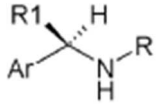
CLAIMS

1. Use of a C5aR inhibitor in the manufacture of a medicament for the prevention and/or treatment of chemotherapy-induced iatrogenic pain, wherein the medicament is to be administered orally.
2. The use according to claim 1, wherein the medicament is for the prevention and/or treatment of allodynia associated to chemotherapy-induced iatrogenic pain.
3. The use according to claim 1 or claim 2, wherein said C5aR inhibitor is selected from a compound of formula (I)



(I)

or a pharmaceutically acceptable salt,

wherein

R is selected from:

- 2 -thiazolyl or 2-oxazolyl, unsubstituted or substituted by a group selected from methyl, tert -butyl or trifluoromethyl group;
- C(Ra)=N-W wherein W is linear or branched C_1-C_4 alkyl,
- CORa, SORa, SO_2Ra, PORa, PO_2Ra,

wherein

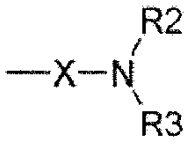
Ra is selected from

- C_1-C_5-alkyl, C_3-C_6-cycloalkyl, C_2-C_5-alkenyl, unsubstituted or substituted phenyl with a group selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halo-C_1-C_4-alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino;
- a heteroaryl group selected from pyridine, pyrimidine, pyrrole, thiophene,

furane, indole, thiazole, oxazole, such heteroaryl being unsubstituted or substituted with a group selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halo-C_1-C_4-alkoxy, hydroxy, C_1-C_4- acyloxy, phenoxy, cyano, nitro, amino;

- a α or β carboxyalkyl residue consisting of straight or branched C_1- C_6-alkyl, C_3-C_6-cycloalkyl, C_2-C_6-alkenyl, C_1-C_6-phenylalkyl, optionally substituted with a further carboxy (COOH) group;

- an ω-aminoalkylamino group of formula II:



(II)

wherein

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_2R4 group or by a CONHR5 group, wherein R4 represents hydrogen or a linear or branched C_1-C_6 alkyl group or a linear or branched C_2-C_6 alkenyl group, wherein R5 represents hydrogen, linear or branched C_2- C_6 alkyl or an OR4 group, R4 being defined as above;

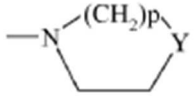
- a $(CH_2)_m$-B-$(CH_2)_n$, group, optionally substituted by a CO_2R4 or CONHR5 group, as defined above, wherein B is an oxygen, or sulfur atom, or nitrogen atom optionally substituted by a C_1-C_4 alkyl group, m is zero or an integer from 2 to 3 and n is an integer from 2 to 3, or B is a CO, SO or 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 R2 group forms a nitrogen containing 3-7 membered heterocyclic, monocyclic or polycyclic ring, and R3 represents hydrogen, C_1-C_4 alkyl, C_1-C_4 acyl, unsubstituted or substituted phenyl with a group selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, hydroxy, C_1-C_4- acyloxy, phenoxy, cyano, nitro, amino;

R2 and **R3** are independently:

hydrogen, linear or branched C_1-C_6 alkyl, optionally interrupted by an oxygen or sulfur atom, a C_3-C_7 cycloalkyl, C_3-C_6 alkenyl, C_3-C_6-alkynyl, aryl-C_1-C_3-alkyl, hydroxy-C_2-C_3-alkyl group;

or R2 and R3 together with the N atom to which they are bound, form a 3-7 membered nitrogen heterocyclic ring of formula (III)



(III)

wherein

Y represents:

- a single bond, CH_2, O, S, or a N-R6 group, where R6 represents hydrogen, C_1-C_4 alkyl, C_1-C_4 acyl, unsubstituted or substituted phenyl with a group selected from halogen, C_1-C_4-alkyl, C_1-C_4- alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino,

and p represents an integer from 0 to 3;

- a residue of formula SO_2R7 wherein R7 is C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_2-C_6-alkenyl, aryl and heteroaryl;

R1 is linear or branched C_1-C_5 alkyl, C_3-C_5 cycloalkyl;

Ar is a phenyl group unsubstituted or substituted by one or more groups independently selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino, C_1-C_4-acylamino, halo-C_1-C_3-alkyl, halo-C_1-C_3-alkoxy, benzoyl, heteroaryl carbonyl, heteroaryl, linear or branched C_1-C_8-alkanesulfonate, linear or branched C_1-C_8-alkanesulfonamides, linear or branched C_1-C_8 alkyl sulfonylmethyl;

or Ar is a heteroaryl ring selected from pyridine, pyrrole, thiophene, furan, indole.

4. The use according to claim 3, wherein

R is selected from:

- 2-thiazolyl or 2-oxazolyl, unsubstituted or substituted by a group selected from methyl, tert-butyl or trifluoromethyl group;
- C(Ra)=N-W wherein W is linear or branched C_1-C_4 alkyl,
- CORa, SORa or SO_2Ra,

wherein Ra is as defined above;

Ar is selected from:

3 ‘-benzoylphenyl, 3 '-(4-chloro-benzoyl)-phenyl, 3 '-(4-methyl-benzoyl)-phenyl, 3 '-acetyl-phenyl, 3'-propionyl-phenyl, 3'-isobutanoyl-phenyl, 4'-isobutyl-phenyl, 4' -trifluoromethanesulfonyloxy-phenyl, 4'-benzenesulfonyloxy-phenyl, 4'-trifluoromethanesulfonylamino-phenyl, 4'-benzenesulfonylamino-phenyl, 4'-benzenesulfonylmethyl-phenyl, 4'-acetoxyphenyl, 4'-propionyloxy-phenyl, 4'-benzoyloxy-phenyl, 4'-acetylamino-phenyl, 4'-propionylamino-phenyl, 4'-benzoylamino-phenyl, 3 '-(furan-2-carbonyl)-phenyl, 3 '-(benzofuran-2-carbonyl)-phenyl, 3 '-(thiophen-2-carbonyl)-phenyl, 3 '-(pyridine-2-carbonyl)-phenyl, 3 '-

(thiazole-2-carbonyl)-phenyl, 3'-(oxazole-2-carbonyl)-phenyl, 3'-(2-furyl)-phenyl, 3'-(2-oxazolyl)- phenyl, 3'-(3-isoxazolyl)-phenyl, 3'-(2-benzoxazolyl)-phenyl, 3'-(3-benzoisoxazolyl)-phenyl, 3'-(2-thiazolyl)-phenyl, 3'-(2-pyridyl)-phenyl, 3'-(2-thiophenyl)-phenyl;

or Ar is a heteroaryl ring selected from pyridine, pyrrole, thiophene, furan or indole.

5. The use according to claim 3, wherein

R is

- 2-thiazolyl, unsubstituted or substituted by a group selected from methyl or trifluoromethyl group;

- CORa, SO_2Ra, SORa;

wherein

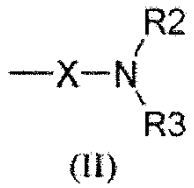
Ra is selected from:

- C_1-C_5-alkyl, C_3-C_5-cycloalkyl;

- phenyl, 2-pyridyl, 2-thiazolyl, 2-furyl, 2-pyrrolyl, 2-thiofenyl, 2-indolyl groups;

- a carboxylalkyl group consisting of straight or branched C_1-C_6-alkyl, C_1-C_6-phenylalkyl group;

- an ω-alkylamino group of formula II,



(II)

(II)

wherein

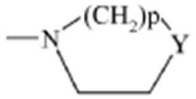
X represents:

linear or branched C_1-C_6 alkylene, C_4-C_6 alkenylene, C_4-C_6 alkynylene;

or X together with the nitrogen atom to which it is bound and with the R2 group forms a nitrogen containing 3-7 membered heterocyclic monocyclic ring and R3 represents hydrogen or C_1-C_4 alkyl;

R2 and **R3** are independently hydrogen, linear or branched C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_6 alkenyl, C_3-C_6-alkynyl;

or R2 and R3 together with the N atom to which they are bound, form a 4-6 membered nitrogen containing heterocyclic ring of formula (III)



(III)

wherein **Y** represents CH_2, O, S, or a N-R6 group, where R6 represents hydrogen, C_1-C_4 alkyl, C_1-C_4 acyl, and p represents an integer from 0 to 2;

R1 is methyl;

Ar is selected from:

3 '-benzoylphenyl, 3 '-(4-chloro-benzoyl)-phenyl, 3 '-(4-methyl-benzoyl)-phenyl, 3 '-acetyl-phenyl, 3'-propionyl-phenyl, 3'-isobutanoyl-phenyl, 4'-isobutyl- phenyl, 4' -trifluoromethanesulfonyloxy-phenyl, 4'-benzenesulfonyloxy-phenyl, 4'-trifluoromethanesulfonylamino-phenyl, 4'-benzenesulfonylamino-phenyl, 4'-benzenesulfonylmethyl-phenyl, 4'-acetoxyphenyl, 4'-propionyloxy-phenyl, 4'-benzoyloxy-phenyl, 4'-acetylamino-phenyl, 4'-propionylamino-phenyl, 4'-benzoylamino-phenyl; 3 '-(furan-2-carbonyl)-phenyl; 3 '-(benzofuran-2-carbonyl)-phenyl; 3 '-(thiophen- 2-carbonyl)-phenyl; 3 '-(pyridine-2-carbonyl)-phenyl, 3 '-

(thiazole-2-carbonyl)- phenyl, 3'-(oxazole-2-carbonyl)-phenyl; 3'-(2-furyl)-phenyl, 3'-(2-oxazolyl)- phenyl, 3'-(3-isoxazolyl)-phenyl, 3'-(2-benzoxazolyl)-phenyl, 3'-(3-benzoisoxazolyl)-phenyl, 3'-(2-thiazolyl)-phenyl, 3'-(2-pyridyl)-phenyl, 3'-(2-thiophenyl)-phenyl.

6. The use according to claim 3, wherein

R is

- 2-thiazolyl, unsubstituted or substituted by a group selected from methyl or trifluoromethyl;

- CORa,SO_2Ra

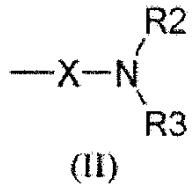
wherein

Ra is selected from:

- C_1-C_5-alkyl, C_3-C_5-cycloalkyl;

- phenyl, 2-pyridyl, 2-furyl, 2-thiophenyl groups;

- a group of formula II,



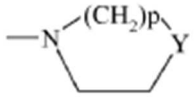
(II)

wherein

X represents:

linear or branched C_1-C_6 alkylene,

R2 and **R3** together with the N atom to which they are bound, form a 4-6 membered nitrogen containing heterocyclic ring of formula (III)



(III)

wherein **Y** represents CH_2, and p represents an integer from 0 to 2;

R1 is methyl;

Ar is selected from:

3'-benzoylphenyl, 3' -(4-chloro-benzoyl)-phenyl, 3 '-(4-methyl-benzoyl)-phenyl, 4'-trifluoromethanesulfonyloxy-phenyl, 4'-benzenesulfonyloxy-phenyl, 3'-(furan-2-carbonyl)-phenyl.

7. The use according to any one of the previous claims, wherein the C5aR inhibitor is selected from:

4-{(1R)-1-[(phenylsulfonyl)amino]ethyl}phenyl trifluoromethanesulfonate

N-[(1R)-1-(3-benzoylphenyl)ethyl]benzenesulfonamide

4-{(1R)-1-[(pyridine-3-ylsulfonyl)amino]ethyl}phenyltrifluoromethanesulfonate

N-[(1R)-1-(3-benzoylphenyl)ethyl]methanesulfonamide

N-{(1R)-1-[3-(2-furoyl)phenyl]ethyl}thiophene-2-sulfonamide

N-{(1R)-1-[3-(2-furoyl)phenyl]ethyl}methanesulfonamide

4-{(1R)-1-[(thien-2-ylsulfonyl)amino]ethyl}phenyl trifluoromethanesulfonate

N-[(1R)-1-(3-benzoylphenyl)ethyl]thiophene-2-sulfonamide

N-[(1R)-1-(3-benzoylphenyl)ethyl]-3-pyrrolidin-1-ylpropane-1-sulfonamide

methyl 5-({[(1R)-1-(3-benzoylphenyl)ethyl]amino}sulfonyl)-2-furoate

5-({[(1R)-1-(3-benzoylphenyl)ethyl]amino}sulfonyl)-2-furoic acid

4-{(1R)-2-methyl-1-[(methylsulfonyl)amino]propyl}phenyltrifluoromethanesulfonate

N-((1R)-1-{4-[1-methyl-1-(phenylsulfonyl)ethyl]phenyl}ethyl)methanesulfonamide

4-[(1R)-1-(isobutyrylamino)ethyl]phenyltrifluoromethanesulfonate

4-{[(1R)-1-(pyridine-3-ylcarbonyl)amino]ethyl]}phenyltrifluoromethanesulfonate

N-[(1R)-1-(3-benzoylphenyl)ethyl]benzamide

N-[(1R)-1-(3-benzoylphenyl)ethyl]-2-furamide

N-[(1R)-1-(3-benzoylphenyl)ethyl]cyclobutanecarboxamide

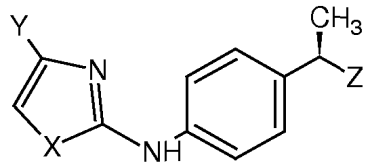
N-[(1R)-1-(4-trifluoromethanesulfonyloxy)phenylethyl]-4-piperidin-1-ylbutanamide

4-{(1R)-1-[(4-pyrrolidin-1-ylbutanoyl)amino]ethyl]}phenyl trifluoromethanesulfonate

3-{(1R)-1-[4-(4-trifluoromethyl-1,3-thiazol-2-yl)amino]ethyl}phenyl)

(phenyl)methanone and pharmaceutically acceptable salts thereof, preferably selected from N-[(1R)-1-(4-trifluoromethanesulfonyloxy)phenylethyl]-4-piperidin-1-ylbutanamide and its chloride salt.

8. The use according to claim 1 or claim 2, wherein said C5aR inhibitor is selected from a compound of formula (II)



(II)

or a pharmaceutically acceptable salt thereof,

wherein

X is a heteroatom selected from

- S, O and N

Y is H or a residue selected from the group consisting of:

- halogen, linear or branched C_1-C_4-alkyl, C_2-C_4-alkenyl, C_1-C_4-alkoxy, hydroxy, -COOH, C_1-C_4-acyloxy, phenoxy, cyano, nitro, $-NH_2$, C_1-C_4-acylamino, halo-C_1-C_3-alkyl, benzoyl, linear or branched C_1-C_8-alkanesulfonate, linear or branched C_1-C_8-alkanesulfonamides, linear or branched C_1-C_8-akyl sulfonylmethyl;

Z is an heteroaryl ring selected from the group consisting of:

unsubstituted tetrazole and triazole, pyrazole, oxazole, thiazole, isooxazole, isothiazole, thiadiazole and oxadiazole substituted by one hydroxy group and optionally further substituted by one or more groups selected from the group consisting of halogen, linear or branched C_1-C_4-alkyl, C_2-C_4-alkenyl, C_1-C_4-akylamino, C_1-C_4-alkoxy, C_1-C_4-alkylthio, C_1-C_4-acyloxy, cyano, nitro, NH_2, C_1-C_4-acylamino, halo-C_1-C_3-alkyl, halo-C_1-C_3-alkoxy, linear or branched C_1-C_8-alkanesulfonate and linear or branched C_1-C_8-alkanesulfonamides.

9. The use according to claim 8, wherein:

X is a heteroatom selected from

- S and O

Y is H or a residue selected from the group consisting of:

- halogen, linear or branched C_1-C_4-alkyl and halo-C_1-C_3-alkyl; preferably selected from the group consisting of trifluoromethyl, chlorine, methyl and tert-butyl;

Z is an heteroaryl ring selected from the group consisting of:

unsubstituted tetrazole and triazole, pyrazole, isooxazole, isothiazole, thiadiazole and oxadiazole substituted by one hydroxy group and optionally further substituted by one or more groups selected from the group consisting of halogen, linear or branched C_1-C_4-alkyl, C_1-C_4-alkylthio and halo-C_1-C_3-alkyl; preferably selected from the group consisting of methyl, trifluoromethyl and chlorine.

10. The use according to claim 8 or claim 9, wherein the C5aR inhibitor is selected from:

N-{4-[(1R)-1-(1H-tetrazol-5-yl)ethyl]phenyl}-4-(trifluoromethyl)-1,3-thiazol-2-amine;

4-methyl-N-{4-[(1R)-1-(1H-tetrazol-5-yl)ethyl]phenyl}-1,3-thiazol-2-amine;

4-tert-butyl-N-{4-[(1R)-1-(1H-tetrazol-5-yl)ethyl]phenyl}-1,3-thiazol-2-amine;

N-{4-[(1R)-1-(1H-tetrazol-5-yl)ethyl]phenyl}-1,3-thiazol-2-amine;

N-{4-[(1R)-1-(1H-tetrazol-5-yl)ethyl]phenyl}-4-(trifluoromethyl)-1,3-oxazol-2-amine;

4-methyl-N- {4-[(1R)-1-(1H tetrazol-5-yl)ethyl]phenyl}-1,3-oxazol-2-amine;

5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]-1H pyrazol-1-ol;

4-methyl-5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl) ethyl]-1H-pyrazol-1-ol;

5-[(1R)-1-(4-([4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]-1H-1,2,3-triazol-1-ol;

5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl] isoxazol-3-ol;

4-methyl-5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl) ethyl]isoxazol-3-ol;

5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl] isothiazol-3-ol;

4-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]-1,2,5-oxadiazol-3-ol;

4-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]-1,2,5-thiadiazol-3-ol;

5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]-1H 1,2,4-triazol-1-ol and pharmaceutically acceptable salts thereof, preferably selected from 1-N-[4-[(1R)-1-(1H-tetrazol-5-yl)ethyl]phenyl}-4-(trifluoromethyl)-l1,3-thiazol-2-amine and its sodium salt.

11. The use as claimed in any one of the previous claims, wherein said chemotherapy-induced iatrogenic pain is induced by a chemotherapeutic agent selected from platinum based drugs, taxanes, epothilones, plant alkaloids, thalidomide, lenalidomide and pomalidomide, carfilzomib, bortezomib and eribulin, preferably taxanes and platinum based drugs.
12. The use according to claim 11, wherein said chemotherapeutic agent is selected from cisplatin, carboplatin, oxaliplatin, paclitaxel, cabazitaxel, docetaxel, ixabepilone, vinblastine, vincristine, vinorelbine, etoposide, thalidomide, lenalidomide, pomalidomide, carfilzomib, bortezomib and eribulin, preferably paclitaxel.
13. The use according to any one of claims 1 to 10, wherein the medicament is in the form of a pharmaceutical composition including at least a pharmaceutically acceptable excipient.

~~14. The use according to any one of the preceding claims, wherein the medicament is to be administered orally.~~