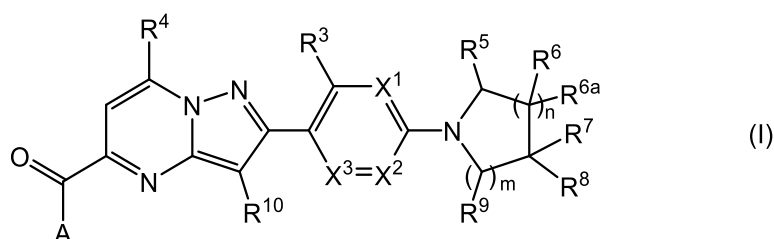


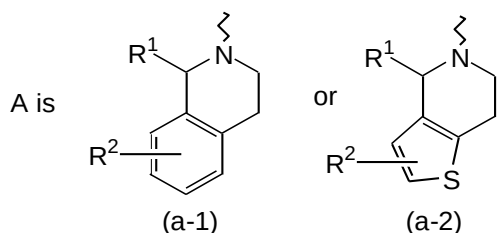
The compounds of the present invention have unexpected better plasma concentration profiles than the pyrazolopyrimidine compounds of WO-2016/174079 bearing a substituted pyrrolidine moiety as demonstrated in Pharmacological Example E.2.

Summary

In one aspect, there is provided a compound of formula (I), including any stereochemically isomeric form thereof, wherein



including any stereochemically isomeric form thereof, wherein



n is 0, 1, or 2;

m is 1 or 2;

X¹, X² and X³ are selected from X¹ is CR¹¹ and X² is CR¹¹ and X³ is CR¹¹,

or X¹ is N and X² is CR¹¹ and X³ is CR¹¹,

or X¹ is CR¹¹ and X² is N and X³ is CR¹¹,

or X¹ is CR¹¹ and X² is CR¹¹ and X³ is N,

or X¹ is N and X² is CR¹¹ and X³ is N,

wherein each R¹¹ is independently selected from the group consisting of hydrogen, halo, hydroxy, C₁₋₄alkyl,

C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, hydroxyC₁₋₄alkyl, and hydroxyC₁₋₄alkyloxy;

R¹ is CH₃ or CH₂CH₃;

R² is hydrogen, halo or C₁₋₄alkyl;

R³ is halo or CH₃O;

R⁴ is C₃₋₆cycloalkyl; phenyl; phenyl substituted with 1, 2 or 3 substituents each individually selected from halo, hydroxy, cyano, C₁₋₄alkyl, polyhaloC₁₋₄alkyl, and C₁₋₄alkyloxy; Heteroaryl; or C₁₋₄alkyl substituted with Heteroaryl;

R⁵ is hydrogen, C₁₋₄alkyl or hydroxyC₁₋₄alkyl;

each R⁶ is independently selected from the group consisting of hydrogen, C₁₋₄alkyl, hydroxy, halo and C₁₋₄alkyloxy;

each R^{6a} is independently selected from the group consisting of hydrogen and halo;

R⁷ is hydrogen, C₁₋₄alkyl, or hydroxyC₁₋₄alkyl;

R⁸ is -OH,

-CN,

-O-(CO)-NR¹²R¹³,

-C₁₋₄alkyl-(CO)-NR¹²R¹³,

-(CO)-NR¹²R¹³,

-(CS)-NR¹²R¹³,

-(CO)-NR¹²-CN,

-(CO)-NR¹²-SO₂-R¹⁴,

-NR¹²-(CO)-R¹⁴,

-NR¹²-(CO)-O-R¹⁴,

-NR¹²-SO₂-R¹⁴,

-NH₂,

-NR¹²-R¹⁵;

-SO₂-R¹⁴,

-SO₂-NR¹²R¹³,

-SO₂-NR¹²-(CO)-R¹⁴, or

-SO(=NH)(-R¹⁴), or

Heteroaryl¹;

wherein

R¹² and R¹³ are each independently selected from hydrogen and C₁₋₄alkyl, and;

R¹⁴ is C₁₋₄alkyl, or polyhaloC₁₋₄alkyl;

R¹⁵ is di(C₁₋₄alkyl)-(P=O)- or polyhaloC₁₋₄alkyl;

or R⁷ and R⁸ may be taken together to form -CH₂-(SO₂)-CH₂- or -CH₂-O-CH₂- ;

each R⁹ is independently selected from the group consisting of hydrogen and C₁₋₄alkyl;

R¹⁰ is hydrogen, halo or C₁₋₆alkyl;

when n = 1 and m=1, R⁸ and R⁹ may be taken together to form -CH₂- ;

when n = 1 and m=1, R⁵ and R⁹ may be taken together to form -CH₂CH₂- ;

when n=1 and m=1, R⁸ and R⁹ may be taken together to form -CH₂-(CO)-O- ;

Heteroaryl is pyridinyl or pyrimidinyl, wherein each Heteroaryl is optionally substituted with one or two substituents each independently selected from C₁₋₄alkyl, halo, amino, and aminocarbonyl;

Heteroaryl¹ is tetrazolyl or oxadiazolyl;

or a pharmaceutically acceptable acid addition salt thereof.

In another aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as defined herein.

In another aspect, there is provided a process for preparing a pharmaceutical composition as defined herein wherein a therapeutically active amount of a compound as defined herein is intimately mixed with a pharmaceutically acceptable carrier.

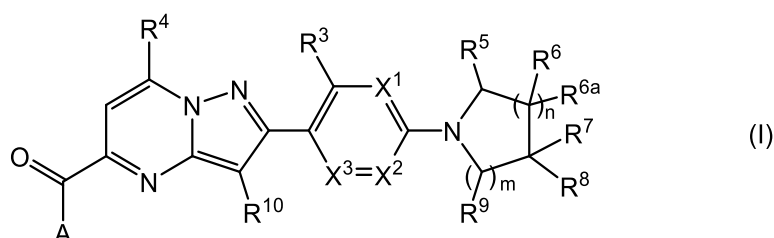
In another aspect, there is provided a compound as defined herein for use as a medicine.

In another aspect, there is provided a compound as defined herein, or a pharmaceutical composition as defined herein, for use in the treatment of a respiratory syncytial virus infection.

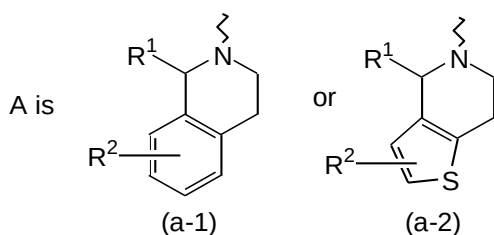
In another aspect, there is provided use of a compound of formula (I) as defined herein in the manufacture of a medicament for the treatment of a respiratory syncytial virus (RSV) infection.

Detailed description of the Invention

The present invention relates to compounds of formula (I)



including any stereochemically isomeric form thereof, wherein



n is 0, 1, or 2;

5 m is 1 or 2;

X^1 , X^2 and X^3 are selected from X^1 is CR^{11} and X^2 is CR^{11} and X^3 is CR^{11} ,

or X^1 is N and X^2 is CR^{11} and X^3 is CR^{11} ,

or X^1 is CR^{11} and X^2 is N and X^3 is CR^{11} ,

or X^1 is CR^{11} and X^2 is CR^{11} and X^3 is N,

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or X^1 is N and X^2 is CR^{11} and X^3 is N,

wherein each R^{11} is independently selected from the group

consisting of hydrogen, halo, hydroxy, C_{1-4} alkyl,

C_{1-4} alkyloxy, C_{1-4} alkyloxy C_{1-4} alkyloxy, hydroxy C_{1-4} alkyl

and hydroxy C_{1-4} alkyloxy;

15 R^1 is CH_3 or CH_2CH_3 ;

R^2 is hydrogen, halo or C_{1-4} alkyl;

R^3 is halo or CH_3O ;

R^4 is C_{3-6} cycloalkyl; phenyl; phenyl substituted with 1, 2 or 3 substituents each

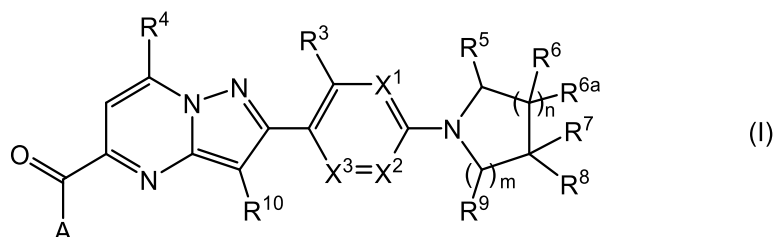
individually selected from halo, hydroxy, cyano, C_{1-4} alkyl, polyhalo C_{1-4} alkyl, and

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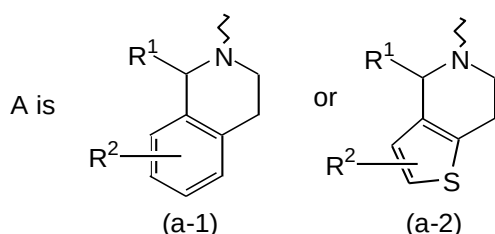
C_{1-4} alkyloxy; Heteroaryl; or C_{1-4} alkyl substituted with Heteroaryl;

Claims

1. A compound of formula (I), including any stereochemically isomeric form thereof, wherein



including any stereochemically isomeric form thereof, wherein



n is 0, 1, or 2;

m is 1 or 2;

X¹, X² and X³ are selected from X¹ is CR¹¹ and X² is CR¹¹ and X³ is CR¹¹,

or X¹ is N and X² is CR¹¹ and X³ is CR¹¹,

or X¹ is CR¹¹ and X² is N and X³ is CR¹¹,

or X¹ is CR¹¹ and X² is CR¹¹ and X³ is N,

or X¹ is N and X² is CR¹¹ and X³ is N,

wherein each R¹¹ is independently selected from the group consisting of hydrogen, halo, hydroxy, C₁₋₄alkyl,

C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, hydroxyC₁₋₄alkyl, and hydroxyC₁₋₄alkyloxy;

R¹ is CH₃ or CH₂CH₃;

R² is hydrogen, halo or C₁₋₄alkyl;

R³ is halo or CH₃O;

R⁴ is C₃₋₆cycloalkyl; phenyl; phenyl substituted with 1, 2 or 3 substituents each individually selected from halo, hydroxy, cyano, C₁₋₄alkyl, polyhaloC₁₋₄alkyl, and C₁₋₄alkyloxy; Heteroaryl; or C₁₋₄alkyl substituted with Heteroaryl;

R⁵ is hydrogen, C₁₋₄alkyl or hydroxyC₁₋₄alkyl;

each R⁶ is independently selected from the group consisting of hydrogen, C₁₋₄alkyl, hydroxy, halo and C₁₋₄alkyloxy;

each R^{6a} is independently selected from the group consisting of hydrogen and halo;

R^7 is hydrogen, C_{1-4} alkyl, or hydroxy C_{1-4} alkyl;

R^8 is -OH,

-CN,

-O-(CO)-NR¹²R¹³,

-C₁₋₄alkyl-(CO)-NR¹²R¹³,

-(CO)-NR¹²R¹³,

-(CS)-NR¹²R¹³,

-(CO)-NR¹²-CN,

-(CO)-NR¹²-SO₂-R¹⁴,

-NR¹²-(CO)-R¹⁴,

-NR¹²-(CO)-O-R¹⁴,

-NR¹²-SO₂-R¹⁴,

-NH₂,

-NR¹²-R¹⁵;

-SO₂-R¹⁴,

-SO₂-NR¹²R¹³,

-SO₂-NR¹²-(CO)-R¹⁴, or

-SO(=NH)(-R¹⁴), or

Heteroaryl¹;

wherein

R¹² and R¹³ are each independently selected from hydrogen and

C₁₋₄alkyl, and;

R¹⁴ is C₁₋₄alkyl, or polyhaloC₁₋₄alkyl;

R¹⁵ is di(C₁₋₄alkyl)-(P=O)- or polyhaloC₁₋₄alkyl;

or R^7 and R^8 may be taken together to form -CH₂-(SO₂)-CH₂- or -CH₂-O-CH₂- ;

each R^9 is independently selected from the group consisting of hydrogen and

C₁₋₄alkyl;

R¹⁰ is hydrogen, halo or C₁₋₆alkyl;

when n = 1 and m=1, R⁸ and R⁹ may be taken together to form -CH₂- ;

when n = 1 and m=1, R⁵ and R⁹ may be taken together to form -CH₂CH₂- ;

when n=1 and m=1, R⁸ and R⁹ may be taken together to form -CH₂-(CO)-O- ;

Heteroaryl is pyridinyl or pyrimidinyl, wherein each Heteroaryl is optionally

substituted with one or two substituents each independently selected from

C₁₋₄alkyl, halo, amino, and aminocarbonyl;

Heteroaryl¹ is tetrazolyl or oxadiazolyl;

or a pharmaceutically acceptable acid addition salt thereof.

2. The compound as claimed in claim 1 wherein

wherein

n is 0, 1, or 2;

m is 1 or 2;

X¹, X² and X³ are selected from X¹ is CR¹¹ and X² is CR¹¹ and X³ is CR¹¹,

or X¹ is N and X² is CR¹¹ and X³ is CR¹¹,

or X¹ is CR¹¹ and X² is N and X³ is CR¹¹,

or X¹ is N and X² is CR¹¹ and X³ is N,

wherein each R¹¹ is independently selected from the group

consisting of hydrogen, halo, hydroxy, C₁₋₄alkyl,

C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, and

hydroxyC₁₋₄alkyloxy;

R¹ is CH₃;

R² is hydrogen, or halo;

R³ is halo;

R⁴ is C₃₋₆cycloalkyl; phenyl; phenyl substituted with 1 substituent selected from halo, cyano, C₁₋₄alkyl, polyhaloC₁₋₄alkyl, and C₁₋₄alkyloxy; or Heteroaryl;

R⁵ is hydrogen, C₁₋₄alkyl or hydroxyC₁₋₄alkyl;

each R⁶ is independently selected from the group consisting of hydrogen, C₁₋₄alkyl,

hydroxy, halo and C₁₋₄alkyloxy;

each R^{6a} is independently selected from the group consisting of hydrogen and halo;

R⁷ is hydrogen, C₁₋₄alkyl, or hydroxyC₁₋₄alkyl;

R⁸ is -OH,

-CN,

-O-(CO)-NR¹²R¹³,

-C₁₋₄alkyl-(CO)-NR¹²R¹³,

-(CO)-NR¹²R¹³,

-(CS)-NR¹²R¹³,

-(CO)-NR¹²-CN,

-(CO)-NR¹²-SO₂-R¹⁴,

-NR¹²-(CO)-R¹⁴,

-NR¹²-(CO)-O-R¹⁴,

-NR¹²-SO₂-R¹⁴,

-NH₂,

-NR¹²-R¹⁵;

-SO₂-R¹⁴,

-SO₂-NR¹²R¹³,

-SO₂-NR¹²-(CO)-R¹⁴, or

-SO(=NH)(-R¹⁴), or
Heteroaryl¹;

wherein

R¹² and R¹³ are each independently selected from hydrogen and C₁₋₄alkyl, and;

R¹⁴ is C₁₋₄alkyl or polyhaloC₁₋₄alkyl;

R¹⁵ is di(C₁₋₄alkyl)-(P=O)- or polyhaloC₁₋₄alkyl;

or R⁷ and R⁸ may be taken together to form -CH₂-(SO₂)-CH₂- or -CH₂-O-CH₂- ;

each R⁹ is independently selected from the group consisting of hydrogen and
C₁₋₄alkyl;

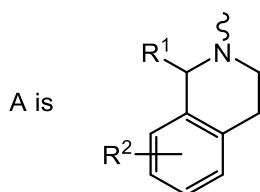
R¹⁰ is hydrogen;

when n=1 and m=1, R⁸ and R⁹ may be taken together to form -CH₂-(CO)-O- ;

Heteroaryl is pyridinyl or pyrimidinyl, wherein each Heteroaryl is optionally
substituted with one substituent selected from halo;

Heteroaryl¹ is tetrazolyl or 5-oxo-4,5-dihydro-1,2,4-oxadiazolyl;

3. The compound as claimed in claim 1 wherein X¹ is CR¹¹ and X² is CR¹¹ and X³ is CR¹¹.
4. The compound as claimed in claim 1 wherein wherein X¹ is N and X² is CR¹¹ and X³ is CR¹¹; or X¹ is CR¹¹ and X² is N and X³ is CR¹¹; or X¹ is CR¹¹ and X² is CR¹¹ and X³ is N; or X¹ is N and X² is CR¹¹ and X³ is N.
5. The compound as claimed in any one of claims 1 to 4 wherein radical A is of formula (a-1).
6. The compound as claimed in any one of claims 1 to 5 wherein n is 0 and m is 1.
7. The compound as claimed in any one of claims 1 to 5 wherein n is 1 and m is 1.
8. The compound as claimed in claim 1 wherein



n is 0 or 1;

m is 1;

X¹, X² and X³ are selected from X¹ is CR¹¹ and X² is CR¹¹ and X³ is CR¹¹, wherein
each R¹¹ is hydrogen;

R^1 is CH_3 ;

R^2 is hydrogen;

R^3 is halo;

R^4 is C_{3-6} cycloalkyl or Heteroaryl;

R^5 is hydrogen;

each R^6 is independently selected from the group consisting of hydrogen, hydroxy,
and halo;

each R^{6a} is hydrogen;

R^7 is hydrogen or hydroxy C_{1-4} alkyl;

R^8 is $-OH$,

$-C_{1-4}$ alkyl-(CO)- $NR^{12}R^{13}$, or

$-(CO)-NR^{12}R^{13}$,

wherein

R^{12} and R^{13} are each independently selected from hydrogen and C_{1-4} alkyl,

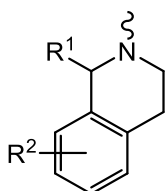
R^{10} is hydrogen;

Heteroaryl is pyridinyl;

or a pharmaceutically acceptable acid addition salt thereof.

9. The compound as claimed in claim 1 wherein

A is



n is 1;

m is 1;

X^1 , X^2 and X^3 are selected from X^1 is CR^{11} and X^2 is CR^{11} and X^3 is CR^{11} , wherein

each R^{11} is hydrogen;

R^1 is CH_3 ;

R^2 is hydrogen;

R^3 is halo;

R^4 is C_{3-6} cycloalkyl;

R^5 is hydrogen;

each R^6 is independently selected from the group consisting of hydrogen, hydroxy,
and halo;

each R^{6a} is hydrogen;

R^7 is hydrogen or hydroxy C_{1-4} alkyl;

R^8 is $-OH$, or

-(CO)-NR¹²R¹³,

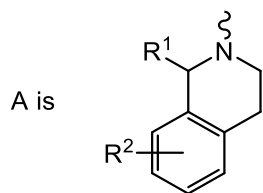
wherein

R¹² and R¹³ are each independently selected from hydrogen and C₁₋₄alkyl,

R¹⁰ is hydrogen;

or a pharmaceutically acceptable acid addition salt thereof.

10. The compound as claimed in claim 1 wherein



n is 1;

m is 1;

X¹, X² and X³ are selected from X¹ is CR¹¹ and X² is CR¹¹ and X³ is CR¹¹, wherein
each R¹¹ is hydrogen;

R¹ is CH₃;

R² is hydrogen;

R³ is halo;

R⁴ is C₃₋₆cycloalkyl;

R⁵ is hydrogen;

each R⁶ is independently selected from the group consisting of hydrogen and hydroxy;

each R^{6a} is hydrogen;

R⁷ is hydrogen;

R⁸ is -OH, or

-(CO)-NR¹²R¹³,

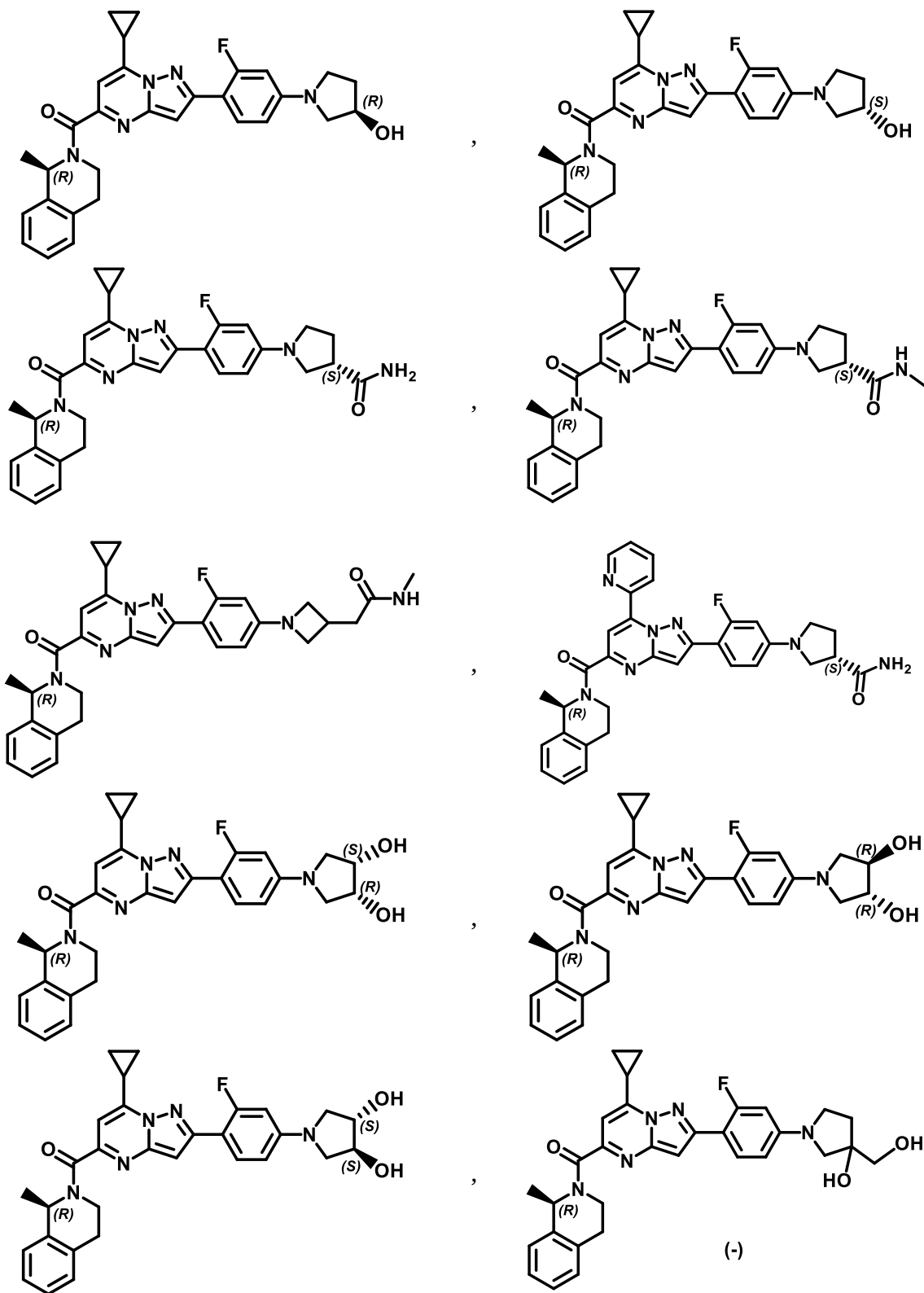
wherein

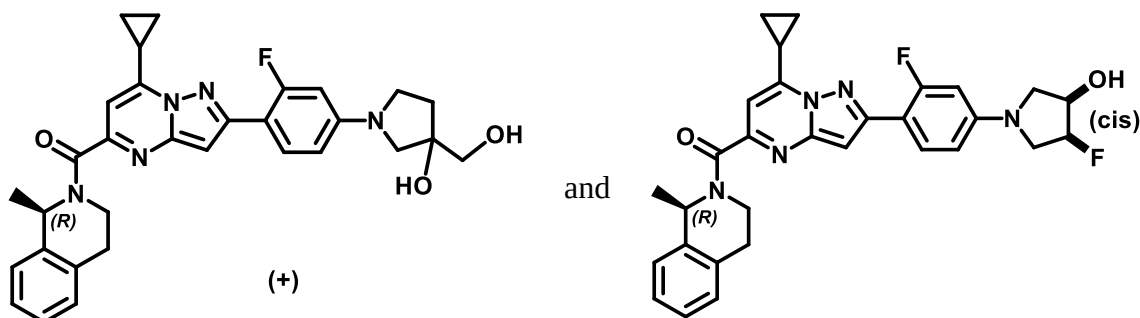
R¹² and R¹³ are each independently selected from hydrogen and C₁₋₄alkyl,

R¹⁰ is hydrogen;

or a pharmaceutically acceptable acid addition salt thereof.

11. The compound according to claim 1, wherein the compound is selected from





or a pharmaceutically acceptable acid addition salt thereof.

12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as claimed in any one of claims 1 to 11.
13. The pharmaceutical composition according to claim 12, which further comprises another antiviral agent.
14. The pharmaceutical composition according to claim 13, wherein the other antiviral agent is a respiratory syncytial virus (RSV) inhibiting compound.
15. A process for preparing a pharmaceutical composition as claimed in any one of claims 12 to 14 wherein a therapeutically active amount of a compound as claimed in any one of claims 1 to 11 is intimately mixed with a pharmaceutically acceptable carrier.
16. A compound as claimed in any one of claims 1 to 11 for use as a medicine.
17. A compound as claimed in any one of claims 1 to 11, or a pharmaceutical composition as claimed in any one of claims 12 to 14, for use in the treatment of a respiratory syncytial virus infection.
18. Use of a compound of formula (I) as defined in any one of claims 1 to 11 in the manufacture of a medicament for the treatment of a respiratory syncytial virus (RSV) infection.