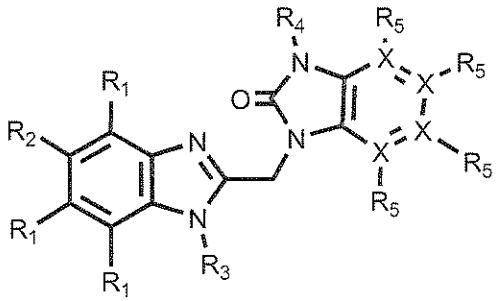
with limited success. Clearly there is a need for an efficacious non-toxic and easy to administer drug against RSV replication. It would be particularly preferred to provide drugs against RSV replication that could be administered perorally.

A reference on benzimidazole antiviral agents is WO 01/95910. Herein compounds are presented to have antiviral activity, yet with EC_{50} values over a wide range of from 0.001 μm to as high as 50 μM (which does not normally represent the desired biological activity). Another reference, relating to substituted 2-methyl-benzimidazole RSV antiviral agents, in the same range of activities is WO 03/053344. Another related background reference on compounds in the same range of activities, is WO 02/26228 regarding benzimidazolone antiviral agents. A reference on structure-activity relations, in respect of RSV inhibition, of 5-substituted benzimidazole compounds is X.A. Wang et al., Bioorganic and Medicinal Chemistry Letters 17 (2007) 4592-4598.

It is desired to provide new drugs that have antiviral activity. Particularly, it would be desired to provide new drugs that have RSV replication inhibitory activity. Further, it would be desired to unravel compound structures that allow obtaining higher antiviral biological activities than disclosed in the art, and particularly having activities represented by EC_{50} values below 0.001 μM. A further desire is to find compounds having oral antiviral activity.

Summary ~~of the Invention~~

In order to better address one or more of the foregoing desires, the disclosure~~invention, in one aspect,~~ presents antiviral benzimidazole compounds represented by formula I, a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex, or a stereochemically isomeric form thereof;



formula (I)

wherein

each X independently is C or N;

R_1 is H;

R_2 is selected from the group consisting of Br and Cl;

R_3 is $-(CR_6R_7)_n-R_8$;

R_4 is selected from the group consisting of H, C_3-C_7cycloalkyl, C_2-C_{10} alkenyl, $-(CR_6R_7)_n-R_8$;, $-CH_2$-p-Fluorophenyl, CH_2CF_3 and $-SO_2CH_3$;

R_5 is present where X is C, whereby each R_5 is selected, each independently, from the group consisting of H, C_1-C_6alkyl, C_1-C_6alkoxy, halogen, and CN;

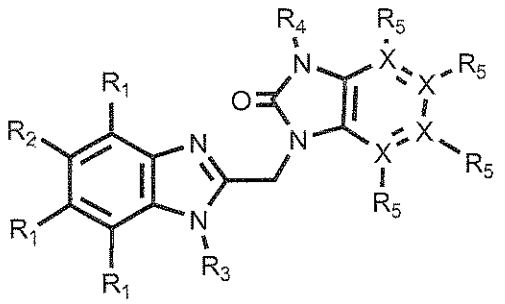
R_5 is absent where X is N;

R_6 and R_7 are each independently chosen from H and C_1-C_{10} alkyl, C_3-C_7cycloalkyl; or R_6 and R_7 taken together form a 5 to 6 membered aliphatic or aromatic ring that optionally contains one or more heteroatoms selected from the group N, S, O.

R_8 is selected from the group consisting of H, OH, CF_3, CHF_2, F, Cl, SO_2CH_3, SO_2C_3-C_7cycloalkyl, $NR_6SO_2R_6$, $SO_2NR_6R_7$, $NR_6SO_2C_3$-C_7cycloalkyl, CN, NR_6R_7, COOH, $COOR_6$, $CONR_6R_7$, $OCOC_1$-C_6alkyl, $CONR_6SO_2R_7$, $CONHR_6SO_2R_7$, $CONHR_6SO_2NR_6R_7CONR_6SO_2NR_6R_7$, phtalimido or a 5 to 6 membered aliphatic or aromatic ring that optionally contains one or more heteroatoms selected from the group N, S, O;

n is an integer having a value from 1 to 6.

In one aspect, there is provided a compound represented by formula I, a *N*-oxide, addition salt, quaternary amine, metal complex, or a stereochemically isomeric form thereof;



formula (I)

wherein

each X independently is C or N;

R_1 is H;

R_2 is selected from the group consisting of Br and Cl;

R_3 is $-(CR_6R_7)_n-R_8$;

R_4 is selected from the group consisting of C_3-C_7cycloalkyl, C_2-C_{10} alkenyl, CH_2CF_3 and $-SO_2CH_3$;

R_5 is present where X is C, whereby each R_5 is selected, each independently, from the group consisting of H, C_1-C_6alkyl, C_1-C_6alkoxy, halogen, and CN;

R_5 is absent where X is N;

R_6 and R_7 are each independently chosen from H and C_1-C_{10} alkyl, C_3-C_7cycloalkyl; or R_6 and R_7 taken together form a 5 to 6 membered aliphatic or aromatic ring that optionally contains one or more heteroatoms selected from the group N, S, O.

R_8 is selected from the group consisting of H, OH, CF_3, CHF_2, F, Cl, SO_2CH_3, SO_2C_3-C_7cycloalkyl, $NR_6SO_2R_6$, $SO_2NR_6R_7$, $NR_6SO_2C_3$-C_7cycloalkyl, CN, NR_6R_7, COOH, $COOR_6$, $CONR_6R_7$, $OCOC_1$-C_6alkyl, $CONR_6SO_2R_7$, CONH-R_6-SO_2R_7 , CONH-R_6-$SO_2NR_6R_7CONR_6SO_2NR_6R_7$, phtalimido or a 5 to 6 membered aliphatic or aromatic ring that optionally contains one or more heteroatoms selected from the group N, S, O;

n is an integer having a value from 1 to 6.

In another embodiment,

each X independently is C or N;

R_1 is H;

R_2 is selected from the group consisting of Br and Cl;

R_3 is $-(CR_6R_7)_n-R_8$;

R_4 is selected from the group consisting of H, C_3-C_7cycloalkyl, C_2-C_{10}alkenyl, and $-SO_2CH_3$;

R_5 is present where X is C, whereby each R_5 is selected, each independently, from the group consisting of H, C_1-C_6alkyl, C_1-C_6alkoxy, halogen, and CN;

R_5 is absent where X is N;

R_6 and R_7 are each independently chosen from H and C_1-C_{10} alkyl; or R_6 and R_7 taken together form a 5 to 6 membered aliphatic ring that optionally contains a heteroatom selected from the group N, S, O.

R_8 is selected from the group consisting of H, OH, CF_3, CHF_2, F, SO_2CH_3, SO_2C_3-C_7cycloalkyl, $NR_6SO_2R_6$, $SO_2NR_6R_7$, $NR_6SO_2C_3$-C_7cycloalkyl, CN, NR_6R_7, COOH, $COOR_6$, $CONR_6R_7$, $OCOC_1$-C_6alkyl;

n is an integer having a value from 2 to 6;

T~~In another aspect, t~~he ~~invention~~disclosure relates to the foregoing compounds for use in the treatment of RSV infections in warm-blooded animals, preferably humans. In another aspect, there is provided a compound as defined above for use as a medicine.~~In yet~~

Tanother aspect, the inventiondisclosure presents a method of treatment of viral RSV infections in a subject in need thereof, comprising administering to said subject an effective amount of a compound as defined above. TIn still another aspect, the inventiondisclosure resides in the use of a compound as defined above, for the manufacture of a medicament in the treatment of RSV infections. In another aspect, there is provided a compound as defined above for use as a medicament for inhibiting RSV replication. In another aspect, there is provided the use of a compound as defined above for the manufacture of a medicament for inhibiting RSV replication.

TIn a further aspect, the inventiondisclosure relates to a pharmaceutical composition comprising a compound as defined above, and a pharmaceutically acceptable excipient. In another aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as defined above.

TIn a still further aspect, the inventiondisclosure provides methods for preparing the compounds defined above. In another aspect, there is provided a process for preparing a pharmaceutical composition as defined above, said process comprising mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound as defined above.

Detailed description of the invention

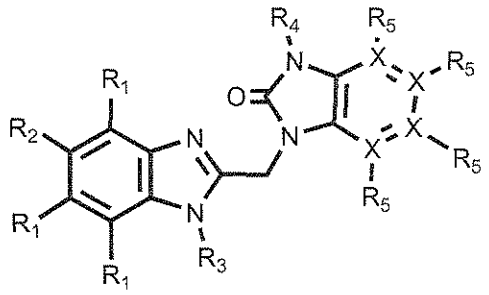
The invention is based on the unexpected finding that, on certain 5-substituted benzimidazole compounds, a specifically chlorine or bromine substituent R_2 provides compounds with unexpectedly strong biological activities against RSV. Even in a scientific presentation of structure activity (the Wang reference mentioned above), the judicious combination of the present invention does not surface. None of the results presented by Wang suggests biological activity outperforming the aforementioned range of 0.001 μM – 50 μM.

The present invention will further be described with respect to particular embodiments and with reference to certain examples but the invention is not limited thereto but only by the claims. Where the term "comprising" is used in the present description and claims, it does not exclude other elements or steps. Where an indefinite or definite article is used when referring to a singular noun e.g. "a" or "an", "the", this includes a plural of that noun unless something else is specifically stated.

The term 'prodrug' as used throughout this text means the pharmacologically acceptable derivatives, e.g. esters and amides, such that the resulting biotransformation product of the derivative is the active drug as defined in the compounds of formula (I). The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p. 13-15) describing prodrugs generally, is hereby incorporated. Prodrugs are characterized by a good aqueous solubility and bioavailability, and are readily metabolized into the active inhibitors *in vivo*.

Claims

1. A compound represented by formula I, a *N*-oxide, addition salt, quaternary amine, metal complex, or a stereochemically isomeric form thereof;



formula (I)

wherein

each X independently is C or N;

R_1 is H;

R_2 is selected from the group consisting of Br and Cl;

R_3 is $-(CR_6R_7)_n-R_8$;

R_4 is selected from the group consisting of C_3-C_7cycloalkyl, C_2-C_{10} alkenyl, CH_2CF_3 and $-SO_2CH_3$;

R_5 is present where X is C, whereby each R_5 is selected, each independently, from the group consisting of H, C_1-C_6alkyl, C_1-C_6alkoxy, halogen, and CN;

R_5 is absent where X is N;

R_6 and R_7 are each independently chosen from H and C_1-C_{10} alkyl, C_3-C_7cycloalkyl; or R_6 and R_7 taken together form a 5 to 6 membered aliphatic or aromatic ring that optionally contains one or more heteroatoms selected from the group N, S, O.

R_8 is selected from the group consisting of H, OH, CF_3, CHF_2, F, Cl, SO_2CH_3, SO_2C_3-C_7cycloalkyl, $NR_6SO_2R_6$, $SO_2NR_6R_7$, $NR_6SO_2C_3$-C_7cycloalkyl, CN, NR_6R_7, COOH, $COOR_6$, $CONR_6R_7$, $OCOC_1$-C_6alkyl, $CONR_6SO_2R_7$, CONH-R_6-SO_2R_7 , CONH-R_6-$SO_2NR_6R_7CONR_6SO_2NR_6R_7$, phtalimido or a 5 to 6 membered aliphatic or aromatic ring that optionally contains one or more heteroatoms selected from the group N, S, O;

n is an integer having a value from 1 to 6;