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.

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

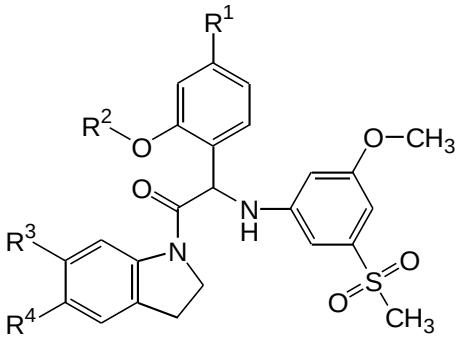
The present disclosure is based on the unexpected finding that at least one of the above-mentioned problems can be solved by the current compounds of the disclosure.

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 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 compounds of formula (I), including any stereochemically isomeric form thereof, :

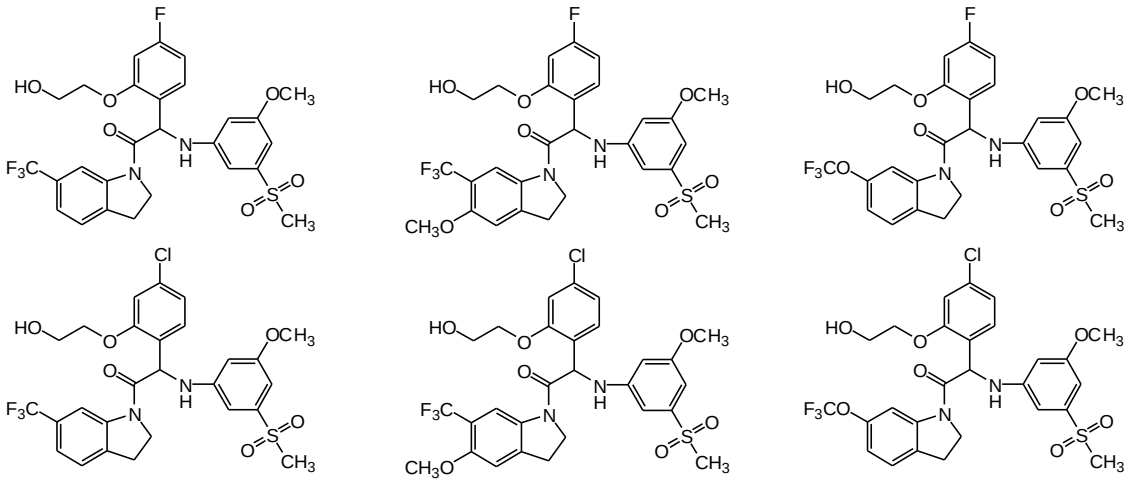


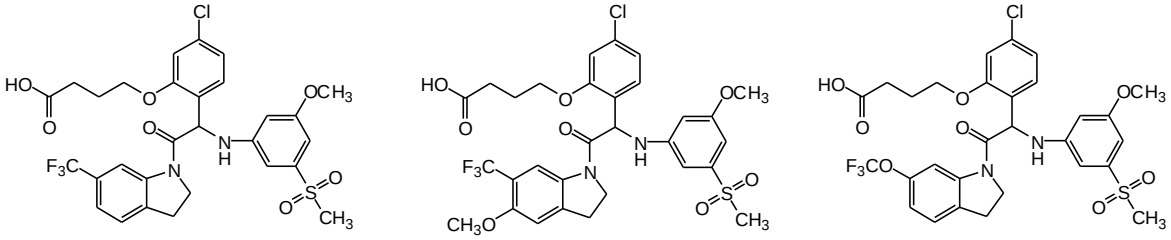
(I)

wherein

R^1 is fluoro, R^2 is $-CH_2CH_2OH$, R^3 is trifluoromethyl, and R^4 is hydrogen, or
R^1 is fluoro, R^2 is $-CH_2CH_2OH$, R^3 is trifluoromethyl, and R^4 is methoxy, or
R^1 is fluoro, R^2 is $-CH_2CH_2OH$, R^3 is trifluoromethoxy, and R^4 is hydrogen, or
R^1 is chloro, R^2 is $-CH_2CH_2OH$, R^3 is trifluoromethyl, and R^4 is hydrogen, or
R^1 is chloro, R^2 is $-CH_2CH_2OH$, R^3 is trifluoromethyl, and R^4 is methoxy, or
R^1 is chloro, R^2 is $-CH_2CH_2OH$, R^3 is trifluoromethoxy, and R^4 is hydrogen, or
R^1 is chloro, R^2 is $-(CH_2)_3COOH$, R^3 is trifluoromethyl, and R^4 is hydrogen, or
R^1 is chloro, R^2 is $-(CH_2)_3COOH$, R^3 is trifluoromethyl, and R^4 is methoxy, or
R^1 is chloro, R^2 is $-(CH_2)_3COOH$, R^3 is trifluoromethoxy, and R^4 is hydrogen;
or a pharmaceutically acceptable salt, solvate or polymorph thereof.

Specifically above mentioned compounds are selected from the group comprising :





Part 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. In another aspect, there is provided a pharmaceutical composition comprising a compound mentioned above 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.

The pharmaceutically acceptable acid salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms that the compounds of formula (I) are able to form. These pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (*i.e.* butane-dioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-amino-salicylic, pamoic acid and the like acids.

In another aspect, there is provided a compound of formula (I) mentioned above for use as a medicine.

In another aspect, there is provided a compound of formula (I) mentioned above for use in the treatment of Dengue infection and for the prevention or treatment of disease associated with Dengue infection.

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 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