infections, higher viral titres are associated with more severe dengue disease. Since maternal antibodies can easily pass on to infants by breast feeding, this might be one of the reasons that children are more affected by severe dengue disease than adults.

In locations with two or more serotypes circulating simultaneously, also referred to as hyperendemic regions, the risk of serious dengue disease is significantly higher due to an increased risk of experiencing a secondary, more severe infection. Moreover, in a situation of hyper-endemicity, the probability of the emergence of more virulent strains is increased, which in turn augments the probability of dengue hemorrhagic fever (DHF) or dengue shock syndrome.

The mosquitoes that carry dengue, including *Aedes aegypti* and *Aedes albopictus* (tiger mosquito), are moving north. According to the United States (US) Centers for Disease Control and Prevention (CDC), both mosquitoes are currently omnipresent in southern Texas. The spread north of dengue-carrying mosquitoes is not confined to the US, but has also been observed in Europe.

Despite large efforts over the past 3 decades, there is currently no vaccine available to protect against dengue virus disease. The main problem is to develop a vaccine that offers protection against all four serotypes (a tetravalent vaccine) to the same extent. Furthermore, today, specific antiviral drugs for the treatment or prevention of dengue fever virus infection are not available. Clearly, there is still a great 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. Therapeutics with good potency, no or low levels of less side-effects, a broad spectrum activity against multiple Dengue virus serotypes, a low toxicity and/or good pharmacokinetic or –dynamic properties are very welcome. The present invention provides novel compounds which show activity against Flaviviruses, including Dengue virus. The prior art does not lead a person skilled in the art to the compounds of the present invention, nor to their use as antiviral compounds.

SUMMARY ~~OF THE INVENTION~~

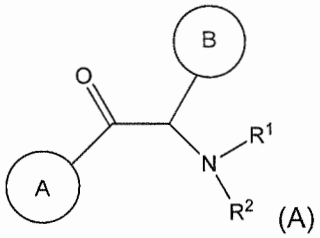
The present ~~invention~~ disclosure is based on the unexpected finding that at least one of the above-mentioned problems can be solved by a novel class of compounds.

The present ~~invention~~disclosure provides new compounds which have been shown to possess antiviral activity. The present ~~invention~~disclosure furthermore demonstrates that these compounds efficiently inhibit proliferation of viruses, especially Flaviviruses, more specifically Dengue virus (DENV) and Yellow Fever virus (YFV). Therefore, these compounds constitute a useful class of new 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 viruses belonging to the family of the Flaviviruses, and yet more particularly infections with Dengue viruses or yellow fever virus.

The present ~~invention~~ disIcosure 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 Flaviviruses, and yet more particularly infections with Dengue viruses or yellow fever virus, in animals or mammals, more in particular in humans. The ~~invention~~disclosure also relates to methods for the preparation of all such compounds and to pharmaceutical compositions comprising them in an effective amount.

The present ~~invention~~disclosure also relates to a method of treatment or prevention of viral infections in humans by the administration of one or more such compounds, optionally in combination with one or more other medicines, to a patient in need thereof. Particularly, the present ~~invention~~disclosure also relates to a method of treatment or prevention of viral infections, especially Flaviviral infections, in humans by the administration of an effective amount of one or more such compounds or a pharmaceutically acceptable salt thereof, optionally in combination with one or more other medicines, to a patient in need thereof. More particularly, the present ~~invention~~disclosure also relates to a method of treatment or prevention of infections by the Dengue virus or yellow fever virus in humans by the administration of an effective amount of one or more such compounds or a pharmaceutically acceptable salt thereof, optionally in combination with one or more other medicines, to a patient in need thereof.

One ~~aspect~~embodiment of the ~~invention~~disclosure is the provision of new compounds of formula (A),



(A)

wherein,

- cycle A is a heterocycle, which can be unsubstituted or substituted with one or more Z^1;
- cycle B is selected from aryl; and heterocycle; wherein said aryl and heterocycle can be unsubstituted or substituted with one or more Z^{1a};
- R^1 is selected from cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; heterocycle-alkyl; heterocycle-alkenyl; heterocycle-alkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heterocycle-heteroalkyl; heterocycle-heteroalkenyl; heterocycle-heteroalkynyl;

  and wherein said cycloalkyl; cycloalkenyl; cycloalkynyl; aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl and heterocycle-heteroalkynyl can be unsubstituted or substituted with one or more Z^{1b};
- R^2 is selected from hydrogen; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; and

alkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, -O-alkyl, $-OCF_3$, cyano, nitro, -C(O)OH or NH_2;

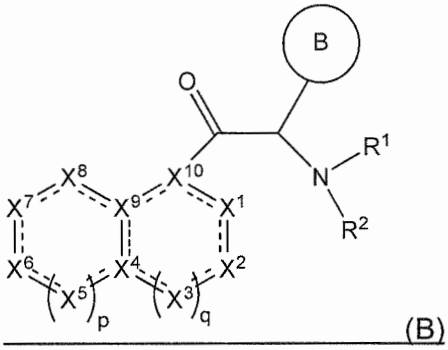
- each Z^4 and Z^5 is independently selected from hydrogen; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heterocycle-alkyl; heterocycle-alkenyl; heterocycle-alkynyl; heterocycle-heteroalkyl; heterocycle-heteroalkenyl; or heterocycle-heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, or heterocycle-heteroalkynyl can be unsubstituted or substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, -O-alkyl, $-OCF_3$, cyano, nitro, -C(O)OH or NH_2;

and wherein Z^4 and Z^5 can be taken together in order to form a (5-, 6-, or 7-membered) heterocycle which can be unsubstituted or substituted with alkyl, alkenyl, alkynyl, hydroxyl, halogen, -SH, trifluoromethyl, -O-alkyl, $-OCF_3$, cyano, nitro, -C(O)OH or $-NH_2$;

and isomers (in particular stereo-isomers or tautomers), solvates, salts (in particular pharmaceutically acceptable salts) or prodrugs thereof.

In one aspect, there is provided a compound of formula (B) for use in the prevention or treatment of a flavivirus infection in an animal, mammal or human,



(B)

wherein

- each dotted line represents an optional double bond whereby maximally 6 non-adjacent dotted lines can form a double bond;
- each of X^1, X^2, X^3, X^5, X^6, X^7, and X^8 is independently selected from CR^3, N, NR^4, O, and S;
- each of X^4 and X^9 is independently selected from C, CH, and N;
- X^{10} is selected from C, CH, and N;

whereby at least five of X^1 to X^{10} are selected from CR^3, C, and CH; and at least one of X^1 to X^{10} is a heteroatom;

- p is 0, 1, or 2;

- q is 0, 1, or 2;

- cycle B is selected from aryl and heterocycle, wherein said aryl and heterocycle are optionally substituted with one, two, or three Z^{1a};

- R^1 is selected from alkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-hetero alkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

and wherein said alkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl, are optionally substituted with one, two, or three Z^{1b};

- R^2 is selected from hydrogen, $-C(O)Z^3$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl;

and wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl, are optionally substituted with one, two, or three Z^{1c};

- each R^3 is independently selected from hydrogen and Z^1;

- each R^4 is independently selected from hydrogen, hydroxyl, sulfhydryl, $-S(=O)Z^2$, $-S(=O)_2Z^3$, $-S(=O)_2NZ^4Z^5$, trifluoromethyl, $-C(=O)Z^3$, $-C(=O)OZ^2$, $-C(=O)NZ^4Z^5$, -C(=O)H, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

and wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl are optionally substituted with one, two, or three substituents selected from alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, $-OCF_3$, cyano, nitro, -C(=O)OH, -C(O)Oalkyl, and $-N(CH_3)_2$, $-NH_2$, -NH-C(=O)O-C_{1-4}alkyl, –O-alkyl;

- each Z^1, Z^{1a}, Z^{1b}, and Z^{1c} is independently selected from the group consisting of halogen, hydroxyl, sulfhydryl, $-OZ^2$, $-O-C(=O)Z^3$, =O, $-SZ^2$, =S, $-S(=O)Z^2$, $-S(=O)_2Z^3$, $-S(=O)_2NZ^4Z^5$, trifluoromethyl, trifluoromethoxy, nitro, $-NZ^4Z^5$, $-NZ^4S(=O)_2Z^2$, $-NZ^4C(=O)Z^2$, $-NZ^4C(=O)-OZ^2$, $-NZ^4C(=O)NZ^4Z^5$, cyano, $-C(=O)Z^3$, $-C(=O)OZ^2$, $-C(=O)NZ^4Z^5$, -C(=O)H, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

and wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl, are optionally substituted with one, two, or three substituents selected from alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, $-OCF_3$, -O-C(O)Me, cyano, nitro, -C(O)OH, -C(O)Oalkyl, $-NH_2$, $-NHCH_3$; $-N(CH_3)_2$, -NH-C(=O)O-C_{1-4}alkyl, morpholinyl, $-S(O)_2C_{1-4}$alkyl, and –O-alkyl;

- each Z^2 is independently selected from alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl, are optionally substituted with one, two, or three substituents selected from alkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, difluoromethyl, -O-alkyl, $-OCF_3$, $-S(=O)_2C_{1-4}$alkyl, cyano, nitro, -C(=O)OH, -C(=O)O-C_{1-4}alkyl, $-NH_2$, and $-N(CH_3)_2$, pyrrolidinyl, piperidinyl, and piperazinyl;

- each Z^3 is independently selected from hydroxyl, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl,

arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl, are optionally substituted with one, two, or three substituents selected from alkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, -O-alkyl, $-OCF_3$, cyano, nitro, -C(=O)OH, $-NH_2$, and $-N(CH_3)_2$;

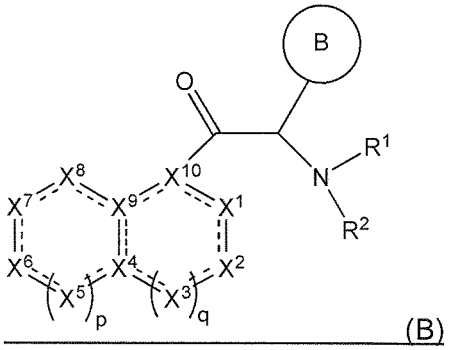
- each Z^4 and Z^5 is independently selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl, are optionally substituted with one, two, or three substituents selected from alkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, -O-alkyl, $-OCF_3$, cyano, nitro, -C(=O)OH or $-NH_2$;

and wherein Z^4 and Z^5 can be taken together in order to form a (5-, 6-, or 7-membered) heterocycle which is optionally substituted with alkyl, alkenyl, alkynyl, hydroxyl, halogen, -SH, trifluoromethyl, -O-alkyl, $-OCF_3$, cyano, nitro, -C(=O)OH, or $-NH_2$;

and isomers (in particular stereo-isomers or tautomers), solvates, salts (in particular pharmaceutically acceptable salts) or prodrugs thereof.

In another aspect, there is provided a compound of formula (B) for use as a medicine,



(B)

wherein

- each dotted line represents an optional double bond whereby maximally 6 non-adjacent dotted lines can form a double bond;

- each of X^1, X^2, X^3, X^5, X^6, X^7, and X^8 is independently selected from CR^3, N, NR^4, O, and S;
- each of X^4 and X^9 is independently selected from C, CH, and N;
- X^{10} is selected from C, CH, and N;

whereby at least five of X^1 to X^{10} are selected from CR^3, C, and CH; and at least one of X^1 to X^{10} is a heteroatom;

- p is 0, 1, or 2;
- q is 0, 1, or 2;

- cycle B is selected from aryl and heterocycle, wherein said aryl and heterocycle are optionally substituted with one, two, or three Z^{1a};

- R^1 is selected from alkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-hetero alkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

and wherein said alkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl, are optionally substituted with one, two, or three Z^{1b};

- R^2 is selected from hydrogen, $-C(O)Z^3$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl;

and wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl, are optionally substituted with one, two, or three Z^{1c};

- each R^3 is independently selected from hydrogen and Z^1;

- each R^4 is independently selected from hydrogen, hydroxyl, sulfhydryl, $-S(=O)Z^2$, $-S(=O)_2Z^3$, $-S(=O)_2NZ^4Z^5$, trifluoromethyl, $-C(=O)Z^3$, $-C(=O)OZ^2$, $-C(=O)NZ^4Z^5$, -C(=O)H, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

and wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl,

heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl are optionally substituted with one, two, or three substituents selected from alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, $-OCF_3$, cyano, nitro, -C(=O)OH, -C(O)Oalkyl, and $-N(CH_3)_2$, $-NH_2$, -NH-C(=O)O-C_{1-4}alkyl, –O-alkyl;

- each Z^1, Z^{1a}, Z^{1b}, and Z^{1c} is independently selected from the group consisting of halogen, hydroxyl, sulfhydryl, $-OZ^2$, -O-C(=O)Z^3, =O, $-SZ^2$, =S, -S(=O)Z^2, $-S(=O)_2Z^3$, $-S(=O)_2NZ^4Z^5$, trifluoromethyl, trifluoromethoxy, nitro, $-NZ^4Z^5$, $-NZ^4S(=O)_2Z^2$, $-NZ^4C(=O)Z^2$, $-NZ^4C(=O)-OZ^2$, $-NZ^4C(=O)NZ^4Z^5$, cyano, -C(=O)Z^3, -C(=O)OZ^2, -C(=O)NZ^4Z^5, -C(=O)H, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

and wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl, are optionally substituted with one, two, or three substituents selected from alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, $-OCF_3$, -O-C(O)Me, cyano, nitro, -C(O)OH, -C(O)Oalkyl, $-NH_2$, $-NHCH_3$; $-N(CH_3)_2$, -NH-C(=O)O-C_{1-4}alkyl, morpholinyl, $-S(O)_2C_{1-4}$alkyl, and –O-alkyl;

- each Z^2 is independently selected from alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl, are optionally substituted with one, two, or three substituents selected from alkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, difluoromethyl, -O-alkyl, $-OCF_3$, $-S(=O)_2C_{1-4}$alkyl, cyano, nitro, -C(=O)OH, -C(=O)O-C_{1-4}alkyl, $-NH_2$, and $-N(CH_3)_2$, pyrrolidinyl, piperidinyl, and piperazinyl;

- each Z^3 is independently selected from hydroxyl, alkyl, alkenyl, alkynyl, heteroalkyl,

heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl, are optionally substituted with one, two, or three substituents selected from alkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, -O-alkyl, $-OCF_3$, cyano, nitro, -C(=O)OH, $-NH_2$, and $-N(CH_3)_2$;

- each Z^4 and Z^5 is independently selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

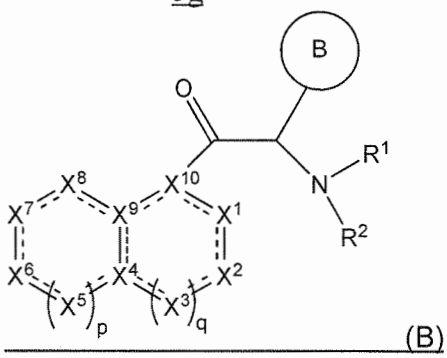
wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl, are optionally substituted with one, two, or three substituents selected from alkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, -O-alkyl, $-OCF_3$, cyano, nitro, or $-NH_2$;

and wherein Z^4 and Z^5 can be taken together in order to form a (5-, 6-, or 7-membered) heterocycle which is optionally substituted with alkyl, alkenyl, alkynyl, hydroxyl, halogen, -SH, trifluoromethyl, -O-alkyl, $-OCF_3$, cyano, nitro, -C(=O)OH, or $-NH_2$;

and isomers (in particular stereo-isomers or tautomers), solvates, salts (in particular pharmaceutically acceptable salts) or prodrugs thereof.

In another aspect, there is provided a compound of formula (B),

5g



(B)

wherein

- each dotted line represents an optional double bond whereby maximally 6 non-adjacent dotted lines can form a double bond;
- each of X^1, X^2, X^3, X^5, X^6, X^7, and X^8 is independently selected from CR^3, N, NR^4, O, and S;
- each of X^4 and X^9 is independently selected from C, CH, and N;
- X^{10} is selected from C, CH, and N;

  whereby at least five of X^1 to X^{10} are selected from CR^3, C, and CH; and at least one of X^1 to X^{10} is a heteroatom;
- p is 0, 1, or 2;
- q is 0, 1, or 2;

- cycle B is selected from aryl and heterocycle, wherein said aryl and heterocycle are optionally substituted with one, two, or three Z^{1a};

- R^1 is selected from alkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-hetero alkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

  and wherein said alkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl, are optionally substituted with one, two, or three Z^{1b};

- R^2 is selected from hydrogen, $-C(O)Z^3$, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl;

  and wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl, are optionally substituted with one, two, or three Z^{1c};

- each R^3 is independently selected from hydrogen and Z^1;

- each R^4 is independently selected from hydrogen, hydroxyl, sulfhydryl, $-S(=O)Z^2$, $-S(=O)_2Z^3$, $-S(=O)_2NZ^4Z^5$, trifluoromethyl, $-C(=O)Z^3$, $-C(=O)OZ^2$, $-C(=O)NZ^4Z^5$, -C(=O)H, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

and wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl are optionally substituted with one, two, or three substituents selected from alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, $-OCF_3$, cyano, nitro, -C(=O)OH, -C(O)Oalkyl, and $-N(CH_3)_2$, $-NH_2$, -NH-C(=O)O-C_{1-4}alkyl, –O-alkyl;

- each Z^1, Z^{1a}, Z^{1b}, and Z^{1c} is independently selected from the group consisting of halogen, hydroxyl, sulfhydryl, $-OZ^2$, -O-C(=O)Z^3, =O, $-SZ^2$, =S, $-S(=O)Z^2$, $-S(=O)_2Z^3$, $-S(=O)_2NZ^4Z^5$, trifluoromethyl, trifluoromethoxy, nitro, $-NZ^4Z^5$, $-NZ^4S(=O)_2Z^2$, $-NZ^4C(=O)Z^2$, $-NZ^4C(=O)$-OZ^2, $-NZ^4C(=O)NZ^4Z^5$, cyano, $-C(=O)Z^3$, $-C(=O)OZ^2$, $-C(=O)NZ^4Z^5$, -C(=O)H, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

and wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl, are optionally substituted with one, two, or three substituents selected from alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, $-OCF_3$, -O-C(O)Me, cyano, nitro, -C(O)OH, -C(O)Oalkyl, $-NH_2$, $-NHCH_3$; $-N(CH_3)_2$, -NH-C(=O)O-C_{1-4}alkyl, morpholinyl, $-S(O)_2C_{1-4}$alkyl, and –O-alkyl;

- each Z^2 is independently selected from alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl,

heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl, are optionally substituted with one, two, or three substituents selected from alkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, difluoromethyl, -O-alkyl, $-OCF_3$, $-S(=O)_2C_{1-4}$alkyl, cyano, nitro, -C(=O)OH, $-C(=O)O-C_{1-4}$alkyl, $-NH_2$, and $-N(CH_3)_2$, pyrrolidinyl, piperidinyl, and piperazinyl;

- each Z^3 is independently selected from hydroxyl, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl, are optionally substituted with one, two, or three substituents selected from alkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, -O-alkyl, $-OCF_3$, cyano, nitro, -C(=O)OH, $-NH_2$, and $-N(CH_3)_2$;

- each Z^4 and Z^5 is independently selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heterocycle-alkyl, heterocycle-alkenyl, heterocycle-alkynyl, heterocycle-heteroalkyl, heterocycle-heteroalkenyl, and heterocycle-heteroalkynyl, are optionally substituted with one, two, or three substituents selected from alkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, trifluoromethyl, -O-alkyl, $-OCF_3$, cyano, nitro, or $-NH_2$;

and wherein Z^4 and Z^5 can be taken together in order to form a (5-, 6-, or 7-membered) heterocycle which is optionally substituted with alkyl, alkenyl, alkynyl, hydroxyl, halogen, -SH, trifluoromethyl, -O-alkyl, $-OCF_3$, cyano, nitro, -C(=O)OH, or $-NH_2$;

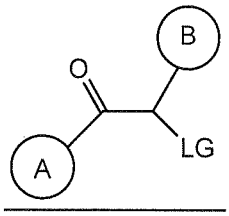
and isomers (in particular stereo-isomers or tautomers), solvates, salts (in particular pharmaceutically acceptable salts) or prodrugs thereof;
with the proviso that compound per se of formula (B) is not

- N-(5-(2-(7-ethyl-1H-indol-3-yl)-2-oxo-1-phenylethylamino)-2-methoxyphenyl)-methanesulfonamide (CAS nr. 1294288-37-1);
- 3-(2-(1H-indol-3-yl)-2-oxo-1-phenylethylamino)benzenesulfonamide (CAS nr. 1211427-21-2);
- 2-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-ylamino)-1-(1H-indol-3-yl)-2-phenylethanone (CAS nr. 1090733-87-1);
- 1-(1H-indol-3-yl)-2-phenyl-2-(pyridin-3-ylmethylamino)ethanone (CAS nr. 875860-58-5); or
- 2-(benzo[d][1,3]dioxol-5-ylmethylamino)-1-(1H-indol-3-yl)-2-phenylethanone (CAS nr. 920816-95-1).

In another aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier, and as active ingredient an effective amount of the compound as defined herein or a pharmaceutically acceptable salt thereof.

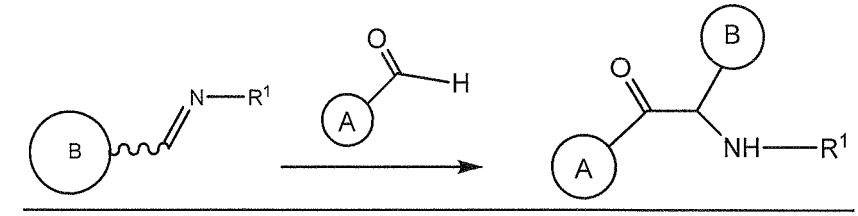
In another aspect, there is provided a method for the preparation of the compound as defined herein comprising the step of

- reacting compound of formula (X1) with the amine R^1R^2NH in a suitable solvent, wherein cycle A, cycle B, R^1, and R^2 have the meaning according to any one of the embodiments presented herein, and LG is a leaving group as known by the skilled in the art, preferably selected from chlorine, bromine, and iodine; or



(X1)

- reacting the imine of formula (X2) with an aldehyde of formula (X3) in the presence of a catalyst and a suitable solvent to obtain compound of formula (A1), wherein cycle A, cycle B, and R^1, have the meaning according to any one of the embodiments presented herein, and provided that in cycle A of formulae (X3) and (A1), a carbon atom is binding to the carbonyl.



(X2) (X3) (A1)

In another aspect, there is provided a use of a compound as defined herein or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treatment or prevention of Flaviviral infections in humans, wherein the medicament is to be optionally administered in combination with one or more other medicines, to a patient in need thereof

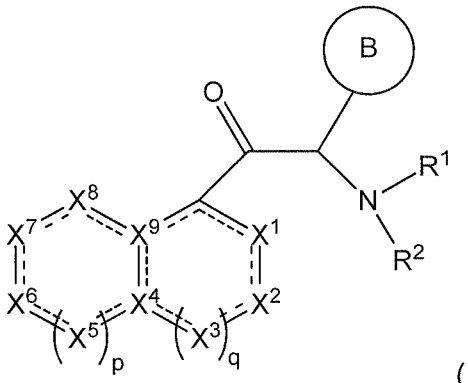
DETAILED DESCRIPTION OF THE FIGURES

Figure 1: Kaplan Meier plot of dengue virus induced mortality/euthanasia in AG129 mice and the effect of treatment with Celgosivir and CPD-242. The red dotted line indicates end of treatment.

DETAILED DESCRIPTION OF THE INVENTION

The present invention will be described with respect to particular embodiments but the invention is not limited thereto.

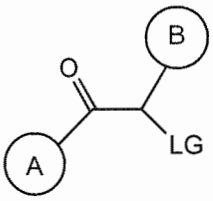
A first embodiment of the present invention relates to a compound according to formula (D),



(D)

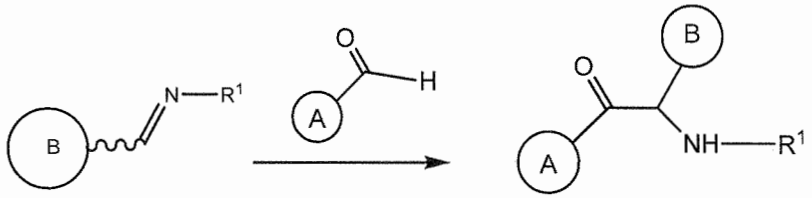
wherein

- each dotted line represents an optional double bond whereby maximally 6 non-adjacent dotted



(X1)

– reacting the imine of formula (X2) with an aldehyde of formula (X3) in the presence of a catalyst and a suitable solvent to obtain compound of formula (A1), wherein cycle A, cycle B, and R^1, have the meaning according to any one of the embodiments presented herein, and provided that in cycle A of formulae (X3) and (A1), a carbon atom is binding to the carbonyl.



(X2) (X3) (A1)

16. ~~A method of treatment or prevention of Flaviviral infections, in humans by the administration of an effective amount of~~ Use of a compound according to any one of claims 1-12 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treatment or prevention of Flaviviral infections in humans, wherein the medicament is to be optionally administered in combination with one or more other medicines, to a patient in need thereof.

17. The ~~method~~ use according to claim 16, wherein the Flaviviral infection is an infection by the Dengue virus or yellow fever virus.