A pharmaceutical composition comprising a $P2X_7$-receptor antagonist and a tumour necrosis factor α

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

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 inflammatory mediators, the cytokines IL-1 and TNFalpha (TNFα), 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.

In accordance with the present invention, there is provided a pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a $P2X_7$ receptor antagonist which $P2X_7$ receptor antagonist is an adamantyl derivative, and a preparation of a second active ingredient which is a tumour necrosis factor α (TNFα) inhibitor, 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 $P2X_7$ receptor antagonist which $P2X_7$ receptor antagonist is an adamantyl derivative, a preparation of a second active ingredient which is a tumour necrosis factor α (TNFα) inhibitor, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

The $P2X_7$ 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 $P2X_7$ receptor by extracellular nucleotides, in particular adenosine triphosphate, is known to lead, amongst other things, to the release of interleukin-1β (IL-1β).

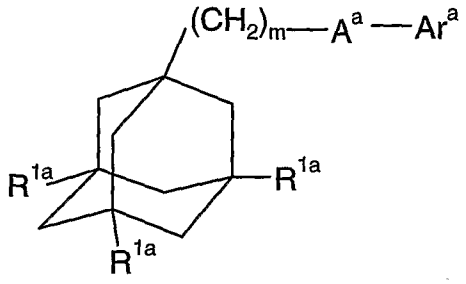
An antagonist of the $P2X_7$ receptor is a compound or other substance that is capable of preventing, whether fully or partially, activation of the $P2X_7$ receptor.

Methods for assaying for $P2X_7$ receptor antagonism are known in the art, for example from WO 01/42194 which describes an assay based on the observation that when the $P2X_7$ 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 $P2X_7$ receptor activation and therefore to quantify the effect of a compound or substance on the $P2X_7$ 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 (2.5×10^6 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 $P2X_7$ receptor agonist), and 25 µl of the high potassium buffer solution containing 3×10^{-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 $P2X_7$ receptor agonist) and pyridoxal 5-phosphate (a $P2X_7$ receptor antagonist) are used separately in the test as controls. From the readings obtained, a pIC_{50} 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_{50} figure greater than 5.5 is normally indicative of an antagonist.

Examples of $P2X_7$ 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 $P2X_7$ receptor antagonist is a compound of formula



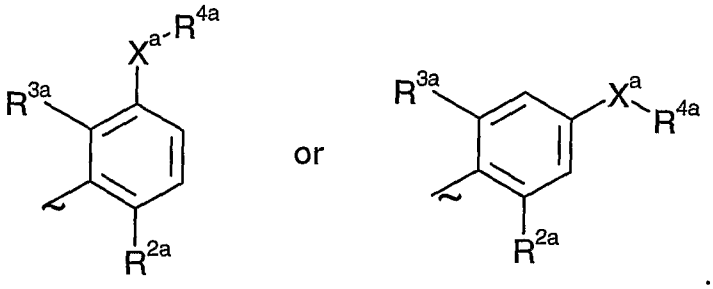
(I)

wherein m represents 1, 2 or 3;

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

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), $(CH_2)_{1-3}O(CH_2)_{1-3}$, $(CH_2)_{1-3}O(CH_2)_{2-3}O$, 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;

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 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 $-CONR^{6a}R^{7a}$,

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;

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 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

(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

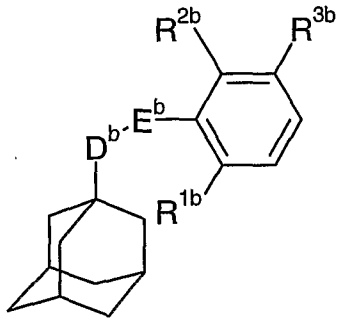
(d) when A^a represents NHC(O) and X^a represents $O(CH_2)_{1-6}$, $NH(CH_2)_{1-6}$ or SCH_2, then R^{4a} does not represent an unsubstituted 1-piperidinyl or unsubstituted 1-pyrrolidinyl group, and

(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.

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

In a second embodiment of the present invention the $P2X_7$ receptor antagonist is a compound of formula



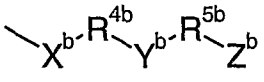
(II)

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



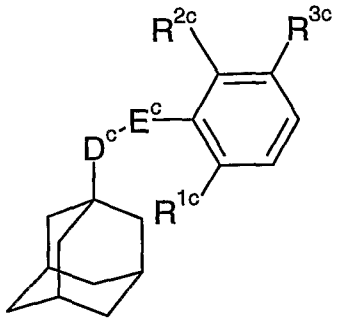
(III);

X^b represents an oxygen or sulphur atom or a group NH, SO or SO_2;

Y^b represents an oxygen or sulphur atom or a group NR^{11b}, SO or SO_2;
Z^b represents a group -OH, -SH, $-CO_2H$, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, $-NR^{6b}R^{7b}$, $-C(O)NR^{8b}R^{9b}$, imidazolyl, 1-methylimidazolyl, $-N(R^{10b})C(O)$-C_1-C_6 alkyl, C_1-C_6 alkylcarbonyloxy, C_1-C_6 alkoxycarbonyloxy, $-OC(O)NR^{12b}R^{13b}$, $-OCH_2OC(O)R^{14b}$, $-OCH_2OC(O)OR^{15b}$ or $-OC(O)OCH_2OR^{16b}$;
R^{4b} represents a C_2-C_6 alkyl group;
R^{5b} represents a C_1-C_6 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_1-C_6 alkyl group optionally substituted by at least one hydroxyl group;
R^{11b} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by at least one substituent independently selected from hydroxyl and C_1-C_6 alkoxy; and
R^{14b}, R^{15b} and R^{16b} each independently represent a C_1-C_6 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_1-C_6 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_2CH_2, 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 $P2X_7$ receptor antagonist is a compound of formula



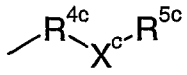
(IV)

wherein D^c represents CH_2 or CH_2CH_2;

E^c represents C(O)NH or NHC(O);

R^{1c} and R^{2c} each independently represent hydrogen, halogen, amino, nitro, C_1-C_6 alkyl or trifluoromethyl, but R^{1c} and R^{2c} may not both simultaneously represent hydrogen;

R^{3c} represents a group of formula

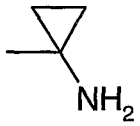


(V);

R^{4c} represents a C_1-C_6 alkyl group;

X^c represents an oxygen or sulphur atom or a group NR^{13c}, SO or SO_2;

R^{5c} represents hydrogen, or R^{5c} represents C_1-C_6 alkyl or C_2-C_6 alkenyl, each of which may be optionally substituted by at least one substituent selected from halogen, hydroxyl, (di)-C_1-C_6-alkylamino, $-Y^c-R^{6c}$,



, and

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 C_1-C_6 alkyl;

Y^c represents an oxygen or sulphur atom or a group NH, SO or SO_2;

R^{6c} represents a group $-R^{7c}Z^c$ where R^{7c} represents a C_2-C_6 alkyl group and Z^c represents an -OH, $-CO_2H$, $-NR^{8c}R^{9c}$, $-C(O)NR^{10c}R^{11c}$ or $-N(R^{12c})C(O)$-C_1-C_6 alkyl group, and, in the case where Y^c represents an oxygen or sulphur atom or a group NH, R^{6c} additionally represents hydrogen, C_1-C_6 alkyl, C_1-C_6 alkylcarbonyl, C_1-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_1-C_6 alkyl group;

R^{13c} represents hydrogen, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkylmethyl, or R^{13c} represents a C_1-C_6 alkyl group optionally substituted by at least one substituent selected from hydroxyl and C_1-C_6 alkoxy; and

R^{14c}, R^{15c}, R^{16c}, R^{17c} and R^{18c} each independently represent a C_1-C_6 alkyl group;

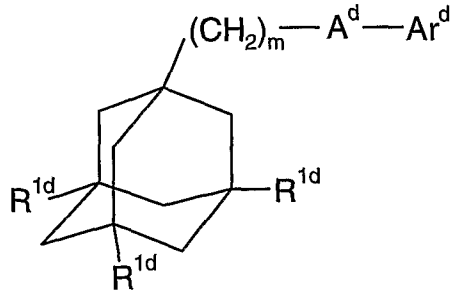
with the proviso that when E^c is C(O)NH, X^c is O, NH or N(C_1-C_6 alkyl), then R^{5c} is other than a hydrogen atom or an unsubstituted C_1-C_6 alkyl group;

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-memberered heteroaromatic ring comprising from 1 to 4 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 compound of formula



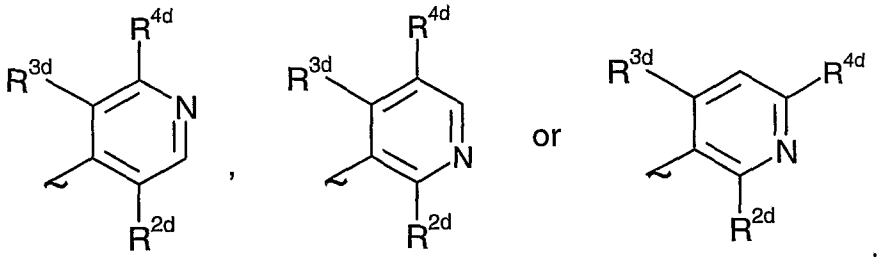
(VI)

wherein m represents 1, 2 or 3;

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

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

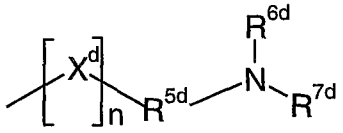
Ar^d represents a group



(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);

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:

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

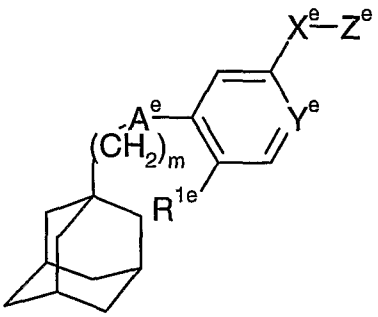
(b) when n is 1, X^d represents oxygen and A^d is C(O)NH, then R^{6d} and R^{7d} do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1-C_6 alkyl, or when one of R^{6d} and R^{7d} represents a hydrogen atom, then the other of R^{6d} and R^{7d}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

(c) 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_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 or $-CH_2CH_2OH$;

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 $P2X_7$ receptor antagonist is a compound of formula



(XI)

wherein m represents 1, 2 or 3;

A^e represents C(O)NH or NHC(O);

Y^e represents N or CH;

X^e represents a bond, CO, $(CH_2)_{1\text{-}6}$, $O(CH_2)_{1\text{-}6}$, $(CH_2)_{1\text{-}6}NH(CH_2)_{1\text{-}6}$, $(CH_2)_{1\text{-}6}O(CH_2)_{1\text{-}6}$, $NH(CH_2)_{1\text{-}6}$;

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

R^{1e} represents halogen, cyano, nitro, amino, hydroxyl, C_1-C_6 alkyl or C_3-C_8 cycloalkyl, which alkyl or cycloalkyl group group can be optionally substituted by one or more fluorine atoms;

R^{2e} and R^{3e} each independently represent a hydrogen atom, C_1-C_6 alkyl or C_3-C_8 cycloalkyl, which alkyl or cycloalkyl group can be optionally substituted by one or more groups selected from hydroxyl, halogen or C_1-C_6 alkoxy,

or R^{2e} and 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 substituted by one or more groups selected from hydroxyl, halogen or C_1-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.

In a further aspect of the present invention the $P2X_7$ receptor antagonist is:-

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

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^{3,7}]dec-1-ylmethyl)-benzamide,

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

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

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

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

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

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

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]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^{3,7}]dec-1-ylmethyl)-benzamide,

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

2-Chloro-5-(piperidin-4-ylsulfinyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

2-Chloro-5-[3-[[(1*R*)-2-hydroxy-1-methylethyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridinecarboxamide,

5-Chloro-2-[3-(ethylamino)propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

5-Chloro-2-[3-[(2-hydroxyethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

5-Chloro-2-[3-[[(2*S*)-2-hydroxypropyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]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^{3,7}]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 $P2X_7$ receptor antagonists that may be used in the present invention include:-

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

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^{3,7}]dec-1-ylmethyl)-benzamide, hydrochloride

2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate (1:1) salt

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

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

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, acetate (1:1) salt

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

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

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

2-Chloro-5-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]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^{3,7}]dec-1-ylmethyl)-benzamide

5-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

2-Chloro-5-[3-[[(1*R*)-2-hydroxy-1-methylethyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridinecarboxamide,

5-Chloro-2-[3-(ethylamino)propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide, hydrochloride

5-Chloro-2-[3-[(2-hydroxyethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide, hydrochloride

5-Chloro-2-[3-[[(2*S*)-2-hydroxypropyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]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^{3,7}]decane-1-acetamide, hydrochloride.

The P2X$_7$ receptor antagonist 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 ingredient and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The second active ingredient in the produdct or kit of the present invention is a tumour necrosis factor α (TNFα) inhibitor. A TNFα inhibitor is a compound or other substance that is capable of inhibiting TNFα activity, whether fully or partially. A detailed

description of compounds or substances that may be used in the present invention as TNFα inhibitors can be found, for example, in published International patent application no. WO 98/05357, the entire contents of which are incorporated herein by reference.

In an embodiment of the invention the tumour necrosis factor α (TNFα) inhibitor is a receptor molecule capable of binding to TNFα. Such receptor molecules are known in the art and a detailed description of receptor molecules that may be used in the present invention can be found, for example, on pages 32 to 35 of WO 98/05357. An example of a receptor molecule that gives especially good results in the present invention is Etanercept (*Expert Opin. Pharmacother. (2001) 2(7); 1137-1148*). Etanercept is a fusion protein consisting of the extracellular ligand-binding portion of the human tumor necrosis factor receptor linked to the Fc portion of human IgG. It is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. Etanercept is considered to attenuate the biological activity of the pro-inflammatory cytokine tumor necrosis factor (TNF) by binding the protein and blocking its interaction with cell surface TNF receptors. Etanercept is marketed by Amgen and Wyeth Pharmaceuticals under the tradename 'Enbrel'. A further example of a TNFα inhibitor that is a receptor molecule and that may be used in accordance with the present invention is Pegsunercept, a PEGylated soluble TNFα inhibitor receptor (*Arth. Rheum. (2003) 48, S121*).

In another embodiment of the invention, the tumour necrosis factor α (TNFα) inhibitor is an anti-TNFα antibody. Examples of anti-TNF antibodies according to the present invention include monoclonal, chimeric, humanized, resurfaced and recombinant antibodies and fragments thereof that are capable of inhibiting TNFα activity, whether fully or partially. Such antibodies are known in the art and are described, for example, on pages 13 to 32 of of WO 98/05357. Specific examples of anti-TNFα antibodies that may be used in the present invention are monoclonal antibodies Infliximab and Adalimumab (D2E7). Infliximab is a chimeric IgG1k monoclonal antibody composed of human constant and murine variable regions and is marketed by Centocor under the tradename 'Remicade'.

Adalimumab (D2E7) is a recombinant human IgG1 monoclonal antibody prepared using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:k constant regions. Adalimumab (D2E7) is is marketed by Abbott Laboratories under the tradename 'Humira'. A further example of an anti-TNFα antibody fragment that may be used in accordance with the present invention is CDP-870, a PEGylated humanized antiboby fragment that binds with high affinity to TNFα (*Cur. Opin. Investig. Drugs. (2003) 4; 588-592*).

In a further embodiment of the invention, the tumour necrosis factor α (TNFα) inhibitor may bind the TNFα receptor and includes anti-TNFα receptor antibodies.

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. Treatment of inflammatory disorders may involve a reduction in swelling and/or alleviation of pain associated with the condition. In this regard the products of the present invention have proven especially beneficial in lowering or alleviating pain caused by inflammatory disorders, in particular rheumatoid arthritis.

A further advantageous aspect of the present invention is that it may allow effective treatment using lower doses of TNFα inhibitor than is possible using a TNFα inhibitor alone. This is significant as use of biological therapeutic agents such as TNFα inhibitors can leave patients susceptible to opportunistic infections. Moreover, established anti-TNFα therapies such as Etanercept have the added complication that they have a long "wash-out" period before the drug is removed from the system. Co-administration with a $P2X_7$ antagonist that allows the dose of TNFα inhibitor to be lowered without compromising efficacy reduces these safety concerns and potentially allows anti-TNFα therapies to be applied to patient populations where their use has to date been considered inappropriate.

In a preferred embodiment of the present invention, the second active ingredient is the tumour necrosis factor α (TNFα) inhibitor Etanercept and the first active ingredient which is a $P2X_7$ receptor antagonist is selected from

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

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^{3,7}]dec-1-ylmethyl)-benzamide,

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

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

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

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

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

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

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]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^{3,7}]dec-1-ylmethyl)-benzamide,

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

2-Chloro-5-(piperidin-4-ylsulfinyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

2-Chloro-5-[3-[[(1*R*)-2-hydroxy-1-methylethyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridinecarboxamide,

5-Chloro-2-[3-(ethylamino)propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

5-Chloro-2-[3-[(2-hydroxyethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

5-Chloro-2-[3-[[(2*S*)-2-hydroxypropyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]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^{3,7}]decane-1-acetamide,

or a pharmaceutically acceptable salt or solvate of any one thereof. The products of this embodiment may in particular be used to reduce or alleviatie pain caused by inflammatory disorders, especially rheumatoid arthritis.

The first and second active ingredients are administered simultaneously (other than in admixture), 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.

The first and second active ingredients are conveniently administered by oral or parenteral (e.g. intravenous, subcutaneous , intramuscular, intraarticular or inhalled) 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. As will be understood by those skilled in the art, the most appropriate method of administering the active ingredients is dependent on a number of factors. However, in

general, oral administration of the first active ingredient is preferred, whilst subcutaneous administration of the second active ingredient 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, dosage of first and second active ingredients 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, 600, 500 or 400 mg.

The pharmaceutical product or kit of the invention may be administered as divided doses. When administered by divided doses the first and second ingredients may be administered at a different frequency from one another. However, in general, frequency of administration of each of the active ingredients will independently be in the range of from one dose every 7 days to 4 doses a day

In an embodiment of the present invention the dosage of the first active ingredient in the pharmaceutical product or kit is in the range of from 5 to 1000 mg, preferably from 20, 50, 100, or 200, to 800, 600, 500 or 400 mg per day, which daily dose may be administered as divided doses from 1 to 4 times a day, preferably once or twice a day; whilst the dose of the second active ingredient is in the range of from 1 to 100 mg, preferably from 5, 10, or 20 to 80, 50 or 40 mg, which dose is administered at a frequency in the range of from one dose every 7 days to one dose daily. The dosing routine of this embodiment may in particular be used when the first active ingredient is delivered by oral administration or inhalation and the second active ingredient is administered by subcutaneous injection. Subcutaneous injection of the second active ingredient and the dosing regime of this embodiment may in particular be employed when the second active ingredient is Etanercept.

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

Still further, the present invention provides a method of treating an inflammatory disorder which comprises simultaneously, sequentially or separately administering:
(a) a (therapeutically effective) dose of a first active ingredient which is a $P2X_7$ receptor antagonist which $P2X_7$ receptor antagonist is an adamantyl derivative; and
(b) a (therapeutically effective) dose of a second active ingredient which is a tumour necrosis factor α (TNFα) inhibitor,
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 "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 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 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 product or kit of the invention 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 product or kit of the 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. Cylco-oxygenase inhibiting nitric oxide donors (CINOD's) and "disease modifying agents" (DMARDs) such 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 product or kit of the invention together with a leukotriene biosynthesis inhibitor, 5-lipoxygenase (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-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 product or kit of the invention together with a receptor antagonist for leukotrienes LTB_4, LTC_4, LTD_4, and LTE_4 selected 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.

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

The present invention still further relates to a pharmaceutical product or kit of the invention together with a antihistaminic H_1 receptor antagonists including cetirizine, loratadine, desloratadine, fexofenadine, astemizole, azelastine, and chlorpheniramine.

The present invention still further relates to a pharmaceutical product or kit of the invention together with a gastroprotective H_2 receptor antagonist or the proton pump inhibitors (such as omeprazole)

The present invention still further relates to a pharmaceutical product or kit of the invention together with an α_1- and α_2-adrenoceptor agonist vasoconstrictor sympathomimetic agent, including propylhexedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, and ethylnorepinephrine hydrochloride.

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

The present invention still further relates to a pharmaceutical product or kit 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 product or kit 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_3CR1 for the C-X_3-C family.

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

The present invention still further relates to a pharmaceutical product or kit 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_1 - and B_2 -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_1 and NK_3 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 product or kit 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 cylco-oxygenase inhibiting nitric oxide donors (CINOD's) analgesics (such as paracetamol and tramadol), cartilage sparing agents such as diacerein, doxycyline and glucosamine, and hyaluronic acids such as hyalgan and synvisc.

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

The pharmaceutical product or kit of the invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, 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 product or kit of the invention may also be used in combination with antiviral agents such as Viracept, AZT, aciclovir and famciclovir, and antisepsis compounds such as Valant.

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

The pharmaceutical product or kit 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, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide

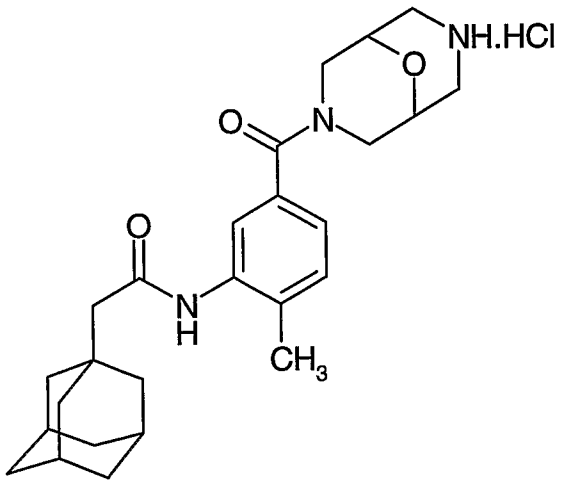
synthase), and anti Alzheimer's drugs such as donepezil, tacrine, propentofylline or metryfonate.

The pharmaceutical product or kit 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.

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

The following $P2X_7$ 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^{3,7}]decane-1-acetamide, hydrochloride



$P2X_7$ antagonist **1.** (*N*-[2-Methyl-5-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-ylcarbonyl)phenyl]-tricyclo[3.3.1.1^{3,7}]decane-1-acetamide, hydrochloride) was prepared as follows.

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 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 bicarbonate (aq) (3x150ml) then dried ($MgSO_4$), filtered and concentrated to afford the sub-titled compound (18.5g).

m/z = 382

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. 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 ($MgSO_4$) and concentrated *in vacuo* to afford the sub-title compound (14.5g).

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^{3,7}]decane-1-acetamide

Prepared by the method of step a) using 1-adamantaneacetic acid and the product of step 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]-tricyclo[3.3.1.1^{3,7}]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 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).

m/z 438 $(M+H)^+$

δ_H (400MHz, d_6-DMSO, Me_4Si, 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).

Example 1

Pharmacological analysis to determine the effect of TNFα inhibitor / $P2X_7$ antagonist combinations (without addition of a $P2X_7$ 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. Lipopolysacharide (LPS) was then added to the cell suspension in tissue culture and this was incubated for 4 - 12 hours at 37 degrees centigrade. TNFα inhibitor and / or a $P2X_7$ 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, TNFα and for other mediators including PGE2, NO and matrix metalloproteinases (MMPs). The levels of mediators released in the presence of a $P2X_7$ receptor antagonist alone, or in the presence of TNFα inhibitor alone, or in the presence of a combination of a $P2X_7$ receptor antagonist with TNFα inhibitor were determined. The effects of the antagonists / TNFα inhibitor alone and in combination were then compared. Statistically significant levels of inhibitory activity against a single mediator (IL-1 or TNFα) or on multiple mediators by $P2X_7$ antagonist / TNFα inhibitor combinations, in comparison to that achieved by either a $P2X_7$ antagonist or TNFα inhibitor alone, is an indicator for increased efficacy in the treatment of disease.

Example 2

Pharmacological analysis to determine the effect of TNFα inhibitor / $P2X_7$ anatagonist combinations (with addition of a $P2X_7$ 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. Lipopolysacharide (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 $P2X_7$ receptor agonist BzATP. Test mixtures can comprise of vehicle as control, a $P2X_7$ receptor antagonist, or a combination of a $P2X_7$ receptor antagonist together with TNFα inhibitor. 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, TNFα and for other mediators including PGE2, NO and matrix metalloproteinases (MMPs). The levels of mediators released in the presence of a $P2X_7$ receptor antagonist alone, or in the presence of a combination of a

$P2X_7$ receptor antagonist with TNFα inhibitor were determined. The effects produced by a $P2X_7$ antagonist alone and in combination with TNFα inhibitor were then compared. Statistically significant levels of inhibitory activity against a single mediator (IL-1 or TNFα) or on multiple mediators by $P2X_7$ antagonist / TNFα inhibitor combinations in comparison to that achieved by a $P2X_7$ antagonist alone is an indicator for increased efficacy in the treatment of disease.

Example 3

Assessment of anti-inflammatory activity of TNFα inhibitor / $P2X_7$ anatagonist combinations in rat Streptococcal cell wall-induced arthritis. [1]

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 μg (in 20 μL) 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 μg in 500 μL 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.*

In this example the $P2X_7$ antagonist **1**, was orally dosed at 30mg/kg (4 mL/kg, bid). The compound was dosed as a suspension in 1% (w/v) methylcellulose in deionised water and was freshly prepared on a daily basis. Dosing commenced 1 day prior to induction of arthritis and continued through to termination on day 6 post-induction. Etanercept (0.5 mg/kg) was administered by subcutaneous injection (1 mL/kg) 1 day prior to induction of arthritis and then on days 1, 3 and 5 post-induction.

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

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. The size and direction of the interaction was calculated and data analysis performed by ANOVA followed by Dunnett's test on the AUC data (SAS version 8.01). Results are summarised in the Table below:

	% reduction of AUC (compared to arthritic vehicle control)	
	Ankle swelling	Von Frey threshold
$P2X_7$ antagonist **1**	28.5 ± 13.5	21.1 ± 10.9
Etanercept	44.0 ± 4.7*	7.4 ± 6.8
$P2X_7$ antagonist **1** + Etanercept	47.5 ± 4.7*	67.4 ± 13.7** Test of interaction p=0.085***

*p<0.01, **p<0.001 vs arthritic vehicle control,

*** an interaction score indicating a greater than additive benefit for the combination.

From the above results it can be seen that the combination of the $P2X_7$ antagonist **1** and Etanercept showed a positive interaction to produce a significantly greater reduction in mechanical threshold than could be expected based on their use alone. The finding that the two drugs have a positive effect on von Frey threshold in a combination which shows no additional benefit on ankle swelling indicates that this combination of drugs has a profound and unexpectedly positive effect on inflammatory joint pain.

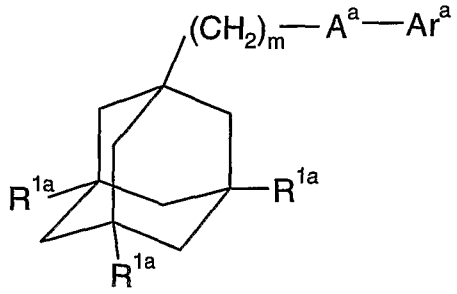
1. Experimental procedure based on that described by Carlson RP, Jacobsen PB; 'Comparison of adjuvant and streptococcal cell wall-induced arthritis in the rat' in Morgan DW, Marshall LA, editors; *In Vivo* Models of Inflammation. Basel: Birkhauser Verlag; 1999.

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CLAIMS

1. A pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a $P2X_7$ receptor antagonist which $P2X_7$ receptor antagonist is an adamantyl derivative, and a preparation of a second active ingredient which is a tumour necrosis factor α (TNFα) inhibitor, for simultaneous, sequential or separate use in therapy.

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



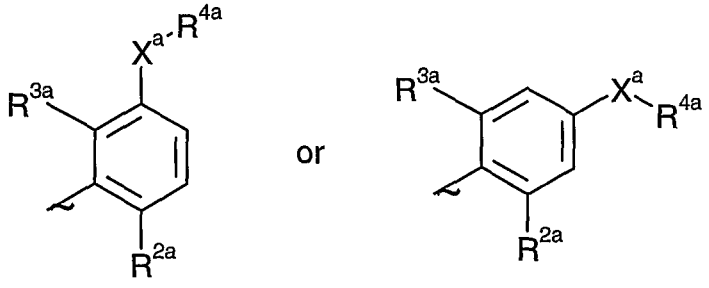
(I)

wherein m represents 1, 2 or 3;

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

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), $(CH_2)_{1-3}O(CH_2)_{1-3}$, $(CH_2)_{1-3}O(CH_2)_{2-3}O$, 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;

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 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 $-CONR^{6a}R^{7a}$,

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;

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 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

(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

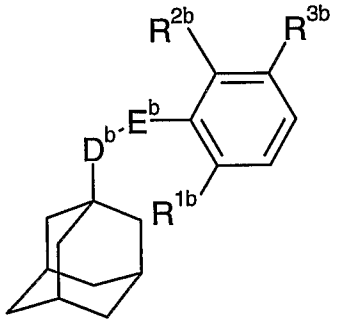
(c) when A^a represents NHC(O) and R^{4a} represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X^a is other than a bond, and

(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



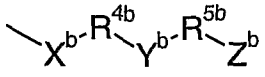
(II)

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



(III);

X^b represents an oxygen or sulphur atom or a group NH, SO or SO_2;

Y^b represents an oxygen or sulphur atom or a group NR^{11b}, SO or SO_2;

Z^b represents a group -OH, -SH, $-CO_2H$, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, $-NR^{6b}R^{7b}$, $-C(O)NR^{8b}R^{9b}$, imidazolyl, 1-methylimidazolyl, $-N(R^{10b})C(O)$-C_1-C_6 alkyl, C_1-C_6 alkylcarbonyloxy, C_1-C_6 alkoxycarbonyloxy, $-OC(O)NR^{12b}R^{13b}$, $-OCH_2OC(O)R^{14b}$, $-OCH_2OC(O)OR^{15b}$ or $-OC(O)OCH_2OR^{16b}$;

R^{4b} represents a C_2-C_6 alkyl group;

R^{5b} represents a C_1-C_6 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_1-C_6 alkyl group optionally substituted by at least one hydroxyl group;

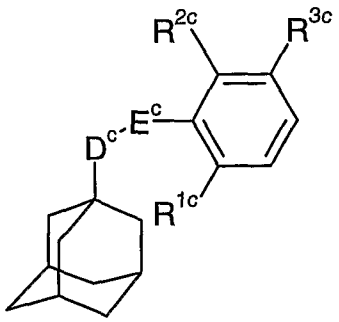
R^{11b} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by at least one substituent independently selected from hydroxyl and C_1-C_6 alkoxy; and

R^{14b}, R^{15b} and R^{16b} each independently represent a C_1-C_6 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_1-C_6 alkyl group substituted by at least one hydroxyl group, and (ii) when E^b represents NHC(O), X^b represents O, S or NH, Y represents NH and R^{5b} represents CH_2CH_2, then Z^b is not -OH or imidazolyl;

or a pharmaceutically acceptable salt or solvate thereof.

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



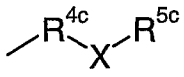
(IV)

wherein D^c represents CH_2 or CH_2CH_2;

E^c represents C(O)NH or NHC(O);

R^{1c} and R^{2c} each independently represent hydrogen, halogen, amino, nitro, C_1-C_6 alkyl or trifluoromethyl, but R^{1c} and R^{2c} may not both simultaneously represent hydrogen;

R^{3c} represents a group of formula

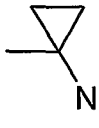


(V);

R^{4c} represents a C_1-C_6 alkyl group;

X^c represents an oxygen or sulphur atom or a group NR^{13c}, SO or SO_2;

R^{5c} represents hydrogen, or R^{5c} represents C_1-C_6 alkyl or C_2-C_6 alkenyl, each of which may be optionally substituted by at least one substituent selected from halogen, hydroxyl, (di)-C_1-C_6-alkylamino, $-Y^c-R^{6c}$,



, and

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 C_1-C_6 alkyl;

Y^c represents an oxygen or sulphur atom or a group NH, SO or SO_2;

R^{6c} represents a group $-R^{7c}Z^c$ where R^{7c} represents a C_2-C_6 alkyl group and Z^c represents an -OH, $-CO_2H$, $-NR^{8c}R^{9c}$, $-C(O)NR^{10c}R^{11c}$ or $-N(R^{12c})C(O)$-C_1-C_6 alkyl group, and, in the case where Y^c represents an oxygen or sulphur atom or a group NH, R^{6c} additionally represents hydrogen, C_1-C_6 alkyl, C_1-C_6 alkylcarbonyl, C_1-C_6

alkoxycarbonyl, -C(O)NR^{14c}R^{15c}, -CH$_2$OC(O)R^{16c}, -CH$_2$OC(O)OR^{17c} or -C(O)OCH$_2$OR^{18c};

R^{8c}, R^{9c}, R^{10c}, R^{11c} and R^{12c} each independently represent a hydrogen atom or a C$_1$-C$_6$ alkyl group;

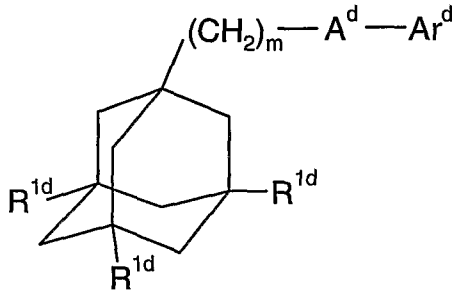
R^{13c} represents hydrogen, C$_3$-C$_8$ cycloalkyl, C$_3$-C$_8$ cycloalkylmethyl, or R^{13c} represents a C$_1$-C$_6$ alkyl group optionally substituted by at least one substituent selected from hydroxyl and C$_1$-C$_6$ alkoxy; and

R^{14c}, R^{15c}, R^{16c}, R^{17c} and R^{18c} each independently represent a C$_1$-C$_6$ alkyl group;

with the proviso that when E^c is C(O)NH, X^c is O, NH or N(C$_1$-C$_6$ alkyl), then R^{5c} is other than a hydrogen atom or an unsubstituted C$_1$-C$_6$ alkyl group;

or a pharmaceutically acceptable salt or solvate thereof.

5. A composition according to claim 1 wherein the P2X$_7$ receptor antagonist is a compound of formula



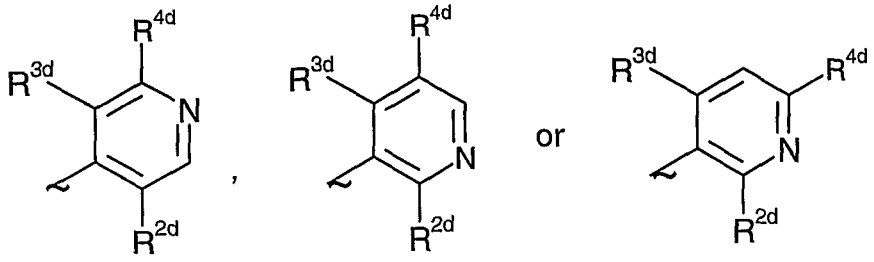
(VI)

wherein m represents 1, 2 or 3;

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

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

Ar^d represents a group

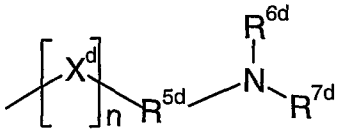


;

(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);

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

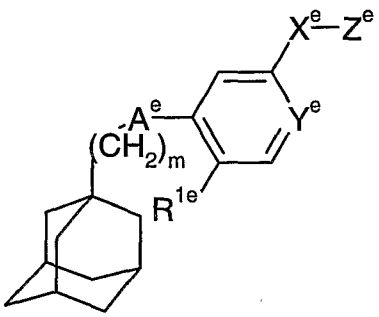
(e) when n is 1, X^d represents oxygen and A^d is C(O)NH, then R^{6d} and R^{7d} do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1-C_6 alkyl, or when one of R^{6d} and R^{7d} represents a hydrogen atom, then the other of R^{6d} and R^{7d} 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_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 or $-CH_2CH_2OH$;

or a pharmaceutically acceptable salt or solvate thereof.

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



(XI)

wherein m represents 1, 2 or 3;

A^e represents C(O)NH or NHC(O);

Y^e represents N or CH;

X^e represents a bond, CO, $(CH_2)_{1\text{-}6}$, $O(CH_2)_{1\text{-}6}$, $(CH_2)_{1\text{-}6}NH(CH_2)_{1\text{-}6}$, $(CH_2)_{1\text{-}6}O(CH_2)_{1\text{-}6}$, $NH(CH_2)_{1\text{-}6}$;

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

R^{1e} represents halogen, cyano, nitro, amino, hydroxyl, C_1-C_6 alkyl or C_3-C_8 cycloalkyl, which alkyl or cycloalkyl group group can be optionally substituted by one or more fluorine atoms;

R^{2e} and R^{3e} each independently represent a hydrogen atom, C_1-C_6 alkyl or C_3-C_8 cycloalkyl, which alkyl or cycloalkyl group can be optionally substituted by one or more groups selected from hydroxyl, halogen or C_1-C_6 alkoxy,

or R^{2e} and 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 substituted by one or more groups selected from hydroxyl, halogen or C_1-C_6 alkoxy; or a pharmaceutically acceptable salt or solvate thereof.

7. A composition according to claim 1 wherein the $P2X_7$ receptor antagonist is:

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

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^{3,7}]dec-1-ylmethyl)-benzamide,

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

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

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

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

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

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

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]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^{3,7}]dec-1-ylmethyl)-benzamide,

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

2-Chloro-5-(piperidin-4-ylsulfinyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

2-Chloro-5-[3-[[(1*R*)-2-hydroxy-1-methylethyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridinecarboxamide,

5-Chloro-2-[3-(ethylamino)propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

5-Chloro-2-[3-[(2-hydroxyethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

5-Chloro-2-[3-[[(2*S*)-2-hydroxypropyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]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^{3,7}]decane-1-acetamide,

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

8. A product according to any one of claims 1 to 7, wherein the second active ingredient is a receptor molecule capable of binding to TNFα.

9. A product according to claim 8 wherein the second active ingredient is Etanercept.

10. A product according to any one of claims 1 to 7, wherein the second active ingredient is an anti-TNFα antibody.

11. A product according to claim 10, wherein the second active ingredient is selected from Infliximab and Adalimumab (D2E7).

12. A kit comprising a preparation of a first active ingredient which is a $P2X_7$ receptor antagonist which $P2X_7$ receptor antagonist is an adamantyl derivative, a preparation of a second active ingredient which is a tumour necrosis factor α (TNFα) inhibitor, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

13. A kit according to claim 12 wherein the $P2X_7$ receptor antagonist is:

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

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^{3,7}]dec-1-ylmethyl)-benzamide,

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

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

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

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

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

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

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]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^{3,7}]dec-1-ylmethyl)-benzamide,

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

2-Chloro-5-(piperidin-4-ylsulfinyl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

5-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

2-Chloro-5-[3-[[(1*R*)-2-hydroxy-1-methylethyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-3-pyridinecarboxamide,

5-Chloro-2-[3-(ethylamino)propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

5-Chloro-2-[3-[(2-hydroxyethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-4-pyridinecarboxamide,

5-Chloro-2-[3-[[(2*S*)-2-hydroxypropyl]amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]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^{3,7}]decane-1-acetamide,

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

14. A kit according to any one of claims 12 to 13, wherein the second active ingredient is a receptor molecule capable of binding to TNFα.

15. A kit according to claim 14 wherein the second active ingredient is Etanercept.

16. A kit according to any one of claims 12 to 13, wherein the second active ingredient is an anti-TNFα antibody.

17. A kit according to claim 16, wherein the second active ingredient is selected from Infliximab and Adalimumab (D2E7).

18. Use of a pharmaceutical product or kit according to any one of the preceding claims in the manufacture of a medicament for the treatment of an inflammatory disorder.

19. Use according to claim 19, wherein the inflammatory disorder is rheumatoid arthritis.

20. A method of treating an inflammatory disorder which comprises simultaneously, sequentially or separately administering:

(a) a (therapeutically effective) dose of a first active ingredient which is a $P2X_7$ receptor antagonist which $P2X_7$ receptor antagonist is an adamantyl derivative; and

(b) a (therapeutically effective) dose of a second active ingredient which is a tumour necrosis factor α (TNFα) inhibitor,

to a patient in need thereof.

21. A method according to claim 20, wherein the inflammatory disorder is rheumatoid arthritis.

IONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 45/06, A61K 31/165, A61K 31/465, 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

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, EPO-INTERNAL, PAJ, MEDLINE, BIOSIS

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), 14 May 2003 (14.05.2003), see paragraph [0100]	1-21
X	WO 03042191 A1 (PFIZER PRODUCTS), 22 May 2003 (22.05.2003), page 40, line 13 - line 18	1-21
A	WO 03041707 A1 (ASTRAZENECA AB), 22 May 2003 (22.05.2003)	1-21
A	WO 0144170 A1 (ASTRAZENECA AB), 21 June 2001 (21.06.2001)	1-21

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search	Date of mailing of the international search report
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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) --	1-21
A	WO 0061569 A1 (ASTRAZENECA AB), 19 October 2000 (19.10.2000) --	1-21
