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

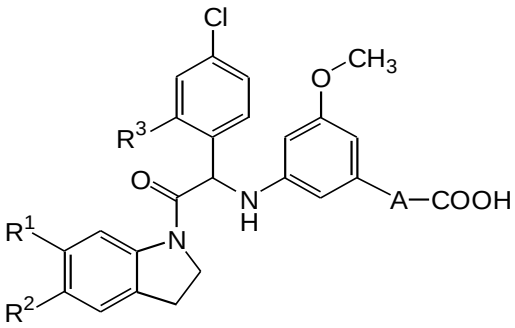
The present disclosure is based on the unexpected finding that at least one of the above-mentioned problems can be solved by the current compounds of the disclosure.

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



(I)

wherein

R^1 is trifluoromethyl, trifluoromethoxy, or chloro;

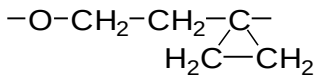
R^2 is hydrogen, fluoro, or methoxy;

R^3 is hydrogen, or methoxy;

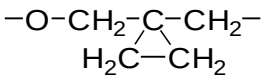
A represents $-(CH_2)_n-$ wherein n is 3 or 4;

$-O-(CH_2)_n-$ wherein n is 2 or 4;

$-O-(CH_2)_n-$ wherein n is 3 and one or two CH_2 are substituted with one or two CH_3;



or



$-CH_2-O-(CH_2)_n-$ wherein n is 2; or

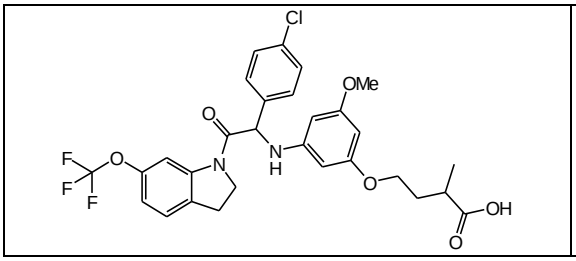
-X-Y- wherein X is a -O-, $-OCH_2-$, or -NH-; and

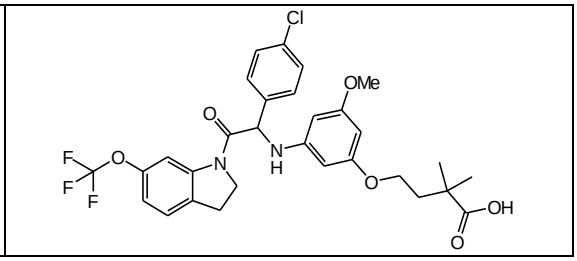
Y is C_{3-4}cycloalkyl optionally substituted with fluoro, or

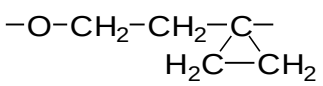
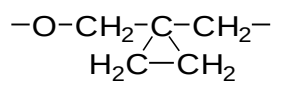
Y is bicyclo[1.1.1]pentanyl;

or a pharmaceutically acceptable salt, solvate or polymorph thereof.

Specifically above mentioned compounds are selected from the group comprising :





A third group of compounds are compounds of formula (I) wherein A represents -O-$(CH_2)_n$- wherein n is 3 and one or two CH_2 are substituted with one or two CH_3; or A represents  or  .

A fourth group of compounds are compounds of formula (I) wherein A represents -CH_2-O-$(CH_2)_n$- wherein n is 2.

A fifth group of compounds are compounds of formula (I) wherein A represents -X-Y- wherein X is a -O-, -OCH_2-, or -NH-; and Y is C_{3-4}cycloalkyl optionally substituted with fluoro.

A sixth group of compounds are compounds of formula (I) wherein A represents -X-Y- wherein X is a -O-, -OCH_2-, or -NH-; and Y is bicyclo[1.1.1]pentanyl.

A seventh group of compounds are compounds of formula (I) wherein R^1 is trifluoromethoxy, R^2 is hydrogen, and R^3 is hydrogen.

An eighth group of compounds are compounds of formula (I) wherein R^1 is trifluoromethoxy, R^2 is hydrogen, and R^3 is methoxy.

A ninth group of compounds are compounds of formula (I) wherein R^1 is trifluoromethyl, R^2 is methoxy, and R^3 is hydrogen.

A tenth group of compounds are compounds of formula (I) wherein R^1 is trifluoromethoxy, R^2 is fluoro, and R^3 is hydrogen.

An eleventh group of compounds are compounds of formula (I) wherein R^1 is chloro, R^2 is methoxy, and R^3 is hydrogen.

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, the present disclosure relates to a pharmaceutical composition comprising a compound as defined herein together with one or more pharmaceutically acceptable excipients, diluents or carriers.

In another aspect, the present disclosure relates a compound of formula (I) as defined herein for use as a medicine.

In another aspect, the present disclosure relates a compound of formula (I) as defined herein for use in the treatment of Dengue infection and for the prevention or treatment of disease associated with Dengue infection.

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.