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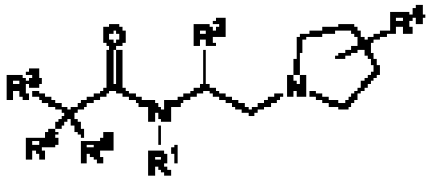
(54) Title: SUBSTITUTED HETEROCYCLIC ACETAMIDES AS KAPPA OPIOID RECEPTOR (KOR) AGONISTS



(I)

(57) Abstract: The present invention relates to a series of substituted compounds having the general formula (I), including their stereoisomers and/or their pharmaceutically acceptable salts, wherein R^1, R^2, R^3. R^4, R^5, and R^6 are as defined herein. This invention also relates to methods of making these compounds including intermediates. The compounds of this invention are effective at the kappa (κ) opioid receptor (KOR) site. Therefore, the compounds of this invention are useful as pharmaceutical agents, especially in the treatment and/or prevention of a variety of central nervous system disorders (CNS), including but not limited to acute and chronic pain, and associated disorders, particularly functioning peripherally at the CNS.

WO 2013/131408 A1

StJBSmUTED HETEROCYCLIC ACETAMDES AΞ KAPPA OPIOID RECEPTOR (KOR) AGONISTS

TECHNICAL FIELD

The present application relates to novel compounds of formula (I), stereoisomers thereof or pharmaceutically acceptable salts thereof as κ (kappa) opioid receptor (KOR) agonists. The present application also describes method of making such compounds and pharmaceutical compositions comprising such compounds.

BACKGROUND

The endogenous opioid system comprises of three principal opioid receptor types in the central neivous system and in the periphery designated as μ (Mu), κ (Kappa) and 5 (Delta). The pharmacological response is elicited by binding of a multitude of endogenous opioid ligards to these receptors, the principal ligands being - the enkepMlins, endorphins, and dynorphins. The exogenous opioids/opiates exert their activity by numicking and/or antagonizing the activity of the endogenous opioid ligands at these receptors. Since the anatomical location, distribution and function of the opioid receptors is wide and varied (Neuropharmacology, 21, 487- 497; Med. Res. Rev, 11, 357-374), the pharmacological effects elicited by their agonism and antagonism are diverse as well.

The μ receptors which bind niorphine and its derivatives are responsible for analgesia, respiratory and gastrointestinal functions, sedation, neuroendocrine functions and mediate opiate dependence. The 5 receptors are abundant in the CNS and mediate analgesia, feeding and various hormonal functions. The κ receptors have a wide distribution in the CNS and the PNS; for example, centrally, these receptors are expressed in caudate-putamen, nucleus accumbens, amygdale, neural lobe of the pituitary gland, etc, and peripherally, they are expressed in the sensory neuron DRG, stomach, duodenum, jejunum, oleum, proximal and distal colon (Acta Neurobiol Exp, 71: 129-138). The κ receptors are responsible for functions including analgesia, gastrointestinal functions like food intake, gut motility, water balance, Iriermoregulation and various neuroendocrine functions. (J. Pharmacol. Exp. Ther. 234, *463-469;* Peptides 4, 797- 800; Goodman and Gilman's The Pharmacological Basis of Therapeutics (11th Edition) Chapter 21, Pp 547 - 590).

Pharmacologic studies with receptor selective ligands have shown that analgesia can be produced by selective activation of each of the three types of opioid receptors. Most clinically used opioid analgesics such as morphine and codeine act as μ receptor agonists. These opioids have well-known, undesirable and potentially dangerous dependence forming side effects associated with their CNS activity. κ opioid receptors, on the other hand, have attracted special attention due to their ability to act peripherally and produce analgesia without causing dependence and respiratory depression that is typically associated with μ receptor activation by morphine (Pharmaceutica Acta Helvetiae, 74, 2-3, Pp 337-344).

The opioid receptors are members of the superfamily of G-protein-coupled receptors (GPCRs). Agonist binding to the κ receptor activates the intracellularly associated G protein, which decreases Ca^{2+} channel conductance or inhibits adenjjiyl cyclase (AC). In addition to analgesia, potential applications of κ selective agonists include the areas of diuresis (Pharmacology Biochemistry and Behavior, 65, 1, Pp 53-59), eating disorders, motion sickness, and neuroprotection (Peptides 29, 12, Pp 2292-2375). Therefore, the κ receptors represent important therapeutic targets. Ligands selective for the κ receptors can serve as important pharmacologic tools. For example, such compounds can be used in competition assays to determine the relative specificity and selectivity of other compounds for the κ receptor, as well as for μ and 5 receptors.

A large number of classes of compounds which act as KOR agonists have been described in the art including the following illustrative classes of compounds.

US7112598 describes KOR agonist comprising **2-ptenylbenzothiasolirLe** derivatives.

US5681830 describes dkrylmethyl piperasane compounds having utility as exogenous receptor combinant species for binding with opioid receptors such as kappa receptors.

EP663401 describes morphinan derivatives as selective KOR agonists and their application as an analgesic, diuretic, antitussive and brain cell protective agent.

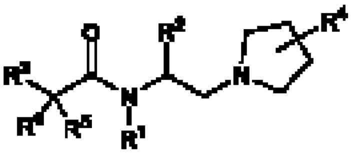
κ opioid receptor (commonly known as KOR) modulation has also been reported to be useful in the treatment of arthritis (Life Sciences, 57, 4, Pp 371-378), hypertension, pain, particularly pain which is inflammatory in origin and post-operative pain, (European Journal of Pharmacology, 429, 1-3, Pp 79-91) inflammation, migraine, inflammatory disorders of the gastrointestinal tract, psoriasis, and irritable bowel syndrome (IBS), Parkinsonism. (European

Journal of Pharmacology 396, *2-3,* Pp 101-107, Molecular Brain Research, 44, 1, Pp 12-20) and stroke.

Accordingly, it is an object of the application to provide compounds as KOR agonists.

SUMMARY

The present application relates to compounds of formula (I),


(I)

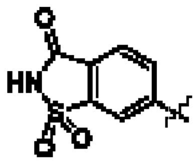
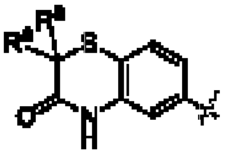
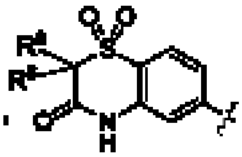
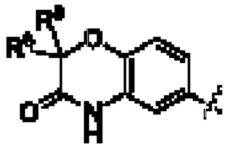
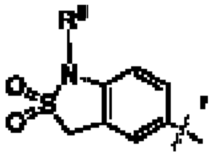
stereoisomers thereof or pharmaceutically acceptable salts thereof;

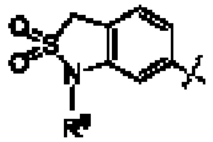
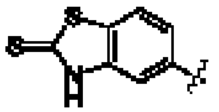
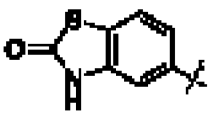
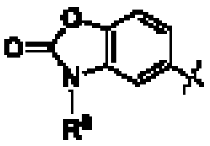
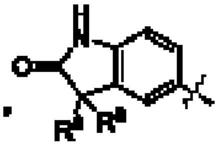
wherein,

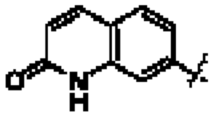
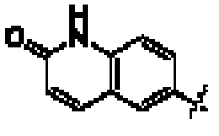
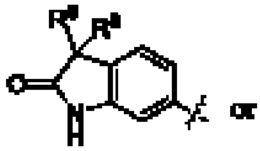
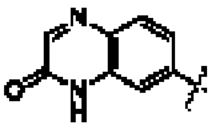
R^1 represents hydrogen, alkyl, haloalkyl or -(C¾)$_m$-cycloalkyl;

R^2 represents (1) cycbalkyl, (2) an group selected from heterocyclyL heteroaryl or aryl, wherein such group is optionally substituted with 1 to *3* substituents selected independently from cyano, hydioxyl, alkji, alkynyl, alkoxy, halogen, haloalkji, haba.ko.iy, -C00R ^{a}, -CONR^{e}R^f, -O-(CH$_2$)$_n$-R^7 or R^{11};

R^3 is an optionally substituted group selected from

, , , , ,

, , , , ,

, ,  or ;

Optional substituent on R^3, in each occurrence, independently selected from halogen, alkyl or haloalkyl;

R^+ is selected from hydrogen, hydroxyl, habgen, alkyl, alkoxy, or habalkyl,

R^5 and R', each are independently selected from hydrogen or alkyl;

R^7 is selected from cyano, tetrazolyL -COOR^4, -C0 NR^{e}R^f or  ;

R^8, in each occurrence, is independently selected from hydrogen, halogen, alkyl or -(CH$_2$)$_q$-R^9;

R^9 is -COOR^4 or  ;

R^{10} is selected from hydrogen, cyano, -COOR^c, -CONR^{e}R^f or tetrazolyl;

R^{11} is selected from (1) (Cs-COcycloalkyL benzyl,  or (2) ***5-6*** membered heteroaryl optionally substituted with 1 to 2 substituents selected independently from alkyl, haloalkyl, haloalkoxyor **-(CH2)nr(C3** -Cc)cycbalkyl;

R^4 and R^c, in each occurrence, iridependently selected from hydrogen, alkyL **heterocyclyi** or heteroaryl;

R¾, in each occurrence, irdependently selected from hydrogen, alkyl or alkoxy,

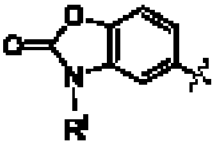
R^6, in each occurrence, independently selected from hydrogen, alkyL haloalkyl or -S(0)$_2$-alkyl;

R^f, in each occurrence, independently selected from hydrogen or alkyl;

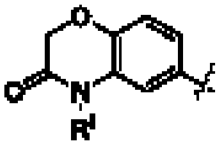
m is selected from 0, 1, 2, ***3*** or 4;

nand ¾ each independently selected from 1 or 2;

provided that when R^2 is pihenyl optionally substituted with alkyL alkoxy or halogen, R^1 is alkyl and one of R^J and R^4 represents hydrogen, then R^3 does not represent the following rings



or



;

wherein R^i, in each occurrence, represents hydrogenor alkyl.

In another embodiment, the apiplication is directed to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an effective amount of a compound of formula (I), stereoisomer thereof or pharmaceutically acceptable salt thereof.

In one embodiment the application is directed to novel compounds of formula (I), stereoisomers thereof or pharmaceutically acceptable salts thereof as κ opioid receptor (KOR) agonists.

In other embodiment, the application is directed to a method for binding opioid receptor, in a patient in need thereof, comprising administering to said patient a composition comprising an effective amount of a compound of formula (I) or a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

In another embodiment, the application is directed to a method of treating or preventing gastrointestinal dysfunction, in a patient in need thereof, comprising administering to said patient a composition comprising an effective amount of a compound of formula (I), a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

In another embodiment, the application is directed to a method of treating or preventing pain, to a patient in need thereof, comprising administering to said patient a composition comprising an effective amount of a compound of formula (I), a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

In another embodiment, the application is directed to a method of administering KOR agonists in a subject, which comprises administering to the subject a therapeutically effective amount of a compound of formula (I), a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION

'Halogen represents fluorine, chlorine, bromine, or iodine.

'Hydroxyl' represents -OH.

'Alkyl' group refers to linear or branched alkyl group with 1 to 10 carbon atoms. Exemplary alkyl group includes, but is not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl, heptyl, octyl and the like.

'Alkynyl' group refers to linear or branched alkynyl group with 1 to 10 carbon atoms. Exemplary alkyl group includes, but is not limited to, ethynyl, prop-1-ynyl, but-2-ynyl, 4-methylpent-2-ynyl and the like.

'Alkoxy' group refers to an -O(alkyl) group, wherein alkyl group is as defined above. Exemplary alkoxy groups include methoxy, ethoxy, n-propoxy iso-propoxy n-butoxy, isobutoxy t-butoxy, and the like. Unless otherwise specified, an alkoxy group has from 1 to 10 carbon atoms.

'Aryl' is a monocyclic or polycyclic aromatic ring system. Exemplary aryl groups include, but are not limited to, phenyl, naphthyl, and the like. Unless otherwise specified, an aryl group typically has from 6 to about 14 carbon atoms but the application is not limited in that respect.

'Cycloalkyl' group refers to a cyclic alkyl group which may be mono, bicyclic, polycyclic, or a fused/bridged ring system. Exemplary cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. Unless otherwise specified, a cycloalkyl group typically has from 3 to about 10 carbon atoms. Typical bridged cycloalkyls include, but are not limited to adamantyl, noradamantyl, bicyclo[1.1.0]butanyl, norbomylibicycloP^llheptanyi), and the like. '(CVCiJcycloalkyT refers to cycloalkyl group having 3 to 6 carbon atoms.

'Haloalkyl' means at least one halogen atom is substituted on an alkyl group. Both halogen and alkyl have the meaning as defined above. Representative examples of haloalkyl groups include, but are not limited to, fluoromethyl, chloromethyl, fluoroethyl, chloroethyl, difluoromethyl, difluoroethyl, trifluoromethyl, dichloroethyl, trichloroethyl and the like. Unless otherwise specified, a haloalkyl group typically has from 1 to 10 carbon atoms.

'Haloalkoxy' means at least one halogen atom is substituted on an alkoxy group wherein alkoxy and halogen groups are as defined above. Exemplary haloalkoxy groups include, but not limited to, fluoromethoxy, chloromethoxy trifluoromethoxy, difluoromethoxy trichloroethoxy fluoroethoxy chloroethoxy difluoroethoxy tnfbroethoxy, perfluoroethoxy (-QCFjCFj), trilluoro-fbutoxy, hexafluoro-i-butoxy, perfluoro-i-butoxy (-$OC(CF_3)_3$), and the like. Unless otherwise specified, an haloalkoxy group typically has from 1 to 10 carbon atoms.

'Heterocyclyl' is a saturated monocyclic or polycyclic ring system of 3 to 10 members having at least one heteroatom or heterogroup selected from one or more of -0-, -N-, -Ξ-, -SO_2, or -CO. Exemplary heterocyclyl groups include one or more of, but not limited to, asetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydro-2H-pymnyl, thbmorpholinyl thtomorphohne-l, 1-dioxide, thiaaohdinyl, 1,3-dioxolanyl, 1,4-dioxanyl, and the like. Unless otherwise specified, a heteiocyclyl group typically has from 3 to about 10 carbon atoms but the application is not limited in that respect.

'Heteroaryl' is an unsaturated, aromatic or non-aromatic, monocyclic or polycyclic ring system of 3 to 10 members having at least one heteroatom or heterogroup selected from one or more of -0-, -N-, -Ξ-, -SO_2, or -CO where R_4 is H, alkyl or a bond. Exemplary lieten aryl groups include one or more of, but not limited to, pyridinyL tluazinyl, pyrazmyL, pyrazolyl, thiazolyl, tetrazolyi, 1,3,4-oxadiazolyl, imidaaolyi, 1,3,4-tMadiazolyl, imidazothiazolyl, indoli.ddin.yl, indolyi, quinolinyL quinoxalinyL 2-oxoiridolinyL 1H-benzo[d]imidazol-2 (3H)-onyl_ benzo[d]oxazol-2 (3H)-onyl_ benzo[d]thiazol-2 (3H)-only, quinolin-2 (lH)-only, 1,3-dihydrobenzo[c] isothiazole 2,2-dioxide-yl, 2H-benzo[b] [1,4]1hiazin-3(4H)-one 1, 1-dioxide-yl, ben2D[d]isomk2ol-3(21 ¾ -one 1,1 -dioxide-yl, benzo[d]thiaaole-2 (3H)-thionyL 2H-benzo[b] [l,4] thiazin-3(4Hi -onyL qumoxalin-2 (1H)-onyi, 2H-benzo[b] [1,4]oxazin-3(4H)-onyl, and the like. Unless otherwise specified, a heteroaryl group typically has from 3 to about 10 carbon atoms.

'5-6 membered heteroaryT is a heteroaryl group as defined above, having 5 to 6 ring atoms and is monocyclic. Exemplary heteroaryl groups include one or more of, but not limited to, pyridinyL thiazinyL pyrazinyL pyrazolyL thiazolyl, tetrazolyi, 1,3,4-oxadiazolyl, imidazolyl and the like.

The KOR maybe an animal or a mammalian or rion-mammalian receptor, such as a human receptor

Optionally substituted' means that the substitution is optional and therefore it is possible for the designated atom or group to be unsubstituted. In the event a substitution is desired, then such substitution means that any number of hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the normal valence of the designated atom is not exceeded, and that the substitution results in a stable compound. For example, in formula (I) when a substituent is oxo (i.e., =0), then two hydrogens on the atom are replaced and when the substitution is fluoro, then one hydrogen on the atom is replaced and the like. When more than one substituent is present on an atom or group, the chosen substituents are independent of each other (i.e same or different).

As used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly indicates otherwise.

As used herein, the term 'subject' or 'patient' means mammals, such as humans and other animals, including horses, dogs, cats, rats, mice, sheep, pigs, etc. In exemplary embodiments, the subject may include subjects for which treatment and/or prevention of the conditions described herein would be beneficial.

The terms 'treating' or 'to treat' means to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms.

The term 'treatment' includes alleviation, elimination of causation of or prevention of any ofthe diseases or disorders described below. Besides being useful for human treatment, these combinations are also useful for treatment of other mammals, including horses, dogs, cats, rats, mice, sheep, pigs, etc.

The compounds described herein are typically administered in admixture with one or more pharmaceutically acceptable excipients or carriers in the form of a pharmaceutical composition. A 'composition' may comprise one compound or a mixture of compounds. A 'pharmaceutical composition' is any composition useful in producing at least one physiological response in a subject to which such pharmaceutical composition is administered.

For ease of reference, in this application it will be described in terms of administration to human subjects. It will be understood, however, that such descriptions are not limited to administration to humans, but will also include administration to other animals unless explicitly stated otherwise.

A 'therapeutically effective amount' is the amount of compound of the present application that is effective in generating biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease.

In one embodiment the term 'a therapeutically effective amount' refers to the amount ofthe compound of formula (I) ofthe present application that, when administered to a subject is effective in at least partially alleviating, inhibiting, preventing and/or ameliorating a condition, or a disorder or a disease associated with KOR.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art.

One or more compounds of formula (I) can be supplied in the form of a therapeutic composition that is within the scope ofthe present application

One or more compounds of formula (I) can be supplied in the form of a novel therapeutic composition that is within the scope of the pre sent application.

One or more compounds of formula (I) can be supplied in the form of a therapeutic composition that is within the scope of the present application

The term 'Pharmaceutically acceptable salts' refers to any acid or base salt, pharmaceutically acceptable solvates, or any complex of the compound thai, when administered to a recipient, is capable of providing (directly or indirectly) a compound as described herein. It should be appreciated, however, salts that are not pharmaceutically acceptable also he within the scope of the application. The preparation of salts can be carried out using known methods.

For example, pharmaceutically acceptable salts of compound of formula (I) contemplated refers to salts prepared from acids or bases including inorganic or organic acids and inorganic or organic bases by conventional chemical methods using a compound of formula (I). Generally such salts maybe prepared, for example, by making free base of the compounds and reacting with a stoichiometric quantity of the appropriate acid and *vice-versa* in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media such as one or more of ether, ethyl acetate, methanol, ethanol, isopropanol or acetonitrile may be utilized.

When the compound of formula (I) is basic, salts may be prepared from acids, including inorganic or organic acids (acid addition salts). Examples of such acids include, but not limited toformic, acetic, trifluoroacetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspaitic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hyiroxybenzoic, phenylacetic, mandelic, embonic (pamoic),nitric, hydrochloride, hydrobromide, isoethionic, hydrtiodide, phosphoric, sulfuric, succinic, tartaric, methane sulfonic, ethanesulfonic, benzene sulfonic, benzoic, mucic, pantothenic, p-toluenesulfonic, camphorsulfonic, 2-hydroxyethanesulfonic, sulfanilic, cycfohexylantinosulfonic, algenic, β-hydroxybutyric, galactaric, and galacturonic acid, and the tike.

Salts formed from inorganic bases include sodium, potassium, hthium, calcium, copper, magnesium, manganic salts, manganous, zinc, aluminum, ammonium, ferric, ferrous and the like.

Salts derived from organic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimemyknunDetlianol, ethanolamine, ethylenediamine, N-ethylmorphohne, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylgiucamine, morpriDline, piperazine, piperide, polyamine resins, pocaine, purines, 1]¾obromine, trielhykmine, trimethykmine, tripropylamine, tromethamine, and the like.

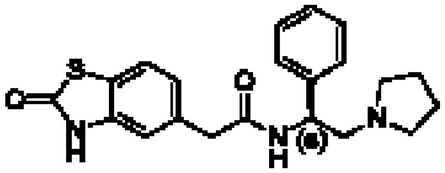
Tharmaceutically acceptabl salts' in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates.

Pharmaceutically acceptable solvates of compound of formula (I) maybe hydrates or comprising other solvents of crystallisation such as alcohols. Pharmaceutically acceptable solvates of compound of formula (I) may be prepared by conventional methods such as dissolving the compounds of formula (I) in solvents such as water, methanol, ethanol etc., preferably w¾ter and recrystallising by using different crystallisation techniques.

The term 'stereoisomers' is a general term used for all isomers of an individual molecule that differ only in the orientation of their atoms in space. Where the compounds according to the present application possess one or more asymmetric centers and compounds with asymmetric centers give rise to enantiomers, diastereomers or both as pure or partially purified compounds . 11is to be understood that all stereoisomenc forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropsiomers, as w¾ll as mixtures thereof such as forms, are included in the scop; of the present application Preparation of such stereo isomeric forms of compurd of formula (I), may be achieved by appropriate modification of the methodology known in the art. Their absolute stereochemistry maybe determined by the suitable methods. If required, racemic mixtures of the compound of formula (I) may be separated to isolate individual enantiomers or diastereomers. Such separation can be carried out by methods known in the art, such as the coupling of a racemic mixture of compound of formula (I) to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallisation or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chital residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods using chiral stationary phases, which methods are will known in the art. Alternatively any enantiomer or diastereomer of a compound maybe obtained by stereoselective synthesis using optically pure starting materials or known reagents.

For any particular compound disclosed herein, wherein the stereochemistry of any particular chiral atom is not specified, then all stereoisomers are contemplated and included as the compounds of the application. Where stereo chemistry is specified by a solid wedge or a dashed wedge bond or dashed line representing a particular configuration then that stereoisomer is so specified and defined. Following the standard chemical literature description practice and as used herein, a full wedge bond means above the ring plane, and a dashed wedge bond or dashed line means below the ring plane.

Furthermore the configuration of a chiral atom maybe denoted as (R) or (Ξ) by the symbols (R) and (Ξ) written next to the chiral atom. For example, a compound (Ξ)-2-(2-oxo-2,3-dihydrobenzo[d]thiazol-5-yl)-N-(1-phenyl-2-(pyrrolidin-1-yl)ethyl)acetamide may be represented as provided below.



Further certain individual molecules may exist as geometric isomers (cisitrans). Similarly, certain compounds of this application may exist in a mixture of two or more structurally distinct forms that are in rapid equilibrium, commonly known as tautomers. Representative examples of tautomers include keto-enol tautomers, phenol-keto tautomers, rdtroso-oxime tautomers, imine-enamine tautomers, etc. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present application.

In the formulae depicted herein, a bond to a substituent and/or a bond that links a molecular fragment to the remainder of a compound maybe shown as intersecting one or more bonds in a ring structure. This indicates that the bond may be attached to any one of the atoms that constitutes the ring structure, so long as a hydrogen atom could otherwise be present at that atom. Where no particular substituent(s) is identified for a particular position in a structure, then hydrogens) is present at that position.

For any particular compound disclosed herein, any general structure presented also encompasses all conformational isomers, regioisomers and tautomers that may arise from a particular set of substituents.

Compounds of the application, such as a compound of formula (I) and salts thereof, also include other forms, such as their stereoisomers (except where specifically indicated), prodrugs, hydrates, solvates, acid salt hydrates, or any isomorphic crystalline forms thereof.

Compounds employed in the methods and compositions of the present application may exist in prodrug form. As used herein, "prodrug" is intended to include any covalently bonded carriers which release the active parent drug, for example, the compound of Formula (I), or other formulas or compounds employed in the present methods and compositions in vivo when such prodrug is administered to a mammalian subject. The term "prodrug" also includes compounds which may be specifically designed to maximize the amount of active species that reaches the desired site of reaction and which themselves may be inactive or minimally active for the activity desired, but through biotransformation are converted into biologically active metabolites. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds employed in the present methods may, if desired, be delivered in prodrug form. Thus, the present application contemplates methods of delivering prodrugs. Prodrugs of the compounds employed in the present application, for example a compound of Formula (I), may be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound.

Accordingly prodrugs include, for example, compounds described herein in which a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or carboxylic acid, respectively. Examples include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups; and alkyl, carbocyclic, aryl, and alkylaryl esters such as methyl, ethyl, propyl, iso-propyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, phenyl, benzyl, and phenethyl esters, and the like.

'Pain' refers to the perception or condition of unpleasant sensory or emotional experience, associated with actual or potential tissue damage or described in terms of such damage. 'Pain' includes, but is not limited to, two broad categories of pain acute and chronic pain. Buschmann, H.; Christoph, T; Friderichs, E.; Ivhul, C ; Sundermann, B; eds.; Analgesics, Wiley-VCH, Verlag GMbH & Co. KgaA, Weinheim, 2002; Jam, K. K., 'A Guide to Drug Evaluation for Chronic Pain'; Emerging Drugs, 5(2), 241-257 (2000), the disclosures of which are hereby incorporated herein by reference in their entireties. Non-limiting examples of pain include, for example, nociceptive pain, inflammatory pain, visceral pain, somatic pain, neuralgias, neuropathic pain, AIDS pain, cancer pain, phantom pain, and psychogenic pain, and pain resulting from hyperalgesia, pain caused by rheumatoid arthritis, migraine, allodynia and the like.

The term 'gastrointestinal dysfunction', as used herein, refers collectively to maladies of the gastrointestinal system, particularly the stomach and small and large intestines. Non-limiting examples of gastrointestinal dysfunction include, for example, diarrhea, nausea, emesis, post-operative emesis, opioid-induced emesis, irritable bowel syndrome, opioid-bowel dysfunction, opioid induced constipation, ileus, including post-operative ileus, post-partum ileus and opioid-induced ileus, colitis, decreased gastric motility, decreased gastric emptying, inhibition of small intestinal propulsion, inhibition of large intestinal propulsion, increased amplitude of non-propulsive segmental contractions, constriction of sphincter of Oddi, increased anal sphincter tone, impaired reflex relaxation with rectal distention, diminished gastric, biliary, pancreatic or intestinal secretions, increased absorption of water from bowel contents, gastroesophageal reflux, gastroparesis, cramping, bloating, distension, abdominal or epigastric pain and discomfort, non-ulcerogenic dyspepsia, gastritis, constipation, or delayed absorption of orally administered medications or nutritive substances.

The term 'peripheral' designates that the compound acts primarily on physiological systems and components external to the central nervous system (CNS). In preferred form, the compounds of the present application employed in the methods of the present application exhibit high levels of activity with respect to peripheral tissue, such as, gastrointestinal tissue, while exhibiting reduced, and preferably substantially no CNS activity at therapeutically relevant doses.

The phrase 'does not substantially cross,' as used herein, means that less than about 20% by weight of the compound employed in the present methods crosses the blood-brain barrier, preferably less than about 15% by weight more preferably less than about 10% by weight, even more preferably less than about 5% by weight and still more preferably a non-detectible, de minimus, or even 0% by weight of the compound crosses the blood-brain barrier at therapeutically relevant doses. Selected compounds can be evaluated for CNS penetration by determining plasma and brain levels following i.v., oral, subcutaneous or intraperitoneal administration.

The compounds described herein are typically administered in admixture with one or more pharmaceutically acceptable excipients or carriers in the form of a pharmaceutical composition. A 'composition' may contain one compound or a mixture of compounds. A 'pharmaceutical composition' is any composition useful or potentially useful in producing at least one physiological response in a subject to which such pharmaceutical composition is administered.

The pharmaceutical compositions of compounds of formula (I) maybe administered enterally and/or parenterally Parenteral administration includes subcutaneous, intramuscular, intradermal, intmmammary, intravenous, and other administrative methods known in the art. Enteral administration includes solution, tablets, sustained release capsules, enteric coated capsules, syrups, beverages, foods, and other nutritional supplements. When administered, the present pharmaceutical compositions may be at or near body temperature. In some embodiments, the present pharmaceutical compositions maybe below body temperatures. In other embodiments, the present pharmaceutical compositions may be above body temperatures.

The compounds of the present application maybe administered in a wide variety of different dosage forms. For example, they may be combined with various pharmaceutically acceptable inert carriers in the form of one or more of, but not limited to, tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers may include one or more of solid diluents or fillers, sterile aqueous media, and various nontoxic organic solvents, etc. Moreover, oral pharmaceutical compositions may be sweetened and/or flavored. In general, the compounds of the application maybe present in such dosage forms at concentration levels ranging from about 0.1 % to about 90% by weight.

For oral administration, tablets may contain various excipients such as one or more of nucrocrystalline cellulose, sodium citrate, calcium carbonate, clicalcium phosphate, and glycine, along with various disintegrants such as starch (sue has corn, potato or tapioca starch), algirdc acid and certain complex silicates, together with granulation binders like plyvinylpyrrohdone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulphate and talc maybe employed. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; exemplary materials in this connection may also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or fkvoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, and various combinations thereof.

For parenteral administration (including intrapritoneal subcutaneous, intravenous, intradermal or intramuscular injection), solutions of compounds of the present application in, for example, either sesame or peanut oil or in aqueous propylene glycol maybe employed. The aqueous solutions maybe buffered, if necessary or desirable, and the liquid diluent first rendered isotonic. These aqueous solutions maybe suitable for intravenous injection purposes. The oily solutions may be suitable for intraarticular, intramuscular, and/or subcutaneous injection purposes. The synthesis of such solutions under sterile conditions may be accomplished by standard pharmaceutical techniques known to those having ordinary skill in the art. For parenteral administration, examples of suitable preparations may include solutions, such as oily or aqueous or non-aqueous solutions, as well as suspensions, emulsions, and/or implants, including suppositories. Compounds of the present application may be formulated in sterile form in multiple or single dose formats. For example, the compounds of the present application may be dispersed in a fluid carrier such as sterile saline and/or 5% saline dextrose solutions commonly used with injectables.

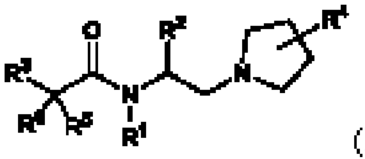
In another enitoodimenl, the compounds of the present application may be administered topically. For example, it maybe desirable to administer the compounds of the present application topically when treating inflammatory conditions of the skin. Non-limiting examples of methods of topical administration include transdermal, buccal, or sublingual application For topical applications, therapeutic compounds maybe suitably admixed in a pharmacologically inert topical carrier such as a gel, an ointment, a lotion, and/or a cream. Such topical carriers may include water, glycerol, alcohol, propylene glycol, fatty alcohols, triglycerides, fatty acid esters, and/or mineral oils. Other possible topical carriers may include liquid petrolatum, isopropylpalmitate, polyethylene glycol, ethanol 95%, polyoxyethylene monolaurate 5% in water, sodium lauryl sulphate 5% in water, and the like, and combinations thereof. In addition, materials such as surfactants, anti-oxidants, humectants, viscosity stabilisers, and the like, and combinations thereof, also maybe added if desired.

It will be appreciated by those having ordinary skill in the art that the exemplary amounts of active compounds used in a given therapy will vary according to the specific compound being utilised, the particular compositions formulated, the mode of application, the particular site of administration, etc. Optimal administration rates for a given protocol of administration maybe ascertained by those having ordinary skill in the art using conventional dosage determination tests conducted with regard to the foregoing guidelines.

In general, compounds of the present application for treatment maybe administered to a subject in a suitable effective dose of one or more compounds of the present application maybe in the range of from about 0.01 to about 100 milligrams per kilogram of body weight of recipient per day, in some embodiments, in the range of from about 0.5 to about 50 milligrams per kilogram body weight of recipient per day, in still other embodiments, in the range of from about 0.1 to about 20 milligrams per kilogram body weight of recipient per day. The exemplary dose maybe suitably administered once daily, or several sub-doses, e.g. 2 to 5 sub-doses, may be administered at appropriate intervals through the day, or on other appropriate schedules.

Reference will now be made in detail to the embodiments of the application, one or more examples of which are set forth below. Each example is provided by way of explanation of the application, and not by way of limitation of the application In fact it will be apparent to those skilled in the art that various modification and variations can be made in the present application without departing from the scope or spirit of the application. For instance, features illustrated or described as part of one embodiment can be used on another embodiment to yield a still further embodiment. Thus it is intended that the present application cover such modificatons and variations as come within the scope of the appended claims and their equivalents. Other objects, features, and aspects of the present application are disclosed in, or are obvious from, the following detailed description. It is to be understood by one of ordinary skill in the art that the present discussion is a description of exemplary embodiments only, and is not to be construed as limiting the broader aspects of the present application.

The present application relates to compounds of formula (I),



(I)

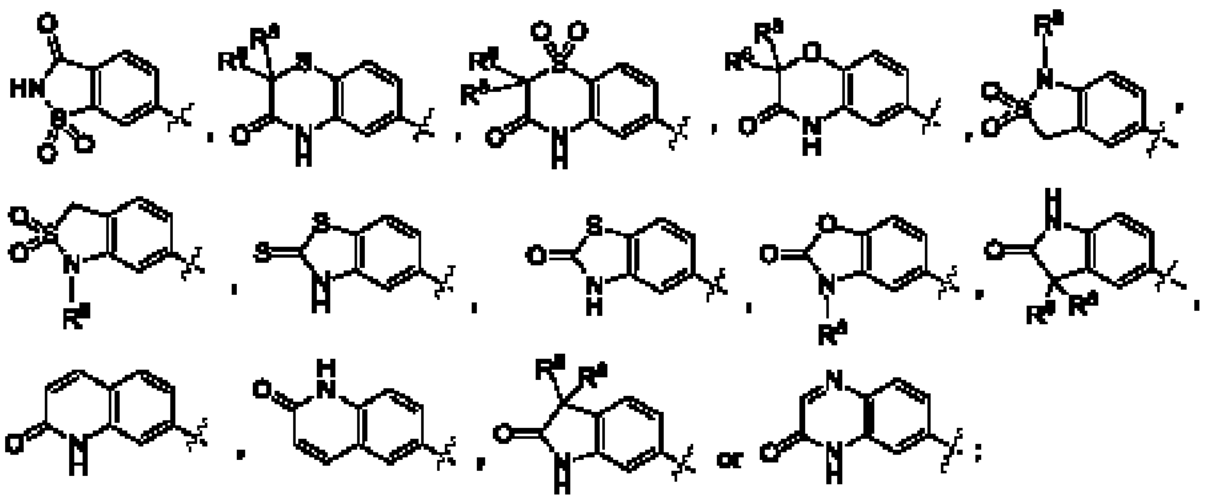
stereoisomers thereof or pharmaceutic ally acceptable salts thereof;

wherein,

R^1 represents hydrogen, alkyl, haloalkyl or -(CHj)nrcycloalkyl;

R^2 represents (1) cycloalkyL (2) an group selected from heterocyclyL heteroaryl or aryl, wherein such group is optionally substituted with 1 to *3* substituents selected independently from cyano, hydroxyl, alkyl, alkynyl, alkoxy, halogen, haloalkyl, haloalko-iy, -COOR^4, -CONR^R*, -CKCH^-R ^{7} or R^{11};

R^3 is an optionally substituted group selected from



Optional substituent on R^3, in each occurrence, independently selected from halogen, alkyl or haloalkyl;

R^{+} is selected from hydrogen, hydroxyl, halogen, alkyl, alko-iy, or haloalkyl;,

R^{5} andR' , each are independently selected from hydrogen or alkyl;

R^{7} is selected from cyano, tetrazolyl, -COOR4, -CONR^{e}R^{f} or 

;

R^{8}, in each occurrence, is independently selected from hydrogen, halogen, alkyl or -$(CH_2)_q$-R^{9};

R^{9} is -COOR^{a} or 

;

R^{10} is selected from hydrogen, cyano, -COOR^{c}, -CONR^{e}R^{f} or tetrazolyl;

R^{11} is selected from (1) $(C_3$-$C_6)$cycloalkyl, benzyl, 

or (2) 5-6 membered heteroaryl optionally substituted with 1 to 2 substituents selected independently from alkyl, habalkyl, haloalkoxyor -$(CH_2)_m$-$(C_3$-$C_6)$cycloalkyl;

R^{4} and R^{c},in each occurrence, independently selected from hydrogen, alkyL heterocyclyl or heteroaryl;

R^{b}, in each occurrence, independently selected from hydrogen, alkyl or alkoxy,

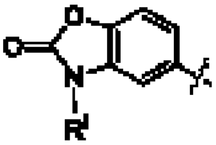
R^{6}, in each occurrence, independently selected from hydrogen, alkyl, haloalkyl or -S(0)$_2$-alkyl;

R^{f}, in each occurrence, independently selected from hydrogen or alkyl;

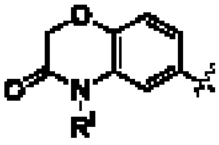
m is selected from 0, 1, 2, 3 or 4;

nand ¾ each independently selected from 1 or 2;

provided that when R^{2} is phenyl optionally substituted with alkyl, alkoxy or halogen, R^{1} is alkyl and one of R^{J} and $R^{'}$ represents hydrogen, then R^{3} does not represent the following rings



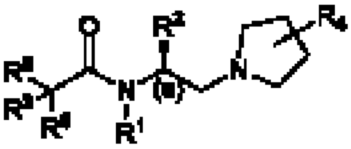
or



;

wherein R^{i}, in each occurrence, represents hydrogen or alkyl.

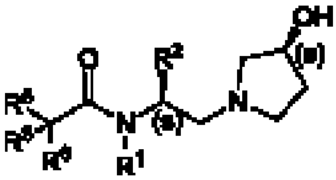
One embodiment of formula (I) includes compunds of formula (lb),



(Ib)

stereoisomers thereof or pharmaceutically acceptable salts thereof

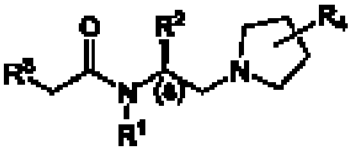
Another embodiment of formula (I) includes compounds of formula (Ib*),



(Ib*)

stereoisomers thereof or pharmaceutically acceptable salts thereof

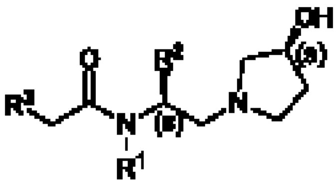
Another embodiment of formula (I) includes compounds of formula (Ic),



(Ic)

stereoisomers thereof or pharmaceutically acceptable salts thereof

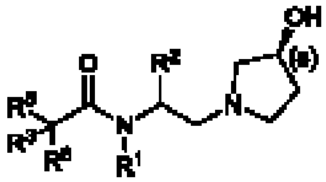
Another embodiment of formula (I) includes compounds of formula (Ic*).



(Ic*)

stereoisomers thereof or pharmaceutically acceptable salts thereof

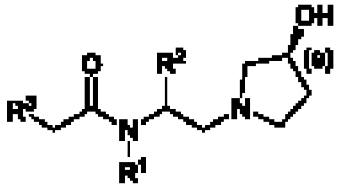
Another embodiment of formula (I) includes compounds of formula (Id),



(Id)

stereoisomers thereof or pharmaceutically acceptable salts thereof

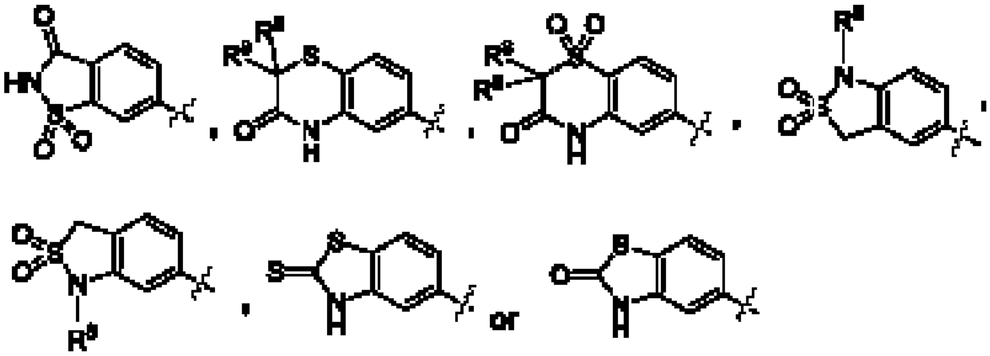
Another embodiment of formula (I) includes compounds of formula (Id^1),



(Id^1)

stereoisomers thereof or pharmaceutically acceptable salts thereof

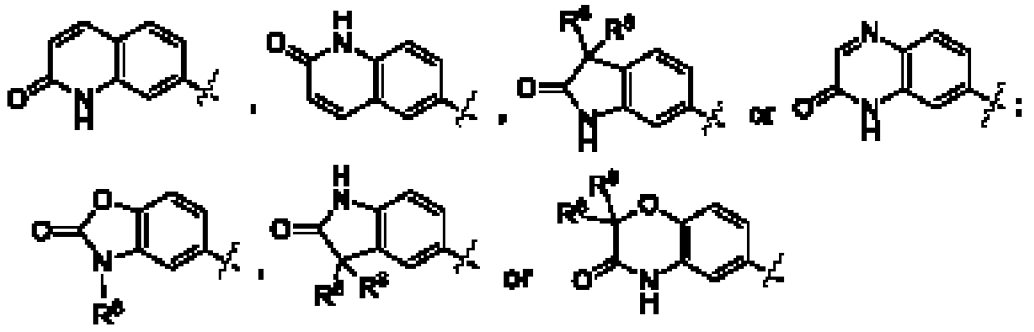
Another embodiment of formula (I) includes compounds of formula (I), stereoisomers thereof or pharmaceutically acceptable salts thereof, wherein R^3 is selected from,



and

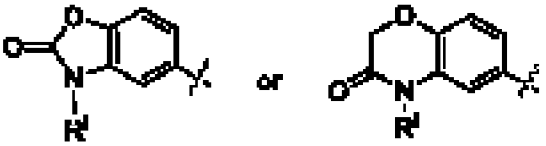
R^8 is as defined in formula (I).

Another embodiment of formula (I) includes compounds of formula (I), stereoisomers thereof or pharmaceutically acceptable salts thereof, wherein R^3 is selected from,

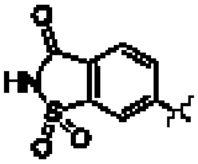


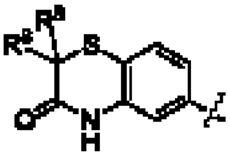
and R^8 is as definedin formula (I).

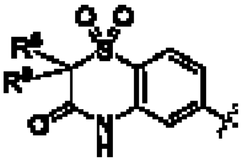
Another embodiment of formula (I), (lb), (Ibi), (Ic), (Ici), (Id) or (Idi), wherein R^2 is phenyl optionally substituted with 1 to 3 groups independently selected from cyano, hydroxy!, alkyl, alkynyl, alkoxy, halogen, haloalky^ haloalkoxy, -COOR^a, -CONR^{e}R^f, -O-(CH$_2$)$_n$-R^7 or R^{11} and all other groups are as defined in formula (I); provided that when R^2 is phenyl optionally substituted with alkyl, alkoxy or halogen, R^1 is alkyl and R^5 and R' independently represents alkyl, then R^3 does not represent the following rings

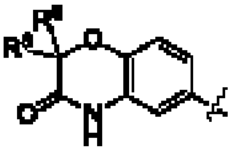


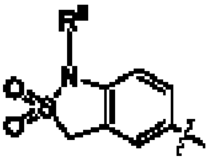
, wherein, in each occurrence, R^i represents hydrogen or alkyl.

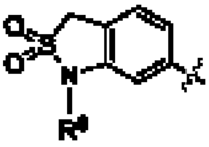
In one aspect of the above embodiment R^3 represents  .

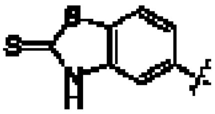
Inanother aspect of the above embodiment R^3 represents  .

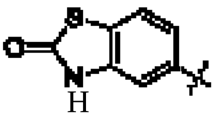
Inanother aspect of the above embodiment R^3 represents  .

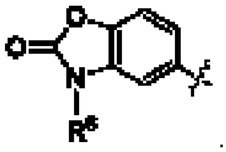
Inanother aspect of the above embodiment R^3 represents  .

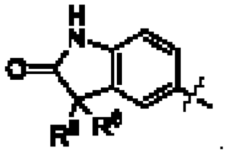
Inanother aspect of the above embodiment R^3 represents  .

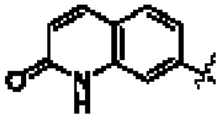
Inanother aspect of the above embodiment R^3 represents  .

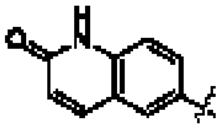
Inanother aspect of the above embodiment R^3 represents  .

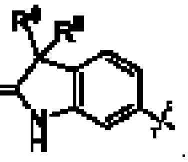
Inanother aspect of the above embodiment R^3 represents  .

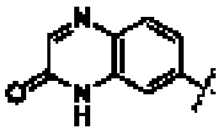
In another aspect of the above en±ıodiment R^3 represents  .

In another aspect of the above embodiment R^3 represents  .

In another aspect of the above embodiment R^3 represents  .

In another aspect of the above embodiment R^3 represents  .

In another aspect of the above embodiment R^3 represents  .

In another aspect of the above embodiment R^3 represents  .

In an embodiment, specific compounds of formula (I) without any limitation are enumerated in Table (1):

Table (1)

N-((3)-2-((S)-3-hydroKypyrrohdin-l -yl)-l -phenyleth7l)-N-meth7l-2-(2-OKoiiidolin-o-ji)acetamide;

N-[(1Ξ)-2-[(3Ξ)-3-hydroKypyrrolidin-1-yl]-1-phenjlethylj -2-(3-oχü-3,4-dihydrü-2H-l,4-benzoxazin-6-yl)acetamide;

N-((S)-2-((S)-3-hydroKypyrrohdin-l -yl)-*l* -phenylethyl)-N-methyl-2-(3-oxo-3,4-dihydrocjuinoxalm-6-yl)acetamide ;

(S)-2-(2-o io-2,3-dih^drobenzo[d]thiaaol-i -yl)-N-(1-phenyl-2-(pyrrolidin-1-ji)ethyl)acetamide ;

2-(1,1^oxido-3-oxo-3,4-dihydro-2H-benso[b][1,4]thiazin-6-yl)-N-((S)-2-((Ξ)-3-

hydroxypyiiOlidin- 1-*yi)* -1-(3-(trifluoron¾tliDxy)phenyl)ethy^ N-methylacetamide ;

N-((S)-1-(3-cyanophenyl)-2-((S)-3-hydto xypyiTdidin-1 -yl)ethyl)-2-(1, 1-dioxido-3 -oxo-3,4-dihydro-2H-benzo[b] [1,4]thiazin-6-yl)-N-methylacetamide ;

N-((Ξ)-2-((Ξ)-3-hyda xypyro lidirL1-yl)-l -phenylethyl)-N-n¾thyl-2 -(3-oxo-3 ,4-dihydro -2H-benzo[b*/* [1,4] thiazin-6-yl)acetamide;

2-(1,1-dioxido-3-oxo-2,3-diJiydrobenzo[d] isothiazol-6i-yl)-N-((Ξ)-2 -((Ξ)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methylacetamide ;

2-(2,*2*-dioxido- 1,3-dihydrobenzo[c] isothiasd-i5-yl)-N-((S) -2-((S)-3-hydroxypyrroHdin- 1-yl)-1-(3-(trifluoromethyl)pl¾nyl)ethyl)-N-methylacetamide;

5-(2 -(((Ξ)-2-((Ξ)-3-hydroxypyrrolidm-l -*y\)*- 1-phenylethylX me1hyl)aniLno)-2-oxoe1hyl)-1,3-dihydroben2o[c] isdhiaml-l -iuin 2,2-dioxide 2,2,2-trifluoroacetate;

N-((Ξ)-1-(3-(diiluoa methoxy)phenyl)-2-((S) -3-hydr oxypyirdidin-l -y.)ethyl)-2-(1,1-dioxido-3-oxo-3.4-dih^diio-2H-benso[b] [1,4]thiazin-6-yl)-N-methylacetamide;

2-(3,3-difluora-2-oxomdolin- ≤-5il)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-*yi)* -1-phenyiethyl)-N-melhylacetainide ;

2-(3,3-dif uoro-2-oxoindolin-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-*yi)* -1-phenylethyi)ac etainide ;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-ethyl-N-((S)-2-((S)-3-hydroxypyrrolidin- 1-*yi)* -1-(3-(trifluor omethoxy)phenyl) ethyl)acetanude ;

2-(1,1-dioxido-3-oxo-3,4-d^ydro -2H-ben:m[b] [1,4]thiazin-6-yl)-N-((3)-2-((Ξ)-3-methoxypyirokdin-1 -*yi)*- 1-(3-(trifluoron¾thoxy) plienyl)ethyl)-N-n¾ethylacetainide

2-(1,1-dioxido-3-oxo-3,4-dihydiO -2H-ben3o[b] [1,4]thiazin-6-yl)-N-((3)-2-((Ξ)-3-liiydroxypynOlidiiL-1-yl)-1-(3-(trifluor oinetho xy)phenyL)ethyl)-N-(2.2,2-trifluoiOe1hyl)acetainide 2,2,2-trifluoroacetate;,

2-(1,1-dioxido-3-oxo-3,4-diliydiO -2H-benao[b] [1,4]thiazin-6-yl)-N-(2 ***i(3)-3-*** liydrQxypyrrolidin- 1-yl)-1-(tetiiahydio-2H-pyi™-4-yl)ethy^ N-methylacetamide-2,2,2-trifluoroacetate;

3-((Ξ)-2-((Ξ)-3-hydroxypyiiD lidin- 1-*yi)*- 1-(N-methyl-2-(2-oxo-2,3-dihydrobenzo [d] thiasol-5-yl)acetamido)ethyl)ben3oic acid;

3-((Ξ)-2-((Ξ)-3-hydroxypyiiD lidin- 1-yl)- 1-(N-niethyl-2-(2-oxo-2,3-diriydrobenzo [d] thiaml-5-yl)acetaniLdo)ethyi)ben2ainide ;

(S)-2-(3-benzyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)-N-(1-(3-hydroxyphenyl)-2-(pynOlidin- 1-yl) ethyl)acetamide;

N-((S)-1-(3-(1H-tetraml-i-yl) phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(1-methyl-2,2-dioxido -1,3-dihydiiobenao[c]isothiazol-f -yl)acetamide ;

2-(3-((Ξ)-1-(2-(1,1-dioxido-3-oxo-3,4-dihydn>2H-ben2o [b] [1,4J thiazin-Q-yl)-N-methyl acetainido)-2-((S) -3-hydroxypynO lidin- 1-yI)ethyI)phenoxy)acetic acid;

3-((Ξ)-2-((Ξ)-3-hydroxypyrto lidin- 1-yl)- 1-(N-i™thyl-2-(2-oxomdolin-6-yl)acetamido) ethyl) benzoic acid;

3-((Ξ)-2-((Ξ)-3-hydroxypyrto lidin- 1-yl)- 1-(N-methyl-2-(2-oxomdolm-0-yl)acetaniido) ethyl) benzamide;

N-((S)-1-(3-cyaiiophe nyl)-2-((S)-3-fluo-Opynolidin- 1-yl)ethyl)-N-methyl-2-(2 -oxoindolin-o-yl)acetamide;

N-((S)-1-(3-(2-amino-2-oxoethoxy)phenyl)-2-((3) -3-hydroxypyriolidin-1 -yl)ethyl)-N-n¾tl^-2-(2-oxomdohn- ≤-yi)acetaniide ;

N-((3)-2-((3)-3-hydroxypynDhdirL-l -yl)-l -(3-(2-(methylSulfonamido)-2-oxo ethoxy)phenyl)ethyl) -N-methyl-2 -(2-oxoindolin-6-yl)acetanude ;

3-((Ξ)-2-((Ξ)-3-fluoropyrrolidin-1-yl)-1-(N-memyl-2-(2-oxoindo lin-ö-yl)ace tamido)ethyl) benzoic acid;

2-(3-((Ξ)-2-((Ξ)-3-flTioropyiTolidin-1-yl)-1-(N-me thyl-2-(2-oxoindo lin-6-yl) acetamido) ethyl) phenoxy)acetic acid;

N-((S)-1-(3-(2-amino-2-oxoethoxy)phenyl)-2-((3) -3-fluoropyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxoindolin-6-yi)ace tamide ;

3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin- 1-yl)- 1-(N-methyl-2-(3-oxo-3 ,4-dihydmqiiimxalirL-0-yi)acetamido)ethyl **)beri2Dic** acid;

3-((Ξ)-2-((Ξ)-3-hydroxypyno lidin- 1-yl)- 1-(N-methy_-2-(3-oxo-3,4-dihydro-2H-benao[b] [1,4J thiazin-6-yl)ac etamido)ethyl)benzamide ;

N-((S)-1-(3-ethynylphenyl)-2-((S)-3-hydioxypynohdin- 1-yl)ethyl)-N-methyl-2 -(2-oxo-2,3-dihydrobenao [d] thasol-5-yl)acetamide ;

N-((Ξ)-2-((Ξ)-3-hydroxypynOhdin-l -yl)-l -(3-(5-(trifluoromethyl)- 1,2,4-oxadiaaol-3-yl)phenyl) ethyl)-N-memyl-2-(3-oxo-3.4dihydro^ uinoxalin-6-yl)acetamide ;

N-((Ξ)-2-((Ξ)-3-hydroxypytTohdin-l -yl)-l -(3-(5-methy±- 1,2,4-oxadiaaol-3-yl)phenyl) ethyl)-

N-methyl-2 -(2-o xoindolin-o -yi)acetamide ;

N-((S)-2-((Ξ)-3 **-hydroxypyrrokdin -l** -yl)-l -(3 **-(thia**..ol-2-yi) **phenyl)ethy** -)-**N -:methyl-2**-(**2-oxoindolin-ij** -yL)ac **etamide ;**

N-((S)-1-(3-(but- 1-yn- 1-yl)phenyl)-2-((3) -3 -hydroxypytrdidin-l *-yl)eihyi)-2-(2,2-dioxi&o*-1,3-dihydrobenzo [c] isothiazol-fi-yl) -N-methylacetamide ;

3-((Ξ)-2-((Ξ)-3 -hydroxypyrrolidin-1 -yl)- 1-(N -methyl-2-(2-oxoiiuiolin-6-yl)acetam **dD)** ethyl) -N-(2,2,2-trifluoroethyl)benzamide ;

N,N-diethyi-3-((3)-2-((Ξ)-3-hydioxypynOHdin-l -yi)- 1-(N-methyl-2 -(2 -ox oindolin-o"-yl)acetamido)etl^l)benzamide ;

3-((Ξ)-2-((Ξ)-3 -hydroxypyrto lidin-1 -yl)- 1-(N-methyl-2-(2-oxo-2 ,3-dihydrobenzo [d] thiam l-5-yl **)acetaraidD**)ethyl)-N-N-dimetl^Ibensamide 2,2,2-triflTioroac etate ;

N-((Ξ)-1-(3-(2-(diethylaniino)-2-oxoethoxy) **ph**enyl)-2-((S)-3-hydroxypyriOlidin- 1-yl)ethyl)-N-methyi-2 -(2-o xoindolin-6-yl)acetamide ;

N-((Ξ)-1-(**3**-(**2-(diethylantino**)-**2-oxoethoxy) phe nyl**)-2-((S)-**3-hydroxypyriOlidin-** 1-**yl)ethyl)-N-methyi -2**-(2-o **xo-2**,**3-dihydrobenzo** [d] **thiazol -5-yl)acetamide ;**

N-((S)-1-(3-f uo ro-5-(thLazd-2-yl)phenyl)-2-((S)-3-hydioxypyrrolidin-1-yl) ethyl) -N-methyi-2-(2 -oxoindolin-6-yl)ace tamide ;

N-((S)-2-((Ξ)-3 -hydtOxypynOlidin-l -yl)-l -(3-(2-methyl-2H-tetrazol-5 -yl)phenyl)e thyl) -N-n¾thyl-2-(2-oxoindolin-6-yl)acetamide ;

N-((S)-2-((3)-3-hydtOxypynOHdin-l -yl)-l -phenylethyl)-2-(3 -methyl -2-oxo-2 ,3-dihydrobenzo [d] oxazol-5 -yi)acetamide ;

(3)-2-(3-(3-c **yanobenzyl**)-**2-oxo -2**,**3-dihydiObenzo** [dJ oxazol-5 -yl)-N-(1-phenyl **-2-(pyrrolidm-1-yl**)**ethyl)acetamide ;**

(S)-N **-methyi** -2-(2-oxo- 1,**2-dihydioquinolin** -6-yl)-N-(1-**phe nyl-2-(pyiTolidin-** 1-**yl)ethyl)acetamide;**

N-((3)-2-((3)-3-hydtOxypyrroHdin-l -yi)-l -phenylethyl)-N-niethyl-2-(2-oxo-l ,2-dihydroquinolin-il-yl)ac etamide ;

(S)-N-methyi-2-(2-oxo- 1.2-dihydroquinolin-7 -yl)-N-(1-phe nyl-2-(pyrrolidin- 1-yl)ethyl)acetamide ;

(S)-N-methyl-2-(3-nie thyl -2,2 -dioxido- 1,3-dihydrob enzo [c] isothiazol-5-yi)-N-(1-phenyl -2 -(pyrrolidin- 1-yl) ethyl)ace tam ide;

N-((S)-2-((R)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-2-(2-oxo-1,2-dihydroquinolin-6-yi)acetamide;

N-((S)-2-((S)-3-hydn xypyrrolidirL-l-yl)-1-phen5leth5l)-N-meth5l-2-(2-oxo-1,2-dihydroquinolin-7-yl)acetamide;

N-((S)-2-((S)-3-hydn xypyrrolidirL-l-yl)-*l*-p¾nylei hyl)-N-2-dirΩeth51-2-(2-oxo-2,3-d-hydrobenzo [d] oxazol-5-jil JprOpanamide;

N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-2-(2-oxo-1,2-dihydroquinolin-7-yi j acetamide;

N-((S)-2-((S)-3-hydo xypyrrolidirL-l-yl)-l-phfinyiethyi)-2-meth5ii-2-(2-oxo-2,3-d-hydrobenzo [d] oxazol-5-yl)propanamide;

(S)-2-(2-oxo-2,3-dih jdrobe nzo [d] oxazd-.5-y)-N-(1-phenyl-2-(pyadidin-l -yi)ethyl) acetainicLe;

N-((S)-2-((S)-3-hyd.Oxypyro lidirL-l-yl)-l-phenyiethyi)-2-(2-oxo-2,3-dihydrobenzo [d] oxazol-5-yl)acetainide;

(S)-2-(3-benzyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)-N-(1-(3-(4-methoxybenzyloxy)phenyl)-2-(pyrrolidin-1-yl)ethyl)acetamide;

2-(3-(4-cyanobenzyl)-2-oxo-2.3-dih;ydiiobe nzo [d] oxazol-5-yl)-N-((Ξ)-2-((Ξ)-3-tyjdroxypyrra lidin-1-5rl)-1-phenylethyl)acetamide;

N-((S)-2-((S)-3-hydrOxypyro lidirL-l-yl)-l-p¾nylethyl)-2-(2-oxoiid d in-6-yl)acetamide

(S)-2-(3-inethyl-2-oxo-2,3-dihydrobenzo [d] oxazol-5-yl)-N-(1-phenyl-2-(pyrrolidin-1-yl)ethyl)acetamide;

N-(1-(1-benzol-1H-pyrazol-4-ji)-2-(pyirolidin-1-*yi)e* thy.)-2-(2-oxo-2,3-dihydrobenzo [d] oxazol-5-yl)acetainide;

(3)-t-butyl-2-(3-(1-(2-(3-benzyl-2-oxo-2,3-dih;ydiObenzo [d] oxazol-5-yl)acetamido)-2-(pyrrolidin-1-yl)ethyl)phenoxy)acetate;

(S)-2-(3-benzyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)-N-(1-(3-(benzyloxy)phenyl)-2-(jyrrolidin-1-*yi)* ethyi)-N-methylacetamide;

N-((S)-1-cyclohexyl-2-((Ξ)-3-hydroxypyrrolidin-1-yl)ethyl)-N-n¾thyl-2-(2-oxoindDlin-D-yi j acetamide;

2-(3-(3-cyanobenzyl)-2-oxo-2.3-dih;ydiiobe nzo [d] oxazol-5-yl)-N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-phenyiethyi)-N-methyiacetamide ;

N-((S)-1-cyclohexyL-2-((Ξ)-3-hydiOxypyirohdm-1-yl)ethyl)-2-(2-oxo-2,3-dihydrobenzo [d] oxazol-5-yl)acetainide ;

(S)-tert-butyl-2-(3-(1-(2-(3-benzyl-2-oxo-2,3-dmydiObenzo[d] oxazol-5-yl)-N-methyl acetaimdo)-2-(pyrralidin-l-yl)ethyl)phenoxy)acetate ;

N-((Ξ)-1-cyclohexyL-2-((Ξ)-3-hydroxypyrrolidin-1-yl)ethyl)-2-(2-oxomdoliii-≤-yl)acetamide

N-((S)-1-cyclohexyL-2-((Ξ)-3-hydiOxypyirohdm-1-yl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydrobenzo [d] oxazol-5-yl)acetamide ;

(S)-N-(1-(3-cyanophenyl)-2-(pyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydrobenzo [d] oxazol-5-yl)acetamide ;

2-(3-(3-cyaiMbeiKyl)-2-oxo-2,3-dmydiiobenzo [d] oxazol-5-yl)-N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-phenyiethyi)acetamide;

N-((Ξ)-1-(3-cyanophenyl)-2-((S)-3-hydtoxypyiididin-1-y-)ethyl)-N-inethyl-2-(2-oxo-2.3-dihydrobenzo [d] oxazol-5-yl)acetamide ;

(S)-tert-butyl **2**-(**3**-(**2**-(**3-hydn ıx ypynOHdirL -l** -^)-l-(2-(2-oxo-2,3-dih5idro benzo[d]oxazol-5-yl)acetamido)ethyl)phenoxy)acetate;

2-(3-(4-cyanobenzyl)-2-oxo-2.3-dmydiiobenzo [d] oxazol-5-yl)-N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methykcetaniLde ;

N-(1-(3-(cyanomethoxy) phenyL)-2-(3-hydroxypynOliditi-1-yl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydrobenzo [d] oxazol-5-yl)acetamide ;

tert-butyl 2-(3-((S)-2-((R)-3-hydroxypynolidin-1-yl)-1-(N-methyl-2-(2-oxo-2,3-dihydrobenzo [djoxaaol-i-yljacetaraidojethyljpl^iioxyjacetate ;

N-((S)-1-(3-cyanophenyl)-2-((3)-3-hydioxypyrrolidin-l-yl)ethyl)-N-methyl-2-(3-methyl-2-oxo-2,3-dihydrobenzo [d] oxazol-5-yL)acetainide ;

N-((S)-1-(3-(1H-tetrazol-5-yl) phenyl)-2-((3)-3-hydiOxypyrrolidin-1-yl)ethyl)-2-(2,2-dioxido-1,3-dihydrobenzo [c] i_Btluazol-≤-yl)-N-inethylacetamide ;

2-(3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-l-yl)-1-(N-methyl-2-(1-methyl-2,2-dioxido-1,3-dihydiObenzo[c] isotlua..ol-6-yl)a^^tamido)ethyl)phenoxy) acetic acid;

(S)-methyl 3-((2-oxo-5-(2-oxo-2-(1-phenyl-2-(pyjrohdin-1-yl)ethykinino) ethyl)benzo[d] oxazol-3(2H)-yl) methyl)benzoate ;

(S)-tert-butyl 2-(2-oxo-5-(2-oxo-2-(1-phenyl-2-(pyiTolidin-1-yl)ethylamino) ethyl)benzo[d] oxazol-3(2H)-yl)acetate ;

(S)-2-(2-oxo-5-(2-oxo-2-(1-phenyl-2-(pyrrolidin-1-yl)ethylarnirio)ethyl) benao [d] oxaaol-3(2H)-yi)acetic acid hydrochloride;

(Ξ)-N-(1-(3-hydiOxyptenyl)-2-(pyrrolidin-1-yl)ethyl) -2-(2-oxo-2,3-dihydroberizo[d] oxaaol-5-yl)acetamide;

(Ξ)-2-(3-(1-(2-(2-oxo-2,3-dihydroberizo [d] oxazd-i-yljacetamido) -2-(pyrrdidirL -1-yl)ethyl)piherioxy)acetic acid hydrochloride ;

2-(5-(2-(((Ξ)-2-((Ξ)-3-hydimypyrrdidirL -1-yl)- 1-phenyiethyi)(me1hyl)arnirb)-2-oxoethyl)-2-oxobe riao [d] oxaad -3(2H)-yl)acetic acid;

2-(3-(1-(N-me thyi-2-(2-oxoindolin-6-yl)acetamido)-2-(pyrrohdiri- 1-yi)e thyl)phenoKy)acetic acid hydrochloride;

3-((5-(2-(((Ξ)-2-((Ξ)-3-hydroxyj^no lidin-l -yl)- 1-phenyiethyl)(methyl)amirio)-2-oxoe1hyl)-2-ox obe nao [d] oxaad -3(2H)-yi)me1hyl)berGamide;

(3)-2-(3-bertzyl-2-oxo-2,3-dihydrobe nao [d] oxazol -5-yl)-N-(1-(3-hydroxyptenyl)-2-(pyrrolidin- 1-yl) ethylJ -N-methykcetairiide;

(R)-2-(3-(1-(N-methyl-2-(2-oxo-2,3-dihydroberiao [d] oxazol -5-yl)acetarddD)-2-(pyrrolidin-1-yl)ethyl)phenoxy)acetic acid;

(Ξ)-3-((2-oχo -5-(2-oχo -2-(1-phenyl-2-(pyrrolidin-l -yl)ethykttu rio)ethyl)berizo [d] oxaaol-3(2H)-yl)me1hyl)benzarnide;

2-(3-(1-(2-(2-o xoiridDlin -0-yi)acetarddo)-2-(pyrmhdirL- 1-yl)e thyi)phenoxy)acetic acid;

(Ξ)-N-(1-(3-(2H-tetraaol-5-yl) phenyi)-2-(pyrtOhdirL-l-yl) ethyl) -N-methyl-2-(2-oxo-2.3-dihydroberiao [d] oxazol -5-yi)acetamide ;

(3)-2-(3-(2-(3-hydroxypyrrohdir.-1-yl)- 1-(N-me thyi-2-(2-oxo-2,3-dmydroberizo [d] oxaaol -5-yl)acetam ido)ethyl)pherioxy)acetic acid tr flouro ac etate ;

(3)-2-(3-(2-(3-hydroxypyrrohdm-1-yl)- 1-(N-mef yl-2-(2-oxoindolin-6-yl) acetamido) ethyl) phe noxy) acetic acid hydrochloride ;

2-(3-((Ξ)-2-((R)-3-hydroxypyrrohdm- 1-yi)- 1-(N-methyl-2-(2-oxo-2,3-dihydrobe nao [d] oxaml -5-yl)acetaimdD)eftyl)pherLOxy)acetic acid;

2-(5-(2-(((S)-1-cyclohexyl -2-((3)-3-hydroxypyrrokdin- 1-yi) ethyi)(niethyl)aniLno)-2-oxo ethyl) -2-ox obe nao [d] oxaaol -3(2H)-yi)acetic acid;

Methyl 4-((5-(2-(((Ξ)-2-((S)-3-hydroxypyrrolidin- 1-yl)-1-phenytethyi)(niethyl)amino)-2-oxo ethyl) -2-ox obe nao [d] oxaaol -3(2H)-yi)me thyi)benaoate ;

N-((S)-1-(3-(2H-tetraaol-5-yl) phenyl)-2-((S)-3-hydiOxypyrrolidm- 1-yl)ethyl)-N-methyl-2 - (2-ox o-2,3-dihydiiobenao [d] oxaaol-5 -yl)acetamide ;

(S)-2-(3-(2-(3-hydroxypynOhdin- 1-yl)- 1-(2-(2-oxoiridolin-6-ylJacetamido) emyl)phenoxy)acetic acid hydrochloride ;

(S)-2-(3-(2-(3-hydroxypynOkdin- 1-yl)- 1-(2-(2-oxo-2,3 -dihydrobenao [d] o-iaaol-5-yl)acetamido)ethyl)phenoxy)acetic acid;

2-(3 -(3-(2H-te trazol-5-yl)b enzyl)-2-oxo-2,3 -dihydrobei™ [d] oxaaol-5 -yl) -N-((Ξ)-2-((Ξ)-3 - hydroxypyrrolidin-1-yl)-1 -phenylemyl)acetamide;,

2-(3 -<3-(2H-te trazol-5-yl)b enzyl)-2-oxo-2,3 -dihydrobei™ [d] oxaaol-5 -yl) -N-((Ξ)-2-((Ξ)-3 - hydroxypyrrolidin-1-yl)-1 -phenylemyl)-N-memykcetamide ;

2-(3 -(4-(1H-te traaol-5-yl)b enay.)-2-oxo-2 ,3 -dihydrobenzo [d] oxaaol-5 -yl) -N-((Ξ)-2-((Ξ)-3 - hydroxypyrrolidin- 1-yl) -1 -phenylethyl) -N-methylacetamide ;

(R) -N-(1-(3-((2H-tetraaol-5 -yl)methoxy)phenyl) -2 -(3 -hydroxypyrrdidin-l -yl)ethyl)-N- methyl-2-(2-oxo-2 ,3 -dihydrobenzo[dJ oxazol-5 -yl)acetamide ;

2-(3 -(4-(1H-te traaol-5-yl)b enayl)-2-oxo-2,3 -dLhydrobenao [d] oxaaol-5 -yl) -N-((Ξ)-2-((Ξ)-3 - hydroxypyrrolidin- 1-yl) -1 -phenylethyl)acetamide;

N-((3)-1-(3-(2H-tetraaol-5-yl) phenyl)-2-((3)-3-hydroxypyrrolidin- 1-yl)ethyl)-N-methyl-2 - (3-methyl-2 -oxo-2,3 -dihydrobeiiao [dj oxaaol-5 -yl)acetamide ;

N-((S)-1-(3-cyanophe nyl)-2-((3)-3 -fluoropyrrolidin- 1-yl)ethyl)-N-methyl-2-(2 -oxo-2,3- dihydrobenao [d] oxaaol-5 -yl)acetamide ;

N-((3)-1-(3-(2H-tetraaol-5-yl) phenyl)-2-((S)-3-nuoropyrrokdin-l -yl) ethyl) -N-methyl-2 -(2- oxo -2,3 -dihydrobenao [d] oxaaol-5 -yl)acetamide ;

N-((Ξ)-1-(3-(2H-tetraaol-5-yl) phenyl)-2-((S)-3-hydroxypyrrolidin- 1-yl)ethyl)-N-methyl-2 - (2-ox oindolin-o-yl)ac eta mide ;

N-((Ξ)-1-(3-(2H-tetraaol-5-yl) phenyl)-2-((S)-3-hydroxypyrrolidin- 1-yl)ethyl)-N-methyl-2 - (1-methyl -2 -oxoindolin-S-ylJac etamide ;

(R) -N-(1-(3-((2H-tetraaol-5 -yl)inethoxy)phenyl) -2 -(3 -hydroxypyrrolidin-1 -yl)ethyl)-N- methyl-2-(2-oxo-2 ,3 -dihydrobenao [dj oxaaol-5 -yl)acetamide ;

N-((S)-1-(3-(2H-tetraaol-5-yl) phenyl)-2-((3)-3-nuoropyrrokdin-l -yl) ethyl) -N-methyl-2 -(2- oxoiridolirL-6 -yl)ac etamide ;

(S)-2-(3-oxo-3 ,4-dih yi ro -2H-benao [b] [1,4] oxaam-6 -yl)-N-(1-phenyl-2 -(pyrrolidin-1-

yl)ethyl)acetamide ;

(S)-N-methyl-2-(2-oxo-2,3-dihydrobenzo[d]thiaaol-5-yl)-N-(1-phenyl -2-(pyn olidin-1-yl)etl^)acetamide ;

2-(2,2-dioxido-1,3-dihjdrobenao[c]isothiasol-6-^i)-N-((3) -2-((Ξ)-3-hydroxypyn olidin-1-yl)-1-phenylethyl)-N-methylacetamide;

N-((S)-2-((S)-3-hydra xypyrro lidirL-l -yl)-l -phenyiethyl)-N-methyl-2-(2-oxo-2,3-dihydrober™ [d]thiaaol-5-yl)acetamide;

N-((S)-2-((S)-3-hydra xypyrro lidirL-l -yl)-l -phen^ieth^i)-2-(2-thioKO-2.3-dihydrober™ [d]thiaaol-5-yl)acetamide;

N-((S)-2-((S)-3-hydra xypyrro lidirL-l -yl)-l -phenylethyl)-N-methyl-2-(2-thioxo-2,3-dih^drobenao [dj thaaol-5-yl)acetamide ;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methylacetamide;

(Ξ)-2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-be_™[b][1,4]tMazin-6-yl)-N-(1-phenyl-2-(pyrrolidiTL-1-yl)ethji)acetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benao[b][1,4]thiazin-6-yl)-N-((3)-2-((Ξ)-3-liydrQKypyrrolidirL-1-yl)-1-phenylethyl)acetainide;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benao[b][1,4]thiazin-6-yl)-N-((3)-2-((Ξ)-3-liydrQKypynOlidirL-1-yl)-1-(3-(trifluQroinetliyl)phenyl)ethyl)-N-methykcetamide ;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-1-(3-fluorophenyl)-2-((Ξ)-3-hydiOxypytTolidin-1-yl)ethyl)-N-methylacetamide;

N-((S)-1-cyclohexyl-2-((Ξ)-3-hydiOxypytTolidin-1-yl)ethyl)-2-(1,1-dioxido-3-OKO-3,4-dihydro-2H^benzo[b][1,4]thiazin-6-ylJ-N-methylacetamide;

2-(1,1^oxido-3-oxo-3A dihydro-2H-benao[b][1,4]thiaain-6-yl)-N-((3)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(3-methoxyphenyl)ethyl)-N-methylacetamide;

(S)-2-(3-oxo-3,4-dihyiro-2H-benao[b][1,4]thiazin-6-yl)-N-(1-phenyl-2-(py.rolidin-1-3ii)et]^)acetamide;

N-((3)-2-((3)-3-hydraKypynDHdirL-l -yl)-l -phenylethyl)-2-(3-oxo-3,4-dihydro-2H-benao[b][1,4]thkzin-6-yl)acetamide;

(S)-N-inethyl-2-(3-oxo-3A^nydro-2H-benzo[b][1,4]thiazin-6-yl)-N-(1-pher¾l-2-(pyrrolidirL-1-yl)ethyl)acetamide ;

N-(2-((S)-3-hydroxypyrrolidin-1-yl)-1-(tetrahydro-2H-pyran-4-yl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydro-2H-b eriao[b][1,4]thiaain-6-yl)acetamide;

N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-:n¾tliQxy]&enyl)ethyl)-N-methyl-2-(3-oxo-3,4-dih^dro-2H-benzo[b][1,4]thiaain-6-yl)acetamide;

N-((S)-2-((S)-3-hydroxyp3^HdirL-l -yl)-l-(3-(triiluorometh^)phien^)em^)-N-mem^-2-(3-oKo-3,4-dihydro-2H-b eriao[b][1,4]thiaain-6-yi)acetamide;

N-((S)-1-(3-f uorophenyl)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)emyl)-N-meth.yl-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiaain-6-yl)acetamide;

N-((S)-2-((S)-3-hydrox;^^Hdm-l -yl)-l-(3-(trifluQromeftox3^pl¾n^)eth^)-N-methyl-2-(3-oxo-3,4-dihydro-2H-b eriao[b][1,4]thiaain-6-yl)acetamide;

2-(1-benayl-2,2-dioxido-1,3-dihydrob eriao[c]isothiaaol-^-yl)-N-((Ξ)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methylacetamide;

2-(2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methylacetamide;

2-(l,l ^oxido-3-oxo-3,4-dmydro-2H-benao[b][1,4]thiaain-o˙-yl)-N-((3)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(3-(trifluor ometlio xy)jihenylJethyiJ-N-propylacetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-2-((S)-3-tydroxyjyrrolidin-1-yl)-1-(3-(trifluor ometlio xy)jlienyl)ethyi)-N-iso propylacetamide;

N-cycb propyl-2-(1,1-dioxido-3-oxo-3,4-dmydra-2H-benao[b][1,4]thiaam-ii-yl)-N-((Ξ)-2-((S)-3-hydroxypyrrolidin-l-yl)-l-(3-(trifluoromethoxy)phenyl)ethyl)acetamide;

2-(1,1-dioxido-3-oxo-3,4-diliydiO-2H-benao[b][1,4]tluaam-6-yl)-N-((S)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(3-(trifluor ometlio xy)jiienyl)ethyi)-N-isobutykcetamide;

N-(cyclopropylmethyl)-2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-be nao[b][1,4]tuaain-6-yl)-N-((Ξ)-2-((Ξ)-3-hydroxypyiiolidirL-1-yl)-1-(3-(trifluorome thoxyjphenyl) ethyl)acetamide;

2-(1,1-dioxido-3-oxo-3,4-diliydro-2H-benao[b][1,4]tluazin-6-yl)-N-((S)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(4-(trifluorometlioxy)ilienyl)ethyi)-N-ri¾mykcetamide;

2-(2,2-dimfithyl-3-oxo-3,4-dmydiO-2H-berEo[b][1,4]tliazin-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(trifluor ometlio xy)ilienyl)ethyi)-N-ri¾mykcetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzD[b][1,4]tliiaam-6-yl)-N-((S)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(3-(2,2,2-trinuoroetrLOxy)phenyl)ethyl)-N-methyiacetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzD[b][1,4]thiaain-o˙-yl)-N-((S)-2-((Ξ)-3-

hydroxypyrrolidin-1-yl)-1-(m-tolyl)ethyl)-N-methylacetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-1-(4-fluoro-3-(trifluoromethoxy)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methylacetamide;

N-((S)-1-(3,5-dimethylphenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethji)-2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] 1hiazin-6-yl)-N-methjjiacetamide;

2-(2,2-dimethyl- 1,1-dioxido-3-oxo-3,4-dih^-2H **-benzo** [b] [1,4] Hiiazin-6-3?l)-N-((S)-2-((S)-3-**hydroxypynOlidin -l** *-y\)-l* -(3-(trifluoromethoxy)phenyl)ethyl)-N-methylacetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benao[b] [1,4] thiazin-6-^i)-N-((S)-1-(3-fluon>5-(2,2,2-**triflnoiD** ethoxy)phenyl)-2-((S)-3-hyiroxypynolidin-l *-yi)* ethyl)-N-meth^iacetamide ;

N-((S)-1-(3-cy?d opropylphenyl)-2-((S)-3-hydroxypyirolidin-l -yl)ethyl)-2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-b enzo [b] [1,4] tluasin-6-^i)-N-meth^iac etamide;

N-((Ξ)-1-(3-cyanophenyl)-2-((S)-3-hydroxypyrrdidin-1 -yl)ethyl)-N-n¾t'iyl-2-(2-oxo-2.3-**dihydrobenzo [dj** thiazol-5- j i)acetamide;

N-((Ξ)-1-(3-cyanophenyl)-2-((S)-3-hydroxypyrrdidin-1 -yl)ethyl)-N-n¾t'iyl-2-(3-oxo-3.4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)acetamide;

N-((S)-1-(3-c^anoplie nyl)-2-((S)-3-hydroxypyrrd idin-l -yl)ethyl)-N-**iM thyl**-2-(3-oxo-3.4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)acetamide;

3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin- 1*-y\)*- 1-(N-meth^-2-(3-oxo-3,4-dihydm-2H-benzo[b] [1**A** thiazin-6-5l)acetamido)ethyl)benzoic acid;

3-((Ξ)-2-((Ξ)-3-**hydr**oxypyrrolidin- 1*-y\)*- 1-(N-meth^-2-(3-oxo-3,4-dihydo -2H-benzo[b] **[l** ,4Joxazin-0-^)acetaimdo)eth^)ben3oic acid;

N-((S)-1-(3-cyaroplie nyl)-2-((3)-3-hydtoxypyrdidin-l -yl)ettyl)-N-:n¾thyl-2-(2-oxoindolin-6-yl)acetamide;

N-((3)-2-((3)-3-hydroxypyrroHdm-l -yl)-l -phen^th^)-2-(2-oxoiiddm-5-^)acetamide;

N-((Ξ)-1-(3-cyaiiophe nyl)-2-((S)-3-hydroxypyirdidin **-l** -yl)et%l)-N-:n¾thyl-2-(3-oxo-3.4-dih^droqiiiiu3xalm-6-^)acetamide ;

2-(3-((Ξ)-2-((Ξ)-3-hydroxypynOlidin-l ***-yl)***- 1-(N-meth^-2-(2-oxomdolin-6-yl)acetamido)ethyl)phenoxy)acetic acid;

3-((Ξ)-2-((Ξ)-3-hydroxypyrtDlidin- 1-yi)- 1-(N-meth^-2-(2-oxo-2,3-dihydrobenzo [d] oxazol-5-yl)acetamido)ethyI)ben^mide ;

N-((S)-2-((3)-3-hydrox^p^rroHdm-l -yl)-l -phenylethyl)-N-methyl-2-(2-oxoiiiddLn-5-

yl)acetamide;

N-((S)-2-((S)-3-fluoropyrrolidin-1-yi)-1-(3-(2-(me1hyisulforiamido)-2-oxoethoxy)phenyl)ethyl)-N-methyl-2-(2-oxoindolin-o-yl)acetamide;

N-((S)-1-(3-cyanophenyi)-2-((3)-3-hydroxypyiTdidin-1-yi)ethyl)-N-methyl-2-(2-oxo-2,3-dihydrobenzo[dj oxazol-5-yi)acetaniide;

3-((S)-2-((S)-3-hydroxypyno lidin-1-*yi)*-1-(N-methyl-2-(3-oxo-3,4-dihydro quimxalin-6-3ii)acetamido)ethyl)benzamide;

3-((S)-2-((S)-3-fluoropyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindolin-6-yl)acetamido)ethyl)benzamide;

2-(3-((S)-2-((S)-3-hydroxypyrrolidin-l-yi)-1-(N-methyl-2-(2-oxo-2,3-dihydrobenzo[d] thasol-i-yijacetaniido) ethyi)pnenoxy)acetic acid;

2-(3-((S)-2-((S)-3-hydroxypyrrolidin-l-yl)-1-(N-mMhyl-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxann-fj-yi)acetamLdo)e1hyl)phe^xy)acetic acid;

N-((S)-1-(3-(2-amino-2-oxoe1hQxy)phenyl)-2-((S)-3-hydroxypyriolidin-1-yl)ethyl)-2-(1,1-dioxido-3-oxo-3.4-dihydiio-2H-beriso[b][1.4]1hiazin-fj-yi)-N-me1hykce1amide;

2-(3-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindolin-5-yl)acetamido)ethyl)phermy)acetic acid;

N-((S)-1-(3-(2-anuno-2-oxoe1hoxy)phenyl)-2-((S)-3-hydroxypyriolidin-l-yl)ethyi)-N-methyl-2-(2-oxo-2,3-dihydrobenao[dj thiazol-i-yijacetamide;

2-(3-((S)-2-((S)-3-hydroxypyrrolidin-l-yl)-1-(N-methyl-2-(3-oxo-3.4-dihydroqui^xalin-6-yl)acetamido)ethyl)phenoxy)acetic acid;

2-(3-((S)-2-((S)-3-hydroxypyrrolidin-l-yi)-1-(N-methyl-2-(3-oxo-3,4-dihydro-2H-benao[b][1,4]thiazin-6-yl)acetaiTLido)eth^)phenoxy)acetic acid;

N-((S)-1-(3-(2-aniino-2-oxoethoxy)phenyl)-2-((3)-3-hydroxypyriolidin-1-yl)ethyi)-N-methyi-2-(3-oxo-3,4-dihydro-2H-benao[b][1,4]oxazin-fj-yi)acetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benao[b][1,4]thiazin-6-yi)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yi)-1-(3-(2-(inethyi-^fonamido)-2-oxoethoxy)phenyi)ethyi)-N-rnethyiacetamide;

N-((S)-1-(3-(2-anuno-2-oxoe1hoxy)phenyl)-2-((S)-3-hydroxypyriolidin-1-yl)ethyi)-N-methyi-2-(3-oxo-3,4-dihydro-2H-benz0[b][1,4]thiazin-6-yijacetairiide;

3-((S)-2-((S)-3-hydroxypyno lidin-1-yl)-1-(N-mfithyl-2-(2-oxo-2,3-dihydroberLZO[d] oxaaol-

5-yl)acetamido)ethyl)ben2oic acid;

3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindolin-6-yl)acetamido)ethyl)-N-(memyl^ionyl)benzamide;

N-((S)-1-(3-ethynylphenyl)-2-((3)-3-hydroxypyoOlidin-1-yl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydroquinoxalin-6-yl)acetamide;

N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)phenyl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetamide;

N-((S)-1-(3-eth.ynylphenyl)-2-((S)-3-hydroxypyoOlidin-1-yl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetamide;

2-(2,2-dioxido-1,3-dihyi.iobenzo[c]iso1hiazol-6-yl)-N-((S)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(3-(5-methyl-1,2,4-oxadiazDl-3-yl)phenyl)ethyl)-N-methykcetamide;

2-(2,2-dioxido-1,3-dihyi.Obenzo[c]i-othiazol-6-yL)-N-((S)-1-(3-ethynylphenyl)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methylacetainide;

N-((Ξ)-2-((Ξ)-3-hydroxypynOkdin-l-yl)-l-(3-(5-methyl-1,2,4-oxadia2ol-3-yl)phenyl)ethyl)-N-methyl-2-(2-oXD-2,3-dihydroben20[d]thiazol-5-yl)acetamide;

N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-l-(3-(5-(trifluoromethyl)-1,2,4-oxadia..ol-3-yl)phenyl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydrobenzo[d]thiazol-5-yl)acetainide;

N-((S)-1-(3-(1,2.4-üXadia..ü1-3-yl)phenyl)-2-((Ξ)-3-hydmxypyrrolidin-1-yl)ethyl)-N-methyi-2-(2-oxtiridolirL-6-yl)acetamide 2,2,2-trifluoroacetate;

N-((S)-1-(3-(1,2,4oxadiazDl-3-yl)phenyl)-2-((Ξ)-3-hydiOxypynolidin-1-yl)ethyl)-2-(2,2-dioxido-1,3-dihydrobenso[c]isothiaaol-6-yl)-N-methykcetamide;

2-(2,2-dioxido-1,3-dihyi.iobenzo[c]isothiazol-6-yl)-N-((3)-2-((S)-3-hydroxypyiiOhdiii-1-yl)-1-(3-(5-(trifluoromethyl)-1,2,4-oxadia2ol-3-yl)pl¾nyl)ethyl)-N-methykcetamide 2,2,2-trifluoroacetate;

N,N-diethyl-3-((S)-2-((Ξ)-3-hydioxypyrrokdin-l-yl)-1-(N-methyl-2-(2-oxo-2,3-dihydrobeinD[d]thiazol-5-yl)acetamido)ethyl)bensamide;

N-((S)-1-(3-(1,2.4-oxadia._ol-3-yl)phenyl)-2-((Ξ)-3-hydmxypyrrolidin-1-yl)ethyl)-N-methyl-2-(2-ox0-2,3-dihydrobenzo[d]thiazol-5-yl)acetamide 2,2,2-tiifluoroacetate;

N-((S)-1-(3-(1,2,4-oxadiazDl-3-yl)phenyl)-2-((Ξ)-3-hydroxypynolidin-1-yl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydroquinoxalin-6-yl)acetamide 2,2,2-tiifluoroacetate;

N-((S)-1-(3-(1H-imidazol-2-yl)phenyl)-2-((Ξ)-3-hydmxypytTohdin-1-yl)ethyl)-N-methyl-2-

(2-ox 0-2,3 -dihydrobenao [d] thiazol-5-yl)acetaniide ;

N-((S)-2-((Ξ) -3 -hydroxypyrrondin-l -yl)-l -(3-(thiazDl-2-yl) phenyl)ethyl)-N-methyl-2-(2-oxo -2,3 -dhydrobenao [dj thiazol-5-yl)acetaniide ;

N-((S)-1-(3 -cyarci-.5 -fluorophenyl)-2-((3)-3 -hydroxypyrrolidin-1-yl)ethyl)-N-niethyl -2-(2-oxo -2,3 -dhydrobenao [dj thiazol-5-yl)acetaniide hydrochloride ;

N-((Ξ)-2-((Ξ) -3 -hydimypyrrohdin-l -yl)-l -(3-(5 -methyl- 1,2,4 -oxadia..ol -3 -yl)phenyl) ethyl) -N-niethyl -2 -(3-oxo-S,4-dihydroquinW-ialin-6-yl)acetamid- ;

3-((S)-1-(2-(2,2 -dioxido-l ,3 -diliydrobenso[c] isothiaiiol -6 -y^-N -methylac etaniido) -2-((Ξ)-3-liydroxyp3^1idi i- 1 -yl) ethyl)-N-(2,2,2 -trifluoroethyl)benzamide;

3-((Ξ)-2 -((Ξ)-3 -hydr oxypyrtD lidin- 1-yl)- 1-(N-i™thyı-2-(3-oxo-3,4-dihydroquim xalin-6-yl)acetamido)ethyl)-N -(2 ,2 ,2 -tiifluoroethyl)b enzaniide;

N-((Ξ)-1-(3 -cyaiiD-5 -fluorophenyl)-2 -((S)-3 -hydioxypynralidin- 1-yl)ethyl)-N-methyl -2-(2-oxoindolin -ḝ -yl)ac etaniide ;

N-((Ξ)-1-(3-(1H-imida3ol -2 -yl) phenyl) -2 -((Ξ)-3 -hydiOxypyrrotidin- 1-yl)ethyl)-N-niethyl-2-(2-ox oindolin-o˘ -yl)ac etaniide 2,2,2 -trifluoroacetate ;

N-((S)-1-(3 -cyano-5 -fluorophenyl)-2 -((S)-3 -hydroxypyrrolidin-1-yl)ethyl)-2-(2,2 -dioxido-1,3-dihydroben20 [c] isothiaaol -6-yl) -N-methykcetaniide ;

N-((S)-1-(3 -cyano-5 -fluorophenyl)-2 -((S)-3 -hydroxypyrrolidin-1-yl)ethyl)-N-methyl -2-(3-oxo -3,4 -dihydroquinoxaHn-di-yl)acetaniLde ;

2-(1,1-dioxido -3-oxo -3,4 -dihydro -2H -ben2o[b] [1,4] thiazin -6-yl)-N-((S)- 1-(3-ethynylphe nyl)-2 -((S) -3 -hydroxypyaohdin- 1-ylJethy^-N-methylac etaniide ;

N-((S)-1-(3-(1H-inuda3ol -2 -yl) phenyl) -2 -((Ξ)-3 -hydroxypyrrolidin- 1-yl)ethyl)-2-(2,2-dioxido- 1,3-dihydrobenzo[c]isothiazol-6-yl)-N-nie thylacetamide ;

N-((S)-1-(3 -cyanophenyl)-2-((3)-3 -hydro xypycrdidin-1 -yl)ethyl)-2-(2,2 -dioxido -1,3 -dihydroben3o[c] isothksnl-di-ylJ-N-methylacetamide;

N-((S)-1-(3 -(but- 1-yn- 1-yr)phenyl)-2 -((S) -3 -hydroxypyaolidin -1 -yl)ethyl)-N-methyl -2-(2-axoindolin-i5 -yl)ac etaniide ;

N-((S)-1-(3 -Cbut- 1-yn- 1-yr)phenyl)-2 -((S) -3 -hydroxypya-olidin -1 -yl)ethyl)-N-methyl -2-(2-oxo -2,3 -dihydrobenao [d] thiazol-5-yl)acetaniide ;

N-((S)-1-(3 -Cbut- 1-yn- 1-yr)phenyl)-2 -((S) -3 -hydroxypya-olidin -1 -yl)ethyl)-N-methyl -2-(3-oxo -3,4 -dihydroquinoxahn -fj -yl)acetaniide ;

3-{(Ξ)-2-((Ξ)-3-hydroxypyrto lidin-1-yl)-1-(N-methyl-2-(2-oxoindolin-f-ylJacetamido)ethyl)-N,N-dimethyib enEainide;

3-{(Ξ)-1-(2-(2.2-dioxido-l ,3-dihydrobenzo[c] isothiaaol-o-yl)-N-methylac etamido)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)ethyl)-N,N-diethylbenzamide;

N,N-diethyl-3-((S)-2-((Ξ)-3-hydioxypyiiOhdin-l -yl)-1-(N-methyl-2 -(3-oxo-3,4 dihydiOqm^xalm-6-yl)acetamido) ethylJbensamide 2,2,2-trifluoroacetate ;

3-((S)-1-(2-(2.2-dioxido-l ,3-dihydrobenzo[c]isothiaaol-6 -yl)-N-methylac etainido)-2-((Ξ)-3-hydroxypyrrolidin-1-ylJethylJ-N,N-dii^thyiberizamide ;

3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(3-oxo-3 J4-diJ¾ydraqTiinoxahn-0-yl)acetamido)ethyl)-Ni^-dimethy!b^ nzamide ;

N-((S)-1-(3-(1,2,A-oxadiazDl-3-yl)phenyl)-2-((Ξ)-3-hydraxypyrrolidin- 1-yl)ethyi)-2-(1, 1-doxido-3-oxo-3.4dihydro-2H-benzo[b] [1,4]thiazin-≤-yl)-N-methylacetaniide2 ,2.2-trifluoroacetate;

N-((Ξ)-2-((Ξ)-3-hydtOxypyrrolidm-l -yl)-l -(3-(1-methyl- 1H-imidaaol-2-yl)phenyl) ethyl)-N-methyl-2-(2-oxoindohn-0 -yl)acetamide ;

N-((S)-1-(3-(5-ethyl-l ,2,4-oxadiazol-3-yl)phenyl)-2-((S)-3-hydroxypyrrolidin- 1-yl)ethyl)-N-methyl-2-(2-oxoindohn-o "-yl)acetamide ;

N-((Ξ)-2-((Ξ)-3-hydtDxypyrrohdirL-l -yl)-l -(3-(5-methylthiaaol-2 -yl)phenyl)ethyl)-N-methyi-2-(2-oxoindolin-6 -yl)acetamide ;

N-((Ξ)-2-((Ξ)-3-hydroxypyrrohdin-l -yl)-l -(3-(thiazol-5-yl) phenyl)ethyi)-N-methyi-2-(2-axoiridolin-6 -yi)acetamide ;

N-((Ξ)-2-((Ξ)-3-hydroxypyrrohdin-l -yl)-l -(3-(thia..ol-4-yi) phenyl)ethyi)-N-methyi-2-(2-**oxoindolirL-6**-yl)ac**etaniide ;**

N-((Ξ)-2-((Ξ)-3-hydroxypyrrohdin-l -yl)-l -(3-(4-methylthia3ol-2 -yl)phenyl)ethyl)-N-methyi-2-(2-oxoindolin-6-yl)acetamide ;

N-((Ξ)-2-((Ξ)-3-hydrax ypyrrohdin-l -yi)-l -(3-(2-methylthia3ol-5 -yl)phenyl)ethyl)-N-methyi-2-(2-oxoindolin-6-yl)acetamide ;

N-((Ξ)-2-((Ξ)-3-hydraxypyrrolidm-1 -yi)-l -(3-(2-methylthia3ol4-yl)phenyl)e thyl)-N-methyi-2-(2-oxoandolin-6-yl)acetamide ;

N-((Ξ)-2-((Ξ)-3-hydraxypyrrolidm-1 -yi)-l -(3-(5-methyl- 1,3^tmadia..ol-2-yi)phe nyl)ethyi)-N-methyi-2 -(2-oxoindolin-o-yi)acetamide ;

N-((Ξ)-2-((Ξ)-3-hydroxypyrrokdrn-l -yl)-l -(3-(1-methyl-1H-inudazol-5-y_)phenyl) ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetar™de;

N-((Ξ)-1-(3-(1,3.4-oxadia2ol-2-yl)phenyl)-2-((Ξ)-3-hydroxypynolidin- 1-yl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetainide;

N-((Ξ)-2-((Ξ)-3-hyd.DxypynOkdin-1-yl)-l -(3-(5-methyI-1,3,4-oxadia2ol-2-yOphenyl) ethyl)-N-methyl-2-(2-oxoindolin-ö-yl)acetamide;

N-((S)-2-((Ξ)-3-hydtoxypyrrohdrn-l -yl)-l -(3-(1-methyl-1H-inuda..ol-4-y-)phenyl) ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetam:de;

N-((S)-1-(3-(1-(cyclopropyh^thyl) -1H-imidazol-2-yl)phenyl)-2-((S)-3-hyiioxypynOlidin-1-ylJethylJ-N-n^thyiJ -(2-oxdndolin-o -yi)acetamide;

N-((Ξ)-2-((Ξ)-3-hyd.oxypyrrokdin-1 -yl)-l -(3-(3-methy±-1,2,4-oxadiaaol-5-yOphenyl) ethyl)-N-methyl-2-(2-oxoindolin-ö-yl)acetamide; and

3-((Ξ)-2-((Ξ)-3-hydroxypynolidin-1-*yi)*-1-(N-miethyl-2-(2-oxo-2,3-dihydrobenso [d] thiazol-5-yl)acetamido)ethyi)-N-(2,2,2-trifiuoroethyl)benzamide;

or stereoisomers thereof or pharmaceutically acceptable salts thereof.

In one embodiment compounds of formula (I) are

2-(3,**3**-difluoro-2-oxoindolin-il-yl)-N-((S) -2-((Ξ)-3-hydroxypyirolidin- 1-yl)-1-phenylethyl)-N-methylacetamide;

2-(3,**3**-difluoro-2-oxoindolin-ii-yl)-N-((S) -2-((Ξ)-3-hydroxypyirolidin- 1-yl)-1-phenylethyl) acetamide;

3-((Ξ)-2-((Ξ)-3-hydroxypynolidin-1-yl)-1-(N-n¾thyi-2-(2-oxoindolm-0-yl)acetamido) ethyl) benzoic acid;

3-((Ξ)-2-((Ξ)-3-hydroxypynolidin-1-yl)-1-(N-n¾thyi-2-(2-oxoiridolm-0-yl)acetamidD) ethyl) benzamide;

N-((3)4-(3-(2-anuno-2-oxoemoxy)phenyI)-2-((3^ -hydroxypyrrolidin-1-yl)etli5ii)-N-methyl-2-(2-oxoindolin-ö-yl)acetamide;

N-((3)-2-((3)-3-hydraxypyrrohdin-l -yl)-l -(3-(2^methylsulfonamido)-2-oxoethoxy) phenyl) ethyl)-N-methyl-2-(2-oxoindolrn-fi-yl)acetamide;

3-((Ξ)-2-((Ξ)-3-fluoropyrrohdin- 1-yl)-1-(N-methyl-2-(2-oxoindolin-ö-yl)acetamido)ethyl) benzoic acid;

N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidirLl-yl)-l-(3-(5-methyl-1,2,4-oxadiazol-3-yl)]aherLyi)ethyl)-N-methyl-2-(2-oXDiridolin-ŏ-yljacetamide ;

N-((Ξ)-2-((Ξ)-3-hydroxypyrrohdirL-1-yl)-l-(3-(trLiaml-2-yl)phenyl)ethyl)-N-methyl-2-(2-axoiridolin-D̆-yl)acetamide ;

3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(N-:methyi-2-(2-oxoiridQlm-6-yl)ace^mido)ethyl)-N-(2,2,2-trifluomet]^l)berizamide ;

N,N-diethyl-3-((S)-2-((Ξ)-3-hydroxypynolidin-l-yl)-1-(N-methyl-2-(2-oκoindolm-6-yl)acetamido)ethyl)benzamide;

N-((S)-1-(3-(2-(diethyiamirLo)-2-oxoethoxy)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oXDiridolirL-ŏ-yl)acetamide ;

N-((S)-1-(3-fuoro-5-(thiazQ-2-yi)phenyi)-2-((S)-3-hydroxypynOhdm-1-yl)ethyl)-N-methyl-2-(2-oxoiridolirL-ŏ-yl)acetamide;

N-((S)-2-((Ξ)-3-hydroxyj-yrrohdm-l-yl)-l-(3-(2-meth^-2H-tetrazol-5-yl)phenyl)ethyl)-VI-methyl-2-(2-oxoiridQkn-6-yi)acetamide;

N-((3)-2-((3)-3-hydroxypynDHdirL-l-yl)-l-pl¾nyl]ethyl)-2-(2-oxoiiddin-6-yl)acetamide ;

N-((S)-1-cyclohexyl-2-((Ξ)-3-hydroxypyrrolidin-1-yl)ethyl)-N-m¾thyl-2-(2-oxomdolrn-6-yl)acetamide ;

N-((S)-1-cyclohexyl-2-((Ξ)-3-hydmxypyirohdin-1-yl)ethyl)-2-(2-oxoindolin-6-yl)acetamide;

2-(3-(1-(N-methyl-2-(2-oxoiridolirL-6-yi)acetamido)-2-(pynOlidin-1-yl)ethyl)phenoxy)acetic acid hydrochloride ;

2-(3-(1-(2-(2-oxoiridoliiL-ŏ-yl)acetamido)-2-(pyrrolidin-1-yl)emyi)phenoxy)acetic acid;

(3)-2-(3-(2-(3-hydroxypynolidm-1-yl)-1-(N-methyl-2-(2-oxoirdolirL-o~-yl)acetamido)ethyl)phenoxy)acetic acid hydrochloride ;

(3)-2-(3-(2-(3-hydroxypynOhdiri-1-yl)-1-(2-(2-oxoiridoliiL-D̆-yl)acetamido)ethyl)phenoxy)acetic acid hydrochloride ;

N-((3)-1-(3-(2H-tetrazol-5-yl)phenyl)-2-((3)-3-hydroxypyrrolidm-1-yl)ethyl)-N-methyl-2-(2-oxoindolm-6-yl)acetamide ;

N-((3)-1-(3-(2H-tetrazol-5-yl)phenyl)-2-((3)-3-hydroxypyrrolidm-1-yl)ethyl)-N-methyl-2-(1-methyl-2-oxomdolin-6~-yl)acetamide ;

N-((S)-1-(3-(2H-tetrazol-5-yl)phenyl)-2-((S)-3-nuoropyrrohdm-l-yl)ethyl)-N-methyl-2-Q-oxoindolin-6-yl)acetamide ;

N-((S)-1-(3-cyarophe nyi)-2-((3)-3-hydro xypyrrdidin -1-yi)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetainide;

N-((S)-2-((S)-3-hydraxyp3^HdirL -l-yl)-l-phenyiethyl)-2-(2-oxoinddm -5-yi)acetarride;

2-(3-((S)-2-((S)-3-hydroxypyrrolidin-l -yi)- 1-(N-™ thyl-2-(2-oxoindolin-6-yl)acetamido) e1hyl)phenoxy)acetic acid,

N-((3)-2-((3)-3-hydroxypyrroHdirL -l-yl)-l -phsnylethyl)-N-methyl-2-(2-oxoi tvi ol m.-5-yl)acetamide;

N-((S)-2-((S)-3-fluoropyrrdidin-l -yi)- 1-(3-(2-(methyisulfonamido)-2-oxoethoxy^phenyl) ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetamide;

3-((S)-2-((S)-3-fluoropyrrolidin- 1-yi)-1-(N-methyi-2-(2-oxoin± ılin-ō-yi)ace tamido)ethyi) lensamide;

2-(3-((S)-2-((S)-3-hydroxypyrrolidin-l -yl)- 1-(N-methyl-2-(2-oxoindQkn--%yl)acetar^ ido) e1hyi)phenoxy)acetic acid;

3-((S)-2-((S)-3-hydr oxypyrto lidin- 1-yl)- 1-(N-methyl-2-(2-oxomdDlin-6-yl)acetam_do) ethyl)-N-(methylsulfonyi)benzanude;

N-((S)-2-((S)-3-hydtOxypyrrokdin-l -yl)-l -(3-(5-(trifluoromethyl)- 1,2,4-oxadia!_ol-3-yl)phenyi) ethyl)-N-methyi-2-(2-oxoindolin-o-yl)acetamide;

N-((S)-1-(3-ethynylphenyl)-2-((S)-3-hydroxypyirolidin- 1-yl)ethyl)-N-methyl-2-(2-oxoindolin-fj-yi)ac etaniide;

N-((S)-1-(3-(1,2,4-oxadiazDl-3-yl)phenyl)-2-((S)-3-hydroxypyrrohdin- 1-yl)e thyi)-N-rne thyi-2-(2-oxoindolin-6-yl)ace tamide 2,2,2-trifluoroacetate;

N-((S)-1-(3-cyaro-5-fluorophenyl)-2-((3)-3-hydroxypyrrolidin- 1-yl)ethyl)-N-methyl-2-(2-oxoindolin-o-yl)ac etaniide;

N-((S)-1-(3-(1H-imida3ol-2-yi) phenyl)-2-((S)-3-hydiOxypyirohdin- 1-yi)ethyi)-N-methyi-2-(2-ox oinddin-o-yl)ac etaniide 2.2,2-trifluoroacetate;

N-((S)-1-(3-(but-1-yn-1-yi)phenyl)-2-((S)-3-hydroxypyrrdidin -1-yl)ethyi)-N-methyi-2-(2-axoindolin-6-yi)ac etaniide;

3-((S)-2-((S)-3-hydr oxypyrto lidin- 1-yl)- 1-(N-methyl-2-(2-oxoindolin-6-yi)acetaniidD) ethyi)-N,N-dimethyib ensatnide;

N-((S)-2-((S)-3-hydroxypyrrolidm-l -yi)-l -(3-(1-methyl- 1H-iinida3ol-2-yl)phenyi) ethyi)-N-methyl-2-(2-oxoindolin-6-yl)acetamide;

N-((S)-1-(3-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-n¾thyl-2-(2-oxoindokn-0˙-yl)acetanUde;

N-((3)-2-((3)-3-hydroxypyrrohdm-l -yl)-l -(3-(5-methylthia2ol-2 -yl)phenyl) ethyl) -N-methyl-2-(2 -oxoindolirL-6 -yl)acetainide ;

N-((3)-2-((3)-3-hydroxypyrrohdm-l -yl)-l -(3-(thia2Dl-5-yl)phenyl)ethyl)-N-methyl-2-(2-oxoindolin-6 -yl)acetamide ;

N-((3)-2-((3)-3-hydraxypy™kdm-l -yl)-l -(3-(1hia!.ol-4yl)phenyl)ethyl)-N-methyl-2-(2-oxoindolin-6 -yl)acetaniide ;

N-((3)-2-((3)-3-hydraxypy™kdm-l -yl)-l -(3-(4-methylthiaaol-2 -yi)phenyl)ethyl) -N-methyl-2-(2 -oxdndolin- 6 -yl)acetarnide ;

N-((S)-2-((S)-3-hydroxypynOkdin-l -yl)-l -(3-(2-methylthia2Dl-5 -yl)phenyl)ethyl) -N-methyl-2-(2 -oxoindolin-6 -yl)acetamide ;

N-((S)-2-((S)-3-hydroxypyrrokdm-l -yl)-l -(3-(2-methyl thiazol-4-yl)phenyl)ethyl) -N-methyl-2-(2 -oxoindolin-6 -yl)acetainide ;

N-((S)-2-((S)-3-hydroxypyrrokdm-l -yl)-l -(3-(5-methyl-1^4-thkdia..ol-2-yl)pre nyl)ethyl)-N-methyl-2 -(2-oxoindolin-o˙ -yl)acetamide ;

N-((3)-2-((S) -3 -hyda xypyrrolidin -1-yl)-l -(3-(1-methyl 1H-inuidazol-5-yl)phenyl) ethyl) -N-methyl-2-(2-oxoindokn-0˙-yl)acetamide;

N-((3)-1-(3-(1,3.4-oxadia._ol-2 -yl)phenyl) -2 -((S)-3-hydiOxypyrrolidin- 1-yl)ethyl) -N-methyl-2-(2 -oxoindolin-6 -yl)acetarnide ;

N-((3)-2-((Ξ) -3 -hyda xypyrolidin -l -yl)-l -(3-(5-methy,-1,3,4-oxadia._ol-2 -yl)phenyl) ethyl) -N-methyl-2 -(2-oxoindolin-o˙ -yl)acetamide ;

N-((S)-2-((S) -3 -hydroxypyrrohdin-1 -yl)-l -(3-(1-methyl- 1H-iinidaaol-4-yl)phenyl) ethyl) -N-methyl-2-(2-oxomdolin-6-yl)acetamide ;

N-((3)-1-(3-(1-(cyclopropyhnethyl) -1H-imidazol-2-yl)phenyl)-2-((3) -3 -hydioxypynOlidin-l-yl)ethyl)-N-methyl-2 -(2 -oxdndolin-o˙-yi)acetamide ; and

N-((3)-2-((3) -3 -hydroxypynDhdin-l -yl)-l -(3-(3-methyl- 1,2,4-oxadia._ol-5 -yl)phenyl) ethyl) -N-inethyl-2 -(2-oxoindolin-o˙ -yl)acetamide ;

stereoisomers thereof or pharmaceutically acceptable salts thereof.

In one embodiment compounds of formula (I) are

N-((S)-1-(3-cyarophenyl)-2-((S)-3 -hydtoxypycrdidin-1 -yl)ethyl)-2-(1, 1-dioxido-3 -oxo-3 ,4-

dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-methylacetamide;

N-((S)-1-(3-(difluoromethoxy)phenyl)-2-((S)-3-hydroxypyrrolidin-l-yi)ethyl)-2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1.4J thiazin-6-yl)-N-memylacetamide ;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-ethyl-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(trifluoromethoxy)phenyl)ethyl)acetamide ;

N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-l-yl)-l-phenylethyl)-N-methyl-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4J thiazin-6-yl)acetamide;

N-((3)-1-(3-(1,2A oxadiazol-3-yl)phenyl)-2-((Ξ)-3-hydroxypiynolidm- 1-yl)ethyl)-2-(1, 1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-mef ylacetamide 2_J2,2-triflnoroacetate;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-ben:m[b][1,4J thiazin-6-yl)-N-((S)-2-((Ξ)-3-metlioxypyirolidin-l-yi)- 1-(3-(trifliiaromethoxy) phen5d)ethyl)-N-methylacetamide ;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benso[b][1,4J tmazm- 6-yl)-N-((3)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(3-(trifluoromethoxy)phenyl)ethyl)-N-(2,2,2-trifluoroethyl) acetamide 2,2,2-trifluoroacetate;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benao[b][1,4J tmazm-6 -yl)-N-(2-((Ξ)-3-hydiOxy pyrrolidin-1-yl)-1-(tetrahydro-2H-pyran-4-yl)ethyl)-N-methylacetamide-2,2,2-trifluoiDacetate;

2-(3-((Ξ)-1-(2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4J thiazin-E5-yl)-N-metftylacetamido)-2-((S)-3-hydroxypyoO lidin- 1-yi)ethyl)p½noxy)acetic acid;

3-((Ξ)-2-((S)-3-hydroxypyno lidin- 1-y\)- 1-(N-methyl-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4J thiazm-6-yl)acetamido)ethyl)benzamide ;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-2-((S)-3-tydrcKyjyrro lidin-1-yl)-1-p¾nylethyl)-N-methylacetamide;

(Ξ)-2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-bensD[b][1,4]tMazin-6-yl)-N-(1-phenyl-2-(l^/rrolidm- 1-yl) ethyl)acetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benao[b][1,4]thiazm-6-yl)-N-((S)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)acetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-2-((S)-3-tydrcKyjyrro lidin-1-yl)-1-(3-(trifluQromethyl)phenyl)ethy.)-N-memykcetamide ;

2-C1.1 -dioxido -3-oxo -3,4-di.LydiO-2H-benao[b] [1,4] thkzin -6-yl)-N-((S)- 1-(3-fluorophenyl)-2-((Ξ)-3-hydroxypyrrolidin- 1-yl) e1hyl)-N-me mykcetamide ;

N-((Ξ)- 1-cyclohexyl -2-((Ξ)-3-hydroxypyrrolidin- 1-yl)ethyl) -2-(1, 1-dioxido -3-oxo -3,4-dihydro-2H-benzo[b] [1,4] thiazin-6-yl)-N-methylacetamide ;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] thiazin-6-yl)-N-((S)-2-((S)-3-liydroxypynOlidin- 1-yl) -1 -(3 -methoxyphenylJethylJ-N-nrethy^ cetamide ;

(S)-2-(3-oxo -3,4-dihydro -2H-benzo [b] [1,4] thiazin-6-yl)-N-(1-phenyl-2-(pynOlidin- 1-yl)ethyl)acetamide;

N-((S)-2-((S)-3-hydroxypyrrolidinL1 -yl)-l -p]¾n^th^)-2-(3 -oxo -3,4-dih^dro-2H-benzo [b] [1,4] thiazin-6 -yL)acetamide;

(S)-N-methyl-2-(3-oxo-3,4-dihyriKl -2H-Benzo[b] [1,4] thiazin-6-3/i)-N -(1-phe nyl-2-(pyrrolidirL 1-yl) ethjl)acetamide ;

N-(2-((S)-3-hydroxypyrrolidin-1-yl)-1-(tetrahydro-2H-pyran-4-yl)ethyl)-N-methyl-2-(3-oxo-3.4-dihydro-2H -b enzo [b] [1,4] thiazin-6 -yl)acetamide ;

N-((Ξ)-2-((Ξ)-3 -hydro xypyrro lidirL1 -yl) -1 -(3-metk3xyphenyl)ethyl) -N-methyl -2-(3-oxo -3,4-dihydro -2H^be nao [b] [1,4] thkain -6-yl)acetamide ;

N-((S)-2-((S)-3 -hydro xypyrro lidirLl -yl)-l -(3-(trifluoromethyl)phenyl) eth^)-N-meth5ii-2-(3-oxo -3,4-dihydro-2H -b enao [b] [1,4] thia ain -6 -yl)acetamide ;

N-((S)-1-(3-fluorophenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydro-2H ^be nao [b] [1.4] thkzin- 6-yl)acetamide ;

N-((S)-2-((S)-3 -hydrOxypyrro lidirL1 -yl) -1 -(3-(trifluorome1hox^pl ¾n5d)eth ^)-N -meth ^i-2-(3-ox o-3,4-dihydiio-2H-b enao [b] [1,4] Iniaain -6 -yl)acetamide ;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] thiazin-6-yl)-N-((S)-2-((S)-3-hydroxypynOlidin- 1-yl) -1 -(3 -(tiifluor ometho xy) phenyl)ethyi)-N-propylacetamide ;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] thiazin-6-yl)-N-((S)-2-((S)-3-hydroxypynOlidin- 1-yl) -1 -(3 -(trifluor ometho xy) phenyl)ethyl)-N-:isopiOpylacetamide ;

N-cyclopropyl-2 -(1,1 -dioxido -3-oxo -3,4-dihydro-2H-benso[b] [1,4] thiaain -6-yl) -N-((Ξ)-2-((S)-3-hydiOxypynohdin- 1-yl) -1 -(3 -(trifluoromethoxy) phenyl) ethyl)ace tam ide ;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-2-((S)-3-hydroxypynolidin- 1-yl)-1-(3-(tiifluoiOmethoxy)phenyl)ethy!)-N-:isobutykcetamide ;

N-(cyclopropylmethyl) -2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]t iazin-6-yl)-N-((Ξ)-2-((Ξ)-3-hydroxypyffolidirL- 1-yl)- 1-(3-(tiifluo-iomethoxy)phenyl)ethyl) acetamide ;

2-(1,1-dioxido-3-oxo-3,4-dihydrO-2H-benso[b][1,4]thiazin-6-yl)-N-((S)-2-((Ξ)-3-hydroxypynolidm- 1-yl)-1-^-(trifluoromethox^phenylJethyiJ -N-:.^ thylacetamide ;

2-(2,2-dimethyl-3-oxo-3,4-dihydrO-2H-beiEo [b][1,4]thiazm-o'-yl)-N-((S)-2-((S)-3-hydroxypynolidin- 1-yl)-1-(3-(tiifluoromethoxy)phenyL)ethyl)-N-methykcetamide ;

2-(1,1^oxido -3-oxo-3,4-dihydro-2H-benao[b][1,4]thiazin-6-yl)-N-((S)-2-((Ξ)-3-hydroxypynolidin- 1-yl)-1-(3-(2,2,2-triflTioroetlMxyJphenylJethyl) -N-methyiacetamide ;

2-(1,1^oxido -3-oxo-3,4-dihydio -2H-bensD [b][1,4J thiazin -6-yl)-N-((S)-2-((Ξ)-3-hydroxypynoliditv- 1-yl)-1-(m-tolyl)ethyl)-N-methylacetamide ;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-1-(4-fluoro-3-(tiifluoromethoxy)phenyl)-2-((S)-3-hydroxypytrolidin- 1-yl)ethyl)-N-methylacetamide ;

N-((S)-1-(3,5-dimethylphenyl)-2-((3)-3-hydroxypyrrolidin-1-yl)ethyl)-2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-methylacetamide;

2-(2,2-dimethyl- 1,1-dioxido-3 -oxo-3,4-dihydiO-2H-ben2D[b][1,4]thiazin-6-yl)-N-((S)-2-((S)-3-hydroxypyiiOlidm -l-yl)-l-(3-(trifluoromethoxy)phenyl)ethyl)-N-methylacetamide;

2-(1,1-dioxido-3-oxo-3,4-dihyda -2H-benao[b][1,4]thiazin-6-yl)-N-((S)-1-(3-fluoro-5-(2,2,2-triflnoiD ethoxy)phenyl) -2-((S)-3 -hyiroxypynolidm-l -yl)ethyl) -N-methykcetamide ;

N-((S)-1-(3-cyclopropylphenyl) -2-((3)-3 -hyd]mypyiTohdin-l-yl)ethyl) -2-(1,1-dioxido-3-oxo-3,4-dihydiO -2H-benzo[b][1,4]thiazin-6-yl)-N-methyiacetamide ;

N-((Ξ)-1-(3-cyaiioplienyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydro -2H ^benzo[b][1,4]thiazin-6-yl)acetamide ;

2-{(S)-2-({S) -3-hydroxypyrtolidin- 1-yl)- 1-(N-methyl-2-(3 -oxo-3,4-dihydiO-2H-benzo[b][l,4Jthkzin-6 -yl)acetamido)ethyl)ben3oic acid;

N-((S)-1-(3-(2-ami]M-2-oxoethoxy)phenyi)-2-((S) -3-hydroxypyri^idin -l-yl)ethyl)-2-(1,1-dioxido-3 -oxo-3,4dmydro-2H-benso [b][1.4]thiazin-6-yl)-N-memykcetamide;

2-(3-((Ξ)-2-((Ξ)-3 -hydroxypynolidm -1-yl)- 1-(N-methy^2-(3 -oxo-3,4-dihydro-2H-benzo[b][l,4J1hkzin-6-yl)acetamido)ethyl)phe]Mxy)acetic acid;

2-(1,1-dioxid>3 -oxo -3,4-dihydro-2H½e nzo [b] [1,4] tluazin-0-yl)-N-((Ξ)-2 -((Ξ)-3-hydroxypyiTohdin-l *-yl)*- 1-^-^-(memylsulfonamido)^ -oxoethoxy)phenyi) ethyl) -N-methylac etamide;

N-((Ξ)- 1-(3-(2-amino-2-oxoethoxy)phenyl)-2-((3)-3-hydiOxypyrroMin- 1-yl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydr o-2H-benzo|T-ı [1,4] thiazin -6-yl)acetamide ;

2-(1,1-dioxido-3 -om -3,4-dihydro-2H¼e nzo [b] [1,4] thiazin-0-yl)-N-((Ξ)-1-(3-ethynyl phenyl) -2 -((Ξ)-3-hydroxypyriOhdin- 1-yl)e 1hyl)-N-me mykcetamide ;

stereoisomers thereof or pharmaceutically acceptable salts thereof.

In one embodiment, compounds of formula (I) are

2-(1,1-dioxido-3 -oxo -2,3 -dihydrobenzo [d] isothiazol-o-yi) -N-((Ξ)-2 -((S) -3-hydroxypyrrolidin-1 -yl)- 1-phenylethyl)-N-methylace tamide ;

2-(2,2-dioxido- 1,3 -dihydrobenzo[c] iso thiazol-o -yl)-N-((S)-2-((3)-3 -hydro xypyrrdidm-1 -yl)- 1-(3-(Mfluoromethyl)p]¾nyi)ethyi)-N-methykcetam _de ;

5-(2-(((Ξ)-2 -((Ξ)-3-hydiOxypyrrohdm- 1-yl)- 1-pie nylethyiXiue myl)amino)-2 -oxoe thyl)-1,3-dihydrobe nzo[c] isothiazol- 1-ium 2,2-dioxide 2,2.2-trifluoroacetate ;

N-((S)- 1-(3-(1H-tetrazol-5-yl)phenyl) -2 -((S) -3 -hydroxypyrrolidm- 1-yl) ethyl)-N-methyl-2 -(1-methyl-2,2-dioxido- 1,3 -dmydrobenzo[c] isothiazol-0-yl)ac etamide ;

N-((Ξ)- 1-(3-(but- 1-yn-1 -yl) phenyl)-2 -((Ξ)-3-hydroxypyrrohdin- 1-yl)ethyl)-2 -(2,2 -dioxido-1,3-dihydrobe nzo[c] isothiazol-^-ylJ-N-methylac etamide ;

(Ξ) -N-methyl-2 -(3 -meth yl-2,2-dioxid o-l ,3-dihydrobenzo [c]isothiazol-5-yl) -N-(1-phe nyl-2-(pyrrolidin- 1-yl)ethyi)ac etamide ;

N-((Ξ)- 1-(3-(1H-tetrazol-5-yl)phenyl) -2 -((Ξ) -3 -hydroxypyrrolidm- 1-yl) ethyl)-2 -(2 ,2 -dioxido-1 ,3 -dmydrobenzo [c] isothiazol-o-yl) -N-methylac etamide ;

2-(3-((Ξ)-2 -((S)-3-hydroxypyrrohdin- 1-yl)- 1-(N-methyl-2 -(1-methyl-2,2 -dioxido- 1,3 -dihydrobe nzo[c] isothiazol-6-yl)ac etamido) ethyl)phenoxy) acetic acid;

2-(2,2-dioxido- 1,3 -dihydrobenzo[c] iso thiazol-6 -yl)-N-((S)-2-((Ξ)-3 -hydro xypyrmlidm-1 -yl)- 1-phe nylethyi) -N-methylac etamide ;

2-(1-benzyl -2 ,2-dioxido -1,3 -dihydrobenzo [c] isothiazol-6 -yl)-N-((S)-2-((Ξ)-3-hydroxypyrrolidin-1 -yl)- 1-phenylethyl)-N-methylace tamide ;

2-(2,2-dioxido- 1,3 -dihydrobenzo[c] iso thiazol-o -yl)-N-((3)-2-((Ξ)-3 -hydro xypyrrdidm-1 -

yl)- **1**-phe nylethyi) -**N** -methylac etamide ;

2-(2,2-dioxido- **1,3**-dihydrobenzD **[c] iso** thiazol -6-yl) -N -((Ξ)-2-((Ξ)-**3** -hydrox ypyriolidin -**1** - yl)- **1-(3-(5 -me** thyl- **1.2,4** -QKad.a2Dl-**3**-yl)phenyi)ethyi)-**N** -methyiace tamide ;

2-(2.2 -dioxido- **1,3**-dihydrobenao **[c]** iso thiazol-o-yl) -N -((S)- **1-(3**-ethynyl phenyl) -**2** -((Ξ)-3- hydroxypynOlidin -**1** -yl)ethyl)-**N** -n¾thylac etamide ;

N-((Ξ)- **1**-(3-(**1,2,4**-oxadiaml -**3** -yl)phenyl)-**2-((S)** -**3** -hydroxypyrrohdin-l -yl)ethyl)-**2-(2 ,2**- dioxido -**1,3** -dihydrob enzo [c] isothia..ol -6-yl) -**N** -methylac etamide ;

2-(2,2 -dioxido- **1,3**-dihydrobenzo[c] iso thia zol-6 -yl)-**N** -((S)-2-((Ξ)-**3** -hydro xypyrmlidin -**1** - yl)- **1-(3-(5** -(trifluorome **thyl)- 1,2,4- o xadiazol-3 -yl)phe nyl)ethyl)-N -methyiac etamide 2,2,2 - trifluoroacetate;**

3-((Ξ) -**1** -**(2** -**(2,2** -dioxido- **1,3**-dihydrobe nzo [c] isothiazDl -6-yl) -**N-me1hykcetamido)-2-((S)-** **3**-hydroxypyiTolidin- **1-yl)ethyi)-N-(2.2** ,2 -trill uor oethyl)b ensamide ;

N-((Ξ)- **1**-(3-(**1H**-imida3ol -**2** -yl)phenyI)-**2** -((Ξ)-**3** -hydroxypyrrohdin -**1** -yl)ethyl) -**2** -**(2,2** - dioxido -**1,3** -dihydrob enzo [c] isothia2ol -6-yl) -**N**-methylac etamide ;

N-((Ξ)- **1**-(**3** -cyanophenyl) -**2** -((Ξ)-**3** -hydroxypyrrolidin- **1**-yl) ethyl) -**2** -**(2,2** -dioxido- **1,3**- dihydrobe i™[c] isothiazol-6-yl)-N-methylacetamide **;**

3-((Ξ) -**1** -**(2** -**(2,2** -dioxido- **1,3**-dihydrobe nzo [c] isothia3ol -6-yl) -**N** -memykcetamido **)-2-((S)-** **3**-hydroxypynOlidin- **1**-yl)ethyl **)-N-N** -diemylbe]^mide ;

3-((Ξ) -**1** -**(2** -**(2,2** -dioxido- **1,3**-dihydrobe nzo [c] isothiazol-6-yl) -**N** -memykcetamido **)-2-((S)-** **3**-hydroxypyiTolidin- **1**-yl)ethyl **)-N-N** -dii™thyIbei™i™de ;

N-((Ξ)- **1**-(**3 -cyano-5** -fluorophenyl) -*2* -((Ξ)-**3** -hydroxypyrroliditi- **1**-yl) ethyl) -**2** -*(2* ,2 -dioxido - **1,3**-dihydrobe **IIEO[C]** isolhiaml -**fj** -ylJ -**N** -methylac etairiide ;

stere oisomers there of or pharmaceutically ac ceptable salts there of

In one en^odime nt, compounds of formula **(I)** are

3-((Ξ) -**2-((Ξ)-3** -hydroxypyiTohdin- **1**-yl)- **1-(N -me thyl-2-(2 -oxo-2,3** - dihydrobensotd] thiazol-**5** -yl)acetarnido)ethyl)benaoic acid;

(S) -**N** -methyl -**2-(2** -o **xo-2,3** -dihydr ob enzo [d] thiazol -5-yl)-**N-(** **1**-phenyl -**2** -(pyirolidin -**1** - $?l)ethyl)ac etamide ;

N -((Ξ)-2-((Ξ)-3 -hydroxypyrrolidin-l -yl)- **1**-phenylethyl) -**N** -methyl -**2** -(2 -o **xo-2,3-** iihydroben2o[d] thia3ol -**5** -yl)acetamide ;

N-N-difithyl-3i(S)-2-((S)-3-hydroxypynolidin-1-yi)-1-(N-methy_-2-(2-oxo-2,3-i ihydrobenzo[d]thiazol-i-yl)acetamido)emyl)ben2amide;

N-((Ξ)-1-(3-(1,2,4-oxadia3ol-3-yijphenyl)-2-((Ξ)-3-hydroxypyrrolidin-1-yi)ethyl)-N-n¾th^-2-(2-oio-2,3-dihyriObenzo[d]thiaaol-i-yl)acetamide 2,2.2-trifluoroacetate;

N-((Ξ)-1-(3-(but-1-yn-1-yi)phenyl)-2-((S)-3-hydroxypynOlidin-1-yl)ethyl)-N-methyl-2-'2-oxo-2,3-dmydrobenzo[d|thkml-5-yl)acetamide;

3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yi)-1-(N-methyl-2-(2-oxo-2,3-dihydrabenzo[d]thia3ol-5-yi)acetamido)eth5i)-N-(2,2,2-trifluoroemyl)berizamide;

N-((Ξ)-1-(3-(1H-imida2Dl-2-yL)phenyl)-2-((Ξ)-3-hydioxypynOudin-1-yi)ethyl)-N-methyl-2-(2-oxo-2,3-dihydiOberizo[d]tliazol-5-yl)acetamide;

N-((S)-2-((S)-3-hydioxypy.Tolidin-l-yi)-1-(3-(thkzDl-2-yl)phenyl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydiOberizo[dJthiaaol-5-yl)acetamide;

N-((S)-1-(3-cyano-5-fluorophenyl)-2-((S)-3-hydroxypynohdin-1-yl)ethyl)-N-methyl-2-i2-oxo-2,3-dmydrobeiiEo[dJthiaml-5-yl)acetamide hydrochloride

stereoisomers thereof or pharmaceutically acceptable salts thereof.

In another embodiment, compounds of formula (I) are

3-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(3-oxo-3,4-dihydroquinoxalin-6-yl)acetamido)ethyl)-N-(2,2,2-trifluoroethyl)benzamide;

N-((Ξ)-1-(3-cyanophenyi)-2-((3)-3-hydroxypyjrohdin-1-yl)ethyl)-N-methyl-2-(3-ox0-3,4-dihydroquinoxalin-0-yl)acetamide;

3-((3)-2-((3)-3-hydroxypyiToli^n-1-yl)-l-(N-methyl-2-(S-oio-S,4-dihyda quinoxalin-6-yl)acetamido)ethyl)ben^mide;

2-(3-((3)-2-((3)-3-hy±oxypyriOlidin-l-yl)-l-(N-methyl-2-(3-oxo-3,4-dihydroquiriDKahn-≤-yl)acetamido)ethyl)phenoxy)acetic acid;

N-((Ξ)-1-(3-ethynylphenyi)-2-((3)-3-hydroxypyrrolidin-l-yl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydroquinoxalin-0-yl)acetamide;

N-((Ξ)-1-(3-(1,2,4-0xadiasol-3-yl)phenyl)-2-((3)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydroquiriDxalm-0-yl)acetamide 2,2,2-trifluoroacetate;

N-((Ξ)-2-((Ξ)-3-hydroxypyriOlidin-1-yl)-1-(3-(5-methyl-1,2,4-oxadiaml-3-yl)phenyl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydroquinoxalin-6-yl)acetamide;

N-((Ξ)-1 -(3-cyano-5-fluorophenyl)-2-((3)-3-hydroxy^ rolidin-1 -yi)ethyl)-N-methyl-2-(3-oxo-3,4-dmydraquinoxahn-0-yl)acetam^ ;

N-((Ξ)-1-(3-(but-1-yn-1-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl) ethyi)-N-methyi-2-(3-oxo-S,4-dihydroquinoxalin-6-yl)acetamide ;

N,N-diethyl-3-((S) -2 i (S)-3-hydroxypynOhdin- 1-yi)-1-(N-methyl-2-(3-oxo-3,4-dihydroqTiiriDxaHn-di-yi)aceta]™io)ethyl)benzamide 2,2,2-trifluoroacetate ;

3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(3-oxo-3,4-dihydroquinoxalin-6-yiJacetamidoJethylJ-N,N-diinethylbenzaini i ;

stereoisomers thereof or pl^maceuticallyacceptable alts thereof.

In another embodiment, compounds of formula (I) are

(Ξ)-N-methyl-2-(2-oxo- 1,2-dihydroquindin-7-yi) -N-(1-phenyl-2-(pyrrolidin- 1-yijethyl) acetamide;

N-((Ξ)-2-((R)-3-hydroxypytididin-l -yi)- 1-phenyiethyi) -2-(2-oxo-l,2-dihydroquinolin-6-yl)acetamide;

N-((Ξ)-2-((S)-3-hydroxypyrrohdin- 1-yi)-1-phenylethyi)-N-methyi-2-(2-oxo- 1,2-dihydroquinolin-7 -yl)acetamide;

stereoisomers thereof or pharmaceutic ally acceptable salts thereof

In another embodiment, compounds of formula (I) are

N-((Ξ)-2-((S)-3-hydroxypyrrohdin- 1-yi)-1-phenylethyi)-2-(3-methyi-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yi)acetamide ;

(Ξ)-2-(3-methyi-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yi) -N-(1-phenyl-2-(pyrrolidin- 1-yl)ethyl)acetamide ;

N-(1-(1-benzyl- 1H-pyrazol4-yi) -2-(pyrrolidin- 1-yi)ethyl)-2-(2-oxo-2,3-dihydrobenzo[d]oxazol-5-yi)acetamide ;

(Ξ)-t-butyl-2-(3-(1-(2-(3-benzyl-2-oxo-2,3-dihydrobenzotdlo xazol-5-yl)acetamido)-2-(pyrrolidin- 1-yi)ethyi)phenoxy)acetate;

(Ξ)-2-(3-benzyl-2-oxo-2,3-dihydrobenzo[dJ oxazol-5-yi)-N-(1-(3-(benzyioxy)phenyi)-2-(pyrrohdin- 1-yi)ethyi)-N-methyiacetamide ;

N-((Ξ)-2-((Ξ)-3-hydraxypyrrolidin-l -yi)- 1-phenyiethyi) -2-(2-oxo-2,3-dihydrobenzo [d|

Dxazol -.5-yl)acetamide ;

(S)-2-(3-benzyl-2-oxo-2,3-dihydrobenzo [d] oxazol -5-yl) -N-(1-(3-(4-methoxybenzyloxy) phenyl)-2-(pyrrolidin-1-yl)emyl)acetamide ;

2-(3-(4-cyanobenzyl) -2-oxo -2,3-dihydtobenzo [d] oxazol -5-yl)-N-((3)-2-((3)-3-hydroxy p^rolidin -1-yl)- l-phenyle1hyl)acetamide;

2-(3-(3-cyanobenzyl) -2-QKO-2,3-dihydtobenzo [d] oxazol -5-yl)-N-((S)-2-((Ξ)-3-hydroxy pyrrolidin-1-yl)-1-phenylethyl)-N-methylacetamide;

N-((S)-1-cyclohexyl -2-((Ξ)-3-hydroxypyrrohdin- 1-yl) ethyl) -2-(2-oxo-2,3-imydrobenzo[d] oxazol -5-yl)acetamide ;

(S)-tert-bTityl -2-(3-(1-(2-(3-benzyl-2-oxo-2,3-dmydrobenzo [d] oxazol -5-yl)-N-methyl acetamido)-2-(pynOhdin-1-yl)ethyl)phenoxy)acetate ;

N-((S)-1-cyclohexyl -2-((Ξ)-3-hydroxypynOkdin- 1-yl) ethyl) -N-methyl-2-(2-oxo -2,3-imydrobenzo[d] oxazol -5-yl)acetainide ;

[5)-N-(1-(3-cyanophenyl)-2-(pyrtDlidin- 1-yl) ethyl) -N-methyl-2-(2-oxo -2,3-imydrobenzo[d] oxazol -5-yl)acetamide ;

2-(3-(3-cyanobenzyl) -2-oxo -2,3-dihydtobenzo [d] oxazol -5-yl)-N-((S)-2-((Ξ)-3-hydroxy pyrrolidin-1-yl)- l-plienylemyl)acetamide ;

N-((S)-1-(3-cyanophenyl)-2-((Ξ)-3-hydroxypyiTolidin-1-yOethyl) -N-inethyl-2-(2-oxo-2,3-imydrobenzo[d] oxazol -5-yl)acetamide ;

(Ξ)-tert -butyl 2-(3-(2-(3-hydroxypyndidin -1-yl)- 1-(2-(2-oxo -2β-dihydro benzo [d] oxazol-5-yl)acetamido) emyl)phenoxy)acetate ;

2-(3-(4-cyanobenzyl)-2-oxo -2,3-dihydrobenzo [d] oxazol -5-yl)-N-((S)-2-((Ξ)-3-hydroxy pyrrolidin- 1-yl)- 1-phenylethyl) -N-methylacetamide ;

N-(1-(3-(cyanome1hoxy)phenyl)-2-(3-hydroxy^^olidin-1-yl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydrobe rEo[d] oxazol -5-yl)acetaniide ;

tert -butyl 2-(3-((Ξ)-2-((R)-3-hydroxypyxrolidin- 1-yl) -1-(N-methyl-2-(2-oxo -2,3-dihydro benzo[d] oxazol -5-yl)acetanudo)ethyl)phenoxy)acetate ;

N-((Ξ)-1-(3-cyanophenyl)-2-((Ξ)-3-hydroxypyrrolidin-1-yl) ethyl) -N-methyl -2-(3-methyl-2-oxo-2,3-dihydrobenzo[d] oxazol -5-yl)acetamide;

(Ξ)-methyl 3-((2-oxo-5-(2-oxo -2-(1-phenyl-2-(pyrrohdin-1-yl) emykmino)ethyl)benzo[d] oxazol -3(2H)-yl)methyl)benzoate ;

(Ξ)-tert-butyi-2-(2-oxo-.5-(2-oxo-2-(1-phenyi-2-(pyrrd idirLl -yiJethylamirLo) ethyl)berizo [d] oxa2ol-3(2H)-yl)acetate;

(Ξ)-2-(2-oxo-5-(2-oxo-2-(1-phenyl-2-(pyrrolidin-1-yl)ethylamino)ethyl) benzo [d] oxazo1-3(2H)-yl)acetic acid hydrochloride;

3-((5-(2-(((Ξ)-2-((Ξ)-3-hydroxypyrrokdin- 1-yl)- 1-phe nyiethylXniethyiJamiflio) -2-oxoethyi)-2-oxoberzo [d] oxa2ol-3(2H)-yl) methyi)berisamide;

(Ξ)-2-(3-benzyi-2-oxo-2,3-dihydroberzo [d] oxazol-5-yl)-N-(1-(3-hydroxyphenyl) -2-(pyrrolidin-1 -yl)ethyi)-N-methyiacetamide;

2-(3-((Ξ)-2-((R)-3-hydroxypyrrolidirL1-yl)- 1-(N-methyi-2-(2-oxo-2.3 -dihydrobenao [d] o.iazol-5-yi)acetamido)ethyi)pl^noxy^acetic acid;

2-(5-(2-(((Ξ)-1-cycbl¾Kyl-2-((S)-3-hydroKypyrrolidiri-l -ylJethylXrMthylJanurio) -2-oxoethyi)-2-oxoberiZD[d] oxai.ol-3(2H)-yl)acetic acid;

Methyi 4-((5-(2-(((Ξ)-2-((Ξ)-3-hydroxypyrrdidirL- 1-yl)- 1-phe nylethyl)(methyl)amino)-2-oxoethyi)-2-oxoberiZD [d] oxa2ol-3(2H)-yl) methyl)berLaoate;

N-((Ξ)- 1-(3-(2H-tetra3Dl-5-yi)phenyi) -2-((S)-3-hydiOxypyrrolidirL- 1-yi) ethyl)-N-methyl-2 -(2-oxo-2,3-dihydrobe rGo[d] oxazol-5-yl)ac etamide ;

(Ξ)-2-(3-(2-(3-hydro xypytrolidirL-l -yl) -1-(2-(2-oxo-2,3 -dihydroberizo[dJ oxa2ol-5 -yl)acetamido)emyl)pheriDxy)acetic acid;

2-(3-(3-(2H-tetm3ol-5 -yl)benzyi) -2-***oxo-2***,3-dihydrobenzo[(3 oxazol-5-yl)-N-((***S)-2***-((S)-3-hydroxypyrrolidin-1 -yij-l-phenylethyljacetamide;

2-(3-(3-(2H-tetmml-5 -yl)benzyi) -2-oxo-2,3-dmydroberizo[dJ oxasol-i -yl)-N-((Ξ)-2-((S)-3-hydiOxypyrrolidin-1 -yl)- 1-phenylethyl)-N-iriethylace tamide;

2-(3-(4(1H-tetraml-5 -yl)benzyi)-2-oxo-2,3-dihydrobenzo[dJ oxaaol-5 -yl)-N-((Ξ)-2-({$)-3-hydiOxypyrrolidin-1 -yl)- 1-phenylethyl)-N-iriethylace tamide;

(R)-N-(1-(3-((2H-tetrazd-5-yl)methoxy)phe nyl)-2-(3-hydroxypyrrokdn- 1-yl)e thyl) -N-methyi-2-(2-oxo-2,3-dihydr obe irao [d] oxazd-5-yi)acetairiide ;

2-(3-(4-(1H-tetraml-5 -yl)benzyi) -2-oxo-2,3-dihydroberLZo[dJ oxazol-5-yl)-N-((Ξ)-2-((Ξ)-3-hydiOxypyrrolidin-1 -yi)-l-phenylethyl)acetamide;

N-((Ξ)- 1-(3-(2H-tetraml-5-yl)p½nyl) -2-((S)-3-hydroxypyrrolidrn- 1-yi) ethyl)-N-methyl-2 -(3-methyi-2-oxo-2,3-dihydr obenzo [d] oxazd-5-yi)acetairiide ;

N-((Ξ)- 1-(3-cyariophenyi) -2-((Ξ)-3-fluoropyriOlidirL- 1-yl) ethyl) -N-methyi-2 -(2-oxo-2,3-

dihydrobe rEo[d] oxaml -^yljacetamide;

N-((Ξ)-1-(3-(2H-tetrazol-5-yl)phenyl) -2-((S)-3-fhioropyrro Min- 1-y_)ethy.)-N-methyl-2-(2-oxo-2,3-dmydrobe **rEo[d]** oxasol-.5-yi)ac etamide ;

(R)-N-(1-(3-((2 H-tB h^d-.5-yl)methoxy)phe nyl)-2-(3-hydroxypyn olidin-1-yl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydr obe nzo[d] oxazd-5-yl)acetamide ;

3-((Ξ)-2-((Ξ)-3-hydroxypyrrok 'drn-1-yl)-1-(N-me thyl-2-(2-oxo-2,3-dihydrob enzo[d]oxam l-5-yl)acetamido)ethyl)benzamide;

N-((Ξ)-1-(3-cyanophenyl) -2-((Ξ)-3-hydroxypyrrolidin- 1-yl) ethyl) -N-me thyl-2-(2-oxo-2,3-dihydrob enzo[d]oxaml-.5-yl)ac etamide;

3-((Ξ)-2-((Ξ)-3-hydroxypyrrokdrn- 1-yl)-1-(N-me thyl-2-(2-oxo-2,3-dihydrob enzo[d] oxam l-i -ylJacetamido Jethyl)benzoic acid;

stereoisomers thereof or pharmaceutically acceptable salts thereof.

In another embodiment, compounds of formula (I) are

(S)-2-(3-oxo-3,4-dihydro -2H-benzo [b] [1,4] oxazin-o-yl)-N-(1-phenyl-2 -(pyrrolidin-1-ji)ethyl)acetamide ;

N-((S)-1-(3-cyarophe nyl)-2-((3)-3-hydro xypyrdidrn-l -yl)ethyl)-N-methyl-2 -(3-oxo-3,4-dihydro-2H^benao[b] [l,4]oxazin .6-yl)acetamide;

3-((Ξ)-2-((Ξ)-3-hydr oxypyno lidin- 1-yl)-1-(N-nttthy_-2-(3-oxo-3,4-dmydro-2H-ben2o[b] [l,4Joxazin-0-yl)acetamido)ethyl)ben3oic acid ;

2-(3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1 -yl)-1-(N-methyI-2-(3-oxo-3 Adihydro-2H-ben2o[b] [l,4Joxazin-0-yl)acetamido)ethyl)phenoxy)acetic acid;

N-((S)-1-(3-(2-amino-2-oxoethoxy)phenyl)-2-((S) -3-hydr oxypyrmlidrn-l -yI)ethyl)-N-methyl-2-(3-oxo-3 ,4-dihydro-2H-ben2D ob] [1,4] oxazin-o-yl)acetamide ;

stereoisomers thereof or pharmaceutic ally acceptable salts thereof.

In one embodiment the present application provides compounds of formula (I) as κ opioid receptor (KOR) agonists.

In another embodiment, the application is directed to pharmaceutical compsitions comprising a pharmaceutically acceptable carrier and an effective amount of a compound of formula (I), stereoisomer thereof or pharmaceutically acceptable salt thereof.

In another embodiment the application is directed to a method for binding opioid receptor, in a patient in need thereof, comprising administering to said patient a composition comprising an effective amount of a compound of formula (I) or stereoisomer thereof or pharmaceutically acceptable salt thereof.

In other embodiment the application is directed to a method of treating or preventing gastrointestinal dysfunction, in a patient in need thereof, comprising administering to said patient a composition comprising an effective amount of a compound of formula (I), stereoisomer thereof or pharmaceutically acceptable salt thereof.

In other embodiment the application is directed to a method of treating or preventing pain, to a patient in need thereof, comprising administering to said patient a composition comprising an effective amount of a compound of formula (I), stereoisomer thereof or pharmaceutically acceptable salt thereof.

In another embodiment the pain is selected from chronic pain or acute pain

In another embodiment the pain is selected from the group consisting of nociceptive pain, inflammatory pain, visceral pain, somatic pain, neuralgia, neuropathic pain, AIDS pain, cancer pain, phantom pain, psychogenic pain, pain resulting from hyperalgesia, pain caused by rheumatoid arthritis, migraine and allodynia.

In another embodiments, the application is directed to a method of treating or preventing ileus, in a patient in need thereof, comprising administering to said patient a composition comprising an effective amount of a compound of formula (I), stereoisomer thereof or pharmaceutically acceptable salt thereof.

In another embodiment the compounds of formula (I), stereoisomers thereof or pharmaceutically acceptable salt thereof, are directed to the use in treating or preventing diseases or disorders that maybe associated with and/or modulated by opioid receptors.

In another embodiment the compounds of formula (I), stereoisomer thereof or pharmaceutically acceptable salt thereof, are directed to the use in treating or preventing diseases or disorders that maybe associated with and/or modulated by KOR agonists.

Another embodiment provides a method, wherein the compound of formula (I), stereoisomer thereof or pharmaceutically acceptable thereof, binds κ opioid receptors.

Another embodiment provides a method, wherein the κ opioid receptors are located in the central nervous system.

Another embodiment provides a method, wherein the κ opioid receptors are located peripherally.

In other embodiments, the compounds of the present application act peripherally.

In yet another embodiment, the application is directed to a method of treating or preventing arthritis, hypertension, post-opeartive pain, inflammation, magraine, disorders of gastrointenstinal tract psoriasis, Parkinsonism and stroke, comprising administering to a patient in need thereof, a composition comprising an effective amount of a compound of formula (I), stereoisomer thereof or pharmaceutically acceptable salt thereof.

In another embodiment the compounds of the present application 'does not substantially cross' the blood-brain barrier.

In other embodiment the compounds of the application maybe used in methods for preventing or treating post-operative or opioid-induced ileus.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art at the time this application was made.

All publications, patent applications and patents mentioned herein are incorporated herein by reference for the purpose of describing and disclosing, for example, the constructs and methodologies that are described in the publications, which might be used in connection with the presently described application. An embodiment of the present application provides the process for preparing compounds of formula (I) according to the procedures of the following examples, using appropriate materials. Those skilled in the art will understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. Moreover, by utilizing the procedures described in detail, one of ordinary skill in the art can prepare additional compounds of the present application claimed herein. All temperatures are in degrees Celsius unless otherwise noted.

EXAMPLES

The following acronyms, abbreviations, terms and definitions have been used throughout the reaction scheme and experimental section.

AD-mix-alpha [Mixture containing Hydroquinine l,4-phti^azinediyl diether (0.0016 mole), BocjO (Dd-tert-butyl dicarbonate), BSA (Bovine serum albumin), BOP (Benzotriazole-l -yl-oxy-tris-(dimethyk mino)-phosphonium hexafluorophosphate), Bn (Benzyl), BnBr (Benzyl bromide), cDNA (complementary DNA), DCC (N,N'-Dicycbhexylcarbodiiimde), DIEA or DIPEA [(N,N-diisopropylethyknune) (Hunig's base)], DMF (N,N-dimemyllDrmamide), DMSO (dimethyl sulfoxide), DCM (Diehloromethane), DMAP (Dimethyl amino pyridine), EC_{50} (half maximal effective concentration), EtOAc (Ethyl acetate), Ether / EtjO (diethyl ether), EDCI (l-ethyl-3-(3-din¾thylaminopropyl) carbodumide hydrochloride, HOBt (1-hydroxyberizotriazole), HC1 (hydrochloric acid), HATU [O-(-7-azabenzotriazol-l -yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate], HEPES (4-(2-hydroxyethyl)-l-piperazine ethane sulfonic acid), HTRF(homogeneous time resolved fluorescence), i-PrjNEt (Dusopropyl-emykmine) MeOH (Methanol), MsCl (Meltanesulfonyl chloride), n-BuLi (n-butyl hthium), OTBDMS (tertiary butyidimethyisiryloxy), PyBOP (benzotriazol-1 -yl-oxytripyimhdinoplMsplMnium hexafluorophosphate), Q-Phos (pentapheny¾di-tert-butylplMsphinoJferrocene), $Pd_2(dba)_3$ (Tris(dibenzylideneacetone) dipalladium(0)), PMB (p-methoxyoenzyl), PE (Petroleum ether), Pd(PPhj)+ (Teti^s(trip]¾nylphosp]ure)pilkdiun^O)) , SEM-Cl (Q-Trimethyteuyljethoxyrnethyl chloride), $P(OMe)_3$ (Trimethylphosphite), TBAI (Tetmbutykmmonium iodide), TBAF (Tetrabutyi ammonium Fluoride), TEA (Triemykmine), THF (tetiahydrofuran), TMS-Cl (Trimethylsilyl chloride), TFA (Tnfluoroacetic acid), h (hour), min (minute), X-Phos (2-DicyclotexylphDsphino-2 ',4^ triisopropylbiphenyl), TLC (thin layer chromatography, MS (mass spectroscopy), NMR (nuclear magnetic resonance), IR (Infrared Spectroscopy), Mp/mp (melting point), aq (aqueous), psi (pound per square inch).

NMR abbreviations: MHz (Megahertz), br (broad), apt (apparent), s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet).

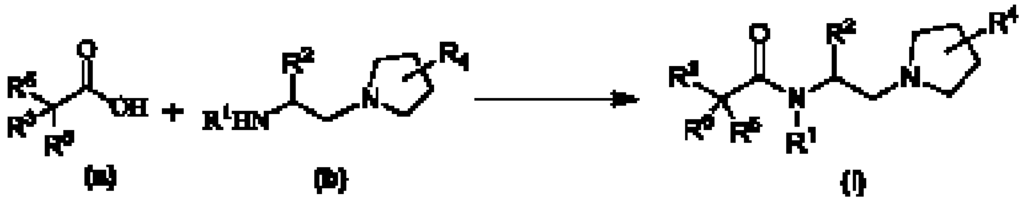
Room temperature is defined as an ambient temperature range, typically from about 20°C to about 35°C. An ice bath (crushed ice and water) temperature is defined as a range, typically from about -5°C to about 0 °C. Temperature at reflux is defined as ±15°C of the boiling point of the primary reaction solvent. Overnight is defined as a time range of from about 8 to about 16 hours. 'Dried/concentrated in vacuo' or 'dried/concentrated under reduced pressure' is defined as using a high vacuum pump at a range of pressures, typically from about 0.1 mm Hg to about 5 mm Hg. Brine is defined as a saturated aqueous sodium chloride. Nitrogen atmosphere is defined as positive static pressure of nitrogen gas passed through a Drierite™ column with an oil bubbler system. Melting points were measured against a mercury thermometerand are not corrected.

All eluents for column or thin layer chromatography were prepared and reported as volume:volume (v:v) solutions. The solvents, reagents, and the quantities of solvents and/or reagents used for reaction work-up or product isolation can be those that typically would be used by one of ordinary skill in organic chemical synthesis, as would be determined for the specific reaction or product to be isolated. For example: 1) crushed ice quantity typically ranged from about 10 g to about 1000 g depending on reaction scale; 2) silica gel quantity used in column cluomatography depended on material quantity, complexity of mixture, and size of chromatography column employed and typically ranged from about 5 g to about 1000 g; 3) extraction solvent volume typically ranged from about 10 mL to about 500 mL, Spending upon the reaction size; 4) washes employed in compound isolation ranged from about 10 mL to about 100 mL of solvent or aqueous reagent depending on scale of reaction; and 5) drying reagents (potassium carbonate, sodium carbonate or magnesium sulfate) ranged from about 5 g to about 100 g depending on the amount of solvent to be dried and its water content.

The following general schemes and examples describe various embodiments of the present application Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the application as disclosed herein. It is intended that the specification, together with the examples, be considered to be exemplary only, with the scope and spirit of the application being indicated by the claims which follow the examples.

The compound of formula (I) can be synthesized by following the processes explained in following general schemes, wherein all symbols/variables are as defined earlier unless otherwise stated:

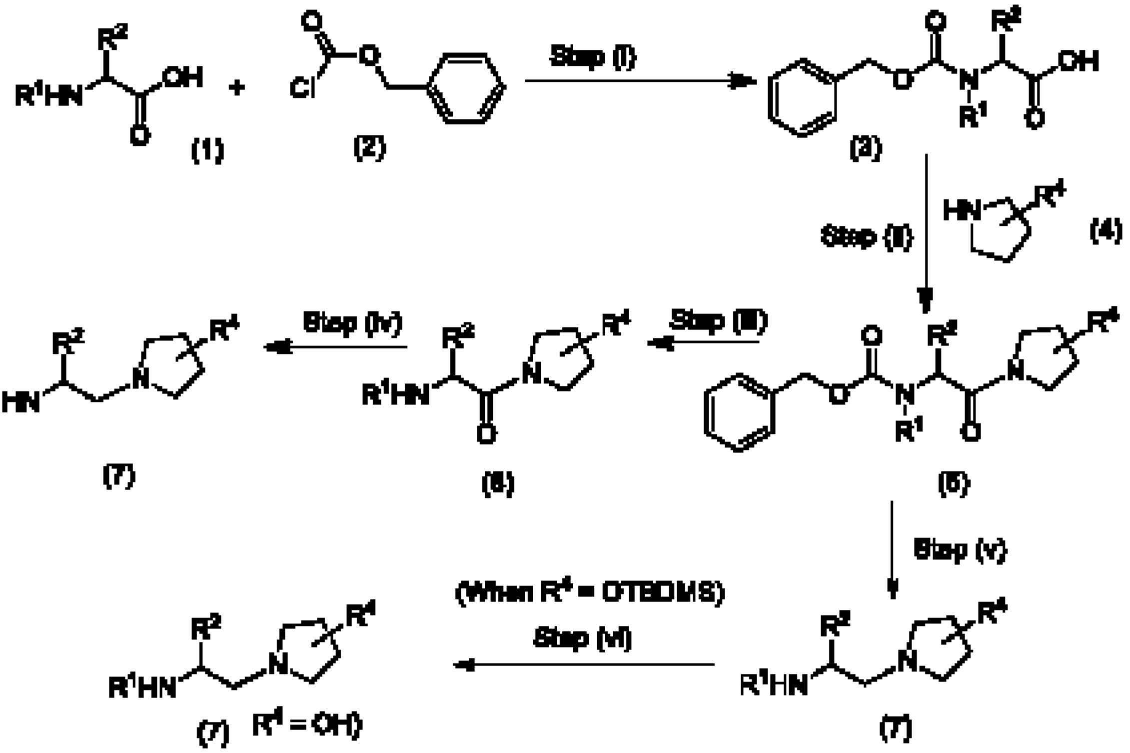
General Scheme (1) for synthesis of compounds of formula (I)



Condensation of reactant (a) with reactant (b) using suitable coupling agents such as EDCI/HOB1, HATU, BOP, PyBOP, DCC/HOBt, and the like in a suitable solvent like DCM, DMF and the like in the presence or absence of base like DMAP, DIPEA, triethylamine and the like can yield a compound of general formula (I) wherein R^1, R^2, R^3, R^+, R^i and R^6 are as defined in the specification

The compounds of general formula (I), wherein optional substitutions on R^2 and R^3 independently contains cyano, can be further converted to the corresponding tetrazolyl, amide and or carboxylic acid group(s) by using general procedures known in the art. When the optional substitutions on R^2 and R^3 independently contains an ester functionality the same can be further converted to the corresponding caiboxylic acid group by using general procedures known in the art. When the optional substitutions on R^2 and R^3 mdependently contains a caiboxylic acid moiety, the same can be further converted to the corresponding caiboxamides. N^cylsulforamides and related derivatives by foliowing general procedures known in the art. The compunds of general formula (I), wherein optional substitutions on R^2 and R^3 independently contains a benzyl group like Bn, PMB etc and or benzyl ether (OBn, OPMB), the benzyl group can be hydrogenolytically removed by using general procedures known in the art. Similarly NBn or NPMB can be hydrogenolytically converted to their NH groups. When R^+ is a silyloxy group for example, OTBDMS, it can be further deprotected to the conesponding hydroxyl group by using general procedures known in the art. When R^+ represents hydroxy! group, it can be further converted to the corresponding fluoio derivatives by following general procedures known in the art.

General Scheme (2) for Synthesis of the Reactant (b)



Step (i): The protection of nitrogen in the compound of general formula (1), wherein R^1 and R^2 are as described in the compound of general formula (I) in the specification, can be effected by reacting with a protecting agent such as benzyl chloroformate (2) in presence of a mild base such as sodium bicarbonate under suitable conditions of solvent and temperature, to yield a compound of general formula (3).

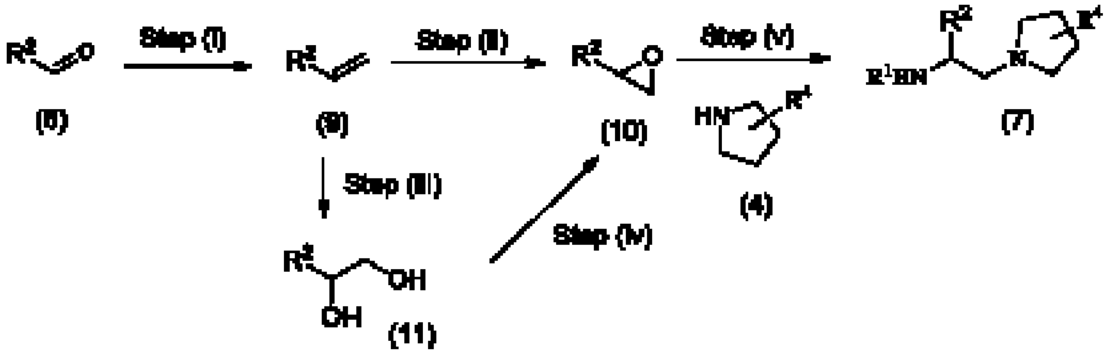
Step (ii): Condensation of the compound (3) with a compound of general formula (4) which represents a nitrogen containing saturated heterocycle substituted with R^+, using suitable coupling agents such as EDCI/HOBt, HATU, BOP, PyBOP, DCC/HOBt, and the like in a suitable solvent like DCM, DMF and the like in the presence or absence of base like DMAP, DIPEA and the like can yield a compound of general formula (5). R^+ is as defined in the general formula (I) in the specification.

Step (iii): Deprotection of the nitrogen i.e removal of the benzyloxycarbonyl (Cbz) group can be effected under hydrogenolytic conditions by treating the compound of general formula (5) with hydrogen in presence of a suitable catalyst such as Pd/C under suitable conditions of solvent and temperature to obtain a compound of formula (6).

Step (iv): A compound of general formula (7) can be obtained by reduction of the compound of formula (6) using suitable reducing agents such as LiAlH+, NaBH+ and the like under suitable conditions of solvent and temperature .

Step (v): A compound of general formula (7) can be obtained by reduction of the compound of formula (5) using suitable reducing agents such as LiAlH+, and the like under suitable conditions of solvent and temperature .

General Scheme (3) for Synthesis of the Reactant (b)



Step (i): A compound of general formula (9) can be obtained from a compound of formula (8) wherein R^2 is as described in the compound of general formula (I) in the specification by the treatment with NaH, and methyltriphenylphosphonium bromide in a suitable solvent like THF, ether and the like at a suitable temperature of 0-25*0.

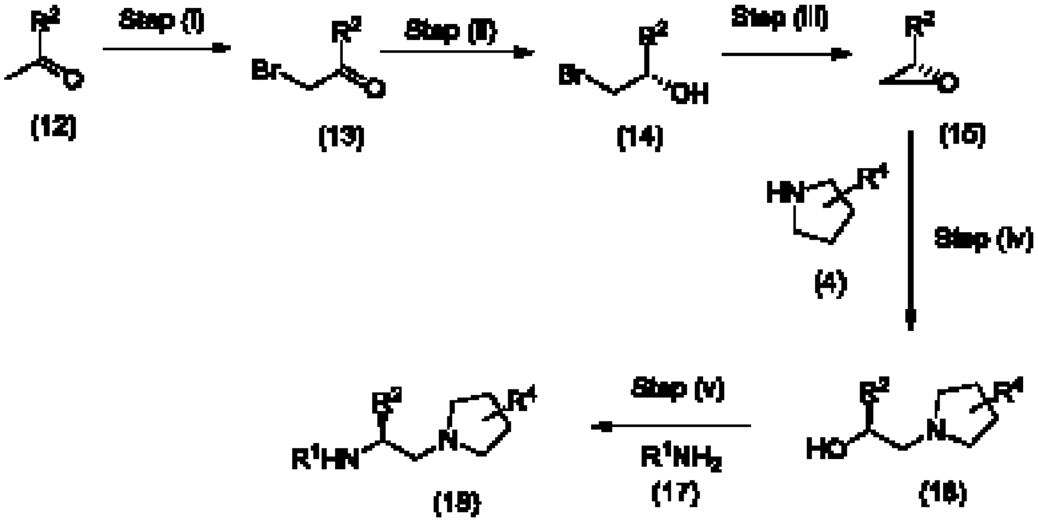
Step (ii): A compound of formula (10) can be synthesized by reacting compound of formula (9) with m-chloroperbenzoic acid and NaHCOj in a suitable solvent like DCMand the like.

Step (iii): A compound of formula (11) can be synthesized from compound of formula (10) by following standard procedure of Sharpless' dihydroxylation method known in the art.

Step (iv): A compound of formula (10) can also be obtained from various diols of formula (11) by standard procedures.

Step (v): A compound of formula (7) can be obtained by the reaction of compound of formula (10) with compound of formula (4) and R^1NH_2, wherein R^1 is described as before, under suitable reaction conditions.

General Scheme (4) for Synthesis of the Reactant (b)



Step (i): A compound of general formula (13) can be obtained from a compound of formula (12) wherein R_2 is as described in the compound of general formula (I) in the specification by using a suitable brominating agent as known in the literature.

Step (ii): A compound of formula (14) can be synthesized from compound of formula (13) by following standard procedure of CBΞ reduction method known in the art.

Step (iii): A compound of formula (15) can be synthesized from compound of formula (14) by following standard procedures.

Step (iv): A compound of formula (16) can be obtained from compound of formula (15) by the treatment with compound of formula (4) under suitable reactions conditions.

Step (v): A compound of formula (IS) can be obtained by the reaction of compound of formula *(16)* with mesyl chloride and the like under suitable condition followed by the treatment of various amines of formula (17) using suitable reaction conditions as known in the art.

The R^2 and R^4 in general formula (7) or general formula (IS) can be further converted to the Reactant (b) with different functional groups. For example when R^2 is a bromophenyl moiety the bromo group can be concerted to (a) acetylenic derivatives following Sonogashira reactions; (b) a cyano group or borate compounds which can be further converted to various 5-membered heteroaryl compounds following standard procedures known in the art. When the optional substitutions on R^2 in the compounds of general formula (7 or IS) independently contains an ester functionality the same can be converted to the corresponding carboxylic acids, amides, hydrazide, N-acylsulfonamides and the related compounds followed by further modifications as desired by using general procedures known in the art. A compound of general formula (7) or general formula (IS) wherein R^+ represent a silyl ether such as OTBDMS group can be converted to the corresponding hydroxy! group by following standard deprotection protocol of silyl ethers.

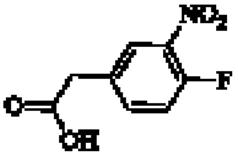
Examples

Following are the non-limiting examples of the reactant of formula (a):

Example 1-a

2-(2-oxoindolLnr6-yl) acetic acid

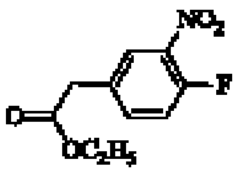
Step (i): Synthesis of 2-(4-fluoro-3-nLtropheny±) acetic acid



To a suspension of 2-(4-fluorophenyl) acetic acid (100 g, 0.648mol) in H_2SO_4 (750 ml); $KN0_3$ *(65.5* g, 0.648 mol) was added portion wise and stirred for 1.5 hr at 0 °C. The reaction mixture was quenched with ice and filtered. The solid residue obtained was dried to get 2-(4-fluoro-3-rdtiOphenyl) acetic acid (SO g).

^{1}H-NMR (400 MHz, DMSO-d_6): 5 12.30 (bs, 1H), S.10-S.0S (d, 1H), 7.73-7.71 (m, 1H), 7*.56-1 5* 1 (m, 1H), 3'1 *6 {s,* 2H); IvE (ES): *m/z* 200 (M+l).

Step (ii): Synthesis of ethyl 2-(4-fluoro-3-nitrophenyl)acetate

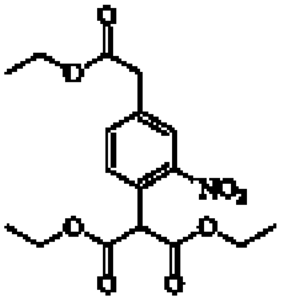


To a suspension of 2-(4-fluoro-3-rtitrophenyl)acetic acid (SO g, 0.402 mol) in ethanol (560 ml). SOCli (142.3 g, 1.206 mol) was added drop wise at 0 °C and stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the crude was dissolved in EtOAc (500 ml), washed with 5% NaHCOj solution (100 ml),, water

(100 ml), brme (100 ml) sequentially dried over Na$_2$SO+, filtered and concentrated to get ethyl 2-(4-fluoro-3-iutrophenyl)acetate (85 g).

^{1}H-NMR (400 MHz, DMSO-d_6): 5 8.01-7.99 (d, 1H), 7.58-7.56 (m, 1H), 7.28-7.23 (m, 1H), 4.214.1 9 (m, 2H), 3.67-3.58 (s, 2H), 129-1 2 5 (m, 3H); IvIS (ES): m/z 226 (M-l).

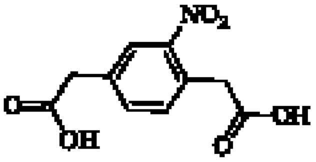
Step (iii): Synthesis of diethyl 2-(4-(2-ethDxy-2-OKoeth^)-2-rLitrophenyl) malonate



A suspension of ethyl 2-(4-fluoro-3-nitrophenyl) acetate (50 g, 0.220 mol), K$_2$CO$_3$ (45.6 g, 0.336 mol), diethyl malonate (42.3 g, 0.264 mol) in DMF (350 ml) was heated to 60°C and stirred for 4 hours. The reaction mixture was concentrated under reduced pressure and the crude was dissolved in EtOAc (500 ml) and washed with water (100 ml), brine (100 ml) dried over NajSO+, filtered and concentrated to diethyl 2-(4-(2-ethoxy-2-oxoeth;jji)-2-nitrophenyl) malonate. The crude compound was purified by column chromatography using 100-200 silica gel as stationary phase and 10% EtOAc in n-hexane as eluent (38 g).

^{1}H-NMR (400 MHz, DMSO-d_6): 5 8.07-8.07 (s, lH), 7.70-7.67 (d, 1H), 7.48-7.46 (d, lH), 5.38 (s, 1H), 420408 (m, 6H), 3.88 (s, 2H), 1.25-1.18 (m, 9H); MS (ES): m/z 368 (M+l).

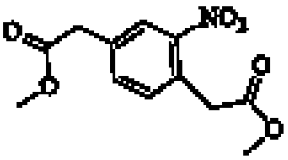
Step (iv): Synthesis of 2,2'-(2-nitro-1,4-phenylene) diacetic acid



A suspension of diethyl 2-(4(2-e1hoxy-2-oxoe1nyl)-2-nitrophenyl) malonate (38 g, 0.103 mol) in 6N AqHCl (380 ml) was stirred overnight at 120 °C. The reaction mixture was dissolved in EtOAc (500 ml); washed with water (100 ml) and brine (100 ml); dried over NajSO+; filtered and concentrated to get 2,2X2-mtro-l,4-phenylene)diacetic acid (17 g).

1H-NMR (400 MHz, **DMSO-rfi**): 5 12.53 (bs, 1H), 8 J01 (s, 1H), 7.60-7.58 (d, 1H), 7.49-7.47 (d, 1H), 3.97 (s, 2H), 3.75 (s, 2H); MS (ES): m/z 262 (M+23).

Step (v): Synthesis of dimethyl 2^'-(2-nitro-l ,4-phenylen;) diacetate



To a suspension of 2,2'-(2-nitro-l ,4-phenylene)diacetic acid (17 g, 0.071 iriol) in methanol (170 ml) at 0℃, ΞOClj (25 g, 1.20 mol) was added drop wise and stirred for 8 hours at room temperature. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in EtOAc (400 ml); washed with water (100 ml) and brine (100 ml); dried over Na_2S0 +; filtered and concentrated to obtain the titled compound (17.5 g).

^{1}H-NMR (400 MHz, DIvEO*-di)*: 5 8.06 (s, 1H), 7.64-7*.62* (d, 1H). 7.53-7.51 (d, 1H), *406*-4.02 (s, 2H), 3.87 (s, 2H), 3*.64* (s, 3H), 3.61 (s. 3H); MS (EΞ): m/z 266(M-1).

Step (vi): Ξynthesis of methyl 2-(2-oxoindolin-6-yl)acetate

To a suspension of diethyl dimethyl 2, 2'-(2-iutro-1.4-phenylene)diacetate (17 g, 0.0^3 mol) in acetic acid (170 ml), Pd/C was added and hydrogen gas pressure was applied to the reaction mixture and it was stirred overnight at room temperature. The reaction mass was filtered through celite plug; extracted with EtOAc (400 ml); washed with 5% NaHC0 $_3$ solution (100 ml), water (100 ml), brine (100 ml); dried over Na_2SO+; filtered and concentrated to get methyl 2-(2-oxoindolin-0ˉ-yl)acetate (10 g).

^{1}H-NMR (400 MHz, DIvEO-tii): 510.36 (s, 1H), 7.13-7.1 1 (d, 1H), 6.81-6.79 (d, 1H), *6.1 2* (s, lH), 3 j63 (s, 3H), 3.60 (s, 2H), 3.43 (s, 2H); MS (ES) : m/z 206 (M+l).

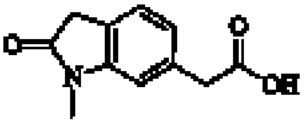
3tep (vii): Synthesis of 2-(2-oxoindolin-6-yl) acetic acid

A suspension of methyl 2-(2-OMoindolrn-6-yl) acetate (10 g, 0.048 mol) in 6N Aq.HCl (ISO ml) was stirred for 2 hours at 90°C. The reaction mixture was cooled to room temperature and filtered to obtain a solid residue which was dried to obtain 2-(2-oxoindolin-oˉ-yl) acetic acid(6.5 g).

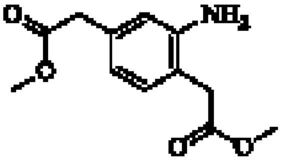
^{1}H-NMR (400 MHz, DMSO-di): δ12.30 (bs, 1H), 10 34 (s, 1H), 7.12-7.10 (d, 1H), 6.80-6.78 (m, 1H), *6.13* (s, 1H), 3.51 (s, 2H), 3.42 (s, 2H); MΞ (EΞ): m/z 192 (M+l).

Example 2-a

î-(l-methyl-2-o\ oindolin-6-yl) acetic acid



Step (i) Synthesis of dimethyl 2, 2'-(2-amino-1,4-phenylene)diacetate



Dimethyl 2^'^2-nitro-l,4-phenylene)diacetate (5 g, 0.018 mol), obtained in Step (iv) of Example (1-a), was dissolved in methanol (50 ml) and 10% Pd-C (3 g) was added to it. Therafter hydrogen gas was introduced in it and the reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was then filtered through celite, washed with methanol and concentrated under reduced pressure to get dimethyl 2, 2^2-amino-l,4-phenyiene)diacetate (4 g).

^{1}H-NMR (400 MHz, DMSO-ti$_6$): 5 6.88-6.So (m, 1H), 6.50-6.54 (m, 1H), 6.39-6.40 (m, 1H), 4.91 (s, 2H), 3.60 (s, 6¾ 3.50 (s, 4H); MS (ES): m/z 238 (M+l).

Step (ii) Synthesis of methyl 2-(1-n^thyl-2-oxomdolin-ii-yl)acetate

Propanol (40 ml) was added to a mixture of 10% Pd/C (1 g) ammoniumformate (10.7 g, 0.168 mol) dissolved in water (4 ml) and the mixture was stirred for about a minute to activate palladium carbon. Dimethyl 2,2'-(2-amino-l ,4-phenylene)diacetate compound (4 g, 0.016 moles) and formaldehyde (4 nil, 0.033 moles) were added to the reaction mixture. The reaction mixture was stirred at room temperature, then filtered through celite bed, washed with methanol, removed the solvent in vacuo to obtain a residue which was dissolved in ethyl acetate, washed, dried, purified by column chromatography using 230-400 silica gel as stationary phase and 35% ethyl acetate in n-hexane as eluent to get methyl 2-(l-methyl-2-oxoindolin-&-yl)acetate (1.8 g).

^{1}H-NMR (400 MHz, DMSO-d_6): 5 7.26 (s, 1H), 6.94-6.95 (m, 1H), 6.76 (s, 1¾ 3.71 (s, 6H), 3.50 (s, 2H), 3.20 (¾ 3H); MS (ES) : m/z 220 (M+l).

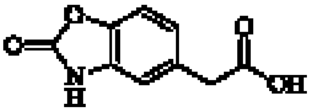
Step (iii) Synthesis of 2-(l-methyl-2-oxoindolin-6-yl) acetic acid

A suspension of methyl 2-(l -methyl-2-oxoindolin-6-yl)acetate (1.8 g, 0.008 moles) in 6N Aq.HCl (25 ml) was heated at 100°C for S hours. Thereafter the reaction mixture was allowed to cool to room temperature. The mixture was filtered to obtain a solid which was dried well to get 2-(l-n¾thyl-2-oxoindolin-6-yl) acetic acid (1.2 g).

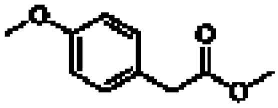
^{1}H-NMR (400 MHz, DIvEO-ii$_6$): 5 12.40 (¾ 1H), 7.17 (s. 1H), 6.87-6.90 (m_ 2H), 3.71 (s. 2H), 3.50 (s, 2H), 3.10 (s, 3H); MS (ES): m/z 206 (M+l).

Example 3-a

2-(2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)acetic acid



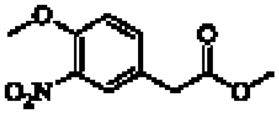
Step (i) Synthesis of n¾thyl 2-(4-methoxyphenyl)acetate



To a solution of 2-(4-metho.iyphenyl)acetic acid (30 g, 0.180 mol) in methanol (350 ml), thionyL chloride was added drop-wise at 0 C; and the mixture was refluxed for 1.5 hours. The reaction mixture was concentrated and treated with saturated sodium bicarbonate, extracted with ethyl acetate . The organic layer was separated, washed, dried and concentrated to get methyi 2-(4-methoxyphenyl)acetate (38 g of crude).

1H-NMR (400 MHz, DMSO-ii.): 5 7.19 (d, J = 8.6 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 3.73 (s, 2H), 3.60 (s, 6H); MS (ES): m/z 266 (M+l).

Step (ii) Synthesis of methyl 2-(4-methoxy-3-nitrophenyl) acetate



A mixture of nitric acid (9 ml) and acetic acid (83 ml) was added drop-wise to a solution of methyl 2-(4-methai:yphenyl)acetate (33 g) in acetic anhydride (50 ml) at -30 C. The reaction mixture was stirred and the temperature of the mixture was gradually raised from -30 to room temperature in a period of 2 hours. Ice-cold water was added portion-wise to the reaction mixture to obtain a yellow solid which was filtered and dried to get methyl 2-(4-n¾trDxy-3-nitrophenyl) acetate (42 g).

^{1}H-NMR (400 MHz, DMSO-d_6): 5 7.80 (s, 2H), 7.58 (d, *J* = 8.6 Hz, 1H). 7.33 (d, *J* = 8.8 Hz, 1H), 3.75 (s, 2H), 3.75 (s, 3H), 3.62 (s, 3H); MS (ES): m/z 226 (M+l).

Step (iii) Synthesis of methyl 2-(4-hydroxy-3-nitrophenyl)acetate

Fresh boron tribromide (27 nil, 70 g, 0.28 mol) was added drop-wise to a solution of methyl 2-(4-methoxy-3-nitrophenyl)acetate (42 gm, 0.186 mol) in DCM (200 ml) at -70°C on dry ice bath. The temperature of the mixture was gradually raised from -30°C to room temperature with stirring in a period of 4 hours. Thereafter the solvent was evaporated, the residue obtained was treated with ice-cold water and the precipitate thus obtained was dissolved in ethyl acetate. This organic layer was washed with brine, concentrated under reduced pressure and purified by column chromatography to obtain methyl 2-(4-hydroxy-3-rdtrophenyl)acetate (23 g).

1H-NMR (400 MHz, DMSO-iii): δ 10.88 (bs, 1H), 7.82 (s, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.01 (d, *J* = S.5 Hz, lH), 3.70 (s, 2H), 3.62 (s, 3H); MS (ES): m/z 212 (M+l).

Step (iv) Synthesis of n¾ethyl 2-(3-amino-4-tydroxyphenyl) acetate

Raney nickel (20 g) was added to a suspension of methyl 2-(4-hydroxy-3-rdtrophenyl)acetate in methanol (250 ml) at room temperature and the reaction mixture was stirred for 12 hours under hydrogen gas. Thereafter the reaction mixture was filtered through celite bed, washed with methanol and concentrated to get methyl 2-(3-amino-4-hydroxyphenyl) acetate (19.7 g) as a black solid.

^{1}H-NMR (400 MHz, DMSO-d_6): 5 9.00 (bs, 1H), 6.56 (d, J = 7.6 Hz, 1H), 6.41 (s, 1H) 6.27 (d, J = 7.6 Hz, 1H), 3.70 (s, 2H), 3.62 (s, 3H); MS (ES): m/z 182 (M+l).

Step (v) Synthesis of methyl 2-(2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)acetate

To methyl 2^3-aminD-4-hydroxyphenyl)acetate (19.5 g, 0.107 moles) in THF, was added triphosgene (45 g, 0.15 moles) portonwise at about 0*C in an hour. Thereafter the solvent was vaporised, the residue was treated with ice-cold water. The solid precipitate thus obtained was filtered, dried in vacuo to obtain methyl 2-(2-oxo-2,3-dinydrobenzo[d]o iasol-5-yl)acetate (10 g).

^{1}H-NMR (400 MHz, DMSO-.i_6): δ 11.60 (bs, 1H), 7.21 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 3.70 (s, 2H), 3.62 (s, 3H); MS (ES): m/z 208 (M+l).

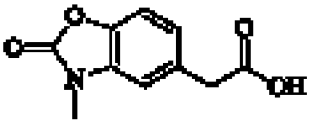
Step (vi) Synthesis of 2-(2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)acetic acid

150 ml of 5% sodium hydroxide was added drop wise to methyl 2-(2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)acetate (10 g, 0.05 moles) in methanol (75 ml), and the resultant mixture was stirred for about an hour. The solvent was vaporized and the residue was treated with 3N aq.HCl. The mixture was filtered in vacuo and dried to obtain 2-(2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)acetic acid (7 g).

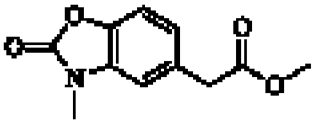
^{1}H-NMR (400 MHz, DMSO-d_6): 5 11.60 (bs, 1H), 7.20 (d, J = 8.3 Hz, 1¾ 7.00 (s, 1H), 6.96 (d, J = 8.5 Hz, 1H), 3.6Q (s, 2H); MS (ES): m/z 192 (M+l).

Example 4-a

2-(3-methyl-2-oxo-2,3-dihydrobenzo[d]oxaxo]r5-yl)acetic acid



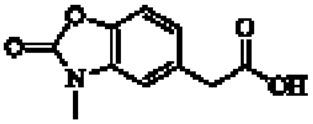
Step (i) Synthesis of memyl 2^3-memyl-2-oxo-2,3-dihydroberizo[d]oxazol-5-yl)acetate



To methyl 2-(2-oxo-2,3-dmydroberLZo[dJ oxazol-5-yl)acetate obtained in Step (v) of example 4-a, (500 mg, ***2.26*** moles) in DMF (10 ml), was added ptassi urn carbonate ***(936*** mg, 6.78 moles) at room temperature and the mixture was stirred for 10-15 minutes. The reaction mixture was then cooled to 0°C; methyl iodide (168 µl, *2*.71 moles) was added drop wise to it and the resultant mixture was stirred for 3 hours at room temperature. After completion of the reaction, the reaction mixture was poured into ice-cold water and extracted with ethyl acetate twice. Combined ethyl acetate layer was washed once with brine and water each respectively dried over sodium sulphate and concentrated in vacuo to give the crude methyl 2-(3-methyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)acetate which was purified by flash chromatography using 230400 mesh silica gel as stationary phase and 20% ethyl acetate in hexane as eluent to obtain the titled product (311 mg).

^{1}H-NMR (400 MHz, DMSO-d_6): ***5 1.26*** (d, ***J*** = 7.8 Hz, 1H), 7.16 (bs, 1H), 7D3-7.01 (m, 1H), 4.11-4.0*5* (q, 2H), 3.70 (s, 2H), 3.32 (s, 3H), 1.20-1.17 (t, 3H); IvE (ES): m/z 23*6* (M+l).

Step (ii) Synthesis of 2-(3-memyl-2-oxo-2^-dihydrobenzo[dJ oxazol-5-yI)acetic acid



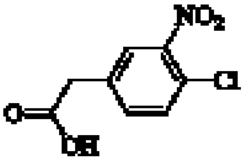
6N aq.HCl was added to methyl 2-(3-n¾thyl-2-oxo-2,3-dmydrobenzo[d]oxazol-5-yl)acetate (311 mg, 1.32 moles) at room temperature and the mixture was refluxed for 2 hours. After completion of the reaction, the reaction mixture was extracted twice with ethyl acetate. Combined ethyl acetate layer washed with brine and water onee each respectively dried over sodium sulphate and concentrated in vacuo to give the pure 2-(3-methyl-2-oxo-2,3-dihydroberLZo[d]oxazol-5-yl)acetic acidj(200 mg).

^{1}H-NMR (400 MHz, DMSO-d_6): 5 12.50 (bs, 1H), 7.23 (**d**, ***J*** = 8.3 Hz, 1H), 7.10 (bs, 1H), ***6.99*** (d, ***J*** = 8.3 Hz, 1H), ***3.60*** (s, 2H), ***3.29*** (s, 3H); MS (ES): m/z 208 (M+l).

Example 5-a

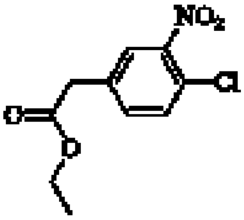
2-(2-o.«)-2,3-dihydiobeiu o[d]thia2Dl-5-yl)acetic acid

Step (i) Synthesis of 2-(4-chloro-3-nitrophenyl)acetic acid



KNOj (IS.7 g, 0.1S5 mol) was added portion-wise to a suspension of 2-(4-chtorophenyl)acetic acid (30 g, 0.176 mol) in H_2SO_4 (150 ml) at 0 °C and the resultant mixture was stirred for 1.5 hour maintaining the temperature at 0 °C. The reaction mixture was quenched with ice and filtered. The solid residue was dried to get the titled compound (26 g). ^{1}H-NMR (400 MHz, **DMSO-d_6**): 5 8.0 (s, 1H), 7.73 (d, *J* = 3.4 ¾ 1H), **7.62** (d, *J* =6.4 Hz, lH), 3.76 (s, 2H); MS (ES): m/z 200 (M+18).

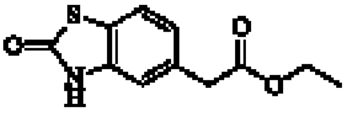
Step (ii): Synthesis of ethyl 2-(4-chloro-3-nitrophenyl)acetate



¾ ΞO$_4$ (25 ml) was added drop wise to a suspension of 2-(4-chloro-3-rdtrophenyl)acetic acid (25 g, 0.116 mol) in ethanol (125 ml) at 0°C and the reaction mixture was stirred for 4hrs at 85°C. The reaction mi-iture was then cooled to room temperature and concentrated under reduced pressure. The crude product was dissolved in EtOAc (500 ml), dried over NajS0+, filtered and concentrated to get the titled compound (27 g).

1H-NMR (400 MHz, DMSO-ti.): 5 7.83 (s, 1H), 7.52-7.44 (m, 2H), 426-4.15 (m, 2H), 3.72 (s, 2H), 127-1 .23 (m, 3H); MS (ES): m/z 242 (M-l).

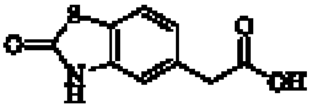
Step (iii): Synthesis of ethyl 2-(2-oxo-2,3-dihydrobenzo[d]thiazol-5-yl)acetate



A suspension of ethyl 2-(4-chloro-3-nitrophenyl)acetate (27 g, 0.111 mol), sulfur powder (17 8 g,0.555 mol), triethylamine (44.9 g, 0.44 mol), water (12 ml, **0.66** mol) in THF (135 ml) was loaded in autoclave; CO Gas pressure of up to 10 kg was applied and the mixture was stirred overnight at 80℃. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, dissolved in EtOAc (600 ml), washed with brine (100 ml), dried over NajSG+, filtered and concentrated to get the crude compound. The crude compound was purified by column chromatography using 100-200 silica gel as stationary phase and 15% EtOAc in n-hexane as eluent to afford the titled compound (10 g).

^{1}H-NMR (400 MHz, DMSO-_i$_6$): 5 11.88 (s, 1H), 11.86 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.047 Dl (m, 2H), 4.104.05 (m, 2H), 3.69 (s, 2H), 1.20-1.16 (m, 3H); MS (ES): m/z 238 (M+l).

Step (iv): Synthesis of 2-(2-oxo-2,3-dihydrobenio[d]thiasol-5-yl)acetic acid

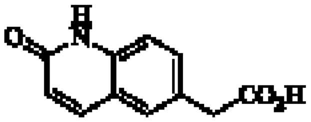


5% aq.NaOH solution (5 ml) was added to a suspension of ethyl 2-(2-oxo-2,3-dihydroberLZo[d]thazol-5-yl)acetate (10 g,0.042 mol) in methanol (50 ml) and the mixture was stirred for about an hour at room temperature. The reaction mixture was concentrated under reduced pressure. Water (10 ml) was added to the reaction mixture and it was adjusted to a pH 2-3 with 6N Aq.HCl; the solid precipitate thus obtained was filtered and dried to get title compound (8 g).

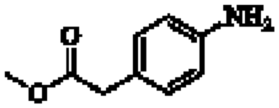
^{1}H-NMR (400 MHz, DMSO-d$_6$): 5 12.37 (bs, 1H), 11.86 (s, 1H), 7.49 (d, *J* =7.6 Hz, 1H), 7.03-7.03 (m, 2H), 3.59 (s, 2H); MS (ES): m/z 209.9 (M+l).

Example 6-a

2-(2-oxo-1,2-dihydroquinolin-6-yl)acetic acid



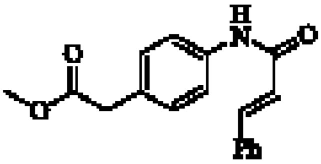
Step (i) Synthesis of methyl 2-(4-aminophenyl)acetate



Thionyl chloride (1 ml) was added dropwise to a mixture of 2-(4-aminophenyl)acetic acid (1 g, 0.0062 moles) in MeOH (20 ml) at 0℃. The reaction was then stirred for 12 hours raising the temperature gradually from 0℃ to room temperature. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, quenched with water, basified with saturated aqueous sodium bicarbonate solution and extracted 2-3 times with ethyl acetate. Combined ethyl acetate layer was washed twice with brine and water each respectively dried over sodium sulphate and concentrated in vacuo to give the title compound (0.9 g).

^{1}H-NMR (400 IvIHz, DMSO-d_6): 5 6£8 (d, *J* = 8.4 Hz, 2H), *6.49* (d, *J* = 8.3 Hz, 2H), *4.96* (s, 2H), 3.57 (s, 3H), 3.43 (s, 2H).

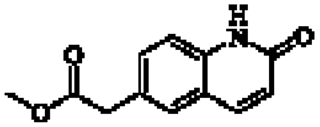
Step (ii) Synthesis of (E)-methyl 2-(4-cinramamidophenyi)acetate



To methyl 2-(4-aminophenyi)acetate (1.88 g, 0.0109 moles) in dichloromethane (30 ml), pyridine (1.6 ml) was added slowly in portions at 0°C under inert nitrogen atmosphere. To the reaction mixture at the same temperature, cinnamoyl chloride (2.7 g, 0.0163 moles) was added. The reaction mixture was then stirred at room temperature for 2 hours. After completion of the reaction, the reaction mixture was diluted with dichloromethane (60 ml), washed with saturated aqueous sodium bicarbonate solution, brine and water once respectively, dried over sodium sulphate and concentrated in vacuo to give the crude product which was then purified by flash chroamatography using 40% ethyl acetate in n-hexane as eluent to obtain the titled compound (4.0 g).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), *1.65*-1*.56* (m, 5H), 7.45-7.42 (m, 3H), 7.23-7 2 1 (m, 2H), *6*.85-6.81 (m, 1H), 3*.63* (s, 2H), 3.61 (s, 3H); IvE (ES): m/z *296* (M+l).

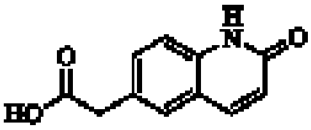
Step (iii) Synthesis of methyl 2-(2-oxo-l,2-dmydroquinolin- ≤-yl)acetate



Anhydrous and freshly sublimed AlCl$_3$ (4.5 g, 0.0338 moles) was added to (E)-methyl 2-(4-cmmmamidophenyl)acetate (2 g, 0.0067 moles) at room temperature under inert nitrogen atmosphere. The reaction mixture was then heated at 90-100°C for 2-3 horns. After completion of the reaction, the reaction mixture was poured into ice-cold water at 0°C and stirred for 30 min. A solid precipitate was obtained which was filtered in vacuo, washed 3-4 times with ethyl acetate. This organic layer washed once with brine and water each respectively, dried over sodium sulphate and concentrated in vacuo to give the titled compound (0.28 g).

^{1}H-NMR. (400 MHz, DIvEO-tit): 5 11.67 (bs, 1H), 7.85 (d, *J* = 9.3 Hz, 1H), 7.50 (s, 1H), 7.37 (d, *J* = *1.9* Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 1H), 6.46 (d, *J* = *9.3* Hz, 1H), 3.50 (s, 3H); MS (ES): m/z 218 (M+l).

Step (iv) Synthesis of 2-(2-oxo4,2-ditydroquinolin-6-yl)acetic acid

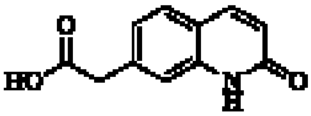


10% aqueous sodium hydroxide solution (10 ml) was added to methyl 2-(2-oxo-l,2-dihydroquinohn-6-yi)acetate (0.5 g, 2.46 moles) in MeOH (10 ml) at 0°C. The reaction mixture was then stirred at room temperature for 2 hours. After completion of the reaction, the solvent was removed in vacuo and the reaction mixture (aqueous layer) was washed twice with ethyl acetate. The aqueous layer was then cooled to 0°C and acidified to pH 2 with 3N Aq.HCl to obtain a solid precipitate. This precipitate was filtered in vacuo, washed with water and dried to obtain get pure 2^2-oxo-l,2-dihydroquinohn-6-yl)ethaneperoxoic acid product.(0.35 g).

^{1}H-NMR. (400 MHz, DMSO-rf.): S 12.33 (bs, 1H), 11.70 (bs, 1H), 7.86 (d, *J* = *9.3* Hz, 1H), 7.52 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = S 3 Hz, 1H), 6.4S (d, *J* = *93* Hz, lH), 3.60 (s, 2H); MS (ES): m/z 204 (M+l).

Example 7-a

2-(2-oxo-1,2,3,4-tetiahydroquinolin-7-yl)ethanepeioxoic acid



Step (i) Synthesis of methyl 2-(3-nitrophenyl)acetate

To 2^3-nitrophenyl)ethareperoxoic acid (1 g, 0.0055 moles) in MeOH (20 ml), thionyl chloride (1 ml) was added slowly dropwise at 0°C. The reaction was then stirred for

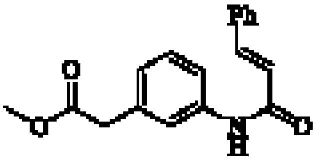
12 hours at 0°C-RT. After completion of the reaction, the volatiles were removed under reduced pressure and the reaction mixture was quenched with water, basified with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate 2-3 times. Combined ethyl acetate layer was washed twice with brine and water each respectively dried over sodium sulphate and concenterated in vacuo to give the pure methyl 2-(3-rdtrophenyl)acetate.(0.9 g)

^{1}H-NMR (400 MHz, DMSO-d_6): 5 8.20 (s, lH), 8.16-8.13 (m, 1H), 7.77-7.75 (m, 1H), 7.65-7.61 (m, 1H), 3.92 (s, 2H), 3.65 (s, 3H)

Step (ii) Synthesis of methyl 2-(3-aminophenyl)acetate

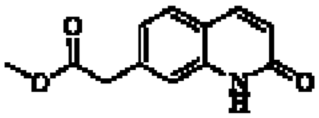
To methyl 2-(3-nitraphenyl)acetate (13 g, 0.978 moles) in MeOH (250 ml), 10%PdiC (6 g) was added under inert nitrogen atmosphere. The reaction mixture was then subjected to hydrogen gas pressure at 60 psi by using par apparatus for 1 hour. After completion of the reaction, the reaction mixture was filtered through celite in vacuo, the celite bed was washed with little excess of MeOH and the filteiate was concenterated in vacuo to give the crude methyl 2-(3-aminophenyl)acetate.(1 0.5 g)

Step (iii) Synthesis of(E)-memyl 2-(3-cinnamamidophenyl)acetate



To methyl 2-(3-aminophenyl)acetate (1.88 g, 0.0109 moles) in dichloromethane (30 ml), pyridine (1.6 ml) was added slowly portionwise at 0°C under inert nitrogen atmosphere. To the reaction mixture at same temperature ,cinnamoyl chloride (2.7 g, 0.0163 moles) was added. The reaction mixture was then stirred at room temperature for 2 hours. After completion of the reaction, the reaction mixture was diluted with dichloromethane (60 ml), washed with saturated aqueous sodium bicarbonate solution, brine and water once respctively, dried over sodium sulphate and concenterated under vacuo to give crude (E)-methyl 2-(3-cinnamamidophenyl)acetate poduct which was then purified by flash chromatography using 40% ethyl acetate in n-hexane as eluent.(4.0 g)

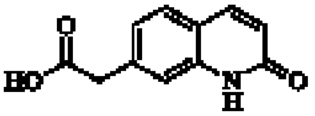
Step (iv) Synthesis of n¾thy! 2-(2-oxo-l,2-dihydroquir olm-7-yl)acete^e



To (E)-methyl 2-(3-cintiamamLdophenyl)acetate (2 g, 0.0067 moles) was added anhydrous and freshly sublimed $AlCl_3$ (4.5 g, 0D338 moles) at room temperature under inert nitrogen atmosphere. The reaction mixture (neat reaction) was then heated at 90-100°C for 2-3 hours .After completion of the reaction, the reaction mixture was poured into ice-cold water at 0°C and stirred for half an hour. A solid precipitated out which was filtered in vacuo. The cake (solid bed) was washed with ethyl acetate 3-4 times. The aqueous layer was separated from ethyl acetate. The organic layer was washed with brine and water once respectively dried over sodium sulphate and concenterated under vacuo to give pure methyl 2-(2-oxo-1,2,3,4tetrahydroquinonn-7-yl)ac etate.(0.280 g).

^{1}H-NMR (400 MHz, DMSO-rf$_6$): 5 11.72 (bs, 1H), 7.87 (d, *J* = *9.5* Hz, 1H), 7.58 (d, *J* = 8.0 Hz, lH), 7.1S (s, 1H), 7.07-7.05 (m, lH), 6.45 (d, *J* = *9.5* Hz, 1H), 3.64 (s, 3H), 3.68 (s, 2H).

Step (v) Synthesis of 2-(2-oxo-1,2-dihydroquinolin-7-yl)acetic acid

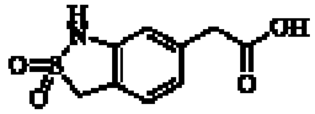


To methyl 2-(2-oxo-l,2,3,4-tetmhydroquinDhn-7-yl)acetate (05 g, *2.46* moles), in MeOH (10 ml), was added 10% aqueous sodium hydroxide solution (10 ml) at 0°C. The reaction mixture was then stirred at room temperature for 2 hours. After completion of the reaction, solvent was removed in vacuo and the reaction mixture (aqueous layer) was washed twice with ethyl acetate. The aqueous layer was then cooled to 0°C and acidified to pH 2 with 3N Aq. HCl. A Solid precipitated out which was filtered in vacuo, washed with water and dried to obtain pure 2-(2-oxo-l^^,4-tetmhydroquinohn-7-yl)ethaneperoxoic acid(0.35 g).

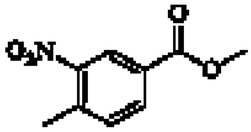
^{1}H-NMR (400 MHz, DMSO-ti$_6$): 5 12.43 (bs, 1H), 11.72 (bs, 1H), 7.87 (d, *J* = *9.5* Hz, 1H), 7.58 (d, *J* = 8.0 Hz, lH), 7.18 (s, 1H) 7.07-7.05 (m, 1H), *6.45* (d, *J* = 95 Hz, lH), 3.64 (s, 2H); MS (ES): m/z 204 (M+l).

Example 8-a

2-(2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-6-yl)acetic acid



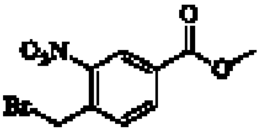
Step (i) Synthesis of methyl 4-me1hyi-3-nitrobenzoate



Thionyl chloride (33 ml, 0.447 moles) was added dropwise to 4-ii¾thyi-3-mtroberLZoic acid (27 g, 0.149 moles) in MeOH (500 ml) at 0°C and the reaction mixture was then stirred for 12 hours in the temperature range of O^-room temp nature. Thereafter the reaction mixture was concentrated in vacuo, quenched with water, basified with saturated aqueous sodium bicarbonate solution and extracted 2-3 times with ethyl acetate. Combined ethyl acetate layer was washed twice with brine and water each respectively, dried over sodium sulphate and concentrated in vacuo to afford the titled product (29.7 g).

^{1}H-NIvR (400 MHs, DMSO-d_6): δ 8.43 (s, lH), 8.16-8.13 (m, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 3.90 (s, 3H), 2.60 (s, 3H).

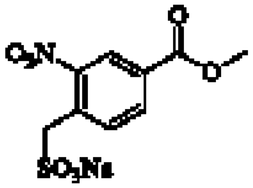
Step (ii) **Synthesis of methyl 4-(broriMmethyl)-3-nitroberLZoate**



To the methyl **4-methyl-3-nitroberL2Date** (29.7 g, 0.152 moles) in CCl_4 (450 ml), was added benzoyl peroxide (2 g, 0.0091 moles) and N-bromosuccirrimide (32.5 g, 0.182 moles) at room temperature. The reaction mixture was then kept for refluxing at 90-100 °C for 15 hours. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered in vacuo to remove succinimide precipitate. The filterate was then concentrated in vacuo to give crude product which was purified by column chromatography using silica gel 230-400 mesh as stationary phase and 5% ethyl acetate in n-hexane as eluent to afford the titled product (23 g).

^{1}H-NMR (400 MHz, DMSO-ti.): δ 8.48 (s, 1H), 8.27-8.25 (m, 1H), 7.93-7.91 (m, 1H), 4.98 (s, 2H), 3.92 (s, 3H).

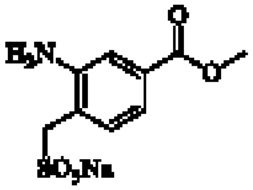
Step (iii) Synthesis of sodium (4-**(methoxycarbonyi**)-2-**nitiophenyl**)me1¾ **nesulforate**



Tetrabutylammonium bromide (0.3 g, 0.000S7 moles) was added to a mixture of sodium sulphite (14.5 g, 0.1 13 moles) in water (150 ml) at room temperature . To this reaction mixture, methyl 4-(bronMmemyl)-3 **-mtroberL3oate** (24 g, 0.087 moles) in MeOH (30 ml) was added at room temperature. The resultant mixture was then refluxed at 90-100 °C for 3 hours. After completion of the reaction, water and methanol were removed in vacuo. The residual water was then aaeotrophed with toluene 3-4 times and the reaction mixture was dried thoroughly to obtain a crude solid product which was triturated twice with each of acetone, ethyl acetate and diethyl ether respectively decanted and dried to obtain sodium (4-(n¾**thDxycarbonyl**)-2-mtrophenyl)n¾thanesulfon^ te (27 g) to be used as such for the **next** reaction without further purification.

^{1}H-NMR (400 MHz, DMSO-d₆): 5 8 2 8 (s, 1H), 8.14-8.12 (m, 1H), *1.66* (d, *J* = 8.3 *Hz*, 1H), 4.27 (s, 2H), 3 9 0 (s, 3H).

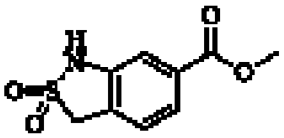
Step (iv) Synthesis of sodium (**2-amino-4-(n¾1hDxycarbonyl)phenyi**)methanesulfonate



10% Pd/C (30% w/w, *3.6* g) was added to sodium (4-(methoxycarbonyI)-2-rdtrophenyl)n¾thane sulfonate (12 g, 0 D40 moles) in IvfeOH (100 **ml)** under inert nitrogen atmosphere. The reaction mixture was then subjected to hydrogen gas pressure at 60 psi by using hydrogen bladder for 12 hours. After completion of the reaction, the reaction mixture was filtered through celite in vacuo. The filtrate was concentrate d in vacuo to give the crude product which was triturated twice with each of ethyl acetate and diethyl ether respectively decanted and dried to obtain sodium (2-andno-4-(n¾tlMxycarbonyl)phenyl **)me1hanesulfonate** as such for the next reaction without further purification *(9* g).

1H-NIvR (400 MHz, DIvEO-d0 : 5 7 3 1 (s, 1H), 7.14-7.12 (m, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 5.42 (s, 2H), 3 £ 0 (s, 3H), 3.74 (s, 2H).

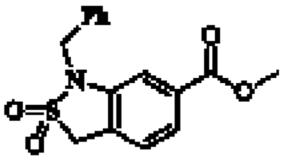
Step (v) Synthesis of methyl **l,3-dmydroben5.o[c]isotha3ole -≤-carboxylate** 2,2-dioxide



POCl$_3$ (55 nil) was added to sodium (2-amino-4-(methoxycarbonyl)phen5l) methanesulfonate (11 g, 0.041 moles) at room temperature and the reaction mixture was then heated to reflux at 140-150^ for 2-3 hours. After completion of the reaction, the reaction mixture was allowed to cool to room temperature. POCb was then distilled off under vacuo. Traces of POCl$_3$ were then removed by co-distilling with dichloro methane and diethyl ether respectively. The crude product thus obtained, was purified by flash chromatography using silica gel 230-400 mesh as stationary phase and 1% methanol in diehloromethane as eluent to afford methyl l,3-dmydrobenm[c]iso1lu™le-0-carboxylate 2,2-dioxide (3 g).

^{1}H-NMR (400 MHz, DMSO-d_i): δ 10.8 (s, 1H), 7.58 (d, *J* = 7.9 Hz, **lH), 7.43 (d, *J* =** 7.8 Hz, **1H),** 7**.32** (s, **1Hi, 4**.66 (s, **2H), 3.85** (s, **3H)**; MS (EΞ): m/z 226 (M-l).

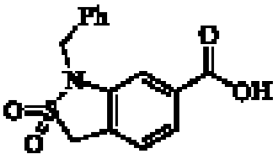
Step (vi) Synthesis of methyl 1-benzyl-l,3-dmydroben2D[c]isolMa3ole-6-carboxylate 2,2-dioxide



To methyl l^-dihydrobensoCclisolliiamle-S-carboxylate 2,2-dioxide (1.8 g, 0.0079 moles) in DMF (15 ml), was added potassium carbonate (2.2 g, 0.0158 moles) at room tempsrature and stirred for 10 minutes. Benzyl bromide (1.36 g, 0.0079 moles) was then added at 0 °C and reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, ice-cold water was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate (3x100 ml). Combined organic layer was washed twice with each of brine and water respectively dried over sodium sulphate and concentrated in vacuo to give crude methyl 1-benzyl-l,3-dihydrobenzo[c]isothiazole-6-carboxylate 2,2-dioxide which was then triturated with petroleum ether to removes traces of benzyl bromide (1.92 g).

1H-NMR (400 MHz, DMEO-*dt*): 5 **7**.60 (s, 1H), 7.58 (s, 1H), 7.49-7.45 (m, 2H), 7.40-7.36 (m, 2H), 73 1 (d, ***J*** = 7.3 Hz, 1H), 7.16 (s, 1H), 4.91 (s, 2H), 4.84 (s, 2H), 4.274.21 (q, 2H), 1.26 (t, 3H).

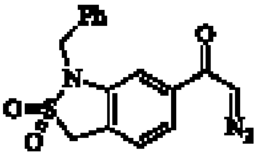
Step (vii) Synthesis of 1-¾enzyl-1,3-dihydrobenzo[c]isothiazole-6-carboxylic acid 2,2-dioxide



To methyl 14Denzyl4,3-dihydroben2D[c]isotn^ ole-6-carboxylate-2,2-dioxide (1.92 g, 0.068 moles) in MeOH (15 ml), was added 10% aqueous sodium hydroxide solution (15 ml) at 0°C. The reaction mixture was then heated at 50°C for 2 hours. After completion of the reaction, the solvent was removed in vacuo and the reaction mixture (aqueous layer) was washed twice with ethyl acetate. The aqueous layer was then cooled to 0°C and acidified to pH 2 with 3N Aq.HCl to obtain a solid precipitate which was filtered in vacuo, washed with water and dried to get l-benzyl4.3-dmydrobenm[c]isotMamle-0-carboxyiic acid 2,2-dioxide (1.2 g).

H -NMR (400 MHz, DMSO-di): 5 13.0 (bs, lH), 7.59 (s, 1H), 7.57 (s, 1H), 7.40-7.40 (m, 2H), 7.38-7.32 (m, 2H), 7.29 (d, J = 7.3 Hz, 1H), 7.15 (s, 1H), 4.89 (s, 2H), 4.83 (s, 2H).

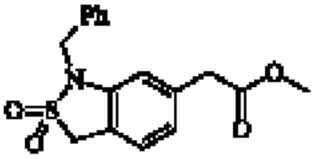
Step (viii) Synthesis of l-(l-benayl-2,2-dioxido-l,3-dmydrobenm [c^isothiazol-6-yl)-2-diaaoethanone



To benzyl-1.3-dihydroberL-B[c]isothksDle-0-carboxyiic acid-2,2-dioxide (0.8 g, 0.0026 moles), SOClj (20 ml) was added at room temperature under inert atmosphere. The reaction mixture was then refluxed for 6-8 hours. After complete conversion of acid into acid chloride, the reaction mixture was cooled to room temperature. SOClj was distilled off completely in vacuo under inert nitrogen atmosphere. The reaction mixture was then cooled to 0°C and diethyl ether (10 ml) was added to the crude acid chloride at 0°C under inert atmosphere. A freshly prepared ethereal diazomefhane solution (45 ml) (prepared from N-rdtrosoN-methyl urea (1.5 g), 40% aq KOH solution (15 ml) was added slowly to the reaction mixture at 0°C under inert nitrogen atmosphere. Finally, THF (10 ml) was added and reaction mixture was then kept for stirring at room temperature for 12 hours. After completion of the reaction, ether and THF were removed in vacuo at low temperature to give the crude product which was then purified by flash chromatography using 30% ethyl acetate in n-hexane as eluent to give l-(l-benzyl-2.2-dioxido-l,3-dihydrober^ [c]isothiazol-6-yl)-2-diazoethanone (0.7 g)

^{1}H-NMR (400 MHz, DMSO-.i$_6$): 5 7.46-7.39 (m, 5H), 7.37-7.35 (m, 2H), 7.1 1 (s, 1H), 6.88 (s, lH), 4.88 (s, 2H), 4.85 (s, 2H).

Step (ix) Synthesis of methyl 2-(1-benzyl-2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-6-yl)acetate



To 1-(1 ½enzyl-2,2-dioxidQ-l,3-dmydrobenzo^ sothiazol-6-yl)-2-diazoethanone (0.8 g, 0.0024 moles) in methanol (15 ml), was added silver benzoate solution in triethylamirie (3.5 ml) (prepared by dissolving 400 mg of silver bensoate in 4 ml of triethylamine) at room temperature. The reaction mixture was then heated at 50 *C for 1 hour. After completion of the reaction, the reaction mixture was cooled to room temperature and diluted with methanol, filtered through celite bed in vacuo. The filterate was concentrated in vacuo at low temperature to give crude solid which was then purified by purified by flash chromatography using silica gel 230-400 mesh as stationary phase and 20% ethyl acetate in n-hexane as eluent to give methyl 2-(1-benzyl-2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-6-yl)acetate (0.53 g).

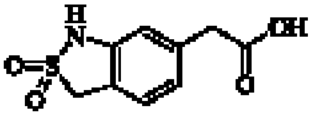
H -NMR (400 MHz, DMSO-rf.): δ 7.45-7.43 (m, 2H), 7.38-7.35 (m, 2H), 7.29-7.26 (m, 2H), 6.87 (d, *J* = 8.0 Hz, 1H), *6.64* (s, 1H), 4.73 (s, 4H), 3.58 (s, 2H), 3.53 (s, 3H).

Step (x) Synthesis of metl^l 2-(2,2-dioxido-l,3-dmydrobei™ [c]isothiazol-6-yl)acetate

To methyl 2-(l-benayl-2,2-diDxido-l,3-dihydroberLao[c] isolMazol-6-yl)acetate (0.5 g, 1.51 moles) in MeOH (10 ml), was added 10% Pd/C (50% w/w, 0.25 g) under inert nitrogen atmosphere. The reaction mixture was then subjected to hydrogen gas pressure at 70 psi for *6*-8 hours. After completion of the reaction, the reaction mixture was filtered through celite in vacuo, and the filtrate was concentrated in vacuo to give the crude solid. The crude product was then purified by flash chromatography using silica gel 230-400 mesh as stationary phase and 30% ethyl acetate in n-hexare as eluent to afford methyl 2-(2,2-dioxido-l,3-dihydrobenzo[c] isotluazol-6-yl)acetate. (0.270 g)

^{1}H-NMEl (400 MHz, DIvE 0 -d ₆) : δ 10.48 (s, 1H), 7.21 (d, J = 7.8 Hz, 1¾ 6.85 (d, J = 7.8 Hz, lH), 6.73 (s, 1H), 4.49 (s. 2H), 3.66 (s, 2H), 3.60 (s, 3H).

Step (xi) Synthesis of 2-(2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-6-yl)acetic acid

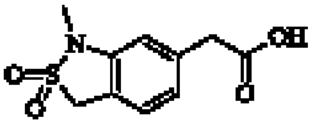


To methyl 2-(2^-dioxido-l,3-dihydrobei™[c]isrt hiazol-6-yl)acetate (2.5 g, 0.01 1 moles) in MeOH (25 ml) was added 10% aqueous sodium hydroxide solution (25 ml) at 0°C. The reaction mixture was then heated at 50°C for 2 hours. After completion of the reaction, the solvent was removed in vacuo and the reaction mixture (aqueous layer) washed with ethyl acetate . The aqueous layer was then cooled to 0°C, acidified to pH 2 with 3N aq.HCl to obtain a solid precipitate which was filtered in vacuo, washed with water and dried to afford 2-(2,2-dioxido-l,3 -dihydrobenzo [c]isotha2Dl-6-yl)aceuc acid (2 g).

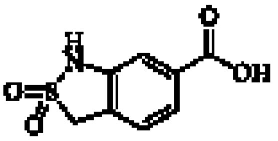
^{1}H-NMEl (400 MHz, **DMSO-rfi)** : 5 13.10 (bs, 1H), 10.80 (bs, 1H), 7.57-7.55 (m, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.31 (s, l H), 4.64 (s, 2H).

Example 9-a

2-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-6-yl)acetic acid



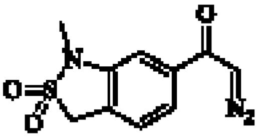
Step (i) Synthesis of l,3-dmydrobenzo[c]isothiazole-6-carboxylic acid 2,2-dioxide



To methyl l,3-dmydraberLZo[c]isotluazole-6-carboxylate 2,2-dioxide (2.5 g, **0.01 1** moles) in MeOH (25 ml) was added 10% aqueous sodium hydroxide solution (25 ml) at 0°C. The reaction mixture was then heated at 50°C for 2 hours. After completion of the reaction, the solvent was removed in vacuo and the reaction mixture (aqueous layer) was washed twice with ethyl acetate. The aqueous layer was then cooled to Q°C and acidified to pH 2 with 3N Aq.HCl. The precipitated solid was filtered, washed with water and dried to get pure 1,3-dihydrobenzo[c] isothkzole-6-carboxylic acid 2,2-dioxide (2 g).

^{1}H-NMEl (400 MHz, DIvE O-d_6): δ 13.10 (bs, 1¾ 10.8 (bs, 1H), 7.57-7.55 (m, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.31 (s, 1H), 4.64 (s, 2H).

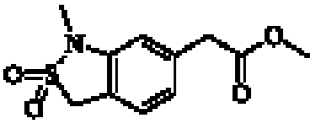
Step (ii) Synthesis of 2-dkzo-l-(l-memyl-2.2-dioxidQ-1.3-dmyd^ benzo[c]isothiazol-6-yl)ethanone



To l,3-dihydrobeiv-o[c]isothiazole-6-car¼oxylic acid 2,2-dioxide (1 g, 0.0046 moles), was added SOClj (20 ml) at room temperature under inert nitrogen atmosphere. The reaction mixture was then refluxed for 6-8 hours and cooled to room temperature. The SOClj was distilled off in vacuo under inert nitrogen atmosphere . The reaction mixture was then cooled to 0°C and diethyl ether (10 ml) was added to the crude acid chloride at 0°C under inert atmosphere. A freshly prepared ethereal diazomethane solution (45 ml) (prepared from N-rdtrosoN-methyl urea (1.5 g), 40% aq KOH solution (15 ml) was added slowly to the reaction mixture at 0°C under inert nitrogen atmosphere. Finally THF (10 ml) was added and reaction mixture was then stirred at room temperature for 12 hours. After completion of the reaction, ether and THF were removed in vacuo at low temperature to give the crude product which was then purified by flash chromatography using 30% ethyl acetate in n-hexane as eluent to give 2-dkzo-l-(l -methyl-2,2-dioxido-l,3-dmyd^ benzo[c]isothiazol-6-yl)ethanone.(0.8 g).

1H-NMR (400 MHz, DMSO-d_6): 5 7.52-7.45 (m, 2H), 7.33 (s, 1H), 7.04 (s, 1H), 4.76 (s, 2H), 3.1 1 (s, 3H) .

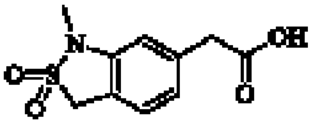
Step (iii) Synthesis of methyl 2-(l-meftyl-2.2-dioxidQ-1.3-dmydrober zo[c]isothiazol-6-yl)acetate



To 2,2-diazo-1-(1-methyl-2,2-dioxido-l ,3-dihydrobenzo [c] isothiazol-6-yl)ethanone, (0.8 g, 0.0032 moles) in methanol (15 ml) was added 4.6 ml of silver benzoate solution in triethykmine (prepared by dissolving 500 mg of silver benzoate in 5 ml of triethylamine). The reaction mixture was heated at 50°C for 1 hour. After completion of the reaction, the reaction mixture was cooled to room temperature and diluted with little excess of methanol. The solid was filtered through a short pad of celite and washed with excess of methanol . The filterate was then concentrated under vacuo at low temp nature to give crude solid which was purified using column chromatography over silica gel using 25% ethyl acetate in n-hexane as eluent to give methyl 2-(l-methyl-2^-diQxido4,3-dihydrober^ [c]isothiazol-6-yl)acetate (0.60 g).

H -NMR (400 MHz, DMSO-d_6): δ 7 2 6 (d, *J* = 7.3 Hz, 1H), 6 9 2-6 90 (m, 1H), *6.25* (s, 1H), 4.62 (s, 2H), 3 *6 9* (s, 2H), 3.61 (s, 3H), 3,01 (s, 3H).

Step (iv) Synthesis of 2-(1-methyl-2,2-dioxido-1,3-dihyd^ benzo[c]isothiazol-6-yl)acetic acid

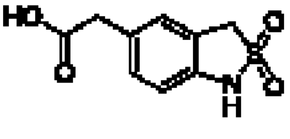


To a solution of methyl 2-(l-meftyl-2,2-dioxido4,3-dihy^ benzo[c]isothiazol-6-yi)acetate (0.42 g, 0.0016 moles) in MeOH (15 ml) was added 10% aqueous sodium hydroxide solution (15 ml) at 0°C. The reaction mixture was then stined at room temperature for 2 hours. After completion of the reaction , the solvent was removed in vacuo, the residue was dissolved in water and extracted with ethyl acetate twice . The aqueous layer was cooled to 0°C and acidified to pH 2 with 3N AqHCl. The precipitated solid was filtered and washed with water and dried get pure 2-(2.2 -diQxido-1,3-dihydrobenzo[c]isothiazol-6-yl)acetic acid (0.27 g).

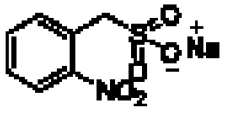
^{1}H-NMR (400 MHz, DMSO-.i $_6$): 5 12.37 (bs, 1H), 7 2 5 (d, *J* = 7.8 Hz, 1H), *6.92-629* (m, 1H), 6.83 (s, 1H), 4.61 (s, 2H), 3.58 (s, 2H), 3.01 (s, 3H).

Example 10-a

2-(2,2-dioxido-1,3-dihydrobenzo [c]isothiazol-5-yl)acetic acid



Step (i) Synthesis of sodium (2-nitrophenyl)methane sulfonate



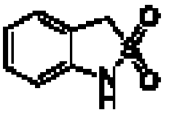
A mixture of Na_2SO_3 (25.6 g. 1.30 equiv), TBAI (600 mg, 1.62 mmol, 0.01 equiv), 1-(bromomethyl)-2-nitrobenzene (33.8 g, 1.00 equiv) and water (250 mL) was stirred for 15 h at 90*C in an oil bath. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was washed once with each of acetone, ethyl acetate and diethyl ether respectively. The solid was dried in an oven under reduced pressure to obtain 34 g (90%) of the title compound as a light yellow solid.

Step (ii) Synthesis of sodium (2-aminophenyl)methanesulfonate

In an inert atmosphere of nitrogen, a solution of sodium (2-rdtrophenyl)methane sulfonate (3 g, 12.54 mmol, 1.00 equiv) in methanol (50 mL) was treated with Palladium carbon hydrogen (0.5 g). The reaction mixture was then stirred under a hydrogen atmosphere for 16 h at 25*C, filtered, concentrated in vacuo to obtain 2 g (76%) of the title compound as a white solid.

LC-IvB : (ES, *m/z*): 188 (M+1).

Step (iii) Synthesis of l,3-dihydrobenzo[c]iso11tiamle 2,2-dioxide

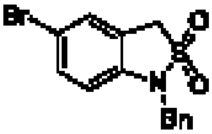


A solution of sodium (2-aminophenyi)methane sulfonate (5.2 g, *24.26* mmol, 1.00 equiv) in PQCL. (148.2 g) was heated to reflux for 2 hr. The resulting mixture was concentrated in vacuo , quenched by the addition of 2N sodium hydroxide and the resulting basic solution was extracted with ethyl acetate and the aqueous layers were combined. The pH value of the solution was adjusted to 2 with 2N HCl. The solids were filtered, dried in an oven under reduced pressure to obtain 15 g (36%) of the title compound as a white solid

Step (iv) Synthesis of 5-bromo-l,3-dihydrobenzo[c]isothiazole 2,2-dioxide

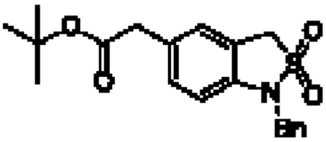
To a solution of l,3-dmydroberL3D[c]iso1hiazole *2^2*-dioxide (1.7 g, 10.05 mmol, 1.00 equiv) in acetic acid (15 mL) was added a solution of Br_2 (1*.69* g, 10*.56* mmol, 1.05 equiv) in acetic acid (1 mL) dropwise with stirring. The resulting solution was stirred for 2 h at 25*C. The resulting mixture was concentrated in vacuo followed by purification with column chromatography with silica gel as stationary phase and ethyl acetate/hexane (1:10) as eluent. This resulted in 1.6 g (64%) of the titled compound as a light yellow solid.

Step (v) Synthesis of 1-benzyl-5-bromo-l,3-dmydrobenm[^ sothiazole-2,2-dioxide



To a suspension of 5-bromo-l,3 -**dihydroben2E** [c]isotluazole 2,2-dioxide (1.5 g, 6.05 mmol, 1.00 equiv) and potassium carbonate (1.67 g, 12.08 mmol, 2.00 equiv) in N,N-din^thylfornrantide (15 mL) was added BnBr (1.OS g, 6.31 mmoL 1.05 equiv) drop wise with stirring at 0*0. The resulting solution was stirred for 1 h at 25*0 and then diluted with water. The resulting solution was extracted with 3x50 mL of ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography using silica gel as stationary phase and ethyl acetate/petroleum ether (1:15) as eluent. This resulted in 1.6 g (7S%) of the titled compound as a white solid.

Step (vi) Synthesis of tert-butyl 2-(l -**benzyl**-2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-5-yl)acetate

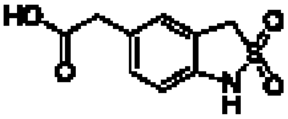


In an inert atmosphere of nitrogen, a solution of 1-benzyl-5-biomo-1,3-dihydrobenao[c] isothiazDle-2,2-dioxide (600 mg, 1.77 mmol, 1.00 equiv), X-Phos (170 mg, 0.36 mmoL 0.20 equiv), $Pd_2(dba)_3$ (160 mg, 0.17 mmol, 0.10 equiv) and tert-butyl 2-(bromozincio)acetate (1.62 g, 6.22 mmol, 3.50 equiv) in tetrahydrofuran (40 mL) was stirred for 16 h at 72*C. The reaction was then quenched by the addition of 40 mL of water, filtered, extracted with 3x50 mL of ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography using silica gel as stationary phase and ethyl acetate/petroleum ether (1:20) as eluent to obtain 0.37 g (56%) of the titled compound as an off-white solid.

Step (vii) Synthesis of tert-butyl 2-(2,2-dimido-l,3-dmydrobenzo [c]iso1niazDl-5-yl)acetate

In an inert atmosphere of nitrogen, to a solution of tert-butyl 2-(l-benz3il-2,2-dioxido-1.3^h^droberL-B [c]isothia2Dl-5-yl)acetate (370 mg, 0.99 mmol, 1.00 equiv) in methanol (20 mL) was added palladium carbon (50 mg). The reaction was stirred under a hydrogen atmosphere for 1.5 h at 25*C ard then filtered, concentrated in vacuo to obtain the titled compound (360 mg) as yellow oil.

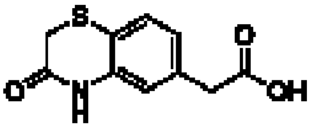
Step (viii) Synthesis of 2-(2,2-dioxido-l,3^hydrobenm[c] isothkml-5-yl)acetic acid



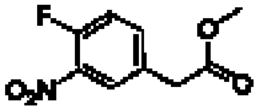
A solution of tert-butyl 2-(2^-dio_iido-l **,3-dihydroben2o**[c]isoth_azol-5-yl)acetate **(360** mg, 1.27 mmol, 1.00 equiv) and trifluoroacetic acid (5 ml_)in dichloromethane (5 mL) was stirred for 2 h at 25*0. The resulting mixture was concentrated in vacuo The residue was dissolved in water. Then the solution was lyophilised to yield 0.29 g of the title compound as an off-white solid-

Example 11-a

2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)acetic acid

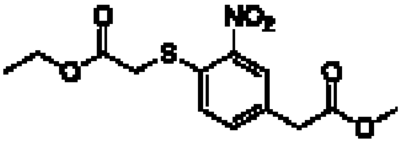


Step (i) Synthesis of methyl 2^4-fluoiO-3-nitrophenyl)acetate



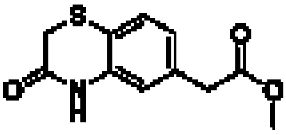
A solution of 2-(4-uuoro-3-nitrophenyi)acetic acid (90 g, *452.26* mmol, 1.00 equiv) in methanol (400 mL) and cone H_2S0 +(10 mL) was refluxed for 4 h in an oil bath. The reaction was then quenched by the addition of 1200 mL of ice-cold water. The resulting solution was extracted with ethyl acetate (3x500 mL). The combined organic layers were washed with sat $NaHCO_3$ (2x400 mL), dried over anhydrous sodium sulfate and concentrated in vacuo to obtain methyl 2-(4-fluoro-3-nitrophenyl)acetate (90 g) as brown oil.

Step (ii) Synthesis of ethyl 2-((4-(2-me1hDxy-2-oxoemyl)-2-mtrophenyl)th_o)acetate



A solution of methyl 2-(4-fluoro-3-iiitrophen;ji)acetate (90 g, 422.54 mmol, 1.00 equiv) in tetrahydrofuran (400 raL), triethylamine (85 g, 841.58 mmol, 2.01 equiv) and ethyl 2-mercaptoacetate (65 g, 541.67 mmoL 1.28 equiv) was stirred for 12-16 h at 15°C and concentrated in vacuo The solids were collected by filtration. This resulted in 80 g (crude) of methyl 2-(4-(2-e1hoxy-2-ctfoemylthio)-3-mtm phenyl)acetate as a yellow solid

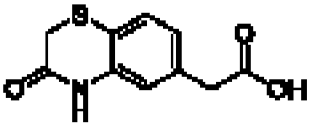
Step (iii) Synthesis of methyl 2-(3-oxo-3,4-dihydro-2H-benzo[b] [1,4]thiazin-0-yl)acetate



A solution of methyl 2-(4-(2-ethoxy-2-OKoeth^lMo)-3-nitrophenyl)acetate (5 g, 15.97 mmol, 1.00 equiv) in methanol (100 mL) and Zn (5 g, 76.92 mmol, 4.82 equiv), acetic acid (5 mL) was heated under reflux for 2 h in an oil bath. The solids were filtered out. The resulting mixture was concentrated in vacuo , diluted with 400 mL of sat. NaHCQj. The resulting solution was extracted with 3x200 mL of ethyl acetate. The combined oi^anic layers were washed with 2x200 mL of brine, dried over sodium sulfate and concentrated in vacuo. The crude product was purifiedbyre-crystdlization from ethyl acetate to obtain methyl 2-(3-oxo-3.4-dihydro-2H-benao[b] [l,4]1hiazin-6-yl)acetate (2.8 g) as a white solid.

IvE (ESI) m/z: 238 (M+l).

Step (iv) Synthesis of 2-(3-oxo-3,4-dmydro-2H-benso[b] [1,4]thiazin-6-yl)acetic acid

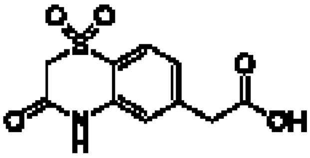


A solution ofmethji 2-(3-oxo-3,4-dmydro-2H-ben3o[b] [l,4]thiazin-o"-yl)acetate (7.8 g, 32.91 mmoL 1.00 equiv) in methanol : water (3: 1) (160 mL) and LiOH·¾0(7 g, 166.61 mmol, 5.06 equiv) was stirred for 2 h at 25°C and then diluted with 100 mL of water. The pH value of the solution was adjusted to 3-4 with 2N HC1 to obtain a solid precipitate which was collected by filtration. The crude product was purified by re-crystallization from methanol. This resulted in 2-(3-oxo-3,4-dihyiro-2H-benzo[b] [l,4]1hiazin-0-yl)acetic acid (7 g) as a white solid.

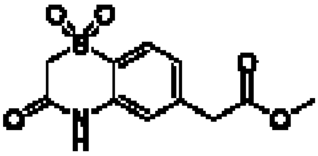
IvE (ESI) m/z : 224 **(MM).**

Example 12-a

2-(1, l-dioxido-3-oM -3,4-dihydio-2H-benzo[b] [l,4]t^ azin-6-yl)acetic acid



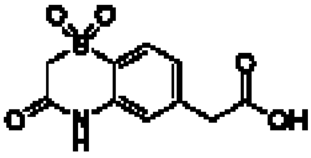
Step (i) Synthesis of methyl 2-(l, l-dio iido-3-o io-3,4-clihydra-2H-benm[b] [l,4]thiazin-6-ji)acetate



A solution of methyl 2-(3-oxo-3,4-dmydro-2H -**berEo**[b][l,4]thiazin-0'-yi)acetate (5 g, 21.10 mmol, 1.00 equiv) in dicluoromethare (120 mL) and m-CPBA (11 g, *63 9 5* mmoL, 3.03 equiv) was stined for 20 h at 25°C, diluted with 300 mL of dichloromethane., washed with 2x250 mL of sat.NaHCGj. The aqueous phase was extracted with 2x150 mL of dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo .The residue was purified by column chromatography using silica gel as stationary phase and ethyl acetate : petroleum ether (1:3) as eluent to obtain 4 *5* g of methyl 2-(3-oxo-3,4-dihydro-2H-ben3o[b] [l,4]thiazin 1, 1-dioxide-6-;jji)acetate as a white solid.

IvE (ESI) m/z : 270 **(MM).**

Step (ii) Synthesis of 2-(l, l-drixido-3-oxo-3,4-dihydro-2H-benmM [1,4]thiazin-6-yl)acetic acid

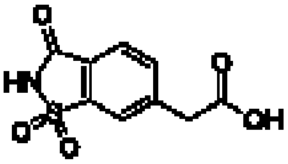


A solution of methyl 2-(3-oxo-3,4-dmydro-2H-benzo[b] [l,4]thiazin 1, l-dioxide-o'-ji)acetate (*6.5* g, 24.16 mmol, 1.00 equiv) in tetmhydrofuian:MeOH:H$_2$O(4:1 :1) (120 mL) and LiOH·H$_2$O(5 g, 119.05 mmol, 4.93 equiv) was stirred for 2 h at 20°C. The resulting mixture was concentrated in vacuo.The reaction was then quenched by the addition of 150 mL of ice-cold water. Tie pH of the solution was adjusted to 3-4 with 2N HC1. The solution was filtered to obtain 2-(3-oxo-3.4-dihydro-2HJ-ienzo[b] [1.4]thiazin 1, 1-dioxide-Q-yi)acetic acid (5.5 g) as a white solid

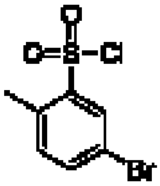
IvE (ESI) m/z : *256* (IvH-1).

Example 13-a

2-(l, l-dioxido-3-oxo-2,3-dihydrobenzo[d]isothiazol-6-yl)acetic acid

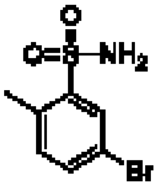


Step (i) Synthesis of 5-bronKi-2-methylberLaerLe-l-sulfonyl chloride



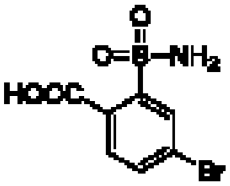
To **l-bromo-4-inethylberEerLe** (40 g, 233.92 mmoL, 1.00 equiv) was added sulfuroc**hloridic** ac**id** (53.8 g) drop**wise with stirring** at **about** 30°C. The re**suiting solution** was stirred for 3 h at 60*C in an oil bath and then poured into 300 g of ice-cold water. The resulting solution was extracted with 3x200 ni of **ethyl** acetate. The combined organic **layers** were dried over anhydrous sodium sulfate and concentrated in vacuo. This resulted **in** 5-bromo-2-methylberEene-l-sulfonyl **chloride** (30 g) as light yellow oil.

Step (ii) Synthesis of 5-bromo-2-methyIbensenesulfonamide



A solution of 5-bromo-2-methylberGene-l-sulfonyl chloride (14 g, 51.85 mmol, 1.00 equiv) in dioxane (300 mL) and NH+OH (600 mL) was stirred overnight at 0-10*0. The solids were filtered out. The resulting mixture was concentrated in vacuo to obtain 5^bromo-2-methyibenae nesuJfonamide (*9* g) as a white solid.

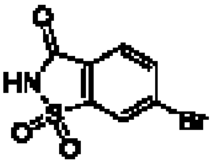
Step (iii) Synthesis of 4-broino-2-sulfamoylbenzoic acid



A solution of 5-bramo-2-n¾th^benzeniesuliDnanude (9 g, 36.00 mmol, 1.00 equiv) and KIvInO+(29 g. 183.54 mmol, 4.98 equiv) in sodium hydroxide (10%) (60 mL) was stirred for 5 h at 40°C. The reaction was then quenched by the addition of NaHSG$_3$ (5 g). The solids were filtered out. The pH value of the filtrate was adjusted to 2 which resulted in precipitation of the product 4-bromo-2-sulfamoylbenzoic acid (10 g) as a white solid.

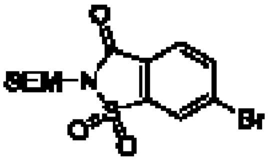
LC-IvE (ES, *m/z)*: 278, 280 (M-l) $^-$

Step (iv) Synthesis of 6-bromobenzo[d]isothiazol-3(2H)-one-l, 1-dioxide



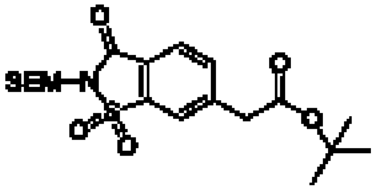
A solution of 4-bromo-2-sulfamoylbenzoic acid (4 g, 14.29 mmol., 1.00 equiv) in plyphosphoric acid (200 mL) was stirred for 4 h at 100*0. The reaction was then quenched by the addition of ice-cold water (100 mL). The resulting solution was extracted with 3x100 mL of ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated in vacuo This resulted **in 6-brornobenzo[d] isotha3ol -3(2H)**-one 1, 1-dioxide (3.5 g) as a white solid.

Step (v) Synthesis of 6-bromo-2^(2^triniethylsn^)ethoxy)n¾tn^)benzo[d]isothiazol-3(2H)-one 1, 1-dioxide



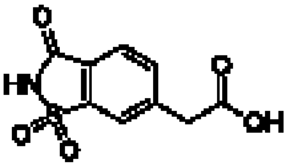
In an inert atmosphere of nitrogen, to a solution of **6-bromoberLZo[d]** iso1hiazol-3(2H)-one 1, 1-dioxide (1 g, 3.83 mmol, 1.00 equiv) in THF (10 mL) was added sodium hydride (310 mg, 12.92 mmol, 1.54 equiv) at 0°C. After 30 min, SEM-Cl (890 mg, *1.63* mmol, 1.50 equiv) was added. The resulting solution was stirred overnight at 20-35^. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 3x30 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography using silica gel as stationary phase and ethyl acetate/petroleum ether(l :50) as eluent to obtain the titled compound (0.8 g) as a white solid.

Step (vi) Synthesis of tert-butyl 2-(l, l-dioxido-i -o-i o-S-((S-(trimethylsilylJethoxyJmethyl)-2.3-dihydrobenso [d] isothiaaol-6-yl)acetate



In an inert atmosphere of nitrogen, a solution of 6-bromo-2-((2-(triri¾mylsnyl)ethoKy)memyl)benso[dJiso^hiazol-3(2H)-one 1, 1-dioxide (500 mg, 12 8 mmol, 1.00 equiv), (2-tert-butoxy-2-oxoetl^)zinc (II) bromide (1180 mg. 454 mmol, 256 equiv), Pdi (dba)$_3$ (40 mg, 0.04 mmol, 0.23 equiv) and Q-phos (28 mg, 0.04 mmol, 0.40 equiv) in THF (10 mL), was stirred for 5 h at 70*0. The resulting solution was then concentrated in vacuo. The residue was purified by column chromatography using silica gel as stationary phase and ethyl acetate/petroleum ether (1:15) as eluent to obtain the titled compound (200 mg) as a light yellow solid.

Step (vii) Synthesis of 2-(1, l-dioxido-3-oxo-2,3-dihydrobenzo[d]isothiazol-6-yl)acetic acid

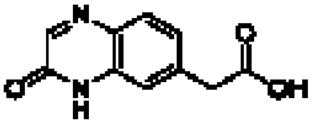


A solution of tert-butyl 2-(l, l-dioxido-3-oxo-2-((2-(trimethylsilyl)ethoxy)methyl)-2,3-dihydroberLzo [d]**isothia2Dl**-0-yl)acetate (500 mg, 1.17 mmol, 1.00 equiv) in dichloro methane (8 mL) and CF$_3$COOH (800 mg, 7 J02 mmol, 5.99 equiv) was stirred for 24 h at room temperature. The resulting mixture was then concentrated in vacuo to obtain the crude product which was further purified by Prep-HPLC to result in the title compound (170 mg) as a white solid.

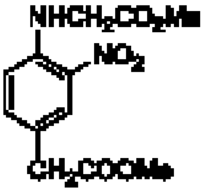
LC-IvE (ES, m/z): 240 (M-l) $^-$; ^-NMR: (CD$_3$OD, 400MHz) 5 7961-7989 (m, 2H), 7.830-7.890 (m, 1H), 3.929 (s, 2H).

Example 14-a

2-(3-oxo-3,4-dihydro¾u™ xalin-6-yl)acetic acid

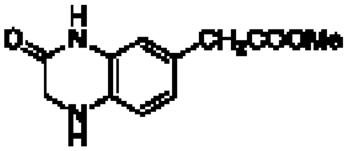


Step (i) Synthesis of methyl 2-((4-(2-methoxy-2-oxoethyl)-2-nitrophenyl)amino)acetate



A solution of methyl 2-(4-fluoro-3 -iiitiOphenyl)acetate (6 g, 28.15 mrnol, 1.00 equiv), $NH_2CH_2CO_2Me$ HC1 (3.9 g, 30.95 mrnol, 1.10 equiv) and i-PrjNEt (10.8 g, 83.72 mrnol, 3.00 equiv) in N,N-dimethylfonnamide (100 mL) was stirred overnight at 30*0. The reaction was then quenched by the addition of 50 mL of water. The resulting solution was extracted with 3x1 GG mL of ethyl acetate. The combined organic layers were washed with 6x100 mL of brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether(l :5). This resulted in 4 g of methyl 2-(4-(2-n¾thoxy-2-oxoemyl)-2-nitrophenylamino)acetate as a yellow solid.

Step (ii) Synthesis of methyl 2-(3-oxo-l ,2,3,4-tetrahydroquinoxdin-o -yi)acetate



In an inert nitrogen atmosphere, a suspension of methyl 2-(4-(2-metho.iy-2-oxoethyl)-2-rLitrophenylamino)acetate (2 g, 7.09 mrnol, 1.00 equiv), 10% Palladium carbon (1 g) and HCO_2NH_+ (6.1 g, 106.35 mrnol, 15.00 equiv) in ethanol (60 mL) was stirred overnight at room temperature. The solids were filtered out. The filtrate was concentrated under vacuum. The residue was dissolved in EtOAc (100 ml), washed with water, dried over $NajSO_+$ and concentrated under vacuum. This resulted in 1.5 g of methyl 2-(3-oxo- 1,2,3,4-tetmhydroquinoxalin-^-yl) - acetate as a white solid.

IvE (ESI): m/z : 221 (MH).

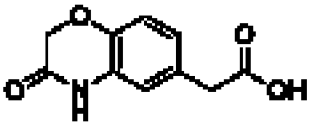
Step (iii) Synthesis of2-(3-oxo-3,4-dihydroquir oxalin-6-yl)acetic acid

3% H_20_2 (6.78 g, 2.00 equiv) was added to a solution of 2-(3-oxo-1,2,3,4-tetrah^oquiimalm-6-yl)acetic acid (600 mg. 251 mmol, 1.00 equiv) in 8% sodium hydroxide (7.50 g, 5.00 equiv) solution and the resulting solution was heated to reflux for 2 hours. To this hot solution was added slowly acetic acid until pH 3-4. The resulting solution was cooled to room temperature and the precipitated product was collected by filtration and washed with water. The product was dried in an oven under reduced pressure. This resulted in 510 mg of2-(3-oxo-l ,2,3,4-tetmhydioquinoxdm-6-yl)acetic acid as a yellow solid.

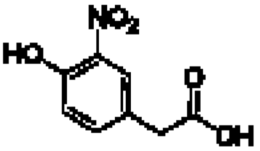
MS(ES, *m/z)*: 205(M+1); ^{1}H-NMR (DMSO-d_6, 300 MHz): 5 12.439 (br, 1H), 8.148 (s, 1H), 7.717-7.746 (d, 1H, *J*=8.7Hz), 7.207-7.224 (m, 2H), 3.710 (s, 2H).

Example 15-a

2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)acetic acid



Step (i) Synthesis of 2-(4-hydroxy-3-nitrophenyl)acetic acid

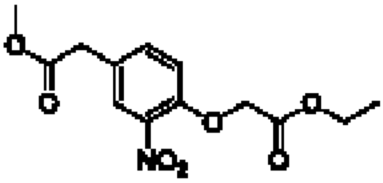


Into a 250-mL 3-necked round^bottom flask, was placed a solution of 2-(4-hydroxyphenyl)acetic acid (30 g, 197.37 mmol, 1.00 equiv) in acetic acid (100 mL). A solution of HNC¼(65%) (19 g, 301.59 mmol, 1.53 equiv) in acetic acid (25 mL) was then added dropwise with stining while the temperature not exceeding 10°C. The resulting solution was stirred for 1 h at 15*0. The solids were collected by filtration and washed with 3x50 mL of water. This resulted in 20 g of 2-(4-hydroxy-3-nitrophenyl)acetic acid as a yellow solid.

Step (ii) Synthesis of methyl 2-(4-hydroxy-3-nitrophen5i)acetate

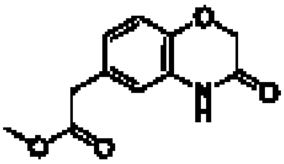
Into a 500-niL 3-necked round-bottom flask, was placed a solution of 2-(4-hydroxy-3-ritrophenyl)acetic acid(1 0 g, 50.76 mmol, 1.00 equiv) in methanol (50 ni). Thionyl chloride (12 g, 100.34 mmol, 1.99 equiv) was then added dropwise at 0°C. The resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 2 niL of water. The resulting mixture was concentrated under vacuum. This resulted in 10 g of methyl 2-(4-hydroxy-3-nLtrophenyl) acetate as a yellow solid.

Step (iii) Synthesis of ethyl 2-(4-(2-methoxy-2-o ioe1hyl)-2-nitrophenoxy)acetate



Into a 250-mL 3-necked round-bottom flask, was placed a suspension of methyl 2-(4-l^oxy-3-mtrophenyl)acetate (5 g, 23.70 mmoL 1.00 equiv) and Cs_2CO_3 (15.45 g, 47.39 mmoL 2.00 equiv) in tetrahydrofuran (100 mL). This was followed by the dropwise addition of a solution of ethyl 2-bromoacetate (4.75 g, 23.44 mmoL 1.20 equiv) in tetrahydrofuran (20 niL) with stirring at room temperature. The resulting solution was heated under reflux for 2 hr. The reaction mixture was cooled to room temperature and diluted with 50 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 3 g of methyl 2-(4^2-emoxy-2-oxoemoxy)-3-nitrophenyl)acetate as a pale yellow solid.

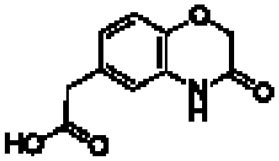
Step (iv) Synthesis of methyl 2-(3-oxo-3,4-dihydro-2H4 .enzo [b] [l,4]oxazin-6-yl)acetate



Into a 250-mL 3-necked round-bottom flask, was placed a solution of methyl 2-(4-(2-ethDxy-2-oxoethoxy)-3-nitrophenyl)acetate (3 g, 10.10 mmoL 1.00 equiv) in HOAc (30 niL). This was foliowed by the addition of iron (1.7 g, 30 36 mmoL 3.01 equiv) in several portionss. The resulting solution was stirred for 2 h under reflux. The solids were filtered out. The reaction was then diluted with 50 niL of water. The resulting solution was extracted with 3x50 niL of ethyl acetate. The combined organic layers combined were washed with 3x30 niL of brine, dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in

1.5 g of methyl 2-(3-oxo-3,4-dmydro-2H-berLZo[b] [1,4]oxazin-6-yl)acetate as a light yellow solid.

Step (v) Synthesis of 2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)acetic acid

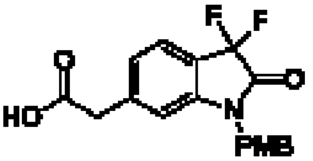


Into a 100-mL round-bottom flask, was placed a solution of methyl 2-(3-oxo-3,4-dihydro-2H-benzo[b] [l,4]oxazin-o'-yl)acetate (2 g, 9.05 mmol, 1.00 equiv) in methanol (20 mL). Then a solution of sodium hydroxide (720 mg, 18.00 mmol, 1.99 equiv) in water(20 mL) was added. The resulting solution was stirred for 3 h at room temperature. The resulting mixture was concentrated under vacuum, diluted with 30 mL of HjO. The pH value of the resulting solution was adjusted to 2-3 and then extracted with 5x50 mL of ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:2). This resulted in 1 g of 2-(3-oxo-3,4-dihydro-2H-benzo[b] [l,4]oxazin.6-yl)acetic acid as a yellow solid.

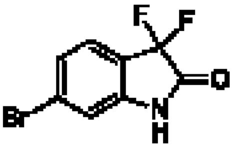
LC-IvE (ES-, m/z): 206 (M-1)" ; 1H-NMR (DIvEO-df5, 300 MHz): 5 12.290 (br, 1H), 10.707 (s, 1H), 6.793-6.910 (m, 3H), 4 5 59 (s, 2H), 3.490 (s, 2H).

Example 16-a

2-(3,3-difluoro-1-(4-methoxybenzyl)-2-oxoindolin-6-yl)acetic acid



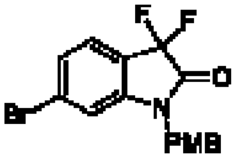
Step (i) Synthesis of 6-brorno-3,3-difluoromdolin-2-one



Into a 50-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 6-bromo-2,3-dihydro-l H-mdole-2,3-dione (2.5 g, 11.06 mmol, 1.00 equiv) in dichlorometharie (15 mL). This was followed by the addition of DAST (*6.26* g, 38.84 nunoL, 3.51 equiv) dropwise with stirring at 0°C. The resulting solution was stirred for 5 h at 25°C. The resulting solution was quenched with 150 mL of aqueous saturated NaHCGj. The resulting aqueous solution was extracted with 3x150 mL of dichloromethane. The organic lasers were combined and dried over ar-hydrous sodium sulfate , concentrated under vacuum. The residue was applied onto silica gel column and eluted with Petroleum ether : Ethyl acetate=50: 1-25:1 to give 1.95 g (71%) of 6-bromo-3,3-difluoiO-2.3-dihydiO4H-mdol-2-one as a yellow solid.

^{1}H-NMR (CDC¾ 300 MHz): 5 7.91 (s, lH), 7.43-7.40 (d, *J* = 8.1 Hz, 1H), 7.34-7.32 (d, *J* = 8.1Hz, 1H), 7.13 (S, 1H).

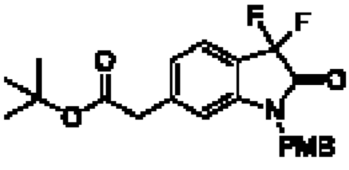
Step (ii) Synthesis of 6-bromo-33-difluoro-l -(4-methoxybenzyl)irddin-2-one



Into a solution of ≤-bromo-3,3-difluoro-2,3-dmydro-lH-in^ l-2-one (1.36 g, 5.48 mmoL, 1.00 equiv) inN,N-dimethylformamide (5 mL) was added potassium carbonate (2.28 g, 16.50 mmol, 3.01 equiv). then l-(bromon¾thyl)-4-metho iybenzerie (1.328 g, 6.60 mmoL, 1.20 equiv) was added at room temperature. The resulting solution was stirred for 1 h at 25°C. The resuiting mixture was quenched with 50 mL of H_20. The resulting aqueous solution was extracted with 2x80 mL of ethyl acetate. The organic layers were combined. The resulting organic layer was washed with 3x100 mL of brine and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate /petroleum ether (1:50-1 :20). This resulted in 1.7 g (84%) of 6-bromo-3,3-dfluoro-l-[(4 **-metlMxypl**¾nyl)n¾myl]-2,3-dihydro-1H-indol-2-one as a white solid.

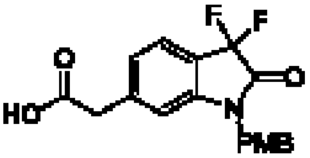
H -NMR (DMSO-d_6, 300 MHz): 5 7.70-7.67 (d, *J* = 7.8 Hz, 1H), 7.53(s, 1H), 7.45-7.42 (d, *J* = 7.8 Hz, 1H), 7.31-7.28 (d, *J* = 8.7Hz, 1H), *6.95-6.92* (d, *J* = 8.4Hz, 1H), 4.38 (s, 2H), 3.73 (¾ 1H).

Step (iii) Synthesis of tertJDutyl 2-(3,3-difuoro-1-(4-methoxybenzyl)-2-oxoindolin-6-yl)acetate



Into a solution of 6-bromo-3,3-difluoro-l -[(4-:imthoxypheny¾ methyl]-2,3-dihydro-lH-indol-2-one (700 nig. 1.90 mmol. 1.00 equiv) in degassed tetrahydrofuran (20 mL) was added Pdj(dba)3 (262 mg, 0.29 mmol, 0.15 equiv), X-Phos (242 mg, 0.51 mmol, 0.27 equiv). Then (2-tert-butoxy-2-oxoethyl)zinc(II) bromide (1.48 g, 5.68 mmol, 2.99 equiv) was added. The resulting solution was stirred overnight at 70*C under nitrogen atmosphere and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1/20). This resulted in 400 mg (52%) of tert-butyl 2-[3,3-difluon>l -[(4-methoxyphenyl)memy^ 2-oxo-2,3-dihydro-1H-indol-6-yl]acetate as a off-white solid.

Step (iv) Synthesis of 2-(3.3-difluon.i-l-(4-methoxybenzyl)-2-oxoindolin-6-yl)acetic acid

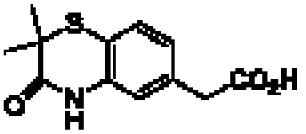


Into a solution of tert-butyl 2-[3,3-difluoro-l -[(4-metho iyphenyl)methyl]-2-oxo-2,3-dihydro-lH-indol -6-yiJ acetate (380 mg, 0.94 mmol, 1.00 equiv) in dichloromethane (20 mL) was added trifluoroacetic acid (5 mL). The resulting solution w¾s stirred overnight at 35*C. The resulting mixture was concentrated under vacuum. The residue was triturated with hexane/ether (5/1). This resulted in 300 mg (crude) of 2-P.3-difluoro-l -[(4-methoxyphenyl)methyl] -2-oxo-2,3-dihydio-lH-indol -6-yiJ acetic acid as a dark-grey solid

IvE (ES. m/z): 348 (IvH-1).

Example 17-a

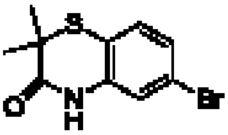
2-(2,2-dimethyl-3-oxo-3,4-dihydio-2H-beinzo[b][l,4]thiazinr6-yl)acetic acid



Step (i) Synthesis of ethyl 2-((4-bromo-2-mtrophenyl)thiD)-2-memylpropar^ ate

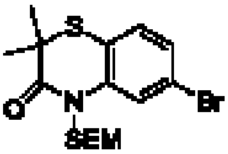
K_2CO_3 (5.8 g, 41.97 mmol, 250 equiv) was added to a solution of 4-bromo-l-fluoro-2-nitrobenzene (3.7 g, 16.82 mmol, 1DO equiv) in DMF (50 mL), then ethyl 2-methyl-2-sulianylpropanoate (3.5 g, 23.61 mmol, 1.40 equiv) was added. The reaction mixture was stirred for 4 h at 30*C. The solution was diluted with 200ml_ of EA and filtered and washed with 5x20mL of brine . The organic layer was dried over anhydrous sodium sulfate and concentrated ***in vacuo.*** The residue was purified by flash column with petroleum ether : EtOAc 100:1 to 20:1. This resulted in 4 g (68%) of ethyl 2-[(4-bromo-2-rdtropher^)sulfanyi]-2-methylpropinoate as a white solid. 1H-NMR (DMSO- i3i, 300MHz): 1.23-1 32 (m, 6H), 1.52-2.0 (m, 1OH), 4.1-4.21 (m, 3H), 7.42 (d, ***J***=l 2 Hz, 1H), 7.62 (d, ***J***=12 ¾ 1H), 8.00 (s, lH).

Step (ii) Synthesis of 6-bromo-2,2-dimethyl-2H-benzo [b] [1,4] thiazin-3(4H)-one



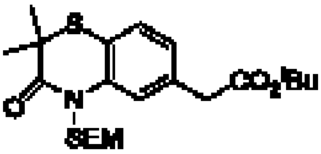
To a solution of ethyl 3-(4-bromo-2-mtophenyl)-2,2-din^ hylpropanoate (4 g, 12.11 mmol, 1.00 equiv) in acetic acid (50 mL) was added Fe powder (6.4 g, 11429 mmol, 9.43 equiv) in small portions. The resulting solution was stirred for 2 h at 80*0. The mixture was diluted with 200mL of EtOAc and filtered. The organic layer was concentrated under vacuum. The residue was purified by flash column with petroleum ether : ethyl acetate (20:1). This resulted in 2.1 g (64%) of 6-bromo-2,2-din¾thyl-3 ,4dihydro-2H-l,4-berLZothk zin-3-one as a oil. ^{1}H-NMR (DMSO-d_6, 300MHz) 5 1.51 (s, 6H), 7.05 (s, 1H), 7.13-7.19 (m, 2H), 8.64 (s, 1H).

Step (iii) Synthesis of 6-bronio-2,2-dmethyl-4-((2-(trimethylsilyl)ethoxy)methyl)-2H-benzo [b] [1,4] thiazin-3 (4H) -one



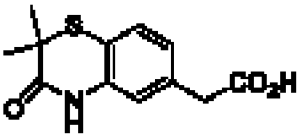
To a solution of 6-bromo-2,2-dme1hyl-3,4-dihydro-2H-^ ,4-benzothiazin-3-one (2.6 g, 9.55 mmol, 1.00 equiv) in THF (30 mL), was added NaH(573 mg, 23.88 mmol, 2.50 equiv). After 30 min, SEMCl (3.2 g, 19.16 mmol, 2.01 equiv) was added. The resulting solution was stirred for 3 h at room temperature. The reaction was quenched by lOmL of HjO. The mixture was extracted with 3x20 mL of ethyl acetate . The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica column with petroleum : ethyl acetate = 100:1 . This resulted **in** 3.8 g *(99%)* of 6-bromo-2,2-dimethyl-4-[[2-(trin¾thylsilyl)ethoxy] methyl]-3.4^hydro-2H4.4-bei ™**irLiazin**-3-one as oil.

Step (iv) Synthesis of tertJ-utyl 2-(2,2-di™ thyl-3-oxo-4-((2-(trimethylsilyl)ethoxy) methyl)-3.4-dihydro-2H-b enzo[b] [1,4] thiazin-6-yl)acetate



A solution of 6-bromo -2,2 -dimethyl-4- [[2-(trimethylsilyl) ethoxy] methyl] -3, 4-dihydio-2H-1,4-benzothiazin-3-one (800 mg, 1.99 mmol, 1.00 equiv), tert-butyl 2-(bromozirLcio)acetate (2.08 g, 7.99 mmol, 4.02 eqiiiv), Pd2 (dba)3 (274 mg, 0.30 mmol, 0.15 equiv), Xphos (286 mg, 0.60 mmol, 0.30 equiv) in THF (40 mL) was stirred overnight at 70°C. The mixture was diluted with lOOmL of EtOAc and filtered. The organic layer was concentrated under vacuum. The residue was purified by silica column with PE:EA (20:1). This resulted in 880 mg of tert-butyl 2-(2,2-dimetliyl-3-oxo4-[[2-(trime thylsilyl)ethoxy] methyl] -3,4-dihydro -2H- 1,4-ber_zothiazin-0 -yl)acetate as yellow oil. ^{1}H-NMR (**DMEO-*d*i,** 300MHz) 5 0.95 (t, *J*=7 S ¾ 2H), 1.*46* (s, 15¾ 3.54 (s, 2H), *3.66* (1, *J*=7 8Hz. 2H), 5.38 (s, 2H), 6.98 (d, *J=6 9Hz,* 1H), 7.25 (d, *J*=8.1Hz, 1H), 7.43 (s, 1H).

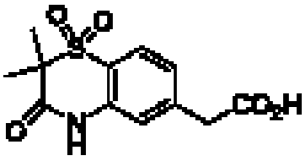
Step (v) Synthesis of 2-(2,2-dm¾myl-3-oxo-3,4-dihydro-2H-ben2D[b] [l,4]lMazin-6-yl)acetic acid



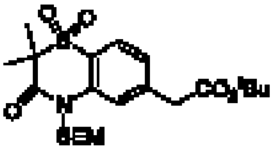
To a solution of tert-butyl 2-(2,2-di™thyl-3-oxo4 -[P-(tnn¾thykilyl)ethoxy] methyl] -3,4-dihydro-2H-l ,4-benzothiazin-6-yl)acetate (200 mg, 0.46 mmol, 1.00 equiv) in DCM (4mL), was added TFA(2 mL) at 0 °C. The resulting solution was stirred for 2 h at room temperature. The solution was concentrated. The residue was washed with PE and EtjO. This resulted in 108 mg (94%) of 2-(2,2-dimemyl-3-oxo-3,4-dihydra-2H4 ,4-benzothiazin-6-yl)acetic acid as a yellow solid. MS (ES, m/z): 252 (M+l).

Example 18-a

2-(2,2-dimethyl-1, 1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)acetic acid

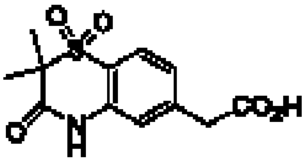


Step (i) Synthesis of tert-butyl 2-(2,2-dimethyl-1, l-dioxido-3-oxo-4-((2-(trimemylsHyl)etMxy)n¾thyi)-3,4-dihydro-2H-benso[b] [1,4]thiazin-6-yl)acetate



To a solution of tert-butyl 2-(2,2-din¾thyl-3-oxo4-((2-(tnn¾thyknyi)eth^ y)methyl)-3.4dihydro-2H-ben3D[b] [l,4]tlua._in-0-yl)acetate (200 mg, 0.46 mmol, 1.00 equiv) in CH_3CN (2 mL) and DCM (2 mL), was added $RuCl_3$ (0.58 mg)Then a solution of $NaIO_{+}$ (28° mg, 1.35 mmol, *2.96* equiv) in H_2O (4 mL) was added dropwise at 0°C. The resulting solution was stirred for 30 min at 0*C. The mixture was extracted with 3x10 mL of EtOAc. The organic layer was washed with 3*5 mL of brine and concentrated. The residue was purified by Prep-TLC with PE:EtOAc= 10:1 . This resulted in 150 mg (70%) of tertJDutyl 2-(2,2-dimethyl-l, 1-dioxido-3-oxo-4-((2-(trimethylsilyl)ethoxy)methyl) -3,4-dihydro-2H-ben30 [b] [1,4]tliazin-o -yl)acetate as colorless oil.

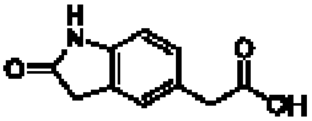
Step (ii) Synthesis of 2-(2,2-dimethyl-l, 1-dioxidD-3-oxo-3,4-dihydro-2H-ben2o[b] [l,4]1niazin-0-yl)acetic acid



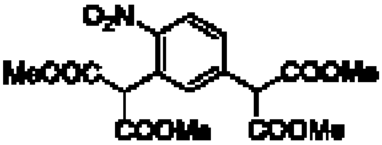
To a solution of tert-butyl 2-(2,2-dimethyl-l, l-dioxido-3-oxo-4-((2-(trimemylsHyl)et]Mxy)me1nyi)-3,4-dmydro -2H-benzo[b] [1,4]thiazin-6-yl)acetate (150 mg, 0.32 mmol, 1.00 equiv) in DCM (5 mL), was added TFA (2 mL). The resulting solution was stirred for 3 h at room temperature. The mixture was concentrated. The residue was triturated with PE. The resulting solid was collected by nitration and dried under vacuum. This resulted in 100 mg of 2-(2^-dtinethyl-l. l-dioxido-3-oxo-3,4-dihydro-2H-benm[¾ [1,4]thiazin-6-yl)acetic acid as a yellow solid.

Example 19-a

2-(2-oxoindDlin-5-yl)acetic acid

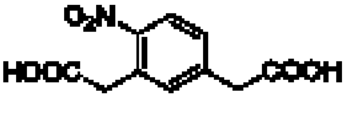


Step (i) Synthesis of tetramethyl 2,2'-(4-nitro-1,3 -phenylene)dimalonate



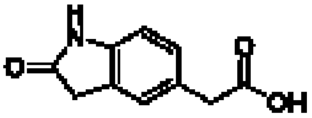
Into a 500-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of sodium hydride (18.88 g, 786.67 mmoL, 5.50 equiv) in DMSO (300 mL) at 0°C. This was followed by the addition of 1,3-dimethyI propanedioate (61.36 g, 464.45 mmol, 3.25 equiv) dropwise with stirring at 0*C. After stirred for 5 min at 0*C, to this was added 2,4-difluoro-l -nitroberLzerie (22.756 g, 143.04 mmoL, 1.00 equiv) dropwise with stimng at 0*C. The resulting solution was stirred overnight at 100*0 in an oil bath. The reaction was then quenched by the addition of NH+C1. The resulting solution was extracted with ethyl acetate (3x300 mL). The organic combined layers were washed with brine (lx200r.iL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (0:1-1 :2). This resulted in 20 g (36%) of 1,3-dimethyl 2-[3-(l,3-dime1hoxy-l,3-dimopropan-2-yl)-4-nitrophenyi] propanedioate as a tight yellow solid.

Step (ii) Synthesis of 2,2'-(4-rdtro-l ,3-phenylene)diacetic acid



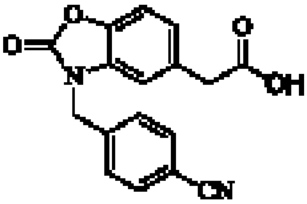
Into a 250-mL round-bottom flask, was placed a solution of 1,3-dimethyl 2-[3-(13-dimethoxy-1,3-dioxopropan-2-yl)-4-mtrophenyl]propanedioate (20 g, 52.18 mmoL, 1.00 equiv) in methanol (40 mL). This was followed by the addition of a solution of sodium hydroxide (8.355 g, 203.89 mmoL, 4.00 equiv) in water (20 mL) dropwise with stirring. The resulting solution was stirred for 1 h at 75°C in an oil bath. The pH value of the solution was adjusted to 1 with hydrochloric acid aqueous. The resulting solution was extracted with ethyl acetate (3x100mL) and the organic layers combined. The resulting mixture was washed with brine (1x100mL). dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (0:1-1:5). This resulted in 1.3 g (10%) of 2,2'-(4-nitro-1,3-phenylene)diacetic acid

Step (iii) Synthesis of 2-(2-oxoindolin-5-yl)acetic acid



Into a 100-mL round-bottom flask, was placed a solution of 2,2'-(4-nitro-1,3-phenylene)diacetic acid (1.2 g, 5.02 mmol, 1.00 equiv) in acetic acid (50 mL). This was followed by the addition of iron (**1.1238** g, 20.12 mmol, 4.00 equiv) in portions. The resulting solution was stirred for 1 h at 100°C in an oil bath. The solids were filtered out. The resulting mixture was concentrated under vacuum. This resulted in 0.56 g (58%) of 2-(2-oxoindolin-5-yl)acetic acid.

Further examples of the acid intermediates of formula (a), which can be paepared by substantially similar procedures as described above or procedures known in the art, include:



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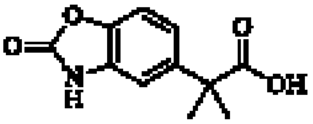

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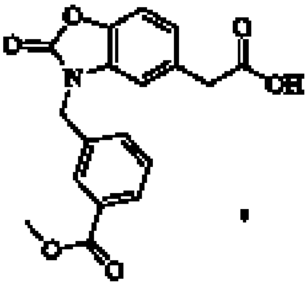

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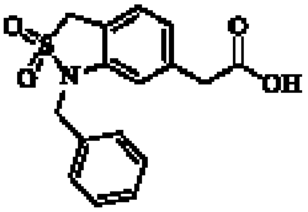

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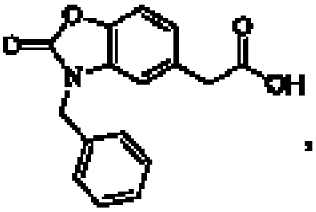

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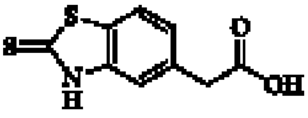
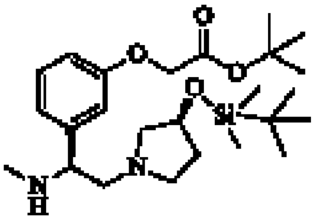


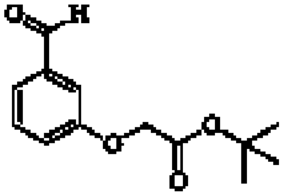
Following are the non-limiting examples of the reactant b:

Example 1-b

tert-butyl 2-(3-((S)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-1-(methylamino)ethyl)phenoxy)acetate



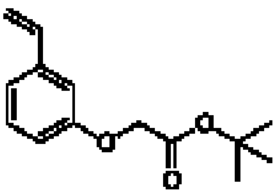
Step (i): Synthesis of tert-butyl 2-(3-formylphenoxy)acetate



A mixture of 3-hydroxybensaldehyde (20.0 g, 0.163 moles), tert-butyl bromoacetate (26 ml, 0.18 moles) and potassium carbonate (57 g, 0.4 moles) in DMF (270 ml) was stirred at room temperature for 4 hours. Thereafter, DMF was removed in vacuo; water was added to the reaction mixture and it was extracted with ethyl acetate (2x500 ml). The combined organic layer was washed with saturated brine solution and the combined organic layer was dried over sodium sulphate and concentrated in vacuo to give crude product. The residue was purified by flash chromatography using silica gel 230-400 mesh as stationary phase and 30 % ethyl acetate in n-hexane as eluent to obtain the titled compound (26.1 g).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.98 (s, 1H), 7.55-7.52 (m, 2H), 7.39 (s, 1H), 7.38 (m, 1H), 4.76 (s, 2H), 1.43 (s, 9H).

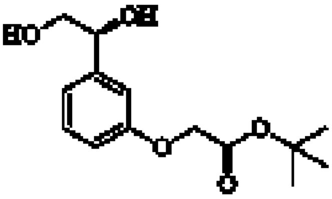
Step (ii): Synthesis oftert-butyl 2-(3-vinylphenoxy)acetate



To a suspension of NaH (26 g, 0.11 moles) in THF (300 ml) at 0°C was added metl^ripl^nylphophonium bromide (45 g, 0.12 mol) in portions and stirred for 1 h. To this mixture was added dropwise a solution of 2-(3-form^phenoxy)acetonitrile (43 g, 0.12 moles) in THF (100 ml) at 0°C. The reaction mixture was stirred at 25°C for 2 hours. Thereafter the reaction mixture was poured into crushed ice then partitioned with ethyl acetate (500 ml); the combined organic layer was dried over sodium sulphate and concentrated in vacuo to give crude product.The residue was purified by flash chromatography using silica gel 230-400 as stationary phase and 30 % ethyl acetate in n-heKane as eluent to obtain the titled compound (12 g).

1H-NMR (400 MHz, DMSO-d_6): 5 7.32-7.27 (m, 1H), 7.25-7.0 (m, 2H), *6.22-6.65* (m, 2H), 5 82 (d, *J* = 17.6 Hz, 1H), 5.23 (d, *J* = *19.6* Hz, lH), 4jo6 (s, 2H), 1.42 (s, 9H).

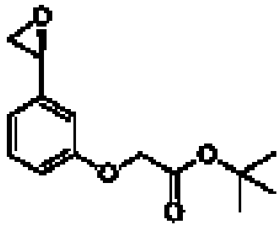
Step (iii): Synthesis of (S)-tert-butyl 2-(3-(l,2-dihydroxyemyl)phenoxy)acetate



At 0°C, to a mixture of tert-butyl alcohol (250 ml), water (250 ml), and AD-mix-alpha (Aldrich TM (84 g) was added tert-butyl2-(3-vinylphenoxy)acetate (12 g, 0.05 moles) and the resultant mixture was stirred for 3.5 hours at room temperature . Sodium sulphite *(96* g, 0.07 moles) was added and the reaction mixture stirred for another hour at room temperature. The reaction mixture was poured into ethyl acetate (500 ml); the aqueous layer was extracted with ethyl acetate (2x 500 ml). The combined organic layer was washed with saturated brine solution, dried over sodium sulphate and concentrated in vacuo to obtain the crude product which was purified by flash chromatography using silica gel 230-400 mesh as stationary phase and 50 % ethyl acetate in n-hexane as eluent to obtain the titled compound (1.6 g).

^{1}H-NMR (400 MHz, DMSO-d_6): 5 7.22-7.20 (m, 1H), 6 93-6.72 (m, 3H), 5.75 (s, 1H) 5 21 (m, 1H), 4 67 (m, 1H), 4.60 (s, 1H), 4.724.50 (m, 1H), 1.42 (s, 9H).

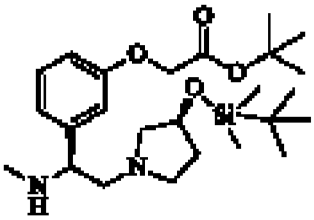
Step (iv): Synthesis of(S)-tert-butyl 2-(3-(oxiran-2-yl)phenoxyjacetate



To a solution of (S)-tert-butyl 2-(3-(l,2-dinydroxyethyl)**pheriDxy**)acetate (5 g, 0.01 moles) in DCM (50 ml); trimethybrthoacetate (5.7 niL,0.04 moles) and chlorotrimethylsilane (5.7 ml, 0.04 moles) were added at room temperature. The reaction was stirred at room temperature under nitrogen for 1 hour, and then the solvent was removed in vacuo. Potassium carbonate (3.31 g. 0.02 moles) and methanol (10 ml) were added, and the reaction was stirred at room temperature under nitrogen for 3 hours. The reaction was then poured into saturated ammonium chloride solution (50 ml) and extracted with dichloromethane (2x 200 ml). The combined organic layer was washed with saturated brine solution, dried over sodium sulphate and concentrated in vacuo to obtain the crude product which was purified by flash chromatography using silica gel 230-400 mesh as stationary phase and 30 % ethyl acetate in n-hexane as eluent to obtain the titled compound (1.7 g).

H -NMR (400 MHz, DIvEO^): 5 7.2S-7.24 (m, 1H), *6.92-6.Z5* (m, 3H), 4.64 (s, 2H), 3.S9 (m, 1H), 2.81 (m, 1H), 1.42 (s, 9H).

Step (v): Synthesis oftert -butyl 2-(3-((3)-2-((S)-3-((tert-butyldimethylsilyl)o iy) pyrrolidin-1-yl)-l -(methyl amino) ethyl)phenoxy)acetate

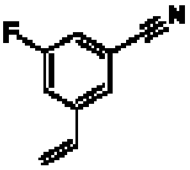


To a stirred solution of (S)-3-(oxiran-2-yl) benzonitrile (*6* g, 41.3 mmol) in ethanol (*6*0 ml); (S)-3-(tert-butyldimethyisilyloxy) pyrrolidine (12.5 g, *62*.1 mmol) was added.The reaction was heated to reflux for 5 houE. Then ethanol was removed in vacuo. The ciude reaction mixture was then dissolved in diethyl ether (120 ml), cooled to 0°C and flushed with nitrogen. Triethylamine (24 ml, 132.16 mmol) was added followed by methanesulphony! chloride (4.5 ml, 57.S mmol) at 0°C and reaction was stirred at 0°C for half an hour. Some more triethylamine (12 ml, *22.6* mmol) was added, the reaction was warmed to room temperature over half an hour, then an aqueous solution of methyl amine (40% w/w) (72 ml, *226* mmol) and water (35 ml) were added. After stirring at room temperature under nitrogen for 1*6* hours, layers were separated and the aqueous layer was extracted with diethyl ether (3x 200 ml). The combined organic layer was washed with 10% sodium bicarbonate solution (100 ml), water (100 ml) and brine (100 ml), dried over sodium sulphate and concentrated in vacuo to give crude product as yellow oil. The residue was purified by flash chromatography using silica gel 2304 00 mesh as the stationaiy phase and 10 % MeOH in DCM as eluent to obtain the titled compound (1.5 g).

Example 2-b

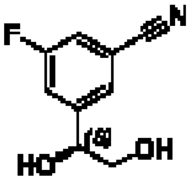
3-((S)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pyTiolidin-1-yl)-1-(methylamino)ethyl)-5-fluorobenxonitrile

Step (i) Synthesis of 3-fluoro-5-vinylberizonitrile



Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 3-bromo-5-fluombenmnitrile (5 g, 25.00 mmol, 1.00 equiv) in ethanol (50 mL). To the solution were added TEA (5.05 g, 49.91 mmol, 2.00 equiv), Pd(dppf)Cl2 (918 mg, 0.05 equiv), and potassium vinyl trifluoroborate (9.98 g, 82.53 mmol, 3.00 equiv). The resulting solution was stirred for 3 hours at 80℃ in an oil bath. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 80 mL of ethyl acetate. The resulting mixture was wasted with brine (2x30 mL), dried over with NajSO+ and concentrated. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:100-1:10). This resulted in 4.21 g of3-ethenyl-5-fluoroberimmtrile as a white solid

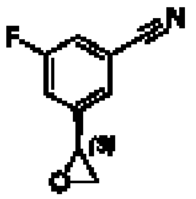
Step (ii) : Synthesis of (SJ-S-il^-dihydroxyemylJ^-fluorobenmrdtrile



Into a 50-mL round-bottom flask, was placed a solution of 3-ethenyl-5-tluorobensonitrile (1 g, 6.80 mmol, 1.00 equiv) in water/t-BuOH (vfv=1:1, 50 mL). To the solution was added AD-mix alpha (10 g). The resulting solution was stirred for 24 hours at room temperature. The resulting solution was diluted with 100 mL of water. The resulting solution was extracted with ethyl acetate (3x30 mL) and the organic layers combined. The resulting mixture was washed with brine (2x30 mL), dried over sodium sulfate and concentrated under vacuum. The resulting crude solid was washed with PE. This resulted in 1.3 g (crude) of 3-[(1S)-1,2-dihydroxyethyl]-5-fluorober^ onitrile as a white solid.

LC-MS: (ES, m¾): 182 (M+l).

Step (iii): Synthesis of (3)-3-fluoro-5-(oxiran-2-yl)bercEorLitrile



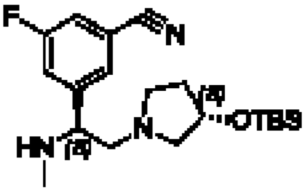
Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 3-[(lS)-l,2-dihydroKyethyI] -5-tluorobenzonitrile (4.4 g, 24.2° mmol, 1.00 equiv) and CH$_3$C(OCH$_3$)$_3$ (13.25 g) in dichloromethane (50 mL). TIvECl (14.58 g, 134.20 mmol, 5.53 equiv) was added dropwise at 0°C. The resulting solution was stirred for 5 hours at room temperature. The resulting nurture was concentrated under vacuum. The residue was diluted in MeOH (50 mL). To the mixture was added potassium carbonate (16.77g, 121.5 mmol, 5.00 equiv), in portions at 0°C. The resulting solution was allowed to read, with stirring, for an additional 1.5 hours at room temperature. The solids were filtered out. The filtrate was concentrated and then dissolved in DCM (100 mL), washed with water (3x30 mL), then dried over with Na$_2$SO+. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column with ethyl acetate/petroleum ether (1:50-l :20). This resulted in 0.8 g (20%) of3-fluoiO-5-[(23)-oxiran-2-yl]ben2Dnitrile as a white solid.

Step (iv): 3-((S)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-l -hydroxyethyl)-5-fluoroberuzonitrile

Into a 50-mL round-bottom flask, was placed a solution of 3-fluoro-5-[(2S)-oxiran-2-yljbenzonitrile (800 mg, 4.90 mmol, 1.00 equiv) in ethanol (20 mL). To the mixture was added (33)-3-[(tert-butyldimethylsilyl)oxy] pyrrolidine (1.97 g, 9.78 mmol, 1.99 equiv).

The resulting solution was stirred for 3 h at 80°C. The resulting nuxture was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with petroleum ether/ethyl acetate (100:l)^chbrometliane/methanol (50 :1). This resulted in OS g (45%) of 3-[(1S)-2-[(3Ξ)-3-[(tert Jautyldimethylsilyljo-iy] pyrrolidin- 1-yl]-1-hydoxyemyQ -5-fluorobenzonitrile as yellow oil. LC-MS : (EΞ, m/z): *365* (M+1).

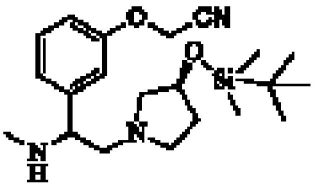
Step (v): Synthesis of 3-((3)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pym lidin-1-yl)-1-(mettylammo)etliyl)-5 **-fluDroben2Dnitrile**



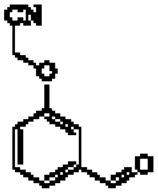
Into a 100-mL 3-neeked round-bottom flask, was placed a solution of 3-[(1Ξ)-2-[(3Ξ)-3-Etert-butyldimethylsilyl) oxy] pyrrolidin-1 -yl]-1-hydroxyethyl] -5-fluorobe nzonitiile (SO0 mg, 2.19 mmol, 1.00 equiv) and TEA (1.8 g, 17*.19* mmol, 8.1 1 equiv) in dchloromethane (20 mL). To the solution was added MsCl (1.22 g, 10.70 mmol, 4.88 equiv) dropwise at 0*C. The solution was stirred for 1 hour at room temperature. Then to this was added IvfeNHj aqueous (30%, 5 ml_) dropwise with stirring. The resulting solution was stirred overnight at room temperature. The resulting solution was extracted with dchloromethane (2x20 mL). The combined oiganic layers were washed with brine (1x20 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with dichloron¾thar.e/methanol (1:0-50:1). This resulted in 0.55 g *(66%)* of 3-[(13)-2-[(33)-3-Etert-butyldir^ thylsilyl)oxy] pyrrolidin-1 -yl]-1-(n¾thykmirio)etr^]-5 **-fluorobensDnitnle** as yellow oil. LC-MΞ: (EΞ, m/z): 378 (M+l).

Example 3-b

2-(3-(2-((S)-3-((e rt-butyldimethylsilyl)Dxy)pyrrolilin-1-yl)-l-methylamino)ethyl) phenoxy) acetonitrile



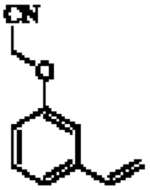
Step (i) Preparation of 2-(3-formylphenoxy)acetonitrile



3-Hydroxybenzaldehyde (5.0 g, 0.04 moles), **bronrLoacetoiiitrile** *{6.4* g, 0.05 mol) and ptassium caibonate (15.IS g, 0.11 mol) in DMF (50 ml) were placed in a 2 neck round bottom flask under nitrogen inlet. The reaction mixture stirred at room temperature for ***6*** h. Thereafter the reaction mixture was concentrated under reduced pressure, treated with water; **and extracted with** ethyl acetate (2x200 ml). The **combined** organic layer was washed **with** saturated **brine** solution; dried over sodium sulphate and concentiated under reduced pressure to give the crude product which was purified by Flash chromatography using silica gel 230-400 mesh and 20% ethyl acetate in **n-hexane** as eluent to obtain 2-(3-formylphenoxy)acetonitrile (2.1 g)

^{1}H-NMR (400 MHz, DMSO-d_6) : 5 10.01 (s, 1H), 7.67-7.43 (m, 4H), 5.29 (s, 2H).

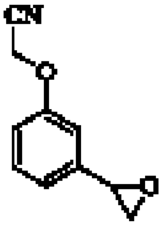
Step (ii) : Pre**paration** of **2-(3-vinylpheriDxy)ace tonitrile**



To a suspension of NaH (13.3 g, 0.55 mol) in THF (200 ml) at 0°C was added methytriphenyl phophonium bromide ***(53.6*** g, 0.15 mol) in portions and stirred for 1 h. To this mixture was added dropwise a solution 2-(3-ibrmylphenoxy) acetonitrile (19.8 g, 0.12 moles) in THF (100 ml) drop wise at 0°C. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was poured in to crushed ice and the mixture was then extracted with ethyl acetate (500 ml). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to get the cmde product which was purified by flash chromatography using silica gel 230-400 mesh and 20% ethyl acetate in n-hexane as eluent to obtain 2-(3-vinylphenDxy)acetonitrile (8.0 g)

^{1}H-NMR (400 MHz, DIvE O-d_6): 5 7.36-7.18 (m, 3H), 7.16-6.°0 (m, 1H), 5.89 (d, *J* = 111 *Hz*, 1H), 5.31 (d, *J* = 11 *Hz*, *Hi)*, 5.19 (*s*, 2H).

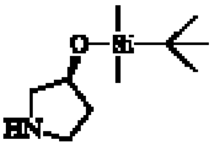
Step (iii) : Preparation of 2-(3-(oxiran-2-yl)phenoxy)acetonitrile



m-Chloroperbenzoic acid (7.2 g, 41.8 moles) and (40 ml) 10% aqueous saturated NaHCOs was added to a solution of 2-(3-vinylpheno iy)acetonitrile (1.9 g. 11.9 moles) in dichloromethane (40 ml). The reaction mixture was stirred at room temperature under nitrogen for 2 h. Thereafter the reaction mixture was concentrated under reduced pressure. It was diluted with 10 % aqueous $Na_2S_2O_3$ solution and extracted with diehloromethane (2x200 ml). The organic layer was washed with saturated NaHCOs solution; dried over sodium sulphate and concentrated under reduced pressure to get the crude product which was purified by flash chromatography using silica gel 230-400 mesh and 20% ethyl acetate in n-hexane as eluent to obtain 2-(3-(oxiran-2-yl)ptenflxy)acetonitrile (0.82 g).

H -NMR (400 MH¾ DIvEO^): 5 7.38 (m, 1H), 7.03-6.97 (m, 3H), 5.17 (s, 2H), 3.94-3.93 (m, 1H), 3.13-3.12 (m, 1H), 2.86-2.84 (m, 1H).

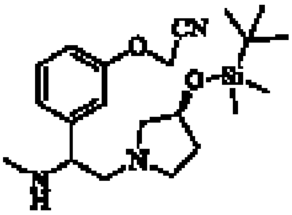
Step (iv): Prepaiation of - (S)-3-(tert-butyldimethylsilyloxy) pynolidine from (S)-pymolidin-3-ol



Imidaaole (4.85 g, 0.07 moles) and tert-butyldimethylsilyl chloride (8.6 g, 0.05 moles) were added to a solution of (S)-pyrrolidin-3-ol (2.5 g, 0 D2 moles) in diehloromethane (30 ml) at 20-35*0 under nitrogen and stirred for 3 h. The reaction was then diluted with dichloromethane (100 ml). The organic layer was washed with water; saturated aqueous sodium bicarbonate and brine. The organic layer was dried over sodium sulphate and concentrated under reduced pressure to get the product as yellow oil (5.1 g).

^{1}H-NMR (400 MHz, DIvEO-d_6): 5 5.30 (bs, 1H), 4.35-4.31 (m, 1H), 2.90-2.84 (m, 2H), 2.76-2.70 (m, 1H), 2.57-2.54 (m, 1H). 1.85-1.77 (m, 1H), 1.57-1 5 0 (m, 1H), 0.90 (s, 9H), 0.14 (s, 6H).

Step (v): Preparation of - 2-(3-(2-((3)-3-((tert-butyldiri¾th;^a lyl)oxy)pyrrolidin-1-yl)-1-(methyl amino) ethyi)phe nosy) ace tonitrile

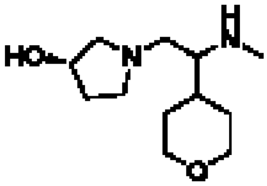


(S)-3-(tert-butyldin¾mylsnytoxy)py^ lidine (2.57 g, 12.8 moles) was added to a stirred solution of 2-(3-(oxiran-2-yl)pheroxy)acetDnitrile (1.6 g, 9.14 moles) in ethanol (60 ml). The reaction mixture was reflu:* d for 8 h and then concentrated under reduced pressure. The reaction mixture was then dissolved in diethyl ether (30 ml) and cooled to 0°C. Triethylamine (2.8 g, 27.42 moles) was added foliowed by methane sulphonyl chloride (1.36 g, 11.88 moles) at 0°C and reaction was stirred at 0°C for 30 minutes. Another portion of triethykmine (1.85 g, 18.28 moles) was added, the reaction was warmed to room temperature over 30 minutes, then an aqueous solution of methyl amine (40% w/w) (5.0 g, 161 2 moles) and water (10 ml) were added. After stirring at room temperature under nitrogen for 16 h, layers were separated and the aqueous layer was extracted with diethyl ether (3×200 ml). The organic layer was dried over sodium sulphate and concentrated under reduced pressure to get the crude product as yellow oil which was further purified by flash chromatography, using silica gel 230-400 mesh and 10 % MeOH in DCM as the eluent to obtain 2-(3-(2-((Ξ)-3-((tert-butyidimemylsnyl)oxy)pyrrohdin-l -yl)-1-(methylanuno)ethyi)phenoxy)ac etonitrile.

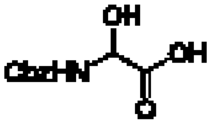
1H-NMR (400 MHz, DMSO-d_6): 5 7.32-7.29 (m, 1H), 7.05-6.94 (m, 3H), 5.14 (s, 2H), 4.34 (s, 1H), 3.61-3.59 (s, 1H). 2.90-2.76 (m, 2H), 2.39-2.32 (m, 3H), 2.17-2.05 (m, 1H), 1.57-1.54 (m, 1H), 0.85-0.81 (m, 9H), 0.04 (s, 6H).

Example 4-b

(3S)-1-(2-(methylamir»)-2-(tetrahydro-2H-pyran-4-yl)ethyl)pyrrolidin-3-ol

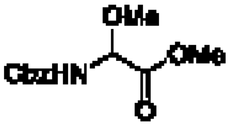


Step (i) Synthesis of 2-(((ben;.yioxy)carbonyi)amLno)-2-hydro^ yacetic acid



Into a 500-mL round-bottom flask, was placed a solution of benzyl carbamate (30 g, 198.47 mmol, 1.00 equiv) and 2-oxoacetic acid (22 g, 297.14 mmol, 1.20 equiv) in ether (300 mL). The resulting solution was stirred for 2 days at room temperature. The solids were collected by filtration. This resulted in the titled compound (30 g, 67%) as a white solid.

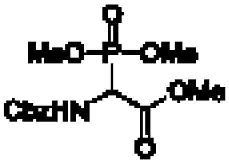
Step (ii) Synthesis of Methyl 2-[[(benzyxoxyjcarbonyi]amino]-2-methoxyacetate



Into a 1000-mL round^bottom flask, was placed a solution of 2-[[(benzyloxy)carbonyI]amino]-2-hydroxyacetic acid (30 g, 133.22 mmol, 1.00 equiv) and sulfuric acid (30 mL) in methanol (300 mL). The resulting solution was stirred overnight at 25*C. The reaction mixture was cooled with an ice-cold water bath. The solids were collected by filtration. This resulted in 33 g (98%) of the title compound as a white solid.

LC-IvE : (ES, m/z): 254 (M+1).

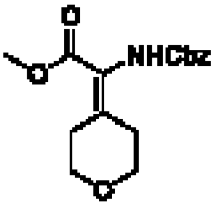
Step (iii) Synthesis of methyl 2-(((benzyloxy)carbonyl)aminD)-2-(dimethoxyphosphoryl)acetate



Into a 500-mL round-bottom flask, was placed a solution of methyl 2-(benzyloxycarbonykmino)-2-n¾1hoxyacetate (33 g, 130.31 mmol, 1.00 equiv) in toluene (250 mL). This was followed by the dropwise addition of PCb (18 g, 131.39 mmol, 1.00 equiv). The resulting solution was stirred for 16 h at 70℃. To this P(OMe)j (16.2 g, 130.65 mmol, 1.10 equiv) was added dropwise. The resulting solution was stirred for an additional 2 h at

70°C. The resulting mixture was concentrated in vacuo .The residue was diluted with 300 mL of ethyl acetate and the organic layer was washed with 3x250 mL of sodium bicarbonate solution and concentrated in vacuo. The crude product was re-crystallised from hexare -ethyl acetate (1:1). This resulted in 28 g (65%) of the title compound as a white solid.

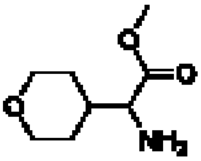
Step (iv) Synthesis of methyl 2-(((benzyloxy)carbonyl)amino)-2-(dihydro-2H-pyran-4(3H)-ylidene)acetate



A solution of methyl 2-(((benzyloxy)caibonyl)amino)-2-(**din¾tlMxyphosphoryl)acetate** (28 g, 84.59 mmol, 1.00 equiv) and 1, 1,3,3-tetmmethylguanidine *(16.5* g, 143.25 mmol, 1.70 equiv) in ethyl acetate (150 mL) was stirred for 30 min at room temperature. To this reaction mixture, a solution of tetmhydropyran4-one *(16.5* g, 164.80 mmol, 1.95 equiv) in ethyl acetate (100 mL) was added The resulting solution was stirred for 2 days at room temperature. The reaction was then quenched by the addition of 500 mL of 5% aqueous citric acid. The resulting solution was extracted with 3x200 mL of ethyl acetate and the combined organic layers were washed with 2x200 mL of brine and concentrated in vacuo. The residue was purified by column chromatography using silica gel as stationary phase and EtOAc: petroleum ether (1:8) as eluent. This resulted in the titled compound (22 g, 85%) as a white solid.

LC-IvE : (ES, *m/z)*: 306 (M+l).

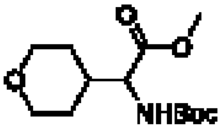
Step (v) Synthesis of methyl 2-amino-2-(tetrahydro-2H-pyran-4-yl)acetate



Under nitrogen atmosphere, palladium carbon (1 g) was added to a solution of methyl 2-[[(benzyloxy)caAonyl]amino]-2-^ oxan-4-ylidene)acetate (10 g, 32.75 mmol, 1.00 equiv) in methanol (200 mL). The resulting solution was stirred overnight at 25*C under hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated in vacuo .This resulted in 5 5 g (97%) of the titled compound as a white solid.

LC-IvE : (*ES, m/z*): 174(M+1).

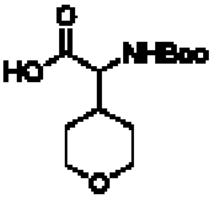
Step (vi) Synthesis of methyl 2-((tert-butoxycaibonyi)amino)-2-(tetra^ ydro-2H-pyran-4-yl)acetate



A mixture of methyl 2-amino-2-(oxan4-yl)acetate (5.5 g, 31.75 mmol, 1.00 equiv),, di-tert-butyl dicarbonate (7 g, 32.07 mmoL 1.03 equiv) and sodium carbonate (10.1 g, 95.28 mmoL 3.00 equiv) in HiO/dioxane (80/30 mL) was stirred for 2 h at 25°C and then diluted with 100 mL of water. The resulting solution was extracted with 200 ml of ethyl acetate and the combined organic layers were concentrated in vacuo. This resulted in 8 g (92%) of the titled compound as a white solid.

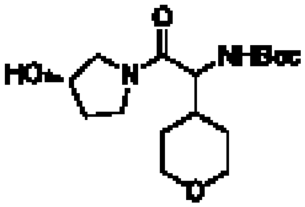
LC-IvE : (ES, m/z): 274 (M+l).

Step (vii) Synthesis of 2-((tert-butoxycaibonyl)anuno)-2-(tetrahyd^ -2H-pyran-4-yl)acetic acid



A solution of methyl 2-[[(tert-buto ^carbony5amino] -2-(oxan-4-yi)acetate (8 g, 29.27 inmoL 1.00 equiv) and NaOH (2.2 g, 55.00 mmol, 1.82 equiv) in a mixture of methanol (20 mL) and H_2O (90 mL) was stirred for 2 h at 25°C. The organic solvent was removed in vacuo. The pH value of the aqueous layer was adjusted to 3 with 2N HC1. The resulting solution was extracted with 50 mL of EtOAc and the organic layer was washed with 2x20 mL of brine and concentrated in vacuo. This resulted in 5 g of the title compound as a white solid which was used in the next step without further purification.

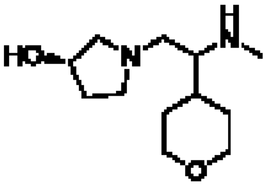
Step (viii) Synthesis of tert-butyl (2-((S)-3-hydroxypyrrolidin-l -yi)-2-oxo-l-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate



A solution of 2-[[(tert-butoxy)carbonyl]amino]-2-(o_an-4-yl)acetic acid (5 g. 19.28 mmol, 1.00 equiv), (3S)-py_Tolidin-3-ol (1.67 g, 19.17 mmol, 1.02 equiv). EDCI (3.67 g, 19.14 mmol, 1.06 equiv) and HOBT (2.6 g, 19.26 mmol, 1.02 equiv) in diehloromethane (80 mL) was stirred for 16 h at 25*0. The solids were filtered off and the filtrate was concentrated in vacuo. This results din 3 g (47%) of the title compound as a white solid.

LJC-IVE : (ES, m/z) 329 (IvH+1).

Step (ix) Synthesis of (3S)-l-(2^memykmmo)-2^teti^ydro-2H-pyran-4-yl)ethyl)pyrrolidin-3-ol

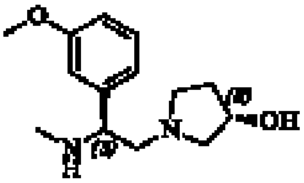


To a solution of tert-butyl N-P-[(3S)-3-hydraxypyrrohdin-l-ylJ-l-(oKan-4-yl)-2-oxoethylJcarbamate (3 g, 9.14 mmoL, 1.00 equiv) in tetrahydrofuran (50 mL), LiAlH+(2 g, 52.63 mmol, 5.76 equiv) was added portionwise. The resulting solution was stirred overnight at 65°C. The reaction was then quenched by the addition of ice-cold water. The solids were filtered off. The nitrate was extracted with 2x100 of ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. This resulted in 1.4 g (67%) of the title compound as a light yellow solid.

IX -IvE : (EΞ,m/5):229 (M+l).

Example 5-b

(3S)-1-[(2S)-2-(3-methoxyphenyl)-2-(methylamino)ethyl]pyrrolidin-3-ol



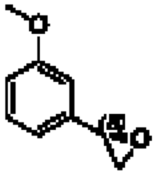
Step (i) Synthesis of l-n¾thoxy-3-vinylben3ene

In an inert atmosphere of nitrogen, n-BuLi(2.5M) (22 mL, 1.10 equiv) was added dropwise with stirring to a solution of methyltriphenylphosphonium bromide(19.6 g, 54.90 mmol, 1.10 equiv) in tetrahydrofuran (100 mL) in a temperature range of -5 to 0°C. The suspension was stirred for 30 min at 0*0. A solution of 3-methoxybenzaldehyde (6.8 g, 49.95 mmol, 1.00 equiv) in tetrahydrofuran (5 mL) was added dropwise with stirring at 0*C. The resulting solution was stirred for 3 h at 25*0. The reaction was then quenched by the addition of sat. HH+C1. The resulting solution was extracted with 3x50 mL of ether and the combined organic layers were washed with 3x50 mL of brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography using silica gel as stationary phase and ethyl acetate/petroleum ether (1:50) as eluent. This resulted in 6 g (90%) of the title compound as a colorless oil.

Step (ii) Synthesis of (S)-1-(3-methoxyphenyl)ethane-1,2-diol

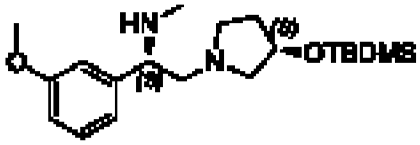
A suspension of AD-mix-alpha (25 g) in tert-Butanol/H_2O (40/40 mL) was stirred at 0*C for 30 min. This was followed by the addition of 1-ethenyl-3-methoxybenzene (2.5 g, 18.63 mmol, 1.00 equiv) to it. The resulting solution was stirred for 16 h at 25*C. The reaction was then quenched by the addition of 20 g of Na_2SO_3 and then stirred for 1 h at 25°C. The resulting solution was extracted with 2x50 mL of ethyl acetate and the combined organic layers were washed with 2x30 mL of brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography using silica gel as a stationary phase and petroleum ether:EtOAc (3:1) to yield 2.9 g of the title compound as colorless oil.

Step (iii) Synthesis of(S)-2-(3-methoxyphenyi)oxirane



In an inert atmosphere of nitrogen, TIvE-Cl (9.4 g, 86.64 mmol, 5.00 equiv) dropwise with stirring to a solution of (lSJ-l -(i -methoxyphenylJethane-1,2-diol (2.9 g, 17.24 mmol, 1.00 equrv) in anhydrous dichloromethane (30 mL) at 25*C. Then $CH_3C(OCH_3)_3$ (10.4 g, 86.67 mmol, 5.00 equiv) was added dropwise at 25*0 and the reaction was stirred at 25*C for 1.5 h The solvent was removed in vacuo and the residue was dissolved in 60 ml of anhydrous methanol. To the solution was added potassium carbonate (4.8 g, 34.78 mmol, 2.00 equiv). The resulting mixture was stiired for 2 h at 25*C and then quenched with sat NH+C1. The resulting solution was extracted with 2x50 mL. of dichloromethane and the combined organic layers were washed with 2x25 mL of brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography using silica gel as stationary phase and ethyl acetate/petroleum ether (1:25) to yield 2 g of the title compound as colorless oil.

Step (iv) Synthesis of (3)-2-((3)-3-((tert-butyldime1hyi^^ yl)oxy)pyrrolidin-1-yl)-1-(3-methoxyphenyl)-N-methylethanamine



In an inert atmosphere of nitrogen, (33)-3-[(tert-butyddin¾thyialyl)oxy] pyrrolidine (4.02 g, *19.96* mmoL 1.50 equiv) was added to a solution of (2Ξ)-2^3-methoxyphe nyl)oxirane (2 g, 1332 mmol, 1.00 equiv) in anhydrous ethanol (100 mL). The reaction was refluxed for 8 h Then the solvent was removed in vacuo and the residue was dissolved in ether (SO ml). To this TEA (4.04 g, *39.92* mmoL 3.00 equiv) was added dropwise at 0°C, followed by the addition of MsCl (1.93 g, 17.29 mmol, 130 equiv) dropwise at 0*C. Then the reaction was stirred at 0*C for 1 h and at 25*C for 1 h. To this reaction mixture CH_3NH_2 (aq, 40%) (21 mL, 20.00 equiv) was added followed by 20 mL of water. The resulting solution was stirred for 1*6* h at 25°C. The resulting solution was extracted with 100 mL of ether. The combined organic layers were washed with 3x25 mL of 10% sodium bicaibonate and 3x25 mL of water, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography using silica gel as stationary phase and DCMIv]eOH(with 0.5% ammonia) (25:1) to yield 1.*6* g of the title compound as colorless oil.

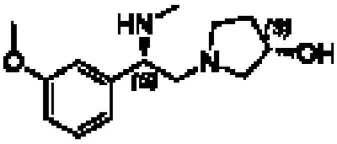
LC-IvE: (EΞ, *m/z): 366* (M+l).

Step (v) Synthesis of tert-butyl ((S)-2-((S)-3-((tert-butyldin¾th;^sil^ oxy)pyrrolidin-1-yl)-1-(3-n¾thoxyphenji)eth5ii)(methyl)caibaniate

A solution of potassium carbonate (1.52 g, 11.01 minol, 2.00 equiv) in water (20 mL) was added to a solution of [(lS)-2-[(3S)-3-[(tert-butyldimem^sny^^ oxy]pyrrolidin-1-yl]-1-(3-n¾tho.iyphenyl)ethyl](methyl)amine (1.6 g, *4.39* mmol, 1.00 equiv) in tetiahydrofuran (20 mL). This was followed by the addition of BocjO (1.3 g, 6.02 mmol, 1.10 equiv) at 0*0. The resulting solution was stirred for 16 h at 25*0. The resulting solution was extracted with 3x50 ml of ethyl acetate . The combined organic layers were washed with 2x20 mL of brine, dried and concentrated in vacuo. The residue was purified by column chromatography using silica gel as stationary phase and petroleum ether:EtOAc (15:1) to result in 2 g (98%) of the title compound as an off-wiute solid.

LC-IvE : (ES, *m/z)*: 466 (M+l).

Step (vi) Synthesis of (S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-methoxyphenyl)-N-nwthylel^naminium 2,2,2-trifluoroacetate

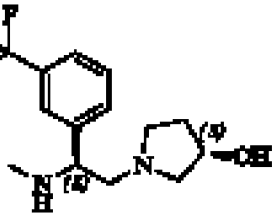


Trifluoroacetic acid (10 mL) was added to a solution of tert-butyl N-[(l S)-2-[(3S)-3-[(tert^utyldmethylsnyl)ox^py™ lidin-1-yl]-1-(3-methoxyphenyl)ethyI]-N-memylcarbamatB (2 g, 4.30 mmol, 1.00 equiv) in dichloromethane (15 mL). The resulting solution was stirred for 5 h at 25*C. The resulting mixture was concentrated in vacuo and the residue was diluted with ether and n-hexane. The solids were collected by filtration and then washed with n-hexane. This resulted in 1 g (64%) of the title compound as an off-white solid.

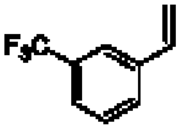
LC-IvE : (ES, m/z): 251 (M+1); H -NMR (300 MHz, CE¾OD) : δ7.487-7539 (m, 1H), 7.142-7.168 (m, 3H), 4.503-4.613 (m, 2H), 3.600-3.884 (br, 5H), 3.461 -3.548 (m, 2H), 3.203-3.237 (m, 2H), 2.612 (s, 3H), 2.181 -2 243 (m, 1H), 2D02-2.223 (m, 1H).

Example *6*-b

(3 S)-1-[(2 S>2-(methylajnijuo)-2-[3-(trifluoromethyl)phenyl]ethyl]pyrrolidin-3-ol

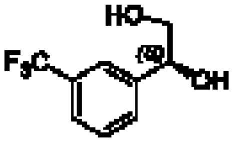


Step (i) Synthesis of l-(tiifluoromethyl)-3-vinylbenzene



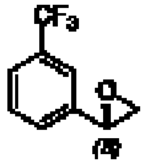
n-BuLi (30 mL) was added dropwise with stirring to a solution of 3-(trifluoromethyI) benzaldehyde (10 g, 57.43 mmol, 1.00 equiv) in tetrahydrofuran (100 mL) at 0°C. The resulting solution was stirred for 0.5 h at 0*0. To this was added a suspension of PPhjCHjBr *(24.6* g, 68.86 mmol, 1.20 equiv) in tetrahydrofuian (250 mL) at 0*C. The resulting solution was stirred for 1 h at room temperature in an oil bath The reaction was then quenched by the addition of Ξat. NH+C1 (50 mL). The resulting solution was extracted with 3x100 mL of ethyl acetate and the combined organic layers were washed with 1x100 mL of brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was applied onto a silica gel column eluting with petroleum ether. This resulted in 4 g (40%) of the title compound as cobrless oil.

Step (ii) Ξynthesis of (S)-1-(3-(trifluoromethyl)phenyl)ethane-1,2-diol



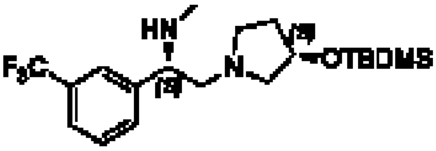
l-e11ienyl-3-(trifluoromethyl **)ben3ene** (3.1 g, 18.01 mmol, 1DO equiv) was added to a solution of AD-rnix a (25 g) in tert-Butanol (90 mL) and water (90 mL) at 0°C. The resulting solution was stirred overnight at 0°C in an ice/salt bath. Then the reaction was quenched by the addition of Na_2SO_3. After stirring for 1 h. the resulting solution was diluted with 25 mL of sodium bicarbonate; extracted with 2x100 mL of ethyl acetate; the combined organic layers were washed with 1x50 mL of brine and 1x50 mL of H_2O and concentrated in vacuo. The residue was purified by column chromatography using silica gel as stationary phase and diclu^romethane/methanol(10:1 -50: 1) as eluent. This resulted in 3.1 g (84%) of the title compound **as** **a** colorless oil.

Step (iii) Synthesis of (S)-2-(3-(trif uoron¾thyl)p]¾nyl)**oKiiane**



In an inert atmosphere of nitrogen, CHsC(OC¾)s (5.4 g) and TIvE-Cl (4.9 g) were added to a solution of (lS)-l-[3-(MnuDromethyl)pher^]ethane-l ,2-diol (3.1 g, 15 D4 mmol, 1.00 equiv) in dichbromethane (60 mL) at 0°C. The reaction was stirred at 25 °C for 2 h. Thereafter the solvent was removed in vacuo, the crude product was dissolved in MeGH (20 niL) and then potassium carbonate (4.1 g) was added. The resulting solution was stirred at 25*C for 0.5 h. The reaction was then poured into saturated ammonium chloride solution and extracted with dichloromethare . The combined organic layers were washed with brine and water, dried over Na_2SO_4 and concentrated in vacuo. The residue was further purified by column chromatography using silica gel as stationary phase and ethyl acetate/petroleum ether(l :5) as eluent to obtain 1.5 g (53%) of the title compound as colorless oil.

Step (iv) Synthesis of (S)-2-((S)-3-((tert-butyldime1hylsnyl)^ y)pyrrolidin-1-yl)-N-methyl-1-(3-(trifluoro methyl)phenyl)e lhanamine

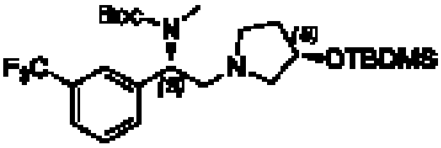


In an inert atmosphere of nitrogen, (3S)-3-[(tert-butyldin¾thyialyl)o^ y]pyrrolidine (322.3 ing, 1.60 nunol, 1.50 equiv) was added to a solution of (2S)-2-[3-(trifluoromemyl)p]¾nyl]oxirane (201 mg, 1.07 mmol, 1.00 equiv) in ethanol (4 mL). The resulting solution was heated to reflux for 4 h. The solvent was removed in vacuo and the residue was diluted with 4 mL of ether. To this was added triethykmine (323 mg, 3.19 mmol, 2.99 equiv) at 0*C. The resulting solution was stirred for 0.5 h at room temperature. To the mixture was added IvIsCl (170 mg, 1.49 mmol, 1.40 equiv). After stirred for l h at 0°C, triethykmine (215 mg, 2.12 mmol, 2.00 equiv) was added. After stirred for 0.5 h at 25*0, a solution of CH_3NH_2 (2.22 g, 21.48 mmol, 20.00 equiv, 30%) in water (3 mL) was added. The resulting solution was stirred for 2 h at 25*0. The resulting solution was extracted with ether and the organic layers combined The combined organic layers were washed with 10%

sodium bicarbonate, water and brine. The mixture was dried over sodium sulfate and concentrated in vacuo. The residue further purified by column chromatography using silica gel as stationary phase and DCM/MeOH (30: 1) as eluent to yield 200 mg of the title compound as colorless oil.

LC-M5 : (ES, *m/z)*: 403 (M+l)

Step (v) Synthesis of tert-butyl ((S)-2-((S)-3-((tert-butyldin¾thyIsil^ oxy)pyrrolidin-1-yl)-1-(3-(trifluoiO me1hyl)phenyl)e thyl)(methyl) carbamate



Sodium carbonate (109 mg, 1.03 mmol, *4.99* eq) was added to a solution of [(1S)-2-[(3S)-3-[(tert-butyldimethylsilyi)oxy]pyrrolidin-1-yl]-1-|3-(trifluoromethyl)phenyr] ethyl](methyl)amine (S3 mg, 0.21 mmol, 1.00 equiv) in tetmhydrofuran/ water (4/4 mL). After stirring for 15 min at room temperature, **B0C$_2$O** (45 mg, 0.21 mmol, 1.00 eq.) was added. The resulting solution was stirred for 10 h at 25°C in an oil bath. The organic solvent was removed in vacuo. The aqueous layer was extracted with 3x5 mL of ethyl acetate. The combined organic layers were washed with 3x10 mL of **H2O** and 3x10 mL of brine, dried over anhydrous sodium sulfate and concentrated in vacuo. This resulted in 100 mg (crude) of the title compound as a light yellow solid.

LC-M5 : (ES, *mfz)*: 503 (M+l).

Step (vi) Synthesis of (S)-l-((S)-2-(me1]nyknuno)-2-(3-(trifluoromethyl) phenyl)ethyl)pyrrohdin-3-ol

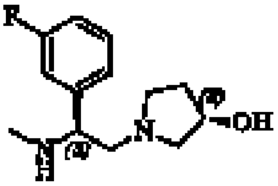
A solution of tert-butyl N-[(1S)-2-[(3S)-3-[(tert-butyldimethylsilyl)oxy]pyrrolidin-1-yl]-l-[3-(trifluoromethyi)phenyl] ethyl]-N-methylcarbamate (780 mg, 1.55 mmol, 1.00 equiv) in dichloromethane (5 mL) and trifluoroacetic acid (2 5 mL) was stirred for 2 h at 15*0. The solids were collected by filtration. The crude product was combined with the previous batches and purified by Prep-HPLC with the following conditions (l#-Pre-HPLC-0 16(Waters)): Column, Xbridge Prep CIS, 5um, 19*150mm; mobile phase, WATER WITH 0 05%

CFjCOOH and CHjCN (10.0% C¾CN up to 31.0% in 15 min, up to 100.0% in 2 min,down to 10.0% in 1 min); Detector, UV 254&220nm. This resulted in 675 mg of the titled compound as a brown solid.

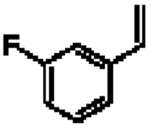
LJC-IVE : (ES, *m/z)*: 289 (M+1); ^{1}H-NMR (300 MHz, CHjOD) S8 J023 (IH, s), 7.913-7.938 (2H, m), 7.787-7.839 (IH, m), 4.8684.893 (IH, m), 4.5334.548 (IH, m), 4.0254.048 (IH, m), 3.320-3.*634* (4H, m), 2.630 (3H, s), 2.1*66*-2.288 (IH, m), 2 0 16-2.226 (1H, m).

Example 7-b

(3S)-1-*[(2*S>2-(3-fluorophenyl)-2-(methylamino)ethyl]pyrroMin-3-ol



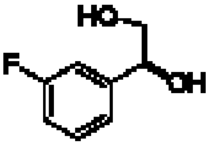
Step (i) Synthesis of l-fluoro-3-vinyIbenzene



In an inert atmosphere of nitrogen, n-BuLi(2.4M) (69 mL, 1.10 equiv) was added to a suspension of PPh_3CH_3Br (64.2 g, 179.83 mmol, 1.20 equiv) in tetrahydrofuran (300 mL) at 0°C. After stirring for 30 min, a solution of 3-nuorobensaldehyde (18.6 g, 149.86 mmol, 1DO ecjuiv) in tetrahydrofuran (50 mL) was added dropwise. The resulting solution was stirred for 1.0 h at room temperature in an oil bath. The reaction was then quenched by the addition of saturated aqueous NH+C1. The resulting solution was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified further by column chromatography using silica gel as stationary phase and petroleum ether as eluent to get the tilled compound 13 g (71%) as a cobrless liquid.

^{1}H-NMR($CDCl_3$, 400MHz): 7.32-7.29 (m, IH), 7 21-7.13 (m, 2H), 7 0 1-6.96 (m, 1H), 6.75-6.71 (q *J*=10.8¾ 17.6¾ 1H), 5.79 (**d,** ***J***=17.6H¾ IH), ***533*** (**d,** ***J***= 11.2H._, IH).

Step (ii) Synthesis of (S)-1-(3-fluorophenyl)ethane-1,2-diol



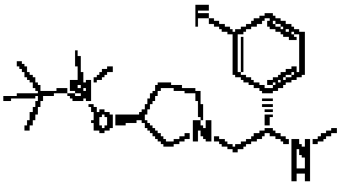
l-e11ienyi-3-:fluorobenzene (2.1 g, 17.19 mmol, 1.00 equiv) was added to a mixture of water (90 mL), t-BuGH (90 mL) and AD-Mix alpha (50 g) at 0°C. The resulting solution was stirred overnight at 0°C. The reaction was quenched with solid Na_2SO_3. After stirring for 1.0 lour at 25*C, the resulting solution was diluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography using silica gel as stationary phase and petroleum ether/EtOAc (1:1) as eluent to obtain 1.6 g (61%) of the titled compound as a white solid.

^{1}H-NMR. (DMSO-di, 300 MHz): 5 7.93-7.32 (m, 1H), 720-7.13 (m, 2H), 7.09-7.02 (m, 1H), 5.38 (d, *J*=4.5Hz, 1H), 4.76 (t, *J*=5.7Hz, 1H). 4.76 (q, *J*=5.7Hz, 9.9Hz, 1H). 3.45 (t, *J*=5.7Hz, 2H).

Step (iii) Synthesis ofiSJ^-iS-fluorophenylJo-iirane

In an inert atmosphere of nitrogen, TMS-Cl (12.58 g, 115.80 mmol, 5.00 equiv) and CH_3C(OC¾)$_3$ (13.85 g, 115.42 mmol, 5.00 equiv) were added to a solution of (13)-l-(3-fluorophenyl)ethane-l ^-diol (3.6 g, 23.05 mmol, 1.00 equiv) in dichloromethane (40 mL) at 0*C. The resulting solution was stirred for 2.0 h at 25*0. The solvent was evaporated in vacuo. The residue was dissolved in dry methanol (50 mL) and then potassium carbonate (15.9 g, 115.22 mmol, 5.00 equiv) was added. The resulting solution was stirred for lhr at 25*0. The reaction was quenched by addition of saturated NH+C1. The resulting solution was extracted with dichloromethane. The combined organic layers were washed with brine and water, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was applied onto a silica gel column eluting with ethyl acetate/petroleum ether (1:30). This resulted in 2.38 g (75%) of the titled compound as light yellow oil.

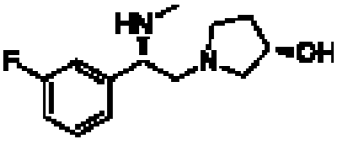
Step (iv) Synthesis of (S)-2-((S)-3-((tert-butyldimemyisn^ oxy)pyrrolidin-1-yl)-1-(3-iluorophenyl)-N-n¾thylethanamine



In an inert atmosphere of nitrogen, a solution of (23)-2-(3-fluorophenyi)oxirane (1.2 g, 3.69 mmoL 1.00 equiv) and (33)-3-[(tert-butyidimemylsnyl)oxy^ pyrrolidine (2.62 g, 13.01 mmol, 1.50 equiv)in ethanol (20 mL) was heated to reflux for 0.5 hr. The ethanol was removed in vacuo. The crude reaction mixture was then dissolved in 30 mL of EtjO. Triethy_amine (2.64 g, 26.14 mmoL 3.00 equiv) and MsCl (1.5 g, 13.04 mmoL 1.50 equiv) were added at 0*C and stirred for 30 min. Another portion of triethykmine (1.76 g, 17.42 mmol, 2.00 equiv) was added. The reaction was warmed to room temperature over 30 min and then CH_3NH_2 (30% aq.) (18 g, 174.19 mmoL 20.00 equiv) and water (1.0 mL) were added. The resulting solution was allowed to react for 5.0 h at 25*0. The organic kyers were separated and aqueous kyer was extracted with 2x100 mL of ether. The combined organic kyers were washed with 2x100 mL of sodium bicarbonate, 2x100 mL ofwater and 2x100 mL of brine, dried over anhydrous sodium sulfate and concentrated in vacuo .The residue was purified further by column chromatography using silica gel as stationary phase and dchbromethane/methanol (30:1) as eluent. This resulted in 1.9 g (62%) of the titkd compound as yellow oil.

LC-IvE : (ES, m¾ : 353 (M+1).

Step (v) Synthesis of (S)-1-((S)-2-(3-fluorophenyl)-2-(methyk mino)ethyl)pyrrolidin-3-ol

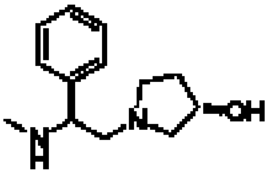


TBAF (1.0 M) (5.5 mL, 3.00 equiv) was added to a solution of [(13)-2-[(33)-3-[(tert-butyldimemylsnyl)oxy]pyrrolidin-1-yl]-1-(3-fluorophenyl)ethyl](methyl)amine (650 mg, 1.84 mmol, 1.00 equiv) in tetrahydrofuran (10 mL) at 0*0. The resulting solution was stirred for 1.0 h at room temperature . The solvent was removed in vacuo. The residue was purified by Fksh-HPLC to give 360 mg (82%) the product (TFA salt) as yellow oil.

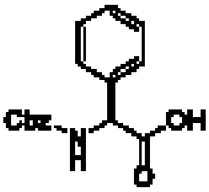
LC-MS: (ES, *mfs)*: 239 (M+l); ^{1}H-NMR (CDjOD, 300 MHz): 5 7.67-7.**60** (m, 1H), 7.46-7.32 (m, 3H), 4.74-4.69 (m, 1H), 4.534.50 (m, 1H), 3.96-3.82 (m, 2H), 3.59-3.49 (m, 1H). 3.42-3.36 (m, lH), 3.32-3.25 (m, 2H), 2.62 (s, 3H), 2.25-2.16 (m, 1¾ 2.06-2D 1 (m, lH).

Example 8-1}

(S)-1-((S)-2-(methylamino)-2-phenylethyl)pyrrolidin-3-ol



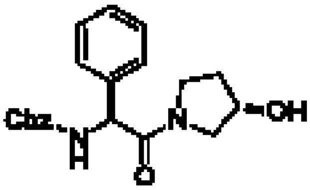
Step (i) Synthesis **of (SJ-2-(((benzylo-iy)carbonylJaminJJ -phenylacetic acid**



Into a 1000-niL round J-ottom flask, were placed a solution of sodium hydroxide (16 g, 400.00 mmol, 2.01 equiv) in water (400 ml_) and (S)-2-amino-2-phenylacetic acid (30 g, 198.68 mmol, 1.00 equiv). This was followed by the dropwise addition of Cbz-Cl (36 g, 210.53 mmol, 1.10 equiv) with stirring at 5*C. The resulting solution was stirred for 4 h at room temperature. The resulting solution was extracted with 2x200 ml of ethyl acetate. The pH value of the aqueous phase was adjusted to 3 with cone. hydrochloric acid. The resulting solids were collected by filtration. The solid was dried in an oven under reduced pressure. This resulted in 35 g (62%) of (3)-2-(benzyloxycarbonylamino)-2-phenyiacetic acid as a white solid.

MS (ESI) m/z 286 (M+l).

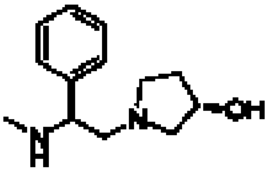
Step (ii) Synthesis of benzyl ((S)-2-((S)-3-hydroxypyrrolidin-l-jd)-2-oxo-l-phenylethyi)carbamate



Into a 500-mL round-bottom flask, was placed a solution of (Ξ)-2-(berizylo-iycarbonylamiMj-S-phenjlacetic acid (10 g, 35.09 mmol, 1.00 equiv) in dichloromethane (200 mL). This was foliowed by the addition of DCC (S.7 g, 42.23 mmoL, 1.20 equiv) at -10*C. To this was added HOBt (5.7 g, 42.22 mmol, 1.20 equiv) at -10*C. The resulting solution was stirred for 1 h at -10*C. To the mixture was added (S)-pyrrdidin-3-ol (3.66 g, 42.07 mmoL, 0.33 equiv) at -10*C. The resulting solution was alb wed to react with stirring, for an additional 1 h at -10*0. The resulting solution was allowed to react, with stirring, overnight at 10*C. The solids were filtered out. The filtrate was washed with 1x100 mL of sat.NaHCCb and 1x200 mL of brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with dichloromethane : CH30H (50:1-20:1). This resulted in 6.7 g of benzyl (S)-2-((S)-3-hydroxypyrrolidin-1-yl)-2-oxo-l-phenylethylcarbamate as a white foamy solid.

MS(ESI) nJz: 355 (MH).

Step (iii) Synthesis of(S)-l -((S)-2-(methykmino)-2-ptenyi^ thyl)pyrrolidin-3-ol

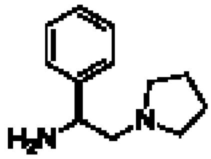


To a solution of LiAlH+ (4.8 g, 126.32 mmoL, 7.40 equiv) in tetrahydrofuran (100 mL) was added a solution of benzyl (S)-2-((S)-3-hydroxypy-ididin-l-yI)-2-oxo-l-phenylethyicarbamate (6 g, 16.95 mmoL, 1.00 equiv) in tetrahydrofuran (50 mL) at room temperature under N2. The resulting solution was heated under reflux overnight in an oil bath. The reaction was then quenched by the addition of 200 ML of water/ice. The solids were filtered out. The filtrate was extracted with 2x200 ML of ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residue was applied onto a A1203 column and eluted with EtOAc/Petroleum Etrher (5:1) and then DCM/MeGH (S0:1-20:1). This resulted in 3 g of (S)-l-((S)-2-(methylamino)-2-plranylethyi)pyrrohdin-3-ol as jellow oil.

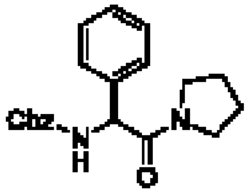
MS (ESI) m/z: 221 (MH).

Example 9-b

(S)-1-phenyl-2-(pyrrolidin-1-yl)ethanamine

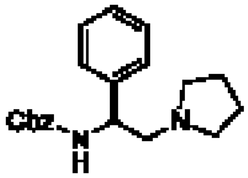


Step (i) Synthesis of (S)-benzyl (2-oxo-1-phenyl-2-(pyimlidin-l-yl)e1nyl)caA amate



Into a 500-mL round-bottom flask, was placed a solution of (S)-2-(benzylo-iycaibonyknumj^-phenyiaceuc acid (10 g, 35.09 mmol, 1.00 equiv) in dichloromethane (200 inL). This was foliowed by the additon of DCC (8.7 g) at -10*C. To this was added HOBt (5.7 g) at -10*C. The resulting solution was stirred for 1 h at -10*C. To the mixture was added pymkdine (3 g. 42.25 mmol, 120 equiv) at -lO^C. The resulting solution was allowed to react, with stirring, for an additional 1 h at -10°C. The resulting solution was alb wed to react, with stirring, overnight at 10°C. The solids were filtered out. The filtrate was washed with 1x100 mL of NaHCG3, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:5) and then dicHomn^ethane/methanol (50:1). This resulted in 10 g (S4% yield) of (S)-benzyl 2-oxo-1-phenyl-2-(pyrrolidin-1-yl)ethylcarbamate as oil. MS (ESI) m/z : 339 (M+l).

Step (ii) Synthesis of (S)-benzyl (1-phenyl-2-(pyrrolidin- 1-yl)ethyl)caibamate



To a solution of LiAlH+ (4.8 g, 126.32 mmol, 7.40 equiv) in tetrahydrofuran (100 mL) was added a solution of benzyl (S)-2-((S)-3-hydroxypyrrolidin-l-yi)-2-oxo-l-phenylethyicarbamate (6 g, 16.95 mmol, 1.00 equiv) in tetrahydrofuran (50 mL) at room temperature under N_2. The resulting solution was heated under reflux overnight in an oil bath. The reaction was then quenched by the addition of 200 ML of water/ice. The solids were filtered out. The filtrate was extracted with 2x200 ML of ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residue was applied onto a A1203 column and eluted with EtOAc/Petroleum Etrher (5:1) and then DCM/MeOH (80:1 -20 :1). This resulted in 3 g of (S)-l-((S)-2-(methylamino)-2-phenylethy-)pyrrolidin-3-ol as jellowoil. MS (ESI) m/z: 221 (MH).

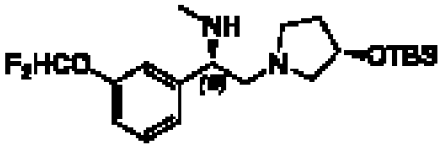
Step (iii) Synthesis of(S)-l -phenyl-2-(pyrrolidin-1-yl)ethanamine

Into a 100-mL round-bottom flask, was placed a solution of (2S)-2-antino-2-phenyi-l-(pynOlidin-1-yl)ethyl borinate (5 g, 22.92 mmol, 1.00 equiv) in aq. HC1 (50 mL). The resulting solution was stirred overnight at 70*0. The resulting solution was extracted with 2x50 mL of ethyl acetate and the aqueous layers combined. The pH value of the aq. solution was adjusted to 10 with sodium hydroxide. The resulting solution was extracted with 3x50 mL of ethyl acetate. The combined organic layers were washed with 100 ml of brine, dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 3 g (69% yield) of (1S)-1 -phenyl-2 -(pyrrolidin-1 -yl)ethan-l -amine as yellow oil.

¾ NMR (DMSO-d_6, 400 MHz): 5 7.46-7.35 (m, 2H), 7.30-7.24 (m, 2H), 7.21 -7.18 (m, 1H). 3.98-3 37 (m, 1H), 2.58-2.45 (m, 3H), 2.42-2.40 (m, 2H), 2.29 (dd. ***J* = 4.6** & 11.5 Hz, 1H), 2.31-2 27 (m, 1H), 2.00 (bs, 2H), 1.77-1 59 (m, 4H); MS (ES): m/z 191 .4 (M+l).

Example 10-b

(S)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-1-(3-(difluoromethoxy)phenyl)-N-methylethanamine



Step (i). Synthesis of 1-(difluoromethoxy)-3-iodobenzene

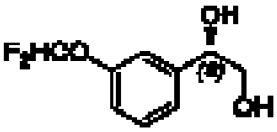
Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 3-iDdophenol (22 g, 100.00 mmol, 1.00

equiv) inN,N-di™thylformamide (100 mL). Then Cs_2CO_3 *(65.2* g, 200.1 1 mmol, 2.00 equiv) and ClFiCCCONa (30.4 g, 200.00 mmol, 2.00 equiv) were added at room temperature. The resulting solution was stirred for 5.0 h at 100*C. The solids were filtered out and washed with 2x200 inL ofEtOAc . The organic lasers were combinedand washed with *6x* 150 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with petroleum ether. This resulted in 15.5 g (57%) of 1-(difluoromelhDxyJ-S-iodobensene as colorless oil.

Step (ii) Synthesis of 1-(difluoromethoxy)-3-vinylbenzene

Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of potassium vm^trifluoroborate (3.17 g, *23.61* mmol, 1.10 equiv) in tetrahydrofuraWHiO (9/1) (60 mL), PhjP (338 mg, 0.06 equiv), PdCli (75 mg, 0.02 equiv), Cs_2CO_3 (21 g, 64.45 mmol, 3.00 equiv). To this was added a solution of l-(difluoromethoxy)-3-iodoben3ene (5.SI g, 21.52 mmol, 1.00 equiv) in tetrahydrofurarIH$_2$O(9/1) (5 mL). The resulting solution was stirred for 24 h at 85°C. The reaction mixture was cooled and the solids were filtered out. The filtrate was extracted with 2x200 ml of petroleum ether and the organic layers combined and dried over ar-hydtous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with petroleum ether. This resulted in 3.1 g (85%) of 1-(difluoromethoxy)-3-ethenylbenzene as yellow oil.

Step (iii) Synthesis of(S)-1 -(3-(difluoromethoxy)phenyl)ethane-1,2-diol

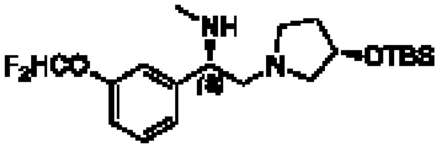


Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of AD-Mix alpha (25.5 g) in tBuOH/H$_2$0(l :l) (148 mL). This was followed by the addition of a solution of l-(difluoromethoxy)-3-ethenylbenzene (3.1 g, 18.22 mmol, 1.00 equiv) in tBuOH/H$_2$0 (1:1) (10 mL) dropwise with stirring at 0*C. The resulting solution was stirred for 2-3 h at room temperature. The NajS0$_3$ was added at stirred for 1 h at room temperature. The resulting solution was extracted with 2x200 mL of ethyl acetate and the organic layers combined The resulting mixture was washed with 2x200 mL of brine. The mixture was dried over sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with DCM/MeOH (200:1 -150/1). This resulted in 3.05 g (82%) of (1Ξ)-1-[3-(difluoromethoxy)phenyi] ethane- 1,2-diol as yellow oil.

Step (iv) Synthesis of (S)-2-(3-(d fluoromethoxy)phenyl)oxirane

Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of (1S)-1-[3-(difluoromethoxyjphenyl] ethane-1,2-diol (3.05 g, 14.94 mmol, 1.00 equiv) in dichloromethane (50 mL), $CH_3C(OCH_3)_3$ (9.0 g, 75.00 mmol, 5.02 equiv). This was followed by the addition of TMSCl (8.2 g, 75.48 mmol, 5.05 equiv) dropwise with stirring at 0°C. After stirred for 5 h at room temperature, the mixture was concentrated. The residue was diluted in 50 mL of methanol. To this was added potassium carbonate (10.3 g, 74.52 mmol, 4.99 equiv) at 0°C. The resulting solution was stirred for 0.5 h at room temperature. The solids were filtrate out. The filtrate was concentrated under vacuum. The resulting solution was extracted with dichbromethane and the organic layers combined and dried over sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel colunm and eluted with ethyl acetate/petroleum ether (1:70-1:50). This resulted in 1.94 g (70%) of (2S)-2-P-(difuoron¾thoxy)phenyl]oxirane as yellow oil.

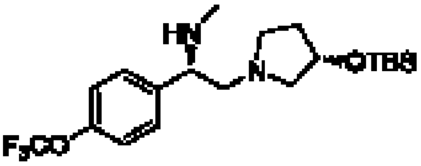
Step (v). Synthesis of (S)-2-((S)-3-((tert-butyldimemyisnyl)oxy)pyrrohdm -1-yl)-1-(3-(difluoromethoxy) phenyl) -N-methylethanamine



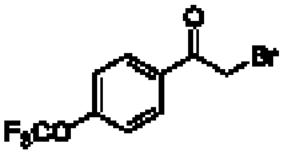
Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of (2S)-2-P-(difluorome1hDxy)phenyl]oxirane (390 mg, 2.10 mmol, 1.00 equiv) in ethanol (10 mL). This was followed by the addition of (3S)-3-[(tert-butyldir[Wthyknyi)oxy]pyrrohdirie (625 mg, 3.10 mmol, 1.50 equiv). The resulting solution was heated to reflux for 2D h and then the solution was concentrated under vacuum. The residue was diluted in 10 mL of ether. To this was added triethykmine (629 mg, 6.21mmol, 3.00 equiv). Then MsCl (358 mg, 3.11mmol, 1.50 equiv) was added dropwise at 0*C and stirred for 30 min. Then triemykmine (418 mg, 4.14 mmol, 2.00 equiv) and CH_3NH_2 (4.3 g, 41.4mmol, 20equiv, 30%) was added. The resulting solution was stirred for 24 h at 25*C. The reaction was then quenched by the addition of 20 mL of water. The resulting solution was extracted with ethyl acetate and the organic layers combined. The resulting mixture was washed with aqueous sodium bicarbonate, brine, dried over sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with DCM/MeOH (70:1-50:1) to obtain the title compound as yellow oil.

Example 11-b

(S)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-N-methyl-1-(4-(trifluoromethoxy)phenyl)ethanamine

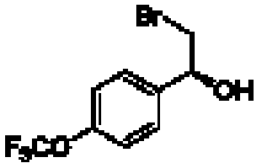


Step (i) Synthesis of 2-bromo-l ^4-(trifluorome1hoxy)phenyl)ethanone



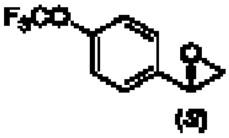
Br_2 (15.2 g, 95.11 mmol, 1.20 equiv) was added dropwise to a solution of l-[4-(trifluorometluixy)phenyl]ethan-l-one (15 g, 73.48 mmol, 1.00 equiv) in ether (200 mL). The resulting solution was stirred for 5 hat room temperature. The reaction was then quenched by the addition of aqueous sodium thiosulfate pentahydrate. The resulting aqueous solution was extracted with 3x100 mL of ethyl acetate. The organic layers was combined and dried over Na2S04 ard concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:70). This resulted in 11.4 g (55%) of 2-bromo-l-[4-(trifluoromethDxy)phenyl]ethan-l-one as a white solid

Step (ii) Synthesis of (S)-2-bromo-1-(4^trifluoromethoxy)phenyl)ethanol



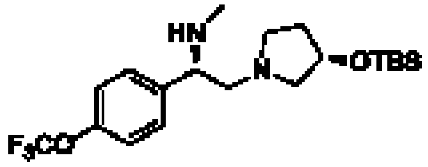
Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed (S)-Me-CBS (587 mg, 2.12 mmol, 0.10 equiv), a solution of N,N-diethylaniline borane (3.5 g, 21.44 mmol, 1.00 equiv) in MTBE (20 mL). The mixture was followed by the addition of a solution of 2-bromo-l -[4-(trifluorome†hoxy)phenyi]ethan-1-one *(6* g, 21.20 mmol, 1.00 equiv) in MΓBE (60 mL) dropwise with stirring at 40°C in 3 hr. After addition, continued to stirring 40*C for 1 hr. The resulting solution was stirred for 14 h at room temperature. The reaction was quenched by the addition of 10ml of methanol below 20*C and 1hen stirred for 30 min at room temperature. The resulting solution was added 60 ml of aqueous HC1 (2.5H) below 20*C and stirred for 30 min at room temperature. The resuiting aqueous solution was extracted with 3x100 mL of ethyl acetate. The organic layers were combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:100). This resultsd in 5.5 g (91%) of (IS) -2-bromo-l -[4-(trifluoromethoxy)phenyIJethan-l -ol as a white solid.

Step (iii) Synthesis of (S)-2-(4-(ti fluoromethoxy)phenyl)oxirane



Potassium carbonate (**5.2** g, 37.62 mmol, **2.00** equiv) was added to a solution of **(1**S)-**2JDromo**-l-[4-(trifluoromethoxy) phenyl]ethan-l-ol (5.4 g, 18.94 mmol, **1.00** equiv) in methanol **(100** mL) in portions at **0**°C. The resulting solution was stirred for **20** min at **0**°C. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was dissolved in EA. The resulting mixture was washed with **2x100** mL of bine. The organic layer was concentrated under vacuum. This resulted in 2**.6** g (67%) of (2S**)-2**-[4-(tritluoromethoxy)phenyl]oxirarLe as a white solid.

Step (iv) Synthesis of (S**)-2**-((S)-3-((†ert-butyldime†hylsny^^oxy)pyrrolidin-1-yl)-N-methyl-1-(4-(trifluoro methoxy)phe nyl)ethanamine



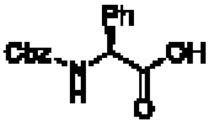
Into 250ml round-bottom flash, a solution of (2S)-2-[4-(trifluoromethoxy)phenyl]oxirane (2.5 g, 12.25 mmol, 1.00 equiv) and (3S)-3-[(tert-butyldimethylsilyl)oxy]pyrrolidine (3.9 g, 19.37 mmol, 1.50 equiv) in ethanol (100 mL) was added. The resulting solution was allowed to react with stirring for overnight at reflux in oil bath. Then the mixture was concentrated and the residue was purified by silica-gel (DCM/MeOH=10/1) to afforded 4.1 g of (S)-2-((S)-3-(tert-butyldimethykflylox^pyiTOlidin-l-yl)-l-(4-(trifluoron¾thoxy)phenyl)ethanol which was dissolved in DCM (150 ml). triethykmine (5.05 g, 49.91 mmol, 2.00 equiv) was added. This resulting solution was followed by the addition of a solution of IvlsCl (2.28 g, 20.00 mmol, 5 DO equiv) in dichloromethane (50 mL) dropwise with stirring at 0°C .Then this resulting solution was aliowed to react with stimng for ***6*** h at room temperature and added 40% aqueous CH_3NH_2 (3.1 g) .The resulting solution was stirred for 14 h at room temperature. The resulting solution was extracted with 2x30 mL. of ethyl acetate. The organic layers were combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (10:1). This resulted in 2.4 g (47%) of [(1S)-2-[(33)-3-[(tert-butyldimetnylsilyi)oxy]pyrrolidin-1-y_]-1-[4-(tnQuorometlMxy)phenyI]ethyl](methyl) amine as yellow oil.

LC-IvE (ES, m/s): 419 (M+1).

Example 12-b

(S)-2-((S)-3-methoxypyrrolidin-1-yl)-N-methyl-1-phenylethanamine

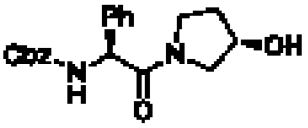
Step (i) Synthesis of (S)-2-(((benzyloxy)caibonyl)amiro)-2-phenylacetic acid



Into a solution of (2S)-2-amirLo-2-phenylacetic acid (10 g, 66.15 mmol, 1.00 equiv) in water(200 mL) was added aqueous sodium hydroxide (5.3 g, 132.50 mmol, 2.00 equiv) in water (100ml). This followed by the addition of CbzCl (12.4 g, *12.69* mmol, 1.10 equiv) at 5°C dropwise. The resulting solution was stirred for 3 h at room temperature. The resulting solution was extracted with ethyl acetate and the aqueous layers were combined. The pH value was adjusted to 3 with aqueous HC1 (1 mol/L). The resulting aqueous solution was extracted with DCMMeOH(10/l) . The organic layers were combined and dried over anhydrous sodium sulfate, concentrated under vacuum. This resulted in 1*6.2* g(crude) (86%) of(2S)-2-[[(benzyloxy)carbonyi]ardno]-2-phenykcetic acid as a white solid.

LC-IvE (ES, m/z): 284 (M-l)$^{-}$

Step (ii) Synthesis of benzyl ((S)-2-((S)-3-hydroxypyrrolidin-l-yl)-2-oxo-l-phenylethyl)carbamate



Into a solution of (2S)-2-[[(benzyloxy)carbonylJamirD] -2-phenylacetic acid (5.7 g, 19.98 mmol, 1.00 equiv) in dichloromethane (100 mL) was acUed DCC (4.94 g, 23.94 mmol, 1.20 equiv). This was followed by the addition of HOBt (3.24 g, 23.98 mmol, 1.20 equiv). The resulting solution was stirred for 30 min at room temperature. To this was added (3S)-pyjTolidin-3-ol (1.91 g, 21.92 mmol, 1.10 equiv) at 0*0. The resulting solution was stirred overnight at room temperature. The resulting mixture was washed with 2x50mL of aqueous sat. sodium bicarbonate. The organic layers were separated and dried over anhydrous sodium sulfate , concentrated under vacuum. The residue was applied onto a silica gel column with dicluoromethane/methanol (50:1). This resulted in 4.2 g (59%) of benzyl N-[(1S)-2-[(3S)-3-hydroxypyrrolidin- 1-ylj -2-oxo-l -phenylethylj carbamate as yellow oil.

LC-IvE (ES, m/z): 355 (M+l).

Step (iii) Synthesis of benzyl ((S)-2-((S)-3-n¾thoxypyrrolidin-l-yl)-2-oxo-l-phenylethyl)(methyl)carbamate

Into a solution of benzyl N-[(1 S)-2-[(3S)-3 -hydroxypyrdidin-l -yl] -2-oxo-l -phenylethyl] carbamate (1.1 g, 3.10 mmol, 1.00 equiv) in tetrahydrofuran (40 mL) was added sodium hydride (250 mg, *6.25* mmol, 2.01 equiv) portionwise at 0°C in ice bath. The mixture was stirred for 10 min at room temperature . To this was added iodomethane (1.3 g, 9.15 mmol, 2.95 equiv) dropwise with stirring. The resulting solution was stirred for 2 h at 30°C. The reaction was then quenched by the addition of water/ice. The resulting aqueous solution was extracted with of ethyl acetate . The organic layers were combined and dried over anhydrous sodium sulfate, concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). This resulted in 730 mg (61%) of benzyl N-[(1S)-2-[(33)-3-memoxypynOhdin-l-yI]-2-oxo-l -phenylethyl]-N-methylcarbamate as colorless oil.

LJC-IVE (ES, m/z): 383 (M+1)

Step (iv) Synthesis of (S)4-((S)-3-memoxypyrrolidin-l -yl)-2-(methylamino)-2-phenylethanone

Into a solution of benzyl N-[(lS)-2-[(3S)-3-n¾thoxypyrrdidin-l -yl]-2-oxo-l-phenylethyi]-N-methyicarbamate (580 mg, 1.52 mmol, 1.00 equiv) in methanol (20 mL) was added Palladium on carbon (290 mg, 10%) under nitrogen atmosphere. The resulting solution was hydrogerated overnight at 25*0. After the completion of the reaction, the reaction mixture was filtered. The filtrate was concentrated to dryness. This resulted in 300 mg (80%) of (2S)-l-[(3S)-3-n¾thoxypyrrdidin-l -yl]-2-(n¾thylamino)-2-phenylethan-l-one as a yellow solid.

LJC-IVE (ES, m/z): 249 (M+l).

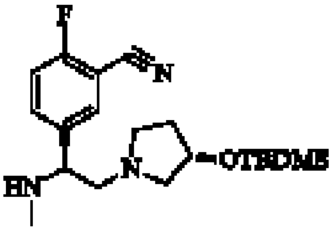
Step (v) Synthesis of (S)-2-((S)-3-methoxypyrrolidin-1-yl)-N-methyl-1-p]¾nyk thanamine

Into a solution of (2S)-l-[(3S)-3-memoxypyrrolidm4 -y^-2-(methylamino)-2-phenylethan-l-one (300 mg, 1.21 mmol, 1.00 equiv) in tetrahydrofuran (25 mL) was added LiAlH+ (184 mg, 4.85 mmol, 4.01 equiv) with stirring at 0°C in ice bath. The resulting solution was stirred for 3 h at room temperature. The reaction was then quenched by the careful addition of water/ice at 0°C. The resulting aqueous solution was extracted with of ethyl acetate. The organic layers were combined and dried over anhydrous sodium sulfate, concentrated under vacuum. This resulted in 160 mg (57%) of [(1Ξ)-2-[(3Ξ)-3-metlioiypyrrolidin-l-yl]-1-phenylethyl](memyl)amine as yellow oil.

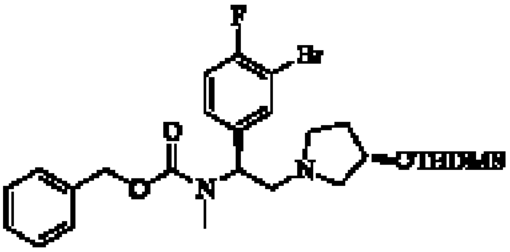
LC-IvE (ES, m/z): 235 (M+l).

Example 13-1}

5-((£j)-2-((¾)-3-((tert-buiyidimethylsily])oxy)pyTrf lidin-1-y]>-l-(methylamino)ethyl)-2-fluorobenzonitrile



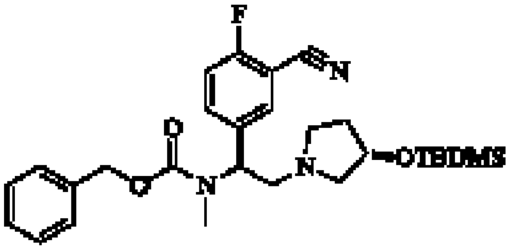
Step (i) Synthesis of benzyl ((S)-l-(3-bromo-4- fluorophenyl) -2-((S)-3-((tert-butyldimethylsilyl) oxy) pyiTolidin-l-yl)emyl)(n¾th^)carbamate



Into a 100-mL 3-necked round-bottom flask, was placed a solution of [(1Ξ)-1-(3-bromo-4- fluorophenyl) -2-[(3S)-3- [(tert-butyldimethylsilyl)oxy]pyrrohdin- 1-yl]ethyl](meth^)amine (2.4 g, ***5.56*** mmoL 1.00 equiv), obtained by following a suitable procedure(s) similar to that mentioned in example 8 by using appropriate starting materials; in EtOAc/H_2O (40/8 mL). This was foliowed by the addition of potassium caibonate (1 g, 7.24 mmoL 1.30 equiv) in portions at 0°C. Then Cbz-Cl (1.14 g, ***6***.68 mmoL 1.20 equiv) was added dropwise with stirring at 0°C. The resulting solution was stirred for 3 h at room temperature. The resulting solution was diluted with 10 mL of water. The resulting aqueous solution was extracted with 3x5 mL of ethyl acetate and the organic layers were combined. The organic layers were washed with 2x15 mL of brine and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a sihca gel column with ethji acetate/petroleum ether (1:10-1:5). This resulted in 2.5 g ***{19%)*** of benzyl N-[(lS)-l-(3-bromo-4- fluorophenyl) -2-[(3S)-3- [(tert-butyldimethylsilyl)oxy] pyrrohdin- 1-yl]ethylj-N-methylcarbamate as yellow oil.

LJC-IVE (ES , m/z): *565, 567* (M +l).

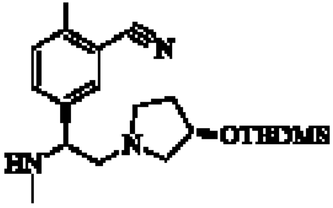
Step (ii) Synthesis of benzyl ((S)-2-((S)-3-((tert-butyldimethyisn^^ oxy) pyrrolidin-1-yl)-1-(3-cydno-4-fluoro phenyl)ethyl)(me thyOcarbamate



Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of benzyl N-[(1Ξ)-1-(3-bromo-4- fluorophenyl) -2-[(3S)-3-[(tertJDutyldimethylsnyl)oxy]py™ lidin-1-yl] ethyl] -N-methylcarbamate (500 mg, 0.88 mmol, 1.00 equiv) in N,N-dimethy,fonnamide (15 mL).Then Zr(CN)$_2$ (207 mg) was added. Following **Fd(PPh3)+** (1.02 g, 0.88 mmol, 0.98 equiv) was added The resulting solution was stirred overnight at 95*C in an oil bath. The reaction was then quenched by the addition of 20 mL of aqueous saturated FeSO+. The resulting solids were filtered out. The filtrate was extracted with 3x10 mL of ethyl acetate and the organic lasers were combined. The organic layers were washed with 1x20 mL of brine and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10-1 :8). This resulted in 350 mg (77%) ofbenzyl N-[(l S)-2-[(3S)-3-[(tert-butyldimemylsilyl)oxy]pynOhdm-l-yI] -1-(3-cyano^l-fluorophenyl)ethyI] -N-methylcarbamate as yellow oil.

LC-IvE (ES, m/z): 512 (IvI+l).

Step (in) Synthesis of 5-((S)-2-((S)-3-((tert-bu1yidiri¾thylsi^ yl)oxy) pyrrolidin-1-yl)-1-(methyl amino) ethyl) -2-fluorobenzonitrile



Into a 25-mL round-bottom flask, was placed a solution of benzyl N-[2-[(3S)-3-[(tert-butyldimethylsilyl)oxy] pyrrolidin-1-yl] - 1-(3-cyano-4-fluorophenyl)ethyI] -N-methylcarbamate

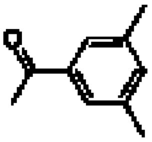
(ISO mg, 0.35 mmol, 1.00 equiv) in ethyl acetate (15 mL) . This was followed by addition of Palladium on caibon (6O mg, 10%) .The resulting solution was hydrogenated at room temperature. After the completion of the reaction, the reaction mixture was filtered The filtrate was concentrated under vacuum. The residue was applied onto Prep-TLC by DCM: IvfeOH (10:1). This resulted in 100 mg (75%) of 5-[2-[(3S)-3-[(tert-butyldimethylsuyljoxylpym lidin-1 -yl]-1-(methylamino)ethyl]-2-fluorobenzonitrile as yellow oil.

LC-IvE (F_S, m/z): 378 (M+l).

Example 14-b

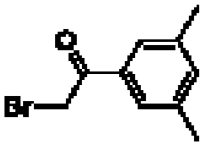
(S)-2-((S)-3-((te rt-butyldijnethylsilyl)oxy)pyTiolidin-1-yl)-1-(3,5-dimfithy]phenyl)-N-methylethanajnine

Step (i) Synthesis of 1-(3,5-dimethylphenyl)ethanone



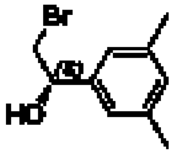
Into a 250-mL 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed Iv% (3.2 g, 1.20 equiv) in teti^ydrofiiran (100 ml_). Then 2mL of l-bromo-3,5-dimethyibenzene and three grains of iodine were added When the reaction was initiated, the rest of l-bromo-3,5-dimethylbenaene (20 g, 108.07 mmol, 1.00 equiv) was added. The resulting solution was stirred for 2 h at 80*C and then cooled to 25*C. To the solution, N-methoxy-N-methylacetainide (16.4 g, 159.04 mmol, 1.50 equiv) was added and the resulting solution was stirred for 2 h at 80*0. The reaction was then quenched by the addition of 50 mL of NH+C1 aqueous and the solution was extracted with ethyl acetate (3xl 20mL). The combined oi^anic layers were washed with brine (3x100 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to give of 15.18 g (95%) 1-(3,5-dimethyl phenyl) ethan-1 -one as yellow oil.

Step (ii) Synthesis of 2-bromo-1-(3,5-dimethylphenyl)ethanone



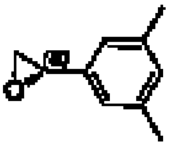
Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 1-(3,5-dimethylphenyl)ethan-l-one (13.04 g, 87.99 mmol, 1.00 equiv) and conc. H_2SG_4 aqueous (4.40 g) in acetic acid (50 ml). This was followed by the addition of NBS (17.23 g, 96 2 1 mmol, 1.10 equiv), in **pDitions** at 0°C in 30 min The resulting solution was stirred for 3 h at room temperature and quenched by the addition of 50 mL of HH+C1 aqueous. The solution was extracted with ethyl acetate (3x50 mL). The combined organic layers were and washed with aq. $Na_2S_2O_3$ (3x50 mL). aq. $NaHC0_3$ (3x50mL) and brine (3x50 mL). The organic solution was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethylacetate : petroleum ether (1:80) to give of 11.3 g (57%) 2-bromo-l-(3,5-dimethyl phenyl) ethan-1 -one as a yellow solid.

Step (iii) Synthesis of (S)-243romo-l-(3,5-dimethylphenyl)ethanol



Into a 50-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 1-imthyi-S^-diphenyl-hexahydropyrrolo[1,2-c][i,3,2]oxazaborole (2.44 g, 8.80 mmol, 1.00 equiv) and N,N-diethylaniline borane (1.44 g, 8.83 mmol, 1.00 equiv) in IvΓΓBE (6 mL). This was followed by the addition of a solution of 2-bromo-l -(3,5-dimethyl phenyl) ethan-1 -one (2.00 g, 8.81 mmol, 1.00 equiv) in **IvITBE** *(6* mL) dropwise with stirring at 40*0 in 3 hr. The resulting solution was stirred for 1 h at 40*0 and cooled down to 25 °C. The reaction was then quenched by the addition of 10 mL of methanol and the pH value of the solution was adjusted to 3-4 with hydrogen chloride aqueous (1 mol/L). The resulting solution was extracted with ethyl acetate (3x10 mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to give of 2.15 g (crude) (1Ξ)-2-bromo-l-(3,5-din¾thylphenyl)ethan-l-ol as a yellow crystal.

Step (iv) Synthesis of (2S)-2-(3,5-dimethylphe nyljoxirane



Into a 50-mL round-bottom flask, was placed a solution of (l S)-2-bromo-l-(3,5-din¾thylptenyi)ethan-l -ol (1.18 g, 5.15 mmol, 1.00 equiv) in methanol (10 mL). To the solution was added potassium carbonate (1.42 g, 1027 mmol, 1.99 equiv). The mixture was stirred for 1-2 h at 0*C .The solids were filtered out and the resulting mixture concentrated under vacuum. The residue was dissolved in lOmL of ethyl acetate. The solution was washed with brine (3x10 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to give of 0.748 g (98%) of (2S)-2-(3,5-dimeth^phen^i)oxirane as yellow oil.

Step (v) Synthesis of (S)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-1-(3,5-dimethylphenyl) ethanol

Into a 50-mL round-bottom flask, was placed a solution of (2Ξ)-2-(3,5-dimethylphenyl) oxirane (750 mg, 5.06 mmol, 1.00 equiv) and (3S)-3-[(tert-butyidimemylsnyl)oxy3pyrrohdme (1.15 g, 5.71 mmol, 1.13 equiv) in ethanol (10 mL). The solution was stirred overnight at 80*0. The resulting mixture was concentrated under vacuum. The residue was dissolved in 40 mL of dichloromethare . The organic layer was washed with brine (3x10 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with dicMoroniethane/methanol (100:1) to give of 0.99 g (56%) (1S)-2-[(3Ξ)-3-[(tert-butyldimethylsilyl)oxy] pyrrolidin-1 -yi]-1-(3,5-dimethylp]¾nyi)ethan-l -ol as yellow oil.

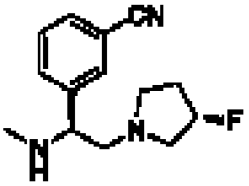
Step (vi) Synthesis of (S)-2-((3)-3-((tert-butyldimethylsilyl)oxy) pyrrolidin-1 -yl)-l -(3,5-dimethylphenyl) -N-methylethanamine

Into a 50-mL round-bottom flask, was placed a solution of (1Ξ)-2-[(3Ξ)-3-[(tert-butyldimethylsilyl)oxy]pyrrolidin-1-yl]-1-(3,5-dimethylphenyl)ethan-1-ol (990 mg, 2.83

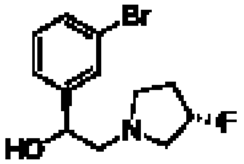
mmol, 1.00 equiv) and TEA (1.43 g, 14.13 rnmoL, 4.99 equiv) in dicMoromethane (15 niL). To the solution was added MsCl (0.97 g) and the mixture was stirred for 0.5 hour while the temperature was maintained at 0°C. Then to the solution was added 30% C¾ NH_3 aqueous (5.86 g. 56.7 mmol, 20 equiv) and the mixture was stirred overnight at room temperature. The resulting solution was extracted with dichloromethane (3x15 ml_). The combined organic layers were washed with brine (3x15 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with dicMoromethane/methanol (100:1) to give of 0.68 g *{66%)* [(lS)-2-[(3S)-3-[(tert-butyldir^^^ silyl)oxy]pyrrolidin-1-yl]-1^3,5^methylp]¾nyl)emyl](meftyl)amine as yellow oil.
LC-IvE (ES, m/z): 363 3 (M+l).

Example 15-b

3-((S)-2-((S)-3-fluoropyrrolidin-1-yl)-1-(methylamino)ethyl)benzonitrile

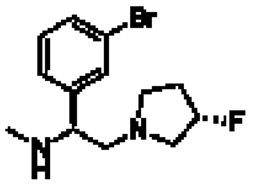


Step (i) Synthesis of(S)-l -(3-biromophenyl)-2-((S)-3-fluoropy-rd idin-l -yLjethanol



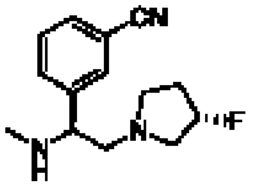
Into a 100 mL round-bottom flask, was placed a solution of (3S)-3-fluoropyrrolidine hydrochloride (2.12 g, 16.88 rnmoL, 1.00 equiv) in ethanol (25 niL). Then sodium carbonate (1.78 g, 16.79 mmol, 1.00 equiv) was added. The resulting solution was stirred at room temperature for 30 min and filtered. The filtrate was added (2S)-2-(3-bromophenyl)oxiiane (3.35 g. 16.83 mmol, 1.00 equiv). The resulting solution was stirred at refluxing for 16 h in oil bath and concentrated to dryness. The residue was purified by column chromatography to get 2.93 g (60%) of the title compound as tight yellow solid.

Step (ii) Synthesis of (S)-1-(3-bromophe nyi)-2-((S)-3-fluoropyrrolidin- 1-yl)-N-methylethanamine



Into a 100 ml_ round-bottom flask, was placed a solution of (S)-l -^3-bromophenyl)-2-((3)-3-fluoropyirolidin-l -yl)ethanol (1.25 g, 4.34 mmol, 1.00 equiv) in dicHoromethane (30 mL).Then TEA (1.31 g, 13.02 mmol, 3.00 equiv) was added Following MsCl (990 mg, 8.68 mmol, 2.00 equiv) was added dropwise at 0*C. The resulting solution was stirred for 30 min at 0*C. Then another part of TEA (0.88 g, 8.713 mmol, 2.00 equiv) was added. The resulting solution was stirred for 4 h at room temperature. Following CH_3NHj (aq) (4.48 g, 43.35 mmol, 9.99 equiv, 30%) was added dropwise . The resulting solution was stirred for 16 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate: petroleum ether (1:2). This resulted in 1.1 g (84%) of the title compound as light yellow oil.

Step (iii) Synthesis of 3-((S)-2^(S)-3-fluoropynolidm4-yl)4 -(methylamino)ethyl) benzonitrile

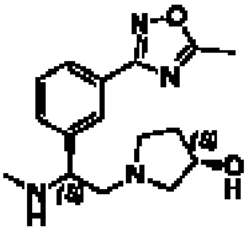


Into a 40-mL sealed tube, was placed a solution of [(l S)-l -(3-bromophenyl)-2-[(3S)-3-fluorop^rrohdin4-y¾eth^(n¾th^)amine obtained by foliowing a procedure similar to that in Example 8, (1.0 g, 3.32 mmol, 1.00 equiv) in N,N-dimeftylformamide (20 niL).Then Zn(CN)2 (387 mg, 3 3 1 mmol, 1.00 equiv) and Pd(PPh3)4 (382 mg, 0.33 mmol, 0.10 equiv) were added under nitrogen atmosphere. The resulting solution was stirred for 16 h at 100*C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 570 mg *(69%)* of the titled compound as an off-white solid.

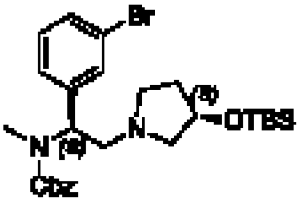
LJC-IVE (ES, m/z): 248 (M+l).

Example 16-b

(S)-1-((¾-2-(3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-2-(methylajnino)ethyl)pyrrolidi iv 3-ol



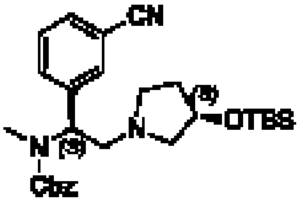
Step (i) Synthesis of benzyl ((S)-l -(3JDromophenyl)-2-((S)-3-((tert-butyldimemylsnyl)oxy) pyrrol din-1-yl)ethyl)(methyl)carbamate



Into a 500-mL 3-necked round-bottom flask, was placed a solution of [(1Ξ)-1-(3-bromophenyl) -2-[(3Ξ)-3-[(tert-buryldmethylsilyijo-iy] pyrrolidin-1-yl]ethylj (memyl)amine *(6.6* g, 15.96 mmol, 1.00 equiv) in ethyl acetate (200 ml_). To the mixture was added a solution of ptassium carbonate (2.8 g, 20.26 mmoL, 1.29 ecjuiv) in water (40 mL). This was folbwed by the addition of CbzCl (3.3 g, 19.34 mmol, 1.21 ecjuiv) dropwise with stirring at 0°C in 30 min. The resulting solution was stirred for 4 h at room temperature. The organic layer was separated and concentrated. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:50). This resuited in § g (92%) of benzyl N-[(1S)-1-(3-bromophenyl)-2- [(3Ξ)-3-[(tert-buryldimemylsilyijo-iy] pyrrolidin- 1-yl]ethylj-N-methylcarbamate as green oil.

LC-IvE (ES, *m/z*): 547 (M+l).

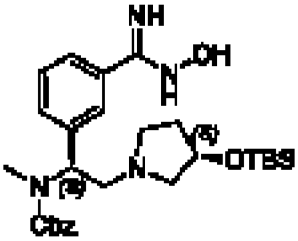
Step (ii) Synthesis of benzyl ((S)-2-((S)-3-((tert-butyldimethyisilyl)oxy)pyrrolidin-1-yl)-1-(3-cyanophenyl) ethyl)(methyl)carbamate



Into a 250-mL 3-necked round-bottom flask, was placed a solution of benzyl N-[(1S)-1-(3-bromophenyl)-2- [(3S)-3-[(tert-butyldimemylsilyijo-iy] pyrrolidin- 1-ylj ethylj-N-methylcarbamate (6 g, 10.96 mmol, 1.00 equiv) in N,N-dimethylformamide (1 10 mL). To the solution were added Zn(CN)2 (1.29 g, 1.00 equiv) and Pd(PPl¾)+ (1.27 g, 1.10 mmol, 0.10 equiv) under nitrogen gas. The resulting solution was stirred for 12 hours at S0°C in an oil bath. 100mL of water was added to the mixture. The resulting solution was extracted with dichloro methane (2xl 00mL) and the organic layers combined. The resulting mixture was washed with water (2x100 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:10). This resulted in 4.5 g (83%) of benzyl N-[(1 3)-2-[(3S)-3-[(tert^utyldirnethylsilyljoxy] pyrrokdin-1 -ylj -1-(3-cyanophe nyl)ethylj -N-methylcarbamate as cobrless oil.

LJC-IVE (ES, m/z): 494 (M+l)

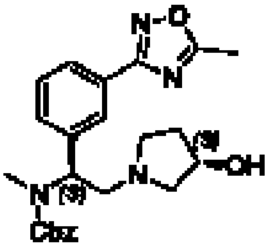
Step (iii) Synthesis of benzyl ((S)-2-((S)-3-((tert-butyldimemylsnyl)oxy)pyrrohdm -1-yl)-1-(3-(N-hydroxycarbarrimidoyl) phe nyl)ethyl)(methyl)carbamate



Into a 100-mL round-bottom flask, was placed a solution of benzyl N-[(l S)-2-[(3S)-3-[(tertJ3utyldirnemylsnyl)oxy]pyrrohdm -1-yl] -1-(3-cyanophe nyl)ethylj -N-methylcarbamate (2.9 g, 5.87 mmol, 1.00 equiv) in ethanol (50 mL). To the solution were added NHiOH.HCl (750 mg, 14.71 mmol, 2.50 equiv) and triethylamine (1.18 g, 11.66 mmol, 2.00 equiv). The resulting solution was stirred for 16 hours at 80°C. The resulting mixture was cooled to room temperature and concentrated under vacuum. This resulted in 4.8 g of benzyl N-[(1S)-2-[(33)-3-[(tert-butyldimemylsilyl)oxy]pyrrohdm-l-yI] -1-[3-(N-hydroxycarbanumidoyl)plienyi] ethyl] -N-methylcarbamate as a white crude solid.

LC-IvE (E3, m/z): 547 (M+l)

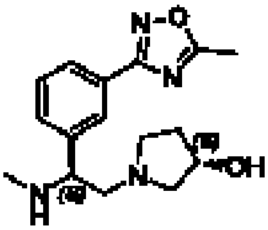
Step (iv) Synthesis of benzyl ((S)-2-((S)-3-hydroxypyrrohdm-l -yl)-l -(3-(5-methyl-l,2,4-oxadiazol-3-yl)phenyl)ethyl)(methyl)carbamate



Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of benzyl N-[(13)-2-[(3S)-3-[(tert-butyldimethylsnyl)oxy] pyrrokdin-1 -yl]-1-**P**-(N-hylroK^arbaminudojii)phenyi] ethyl]-N-methylcaibamate (4.S g, 9.1 1 mmol, 1.00 equiv) in Toluene (70 mL). To the mixture was added acetic anhydride (4 g, 4.00 equiv). The resulting solution was stirred for 3 hours at room temperature. The resulting mixture was concentrated under vacuum. The residue was dissolved in tetrahydro furan (50 mL). Then TBAF (7.2 g, 27.54 mmol, 5.00 equiv) was added. The resulting solution was allowed to react, with stimng, for an additional *36* hours at room temperature. The resulting nurture was concentrated under vacuum. The resulting solution was diluted with 250 mL of water and the resulting solution was extracted with dichloro methane (5x100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 2.78 g (70%) of benzyl N-[(1Ξ)-2-[(3Ξ)-3-hydnoxypyrrolidin-l -yl]-1-[3-(5-methyl-1,2,4-oxadiazo l-3-yi)phenyI] ethyl]-N-methylcarbamate as yellow crude oil.

LC-IvE (E*S, m/z)*: 437 (M+l) .

Step (v) Ξynthesis of (S)-1-((Ξ)-2-(3-(5-methyl- 1,2,4-oxadiazol-3 -yl)phenyl)-2 -(metl^lamino) e1hyl)pyrrokdin-3 -ol

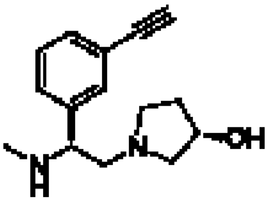


Into a 50-mL round-bottom flask, was placed a solution of benzyl N-[(1Ξ)-2-[(3Ξ)-3-hydroxypyrrolidin- 1-yl]-1-[3-(5-methyl- 1,2,4-oxadiazol-3 -yl)phenylj ethyl] -N-methylcaibamate (400 mg, 0.92 mmol, 1.00 equiv) in concentrated hydrogen chloride aqueous (10 mL) . The resulting solution was stirred for 3 hours at 80°C in an oil bath. The reaction mixture was cooled to room temperature. The resulting solution was washed with dichloro methane (4x20 ml_) and the aqueous layer was concentrated under vacuum. The residue was diluted with 20 mL of methanol. The pH value of the solution was adjusted to 8-9 with ammonia. The resulting mixture was concentrated under vacuum. The residue was applied onto a sihca gel column and eluted with dicMoromethane/methanol (10/1). This resulted in 110 mg (40%) of (3S)-1 -[(2S)-2-(3-(5-n¾th^4.2,4-oxadiasd-3-^)pher5il]-2-(meth^amino)em^p^didin-3-ol as yellow oil.

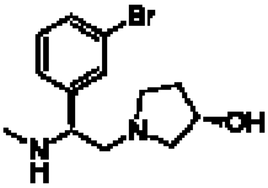
LJC-IVE (ES, m/z): 303 (M+l).

Example 17-b

(S)-1-((S)-2-(3-ethynylphenyl)-2-(methylamino)ethyl)pyrrolidin-3-ol



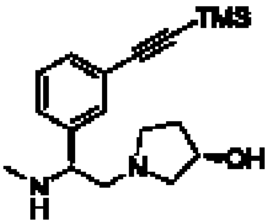
Step (i) Synthesis of (S)-l -((S)-2-(3Jbromophenyl)-2-(methylamino)ethyl)pyrrolidin-3-ol



To a solution of [(13)-l-(3JDromophenyl)-2-[(33)-3-[(tert-l¾tyldimethylsilyl)oxy]pyrrolidin-1-yl]ethyl](methyl)amine (3 g, *1.26* mmol, 1.00 equiv) in methanol (25 mL). This was followed by the addition of hydrogen chloride aqueous (12N in water, 4g) dropwise with stirring at 0°C. The resulting solution was stirred for 1 h at 20℃. The pH value of the solution was adjusted to 8 with saturated aqueous sodium bicarbonate. The resulting aqueous solution was extracted with DCM:MeOH(10:1,5x20 mL) and the organic layers combined. The resulting organic layer was washed with brine (2x60mL), dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 2.8 g (crude) of (3S)-1-[(2S)-2-(3-bromophenyi) -2-(methykmino)ethyl] pyrrolidin-3-ol as brown crude oil.

LC-IvE (ES, m/z): *299* (M+l).

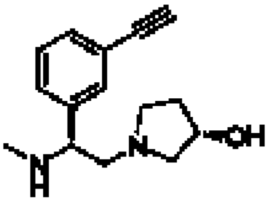
Step (ii) Synthesis of (S)4-((S)-2-(methylamino)-2-(3-((trimemylsilyl)ethynyl)phenyl) emyl)pyrrohdin-3 -ol



To a solution of (3S)-l-[(23)-2-(3-bromophenyl)-2-(]nethy^^ no)ethyl]pyrrolidin-3-ol (2.8 g, *9.36* mmol, 1.00 equiv) in TEA (15 ml_), **were** added **eu\ynyltrime1hylsilane** (54 mg, 0.55 mmol, □.03 equiv) and CuI (200 nig, 1.05 mmol, 0.02 equiv) under nitrogen. Following **Pd(PPh3)+** *{93* mg, 0.01 mmol) was added. The resulting solution was stirred for 40 h at 50℃ in an oil bath. The resulting mixture was concentrated under vacuum. The residue was purifie d by silica gel column and eluted with dichlorome Ihane/methanol = 20: 1. This resulted in 1.3 g (44%) of (3S)4-[(2S)-2^methykmino)-2-[3-[2-(trime mylsHyl)ethynyI] phenyl] ethylj pyrrdidin-3-ol as brown oil.

LJC-IVE (ES, m/z): 317 (MH).

Step (iii) Synthesis of (Ξ)-1-((Ξ)-2-(3-ethynylphenyl)-2-(methylamino)etr^)pyrrolidin-3-ol

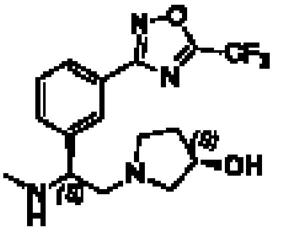


Into a 50-mL round-bottom flask, was placed a solution of (3S)-1-[(2Ξ)-2-(methylamino)-2-[3-P-(trimethyl^yl)ethynyl]phenyl]ethyl]pyrrolidin-3-ol (1.08 g, 3.41 mmoL 1.00 equiv) in methanol (15 mL). This was followed by the addition of potassium hydroxide in water (20%, 10 mL) dropwise with stirring at 0℃. The resulting solution was stirred for 2-3 h at 20℃. The pH value of the solution was adjusted to S with hydrogen chloride aqueous (2.5M). The resulting mixture was concentrated under vacuum and diluted with of water. The resulting aqueous solution was extracted with dichbromelhane/mellianol (10:1, 5x1OmL) and the organic layers combined. The resulting organic layer was washed with brine (2x30mL). dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by Prep-TLC with dicluoromethane/methanol/ TEA(20:l :0.003,v/v/v). This resulted in 460 mg (55%) of(3S)-l -[(2S)-2-(3-ethynylphenyl)-2-(methylamino) ethyi] pyrrdidin-3 -ol as yellow oil.

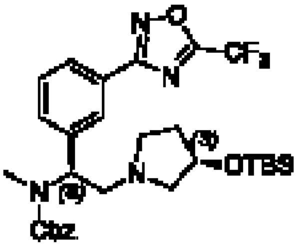
LC-IvE (ES, m/z): 245(M+l).

Example 18-b

(S)-1-((S)-2-(methylamino)-2-(3-(5-(trifluoro methyl)-1,2,4-oxadiazol-3-yi)phenyl)ethji)pjrrolidin-3-ol



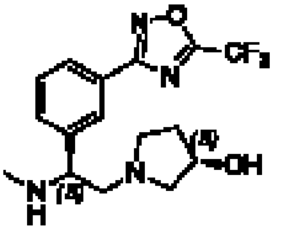
Step (i) Synthesis of benzyl ((S)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-1-(3-(5-(trifluoro methyl)- 1,2,4-oxadia3ol -3 -yl)phenyl)ethyi)(nie thyi)c arbamate



Into a 100-niL round-bottom flask, was placed a solution of benzyl N-[(1S)-2-[(3Ξ)-3-[(tertJDutyldmemylsnyl)oxy]py^ lidin-1-yl] -1-P-(N-hydroxycarbamimidoyl)phenyl] ethylj -N-methylcarbamate (1 g, 190 mmol., 1.00 equiv) in pyridine (10 mL) . To the solution was added (CFsCO)iO (1.2 g, 3.00 equiv). The resulting solution was stirred for 3 hours at 110*C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC with dicMoromethane/methanol (10:1). This resulted in 0.39 g (34%) of benzyl N-[(1Ξ)-2-[(3Ξ)-3-[(tert-butyldimMh^silyl)oxy] pyrrolidin-1 -yl]-1-[3-[5-(trifluoro metl^J-l^^oxadiazol-S-^phenyl] ethyl] -N-methylcarbamate as yellow oil.

LJC-IVE (ES, m/z): 605 (M+1).

Step (ii) Synthesis of (S)-1-((S)-2-(n¾thykmino)-2-(3-(5-(trifluoromethyl) -1,2,4-oxadiazol-3-yl)phenyl) ethyi)pyrrohdin-3-ol

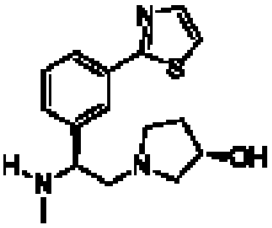


Into a 25-mL sealed tube, was placed a solution of benzyl N-[(lS)-2-[(3S)-3-[(tert-butyldimethylsHylJoxy] pymkdin-1 -yl]-1-[3-[5-(trifluoromethyl)- 1,2,4-oxadiazol-3-yl]phenyl] ethyl] -N-methylcarbamate (1.4 g, 2.32 mmol, 1.00 equiv) in concentrated hydrogen chloride aqueous (15 niL). The resulting solution was stirred for 3 hours at S0°C in an oil bath. The resulting mixture was concentrated under vacuum. The crude product (2 g) was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, CIS silica gel; mobile phase, 0.5% ammonia water/acetordtrile=100:1 increasing to 5% ammonia water/acetordtrile= 100:45 within 30 min; Detector, UV 254 urn. This resulted in 0.S g (97%) of (3S)-1-[(2Ξ)-2-(methylamino)-2- [3-[5-(trifluoromethyl) -1,2,4-oxadiazol-3-yl]phenyl] emyI]pyrrohdin-3-ol as yellow oil.

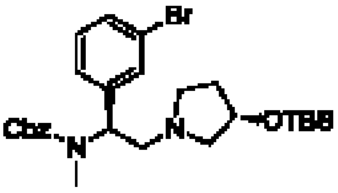
LC-IvE (ES, πɏζ): 357 (IvH+1).

Example 19-b

(S)-1-((¾-2-(nethyi amino)-2-(3-(thiaMl-2-yl)phenyDethyl)pyτroïü iη-3-ol



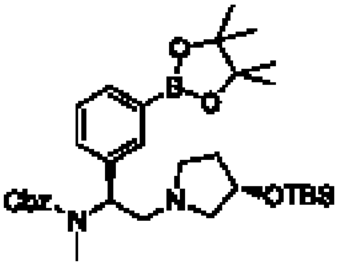
Step (i) Synthesis of benzyl ((SJ-1-(S-bromophenylJ-2-((SJ-S-((tert-butyldimethylsilylJo-iy) pyrrolidin- 1-yl)ethyi)(methyl)carbamate



Into a 250-mL round-bottom flask, was placed a solution of [(lS)-l-(3-bromophenyl)-2-[(33)-3-[(tert-butyidin¾thylsnyI)oxy]p^ rolidin-1-yl]ethyl](methyl)amine (6.2 g, 15.00 mmol, 1.00 equiv) in ethyl acetate :water(5: 1) (60 mL). To it was added potassium carbonate (2.7 g, 19.54 mmol, 1.30 equiv) followed by benzyl chloroformate (3.1 g, IS.17 mmol, 1.21 equiv) dropwise at 5-10°C in ice-water bath. The resulting solution was stirred for 2 hours at 25*C and diluted with 50ml of brine. The resulting aqueous solution was extracted with ethyl acetate (3x100 mL) and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 7.5 g (crude) of benzyl N-[(lS)-l-(3-bromophenyl) -2 -[(3S)-3- [(tert-butyldimethylsiljiijo-iy] pyrrolidin- 1-yl] ethyl] -N-methylcarbamate as yellow oil.

LJC-IVE (ES, m/z): 549 (M+l).

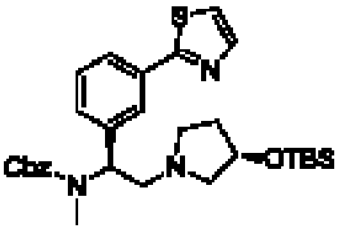
Step (ii) Synthesis of benzyl ((S)-2-((S)-3-((tert-bu ¾^ri ¾thyisily^ xy) pyrrolidin-1 -yl)-1-(3-(4,4,5,5 -tetramethyl- 1,3,2-dio xaboio lan-2 -yl) phenyl)ethyi)(me thyi)carbamate



Into a 250 -mL 3-necked round ^bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of benzyl N-[(1S)-1 -(3-bromophenyl)-2-[(3S)-3-[(tert-butyldimemylsilyi)o: yl] pyrrolidin-1-yl] ethyl] -N-methylcarbamate (2.0 g, *3.65* mmol, 1.00 equiv) in 1,4-dioxane (100 mL). Then KOAc (720 mg, 7.34 mmol, 2.01 equiv) and 4,4,5,54etramethyl-2-(3,3,4,4-te tramethylbor olan-1 -yi)-l ,3,2 -dioxaborolane (1.85 g, 7.40 mmol, 2.03 equiv) were added. Following FdidppfjClj (530 mg, 0.72 mmol, 0.20 equiv) was added. The resulting solution was stirred overnight at S0°C in an oil bath under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:5). This resulted in 1.95 g (90%) of benzyl N-[(lS)-2-[(3S)-3-[(tert-butyldimethylsnyl)oxy] pyrrohdin-l -yi]-l-[3-(tetra methyl- 1,3,2-dioKabor olan-2-yl) phenyl] ethyl] -N-methylcarbamate as yellow oil.

LC-M3 (ES, m/z): 595 (MM)

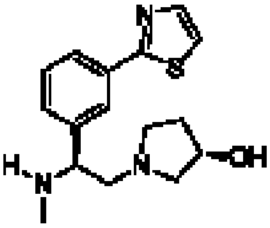
Step (iii) Synthesis of benzyl ((S)-2-((S)-3-((tert-butyldin¾thyisil^ oxy) pyrrolidin-1 -yl)-1-(3^thkzol-2-yl)phenyi)ethyi)(n¾thyl)carbamate



Into a 250 -mL 3-necked round -bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of benzyl N-[(lS)-2-[(3S)-3-[(tert-butyldimemylsnyl)oxy] pyirohdin-1 -yl]-1-P-(tetramethyl-1,3.2-dioxaborolan-2 -ji)phenyT] ethy[] -N-memylcarbamate (1.9 g, 3.20 mmol, 1.00 equiv) in tetrahydrofuran: water (5:1) (120 ml_). Then potassium carbonate (330 mg, 6.37 mmoL 1.99 equiv) and 2 Jbro mo-1,3-thiazole (1.05 g, 6.40 mmol, 2.00 equiv) were added. Following Pd(PPh3)4 (740 mg, 0.64 mmoL 0.20 equiv) was added. The resulting solution was stirred overnight at 80°C in an oil bath under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). This resulted in 560 mg (32%) of benzyl N-[(lS)-2-[(3S)-3-[(tert-butyldimethylsilyl)oxy] pyrrohdin-1 -yl]-1-[3-(1,3-thiazol-2 -yl)phenyl] ethyl] -N-methylcarbamate as yellow oil.

LC-IvE *(ES, m/s)*: 552 **(M+l).**

Step (iv) Synthesis of **(S)-l** -((S)-2-(methykmino)-2-(3-(thiazol-2-**ji)phenyl) emyl)pyiTohdin-3**-ol

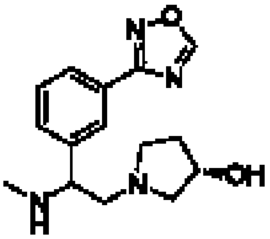


Into a 50-mL sealed tube, was placed a solution of benzyl N-[(lS)-2-[(3S)-3-[(tert-butyldimethylsilyl)oxy] pyrrohdin-1 -yl]-1-[3-(1,3-thiazol-2 -yl)phenyl] ethyl] -N-methylcarbamate (560 mg, 1.01 mmoL 1DO equiv) in methanol (1 mL) and concentrated hydrogen chloride aqueous (6 mL). The resulting solution was stirred for 6 hours at 80°C in an oil bath The resulting solution was concentrated under vacuum and diluted with methanol. The PH value of the methanol solution was adjusted to 8 with ammonia water (30% in water) . The resulting solution was concentrated and purified by silica gel colum(dichloromethane/methanol=100/1). This resulted in 350mg of (S)-1-((S)-2-(methylanuno)-2-(3-(1hkml-2-yl)ph^ nyl)ethyl)pyrrolidin-3-ol as yellow oil.

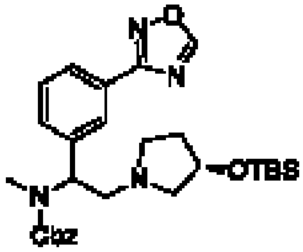
LC-IvE (ES, m/s): 303 (M+l).

Example 20-b

(3S)-1-(2-(3-(1,2,4-oxadiaz»l-3-yl)phenyl)-2-(methylajnino)ethyl)pyrivlidin-3-ol



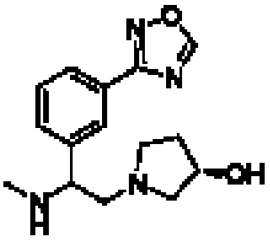
Step (i) Synthesis of benzyl (l-(3-(l,2,4-oxadkzol-3-yl)ptenyi)-2-((S)-3-((tert-butyldimemylsnyl)oxy)pyno^ din-1 -yl)ethyl)(methyl)carbamate



Into 50ml round-bottom flash purged, was placed a solution of benzyl N-[(1S)-2-[(3S)-3-[(tert-butyldin¾ethylsilyl)oKy3pyrmhdin-l-yiJ -1-[3-(N-hydroxycarbamimidoyl) phenyl]ethyl]-N-methylcarbamate (300 mg, 0.56 mmol, 1.00 equiv) in trimethyl ortho formate (8 mL). Following boron trifiuoride ethyl ether (2 drops) was added The resulting solution was stirred for 2 hours at 80°C. The mixture was diluted with 40 mL of ethyl acetate and the result solution was washed with water (3x10 mL) and sodium bicarbonate (2x10 mL). The organic layer was dried and concentrated The residue was purified by prep-TLC with petroleum ether/ethyl acetate=4:l . This resulted in 250 mg ofbenzyl N-[(lS)-2-[(3S)-3-[(tert-butyidimethylsilyl)oxy] pyrrohdin-1 -yi]-1-[3-(1,2,4-oχadiaζo1-3-yl)phenyij ethyl]-N-methyicarbamate as yellow oil.

LC-IvE (ES, m/z): 537 (M+l).

Step (ii) Synthesis of (3S)-1-(2-(3-(1,2,4-oxadiazol-3-yl)phenyl)-2-(n¾thylamino)ethyl) pyrrolidin-3-ol

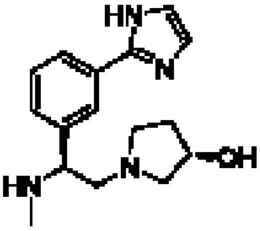


Into 50ml of sealed tube, was placed a solution of benzyl N-[(lS)-2-[(3S)-3-[(tert-butyldime1hylsilyl)oxy] pynohdin-1 -yl]-1-[3-(1,2,4-oχadi¾ζo1-3-yl)phenyi]ethyl]-N-

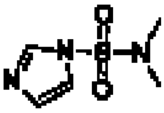
methylcarbamate (1.5 g, 2.79 mmol, 1.00 equiv) in concentrated hydrochloride aqueous (30 mL). The resulting solution was stirred for 3 hours at 80°C. The mixture was concentrated under vacuum. The residue was dissolved in DCM (20mL) and basified with Et^N. The mixture was concentrated under vacuum. This resulted in 1.6 g (crude) of (3S)-1-[(2S)-2-(methylamino)-2-[3-(1,2,4-oxadiazol-3-yl)phenyl]ethyl] pyrrolidin-3-ol as a brown solid.
LC-IvE (ES, m/z): 289 (M+l)

Example 21-b

(S)-1-((S)-2-(3-(1**H-imida2ol-2**-yl)phenyl)-2-(methykmino) ethyl) pyrrolidin-3-ol



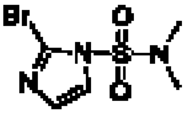
Step (i) Synthesis of N,N-din¾thyl-lH-imida3ole-l -sulfonamide



Into a 250-ml, 3-necked round ^bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of lH-imidazole (3 g, 44.07 mmol, 1.16 equiv) in dichloromethane (100 mL), TEA (4.15 g, 41.01 mmol, 1.08 equiv). This was followed by the addition of N,N-dimethyisultamoyl chloride (5.46 g, 38.02 mmol, 1.00 equiv) dropwise with stirring at 0°C. The resulting solution was stirred for 20 h at room temperature. The solids were filtered out. The filtrate was washed with water (3x100mL) and brine (1xlOOmL). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dicl^romelhane/methanol (0-100/1). This resulted in 5.77 g (87%) of N.N-din^thyl-lH-iimdazde-l-sulfommide as light yellow oil.

LC-M5 (ES, m/z): 176 (M+l) .

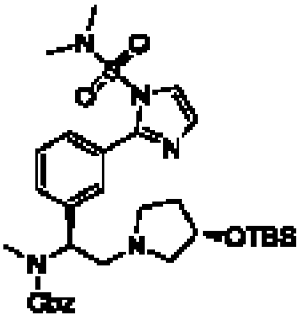
Step (ii) Synthesis of 2-bromo-N,N-dimethyl- 1H-imidaaole -1-sulfonamide



Into a 250-niL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of N,N-dimethyl-l H-imidazole-1-sulfonamide (3.77 g, 21.52 mmol, 1.00 equiv) in tetrahydrofuran (50 mL). This was followed by the addition of n-BuLi (9.5 mL, 1.10 equiv, 2.5 N) dropwise with stirring at -78°C. The resulting solution was stirred for 30 min at -78°C. To this was added a solution of tetrabromomethane (7.86 g, 23.70 mmol, 1.10 equiv) in tetrahydrofuran (20 mL) dropwise with stirring at -78*C. The resulting solution was allowed to react, with stirring, for an additional 30 min at -78*C. The resulting solution was allowed to react, with stirring, for an additional 2 h at room tempsrature. The reaction was then quenched by the addition of 100 mL of water/ice. The resulting solution was extracted with ethyl acetate (4x70mL) and the organic layers combined. The resulting mixture was washed with water (2x70mL) and brine (2x70mL). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (0-1/1). This resulted in 3.47 g (63%) of 2-bromo-N,N-din¾thyl-lH -imida2Dle-1-sulfonamide as a brown solid.

LC-IvE (E5, m/z): 254 (M+1).

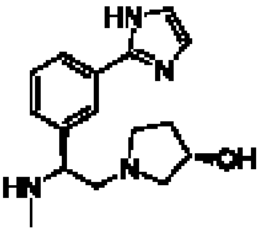
Step (iii) Synthesis of benzyl ((S)-2-((S)-3-((tert-butyldiri¾thylsilyl)oxy)pyrrolidm -1-yl)-1-(3-(1-(N,N-dimethylsulfamoyl)- 1H-imidazol-2-yl)phenyl)ethyiX methyl)carbamate



Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of benzyl N-[(lS)-2-[(3S)-3-[(tert-butyldimethylsilyl)oxy] pyrrohdin-l -yl]-1-[3-(tetramethyl- 1,3,2-dioxaborolan-2 -yl)phenyl] ethyl]-N-methylcarbamate (2.0 g, 3.36 mmol, 1.00 equiv) in dioxane/H_2O (60/lOmL), 2-bramo-N-N-dimelhyl-l H-imidazole-l-sulfonamde (1.27 g, 5.00 mmol, 1.50 equiv), ptassium carbonate (930 mg, 6.73 mmol, 2.00 equrv), Pd(PPh3)+ (770 mg, 0.67 mmol, 0.20 equiv). The resulting solution was stirred for 16 h at 80°C in an oil bath. The reaction mixture was cooled. The reaction was then quenched by the addition of lOOmL of water/ice. The resulting solution was extracted with ethyl acetate (4x50 mL) and the organic layers combined. The resulting mixture was washed withbrine (4x50 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate /petroleum ether (0-1/1). This resulted in 1.1 g (51%) of benzyl N-[(1S)-2-[(3Ξ)-3-[(tertJDutyldimethylsnyl)oxy]py™ lidin-1-yl]-1-[3-[l -(dn¾thylsulfamoyl)-lH-imidazol-2-yV] phenyl] ethyl]-N-methykarbamate as yellow oil.

LC-IvE (ES, m/z): 642 (M+l).

Step (iv) Synthesis of (Ξ)-1 -((S)-2-(3-(lH-:irridazol-2-yl)phen^ -2-(methylamino) e1hyl)pytToudin-3 -ol

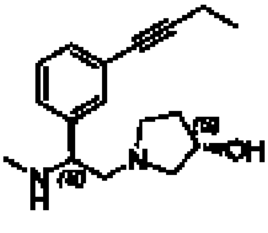


Into a 100-mL round-bottom flask, was placed a solution of benzyl N-[(1S)-2-[(3Ξ)-3-hydroxypynolidin- 1-yl]-1-[3-(1 H-imidazol-2-yl) phenyl] ethyl] -N-methykarbamate (1.1 g, *2.62* mmol, 1.00 equiv) in core . hydrogen chloride aqueous (30 mL). The resulting solution was stirred for 2 h at 80°C in an oil bath The reaction mixture was cooled to room temperature. The resulting solution was washed with dichloromethane (4x20mL) and the aqueous layer was concentrated under vacuum. This resulted in 800 mg of (3Ξ)-1-[(2Ξ)-2-[3-(lH-imidazol-2-yl)phenyl]-2 -(ri¾thyk mino)ethyl]pyrrolidin-3-ol as a brown crude solid.

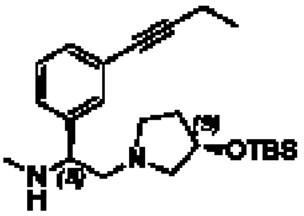
LC-IvE (ES, m/s): 287 (M+l).

Example *22*-b

(S)-1-((S)-2-(3-(but-1-jTi-1-y¾ henyl)-2-(methylajnino)ethyl)pyrrolidin-3-ol



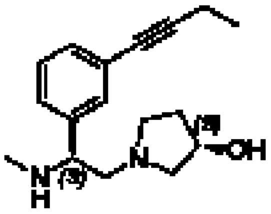
Step (i) Synthesis of (S)-l-(3-(but-l -yn-l -yl)phenyl)-2-((S)-3-((tert-butyldime1hylsnyl)oxy)pyiro lidin-1-yl)-N-methyletharamine



To a solution of [(1S)-1-(3-bromophenyl)-2-[(3S)-3-[(tert-butyldimethylsilyl) oxy] pyrrolidin -1-yl]ethyl](methyl)amine (2.5 g, 6.05 mmol, 1.00 equiv), Pdj (dba)$_3$CHCl$_3$ (634 mg, 0.60 mmol, 0.10 equiv), PPhs (631 mg, 2.41 mmoL 0.40 equiv) and Cul (229 mg, 1.20 mmol, 0 20 equiv) in TEA (25 mL), was introduce d but- 1-yne (1.62 g, *29.95* nunol. 4.95 equiv). The resulting solution was stirred for 60 hours at 80°C in a 50-mI_ sealed tube. The solution was concentrated and the residue was applied onto silica gel column (EA:PE=1 :5). This resulted in 1.4 g (60%) of [(13)-l -[3-(but-1 -^-l -3l)phenyl] -2-[(3S)-3-[(tert-butyldimethylsilyl)oxy] pyrrolidin -l -yl]emyl](methyl)anune as yellow oil.

LC-IvE (ES, m/z): 387 (M+l)

Step (ii) (S)-1-((Ξ)-2-(3-(but- 1-yn- 1-yi)phe n^)-2-(meth^mino)eth^)p^r Olidin-3-ol

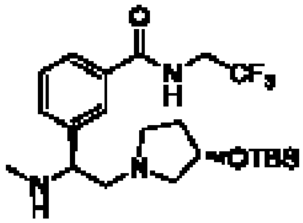


To a solution of [(1Ξ)-1-[3-(but-1 -5m.- 1-yl)phenyl] -2 -[(3Ξ)-3- [(tert-butyldimemylsilyl)oxy] pyrrolidin- 1-yl]e1hyl](n¾thyi)amine (1.4 g, 3 J62 mmol, 1.00 equiv) in methanol (60 mL), was added concentrated hydrogen chloride aqueous (10 mL) at 0°C. The resulting solution was stirred for 2 hour at 25"^ . The resulting mixture was adjusted pH to 7 with saturated aqueous NaHCOs. The mixture was concentrated under vacuum. The resulting aqueous phase was extracted with ethyl acetate. The combined 0-¾anic layers were dried over Na$_2$SO+ ard concentrated under vacuum. The residue was applied on to prep-TLC (dicMoromethane:me1harid:ar ammonia =100: 10:1). This resulted in 550 mg (56%) of (3Ξ)-1-[(2Ξ)-2- [3-(but-l -yn-1 -yl)phenyl] -2^methylanuno) ethyl]pyrrohdin-3 -ol as yellow oil.

LC-IvE (ES, m/z): 273 (M+l).

Example 23-b

3-((S)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-1-(methylamino)ethyl)-N-(2,2,2-trifluoroethyl)benzamide

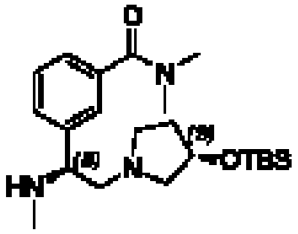


Into a 100-mL round-bottom flask, was placed a solution of 3-[(1S)-2-[(3S)-3-[(tert-butyldimethylsilyl)oxy]pyrrolidin-1-yl]-1-(methylamino)ethyl]benzoic acid (2.04 g, 539 mmol, 1.00 equiv), $CF_3CH_2NH_2$ (2.67 g, 26.97 mmol, 5.00 equiv) and DIEA (2.09 g, 16.17 mmol, 3.00 equiv) in N,N-dimethylforniamide (20 *mL).* To the solution was added HATU (2.26 g, 5.94 mmol, 1.10 equiv). The resulting solution was stirred for 1 hour at 25°C. The resulting solution was diluted with 100 mL of ethyl acetate. The resulting mixture was washed with water (3x50 mL). brine (3x50 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (100: 1). This resulted in 1.2 g (48%) oi 3-[(1S)-2-[(3S)-3-[(tert-butyldimethylsilyI)oxy3pyrrohdin-1 -yl]-1-(methylamino)ethyl] -N-(2,2,2-triiluoroethyi)ben2amide as tight brown oil.

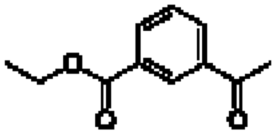
LC-IvE (ES, m/z): 460 (M+l)

Example 24-b

3-((S)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-1-(methylamino)ethyl)-N,N-dimethylbenzamide

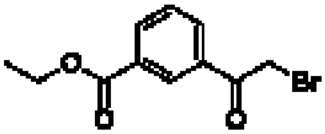


Step (i) Synthesis of ethyl 3-acetylbenmate



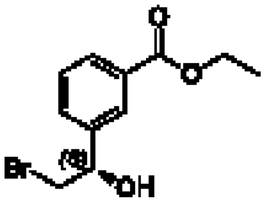
Into a 1-L round-bottom flask, was placed a solution of 3-acety-bensoic acid (50 g, 304.58 mmoL, 1.0 equiv) in etVianol (500 mL). This was followed by the addition of sulfuric acid (30 g, 305.88 mmoL, 1.00 equiv, 98%) dropwise with stirring at Q℃. The resulting solution was stirred for 16 hours at 80℃. The resulting mixture was concentrated under vacuum. The residue was dissolved in 100 mL of H_2O. The resulting solution was extracted with ethyl acetate (3x200 mL) and the organic layers combined The resulting mixture was washed with water (2x100 mL), brine (2x100 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 53 g (crude) of ethyl 3-acetylben2oate as brown oil.

Step (ii) Synthesis of ethyl 3-(2-bromoacetyl)benzoate



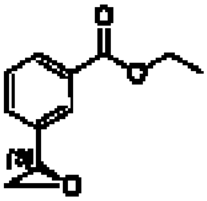
Into a 1000-mL round-bottom flask, was placed a solution of ethyl 3-acetylbenzoate (48 g, 249 .73 mmol, 1.00 equiv) in MΓBE (600 mL). To the solution was added PTAP *{95.9* g. *255 0 5* mmoL, 1.02 equiv). The resulting solution was stirred for 1.5 hours at 0°C. The resulting mixture was washed with saturated $Na_2S_2O_3$ aqueous (4x400 mL), water (3x300 mL) and brine (2x300 mL). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in *63.3* g (crude) of ethyl 3-(2-bromoacetyl **)ben2oate** as brown oil.

Step (iii) Synthesis of (S)-ethyl 3-(2-bromo-1-hydroxyethyl)**berL2Date**



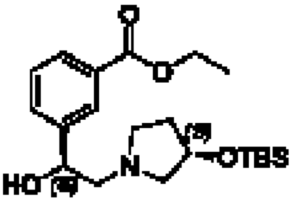
Into a 250-mL round-bottom flask, was placed a solution of S-Met-CBS (9.2 g, 40.53 mmoL, 0.50 equiv) and DEA.BHj (13.2 g, 80.98 mmoL, 1.00 equiv) ln MTBE (84 mL). This was followed by the addition of a solution of ethyl 3-(2-bromoacetyl)benzoate (22 g, 81.15 mmoL, 1.00 equiv) in MΓBE (20mL) dropwise with stirring at 40*0 in 1 hour. The resulting solution was stirred for 8 hours at 25℃. The reaction was then quenched by the addition of 44 mL of methanol and 57 mL of hydrogen chloride aqueous (3N) at 0℃. The resulting solution was extracted with ethyl acetate (3x200 mL) and the organic layers combined. The resulting mixture was washed with water (3x100 mL), brine (3x100 mL). dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in *19.5* g (88%) of ethyl 3-[(lS)-2-bromo-l-hydroxyethyl]berLiDate as yellow oil.

Step (iv) Synthesis of (S)-ethyl 3-(oxiran-2-yl)ben2Date



Into a 250-mL round-bottom flask, was placed a solution of ethyl 3-[(lS)-2-bromo-l-hydroxyethyI]ben3oate (12 g, 43.94 mrnol, 1.00 ecjuiv) in ethanol (120 mL). To the solution was added potassium carbonate (12 g, 86.82 mmol, 2.00 equiv). The resulting solution was stirred for 30 min at 0*0. The resulting solution was allowed to react, with stirring, for an additional 30 min at 25°C. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was dissolved in 100 mL of ethyl acetate. The resulting mixture was washed with water (3x50 mL), brine (3x50 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 7.3 g (crude) of ethyl 3-[(2S)-oxiran-2-yl]benzoate as brown oil.

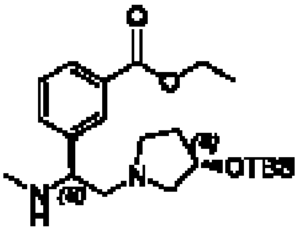
Step (v) Synthesis of ethyl 3-((S)-2-((S)-3-((tert-butyldin¾thyisi^ oxy)pyrrolidin-1-yl)-1-hydroxyethyl)be naoate



Into a 250-mL round-bottom flask, was placed a solution of ethyl 3-[(2S)-oxiran-2-yTJbensoate (*5.9* g, 30.70 mmoL 1.00 equiv) in ethanol (*60* mL). To the solution was added (3S)-3-[(tert-butyldimethylsilyi)oxy] pyrrolidine (7.5 g, 37.24 mmol, 1.20 equiv). The resulting solution was stirred for 15 hours at 70*C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was dissolved in 80 mL of ethyl acetate. The resulting mixture was washed with 0.5N hydrogen chloride aqueous (2x50 mL), water (3x30 mL) and brine (3x30 mL). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 7 0 g (crude) of ethyl 3-[(lS)-2-[(3S)-3-[(tert-butyldimemylsuyljoxy] pyirohdrn-1 -yl] - 1-hydroxyemyl] benzoate as brown oil.

LC-M5 (ES, m/z): 394 (M+l).

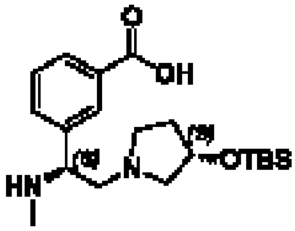
Step (vi) Synthesis of ethyl 3-((S)-2-((S)-3-((tert-butyldin¾thyisi^ oxy)pyrrolidin-1-yl)-1-(methyl ami no) ethyl)b enzoate



Into a 250-mL round-bottom flask, was placed a solution of ethyl 3-[(l S)-2-[(3S)-3-[(tertJautyldmemylsnylJo-iylpyrrohdm -1-yl]-1-hydroxyethyl]benzoate (7.0 g, 17.7S mmol, 1.00 equiv) and TEA (9.1 g, 88.93 mmol, 5.0o equiv) in dichloromethane (70 mL). To the solution was added MsCl (6.2 g, 3.00 equiv) at 0*C. The mixture was stirred at 0*C for 30 min, and stirred for 1 hour at 25*C. Then methanamine (37.2 g, 1.20 mol, 20.00 equiv) was added. The resulting solution was stirred for 20 hours at 30°C. The resulting solution was diluted with 100 mL of DCM. The resulting mixture was washed with water (3x50 mL) and brine (3x50 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 8.1 g (crude) of ethyl 3-[(13)-2-[(33)-3-[(tert-butyldimethylsilyl)ox^ pyriOlidin-l-yVJ-l-(n¾thylarniriQ)ethyI]benzoate as brown oil.

LC-MS (ES, m/z): 407 (M+l).

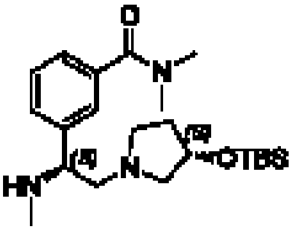
Step (vii) Synthesis of 3-((S)-2-((S)-3-((tert-butyldiri¾thyia^ oxy)pyrrolidin-1-yl)-1-(methylamLno)emyl)benzoic acid



Into a 100-mL round-bottom flask, was placed a solution of ethyl 3-[(1Ξ)-2-[(3Ξ)-3-[(tertJDutyldmemylsnyl)oxy]pynohdm-l-y^ -1-(methylamino)ethyl]benzoate (2.2 g, 5.41 mmol, 1.00 equiv) in methanol/HjO(5/l) (12 mL). To the solution was added LiOH.HjO (1.14 g, 27.17 mmol, 5.00 equiv). The resulting solution was stirred for 1 hour at 25^. The resulting mixture was concentrated under vacuum. This resulted in 2.56 g (crude) of 3-[(lS)-2-[(3S)-3-[(tert-butyldin¾thylsil;ji)oxy] pyrrolidin- 1-yl]-1-(memykmino)e thyQbenzoic acid as yellow solid.

LJC-IVE (ES , m/z): 379 (M+1).

Step (viii) Synthesis of 3-((S)-2-((S)-3-((tert-bu1yldin¾thytsi^ oxy)pyrrolidin-1-yl)-1-(methyl amino) ethyl) -N,N-dim ethylb ensamide

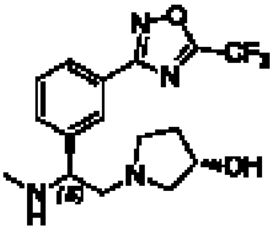


Into a 100-mL round-bottom flask, was placed a solution of 3-[(1S)-2-[(3S)-3-[(tert-butyldime1hylsnyl)oxy]pym lidin-1-yl]-1-(methylamino)ethyl]benzoic acid (93.1 mg, 0.25 mmol, 1.00 equiv), NHMe$_2$.HCl(40 mg. 0.49 mmol, 2.00 equiv) and DIEA (95 mg. 0.74 mmol, 3.00 equiv) in N,N-dimethylformamide (4 mL). To the solution was added HATU (140 mg, 0.37 mmol, 1.50 equiv). The resulting solution was stirred for 1 h at 25^. The resulting solution was diluted with 50 mL of ethyl acetate and the organic layer was washed with brine (4x50 ml), dried over Na$_2$SO$_4$ and concentrated under vacuum. This resulted in 101.7 mg (crude) of 3-[(lS)-2-[(3S)-3-[(tert-butyldimemyla^ yl)oxy]pyrrolidin-1-yl]-1-(methylamino) ethyl] **-N,N-dimef ylbenzamide** as **brown oil.**

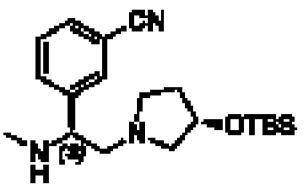
LC-IvE (ES, m/z): 406 (M+l).

Example 25-b

(S)-1-((S)-2-(methylajnino)-2-(3-(5-(trifluoiomethyl)-1,2,^oxadiaz>ol-3 -yl)phenyl)ethyl) pyrrolidiii-3-ol



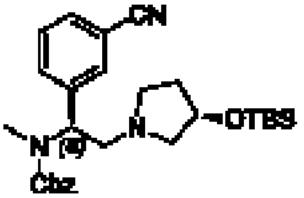
Step (i) Synthesis of 3-((S)-2-((S)-3-((tert-butyldin¾thyisi^ oxy)pyrrolidin-1-yl)-1-(methyl amino) ethyl)b enzonitrile



Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of [(1 3)-l-(34Dromophenyl)-2-[(3S)-3-[(tert-butyldimemylsilyl) o.i^pyirolidin-l -^eth^(mem^)amLne (20 g, 4S.36 mmoL 1.00 equiv) in N,N-dimethyiformamide (30 *mL)* . To the solution were added Zn(CN)$_2$ (7.1 g, 60.68 mmol, 1.25equiv) and Pd(P¾)+*(5 6* g, 4.34 mmol, 0.10 equiv). The resulting solution was stirred ovemight at 100°C in an oil bath. The reaction was then quenched by the addition of 50 mL of water. The resulting solution was extracted with ethyl acetate (5x10 mL), and the organic layers combined. The resulting mixture was washed with water (2x150 mL) and brine (3x100 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dicMoromethane/methanol (30:1). This resulted in 13 g (76%) of 3-[(lS)-2-[(33)-3-[(tert-buty^ ethylsilyl)oxy] pyrrolidin-1-yl]-1-(meth^aminD)emyI]b erL-Bmtrile as a light yellow solid.

LC-IvE (ES, m/z): 360 (M+l).

Step (ii) Synthesis of benzyl ((3)-2-((3)-3-((tert-butyldimemyisn^^ oxy)pyrrolidin-1-yl)-1-(3-cyinophenyl) ethyl)(methyl)carbamate

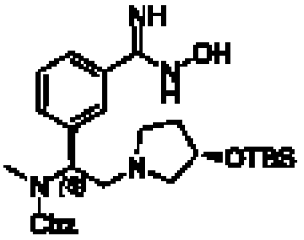


Into a 100-mL round-bottom flask, was placed a solution of 3-(2-[3-[(tert-butyldimemylsnyl)oxy]pyjro lidin-1-yl]-1-(methylamino)ethyl)benzonitrile (7 g, 19.47 mmol, 1.00 equiv) in ethyl acetate/water (50/10 mL). This was followed by the addition of potassium carbonate (3.5 g, 25 32 mmol, 1.30 equiv) for portions with stirring at 0*C in a water/ice bath. The resulting solution was stirred for 20 min at 0°C in a water/ice bath. Then benzyl carbonchloridate (4 g, 23.45 mmol, 12 0 equiv) was dropwised at 0*C in a water/ice bath Then it was warmed to 20*C and stirred for 3 h at 20*C. The reaction was done, the resulting solution was extracted with ethyl acetate (3x100 mL) and the organic layers combined. The resulting solution was dried over anhydrous sodium sulfate and concentrated under vacuum.

The residue was applied onto a silica gel column and eluted with ethyl acetate /petroleum ether **(1:4).** This resulted in **4** g **(42%)** of benzyl N-**(2-[3** -[(tert-butyldimethylsil yl)oxy] pyoolidrn-l - ^^-(i-cyamplinylJethylJ-N-methylcarbamate as yellow oil

LJC-IVE (EΞ, m¾ : 494 (M+1).

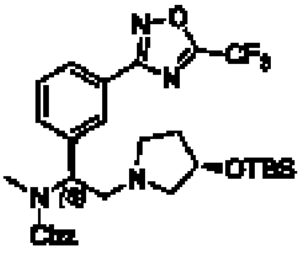
Step (iii) Synthesis of benzyl ((S)-2-((S)-3-((tert-butyldimemyisn^ oxy)pyrrolidin-1-5ii)-1-(3-(N-hydroxycarbarrimLdoyl) phenyl)ethyl)(methyl)carbamate



Into a **100-mL** round bottom flask, was placed a solution of benzyl N-**(2-[3** -[(tert-butyldimethylsilyl)ox y] pyrrokdrn -**1**-yl]-**1-(3**-cyanophe nyl)ethyl)-N-methylcarbamate **(3.4** g, **6.S9** mmol, **1.00** equiv) in ethanol **(50** mL). To the solution were added NHiOH HCl **(1.2 g, 2.50** equiv) and triemykmine **(1.4** g, **13.84** mmol, **2.00** equiv). The resulting solution was stirred for **12** h at **S0°C** in an oil bath. The resulting mixture was concentrated under vacuum. This resulted in **5.1** g (crude) ofbenzyl N-(2-[3-[(tert-butyldimet^ ylsilyl)oxy]pyrrolidin-1-yl]-1-P-(N-hydroxycarbamimidoyl)phenyl]ethyl)-N-methylcarbamate as a solid.

LC-MS (ES, m/z): 527 (M+1).

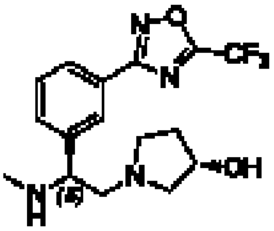
Step (iv) Synthesis of benzyl ((S)-2-((S)-3-((tert-butyldiri¾thylsilyl)o iy)pyra lidin-1-yl)-1-**(3-(5** -(trifluoro methyl)- **1,2,4** -oxadiazol -**3**-yl)phenyl)ethyl)(methyl)carbamate



Into a **100-mL** round bottom flask, was placed a solution of benzyl N-**(2-[3** -[(tert-butyldimethylsilyl)oxy] pyiTokdrn-l -yl]-**1**-P-iN-hydraxycarbaminmic^lJphenyl]ethyl)-N-methylcarbamate **(2** g, **3.8o** mmol, **1.00** equiv) in pyridine **(20** mL). To the solution was added $(CF_3CO)_2O$ **(2.4** g, **11.4** mmol, **3.00** equiv). The resuiting solution was stirred for **3** h at **110°C** in an oil bath. The resuiting mixture was concentrated under vacuum. The residue was applied onto a preparation TLC with dichbrometrarie/methanol **(10: 1).** This resulted in **1.6** g (crude) of 1-P-(methykmino)-2-[3-[5-(trifluoromethyl) -1,2,4-oxadiazol-3-yl] phe nyi] ethyl] pyiTolidin-3-ol as yellow oil.

LC-MS (ES, m/z): 605 (M+1).

Step (v) Synthesis of (S)-1-((3)-2-(methylamino)-2-(3-(5-(trifluoromethyl) -1,2,4-oxadiazol-3-yl)phenyl) ethyl)pyrrolidin-3 -ol

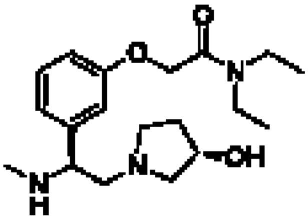


Into a 50-niL sealed tube, was placed a solution of benzyl N-[(13)-2-[3-[(tert-butyldimethylsilyijoxy] pyiroudin-1 -yl]-1-[3-[5-(trifluoromethyl)- 1,**2**,**4-oxadia2ol-3**-yl]p]¾nyIJ ethyIJ-N-me1nylcaibamate (1.6g, *2.56* mmol, 1.00 equiv) in methanol (50 ml_). To the solution was added concentrated hydrogen chloride aqueous (8 mL). The resulting solution was stirred for 3 h at 80℃ in an oil bath. The resulting mixture was concentrated under vacuum. This resulted in 800 mg (87%) of 1-P-(methykmino)-2-[3-[5-(trifluoromethylj-1,2,4-oxadiam l-3-yi]phenyl] ethyIJpyirolidin-3-ol as oil.

LC-IvE (ES, m/z): 357 (M+l).

Example 26-1}

IHN-4iethylr2-(3-((S)-2-((S)-3-hydroxypyn olidin-1-yl)-1-(methylamino)ethyl)pheiu)xy) acetamide

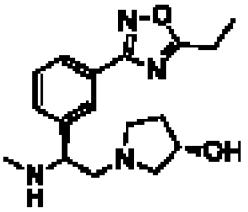


Into a 100-niL round-bottom flask, was placed a solution of 2-[3-[(l S)-2-[(3S)-3-hydroxypyrrolidin-1-yl]-1-(methylamino)ethyl]phenoxy]acetic acid (432 mg, 1.47 mmol, 1.00 equiv) in N,N-dimemylf0rmamide (20 mL). To the solution were added DIEA *(569* mg, 4.40 mmol, 3.00 equiv), NEtj (537 mg, 1.*36* mmol, 5.00 equiv) and HATU (615 mg, 1.62 mmol, 1.10 equiv). The resulting solution was stirred for 1 h at 25*0. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (20: 1). This resulted in 580 mg of N,N-diethyi-2-[3-[(13)-2-[(33)-3-hydroxypyrrolidin-l-yl] -l-imeth^niinojeth^pherio-i^acetamide as light yellow oil.

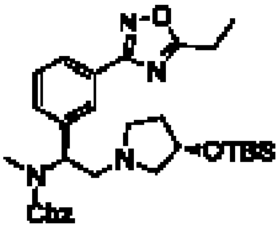
LJC-IVE (EΞ, m/z): 350 (M+1)

Example 27-b

(S)-1-((¾-2-(3-(5-ethyl-l,2,4-oxadiamt3- yl)phenyl)-2-(n* thylajnino)ethyl)pyra lidm-3-ol



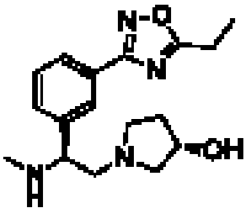
Step (i) Synthesis of benzyl ((S)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-1-(3-(5-ethyl-l,2,4-oxadiazol-3-yi)phenyl)ethyl)(methyl)carbamate



Into a 100-mL round-bottom flask, was placed a solution of benzyl N-[(1S)-2-[(3Ξ)-3-[(tert-butyldimethylsilyl)oxy]pyrrolidin-1-yl]-1-[3-(N-hydroxycarbamimidoyl)phenyl]ethyl]-N-methyicarbamate (2.3 g, 4.37 mmol, 1.00 equiv) in pyridine (30 ml_). To the solution was added propanoyi propanoate (1.7 g, 13.06 mmol, 3.00 equiv). The resulting solution was stirred overnight at 110*0. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (0/100-1/30). This resulted in 1.2 g (49%) of benzyl N-[(13)-2-[(33)-3-[(tert-butyldimethylsilyljoxy] pyrrohdin-1 -yi]-1-[3-(5-ethyl-l,2,4-oxadiazol-3-yl)phenyl]ethyl]-N-methyicarbamate as orange oil.

LJC-IVE (ES, m/z): 565 (M+l)

Step (ii) Synthesis of (S)-l-((S)-2-(3-(5-ethyl-1.2,4-oxadiazol-3-yl)phenyl)-2-(methylamino) emyi)pyjrdidin-3 -ol

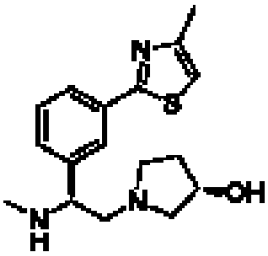


Into a 10-ml_ round-bottom flask, was placed a solution of [(lS)-2-[(3S)-3-[(tert-butyidimemylsnyl)oxy] pyrrohdin-1 -yi]-1-[3-(5-ethyL-1,2,4-oxadiazol-3-yl)phenyl] emyij(nttmyl)amine (230 mg, 0.53 mmol, 1.00 equiv) in concentrated hydrogen chloride aqueous (2 mL). The resulting solution was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 170 mg (crude) of (3S)-1-[(2S)-2-[3-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyi]-2-(memylaminojelhyi] pyrrolidin-3-ol as a black solid.

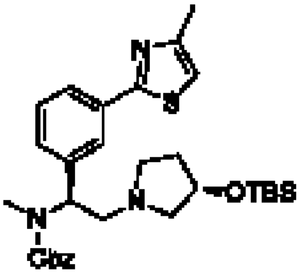
LJC-IVE (ES, m/z): 317 (M+l).

Example 28-b

(S)-1-((S)-2-(methylamino)-2-(3-(4-methylthiazol-2-yl)phenyl)ethyl)pyrrolidin-3-ol



Step (i) Synthesis of benzyl ((S)-2-((S)-3-((tert-buryldimemylsn^ oxy)pyrrolidin-1-yl)-1-(3-(4-methyl 1hiazol-2-yl)phenyi) ethyl)(methyl)carbamate

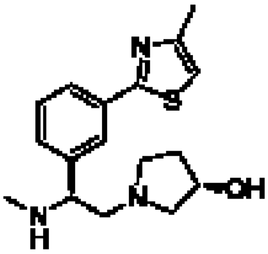


Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of benzyl N-[(lS)-2-[(3S)-3-[(tert-butyldimethylsilyl)oxy] pyrrolidin-1 -yi]-1-[3-(tetramethyl-1,3,2-diaxaborolan-2 -yl)phenyij ethyij-N-methylcarbamate (800 mg, 1.35 mmol, 1.00 equiv) in 1,4-dio.iane:H20 (10/2 mL).

To the solution were added 2-bromo-4-n¾thyl-l,3-thkzole (358 mg, 2.01 mmol, 1.50 equiv), potassium carbonate (316 mg, 2.72 mmol, 2.00 equiv) and Pd(PPhs)+ (316 mg, 0.27 mmol, 0.20 ecjuiv). The resulting solution was stirred for 16 hours at 80°C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate /petroleum ether (1:10). This resulted in 0.32 g (42%) of benzyl N-[(l S)-2-[(3S)-3-[(tertJautyidimemylsnylJo-iylpyrrolidm-1-yl]-1-[3-(4-methyl-l,3-thiaml-2-yi)pd¾nyi] ethyl]-N-methylcarbamate as yellow oil.

LC-IvE (ES, m/z): 566 (M+l).

Step (ii) Synthesis of (S)-1-((S)-2-(methylamino)-2-(3-(4-memylmiasd-2-yl)pJienyl) emyl)pyrrohdin-3-ol

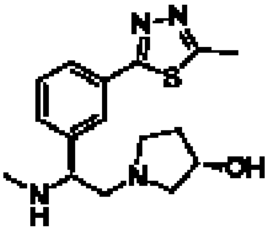


Into a 25-mL round-bottom flask, was placed a solution of benzyl N-[(l S)-2-[(3S)-3-[(tertJautyldimemylsnylJo-iylpyrrohdm-1-yl]-1-[3-(4-methyl-l,3-thiazol-2-yl)phenyiJ ethyij-N-methylcarbamate (160 mg, 0.28 mmol, 1.00 equiv) in concentrated HCl aqueous (5 mL). The resulting solution was stirred for 2 h at 80°C. The resulting mixture was concentrated under vacuum. This resulted in 150 mg (crude) of (33)-l-[(23)-2-P-(4-memyl-l,3-thiazol-2-yl)phenyij-2-(methyiamino)ethyiJ pynQlidin-3-ol as yellow oil.

LC-IvE (ES, m/z): 318 (M+l).

Example 29-b

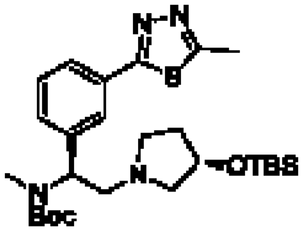
(S)-1-((¾-2-(3-(5-methyl-1,3,4-thiadiazol-2-yl)phenyl)-2-(methylamino)ethyl)pyrrolidin-3-ol



Step (i) Synthesis of 2-bronKi-5-memyl-l,3,4-thkdiazole

Into a 250-mL 3-necked round-bottom flask, HBr (20 ml, 10.00 equiv, 40%) was added. 5-n^myl-1 ,3,4-thkdkml-2-ar[une (2 g, 17.37 mmol, 1.00 equiv), water (20 ml) and CuBr (250 mg, 0.10 equiv) were added in sequence. A solution of sodium nitrite (1.2 g. 17.39 mmol, 1.00 equiv) in water (50 ml) was added dropwise with stirring at 0*C in 30mins. The reaction was stirred for additional 30 nun at 25*C. The resulting solution was extracted with ethyl acetate (2x50 mL) and the organic layers combined. The resulting mixture was washed with sodium bicarbonate aqueous (2x40 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 2.2 g (71%) of 2-**iromo**-5-methyI-l,3,4-thiadiaaole as a yellow solid.

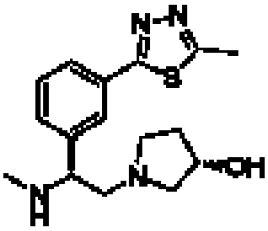
Step (ii) Synthesis of tert-butyl ((S)-2-((S)-3-((tert-butyldin^ hylsilyl)oxy)pyrrolidin-1-yl)-1-(3-(5 -methyl-1 ,3,4-thkdksDl-2-yl)phenyl)ethyl)(n¾thyl)carbamate



Into a 50-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, N,N-dimemylforrnamide (3 ml), tert-butyl (1R)-2-[(3S)-3-[(tert-brityldimethylsilyl)oxy] pymhdin-1 -yl]-1-[3-(tetramethyl- 1,3,2-dioxaborolan-2 -yl)phenyl] ethyl N-methylcarbamate (300 mg, 0.53 mmol, 1.00 equiv), 2-bromo-5-methyl-**1,3,4-thiadia2ole** (105.48 mg, 0 5 9 mmol, 1.10 equiv), tetrakis(triphenylpliosphane) palladium (30 mg, 0.03 mmol, 0.05 equiv), potassium phosphate (228 mg, 1.07 mmol, 2.01 equiv) were added. The resulting solution was stirred for 16 h at 80*C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (10;1). This resulted in 120 mg (42%) of tert-butyl (1R)-2-[(3Ξ)-3-[(tert^utyldimethylsilyl)oxy] pyrrohdin-1 -ylj -1-[3-(5-methyl- 1,3,4-1hiadia!_ol-2 -yl)phenyl] ethyl N-methylcarbamate as light yelbw oil.

LC-IvE (ES, m/z): 533 (M+l)

Step (iii) Synthesis of (Ξ)-1-((Ξ)-2-(3-(5-methyl-l ,3,4-thiadiazol-2-yl)phenyl)-2-(methylamino) emyi)pyrrolidin-3-ol

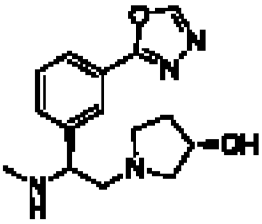


Into a 50-mL round-bottom flask, concentrated hydrogen chloride aqueous (1.2 mL) and tert-butyl (1R)-2-[(3S)-3-[(tert^utyldirnemylsiiyrjoxy] pyrrolidin-1-yl]-1-[3-(5-methyl-l,3,4-thiadiazol-2-yl)phenyi] ethyl N-methylcarbamate (120 mg, 0.22 mmol, 1.00 equiv) were added. The resulting solution was stirred for 30 nuin at 40°C. The pH value of the solution was adjusted to 8-9 with sodium bicarbonate. The resulting mixture was concentrated under vacuum. This resulted in 72 mg (crude) of (3S)-l-[(2S)-2-P-(5-memyl-l,3,4-1hkdiazol-2-yl)phenyij-2-(methylamino)ethyl]pyrrolidin-3-ol as a yellow solid.

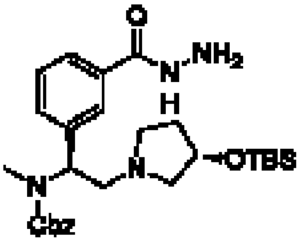
LC-IvE (ES, m/z): 319 (M+l).

Example 30-1}

(S)-1-((S)-2-(3-(1,3,4-oxadiazol-2-yl)phenyl)-2-(methylamino)ethyl)pyrrolidin-3-ol



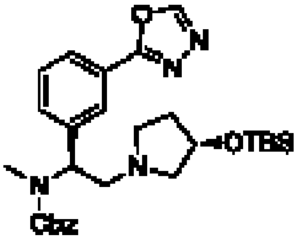
Step (i) Synthesis of benzyl ((S)-2-((S)-3-((tert-butyldimemylsn^^ oxy)pyrrolidin-1-yl)-1-(3-(hydrazine carbonyi) phenyl)ethyi)(memyl)carbamate



Into a 500-niL round-bottom flask, was placed a solution of ethyl 3-[(1Ξ)-1-[[(benzyloxy)carbonyi] (methyl) amino]-2-[(3Ξ)-3-[(tert-butyldirnethylsilyljoxy] pyrrohdin-1-yl]ethyl]benzoate (5.6 g, 10.36 mmol, 1.00 equiv) in ethanol (100 mL). To the solution were added hydrazine (16.3 g, 508.66 mmol, 25.00 equiv). The resuiting solution was stirred for 16 h at 80°C in an oil bath. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 100 mL of ethyl acetate. The resulting mixture was washed with water (3x50 mL) and brine (3x50 mL). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 6.0 g (crude) of benzyl N-[(1S)-2-[(3Ξ)-3-[(tertJautyldimethylsilyi)oxyJ pyrrohdin-1 -yl]-1-[3-(hydrazinecarbonyL)phenyl] ethyl] -N-methylcarbamate as light yellow oil.

LC-IvE (ES, m/z): 527 (M+l)

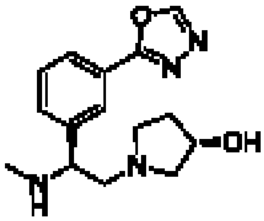
Step (ii) Synthesis of benzyl ((3)-l-(3-(1.3,4-oxadiazol-2-yl)phenyl)-2-((3)-3-((tert-butyldimemylsnyl)oxy)py™ lidin-1-yl)ethyl)(methyl)carbamate



Into a 100-mL round-bottom flask, was placed a solution of benzyl N-[(1S)-2-[(3Ξ)-3-[(tertJDutyldimethylsilyl)oxyJ pyrrahdin-l -yl]-1-[3-(hydrazinecarbonyl) phenyl] ethyl] -N-methylcarbamate (1.0 g, 1.90 mmol, 1.00 equiv) in CH(OCHj)3 (15 mL). The resulting solution was stirred for 16 h at 100*0 in an oil bath. The resulting mixture was concentrated under vacuum. Purification by a silica gel column with diehlorome thane :MeOH (100:0-1 00:1) resulted in 0.8 g (79%) of benzyl N-[(13)-2-[(33)-3-[(tert-but^ methylsilyl)oxy] pyrrolidin-1-yl]-1-[3-(1,3,4-oxadiazol-2-yl)phenyl] ethyl]-N-methylcarbamate as light brown oil.

LC-IvE ***(ES, m/z)**: **531*** (M+l).

Step (iii) Synthesis of (S)-l-((S)-2-(3-(l,3.4-oxaiazol-2-yl)pltenyl)-2-(methylamino)ethyl) pyrrolidin-3-ol

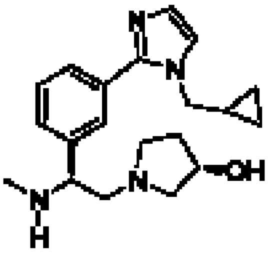


Into a 100-mL round-bottom flask, was placed a solution of benzyl N-[(1S)-2-[(3Ξ)-3-[(tertJ3utyldmethylsilyl)oxy] pyrrohdin-1 -yl]-1-[3-(1,3,4-oxadiazol-2-yl) phenyl] ethyl]-N-methylcarbamate (612 mg, 1.14 mmol, 1.00 equiv) in tetrahydrofuran (10 mL) . To the

mixture was added TBAF (2 mL, 2.28 mmol, 2.00 equiv, 1M in THF). The resulting solution was stirred for 4 h at 25*C, then diluted with 20 mL of ethyl acetate. The resulting solution was washed with water (2x10 mL) and brine (2x10 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by Prep-TLC (dicluoromethane:methanol = 18:1) to result in 244 mg product. A solution of the product(244mg) in MeOH (10mL)was hydrogenated in the presence of 20% Pd/C(40mg) at 25*C for 12h. The mixture was filtered (through Celite) and washed with methanol. The solvent was evaporated to afford 168 mg (51%) of *(3S)-1-[(2S)-2-(methylamino)-2-[3-(1,3,4-*oxadkml-2-3?l)phenyI] ethyl]pynolidin-3-ol as light yellow oil.
LC-IvE *(ES, m/z)*: *2%9* (M+l).

Example 31-b

(S)-1-((S)-2-(3-(1-(cyclopropylmethyl)-1H-imidazol-2-yl)phenyl)-2-(methylamino)ethyl)pyrrolidin-3-ol



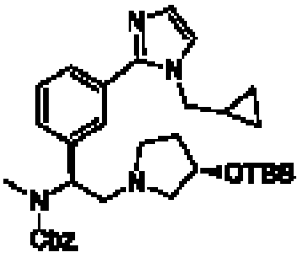
Step (i) Synthesis of 1-(cyclopropylmethyl)-1H-imidazole

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of lH-imidarole (3 g, 44.07 mmol, 1.00 equiv) and potassium hydroxide (11.8 g, 210.30 mmol, 5.00 equiv) in acetone (100 mL),. The resulting solution was stirred for 30 min at 25*C.This was followed by the addition of (bromomethyl) cyclopropane *(6.9* mL, 1.10 equiv) dropwise with stirring at *25'C*. The resulting solution was alb wed to react, with stirring, for an additional 30 min at 25*0. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 100/100 mL of dichbromethane/HjO. The pH value of the solution was adjusted to *2*Λ with concentrated HC1 aqueous (12 mol/L). The aqueous layer was separated and the pH value was adjusted to 9-10 by sodium hydroxide aqueous. The resulting solution was extracted with dichbromethane (2x150 mL) and the organic layers combined. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The resdue was applied onto a silica gel column with petroleum ether/ethyl acetate(1:2), This resulted in 3.19 g *(59%)* of l -(cycbpropylmfithyl)-lH-imidazole as yellowoil.

Step (ii) Ξynthesis of 1-(cyclopropylmethyl)-2-iodo-1H-imidazole

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 1-(cycb propylmethyl)-1H-imidazole (3.19 g, 26.11 mmol, 1.00 equiv) in tetrahydrofuran (100 mL). This was followed by the addition of n-BuLi (11.4 mL, 1.10 equiv) at -78*C. The resulting solution was stirred for 1 h at -78*C. To this was added a solution of I_2 *(6.6* g, 26.09 mmol, 1.00 equiv) in tetrahydrofuran (30 mL) dropwise with stirring at -78*X*C. The resulting solution was allowed to react, with stirring, for an additional 1 h at 25*C. The reaction was then quenched by the addition of 10 mL of saturated NH+C1 aqueous. The resulting solution was extracted with ethyl acetate (2x100 mL) and the organic layers combined The resuiting mixture was washed with water (2x 100 mL) and brine (2x100 mL). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:7). This resulted in 5 g (77%) of 1-(cyclopropylri¾t]^)-2 **-iDdD4H-imida2Dle** as yellow oil. LC-IvE (ES, m/z): 249 (M+l).

Step (iii) Synthesis of benzyl ((S)-2-((S)-3-((tert-butyldiri¾thylsily^^ oxy)pyrrolidin-1-yl)-1-(3-(1-(cycbpropylmethyl)- 1H-imidazol-2 -yOphenyl) ethyl)(methyl) carbamate

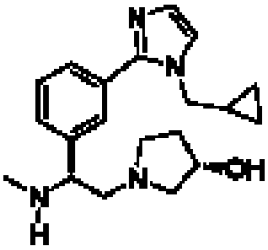


Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen. was placed a solution of benzyl N-[(lS)-2-[(3S)-3-[(tert-butyldimethylsilyl)oxyJ pyrrotidin-l -yl]-1-[3-(tetramethyl- 1,3,2-dioxaborolan-2 -yi)phenyl] ethyl]-N-methylcarbamate (500 mg, 0.84 mmol, 1.00 equiv) in 1,4-dioxane/H_2O

(30/3 mL). To the solution were added l -(cyclop:opylmethyl)-2-iodo-l H-inudazole (230 mg, 0.93 mmol, 1.10 equiv), PdfdppfjCli (62 mg, 0 0 8 mmol, 0.10 equiv), Potassium tert-buto-iide (188 mg, 1.6S mmol, 2.00 equiv) and Xphos (SO mg, 0.17 mmol, 0.20 equiv). The resulting solution was stirred for 16 h at 90*0. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC. This resulted in 270 mg (55%) of benzyl N -[(1 Ξ)-2-[(3Ξ)-3- [(tert-butyldimethylsilyi)oxy]pyrrolidin- 1-yl] -1 -[3 -[1 -(c ycbpropylmethyl)- 1H-imidazol-2-yl] phenyl] ethyl] -N-methylcarbamate as yellow oil.

LC-IvE (ES, m/z): 5%9 (M+l).

Step (iv) Synthesis of (S)-l-((S)-2-(3-(l-(cyclopiopyimethyl)-lH-irri dazol-2-yl)phenyl)-2-(methyl amino) ethyi)pyrrolidin -3 -ol

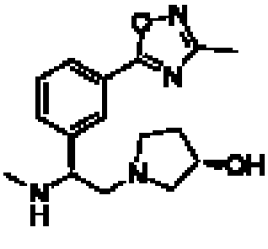


Into a 50-mL round-bottom flask, was placed a solution of benzyl N-[(1 S)-2-[(3 Ξ)-3-[(tert^utyldimethylsilyljo-iy] pynoudin-1 -yl] -1 -[3 -[1 -(cyclopropylmethyl)- 1H-imidazol-2-yl] phenyl] ethyl] -N-methylcarbamate (270 mg, *0 .46* mmol, 1.00 equiv) in concentrated HC1 aqueous (5 mL). The resulting solution was stirred for 2 h at 80°C. The resulting mixture was concentrated under vacuum. This resulted in 200 mg (crude) of (3Ξ) -1-[(2Ξ)-2-[3-[1-(cycbpropylmethyl)- 1H-imidazol-2 -yl] phenyl] -2 -(niethylamino)ethyl] pyrrolidin-3-ol as yellow oil.

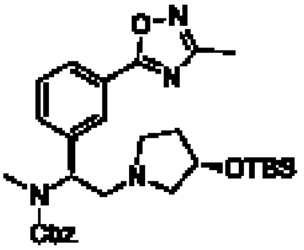
LC-IvE (ES, m/z): 341 (M+l).

Example 32-b

(S)-1-((¾-2-(3-(3-methyl-1,2,4-oxadiazol-5-yl)p]*ny]J-2-(methylajnino)ethyl)pyrrolidin-3-ol



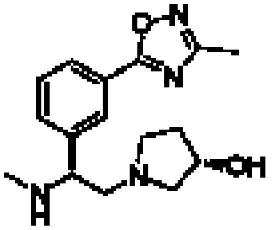
Step (i) Synthesis of benzyl ((S)-2-((S)-3-((tert-butyidime1hylsn^^ oxy)pyrrolidin-1-yl)-1-(3-(3-methyi-l ,2,4-oxadiazol-5 -yl)phenyl)ethyl)(methyl)carbamate



Into a 50-mL round-bottom flask, was placed a solution of ethyl 3-[(lS)-l-[[(benzyloxy)carbonyi] (memyi)amino] -2 -[(3Ξ)-3- [(tert-butyldimethylsilyl)oxy] pyrrolidin- 1-yl] ethyTJbenzoate (1.0 g, 1.85 mmol, 1.00 equiv) in toluene (10 mL). To the solution were added (E)-N_ydroxyethenimidamide (2.74 g, *36.99* mmol, 20.00 equiv), potassium carbonate (1.27 g, *9.19* mmol, 4.97 equiv) and 4-dinttthykminopyridine (23 mg. 0.19 mmol, 0.10 equiv). The resulting solution was stirred for 24 hours at 110*C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was dissolved in 20 mL of ethyl acetate. The resulting mixture was washed with water (2x10 mL) and brine (2x10 ml_). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:100-1 :5). This resulted in 0.796 g (78%) of benzyl N-[(lS)-2-[(3S)-3-[(tert-butyld^ hylsilyl)oxy]pyrrolidin-1-yl]-1-[3-(3-methyl-l ^,4 -oxadiazol-5-yl)phenyi] emyiJ-N-methylcarbamate as yellow oil.

LC-IvE *(ES*, *m/z*): *551* (M+l).

Step (ii) Synthesis of (S)-l -((S)-2-(3-(3-n¾thyl-l,2,4-oxadiazol-5-yl)phenyl)-2-(methylamino)emyi)pyrrdidin-3 -ol



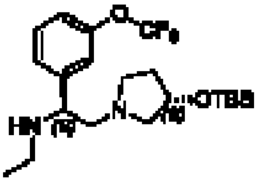
Into a 25-mL round-bottom flask, was placed a solution of benzyl N-[(l S)-2-[(3S)-3-[(tertJ3utyldimethylsilyl)oxy] pyrrokdin-1 -yij -1 -[3 -(3 -methyl- 1,2,4-oxadiazol-5 -yl)phenyi] ethyi] -N-methylcaibamate (400 mg, 0.73 mmol, 1.00 equiv) in concentrated HC1 aqueous (3 mL). The resulting solution was stirred for 1 hour at 70°C in an oil bath. The resulting solution was diluted with 20mL of water. The resulting mixture was washed with

DCM (3xlO nil-) and concentrated under vacuum. This resulted in 198 mg (crude) of(33)-l-[(2Ξ)-2- P-(3-methyl-l,2,4-oxadiazol-5-yl)phenyl]-2-(me 1hykmino)ethyI] pynOudin-3 -ol as light yellow oil.

LJC-IVE (ES , m/z): 303 (M+l).

Example 33-b

(S)-2-((¾-3-((tert-butyidijnethylsilyl)oxyjpyTrolidirv1-yl)-N-ethyl-1-(3-(trifluoromethoxy)phenyi)ethajiamine



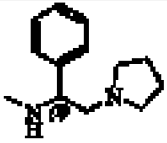
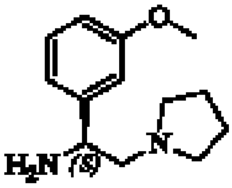
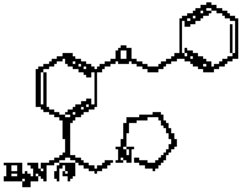
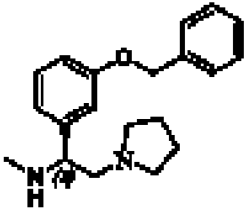
Into a 250-nil- 3-necked round ^bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of (13)-2-[(33)-3-[(tert-butyldime1hylsnyl)oxy]pymlidin-1-yl]-1-[3-(trifluoromethoxy)phenyl]ethan-1-ol (5 g, 12.33 mmol, 1.00 equiv) in dichloro methane (140 mL). This was followed by the addition of TEA *(6.2* g, 61.27 mmol, 5.00 equiv) and IvIsCl (4.2 g, *36*.S4 mmol, 3.00 equiv) at 0*C. The mixture was stirred at 25°C for 2 h. To the mixture was added ethanamine (7.9 g, 175.23 mmol, 10.00 equiv) dropwise with stirring at 0-5*0. The resulting solution was stirred **for** I8 h at 25°C. The resulting mixture was washed with water (3x50mL) and brine (3x50 mL). The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:4). This resulted in 4 g (75%) of [(1Ξ)-2-[(3Ξ)-3-[(tert-butyldimethylsilyl)oxy]pyrrolidin-1-yl]-1-[3-(trifluoromethoxy)phenyl]ethyl](ethyl)amine as light yellow oil

LJC-IVE (ES, m/ζ): 433.3 (M+l).

Further examples of the amine intermediates of formula (b), as in **Table 2**, can be prepared by the following procedures substantially similar to those described previously using suitable starting materials:

Table 2

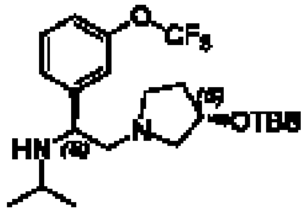
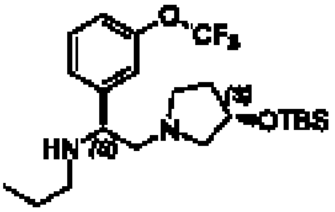
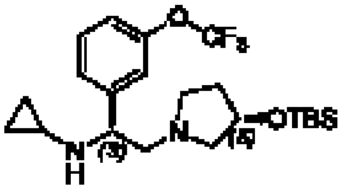
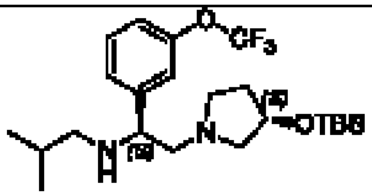
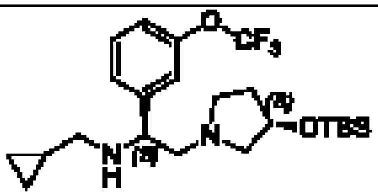
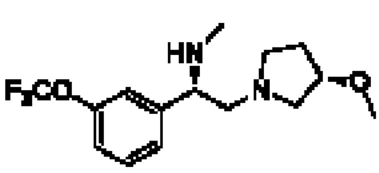
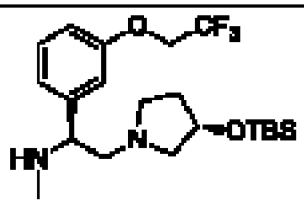
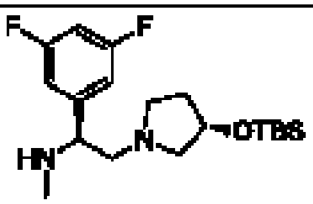
Ex No.	Amine intermediate	Analytical data

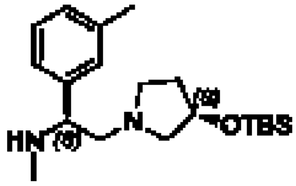
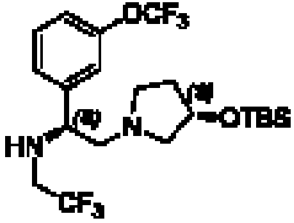
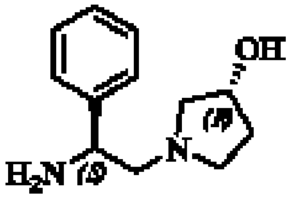
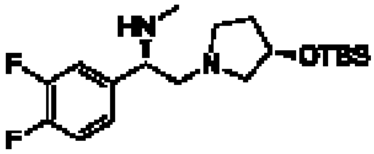
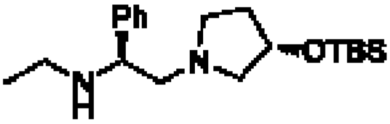
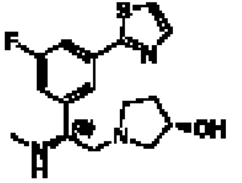
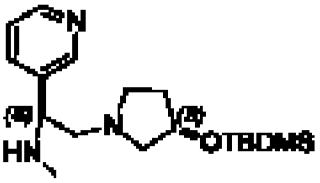
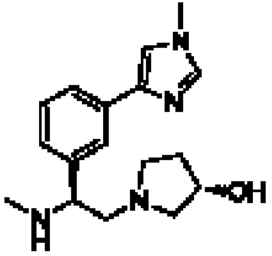
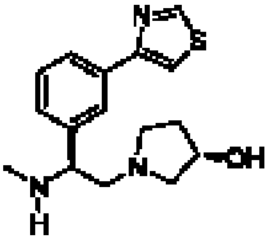
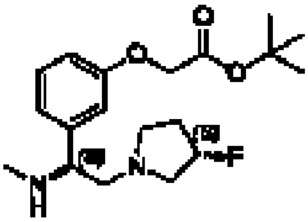
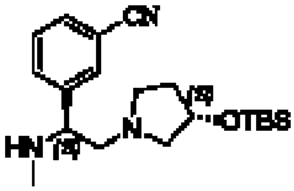
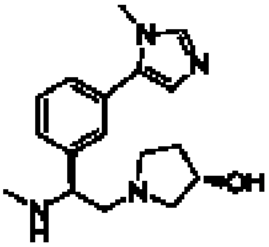
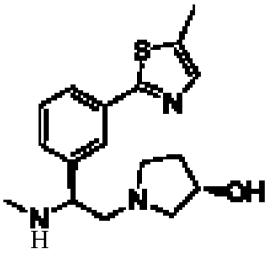
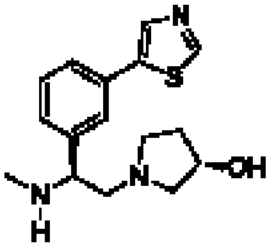
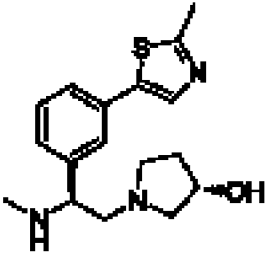
	of formula (b)	
34-b		^{1}H-NMR (*dt* - DMSO, 400 MHz): 5 7.36-7.28 **(in,** 4H), 7.24-7.22 (m, 1H), 3 55-3.51 (m, 1¾ 2.66-2.61 (m, 1H).
35-b		¾ NMR (*dt* -DMSO, 400 MHz): 5 7.37-7 3 0 (m, 2H), 7.29-7.24 (m, 2H), 7.23-7.19 (m, 1H), 4.19-4.14 (m, 1H), 3.96-3.92 (m, 1H), 3.32 (bs, 2H), 2.80-2.76 (m, 1H), 2.69-2.65 (m, 1H), 2.43-2.38 (m, lH), 2 32-2.26 (m, 2H), 2.00-1 .91 (m, 2H), 1.56-1 .49 (m, 1H).
36-b		¾-NMR (400 MHz. CDCI3+ *dt* -DM50): 5 3 3 2 (bs, 2H), 2.60-2.57 (m, 1H), 2.56-2.47 (m, 5H), 2.35-2.30 (m, 2H), 2.21-2.1 l(m, 1H), 1.58-1 .76 (m, 4H), 1.19-1 .00 (m, 6H); MS (EΞ): m/z 197 (M+l).
37-b		'H -NMR (*d*, -DM30, 400 MHz): S 7.19 (t, *J* = 7.9Hz, 1H), 6.96-6.91 (m, 2H), 6.77-6.75 (m, 1H), 3.95-3.92 (m, 1H), 3.73 (s, 3H), 2.45-2 .40 (m, 2H), 2 .33-2 .36 (m, 2H), 1.93-1 .81 (m, 2H); MΞ (EΞ): m/z 2 2 1.2 (M+l).
3S-b		^{1}H-NMR (*dt* -DM30, 400 MHz): *5* 7.44-7.31 (m, 5H), 7.24-7.19 (m, 1H), 6.92-6.86 (m, 2H), 6.77 (d, *J* = 7.3Hz, 1H), 5.08 (s, 2H), 4.62-4.58 (m, 1H), 2.38-2.29 (m, 2H), 1.*65-1 .59* (m, 4H), 1.34-1 .24 (m, 4H); MS (EΞ): m/z 298 (M+l).
39-b		^{1}H-NMR (*dt* - OMΞO, 400 MHz): 5 7.46-7.30 (m, 5H), 7.22 (t, *J* =7.9 Hz, 1H), 7.0 (s, 1H), 6.87 (dd, J_1 = 2.6 Hz, J_2 = 8.0 Hz, 2H), 5.07 (*s,* 2H), 3.57-3.53 (m, 1H), 2.66 (t, *J* = 10.8 Hz, 1H), 2.57 (d, *J* = 5.2 Hz, 3H), 2.43-2.24 (m, 4H), 2.14 (s, 2H), 1.68 (s, 4H); MΞ (EΞ): m/z 3 1 1 (M+l).
40-b		^{1}H-NMR: (CDCb): S 7.75-7.52 (m, 4H), 4.84-4.58 (m, 1H), 4.53 (m, 2H), 4.15 (s, 1H), 4.07-3.95 (m, 2H), 3.62-3.42 (m, 4H), 2.63 (s, 3H), 2.27-2.16 (m, 1H), 2.06-2.01 (m, 1H); LC-MΞ: (EΞ, m/s): 305 (M+l).

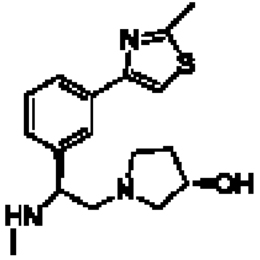
41-b		^{1}H-NMR (d_6 –DMSO, 400 MHz): δ 7.82-7.62 (m, 3H), 7.59-7.54 (m, 1H), 4.74 (t, J = 7.3 Hz, 1H), 2.50-2.49 (m, 4H), 2.33-2.18 (m, 2H), 1.83-1.56 (m, 4H); MS (ES): m/z 216.2 (M+1)
42-b		^{1}H-NMR (d_6 –DMSO, 400 MHz): δ 7.64 (s, 1H), 7.39 (s, 1H), 7.32-7.27 (m, 3H), 7.21-7.20 (m, 2H), 5.24 (s, 2H), 3.91-3.87 (m, 1H), 2.40-2.38 (m, 4H), 1.89-1.80 (m, 2H), 1.67-1.62 (m, 4H); MS (ES): m/z 271 (M+1).

Further examples of the amine intermediates of formula (b), as in **Table 3**, can be prepared by the following procedures substantially similar to those described previously, using suitable starting materials:

Table 3

Example No. / Structure / Characterization		
 MS (ES): m/z 227 (M+1) Example No. 43-b	 LC-MS (ES, m/z): 447 (M+1) Example No. 44-b	 LC-MS (ES, m/z): 447 (M+1) Example No. 45-b
 LC-MS (ES, m/z): 445 (M+1) Example No. 46-b	 LC-MS (ES, m/z): 461 (M+1) Example No. 47-b	 LC-MS (ES, m/z): 459 (M+1) Example No. 48-b
 LC-MS (ES, m/z): 319 (M+1) Example No. 49-b	 LC-MS (ES, m/z): 433 (M+1) Example No. 50-b	 LC-MS (ES, m/z): 371 (M+1) Example No. 51-b

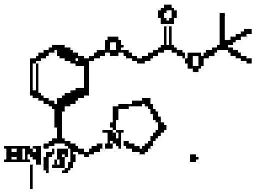
 LC-MS (ES, m/z): 349 (M+1) Example No. 52-b	 LC-MS (ES, m/z): (M+1) 487 Example No. 53-b	 MS (ES): m/z 207.1(M+1). Example No. 54-b
 LC-MS (ES, m/z): 371 (M+1) Example No. 55-b	 LC-MS (ES, m/z): 349 (M+1) Example No. 56-b	 LC-MS (ES, m/z): 322 (M+1) Example No. 57-b
 LC-MS (ES, m/z): 336 (M+1) Example No. 58-b	 LC-MS (ES, m/z): 301 (M+1) Example No. 59-b	 LC-MS (ES, m/z): 304 (M+1) Example No. 60-b
 LC-MS (ES, m/z): 353.2 (M+1) Example No. 61-b	 LC-MS (ES, m/z): 360.2 (M+1) Example No. 62-b	 LC-MS (ES, m/z): 301 (M+1) Example No. 63-b
 LC-MS (ES, m/z): 318 (M+1) Example No. 64-b	 LC-MS (ES, m/z): 304 (M+1) Example No. 65-b	 LC-MS (ES, m/z): 318 (M+1) Example No. 66-b



LC-MS (ES, m/z): 318 (M+1)

Example No. 67-b

Further examples of the amine intermediates of formula (b) which can be prepared by substantially similar procedures as described above, include: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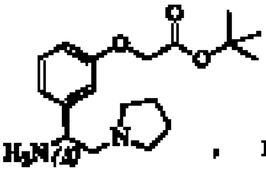
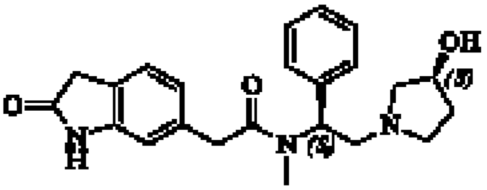

,


Following are the non-limiting examples of compounds of general formula (I)

Example 1

N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetamide



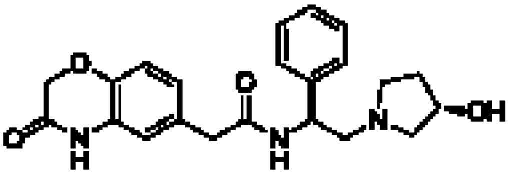
To a solution of 2-(2-oxoindolin-6-yl)acetic acid (4 g, 20.9 mmoles) in dichloromethane were added at room temperature, dicyclohexane carbodiimide (4.2 g, 20.9 mmoles) in DCM (30 mL) and 1-hydroxy benzo triazole (2.7 g, 20.9 mmoles) and the mixture was stirred at room temperature for 10 minutes. To this mixture was added (S)-1-((S)-2-(methylamino)-2-phenylethyl) pyrrolidin-3-ol (4.5 g, 20.9 mmoles) and the contents were allowed to stir for 12 h at room temperature. The reaction mixture was filtered and the filtrate was diluted with DCM (50 mL). The organic layer was washed with sat.$NaHCO_3$ solution (50 mL), brine solution (2x50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude. The crude was purified by flash column chromatography over silica gel

(230-400 mesh) using 10% IvfeOH in DCM to furnish the desired compound as a cream colour solid (3 g).

Mating point: 166-168 °C; ^{1}H-NMR (400 MHz, DMSO-di): δ 10-43 (s, 1H), 7.42-7.26 (m, 5H), 7.18 (d, *J* = 7.5 Hz, 1H), 6 £9-6 81 (m, 2H), *5.93* (d, *J* = 5.4 Hz, 1¾ 4.96 (s, 1H), 4.26 (s, 1H), 3.88-3.84 (m, 1H), 3.74-3.70 (m, 1H), 3.49 (s, 2H), 3.14 (s, 1H), 2.92-2.76 (m, 6H), 2.45-2.40 (m, 2H), 2.06-1.98 (m, 1H), 1.58 (s, 1H); IR (KBr, cm^{-1}): 3325, 2938, 2793, 2769, 1713, 1618, 1462, 1383; IvE (ESI): m/z 394.0 (M+l).

Example 2

N-[(1S)-2-[(3S)-3-hydroxypyrrolidin-1-yl]-1-phenylethyl]-2-(3-oxo-3,4-dihydro-2H-1,4-benxDxaxin-6-yl)acetajriide

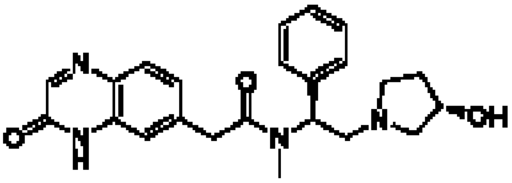


Into a 8-mL round-bottom flask, were placed 2-(3-oxo-3,4-dmydro-2H-l,4-benzoxazin-6-yl)acetic acid (50 mg, 0.24 mmoL 1.00 equiv), (3S)-l-[(2S)-2-amino-2-phenylethyl]pyrrohdin-3-ol (52.2 mg, 0.25 mmol, 1.05 equiv), EDCI (48.7 mg, 0.25 mmol, 1.05 equiv), HOBT (34.2 mg, 0.25 mmol, 1.05 equiv), DIEA (46.7 mg, 0.36 mmol, 1.50 equiv) and tetrahydrafuran (3 mL). The resulting solution was stirred overnight at 28 °C. The crude product (100 mg) was directly purified by Prep-HPLC with the following conditions (Waters): Column, Xbridge Prep CI8, 5um, 19*150mm; mobile phase, water with 0.03%NH_3H_2O and CH^CN (15.0% CH_3CN up to 34.0% in 8 min, up to 100.0% in 2 min, down to 15.0% in 2 min); Detector, UV 254&220nm. This results d in 61.4 mg (64%) of N-[(1Ξ)-2-[(3S)-3-hydroxypyrrolidin-l-yl]-1-phenylethyl]-2-(3-oxo-3,4-dihydro-2H-1,4-berizoxazm-6-yl)acetamide as a white solid.

IvE (ESI) m/z: 396 (Mfl); ^{1}H-NMR (DMSO-d_6, 400MHz): 5 10.7 (s, 1H), 8.46 (d, 1H, *J* = S.4Hz), 7.29 (m, 4H), 7.22 (m, 1H), 6.81-6.86 (m, 3¾ 4.75-4.88 (br, 2¾ 4.51 (s, 2H), 4.15 (br, 1H), 3.29-3.42 (m, 4H), 2.32-2.72 (m, 4H), 1.95 (m, 1H), 1.51 (m, 1H).

Example 3

N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methyl-2-(3-oxo-3,4-dihydro¾uino xalijı-6-yl)acetamide

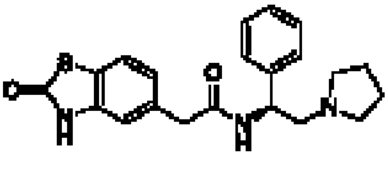


A solution of 2-(3-oxo-3,4-dihydroquirLOxahn-6-y^ cetic acid (50 mg, 0.24 mmol, 1.00 equiv) in tetrahydiOfuran/DMF (1 mL/1 mL), EDCI (49.4 mg, 0.26 mmol) and HOBt (34.7 mg, 0.26 mmol, 1.05 equiv) was stirred for 30 min at room temperature. To this was 1hen added (3S)-l -[(2S)-2-(n¾mykmmo)-2-pheny^ thyl]pyrrolidin-3-ol (56.6 mg, 0.26 mmol, 1.05 equiv). The resulting solution was allowed to react for an additional 3.0 h at 25*0. The solution was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (1#-Fte-HPLC-016(Waters)): Column, Xbridge Prep CIS, 5um, 19*150 mm; mobile phase, WATER WITH 0.03%NH_3H_2O and CHsCN (10 0 % CH_3CN up to 34.0% in 15 min, up to 100.0% in 2 min,down to 10.0% in 1 min); Detector, UV 254&220nm. This resulted in N-[(1S)-2-[(3S)-3-hydroxypyrrohdin-1-yl]-1-phenylethyl]-N-methyl-2-(3-o-io-S,4-dihydroquinoxalin-6-yl]acetar-uide (45 mg) as a white solid

LC-IvE (EΞ, *m/z)* 407 (M+1J; ^{1}H-NMR (DIvISO-dt, 300MHz): 5 12.43 (s, 1H) , 8.14 (s, 1H), 7.74 (d, *J* =8.7Hz, 1H), 7.38-7.22 (m,7H), 5.88 (s, 1H), 4.84 (s, 1H), 4.20 (s, 1H), 3.99-3.82 (m, 2H), 2.75-2.60 (m, 4H), 2.75 (s, 3H), 1.95-1 .93 (m, lH), 1.55 (s, lH).

Example 4

(S)-2-(2-oxo-2,3-dihydrobenzo[djthiazol-5-*y*l)-N-(1-phenyl-2-(pyrrolidin-1-yl)ethyl)acetajnide



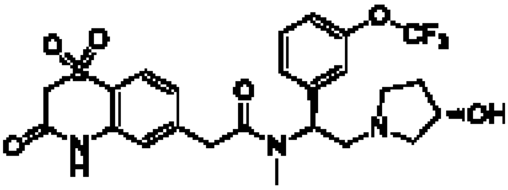
Into a 8-mL vial, were placed a solution of 2-(2-om-2,3-dihydro-l ^-benzothiasol-5-yl)acetic acid (40 mg, 0.19 mmol, 1 0 0 equiv, obtained in scheme 6) in tetmhydrofuran (1 mL), (13)-l -phenyl-2-(pyrrohdin-l -yl)ethan-l -amine (36 mg, 0.1 9 mmol, 0.99 equiv), EDCI

(40 mg, 0.21 mmol, 109 equiv) and HOBt (28 mg, 0.21 mmol, 1.08 equiv). The resulting solution was stirred overnight at 25*C. The reaction was then quenched by the addition of 1 mL of sat. aq. NaHCOs . The resulting solution was extracted with 8x2 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give crude product which was purified by Prep-TLC (MeGH/DCM=l/20). This resulted in 30 mg of the titled compound as a white solid.

LC-IvE (EΞ, *m/z)* 382 (M+1); ^{1}H-NMR(DMSO-d_6, 300 MHz): 5 11.823 (1H, s), 8.527 (1H, d, *J*=8.1 Hz), 7.457 (1H, d, *J*=S.4Hz), 7.380-7.120 (5H, m), 7.036 (2H, d, *J*=5.1 Hz), 4.955-4.875 (1H, m), 3.550-3.440 (2H, m), 2.880-2.690 (1H, m), 2.680-2.550 (5H, m), 1.770-1.5 (4H, m).

Example 5

Synthesis of 2-(1, 1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(trifluoromethoxy)phenyl)ethyl)-N-methylacetamide



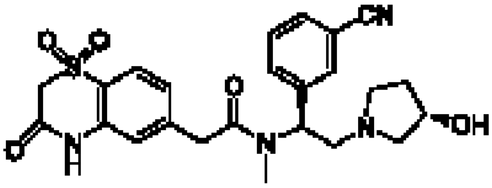
Into a 5-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2-(1, 1,3-trioxo-3,4-dihydro-2H-1-[6],4-berEohiazin-6-yi)acetic acid (50 mg, 0.20 mmol, 1.00 equiv) in N,N-dimethylformamide (1 mL), EDCI (41.4 mg, 0.22 mmol, 1.10 equiv), HOBt (29.1 mg, 0.22 mmol, 1.10 equiv), triethylamme (20.8 mg, 0.21 mmol, 1.05 equiv). Then (33)-l-[(23)-2-(methylamino)-2-[3-(trifluoromethoxy)phenyl]e1hy^ pyrrolidin-3-ol-2,2,2-trifluoroacetate (82.6 mg, 0.2*1* mmol, 1.05 equiv) were added at 0°C. The resulting solution was stirred for 2.0 h at 25°C. The resulting solution was diluted with 30 mL of dichloromethane, washed with 1x10 mL of sodium bicarbonate. The aqueous solution was extracted with 3x30 mL of dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product (70 mg) was purified by Prep-HPLC with the following conditions: Column, prep CIS 5um; 19*150mm; mobile phase, 0.03%NH$_3$H$_2$O ard CH$_3$CN;ratio:l 5%-

60%;time;10 min; Detector. UV 254 nm. This resulted in 25.7 mg (24%) of the title compound as a white solid.

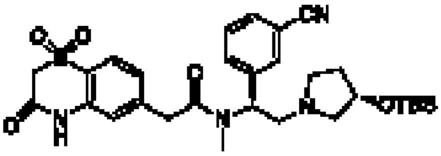
LC-IvE : (ES, m/z): 542 (M+IJ;^{1}H-NMR: (DIvEO) 5 11.23 (d, *J*=10.*5Hz,* 1H), 7.78-7.73 (m, 1H), 7.54-7.48 (m, 1H),7.37-7.28 (m, 3H), 7.22-7.17 (m, 1H), 7.12 (s, 1H), 5.85 (s, 1H), 4.754.7 1 (m, 3H), 4.20 (s, 1H), 4.05-3.83 (m, 2H), 2.91-2.*64* (m, 6H), 2.50-2.42 (m, 1H), 1.98-1 *94* (m, 1H), 1.58-1 .49 (m, 1H).

Example 6

N-((S)-l-(3-cyar» phenyl)-2-((S)-3-hydro xyp ynvlttin- l-yl)ethyl)-2-(l, l-dioxido-3-oxo-3,4-dihydro-2H-benxo[b][l,4]tMadn-6-yl)-N-methylacetamide

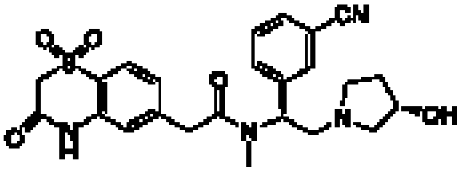


Step (i) Synthesis of N-((3)-2-((3)-3-((tert-butyldimemy^ yl)oxy)pyrrolidin-1-yl)-1-(3-cyinophenyl) ethyl)-2-(1, 1-did xido-3-oxo-3,4-dmydro-2H -benzo[b] [1,*4]* thiazin-o-yl)-N-methylacetamide



Into a 10-mL sealed tube, was placed a solution of 2-(l,l-diDxido-3-oxo-3,4-dihydro-2H-ben3o[b] [l,4]thkzin-0 -yl)acetic acid (76.5 mg, 0.30 mmol, 1.00 equiv) in tetrahydrofuran (2 mL). Then EDCI (63.4 mg. 0.33 mmol. 1.10 equiv), HOBt (44.6 mg, 0.33 mmol, 1.10 equiv), 3-[(1Ξ)-2-[(3Ξ)-3-[(tert-butyldimemylsilyl)oxy] pyrrolidin-1-yl]-1-(methylamino) emy^benmnitrile (118.8 mg, 0.33 mmol. 1.10 equiv) were added at 0°C. The resulting solution was stirred for 2.0 h at 25°C. The resulting solution was diluted with 50 mL of dichloro methane. The resulting mixture was washed with 1x10 mL of sodium bicarbonate. The aqueous solution was extracted with 2x50 mL of dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was used in the next step without further purification.

Step (ii) Synthesis of N-((S)-1 -(3-cyanophen^)-2-((S)-3-h^o.iyp^didin-l-yl)eth5ii)-2-(l. 1-dioxido-3-oxo-3,4-dihydro-2H-benzo [b] [l^tkiazm-^-^J-N-methyiacetaniLde

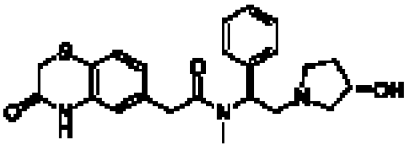


Into a 50-niL round-bottom flask, was placed a solution of N-((S)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1 -yl)- 1-(3-cyanophenyl)ethyl)-2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b] [1,4]thiazin-6-yl)-N-methylacetamide (30 mg, 0.05 mmol, 1.00 equiv) in tetrahydrofuran (1 mL). Then TBAF (39.4 mg, 0.15 mmol, 3.00 equiv) was added. The resulting solution was stirred for 3.0 h at 25*0. The resulting mixture was concentrated in 'va cuo.The crude product (150 mg) was purified byPrep-HPLC with the following conditions: Column, prep CIS 5urn; 19*150mm; mobile phase, 0.05%NH ;O and CHBCN ; ratio :10%-50%;timej0-10 mim Detector, UV 254 nm. This resulted in 17.2 mg (71%) of the titled compound as a white solid.

LC-IvE : (EΞ, m/s): 483 (M+1), ^{1}H-NMR: (300M¾ DIvE O-d_6) 5 11.23 (s, 1H), 7.85-7.76 (m, 3H), 7.67-7.65 (m, 1H), 7.59-7.55 (m, 1¾ 7.21-7.19 (m, 1H), 5.82-5.80 (m, 1H), 4.73-4.70 (m, 3H), 4.18 (s, 1H), 4.02-3.87 (m, 2H), 2 58-2.81 (m, 4H), 2.79-2.60 (m, 3H), 2.49-2.32 (m, 2H), 2.02-1.89 (m, 1H), 1.58-1.50 (m, 1H).

Example 7

Synthesis of N-((S)-2-((S)-3-hydroxypyrrolidiiv l -yl)-1-phenylethyl)-N-methyl-2-(3-oxo-3,4-dihydro-2H-benxo [b] [l,4]tMa_rin-6-yl)acetamide

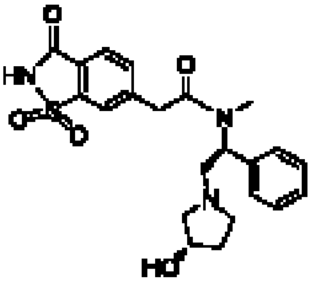


Into a 10-mL round-bottom flask, were placed a solution of 2-(3-oxo-3,4-dmydro-2H-l,44)enmtMazin-6-yi)acetic acid (Example 21-a, 20 mg, 0.09 mmol, 1.00 equiv) in tetrahydrofuran (1 mL), (3S)-1 -[(2S)-2-**(me1hykmirD**)-2-prenylethyI]pyrrolidin-3-ol (20 mg, 0.09 mmol, 1.01 equiv), EDCI (17.2 mg, 0.09 mmol, 1.00 equiv) and HOBT (12 mg, 0.09 mmol, 0 5 9 equiv). The resulting solution was stirred for 2 h at 25*C, diluted with 1 mL of water, extracted with 6x5 mL of dichloromethare . The combined organic layers were concentrated in vacuo .The crude product was purified by Prep-HPLC with the following conditions (Waters): Column., Xbridge Prep CIS, 5 urn, 19*150mm; mobile phase. WATER WITH 0.03%NH_3H_2O and CH_3CN (10.0% CH_3CN up to 34.0% in 15 nuin, up to 100.0% in 2 min,down to 10.0% in 1 nun);, Detector., UV 254 & 220nm. This resulted in 23 mg of the titled compound as a white solid.

LJC-IVE (EΞ, *m/z*): 426 (M+1); ^{1}H-NMR (DMSO-d_6, 300MHz) δ 1.5 (1H, s), 1.9 (1H, M), 2.5 (2H, m), *2.6* (8H, m), 3.6 (2H. m), 4.1 (lH, s), 4.5 (1H, s), 5.8 (1H, m), 6.8 (2H, m), 7.3 (6H, m), 10.5 (lH, s).

Example 8

2-(1, 1-dioxido-3-oxo-2,3-dihydrobenzo[d]isothiazol-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyli-N-methylacetamide

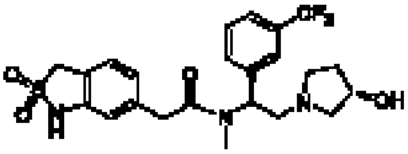


Into a 10-mL round-bottom flask, were placed a solution of 2-(1,1-dioxido-3-oxo-2,3-dih^drobei™[d]isothia--ol-6-7l)acetic acid (30 mg, 0.12 mmol, 1.00 equiv) in tetrahydrofuran (1 ML), EDC1 (26.3 mg, 0.14 mmol, 1.10 equiv), HOBt (18.5 mg, 0.14 mmol, 1.10 equiv), DIEA (24.1 mg, 0.19 mmol, 1.50 equiv) and (3S)-l-[(2S)-2-(methylamino)-2-phenylethyi]pyrrohdin-3-ol (30.1 mg, 0.14 mmol, 1.10 equiv). The resulting solution was stirred overnight at 25°C. The precipitate formed was collected by filtration, washed with dichloro methane and dried in an oven under reduced pressure. This resulted in 16.5 mg of the titled compound as a white solid.

LC-M5 (ES, *m/z)* 444(M+1); ^{1}H-NMR: (DMSO-^ 300MHs)5 9.364 (s, 1H), 9.355 (s, 1H), 7.236-7.967 (m,8H), 6.146-6.178 (m, lH), 5.461-5.548 (m, 1H), 3.8664.079 (m, 3H), 3.686-3.606 (m, 3H), 3.606 (m, 1H), 2.894 (m, 3H), 2.273 (m, lH), 1.764-2.082 (m, 2H).

Example 9

2-(2,2-dio sido -1,3 -df ıydrobenzo [c]isothia™l-6-y])-N -((S)-2-((S)-3-hydroxypyrroMin- 1-yl)-1-(3 -(trifluo romethyljp henyl)ethyl)-N- methylacetamide

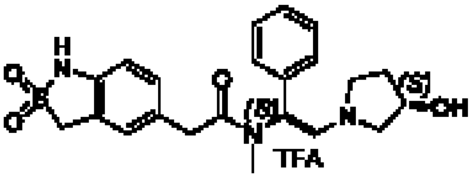


Into a 10-mL sealed tube, was placed a solution of 2-(2,2-dioxi ioo-1,3-dihydrobenzo[c] isothiazol-6-yl)acetic acid (34 nig, 0.15 mmoL 1.00 equiv) in N,N-dimethyiformamide (1 mL). Then EDCI (32 mg, 0.17 mmol, 1.10 ecjuiv), HOBt (22 mg, 0.16 mmol, 1.10 equiv), triethylamine (16 mg, 0.16 mmol, 1.05 equiv) and (3Ξ)-1 -[(2Ξ)-2-(methylam ino)-2 -P-(trifluorometh^phenyl]ethyl] pyrrolidin-3-ol 2^,2-trifluoroacetic acid (62 mg, 0.15 mmol, 1DO equiv) were added at 0*0. The resulting solution was stirred for 2.0 h at 25*0. The resulting solution was diluted with 20 ml_ of diehlorome thane, washed with 1:i 10 mL of sodium bicarbonate. The aqueous solution was extracted with 2x30 mL of dichloromethane. The combined organic lasers were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product (70 mg) was purified by Prep-HPLC with the following conditions: Column, prep CIS 5um; 19*150mm; mobile phase, 0.03%$NH_3.H_2O$ and C¾CN; ratio: 10%-29%;time;0-9 min; Detector, UV 254 nm. This resulted in 31.6 mg (40%) of the titled compound as an off-white solid

LC-IvE : (EΞ, *m/z*): 498 (MH); ^{1}H-NMR: (300MHs, DMSO-d_6) 510.44-10.36 (m, 1H), 7.63-7 .47 (m, 4H), 7 2 1-7.18 (m, 1H), *625-23* (m, 1H), 6.75 (s, 1H), 5.91 -5.86 (m, 1H), 4.4S (s, 2H), 4 .1 9 (s, 1H), 3.85-3.68 (m, 2H), 3.11-3 0 7 (m, 1H), 2 9 4-2 .80 (m, 2H), 2.65-2 .62 (m, 4H), 2.59 (s, 1H), 2.42-2.38 (m, 1H), 1.98-1.9 1 (m, 1H), 1.57-1.52 (m, 1H).

Example 10

5-(2-(((S)-2-((S)-3 -hydroxypyrrolidin-1 -yl)-1-p henyle thyl)(methyl)ajnino)-2-oxoethyl)-1,3-djhydrobeii-zo[c]isDthiazol-1 -iuJ.i 2,2-dioxide 2,2,2-trifluoroacetate

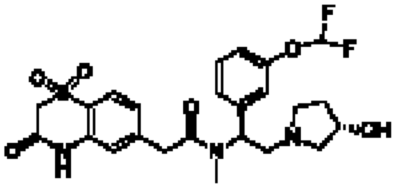


Into a 20-mL round-bottom flask, was placed a solution of 2-(2,2-dio iido-l,3-dihydrobenzo[c] isotkiazol-5-yl)acetic acid (SO mg, 0.35 mmol, 1.00 equiv), HOBt (50 mg, 0.37 mmol, 1.05 equiv), EDCI (74 mg, 0.39 mmol, 1.05 equiv) and (Ξ)-1-((Ξ)-2-(methylamino)-2-phenylethyl)pyrrolidin-3-ol (74 mg, 0.34 mmol, 1.10 equiv) in tetrahydrofuran (5 mL). The resulting solution was stirred for *6* h at 25*C. The resulting mixture was concentrated in vacuo The residue was purified by Prep-HPLC with the following conditions (l#-Pre-HPLC-01o ¯(Waters)): Column, Xbridge Prep CIS, 5um, 19*150mm; mobile phase, WATER WITH 0.05%TFA and CHjCN (10.0% CHjCN up to 30% in 15 mm, up to 100.0% in 2 mm,dowii to 10.0% in 1 min); Detector, UV 254&220nm to result in 166 mg (11%) of the title compoundas a white solid.

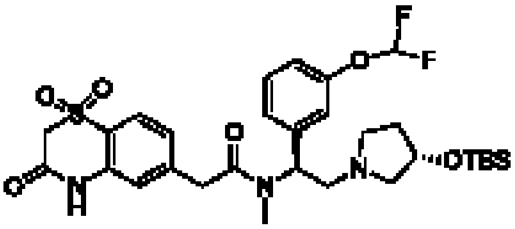
LC-IvE : (EΞ, m/z) 430 **(M+1);** ^{1}H-NMR(DMSO-d_6, 300MHz) δ 7.373-7.449 (m, 3H), 7.1S4-7.2S3 (m, 4H), *6223-6.249* (m, 1H), *6.252-6.299* (m, lH), 4.5S5 (s, 1H), 4.399 (s, 2H), 3.73S-3.SS3 (m, 6H), 3.400-3.576 (m, 2H), 2.7S7 (s, 3H), 1.S00-2.400 (br, 2H).

Example 11

N-((S)-1-(3-(difluoromethoxy)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-2-(1, 1-dioxido-3-oxo-3,4-dihydro-2H-heiu» [b] [l,4]thiaznL-6-yi)-N-methylacetamide

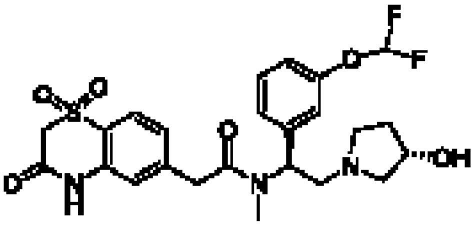


Step (i) Synthesis of N-((S)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-1-(3-(difluorometno-i^phen^l) ethyl)-2-(1, 1-dioKido-3-oxo-3,4-dmydro-2H-benzo [b] [1,4] tlidazin-6-yl)-N-methylacetamide



Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2-(l,l -dio ddo-3-oxo-3,4-dmyd o-2H-benzo[b] [l,4]11uazin-Q-yl)acetic acid (482 mg, 1.S9 mmol, 1.00 equiv) in N,Ndiniethylformamide (15 ml_). Then EDCI (397 mg, 2.07 mmol, 1.10 ecjuiv) and HOBt (279 mg, 2.06 mmol., 1.10 equiv) was added at 0-5oC.The resulting solution was stirred for 20 min at OoC. To this was added a solution of [(lS)-2-[(3S)-3-[(tert-butyldimemylsuyljoxy] pyrrohdin-1 -yl]-1-P-(difluoromethoxy) phenyl] ethylj (memyl)anune (754 nig, 1.88 mmol, 1.00 equiv) in N,N-dimethylformamide (5 mL) at O-5oC. The resulting solution was stirred for 2 h at 0-25oC. The reaction was then quenched by the addition of water. The resulting solution was extracted with ethyl acetate and the organic layers combined. The resulting mixture was washed with sodium bicarbonate(aq) and brine. The organic layers dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with dichloromethane/methanol (60/1-40/1). This resulted in 1.16 g (96%) of the titled compound as a yellow solid.

Step (ii) N-((S)-1-(3-(difluoro methoxy)pheny±)-2-((S) -3-**hydroxypy-Tolidin-**1-yl)ethyl)-2-(1, 1-di oxido-3-oxo-3,4-dihydro-2H-**ben30** [b] [1,4]tluazm-6-yl)-N **-memykcetamLde**

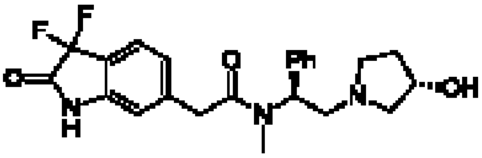


Into a 100-mL purged and maintaired with an inert atmosphere of nitrogen, was placed a solution of N-((3)-2-((S)-3-((tert-butyldimemy^^ ilyl)oxy)pyrrolidin-1-yl)-1-(3-(difluoromethoxyjphenyl) ethyl)-2-(1, 1-dioxido-3 -oxo-3,4-dmydro-2H-benzo [b] [1,4] thiazin-6-yl)-N-methylacetamide , obtained in the previous step, (553 mg, 0.87 mmol, 1.00 equiv) in tetmhydroiuran (8 niL), TBAF.3HjO (549 mg, 2.00 equiv). The resulting solution was stirred for 5 h at 25*0. The resulting mixture was concentrated under vacuum. The resulting solution was extracted with ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product (300 mg) was purified by Prep-HPLC with the following conditions (Bridge): Column, RP CIS 5um; 19*150mm; mobile phase, 0.03%NH$_3$.H2O and CHjCN; ratio: 20%-52%; timefl-lO min; Detector, UV 254 nm. This resulted in 151 mg (34%) of the title compound as a white solid.

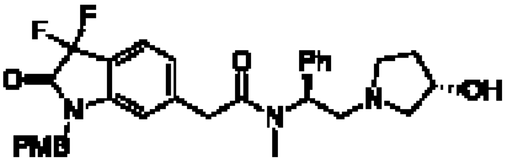
LC-IvE (ES, m/z): 524(M+1) ^H-NMR (CDjOD, 300MHz) 5 7.84 (d, *J*= 8.0Hz, l H), 7.42-7.38 (m, 1H), 7.27 (d, *J*= 8.0Hz, 1H), 7.22-7.20 (m, 2H). 7.18-7.10 (m, 2H), *623* (t, *J*= 74.0Hz , 1H), 6.05-6.01 (m, lH), 4.87 (s, 2H), 4.83 (s, 1H), 4.384.34 (m, lH), 4J06-3*99* (m, 1H), 3.91-3.87 (m, 1H). 3.10-2.94 (m, 2H), 2.86 (s, 3H), 2.84-2.78 (m, 1H), 2.61-2.52 (m, 2H). 2.17-2.12 (m, 1H). 1.75-1.71 (m. 1H).

Example 12

2-(3,3-difluoro-2-oxoindolin-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethylj-N-methylacetamide

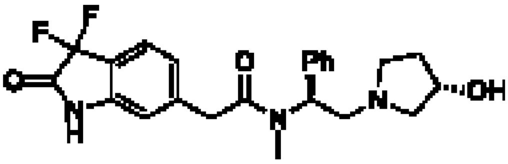


Step (i) Ξynthesis of 2-(3.3-difluoiO-l-(4-n¾tlioxybenzyl)-2-ox^ indolin-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin- 1-yl)-1-phenylethyl)-N-methykcetamLde



Into a 8-mL sealed tube, was placed 2-[3,3-difluoro-1-[(4-methoxyphenyl)methyl]-2-oxo-2,3-dihydro-lH-indol-6-yI] acetic acid (280 mg, 0.81 mmol, 1.00 equiv) in N,N-din¾thylfornramide (5 ml,). This was following by addition of EDCI (310 mg, 1.62 mmol, 2.01 equiv) andHOBt (163 mg, 1.21 mmol, 1.50 equiv). The resulting solution was stirred for 30mins at OoC.Then (3S)-1-[(2S)-2-(n¾thykmino)-2-phenylethyl]pyrrolidin-3-ol (178 mg. 0.81 mmol, 1.00 equiv) was added The resulting solution was stirred for 2 h at 25oC. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel colunm and eluted with dichloromethane/nwthanol/'amnioria (50: 1:1). This resulted in 330 mg (74%) of 2-[3,3-difluQro-l-[(4-methoxyphenyl)methyl]-2-oxo-2,3-dihydro-1H-indol-6-yl]-N-[(1Ξ)-2-[(3Ξ)-3-hydroKypyrrohdin-l-yl]-1-phenylethyl]-N-methylacetamide as brown oil.

Step (ii) Ξynthesis of 2-(3,3-difluoro-2-oxoindolin-6-yl)-N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methylacetamide

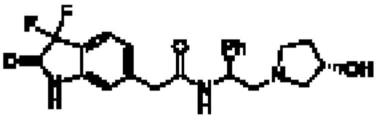


Into a 50-mL round-bottom flask, was placed 2-[3,3-difluoiO-l-[(4-n¾1noxyphen^)methyl]-2-oxo-2,3-dihydro-1 H-indol-6-yi] -N-[(1S)-2-[(3S)-3-hydroxypytrohdin- 1-yl]-1-phenyle thylj-N-memykcetamide (300 mg, 0.55 mmol, 1.00 equiv) in CH3CN (8 mL) Then a solution of (NH4)2Ce(NCG)6 (900 mg, 1.64 mmol, 3.01 equiv) in water(4 mL) was added. The resulting solution was stirred for 1 h at 30oC. The resulting solids were filtered out and washed with ethyl acetate. The filtrate was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with dichloromethane/methanol (100/1). This resulted in 13 mg (6%) of 2-(3,3-diiluoro-2-oKo-2,3-dihydro -1H-indol-6 -yl)-N-[(1S)-2-[(3S)-3-hydraxypyrrolidin- 1-yl]-1-phenylethyl] -N-methylacetamide as a white solid.

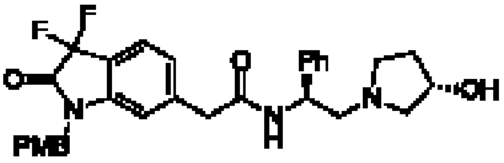
IvE (ES, m/z): 430 (M+1); ^{1}H-NMR (DMSO-d$_{6}$, 300MHz) 5 11.18 (s, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.40-7.20 (m, 5H), 7.05 (d, *J* = 7.8 Hz, 1H), 700-6.85 (m, 1H), 5.85 (s, 1H), 5.20-4.60 (m, 1H), 4.18 (s, 1H), 3.95 (d, *J* = 14.7 Hz, 1H), 3.75 (d, *J* = 15.9 Hz, 1H), 3.15-3.00 (m, 1H), 3.00-2.90 (m, 1H), 2.90-2.78 (m, 1H), 2.78-2.60 (m, 4H), 2.50-2.30 (m, 2H), 2.05-1.85 (m, lH), 1.50 (bs, 1H), F-NMR: (DMSO-di , 300MHz) : -110 (s, 2F).

Example 13

2-(3,3-difluoro-2-oxoindolin-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)acetamide

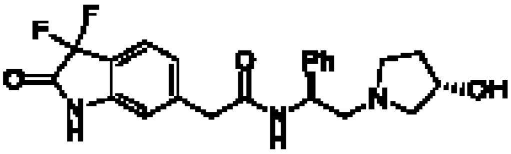


Step (i) Synthesis of 2-(3,3-dinuoro-l-(4-n¾thoxybenzyl)-2-oxoi^^ lin-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin- 1-yl)-1-phenylethyl)acetamide



Into a solution of 2-[3,3-difluoiO-l -[(4-methDxyphenyl)meth.yI] -2-o.io-2,3-dihydiO-lH-inlol-6-yI] acetic acid (300 mg, 0.86 mmol, 1.00 equiv) in N,N-dimethylformamide (3 ml_) was added EDCI (332 mg, 1.73 mmol, 2.01 equiv), HOBt (175 mg, 1.30 mmol, 1.50 equiv). After stirring for 10 min, (3S)-l-[(2S)-2-ammo-2-phenylethylIJpyrrohdin-3-ol (190 mg, 0 92 mmol, 1.07 equiv) was added. The resulting solution was stirred for 2 h at room temperature and concentrated under vacuum. The residue was applied onto a silica gel column with dichbrame1hiarie/me1hanol=50 :l . This resulted in 370 mg (80%) of 2 -[3-3-difluoro-l-[(4-methoxyphenyl)methyT] -2 -oxo -2,3 -dihydro - 1H-indol-6 -yl] -N- [(1S)-2- [(3 S)-3 -hydroxypytrolidin- 1-yl] -1 -phenyle1hyl]acetamide as a white solid. IvE (ES, m/z): 536 (M+l)

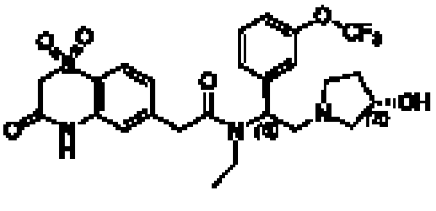
Step (ii) Synthesis of 2-(3,3-di luoro-2-oxoir dohn-6-yl)-N^ (S)-2-((S)-3-hydroxypyrrolidin-1-y!)- 1-phenyle thyl)acetamide



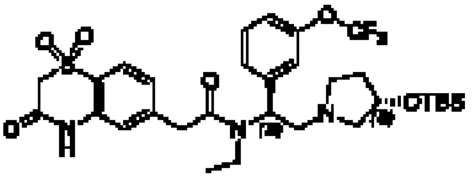
Into a solution of 2-[3,3-difhioro-l -[(4-methoxyphenyl)methyi] **-2 -oxo -2,3-dihydiO-**lH-iriiol-6 **-yl**]-N-[(lS)-2-[(3S)-3 **-hydrox^** rrolidin-1-yl]-1-phenylethyl]acetamide (370 mg, 0.69 mmol, 1.00 equiv) in CH_3CN (8 mL)/water(4 mL) was adcfed (NH+).Ce**(NQ5) i** (1.14 g, 2.0s mmol, 3.01 equiv). The resulting solution was stirred for 1 h at 30*0. The resulting solids were filtered out. The filtrate was concentrated under vacuum. The residue was applied onto a silica gel column with die Horomethane/methanol (100/1). This resulted in 14.1 mg (5%) of 2-(3,3-difluoro-2-oxo-2,3-dihydro-l H-indol-6-yl)-N-[(1S)-2 -[(3S)-3-hydroxypyrrolidin- 1-yl]-1-phenytethy^acetamide as a white solid. IvE (ES, m/z): 416 (M+1); ^{1}H-N IvIR (DMSO-d6, 300 MHz)5 11.1 7 (s, 1H), 8.58 (**d,** ***J*** = 7.8 Hz, 1H), 7.54 (**d,** ***J*** **=** 7.8 Hz, 1H), 7.48-7.18 (m, 5H), 7.05 (**d,** ***J*** = 7.8 Hz, 1H), 6.97 (s, lH), 4 S9 (s, lH), 4.16 (s, 1H), 3.63-3.42 (dd, ***J*** **=** 14.4, 21.5 Hz, 2H), 2.84-2.5° (m, 3H), 2.46-2.30 (m, 2H), 2.05-1 .85 (m, 1H), 1.50 (bs, 1H); F-NMR- (DMSO-d6, 300MHz): -1 10 (s, 2F).

Example 14

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-ethyl-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(trifluoromethoxy)phenyl)ethyl)acetamide

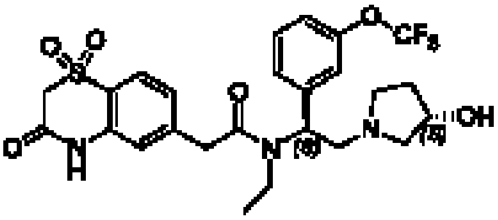


Step (i) Synthesis of N-((S)-2-((S)-3-((tert-butyidimemylsu^^ oxy)pyrrolidin-1-yl)-1-(3-(triiluoromethoxy)phenyl)ethyi)-2-(1, 1-dioxido-3-oxo-3,4-dmydro-2H-benso [b][1,4]thiazin-6-yl)-N-emykcetamide



Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2-(1,1-dioxido-3-oxo-3,4-dmydn>2H-benzo[b][1,4]thiazin-6-yl)acetic acid (62.0 mg, 0.24 mmoL, 1.05 equiv) in N-N-dimemylformanude (10 mL). Then EDCI (*61* mg, 0.35 mmol, 1.51 equiv) and HOBt (*46* mg, 034 mmol, 1.47 equiv) were added at OoC. After stirred for 5 min, [(lS)-2-[(3S)-3-[(tert-butyldimethylsi^ oxy]pyrrolidin-1-yl]-1-P-(trifluoromethoxy)phenyl]ethyl](ethyl)amine (100 mg, 0.23 mmol, 1.00 equiv) was added. The resulting solution was stirred for 2 h at room temperature. The resulting solution was diluted with 60mL of ethyl acetate. The resulting mixture was washed with water (3x2 OmL). brine (2x20mL), 10% ammonia aqueous (4x20mL) and brine (3x20mL). The mixture was dried over anhyirous sodium sulfate and concentrated under vacuum. This resulted in 143 mg (crude) of the title compound as a light yellow solid. MΞ (EΞ, m/z): 670 (M+1).

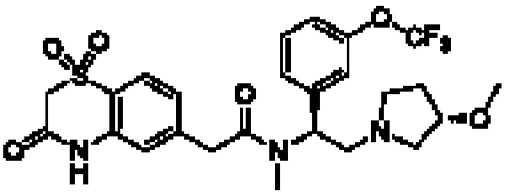
Step (ii) Ξynthesis of 2-(l, l-dioxidD-3-oxo-3,4-dmydro-2H-benzo[b][1,4]tMazin^-yl)-N-ethyl-N-((S)-2-((S)-3-hyioxypyrrolidin-1-yl)-1-(3-(trifluoromethoxy)phenyi)ethyl)acetamide



Into a 50-mI_ round-bottom flask, was placed a solution of N-((S)-2-((S)-3-((tert-butyldimemylsnyl)oxy)pyiTohdin-l -yl)-1-(3-(trifluoromethoxy)phenyl)ethyl)-2-(1, 1-dioxido-**3-oxo-3,4-dihydro**-2H-ierLZo [b][1,4]thiazin-6-yl)-N-ethylacetamide (*459* mg, 0b9 mmoL, 1.00 equiv) in methanol (15 mL). This was followed by the addition of cone. HC1 aqueous (1.5 mL) dropwise with stirring at 0*0. The resulting solution was stirred for 3 h at room temperature. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 50mL of HjO. The pH value of the solution was adjusted to 7-8 with saturated aqueous sodium bicarbonate. The resulting solution was extracted with dichloromethane (5x20mL) and the organic layers combined. The resulting mixture was washed with brine (3x20mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18; mobile phase, H_2O:MeCN=100:0 at 5min, then increasing to H_2O:MeCN=50:50 within 40 min; Detector, UV 254 nm. That resulted in 25 mg of Synthesis of 2-(1, 1-dioxido-3-oxo-3,4dmydro-2H -ben2D [b] [1,4] thiazm-6-yl)-N-ethyl-N-((S)-2-((S)-3-hydroxypyrrolidm- 1-yl)-1-(3-(trifluoromethoxy)phenyl)ethyl)acetamide as a white solid. MΞ (EΞ, m/z): 556 (M+1); 1H-NMR (DIvEO, 400Hz) S 11.23 (s, 1H), 7.76-7.74 (m, 1H), 7.50-7.14 (m, 6H), *5.69* (m_ 1H), 4.70-4.74 (m, 3¾ 4.16 (m, 1H), 4.01-4.05 (m, 1H), 3.79-3.90 (m, 1H), 3.22-3.32 (m, 2H), 2.99 (m, 1H), 2.80-2.82 (m, 1H¾ 2.67-2.68 (m, 1H), 2.33-2.51 (m, 2H), 1.91-1.*96* (m, 1H), 1.52 (m, 1H), 0.88-0.92 (m, 2H), 0.67-0.70 (m, 1H)

Example 15

2-(1, 1-du xido-3-o» -3,4-dihydro-2H-lli en o[b] [l,4]thiazin-6-yl)-N-((S)-2-((!$)-3-methoxypyrrolidin-1-yl)-1-(3-(trifluoromethoxy)phenyl)ethyl)-N-methylacetamide

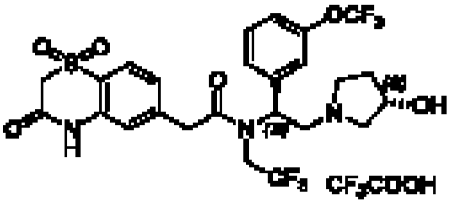


Into a solution of 2-(l , l-dioxido-3-oxo-3,4-dihydro-2H-benzo[b] [l,4]mkzin-6-yl)aceuc acid (200 mg, 0.78 mmol, 1.10 equiv) in N,N-dimethylformamide (30 mL) was added EDCI (204 mg, 1.06 mmoL 1.49 equiv), HOBT (140 mg, 1.04 mmol, 1.45 equiv). Then [(1Ξ)-2-[(3Ξ)-3-methoxypyrrolidin-1-yl]-1-|3-(tritluoromethoxy)phenyI] ethyl](n¾myl)amine (227 mg, 0.71 mmol, 1.00 equiv) was added The resulting solution was stirred for 6 h at room temperature. The reaction was then quenched by the addition 10ml of water. The resulting aqueous solution was extracted with 3x30 mL of ethyl acetate. The organic layers was combined and dried over sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with dichloromelhane/methanol (10: 1). This resulted in 28.9 mg (7%) of2-(l, l-dioxido-3-oxo-3,4-dihydro-2H½5nzo^ ,4]thiazin-6-yl)-N-((Ξ)-2-((Ξ)-3-methoxypyirolidin-1-yl)-1-(3-(trifluoromethoxy)phenyl)ethyl)-N-methylacetamide as a white solid.

MS (ES, m/z): 556 (M+l); ^{1}H-NMR (DMSO-d_6, 400 MHz) 5 11.23 (1, 1H), 7.76 (m, 7H), 5.82 (t, J=7.2Hz, 1H), 4.70 (s, 2H), 3.99-3.SI (m, 3H), 3.32-2.33 (m, 12H), 1.99-1.91 (m. 1H), 1.63 (s, lH).

Example 16

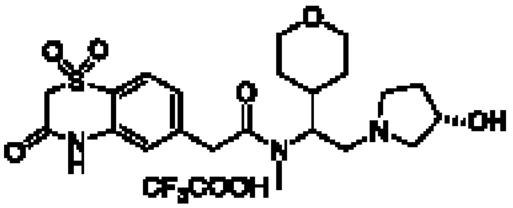
2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-b emo [b][l,4]thiazin-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(trifluoromethoxy)phenyl)ethyl)-N-(2,2,2-trifluoroethyl)acetamide 2,2,2-trifluoroacetate



2,2-(l, l-dioxido-3-oxo-3,4-dmydro-2H-berLZo|T -][1,4]thiazin-6-yl)acetic acid (1 g, 3.92 nunol 1.00 equiv) was added into 10ml of phosphroyl trichloride at room temperature. The resuiting solution was stirred for 30 min at 85*C in an oil bath. The resuiting mixture was concentrated under vacuum. The crude product was dissolved in 5ml THF. The resulting solution was added into a solution of [(lS)-2-[(3S)-3-[(tert-butyldimemylsilyl)oxy] pyrrolidin-1-yl]-1-[3-(triiluoromethoxy) phenyO ethyl] (2,2,2-triiluoroemyl)amine (1.9 g, 3.90 mmoL 1.00 equiv) in THF (lOmL), dropwished with stirring at 0 °C under nitrogen gas. The mixture was stirred for 2 hours at room temperature. Removing the solvent, the residue was purified by Prep-HPLC with the following conditions (waters): Column, SunFire Prep CIS, 19*150mm 5um; Mobile phase: WATER WITH 0.05% TFA and MeCN (30% MeCN up to 70% in 30 min, up to 100% in 2 min); Etetector, UV 254 nm. This resulted in 14 mg of the title compound as a white solid .LJC-MΞ (EΞ, mfz): (M+l) 610; ^{1}H-NMR (300MHz, DMSO-df.): 5 11.20 (s, 1H), 7.76 (d, J=8.1Hz, 1H), 7.39-7.55 (m, 4H), 7.08-7.15 (m, 2H), 5.57 (br, 1H), 4.72 (s, 2H), 4.41-4.58 (m, 3H) 3.78-4.16 (m, 5H), 3.65 (t, J=6.3HZ, 1H), 2.02 (br, 1H), 1.70-1.80 (m, 1H), 1.55-1.64 (m, 2H), 1.22 (s, 1H);

Example 17

2-(l, 1-di ı xido-3-Oxo-3,4-dihydro-2H-li enzo[b][1,4]thiazin-6-yl)-N-(2-((S)-3-hydroxypyrrolidin-1-yl)-1-(tetrahydro-2H-pyran-4-yl)ethyl)-N-methylacetamide-2,2,2-trifhioroacetate

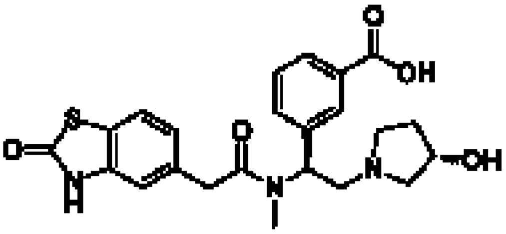


Into a solution of 2-(l, l-dio iido-3-o io-3,4-dh^dm-2H-benm[b] [1,4]thiazin-6-yl)acetic acid (127 mg, 0.50 mmol, 1.00 equiv) in N,N-dimethylformamide (5 mL) was added N-(3-dimethylantinopropyl)-N'-em^ arbodiimide hydrochloride (105 nig, 0.55 mmol, 1.10 equiv), l-Hydroxybenzotrizole(74 nig. 0.55 mmol, 1.10 equiv). The resulting solution was stirred for 30 min at 0°C in a water/ice bath. Then (3S)-l-[2-(mem^aniino)-2-(oKan-4-yI)ethyl]pyiTolidin-3-ol (120 mg, 0.53 mmoL 1.05 equiv) was added. The resulting solution was allowed to react, with stirring, for an additional 2 h at room temperature. The resulting mixture was concentiated under vacuum. The crude product (150 mg) was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, CIS silica gel; mobile phase, CH3CN/0.5¾ aq TFA=1:100 increasing to CH3CN/0.5% aq TFA=35:100 within 22 min; Detector, UV 254 nm. This resulted in 60 mg (21%) of the title compurd as a white solid.

IvE (ES, *m/z*): 466 [M-CF3COOH+H]$^+$; H -NMR (CDjOD, 400 MHz) 5 7.S2-7.S4 (d, ***J***=8Hz, 1H), 7 22-7.24 (d. ***J***=8Hz, 1H), 7.12 (s, 1H), 4.71-4.88 (m, 1H), ***4.564.69*** (m, 1H), 4.43-4.45 (m, 1H), 3.784.01 (m, 5H), 3.42-3.67 (m, 5H), 3.19-3.22 (m, lH), 3.02 (s, 3H), 1.92-2.45 (m, 2H), 1.***61***-1.SS (m, 2H), 1.35-1.45 (m, 2H), 1.21-1.25 (m, 1H).

Example 18

3-((S)-2-((S)-3-hydroxypyrroMin-l-yl>-l-(N-methyl-2-(2-oM-2,3-dihydiobenzo[d]thiazol-5-yl)acetamido)ethyl)benzoic acid

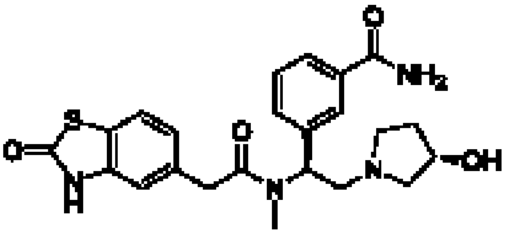


Into a S.OmL sealed tube, was placed a solution of N-[(13)-2-[(33)-3-[(tert-butyidimemylsu-yljox^pyrroh din-1 -yl]-l -(3-c5ianophen^)ethyl]-N-methyl-2-(2 -oxo-2,3-dihyda -1,3-**ben2othiazol** -5-^l)a-cetamide (200 mg, 0.36mmoL, 1.00 equiv) in tetrahydrofuran (l .OmL) and methanol (l .OmL). Then water (2.0mL) and potassium hydroxide (245 3mg, 4.37mmoL, 12.04 equiv) were added. The resulting solution was stirred for 15 h at 75°C and cooled to room temperature naturally. The pH value of the solution was adjusted to 2 with aqueous hydrogen chloride (2 moUL) and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column, X-Bridge, CI8, 15cm; mobile phase, Wate^contained 0.2% of NH+HCOj) and acetonitrile (5% acetonitrile up to 25% in lOmin, up to 100% in lmin, down to 5% in lmin); Detector, UV220/254 nm. This le suite din 70 mg (42%) of title compound as a white solid.

IvE (ES, *m/z*): 456 (M+l); ^{1}H-NMR (DIvE O-d_6, 400MHz) δ 7.85-7.84 (m, 2H), 7 5 3-7.44 (m, 3H), 7.10 (s, 1H), 7.04-6.95 (m, 1H), 5.91 (t, *J*=8.0Hz, 1H), 4.21-4.17 (m, 1H), 3£7 (d_ *J*=15.6Hz, 1H), 3.73 (d, *J*=16.0Hz, 1H), 3.16 (t, *J*=8.0Hz, 1H), 2.84-2.72 (m, 3H), 2.62-2.54 (m, 3H), 2.47-2.39 (m, 2H), 1.98-1 .93 (m, 1H), 1.54-1.45 (m, 1H)

Example 19

3-((S)-2-((¾)-3-hydroxypyrrolidin-l-yl)-l-(N-methyt2-(2-oxo-2,3-dihydrobenzo[d]thiazol-5-yl)acetamido)ethyl)benzamide

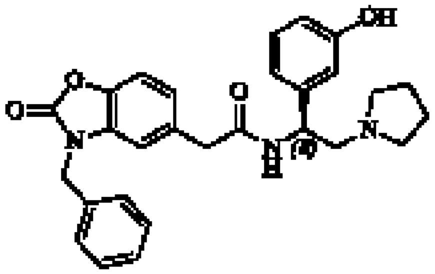


Into a S.OmL sealed tube, was placed a solution of N-[(lS)-2-[(3S)-3-[(tert-butyidimemylsnyl)ox-^pyrrohdin-l -yl]-l -(3-cyarDphenyl)ethyI]-N-methyl-2-(2-oxo-2,3-dihydro-l,3-beri2Dthiazol-5-yl)aceta-mide (SOmg, 0.15mmoL, 1.00 equiv) in tetrahydrofuran

(0.4mL) and methanol (0.4mL).Then water(0.8niL) and potassium hydroxide (98 .1 mg, 1.7mmol, 12.04 equiv) were added. The resulting solution was stirred for 15 h at 50 *C and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column, X-Bridge, CIS, 15cm; mobile phase, Wate^contained 0.2% of HH+HCOj) and acetonitrile (7% acetonitrile up to 25% in lOmin, up to 100% in lmin, down to 7% in lmin); Detector, UV220/254 nm. This resulted in 32 mg (48%) of 3 -((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl) -1 -(N-memyl-2-(2 -oxo-2 $_J$3-dihydroberLZo[d]thiazol-5-ylJacetamidoJethyDbenzamide as a white solid. MS (EΞ, *m/z*): 455(M+1); ^{1}H-NMR (DIvBO-*d*$_6$, 300MHz) 5 11.80-1 1.79 (m, 1H), 7.97 (s, 1H), 7.80-7.73 (m, 2H), 1.45-7.32 (m, 4¾ 7.08-6 9 5 (m, 2H), 5.88-5.82 (m, 1H), 492-4.83 (m, 1H), 4.18-4.05 (m, 1H), 3.86-3.81 (m, 1H), 3.70-3.64 (m, 1H), 3.08 (t, J=l 1.4Hz, 1¾ 2.82-2.55 (m, 6H), 2 38-2.22 (m, 3H), 195-182 (m, l H), 1.43-1 .35 (m, 1H)

Example 20

(*S*)-2-(3-benzyl-2-oxo-2,3-Aihydrobenzo[*d*]oxazol-5-yl>-*N*-(*l*-(3-hydroxyp l¾i^I)-2-(pyrrolidin-1-yl)ethyl)acetamide

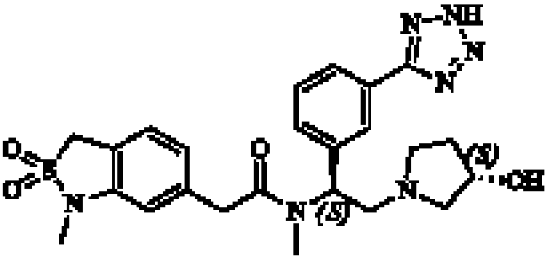


Hydrogenolysis of (S)-2-(3-bercyl-2-o io-2 $_J$3-diliydrobenm[d]oxazol-5-yl)-N-(l-(3-(benzylo iyipheryl)-2-(pyrrohdin-l-yl)emyl)ace^ mide in methanol at room temperature afforded the title compound in 64% yield as a while solid.

Melting point: 104-106 °C; 1H-NMR (400 MHz, DMSO-*d*$_6$): 5 12.00 (bs, 1H), 9.36 (bs, 1¾ 8.45 (d, *J* = 8.0 Hz, 1H), 7 .42-7.33 (m, 6H), 7 .1 3-7 D7 (m, 3H), 6.74 (d, *J* = 75 Hz, 2H), 6.66 (d, *J* = 9.1 Hz, 1H), 5.04 (s, 2H), 4.84 (d, *J* = 5.9 Hz, 1H), 3.50 (d, *J* = 5.9 Hz, 2H), 2.72 (s, 1H), 2.59-2.38 (m, 4H), 1.66 (bs, 4H); IR (KBr, cm^{-1}): 3275, 3064, 2970, 1774, 1659, 1589, 1550, 1492, 1466, 1384, 1350 ; MS (ESI) m/z: 472.0 (M+l).

Example 21

N-((S)-1-(3-(1H-tetrazol-5-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(1-methyi-2,2-dioxido-1,3-dihydrobenzo[c]isothiaxol-6-yl)acetamide

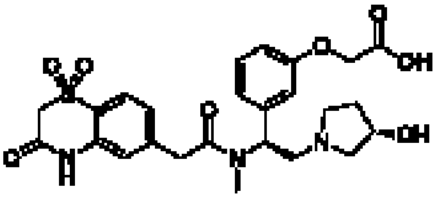


The title compound was obtained as white solid by treating N-((S)-l-(3-cyanoprenyL)-2-((S)-3-hydroxypyjrolidin- 1-yl)ethyl)-N-methyL-2-(1-methyl-2,2 -dio-iido- 1,3-dihydrobenzo[c] isotluazol-6-yl)acetamide with sodium azide following standard procedure known in the literature.

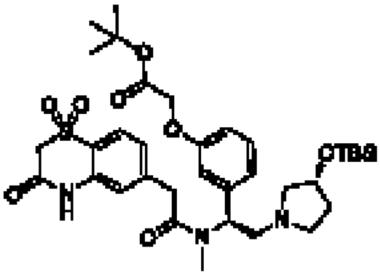
^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.92 (s, IH), 7.86 (d, J = 7.9 Hz, IH), 7.35-7.31 (m, IH), 7.24 (4 J = 7.4 Hz, IH), 7.17 (d, J = 7.3 Hz, IH), 6.95 (d, J = 7.3 Hz, IH), 6.76 (s, IH), 5.93-5.89 (m, IH), 4.61 (bs, IH), 4.60 (s, 2H), 4.17-4.16 (m, IH), 3.81-3.71 (m, 2H), 3.22-3.15 (m, 2H), 3.12-3.09 (m, 2H), 2.97 (s, 3H), 2.74 (s, 3H), 2.45-2.32 (m, 1¾ 2.31-2.29 (m, IH), 1.97-1.92 (m, IH), 1.53-1.50 (m, 1H); IR (Neat, cm^{-1}): 2978, 1641, 1402, 1321, 1217, 1139, 1056; MS (ESI) m/z: 512 (M+l).

Example 22

2-(3-((£^ 1-(2-(1,l-dioxido-i-oxo -^dihydro -2H-benzo[h] [l,4]tMazin-6-y])-N-methylacetamido)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)phenoxy)acetic acid

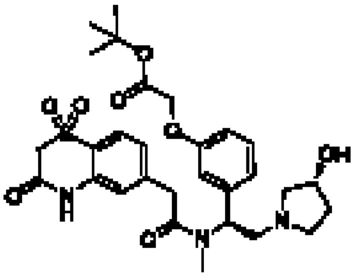


Step (i) Synthesis of tert-butyl 2-(3-((S)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-1-(2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-n^thylacetamidoJethylJpheno -iyJacetatB



Into a 50-mL roundJaottom flask purged and maintained with an inert atmosphere of nitrogen. was placed a solution of 2-(l, 1-dioxidD-3-oxo-3,4-dmydro-2H-benzo[l-ij [l,4]11uazLn-6-yl)aceti c acid (300 mg, 1.18 mmol, 1.10 equiv) in N,N-dimethylfornramide (10 mL). This was followed by the addition of EDCI (309 mg, 1.61 mmol, 1.50 equiv) at 0-5°C. To this was added HOBT (217 mg, 1.61 mmol, 1.50 equiv) at O-5*C. To the mixture was added tert-butyl 2-[3-K1S)-2-[(3Ξ)-3-[(tert-butyldimethylsilyljoxy]pyrrolidm-l-yl]-1-(methylamino)ethyl]phenoxy] acetate (500 mg, 1.0S mmol, 1.00 equiv). The resulting solution was stirred for 3 h at room temperature. The resulting solution was diluted with 150 mL of ethyl acetate. The resulting mixture was washed with 3x50 mL of water and 2x50 mL of brine. The resulting mixture was washed with 3x50 mL of 10% ammonia and 3x50 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. This resuited in 700 mg (93%) of the title compound as a light yellow cmde solid.

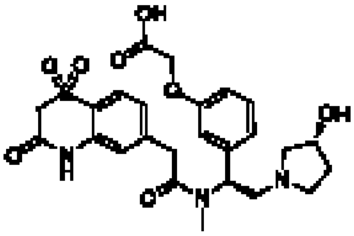
Step (ii) Synthesis of methyl 2-(3-((S)-l -(2-(l, 1-dioxidQ-3-oxo-3,4-dmydro-2H-benzo[b] [1,4]thiazin-6-yl)-N-methylacetamido)-2-((S)-3-hydraxypyrrolidin- 1-yi)ethyl)phenoxy)acetate



Into a 50-mL round-bottom flask, was placed a solution of tert-butyl 2-(3-((S)-2-((S)-3-((tert-butyldime1hylsilyl)oxy)p^ rolidin-1-yl)-1-(2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-ben3o[b] [l,4]tMazin-6-yl)-N-:imthykcetanu\^)ethyl)phenoxy)acetate (400 mg, 0 5 7 mmol, 1.00 equiv) in methanol (15 mL). This was followed by the addition of cone . HC1 (1.5 mL) dropwise with stirring at 0-5*0. The resulting solution was stirred for 2 h at room temperature.

The resulting mixture was concentrated under vacuum. This resulted in 366 mg (118%) of the title compound as a light yellow crude solid which was used in the next step without further purification.

Step (iii) Synthesis of 2-(3-((Ξ)-1-(2-(1,1-dioxidD-3-oxo-3,4-dmydro-2H-benzo[b][1,4]thiazin-6-yl)-N-methylacetamido)-2-((Ξ)-3-hydiDxypyrrolidin-1-yl)ethyl)phenoxy)acetic acid

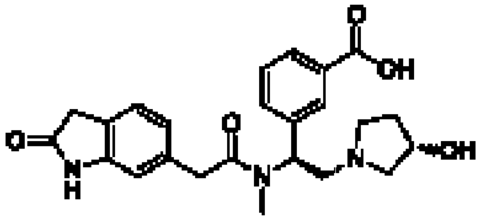


Into a 50-mL round-bottom flask, was placed a solution of methyl 2-(3-((S)-l-(2-(l,1-doxido-3-oxo-3,4dihydro-2H-benzo [b][1,4]thiazin-^-yl)-N-methylacetamido)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)phenoxy)acetate (100 mg, 0.18 mmol, 1.00 equiv) in methanoUwater (15 mL/2.5 mL). This was followed by the addition of LiOH.HjO (77 mg, 1.84 mmol, 10.00 equiv), in portions at 0*C in ice/salt bath. The resulting solution was stirred for 2 h at 25*0 . The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 60 mL of H_2O. The resulting solution was washed with ethyl acetate (3x30 mL) and the pH value of the solution was adjusted to 2-3 with cone. hydrogen chloride aqueous. The resulting mixture was concentrated under vacuum. The crude product (170 mg) was purified by Prep-HPLC with the following conditions (x-bridge): Colunm(5 nm 19*150mm), mobile phase, 0.2% NH_4HCO_3 solution and CH_3CN, 3% CH_3CN up to 20% in 10 min; Detector, 220nm&254nm. 20 mg product was obtaired. This resulted in 20 mg (21%) of the title compound as a white solid.

MS *(ES, m/z):* 532.1 (M+1); ^{1}H-NMR (400 MHz, DMSO-c¾ 5 11.47 (brs, 1H), 7.71-7.77 (m, 1H), 7.13-7.27 (m, 3H), 6.79-6.88 (m, 3H), 5.79-5.83 (m, 1H), *4.69* (s, 2H), 459-4.62 (m, 2H), 4.18-4.19 (m, 1H), 3.81-3.88 (m, 2H), 3.14 (t, *J*=l 1.2H¾ 1H), 2.74-2.89 (m, 5H), *2.65-2.6%* (m, 1H), 2.41-2.43 (m, 2H), 1.95-2.00 (m, 1H), 1.53-1.56 (m, 1H).

Example 23

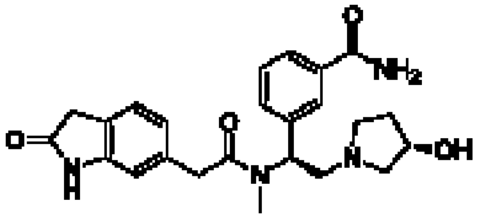
3-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindolijvf-yl)acetamido)ethyl)benzoic acid



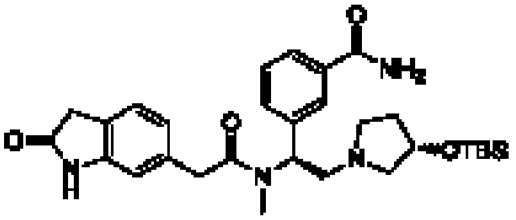
Into a 80mL sealed tube, was placed a solution of N-((S)-2-((S)-3-((tert-butyldimemylsnyl)oxy)pyrroh din-1-yl)-1-(3-cyanophe nyl)ethyl)-N-methyl-2-(2-oxoirdolin-6-yl)acetamide (200mg, 0.38mmo, 1.00 equiv) in Conc. HC1 (2.0mL). The resulting solution was stirred for 5h at 100°C and concentrated under vacuum. The residue was purified by Prep-TLC and eluted with dichloramelJaane-methanol (3:1).This resulted in 60 mg (37%) of the title compound as a off-white solid. MS (ES, *m/z*): 438 (M+l); 1H-NMR (DMSO-d_6, 300MHz) 5 10.31 (s, 1H), 7.87-7.84 (m, 2H), 7.53-7.45 (m, 2H), 7.11 (d, *J* =7.*5Hz,* 1H), 6.82-6.74 (m, 2H), 5.98-5.96 (m, 1H), 5.08-5.02 (m, 1H), 4.28-4.20 (m, 1H), 3.83-3.78 (m, 1H), 3.70-3.59 (m, 1H), 3.43 (s. 2H), 2.98-2.80 (m, 3H), 2.71 (s, 3H), 2.65-2.58 (m, 2¾ 2.08-1.92 (m, 1H), 1.66-1.44 (m, 1H)

Example 24

3-((¾>-2-((£)-3-hydroxypyrroftlm-1-yl)-1-(N-methyl-2-(2-oxoijdolijv6-yl)acetamido)ethyl)benzamide



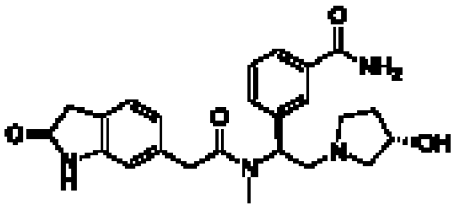
Step (i) Synthesis of 3-((3)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindohn-6-yl)acetamido)ethyl)benzamide



Into a S.OmL sealed tube, was placed a solution of N-[(lR)-2-[(33)-3-[(tert-butyldimethylsilyl)ox-y]cycb pentyl]-1-(3-cyanophenyl) ethylj -N-methyl-2-(2-oxo-2,3-

dihydro-lH-indol-6-yl)acetamide (150 mg, 0.28mmol, 1.00 equiv) in DIvEO (2.0mL) .Then potassium carbonate (11.7 mg, O.08mmol, 0.30 equiv) was added. This was followed by the addition of hydrogen peroxide (30% in water, 0.15mL) dropwise with stirring at 0-10°C. The resulting solution was stirred for 3 h at 18°C and diluted with 20mL of water. The resulting aqueous solution was extracted with 3x10mL of ethyl acetate and the organic layers combined The resulting organic layer was washed with 2x20mL of brine, then dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 120mg of the title compound as a light yellow solid which was used in the next step without further purification MS (ES, m/z): 437(M+1).

Step (ii) **Synthesis** of **3-((S)-2-((S)-3-hydroxypyrrdidin -l -y^** -(N-methyl-2-(2-oxoindolin-**6-yl)acetar rudo)ethy l)b erlZaiтlid e**

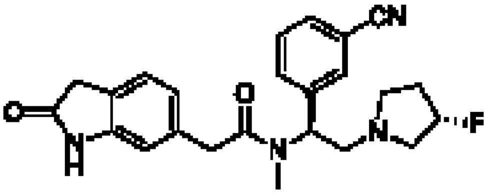


Into a 8.0 mL sealed tube, was placed a solution of 3-((S)-2-((S)-3-((tertJ-utyldimethyl sHyl)oxy)pyrrolidin- 1-yl)-1-(N-methyl-2-(2-o xoindolin-6-yl)acetamido)ethyl)**berL2anude** (l lOmg, 0.20mmol, 1.00 equiv) in methanol (l .OmL) and Cone. hydrogen chloride (0.25mL). The resulting solu-tion was stirred for 30 min at 18°C and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column, X-Bridge, CIS, 15cm; mobile phase, Water(contained 0.2% of NH+HCO$_3$) and acetonitrile (5% acetonitrile up to 28% in lOmin, up to 100% in 1min, down to 5% in 1min); Detector, UV 220/254 nm. This resulted in 13 mg (15%) of title compound as a white solid.

IvE (ES, *m/z*): 437 (M+l); ^{1}H-NMR (DMSO-d_6, 300MHz) 5 10.35 (s, 1H), 8.95 (s, 1H), 7 £ 5 (s, 2H) \ 7.47-7.32 (m, 3H), 7.06 (d, *J* =6.0Hz, 1H), 6.78-6.65 (m, 2H), 5 93-5.82 (m, 1H), 4.95-4.80 (m, 1H), 4.19-4.05 (m, 1H), 3.80-3.52 (m, 2H), 3.42 (s, 2H), 3 .14-3.02 (m, 1H), 2.95-2 j67 (m, 2H), 2.65 (s, 3H), 2.55 (s, 1H), 2.38-2.22 (m, 1H), 2.05-1 .75 (m, 1H), 1.56-1 .32 (m, lH).

Example 25

N-((S)-1-(3-cyanophenyl)-2-((S)-3-fluoropyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxoindolin-6-yi)acetamide

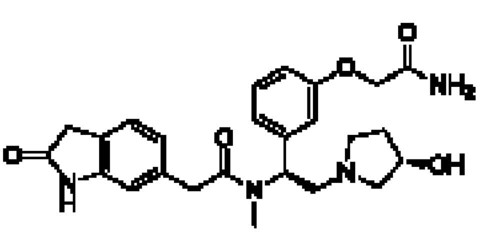


Into a 25-mL round-bottom flask, was placed a solution of 2-(2-oxo-2,3-dmydio-lH-indol-6-yl)acetic acid (155 mg, 0.81 mmol, 1.00 equiv) in N,N-dimem^ormamide (5 mL).Then EDCI (186 mg, 0.97 mmol, 12 0 equiv) and HOBt (132 mg, 0.9S mmol, 1.20 equiv) were added. The resulting solution was stirred for 20mins at room temperature. Following 3-[(lS)-2-[(3S)-3-fluoropy.TOhdm-l-^-l-(mem^mino)em^ benzonitrile (200 mg, 0S 1 mmol, 1.00 equiv) was added. The resulting solution was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with of ethyl acetate. The resulting ethyl acetate layer was washed with aqueous sat. sodium bicarbonate and brine. The ethyl acetate layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified onto prep-TLC (dichloromethane:MeOH=15:1). This resulted in 160 mg (49%) of the title compound as a white solid.

IvE (ES, *m/z*): 443 (M+23); 1H-NMR (DM30, 300 MHz): 5 10.33 (s, 1H), 7.81-7.67 (m, 2H), 7.67-7 50 (m, 2H), 7.18-7.07 (m, 1H), 6.88-6.78 (m, 1H), 6.78-6.67 (m, 1H), 5.90-5.77 (m, 1H),5.29-4.99 (m, 2H), 3.95-3.65 (m, 2H), 3.42 (s, 2H), 3.15-3.00 (m, 1H), 293-2.79 (m, 3H), 2.79-2 33 (m, 5H), 2.18-1.92 (m, l H), 1.92-1.70 (m, 1H).

Example 26

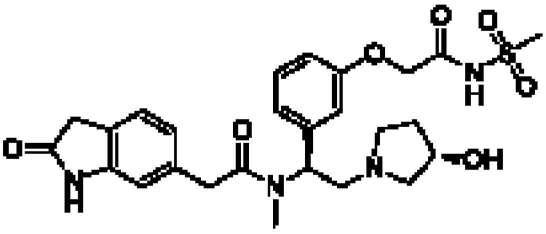
I* ((S)-1-(3-(2-ajnino-2-oxoethoxy)phenyl)-2-((S)-3-hydroxypyrif lidin-1-yl)ethyl)-N-methgl-2-(2-oxoindolin-6-yl)acetamide



Into a 25-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2-(3-((S)-2-((3)-3-h;ydroxypyrrolid^ -1-yl)-1-(N-methyl-2-(2-oxoindolin-6-yl)acetar[tidQ)ethyl)p^ noxy)acetic acid (100 mg, 0.21 mmol, 1.00 equiv) in N,N-din¾thylformamide (6 mL). To the mixture were added HATU (90 mg, 0.24 mmol, 1.10 ecjuiv) and DIEA (S3 mg, 0.64 mmol, 5.00 equiv). The resulting solution was stirred for 5 min at room temperature. Then AcONH+ (33 mg, 0.43 mmol, 10.00 equiv) was added. The resulting solution was allowed to react, with stirring, for an additional 3 h at room temperature. The resulting mixture was concentrated and the crude product (100 mg) was purified by Prep-HPLC with the following conditions (pep HPLC): Column, X-bridge, 19*150 μm; mobile phase, water with 0.05% ammonia and CH_3CN(5% CHjCN up to 19% in 12 min, up to 100% in 2 min, down to 5% in 2 min); Detector, UV 254 nm&220 nm. 20 mg product was obtained. This resulted in 20 mg (20%) of the title comppound as a white solid. 1VE (EΞ, rote): 467.1 (M+1); ^{1}H-NMR (DMSO-d_6, 400 MHz) 5 10.32-10.36 (m, 1H), 7.54 (s, 1H), 7.40 (s, 1H), 7.25 (t, J=8.4Hz, 1H), 7.12 (t, J=7.6, 1H), 6.80-6.89 (m, 5H), 5.£2-5.87 (m, 1H), 4.91 (s, 2H), 4.35-4.38 (m, 2¾ 4.20 (brs, 1H), 3.76-3.82 (m, 1H), 3.59-3.67 (m, 1H), 3.43-3.45 (m, 2H), 3.15 (brs, 1H), 2.64-2.82 (m, 6H), 2.33-2.52 (m, 2H), 1.95-2.00 (m, 1H), 1.52-1.54 (m, lH).

Example 27

N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(2-(ηιβthylsulfonaηιido>-2-oxoethoxy)phenyl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetajnide



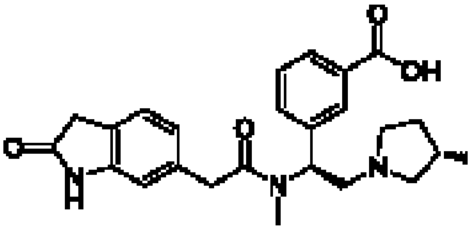
Into a 25-mL roundJaottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2-(3-((S)-2-((3)-3-h;ydroxypyrrolid^ -1-yl)-1-(N-methyl-2-(2-oxoindolin-6-yl)acetamido)ethyl)phenoiy)acetic acid (100 mg, 0.21 mmol, 1.00 equiv) in N,N-din¾thylformamide (5 mL). To the mixture were added HATU (90 mg, 0.24 mmol, 1.10 equiv) and DIEA (83 mg, 0.64 mmol, 5.00 equiv). The resulting solution was stirred for 5 min at room temperature. Then memanesulforamide (160 mg, 1.68 mmol, 7.86 equiv) was added.

The resulting solution was allowed to react, with stirring, for an additional 2 h at room temperature. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Waters): Column, X-bridge, 19*150 run ; mobile phase, water with 0.05% ammonia and CH_3CN(5% CH_3CN up to 25% in 12 ruin, up to 100% in 2 min, down to 5% in 2 min, Detector,UV 254 nm&220 nm. 30 mg product was obtained. This resulted in 30 mg (26%) of the title compound as a white solid.

IvE (ES, m/z): 545.1 (M+l); ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) 510.33 (s, 1H), 7.31 (**t,** ***J***=7.8Hz, lH), 7.22 (d, ***J***=7.5Hz, lH), 6.72-7.04 (m, 6H), 5.99-6.03 (m, 1H), 5.23-5.31 (m, 1H), 4.34-4.44 (m, 3H), 3.61-3.80 (m, 3H), 3.31-3.43 (m, 3H), 3.04-3 2 3 (m, 3H), 2.90-2.93 (m, 3H), 2.65-2 £ 5 (m, 3H), 2.10-2.12 (m, 1H), 1.75-1.78 (m, lH).

Example 28

3-((S)-2-((S)-3-fluoropyrrolidin-*I*-yl)-1-(N-methyl-2-(2-oxomdo1m-6-yl)acetajitiio>ethyl]) benzoic acid

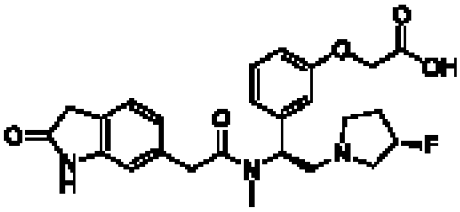


Into a 8-mL sealed tube, was placed a solution of N-((S)-l-(3-cyarophenyi)-2-((S)-3-fluoropyrrohdin-l-yl)ethyl)-N-nttth^ -2-(2-oxoindolin-6-yl)acetamide (200 mg, 0.48 mrnol, 1.00 equiv) in cone hydrogen chloride (4 mL). The resulting solution was stirred for 1.5 h at 100*C. After cooling to room temperature, the reaction mixture was concentrated to dryness. The residue was applied onto prep-TLC (dichtoromethane:MeOH = 10: 1). This resulted in 11 mg of the title compound as a tight yellow solid

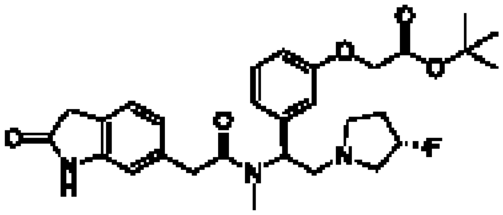
IvE (EΞ, m/z): 440 (M+l); ^{1}H-NMR (DMSO-*d*$_6$, 300 MHz): 5 10.44 (s, 1H), 7.90-7.67 (m, 2H), 7.45-7.30 (m, 2H), 7.09 (d, ***J*** = 7.8 Hz, 1H), 6.88-6.65 (m, 2H), 6.00-5.80 (m, 1H), 5 29-5.01 (m, 1H), 3.86-3.65 (m, 2H), 3.47-3.38 (m, 2H), 3.20-3.10 (m, 1H), 3 02-2 5 6 (m, 7H), 2.40-2 2 7 (m, 1H), 2.15-1.96 (m, 1H), 1.96-1.70 (m, 1H); F-NMR (DMSO-*d*$_6$, 400 MHz) 5 167 (s).

Example 29

2-(3-((S)-2-((S)-3-fluoropyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindolin-6-yl)acetamido)ethyl)phenoxy)acetic acid

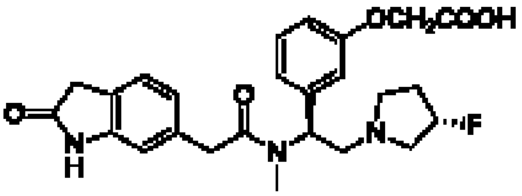


Step (i) Synthesis of tert-butyl 2-(3-((S)-2-((S)-3-fluoropyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindolin-6-yl)acetamido)ethyl)phenoxy)acetate



Into a 25-mL round-bottom flask, was placed a solution of 2-(2-oxo-2,3-dmydro-lH-iridol-ŏ-yl)acetic acid (250 mg, 1.31 mmol, 1.00 equiv) in N,N-din¾thylformamide (10 mL). To the solution were added EDCI (204 mg, 1.06 mmol, 1.50 equiv), HOBt (144 mg, 1.07 mmol, 1.50 equiv) and tert^utyl 2-(3-**P**-[(3S)-3-fluoropyrrdidin-l -yij-l-(n¾ethylamino)eth.yI]phenoKy) acetate (136 mg, 0.39 mmol, 1.00 equiv). The resulting solution was stirred for 2 h at 25*0. The resulting solution was diluted with 50 mL of dichloromethane. The resulting mixture was washed with ammonia (10%) (1x20 mL), H_2O (3x20 mL) and (3x20 mL). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 430 mg of tertJ-utyl 2-[3-[(lS)-2-[(3S)-3-fluoropyrrolidin-1-yl]-1-[N-n¾thyl-2-(2-oxo-2,3-dihydro-1H-indol-ŏ-yi)acetamido]ethyIJphenoxy] acetate as brown crude oil.

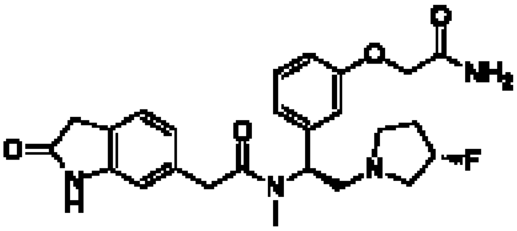
Step (ii) Synthesis of 2-(3-((S)-2-((S)-3-fluoropyrrolidin-l-yl)-1-(N-methyl-2-(2-oxoindolin-6-yl)acetamido)ethyl)phenoxy)acetic acid



Into a 25-mL round-bottom flask, was placed a solution of tert-butyl 2-[3-[(lS)-2-[(3S)-3-fluDropyrrolidin-l -yl]-1-[N-methyl-2-(2-oxo-2,3-dihydro-1H-indol-ŏ-yl)acetamido]ethyl] phenoxy] acetate (100 mg, 0.19 mmol, 1.00 equiv) in diehloromethane (5 mL). To the mixture was added trifluoroacetic acid (1 mL). The resulting solution was stirred for 3 h at 25 degree C. The resulting mixture was concentrated under vacuum. The crude product (SO mg) was purified by Prep-HPLC with the following conditions (prep-HPLC): Column, X-bridge prep C18; mobile phase, water and CH_3CN(10% CHjCN up to S0% in lOmin, up to 100% in 1 min, down to 10% in 1 min); Detector., 254&220. 17.3 mg product was obtained. This resulted in 17.3 mg (19%) of 2-P-[(lS)-2-[(3S)-3-fluorop^olidin-l-yIJ-l-[H-methyl-2-(2-O xo-2,3-dihydro-l H-indd-di-yl)acetamLdo] ethyl] phenoxy] acetic acid as a white solid. IvE (EΞ, m/z): 470 (M+1); ^{1}H-NMR (DMSO-d_6, 300MHz) 5 10.34 (s, 1H), 7.22-7.26 (m, 1¾ 7.09-7. IS (m_ 1¾ *6.19-621* (m, 4H), *6.12-6.13* (m, 1H), 5.*19-5*.S3 (m, 1H), 5.0S-5 2 3 (m, 1H), 4.62 (S, 2H), *3.65-3.11* (m, 2H), 3.43 (s, 2H), 3.06-3.12 (m, 1H), 2.71-2.86 (m, 6H), *2.65-2.61* (m, 1H), 2.33-2.3c (m, 1H), 2.01-2.OS (m, 1H), 1.75-1.90 (m, 1H)

Example 30

rN-((S)-1-(3-(2-amino-2-oxoethoxy)phenyl)-2-((S)-3-fluoropyrroMin-1-yl)ethyl)-N-methyl-2-(2-oxoindolii-6-yl)acetamide

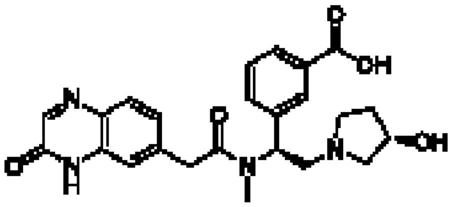


Into a 10-mL round-bottom flask, was placed a solution of 2-(3-((Ξ)-2-((Ξ)-3-fluoropyrrolidin- 1-yl)- 1-(N-methyl-2-(2-oxoindolm-0-yl)acetamido) ethyl) phenoxy)acetic acid (100 mg, 0 2 1 mmol, 1.00 equiv) in N,N-dimethylforniamide (3 mL), HATU (S9 mg, 0.23 mmol, 1.10 equiv), DIEA (137 mg, 1*06* mmol, 5.00 equiv), ammonia aqueous (1.5 mL). The resulting solution was stirred for I8 h at 25^. The resulting mixture was concentrated under vacuum. The crude product (3 mL) was purified by Prep-HPLC with the following conditions (Prep-HPLC): Column, XJmdge prep CIS; mobile phase, water and CH_3CN (10% C¾CN up to S0% in lOmin, up to 100% in 1 min, down to 10% in 1 min); Detector, 254&220. 9 mg product was obtained. This resulted in 9 mg of the title compound as a white solid

IvE (EΞ, m/z): *469* (MH); ^{1}H-NMR (DMSO-d_6, 400MHz) *8* 10 3 2 (s, lH), 753 (s, 1H), 7.40 (s, 1¾ 7.23-7.27 (m, 1H), 7.09-7.1 1 (m, 1H), 6.81-6.89 (m, 4H), *6.12-6.13* (m, 1H), 5.80-5 £ 4 (m, 1H), 5.08-5.23 (m, 1H), 4.38 (s, 1H), 3 65 (m, 2H), 3 .42-3.44 (m, 2H) , 3.06-3.1 1 (m, 1H), 2.66-2.95 (m, 7H), 7.40 (s, 1H), 2 3 1- 2.40 (m, 1H), 1.65-2 .1 8 (m, 2H)

Example 3 1

3-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(3-oxo-3,4-dihydroquinoxalin-6-yl)acetamido)ethyl)benzoic acid

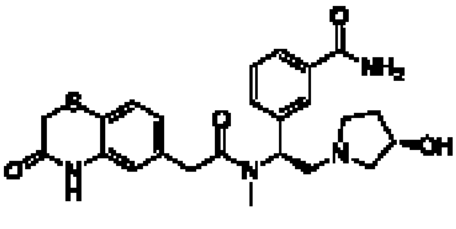


Into a 8-mL vial, was placed a solution of N-((3)-2-((3)-3-((tert-butyldime1hylsnyl)oxy)pym lidin-1 -yl)- 1-(3-cyanophe ηyl)βi 1yı)-N-ηβi 1ß1-2-(3-oxo-3,4-dihydracjuinoKalm-6-yl)acetamide (100 mg, 0.18 mmol, 1.00 equiv) in cone . HC1 (2 nil). The resulting solution was stirred overnight at 75°C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column, X-Bridge, CIS, 15cm; mobile phase, Water(contained 0.5% of ammonium bicarbonate) and CH3CN (5% acetonitrile up to 32% in 12min, up to 100% in lmin, down 5% in l min); Detector, UV22 0/254 nm. This resulted in 8 mg of the title compound as a light yellow solid.

IvE (EΞ, m/z): 451(M+1); 1H-NMR (DMSO-^ 400MHz): 5 12.09-12 .49 (s, lH), 8.13 (s, 1H¾ 7.85-7 61 (m, 3H), 7.55-7.44 (m, 2H), 7.22-7.21 (m, 2H), 5.91 -5.87 (m, 1H), 4.64-4.91 (m, 1H). 4.1 6 (s. 1H), 3.834.00 (m, 2H), 3.13-3.07 (m, 1H). 2.86-2 .64 (m, 6¾ 2.48-2.34 (m, 2H), 1.96-1 .91 (m, 1H), 1.53-1 .50 (m, 1H).

Example 32

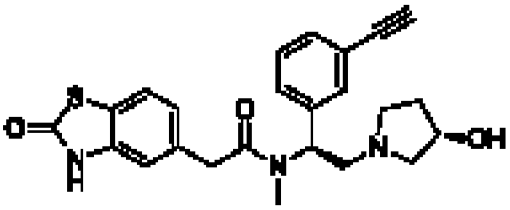
3-((£)-2-((¾)-3 -hydroxypyrrolidin-1-yl)-1-(N-methyt2-(3-oxo-3 ,4-dfliydro-2H-beiu»[b][l,4] thiazin-6-yl)acetamido)ethyl)benzamide



Into a 8.0nil_ sealed tube, was placed a solution of N-((S)-2-((S)-3-((tert-butyldimelhylsil yl)oxy)pyrrohdin-l -yl)- 1-(3-cyanophe nyl)ethyl)-N-n¾thyl-2-(3-o:{o-3,4-dihydro-2H-benzo[b] [l,4]1hk.dn-6-y-)acetamide (60mg, 0.1 1mmol, 1.00 equiv) in tetrahydrofuran (0.4niL) and methanol (0.4mL). Then water (O.SmL) and potassium hydroxide (59.6 mg, 1.06mmol, 10.00 equiv) were added. The resulting solution was stirred for 7 tours at 50*C and concentrated under vacuum. The residue was purified by Flash- Prep-HPLC with the following conditions (IntelFlash-1): Column, CIS silica gel; mobile phase, H_2O/MeCN=100:5 increasing to H_2O/MeCN=100:25 within 15 min; Detector, UV 254 nm. This resulted in 35 mg (70%) of 3-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(3-oxo-3,4-dihydro-2H -benzo[b] [l,4]thk zin-6-yl)acetamido)ethyl)benzamide as a white solid. IvE (EΞ, *m/z)*: 533 (M+I); ^{1}H-NMR (DIvEO^, 300 MHz): 5 10.49 (s, 1H), 7.96 (s, 1H), 7.72 (m, 2h), 7.38-7.36 (m, 3H), 7.19 (d, J=7£Hz, 1H), ***6.25-6*** SO (m, 2H), 5.86-5.78 (m, 1H), 4.724.65 (m, 1H), 4.18-4.06 (m, 1H), 3.75-3.56 (m, 2H), 3.34 (s, 2H), 3.11-2.90 (m, 1H), 2.86-2.60 (m, 6H), 2.28-2.16 (m, 1H), 1.95-1.82 (m, 1H), 1.48-1 .32 (m, 1H).

Example 33

I* ((S)-l -(3-ethynylphenyl)-2-((S)-3-hydroxjpyττolidin-1-yl)ethyl)-N-methyJr2-(2 -oxo-2,3 -dihydrobenzo [d]miazol-5- yl)aceta_mide

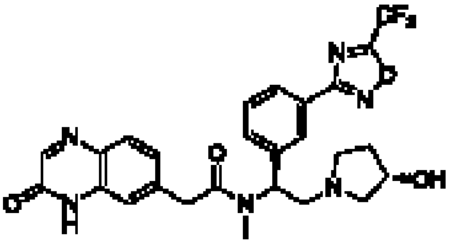


To a solution of 2-(2^.io-2,3-dihydro-l,3 -benzothiazol-5-yl)acetic acid (50 mg, 0.24 mmol, 1.10 equiv) in N,N-dime1hy-formamide (2 mL), were added EDCI (62.6 mg, 0.33 mmol, 1.51 equiv) and HOBt (44 mg, 0.33 mmol, 1.50 equiv). The resulting solution was stirred for 30 min at 20℃. This was followed by addition of a solution of (3Ξ)-1-[(2Ξ)-2-(3-emynylphenyl)-2-(memykmLno)emyIJpym lidin-3-ol (53 mg, 0.22 mmol, 1.00 equiv) in N,N-din^thylforn^mide (1 mL) dropwise with stirring. The resulting solution was allowed to react, with stirring, for an additional 1.5 h at 20℃. The reaction was concentrated and the residue was purified by Prep-HPLC with the following conditions: Column, X-Bridge, CIS, 15cm; mobile phase, Water(contained 0.5% of ammonium bicarbonate) and CH_3CN (5% CHjCN up to 45% in 12min, up to 100% in 1min, down 10% in 1 min); Detector, UV 220/254 nm. This resulted in 22.4 mg (24%) of the title compound as a off-white solid.

MS (ES, *m/s*): 436 (M+1), ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 7.49-7.64 (d, *J*=7.8Hz, 1H), 7.31-7.33 (m, 4H), 7.08-7.00 (m, 2H), 5.84-5.78 (m, 1H), 4.18-4.17 (m, 2H), 3.89-3.70 (m, 2H), 3.09-3.00 (m, 1H), 2.81-2.69 (m, 5H), 2.42-2.35 (m, 2H), 2.12-1.83 (m, 1H), 159-1.41 (m, 1H).

Example 34

N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)phenyl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydroquinoxalin-6-yl)acetamide

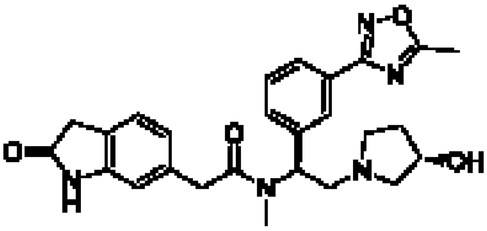


To a solution of 2-(3-oxo-3,4-dihydroquinoxalin-6-yl)acetic acid (70 mg, 0.34 mmol, 1.20 equiv) in N,N-dimethylformamide (3mL), were added EDCI (60 mg, 0.31 mmol, 1.10 equiv) and HOBT (42 mg, 0.31 mmol, 1.10 equiv). The resulting solution was stirred for 10 min at room temperature. Then a solution of 1-[2-(methylamino)-2-[3-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]ethyl]pyrrolidin-3-ol (100 mg, 0.28 mmol, 1.00 equiv) in N,N-dimethylformamide (2mL) was added. The resulting solution was stirred for 3 hours at 20°C. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC with dichloromethane/methanol (10:1). This resulted in 41.4 mg (27%) of N-[(1S)-2-(3-hydroxypyrrolidin-1-yl)-1-[3-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]ethyl]-N-methyl-2-(3-oxo-3,4-dihydroquinoxalin-6-yl)acetamide as a white solid.

MS (ES, *m/z*): 543 (M+1); ^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.098 (s, 1H), 7.989-7.921 (m, 2H), 7.765-7.603 (m, 4H), 7.225-7.130 (m, 2H), 5.939-5.888 (m, 1H), 4.795-4.715 (m, 1H), 4.180 (s, 1H), 4.026-3.832 (m, 2H), 3.323-2.368 (m, 9H), 1.989-1.898 (m, 1H), 1.537-1.462 (m, 1H).

Example 35

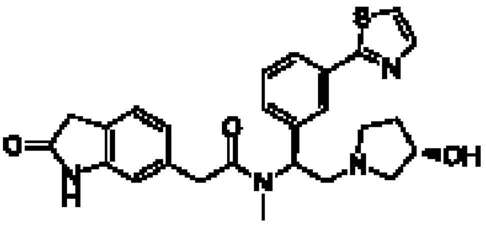
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(5-methyl-1,2,4-oxadia™l-3-yl)phenyl)ethj1)-N-methyl-2-(2-oxoindolij1-6-yl)acetajnide



To a solution of 2-(2-oxo-2.3-dihydro-l H-indol-6-yl)acetic acid (44.S9mg, 0.23mmoL, 1.OOequiv) in N,N-dimemylfcimamide (2.0mL), were added EDCI (67.41mg, 0.35mmol., 1.50 equiv) and HOBt (47.52ing, 0 35mmol, 1.50equiv). The mixture was stirred for 20min at 25. To this was added (3Ξ)-1 -[(2S)-2-P-(5-i^thyl4.2 j4-0Kadiasd-3-yl)pheii5ii]-2-(metr^amino) ethyl] pyrrdidin-3 -ol di-hydrochbride (SO mg, 0.21mmol, 0.91equiv) and triethykmine (172mg, 1.70mmoL, 7.24equiv) . The resulting solution was stirred for 2 hours at 25℃, and then 20ml_ of water/ice was added to quench the reaction. The resulting aqueous solution was extracted with dichloromethane (3x15mL) and the organic layers combined. The resulting organic layers was washed with brine (Ix20mL), dried over anhydrous sodium sulfate and concentiated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column; X-Bridge, CIS, 19*150mm; mobile phase : Water(contained 0.2% ofNH+HCOs) andacetonitiile (5% acetonitrile up to 45% in lOmin, up to 100% in lmin, down to 5% in l min); Detector: UV220/254 nm. This resulted in 50 mg (46%) of the title compound as a white solid. MΞ (EΞ, *m/z*): 476(IvI+l); ^{1}H-NMR (D IvE O-d_6, 300MHz): 5 10.35 (s, 1H), 7.91 -7.SS (m, 2H), 7.65-7.45 (m, 2H), 7.10 (d, *J*=7.2Hz, 1H), *5.95-5.90* (m, 1H), 4.SS (d, *J* =3*.9Hz,* 1H), 4.25-4.1S (m, 1H), 3.S4-3.79 (m, 1H), 3.*69*-3.64 (m, 1H), 3.42 (s, 2H), 3.16-3.OS (m, 1H), 2.S4-2.77 (m, 2H), 2.72 (s, 3H), *2*.67 (s, 3H), 2.42-2.30 (m, 2H), 2.02-1.86 (m, 1H), 1.53-1.40 (m, l H).

Example 36

N-((S)-2-((S)-3-hydroxypyrrolidiiv1-yl)-1-(3-(thiazol-2-yl^henyl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetanii de

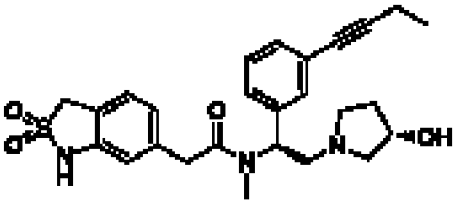


Into a 8-mL sealed tube, was placed a solution of 2-(2-oxo-2,3-dmydro-lH-mdol-6-yl)acetic acid (40 mg, 0.21 mmol, 1.00 equrv) in N,N-dimethylformamide (3 ml_). Then EDCI (45 mg, 0.23 mmol, 1.20 equiv) and HOBt (32 mg, 0.24 mmol, 120 equiv) were added Following triethylamine (60 mg, 0.59 nunol, 3.00 equiv) was added. The resulting solution was stirred for 10 min at room temperature. Then (3S)-l-[(2S)-2-(meth5ilar iLno)-2-[3-(l,3-thiazol-2-yl)phenyl]ethyl]pyrrolidin-3-ol (60 mg, 0.20 nunol, 1.00 equiv) was added The resulting solution was albwed to react, with stirring, for an additional 2 hours at room temperature. The resulting mixture was concentrated under vacuum and the residue was purified by prep-HPLC with the following conditions: Colun%X-Bridge,C 18, 15cm; mobile phase, water(contained 0.5% ammonium bicarbonate) andacetonitrile (10% acetonitrile up to 45% in 12mins,up to 100% in lmin,down to 10% in l inin); detector, UV220/254nm. This resulted in 10 mg of the title compound as a white solid.

IvE (ES, m/z): 477 (M+1); ^{1}H-NMR (CD$_3$OD-d,, 300MHz): δ 7.76-7.73 (m, 3H), 7.52-7.50 (m, 1H), 739-7 3 1 (m, 2H), 7.07-7.05 (m, 1H), 6.87-6.82 (m, 2H), 6.04-5.92 (m, 1H), 4.27-4.25 (m, 1H), 3.82-3.67 (m, 2H), 3.37-3.35 (m, 1H), 3.28-3.22 (m, 2H), 2 95-2.83 (m, 2H), 2.77-2.72 (m, 4H), 2.55-2.38 (m, 2H), 2.06-2.03 (m, 1H), 14.71-1.52 (m, 1H).

Example 37

N-((S)-1-(3-(but-1-yn-1-yl)p¾nyl)-2-((¾>-3-hydroxypyrrolidin-1-y)ethyl)-2-<2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-6-yl)-N-methylacetamide

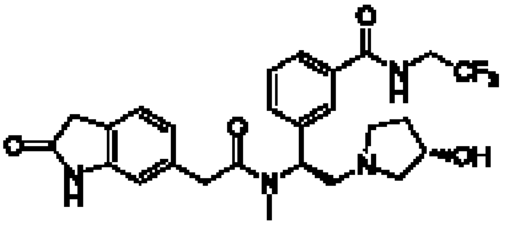


Into a 25-mL round-bottom flask, was placed a solution of 2-(2,2-dioiido-l,3-dihydrobenzo[c]isothiaml^-yljacetic acid (70 mg, 0 3 1 mmol, 1.10 equiv) in N,N-dinieth^forn^mide (10 mL), EDCI (84 mg, 0.44 mmol, 1.50 equiv), HOBT (60 mg, 0.44

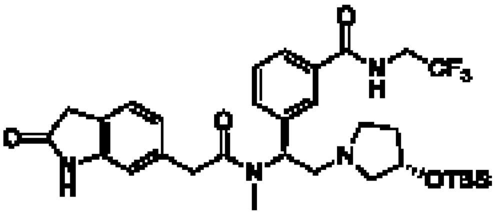
mmoL, 1.50 equiv). The resulting solution was stirred for 5 min at room temperature. Then (3S)-l-[(2S)-2-|>(l_ait-l-yn-l-yl)phmyI]-2^ thylamino)ethyl]pyrrolidin-3-ol (SO mg, 0.29 mmoL, 1.00 equiv) was added. The resulting solution was allowed to read, with stirring, for an additional 3 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC with dicHoromethane/methanol (10/1). That resulted in 60mg crude product. The crude product was purified by Prep-HPLC with the following conditions (Waters): Column, X-bridge Prep CIS 19*150 nm; mobile phase, water with 0.0S% NH+HCO$_3$ and CH$_3$CN(10% C¾CN up to 42% in S min, up to 100% in 1 min, down to 10% in 1 min); Detector, 254&220 nm. This resulted in 45 mg (32%) of the title compound as a white sotid. MS (ES, *m/z*): 4S2 (M+1); ^{1}H -NMR (300 MHz, DMSO-d_6): 7.17-7.31 (m, 5H), *624* (d, *J*=7.5Hz, 1H), *6*.73-*6*.75 (m, 1H), 5.77-5.S3 (m, 1H), 4.47 (m, 2H), 4.IS (brs, lH), 3.7S-3 S4 (m, 1H), 3.63-3.69 (m, 1H), 3.03-3.1 1 (m, 1H), 2.62-*2*.S3 (m, 5H), 2.59 (s, 1H), 2.34-2 .49 (m, 4H), 1.91 -1.99 (m, 1H), 1.47 (brs, 1H), 1.16 (t, *J*=7.5Hz, 3H).

Example 38

3-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindolin-6-yl)acetamido)ethyl)-N-(2,2,2-trifluoroethyl)benzamide



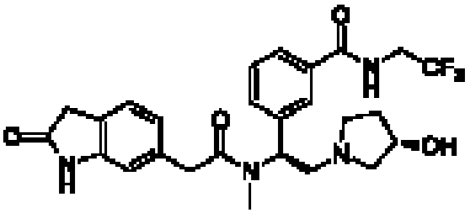
Step (i) Synthesis of 3-((S)-2-((S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindolin-0"-yi)acetamido)ethyl)-N-(2,2,2-trifluoroethyi)benzamide



Into a 5-mL vial, was placed a solution of 3-[(lS)-2-[(3S)-3-[(tert-butyldimethylsilyl)oxy]pyrrahdin-1 -yl] - 1-(methylamino)ethyi] -N-(2,2,2-tnfluoroethyl)bensamide (100 mg, 0.22 mmoL, 1.00 equiv) in Ni^-dimellnylformamide (1 niL). To the solution were added 2-(2-oxo-2,3-dihydro-l H-indol-6-yl)acetic acid (42 mg, 0.22

mmol, 1.00 equiv), HOBt (44.2 mg, 0.33 mmol, 1.50 equiv) and EDCI *(62.5* mg, 0.33 mmol, 1.50 equiv). The resulting solution was stirred for 1 hour at 25*C. The resulting solution was diluted with 20 mL of ethyl acetate. The resulting mixture was washed with ammonia (5%, 2x10 mL), brine (3x10 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 139 of the title compound as yellow oil which was used without further purification. IvE (EΞ, m/z): 633 (M+l).

Step (ii) Synthesis of 3-((S)-2-((S)-3-hydroxypyrrolidin-l -yl)-1-(N-n¾thyl-2-(2-oxoindolin-6-yl)acetamido)ethyl)-N-(2,2,2-trifluoroethyl)bensamide

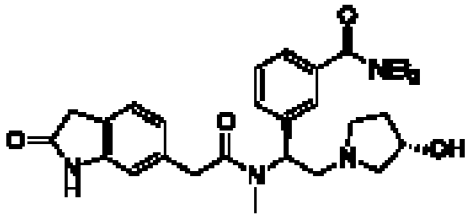


Into a 50-mL round J-ottom flask, was placed a solution of 3-[(lS)-2-[(3S)-3-[(tert-butyldimethylsilyl)oxy] pyrrohdin-1 -yl]-1-[W-methyl-2-(2-oxo-2,3-dihydro- 1H-indol-6-yl)acetamido]ethyl]-N-(2,2,2-trifluoroethyl)benzamide (138.5 mg, 0.22 mmol, 1.00 equiv) in methanol (3 mL). To the solution was added cone. hydrogen chloride aqueous (0.3 mL). The resulting solution was stirred for 2 hours at 25*C. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column, X-Bridge. prep CIS 5um OBD 19*150mm; mobile phase, water with 0.5% NH_3.¾0 and CHjCN (5% of CH_3CN up to 52% in 8 mins); Detector, UV 254,220 urn. This resulted in 6 mg of the title compound as a white solid.

IvE (ES, m/z): 519 (M+1); H -NMR (400MH¾ ΩMSO-*dt*): 10.35 (s, 1H), 9.13-9.09 (m, 1H), 7.8 (s, 2H), 7.49-7.46 (m, 2H), 7.10-7.13 (m, 1H), 6.83-6.73 (m, 2H), 5.94-5.89 (m, 1H), 5.20-5.13 (m, 1H), 4.91-4.89 (m, 1H), 4.20-4.05 (m, 3H), 3.84-3.80 (m, 1H), 3.67-3.3.63 (m, 1H), 3.42 (s, 2H), 3.12-3.08 (m, 1H), 2.85-2.81 (m, 2H), 2.76-2.74 (m, 2H), 2.63 (s, 1H), 2.52-2.50 (m, 2H), 1.98-1.95 (m, 1H), 1.52 (m, 1H).

Example 39

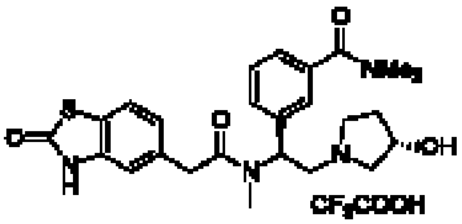
N,N-diethyl-3-((S)-2-((¾-3-hydroxypyrrolidin-1-yl)-1-(N-methylr2-(2-oxoindolin-6-yl)acetamido)ethyl)bera amide



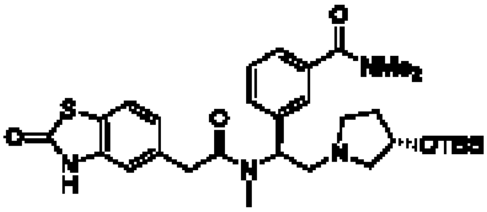
Into a 10-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 3-[(lS)-2-[(3S)-3-hydroxypyrrolidm-l -yl]-1-[N-methyl-2-(2-oxo-2,3-dih^dro4H-indol-6-^)acetan^do] e1h3¾benzoic acid (200 mg, 0.46 mmol, 1.00 equiv) in N,N-din^th^formamide (2 mL). To the mixture were added HATU (225 mg, 0.59 mmoL, 1.20 equiv), DIE A (381 mg, 2.95 mmoL, 6.00 equiv) and diethykmine (180 mg, 2.46 mmol, 5.00 equiv). The resulting solution was stirred for 6 hours at 25°C. The mixture was purified by Prep-HPLC with the following conditions (Waters): Column, X-bridge prep CIS; mobile phase, water with 0.5% N¾HjO and CH_3CN(10% CH_3CN up to 80% in lOmin, up to 100% in 1 min, down to 10% in 1 min); Detector, 254&220 . This resulted in 5 mg of the title compound as a white solid MS (EΞ, m/z): 493 (M+l); ^{1}H-NMR (DMSO-d_6, 400MHz): 5 10.33-10.36 (m, 1H), 7.33-7.41 (m, 2H), 7.20-7.24 (m, 2H), 7.10-7.19 (m, 1H), 6.74-6.S1 (m, 2H), 5.88 (m, 1H), 4.704.90 (m, 1H), 4.17 (m, 1H), 3.77-3.81 (m, 1H), 364-3 68 (m, 1H), 3.40-3.41 (m, 4H), 3.04-3.10 (m, 3H), 2.70-2.79 (m, 5H), 2.33-2.38 (m, 2H), 193-196 (m, 1H), 1.51 (m, 1H), 1.00-1.14 (m, 6H).

Example 40

3-((S)-2-((S)-3-hydroxypyrrolidin-1-yJ)-l-(N-methyt2-(2-oxo-2,3-i-hydrobenzo[d]thiazol-5-yl)acetajnido)ethyl)-N,N-dijnethylbenxamide- 2,2,2-trifhioroacelate

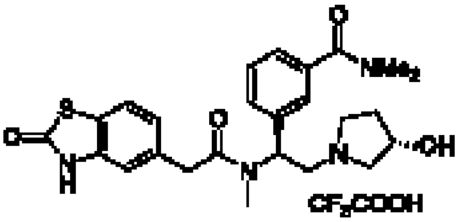


Step (i) Synthesis of 3-((S)-2-((S)-3-((tert-butyldirnethylsilyi)oxy)pyiTohdin-l-yl)-l-(N-methyl-2-(2-oxo-2,3-dihydrobenao[d| thiazoi-5-ylJacetarddoJethylJ-HN-dimethylbensamide



Into a 8-mL sealed tube, was placed a solution of 3-[(13)-2-[(3S)-3-[(tert-butyldimemylsilyl)oxy] pyirokdin-1 -yi]-1-(n¾th^amino)ethyV| -N^-din^thylbensamide (lOOmg, 0.25mmoL, 1.OOequiv) in N,N-din¾mylformamide (3 mL). To the solution were addede 2^2-oxo-2 ,3-dih^o-l ,3J-enzothiaz Q-5-5il)aceuc acid (52.3 mg, 0.25 mmol, I.00 equiv), EDCI (73 mg, 0.38 mmol, 150 equiv) ard 1H-1,2,3-benzotr aaol-l -ol (51.3 mg, 0.38 mmol, 1.50 equiv). The resulting solution was stirred for 1 h at room temperature. The resulting mixture was diluted with 50mL of ethyl acetate. Then the resulting solution was washed with ammonia (1x10 mL), brine (3x30 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 80 mg (54%) of the title compound as orange oil. IvE (ES, m/z): 597 (IvH-1).

Step (ii) Synthesis of 3^(S)-2-((S)-3-hydroxypyirolidin-l-yl)4-(N-methyl-2-(2-oxo-2,3-dihydrobensD[d]thiazol-5-yl)acetamido)ethyl)-N,N-dimethylbenzamide 2,2,2 -trifluoroacetate

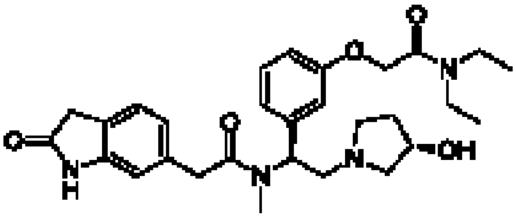


Into a 25-mL round Jaottom flask, was placed a solution of 3-[(lS)-2-[(3S)-3-[(tert-butyldimethylsilyljoxy] **pyirokdin -1**-yl]-1-[N-methyl-2 -(2 -oxo-2,3 -dihydro- 1,3-benzo thiazol-5-yl)acetamido] ethyl]-N,N-dimethylbenzamide (80 mg, 0.13 mmol, 1.00 equiv) **in** methanol (2 mL). To the solution was added concentrated hydrogen chloride aqueous (0.2 mL). The resulting solution was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (prep-HPLC): Cdumn,X-bridge prep CIS ; mobile phase, water (0.5¾TFA) and CH_3CN (5% CHjCN up to 38% in lOmin, up to 100% in 1 min, down to 5% in 1 min); Detector,254&220 nm. This resulted in 17 mg (26%) of the title compound as a white solid.

MS (EΞ, *m/z*): 483 (M+l); ^{1}H-NMR (DMSO-d_6, 300MHz): S 11.89 (s, 1H) , 10.08-9.61 (m, 1H), 7.58-6.91 (m, 7H), 6.28-6.13 (m, 1H), 5.63-5.43 (m, 1H), 4.52-4.33 (m, 1H), 4.18-4.02 (m, 1H;i, 393-3.57 (m, 5H), 3.08-2.91 (s, 3H), 2.83-2.61 (m, 6H), 2.42-2.23 (s, 1H), 2.13-1.72 (m, lH).

Example 41

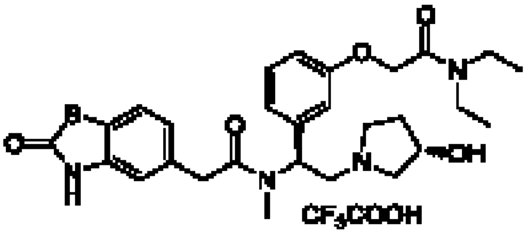
N-((S)-1-(3-(2-(diethylamino)-2-oxoethoxy)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yi)ethyi)-N-methyl-2-(2-oxoindolin-6-yl)acetajnide



Into a 10-mL vial, was placed 2-(2-oxo-2,3-dmydro-l H-irdd-6-yl)acetic acid (548 mg, 0.29 mmol, 1.00 equiv) in DMF (1 ml). To the solution weie added HGBt (58.1 mg, 0.43 mmol, 150 equiv) and EDCI (82.2 mg, 0.43 mmol, 1.50 equiv), then followed by the addition of N,N-diethyl-2- [3-[(1S)-2-[(3Ξ)-3-hydroxypyrroMin- 1-yl]-1-(memykmino) ethyl] phenoxy] acetamide (100.0 mg, 0.29 mmol, 1.00 equiv). After stirring for 1 h at 25 degree C, the resulting solution was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions : Column, X-Bridge prep CIS; mobile phase, water with 0.5% NH_3*H_20 and C¾CN (15% CH_3CN up to 45% in 10 min, up to 100% in 1 min, down to 15% in 1 min); Detector, UV 254^320 nm. This resulted in 26 mg of the title compound as a white solid. MS (ES, *m/z*): 541 (M+l/H-NMR. (DMSO-^ 300MHZ): 10.35-10.31 (m, 1¾ 7 24-7.20 (t, *J*=SJ0Hz, 1¾ 7.12-7.10 (d, *J*=7.2Hz, 1H), 6.85-6.68 (m, 5¾ 5.83-5.80 (m, 1H), 4.88 (s, 1H), 4.73 (s, 2H), 4.18 (s, 1H), 3.80-3.75 (m, 1H), 3J66-3.62 (m, 1H), 3.42 (s, 2H), 3.35-3.25 (m, 4H), 3.02 (1, 1H), 2.89-2.78 (m, 2H), 2.76-2.63 (m, 4H), 2 37-2 36 (s, 2H), 1.9S-1.93 (m, 1H), 1.50 (m, 1H), 1.16-1.12 (t, *J*=7.2Hz, 3H), 1.04-1.01 (t, *J*=7.2Hz, 3H)

Example 42

N-((S)-1-(3-(2-(diethylamino)-2-oxoethoxy)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydrobenzo[d]thiazol-5-yl)acetamide

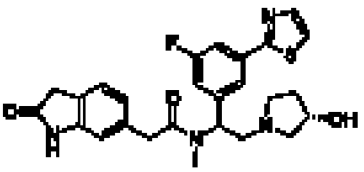


Into a 10-mL vial, was placed a solution of 2-(2-o:m-2,3-dihydro-l ,3-benzothiazol-5-ji)acetic acid (60.0 mg, 0.29 mmol, 1.00 equiv) in N,N-dimethylformamide (1 ml_). To the solution were added HOBt (58.1 mg, 0.43 mmol, 1.50 equiv) EDCI (82.2 mg, 0.43 mmol, 1.50 equiv), and N,N-diethyl-2 -P-[(13)-2-[(33)-3-hyd^xypyrrolidin-1-yl]-1-(methylamino) ethyl] pheno-iy]acetamide (100 mg, 0.29 mmol., 1.0□ equiv). After stirring for 1 h at 25*C., the resulting solution was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column, X-Bridge prep CIS; mobile phase, water with 0.5%TFA and CH£N(10% C¾CN up to 28% in 6min, stay 28% in 5min, up to 100% in 1 min, down to 10% in 1 min); Detector, UV 254,220 nm. This resulted in 15 mg of the title compound as a white solid. IvE (EΞ, m/≤): 541 [MfH-CF3COOH] +

H -NMR: (**DMSO-iJi,** 300MHz): 5 11.90 (s, 1H), 9.97-9.51 (m, 1H), 7.51-7.49 (d, *J*=8.0 ¾ 1H), 7.31 -7.25 (m, 1H), 7.12-6.99 (m, 2H), 6.87-6.76 (m, 3H), 6.1 1 (brs, 1H), 5.58-5.49 (m, 1H), 4.76 (s, 2H), 4.48-4.41 (m, 1H), 4.07-3.98 (m, 1H), 3 J89-3.49 (m, 5H), 3.37-3.18 (m, 5H), 2.74 (s, 3H), 2.34-1 .84 (m, 2H), 1.16-1 .12 (t, *J* =7.2 ¾ 3¾ 1.05-1 .01 (t, *J*=1 2 Hz, 3H)

Example 43

N-((S)-1-(3-fluoro-5-(thiazol-2-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oMindolin-6-yl)acetajnide

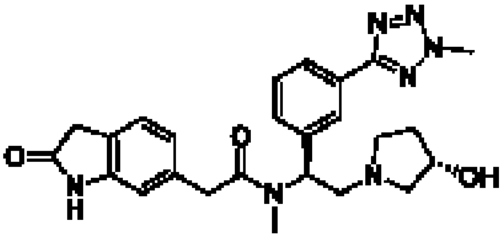


Into a 8-mL round-bottom flask, was placed a solution of (S)-l-((S)-2-(3-fluoro-5-**(tlm3ol** -2-yl)phenyi)-2-(methykmino)ethyl)py^ lidin-3-ol (60 mg, 0.14 mmol, 1.00 equiv) in N,N-dimethylformamide (2 mL). To the solution were added 2-(2-oxo-2,3-dihydm-lH-indol-6-yl)acetic acid (35.3 mg, 0.18 mmol, 1.10 equiv), EDCI (48.4 mg, 0.25 mmol, 1.50 equiv). HOBt (34 mg, 0 25 mmol, 1.50 equiv) and TEA (51 mg, 0.50 mmol, 3.00 equiv). The resulting solution was stirred for 2 hours at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified with Prep-HPLC with the following conditions (X-bridge Prep-HPLC): Column, Prep CIS 19*150 mm; mobile phase, water with 0.5% NH_3*$H_2$0 and CH_3CN(5% C¾CN up to 35% in 10 nün, up to 100% in 1 min, down to 5% in 1 min), Detector, 254&220 nm. This resulted in 2S.5 mg (41 %) of the title compound as a white solid.

IvE (ES, m/z): 495 (M+l); ^{1}H-NMP.: (300MHz, d_6-DIvEO): 5 10.33 (s, 1H), 7.96 (s, 1H), 7.85 (s, 1H), 7.65 (s, 2H), 7.41 -7.12 (m, 2H), 6.84-6 S0 (m, 2H), 5 90 (s, 1H), 4.87 (s, 1H), 4.19 (s, 1H), 3.S3-3.67 (m, 2H), 3.42 (s, 2H), 3 .1S-3.06 (m, 1H), 2.S7-2.63 (m, 5H), 2.40-2.27 (m, 2H), 2.02-1 .95 (m, 1H), 1.53-1 .4S (m, 1H).

Example 44

N-((S)-2-((S)-3-hydroxypyrrolidiii 1-yl)-1-(3-(2-methyl-2H-tetra™l-5-y¾ l* nyl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetamide



Into a S-mL, was placed a solution of (33) -1-[(2Ξ)-2-[3-(2-methyl-2H- 1,2,3,4-tetrazol-5-yl)pheny[] -2-(methylamino)ethyl] pyiTolidin-3-ol *(160* mg, 0.53 mmoL, 1.00 equiv) and 2-(2-oxo-2,3-dih^dro-lH-indol-6-^l)acetic acid (101 mg, 0.53 mmoL, 1.00 equiv) in N,N-dimeth^fonmmide (2mL). To the solution were added EDC (152 mg) and 1H-1,2,3-benzotriazol-l-ol (107 mg, 0.79 mmoL, 1.50 equiv). The resulting solution was stirred for 2 hours at room temperature. The resulting mixture was concentrated under vacuum. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (X-bridge): Column, prep CIS 19*150mm; mobile phase, water with 0.5% ammonia and CH_3CN (10% CHjCN up to 45% in 10 min; up to 100% in 1 min; down to 10% in 1 min) ; Detector, 254,220. This resulted in 17 mg of the title compound as a white solid.

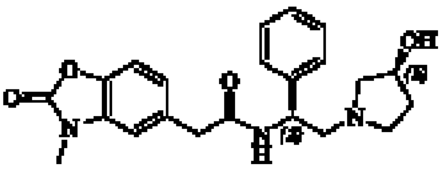
IvE (ES, m/z): 4l 6 (M+l); ^{1}H-NMR (300MHz, DM50 -i $_6$): 5 10.366 (1H, s), 7.943-7.972 (2H, d, J=8.7Hz), 7.475-7.537 (2H, m), 7.095-7.121 (1H, d, J=7.£Hz), 6£00-6.840 (2H, m), 5.95

(IH, m), 4.9074.921 (IH, d, J=4.2Hz), 4.431 (3H, s), 4.19 (IH,m), 3.801-3.852 (IH, d, J=15.3Hz), 3.642-3.693 (IH, d, J=15.3Hz), 3.394-3 .423 (2H, s), 3.142 (IH, m), 2.731-2.829 (5H, m), 2.652 (IH, s), 2.383-2.425 (2H, m), 1.94 (1H, m), 1.55 (IH, m).

The following examples 45-228 were prepared by following suitable procedure(s) similar to that mentioned in above examples 1-44, by taking appropriate starting materials:

Example 45

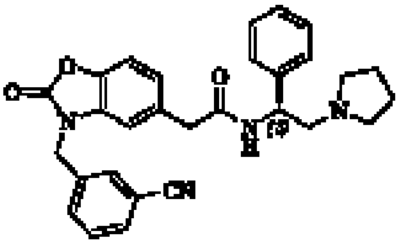
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-pl¾nyl thyl)-2-(3-methyl-2-oxo-2,3-dihydrobenzo [ti]oxazo1-5-yl)acetamide



Melting point: 105-106 °C; ^{1}H-NMR (400 MHz, DMSO-.i$_6$): 5 8.49 (d, J = 8.0 Hz, IH), 7.30-7.29 (m, 3H), 7.24-7.20 (m, 2H), 7.09 (s, 1¾ 7.04-7.03 (m, IH), 4.89-4.88 (bs, 2H), 4.66 (bs, IH), 4.12 (bs, I H), 3.55-3.50 (m, 2H), 3.29 (s, 3H), 2.73 (d, J = 8.0 Hz, 2H), 2.55-2.54 (m, 2H), 2.30 (bs, 2H), 191-1.90 (m, IH), 1.49-1 .48 (m, IH); IR (KBr, cm^{-1}): 3286, 2945, 1766, 1651, 1494, 1384; M5 (ESI): m/z 396 (M+l).

Example 46

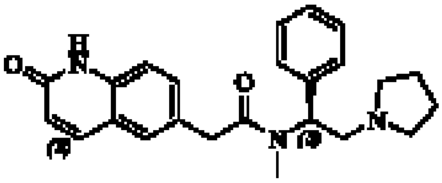
(S)-2-(3-(3-cyanobenzyl)-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)-N-(1-phenyl-2-(pyrτOlidπ-1-yl)ethyl)acetamide



Melting point: 109-110 °C; ^-NMR (400 MHz, DMS0-_i$_6$): 5 8.48 (bs, 1H), 7.9 (s, 1H), 7.79 (d, J = 7.3 Hz, I H), 7.67 (d, J = 7.6 Hz, I H), 7.57 (m, IH), 7.29-7.21 (m, 6H), 7.11 (s, IH), 7.06 (d, J = 8.2 Hz, IH), 5.07 (s, 2H), 4.92 (m, 1H), 3.52 (s, 2H), 2.63-2.54 (m, 2¾ 2.50 (bs, 4H), 1.63 (bs, 4H) ; IR (KBr, cm^{-1}): 3293, 3061, 2962, 2794, 2230, 1769, 1643, 1385, 1246; IvE (ESI): m/z 481.22 (M+1).

Example 47

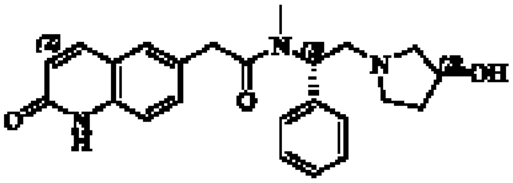
(*S*)-*N*-methyl-2-(2-oxo-1,2-dihydroquinolin-6-yl)-*N*-(1-phenyl-2-(pyrrolidin-1-yl)ethyl)acetamide



^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.69 (bs, 1H), 7.83 (d, ***J*** = 9.8 Hz, 1H), 7.47 (s, 1H), 7.40-7.23 (m, 7H), 6.48 (d, ***J*** = 9.8 Hz, 1H), 5.93-5.90 (m, 1H), 3.91-3.98 (m, 1H), 3.78-3.74 (m, 1H), 3.18 (s, 1H), 2.74 (s, 3H), 2.67 (s, 1H), 2.51-2.50 (m, 4H), 1.64 (bs, 4H); IR (KBr, cm^{-1}): 3447, 2963, 1655, 1430, 1365, 1265, 1120; MS (ESI) m/z: 390 (M+1).

Example 48

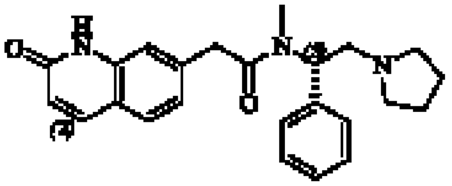
N-((*S*)-2-((*S*)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methyl-2-(2-oxo-1,2-dihydroquinolin-6-yl)acetamide



^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.69 (bs, 1H), 7.85 (d, ***J*** = 9.8 Hz, 1H), 7.47 (s, 1H), 7.39-7.23 (m, 7H), 6.47 (d, J = 9.3 Hz, 1H), 5.92 (bs, 1H), 4.70 (bs, 1H), 4.15 (bs, 1H), 3.85-3.76 (m, 2H), 3.18-3.16 (m, 2H), 2.73 (bs, 3H), 2.63 (s, 2H), 2.51-2.50 (m, 2H), 1.90 (s, 1H), 1.50 (s, 1H) ; IR (KBr, cm^{-1}): 3333, 2905, 1219, 1109, 1026 ; MS (ESI) m/z: 406 (M+1).

Example 49

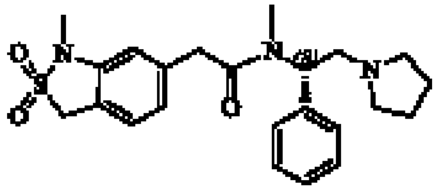
(*S*)-N-methyl-2-(2-oxo-1,2-dihydroquinolin-7-yl)-*N*-(1-phenyl-2-(pyrrolidin-1-yl)ethyl) acetamide



Melting point: 170-172 ℃; ^{1}H-NMR (400 MHz, DMSO-d_6): 5 11.70 (s, 1H), 7.86 (d, *J* = *9.2* Hz, 1H), 7.57 (d, i = 8 ¾ 1H), 7.35-7.25 (m, 5H), 7.19 (s, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.44 (d, *J* = *9.6* Hz, 1H), 60-5.80 (bs, 1H). 3.91-3.80 (m, 2¾ 2.81 (s, 1H), 2.73 (s, 3H), 2.64 (s, 1H), 2.44 (s, 4H), 1.63 (s, 4H), IR (KBr, cm^{-1}): 2964, 2794, 1656, 1560, 1413, 1282, 1122; IvE (ESI) m/z: 390 (M+l).

Example 50

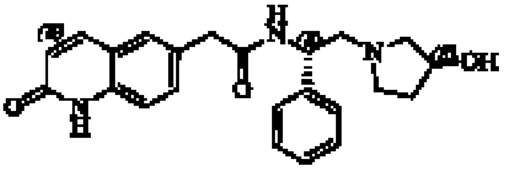
(S)-N-methyl-2-(3-methyl-2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-5-yl)-N-(1-phenyl-2-(pyrrolidin-1-yl)ethyl)acetamide



Melting point: 154-156 ℃; ^{1}H-NMR (400 MHz, DIvEO-ti.): 5 7.34-7.22 (m, 6H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.75 (s, lH), 5.87 (d, *J* = 5.2 Hz, 1H), 4.61 (s, 2H), 3.86-3.74 (m, 2H), 3.32-3.08 (m, 1H), 2.98 (s, 3H), 2.74-3.63 (m, 3H), 2.57-2.43 (m, 5H), 1.59-1.65 (m, 4H); IR (KBr, cm^{-1}): 3329, 2926, 2850, 2791, 1625, 1585, 1500, 1444, 1400, 1323, 1205; MS (ESI) *m/z*: 428 (M+l).

Example 51

M-((5)-2-((R)-3-hydroxypyrroMm-1-yl)-1-phenylefhyl>-2-(2-oxo-1,2-dihydroquinolin-6-yi)acetamide

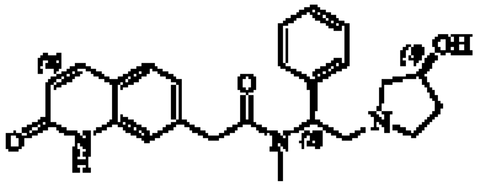


Malting point: 196-198 *C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.67 (bs, 1H), 8.51 (bs, 1¾ 7.78 (d, *J* = *9.2* Hz, 1H), 7.48 (s, 1H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.30-7.22 (m, 6H), 6.45 (d, *J* =

9.2 Hz, 1H), 4.97 (bs, 1H), 4.80400 (bs, 1H), 4.19 (bs, 1H), 3.53 (¾ *J* = 12.5 Hz, 2H), 3.40 (d, *J* = 6.8 Hz, 2H), 2.79-2.65 (in, 2H), 2.35 (bs, 2H), 1.96 (bs, 1H), 1.59 (bs, 1H); IR (KBr, cm^{-1}): 3032, 2806, 1660, 1604, 1546, 1425, 1382, 1261, 1220, 1153, 1095; MΞ (ESI) m/z: 392 (M+l).

Example 52

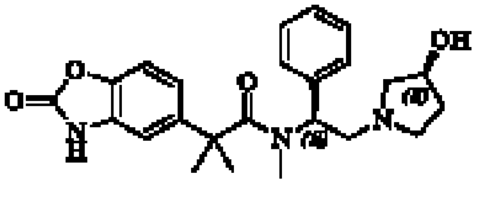
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-.V methyl-2-(2-oxo- 1,2-dihydro¾uinoLin-7-yl)acetamide



Melting pint: 176-177 ℃; 1H-NMR (400 MHz, **DIvE** O-d_6): 5 11.70 (bs, 1H), 7.86 (d, *J* = 9.2 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.33-7.29 (bs, 5H), 7.19 (s, 1H), 7.06 (d, *J* = 5.6 Hz, 1H), 6.44 (d, *J* = 8.4 Hz, 1¾ 5.84 (bs, 1H), 4.73-4.69 (bs, 1H), 4.15 (bs, 1H), 3.92-3.75 (in, 2H), 3.06-3.01 (in, 1H), 2.85 (bs, 1H), 2.63-2.72 (in, 3H), 2.50 (bs, 2H), 2.31 (bs, 2H), 1.91 (bs, 1H), 1.50 (bs, 1H); IR (KBr, cm^{-1}): 3338, 3184, 3057, 2964, 2918, 2769, 1666, 1631, 1415, 1346, 1274, 1138; **IvE** (ESI) m/z: 406 (M+l).

Example 53

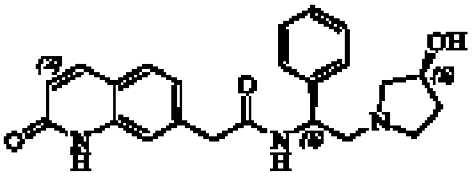
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-_V2-dimethyt2-(2-o «i-2,3-dihydrobenzo[d]oxazol-5-yl)propanajiiide



1H-NMR (400 MHz, DMSO-ii.): 5 7.30-7.22 (in, 5H), 7.05-6.99 (in, 3H), 5.07-5.05 (in, 1H), 3.55-3.51 (in, 1H), 2.82-2.76 (in, 2H), 2.69-2.67 (m, 2¾ 2.42-2.40 (d, *J* = 10.4 Hz, 1H), 2.39-2.34 (m, 1H), 2.24-2.21 (in, 3H), 2.19 (s, 3H), 1.64-1.60 (bs, 1H), 1.49 (s, 6H); IR (KBr, cm^{-1}): 2972, 2798, 1776, 1496, 1467, 1388, 1350, 1257, 1147, 1147, 1074; MS (ESI) m/z: 424 (M+l).

Example 54

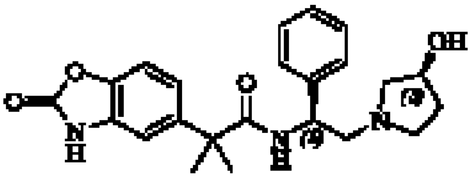
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-2-(2-oxo-1,2-dihydroquinolin-7-yl)acetamide



Melting point: 174-176 °C; ^{1}H-NMR (400 MHz, DMSO-di): S 11.72 (s, 1H), 8.54 (d, *J* = 8.4 Hz, 1H), **7.S4 (d, *J* =** 10.0 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 730-7.27 (m, 4H), 7.24-7.19 (m, 2H), 7.11 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 6.43 (dd_ *J*, = 1.6 Hz, J_2 = 8.0 Hz, 1¾ 4.89 {q, *J* = 7.5 Hz, 1H), 4.7 (bs, 1H), 4.13-4.08 (m, 1H), 3.54 (¾ *J* = 13.6 Hz, 2H), 2.77-2.67 (m, 2H), 2.59-2.54 (in, 1H), 2.44-2.40 (m, 1H), 2.33-2.29 (in, 2H), 1.93-1.88 (in, 1H), 1.51-1.49 (in, lH); IR (KBr, cm^{-1}): 3061, 2964, 2806, 1658, 1604, 1552, 1415, 1346, 1276, 1219, 1149; MS (ESI) m/z: 392 (M+l).

Example 55

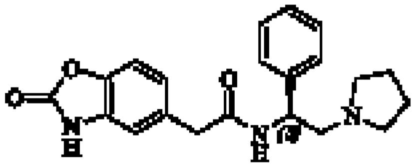
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-2-methyl-2-(2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)propanamide



^{1}H-NMR (400 MHz, DMSO-tii): δ 11.6 (bs, 1H), 7.52-7.50 (d, *J* = 7.3 Hz, 1H), 7.28-7.24 (in, 6H), 7.28-7.17 (in, 2H), 4.934.90 (in, 1H), 409-4.12 (m, 1H), 2.94-2.67 (m, 4H), 254-2.30 (in, 3H), 1.95-1.90 (m, 1H), 1.52-1.48 (s, 3H), 1.47-1.43 (s, 3H); IR (KBr, cm^{-1}): 3305, 3084, 2929, 2810, 1766, 1664, 1494, 1467, 1259, 1159; MS (ESI) m/z: 410 (M+l).

Example 56

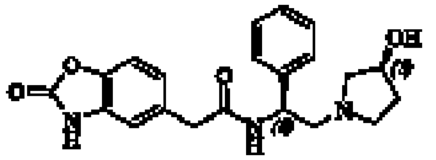
(S)-2-(2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)-N-(1-phenyl-2-(pyrrolidin-1-yl)ethyl)acetamide



Melting point: 129-130 °C; 1H-NMR (400 MHz, DMSO-d_6): δ 12.0-11.0 (bs, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 7.30-7.28 (m, 5H). 7.23-7.19 (m, 1H), 7.11 (m, 1H), 6.96-6.91 (m, 1H), 4.91-4.85 (m, 1H), 3.45 (s, 2H), 2.76-2.67 (m, 2H), 2.42 (bs, 4H), 1.62 (bs, 4H); IR (KBr, cm^{-1}): 3064, 2796, 1764, 1658, 1535, 1261; MS (ESI) m/z: 366.2 (M+l).

Example 57

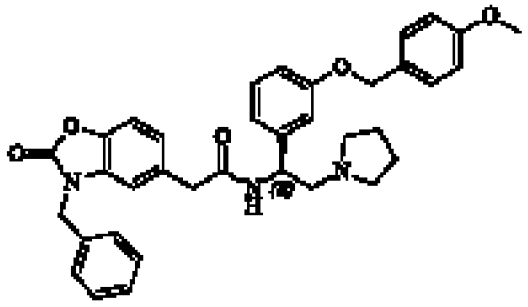
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-2-(2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)acetamide



Melting point: 210-211 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.5-11.0 (bs, 1H), 8.49 (d, *J* = 8.3 Hz, 1H), 7.30-7.16 (m, 6H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.06 (s, 1H), 6.97 (d, *J* = 7.3 Hz, 1H), 4S9 (q, *J* = 8.5 Hz, 1H), 4.13 (bs, 1H), 3.52-3.42 (m, 2H), 2.76-2.68 (m, 2H), 2.60-2.50 (in, 2H), 2.43-2.40 (m, 1H), 2.33-2.30 (m, 1H), 1.96-1.91 (m, 1H), 1.50-1.40 (m, 1H); IR (KBr, cm^{-1}): 3420, 3120, 1640, 1339, 1219; MS (ESI) m/z: 382.0 (M+l).

Example 58

(S)-2-(3-benzyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)-N-(1-(3-(4-methoxybenzyloxy)phenyl)-2-(pyrrolidin-1-yl)ethyl)acetamide

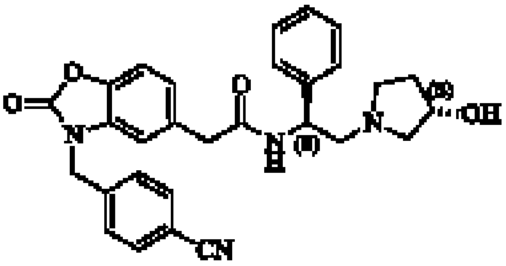


Melting point: 72-74 °C; ¾-NMR (400 MHz, DMSO-d_6): δ S.45 (d, *J* = 7.0 Hz, 1H), 7.36-7.39 (m, 7H), 7.31-7.25 (m, 1H), 7.21-7.17 (m, 1H), 7.11 (s, 1H), 7.06-7.04 (m, 1H), 6.95-

6.93 (m, 3H), 6.85 (d, *J* = 5.9 Hz, 2H), 4.97 (s, 2H), 4.94 (s, 2H), 490 (bs, 1H), 3.76 (s, 3H), 3.47 (s, 2H), 2.50 (bs, 4H), 2.45 (bs, 2H), 1.63 (bs, 4H); IR (KBr, cm^{-1}): 3313, 3034, 2962, 2794, 1774, 1664, 16 10, 1585, 15 14, 1492, 1465; MΞ (ESI) m/z: 591 .8 (M+l).

£xamp]e 59

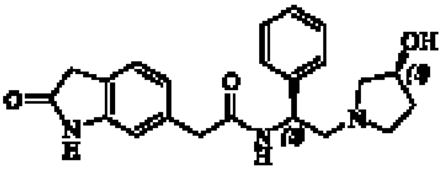
2-(3-(4-cyanobenzyl)-2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)-*N*-((*S*)-2-((*S*)-3-hydroxy pyrrolidin-1-yl)-1-phenylethyl)acetamide



Mating point: 194-194 °C; 1H-NMR (400 MHz, DIvEO-tit) : δ 8.47-8.45 (m, 1H), 7.84-7.82 (m, 2H), 7.53-7.51 (m, 2H), 7.31-7.21 (m, 6H), 7.08-7.06 (m, 2H), 5.20-5.18 (m, 2H), 4.90-4.80 (m, 1H), 4.71-4.61 (m, 1H), 4.134.20 (m, lH), 3.50-3.38 (m, 4H), 2.80-2.7 1 (m, 2H), 2.67-2 3 3 (m, 2H), 1.91 - 1.89 (m, 1H), 1.50- 1.50 (m, 1H) ; IR (Neat, cm^{-1}): 3304, 2943, 2230, 1768, 1495; IvE (ESI): m/z 497 (M+l).

Example 60

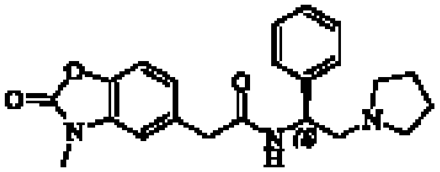
iV-((*S*)-2-((*S*)-3-hydroxypyrrolidin-1-yl)-1-phenylethyI)-2-(2-oxomdo lm-6-yl)acetamide



lilting point: 207-209 °C; ^{1}H-NMR (400 MHz, DIvEO-rf$_6$): 5 10.35 (s, 1H), 8.49 (d, *J* = 7.2 Hz, 1H), 737-7.22 (m, 5H), 7.08 (d, *J* = 7.2 Hz, 1H), 6.81 (s, 2H), 4.90 (s, 1H), 4.84 (s, 1H), 4.16 (s, lH), 3 .47-3 32 (m, 4H), 2.77-2.67 (m, 3H), 2.50 (bs, 1H), 2.38 (bs, 2H), 1.95-1 91 (m, 1H), 1.53 (bs, 1H); IR (KBi; cm^{-1}): 3275, 3065, 2941, 2804, 1691, 1630, 1547; MS (ESI) m/z : 380.6 (M+l).

Example 6 1

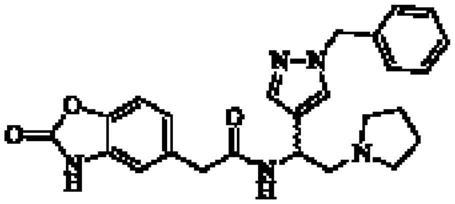
(S')-2-(3-methylr2-oxo-2,3-dihydrobenzo[.¾oxainl-5-yl)-iV-(l-phieiiylr2-(pyrrolidin-1-yl)ethyl)acetamide



Melting punt: 105-107 °C; ^{1}H-NMR (400 MHz, OMEO-iii): δ 8.49 (d, J = 8.3 Hz, 1H), 7.30-7.29 (in, 4H), 7.27-7.20 (m, 2H), 7 0 9 (d, J = 1.3 Hz, 1H), 7.03 (dd, J_1 = 1.6 Hz, J_2 = 8.3 Hz , 1H), 4.93-4.87 (m, 1H), 3.51 (d, J = 2.4 Hz, 2H), 3.31 (s, 3H), 2.79-2.73 (m, 1H), 2.51 (bs, 1H), 2 50-2.44 (in, 4H), 1.64-1 .23 (in, 4H); IR (KBr, cm^{-1}): 3286, 3061, 2954, 2794, 1764, 1649, 1535, 1494, 1384, 1064; MS (ESI) m/z: 380 (M+l).

Example 62

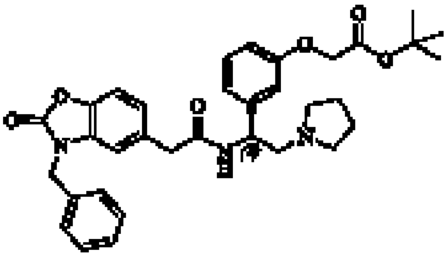
N-(1-(1-benzyl-1H-pyrazol-4-yl)-2-(pyrrolidin-1-yl)ethyl)-2-(2-oxo-2,3-dihydro henxo [d]oxazol-5-yl)acetamide



1H-NMR (400 MHz, DMSO-d_6): δ 11.52 (bs, 1H), 8.26 (d, J = 8.32 Hz, 1H), 7.62 (s, 1H), 7.32-7 .1 5 (in, 7H), 6.95 (d, J = 8.32 Hz, 2¾ 5.24 (s, 2H), 4.93-4.92 (in, 1H), 3.43 (s, 2H), 2.71-2 .67 (m, 2H), 2.50-2.33 (in, 4H), 1.63 (bs, 4H), IR (KBr, cm^{-1}): 3064, 2962, 1774, 1656, 1496, 1261 ; IvE (ESI) m/z: 446 (M+l).

Example 63

(S)-t-butyl-2-(3-(1-(2-(3-benzyl-2-oxo-2,3-dihydrabeiiz» [d]oxaxol-5-yl)acetamido)-2-(pyrrolidm.-1-yl)ethyl)phenoxy)acetate

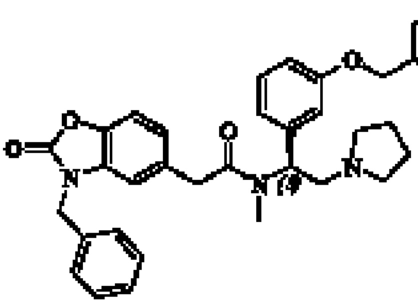


Melting pzdnt: 68-70 *C; 1H-NMR (400 MHz, DMSO-ti.): δ 8.50 (bs, 1H), 7.38-7.30 (m, 5H), 7.2S-7 3 0 (m, 2H), 7.12 (s, 1H), 7 0 4 (d, J = 8.3 Hz, 1H), 6.91 (bs, 2H), 6 .76 (bs, 1H), 4.99

(bs, 3H), 4.60 (s, 2H), 3.49 (bs, 2H), 3.20-2.60 (m, 2H), 2.50 (bs, 4H), 1.68 (bs, 4H), 1.42 (s, 9H); IR (KBr, cm^{-1}): 3248, 2974, 2796, 1776, 1664, 1587, 1492, 1467, 1384, 1369, 1246; MS (ESI) m/z: 586.5 (M+l).

Example 64

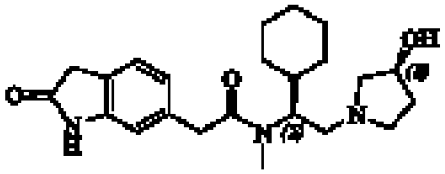
(*S*)-2-(3-benzyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)-*N*-(1-(3-(benzyloxy)phenyl)-2-(pyrrolidin-1-yl)ethyl)-*N*-methylacetamide



1H-NMR (400 MHz, **DMSO-rfi**): ***8*** 7.43-7.20 (m, 13H), 7.08 (s, 1H), 7.02 (d, ***J*** = 8.2 Hz, 1H), 6.91 (d, ***J*** = 7.0 Hz, 1H), 6.89-6.84 (m, 1H), 5.80-5.77 (m, 1H), 5.044.99 (m, 4H), 3.81-3.68 (m, 2H), 3.04-2.98 (m, 1H), 2.70 (s, 3H), 2.59 (s, 1H), 2.40 (bs, 4H), 1.60 (bs, 4H); IR (KBr, cm^{-1}): 2931, 2791, 1774, 1631, 1494, 1467, 1382, 1352, 1244, 1134; MS (ESI) m/z: 576 (M+l).

Example 65

N-((*S*)-1-cyclohexyl-2-((*S*)-3-hydroxypyrrolidin-1-yl)ethyl)-*N*-methyl-2-(2-oxoindolin-6-yl)acetamide

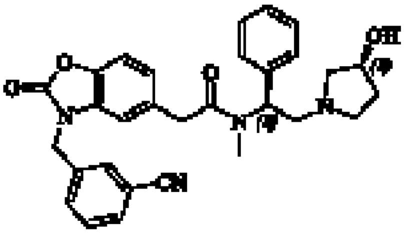


1H-NMR (400 MHz, **DMSO-rfi**): δ 10.36 (s, 1H), 7.10 (d, ***J*** = 7.3 Hz, 1H), 6.82-6.70 (m, 2H), 4.90 (bs, 1H), 4.39 (bs, lH), 4.14 (s, 1H), 3.77-3.73 (m, 1¾ 3.65 (s, 1H), 3.58-3.54 (m, 1H), 3.42 (s, 1H) 2.72 (s, 3H), 2.69-2.61 (m, 2H), 2.24-2.16 (m, 3H), 1.95-1.90 (m, 1H), 1.76-1.57 (m, 4H), 1.46-1.43 (m, 2H), 1.37-1.34 (m, lH), 1.13-1.00 (m, 4H), 0.97-0.93 (m, 1H), 0.84-

0.81 (m, 1H) ; IR (KBr, cm"1): 3306, 3182, 2928, 2856, 2783, 1710, 1630, 1605, 1460; MS (ESI): m/z 400.4 (M+1).

Example 66

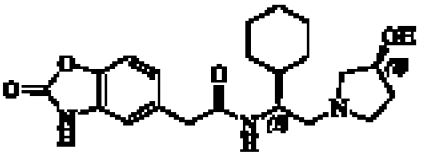
2-(3-(3-cyanoben.yl)-2-oxo-2,3-dihydrobenzo[.i]oxaml-5-yI)-iV-((^-2-((£)-3-hydroxypyrrolidiii-l-yl)-1-phenylethyl)-N-methylacetamide



^{1}H-NMR (400 MHz, DMSO-tii): 5 7.87 (s, 1H), 7.79 (d, *J* = 7.69 Hz, 1H), 7.67 (d, *J* = 8D5 Hz, 1H), 7.59-7.57 (m, 1H), 7.31-7.24 (in, 5H), 7.18 (d, *J* = 6.96 Hz, 1H), 7.07 (d, *J* = 10.9 Hz, 1H), 7.04-6.99 (in, 1¾ 5.80 (in, 1H), 5.08 (s, 2H), 4.67 (d, J = 8.42 Hz, 1H), 4.12 (bs, 1H), 3.843.68 (m, 2H), 2.99-2.80 (m, 2H), 2.70 (s, 2H), 2.60 (bs, 3H), 2.40-2.33 (m, 1H), 2.32-2.29 (in, 1H), 190-1 £7 (in, 1H), 1.47-1.35 (in, 1H) ; IR (KBr, cm"1): 3419, 2924, 2852, 2804, 2229, 1772, 1627, 1494, 1355, 1244, 1022, 754; MS (ESI): m/z 511 (M+1).

Example 67

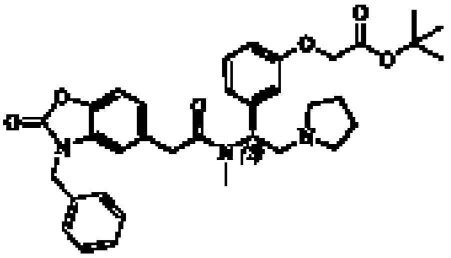
N-((S)-1-cyclohexyl-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-2-(2-oxo-2,3-dihydrobenxo[d]oxazo1-5-yl)acetamide



Melting pzdnt: 173-174 °C; ^{1}H-NMR (400 MHz, DMSO-d$_6$): 5 11.5 (bs, 1H), 7.72 (s, *J* = 824 Hz, 1H), 7.17 (d, *J* = 7.94 Hz, 1H), 7.07 (s, 1H), 6.96 (d, *J* = 7.94 Hz, 1H), 4.80 (bs, 1H), 4.12 (bs, 1H), 3.73 (bs, 1H), 3.41-3.37 (in, 2H), 2.65 (d, *J* = 85 Hz, 1H), 2.43-2.23 (m, 4H), 1.92 (d, *J* = 6.41 Hz, 1H), 1.59 (in, 7H), 12-1.08 (in, 6H); IR (KBr, cm"1): 3065, 2797, 1765, 1649, 1535, 1262; MS (ESI): m/z 388 (M+1).

Example 68

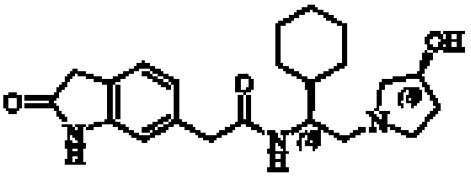
(*S*)-tert-butyl 2-(3-(1-(2-(3-benzyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)-.V-methyl acetamido)-2-(pyrrolidin-1-yl)ethyl)phenoxy)acetate



Melting pint: 111-113 °C; 1H-NMR (400 MHz, DMSO-d_6): 5 7.35-7.26 (m, 6H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.07 (s, 1H). 7.05-7.01 (m, 1H), 6.86 (d, *J* = 7.2 Hz, 1H), 6.79-6.73 (in, 2H), 5.79 (bs, 1H), 5.00 (s, 2H), 4.61 (s, 2H), 3.81-3.79 (m, 1H), 3.75-3.68 (in, 1H), 3.01 (bs, 1H), 2.89 (s, 1H), 2.71 (s, 3H), 2.61-2.54 (m, 2H), 2.49-2.33 (in, 2H), 1.61 (bs, 4H), 1.41 (s, 9H); IR (KBr, cm^{-1}): 3399, 2922, 2851, 1776, 1641, 1493, 1462, 1389, 1289; MS (ESI): m/z 600 (M+l).

Example 69

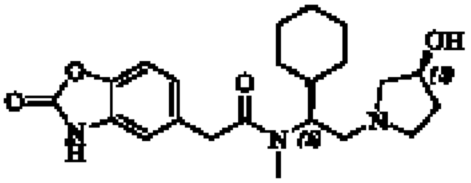
-V((*S*)-1-cyclohexyl-2-((*S*)-3-hydroxypyrrolain-1-yl)ethyl)-2-(2-oxoindolin-6-yi)acetamide



lilting point: 132-133 °C; ^{1}H-NMR (400 MHz, DIvE O-d_6): 5 10 3 2 (s, 1H), 7.63 (d, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 1H), 6.91-6.81 (in, 2H), 4.86 (bs, 1H), 4.18 (bs, 1H), 3.78 (s, 1H), 3.46-3.31 (in, 4H), 2.68 (s, 2H), 2.21-2.19 (in, 4H), 1.96 (s, 1H), 1.67-1.60 (m, 6H), 1.52-0 9 7 (m, 6H) ; IR (KBr, cm^4): 3262, 2928, 2853, 2799, 1703, 1632; IvE (EΞI): m/z 386 (M+l).

Example 70

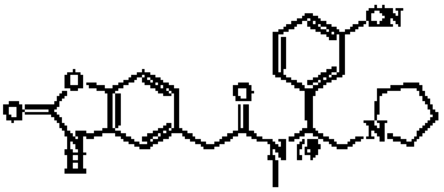
N-((*S*)-1-cyclohexyt2-((£)-3-hydroxypyrrolain-1-yl)ethyl)-*N*-methyl-2-(2-oxo-2,3-dihydrobenzo[ti]oxazol-5-yl)acetamide



Melting point: 130-131°C; ^-NMR. (400 MHz, DM50-ti ,): 5 11.5 (bs, 1H). 7.IS (d, *J* = 7.8 Hz, 1H), 7.16 (s, 1H), 7.03-6.96 (m, 1H), 4J6 (bs, 1H), 4.3 (bs, 1H), 4.14 (bs, 1H), 3.8-3.6 (m, 4H). 2.73 (s, 3H). 2.7-2.6 (m, 2H). 2.2 (bs, 2H). 1.93-1.90 (in, 2H), 1.8-1.71 (in, 7H), 1.20-1.02 (m, 4H) ; IR (KBr, cm^{-1}): 2927, 2852, 1774, 1618, 1261 ; MS (EΞI): m/z 402 (M+l).

Example 71

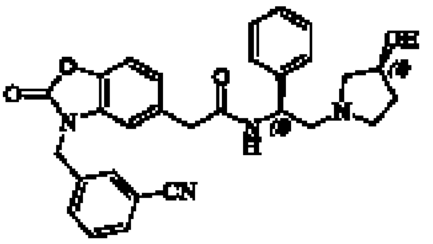
(*S*)-*N*-(1-(3-cyanophenyl)-2-(pyrrolidin-1-yl)ethyl)-*N*-methyl-2-(2-oxo-2,3-dihydrobenzo[*d*]Oxazol-5-yl)acetajiiide



Malting pint: 116-118 °C; 1H-NMR (400 MHz, DMSO-*d*$_6$): δ 11.5 (bs, l H), 7.75-7.63 (in, 2H), 7.61- 7.52 (m, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.95-6.93 (m, 2H), 5.82-5.79 (m, 1H), 3.79-3.76 (in, 2H), 3.01-2.97 (in, 1H), 2.86-2 S3 (m, 1H), 2.76 (s, 3H), 2.50 (bs, 4H), 1.6 (bs, 4H) ; IR(KBr, cm^{-1}): 2958, 2794, 2227, 1774, 1629, 1465, 1400, 1261 ; MS (ESI): m/z 405 (M+l).

Example 72

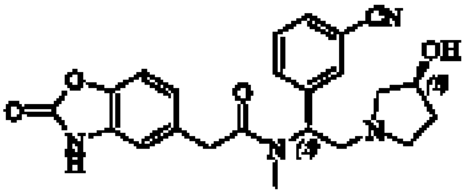
2-(3-(3-cyanobenzyl)-2-oxo-2,3-dihydrobenzo[.i]oxaiol-5-yl>jV-((^-2-((i)-3-hydroxyp ynnlidin- l-yl)- 1-phenylethyl)acetamide



Mslting pint: 65-68 °C; ^{1}H-NMR (400 MHz, DMS0 -*d*$_6$): δ 8.43 (d, *J* = 8.3 Hz, 1¾ 7.88 (s, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.67 (d, J = 8.1 Hz, lH), 7.59-7.55 (m, 1H), 7.29-7.25 (m, 5H), 7.23-7.18 (in, 1H), 7.09-7.05 (in, 2H), 5.06 (s, 2H), 4.87-4.81 (m, 1H), 4.64 (d, *J* = 4.3 Hz, 1H), 4.12-4.08 (m, lH), 3.50-3.41 (m, 2H), 2.70-2.66 (m, 2H), 2.53-2.51 (m, 2H), 2.47-2.37 (m, 1H), 2.29-2.26 (m, 1H), 1.91-1.86 (m, 1H), 1.49-1.44 (m, lH) ; IR (KBr, cm^{-1}): 3304, 3062, 2943, 2806, 2229, 1774, 1658, 1535, 1494, 1354, 1246; MS (ESI): m/z 497 (M+l).

Example 73

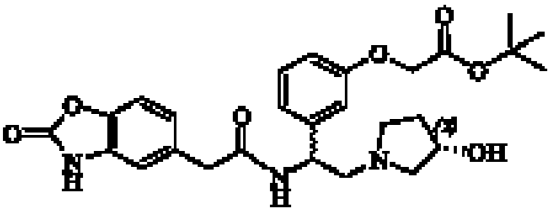
N-((S)-l-(3-cyanophenyl)-2-((S)-3-hydroxypyTrolidin-l-yl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydrobenzo[d]oxazol-5-yljacetamide



Ivfelting pint: 203-206 °C; ¾ -NMR (400 MHz, DMSO-ti.) : 5 11.58 (bs, lH), 7.74 (d, *J* = 6.8 Hz, 1H), 7.70 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.58-7.53 (m, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 7.02 (s, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 5.86-5.82 (m, 1H), 490 (bs, 1H), 4.23-4.18 (m, lH), 3.89-3.75 (m, 2H), 3.18-3.0 (m, 1H), 2.87-2.83 (m, 2H), 2.76 (s, 3H), 2.74-2.71 (m, 1H), 2.50-2.42 (m, 2H), 199-1.92 (m, lH), 1.59-1.51 (m, 1H) ; IR (KBr, cm^{-1}): 333 1, 2920, 2798, 2229, 1764, 1597, 1465, 1261, 1138; IvE (ESI): m/z 421 (M+l).

Example 74

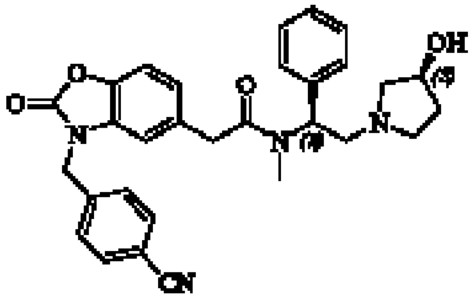
(S)-tert-butyl 2-(3-(2-(3-hydroxypyrrolidin-l-yl>-1-(2-(2-oxo-2,3-dihydrobenzo[^oxaxol-5-yi)acetamido)ethyl)phenoxy)acetate



^-NMR (400 MHz, DMSO-ti): *5* 11.55 (bs, 1H), 8.47 (t, *J* = 8.8 Hz, 1H), 7.22-7.15 (m, 2H), 7.06-6.70 (m, 5H), 4.88 (bs, 1H), 4.59 (d, *J* = 2.0 Hz, 2H), 4.16 (bs, 1H), 3.53-3.40 (m, 2H), 3.18-3.14 (m, 1H), 2.84-2.60 (m, 3H), 2.40-2.35 (m, 2H), 1.96-1.86 (m, 1H), 1.58-1.52 (m, 1H), 1.42 (s, 9H) ; IR (KBr, cm^{-1}): 3288, 3055, 2974, 2808, 1764, 1656, 1492, 1467, 1369, 1261, 1153, 1087; IvE (ESI): m/z 512 (M+l).

Example 75

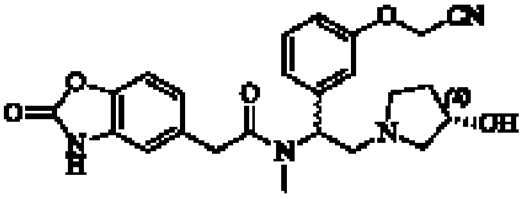
2-(3-(4-cyanobenzyl)-2-oxo-2,3-dihydroberUD[*d*]oxazol-5-yl)-iV-((*S*)-2-((*S*)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-*N*-methylacetamide



1H-NMR (400 MHz, DMSO-d_6): 5 7.83 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.33-7.25 (m, 5H), 7.24-7.16 (m, 1H), 7.06-7.04 (m. 2H), 5.80 (m, 1H), 5.08 (s, 2H), 4.67 (d, *J* = 8.42 Hz, 1H), 4.12 (bs, 1H), 3.84-3.68 (m, 2H), 2.99-2.80 (m, 2H), 2.70 (s, 2H), 2.60 (bs, 3H), 2.40-2.33 (m, 1H), 2.32-2.29 (m, 1H), 1.90-1.87 (m, 1H), 1.47-1.35 (m, 1H); IR (KBr, cm^{-1}): 3062, 2920, 2852, 2804, 2227, 1774, 1631, 1494, 1467, 1384, 1244, 1095;
IvE (ESI): m/z 511 (M+l).

Example 76

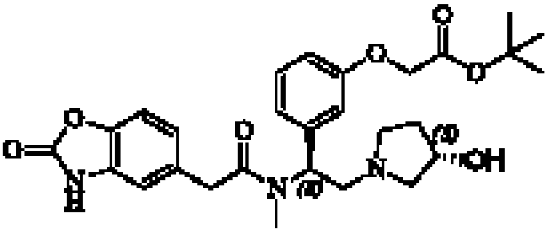
iV-(1-(3-(cyanomethoxy)phenyl)-2-(3-hydroxypyrrolidin-1-yl)ethyl)-iV-methyl-2-(2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)acetamide



1H-NMR (400 MHz, **DMSO-d_6**): 5 11.54 (bs, 1H), 7.35-7.31 (m, lH), 7.30-7.20 (m, 1H), 7.17-6.90 (m, 5H), 5.82 (bs, 1H), 5.15-5.14 (s, 2H), 4.90 (bs, 1H), 4.68 (bs, 1H), 4.16-3.86 (bs, 1H), 3.82-3.72 (m, 2H), 329-3.17 (m, 1H), 2.96-2.78 (m, 2H), 2.73-2.62 (s, 3H), 2.5-2.37 (m, 2H), 1.98-1.94 (m, 1H), 1.60-1.40 (bs, 1H); IR (Neat cm^{-1}): 2949, 2808, 1766, 1604, 1467, 1400, 1263, 1172, 1138, 1099; MS (EΞI): m/z 451 (M+l).

Example 77

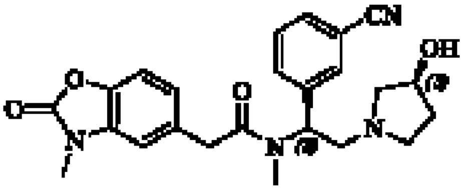
tert-butyl 2-(3-((*S*)-2-((*R*)-3-hydroxypyrrolidin-1-yl)-1-(jV-iuethyJr2-(2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)acetamido)ethyl)phenoxy)acetate



Mating point: 124-125 °C; 1H-NMR (400 MHz, DMSO-ci.): 5 12.0-1 1.0 *(bs,* 1H), 7.26-7.17 **(in,** 2H), 7.04 (s, IH), *6.96-6.95* (m, IH), 6.88-6.86 **(in,** 1H). 6.83-6.80 (m, IH), 6.77-6.74 (m, 2H), 5 £4-5.80 **(in,** 1H), 4.83 (bs, IH), 4.61 (s, 1H), 4.20-4.16 **(in,** IH), 3.86-3.84 **(in,** IH), 3.82-3.71 **(in,** I H), 3.10-3.00 (m, IH), 2.81-2.74 **(in,** 2H), 2.71 (s, 3H), 2.68-2.67 **(in,** IH), 2.50-2.49 **(in,** 2H), 1.98-1.91 **(in,** IH), 1.52-1.51 (m, 1H), 1.49 (s, 9H); IR (Neat, cm^{-1}): 3339, 2980, 2797, 1773, 1597, 1467; MS (ESI): m/z 526 (M+l).

Example 78

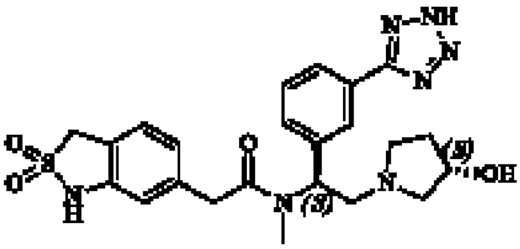
N-((S)-1-(3-cyanophenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(3-methyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)acetamide



Melting point: 83-85 °C; ¾-NMR (400 MHz, DMSO-d_6): δ 7.74 (d, *J* = 6.8 Hz, IH), 7.70 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.58-7.53 **(in,** IH), 7.20 (d, *J* = 8.3 Hz, 1¾ 7.02 (s, 1H), 6.95 (d, *J* = 8.3 Hz, IH), 5.86-5.82 **(in,** IH), 4.90 (bs, 1¾ 4.23-4.18 (m, IH), 3.89-3.75 (m, 2H), 3.31 (s, 3H), 3.18-3.0 **(in,** IH), 2 £7-2.83 **(in,** 2H), 2.76 (s, 3H), 2.74-2.71 **(in,** I H), 2.50-2.42 **(in,** 2H), 1.99-1.92 **(in,** IH), 1.59-1.51 **(in,** IH); IR (Neat, cm^{-1}): 2943, 2802, 2227, 1776, 1631, 1479, 1384, 1265; MS (ESI): m/z 435 (M+l).

Example 79

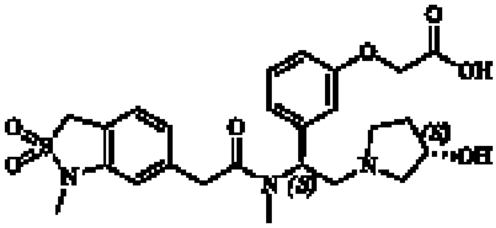
N-((S)-1-(3-(1H-tetrazol-5-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-2-(2,2-dioxido-1,3-dihydrobenzo[c]iothiaml-6-yl)-N-methylacetamide



^{1}H-NME (400 MHz, DIvEO-d.): 5 7.93 (s, IH), 7.90 (d, J = 7.3 Hz, IH), 7.45-7.41 (m, IH), 7.31 (s, 1¾ 7.17 (d, J = 7.S Hz, IH), 6.86 (d, J = 7.8 Hz, IH), 6.79 (a. IH), 5.95 (m, IH), 5.21 (bs, IH), 4.40 (s, 2H), 4.23 (a. I H), 3.81-3.71 (m, 2H), 3.22-3.15 (m, 2H), 3.12-3.09 (m, 2H), 2.74 (s, 3H), 2.45-2.32 (m, 1¾ 2.31-2.29 (m, IH), 1.97-1.92 (m, 1¾ 1.53-1.50 (m, lH);IR(Neat cm^{-1}): 2926, 1708, 1641, 1583, 1444, 1402, 1309, 1136;
IvE (ESI) m/z: 498 (M+l).

Example 80

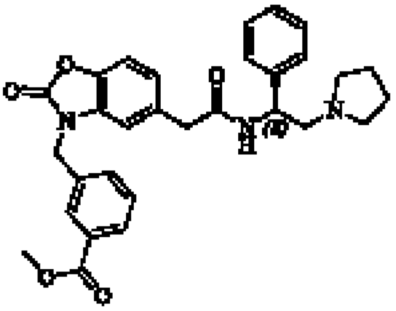
2-(3-((S)-2-((S)-3-hydroxy yrroMin- 1-yl)-1-(N-methyl-2-(1-methyl-2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-5-yl)acetajnido)ethyl)phenoxy)acetic acid



^{1}H-NMR (400 MHz, DMSO-d_6): δ 13.00 (s, IH), 9.94-9.76 (m, IH), 7.31-7.25 (m, 2H), 6.91-6.77 (m, 5H), 6.13-6.12 (m, IH), 6.10 (s, IH), 4.804.75 (s, 2H), 4.604.45 (s, 2H), 4.44 (d, 1H; j= 28.3), 4.12-4.09 (m, 1H), 4.0-3.60 (m, 5H), 3.20-3.10 (s, 3H), 2.82-2.73 (s, 3H), 232-2.28 (m, IH), 2.26-1.84 (m, IH); IR (Neat, cm^{-1}): 2927, 1678, 1612, 1587, 1492, 1442, 1400, 1321, 1203, 1139; IvE (ESI) m/z: 518 (M+l).

Example 81

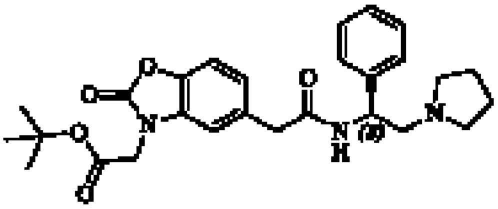
(5)-methyl 3-((2-DM-5-(2-OXO-2-(1-phenyl-2-(pyrrolidin-1-yl)ethylamino)ethyl)benzo[d]oxazol-3(2H)-yl)methyl)benzoate



1H-NMR (400 MHz, DMSO-tit): δ 8.80-8.60 (m, 1H), 7.95 (s, 1H), 790 (d, *J* = 7.8 Hz, 1H), 7.63 (**d**, *J* = 7.5 Hz, 1H) 7.51 (**t**, *J* = 7.8 Hz, 1H), 7.30-7.28 (m, 6H), 7.15 (s, 1H), 7.05 (**d**, *J* = 8.33 Hz, 1H), 5.09 (m, 3H), 3.84 (s, 3H), 3.50 (s, 2H), 3.20 (m, 2H), 2.54-2.50 (m, 4H), 1.75 (bs, 4H); IR (**KBr,** cm⁻¹): 3360, 2951, 1776, 1722, 1658, 1492, 1286, 1203, 1107, 1020; MS (ESI) m/z: 514.0 (M+1).

Example 82

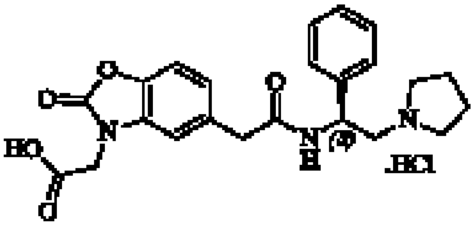
(*S*)-tert-butyl-2-(2-oxo-5-(2-oxo-2-(1-phenyl-2-(pyrrolidin-1-yl)ethylamino)ethyl)benzo[*d*]oxazol-3(2*H*)-yl)acetate



¾-NMR (400 MHz, DMSO-d_6): δ 8.51 (bs, 1H), 7.30-7.05 (m, 8H), 4.92 (m, 1H), 4.58 (s, 2H), 3.52-3.37 (bs, 2H), 2.89-2.67 (m, 2H), 2.54-2.32 (m, 4H), 1.91-1.57 (m, 4H), 1.41 (s, 9H); IR (Neat, cm⁻¹): 2976, 1784, 1743, 1658, 1546, 1494, 1467, 1390, 1367, 1244, 1155; MS (ESI) m/z: 480 (M+1).

Example 83

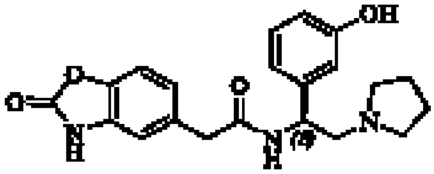
(*S*)-2-(2-oxo-5-(2-oxo-2-(1-phenyl-2-(pyrrolidin-1-yl)ethylamino)ethyl)benzo[*d*]oxazol-3(2*H*)-yl)acetic acid hydrochloride



^{1}H-NMR. (400 MHz, DMSO-ii$_6$): 5 10.1 (bs, IH), S.90 (d_ *J* = 8.3 Hz, IH), 7.2-7.4 (m, 7H), 7.06 (m, 1H), 5.25-5.29 (m, IH), 4.26 (s, 2H), 3.61 (s, 2H), 3.53-3.38 (m, 4H), 3.32-3.06 (m, 2H), 2.32-1.90 (m, 4H); IR (Neat cm^4): 3030, 2601, 1778, 1670, 1535, 1496, 1467, 1390, 1357, 1246, 1219; Mi (ESI) m/z: 424 (M+l).

Example 84

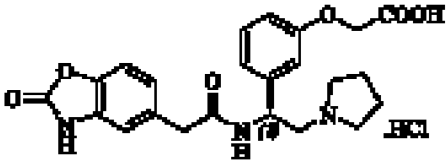
(*S*)-.V-(l-(3-hydroxyphenyl)-2-(pyrrolidin-1-yl)ethyl)-2-(2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)acetamide



Melting point: 140-142 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): 5 11.57 (bs, IH), 9.33 (bs, IH), 8.43 (bs, IH), 7.17 (d, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, IH), ***6.99-6.95*** (m, 2H), 6.73 (s, IH), 6.69 (s, IH), 6.62 (d, *J* = 8.0 Hz, IH), 4.82 (bs, IH), 3.47 (d, *J* = ***5.9*** Hz, 2H), 3.17 (d, *J* = 5.2 Hz, I H), 2.54 (bs, 4H), 2.44 (bs, IH), 1.65 (bs, 4H); IR (KBr, cm^{-1}): 3066, 2972, 2823, 1764, 1658, 1589, 1546, 1500, 1467, 1382, 1263; MS (ESI) m/z: 382.4 (M+l).

Example 85

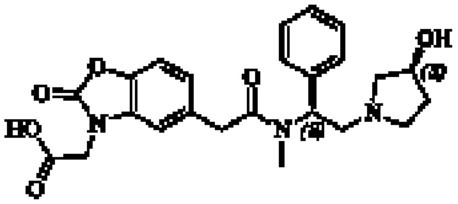
(*S*)-2-(3-(1-(2-(2-oxo-2,3-dihydrobenzo[*d*]oxazol 5-yl)acetamido)-2-(pyrrolidin-1-yl)ethyl)phenoxy)acetir acid hydrochloride



1H-NMR (400 MHz, DMSO-rf.): δ 13.05 (bs, IH), 11.60 (s, IH), 10.20 (bs, IH), 8.87 (d, *J* = 8.6 Hz, I H), 7.28-7.24 (m, IH), 7.18 (**d,** *J* = 8.3 Hz, IH), 7.04-6.97 (m, 4H), 6.84-6.81 (m, IH), 5.26-5.21 (m, IH), 4.65 (s, 2H), 3.60 (s, IH), 3.37-3.05 (m, 2¾ 2.67-2.50 (m, 4H), 1.96-1.90 (m, 4H); IR (KBr, cm^{-1}): 3525, 3444, 2638, 1766, 1564, 1259, 1024, 792; MS (ESI) m/z: 440 (M+l).

Example 86

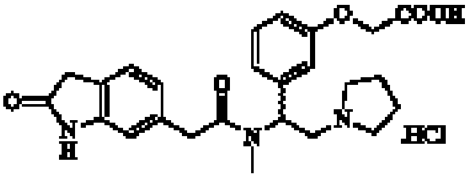
2-(5-(2-(((*S*)-2-((*S*)-3 -hydroxypyrrolidin-l-yl)-1-phenylethyl)(methyl)amino)-2-oxoethyl)-2-oxobenzo[*d*]oxazol-3(2*H*)-yl)acetic acid



¾-NMR (400 MHz, DMSO-ii₆): 5 7.35-7.25 (m, 6H), 7.09-6.99 (m, 2H), 5.91-5.39 (m, 1H), 4.35 (bs, 2H), 4.19 (bs, l H), 3.87-3.65 (m, 4H), 3.16-2.85 (m, 4H), 2.34-2.62 (m, 4H), 2.0-1.96 (m, 1H), 1.58-1.43 (m, 1H), 1.23-1.13 (m, 1H); IR (Neat, cm^{-1}): 3167, 2945, 1782, 1631, 1604, 1496, 1469, 1396, 1381, 1359, 1307; IvE (ESI): m/z 454 (M+l).

Example 87

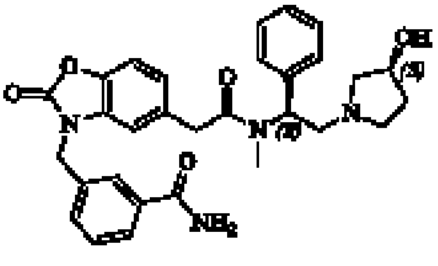
2-(3-(1-(*N*-methylr2-(2-oxoindDlin-6-yl)acetajnido)-2-(pyrrolidm-1-yl)ethyl)phenoxy) acetic acid hydrochloride



lilting point: 169-171 *V* ; 1H-NMR (400 MHz, DMSO-*d*₆): S 10.59 (s, 1H), 7.21 (t, *J* = 1.Q Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.84-6.77 (m, 4H), 6.72 (s, 1H), 5.37-5.83 (m, 1H), 4.51 (s, 2H), 3.75 (d, *J* = 5.6 Hz, l H), 3.70 (s, lH), 3.17 (s, 1H), 3.14-3.09 (m, 1H), 2.83-2.82 (m, 1H), 2.68 (s, 3H), 2.50 (bs, 4H), 2.44 (bs, 1H), 1.70 (bs, 4H); IR (KBr, cm^{-1}): 3018, 1699, 1629, 1215, 756, 669; MS (ESI): m/z 452 (M+l).

Example 88

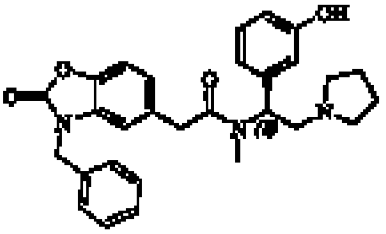
3-((5-(2 -(((5)-2-((5>3-hydiroxypyrroMm-l-yl)-l -phenylethyl)(methyl)amino>2-o¾ethy^2 - oxoheitzo[*d*]oxazol-3(2*H*)-yl)methyl)benzamide



Melting point: 181-1S3 °C; ^{1}H-NMR (400 MHz. DMSO-d$_6$): 5 7 9 9 (s, 1H), 7.84 (s, 1H), 7.79 (d, J = 7.33 Hz, 1H), 7 50-7.21 (in, 7H), 7.19-7 02 (m, 2H), 6.09 (bs, 1H), 5.81 (bs, 1H), 5.07 (s, 2H), 4.91 (*bs*, 1H), 4.56 (in, 1H), 4.03 (*bs*, 1H), 3.83-3.7 1 (m, 2H), **2.69** (s, 4H), 2.67-2.53 (in, 3H), 2 29-2.0 (in, 2H), 1.98-1 .72 (in, 1H), 1.33-1 .29 (in, 1H); IR (KBr, cm^{-1}): 3375, 3034, 2927, 2723, 1768, 1666, 1494, 1384, 1246; MS (EΞI): *miz* 529 (M+l).

Example 89

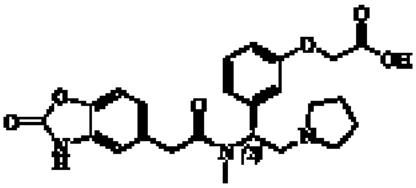
(*S*)-2-(3-benzy]r2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl>-*N*-(*l*-(3-hydroxyp¾ nyl)-2-(pyTrolidin-l-yl)ethyl)-*N*-methylacetamide



Melting point: 165-167 *C; 1H-NMR (500 MHz, DMSO-*dt)*: 5 9 3 6 (*bs*, 1H), 7.36-7.27 (m, 6H), 7.12-7.02 (m, 3H), 6.68-6.61 (in, 3H), 5.76 (*s*, 1H), 5.00 (*s*, 2H), 3.79-3.69 (in, 2H), 2.71 (s, 2Hi 2.65-2.64 (m, 1H), 2.43-2.36 (*bs*, 2H), 2.51-2.49 (bs, 4H), 1.64-1 .58 (bs, 4H); IR (KBr, cm$^{"1}$): 3523, 1770, 1620, 1492, 1454, 1390, 1357, 1271, 1244, 1016; MS *(ESI): miz* 486.2 (M+l).

Example 90

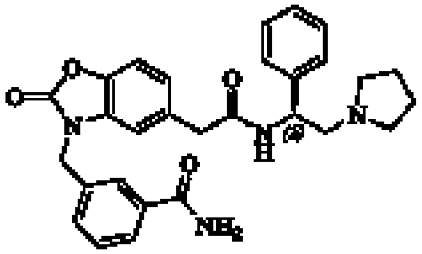
(*R*)-2-(3-(1-(*N*-methyl-2-(2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)acetamido)-2-(pyrrolidin-1-yl)ethyl)phenoxy)acetic acid



Melting point: 227-229 °C; 1H-HMR (400 MHz, DMSO-d_6): S 13.03 (bs, 1H), 11.58 (s, 1H), 10.10 (bs, 1H), 7.30 (t, J = S.O Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.05 (s, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.8S (d, J = 1.6 Hz, 1H), 6.86 (*d*, J = 1.6 Hz, 1H), 6.82 (d, J = 7.2 Hz, 1H), 6.10-6.07 (in, 1H), 4.65 (s, 2H), 4.05 (t, J = 12.4 Hz, lH), 3.94-3.7S (m, 2H), 3.63 (d, J = 12.0 Hz, 2H), 3.52 (s, IH), 3 .16 (bs, 1¾ 2.79 (s, 3H), 1.99 ***(bs,*** 4H); IR (KBr, cm"1): 3477, 2949, 1759, 1612, 1462, 1265, 1172, 1074, 920, 781, 705; MS (ESI): m/z 454.3 (M+l).

Example 9 1

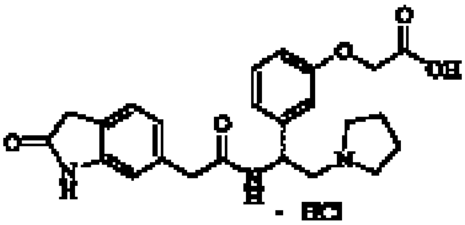
(.£)-3-((2-oxo-5-(2-oxo-2-(l-p henyl-2-(pyTi:olidi n-1-yl)ethji amin o)ethyl)i) enzo *[d]* oxazol-3(2*Hi*-yl)methyl)i) enzami de



Melting point: 171-172 °C; ^{1}H-NMR (400 MHz, DMSO-*d*6): 5 8.61 (bs, IH), 8.02 ***(bs,*** IH), 7.85 ***(bs,*** IH), 7.82 (d, ***J*** = 7.3 Hz, IH), 7.47 ***(bs,*** IH), 7.45-7.40 (m, 2H), 7 .39-7.23 (in, 6H), 7.1 1 ***(s,*** IH), 7.05 (d, ***3*** = 8 ***2*** Hz, IH), 5.03 ***(s,*** 2H), 4.95 (bs, 1¾ 3.49 (s, 2¾ 2.91-2.74 (in, 2H), 2 50 (bs, 4H), 1.67 (bs, 4H); IR (KBr, cm"1): 3304, 3188, 3059, 2964, 2799, 1769, 1659, 1495, 1246; MS (ESI): m/z 499.0 (M+l).

Example 92

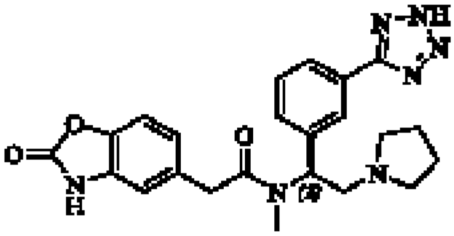
2-(3-(1-(2-(2-oxoindolin-6-yl)acetamido)-2-(pyrrolidin-1-yl)ethyl)phenoxy)acetic acid



Melting point: 104-106 °C; ^{1}H-NMR (400 MHz, DMSO-*d*6): 5 13.00 (bs, IH), 10.35 (s, IH), 10.19 (bs, IH), 8.85 (d, ***J*** = 8.8 Hz, IH), 7.26 *(*t, ***J*** = 8.0 Hz, IH), 7.09 (d, ***J*** = 7.2 Hz, IH), 7.0-7.06 (m, 2H), 6 £5-6 £ 1 (in, 2H), 6.75 (s, I H), 5.23 (m, IH), 4.63 (s, 2H), 3.56 (s, 3H), 3.53 (s, 2H), 3.44 (d, ***J*** = 12.0 Hz, 2H), 3.30 (bs, IH), 3.10 (bs, IH), 1.98-1 .88 (m, 4H) ; IR (KBr, cm"1): 3020, 2401, 1535, 1217, 929, 759, 673; MS (ESI): m/z 438 (M+l).

Example 93

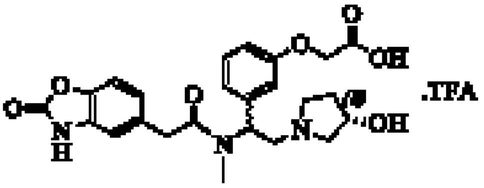
(*S*)-*N*-(1-(3-(2*H*-tetrazol-5-yl)phenyl)-2-(pyrrolidin-1-yl)ethyl)-*N*-methyl-2-(2-oxo-2,3-dihydrobenxo[*d*]oxazo1-5-yl)acetamide



Melting point: 240-242 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): 5 11.57 (s, IH), 10.1 (bs, IH), 8.01 (d, *J* = 7.0 Hz, 2H), 7.98 (s, I H), 7.65-7.62 (m, 1¾ 7.45 (d, *J* = 7.0 Hz, IH), 7.17 (d, *J* = 7.6 Hz, IH), 7.07-6.98 (in, IH), 6.24 (d, *J* = 10.2 Hz, 1¾ 4.204.13 (m, 2H), 3.99-3.82 (in, 2H), 2.85 (s, 3H), 2.50 (bs, 4H), 2.0 (bs, 4H) ; IR (KBr, cm^{-1}): 3373, 3035, 1778, 1629, 1550, 1467, 1388, 1269, 1103; IvE (ESI): m/z 448 (M+l).

Example 94

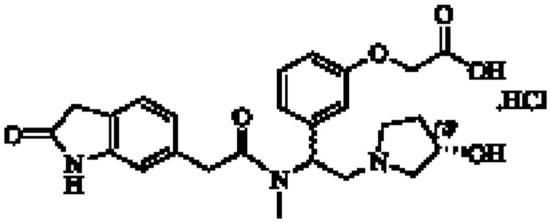
(*S*)-2-(3-(2-(3-hydroxypyrrolidin-1-yl)-1-(*N*-methyl-2-(2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yi)acetamido)ei hyl)phenoxy)acetic acid triflouro acetate



1H-NMR (400 MHz, DIvSO-d_6): δ 13.10 (bs, IH), 11.60 (s, IH), 9.80-9.60 (in, IH), 7.30 (in, IH), 7.20 (d, *J* = 8.3 Hz, IH), 6.99 (s, IH), 6.95-6.76 (m, 4H), 6.18-6.05 (m, IH), 5.50 (bs, IH), 4.64 (s, 2H), 4.42 (bs, IH), 4.20-3.60 (in, 5H), 3.50-3.20 (in, 3H), 2.73 (s, 3H), 2.30-2.20 (in, IH), 190-1.80 (in, IH) ; IR (KBr, cm^{-1}): 3062, 1766, 1672, 1469, 1265, 1199, 1134, 1095; IvE (ESI): m/z 470 (M+l).

Example 95

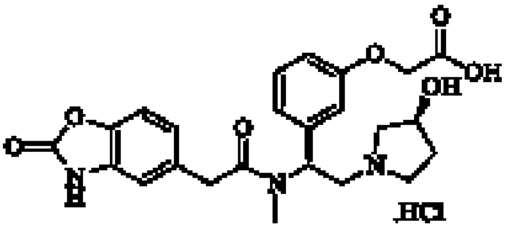
(*S*)-2-(3-(2-(3-hydro?ypyrriolidi n-1-yl)-1-(-Vmethylr2-(2-o roijidohn-6-y l) acetamido) ethyl) pheiiDxy) acetic acid hydrochloride



1H-NMR (400 MHz, DMSO-*d*6): 5 13.10 (bs, IH), 10.35 (s, 1¾ 9.90-9.65 (in, IH), 7 30-7.27 (in, IH) 7.12 (d, *J* = 7.4 Hz, I H), 6.86 (d, *J* = 8.3 Hz, IH), 6.81-6.70 (m, 4H), 6.2-6.13 (in, 1H), 5 5 0 (bs, 1H), 4.63 (s, 2H), 4.42 (s, I H), 4.15-4.10 (m, I H), 3.85-3.60 (in, 5H), 3.40-4.20 (in, 4H), 2.70 (s, 3H), 2.30-2.20 (m, IH), 1.90-1.80 (in, 1H) ; IR (KBr, cm^{-1}): 3238, 2951, 1678, 1631, 1452, 1462, 1203, 1136; IvE (ESI): m/z 468 (M+l).

Example 96

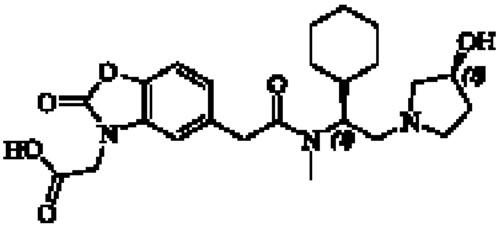
2-(3-((S)-2-((R)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(2-oxo-2,3-dihydrobenzo[d] oxazot!?-yljacetamido)ethyl)phenoxy)acetic acid



Melting point: *95-96* °C; ^{1}H-NMR (400 MHz, DMSO-.i$_6$): 5 13.00 (bs, IH), 11.60 (bs, I H), 9.84 (bs, IH), 7.31-7.27 (in, IH), 7.21 (d, *J* = 7.8 Hz, I H), 7.00 (s, IH), 6.96 (d, *J* = 8.3 Hz, IH), 6.88 (d, *J* = 8.3 Hz, IH), 6.82-6.75 (in, 2H), 6.11 (d, *J* = 10.7 Hz, I H), 5.50 (bs, 1¾ 4.65 (s, 2H), 4.47 (s, 1¾ 4.40-4.02 (m, 2H), 3 99-3.98 (in, IH), 3.82 (s, 3H), 3.43-3.18 (m, 2H), 2.74 (s, 2H), 2.32-2.27 (in, IH), 2 20-1.83 (m, 2H) ; IR (Neat, cm^{-1}): 2959, 1756, 1611, 1468, 1219; IvE (ESI): m/z 470.2 (M+l).

Example 97

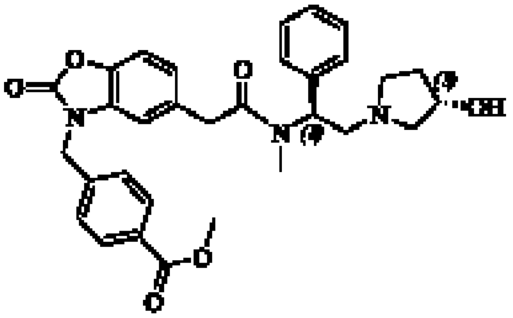
2-(5-(2-(((*S*)-1-cyclohexyl-2-((*S*)-3-hydroxypyrrolidin-1-yl)ethyl)(methyl)amino)-2-oxoethyl)-2-oxobenzo[*d*]oxazol-3(2*H*)-yl)acetic acid



Melting point: 233-234 °C; 1H-NMR (400 MHz, DIvEO-*dt*): 5 7.18 (d, *J* = 8.2 Hz, 1H), 6.9-6.8 (m, 2H), 4.45 (s, 1H), 4.2-4.19 (m, 3H), 3.69-3.04 (m, SH), 2.68 (s, 3H), 2.36-2.01 (m, IH), 1.69-1.53 (m, 5H), 1.37-1.07 (m, 6H), 0.94-0.90 (m, IH), 0.88-0.69 (m, lH); IR (KBr, cm^{-1}): 3290, 2929, 2852, 1768, 1620, 1620, 1496, 1377, 1246, 1101, 1024; MS (ESI): m/z 460 (M+l).

Example 98

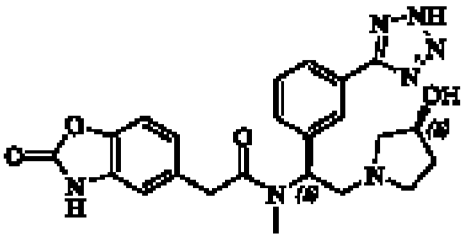
Methyl 4-(β-(2-(((*S*)-2-((*S*)-3-hydroxypyrrolidin-1-yl)-1-phenylethylXmethyi)amino)-2-oxoethyl)-2-oxobenzo[*d*]oxazol-3(2*H*)-yl)methyl)benzoate



¾-NMR (400 MHz, DMSO-_i$_6$): δ 7.94 (d, *J* = 7.8 Hz, 2H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.30-7.20 (m, 6H), 7.04 (s, 2H), 5.80 (bs, IH), 5.11 (s, 2H), 4.65 (bs, IH), 4.15 (*bs*, IH), 3.83 (s, 3H). 3.80-3.60 (m, 2H), 3.0-2.60 (m, 7H), 2.45-2.25 (m, 2H), 1.90 (bs, IH), 1.50 (bs, IH) ; IR (KBr, cm^{-1}): 3420, 3032, 2949, 2800, 1774, 1720, 1612, 1495, 1385, 1280, 1244; MS (ESI): m*ix* 544 (M+l).

Example 99

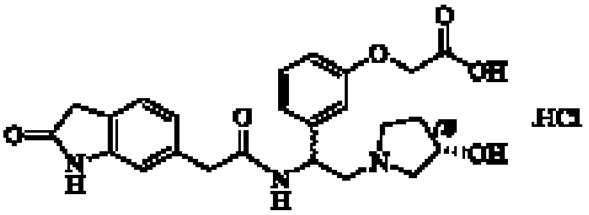
***N*-((*S*)-1-(3-(2*H*-tetrazol-5-yl)phenyl)-2-((*S*)-3-hydroxypyrrolidin-1-yl)ethyl)-*N*-methyl-2-(2-0X0-2,3-dihydrobenzo [[iloxa™l -5-yl)acetamide**



Melting point: 228-230 °C; 1H-NMR (400 MHz, DMSO-d_6): δ 11.59 (bs, IH), 7.97-7.93 (in, 2H), 7 55-7.52 (in, IH), 7.33 (d, *J* = 7.9 Hz, IH), 7.18 (d, *J* = 8.3 Hz, 1¾ 7.05 (s, IH), 6.97 (d, *J* = 7.9 Hz, IH), 6.18-6.16 (m, IH), 5.47-5.40 (m, IH), 4.40 (s, IH), 3.94-3.86 (in, IH), 3.83 (s, 2H), 3.59-3.56 (in, IH), 3.43-3.31 (in, 3H), 3.18-3.16 (in, IH), 2.78 (s, 3H), 2.18-2.14 (in, IH), 1.83-1.82 (in, IH) ; IR (KBr, cm^{-1}): 3064, 2725, 1766, 1629, 1560, 1467, 1392, 1265; *MS* (ESI): m/z 464 (M+l).

Example 100

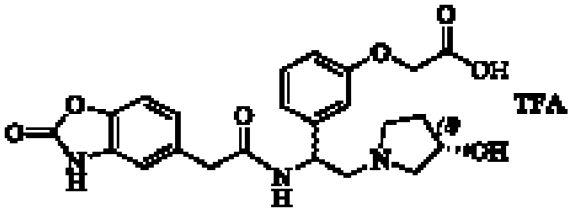
(*S*)-2-(3-(2-(3-hydroxypyrrolidin-1-yl)-1-(2-(2-oxoindolin-6-yl)acetamido)ethyl)phenoxy)acetic acid hydrochloride



1H-NMR (400 MHz, DMSO-d_6): *8* 10.43 (s, IH), 8.47 (t, *J* = 8.8 Hz, IH), 7.21 (d, *J* = 2.0 Hz, 1H), 7.19 (d, *J* = 1.4 Hz, IH), 6.88-6.73 (m, 5H), 4.90-4.87 (m, IH), 457 (d, *J* = 2.4 Hz, 2H), 4.184.1 5 (in, IH), 3.46-3.36 (m, 4H), 2.84-2.54 (in, 4H), 2.50-2.40 (m, 2H), 1.97-1.88 (in, IH), 1.53-1.45 (m, lH); IR (KBr, cm^{-1}): 3334, 2922, 1726, 1535, 1467, 1379, 1251, 1016; *MS* (ESI): m/z 454 (M+l).

Example 101

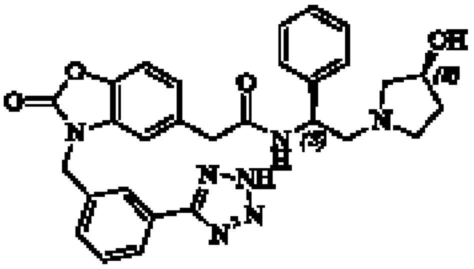
(*S*)-2-(3-(2-(3-hydroxypyrrolidin-1-yl)-1-(2-(2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)acetamido)ethyl)phenoxy)acetic acid



^{1}H-NMR (400 MHz, OMEO-*di*): δ 13.1 (bs, 1H), 11.6 (s, 1H), 10.0-9.6 (m, 1H), 8.7 (1, *J* = 8.8 Hz, 1H) 7.3-6S **(m,** 7H), 5.5 (bs, 1H), 5.27 (s, 1H), 4.6 (s, 2H), 4.4 (d, *J* = 15.6 Hz, 1H), 3.60-3 .1 4 (m, 6H), 2.23 (bs, 1H), 1.98-1 .80 (m, 2H), 1.58-1 .54 **(in,** 1H) ; IR (KBr, cm^{-1}):3059, 2966, 1764, 1678, 1599, 1493, 1441, 1263, 1201, 1139, 1085; MS (ESI): m/z 456 (M+l).

Example 102

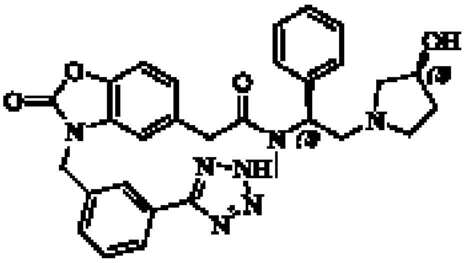
2-(3-(3-(2*H*-e trazolr5-yl)b enzyl)-2-oxo-2,3-dihydrob enzo [*d*]oxazo l-5-yl)-*N*-((*S*)-2-((*S*)-3-hydroxyp yiTolidiii-1-yl)-1-p henylethyl)acetamide



Melting point: 235-237 °C; ^{1}H-NMR (400 MHz, DMSO-ci$_6$): 5 8.62 (d, *J* = 8.8 Hz, 1H), 7.97 (s, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.46-7.42 (m, 1H), 7.34 (d, *J* = 7.8 Hz, l H), 7.31-7.29 (m, 5H), 7.27-7.23 (m, 1H), 7.09 (s, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 5.12-5.09 **(in,** lH), 5.06 (s, 2¾ 4.25 (d, *J* = 2.9 Hz, 1H), 4.23 (s, 1H), 3.49 (s, 2H), 3.16-3.03 **(in,** 4H), 2.96-2.93 **(in,** 1H), 2.92-2 SO(m, 1H), 2.01 -1 *9 6* (m, 1H), 1.67-l .64 (m, lH); IR (KBr, cm^{-1}): 3379, 3028, 1764, 1658, 1546, 1494, 1357, 1246 ; MS (ESI): m/z 540 (M+l).

Example 103

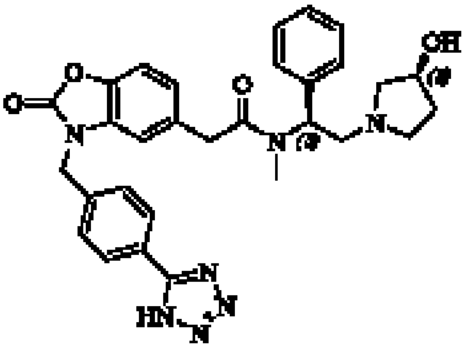
2-(3-(3-(2*H*-tetrazol-5-yl)b enzyl)-2-oxo-2,3-dihydrob enzo [*d*]oxazo l-5-yl)-*N*-((*S*)-2-((*S*)-3-hydroxyp yiTolidiii-l-yl)-1-p henylethyl)-*N*-methylacetamide



Melting point: 123-125 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.0-7.80 (in, 2H), 7.40-7.20 (in, 8H), 7.10-7.0 (in, 2H), 5.80 (in, IH), 5.08 (s, 2H), 4.67 (d, *J* = 8.42 Hz, lH), 4.12 (bs, IH), 3.84-3.68 (in, 2H), 2.99-2.80 (in, 2H), 2.70 (s, 2H), 2.60 (bs, 3H), 2.40-2.33 (in, 1H), 2.32-2.29 (in, 1H), 1.90-1.87 (m, 1H), 1.47-1.35 (m, 2H), IR (KBr, cm^{-1}): 3138, 1766, 1641, 1494, 1390, 1244, 1091, 1016; MS (ESI): m/z 554 (M+l).

Example 104

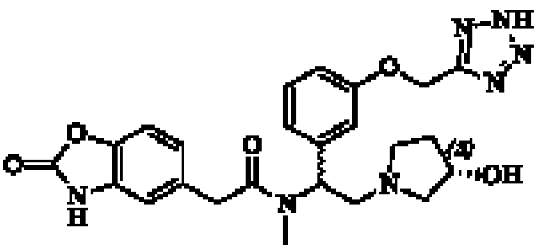
2-(3-(4-(1*H*-tetrazol-5-yl)benzyl)-2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)-iV-((*S*)-2-((*S*)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-*N*-methylacetamide



Melting point: 218-220 °C; 1H-NMR (400 MHz, DMSO-d_6): S 7.83 (d, J = 8.3 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.33-7.25 (m, 5H), 7.24-7.16 (in, IH), 7.06-7.04 (m, 2H), 5.80 (m, 1H), 5.08 (s, 2H), 4.67 (d, *J* = 8.42 Hz, IH), 4.12 (bs, IH), 3.84-3.68 (in, 2H), 2.99-2.80 (in, 2H), 2.70 (s, 2H), 2.60 (bs, 3H), 2.40-2.33 (m, IH), 2.32-2.29 (m, 1H), 1.90-1.87 (m, IH), 1.47-1.35 (in, 2H); IR (Neat cm^{-1}): 2920, 1764, 1629, 1492, 1390, 1346, 1219, 1089, 1012; MS (ESI): m/z 554 (M+l).

Example 105

(*R*)-*N*-(l-(3-((2*H*-tetrazol-5-yl)methoxy)phenyl)-2-(3-hydroxypyrrolidin-1-yl)ethyl)-*N*-methyl-2-(2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)acetamide

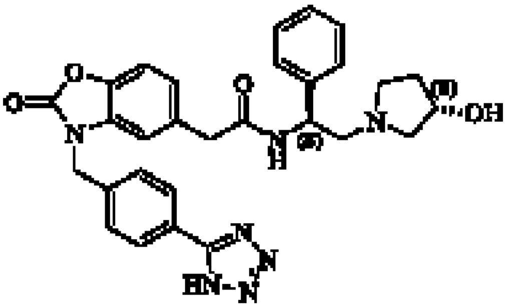


^{1}H-NMR (400 MHz, DMSO-rf.) : δ 11 -S-1 1.6 (bs, IH), 7.28-7.26 (in, I H), 7.24-7.20 (in, IH), 7.02-6 9 8 (in, 5H), 6.81-6.80 (m, IH), 60-5.98 (m, IH), 5.26-5.24 (m, 3H), 4.35-4.27 (bs, IH), 3.89-3.78 (m, 2H), 3 .45-3 29 (m, 4H), 3.06-2.69 (in, 4H), 2.19-2.17 (in, IH), 1.86 (in, IH) ;

IR (Neat, cm^{-1}): 3039 , 2723, 1757, 1629, 1467, 1392, 1292, 1267, 1236, 1168, 1101 ; IvE (ESI): m/z 494 (M+1) .

Example 106

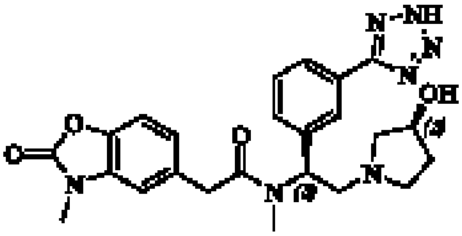
2-(3-(4 (1*H*-tetraz»l-5-yl)benzyl)-2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)-iV-((*S*)-2-((*S*)-3-hydraxyp ynvlidin- *l*-yl)-1-phenylethyl)acetamide



Melting point: 296-297 °C; 1H-NMR (400 MHz, DM5O-d_6) : δ 8.01-7.98 (m, 2H), 739-7.42 (in, 2H), 7.35-7.26 (m, 6H), 7.08-7.03 (m, 2H), 5.19-5.16 (m, IH), 5.02-4.98 (in, 2H), 4.40-4.33 (m, IH), 3.64-3.53 (m, 2H), 3.35-3.25 (in, 3H), 3.17-3.15 (in, 2H), 3 05-3 01 (in, IH), 2.09-2 0 4 (in, IH), 1.78-1 .75 (in, IH) ; IR (Neat, cm^{-1}): 3242, 3061, 1766, 1494, 101 1; IvE (ESI): m/z 540 (M+1) .

Example 107

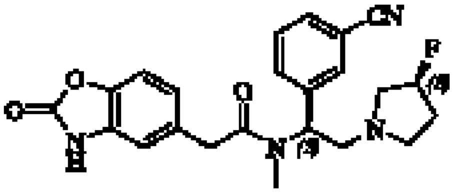
***N*-((*S*)-1-(3-(2*H*-tetrazol-5-yl)phenyl)-2-((*S*)-3-hydroxypyrrolidin-1-yl)ethyl)-*N*-methyl-2-(3-methyl-2-03D -2,3-dihydrobenzo[*d*]oxazol-5-yliacetajnide**



Melting point: 130-132 °C; 1H-NMR (400 MHz, DMSO-d_6): 5 7.97-7.93 (m, 2H), 7.55-7.52 (m, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.18 ((3, *J* = 8.3 Hz, 1H), 7.05 (s, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.18-6.16 (m, 1H), 5.47-5.40 (m, 1H), 4.40 (s, 1H), 3.94-3 £6 (m, 1H), 3.83 (s, 2H), 3.60 (s, 3H), 3.59-3.56 (m, 1H), 3.43-3.31 (m, 3H), 3.18-3.16 (m, 1H), 2.78 (s, 3¾ 2.18-2.14 (m, 1H), 1.83-1.82 (m, 1H) ; IR (Neat cm^{-1}): 2964, 1774, 1641, 1479, 1384, 1267, 1219; MS (ESI): m/z 478 (M+l).

Example 108

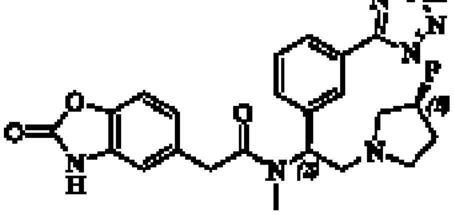
N-((S)-1-(3-cyanophenyl)-2-((5)-3-fluoropyrrolidin-1-yl)ethyl)-iV-mfthyl-2-(2-oxo-2,3-dihydrobenzo [ti]oxazol-5-yl)acetamide



Melting point: 133-134 °C; 1H-NMR (400 MHz, DMSO-d_6): 5 11.5 (s, 1H), 7.75-7.53 (m, 4H), 7.17 (d, *J* = 8.8 Hz, 1H), 6.98-6.94 (m, 2H), 5.83-5.81 (m, 1H), 5.20-5.0 (m, 1H), 3.83-3.80 (m, 2¾ 2.88-2.81 (m, 4H), 2.76 (s, 3H), 2.42-2.46 (m, 2H), 2.1-2.0 (m, 1H), 1.98-1.80 (m, 1H) ; IR(Neat cm^{-1}): 2927, 2852, 1774, 1618, 1261 ; MΞ (EΞI): m/z 421 (M-l).

Example 109

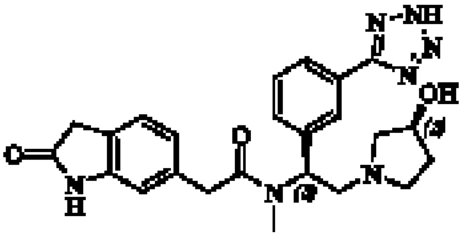
N-((S)-1-(3-(2H-tetrazol-5-yl)phenyl)-2-((S)-3-fluoropyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxo-2,3-dDiydrol>eiza>[d]oxazol-5-yl)acetamide



Melting point: 133-134 °C; ^-NMR (400 MHs, DMSO-d_6): 5 11.59 (a. IH), 10.2 (bs, IH), 7.99 (d, ***J*** = 7.8 Hs, 2H), 7.65 (**d**, ***J*** = 7.8 Hs, IH), 7.43 (d. ***J*** = 7.8 Hs, 1H), 7.18 (d, ***J*** = 7.9 Hs, IH), 7.01-6.96 (in, 2H), 6.27 (m, 1H), 5.56-5.43 (m, 1H), 4.1 9 (s, 1H), 3.96-3 6 9 (m, 7H), 2.77 (s, 3H), 2.33 (bs, 2H) ; IR (Neat, cm^{-1}): 2980, 1764, 1678, 1467, 1205, 1265, 1138; MS (ESI): ***miz*** 466 (M+1).

Example 1 10

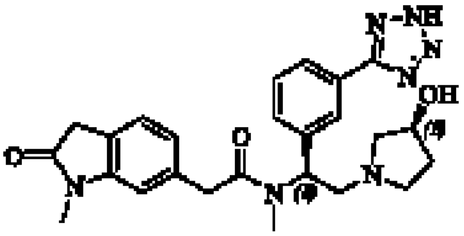
-V((S)-1-(3-(2H-tetrazo Jr5 -yl)phenyl)-2-((S)-3-hydroxypyTTolidin-1-yl)ethyl)-N-metiiyl-2-(2-oxomdolIn-6-yl)acetamide



Melting point: 208-210 °C; ^{1}H-NMR (400 MHs, DMSO-d_6): 5 10.35 (bs, I H), 10.06 (bs, IH), 9.93 (bs, IH), 7.99 (d, ***J*** = 7.8 Hs, 1H), 7.94 (s, IH), 7.64-7.60 (m, IH), 7.42 (d, ***J*** = 7.8 Hz, 1H), 7 09 (**d**, ***J*** = 7.8 Hs, IH), 6.82 (**d**, ***J*** = 7.8 Hs, 1H), 6.76 (s, IH), 6.25-6.23 (in, IH), 5.51 (bs, IH), 4.45 (bs, IH), 4.1 1 (bs, IH), 3.79-3.77 (in, 4H), 3.73-3.42 (m, 4H), 2.76 (s, 3H), 2.32 (s, IH), 2.08-1 .90 (in, IH) ; IR (Neat, cm^{-1}): 3053, 2752, 1689, 1629, 1483, 1460, 1400, 1271, 1246, 1116; MS (E5I): m/s 462 (M+l).

Example 1 11

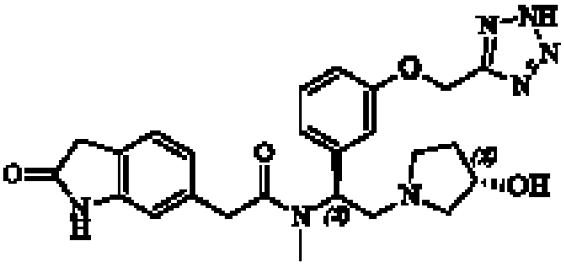
N-((S)-1-(3-(2H-e trazo Jr5 -yl)phenyl)-2-((S)-3-hydroxypyTTolidm-1-yl)ethyl)-N-methyl-2-(l-methyl-2-oxo indolin-6-yl)acetamide



Melting point: 198-200 °C; 1H-NMR (400 MHs, DMSO-iii): δ ***9.99*** (bs, IH), 9.69 (bs, IH), 7.99 (**d**, ***J*** = 7.8 Hs, lH), 7.94 (s, 1¾ 7.64-7.60 (m, 1¾ 7.42 (**d**, ***J*** = 7.8 Hs, IH), 7.09 (d, ***J*** = 7.8 Hs, IH), 6.82 (d_ ***J*** = 7.8 Hs, IH), 6.76 (s, IH), 6.25-6.23 (in, IH), 5.51 (bs, IH), 4.45 (bs, IH), 4.1 1 (bs, IH), 3 .79-3.77 (m, 4H), 3.73-3.42 (m, 4H), 3.05 (s, 3H), 2.77 (s, 3H), 2.32 (s, IH), 2.08-1 .90 (m, IH) ; IR (Neat, cm^{-1}): 3022, 2746, 1681, 1618, 1562, 1450, 1375, 1350, 1274, 1105; MS (ESI): m/z 476 (M+l).

Example 112

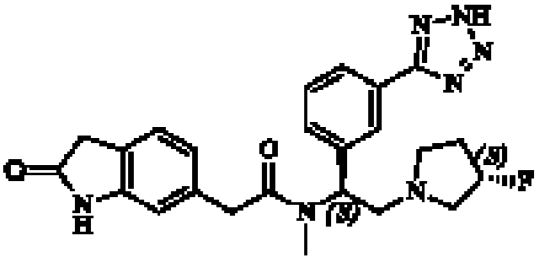
(*R*)-*N*-(1-(3-((2*H*-tetrazol-5-yl)methoxy)phenyl)-2-(3-hydroxypyrrolidin-1-yl)ethyl)-*N*-methyl-2-(2-oxo-2,3-dihydrobenzo[*d*]oxazol-5-yl)acetamide



^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, IH), 10.38-10.35 (d, *J* = 15.0 Hz, IH), 7.23-7.21 (m, IH), 7.09-6.95 (m, I H), 6.95-6.80 (m, 5H), 5.87-5.85 (m, IH), 5.13-5.08 (s, 2H), 4.26-4.23 (bs, IH), 3.79-3.72 (m, 2H), 3.40-3.32 (bs, 2H), 3.16-2.63 (m, 6H), 2.63-2.59 (s, 3H), 1.99-1 9 0 (m, 2H), 1.6-1 .55 (m, IH) ; IR (Neat, cm^{-1}): 3053, 2953, 2773, 1703, 1643, 1589, 1492, 1462, 1413, 1269, 1043 ; MS (ESI): m/z 492 (M+l).

Example 113

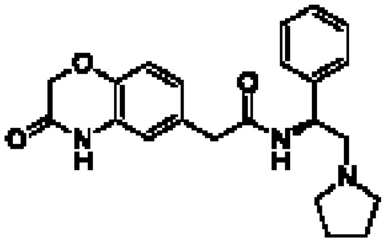
N-((S)-1-(3-(2H-tetrazol-5-yl)phenyl)-2-((S)-3-fluoropyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetamide



Milting point: 175-177 °C; 1H-NMR (400 MHz, DMSO-d_6): δ 10.35 (s, IH), 7.98 (d, *J* = 7.8 Hz, IH), 7.92 (s, 1H), 7.64 (d, *J* = 7.8 Hz, IH), 7.44 (d, *J* = 7.8 Hz, 1H), 7.09 (d, J = 7.8 Hz, lH), 6.S2 (d, *J* = 7.8 Hz, l H), 6.75 (s, 1H), 6.26-6.23 (m, IH), 5.55-5.41 (m, lH), 4.12 (s, 1¾ 3.93-3 .73 (m, 4H), 3.69-3.16 (m, 7H), 2.75 (s, 3H) ; MS (ESI): m/z 464 (M+l).

Example 114

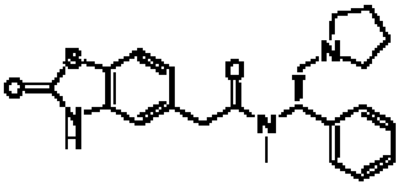
(S)-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-N-(1-phenyl-2-(pyrrolidin-1-yi)ethyl)acetamide



IvE (EΞI): m/z 380 (M+l); ^{1}H-NMR (300MHz. CD$_3$OD)5 7.35-7 2 3 (m, 5H);6.92-6.85 (m, 3H); 5 D9 -5 .04 (m, 1H); 45 4 {s, 1H); 3.55 (¾ 1H); 3.09-2 .87 (m, 1H); 2.71 -2.58 (m, 5H); 1.79 (s, lH).

Example 115

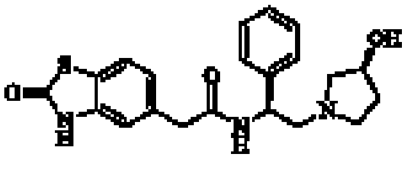
(S)-N-nïe∧ yl-2-(2-oxo-2,3-dïhydr obenzo [d]thiazol-5-yl)-N-(l-phenyl-2-(pyrrolidin-1-yi)ethyl)acetamide



LC-MS (EΞ, *mfs)* 396(M+l); ¾ -NMR(DM30 -i$_{¾}$ 300 MHz)δ 11.736 (1H, s), 7.650-7.210 (6H, m), 7.160-6.920 (2H, m), 5.940-5.105 (1H, m), 3.970-3.680 (2H, m), 3.150-2.975 (1H, m), 2.860-2.615 (4H, m), 2.500-2.355 (3H, m), 2.180-2 0 05 (1H, m), 1.770-1.450 (4H. m).

Example 116

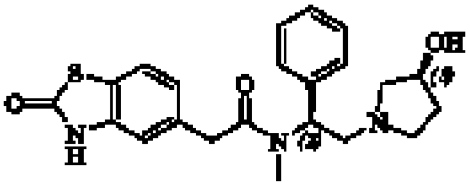
2-(2,2-dioxido-1,3-dihydiobenzo[c]isothiazol-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolilin- 1-yi)-l-phenylethyl)--^ methylacetamide



LC-MS (EΞ, *m/z)* 382 (M+l).

Example 117

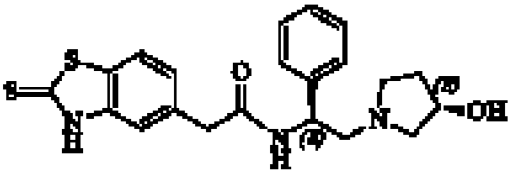
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl>-1-p¾nylethyl)-V methyl-2-(2-oxo-2,3-dihydrobenzo[ti]thiazol-5-yljacetamide



^{1}H-NMR (400 MHz, DMSO-.i$_6$): 5 11.8 (bs, IH), 7.49-7.47 (m, IH), 7.35-7.23 (m, 5H), 7.08-7.01 (m, 2H), 5.86 (bs, IH), 4.94-4.91 (m, IH), 4.18 (bs, IH), 3 £7-3.70 (m, 2H), 3.29 (bs, IH), 2.75-2.62 (m, 6H), 2.50 (bs, 2H), 1.99-1.93 (bs, IH), 151 (bs, IH); IR (Neat cm^{-1}): 3284, 2924, 2852, 2771, 1693, 1620, 1573, 1469, 1402, 1346, 1276; IvE (ESI) m/z: 412 (M+l).

Example 118

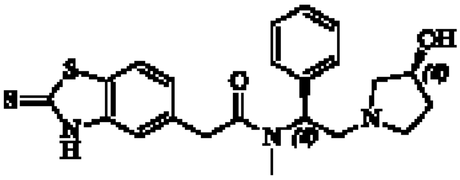
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-2-(2-thioxo-2,3-dihydrobenzo[ti]thiazol-5-yljacetamide



1H-NMR (400 MHz, DMSO-ti.): 5 13.0 (bs, lH), 856 (d, J = 8.56 Hz, IH), 7.57 (d, J = 7.8 Hz, IH), 7.30-7.17 (m, 7H), 4.93 (d, J = 5.4 Hz, IH), 4.17-4.15 (m, IH), 3.54 (d, J = 8.3 Hz, 2H), 2£1-2.50 (m, 5H), 2.42 (d, J = 3.0 Hz, IH), 1.9-1.85 (m, IH), 1.6-1.55 (m, IH); IR (Neat cm^{-1}): 3240, 3030, 2930, 1658, 1529, 1452, 1365, 1323, 1261, 1157, 1082; MS (ESI) mix: 414 (M+l).

Example 119

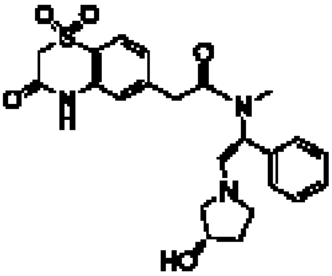
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methyl-2-(2-thioxo-2,3-dihydrobenzo[d]thiazolr5-yljacetamide



1H-NMR (400 MHz, DMSO-ii.): 7 28-7.16 (m, 7H), 6.79-6.77 (m, IH), 5.86 (b¾ IH), 4.16-4.01 (ts, IH), 3.78-3.64 (m, 3H), 3.142.90 (m, 2H), 2.85-2.62 (m, 7H), 2 37-2 3 5 (m, IH), 1.941 83 (bs, IH), 159-1 5 5 (bs, IH); IR (Neat cm^{-1}): 3537, 2926, 2812, 1581, 1382, 1315, 1136; MS (ESI) m/z: 428 (M+l).

Example 120

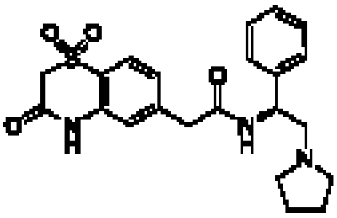
2-(1, 1-dioxido-3-oxo-3,4-dihydra-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-2-((£^3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methylacetamide



LJC-MS (ES, m/z) 458 (M+l ^H-NMR (DMSO-^ 300MHz) 5 11.255 (s, IH), 7.107-7.778 (m, 8H), 5.890-5.170 (in, IH), 4.713 (s, 2H) , 4.204 (s, IH), 3.979-3.804 (m, 2H), 3.338-2.628 (m, 7H), 2.078-1 .998 (m, IH), 1.557-1 .453 (m, I H).

Example 121

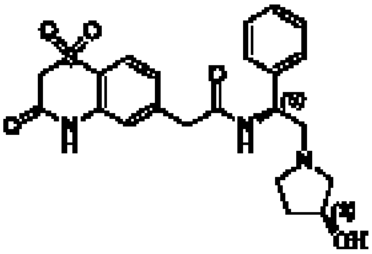
(S)-2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-(1-phenyl-2-(pyrrolidin-1-yl)ethyl)acetamide



LC-MS (ES, m/z) 428 (M+l); ¾ -NMR (DMSO-d_6, 300MHz) 5 11.33 (br, ¾ IH), 8 89-6 .95 (m, 9H), 5.01 -4.49 (m, 3H), 3.71 -3.51 (m, 2H), 2.91-2.21 (m, 6H), 1.91-1 .41 (m, 4H).

Example 122

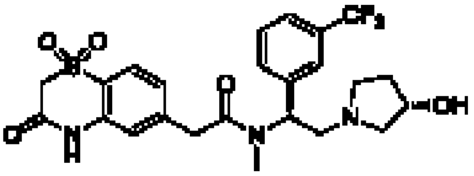
2-(l, 1-dioxido-3-Oxo-3,4-dihydro-2H -benm [b] [1,4]thiazin-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)acetamide



LC-IvE (ES, m/z) 444 (M+l); ^{1}H-NMR(DMSO-d_6, 400MHz): 5 11.24 (s, 1¾ 8.64 (d, 1H, >8.4Hz), 7.73 (d, lH, J=8.4Hz), 7.31 (d, 4H, J=4Hz), 7.23 (d, 2H, J=7.6Hz), 7.12 (s, 1H), 4.6749 1 (m, 4¾ 4.16 (bs, 1H), 3.52-3.62 (m, 2H), 2.63-2.78 (m, 3H), 2.27-2 3 6 (m, 1H), 1.94-1 9 9 (m, 1H), 1.53 (bs, 1H).

Example 123

2-(1, 1-dioxido-3-OM-3,4-dihydro-2H-benzo [b] [1,4]thiazin-6-yl)-N-((S)-2-((£^3-hydroxypyrrolidin-1-yl)-1-(3-(trifluoromethyl)phenyl)ethyl)-N-methylacetamide

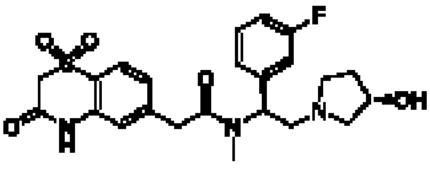


LC-IvE : (ES, m/z): 526 (M+l) ;

1H-NMR. (DMSO-d_6, 300 MHz): 5 11.21 (d, J=12Hz, 1H), 7.77-7.61 (m, 5H), 7.19 (d, J=6.6Hz, 1H), 7.1 1 (a. 1H), 5.90-5.85 (m, 1H), 4.69 (s, 2H), 4.18 (s, 1H), 4.03-3 £ 2 (m, 2H), 3.15-2 9 8 (m, 1H), 2.79-2.62 (m, 6H), 2.49-2.33 (m, 1H), 1.96-1 .95 (m, 1H), 1.55 (s, 1H).

Example 124

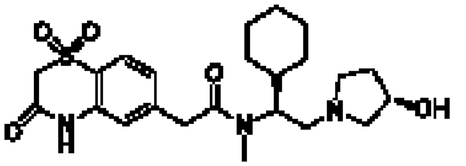
2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][l,4]thiazin-6-yl)-N-((S)-1-(3-fluoro phenyI)-2-((S)-3 -hydroxypyrrolidiII-1-yl)ethyl)-N-methylacetamide



LC-IvE : (ES, mfs): 476 (M+l);^-NMR. (DMSO-$d_{\&}$): 11.22 (d, J=9.9Hz, 1H), 7.77-7.72 (m, 1H), 1.42-7.35 (m, 1H), 7.21-7.10 (m. 5H). 5.80 (s, 1H), 4.744.70 (m, 3H), 3.98 (s, 1H). 3.96-3 £ 0 (m, 2H), 3.05-2.97 (m, 1H), 2.77-2.73 (m, 5H), 2.63 (s, 1H), 2.42-2.32 (m, 1H), 1.98-1 9 2 (m, 1H), 1.52 (s, 1H).

Example 125

N-((S)-1-cyclohexyl-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo [b] [1,4]thiazin-6-yl)-N-methylacetamide



LC-IvE : (EΞ, m/z): 464 (M+1); ^{1}H-NME.: (DMSO-d6, 300 MHz): S 11.23 (s, 1H), 7.77-7.71 (m, 1H), 7.21-7.13 (m, lH), 7.13 (s, 1H), 4.71-4.69 (in, 1H), 4.39-4.31 (m, 1H), 3.90-3.70 (m, 2H), 2.78-2.50 (m, 7H), 2.31-2.16 (m, 3H), 1.95-1.89 (m, 1H), 1.78-1.41 (m, 7H), 1.22-1 D7 (m, 3H), 1.05-0.82 (m, 2H).

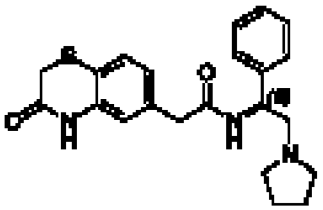
Example 126

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-l(i enzo |b]|1,4]thiazin-6-yl)-N-((S)-2-((!5)-3-hydraxy pyrrolidin-1-yl)-1-(3-methoxyphenyl)ethyl)-N-methylacetamide

LC-MS : (ES, m/s): 488 (M+1); ^{1}H-NMR(DMSO-d_6, 300 MHz): 11.23 (d, J=10.2Hz, 1H), 7.79-7.74 (m, 1H), 7.31-7.18 (m, 2H), 7.13 (s, lH), 6.90-6.82 (m, 3H), 5.81-5.78 (m, 1H). 4.72 (s, 2H), 4.20 (s, 1¾ 3.98-3.81 (m, 2H), 3.74 (¾ 3H), 3.07-3.00 (m, 2H), 2.89-2.77 (m, 4H). 2.66 (s, 1H), 2.52-2.33 (m, 1H). 1.99-1.97 (m, 1H), 1.55 (s. 1H).

Example 127

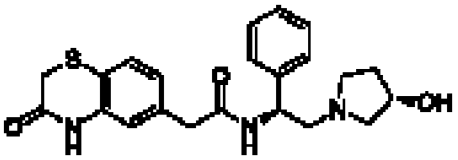
(S)-2-(3-oxo-3,4-dihydm-2H-heiizo [b] [l,4]thiazin-6-y)>N-(l-phenyl-2-(pyrrolidin-1-ji>ethyl)acetamjde



LC-IvE (ES, *mfs)* : 396(M+1); ^{1}H-NMR (DMSO-d_6, 300MHz) 5 10.56 (s, 1¾ 8.51 (d, 1H, *J*=8.7Hz), 7.20-7.31 (m, 6H), 8.62-8.69 (m, 2H), 4.90 (bs, 1H), 3.42 (bs, 4H), 2.73-2.76 (m, 1H), 2.45-2.68 (m, 5H), 1.65 (m, 4H).

Example 128

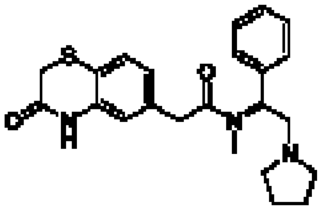
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-2-(3-OM -3y4-dihydro-2H-benxo[b][l,4]thiazinr6- yl)acetamide



1H-NMRj(DMSO-ik 300 MHz): 5 10.576 (1H, *s*), 8.523 (1H, d, *J*=8.1 Hz), 7.370-7.175 (6H, m), 6.985-6.820 (2H, m), 4.9854.820 (1H, m), 4.815-4.650 (1H, m), 4.235-4.095 (lH, m), 3.520-3.380 (4H, m), 2.850-2.675 (2H, m), 2.672-2 585 (1H, m), 2.460-2.375 (1H, m), 2.370-2.250 (1H, m), 2.040-1 .850 (1H, m), 1.590-1 .435 (1H, m).

Example 129

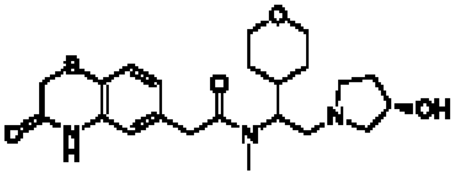
(S)-N-mfthyl-2-(3-oM-3,4-dihydro-2H-benf [b][1,4]thiazin-6-yl)-N-(l -pheiiylr2-(pyrrolidin-1-yl)ethyl)acetamide



IX-MS (EΞ, *m/z)*: 410 (M+l); ^{1}H-NMR (DMSO-d_6, 300MHz) *5* 10.57 (s, lH), 7.23-7.35 (m, 6H), 6.89 (s, 2H), 5.87 and 5.12 (2bs, 1H), 3.63-3.79 (m, 2H), 3.46 (s, 2H), 2.643 D8 (m, 6H), 2.35-2 .45 (m, 3H), 1.67 (bs, 4H).

Example 130

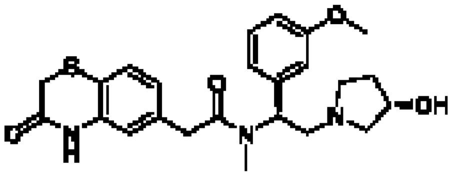
N-(2-((S)-3-hydroxypyrrolidin-1-yl)-1-(tetrahydro-2H-pyran-4-yl)ethyl)-N-methyl-2-(3-oxo-3,4-dfıydro-2H-benzo[b][l,4]thiazin-6-yl)acetajiiide



LJC-IVE : (EΞ, m/z): 434 (M+l); 'H -NMR (DIvE O-rf$_6$, 300 MHz): 1.2-1.5 (3H, br), 1.5-1.7 (3H, m), 19-2.5 (6H, br), 2.7 (3H, m), 3.2-3.8 (8H, br). 4.1 (1H, m), 4.4 (1H. m), 4.7 (1H, m), 6.8 (2H, d, J=4.8Hz), 7.2 (1H, m), 10.5 (1H, m).

Example 131

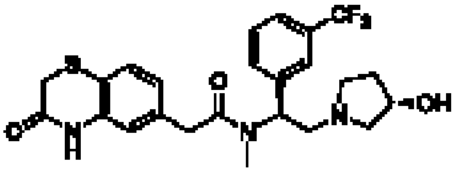
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-methoxyphenyl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydro-2H-ljenzo[b][l,4]thiazin-6-yl)acetamide



LC-MΞ: (ES , m/z): 456 (M+1); ^{1}H-NMR(DMSO-d_6, 300 MHz): δ 10.53 (d, J=5.4Hz, 1H), 7.27-7 2 2 (m, 2H), 6 2,9-6.61 (m, 5H), 5.78 (s, 1H), 4.70 (s, 1H), 4.15 (s, 1H), 3.76-3.67 (m, 5H), 3.43 (s, 2H), 3.31 (d, J=7.2Hz, 2H), 3.01-2.81 (m, 2H), 2.71 (a. 3H), 2.62 (s, 1H), 2.31-2.27 (m, 1H), 1.94-1.92 (in, 1H), 1.50 (s, 1H).

Example 132

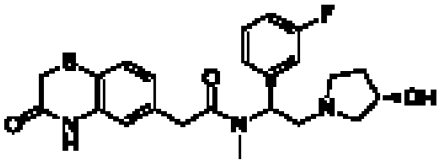
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(trifluoromethyl)phenyl)ethyl)-N-methyl-2-(3-0X0-3,4-dihydro-2H-benzo[b][l,4]tMaim-6-yI)aceta_nijde



LJC-MΞ: (EΞ, m/z): 494(M+1); ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 11.52 (d,J=7.5Hz, 1H), 7.63-7 5 5 (m, 4H), 7.24 (d, J=8.4Hz, 1H), 6.87 (6, J=6.6Hz, 2H\ 5.85 (s, 1H), 4.71 (s, 1H), 4.16 (s, 1H), 3.81-3.64 (m, 2H), 3.41-3.32 (m, 2H), 3.30 (s, 2H), 3.06-2.82 (m, 3H), 2.74 (s. 3H), 2.67 (s, 1H), 2.50-2.27 (m, 1H), 1.96-1.92 (m, 1H), 1.52-1.50 (m, 1H).

Example 133

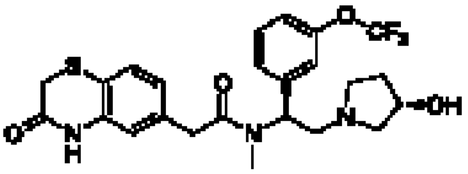
N-((S)-1-(3-fluorophenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)acetamide



LC-IvE : (ES, m/z): 444 (M+1); ^{1}H-NMR (DMSO-d_6, 300 MHz): δ10.53 (d, J=6.6Hz, 1H), 7.41-7.34 (m, 1H), 7.26-7.23 (m, 1H), 7.13-7.07 (m, 3¾ 6.88-6.84 (m, 2H), 5.82 (d, J=9.0 Hz, 1H), 6.70 (d, J=3.3 Hz, 1H), 4.15 (s, 1H), 3.78-3.63 (m, 2¾ 3.42 (s, 2H), 3.01-2.90 (m, 1H), 2.£5-2.81 (m, 1H), 2.73 (s, 3H), 2.62-2.56 (m, 1H), 2.50-2.28 (m, 1¾ 1.93-1.89 (m, 1H), 1.62-1.58 (m, 1H).

Example 134

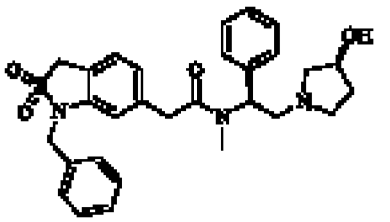
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(trifluoiomfthoxy)i ¾nyl)ethyl)-N-methyl-2-(3-oxo-3,4-dihyd.ro-2H-benzo[b][1,4]thiazin-6-yl)acetamide



LC-IvE : (EΞ, m¾ : 510 (M+1); H -NMR: (DMSO-d_6, 300 MHz) : δ 10.54 (d, J=6.0Hz, 1H), 7.52-7.46 (in, 1H), 7.36-7.24 (m, 4H), 6.89-6.87 (m, 2H), 5.86-5.80 (m, 1H), 4.724.71 (m, lH), 4.16 (s, 1H), 3.80-3.65 (m, 2H), 3.45 (s, 2H), 3.07-2.99 (m, 1H), 2.86-2.81 (m, 2H), 2.76 (¾ 2H), 2.71-2.62 (m, 2H), 2.42-2.41 (m, 1H), 2.36-2.29 (m, 1H), 1.98-1.94 (m, 1H), 1.58-1.49 (m, 1H).

Example 135

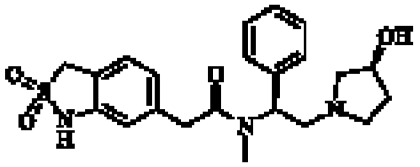
2-(1-benzyl-2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methylacetamide



^{1}H-NMR (400 MHz, DMSO-rf.): δ 7.41-7.35 (m, 2H), 7.33-7.21 (m, SH), 7.08 (d, *J = 6.9* Hz, IH), 6.89-6.84 (m, IH), 6.58-6.55 (m, IH), 5 .78-5.73 (bs, 1H), 4.93 (bs, 1H), 4.71 -4.69 (m, 4H), 4.13 (bs, IH), 3.71 -3.58 (m, 2H), 3.39-3.28 (m, 2H), 2.842.77 (m, IH), 2.62 (s, 3H), 2.542 .48 (m, 2H), 2.31 -2.28 (m, IH), 1.90-1 .89 (m, IH), 1.49 (bs, lH); IR (KBr, cm^{-1}): 3414, 2928, 2799, 1624, 1450, 1323, 1202, 1142, 1099; MS (ESI) m/z: 520 (M+l).

Example 136

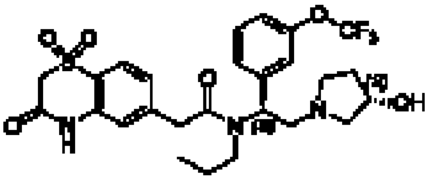
2-(2,2 -di> xido-1,3-dihydrobeizo[c]isothiazol-6-yl)-N-((S>2 -((S)-3-hydroxypyrroli ii n-1-yi)-1-phenylethyl)--^ methylacetamide



Mating point: 232-234 °C; ^{1}H-NMR (400 MHz, DMSCkii): δ 10.30 (bs, I H), 7.35-7.26 (m, 5H), 7 24-7.18 (m, IH), 6.85-6.82 (m, IH), 6.75-6.73 (m, IH), 5.87-5.83 (m, IH), 5.10 (t, *J* = 7.6 Hz, IH), 4.47 (s, 2H) 4.21 4.16 (m, IH), 3.81-3.77 (m, I H), 3.69-3.65 (m, IH), 3.16-3.05 (m, IH), 2 £5-2.81 (m, IH), 2.78-2.64 (m, 4H), 2.61 (s, IH), 2.42-2.32 (m, 2H), 2.01-1 .91 (m, IH), 156-1 .49 (m, IH); IR (KBr, cm^{-1}): 3294, 2938, 2787, 1612, 1450, 1313, 1196, 1134, 1091 ; MS (ESI) m/z: 428 (M+l).

Example 137

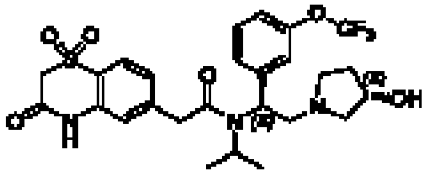
2-(1, 1-di ı xido-3 -OM -3,4 -dihydro-2H -bea o[b] [l,4]thUziit6-yl)-N-((S)-2-((S)-3-hydroxypyiTolidin-l-yl)- l-(3-(trifluoiomethoxy)phenyl)ethyl)-N-propylacetamide



MS (EΞ, *mfs)*: 570 (M+l); 'H -NMR: (DMSO-d_6, 400MHz): 5 11.23 (s, 1H), 7.74-7.76 (m, 1H), 7 .45-7.49 (in. 1H), 7.27-7.39 (in, 3H), 7.19-7.21 (m, 1H), 7.12 {s, 1¾ 5.64 (in, 1¾ 4.704.73 (m, 3H), 3.77-4.16 (m, 3H), 2 J64-3.17 (in, 6H), 2.33-2.45 (in, 2H), 1.90-1 .95 (in, 1H), 1.04-1 .51 (m, 3H), 0.52-0.73 (in, 3H).

Example 138

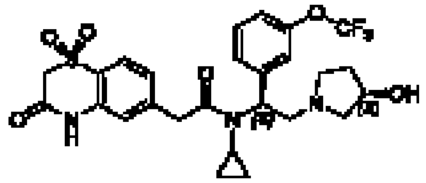
2-(1, 1-du xido -3 -oM -3,4-dihydro-2H-lli en o [b] [l ,4]thiazin-6-yl)-N-((S)-2-((S)-3-hydroxyp yrrolidi n-1-yl)-1-(3-(trifluoromethoxy)phenyl)ethyl)-N-isopropylacetamide



LC-MS : (ES, *mfs)*: 570 (M+l); ^{1}H-NMR : (DM5 O-d_6, 400MHz) : 5 11.24 (s, 1H), 7.73-7 .77 (m, 1H), 7.30-7.50 (m, 4H), 7 .1 6-7.28 (in, 2H), 7 J09 (s, 1H), 4.734.76 (in, 1H), 4.70 (s, 2H), 4.18 (in, 2H), 3.89 (s, 2H), 3.30 (in, 1H), 2.61 -2.85 (in, 4H), 2.40-2.49 (m, 1H), 1.93-1 5 9 (in, 1H), 1.53-1 .55 (m, 1H), 1.23-1 .31 (in, 3H), 1.06-1 .09 (m, 2H), 0 80 (in, 1H).

Example 139

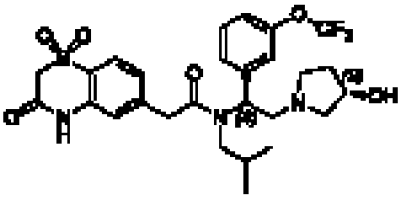
N-cyc b propyl-2-(l, 1-dioxid o-3-oxo-3,4- dihydro -2H-H»eiu» [b] [1 ,4]thi azm-6-yl)-N -((S)-2-((S)-3-hyd_o xypyrroEdi n-1-yl)-1-(3 -(tri Quorome thoxy)phenyDet hyljac etajnide



LC-MS (ES, *mfs):* 568 (M+1); ^{1}H-NMR (DMSO-d_6, 400MHz) *5* 11.24 (s, 1H), 7.77 (d, J=SHz, 1H), 7 .44 (in, 1H), 7.30 (m, *IK)*, 7 23 (in, 3H), 7.14 (in, 1H), 5.44 (¾ 1H), 4.75-4.71 (in, 3H), 4.15-3.98 (in, 3H), 3.30-3.27 (in, 2H), 3D0 (in, 1H), 2.74 (in, 3H), 2.39-2.33 (m, 2H), 1.95 (m, 1H), 1.55 (m, 1H), 0.84-0.71 (in, 3H), 0.38 (s, 1H)

Example 140

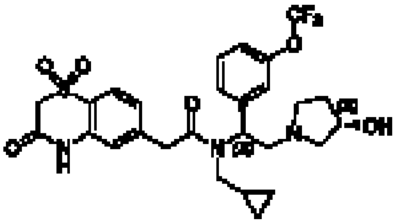
2-(1, 1-du xido -3 -OM -3,4-dihydro-2H-h erao [b] [l ,4]thia zin-6-yl)-N-((S)-2-((S)-3-hydraxyp yrrolidi n- 1-yD- l -(3 -(tri luoi om eth o\y)p heny l)et hy l)-N-isobutylacetamide



IvE (EΞ, m/z): 584 (IvI+1); ^{1}H-NMR: (DMSO-d_6, 400MHz) 5 11.23 (m, 1H), 7.77-7.73 (in, 1H), 7.49-7.39 (m, 3H), 7.26-7.1 1 (m, 3H), 5 32-5.15 (m, 1H), 4.754.70 (m, 3H), 390-3.01 (in, 3H), 2.75-2.67 (m, 3H), 2.41-2.38 (in, 2H), 1.92 (in, 1H), 1.54-1 5 2 (m, 2H), 0.79-0.72 (in, 4H), 0.63-0.61 (in, 1H), 0.36-0.34 (m, 1H)

Example 141

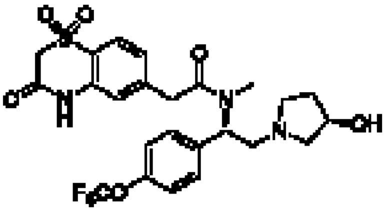
N-(cyclopropylmethyl)-2-(1,l-dioxido-3-o xo-3,4-dihydra-2H-beiizD [b] [l,4]thiazm-6-yl)-N-((S)-2-((S)-3-hydToxypyrrofdin-1-yl)-1-(3-(trifluoromethoxy)phenyl)ethyl) acetamide



MS (ES, m/z): 582 (M+1); ¾-NMR (CDCb, 400 MHz): 5 11.23 (in, 1H), 7.76-7.74 (in, 1H), 7.50-7.13 (in, 6H), 5.32-5.15 (in, 1H), 4.74-4.71 (in, 3H), 4.17-3.90 (in, 3H), 3.33-3.10 (in, 4H) 2.85-2.79 (m, 2H), 2.40 (m, 2H), 195-1 .93 (m, 1H), 1.53-1 .52 (in, 1H), 0.88-0.65 (m, 1H), 0.38-0.08 (m, 4H).

Example 142

2-(1, 1-dioxido-3-oxo-3,4-dihydro-2H-l(i enzo[b] [l,4]thiazin-6-yl)-I^((S>-2-((!$)-3-hydroxyp yiralidin- l-yl)- 1-(4-(trifluoromethoxy)phenyl)ethyl)-N-methylacetamide



MS (ES, mfz): 542 (M+1); 1H-NMR (DM3O-ii,400MHz) 5 11.236 (s, 1H),7.774-7.097 (in, 7H), 5.327 (s, 1H), 4.7444.707 (in, 3H), 4.177 (s, 1H), 3.989-3305 (m, 2H), 3.028-2.333 (in, 9H), 2.079 (in, 1H), 1.979-1 .962 (in, 1H).

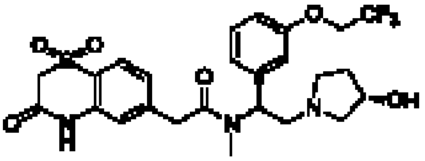
Example 143

2-(2,2-dime%l-3-oxo-3 ,+dihydro-2 H-benm [b] [l,4]thiazm-6 -yIW (S)-2-((S)-3-hydroxyp yrrolidin-1-yl)-1-(3-(trifluoromethoxy)phenyl)ethyl)-N-methylacetamide

MS (EΞ, m/z): 538 (M+l); ^{1}H-NMER (DMSO-d6, 300MHz) B1.34 (s, 6H), 1.50-1 .52 (m, 1H), 1.90-1 95 (in, 1H). 2.30-2.33 (m, 1H). 2.46-2.50 (m, 3H). 2.60-2.85 (m, 4H), 2.99-3.04 (m, 1H), 3.70 (q, J=12 Hz, 2H), 4.15 (s, 1H), 4.71 (s, 1H), 5.81 (m, 1H), 6 £3-7.48 (m, 7H), 10.52 (¾ 1H).

Example 144

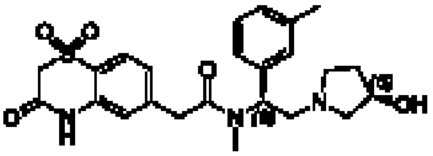
2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-2-((S)-3-hydroxy pyrrolidiii- 1-yI)-1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)-N-methylacetamide



MS (EΞ, m/s): 556 (M+l); 1H-NMR (300 MHz, DMSO-di) 5 11.20 (a, 1H), 7.75 (d, 7=8.1, 1H), 7.32 (t, J=8.4, 1H), 7.18 (d, J=8.7, 1H), 7.16 (s, 1H), 6.95-7.10 (m, 3H), 5.77-5.83 (m, 1H), 4.70-4.80 (m, 5H), 4.17 (s, 1H), 3.78-3.98 (m, 2H), 3.04-3.12 (m, 1H), 2.50-3.00 (m, 6H), 2.33-2.50 (m, 2H), 1.92-1 .98 (m, 1H), 1.53 (s. 1H).

Example 145

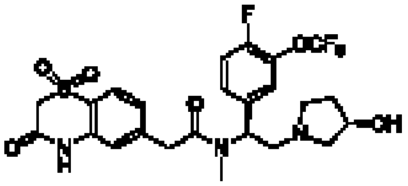
2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-li enzo [b] [l,4]thiaziit6-yl>-I^((S>-2-((£^3-hydroxy pyrroMdm-1-yI)-1-(m-tolyl)ethyl)-N-methylacetamide



MS (EΞ, m/z): 472 (M+l); 1H-NMRj(DM3O-d6, 400MHz) 5 11.20-1 1.23 (m, 1¾ 7.73-7.77 (m, 1H), 7.20-7.26 (m, 2H), 7.05-7.16 (m, 4H), 5.78-5 .79 (m, 1H), 4.704.74 (m, 3H), 4.17 (m, 1H), 3 *19-3.96* (m, 2H), 3.09 (in, 1H), 2.82 (m, 1H), 2.73 (s, 3H), 2 £3-2.67 (m, 1H), 2.41 (in, 3H), 2.33 (s, 3H), 1.98 (in, 1H), 1.50 (in, 1H).

Example 146

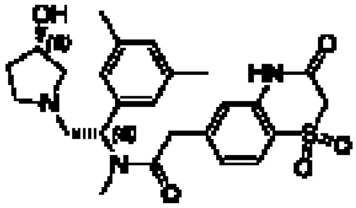
2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-1-(4-fluoro-3-(trifluoromethoxy)phenyi)-2-((S)-3-hydroxypyrrolidin-1-yljethylVN-methylacetamide



IvE (ES, *m/i)*: *559.9* (M+1); 'H -NMR (300 MHz, DMSO-*d*₆) 5 11.20 *(s,* 1H), 7.71 (d, *J*=7.8Hz, 1H), 7.32-7.50 (in, 3H), 7.13 (d, *J*=8.1Hz, 1H), 7.04 (s, 1H), 5.73 (t, *J*=6.6Hz, 1H), 4.654 .71 (m, 3H), 4.12 (*s,* lH), 3.75-3.96 (in, 2¾ 2.73 (br¾ 1¾ 2.44-2.68 (m, 6H), 2 33-2.40 (in, 2H), 1.86-1 .93 (in, 1H), 1.45 (bis, 1H).

Example 147

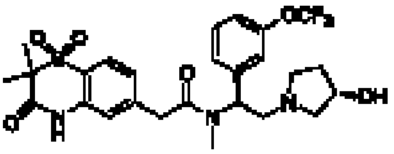
N-((S)-1-(3,5-di™thylp ¾ nyl)-2-((S)-3-h.ydroxypyrrolidin-1-yl)ethyl)-2-(1,l-dijxidij-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-methylacetamide



MS (ES, m/z): 486.12; 1H-NMR (DM30, 300MHz) 5 11.19 (s, 1H,), 7.731-7.71 (in, 1H), 7.18-7.16 (m, 1H), 7.07 (in, 1H), 6.84-6.79 (m, 3H), 5.71 (m,0.8H), 4.95 (m, 0.2H), 4.71-4.65 (in, 3H), 4.13 (in, 1H), 3.91-3.78 (in, 2H), 3.15-2.19 (in, 15H), 1.95-1 £5 (in, 1H), 1.48-1 .42 (m , IH)

Example 148

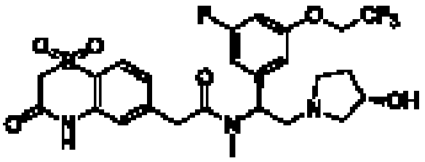
2-(2,2-dimethyl-1,1-dioxido-3-OSD-3,4-dihydra-2H-hei™ |>][1,4]thiazin-6-yI)-N-« S)-2-((S)-3-hyd_roxypyrroEdin-1-yl)-1-(3-(trifruorometho xy)phenyDet hyl)-N-methylacetamide



MS (ES, m/z): 570 (M+1); ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 11.21 (s. 1H), 7.75-7.17 (m, 6H), 7.04 (s, 1H). 5.77 (t, J=8 Hz, 0.8H), 5.14 (t, J=8 Hz, 0.2H), 4.70 (s, 1H). 4.12 (s, 1H), 3.92 (d, J=12 Hz, 2H), 3.04 (br, 1H). 2.99-2.67 (m, 6H), 2.45-2.26 (m, 1H). 1.92-1.85 (m, 1H), 1,47 (s, 7H).

Example 149

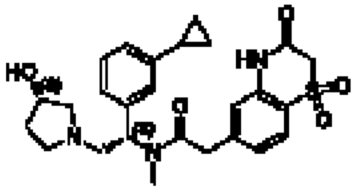
2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-1-(3-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methylacetamide



MS (ES, m/z): 573.9 (MH); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.20 (s, 1H), 7.75 (d, J=8.4Hz, 1H). 7.15-7.20 (m, 1H). 7.09 (s, 1H), 6.78-6.95 (m, 3H), 5.73 (brs, 1H), 4.69-4.84 (m, 5H), 4.15 (brs, 1H), 3.79-3.98 (m, 2H), 3.29 (s, 1H), 2.96-3.01 (m, 1H), 2.63-2.79 (m, 5H), 2.26-2.35 (m, 2H), 1.52-1.98 (m, 1H), 1.48 (m, 1H).

Example 150

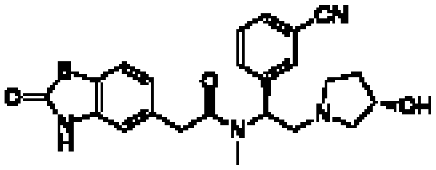
N-((S)-1-(3-cyclopropylphenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-methylacetamide



MS (ES, m/z): 498 (M+1); 1H-NMR (DMSO-d_6, 300MHz) δ 11.16 (m, 1H), 7.73-7.68 (m, 1H), 7.18-6.87 (m, 6H), 5.78-5.71 (m, 0.7H), 5.08-5.02 (m, 0.2H), 4.70-4.66 (m, 3H), 4.13 (m, 1H), 3.92-3.80 (m, 2H), 3.06-2.23 (m, 8H), 1.92-1.81 (m, 2H), 1.49 (m, 1H), 0.90-0.87 (m, 2H), 0.60-0.55 (m, 2H).

Example 151

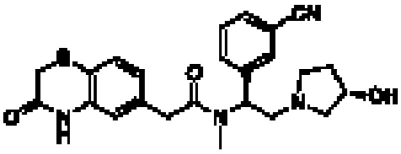
N-((S)-1-(3-cyanophenyl)-2-((S)-3-hydroxypyTrolidin-1-yl)ethjl)-I* methyl-2-(2-oxo-2,3-djhydrobenzo[dJthiazolr5-yl)acetamide



IvE {EΞ, mfz): **437 (IvH-1)**; ^{1}H-NMR. (DMSO -d_6, **400** MHz) **5 11.84** (s, **1H), 7.76-7.73** (m, **2H), 7.65-7.46** (m, **3H), 7.07-7.01** (m, **2H), 5.85-5S 1** (m, **0.8H), 5.18** (m, **0.2H), 4.89-4.70** (m, **1H), 4.18** (s, **1H), 3.92-3.74** (m, **2H), 3.12-2.56** (m, **7H), 2.40-2.33** (m, **2H), 1.97-1.94** (m, **1H), 1.42-1.49** (s, lH).

Example 152

N-((S)-1-(3-cyar» phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-I* methyl-2-(3-oxo-3,4-dihydro-2H-bennj [b] [l,4]thiazinr6-yl)acetamide



IvE (EΞ, m/z): 451 (M+l); ^{1}H-NM (CDjOD ,300MHz) *5* 7.67-7.64 (m, 3H), 7.56-7.50 (m, 1H), 6 98-6.91 (m, 2H), 6.02 (t, *J*=5.2Hz, 1¾ 4.36-4.32 (m, 1H), 3.82 (¾ *J*=15.6Hz, 2H), 3.43 **(s,** 2H), 3.28-3.22 **(m,** 1H). 2.95-2.90 **(in,** 2H), 2.82 **(s,** 3H), 2.76-2.72 **(m,** 1¾ 2.54-2.46 (m, 2H), 2.15-2.02 (m, lH), 1.73-1.62 (m, 1H).

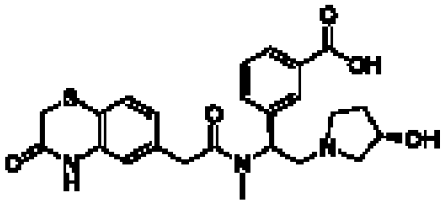
Example 153

N-((S)-1-(3-cyanophenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(3-oxo-3,4-djhydio-2H-benzo[b] [l,4]oxazm-ti- yl)aceiamide

IvE (EΞ, *m/z): 435* (M+l); ¾-NMR (CDjOD, 400MHz) 5 7.75-7.58 (m, 4H), *6.95-629* (m, 3H), *6 33-6.31* (d, *J*=10 8Hz, 1H), 4.60-4.58 (m, 3H), 4.144.06 (m, 1H), 3.87-3.46 (m, 7H). 2.83-2 S O (m, 3H), 2.31 -2.1 1 (m, 2H).

Example 154

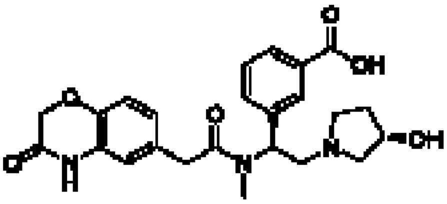
3-((S)-2-((¾)-3 -hydroxypyrrolidin-l -yl)-l -(N-methyl-2-(3-oxo-3,4-dfliydT0-2H-beinzo [b] [l,4]thiazin-6-yl)acetamido)ethyl)benzoic acid



IvE (ES, *m/z*): 470(M+1); ^{1}H-NMR (DMSO-^, 300MHz) 5 10.46 (a. 1H), 7.74 (d, *J*= 13.5Hz, 2H), 7.46-7.38 (m, 2H), 7.20-7.16 (m, 1H), 6.84-6.79 (m, 2¾ 5.80 (dd, *J* =6.0Hz, *J*=9.6Hz. 1H), 467 (m, 1H), 4.1 1 (m, 1H), 3.72 (d, *J*=15.3Hz, 1H), 3.59 (d, *J* = 156Hz, 1H), 3.39 (a. 2H), 3.04 (t, *J* =5 9Hz. 1H), 2.82-2.54 (m, 6H), 2 30-2.25 (m, 1H), 192-1.80 (m, 1¾ 1.43-1 3 5 (m, 1H)

Example 155

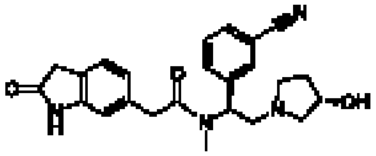
3-((S)-2-((S)-3 -hydroxypyrrolidin- l-yl)- l-(N-methyt2-(3-oxo-3 ,4-dfliydro-2H-benzo [b] [l,4]oxazin-6-yl)¾ etamido)ethyl)benzoic acid



IvE (EΞ, *mfs):* 454(M+1); ^{1}H-NMR (DMSO -d_6, 400MHz) 5 10.72 (s, 1H), 7.84 (s, 2H), 7.51-7 .42 (m, 2H), 6 £8-6.80 (m, 3H), 5.8 S (m, 1H), 4.53 (s, 2H), 4.184.16 (m, 1H), 3.73 (d, J=15.2Hz, 1H), 3.62 (d, *J*=15.2Hz, 1H). 3.1 1-3.08 (m, 1H), 2.86-2.81 (m, 3H), 2.80 (s, 3¾ 2.62 (s, 1H), 2.46 (d, *J*=6.0Hz, 1H), 2.37-2.34 (dd, *J*=4.0Hz, *J* =4.4Hz, 1H). 1.94 (m, 1¾ 1.541 5 1 (m, 1H)

Example 156

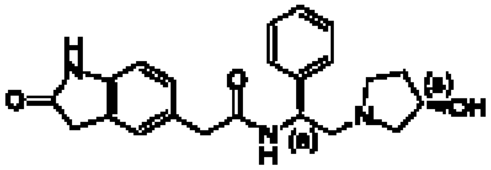
N-((S)-l -(3-cyanophenyl)-2-((S)-3-hydroxypyTrolidin-l-yl)ethjl)-I* methyl-2-(2-oxo indolin-6- yl)acetamide



IvE (ES, m/z): 419 (MH); 1H-NMR 1H-NMR(CDCb,300MHs) δ 10.35 (s, lH), 7 .75-7.54 (m, 4H), 7.1 1 (d, J=6.3Hz, IH), 6.81-6.76 (m, 2H), 5.82 (t, J=6.0H._, IH), 4.85 (d, J=3.6Hz, IH), 4.16 (s, IH), 3.81 -3.64 (m, 2H), 3.51-3.42 (m, 2H), 3.06-2.94 (m, IH), 2 .82-2.72 (m, 6H), 2.57 (s, IH), 2.35-2 2 8 (m, 2H), 1.95-1 .90 (m, 1¾ 1.51 - 1.49 (m, IH)

Example 157

N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-2-(2-oxoindolin-5-yl)acetamide

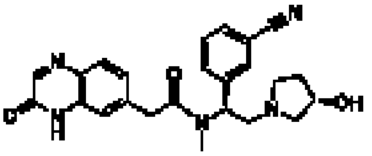


M S (ES, m/z) : (_vH-l) 380

^{1}H-NMR (DMSO-d_6, 300MHz) 5 10.28 (IH, s), 8.42-8.40 (IH, m), 7.29-7 .19 (5H, m), 7.09-7.04 (2 H, s) 6.71-6.69 (I H, m), 4.88-4.85 (IH, m), 4.66 4.65 (IH, m), 4.1 34.1 1 (IH, m), 3.43-3 3 2 (4H, m), 2.74-2.69 (2H, m), 2.57-2.47 (IH, m), 2.45-2.43 (IH, m), 2.29-2.25 (IH, m), 1.93-1 £ 8 (lH, m), 157-1 .47 (l H, m)

Example 158

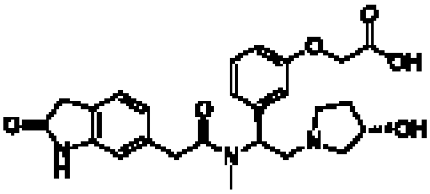
N-((S)-1-(3-cyanophenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydro¾uinoxalin-6-yl)acetamide



IvE (ES , m/z): 432 (M+1); ^{1}H-NMR(DMSO-d_6,300MHz) 5 12 .262 (s, I H), 9 .353 (s, I H), 8 .122-7 .525 (m, 4H), 7 .19 8 (s, 2H,), 5 .835-5 .7 10 (m, I H), 4.830 4.622 (m, I H), 4 .15 0 (s, I H), 4.02 1-3 .830 (m, 2H), 3.154-2 .27 0 (m, 9H), 1.998- 1.854 (m, 1H), 1.587 -1 .375 (in, I H)

Example 159

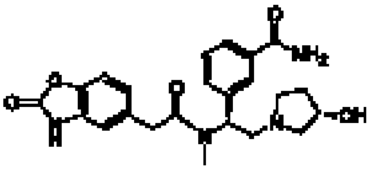
2-(3-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindolin-6-yl) acetamido)ethyl)phenoxy)acetic acid



IvE *(ES, m/z)*: 467.9 (M+l); ^{1}H-NMR (DMSO-d_6, 300 MHz): 5 10.36-10.45 (m, IH), 7.24 (d, *J*=S.8Hz, 1H), 7.1 1 (d, ***J=1.6,*** I H), 6.70-6.86 (m, 5H), 5.83-5.88 (m, IH), 4.58 (s. 2H), 4.20-4.23 (m, IH), 3.76-3.79 (m, IH), 3.64-3.69 (m, 2H), 3.30-3.42 (s, 4H), 3.12-3.18 (m, IH), 2.76-2 £ 9 (m, 3H), 2.63-2.69 (m, 3H), 2.50-2.52 (m, IH), 1.99-2.01 (m, IH), 1.54-1.57 (m, IH).

Example 160

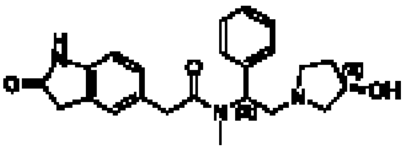
3-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(N-methy]r2-(2-oxo-2,3-dmydroh enzo[d] oxazo1-5-yljacetanudo)ethyl)benzamide



MS (EΞ, *m/z)*: 439 (M+l); 1H-NMR (DMSO-d_6, 300MHz) 5 11.35-1 1.69 (s, IH), 8.00 (s, 1H), 7.77-7.74 (m, 2H), 7.42-7 3 9 (m, 3H), 7.2 1-7.17 (m, 1¾ 7.05-6.96 (m, 2H), 5.92-5.87 (m, 0.8H), 5.12-5.25 (in, IH), 5.09-4.89 (m, I H), 4.18 (s, I H), 3.89-3.84 (m, IH), 3.72-3.67 (m, IH), 3.17-3.09 (m, IH), 2.85-2.62 (m, 6H), 2.39-2.36 (m, 2H), 1.99-1.92 (m, IH), 1.42-1.59 (m, lH)

Example 161

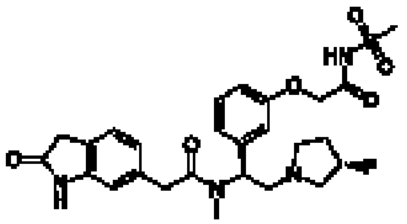
I^((S>-2-((!Si)-3-hydroxyp yrroHdnv1-yl)-1-phenylethyl)-N-methyl-2-(2-DXDmdolm-5-yl)acetamide



IvE (ES, *mfz):* (M+l) 394; ^{1}H-NMR (DMSO-d_6, 300MHz) 5 10 3 1 (lH,s), 7.36-7.22 (5H.m), 6.75-6 .73 (2H,m), 5.86 (0.7H,m), 4.69 (0.2H,m), 4.16 (lH,m), 3.75-3.71 (1H,m), 3.64-3.60 (lH-m), 3.44 (2H,m), 3.09-2.89 (2H,m). 2.62-2.69 (4H,m), 2.49-2.51 (IH,m), 1.92-1 .93 (lH,m), 1.52 (lH.m)

Example 162

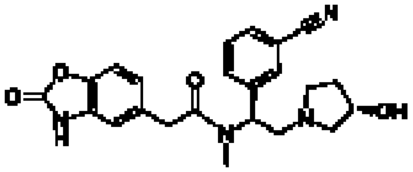
N-((S)-2-((S)-3-fluoropyrrolidin-1-yl> 1-(3-(2-(methylsulfonamido>2-oxoethoxy)phenyl) ethyl)-N-methyi -2-(2-oxoindolin-6-yl)acetamide



IvE (EΞ, *mfz):* 547 (M+1); ^{1}H-NMR (DMSO-d., 400MHz) 5 10.35 (¾ 1H) , 7.23-7.27 (m, IH), 7.10-7.13 (m, IH), 6.78-6.96 (m, 3H), 6 .73 (s, IH), 5.87-5.89 (m, IH), 5 D9-5 .29 (m, IH), 4.54 (s, 2H), 3.67-3.77 (m, 2H), 3.42 (s, 2H), 3.13 (s, 3H), 2.81-3.13 (m, 3H), 2.63-2.71 (m, 3H), 1.76-2. 14 (m, 2H).

Example 163

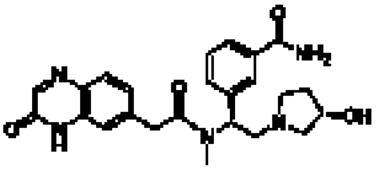
N-((S)-1-(3-cyanophenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-_™;thyl-2-(2-om-2,3-dihydrobenzo[d]oxazol-5-yl)acetamide



IvE (ES, *mfz):* 421 (M+1); ^{1}H-NMR (DMSO-d_6, 400MHz) S 11.56 (a. IH), 7.76-7.71 (m, 2H), 7.647 .62 (in, IH), 7.59-7.54 (m, 1¾ 7.22-7.17 (m, IH), 7.03 (s, IH), *6.99-6 95* (m, IH), 5.85-5 .13 (m, IH), 5.05-4.66 (m, IH), 4.60-5.02 (m, IH), 4.17 (a. IH), 3 .90-3.72 (m, 2H), 3.33-3.00 (m, IH), 2.85-2 .60 (m, 6H), 2.42-2 .36 (m, 2H), 1.55-1.41 (m, IH).

Example 164

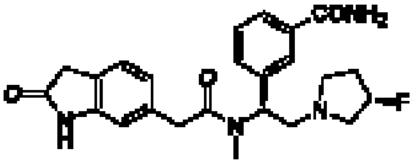
3-((£i)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(3-oxo-3,4-dihydroquinoxalin-6-yl)acetamido)ethyl)benzamide



IvE (ES, m/∑): 450 (M +l); 1H-NMR (DIvEO -d_6, 300MHz) 5 S.01-7.6S (m, 5H), 7.43-7.39 (m, 3H), 7 2 2-7 .20 (m, 2H), 5.91-5.85 (m, 1H), 4.16 (s, 1¾ 3.99-3.79 (m, 2H), 3.14-3.06 (in, 1H), 2.S6-2.54 (m, 6H), 2.44-2.31 (m, 2H), 1.96-1 .89 (m, 1H), 1.53-1 .50 (m, 1H)

Example 165

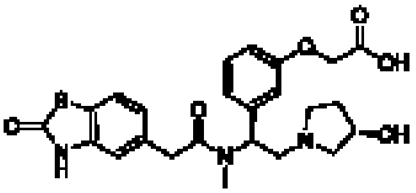
3-((S)-2-((S)-3-fluoropyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindolin-6-yl)acetamido)ethyl)benzamide



IvE (EΞ, m/z): 439 (M+l); ^{1}H-NMER (DIvEO-d_6, 300 MHz): δ 10.31 (s, 1H). 7.99 (s, 1H), 7.77 (s, 2¾ 7.47-7.31 (m, 3H), 7.09 (d, J = 7 2 Hz, 1H), 6 82 (d, J = 7.2 Hz, 1H), 6.71 (s, 2H). 5 96-5.84 (m, 1H), 5.30-5.00 (m, 1H), 3 86-3 ,60 (m, 2H), 3.42 (s, 2H), 3 20-3.06 (m, 1H), 2 9 1-2.62 (m, 7¾ 2.42-2.27 (m, 1H), 2.15-1 .93 (m, 1H), 1.93-1 .66 (m, 1H); ^{19}F-NMR-(DMSO-d_6, 400 MHz) δ166 (s)

Example 166

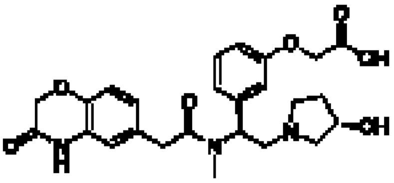
2-(3-((⅟4)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(2-o«i-2,3-dihydrobenzo[d]thiazol-5-yl)acetamido)ethyl)phenoxy)acetic acid



IvE (EΞ, *m/z)*: 486.00 (M+l); ¾ -NMR (DMSO-^OOMHz) 5 12.51 (m, 1H), 7.49-7.46 (d, *J*=4.0Hz, I H), 7.26-7.22 (t. *J*=6.0Hz, IH), 7.06-7.01 (m, 2H), 6.87-6.79 (m, 3H). 5.88-5.85 (m, IH), 5.10 (m, IH), 4.604 5 8 (m, 2H), 4.22 (m, I H), 3.85-3.74 (m, 2H), 3.32-3.17 (m, IH), 2.95-2.70 (m, 3H), 2.68-2.65 (m, 3H), 2.54-2.50 (m, IH), 2.01 (m, IH), 1.57-1.56 (m, IH).

Example 167

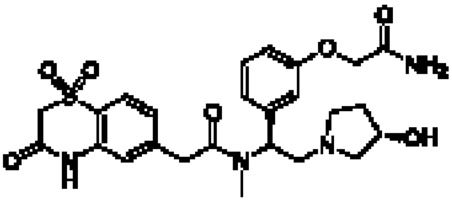
2-(3-((S)-2-((S)-3-hydroxypyrrolidin-l-yl)-l-(N-methyl-2-(3-o«j-3,4-dihydro-2H-benzo[b][l,4]oxazin-6-yl)acetamido)ethyl)phenoxy)acetic acid



IvE (EΞ, *m/z*): 484 (M+l); 1H-NMR (DMSO-d_6, 300MHz) 5 10.87 (m, I H), 7.25-7.20 (m, IH), 6.88-6.74 (m, 6H), 5.83-5.79 (m, 0.8H), 5.07-5.01 (m, 0.2H), 4.57-4.53 (m, 4H), 4.18-4.15 (m, IH), 3.72-3.60 (m, 2H), 3.10-3.04 (m, IH), 2.91-2.83 (m, IH), 2.79-2.73 (m, IH), 2.70-2.64 (m, 2H), 2.55 (m, IH), 2.38-2.33 (m, IH), 2.50-2.51 (m, IH), 193-1 98 (m, IH), 1.51-1 5 3 (m, IH).

Example 168

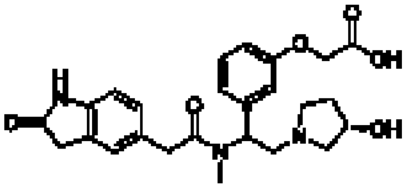
N-((S)-l-(3-(2-amiiu)-2-oxoethDxy^ henyl>2-((S>-3-hydroxypyrrolidinr l-yl)ethyl)-2-(l,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][l,4]thiazin-6-yl)-N-methylacetamide



MS (ES, *m/z*): 531 (M+l); ^{1}H-NMR (DMSO-d6,300 MHz): 5 11.19 (bra, I H), 7.71-7.77 (m, IH). 7 54 (bis, IH), 7.40 (bis, IH), 7.15-7.29 (m, 2H), 7.10 (s, IH), 6.83-6.93 (m, 3H), 5.80-5.82 (m, lHi 4.69-4.75 (m, 3H), 4.40-4.42 (m, 2H), 4.17 (brs, IH), 3.77-3.96 (m, 2H), 2.96-3.06 (m, 1H), 2.65-2.85 (m, 5H), 2.32-2.45 (m, 2H), 1.92-1.99 (m, IH), 1.51-1.53 (m, 1H)

Example 169

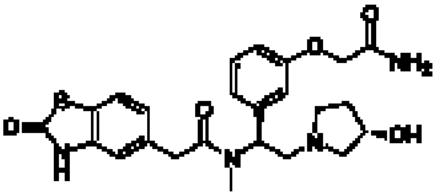
2-(3-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindolin-5-yl)acetamido) ethyl)phenoxy)acetic acid



IvE (ES, *m/z*): 468 (MH); ^{1}H-NMR(DMSO-d_6, 300MHz) S 10.31 (s, lH), 7.25-7.21 (m, 1H), 7.06-7.02 (m, 2H), 6.86-6.73 (m, 4H), 5 &4-5.80 (m, 1H), 4.59 (a. 1H), 4.15 (m, 1H), 3.75-3.60 (m, 2H), 3.54-3.32 (m, 2H), 3.10-3.04 (m, 1H), 2.942.87 (m, 1H), 2.75-2.50 (m, 5H), 2.37-2.31 (m, 1H), 1.97-1.91 (m, l H), 1.76-1.52 (m, 1H).

Example 170

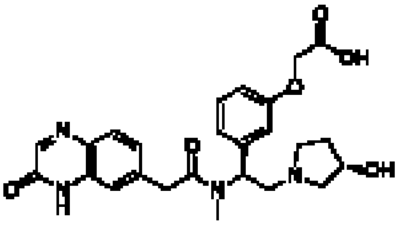
N-((S)-1-(3-(2-amino-2-oxoethoxy)phenyl>2-((S>-3-hydroxypyrrolidinr1-yl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydrobenzo[djthiazol-5-yljacetamide



IvE (ES, *m/z*): 485 (M+l); 1H-HMR (DMSO-d_6, 400MHZ) *5* 11.86 (brs. 1H), 7.54-7.40 (m, 3H), 7.28-7.24 (m, 1H), 7.09-7.02 (m, 2H), 6 9 0-6.84 (m, 3H), 5.85-5.81 (m, 1H), 5.14-4.73 (m, 1H), 4.40 (s, 2H), 4.18-4.17 (m, 1H), 3.90-3.70 (m, 2H), 3.10-2.66 (m, 6H), 2.39-2.35 (m, 2H), 1.97-1.93 (m, 1H), 1.53-1.51 (m, 1H).

Example 171

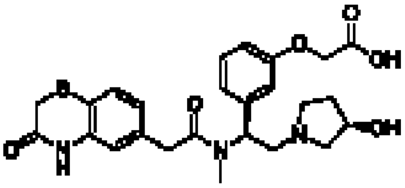
2-(3-((S)-2-((S)-3-hydroxy yrrolidin-1-yl)-1-(N-methyt2-(3-oxo-3,4-dihydro¾uinoxalin-6-yl)acetamido)ethyl)phenoxy)acetic acid



IvE (EΞ, m/z): 481 (M+l^H-NMR (DMSO-d_6, 300MHz) 5 8.13 (*s,* 1H), 7.72-7.68 (m, 1H), 7.25-7.17 (m, 3H), 6.87-6.78 (in, 3H). 5.85-5.80 (in, 0.8H), 5.13-5.08 (in, 0.2H), 4.55 (s, 2H), 4.17 (***bis,*** 1H), 4.00-3.82 (m, 2H), 3.16-3.06 (m, 1H), 3.00-2.61 (m, 7H), 2.50-2.41 (m, 1H), 2.08-1.89 (in, lH), 1.54-1.53 (m, 1H)

Example 172

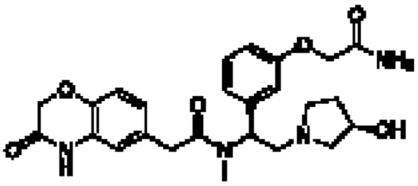
2-(3-((!S)-2-((S)-3-hydroxypyrro*Mm*-1-yl)-1-(N-methyl-2-(3-o«)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)acetamido)ethyl)phenoxy)acetic acid



MS (ES, m/s): 500 (M+l); 1H-NMR (DMSO-d_6, 400MHz) 5 10.62 (s, 1H), 7.21-7.25 (in, 2H), 6.78-6.88 (m, 5H), 5.73-5.82 (in, 1H), 4.58 (*s,* 2H), 4.15-4.17 (m, 1H), 3.62-3.76 (m, 3H), 3.07-3.10 (in, 2H), 2.84-2.92 (in, 2H), 2.84 (in, 2H), 2.67-2.73 (s, 3H), 2.33-2.38 (in, 2H), 1.90-2.07 (m, 1H), 1.50 (in, 1H)

Example 173

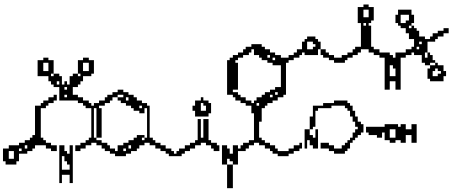
N-((S)-1-(3-(2-amino-2-oxoethoxy)phenyl>2-((S)-3-hydroxypyriflidinr 1-yl)ethyl')-N-methyl-2-(3-oxo-3,4-dihydro-2H-beriZD[i][l,4]oxaziiir6 -yl)acetamide



MS (EΞ, m/z): 483 (M+l); 1H-NMR (DMSO-d_6, 300MHz) 5 10.68-10.65 (m, 1H), 7.54 (s, 1H), 7.40 (*s,* 1H), 7.27-7.23 (in, 1H), 6.89-6.81 (m, 6H), 5.81-5.78 (in, 0.8H), 5.07-5.04 (in, 0.2H), 4.75-4.74 (m, 1H), *454* (*s,* 2H), 4.39 (*s,* 2H), 3.75-3.58 (in, 2H), 3.01-2.65 (in, 7H), 2.45-2.29 (m, 2H), 1.95-1.92 (m, 1H), 1.52-1.50 (in, 1H).

Example 174

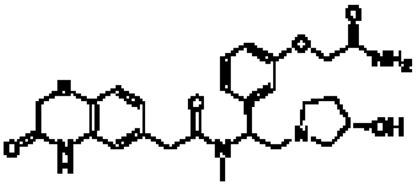
2-(1, 1-di ı xido -3 -oxo -3,4-dihydro-2H-b e a ,o [b] [1 ,4]thiaz in-6-yl)-N-((S)-2-((S)-3-hydroxyp yrroli di n- *l* -yl)-1 -(3-(2-(methylsulfonamido)-2-oxoetho *xy*)p henyl)ethyl)-N-me thylac etajiiide



IvE (EΞ, *m/z*): 609 (M+1); ^{1}H-NMR (DMSO-d_6, 300 MHz): 5 11.21 (*s*, 1H), 7.72-7.77 (m, 1H), 7 .1 2-7.29 (m, 4H), 6.74-6.82 (m, 3H), 5.98-6 .01 (m, 1H), 5.28-5.32 (m, 1H). 4.70 (a. 2H), 4.25-4.42 (m, 3¾ 3.81 -3.98 (m, 3H), 3.07-3.32 (m, 3H), 2.90-2.94 (m, 4H), 3.81-3.86 (m, 3H), 2.10-2.28 (m, 1 H), 1.75-1 .78 (m, 1H).

Example 175

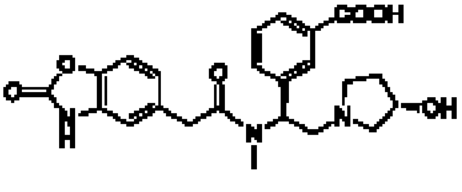
N-((S)-1-(3-(2-amin0-2-oxoeth0xyty henyl>2-((S)-3-hydroxypyriflliding 1 -yl)ethyl)-N-methyl-2-(3 -oxo -3,4-dihydro-2H-bena ı [b] [1 ,4]thiazin-6-yi)aceta mide



MΞ (EΞ, m/z): 499 (M+l); 1H-NMR (DMSO-d_6, 400MHz) : 5 10.54 (s, 1H), 7.55 (s, 1H), 7.41 (*s*, 1H). 7.27-7.24 (m, 2H), 6.89-6.83 (m, 5¾ 5.81-5.78 (m, 1H). 4.724.7 1 (m, 1H). 4.40430 (in, 2H), 4.15 (br, 1H), 3.78-3.61 (m, 2H), 3 .44-3 2 6 (m, 2H), 3.05-2.65 (m, 7H), 2.51-2 2 8 (m, 2H), 1.87-1 .97 (m, l H), 1.50 (m, l H).

Example 176

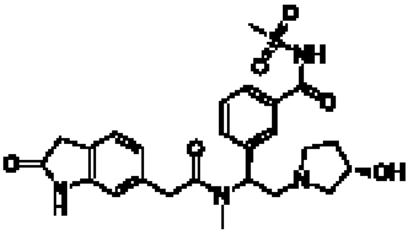
3-((S)-2-((S)-3 -hydroxyp yrrolidin-1 -yl)-1-(N-methylr2-(2-oxo-2 ,3-dihydroh enzo [d] osazol-i -yl>afetamido)ethyl)benxoic acid



IvE (ES, m/z): 440 (M+l); ^{1}H-NMR (DMSO-d6, 300 MHz): 5 7.80 (m, 2H), 7.53-7.43 (m, 2H), 7.21-7.15 (in, IH), 7.04-6.93 (m, 2H), 5.92-5.87 (m, 0.8H), 4.19-4.17 {s, I H), 3.88-3.69 (m, 2H), 3.15-3.00 (m, 2H), 2.91-2.72 (m, 5H), 2.61 (a. 1H), 2.45-2.36 (m, 2H), 1.99-1.92 (m, 1H), 1.52-1.50 (m, 1H).

Example 177

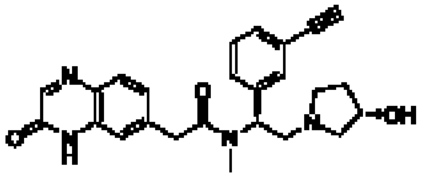
3-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindolin-6-yl)acetamido)ethyl)-N-(methylsulfonyl)benxamide



ME (ES, m/z): 515(M+1); ^{1}H-NMR **(DIvE** O-d_6, 400MHz) : 5 10.34-10.30 (m, IH), 7.87-7.86 (s, 2H), 7.36-7.27 (m, 2H), 7.14-7.12 (d, J=7.6Hz, IH), 6.08-5.97 (m, IH), 5.10-5.35 (m, 1H), 4.414.15 (m, IH), 3.79-3.74 (m, 2H), 3.43 (s, 2H) .307-2.98 (m, 2H), 294-2.92 (m, 4H), 2.73 (¾ 2H), 2 j67-2.64 (m. 3¾ 2.11-2.08 (m, IH), 1.76-1.67 (m, 1H).

Example 178

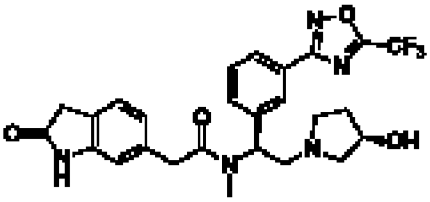
N-((S)-1-(3-ethynylphenyl)-2-((S)-3-hydroxjpyrrolidin-1-yl)ethyl)-N-methyl-2-(3-oxo-3,4-djhydrDquinoxalin-6-yl)acetamide



IvE (ES, mfs): 431(M+1) ; ^{1}H-NMR **(DIvEO** -d_6, 300MHz): 5 12.48-12.32 (s, IH), 8.13 (s, 1H), 7.73-7.70 (m, IH), 7.38-7.35 (m, 4H), 7.21-7.20 (m, 2H), 5.69-5.95 (s, IH), 4.J65-4.90 (m, IH), 4.194.16 (m, 2H), 4.00-3.89 (m, 2H), 3.12-2.94 (m, 1H), 2.92-2.75 (m, 5H), 2.62 (s, IH), 2.21-2.31 (m, 2H), 2.12-1.92 (m, IH), 2.52-2.41 (m, IH).

Example 179

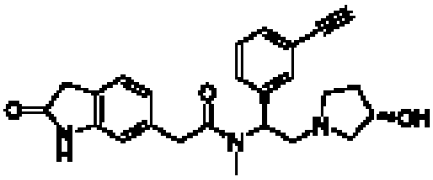
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(5-(trif ı» romethyl)-1,2,4-oxadiazol-3-yl)phenyl)ethjl)-N-methyl-2-(2-oxoindoli ii-6-yl)acetamide



IvE (EΞ, m/z): 530 (Mfl); ^{1}H-NMR (DIvEO -d_6, 300MHz): 5 10.35 (s, 1H), 7.97 (d, J=3Hz, 1H), **7.60** (d, J=4.8Hz, 2H), 7 0 S (d, J=4.8Hz, 1H), 6.83-6.79 (m, 2H), 5 .96-5.24 (m, 1H), 4.88 (s, lH), 4.19 (s, 1H), 334-3 **.65** (m, 2H), 3.42 (s, 2H), 3 .16-2.40 (m, 9H), 2 00-1 .93 (m, 1H), 1.541 .49 (m, 1H).

Example 180

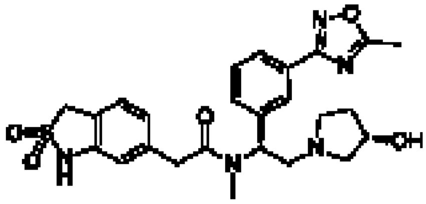
N-((S)-1-(3-ethynylphenyl)-2-((S)-3-hydro3ypyrrolidi ii-1-yl)ethyl)-N-methyJr2-(2-oxoindolijın6-yl)acetamide



IvE (EΞ, m/z): 418 (M+1J; ^{1}H-NMR (DMSO-d_6, 300MHz): 5 10.41-1 0.31 (in, 1H), 7.37-7.27 (m, 4H), 7.13-7.10 (d, J=6.9Hz, 1H), 6.82-6.74 (m, 2H), 5.85-5.80 (m, 1H), 4.89-4.87 (d. J=4.2Hz, 1H), 4.19-4.17 (m, 2H), 3.83-3.63 (m, 2H), 3.43 (s, 2H), 3.09-3.01 (m, 1H), 2.81-2.70 (m, 4H), 2.60-2.58 (m, 1H), 2.40-2.33 (m, 2H), 2.00-1.90 (m, 1H), 1.52-1 .49 (m, 1H).

Example 181

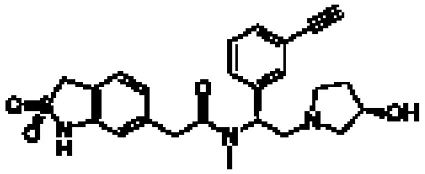
2-(2,2-4» xido-1,3-dfıydrobenzo[c]isothiazol-6-yl)-N-((S> 2-((S)-3-hydrox)pyrrolilin-1-yl)-1-(3-(5-methyl-1,2,4 oxadiazol-3-yl)phenyl)ethyl)-N-methylacetamide



IvE (ES. m/z): 512 (M+1); ^{1}H-NMR (DMSO-d_6, 300MHz): δ 7.89 (d, J=1.2 Hz, 1H), 753 **(4** J=7.5 Hz, 1H), 7.20 (d, J= 7.8 Hz, 1H), 6.86 (d, J=6.6 Hz, 1H), 6.75 (s, 1H), 5.95-5.85 (m, 0.8H), 5.25 (m, 0.2H), 4.45 (s, 2H), 4.24-4.13 (m, 1H), 3.75 (q, 7=15.6 Hz, 2H), 3.1 1 (t, 7=11.4 Hz, 1H), 2.95-2.35 (m, 11H). 2.04-1.86 (m, 1H), 1.60-1.45 (m, 1H).

Example 182

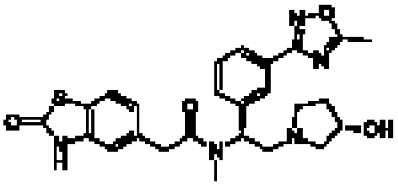
2-(2,2-dx xido-1,3-dihydrobenzo[c]isothiaml-6-yl)-N-((S)-1-(3-ethynylphenyi)-2-((S)-3-hydroxypyT rondin-1-yl)ethyl)-N-methylacetaniide



IvE (ES, m/z): 454 (M+1); ^{1}H-NMR (DMSO-d_6, 300MHz) : 5 7.38-7.18 (m, 5H), 6.85-6.75 (m, 2H), 5£45.79 (m, 1H), 4.48 (s, 2H), 4.25-4.18 (m, 2H), 3.843.65 (m, 2H), 3.18-3.03 (m, 2H), 2.842 .72 (m, 5H), 2.442 .36 (m, 2H). 2.00-1.93 (m, 1H), 1.58-1.45 (m, 1H).

Example 183

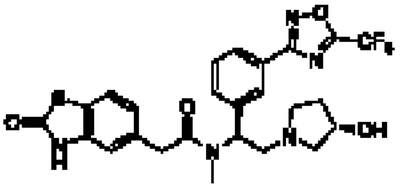
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(5-methyt l,2,4-oxadiaml-3-yl)phenyl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydrobenzo[d]thiazol-5-yl)acetamide



IvE (ES, m/z): 494 (M+l); 1H-NMR (DIvEO -di, 300MHz): 5 852-7.02 (m, 7H), 5.95-5.76 (m, 0.8H), 5.23 (m, 0.2H), 4.22-4.10 (m, 1H), 3.80 (q, 7=15.6 Hz, 2H), 3.12 (t, 7 =11.4 Hz, 1H), 2.80-2.35 (m, 11H), 2.00-1.89 (m, 1H), 1.60-1.45 (m, 1H).

Example 184

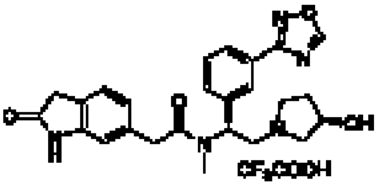
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(5-(trif v» romethyl)-1,2,4-oxadiazol-3-yl)phenyl)ethyl)-Ni meihyl-2-(2-oxo-2,3-dihydrobenzo[d]thiazolr5-yljacetaniide



IvE (ES, *mfs)*: 548 (M+l); ^{1}H-NMR (DIvEO-^ 400MHz): δ 11.84 (s, 1H), 7.99-7.93 (m, 2H), 7.62-7.41 (m, 3H), 7.04-7.00 (m, 2H), 5.95-5.91 (m, 1H), 4.91 *{s,* 1H), 4.19 (¾ 1H), 3.92-3.78 (m, 2H), 3.17-2.40 (m, 9H), 1.98-1 .92 (m, 1H), 1.54-1 .51 (m, 1H).

Example 185

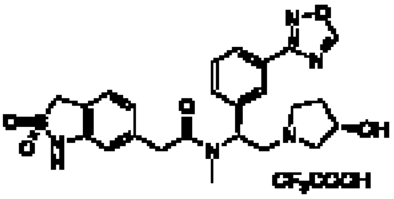
N-((S)-1-(3-(1,2,4-oxadiazol-3-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oMindolin-6-yl)acetamide 2,2,2-tr fhnroacetate



MS(ES, *m/z*): 462 (M+l), ^{1}H-NMR (DMSO-d_6, 300MHZ): S 10.40 (s, 1H), 9.95 (br, 0.5¾ 9.75 (s¾ 1H), 9.60 (br, 0.3H), 8.02 (d, *J*=5.7 Hz, 1H), 7.90 (s, 1H), 7.62 (t, *J*=8.7 Hz, 1H), 7.43 (t, *J*=5.7 Hz, 1H), 7.11 (d, *J*=5.4 Hz, 1H), 6.81 (d, *J*=5.7 Hz, 1H), 6.75 *(s,* 1¾ 6.25 (m, 1H), 5.70-5.40 (m, 1H), 4.52-3.21 (m, 13H), 2.74 (s, 3¾ 2.35-1.82 (m, 3H).

Example 186

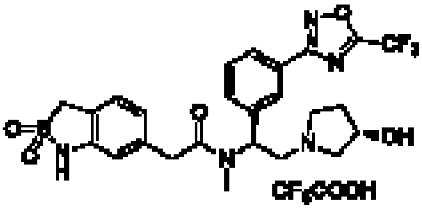
N-((S)-1-(3-(1,2,4-oxadiamt3-yl)phenyl)-2-((S)-3-hydroxypyTrolidin-1-yl)eihyl)-2-(2,2-dioxido-1,3-dihydrobenzo[c]isothiaiol-6-yD-N-methylacetamide



IvE (ES, *mfs):* 498 (M+l); ^{1}H-NMR (DMSO -d_6, 300MHz): S 10.49 (s, 1¾ 10.00 (br, 0.6H), 9.75 (s, 1H), 8.02 (d, *J*=7.5 Hz, 1¾ 7.90 (¾ 1H), 7.60 (t, *J*=7.8 Hz, 1H), 7.43 (in, 1H), 7.20 (d, *J*=7.8 Hz, 1H), 6.75 (s, 1H), 6.30-6.17 (m, 1H), 5.64-5.40 (m, 1H), 450 *(s,* 3H), 4.30-3.35 (m, 6H), 2.75 (s, 3H), 2.30-1.75 (m, 3H).

Example 187

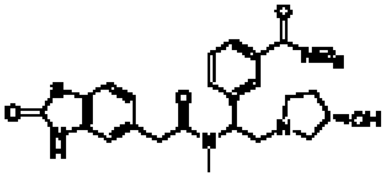
2-(2,2-dioxido-1,3-dfhydrobenzo[c]isothiazot6-y^N-((S)-2-((!^3-hy4roxyp yrrolilifv 1-yl)-1-(3-(5-(trifluoromethyi)-1,2,4-oxadiazD.r3-yl)p¾nyl)ethyl)-N-methylacetamide 2,2,2-trifhioroac etate



M5 (EΞ, *m/z)*: 566 (M+1); ^{1}H-NMR (DMSO-d_6, 400MHz): δ 10.47 (**d**, ***J*** = 4.5Hz, 1H), 10.09 (¾ 1H), 8.06 (**d**, ***J*** = 6Hz, 1H), 7.69 (**d**, ***J*** = 4.5Hz, 1H), 7.67-6.85 (m, 4H), 6.76 (¾ 1H), 6.28-6.25 (m, 1H), 5.73-5.46 (a. 1H), 4.49-3.25 (m, 11H), 2.78 (a. 3H), 2.33-1.87 (m, 3H).

Example 188

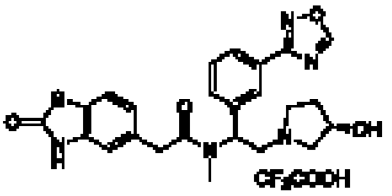
N,N-diethyl-3-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(2-oxo-2,3-dihydrobenzo [d]thiazolr5-yi)acetamido)ethyl)benEimide



MS (EΞ, *m/z*): 51123 (M+1); ^-NMR (300MHz, DMSO-d_6): 5 7.45 (d, ***J*** =4.5 Hz, 1H). 7.40-7.33 (m, 2H), 7.24-7.19 (m, 2H),7.07-7.00 (m, 2H) , 5.87-5.85 (t, J=3 Hz, 1H), 4.88-4.77 (br, 1H), 3.88-3.71 (m, 2H), 3.32 (m, 2H), 3.11-3.10 (m, 3H), 2.92-2.79 (m, 4H), 2.49-2.23 (m, 2H), 2.04-1.95 (m, 1H), 1.54 (m, 1H), 1.24-0.99 (m, 6H)

Example 189

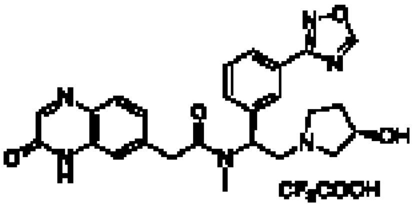
N-((S)-1-(3-(1,2,4-oxadiazol-3-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(2-OM-2,3-dihydrobenzo [d]thiazolr5 -yljacetamide 2,2,2-trifhioroacetale



MS (E5, m/s): 4S0 (M+l); H -NMR (CD$_3$OD-d_4, 300 MHz): 5 9.32 (s, 1H), S.11 (**d**, ***J*** =7.2 Hz, 1H), 7.95 (s, 1H), 7.60 (t, *J*=7.8 Hz, 1H), 7.50-7.10 (m, 4H), 6.40 (d, ***J*** =8.4 Hz, 1H), 4.60 (s, 1H), 4.35-3.50 (m, 7H), 2.82 (a. 3H), 2.50-2.00 (m, 2H).

Example 190

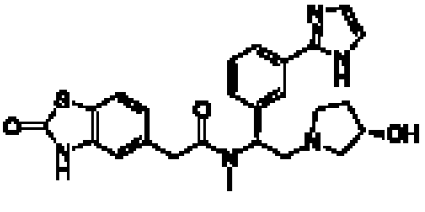
N-((S)-1-(3-(1,2,4-oxadiazol-3-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydroquinoxalin-6-yl)acetamide 2,2,2-trifluoroacetate



IvE (ES, m/z) : 475 (M+1); ^{1}H-NMR (CD$_3$OD-d+, 300 MHz) : 5 9.30 (a, IH), 8.20 (s, 1¾ 8.10 (4 J=7.5Hz, IH), 7.96 (s, IH), 7.80 (4 J=8.1 Hz, IH). 7.60 (1, J=7.S Hz, I H), 7.50-7.30 (m, 4H), 6.40 (d, J=8.7 Hz, 1H), 4.62 (s. IH), 4 35-3.40 (m, 7H), 2.85 (s, 3H), 2.50-1 95 (m, 2H). 1H-NMR (CD$_3$OD-d$_4$, 300 MHz): 5 9.30 (s, IH), 8.20 (s, IH), 8.10 (4 J=7.5Hz, I H), 7.96 (s, IH), 7.80 (4 J=8.1 Hz, IH), 7.60 (t, J=7.8 Hz, IH), 7.50-7.30 (m, 4H), 6.40 (d, J= 8.7 Hz, 1H), 4.62 (s, 1H), 4.35-3.40 (m, 7H), 2.85 (s, 3H), 2.50-1 95 (m, 2H).

Example 191

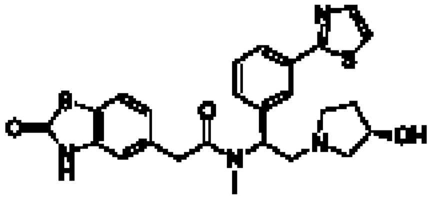
N-((S)-1-(3-(1H-imidazol-2-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydn)beiizD [d]thiazolr5-yl)acetamide



MS (ES, mfs) : 478.18 (M+1); ^{1}H-NMR (300MHz, DM3O-d$_6$): 5 7.86-7.84 (m, 2H), 7.49-7.40 (m, 2H), 7.26-7.23 (m, 2H), 7.10 (s, IH). 7.06-7 D3 (m, 2H), 5.82-5.87 (m, IH), 425-4.14 (br, 1H), 3.87 (m, IH), 3.75 (4 lH), 2.77 (m, lH), 2.74 (m, IH), 2.67 (m, IH), 2.62 (m, 4H), 2.41-2.40 (m, 2H), 2.27-2.02 (m, IH), 1.50-1.60 (m, IH).

Example 192

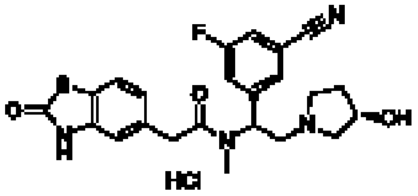
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl>-1-(3-(thiazolr2-yl)phenyl)ethyl)-N-methyl-2-(2-oxo-2,.3-dihydrohen_nj [d]thiaxolr5-yl)acetamide



IvE (ES, *m/z)*: 495.1 **(M+l)**; ^{1}H-NMR (300MHz, DMSO-d6) : 5 11.90-1 1.82 (br, 1**H)**, 7.92 (d, J=1 .5H¾ 1H), 7.85-7.78 (m, 3H), 7.48-7.39 (m, 3H), 7.10-7.03 (m, 2H), 5.87-5.85 (1, J=3Hz, 1H), 4.88-4.77 (br, 1H), 3.85 (m, 2H), 2.83 (¾ 1H¾ 2.80-2.77 (m, 5H), 2.73-2.64 (s, 1H), 2.04 1.95.(m, 1H), 1.54 (m, 1H).

Example 193

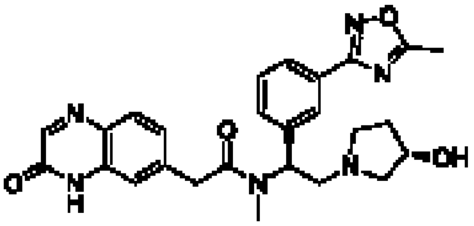
N-((S)-l-(3-cyai» -5-fluorophenyl)-2-((S)-3-hydroxypyττoϊidin-l-yi)ethyl)-N-methyl-2-(2-oxo -2,3-dihydrobeiiz>o [d]thiaxolr5- ji>acetamide hydrochioride



IvE (EΞ, *m/z*): 455 (M+l); ^{1}H-NMEt (300MHz. d6-DMSO): 5 11.90-1 1.88 (m, 1H), 9.95-10.05 (m, 1H), 7.89-7.87 (m, 1H), 7 5 8 (a. 1H), 7 .43-7.58 (m, 2H), 7.08-7.04 (m, 1H), 6.14 6.1 1 (m, 1H), 5.58-5.48 (d, 1H). 4.494.41 (m, 1H), 3.95-3 £ 2 (m, 5H), 3.56-3.43 (m, 3H), 3.27-3 .1 7 (m, 2H), 2.83 (s, 3H), 2.49-2.33 (m, 1H), 19 1-1 £ 7 (m, 1H).

Example 194

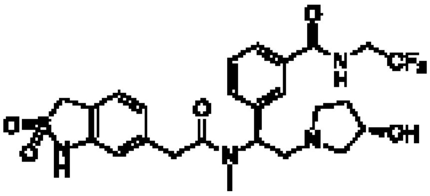
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl) ethyD-IN^methjl-2-(3-o\o-3,^dihydM quinoxalm-6-yI)acetamide



IvE (*ES, m/z)*: 489 (M+l); ^{1}H-NMR (300 MHz. DMSO-d6): *5* 12.41 *(bis,* 1H), 8.1 1 (s, 1H), 7.86-7 9 1 **(in,** 2H), 7.647.73 (m, 1H), 7.51 -7.54 (m, 2H), 7.21 -7.23 (m, 2H), 5.87-5.93 (m, 1H), 4.70-4.85 (m, 1H\ 4.17 (br¾ 1H), 3.82-3.99 (m, 2H), 3.07-3.15 (m, 1H), 2.66-2.87 (m, SH), 2.34-2.50 (m, 2H). 1.89-1 .96 (m, 1H), 1.49-1 .53 (m, 1H);

Example 195

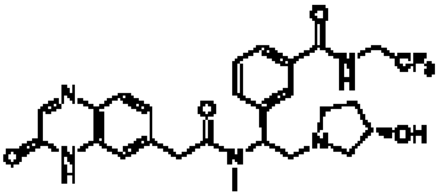
3-((S)-1-(2-(2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-6-yl)-N-methylacetamido)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-(2,2,2-trifluoroethyl)benzamide



MS (ES, m/z): 555 (M+1); ^{1}H-NMR (DMSO-ii, 400MHz) : 10.50 (a. 1H), 9.13-9.09 (m, 1H). 7.80-7 .77 (m, 2H), 7.48-7.44 (m, 2H). 7 20-7.18 (m, 1H). 6.86-6.73 (m, 2H), 5.92-5.88 (m, 1H), 5 20-5.15 (m, 1H), 4.47 (s, 2H), 4.19-4.08 (m, 3H), 3.84-3 8O (m, 1H), 3.69-3.65 (m, 1H), 3.12-3.09 (m, 1H), 2.87-2.74 (m, 2H), 2 .72 (s, 3H), 2.63 (s, 1H), 2.45-2.36 (m, 2H), 2.00-1 9 5 (m, 1H), 1.54-1 .53 (m, 1H).

Example 196

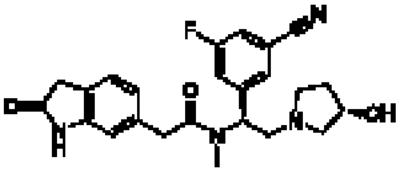
3-((¾-2-((S)-3-hydroxypyrroBdm-1-yl)-l-(N-methylr2-(3-oxo-3,^dmyidr o¾uinoxalin-6-yi)acetamido)ethyl)-N-(2,2,2-trifluoroethyl)benzamide



IvE (ES, mfs): 532 (M+1); H -NMR (DMSO-d₆, 400MHz): 5 12.39 (¾ 1H), 9.1 1-9.10 (m, 1H). 8.12 (s, 1H), 7.80-7.70 (m, 3H), 7.49-7.47 (m, 2H), 7 22-7.20 (m, 2¾ 5.90 (m, 1¾ 4.79 (m, 1H), 4.16-4.10 (m, 3H), 4.08-3.81 (m, 2H), 3.17-3.01 (m, 1H), 2.92-2.85 (m, 2¾ 2.83 (¾ 2H), 2.75 (m, 2H), 2.46 (m, 2H), 1.92 (m, 1H), 1.51 (m, 1H).

Example 197

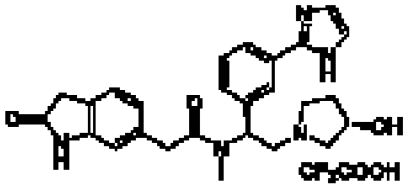
N-((S)-l-(3-cyai» -5-fluorophenyl)-2-((£^3-hydroxyp yrroliiifi- l-yl>ethyl)-N-methy]r 2-(2-oxoindolin-6-yljacetamide



MS (EΞ, ***mfs)***: 438 (M+1); ^{1}H-NMR (300MHz, DMSO-d_6): δ 10.36 (s, 1H), 7.78-7.73 (m, 1H), 7.59-7.48 (m, 2H), 7.13-7.11 (d, 1H, J=7.5Hz), 5.75 (s, 1H), 4.83 (s, 1H), 4.17 (s, 1H), 3.89-3.82 (m, 2H), 3.43 (s, 2H), 2.94-2.91 (m, 2H), 2.77 (in, 4H), 2.36-2.34 (m, 2H), 1.95-1.91 (m, 1H), 1.59-1.56 (m, 1H).

Example 198

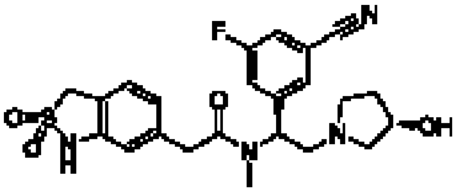
N-((S)-1-(3-(1H-imidazol-2-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetamide 2,2,2-irif uoroacelate



IvE ***{FS, m/z)***: 574.22 (M+1); ^{1}H-NMR. (300MH¾ DMSO-^): 5 7.84 (d, J=4.5Hz., 1H), 7.70-7.58 (m, 4H), 7.44 (d, J=7.5Hz, 1H), 7.11 (d, J=1.5Hz, 1H), 6.3 (d, J=1.5Hz, 1H), 6.75-6.72 (s, lH), 6.2 (d, J=1.5Hz, 1H), 4.46 (s, 2H), 3.76-3.55 (m, 4H), 3.39-3.36 (m, 4H), 2.88 (s, 3H), 2.46-1 9 6 (m, 2H).

Example 199

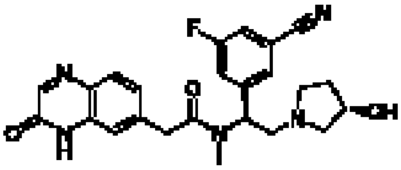
N-((S)-1-(3-cyano-5-fluorophenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-2-(2,2-dioxido-1,3-djhydrohenxD [c]isothiazol-6-yl)-N-methylacetamide



MS (EΞ, m/z): 473 (M+1); ^{1}H-NMR (300MHz, d_6-DMSO): 5 10.43 (brs, 1H), 7.78-7.75 (m, 1H), 7.61-7.49 (m, 2H), 7.21-7.18 (m, 1H), 6.85-6.82 (d, 1H, J=7.5Hz), 6.73 (s. 1H), 5.79-5.74 (m, 1H), 4.854.75 (m, 1H), 4.47 (s, 2H), 4.17 (s, 1H), 3 34-3.68 (q, 2H), 2.97-2.88 (m, 2H), 2.78-2.60 (m, 5H), 2.38-2.35 (m, 2H), 1.99-1.94 (m, 1H), 1.54 (¾ 1H).

Example 200

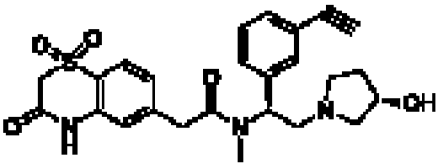
N-((S)-l-(3-cyai» -5-fluorop henyl)-2-((S)-3-hydroxyp yrrolidijı 1-yl)ethyl)-N-methyl-2-(3-oxo-i ,4-dihydroquijıoxalijı-6-yl)acetajnide



IvE (ES, m/z): (M+1) 450; ^{1}H-NMR (300MHz, d6-DM3O): 5 8.15 (s, 1H), 7.89-7.85 (m, 2H). 7.58-7 5 1 (m, 2H), 7.18 (m, 2H), 5.78-5.74 (m, 1H), 4.79-4.71 (m, 1H). 4.16 (s, 1H), 403-3.83 (m, 2H), 3.93-3.87 (m, 1H), 2.81 (s, 4H), 2.75-2.64 (m, 1H), 2.41-2.32 (m, 2H), 1.91-1.87 (m, l H), 1.63-1.58 (m, 1H).

Example 201

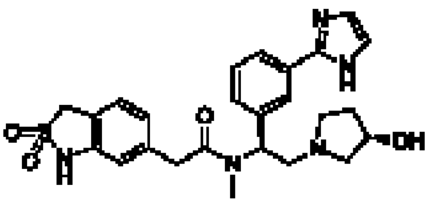
2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-1-(3-ethynyl phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methylacetamide



MT (ES, m/≤): 4S2 (M+1); ^{1}H-NMR (DMSO, 400 MHz): 5 1120-1 12 2 (m, 1H). 7.72-7.77 (in, lH), 7 35-7.44 (m, 4H), 7.17-7.21 (m, 1H), 7.10 (s, 1H), 5.79 (m, lH), 4.704.73 (m, 3H), 4.17422 (m, 2H), 3.80-3.99 (m, 2H), 2.93-3.14 (s, lH), 2.76-2.79 (m, 4H), 2.62-2.71 (m, 2H), 2.33-2.43 (m, 2H), 1.93-2.08 (m, 1H), 1.40-1.60 (m, 1H).

Example 202

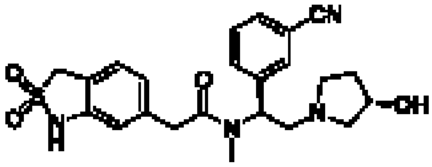
N-((S)-1-(3-(1H-imidazol-2-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-2-(2,2-dioxido-1,3-dihydrobenzo[c]isothi__ral-6-yI)-N-methylacetamide



IvE (EΞ, *mfs)*: 496 (M+l); ^-NMR (300 MHz. DMSO-d_6): 5 7.81-7.86 (m, 2H), 7.40 (1, *J*=7.8Hz, 1H), 7.13-7.25 (m, 4H), 6.85 (d, *J*=7.8Hz, 1H), 6.76 (¾ 1H), 5.85-6.00 (in, 1H), 4.46 (s, 2H), 4.20 ***(bis,*** 1H), 3.81-3.86 (m, 1H), 3.60-3.69 (m, 1H), 2.95-3.20 (m, 1H), 2.80-2.85 (m, 1H), 2.73-2.73 (m, 4H), 2.66 (s, 1H). 2.38-2.49 (m, 2H), 1.90-2.10 (m, 1H). 1.50 (br¾ 1H) .

Example 203

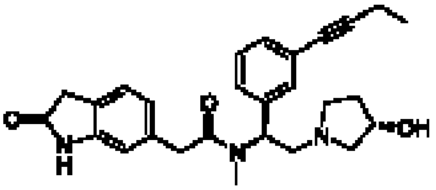
N-((S)-1-(3-cyanophenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-2-(2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-6-yl)-N-methylacetamide



MS (EΞ, m/z): 455 (M+l); ¾-NMR (DMSO-d_6, 300 MHz): 5 7.30-7.69 (m, 2H), 7.69-7.46 (m, 2H), 720 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.73 (s, 1H), 5.83-5.74 (m, 1H), 4.47 (s, 2H), 4.18 (br *s,* lH), 4.00-3.60 (m, 2H), 3.17-2.90 (m, 1H), 2.90-2.55 (m, 7H), 2.48-2.32 (m, 1H), 2.16-1.79 (m, l H), 1.60-1.40 (m, 1H).

Example 204

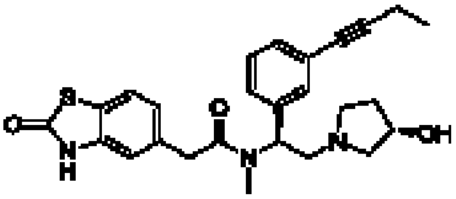
N-((S)-1-(3-(but-1-yn-1-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetamide



MS (EΞ, *m/z):* 446 (M+l^H-NMR. (DMSO-^ 300 MHz) : 5 10.34 (m, 1H), 7.36-6.90 (m, 5H), 6.90-6.70 (m, 2H), 597-5.62 (m, 1H), 4.97-4.31 (m, 1H), 4.25-4.01 (br s, lH), 337-3.55 (m, 2H), 3.42 (s, 2H), 3.20-2.36 (m, 1H), 2.83-2.62 (m, 5H), 2.43-2.22 (m, 4H), 2.01-1.84 (m, 1H), 1.65-1.40 (m, 1H), 1.29-1.08 (1, *J* = 7.5 Hz, 3H).

Example 205

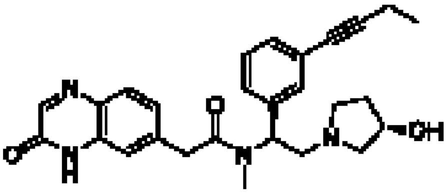
N-((S)-1-(3-(but-1-yn-1-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydrobenzo[d]thiazol-5-yl)acetamide



IvE (EΞ, *mfz)*: 464 (M+l) ; H -NMR (DMSO-d_6, 300 MHz) : 5 7.47 (d, ***J*** = 7.2 Hz, lH), 7.38-7.15 (m, 4H), 7.12-6.97 (m, 2H), 5.90-5.73 (in, 1H), 4.244.01 (m, 1H), 3 92-3 5 8 (m, 2H), 3.20-2 9 6 (s, 1H), 2.80-2.55 (m, 6H), 2.45-2.30 (m, 4H), 1.99-1 .82 (m, 1¾ 1.58-1 .45 (m, 1H), 1.21-1 .12 (t, ***J*** = 7.5 Hz, 3H).

Example 206

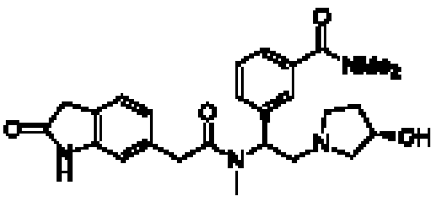
N-((S)-1-(3-(but-1-yn-1-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydi o¾uinoxalin-6-yl)acetamide



MS (ES, *m/z*): 459 (M+l); ^{1}H-NMR (DMSO-d_6, 300MHz): 5 8.1 2 (s, 1H), 7.73-7.70 (m, 1H), 7.28-7.19 (m, 6H), 5.79-5.78 (m, 1H), 4.79-4.67 (m, 1H), 4.14 (brs, 1H), 3.98-3.90 (m, 2H), 3.043.01 (m, 1H), 2.83-2.61 (m, 5H), 2.38-2 30 (m, 4H), 1.93-1 .89 (m, 1H), 1.51 (brs, 1H), 1.18-1 .13 (I, ***J***=7.5Hz, 3H).

Example 207

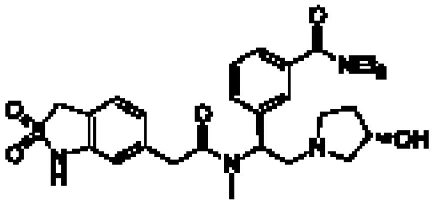
3-((S)-2-((S)-3 -hydroxypyrrohdin-1-yl)-1-(N-methyl-2-(2-oxoindolm -6-yl>afetajnido) ethyD-N,N-diniethy¾ enzamide



MS (EΞ, ***mfz):*** 465 (M+l); ¾-NMR. (DMSO-^ 400MHz): 5 7.46-7.44 (m, 2H) , 736-7.31 (m, 2H), 7.21-7.19 (m, 1H), 6.94-6 9 2 (m, 2H), 6.10-6.08 (m, 1H), 4.39-4.36 (m, 1H), 3 90-3.76 (m, 2H), 3.50-3.48 (m, 1H), 3.33-3.30 (m, 2H), 3.12-3.10 (m, 3H), 3 D3-2 9 0 (m, 5H), 2.842 .76 (m, 4H), 2.64-2.50 (m, 2H), 2.16-2.13 (m, 1H), 1.73 (m, 1H)

Example 208

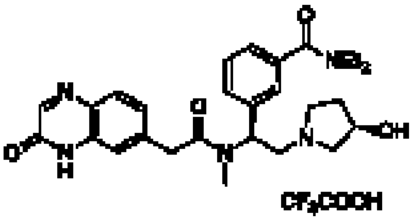
3-((S)-1-(2-(2,2-d» xi l o-1,3-dihydrobenzo [c]isothia™t6 -yl)-N-ni ethylacetajni l o)-2-((S)-3-hydroxyp yrrolidiri-l -yl)ethyl)-N,N-diethyl)eiixarnide



IvE (EΞ, m/z): 529 (M+l); ^{1}H-NMR (DIvEO-^ 400MHz): 5 10.43 (tars, 1H), 7.42-7.33 (m, 2H), 7.25-7.20 (m, 3H), 6.85-633 (m, 1H), 6.75 (s, l H), 5.89-5 £ 5 (m, 1H), 4.48 (s, 2¾ 4.19 (tars. 1H), 3.83-3.66 (m, 2H), 3.40 (m, 2H), 3.23-3.13 (m, 3H), 2.86-2.51 (m, 6H), 234-2.33 (m, 1H), 2.00-1 .95 (m, I H), 1.54 (brs, 1H), 1.14-1 .01 (m, 6H).

Example 209

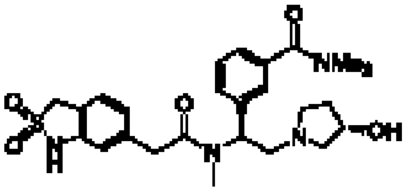
N,N -diethyl-3-((S)-2-((¾-3-hydroxypyrrolidin-l -yl)-1-(N-methyl-2-(3-OXO-3,4-dihyd roquinoxalin-6-yl)acetamido)ethyl)benzamide 2,2,2-trifluoroacetate



IvE (EΞ, m/z): 620 [M+H-CF$_3$COOH]$^+$; ^{1}H-NMR (D$_2$O, 300MHz): 5 8.13 (s, lH), 7.72-7.69 (d, J=8 .4Hz, 1H), 7.44-7.34 (m, 1H), 7.29-7.20 (m, 4H). 6.87 (s. 1H), 6 .19-6.15 (in, 1H). 4.784.75 (m, 1H), 4.10-3.78 (m, 5H), 3.64-3.19 (m, 4H), 3.01-2.94 (m, 2H), 2.89 (s, 3H), 2 .34-1 98 (m, 2H), 1.08-1 .03 (t, J=7 .2Hz, 3H), 0.75-0.70 (t, J=7 .2Hz, 3H).

Example 2 10

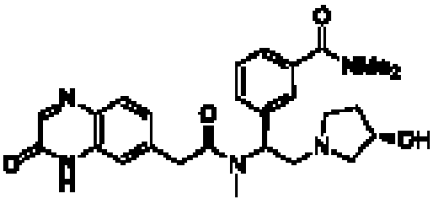
3-(($- 1-(2-(2,2-d»xilo -1,3-dihydrvbenzo [c]isothiazol-6 -yl)-N-methylacetam-ko)-2-((S)-3-hydroxyp yrriolidiri-l -yl)ethyl)-N,N-dijnethylbenzamide



IvE (ES, m/z): 501 (IvI+1); H -NMR (DMSO-d_6, 300MHz): δ 7.40-7.38 (s, 2H), 7.36-7.34 (s, 2H), 7 20-7.18 (in, 1H), 6.84-6.83 (s, 1H), 6.74 (m, 1H), 5.86 (m, 1H), 4.47 (m, 2H), 4.18 (m, 1H), 3.32 (m, 1H). 3.73-3.67 (s, 1H), 3.03 (s, 1H), 3.05 (s, 3H), 2.93-2 S5 (s, 3H), 2.82-2.80 (m, 2H), 2.S3 (s, 3H), 2.51 (s, 1H) ,2.43-2.36 (s, 2H), 1.92 (s, 1H), 1.42 (s, 1H) 1.12 (s, 1H).

Example 211

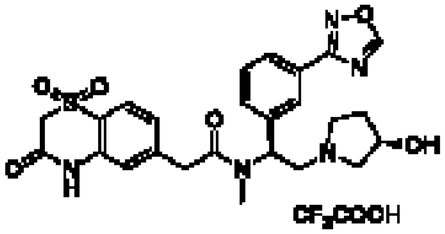
3-((S)-2-((S)-3-hydroxypyrrolidin-l-yl)-1-(N-mf thylr2-(3-oxo-3,4-dihydroquinoxalin-6-yl)acetamido)ethyl)-N,N-dimethylbenzamide



IvE (EΞ, m/s): 478 (M+1); ^{1}H-NMR (DMSO-rfi, 300MHz): 12.43-12.27 (m, 1H), 3.13 (s, 1H), 7.76-7.68 (m, 1H), 7.35-7.03 (m, 6H), 5.87 (m, 1H), 4.83-4.63 (m, 1H), 4.15 (s, 1H), 3.88-3.72 (m, 2H), 3.18-2.76 (m, 12H), 2.01 -1.88 (m, 1H), 1.53 (s, 1H).

Example 212

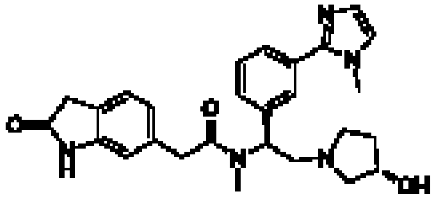
N-((S)-l-(3-(l,2,4-oxadi™ J3-yl)phenyl)-2-((S)-3-hydrf xypyrrolidin-l-yl)ethyl)-2 (l, 1-dioxido-3-oxo-3,4-dihydro-2H-heiu» [b][l,4]thjaim-6-yi)-N-methylaceta_niide2,2,2-trifhioroacetate



IvE (EΞ, m/z): 526 [IvI+H-CF3COOH]$^+$; H -NMR (DMSO-d_6, 300MH z): 5 11.30 (s, 1H), 9.75 (s, 1H), 8.05-8J02 (d, 1H), 1 9 1 (m, 1H), 7.58 (s, 1H), 7.73-7.77 (m, 1H), 7.75-7.66 (m, 1H), 7.64-7.61 (m, 1H), 7.27-7.21 (m, 1H), 7.17-7.1 1 (m, 1H), 6.26-6.22 (m, 1H), 5.58-5.48 (m, 1H), 4.72 (s, 2H), 4.51-4.42 (m, 1H). 4.25-4.17 (m, 1H), 3.95-3.82 (m, 5H), 3.70-3.52 (m, 2H), 2.80 (*s*, 3H), 2.49-2.27 (m, 1H), 230-2 2 6 (m, 2H).

Example 2 13

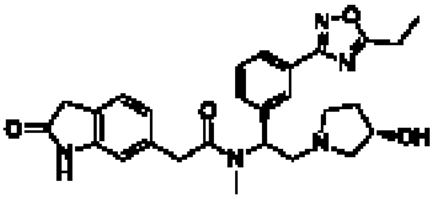
N-((S)-2-((S)-3-hydroxyp yrntlidm- 1-yl>-1-(3-(1-methyl-1H-imida™l-2-yl)phenyl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetamide



IvE (EΞ, *m/z*): 474 (M+l); 1H-NMR (DIvEO-d_6, 300MHz) : 510.415 (1H, s), 7.590-6.760 (9H, m), 5.924 (lH,br), 4.894 (1H, m), 4.199 (1H, m), 3£23 (IK m), 3.785 (3H, s), 3.703 (1H, m), 3.436-2.520 (11H, m), 1.990 (1H, m), 1.524 (1H, m).

Example 2 14

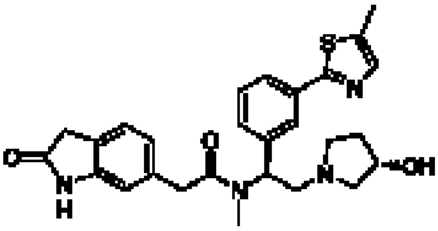
N-((S)-1-(3-(5-ethyl-1,2,4-oxadiaz»l-3 -yl)p¾nyl)-2-((S)-3-hydroxyp yrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetamide



IvE (EΞ, m/z): 490 (IvI+1); ¾ -NMR (DMS0 -d_6, 300MHz): 510.41-10.28 (m, 1H), 7.93 (m, 2¾ 7 J61 -7.43 (m, 1H), 7.14 (m, 1H), 608-6 .75 (m, 2H), 593 (m, 1H), 4.95 (¾ 1H), 4.13 (m, 1H), 3.83-3.58 (m, 2H), 3.34 (m, 2H), 3.1 1-2.92 (m, 3¾ 2.83-2.59 (m, 6H), 2.51 -2.33 (m, 2H), 1.92 (m, 1H), 1.31 (m, 3H).

Example 2 15

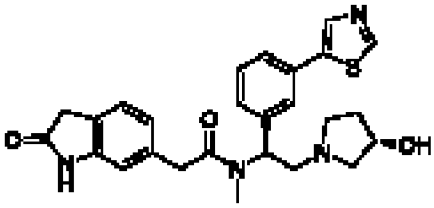
N-((S)-2-((S)-3-hydroxyp yrntlidm- 1-yl>-1-(3-(5-methylthiazol-2-yl)p¾nyl)ethyl)-N-methyl-2-(2-oM mdo lin-6-yl)acetamide



IvE (E.S, m/z): 49 1 (M+1); H -NMR (300MHz, DMSO-di): δ 10.38 (s, 1H). 7 .76-7.74 (d, *J* = 8¾ 1H), 7.61-7.60 (d, *J* = 4Hz, 1H), 7.12-7.10 (d, *J* = 8H¾ 1H), 6.82 (t, *J*=6¾ 2H), 5.93-5.89 (m, 1H), 4.904.89 (s, 1H). 4.20 (s, 1H). 3.83-3.67 (m, 1H). 3.43 (s, 2H), 3 3 4 (s, 3H), 3.13-3 .08 (m, 1H), 2.85-2.73 (m, 6¾ 242-2.40 (m, 1H), 1.53 (m, 1H).

Example 2 16

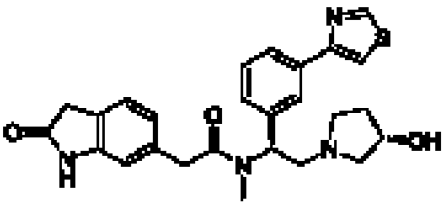
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(thiazol-5-yl)phenyl)ethyl)-N-methyl-2-(2-oxoindoKiirfi-yl)acetamide



IvE (ES, m/z): 477 (M+l); 'H -NMR (300MHz, DMSO-_i): 5 10.40-10 30 (in, 1H), 9.08 (s, 1H), 8.23 (s, 1H). 7.63-7.7.55 (m, 1H), 7.48-7.37 (m, 2H), 7.32-7.22 (m, 1H), 7 .1 5-7.05 (m, 1H), 6.86-6.75 (m, 2H), 5.94-5.80 (m, 1H). 4.95-4.85 (m, 1H), 4.254.10 (m, 1H), 3.91-3.62 (m, 2H), 3.45-3.40 (m, 2H), 3.18-3.00 (m, 1H), 2.87-2.71 (m. 5H), 2.63-2.59 (m, 1H), 2.46-2.35 (m,2H), 2.05-1.89 (m, 1H), 1.60-1 .45 (m, 1H).

Example 2 17

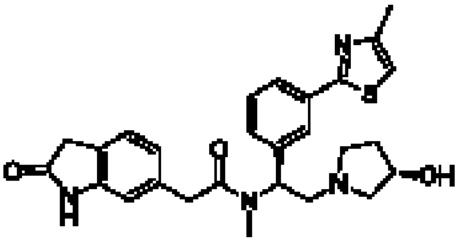
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(tlώ ™l-4-yl)phenyl)ethyl)-N-methyl-2-(2-oxoindolinr6-yl)acetamide



IvE (EΞ, m/z): 477 (M+1); ^{1}H-NMR (300MH¾ **DIvEO-d**): δ 10.40-1 0.30 (m, 1H), 9.20-9.19 (m, 1H), 8 .1 2 (s, 1H), 7.82-7.91 (m, 2H), 7 .48-7.37 (m, 1H). 7.28-7.18 (m, 1H), 7.15-7.05 (m, 1H), 6.86-6.75 (m, 2H), 5.97-5.85 (m, IH), 4.95-4.85 (m, IH), 4.25 4.10 (m.lH), 3.91-3.62 (m, 2H), 3.45-3.40 (m, 2H), 3.18-3.00 (m, IH), 2.87-2.71 (m. 5H), 2.63-2.59 (m, IH), 2.46-2.35 (m, 2H), 2.05-1.89 (m, IH), 1.60-1 4 5 (m, IH).

Example 2 18

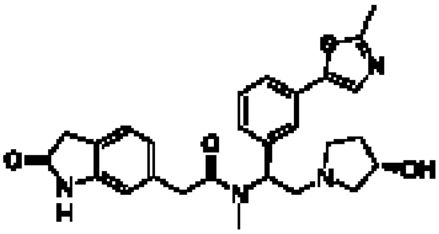
N-((S)-2-((S)-3-hydroxypyrntlidm-1-yl>-1-(3-(4-methylthiazol-2-yl)p¾nyl)ethyl)-N-methyl-2-(2-oMindoli n-6-yl)acetamide



IvE (ES, m/z): 491 (M+l); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.36 (m, IH), 7.82-7.71 (m, 2H), 7.48-7.37 (m, 2H), 7.32 (s, 1H), 7.12-7.08 (in, IH), 6.84-6 .75 (m, 2H), 5.97-5.83 (m, IH), 4 9 54.85 (m, 1¾ 4.254.12 (m, IH), 3.32-3.61 (m, 2H), 3.45-3.40 (m, 2H), 3.30 (s, 3H). 3.18-3.00 (m, 1¾ 2.85-2.71 (m, 4H), 2.63-2.63 (m, IH), 2.42 (s, 3H), 2.05-1.89 (m, IH), 1.60-1 .47 (m, IH).

Example 2 19

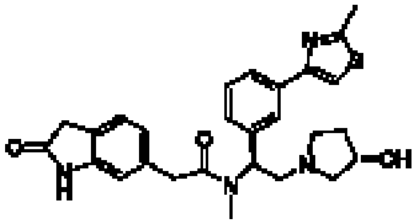
I^(S)-2-((^3-hydroxyp yriolidm-1-yl)-1-(3-(2-methylthiazol-5-yl)phenyl)ethyl)-N-methyl-2-(2-oMmdoli n-6-yl)acetajnide



IvE (ES, m/z): 491 (M+l); 1H-NMR (400MHz, DMSO-d_6): 5 10.37 (s, IH), 7.98-7.94 (s, IH), 7.50-7.51 (d, J=7.6Hz, I H), 7.37-7.41 (m, 2H), 7.21-7.27 (m, IH), 7.07-7.15 (m, IH), 6.79-6.85 (m, IH), 5.35-5.39 (m, IH), 4.88 (s, IH), 4.20 (s, IH), 3.68-3.37 (m, 2H), 3.43 (s, 2H), 3.32-3 3 4 (d, J = SHz, IH), 3.07-3.12 (m, IH), 2.88-2.90 (m, 2H), 2.74-2.81 (m, 2H), 2.6S (s, 3H), 2.59-2 .64 (s, 1H), 2.42-2.51 (m, 2H), 1.96-2.00 (m, IH) , 1.54 (m, 1H).

Example 220

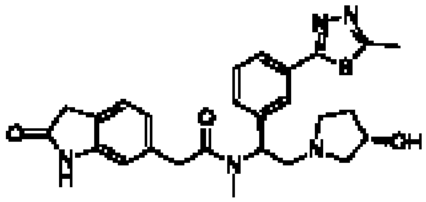
N-((S)-2-((S)-3-hydroxypyriolidm-1-yl)-1-(3-(2-methylthiazol-4-yl)phenyl)ethyl)-N-methyl-2-(2-oxDindolin-6-yl)acetamide



MS (EΞ, m/z): 491 (M+1); H -NMR (400MHz. DMSO-^: 5 10.36 (m, 1H), 7.86-7.79 (m. 2H), 7 3 8 (s, 1H), 7.22-7.10 (m, 1H), 6.83-6.75 (in, 2H), 5.93-5 88 (m, 1H), 4.90-4.68 (m, 1H), 4.19 (m, 1H), 3.82-3.77 (m, 1H), 3.67-3.62 (m, 1¾ 3.41-3.32 (m, 2H), 3.30-3.14 (m. 1H). 2.94-2.76 (m. 2H). 2.76-2 .7 1 (m. 6H), 2.64 (m. 1H¾ 2.50-2.41 (m. 1H), 2.00-1 .91 (m, 1H), 1.50 (m, lH).

Example 221

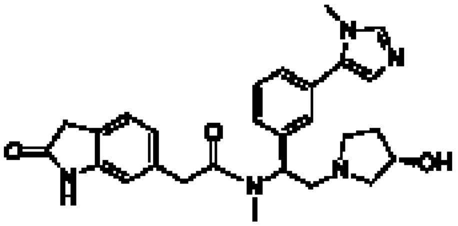
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(5-methyl-1,3,4-thiadiazDl-2-yl)phenyl) ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetamide



MS (EΞ, m/s): 492 (M+1); ^{1}H-NMR (300MH¾ DMSO-d_6): 5 10.37 (brs, 1H), 7.83-7.77 (m, 2H), 7.52-7.46 (m, 2H), 7.13-7.1 1 (m, 1H), 6.84-6.77 (m, 2¾ 5.944.71 (m, 1H), 4.25-4.14 (brs, 1H), 3.85-3 6 8 (m, 3H), 3.60-3.02 (m, 5H), 2.81-2.78 (m, 8H), 2.68-2.34 (m, 1H), 2.28-1.98 (m, I H), 1.60-1 .55 (m, 1H).

Example 222

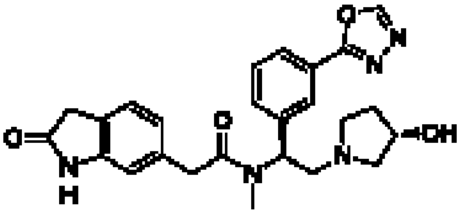
I^(S)-2-((^3-hydroxyp yriulidm-1-yl)-1-(3-(1-meihyJr1H-im-daznlrS-yl)pheriyl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetamide



IvE (EΞ, *m/z*): 514 (MM); 1H-NMR (300MH.; DM3O-*di*): *5* 10.41-1 0.28 (m, 1H). 7.74-7.63 (m, 1H), 7.48-7.31 (m, 2H), 7.31-7.19 (m, 2H), 7.14-7.03 (m, 1H), 7.03-6.91 (m, 1H), 6.88-6.70 (m, 2H), 5.98-5.80 (m, 1H), 4.954.85 (m, 1H). 4.25-4.08 (m, 1H). 3 .89-3 5 8 (m, 5H), 3.46-3 3 7 (m, 2H), 3.16-2.97 (in, 1H), 2.90-2.80 (m, 2H). 2.79-2.72 (m, 3H), 2 6 2 (m, 1H). 2.46-1 3 1 (m, 2¾ 2.03-1 .88 (m, l H), 1.62-1 .49 (m, 1H).

Example 223

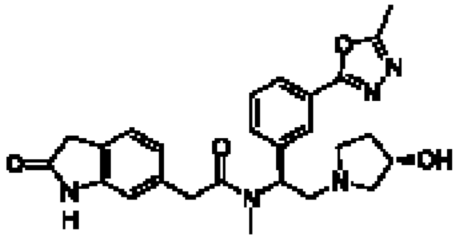
N-((S)-1-(3-(1,3,4-oxadiazol-2-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxo.ndoli n-6-yl)acetamide



MS (EΞ, *mfs*): 462 (M+1); ^{1}H-NMR (300MHz, DMSO-*d6*): δ 10.36 (*s*, 1H), 9.34 (*s*, 1H), 7.95-7.89 (m, 2H), 7.72-7.45 (m, 2H), 7.12-7.10 (d, *J*=7.5Hz, 1H), 6.88-6.68 (m, 2H), 5.96-5.90 (m, 1H), 4.91-4.89 (**d**, *J*=3.9Hz, 1H), 4.19 (bn¾ 1H), 3.84-365 (m, 2H), 3.42 (s, 2H), 3.18-3 0 3 (m, 1H), 2.89-2.74 (m, 6H), 2.51 -2.40 (m, 2H), 1.98-1 .93 (m, 1H). 1.53 (m, 1H).

Example 224

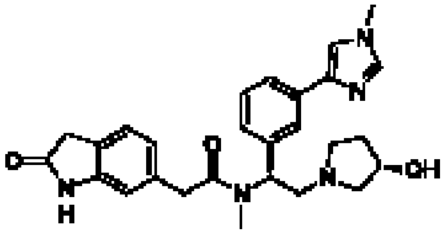
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)ethyl)-N-methyl-2-(2-oxomdolin-6-yl)acetamide



MS (ES, *mfs)*: 476 (M+l); ^{1}H-NMR (300MHz. DMSO-^: 5 10.36 (s, 1H), 7.90-7.84 (m, 2H), 7.72-7.40 (m, 2H), 7.12-7.07 (m, 1H), 6.83-6.70 (m, 2H), 5.96-5.90 (m, 1H), 4.91-4.89 (d, *J*=3.9Hz, 1H), 4.19 (bis, 1H), 3.84-3.60 (m, 2H), 3.42 (s, 2H), 3.18-3.09 (m, 1H), 2.89-2.73 (m, 6H), 2.64 (s, 3¾ 2.51-2.40 (m, 2H), 198-1.91 (m, lH), 1.53 (m, 1H).

Example 225

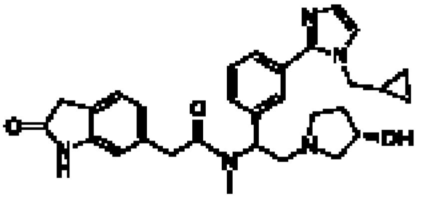
N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(1-methyl-1H-imidazol-4-yl)phenyl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetamide



MS (ES, *m/z):* 474 (M+1); ^{1}H-NMR. (400MHz, DMSO-^: 5 10.35-10.37 (s, 1H), 7.48-7.63 (m, 4H), 7.29-7.32 (t, 1H;J=15.6HZ), 7.02-7.12 (m, 2H), 6.78-6.83 (m, 2H), 5.92-5.93 (s, 1H), 4.97 (s, 1H), 3.79-3.83 (m, 1H), 3.69-3.80 (m, 2H), 3.61-3.65 (m, 4H), 3 5 1 (m, 2H), 3.42 (¾ 1H).2 £2-2.98 (m, 3H), 2.65-2.77 (m, 3¾2.68 (¾ 2H), 1.98-2.00 (m, l H), 1.55 (m, 1H).

Example 226

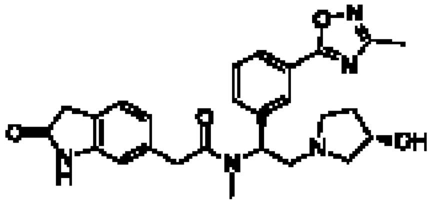
N-((S)-1-(3-(1-(cyclopropylmethyl)-1H-imidazol-2-y^heny]>2-((S)-3-hydroxy pyrrolidin-1-yl)ethyl)-r+ methyl-2-(2-oM indolin-6-yl)acetamide



MS (EΞ, m/≤): 514 (M+l); 1H-NMR (300MHz, DMSO-d_6): 5 10.41 (s, 1H), 7.55-7.41 (m, 3H), 7.40-7.25 (m, 2H), 7.15-7.05 (m, 1H), 6.99 (m, 1¾ 6.83-6.73 (m, 2H), 5.95-5.85 (m, 1H), 4954.85 (m, 1¾ 4.25-4.08 (m, 1H), 3.90-3.60 (m, 4H), 3.41 (¾ 2H), 3.13-3.01 (m. 1H), 2.87-2.75 (m, 2H), 2.72 (s, 3H), **2.63** (s, lH), 2.45-2.35 (m, 2H), 2.07-1.85 (m, 1H). 1.60-1.42 (m, 1H), 1.12-1.00 (m, 1H), 0.50-0.40 (m, 2H), 0.30-0.15 (m, 2H).

Example 227

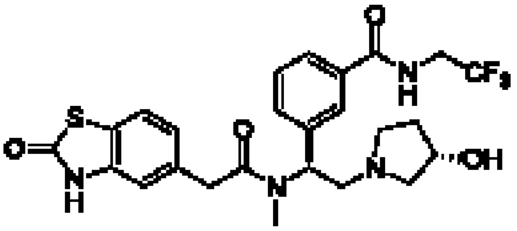
N-((S)-2-((^3-hydroxyp yrrondin- 1-yl)-l-(3-(3-methyJr l,2,4-oxadiaz>ol-5-y¾ henyl) ethyD-N-methyi-2-(2-oxomdolin-6-yl)acetamide



IvE (ES, m/z): 476 (M+l); ^{1}H-NMR (300MHz. DMSO-iJJ: 5 10.35 (s, 1H), 7.98-7.94 **(m,** 2H), 7.61 (m, 2H), 7.12-7.09 (m, 1H), 6.83-6.81 (m, 2H), 5.92 (m, 1H). 4.85 (s, 1H), 4.17 (brs, 1H), 3.S4-3.70 (m, 2H), 3.42 (s, 2H), 3.1 2-3.05 (m, 1¾ 2.81 -2.63 (m, 6H), 2.49-2.42 (m, 5H), 1.99-1 .93 1 (m, 1H), 1.52 (m, 1H).

Example 228

3-((S)-2-((S)-3-hydroxyp yrrotidin- 1-yJ)-l-(N-methylr2-(2-oxo-2 ,3-dfliydroh enzo[d] thiazol-5-yl)acetairudo)ethyl)-N-(2,2,2-trif]UDToethyl)b emamide



M5 (ES, m/z): 537 (M+l); ^{1}H-NMR (400MHz, DMSO-ii$_6$): 5 11.82 (s, 1H), 9.13-9.10 (m, 1H), 7.81-7.79 (m, 2H), 7.48-7.45 (m, 3H), 7.0S (s, 1¾ 7.04-7.01 (m, 1H), 5.92-5.88 (m, 1H), 5.20 (m, 1H), 4.68 (m, 1H), 4.18-4.05 (m, 3H), 3.92-3 £8 (m, 1H). 3.86-3.70 (m, 1H). 3.15-3.09 (m, 1H), 2.84-2.80 (m, 2H), 2.76 (s, 2H), 2.74-2.63 (m, 1H), 2.43-2.33 (m, 2H),1 .98-1 .93 (m, 1H),1 .52-1 .51 (m, 1H).

Example 229

In vitro assay to evaluate potency of KOR agonists of formula (I) using IF- One assay

The potency of the test compounds to the human KOR receptor was determined by performing dose-response experiments in COS-7 cells transiently transfected with the human KOR receptor cDNA using IP-One HTRF assay.

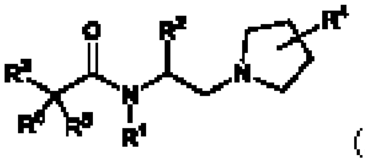
IP-One assay: One day following tiansfection cells were seeded in ½-area 96 well plates (Corning Costar, #675083) with 40,000 cells/well in DMEM medium supplemented with 10% fetal calf serum, 2 mM glutamine and 0.01 mg/ml gentamicin The following day, media was aspirated and 50 µï Stimulation buffer (10 mM HEPEΞ, 1 mMCaClj, 0.5 mM MgClj, 4.2 mM KCl, 146 mM NaCl, 5.5 mM glucose, 50 mM LiCL 0.1% BΞA, pH 7.4) were added to each well. Test compurds were dissolved in DMS0 in various concentrations and 1 µl was added to each well to stimulate cells. Following an incubation of about 60 minutes at 37 °C, 10 µI_ IPl -d2 (Cisbio) and 10 µï anti IPl -Cryptate (Cisbio) were added to each well. Plates were incubated at about 20-35"^ for a minimum of 60 minutes and counts d on HTRF compatible Alpha-Fusion (Packard). Determinations were made in duplicates. EC50 values were calculated using AssayExplorer 3.2 (Symyx), a standaid pharmacological data handling software. Using this protocol, various compounds as described in Table 4 defined above were found to exhibit KOR agonistic activity.

Using this protocol, various compounds as described herein were found to exhibit binding affinity towards KOR. For instance, examples 2, 5, *6*, 7, 12, 15, 16, 18, 19, 20, 22, 23, 24, 25, 26, *29*, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 45, 46, 52, 53, 59, 55, 56, 57, 58, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 82, S3, 84, 85, 86, 87, 88, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 113, 114, 115, 116, 117, 118, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 193, 194, 195, 196, 198, 199, 200, 201, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, and 228 as described herein, exhibited a KOR agonistic binding in-vitro EC_{50} values of less than or equal to 50 nM; examples 1, 4, 21, 27, 36, 44, 48, 50, 61, 90, 112, 138, 197 and 202 as described herein exhibited a KOR agonistic binding in-vitro EC_{50} values between 51-100 nM; examples 3, 9, 10, 17, 28, 47, 51, 89, 165 and 192 as described herein exhibited a KOR agonistic binding in-vitro EC50 values between 101nM -1 µM; and examples 8, 11, 13, 14, 30 and 49 as described herein exhibited a KOR agonistic binding in-vitro EC_{50} values greater than or equal to 1 µM.

Although the present application has been illustrated by certain of the preceding examples, it is not to be construed as being limited thereby, but rather, the present application encompasses the generic area as hereinbefore disclosed. Various modifications and embodiments can be made without departing from the spirit and scope thereof For example, the following compounds are also included in the scope of the present application

What is claimed is:

1. A compound of formula (I),



(I)

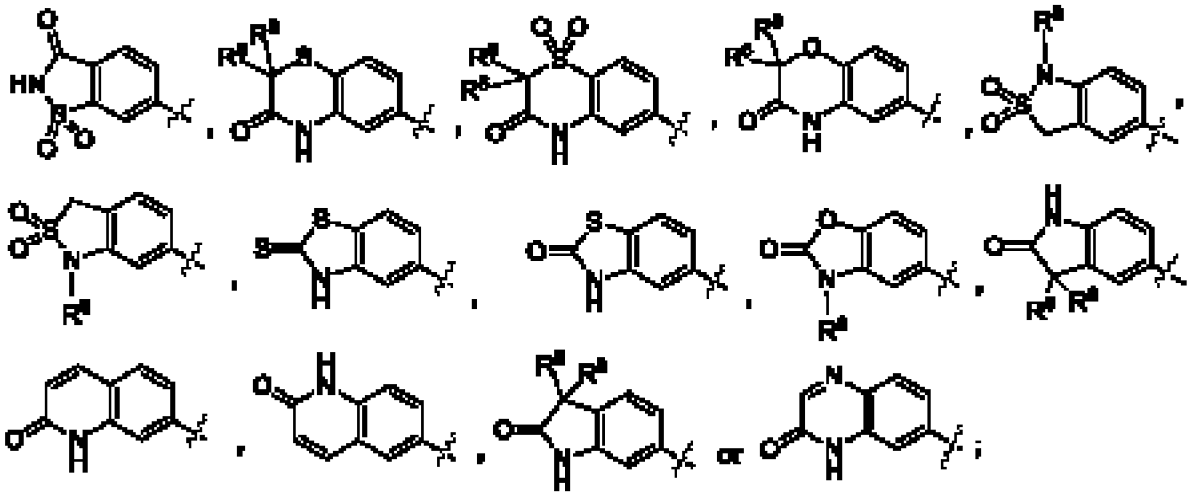
stereoisomers thereof or pharmaceutic ally acceptable salts thereof;

wherein,

R^1 represents hydrogen, alkyl, haloalkyl or -(CH2)$_m$-cycloalkyl;

R^2 represents (1) cycbalkyL, (2) an group selected from heterocyclyL heteroaryl or aryL wherein such group is optionally substituted with 1 to 3 substituents selected independently from cyano, hydroxy!, alkyl, alkynyL alko.iy, habgen, habalkyl, habalkoxy, -COOR^4, -CONR^{e}R^f, -O-(CH$_2$)$_n$-R^7 or R^{11};

R^3 is an optionally substituted group selected from



Optional substituent on R^3, in each occurrence, independently selected from habgen, alkyl or habalkyl;

R^+ is selected from hydrogen, hydroxy!, habgen, alkyl, alkoxy, or haloalkyl;

R^5 andR', each are independently selected from hydrogen or alkyl;

R^7 is selected from cyano, tetrazolyl, -COOR^4, -C0 NR^{e}R^f or  ;

R^8, in each occurrence, is independently selected from hydrogen, halogen, alkyl or $-(CH_2)_q-R^9$;

R^9 is $-COOR^a$ or  ;

R^{10} is selected from hydrogen, cyano, $-COOR^c$, $-CONR^eR^f$ or tetrazolyl;

R^{11} is selected from (1) (C_3-C_6)cycloalkyl, benzyl,  or (2) 5-6 membered heteroaryl optionally substituted with 1 to 2 substituents selected independently from alkyl, haloalkyL haloalkoxyor $-(CHj)_m-(C_3-Ci)$cycloalkyl;

R^a and R^c,in each occurrence, independently selected from hydrogen, alkyl, heterocyclyi or heteroaryl;

R^b, in each occurrence, irdependently selected from hydrogen, alkyl or alkoxy,

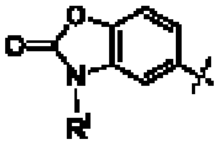
R^6, in each occurrence, independently selected from hydrogen, alkyl, haloalkyl or $-S(0)_2$-alkyl;

R^f, in each occurrence, independently selected from hydrogen or alkyl;

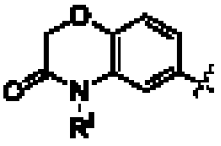
m is selected from 0, 1, 2, 3 or 4;

nand ¾ eachindeperdently selected from 1 or 2;

provided that when R^2 is pihenyl optionally substituted with alkyL alkoxy or halogen, R^1 is alkyl and one of R^J and R^4 represents hydrogen, then R^3 does not represent the following rings



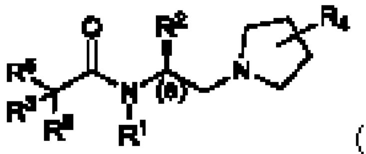
or



;

wherein R^i, in each occurrence, represents hydrogen or alkyl.

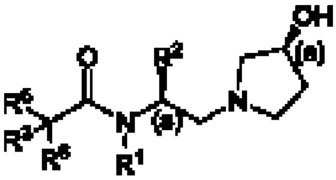
2. The compound according to claim 1, having the formula (lb),



(Ib)

stereoisomers thereof or pharmaceutically acceptable salts thereof

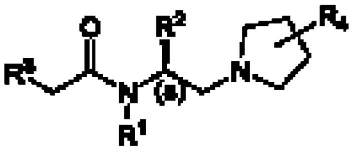
3. The compound according to claim 1, having the formula (Ib^,



(Ib^1)

stereoisomers thereof or pharmaceutically acceptable salts thereof

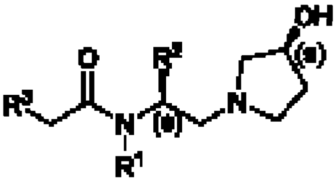
4. The compound according to claim 1, having the formula (Ic),



(Ic)

stereoisomers thereof or pharmaceutically acceptable salts thereof.

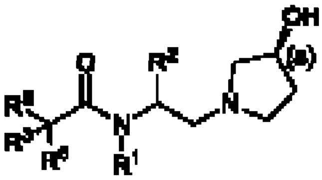
5. The compound according to claim 1, having the formula (Ic^1),



(Ic^1)

stereoisomers thereof or pharmaceutically acceptable salts thereof

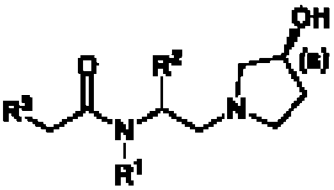
6. The compound according to claim 1, having the formula (Id),



(Id)

stereoisomers thereof or pharmaceutically acceptable salts thereof

7. The compound according to claim 1, having the formula (Id^1),



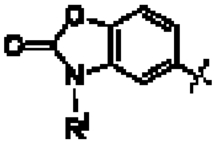
(Id^1)

stereoisomers thereof or pharmaceutically acceptable salts thereof

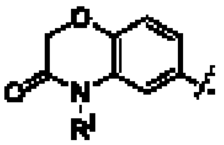
S. The compound according to claim 1,

wherein R^2 is phenyl optionally substituted with 1 to 3 groups independently selected from cyano, hydroxy., alkyl, alkynyL, alkoxy halogen, haloalkyL, haloalkoxy, **-COOR^4, -CONR^{e}R^f, -0 -(CH$_2$)$_n$-R^7** or **R^{11}** ; and all other groups are as defined in formula **(I);**

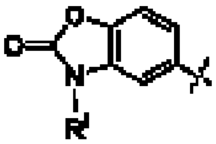
provided that when R^2 is phenyl optionally substituted with alkyl, alkoxy or halogen R^1 is alkyl and R^5 and R^6 independently represents alkyl, then R^3 does not represent the following rings



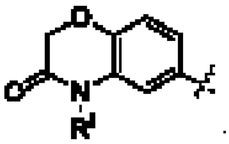
or



, wherein, in each occurrence, R^i represents hydrogen or alkyl.



or

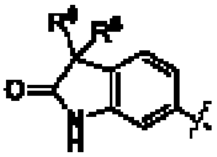


;

wherein, R^i represents hydrogen or alkyl.

9. The compound according to claim 1, wherein R^t represents hydrogen or hydroxy!.

10. The compound according to claim 1, wherein R^3 represents



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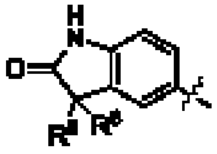
11. The compound according to claim 1, wherein R^3 represents



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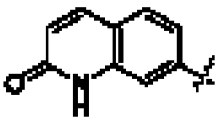
12. The compound according to claim 1, wherein R^3 represents



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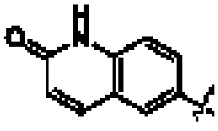
13. The compound according to claim 1, wherein R^3 represents



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14. A compound selected from

N-((S)-2-((S)-3-hydo xypyr o lidirL-l -yl)-l -phenylethylJ-N-methyl-S-(2-oxoindolin-6-yi)acetamide;

N-[(1Ξ)-2-[(3Ξ)-3-hydroxypyrrolidin-1-yl]-1-phenylethyl]-2-(3-oxo-3,4-dihydro-2H-l,4-be1™ xazin-≤-5l)acetamide;

N-((S)-2-((S)-3-hydo xypyra lidirL-l -yl)-l -phen^ieth^l)-N-meth^l-2-(3-OKO-3,4-dihydroquinoxalin-6-yl)acetamide;

(S)-2-(2-o io-2,3-dihyi ob eirao[d] thiamin -yl)-N-(1-phenyl-2-(pyrrolidm-1-3ii)etl^)acetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benao[b] [1,4] thiazin-6-yl)-N-((S)-2-((Ξ)-3-hydroxypyrrolidin-1-*yi)* -1-(3-(tri fuoromethoxy)phenyl)ethyl)-N-methylacetamide;

N-((Ξ)-1-(3-cyanophenyl)-2-((S)-3-hydroxypyrrd idin-l -yl)ethyl)-2-(1, 1-dioxido-3-oxo-3,4-dih^dro-2H-benzo[b] [1,4]thiazin-6-yl)-N-iMthylacetamide;

N-((Ξ)-2-((Ξ)-3-hyda xypyrrolidirL-1-yl)-1-phen5leth5l)-N-meth5l-2-(3-oxo-3,4-dihydro-2H-benzo[b] [1,4] thiazin-6-yl)acetamide;

2-(1,1-dioxido-3-oxo-2,3-dihy?l-obenzo[d] isothiazol-i -yl)-N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methykcetamide ;

2-(2,*2*-dioxido-1,3-dihydrobenzo[c]isothiazol-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(trifluoro methyl) pl¾nyl)ethyl)-N-ітіethylacetamide;

5-(2-(((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-l-*yi)*- 1-phenylemylX memyl)amiiM)-2-oxoe1hyl) -1,*3*-dih^drobenao[c] isothiaml-l -iuin 2,2-dioxide 2,2.2-trifluoiOacetate;

N-((S)-1-(3-(difluoa methoxy)phenyl)-2-((3) -3-hydroxypya didin-1 -;ji)ethyl)-2-(1,1-dioxido-3-oxo-3,4-dihydiO-2 HJ₃enzo[b] [1,4] thiazin-6-yl)-N-methylacetamide;

2-(3,*3*-difluDra-2-oxoiidDlin-ii-^l)-N-((3) -2-((S)-3-hydiOxypytrolidin- 1-*yl)* - 1-phenylethyl)-N-methylacetamide;

2-(3,*3* ^fluDra-2-oxomdDlin-di-^l)-N-((S) -2-((S)-3-hydiOxypytrolidin- 1-*yi)* - 1-phenylethy^ac etamide ;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-ethyl-N-((S)-2-((S)-3-hydroxypytrolidirL-1-*yi)* -1-(3-(tiifluor ometliDxy)phenyl) ethyl)acetamide ;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-2-((S)-3-metlioxypyrrolidm-l -*yi)*- 1-(3-(trifluoromethoxy) phenyl)ethyl)-N-methylacetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(trifluoiOmethoxy)phenyl)ethyl)-N-(2,2,2-trifluoroethylJacetamide 2,2,2-trifluoroacetate;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benao[b][1,4Jthiazin-6-yl)-N-(2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(tetrahydro-2H-pyran-4-yl)ethyl)-N-methylacetamide-2,2,2-trifluoroacetate;

3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(N--™th^-2-(2-oxo-2,3-dihydrobenzo[d]thiazol-5-yl)acetamido)ethyl)benzoic acid;

3-((Ξ)-2-((Ξ)-3-hydroxypyrtolidin-1-yl)-1-(N-_™th^-2-(2-oxo-2,3-dihydrobenzo[d]thiazol-5-yl)acetamido)ethyl)benzamide;

(3)-2-(3-beiiE5ii-2-oxo-2,3-dil5idrObenzo[d]oxaaol-5-yl)-N-(1-(3-hydroxyphenyl)-2-(pyrrolidin-1-yl)ethjl)acetamide;

N-((S)-1-(3-(1H-tetrasol-5-yl)phenyl)-2-((3)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(1-methyl-2,2-dioxicb-1,3-dihydrobenao[c]isothiaaol-≤-yl)acetamide;

2-(3-((Ξ)-1-(2-(1,1-dio(xido-3-oxo-3,4-dmydnɔ-2H-ben2o[b][1,4Jthiazin-6-yl)-N-metliylacetamido)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)phenoxy)acetic acid;

3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindolin-6-yl)acetamido) ethyl) benzoic acid;

3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindolin-6-yl)acetamido) ethyl) bensamide;

N-((S)-1-(3-cyaiiophenyl)-2-((3)-3-fluoropyrrolidin-1-yl)ethyl)-N-n¾thyl-2-(2-oxoindolin-o˙-yl)acetamide;

N-((S)-1-(3-(2-amino-2-oxoethoxy)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetamide;

N-((S)-2-((S)-3-hydroxypynOndin-l-yl)-l-(3-(2-(methylsulfonamido)-2-oxoettoxy)pbenyl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetanude;

3-((Ξ)-2-((Ξ)-3-fluoropyrrolidin-1-yl)-1-(N-me1hyl-2-(2-oxoindDlin-o~-yl)acetamido)ethyl) benzoic acid;

2-(3-((Ξ)-2-((Ξ)-3-fluoa pyrrolidin-1-yl)-1-(N-methyl-2-(2-oxoindolin-6-yl) acetamido) ethyl) phenoxy)acetic acid;

N-((S)-1-(3-(2-amino-2-oxoethoxy)phenyi)-2-((S)-3-fluoropytTolidin-1-yl)ethyl)-N-methyl-2-

(2-ox dnddin-o ¯-yl)ac etamide;

3-((Ξ)-2-((Ξ)-3-hydr oxypynolidin- 1-yl)- 1-(N-methyl-2-ii -o-io-i ,4-dihyda quim xalin-f -yl)acetamido)ethyl)berizoic acid,

3i(S)-2-((3) -*3*-hydr oxypyrrolidin- 1-yl)- 1-(N-meth^-2-(3 -oxo-3,4-dihydrc ı-2H-benzo [b] [1,4] thiazm-6-yl)acetamidQ)ethyl)benzan^ le;

N-((S)-1-(3-ethynyiphenyl)-2-((S)-3-hydioxypynOlidin- 1-yl)ethyl)-N-methyl -2-(2-oxo-2,3-dihydrobenzo [d] thiazol-5-yl)acetamide;

N-((Ξ)-2-((Ξ)-3-hyd-OxypyrroHdin-l -yl)-l -(3-(5-(trifluoromethyl)- 1,2,4-oxadiazol -3-yl)phenyl) ethyi)-N-memyi -2-(3-oxo-3,4-dihydroquinoxalin-6-yl)acetamide;

N-((Ξ)-2-((Ξ)-3-hyd-OxypyrroHdin-l -yi)-l -(3-(5 -methyl- 1,2,4-oxadiazol -3-yi)phenyi) ethyi) -N-methyl -2-(2-o XDindolin-ō-yi)acetamide ;

N-((Ξ)-2-((Ξ)-3-hydtOxypyrrondin-l -yl)-l -(3-(thia zol-2-yi) phenyl)ethy _)-N-:nethyl-2-(2-oxoiridolin-D̄-yl)ac etainide ;

N-((Ξ)-1-(3-(but- 1-*ya.*- 1-yL)phenyi)-2-((S)-3-hydroxypyndidin-l -yl)ethyl)-2-(2,2 -dioxido-1,3-dihydrobenzo [c] isdluazol-o ¯-yl)-N-n¾thyiacetainide ;

3-((Ξ)-2-((Ξ)-3-hydr oxypyrto lidin- 1-yl)- 1-(N-meth ^-2-(2 -oxomdDlin -6-3^)acetaniido) ethyl) -N-(2,2,2 -trifluoroethyl)berizamide ;

N,N-diethyl -3-((S)-2-((Ξ)-3-hydroxypyrrohdin-l -yl)- 1-(N-methyl -2-(2-oк oindolin-6-yl)acetamido)ethyl)berizamide ;

3-((Ξ)-2-((Ξ)-3-hydr oxypyrto lidin- 1-yl)- 1-(N-methyl -2-(2 -oxo -2,3-dihydrobenzo [d] thiazol-5-yl)ace tamido)ethyl)-N ^-din¾thylbenzaniLde 2,2,2 -trifluoroac etate;

N-((S)-1-(3-(2 -(diethylamino)-2-oxoethoxy) phenyl)-2-((3)-3-hydroxypynolidin- 1-yTjethyl)-N-methyl -2-(2-o xoindolin-o¯-yl)acetamide ;

N-((S)-1-(3-(2 -(diethylamino)-2-oxoethoxy) phenyl)-2-((3)-3-hydroxypynolidin- 1-yTjethyl)-N-methyl -2-(2-o xo-2,3 -dihydrobenzo [d] tluazol -5-yl)acetamide ;

N-((S)-1-(3-f uoro-5-(thiazd -2-yl)phenyl)-2-((S)-3-hydroxypyriOhdrn- 1-yl) ethyl) -N-methyi-2-(2 -ox oindolin-6-yl)ace tamide ;

N-((3)-2-((Ξ)-3-hydtOxypyrrokdm -ı-yi)-l -(3-(2 -methyl -2H-tetrazol -5-yl)phenyi)e thyl)-N-methyl -2-(2 -oxoindolin-6-yl)acetamide;

N-((3)-2 -((S)-3-hydraxypyrrohdirL-l -yi)-l -phenylethyl)-2-(3 -methyl -2-oxo -2,3-dihydrobenzo [d] oxazol -5-yl)acetamide ;

(S)-2-(3-(3-c yinobenayl)-2-oxo-2 ,3-dihydiiobenao[d] oxaaol-5-yl)-N-(1-phenyl-2-(pynohdin-1-yl)ethyl)acetamide ;

(S)-N-methyl-2-(2-oxo- 1,2-dihydroquinolin-6-yl)-N-(1-phenyl-2-(pytrolidin- 1-yl)ethyl)acetamide;

N-((S)-2-((S)-3-hydraKypynDHdirL-l -yl)-l -ptenylethyl)-N-n¾thyl-2-(2-oxo-l ,2-dihydroquinolin-6-yl)acetamide ;

(S)-N-methyl-2-(2-oxo- 1,2-dihydroquinolin-7-yl)-N-(1-phenyl-2-(pyrtiolidin-1-y!)ethyl)acetamide;

(S)-N-methyl-2-(3-methyi-2,2-dioxido-1,3-dihydrobenao[c]isothiaaol-5-yl)-N-(1-phenyl-2-(pyrrolidin- 1-yl)ethyl)acetamide;

N-((Ξ)-2-((E) -3-hydroxypytrolidin- 1-yl)-1-phenylethyl)-2-(2-oxo-1,2-dihydroquinolin-^-yl)acetamide;

N-((3)-2-((3)-3-hydraxypynOhdin-l -yl)-l -phenylethyl)-N-niethyl-2-(2-oxo-l ,2-dhydroquinolin-7-yl)ac etamide ;

N-((3)-2-((3)-3-hydraxypynOhdin-l -yl)-l -pl¾nylethyl)-N-2-dimethyl-2-(2-QKO-2J3-dihydrobenao [d] oxaaol-5 -yl)propnamide ;

N-((Ξ)-2-((Ξ)-3-hydraxypyrrohdin-1 -yl)-l -phenylethyl)-2-(2 -oxo-1,2-dihydroquinolin-7-yl)acetamide;

N-((3)-2-((3)-3-hydraxypyrrohdin-l -yl)-l -phenylethyl)-2-methyl-2-(2-oxo-2 J3-dihydrobenao [d] oxaaol-5 -yl)propanamide;

(S)-2-(2-oxo-2,3-dihyi obenao [d] oxaaol-.5-yl)-N-(1-phenyl-2-(pyrrolidin-l -y<)ethyl) acetamide;

N-((Ξ)-2-((Ξ)-3-hydiOxypymndin-l -yl)-l -phenylethyl)-2-(2 -oxo-2,3-dihydrobenzo [d] oxaaol-5-yl)acetamide;

(S)-2-(3-benzyl-2-oxo-2,3-dihyd Obenao [d] oxazol-.5-yl)-N-(1-(3-(4-methoxybenaytoxy)phenyl)-2-(pynoHdin- 1-yl)efhyl)acetamide ;

2-(3-(4-cyanobenayl)-2-oxo-2.3-dihydrobe nao [d] oxaaol-5-yl) -N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)acetamide;

N-((S)-2-((3)-3-hydrox jpynrahdin-l -yl)-l -pl¾nylethyl)-2-(2-oxoinddm-ii-yl)acetamide;

(S)-2-(3-methyl-2 -oxo-2,3-dihydrobenao [d] oxaaol-5 -yl)-N-(1-phenyl-2-(pytTolidin- 1-yl)ethyl)acetamide;

N-(1-(1-benzyl- 1H -pyrazol -4-yl)-2 -(pyriOlidin- 1-yl)e thy.)-2-(2 -oxo-2,3- d-hydrobenzo [d] oxazol -5 -yl)acetainide ;

(S)-t-butyl-2-(3-(1-(2-(3 -benzyl-2 -oxo -2,3 -dihydiObenzo [cL] oxazol -5-yl)acetamidD)-2 -(pyrrolidirL- 1 -yl) ethyl)phenoxy)ac etate;

(S)-2-(3 -benzyl-2 -oxo -2,3 -dihy(irobe nzo [cL] oxazol -5-yl)-N-(1-(3 -(benzyloxy)phenyl) -2 -(pyrrolidirL- 1 -yl) ethyl)-N -methykcetainide ;

N-((S)-1-cyclohexyl -2 -((Ξ)-3 -hydmxypytrolidin- 1-yl)ethyl) -N -^thyl -2-(2 -oxoindolin-i5-yl)acetamide;

2-(3 -(3 -cyanobei^yl)-2 -oxo -2.3 -dihydiiobe nzo [d] oxazol -5-yl) -N -((Ξ) -2 -((Ξ)-3-hydroxypyrralidin- 1 -yl) -1 -phenylethyl)-N -methylacetaniide ;

N-((S)-1-cyclohexyl -2 -((Ξ)-3 -hydraxypyrrolidin- 1-yl)ethyl) -2-(2 -oxo-2,3-dihydrobenzo [d] oxazol -5 -yljacetainide ;

(S)-tert-butyl -2-(3-(1-(2-(3 -benzyl -2 -oxo -2,3-dihydrobenzo [dJ oxazol -5 -yl)-N -inethyl acetaniido)-2 -(pyfrolidin-l -yl)ethyl)phenoxy)ac etate ;

N-((S)-1-cyclohexyl -2 -((Ξ)-3 -hydraxypyrrolidin- 1-yl)ethyl) -2-(2 -oxoindolin-o -yl)ace tamide;

N-((S)-1-cyclohexyl -2 -((Ξ)-3 -hydmxypyrrolidin- 1-yl)ethyl) -N -inethyl-2-(2 -oxo-2,3-dihydrobenzo [d] oxazol -5 -yl)acetainide ;

(Ξ)-N -(1-(3 -cyaiiophe nyl)-2 -(pyrrolidin- 1-yl)ethyl)-N -methyl -2 -(2 -oxo -2,3-dihydrobenzo [d] oxazol -5 -yl)acetainide ;

2-(3 -(3 -cyanobenzyl)-2 -oxo -2.3 -dihydrobe nzo [d] oxazol -5-yl) -N -((Ξ) -2 -((Ξ)-3-hydroxypyrralidin- 1 -yl) -1 -phenylethyl)acetanTide;

N-((S)-1-(3 -cyanophe nyl)-2-((3)-3 -hydio xypyrrolidin -1 -yl)ethyl)-N -methyl -2 -(2 -oxo-2.3-dihydrobenzo [d] oxazol -5 -yljacetainide ;

(S)-tert-butyl 2 -(3 -(2-(3 -hydraxypyrrolidin-l -yl)- 1-(2-(2 -oxo-2,3-dihycLro benzo [d] oxazol -5-yl)ace tamido)ethyl)phenoxy)ac etate;

2-(3 -(4-cyanobenzyl)-2 -oxo -2.3 -dihydrobe nzo [d] oxazol -5-yl) -N -((Ξ) -2 -((Ξ)-3-hydroxypymlidin- 1 -yl) -1 -phenylethyl)-N -methylacetanLide ;

N-(1-(3 -(cyanomethoxy) phe nyl)-2 -(3 -hydraxypyriOlidin- 1-yl) ethyl) -N -methyl -2 -(2 -oxo -2,3-dihydrobenzo [d] oxazol -5 -yl)acetamide ;

tert-butyl 2-(3-((Ξ)-2-((R)-3 -hydiDxypyirolidin -1 -yl)- 1-(N -methyl-2-(2 -oxo -2,3 -dihydrobe nzo [dj oxazol -5 -yl)acetaniido)ethyl)phenoxy)acetate;

N-((S)-1-(3-cyaiiophenyl)-2-((3)-3-hydtoxypyrrolidin-1-yl)ethyl)-N-methyl-2-(3-methyl-2-oxo-2,3-dihydiiobenao[d]oxaaol-5-yl)acetamide;

N-((S)-1-(3-(1H-tetraml-5-yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-2-(2,2-dioxido-1.3-dihydroben30[c]isothiai.ol-6-yl)-N-methyiacetainide;

2-(3-((Ξ)-2-((Ξ)-3-hydroxypynOlidin-l-yl)-1-(N-methyl-2-(1-meIhyl^^-dioxido-1,3-dihydrobei™[c]isothiaml-^yl)acetamido)ethyl)phenoxy)acetic acid;

(S)-methyl 3-((2-oxo-5-(2-oxo-2-(1-phenyl-2-(pyrrolidin-1-yl)ethylamino)ethyl)benzo[d]oxazol-3(2H)-yl)methyl)benzoate;

(S)-tert-butyl 2-(2-oxo-5-(2-oxo-2-(1-phenyl-2-(pyiTohdin-1-yl)ethykmino)ethyl)benso[dj oxa2ol-3(2H)-yl)acetate;

(Ξ)-2-(2-oχo-5-(2-oχo-2-(1-phenyl-2-(pyoOlidin-l-yl)e1hylainino)ethyl)benzo[d]oxaaol-3(2H)-yl)acetic acid hydrochloride;

(Ξ)-N-(1-(3-hydiDxyphenyl)-2-(pyrroHdirL-l-yl)ethyl)-2-(2-oxo-2,3-dihydiObenso[d]oxaaol-5-yl)acetamide;

(Ξ)-2-(3-(1-(2-(2-oxo-2,3-dihydrobeIIEO[d]oxaad-5-yl)acetamido)-2-(pyrrdidin-1-yl)ethyl)pl¾noxy)acetic acid hydrochloride;

2-(5-(2-(((Ξ)-2-((Ξ)-3-hydroxypyc^idin-1-yl)-1-phenylethylX methyl)amino)-2-oxoethyl)-2-oxober™[d]oxaad-3(2H)-yl)acetic acid;

2-(3-(1-(N-methyl-2-(2-oxoindolin-di-yl)acetamido)-2-(pynOlidin-1-yl)ethyl)phenoxy)acetic acid hydrochloride;

3-((5-(2-(((Ξ)-2-((Ξ)-3-hydroxypyrtolidin-1-yl)-1-phenylemyl)(methyl)amino)-2-oxoe1hyl)-2-Qxobenao[d]oxaad-3(2H)-yl)methyl)benaamide;

(S)-2-(3-berEyl-2-oxo-2,3-dili5idrobenao[d]oxazd-.5-yl)-N-(1-(3-hydiOxyphenyl)-2-(pyrrolidiTL-1-yl)ethyl)-N-methylacetainide;

(R)-2-(3-(1-(N-methyl-2-(2-oxo-2,3-dihydroberiao[d]oxazol-5-yl)acetamido)-2-(pyrralidirLl-yl)ethyl)phenoxy)acetic acid;

(Ξ)-3-((2-oχo-5-(2-oχo-2-(1-phenyl-2-(pya.olidin-l-yl)ettykmiiio)ethyl)ben2JO[d]oxaaol-3(21¾-yl)i™thyl)beimmide;

2-(3-(1-(2-(2-oxoii^Lin-0-yl)acetamLdD)-2-(pynoHdin-1-yl)ethyl)phenoxy)acetic acid;

(Ξ)-N-(1-(3-(2H-tetraaol-5-yl)phenyl)-2-(pyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydrobenao[d]oxaaol-5-yl)acetamide;

(S)-2-(3-(2-(3-hydioxypyrrohdin- 1-*yi)*- 1-(N-rne thyl-2-(2 -oxo-2,3 -dmydroberiao [d] oxaaol-5 -y})acetamido)ethyl)]ahermy)acetic acid triflouro acetate;

(S)-2-(3-(2-(3-hydroxyp3rrolidin-1-yl)- 1-(N-rne thyl-2-(2 -oxoirdolirL-o-yi) acetamido) ethyl) pherioxy) acetic acid hydrochloride ;

2-(3-{(Ξ)-2-((R)-3-hydroxypynOhdm- 1-*yi)*- 1-(N-methyl-2 -(2-oxo-2 ,3-dihydrobe nzo [d] oxaaol-5 -yl)acetamido)emyi)]aherLOxy)acetic acid;

2-(5-(2-(((Ξ)-1-c yclonexyl-2 -((S)-3-hydroxypynOhdin- 1-*yi)* ethylX methyl)amino)-2-oxo ethyl) -2 -ox obe nao [d] oxazol-3(2H)-yl)ac etic ac id;

Ivfethyi 4-d(5-(2-(((S)-2-((Ξ)-3 -hydro« ypyn olidin -l -yi)- 1-phenylethyl) (methyl)amrno)-2-oxo ethyl) -2 -ox obe nao [d] oxaaol-3(2H)-yl)me myi)benaoate ;

N-((S)-1-(3-(2H-tetraaol-5-yl) phenyl)-2-((3)-3-hydroxypyrrolMm- 1-yl)ethyl)-N-methyl-2 -(2 -oxo -2,3 -dhydroberiao [d] oxaaol-5 -yl)acetamide ;

(3)-2-(3-(2-(3-hydioxyt-yriOHdiri- 1-yl)- 1-(2-(2-oxoiridolm -6-yl)acetamido) ethyl)phenoxy)acetic acid hydrochloride ;

(3)-2-(3-(2-(3-hydioxyt.ynOHdiri- 1-yl)- 1-(2-(2-oxo-2,3 -dihydroberiao [d] oxa3ol-5-yi)acetamido)ethyl)pheroxy)acetic acid ;

2-(3 -(3-(2H-te trazol-5-yl)b enzyl)-2-oxo-2,3 -dihydroberrao [d] oxaaol-5 -yl) -N-((Ξ)-2-((Ξ)-3 -hydroxyj^^lidrn- 1-yl) -1 -phenylemyl)acetamide;

2-(3 -(3-(2H-te trazol-5-yl)b enzyl)-2-oxo-2,3 -dihydroberrao [d] oxaaol-5 -yl) -N-((Ξ)-2-((Ξ)-3 -hydroxyj^rrolidin- 1-yl) -1 -]al¾nylemyl)-N-memykcetamide ;

2-(3-(4-(1H-te traaol-5-yl)b enzyl)-2-oxo-2,3 -dihydrobenao [d] oxaaol-5 -yl) -N-((Ξ)-2-((Ξ)-3 -hydroxyj^rrolidin- 1-yl) -1 -]al¾nylemyl)-N-memykcetarmde ;

(R) -N-(1-(3-((2H-tetraaol-5 -yi)rnethoxy)phenyl) -2 -(3 -hyiio xypyrrolidin-1 -yl)et %1)-N-rnethyl-2-(2-oxo-2 ,3-dmydroberiao [dj oxaaol-5 -yl)acetamide ;

2-(3 -(4(1H-te traaol-5-yl)b enzyl)-2-oxo-2,3 -dihydrobenaD [d] oxaaol-5 -yl) -N-((Ξ)-2-((Ξ)-3 -hydroxyi^/rrolidin- 1-yl) -1 -]atenylemyl)acetamide;

N-((S)-1-(3-(2H-tetraaol-5-yl) phenyl)-2-((S)-3-hydroxypyrrolidin- 1-yl)ethyl)-N-methyl-2 -(3 -rnethyl-2-oxo-2 ,3-dihydroberizo [dj oxaaol-5 -yl)ac etamide ;

N-((S)-1-(3-cyanophe nyl)-2-((S)-3 -fluoropyrrolidin- 1-yl)ethyl)-N-iriethyl-2-(2 -oxo-2 ,3 -dihydroberiao [d] oxaaol-5 -yl)acetamide ;

N-((S)-1-(3-(2H-tetraaol-5-yl) phenyl)-2-((3)-3-HviororjyrrohdirL-l -yl) ethyl) -N-methyl-2 -(2-

окo-2,3-dihydrobenzo[d]oxazol-5-yl)acetamide;

N-((S)-1-(3-(2H-tetmml-5-5ii) phenyl)-2-((S)-3-hydroxypyr.oJidin-1-yl)ethyl)-N-methyl-2-(2-OKoiridolirL-6-yl)acetamide ;

N-((S)-1-(3-(2H-tetraml-5- yl)phenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(1-methyl-2-oxoindolin-6-yl)acetamide;

(R)-N-(1-(3-((2H-teti¾2Dl-5-yl)methoxy)phenyl)-2-(3-hydroxypyrrolidin-1-yl)eti¾l)-N-metli5ii-2-(2-oxo -2,3-dihydrober™ [dj oxazol-5-^acetamide ;

N-((S)-1-(3-(2H-tetrazol-5-5ii)phenyi)-2-((S)-3-fluoropyrrolidin-l-*yi)*ethyl) -N-methyl-2-(2-oxoindolin-6-yl)acetamide;

(S)-2-(3-oxo -3,4-dihyi.o-2H-benso[b][1,4J oxazin -6-yl)-N-(1-phenyl-2-(pynolidin-1-yi)ethyl)acetamide;

(S)-N-meth^-2-(2 -oxo -2.3-dili5idrobenzo[d]thiazol-i -yl)-N-(1-phenyl-2-(pyrrolidm-1-ji)etl^)acetamide ;

2-(2,2-dioxido- 1,3-dihyi .Obenzo[c]isothiazol-6-yl)-N-((S)-2-((Ξ)-3-hydroxypyrrolidin-1-*yi)*-1-phenyleth^)- N-methylacetamide;

N-((S)-2-((S)-3-hydrOxypyrrolidirL1 -yl)-l -phenyiethyl)-N-methyl-2-(2-oχo-2,3-dihydrobenzo[d]thiazol-5-yl)acetamide;

N-((S)-2-((S)-3-hydrOxypyrrolidirL1 -yl)-l -phenyiethyl)-2-(2-thioxo-2,3-dihydrobenzo[d]thiazol-5-yl)acetamide;

N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methyl-2-(2-thioxo-2,3-dihydrobenzo[d] thiazol -5-5ii)acetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methylacetamide;

(S)-2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-(1-phenyl-2-(pyrrolidin-1-yl)ethyl)acetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-2-((S)-3-tydroxypyrrolidin-1-5d)-1-phenylethyl)acetamide;

2-C1.1 -dioxido-3 -oxo -3,4-diV iro-2H-ben3o[b][1,4J thiazin-6-*yi)*-N-((S)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(3-(trifluoromethyl)phenyl)ethyl)-N-methylacetamide;

2-C1.1 -dioxido -3-oxo-3,4-dih^iro-2H-benao[b][1,4]thiazin-6-^i)-N-((S)-1-(3-fluorophe*nyi)-2-*((SJ-S-hydioxypyiro lidin-1-*yi)* ethyl) -N-melhylacetamide;

N-((S)-1-cyclohexyl-2-((Ξ)-3-hydroxypyrrolidm-1-yl)ethyl)-2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-methylacetamide

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-methoxyphenyl)ethyl)-N-methylacetamide;

(S)-2-(3-oxo-3,4-dihyi iXi-2H-benzo[b][1,4]thiazin-6-yl)-N-(1-phenyl-2-(pyrrolidin-1-y!)ethyl)acetamide;

N-((S)-2-((S)-3-hydo xypyrrolidirL-l-yl)-l-p^n^th^)-2-(3^xo-3,4-dih^dro-2H-benzo[b][1,4]thiazin-6-yl)acetamide;

(S)-N-]^th^-2-(3-oxo-3.4-dili5idro-2H-benso[b][1,4]thiazin-6-yl)-N-(1-phe^l-2-(pytrolidin-1-yl)ethyl)acetamide;

N-(2-((S)-3-hydroxypyrrolidin-1-yl)-1-(tetrahydro-2H-pyran-4-yl)ethyl)-N-methyl-2-(3-oxo-3.4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)acetamide;

N-((Ξ)-2-((Ξ)-3-hyd-OxypynOHdin-l-yl)-l-(3-methoxyphenyi)ethyi)-N-methyl-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-0-jd)acetamide;

N-((S)-2-((SJ-S-hydroxypyrrolidin-l-yl)-l-(3-(trifluoromethyl)phenyl)eth^)-N-me1h^i-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiaain-6-yl)acetamide;

N-((S)-1-(3-fluorophenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-ji)acetamide;

N-((S)-2-((S)-3-hyd.Oxypyrrolidirl-l-yl)-l-(3-(trifluo(romet]iox^pl¾n5d)eth^)-N-meth^i-2-(3-oxo-3,4-dihydiio-2H-benzo[b][1,4J ti-iazin-6-yl)acetamide;

2-(1-¾enz5ii-2,2-dioxido-1,3-dihydiiobenzo[c]isothiaaol-S-^i)-N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-phenylethyl)-N-methylacetamide;

2-(2,2-dioxido-1,3-dihyi .Obenzo[c]isothiazol-6-^l)-N-((S)-2-((Ξ)-3-hydroxypynraHdin-1-yl)-1-phen^eth^)-N-meth^cetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-2-((S)-3-liydraxypynOlidin-1-yl)-1-(3-(tiifluoromethoxy)phenyl)ethyl)-N-propylacetamide;

2-(1,1-dioxido-3-oxo-3,4-di^^dra-2H-benao[b][1,4]thiazin-6-yl)-N-((S)-2-((Ξ)-3-liydraxypynOlidin-1-yl)-1-(3-(tiifluoromethoxy)phenyl)ethyl)-N-:isopropylacetamide;

N-cyclopropyl-2-(1,1-dioxido-3-oxo-3,4-dihydiro-2H-benso[b][1,4J thiazin-0'-yl)-N-((Ξ)-2-((S)-3-hydiOxypyniolidin-l-yl)-l-(3-(tiifluoromethoxy)phenyl)ethyl)acetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydra-2H-bensD[b][1,4]thiazin-6-yl)-N-((S)-2-((Ξ)-3-

hydroxypynolidin-1-yl)-1-(3-(trifluoromethoxy)phenyl)ethylJ-N-isobutylacetamide;

N-(cyclopropylmethyl)-2-(1,\-dioxido-3-oxo-3,4dihydro-2H-benzo[b] [1.4] thkzin-6-yl)-N-((Ξ)-2-((Ξ)-3-hydroxypyiiolidirL-1-yl)-1-(3-(tri.liiQromethoxyjphenyl) ethyl) acetamide;

2-(1,1-dioxido-3-oxo-3,4-dihydro.2H-ben3o[b] [1,4] thiazin-6-yl)-N-((3)-2-((Ξ)-3-hydroxypynolidm-1-yl)-1-(4-(trifluoromethoxy)phenyl)ethyl)-N-methylacetamide;

2-(2,2-dimethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-N-((S)-2-((S)-3-hydroxypyrrolidin-1-yl)-1-(3-(trifluoromethoxy)phenyl)ethyl)-N-methylacetamide;

2-C1.1-dioxido-3-oxo-3,4-dihydro-2H-benao[b] [1,4] thiazin-6-yl)-N-((S)-2-((Ξ)-3-hydroxypynolidin-1-yl)-1-(3-(2,2,2-trifluoroethoxyJphenylJethyl)-N-methylacetamide;

2-C1.1-dioxido-3-oxo-3,4-dihydro-2H-benao[b] [1,4] thiazin-6-yl)-N-((S)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(m-tolyl)ethyl)-N-methylacetamide

2-(1,1-dioxido-3-oxo-3,4dihydro-2H-benao[b] [1,4J thiazin-6-yl)-N-((S)-1-(4-fluoro-3-(trifluoromethoxy)phenyl)-2-((3)-3-hydroxypyrrolidin-1-yi)ethy-)-N-:n¾thy-acetamide

N-((S)-1-(3,5-dimethylphenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyi)-2-(1,1-dioxido-3-oxo-3.4dihydro-2H-benzo[b] [1,4] thiazin-6-yl)-N-methylacetamide

2-(2,2-dimethyl-1,1-dioxido-3-oxo-3,4dihydro-2H-berL7D[b] [1,4J thiazirL6-yl)-N-((S)-2-((Ξ)-3-hydroxypynOliditi-l-yl)-l-(3-(trifluoromethoxy)phenyl)ethyl)-N-methylacetamide

2-(1,1-dioxido-3-oxo-3,4 dihydro-2H-benao[b] [1,4J thiazin-o˙-yl)-N-((S)-1-(3-fluoro-5-(2.2,2-triflnoro ethoxy)phenyl)-2-((S)-3-hyJroxypyriOhdi-i-l-yl) ethyl)-N-methylacetamide

N-((S)-1-(3-cyclopropylphenyl)-2-((3)-3-hydroxypyjrohdin-l-yl)ethyl)-2-(1,1-dioxido-3-oxo-3.4dihydro-2H-benzo[b] [1,4] thiazin-6-yl)-N-methyiacetamide

N-((S)-1-(3-cyanophenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxo-2.3-dihydrobenao [d] thiazol-5-yl)acetamide

N-((S)-1-(3-cyanophenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(3-oxo-3,4 dihydro-2H-benzo[b] [1,4J thiazin-6-yi)acetamide

N-((S)-1-(3-cyanophenyl)-2-((S)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(3-oxo-3,4 dihydro-2H ^ben2D[b] [1,4Joxazin -6-yl)acetamide

3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-1-(N-methyl-2-(3-oxo-3,4 dihydro-2H-ben2o[b] [1,4J thiazin-6-yl)acetamido)ethyl)benaaic acid

3-((Ξ)-2-((Ξ)-3-hydroxypyrtolidin-1-yl)-1-(N-methyl-2-(3-oxo-3,4 dihydro-2H-benzo[b] [1 ^oxazin-^-ylJacetaimdoJemylJberL-Bic acid

N-((S)-1-(3-cyaropre nyi)-2-((3)-3-hydro xypyrrdidin-1 -yl)ethyl)-N - n¾thyl-2-(2-oxoindolin-6-yl)acetamide

N-((S)-2-((S)-3-hyda xypymolidinL-l -yl)-l -pl¾nylethyl)-2-(2-oxoind din-5-yl)acetamide

N-((S)-1-(3-cyaropre nyi)-2-((3)-3-hydro xyp yrrdidin-1 -yl)ethyl)-N- n¾thyl-2-(3-oxo-3.4-dihjrdroquinoxd in-f -yl)acetamide

2-(3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin -1-yl)- 1-(N-:n¾thyl-2-(2-oxoindolLn-fj-yl)acetamido)ethyl)pherioxy)acetic acid

3-((Ξ)-2-((Ξ)-3-hydr oxypyrto lidin- 1-yl)- 1-(N-imethyl-2-(2-oxo-2 ,3-dihydrobenso [d] oxa3ol-5-yl)acetamido)ethyl)benzamide

N-((3)-2-((S)-3-hydraxypyrroHdiTL-l -yi)-l -p]¾nyiethyl)-N-n¾thyl-2^2 -oxoind in-5-yl)acetamide

N-((S)-2-((S)-3-fluoropyrrolidin-1-yl)-1-(3-(2-(methylsulfonamido)-2-oxoethoxy)phenyl) ethyl)-N-methyl-2-(2-o xoindolrn-fj-yl)acetamide

N-((Ξ)-1-(3-cyaropre nyi)-2-((S)-3-hydro xypyrrdidin -1-yl)ethyl)-N-methyl-2-(2-oxo-2.3-dihydrobenao [d] oxasol -5-yi)acetarriide

3-((Ξ)-2-((Ξ)-3-hydroxypyrto lidin- 1-yl)- 1-(N-_™thyl-2-(3-oxo-3 ,4-dihydraqTiimxalin -6-yl)ace tamido)ethyl)berizaniide

3-((Ξ)-2-((Ξ)-3-fluoropyiTolidin- 1-yl)-1-iN-methyi-2-(2-oxoindo lin-6-yl)ace tamido)ethyl)berizaniide

2-(3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1 -yl)- 1-(N-methyl-2-(2-oxo-2.3-dihydrobenao [d] thiazol-5-yi)acetaniido) ethyl)phenoxy)acetic acid

2-(3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1 -yl)- 1-(N-methyI-2-(3-oxo-3,4dihydro-2H-benao[b] [l,4]oxazin-6j-yl)acetamido)ethyl)phenoxy)acetic acid

N-((S)-1-(3-(2-anTino-2-oxoethoxy)phenyl)-2-((3) -3-hydroxypyrmlidin -1-yl)ethyi)-2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-benzo [b] [1.4] thiazin-≤-yl)-N-me1hylacetaniide

2-(3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin -1-yl)- 1-(N-methyl-2-(2-oxoindohn -5-yl)acetamido)ethyl)phenoxy)acetic acid

N-((S)-l-(3-(2-amino-2-oxoethoxy)phenyl^ -((S)-3-hydroxypyrrolidin-1 -yl)ethyi)-N-methyi-2-(2-ox 0-2,3-dihydrobenzo [d] trriasd-i-yljacetanude

2-(3-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1 -yl)- 1-(N-n¾thyl-2-(3-oxo-3.4dihydroquinoxalin-fj-yl)acetamido)ethyl)phermy)acetic acid

2-0 -((Ξ)-2-((Ξ)-3 -hydroxypyrrolidrn-l -yi)- 1-(N-methyl-2-(3-oxo-3A dihydro-2H-benao [b] [1,4] 1hkain -6 -yl)acetamido)ethyl)phenoxy)acetic acid

N-((S)-1-(3-(2-amino-2-oxoethoxy)phenyl)-2-((S)-3-hydroxypyrrolidin-1 -yl)ethyl)-N-methyl-2-(3 -ox o -3,4-dihydro-2 H-benao [b] [1,4] oxaam-o ˆ-yl)acetamide

2-(1,1 -dioxido-3-oxo-3,4-dihydro-2H-benzo[b] [1,4] thiazin-6 -yl)-N-((S)-2-((S)-3-hydroxypyrrolidin- 1-yl) -1 -(3 -(2 -(methylsulfonamido)-2-oxoethoxy)]dienyl)ethyl) -N-methylacetamide

N-((3)-1 -(3-(2-amino-2-oxoethoxy)pl¾nyl)-2-((S)-3-hydroxypyrrolidin-1 -yl)ethyl)-N-:methyl-2-(3 -OK o -3,4-dihydro-2 H-benao [b] [1,4] thia ain -6 -yl)acetanude

3-((Ξ)-2-((Ξ)-3 -hydroxypyrto lidin- 1-yl)- 1-(N-i™thyl-2-(2-oxo-2,3-dihydiObenzo [d] oxaaol -5-yl)ace tamido)ethyl)benao ic acid

3-((Ξ)-2-((Ξ)-3 -hydroxypyrto lidin- 1-yl)- 1-(N-methyl-2-(2-oxomdolin-0-yl)acetaniido) ethyl) -N-(me myl^fonyljbenaanude

N-((Ξ)- 1-(3-ethyiiylphenyl)-2-((S)-3-hydroxypyrrolidin- 1-yl)ethyl)-N-methyl-2 -(3 -oxo -3,4-dihydroquinoxalin -0-yl)acetamide

N-((Ξ)-2-((Ξ)-3 -hydtOxypyrrohdin-l -yl)-l -(3-(5-(trifluoromethyl)- 1,2,4-oxadia!ol-3 -yl)phenyi) ethyl) -N-methyl-2-(2 -oxoindolm-o ˆ-yl)acetamide

N-((S)- 1-(3-emynyiphenyl)-2-((S)-3-hydroxypyrrohdin- 1-yl)ethyl)-N-methyl-2 -(2 -oxoindolin-D ˆ-yi)ac etainide

2-(2,2 -dioxido- 1,3-dihydrobe nao [c] isothiasol -6-yl)-N-((3) -2 -((S)-3 -hydroxypyrrohdin- 1-yl) -1-(3 -(5-methyi-l ,2 ,4-oxadiaaol-3-yi) pl¾nyl)ethyi)-N -methylacetamide

2-(2,2 -dioxido- 1,3-dihydrobe nao [c] iso1hiaaol -6-yi)-N-((3) -1 -(3 -ethynylphenyl) -2 -((Ξ)-3 -hydroxypyrrolidin - 1-yl) ethyl)-N-methylacetainide

N-((Ξ)-2-((Ξ)-3 -hydiOxypyrrohdin-l -yl)-l -(3-(5-methyl- 1,2,4-oxadiazol-3 -yl)phenyl) ethyl) -N-methyl-2 -(2-o xo -2,3-dihydroben30 [d] thiazol-5-yi)acetamide

N-((Ξ)-2-((Ξ)-3 -hydiOxypyrrohdin-l -yi)-l -(3-(5-(trifluoromethyl)- 1,2,4-oxadia5ol-3 -yl)phenyi) ethyl) -N-methyl-2-(2 -oxo -2,3 -dihydrobenao [d] thiaaol-5-yl)acetamide

N-((S)- 1-(3-(1,2.4-oxadiaaol-3 -yl)phenyl) -2 -((Ξ)-3-hydiOxypyrrolidin- 1-yl)ethyi) -N-me fhyi-2-(2-oxoindolin-6-yl)ace tamide 2,2,2-trifluoroacetate

N-((S)- 1-(3-(1,2,4-°xadkaol-3 -yl)phenyl) -2 -((S)-3-hydroxypyrrolidin- 1-yl)ethyi) -2 -(2,2-dioxido- 1,3-dihydrobe nao [c] isothiaao l-6-yi)-N-me thylacetamide

2-(2,2-dioxido-1,3-dihydrobenzo[c]iso1hiazd-0-yi)-N-((S)-2-((Ξ)-3-hydroxypyr-Ohdin-1-yl)-1-(3-(5-(triflnoiD methyl)-1,2,4-oxadiazDl-3-yl)p¾nyl)ethyl)-N-methylacetamide 2,2,2-trifliioroacetate

N,N-diethyl-3-((3)-2-((Ξ)-3-hydroxypyriOhdirL-l -yl)-1-(N-methyl-2-(2-oxo-2,3-dihydrobenzo[d]thiazol-i-yl)acetamido)ethyl)berizairiide

N-((S)-1-(3-(1,2.4-oxadia5_ol-3-yl)phenyl)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydrober zo[d]thiazol-5-yl)acetamide 2,2,2-tiifluoroacetate

N-((S)-1-(3-(1,2,4-oxadia..ol-3-yl)phenyi)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)ethyl)-N-methyl-2-(3-oxo-3,4-dihydroquiMxalin-6-yl)acetamide 2,2,2-triiTuoroacetatie

N-((S)-1-(3-(1H-imida3ol-2-yl)phenyl)-2-((Ξ)-3-hydroxypyrrolidin-1-5l)ethyl)-N-methyl-2-(2-oxo-2,3-dihydrobenzo[d]thiaml-5-yi)acetamide

N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidirLı-yl)-l-(3-(thia2ol-2-yi)ptenyl)ethyl)-N-methyl-2-(2-oxo-2,3-dihydroben20[d]thiazol-5-yi)acetamide

N-((Ξ)-1-(3-cyaro-.5-fluorophenyl)-2-((S)-3-hydroxypynOL.din-1-yl)ethyl)-N-methyl-2-(2-oxo-2,3-d-hydrobenao[d]thazol-5-yl)acetamide hydrochloride

N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-l-(3-(5-methyl-1,2,4-oxadia..ol-3-yi)phenyi)ethyl)-N-methyl-2-(3-oXD-3,4-dihydroquiiioxahn-0-yi)acetamicle

3-((S)-1-(2-(2.2-dioxido-l,3-dmydrobenzo[c]isothiaaol-6-yl)-N-methylacetamido)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)ethyl)-N-(2,2,2-trifluoroethyl)benzamide

3-((Ξ)-2-((Ξ)-3-hydroxypyrtolidin-1-yl)-1-(N-methyl-2-(3-oxo-3,4-dihydroqTrirDxalirL-0-yl)acetamido)ethyl)-N-(2,2,2-trifluoroethyi)bensamide

N-((S)-1-(3-cyaro-5-fluorophenyi)-2-((3)-3-hydroxypyriOlidin-1-yi)ethyi)-N-inethyl-2-(2-**OKoiridolirL**-6-yi)acetamide

N-((S)-1-(3-(1H-imida2ol-2-yi)phenyl)-2-((Ξ)-3-hydroxypyrrolidm-1-yl)ethyi)-N-inethyl-2-(2-oxoindolin-6-yl)acetamide 2.2,2-trifluoroacetate

N-((S)-1-(3-cyaro-5-fluorophenyi)-2-((S)-3-hydroxypyriOlidin-1-yi)ethyl)-2-(2,2-dioxido-1,3-dihydroberLTJO[c]isothiaaol-6-yl)-N-methylacetainide

N-((S)-1-(3-cyaro-5-fluorophenyi)-2-((S)-3-hydroxypyriOlidin-1-yi)ethyi)-N-methyl-2-(3-oxo-3,4-dihydroquirioxalin-6-yl)acetamide

2-(1,1-dioxido-3-oxo-3,4-dihydro-2H-ben3o[b][1,4]thiazin-o-yl)-N-((S)-1-(3-ethynylphenyl)-2-((Ξ)-3-hydroxypyrrohdin-1-yl)ethyi)-N-methykcetamide

N-((S)-1-(3-(1**H-imida2Dl-2**-yi) phenyl)-2-((Ξ)-3-hydroxypyrrolidm- 1-yl)ethyl)-2-(2,2-dioxido-1,3-dihydrobenzo[c] isothiazDl-6-yi)-N-me thylacetamide

N-((Ξ)-1-(3-cyanophenyl)-2-((S)-3-hydio xypyjrdidin-1 -yl)ethyl)-2-(2,2-dioxido -1,3-dihydiioben2D[c] isothiaml-tf-yiJ-N-memyiacetaniLde

N-((S)-1-(3-(but- 1-yn- 1-yl)phenyI)-2-((S) -3-hydroxypy.rdidin-1 -yI)ethyl)-N-methyl-2-(2-oxoindolin-D-yl)ac etamide

N-((S)-1-(**3-Cbut-** 1-yn- 1-yl)phenyI)-2-((S) -3-hydroxypy.rdidin-1 -yI)ethyl)-N-methyl-2-(2-oKo-2,3-dihydrobenzo[d]thiazol-5-yi)acetamide

N-((S)-1-(**3-Cbut-** 1-yn- 1-yl)phenyI)-2-((S) -3-hydroxypyiididin-l -yI)ethyl)-N-methyl-2-(3-oKo-3,4-d hydroquinoxalin-6-yl)acetamide

3-((Ξ)-2-((Ξ)-3-hydroxypyrto lidin- 1-yl)-1-(N-methyl-2-(2-oxoindolm-0-yi)acetan^ lo) ethyl)-N,N-diniethylb enzamide

3-((S)-1-(2-(2.2-dioxido-l ,3-dmydrobenso[c] isothiaaol-6-yl)-N-methylac etamido)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)ethyl)-N,N-diethyibenzamide

N,N-diethyl-3-((3)-2-((Ξ)-3-hydioxypyrrohdin-l -yl)-1-(N-methyl-2 -(3-oxo-3,4-dihydroquiiMxalm-0-yl)acetamido) e1hyl)beiramide 2,2,2-trifluoroacetate

3-((S)-1-(2-(2.2-dioxido-l ,3-dmydrobenso[c] isothiazol-6-yl)-N-methylac etainido)-2-((Ξ)-3-hydroxypyrrolidin-1-yi) ethyl)-N,N-din¾mylbenzamide

3-((Ξ)-2-((Ξ)-3-hydroxypyrto lidin- 1-yl)-1-(N-n¾thyl-2-(3-oxo-3 ,4-dihydroqTiinoxalin-di-yl)acetamido)etl^l)-N^-din ¾**thylbenzamide**

N-((S)-1-(3-(1,2,4-oxadiam l-3-yl)phenyl)-2-((S)-3-hydroxypyrrolidm- 1-yl)ethyl)-2-(1, 1-dioxido-3-oxo-3.4-dihydro-2H-benso[b] [1.4] lh;aain-6-yl)-N-me1hylacetamide2 ,2,2-tnfluoroacetate

N-((S)-2-((3)-3-hydrox ypyrrolidin-l -yi)-l -(3-(1-methyl- 1H-**iinida3ol** -2-yl)phenyi) ethyl)-N-n¾thyl-2-(2-oxoindolin- ≤-yl)ac etamide

N-((3)-1-(3-(5-ethyl-l ,2,4-oxadia3ol-3-yl)phenyl)-2-((S)-3-hydioxypyn olidin- 1-yl)ethyl)-N-n¾thyl-2-(2-oxoindohn-fj-yl)ac etamide

N-((Ξ)-2-((Ξ)-3-hydraxypyrrohdin-1 -yi)-l -(3-(5-methylthia3ol-2 -yl)phenyl)e thyl)-N-methyi-2-(2-ox oindolin-6-yl)acetamide

N-((S)-2-((Ξ)-3-hydroxypyrrohdin-1 -yi)-l -(3-(thiaml-5-yl) phenyl)ethyi)-N-methyi-2-(2-oxoindolin-6-yi)ac etamide

N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-l-yl)-l-(3-(thia;.ol-4yl)phenyl)ethyl)-N-:methyl-2-(2-oxoindolin-6-yl)acetamide

N-((Ξ)-2-((Ξ)-3-hydiOxypyrrohdin-l-yl)-l-(3-(4methyIthiaaol-2-y_)phenyl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetarnide

N-((Ξ)-2-((Ξ)-3-hydiOxypynOhdin-l-yl)-l-(3-(2-™thylthiazol-5-yi)phenyl)ethyl)-N-methyi-2-(2-oxoindolin-6-yl)acetarnide

N-((S)-2-((Ξ)-3-hydroxypyrrolidin-l-yl)-l-(3-(2-methylthiazol-4-yl)phenyl)ethyl)-N-methyl-2-(2-*ox*oindolin-6-yl)acetarnide

N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-l-yl)-l-(3-(5-methyI-1,3,4-thiadiazol-2-yl)phenyl)ethyl)-N-methyl-2-(2-oxoindolin-o-yl)acetamide

N-((Ξ)-2-((Ξ)-3-hyd.OxypynOhtiin-1-yl)-l-(3-(1-methyl-1H-imida..ol-5-y-)phenyl)ethyl)-N-methyl-2-(2-oxoindQkn-o-y-)acetamide

N-((S)-1-(3-(1,3.4oxadia..ol-2-yi)phenyl)-2-((Ξ)-3-hydiOxypynolidin-1-yl)ethyl)-N-methyl-2-(2-oxtindolin-o-yl)acetarnide

N-((Ξ)-2-((Ξ)-3-hydiOxypyrrokdin-l-yl)-l-(3-(5-methyi-1,3,4-oχaüAzol-2-yl)phenyl)ethyl)-N-methyl-2-(2-oxoindolin-o-yl)acetamide

N-((Ξ)-2-((Ξ)-3-hydroxypyrrolidin-1-yl)-l-(3-(1-methyl-1H-imida..ol-4y-)phenyl)ethyl)-N-methyl-2-(2-oxoindolin-6-yl)acetamide

N-((S)-1-(3-(1-(cyclopropymiethyl)-1H-imidazol-2-5ii)pihenyl)-2-((S)-3-hydioxypyriOlidirL-1-^)etl^)-N-metl^-2-(2-oxomdolin-0-5ii)acetamide

N-((Ξ)-2-((Ξ)-3-hydiOxypyrrokdin-l-yl)-l-(3-(3-methyi-1,2,4-oxadiazol-i-yOphenyi)ethyl)-N-methyl-2-(2-oxoindolin-o-yl)acetamide

3-((Ξ)-2-((Ξ)-3-hydroxypynolidin-1-yl)-1-(N-meth^-2-(2-oxo-2,3-dih5idrobenzo[d]thiazol-5-yl)acetamido)ethyl)-N-(2,2,2-trifluoroe1hyl)benzamide

or a stereoisomer thereof or a pharmaceutically acceptable alt thereof.

15. A pharmaceutical composition comprising one or more compounds according to claim 1 or a stereoisomer thereof or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

16. A pharmaceutical composition comprising one or more compounds according to claim 14 or a stereoisomer thereof or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

17. A compound according to claim 1, which is *kappa (κ)* opioid receptor (KOR) agonist.

18. A compound according to claim 14, which is *kappa (κ)* opioid receptor (KOR) agonist.

19. A method of binding a κ opioid receptor (KOR) in a patient, comprising administering to the patient in need thereof a therapeutically effective amount of a compound according to claim 1, or a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

20. The method according to claim 19, wherein the compound binds κ opioid receptor site.

21. The method according to claim 20, wherein the κ opioid receptor site is located in the central nervous system.

22. The method according to claim 20, wherein the κ opioid receptor site is located peripherally to the central nervous system.

23. A method of treating gastrointestinal dysfunction in a patient comprising administering to the patient a therapeutically effective amount of a compound according to claim 1 or a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

24. A method of treating ileus in a patient comprising administering to the patient a therapeutically effective amount of a compound according to claim 1 or a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

25. A method of treating pain in a patient comprising administering to the patient a therapeutically effective amount of a compound according to claim 1 or a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

26. A method of binding an opioid receptor in a patient, comprising administering to the patient a therapeutically effective amount of a compound according to claim 14, or a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

27. The method according to claim 26, wherein the compound binds κ opioid receptor site.

28. The method according to claim 27, wherein the κ opioid receptor site is located in the central nervous system.

29. The method according to claim 28, wherein the κ opioid receptor site is located peripherally to the central nervous system.

30. A method of treating gastrointestinal dysfunction in a patient comprising administering to the patient a therapeutically effective amount of a compound according to claim 14 or a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

31. A method of treating ileus in a patient comprising administering to the patient a therapeutically effective amount of a compound according to claim 14 or a stereoisomer thereof or a pharmaceutically acceptable salt thereof

32. A method of treating pain in a patient comprising administering to the patient a therapeutically effective amount of a compound according to claim 14 or a stereoisomer thereof or a pharmaceutically acceptable salt thereof

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2013/000230

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D207/-; C07D217/-; A61K31/-;

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI,EPODOC,CNKI,CNPAT,: kappa, opioid, opiate, receptor, KOR, agonist?, analgesia, gastrointestinal, analgesic, pyrrolidines

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US5232978A(MERCK PATENT GESELLSCHAFT MIT BESCHRANKTER HAFTUNG) 03 Aug.1993 (03.08.1993), column 1,lines 15-44; column 2,lines 4-28	1-18,25,32
Y		19-24,26-31
Y	CN1145781A(MERCK PATENT GESELLSCHAFT MIT BESCHRANKTER HAFTUNG) 26 Mar.1997(26.03.1997), pages 1-2,7	19-24,26-31
A	WO0014065Al(ADOLOR CORPORATION) 16 Mar.2000(16.03.2000), the whole document	1-32

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"document member of the same patent family

Date of the actual completion of the international search 24 Apr. 2013(24.04.2013)	Date of mailing of the international search report **13 Jun. 2013 (13.06.2013)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer SHIJie Telephone No. (86-10)82246672

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2013/000230

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

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

1. ☒ Claims Nos.: 19-32
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 19-32 are directed to methods of treatment. The search report has been carried out and based on the application of compounds for preparing compositions for use in a medical treatment.

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

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

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

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

Remark on protest

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

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/000230

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
US5232978A	03.08.1993	EP0483580A	06.05.1992
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		AU8553891A	07.05.1992
		CA2054648A	03.05.1992
		CA2006413A	23.06.1990
		ZA9108716A	26.08.1992
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		PT99383A	30.09.1992
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		EP0483580A3	02.09.1992
		EP0374756A	27.06.1990
		DE3935371A	05.07.1990
		JP2215769A	28.08.1990
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/000230

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
		AU708699B	12.08.1999
		US5977161A	02.11.1999
		NO309674B1	12.03.1999
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		ZA200102853A	26.06.2002
		JP2002524444A	06.08.2002
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		US6054445A	25.04.2000
		US6057323A	02.05.2000

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/000230

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2013/000230

Continuation of A : CLASSIFICATION OF SUBJECT MATTER

C07D207/1 2(2006.01)i

A61K3 l/40(2006.01)i

C07D207/04(2006.01)i

C07D2 17/1 2(2006.01)i