

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.

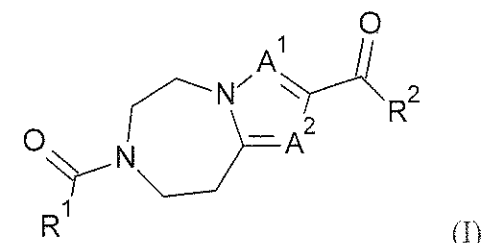
5 In accordance with the ~~invention~~disclosure, the compounds of formula (I) or their pharmaceutically acceptable salts and esters can be used for the treatment or prophylaxis of diseases, disorders or conditions that are associated with the activity of autotaxin and/or the biological activity of lysophosphatidic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

10 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
15 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.

20 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
25 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
30 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)



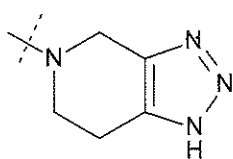
5 wherein

R¹ is alkyl, haloalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylalkoxy, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, 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 phenylalkoxy, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isoindol-2-yl, substituted 1H-indol-2-yl and substituted benzofuran-2-yl are substituted with R³, R⁴ and R⁵;

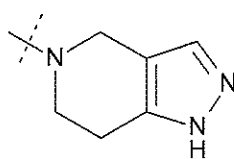
A¹ is -N- or -CR⁷-;

20 A² is -N- or -CR⁸- and at least one of A¹ and A² is -N-;

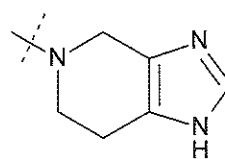
R² is selected from the ring systems A, B, C, D, E, F, G, H, I, K and L;



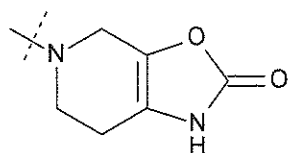
A



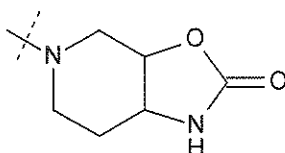
B



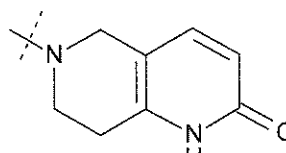
C



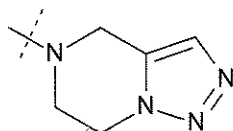
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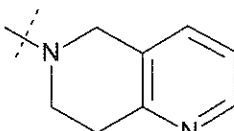
E



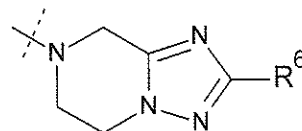
F



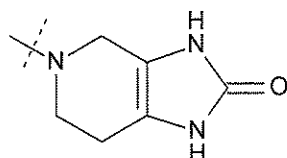
G



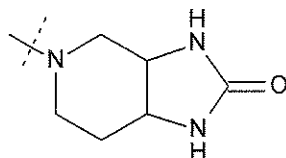
H



I



K



L

R^3 , R^4 and R^5 are independently selected from H, alkyl, hydroxyalkyl, haloalkyl, hydroxyhaloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkoxy, cycloalkoxy, cycloalkoxyalkyl, cycloalkylalkoxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkoxyalkoxy, alkoxyalkoxyalkyl, heterocycloalkylalkoxy, phenyl, substituted phenyl, pyridinyl, substituted pyridinyl, halogen, hydroxy, cyano, alkylsulfanyl, haloalkylsulfanyl, cycloalkylsulfanyl, alkylsulfinyl, haloalkylsulfinyl, cycloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, alkylcarbonylamino, 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

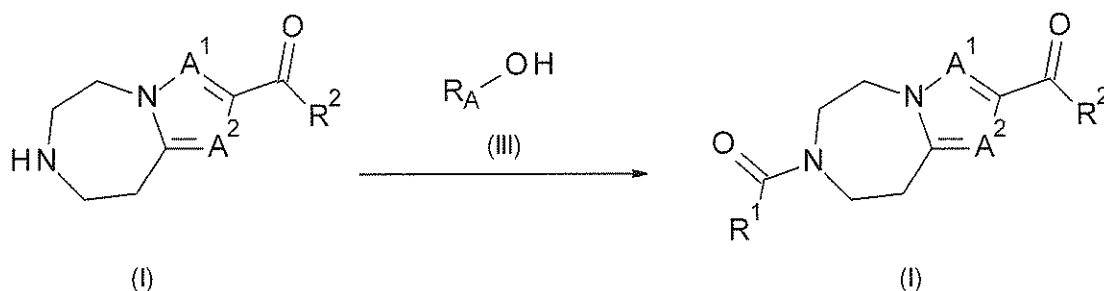
substituted with one to three substituents independently selected from alkyl, halogen, haloalkyl, alkoxy and haloalkoxy;

R^6 is H, alkyl, haloalkyl or cycloalkyl;

R^7 and R^8 are independently selected from H, alkyl, haloalkyl or cycloalkyl;

5 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 is phenylalkoxy substituted with R^3 , R^4 and R^5 , R_A is phenylalkyl substituted with R^3 , R^4 and R^5 and R^2 , R^3 , R^4 , R^5 , A^1 and A^2 are as defined herein

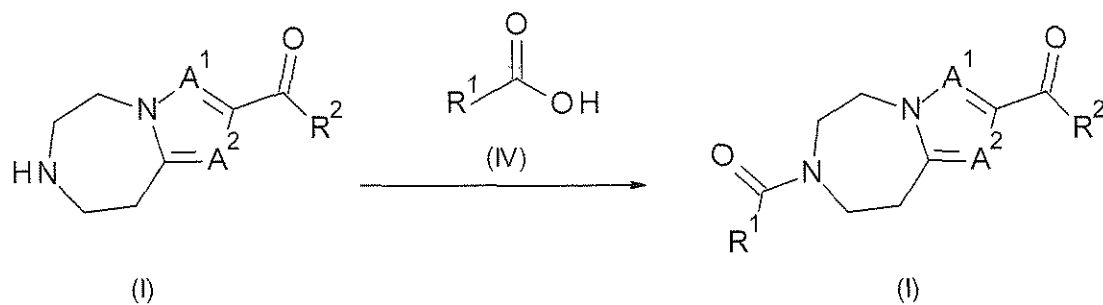


In another aspect, there is provided a process to prepare a compound as defined herein comprising the reaction of a compound of formula (II) in the presence of a compound of formula (IV), wherein R^1 is alkyl, haloalkyl, substituted cycloalkyl, substituted cycloalkylalkyl, substituted phenyl, substituted phenylalkyl, substituted phenoxyalkyl, substituted phenylcycloalkyl, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, 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 pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isoindol-2-yl, substituted 1H-indol-2-yl and

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substituted benzofuran-2-yl are substituted with R^3 , R^4 and R^5 and R^2 , R^3 , R^4 , R^5 A^1 and A^2 are as defined herein



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 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 the use of a compound as defined herein for 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.

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.

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

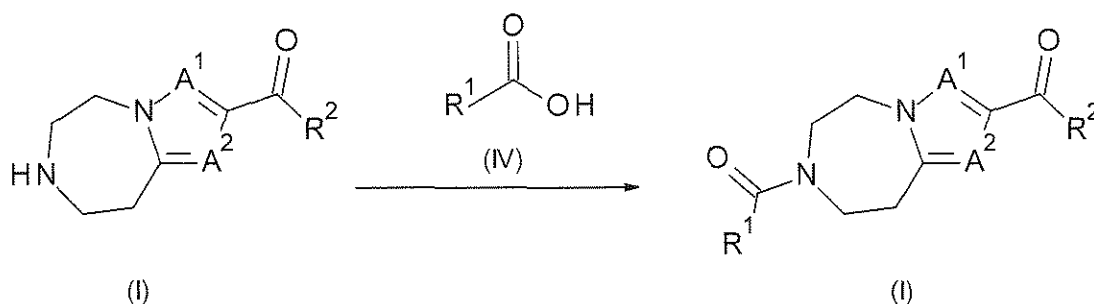
The term “alkoxyalkoxy” denotes an alkoxy group wherein at least one of the hydrogen atoms of the alkoxy group has been replaced by another alkoxy group. Examples of alkoxyalkoxy group include methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy and ethoxypropoxy. Particular alkoxyalkoxy groups include methoxymethoxy and methoxyethoxy.

The term “alkoxyalkoxyalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by an alkoxyalkoxy group. Examples of alkoxyalkoxyalkyl group include methoxymethoxymethyl, ethoxymethoxymethyl, methoxyethoxymethyl, ethoxyethoxymethyl, methoxypropoxymethyl, ethoxypropoxymethyl, methoxymethoxyethyl, ethoxymethoxyethyl, methoxyethoxyethyl, ethoxyethoxyethyl, methoxypropoxyethyl and ethoxypropoxyethyl.

The term “alkoxyalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by an alkoxy group. Exemplary alkoxyalkyl groups include methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, methoxypropyl, ethoxypropyl and isopropoxymethyl. Particular alkoxyalkyl group include include methoxymethyl, methoxyethyl and isopropoxymethyl.

The term “alkoxycarbonyl” denotes a group of the formula $-C(O)-R'$, wherein R' is an alkoxy group. Examples of alkoxycarbonyl groups include groups of the formula $-C(O)-R'$, wherein R' is methoxy or ethoxy. Particular alkoxycarbonyl group include groups of the formula $-C(O)-R'$, wherein R' is methoxy.

phenylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted 2,3-dihydro-1H-isoindol-2-yl, substituted 1H-indol-2-yl and substituted benzofuran-2-yl are substituted with R^3 , R^4 and R^5 and R^2 , R^3 , R^4 , R^5 , A^1 and A^2 are as defined in any one of claim 1 to 18.



25. A compound according to any one of claims 1 to 22 for use as therapeutically active substance.
26. A pharmaceutical composition comprising a compound according to any one of claims 1 to 22 and a therapeutically inert carrier.
- ~~27. The use of a compound according to any one of claims 1 to 22 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.~~
- ~~28~~27. A compound according to any one of claims 1 to 22 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.
- ~~29~~28. 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 renal conditions, liver conditions, inflammatory conditions, conditions of the nervous system, fibrotic diseases and acute and chronic organ transplant rejection.
- ~~30. 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 22.~~

~~3129.~~ A compound according to any one of claims 1 to 22, when manufactured according to a process of claim 23 or 24.