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- (71) Applicant (for all designated States except US): **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): **BOUGHTON-SMITH, Nigel** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB).
- (74) Agent: **ASTRAZENECA**; Global Intellectual Property, S-151 85 Södertälje (SE).
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(54) Title: A PHARMACEUTICAL COMPOSITION CONTAINING A P2X<sub>7</sub> RECEPTOR ANTAGONIST AND METHOTREXATE

(57) Abstract: The invention provides a pharmaceutical composition, pharmaceutical product or kit comprising a first active ingredient which is a P2X<sub>7</sub> receptor antagonist and which P2X<sub>7</sub> receptor antagonist is an adamantyl derivative, and a second active ingredient which is *N*-[4-[[2,4-diamino-6-pteridiny]methyl]methylamino]benzoyl]-L-glutamic acid (methotrexate) or a pharmaceutically acceptable derivative thereof, for use in the treatment of inflammatory disorders.

WO 2004/105796 A1

## NEW COMBINATION

The present invention relates to combinations of pharmaceutically active substances for use in the treatment of inflammatory conditions/disorders, especially rheumatoid arthritis.

5

Chronic inflammatory disorders such as rheumatoid arthritis are polygenic, highly complex, and involve multiple inflammatory and immune mechanisms. Treatment of these disorders has been largely empirical with a variety of therapeutic agents being used with little understanding of the mechanisms involved. Recent research suggests that two  
10 inflammatory mediators, the cytokines IL-1 and TNF $\alpha$  (TNF $\alpha$ ), may play key roles in the inflammatory process in rheumatoid arthritis.

It would be desirable to develop new pharmaceuticals for use in treating inflammatory conditions/disorders.

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In accordance with the present invention, there is therefore provided a pharmaceutical composition comprising, in admixture, a first active ingredient which is a P2X<sub>7</sub> receptor antagonist and which P2X<sub>7</sub> receptor antagonist is an adamantyl derivative, and a second active ingredient which is *N*-[4-[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-  
20 L-glutamic acid (methotrexate) or a pharmaceutically acceptable derivative thereof.

25

The P2X<sub>7</sub> receptor (previously known as P2Z receptor) is a ligand-gated ion channel that 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 P2X<sub>7</sub> receptor by extracellular nucleotides, in particular adenosine triphosphate, is known to lead, amongst other things, to the release of interleukin-1 $\beta$  (IL-1 $\beta$ ).

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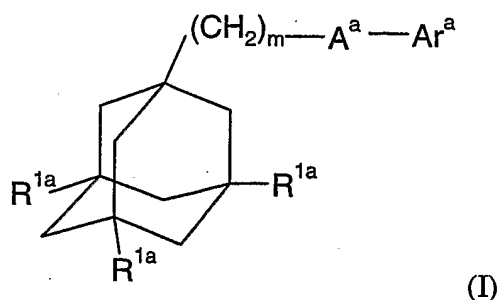
An antagonist of the P2X<sub>7</sub> receptor is a compound or other substance that is capable of preventing, whether fully or partially, activation of the P2X<sub>7</sub> receptor.

Methods for assaying for P2X<sub>7</sub> receptor antagonism are known in the art, for example from WO 01/42194 which describes an assay based on the observation that when the P2X<sub>7</sub> receptor is activated using a receptor agonist in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. Thus, an increase in fluorescence can be used as a measure of P2X<sub>7</sub> receptor activation and therefore to quantify the effect of a compound or substance on the P2X<sub>7</sub> receptor.

In WO 01/42194, the assay is carried out by taking a 96-well flat bottomed microtitre plate and filling the wells with 250 µl of test solution comprising 200 µl of a suspension of THP-1 cells ( $2.5 \times 10^6$  cells/ml) containing  $10^{-4}$  M ethidium bromide, 25 µl of a high potassium buffer solution containing  $10^{-5}$  M benzoylbenzoyl adenosine triphosphate (bbATP, a known P2X<sub>7</sub> receptor agonist), and 25 µl of the high potassium buffer solution containing  $3 \times 10^{-5}$  M test compound. The plate is covered with a plastics sheet and incubated at 37 °C for one hour. The plate is then read 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 P2X<sub>7</sub> receptor agonist) and pyridoxal 5-phosphate (a P2X<sub>7</sub> receptor antagonist) are used separately in the test as controls. From the readings obtained, a pIC<sub>50</sub> figure is calculated for the test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. A pIC<sub>50</sub> figure greater than 5.5 is normally indicative of an antagonist.

Examples of P2X<sub>7</sub> receptor antagonists which may be used in accordance with present invention include the compounds described in WO 00/61569, WO 01/42194, WO 01/44170 and WO 03/41707 the entire contents of which are incorporated herein by reference.

More specifically, in a first embodiment of the present invention the P2X<sub>7</sub> receptor antagonist is a compound of formula

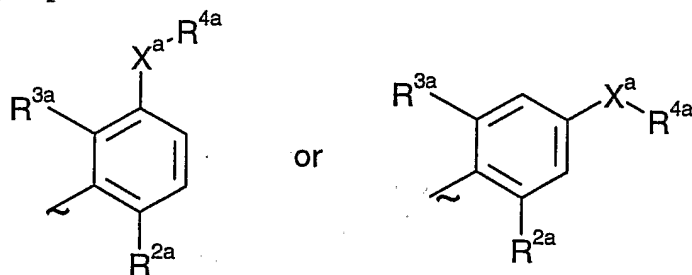


wherein m represents 1, 2 or 3;

each  $R^{1a}$  independently represents a hydrogen or halogen atom;

5  $A^a$  represents  $C(O)NH$  or  $NHC(O)$ ;

$Ar^a$  represents a group



$X^a$  represents a bond, an oxygen atom or a group  $CO$ ,  $(CH_2)_{1-6}$ ,  $CH=$ ,  $(CH_2)_{1-6}O$ ,

$O(CH_2)_{1-6}$ ,  $O(CH_2)_{2-6}O$ ,  $O(CH_2)_{2-3}O(CH_2)_{1-3}$ ,  $CR'(OH)$ ,  $(CH_2)_{1-3}O(CH_2)_{1-3}$ ,

10  $(CH_2)_{1-3}O(CH_2)_{2-3}O$ ,  $NR^{5a}$ ,  $(CH_2)_{1-6}NR^{5a}$ ,  $NR^{5a}(CH_2)_{1-6}$ ,  $(CH_2)_{1-3}NR^{5a}(CH_2)_{1-3}$ ,

$O(CH_2)_{2-6}NR^{5a}$ ,  $O(CH_2)_{2-3}NR^{5a}(CH_2)_{1-3}$ ,  $(CH_2)_{1-3}NR^{5a}(CH_2)_{2-3}O$ ,  $NR^{5a}(CH_2)_{2-6}O$ ,

$NR^{5a}(CH_2)_{2-3}O(CH_2)_{1-3}$ ,  $CONR^{5a}$ ,  $NR^{5a}CO$ ,  $S(O)_n$ ,  $S(O)_nCH_2$ ,  $CH_2S(O)_n$ ,

$SO_2NR^{5a}$  or  $NR^{5a}SO_2$ ;

n is 0, 1 or 2;

15  $R'$  represents a hydrogen atom or a  $C_1$ - $C_6$  alkyl group;

one of  $R^{2a}$  and  $R^{3a}$  represents a halogen, cyano, nitro, amino, hydroxyl, or a group

selected from (i)  $C_1$ - $C_6$  alkyl optionally substituted by at least one  $C_3$ - $C_6$  cycloalkyl,

(ii)  $C_3$ - $C_8$  cycloalkyl, (iii)  $C_1$ - $C_6$  alkyloxy optionally substituted by at least one

$C_3$ - $C_6$  cycloalkyl, and (iv)  $C_3$ - $C_8$  cycloalkyloxy, each of these groups being optionally

20 substituted by one or more fluorine atoms, and the other of  $R^{2a}$  and  $R^{3a}$  represents a

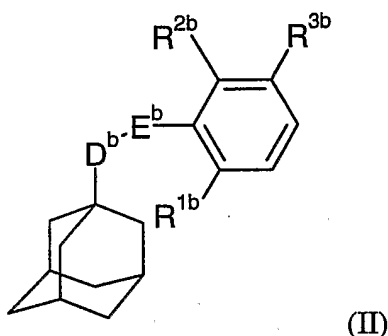
hydrogen or halogen atom;

- either  $R^{4a}$  represents a 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system containing one or two nitrogen atoms and optionally an oxygen atom, the heterocyclic ring system being optionally substituted by one or more substituents independently selected from fluorine atoms, hydroxyl, carboxyl, cyano,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  hydroxyalkyl,  $-NR^{6a}R^{7a}$ ,  $-(CH_2)_rNR^{6a}R^{7a}$  and  $-CONR^{6a}R^{7a}$ ,  
5 or  $R^{4a}$  represents a 3- to 8-membered saturated carbocyclic ring system substituted by one or more substituents independently selected from  $-NR^{6a}R^{7a}$ ,  $-(CH_2)_rNR^{6a}R^{7a}$  and  $-CONR^{6a}R^{7a}$ , the ring system being optionally further substituted by one or more substituents independently selected from fluorine atoms, hydroxyl and  $C_1$ - $C_6$  alkyl;
- 10  $r$  is 1, 2, 3, 4, 5 or 6;  
 $R^{5a}$  represents a hydrogen atom or a  $C_1$ - $C_6$  alkyl or  $C_3$ - $C_8$  cycloalkyl group;  
 $R^{6a}$  and  $R^{7a}$  each independently represent a hydrogen atom or a  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  hydroxyalkyl or  $C_3$ - $C_8$  cycloalkyl group, or  $R^{6a}$  and  $R^{7a}$  together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic  
15 ring;
- with the provisos that,
- (a) when  $A^a$  represents  $C(O)NH$  and  $R^{4a}$  represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then  $X^a$  is other than a bond, and  
20 (b) when  $A^a$  represents  $C(O)NH$  and  $X^a$  represents a group  $(CH_2)_{1-6}$  or  $O(CH_2)_{1-6}$ , then  $R^{4a}$  does not represent an unsubstituted imidazolyl, unsubstituted morpholinyl, unsubstituted piperidinyl or unsubstituted pyrrolidinyl group, and  
(c) when  $A^a$  represents  $NHC(O)$  and  $R^{4a}$  represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then  $X^a$  is other  
25 than a bond, and  
(d) when  $A^a$  represents  $NHC(O)$  and  $X^a$  represents  $O(CH_2)_{1-6}$ ,  $NH(CH_2)_{1-6}$  or  $SCH_2$ , then  $R^{4a}$  does not represent an unsubstituted 1-piperidinyl or unsubstituted 1-pyrrolidinyl group, and  
(e) when  $A^a$  represents  $NHC(O)$  and  $X^a$  represents  $O(CH_2)_{2-3}NH(CH_2)_2$ , then  $R^{4a}$  does  
30 not represent an imidazolyl group;

or a pharmaceutically acceptable salt or solvate thereof.

Compounds of formula (I) are described in WO 00/61569.

- 5 In a second embodiment of the present invention the P2X<sub>7</sub> receptor antagonist is a compound of formula

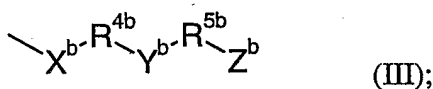


wherein D<sup>b</sup> represents CH<sub>2</sub> or CH<sub>2</sub>CH<sub>2</sub>;

10 E<sup>b</sup> represents C(O)NH or NHC(O);

R<sup>1b</sup> and R<sup>2b</sup> each independently represent a hydrogen or halogen atom, or an amino, nitro, C<sub>1</sub>-C<sub>6</sub> alkyl or trifluoromethyl group;

R<sup>3b</sup> represents a group of formula



15

X<sup>b</sup> represents an oxygen or sulphur atom or a group NH, SO or SO<sub>2</sub>;

Y<sup>b</sup> represents an oxygen or sulphur atom or a group NR<sup>11b</sup>, SO or SO<sub>2</sub>;

Z<sup>b</sup> represents a group -OH, -SH, -CO<sub>2</sub>H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylthio,

C<sub>1</sub>-C<sub>6</sub>-alkylsulphinyl, C<sub>1</sub>-C<sub>6</sub>-alkylsulphonyl, -NR<sup>6b</sup>R<sup>7b</sup>, -C(O)NR<sup>8b</sup>R<sup>9b</sup>, imidazolyl,

20 1-methylimidazolyl, -N(R<sup>10b</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylcarbonyloxy,

C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyloxy, -OC(O)NR<sup>12b</sup>R<sup>13b</sup>, -OCH<sub>2</sub>OC(O)R<sup>14b</sup>, -OCH<sub>2</sub>OC(O)OR<sup>15b</sup>

or -OC(O)OCH<sub>2</sub>OR<sup>16b</sup>;

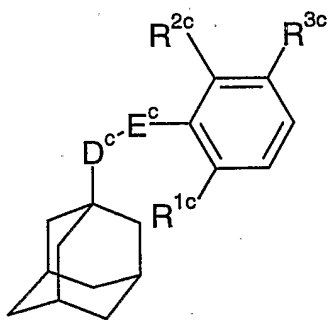
R<sup>4b</sup> represents a C<sub>2</sub>-C<sub>6</sub> alkyl group;

R<sup>5b</sup> represents a C<sub>1</sub>-C<sub>6</sub> alkyl group;

- $R^{6b}$ ,  $R^{7b}$ ,  $R^{8b}$ ,  $R^{9b}$ ,  $R^{10b}$ ,  $R^{12b}$  and  $R^{13b}$  each independently represent a hydrogen atom, or a C<sub>1</sub>-C<sub>6</sub> alkyl group optionally substituted by at least one hydroxyl group;
- $R^{11b}$  represents a hydrogen atom, or a C<sub>1</sub>-C<sub>6</sub> alkyl group optionally substituted by at least one substituent independently selected from hydroxyl and C<sub>1</sub>-C<sub>6</sub> alkoxy; and
- $R^{14b}$ ,  $R^{15b}$  and  $R^{16b}$  each independently represent a C<sub>1</sub>-C<sub>6</sub> alkyl group;
- with the provisos that (i) when  $E^b$  represents NHC(O),  $X^b$  represents O, S or NH and  $Y^b$  represents O, then  $Z^b$  represents  $-NR^{6b}R^{7b}$  where  $R^{6b}$  represents a hydrogen atom and  $R^{7b}$  represents either a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl group substituted by at least one hydroxyl group, and (ii) when  $E$  represents NHC(O),  $X^b$  represents O, S or NH,  $Y^b$  represents NH and  $R^{5b}$  represents CH<sub>2</sub>CH<sub>2</sub>, then  $Z^b$  is not -OH or imidazolyl;
- or a pharmaceutically acceptable salt or solvate thereof.

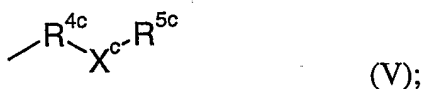
Compounds of formula (II) are described in WO 01/42194.

- In a third embodiment of the present invention the P2X<sub>7</sub> receptor antagonist is a compound of formula



(IV)

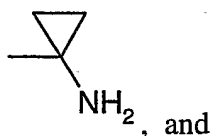
- wherein D<sup>c</sup> represents CH<sub>2</sub> or CH<sub>2</sub>CH<sub>2</sub>;
- E<sup>c</sup> represents C(O)NH or NHC(O);
- $R^{1c}$  and  $R^{2c}$  each independently represent hydrogen, halogen, amino, nitro, C<sub>1</sub>-C<sub>6</sub> alkyl or trifluoromethyl, but  $R^{1c}$  and  $R^{2c}$  may not both simultaneously represent hydrogen;
- $R^{3c}$  represents a group of formula



$\text{R}^{4c}$  represents a C<sub>1</sub>-C<sub>6</sub> alkyl group;

$\text{X}^c$  represents an oxygen or sulphur atom or a group  $\text{NR}^{13c}$ , SO or SO<sub>2</sub>;

5  $\text{R}^{5c}$  represents hydrogen, or  $\text{R}^{5c}$  represents C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>2</sub>-C<sub>6</sub> alkenyl, each of which may be optionally substituted by at least one substituent selected from halogen, hydroxyl, (di)-C<sub>1</sub>-C<sub>6</sub>-alkylamino,  $-\text{Y}^c-\text{R}^{6c}$ ,



a 5- or 6-membered heteroaromatic ring comprising from 1 to 4 heteroatoms independently  
10 selected from nitrogen, oxygen and sulphur which heteroaromatic ring may itself be optionally substituted by at least one substituent selected from halogen, hydroxyl and C<sub>1</sub>-C<sub>6</sub> alkyl;

$\text{Y}^c$  represents an oxygen or sulphur atom or a group NH, SO or SO<sub>2</sub>;

15  $\text{R}^{6c}$  represents a group  $-\text{R}^{7c}\text{Z}^c$  where  $\text{R}^{7c}$  represents a C<sub>2</sub>-C<sub>6</sub> alkyl group and  $\text{Z}^c$  represents an -OH, -CO<sub>2</sub>H,  $-\text{NR}^{8c}\text{R}^{9c}$ ,  $-\text{C}(\text{O})\text{NR}^{10c}\text{R}^{11c}$  or  $-\text{N}(\text{R}^{12c})\text{C}(\text{O})-\text{C}_1-\text{C}_6$  alkyl group, and, in the case where  $\text{Y}^c$  represents an oxygen or sulphur atom or a group NH,  $\text{R}^{6c}$  additionally represents hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl,  $-\text{C}(\text{O})\text{NR}^{14c}\text{R}^{15c}$ ,  $-\text{CH}_2\text{OC}(\text{O})\text{R}^{16c}$ ,  $-\text{CH}_2\text{OC}(\text{O})\text{OR}^{17c}$  or  $-\text{C}(\text{O})\text{OCH}_2\text{OR}^{18c}$ ;

20  $\text{R}^{8c}$ ,  $\text{R}^{9c}$ ,  $\text{R}^{10c}$ ,  $\text{R}^{11c}$  and  $\text{R}^{12c}$  each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl group;

$\text{R}^{13c}$  represents hydrogen, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkylmethyl, or  $\text{R}^{13c}$  represents a C<sub>1</sub>-C<sub>6</sub> alkyl group optionally substituted by at least one substituent selected from hydroxyl and C<sub>1</sub>-C<sub>6</sub> alkoxy; and

25  $\text{R}^{14c}$ ,  $\text{R}^{15c}$ ,  $\text{R}^{16c}$ ,  $\text{R}^{17c}$  and  $\text{R}^{18c}$  each independently represent a C<sub>1</sub>-C<sub>6</sub> alkyl group;

with the proviso that when  $\text{E}^c$  is C(O)NH,  $\text{X}^c$  is O, NH or N(C<sub>1</sub>-C<sub>6</sub> alkyl), then  $\text{R}^{5c}$  is other than a hydrogen atom or an unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl group;

or a pharmaceutically acceptable salt or solvate thereof.

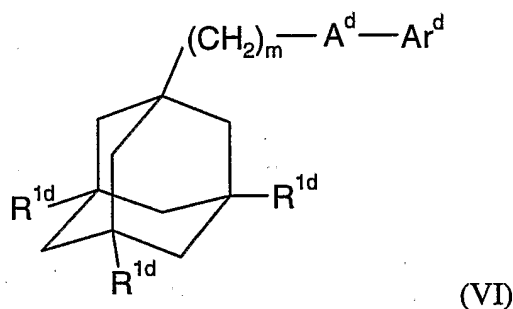
Preferred compounds of formula (IV) are those wherein  $R^{5c}$  represents an optionally substituted  $C_1$ - $C_6$  alkyl group, a preferred substituent being  $-Y^c-R^{6c}$ . When  $R^{5c}$  is substituted with a 5- or 6-membered heteroaromatic ring comprising from 1 to 4

5 heteroatoms, it is preferred that the number of heteroatoms in the ring is not greater than 2.

Compounds of formula (IV) are described in WO 01/44170.

In a fourth embodiment of the present invention the  $P2X_7$  receptor antagonist is a

10 compound of formula

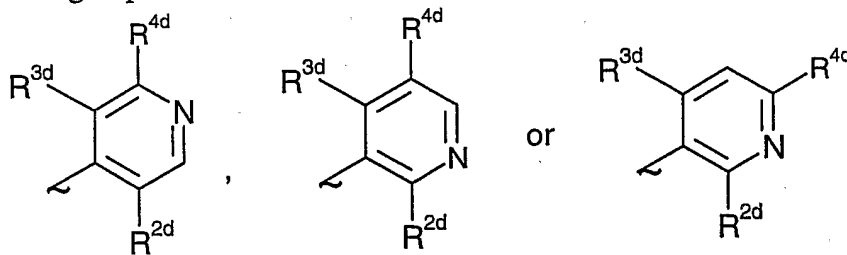


wherein  $m$  represents 1, 2 or 3;

each  $R^{1d}$  independently represents a hydrogen or halogen atom;

15  $A^d$  represents  $C(O)NH$  or  $NHC(O)$ ;

$Ar^d$  represents a group



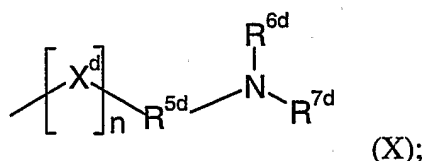
one of  $R^{2d}$  and  $R^{3d}$  represents halogen, nitro, amino, hydroxyl, or a group

20 selected from (i)  $C_1$ - $C_6$  alkyl optionally substituted by at least one halogen atom,

(ii)  $C_3$ - $C_8$  cycloalkyl, (iii)  $C_1$ - $C_6$  alkoxy optionally substituted by at least one halogen

atom, and (iv) C<sub>3</sub>-C<sub>8</sub> cycloalkyloxy, and the other of R<sup>2d</sup> and R<sup>3d</sup> represents a hydrogen or halogen atom;

R<sup>4d</sup> represents a group



5 X<sup>d</sup> represents an oxygen or sulphur atom or a group >N-R<sup>8d</sup>;

n is 0 or 1;

R<sup>5d</sup> represents a C<sub>1</sub>-C<sub>5</sub> alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C<sub>1</sub>-C<sub>6</sub> alkoxy;

10 R<sup>6d</sup> and R<sup>7d</sup> each independently represent a hydrogen atom, C<sub>1</sub>-C<sub>6</sub> alkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen, C<sub>1</sub>-C<sub>6</sub> alkoxy, and (di)-C<sub>1</sub>-C<sub>4</sub> alkylamino (itself optionally substituted by at least one hydroxyl group)), or C<sub>3</sub>-C<sub>8</sub> cycloalkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen and C<sub>1</sub>-C<sub>6</sub> alkoxy); and

15 R<sup>8d</sup> represents a hydrogen atom or a C<sub>1</sub>-C<sub>5</sub> alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C<sub>1</sub>-C<sub>6</sub> alkoxy; with the provisos that:

(a) when n is 0, then A<sup>d</sup> is NHC(O), and

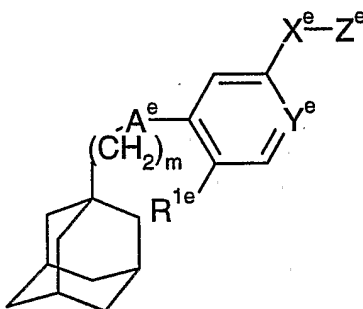
20 (b) when n is 1, X<sup>d</sup> represents oxygen and A<sup>d</sup> is C(O)NH, then R<sup>6d</sup> and R<sup>7d</sup> do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, or when one of R<sup>6d</sup> and R<sup>7d</sup> represents a hydrogen atom, then the other of R<sup>6d</sup> and R<sup>7d</sup> does not represent an unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl; and

25 (c) when n is 1, X<sup>d</sup> is oxygen, sulphur or >NH and A<sup>d</sup> is NHC(O), then R<sup>6d</sup> and R<sup>7d</sup> do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, or when one of R<sup>6d</sup> and R<sup>7d</sup> represents a hydrogen atom, then the other of R<sup>6d</sup> and R<sup>7d</sup> does not represent an unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl or -CH<sub>2</sub>CH<sub>2</sub>OH;

or a pharmaceutically acceptable salt or solvate thereof.

Compounds of formula (VI) are described in WO 03/41707.

In another aspect of the present invention the P2X<sub>7</sub> receptor antagonist is a compound of  
5 formula



(XI)

10 wherein  $m$  represents 1, 2 or 3;

$\text{A}^e$  represents  $\text{C}(\text{O})\text{NH}$  or  $\text{NHC}(\text{O})$ ;

$\text{Y}^e$  represents  $\text{N}$  or  $\text{CH}$ ;

$\text{X}^e$  represents a bond,  $\text{CO}$ ,  $(\text{CH}_2)_{1-6}$ ,  $\text{O}(\text{CH}_2)_{1-6}$ ,  $(\text{CH}_2)_{1-6}\text{NH}(\text{CH}_2)_{1-6}$ ,  $(\text{CH}_2)_{1-6}\text{O}(\text{CH}_2)_{1-6}$ ,  
 $\text{NH}(\text{CH}_2)_{1-6}$ ;

15  $\text{Z}^e$  represents  $\text{NR}^{2e}\text{R}^{3e}$ ;

$\text{R}^{1e}$  represents halogen, cyano, nitro, amino, hydroxyl,  $\text{C}_1\text{-C}_6$  alkyl or  $\text{C}_3\text{-C}_8$  cycloalkyl,  
which alkyl or cycloalkyl group can be optionally substituted by one or more  
fluorine atoms;

$\text{R}^{2e}$  and  $\text{R}^{3e}$  each independently represent a hydrogen atom,  $\text{C}_1\text{-C}_6$  alkyl or  $\text{C}_3\text{-C}_8$

20 cycloalkyl, which alkyl or cycloalkyl group can be optionally substituted by one or more  
groups selected from hydroxyl, halogen or  $\text{C}_1\text{-C}_6$  alkoxy,

or  $\text{R}^{2e}$  and  $\text{R}^{3e}$  together with the nitrogen atom to which they are attached form a 3- to 9-  
membered saturated mono- or bicyclic heterocyclic ring comprising from 1 to 2 nitrogen  
atoms and optionally an oxygen atom, which heterocyclic ring can be optionally

25 substituted by one or more groups selected from hydroxyl, halogen or  $\text{C}_1\text{-C}_6$  alkoxy;

or a pharmaceutically acceptable salt or solvate thereof.

Compounds of formula (XI) may be prepared by chemistry according or analogous to that described in the references cited herein above.

5

In a further aspect of the present invention the P2X<sub>7</sub> receptor antagonist is:-

2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-*N*-  
(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-benzamide,

10 2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-  
benzamide,

(*R*)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-*N*-  
(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-  
ylmethyl)-benzamide,

15 2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-  
ylmethyl)benzamide,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-  
ylmethyl)-benzamide,

20 2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-  
ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-  
ylmethyl)-benzamide,

2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-  
ylmethyl)-benzamide,

25 2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-  
(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-benzamide,

2-Chloro-5-piperazin-1-ylmethyl-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-*N*-(tricyclo[3.3.1.1]dec-1-

30 ylmethyl)-benzamide,

2-Chloro-5-(piperidin-4-ylsulfinyl)-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-benzamide,

5-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-4-pyridinecarboxamide,

2-Chloro-5-[3-[[*(1R)*]-2-hydroxy-1-methylethyl]amino]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-3-pyridinecarboxamide,

5-Chloro-2-[3-(ethylamino)propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-4-pyridinecarboxamide,

5-Chloro-2-[3-[(2-hydroxyethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-4-pyridinecarboxamide,

5-Chloro-2-[3-[[*(2S)*]-2-hydroxypropyl]amino]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-4-pyridinecarboxamide,

*N*-[2-Methyl-5-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-ylcarbonyl)phenyl]-tricyclo[3.3.1.1<sup>3,7</sup>]decane-1-acetamide,

or a pharmaceutically acceptable salt or solvate of any one thereof.

Pharmaceutically acceptable salts include, where applicable, acid addition salts derived from pharmaceutically acceptable inorganic and organic acids such as a chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salt; and salts prepared from pharmaceutically acceptable inorganic and organic bases. Salts derived from inorganic bases include aluminium, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and bismuth salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic bases include salts of primary, secondary and tertiary amines, cyclic amines like arginine, betaine, choline and the like. Examples of pharmaceutically acceptable solvates include hydrates.

Examples of P2X<sub>7</sub> receptor antagonists that may conveniently be used in the present invention include:-

2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-*N*-  
(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-benzamide, dihydrochloride

5 2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-  
benzamide, hydrochloride

(*R*)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-*N*-  
(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-benzamide, hydrochloride

10 2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-  
ylmethyl)-benzamide, acetate (1:1) salt

2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-  
ylmethyl)benzamide, hydrochloride

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-  
ylmethyl)-benzamide, hydrochloride

15 2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-  
ylmethyl)-benzamide, acetate (1:1) salt

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-  
ylmethyl)-benzamide

20 2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-  
ylmethyl)-benzamide, hydrochloride

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-  
(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-benzamide

2-Chloro-5-piperazin-1-ylmethyl-*N*-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,  
dihydrochloride

25 2-Chloro-5-(4-piperidinyl)oxy)-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-benzamide,  
hydrochloride

2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-*N*-(tricyclo[3.3.1.1]dec-1-  
ylmethyl)-benzamide, hydrochloride

2-Chloro-5-(piperidin-4-ylsulfinyl)-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-benzamide

5-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-4-pyridinecarboxamide,

2-Chloro-5-[3-[[*(1R)*]-2-hydroxy-1-methylethyl]amino]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-3-pyridinecarboxamide,

5-Chloro-2-[3-(ethylamino)propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-4-pyridinecarboxamide, hydrochloride

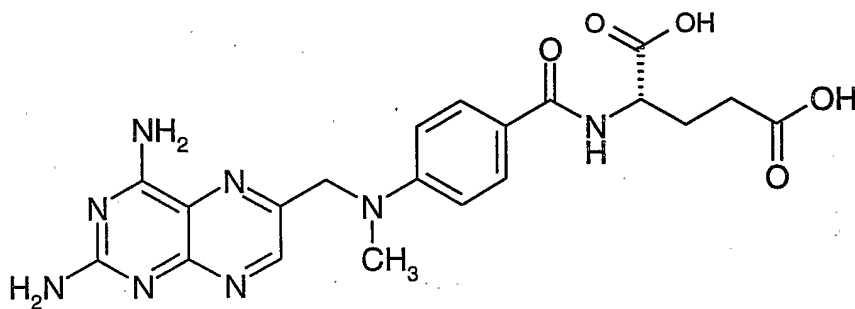
5-Chloro-2-[3-[(2-hydroxyethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-4-pyridinecarboxamide, hydrochloride

5-Chloro-2-[3-[[*(2S)*]-2-hydroxypropyl]amino]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-4-pyridinecarboxamide, dihydrochloride, and

*N*-[2-Methyl-5-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-ylcarbonyl)phenyl]-tricyclo[3.3.1.1<sup>3,7</sup>]decane-1-acetamide, hydrochloride.

*N*-[4-[[*(2,4-diamino-6-pteridinyl)*methyl]methylamino]benzoyl]-*L*-glutamic acid

(methotrexate) has the following chemical structure:



In the context of the present specification, unless otherwise stated, a pharmaceutically acceptable derivative of methotrexate means a pharmaceutically acceptable ester, salt or solvate of methotrexate or a pharmaceutically acceptable solvate of such an ester or salt.

Examples of suitable esters include lower alkyl (C<sub>1</sub>-C<sub>6</sub> alkyl) esters.

Pharmaceutically acceptable salts include acid addition salts derived from pharmaceutically acceptable inorganic and organic acids such as a chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salt; and salts prepared from pharmaceutically acceptable inorganic and organic bases. Salts derived from inorganic bases include aluminium, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and bismuth salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic bases include salts of primary, secondary and tertiary amines, cyclic amines like arginine, betaine, choline and the like.

Examples of pharmaceutically acceptable solvates include hydrates.

The preparation of methotrexate is described, for example, by Seeger *et al.*, *J. Am. Chem. Soc.*, 71, 1753 (1949). Pharmaceutically acceptable derivatives of methotrexate may be prepared by methods conventional in the art.

Presently available oral and intravenous formulations of methotrexate include "Rheumatrex" (trade mark) methotrexate dose pack (Lederle Laboratories, Wayne, New Jersey, USA); methotrexate tablets (Mylan Pharmaceuticals Inc., Morgantown, West Virginia, USA; Roxane Laboratories, Inc., Columbus, Ohio, USA); methotrexate sodium tablets for injection (Immunex Corporation, Seattle, Washington, USA); and "methotrexate LPF" (trade mark) sodium injection (Immunex Corporation, Seattle, Washington, USA). Methotrexate is also commercially available from Pharmacochemie (Netherlands).

The active ingredients used in the present invention may be capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric

and optical isomers of the active ingredients and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The invention also provides a pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a P2X<sub>7</sub> receptor antagonist and which P2X<sub>7</sub> receptor antagonist is an adamantyl derivative, and a preparation of a second active ingredient which is *N*-[4-[[2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid (methotrexate) or a pharmaceutically acceptable derivative thereof, for simultaneous, sequential or separate use in therapy.

In another aspect, the invention provides a kit comprising a preparation of a first active ingredient which is a P2X<sub>7</sub> receptor antagonist and which P2X<sub>7</sub> receptor antagonist is an adamantyl derivative, a preparation of a second active ingredient which is *N*-[4-[[2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid (methotrexate) or a pharmaceutically acceptable derivative thereof, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

It has been found that the choice of active ingredients according to the invention is advantageous because it results in a beneficial anti-inflammatory effect and, accordingly, can be used to treat various acute and chronic inflammatory conditions/disorders such as rheumatoid arthritis.

The pharmaceutical composition of the invention may be prepared by mixing the first active ingredient with the second active ingredient. Therefore, in a further aspect of the present invention, there is provided a process for the preparation of a pharmaceutical composition which comprises mixing a first active ingredient which is a P2X<sub>7</sub> receptor antagonist and which P2X<sub>7</sub> receptor antagonist is an adamantyl derivative, with a second active ingredient which is *N*-[4-[[2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid (methotrexate) or a pharmaceutically acceptable derivative thereof.

The first and second active ingredients may alternatively be administered simultaneously (other than in admixture as described above), sequentially or separately to treat inflammatory conditions. By sequential is meant that the first and second active ingredients are administered, in any order, one immediately after the other. They still have the desired effect if they are administered separately but less than about 4 hours apart, preferably less than about 2 hours apart, more preferably less than about 30 minutes apart.

The first and second active ingredients are conveniently administered by oral or parenteral (intraarticular or inhaled) administration using conventional systemic dosage forms, such as tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions and sterile injectable aqueous or oily solutions or suspensions. These dosage forms will usually include one or more pharmaceutically acceptable ingredients which may be selected, for example, from adjuvants, carriers, binders, lubricants, diluents, stabilising agents, buffering agents, emulsifying agents, viscosity-regulating agents, surfactants, preservatives, flavourings and colorants.

Oral administration is preferred.

For the above-mentioned therapeutic uses the dosages administered will, of course, vary with the first and second active ingredients employed, the mode of administration, the treatment desired and the condition or disorder indicated. However, in general, satisfactory results will be obtained when the total, combined, daily dosage of first and second active ingredients, when taken orally, is in the range from 10 to 2000 milligrammes (mg), particularly from 10, 20, 30, 40, 50, 100, 150, 200 or 300 to 1800, 1500, 1200, 1000, 800, 700, 600, 500 or 400 mg.

The pharmaceutical composition, pharmaceutical product or kit according to the invention may be administered as divided doses from 1 to 4 times a day, and preferably once or twice a day.

The present invention further provides the use of a pharmaceutical composition, pharmaceutical product or kit according to the invention in the manufacture of a medicament for the treatment of an inflammatory disorder.

5 Also, the present invention provides a method of treating an inflammatory disorder which comprises administering a therapeutically effective amount of a pharmaceutical composition of the invention to a patient in need thereof.

Still further, the present invention provides a method of treating an inflammatory disorder  
10 which comprises simultaneously, sequentially or separately administering:

(a) a (therapeutically effective) dose of a first active ingredient which is a P2X<sub>7</sub> receptor antagonist and which P2X<sub>7</sub> receptor antagonist is an adamantyl derivative; and

(b) a (therapeutically effective) dose of a second active ingredient which is *N*-[4-[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid (methotrexate) or a  
15 pharmaceutically acceptable derivative thereof,  
to a patient in need thereof.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and  
20 "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the condition or disorder in question. Persons at risk of developing a particular condition or  
25 disorder generally include those having a family history of the condition or disorder, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition or disorder.

The invention further relates to triple combination therapies for the treatment of any one of  
30 rheumatoid arthritis, osteoarthritis, osteoporosis, psoriasis, inflammatory bowel diseases,

COPD, asthma, allergic rhinitis or cancer or the neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease or stroke.

For the treatment of rheumatoid arthritis, the pharmaceutical composition of the invention  
5 may be combined with "biological agents" such as IL-1 receptor antagonists (e.g. Anakinra) and IL-1 trap, IL-18 receptor, anti-IL-6 Ab, anti-CD20 Ab, anti-IL-15 Ab and CTLA4Ig.

Suitable agents to be used in combination with the pharmaceutical composition of the  
10 invention include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin. Cyclo-oxygenase inhibiting nitric oxide donors (CINOD's) and "disease modifying agents" (DMARDs) such  
15 as cyclosporine A, leflunomide; ciclesonide; hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold may also be used.

The present invention still further relates to the combination of a pharmaceutical composition of the invention together with a leukotriene biosynthesis inhibitor, 5-  
20 lipooxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist selected from the group consisting of zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; N-(5-substituted)-thiophene-2-alkylsulfonamides; 2,6-di-tert-butylphenol hydrazones; methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; pyridinyl-substituted 2n cyanonaphthalene compounds such as L-  
25 739,010; 2-cyanoquinoline compounds such as L-746,530; indole and quinoline compounds such as MK-591, MK-886, and BAY x 1005.

The present invention still further relates to a pharmaceutical composition of the invention together with a receptor antagonist for leukotrienes LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub> selected  
30 from the group consisting of the phenothiazin-3-ones such as L-651,392; amidino

compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

5

The present invention still further relates to a pharmaceutical composition of the invention together with a PDE4 inhibitor including inhibitors of the isoform PDE4D.

10

The present invention still further relates to a pharmaceutical composition of the invention together with a antihistaminic H<sub>1</sub> receptor antagonists including cetirizine, loratadine, desloratadine, fexofenadine, astemizole, azelastine, and chlorpheniramine.

15

The present invention still further relates to a pharmaceutical composition of the invention together with a gastroprotective H<sub>2</sub> receptor antagonist or the proton pump inhibitors (such as omeprazole)

20

The present invention still further relates to a pharmaceutical composition of the invention together with an  $\alpha_1$ - and  $\alpha_2$ -adrenoceptor agonist vasoconstrictor sympathomimetic agent, including propylhexedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, and ethylnorepinephrine hydrochloride.

25

The present invention still further relates to a pharmaceutical composition of the invention together with anticholinergic agents including ipratropium bromide; tiotropium bromide; oxitropium bromide; pirenzepine; and telenzepine.

30

The present invention still further relates to a pharmaceutical composition of the invention together with methylxanthanines including theophylline and aminophylline; sodium cromoglycate; or muscarinic receptor (M1, M2, and M3) antagonist.

The present invention still further relates to a pharmaceutical composition of the invention together with a modulators of chemokine receptor function such as CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7; CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX<sub>3</sub>CR1 for the C-X<sub>3</sub>-C family.

The present invention still further relates to a pharmaceutical composition of the invention together with an insulin-like growth factor type I (IGF-1) mimetic.

The present invention still further relates to a pharmaceutical composition of the invention together with (a) tryptase inhibitors; (b) platelet activating factor (PAF) antagonists; (c) interleukin converting enzyme (ICE) inhibitors; (d) IMPDH inhibitors; (e) adhesion molecule inhibitors including VLA-4 antagonists; (f) cathepsins; (g) glucose-6 phosphate dehydrogenase inhibitors; (h) kinin-B<sub>1</sub> - and B<sub>2</sub> -receptor antagonists; (i) anti-gout agents, e.g., colchicine; (j) xanthine oxidase inhibitors, e.g., allopurinol; (k) uricosuric agents, e.g., probenecid, sulfinpyrazone, and benzbromarone; (l) growth hormone secretagogues; (m) transforming growth factor (TGFβ); (n) platelet-derived growth factor (PDGF); (o) fibroblast growth factor, e.g., basic fibroblast growth factor (bFGF); (p) granulocyte macrophage colony stimulating factor (GM-CSF); (q) capsaicin cream; (r) Tachykinin NK<sub>1</sub> and NK<sub>3</sub> receptor antagonists selected from the group consisting of NKP-608C; SB-233412 (talnetant); and D-4418; and (s) elastase inhibitors selected from the group consisting of UT-77 and ZD-0892 (t) induced nitric oxide synthase inhibitors (iNOS) or (u) chemoattractant receptor-homologous molecule expressed on TH2 cells, (CRTH2 antagonists).

The pharmaceutical composition of the invention may also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen,

fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, induced nitric oxide synthase inhibitors (iNOS inhibitors), and the cyclo-oxygenase inhibiting nitric oxide donors (CINOD's) analgesics (such as paracetamol and tramadol),  
5 cartilage sparing agents such as diacerein, doxycycline and glucosamine, and hyaluronic acids such as hyalgan and synvisc.

The pharmaceutical composition of the invention may also be used in combination with existing therapeutic agents for the treatment of inflammatory bowel diseases (Ulcerative  
10 colitis and Crohn's disease). Suitable agents to be used include 5-amino-salicylates, the thiopurines, azathioprine and 6-mecaptopurine.

The pharmaceutical composition of the invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin,  
15 daunomycin, cis-platinum, etoposide, taxol, taxotere and farnesyl transferase inhibitors, VegF inhibitors, and antimetabolites such as antineoplastic agents, especially antimitotic drugs including the vinca alkaloids such as vinblastine and vincristine.

The pharmaceutical composition of the invention may also be used in combination with  
20 antiviral agents such as Viracept, AZT, aciclovir and famciclovir, and antiseptis compounds such as Valant.

The pharmaceutical composition of the invention may also be used in combination with calcium channel blockers, lipid lowering agents such fibrates, beta-blockers, Ace  
25 inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

The pharmaceutical composition of the invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline,  
30 comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA

antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti Alzheimer's drugs such as donepezil, tacrine, propentofylline or metryfonate.

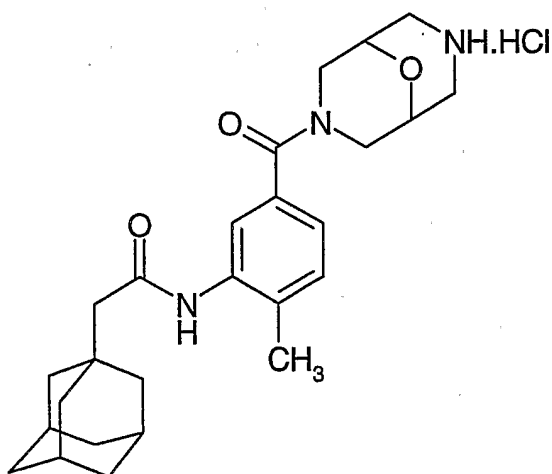
- 5 The pharmaceutical composition of the invention may also be used in combination with osteoporosis agents such as roloxifene, droloxifene, lasofoxifene or fosomax and immunosuppressant agents such as FK-506, rapamycin, cyclosporine, and azathioprine.

10

The present invention will now be further understood by reference to the following illustrative examples.

- 15 The following P2X<sub>7</sub> antagonists were employed in the examples:-

**1. N-[2-Methyl-5-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-ylcarbonyl)phenyl]-tricyclo[3.3.1.1<sup>3,7</sup>]decane-1-acetamide, hydrochloride**



20

P2X<sub>7</sub> antagonist **1**. (*N*-[2-Methyl-5-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-ylcarbonyl)phenyl]-tricyclo[3.3.1.1<sup>3,7</sup>]decane-1-acetamide, hydrochloride ) was prepared as follows.

5 **a) 3-(4-Methyl-3-nitrobenzoyl)-7-(phenylmethyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane**

Oxalyl chloride (9.6ml) in dichloromethane (30ml) was added dropwise over 45 minutes to an ice-cooled solution of 4-methyl-3-nitro-benzoic acid (10.0g) in dichloromethane (320ml) containing DMF (0.1ml). The reaction mixture was stirred at room temperature for 10 1 hour then concentrated *in vacuo*. The acid chloride was taken into THF (320ml) and cooled in an ice-bath before adding *N,N*-diisopropylethylamine (38ml) then 3-(phenylmethyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane, dihydrochloride (16.0g) (prepared as described in WO 01/028992) portionwise. The reaction was stirred for 18 hours then diluted with ethyl acetate (600ml) and washed with water (2x200ml) and saturated sodium 15 bicarbonate (aq) (3x150ml) then dried (MgSO<sub>4</sub>), filtered and concentrated to afford the sub-titled compound (18.5g).

$m/z = 382$

20 **b) 3-(3-Amino-4-methylbenzoyl)-7-(phenylmethyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane**

Reduced iron powder (7.9g) was added over 15 minutes to a stirred solution of the product of step a) (18.0g) and ammonium chloride (7.5g) in ethanol/water (3:1, 320ml) at 70°C. 25 The reaction mixture was heated at reflux for 2 hours then filtered and concentrated *in vacuo*. The residue was taken into ethyl acetate (400ml), washed with water (2x150ml) then the organic phase dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to afford the sub-title compound (14.5g).

30  $m/z = 352$

c) *N*-[2-Methyl-5-[[7-(phenylmethyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]carbonyl]phenyl]-tricyclo[3.3.1.1<sup>3,7</sup>]decane-1-acetamide

Prepared by the method of step a) using 1-adamantaneacetic acid and the product of step

5 b). Recrystallisation (ethyl acetate) afforded the sub-title compound.

*m/z* 528

d) *N*-[2-Methyl-5-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-ylcarbonyl)phenyl]-  
10 tricyclo[3.3.1.1<sup>3,7</sup>]decane-1-acetamide, hydrochloride

4M HCl in 1,4-dioxane (8ml) was added to a solution of the product of step c) (13.0g) in ethyl acetate (300ml). The resulting precipitate was isolated by filtration then suspended in ethanol (300ml) and 5% palladium on carbon (1.2g) added. The reaction mixture was  
15 stirred under 3 atmospheres pressure of hydrogen for 36 hours. Methanol was then added under an atmosphere of nitrogen, then the catalyst removed by filtration and the filtrate concentrated *in vacuo*. Recrystallisation (isopropanol: methanol 25:1, 800ml) gave the title compound (9.1g).

20 *m/z* 438 (M+H)<sup>+</sup>

$\delta_{\text{H}}$  (400MHz, *d*<sub>6</sub>-DMSO, Me<sub>4</sub>Si, 90°C) 9.06 (1H, s), 7.64 (1H, s), 7.25 (1H, m), 7.19 (1H, m), 4.15 (2H, s), 3.96 (2H, d, *J* 14Hz), 3.35-3.23 (6H, m), 2.26 (3H, s), 2.14 (2H, s), 1.96 (3H, br s), 1.69-1.62 (12H, m).

25

### Example 1

Pharmacological analysis to determine the effect of methotrexate / P2X<sub>7</sub> antagonist combinations (without addition of a P2X<sub>7</sub> agonist).

Human peripheral blood monocytes were prepared from the blood of healthy human volunteers collected in EDTA blood tubes. Monocytes were isolated by serial gradient centrifugation and washing to produce a pure population of cells. Lipopolysaccharide (LPS) was then added to the cell suspension in tissue culture and this was incubated for 4 - 12 hours at 37 degrees centigrade. Methotrexate and / or a P2X<sub>7</sub> antagonist or vehicle was then added to the cells. After incubation, samples of cell supernatants were transferred to a 96-well plate for subsequent cytokine and mediator measurements. The formation of inflammatory mediators was measured in the cell supernatants by specific ELISA assays for the cytokines IL-1, IL-18, TNF $\alpha$  and for other mediators including PGE<sub>2</sub>, NO and matrix metalloproteinases (MMPs). The levels of mediators released in the presence of a P2X<sub>7</sub> receptor antagonist alone, or in the presence of methotrexate alone, or in the presence of a combination of a P2X<sub>7</sub> receptor antagonist with methotrexate were determined. The effects of the antagonists / methotrexate alone and in combination were then compared. Statistically significant levels of inhibitory activity against a single mediator (IL-1 or TNF $\alpha$ ) or on multiple mediators by P2X<sub>7</sub> antagonist / methotrexate combinations, in comparison to that achieved by either a P2X<sub>7</sub> antagonist or methotrexate alone, is an indicator for increased efficacy in the treatment of disease.

### Example 2

**Pharmacological analysis to determine the effect of methotrexate / P2X<sub>7</sub> antagonist combinations (with addition of a P2X<sub>7</sub> agonist).**

Human peripheral blood monocytes were prepared from the blood of healthy human volunteers collected in EDTA blood tubes. Monocytes were isolated by serial gradient centrifugation and washing to produce a pure population of cells. Lipopolysaccharide (LPS) was then added to the cell suspension in tissue culture and this was incubated for 4 - 12 hours at 37 degrees centigrade. Test mixtures were then added followed by the addition of the P2X<sub>7</sub> receptor agonist BzATP. Test mixtures can comprise of vehicle as control, a P2X<sub>7</sub> receptor antagonist, or a combination of a P2X<sub>7</sub> receptor antagonist together with methotrexate. After incubation, samples of cell supernatants were

transferred to a 96-well plate for subsequent cytokine and mediator measurements. The formation of inflammatory mediators was measured in the cell supernatants by specific ELISA assays for the cytokines IL-1, IL-18, TNF $\alpha$  and for other mediators including PGE2, NO and matrix metalloproteinases (MMPs). The levels of mediators released in the presence of a P2X<sub>7</sub> receptor antagonist alone, or in the presence of a combination of a P2X<sub>7</sub> receptor antagonist with methotrexate were determined. The effects produced by a P2X<sub>7</sub> antagonist alone and in combination with methotrexate were then compared. Statistically significant levels of inhibitory activity against a single mediator (IL-1 or TNF $\alpha$ ) or on multiple mediators by P2X<sub>7</sub> antagonist / methotrexate combinations in comparison to that achieved by a P2X<sub>7</sub> antagonist alone is an indicator for increased efficacy in the treatment of disease.

### **Example 3**

**Assessment of anti-inflammatory activity of methotrexate / P2X<sub>7</sub> antagonist combinations in rat Streptococcal cell wall-induced arthritis.**<sup>1</sup>

Streptococcal cell wall (SCW)-induced arthritis was induced in the left ankle of female Lewis rats. Animals were sensitised by intra-articular injection of 5  $\mu$ g (in 20  $\mu$ L) SCW (Lee Laboratories) into the left ankle. Ankle swelling was assessed 3 days after injection and non-responders (animals with no apparent ankle swelling) were rejected. Responding animals were randomly allocated to the test groups.

Arthritis was induced 21 days after sensitisation by intravenous (iv) injection of SCW (100  $\mu$ g in 500  $\mu$ L saline). Animals were monitored and assessed on a daily basis through to termination 6 days after induction. The rats were housed on sawdust and provided with food and water *ad libitum*.

Oral dosing suspensions were in 1% (w/v) methylcellulose in deionised water and were freshly prepared on a daily basis. Compounds were administered by oral (4 mL/kg) prophylactic dosing, commencing 1 day prior to induction of arthritis through to

termination on day 6 post-induction. The P2X<sub>7</sub> antagonist **1**, was dosed at 30mg/kg (bid) and the Methotrexate dosed at 0.3 mg/kg (bid).

Ankle diameters were measured with vernier callipers on a daily basis from day -1.

5 Mechanical thresholds were assessed using von Frey filaments on days -1, 1, 3 and 5. The filaments were applied in increasing weights to the ankle region on the footpad of both feet. The first filament to induce a withdrawal response was considered to be the threshold.

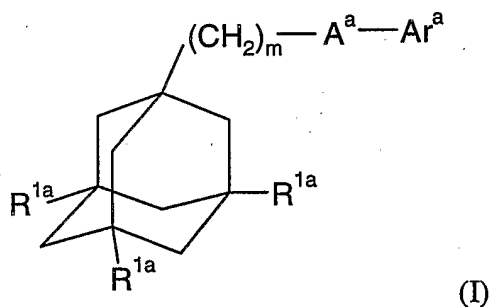
10 Effects on ankle swelling and mechanical threshold were calculated on an area under the curve (AUC) basis, as the sum of the differences from individual day -1 values. Data analysis was by one-way ANOVA followed by Dunnett's test (ankle diameter) or Dunn's test (von Frey threshold) on the raw data (GraphPad InStat).

15 The left hind limbs were taken and X-rays of the tibio-tarsal compartment examined and scored (blinded) for radiologically evident lesions. Tissues were then processed for histopathological assessment. Data analysis was by a non-parametric one-way analysis of variance (ANOVA), followed by Kruskal-Wallis post-test.

20 1. Experimental procedure based on that described by Carlson RP, Jacobsen PB; 'Comparison of adjuvant and streptococcal cell wall-induced arthritis in the rat' in Morgan DW, Marshall LA, editors; *In Vivo Models of Inflammation*. Basel: Birkhauser Verlag; 1999.

## CLAIMS

1. A pharmaceutical composition comprising, in admixture, a first active ingredient which is a P2X<sub>7</sub> receptor antagonist and which P2X<sub>7</sub> receptor antagonist is an adamantyl derivative, and a second active ingredient which is *N*-[4-[[2,4-diamino-6-pteridiny]methyl]methylamino]benzoyl]-L-glutamic acid or a pharmaceutically acceptable derivative thereof.
2. A composition according to claim 1, wherein the P2X<sub>7</sub> receptor antagonist is a compound of formula

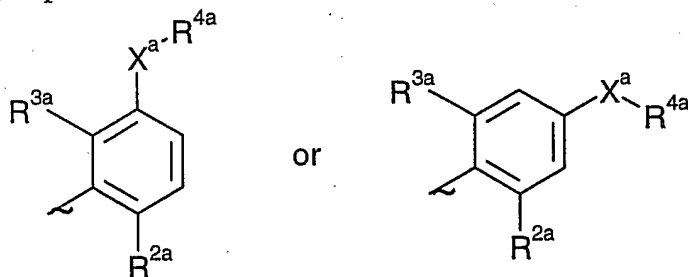


wherein *m* represents 1, 2 or 3;

each R<sup>1a</sup> independently represents a hydrogen or halogen atom;

A<sup>a</sup> represents C(O)NH or NHC(O);

Ar<sup>a</sup> represents a group



X<sup>a</sup> represents a bond, an oxygen atom or a group CO, (CH<sub>2</sub>)<sub>1-6</sub>, CH=, (CH<sub>2</sub>)<sub>1-6</sub>O, O(CH<sub>2</sub>)<sub>1-6</sub>, O(CH<sub>2</sub>)<sub>2-6</sub>O, O(CH<sub>2</sub>)<sub>2-3</sub>O(CH<sub>2</sub>)<sub>1-3</sub>, CR'(OH), (CH<sub>2</sub>)<sub>1-3</sub>O(CH<sub>2</sub>)<sub>1-3</sub>, (CH<sub>2</sub>)<sub>1-3</sub>O(CH<sub>2</sub>)<sub>2-3</sub>O, NR<sup>5a</sup>, (CH<sub>2</sub>)<sub>1-6</sub>NR<sup>5a</sup>, NR<sup>5a</sup>(CH<sub>2</sub>)<sub>1-6</sub>, (CH<sub>2</sub>)<sub>1-3</sub>NR<sup>5a</sup>(CH<sub>2</sub>)<sub>1-3</sub>,

$O(CH_2)_{2-6}NR^{5a}$ ,  $O(CH_2)_{2-3}NR^{5a}(CH_2)_{1-3}$ ,  $(CH_2)_{1-3}NR^{5a}(CH_2)_{2-3}O$ ,  $NR^{5a}(CH_2)_{2-6}O$ ,  
 $NR^{5a}(CH_2)_{2-3}O(CH_2)_{1-3}$ ,  $CONR^{5a}$ ,  $NR^{5a}CO$ ,  $S(O)_n$ ,  $S(O)_nCH_2$ ,  $CH_2S(O)_n$ ,  
 $SO_2NR^{5a}$  or  $NR^{5a}SO_2$ ;

n is 0, 1 or 2;

- 5 R' represents a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl group;  
 one of R<sup>2a</sup> and R<sup>3a</sup> represents a halogen, cyano, nitro, amino, hydroxyl, or a group  
 selected from (i) C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted by at least one C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  
 (ii) C<sub>3</sub>-C<sub>8</sub> cycloalkyl, (iii) C<sub>1</sub>-C<sub>6</sub> alkyloxy optionally substituted by at least one  
 C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and (iv) C<sub>3</sub>-C<sub>8</sub> cycloalkyloxy, each of these groups being optionally  
 10 substituted by one or more fluorine atoms, and the other of R<sup>2a</sup> and R<sup>3a</sup> represents a  
 hydrogen or halogen atom;  
 either R<sup>4a</sup> represents a 3- to 9-membered saturated or unsaturated aliphatic heterocyclic  
 ring system containing one or two nitrogen atoms and optionally an oxygen atom, the  
 heterocyclic ring system being optionally substituted by one or more substituents  
 15 independently selected from fluorine atoms, hydroxyl, carboxyl, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl,  
 C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl,  $-NR^{6a}R^{7a}$ ,  $-(CH_2)_rNR^{6a}R^{7a}$  and  $-CONR^{6a}R^{7a}$ ,  
 or R<sup>4a</sup> represents a 3- to 8-membered saturated carbocyclic ring system substituted by one  
 or more substituents independently selected from  $-NR^{6a}R^{7a}$ ,  $-(CH_2)_rNR^{6a}R^{7a}$  and  
 $-CONR^{6a}R^{7a}$ , the ring system being optionally further substituted by one or more  
 20 substituents independently selected from fluorine atoms, hydroxyl and C<sub>1</sub>-C<sub>6</sub> alkyl;  
 r is 1, 2, 3, 4, 5 or 6;

R<sup>5a</sup> represents a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>8</sub> cycloalkyl group;

R<sup>6a</sup> and R<sup>7a</sup> each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl,

C<sub>2</sub>-C<sub>6</sub> hydroxyalkyl or C<sub>3</sub>-C<sub>8</sub> cycloalkyl group, or R<sup>6a</sup> and R<sup>7a</sup> together with the

- 25 nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic  
 ring;

with the provisos that,

(a) when A<sup>a</sup> represents C(O)NH and R<sup>4a</sup> represents an unsubstituted 3- to 8-membered

saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X<sup>a</sup> is other

- 30 than a bond, and

(b) when  $A^a$  represents  $C(O)NH$  and  $X^a$  represents a group  $(CH_2)_{1-6}$  or  $O(CH_2)_{1-6}$ , then  $R^{4a}$  does not represent an unsubstituted imidazolyl, unsubstituted morpholinyl,

unsubstituted piperidinyl or unsubstituted pyrrolidinyl group, and

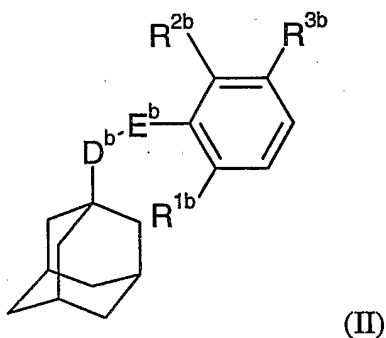
(c) when  $A^a$  represents  $NHC(O)$  and  $R^{4a}$  represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then  $X^a$  is other than a bond, and

(d) when  $A^a$  represents  $NHC(O)$  and  $X^a$  represents  $O(CH_2)_{1-6}$ ,  $NH(CH_2)_{1-6}$  or  $SCH_2$ , then  $R^{4a}$  does not represent an unsubstituted 1-piperidinyl or unsubstituted 1-pyrrolidinyl group, and

(e) when  $A^a$  represents  $NHC(O)$  and  $X^a$  represents  $O(CH_2)_{2-3}NH(CH_2)_2$ , then  $R^{4a}$  does not represent an imidazolyl group;

or a pharmaceutically acceptable salt or solvate thereof.

3. A composition according to claim 1, wherein the  $P2X_7$  receptor antagonist is a compound of formula

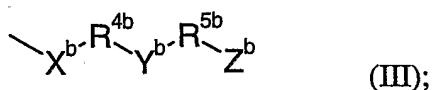


wherein  $D^b$  represents  $CH_2$  or  $CH_2CH_2$ ;

$E^b$  represents  $C(O)NH$  or  $NHC(O)$ ;

$R^{1b}$  and  $R^{2b}$  each independently represent a hydrogen or halogen atom, or an amino, nitro,  $C_1$ - $C_6$  alkyl or trifluoromethyl group;

$R^{3b}$  represents a group of formula



$X^b$  represents an oxygen or sulphur atom or a group NH, SO or SO<sub>2</sub>;

$Y^b$  represents an oxygen or sulphur atom or a group NR<sup>11b</sup>, SO or SO<sub>2</sub>;

$Z^b$  represents a group -OH, -SH, -CO<sub>2</sub>H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylthio,

5 C<sub>1</sub>-C<sub>6</sub>-alkylsulphinyl, C<sub>1</sub>-C<sub>6</sub>-alkylsulphonyl, -NR<sup>6b</sup>R<sup>7b</sup>, -C(O)NR<sup>8b</sup>R<sup>9b</sup>, imidazolyl, 1-methylimidazolyl, -N(R<sup>10b</sup>)C(O)-C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylcarboxyloxy,

C<sub>1</sub>-C<sub>6</sub> alkoxy-carboxyloxy, -OC(O)NR<sup>12b</sup>R<sup>13b</sup>, -OCH<sub>2</sub>OC(O)R<sup>14b</sup>, -OCH<sub>2</sub>OC(O)OR<sup>15b</sup> or -OC(O)OCH<sub>2</sub>OR<sup>16b</sup>;

R<sup>4b</sup> represents a C<sub>2</sub>-C<sub>6</sub> alkyl group;

10 R<sup>5b</sup> represents a C<sub>1</sub>-C<sub>6</sub> alkyl group;

R<sup>6b</sup>, R<sup>7b</sup>, R<sup>8b</sup>, R<sup>9b</sup>, R<sup>10b</sup>, R<sup>12b</sup> and R<sup>13b</sup> each independently represent a hydrogen atom, or a C<sub>1</sub>-C<sub>6</sub> alkyl group optionally substituted by at least one hydroxyl group;

R<sup>11b</sup> represents a hydrogen atom, or a C<sub>1</sub>-C<sub>6</sub> alkyl group optionally substituted by at least one substituent independently selected from hydroxyl and C<sub>1</sub>-C<sub>6</sub> alkoxy; and

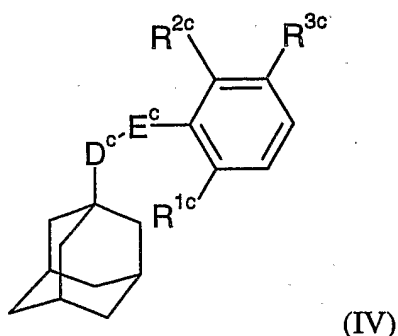
15 R<sup>14b</sup>, R<sup>15b</sup> and R<sup>16b</sup> each independently represent a C<sub>1</sub>-C<sub>6</sub> alkyl group;

with the provisos that (i) when E<sup>b</sup> represents NHC(O), X<sup>b</sup> represents O, S or NH and Y<sup>b</sup> represents O, then Z<sup>b</sup> represents -NR<sup>6b</sup>R<sup>7b</sup> where R<sup>6b</sup> represents a hydrogen atom and R<sup>7b</sup> represents either a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl group substituted by at least one hydroxyl group, and (ii) when E<sup>b</sup> represents NHC(O), X<sup>b</sup> represents O, S or NH, Y

20 represents NH and R<sup>5b</sup> represents CH<sub>2</sub>CH<sub>2</sub>, then Z<sup>b</sup> is not -OH or imidazolyl;

or a pharmaceutically acceptable salt or solvate thereof.

4. A composition according to claim 1, wherein the P2X<sub>7</sub> receptor antagonist is a compound of formula

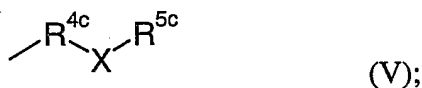


wherein  $D^c$  represents  $\text{CH}_2$  or  $\text{CH}_2\text{CH}_2$ ;

$E^c$  represents  $\text{C}(\text{O})\text{NH}$  or  $\text{NHC}(\text{O})$ ;

$R^{1c}$  and  $R^{2c}$  each independently represent hydrogen, halogen, amino, nitro,  $\text{C}_1$ - $\text{C}_6$  alkyl  
 5 or trifluoromethyl, but  $R^{1c}$  and  $R^{2c}$  may not both simultaneously represent hydrogen;

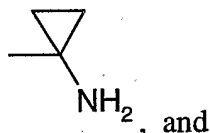
$R^{3c}$  represents a group of formula



$R^{4c}$  represents a  $\text{C}_1$ - $\text{C}_6$  alkyl group;

10  $X^c$  represents an oxygen or sulphur atom or a group  $\text{NR}^{13c}$ ,  $\text{SO}$  or  $\text{SO}_2$ ;

$R^{5c}$  represents hydrogen, or  $R^{5c}$  represents  $\text{C}_1$ - $\text{C}_6$  alkyl or  $\text{C}_2$ - $\text{C}_6$  alkenyl, each of which  
 may be optionally substituted by at least one substituent selected from halogen, hydroxyl,  
 (di)- $\text{C}_1$ - $\text{C}_6$ -alkylamino,  $-\text{Y}^c-\text{R}^{6c}$ ,



15 a 5- or 6-membered heteroaromatic ring comprising from 1 to 4 heteroatoms independently  
 selected from nitrogen, oxygen and sulphur which heteroaromatic ring may itself be  
 optionally substituted by at least one substituent selected from halogen, hydroxyl and  
 $\text{C}_1$ - $\text{C}_6$  alkyl;

$Y$  represents an oxygen or sulphur atom or a group  $\text{NH}$ ,  $\text{SO}$  or  $\text{SO}_2$ ;

20  $R^{6c}$  represents a group  $-\text{R}^{7c}\text{Z}^c$  where  $R^{7c}$  represents a  $\text{C}_2$ - $\text{C}_6$  alkyl group and  $Z^c$  represents  
 an  $-\text{OH}$ ,  $-\text{CO}_2\text{H}$ ,  $-\text{NR}^{8c}\text{R}^{9c}$ ,  $-\text{C}(\text{O})\text{NR}^{10c}\text{R}^{11c}$  or  $-\text{N}(\text{R}^{12c})\text{C}(\text{O})-\text{C}_1$ - $\text{C}_6$  alkyl group, and,  
 in the case where  $Y^c$  represents an oxygen or sulphur atom or a group  $\text{NH}$ ,  $R^{6c}$   
 additionally represents hydrogen,  $\text{C}_1$ - $\text{C}_6$  alkyl,  $\text{C}_1$ - $\text{C}_6$  alkylcarbonyl,  $\text{C}_1$ - $\text{C}_6$

alkoxycarbonyl,  $-C(O)NR^{14c}R^{15c}$ ,  $-CH_2OC(O)R^{16c}$ ,  $-CH_2OC(O)OR^{17c}$  or  $-C(O)OCH_2OR^{18c}$ ;

$R^{8c}$ ,  $R^{9c}$ ,  $R^{10c}$ ,  $R^{11c}$  and  $R^{12c}$  each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl group;

5  $R^{13c}$  represents hydrogen, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkylmethyl, or  $R^{13c}$  represents a C<sub>1</sub>-C<sub>6</sub> alkyl group optionally substituted by at least one substituent selected from hydroxyl and C<sub>1</sub>-C<sub>6</sub> alkoxy; and

$R^{14c}$ ,  $R^{15c}$ ,  $R^{16c}$ ,  $R^{17c}$  and  $R^{18c}$  each independently represent a C<sub>1</sub>-C<sub>6</sub> alkyl group;

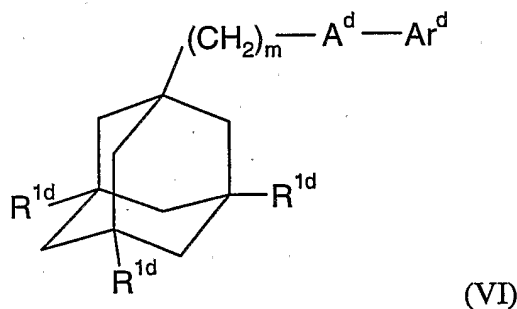
with the proviso that when E<sup>c</sup> is C(O)NH, X<sup>c</sup> is O, NH or N(C<sub>1</sub>-C<sub>6</sub> alkyl), then R<sup>5c</sup> is

10 other than a hydrogen atom or an unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl group;

or a pharmaceutically acceptable salt or solvate thereof.

5. A composition according to claim 1, wherein the P2X<sub>7</sub> receptor antagonist is a compound of formula

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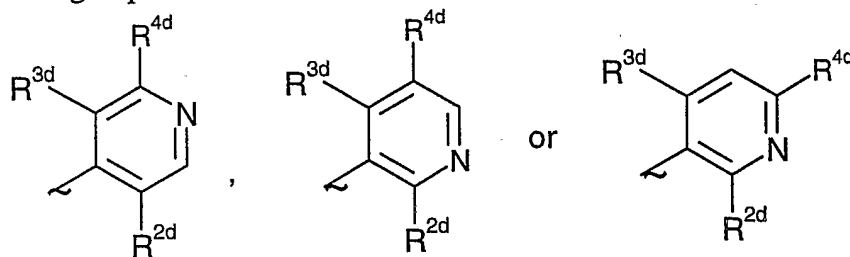


wherein m represents 1, 2 or 3;

each R<sup>1d</sup> independently represents a hydrogen or halogen atom;

20 A<sup>d</sup> represents C(O)NH or NHC(O);

Ar<sup>d</sup> represents a group



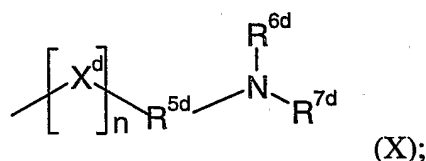
(VII)

(VIII)

(IX)

one of  $R^{2d}$  and  $R^{3d}$  represents halogen, nitro, amino, hydroxyl, or a group selected from (i)  $C_1$ - $C_6$  alkyl optionally substituted by at least one halogen atom, (ii)  $C_3$ - $C_8$  cycloalkyl, (iii)  $C_1$ - $C_6$  alkoxy optionally substituted by at least one halogen atom, and (iv)  $C_3$ - $C_8$  cycloalkyloxy, and the other of  $R^{2d}$  and  $R^{3d}$  represents a hydrogen or halogen atom;

$R^{4d}$  represents a group



$X^d$  represents an oxygen or sulphur atom or a group  $>N-R^{8d}$ ;

$n$  is 0 or 1;

$R^{5d}$  represents a  $C_1$ - $C_5$  alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and  $C_1$ - $C_6$  alkoxy;

$R^{6d}$  and  $R^{7d}$  each independently represent a hydrogen atom,  $C_1$ - $C_6$  alkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen,  $C_1$ - $C_6$  alkoxy, and (di)- $C_1$ - $C_4$  alkylamino (itself optionally substituted by at least one hydroxyl group)), or  $C_3$ - $C_8$  cycloalkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen and  $C_1$ - $C_6$  alkoxy); and

$R^{8d}$  represents a hydrogen atom or a  $C_1$ - $C_5$  alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and  $C_1$ - $C_6$  alkoxy;

with the provisos that:

(d) when  $n$  is 0, then  $A^d$  is  $NHC(O)$ , and

(e) when  $n$  is 1,  $X^d$  represents oxygen and  $A^d$  is  $C(O)NH$ , then  $R^{6d}$  and  $R^{7d}$  do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted  $C_1$ - $C_6$  alkyl, or when one of  $R^{6d}$  and  $R^{7d}$  represents a hydrogen atom, then the other of  $R^{6d}$  and  $R^{7d}$  does not represent an unsubstituted  $C_1$ - $C_6$  alkyl; and

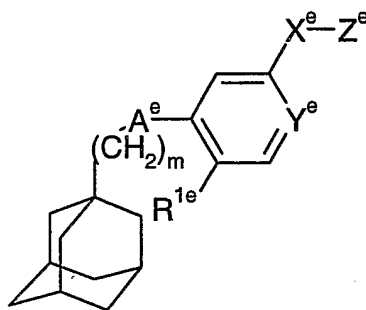
(f) when  $n$  is 1,  $X^d$  is oxygen, sulphur or  $>NH$  and  $A^d$  is  $NHC(O)$ , then  $R^{6d}$  and  $R^{7d}$  do not both simultaneously represent a hydrogen atom or do not both

simultaneously represent an unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, or when one of R<sup>6d</sup> and R<sup>7d</sup> represents a hydrogen atom, then the other of R<sup>6d</sup> and R<sup>7d</sup> does not represent an unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl or -CH<sub>2</sub>CH<sub>2</sub>OH;

or a pharmaceutically acceptable salt or solvate thereof.

5

6. A composition according to claim 1, wherein the P2X<sub>7</sub> receptor antagonist is a compound of formula



10

(XI)

wherein m represents 1, 2 or 3;

$\text{A}^e$  represents C(O)NH or NHC(O);

$\text{Y}^e$  represents N or CH;

15  $\text{X}^e$  represents a bond, CO,  $(\text{CH}_2)_{1-6}$ ,  $\text{O}(\text{CH}_2)_{1-6}$ ,  $(\text{CH}_2)_{1-6}\text{NH}(\text{CH}_2)_{1-6}$ ,  $(\text{CH}_2)_{1-6}\text{O}(\text{CH}_2)_{1-6}$ ,  $\text{NH}(\text{CH}_2)_{1-6}$ ;

$\text{Z}^e$  represents  $\text{NR}^{2e}\text{R}^{3e}$ ;

$\text{R}^{1e}$  represents halogen, cyano, nitro, amino, hydroxyl, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>8</sub> cycloalkyl, which alkyl or cycloalkyl group can be optionally substituted by one or more

20 fluorine atoms;

$\text{R}^{2e}$  and  $\text{R}^{3e}$  each independently represent a hydrogen atom, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>8</sub> cycloalkyl, which alkyl or cycloalkyl group can be optionally substituted by one or more groups selected from hydroxyl, halogen or C<sub>1</sub>-C<sub>6</sub> alkoxy,

or  $\text{R}^{2e}$  and  $\text{R}^{3e}$  together with the nitrogen atom to which they are attached form a 3- to 9-

25 membered saturated mono- or bicyclic heterocyclic ring comprising from 1 to 2 nitrogen

atoms and optionally an oxygen atom, which heterocyclic ring can be optionally substituted by one or more groups selected from hydroxyl, halogen or C<sub>1</sub>-C<sub>6</sub> alkoxy; or a pharmaceutically acceptable salt or solvate thereof.

5 7. A composition according to claim 1, wherein the P2X<sub>7</sub> receptor antagonist is:

2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-*N*-  
(tricyclo[3.3.1.1<sup>3,7</sup>]<sub>1</sub>dec-1-ylmethyl)-benzamide,

2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]<sub>1</sub>dec-1-ylmethyl)-  
benzamide,

10 (R)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-*N*-  
(tricyclo[3.3.1.1<sup>3,7</sup>]<sub>1</sub>dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]<sub>1</sub>dec-1-  
ylmethyl)-benzamide,

15 2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]<sub>1</sub>dec-1-  
ylmethyl)benzamide,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]<sub>1</sub>dec-1-  
ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]<sub>1</sub>dec-1-  
ylmethyl)-benzamide,

20 2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]<sub>1</sub>dec-1-  
ylmethyl)-benzamide,

2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]<sub>1</sub>dec-1-  
ylmethyl)-benzamide,

25 2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-  
(tricyclo[3.3.1.1<sup>3,7</sup>]<sub>1</sub>dec-1-ylmethyl)-benzamide,

2-Chloro-5-piperazin-1-ylmethyl-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]<sub>1</sub>dec-1-ylmethyl)-benzamide,

2-Chloro-5-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]<sub>1</sub>dec-1-ylmethyl)-benzamide,

2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]<sub>1</sub>dec-1-  
ylmethyl)-benzamide,

30 2-Chloro-5-(piperidin-4-ylsulfinyl)-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]<sub>1</sub>dec-1-ylmethyl)-benzamide,

5-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-4-pyridinecarboxamide,

2-Chloro-5-[3-[[*(1R)*]-2-hydroxy-1-methylethyl]amino]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-3-pyridinecarboxamide,

5 5-Chloro-2-[3-(ethylamino)propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-4-pyridinecarboxamide,

5-Chloro-2-[3-[(2-hydroxyethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-4-pyridinecarboxamide,

10 5-Chloro-2-[3-[[*(2S)*]-2-hydroxypropyl]amino]propyl]-*N*-(tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylmethyl)-4-pyridinecarboxamide,

*N*-[2-Methyl-5-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-ylcarbonyl)phenyl]-tricyclo[3.3.1.1<sup>3,7</sup>]decane-1-acetamide,

or a pharmaceutically acceptable salt or solvate of any one thereof.

15 8. A composition according to any one of claims 1 to 7, wherein the second active ingredient is *N*-[4-[[*(2,4*-diamino-6-pteridinyloxy)methyl]methylamino]benzoyl]-*L*-glutamic acid.

9. A composition according to any one of claims 1 to 8 which is formulated for oral  
20 administration.

10. A process for the preparation of a pharmaceutical composition as defined in any one of claims 1 to 8 which comprises mixing the first active ingredient with the second active ingredient.

25

11. Use of a composition according to any one of claims 1 to 8 in the manufacture of a medicament for the treatment of an inflammatory disorder.

12. Use according to claim 11, wherein the inflammatory disorder is rheumatoid arthritis.

30

13. A method of treating an inflammatory disorder which comprises administering a therapeutically effective amount of a pharmaceutical composition as defined in any one of claims 1 to 8 to a patient in need thereof.

5 14. A method according to claim 13, wherein the inflammatory disorder is rheumatoid arthritis.

15. A pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a P2X<sub>7</sub> receptor antagonist and which P2X<sub>7</sub> receptor antagonist is an adamantyl derivative, and a preparation of a second active ingredient which is *N*-[4-[[2,4-diamino-6-pteridiny]methyl]methylamino]benzoyl]-L-glutamic acid or a pharmaceutically acceptable derivative thereof, for simultaneous, sequential or separate use in therapy.

15 16. A kit comprising a preparation of a first active ingredient which is a P2X<sub>7</sub> receptor antagonist and which P2X<sub>7</sub> receptor antagonist is an adamantyl derivative, a preparation of a second active ingredient which is *N*-[4-[[2,4-diamino-6-pteridiny]methyl]methylamino]benzoyl]-L-glutamic acid or a pharmaceutically acceptable derivative thereof, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 45/06, A61K 31/485, A61K 31/519, A61P 29/00  
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)

IPC7: A61K, 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)

WPI DATA, CHEM.ABS.DATA, PAJ, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1310493 A1 (PFIZER PRODUCTS INC.), 14 May 2003 (14.05.2003) --	1-16
X	WO 03042191 A1 (PFIZER PRODUCTS INC.), 22 May 2003 (22.05.2003) --	1-16
A	WO 03041707 A1 (ASTRAZENECA AB), 22 May 2003 (22.05.2003) --	1-16
A	WO 0144170 A1 (ASTRAZENECA AB), 21 June 2001 (21.06.2001) --	1-16

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents:

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

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search  
17 Sept 2004

Date of mailing of the international search report  
17-09-2004

Name and mailing address of the ISA/  
Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM  
Facsimile No. +46 8 666 02 86

Authorized officer  
CAROLINA GÓMEZ LAGERLÖF/BS  
Telephone No. +46 8 782 25 00

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0142194 A1 (ASTRAZENECA AB), 14 June 2001 (14.06.2001)  --	1-16
A	WO 0061569 A1 (ASTRAZENECA AB), 19 October 2000 (19.10.2000)  -- -----	1-16

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE 2004/000815

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

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

1.  Claims Nos.: **13-14**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see extra sheet**
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1.  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.

## Box II.1

Claims 13-14 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

31/07/2004

International application No.

PCT/SE 2004/000815

EP	1310493	A1	14/05/2003	BR	0204588	A	16/09/2003
				CA	2411544	A	12/05/2003
				JP	2003183263	A	03/07/2003
				US	20030144293	A	31/07/2003
				WO	03042190	A	22/05/2003
-----							
WO	03042191	A1	22/05/2003	CA	2466724	A	22/05/2003
				US	20030186981	A	02/10/2003
-----							
WO	03041707	A1	22/05/2003	CA	2464863	A	22/05/2003
				SE	0103836	D	00/00/0000
-----							
WO	0144170	A1	21/06/2001	AT	261933	T	15/04/2004
				AU	2244401	A	25/06/2001
				BR	0016395	A	27/08/2002
				CA	2393352	A	21/06/2001
				CN	1434794	T	06/08/2003
				CZ	20022093	A	15/01/2003
				DE	60009147	D	00/00/0000
				DK	1242364	T	21/06/2004
				EE	200200330	A	15/10/2003
				EP	1242364	A,B	25/09/2002
				SE	1242364	T3	
				EP	1352895	A	15/10/2003
				EP	1352896	A	15/10/2003
				EP	1352897	A	15/10/2003
				GB	0015744	D	00/00/0000
				HU	0300616	A	28/07/2003
				IL	150124	D	00/00/0000
				JP	2003517035	T	20/05/2003
				NO	20022856	A	16/08/2002
				NZ	519378	A	27/02/2004
				PL	355913	A	31/05/2004
				SK	8412002	A	04/02/2003
				US	20030013704	A	16/01/2003
				GB	0017942	D	00/00/0000
				SE	9904651	D	00/00/0000
				ZA	200204125	A	25/08/2003

# INTERNATIONAL SEARCH REPORT

Information on patent family members

31/07/2004

International application No.

PCT/SE 2004/000815

WO	0142194	A1	14/06/2001	AT	263748	T	15/04/2004
				AU	2036301	A	18/06/2001
				BR	0016227	A	01/10/2002
				CA	2394236	A	14/06/2001
				CN	1407968	T	02/04/2003
				CZ	20021982	A	15/01/2003
				EE	200200295	A	15/08/2003
				EP	1240132	A,B	18/09/2002
				SE	1240132	T3	
				HU	0300618	A	28/07/2003
				IL	149762	D	00/00/0000
				JP	2003516382	T	13/05/2003
				NO	20022727	A	29/07/2002
				NZ	518985	A	27/02/2004
				SE	9904505	D	00/00/0000
				SK	7622002	A	09/01/2003
				US	6720452	B	13/04/2004
				US	20020193414	A	19/12/2002
				ZA	200203834	A	14/08/2003

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

31/07/2004

International application No.

PCT/SE 2004/000815

WO	0061569	A1	19/10/2000	AU	774526	B	01/07/2004
				AU	3994700	A	14/11/2000
				AU	5547000	A	02/01/2001
				BR	0009651	A	08/01/2002
				CA	2368829	A	19/10/2000
				CN	1353702	T	12/06/2002
				CZ	20013608	A	15/05/2002
				EE	200100525	A	16/12/2002
				EP	1171432	A	16/01/2002
				GB	0002330	D	00/00/0000
				HU	0202214	A	28/10/2002
				IL	145505	D	00/00/0000
				JP	2002541249	T	03/12/2002
				NO	20014894	A	10/12/2001
				NZ	514477	A	29/04/2003
				PL	350907	A	10/02/2003
				SK	13422001	A	09/05/2002
				TR	200102911	T	00/00/0000
				US	6492355	B	10/12/2002
				AP	200102041	D	00/00/0000
				AT	250036	T	15/10/2003
				AU	751103	B	08/08/2002
				AU	4950499	A	07/02/2000
				BR	9912109	A	02/05/2001
				CA	2336968	A	27/01/2000
				DE	69911415	D,T	08/07/2004
				DK	1095021	T	24/11/2003
				EE	200100010	A	17/06/2002
				EP	1095021	A,B	02/05/2001
				SE	1095021	T3	
				HK	1035715	A	00/00/0000
				HR	20010039	A	31/12/2001
				HU	0103224	A	28/01/2002
				IL	140346	D	00/00/0000
				JP	2002520395	T	09/07/2002
				NO	20010211	A	15/03/2001
				NZ	508923	A	27/09/2002
				PL	345388	A	17/12/2001
				SE	9901270	D	00/00/0000
				ZA	200108265	A	08/01/2003