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(54) Title: 1- [ (4- [BENZOYL (METHYL) AMINO] -3- (PHENYL) BUTYL] AZETIDINE DERIVATIVES FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS 2

(57) Abstract: The present invention relates to new compounds of formula (I) wherein Het has the meaning given in the description, as well as salts and enantiomers thereof. The invention also relates to pharmaceutical compositions comprising said compounds, and to the use of said compounds in therapy, e.g. in the treatment of gastrointestinal disorders. The invention further relates to processes for the preparation of the compounds. The compounds are neurokinin (NK) receptor antagonists.



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1 - [ (4 - [benzoyl (methyl) amino] - 3 - (phenyl) butyl] azetidine  
derivatives for the treatment of gastrointestinal disorders  
2

Field of the Invention

5 The present invention relates to new compounds of formula I, to pharmaceutical compositions comprising 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.

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  
15 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 (NK<sub>1</sub>), neurokinin 2 (NK<sub>2</sub>) and neurokinin 3 (NK<sub>3</sub>) 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  
25 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 certain compounds may cause undesirable effects on cardiac  
30 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<sup>+</sup> 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  
5 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  
10 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.

In particular, it is desirable that the NK receptor antagonist has a suitable balance of pharmacodynamic and pharmacokinetic properties to make it therapeutically useful. In  
15 addition to having sufficient and selective potency, the NK receptor antagonist needs to be balanced with regard to relevant pharmacokinetic properties. Thus, it is necessary that the NK antagonist has: a) sufficiently high affinities at the different NK receptors, b) pharmacokinetic properties (absorption, distribution and elimination properties) that makes it possible for the drug to act at the targeted NK receptors in the periphery as well as in the  
20 CNS. For instance, the NK receptor antagonist needs to have sufficiently high metabolic stability, c) sufficiently low affinities to different ion channels, such as the hERG-encoded potassium channel in order to obtain a tolerable safety profile and d) liver enzyme (such as CYP3A4) inhibiting properties at a low level to prevent drug-drug interactions.

25 Furthermore, in order to enhance the efficacy of the NK receptor antagonist, it is beneficial to have an NK antagonist with a long-lasting competitive mode of action at the receptor.

EP 0625509, EP 0630887, WO 95/05377, WO 95/12577, WO 95/15961, WO 96/24582, WO 00/02859, WO 00/20003, WO 00/20389, WO 00/25766, WO 00/34243,

WO 02/51807 and WO 03/037889 disclose piperidinybutylamide derivatives, which are tachykinin antagonists.

“4-Amino-2-(aryl)-butylbenzamides and Their Conformationally Constrained Analogues.

5 Potent Antagonists of the Human Neurokinin-2 (NK<sub>2</sub>) 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 NK<sub>2</sub> receptor antagonistic properties.

10

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

EP 0790248 discloses azetidinyllazapiperidones and azetidinyloxapiperidones,

15 which are stated to be tachykinin antagonists.

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

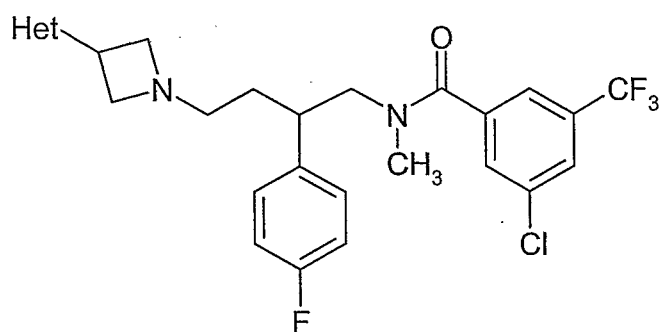
20 EP 0791592 discloses azetidinyllglutarimides with tachykinin antagonistic properties.

WO2004/110344 A2 discloses dual NK<sub>1,2</sub> antagonists and the use thereof.

25 An object of the present invention was to provide novel neurokinin antagonists useful in therapy. A further object was to provide novel compounds having well-balanced pharmacokinetic and pharmacodynamic properties.

Outline of the invention

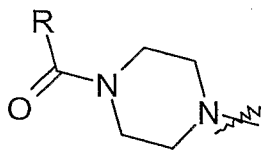
The present invention provides a compound of the general formula (I)



(I)

wherein

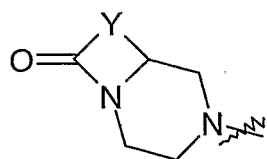
Het is



wherein

R is C<sub>1</sub>-C<sub>4</sub> alkyl; cyclopropyl; C<sub>1</sub>-C<sub>4</sub> methoxyalkyl; C<sub>1</sub>-C<sub>4</sub> ethoxyalkyl; C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl; tetrahydrofuran-2-yl; tetrahydrofuran-3-yl; tetrahydropyran-2-yl; tetrahydropyran-3-yl; or tetrahydropyran-4-yl;

or Het is



wherein

Y is C<sub>1</sub>-C<sub>3</sub> alkylene; -CH<sub>2</sub>-O-CH<sub>2</sub>-; or -CH<sub>2</sub>-CH<sub>2</sub>-O-;

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.

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

As used herein, the term "C<sub>1</sub>-C<sub>4</sub> alkyl" includes straight as well as branched chain C<sub>1-4</sub> alkyl groups, for example methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl.

As used herein, the term "C<sub>1</sub>-C<sub>3</sub> alkylene" includes straight chain C<sub>1-3</sub> saturated hydrocarbon radicals, for example methylene, ethylene or n-propylene.

As used herein, "C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl" is a hydroxyalkyl group comprising 1-4 carbon atoms and a hydroxyl group.

As used herein, "C<sub>1</sub>-C<sub>4</sub> methoxyalkyl" is a methoxyalkyl group comprising 1-4 carbon atoms.

As used herein, "C<sub>1</sub>-C<sub>4</sub> ethoxyalkyl" is an ethoxyalkyl group comprising 1-4 carbon atoms.

#### 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 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 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 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 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 humans in a daily dose of a compound of formula I of from 0.01 to 25 mg/kg body weight. Alternatively, a daily dose of the compound of formula I from 0.1 to 5 mg/kg body weight is administered. This daily dose may be given in divided doses as necessary, the precise amount of the compound administered 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.

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 inhalation, a compound of the formula (I) or a pharmaceutically acceptable salt thereof may be administered in a daily dosage range of from 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 acceptable salt thereof may be used.

#### Medical and pharmaceutical use

5 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 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  
10 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.

The compounds of formula (I) or pharmaceutically acceptable salts or solvates thereof may  
15 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.

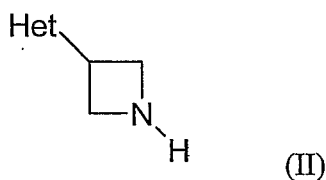
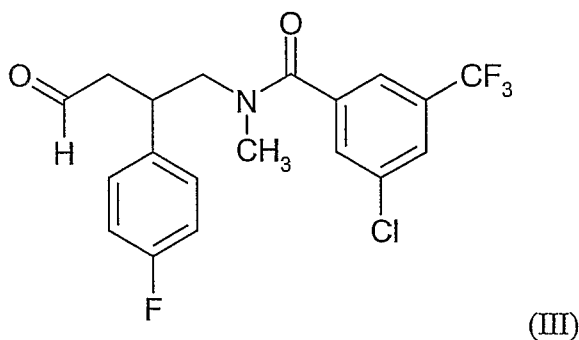
Examples of such disorders are asthma, allergic rhinitis, pulmonary diseases, cough, cold, inflammation, chronic obstructive pulmonary disease, airway reactivity,

20 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 depression, substance dependence, movement disorder, cognitive disorder, obesity, stress disorders, micturition disorders, mania, hypomania and aggression, bipolar disorder,  
25 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 motility disorders, gastro-esophageal reflux disease (GERD) or functional dyspepsia.

Methods of preparation

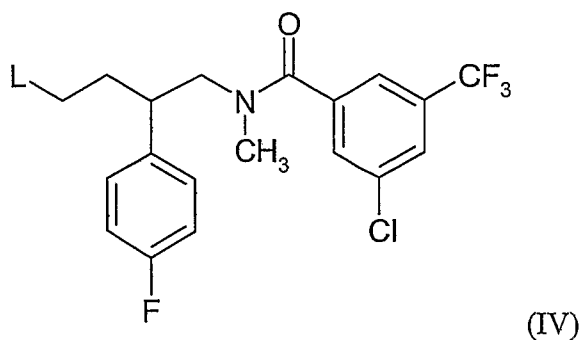
In another aspect the present invention provides a process for preparing a compound of the formula (I) or salts thereof which process comprises:

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



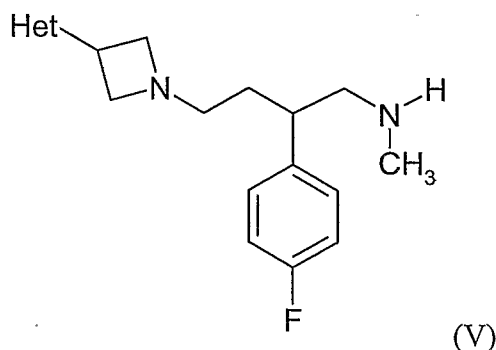
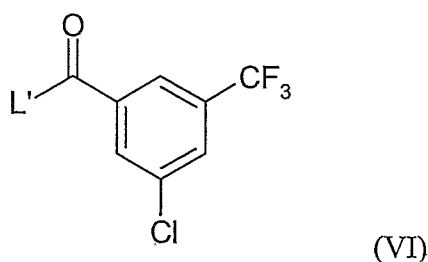
wherein Het is as hereinbefore defined; and the conditions are such that reductive alkylation of the compounds of the formula (II) forms an N-C bond between the nitrogen atom of the azetidine group of the compounds of formula (II) and the carbon atom of the aldehyde group of the compounds of formula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

- 15 b) reacting a compound of the formula (II) with a compound of the formula (IV):



wherein Het is as hereinbefore defined; and L is a group such that alkylation of the compounds of the formula (II) forms an N-C bond between the nitrogen atom of the azetidine group of the compounds of formula (II) and the carbon atom of the compounds of formula (IV) that is adjacent to the L group; or

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



wherein Het is as hereinbefore defined; and L' is a leaving group;  
wherein any other functional group is protected, if necessary, and:

i) removing any protecting groups;

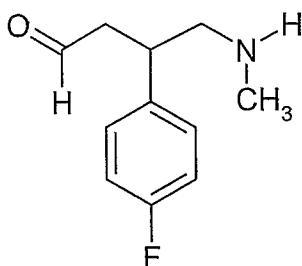
ii) optionally forming a pharmaceutically acceptable salt.

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 chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

The compounds of the formula (II) and (III) are reacted under conditions of reductive 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 formula (II) and (IV) are reacted under conditions of alkylation. Typically in the compounds of the formula (IV) 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.

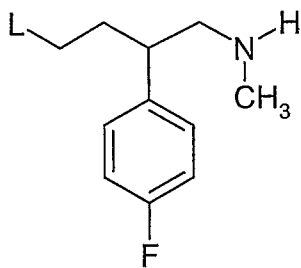
The compounds of the formula (II) are known or may be prepared in conventional manner. The compound of the formula (III) may be prepared, for example, by reacting a compound of the formula (VI) with a compound of the formula (VII):



(VII)

under conventional acylation conditions.

The compounds of the formula (IV) may be prepared, for example, by reacting a compound of the formula (VI) with a compound of the formula (VIII):

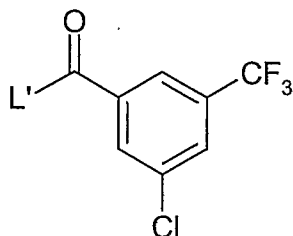


(VIII)

wherein L is as hereinbefore defined, under conventional acylation conditions.

The compounds of the formulae (V) and (VI) 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, 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 (VII) and (VIII) are known or may be prepared in conventional manner.

### Working Examples

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, which may include broad peaks.

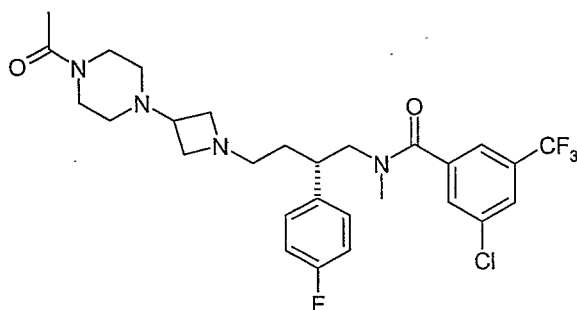
25

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

The following abbreviations are used in the experimental: DMSO (dimethylsulfoxide), THF (tetrahydrofuran), MTBE (methyl-tertbutyleter) and RT (room temperature).

### Example 1

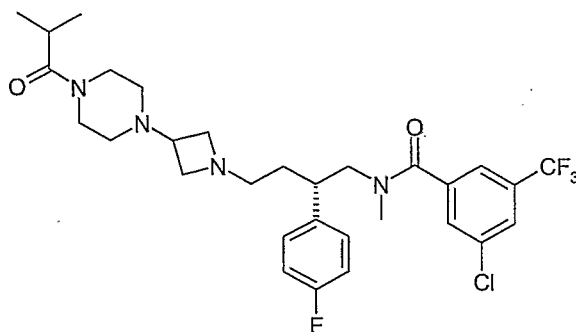
5 3-Chloro-N-[(2S)-2-(4-fluorophenyl)-4-[3-(4-acetypiperazin-1-yl)azetidin-1-yl]butyl]-N-methyl-5-(trifluoromethyl)benzamide



3-Chloro-N-[(2S)-2-(4-fluorophenyl)-4-oxobutyl]-N-methyl-5-(trifluoromethyl)benzamide (see Method 1; 0.25 g, 0.62 mmol) and 1-acetyl-4-azetidin-3-ylpiperazine hydrochloride (see WO 96/05193; 0.20 g, 0.93 mmol) together with triethylamine (0.17 mL, 1.24 mmol) were mixed with methanol (7 mL). The mixture was stirred at RT for 30 min and then sodium triacetoxyborohydride (0.26 g, 1.24 mmol) was added. The reaction mixture was stirred at RT for 1 h. The solvent was removed by evaporation and the residue was partitioned between methylene chloride (5 mL) and an aqueous solution of NaHCO<sub>3</sub> (5 mL 10%). The organic phase was separated by means of a phase separator column, which then was washed with more of methylene chloride. The solvent was removed by evaporation. The product was purified by chromatography on silica gel (ammonia saturated methanol – methylene chloride: 2%-15% methanol). There was obtained 0.21 g (60%) of the title compound as a colorless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 1.3-1.8 (cm, 2H), 2.0 (s, 3H), 2.1-3.7 (cm, 21H), 6.7-7.3 (cm, 6H), 7.5 (s, 1H): m/z 569 (M+1)<sup>+</sup>.

**Example 2**

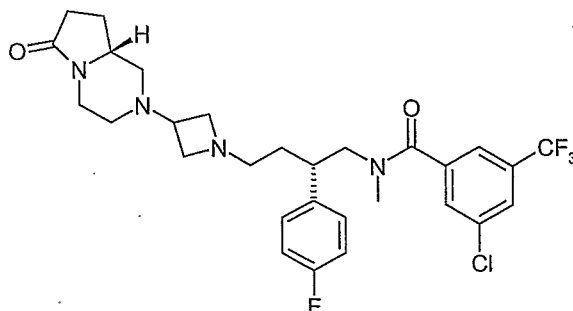
3-Chloro-*N*-[(2*S*)-2-(4-fluorophenyl)-4-[3-(4-isobutyrylpiperazin-1-yl)azetidin-1-yl]butyl]-*N*-methyl-5-(trifluoromethyl)benzamide



- 5 3-Chloro-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-5-(trifluoromethyl)benzamide (see Method 1; 1.57 g, 3.90 mmol) and triethylamine (0.79 g, 7.82 mmol) were mixed with methanol (7 mL). 1-Azetidin-3-yl-4-isobutyrylpiperazine hydrochloride (see Method 2; 1.26 g, 5.08 mmol) was added and the mixture was stirred at RT for 30 min. Sodium triacetoxyborohydride (1.24 g, 5.86 mmol) was added over a period of 15 min. The
- 10 reaction mixture was stirred at RT for 30 min. The solvent was removed by evaporation and the residue was partitioned between methylene chloride (5 mL) and an aqueous solution of NaHCO<sub>3</sub> (5 mL 10%). The organic phase was separated by means of a phase separator column, which then was further washed with methylene chloride. The solvent was removed by evaporation. The product was purified by chromatography on silica gel
- 15 (ammonia saturated methanol – methylene chloride: 2%-15% methanol). There was obtained 0.21 g (60%) of the title compound as a colorless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 1.1 (d, 6H), 1.3-1.8 (cm, 2H), 2.2-3.8 (cm, 22H), 6.8-7.3 (cm, 6H), 7.6 (s, 1H): m/z 597 (M+1)<sup>+</sup>.

**Example 3**

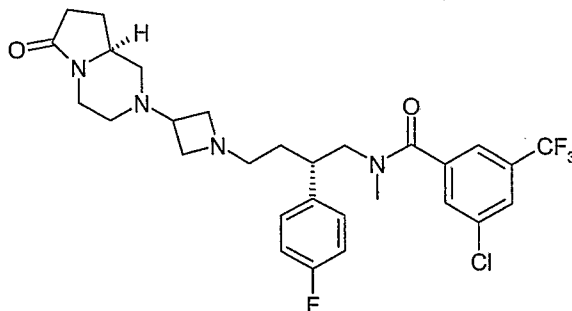
3-Chloro-*N*-((2*S*)-2-(4-fluorophenyl)-4-{3-[(8*aR*)-6-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]azetidin-1-yl}butyl)-*N*-methyl-5-(trifluoromethyl)benzamide



- 5 A mixture of 3-chloro-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-5-(trifluoromethyl)benzamide (see Method 1; 0.54 g, 1.8 mmol), triethylamine (0.5 mL, 3.6 mmol) and (8*aR*)-2-azetidin-3-ylhexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (see Method 3; 0.70 g, 1.8 mmol) in methanol was stirred for 1 h at RT. Triacetoxy sodium borohydride (0.52 g, 3.6 mmol) was added while cooling to 0°C and then the mixture was stirred
- 10 overnight at RT. Water was added and the mixture was extracted with dichloromethane. The organic solution was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed by evaporation and the residue was purified by chromatography on silica gel (methanol – methylene chloride 3:97). There was obtained 0.31 g (29%) of the title compound as a pale yellow gummy oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.6-3.6 (cm, 24H),
- 15 4.0 (d, 2H), 6.8-7.6 (cm, 7H): *m/z* 582 (M+1)<sup>+</sup>.

**Example 4**

3-Chloro-*N*-((2*S*)-2-(4-fluorophenyl)-4-{3-[(8*aS*)-6-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]azetidin-1-yl}butyl)-*N*-methyl-5-(trifluoromethyl)benzamide



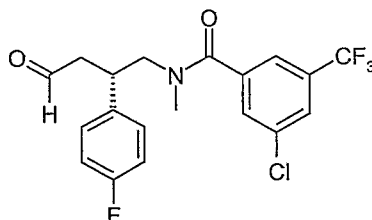
A mixture of 3-chloro-*N*-[(2*S*)-2-(4-fluorophenyl)-4-oxobutyl]-*N*-methyl-5-(trifluoromethyl)benzamide (see Method 1; 0.54 g, 1.8 mmol), triethylamine (0.5 mL, 3.6 mmol) and (8*aS*)-2-azetidin-3-ylhexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (see Method 4; 0.70 g, 1.8 mmol) in methanol was stirred for 1 h at RT. Triacetoxy sodium borohydride (0.52 g, 3.6 mmol) was added while cooling to 0°C and then the mixture was stirred overnight at RT. Water was added and the mixture was extracted with dichloromethane. The organic solution was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed by evaporation and the residue was purified by chromatography on silica gel (methanol – methylene chloride 3:97). There was obtained 0.32 g (30%) of the title compound as a pale yellow gummy oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.6-3.6 (cm, 24H), 4.0 (d, 2H), 6.8-7.2 (cm, 6H), 7.6 (s, 1H); m/z 582 (M+1)<sup>+</sup>.

### 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 reactions are an illustration, but not a limitation, of some of the starting materials.

### Method 1

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



#### (a) *tert*-Butyl 3-cyano-3-(4-fluorophenyl)propanoate

Lithium diisopropylamide (LDA, 52 L, 1.8 M, 93.6 mol) in a solution of THF/heptane and ethylbenzene was charged to a reactor under a nitrogen atmosphere, and THF (52 L) was then added. The temperature was adjusted to an inner temperature (the temperature of the reaction solution) of -48 °C. 4-Fluorophenylacetonitrile (13.0 kg, 96.2 mol) in a THF-solution (25 L) was charged during 1 h and 50 min to the solution comprising LDA, while the temperature of the reaction mixture was kept below -30 °C. The temperature was increased to -6 °C over 1 h, during that time the yellow slurry transformed into a dark

purple solution. THF (5 L) followed by *tert*-butylbromoacetate (20.25 kg, 104 mol) and finally THF (25 L) were charged to a second reactor. The temperature was lowered to an inner temperature of -48 °C. The dark purple solution above was charged to the *tert*-butylbromoacetate-solution over 7.5 h, while the inner temperature was kept below -34°C. The inner temperature was adjusted to -5 °C and the reaction mixture was quenched by adding a solution of ammonium chloride (12.7 kg) and water (55 L) over 15 min. Methyl *tert*-butyl ether (43 L) was charged and the obtained mixture was stirred for 5 min. After phase separation, the aqueous phase was discarded. Brine (7.6 kg sodium chloride in 25 L of water) was charged to the remaining organic phase and the mixture was stirred for 5 min. The aqueous phase was discarded and the remaining solution was concentrated by distillation at reduced pressure to a volume of 150 L. Isooctane (43 L) was charged and the distillation was continued until the resulting volume was 60 L at which point crystallization started. MTBE (25 L) was charged and the jacket temperature was set to 0 °C. After 2 h the batch was filtered (inner temperature 2 °C) and washed with isooctane (2 × 20 L). After drying 16.8 Kg (72%) of *tert*-butyl 3-cyano-3-(4-fluorophenyl)propanoate was obtained. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.51 (app d, *J* = 8 Hz, 1 H), 7.50 (app d, *J* = 8 Hz, 1 H), 7.24 (app t, *J* = 8 Hz, 2H), 4.50 (app dd, *J*<sub>1</sub> = 6 Hz, *J*<sub>2</sub> = 8 Hz, 1 H), 3.02 (app dd, *J*<sub>1</sub> = 8 Hz, *J*<sub>2</sub> = 16 Hz, 1 H), 2.86 (app dd, *J*<sub>1</sub> = 6 Hz, *J*<sub>2</sub> = 16 Hz, 1 H), 1.36 (s, 9 H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 168.4, 161.7 (d, *J*<sub>C,F</sub> = 244 Hz), 131.3 (d, *J*<sub>C,F</sub> = 3 Hz), 129.8 (d, *J*<sub>C,F</sub> = 9 Hz), 120.6, 115.7 (d, *J*<sub>C,F</sub> = 22 Hz), 81.0, 39.1, 31.4, 27.6.

(b) *4-Amino-3-(4-fluorophenyl)butan-1-ol*

*tert*-Butyl 3-cyano-3-(4-fluorophenyl)propanoate (16.7 kg, 67.0 mol) was charged under nitrogen atmosphere to a reactor and THF (50 L) was then added. The temperature was adjusted to an inner temperature of 65 °C. Borane-dimethylsulfide complex (16.6 L, 166 mol) in a THF solution (5 L) was charged to the reaction mixture over a period of 43 minutes. The mixture was then refluxed for 2 hours. The reaction mixture was cooled to 10°C. Water (75 L) and hydrochloric acid (25.5 L) was charged to a second vessel and the reaction solution above was charged to this aqueous phase accompanied by gas evolution (H<sub>2</sub> is formed). When the addition was complete (after 1.5 h), the jacket temperature was increased to 105 °C and the solvents were distilled off until the temperature of the reaction

mixture reached 85 °C. The reaction mixture was refluxed for 12.5 h and then cooled to 24°C. Aqueous sodium hydroxide (50% solution, 32.4 kg) was charged followed by toluene (55 L) and THF (18 L). After phase separation, the aqueous phase was extracted with a mixture of toluene (30 L) and THF (13 L). The organic phases were combined and approximately 65L of solvent mixture was removed by distillation under reduced pressure. Toluene (40 L) and THF (5 L) was charged to the organic phase and the resulting mixture was clear filtered and returned to the reactor. The solvents were distilled off at reduced pressure until 50 L remained. Toluene (20 L) was charged and the distillation was continued until approximately 35 L remained. The inner temperature was lowered from 59 °C to 12 °C over 1 h and seeding crystals (0.2g) were added, which started the crystallization. Heptane (12 L) was charged and the slurry was cooled down to 6°C over 2 h. The slurry was filtered and the solid was washed with heptane (2×10 L) and dried. There was obtained 6.13 kg (50 %) of 4-amino-3-(4-fluorophenyl)butan-1-ol. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.21 (app d, *J*= 8 Hz, 1 H), 7.19 (app d, *J*= 8 Hz, 1 H), 7.10 (app t, *J*= 8 Hz, 2H), 3.13-3.35 (m, 2 H), 2.59-2.81 (m, 2 H), 1.77-1.94 (m, 2 H), 1.50-1.68 (m, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 161.7 (d, *J*<sub>C,F</sub>= 244 Hz), 139.9 (d, *J*<sub>C,F</sub>= 3 Hz), 129.0 (d, *J*<sub>C,F</sub>= 8 Hz), 115.6 (d, *J*<sub>C,F</sub>= 21 Hz), 61.1, 48.2, 46.7, 38.6.

(c) (3*S*)-4-Amino-3-(4-fluorophenyl)butan-1-ol (*R*)-*O*-acetylmandelic acid salt

(*R*)-*O*-Acetylmandelic acid (18.79 kg, 96.76 mol) was charged to a reactor followed by water (845 g) and ethyl acetate (100 L). The solution was stirred at an inner temperature of 17-20 °C for 0.5 h. The clear solution was collected in a drum and the reactor was rinsed with ethyl acetate (20 L). The rinsing solution was then combined with the above clear (*R*)-*O*-acetylmandelic acid solution. 4-Amino-3-(4-fluoro-phenyl)-butan-1-ol (20.64 kg, 112.65 mol) was charged to a reactor followed by absolute ethanol (99.7 % w/w, 19 L) and ethyl acetate (43 L). Stirring was started and the inner temperature was raised to 59 °C. The (*R*)-*O*-acetylmandelic acid solution was charged to the solution of 4-amino-3-(4-fluoro-phenyl)-butan-1-ol over 24 min. The dark yellow solution thus obtained started to crystallize at an inner temperature of 53 °C about 5 min after complete addition of (*R*)-*O*-acetylmandelic acid. The inner temperature was kept at 52-53 °C for 20 min, and the slurry was then cooled down to 25 °C over 1 h and 20 min. The white slurry was filtered and the

solid was washed with ethyl acetate ( $2 \times 37.5$  L) to give, after drying on the filter, 15.33 kg of needle like white crystals having an optical purity of 83 % enantiomeric excess (ee). The ee corrected yield is 66 %. The obtained product (15.33 kg, 40.62 mol) was charged to a reactor followed by absolute 99.5 % ethanol (27.5 L) and ethyl acetate (22.5 L). Stirring was started and the mixture was heated to an inner temperature of 70 °C. Ethyl acetate (105 L) was charged to the mixture over 44 min. The inner temperature was kept between 67-70 °C during the addition. The crystallization started 8 min after the last addition of ethyl acetate (inner temperature 69 °C). The slurry was cooled to an inner temperature of 25 °C over 1 h and 50 min and then filtered. The solid was washed with ethyl acetate ( $2 \times 37.5$  L) and dried giving 11.65 kg (82 % ee corrected yield) of (3*S*)-4-amino-3-(4-fluorophenyl)butan-1-ol as white crystals. The optical purity was 98 % ee according to chiral HPLC. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.41 (app dd,  $J_1 = 7$  Hz,  $J_2 = 1$  Hz, 2 H), 7.16-7.34 (m, 5 H), 7.12 (app t,  $J = 9$  Hz, 2H), 5.53 (app s, 1 H), 3.08-3.33 (m, 2 H), 2.92-3.08 (m, 2 H), 2.78-2.92 (m, 1 H), 2.04 (s, 3 H), 1.77-1.94 (m, 1 H), 1.50-1.69 (m, 1 H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 170.6, 169.7, 168.4, 161.1 (d,  $J_{C,F} = 242$  Hz), 138.3, 137.7 (d,  $J_{C,F} = 3$  Hz), 129.7 (d,  $J_{C,F} = 8$  Hz), 127.9, 127.4, 127.3, 115.2 (d,  $J_{C,F} = 21$  Hz), 77.2, 58.2, 44.0, 38.7, 36.3, 21.1.  $[\alpha]_D$  (*c* 1.0 in methanol, 25°C) -60.4°.

(d) *Ethyl [(2*S*)-2-(4-fluorophenyl)-4-hydroxybutyl]carbamate*

(*S*)-4-Amino-3-(4-fluorophenyl)-butan-1-ol (*R*)-*O*-acetylmandelic acid salt (11.61 kg, 30.76 mol) was charged to a stirred solution of aqueous sodium hydroxide (11.30 kg of 50% sodium hydroxide in water, 141.3 mol, diluted to approximately 70 L) at 16 °C inner temperature under nitrogen atmosphere. THF (7.5 L) and toluene (74 L) was charged resulting in a clear two-phase system. The solution was cooled to -1°C and ethyl chloroformate (3.60 kg, 33.2 mol) in a mixture of THF (1.1 L) and toluene (10 L) was charged to the mixture over 18 min. During the addition the inner temperature rose to 9 °C. The reaction mixture was heated to 18 °C over 1 h and 48 min at which point HPLC analysis indicated that the reaction was complete. Toluene (17.5 L) was charged and good mixing was achieved followed by phase separation. The resulting two phases were separated and the aqueous phase was discarded. The organic phase was washed with water ( $3 \times 8$  L) and concentrated to approximately 50 L by distillation at reduced pressure.

Toluene (25 L) was charged and the distillation was continued until approximately 30 L of the solvents had been distilled off. Toluene (25 L) was charged and the distillation continued until approximately 40 L remained in. The toluene solution containing ethyl [(2*S*)-2-(4-fluorophenyl)-4-hydroxybutyl]carbamate was taken straight into the next step.

(e) (3*S*)-3-(4-Fluorophenyl)-4-(methylamino)butan-1-ol

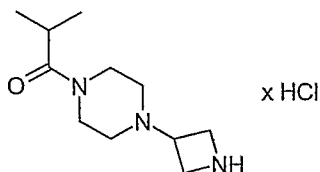
Lithium aluminium hydride (2.11 kg, 55.6 mol) was charged to a reactor containing THF (50 L) at an inner temperature of 20 °C under a nitrogen atmosphere, while stirring. The mixture was heated to an inner temperature of 51 °C and ethyl [(2*S*)-2-(4-fluorophenyl)-4-hydroxybutyl]carbamate in toluene (total volume 43 L) from the previous step was charged to the lithium aluminium hydride slurry in THF over 2 h. The temperature was kept between 51-68 °C during the addition. The charging vessel was rinsed with toluene (5 L) and the batch was then held at 56-58 °C for 2 h. The reaction mixture was cooled to an inner temperature of 2 °C and a solution of aqueous sodium bicarbonate (26 L) was charged over 44 min (inner temperature 15 °C and jacket temperature -25 °C at the end of the quench) after which the jacket was adjusted to 20 °C and the batch was left for 15 h. The slurry in the reactor was filtered and the resulting solid was washed with toluene (30 L) in four portions. The filtrate was returned to the reactor (cleaned from aluminium salts) and washed with water (2 × 10 L) and then clear filtered. The clear filtered solution was returned to the reactor and concentrated to approximately 15 L by distillation under reduced pressure. The distillation was stopped and isooctane (30 L) was charged to the slurry. The slurry was cooled from an inner temperature of 32 °C to 20 °C over 40 min, then filtered and the isolated solid was washed with isooctane (30 L) in four portions. The solid was dried and this resulted in 4.54 kg (75 % over two Steps) of (3*S*)-3-(4-fluorophenyl)-4-(methylamino)butan-1-ol. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.22 (app d, *J* = 8 Hz, 1 H), 7.20 (app d, *J* = 8 Hz, 1 H), 7.08 (app t, *J* = 8 Hz, 2H), 3.11-3.34 (m, 2 H), 3.72-3.88 (m, 1 H), 3.52-3.66 (m, 2 H), 2.21 (s, 3 H), 1.73-1.91 (m, 1 H), 1.48-1.68 (m, 1 H); <sup>13</sup>C NMR δ 160.6 (d, *J*<sub>C,F</sub> = 241 Hz), 140.7 (d, *J*<sub>C,F</sub> = 3 Hz), 129.3 (d, *J*<sub>C,F</sub> = 8 Hz), 114.8 (d, *J*<sub>C,F</sub> = 21 Hz), 58.9, 57.8, 41.3, 37.4, 36.1. [α]<sub>D</sub> (c 1.0 in methanol, 25 °C) +8.8°.

(f) *3-Chloro-N-[(2S)-2-(4-fluorophenyl)-4-hydroxybutyl]-N-methyl-5-(trifluoromethyl)benzamide*

(3S)-3-(4-Fluorophenyl)-4-(methylamino)butan-1-ol (4.0 g, 20.5 mmol) was mixed with an aqueous solution of NaOH (3.3 g in 16 mL of water, 41 mmol). To the formed suspension was added by drops a toluene solution of 3-chloro-5-(trifluoromethyl)benzoyl chloride (5.0 g in 24 mL of toluene, 20.5 mmol) while vigorously stirring. The addition was completed after 15 min. The mixture was stirred for 1 h at RT. The aqueous phase was separated off and the organic solution was washed twice with water. The solvent was dried and then removed by evaporation. There was obtained 8.6 g (100%) of 3-chloro-*N-[(2S)-2-(4-fluorophenyl)-4-hydroxybutyl]-N-methyl-5-(trifluoromethyl)benzamide* as a viscous oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 1.6-2.0 (cm, 2H), 2.7 (s, 3H), 3.0-3.8 (cm, 5H), 6.8-7.3 (cm, 6H), 7.6 (s, 1H); LCMS: m/z 404 (M+1)<sup>+</sup>.

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

3-Chloro-*N-[(2S)-2-(4-fluorophenyl)-4-hydroxybutyl]-N-methyl-5-(trifluoromethyl)benzamide* (8.5 g, 21.0 mmol) was dissolved in DMSO (30 mL) together with triethylamine (8.5 g, 84.2 mmol). Sulfur trioxide pyridine complex (7.4 g, 46.3 mmol) dissolved in DMSO (30 mL) was added by drops over a period of 20 min. The mixture was stirred at RT for 3 h and then another portion of sulfur trioxide pyridine complex (3.5 g, 21.0 mmol) was added. The mixture was stirred at RT overnight and then concentrated on a rotavapor for 2 h in order to remove formed dimethylsulfide. The mixture was diluted with MTBE (50 mL) and then sulfuric acid (2.0 g, 21.0 mmol) dissolved in water (40 mL) was added by drops. The mixture was stirred vigorously for 25 min, the two phases were separated and then the organic solution was washed twice with water. The solution was dried and the solvent was removed by evaporation. The product was purified by chromatography on silica gel (ethyl acetate – heptane, 10% to 100% ethyl acetate). There was obtained 2.6 g (30%) of the title compound as an oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 2.6-3.9 (cm, 8H), 6.8-7.4 (cm, 6H), 7.6 (d, 1H), 9.6-9.8 (d, 1H); LCMS: m/z 400 (M-1)<sup>+</sup>.

**Method 2**1-Azetidin-3-yl-4-isobutyrylpiperazine hydrochloride*(a) 1-[1-(Diphenylmethyl)azetidin-3-yl]piperazine*

5 A mixture of 1-(diphenylmethyl)azetidin-3-yl methanesulfonate (see *J. Org. Chem.*; 56; 1991; 6729; 25 g, 78.6 mmol), piperazine (67.7 g, 0.79 mol) and dry acetonitrile was stirred at 60°C overnight under nitrogen. The mixture was cooled and partitioned between water and methylene chloride. The organic layer was washed with water and brine. The solution was dried over Na<sub>2</sub>SO<sub>4</sub> and then the solvent was removed by evaporation. The residue was purified by column chromatography on silica gel (methanol – methylene chloride 5:95). There was obtained 17.5 g (72%) of 1-[1-(diphenylmethyl)azetidin-3-yl]piperazine as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 2.1-2.4 (m, 4H), 2.8-2.9 (m, 2H), 3.0 (m, 4H), 3.4-3.5 (m, 2H), 3.7-3.9 (m, 1H), 4.4 (s, 1H), 7.2-7.4 (m, 10H); LCMS: m/z 308 (M+1)<sup>+</sup>.

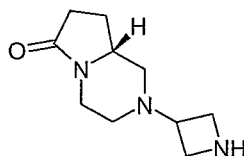
*(b) 1-[1-(Diphenylmethyl)azetidin-3-yl]-4-isobutyrylpiperazine*

To a mixture of 1-[1-(diphenylmethyl)azetidin-3-yl]piperazine (15.0 g, 48.8 mmol), triethylamine (13.5 mL, 97.6 mmol) and methylene chloride (150 mL) was added 2-methylpropanoyl chloride (6.2 g, 58.5 mmol) dissolved in methylene chloride (50 mL).

20 The addition was performed while stirring and was completed within 15 min. The mixture was stirred at RT for 15 min and then the solution was washed with aqueous NaHCO<sub>3</sub>. The organic phase was separated, dried over Na<sub>2</sub>SO<sub>4</sub> and then the solvent was removed by evaporation. There was obtained 18.0 g (97%) of 1-[1-(diphenylmethyl)azetidin-3-yl]-4-isobutyrylpiperazine as a yellow semi-solid material. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 1.1 (d, 6H), 2.2-2.3 (m, 4H), 2.7-2.8 (qn, 1H), 2.9 (t, 2H), 3.0 (qn, 1H), 3.4 (t, 2H), 3.5 (b, 2H), 3.6 (b, 2H), 4.4 (s, 1H), 7.2 (t, 2H), 7.3 (t, 4H), 7.4 (d, 4H); LCMS: m/z 377 (M+1)<sup>+</sup>.

(c) *1-Azetidin-3-yl-4-isobutyrylpiperazine hydrochloride*

1-[1-(Diphenylmethyl)azetidin-3-yl]-4-isobutyrylpiperazine (17.9 g, 47.4 mmol) was dissolved in methylene chloride (100 mL) and to the resultant solution, which was cooled to 0°C, was added 1-chloroethyl chloroformate (10.2 mL, 94.8 mmol) by drops. The addition was performed while stirring and was completed within 10 min. The mixture was stirred at RT for 1.5 h. Methanol (35 mL) was added and the mixture was heated to reflux for 30 min. The solvent was removed by evaporation and the residue was left in a freezer for three days. 2-Propanol (150 mL) was added and the mixture was heated to reflux while stirring, cooled to RT and then filtered. The filter cake was washed twice with 2-propanol and then dried under reduced pressure. There was obtained 12.2 g (100%) of the title compound as an off white powder. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): 1.1 (d, 6H), 2.9-3.0 (m, 1H), 3.2-3.4 (b, 4H), 3.8-4.1 (b, 4H), 4.3-4.4 (m, 3H), 4.7-4.8 (m, 2H).

**Method 3**(8aR)-2-Azetidin-3-ylhexahydropyrrolo[1,2-a]pyrazin-6(2H)-one(a) *(8aR)-2-[1-(Diphenylmethyl)azetidin-3-yl]hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one*

(8aR)-Hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one (see WO 03/066635; 0.17 g, 1.2 mmol), 1-(diphenylmethyl)azetidin-3-yl methanesulfonate (see *J. Org. Chem.*; 56; 1991; 6729; 0.40 g, 1.3 mmol) and triethylamine (0.20 mL, 1.4 mmol) were dissolved in acetonitrile. The mixture was heated for 15 min at 150°C using microwave single node heating and then the solvent was removed by evaporation. The residue was partitioned between ethyl acetate and aqueous NaHCO<sub>3</sub> and the aqueous phase extracted further with ethyl acetate. The organic phase was dried and then the solvent was removed by evaporation. The product was purified by chromatography on silica gel (methanol – methylene chloride 5:95). There was obtained 0.23 g (54%) of (8aR)-2-[1-(diphenylmethyl)azetidin-3-yl]hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one as a pale yellow oil. <sup>1</sup>H NMR (500 MHz,

CDCl<sub>3</sub>): 1.5-1.6 (m, 2H), 1.7-1.8 (m, 1H), 2.1-2.2 (m, 1H), 2.3-2.4 (m, 2H), 2.6-2.7 (d, 1H), 2.8 (m, 1H), 2.8-2.9 (m, 3H), 3.0 (qn, 1H), 3.4 (t, 2H), 3.6 (m, 1H), 4.0 (d, 1H), 4.4 (s, 1H), 7.2 (m, 2H), 7.2-7.3 (m, 4H), 7.4 (m, 4H); LCMS: m/z 362 (M+1)<sup>+</sup>.

(b) (8aR)-2-Azetidin-3-ylhexahydropyrrolo[1,2-a]pyrazin-6(2H)-one

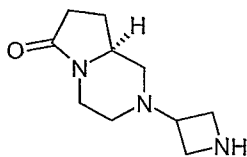
(8aR)-2-[1-(diphenylmethyl)azetidin-3-yl]hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one

(0.23 g, 0.64 mmol) was dissolved in acetic acid (20 mL) and to the resultant solution was added palladium hydroxide on carbon (0.33 g). The mixture was stirred under hydrogen (5 bar) at RT for 48 h 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. The solvent was removed by evaporation and there was obtained 0.10 g (84%) of the title compound. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 1.5-1.6 (m, 2H), 1.8 (m, 1H), 2.1-2.2 (m, 1H), 2.3-2.4 (m, 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)<sup>+</sup>.

#### Method 4

(8aS)-2-Azetidin-3-ylhexahydropyrrolo[1,2-a]pyrazin-6(2H)-one



(a) (8aS)-2-[1-(Diphenylmethyl)azetidin-3-yl]hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one

The title compound was prepared by utilizing the N-alkylation reaction protocol described in Method 1a but using (8aS)-hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one (see WO

03/066635) as the amine (yield, 56%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 1.5-1.6 (qn, 2H), 1.7-1.8 (m, 2H), 2.1-2.2 (m, 1H), 2.3-2.4 (m, 2H), 2.6-2.7 (d, 1H), 2.8 (d, 1H), 2.8-2.9 (m, 2H), 3.0 (qn, 1H), 3.4 (t, 2H), 3.6 (m, 1H), 4.0 (d, 1H), 4.4 (s, 1H), 7.1-7.2 (t, 2H), 7.2-7.3 (t, 4H), 7.4 (t, 4H); LCMS: m/z 362 (M+1)<sup>+</sup>.

(b) (8a*S*)-2-Azetidin-3-ylhexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one

The title compound was prepared by utilizing the hydrogenation reaction protocol described in Method 1b but using (8a*S*)-2-[1-(diphenylmethyl)azetidin-3-

5 yl]hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one as the substrate (yield, 73%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 1.5-1.6 (m, 2H), 1.8 (m, 1H), 2.1-2.2 (m, 1H), 2.3-2.4 (m, 2H), 2.6-2.8 (d, 1H), 2.8-3.0 (m, 2H), 3.2-3.4 (m, 2H), 3.5-3.7 (m, 4H), 4.0 (dd, 1H); LCMS: m/z 196 (M+1)<sup>+</sup>.

Pharmacology

*Transfection and culturing of cells used in FLIPR and Binding assays*

Chinese Hamster Ovary (CHO) K1 cells (obtained from ATCC) were stably transfected with the human NK<sub>2</sub> receptor (hNK<sub>2</sub>R cDNA in pRc/CMV, Invitrogen) or the human NK<sub>3</sub> receptor (hNK<sub>3</sub>R in pcDNA 3.1/Hygro (+)/IRES/CD8, Invitrogen vector modified at  
15 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 hNK<sub>2</sub>R transfected cells and with Hygromycin (Invitrogen) at 500µg/ml for the hNK<sub>3</sub>R transfected cells. Single cell clones  
20 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 NK<sub>1</sub> receptors originates from AstraZeneca R&D, Wilmington USA. Human NK<sub>1</sub> receptor cDNA (obtained from RNA-PCR from lung tissue) was subcloned into pRcCMV (Invitrogen). Transfection was performed by Calcium Phosphate and selection with 1mg/ml G418.

25 The CHO cells stably transfected with hNK<sub>1</sub>R, hNK<sub>2</sub>R and hNK<sub>3</sub>R were cultured in a humidified incubator under 5% CO<sub>2</sub>, in Nut Mix F12 (HAM) with Glutamax I, 10% Foetal Bovine Serum (FBS), 1% Penicillin/Streptomycin (PEST) supplemented with 200µg/ml Geneticin for the hNK<sub>1</sub>R and hNK<sub>2</sub>R expressing cells and 500µg/ml Hygromycin for the

hNK<sub>3</sub>R expressing cells. The cells were grown in T175 flasks and routinely passaged when 70-80% confluent for up to 20-25 passages.

*Assessing the Activity of Selected test Compounds to Inhibit Human NK<sub>1</sub>/NK<sub>2</sub>/NK<sub>3</sub>*

5 *Receptor Activation (FLIPR assay)*

The activity of a compound of the invention to inhibit NK<sub>1</sub>/NK<sub>2</sub>/NK<sub>3</sub> receptor activation measured as NK<sub>1</sub>/NK<sub>2</sub>/NK<sub>3</sub> receptor mediated increase in intracellular Ca<sup>2+</sup> was assessed by the following procedure:

10 CHO cells stably transfected with human NK<sub>1</sub>, NK<sub>2</sub> or NK<sub>3</sub> receptors were plated in black walled/clear bottomed 96-well plates (Costar 3904) at 3.5x10<sup>4</sup> cells per well and grown for approximately 24h in normal growth media in a 37°C CO<sub>2</sub>-incubator.

Before the FLIPR assay the cells of each 96-well plate were loaded with the Ca<sup>2+</sup> 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 CO<sub>2</sub>-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 (NK<sub>1</sub> specific), NKA (NK<sub>2</sub> specific), or Pro-7-NKB (NK<sub>3</sub> specific) agonist solution (final concentration equivalent to an approximate EC<sub>60</sub> 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 IC<sub>50</sub>s were calculated from ten-point concentration-response curves for each compound. The IC<sub>50</sub>s were then converted to pK<sub>B</sub> values with the following formula:

30 
$$K_B = IC_{50} / 1 + (EC_{60} \text{ conc. of agonist used in assay} / EC_{50} \text{ agonist})$$

$$pK_B = -\log K_B$$

***Determining the Dissociation Constant ( $K_i$ ) of compounds for Human  $NK_1/NK_2/NK_3$  Receptors (Binding Assay)***

5 Membranes were prepared from CHO cells stably transfected with human  $NK_1$ ,  $NK_2$  or  $NK_3$  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  $1 \times 10^8$  cells/ml in Tris-HCl 50 mM, KCl 300 mM, EDTA- $N_2$  10 mM pH 7.4 (4°C). Cell suspensions were  
10 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. 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  
15 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.

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  
20 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  $MnCl_2$ ). Competition binding curves were done by adding increasing amounts of the 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-  
25 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( $O_2$ )-Substance P] (4nM final conc) was used in binding experiments on hNK<sub>1r</sub>. [ $^3H$ -SR48968] (3nM final conc.) for hNK<sub>2r</sub> and [ $^3H$ -SR142801] (3nM final conc) for binding experiments on hNK<sub>3r</sub>. 50µl radioligand, 3µl test compound diluted in DMSO and 47µl incubation

buffer were mixed with 5-10 $\mu$ g cell membranes in 100 $\mu$ l 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 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 MnCl<sub>2</sub>) 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  $\beta$ -Liquid Scintillation Counter (1450 Microbeta, 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.

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

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

### Results

In general, the compounds of the invention, which were tested, demonstrated statistically significant antagonistic activity at the NK<sub>1</sub> receptor within the range of 8-9 for the pK<sub>B</sub>.

For the NK<sub>2</sub> receptor the range for the pK<sub>B</sub> was 7-9. In general, the antagonistic activity at the NK<sub>3</sub> receptor was 7-9 for the pK<sub>B</sub>.

In general, the compounds of the invention, which were tested, demonstrated statistically significant CYP3A4 inhibition at a low level. The IC<sub>50</sub> values tested according to Bapiro et al; Drug Metab. Dispos. 29, 30-35 (2001) were generally greater than 15  $\mu$ M.

*Activity against hERG*

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 significant hERG activity at a low level. The IC<sub>50</sub> values tested as described above were generally greater than 6 µM.

*Metabolic stability*

The metabolic stability of compounds according to formula I can be determined as 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 µM) 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. The parent compound is analysed by HPLC-MS. From the calculated half-life,  $t_{1/2}$ , the intrinsic clearance, Clint, is estimated by taking microsomal protein concentration and liver weight into account.

In general, the compounds of the invention had in vitro metabolic stability at a high level. Intrinsic clearance values tested as above were generally lower than 40 µl/min/mg protein.

The following table illustrates the properties of the compounds of the present invention:

*3-Chloro-N-[(2S)-2-(4-fluorophenyl)-4-[3-(4-isobutyrylpiperazin-1-yl)azetidin-1-yl]butyl]-N-methyl-5-(trifluoromethyl)benzamide (Ex 2):*

5

| pKB<br>(NK1) | pKB<br>(NK2) | pKB<br>(NK3) | IC <sub>50</sub><br>(hERG) | IC <sub>50</sub><br>(CYP3A4) | CL <sub>int</sub><br>(HLM) |
|--------------|--------------|--------------|----------------------------|------------------------------|----------------------------|
| 8.0          | 7.5          | 7.2          | 6.6 $\mu$ M                | 18.3 $\mu$ M                 | 36 $\mu$ L/min/mg          |

#### Biological evaluation

##### ***Gerbil Foot Tap (NK1 specific test model)***

10 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  
15 euthanized immediately after the experiment by heart punctation or a lethal overdose of pentobarbital 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  
20 with agonist.

The gerbils are lightly anaesthetized using isoflurane 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  $\mu$ L using a Hamilton syringe with a needle 4 mm long. The wound is  
25 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)*

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  
5 Journal of Pharmacology and Experimental Therapeutics (2001), pp. 559-564.

*Colorectal distension model*

Colorectal distension (CRD) in gerbils is performed as previously described in rats and mice (Tammperä A, Brusberg M, Axenborg J, Hirsch I, Larsson H, Lindström E.

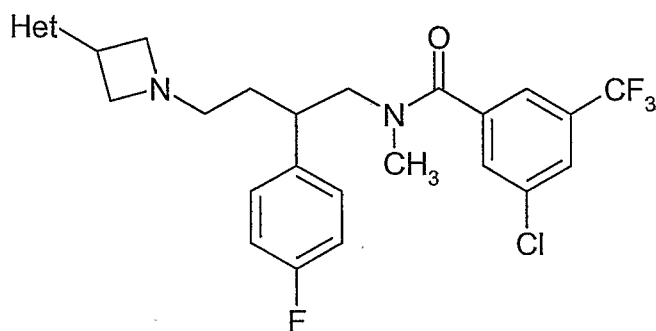
10 Evaluation of pseudo-affective responses to noxious colorectal distension in rats by manometric recordings. Pain 2005; 116: 220-226; Arvidsson S, Larsson M, Larsson H, Lindström E, Martinez V. Assessment of visceral pain-related pseudo-affective responses to colorectal distension in mice by intracolonic manometric recordings. J Pain 2006; 7: 108-118) with slight modifications. Briefly, gerbils are habituated to Bollmann cages 30-  
15 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 catheter is inserted in the distal colon, 2 cm from the base of the balloon to the anus, during light isoflurane anaesthesia (Forene<sup>®</sup>, Abbott Scandinavia AB, Solna, Sweden). The catheter is fixed to the tail with tape. The balloons are connected to pressure transducers  
20 (P-602, CFM-k33, 100 mmHg, Bronkhorst HI-TEC, Veenendaal, The Netherlands). Gerbils are allowed to recover from sedation in the Bollmann cages for at least 15 min before the 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  
25 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 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  
30 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.

Claims

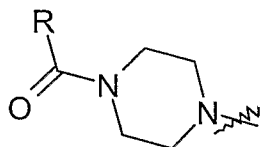
1. A compound of formula (I)



(I)

wherein

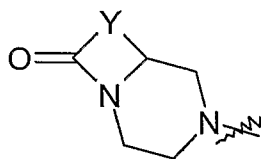
Het is



wherein

R is C<sub>1</sub>-C<sub>4</sub> alkyl; cyclopropyl; C<sub>1</sub>-C<sub>4</sub> methoxyalkyl; C<sub>1</sub>-C<sub>4</sub> ethoxyalkyl; C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl; tetrahydrofuran-2-yl; tetrahydrofuran-3-yl; tetrahydropyran-2-yl; tetrahydropyran-3-yl; or tetrahydropyran-4-yl;

or Het is

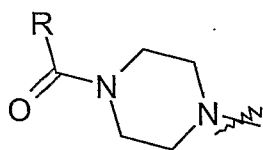


wherein

Y is C<sub>1</sub>-C<sub>3</sub> alkylene; -CH<sub>2</sub>-O-CH<sub>2</sub>-; or -CH<sub>2</sub>-CH<sub>2</sub>-O-;

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

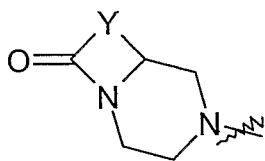
2. A compound according to claim 1 wherein Het is



wherein

R is C<sub>1</sub>-C<sub>4</sub> alkyl; cyclopropyl; C<sub>1</sub>-C<sub>4</sub> methoxyalkyl; C<sub>1</sub>-C<sub>4</sub> ethoxyalkyl; C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl; tetrahydrofuran-2-yl; tetrahydrofuran-3-yl; tetrahydropyran-2-yl; tetrahydropyran-3-yl; or tetrahydropyran-4-yl.

3. A compound according to claim 1 wherein Het is



wherein

Y is C<sub>1</sub>-C<sub>3</sub> alkyl; -CH<sub>2</sub>-O-CH<sub>2</sub>-; or -CH<sub>2</sub>-CH<sub>2</sub>-O-.

4. A compound according to claim 2, wherein R is C<sub>1</sub>-C<sub>3</sub> alkyl.

5. A compound according to claim 4, wherein R is C<sub>1</sub>-C<sub>2</sub> alkyl.

6. A compound according to claim 2, wherein R is C<sub>1</sub>-C<sub>2</sub> methoxyalkyl.

7. A compound according to claim 2, wherein R is C<sub>1</sub>-C<sub>2</sub> ethoxyalkyl.

8. A compound according to claim 3, wherein Y is C<sub>2</sub>-C<sub>3</sub> alkylene.

9. A compound according to claim 3, wherein Y is -CH<sub>2</sub>-O-CH<sub>2</sub>-.

10. A compound according to any one of claims 1-9 wherein the compound is the (*S*)-enantiomer.

5

11. A compound according to claim 1 selected from

3-Chloro-*N*-{(2*S*)-2-(4-fluorophenyl)-4-[3-(4-acetylpiperazin-1-yl)azetidin-1-yl]butyl}-*N*-methyl-5-(trifluoromethyl)benzamide;

10 3-Chloro-*N*-{(2*S*)-2-(4-fluorophenyl)-4-[3-(4-isobutyrylpiperazin-1-yl)azetidin-1-yl]butyl}-*N*-methyl-5-(trifluoromethyl)benzamide;

3-Chloro-*N*-((2*S*)-2-(4-fluorophenyl)-4-{3-[(8*aR*)-6-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]azetidin-1-yl}butyl)-*N*-methyl-5-(trifluoromethyl)benzamide and

3-Chloro-*N*-((2*S*)-2-(4-fluorophenyl)-4-{3-[(8*aS*)-6-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]azetidin-1-yl}butyl)-*N*-methyl-5-(trifluoromethyl)benzamide.

15

12. A compound according to any one of claims 1-11 for use in therapy.

13. Use of a compound according to any one of claims 1-11 for the manufacture of a medicament for the treatment of a functional gastrointestinal disorder.

20

14. Use of a compound according to any one of claims 1-11 for the manufacture of a medicament for the treatment of IBS.

15. Use of a compound according to any one of claims 1-11 for the manufacture of a medicament for the treatment of functional dyspepsia.

25

16. A pharmaceutical formulation comprising a compound according to any one of claims 1-11 as active ingredient and a pharmaceutically acceptable carrier or diluent.

17. A compound selected from

3-Chloro-*N*-[(2*S*)-2-(4-fluorophenyl)-4-hydroxybutyl]-*N*-methyl-5-  
5 (trifluoromethyl)benzamide;

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

1-Azetidin-3-yl-4-isobutyrylpiperazine hydrochloride;

1-[1-(Diphenylmethyl)azetidin-3-yl]piperazine;

1-[1-(Diphenylmethyl)azetidin-3-yl]-4-isobutyrylpiperazine; and

10 1-Azetidin-3-yl-4-isobutyrylpiperazine hydrochloride.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2007/000483

## 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, A61P

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 (INCL.PAJ), WPI DATA, CAPLUS

## 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),<br>23 December 2004 (23.12.2004), page 16,<br>line 21 - page 17, line 12, page 35, Exemple 19;<br>page 37, Exemple 21; page 51, Example 53; claims<br>1-2,4-10,14-19,21,25-32<br>--                                                | 1-16                  |
| A         | MACKENZIE A. ET AL, "4-Amino-2-(aryl)-butylbenz-<br>amides and Their Conformationally Constrained<br>Analogues. Potent Antagonists of the Human<br>Neurokinin-2 (NK2) Receptor", Bioorganic & Medicinal<br>Chemistry Letters 7 July 2003, Vol.13, pp. 2211-2215<br>-- | 1-16                  |
| P,X       | WO 2006137790 A1 (ASTRAZENECA AB),<br>28 December 2006 (28.12.2006)<br>--                                                                                                                                                                                             | 1-16                  |

☒ 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

"&amp;" document member of the same patent family

Date of the actual completion of the international search

26 Sept 2007

Date of mailing of the international search report

27-09-2007

Name and mailing address of the ISA/

Swedish Patent Office

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Telephone No. +46 8 782 25 00

## INTERNATIONAL SEARCH REPORT

International application No.

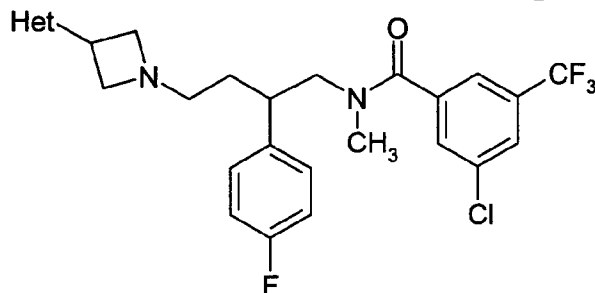
PCT/SE2007/000483

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|------------------------------------------------------------------------------------|-----------------------|
| P,X       | WO 2006137791 A1 (ASTRAZENECA AB),<br>28 December 2006 (28.12.2006)<br><br>--      | 1-16                  |
| P,X       | WO 2007037742 A1 (ASTRAZENECA AB), 5 April 2007<br>(05.04.2007)<br><br>--          | 1-16                  |
| P,X       | WO 2007037743 A1 (ASTRAZENECA AB), 5 April 2007<br>(05.04.2007)<br><br>--<br>----- | 1-16                  |

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

The present invention relates to new compounds of formula I



(I)

wherein Het has the meaning given in the description, as well as salts and enantiomers thereof. The invention also relates to pharmaceutical compositions comprising said compounds, and to the use of said compounds in therapy, e.g. in the treatment of gastrointestinal disorders. The invention further relates to processes for the preparation of the compounds. The compounds are neurokinin (NK) receptor antagonists.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE2007/000483

## 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:

- 1: Claims 1-16, directed to compounds of formula I and to the use of these compounds for the manufacture of a medicament for the treatment of gastrointestinal disorders.
- 2: Parts of claim 17, directed to certain intermediates lacking the azetidine part of the molecule.
- 3: Parts of claim 17, directed to certain intermediates lacking the benzamide part of the molecule.

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 - 16

### 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 patent classification (IPC)**

**C07D 205/04** (2006.01)  
**A61K 31/496** (2006.01)  
**A61K 31/498** (2006.01)  
**A61K 31/4985** (2006.01)  
**A61P 1/00** (2006.01)  
**C07D 487/04** (2006.01)  
**C07D 498/04** (2006.01)

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- In English/Searches and advisory services/Cited documents (service in English) or
- e-tjänster/anförda dokument (service in Swedish).

Use the application number as username.

The password is **RTYXEOAUSP**.

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**

Information on patent family members

International application No.

01/09/2007

PCT/SE2007/000483

|    |            |    |            |    |             |   |            |
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