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

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 derivates for use in the treatment of dengue viral infections.

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.

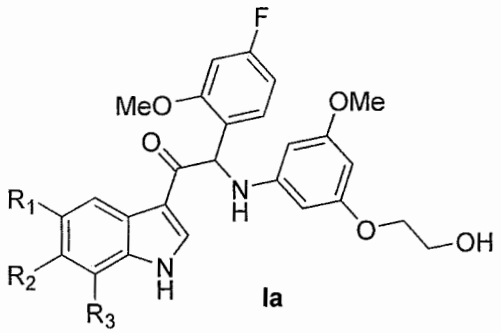
The present disclosure provides compounds which have been shown to possess potent antiviral activity against all four (4) serotypes currently known. The present disclosure furthermore demonstrates that these compounds efficiently inhibit proliferation of Dengue virus (DENV). Therefore, these compounds 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.

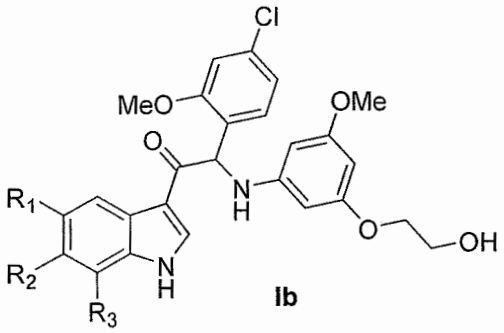
The present disclosure also relates to a method of treatment or prevention of dengue viral infections in humans by the administration an effective amount of one or more such compounds, or a pharmaceutically acceptable salt thereof optionally

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 compounds of formula (Ia or Ib)



Ia

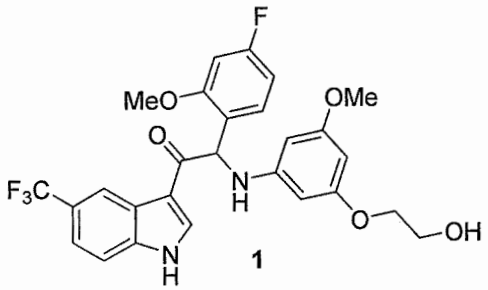


Ib

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_1 is CF_3 or OCF_3, R_2 is H or OCH_3 or F, R_3 is H;
and when R_2 is H than R_3 can also be CH_3.

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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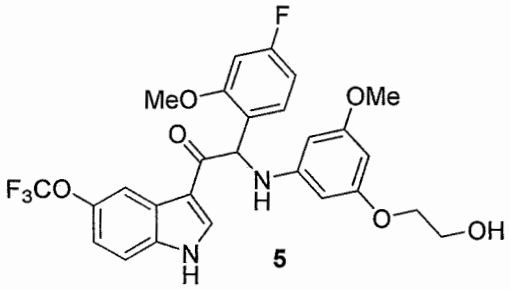

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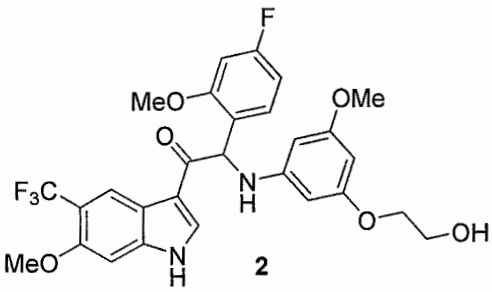

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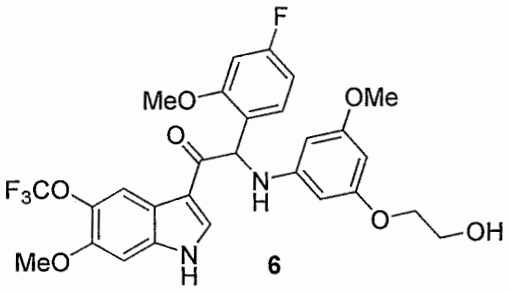

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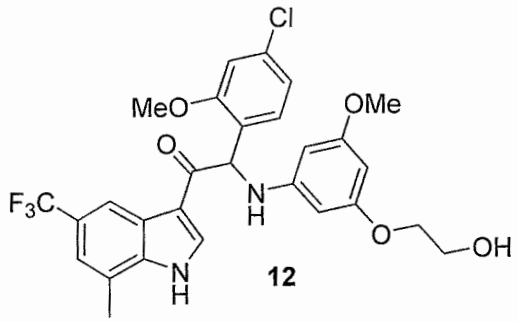

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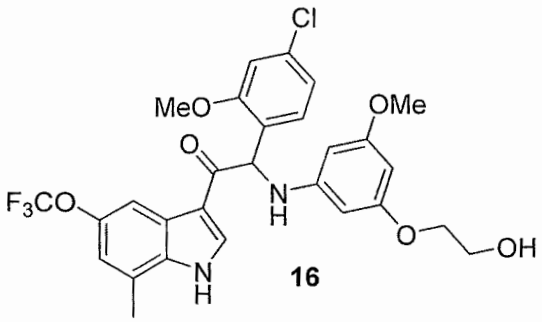


16

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

Pharmaceutically acceptable salts of the compounds of formula (Ia or Ib) 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 present disclosure is a compound of formula (Ia or Ib) 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 present disclosure is a compound of formula (Ia or Ib) 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 present disclosure is use of a compound 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 present disclosure is use of a compound 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 disclosure 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 disclosure and one or more pharmaceutically acceptable solvent molecules, for example, ethanol.

The term “polymorph” refers to the ability of the compound of the disclosure to exist in more than one form or crystal structure.

The compounds of the present disclosure 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 disclosure 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 disclosure. 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 disclosure 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 disclosure, 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, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. Also included are solid form preparations that can be converted, shortly before use, to liquid forms.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

Those of skill in the treatment of infectious diseases will be able to determine the effective amount from the test results presented hereinafter. In general it is contemplated that an effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, more preferably from 0.1 mg/kg to 10 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (Ia or Ib) used, the particular condition being treated, the

severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that the effective amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant disclosure. The effective amount ranges mentioned above are therefore only guidelines and are not intended to limit the scope or use of the disclosure to any extent.

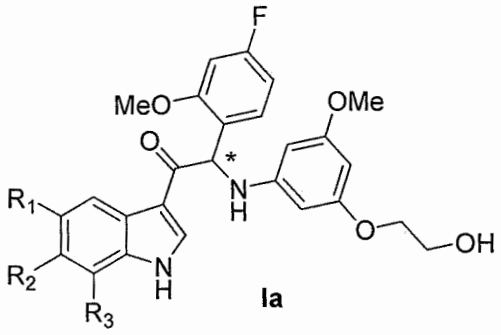
The present disclosure is also intended to include any isotopes of atoms present in the compounds of the disclosure. For example, isotopes of hydrogen include tritium and deuterium and isotopes of carbon include C-13 and C-14.
The present compounds used in the current disclosure may also exist in their stereochemically isomeric form, defining all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures, which are not interchangeable. Unless otherwise mentioned or indicated, the chemical designation of compounds encompasses the mixture of all possible stereochemically isomeric forms, which said compounds might possess.
Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds used in the present disclosure either in pure form or in admixture with each other are intended to be embraced within the scope of the present disclosure including any racemic mixtures or racemates.

Pure stereoisomeric forms of the compounds and intermediates as mentioned herein are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term 'stereoisomerically pure' concerns compounds or intermediates having a stereoisomeric excess of at least 80% (i. e. minimum 90% of one isomer and maximum 10% of the other possible isomers) up to a stereoisomeric excess of 100% (i.e. 100% of one isomer and none of the other), more in particular, compounds or intermediates having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a stereoisomeric excess of 97% up to 100%. The terms 'enantiomerically pure' and 'diastereomerically pure' should be understood in a similar way, but then having regard to the

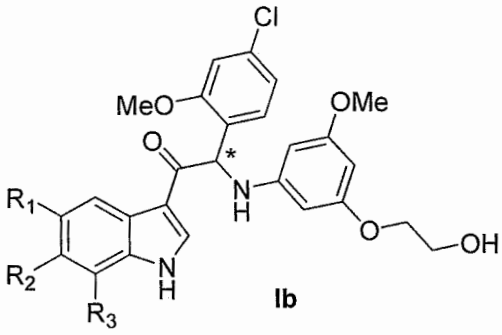
enantiomeric excess, respectively the diastereomeric excess of the mixture in question.

Pure stereoisomeric forms of compounds and intermediates used in this disclosure may be obtained by the application of art-known procedures. For instance, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids or bases. Examples thereof are tartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid and camphosulfonic acid. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably, if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (Ia) or (Ib) of the present disclosure all have at least one chiral carbon atom as indicated in the figure below by the carbon atom labelled with * :



Ia



Ib

Due to the presence of said chiral carbon atom, a "compound of formula (Ia) or (Ib)" can be the (R)-enantiomer, the (S)-enantiomer, the racemic form, or any possible combination of the two individual enantiomers in any ratio. When the absolute (R)- or (S)-configuration of an enantiomer is not known, this enantiomer can also be identified by indicating whether the enantiomer is dextrorotatory (+)- or levorotatory (-)- after measuring the specific optical rotation of said particular enantiomer.

The present disclosure also relates to a first group of compound of formula (I) wherein the compounds of formula (I) have the (+) specific rotation.

The present disclosure also relates to a second ground of compounds of formula (I) wherein the compounds of formula (I) have the (-) specific rotation.

Examples

LC/MS methods

The High Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below).

Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time...) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software.

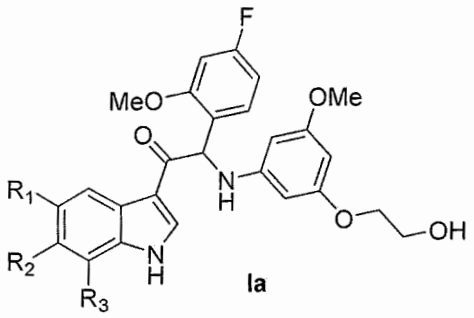
Compounds are described by their experimental retention times (R_t) and ions. If not specified differently in the table of data, the reported molecular ion corresponds to the $[M+H]^+$ (protonated molecule) and/or $[M-H]^-$ (deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e. $[M+NH_4]^+$, $[M+HCOO]^-$, etc...). For molecules with multiple isotopic patterns (Br, Cl), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used.

Hereinafter, "SQD" means Single Quadrupole Detector, "MSD" Mass Selective Detector, "RT" room temperature, "BEH" bridged ethylsiloxane/silica hybrid, "DAD" Diode Array Detector, "HSS" High Strength silica.

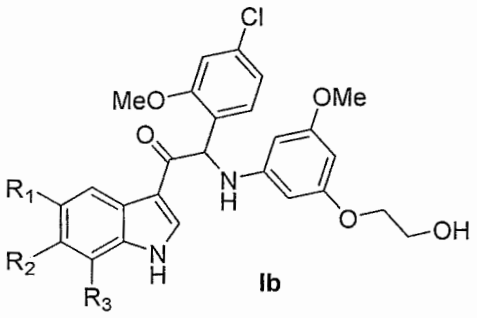
LC/MS Method codes (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes)

Method code	Instrument	Column	Mobile phase	Gradient	Flow --- Col T	Run time (min)
LC-A	Waters: Acquity® UPLC® - DAD-SQD	Waters: BEH C18 (1.7µm, 2.1x50mm)	A: 10mM CH_3COONH_4 in 95% H_2O + 5% CH_3CN B: CH_3CN	from 95% A to 5% A in 1.3 min, held for 0.7 min.	0.8 mL/min --- 55°C	2

6. A use of a compound represented by the following structural formula (Ia or Ib)



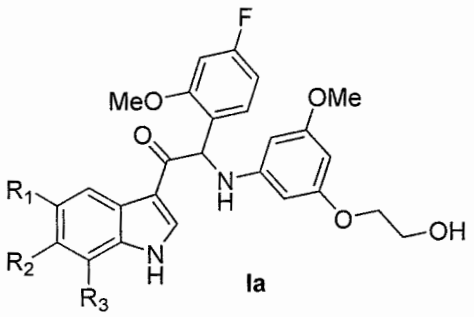
Ia



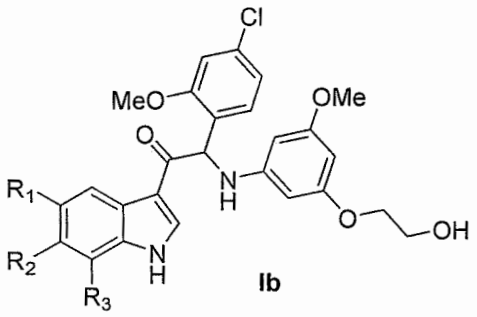
Ib

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_1 is CF_3 or OCF_3, R_2 is H or OCH_3 or F, R_3 is H;
and when R_2 is H than R_3 can also be CH_3
in the manufacture of a medicament for inhibiting the replication of dengue virus(es) in a patient.

7. A use of a compound represented by the following structural formula (Ia or Ib)



Ia



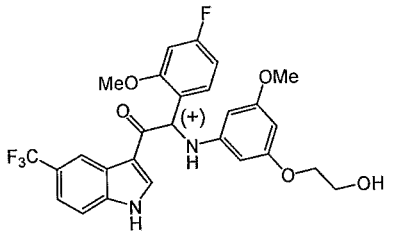
Ib

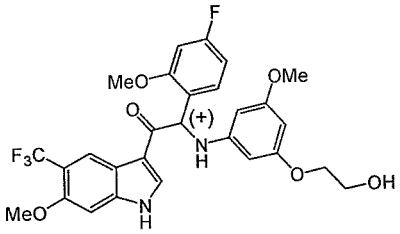
a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof comprising a mono- or di-substituted indole group; said compound is selected from the group wherein:
R_1 is CF_3 or OCF_3, R_2 is H or OCH_3 or F, R_3 is H;
and when R_2 is H than R_3 can also be CH_3
for inhibiting the replication of dengue virus(es) in a biological sample.

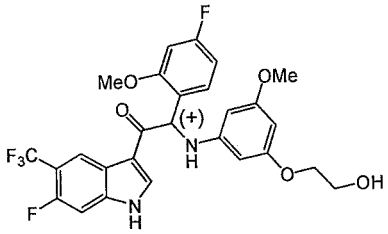
8. The use of a compound according to claim 6 or 7 further comprising an additional therapeutic agent.

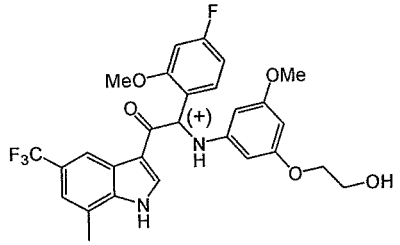
9. The use of claim 8 wherein said additional therapeutic agent is selected from an antiviral agent or dengue vaccine, or both.

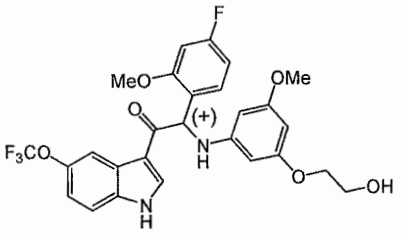
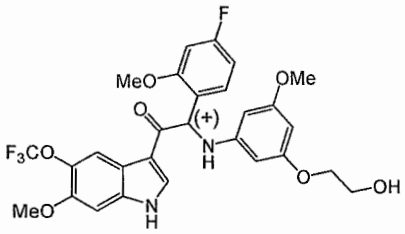
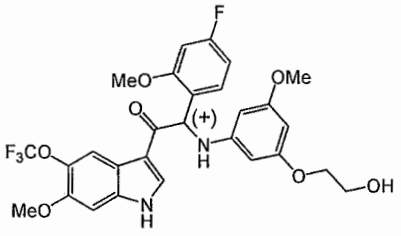
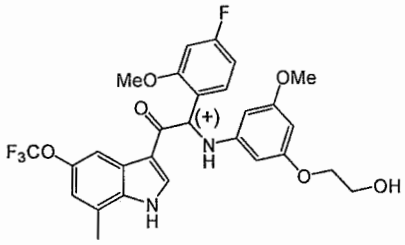
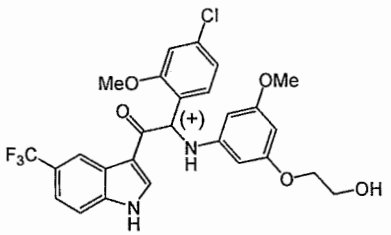
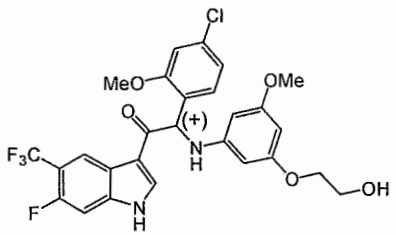
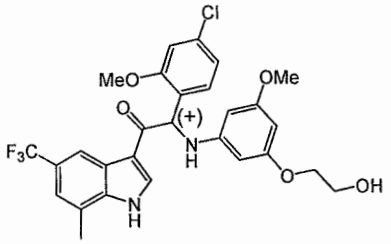
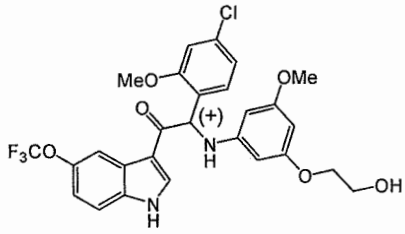
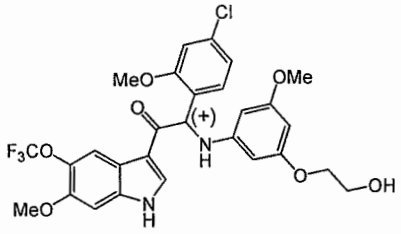
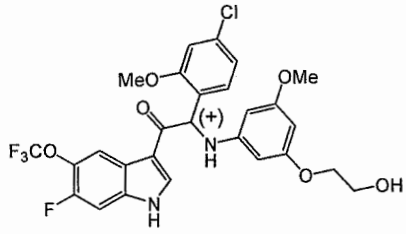
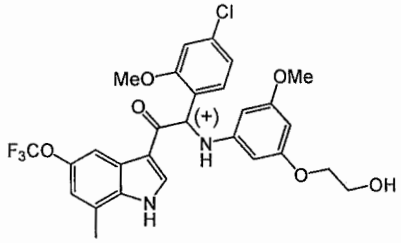
10. The compound as claimed in claim 1 wherein the compound is selected from









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 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 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 16 wherein said additional therapeutic agent is selected from an antiviral agent or dengue vaccine, or both.