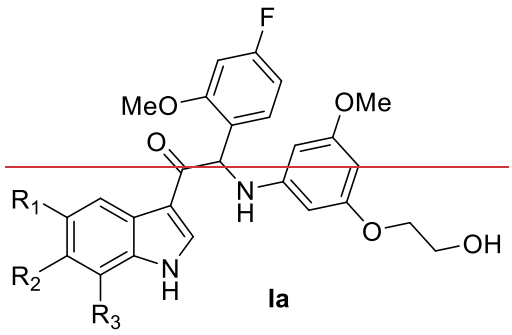
One aspect of the disclosure is the provision of a compound of formula (Ia, Ib, II, III or IV) wherein formula (Ia) is represented by:



Ia

a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof; said compound is selected from the group wherein:

R_1 is Cl, R_2 is H, R_3 is CH_3;

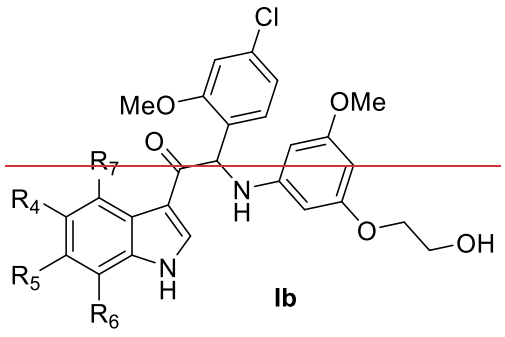
R_1 is Cl, R_2 is OCH_3 , R_3 is H;

R_1 is CH_3, R_2 is F or OCF_3 or H or OCH_2CH_3 and R_3 is H;

R_1 and R_2 are connected forming a heterocycle of 5 members having one oxygen atom, R_3 is H;

R_2 and R_3 are connected forming a heterocycle of 5 members having one oxygen atom, R_1 is H;

or wherein formula (Ib) is represented by:



Ib

a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof; said compound is selected from the group wherein:

R_4 is CH_3, R_5 is F, R_6 and R_7 are both H;

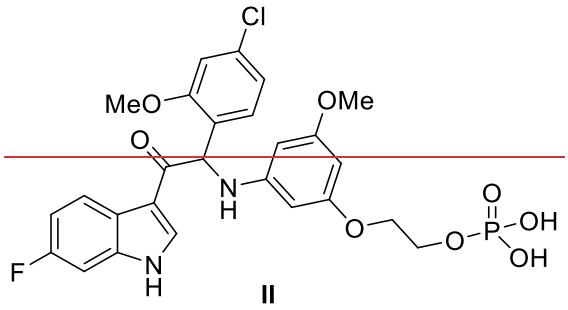
R_4 is CH_3, R_5 is OCH_3, R_6 is H, R_7 is F;

R_4 is SF_5, $R_5 = R_6 = R_7$ are all H;

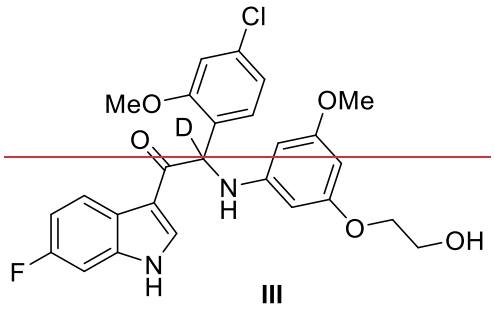
R_4 and R_5 are connected forming a heterocycle of 5 members having one oxygen atom, R_6 and R_7 are both H;

R_5 and R_6 are connected forming a heterocycle of 5 members having one oxygen atom, R_4 and R_7 are both H

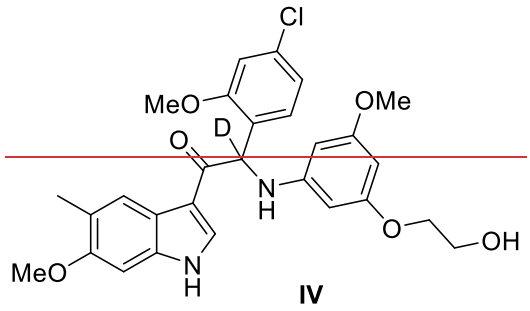
and wherein compounds (II, III and IV) respectively are represented by:



II



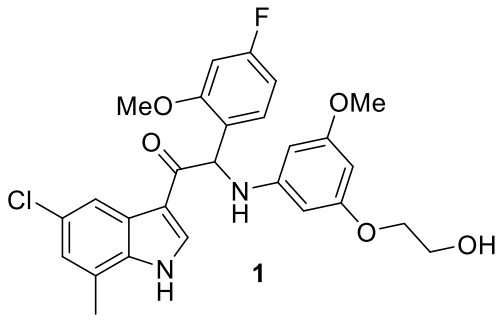
III



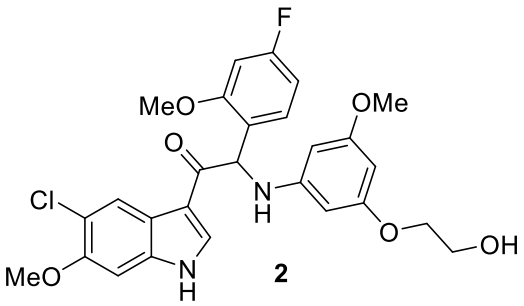
IV

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

One aspect of the disclosure is the provision of a compound or its stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof wherein said compound is selected from the group:



1



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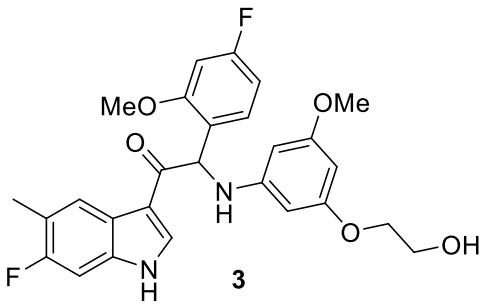

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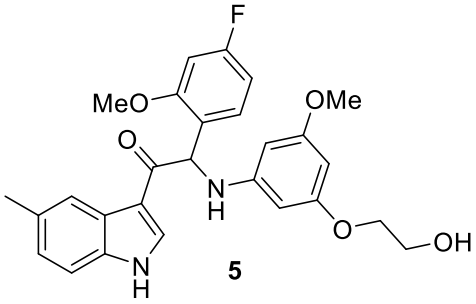

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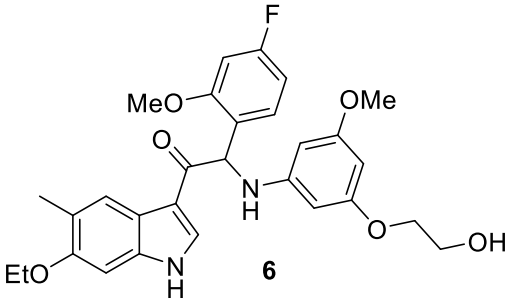

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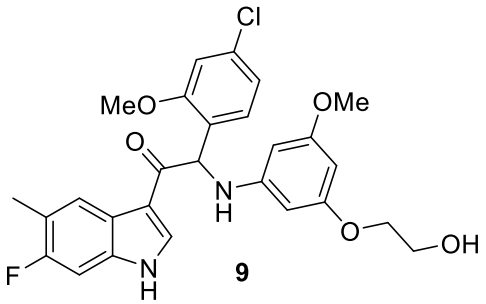

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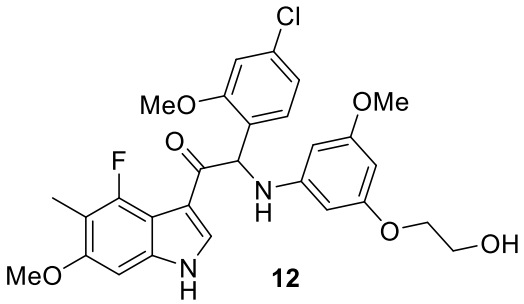

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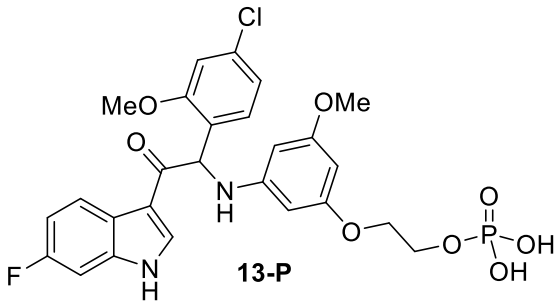
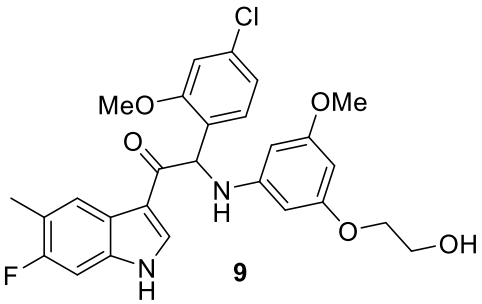


13-P

One embodiment of the disclosure is the provision of compounds of formula (Ia or Ib).



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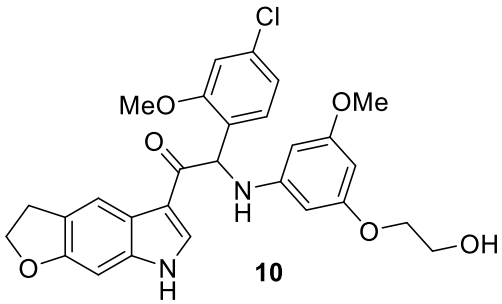

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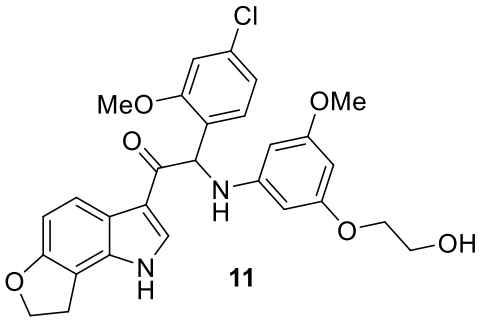

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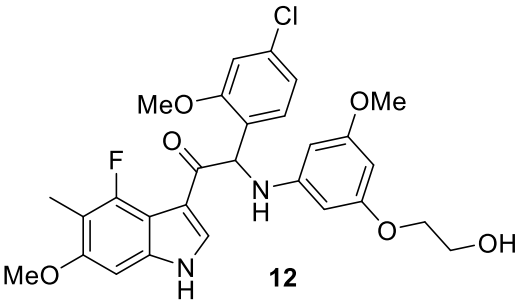

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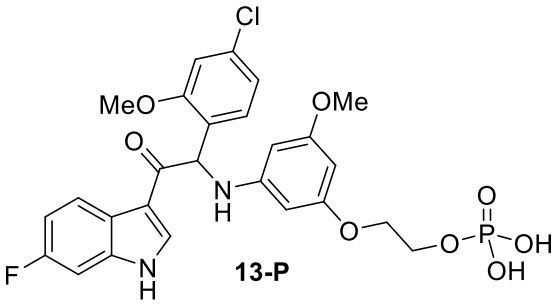
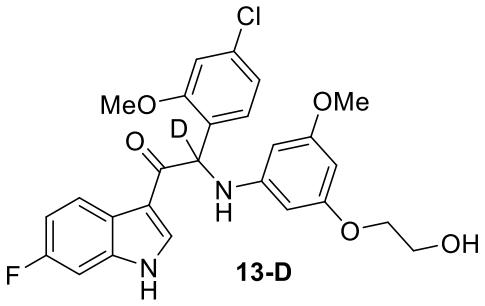
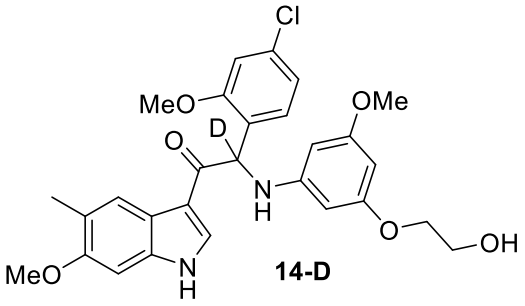


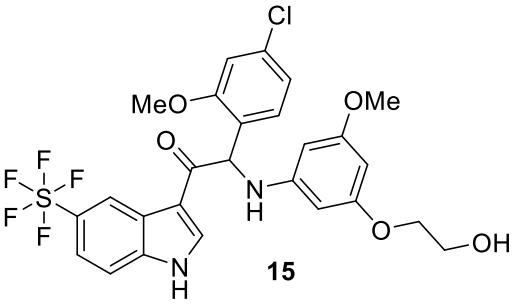
13-P



13-D



14-D



15

Another aspect of the current disclosure is also a pharmaceutical composition comprising a compound of formula (Ia, Ib, II, III or IV) or a compound as defined herein 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 the compounds of formula (Ia, Ib, II, III or IV) 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.

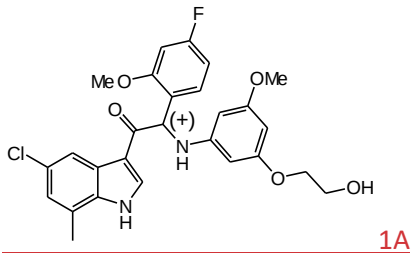
Another aspect of the current disclosure is a compound as defined herein ~~of formula (Ia, Ib, II, III or IV)~~ or a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof ~~as defined herein~~ or a pharmaceutical composition as defined herein for use as a medicament.

Another aspect of the current disclosure is a compound ~~of formula (Ia, Ib, II, III or IV)~~ as defined herein or a stereoisomeric 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.

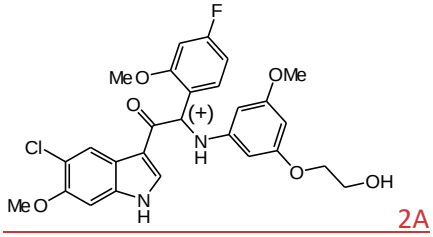
Another aspect of the current disclosure is use of a compound as represented by any of the structural formula as defined herein, a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof in the manufacture of a medicament for inhibiting the replication of dengue virus(es)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

Another aspect of the current disclosure is 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.

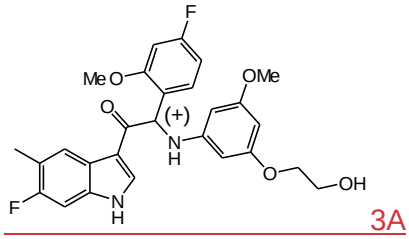
Another aspect of the current disclosure is a compound selected from



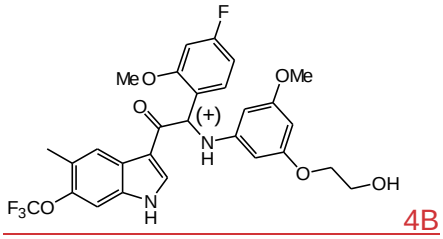
1A



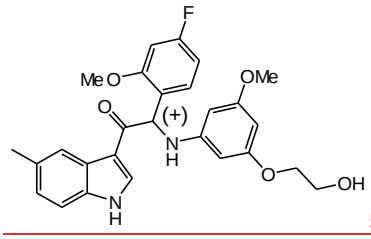
2A

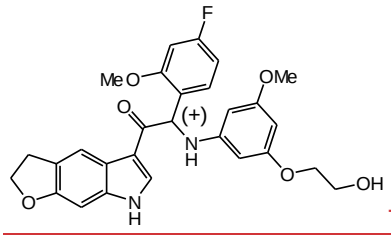


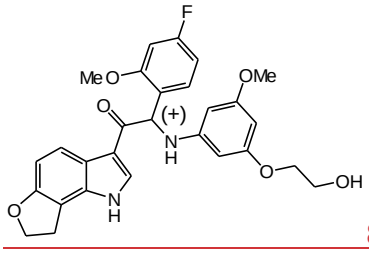
3A

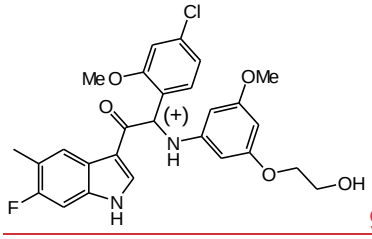


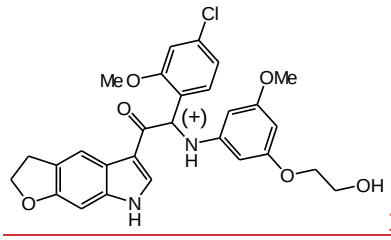
4B


5A


7A


8A


9B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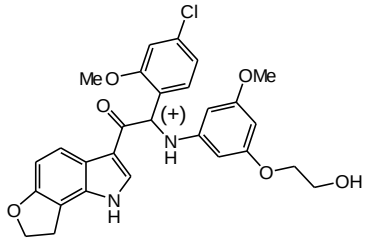
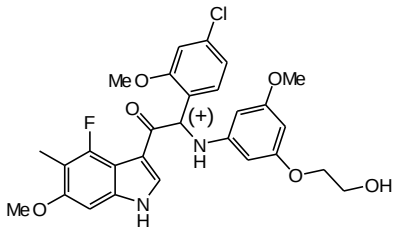
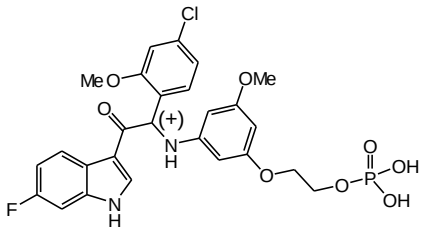
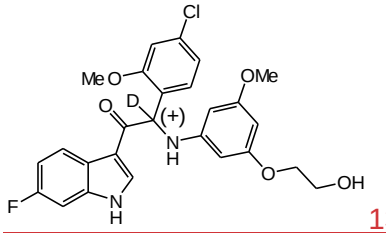
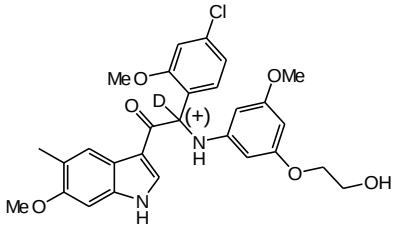
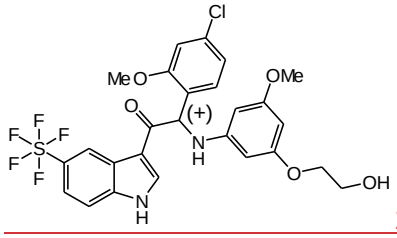

11A

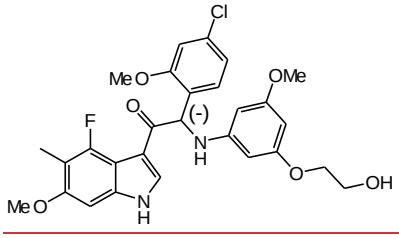

12B


13A-P


13A-D


14A-D


15A


12A

or a pharmaceutically acceptable salt, solvate or polymorph thereof.

Another aspect of the current disclosure is a pharmaceutical composition comprising a compound as defined herein, a pharmaceutically acceptable salt, solvate or polymorph thereof together with one or more pharmaceutically acceptable excipients, diluents or carriers.

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

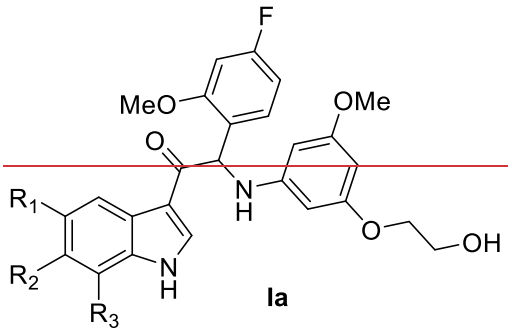
The compounds of the invention may also exist in un-solvated and solvated forms. The term “solvate” is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol.

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.

Claims

1. A compound of formula (Ia, Ib, II, III or IV) wherein formula (Ia) is represented by:



Ia

a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof; said compound is selected from the group wherein:

R_1 is Cl, R_2 is H, R_3 is CH_3;

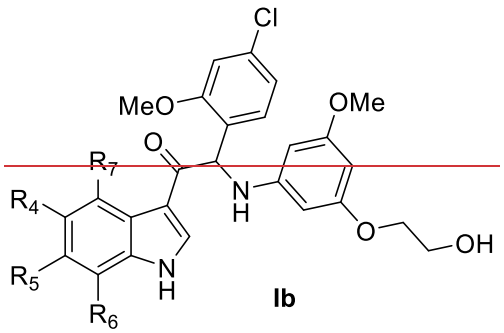
R_1 is Cl, R_2 is OCH_3 , R_3 is H;

R_1 is CH_3, R_2 is F or OCF_3 or H or OCH_2CH_3 and R_3 is H;

R_1 and R_2 are connected forming a heterocycle of 5 members having one oxygen atom, R_3 is H;

R_2 and R_3 are connected forming a heterocycle of 5 members having one oxygen atom, R_1 is H;

or wherein formula (Ib) is represented by:



Ib

a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof; said compound is selected from the group wherein:

R_4 is CH_3, R_5 is F, R_6 and R_7 are both H;

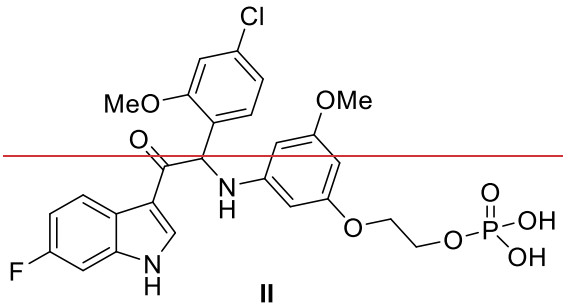
R_4 is CH_3, R_5 is OCH_3, R_6 is H, R_7 is F;

R_4 is SF_5, R_5 = R_6 = R_7 are all H;

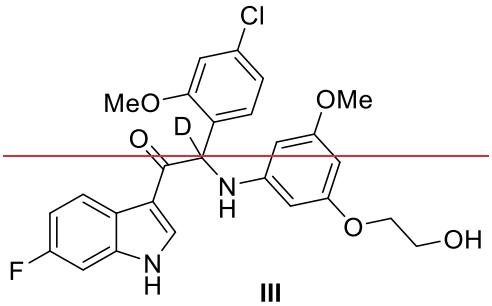
~~R_4 and R_5 are connected forming a heterocycle of 5 members having one oxygen atom, R_6 and R_7 are both H;~~

~~R_5 and R_6 are connected forming a heterocycle of 5 members having one oxygen atom, R_4 and R_7 are both H~~

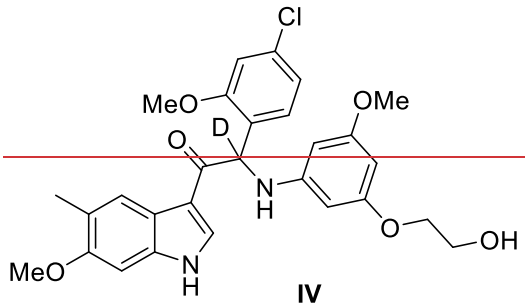
~~and wherein compounds (II, III and IV) respectively are represented by:~~



II



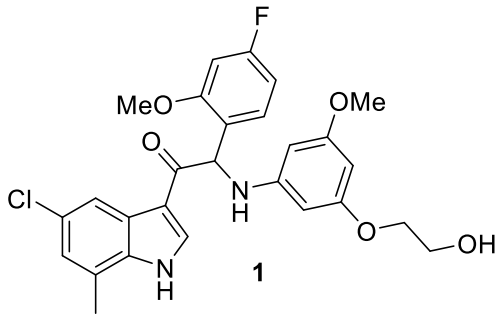
III



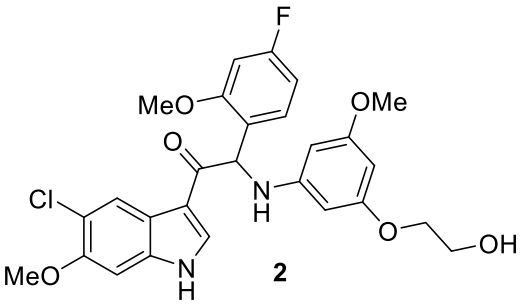
IV

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

~~2.~~1. A compound or its stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof ~~according to claim 1~~ wherein said compound is selected from the group:



1



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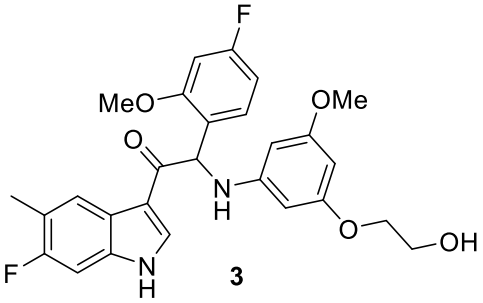

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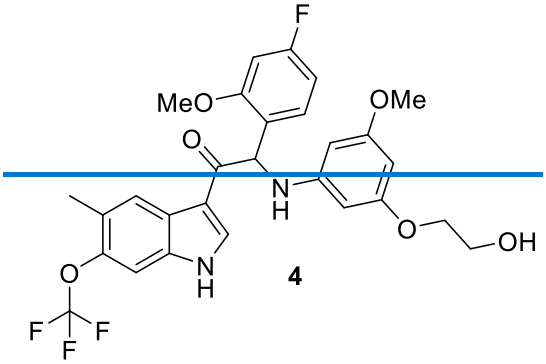

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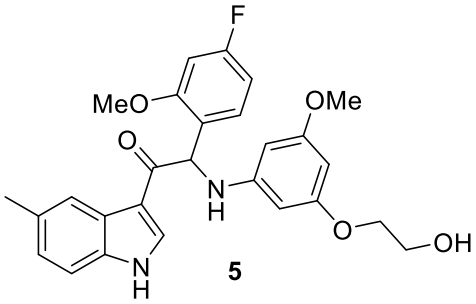
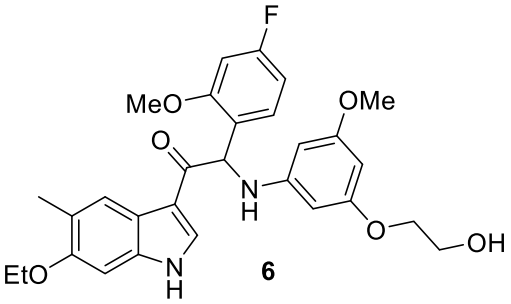


5



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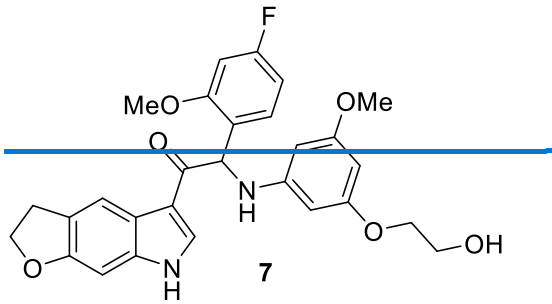

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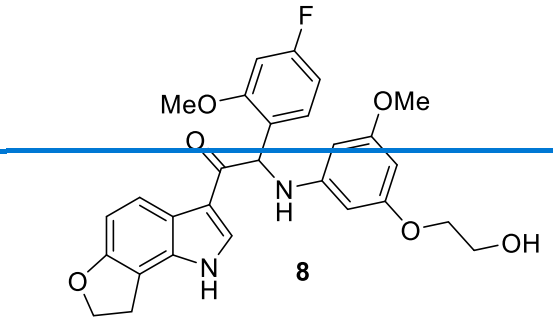

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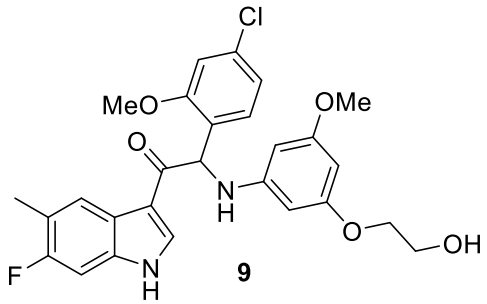

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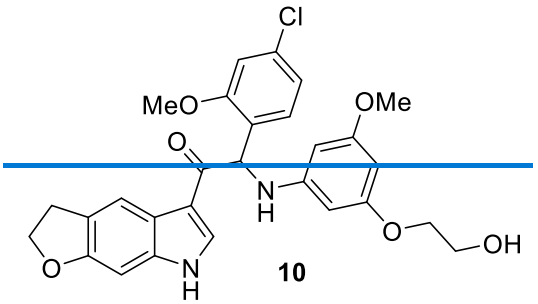

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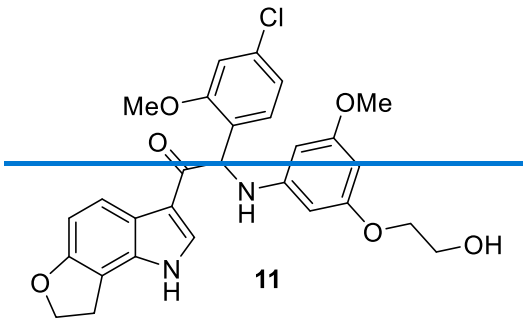

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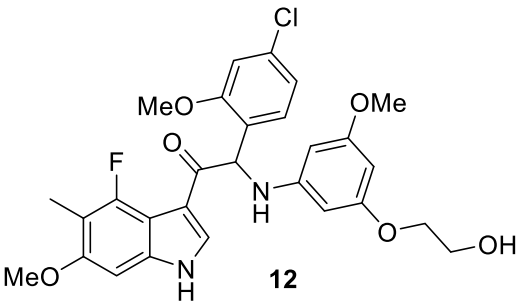
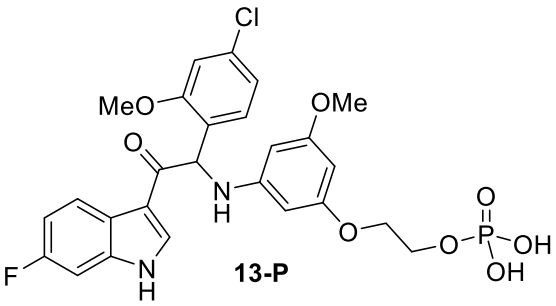
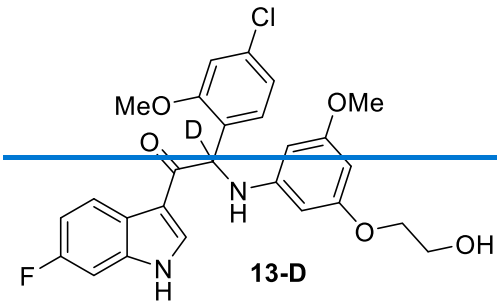


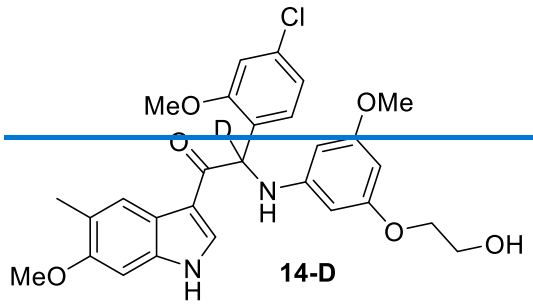
12



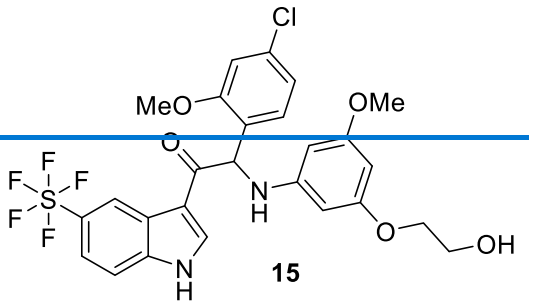
13-P



13-D



14-D



15

3.2. A pharmaceutical composition comprising a compound ~~of formula (Ia, Ib, II, III or IV)~~ according to claim 1 or a stereoisomeric form~~-~~, a pharmaceutically acceptable salt, solvate or polymorph thereof ~~according to claim 1 or 2~~ together with one or more pharmaceutically acceptable excipients, diluents or carriers.

4.3. A compound ~~of formula (Ia, Ib, II, III or IV)~~ according to claim 1 or a stereoisomeric form~~-~~, a pharmaceutically acceptable salt, solvate or polymorph thereof ~~according to claim 1~~ or a pharmaceutical composition according to claim ~~3~~ 2 for use as a medicament.

5.4. A compound ~~of formula (Ia, Ib, II, III or IV)~~ according to claim 1 or a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof ~~according to claim 1~~ or a pharmaceutical composition according to claim ~~3~~ 2 for use in the treatment of dengue.

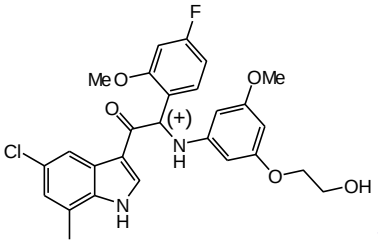
6.5. A use of a compound as represented by any of the structural formula from claim~~s~~ 1~~-5~~, a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof in the manufacture of a medicament for inhibiting the replication of dengue virus(es) in a patient.

7.6. A use of a compound as represented by any of the structural formula from claim~~s~~ 1~~-5~~, a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof for inhibiting the replication of dengue virus(es) in a biological sample.

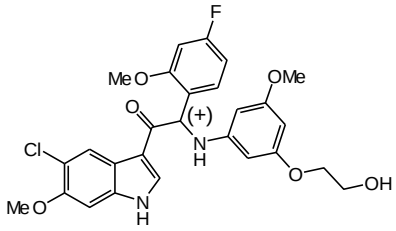
8.7. The use of a compound according to claim ~~6~~ 5 or ~~7~~ 6 further comprising an additional therapeutic agent.

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

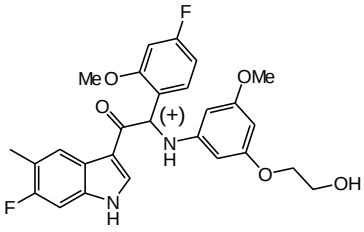
~~10.~~9. ~~The~~ A compound ~~as claimed in claim 1 wherein the compound is~~ selected from



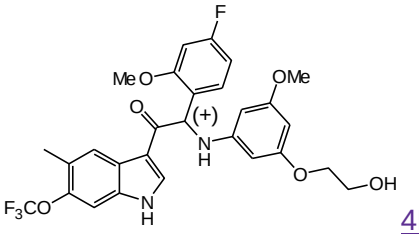
1A



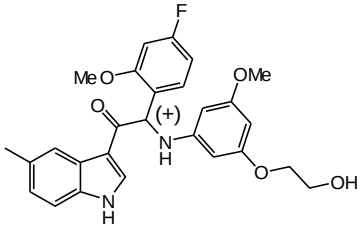
2A



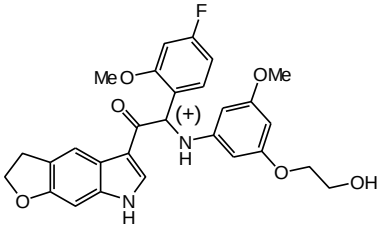
3A



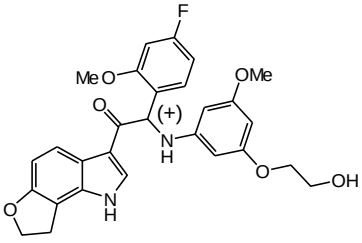
4B



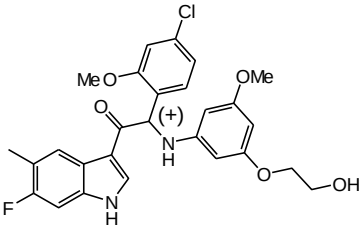
5A



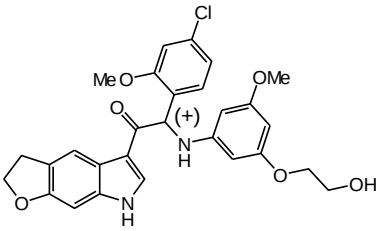
7A



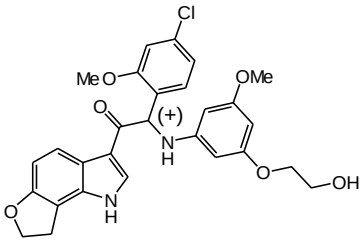
8A



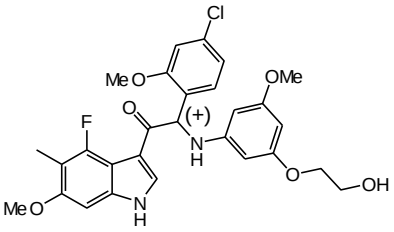
9B



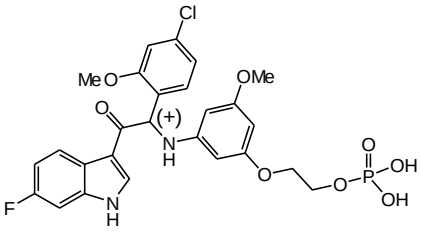
10B



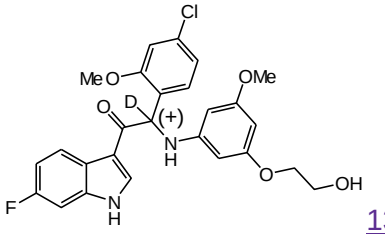
11A



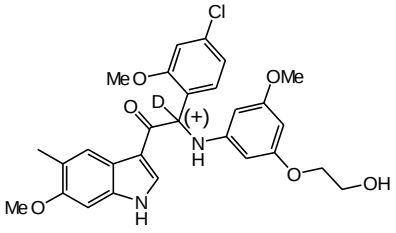
12B



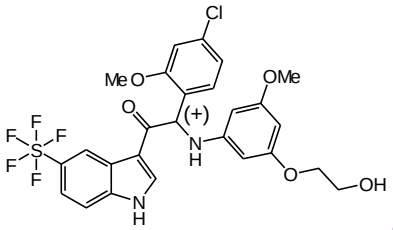
13A-P



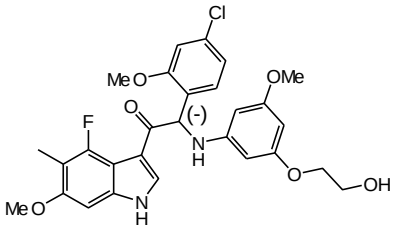
13A-D



14A-D



15A



12A

or a pharmaceutically acceptable salt, solvate or polymorph thereof.

10. ~~11.~~ A pharmaceutical composition comprising a compound according to claim ~~10~~9, a pharmaceutically acceptable salt, solvate or polymorph thereof together with one or more pharmaceutically acceptable excipients, diluents or carriers.

~~12~~11. A compound according to claim ~~10~~9, a pharmaceutically acceptable salt, solvate or polymorph thereof or a pharmaceutical composition according to claim ~~11~~ 10 for use as a medicament.

~~13~~12. A compound according to claim ~~10~~9, a pharmaceutically acceptable salt, solvate or polymorph thereof or a pharmaceutical composition according to claim ~~11~~ 10 for use in the treatment of dengue.

~~14~~13. A use of a compound as represented by any of the structural formula from claim ~~10~~9, 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.

~~15~~14. A use of a compound as represented by any of the structural formula from claim ~~10~~9, a pharmaceutically acceptable salt, solvate or polymorph thereof for inhibiting the replication of dengue virus(es) in a biological sample.

~~16~~15. The use according to claim ~~14~~ 13 or ~~15~~ 14 which use further comprises an additional therapeutic agent.

~~17~~16. The use according to claim ~~16~~ 15 wherein said additional therapeutic agent is selected from an antiviral agent or dengue vaccine, or both.