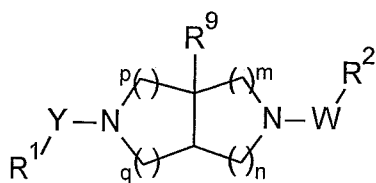


The compounds of formula (I) or their pharmaceutically acceptable salts and esters herein inhibit autotaxin activity and carbonic anhydrase activity therefore inhibit LPA production and modulate LPA levels and associated signaling. Dual ATX/CA-II inhibitors described herein are useful as agents for the 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 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 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 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. More particularly, 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 ocular conditions, furthermore particularly glaucoma.

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



wherein

- R¹ is substituted phenyl, substituted phenyl-C₁₋₆-alkyl, substituted phenoxy-C₁₋₆-alkyl, substituted phenyl-C₂₋₆-alkenyl, substituted phenyl-C₂₋₆-alkynyl, substituted pyridinyl, substituted pyridinyl-C₁₋₆-alkyl, substituted pyridinyl-C₂₋₆-alkenyl, substituted pyridinyl-C₂₋₆-alkynyl, substituted thiophenyl, substituted thiophenyl-C₁₋₆-alkyl, substituted thiophenyl-C₂₋₆-alkenyl or substituted thiophenyl-C₂₋₆-alkynyl, wherein substituted phenyl, substituted phenyl-C₁₋₆-alkyl, substituted phenoxy-C₁₋₆-alkyl, substituted phenyl-C₂₋₆-alkenyl, substituted phenyl-C₂₋₆-alkynyl, substituted pyridinyl, substituted pyridinyl-C₁₋₆-alkyl, substituted pyridinyl-C₂₋₆-alkenyl, substituted pyridinyl-C₂₋₆-alkynyl, substituted thiophenyl, substituted thiophenyl-C₁₋₆-alkyl, substituted thiophenyl-C₂₋₆-alkenyl and substituted thiophenyl-C₂₋₆-alkynyl are substituted by R³, R⁴ and R⁵;

Y is -OC(O)- or -C(O)-;

- W is -C(O)-, -S(O)₂- or -CR⁶R⁷-;

R² is substituted phenyl, substituted pyridinyl or substituted thiophenyl, wherein substituted phenyl, substituted pyridinyl and substituted thiophenyl are substituted by R⁶, R⁷ and R⁸;

- R³ is halogen, hydroxy, cyano, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₃₋₈-cycloalkyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl, C₃₋₈-cycloalkyl-C₁₋₆-alkoxy, C₃₋₈-cycloalkoxy, C₃₋₈-cycloalkoxy-C₁₋₆-alkyl, C₁₋₆-alkylamino, C₁₋₆-alkylcarbonylamino, C₃₋₈-cycloalkylcarbonylamino, C₁₋₆-alkyltetrazolyl, C₁₋₆-alkyltetrazolyl-C₁₋₆-alkyl or heterocycloalkyl-C₁₋₆-alkoxy;

- R⁴ and R⁵ are independently selected from H, halogen, hydroxy, cyano, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₃₋₈-cycloalkyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl, C₃₋₈-cycloalkyl-C₁₋₆-alkoxy, C₃₋₈-cycloalkoxy, C₃₋₈-cycloalkoxy-C₁₋₆-alkyl, C₁₋₆-alkylcarbonylamino, C₃₋₈-cycloalkylcarbonylamino, C₁₋₆-alkyltetrazolyl, C₁₋₆-alkyltetrazolyl-C₁₋₆-alkyl or heterocycloalkyl-C₁₋₆-alkoxy;

R^6 is aminosulfonyl;

R^7 and R^8 are independently selected from H, halogen, hydroxy, cyano, C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkoxy- C_{1-6} -alkyl, halo- C_{1-6} -alkoxy, halo- C_{1-6} -alkyl, hydroxy- C_{1-6} -alkyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkoxy, C_{3-8} -cycloalkoxy and C_{3-8} -cycloalkoxy- C_{1-6} -alkyl;

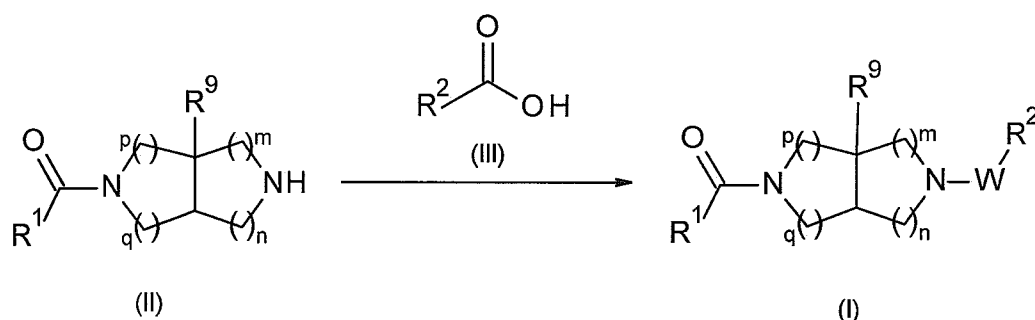
R^9 is C_{1-6} -alkyl, C_{1-6} -alkoxy or halogen;

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 , R^9 , m, n, p and q are as defined herein and W is -C(O)-



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.

In another aspect, there is provided a compound as defined herein for the treatment or prophylaxis of ocular conditions.

In another aspect, there is provided the use of a compound as defined herein for the preparation of a medicament for the treatment or prophylaxis of ocular conditions.

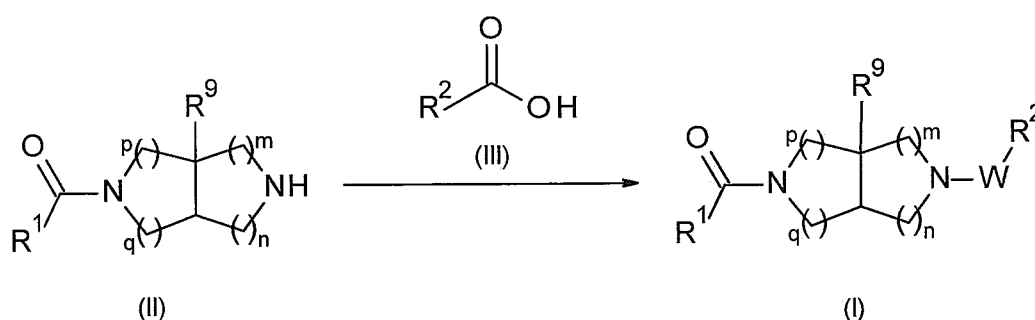
In another aspect, there is provided a compound as defined herein, when manufactured according to a process as defined herein.

The term “C₁₋₆-alkoxy” denotes a group of the formula -O-R’, wherein R’ is an C₁₋₆-alkyl group. Examples of C₁₋₆-alkoxy group include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy and tert-butoxy. Particular example is methoxy.

trans-4-[5-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]-3a-fluoro-3,4,6,6a-tetrahydro-1H-pyrrolo[3,4-c]pyrrole-2-carbonyl]-3-fluorobenzenesulfonamide;

and pharmaceutically acceptable salts thereof.

22. A process to prepare a compound according to any one of claims 1 to 22 comprising the reaction of a compound of formula (II) in the presence of a compound of formula (III), wherein R^1 , R^2 , R^9 , m, n, p and q are as defined in any one of claim 1 to 22 and W is -C(O)-.



23. A compound according to any one of claims 1 to 22 for use as therapeutically active substance.

24. A pharmaceutical composition comprising a compound according to any one of claims 1 to 22 and a therapeutically inert carrier.

25. A compound according to any one of claims 1 to 22 for the treatment or prophylaxis of ocular conditions.

26. The use of a compound according to any one of claims 1 to 22 for the preparation of a medicament for the treatment or prophylaxis of ocular conditions.

27. A compound according to any one of claims 1 to 22, when manufactured according to a process of claim 22.