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.

WO-2010/021878 discloses 2-phenylpyrrolidine and indoline derivatives as cold menthol receptor antagonists for treatment of inflammatory and central diseases. WO-2013/045516 discloses indole and indoline derivatives for use in the treatment of dengue viral infections.

The present invention now provides compounds, substituted indoline derivatives, which show high potent activity against all four (4) serotypes of the Dengue virus.

SUMMARY

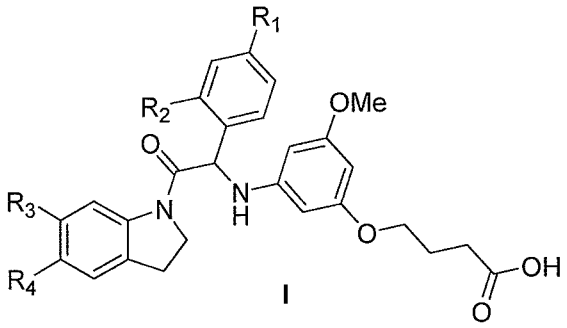
The present disclosure is based on the unexpected finding that at least one of the above-mentioned problems can be solved by the current compounds of the disclosure.

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.

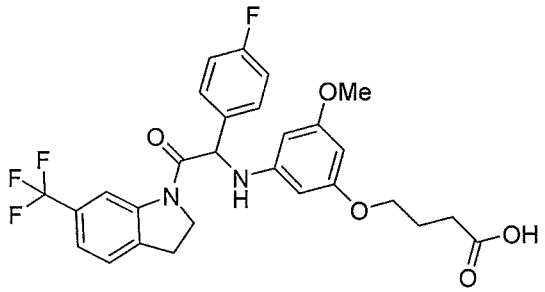
The present disclosure also relates to a method of treatment or prevention of dengue viral infections in humans by the administration of an effective amount of one or more such compounds, or a pharmaceutically acceptable salt thereof optionally in combination with one or more other medicines, like another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

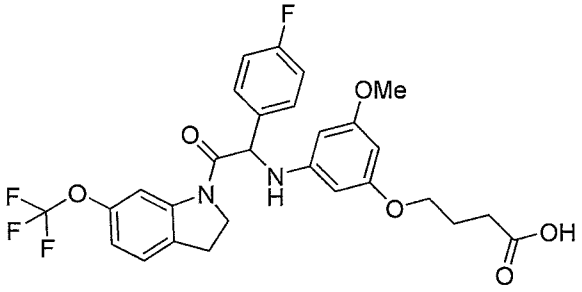
One aspect of the disclosure is the provision of compounds having formula (I), a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof:

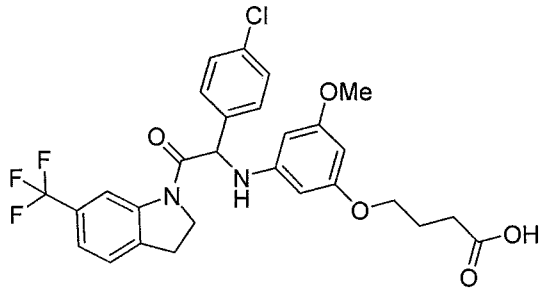


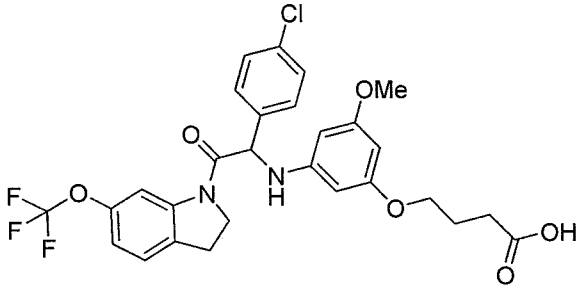
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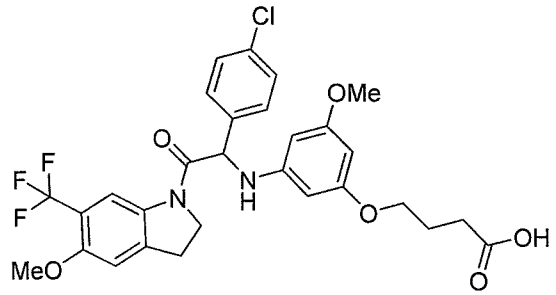
wherein the compounds are selected from the group comprising:

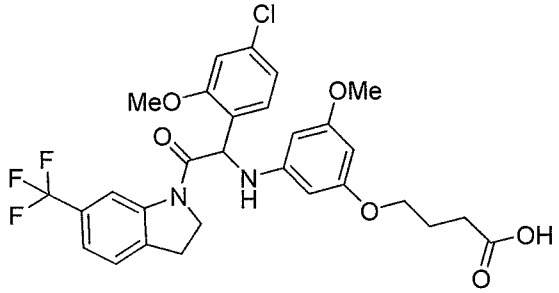


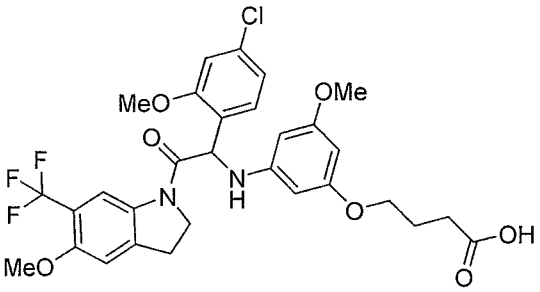
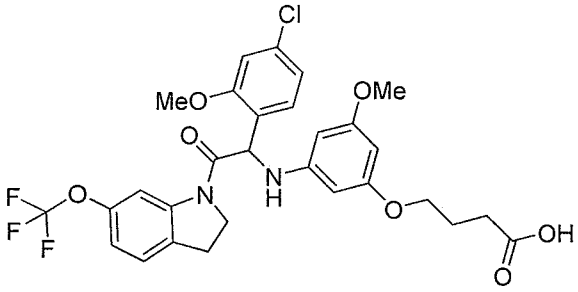
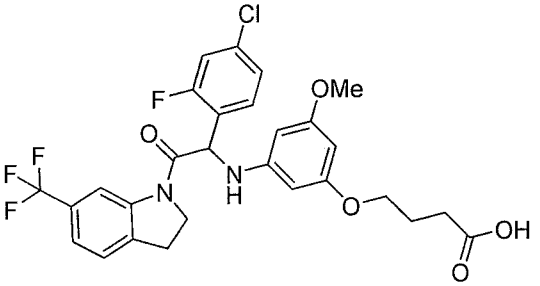
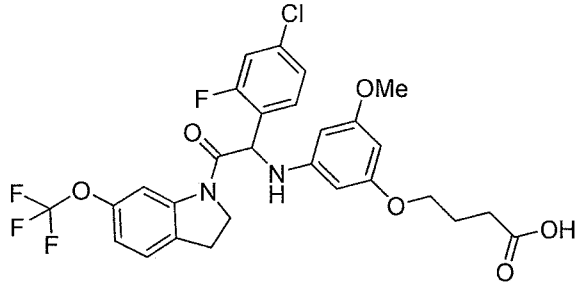
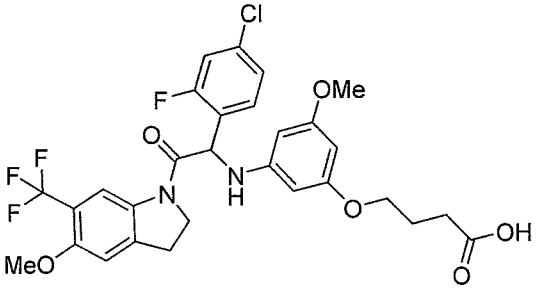
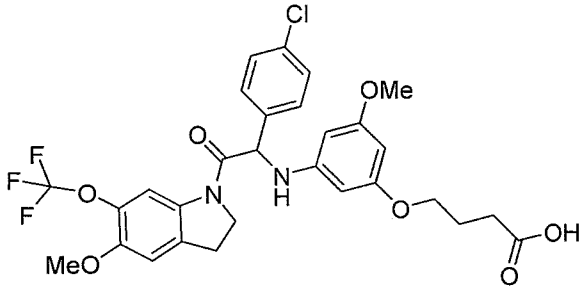




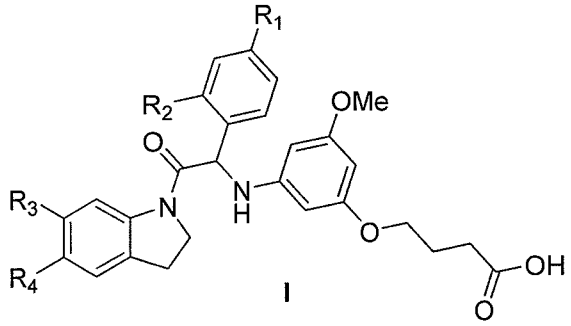






In an alternative embodiment, the present disclosure relates to a compound having formula (I)



I

a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein

R_1 is fluoro, R_2 is hydrogen, R_3 is trifluoromethyl, and R_4 is hydrogen; or

R_1 is fluoro, R_2 is hydrogen, R_3 is trifluoromethoxy, and R_4 is hydrogen; or

R_1 is chloro, R_2 is hydrogen, R_3 is trifluoromethyl, and R_4 is hydrogen; or

R_1 is chloro, R_2 is hydrogen, R_3 is trifluoromethoxy, and R_4 is hydrogen; or

R_1 is chloro, R_2 is hydrogen, R_3 is trifluoromethyl, and R_4 is methoxy; or

R_1 is chloro, R_2 is methoxy, R_3 is trifluoromethyl, and R_4 is hydrogen; or
R_1 is chloro, R_2 is methoxy, R_3 is trifluoromethyl, and R_4 is methoxy; or
R_1 is chloro, R_2 is methoxy, R_3 is trifluoromethoxy, and R_4 is hydrogen; or
R_1 is chloro, R_2 is fluoro, R_3 is trifluoromethyl, and R_4 is hydrogen; or
R_1 is chloro, R_2 is fluoro, R_3 is trifluoromethoxy, and R_4 is hydrogen; or
R_1 is chloro, R_2 is fluoro, R_3 is trifluoromethyl, and R_4 is methoxy; or
R_1 is chloro, R_2 is hydrogen, R_3 is trifluoromethoxy, and R_4 is methoxy.

Another aspect of the current disclosure is also a pharmaceutical composition comprising a compound mentioned above or a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof together with one or more pharmaceutically acceptable excipients, diluents or carriers.

Pharmaceutically acceptable salts of said compounds 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 current disclosure is a compound as defined herein or its stereoisomeric 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 current disclosure is a compound as defined herein or its stereoisomeric 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 current disclosure is a use of a compound as represented by any of the structural formula as defined herein, a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof in the manufacture of a medicament for inhibiting the replication of dengue virus(es) in a patient.

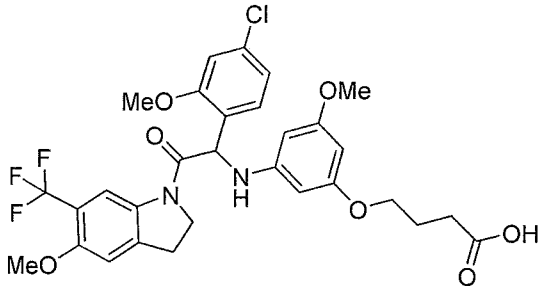
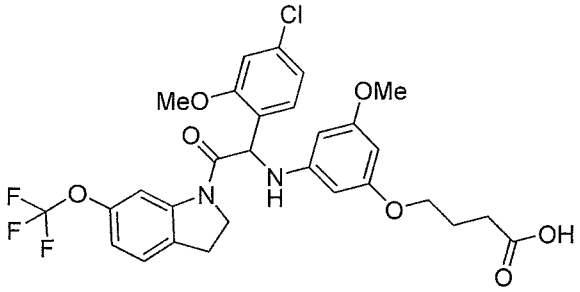
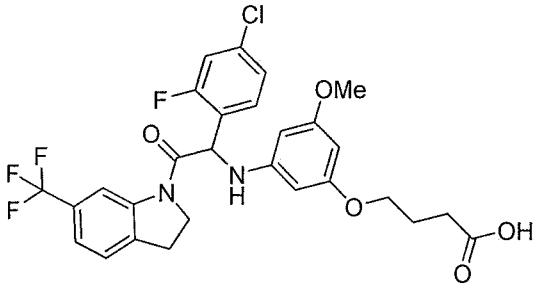
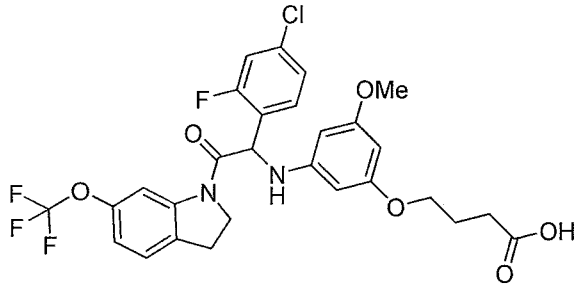
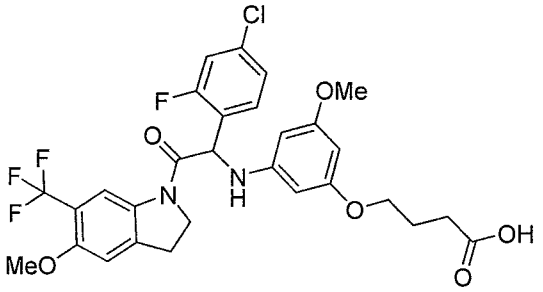
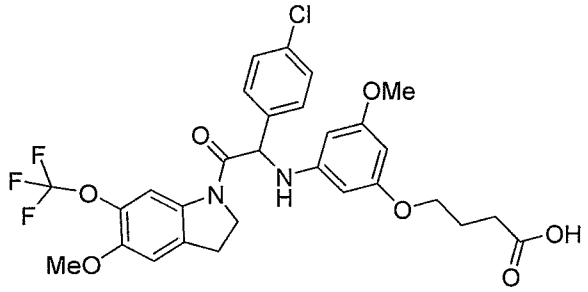
Another aspect of the current disclosure is a use of a compound as represented by any of the structural formula as defined herein, a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof for inhibiting the replication of dengue virus(es) in a biological sample.

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

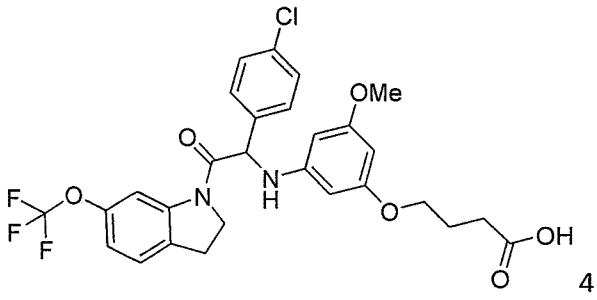
The term "polymorph" refers to the ability of the compound of the invention to exist in more than one form or crystal structure.

The compounds of the present invention 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 invention 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 invention. 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 invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As

2. A compound of formula 4 according to claim 1



4

a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof.

3. A compound, a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof according to any one of claims 1 or 2, wherein said compound is: Enantiomer 4A,
wherein

^{1}H NMR (500 MHz, DMSO-*d6*) δ ppm 1.87 (quin, *J*=6.7 Hz, 2 H) 2.34 (br t, *J*=7.3 Hz, 2 H) 3.08 - 3.27 (m, 2 H) 3.62 (s, 3 H) 3.85 (br t, *J*=6.3 Hz, 2 H) 3.99

- 4.11 (m, 1 H) 4.47 - 4.57 (m, 1 H) 5.57 (br s, 1 H) 5.76 (s, 1 H) 5.95 (br d, *J*=10.1 Hz, 2 H) 6.45 (br s, 1 H) 7.01 (br d, *J*=7.6 Hz, 1 H) 7.34 (br d, *J*=7.9 Hz, 1 H) 7.44 (br d, *J*=8.5 Hz, 2 H) 7.55 (br d, *J*=8.2 Hz, 2 H) 8.04 (br s, 1 H) 12.12 (br s, 1 H);
LC/MS (method LC-A): R_t 2.95 min, MH^+ 579;
$[\alpha]_D^{20}$: -48.5° (c 0.27, DMF);
Chiral SFC (method SFC-A): R_t 1.13 min, MH^+ 579, chiral purity 100%.

4. A compound, a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof according to any one of claims 1 or 2, wherein said compound is: Enantiomer 4B,
wherein,

^{1}H NMR (500 MHz, DMSO-*d6*) δ ppm 1.87 (br t, *J*=6.8 Hz, 2 H) 2.34 (br t, *J*=7.3 Hz, 2 H) 3.09 - 3.27 (m, 2 H) 3.62 (s, 3 H) 3.85 (br t, *J*=6.1 Hz, 2 H) 3.99 - 4.10 (m, 1 H) 4.46 - 4.59 (m, 1 H) 5.57 (s, 1 H) 5.76 (br s, 1 H) 5.95 (br d, *J*=10.1 Hz, 2 H) 6.45 (br s, 1 H) 7.01 (br d, *J*=7.9 Hz, 1 H) 7.34 (br d, *J*=7.9 Hz, 1 H) 7.44 (br d, *J*=8.2 Hz, 2 H) 7.55 (br d, *J*=8.2 Hz, 2 H) 8.04 (br s, 1 H) 12.12 (br s, 1 H)
LC/MS (method LC-A): R_t 2.94 min, MH^+ 579
$[\alpha]_D^{20}$: +42.9° (c 0.28, DMF)
Chiral SFC (method SFC-A): R_t 2.13 min, MH^+ 579, chiral purity 100%

5. A compound, a pharmaceutically acceptable salt, solvate, or polymorph thereof according to any one of claims 1 to 4, wherein said compound is in a crystalline form.

6. A compound, a pharmaceutically acceptable salt, or solvate thereof according to any one of claims 1 to 4, wherein said compound is in an amorphous form.

7. A compound, a pharmaceutically acceptable salt, solvate, or polymorph thereof according to any one of claims 1 to 4, wherein said compound is in an un-solvated form.

8. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7 or its stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof together with one or more pharmaceutically acceptable excipients, diluents or carriers.

9. A compound according to any one of claims 1 to 7 or its stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof or a pharmaceutical composition according to claim 8 for use as a medicament.

10. A compound according to any one of claims 1 to 7 or its stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof or a pharmaceutical composition according to claim 8 for use in the treatment of dengue.

11. A use of a compound as represented by any of the structural formula from any one of claims 1 to 7, a stereoisomeric form, a pharmaceutically acceptable salt, solvate or

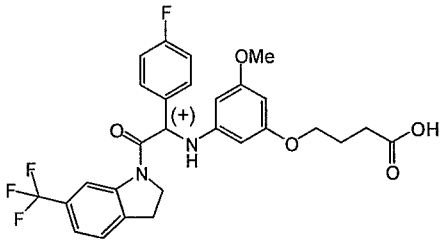
polymorph thereof in the manufacture of a medicament for inhibiting the replication of dengue virus(es) in a patient.

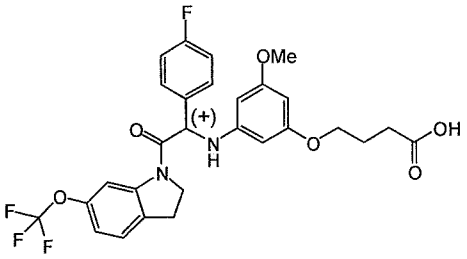
12. A use of a compound as represented by any of the structural formula from any one of claims 1 to 7, a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof for inhibiting the replication of dengue virus(es) in a biological sample.

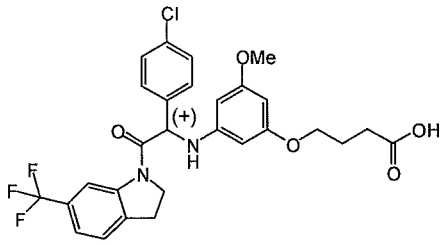
13. The use of a compound according to claim 11 or 12 further comprising an additional therapeutic agent.

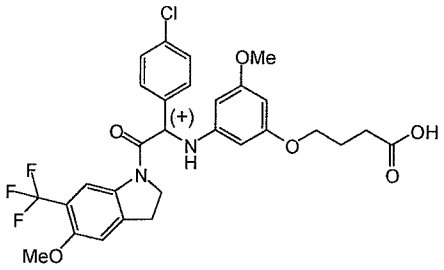
14. The use of claim 13 wherein said additional therapeutic agent is selected from an antiviral agent or dengue vaccine, or both.

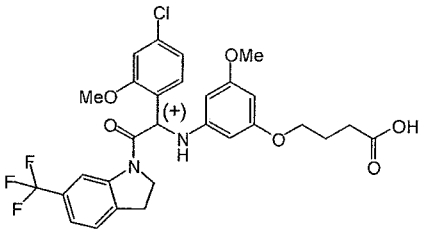
15. The compound as claimed in any one of claims 1 or 5-7, wherein the compound is

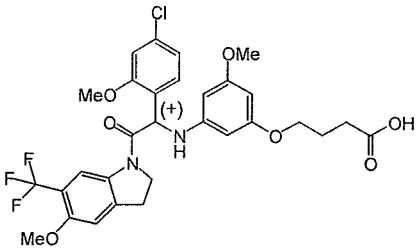


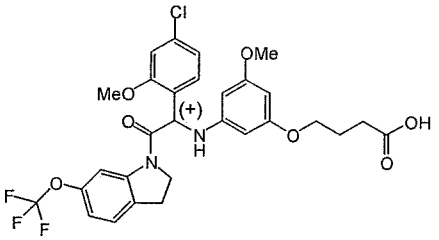


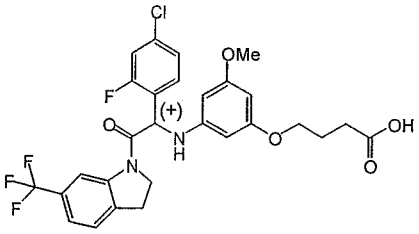


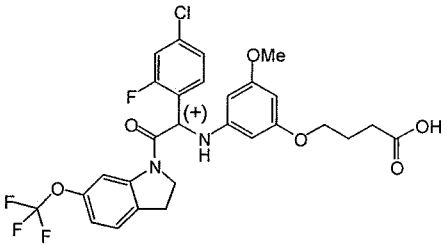


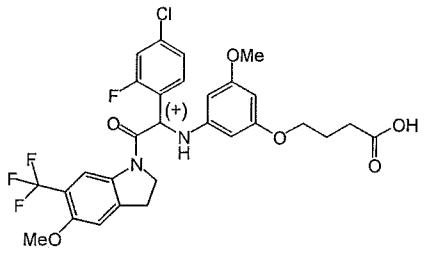
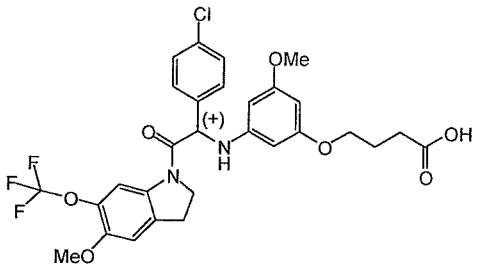






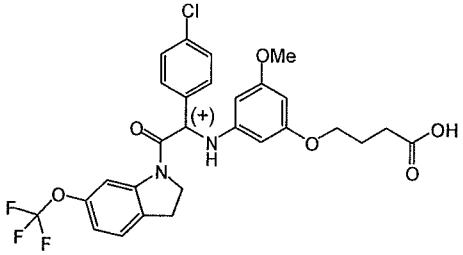




or a pharmaceutically acceptable salt, solvate or polymorph thereof.

16. The compound as claimed in any one of claims 1-2 or 5-7, wherein the compound is



or a pharmaceutically acceptable salt, solvate or polymorph thereof.

17. A pharmaceutical composition comprising a compound according to any one of claims 15 or 16, a pharmaceutically acceptable salt, solvate or polymorph thereof together with one or more pharmaceutically acceptable excipients, diluents or carriers.

18. A compound according to any one of claims15 or 16, a pharmaceutically acceptable salt, solvate or polymorph thereof or a pharmaceutical composition according to claim 17 for use as a medicament.

19. A compound according to any one of claims15 or 16, a pharmaceutically acceptable salt, solvate or polymorph thereof or a pharmaceutical composition according to claim 17 for use in the treatment of dengue.

20. A use of a compound as represented by any of the structural formula from any one of claims15 or 16, a pharmaceutically acceptable salt, solvate or polymorph thereof in the manufacture of a medicament for inhibiting the replication of dengue virus(es) in a patient.

21. A use of a compound as represented by any of the structural formula from any one of claims 15 or 16, a pharmaceutically acceptable salt, solvate or polymorph thereof for inhibiting the replication of dengue virus(es) in a biological sample.

22. The use according to claim 21 which use further comprises an additional therapeutic agent.

23. The use according to claim 22 wherein said additional therapeutic agent is selected from an antiviral agent or dengue vaccine, or both.