

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 US-A-3,789,072 as serotonin inhibitors, from Chem. Abs. (1974), Vol. 80, No.5 (26871m) as inflammation and edema inhibitors or analgesics, from Chem. Abs. (1975), Vol. 82, No.1 (3853j) and Chem. Abs. (1977), Vol. 86, No.17 (120855e) as antiviral agents, and also from Chem. Abs. (1968), Vol. 69, No.1 (2562h), Chem. Abs. (1975), Vol. 82, No.3 (16510v) and Tetrahedron (1988), 44, No. 23, 7234-7242.

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.



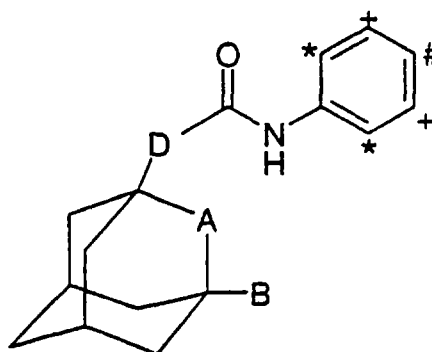
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group substituted by an amino, (di)C₁-C₆-alkylamino, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group;
or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, unless otherwise indicated, an alkyl
5 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. When D represents a
group OCH₂ or NHCH₂, the group is orientated such that the oxygen or nitrogen atom is
directly attached to the adamantyl group. A 3- to 8-membered heterocyclyl group should
10 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 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":



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Similarly, meta and para positions in the phenyl group R are defined relative to the point of
attachment of the amide linking group to R and are indicated in the above formula by the
symbols + and # respectively.

Preferably, R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl,
20 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 a cyano, carboxyl, hydroxyl, nitro, halo-C₁-C₆-alkyl (e.g.
trifluoromethyl), -N(R¹)-C(=O)-R², -C(O)NR³R⁴, -NR⁵R⁶, C₃-C₈-cycloalkyl (e.g.
cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), 3- to 8-membered heterocyclyl (e.g.

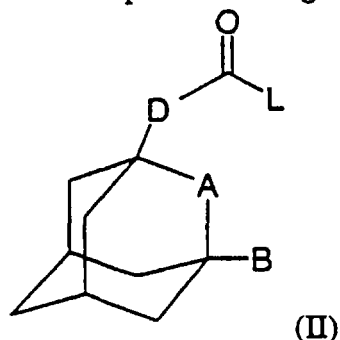
Preferably, R^3 , R^4 , R^5 and R^6 each independently represent a hydrogen atom or a C_1 - C_4 -alkyl (e.g. methyl, ethyl, propyl or butyl) or C_3 - C_6 -cycloalkyl (e.g. cyclopentyl or cyclohexyl) group.

Preferred compounds of the invention include:

- 5 *N*-(2-Methyl-6-benzothiazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(3-(3-(Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
N-(2-Chlorophenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
10 *N*-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2,3-Dimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(5-Indolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2,3-Dimethyl-5-indolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-[5-(3-*N,N*-Dimethylaminopropoxy)-2-methylphenyl]-tricyclo[3.3.1.1^{3,7}]decane-1-
15 acetamide, hydrochloride,
N-(5-Indazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(6-Indazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(1*H*-Indol-4-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
20 4-Methyl-3-[[1-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]phenoxy-acetic acid,
hydrochloride salt,
N-(1-Methyl-1*H*-indol-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(1-(*N,N*-Dimethylamino)ethyl-1*H*-indo-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
5-[[1-Oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]-1*H*-indole-1-acetic acid,
25 1,1-dimethylethyl ester,
N-(3-(2-Chloropyridyl))-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(3-(*N,N*-Dimethylamino)methyl-1*H*-indo-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(4-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2-Chloro-5-methoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
30 *N*-(4-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

- N*-(3-(3-(*N*-Methylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.^{3,7}]decane-1-acetamide, hydrochloride,
- N*-(5-(3-(*N,N*-Dimethylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.^{3,7}]decane-1-acetamide, hydrochloride,
- 5 *N*-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.^{3,7}]decanyloxy-1-acetamide,
- N*-(5-Methoxy-2-methylphenyl)-(3-bromo-tricyclo[3.3.1.^{3,7}]decane)-1-acetamide,
- N*-(5-Methoxy-2-methylphenyl)-(2-oxa-tricyclo[3.3.1.^{3,7}]decane)-1-acetamide,
- N*-(5-Methoxy-2-methylphenyl)-2-(tricyclo[3.3.1.^{3,7}]decan-1-amino)acetamide,
- N*-(3,5-Dimethoxyphenyl)-tricyclo[3.3.1.^{3,7}]decane-1-acetamide,
- 10 *N*-(3,5-Dihydroxyphenyl)-tricyclo[3.3.1.^{3,7}]decane-1-acetamide,
- N*-(3,5-Dimethoxyphenyl)-tricyclo[3.3.1.^{3,7}]decanyloxy-1-acetamide,
- N*-(3,5-Bis-(3-aminopropyloxy)phenyl)-tricyclo[3.3.1.^{3,7}]decane-1-acetamide,
- N*-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.^{3,7}]decanyloxy-1-acetamide,
- N*-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.^{3,7}]decanyloxy-1-acetamide,
- 15 *N*-(5-(2-(*N*-Methylamino)ethyloxy)-2-methylphenyl)-tricyclo[3.3.1.^{3,7}]decane-1-acetamide, hydrochloride,
- N*-(5-(2-(*N*-Methylamino)ethyloxy)-2-methylphenyl)-tricyclo[3.3.1.^{3,7}]decanyloxy-1-acetamide,
- N*-(5-(3-(*N*-Methylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.^{3,7}]decanyloxy-1-acetamide, and
- 20 *N*-(3,5-Dihydroxy-2-methylphenyl)-tricyclo[3.3.1.^{3,7}]decane-acetamide.

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



The compounds of the present invention are advantageous in that they possess pharmacological activity. They are therefore indicated as pharmaceuticals for use in the treatment or prevention of rheumatoid arthritis, osteoarthritis, psoriasis, allergic dermatitis, asthma, hyperresponsiveness of the airway, septic shock, glomerulonephritis, irritable
5 bowel disease, Crohn's disease, ulcerative colitis, atherosclerosis, growth and metastases of malignant cells, myocardial ischaemia, myoblastic leukaemia, diabetes, Alzheimer's disease, osteoporosis, burn injury, stroke, varicose veins and meningitis.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in
10 therapy.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

The invention further provides a method of effecting immunosuppression (e.g. in the
15 treatment of rheumatoid arthritis, irritable bowel disease, atherosclerosis or psoriasis) which comprises administering a therapeutically effective amount of a compound of 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,
20 vary with the compound employed, the mode of administration, the treatment desired and 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
25 ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. 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
30 based on total composition.

b) *N*-(2-Methyl-6-benzothiazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide

To a solution of 1-adamantaneacetyl chloride (0.5 g) prepared as described in a) above in acetonitrile (10 ml) was added triethylamine (0.38 ml) and 6-amino-2-methylbenzothiazole (0.39 g). The reaction mixture was stirred at ambient temperature for 1 hour before being diluted with ethyl acetate. The organic phase was then washed with dilute hydrochloric acid and water, dried over magnesium sulphate (MgSO₄) and finally concentrated under reduced pressure to give the title compound as a white solid (0.12 g).

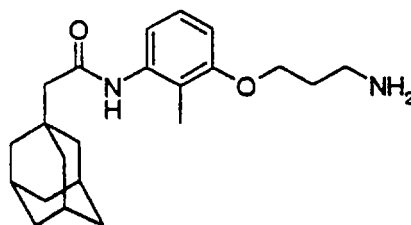
Melting point: 172 °C

MS (APCI +ve) 341 (M+H)⁺

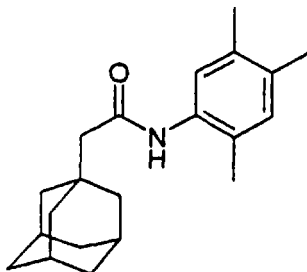
¹H NMR (CDCl₃) δ 8.45 (1H, d), 7.84 (1H, d), 7.19 (2H, m), 2.81 (3H, s), 2.13 (2H, s), 2.00 (3H, s), 1.75 (12H, m)

Example 2

***N*-(3-(3-(Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



Diethyl azodicarboxylate (1.0 ml) was added to a solution of *N*-(3-hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (0.408 g, Example 26), tert-butyl *N*-(3-hydroxypropyl)carbamate (1.11 g) and triphenylphosphine (1.74 g) in tetrahydrofuran (5 ml). After stirring overnight at room temperature the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography over silica eluting with dichloromethane : ethyl acetate (9:1) and then further purified by HPLC over a Dynamax® column using a Waters Prep 4000 eluting with iso-hexane : ethyl acetate (7:3) to give the Mitsunobu reaction product (0.34 g) which was dissolved in methanol (10 ml). A solution of hydrogen chloride (generated by slow addition of acetyl chloride (12 ml) to

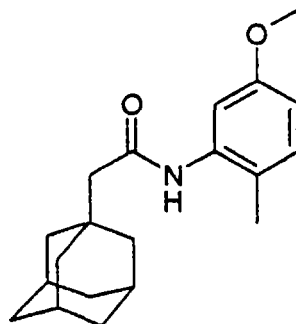
Example 4***N*-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
5 (0.2 g) and 2,4,5-trimethylaniline (0.13 g) to give the title compound as a white solid
(0.042 g).

Melting point: 158 °C

MS (APCI +ve) 312 (M+H)⁺

10 ¹H NMR (DMSO-d₆) δ 9.00 (1H, s), 7.08 (1H, s), 6.94 (1H, s), 2.14 (6H, s), 2.10 (3H, s),
2.04 (2H, s), 1.98 (3H, s), 1.75 (12H, m)

Example 5***N*-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

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Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
(0.2 g) and 5-methoxy-2-methylaniline (0.13 g) to give the title compound as a white solid
(0.043 g).

20 Melting point: 147 °C

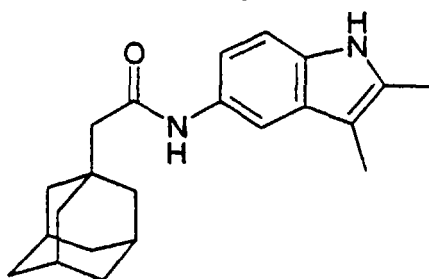
MS (APCI +ve) 314 (M+H)⁺

MS (APCI +ve) 309 (M+H)⁺

¹H NMR (DMSO-d₆) δ 10.95 (1H, s), 9.51 (1H, s), 7.85 (1H, s), 7.28 (2H, m), 7.16 (1H, dd), 6.35 (1H, t), 2.04 (2H, s), 1.94 (3H, s), 1.70-1.50 (12H, m)

5 Example 8

N-(2,3-Dimethyl-5-indolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide

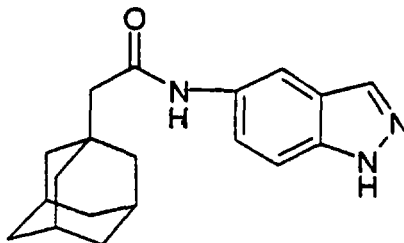


To a solution of 1-adamantaneacetic acid (0.30 g) in dichloromethane (10 ml) were added 4-dimethylaminopyridine (0.19 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.30 g). The reaction mixture was stirred for 0.5 hour before addition of 5-amino-2,3-dimethylindole (0.25 g). Stirring was then continued overnight at ambient temperature. The next day the reaction mixture was washed with dilute hydrochloric acid, water and brine, dried over sodium sulphate (Na₂SO₄) and finally concentrated under reduced pressure to leave a residue. Purification of the residue by silica gel chromatography, eluting with 40% ethyl acetate in *isohexanes*, gave the title compound as a white solid (0.14 g).

Melting point: 234-235 °C

MS (APCI +ve) 337 (M+H)⁺

¹H NMR (DMSO-d₆) δ 10.50 (1H, s), 9.46 (1H, s), 7.67 (1H, s), 7.08 (2H, m), 2.28 (3H, s), 2.03 (3H, s), 1.99 (2H, s), 1.94 (3H, s), 1.70-1.50 (12H, m)

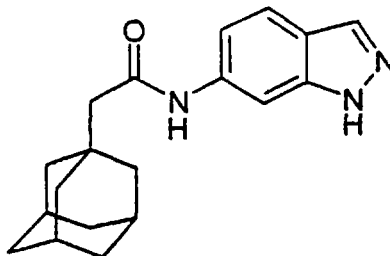
Example 10***N*-(5-Indazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
5 (0.1 g) and 5-aminoindazole (0.067 g) to give the title compound as a white solid (0.12 g).

Melting point: 265 °C

MS (APCI +ve) 310 (M+H)⁺

¹H NMR (DMSO-d₆) δ 12.93 (1H, s), 9.73 (1H, s), 8.12 (1H, s), 7.99 (1H, s),
10 7.40 (2H, m), 2.04 (2H, s), 1.94 (3H, s), 1.70-1.50 (12H, m)

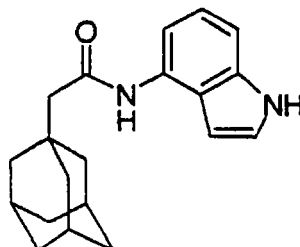
Example 11***N*-(6-Indazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

15 Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
(0.2 g) and 6-aminoindazole (0.13 g) to give the title compound as a white solid (0.064 g).

Melting point: 245 °C

MS (APCI +ve) 310 (M+H)⁺

¹H NMR (DMSO-d₆) δ 12.84 (1H, s), 9.87 (1H, s), 8.16 (1H, s), 7.94 (1H, s),
20 7.62 (1H, d), 7.05 (1H dd), 2.04 (2H, s), 1.94 (3H, s), 1.70-1.50 (12H, m)

Example 13***N*-(1*H*-Indol-4-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
 5 (0.074 g) and 4-aminoindole hydrochloride (0.059 g) to give the title compound as a white
 solid (0.068 g).

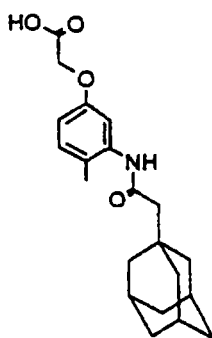
Melting point: 211-213 °C

MS (APCI +ve) 309 (M+H)⁺

10 ¹H NMR (DMSO-d₆) δ 11.07 (1H, s), 9.35 (1H, s), 7.53 (1H, d), 7.27 (1H, t), 7.12 (1H, d),
 6.99 (1H, t), 6.66 (1H, s), 2.19 (2H, s), 1.94 (3H, s), 1.68 (6H, d), 1.68-1.58 (6H, m).

Example 14

4-Methyl-3-[[1-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]phenoxy-acetic acid,
 15 **hydrochloride salt**



To a solution of *N*-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide
 from Example 12 (0.20 g) was added potassium carbonate (0.106g) and ethyl bromoacetate
 (0.3ml). The reaction mixture was stirred and heated at 80°C for 24 hours. Once cooled,
 20 the reaction mixture was diluted with ethyl acetate and washed with saturated brine. The
 organic phase was separated, dried over magnesium sulphate (MgSO₄) and evaporated

¹H NMR (DMSO-d₆) δ 8.58 (1H, d), 8.04 (1H, dd), 7.65 (1H, d), 7.61 (1H, d), 6.75 (1H, dd), 3.88 (3H, s).

b) *N*-(1-Methyl-1*H*-indol-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide

To a solution of 1-methyl-5-nitroindole from step a) (0.11 g) in ethanol (10 ml) was added 10% palladium on carbon (0.023 g) and resulting suspension stirred under 4 bar pressure of hydrogen for 0.75 h before filtering off the catalyst and concentration at reduced pressure. The resulting residue was condensed with 1-adamantanecetyl chloride (0.10 g) according to the method of Example 1b) to give the title compound as a white solid (0.11 g).

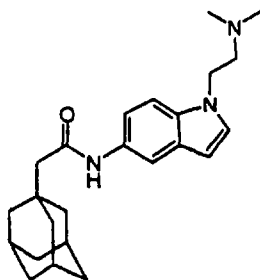
Melting point: 183-184 °C

MS (APCI +ve) 323 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.55 (1H, s), 7.87 (1H, d), 7.32 (1H, d), 7.26 (1H, d), 7.23 (1H, dd), 6.34 (1H, dd), 3.75 (3H, s), 2.04 (2H, s), 1.94 (3H, s), 1.75-1.50 (12H, m).

Example 16

***N*-(1-(*N,N*-Dimethylamino)ethyl-1*H*-indol-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**



a) 1-(*N,N*-Dimethylamino)ethyl-5-nitro-1*H*-indole

Prepared according to the method of Example 15a) from 5-nitroindole (0.217 g) and dimethylaminoethyl chloride hydrochloride (0.21 g) to leave sub-title compound as an orange/brown solid (0.24 g).

¹H NMR (DMSO-d₆) δ 8.56 (1H, d), 8.02 (1H, dd), 7.71 (1H, d), 7.61 (1H, d), 6.74 (1H, dd), 4.35 (2H, t), 2.62 (2H, t), 2.17 (6H, s).

b) 5-[[1-Oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]-1*H*-indole-1-acetic acid, 1,1-dimethylethyl ester

Prepared according to the method of Example 15b) from 5-nitro-1*H*-indole-1-acetic acid, 1,1-dimethylethyl ester (0.29 g) and 1-adamantaneacetyl chloride (0.20 g) to give the
5 title compound as a white solid (0.24 g).

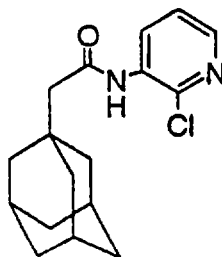
Melting point: 199 °C

MS (APCI +ve) 423 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.56 (1H, s), 7.86 (1H, d), 7.27 (1H, d), 7.22 (2H, m), 6.38 (1H, d),
10 4.94 (2H, s), 2.04 (2H, s), 1.94 (3H, s), 1.65 (12H, m), 1.41 (9H, s).

Example 18

***N*-(3-(2-Chloropyridyl))-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

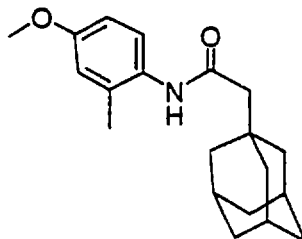


15 Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride (0.5g) and 2-chloro-3-aminopyridine (0.31 g) to give the title compound as a white solid (0.27 g).

Melting point: 135-136 °C

20 MS (APCI +ve) 305 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.51 (1H, s), 8.22 (1H, dd), 8.15 (1H, dd), 7.4 (1H, dd),
2.20 (2H, s), 1.98 (3H, s), 1.60 (12H, m)

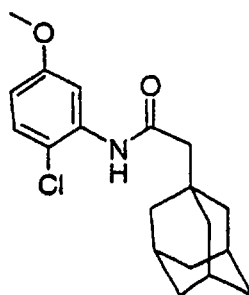
Example 20***N*-(4-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
5 (2.0g) and 4-methoxy-2-methylaniline (1.29 g) to give the title compound as a white solid
(1.37 g).

Melting point: 156-157 °C

MS (APCI +ve) 314 (M+H)⁺

10 ¹H NMR (DMSO-d₆) δ 9.01 (1H, s), 7.15 (1H, d), 6.80 (1H, d), 6.7 (1H, dd), 3.7 (3H, s),
2.20 (3H, s), 2.05 (2H, s), 1.95 (3H, s), 1.60 (12H, m)

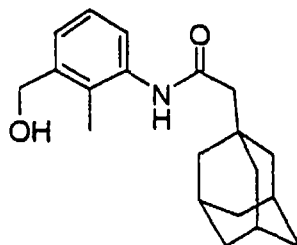
Example 21***N*-(2-Chloro-5-methoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

15

Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
(2.0g) and 2-chloro-5-methoxyaniline (1.49 g) to give the title compound as a white solid
(0.60 g).

20 Melting point: 122-123 °C

MS (APCI +ve) 334 (M+H)⁺

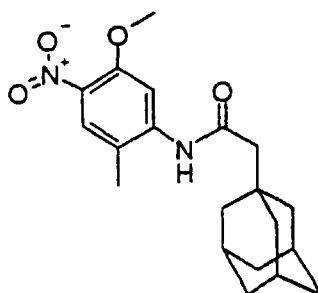
Example 23***N*-(3-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
 5 (2.0g) and 3-amino-2-methylbenzyl alcohol (1.29 g). Silica gel chromatography, eluting
 with 5% ethylacetate in dichloromethane gave the title compound as a white solid (0.80 g).

Melting point: 205-206 °C

MS (APCI +ve) 314 (M+H)⁺

10 ¹H NMR (DMSO-d₆) δ 9.16 (1H, s), 7.20-7.05 (3H, m), 5.07 (1H, bs), 4.47 (2H, s),
 2.09 (2H, s), 2.08 (3H,s), 1.95 (3H, s), 1.60 (12H, m)

Example 24***N*-(5-Methoxy-2-methyl-3-nitrophenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

15

Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride
 (2.0g) and 5-methoxy-2-methyl-4-nitroaniline (1.71 g). Silica gel chromatography, eluting
 with iso-hexane/diethyl ether (1:1), gave the title compound as a yellow solid (1.10 g).

20 Melting point: 141-142 °C

MS (APCI +ve) 359 (M+H)⁺

Melting point: 211 °C

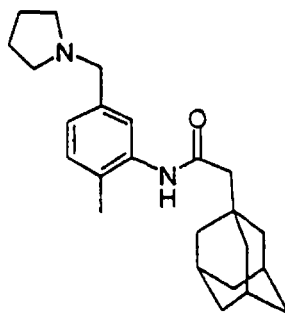
MS (APCI +ve) 300 (M+H)⁺

¹H NMR (DMSO- d₆) δ 9.28 (1H, bs), 9.04 (1H, bs), 6.91 (1H, t), 6.8 (1H, d), 6.6 (1H, d), 2.05 (2H, s), 1.98 (3H, S) 1.94 (3H, bs), 1.6 (12H, m)

5

Example 27

***N*-(2-Methyl-5-(1-pyrrolidinemethyl)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



10 To a solution of *N*-(5-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide from Example 25) (1.0 g) in acetonitrile was added triphenylphosphine (0.93g) and carbon tetrabromide (1.2g). The reaction mixture was stirred at ambient temperature for 24 hours and evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with iso-hexane/diethyl ether to give a white solid. A portion
15 (0.1g) of the solid was dissolved in acetonitrile (3ml) and treated with pyrrolidine (0.2ml). The reaction mixture was stirred and heated at 80°C for 24 hours. Once cooled, the reaction mixture was diluted with ethyl acetate and washed with saturated brine. The organic phase was separated, dried over magnesium sulphate (MgSO₄), treated with a solution of hydrogen chloride in diethyl ether (1ml of 1.0M) and evaporated under
20 reduced pressure to leave a residue which was triturated with iso-hexane to give the title compound as an off-white solid. (0.030g)

Melting point: 214-215 °C

MS (APCI +ve) 367 (M+H)⁺ for free base.

Melting point: 224-225 °C

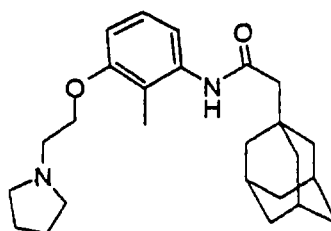
MS (APCI +ve) 320 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.65 (1H, s), 9.09 (1H, s), 7.23 (2H, m), 6.55 (1H, dd),
2.20 (2H, s), 1.95 (3H, s), 1.60 (12H, m)

5

Example 30

***N*-(2-Methyl-3-(2-(1-pyrrolidino)ethoxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



10 To a solution of *N*-(3-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide from Example 26 (0.060g), in acetonitrile (3ml), was added caesium carbonate (0.196g) and *N*-(2-chloroethyl)-pyrrolidine hydrochloride (0.068g). The reaction mixture was stirred and heated at 80°C for 24 hours. After cooling, the reaction mixture was diluted with ethyl acetate and washed with water. The organic phase was dried over magnesium
15 sulphate and evaporated under reduced pressure to leave a residue which was purified by Supercritical Fluid Chromatography using a gradient elution of 0.1% v/v solution of diethylamine in methanol and supercritical carbon dioxide on a Cyano column. The pure product was dissolved in dichloromethane, treated with 1.0M solution of hydrogen chloride in diethyl ether and evaporated under reduced pressure to leave the title compound as a
20 white solid. (0.010g)

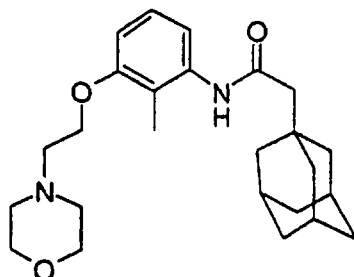
Melting point: 105-106 °C

MS (APCI +ve) 397 (M+H)⁺ for free base.

¹H NMR (DMSO-d₆) δ 9.22 (1H, s), 7.12 (1H, t), 6.97 (1H, d), 6.81 (1H, d), 4.30 (2H, t),
25 3.60 (4H, m), 3.10 (2H, m), 2.05 (6H, s), 1.95 (6H, m), 1.60 (12H, m)

Example 32

***N*-(2-Methyl-3-(2-(1-morpholino)ethoxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



- 5 Prepared according to the method of Example 30 from *N*-(3-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (0.060g) and *N*-(2-chloroethyl)-morpholine hydrochloride (0.075g) to give the title compound as a white solid. (0.024g).

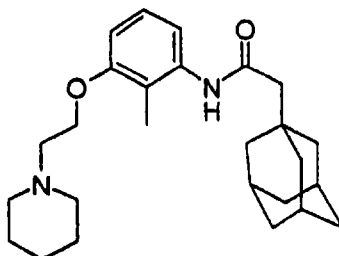
Melting point: 195-197 °C

- 10 MS (APCI +ve) 413 (M+H)⁺ for free base.

¹H NMR (DMSO-d₆) δ 11.36 (1H, bs), 9.23 (1H, s), 7.15 (1H, t), 6.99 (1H, d), 6.83 (1H, d), 4.42 (2H, t), 4.10-3.0 (12H, m), 2.08 (2H, s), 2.07 (3H, s), 1.95 (3H, s), 1.60 (12H, m)

15 **Example 33**

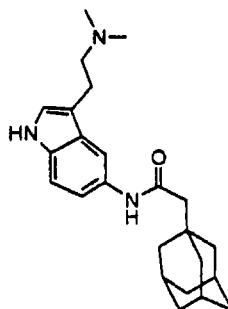
***N*-(2-Methyl-3-(2-(1-piperidino)ethoxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



- 20 Prepared according to the method of Example 30 from *N*-(3-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (0.060g) and *N*-(2-chloroethyl)-piperidine hydrochloride (0.074g) to give the title compound as a white solid (0.036g).

Example 35

***N*-(5-(3-(2-*N,N*-dimethylaminoethyl)indolyl))-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**

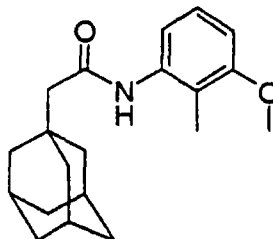


5 Prepared according to the method of Example 1b) from 1-adamantaneacetyl chloride (0.040g) and 5-amino-3-(2-dimethylaminoethyl)indole dihydrochloride (0.18 g). Supercritical Fluid chromatography using a gradient elution of 0.1% v/v solution of diethylamine in methanol and supercritical carbon dioxide on a Cyano column gave the pure product which was dissolved in dichloromethane, treated with 1.0M solution of
 10 hydrogen chloride in diethyl ether and evaporated under reduced pressure to leave the title compound as a pale yellow solid. (0.031g).

Melting point: 145-147 °C

MS (APCI +ve) 380 (M+H)⁺ for free base

15 ¹H NMR (DMSO-d₆) δ 10.89 (1H, s), 9.58 (1H, s), 7.95 (1H, d), 7.25 (1H, dd), 7.15 (1H, d), 7.12 (1H, dd), 3.33 (2H, m), 3.05 (2H, m), 2.85 (6H, 2s), 2.03 (2H, s), 1.95 (3H, s), 1.60 (12H, m)

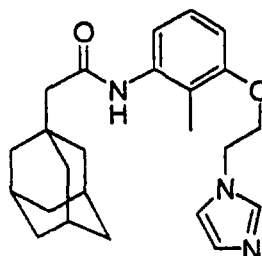
Example 37***N*-(3-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

Diethyl azodicarboxylate (0.20 ml) was added to a solution of *N*-(3-hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (0.20 g, Example 26), methanol (0.10 ml) and triphenylphosphine (0.41 g) in toluene (10 ml) and tetrahydrofuran (5 ml). After 2 hours stirring at room temperature further triphenylphosphine (0.20 g) and diethyl azodicarboxylate (0.10 ml) were added and the solution stirred for 2 hours. The reaction mixture was concentrated under reduced pressure and the residue purified by silica gel chromatography eluting with dichloromethane : ethyl acetate (19:1) to give the title compound as a colourless solid (0.20 g).

Melting point: 173-175 °C

MS (APCI +ve) 314 (M+H)⁺

¹H NMR (CDCl₃) δ 7.48 (1H, d), 7.16 (1H, t), 6.86 (1H, bs), 6.69 (1H, d), 3.82 (3H, s), 2.13 (5H, s), 2.00 (3H, s), 1.75-1.6 (12H, m).

Example 38***N*-(2-Methyl-3-(2-(1-imidazol)ethoxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

20

Diethyl azodicarboxylate (0.060 ml) was added to a solution of *N*-(3-hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (0.100 g, Example 26), 1-(2-

dichloromethane then dichloromethane : ethyl acetate (9:1) to give the title compound as a colourless solid (0.469 g).

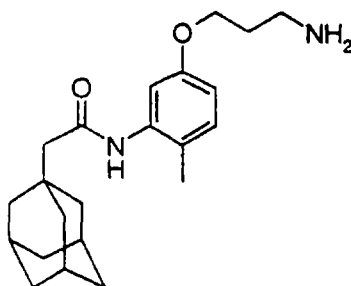
Melting point: 212-215 °C

5 MS (APCI +ve) 312 (M+H)⁺

¹H NMR (DMSO-d₆) δ 8.97 (1H, s), 6.85 (2H, s), 2.21 (3H, s), 2.10 (6H, s), 2.06 (2H, s), 1.95 (3H, s), 1.8-1.5 (12H, m).

Example 40

10 *N*-(5-(3-Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride



Prepared according to the method of Example 2 using diethyl azodicarboxylate (1.05 ml), *N*-(5-hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (0.506 g,

15 Example 12), tert-butyl *N*-(3-hydroxypropyl)carbamate (1.15 g) and triphenylphosphine (1.75 g) to give the title compound as a yellow solid (0.21 g).

Melting point: 145 °C (dec.)

MS (APCI +ve) 357 (M-HCl+H)⁺

20 ¹H NMR (DMSO-d₆) δ 9.05 (1H, s), 7.91 (3H, bs), 7.15-7.05 (2H, m), 6.66 (1H, dd), 3.99 (2H, t), 2.94 (2H, t), 2.13 (3H, s), 2.10 (2H, s), 2.05-1.9 (5H, m), 1.75-1.55 (12H, m).

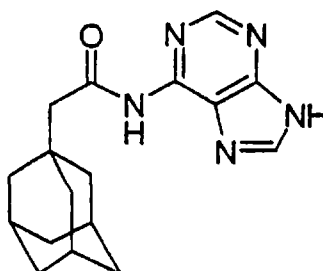
MS (APCI +ve) 371 (M-HCl+H)⁺

¹H NMR (DMSO-d₆) δ 9.05 (1H, s), 8.76 (2H, bs), 7.15-7.05 (2H, m), 6.66 (1H, dd), 3.99 (2H, t), 3.1-2.95 (2H, m), 2.6-2.5 (3H, m), 2.13 (3H, s), 2.10 (2H, s), 2.1-2.0 (2H, m), 1.94 (3H, m), 1.75-1.55 (12H, m).

5

Example 42

N6-(Tricyclo[3.3.1.1^{3,7}]decane-1-acetyl)adenine



To a solution of 1-adamantaneacetyl chloride from Example 1a) (0.226 g) in
10 dichloromethane (5 ml) was added 4-nitrophenol (0.149 g) and reaction mixture stirred at room temperature for 1 hr before concentration at reduced pressure. The resulting 4-nitrophenol ester was used without further purification.

To a suspension of the 4-nitrophenol ester (0.209 g), adenine (0.09 g) in
dimethylsulphoxide (1.4 ml) was added triethylamine (0.19 ml) and reaction mixture
15 heated to 90 °C for 2 days before cooling to room temperature. Reaction mixture was poured into aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. Organic extracts combined, washed with water (x 3), brine, dried (Na₂SO₄) and concentrated at reduced pressure. Trituration of the residue with isohexane and ether left the product as a pale yellow solid (0.036 g).

20

Melting point: 309 °C (dec.)

MS (APCI +ve) 312 (M+H)⁺

¹H NMR (DMSO-d₆) δ 12.10 (1H, s), 11.06 (1H, s), 8.61 (1H, s), 8.40 (1H, s), 2.29 (2H, s), 1.92 (3H, s), 1.66 (6H, d), 1.60 (6H, m).

25

room temperature for 1 hour. The reaction was concentrated under reduced pressure and the residue partitioned between an aqueous solution of saturated sodium hydrogen carbonate (100 ml) and dichloromethane (100 ml). The organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give an oil (0.5 g) which was dissolved in dichloromethane (10 ml) and triethylamine (2 ml). A solution of 1-adamantaneacetyl chloride (generated from 1-adamantaneacetic acid (0.50 g) and thionyl chloride) in dichloromethane (5 ml) was added to the latter solution and the mixture stirred at room temperature for 2 hours. The reaction was diluted with dichloromethane (100 ml) and the solution washed with aqueous hydrochloric acid (2M, 50 ml) then an aqueous solution of saturated sodium hydrogen carbonate (50 ml). The organic phase was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography over silica eluting with dichloromethane then dichloromethane : ethyl acetate (19:1) to give the title compound as a colourless solid (0.54 g).

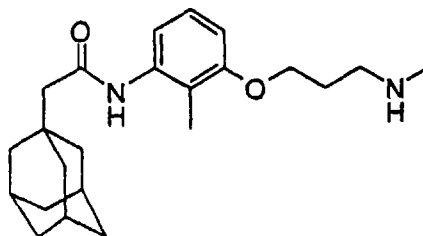
Melting point: 201-203 °C

MS (APCI +ve) 344 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.08 (1H, s), 6.61 (1H, d), 6.38 (1H, d), 3.76 (3H, s), 3.70 (3H, t), 2.07 (2H, s), 1.94 (6H, s), 1.75-1.55 (12H, m).

Example 44

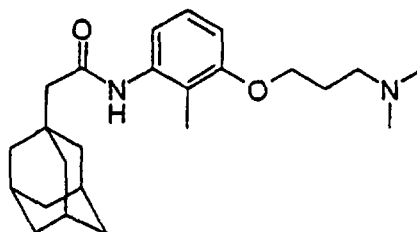
N-(3-(3-(*N*-Methylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride



Dry dichloromethane (40 ml), triphenylphosphine (3.28 g), imidazole (1.05 g) and iodine (3.85 g) were combined in that order. A solution of *tert*-butyl *N*-(3-hydroxypropyl)-

Example 45

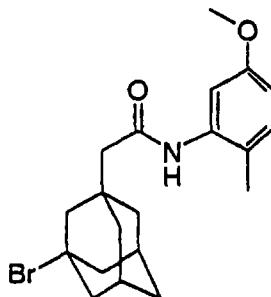
***N*-(5-(3-(*N,N*-Dimethylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride**



5 Caesium carbonate (1.31 g) was added to a suspension of *N*-(3-hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (0.473 g, Example 26) in acetonitrile (35 ml) and the mixture heated at 80°C for 5 minutes. After cooling to room temperature solid *N,N*-dimethyl-3-chloropropylamine (0.274 g) was added and the reaction heated at reflux overnight. The reaction was concentrated under reduced pressure and the residue
 10 partitioned between dichloromethane (100 ml) and water (100 ml). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography over silica eluting with dichloromethane : ethanol : triethylamine (95:4:1) to give a yellow gum. This was dissolved in methanol (10 ml) and treated with an excess of ethereal hydrogen chloride
 15 (1M, 5 equivalents). The solution was concentrated under reduced pressure to give a gum that was stirred for 2 days in ether (20 ml) to give a solid which was isolated by filtration (0.588 g).

MS (APCI +ve) 385 (M-HCl+H)⁺

20 ¹H NMR (DMSO-d₆) δ 10.33 (1H, bs), 9.21 (1H, s), 7.10 (1H, t), 6.94 (1H, d), 6.78 (1H, d), 4.04 (2H, t), 3.3-3.1 (2H, m), 2.79 (6H, d), 2.2-2.1 (2H, m), 2.08 (2H, s), 2.05 (3H, s), 1.95 (3H, s), 1.75-1.55 (12H, m).

Example 47***N*-(5-Methoxy-2-methylphenyl)-(3-bromo-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide**

To a solution of 3-bromoadamantane acetic acid (CN 17768-34-2) (0.123 g) in
 5 dichloromethane (5 ml) was added oxalyl chloride (0.5 ml) and resulting reaction mixture
 heated to reflux temperature for 2 hr before concentration at reduced pressure. Residue
 was dissolved in dichloromethane (5 ml) and a mixture of 5-methoxy-2-methylaniline
 (0.062 g) and triethylamine (0.2 ml) in dichloromethane (2 ml) was added dropwise and
 reaction mixture stirred at room temperature for 18 hr before being poured into dilute HCl
 10 and extracted with diethyl ether. Organic extracts combined, washed with water, 15%
 NaOH solution, brine, dried (Na₂SO₄) and concentrated to leave a solid that was triturated
 with ether to leave the title compound as a white solid (0.07 g).

Melting point: 133 °C

15 MS (APCI +ve) 392/394 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.13 (1H, s), 7.09 (1H, d), 7.05 (1H, d), 6.66 (1H, dd),
 3.70 (3H, s), 2.28-2.13 (11H, m), 2.18 (2H, s), 1.68-1.55 (6H, m).

pressure and the residue was then dissolved in dichloromethane (5 ml). This solution was then added over 1 minute to a solution of 5-methoxy-2-methylaniline (69 mg) in dichloromethane (5 ml) and triethylamine (1 ml) at room temperature for 20 minutes. The reaction mixture was diluted with dichloromethane to 60 ml and then washed with aqueous
 5 hydrochloric acid (2M, 30 ml). The organic phase was dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography over silica eluting with dichloromethane then dichloromethane : ether (19:1) to give, after trituration with iso-hexane, a colourless solid (0.05 g).

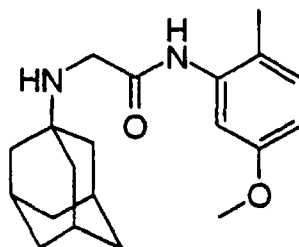
10 Melting point: 108-109.5 °C

MS (APCI +ve) 316 (M+H)⁺

¹H NMR (DMSO-d₆) δ 9.12 (1H, s), 7.39 (1H, d), 7.08 (1H, d), 6.61 (1H, dd), 4.09 (1H, bs), 3.69 3H, s), 2.37 (2H, s), 2.15-2.05 (2H, m), 2.13 (3H, s), 1-9-1.55 (10H, m).

15 **Example 49**

***N*-(5-Methoxy-2-methylphenyl)-2-(tricyclo[3.3.1.1^{3,7}]decan-1-amino)acetamide**



a) *N*-(5-Methoxy-2-methylphenyl)-2-chloroacetamide

To a solution of 5-methoxy-2-methylaniline (7.62 g) and triethylamine (15.5 ml) in
 20 dichloromethane (150 ml) at 0-5 °C was added chloroacetyl chloride (5.0 ml) dropwise and the ice bath removed. The resulting reaction mixture was stirred for 45 min before being poured into dil HCl and extracted with dichloromethane. Organic extracts were combined, washed with water, dried (Na₂SO₄) and concentrated to give a brown solid that was triturated with diethyl ether to leave the sub-title compound as a beige solid (5.7 g).

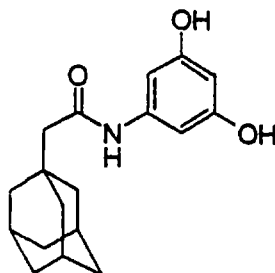
25

Melting point: 89-91 °C

^1H NMR (DMSO- d_6) δ 9.69 (1H, s), 6.86 (2H, d), 6.18 (1H, t), 3.70 (6H, s), 2.02 (2H, s), 1.93 (3H, s), 1.68-1.57 (12H, m).

Example 51

5 *N*-(3,5-Dihydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide

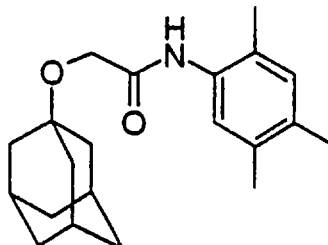


To a solution of *N*-(3,5-dimethoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide (2.22 g) in dichloromethane (200 ml) at -78 °C was added boron tribromide (60 ml of a 1M solution in dichloromethane). Cooling bath was removed and reaction stirred at room
10 temperature for 3 days. Reaction was quenched by addition of ice (230 g). After stirring vigorously for 30 min ethyl acetate (700 ml) added and the organic layer separated, dried (MgSO_4) and concentrated. The residue was purified by column chromatography over silica eluting 5% ethanol in dichloromethane to give the leave a white solid (1.95 g). A portion of this was recrystallised from hot ethyl acetate to leave the title compound as an
15 off-white solid.

Melting point: 239-242 °C

MS (APCI +ve) 302 ($\text{M}+\text{H}$)⁺

^1H NMR (DMSO- d_6) δ 9.42 (1H, s), 9.09 (2H, s), 6.55 (2H, d), 5.87 (1H, t), 1.99 (2H, s),
20 1.92 (3H, s), 1.69-1.56 (12H, m).

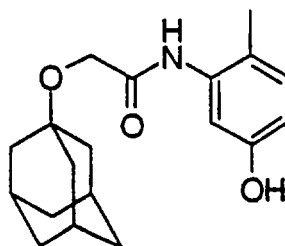
Example 54***N*-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide**

The title compound was prepared as in Example 46 from 2,4,5-trimethylaniline
 5 (0.30 g) and 1-adamantyloxyacetic acid (0.38 g, CA 1966, 65, 2149a) as a colourless solid
 (0.41 g).

Melting point: 138-140 °C

MS (APCI +ve) 328 (M+H)⁺

10 ¹H NMR (DMSO-d₆) δ 8.76 (1H, s), 7.42 (1H, s), 6.98 (1H, s), 4.00 (2H, s),
 2.2-2.1 (12H, m), 1.8-1.75 (6H, m), 1.65-1.55 (6H, m).

Example 55***N*-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide**

15

Thionyl chloride (5 ml) was added to 1-adamantyloxyacetic acid (2.00 g, CA 1966, 65,
 2149a) and the reaction heated at reflux for 5 minutes. The excess thionyl chloride was
 removed by concentration under reduced pressure and the residue was then dissolved in
 dichloromethane (10 ml). This solution was then added over 5 minutes to a solution of
 20 2-methyl-5-hydroxyaniline hydrochloride (1.00 g *J.Chem.Soc. Perkin Trans. 2*, 1972, 539)
 in dichloromethane (20 ml) and triethylamine (10 ml) at 0 °C. The solution was then
 allowed to warm to room temperature and, after 30 minutes stirring, was concentrated

tert-butyl *N*-(2-hydroxyethyl)-*N*-methylcarbamate (1.04 g) and tributylphosphine (1.35 ml) were added and the solution recooled in ice/water before addition of 1,1'-(azodicarbonyl)dipiperidine (1.39 g) and stir in ice/water for 10 minutes then at room temperature overnight. The reaction mixture was diluted with iso-hexane (50 ml) and filtered. The residue was washed with ether (100 ml) and the combined organics concentrated under reduced pressure. The residue was purified by column chromatography over silica eluting with iso-hexane : ethyl acetate (7:3) and further purified by column chromatography over silica eluting with dichloromethane : ethyl acetate (9:1) to give the coupled product (0.57 g) which was dissolved in methanol (10 ml). A solution of hydrogen chloride (generated by slow addition of acetyl chloride (10 ml) to methanol (15 ml) at 0°C **CARE - Very Exothermic**) was then added to the latter solution and the reaction stirred at room temperature for 2 hours. The reaction was then concentrated under reduced pressure and then triturated with ether (100 ml) give the title compound as colourless solid (0.35 g).

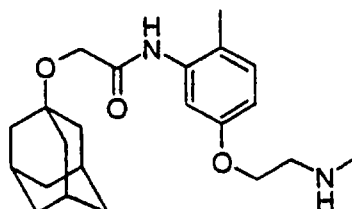
Melting point: 193-195 °C

MS (APCI +ve) 357 (M+H)⁺ as free base

¹H NMR (DMSO-d₆) δ 9.06 (1H, s), 8.91 (2H, bs), 7.19 (1H, 6), 7.12 (1H, d), 6.70 (1H, dd), 4.17 (2H, t), 3.4-3.25 (2H, m), 2.61 (3H, s), 2.15 (3H, s), 2.11 (2H, s), 1.95 (3H, s), 1.75-1.55 (12H, m).

Example 57

N-(5-(2-(*N*-Methylamino)ethoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide



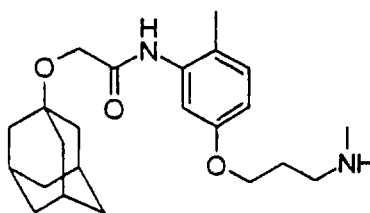
a) *N*-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide

Thionyl chloride (5 ml) was added to 1-adamantyloxyacetic acid (2.00 g, CA 1966, 65, 2149a) and the reaction heated at reflux for 5 minutes. The excess thionyl chloride was

^1H NMR (DMSO- d_6) δ 9.07 (2H, bs), 8.84 (1H, s), 7.57 (1H, d), 7.16 (1H, d), 6.71 (1H, dd), 4.20 (2H, t), 4.05 (2H, s), 3.30 (2H, t), 2.60 (3H, t), 2.17 (3H, s), 2.13 (3H, s), 1.78 (6H, d), 1.65-1.55 (6H, m).

5 **Example 58**

***N*-(5-(3-(*N*-Methylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide**



Prepared using the method described in Example 56 from *tert*-butyl *N*-(3-hydroxypropyl)-*N*-methylcarbamate (1.01 g, J. Org. Chem., 1988, 53(10), 2229) and *N*-(5-hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide (1.00 g, Example 55) to give the title compound as a colourless solid (0.50 g).

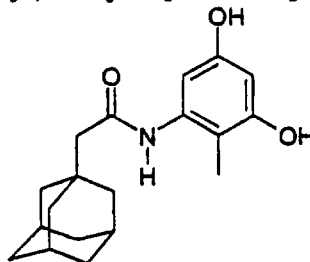
Melting point: 151-154 °C (dec.)

15 MS (APCI +ve) 387 (M-HCl+H)⁺

^1H NMR (DMSO- d_6) δ 8.91 (2H, bs), 8.82 (1H, s), 7.49 (1H, d), 7.13 (1H, d), 6.67 (1H, dd), 4.04 (2H, s), 4.01 (2H, t), 3.03 (2H, quintet), 2.55 (3H, t), 2.15 (3H, s), 2.13 (3H, s), 2.06 (2H, quintet), 1.78 (6H, d), 1.65-1.55 (6H, m).

20 **Example 59**

***N*-(3,5-Dihydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-acetamide**



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 necessary to reduce the bbATP agonist activity by 50%. Each of the compounds of

5 Examples 1 to 59 demonstrated antagonist activity, having a pIC₅₀ figure > 4.50.

group substituted by an amino, (di)C₁-C₆-alkylamino, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group;
or a pharmaceutically acceptable salt or solvate thereof.

- 5 2. A compound according to claim 1, wherein A represents a group CH₂.
3. A compound according to claim 1 or claim 2, wherein B represents a hydrogen atom.
4. A compound according to any one of claims 1 to 3, wherein D represents a group
10 CH₂, OCH₂ or NHCH₂.
5. A compound according to any one of claims 1 to 4, wherein R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl or thiophenyl group, each of which may be optionally substituted by one, two or three substituents independently selected from a
15 halogen atom or a hydroxyl, nitro or C₁-C₄-alkoxycarbonyl group, or a C₁-C₄-alkyl or C₁-C₄-alkoxy group optionally substituted by one or two substituents independently selected from a halogen atom or an amino, carboxyl, hydroxyl, C₁-C₄-alkoxy, (di)C₁-C₄-alkylamino, C₁-C₄-alkoxycarbonyl, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group.
- 20 6. A compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, being:
N-(2-Methyl-6-benzothiazolyl)-tricyclo[3.3.1.^{1,3,7}]decane-1-acetamide,
N-(3-(3-(Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.^{1,3,7}]decane-1-acetamide,
25 hydrochloride,
N-(2-Chlorophenyl)-tricyclo[3.3.1.^{1,3,7}]decane-1-acetamide,
N-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.^{1,3,7}]decane-1-acetamide,
N-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.^{1,3,7}]decane-1-acetamide,
N-(2,3-Dimethylphenyl)-tricyclo[3.3.1.^{1,3,7}]decane-1-acetamide,
30 N-(5-Indolyl)-tricyclo[3.3.1.^{1,3,7}]decane-1-acetamide,

- N*-(2-Methyl-3-(2-(1-morpholino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- N*-(2-Methyl-3-(2-(1-piperidino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- 5 *N*-(2-Methyl-5-(1-morpholinomethyl)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- N*-(5-(3-(2-*N,N*-dimethylaminoethyl)indolyl))-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- Methyl 4-methyl-3-[[1-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]thiophene-2-
- 10 carboxylate,
- N*-(3-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(2-Methyl-3-(2-(1-imidazolo)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(2,4,6-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(5-(3-Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- 15 hydrochloride,
- N*-(5-(3-(*N*-Methylamino)propoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- N*6-(Tricyclo[3.3.1.1^{3,7}]decane-1-acetyl)adenine,
- N*-(3,5-Dimethoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- 20 *N*-(3-(3-(*N*-Methylamino)propoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- N*-(5-(3-(*N,N*-Dimethylamino)propoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- N*-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
- 25 *N*-(5-Methoxy-2-methylphenyl)-(3-bromo-tricyclo[3.3.1.1^{3,7}]decane)-1-acetamide,
- N*-(5-Methoxy-2-methylphenyl)-(2-oxa-tricyclo[3.3.1.1^{3,7}]decane)-1-acetamide,
- N*-(5-Methoxy-2-methylphenyl)-2-(tricyclo[3.3.1.1^{3,7}]decan-1-amino)acetamide,
- N*-(3,5-Dimethoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decan-1-acetamide,
- N*-(3,5-Dihydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decan-1-acetamide,
- 30 *N*-(3,5-Dimethoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,

or solvate thereof, as defined in any one of claims 1 to 6 with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof,
5 as claimed in any one of claims 1 to 6 for use in therapy.

11. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof,
as claimed in any one of claims 1 to 6 for use in the treatment of rheumatoid arthritis.

10 12. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6 in the manufacture of a medicament for use in therapy.

13. A method of effecting immunosuppression which comprises administering to a
15 patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/02189

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07C 233/25, C07D 209/04, C07D 231/54, C07D 277/62, C07D 221/22,
A61K 31/16, A61K 31/40, A61K 31/415, A61K 31/425, A61K 31/445
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)

IPC6: C07C, C07D

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)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Journal of Medical Chemistry, Volume 15, No 11, 1972, V.L. Narayanan, "Adamantyl Analogs of 2'-(3-Dimethylaminopropylthio)cinnamanilide" page 1180 - page 1182 --	1-13
X	EP 0395093 A1 (KYOWA HAKKO KOGYO CO., LTD.), 31 October 1990 (31.10.90), compounds 109 and 128 --	1-10,12
X	STN International, File CAPLUS, CAPLUS accession no. 1975:592744, Document no. 83:192744, Kreutzberger, A. et al: "Antiviral agents. 4. Aromatically substituted carbonic acid amide structure in potentially virustatic compounds"; Arzneim.-Forsch. (1975), 25(7), 994-7 --	1-5,7-10,12

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents	"I" 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
A document defining the general state of the art which is not considered to be of particular relevance	"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
"I" earlier document but published on or after the international filing date	"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
"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date or another citation or other special reason (as specified)	"&" document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
"P" document published on or to the international filing date or later than the priority date claimed	

Date of the actual completion of the international search

24 March 1999

Date of mailing of the international search report

30 MAR 1999

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/02189

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 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.: 13
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 13 relates to a method of treatment of the human or animal body by surgery or by therapy (Rule 39.1(iv)). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.
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 II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional 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.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest

☐

No protest accompanied the payment of additional search fees

NOVEL COMPOUNDS

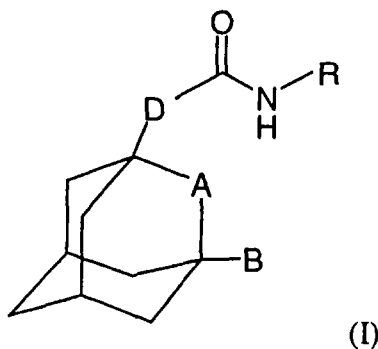
The present invention relates to adamantane derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

Adamantane derivatives are known in the art, e.g. from US-A-3,789,072 as serotonin inhibitors, from Chem. Abs. (1974), Vol. 80, No.5 (26871m) as inflammation and edema inhibitors or analgesics, from Chem. Abs. (1975), Vol. 82, No.1 (3853j) and Chem. Abs. (1977), Vol. 86, No.17 (120855e) as antiviral agents, and also from Chem. Abs. (1968), Vol. 69, No.1 (2562h), Chem. Abs. (1975), Vol. 82, No.3 (16510v) and Tetrahedron (1988), 44, No. 23, 7234-7242.

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.

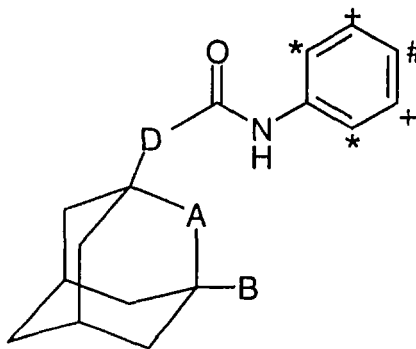
In accordance with the present invention, there is therefore provided a compound of general formula



- wherein A represents a group CH₂ or an oxygen atom; B represents a hydrogen or halogen atom (e.g. fluorine, chlorine, iodine and especially bromine);
- D represents a group CH₂, OCH₂, NHCH₂ or CH₂CH₂, in particular a group CH₂, OCH₂ or NHCH₂;
- 5 R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl, pyrimidinyl or thiophenyl group, each of which may be optionally substituted by one or more substituents independently selected from a halogen atom or a cyano, carboxyl, hydroxyl, nitro, halo-C₁-C₆-alkyl, -N(R¹)-C(=O)-R², -C(O)NR³R⁴, -NR⁵R⁶, C₃-C₈-cycloalkyl, 3- to 8-membered heterocyclyl, C₃-C₈-cycloalkyloxy, C₁-C₆-alkylcarbonyl, phenoxy,
- 10 benzyl, C₁-C₆-alkylthio, phenylthio, C₁-C₆-alkoxycarbonyl, C₁-C₆-alkylsulphinyl or C₁-C₆-alkylsulphonyl group, or a C₁-C₆-alkyl or C₁-C₆-alkoxy group optionally substituted by one or more substituents independently selected from a halogen atom or an amino, carboxyl, hydroxyl, C₁-C₆-alkoxy, (di)C₁-C₆-alkylamino, C₁-C₆-alkoxycarbonyl, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group;
- 15 R¹ represents a hydrogen atom or a C₁-C₆-alkyl or C₃-C₈-cycloalkyl group; R² represents a C₁-C₆-alkyl or C₃-C₈-cycloalkyl group; and R³, R⁴, R⁵ and R⁶ each independently represent a hydrogen atom or a C₁-C₆-alkyl or C₃-C₈-cycloalkyl group;
- with the provisos that
- 20 (i) when A is CH₂, B is H and D is CH₂, then R does not represent a phenyl, ortho-carboxyphenyl, ortho-nitrophenyl, ortho-aminophenyl, ortho-(dimethylaminoethyl)phenyl, methylphenyl or para-phenoxyphenyl group, and
- (ii) when A is CH₂, B is Br and D is CH₂, then R does not represent an ortho-carboxyphenyl group, and
- 25 (iii) when A is CH₂, B is H and D is CH₂CH₂, then R does not represent a phenyl group, and
- (iv) when A is CH₂, D is CH₂ or CH₂CH₂ and R represents a substituted phenyl group, the substituent or substituents present do not comprise, in an ortho position, a C₁-C₆-alkoxy group substituted by an amino, (di)C₁-C₆-alkylamino, imidazolyl,
- 30 morpholinyl, piperidinyl or pyrrolidinyl group;

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. When D represents a group OCH_2 or NHCH_2 , the group is orientated such that the oxygen or nitrogen atom is directly attached to the adamantyl group. A 3- to 8-membered heterocyclcyl 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 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":

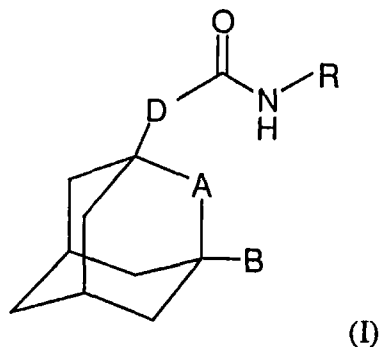


Similarly, meta and para positions in the phenyl group R are defined relative to the point of attachment of the amide linking group to R and are indicated in the above formula by the symbols + and # respectively.

Preferably, R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl, 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 a cyano, carboxyl, hydroxyl, nitro, halo- C_1 - C_6 -alkyl (e.g. trifluoromethyl), $-\text{N}(\text{R}^1)-\text{C}(=\text{O})-\text{R}^2$, $-\text{C}(\text{O})\text{NR}^3\text{R}^4$, $-\text{NR}^5\text{R}^6$, C_3 - C_8 -cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), 3- to 8-membered heterocyclcyl (e.g.

CLAIMS

1. A compound of general formula



- 5 wherein A represents a group CH_2 or an oxygen atom;
 B represents a hydrogen or halogen atom;
 D represents a group CH_2 , OCH_2 , NHCH_2 or CH_2CH_2 ;
 R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl, pyrimidinyl or
 thiophenyl group, each of which may be optionally substituted by one or more substituents
 10 independently selected from a halogen atom or a cyano, carboxyl, hydroxyl, nitro,
 halo- C_1 - C_6 -alkyl, $-\text{N}(\text{R}^1)-\text{C}(=\text{O})-\text{R}^2$, $-\text{C}(\text{O})\text{NR}^3\text{R}^4$, $-\text{NR}^5\text{R}^6$, C_3 - C_8 -cycloalkyl,
 3- to 8-membered heterocyclyl, C_3 - C_8 -cycloalkyloxy, C_1 - C_6 -alkylcarbonyl, phenoxy,
 benzyl, C_1 - C_6 -alkylthio, phenylthio, C_1 - C_6 -alkoxycarbonyl, C_1 - C_6 -alkylsulphinyl or
 C_1 - C_6 -alkylsulphonyl group, or a C_1 - C_6 -alkyl or C_1 - C_6 -alkoxy group optionally
 15 substituted by one or more substituents independently selected from a halogen atom or an
 amino, carboxyl, hydroxyl, C_1 - C_6 -alkoxy, (di) C_1 - C_6 -alkylamino,
 C_1 - C_6 -alkoxycarbonyl, imidazolyl, morpholiny, piperidinyl or pyrrolidinyl group;
 R^1 represents a hydrogen atom or a C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl group;
 R^2 represents a C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl group; and
 20 R^3 , R^4 , R^5 and R^6 each independently represent a hydrogen atom or a C_1 - C_6 -alkyl or
 C_3 - C_8 -cycloalkyl group;
 with the provisos that
 (i) when A is CH_2 , B is H and D is CH_2 , then R does not represent a phenyl, ortho-
 carboxyphenyl, ortho-nitrophenyl, ortho-aminophenyl, ortho-
 25 (dimethylaminoethyl)phenyl, methylphenyl or para-phenoxyphenyl group, and

- (ii) when A is CH₂, B is Br and D is CH₂, then R does not represent an ortho-carboxyphenyl group, and
- (iii) when A is CH₂, B is H and D is CH₂CH₂, then R does not represent a phenyl group, and
- 5 (iv) when A is CH₂, D is CH₂ or CH₂CH₂ and R represents a substituted phenyl group, the substituent or substituents present do not comprise, in an ortho position, a C₁-C₆-alkoxy group substituted by an amino, (di)C₁-C₆-alkylamino, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group; or a pharmaceutically acceptable salt or solvate thereof.
- 10
2. A compound according to claim 1, wherein A represents a group CH₂.
3. A compound according to claim 1 or claim 2, wherein B represents a hydrogen atom.
- 15 4. A compound according to any one of claims 1 to 3, wherein D represents a group CH₂, OCH₂ or NHCH₂.
5. A compound according to any one of claims 1 to 4, wherein R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl or thiophenyl group, each of which may
- 20 be optionally substituted by one, two or three substituents independently selected from a halogen atom or a hydroxyl, nitro or C₁-C₄-alkoxycarbonyl group, or a C₁-C₄-alkyl or C₁-C₄-alkoxy group optionally substituted by one or two substituents independently selected from a halogen atom or an amino, carboxyl, hydroxyl, C₁-C₄-alkoxy, (di)C₁-C₄-alkylamino, C₁-C₄-alkoxycarbonyl, imidazolyl, morpholinyl, piperidinyl or
- 25 pyrrolidinyl group.
6. A compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, being:
- N*-(2-Methyl-6-benzothiazolyl)-tricyclo[3.3.1.^{3,7}]decane-1-acetamide,

- N*-(3-(3-(Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- N*-(2-Chlorophenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- 5 *N*-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(2,3-Dimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(5-Indolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(2,3-Dimethyl-5-indolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-[5-(3-*N,N*-Dimethylaminopropoxy)-2-methylphenyl]-tricyclo[3.3.1.1^{3,7}]decane-1-
- 10 acetamide, hydrochloride,
- N*-(5-Indazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(6-Indazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(1*H*-Indol-4-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- 15 4-Methyl-3-[[1-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]phenoxy-acetic acid, hydrochloride salt,
- N*-(1-Methyl-1*H*-indol-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(1-(*N,N*-Dimethylamino)ethyl-1*H*-indo-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- 5-[[1-Oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]-1*H*-indole-1-acetic acid,
- 20 1,1-dimethylethyl ester,
- N*-(3-(2-Chloropyridyl))-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(3-(*N,N*-Dimethylamino)methyl-1*H*-indo-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(4-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(2-Chloro-5-methoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- 25 *N*-(4-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(3-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(5-Methoxy-2-methyl-3-nitrophenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(5-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(3-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

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- N*-(2-Methyl-5-(1-pyrrolidinemethyl)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
- N*-(2-Chloro-5-hydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(2-Chloro-4-hydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- 5 *N*-(2-Methyl-3-(2-(1-pyrrolidino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
- N*-(5-Methoxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(2-Methyl-3-(2-(1-morpholino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
- 10 *N*-(2-Methyl-3-(2-(1-piperidino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
- N*-(2-Methyl-5-(1-morpholinomethyl)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
- N*-(5-(3-(2-*N,N*-dimethylaminoethyl)indolyl))-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
15 hydrochloride,
- Methyl 4-methyl-3-[[1-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]thiophene-2-
carboxylate,
- N*-(3-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(2-Methyl-3-(2-(1-imidazolo)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- 20 *N*-(2,4,6-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(5-(3-Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
- N*-(5-(3-(*N*-Methylamino)propoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-
acetamide, hydrochloride,
- 25 *N*6-(Tricyclo[3.3.1.1^{3,7}]decane-1-acetyl)adenine,
- N*-(3,5-Dimethoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(3-(3-(*N*-Methylamino)propoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-
acetamide, hydrochloride,
- N*-(5-(3-(*N,N*-Dimethylamino)propoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane 1
30 acetamide, hydrochloride,

AMENDED SHEET

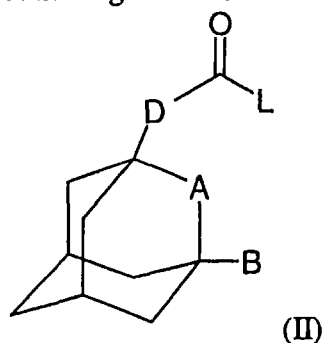
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- N*-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
N-(5-Methoxy-2-methylphenyl)-(3-bromo-tricyclo[3.3.1.1^{3,7}]decane)-1-acetamide,
N-(5-Methoxy-2-methylphenyl)-(2-oxa-tricyclo[3.3.1.1^{3,7}]decane)-1-acetamide,
N-(5-Methoxy-2-methylphenyl)-2-(tricyclo[3.3.1.1^{3,7}]decan-1-amino)acetamide,
 5 *N*-(3,5-Dimethoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decan-1-acetamide,
N-(3,5-Dihydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decan-1-acetamide,
N-(3,5-Dimethoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
N-(3,5-Bis-(3-aminopropoxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
 10 *N*-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
N-(5-(2-(*N*-Methylamino)ethyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-
 acetamide, hydrochloride,
N-(5-(2-(*N*-Methylamino)ethyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-
 acetamide,
 15 *N*-(5-(3-(*N*-Methylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-
 acetamide, or
N-(3,5-Dihydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-acetamide.

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



wherein L represents a leaving group and A, B and D are as defined in formula (I), with a
 compound of general formula (III), R-NH₂, wherein R is as defined in formula (I); and
 optionally forming a pharmaceutically acceptable salt or solvate thereof.

25

8. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.
- 5 9. A process for the preparation of a pharmaceutical composition as claimed in claim 8 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 6 with a pharmaceutically acceptable adjuvant, diluent or carrier.
- 10 10. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6 for use in therapy.
11. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6 for use in the treatment of rheumatoid arthritis.
- 15 12. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6 in the manufacture of a medicament for use in therapy.
- 20 13. A method of effecting immunosuppression which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 6.

REPLACEMENT SHEET

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wherein A represents a group CH_2 or an oxygen atom; B represents a hydrogen or halogen atom (e.g. fluorine, chlorine, iodine and especially bromine);

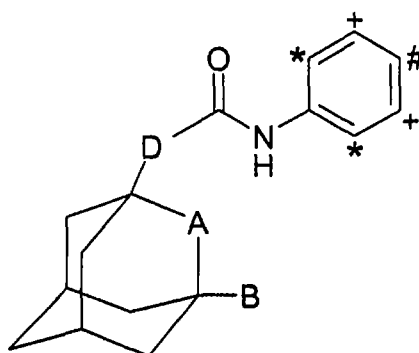
D represents a group CH_2 , OCH_2 , NHCH_2 or CH_2CH_2 , in particular a group CH_2 , OCH_2 or NHCH_2 ;

- 5 R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl, pyrimidinyl or thiophenyl group, each of which may be optionally substituted by one or more substituents independently selected from a halogen atom or a cyano, carboxyl, hydroxyl, nitro, halo- C_1 - C_6 -alkyl, $-\text{N}(\text{R}^1)-\text{C}(=\text{O})-\text{R}^2$, $-\text{C}(\text{O})\text{NR}^3\text{R}^4$, $-\text{NR}^5\text{R}^6$, C_3 - C_8 -cycloalkyl, 3- to 8-membered heterocyclyl, C_3 - C_8 -cycloalkyloxy, C_1 - C_6 -alkylcarbonyl, phenoxy,
- 10 benzyl, C_1 - C_6 -alkylthio, phenylthio, C_1 - C_6 -alkoxycarbonyl, C_1 - C_6 -alkylsulphinyl or C_1 - C_6 -alkylsulphonyl group, or a C_1 - C_6 -alkyl or C_1 - C_6 -alkoxy group optionally substituted by one or more substituents independently selected from a halogen atom or an amino, carboxyl, hydroxyl, C_1 - C_6 -alkoxy, (di) C_1 - C_6 -alkylamino, C_1 - C_6 -alkoxycarbonyl, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group;
- 15 R^1 represents a hydrogen atom or a C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl group; R^2 represents a C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl group; and R^3 , R^4 , R^5 and R^6 each independently represent a hydrogen atom or a C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl group;
- with the provisos that
- 20 (i) when A is CH_2 , B is H and D is CH_2 , then R does not represent a phenyl, ortho-carboxyphenyl, ortho-nitrophenyl, ortho-aminophenyl, ortho-(dimethylaminoethyl)phenyl, ortho-hydroxyphenol, ortho-(3-chloropropoxy)phenyl, methylphenyl or para-phenoxyphenyl group, and
- (ii) when A is CH_2 , B is Br and D is CH_2 , then R does not represent an ortho-carboxyphenyl group, and
- 25 (iii) when A is CH_2 , B is H and D is CH_2CH_2 , then R does not represent a phenyl group, and
- (iv) when A is CH_2 , D is CH_2 or CH_2CH_2 and R represents a substituted phenyl group, the substituent or substituents present do not comprise, in an ortho position, a
- 30 C_1 - C_6 -alkoxy group substituted by an amino, (di) C_1 - C_6 -alkylamino, imidazolyl,

morpholinyl, piperidinyl or pyrrolidinyl group;

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. When D represents a group OCH_2 or NHCH_2 , the group is orientated such that the oxygen or nitrogen atom is directly attached to the adamantyl group. 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 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":

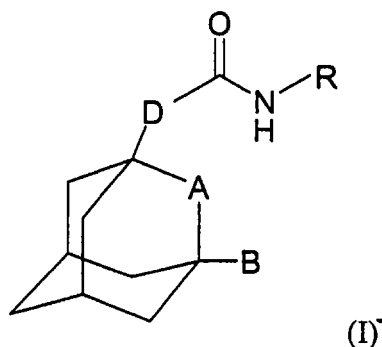


- Similarly, meta and para positions in the phenyl group R are defined relative to the point of attachment of the amide linking group to R and are indicated in the above formula by the symbols + and # respectively.

- Preferably, R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl, 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 a cyano, carboxyl, hydroxyl, nitro, halo- C_1 - C_6 -alkyl (e.g. trifluoromethyl), $-\text{N}(\text{R}^1)-\text{C}(=\text{O})-\text{R}^2$, $-\text{C}(\text{O})\text{NR}^3\text{R}^4$, $-\text{NR}^5\text{R}^6$, C_3 - C_8 -cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), 3- to 8-membered heterocyclyl (e.g.

CLAIMS

1. A compound of formula



wherein A represents a group CH_2 or an oxygen atom;

B represents a hydrogen or halogen atom;

5 D represents a group CH_2 , OCH_2 , NHCH_2 or CH_2CH_2 ;

R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl, pyrimidinyl or thiophenyl group, each of which may be optionally substituted by one or more substituents independently selected from a halogen atom or a cyano, carboxyl, hydroxyl, nitro, halo- $\text{C}_1\text{-C}_6\text{-alkyl}$, $-\text{N}(\text{R}^1)\text{-C(=O)-R}^2$, $-\text{C(O)NR}^3\text{R}^4$, $-\text{NR}^5\text{R}^6$, $\text{C}_3\text{-C}_8\text{-cycloalkyl}$,

10 3- to 8-membered heterocyclyl, $\text{C}_3\text{-C}_8\text{-cycloalkyloxy}$, $\text{C}_1\text{-C}_6\text{-alkylcarbonyl}$, phenoxy, benzyl, $\text{C}_1\text{-C}_6\text{-alkylthio}$, phenylthio, $\text{C}_1\text{-C}_6\text{-alkoxycarbonyl}$, $\text{C}_1\text{-C}_6\text{-alkylsulphinyl}$ or $\text{C}_1\text{-C}_6\text{-alkylsulphonyl}$ group, or a $\text{C}_1\text{-C}_6\text{-alkyl}$ or $\text{C}_1\text{-C}_6\text{-alkoxy}$ group optionally substituted by one or more substituents independently selected from a halogen atom or an amino, carboxyl, hydroxyl, $\text{C}_1\text{-C}_6\text{-alkoxy}$, (di) $\text{C}_1\text{-C}_6\text{-alkylamino}$,

15 $\text{C}_1\text{-C}_6\text{-alkoxycarbonyl}$, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group;

R^1 represents a hydrogen atom or a $\text{C}_1\text{-C}_6\text{-alkyl}$ or $\text{C}_3\text{-C}_8\text{-cycloalkyl}$ group;

R^2 represents a $\text{C}_1\text{-C}_6\text{-alkyl}$ or $\text{C}_3\text{-C}_8\text{-cycloalkyl}$ group; and

R^3 , R^4 , R^5 and R^6 each independently represent a hydrogen atom or a $\text{C}_1\text{-C}_6\text{-alkyl}$ or $\text{C}_3\text{-C}_8\text{-cycloalkyl}$ group;

20 with the provisos that

- (i) when A is CH₂, B is H and D is CH₂, then R does not represent a phenyl, ortho-carboxyphenyl, ortho-nitrophenyl, ortho-aminophenyl, ortho-(dimethylaminoethyl)phenyl, ortho-hydroxyphenyl, ortho-(3-chloropropoxy)phenyl, methylphenyl or para-phenoxyphenyl group, and
- 5 (ii) when A is CH₂, B is Br and D is CH₂, then R does not represent an ortho-carboxyphenyl group, and
- (iii) when A is CH₂, B is H and D is CH₂CH₂, then R does not represent a phenyl group, and
- (iv) when A is CH₂, D is CH₂ or CH₂CH₂ and R represents a substituted phenyl group,
- 10 the substituent or substituents present do not comprise, in an ortho position, a C₁-C₆-alkoxy group substituted by an amino, (di)C₁-C₆-alkylamino, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group;
- or a pharmaceutically acceptable salt or solvate thereof.
- 15 2. A compound according to claim 1, wherein
- A represents a group CH₂ or an oxygen atom;
- B represents a hydrogen or halogen atom;
- D represents a group CH₂, OCH₂, NHCH₂ or CH₂CH₂;
- R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl, pyrimidinyl or
- 20 thiophenyl group, each of which may be optionally substituted by one or more substituents independently selected from a halogen atom or a cyano, hydroxyl, nitro, halo-C₁-C₆-alkyl, -N(R¹)-C(=O)-R², -C(O)NR³R⁴, -NR⁵R⁶, C₃-C₈-cycloalkyl, 3- to 8-membered heterocyclyl, C₃-C₈-cycloalkyloxy, C₁-C₆-alkylcarbonyl, phenoxy, benzyl, C₁-C₆-alkylthio, phenylthio, C₁-C₆-alkoxycarbonyl, C₁-C₆-alkylsulphinyl or
- 25 C₁-C₆-alkylsulphonyl group, or a C₁-C₆-alkyl or C₁-C₆-alkoxy group optionally substituted by one or more substituents independently selected from a halogen atom or an amino, carboxyl, hydroxyl, C₁-C₆-alkoxy, C₁-C₆-alkoxycarbonyl, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group;
- R¹ represents a hydrogen atom or a C₁-C₆-alkyl or C₃-C₈-cycloalkyl group;
- 30 R² represents a C₁-C₆-alkyl or C₃-C₈-cycloalkyl group; and

R^3 , R^4 , R^5 and R^6 each independently represent a hydrogen atom or a C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl group;

with the provisos that

- (i) when A is CH_2 , B is H and D is CH_2 , then R does not represent a phenyl, ortho-nitrophenyl, ortho-aminophenyl, ortho-hydroxyphenyl, ortho-(3-chloropropoxy)phenyl, methylphenyl or para-phenoxyphenyl group, and
 - (ii) when A is CH_2 , B is H and D is CH_2CH_2 , then R does not represent a phenyl group, and
 - (iii) when A is CH_2 , D is CH_2 or CH_2CH_2 and R represents a substituted phenyl group, the substituent or substituents present do not comprise, in an ortho position, a C_1 - C_6 -alkoxy group substituted by an amino, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group.
3. A compound according to claim 1 or claim 2, wherein A represents a group CH_2 .
 4. A compound according to any one of claims 1 to 3, wherein B represents a hydrogen atom.
 5. A compound according to any one of claims 1 to 4, wherein D represents a group CH_2 , OCH_2 or $NHCH_2$.
 6. A compound according to claim 1, wherein R represents a phenyl, benzothiazolyl, indolyl, indazolyl, purinyl, pyridyl or thiophenyl group, each of which may be optionally substituted by one, two or three substituents independently selected from a halogen atom or a hydroxyl, nitro or C_1 - C_4 -alkoxycarbonyl group, or a C_1 - C_4 -alkyl or C_1 - C_4 -alkoxy group optionally substituted by one or two substituents independently selected from a halogen atom or an amino, carboxyl, hydroxyl, C_1 - C_4 -alkoxy, (di) C_1 - C_4 -alkylamino, C_1 - C_4 -alkoxycarbonyl, imidazolyl, morpholinyl, piperidinyl or pyrrolidinyl group.

7. A compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, being:
- N*-(2-Methyl-6-benzothiazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(3-(3-(Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
5 hydrochloride,
N-(2-Chlorophenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2,3-Dimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
10 *N*-(5-Indolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2,3-Dimethyl-5-indolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-[5-(3-*N,N*-Dimethylaminopropoxy)-2-methylphenyl]-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
N-(5-Indazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
15 *N*-(6-Indazolyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(1*H*-Indol-4-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
4-Methyl-3-[[1-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]phenoxy-acetic acid,
hydrochloride salt,
20 *N*-(1-Methyl-1*H*-indol-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(1-(*N,N*-Dimethylamino)ethyl-1*H*-indo-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
5-[[1-Oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]-1*H*-indole-1-acetic acid,
1,1-dimethylethyl ester,
N-(3-(2-Chloropyridyl))-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
25 *N*-(3-(*N,N*-Dimethylamino)methyl-1*H*-indo-5-yl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(4-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2-Chloro-5-methoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(4-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(3-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
30 *N*-(5-Methoxy-2-methyl-3-nitrophenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,

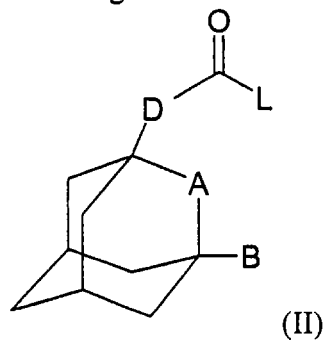
- N*-(5-Hydroxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(3-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2-Methyl-5-(1-pyrrolidinemethyl)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
- 5 *N*-(2-Chloro-5-hydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2-Chloro-4-hydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2-Methyl-3-(2-(1-pyrrolidino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
N-(5-Methoxymethyl-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- 10 *N*-(2-Methyl-3-(2-(1-morpholino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
N-(2-Methyl-3-(2-(1-piperidino)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
N-(2-Methyl-5-(1-morpholinomethyl)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- 15 hydrochloride,
N-(5-(3-(2-*N,N*-dimethylaminoethyl)indolyl))-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
Methyl 4-methyl-3-[[1-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]thiophene-2-
carboxylate,
- 20 *N*-(3-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2-Methyl-3-(2-(1-imidazolo)ethyloxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(2,4,6-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(5-(3-Aminopropoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
hydrochloride,
- 25 *N*-(5-(3-(*N*-Methylamino)propoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-
acetamide, hydrochloride,
*N*6-(Tricyclo[3.3.1.1^{3,7}]decane-1-acetyl)adenine,
N-(3,5-Dimethoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
N-(3-(3-(*N*-Methylamino)propoxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-
- 30 acetamide, hydrochloride,

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- N*-(5-(3-(*N,N*-Dimethylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- N*-(5-Methoxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
- N*-(5-Methoxy-2-methylphenyl)-(3-bromo-tricyclo[3.3.1.1^{3,7}]decane)-1-acetamide,
- 5 *N*-(5-Methoxy-2-methylphenyl)-(2-oxa-tricyclo[3.3.1.1^{3,7}]decane)-1-acetamide,
- N*-(5-Methoxy-2-methylphenyl)-2-(tricyclo[3.3.1.1^{3,7}]decan-1-amino)acetamide,
- N*-(3,5-Dimethoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decan-1-acetamide,
- N*-(3,5-Dihydroxyphenyl)-tricyclo[3.3.1.1^{3,7}]decan-1-acetamide,
- N*-(3,5-Dimethoxyphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
- 10 *N*-(3,5-Bis-(3-aminopropoxy)phenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide,
- N*-(2,4,5-Trimethylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
- N*-(5-Hydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
- N*-(5-(2-(*N*-Methylamino)ethyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride,
- 15 *N*-(5-(2-(*N*-Methylamino)ethyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide,
- N*-(5-(3-(*N*-Methylamino)propyloxy)-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decanyloxy-1-acetamide, or
- N*-(3,5-Dihydroxy-2-methylphenyl)-tricyclo[3.3.1.1^{3,7}]decane-acetamide.

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8. 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 L represents a leaving group and A, B and D are as defined in formula (I), with a compound of general formula (III), $R-NH_2$, wherein R is as defined in formula (I); and optionally forming a pharmaceutically acceptable salt or solvate thereof.

- 5 9. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.
- 10 10. A process for the preparation of a pharmaceutical composition as claimed in claim 9 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 7 with a pharmaceutically acceptable adjuvant, diluent or carrier.
- 15 11. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 for use in therapy.
12. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 for use in the treatment of rheumatoid arthritis.
- 20 13. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in treating rheumatoid arthritis.
- 25 14. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in treating irritable bowel disease.
- 30 15. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in treating atherosclerosis.

16. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in treating psoriasis.