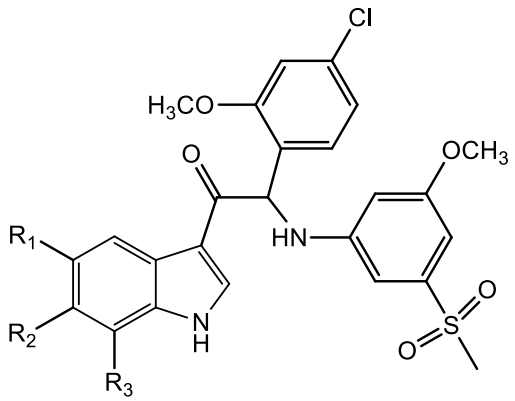
a stereo-isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof; wherein:

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~~.

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 the treatment of dengue viral infections.

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:

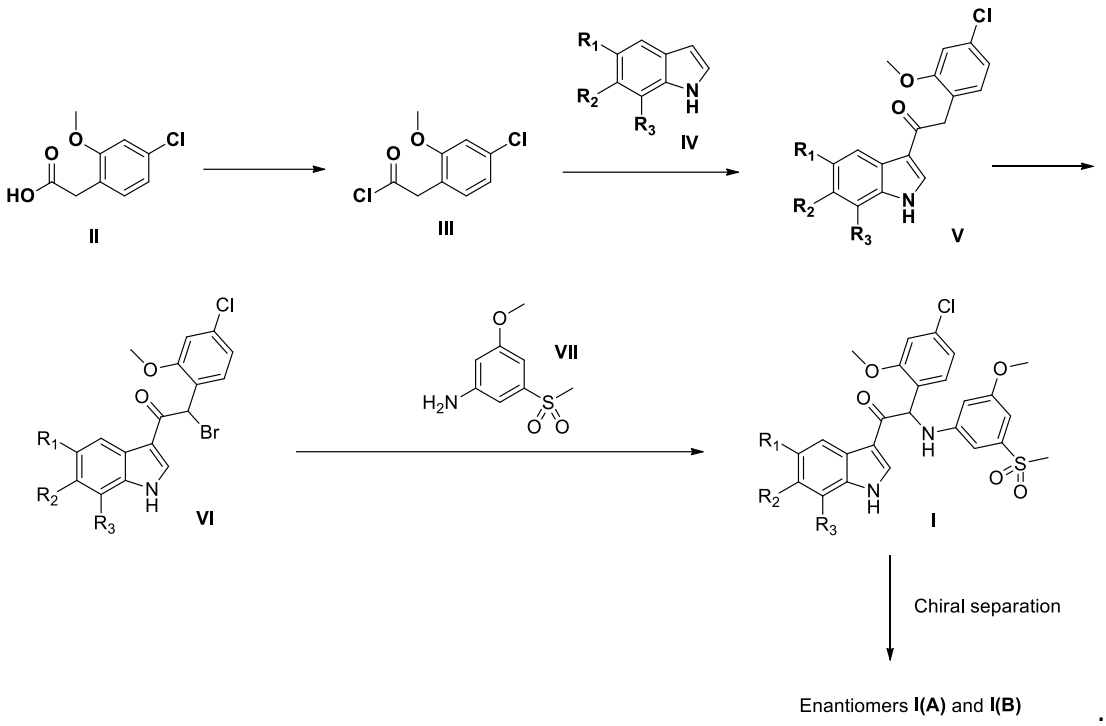
a) converting 2-(4-chloro-2-methoxyphenyl)acetic acid (**II**) to the corresponding 2-(4-chloro-2-methoxyphenyl)acetyl chloride (**III**) with a chlorination reagent;

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;

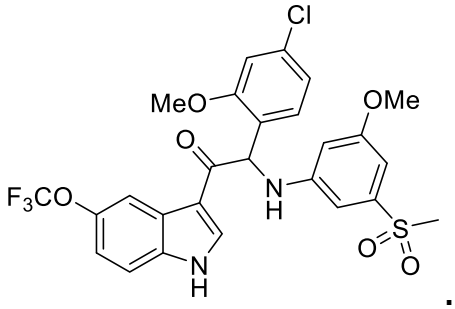
e) chiral separation of the compounds of general formula **I** to provide the enantiomers **A** and **B** of general formula **I**, wherein R_1 is OCF_3, R_2 is H and R_3 is H,



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%.

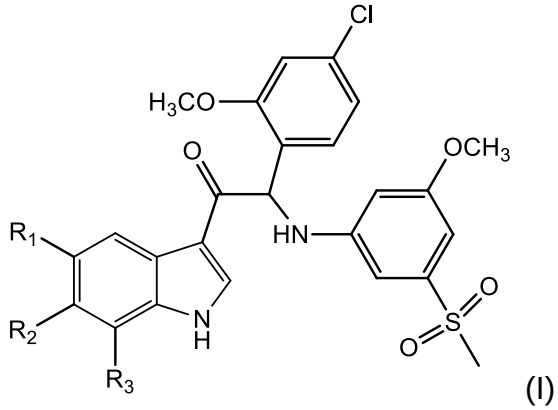
4. A pharmaceutical composition comprising a compound according to any one of claims 1-3 or a stereo- isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof, together with one or more pharmaceutically acceptable excipients, diluents or carriers.

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)



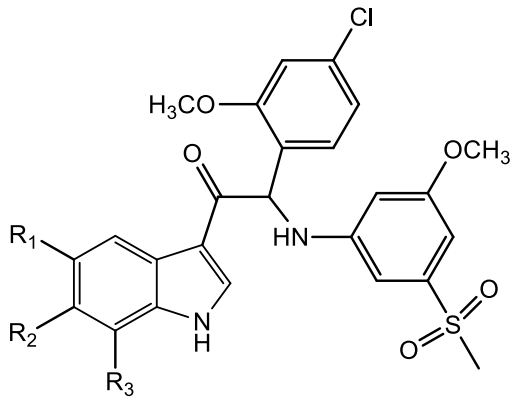
(I)

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



(I)

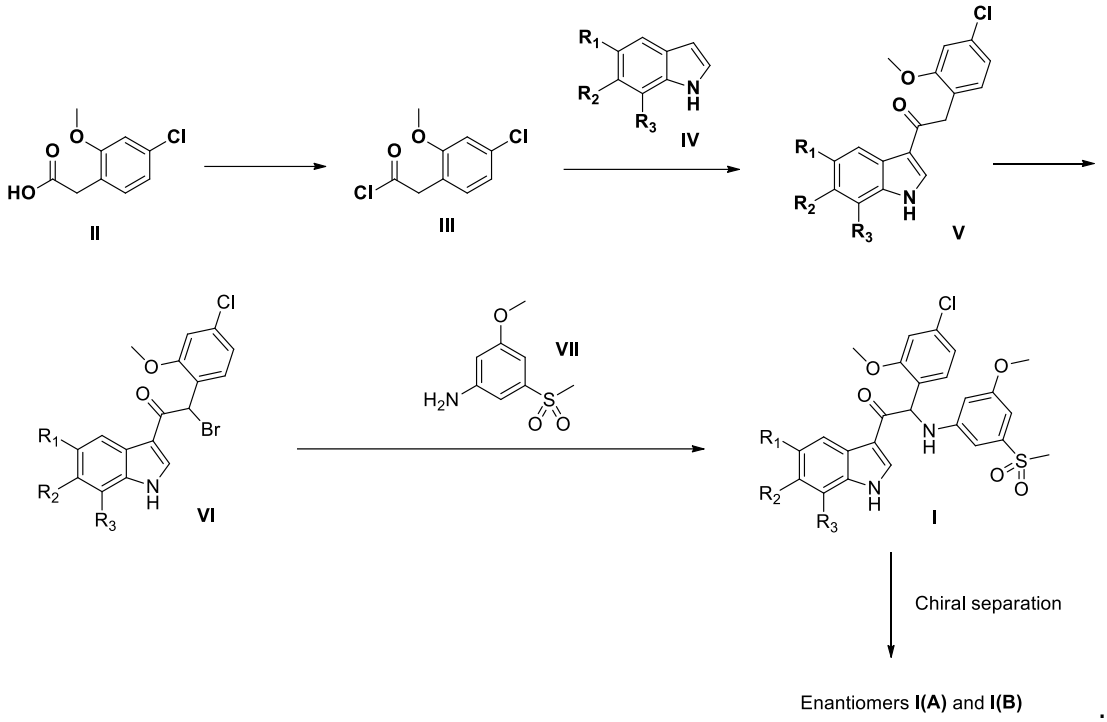
a stereo-isomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof; wherein:
R_1 is OCF_3, R_2 is H and R_3 is H,
in the manufacture of a medicament for the treatment of dengue viral infections.

~~9.~~10. The use of a compound according to claim ~~8~~ 9 further comprising an additional therapeutic agent to be co-administered.

~~10.~~11. The use of claim ~~9~~ 10 wherein said additional therapeutic agent is selected from an antiviral agent or dengue vaccine, or both.

~~11~~12. 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,


II
III
IV
V
VI
VII
I
Chiral separation
Enantiomers I(A) and I(B)