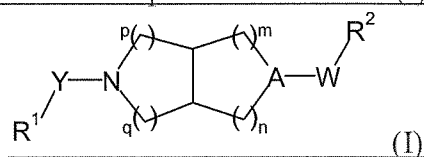


The compounds of formula (I) or their pharmaceutically acceptable salts and esters herein inhibit autotaxin activity and therefore inhibit LPA production and modulate LPA levels and associated signaling. Autotaxin inhibitors described herein are useful as agents for the treatment or prevention of diseases or conditions in which ATX activity and/or LPA signaling participates, is involved in the etiology or pathology of the disease, or is otherwise associated with at least one symptom of the disease. The ATX-LPA axis has been implicated for example in angiogenesis, chronic inflammation, autoimmune diseases, fibrotic diseases, cancer and tumor metastasis and progression, ocular conditions, metabolic conditions such as obesity and/or diabetes mellitus, conditions such as cholestatic or other forms of chronic pruritus as well as acute and chronic organ transplant rejection.

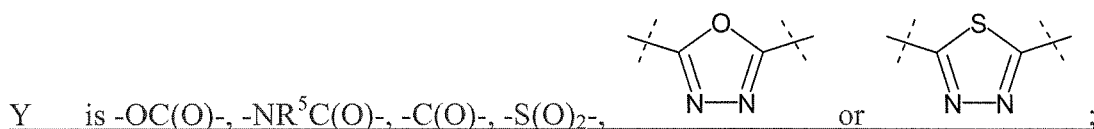
Objects of the ~~present invention~~ embodiments disclosed herein are the compounds of formula (I) and their aforementioned salts and esters and their use as therapeutically active substances, a process for the manufacture of the said compounds, intermediates, pharmaceutical compositions, medicaments containing the said compounds, their pharmaceutically acceptable salts or esters, the use of the said compounds, salts or esters for the treatment or prophylaxis of disorders or conditions that are associated with the activity of ATX and/or the biological activity of lysophosphatidic acid (LPA), particularly in the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, conditions of the respiratory system, vascular and cardiovascular conditions, fibrotic diseases, cancer, ocular conditions, metabolic conditions, cholestatic and other forms of chronic pruritus and acute and chronic organ transplant rejection, and the use of the said compounds, salts or esters for the production of medicaments for the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, conditions of the respiratory system, vascular and cardiovascular conditions, fibrotic diseases, cancer, ocular conditions, metabolic conditions, cholestatic and other forms of chronic pruritus and acute and chronic organ transplant rejection.

In one aspect, there is provided compounds of formula (I)



wherein

- R¹ is substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted naphthyl, substituted naphthylalkyl, substituted naphthyloxyalkyl, substituted naphthylalkenyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted indolyl, substituted quinolyl, substituted isoquinolyl, substituted 2,3-dihydro-1H-isoindol-2-yl, substituted 1H-indol-2-yl or substituted benzofuran-2-yl wherein substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted naphthyl, substituted naphthylalkyl, substituted naphthyloxyalkyl, substituted naphthylalkenyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted indolyl, substituted quinolyl, substituted isoquinolyl, substituted 2,3-dihydro-1H-isoindol-2-yl, substituted 1H-indol-2-yl and substituted benzofuran-2-yl are substituted with R⁷, R⁸ and R⁹;
- R² is substituted phenyl, substituted pyridinyl, substituted pyrrolyl, oxodihydropyridinyl or substituted thiophenyl, wherein substituted phenyl, substituted pyridinyl, substituted pyrrolyl and substituted thiophenyl are substituted with R¹⁰, R¹¹ and R¹²;



A is -N- or CH-;

- W is -O-, -S-, -NR⁶-, -C(O)-, -S(O)₂-, or -CR³R⁴-;

R³ and R⁴ are independently selected from H, halogen, alkyl and cycloalkyl;

R⁵ and R⁶ are independently selected from H, alkyl and cycloalkyl;

R⁷, R⁸ and R⁹ are independently selected from H, alkyl, hydroxyalkyl, haloalkyl, hydroxyhaloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkoxy, cycloalkoxy, cycloalkoxyalkyl, cycloalkylalkoxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkoxyalkoxy, alkoxyalkoxyalkyl, phenyl, substituted phenyl, pyridinyl, substituted pyridinyl, halogen, hydroxy, cyano, alkylsulfanyl, haloalkylsulfanyl, cycloalkylsulfanyl, alkylsulfinyl, haloalkylsulfinyl, cycloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, substituted aminosulfonyl, substituted amino and substituted aminoalkyl, wherein substituted aminosulfonyl, substituted amino and substituted aminoalkyl are substituted on the nitrogen atom with one to two substituents independently selected from H, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl and cycloalkylcarbonyl, and wherein substituted phenyl and substituted pyridinyl are optionally substituted with one to three substituents independently selected from alkyl, halogen, haloalkyl, alkoxy and haloalkoxy, wherein at least one of R⁷, R⁸ and R⁹ is not H;

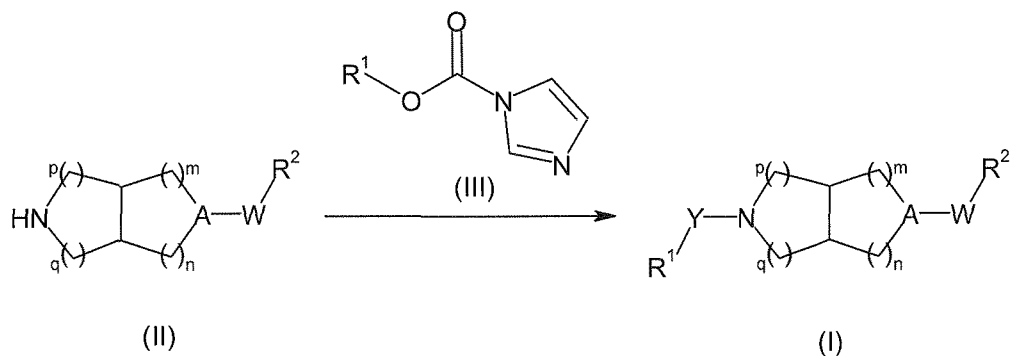
15 R¹⁰ is substituted aminosulfonyl, alkoxycarbonyl, alkylcarbonylamino, alkylsulfonylamino, substituted amino, carboxy, cyano, hydroxy or tetrazolyl, wherein substituted amino is substituted on the nitrogen atom with one to two substituents independently selected from H, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl and alkoxyalkyl;

R¹¹ and R¹² are independently selected from H, alkyl, cycloalkyl, alkoxy, halogen and haloalkyl;

20 m, n, p and q are independently selected from 1 or 2;

or pharmaceutically acceptable salts.

In another aspect, there is provided a process to prepare a compound as defined herein comprising the reaction of a compound of formula (II) in the presence of a compound of formula (III), wherein R^1 , R^2 , A, W, m, n, p and q are as defined above, Y is -OC(O)-.



5 In another aspect, there is provided a compound as defined herein for use as therapeutically active substance.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a therapeutically inert carrier.

10 In another aspect, there is provided a compound as defined herein for use in the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, fibrotic diseases and acute and chronic organ transplant rejection.

15 In another aspect, there is provided use of a compound as defined herein in the preparation of a medicament for the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, fibrotic diseases and acute and chronic organ transplant rejection.

In another aspect, there is provided a compound as defined herein, when manufactured according to a process as defined herein.

20 The term “alkenyl” denotes a monovalent linear or branched hydrocarbon group of 2 to 7 carbon atoms with at least one double bond. In particular embodiments, alkenyl has 2 to 4 carbon atoms with at least one double bond. Examples of alkenyl include ethenyl, propenyl, prop-2-enyl, isopropenyl, n-butenyl and iso-butenyl. Particular alkenyl group is ethenyl.

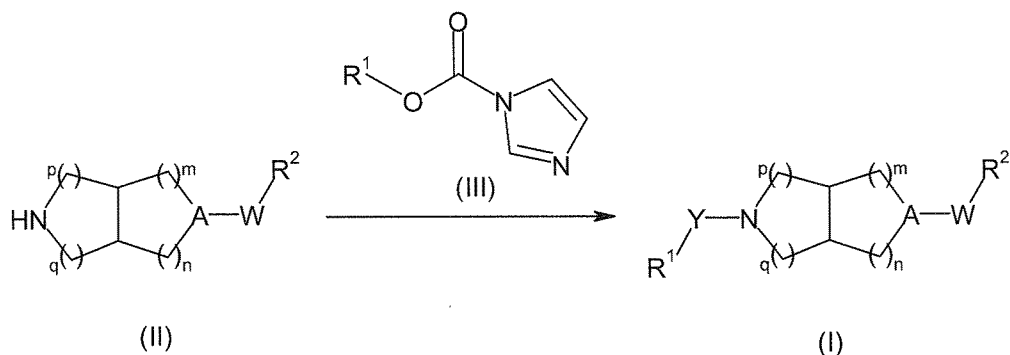
(3aS,6aS)-5-(4-sulfamoyl-benzoyl)-hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid 4-trifluoromethoxy-benzyl ester;

4-{(3aR,6aR)-5-[3-(4-trifluoromethoxy-phenyl)-propionyl]-hexahydro-pyrrolo[3,4-c]pyrrole-2-carbonyl}-benzenesulfonamide;

5 (3aS,6aS)-5-(5-sulfamoyl-pyridine-2-carbonyl)-hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid 4-cyano-2-(2,2-dimethyl-propionylamino)-benzyl ester;

and pharmaceutically acceptable salts thereof.

26. A process to prepare a compound according to any one of claims 1 to 25 comprising the reaction of a compound of formula (II) in the presence of a compound of formula (III),
10 wherein R^1 , R^2 , A, W, m, n, p and q are as defined above, Y is -OC(O)-.



27. A compound according to any one of claims 1 to 25 for use as therapeutically active substance.

28. A pharmaceutical composition comprising a compound according to any one of claims 1 to
15 25 and a therapeutically inert carrier.

~~29 The use of a compound according to any one of claims 1 to 25 for the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, fibrotic diseases and acute and chronic organ transplant rejection.~~

30 29. A compound according to any one of claims 1 to 25 for use in the treatment or prophylaxis
20 of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, fibrotic diseases and acute and chronic organ transplant rejection.

3130. The use of a compound according to any one of claims 1 to 25 ~~for~~in the preparation of a medicament for the treatment or prophylaxis of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, fibrotic diseases and acute and chronic organ transplant rejection.

~~32. A method for the treatment or prophylaxis a renal condition selected from the group consisting of renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, fibrotic diseases and acute and chronic organ transplant rejection, which method comprises administering an effective amount of a compound according to any one of claims 1 to 25.~~

~~33~~31. A compound according to any one of claims 1 to 25, when manufactured according to a process of claim 26.