Fluorinated Aminotriazole Derivatives

The present invention relates to fluorinated aminotriazole derivatives 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 especially their use as ALX receptor agonists.

ALXR (alias Lipoxin A4 Receptor, FPRL1, FPR2; disclosed in WO2003/082314 as nucleotide sequence SEQ ID NO:1 and amino acid sequence SEQ ID NO:2) is a member of the G-protein coupled receptor family. ALXR was found to mediate calcium mobilisation in response to high concentration of the formyl-methionine-leucyl-phenylalanine peptide. Furthermore, a lipid metabolite, lipoxin A4 (LXA4), and its analogs, were found to bind ALXR with high affinity and increase arachidonic acid production and G-protein activation in ALXR transfected cells (Chiang *et al.,* Pharmacol. Rev., 2006, 58, 463-487). The effects of LXA4 have been evaluated in a variety of animal models of diseases; and LXA4 was demonstrated to have potent anti-inflammatory and pro-resolution activities. The disease models where LXA4, or derivatives, or stable analogs, demonstrated *in vivo* activities are for example dermal inflammation, dorsal air pouch, ischemia/reperfusion injury, peritonitis, colitis, mesangioproliferative nephritis, pleuritis, asthma, cystic fibrosis, sepsis, corneal injury, angiogenesis, periodontitis, carrageenan-induced hyperalgesia, and graft-vs-host disease (GvHD) (Schwab and Serhan, Current Opinion in Pharmacology, 2006, 414-420). ALXR was also identified as a functional receptor of a various number of peptides, including a fragment of the prion protein, a peptide derived from gp120 of the Human Immunodeficiency Virus (HIV)-1_{LAI} strain, and amyloid-beta 1-42 (Ab42) (for review, Le *et al.*, Protein Pept Lett., 2007, 14, 846-853), and has been suggested to participate in the pathogenesis of Alzheimer's Disease (AD) in several crucial ways (Yazawa *et al.*, FASEB J., 2001, 15, 2454-2462). Activation of ALXR on macrophages and microglial cells initiates a G protein-mediated signalling cascade that increases directional cell migration, phagocytosis, and mediator release. These events may account for the recruitment of mononuclear cells to the vicinity of senile plaques in the diseased areas of AD brain where Ab42 is overproduced and accumulated. Although accumulation of leukocytes at the sites of tissue injury may be considered an innate host response aimed at the clearance of noxious agents, activated mononuclear phagocytes also release a variety of substances such as superoxide anions that may be toxic to neurons. Thus, ALXR may mediate pro-inflammatory responses elicited by Ab42 in AD brain and exacerbate disease

progression. It was also reported that humanin (HN), a peptide with neuroprotective capabilities, shares the human ALXR with Ab42 on mononuclear phagocytes and neuronal cell lines and it has been suggested that the neuroprotective activity of HN may be attributed to its competitive occupation of ALXR (Ying *et al.*, J. Immunol., 2004, 172, 7078-7085).

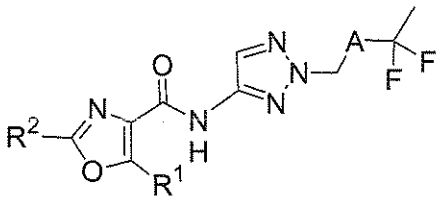
The biological properties of ALXR agonists include, but are not limited to, monocyte/macrophage/microglia/dendritic cell migration/activation, neutrophil migration/ activation, regulation of lymphocyte activation, proliferation and differentiation, regulation of inflammation, regulation of cytokine production and/or release, regulation of proinflammatory mediator production and/or release, regulation of immune reaction.

The present invention provides fluorinated aminotriazole derivatives, which are non-peptide agonists of human ALX receptor. The compounds are useful for the prevention or treatment of diseases, which respond to the modulation of the ALX receptor such as inflammatory diseases, obstructive airway diseases, allergic conditions, HIV-mediated retroviral infections, cardiovascular disorders, neuroinflammation, neurological disorders, pain, prion-mediated diseases and amyloid-mediated disorders (especially Alzheimer's disease); in addition they are useful for the prevention or treatment of autoimmune diseases and for the modulation of immune responses (especially those elicited by vaccination).

Compared to aminotriazole derivatives disclosed in WO 2009/077990, which are also ALX receptor agonists, compounds of the present application demonstrated a significantly improved profile when tested in a covalent binding assay, which is expected to correlate to an improved safety profile (Evans et al. *Chem. Res. Toxicol.*, 2004, *17*, 3-16).

Various embodiments of the invention are presented hereafter:

1) The present disclosure~~invention~~ relates to fluorinated aminotriazole derivatives of formula (I). In one aspect, there is provided a compound of formula (I),



(I)

wherein

A represents a heteroaryl-group, wherein the two attachment-points of said heteroaryl-group are in a 1,3-arrangement;

R^1 represents phenyl which is unsubstituted, mono- or di-substituted (notably unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of halogen, methyl, methoxy, trifluoromethyl, trifluoromethoxy and dimethylamino; and

R^2 represents hydrogen, methyl, ethyl or cyclopropyl (notably hydrogen or methyl);

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

In another aspect, there is provided a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for use as a medicament.

In yet another aspect, there is provided a pharmaceutical composition containing, as active principle, a compound of formula (I) as defined above or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

In still another aspect, there is provided the use of a compound of formula (I) as defined above, or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or treatment of a disease selected from inflammatory diseases, obstructive airway diseases, allergic conditions, HIV-mediated retroviral infections, cardiovascular disorders, neuroinflammation, neurological disorders, pain, prion-mediated diseases and amyloid-mediated disorders; and for the modulation of immune responses.

In another aspect, there is provided a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for the prevention or treatment of a disease selected from inflammatory diseases, obstructive airway diseases, allergic conditions, HIV-mediated retroviral infections, cardiovascular disorders, neuroinflammation, neurological disorders, pain, prion-mediated diseases and amyloid-mediated disorders; and for the modulation of immune responses.

The following paragraphs provide definitions of the various chemical moieties for the compounds according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a broader or narrower definition.

The term halogen means fluoro, chloro, bromo or iodo, preferably fluoro, chloro or bromo and most preferably fluoro or chloro.

The term "heteroaryl", used alone or in combination, means a 5-membered monocyclic aromatic ring containing 1, 2 or 3 (preferably 1 or 2) heteroatoms independently selected from oxygen, nitrogen and sulfur. Examples of such heteroaryl groups are furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl and triazolyl. Preferred examples are furanyl (notably furan-2,5-diyl), oxazolyl (notably oxazol-2,4-diyl) and thiazolyl (notably thiazol-2,4-diyl). Most preferred examples are furan-2,5-diyl, oxazol-2,4-diyl with 1,1-difluoroethyl being attached to the 4-position and thiazol-2,4-diyl with 1,1-difluoroethyl being attached to the 4-position (and especially oxazol-2,4-diyl with 1,1-difluoroethyl being attached to the 4-position). A further most preferred example is oxazol-2,4-diyl with 1,1-difluoroethyl being attached to the 2-position.

The term "1,3-arrangement" as used in the specification of "**A**" means that the two atoms of the heteroaryl-group which are attached to the triazole-methyl moiety and to the 1,1-difluoroethyl moiety are separated from each other by one atom; for example, if "**A**" represents furan-2,5-diyl the arrangement of the substituents is as shown in the figure below

[1,2,3]triazol-4-yl}-amide;
2-Methyl-5-(3-trifluoromethyl-phenyl)-oxazole-4-carboxylic acid {2-[5-(1,1-difluoro-ethyl)-furan-2-ylmethyl]-2H-[1,2,3]triazol-4-yl}-amide;
5-(4-Fluoro-phenyl)-oxazole-4-carboxylic acid {2-[4-(1,1-difluoro-ethyl)-thiazol-2-ylmethyl]-2H-[1,2,3]triazol-4-yl}-amide;
5-(3-Fluoro-5-methyl-phenyl)-2-methyl-oxazole-4-carboxylic acid {2-[5-(1,1-difluoro-ethyl)-furan-2-ylmethyl]-2H-[1,2,3]triazol-4-yl}-amide;
2-Methyl-5-(3-trifluoromethoxy-phenyl)-oxazole-4-carboxylic acid {2-[5-(1,1-difluoro-ethyl)-furan-2-ylmethyl]-2H-[1,2,3]triazol-4-yl}-amide;
5-Phenyl-oxazole-4-carboxylic acid {2-[5-(1,1-difluoro-ethyl)-furan-2-ylmethyl]-2H-[1,2,3]triazol-4-yl}-amide;
5-(3-Chloro-phenyl)-2-methyl-oxazole-4-carboxylic acid {2-[4-(1,1-difluoro-ethyl)-thiazol-2-ylmethyl]-2H-[1,2,3]triazol-4-yl}-amide;
2-Ethyl-5-phenyl-oxazole-4-carboxylic acid {2-[4-(1,1-difluoro-ethyl)-thiazol-2-ylmethyl]-2H-[1,2,3]triazol-4-yl}-amide; and
2-Methyl-5-m-tolyl-oxazole-4-carboxylic acid {2-[4-(1,1-difluoro-ethyl)-oxazol-2-ylmethyl]-2H-[1,2,3]triazol-4-yl}-amide;
or a salt of such a compound.

12. A compound of formula (I) according to claim 1, selected from the group consisting of:
N-(2-((2-(1,1-Difluoroethyl)oxazol-4-yl)methyl)-2*H*-1,2,3-triazol-4-yl)-2-methyl-5-(m-tolyl)oxazole-4-carboxamide;
2-Methyl-5-phenyl-oxazole-4-carboxylic acid {2-[4-(1,1-difluoro-ethyl)-oxazol-2-ylmethyl]-2*H*-[1,2,3]triazol-4-yl}-amide;
5-(3-Dimethylamino-phenyl)-oxazole-4-carboxylic acid {2-[4-(1,1-difluoro-ethyl)-oxazol-2-ylmethyl]-2*H*-[1,2,3]triazol-4-yl}-amide;
5-(3-Dimethylamino-4-fluoro-phenyl)-oxazole-4-carboxylic acid {2-[4-(1,1-difluoro-ethyl)-oxazol-2-ylmethyl]-2*H*-[1,2,3]triazol-4-yl}-amide; and
5-(3-Dimethylamino-4-fluoro-phenyl)-2-methyl-oxazole-4-carboxylic acid {2-[4-(1,1-difluoro-ethyl)-oxazol-2-ylmethyl]-2*H*-[1,2,3]triazol-4-yl}-amide;
or a salt of such a compound.

13. A compound of formula (I) according to claim 1, wherein the compound is 2-Methyl-5-phenyl-oxazole-4-carboxylic acid {2-[5-(1,1-difluoro-ethyl)-furan-2-ylmethyl]-2*H*-[1,2,3]triazol-4-yl}-amide or a salt of such a compound.

14. A compound of formula (I) according to claim 1, wherein the compound is 2-Methyl-5-phenyl-oxazole-4-carboxylic acid {2-[4-(1,1-difluoro-ethyl)-thiazol-2-ylmethyl]-2*H*-[1,2,3]triazol-4-yl}-amide or a salt of such a compound.

15. A compound of formula (I) according to claim 1, wherein the compound is 5-(3-Chloro-phenyl)-2-methyl-oxazole-4-carboxylic acid {2-[4-(1,1-difluoro-ethyl)-thiazol-2-ylmethyl]-2*H*-[1,2,3]triazol-4-yl}-amide or a salt of such a compound.

16. A compound of formula (I) according to claim 1, wherein the compound is 2-Methyl-5-*m*-tolyl-oxazole-4-carboxylic acid {2-[4-(1,1-difluoro-ethyl)-oxazol-2-ylmethyl]-2*H*-[1,2,3]triazol-4-yl}-amide or a salt of such a compound.

17. A compound of formula (I) according to claim 1, wherein the compound is 2-Methyl-5-phenyl-oxazole-4-carboxylic acid {2-[4-(1,1-difluoro-ethyl)-oxazol-2-ylmethyl]-2*H*-[1,2,3]triazol-4-yl}-amide or a salt of such a compound.

18. ~~As a medicament, a~~A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, for use as a medicament.

19~~3~~4. A pharmaceutical composition containing, as active principle, a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

15~~2~~20. Use of a compound of formula (I) according to claim 1, or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or treatment of a disease selected from inflammatory diseases, obstructive airway diseases, allergic conditions, HIV-mediated retroviral infections, cardiovascular disorders, neuroinflammation, neurological disorders, pain, prion-mediated diseases and amyloid-mediated disorders; and for the modulation of immune responses.

16~~2~~21. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, for the prevention or treatment of a disease selected from inflammatory diseases, obstructive airway diseases, allergic conditions, HIV-mediated retroviral infections, cardiovascular disorders, neuroinflammation, neurological disorders, pain, prion-mediated diseases and amyloid-mediated disorders; and for the modulation of immune responses.