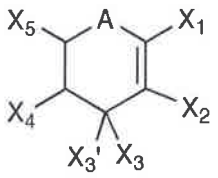
Claims

1. A compound of general formula (I) which is a selective inhibitor of influenza A virus group 1 sialidases:



I

or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein

A is O, S or NR_1;

where R_1 is hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted acyl or optionally substituted sulfonyl;

X_1 is CO_2H, $P(O)(OH)_2$, NO_2, SO_2H, SO_3H, $-C(O)NHOH$ or tetrazole;

X_2 is alkyl, aralkyl, alkenyl, alkynyl, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, optionally substituted alkynyl, OR_2, SR_2, NR_2R_2', or substituted triazole,

where R_2 and R_2' are selected independently from optionally substituted acyl, optionally substituted sulfonyl, alkyl, alkenyl, alkynyl, optionally substituted alkyl, or optionally substituted alkenyl,

or R_2' is hydrogen;

X_3 and X_3' are selected independently from hydrogen, R_3, halogen, CN, OR_3, NR_3R_3', $NHC(NR_3)N(R_3)_2$, N_3, SR_3, $-O-CH_2-C(O)-NR_3R_3'$, $-O-CH_2-C(NH)-NR_3R_3'$, $-O-CH_2-C(S)-NR_3R_3'$

and optionally substituted triazole,

or X_3 and X_3' together are =O, $=N-OR_3$, or $=CH-R_3$

where R_3 and R_3' are selected independently from hydrogen, optionally substituted acyl, optionally substituted sulfonyl, alkyl, aralkyl, alkenyl, alkynyl, heteroalkyl, heterocyclyl, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, $-C(O)R_8$ and $-S(O)_2R_8$,

where R_8 is selected from optionally substituted alkyl and optionally substituted alkenyl;

X_4 is NR_4R_4', ~~$-OR_4$,~~ SR_4, $CH_2C(O)R_4$, $CH_2C(O)OR_4$, $CH_2C(O)NR_4R_4'$, CHR_4NO_2, CHR_4CN, CHR_4R_4', or CH_2NHR,

where R_4 and R_4' are selected independently from hydrogen optionally substituted acyl, optionally substituted thioacyl, optionally substituted sulfonyl, alkyl, alkenyl, alkynyl, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, optionally substituted heteroaryl, and optionally substituted heterocyclyl;

X_5 is optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-C(O)R_5$, $-CO_2R_5$, $-C(O)NR_5R_5'$, $-P(O)(OR_5)(OR_5')$, $-P(O)(OR_5)(NR_5R_5')$, $-P(O)(NR_5R_5')_2$, CN, OR_6, azide, NHR_6, NR_6R_6', SR_6, or optionally substituted triazole,

where R_5 and R_5' are independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, or heteroaryl, and

R_6 and R_6' are independently selected from optionally substituted acyl, optionally substituted sulfonyl, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, optionally substituted aryl, heteroaryl, or heterocyclyl.

2. A compound as claimed in claim 1 wherein A is O.

3. A compound as claimed in either one of claims 1 or 2 wherein X_1 is CO_2H or $P(O)(OH)_2$ or an ester thereof.

4. A compound as claimed in claim 3 wherein X_1 is CO_2H.

5. A compound as claimed in any one of claims 1 to 4 wherein X_2 is alkyl, aralkyl, alkenyl, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted alkenyl.

6. A compound as claimed in any one of claims 1 to 4 wherein X_2 is OR_2, SR_2, NR_2R_2'.

7. A compound as claimed in any one of claims 1 to 6 wherein X_3' is hydrogen and X_3 is selected from R_3, OR_3, NR_3R_3', $NHC(NR_3)N(R_3)_2$, N_3, SR_3, and optionally substituted triazole,

where R_3 and R_3' are independently selected from hydrogen, alkyl, alkenyl, alkynyl, optionally substituted alkyl, optionally substituted alkenyl, $-C(O)R_8$ or $-S(O)_2R_8$,

where R_8 is selected from optionally substituted alkyl and optionally substituted alkenyl.

8. A compound as claimed in any one of claims 1 to 7 wherein X_4 is $-NR_4R_4'$, R_4 is optionally substituted acyl and R_4' is hydrogen.

9. A compound as claimed in claim 8 wherein R_4 is acyl.

10. A compound as claimed in any one of claims 1 to 9 wherein X_5 denotes CH_2YR_7, $CHYR_7CH_2YR_7$ or $CHYR_7CHYR_7CH_2YR_7$,

where Y is O, S, or NR_7', and successive Y moieties in an X_5 group are the same or different, or

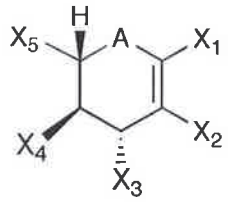
where the substituent YR_7 is =O, $=N-OR_7$, or $=CHR_7$,

or

where two adjacent YR_7 groups together form part of a ring structure which optionally includes at least one heteroatom selected from O, S and N and is optionally substituted; in particular, an epoxide, aziridine, 5 or 6 membered cyclic ether group,

and R_7 and R_7' are independently selected from hydrogen, optionally substituted acyl, optionally substituted sulfonyl, $-S(O)_2OH$, $-P(O)(OH)_2$, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, optionally substituted aralkyl, and optionally substituted alkenyl.

11. A compound of general formula (II) which is a selective inhibitor of influenza A virus group 1 sialidases:



II

wherein,

A is O, S or NR_1;

where R_1 is hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted acyl or optionally substituted sulfonyl;

X_1 is CO_2H, $P(O)(OH)_2$, NO_2, SO_2H, SO_3H, $-C(O)NHOH$ or tetrazole;

X_2 is alkyl, aralkyl, alkenyl, alkynyl, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, optionally

substituted alkynyl, OR_2, SR_2, NR_2R_2', or substituted triazole,

where R_2 and R_2' are selected independently from optionally substituted acyl, optionally substituted sulfonyl, alkyl, alkenyl, alkynyl, optionally substituted alkyl, or optionally substituted alkenyl,

or R_2' is hydrogen;

X_3 and X_3' are selected independently from hydrogen, R_3, halogen, CN, OR_3, NR_3R_3', $NHC(NR_3)N(R_3)_2$, N_3, SR_3, $-O-CH_2-C(O)-NR_3R_3'$, $-O-CH_2-C(NH)-NR_3R_3'$, $-O-CH_2-C(S)-NR_3R_3'$
and optionally substituted triazole,

or X_3 and X_3' together are $=O$, $=N-OR_3$, or $=CH-R_3$

where R_3 and R_3' are selected independently from hydrogen, optionally substituted acyl, optionally substituted sulfonyl, alkyl, aralkyl, alkenyl, alkynyl, heteroalkyl, heterocyclyl, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, $-C(O)R_8$ and $-S(O)_2R_8$,

where R_8 is selected from optionally substituted alkyl and optionally substituted alkenyl;

X_4 is NR_4R_4', OR_4, SR_4, $CH_2C(O)R_4$, $CH_2C(O)OR_4$, $CH_2C(O)NR_4R_4'$, CHR_4NO_2, CHR_4CN, CHR_4R_4', or CH_2NHR,

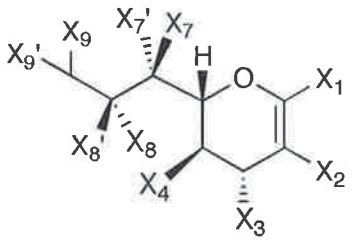
where R_4 and R_4' are selected independently from hydrogen optionally substituted acyl, optionally substituted thioacyl, optionally substituted sulfonyl, alkyl, alkenyl, alkynyl, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, optionally substituted heteroaryl, and optionally substituted heterocyclyl;

X_5 is optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-C(O)R_5$, $-CO_2R_5$, $-C(O)NR_5R_5'$, $-P(O)(OR_5)(OR_5')$, $-P(O)(OR_5)(NR_5R_5')$, $-P(O)(NR_5R_5')_2$, CN, OR_6, azide, NHR_6, NR_6R_6', SR_6, or optionally substituted triazole,

where R_5 and $R_{5'}$ are independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, or heteroaryl, and

R_6 and R_6' are independently selected from optionally substituted acyl, optionally substituted sulfonyl, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, optionally substituted aryl, heteroaryl, or heterocyclyl~~X_1, X_2, X_3, X_4 and X_5 are as defined in any one of claims 1 to 10~~.

12. A compound of general formula (III) which is a selective inhibitor of influenza A virus group 1 sialidases:



III

wherein

~~A~~ is O, S or NR_1;

where R_1 is hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted acyl or optionally substituted sulfonyl;

X_1 is CO_2H, $P(O)(OH)_2$, NO_2, SO_2H, SO_3H, $-C(O)NHOH$ or tetrazole;

X_2 is alkyl, aralkyl, alkenyl, alkynyl, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, optionally substituted alkynyl, OR_2, SR_2, NR_2R_2', or substituted triazole,

where R_2 and R_2' are selected independently from optionally substituted acyl, optionally substituted sulfonyl, alkyl, alkenyl, alkynyl, optionally substituted alkyl, or optionally substituted alkenyl,

or R_2' is hydrogen;

X_3 and X_3' are selected independently from hydrogen, R_3, halogen, CN, OR_3, NR_3R_3', $NHC(NR_3)N(R_3)_2$, N_3, SR_3, $-O-CH_2-C(O)-NR_3R_3'$, $-O-CH_2-C(NH)-NR_3R_3'$, $-O-CH_2-C(S)-NR_3R_3'$ and optionally substituted triazole,

or X_3 and X_3' together are $=O$, $=N-OR_3$, or $=CH-R_3$

where R_3 and R_3' are selected independently from hydrogen, optionally substituted acyl, optionally substituted sulfonyl, alkyl, aralkyl, alkenyl, alkynyl, heteroalkyl, heterocyclyl, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, $-C(O)R_8$ and $-S(O)_2R_8$,

where R_8 is selected from optionally substituted alkyl and optionally substituted alkenyl;

X_4 is NR_4R_4', OR_4, SR_4, $CH_2C(O)R_4$, $CH_2C(O)OR_4$, $CH_2C(O)NR_4R_4'$, CHR_4NO_2, CHR_4CN, CHR_4R_4', or CH_2NHR,

where R_4 and R_4' are selected independently from hydrogen optionally substituted acyl, optionally substituted thioacyl, optionally substituted sulfonyl, alkyl, alkenyl, alkynyl, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, optionally substituted heteroaryl, and optionally substituted heterocyclyl;

X_5 is optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-C(O)R_5$, -

CO_2R_5, $-C(O)NR_5R_5'$, $-P(O)(OR_5)(OR_5')$, $-P(O)(OR_5)(NR_5R_5')$, $-P(O)(NR_5R_5')_2$, CN, OR_6, azide, NHR_6, NR_6R_6', SR_6, or optionally substituted triazole,

where R_5 and R_5' are independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, or heteroaryl, and

R_6 and R_6' are independently selected from optionally substituted acyl, optionally substituted sulfonyl, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted alkenyl, optionally substituted aryl, heteroaryl, or heterocyclyl~~X_1, X_2, X_3, and X_4 are as defined in any one of claims 1 to 10;~~,

one of X_7 and X_7' is hydrogen,

one of X_8 and X_8' is hydrogen,

one of X_9 and X_9' is hydrogen, and

X_7, X_7', X_8, X_8', X_9, and X_9' are the same or different, and are selected from H, OR_7, NR_7R_7', SR_7, or optionally substituted triazole, or

together X_7 and X_7', X_8 and X_8', or X_9 and X_9' form =O, or $=N-OR_7$.

13. A compound selected from the group consisting of:

methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-3-*C*-(prop-2'-enyl)-D-*glycero*-D-*galacto*-non-2-enonate,

5-acetamido-2,6-anhydro-3,5-dideoxy-3-*C*-(prop-2'-enyl)-D-*glycero*-D-*galacto*-non-2-en-onic acid,

methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-3-*C*-(4,4-dimethylpent-2'-enyl)-D-*glycero*-D-*galacto*-non-2-enonate,

5-acetamido-2,6-anhydro-3,5-dideoxy-3-*C*-(4,4-dimethylpent-2'-enyl)-D-*glycero*-D-*galacto*-non-2-enonic acid,

methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-

anhydro-3,5-dideoxy-3-*C*-(3'-cyclohexyl-prop-2'-enyl)-D-*glycero*-D-*galacto*-non-2-enonate,

5-acetamido-2,6-anhydro-3,5-dideoxy-3-*C*-(3'-cyclohexyl-prop-2'-enyl)-D-*glycero*-D-*galacto*-non-2-enonic acid,

methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-3-*C*-(3'-phenyl-prop-2'-enyl)-D-*glycero*-D-*galacto*-non-2-enonate,

5-acetamido-2,6-anhydro-3,5-dideoxy-3-*C*-(3'-phenyl-prop-2'-enyl)-D-*glycero*-D-*galacto*-non-2-enonic acid,

methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-3-*C*-[3'-(*p*-tolyl)-prop-2'-enyl]-D-*glycero*-D-*galacto*-non-2-enonate (8d, R = 4-CH_3Ph),

5-acetamido-2,6-anhydro-3,5-dideoxy-3-*C*-[3'-(*p*-tolyl)-prop-2'-enyl]-D-*glycero*-D-*galacto*-non-2-enonic acid,

methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-3-*C*-[3'-(4-tert-butoxyphenyl)-prop-2'-enyl]-D-*glycero*-D-*galacto*-non-2-enonate,

5-acetamido-2,6-anhydro-3,5-dideoxy-3-*C*-[3'-(4-tert-butoxyphenyl)-prop-2'-enyl]-D-*glycero*-D-*galacto*-non-2-enonanic acid,

methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-3-*C*-(3'-naphthyl-prop-2'-enyl)-D-*glycero*-D-*galacto*-non-2-enonate,

5-acetamido-2,6-anhydro-3,5-dideoxy-3-*C*-(3'-naphthyl-prop-2'-enyl)-D-*glycero*-D-*galacto*-non-2-enonic acid,

methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-3-*C*-[4'-(3,4-dimethoxyphenyl)-but-2'-enyl]-D-*glycero*-D-*galacto*-non-2-enonate,

5-acetamido-2,6-anhydro-3,5-dideoxy-3-*C*-[4'-(3,4-dimethoxyphenyl)-but-2'-enyl]-D-*glycero*-D-*galacto*-non-2-enonic acid,

methyl 5-acetamido-3-*C*-(3'-acetoxypropyl)-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-en-onate,

5-acetamido-3-*C*-(3'-hydroxypropyl)-2,6-anhydro-

3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-enonic acid,

methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-3-*C*-propyl-D-*glycero*-D-*galacto*-non-2-enonate,

5-acetamido-2,6-anhydro-3,5-dideoxy-3-*C*-propyl-D-*glycero*-D-*galacto*-non-2-enonic acid,

methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-3-*C*-propenyl-D-*glycero*-D-*galacto*-non-2-enonate,

methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-3-*C*-(prop-2'-enyl)-D-*glycero*-D-*galacto*-non-2-enonate ,

methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-8,9-*O*-isopropylidene-3-*C*-(prop-2'-enyl)-D-*glycero*-D-*galacto*-non-2-enonate,

methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-4-*O*-ethyl-8,9-*O*-isopropylidene-3-*C*-(prop-2'-enyl)-D-*glycero*-D-*galacto*-non-2-enonate,

methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-4-*O*-ethyl-8,9-*O*-isopropylidene-3-*C*-(prop-2'-enyl)-D-*glycero*-D-*galacto*-non-2-enonate,

5-acetamido-2,6-anhydro-3,5-dideoxy-4-*O*-ethyl-3-*C*-(prop-2'-enyl)-D-*glycero*-D-*galacto*-non-2-enonic acid,

2-methyl-(methyl 7,8,9-tri-*O*-acetyl-2,6-anhydro-3,5-dideoxy-3-C-(prop-2'-enyl)-D-*glycero*-D-*talo*-non-2-enonate)-[4,5-d]-2-oxazoline,

methyl 5-acetamido-7,8,9-tri-*O*-acetyl-2,6-anhydro-4-azido-3-*C*-(prop-2'-enyl)-3,4,5-trideoxy-D-*glycero*-D-*galacto*-non-2-enonate,

methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-3-*O*-ethyl-D-*glycero*-D-*galacto*-non-2-enonate,

5-acetamido-2,6-anhydro-3,5-dideoxy-3-*O*-ethyl-D-*glycero*-D-*galacto*-non-2-enonic acid,

methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-3-*O*-(2'-azidoethyl)-D-*glycero*-D-*galacto*-non-2-enonate, and

methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-

anhydro-3,5-dideoxy-3-*O*-[2'-(4"-isobutyl-[1",2",3"]triazol-1"-yl)ethyl]-D-*glycero*-D-*galacto*-non-2-enonate.

14. A compound which is a multivalent presentation of any one or compounds as claimed in any one of claims 1 to 13 comprising a plurality of said compounds bound through a linker to a multivalent template.

15. A pharmaceutical composition comprising a compound of as claimed in any one of claims 1 to 14 and a pharmaceutically acceptable carrier.

~~16. A method of preventing or treating influenza in a subject comprising administering to said subject a compound as claimed in any one of claims 1 to 14.~~

16~~7~~. Use of a compound as claimed in any one of claims 1 to 14 in the manufacture of a medicament for the prevention or treatment of influenza.

~~18. Use of a compound as claimed in any one of claims 1 to 14 in the prevention or treatment of influenza.~~

19~~7~~. A method of preparing a compound of general formula (I) as claimed in any one of claims 1 to 10, comprising the steps of:

1) providing a compound of general formula (IV), wherein:
X_2, X_3, X_4 and X_5 are as defined in any one of claims 1 to 10,
and may be protected by protecting groups,
X_6 is X_1, or a functional group that can be modified to form X_1, where X_6 can be selected from, but is not limited to, CHO, CN, CH_2OR', thiazole, and
and Z is a group that can be activated to enable beta- elimination;



(IV)

2) eliminating H-Z from the compound of general formula (IV);

3) converting X_6 to X_1 when it is other than X_1;

4) optionally functionalizing X_1, X_2, X_3, X_4 and/or X_5; and

5) optionally deprotecting X_1, X_2, X_3, X_4 and/or X_5.

~~20~~18. A method as claimed in claim ~~19~~ 17 wherein:

Z is a halide and elimination is achieved under basic conditions; or

Z is a halide and elimination is achieved in the presence of a heavy metal reagent; or

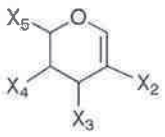
Z is acyloxy and elimination is achieved under Lewis acidic conditions; or

Z is alkoxy and elimination is achieved under acetolysis conditions; or

Z is phosphite and elimination is achieved under Lewis acidic conditions.

~~21~~19. A method of preparing a compound of general formula (I) as claimed in any one of claims 1 to 10, comprising the steps of:

1) providing a compound of general formula (V),



(V)

wherein X_2, X_3, X_4 and X_5 are as defined and may be protected by protecting groups;

2) introducing X_1 to the compound of general formula (V) in a direct C-1 lithiation followed by reaction of the lithiated species with EX_1 wherein E is an electrophile and X_1 may be protected with a protecting group;

3) optionally functionalizing X_1, X_2, X_3, X_4 and/or X_5; and

4) optionally deprotecting X1, X2, X3, X4 and/or X5.