

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

5 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.

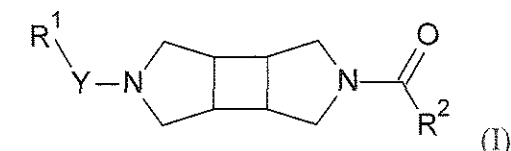
Objects of the ~~present invention~~embodiments disclosed herein are the compounds of

10 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

15 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

20 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.

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

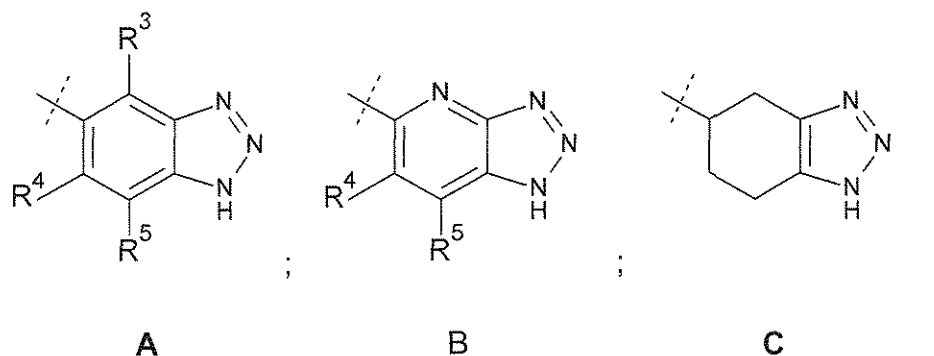


wherein

$R^1$  is substituted quinolinyl, substituted 1,2,3,4-tetrahydroquinolinyl, substituted isoquinolinyl, substituted 1,2,3,4-tetrahydroisoquinolinyl, substituted 9H-carbazolyl, substituted chromanyl, substituted indolyl, substituted naphthyl, substituted oxazolyl, substituted phenyl, substituted phenylalkyl, substituted phenylcycloalkyl, substituted phenoxyalkyl, substituted phenylalkoxy, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridazinyl, substituted pyridazinylalkyl, substituted pyridazinylalkenyl, substituted pyridazinylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted pyridinonyl, substituted pyridinonylalkyl, substituted pyridinonylalkenyl, substituted pyridinonylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted tetralinyl or substituted tetralinonyl, wherein substituted quinolinyl, substituted 1,2,3,4-tetrahydroquinolinyl, substituted isoquinolinyl, substituted 1,2,3,4-tetrahydroisoquinolinyl, substituted 9H-carbazolyl, substituted chromanyl, substituted indolyl, substituted naphthyl, substituted oxazolyl, substituted phenyl, substituted phenylalkyl, substituted phenylcycloalkyl, substituted phenoxyalkyl, substituted phenylalkoxy, substituted phenylalkenyl, substituted phenylalkynyl, substituted pyridazinyl, substituted pyridazinylalkyl, substituted pyridazinylalkenyl, substituted pyridazinylalkynyl, substituted pyridinyl, substituted pyridinylalkyl, substituted pyridinylalkenyl, substituted pyridinylalkynyl, substituted pyridinonyl, substituted pyridinonylalkyl, substituted pyridinonylalkenyl, substituted pyridinonylalkynyl, substituted thiophenyl, substituted thiophenylalkyl, substituted thiophenylalkenyl, substituted thiophenylalkynyl, substituted tetralinyl and substituted tetralinonyl are substituted with  $R^6$ ,  $R^7$  and  $R^8$ ;

$Y$  is -C(O)- or -S(O)<sub>2</sub>-;

$R^2$  is substituted pyridinyl, substituted phenyl or is selected from the ring systems A, B and C, wherein substituted pyridinyl and substituted phenyl are substituted with one substituted aminosulfonyl, wherein substituted aminosulfonyl is substituted on the nitrogen atom with one to two substituents independently selected from H, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl and alkoxyalkyl;

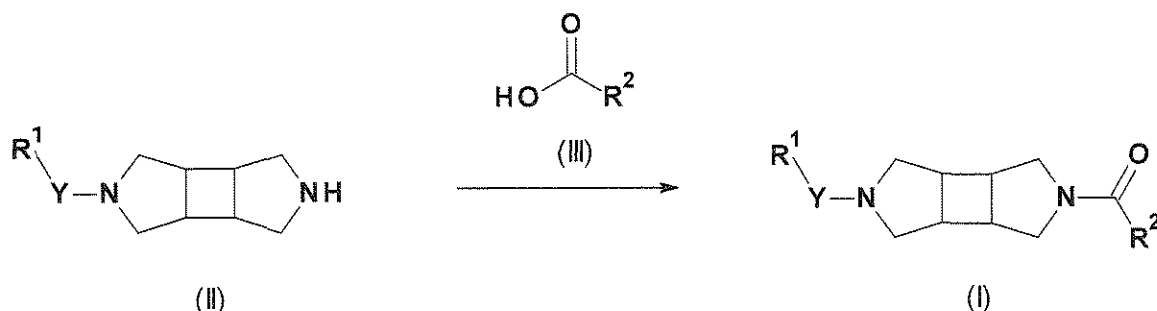


$R^3$ ,  $R^4$  and  $R^5$  are independently selected from H, alkyl, halogen, haloalkyl and alkoxy;

$R^6$ ,  $R^7$  and  $R^8$  are independently selected from H, halogen, cyano, cyanoalkyl, alkyl, hydroxyalkyl, haloalkyl, hydroxyhaloalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkoxy, cycloalkoxy, cycloalkoxyalkyl, cycloalkylalkoxyalkyl, alkoxy, alkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkoxyalkoxy, alkoxyalkoxyalkyl, alkylsulfonyl, furanyl, tetrahydropyranyl, phenyl, substituted phenyl, phenylalkoxy, substituted phenylalkoxy, pyridinyl, substituted pyridinyl, pyrrolyl, substituted pyrrolyl, pyrrolydinyl and substituted pyrrolydinyl, wherein substituted phenyl, substituted phenylalkoxy, substituted pyridinyl, substituted pyrrolyl and substituted pyrrolydinyl are substituted with one to three halogen;

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 and Y are as defined above



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.

5 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, 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.

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

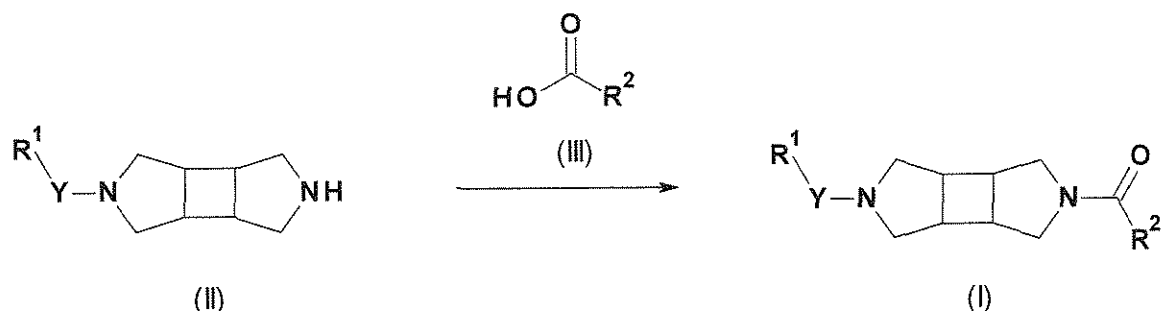
15 The term “alkenyl” denotes a monovalent linear or branched hydrocarbon group of 2 to 7 carbon atoms with at least one double bond. In particular embodiments, alkenyl has 2 to 4 carbon atoms with at least one double bond. Examples of alkenyl include ethenyl, propenyl, prop-2-enyl, isopropenyl, n-butenyl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

20 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 methoxy, ethoxy and isopropoxy. More particular alkoxy group is isopropoxy.

(3aR,3bS,6aR,6bS)-5-(1H-benzotriazole-5-carbonyl)-octahydro-cyclobuta[1,2-c;3,4-c']dipyrrole-2-carboxylic acid 4-trifluoromethoxy-benzyl ester;

and pharmaceutically acceptable salts thereof.

18. A process to prepare a compound according to any one of claims 1 to 17 comprising the reaction of a compound of formula (II) in the presence of a compound of formula (III), wherein  $R^1$ ,  $R^2$ , A and Y are as defined above.



19. A compound according to any one of claims 1 to 17 for use as therapeutically active substance.

20. A pharmaceutical composition comprising a compound according to any one of claims 1 to 17 and a therapeutically inert carrier.

~~21. The use of a compound according to any one of claims 1 to 17 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.~~

~~221.~~ A compound according to any one of claims 1 to 17 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.

~~2322.~~ The use of a compound according to any one of claims 1 to 17 for the preparation of a medicament 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.

24. ~~A method for the treatment or prophylaxis a condition selected from the group consisting~~  
5 ~~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, which method~~  
10 ~~comprises administering an effective amount of a compound according to any one of~~  
~~claims 1 to 17.~~

2523. A compound according to any one of claims 1 to 17, when manufactured according to a process of claim 18.