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.

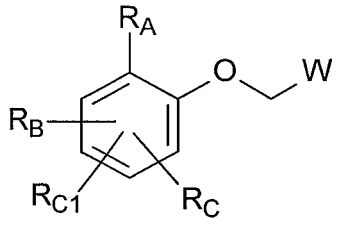
In accordance with the disclosure, the compounds of formula (I) or their pharmaceutically acceptable salts and esters can be used for the treatment or prophylaxis of diseases, disorders or conditions that are associated with the activity of autotaxin and/or the biological activity of lysophosphatidic 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 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 particulary, 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, the present disclosure relates to compounds of formula (I)




(I)

wherein

$R_A$ is selected from the group consisting of

i) $C_1$-$C_6$-alkyl,

ii) cyano-$C_1$-$C_6$-alkyl,

iii) $C_3$-$C_8$-cycloalkyl,

iv) halo-$C_1$-$C_6$-alkoxy,

v) halo-$C_1$-$C_6$-alkyl,

vi) aryl substituted with $R_G$, $R_{G1}$ and $R_{G2}$,

vii) heterocycloalkyl substituted with $R_G$, $R_{G1}$ and $R_{G2}$, and

viii) heteroaryl substituted with $R_G$, $R_{G1}$ and $R_{G2}$;

$R_B$ is selected from the group consisting of

i) $C_1$-$C_6$-alkyl,

ii) $C_3$-$C_8$-cycloalkyl,

iii) $C_1$-$C_6$-alkylsulfonyl,

iv) $C_3$-$C_8$-cycloalkylsulfonyl,

v) $C_1$-$C_6$-alkylsulfonylamino,

vi) $C_3$-$C_8$-cycloalkylsulfonylamino,

vii) aminocarbonyl,

viii) cyano,

ix) halogen,

x) halo-$C_1$-$C_6$-alkoxy,

xi) halo-$C_1$-$C_6$-alkyl,

xii) heterocycloalkyl, and

xiii) heteroaryl substituted with one H, $C_1$-$C_6$-alkyl or trialkylsilyl-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl;

$R_C$ and $R_{C1}$ are independently selected from the group consisting of

i) H,

ii) $C_1$-$C_6$-alkyl,

iii) $C_3$-$C_8$-cycloalkyl,

iv) halo-$C_1$-$C_6$-alkoxy,

v) halo-$C_1$-$C_6$-alkyl, and

vi) halogen;

or $R_B$ and $R_C$ together with the carbon atoms to which they are attached form a ring system selected from the group consisting of

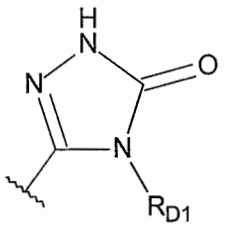
i) $C_3$-$C_8$-cycloalkyl substituted with one to two substituent independently selected from H, $C_1$-$C_6$-alkyl, halo-$C_1$-$C_6$-alkoxy, halo-$C_1$-$C_6$-alkyl and $C_3$-$C_8$-cycloalkyl,

ii) heterocycloalkyl substituted with one to two substituent independently selected from H, $C_1$-$C_6$-alkyl, halo-$C_1$-$C_6$-alkoxy, halo-$C_1$-$C_6$-alkyl and $C_3$-$C_8$-cycloalkyl,

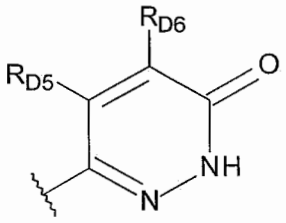
iii) aryl substituted with one to two substituent independently selected from H, halogen, $C_1$-$C_6$-alkyl, halo-$C_1$-$C_6$-alkoxy, halo-$C_1$-$C_6$-alkyl and $C_3$-$C_8$-cycloalkyl, and

iv) heteroaryl substituted with one to two substituent independently selected from H, halogen, $C_1$-$C_6$-alkyl, halo-$C_1$-$C_6$-alkoxy, halo-$C_1$-$C_6$-alkyl and $C_3$-$C_8$-cycloalkyl;

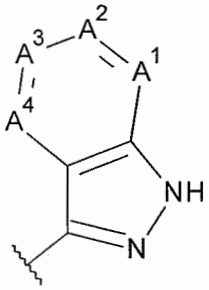
W is selected from the ring systems A, B, C, D, E, F and G;



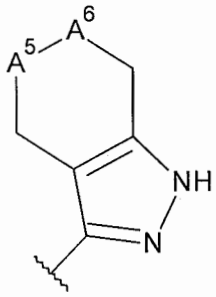

A ;



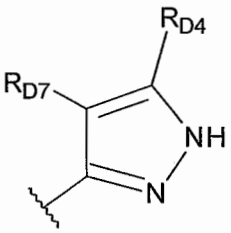

B ;



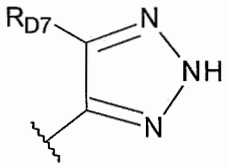

C ;



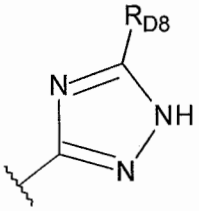

D ;




E ;




F ;




G ;

$A^1$, $A^3$ and $A^4$ are -CH- and $A^2$ is -$CR_{D2}$-,

$A^1$ is -N-, $A^2$ is -$CR_{D2}$-, $A^3$ is -CH- or -N- and $A^4$ is -CH-,

$A^1$, $A^3$ and $A^4$ are -CH- and $A^2$ is -N-,

$A^1$, $A^2$ and $A^4$ are -CH- and $A^3$ is -N-, or

$A^1$ and $A^3$ are -CH-, $A^2$ is -$CR_{D2}$- and $A^4$ is -N-;

one of $A^5$ and $A^6$ is -$NR_{D3}$- and the other one is -$CR_LR_M$-;

$R_{D1}$ is selected from the group consisting of

i) H,

ii) $C_1$-$C_6$-alkyl,

iii) halo-$C_1$-$C_6$-alkoxy,

iv) halo-$C_1$-$C_6$-alkyl, and

v) $C_3$-$C_8$-cycloalkyl,

$R_{D2}$ is selected from the group consisting of

i) H,

ii) halogen,

iii) $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkylcarbonyl,

iv) $C_1$-$C_6$-alkoxycarbonyl,

v) $C_1$-$C_6$-alkylcarbonyl,

vi) $C_3$-$C_8$-cycloalkylcarbonyl,

vii) $C_1$-$C_6$-alkyl,

viii) $C_3$-$C_8$-cycloalkyl,

ix) hydroxy-$C_1$-$C_6$-alkoxy,

x) hydroxy-$C_1$-$C_6$-alkyl($C_1$-$C_6$-alkyl)amino,

xi) hydroxy-$C_1$-$C_6$-alkylamino,

xii) hydroxy-$C_1$-$C_6$-alkyl,

xiii) dihydroxy-$C_1$-$C_6$-alkoxy,

xiv) dihydroxy-$C_1$-$C_6$-alkyl($C_1$-$C_6$-alkyl)amino,

xv) dihydroxy-$C_1$-$C_6$-alkylamino,

xvi) dihydroxy-$C_1$-$C_6$-alkyl,

xvii) halo-$C_1$-$C_6$-alkoxy,

xviii) halo-$C_1$-$C_6$-alkyl,

xix) heterocycloalkyl,

xx) heterocycloalkylcarbonyl, and

xxi) aminocarbonyl substituted on the nitrogen atom with one to two independently selected $C_1$-$C_6$-alkyl;

$R_{D3}$ is selected from the group consisting of

i) H,

ii) $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkylcarbonyl,

iii) $C_1$-$C_6$-alkoxycarbonyl,

iv) $C_1$-$C_6$-alkylcarbonyl,

v) $C_3$-$C_8$-cycloalkylcarbonyl,

vi) $C_1$-$C_6$-alkyl,

vii) $C_3$-$C_8$-cycloalkyl,

viii) halo-$C_1$-$C_6$-alkoxy,

ix) halo-$C_1$-$C_6$-alkyl,

x) hydroxy-$C_1$-$C_6$-alkyl, and

xi) dihydroxy-$C_1$-$C_6$-alkyl;

$R_{D4}$ is selected from the group consisting of

i) H,

ii) $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkylcarbonyl,

iii) $C_1$-$C_6$-alkoxycarbonyl,

iv) $C_1$-$C_6$-alkylcarbonyl,

v) $C_3$-$C_8$-cycloalkylcarbonyl,

vi) $C_1$-$C_6$-alkyl,

vii) $C_3$-$C_8$-cycloalkyl,

viii) halo-$C_1$-$C_6$-alkoxy,

ix) halo-$C_1$-$C_6$-alkyl,

x) heterocycloalkylcarbonyl,

xi) aminocarbonyl substituted on the nitrogen atom with one to two independently selected $C_1$-$C_6$-alkyl, and

xii) aryl substituted with one to thre substituents indenpendently selectefd from H, $C_1$-$C_6$-alkyl, $C_3$-$C_8$-cycloalkyl, halo-$C_1$-$C_6$-alkyl and halo-$C_1$-$C_6$-alkoxy;

$R_{D5}$, $R_{D6}$ and $R_{D7}$ are independently selected from the group consisting of

i) H,

ii) $C_1$-$C_6$-alkyl,

iii) $C_1$-$C_6$-alkoxy

iv) halo-$C_1$-$C_6$-alkoxy,

v) halo-$C_1$-$C_6$-alkyl,

vi) $C_3$-$C_8$-cycloalkyl, and

vii) $C_3$-$C_8$-cycloalkoxy;

$R_{D8}$ is selected from the group consisting of

i) H,

ii) $C_1$-$C_6$-alkyl,

iii) $C_1$-$C_6$-alkoxy

iv) halo-$C_1$-$C_6$-alkoxy,

v) halo-$C_1$-$C_6$-alkyl,

vi) $C_3$-$C_8$-cycloalkyl,

vii) $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkylcarbonyl,

viii) $C_1$-$C_6$-alkoxycarbonyl,

ix) $C_1$-$C_6$-alkylcarbonyl,

x) $C_3$-$C_8$-cycloalkylcarbonyl,

xi) heterocycloalkylcarbonyl, and

xii) aminocarbonyl substituted on the nitrogen atom with one to two independently selected $C_1$-$C_6$-alkyl;

$R_G$ is selected from the group consisting of

i) H,

ii) $C_1$-$C_6$-alkoxy,

iii) $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkylcarbonylamino-$C_1$-$C_6$-alkyl,

iv) $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkylcarbonyl($C_1$-$C_6$-alkyl)amino-$C_1$-$C_6$-alkyl,

v) $C_1$-$C_6$-alkoxycarbonyl,

vi) $C_1$-$C_6$-alkyl,

vii) $C_1$-$C_6$-alkylsulfonyl,

viii) $C_3$-$C_8$-cyloalkylsulfonyl,

ix) carboxy,

x) cyano,

xi) $C_3$-$C_8$-cycloalkyl,

xii) $C_3$-$C_8$-cycloalkoxy,

xiii) $C_3$-$C_8$-cycloalkylcarbonylamino-$C_1$-$C_6$-alkyl,

xiv) $C_3$-$C_8$-cycloalkylcarbonyl($C_1$-$C_6$-alkyl)amino-$C_1$-$C_6$-alkyl,

xv) $C_1$-$C_6$-alkylcarbonylamino-$C_1$-$C_6$-alkyl,

xvi) $C_1$-$C_6$-alkylcarbonyl($C_1$-$C_6$-alkyl)amino-$C_1$-$C_6$-alkyl,

xvii) halo-$C_1$-$C_6$-alkyl,

xviii) halo-$C_1$-$C_6$-alkoxy,

xix) halogen,

xx) hydroxy,

xxi) aminocarbonyl substituted on the nitrogen atom with $R_N$ and $R_O$,

xxii) aminocarbonyl-$C_1$-$C_6$-alkoxy substituted on the nitrogen atom with $R_N$ and $R_O$,

xxiii) heteroaryl substituted with one H, $C_1$-$C_6$-alkyl, $C_3$-$C_8$-cycloalkyl, halo-$C_1$-$C_6$-alkyl, halo-$C_1$-$C_6$-alkoxy, benzyl or aryl, wherein benzyl and aryl are substituted with one to three substituents independently selected from H, $C_1$-$C_6$-alkyl, $C_3$-$C_8$-cycloalkyl, halo-$C_1$-$C_6$-alkyl and halo-$C_1$-$C_6$-alkoxy,

xxiv) heterocycloalkyl-$C_1$-$C_6$-alkoxy substituted with one H, $C_1$-$C_6$-alkyl, $C_3$-$C_8$-cycloalkyl, halo-$C_1$-$C_6$-alkyl, halo-$C_1$-$C_6$-alkoxy, benzyl or aryl, wherein benzyl and aryl are substituted with one to three substituents independently selected from H, $C_1$-$C_6$-alkyl, $C_3$-$C_8$-cycloalkyl, halo-$C_1$-$C_6$-alkyl and halo-$C_1$-$C_6$-alkoxy, and

xxv) heterocycloalkyl-$C_1$-$C_6$-alkyl substituted with one H, $C_1$-$C_6$-alkyl, $C_3$-$C_8$-cycloalkyl, halo-$C_1$-$C_6$-alkyl, halo-$C_1$-$C_6$-alkoxy, benzyl or aryl, wherein benzyl and aryl are substituted with one to three substituents independently selected from H, $C_1$-$C_6$-alkyl, $C_3$-$C_8$-cycloalkyl, halo-$C_1$-$C_6$-alkyl and halo-$C_1$-$C_6$-alkoxy;

$R_{G1}$ and $R_{G2}$ are independently selected from the group consisting of

i) H,

ii) halogen,

iii) $C_1$-$C_6$-alkyl,

iv) $C_3$-$C_8$-cycloalkyl,

v) halo-$C_1$-$C_6$-alkoxy, and

vi) halo-$C_1$-$C_6$-alkyl;

$R_L$ and $R_M$ are independently selected from the group consisting of

i) H, and

ii) $C_1$-$C_6$-alkyl;

$R_N$ is selected from the group consisting of

i) H,

ii) $C_1$-$C_6$-alkoxy,

iii) $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl,

iv) $C_1$-$C_6$-alkoxycarbonyl-$C_1$-$C_6$-alkyl,

v) $C_1$-$C_6$-alkyl,

vi) carboxy-$C_1$-$C_6$-alkyl,

vii) $C_3$-$C_8$-cycloalkyl,

viii) $C_3$-$C_8$-cycloalkyl-$C_1$-$C_6$-alkyl,

ix) hydroxy-$C_1$-$C_6$-alkyl,

x) phenyl, and

xi) heteroaryl-$C_1$-$C_6$-alkyl;

$R_O$ is selected from the group consisting of

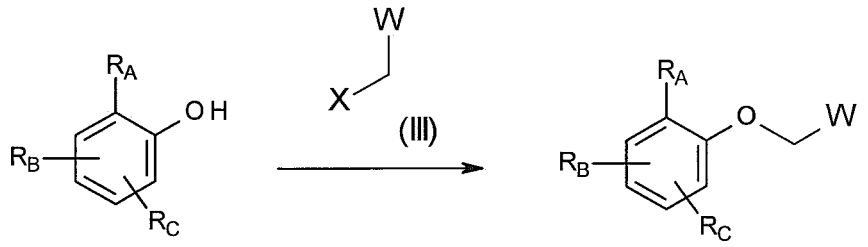
i) H, and

ii) $C_1$-$C_6$-alkyl;

or $R_N$ and $R_O$ together with the nitrogen atom to which they are attached form a heterocycloalkyl;

or pharmaceutically acceptable salts.

In another aspect, the present disclosure relates to 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 $R_A$, $R_B$, $R_C$ and W are as defined herein and X is halogen, mesylate or tosylate.




(II) (I)

In another aspect, the present disclosure relates to a compound as defined herein for use as therapeutically active substance.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a compound as defined herein and a therapeutically inert carrier.

In another aspect, the present disclosure relates to a compound as defined herein for use in the treatment or prophylaxis of ocular conditions.

In another aspect, the present disclosure relates to use of a compound as defined herein for the preparation of a medicament for the treatment or prophylaxis of ocular conditions.

In another aspect, the present disclosure relates a compound as defined herein, when manufactured as defined herein.

The term "$C_{1-6}$-alkoxy" denotes a group of the formula -O-R', wherein R' is an $C_{1-6}$-alkyl group. Examples of $C_{1-6}$-alkoxy group include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy and tert-butoxy. Particular examples are methoxy and isopropoxy.

The term "$C_{1-6}$-alkoxy-$C_{1-6}$-alkyl" denotes a $C_{1-6}$-alkyl group wherein at least one of the hydrogen atoms of the $C_{1-6}$-alkyl group is replaced by a $C_{1-6}$-alkoxy group. Particular examples are methoxymethyl, methoxyethyl, ethoxymethyl, ethoxyethyl, iso-propoxymethyl and iso-propoxyethyl. Particular example is methoxyethyl.

The term "$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkylcarbonyl($C_1$-$C_6$-alkyl)amino-$C_1$-$C_6$-alkyl" denotes an amino-$C_1$-$C_6$-alkyl wherein the nitrogen atom is substituted by a $C_1$-$C_6$-alkyl group and by a $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkylcarbonyl group. Particular example is an aminomethyl wherein the nitrogen atom is substituted by methyl and methoxymethylcarbonyl.

The term "$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkylcarbonyl" denotes a group of the formula -C(O)-R', wherein R' is a $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl group. Examples of $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkylcarbonyl group include groups wherein R' is methoxymethyl, methoxyethyl, ethoxymethyl, ethoxyethyl, iso-propoxymethyl and iso-propoxyethyl. Particular example is group wherein R' is methoxymethyl.

The term "$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkylcarbonylamino-$C_1$-$C_6$-alkyl" denotes an amino-$C_1$-$C_6$-alkyl group wherein the nitrogen atom is substituted by H and by a $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkylcarbonyl group. Particular example is an aminomethyl wherein the nitrogen atom is substituted by H and methoxymethylcarbonyl.

The term "$C_1$-$C_6$-alkoxycarbonyl-$C_1$-$C_6$-alkyl" denotes a $C_{1-6}$-alkyl group wherein at least one of the hydrogen atoms of the $C_{1-6}$-alkyl group is replaced by a $C_1$-$C_6$-alkoxycarbonyl group. Particular examples are groups wherein the $C_1$-$C_6$-alkoxycarbonyl group is methoxycarbonyl or ethoxycarbonyl and the $C_{1-6}$-alkyl group is methyl or ethyl. More particular examples are methoxyoxopropyl and ethoxyoxoethyl.

4-[(2-tert-Butyl-4-chloro-5-methylphenoxy)methyl]-2H-triazole;

3-[(2-tert-Butyl-4-chloro-5-methylphenoxy)methyl]-5-phenyl-1H-pyrazole; and

5-tert-Butyl-2-methyl-4-[(5-phenyl-1H-pyrazol-3-yl)methoxy]benzonitrile.

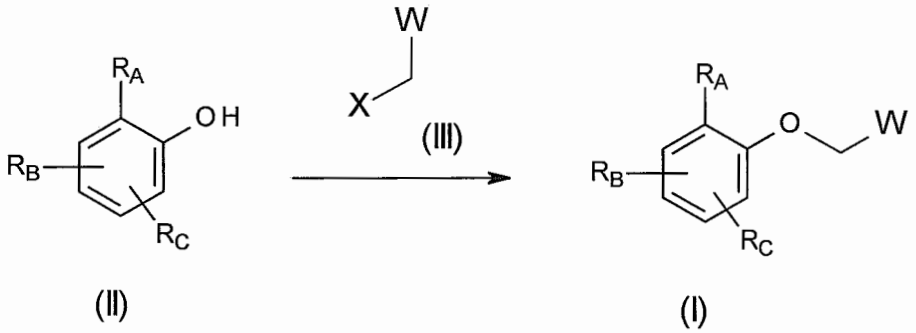
40. A compound according to any one of claims 1 to 36, selected from

5-tert-butyl-2-methyl-4-[(4-methyl-5-oxo-1H-1,2,4-triazol-3-yl)methoxy]benzonitrile ;

5-tert-butyl-2-chloro-4-[(4-methyl-5-oxo-1H-1,2,4-triazol-3-yl)methoxy]benzonitrile; and

5-tert-butyl-2-fluoro-4-[(4-methyl-5-oxo-1H-1,2,4-triazol-3-yl)methoxy]benzonitrile;

41. A process to prepare a compound according to any one of claims 1 to 40 comprising the reaction of a compound of formula (II) in the presence of a compound of formula (III), wherein $R_A$, $R_B$, $R_C$ and W are as defined in any one of claims 1 to 34 and X is halogen, mesylate or tosylate.




42. A compound according to any one of claims 1 to 40 for use as therapeutically active substance.

43. A pharmaceutical composition comprising a compound according to any one of claims 1 to 40 and a therapeutically inert carrier.

44. A compound according to any one of claims 1 to 40 for use in the treatment or prophylaxis of ocular conditions.

45. The use of a compound according to any one of claims 1 to 40 for the preparation of a medicament for the treatment or prophylaxis of ocular conditions.

46. A compound according to any one of claims 1 to 40, when manufactured according to a process of claim 41.