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(54) Title: NEW AZETIDINE DERIVATIVES AS NEUROKININ RECEPTOR ANTAGONISTS FOR THE TREATMENT OF GASTROINTESTINAL DISEASES

(57) Abstract: The present invention relates to new azetidine derivatives of formula I, to pharmaceutical compositions containing said compounds and to the use of said compounds as neurokinin (NK) receptor antagonists in the treatment of gastrointestinal diseases. The invention further relates to processes for the preparation of compounds of formula I and to new intermediates used in the preparation thereof.



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NEW COMPOUNDS FOR THE TREATMENT OF DISORDERS I

Field of the Invention

5 The present invention relates to new compounds of formula I, to pharmaceutical compositions containing said compounds, and to the use of said compounds in therapy. The present invention further relates to processes for the preparation of compounds of formula I and to new intermediates thereof.

10

Background of the invention

The neurokinins, also known as the tachykinins, comprise a class of peptide neurotransmitters which are found in the peripheral and central nervous systems. The three principal tachykinins are Substance P (SP), Neurokinin A (NKA) and Neurokinin B (NKB). At least three receptor types are known for the three principal tachykinins. Based upon their relative selectivities favouring the agonists SP, NKA and NKB, the receptors are classified as neurokinin 1 (NK₁), neurokinin 2 (NK₂) and neurokinin 3 (NK₃) receptors, respectively.

20

There is a need for an orally active NK receptor antagonist for the treatment of e.g. respiratory, cardiovascular, neuro, pain, oncology, inflammatory and/or gastrointestinal disorders. In order to increase the therapeutic index of such therapy it is desirable to obtain such a compound possessing no or minimal toxicity as well as being selective to said NK receptors. Furthermore, it is considered necessary that said medicament has favourable pharmacokinetic and metabolic properties thus providing an improved therapeutic and safety profile such as lower liver enzyme inhibiting properties.

It is well known that severe problems such as toxicity may occur if plasma levels of one medication are altered by the co-administration of another drug. This phenomenon - which is named drug-drug interactions - could happen if there is a change in the metabolism of

30

one drug caused by the co-administration of another substance possessing liver enzyme inhibiting properties. CYP (cytochrome P450) 3A4 is the most important enzyme in the human liver as a majority of oxidised drugs have been biotransformed by this enzyme. Accordingly, it is undesirable to employ a medication having a significant degree of such liver enzyme inhibiting properties. It has been found that many NK receptor antagonists known in the art inhibit the CYP3A4 enzyme to a certain level and consequently there is a possible risk if high doses of those compounds are being used in therapy. Thus, there is a need for a novel NK receptor antagonist with improved pharmacokinetic properties. The present invention provides compounds with CYP3A4 enzyme inhibiting properties at a low level, as comparatively high IC₅₀ values are obtained in a CYP3A4 inhibiting assay. Said method for determining CYP3A4 inhibition is described in Bapiro et al; Drug Metab. Dispos. 29, 30-35 (2001).

It is well known that certain compounds may cause undesirable effects on cardiac repolarisation in man, observed as a prolongation of the QT interval on electrocardiograms (ECG). In extreme circumstances, this drug-induced prolongation of the QT interval can lead to a type of cardiac arrhythmia called Torsades de Pointes (TdP; Vandenberg et al. hERG K⁺ channels: friend and foe. Trends Pharmacol Sci 2001; 22: 240-246), leading ultimately to ventricular fibrillation and sudden death. The primary event in this syndrome is inhibition of the rapid component of the delayed rectifying potassium current (IKr) by these compounds. The compounds bind to the aperture-forming alpha sub-units of the channel protein carrying this current. The aperture-forming alpha sub-units are encoded by the human ether-a-go-go-related gene (hERG). Since IKr plays a key role in repolarisation of the cardiac action potential, its inhibition slows repolarisation and this is manifested as a prolongation of the QT interval. Whilst QT interval prolongation is not a safety concern per se, it carries a risk of cardiovascular adverse effects and in a small percentage of people it can lead to TdP and degeneration into ventricular fibrillation.

Compounds of the present invention have particularly low activity against the hERG-encoded potassium channel. In this regard, low activity against hERG *in vitro* is indicative of low activity *in vivo*.

5 It is also desirable for drugs to possess good metabolic stability in order to enhance drug efficacy. Stability against human microsomal metabolism *in vitro* is indicative of stability towards metabolism *in vivo*.

EP 0625509, EP 0630887, WO 95/05377, WO 95/12577, WO 95/15961, WO 96/24582,
10 WO 00/02859, WO 00/20003, WO 00/20389, WO 00/25766, WO 00/34243, WO 02/51807 and WO 03/037889 disclose piperidinylbutylamide derivatives, which are tachykinin antagonists.

“4-Amino-2-(aryl)-butylbenzamides and Their Conformationally Constrained Analogues.
15 Potent Antagonists of the Human Neurokinin-2 (NK₂) Receptor”, *Roderick MacKenzie, A., et al, Bioorganic & Medicinal Chemistry Letters (2003), 13, 2211-2215*, discloses the compound *N*-[2-(3,4-dichlorophenyl)-4-(3-morpholin-4-ylazetidin-1-yl)butyl]-*N*-methylbenzamide which was found to possess functional NK₂ receptor antagonistic properties.

20 WO 96/05193, WO 97/27185 and EP 0962457 disclose azetidinyllactam derivatives with tachykinin antagonist activity.

EP 0790248 discloses azetidinyllazapiperidones and azetidinyllaxapiperidones,
25 which are stated to be tachykinin antagonists.

WO 99/01451 and WO 97/25322 disclose azetidinyllpiperidine derivatives claimed to be tachykinin antagonists.

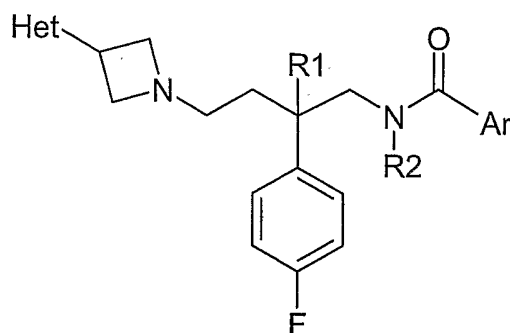
30 EP 0791592 discloses azetidinyllglutarimides with tachykinin antagonistic properties.

WO2004/110344 A2 discloses dual NK1,2 antagonists and the use thereof.

An object of the present invention was to provide novel neurokinin antagonists useful in
5 therapy. A further object was to provide novel compounds having improved
pharmacokinetic and metabolic properties as well as limited interaction with the hERG
channel.

10 Outline of the invention

The present invention provides a compound of the general formula (I)



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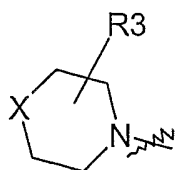
wherein

R1 is hydrogen;

20 R2 is C₁-C₄ alkyl, wherein one or more of the hydrogen atoms of the alkyl group may be substituted for a fluoro atom;

Het is selected from 2,5-diazabicyclo[2.2.1]heptane, octahydropyrrolo[3,4-*c*]pyrrole, 1,4-diazepane, octahydropyrrolo[1,2-*a*]pyrazine, octahydro-2*H*-pyrido[1,2-*a*]pyrazine, octahydropyrazino[2,1-*c*][1,4]oxazine; optionally substituted by C₁-C₄ alkyl, wherein one or more of the hydrogen atoms of the alkyl group may be substituted for a fluoro atom;
25 with the proviso that Het is connected to the azetidine ring at one of its nitrogen atoms;

or Het is



wherein

X is CH₂, O or NR₆;

5 R₃ is (CH₂)_mNR₄R₅ or R₃ is H if X is NR₆;

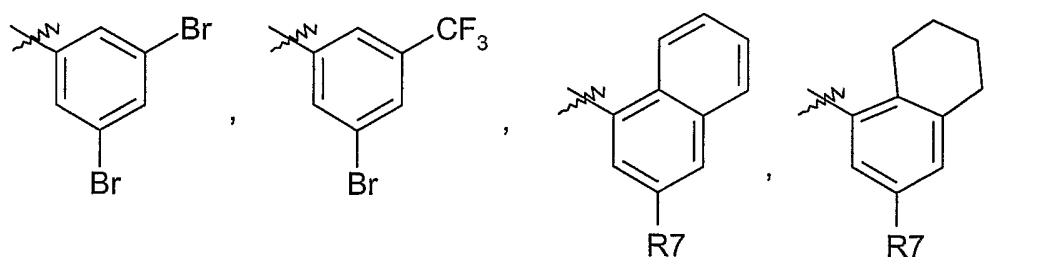
R₄ and R₅ is each and independently selected from hydrogen, C₁-C₄ alkyl or C₂-C₄ hydroxyalkyl, wherein one or more of the hydrogen atoms of the alkyl group or hydroxyalkyl group may be substituted for a fluoro atom;

or R₄ and R₅ may together form an azacycloalkane having 4 to 8 atoms, optionally
10 substituted by one or more fluoro atoms;

m is 0, 1, 2, 3 or 4 with the proviso that if m is 0 then X is CH₂ and R₃ is attached to the 3- or 4-position of the ring;

R₆ is hydrogen, C₁-C₄ alkyl, C₂-C₄ hydroxyalkyl, 2-(dimethylamino)-2-oxoethyl, wherein
15 one or more of the hydrogen atoms of the alkyl group or hydroxyalkyl group may be substituted for a fluoro atom; and

Ar is selected from



wherein

20 R₇ is CN or F;

as well as pharmaceutically and pharmacologically acceptable salts thereof, and enantiomers of the compound of formula I and salts thereof.

The present invention relates to compounds of formula I as defined above as well as to salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I.

5 The compounds of the present invention are capable of forming salts with various inorganic and organic acids and such salts are also within the scope of this invention. Examples of such acid addition salts include acetate, adipate, ascorbate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, citrate, cyclohexyl sulfamate, ethanesulfonate, fumarate, glutamate, glycolate, hemisulfate, 2-
10 hydroxyethylsulfonate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, hydroxymaleate, lactate, malate, maleate, methanesulfonate, 2-naphthalenesulfonate, nitrate, oxalate, palmoate, persulfate, phenylacetate, phosphate, picrate, pivalate, propionate, quinate, salicylate, stearate, succinate, sulfamate, sulfanilate, sulfate, tartrate, tosylate (p-toluenesulfonate), and undecanoate.

15

Pharmaceutically acceptable salts may be prepared from the corresponding acid in conventional manner. Non-pharmaceutically-acceptable salts may be useful as intermediates and as such are another aspect of the present invention.

20 Acid addition salts may also be in the form of polymeric salts such as polymeric sulfonates.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in
25 which the salt is poorly soluble, or in a solvent such as water, which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion-exchange resin.

Compounds of formula I have one or more chiral centres, and it is to be understood that the
30 invention encompasses all optical isomers, enantiomers and diastereomers. The compounds according to formula (I) can be in the form of the single stereoisomers, i.e. the

single enantiomer (the *R*-enantiomer or the *S*-enantiomer) and/or diastereomer. The compounds according to formula (I) can also be in the form of a racemic mixture, i.e. an equimolar mixture of enantiomers.

- 5 It is to be understood that the present invention also relates to any and all tautomeric forms of the compounds of formula I.

The compounds can exist as a mixture of conformational isomers. The compounds of this invention comprise both mixtures of, and individual, conformational isomers.

10

Unless stated otherwise, the term "alkyl" includes straight as well as branched chain C₁₋₄ alkyl groups, for example methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl. One or more of the hydrogen atoms of the alkyl group may be substituted for a fluoro atom, such as in difluoromethyl or trifluoromethyl.

15

As used herein, C₁₋₄ hydroxyalkyl is a hydroxyalkyl group comprising 1-4 carbon atoms and a hydroxyl group. One or more of the hydrogen atoms of the hydroxyalkyl group may be substituted for a fluoro atom.

20

Pharmaceutical formulations

According to one aspect of the present invention there is provided a pharmaceutical formulation comprising a compound of formula I, as a single enantiomer, a racemate or a mixture thereof as a free base or pharmaceutically acceptable salts thereof, for use in
25 prevention and/or treatment of respiratory, cardiovascular, neuro, pain, oncology, inflammatory and/or gastrointestinal disorders.

The pharmaceutical compositions of this invention may be administered in standard
30 manner for the disease condition that it is desired to treat, for example by oral, topical,

parenteral, buccal, nasal, vaginal or rectal administration or by inhalation or insufflation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, pellets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided
5 powders or aerosols or nebulisers for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention the pharmaceutical composition of
10 this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more disease conditions referred to herein.

The pharmaceutical compositions of this invention will normally be administered to
15 humans so that, for example, a daily dose of 0.01 to 25 mg/kg body weight (and preferably of 0.1 to 5 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

20

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention. For example a tablet or capsule for oral administration may conveniently contain up to 250 mg (and typically 5 to 100 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof. In another example, for administration by
25 inhalation, a compound of the formula (I) or a pharmaceutically acceptable salt thereof may be administered in a daily dosage range of 5 to 100 mg, in a single dose or divided into two to four daily doses. In a further example, for administration by intravenous or intramuscular injection or infusion, a sterile solution or suspension containing up to 10% w/w (and typically 5% w/w) of a compound of the formula (I) or a pharmaceutically
30 acceptable salt thereof may be used.

Medical and pharmaceutical use

The present invention provides a method of treating or preventing a disease condition wherein antagonism of tachykinins acting at the NK receptors is beneficial which
5 comprises administering to a subject an effective amount of a compound of the formula (I) or a pharmaceutically-acceptable salt thereof. The present invention also provides the use of a compound of the formula (I) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for use in a disease condition wherein antagonism of tachykinins acting at the NK receptors is beneficial.

10 The compounds of formula (I) or pharmaceutically acceptable salts or solvates thereof may be used in the manufacture of a medicament for use in the prevention or treatment of respiratory, cardiovascular, neuro, pain, oncology and/or gastrointestinal disorders.

15 Examples of such disorders are asthma, allergic rhinitis, pulmonary diseases, cough, cold, inflammation, chronic obstructive pulmonary disease, airway reactivity, urticaria, hypertension, rheumatoid arthritis, edema, angiogenesis, pain, migraine, tension headache, psychoses, depression, anxiety, Alzheimer's disease, schizophrenia, Huntington's disease, bladder hypermotility, urinary incontinence, eating disorder, manic
20 depression, substance dependence, movement disorder, cognitive disorder, obesity, stress disorders, micturition disorders, mania, hypomania and aggression, bipolar disorder, cancer, carcinoma, fibromyalgia, non cardiac chest pain, gastrointestinal hypermotility, gastric asthma, Crohn's disease, gastric emptying disorders, ulcerative colitis, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), emesis, gastric asthma, gastric
25 motility disorders, gastro-esophageal reflux disease (GERD) or functional dyspepsia.

Pharmacology

Transfection and culturing of cells used in FLIPR and Binding assays

Chinese Hamster Ovary (CHO) K1 cells (obtained from ATCC) were stably transfected
5 with the human NK₂ receptor (hNK₂R cDNA in pRc/CMV, Invitrogen) or the human NK₃
receptor (hNK₃R in pcDNA 3.1/Hygro (+)/IRES/CD8, Invitrogen vector modified at
AstraZeneca EST-Bio UK, Alderley Park). The cells were transfected with the cationic
lipid reagent LIPOFECTAMINE™ (Invitrogen) and selection was performed with
Geneticin (G418, Invitrogen) at 1mg/ml for the hNK₂R transfected cells and with
10 Hygromycin (Invitrogen) at 500µg/ml for the hNK₃R transfected cells. Single cell clones
were collected by aid of Fluorescence Activated Cell Sorter (FACS), tested for
functionality in a FLIPR assay (see below), expanded in culture and cryopreserved for
future use. CHO cells stably transfected with human NK₁ receptors originates from
AstraZeneca R&D, Wilmington USA. Human NK₁ receptor cDNA (obtained from RNA-
15 PCR from lung tissue) was subcloned into pRcCMV (Invitrogen). Transfection was
performed by Calcium Phosphate and selection with 1mg/ml G418.

The CHO cells stably transfected with hNK₁R, hNK₂R and hNK₃R were cultured in a
humidified incubator under 5% CO₂, in Nut Mix F12 (HAM) with Glutamax I, 10% Foetal
20 Bovine Serum (FBS), 1% Penicillin/Streptomycin (PEST) supplemented with 200µg/ml
Geneticin for the hNK₁R and hNK₂R expressing cells and 500µg/ml Hygromycin for the
hNK₃R expressing cells. The cells were grown in T175 flasks and routinely passaged when
70-80% confluent for up to 20-25 passages.

25 ***Assessing the Activity of Selected test Compounds to Inhibit Human NK₁/NK₂/NK₃ Receptor Activation (FLIPR assay)***

The activity of a compound of the invention to inhibit NK₁/NK₂/NK₃ receptor activation
measured as NK₁/NK₂/NK₃ receptor mediated increase in intracellular Ca²⁺ was assessed
by the following procedure:

CHO cells stably transfected with human NK₁, NK₂ or NK₃ receptors were plated in black walled/clear bottomed 96-well plates (Costar 3904) at 3.5x10⁴ cells per well and grown for approximately 24h in normal growth media in a 37°C CO₂-incubator.

Before the FLIPR assay the cells of each 96-well plate were loaded with the Ca²⁺ sensitive dye Fluo-3 (TEFLABS 0116) at 4μM in a loading media consisting of Nut Mix F12 (HAM) with Glutamax I, 22mM HEPES, 2.5mM Probenicid (Sigma P-8761) and 0.04% Pluronic F-127 (Sigma P-2443) for 1 h kept dark in a 37°C CO₂-incubator. The cells were then washed three times in assay buffer (Hanks balanced salt solution (HBSS) containing 20mM HEPES, 2.5mM Probenicid and 0.1% BSA) using a multi-channel pipette leaving them in 150μl at the end of the last wash. Serial dilutions of a test compound in assay buffer (final DMSO concentration kept below 1%) were automatically pipetted by FLIPR (Fluorometric Imaging Plate Reader) into each test well and the fluorescence intensity was recorded (excitation 488 nm and emission 530 nm) by the FLIPR CCD camera for a 2 min pre-incubation period. 50μl of the Substance P (NK₁ specific), NKA (NK₂ specific), or Pro-7-NKB (NK₃ specific) agonist solution (final concentration equivalent to an approximate EC₆₀ concentration) was then added by FLIPR into each well already containing 200μl assay buffer (containing the test compound or vehicle) and the fluorescence was continuously monitored for another 2 min. The response was measured as the peak relative fluorescence after agonist addition and IC₅₀s were calculated from ten-point concentration-response curves for each compound. The IC₅₀s were then converted to pK_B values with the following formula:

$$K_B = IC_{50} / 1 + (EC_{60} \text{ conc. of agonist used in assay} / EC_{50} \text{ agonist})$$

$$pK_B = -\log K_B$$

Determining the Dissociation Constant (K_i) of compounds for Human NK₁/NK₂/NK₃ Receptors (Binding Assay)

Membranes were prepared from CHO cells stably transfected with human NK₁, NK₂ or NK₃ receptors according to the following method.

Cells were detached with Accutase® solution, harvested in PBS containing 5% FBS by centrifugation, washed twice in PBS and resuspended to a concentration of 1x10⁸ cells/ml

- in Tris-HCl 50 mM, KCl 300 mM, EDTA-N₂ 10 mM pH 7.4 (4°C). Cell suspensions were homogenized with an UltraTurrax 30 s 12.000 rpm. The homogenates were centrifuged at 38.000 x g (4°C) and the pellet resuspended in Tris-HCl 50 mM pH 7.4. The homogenization was repeated once and the homogenates were incubated on ice for 45 min.
- 5 The homogenates were again centrifuged as described above and resuspended in Tris-HCl 50mM pH 7.4. This centrifugation step was repeated 3 times in total. After the last centrifugation step the pellet was resuspended in Tris-HCl 50mM and homogenized with Dual Potter, 10 strokes to a homogenous solution, an aliquot was removed for protein determination. Membranes were aliquoted and frozen at -80°C until use.
- 10 The radioligand binding assay is performed at room temperature in 96-well microtiter plates (No-binding Surface Plates, Corning 3600) with a final assay volume of 200µl/well in incubation buffer (50mM Tris buffer (pH 7.4 RT) containing 0.1 % BSA, 40 mg/L Bacitracin, complete EDTA-free protease inhibitor cocktail tablets 20 pills/L (Roche) and 3mM MnCl₂). Competition binding curves were done by adding increasing amounts of the
- 15 test compound. Test compounds were dissolved and serially diluted in DMSO, final DMSO concentration 1.5 % in the assay. 50µl Non labelled ZD 6021 (a non selective NK-antagonist, 10µM final conc) was added for measurement of *non-specific binding*. For *total binding*, 50µl of 1.5% DMSO (final conc) in incubation buffer was used. [³H-Sar, Met(O₂)-Substance P] (4nM final conc) was used in binding experiments on hNK_{1r}. [³H-SR48968]
- 20 (3nM final conc.) for hNK_{2r} and [³H-SR142801] (3nM final conc) for binding experiments on hNK_{3r}. 50µl radioligand, 3µl test compound diluted in DMSO and 47µl incubation buffer were mixed with 5-10µg cell membranes in 100µl incubation buffer and incubated for 30 min at room temperature on a microplate shaker.
- The membranes were then collected by rapid filtration on Filtermat B(Wallac), presoaked
- 25 in 0.1% BSA and 0.3% Polyethyleneimine (Sigma P-3143), using a Micro 96 Harvester (Skatron Instruments, Norway). Filters were washed by the harvester with ice-cold wash buffer (50mM Tris-HCl, pH 7.4 at 4°C, containing 3mM MnCl₂) and dried at 50°C for 30-60 min. Meltilex scintillator sheets were melted on to filters using a Microsealer (Wallac, Finland) and the filters were counted in a β-Liquid Scintillation Counter (1450 Microbeta,
- 30 Wallac, Finland).

The K_i value for the unlabeled ligand was calculated using the Cheng-Prusoff equation (Biochem. Pharmacol. 22:3099-3108, 1973): where L is the concentration of the radioactive ligand used and K_d is the affinity of the radioactive ligand for the receptor, determined by saturation binding.

5 Data was fitted to a four-parameter equation using Excel Fit.

$$K_i = IC_{50} / (1 + (L/K_d))$$

Results

10 In general, the compounds of the invention, which were tested, demonstrated statistically significant antagonistic activity at the NK_1 receptor within the range of 7-9 for the pK_B . For the NK_2 receptor the range for the pK_B was 7-9. In general, the antagonistic activity at the NK_3 receptor was 6-9 for the pK_B .

15 In general, the compounds of the invention, which were tested, demonstrated statistically significant CYP3A4 inhibition at a low level. The IC_{50} values tested according to Bapiro et al; Drug Metab. Dispos. 29, 30-35 (2001) were generally greater than 2 μM .

Activity against hERG

20 The activity of compounds according to formula I against the hERG-encoded potassium channel can be determined according to Kiss L, et al. Assay Drug Dev Technol. 1 (2003), 127-35: "High throughput ion-channel pharmacology: planar-array-based voltage clamp".

In general, the compounds of the invention, which were tested, demonstrated statistically
25 significant hERG activity at a low level. The IC_{50} values tested as described above were generally greater than 10 μM .

Metabolic stability

The metabolic stability of compounds according to formula I can be determined as
30 described below:

The rate of biotransformation can be measured as either metabolite(s) formation or the rate of disappearance of the parent compound. The experimental design involves incubation of low concentrations of substrate (usually 1.0 μ M) with liver microsomes (usually 0.5 mg/ml) and taking out aliquotes at varying time points (usually 0, 5, 10, 15, 20, 30, 40 min.). The test compound is usually dissolved in DMSO. The DMSO concentration in the incubation mixture is usually 0.1% or less since more solvent can drastically reduce the activities of some CYP450s. Incubations are done in 100 mM potassium phosphate buffer, pH 7.4 and at 37 °C. Acetonitrile or methanol is used to stop the reaction.

Biological evaluation

Gerbil Foot Tap (NK1 specific test model)

Male Mongolian gerbils (60-80g) are purchased from Charles River, Germany. On arrival, they are housed in groups of ten, with food and water *ad libitum* in temperature and humidity-controlled holding rooms. The animals are allowed at least 7 days to acclimatize to the housing conditions before experiments. Each animal is used only once and euthanized immediately after the experiment by heart punctuation or a lethal overdose of penthobarbital sodium.

Gerbils are anaesthetized with isoflurane. Potential CNS-permeable NK1 receptor antagonists are administered intraperitoneally, intravenously or subcutaneously. The compounds are given at various time points (typically 30-120 minutes) prior to stimulation with agonist.

The gerbils are lightly anaesthetized using isofluorane and a small incision is made in the skin over bregma. 10 pmol of ASMSP, a selective NK1 receptor agonist, is administered icv in a volume of 5 μ l using a Hamilton syringe with a needle 4 mm long. The wound is clamped shut and the animal is placed in a small plastic cage and allowed to wake up. The

cage is placed on a piece of plastic tubing filled with water and connected to a computer via a pressure transducer. The number of hind feet taps is recorded.

Fecal pellet output (NK2 specific test model)

5 The in vivo effect (NK2) of the compounds of formula I can be determined by measuring NK2 receptor agonist-induced fecal pellet output using gerbil as described in e.g. The Journal of Pharmacology and Experimental Therapeutics (2001), pp. 559-564.

10 *Colorectal distension model*

Colorectal distension (CRD) in gerbils is performed as previously described in rats and mice (Tammperre A, Brusberg M, Axenborg J, Hirsch I, Larsson H, Lindström E. Evaluation of pseudo-affective responses to noxious colorectal distension in rats by manometric recordings. Pain 2005; 116: 220-226; Arvidsson S, Larsson M, Larsson H, 15 Lindström E, Martinez V. Assessment of visceral pain-related pseudo-affective responses to colorectal distension in mice by intracolonic manometric recordings. J Pain 2006; 7: 108-118) with slight modifications. Briefly, gerbils are habituated to Bollmann cages 30-60 min per day for three consecutive days prior to experiments to reduce motion artefacts due to restraint stress. A 2 cm polyethylene balloon (made in-house) with connecting 20 catheter is inserted in the distal colon, 2 cm from the base of the balloon to the anus, during light isoflurane anaesthesia (Forene[®], Abbott Scandinavia AB, Solna, Sweden). The catheter is fixed to the tail with tape. The balloons are connected to pressure transducers (P-602, CFM-k33, 100 mmHg, Bronkhorst HI-TEC, Veenendal, The Netherlands). Gerbils are allowed to recover from sedation in the Bollmann cages for at least 15 min before the 25 start of experiments.

A customized barostat (AstraZeneca, Mölndal, Sweden) is used to manage air inflation and balloon pressure control. A customized computer software (PharmLab on-line 4.0) running on a standard computer is used to control the barostat and to perform data collection. The distension paradigm used consists of 12 repeated phasic distensions at 80 mmHg, with a 30 pulse duration of 30 sec at 5 min intervals. Compounds or their respective vehicle are

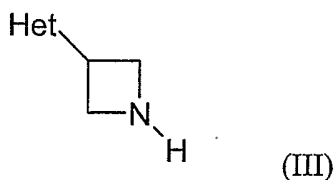
administered as intraperitoneal (i.p.) injections before the CRD paradigm. Each gerbil receives both vehicle and compound on different occasions with at least two days between experiments. Hence, each gerbil serves as its own vehicle control.

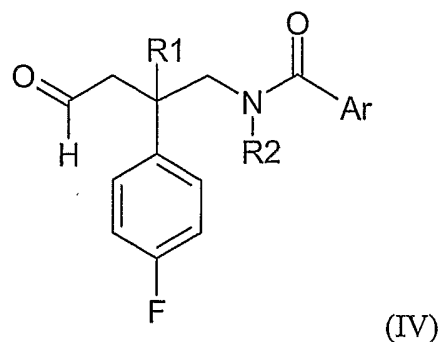
The analog input channels are sampled with individual sampling rates, and digital filtering is performed on the signals. The balloon pressure signals are sampled at 50 samples/s. A highpass filter at 1 Hz is used to separate the contraction-induced pressure changes from the slow varying pressure generated by the barostat. A resistance in the airflow between the pressure generator and the pressure transducer further enhances the pressure variations induced by abdominal contractions of the animal. A customized computer software (PharmLab off-line 4.0) is used to quantify the magnitude of highpass-filtered balloon pressure signals. The average rectified value (ARV) of the highpass-filtered balloon pressure signals is calculated for 30 s before the pulse (i.e baseline response) and for the duration of the pulse. When calculating the magnitude of the highpass-filtered balloon pressure signals, the first and last seconds of each pulse are excluded since these reflect artifact signals produced by the barostat during inflation and deflation and do not originate from the animal.

Methods of preparation

In another aspect the present invention provides a process for preparing a compound of the formula (I) or salts thereof which process comprises:

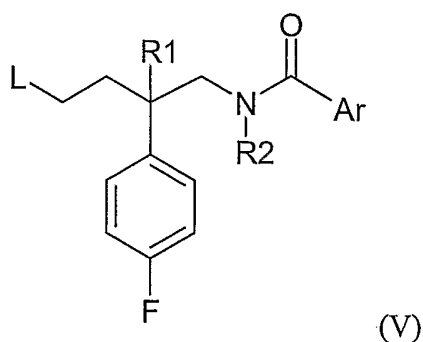
- a) reacting a compound of the formula (III) with a compound of the formula (IV):





wherein R1-R2, Het, and Ar are as hereinbefore defined; and the conditions are such that reductive alkylation of the compounds of the formula (III) forms an N-C bond between the nitrogen atom of the azetidine group of the compounds of formula (III) and the carbon atom of the aldehyde group of the compounds of formula (IV); or

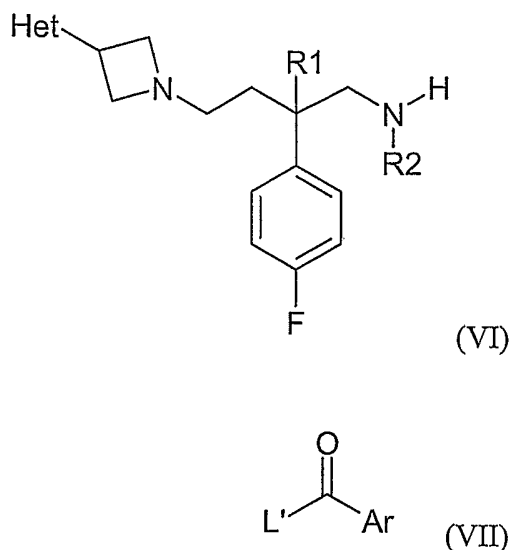
b) reacting a compound of the formula (III) with a compound of the formula (V):



wherein R1-R2, Het, and Ar are as hereinbefore defined; and L is a group such that alkylation of the compounds of the formula (III) forms an N-C bond between the nitrogen atom of the azetidine group of the compounds of formula (III) and the carbon atom of the compounds of formula (V) that is adjacent to the L group; or

c) reacting a compound of the formula (VI) with a compound of the formula (VII):

18



5 wherein R1-R2, Het and Ar are as hereinbefore defined; and L' is a leaving group;
wherein any other functional group is protected, if necessary, and:

- i) removing any protecting groups;
- ii) optionally oxidizing any oxidizable atoms;
- iii) optionally forming a pharmaceutically acceptable salt.

10

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question, and may be introduced and removed by conventional methods; see for example *Protecting Groups in Organic Chemistry*; Theodora W. Greene. Methods of removal are
15 chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

It will also be appreciated that certain of the various optional substituents in the compounds of the formula (I) may be introduced by standard aromatic substitution
20 reactions or generated by conventional functional group modifications either prior to or immediately following the processes described hereinabove. The reagents and reaction conditions for such procedures are well known in the chemical art.

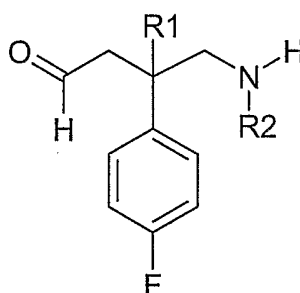
The compounds of the formulae (III) and (IV) are reacted under conditions of reductive
25 alkylation. The reaction is typically performed at a non-extreme temperature, for example

0 - 40 °C, in a substantially inert solvent for example dichloromethane. Typical reducing agents include borohydrides such as sodium cyanoborohydride.

The compounds of the formulae (III) and (V) are reacted under conditions of alkylation.

5 Typically in the compounds of the formula (V) L is a leaving group such as halogen or alkylsulfonyloxy. The reaction is typically performed at an elevated temperature, for example 30 - 130 °C, in a substantially inert solvent for example DMF.

The compounds of the formula (III) are known or may be prepared in conventional
10 manner. The compounds of the formula (IV) may be prepared, for example, by reacting a compound of the formula (VII) with a compound of the formula (VIII):



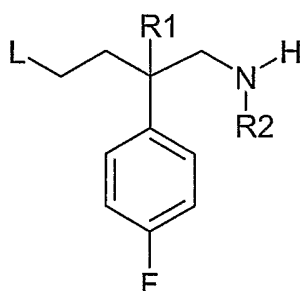
(VIII)

15

wherein R1-R2 are as hereinbefore defined under conventional acylation conditions.

The compounds of the formula (V) may be prepared, for example, by reacting a compound
of the formula (VII) with a compound of the formula (IX):

20

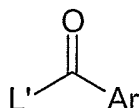


(IX)

wherein R1-R2 and L are as hereinbefore defined under conventional acylation conditions.

The compounds of the formulae (VI) and (VII) may be reacted under conventional acylation conditions wherein

5



is an acid or an activated acid derivative. Such activated acid derivatives are well known in the literature. They may be formed in situ from the acid or they may be prepared,
10 isolated and subsequently reacted. Typically L' is chloro thereby forming the acid chloride. Typically the acylation reaction is performed in the presence of a non-nucleophilic base, for example N,N-diisopropylethylamine, in a substantially inert solvent such as dichloromethane at a non-extreme temperature.

15 The compounds of the formula (VIII) and (IX) are known or may be prepared in conventional manner.

Examples

20 It should be emphasised that the compounds of the present invention most often show highly complex NMR spectra due to the existence of conformational isomers. This is believed to be a result from slow rotation about the amide and/or aryl bond. The following abbreviations are used in the presentation of the NMR data of the compounds: s-singlet; d-doublet; t-triplet; qt-quartet; qn-quintet; m-multiplet; b-broad; cm-complex multiplet,
25 which may include broad peaks.

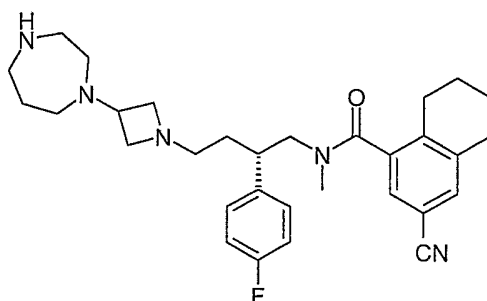
The following examples will describe, but not limit, the invention.

The following abbreviations are used in the experimental: Boc (*tert*-butoxycarbonyl), DCC (1,3-dicyclohexylcarbodiimide), DIPEA (*N,N*-diisopropylethylamine), DMF (*N,N*-dimethylformamide), TBTU (*N,N,N',N'*-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate), THF (tetrahydrofuran) and RT (room temperature).

5

Example 1

3-Cyano-*N*-[(2*S*)-4-[3-(1,4-diazepan-1-yl)azetidin-1-yl]-2-(4-fluorophenyl)butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide



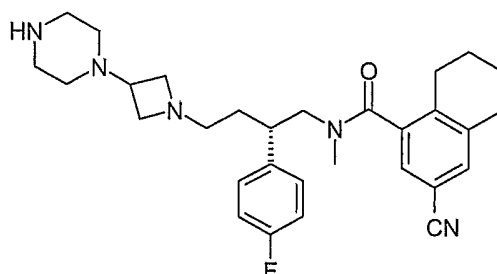
10

tert-Butyl 4-{1-[(3*S*)-4-[[3-(3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl]-(methylamino)-3-(4-fluorophenyl)butyl]azetidin-3-yl}-1,4-diazepane-1-carboxylate (see Method 1; 63 mg, 0.10 mmol) was dissolved in methylene chloride (2 mL) and to the resultant solution was added HCl (4M in dioxane, 1 mL, 4 mmol). The solution was stirred at RT and within a few minutes a precipitate was formed. Methanol (1 mL) was added and stirring continued at RT for 4 h. The solvent was removed by evaporation to yield 70 mg of crude material, which then was dissolved in 1 mL of methanol/methylene chloride (1:9). The product was purified by chromatography on a cation exchange column (Isolute SCX-2, 2 g) (ammonia saturated methanol – methylene chloride 0 to 50%). There was obtained 57 mg (100%) of the title compound. ¹H NMR (500 MHz, CDCl₃): 1.4-2.4 (cm, 8H), 2.5-2.9 (cm, 10H), 3.0-4.0 (cm, 15H), 5.4-6.4 (b, 1H), 6.7-7.1 (cm, 3H), 7.2-7.4 (cm, 3H); LCMS: *m/z* 518 (M+1)⁺.

20

Example 2

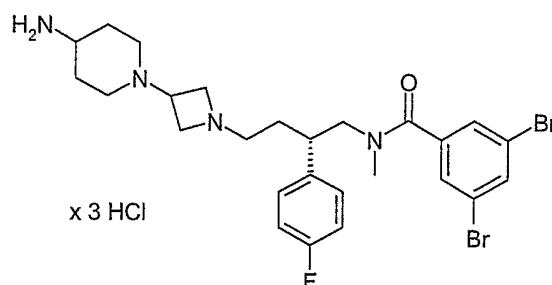
3-Cyano-N-[(2*S*)-2-(4-fluorophenyl)-4-(3-piperazin-1-ylazetidin-1-yl)butyl]-N-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide



5 *tert*-Butyl 4-{1-[(3*S*)-4-[(3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl]-(methyl)amino]-3-(4-fluorophenyl)butyl}azetidin-3-yl}piperazine-1-carboxylate (see Method 3; 320 mg, 0.53 mmol) was dissolved in methylene chloride (10 mL) and to the resultant solution was added HCl (4M in dioxane, 10 mL, 40 mmol). The solution was stirred at RT for 5 h and then the solvent was removed by evaporation. The residue was
 10 dissolved in methylene chloride and the solution was washed with a saturated aqueous NaHCO₃ solution and then with water. The organic phase was separated by means of a phase separator column and then the solvent was removed by evaporation. There was obtained 240 mg (90%) of the title compound. $[\alpha]_D^{20} = -15.3^\circ$ (*c* 0.4 g/mL, methanol); ¹H NMR (500 MHz, CDCl₃): 1.2-2.0 (cm, 6H), 2.1-4.2 (cm, 25H), 6.6-7.1 (cm, 3H), 7.2-7.3 (b, 3H); LCMS: *m/z* 504 (M+1)⁺.
 15

Example 3

N-[(2*S*)-4-[3-(4-Aminopiperidin-1-yl)azetidin-1-yl]-2-(4-fluorophenyl)butyl]-3,5-dibromo-N-methylbenzamide trihydrochloride



20

tert-Butyl (1-{1-[(3*S*)-4-[(3,5-dibromobenzoyl)(methyl)amino]-3-(4-fluorophenyl)-butyl]azetidin-3-yl}piperidin-4-yl)carbamate (see Method 4; 573 mg, 0.82 mmol) was dissolved in a methanol solution of HCl (1.25M, 50 mL, 62.5 mmol). The solution was

stirred at RT for 5 h and then the solvent was removed by evaporation and then co-evaporated with toluene. There was obtained 610 mg (100%) of the title compound. ¹H NMR (500 MHz, DMSO-d₆): 1.8-2.2 (cm, 5H), 2.5-4.8 (cm, 24H), 6.8-8.0 (cm, 6H), 8.4 (b, 1H); LCMS: m/z 597 (M+1)⁺.

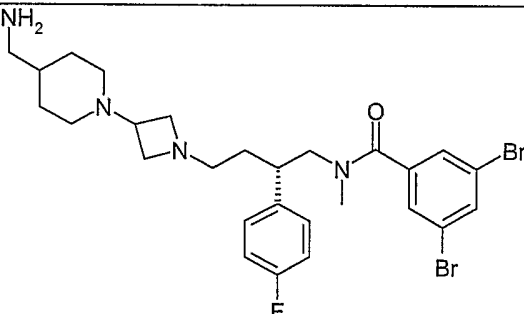
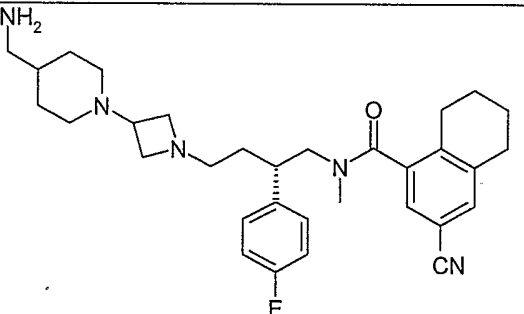
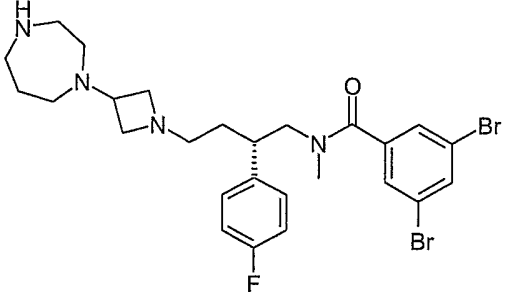
5

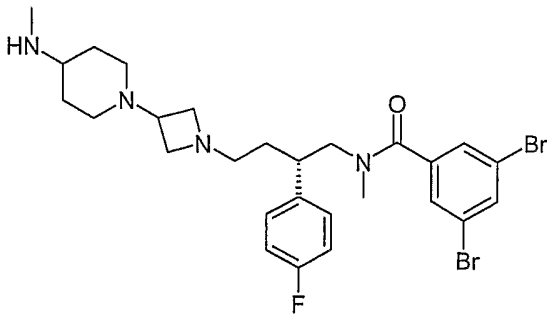
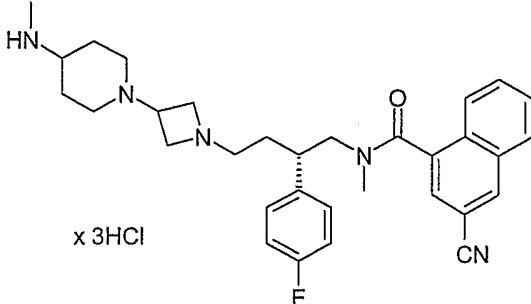
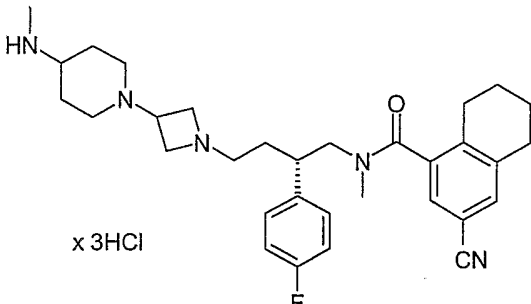
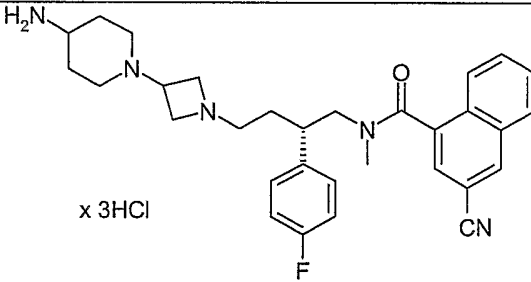
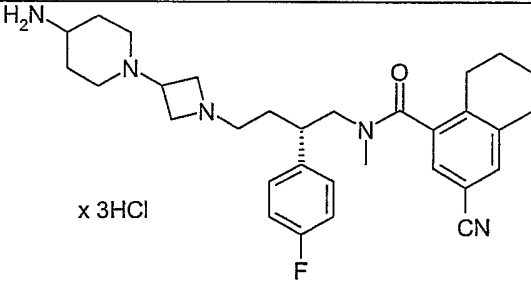
Examples 4-16

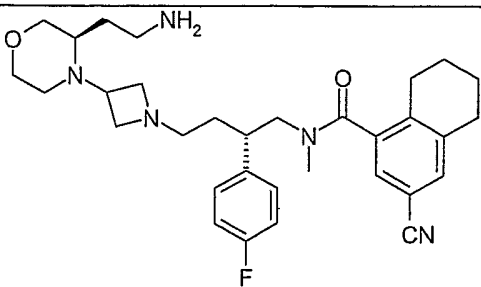
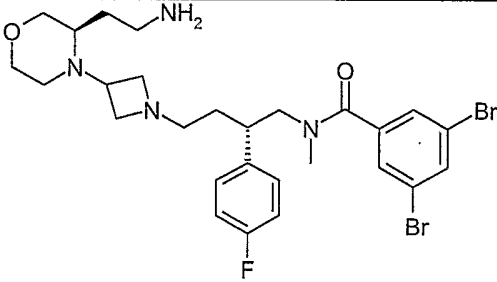
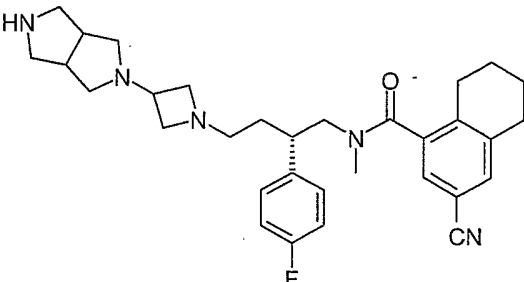
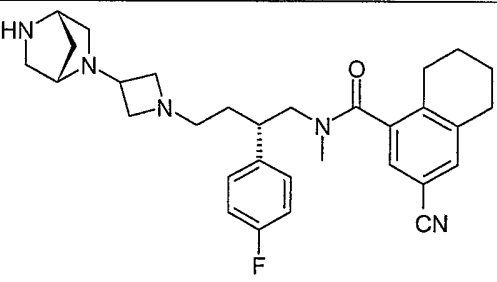
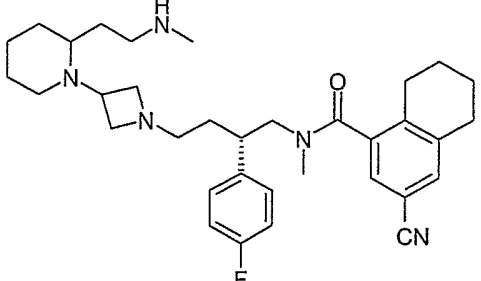
The following compounds, which are tabulated below, were synthesized in an analogous way to that of Example 1, Example 2 and Example 3 using the appropriate Boc protected amine intermediates (see below): *N*-[(2*S*)-4-{3-[4-(aminomethyl)piperidin-1-yl]azetidin-1-yl}-2-(4-fluorophenyl)butyl]-3,5-dibromo-*N*-methylbenzamide (Ex. 4), *N*-[(2*S*)-4-{3-[4-(aminomethyl)piperidin-1-yl]azetidin-1-yl}-2-(4-fluorophenyl)butyl]-3-cyano-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (Ex. 5), 3,5-dibromo-*N*-[(2*S*)-4-[3-(1,4-diazepan-1-yl)azetidin-1-yl]-2-(4-fluorophenyl)butyl]-*N*-methylbenzamide (Ex. 6), 3,5-dibromo-*N*-[(2*S*)-2-(4-fluorophenyl)-4-{3-[4-(methylamino)piperidin-1-yl]azetidin-1-yl}butyl]-*N*-methylbenzamide (Ex. 7), 3-cyano-*N*-[(2*S*)-2-(4-fluorophenyl)-4-{3-[4-(methylamino)piperidin-1-yl]azetidin-1-yl}butyl]-*N*-methyl-1-naphthamide trihydrochloride (Ex. 8), 3-cyano-*N*-[(2*S*)-2-(4-fluorophenyl)-4-{3-[4-(methylamino)piperidin-1-yl]azetidin-1-yl}butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (Ex. 9), *N*-[(2*S*)-4-[3-(4-aminopiperidin-1-yl)azetidin-1-yl]-2-(4-fluorophenyl)butyl]-3-cyano-*N*-methyl-1-naphthamide trihydrochloride (Ex. 10), *N*-[(2*S*)-4-[3-(4-aminopiperidin-1-yl)azetidin-1-yl]-2-(4-fluorophenyl)butyl]-3-cyano-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (Ex. 11), *N*-[(2*S*)-4-{3-[(3*R*)-3-(2-aminoethyl)morpholin-4-yl]azetidin-1-yl}-2-(4-fluorophenyl)butyl]-3-cyano-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (Ex. 12), *N*-[(2*S*)-4-{3-[(3*R*)-3-(2-aminoethyl)morpholin-4-yl]azetidin-1-yl}-2-(4-fluorophenyl)butyl]-3,5-dibromo-*N*-methylbenzamide (Ex. 13), 3-cyano-*N*-[(2*S*)-2-(4-fluorophenyl)-4-[3-(octahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)azetidin-1-yl]butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (Ex. 14), 3-cyano-*N*-[(2*S*)-4-[3-(2,5-diazabicyclo[2.2.1]hept-2-yl)azetidin-1-yl]-2-(4-fluorophenyl)butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (Ex. 15), 3-cyano-*N*-[(2*S*)-2-(4-fluorophenyl)-4-(3-{2-[2-(methylamino)ethyl]piperidin-1-yl}azetidin-1-yl)butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (Ex. 16).

30

The preparation of the Boc protected amino derivatives, used as key intermediates in the syntheses of Examples 4-16, are described in the following referred Methods (Meth.): Ex 4 (see Meth. 5), Ex 5 (see Meth. 6), Ex 6 (see Meth. 2), Ex 7 (see Meth. 7), Ex 8 (see Meth. 8), Ex 9 (see Meth. 9), Ex 10 (see Meth. 10), Ex 11 (see Meth. 11), Ex 12 (see Meth. 12), Ex 13 (see Meth. 13), Ex 14 (see Meth. 14), Ex 15 (see Meth. 15), Ex 16 (see Meth. 16).

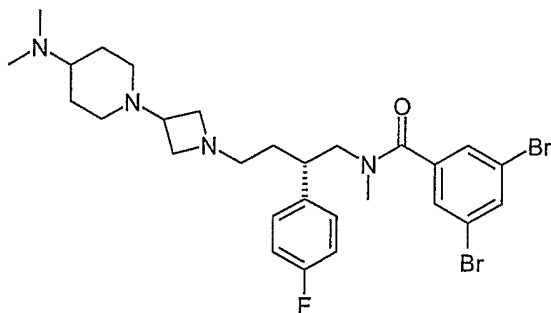
Ex	Compound	¹ H NMR	LCMS	Yield
4		(500 MHz, CDCl ₃): 1.2-2.0 (cm, 7H), 2.2-3.8 (cm, 19H), 5.5-6.5 (b, 2H), 6.8-7.3 (cm, 6H), 7.6 (s, 1H).	611 (M+1) ⁺	100%
5		(500 MHz, CDCl ₃): 1.1-1.8 (cm, 11H), 2.1-4.0 (cm, 23H), 6.8-7.4 (cm, 6H).	532 (M+1) ⁺	96%
6			597 (M+1) ⁺	91%

Ex	Compound	¹ H NMR	LCMS	Yield
7		(500 MHz, CDCl ₃): 1.2-3.8 (cm, 27H), 6.8-7.2 (cm, 6H), 7.6 (s, 1H).	611 (M+1) ⁺	75%
8	 x 3HCl	(500 MHz, CD ₃ OD): 1.6-4.9 (cm, 27H), 6.2-8.1 (cm, 9H), 8.4 (s, 1H).	528 (M+1) ⁺	95%
9	 x 3HCl	(500 MHz, CD ₃ OD): 1.4-4.2 (cm, 35H), 5.8-8.4 (cm, 6H).	532 (M+1) ⁺	84%
10	 x 3HCl	(500 MHz, CD ₃ OD): 1.6-4.9 (cm, 24H), 6.2-7.8 (cm, 8H), 8.0 (m, 1H), 8.4 (s, 1H).	514 (M+1) ⁺	95%
11	 x 3HCl	(500 MHz, CD ₃ OD): 1.5-4.8 (cm, 32H), 5.7-8.4 (cm, 6H).	518 (M+1) ⁺	99%

Ex	Compound	¹ H NMR	LCMS	Yield
12		(500 MHz, CDCl ₃): 1.3-4.1 (cm, 34H), 6.1-7.4 (cm, 6H).	548 (M+1) ⁺	29%
13		(500 MHz, CDCl ₃): 1.3-3.8 (cm, 26H), 6.8-7.3 (cm, 6H), 7.7 (s, 1H).	627 (M+1) ⁺	70%
14		(500 MHz, CDCl ₃): 1.5-4.3 (cm, 33H), 5.9-7.6 (cm, 6H).	530 (M+1) ⁺	27%
15		(500 MHz, CD ₃ OD): 1.5-2.2 (cm, 8H), 2.4-4.3 (cm, 23H), 5.8-7.6 (cm, 6H).	516 (M+1) ⁺	42%
16		(500 MHz, CDCl ₃): 1.2-4.2 (cm, 39H), 6.0-7.4 (cm, 6H).	560 (M+1) ⁺	33%

Example 17

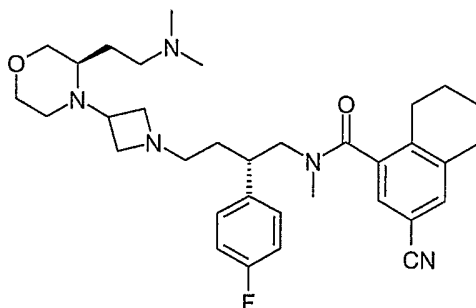
3,5-Dibromo-N-[(2S)-4-{3-[4-(dimethylamino)piperidin-1-yl]azetidin-1-yl}-2-(4-fluorophenyl)butyl]-N-methylbenzamide



- 5 *N*-[(2S)-4-[3-(4-Aminopiperidin-1-yl)azetidin-1-yl]-2-(4-fluorophenyl)butyl]-3,5-dibromo-*N*-methylbenzamide (see Ex. 3; 52 mg, 0.087 mmol) was mixed with formic acid (5 mL) and formaldehyde (36% in water, 0.20 mL, 2.6 mmol). The mixture was stirred at room temperature over night and then refluxed for 1 h. The solvent was removed by evaporation. The residue was purified by means of reversed phase chromatography using a mixture of
 10 acetonitrile and 0.1 M ammonium acetate aq. There was obtained 21 mg (37%) of the title compound. ¹H NMR (500 MHz, CDCl₃): 1.4-1.6 (cm, 3H), 1.7-1.9 (cm, 6H), 2.2-3.8 (cm, 21H), 6.9-7.2 (cm, 5H), 7.3 (t, 1H), 7.8 (d, 1H); LCMS: *m/z* 625 (M+1)⁺.

Example 18

- 15 3-Cyano-N-[(2S)-4-(3-{(3R)-3-[2-(dimethylamino)ethyl]morpholin-4-yl}azetidin-1-yl)-2-(4-fluorophenyl)butyl]-N-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide



- {2-[(3R)-4-Azetidin-3-ylmorpholin-3-yl]ethyl}dimethylamine (see Method 17; 38 mg, 0.18 mmol), 3-cyano-*N*-[(2S)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (see WO 04/110344; 50 mg, 0.13 mmol) and
 20 triethylamine (40 mg, 0.40 mmol) were dissolved in methanol (5 mL). A mixture of

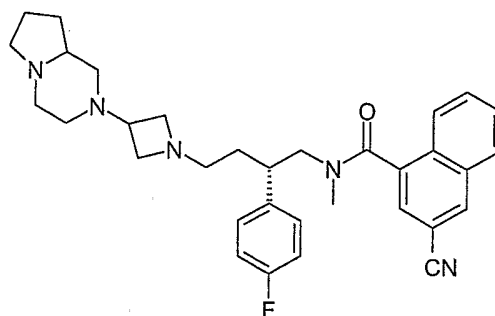
sodium cyanoborohydride (58 mg, 0.92 mmol), zinc chloride (54 mg, 0.40 mmol) and methanol (2 mL) was added and the reaction mixture then stirred at room temperature for 4 h. The solvent was removed by evaporation and the residue dissolved in methylene chloride. The organic solution was washed three times with saturated aqueous NaHCO₃.

- 5 The organic phase was separated by means of a phase separator column and then the solvent was removed by evaporation. The product was purified by chromatography on silica gel (ammonia saturated methanol – methylene chloride 1:6). There was obtained 21 mg (28%) of the title compound as an oil. ¹H NMR (500 MHz, CDCl₃): 0.8-4.2 (cm, 40H), 6.1-7.4 (cm, 6H); LCMS: m/z 576 (M+1)⁺.

10

Example 19

3-Cyano-N-[(2S)-2-(4-fluorophenyl)-4-[3-(octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)azetidin-1-yl]butyl]-N-methyl-1-naphthamide

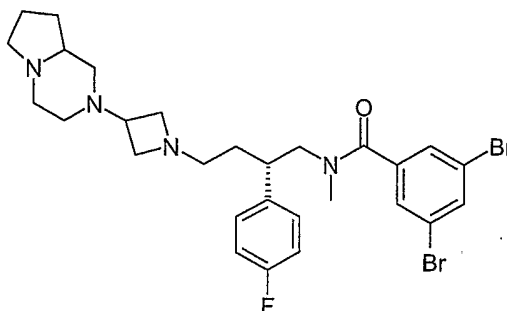


- 15 To a mixture of 2-azetidin-3-yloctahydropyrrolo[1,2-a]pyrazine (see Method 18; 37 mg, 0.20 mmol) and 3-cyano-N-[(2S)-2-(4-fluorophenyl)-4-oxobutyl]-N-methyl-1-naphthamide (see WO 04/110344; 78 mg, 0.20 mmol) in methanol (5 mL) were added sodium cyano borohydride (110 mg, 1.75 mmol) and zinc chloride (115 mg, 0.84 mmol). The reaction mixture was stirred at RT for 30 min and then the solvent was removed by evaporation.
- 20 The residue was partitioned between aqueous NaHCO₃ and ethyl acetate. The organic phase was separated and the aqueous phase extracted with ethyl acetate. The combined organic solutions were concentrated by evaporation and the product purified by reversed phase chromatography using a mixture of acetonitrile and 0.1 M aqueous ammonium acetate. The collected fractions were concentrated on a rotary evaporator and then
- 25 extracted with ethyl acetate. The solution was dried (MgSO₄) and the solvent removed by evaporation. There was obtained 27 mg (23 %) of the title compound as an oil. ¹H NMR

(500 MHz, CD₃OD): 0.8-4.5 (cm, 28H), 6.2-7.8 (cm, 8H), 8.0-8.1 (m, 1H), 8.4 (s, 1H);
LCMS: m/z 534 (M+1)⁺.

5 **Example 20**

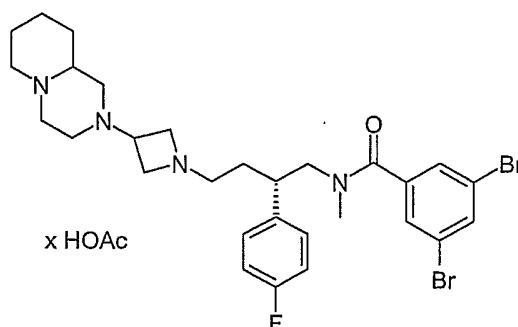
3,5-Dibromo-N-{(2*S*)-2-(4-fluorophenyl)-4-[3-(octahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)azetidin-1-yl]butyl}-N-methylbenzamide



To a mixture of 2-azetidin-3-yloctahydropyrrolo[1,2-*a*]pyrazine (see Method 18; 37 mg,
10 0.20 mmol) and 3,5-dibromo-N-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-N-methylbenzamide
(see WO 04/110344; 92 mg, 0.20 mmol) in methanol (5 mL) were added sodium cyano
borohydride (122 mg, 1.94 mmol) and zinc chloride (115 mg, 0.84 mmol). The reaction
mixture was stirred at RT for 30 min and then the solvent was removed by evaporation.
The residue was partitioned between aqueous NaHCO₃ and ethyl acetate. The organic
15 phase was separated and the aqueous phase extracted with ethyl acetate. The combined
organic solutions were removed by evaporation and the product purified by reversed phase
chromatography using a mixture of acetonitrile and aqueous ammonium acetate (0.1 M).
The collected fractions were concentrated on a rotary evaporator and then extracted with
ethyl acetate. The solution was dried (MgSO₄) and the solvent removed by evaporation.
20 There was obtained 12 mg (9 %) of the title compound as an oil. ¹H NMR (500 MHz,
CD₃OD): 0.9-3.8 (cm, 28H), 6.9-7.2 (m, 5H), 7.3 (t, 1H), 7.8 (d, 1H); LCMS: m/z 623
(M+1)⁺.

Example 21

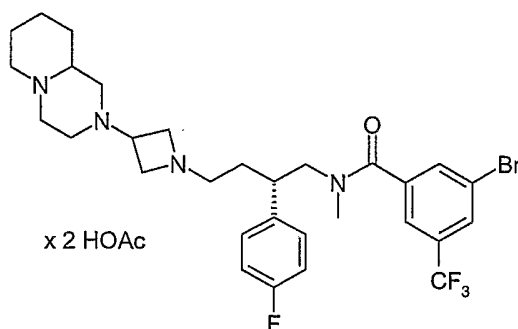
3,5-Dibromo-*N*-{(2*S*)-2-(4-fluorophenyl)-4-[3-(octahydro-2*H*-pyrido[1,2-*a*]pyrazin-2-yl)azetidin-1-yl]butyl}-*N*-methylbenzamide acetate



- 5 To a mixture of 2-azetidin-3-yl octahydro-2*H*-pyrido[1,2-*a*]pyrazine (see Method **19**; 150 mg, 0.55 mmol) and 3,5-dibromo-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methylbenzamide (see *WO 04/110344*; 200 mg, 0.44 mmol), a few drops of acetic acid and methylene chloride (5 mL) were added DIPEA (0.23 mL, 1.31 mmol) and sodium triacetoxyborohydride (124 mg, 0.59 mmol). The reaction mixture was stirred under
- 10 nitrogen at RT for 4 h and then the solvent was removed by evaporation. The residue was partitioned between aqueous NaHCO₃ and ethyl acetate. The organic phase was separated and then washed with aqueous NaHCO₃ ethyl acetate. The solution was dried and the solvent was removed by evaporation. The product was purified by reversed phase chromatography using a mixture of acetonitrile and aqueous ammonium acetate (0.1 M).
- 15 Technical failure during chromatography led to loss of material. However, some fractions were rescued and freeze-dried. There was obtained 5 mg (1.5 %) of the title compound. ¹H NMR (500 MHz, CD₃OD): 1.2-3.8 (cm, 33H), 6.9-7.4 (m, 6H), 7.8 (d, 1H); LCMS: *m/z* 637 (M+1)⁺.

Example 22

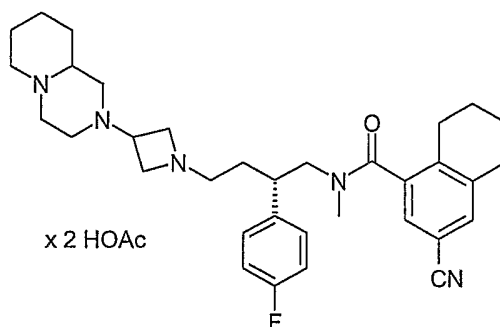
3-Bromo-*N*-{(2*S*)-2-(4-fluorophenyl)-4-[3-(octahydro-2*H*-pyrido[1,2-*a*]pyrazin-2-yl)azetidin-1-yl]butyl}-*N*-methyl-5-(trifluoromethyl)benzamide diacetate



- 5 To a mixture of 2-azetidin-3-yl octahydro-2*H*-pyrido[1,2-*a*]pyrazine (see Method **19**; 134 mg, 0.50 mmol) and 3-bromo-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-5-(trifluoromethyl)benzamide (see Method **20**; 215 mg, 0.48 mmol), a few drops of acetic acid and methylene chloride (5 mL) were added DIPEA (0.24 mL, 1.35 mmol) and sodium triacetoxyborohydride (128 mg, 0.60 mmol). The reaction mixture was stirred under
- 10 nitrogen at RT for 4 h and then the solvent was removed by evaporation. The residue was partitioned between aqueous NaHCO₃ and ethyl acetate. The organic phase was separated and then washed with aqueous NaHCO₃ ethyl acetate. The organic solution was dried and the solvent removed by evaporation. The product was purified by reversed phase chromatography using a mixture of acetonitrile and aqueous ammonium acetate (0.1 M).
- 15 The collected fractions were freeze-dried and there was obtained 110 mg (30 %) of the title compound. ¹H NMR (500 MHz, CD₃OD): 1.3-4.0 (cm, 36H), 6.9-7.6 (m, 6H), 7.9 (d, 1H); LCMS: m/z 626 (M+1)⁺.

Example 23

3-Cyano-*N*-{(2*S*)-2-(4-fluorophenyl)-4-[3-(octahydro-2*H*-pyrido[1,2-*a*]pyrazin-2-yl)azetidin-1-yl]butyl}-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide diacetate



- 5 The title compound was prepared by means of the reductive amination protocol described in Example 22 but using 3-cyano-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (see *WO 04/110344*) as the aldehyde starting material (yield, 15%). ¹H NMR (500 MHz, CD₃OD): 1.4-4.3 (cm, 44H), 5.8-7.5 (cm, 6H); LCMS: *m/z* 558 (M+1)⁺.

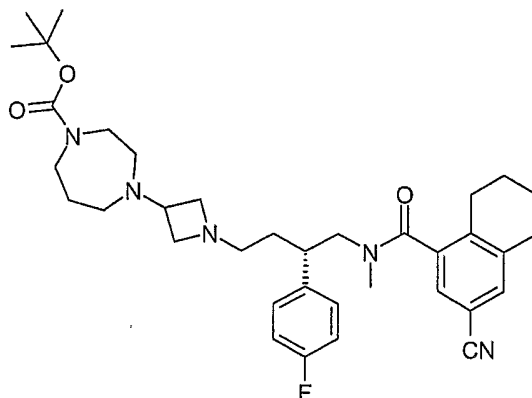
10

Preparation of Starting Materials

- The starting materials for the examples above are either commercially available or are readily prepared by standard methods from known materials. For example, the following
- 15 reactions are an illustration, but not a limitation, of some of the starting materials.

Method 1

tert-Butyl 4-{1-[*(3S)*-4-[[*(3*-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl]-
(methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}-1,4-diazepane-1-carboxylate



5 (a) *tert*-Butyl 4-[1-(diphenylmethyl)azetidin-3-yl]-1,4-diazepane-1-carboxylate

A solution of 1-(diphenylmethyl)azetidin-3-yl methanesulfonate (see *J. Org. Chem.*; 56; 1991; 6729; 1.0 g, 3.15 mmol), 1-Boc-1,4-diazepane (0.76 g, 3.78 mmol), DIPEA (0.49 g, 3.78 mmol) and acetonitrile (25 mL) was heated to 70°C overnight and then the solvent was removed by evaporation. The residue was dissolved in ethyl acetate and the solution
10 was washed with aqueous NaHCO₃ and then with brine. The organic solution was dried over MgSO₄ and then the solvent was removed by evaporation. The product was purified by chromatography on silica gel (ethyl acetate – heptane 10% to 70%). There was obtained 0.98 g (73%) of *tert*-butyl 4-[1-(diphenylmethyl)azetidin-3-yl]-1,4-diazepane-1-carboxylate as a solid. ¹H NMR (500 MHz, CDCl₃): 1.4 (s, 9H), 1.7-1.8 (m, 2H), 2.3-2.4 (m, 4H), 2.8 (dd, 2H), 3.1-3.2 (t, 1H), 3.2-3.3 (m, 6H), 4.4 (s, 1H), 7.2 (m, 2H), 7.3 (m,
15 4H), 7.4 (m, 4H); LCMS: *m/z* 422 (M+1)⁺.

(b) *tert*-Butyl 4-azetidin-3-yl-1,4-diazepane-1-carboxylate hydrochloride

To a solution of *tert*-butyl 4-[1-(diphenylmethyl)azetidin-3-yl]-1,4-diazepane-1-carboxylate (1.0 g, 3.1 mmol) in ethanol (15 mL) and acetic acid (5 mL) was added
20 palladium hydroxide on carbon (0.32 g). The mixture was stirred under hydrogen (5 bar) at RT overnight and then the catalyst was filtered off by means of Celite®. The solvent was removed by evaporation and the residue was partitioned between toluene and diluted aqueous HCl. The two phases were separated and the aqueous solution was freeze-dried
25 overnight. There was obtained 700 mg (100%) of *tert*-butyl 4-azetidin-3-yl-1,4-diazepane-

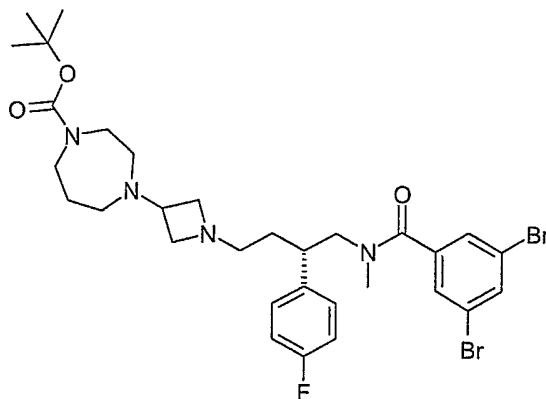
1-carboxylate hydrochloride as a solid. ^1H NMR (500 MHz, CD_3OD): 1.5 (s, 9H), 2.0 (b, 2H), 2.7-3.0 (b, 4H), 3.5 (d, 2H), 3.6 (b, 2H), 3.9-4.1 (b, 1H), 4.1-4.4 m, 4H); LCMS: m/z 292 ($M+1$) $^+$.

- 5 (c) *tert*-Butyl 4-{1-[(3*S*)-4-[[[(3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl]-(methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}-1,4-diazepane-1-carboxylate

tert-Butyl 4-azetidin-3-yl-1,4-diazepane-1-carboxylate (67 mg, 0.26 mmol) was dissolved in methanol (1 mL) and 3-cyano-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-
 10 5,6,7,8-tetrahydronaphthalene-1-carboxamide (see *WO 04/110344*; 100 mg, 0.26 mmol) was dissolved in methylene chloride (1 mL) together with acetic acid (0.2 mL). The two solutions were combined and then mixed with (polystyrylmethyl) trimethylammonium cyanoborohydride (75 mg, 0.4 mmol), which had been pre-washed with methylene chloride. The reaction mixture was stirred at RT for 2 h and then the solution was
 15 separated from the solid support. The mixture was diluted with methylene chloride (2 mL) and then washed with aqueous NaHCO_3 (2M, 2 mL). The organic phase was separated by means of a phase separator column and then the solvent was removed by evaporation. The product was purified by chromatography on silica gel (methanol-methylene chloride 2% to 10%). There was obtained 63 mg (39%) of the title compound as an oil. ^1H NMR (500
 20 MHz, CDCl_3): 1.4 (s, 9H), 1.5-4.1 (cm, 33H), 6.0-7.3 (cm, 6H); LCMS: m/z 618 ($M+1$) $^+$.

Method 2

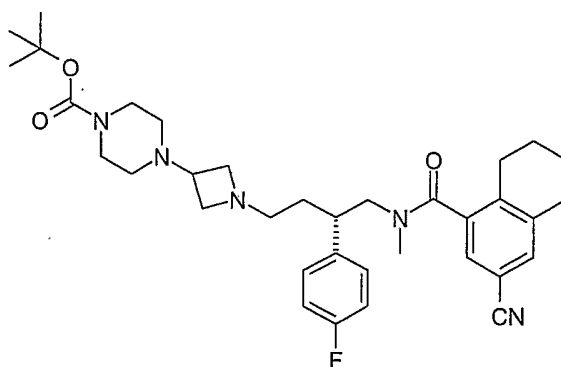
tert-Butyl 4-{1-[(3*S*)-4-[(3,5-dibromobenzoyl)(methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}-1,4-diazepane-1-carboxylate



The title compound was prepared by means of the reductive amination protocol described in Method 1c but using 3,5-dibromo-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methylbenzamide (see WO 04/110344) as the aldehyde starting material (yield, 33%). ¹H NMR (500 MHz, CDCl₃): 1.4 (s, 9H), 1.5-3.8 (cm, 25H), 6.8-7.3 (cm, 6H), 7.6 (s, 1H);
5 LCMS: m/z 697 (M+1)⁺.

Method 3

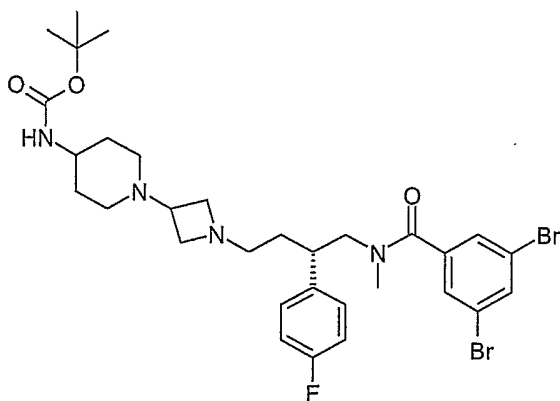
tert-Butyl 4-{1-[(3*S*)-4-[(3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl](methylamino)-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperazine-1-
10 carboxylate



To a solution of *tert*-butyl 4-azetidin-3-ylpiperazine-1-carboxylate (see WO 96/05193; 410 mg, 1.70 mmol) and 3-cyano-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (see WO 04/110344; 500 mg, 1.33 mmol) in
15 methanol (5 mL) were added triethylamine (470 mg, 4.62 mmol) and then a mixture of sodium cyano borohydride (580 mg, 9.24 mmol), zinc chloride (630 mg, 4.62 mmol) and methanol (5 mL). The reaction mixture was stirred at RT for 40 min and then the solvent was removed by evaporation. The residue was dissolved in ethyl acetate and the solution was washed with aqueous NaHCO₃ and then with brine. The organic phase was separated
20 by means of a phase separator column and then the solvent was removed by evaporation. The product was purified by chromatography on silica gel (methanol – methylene chloride 2% to 20%). There was obtained 590 mg (73%) of the title compound as an oil. ¹H NMR (500 MHz, CDCl₃): 1.4 (s, 9H), 1.5-4.1 (cm, 31H), 6.0-7.4 (cm, 6H); LCMS: m/z 604 (M+1)⁺.

Method 4

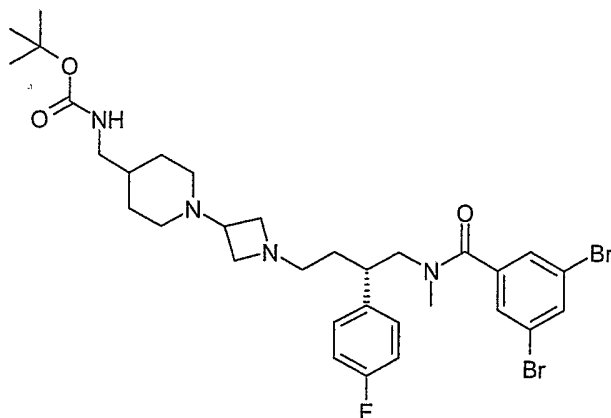
tert-Butyl (1-{1-[(3*S*)-4-[(3,5-dibromobenzoyl)(methyl)amino]-3-(4-fluorophenyl)-butyl]azetidin-3-yl}piperidin-4-yl)carbamate



- 5 The title compound was prepared by means of the reductive amination protocol described in Method 3 but using 3,5-dibromo-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methylbenzamide (see *WO 04/110344*) as the aldehyde starting material and *tert*-butyl (1-azetidin-3-ylpiperidin-4-yl)carbamate (see *WO 96/05193*) as the azetidine starting material (yield, 47%). ¹H NMR (500 MHz, CDCl₃): 1.3-3.5 (cm, 31H), 3.6-3.8 (m, 1H), 4.4 (b, 1H),
10 6.8-7.3 (cm, 6H), 7.6 (s, 1H); LCMS: *m/z* 697 (M+1)⁺.

Method 5

tert-Butyl [(1-{1-[(3*S*)-4-[(3,5-dibromobenzoyl)(methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)methyl]carbamate



15

- (a) *tert*-Butyl ({1-[1-(diphenylmethyl)azetidin-3-yl]piperidin-4-yl}methyl)carbamate
A mixture of *tert*-butyl (piperidin-4-ylmethyl)carbamate (0.81 g, 3.8 mmol), 1-(diphenylmethyl)-azetidin-3-yl methanesulfonate (see *J. Org. Chem.*; 56; 1991; 6729; 1.0

g, 3.2 mmol), acetonitrile (25 mL) and DIPEA (0.50 g, 3.8 mmol) was heated to reflux overnight and then the solvent was removed by evaporation. The residue was dissolved in ethyl acetate and the solution was washed with aqueous 1M NaHCO₃. The organic solution was dried over MgSO₄ and then the solvent was removed by evaporation. There was
5 obtained 0.18 g (13%) of *tert*-butyl ({1-[1-(diphenylmethyl)-azetidin-3-yl]piperidin-4-yl)methyl}carbamate as an oil. ¹H NMR (500 MHz, CDCl₃): 1.2-1.4 (m, 3H), 1.5 (s, 9H), 1.6-1.7 (d, 2H), 1.7-1.8 (t, 2H), 2.7 (d, 2H), 2.9-3.0 (m, 3H), 3.0 (t, 2H), 3.4 (t, 2H), 4.4 (s, 1H), 4.7 (b, 1H), 7.2 (m, 2H), 7.3 (m, 4H), 7.4 (m, 4H); LCMS: m/z 436 (M+1)⁺.

10 (b) *tert*-Butyl [(1-azetidin-3-ylpiperidin-4-yl)methyl]carbamate hydrochloride

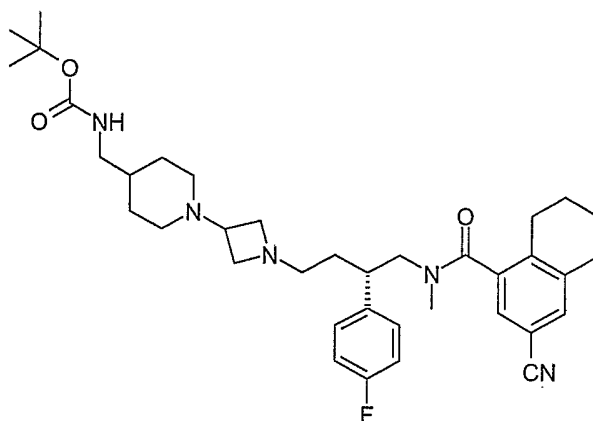
To a solution of *tert*-butyl ({1-[1-(diphenylmethyl)-azetidin-3-yl]piperidin-4-yl)methyl}carbamate (0.18 g, 0.42 mmol) in acetic acid (5 mL) was added palladium hydroxide on carbon (0.06 g). The mixture was stirred under hydrogen (5 bar) at RT overnight and then the catalyst was filtered off by means of Celite®. The solvent was removed by evaporation
15 and the residue was partitioned between toluene and diluted aqueous HCl. The two phases were separated and the aqueous solution was then freeze-dried. There was obtained 0.13 g (98%) of *tert*-butyl [(1-azetidin-3-ylpiperidin-4-yl)methyl]carbamate hydrochloride. ¹H NMR (500 MHz, CD₃OD): 1.2-4.8 (cm, 16H); LCMS: m/z 270 (M+1)⁺.

20 (c) *tert*-Butyl [(1-{1-[(3*S*)-4-[(3,5-dibromobenzoyl)(methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)methyl]carbamate

The title compound was prepared by means of the reductive amination protocol described in Method 1c but using 3,5-dibromo-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methylbenzamide (see WO 04/110344) as the aldehyde starting material and using *tert*-
25 butyl [(1-azetidin-3-ylpiperidin-4-yl)methyl]carbamate as the azetidine starting material (yield, 28%). ¹H NMR (500 MHz, CDCl₃): 1.2 (m, 2H), 1.4 (s, 9H), 1.4-3.8 (cm, 24H), 4.6 (b, 1H), 6.8-7.3 (m, 6H), 7.8 (s, 1H); LCMS: m/z 711 (M+1)⁺.

Method 6

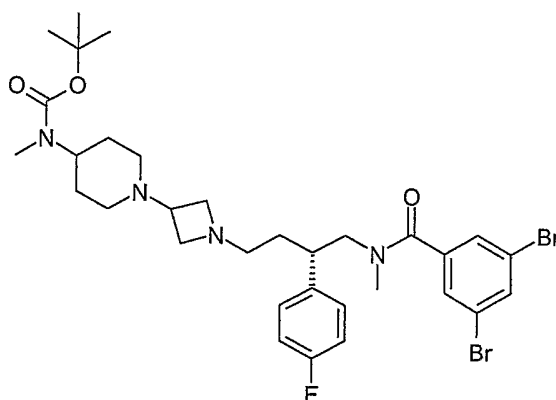
tert-Butyl [(1-{1-[(3*S*)-4-[(3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)methyl]carbamate



The title compound was prepared by means of the reductive amination protocol described in Method 1c but using *tert*-butyl [(1-azetidin-3-yl)piperidin-4-yl)methyl]carbamate (see Method 5c) as the azetidine starting material (yield, 41%). ¹H NMR (500 MHz, CDCl₃): 1.2 (q, 2H), 1.4 (s, 9H), 1.5-4.2 (cm, 32H), 4.7 (b, 1H), 6.0-7.4 (cm, 6H); LCMS: m/z 632 (M+1)⁺.

Method 7

tert-Butyl (1-{1-[(3*S*)-4-[(3,5-dibromobenzoyl)(methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)methylcarbamate



(a) *tert*-Butyl {1-[1-(diphenylmethyl)azetidin-3-yl]piperidin-4-yl}methylcarbamate

A mixture of *tert*-butyl methyl(piperidin-4-yl)carbamate (0.71g, 3.3 mmol), 1-(diphenylmethyl)-azetidin-3-yl methanesulfonate (see *J. Org. Chem.*; 56; 1991; 6729; 0.92

g, 2.9 mmol), acetonitrile (40 mL) and triethylamine (0.36 g, 3.6 mmol) was heated to reflux overnight and then the solvent was removed by evaporation. The residue was dissolved in ethyl acetate and the solution was washed with aqueous NaHCO₃. The organic solution was separated and the solvent removed by evaporation. The product was chromatographed on silica gel (ethyl acetate). There was obtained 0.79 g (63%) of *tert*-butyl {1-[1-(diphenylmethyl)azetidin-3-yl]piperidin-4-yl} methylcarbamate as an oil. ¹H NMR (500 MHz, CDCl₃): 1.4 (s, 9H), 1.5-1.9 (m, 7H), 2.7 (s, 3H), 2.8 (d, 2H), 2.9 (t, 2H), 3.0 (m, 1H), 3.4 (t, 2H), 4.4 (s, 1H), 7.2 (m, 2H), 7.3 (m, 4H), 7.4 (m, 4H); LCMS: m/z 436 (M+1)⁺.

(b) *tert*-Butyl (1-azetidin-3-ylpiperidin-4-yl)methylcarbamate

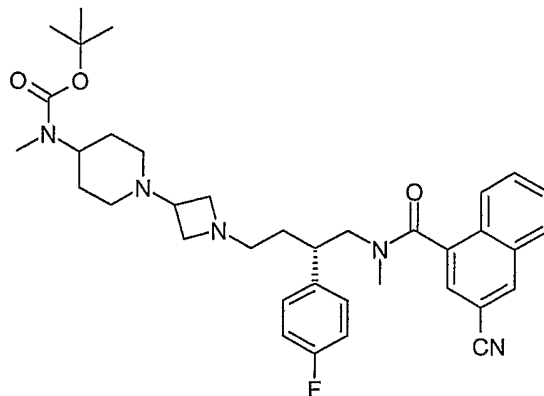
To a solution of *tert*-butyl {1-[1-(diphenylmethyl)azetidin-3-yl]piperidin-4-yl}-methylcarbamate (0.79 g, 1.8 mmol) and acetic acid (40 mL) was added palladium hydroxide on carbon (0.35 g). The mixture was stirred under hydrogen (5 bar) at RT overnight and then the catalyst was filtered off by means of Celite®. The solvent was removed by evaporation and the residue was dissolved in ethanol. The solution was filtered through a cation exchange column (Isolute SCX-2, 10 g). The column was washed with ethanol and then the product was eluted with ammonia-saturated methanol. There was obtained 0.39 g (80%) of *tert*-butyl (1-azetidin-3-ylpiperidin-4-yl)methylcarbamate. ¹H NMR (500 MHz, CDCl₃): 1.4 (s, 9H), 1.6-2.0 (m, 7H), 2.7 (s, 3H), 2.8 (d, 2H), 3.2 (qn, 1H), 3.5-3.7 (m, 4H), 4.0 (b, 1H); LCMS: m/z 270 (M+1)⁺.

(c) *tert*-Butyl (1-{1-[1-(3S)-4-[(3,5-dibromobenzoyl)(methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)methylcarbamate

The title compound was prepared by means of the reductive amination protocol described in Method 3 but using 3,5-dibromo-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methylbenzamide (see WO 04/110344) as the aldehyde starting material and *tert*-butyl (1-azetidin-3-ylpiperidin-4-yl)methylcarbamate as the azetidine starting material (yield, 57%). ¹H NMR (500 MHz, CDCl₃): 1.4 (s, 9H), 1.5-4.1 (cm, 27H), 6.8-7.2 (cm, 6H), 7.7 (s, 1H); LCMS: m/z 711 (M+1)⁺.

Method 8

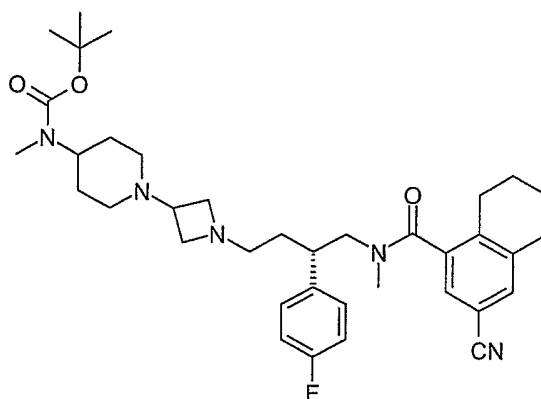
tert-Butyl (1-{1-[(3*S*)-4-[(3-cyano-1-naphthoyl)(methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)methylcarbamate



- 5 The title compound was prepared by means of the reductive amination protocol described in Method 3 but using 3-cyano-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-1-naphthamide (see *WO 04/110344*) as the aldehyde starting material and *tert*-butyl (1-azetidin-3-ylpiperidin-4-yl)methylcarbamate (see Method 7c) as the azetidine starting material (yield, 78%). ¹H NMR (500 MHz, CDCl₃): 1.4 (s, 9H), 1.6-4.1 (cm, 26H), 4.4 (b, 10 1H), 6.4-7.9 (cm, 9H), 8.2 (s, 1H); LCMS: *m/z* 628 (M+1)⁺.

Method 9

- tert*-Butyl (1-{1-[(3*S*)-4-[[3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl]carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)methylcarbamate
- 15



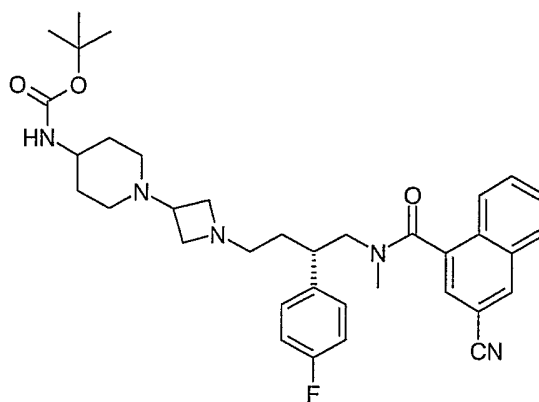
The title compound was prepared by means of the reductive amination protocol described in Method 3 but using 3-cyano-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-5,6,7,8-

tetrahydronaphthalene-1-carboxamide (see *WO 04/110344*) as the aldehyde starting material and *tert*-butyl (1-azetidin-3-ylpiperidin-4-yl)methylcarbamate (see Method 7c) as the azetidine starting material (yield, 25%). ¹H NMR (500 MHz, CD₃OD): 1.4 (s, 9H), 1.5-4.2 (cm, 35H), 5.8-8.4 (cm, 6H); LCMS: m/z 632 (M+1)⁺.

5

Method 10

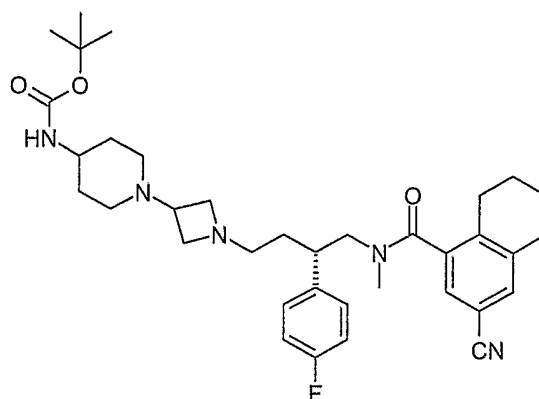
tert-Butyl (1-{1-[(3*S*)-4-[(3-cyano-1-naphthoyl)(methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)carbamate



- 10 The title compound was prepared by means of the reductive amination protocol described in Method 3 but using 3-cyano-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-1-naphthamide (see *WO 04/110344*) as the aldehyde starting material and *tert*-butyl (1-azetidin-3-ylpiperidin-4-yl)carbamate (see *WO 96/05193*) as the azetidine starting material (yield, 60%). ¹H NMR (500 MHz, CDCl₃): 1.0-4.0 (cm, 32H), 4.4 (b, 1H), 6.4-8.0 (cm, 9H), 8.2 (s, 1H); LCMS: m/z 614 (M+1)⁺.
- 15

Method 11

tert-Butyl (1-{1-[(3*S*)-4-[[3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl]carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)carbamate



5

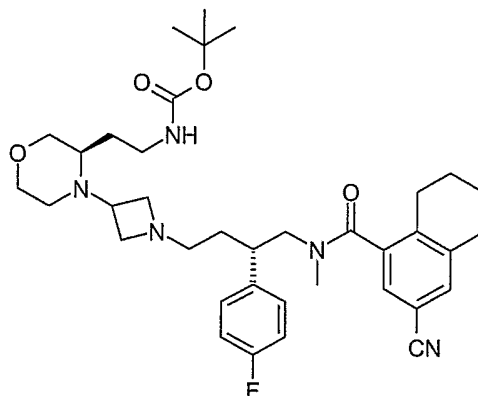
The title compound was prepared by means of the reductive amination protocol described in Method 3 but using 3-cyano-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (see *WO 04/110344*) as the aldehyde starting material and *tert*-butyl (1-azetidin-3-ylpiperidin-4-yl)carbamate (see *WO 96/05193*) as the azetidine starting material (yield, 65%). ¹H NMR (500 MHz, CD₃OD): 1.4 (s, 9H), 1.5-4.2 (cm, 32H), 5.8-7.5 (cm, 6H); LCMS: *m/z* 618 (M+1)⁺.

10

Method 12

tert-Butyl [2-((3*R*)-4-{1-[(3*S*)-4-[[3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl]carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}morpholin-3-yl)ethyl]carbamate

15



(a) *(3S)-4-Benzyl-3-(chloromethyl)morpholine*

To a solution of [(3R)-4-benzylmorpholin-3-yl]methanol (see *J. Med. Chem.*; 29; 1986; 1288-1290; 1.83 g, 8.8 mmol) in dry methylene chloride (15 mL) was added thionyl chloride (3.15 g, 26.5 mmol) and DMF (2 drops). The mixture was heated to reflux for 2 h 30 min and then the solvent was removed by evaporation. The residue was treated with aqueous NaHCO₃ and the solution was extracted with ethyl acetate. The organic solution was separated and the solvent was removed by evaporation. There was obtained 1.88 g (94%) of (3S)-4-benzyl-3-(chloromethyl)morpholine as an oil. ¹H NMR (500 MHz, CDCl₃): 2.3-2.4 (m, 1H), 2.7 (m, 1H), 2.8 (m, 1H), 3.5 (d, 1H), 3.6-3.9 (m, 5H), 4.0 (d, 1H), 7.3 (m, 1H), 7.4 (m, 4H); LCMS: m/z 226 (M+1)⁺.

(b) *(3R)-4-Benzylmorpholine-3-carbonitrile*

To a solution of (3S)-4-benzyl-3-(chloromethyl)morpholine (1.83 g, 8.1 mmol) in methylene chloride (6 mL) was added a mixture of tetrabutylammonium hydrogensulfate (0.14 g, 0.42 mmol), NaOH (0.033 g, 0.83 mmol) and water (6 mL) followed by KCN (0.54 g, 8.3 mmol). The mixture was refluxed for 20 h and then diluted with methylene chloride. The organic phase was washed twice with water and then separated by means of a phase separator column. The solvent was removed by evaporation and the product was purified by chromatography on silica gel (methanol – methylene chloride 0 to 5%). There was obtained 1.66 g (95%) of (3R)-4-benzylmorpholine-3-carbonitrile. ¹H NMR (500 MHz, CDCl₃): 2.4 (m, 1H), 2.6 (dd, 1H), 2.6-2.7 (m, 1H), 2.8 (dd, 1H), 2.9 (m, 1H), 3.4 (d, 1H), 3.7-3.9 (m, 5H), 7.3 (m, 1H), 7.4 (m, 4H); m/z 217 (M+1)⁺.

(c) *{2-[(3R)-4-Benzylmorpholin-3-yl]ethyl}amine*

(3R)-4-Benzylmorpholine-3-carbonitrile (0.64 g, 2.9 mmol) was dissolved in 2-propanol (4 mL) containing KOH (0.08 g, 1.4 mmol) and Raney-nickel (0.58 g, wet), which had been pre-washed with water and 2-propanol. The mixture was heated to reflux while stirring for 6 h. After cooling to RT the catalyst was filtered off by means of Celite® and the filter cake was washed with 2-propanol. The solvent was removed by evaporation and the residue was stirred in aqueous HCl (2M, 6 mL) for 15 min. The mixture was made alkaline by the addition of NaOH (2M) and then extracted with methylene chloride. The organic phase was separated by means of a phase separator column. The solvent was

removed by evaporation and the product was chromatographed on silica gel (methylene chloride – methanol 13:1). There was obtained 0.36 g (60%) of {2-[(3R)-4-benzylmorpholin-3-yl]ethyl}amine as an oil. ¹H NMR (500 MHz, CDCl₃): 1.6-1.8 (m, 2H), 2.2 (m, 1H), 2.5 (m, 1H), 2.6-2.7 (m, 1H), 2.7-2.8 (m, 1H), 2.8-2.9 (m, 1H), 3.2 (d, 1H), 3.5 (dd, 1H), 3.6 (m, 1H), 3.7 (m, 1H), 3.8 (dd, 1H), 4.1 (d, 1H), 7.3 (m, 1H), 7.4 (m, 4H); LCMS: m/z 221 (M+1)⁺.

(d) *tert*-Butyl {2-[(3R)-4-benzylmorpholin-3-yl]ethyl}carbamate

tert-Butyl {2-[(3R)-4-benzylmorpholin-3-yl]ethyl}carbamate (0.36 g, 1.6 mmol) was dissolved in dry THF (5 mL) under nitrogen and to the resultant solution was added triethylamine (0.34 g, 3.3 mmol) and di-*tert*-butyldicarbonate (0.36 g, 1.7 mmol). The mixture was stirred at RT for 1h and then diluted with methylene chloride. The solution was washed twice with aqueous NaHCO₃ and brine. The organic phase was separated by means of a phase separator column. The solvent was removed by evaporation and the product was chromatographed on silica gel (methylene chloride – ammonia saturated methanol 13:1). There was obtained 0.53 g (99%) of *tert*-butyl {2-[(3R)-4-benzylmorpholin-3-yl]ethyl}carbamate as an oil. m/z 321 (M+1)⁺.

(e) *tert*-Butyl {2-[(3R)-morpholin-3-yl]ethyl}carbamate

To a solution of *tert*-butyl {2-[(3R)-4-benzylmorpholin-3-yl]ethyl}carbamate (0.51 g, 1.6 mmol) in ethanol (15 mL) were added palladium hydroxide (20% on carbon, 0.22 g) and a catalytic amount of acetic acid. The mixture was stirred under hydrogen overnight at 5 bar and RT. The catalyst was filtered off and the solvent was removed by evaporation. The residue was re-dissolved in ethanol (1 mL) and THF (10 mL). The solution was filtered through a cation exchange column (Isolute SCX-2, 10 g). The column was washed with THF and then the product was eluted with ammonia-saturated methanol. The solvent was removed by evaporation and there was obtained 0.32 g (86%) of *tert*-butyl {2-[(3R)-morpholin-3-yl]ethyl}carbamate as an oil. ¹H NMR (500 MHz, CD₃OD): 1.4-1.6 (m, 11H), 2.8-3.0 (m, 3H), 3.1-3.3 (m, 3H), 3.5-3.6 (m, 1H), 3.8 (d, 2H); LCMS: m/z 231 (M+1)⁺.

(f) *tert*-Butyl (2-[(3*R*)-4-[1-(diphenylmethyl)azetidin-3-yl]morpholin-3-yl]ethyl)carbamate

To a solution of *tert*-butyl {2-[(3*R*)-morpholin-3-yl]ethyl} carbamate (0.32 g, 1.4 mmol) and 1-(diphenylmethyl)azetidin-3-one (see *Bioorg. Med. Chem. Lett.*; 13; 2003; 2191-2194, 0.31 g, 1.3 mmol) in methanol (5 mL) was added acetic acid (0.5 mL). The solution was mixed with (polystyrylmethyl) trimethylammonium cyanoborohydride (4.2 mmol/g, 0.34 g, 1.8 mmol). The mixture was heated for 8 min at 120°C using microwave single node heating. The solution was filtered and then the solvent was removed by evaporation. The residue was dissolved in methylene chloride and the solution was washed twice with aqueous NaHCO₃ solution. The organic solution was separated by use of a phase separator column. The solvent was removed by evaporation and the product was chromatographed on silica gel (methylene chloride –methanol 11:1). There was obtained 0.49 g (79%) of *tert*-butyl (2-[(3*R*)-4-[1-(diphenylmethyl)azetidin-3-yl]morpholin-3-yl]ethyl)carbamate. LCMS: m/z 452 (M+1)⁺.

(g) *tert*-Butyl {2-[(3*R*)-4-azetidin-3-ylmorpholin-3-yl]ethyl}carbamate

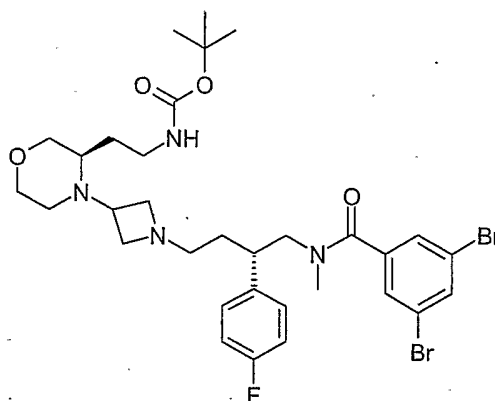
A solution of *tert*-butyl (2-[(3*R*)-4-[1-(diphenylmethyl)azetidin-3-yl]morpholin-3-yl]ethyl)carbamate (0.49 g, 1.1 mmol) in ethanol (10 mL) was mixed with palladium hydroxide (20% on carbon, 0.15 g) and a catalytic amount of acetic acid. The mixture was stirred under hydrogen overnight at 5 bar and RT. The catalyst was filtered off and the solvent was removed by evaporation. The residue was re-dissolved in ethanol (1 mL) and THF (10 mL). The solution was filtered through a strong cation exchange column (Isolute SCX-2, 10 g). The column was washed with THF and then the product was eluted with ammonia-saturated methanol. The solvent was removed by evaporation and there was obtained 0.27 g (86%) of *tert*-butyl {2-[(3*R*)-4-azetidin-3-ylmorpholin-3-yl]ethyl}carbamate as an oil. ¹H NMR (500 MHz, CDCl₃): 1.4 (s, 9H), 1.6 (m, 2H), 2.2 (m, 1H), 2.4 (m, 1H), 2.6 (m, 1H), 3.0-3.2 (m, 2H), 3.5-3.8 (m, 8H), 4.6 (m, 1H); LCMS: m/z 286 (M+1)⁺.

(h) *tert*-Butyl [2-((3*R*)-4-{1-[(3*S*)-4-[[[(3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}morpholin-3-yl)ethyl]carbamate

The title compound was prepared by means of the reductive amination protocol described in Method 1c but using *tert*-butyl {2-[(3*R*)-4-azetidin-3-ylmorpholin-3-yl]ethyl} carbamate as the azetidine starting material (yield, 35%). ¹H NMR (500 MHz, CDCl₃): 1.4 (s, 9H), 1.5-4.2 (cm, 31H), 4.6 (b, 1H), 6.1-7.4 (cm, 6H); LCMS: m/z 648 (M+1)⁺.

Method 13

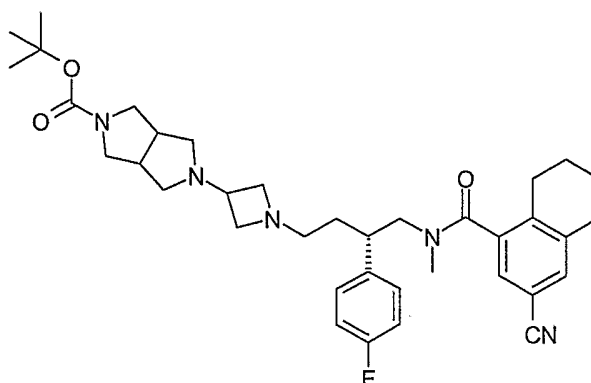
tert-Butyl [2-((3*R*)-4-{1-[(3*S*)-4-[(3,5-dibromobenzoyl)(methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}morpholin-3-yl)ethyl]carbamate



The title compound was prepared by means of the reductive amination protocol described in Method 1c but using 3,5-dibromo-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methylbenzamide (see WO 04/110344) as the aldehyde starting material and *tert*-butyl {2-[(3*R*)-4-azetidin-3-ylmorpholin-3-yl]ethyl} carbamate (see Method 12g) as the azetidine starting material (yield, 35%). ¹H NMR (500 MHz, CDCl₃): 1.4 (s, 9H), 1.5-4.0 (cm, 26H), 4.6 (b, 1H), 6.8-7.2 (cm, 6H), 7.6 (s, 1H); LCMS: m/z 727 (M+1)⁺.

Method 14

tert-Butyl 5-{1-[(3*S*)-4-[[[(3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl]-(methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}octahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate



(a) *tert*-Butyl 5-[1-(diphenylmethyl)azetidin-3-yl]octahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate

tert-Butyl octahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (0.23 g, 1.1 mmol) was dissolved in THF (2 mL) and 1-(diphenylmethyl)azetidin-3-yl methanesulfonate (see *J. Org. Chem.*; 56; 1991; 6729; 0.32 g, 1.0 mmol) was dissolved in THF (1 mL). The two solutions were mixed and triethylamine (0.15 g, 1.5 mmol) was added to the mixture. The reaction mixture was heated to 160°C for 10 min using microwave single node heating. The solvent was removed by evaporation and the product was purified by means of reversed phase chromatography using a mixture of acetonitrile and aqueous 0.1 M ammonium acetate. There was obtained 0.21 g (47%) of *tert*-butyl 5-[1-(diphenylmethyl)azetidin-3-yl]octahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate. LCMS: m/z 434 ($M+1$)⁺.

(b) *tert*-Butyl 5-azetidin-3-yl octahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate

A vial was loaded with palladium hydroxide on carbon (13 mg) and a mixture of *tert*-butyl 5-[1-(diphenylmethyl)azetidin-3-yl]octahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (0.21 g, 0.47 mmol), acetic acid (0.1 mL) and methanol (3 mL). The mixture was stirred under hydrogen for 21 h at 1.6 bar and RT. The catalyst was filtered off by means of Celite® and the filter cake was washed with methanol. The filtrate was concentrated on a rotavapor and the residue was re-dissolved in methanol (3 mL). The solution of *tert*-butyl

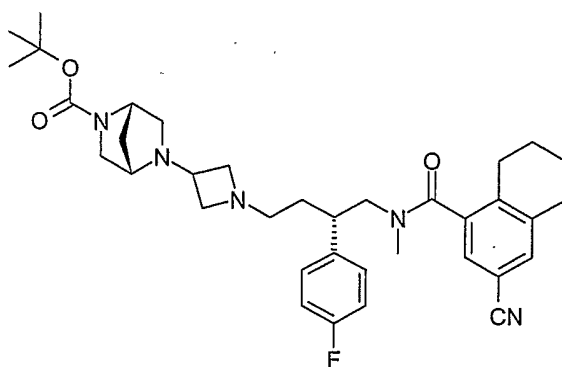
5-azetidin-3-yl)octahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate was used directly in the next step without isolation of the azetidine intermediate. LCMS: m/z 268 ($M+1$)⁺.

(c) *tert*-Butyl 5-{1-[(3*S*)-4-[(3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl]-(methyl)amino]-3-(4-fluorophenyl)butyl}azetidin-3-yl}octahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate

To a methanol (3 mL) solution of *tert*-butyl 5-azetidin-3-yl)octahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (see above) were added 3-cyano-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (see WO 04/110344; 143 mg, 0.38 mmol), (polystyrylmethyl) trimethylammonium cyanoborohydride (93 mg, 0.49 mmol) and acetic acid (0.3 mL). The reaction mixture was shaken for 2 h at RT. The resin was filtered off and the solvent was removed by evaporation. The product was purified by means of reversed phase chromatography using a mixture of acetonitrile and aqueous 0.1 M ammonium acetate and there was obtained 19 mg (8% two steps). LCMS: m/z 630 ($M+1$)⁺.

Method 15

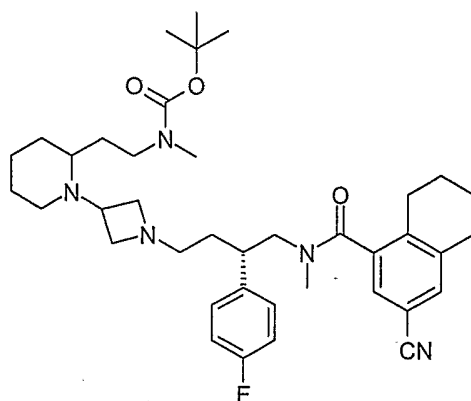
tert-Butyl (1*S*,4*S*)-5-{1-[(3*S*)-4-[(3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl}azetidin-3-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



The title compound was prepared by means of the protocol described in Method 14 but using (1*S*,4*S*)-2-Boc-2,5-diazabicyclo[2.2.1]heptane as the amine starting material (yield, 6%, three steps). LCMS: m/z 616 ($M+1$)⁺.

Method 16

tert-Butyl [2-(1-{1-[(3*S*)-4-[[3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl]carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-2-yl)ethyl]methylcarbamate



(a) *tert*-Butyl methyl(2-pyridin-2-ylethyl)carbamate

N-Methyl-2-pyridin-2-ylethanamine (0.98 g, 7.2 mmol) was dissolved in dry methylene chloride (15 mL) and to the resultant solution was added di-*tert*-butyldicarbonate (2.0 g, 9.0 mmol) at 0°C over a period of 10 min. The mixture was stirred at 0°C for 20 min and then at RT for 15 min. Polystyrene-trisamine (1.02 g) was added and the mixture was stirred at RT for 1 h. The resin was filtered off and washed with methylene chloride. The solvent was removed by evaporation and there was obtained 1.72 g (97%) of *tert*-butyl methyl(2-pyridin-2-ylethyl)carbamate. ¹H NMR (500 MHz, CDCl₃): 1.4 (s, 9H), 2.8 (s, 3H), 3.0 (b, 2H), 3.6 (t, 2H), 7.1 (b, 1H), 7.2 (b, 1H), 7.6 (t, 1H), 8.6 (b, 1H); LCMS: m/z 237 (M+1)⁺.

(b) *tert*-Butyl methyl(2-piperidin-2-ylethyl)carbamate

A reaction vessel was loaded with platinum (IV) oxide (80%, 33 mg), an ethanol (3 mL) solution of *tert*-butyl methyl(2-pyridin-2-ylethyl)carbamate (0.51 g, 2.2 mmol) and acetic acid (0.1 mL). The mixture was stirred under hydrogen (1.6 bar) at RT for 57 h. The catalyst was filtered off by means of Celite® and the solvent was removed by evaporation. There was obtained 0.58 g (94%) of *tert*-butyl methyl(2-piperidin-2-ylethyl)carbamate. ¹H NMR (500 MHz, CDCl₃): 1.4 (m, 1H), 1.5 (s, 9H), 1.6-2.0 (m, 7H), 2.6-2.8 (m, 2H), 2.8 (s, 3H), 3.1 (b, 1H), 3.3 (b, 1H), 3.5 (m, 1H), 3.8 (m, 1H); LCMS: m/z 243 (M+1)⁺.

(c) *tert*-Butyl (2-{1-[1-(diphenylmethyl)azetidin-3-yl]piperidin-2-yl}ethyl)methylcarbamate

To a solution of *tert*-butyl methyl(2-piperidin-2-ylethyl)carbamate (0.57 g, 2.0 mmol) and 1-(diphenylmethyl)azetidin-3-one (see *Bioorg. Med. Chem. Lett.*; 13; 2003; 2191-2194, 0.47 g, 2.0 mmol) in methanol (3 mL) was added acetic acid (0.3 mL). The solution was mixed with (polystyrylmethyl) trimethylammonium cyanoborohydride (4.2 mmol/g, 0.49 g, 2.6 mmol) and the mixture was heated for 5 min at 140°C using microwave single node heating. The resin was filtered off and then the solvent was removed by evaporation. The product was purified by means of reversed phase chromatography using a mixture of acetonitrile and aqueous 0.1 M ammonium acetate. There was obtained 0.55 g (60%) of *tert*-butyl (2-{1-[1-(diphenylmethyl)azetidin-3-yl]piperidin-2-yl}ethyl)methylcarbamate. ¹H NMR (500 MHz, CDCl₃): 1.3-1.4 (m, 2H), 1.4 (s, 9H), 1.5-1.8 (m, 6H), 2.1 (m, 1H), 2.3 (b, 1H), 2.5-2.6 (m, 1H), 2.8 (s, 3H), 2.8-2.9 (m, 2H), 3.0-3.3 (m, 3H), 3.4 (m, 1H), 3.5 (m, 1H), 4.4 (s, 1H), 7.2 (m, 2H), 7.3 (m, 4H), 7.4 (m, 4H); LCMS: m/z 464 (M+1)⁺.

(d) *tert*-butyl [2-(1-azetidin-3-ylpiperidin-2-yl)ethyl]methylcarbamate

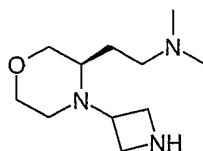
A reaction vessel was loaded with palladium hydroxide (20% on carbon, 165 mg) and a mixture of *tert*-butyl (2-{1-[1-(diphenylmethyl)azetidin-3-yl]piperidin-2-yl}ethyl)methylcarbamate (0.55 g, 1.2 mmol), acetic acid (0.3 mL) and methanol (4 mL). The mixture was stirred under hydrogen for 20 h at 1.6 bar and RT. The catalyst was filtered off by means of Celite® and the filter cake was washed with methanol. The solvent was removed by evaporation and the residue was dissolved in HCl (2M). The mixture was washed with toluene and the pH of the aqueous solution was adjusted to pH 11 by the addition of aqueous NaOH (5M). The mixture was extracted twice with methylene chloride and the combined organic solutions were dried over MgSO₄. The solvent was removed by evaporation and the residue re-dissolved in methylene chloride. The mixture was filtered through a cation exchange column (Isolute SCX-2, 2 g). The column was first washed with THF and then with methylene chloride. The product was eluted with a mixture of ammonia-saturated methanol and methylene chloride (1:9). The solvent was removed by evaporation and there was obtained 32 mg (9%) of *tert*-butyl [2-(1-azetidin-3-ylpiperidin-2-yl)ethyl]methylcarbamate. ¹H NMR (500 MHz, CDCl₃): 1.3-1.7 (m, 17H), 2.1 (m, 1H), 2.3-2.6 (m, 4H), 2.8 (s, 3H), 3.0-3.3 (m, 2H), 3.4-3.7 (m, 4H); LCMS: m/z 298 (M+1)⁺.

(e) *tert*-Butyl [2-(1-{1-[(3*S*)-4-[[[3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl]carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-2-yl)ethyl]methylcarbamate

5 *tert*-Butyl [2-(1-azetidin-3-ylpiperidin-2-yl)ethyl]methylcarbamate (32 mg, 0.11 mmol) was dissolved in methylene chloride (5 mL) together with 3-cyano-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide (see WO 04/110344; 41 mg, 0.11 mmol). To the solution was added acetic acid (0.1 mL) and sodium triacetoxyborohydride (73 mg, 0.33 mmol). The reaction mixture was stirred at RT
10 for 2 h and then washed with aqueous NaHCO₃. The aqueous solution was extracted twice with methylene chloride and the combined organic solutions were separated by means of a phase separator column. The solvent was removed by evaporation and there was obtained 82 mg (69%) of the title compound. LCMS: *m/z* 660 (M+1)⁺.

15 **Method 17**

{2-[(3*R*)-4-azetidin-3-ylmorpholin-3-yl]ethyl}dimethylamine



(a) (2-{(3*R*)-4-[1-(Diphenylmethyl)azetidin-3-yl]morpholin-3-yl}ethyl)amine

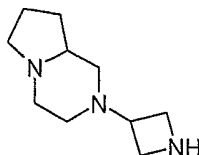
tert-Butyl (2-{(3*R*)-4-[1-(diphenylmethyl)azetidin-3-yl]morpholin-3-yl}ethyl)carbamate
20 (see Method 12f; 190 mg, 0.42 mmol) was dissolved in an HCl-saturated solution of ethyl acetate (2 mL). The reaction mixture was stirred at RT for 1 h, diluted with ethyl acetate and then the solution was washed with aqueous NaHCO₃. The organic phase was separated by means of a phase separator column and then the solvent was removed by evaporation. There was obtained 78 mg (53%) of (2-{(3*R*)-4-[1-(diphenylmethyl)azetidin-3-yl]morpholin-3-yl}ethyl)amine. ¹H NMR (500 MHz, CD₃OD): 1.5-1.6 (m, 2H), 2.2 (m, 1H), 2.4 (m, 1H), 2.5 (m, 1H), 2.6 (m, 2H), 2.9-3.0 (m, 2H), 3.3-3.5 (m, 4H), 3.6-3.7 (m, 3H), 4.4 (s, 1H), 7.2 (m, 2H), 7.3 (m, 4H), 7.4 (m, 4H); LCMS: *m/z* 352 (M+1)⁺.
25

(b) *(2-((3R)-4-[1-(diphenylmethyl)azetidin-3-yl]morpholin-3-yl)ethyl)dimethylamine*
(2-((3R)-4-[1-(Diphenylmethyl)azetidin-3-yl]morpholin-3-yl)ethyl)amine (78 mg, 0.22 mmol) and formaldehyde (36%, 0.14 mL, 1.7 mmol) were dissolved in acetonitrile (2 mL) and to the resultant solution was added sodium cyanoborohydride (28 mg, 0.44 mmol). The mixture was stirred at RT overnight and then diluted with 2M aqueous HCl. The solution was washed with methylene chloride and then rendered alkaline by the addition of 2M aqueous NaOH. The mixture was extracted with methylene chloride and the organic layer was dried over Na₂SO₄. The solvent was removed by evaporation and the product was chromatographed on silica gel (methylene chloride – methanol treated with ammonia 9:1). There was obtained 80 mg (95%) of (2-((3R)-4-[1-(diphenylmethyl)azetidin-3-yl]morpholin-3-yl)ethyl)dimethylamine as an oil. ¹H NMR (500 MHz, CDCl₃): 1.5-1.6 (m, 2H), 2.1-2.3 (m, 9H), 2.4 (m, 1H), 2.6 (m, 1H), 2.8-3.0 (m, 2H), 3.3 (m, 1H), 3.4 (m, 1H), 3.4-3.5 (m, 2H), 3.6-3.8 (m, 3H), 4.4 (s, 1H), 7.2 (m, 2H), 7.3 (m, 4H), 7.4 (m, 4); LCMS: m/z 380 (M+1)⁺.

15

(c) *{2-[(3R)-4-azetidin-3-ylmorpholin-3-yl]ethyl}dimethylamine*
(2-((3R)-4-[1-(Diphenylmethyl)azetidin-3-yl]morpholin-3-yl)ethyl)dimethylamine (80 mg, 0.21 mmol) was dissolved in ethanol (3 mL) together with a catalytic amount of acetic acid and to the resultant solution was added palladium hydroxide on carbon (30 mg). The mixture was stirred under hydrogen (5 bar) at RT overnight and then the catalyst was filtered off. The solvent was removed by evaporation and the residue was dissolved in a mixture of ethanol (1 mL) and THF (10 mL). The mixture was filtered through a cation exchange column (Isolute SCX-2, 10 g). The column was first washed with THF and then the product was eluted with ammonia-saturated methanol. The solvent was removed by evaporation and there was obtained 38 mg (84%) of the title compound. ¹H NMR (500 MHz, CD₃OD): 1.4-4.0 (cm, 22H); LCMS: m/z 214 (M+1)⁺.

25

Method 182-Azetidin-3-ylhexahydropyrrolo[1,2-*a*]pyrazine

(a) 2-[1-(Diphenylmethyl)azetidin-3-yl]hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one
5 Hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (see *WO 03/066635*; 1.7 g, 12.1 mmol) and 1-(diphenylmethyl)azetidin-3-yl methanesulfonate (see *J. Org. Chem.*; 56; 1991; 6729; 3.0 g, 9.4 mmol) were dissolved together in acetonitrile (100 mL). The reaction mixture was heated to reflux for 16 h and then the solvent was removed by evaporation. The residue was dissolved in ethyl acetate and the solution was washed with aqueous NaHCO₃. The organic solution was dried over MgSO₄ and then the solvent was removed by evaporation.
10 The product was purified by chromatography on silica gel (methanol – methylene chloride 5:95). There was obtained 2.1 g (61%) of 2-[1-(diphenylmethyl)azetidin-3-yl]hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one as an oil. ¹H NMR (500 MHz, CD₃OD): 1.5-1.6 (qn, 2H), 1.7 (b, 1H), 1.8 (m, 1H), 2.1-2.2 (m, 1H), 2.3-2.4 (m, 2H), 2.6 (d, 1H), 2.8-2.9 (m, 3H), 3.0 (m, 1H), 3.4 (t, 2H), 3.6 (m, 1H), 4.0 (d, 1H), 4.4 (s, 1H), 7.2 (m, 2H), 7.3 (m, 4H), 7.4 (m, 4H); LCMS: *m/z* 362 (M+1)⁺.
15

(b) 2-Azetidin-3-ylhexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one
2-[1-(Diphenylmethyl)azetidin-3-yl]hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (2.1 g, 5.7
20 mmol) was dissolved in acetic acid (100 mL) and to the resultant solution was added palladium hydroxide on carbon (1 g). The mixture was stirred under hydrogen (5 bar) at RT overnight and then the catalyst was filtered off by means of Celite®. The solvent was removed by evaporation and the residue was partitioned between methylene chloride and diluted aqueous HCl. The two phases were separated and the aqueous solution was then
25 extracted twice with methylene chloride. The pH of the aqueous solution was made alkaline by adding K₂CO₃. An effort to extract the product over to an organic solution by means of methylene chloride was unsuccessful. The aqueous solution was rendered acidic by adding HCl and then the mixture was filtered through a cation exchange column (Isolute SCX-2, 10 g). The column was washed with water and ethanol and then the

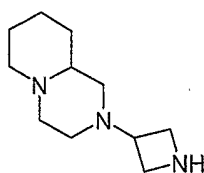
product was eluted with ammonia-saturated methanol. The solvent was removed by evaporation and there was obtained 0.15 g (13%) of 2-azetidin-3-ylhexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one. ¹H NMR (500 MHz, CDCl₃): 1.6 (t, 2H), 1.8 (m, 1H), 2.2 (m, 1H), 2.4 (m, 2H), 2.5 (b, 2H), 2.7 (d, 1H), 2.8-2.9 (m, 2H), 3.2 (qn, 1H), 3.5-3.7 (m, 4H), 4.0 (dd, 1H); LCMS: m/z 196 (M+1)⁺.

(c) *2-Azetidin-3-yloctahydropyrrolo[1,2-a]pyrazine*

2-Azetidin-3-ylhexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (100 mg, 0.51 mmol) was dissolved in dry THF (20 mL) under nitrogen and to the resultant solution was added borane-THF complex (516 mg, 6.0 mmol). The mixture was stirred at RT for 16 h and then ethanol (5 mL) was added by drops. The solvent was removed by evaporation and the residue was dissolved in water. The solution was filtered through a cation exchange column (Isolute SCX-2, 10 g). The column was washed with water and then with ethanol. The product was eluted with ammonia-saturated methanol. The solvent was removed by evaporation and there was obtained 74 mg (80%) of the title compound as an oil. ¹H NMR (500 MHz, CD₃OD): 1.4 (m, 1H), 1.6-2.0 (m, 4H), 2.0-2.5 (m, 4H), 2.5-3.2 (m, 4H), 3.2-3.4 (m, 2H), 3.6-4.0 (m, 3H); LCMS: m/z 182 (M+1)⁺.

Method 19

2-Azetidin-3-yloctahydro-2*H*-pyrido[1,2-*a*]pyrazine dihydrochloride



(a) *2-[1-(Diphenylmethyl)azetidin-3-yl]octahydro-2*H*-pyrido[1,2-*a*]pyrazine*

A mixture of octahydro-2*H*-pyrido[1,2-*a*]pyrazine (1.00 g, 7.1 mmol) and 1-(diphenylmethyl)azetidin-3-one (see *Bioorg. Med. Chem. Lett.*; 13; 2003; 2191-2194, 1.5 g, 6.5 mmol), methanol (13.5 mL) and acetic acid (1.5 mL) was divided into five test tubes (5 mL). To each tube was added (polystyrylmethyl) trimethylammonium cyanoborohydride (4.2 mmol/g, 0.3 g, 1.6 mmol) and each mixture was then heated for 5 min at 120°C using microwave single node heating. The resins were filtered off and then the solutions were combined. The solvent was removed by evaporation. The product was

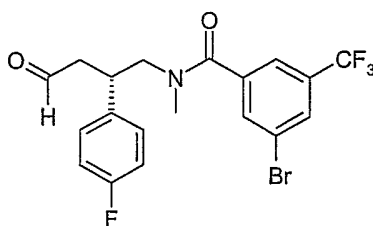
purified by means of silica gel chromatography using a mixture of methanol and methylene chloride (2% – 4%). There was obtained 1.2 g (51%) of 2-[1-(diphenylmethyl)azetidin-3-yl]octahydro-2*H*-pyrido[1,2-*a*]pyrazine. ¹H NMR (500 MHz, CDCl₃): 1.2-1.3 (m, 2H), 1.4-1.5 (d, 1H), 1.6-1.8 (m, 4H), 2.0-2.2 (m, 3H), 2.3 (t, 1H), 2.5 (d, 1H), 2.6-3.0 (m, 6H), 3.4 (t, 2H), 4.4 (s, 1H), 7.2 (t, 2H), 7.3 (m, 4H), 7.4 (m, 4H); LCMS: *m/z* 362 (M+1)⁺.

(b) *2-Azetidin-3-yl*octahydro-2*H*-pyrido[1,2-*a*]pyrazine dihydrochloride

2-[1-(Diphenylmethyl)azetidin-3-yl]octahydro-2*H*-pyrido[1,2-*a*]pyrazine (1.2 g, 3.3 mmol) was dissolved in acetic acid and to the resultant solution was added palladium hydroxide on carbon (1 g). The mixture was stirred under hydrogen (5 bar) at RT overnight and then the catalyst was filtered off by means of Celite®. The filter cake was washed several times with ethanol. The solvent was removed by evaporation and the residue was partitioned between toluene and diluted aqueous HCl. The two phases were separated and the aqueous solution was then extracted with toluene. The solvent was removed by freeze-drying and there was obtained 0.80 g (90%) of the title compound. ¹H NMR (500 MHz, CD₃OD): 1.4-2.2 (cm, 6H), 3.1-3.5 (cm, 2H), 3.5-4.0 (cm, 7H), 4.4-4.9 (cm, 5H); LCMS: *m/z* 196 (M+1)⁺.

Method 20

3-Bromo-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-5-(trifluoromethyl)benzamide



(a) *3-Bromo-N-[(2S)-2-(4-fluorophenyl)pent-4-en-1-yl]-N-methyl-5-(trifluoromethyl)benzamide*

To a solution of [(2*S*)-2-(4-fluorophenyl)pent-4-en-1-yl]methylaniline (see *Bioorg. Med. Chem. Lett*; 2001; 265-270; 0.54 g, 2.8 mmol) and 3-bromo-5-trifluoromethyl benzoic acid (0.81 g, 3.0 mmol) in DMF (7 mL) were added TBTU (0.96 g, 3.0 mmol) and DIPEA (1.41 g, 10.9 mmol). The reaction mixture was stirred under nitrogen overnight at RT and then partitioned between ethyl acetate and an aqueous NaHCO₃ solution. The aqueous

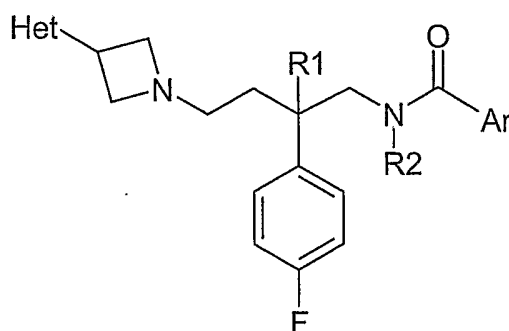
phase was extracted trice with ethyl acetate. The combined organic solutions were washed trice with water and then dried by a phase separator column. The solvent was removed by evaporation and the product was purified by chromatography on silica gel (ethyl acetate – heptane 10% to 17%). There was obtained 0.86 g (68%) of 3-bromo-*N*-[(2*S*)-2-(4-fluorophenyl)pent-4-en-1-yl]-*N*-methyl-5-(trifluoromethyl)benzamide. ¹H NMR (500 MHz, CDCl₃): 2.1-3.8 (cm, 8H), 4.9-5.1 (m, 2H), 5.5-5.8 (m, 1H), 6.8-7.4 (cm, 6H), 7.8 (s, 1H). LCMS: m/z 445 (M+1)⁺.

(b) *3-Bromo-N-[(2S)-2-(4-fluorophenyl)-4-oxobutyl]-N-methyl-5-(trifluoromethyl)benzamide*

To a solution of 3-bromo-*N*-[(2*S*)-2-(4-fluorophenyl)pent-4-en-1-yl]-*N*-methyl-5-(trifluoromethyl)benzamide (0.86 g, 1.9 mmol) in acetone (45 mL) were added OsO₄ (2.5% in *t*-butyl alcohol, 0.49 mL, 0.039 mmol) and 4-methylmorpholine-4-oxide (0.41 g, 3.5 mmol). The solution was stirred under nitrogen at RT overnight and then an aqueous solution of NaHSO₃ (39%, 45 mL) was added. The mixture was stirred for 2 h, diluted with water and then extracted twice with methylene chloride. The combined organic solutions were separated by means of a phase separator column and the solvent was removed by evaporation. The residue (1.08 g) was dissolved in THF (18 mL) and water (4.5 mL) and to the resultant solution was added NaIO₄ (0.73 g, 3.4 mmol). The mixture was stirred under nitrogen overnight at RT. The mixture was partitioned between methylene chloride and water. The aqueous phase was extracted with methylene chloride and then the combined organic solutions were washed with brine and separated by means of a phase separator column. The solvent was removed by evaporation. There was obtained 0.78 g (90%) of the title compound. ¹H NMR (500 MHz, CDCl₃): 2.4-4.4 (cm, 8H), 6.2-8.2 (cm, 7H), 9.8 (s, 1H); LCMS: m/z 447 (M+1)⁺.

Claims

1. A compound of formula (I)



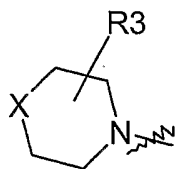
(I)

wherein

R1 is hydrogen;

10 R2 is C₁-C₄ alkyl, wherein one or more of the hydrogen atoms of the alkyl group may be substituted for a fluoro atom;

Het is selected from 2,5-diazabicyclo[2.2.1]heptane, octahydropyrrolo[3,4-*c*]pyrrole, 1,4-diazepane, octahydropyrrolo[1,2-*a*]pyrazine, octahydro-2*H*-pyrido[1,2-*a*]pyrazine, octahydropyrazino[2,1-*c*][1,4]oxazine; optionally substituted by C₁-C₄ alkyl, wherein one
 15 or more of the hydrogen atoms of the alkyl group may be substituted for a fluoro atom;
 with the proviso that Het is connected to the azetidine ring at one of its nitrogen atoms;
 or Het is



wherein

20 X is CH₂, O or NR₆;

R3 is (CH₂)_mNR₄R₅ or R3 is H if X is NR₆;

R4 and R5 is each and independently selected from hydrogen, C₁-C₄ alkyl or C₂-C₄ hydroxyalkyl, wherein one or more of the hydrogen atoms of the alkyl group or hydroxyalkyl group may be substituted for a fluoro atom;

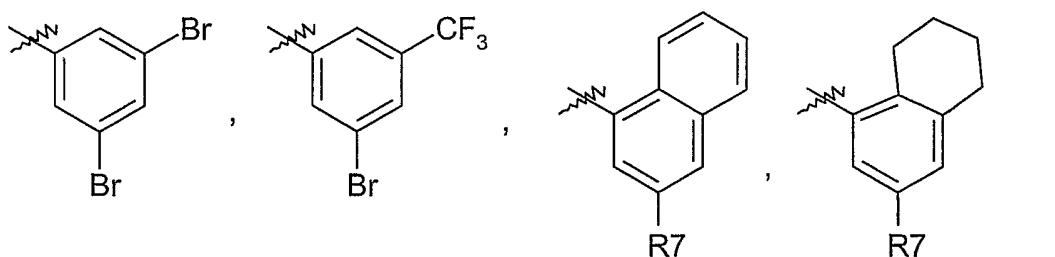
or R4 and R5 may together form an azacycloalkane having 4 to 8 atoms, optionally substituted by one or more fluoro atoms;

m is 0, 1, 2, 3 or 4 with the proviso that if m is 0 then X is CH₂ and R3 is attached to the 3- or 4-position of the ring;

R6 is hydrogen, C₁-C₄ alkyl, C₂-C₄ hydroxyalkyl, 2-(dimethylamino)-2-oxoethyl, wherein one or more of the hydrogen atoms of the alkyl group or hydroxyalkyl group may be

substituted for a fluoro atom; and

Ar is selected from



wherein

R7 is CN or F;

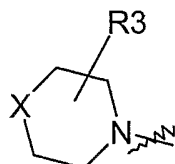
as well as pharmaceutically and pharmacologically acceptable salts thereof, and enantiomers of the compound of formula I and salts thereof.

2. A compound according to claim 1 wherein R2 is methyl, wherein one or more of the hydrogen atoms of the methyl group may be substituted for a fluoro atom.

3. A compound according to claim 1 or 2 wherein Het is selected from octahydropyrrolo[1,2-*a*]pyrazine or octahydro-2*H*-pyrido[1,2-*a*]pyrazine, optionally substituted by C₁-C₄ alkyl, wherein one or more of the hydrogen atoms of the alkyl group may be substituted for a fluoro atom.

4. A compound according to claim 1 or 2 wherein Het is octahydropyrazino[2,1-c][1,4]oxazine, optionally substituted by C₁-C₄ alkyl, wherein one or more of the hydrogen atoms of the alkyl group may be substituted for a fluoro atom.

5. A compound according to claim 1 or 2 wherein Het is



wherein

X is CH₂, O or NR₆;

R₃ is (CH₂)_mNR₄R₅ or R₃ is H if X is NR₆.

10

6. A compound according to claim 5 wherein R₄ is hydrogen or methyl, wherein one or more of the hydrogen atoms of the methyl group may be substituted for a fluoro atom.

7. A compound according to claim 5 or 6 wherein R₅ is hydrogen or methyl, wherein one or more of the hydrogen atoms of the methyl group may be substituted for a fluoro atom.

15

8. A compound according to claim 5 wherein R₄ and R₅ together form an azacycloalkane having 4 to 8 atoms, optionally substituted by one or more fluoro atoms.

9. A compound according to claim 8 wherein R₄ and R₅ together form a five to six membered azacycloalkane optionally substituted by one or more fluoro atoms.

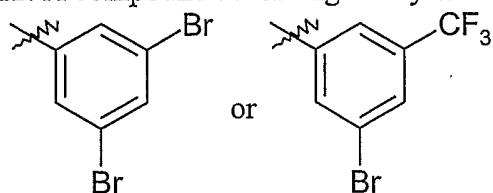
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10. A compound according to any one of claims 5-9 wherein m is 0, 1 or 2.

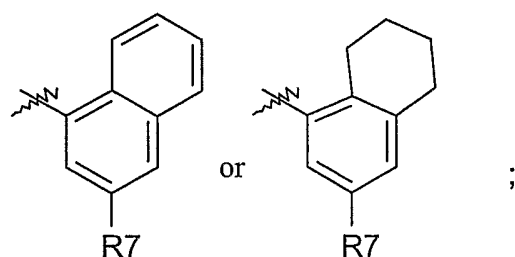
11. A compound according to any one of claims 5-10 wherein R₆ is hydrogen or 2-(dimethylamino)-2-oxoethyl.

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12. A compound according to any one of claims 1-11 wherein Ar is selected from



13. A compound according to any one of claims 1-11 wherein Ar is selected from



wherein R7 is CN or F.

14. A compound according to any one of claims 1-13 wherein the compound is the (*S*)-enantiomer.

15. A compound according to claim 1 selected from

3-Cyano-*N*-[(2*S*)-4-[3-(1,4-diazepan-1-yl)azetidin-1-yl]-2-(4-fluorophenyl)butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide;

3-Cyano-*N*-[(2*S*)-2-(4-fluorophenyl)-4-(3-piperazin-1-ylazetidin-1-yl)butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide;

N-[(2*S*)-4-[3-(4-Aminopiperidin-1-yl)azetidin-1-yl]-2-(4-fluorophenyl)butyl]-3,5-dibromo-*N*-methylbenzamide trihydrochloride;

N-[(2*S*)-4-{3-[4-(aminomethyl)piperidin-1-yl]azetidin-1-yl}-2-(4-fluorophenyl)butyl]-3,5-dibromo-*N*-methylbenzamide;

N-[(2*S*)-4-{3-[4-(aminomethyl)piperidin-1-yl]azetidin-1-yl}-2-(4-fluorophenyl)butyl]-3-cyano-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide;

3,5-dibromo-*N*-[(2*S*)-4-[3-(1,4-diazepan-1-yl)azetidin-1-yl]-2-(4-fluorophenyl)butyl]-*N*-methylbenzamide;

- 3,5-dibromo-*N*-((2*S*)-2-(4-fluorophenyl)-4-{3-[4-(methylamino)piperidin-1-yl]azetidin-1-yl}butyl)-*N*-methylbenzamide;
- 3-cyano-*N*-((2*S*)-2-(4-fluorophenyl)-4-{3-[4-(methylamino)piperidin-1-yl]azetidin-1-yl}butyl)-*N*-methyl-1-naphthamide trihydrochloride;
- 5 3-cyano-*N*-((2*S*)-2-(4-fluorophenyl)-4-{3-[4-(methylamino)-piperidin-1-yl]azetidin-1-yl}butyl)-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide;
- N*-[(2*S*)-4-[3-(4-aminopiperidin-1-yl)azetidin-1-yl]-2-(4-fluorophenyl)butyl]-3-cyano-*N*-methyl-1-naphthamide trihydrochloride;
- N*-[(2*S*)-4-[3-(4-aminopiperidin-1-yl)azetidin-1-yl]-2-(4-fluorophenyl)butyl]-3-cyano-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide;
- 10 *N*-[(2*S*)-4-{3-[(3*R*)-3-(2-aminoethyl)morpholin-4-yl]azetidin-1-yl}-2-(4-fluorophenyl)butyl]-3-cyano-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide;
- N*-[(2*S*)-4-{3-[(3*R*)-3-(2-aminoethyl)morpholin-4-yl]azetidin-1-yl}-2-(4-fluorophenyl)butyl]-3,5-dibromo-*N*-methylbenzamide;
- 15 3-cyano-*N*-{(2*S*)-2-(4-fluorophenyl)-4-[3-(octahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)azetidin-1-yl]butyl}-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide;
- 3-cyano-*N*-[(2*S*)-4-[3-(2,5-diazabicyclo[2.2.1]hept-2-yl)azetidin-1-yl]-2-(4-fluorophenyl)butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide;
- 3-cyano-*N*-[(2*S*)-2-(4-fluorophenyl)-4-(3-{2-[2-(methylamino)ethyl]piperidin-1-yl}azetidin-1-yl)butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide;
- 20 3,5-Dibromo-*N*-[(2*S*)-4-{3-[4-(dimethylamino)piperidin-1-yl]azetidin-1-yl}-2-(4-fluorophenyl)butyl]-*N*-methylbenzamide;
- 3-Cyano-*N*-[(2*S*)-4-(3-{(3*R*)-3-[2-(dimethylamino)ethyl]morpholin-4-yl}azetidin-1-yl)-2-(4-fluorophenyl)butyl]-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide;
- 25 3-Cyano-*N*-{(2*S*)-2-(4-fluorophenyl)-4-[3-(octahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)azetidin-1-yl]butyl}-*N*-methyl-1-naphthamide;
- 3,5-Dibromo-*N*-{(2*S*)-2-(4-fluorophenyl)-4-[3-(octahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)azetidin-1-yl]butyl}-*N*-methylbenzamide;
- 3,5-Dibromo-*N*-{(2*S*)-2-(4-fluorophenyl)-4-[3-(octahydro-2*H*-pyrido[1,2-*a*]pyrazin-2-yl)azetidin-1-yl]butyl}-*N*-methylbenzamide acetate;
- 30

3-Bromo-*N*-{(2*S*)-2-(4-fluorophenyl)-4-[3-(octahydro-2*H*-pyrido[1,2-*a*]pyrazin-2-yl)azetidin-1-yl]butyl}-*N*-methyl-5-(trifluoromethyl)benzamide diacetate; and
3-Cyano-*N*-{(2*S*)-2-(4-fluorophenyl)-4-[3-(octahydro-2*H*-pyrido[1,2-*a*]pyrazin-2-yl)azetidin-1-yl]butyl}-*N*-methyl-5,6,7,8-tetrahydronaphthalene-1-carboxamide diacetate.

5

16. A compound according to any one of claims 1-15 for use in therapy.

17. Use of a compound according to any one of claims 1-15 for the manufacture of a medicament for the treatment of a functional gastrointestinal disorder.

10

18. Use of a compound according to any one of claims 1-15 for the manufacture of a medicament for the treatment of IBS.

19. Use of a compound according to any one of claims 1-15 for the manufacture of a medicament for the treatment of functional dyspepsia.

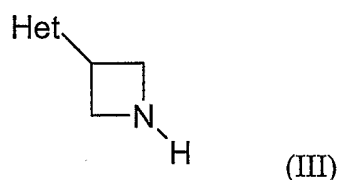
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20. A pharmaceutical formulation comprising a compound according to any one of claims 1-15 as active ingredient and a pharmaceutically acceptable carrier or diluent.

21. Process for preparing a compound of formula (I) comprising the steps of

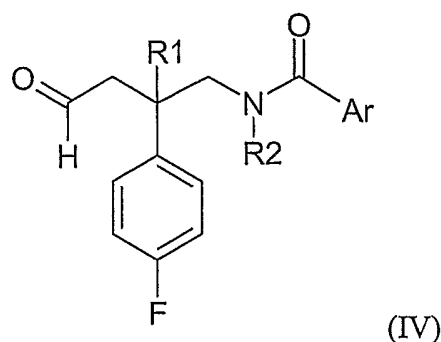
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a) reacting a compound of the formula (III) with a compound of the formula (IV):



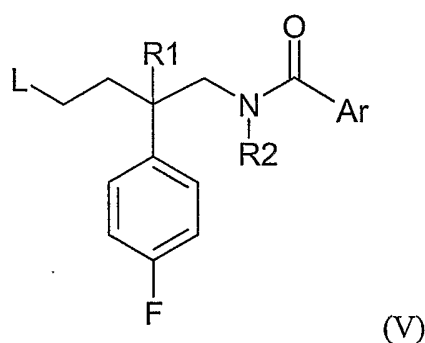
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wherein R1-R2, Het, and Ar are as hereinbefore defined; and the conditions are such that reductive alkylation of the compounds of the formulae (III) forms an N-C bond between
5 the nitrogen atom of the azetidine group of the compounds of formulae (III) and the carbon atom of the aldehyde group of the compounds of formulae (IV); or

b) reacting a compound of the formula (III) with a compound of the formula (V):

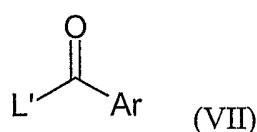
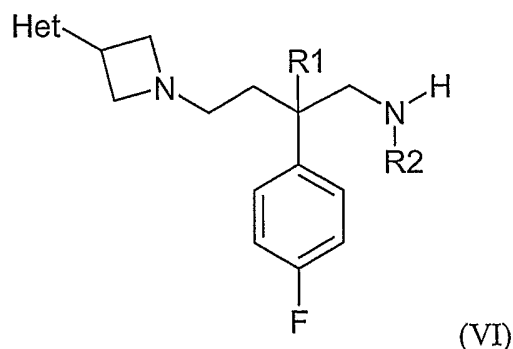


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wherein R1-R2, Het, and Ar are as hereinbefore defined; and L is a group such that alkylation of the compounds of the formulae (III) forms an N-C bond between the nitrogen atom of the azetidine group of the compounds of formulae (III) and the carbon atom of the compounds of formulae (V) that is adjacent to the L group; or

15 c) reacting a compound of the formula (VI) with a compound of the formula (VII):

64



- wherein R1-R2, Het and Ar are as hereinbefore defined; and L' is a leaving group;
 wherein any other functional group is protected, if necessary, and:
- i) removing any protecting groups;
 - ii) optionally oxidizing any oxidizable atoms;
 - iii) optionally forming a pharmaceutically acceptable salt.

10

22. A compound selected from

tert-Butyl-4-{1-[(3*S*)-4-[(3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl]-
 (methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}-1,4-diazepane-1-carboxylate;

tert-Butyl 4-{1-[(3*S*)-4-[(3,5-dibromobenzoyl)(methyl)amino]-3-(4-
 fluorophenyl)butyl]azetidin-3-yl}-1,4-diazepane-1-carboxylate;

tert-Butyl 4-{1-[(3*S*)-4-[(3-cyano-5,6,7,8-tetrahydronaphthalen-1-
 yl)carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperazine-1-
 carboxylate;

tert-Butyl (1-{1-[(3*S*)-4-[(3,5-dibromobenzoyl)(methyl)amino]-3-(4-fluorophenyl)-
 butyl]azetidin-3-yl}piperidin-4-yl)carbamate;

tert-Butyl [(1-{1-[(3*S*)-4-[(3,5-dibromobenzoyl)(methyl)amino]-3-(4-
 fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)methyl]carbamate;

- tert*-Butyl [(1-{1-[(3*S*)-4-[[3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)methyl]carbamate;
- tert*-Butyl (1-{1-[(3*S*)-4-[(3,5-dibromobenzoyl)(methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)methylcarbamate;
- tert*-Butyl (1-{1-[(3*S*)-4-[(3-cyano-1-naphthoyl)(methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)methylcarbamate;
- tert*-Butyl (1-{1-[(3*S*)-4-[[3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)methylcarbamate;
- tert*-Butyl (1-{1-[(3*S*)-4-[(3-cyano-1-naphthoyl)(methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)carbamate;
- tert*-Butyl (1-{1-[(3*S*)-4-[[3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-4-yl)carbamate;
- tert*-Butyl [2-((3*R*)-4-{1-[(3*S*)-4-[[3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl)morpholin-3-yl)ethyl]carbamate;
- tert*-Butyl [2-((3*R*)-4-{1-[(3*S*)-4-[(3,5-dibromobenzoyl)(methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl)morpholin-3-yl)ethyl]carbamate;
- tert*-Butyl 5-{1-[(3*S*)-4-[[3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}octahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate;
- tert*-Butyl (1*S*,4*S*)-5-{1-[(3*S*)-4-[[3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate;
- tert*-Butyl [2-(1-{1-[(3*S*)-4-[[3-cyano-5,6,7,8-tetrahydronaphthalen-1-yl)carbonyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl}piperidin-2-yl)ethyl]methylcarbamate;
- {2-[(3*R*)-4-azetidin-3-ylmorpholin-3-yl]ethyl} dimethylamine;

2-Azetidin-3-yl octahydropyrrolo[1,2-*a*]pyrazine;

2-Azetidin-3-yl octahydro-2*H*-pyrido[1,2-*a*]pyrazine dihydrochloride; and

3-Bromo-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-5-(trifluoromethyl)benzamide.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2006/000760

A. CLASSIFICATION OF SUBJECT MATTER

IPC: 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: C07D, A61K

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

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004110344 A2 (ASTRAZENECA AB), 23 December 2004 (23.12.2004), page 1, line 21 - line 28, examples 2, 9, 14, 20, 27-28, 30-36, 45-46, 51, 52 --	1-21, PARTLY 22
A	MACKENZIE A. RODERICK ET AL, "4-Amino-2-(aryl)-butylbenzamides and Their conformationally constrained analogues. Potent antagonists of the human neurokinin-2 (NK2) receptor", Bioorganic & Medicinal Chemistry Letters, Vol. 13, Issue 13, 7 July 2003, page 2211 - page 2215 --	1-21, PARTLY 22
A	WO 0020003 A1 (ZENECA LIMITED), 13 April 2000 (13.04.2000) --	1-21, PARTLY 22

☒ 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

7 November 2006

Date of mailing of the international search report

08-11-2006

Name and mailing address of the ISA/
Swedish Patent Office
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000760

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

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

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

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

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

In order to fulfil the requirements of unity of invention, it is necessary that the intermediate compounds are closely interconnected with the end products. Such close connection requires that the essential structural part of the end product is incorporated by the intermediate compound. However, the

.../...

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 fee, this Authority did not invite payment of any 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.: 1-21, partly 22

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
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Box III

present application lacks a single general inventive concept based on the above principle. This leads to the presence of the following separate inventions listed below, each falling under its own restricted inventive concept.

1: Claims 1-21 and partly 22 directed to compounds of formula I, to the use of these compounds for the manufacture of a medicament for the treatment of gastrointestinal diseases, to a process for the preparation of these compounds and to BOC-protected intermediates (compounds 1-16 in claim 22).

2: Claim 22 (partly) directed to three heterocycle-substituted azetidine derivatives (compounds 17-19).

3: Claim 22 (partly) directed to 3-bromo-N-[(2S)-2-(4-fluorophenyl)-4-oxobutyl]-N-methyl-5-(trifluoromethyl)-benzamide (compound 20).

The present application has been considered to contain 3 inventions which are not linked such that they form a single general inventive concept, as required by Rule 13 PCT.

A partial search has been carried out, which relates to the invention 1 mentioned above.

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Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to new azetidine derivatives of formula I, to pharmaceutical compositions containing said compounds and to the use of said compounds as neurokinin (NK) receptor antagonists in the treatment of gastrointestinal diseases. The invention further relates to processes for the preparation of compounds of formula I and to new intermediates used in the preparation thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2006/000760

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0002859 A1 (ZENECA LIMITED), 20 January 2000 (20.01.2000) ---	1-21, PARTLY 22
A	WO 9727185 A1 (PFIZER RESEARCH AND DEVELOPMENT COMPANY), 31 July 1997 (31.07.1997) ---	1-21, PARTLY 22
A	WO 9610568 A1 (MERCK & CO., INC.), 11 April 1996 (11.04.1996) -----	1-21, PARTLY 22

International patent classification (IPC)

C07D401/04 (2006.01)
A61K31/397 (2006.01)
A61K31/407 (2006.01)
A61K31/4523 (2006.01)
A61K31/4985 (2006.01)
A61K31/5377 (2006.01)
A61K31/5513 (2006.01)
A61P1/00 (2006.01)
A61P11/00 (2006.01)
A61P25/00 (2006.01)
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- e-tjänster/anförda dokument (service in Swedish).

Use the application number as username.

The password is **SQNRXDKJII**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

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International application No.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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INTERNATIONAL SEARCH REPORT

Information on patent family members

04/10/2006

International application No.

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