Furthermore, today, specific antiviral drugs for the treatment or prevention of dengue fever virus infection are not available. Clearly, there is still a great unmet medical need for therapeutics for the prevention or treatment of viral infections in animals, more in particular in humans and especially for viral infections caused by Flaviviruses, more in particular Dengue virus. Compounds with good anti-viral potency, no or low levels of side-effects, a broad spectrum activity against multiple Dengue virus serotypes, a low toxicity and/or good pharmacokinetic or -dynamic properties are highly needed.

The present invention now provides compounds, mono- or di-substituted indole derivatives, which show high potent activity against all four (4) serotypes of the Dengue virus. Also the compounds according to the invention possess a good pharmacokinetic profile and surprisingly these specific compounds show an improved chiral stability.

SUMMARY

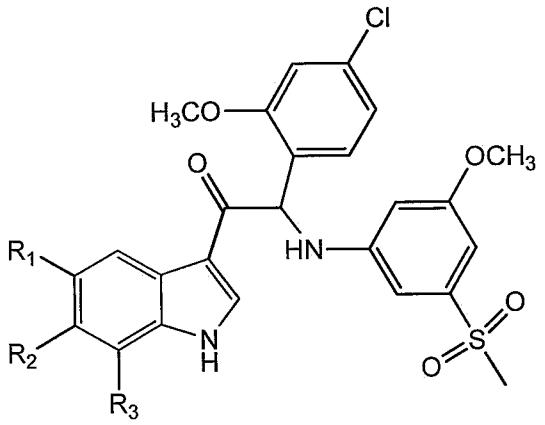
The present disclosure is based on the unexpected finding that at least one of the above-mentioned problems can be solved by the current compounds of the disclosure.

The present disclosure provides compounds which have been shown to possess potent antiviral activity against all four (4) serotypes currently known. The present disclosure furthermore demonstrates that these compounds efficiently inhibit proliferation of Dengue virus (DENV). Therefore, these compounds constitute a useful class of potent compounds that can be used in the treatment and/or prevention of viral infections in animals, mammals and humans, more specifically for the treatment and/or prevention of infections with Dengue viruses.

The present disclosure furthermore relates to the use of such compounds as medicines and to their use for the manufacture of medicaments for treating and/or preventing viral infections, in particular with viruses belonging to the family of the Dengue viruses in animals or mammals, more in particular in humans. The disclosure also relates to methods for the preparation of all such compounds and to pharmaceutical compositions comprising them in an effective amount.

The present disclosure also relates to a method of treatment or prevention of dengue viral infections in humans by the administration of an effective amount of one or more such compounds, or a pharmaceutically acceptable salt thereof optionally in combination with one or more other medicines, like another antiviral agent or dengue vaccine or both, to a patient in need thereof.

One aspect of the disclosure is the provision of compounds of formula (I)

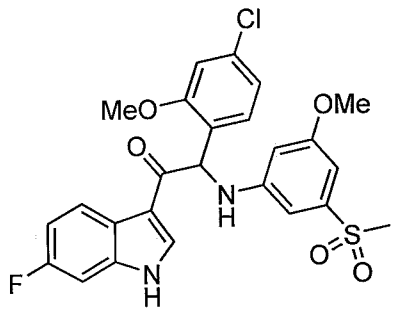


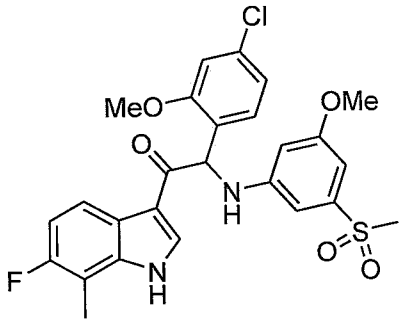
(I)

a stereo-isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof comprising a mono- or di-substituted indole group; said compound is selected from the group wherein:

R_1 is H, R_2 is F and R_3 is H or CH_3,
R_1 is H, CH_3 or F, R_2 is OCH_3 and R_3 is H,
R_1 is H, R_2 is OCH_3 and R_3 is CH_3,
R_1 is CH_3, R_2 is F and R_3 is H,
R_1 is CF_3 or OCF_3, R_2 is H and R_3 is H,
R_1 is OCF_3, R_2 is OCH_3 and R_3 is H and
R_1 is OCF_3, R_2 is H and R_3 is CH_3.

In particular the compounds of the disclosure or their stereo-isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof are selected from the group:

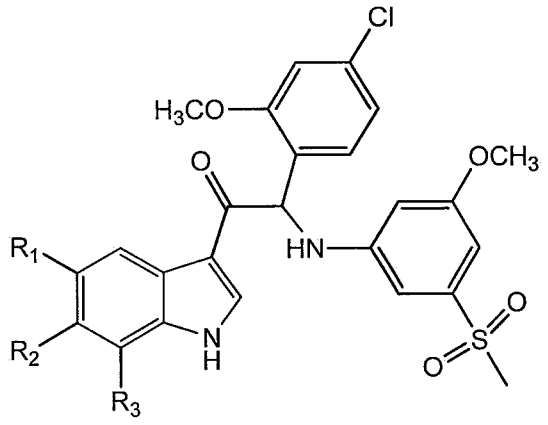




Another aspect of the disclosure is a compound of formula (I) or a stereo- isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof as defind herein or a pharmaceutical composition as defined herein for use as a medicament.

Another aspect of the disclosure is a compound of formula (I) or a stereo- isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof as defined herein or a pharmaceutical composition as defined herein for use in the treatment of dengue.

Another aspect of the disclosure is the use of a compound represented by the following structural formula (I)



(I)

a stereo-isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof comprising a mono- or di-substituted indole group; said compound is selected from the group wherein:

R_1 is H, R_2 is F and R_3 is H or CH_3,

R_1 is H, CH_3 or F, R_2 is OCH_3 and R_3 is H and

R_1 is H, R_2 is OCH_3 and R_3 is CH_3,

R_1 is CH_3, R_2 is F and R_3 is H,

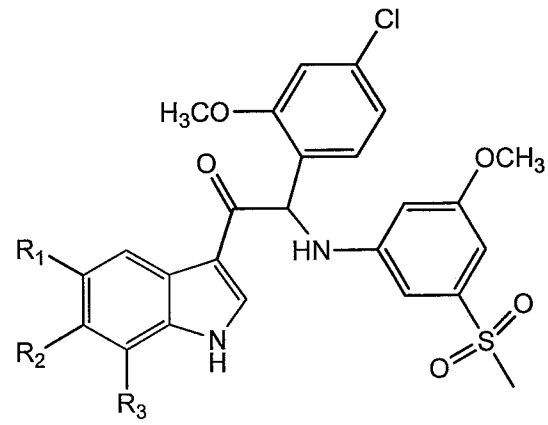
R_1 is CF_3 or OCF_3, R_2 is H and R_3 is H,

R_1 is OCF_3, R_2 is OCH_3 and R_3 is H and

R_1 is OCF_3, R_2 is H and R_3 is CH_3

in the manufacture of a medicament for the inhibition of replication of dengue virus(es) in a patient.

Another aspect of the disclosure is the use of a compound represented by the following structural formula (I)



(I)

a stereo-isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof comprising a mono- or di-substituted indole group; said compound is selected from the group wherein:

R_1 is H, R_2 is F and R_3 is H or CH_3,

R_1 is H, CH_3 or F, R_2 is OCH_3 and R_3 is H and

R_1 is H, R_2 is OCH_3 and R_3 is CH_3,

R_1 is CH_3, R_2 is F and R_3 is H,

R_1 is CF_3 or OCF_3, R_2 is H and R_3 is H,

R_1 is OCF_3, R_2 is OCH_3 and R_3 is H and

R_1 is OCF_3, R_2 is H and R_3 is CH_3

for inhibiting the replication of dengue virus(es) in a biological sample.

Another aspect of the current disclosure is a pharmaceutical composition comprising a compound of formula (I) or a stereo- isomeric form , a pharmaceutically acceptable salt, solvate or polymorph thereof together with one or more pharmaceutically acceptable excipients, diluents or carriers.

Pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition and base salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts. Suitable base salts are formed from bases which form non-toxic salts.

The compounds of the disclosure may also exist in un-solvated and solvated forms. The term “solvate” is used herein to describe a molecular complex comprising the

compound of the disclosure and one or more pharmaceutically acceptable solvent molecules, for example, ethanol.

The term "polymorph" refers to the ability of the compound of the disclosure to exist in more than one form or crystal structure.

The compounds of the present disclosure may be administered as crystalline or amorphous products. They may be obtained for example as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. They may be administered alone or in combination with one or more other compounds of the disclosure or in combination with one or more other drugs. Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the disclosure. The choice of excipient depends largely on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

The compounds of the present disclosure or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this disclosure, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, for example, for oral or rectal administration. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions, and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. Also included are solid form preparations that can be converted, shortly before use, to liquid forms.

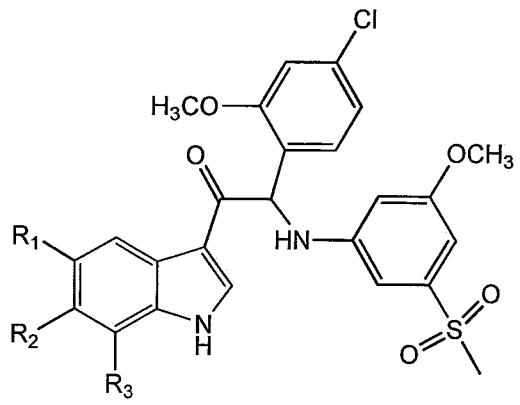
It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of

in the manufacture of a medicament for the inhibition of replication of dengue virus(es) in a patient.

7. The use of a compound according to claim 6 further comprising an additional therapeutic agent.

8. The use of claim 7 wherein said additional therapeutic agent is selected from an antiviral agent or dengue vaccine, or both.

9. A use of a compound represented by the following structural formula (I)



(I)

a stereo-isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof comprising a mono- or di-substituted indole group; said compound is selected from the group wherein:

R_1 is H, R_2 is F and R_3 is H or CH_3,
R_1 is H, CH_3 or F, R_2 is OCH_3 and R_3 is H and
R_1 is H, R_2 is OCH_3 and R_3 is CH_3,
R_1 is CH_3, R_2 is F and R_3 is H,
R_1 is CF_3 or OCF_3, R_2 is H and R_3 is H,
R_1 is OCF_3, R_2 is OCH_3 and R_3 is H and
R_1 is OCF_3, R_2 is H and R_3 is CH_3

for inhibiting the replication of dengue virus(es) in a biological sample.