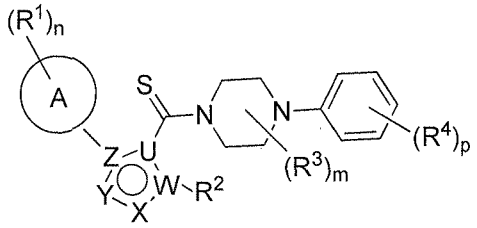
CLAIMS

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

the ring A



is 6-membered aryl or heteroaryl containing 1-3 nitrogen atoms;

n is an integer of from 0 to 3;

m is an integer of from 0 to 2;

p is an integer of from 0 to 3;

each R^1 is independently selected from C1-C6 alkyl; C1-C6 alkoxy; OH; halogen; and R^5R^6N;

R^2 is selected from H and C1-C6 alkyl;

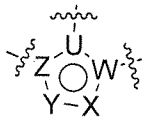
each R^3 is independently selected from C1-C6 alkyl;

each R^4 is independently selected from NO_2; halogen; C1-C6 alkyl and C1-C6 alkoxy;

R^5 and R^6 are independently selected from H and C1-C6 alkyl;

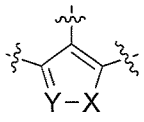
wherein any alkyl and any alkoxy is optionally substituted with one or several halogen atoms; and

the ring of formula (III)

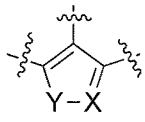


(III)

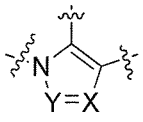
is a ring of formula (IIIa), (IIIb), (IIIc), (IIId), or (IIIe)



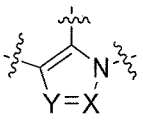
(IIIa)



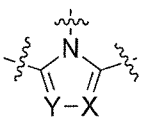
(IIIb)



(IIIc)



(IIId)



(IIIe)

wherein

in formula (IIIa), X is NH or O, and Y is N or CH,

in formula (IIIb), X is N or CH, and Y is NH or O,

in formula (IIIc), X is N or CH, and Y is N or CH,

in formula (IIId), X is N or CH, and Y is N or CH, and

in formula (IIIe), X is N or CH, and Y is N or CH.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein each R^1 is independently selected from C1-C6 alkyl; OH; halogen; and R^5R^6N;

R^2 is selected from H and C1-C6 alkyl;

each R^3 is independently selected from C1-C6 alkyl;

each R^4 is independently selected from NO_2; halogen; and C1-C6 alkyl; and

each R^5 and R^6 is independently selected from H and C1-C6 alkyl;

wherein any alkyl is optionally substituted with one or several halogen atoms.

3. A compound according to claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein m is 0.

4. A compound according to any one of the claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein the ring of formula (III) is a ring of formula (IIIa), (IIIb), (IIIc), or (IIId).

5. A compound according to any one of the claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein the ring of formula (III) is a ring of formula (IIIa).

6. A compound according to any one of the claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein the ring of formula (III) is a ring of formula (IIIc) or (IIId).

7. A compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein the ring of formula (III) is a ring of formula (IIIc).

8. A compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein the ring of formula (III) is a ring of formula (IIId).

9. A compound according to any one of the claims 6 to 8, or a pharmaceutically acceptable salt thereof, wherein both X and Y are N.

10. A compound according to any one of the claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein the ring A is phenyl.

11. A compound according to claim 1, selected from
(4-(2-chloro-4-nitrophenyl)piperazin-1-yl)(5-methyl-3-phenylisoxazol-4-yl)methanethione,
(5-methyl-3-phenylisoxazol-4-yl)(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)methanethione,
(4-(2-chloro-4-nitrophenyl)piperazin-1-yl)(1-(2,6-dimethoxyphenyl)-4-methyl-1H-1,2,3-triazol-5-yl)methanone,
(4-(2-chloro-4-nitrophenyl)piperazin-1-yl)(4-(2-methoxyphenyl)-1-methyl-1H-1,2,3-triazol-5-yl)methanethione,
(4-(2-chloro-4-nitrophenyl)piperazin-1-yl)(4-(2-fluoro-6-methoxyphenyl)-1-methyl-1H-1,2,3-triazol-5-yl)methanethione,
(4-(2-chloro-4-nitrophenyl)piperazin-1-yl)(4-(2,6-dimethoxyphenyl)-1-methyl-1H-1,2,3-triazol-5-yl)methanethione,
(4-(2-chloro-4-nitrophenyl)piperazin-1-yl)(1-(2-methoxyphenyl)-4-methyl-1H-1,2,3-triazol-5-yl)methanethione,
(4-(2-chloro-4-(trifluoromethyl)phenyl)piperazin-1-yl)(1-(2-methoxyphenyl)-4-methyl-1H-1,2,3-triazol-5-yl)methanethione,
(4-(2-chloro-4-nitrophenyl)piperazin-1-yl)(1-(2,4-dimethoxyphenyl)-4-methyl-1H-1,2,3-triazol-5-yl)methanethione, and
(4-(2-chloro-4-nitrophenyl)piperazin-1-yl)(1-(2,6-dimethoxyphenyl)-4-methyl-1H-1,2,3-triazol-5-yl)methanethione,
or a pharmaceutically acceptable salt thereof.

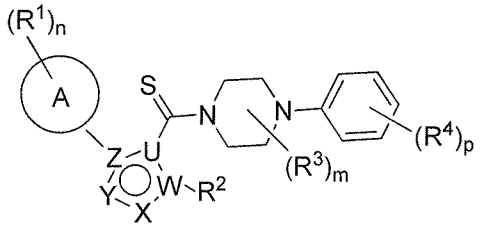
12. A compound according to any one of the claims 1 to 11, or a pharmaceutically acceptable salt thereof, for use in therapy.

13. A pharmaceutical composition comprising a compound according any one of the claims 1 to 11, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

14. Use of a compound according to any one of the claims 1 to 11, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a viral infection.

15. The use according to claim 14, wherein the viral infection is an influenza.

16. A method of preparing a compound of formula (I)



(I)

wherein

the ring A



is 6-membered aryl or heteroaryl containing 1-3 nitrogen atoms;

n is an integer of from 0 to 3;

m is an integer of from 0 to 2;

p is an integer of from 0 to 3;

each R^1 is independently selected from C1-C6 alkyl; C1-C6 alkoxy; OH; halogen; and R^5R^6N;

R^2 is selected from H and C1-C6 alkyl;

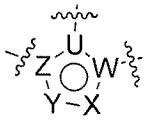
each R^3 is independently selected from C1-C6 alkyl;

each R^4 is independently selected from NO_2; halogen; C1-C6 alkyl and C1-C6 alkoxy;

R^5 and R^6 are independently selected from H and C1-C6 alkyl;

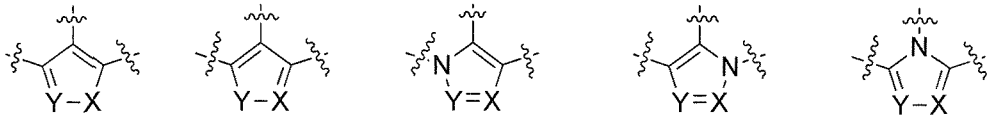
wherein any alkyl and any alkoxy is optionally substituted with one or several halogen atoms; and

the ring of formula (III)



(III)

is a ring of formula (IIIa), (IIIb), (IIIc), (IIId), or (IIIe)



(IIIa) (IIIb) (IIIc) (IIId) (IIIe)

wherein

in formula (IIIa), X is NH or O, and Y is N or CH,

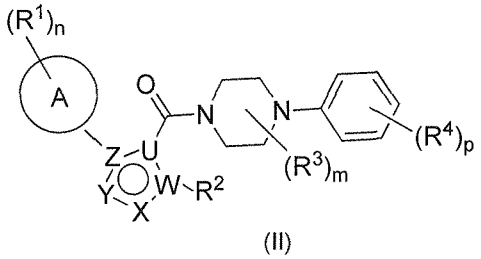
in formula (IIIb), X is N or CH, and Y is NH or O,

in formula (IIIc), X is N or CH, and Y is N or CH,

in formula (IIId), X is N or CH, and Y is N or CH, and

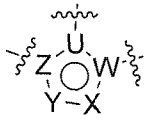
in formula (IIIe), X is N or CH, and Y is N or CH;

comprising reacting a compound of formula (II)



(II)

wherein the ring A, n, m, p, R^1, R^2, R^3, R^4, and the ring of formula (III)



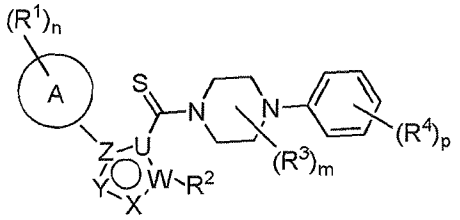
(III)

are as defined herein above,

with $P_2S_5 \cdot 2\ C_5H_5N$ as a thionating agent, in a liquid solvent medium; and optionally preparing a pharmaceutically acceptable salt of the compound of formula (I).

CLAIMS

1. A compound of formula (I)



(I)

wherein

U is C or N;

W is C or N;

X is N, CH, O or NH;

Y is N, CH, O or NH;

Z is C or N;

the ring A



is 6-membered aryl or heteroaryl;

n is an integer of from 0 to 3;

m is an integer of from 0 to 2;

p is an integer of from 0 to 3;

each R^1 is independently selected from C1-C6 alkyl; C1-C6 alkoxy; OH; halogen; and R^5R^6N;

R^2 is selected from H and C1-C6 alkyl;

each R^3 is independently selected from C1-C6 alkyl;

each R^4 is independently selected from NO_2; halogen; C1-C6 alkyl and C1-C6 alkoxy;

R^5 and R^6 are independently selected from H and C1-C6 alkyl;

wherein any alkyl is optionally substituted with one or several halogen atoms;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein
each R^1 is independently selected from C1-C6 alkyl; OH; halogen; and R^5R^6N;
R^2 is selected from H and C1-C6 alkyl;
each R^3 is independently selected from C1-C6 alkyl;
each R^4 is independently selected from NO_2; halogen; and C1-C6 alkyl;
each R^5 and R^6 is independently selected from H and C1-C6 alkyl;
wherein any alkyl is optionally substituted with one or several halogen atoms;
or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or claim 2, wherein any C1-C6 alkyl moiety is selected from C1-C3 alkyl;
or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 3, wherein any C1-C6 alkyl moiety is methyl;
or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of the claims 1-4, wherein n is 0,
or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of the claims 1-5, wherein m is 0,
or a pharmaceutically acceptable salt thereof.

7. A compound according to any one of the claims 1-6, wherein U is C,
or a pharmaceutically acceptable salt thereof.

8. A compound according to any of the claims 1 to 7, wherein Y is N,
or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of the claim 1 to 7, wherein Y is NH, or a pharmaceutically acceptable salt thereof.

10. A compound according to any one of the claims 1 to 7, wherein Y is O, or a pharmaceutically acceptable salt thereof.

11. A compound according to any one of the claims 1 to 10, wherein X is N, or a pharmaceutically acceptable salt thereof.

12. A compound according to any one of the claims 1 to 10, wherein X is NH, or a pharmaceutically acceptable salt thereof.

13. A compound according to any one of the claims 1 to 10, wherein X is O, or a pharmaceutically acceptable salt thereof.

14. A compound according to any one of the claims 1 to 13, wherein W is N, or a pharmaceutically acceptable salt thereof.

15. A compound according to any one of the claims 1 to 13, wherein W is C, or a pharmaceutically acceptable salt thereof.

16. A compound according to any one of the claims 1 to 15, wherein Z is N, or a pharmaceutically acceptable salt thereof.

17. A compound according to any one of the claims 1 to 15, wherein Z is C, or a pharmaceutically acceptable salt thereof.

18. A compound according to any one of the claims 1 to 17, wherein the ring A is phenyl, or a pharmaceutically acceptable salt thereof.

19. A compound according to any one of the claims 1-18, or a pharmaceutically acceptable salt thereof, for use in therapy.

20. A pharmaceutical composition comprising a compound according any one of the claims 1-18, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

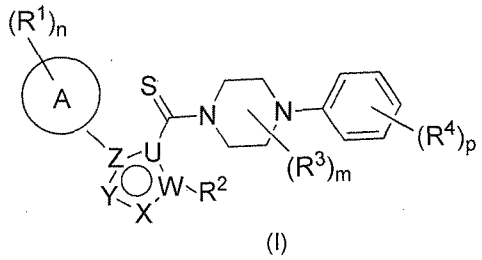
21. Use of a pharmaceutical composition according to claim 20, in the manufacture of a medicament for the treatment of a viral infection.

22. A use according to claim 21, wherein the viral infection is an influenza.

23. Use of a compound according to any one of the claims 1-18, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a viral infection.

24. A use according to claim 23, wherein the viral infection is an influenza.

25. A method of preparing a compound of formula (I)



(I)

wherein

U is C or N;

W is C or N;

X is N, CH, O or NH;

Y is N, CH, O or NH;

Z is C or N;

the ring A



is 6-membered aryl or heteroaryl;

n is an integer of from 0 to 3;

m is an integer of from 0 to 2;

p is an integer of from 0 to 3;

each R^1 is independently selected from C1-C6 alkyl; C1-C6 alkoxy; OH; halogen; and R^5R^6N;

R^2 is selected from H and C1-C6 alkyl;

each R^3 is independently selected from C1-C6 alkyl;

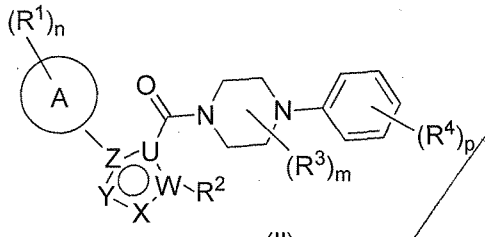
each R^4 is independently selected from NO_2; halogen; C1-C6 alkyl and C1-C6 alkoxy;

R^5 and R^6 are independently selected from H and C1-C6 alkyl;

wherein any alkyl is optionally substituted with one or several halogen atoms;

or a pharmaceutically acceptable salt thereof,

comprising reacting a compound of formula (II)



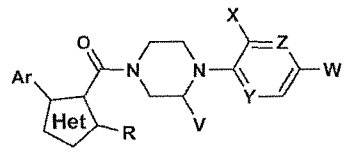
(II)

wherein the ring A, X, Y, Z, U, W, n, m, p, R^1, R^2, R^3 and R^4 are as defined herein above,

with $P_2S_5 \cdot 2\ C_5H_5N$ as a thionating agent in a liquid solvent medium.

linear and branched C_1-C_6 alkoxy, amino, azido, cyano, nitro, nitrile, isonitrile, amide, carboxylate, urea, guanidine, isocyanate, isothiocyanate, and thioether.

International patent application No. PCT/US2011/052965, published as WO/2012/044531, discloses a compound of the formula:

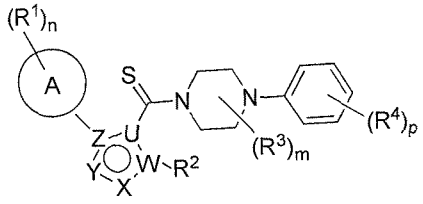


wherein Het is a 5 or 6-membered heterocycle with N, O, or S adjacent to the Ar substituent or adjacent to the point of attachment for the Ar substituent; Ar is aryl or heteroaryl; R is CH_3, CH_2F, CHF_2 or $CH{=}CH_2$; V is H, CH_3 or =O; W is NO_2, Cl, Br, CH_2OH, or CN; X is Cl, Br, F, CH_3, OCH_3, or CN; Y is CH or N; and Z is CH or N, useful in compositions for the prevention and treatment of influenza virus.

There still remains an urgent need for better treatment of viral infections, in particular infections by the influenza virus. Therefore, it is an object of the present invention to provide further antiviral compounds that effectively treat or prevent viral infections, particularly influenza infections, formulations containing these compounds, methods of making the compounds, and methods of using the compounds.

SUMMARY ~~OF THE INVENTION~~

In a first ~~aspect~~embodiment, a compound of formula (I) is provided:



(I)

wherein

U is C or N;

W is C or N;

X is N, CH, O or NH;

Y is N, CH, O or NH;

Z is C or N;

the ring A



is 6-membered aryl or heteroaryl;

n is an integer of from 0 to 3;
m is an integer of from 0 to 2;
p is an integer of from 0 to 3;

each R^1 is independently selected from C1-C6 alkyl; C1-C6 alkoxy; OH; halogen; and R^5R^6N;

R^2 is selected from H and C1-C6 alkyl;

each R^3 is independently selected from C1-C6 alkyl;

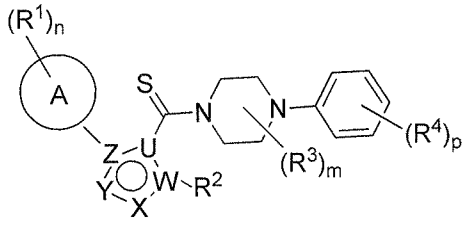
each R^4 is independently selected from NO_2; halogen; C1-C6 alkyl and C1-C6 alkoxy;

R^5 and R^6 are independently selected from H and C1-C6 alkyl;

wherein any alkyl is optionally substituted with one or several halogen atoms;

or a pharmaceutically acceptable salt thereof.

In an aspect, there is provided a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

the ring A



is 6-membered aryl or heteroaryl containing 1-3 nitrogen atoms;

n is an integer of from 0 to 3;

m is an integer of from 0 to 2;

p is an integer of from 0 to 3;

each R^1 is independently selected from C1-C6 alkyl; C1-C6 alkoxy; OH; halogen; and R^5R^6N;

R^2 is selected from H and C1-C6 alkyl;

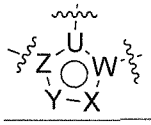
each R^3 is independently selected from C1-C6 alkyl;

each R^4 is independently selected from NO_2; halogen; C1-C6 alkyl and C1-C6 alkoxy;

R^5 and R^6 are independently selected from H and C1-C6 alkyl;

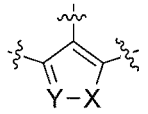
wherein any alkyl and any alkoxy is optionally substituted with one or several halogen atoms; and

the ring of formula (III)

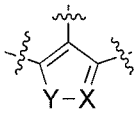


(III)

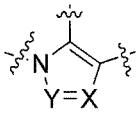
is a ring of formula (IIIa), (IIIb), (IIIc), (IIId), or (IIIe)



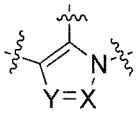
(IIIa)



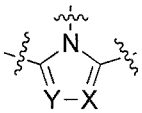
(IIIb)



(IIIc)



(IIId)



(IIIe)

wherein

in formula (IIIa), X is NH or O, and Y is N or CH,

in formula (IIIb), X is N or CH, and Y is NH or O,

in formula (IIIc), X is N or CH, and Y is N or CH,

in formula (IIId), X is N or CH, and Y is N or CH, and

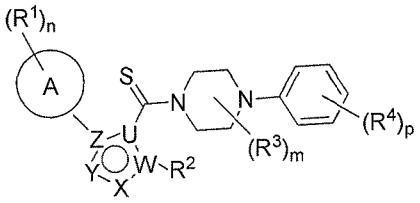
in formula (IIIe), X is N or CH, and Y is N or CH.

In another aspect, a compound of formula (I), as defined herein above, or a pharmaceutically acceptable salt thereof, is provided for use in therapy, e.g. for use in the treatment of a viral infection, such as an infection by an influenza virus.

In still another aspect, a pharmaceutical composition is provided, comprising a compound as defined herein above, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

In still another embodiment a pharmaceutical composition as defined herein above is provided for use in the treatment of a viral infection, such as an infection by an influenza virus. In another ~~aspect~~embodiment, the use of a pharmaceutical composition as defined above, in the manufacture of a medicament for the treatment of a viral infection is provided. In still another aspect, the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a viral infection is provided.

In another ~~aspect~~embodiment, a method is provided for preparing a compound of formula (I)



(I)

wherein

U is C or N;

W is C or N;

X is N, CH, O or NH;

Y is N, CH, O or NH;

Z is C or N;

the ring A



is 6-membered aryl or heteroaryl;

n is an integer of from 0 to 3;

m is an integer of from 0 to 2;

p is an integer of from 0 to 3;

each R^1 is independently selected from C1-C6 alkyl; C1-C6 alkoxy; OH; halogen; and R^5R^6N;

R^2 is selected from H and C1-C6 alkyl;

each R^3 is independently selected from C1-C6 alkyl;

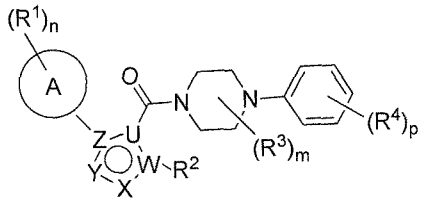
each R^4 is independently selected from NO_2; halogen; C1-C6 alkyl and C1-C6 alkoxy;

each R^5 and R^6 is independently selected from H and C1-C6 alkyl;

wherein any alkyl is optionally substituted with one or several halogen atoms;

or a pharmaceutically acceptable salt thereof;

comprising reacting a compound of formula (II)

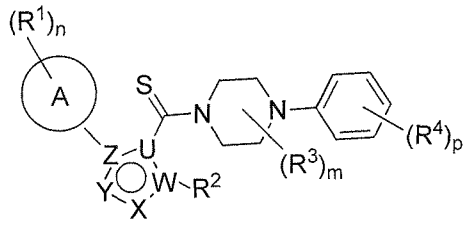


(II)

wherein X, Y, Z, U, W, the ring A, n, m, p, R^1, R^2, R^3 and R^4 are as defined herein above,

with $P_2S_5 \cdot 2\ C_5H_5N$ as a thionating agent, in a liquid solvent medium; and optionally preparing a pharmaceutically acceptable salt of the compound of formula (I).

In another aspect, there is provided a method of preparing a compound of formula (I)



(I)

wherein

the ring A



is 6-membered aryl or heteroaryl containing 1-3 nitrogen atoms;

n is an integer of from 0 to 3;

m is an integer of from 0 to 2;

p is an integer of from 0 to 3;

each R^1 is independently selected from C1-C6 alkyl; C1-C6 alkoxy; OH; halogen; and R^5R^6N;

R^2 is selected from H and C1-C6 alkyl;

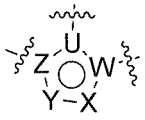
each R^3 is independently selected from C1-C6 alkyl;

each R^4 is independently selected from NO_2; halogen; C1-C6 alkyl and C1-C6 alkoxy;

R^5 and R^6 are independently selected from H and C1-C6 alkyl;

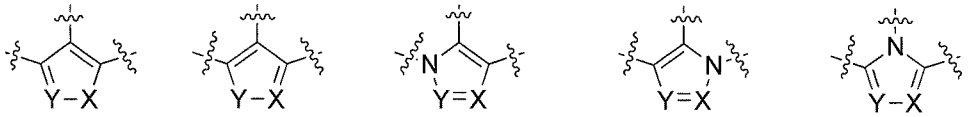
wherein any alkyl and any alkoxy is optionally substituted with one or several halogen atoms; and

the ring of formula (III)



(III)

is a ring of formula (IIIa), (IIIb), (IIIc), (IIId), or (IIIe)



(IIIa) (IIIb) (IIIc) (IIId) (IIIe)

wherein

in formula (IIIa), X is NH or O, and Y is N or CH,

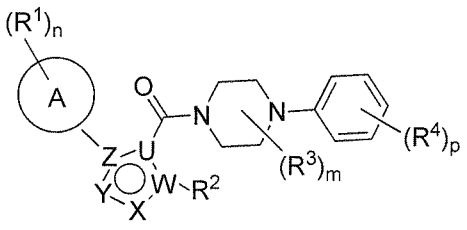
in formula (IIIb), X is N or CH, and Y is NH or O,

in formula (IIIc), X is N or CH, and Y is N or CH,

in formula (IIId), X is N or CH, and Y is N or CH, and

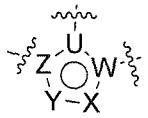
in formula (IIIe), X is N or CH, and Y is N or CH;

comprising reacting a compound of formula (II)



(II)

wherein the ring A, n, m, p, R^1, R^2, R^3, R^4, and the ring of formula (III)


(III)

are as defined herein above,

with $P_2S_5 \cdot 2\ C_5H_5N$ as a thionating agent, in a liquid solvent medium; and optionally preparing a pharmaceutically acceptable salt of the compound of formula (I).

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 is a bar chart diagram showing inhibition experiments performed on (A) Texas influenza virus, (B) H1N1 influenza virus and (C) Vesicular Stomatitis virus.

FIGURE 2 is a bar chart diagram showing inhibition experiments performed on (A) Texas influenza virus, (B) H1N1 influenza virus.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise indicated or apparent from the context, any alkyl group as referred to herein may be branched or unbranched. This also applies to said groups when present in moieties such as alkoxy groups.

The term "alkyl" as employed herein, alone or as part of another group, refers to an acyclic straight or branched alkyl chain radical, unless otherwise specified containing 1, 2, 3, 4, 5, or 6, carbons in the normal chain, which includes methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, and *n*-hexyl. Examples of branched chain radicals, not excluding any of the possible isomers not mentioned, are *iso*-propyl, *sec*-butyl, *tert*-butyl, *iso*-pentyl, 3-methylpentyl, and the like.

Unless otherwise indicated or apparent from the context, in the expression "any alkyl is optionally substituted with one or several halogen atoms", the reference to "any alkyl" includes alkyls which constitute either the radical *per se*, such as in R^3, or which are part of a functional group, e.g. an alkoxy radical.