CXCR7 receptor modulators

The present invention relates to novel CXCR7 receptor modulators of formula (I) and their use as pharmaceuticals. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula (I), and their use as CXCR7 receptor modulators. The invention further relates to the compounds of formula (I) and their use as pharmaceuticals in combination with one or more therapeutic agents and / or radiotherapy in the treatment of cancers, especially in the treatment of malignant glioma, in particular glioblastoma multiforme.

Chemokine receptors are a group of G-protein coupled receptors (GPCRs) that bind peptidic chemokine ligands with high affinity. The predominant function of chemokine receptors is to guide leukocyte trafficking to lymphoid organs and tissues under resting conditions as well as during inflammation, but a role for certain chemokine receptors on non-hematopoietic cells and their progenitors has also been recognized.

Signaling networks and metabolic profiles of cancer cells differ in a microenvironment dependent manner. This is a major reason for lack of therapeutic response of tumors at certain organ sites and of tumor metastases in comparison to primary tumors. CXCL12 (alias stromal cell-derived factor 1, SDF-1; alias Pre-B cell growth stimulating factor, PBSF), a stroma-derived chemo-attractant, exerts anti-apoptotic effects, displays pro-angiogenic properties and plays a key role in seeding circulating tumor cells to metastatic sites. CXCL12 binds and activates two receptors, CXCR7 (alias ACKR3, alias RDC1, alias CMKOR1, alias GPR159) and CXCR4 (alias Fusin, alias Leukocyte-derived seven-transmembrane-domain receptor; LESTR, alias D2S201E, alias seven-transmembrane-segment receptor, alias HM89, alias lipopolysaccharide-associated protein 3; lap3, alias LPS-associated protein 3).

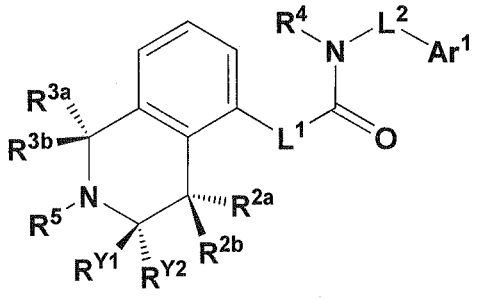
The expression of the CXCL12 receptor CXCR7 correlates with diseases progression in cancer (among others in hormone refractory prostate cancer, in renal cell carcinoma, cervical cancer, papillary thyroid carcinoma, bladder cancer, Ewing's sarcoma, colorectal cancers, lung cancer, meningiomas, MALT lymphoma and in tumors in the brain). CXCR7 is also expressed in hepatocellular carcinoma, breast cancer, osteosarcoma, leukemia, gallbladder cancer, alveolar rhabdomyosarcoma, myeloma, non-small cell lung cancer, oral cancers and pancreas cancer (for review see Sun et al.; CXCL12/CXCR4/CXCR7 Chemokine Axis and Cancer Progression; Cancer Metastasis Rev. 2010, 29(4), 709-722).

(C_{2-3})fluoroalkyl; or (C_{3-6})cycloalkyl or (C_{3-6})cycloalkyl-(C_{1-3})alkyl, wherein in the above groups the (C_{3-6})cycloalkyl group optionally contains one ring oxygen atom, and wherein said (C_{3-6})cycloalkyl group is optionally substituted with methyl;

- -(C_{1-3})alkylene-CO-$\mathbf{R^8}$, wherein $\mathbf{R^8}$ represents (C_{1-4})alkoxy (especially ethoxy); or $\mathbf{R^8}$ represents $NR^{81}R^{82}$ wherein $\mathbf{R^{81}}$ and $\mathbf{R^{82}}$ independently represent hydrogen or (C_{1-4})alkyl, or $\mathbf{R^{81}}$ and $\mathbf{R^{82}}$ together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally substituted with two fluoro substituents (especially such $NR^{81}R^{82}$ represents amino, 3,3-difluoroazetidinyl);
- -(C_{1-3})alkylene-SO_2-$\mathbf{R^9}$ wherein $\mathbf{R^9}$ represents (C_{1-3})alkyl (especially methyl), or amino;
- (C_{3-6})cycloalkyl or (C_{3-6})cycloalkyl-(C_{1-3})alkyl, wherein the cycloalkyl group is optionally mono-substituted with -CO-(C_{1-4})alkoxy or hydroxy;
- (C_{4-7})heterocyclyl or (C_{4-7})heterocyclyl-(C_{1-3})alkyl, wherein in the above groups the (C_{4-7})heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said (C_{4-7})heterocyclyl independently is unsubstituted, or mono-, di-, or tri-substituted wherein the substituents are independently selected from:
  - one oxo substituent attached to a ring carbon atom in alpha position to a ring nitrogen (thus forming together with the nitrogen an amide group, or, in case a ring oxygen is additionaly adjacent, a carbamate group, or, in case second ring nitrogen is additionaly adjacent, a urea group); and / or
  - two methyl substituents attached to a ring carbon atom in alpha position to a ring nitrogen atom (thus forming together with the nitrogen a $-C(CH_3)_2-N-$ group); and / or
  - two oxo substituents at a ring sulfur ring atom (thus forming a $-SO_2-$ group); and / or
  - (C_{1-4})alkyl (especially methyl) or -CO-(C_{1-4})alkoxy attached to a ring nitrogen atom having a free valency; and/or
  - two fluoro substituents attached to a ring carbon atom; and/or
  - in case of a (C_{4-7})heterocyclyl-(C_{1-3})alkyl group, methyl attached to a ring carbon atom which is attached to the linking (C_{1-3})alkyl group;
- 2-oxo-2,3-dihydropyridin-4-yl-(C_{1-2})alkyl;
- phenyl-(C_{1-3})alkyl-, or 5- or 6-membered heteroaryl-(C_{1-3})alkyl-, wherein the phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C_{1-4})alkyl (especially methyl, ethyl), (C_{1-4})alkoxy (especially methoxy), halogen, (C_{1-3})fluoroalkyl (especially trifluoromethyl), (C_{1-3})fluoroalkoxy (especially trifluoromethoxy), and cyano;

or a pharmaceutically acceptable salt thereof.

23) ~~A second aspect~~Another embodiment of the invention relates to compounds of the formula (I) according to embodiment 1) which are also compounds of the formula (II)



Formula (II)

wherein

- one of R^{Y1} and R^{Y2} represents hydrogen, or (C_{1-3})alkyl (especially methyl); and the other represents hydrogen; and
  - R^{3a} and R^{3b} together with the carbon atom to which they are attached to form a carbonyl group, or
  - two of R^{2a}, R^{2b}, R^{3a} and R^{3b} independently represent hydrogen, or (C_{1-3})alkyl (especially methyl);

  and the remaining of R^{2a}, R^{2b}, R^{3a} and R^{3b} represent hydrogen; or
- R^{Y1} and R^{Y2} together with the carbon to which they are attached to form a carbonyl group; and R^{2a}, R^{2b} R^{3a} and R^{3b} all represent hydrogen;

R^5 represents

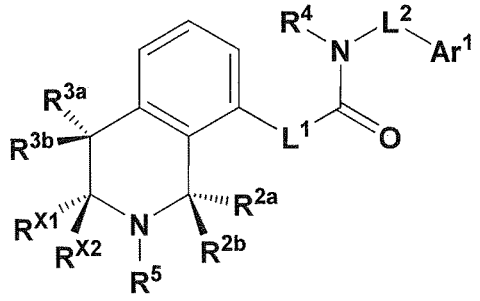
- (C_{1-6})alkyl; [in particular such (C_{1-6})alkyl is methyl, ethyl, propyl, isopropyl, isobutyl, 1-methyl-propyl, 1,2-dimethyl-propyl, 2,2-dimethyl-propyl, 3,3-dimethyl-butyl];
- (C_{1-4})alkyl mono-substituted with (C_{1-3})alkoxy, cyano, vinyl; ethynyl, or (C_{1-3})alkoxy-carbonyl; [in particular such mono-substituted (C_{1-4})alkyl is allyl, prop-2-ynyl, cyanomethyl, 2-methoxy-ethyl, 2-methoxy-1-methyl-ethyl, methoxycarbonyl-methyl, ethoxycarbonyl-methyl];
- -CO-R^{10} wherein R^{10} represents (C_{1-5})alkyl; (C_{1-5})alkoxy; phenyl; phenyl-oxy-; phenyl-(C_{1-3})alkyl-; phenyl-(C_{1-3})alkyl-oxy-; (C_{3-6})cycloalkyl-(C_{1-3})alkyl; (C_{3-4})alkenoxy; (C_{3-4})alkynoxy; (C_{1-3})fluoroalkyl; (C_{1-3})fluoroalkoxy; (C_{1-3})alkoxy-(C_{2-3})alkoxy; (C_{1-3})alkoxy-(C_{1-3})alkyl; (C_{3-6})cycloalkyl optionally containing one ring oxygen atom, wherein said cycloalkyl is optionally mono- or di-substituted wherein the substituents independently are fluoro or (C_1)fluoroalkyl; unsubstituted 5-membered heteroaryl (especially furanyl); or $-NR^{10a}R^{10b}$ wherein R^{10a} and R^{10b} independently represent hydrogen, (C_{1-4})alkyl or (C_{3-6})cycloalkyl, or R^{10a} and R^{10b} together with the nitrogen to

especially the following embodiments are thus possible and intended and herewith specifically disclosed in individualized form:

23, 23+7, 23+10, 23+10+7, 23+13, 23+13+7, 23+13+10, 23+13+10+7, 23+17, 23+17+7, 23+17, 23+17+13, 23+17+13+7, 23+17+13+10, 23+17+13+10+7, 23+19, 23+19+7, 23+19, 23+19+13, 23+19+13+7, 23+19+13+10, 23+19+13+10+7, 23+19+17, 23+19+17+7, 23+19+17, 23+19+17+13, 23+19+17+13+7, 23+19+17+13+10, 23+19+17+13+10+7, 23+21, 23+21+7, 23+21, 23+21+13, 23+21+13+7, 23+21+13+10, 23+21+13+10+7, 23+21+17, 23+21+17+7, 23+21+17, 23+21+17+13, 23+21+17+13+7, 23+21+17+13+10, 23+21+17+13+10+7.

In the list above the numbers refer to the embodiments according to their numbering provided hereinabove whereas "+" indicates the limitations as outlined above.

24) ~~A third aspect~~ Another embodiment of the invention relates to compounds of the formula (I) according to embodiment 1) which are also compounds of the formula (III)



Formula (III)

wherein

- one of R^{X1} and R^{X2} represents hydrogen, or (C_{1-3})alkyl (especially methyl); and the other represents hydrogen; and
  - R^{3a} and R^{3b} together with the carbon atom to which they are attached to form a carbonyl group, or
  - two of R^{2a}, R^{2b}, R^{3a} and R^{3b} independently represent hydrogen, or (C_{1-3})alkyl (especially methyl);

  and the remaining of R^{2a}, R^{2b}, R^{3a} and R^{3b} represent hydrogen; or
- R^{X1} and R^{X2} together with the carbon to which they are attached to form a carbonyl group; and R^{2a}, R^{2b} R^{3a} and R^{3b} all represent hydrogen;

R^5 represents

- (C_{1-6})alkyl; [in particular such (C_{1-6})alkyl is methyl, ethyl, propyl, isopropyl, isobutyl, 1-methyl-propyl, 1,2-dimethyl-propyl, 2,2-dimethyl-propyl, 3,3-dimethyl-butyl];
- (C_{1-4})alkyl mono-substituted with (C_{1-3})alkoxy, cyano, vinyl; ethynyl, or (C_{1-3})alkoxy-carbonyl; [in particular such mono-substituted (C_{1-4})alkyl is allyl, prop-2-ynyl,

difluoropyrrolidin-1-yl)-ethyl, 2-(3,3-difluoropiperdin-1-yl)-ethyl, 2-(4,4-difluoropiperdin-1-yl)-ethyl, (1-(*tert.*-butoxycarbonyl)-pyrrolidin-3-yl)-methyl, 2-(1-(*tert.*-butoxycarbonyl)-piperazin-4-yl)-ethyl];

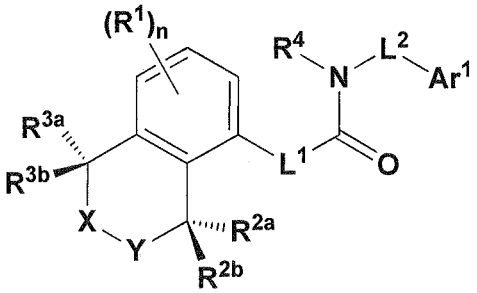
- 2-oxo-2,3-dihydropyridin-4-yl-(C_{1-2})alkyl;
- phenyl-(C_{1-3})alkyl-, or 5- or 6-membered heteroaryl-(C_{1-3})alkyl-, wherein the phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C_{1-4})alkyl (especially methyl, ethyl), (C_{1-4})alkoxy (especially methoxy), halogen, (C_{1-3})fluoroalkyl (especially trifluoromethyl), (C_{1-3})fluoroalkoxy (especially trifluoromethoxy), and cyano;

wherein the characteristics disclosed in embodiments 2) to 21) are intended to apply *mutatis mutandis* also to the compounds formula (III) according to embodiment 24); wherein especially the following embodiments are thus possible and intended and herewith specifically disclosed in individualized form:

24, 24+7, 24+10, 24+10+7, 24+13, 24+13+7, 24+13+10, 24+13+10+7, 24+17, 24+17+7, 24+17, 24+17+13, 24+17+13+7, 24+17+13+10, 24+17+13+10+7, 24+19, 24+19+7, 24+19, 24+19+13, 24+19+13+7, 24+19+13+10, 24+19+13+10+7, 24+19+17, 24+19+17+7, 24+19+17, 24+19+17+13, 24+19+17+13+7, 24+19+17+13+10, 24+19+17+13+10+7, 24+21, 24+21+7, 24+21, 24+21+13, 24+21+13+7, 24+21+13+10, 24+21+13+10+7, 24+21+17, 24+21+17+7, 24+21+17, 24+21+17+13, 24+21+17+13+7, 24+21+17+13+10, 24+21+17+13+10+7.

In the list above the numbers refer to the embodiments according to their numbering provided hereinabove whereas "+" indicates the limitations as outlined above.

25) A further ~~aspect~~ embodiment of the invention relates to compounds of the formula (I) which are also compounds of the formula (I_P),

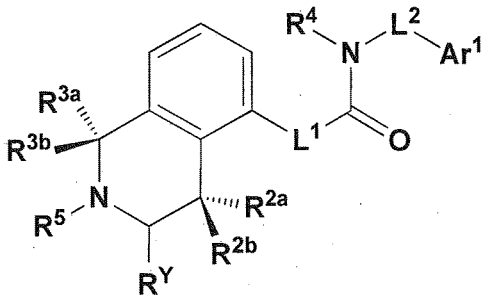


Formula (I_P)

wherein

- **X** represents NR^5, and **Y** represents CHR^Y wherein R^Y represents hydrogen, or (C_{1-3})alkyl (especially methyl); and

30) A further ~~aspect~~ embodiment of the invention relates to compounds of the formula (I) according to embodiment 1) which are also compounds of the formula (II_P)



Formula (II_P)

wherein

R^Y represents hydrogen, or (C_{1-3})alkyl (especially methyl); and

- two of $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$ $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ independently represent hydrogen, or (C_{1-3})alkyl (especially methyl);
  and the remaining of $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$ $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ represent hydrogen;

$\mathbf{R^5}$ represents

- (C_{1-6})alkyl;
- -CO-$\mathbf{R^{10}}$ wherein $\mathbf{R^{10}}$ represents (C_{1-5})alkyl, (C_{1-5})alkoxy, phenyl, phenyl-oxy-, phenyl-(C_{1-3})alkyl-, phenyl-(C_{1-3})alkyl-oxy-, or (C_{3-6})cycloalkyl-(C_{1-3})alkyl,
- -SO_2-$\mathbf{R^{11}}$ wherein $\mathbf{R^{11}}$ represents (C_{1-5})alkyl;
- (C_{2-4})fluroroalkyl;
- (C_{3-6})cycloalkyl optionally containing one ring oxygen atom;
- (C_{3-6})cycloalkyl-(C_{1-3})alkyl, wherein the (C_{3-6})cycloalkyl group optionally contains one ring oxygen atom;
- phenyl-(C_{1-3})alkyl-, wherein the phenyl-(C_{1-3})alkyl-is unsubstituted;

$\mathbf{L^1}$ represents a two-membered linker group selected from -NH-CH_2-*, -N$\mathbf{R^6}$-CH_2-* wherein $\mathbf{R^6}$ represents (C_{1-3})alkyl, -O-CH_2-*, -CH_2CH_2-, -CH=CH-, and -CH=C(CH_3)-*; wherein the asterisks indicate the bond with which the group $\mathbf{L^1}$ is attached to the carbonyl group;

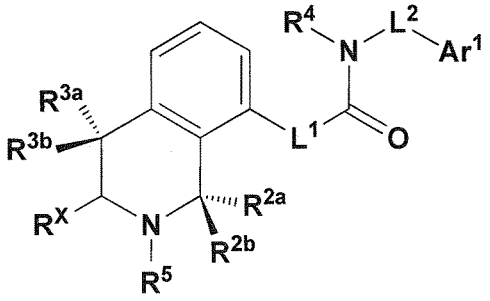
$\mathbf{L^2}$ represents -(C_{1-4})alkylene- or -(C_{3-4})alkenylene- (especially a linker group selected from -CH_2-, -CH(CH_3)-, -CH_2-CH_2-, -CH_2-CH_2-CH_2-, *-CH_2-CH=CH-, and *-CH_2-C(CH_3)=CH-, wherein the asterisks indicate the bond with which the group L^2 is attached to the amide nitrogen atom);

$\mathbf{Ar^1}$ represents phenyl or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, di- or tri-substituted, wherein

30+10+26, 30+1+10, 30+13+10+26, 30+13+10, 30+13+26, 30+13, 30+17+10+26, 30+17+10, 30+17+13+10+26, 30+17+13+10, 30+17+13+26, 30+17+13, 30+17+26, 30+17, 30+26, 30+27+10+26, 30+27+10, 30+27+13+10+26, 30+27+13+10, 30+27+13+26, 30+27+13, 30+27+17+10+26, 30+27+17+10, 30+27+17+13+10+26, 30+27+17+13+10, 30+27+17+13+26, 30+27+17+13, 30+27+17+26, 30+27+17, 30+27+26, 30+27, 30+28+10+26, 30+28+10, 30+28+13+10+26, 30+28+13+10, 30+28+13+26, 30+28+13, 30+28+17+10+26, 30+28+17+10, 30+28+17+13+10+26, 30+28+17+13+10, 30+28+17+13+26, 30+28+17+13, 30+28+17+26, 30+28+17, 30+28+26, 30+28, 30.

In the list above the numbers refer to the embodiments according to their numbering provided hereinabove whereas "+" indicates the limitations as outlined above.

31) A further ~~aspect~~ embodiment of the invention relates to compounds of the formula (I) according to embodiment 1) which are also compounds of the formula (III_P)



Formula (III_P)

wherein

R^X represents hydrogen, or (C_{1-3})alkyl (especially methyl); and

- R^{2a} and R^{2b} together with the carbon atom to which they are attached to form a carbonyl group, or
- two of R^{2a}, R^{2b} R^{3a} and R^{3b} independently represent hydrogen, or (C_{1-3})alkyl (especially methyl);

and the remaining of R^{2a}, R^{2b} R^{3a} and R^{3b} represent hydrogen; or

R^5 represents

- (C_{1-6})alkyl;
- -CO-R^{10} wherein R^{10} represents (C_{1-5})alkyl, (C_{1-5})alkoxy, phenyl, phenyl-oxy-, phenyl-(C_{1-3})alkyl-, phenyl-(C_{1-3})alkyl-oxy-, or (C_{3-6})cycloalkyl-(C_{1-3})alkyl,
- -SO_2-R^{11} wherein R^{11} represents (C_{1-5})alkyl;
- (C_{2-4})fluroroalkyl;
- (C_{3-6})cycloalkyl optionally containing one ring oxygen atom;
- (C_{3-6})cycloalkyl-(C_{1-3})alkyl, wherein the (C_{3-6})cycloalkyl group optionally contains one ring oxygen atom;

N-(2-Dimethylamino-ethyl)-2-[2-(pyrrolidine-1-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;

N-(2-Dimethylamino-ethyl)-2-[2-(2,2-dimethyl-propyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;

N-(2-Dimethylamino-ethyl)-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;

2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;

2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;

N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-N-(2-trifluoromethyl-benzyl)-acetamide;

2-((R)-2-Cyclopropylmethyl-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;

2-((S)-2-Cyclopropylmethyl-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;

N-(2-Dimethylamino-ethyl)-2-[2-((1R,2R)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;

N-(2-Dimethylamino-ethyl)-2-[2-((1S,2S)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;

3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylmethyl)-1-(2-dimethylamino-ethyl)-1-(2-trifluoromethyl-benzyl)-urea;

2-[2-(2,2-Difluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;

N-(2-Dimethylamino-ethyl)-2-[2-(furan-2-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;

N-(2-Dimethylamino-ethyl)-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide.

The compounds of formula (I) according to embodiments 1) to 33) and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral (such especially oral) or parenteral administration (including topical application or inhalation).

In another aspect, there is provided a pharmaceutical composition comprising, as active principle, a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

In a further aspect, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use as a medicament.

In yet another aspect, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament, for the prevention or treatment of diseases selected from the group consisting of cancer, autoimmune disorders, inflammatory diseases, transplant rejection, and fibrosis.

In another aspect, there is provided a use of an effective amount of the compound of formula (I) as disclosed herein, or of a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating tumors, wherein said effective amount leads to a change of tumor properties, and wherein said modification is achieved by modulating the CXCL12 receptor pathway.

In a further aspect, there is provided a use of an effective amount of the compound of formula (I) as disclosed herein, or of a pharmaceutically acceptable salt thereof in the manufacture of a medicament for modulating an immune response, wherein said effective amount modulates an inflammatory disease and wherein said response is mediated by the CXCL12 receptor pathway.

In yet another aspect, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament, for the prevention or treatment of cancer; wherein said compound is optionally used in combination with one or more chemotherapy agents and / or radiotherapy and / or targeted therapy.

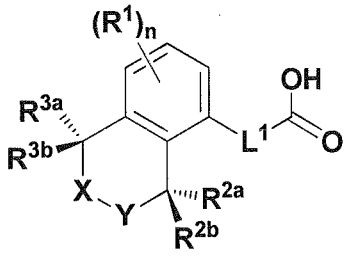
The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, *The Science and Practice of Pharmacy*, 21st Edition (2005), Part 5, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the described compounds of formula

Preparation of compounds of Formula (I)

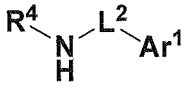
~~A further aspect~~An embodiment of the invention is a process for the preparation of compounds of Formula (I). Compounds according to Formula (I) of the present invention can be prepared from commercially available or well known starting materials according to the methods described in the experimental part, by analogous methods; or according to the general sequence of reactions outlined below, wherein R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^4, L^1, L^2, X, Y and Ar^1 are as defined for Formula (I). Other abbreviations used herein are explicitly defined, or are as defined in the experimental section. In some instances the generic groups R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^4, L^1, L^2, X, Y and Ar^1 might be incompatible with the assembly illustrated in the schemes below and so will require the use of protecting groups (PG). The use of protecting groups is well known in the art (see for example "Protective Groups in Organic Synthesis", T.W. Greene, P.G.M. Wuts, Wiley-Interscience, 1999). For the purposes of this discussion, it will be assumed that such protecting groups as necessary are in place. The compounds obtained may also be converted into salts, especially pharmaceutically acceptable salts thereof in a manner known *per se*.

Amide coupling as last step

Generally examples of Formula (I) are obtained from a carboxylic acid precursor of Structure 1 and an amine of Structure 2 using HATU or another amide coupling reagent in a solvent such as DCM or DMF at room temperature or 0°C in the presence of a base like TEA or DIPEA.



Structure 1



Structure 2

Preparation of compounds of Structure 1

Compounds of Structure 1 are made by ester cleavage of a compound of Structure 3 in which R represents a *tert*-Butyl, Ethyl, Methyl group or the like. In a typical reaction a compound of Structure 3 is stirred with a base such as aq. NaOH soln. or aq. LiOH soln. in a solvent such as EtOH, MeOH or THF at room temperature of reflux. In an alternative method, in particular if R is a *tert*-butyl group a compound of Structure 3 is stirred in DCM at room temperature in the presence of TFA to give a compound of Structure 1.

2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;

N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-N-(2-trifluoromethyl-benzyl)-acetamide;

2-((R)-2-Cyclopropylmethyl-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;

2-((S)-2-Cyclopropylmethyl-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;

N-(2-Dimethylamino-ethyl)-2-[2-((1R,2R)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;

N-(2-Dimethylamino-ethyl)-2-[2-((1S,2S)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;

3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylmethyl)-1-(2-dimethylamino-ethyl)-1-(2-trifluoromethyl-benzyl)-urea;

2-[2-(2,2-Difluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;

N-(2-Dimethylamino-ethyl)-2-[2-(furan-2-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;

N-(2-Dimethylamino-ethyl)-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;

or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising, as active principle, a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

14. A compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use as a medicament.

15. Use of A~~a~~ compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament, for ~~use in~~ the prevention or treatment of diseases selected from the group consisting of cancer, autoimmune disorders, inflammatory diseases, transplant rejection, and fibrosis.

~~16. A compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for the prevention or treatment of diseases selected from the group consisting of cancer, autoimmune disorders, inflammatory diseases, transplant rejection, and fibrosis.~~

~~17~~16. Use of ~~A method of treating tumors comprising administering~~ an effective amount of the compound of formula (I) according to claims 1 or 12, or of a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating tumors, wherein said effective amount leads to a change of tumor properties, and wherein said modification is achieved by modulating the CXCL12 receptor pathway.

~~18~~17. Use of ~~A method of modulating an immmune response comprising the administration of~~ an effective amount of the compound of formula (I) according to claims 1 or 12, or of a pharmaceutically acceptable salt thereof in the manufacture of a medicament for modulating an immune response, wherein said effective amount modulates an inflammatory disease and wherein said response is mediated by the CXCL12 receptor pathway.

~~19. A method of treatment of cancer, autoimmune disorders, inflammatory diseases, transplant rejection, or fibrosis; comprising administering to a patient a compound of formula (I) as defined in any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof.~~

~~20~~18. Use of ~~A~~ a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament, for ~~use in~~ the prevention or treatment of cancer; wherein said compound is optionally used in combination with one or more chemotherapy agents and / or radiotherapy and / or targeted therapy.