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 indole derivatives, which show high potent activity against all four (4) serotypes of the Dengue virus.

SUMMARY

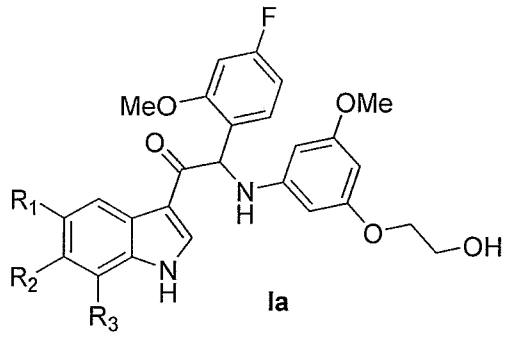
The present disclosure is based on the unexpected finding that at least one of the above-mentioned problems can be solved by the current compounds of the disclosure.

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 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 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 comprising a mono- or di-substituted indole group; said compound is selected from the group wherein:

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

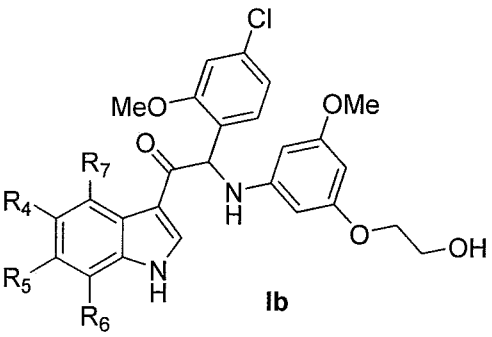
R_1 is Cl, R_2 is OCH_3 , R_3 is H;

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 comprising a mono- or di-substituted indole group; 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;

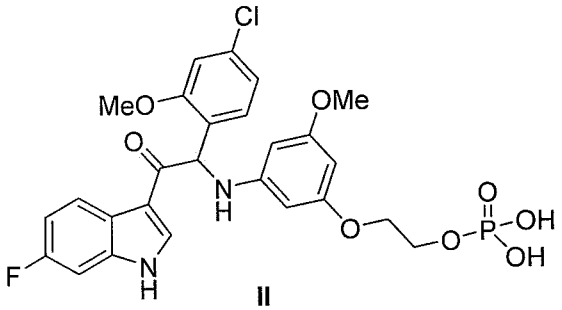
R_4 is CH_3, R_5 is OCH_3, R_6 is H, R_7 is F;

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

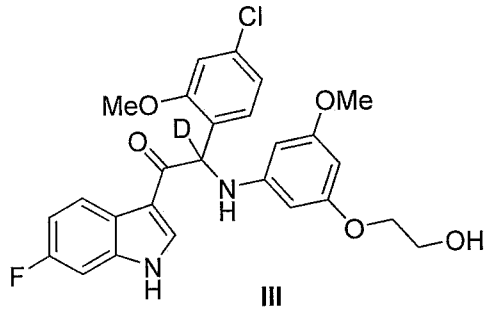
R_4 and R_5 are connected forming a heterocycle of 5 members having one oxygen atom, R_6 and R_7 are both H;

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

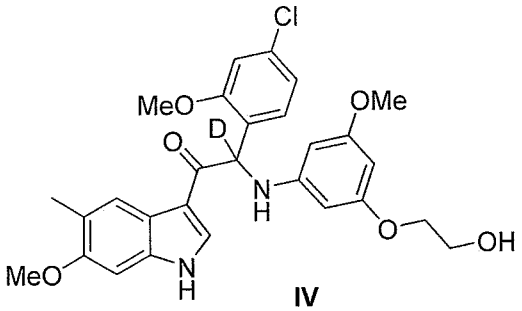
and wherein compounds (II, III and IV) respectively are represented by:



II



III



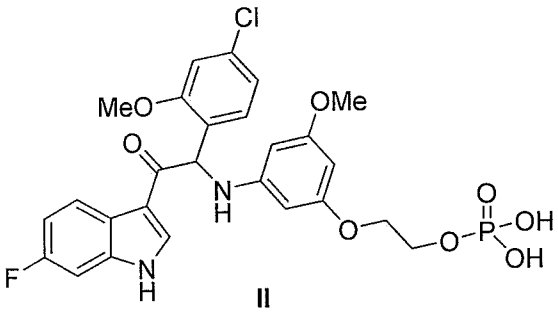
IV

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

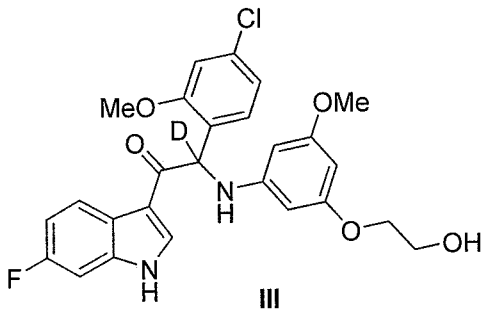
One embodiment of the disclosure is the provision of compounds of formula (Ia or Ib).

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.

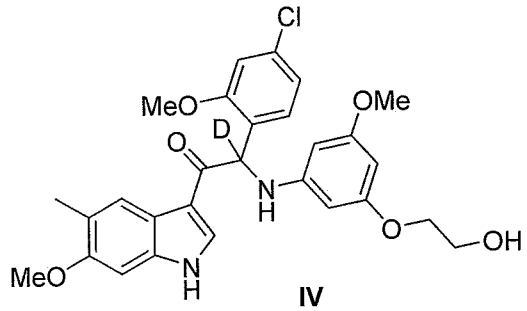
Part of the disclosure are also the following three compounds having the structures (II), (III) and (IV) respectively:



II



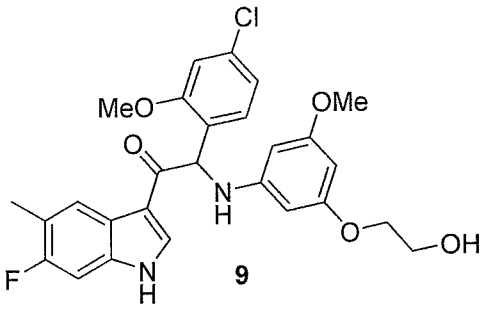
III



IV

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

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



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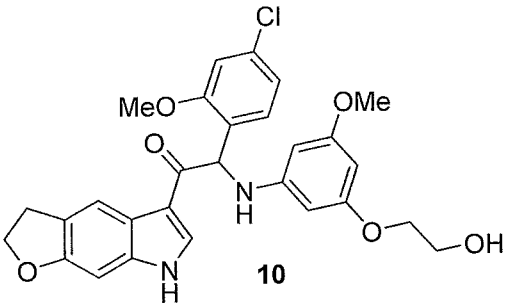

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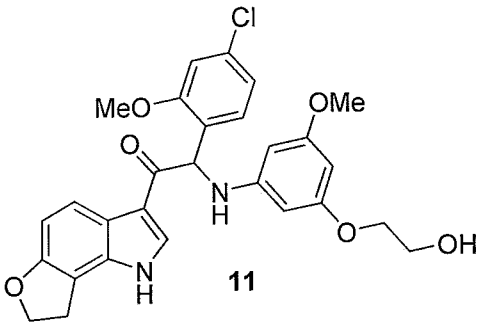

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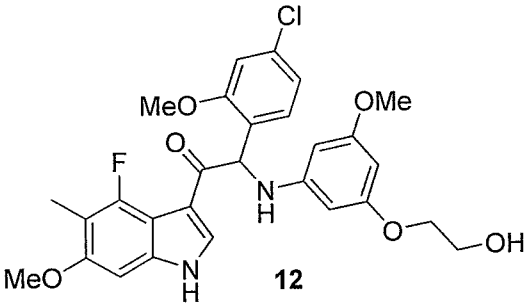

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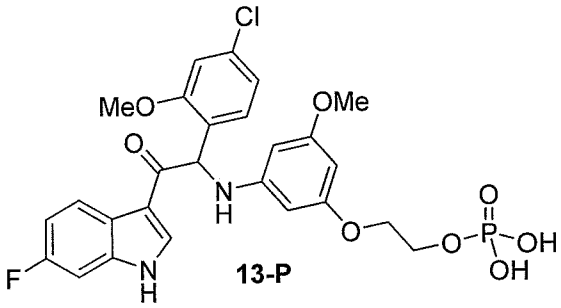
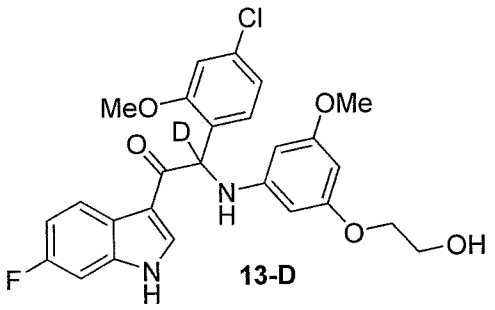
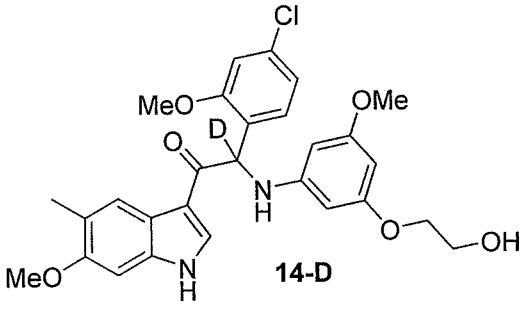


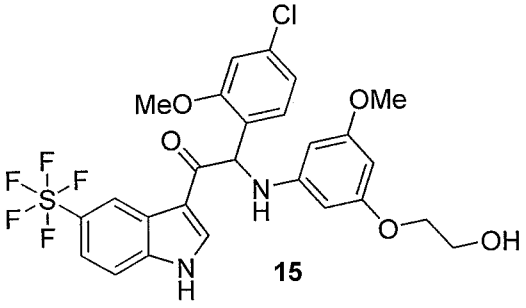
13-P



13-D



14-D



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Another aspect of the current disclosure is also a pharmaceutical composition comprising a compound of formula (Ia, Ib, II, III or IV) 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 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) 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 comprising a mono- or di-substituted indole group 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 comprising a mono- or di-substituted indole group 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 appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, 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,

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

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

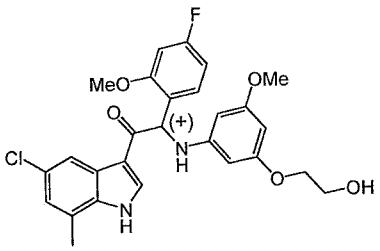
6. A use of a compound as represented by any of the structural formula from claims 1-5, a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof comprising a mono- or di-substituted indole group in the manufacture of a medicament for inhibiting the replication of dengue virus(es) in a patient.

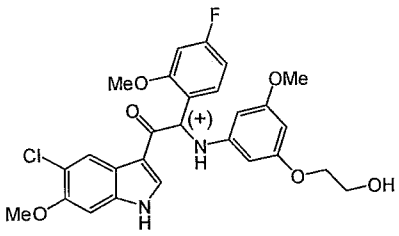
7. A use of a compound as represented by any of the structural formula from claims 1-5, a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof comprising a mono- or di-substituted indole group for inhibiting the replication of dengue virus(es) in a biological sample.

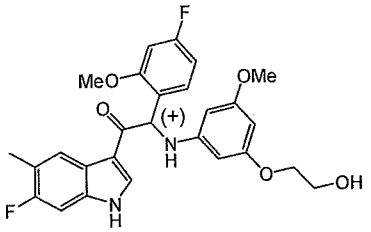
8. The use of a compound according to claim 6 or 7 further comprising an additional therapeutic agent.

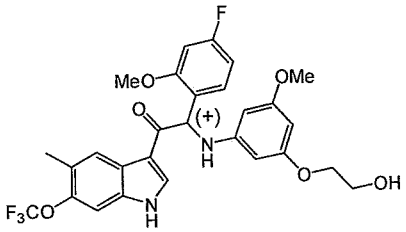
9. The use of claim 8 wherein said additional therapeutic agent is selected from an antiviral agent or dengue vaccine, or both.

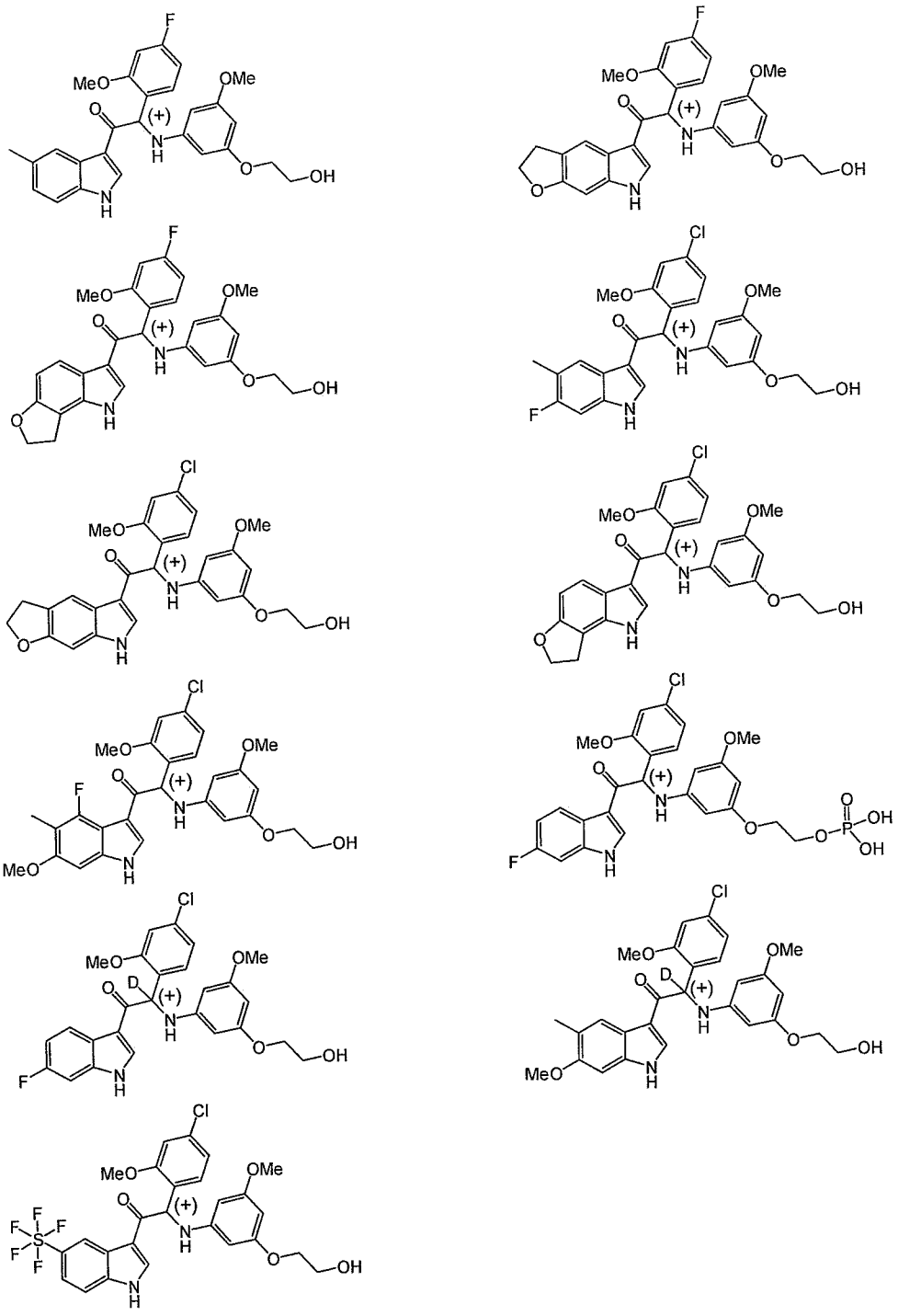
10. The compound as claimed in claim 1 wherein the compound is selected from











or a pharmaceutically acceptable salt, solvate or polymorph thereof.

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

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

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

14. A use of a compound as represented by any of the structural formula from claim 10, a pharmaceutically acceptable salt, solvate or polymorph thereof comprising a mono- or di-substituted indole group in the manufacture of a medicament for inhibiting the replication of dengue virus(es) in a patient.

15. A use of a compound as represented by any of the structural formula from claim 10, a pharmaceutically acceptable salt, solvate or polymorph thereof comprising a mono- or di-substituted indole group for inhibiting the replication of dengue virus(es) in a biological sample.

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

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