(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 March 2005 (24.03.2005)

PCT

(10) International Publication Number
WO 2005/025571 A1

(51) International Patent Classification[7]: A61K 31/465, 31/166, 31/167, 31/395, A61P 19/02, 19/10, 29/00

(21) International Application Number:
PCT/SE2004/001334

(22) International Filing Date:
15 September 2004 (15.09.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0302488-2 18 September 2003 (18.09.2003) SE

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A PHARMACEUTICAL COMPOSITION COMPRISING A P2X7 RECEPTOR ANTAGONIST AND A NONSTEROIDAL ANTI INFLAMMATORY DRUG.

(57) Abstract: The invention provides a pharmaceutical composition, pharmaceutical product or kit comprising a first active ingredient which is a P2X7 receptor antagonist, and a second active ingredient which is a nonsteroidal anti-inflammatory drug, for use in the treatment of inflammatory disorders.

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A pharmaceutical composition comprising a P2X7 receptor antagonist and a nonsteroidal anti-inflammatory drug.

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 therefore provided a pharmaceutical composition comprising, in admixture, a first active ingredient which is a $P2X_7$ receptor antagonist, and a second active ingredient which is a nonsteroidal anti-inflammatory drug (NSAID).

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).

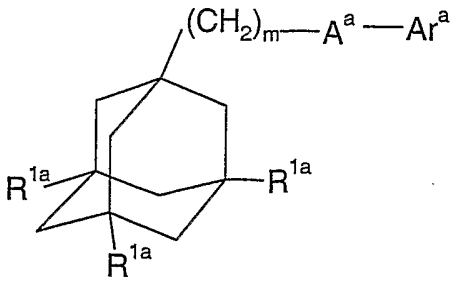
An antagonist of the $P2X_7$ receptor is a compound or other substance that is capable of preventing, whether fully or partially, activation of the $P2X_7$ receptor.

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 include the compounds described in WO 00/61569, WO 01/42194, WO 01/44170 and WO 03/041707, 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



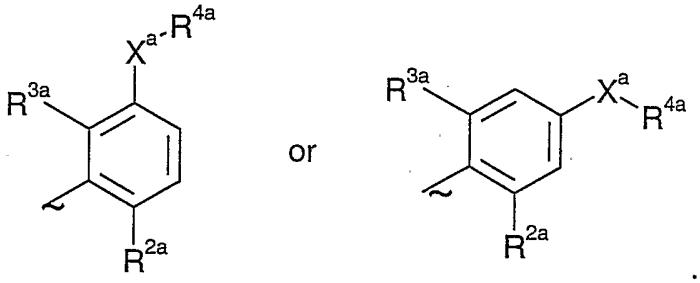
(I)

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

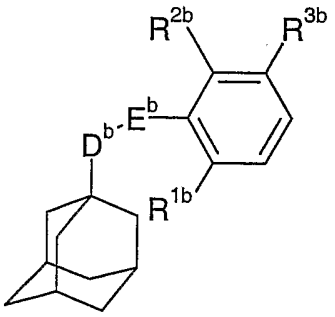
(d) when A^a represents NHC(O) and X^a represents $O(CH_2)_{1-6}$, $NH(CH_2)_{1-6}$ or SCH_2, then R^{4a} does not represent an unsubstituted 1-piperidinyl or unsubstituted 1-pyrrolidinyl group, and

(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



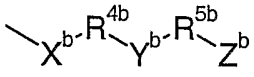
(II)

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;

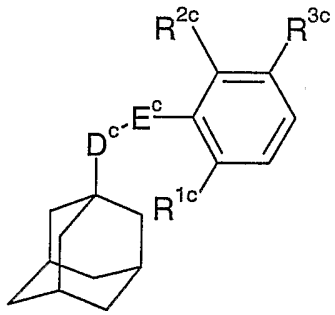
R^{5b} represents a C_1-C_6 alkyl group;

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.

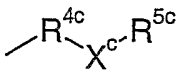
Compounds of formula (II) are described in WO 01/42194.

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

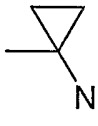


(V);

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;

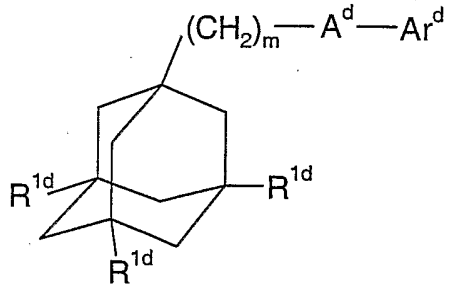
with the proviso that when E^c is C(O)NH, X^c is O, NH or N(C_1-C_6 alkyl), then R^{5c} is other than a hydrogen atom or an unsubstituted C_1-C_6 alkyl group;

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



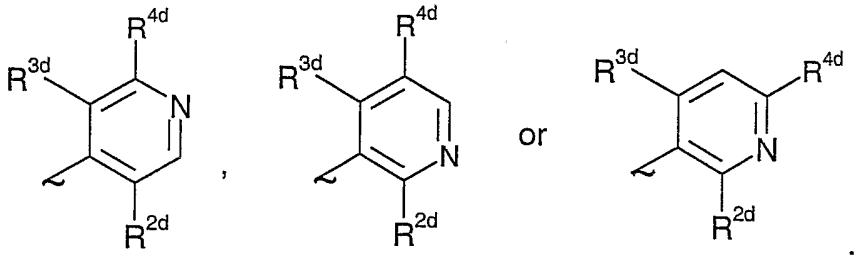
(VI)

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);

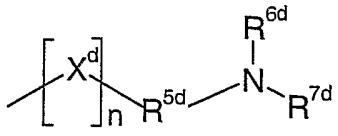
Ar^d represents a group



(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

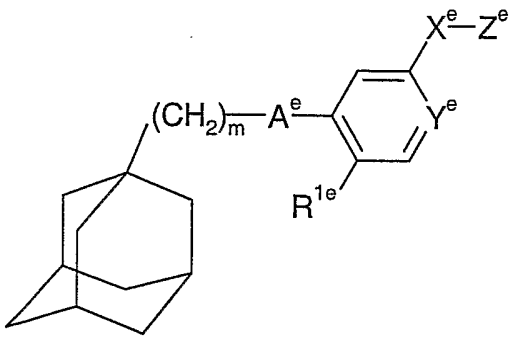
(b) when n is 1, X^d represents oxygen and A^d is C(O)NH, then R^{6d} and R^{7d} do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1-C_6 alkyl, or when one of R^{6d} and R^{7d} represents a hydrogen atom, then the other of R^{6d} and R^{7d} 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, $(CH_2)_{1-6}$, $O(CH_2)_{1-6}$, $(CH_2)_{1-6}NH(CH_2)_{1-6}$, $(CH_2)_{1-6}O(CH_2)_{1-6}$, $NH(CH_2)_{1-6}$;

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 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 second active ingredient in the present invention is a nonsteroidal anti-inflammatory drug (NSAID). An NSAID is a compound or substance that is capable of inhibiting, whether fully or partially, the enzyme cyclooxgenase (COX). The enzyme has at least two isoforms referred to as COX – 1, which is consituitively expressed in and acts to protect the stomach lining and intestine, and COX – 2 which is inducible and which plays an intrinsic role in the inflammatory process. Selective COX – 2 inhibitors are also known as COXIBs.

The NSAID of the invention may inhibit both COX – 1 and COX - 2 but is preferably selective for COX -2.

Examples of NSAIDs that may be used include ibuprofen, naproxen, aspirin, celecoxib (commercially available under the trade mark "Celebrex"), diclofenac (commercially available under the trade mark "Voltaren"), etodolac (commercially available under the

trade mark "Lodine"), fenoprofen (commercially available under the trade mark "Nalfon"), indomethacin (commercially available under the trade mark "Indocin"), ketoprofen (commercially available under the trade mark "Oruvail"), ketoralac (commercially available under the trade mark "Toradol"), oxaprozin (commercially available under the trade mark "Daypro"), nabumetone (commercially available under the trade mark "Relafen"), sulindac (commercially available under the trade mark "Clinoril"), tolmetin (commercially available under the trade mark "Tolectin"), rofecoxib (commercially available under the trade mark "Vioxx"), valdecoxib, lumaricoxib, meloxicam, etoricoxib and parecoxib.

In an embodiment of the invention, the second active ingredient is a selective inhibitor of COX - 2. In the context of this embodiment a selective inhibitor of COX-2 is a compound that displays an in vitro selectivity for COX-2 to COX-1 of at least 2:1 as measured by whole blood assay as described by *Warner, T.D. etal., Proc. Natl. Acad. Sci. USA,1999, **96**, 7563-7568*. Preferably the selective inhibitor of COX - 2 has an in vitro selectivity for COX-2 to COX-1 of at least 5:1, more preferably at least 10:1, even more preferably at least 30:1 and most preferably at least 100:1. Examples of selective inhibitors of COX-2 that may be employed in accordance with this embodiment include celecoxib, rofecoxib, valdecoxib, lumaricoxib, etoricoxib and parecoxib.

In one embodiment of the present invention the second active ingredient is the selective inhibitor of COX – 2, celecoxib. The chemical name for celecoxib is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl] benzenesulfonamide (*Penning, T. etal, J. Med. Chem., 1997, **40**, 1347-1365).* Celecoxib is marketed by Pfizer under the trade mark 'Celebrex'.

In another embodiment of the present invention the second active ingredient is the selective inhibitor of COX – 2, rofecoxib. The chemical name for rofecoxib is 4-[4'-(methylsulfonyl)phenyl]-3-phenyl-(5*H*)-furanone *(Chan, C.C. etal J. Pharmacol. Exp.*

*Ther., 1999, **290**, 551-560).* Rofecoxib is marketed by Merck Sharp & Dohme under the trade mark 'Vioxx'.

In another embodiment of the present invention the second active ingredient is the selective inhibitor of COX – 2, valdecoxib. The chemical name for valdecoxib is 4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide (*Talley, J. J. etal J. Med. Chem., 2000, **43**, 775-777).* Valdecoxib is marketed by Pfizer under the trade mark 'Bextra'.

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 and osteoarthritis. 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 joint disorders.

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 $P2X_7$ receptor antagonist, with a second active ingredient which is a nonsteroidal anti-inflammatory drug.

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 4 hours apart, preferably less than 2 hours apart, more preferably less than 30 minutes apart.

Therefore, the invention also provides a pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a $P2X_7$ receptor antagonist, and a preparation of a second active ingredient which is a nonsteroidal anti-inflammatory drug, for simultaneous, sequential or separate use in therapy. The second active ingredient is preferably a selective inhibitor of COX – 2.

In another aspect, the invention provides a kit comprising a preparation of a first active ingredient which is a $P2X_7$ receptor antagonist, a preparation of a second active ingredient which is a non-steroidal anti-inflammatory drug, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof. The second active ingredient is preferably a selective inhibitor of COX – 2.

The first and second active ingredients are conveniently administered by oral or parenteral 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. Preferably the first and second active ingredients are delivered orally.

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.

In an embodiment of the present invention the daily dosage of the first active ingredient in the pharmaceutical composition, product or kit is in the range from 5 to 1000mg, 5 to 800mg, 5 to 600mg, 5 to 500mg, 5 to 400mg, 5 to 300mg, 5 to 200mg, 5 to 100mg, 5 to 50mg, 20 to 1000mg, 20 to 800mg, 20 to 600mg, 20 to 500mg, 20 to 400mg, 20 to 300mg, 20 to 200mg, 20 to 100mg, 20 to 50mg, 50 to 1000 mg, 50 to 800mg, 50 to 600mg, 50 to 500mg, 50 to 400mg, 50 to 300mg, 50 to 200mg, 50 to 100mg, 100 to 1000 mg, 100 to 800mg, 100 to 600mg, 100 to 500mg, 100 to 400mg, 100 to 300mg, or 100 to 200mg; whilst the daily dose of the second active ingredient is in the range from 1 to 200mg, 1 to 100mg, 1 to 50mg, 1 to 25mg, 5 to 200mg, 5 to 100mg, 5 to 50mg, 5 to 25mg, 10 to 200mg, 10 to 100mg, 10 to 50mg or 10 to 25mg; which daily doses of first and second active ingredient may be administered as divided doses from 1 to 4 times a day, preferably once or twice a day, and which first and second active ingredients may be administered in admixture, simultaneously , sequentially or separately. The dosing regime of this embodiment may conveniently be adopted where both the first and second active ingredients are delivered by oral administration. Second active ingredients that may be used in accordance with this embodiment include celecoxib, rofecoxib and valdecoxib.

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

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, particular inflammatory disorders being rheumatoid arthritis or osteoarthritis.

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; and

(b) a (therapeutically effective) dose of a second active ingredient which is a nonsteroidal anti-inflammatory drug,

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 composition 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 composition of the

invention include 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 composition 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 composition 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 composition of the invention together with a PDE4 inhibitor including inhibitors of the isoform PDE4D.

The present invention still further relates to a pharmaceutical composition 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 composition 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 composition 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 composition 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 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_3CR1 for the $C\text{-}X_3\text{-}C$ 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_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 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 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 composition 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 composition 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 composition 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 composition of the invention may also be used in combination with calcium channel blockers, lipid lowering agents such fibrates, beta-blockers, Ace inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

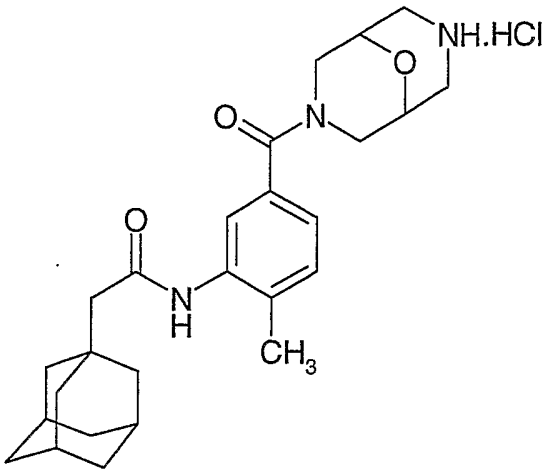
The pharmaceutical composition of the invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors,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

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 NSAID / $P2X_7$ 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. An NSAID 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 NSAID alone, or in the presence of a combination of a $P2X_7$ receptor antagonist with NSAID were determined. The effects of the antagonists / NSAID 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 / NSAID combinations, in comparison to that achieved by either a $P2X_7$ antagonist or NSAID alone, is an indicator for increased efficacy in the treatment of disease.

Example 2

Pharmacological analysis to determine the effect of NSAID / $P2X_7$ 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 an NSAID. 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 NSAID were determined. The effects produced by a $P2X_7$ antagonist alone and in combination with NSAID 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 / NSAID combinations in comparison to that achieved by a $P2X_7$ antagonist alone is an indicator for increased efficacy in the treatment of disease.

Example 3A

Assessment of anti-inflammatory activity of the COX-2 inhibitor, Celecoxib / $P2X_7$ antagonist 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 on a daily basis through to termination on day 6 post-induction. Celecoxib (3mg/kg) was dosed orally under the same regime as for $P2X_7$ antagonist **1**, administration of celecoxib occurring immediately after administration of $P2X_7$ antagonist **1**.

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 Table 1.

Table 1

	% 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
Celecoxib	63.0 ± 3.9**	43.2 ± 15.9*
$P2X_7$ antagonist **1** + Celecoxib	59.4 ± 6.2**	64.2 ± 10.3** Test of interaction p=1.00***

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

*** an interaction score indicating an additive benefit for the combination.

From the above results it can be seen that the combination of the $P2X_7$ antagonist **1** and celecoxib showed a positive interaction to produce a reduction in mechanical threshold.

In further studies, the $P2X_7$ antagonist **1** was dosed at 10 and 30mg/kg in combination with celecoxib at 1, 3 and 10mg/kg, wherein the two active ingredients where co-administered in a single formulation. Experimental endpoints were as previously described. The results from these studies confirm the positive interaction to produce a reduction in mechanical threshold as described above. Moreover, analysis of blood samples from these studies demonstrated that the pharmacokinetic profiles of the two drugs when dosed in combination were identical to those when dosed individually. This indicates that the observed positive effects are not attributable to changes in the pharmacokinetic profiles of the drugs but are the result of a pharmacological interaction.

The finding that $P2X_7$ antagonist **1** and celecoxib have a positive effect on von Frey threshold in a combination which shows little 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.

Example 3B

Assessment of anti-inflammatory activity of the COX-2 inhibitor, Rofecoxib / $P2X_7$ antagonist combinations in rat Streptococcal cell wall-induced arthritis. [1]

The anti-inflammatory activity of the COX-2 inhibitor, rofecoxib in combination with a $P2X_7$ antagonist was assesesd using the protocol described in Example 3A. The $P2X_7$ antagonist **1** was dosed orally at 30mg/kg (4 mL/kg, bid) as a suspension in 1% (w/v) methylcellulose in deionised water, together with rofecoxib (Merck Sharp & Dohme Limited) (1mg/kg) in a single formulation. Dosing commenced 1 day prior to induction of arthritis and continued on a daily baisis through to termination on day 6 post-induction. Results are summarised in Table 2.

Table 2

	% reduction of AUC (compared to arthritic vehicle control)	
	Ankle swelling	Von Frey threshold
$P2X_7$ antagonist **1**	2.6 ± 11.6	26.5 ± 11.4
Rofecoxib	50.6 ± 4.7**	29.8 ± 7.8*
$P2X_7$ antagonist **1** + Rofecoxib	56.1 ± 6.4**	69.5 ± 6.6** Test of interaction p=0.44***

*p<0.05, **p<0.0001 vs arthritic vehicle control

*** an interaction score indicating an additive benefit for the combination.

From the above results it can be seen that the combination of the $P2X_7$ antagonist **1** and rofecoxib showed a positive interaction to produce a reduction in mechanical threshold. The finding that the two drugs have a positive effect on von Frey threshold in a combination which shows little benefit on ankle swelling indicates that this combination of drugs has a profound and unexpectedly positive effect on inflammatory joint pain. Moreover, analysis of blood samples from this study demonstrated that the pharmacokinetic profiles of the two drugs when dosed in combination were identical to those when dosed individually. This indicates that the observed positive effects are not attributable to changes in the pharmacokinetic profiles of the drugs but are the result of a pharmacological interaction.

Example 3C

Assessment of anti-inflammatory activity of the COX-2 inhibitor, Valdecoxib / $P2X_7$ antagonist combinations in rat Streptococcal cell wall-induced arthritis. [1]

The anti-inflammatory activity of the COX-2 inhibitor, valdecoxib in combination with a $P2X_7$ antagonist was assesesd using the protocol described in Example 3A. The $P2X_7$ antagonist **1** was orally dosed at 30mg/kg (4 mL/kg, bid) as a suspension in 1% (w/v) methylcellulose in deionised water, together with valdecoxib (Pfizer) (1mg/kg) in a single formulation. Dosing commenced 1 day prior to induction of arthritis and continued on a daily baisis through to termination on day 6 post-induction. Results are summarised in Table 3

Table 3

	% reduction of AUC (compared to arthritic vehicle control)	
	Ankle swelling	Von Frey threshold
$P2X_7$ antagonist **1**	2.6 ± 11.6	26.5 ± 11.4
Valdecoxib	52.8 ± 3.1**	37.8 ± 8.6*
$P2X_7$ antagonist **1** + Valdecoxib	57.4 ± 6.8**	60.9 ± 6.0** Test of interaction p=0.85***

*p<0.01,**p<0.0001 vs arthritic vehicle control

*** an interaction score indicating an additive benefit for the combination.

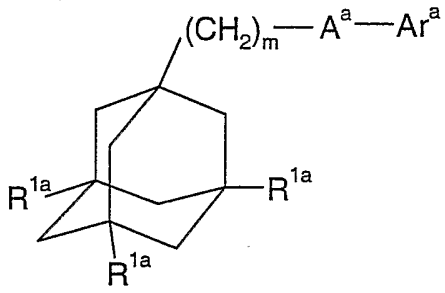
From the above results it can be seen that the combination of the $P2X_7$ antagonist **1** and valdecoxib showed a positive interaction to produce a reduction in mechanical threshold. The finding that the two drugs have a positive effect on von Frey threshold in a combination which shows little benefit on ankle swelling indicates that this combination of drugs has a profound and unexpectedly positive effect on inflammatory joint pain. Moreover, analysis of blood samples from this study demonstrated that the pharmacokinetic profiles of the two drugs when dosed in combination were identical to those when dosed individually. This indicates that the observed positive effects are not attributable to changes in the pharmacokinetic profiles of the drugs but are the result of a pharmacological interaction.

CLAIMS

1. A pharmaceutical composition comprising, in admixture, a first active ingredient which is a $P2X_7$ receptor antagonist, and a second active ingredient which is a nonsteroidal anti-inflammatory drug.

2. A composition according to claim 1, wherein the $P2X_7$ receptor antagonist is an adamantyl derivative.

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



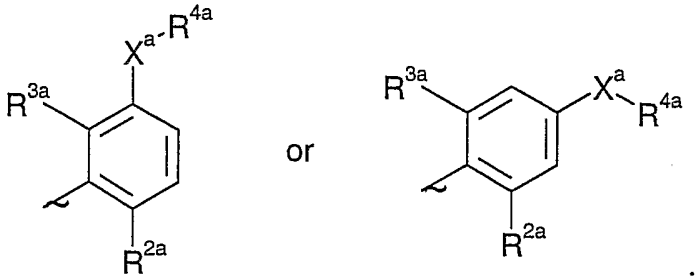
(I)

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

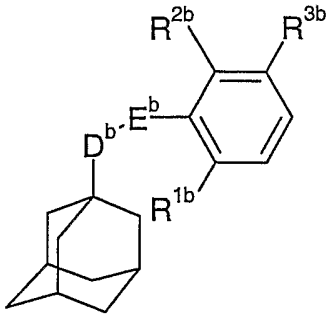
(c) when A^a represents NHC(O) and R^{4a} represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X^a is other than a bond, and

(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.

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



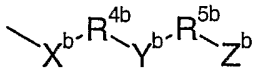
(II)

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;

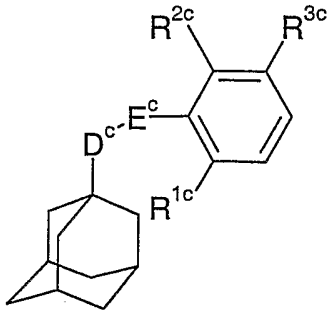
R^{11b} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by at least one substituent independently selected from hydroxyl and C_1-C_6 alkoxy; and

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.

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



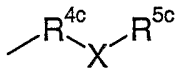
(IV)

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

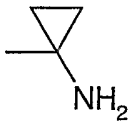


(V);

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

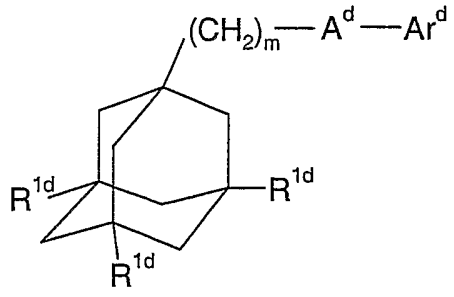
R^{13c} represents hydrogen, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkylmethyl, or R^{13c} represents a C_1-C_6 alkyl group optionally substituted by at least one substituent selected from hydroxyl and C_1-C_6 alkoxy; and

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.

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



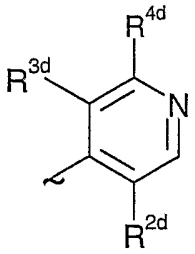
(VI)

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



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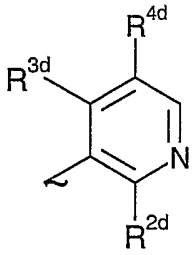

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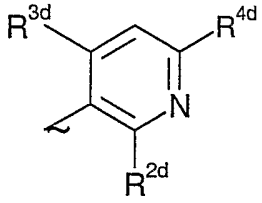
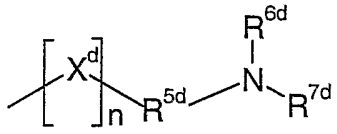


;

(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:

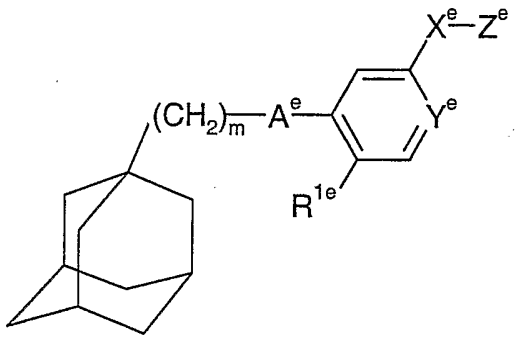
(d) when n is 0, then A^d is NHC(O), and

(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.

7. A composition according to claim 1 or claim 2, 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.

8. A composition according to claim 1 or claim 2, 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.

9. A composition according to any one of claims 1 to 8, wherein the second active ingredient is a selective inhibitor of COX – 2.

10. A composition according to claim 9, wherein the second active ingredient is celecoxib.

11. A composition according to claim 9, wherein the second active ingredient is rofecoxib.

12. A composition according to claim 9, wherein the second active ingredient is valdecoxib.

13. A composition according to any one of claims 1 to 12 which is formulated for oral administration.

14. A process for the preparation of a pharmaceutical composition as defined in any one of claims 1 to 13 which comprises mixing the first active ingredient with the second active ingredient.

15. Use of a composition according to any one of claims 1 to 13 in the manufacture of a medicament for the treatment of an inflammatory disorder.

16. Use according to claim 15, wherein the inflammatory disorder is rheumatoid arthritis or osteoarthritis.

17. 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 13 to a patient in need thereof.

18. A method according to claim 17, wherein the inflammatory disorder is rheumatoid arthritis or osteoarthritis.

19. A pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a $P2X_7$ receptor antagonist, and a preparation of a second active ingredient which is a nonsteroidal anti-inflammatory drug, for simultaneous, sequential or separate use in therapy.

20. A kit comprising a preparation of a first active ingredient which is a $P2X_7$ receptor antagonist, a preparation of a second active ingredient which is a nonsteroidal anti-

inflammatory drug, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001334

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/465, A61K 31/166, A61K 31/167, A61K 31/395, A61P 19/02, A61P 19/10, 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, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPO-INTERNAL, PAJ, CHEM. ABS DATA, MEDLINE

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) --	1-20
X	WO 03042191 A1 (PFIZER PRODUCTS INC.), 22 May 2003 (22.05.2003) --	1-20
A	WO 03041707 A1 (ASTRAZENECA AB), 22 May 2003 (22.05.2003) --	1-20
A	WO 0144170 A1 (ASTRAZENECA AB), 21 June 2001 (21.06.2001) --	1-20

[X] Further documents are listed in the continuation of Box C. [X] 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	Date of mailing of the international search report
11 January 2005	12-01-2005
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 Eva Johansson/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2004/001334

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.: 17-18
because they relate to subject matter not required to be searched by this Authority, namely:

See attached sheet

2. ☒ Claims Nos.: 1-2, 9, 13-16 and 19-20 and partly 3-8, 10-12
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:

Present claims 1-2, 9, 13-16 and 19-20 and partly 3-8,

.../...

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 17-18 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the product.

Box II.2

10-12 relate to a composition defined by reference to a desirable characteristic or property, namely that one of the active compounds inhibits the P2X7 receptor and the other is a nonsteroidal anti-inflammatory drug. The claims cover all compositions having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT for only a very limited number of/ lacks support for such compositions. Additionally, previously known compounds may be included in the scope of the present claims. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the composition by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to adamantly derivatives claims 3-8 with connection to the P2X7 receptor or to the treatment of inflammatory conditions, as well as the compounds mentioned in claims 10-12 in combination with those NSAID or COX-2 compounds mentioned in the description. Furthermore, a limited search concerning the expressions "P2X7 receptor antagonist" and "nonsteroidal anti-inflammatory" or "NSAID" or COX-2" has been performed

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001334

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)	1-20
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A	WO 0061569 A1 (ASTRAZENECA AB), 19 October 2000 (19.10.2000)	1-20
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A	Dell´Antonio, Giacomo et al, "Antinociceptive effect of a new P2z/P2X7 antagonist, oxidized ATP, in arthritic rats", Neuroscience Letters, 2002, vol. 327, page 87 - page 90	1-20
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				WO	03042190	A	22/05/2003
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				CA	2466724	A	22/05/2003
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				SE	0103836	D	00/00/0000
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				CN	1434794	T	06/08/2003
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				DE	60009147	D	00/00/0000
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				EE	200200330	A	15/10/2003
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				EP	1352895	A	15/10/2003
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				GB	0015744	D	00/00/0000
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				TR	200401432	T	00/00/0000
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				BR	0009651	A	08/01/2002
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				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