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

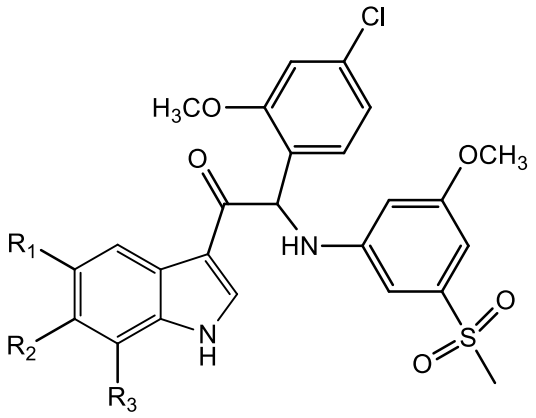
The present disclosure is based on the unexpected finding that at least one of the above-mentioned problems can be solved by the current compounds of the disclosure.

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.

The disclosure provides compounds of formula (I)

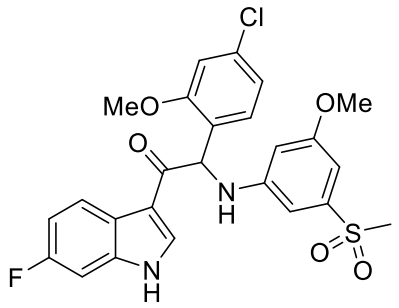


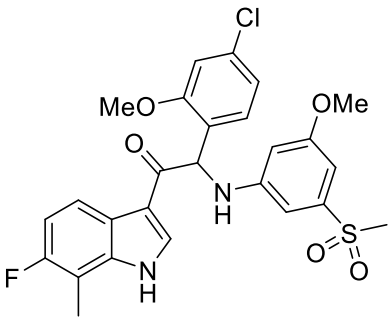
(I)

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:

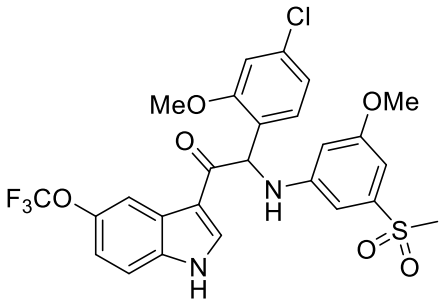
R_1 is H, R_2 is F and R_3 is H or CH_3,
R_1 is H, CH_3 or F, R_2 is OCH_3 and R_3 is H,
R_1 is H, R_2 is OCH_3 and R_3 is CH_3,
R_1 is CH_3, R_2 is F and R_3 is H,
R_1 is CF_3 or OCF_3, R_2 is H and R_3 is H,
R_1 is OCF_3, R_2 is OCH_3 and R_3 is H and
R_1 is OCF_3, R_2 is H and R_3 is CH_3.

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:



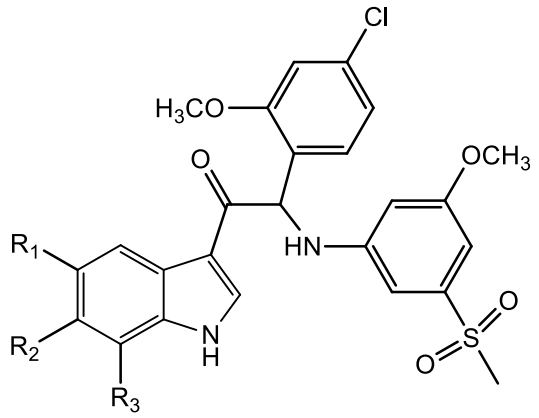


One aspect of the disclosure is a compound or its stereo-isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein said compound is:



.

The disclosure also provides 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,

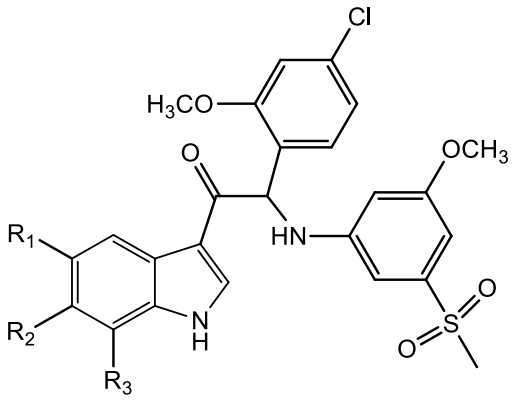
R_1 is CF_3 or OCF_3, R_2 is H and R_3 is H,

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 or patient.

Another aspect of the disclosure is 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; wherein:

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

in the manufacture of a medicament for inhibiting the replication of dengue virus(es) in a biological sample or patient

Part of the current disclosure is also 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. Another aspect of the disclosure is a pharmaceutical composition comprising a compound as defined herein 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.

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

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

Another aspect of the disclosure is a method for the synthesis of a compound as defined herein comprising the steps of:

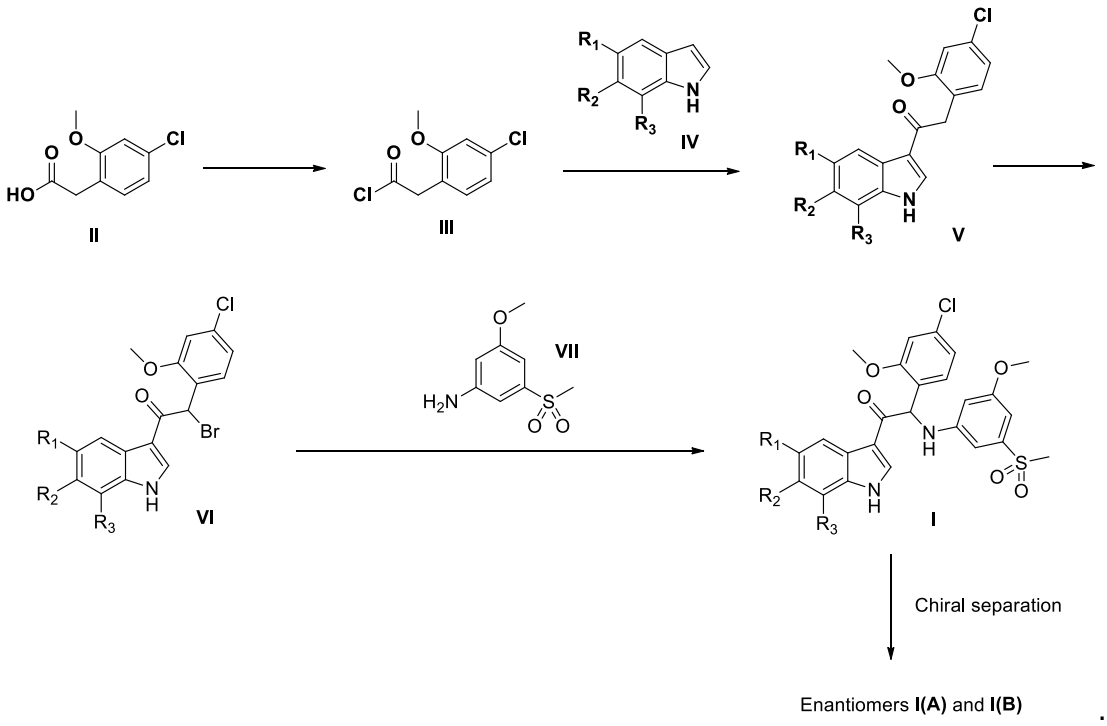
a) converting 2-(4-chloro-2-methoxyphenyl)acetic acid (**II**) to the corresponding 2-(4-chloro-2-methoxyphenyl)acetyl chloride (**III**) with a chlorination reagent;

b) Friedel-Crafts reaction of the acid chloride (**III**) with a substituted indole of general formula (**IV**) performed using a Lewis acid reagent in a suitable solvent and under suitable reaction conditions, to provide the 3-acylated indole of general formula (**V**), wherein R_1 is OCF_3, R_2 is H and R_3 is H;

c) bromination of (**V**) with a reagent in a suitable solvent, to provide the compounds of general formula (**VI**);

d) reaction of the compounds of general formula (**VI**) with 3-methoxy-5-(methylsulfonyl)-aniline (**VII**) in a suitable solvent and using a base to provide the compounds of general formula **I** as racemic mixtures;

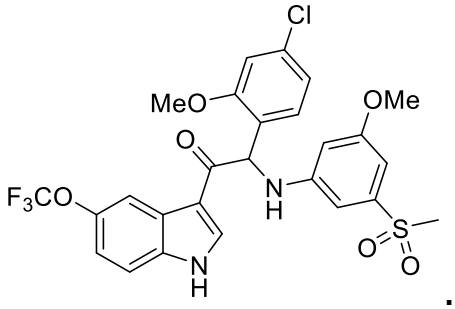
e) chiral separation of the compounds of general formula **I** to provide the enantiomers **A** and **B** of general formula **I**, wherein R_1 is OCF_3, R_2 is H and R_3 is H,



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

Claims

1. A compound or its stereo-isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein said compound is:



.

2. The compound according to claim 1, wherein said compound is: Enantiomer 9A, wherein

   ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.09 (s, 3 H) 3.73 (s, 3 H) 3.99 (s, 3 H) 6.26 (d, *J*=7.9 Hz, 1 H) 6.55 - 6.62 (m, 2 H) 6.91 (t, *J*=1.5 Hz, 1 H) 6.98 (dd, *J*=8.4, 2.0 Hz, 1 H) 7.07 (d, *J*=7.9 Hz, 1 H) 7.13 (d, *J*=2.0 Hz, 1 H) 7.21 (dd, *J*=8.8, 1.8 Hz, 1 H) 7.36 (d, *J*=8.4 Hz, 1 H) 7.59 (d, *J*=8.8 Hz, 1 H) 8.07 (d, *J*=0.9 Hz, 1 H) 8.55 (s, 1 H) 12.29 (br s, 1 H)

   LC/MS (method LC-A): R_t 1.20 min, MH^+ 583

   $[\alpha]_D^{20}$: +130.3° (c 0.555, DMF)

   Chiral SFC (method SFC-E): R_t 3.10 min, MH^+ 583, chiral purity 100%.

3. The compound according to claim 1, wherein said compound is: Enantiomer 9B, wherein

   ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.09 (s, 3 H) 3.73 (s, 3 H) 3.99 (s, 3 H) 6.26 (d, *J*=7.9 Hz, 1 H) 6.56 - 6.62 (m, 2 H) 6.92 (t, *J*=2.0 Hz, 1 H) 6.98 (dd, *J*=8.1, 2.0 Hz, 1 H) 7.07 (d, *J*=7.9 Hz, 1 H) 7.13 (d, *J*=2.0 Hz, 1 H) 7.22 (dd, *J*=8.8, 1.8 Hz, 1 H) 7.36 (d, *J*=8.4 Hz, 1 H) 7.59 (d, *J*=8.8 Hz, 1 H) 8.07 (d, *J*=0.9 Hz, 1 H) 8.55 (s, 1 H) 12.30 (br s, 1 H)

   LC/MS (method LC-A): R_t 1.20 min, MH^+ 583

   $[\alpha]_D^{20}$: -133.2° (c 0.5, DMF)

   Chiral SFC (method SFC-E): R_t 3.50 min, MH^+ 583, chiral purity 100%.

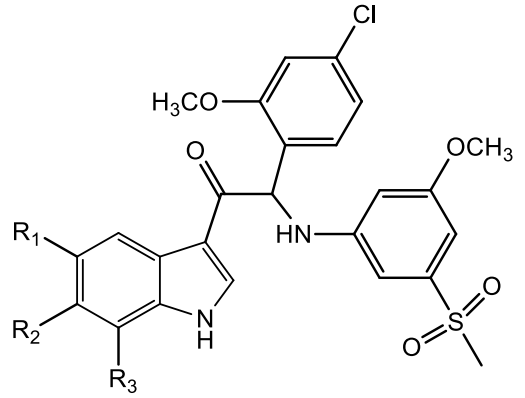
4. A pharmaceutical composition comprising a compound according to any one of claims 1-3 or a stereo- isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof, together with one or more pharmaceutically acceptable excipients, diluents or carriers.

5. A compound according to any one of claims 1-3 or a stereo- isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof, or a pharmaceutical composition according to claim 4 for use as a medicament.

6. A compound according to any one of claims 1-3 or a stereo- isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof, or a pharmaceutical composition according to claim 4 for use in the treatment of dengue.

7. The compound according to claim 6, wherein the compound is to be administered as a crystalline or amorphous product.

8. 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; wherein:
R_1 is OCF_3, R_2 is H and R_3 is H,

in the manufacture of a medicament for inhibiting the replication of dengue virus(es) in a biological sample or patient.

9. The use of a compound according to claim 8 further comprising an additional therapeutic agent to be co-administered.

10. The use of claim 9 wherein said additional therapeutic agent is selected from an antiviral agent or dengue vaccine, or both.

11. A method for the synthesis of a compound according to any one of claims 1 to 3 comprising the steps of:
    a) converting 2-(4-chloro-2-methoxyphenyl)acetic acid (**II**) to the corresponding 2-(4-chloro-2-methoxyphenyl)acetyl chloride (**III**) with a chlorination reagent;
    b) Friedel-Crafts reaction of the acid chloride (**III**) with a substituted indole of general formula (**IV**) performed using a Lewis acid reagent in a suitable solvent and under suitable reaction conditions, to provide the 3-acylated indole of general formula (**V**), wherein R_1 is OCF_3, R_2 is H and R_3 is H;
    c) bromination of (**V**) with a reagent in a suitable solvent, to provide the compounds of general formula (**VI**);
    d) reaction of the compounds of general formula (**VI**) with 3-methoxy-5-(methylsulfonyl)-aniline (**VII**) in a suitable solvent and using a base to provide the compounds of general formula **I** as racemic mixtures;
    e) chiral separation of the compounds of general formula **I** to provide the enantiomers **A** and **B** of general formula **I**, wherein R_1 is OCF_3, R_2 is H and R_3 is H,

