

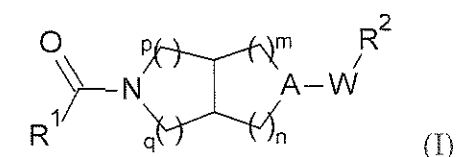
expression and altered responses to LPA may contribute to the initiation, progression and/or outcome of a number of different pathophysiological conditions related to the ATX/LPA axis.

In accordance with the ~~invention~~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).

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)



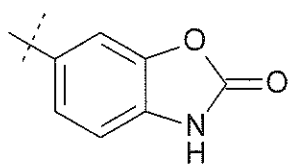
wherein

5 R¹ is substituted phenyl or substituted pyridinyl, wherein substituted phenyl and substituted pyridinyl are substituted with R³, R⁴ and R⁵;

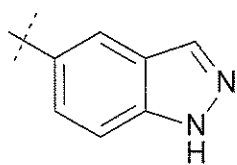
A is -N- or -CH-;

W is -C(O)-, -C(O)O-, -S(O)₂-, -C(O)-NR¹⁰- or -CR⁶R⁷;

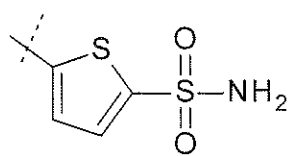
10 R² is selected from the ring systems B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, S, T, U, V, X, Z, AA, AB, AC, AD, AE, AF, AG, AH, AI, AJ, AK, AL, AM, AN, AO, AP, AQ, AR, AS, AT, AU and AV;



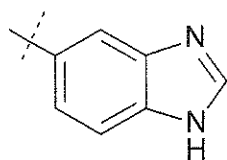
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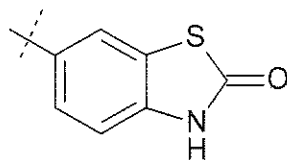
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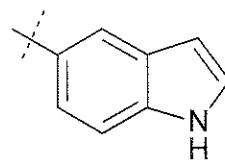
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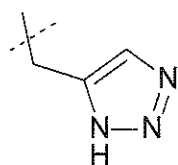
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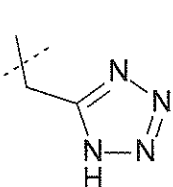
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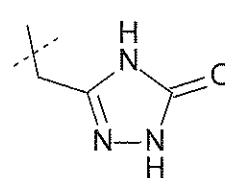
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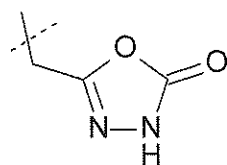
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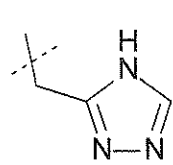
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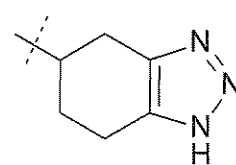
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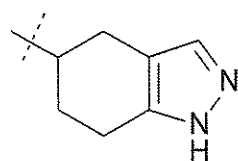
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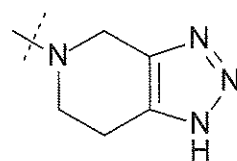
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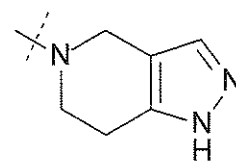
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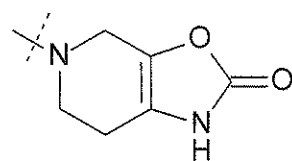
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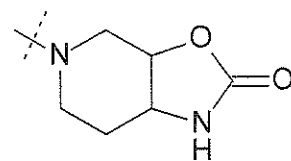
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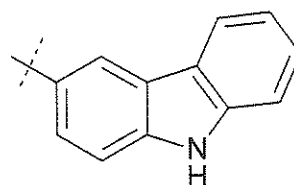
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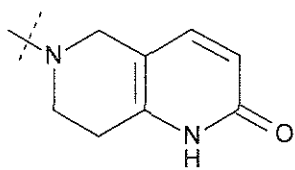
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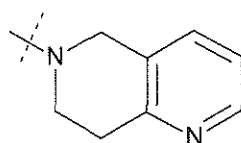
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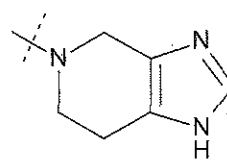
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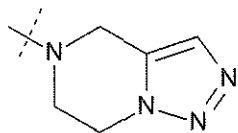
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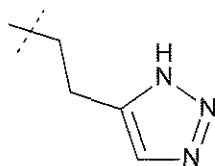
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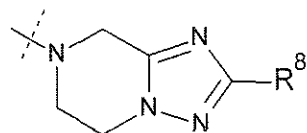
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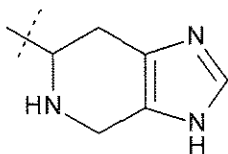
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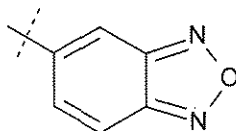
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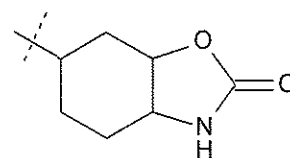
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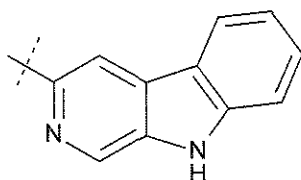
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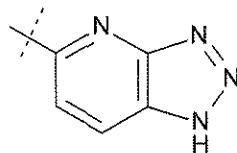
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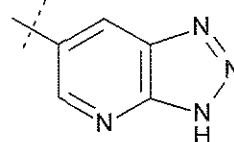
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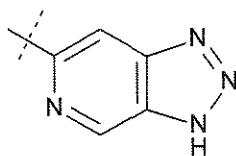
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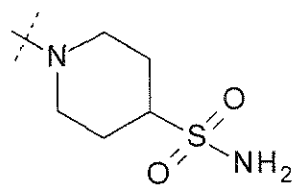
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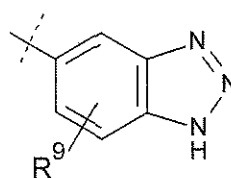
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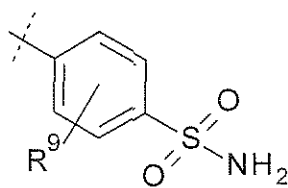
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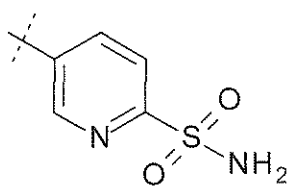
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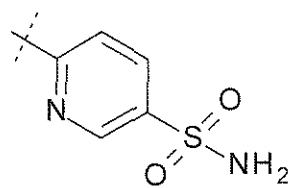
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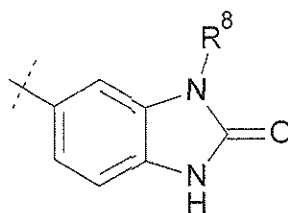
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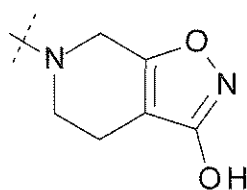
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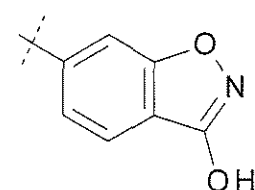
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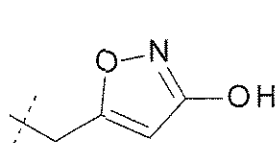
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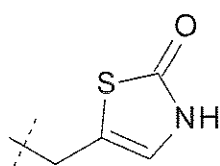
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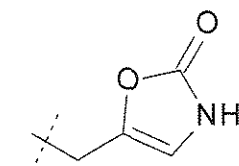
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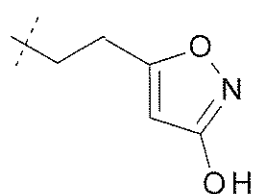
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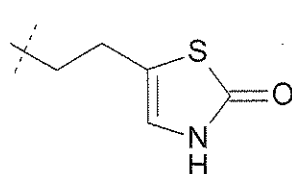
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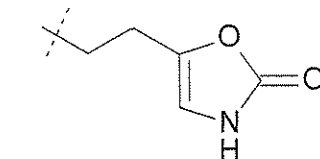
AS



AT



AU



AV

R³ is substituted heterocycloalkoxy, substituted heterocycloalkylalkoxy, substituted heterocycloalkylamino or substituted heterocycloalkylalkylamino, wherein substituted heterocycloalkoxy, substituted heterocycloalkylalkoxy, substituted heterocycloalkylamino and substituted heterocycloalkylalkylamino are substituted with R¹¹, R¹² and R¹³;

R⁴ and R⁵ are independently selected from H, amino, alkylamino, dialkylamino, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, halogen and cyano;

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

R⁶ and R⁷ are independently selected from H or alkyl;

R⁸ is H, alkyl, haloalkyl or cycloalkyl;

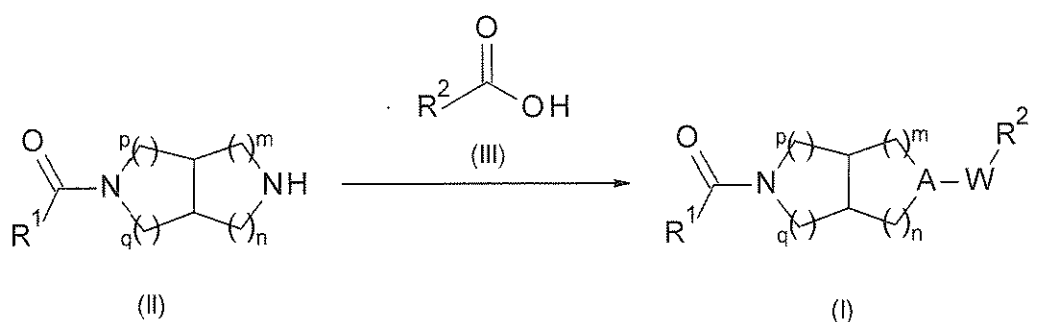
R⁹ is H, alkyl, halogen, haloalkyl and alkoxy;

5 R¹⁰ is H or alkyl;

R¹¹, R¹² and R¹³ are independently selected from H, alkyl, alkoxy, cycloalkyl, cycloalkoxy, halogen, haloalkyl, and cyano;

or pharmaceutically acceptable salts.

10 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 above, A is -N- and W is -C(O)-



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

15 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.

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

- ~~24.~~ The use of a compound according to any one of claims 1 to 20 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.
- ~~25~~24. A compound according to any one of claims 1 to 20 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.
- ~~26~~25. The use of a compound according to any one of claims 1 to 20 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.
- ~~27.~~ 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 20.
- ~~28~~26. A compound according to any one of claims 1 to 20, when manufactured according to a process of claim 21.