(11) Application No. AU 2002338784 B2

(19) AUSTRALIAN PATENT OFFICE

(54) Title

Quaternary ammonium salts of omega-aminoalkylamides of R-2-aryl-propionic acids and pharmaceutical compositions containing them

(51)[6] International Patent Classification(s)

C07D 295/12 (2006.01)
A61K 31/165 (2006.01)
A61K 31/452 (2006.01)
A61K 31/5375 (2006.01)
A61P 1/04 (2006.01)
A61P 9/10 (2006.01)
A61P 11/00 (2006.01)
A61P 13/12 (2006.01)
A61P 17/00 (2006.01)
A61P 17/06 (2006.01)
A61P 19/02 (2006.01)
A61P 19/04 (2006.01)
A61P 29/00 (2006.01)
A61P 43/00 (2006.01)
C07C 231/12 (2006.01)
C07C 233/40 (2006.01)
C07C 233/42 (2006.01)
C07C 233/44 (2006.01)
C07C 233/51 (2006.01)
C07C 235/78 (2006.01)
C07C 237/20 (2006.01)
C07C 237/22 (2006.01)
C07D 295/13 (2006.01)
C07D 295/12 20060101AFI2005122 0BMJP
A61K 31/165 20060101ALI2005122 0BMJP
A61K 31/452 20060101ALI2005122 0BMJP
A61K 31/5375 20060101ALI2005122 0BMJP
A61P 1/04 20060101ALI2005122 0BMJP
A61P 9/10 20060101ALI2005122 0BMJP
A61P 11/00 20060101ALI2005122 0BMJP
A61P 13/12 20060101ALI2005122 0BMJP
A61P 17/00 20060101ALI2005122 0BMJP
A61P 17/06 20060101ALI2005122 0BMJP
A61P 19/02 20060101ALI2005122 0BMJP
A61P 19/04 20060101ALI2005122 0BMJP
A61P 29/00 20060101ALI2005122 0BMJP
A61P 43/00 20060101ALI2005122 0BMJP
C07C 231/12 20060101ALI2005122 0BMJP
C07C 233/40 20060101ALI2005100 8BMEP
C07C 233/42 20060101ALI2005122 0BMJP
C07C 233/44 20060101ALI2005100 8BMEP
C07C 233/51 20060101ALI2005100 8BMEP
C07C 235/78 20060101ALI2005100 8BMEP
C07C 237/20 20060101ALI2005100 8BMEP
C07C 237/22 20060101ALI2005100 8BMEP
C07D 295/13 20060101ALI2005100 8BMEP

(21) Application No: 2002338784

(22) Application Date: 2002.09.25

(87) WIPO No: WO03/029187

(30) Priority Data

(31) Number	(32) Date	(33) Country
MI2001A002025	2001.09.28	IT

(43) Publication Date : 2003.04.14

(43) Publication Journal Date : 2003.06.26

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(56) Related Art

WO 2002/068377

FR 2410641

FR 1593024

WO 20011/058852

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 April 2003 (10.04.2003)

PCT

(10) International Publication Number
WO 03/029187 A1

(51) International Patent Classification: C07C 233/40

(21) International Application Number: PCT/EP02/10746

(22) International Filing Date:
25 September 2002 (25.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2001A002025
28 September 2001 (28.09.2001) IT

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, 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, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

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

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, 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, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*

— *of inventorship (Rule 4.17(iv)) for US only*

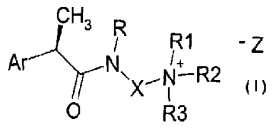
Published:

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.

WO 03/029187 A1

(54) Title: QUATERNARY AMMONIUM SALTS OF OMEGA-AMINOALKYLAMIDES OF R-2-ARYL-PROPIONIC ACIDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(I)

(57) Abstract: (R)-Enantiomers of quaternary ammonium salts of general formula (I) are described: (I) where R, R_1, R_2, R_3, X and Z are as defined in the description. The process for their preparation and pharmaceutical preparations thereof are also described. The quaternary salts of the invention are useful in the inhibition of chemotaxis of neutrophils and monocytes induced by the fraction C5a of the complement and are used in the treatment of psoriasis, pemphigus and pemphigoid, rheumatoid arthritis, intestinal chronic inflammatory pathologies including ulcerative colitis, acute respiratory distress syndrome, idiopathic fibrosis, cystic fibrosis, chronic obstructive pulmonary disease and glomerulonephritis. The compounds of the invention are advantageously used in the prevention and the treatment of injury caused by ischemia and reperfusion.

2002338784 28 Jul 2008

"QUATERNARY AMMONIUM SALTS OF OMEGA-AMINOALKYLAMIDES OF R-2-ARYL-PROPIONIC ACIDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"

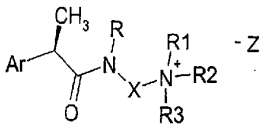
Introduction and background of the invention

The present invention relates to compounds useful in the inhibition of the chemotactic activation induced by the fraction C5a of complement and from other chemotactic proteins (chemokines) that exert their action by activating a 7-transmembrane-domain (7-TM) receptor. Said compounds are quaternary ammonium salts of R-2-arylpropionamides useful in the treatment of pathologies depending on the chemotactic activation of neutrophils and monocytes induced by the fraction C5a of the complement. In particular, the compounds of the invention are useful in the treatment of psoriasis, rheumatoid arthritis, ulcerative colitis, acute respiratory distress syndrome, idiopathic fibrosis, glomerulonephritis and in the prevention of injury caused by ischemia and reperfusion.

Summary of the invention

The present invention provides the following items 1 to 26:

1. (R)-2-aryl-propionamide compound of formula (I-a):



(I-a)

wherein

- Ar is selected from:

  a) an aryl group selected in the group consisting of (+-)-p-((2-Oxocyclopentyl)methyl)phenyl, alpha-(4-(1-Oxo-2-iso-indolinyl)phenyl, 2-(4-(methallylamino)phenyl, 4-thienoylphenyl, 3-chloro-4-(2,5-dihydro-1H-pyrrol-1-yl)phenyl, 3-phenoxyphenyl, 4-isobutylphenyl, 3-benzoylphenyl;

  b) an aryl of formula (IIIb):

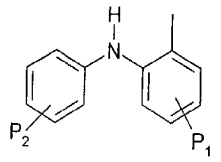
$$\Phi\text{-}Ar_b$$

(IIIb)

wherein:

- Ar_b is a phenyl mono- or poly-substituted by hydroxy, mercapto, C_1-C_3-alkoxy, C_1-C_3-alkylthio, chlorine, fluorine, trifluoromethyl, nitro, amino, optionally substituted C_1-C_7-acylamino;
- Φ is hydrogen; a linear or branched C_1-C_5 alkyl, C_2-C_5- alkenyl or C_2-C_5-alkynyl residue optionally substituted by C_1-C_3-alkoxycarbonyl, substituted or non-substituted phenyl, 2-, 3- or 4-pyridyl, quinolin-2-yl; a C_3-C_6-cycloalkyl; 2-furyl; 3-tetrahydrofuryl; 2-thiophenyl; 2-tetrahydrothiophenyl or a C_1-C_8-(alkanoyl, cycloalkanoyl, arylalkanoyl)-C_1-C_5-alkylamino group;

  c) a 2-(phenylamino)-phenyl of formula (IIIc):



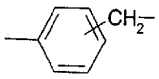
(IIIc)

wherein the substituents P_1 and P_2 indicate that the two phenyl groups bear, each independently, mono- or poly-substitutions with C_1-C_4-alkyl, C_1-C_3-alkoxy groups, chlorine, fluorine and/or trifluoromethyl;

- R represents hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, these groups being optionally substituted by a CO_2R_4 group, wherein R_4 represents hydrogen or a linear or branched C_1-C_6 alkyl group or a linear or branched C_2-C_6 alkenyl group;
- X represents:

linear or branched C_1-C_6 alkylene, C_4-C_6 alkenylene, C_4-C_6 alkynylene, optionally substituted by a CO_2R_4 group or by a $CONHR_5$ group wherein R_5 represents hydrogen, linear or branched C_2-C_6 alkyl or an OR_4 group, R_4 being defined as above, or (CHR')-CONH-$(CH_2)_n$ wherein n is an integer from 2 to 3 and R' is a methyl, having absolute configuration R or S;

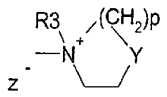
- phenyl or a phenylmethylene group of formula:



- a $(CH_2)_m$-B-$(CH_2)_n$, group, optionally substituted by a CO_2R_4 or $CONHR_5$ group, as defined above, wherein B is an oxygen or sulfur atom, m is zero or an integer from 2 to 3 and n is an integer from 2 to 3; or B is a CO, SO or CONH group, m is an integer from 1 to 3 and n is an integer from 2 to 3;
- or X together with the nitrogen atom to which it is bound and with the R_1 group forms a nitrogen containing 3-7 membered heterocyclic monocyclic or polycyclic ring;
- R_1, R_2 and R_3 are independently linear or branched C_1-C_6 alkyl, optionally substituted by an oxygen or sulfur atom, a C_3-C_7 cycloalkyl, C_3-C_6 alkenyl, C_3-C_6-alkynyl, aryl, aryl-C_1-C_3-alkyl, hydroxy-C_2-C_3-alkyl group;

or R_1 and R_2 together with the N atom to which they are bound, form a nitrogen containing 3-7 membered heterocyclic ring of formula (II) and R_3 independently has the meanings as defined above,

2002338784 28 Jul 2008



(II)

wherein Y represents a single bond, a methylene group, an oxygen atom, a nitrogen atom or a sulfur atom and p represents an integer from 0 to 3;

Z^- represents a pharmaceutically acceptable counter-ion of quaternary ammonium salts,

with the proviso that when Ar is biphenyl, R_2 and R_3 are not ethyl, and with the proviso that when X is (CHR')-CONH-$(CH_2)_n$, R is H.

2. Compound according to item 1, wherein the C_1-C_8-(alkanoyl, cycloalkanoyl, arylalkanoyl)-C_1-C_5-alkylamino group is acetyl-N-methyl-amino or pivaloyl-N-ethyl-amino.

3. Compound according to any one of the previous items wherein:

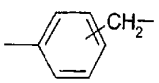
R is hydrogen;

X is:

- a linear C_1-C_6 alkylene, optionally substituted at C_1 by a $-CO_2R_4$ group as defined above;
- a linear C_1-C_6 alkylene optionally substituted at C_1 by a $-CONHR_5$ group wherein R_5 is OH;
- 2-butynylene, cis-2-butenylene, trans-2-butenylene;
- 3-oxa-pentylene, 3-thio-pentylene, 3-oxa-hexylene, 3-thio-hexylene;
- $(CH_2)_m$-CO-NH-$(CH_2)_n$-wherein m and n are each independently an integer from 2 to 3;
- (CHR')-CONH-$(CH_2)_n$ wherein n is an integer from 2 to 3 and R' is a methyl, having absolute configuration R or S;

2002338784 28 Jul 2008

- a phenyl or phenylmethylene group of formula:



- or X, together with the N atom, form an azocycloaliphatic ring.

4. Compound according to item 3, wherein X is a linear C_2-C_4 alkylene.

5. Compound according to any one of items 1 to 3, wherein $NR_1R_2R_3$ group represents a trimethylammonium, triethylammonium, N-methyl-N,N-diethylammonium, N-methyl-N,N-diisopropylammonium, N-cyclohexylmethyl-N,N-dimethylammonium, N-cyclopentylamino-N,N-dimethylammonium, N-methyl-1-piperidinium, N-ethyl-1-piperidinium, N-methyl-4-morpholinium, N-methyl-4 thiomorpholinium, N-benzyl-N,N-dimethylammonium, N-allyl-1-piperidinium, 4-oxy-N-methyl-piperidinium group or X together with the amine N to which it is bound and with the R_1 group, forms a nitrogen containing 5-6 membered heterocyclic ring and the substituents R_2 and R_3 represent independently a methyl or cyclohexyl residue.

6. Compound according to any one of items 1 to 5, wherein Ar is selected from 4-isobutylphenyl, 4-cyclohexylmethylphenyl, 4-(2-methyl)allyl-phenyl, 3-phenoxyphenyl, 3-benzoyl-phenyl, 3-acetyl-phenyl, the single (R) (S) diastereoisomers and the diastereoisomeric (R,S) mixture of 3-C_6H_5-CH(OH)-phenyl, 3-CH_3-CH(OH)-phenyl, 5-C_6H_5-CH(OH)-thienyl, 4-thienyl-CH(OH)-phenyl, 3-(pyrid-3-yl)-CH(OH)-phenyl, 5-benzoyl-thien-2-yl, 4-thienoyl-phenyl, 3-nicotinoyl-phenyl, 2-fluoro-4-phenyl, 6-metoxy-2-naphthyl, 5-benzoyl-2-acetoxy-phenyl, 5-benzoyl-2-hydroxy-phenyl, 4-cyclopentyl-phenyl, 4-(2-oxo-cyclopentyl)-phenyl, 4-(2-oxo-cyclohexyl)-phenyl.

7. Compound according to item 1 or 5, wherein Ar is a phenyl group 3-substituted by isoprop-1-en-1-yl-isopropyl, pent-2-en-3-yl, pent-3-yl; 1-phenylethylen-1-yl; α-methylbenzyl.

8. Compound according to item 1 or 5, wherein the Ar groups in the formula (IIIc) are 2-(2,6-dichloro-phenyl-amino)-phenyl; 2-(2,6-dichlorophenyl-amino)-5-

2002338784 28 Jul 2008

chloro-phenyl; 2-(2,6-dichloro-3-methyl-phenyl-amino)-phenyl; 2-(3-trifluoromethyl-phenylamino)-phenyl.

9. Compound according to any one of the previous items, wherein Z^- is a halide chosen from Cl^-, I^-, Br^-, a sulfate anion, methanesulfonate or p-toluenesulfonate.

10. Compound according to any one of the previous items, selected from:
(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-trimethylammonium iodide;
(R)-{3-[2-(3-benzoylphenyl)-propionylamino] propyl}-trimethylammonium iodide;
(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl} -N-ethyl-N,N-dimethylammonium iodide;
(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-N-cyclohexylmethyl- N,N-dimethylammonium iodide;
(R)-{3-[2-(4-cyclopentylmethylphenyl)-propionylamino] propyl}-trimethylammonium iodide;
(R)-{3-[2-(3-benzoylphenyl)-propionylamino] propyl}-N-isopropyl-N,N-dimethylammonium iodide;
(R)-{3-[2-(4-isobutylphenyl)-propionylamino] butyl-trimethylammonium iodide;
(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-1-methyl-piperidinium iodide;
(R)-{3-[2-(3-benzoylphenyl)-propionylamino] propyl}-1-methyl piperidinium iodide;
(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-4-methyl-morpholinium iodide;
(R)-{3-[2-(3-isopropylphenyl)-propionylamino] propyl}-4-methyl-thiomorpholinium methanesulfonate;
(R)-{3-[2-(4-isobutylphenyl)-propionylamino] ethyl-trimethylammonium bromide;
(R)-2-[(4-isobutylphenyl)-propionylamino]-1,1-dimethyl)piperidinium p-toluenesulfonate;
(R),(S')-2-(4-isobutylphenyl)-N-[(1-carboxy-2"-N,N,N-trimethylammonium)ethyl] propionamide methanesulfonate;
R(-)-2-[(4-isobutylphenyl)-N-(trimethylammoniumethyl) methylamide] propionamide iodide;

2002338784 28 Jul 2008

(R)(3-{2-[2(2,6-dichlorophenylamino)-phenyl]-propionylamino}-propyl)-trimethylammonium methanesulfonate;

(2R), (4"S)1-{4-carboxy-4-[2-(4-isobutyl-phenyl)-propionylamino] butyl}-1-methyl-piperidinium iodide;

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(N-benzyl)-N,N-dimethylammonium iodide;

2R-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(1"methyl-4" carboxyamide) piperidinium iodide;

(2R)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(1"-methyl-4" carbonyl) piperidinium iodide;

R(-)-{3,-[-(4'-isobutylphenyl)-propionylamino]-propyl}-triethylammonium iodide;

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-1-allylpiperidinium bromide;

R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-N,N,N-trimethylaminophenyl] propionamide iodide;

R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-N,N,N-trimethylaminomethylphenyl] propionamide iodide.

11. Compound according to any one of items 1 to 10, for use as a medicament.

12. Compound according to any one of items 1 to 10, for use as an inhibitor of the chemotaxis of neutrophils and monocytes induced by C5a.

13. Compound according to any one of items 1 to 10, for use in the treatment of psoriasis, pemphigus and pemphigoid, rheumatoid arthritis, intestinal chronic inflammatory pathologies, acute respiratory distress syndrome, idiopathic fibrosis, cystic fibrosis, chronic obstructive pulmonary disease and glomerulonephritis.

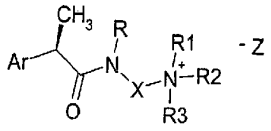
14. Compound according to item 13, wherein the intestinal chronic inflammatory pathology is ulcerative colitis.

15. Compound according to any one of items 1 to 10, for use in the prevention and treatment of injury caused by ischemia and reperfusion.

16. Pharmaceutical composition containing a compound according to any one of items 1 to 10 in admixture with a suitable carrier thereof.

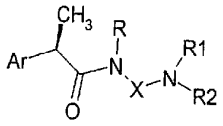
2002338784 28 Jul 2008

17. Process for the preparation of (R)-2-aryl-propionamide compounds of formula (I-a):



(I-a)

wherein Ar, X, R_1 ,R_2 ,R_3 have the meaning as defined in claim 1, comprising reaction of amides of formula (IV-a)



(IV-a)

with compounds of formula R_3Z, wherein Z is a conventional leaving group.

18. Process according to item 17, wherein the leaving group is chloride, bromide, iodide, methanesulfonate, p-toluensulfonate or sulfate.

19. A method of treating psoriasis, pemphigus and pemphigoid, rheumatoid arthritis, intestinal chronic inflammatory pathologies, acute respiratory distress syndrome, idiopathic fibrosis, cystic fibrosis, chronic obstructive pulmonary disease or glomerulonephritis in a patient, the method comprising administering to the patient an effective amount of a compound according to any one of items 1 to 10.

20. A method according to item 19 wherein the intestinal chronic inflammatory pathology is ulcerative colitis.

21. The use of a compound according to any one of items 1 to 10 in the manufacture of a medicament for the treatment of psoriasis, pemphigus and pemphigoid, rheumatoid arthritis, intestinal chronic inflammatory pathologies, acute respiratory distress syndrome, idiopathic fibrosis, cystic fibrosis, chronic obstructive pulmonary disease or glomerulonephritis.

2002338784 28 Jul 2008

22. Use according to item 21 wherein the intestinal chronic inflammatory pathology is ulcerative colitis.

23. A method of preventing or treating an injury caused by ischemia and reperfusion in a patient, the method comprising administering to the patient an effective amount of a compound according to any one of items 1 to 10.

24. Use of a compound according to any one of items 1 to 10 in the manufacture of a medicament for the prevention or treatment of an injury caused by ischemia and reperfusion.

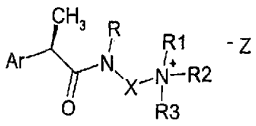
25. A method of inhibiting chemotaxis of neutrophils and monocytes induced by C5a in a patient, the method comprising administering to the patient an effective amount of a compound according to any one of items 1 to 10.

26. The use of a compound according to any one of items 1 to 10 in the manufacture of a medicament for inhibiting chemotaxis of neutrophils and monocytes induced by C5a.

The compound of formula (I-a) described above falls within the scope of the compound of the formula (I) described below. The compound of formula (IV-a) described above falls within the scope of the compound of the formula (IV) described below.

Detailed description of the invention

Described herein are (R)-2-aryl-propionamides of formula (I):



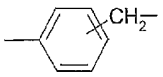
(I)

wherein

- Ar represents a substituted or non-substituted aryl group;
- R represents hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, optionally substituted by a CO_2R_4 group, wherein R_4 represents hydrogen or a linear or branched C_1-C_6 alkyl group or a linear or branched C_2-C_6 alkenyl group;
- X represents:

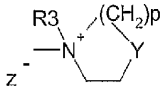
linear or branched C_1-C_6 alkylene, C_4-C_6 alkenylene, C_4-C_6 alkynylene, optionally substituted by a CO_2R_4 group or by a $CONHR_5$ group wherein R_5 represents hydrogen, linear or branched C_2-C_6 alkyl or an OR_4 group, R_4 being defined as above;

- phenyl or a phenylmethylene group of formula:



- a $(CH_2)_m$-B-$(CH_2)_n$, group, optionally substituted by a CO_2R_4 or $CONHR_5$ group, as defined above, wherein B is an oxygen or sulfur atom, m is zero or an integer from 2 to 3 and n is an integer from 2 to 3; or B is a CO, SO or CONH group, m is an integer from 1 to 3 and n is an integer from 2 to 3;
- or X together with the nitrogen atom to which it is bound and with the R_1 group forms a nitrogen containing 3-7 membered heterocyclic monocyclic or polycyclic ring;
- R_1, R_2 and R_3 are independently linear or branched C_1-C_6 alkyl, optionally substituted by an oxygen or sulfur atom, a C_3-C_7 cycloalkyl, C_3-C_6 alkenyl, C_3-C_6-alkynyl, aryl, aryl-C_1-C_3-alkyl, hydroxy-C_2-C_3-alkyl group;

or R_1 and R_2 together with the N atom to which they are bound, form a nitrogen containing 3-7 membered heterocyclic ring of formula (II) and R3 independently has the meanings as defined above.



(II)

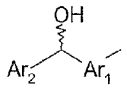
In the general formula (II)

- Y represents a single bond, a methylene group, an oxygen atom, a nitrogen atom or a sulfur atom
- p represents an integer from 0 to 3;
- Z represents conventional anions used as counter-ions of quaternary ammonium salts which are pharmaceutically acceptable, such as, for example, halide ions Cl^-, I^-, Br^-, the sulfate anion or anions derived from sulfonic acids such as methansulfonate or p-toluensulfonate.

In the compounds of general formula (I), the aryl group Ar is preferably chosen among:

a) an Ar_a mono- or poly-substituted aryl group, of the most common (±) 2-aryl-propionic acids in current therapeutic use: alminoprofen, benoxaprofen, carprofen, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, loxoprofen, R-naproxen, pirprofen and its dehydro and dihydro derivatives, pranoprofen, surprofen, tiaprofenic acid, zaltoprofen;

b) an aryl-hydroxymethyl-aryl group of formula (IIIa) both as diastereoisomer mixture, or as single diastereoisomers,



(IIIa)

wherein, when Ar_2 is phenyl Ar_1 is selected from the group consisting of phenyl and thien-2-yl while when Ar_1 is phenyl, Ar_2 is selected from the group consisting of phenyl, 4-thienyl, pyridyl.

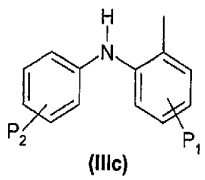
c) an aryl of formula (IIIb):

(IIIb)

wherein:

- Ar_b is a phenyl mono- or poly-substituted by hydroxy, mercapto, C_1-C_3-alcoxy, C_1-C_3-alkylthio, chlorine, fluorine, trifluoromethyl, nitro, amino, optionally substituted C_1-C_7-acylamino;
- Φ is hydrogen; a linear or branched C_1-C_5 alkyl, C_2-C_5- alkenyl or C_2-C_5-alkynyl residue optionally substituted by C_1-C_3-alkoxycarbonyl, substituted or non-substituted phenyl, 2-, 3- or 4-pyridyl, quinolin-2-yl; a C_3-C_6-cycloalkyl; 2-furyl; 3-tetrahydrofuryl; 2-thiophenyl; 2-tetrahydrothiophenyl or a C_1-C_8-(alkanoyl, cycloalkanoyl, arylalkanoyl)-C_1-C_5- alkylamino group e.g. acetyl-N-methyl-amino, pivaloyl-N-ethyl-amino;

d) a 2-(phenylamino)-phenyl of formula (III c):



(IIIc)

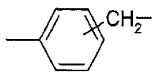
wherein the substituents P_1 and P_2 indicate that the two phenyl groups bear, each independently, mono- or poly-substitutions with C_1-C_4-alkyl, C_1-C_3-alcoxy groups, chlorine, fluorine and/or trifluoromethyl.

Preferred compounds of general formula (I) are those wherein:

R is hydrogen;

X is:

- a linear C_1-C_6 alkylene, preferably C_2-C_4, optionally substituted at C_1 by a -CO_2R_4 group as defined above;
- a linear C_1-C_6 alkylene optionally substituted at C_1 by a -$CONHR_5$ group wherein R_5 is OH;
- 2-butynylene, cis-2-butenylene, trans-2-butenylene;
- 3-oxa-pentylene, 3-thio-pentylene, 3-oxa-hexylene, 3-thio-hexylene;
- $(CH_2)_m$-CO-NH-$(CH_2)_n$-wherein m and n are each independently an integer from 2 to 3;
- (CHR')-CONH-($CH_2)_n$ wherein n is an integer from 2 to 3 and R' is a methyl, having absolute configuration R or S;
- a phenyl or phenylmethylene group of formula:



- or X, together with the N atom, form an azocycloaliphatic ring, preferably 1-methyl-piperidin-4-yl or 1,5-tropan-3-yl;

Preferred compounds are, in addition, those wherein the $NR_1R_2R_3$ group represents a trimethylammonium, triethylammonium, N-methyl-N,N-diethylammonium, N-methyl-N,N-diisopropylammonium, N-cyclohexylmethyl-N,N-dimethylammonium, N-cyclopentylamino-N,N-dimethylammonium, N-methyl-1-

piperidinium, N-ethyl-1-piperidinium, N-methyl-4-morpholinium, N-methyl-4 thiomorpholinium, N-benzyl-N,N-dimethylammonium, N-allyl-1-piperidinium, 4-oxy-N-methyl-piperidinium group.

Examples of particularly preferred aryl groups comprise:

4-isobutylphenyl, 4-cyclohexylmethylphenyl, 4-(2-methyl)allyl-phenyl, 3-phenoxyphenyl, 3-benzoyl-phenyl, 3-acetyl-phenyl, the single (R) (S) diastereoisomers and the diastereoisomeric (R,S) mixture of 3-C_6H_5-CH(OH)-phenyl, 3-CH_3-CH(OH)-phenyl, 5-C_6H_5-CH(OH)-thienyl, 4-thienyl-CH(OH)-phenyl, 3-(pyrid-3-yl)-CH(OH)-phenyl, 5-benzoyl-thien-2-yl, 4-thienoyl-phenyl, 3-nicotinoyl-phenyl, 2-fluoro-4-phenyl, 6-metoxy-2-naphthyl, 5-benzoyl-2-acetoxy-phenyl, 5-benzoyl-2-hydroxy-phenyl, 4-cyclopentyl-phenyl, 4-(2-oxo-cyclopentyl)-phenyl, 4-(2-oxo-cyclohexyl)-phenyl.

Particularly preferred aryl groups of formula (IIIb) are phenyl groups 3-substituted by: isoprop-1-en-1-yl, isopropyl, pent-2-en-3-yl; pent-3-yl; 1-phenylethylen-1-yl; α-methylbenzyl.

Particularly preferred aryls of formula (IIIc) are: 2-(2,6-dichloro-phenyl-amino)-phenyl; 2-(2,6-dichloro-phenyl-amino)-5-chloro-phenyl; 2-(2,6-dichloro-3-methyl-phenyl-amino)-phenyl; 2-(3-trifluoromethyl-phenyl-amino)-phenyl. Examples of P_2 substituted phenyl groups comprise phenyl groups substituted by one to three halogen atoms, C_1-C_4 alkyl groups, methoxy, trifluoromethyl, nitro, cyano, haloalkoxy.

Particularly preferred compounds of general formula (I) are:

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-trimethylammonium iodide;

(R)-{3-[2-(3-benzoylphenyl)-propionylamino] propyl}-trimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl} -N-ethyl-N,N-dimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-N-cyclohexylmethyl- N,N-dimethylammonium iodide;

(R)-{3-[2-(4-cyclopentylmethylphenyl)-propionylamino] propyl}-trimethylammonium iodide;

(R)-{3-[2-(3-benzoylphenyl)-propionylamino] propyl}-N-isopropyl-N,N-dimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] butyl-trimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-1-methyl-piperidinium iodide;

(R)-{3-[2-(3-benzoylphenyl)-propionylamino] propyl}-1-methyl piperidinium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-4-methyl-morpholinium iodide;

(R)-{3-[2-(3-isopropylphenyl)-propionylamino] propyl}-4-methyl-thiomorpholinium methanesulfonate;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] ethyl-trimethylammonium bromide;

(R)-2-[(4-isobutylphenyl)-propionylamino]-1,1-dimethyl)piperidinium p-toluenesulfonate;

(R),(S')-2-(4-isobutylphenyl)-N-[(1-carboxy-2"-N,N,N-trimethylammonium)ethyl] propionamide methanesulfonate;

R(-)-2-[(4-isobutylphenyl)-N-(trimethylammoniumethyl) methylamide] propionamide iodide;

(R)(3-{2-[2(2,6-dichlorophenylamino)-phenyl]-propionylamino}-propyl)-trimethylammonium methanesulfonate;

(2R), (4"S)1-{4-carboxy-4-[2-(4-isobutyl-phenyl)-propionylamino] butyl}-1-methyl-piperidinium iodide;

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(N-benzyl)-N,N-dimethylammonium iodide;

2R-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(1"methyl-4" carboxyamide) piperidinium iodide;

(2R)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(1"-methyl-4" carbonyl) piperidinium iodide;

R(-)-{3,-[-(4'-isobutylphenyl)-propionylamino]-propyl}-triethylammonium iodide;

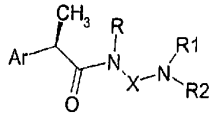
R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-1-allylpiperidinium bromide;

2002338784 28 Jul 2008

R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-N,N,N-trimethylaminophenyl] propionamide iodide;

R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-N,N,N-trimethylaminomethylphenyl] propionamide iodide.

Known methods for the alkylation of tertiary amine groups (Menschutkin reaction) are used for the preparation of formula (I) compounds; compounds of formula (IV), wherein Ar, R, R_1, R_2 and X are as above defined, are reacted with compounds of formula R_3Z where R_3 is defined as above and Z is a conventional leaving group such as chloride, bromide, iodide, methanesulfonate, p-toluensulfonate or sulfate.



(IV)

The alkylation reactions are normally conducted at room temperature, using conventional protic or aprotic preferably anhydrous solvents or their mixtures, optionally in the presence of a strong non-nucleophilic base. Alternatively, some of compounds of formula (I) can be obtained starting from compounds of formula (IV) by reaction with Michael-type unsaturated substrates catalyzed by mineral acids such as HCl or HNO_3.

The preparation of compounds of formula (IV) is described in International Patent Application PCT/EP02/01974. Some of the compounds of formula (IV) are new with respect to specific compounds described in the above patent application, and were prepared with the methods described further below in the Preparations section.

It is understood that is the synthesis of compounds formula (I) starting from the amides of formula (IV) wherein substituents R_1 and R_2 can be -H independently is included in the process. If desired, the primary and secondary amines can be reacted in the conditions of exhaustive alkylation with compounds of formula R_3Z to yield the compounds of formula (I) wherein at least two of the

residues defined as R_1, R_2 and R_3 are the same. The reaction is carried out under the same conditions as described for the conversion of the amides of formula (IV) into the compounds of formula (I).

Alternatively, the primary or secondary amides of formula (IV) can be converted into formula (I) compounds in two consecutive steps. In the first step of mono-or dialkylation, the reaction is carried out at room temperature or by heating in the presence of one or two equivalents of R_2Z alkylating agent, depending on the degree of substitution of the starting amine group. The reactions are carried out in conventional protic or aprotic preferably anhydrous solvents or their mixtures, optionally in the presence of a strong non-nucleophilic base.

The compounds of formula (I) were evaluated *in vitro* for their ability to inhibit chemotaxis of polymorphonucleate leukocytes (hereinafter referred to as PMNs) and monocytes induced by the fractions of the complement C5a and C5a-desArg. For this purpose, to isolate the PMNs from heparinized human blood, taken from healthy adult volunteers, mononucleates were removed by means of sedimentation on dextran (according to the procedure disclosed by W.J. Ming *et al.*, J. Immunol., 138, 1469, 1987) and red blood cells by a hypotonic solution. The cell vitality was calculated by exclusion with Trypan blue, whilst the ratio of the circulating polymorphonucleates was estimated on the cytocentrifugate after staining with Diff Quick.

Human recombinant fractions C5a and C5a-desArg (Sigma) were used as stimulating agents in the chemotaxis experiments, giving practically identical results.

The lyophilized C5a was dissolved in a volume of HBSS containing 0.2% bovin serum albumin BSA so thus to obtain a stock solution having a concentration of 10^{-5} M to be diluted in HBSS to a concentration of 10^{-9} M , for the chemotaxis assays.

In the chemotaxis experiments, the PMNs were incubated with the compounds of formula (I) for 15' at 37°C in an atmosphere containing 5% CO_2.

The chemotactic activity of the C5a was evaluated on human circulating polymorphonucleates (PMNs) resuspended in HBSS at a concentration of $1.5x10^6$ PMNs per mL.

During the chemotaxis assay (according to W. Falket et al., J. Immunol. Methods, 33, 239, 1980) PVP-free filters with a porosity of 5 μm and microchambers suitable for replication were used.

The compounds of formula (I) were evaluated at a concentration ranging between 10^{-6} and 10^{-10} M; for this purpose they were added, at the same concentration, both to the lower pores and the upper pores of the microchamber. The wells in the lower part contain the solution of C5a or the simple carrier, those in the upper part contain the suspension of PMNs.

Inhibition of C5a-induced chemotactic activity by the individual compounds of formula (I) was evaluated by incubating the microchamber for the chemotaxis for 60 min at 37°C in an atmosphere containing 5% CO2.

Evaluation of the ability of the compounds of formula (I) to inhibit C5a-induced chemotaxis of human monocytes was carried out according to the method disclosed by Van Damme J. et al. (Eur. J. Immunol., 19, 2367, 1989). Inhibition of C5a-induced chemotactic activity by the individual compounds of formula (I) towards human monocytes was evaluated at a concentration ranging between 10^{-6} and 10^{-10} M by incubating the microchamber for the chemotaxis for 120 min. at 37°C in an atmosphere containing 5% CO2.

By way of example, the inhibition data of the chemotaxis of PMN ($C=10^{-6}$ M) of some representative compounds of formula (I) are reported in the following table:

COMPOUND	% INHIBITION ($C=10^{-6}$ M)
(R)-(3-{2-[2-(2,6-dielorophenylamino)-phenyl]-propionylamino}-propyl)-trimethylammonium iodide	62±3
R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-trimethylammonium iodide	53±6

R(-)-2-[(4'-isobutylphenyl)-propionylamino]-1,1-dimethylpiperidinium iodide	18±9
R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-l-methyl-piperidinium iodide	24±4
R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-N-cyclohexylmethyl- N,N-dimethyl-ammonium methanesulfonate	57±4
R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(N-benzyil)-N,N-dimethylammonium iodide	22±4

The compounds of formula (I), evaluated *ex vivo* in the blood *in toto* according to the procedure disclosed by Patrignani et al., in J. Pharmacol. Exper. Ther., 271, 1705, 1994, were found to be totally ineffective as inhibitors of cyclooxygenase (COX) enzymes.

In almost all cases, the compounds of formula (I) do not interfere with the production of PGE_2 induced in murine macrophages by lipopolysaccharides stimulation (LPS, 1 μg/mL) at a concentration ranging between 10^{-5} and 10^{-7} M. Inhibition of the production of PGE_2 which may be recorded, is mostly at the limit of statistical significance, and more often is below 15-20% of the basal value.

In view of the experimental evidence discussed above and of the role performed by the complement cascade, and namely its fraction C5a, in the processes that involve the activation and the infiltration of neutrophils, the compounds of formula (I) (including compounds of formula (I-a)) are particularly useful in the treatment of diseases such as psoriasis (R. J. Nicholoff et al., Am. J. Pathol., 138, 129, 1991), pemphigo and pemphigoid, rheumatoid arthritis (M. Selz et al., J. Clin. Invest., 87, 463, 1981), intestinal chronic inflammatory pathologies such as ulcerative colitis (Y. R. Mahida et al., Clin. Sci., 82, 273, 1992), acute respiratory distress syndrome and idiopathic fibrosis (E. J. Miller, previously cited, and P. C. Carré et al., J. Clin. Invest., 88, 1882, 1991), cystic fibrosis, chronic obstructive pulmonary disease, glomerulonephritis (T. Wada et al.,

J. Exp. Med., 180, 1135, 1994) and in the prevention and the treatment of injury caused by ischemia and reperfusion.

The compounds of formula (IV) for their use as medicaments are described in International Patent Application PCT/EP02/01974. The new amides of formula (IV) described below in the Preparations section have biological activity comparable to that of amides described in the above patent application and can be used for the treatment of the same pathologies.

To this purpose, the compounds of formula (I) (including compounds of formula (I-a)) conveniently are formulated in pharmaceutical compositions using conventional techniques and excipients such as those described in "Remington's Pharmaceutical Sciences Handbook" MACK Publishing, New York, 18th ed., 1990.

The compounds of formula (I) (including compounds of formula (I-a)) can be administered by intravenous injection, as a bolus, in dermatological preparations (creams, lotions, sprays and ointments), by inhalation as well as orally in the form of capsules, tablets, syrup, controlled-release formulations and the like.

The average daily dose depends on several factors such as the severity of the disease, the condition, age, sex and weight of the patient. The dose will vary generally from 1 to 1500 mg of compounds of formula (I) per day, optionally divided in multiple administrations. Higher doses can be administered for long periods of time, thanks to the low toxicity of compounds of formula (I).

The following examples and preparations serve to illustrate the invention.

By convention, apices (e.g. R', S', S" etc.) show the absolute configurations present in substituent R_1 in the compounds of formula (I).

Abbreviations: THF: tetrahydrofuran; DMF: dimethylformamide; EtAc: ethyl acetate, HOBZ: hydroxybenzotriazol, DCC:dicyclohexylcarbodiimide.

Materials and methods

The amines used as reagents in the synthesis of compounds of formula (IV) are known products, generally commercially available or they can be prepared according to methods described in the literature.

The synthesis of 2-aryl-propionic acids of formula ϕ-Ar_3-$C(CH_3)H$-CO_2H and of their R-enantiomers is reported in International patent application PCT/EP01/01285.

The optical resolution was carried out by means of salification with R(+)-N-methylbenzylamine according to the method described by Akguen et al,. Arzneim. Forsch., 46:9 891-894, 1996.

PREPARATIONS

Preparation of Omega-aminoalkylamides of R-2-arylpropionic acid as intermediates

The preparation of compounds of formula (IV) is disclosed in International Patent application PCT/EP02/01974. Some compounds of formula (IV) are new and described for the first time in the present patent application.

Examples of the preparation of the new amides of formula (IV) are reported below.

PREPARATION 1

R(-)-2-[(3-benzoyl)phenyl]-N-[3"-(N',N'-dimethylamino)propyl]propionamide

Hydroxybenzotriazol (0.604 g, 3.93 mmol) and N,N-dicyclohexylcarbodiimmide (0.81 g, 3.93 mmol) are added to a solution of R(-)-ketoprofen (1g, 3.93 mmol) in anhydrous dichloromethane (25 mL). The mixture is stirred at r.t. for 30 min; N,N-dimethyl-1,3-propandiamine (0.49 mL, 3.93 mmol) is added to the suspension formed. The resulting suspension is stirred at r.t. overnight. Dicyclohexylurea (DCU) is then filtered off under vacuum and the filtrate is evaporated at reduced pressure; the crude oily residue is taken up in acetonitrile (20 mL) and the mixture left overnight at T=4°C. After the filtration of a further aliquot of DCU, the filtrate is again evaporated at reduced pressure and the residue is purified by means of flash chromatography on silica gel (eluent $CHCl_3/CH_3OH$ 8:2); R(-)-2-[(3'-benzoyl)phenyl]-N-[3"-(N',N'-dimethylamino)propyl]-propionamide (0.997 g, 2.94 mmol) is obtained as a transparent oil.

Yield 75%

$[\alpha]_D$ = -20 (c = 0.9; CH_3OH)

^{1}H-NMR ($CDCl_3$) δ 7.90-7.40 (m, 9H); 7.25 (s, 1H, CONH); 3.65 (m, 1H); 3.36 (m, 2H); 2.38 (m, 2H); 2.20 (s, 6H); 1.62 (m, 5H).

In a similar way the following compounds were also prepared:

R(-)-2-[(3'-benzoyl)phenyl]-N-(3"-N"'-piperidinopropyl)-propionamide

Yield 80%

$[\alpha]_D$ = -47.5 (c = 0.3; CH_3OH)

^{1}H-NMR ($CDCl_3$) δ 7.85-7.42 (m, 9H + CONH); 3.80 (m, 1H); 3.57-3.28 (m, 4H); 2.85 (m, 2H); 2.10 (m, 2H); 1.65 (m, 11H).

R(-)-2-[(4'-isobutyl)phenyl]-N-[3"-N'-(4",4"-piperidinediol)-propyl]-propionamide

$[\alpha]_D$ = -19.5 (c = 1; CH_3OH)

^{1}H-NMR (DMSO-d6) δ 8.05 (t, 1H, J= 6Hz, CONH); 7.25 (d, 2H, J=8Hz); 7.08 (d, 2H, J=8Hz); 3.55 (m, 1H); 3.40 (m, 2H); 3.35-3.25 (m, 6H); 2.38 (d, 2H, J=7Hz); 2.05 (m, 4H); 1.85 (m, 1H); 1.50 (m, 2H); 1.35 (d, 3H, J=7Hz); 0.87 (d, 6H, J=7Hz).

R(-)-2-[(4'-isobutyl)phenyl]-N-[3"-N'-(4"-carboxyamidopiperidin)-propyl]propionamide

$[\alpha]_D$ = -28.5 (c = 1; CH_3OH)

^{1}H-NMR (DMSO-d6) δ 8.45 (d, 2H, J=8Hz), CONH2); 8.10 (t, 1H, J= 6Hz, CONH); 7.35 (d, 2H, J=8Hz); 7.20 (d, 2H, J=8Hz); 3.65 (m, 1H); 3.42 (m, 2H); 3.15-2.90 (m, 6H); 2.35 (d, 2H, J=7Hz); 2.15 (m, 1H); 1.80 (m, 1H); 1.55 (m, 6H); 1.35 (d, 3H, J=7Hz); 0.85 (d, 6H, J=7Hz).

R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-N,N-dimethylaminomethylphenyl]-propionamide

$[\alpha]_D$ = -35 (c=1; CH_3OH)

^{1}H-NMR ($CDCl_3$): δ 7.82 (dd, 1H, J_1=8.4Hz, J_2=2Hz); 7.55 (d, 1H, J=2Hz); 7.20 (m, 2H); 7.10 (m, 2H); 6.85 (d, 2H, J=8.4Hz); 6.15 (bs, 1H, CONH); 3.70 (s, 2H); 3.50 (m, 1H); 3.20 (s, 6H); 2.45 (d, 2H, J=7Hz); 1.88 (m, 1H); 1.50 (d, 3H, J=7Hz); 0.85 (d, 6H, J=7Hz).

EXAMPLES

QUATERNARY SALTS OF OMEGA-AMINOALKYLAMIDES OF R-2-ARYL-PROPIONIC ACIDS

Example 1

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-1-methyl-piperidinium iodide

R(-)-2-[(4' -isobutyl)phenyl]-N-[3"-N' -(N' -methyl)piperidinopropyl]-propionamide (0.095 g; 0.287 mmol) is dissolved in anhydrous tetrahydrofuran (6 mL) under inert atmosphere. Methyl iodide (0.1mL, 1.61 mmol) is added to the solution; the solution is stirred at r.t. for 18 hours until the starting reagent is no longer detectable. The solvent is then evaporated at reduced pressure and the residue is taken up in isopropyl ether. A white precipitate forms which is stirred for 6 hours. The precipitate is filtered and dried under vacuum at T=40°C to yield the R(-)-2-[(4'-isobutyl)phenyl]-N-[3"-N' -(N'-methyl)-piperidinopropyl] propionamide iodide (0.114 g; 0.24 mmol) as a clear yellow waxy solid.

Yield 84%

$[\alpha]_D$ = -12 (c = 0.7; CH_3OH)

^{1}H-NMR (DMSO-d_6) δ 8.05 (t, 1H, J= 6Hz, CONH); 7.25 (d, 2H, J=8Hz); 7.08 (d, 2H, J=8Hz); 3.55 (m, 1H); 3.25-3.02 (m, 8H); 2.90 (s, 3H); 2.38 (d, 2H, J=7Hz); 1.85-1.55 (m, 7H); 1.50 (m, 2H); 1.35 (d, 3H, J=7Hz); 0.88 (d, 6H, J=7Hz).

The following compounds were prepared by using the method reported above:

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-trimetilammonium iodide

m.p. 105-110°C

$[\alpha]_D$ = -17 (c = 1.0; CH_3OH)

^{1}H-NMR ($CDCl_3$) δ 7.42 (d, 2H, J=8Hz); 7.20 (t, 1H, J=6Hz, CONH); 7.07 (d, 2H, J=8Hz); 3.83 (m, 1H); 3.77 (m, 2H); 3.55-3.20 (m, 2H); 3.18 (s, 9H); 2.40 (d, 2H, J=7Hz); 2.05 (m, 2H); 1.83 (m, 1H); 1.45 (d, 3H, J=7Hz); 0.9 (d, 6H, J=7Hz).

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-butyl}-trimethylammonium iodide

m.p. 100-103°C

$[\alpha]_D$ = -25 (c = 1.0; CH_3OH)

^{1}H-NMR ($CDCl_3$) δ 7.25 (d, 2H, J=8Hz); 7.09 (d, 2H, J=8Hz); 6.18 (s, 1H, CONH); 3.61 (m, 1H); 3.28 (m, 2H); 3.12 (m, 2H); 3.08 (s, 9H); 2.44 (d, 2H, J=7Hz); 1.81 (m, 1H); 1.75 (m, 4II); 1.50 (d, 3H, J=7Hz); 0.88 (d, 6H, J=7Hz).

R(-)-2-[(4'-isobutylphenyl)-propionylamino]-l,l-dimethylpiperidinium iodide

m.p. 80-85°C

$[\alpha]_D$ = -7 (c = 1.2; CH_3OH)

^{1}H-NMR (DMSO-d_6) δ 7.91 (d, 1H, J=7Hz, CONH); 7.22 (d, 2H, J=8Hz); 7.08 (d, 2H, J=8Hz); 3.80 (m, 1H); 3.53 (m, 1H); 3.35-3.30 (m, 4H); 3.08 (s, 3H); 3.00 (s, 3H); 2.40 (d, 2H, J=7Hz); 1.95-1.65 (m, 5H); 1.3 (d, 3H, J=7Hz); 0.87 (d, 6H, J=7Hz).

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-4-methylmorpholinium iodide

m.p. 84-87°C

$[\alpha]_D$ = -17 (c = 0.5; CH3OH)

1H-NMR ($CDCl_3$) δ 7.45 (d, 2H, J=8Hz); 7.02 (m, 3H, CONH + 2Har.); 4.25 (m, 2H); 3.92 (m, 1H); 3.88 (m, 1H); 3.80 (m, 1H); 3.53 (m, 1H); 3.35 (m, 2H); 3.15 (m, 1H); 3.00 (s, 3H); 2.92-2.70 (m, 4H); 2.40 (d, 2H, J=7Hz); 2.15 (m, 2H); 1.88 (m, 1H); 1.45 (d, 3H, J=7Hz); 0.92 (d, 6H, J=7Hz).

R(-)-2-[(4'-isobutylphenyl)-N-(trimethylammoniumethyl)-methylamide]-propionamide iodide

m.p. 70-72°C

$[\alpha]_D$ = -18 (c = 1.0; CH3OH)

1H-NMR (DMSO-d_6) δ 7.22 (d, 2H, J=8Hz); 7.11 (d, 2H, J=8Hz); 6.25 (bs, 2H, CONH); 3.57 (m, 1H); 3.30 (m, 2H); 3.10 (s, 9H); 2.45 (d, 2H, J=7Hz); 2.40 (m, 2H); 1.88 (m, 1H); 1.75 (m, 2H); 1.52 (d, 3H, J=7Hz); 0.92 (d, 6H, J=7Hz).

R(-)-{3-[2-(3'-benzoylphenyl)-propionylamino]-propyl}-trimethylammonium iodide

m.p. 62-65°C

$[\alpha]_D$ = -16.3 (c = 1.0; CH_3OH)

^{1}H-NMR (DMSO-d6) δ 8.20 (t, 1H, J=7Hz, CONH); 7.81-7.47 (m, 9H); 3.75 (m, 1H); 3.27-3.05 (m, 4H); 3.00 (s, 9H); 1.85 (m, 2H); 1.37 (d, 3H, J=7Hz).

R(-)-{3-[2-(3-benzoylphenyl)propionylamino]-propyl)]-1-methylpiperidinium iodide

m.p. 69-73°C

$[\alpha]_D$ = -10 (c = 0.6; CH_3OH)

^{1}H-NMR (DMSO-d_6) δ 8.18 (t, 1H, J=7Hz, CONH); 7.80-7.47 (m, 9H); 3.70 (m, 1H); 3.28-3.05 (m, 8H); 2.92 (s, 3H); 1.87-1.53 (m, 6H); 1.42 (m, 2H); 1.38 (d, 3H, J=7Hz).

(R)-{3-{2-[2-(2,6-dichlorophenylamino)-phenyl]-propionylamino}-propyl)-trimethylammonium iodide

$[\alpha]_D$ = -15 (c = 1.0; CH_3OH)

^{1}H-NMR (DMSO-d_6) δ 8.48 (m, 1H, CONH); 8.27 (s, 1H, NH); 7.52 (d, 2H, J=8Hz); 7.18 (q, 2H, J1=8Hz, J2=16Hz); 7.05 (t, 1H, J=7Hz); 6.88 (t, 1H, J=7Hz); 6.30 (d, 1H, J=8Hz); 3.75 (m, 1H); 3.30 (m, 11H); 3.21 (m, 2H); 1.88 (m, 2H); 1.64 (d, 3H, J=7Hz).

(2R), (4"S) 1-{4-carboxy-4-[2-(4-isobutyl-phenyl)-propionylamino]-butyl}-1-methyl-piperidinium iodide

$[\alpha]_D$ = -9.5 (c=1.0; CH_3OH)

^{1}H-NMR (DMSO-d_6): δ 8.66 (bs, 1H, CONH); 7.22 (d, 2H, J=8Hz); 7.5 (d, 2H, J=8Hz); 4.00 (m, 1H); 3.80 (m, 1H); 2.95 (m, 6H); 2.90 (s, 3H); 2.45 (d, 2H, J=7Hz); 1.82 (m, 1H); 1.70-1.33 (m, 10H); 1.31 (d, 3H, J=7Hz); 0.89 (d, 6H, J=7Hz).

(2R)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(1"-methyl-4"carbonyl)-piperidinium iodide

$[\alpha]_D$ = -39 (c = 1; CH_3OH)

^{1}H-NMR (DMSO-d6) δ 8.15 (t, 1H, J= 6Hz, CONH); 7.28 (d, 2H, J=8Hz); 7.12 (d, 2H, J=8Hz); 3.80 (m, 1H); 3.70 (m, 2H); 3.35-3.25 (m, 6H); 3.18 (s, 3H); 2.35 (d, 2H, J=7Hz); 2.12 (m, 4H); 1.85 (m, 1H); 1.50 (m, 2H); 1.37 (d, 3H, J=7Hz); 0.87 (d, 6H, J=7Hz).

2R-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(1"-methyl-4"-carboxyamide)-piperidinium iodide

$[\alpha]_D$ = -25 (c = 1; CH_3OH)

^{1}H-NMR (DMSO-d6) δ 8.74 (d, 2H, J=8Hz, CONH2); 8.18 (t, 1H, J= 6Hz, CONH); 7.30 (d, 2H, J=8Hz); 7.22 (d, 2H, J=8Hz); 3.75 (m, 1H); 3.45 (m, 2H); 3.35 (s, 3H); 3.20-3.00 (m, 6H); 2.38 (d, 2H, J=7Hz); 2.15 (m, 1H); 1.90 (m, 1H); 1.75 (m, 6H); 1.35 (d, 3H, J=7Hz); 0.85 (d, 6H, J=7Hz).

R(-)-2-[(4'-isobutyl)-phenyl]-N-[4"-N,N,N-trimethylaminomethylphenyl]-propionamide iodide

$[\alpha]_D$ = -23 (c=1; CH_3OH)

^{1}H-NMR (DMSO-d_6): δ 7.80 (dd, 1H, J_1=8.4Hz, J_2=2Hz); 7.55 (d, 1H, J=2Hz); 7.24 (m, 2H); 7.10 (m, 2H); 7.00 (d, 2H, J=8.4Hz); 6.20 (bs, 1H, CONH); 3.70 (s, 2H); 3.50 (m, 1H); 3.20 (s, 9H); 2.45 (d, 2H, J=7Hz); 1.88 (m, 1H); 1.50 (d, 3H, J=7Hz); 0.85 (d, 6H, J=7Hz).

Example 2

The following compound was prepared according to the method described in Example 1, but using ethyliodide as the reagent:

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl} triethylammonium iodide

m.p. 100-102°C

$[\alpha]_D$ = -19.5 (c = 1.0; CH_3OH)

^{1}H-NMR ($CDCl_3$) δ 7.43 (d, 2H, J=8Hz); 7.22 (t, 1H, J=6Hz, CONH); 7.10 (d, 2H, J=8Hz); 3.83 (m, 1H); 3.77 (m, 2H); 3.55-3.35 (m, 2H); 3.15 (q, 6H, J=7Hz); 2.95 (t, 9H, J=7Hz); 2.42 (d, 2H, J=7Hz); 2.05 (m, 2H); 1.85 (m, 1H); 1.45 (d, 3H, J=7Hz); 0.9 (d, 6H, J=7Hz).

Example 3

The following compound was prepared according to the method described in Example 1, but using benzyliodide as the reagent :

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(N-benzyl)-N,N-dimethylammonium iodide

m.p. 97-100°C

$[\alpha]_D$ = -12 (c = 1.0; CH_3OH)

^{1}H-NMR ($CDCl_3$) δ 7.42 (d, 2H, J=8Hz); 7.30-7.25 (m, 5H); 7.20 (t, 1H, J=6Hz, CONH); 7.07 (d, 2H, J=8Hz); 3.85 (m, 1H); 3.72 (m, 2H); 3.68 (s, 2H); 3.55-3.32 (m, 2H); 3.20 (s, 6H); 2.40 (d, 2H, J=7Hz); 2.05 (m, 2H); 1.83 (m, 1H); 1.45 (d, 3H, J=7Hz); 0.9 (d, 6H, J=7Hz).

Example 4

The following compound was prepared according to the method described in Example 1, but using cyclohexylmethyl metanesulfonate as the reagent:

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-N-cyclohexylmethyl-N,N-dimethyl-ammonium metaneosulfonate

$[\alpha]_D$ = -23 (c = 1.0; CH_3OH)

^{1}H-NMR (DMSO-d_6) δ 7.44 (d, 2H, J=8Hz); 7.20 (t, 1H, J=6Hz, CONH); 7.08 (d, 2H, J=8Hz); 3.83 (m, 1H); 3.77 (m, 2H); 3.55-3.20 (m, 4H); 3.18 (s, 6H); 3.00 (s, 3H); 2.40 (d, 2H, J=7Hz); 2.05 (m, 2H); 1.83 (m, 1H); 1.75 (m, 5H); 1.48 (m, 1H); 1.45 (d, 3H, J=7Hz); 1.22 (m, 3H); 0.95 (m, 2H); 0.9 (d, 6H, J=7Hz).

Example 5

The following compound was prepared according to the method described in Example 1, but using allyl bromide in lieu of methyl iodide

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-1-allylpiperidinium bromide

$[\alpha]_D$ = -14.5 (c = 0.5; CH_3OH)

^{1}H-NMR (DMSO-d6) δ 8.05 (t, 1H, J= 6Hz, CONH); 7.25 (d, 2H, J=8Hz); 7.08 (d, 2H, J=8Hz); 6.05 (m, 1H); 5.35 (d, 1H, J=2Hz); 5.15 (d, 1H, J=2Hz); 3.80 (d, 2H, J=7Hz); 3.55 (m, 1H); 3.25-3.02 (m, 8H); 2.38 (d, 2H, J=7Hz); 1.85-1.55 (m, 7H); 1.50 (m, 2H); 1.35 (d, 3H, J=7Hz); 0.88 (d, 6H, J=7Hz).

Example 6

The following compound was prepared starting from the (4-aminophenyl)trimethylammonium iodide hydrochloride (commercial reagent) :

R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-NNN-trimethylaminophenyl]-propionamide iodide

Hydroxybenzotriazol (0.62 g; 4.58 mmol) is added, at T=0°C, to a solution of (R)(-)Ibuprofen (1.01 g; 5 mmol) in DMF (4.5 mL). The solution is stirred at T=0°C for 30 min; (4-aminophenyl)-trimethylammonium iodide hydrochloride (1.433g; 4.56 mmol) is then added to the mixture. N,N-dicyclohexylcarbodiimmide (1.02 g; 4.95 mmol) is added gradually in small portions. After stirring at T=0°C for 2 h., the mixture is left to warm to r.t. Then it is stirred for 24 h. The DCU which is formed is filtered off and DMF is distilled off under reduced pressure. The residue is dissolved in H_2O and stirred in diisopropyl ether (30 mL) overnight at room temperature; the precipitate formed is filtered under vacuum and dried in oven at T=40°C for 6 h, yielding a white solid (1.67 g; 3.58 mmol);

$[\alpha]_D$ = -31 (c=1; CH_3OH)

^{1}H-NMR (DMSO-d_6): δ 7.85 (dd, 1H, J_1=8.4Hz, J_2=2Hz); 7.62 (d, 1H, J=2Hz); 7.24 (m, 2H); 7.10 (m, 2H); 7.02 (d, 2H, J=8.4Hz); 6.15 (bs, 1H, CONH); 3.50 (m, 1H); 3.25 (s, 9H); 2.45 (d, 2H, J=7Hz); 1.85 (m, 1H); 1.52 (d, 3H, J=7Hz); 0.90 (d, 6H, J=7Hz).

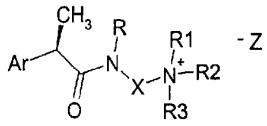
A reference herein to a prior art document is not an admission that the document forms part of the common general knowledge in the art in Australia.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

2002338784 28 Jul 2008

The claims defining the invention are as follows:

1. (R)-2-aryl-propionamide compound of formula (I-a):



(I-a)

wherein

- Ar is selected from:

  a) an aryl group selected in the group consisting of (+-)-p-((2-Oxocyclopentyl)methyl)phenyl, alpha-(4-(1-Oxo-2-iso-indolinyl)phenyl, 2-(4-(methallylamino)phenyl, 4-thienoylphenyl, 3-chloro-4-(2,5-dihydro-1H-pyrrol-1-yl)phenyl, 3-phenoxyphenyl, 4-isobutylphenyl, 3-benzoylphenyl;

  b) an aryl of formula (IIIb):

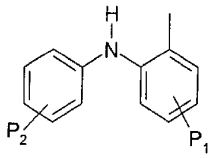
$$\Phi\text{-}Ar_b$$

(IIIb)

wherein:

- Ar_b is a phenyl mono- or poly-substituted by hydroxy, mercapto, C_1-C_3-alkoxy, C_1-C_3-alkylthio, chlorine, fluorine, trifluoromethyl, nitro, amino, optionally substituted C_1-C_7-acylamino;
- Φ is hydrogen; a linear or branched C_1-C_5 alkyl, C_2-C_5- alkenyl or C_2-C_5-alkynyl residue optionally substituted by C_1-C_3-alkoxycarbonyl, substituted or non-substituted phenyl, 2-, 3- or 4-pyridyl, quinolin-2-yl; a C_3-C_6-cycloalkyl; 2-furyl; 3-tetrahydrofuryl; 2-thiophenyl; 2-tetrahydrothiophenyl or a C_1-C_8-(alkanoyl, cycloalkanoyl, arylalkanoyl)-C_1-C_5-alkylamino group;

  c) a 2-(phenylamino)-phenyl of formula (IIIc):

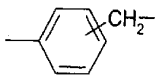


(IIIc)

2002338784 28 Jul 2008

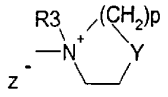
wherein the substituents P_1 and P_2 indicate that the two phenyl groups bear, each independently, mono- or poly-substitutions with C_1-C_4-alkyl, C_1-C_3-alkoxy groups, chlorine, fluorine and/or trifluoromethyl;

- R represents hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, these groups being optionally substituted by a CO_2R_4 group, wherein R_4 represents hydrogen or a linear or branched C_1-C_6 alkyl group or a linear or branched C_2-C_6 alkenyl group;
- X represents:
  linear or branched C_1-C_6 alkylene, C_4-C_6 alkenylene, C_4-C_6 alkynylene, optionally substituted by a CO_2R_4 group or by a $CONHR_5$ group wherein R_5 represents hydrogen, linear or branched C_2-C_6 alkyl or an OR_4 group, R_4 being defined as above, or (CHR')-CONH-$(CH_2)_n$ wherein n is an integer from 2 to 3 and R' is a methyl, having absolute configuration R or S;
- phenyl or a phenylmethylene group of formula:



- a $(CH_2)_m$-B-$(CH_2)_n$, group, optionally substituted by a CO_2R_4 or $CONHR_5$ group, as defined above, wherein B is an oxygen or sulfur atom, m is zero or an integer from 2 to 3 and n is an integer from 2 to 3; or B is a CO, SO or CONH group, m is an integer from 1 to 3 and n is an integer from 2 to 3;
- or X together with the nitrogen atom to which it is bound and with the R_1 group forms a nitrogen containing 3-7 membered heterocyclic monocyclic or polycyclic ring;
- R_1, R_2 and R_3 are independently linear or branched C_1-C_6 alkyl, optionally substituted by an oxygen or sulfur atom, a C_3-C_7 cycloalkyl, C_3-C_6 alkenyl, C_3-C_6-alkynyl, aryl, aryl-C_1-C_3-alkyl, hydroxy-C_2-C_3-alkyl group;
  or R_1 and R_2 together with the N atom to which they are bound, form a nitrogen containing 3-7 membered heterocyclic ring of formula (II) and R_3 independently has the meanings as defined above,

2002338784 28 Jul 2008



(II)

wherein Y represents a single bond, a methylene group, an oxygen atom, a nitrogen atom or a sulfur atom and p represents an integer from 0 to 3;

Z^- represents a pharmaceutically acceptable counter-ion of quaternary ammonium salts,

with the proviso that when Ar is biphenyl, R_2 and R_3 are not ethyl, and with the proviso that when X is (CHR')-CONH-$(CH_2)_n$, R is H.

2. Compound according to Claim 1, wherein the C_1-C_8-(alkanoyl, cycloalkanoyl, arylalkanoyl)-C_1-C_5-alkylamino group is acetyl-N-methyl-amino or pivaloyl-N-ethyl-amino.

3. Compound according to any one of the previous Claims wherein:

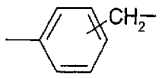
R is hydrogen;

X is:

- a linear C_1-C_6 alkylene, optionally substituted at C_1 by a $-CO_2R_4$ group as defined above;
- a linear C_1-C_6 alkylene optionally substituted at C_1 by a $-CONHR_5$ group wherein R_5 is OH;
- 2-butynylene, cis-2-butenylene, trans-2-butenylene;
- 3-oxa-pentylene, 3-thio-pentylene, 3-oxa-hexylene, 3-thio-hexylene;
- $(CH_2)_m$-CO-NH-$(CH_2)_n$-wherein m and n are each independently an integer from 2 to 3;
- (CHR')-CONH-$(CH_2)_n$ wherein n is an integer from 2 to 3 and R' is a methyl, having absolute configuration R or S;

2002338784 28 Jul 2008

- a phenyl or phenylmethylene group of formula:



- or X, together with the N atom, form an azocycloaliphatic ring.

4. Compound according to Claim 3, wherein X is a linear C_2-C_4 alkylene.

5. Compound according to any one of Claims 1 to 3, wherein $NR_1R_2R_3$ group represents a trimethylammonium, triethylammonium, N-methyl-N,N-diethylammonium, N-methyl-N,N-diisopropylammonium, N-cyclohexylmethyl-N,N-dimethylammonium, N-cyclopentylamino-N,N-dimethylammonium, N-methyl-1-piperidinium, N-ethyl-1-piperidinium, N-methyl-4-morpholinium, N-methyl-4 thiomorpholinium, N-benzyl-N,N-dimethylammonium, N-allyl-1-piperidinium, 4-oxy-N-methyl-piperidinium group or X together with the amine N to which it is bound and with the R_1 group, forms a nitrogen containing 5-6 membered heterocyclic ring and the substituents R_2 and R_3 represent independently a methyl or cyclohexyl residue.

6. Compound according to any one of Claims 1 to 5, wherein Ar is selected from 4-isobutylphenyl, 4-cyclohexylmethylphenyl, 4-(2-methyl)allyl-phenyl, 3-phenoxyphenyl, 3-benzoyl-phenyl, 3-acetyl-phenyl, the single (R) (S) diastereoisomers and the diastereoisomeric (R,S) mixture of 3-C_6H_5-CH(OH)-phenyl, 3-CH_3-CH(OH)-phenyl, 5-C_6H_5-CH(OH)-thienyl, 4-thienyl-CH(OH)-phenyl, 3-(pyrid-3-yl)-CH(OH)-phenyl, 5-benzoyl-thien-2-yl, 4-thienoyl-phenyl, 3-nicotinoyl-phenyl, 2-fluoro-4-phenyl, 6-metoxy-2-naphthyl, 5-benzoyl-2-acetoxy-phenyl, 5-benzoyl-2-hydroxy-phenyl, 4-cyclopentyl-phenyl, 4-(2-oxo-cyclopentyl)-phenyl, 4-(2-oxo-cyclohexyl)-phenyl.

7. Compound according to Claim 1 or 5, wherein Ar is a phenyl group 3-substituted by isoprop-1-en-1-yl-isopropyl, pent-2-en-3-yl, pent-3-yl; 1-phenylethylen-1-yl; α-methylbenzyl.

8. Compound according to Claim 1 or 5, wherein the Ar groups in the formula (IIIc) are 2-(2,6-dichloro-phenyl-amino)-phenyl; 2-(2,6-dichlorophenyl-amino)-5-

2002338784 28 Jul 2008

chloro-phenyl; 2-(2,6-dichloro-3-methyl-phenyl-amino)-phenyl; 2-(3-trifluoromethyl-phenylamino)-phenyl.

9. Compound according to any one of the previous Claims, wherein Z^- is a halide chosen from Cl^-, I^-, Br^-, a sulfate anion, methanesulfonate or p-toluenesulfonate.

10. Compound according to any one of the previous Claims, selected from:

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-trimethylammonium iodide;

(R)-{3-[2-(3-benzoylphenyl)-propionylamino] propyl}-trimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl} -N-ethyl-N,N-dimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-N-cyclohexylmethyl- N,N-dimethylammonium iodide;

(R)-{3-[2-(4-cyclopentylmethylphenyl)-propionylamino] propyl}-trimethylammonium iodide;

(R)-{3-[2-(3-benzoylphenyl)-propionylamino] propyl}-N-isopropyl-N,N-dimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] butyl-trimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-1-methyl-piperidinium iodide;

(R)-{3-[2-(3-benzoylphenyl)-propionylamino] propyl}-1-methyl piperidinium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-4-methyl-morpholinium iodide;

(R)-{3-[2-(3-isopropylphenyl)-propionylamino] propyl}-4-methyl-thiomorpholinium methanesulfonate;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] ethyl-trimethylammonium bromide;

(R)-2-[(4-isobutylphenyl)-propionylamino]-1,1-dimethyl)piperidinium p-toluenesulfonate;

(R),(S')-2-(4-isobutylphenyl)-N-[(1-carboxy-2"-N,N,N-trimethylammonium)ethyl] propionamide methanesulfonate;

R(-)-2-[(4-isobutylphenyl)-N-(trimethylammoniumethyl) methylamide] propionamide iodide;

2002338784 28 Jul 2008

(R)(3-{2-[2(2,6-dichlorophenylamino)-phenyl]-propionylamino}-propyl)-trimethylammonium methanesulfonate;

(2R), (4"S)1-{4-carboxy-4-[2-(4-isobutyl-phenyl)-propionylamino] butyl}-1-methyl-piperidinium iodide;

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(N-benzyl)-N,N-dimethylammonium iodide;

2R-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(1"methyl-4" carboxyamide) piperidinium iodide;

(2R)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(1"-methyl-4" carbonyl) piperidinium iodide;

R(-)-{3,-[-(4'-isobutylphenyl)-propionylamino]-propyl}-triethylammonium iodide;

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-1-allylpiperidinium bromide;

R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-N,N,N-trimethylaminophenyl] propionamide iodide;

R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-N,N,N-trimethylaminomethylphenyl] propionamide iodide.

11. Compound according to any one of Claims 1 to 10, for use as a medicament.

12. Compound according to any one of Claims 1 to 10, for use as an inhibitor of the chemotaxis of neutrophils and monocytes induced by C5a.

13. Compound according to any one of Claims 1 to 10, for use in the treatment of psoriasis, pemphigus and pemphigoid, rheumatoid arthritis, intestinal chronic inflammatory pathologies, acute respiratory distress syndrome, idiopathic fibrosis, cystic fibrosis, chronic obstructive pulmonary disease and glomerulonephritis.

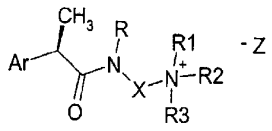
14. Compound according to Claim 13, wherein the intestinal chronic inflammatory pathology is ulcerative colitis.

15. Compound according to any one of Claims 1 to 10, for use in the prevention and treatment of injury caused by ischemia and reperfusion.

16. Pharmaceutical composition containing a compound according to any one of Claims 1 to 10 in admixture with a suitable carrier thereof.

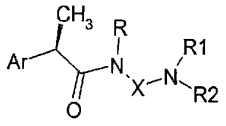
2002338784 28 Jul 2008

17. Process for the preparation of (R)-2-aryl-propionamide compounds of formula (I-a):



(I-a)

wherein Ar, X, R_1, R_2, R_3 have the meaning as defined in claim 1, comprising reaction of amides of formula (IV-a)



(IV-a)

with compounds of formula R_3Z, wherein Z is a conventional leaving group.

18. Process according to Claim 17, wherein the leaving group is chloride, bromide, iodide, methanesulfonate, p-toluensulfonate or sulfate.

19. A method of treating psoriasis, pemphigus and pemphigoid, rheumatoid arthritis, intestinal chronic inflammatory pathologies, acute respiratory distress syndrome, idiopathic fibrosis, cystic fibrosis, chronic obstructive pulmonary disease or glomerulonephritis in a patient, the method comprising administering to the patient an effective amount of a compound according to any one of Claims 1 to 10.

20. A method according to Claim 19 wherein the intestinal chronic inflammatory pathology is ulcerative colitis.

21. The use of a compound according to any one of Claims 1 to 10 in the manufacture of a medicament for the treatment of psoriasis, pemphigus and pemphigoid, rheumatoid arthritis, intestinal chronic inflammatory pathologies, acute respiratory distress syndrome, idiopathic fibrosis, cystic fibrosis, chronic obstructive pulmonary disease or glomerulonephritis.

22. Use according to Claim 21 wherein the intestinal chronic inflammatory pathology is ulcerative colitis.

23. A method of preventing or treating an injury caused by ischemia and reperfusion in a patient, the method comprising administering to the patient an effective amount of a compound according to any one of Claims 1 to 10.

24. Use of a compound according to any one of Claims 1 to 10 in the manufacture of a medicament for the prevention or treatment of an injury caused by ischemia and reperfusion.

25. A method of inhibiting chemotaxis of neutrophils and monocytes induced by C5a in a patient, the method comprising administering to the patient an effective amount of a compound according to any one of Claims 1 to 10.

26. The use of a compound according to any one of Claims 1 to 10 in the manufacture of a medicament for inhibiting chemotaxis of neutrophils and monocytes induced by C5a.

27. Compound according to Claim 1 or process according to Claim 17, substantially as herein described with reference to any one of the Examples.