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(54) Title: ADAMANTANE DERIVATIVES			
(57) Abstract			
The invention provides adamantane derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy. A compound for general formula (I) wherein x represents 1 or 2; A represents a group CH₂ or an oxygen atom; B represents a hydrogen or halogen atom; R represents a phenyl, pyridyl, indolyl, pyrimidinyl or thiophenyl group, each of which may be optionally substituted by one or more substituents.			
		 *G00001*	

ADAMANTANE DERIVATIVES

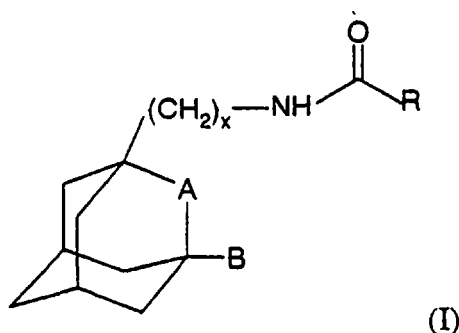
The present invention relates to adamantane derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

Adamantane derivatives are known in the art, e.g. from WO 95/04720 for use as gastrin and cholecystokinin receptor ligands, from Chem. Abs. (1977), Volume 86, No. 13 (86: 89560d) for use as analgesics, and from US-A-3 464 998 as antibiotics.

The P2X₇ receptor (previously known as P2Z receptor), which is a ligand-gated ion channel, is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the P2X₇ receptor by extracellular nucleotides, in particular adenosine triphosphate, leads to the release of interleukin-1 β (IL-1 β) and giant cell formation (macrophages/microglial cells), degranulation (mast cells) and L-selectin shedding (lymphocytes). P2X₇ receptors are also located on antigen-presenting cells (APC), keratinocytes, salivary acinar cells (parotid cells) and hepatocytes.

It would be desirable to make compounds effective as P2X₇ receptor antagonists for use in the treatment of inflammatory, immune or cardiovascular diseases, in the aetiologies of which the P2X₇ receptor may play a role.

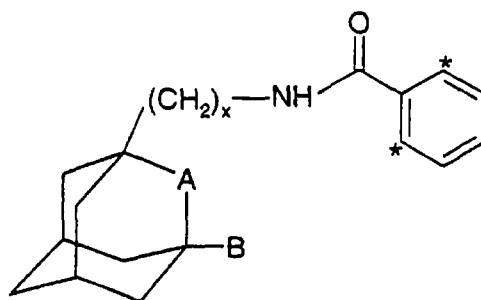
In accordance with the present invention, there is therefore provided a compound of general formula



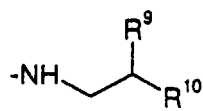
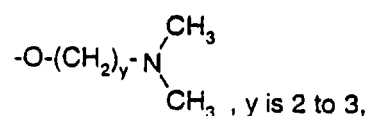
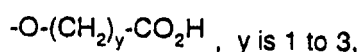
wherein x represents 1 or 2; A represents a group CH₂ or an oxygen atom;
B represents a hydrogen or halogen atom (e.g. fluorine, bromine, iodine or especially chlorine);

substituted phenyl, indolyl or indazolyl group, the substituent or substituents present do not comprise an amido, carboxyl, (di) C₁-C₆-alkylamido or C₁-C₆-alkoxycarbonyl group in an ortho position; or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, unless otherwise indicated, an alkyl substituent or alkyl moiety in a substituent group may be linear or branched. Furthermore, the (cyclo)alkyl moieties in a dialkylamino, dicycloalkylamino, dialkylamido or dicycloalkylamido substituent group may be the same or different. A 3- to 8-membered heterocyclyl group should be understood to mean an aliphatic heterocyclic ring system containing a single heteroatom selected from nitrogen, oxygen or sulphur. The term "in an ortho position" defines the ring position on the phenyl, indolyl or indazolyl ring of R which is adjacent to the point of attachment of the amide linking group to R, e.g., as illustrated in the formula below where the asterisks define the "ortho position":



Preferably, R represents a phenyl, pyridyl, indolyl, indazolyl, pyrimidinyl or thiophenyl group, each of which may be optionally substituted by one, two, three or four substituents independently selected from a halogen atom (e.g. fluorine, chlorine, bromine or iodine) or an amino, cyano, carboxyl, hydroxyl, nitro, C₁-C₆-alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl or hexyl), halo-C₁-C₆-alkyl (e.g. trifluoromethyl), $-N(R^1)-C(=O)-R^2$, $-C(O)NR^3R^4$, $-NR^5R^6$, C₃-C₈-cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), 3- to 8-membered heterocyclyl (e.g. aziridinyl, pyrrolidinyl, piperidinyl), C₃-C₈-cycloalkyloxy (e.g. cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or cyclohexyloxy), C₁-C₆-alkylcarbonyl (e.g. methyl-, ethyl-, propyl-, butyl-, pentyl- or hexylcarbonyl), C₁-C₆-alkoxycarbonyl (e.g. methoxy-, ethoxy-, propoxy-, butoxy-,



It is preferred that R^1 represents a hydrogen atom or a C_1 - C_4 -alkyl (e.g. methyl, ethyl, propyl or butyl) or C_3 - C_6 -cycloalkyl (e.g. cyclopentyl or cyclohexyl) group.

5 Preferably R^2 represents a C_1 - C_4 -alkyl (e.g. methyl, ethyl, propyl or butyl) or C_3 - C_6 -cycloalkyl (e.g. cyclopentyl or cyclohexyl) group.

Preferably, R^3 and R^4 each independently represent a hydrogen atom or a C_1 - C_4 -alkyl (e.g. methyl, ethyl, propyl or butyl) or C_3 - C_6 -cycloalkyl (e.g. cyclopentyl or cyclohexyl) group.

10 It is preferred that R^5 represents a hydrogen atom or a C_1 - C_4 -alkyl (e.g. methyl, ethyl, propyl or butyl, especially methyl) or C_3 - C_6 -cycloalkyl (e.g. cyclopentyl or cyclohexyl) group and that R^6 represents a C_3 - C_6 -cycloalkyl (e.g. cyclopentyl or cyclohexyl) group and, additionally, a C_1 - C_4 -alkyl (e.g. methyl, ethyl, propyl or butyl, especially methyl) group when R^5 is not a hydrogen atom.

15 It is preferred that R^7 represents a hydrogen atom or a C_1 - C_4 -alkyl (e.g. methyl, ethyl, propyl or butyl) or C_3 - C_6 -cycloalkyl (e.g. cyclopentyl or cyclohexyl) group and is especially a methyl group.

Preferably R^8 represents a C_1 - C_4 -alkyl (e.g. methyl, ethyl, propyl or butyl) or C_3 - C_6 -cycloalkyl (e.g. cyclopentyl or cyclohexyl) group and is especially a methyl group.

20 Preferred compounds of the invention include:

2,4-Dichloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide,

3,5-Dichloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide,

2-Chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide,

2,6-Dichloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide,

25 2-Methoxy-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide,

2-Methyl-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide,

- 2-(2-(Pyrrolidin-1-yl)ethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide, dihydrochloride,
- 2-(Methylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide, dihydrochloride,
- 5 2-(Dimethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide, hydrochloride,
- 2-(Pyrrolidin-1-yl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide, dihydrochloride,
- 2-(2,5-Dimethoxyphenylthio)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine
10 carboxamide,
- 2-Chloro-5-methylthio-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
- 2-(2-(*N,N*-Dimethylamino)ethylthio)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
- 2-(4-Methoxyphenylthio)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide,
- 2-Chloro-3-fluoro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
- 15 2-Bromo-5-fluoro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
- 2-Chloro-5-fluoro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
- 2-(2,5-Dihydroxyphenylthio)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide,
- 3-[[*N*-(Tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]carbonyl]pyridyl-2-thioacetic acid,
- 20 (2-Chloro-6-methyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide,
- 3-[[*N*-(Tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]carbonyl]pyridyl-2-(4-phenylthio)oxyacetic acid,
- 2-(4-(3-*N,N*-dimethylamino)propyloxyphenylthio)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide, dihydrochloride,
- 25 (2-Methylthio-6-methyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide,
- 2-[[*N*-(Tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]carbonyl]phenyl-1-oxybutyric acid,
- 2-Chloro-5-hydroxy-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
- 2-Chloro-3-nitro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
- 2-Chloro-5-nitro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
- 30 3-Amino-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

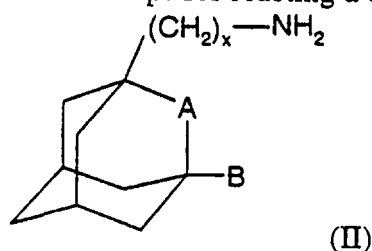
2-Chloro-3-(*N*-(2-[imidazolyl-4-yl]ethyl)-2-aminoethyl)amino-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2,5-Dimethyl-*N*-(3-chloro-tricyclo[3.3.1.1^{3,7}]dec-1ylmethyl)-benzamide,

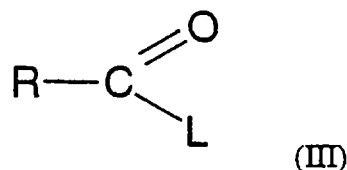
3,5-Dimethoxy-2-methyl-*N*-(3-chloro-tricyclo[3.3.1.1^{3,7}]dec-1ylmethyl)-benzamide, and

5 2-Chloro-5-iodo-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide.

The present invention further provides a process for the preparation of a compound of formula (I) as defined above which comprises reacting a compound of general formula



wherein x, A and B are as defined in formula (I), with a compound of general formula



10 wherein R is as defined in formula (I) and L is a leaving group such as a halogen atom (e.g. chlorine), an imidazole group or an urea; and optionally forming a pharmaceutically acceptable salt or solvate thereof.

The process may conveniently be carried out in a solvent (e.g. dichloromethane, tetrahydrofuran, dioxan or dimethylformamide) and optionally in the presence of a base
15 (e.g. triethylamine or diisopropylethylamine). The process is conveniently operated at a temperature in the range from 0 to 100 °C, preferably in the range from 10 to 80 °C, and especially at ambient temperature (20 °C).

The compounds of formula (II) and (III) are known compounds or may be prepared
20 by processes analogous to those known in the art.

It will be appreciated by those skilled in the art that in the process of the present invention certain functional groups such as hydroxyl or amino groups in the intermediate compounds may need to be protected by protecting groups. Thus, the final stage in the preparation of the compounds of formula (I) may involve the removal of one or more
25 protecting groups.

formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined to a patient.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and
5 the disorder indicated.

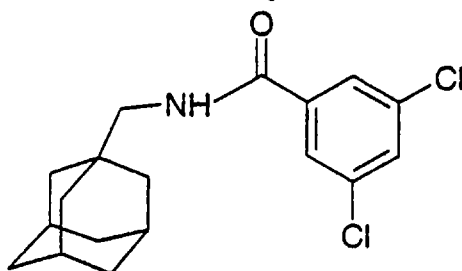
The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

10 Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

15 Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical
20 composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical composition of the invention may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions,
25 heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

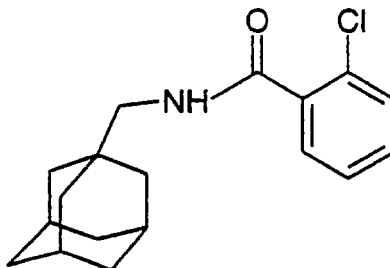
Example 2**3,5-Dichloro-N-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide**

Prepared according to the method of Example 1 from 1-adamantanemethylamine
5 (0.1 ml) and 3,5-dichlorobenzoyl chloride (0.118 g) to give the title compound as a white
solid (0.18 g).

Melting point: 197-198 °C

MS (APCI +ve) 338/340/342 (M+H)⁺

10 ¹H NMR (DMSO-d₆) δ 8.51 (1H, t), 7.87 (2H, d), 7.81 (1H, dd), 2.98 (2H, d), 1.93 (3H, s),
1.65 (3H, d), 1.60 (3H, d), 1.49 (6H, d)

Example 3**2-Chloro-N-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide**

15

Prepared according to the method of Example 1 from 1-adamantanemethylamine
(0.1 ml) and 2-chlorobenzoyl chloride (0.099 g) to give the title compound as a white solid
(0.16 g).

20 Melting point: 148-152 °C

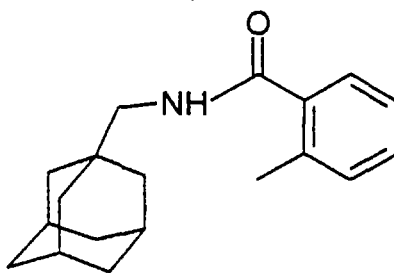
MS (APCI +ve) 304/306 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.33 (1H, t), 7.48 (1H, d), 7.45 -7.37 (3H, m), 2.93 (2H, d),

¹H NMR (DMSO-d₆) δ 8.01 (1H, t), 7.70 (1H, dd), 7.46 (1H, dt), 7.14 (1H, dd), 7.03 (1H, dt), 3.90 (3H, s), 3.00 (2H, d), 1.95 (3H, s), 1.67 (3H, d), 1.61 (3H, d), 1.51 (6H, d)

5 Example 6

2-Methyl-N-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide



Prepared according to the method of Example 1 from 1-adamantanemethylamine (0.1 ml) and 2-methylbenzoyl chloride (0.078 g) to give the title compound as a white solid
10 (0.13 g).

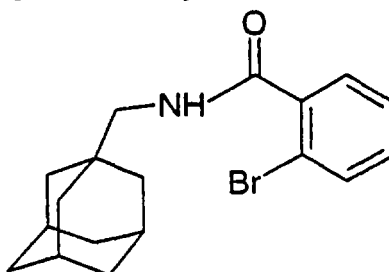
Melting point: 150-152 °C

MS (APCI +ve) 284 (M+H)⁺

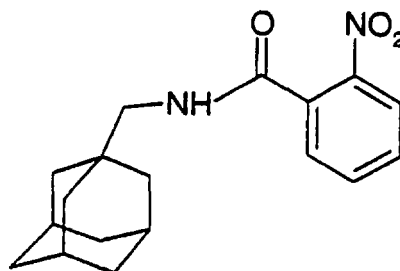
¹H NMR (DMSO-d₆) δ 8.12 (1H, t), 7.31 (2H, m), 7.23 (2H, m), 2.94 (2H, d),
15 2.33 (3H, s), 1.94 (3H, s), 1.66 (3H, d), 1.61 (3H, d), 1.50 (6H, d)

Example 7

2-Bromo-N-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide



Prepared according to the method of Example 1 from 1-adamantanemethylamine (0.1 ml) and 2-bromobenzoyl chloride (0.111 g) to give the title compound as a white solid
20 (0.17 g).

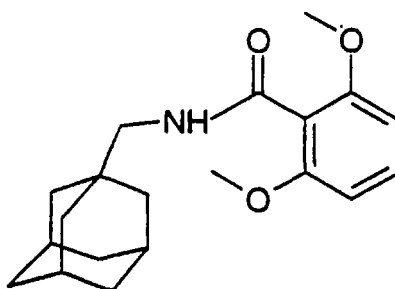
Example 9**2-Nitro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide**

Prepared according to the method of Example 1 from 1-adamantanemethylamine
 5 (0.1 ml) and 2-nitrobenzoyl chloride (0.094 g) to give the title compound as a pale yellow solid (0.13 g).

Melting point: >250 °C

MS (APCI +ve) 315 (M+H)⁺

10 ¹H NMR (DMSO-d₆) δ 8.54 (1H, t), 8.02 (1H, dd), 7.78 (1H, dt), 7.67 (1H, dt),
 7.59 (1H, dd), 2.93 (2H, d), 1.94 (3H, s), 1.67 (3H, d), 1.62 (3H, d), 1.52 (6H, d)

Example 10**2,6-Dimethoxy-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide**

15 Prepared according to the method of Example 1 from 1-adamantanemethylamine
 (0.1 ml) and 2,6-dimethoxybenzoyl chloride (0.102 g) to give the title compound as a white solid (0.13 g).

20 Melting point: 185-186 °C

MS (APCI +ve) 330 (M+H)⁺

Melting point: 162-163 °C

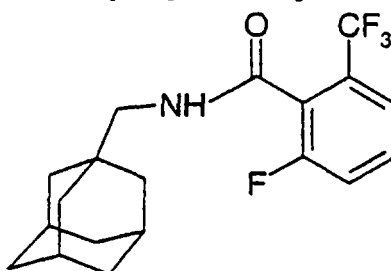
MS (APCI +ve) 306 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.58 (1H, t), 7.50 (1H, m), 7.14 (2H, m), 2.95 (2H, d), 1.94 (3H, s), 1.67 (3H, d), 1.59 (3H, d), 1.50 (6H, d)

5

Example 13

2-(Trifluoromethyl)-6-flouro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide



Prepared according to the method of Example 1 from 1-adamantanemethylamine
(0.1 ml) and 2-(trifluoromethyl)-6-fluorobenzoyl chloride (0.115 g) to give the title
10 compound as a white solid (0.18 g).

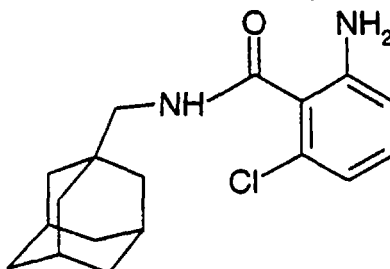
Melting point: 151-153 °C

MS (APCI +ve) 356 (M+H)⁺

15 ¹H NMR (DMSO-d₆) δ 8.57 (1H, t), 7.68-7.59 (3H, m), 2.95 (2H, d), 1.94 (3H, s), 1.66 (3H, d), 1.59 (3H, d), 1.50 (6H, d)

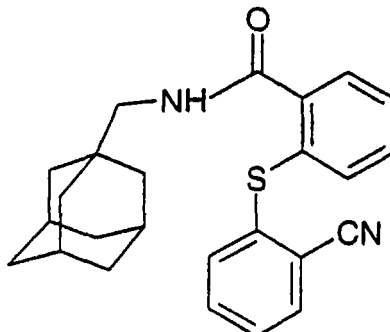
Example 14

2-Amino-6-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide



20

To a solution of 2-amino-6-chlorobenzoic acid (0.087 g) in *N,N*-dimethylformamide (1.5 ml) was added carbonyldiimidazole (0.082 g). The resulting reaction mixture was

Example 16**2-(2-Cyanophenylthio)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide**

Prepared according to the method of Example 14 from 1-adamantanemethylamine
5 (0.1 ml) and 2-(2-cyanophenylthio)benzoic acid (0.144 g) to give the title compound as a
white foam (0.19 g).

Melting point: 62-65 °C

MS (APCI +ve) 403 (M+H)⁺

10 ¹H NMR (DMSO-d₆) δ 8.34 (1H, t), 7.89 (1H, d), 7.81 (1H, d), 7.55 (1H, m), 7.44 (3H, m),
7.25 (1H, d), 7.18 (1H, m), 2.92 (2H, d), 1.88 (3H, s), 1.62 (3H, d), 1.54 (3H, d),
1.41 (6H, d)

Melting point: 171-172 °C

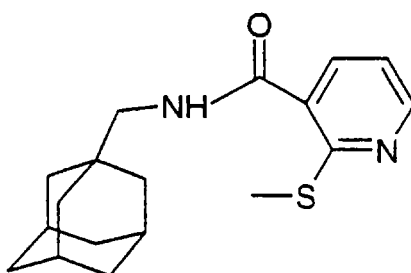
MS (APCI +ve) 316 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.16 (1H, t), 7.4-7.3 (3H, m), 7.18 (1H, dt), 2.91 (2H, d), 2.40 (3H, s), 1.94 (3H, s), 1.67 (3H, d), 1.60 (3H, d), 1.52 (6H, d)

5

Example 19

2-(Methylthio)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-3-pyridine carboxamide



10 Prepared according to the method of Example 14 from 1-adamantanemethylamine (0.1 ml) and 2-methylthiopyridine-3-carboxylic acid (0.095 g) to give the title compound as a white solid (0.17 g).

Melting point: 118-120 °C

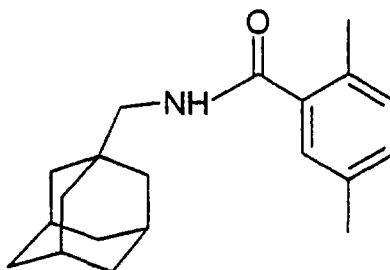
15 MS (APCI +ve) 317 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.51 (1H, dd), 8.34 (1H, t), 7.72 (1H, dd), 7.17 (1H, m), 2.93 (2H, d), 2.44 (3H, s), 1.94 (3H, s), 1.67 (3H, d), 1.61 (3H, d), 1.52 (6H, d)

2.93 (2H, d), 1.94 (3H, s), 1.67 (3H, d), 1.60 (3H, d), 1.52 (6H, d)

Example 22

2,5-Dimethyl-N-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide



To a solution of 2,5-dimethylbenzoic acid (0.12 g) in dichloromethane (2 ml) was added a mixed solution of 4-dimethylaminopyridine and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2 ml of 0.41M solution in dichloromethane). The reaction mixture was stirred for 0.5 hour and then a solution of 1-adamantanemethylamine (2 ml of a 0.45M solution in dichloromethane) was added. Stirring was continued at room temperature overnight. On the following day, the reaction mixture was washed with dilute hydrochloric acid, water and brine, dried over sodium sulphate (Na₂SO₄) and concentrated under reduced pressure to leave a yellow solid that was triturated under diethyl ether to give the title compound as a white solid (0.12 g).

Melting point: 153-154 °C

MS (APCI +ve) 298 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.07 (1H, t), 7.13 (3H, m), 2.92 (2H, d), 2.28 (6H, s), 1.82 (3H, s), 1.63 (6H, dd), 1.50 (6H, d)

mixture was stirred at room temperature for 1.5 hours and then diluted with methanol.

Potassium carbonate (0.50 g) was added and the resulting suspension was stirred at room temperature for 2 hours before being partitioned between diethyl ether and dilute hydrochloric acid. An organic phase was separated, washed with brine, and then dried over sodium sulphate (Na₂SO₄). Concentration of the organic phase under reduced pressure yielded a yellow solid that was triturated under isohexanes to give the sub-title compound as a white solid (0.27 g).

MS (APCI +ve) 286 (M+H)⁺

¹H NMR (DMSO-d₆) δ 12.52 (1H, s), 8.64 (1H, t), 7.89 (1H, dd), 7.39 (1H, dt), 6.91 (2H, m), 3.03 (2H, d), 1.94 (3H, s), 1.66 (3H, d), 1.60 (3H, d), 1.50 (6H, d)

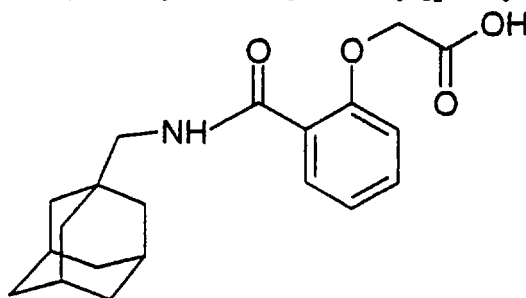
b) 2-(2-(*N,N*-Dimethylamino)ethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide, hydrochloride

To a solution of 2-hydroxy-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide prepared as described in step a) above (0.09 g) in acetonitrile (5 ml) was added caesium carbonate (0.257 g) and the reaction mixture was stirred for 10 minutes. 2-Dimethylaminoethyl chloride hydrochloride (0.055 g) was added and the resulting suspension was heated at reflux for 1.5 hours. The reaction mixture was then cooled to room temperature, diluted with diethyl ether and extracted with water. Drying over sodium sulphate (Na₂SO₄) followed by concentration under reduced pressure gave a residue which was subsequently purified by silica gel chromatography, eluting with 4% methanol in dichloromethane. Fractions containing product were concentrated under reduced pressure and the residue obtained was dissolved in diethyl ether. Hydrogen chloride (1 ml of a 1M solution in diethyl ether) was added dropwise and the resulting solid was triturated under diethyl ether and then dried *in vacuo* to leave the title compound as a white solid (0.098 g).

Melting point: 181-183 °C

MS (APCI +ve) 357 (M+H)⁺ for free base

¹H NMR (DMSO-d₆) δ 10.63 (1H, s), 8.18 (1H, t), 7.51 (1H, dd), 7.46 (1H, dt),

Example 26**2-[[[(Tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]carbonyl]phenyl-1-oxyacetic acid**

To a solution of the ester prepared as described in Example 25 above (0.085 g) in dichloromethane (0.75 ml) was added trifluoroacetic acid (1.5 ml). The reaction mixture was stirred at room temperature for three days and then concentrated under reduced pressure to leave a residue. The residue was thereafter co-evaporated with toluene and the beige solid obtained was triturated under diethyl ether to yield the title compound as a white solid (0.04 g).

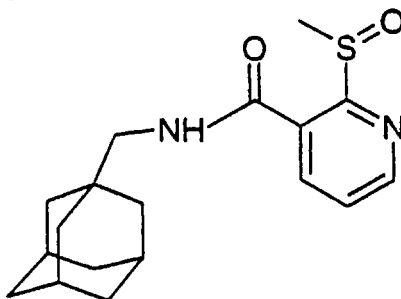
Melting point: 186-187 °C

MS (APCI +ve) 342 (M+H)⁺

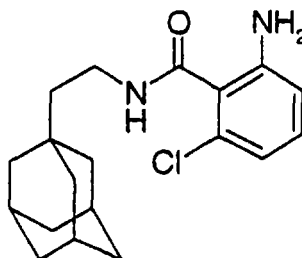
¹H NMR (DMSO-d₆) δ 8.52 (1H, t), 7.88 (1H, dd), 7.46 (1H, dd), 7.14 (1H d),

7.08 (1H, dt), 4.89 (2H, s), 3.05 (2H, d), 1.93 (3H, s), 1.65 (3H, d), 1.59 (3H, d),

1.51 (6H, d)

Example 27**2-(Methylsulphoxide)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-3-pyridine carboxamide**

To an ice-cooled solution of the amide prepared as described in Example 19 above (1.00 g) in 80% aqueous methanol (20 ml) was added potassium peroxymonosulphate

Example 29**2-Amino-6-chloro-N-(2-[tricyclo[3.3.1.1^{3,7}]dec-1-yl]ethyl)-benzamide**

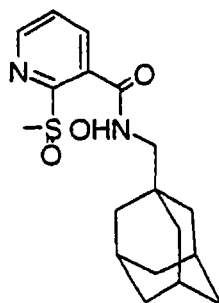
Prepared according to the method of Example 14 from 1-adamantaneethylamine
 5 hydrochloride (CN 26482-53-1) (0.105 g) and 2-amino-6-chlorobenzoic acid (0.132 g) and
 purified by supercritical fluid chromatography eluting with CO₂ in ethanol to give the title
 compound, contaminated with 0.35mol equivalents of imidazole, as a white solid (0.046 g).

Melting point: 132-134 °C

10 MS (APCI +ve) 333/335 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.26 (1H, t), 7.01 (1H, t), 6.72 (1H, dd), 6.67 (1H, dd),

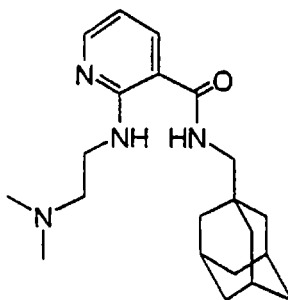
5.14 (2H, s), 3.23 (2H, m), 1.93 (3H, s), 1.70-1.59 (6H, m), 1.51 (6H, d), 1.31 (2H, m).

Example 30**2-(2-Methylsulphonyl)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide**

To an ice-cooled solution of the amide prepared as described in Example 19 (1.00 g) in
 80% aqueous methanol (20 ml) was added potassium peroxymonosulphate (6.00 g) portion
 wise. After stirring for 24 hours, the reaction mixture was poured onto saturated sodium
 20 metabisulphite solution and extracted with ethyl acetate. Combined organic extracts were
 washed with sodium metabisulphite solution and then brine, dried over magnesium

Example 32

2-(2-(*N,N*-Dimethylamino)ethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide, dihydrochloride



5 To a solution of the sulphone from Example 30 (0.1g) in acetonitrile (3ml) was added triethylamine (0.04ml) and *N,N*-dimethylethylenediamine (0.030g). The reaction mixture was stirred and heated at 80 °C in a sealed tube for 48 hours. The reaction mixture was cooled, diluted with ethyl acetate, washed with brine and dried over MgSO₄. A solution of hydrogen chloride in diethyl ether (1.0ml of 1.0M) was added and the solvents evaporated
10 under reduced pressure. The residue was recrystallised from acetonitrile to give the title compound as a white solid. (0.025g).

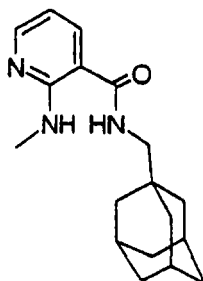
Melting point: 258-260 °C

MS (APCI +ve) 357 (M+H)⁺ for free base

15 ¹H NMR (DMSO-d₆) δ 10.1 (1H, bs), 8.60 (1H, bs), 8.20 (1H, bd), 8.15 (1H, dd), 6.84 (1H, t), 3.90 (2H, bm), 3.30 (2H, bm), 2.95 (2H, d), 1.94 (3H, s), 1.66 (3H, d), 1.62 (3H, d), 1.51 (6H, d)

Example 34

2-(Methylamino)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide, dihydrochloride



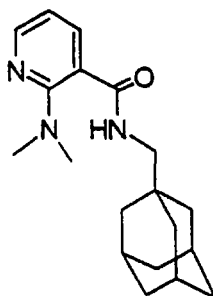
- 5 Prepared according to the method of Example 33 using the sulphone from Example 30 (0.1g) and methylamine (0.2ml of a 2.0M solution in tetrahydrofuran) to give the title compound as a white solid (0.010g).

Melting point: 160-162 °C

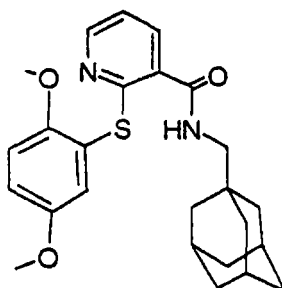
- 10 MS (APCI +ve) 300 (M+H)⁺ for free base
¹H NMR (DMSO-d₆) δ 8.80 (1H, t), 8.40 (1H, d), 8.10 (1H, dd), 6.90 (1H, t), 3.05 (3H, s), 2.98 (2H, d), 1.94 (3H, s), 1.66 (3H, d), 1.62 (3H, d), 1.51 (6H, d)

Example 35

- 15 **2-(Dimethylamino)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide, hydrochloride**



- Prepared according to the method of Example 33 using the sulphone from Example 30 (0.1g) and dimethylamine (0.2ml of a 2.0M solution in tetrahydrofuran) to give the title compound as a white solid (0.025g).
- 20

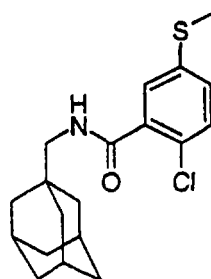
Example 37**2-(2,5-Dimethoxyphenylthio)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide**

Prepared according to the method of Example 14 from 1-adamantanemethylamine (0.77 g) and 2-(2,5-dimethoxyphenylthio)pyridine-3-carboxylic acid (1.36 g) to give the title compound as a white solid (1.20 g).

Melting point: 135-136 °C

MS (APCI +ve) 440 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.45 (1H, t), 8.30 (1H, dd), 7.80 (1H, dd), 7.20 (1H, dd), 6.95 (3H, m), 3.69 (3H, s), 3.62 (3H, s), 2.98 (2H, d), 1.98 (3H, s), 1.66 (3H, d), 1.62 (3H, d), 1.51 (6H, d)

Example 38**2-Chloro-5-methylthio-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide**

To a solution of 2-chloro-5-methylthiobenzoic acid (0.2 g) and 1-hydroxy benzotriazole (0.13 g) in dichloromethane (10 ml) was added 1-adamantanemethylamine (0.17 ml). The mixture was stirred 5 min and then 1,3-dicyclohexylcarbodiimide (0.2 g) was added. Stirring was continued overnight. The resulting precipitate was filtered and

extracted with dichloromethane. The organic extract was washed with water and dried over magnesium sulphate (MgSO_4). Concentration of the organic phase under reduced pressure yielded an oil (0.11 g).

To a solution of the oil in dimethylformamide (5 ml) was added 2-dimethylamino ethyl chloride hydrochloride (0.063 g) and caesium carbonate (0.3 g). The resulting suspension was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and washed with water. Organic extracts were dried over magnesium sulphate (MgSO_4) and concentrated under reduced pressure to give a gum which was purified by silica gel chromatography (eluting with ethyl acetate and 0.1 to 1% ammonium hydroxide) to yield a gum. Hydrogen chloride (2 ml of a 1M solution in diethyl ether) was added dropwise to a solution of the gum in dichloromethane. The solvents were removed under reduced pressure and the residue was triturated under ethyl acetate and ether to leave the title compound as a white solid (0.03 g).

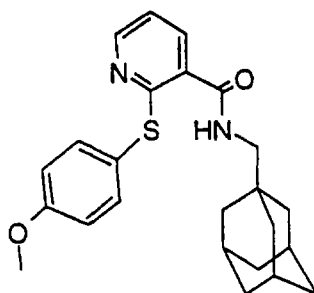
Melting point: 193 - 195°C

MS (APCI +ve) 373/374 ($\text{M}+\text{H}$)⁺ for free base

¹H NMR (CDCl_3) δ 7.62 (1H,d), 7.42 (3H,m), 6.13 (1H,bs), 3.39 (2H,m), 3.17 (4H,m), 2.78 (6H,s), 2.02 (3H,bs), 1.68 (12H,m).

Example 40

2-(4-Methoxyphenylthio)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide

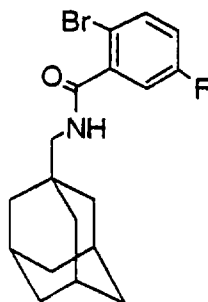


To a solution of the sulphone from Example 30 (1.0g) in acetonitrile (30 ml) was added triethylamine (0.40ml) and 4-methoxythiophenol (0.402g). The reaction mixture was

^1H NMR (DMSO- d_6) δ 8.42 (1H, t), 7.50 - 7.40 (2H, m), 7.29 - 7.24 (1H, m), 2.94 (2H, d), 1.94 (3H, s), 1.64 (6H, dd), 1.53 (6H, m)

Example 42

5 **2-Bromo-5-fluoro-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide**



Prepared according to the method of Example 41 from 1-adamantanemethylamine (0.1 ml) and 2-bromo-5-fluorobenzoic acid (0.123 g) to give the title compound as a white solid (0.140 g).

10

Melting point: 143-144 °C

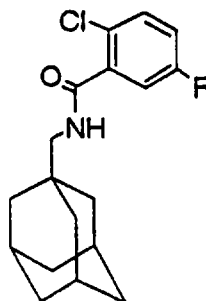
MS (APCI +ve) 322/324 (M+H)⁺

^1H NMR (DMSO- d_6) δ 8.40 (1H, t), 7.56 - 7.52 (1H, dd), 7.34 - 7.27 (2H, m), 2.93 (2H, d), 1.94 (3H, s), 1.63 (6H, dd), 1.52 (6H, m)

15

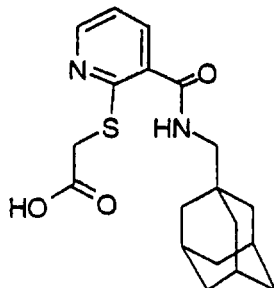
Example 43

2-Chloro-5-fluoro-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



Prepared according to the method of Example 41 from 1-adamantanemethylamine (0.1 ml) and 2-chloro-5-fluorobenzoic acid (0.098 g) to give the title compound as a white solid (0.165 g).

20

Example 45**3-[[[(Tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]carbonyl]pyridyl-2-thioacetic acid**

To a solution of the sulphone from Example 30 (0.1g) in acetonitrile (3ml) was added
 5 triethylamine (0.04ml) and methyl thioglycate (0.050g). The reaction mixture was stirred
 and heated at reflux for 24 hours before cooling to room temperature and the solvent
 evaporated under reduced pressure. The residue was dissolved in ethanol (2ml) and treated
 with 2M sodium hydroxide. The reaction mixture was stirred at ambient temperature for
 24 hours, acidified with 2M hydrochloric acid and extracted into ethyl acetate. The
 10 extracts were dried (MgSO₄) and evaporated under reduced pressure. The product was
 purified by silica gel chromatography eluting with 0-3% methanol in dichloromethane.
 Fractions containing product were combined and evaporated under reduced pressure to
 give the title compound as a white solid (0.008g).

15 Melting point: 147-150 °C

MS (APCI +ve) 361 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.53(1H, t), 8.45 (1H, dd), 7.89 (2 H, bs), 7.20 (1H, dd),
 3.80 (2H, s), 2.94 (2H, d), 1.94 (3H, s), 1.66 (3H, d), 1.62 (3H, d), 1.51 (6H, d)

MgSO₄ and the solvent was removed under reduced pressure to leave a white solid which was dissolved in dimethylformamide (10ml), treated with ethylbromoacetate (0.1ml) and potassium carbonate (0.050g). The mixture was stirred at ambient temperature for 24 hours, diluted with saturated sodium chloride solution and extracted with ethyl acetate.

5 The organic phase was further washed with saturated sodium chloride solution, dried over MgSO₄ and the solvent was removed under reduced pressure to leave a white solid. The residue was dissolved in dioxane (10ml), treated with 2M sodium hydroxide (5ml) solution and stirred at ambient temperature for 24 hours, acidified with 2M hydrochloric acid and filtered to give a white solid which was purified by silica gel chromatography eluting with
10 25% methanol in dichloromethane. Fractions containing product were combined and the solvent removed under reduced pressure to leave the title compound as a white solid (0.045g).

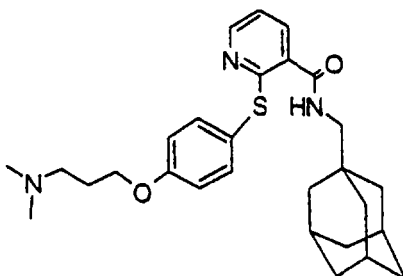
Melting point: 185-186 °C

15 MS (APCI +ve) 453 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.47(1H, t), 8.25 (1H, dd), 7.75 (1H, dd), 7.35 (2H, d), 7.18 (1H, m), 6.80 (2H, d), 4.15 (2H, s), 3.0 (2H, d), 2.0 (3H, s), 1.67 (3H, d), 1.61 (3H, d), 1.53 (6H, d)

20 Example 48

2-(4-(3-*N,N*-dimethylamino)propoxyphenylthio)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide, dihydrochloride



To a solution of the methoxy compound from Example 40 (0.56g) in dichloromethane
25 (10ml) at -78 °C, was added boron tribromide (1.5ml of a 1M solution in dichloromethane). The reaction mixture was stirred for 24 hours, warming to ambient

acetate, washed with saturated sodium chloride solution and dried over MgSO_4 . The solvent was evaporated under reduced pressure and the residue triturated with diethyl ether to give the title compound as a pale yellow solid (0.028g).

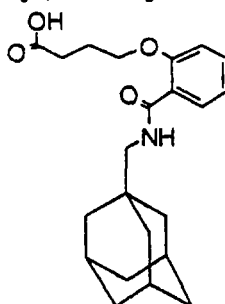
5 Melting point: 160-161 °C

MS (APCI +ve) 331 $(\text{M}+\text{H})^+$

^1H NMR ($\text{DMSO}-d_6$) δ 8.22 (1H, t), 7.64 (1H, d), 7.02 (1H, d), 2.91 (2H, d), 2.51 (3H, s), 2.40 (3H, s), 1.93 (3H, s), 1.65 (3H, d), 1.60 (3H, d), 1.53 (6H, d)

10 **Example 50**

2-[[[(Tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]carbonyl]phenyl-1-oxybutyric acid



a) 2-[[[(Tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]carbonyl]phenyl-1-oxybutyric acid, methyl ester

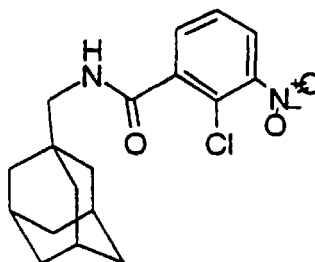
15 A suspension of 2-hydroxy-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, from Example 24 step a) (0.061 g), and caesium carbonate (0.069 g) in acetonitrile (3 ml) was heated at 40 °C until homogeneous. Methyl 4-bromobutyrate (0.032 ml) was added and the resulting mixture was heated at reflux temperature for 0.5 hours. The reaction mixture was cooled to room temperature, poured into water and extracted with ethyl acetate (x 3). The
20 combined organic extracts were washed with water and saturated aqueous sodium chloride solution and dried over sodium sulphate (Na_2SO_4) followed by concentration under reduced pressure to give the sub-title compound as a colourless oil.

MS (APCI +ve) 386 $(\text{M}+\text{H})^+$

^1H NMR (DMSO- d_6) δ 9.85(1H,s), 8.25 (1H, t), 7.24(1H, d), 6.76-6.82(2H, m), 2.90 (2H,d), 1.93(3H, s), 1.67 (3H, d), 1.57 (3H, d), 1.51 (6H, s)

Example 52

5 2-Chloro-3-nitro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



Prepared according to the method of Example 14 from 1-adamantanemethylamine (1.0 g) and 2-chloro-3-nitrobenzoic acid (1.22g) to give the title compound as a yellow solid (1.7 g).

10

Melting point: 185 °C

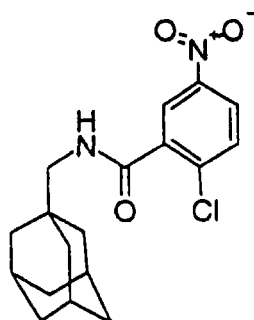
MS (APCI +ve) 348/350 ($M+H$)⁺

^1H NMR (CDCl₃) δ 7.83 (1H, d), 7.74 (1H, d), 7.48 (1H, t), 6.0(1H, bs), 3.18 (2H, d), 2.0 (3H, bs), 1.8 (12H, m)

15

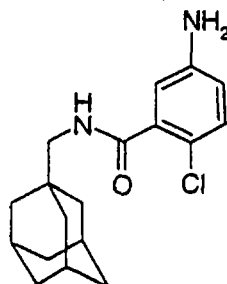
Example 53

2-Chloro-5-nitro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



Prepared according to the method of Example 14 from 1-adamantanemethylamine (1.0g) and 2-chloro-5-nitrobenzoic acid (1.22g) to give the title compound as a yellow solid (1.7 g).

20

Example 55**5-Amino-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide**

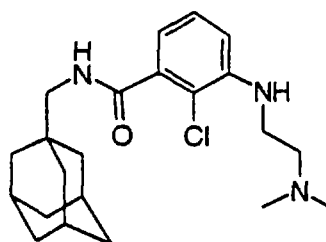
Prepared according to the method of Example 54 from the nitro compound from
5 Example 53 (0.50 g) to give the title compound as a white solid (0.4g).

Melting point: 214 °C

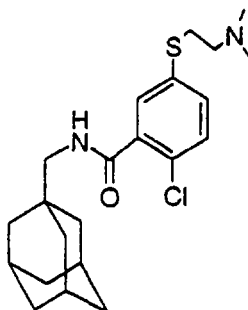
MS (APCI +ve) 319/21 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.14 (1H, t), 7.03 (1H, dd), 6.56 (2H, m), 5.36 (2H, s),

10 2.89 (2H, d), 1.95 (3H, s), 1.7 (12H, m)

Example 56**2-Chloro-3-(*N,N*-dimethylamino)ethylamino-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide**

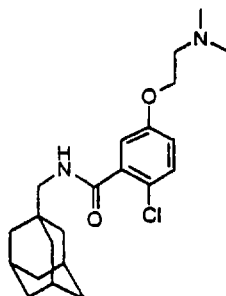
15 A mixture of the amino compound from Example 54 (0.10 g), potassium carbonate (0.087g) and *N*-(2-chloroethyl)dimethylamine hydrochloride was stirred and heated at 138 °C for 72hr. The residue was dissolved in water and the product extracted into ethyl acetate. The organic extract was washed with brine, dried over sodium sulphate (Na₂SO₄)
20 and concentrated to give an oil which was purified by Supercritical Fluid Chromatography eluting with CO₂/methanol/0.1% diethylamine to give an oil. Addition of excess ethereal

Example 58**2-Chloro-5-(*N,N*-dimethylamino)ethylthio-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, fumarate****a) 2-Chloro-5-methylsulphinyl-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide**

A solution of amide from Example 38 (0.2 g) in chloroform (5 ml) was treated with 70% *m* chloroperbenzoic acid (0.14 g). The reaction mixture was stirred for two days, calcium hydroxide (0.09 g) added and after stirring for a further 0.5 h the mixture was filtered. The filtrate was concentrated under reduced pressure to yield the sub-title product as a white solid (0.23 g).

b) 2-Chloro-5-(*N,N*-dimethylamino)ethylthio-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, fumarate.

To a solution of the sulphoxide from step a) (0.22g) in dichloromethane (1 ml) was added trifluoroacetic anhydride (1.1 ml) and the reaction mixture was heated to reflux temperature for 2 h. The reaction mixture was cooled to room temperature and the solvent evaporated under reduced pressure. A solution of the residue in triethylamine / methanol (10 ml 1:1) was treated with 2-dimethylaminoethyl chloride hydrochloride (0.086 g) and the reaction mixture stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue purified by silica gel chromatography (eluting with 10 - 20% methanol in ethyl acetate) to yield the product as a gum. Fumaric acid (0.0045g) was added to a solution of the gum in dichloromethane (10 ml). The solvent was removed under reduced pressure to leave the title compound as a viscous gum (0.023 g).

Example 60**2-Chloro-5-(*N,N*-dimethylamino)ethoxy-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide**

- 5 To a solution of 2-chloro-5-hydroxy-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide from Example 51 (0.05g) in acetonitrile (5 ml) was added potassium carbonate (0.065 g) and 2-dimethylaminoethyl chloride hydrochloride (0.037 g). The reaction mixture was stirred and heated at reflux temperature for 48 hours. The reaction mixture was evaporated under reduced pressure and residue dissolved in ethyl acetate and washed with brine.
- 10 Drying over sodium sulphate (Na₂SO₄), followed by concentration under reduced pressure gave a residue which was subsequently purified by supercritical chromatography, eluting with CO₂/methanol/0.1% diethylamine. Fractions containing product were concentrated under reduced pressure and the residue obtained was dissolved in diethyl ether. Hydrogen chloride (1 ml of a 1M solution in diethyl ether) was added dropwise and the resulting solid
- 15 was triturated under diethyl ether and then dried *in vacuo* to leave the title compound as a white solid (0.020 g).

Melting point: 144-147 °C

MS (APCI +ve) 391 (M+H)⁺ for free base

- 20 ¹H NMR (DMSO-d₆) δ 10.33 (1H, s), 8.33 (1H, t), 7.44-6.99 (3H, m), 4.38 (2H, t), 3.50 (2H, d), 2.90 (2H, m), 2.81 (6H, d), 1.95 (3H, s), 1.66 (3H, d), 1.59 (3H, d), 1.50 (6H, d)

hours at 90°C. The ethanol was removed under reduced pressure, water (20ml) was added to the residue, the product was extracted into ethyl acetate (3 x 50ml), dried over magnesium sulphate and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluting with dichloromethane:ethyl acetate (1:1) to give the title compound as a white solid (0.04g).

Melting point: 163-164 °C

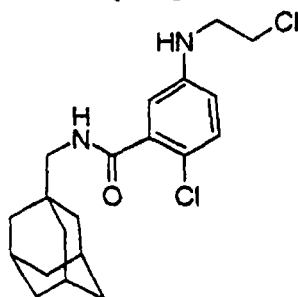
MS (APCI +ve) 333/335 (M+H)⁺

¹H NMR (CDCl₃) δ 7.17(1H, d); 6.96(1H, d); 6.57(1H, dd); 6.35(1H, s); 3.84(1H, s);

3.16(2H, d); 3.83(3H, d); 2.0(3H, s); 1.75-1.62(6H, m); 1.6(6H, d).

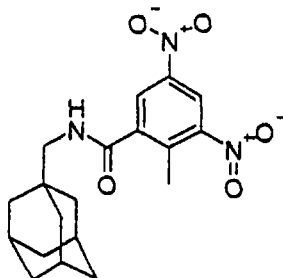
Example 63

2-Chloro-5-(2-chloroethyl)amino-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



Chloroacetaldehyde (50% solution in water) (0.705ml) was added to a solution of amino amide from Example 55 (1.5g) in methanol (15ml). After 10 minutes hydrochloric acid (0.77 ml of a 50% solution in methanol) was added. Solid sodiumcyanoborohydride (0.317g) was added and the mixture stirred at ambient temperature for two days. The solvent was removed under reduced pressure, the residue was dissolved in dichloromethane (50ml) and washed with aqueous sodium hydrogen carbonate (3 x 50ml). The organic extracts were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluting with hexane:diethylether (1:1) to give the title compound as a yellow solid (1.13g).

Melting point: 144-145 °C

Example 65**2-Methyl-3,5-dinitro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide**

Thionyl chloride (30 ml) was added to 3,5-dinitro-*o*-toluic acid (6.0 g) and the reaction
 5 heated at reflux temperature for 18 hours. The excess thionyl chloride was removed by
 concentration under reduced pressure and the residue was dissolved in dichloromethane
 (15 ml). This solution was added to a solution of 1-adamantanemethylamine (2.89 g) in
 dichloromethane (20 ml) and triethylamine (5 ml) at 0°C. After 10 minutes the reaction
 mixture was concentrated under reduced pressure and the residue purified by silica gel
 10 chromatography eluting with dichloromethane : ethyl acetate (9:1) to give a solid which
 was further purified by silica gel column chromatography eluting with dichloromethane to
 give a solid (6.34 g). Part of this material was treated with charcoal in boiling ethyl
 acetate, filtered and concentrated to remove coloured impurities. Washing the product with
 ether gave the title compound as a colourless solid.

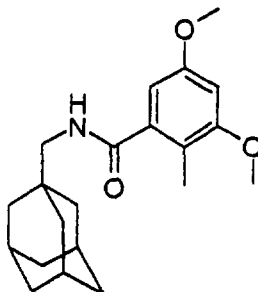
15

Melting point: 171-172 °C

MS (APCI +ve) 374 (M+H)⁺

¹H NMR (CDCl₃) δ 8.71 (1H, d), 8.39 (1H, d), 5.9-5.8 (1H, m), 3.21 (2H, d), 2.67 (3H, s),
 2.04 (3H, s), 1.8-1.7 (3H, m), 1.7-1.6 (3H, m), 1.6-1.55 (6H, m).

20

Example 67**3,5-Dimethoxy-2-methyl-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide****a) 3,5-Dimethoxy-2-methylbenzoic acid**

5 Solid methyl 3,5-dimethoxy-2-methylbenzoate (5.83 g, *J.C.S. Perkin I*, 1973, 2853.) was dissolved in methanol (80 ml). A solution of aqueous sodium hydroxide (10%, 80 ml) was added and the solution stirred at room temperature for 1 hour. The reaction was then concentrated under reduced pressure to approximately half of the original volume before adding aqueous hydrochloric acid (200 ml). The white precipitate that formed was
10 extracted with ethyl acetate (2 x 250 ml). The combined extracts were dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give the sub-title compound as a colourless solid (5.41 g).

¹H NMR (CDCl₃) δ 7.10 (1H, d), 6.64 (1H, d), 3.84 (6H, s), 2.45 (3H, s).

b) 3,5-Dimethoxy-2-methyl-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide

A mixture of 3,5-dimethoxy-2-methylbenzoic acid (0.15 g, part a) and thionyl chloride (2 ml) was heated at reflux for 2 minutes and then cooled to room temperature. The excess thionyl chloride was removed by concentration under reduced pressure and the residue
20 dissolved in dichloromethane (1 ml). This solution was added to a solution of 1-adamantanemethylamine (0.188 g) in dichloromethane (5 ml) and triethylamine (1 ml) and the resulting reaction mixture stirred overnight. The reaction was partitioned between dichloromethane (100 ml) and aqueous hydrochloric acid (1M, 50 ml). The organic phase was washed with a saturated aqueous solution of sodium hydrogen carbonate (50 ml), dried
25 over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to

Melting point: 130-133 °C

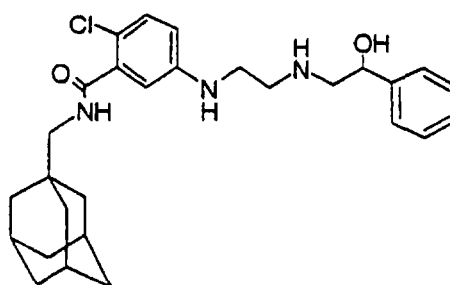
MS (APCI +ve) 330 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.24 (1H, t), 7.01 (2H, d), 6.30 (1H, t), 3.78 (6H, s), 2.97 (2H, d), 1.91 (3H, s), 1.7-1.5 (6H, m), 1.48 (6H, d)

5

Example 69

5-(*N*-(2-Hydroxy-2-phenylethyl)-2-aminoethyl)amino-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide



10 2-Chloro-5-(2-chloroethyl)amino-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide from Example 63 (0.1g), 2-amino-1-phenylethanol (0.539g) and triethylamine (0.5ml) were dissolved in tetrahydrofuran (3ml) and heated at 80°C for 60 hours in a sealed tube. The reaction mixture was concentrated under reduced pressure, the residue was suspended in aqueous sodium hydrogen carbonate (30ml), the product was extracted into ethyl acetate
15 (3 x 30ml), dried over magnesium sulphate filtered and concentrated under reduced pressure. Purification by NPHPLC eluting with 0 to 25% ethanol in dichloromethane gave title compound as a white solid (0.044g).

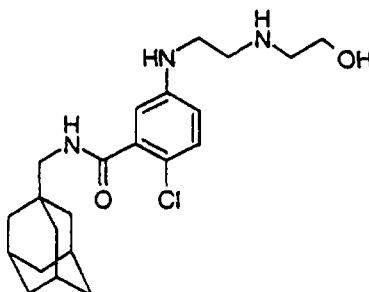
Melting point: 63-64 °C

20 MS (APCI +ve) 482/484 (M + H)⁺

¹H NMR (CDCl₃) δ 7.34(4H, d); 7.30-7.25(1H, m); 7.13(1H, d); 6.94(1H, d); 7.56(1H, dd); 6.39(1H, t); 4.73(1H, dd); 4.30(1H, s); 3.19-3.14(4H, m); 2.93-2.83(3H, m); 2.80-2.75(1H, m); 2.0(3H, s); 1.76-1.62(6H, m); 1.57(6H, m).

Example 71

5-(*N*-(2-Hydroxyethyl)-2-aminoethyl)amino-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, dihydrochloride



- 5 Prepared according to the method described in Example 69 from 2-chloro-5-(2-chloroethyl)amino-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide (0.1g), ethanolamine (0.24g), triethylamine (0.5ml) and tetrahydrofuran (3ml). Purification by flash column chromatography eluting with 10% methanol and 1% triethylamine in dichloromethane gave 2-chloro-5-(2-(piperidin-1-yl)ethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-
10 benzamide as a glass. Conversion to the hydrochloride salt upon treatment with excess ethereal hydrochloric acid (2M) gave the title compound as a cream solid (0.056g).

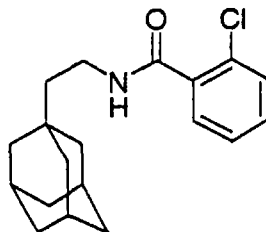
Melting point: 143 °C (Decomposed)

MS (APCI +ve) 406/408 ($M - (\text{hydrochloric acid}) + H^+$)

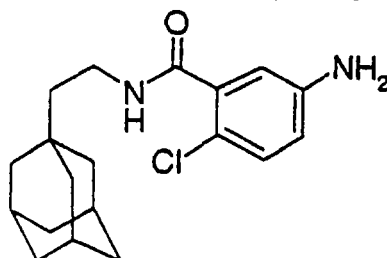
- 15 ¹H NMR (DMSO-d₆) δ 8.94(1H, s); 8.19(1H, t); 7.17(1H, dd); 6.67(1H, dd); 6.11(1H, d); 3.68(2H, t); 3.43-3.37(2H, m); 3.08-3.03(4H, m); 2.90(2H, d); 1.94(3H, s); 1.69-1.61(6H, m), 1.52(6H, d).

Example 72

- 20 **2-Chloro-*N*-(2-[tricyclo[3.3.1.1^{3,7}]dec-1-yl]ethyl)-benzamide**



Prepared according to the method of Example 1 from 1-adamantaneethylamine

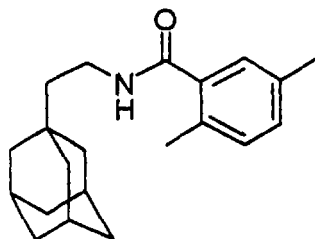
Example 74**5-Amino-2-chloro-N-(2-[tricyclo[3.3.1.1^{3,7}]dec-1-yl]ethyl)-benzamide**

Prepared according to the method of Example 14 from 1-adamantaneethylamine
5 hydrochloride (0.105 g) and 5-amino-2-chlorobenzoic acid (0.132 g) and purified by
supercritical fluid chromatography eluting with CO₂ in ethanol to give the title compound
as a white foam (0.094 g).

Melting point: 147-149 °C

10 MS (APCI +ve) 333/335 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.13 (1H, t), 7.03 (1H, d), 6.56-6.52 (2H, m), 5.36 (2H, s), 3.19
(2H, m), 1.93 (3H, s), 1.66-1.59 (6H, m), 1.50 (6H, d), 1.28 (2H, m).

Example 75**2,5-Dimethyl-N-(2-[tricyclo[3.3.1.1^{3,7}]dec-1-yl]ethyl)-benzamide**

Prepared according to the method of Example 14 from 1-adamantaneethylamine
hydrochloride (0.131 g) and 2,5-dimethylbenzoic acid (0.099 g) to give the title compound
as a white solid (0.163 g).

20 Melting point: 153 °C

MS (APCI +ve) 312 (M+H)⁺

chloroacetaldehyde in water (0.353 ml), sodium cyanoborohydride (0.159 g), 50% hydrochloric acid in methanol (0.385 ml) and methanol (10 ml), giving the subtitled compound as a white solid (0.777 g) after purification by flash column chromatography eluting with 3:1 *iso*-hexane : ethylacetate.

5

Melting point: Decomposed 179-180°C

MS (APCI +ve) 381/383 (M+H)⁺

¹H NMR (CDCl₃) δ 7.18(1H, t); 6.89(1H, dd); 6.70(1H, dd); 5.88(1H, bs); 4.88(1H, t); 3.75-3.70(2H, m); 3.61-3.55(2H, m); 3.15(2H, d); 2.02(2H, bs); 1.71-1.62(5H, m); 1.58(5H, d); 1.55(2H, s).

10

b) 2-Chloro-3-(N-(2-[imidazol-4-yl]ethyl)-2-aminoethyl)amino-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide

Aminoethylchloride from step a) (0.15g), histamine (0.437g), triethylamine (0.5ml) and tetrahydrofuran were combined and heated in a sealed tube for 60 hours at 80°C. The solvent was removed under reduced pressure, aqueous sodium hydrogencarbonate (30ml) was added to the residue which was extracted with ethylacetate (3 x 30ml). The combined organic extracts were dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The crude product was purified by reverse phase HPLC eluting with 85% to 15% of 0.1% aqueous trifluoroacetic acid in methanol to give the title compound as a white foam (0.07g).

15

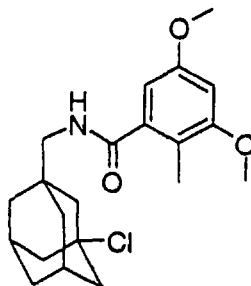
20

Melting point: 86-87°C

MS (APCI +ve) 456/458 (M+H)⁺

¹H NMR (CDCl₃) δ 7.61(1H, s); 7.17(1H, t); 6.79-6.72(2H, m); 6.31(1H, s); 6.02(1H, t); 4.76(1H, t); 3.45-3.30(2H, m); 3.17(2H, d); 2.95-2.85(4H, m); 2.75(2H, t); 2.02(3H, s); 1.80-1.60(6H, m); 1.58(6H, d).

25

Example 79**3,5-Dimethoxy-2-methyl-N-(3-chloro-tricyclo[3.3.1.1^{3,7}]dec-1ylmethyl)-benzamide**

A mixture of 3,5-dimethoxy-2-methylbenzoic acid from Example 67a) (0.15 g) and thionyl chloride (2 ml) was heated to reflux temperature for 2 minutes before cooling to room temperature and concentrated under reduced pressure. The residue was dissolved in dichloromethane (1 ml) and added to a solution of 1-adamantanemethylamine (0.104 g) in dichloromethane (5 ml) and triethylamine (1 ml) and the resulting reaction mixture stirred for 2 days. The reaction was partitioned between dichloromethane (100 ml) and aqueous hydrochloric acid (0.5M, 50 ml). The organic phase was washed with a saturated aqueous solution of sodium hydrogen carbonate (50 ml), dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by HPLC over a Dynamax® column eluting with iso-hexane : ethyl acetate (4:1) to give the title compound as a colourless solid (0.090 g).

Melting point: 173-175 °C

MS (APCI +ve) 378 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.17 (1H, t), 6.58 (1H, d), 6.43 (1H, d), 3.79 (3H, s), 3.76 (3H, s), 3.00 (2H, d), 2.16 (2H, s), 2.1-1.95 (4H, m), 2.05 (3H, s), 1.89 (2H, s) 1.7-1.5 (6H, m).

observed. The increase in fluorescence can be used as a measure of P2X₇ receptor activation and therefore to quantify the effect of a compound on the P2X₇ receptor.

In this manner, each of the title compounds of Examples 1 to 80 were tested for antagonist activity at the P2X₇ receptor. Thus, the test was performed in 96-well flat
5 bottomed microtitre plates, the wells being filled with 250 µl of test solution comprising 200 µl of a suspension of THP-1 cells (2.5×10^6 cells/ml) containing 10^{-4} M ethidium bromide, 25 µl of a high potassium buffer solution containing 10^{-5} M bbATP, and 25 µl of the high potassium buffer solution containing 3×10^{-5} M test compound. The plate was covered with a plastics sheet and incubated at 37 °C for one hour. The plate was then read
10 in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a P2X₇ receptor agonist) and pyridoxal 5-phosphate (a P2X₇ receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC₅₀ figure was calculated for each test compound, this figure being the negative logarithm of the concentration of test compound
15 necessary to reduce the bbATP agonist activity by 50%. Each of the compounds of Examples 1 to 80 demonstrated antagonist activity, having a pIC₅₀ figure > 4.50.

R^3 and R^4 each independently represent a hydrogen atom or a C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl group;

R^5 represents a hydrogen atom or a C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl group;

R^6 represents a C_3 - C_8 -cycloalkyl group and, additionally, a C_1 - C_6 -alkyl group when R^5 is

5 not a hydrogen atom;

R^7 represents a hydrogen atom or a C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl group;

R^8 represents a C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl group;

R^9 represents a hydrogen atom or a hydroxyl group; and

R^{10} represents a hydrogen atom or a phenyl or imidazolyl group;

10 with the provisos that R does not represent an unsubstituted pyridyl group when A represents a group CH_2 and B represents a hydrogen atom, and that when R represents a substituted phenyl, indolyl or indazolyl group, the substituent or substituents present do not comprise an amido, carboxyl, (di) C_1 - C_6 -alkylamido or C_1 - C_6 -alkoxycarbonyl group in an ortho position; or a pharmaceutically acceptable salt or solvate thereof.

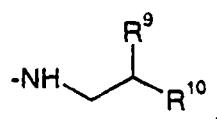
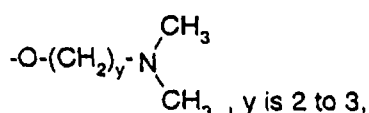
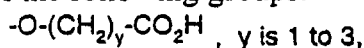
15

2. A compound according to claim 1, wherein R represents a phenyl, pyridyl or indolyl group, each of which may be optionally substituted by one or two substituents

independently selected from a fluorine, chlorine, bromine or iodine atom or an amino, hydroxyl, nitro, aziridiny, pyrrolidinyl, C_1 - C_4 -alkyl, trifluoromethyl, $-NR^5R^6$,

20 C_1 - C_4 -alkylsulphinyl or C_1 - C_4 -alkylsulphonyl group, or a C_1 - C_4 -alkoxy,

C_1 - C_4 -alkylamino, benzyl, C_1 - C_4 -alkylthio or phenylthio group optionally substituted by one or two substituents independently selected from a halogen atom or an amino, cyano, carboxyl, hydroxyl, 1-pyrrolidinyl, 1-piperidinyl, methyl, methoxy, dimethylamino, C_1 - C_4 -alkoxycarbonyl or one of the following groups:



25

- 2-(Phenylmethyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide,
2-(2-(*N,N*-Dimethylamino)ethyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-benzamide,
hydrochloride,
2-[[(Tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]carbonyl]phenyl-1-oxyacetic acid, 1,1-
5 dimethylethyl ester,
2-[[(Tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]carbonyl]phenyl-1-oxyacetic acid,
2-(Methylsulphoxide)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-3-pyridine carboxamide,
N-(tricyclo[3.3.1.1^{3,7}]dec-1-methyl)-5-indole carboxamide,
2-Amino-6-chloro-*N*-(2-[tricyclo[3.3.1.1^{3,7}]dec-1-yl]ethyl)-benzamide,
10 2-(2-Methylsulphonyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide,
2-(2-Aminoethylthio)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide,
trifluoroacetate,
2-(2-(*N,N*-Dimethylamino)ethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine
carboxamide, dihydrochloride,
15 2-(2-(Pyrrolidin-1-yl)ethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine
carboxamide, dihydrochloride,
2-(Methylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide,
dihydrochloride,
2-(Dimethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide,
20 hydrochloride,
2-(Pyrrolidin-1-yl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide,
dihydrochloride,
2-(2,5-Dimethoxyphenylthio)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine
carboxamide,
25 2-Chloro-5-methylthio-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
2-(2-(*N,N*-Dimethylamino)ethylthio)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
2-(4-Methoxyphenylthio)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridine carboxamide,
2-Chloro-3-fluoro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
2-Bromo-5-fluoro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,
30 2-Chloro-5-fluoro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

3,5-Dimethoxy-2-methyl-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

3,5-Dimethoxy-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5-(*N*-(2-Hydroxy-2-phenylethyl)-2-aminoethyl)amino-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5 2-Chloro-5-(2-(piperidin-1-yl)ethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride,

5-(*N*-(2-Hydroxyethyl)-2-aminoethyl)amino-2-chloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, dihydrochloride,

2-Chloro-*N*-(2-[tricyclo[3.3.1.1^{3,7}]dec-1-yl]ethyl)-benzamide,

10 2,3-Dichloro-*N*-(2-[tricyclo[3.3.1.1^{3,7}]dec-1-yl]ethyl)-benzamide,

5-Amino-2-chloro-*N*-(2-[tricyclo[3.3.1.1^{3,7}]dec-1-yl]ethyl)-benzamide,

2,5-Dimethyl-*N*-(2-[tricyclo[3.3.1.1^{3,7}]dec-1-yl]ethyl)-benzamide,

2-Chloro-*N*-(3-chloro-tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

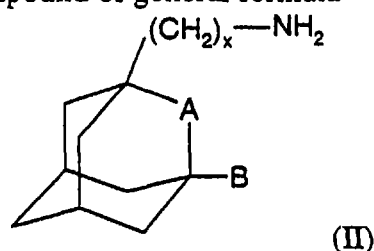
15 2-Chloro-3-(*N*-(2-[imidazol-2-yl]ethyl)-2-aminoethyl)amino-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2,5-Dimethyl-*N*-(3-chloro-tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

3,5-Dimethoxy-2-methyl-*N*-(3-chloro-tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, or

2-Chloro-5-iodo-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide.

20 6. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises reacting a compound of general formula



wherein x, A and B are as defined in formula (I), with a compound of general formula

