

RSV has a seasonal incidence; it is highly predictable and occurs in the winters of both hemispheres, from September to May in Europe and North America, peaking in December and January, and can occur throughout the year in tropical countries. It affects >90% of infants and young children by the age of two years and as natural immunity is short-lived; many will be re -infected each year. As with influenza, in elderly people, RSV causes around 10% of winter hospitalisations with an associated mortality of 10%.

Current anti-RSV treatment involves the use of a monoclonal antibody to RSV, called palivizumab. Such use of palivizumab is a prophylactic, rather than therapeutic, treatment of RSV. Although this antibody is often effective, its use is restricted to preterm infants and infants at high risk. Indeed, its limited utility means that it is unavailable for many people in need of anti-RSV treatment. There is therefore an urgent need for effective alternatives to existing anti-RSV treatment.

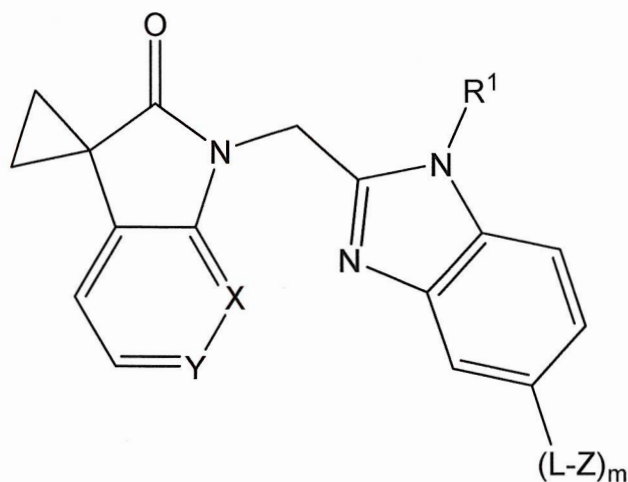
Additionally, several compounds have been proposed as inhibitors of RSV, including benzimidazole-based compounds. For example, K D Combrink et al., Bioorganic & Medicinal Chemistry Letters, 17 (2007), 4784-4790 discloses the compound BMS-433771 and variants thereof. Further benzimidazole-based compounds are disclosed in WO-02/062290, WO-03/053344 and WO-10/103306.

WO 2013/068769 discloses spirocyclic compounds having activity against RSV. However there exists a need to identify further compounds, and in particular compounds having favourable pharmacokinetic profiles.

Summary

It has now been found that a novel series of benzimidazoles are active as RSV inhibitors with favourable pharmacokinetics.

Accordingly, the present disclosure relates to a compound which is a benzimidazole of formula (I):



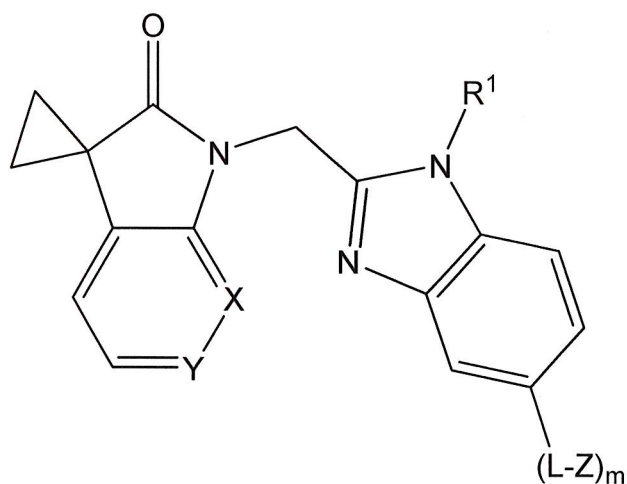
Formula (I)

wherein:

- one of X and Y is an N atom or a substituted C atom, and the other is CH;
- L is a single bond, C₁₋₃ alkylene, C₂₋₃ alkenylene or C₂₋₃ alkynylene;
- R¹ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, 3- to 10-membered cycloalkyl 5- to 10-membered heterocyclyl or 5- to 12- membered heteroaryl, each of which is unsubstituted or substituted;
- Z is halo, C₁₋₆ haloalkyl, nitro, -CN, -N(R²)₂, -OR², -SR², -S(=O)R², or -S(=O)₂R²;
- each R² is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, wherein said alkyl, alkenyl and alkynyl groups are unsubstituted or substituted; and
- m is 0 or 1;

or a pharmaceutically acceptable salt thereof.

In one aspect of the present disclosure, there is provided a compound which is a benzimidazole of formula (I):



Formula (I)

wherein:

- 5 - one of X and Y is an N atom or a substituted C atom, and the other is CH;
- L is a single bond or C₁₋₃ alkylene;
- R¹ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, 3- to 10-membered cycloalkyl, 5- to 10-membered heterocyclyl or 5- to 12- membered
- 10 heteroaryl, each of which is unsubstituted or substituted;
- Z is -N(R²)₂;
- each R² is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, wherein said alkyl, alkenyl and alkynyl groups are unsubstituted or substituted; and
- 15 - m is 1;

or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a pharmaceutical composition which comprises a compound as defined herein and a pharmaceutically

20 acceptable carrier or diluent.

In yet another aspect of the present disclosure, there is provided a compound as defined herein, for use in the treatment of the human or animal body by therapy.

In a further aspect of the present disclosure, there is provided a compound as defined herein for use in the treatment or prevention of an RSV infection.

In yet another aspect of the present disclosure, there is provided a product containing:

5 (a) a compound as defined herein; and

 (b) one or more further therapeutic agents;

for simultaneous, separate or sequential use in the treatment of a subject suffering from or susceptible to an RSV infection.

10 In a further aspect of the present disclosure, there is provided a pharmaceutical composition which comprises (a) a compound as defined herein, and (b) one or more further therapeutic agents, as defined herein, together with a pharmaceutically acceptable carrier or diluent.

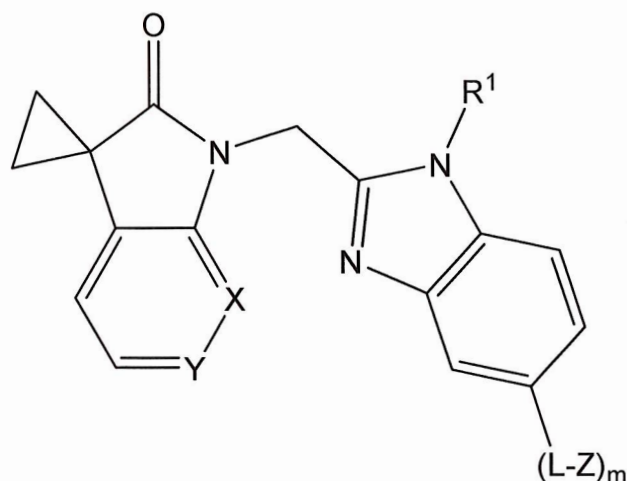
15 **Detailed Description of the Invention**

When any group, ring, substituent or moiety defined herein is substituted, it is typically substituted by Q as defined below.

20 A C₁₋₆ alkyl group or moiety is linear or branched. A C₁₋₆ alkyl group is typically a C₁₋₄ alkyl group, or a C₄₋₆ alkyl group. Examples of C₁₋₆ alkyl groups and moieties include

CLAIMS

1. A compound which is a benzimidazole of formula (I):



Formula (I)

wherein:

- one of X and Y is an N atom or a substituted C atom, and the other is CH;
- L is a single bond or C₁₋₃ alkylene;
- R¹ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, 3- to 10-membered cycloalkyl, 5- to 10-membered heterocyclyl or 5- to 12- membered heteroaryl, each of which is unsubstituted or substituted;
- Z is -N(R²)₂;
- each R² is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, wherein said alkyl, alkenyl and alkynyl groups are unsubstituted or substituted; and
- m is 1;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein one of X and Y is an N atom or a C atom substituted with a halogen atom, and the other is CH.

3. A compound according to claim 1 wherein L is a single bond or C₁ alkylene.

4. A compound according to any one of the preceding claims wherein R¹ is C₃₋₆
5 alkyl, C₃₋₆ alkenyl, 5- or 6-membered cycloalkyl, 5- or 6-membered heterocyclyl or 5-
or 6- membered heteroaryl, each of which is unsubstituted or substituted.

5. A compound according to claim 4 wherein R¹ is C₅₋₆ alkyl which is
10 unsubstituted or substituted with one, two, three or four halogen atoms, R¹ is 6-
membered cycloalkyl substituted with one, two, three or four -OH groups, or R¹ is
unsubstituted 6-membered heterocyclyl.

15 6. A compound according to claim 1 wherein Z is NH₂.

7. A compound according to any one of the preceding claims wherein each R² is
independently hydrogen or C₁₋₄ alkyl.

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8. A compound according to claim 1 wherein, in formula (I):

- one of X and Y is an N atom or C substituted with a fluorine atom, and the other is CH;
- R^1 is C_{5-6} alkyl, which is unsubstituted or substituted with one, two, three or four fluorine atoms, R^1 is cyclohexyl which is unsubstituted or substituted with one or two -OH groups, or R^1 is unsubstituted tetrahydropyran;
- m is 1
- L is a single bond or C_1 alkylene; and
- Z is NH_2 .

9. A compound according to claim 1 which is selected from:

- 1'-{[5-(aminomethyl)-1-(4,4,4-trifluorobutyl)-1H-1,3-benzodiazol-2-yl]methyl}-6'-fluoro-1',2'-dihydrospiro[cyclopropane-1,3'-indole]-2'-one;
- 1'-((5-(aminomethyl)-1-(4,4,4-trifluorobutyl)-1H-benzo[d]imidazol-2-yl)methyl)spiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one;
- 1'-((5-(aminomethyl)-1-isopentyl-1H-benzo[d]imidazol-2-yl)methyl)spiro[cyclopropane-1,3'-pyrrolo[2,3-b]pyridin]-2'(1'H)-one;
- 1'-((5-(aminomethyl)-1-isopentyl-1H-benzo[d]imidazol-2-yl)methyl)spiro[cyclopropane-1,3'-pyrrolo[2,3-c]pyridin]-2'(1'H)-one; and
- 1'-((5-(aminomethyl)-1-(tetrahydro-2H-pyran-4-yl)-1H-benzo[d]imidazol-2-yl)methyl)-6'-fluorospiro[cyclopropane-1,3'-indolin]-2'-one;
- 1'-((5-(Aminomethyl)-1-((1R,4R)-4-hydroxycyclohexyl)-1H-benzo[d]imidazol-2-yl)methyl)-6'-fluorospiro[cyclopropane-1,3'-indolin]-2'-one

and the pharmaceutically acceptable salts thereof.

10. A pharmaceutical composition which comprises a compound as defined in any one of claims 1 to 9 and a pharmaceutically acceptable carrier or diluent.

11. A compound as defined in any one of claims 1 to 9, for use in the treatment of the human or animal body by therapy.
12. A compound as defined in any one of claims 1 to 9 for use in the treatment or
5 prevention of an RSV infection.
13. A product containing:
(a) a compound as defined in any one of claims 1 to 9; and
(b) one or more further therapeutic agents;
10 for simultaneous, separate or sequential use in the treatment of a subject suffering from or susceptible to an RSV infection.
14. A product for use according to claim 13, wherein the further therapeutic agent is :
15 (i) a RSV nucleocapsid(N)-protein inhibitor;
(ii) another protein inhibitor, such as one that inhibits the phosphoprotein (P) protein and/or large (L) protein;
(iii) an anti-RSV monoclonal antibody, such as an F-protein antibody;
(iv) an immunomodulating toll-like receptor compound;
20 (v) another respiratory virus anti-viral, such as an anti-influenza and/or anti-rhinovirus compound; and/or
(vi) an anti-inflammatory compound.
15. A pharmaceutical composition which comprises (a) a compound as defined in
25 any one of claims 1 to 9, and (b) one or more further therapeutic agents, as defined in claim 13 or 14, together with a pharmaceutically acceptable carrier or diluent.