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(54) Benævnelse: **KVATERNÆRE AMMONIUMSALTE AF OMEGA-AMINOALKYLAMIDER AF R-2-ARYL-PROPIONSYRER OG FARMACEUTISKE SAMMENSÆTNINGER INDEHOLDENDE DEM**

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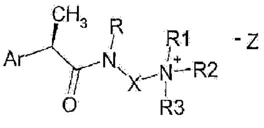
DESCRIPTION

Introduction and background of the invention

[0001] 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. Lanza et al, J Med Chem, 35 (1992), pages 252-258, discloses substituted 4,6-diaminoquinolines as selective antagonist of C5a receptor. The compounds of the invention 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.

Detailed description of the invention

[0002] The present invention relates to (R)-2-aryl-propionamides of formula (I):

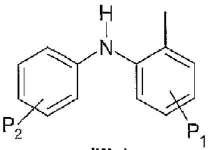


(I)

wherein

$^{-}$Z represents a pharmaceutically acceptable counterion of quaternary ammonium salts and Ar is chosen among:

4-isobutylphenyl, 3-benzoyl-phenyl, a phenyl group 3-substituted by isopropyl and a 2-(phenylamino)-phenyl of formula (III c):



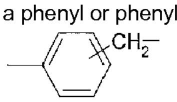
(IIIc)

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;

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 wherein R_4 is H;
- a linear C_1-C_6 alkylene optionally substituted at C_1 by a -$CONHR_5$ group wherein R_5 is OH;
- $(CH_2)_m$-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;

  the $NR_1R_2R_3$ group represents a trimethylammonium, triethylammonium, 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 R1 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.

[0003] The aryl groups comprise, in addition to the above described aryl of formula (IIIC): 4-isobutylphenyl, 3-benzoyl-phenyl, 3 phenyl groups 3-substituted by: isopropyl.

[0004] Particularly preferred aryls of formula (III c) 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.

[0005] Particularly preferred compounds of the invention are:

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

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

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

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

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

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

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

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

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

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

R(-)-2-[(4-isobutylphenyl)-N-(trimethylammonimethyl)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-dimethyl ammonium iodide;

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

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

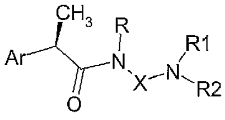
R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-triethylammonium iodide;

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.

[0006] 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)

[0007] 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.

[0008] 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.

[0009] 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 the invention 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 the invention of formula (I).

[0010] 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.

[0011] The compounds of the invention 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.

[0012] Human recombinant fractions C5a and C5a-desArg (Sigma) were used as stimulating agents in the chemotaxis experiments, giving practically identical results.

[0013] 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.

[0014] In the chemotaxis experiments, the PMNs were incubated with the compounds of the invention of formula (I) for 15' at 37°C in an atmosphere containing 5% CO_2.

[0015] 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.

[0016] During the chemotaxis assay (according to W. Fallcet et al., J. Immunol. Methods, 33, 239, 1980) PVP-free filters with a porosity of 5 µm and microchambers suitable for replication were used.

[0017] The compounds of the invention in 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.

[0018] Inhibition of C5a-induced chemotactic activity by the individual compounds of the invention of formula (I) was evaluated by incubating the microchamber for the chemotaxis for 60 min at 37°C in an atmosphere containing 5% CO2.

[0019] Evaluation of the ability of the compounds of the invention 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 the invention 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.

[0020] By way of example, the inhibition data of the chemotaxis of PMN (C=10^{-6} M) of some representative compounds of the invention 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}-1-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

[0021] 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.

[0022] 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.

[0023] It is therefore a further object of the present invention the use of the compounds of the invention as medicaments.

[0024] 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 the invention 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.

[0025] 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.

[0026] To this purpose, the compounds of the invention of formula (I) 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.

[0027] The compounds of the invention 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.

[0028] 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 the invention.

[0029] The following examples and preparations serve to illustrate the invention.

[0030] By convention, apices (e.g. R', S', S".) show the absolute configurations present in substituent R_1 in the compounds of the invention of formula (I). Abbreviations: THF: tetrahydrofuran; DMF: dimethylformamide; EtAc: ethyl acetate, HOBZ: hydroxybenzotriazol, DCC:dicyclohexylcarbodiimide.

Materials and methods

[0031] 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.

[0032] 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.

[0033] 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

[0034] 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.

[0035] 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

[0036] 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

[0037] $[\alpha]_D$ = -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

[0038] $[\alpha]_D$ = -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

[0039] $[\alpha]_D$ = -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-ARYLPROPIONIC ACIDS

Example 1

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

[0040] 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).

[0041] The following compounds were prepared by using the method reported above:

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

[0042] 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

[0043] 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, 4H); 1.50 (d, 3H, J=7Hz); 0.88 (d, 6H, J=7Hz).

R(-)-2-[(4'-isobutylphenyl)-propionylamino]-1,1-dimethylpiperidinium iodide m.p. 80-85°C

[0044] $[\alpha]_D$ = -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

[0045] 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

[0046] 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

[0047] 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

[0048] 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

[0049] $[\alpha]_D$ = -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

[0050] $[\alpha]_D$ = -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

[0051] $[\alpha]_D$ = -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

[0052] $[\alpha]_D$=-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

[0053] $[\alpha]_D$ = -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

[0054] 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

[0055] 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

[0056] 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

[0057] 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

[0058] 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 methanesulfonate

[0059] $[\alpha]_D$ = -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

[0060] 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

[0061] $[\alpha]_D$ = -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

[0062] 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

[0063] 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, CON<u>H</u>); 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).

REFERENCES CITED IN THE DESCRIPTION

Patent documents cited in the description

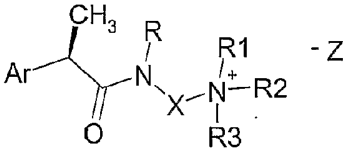
- EP0201974W [0008] [0025] [0034]
- EP0101285W [0032]

Non-patent literature cited in the description

- **LANZA et al.**J Med Chem, 1992, vol. 35, 252-258 [0001]
- **W.J. MING et al.**J. Immunol., 1987, vol. 138, 1469- [0011]
- **W. FALLCET et al.**J. Immunol. Methods, 1980, vol. 33, 239- [0016]
- **VAN DAMME J. et al.**Eur. J. Immunol., 1989, vol. 19, 2367- [0019]
- **PATRIGNANI et al.**J. Pharmacol. Exper. Ther., 1994, vol. 271, 1705- [0021]
- **R. J. NICHOLOFF et al.**Am. J. Pathol., 1991, vol. 138, 129- [0024]
- **M. SELZ et al.**J. Clin. Invest., 1981, vol. 87, 463- [0024]
- **Y. R. MAHIDA et al.**Clin. Sci., 1992, vol. 82, 273- [0024]
- **P. C. CARRÉ et al.**J. Clin. Invest., 1991, vol. 88, 1882- [0024]
- **T. WADA et al.**J. Exp. Med., 1994, vol. 180, 1135- [0024]
- Remington' s Pharmaceutical Sciences HandbookMACK Publishing19900000 [0026]
- **AKGUEN et al.**Arzneim. Forsch., 1996, vol. 46, 9891-894 [0033]

Patentkrav

1. (R)-2-aryl-propionamidforbindelser med formel (I):



(I)

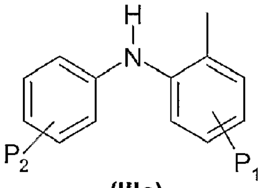
hvor

Ar er valgt fra:

a) en Ar_a der er valgt fra gruppen bestående af 4-isobutylphenyl, 3-benzoyl-phenyl;

b) en phenylgruppe 3-substitueret med isopropyl,

c) en 2-(phenylamino)-phenyl med formel (III c):



(IIIc)

hvor substituenterne P1 og P2 indikerer at de to phenylgrupper bærer, hver uafhængigt, mono-eller poly-substitutioner med C_1-C_4-alkyl, C_1-C_3-alkoxygrupper, chlor, fluor og/eller trifluormethyl.

R er hydrogen;

X er:

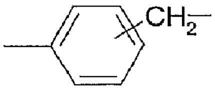
-en lineær C_1-C_6 alkylen, eventuelt substitueret ved C1 med en $-CO_2R_4$ hvor R_4 er H;

-en lineær C_1-C_6 alkylen eventuelt substitueret ved C1 med en $-CONHR_5$-gruppe, hvor R5 er OH;

-$(CH_2)_m$-CO-NH-$(CH_2)_n$-, hvor m og n hver er uafhængigt et helt tal fra 2 til 3;

-(CHR')-CONH-$(CH2)_n$, hvor n er et helt tal fra 2 til 3 og R' er en methyl, med absolut konfiguration R eller S;

-en phenyl-eller phenylmethylen-gruppe med formel:



-eller X, sammen med det N-atom til hvilket det er bundet og R1-gruppen, danner en azocycloalifatisk ring,

$NR_1R_2R_3$-gruppe betegner en trimethylammonium-, triethylammonium-, N-cyclohexylmethyl-, 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-oxo-N-methyl-piperidinium-gruppe eller X sammen med den amin N til hvilken den er bundet og med R1-gruppen, danner et nitrogen indeholdende 5-6 leddet heterocyklisk ring og substituenterne R_2 og R_3 betegner uafhængigt en methyl-eller cyclohexylgruppe,

Z^-betegner en farmaceutisk acceptabel mod-ion af kvaternære ammoniumsalte,

eller forbindelserne er (R)-{3-[2-(3-benzoylphenyl)-propionylamino]propyl}-N-isopropyl-N,N-dimethylammoniumiodid eller (R)-{3-[2-(4-isobutylphenyl)-propionylamino]propyl}-N-ethyl-N,N-dimethylammoniumiodid.

2. Forbindelser ifølge krav 1, hvor X er en lineær C2-C4 alkylen.

3. Forbindelser ifølge krav 1 eller 2, hvor Ar-grupperne i formlen (IIIc) vælges fra 2-(2,6-dichlor-phenyl-amino)-phenyl; 2-(2,6-dichlorphenyl-amino)-5-chlor-phenyl; 2-(2,6-dichlor-3-methyl-phenyl-amino)-phenyl; 2-{3-trifluormethyl-phenylamino)-phenyl.

4. Forbindelser ifølge et hvilket som helst af de foregående krav, hvor Z^- er et halid valgt fra Cl-, I-, Br^-, en sulfatanion, methansulfonat eller p-toluensulfonat.

5. Forbindelser ifølge et hvilket som helst af de foregående krav, valgt fra:

- (R)-(3-{2-[2-(2,6-dichlorphenylamino)-phenyl]propionylamino}propyl)-trimethylammoniumiodid,
- (R)-{3-[2-(4-isobutylphenyl)-propionylamino]propyl}-trimethylammoniumiodid;
- (R)-{3-[2-(3-benzoylphenyl)-propionylamino]propyl}-trimethylammoniumiodid;
- (R)-{3-[2-(4-isobutylphenyl)-propionylamino]propyl}-N-ethyl-N,N-dimethylammoniumiodid;
- (R)-{3-[2-(4-isobutylphenyl)-propionylamino]propyl}-N-cyclohexylmethyl-N,N-dimethylammoniummethansulfonat
- (R)-{3-[2-(4-isobutylphenyl)-propionylamino]propyl}-N-cyclohexylmethyl-N,N-dimethylammoniumiodid;
- (R)-{3-[2-(4-cyclopentylmethylphenyl)-propionylamino]propyl}-trimethylammoniumiodid;
- (R)-{3-[2-(3-benzoylphenyl)-propionylamino]propyl}-N-isopropyl-N,N-dimethylammoniumiodid;
- (R)-{4-[2-(4-isobutylphenyl)-propionylamino]butyl}-trimethylammoniumiodid;

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

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

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

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

- (R)-{2-[2-(4-isobutylphenyl)-propionylamino]ethyl}-trimethylammoniumbromid;

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

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

- R(-)-2-[(4-isobutylphenyl)-N-(trimethylammoniumethyl)methylamid]propionamidiodid;

- (R)(3-{2-[2(2, 6-dichlorphenylamino)-phenyl]-propionylamino}-propyl)-trimethylammoniummethansulfonat;

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

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

- 2R-{3-[2-(4'-isobutylpheny])-propionylamino]-propyl}-(1"methyl-4" carboxyamid)piperidiniumiodid;

- (2R)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(1"-methyl-4"oxo)piperidiniumiodid;

- R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-triethylammoniumiodid;
- R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-1-allylpiperidiniumbromid;
- R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-N,N,N-trimethylaminophenyl]propionamidiodid
- R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-N,N,N-trimethylaminomethylphenyl]propionamidiodid.

6. Forbindelser ifølge et hvilket som helst af kravene 1 til 5, til anvendelse som medikamenter.

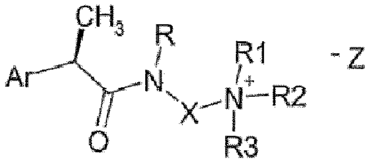
7. Forbindelser ifølge et hvilket som helst af kravene 1 til 5, til anvendelse som inhibitorer af kemotaksi af neutrofiler og monocytter induceret ved C5a.

8. Forbindelser ifølge et hvilket som helst af kravene 1 til 5, til anvendelse i behandlingen af psoriasis, pemphigus og Pemphigoid, rheumatoid arthritis, intestinale kroniske inflammatoriske patologier herunder ulcerativ colitis, akut respiratorisk distress syndrom, idiopatisk fibrose, cystisk fibrose, kronisk obstruktiv pulmonær sygdom og glomerulonephritis.

9. Forbindelser ifølge et hvilket som helst af kravene 1 til 5, til anvendelse i forebyggelsen og behandlingen af skader forårsaget ved iskæmi og reperfusion.

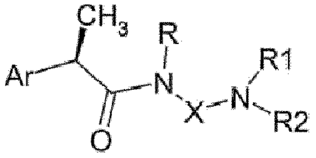
10. Farmaceutiske sammensætningerne indeholdende en forbindelse ifølge kravene 1-5 i blanding med en egnet bærer deraf.

11. Fremgangsmåde til fremstillingen af (R)-2-aryl-propionamidforbindelser med formel (I):



(I)

hvor Ar, X, R_1, R_2, R_3 har betydningen som defineret i krav 1, omfattende omsætning af amider med formel (IV)



(IV)

med forbindelser med formel R_3Z, hvor Z er en konventionel fraspaltningsgruppe.