

enhanced disease during subsequent infection. Live attenuated vaccines have been tried 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.

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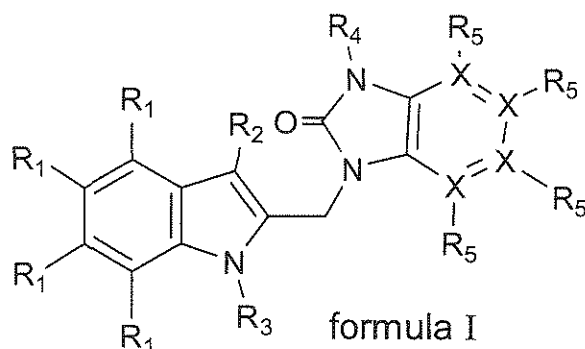
A reference entitles "imidazopyridine and imidazopyrimidine antiviral agents" is WO 01/95910 which, in fact, relates to benzimidazole antiviral agents. Herein compounds are presented to have antiviral activity, yet with EC₅₀ values over a wide range of from 0.001 μ M to as high as 50 μ M (which does not normally represent the
10 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 ohm 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
15 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
20 would be desired to retrieve compound structures that allow obtaining antiviral biological activities of the order of magnitude in the stronger regions of the prior art (i.e. at the bottom of the above-mentioned range of up to 50 μ M), and preferably at a level of about the most active, more preferably of even stronger activity, than the compounds disclosed in the art. A further desire is to find compounds having oral
25 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 indole compounds represented by **formula I**, a
30 prodrug, *N*-oxide, addition salt, quaternary amine, metal complex, or a stereochemically isomeric form thereof;

In one aspect, there is provided a compound of formula (I), an addition salt, or a stereochemically isomeric form thereof;



wherein each X independently is C or N;

R₁ is selected from the group of H, halogen, C₁-C₆alkoxy, CF₃, and OCF₃;

R₂ is selected from the group consisting of H, halogen, and CO(R₇);

R₃ is -(CR₈R₉)_n-R₁₀;

R₄ is selected from the group consisting of H, C₁-C₁₀alkyl, C₃-C₇cycloalkyl, C₂-C₁₀alkenyl, SO₂-R₈, CH₂CF₃, SO₂CH₃ or a 4 to 6 membered saturated ring containing an oxygen atom;

R₅ is present where X is C, and is selected from the group consisting of H, C₁-C₆alkoxy, CO(R₇), and halogen;

R₅ is absent where X is N;

R₇ is selected from the group consisting of OH, O(C₁-C₆alkyl), NH₂, NHSO₂NHCH₃, NHSO₂(C₁-C₆alkyl), NHSO₂(C₃-C₇cycloalkyl), NR₈R₉, and NR₉R₁₀;

n is an integer from 2 to 6;

R₈ and R₉ are each independently chosen from H, or C₁-C₁₀alkyl;

R₁₀ is selected from the group consisting of H, C₁-C₆alkyl, OH, CN, F, CF₂H, CF₃, CONR₈R₉, COOR₈, SO₂R₈ and a 4 to 6 membered saturated ring containing an oxygen atom.

In a preferred embodiment, R_7 is selected from the group consisting of OH, $O(C_1-C_6\text{alkyl})$, NH_2 , $NHSO_2N(C_1-C_6\text{alkyl})_2$, $NHSO_2NHCH_3$, $NHSO_2(C_1-C_6\text{alkyl})$, $NHSO_2(C_3-C_7\text{cycloalkyl})$, and $N(C_1-C_6\text{alkyl})_2$;

R_8 and R_9 are each independently chosen from H, $C_1-C_{10}\text{alkyl}$, $C_3-C_7\text{cycloalkyl}$ or R_8 and R_9 taken together form a 4 to 6 membered aliphatic ring that optionally contains a heteroatom selected from the group N, S, O;

R_{10} is selected from the group consisting of H, $C_1-C_6\text{alkyl}$, OH, CN, F, CF_2H , CF_3 , $CONR_8R_9$, $COOR_8$, $CONR_8SO_2R_9$, $CON(R_8)SO_2N(R_8R_9)$, NR_8R_9 , NR_8COOR_9 , $OCOR_8$, $NR_8SO_2R_9$, $SO_2NR_8R_9$, SO_2R_8 or a 4 to 6 membered saturated ring containing an oxygen atom.

Preferably, R_4 is selected from the group consisting of H, $C_1-C_{10}\text{alkyl}$, $C_3-C_7\text{cycloalkyl}$, $C_2-C_{10}\text{alkenyl}$, SO_2-R_8 , or a 4 to 6 membered saturated ring containing an oxygen atom.

~~In another aspect, the disclosure also relates to the foregoing compounds for use in the treatment of RSV infections in warm-blooded animals, preferably humans. In yet another aspect, the disclosure also 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. In still another aspect, the disclosure also 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 medicine.

In another aspect, there is provided a compound as defined above for use as a medicament for inhibiting RSV replication.

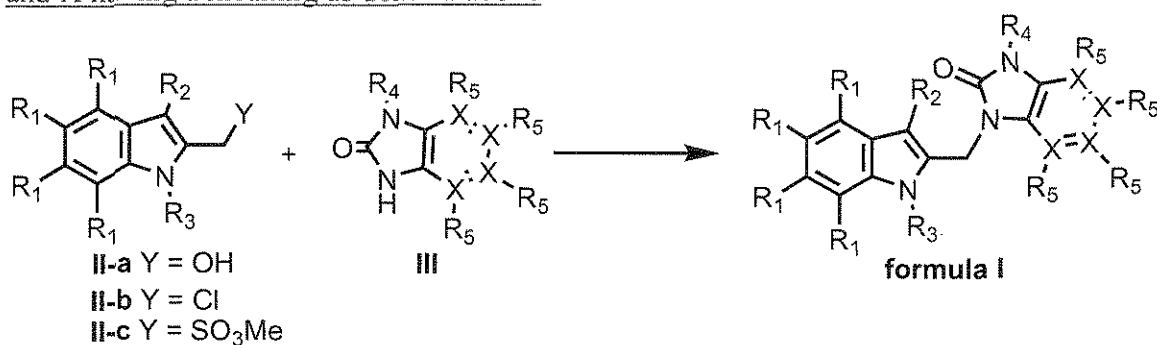
In another aspect, there is provided the use of a compound as defined above for the manufacture of a medicament for inhibiting RSV replication.

~~In a further aspect, the disclosure also 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.~~

~~In a still further aspect, the disclosure also~~ invention provides methods for preparing the compounds defined above.

In another aspect, there is provided a process for preparing a pharmaceutically composition as defined above, said process comprising intimately mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound as defined above.

In another aspect, there is provided a process for preparing a compound as defined above, said process comprising coupling a compound selected from the group consisting of II-a, II-b, and II-c with a compound III, resulting in derivatives of formula (I) with all substituents R and X having a meaning as defined above



Detailed description of the invention

The molecules of formula I, in deviation from the prior art, have on one side (the left side in the formula as depicted) a substituted indole moiety. The invention, in a broad sense, is based on the judicious recognition that these substituted indole compounds generally possess an interesting RSV inhibitory activity. Moreover, these compounds enable access to anti-RSV activities at the higher regions (i.e. the lower end of the EC₅₀ values) of the range available in the aforementioned references. Particularly, on the