

purinergic receptors than to the prototypic LPA1-3 receptors. The ATX-LPA signaling axis is involved in a large range of physiological and pathophysiological functions, including, for example, nervous system function, vascular development, cardiovascular physiology, reproduction, immune system function, chronic inflammation, tumor metastasis and progression, organ fibrosis as well as obesity and/or other metabolic diseases such as diabetes mellitus. Therefore, increased activity of ATX and/or increased levels of LPA, altered LPA receptor expression and altered responses to LPA may contribute to the initiation, progression and/or outcome of a number of different pathophysiological conditions related to the ATX/LPA axis.

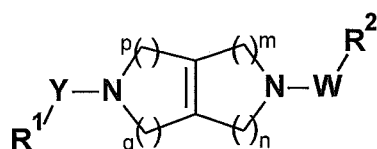
In accordance with the invention, the compounds of formula (I) or their pharmaceutically acceptable salts and esters can be used for the treatment or prophylaxis of diseases, disorders or conditions that are associated with the activity of autotaxin and/or the biological activity of lysophosphatidic acid (LPA).

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 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. 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)



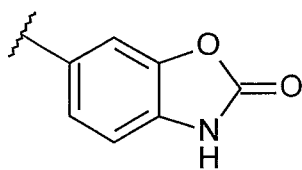
wherein

R^1 is substituted phenyl, substituted phenyl- C_{1-6} -alkyl, substituted phenoxy- C_{1-6} -alkyl, substituted phenyl- C_{2-6} -alkenyl, substituted phenyl- C_{2-6} -alkynyl, substituted pyridinyl, substituted pyridinyl- C_{1-6} -alkyl, substituted pyridinyl- C_{2-6} -alkenyl, substituted pyridinyl- C_{2-6} -alkynyl, substituted thiophenyl, substituted thiophenyl- C_{1-6} -alkyl, substituted thiophenyl- C_{2-6} -alkenyl or substituted thiophenyl- C_{2-6} -alkynyl, wherein substituted phenyl, substituted phenyl- C_{1-6} -alkyl, substituted phenoxy- C_{1-6} -alkyl, substituted phenyl- C_{2-6} -alkenyl, substituted phenyl- C_{2-6} -alkynyl, substituted pyridinyl, substituted pyridinyl- C_{1-6} -alkyl, substituted pyridinyl- C_{2-6} -alkenyl, substituted pyridinyl- C_{2-6} -alkynyl, substituted thiophenyl, substituted thiophenyl- C_{1-6} -alkyl, substituted thiophenyl- C_{2-6} -alkenyl and substituted thiophenyl- C_{2-6} -alkynyl are substituted by R^3 , R^4 and R^5 ;

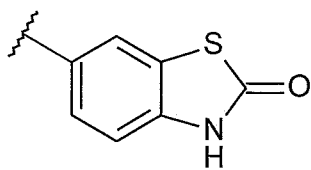
Y is $-OC(O)-$ or $-C(O)-$;

W is $-C(O)-$, $-S(O)_2-$ or $-CR^6R^7-$;

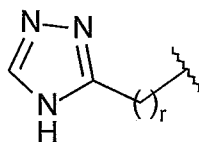
R^2 is selected from the ring systems B, F, L, M, O, Z, AF, AG, AH, AJ, AN, AO, AP, AQ, AR, AS, AT, AU, AV, AW, AX, AY, AZ, BA, BC and BD;



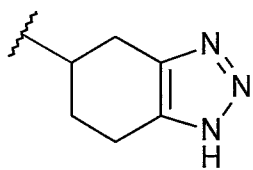
B



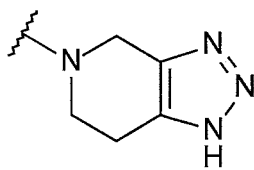
F



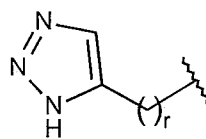
L



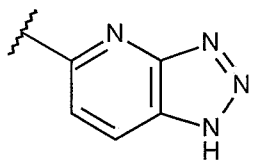
M



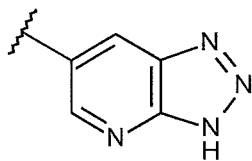
O



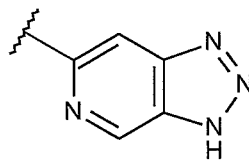
Z



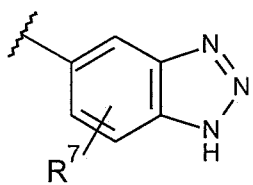
AF



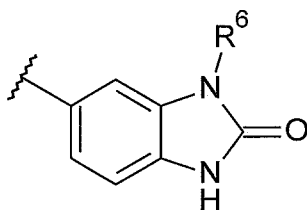
AG



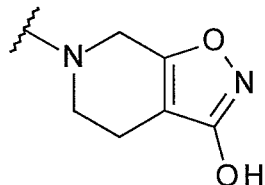
AH



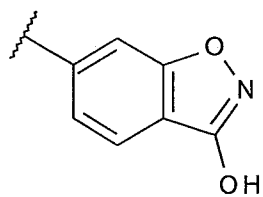
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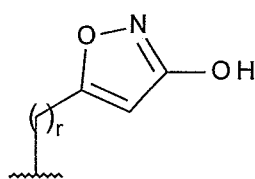
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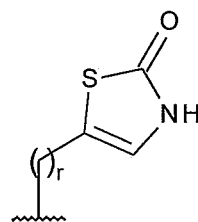
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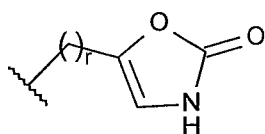
AP



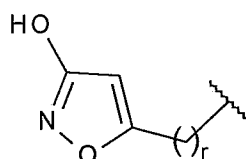
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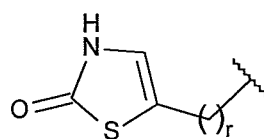
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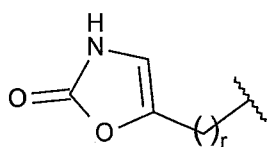
AS



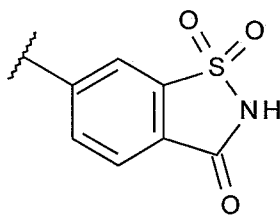
AT



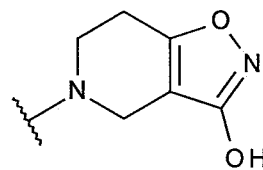
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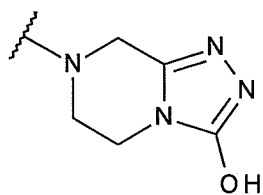
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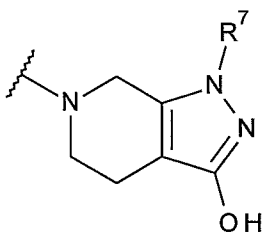
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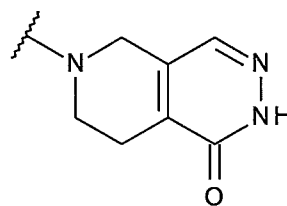
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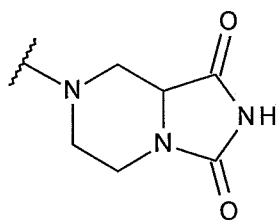
AY



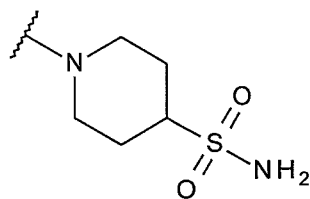
AZ



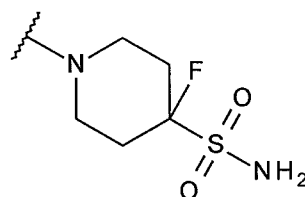
BA



BB



BC



BD

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;

R⁶ is H or C₁₋₆-alkyl;

R⁷ is H, C₁₋₆-alkyl, halogen, halo-C₁₋₆-alkyl or C₁₋₆-alkoxy;

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

r is 1, 2 or 3;

and 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 R₁, R₂, 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.

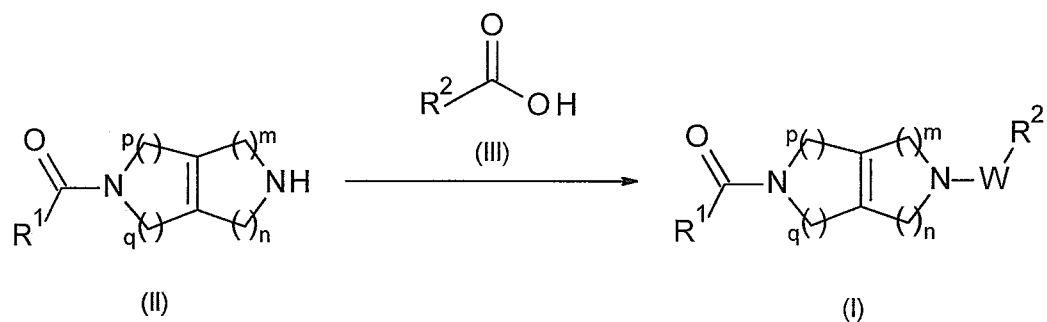
The term “C₂₋₆-alkenyl” denotes a monovalent linear or branched hydrocarbon group of 2 to 6 carbon atoms with at least one double bond. Particular example is ethylenyl.

The term “C₁₋₆-alkoxy-C₁₋₆-alkyl” denotes a C₁₋₆-alkyl group wherein at least one of the hydrogen atoms of the C₁₋₆-alkyl group is replaced by a C₁₋₆-alkoxy group. Particular examples are methoxymethyl, methoxyethyl, ethoxymethyl, ethoxyethyl, iso-propoxymethyl and iso-propoxyethyl.

The term “C₁₋₆-alkyl” denotes a monovalent linear or branched saturated hydrocarbon group of 1 to 6 carbon atoms. Examples of C₁₋₆-alkyl include methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl and pentyl. Particular alkyl groups include methyl, ethyl, isopropyl, n-butyl and sec-butyl.

The term “C₁₋₆-alkylamino” a group of the formula -NH- R', wherein R' is an C₁₋₆-alkyl group. Particular C₁₋₆-alkylamino is a group of the formula -NH- R', wherein R' is ter-butyl.

The term “C₁₋₆-alkylcarbonylamino” denotes a group of the formula -NH-C(O)-R', wherein R' is an C₁₋₆-alkyl group. Particular C₁₋₆-alkylcarbonylamino is a group of the formula -NH-C(O)-R', wherein R' is ter-butyl.



28. A compound according to any one of claims 1 to 26 for use as therapeutically active substance.
29. A pharmaceutical composition comprising a compound according to any one of claims 1 to 26 and a therapeutically inert carrier.
30. A compound according to any one of claims 1 to 26 for the treatment or prophylaxis of ocular conditions.
31. The use of a compound according to any one of claims 1 to 26 for the preparation of a medicament for the treatment or prophylaxis of ocular conditions.
32. A compound according to any one of claims 1 to 26, when manufactured according to a process of claim 27.
