CLAIMS:

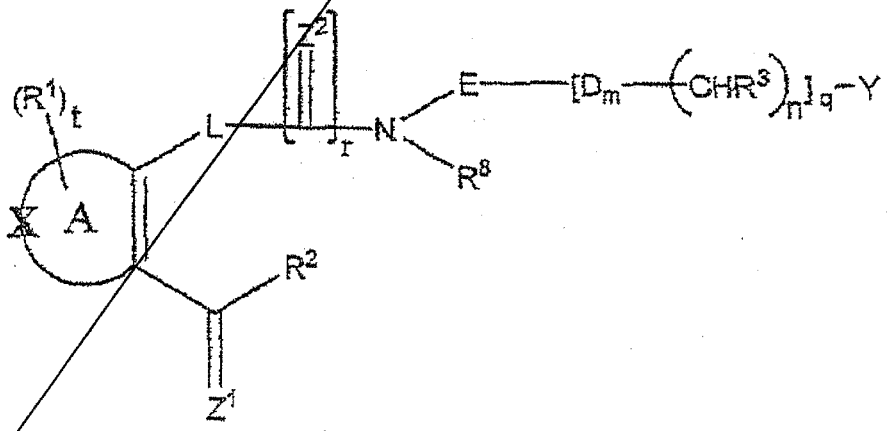
1. Use of a dihydroorotate-dehydrogenase inhibitor in the manufacture of a medicament for the treatment or amelioration of a disease or medical condition caused by a viral infection by

a virus selected from the group comprising Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Hepatitis B Virus (HBV), and Influenza, BK- Polyomavirus (BKV), Human Cytomegaly Virus (HCMV), Rift Valley Fever *Virus (RVFV), Norovirus (NV), Lassa Virus (LV), Ebolavirus (BBOV), West Nile Virus (WNV), Dengue Virus (DV), Human Respiratory Syncytial Virus (RSV), Yellow fever virus (YFV),

wherein the dihydroorotate-dehydrogenase inhibitor is a compound of the general formula (I) or a physiologically functional derivative,

wherein in said physiologically functional derivative one or more of the chemical groups of the compound of the general formula (I) are modified by a modification selected from the group comprising ester, phosphate or sulfate derivatives of hydroxyl groups; ester or amide derivatives of carboxylic groups; and imine, amide or urea derivatives of amino groups,

or a pharmacologically tolerable salt thereof,



(Formula I)

wherein

A is an aromatic or non-aromatic 5- or 6-membered hydrocarbon ring wherein optionally one or more of the carbon atoms are replaced by a group X, wherein X is independently selected from the group consisting of S, O, N, NR^4, SO_2 and SO;

L is a single bond or NH

D is O, S, SO_2, NR^4, or CH_2;

Z^1 is O, S, or NR^5;

Z^2 is 0, S, or NR^5;

R^1 independently represents H, halogen, haloalkanyl, haloalkenyl, haloalkynyl, haloalkanyloxy, haloalkenyloxy, haloalkynyloxy, $-CO_2R``$, $-SO_3H$, -OH, -CONR*R``, -CR``O, $-SO_2$-NR*R``, $-NO_2$, $-SO_2$-R`` -SO-R*, -CN, alkanyloxy, alkenyloxy, alkynyloxy, alkanylthio, alkenylthio, alkynylthio, aryl, -NR``-CO_2-R`, -NR``-CO-R*, -NR``-SO_2-R`, -O-CO-R*, -O-CO_2R*, -O-CO-NR*R``; cycloalkyl, heterocycloalkyl, alkanylamino, alkenylamino, alkynylamino, hydroxyalkanylamino, hydroxyalkenylamino, hydroxyalkynylamino, -SH, heteroaryl, alkanyl, alkenyl or alkynyl;

R* independently represents H, alkanyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aminoalkanyl, aminoalkenyl, aminoalkynyl, alkanyloxy, alkenyloxy, alkynyloxy, -OH, -SH, alkanylthio, alkenylthio, alkynylthio, hydroxyalkanyl, hydroxyalkenyl, hydroxyalkynyl, haloalkanyl, haloalkenyl, haloalkynyl, haloalkanyloxy, haloalkenyloxy, haloalkynyloxy, aryl or heteroaryl;

R` independently represents H, -C0$_2$R``, -CONR``R```, -CR``O, -$SO_2$NR``, -NR``-CO-haloalkanyl, haloalkenyl, haloalkynyl, $-NO_2$, -NR``-SO_2-haloalkanyl, haloalkenyl, haloalkynyl, -NR``-$SO_2$-alkanyl, -NR``-SO_2-alkenyl, -NR``-$SO_2$-alkynyl, -$SO_2$-alkanyl, -$SO_2$-alkenyl, -$SO_2$-alkynyl, -NR``-CO-alkanyl, -NR``CO-alkenyl, -NR``-CO-alkynyl, -CN, alkanyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aminoalkanyl, aminoalkenyl, aminoalkynyl, alkanylamino, alkenylamino, alkynylamino, alkanyloxy, alkenyloxy, alkynyloxy, -cycloalkyloxy, -OH, -SH, alkanylthio, alkenylthio, alkynylthio, hydroxyalkanyl, hydroxyalkenyl, hydroxyalkynyl, hydroxyalkanylamino, hydroxyalkenylamino, hydroxyalkynylamino, halogen, haloalkanyl, haloalkenyl, haloalkynyl, haloalkanyloxy, haloalkenyloxy, haloalkynyloxy, aryl, aralkyl or heteroaryl;

R`` independently represents hydrogen, haloalkanyl, haloalkenyl, haloalkynyl, hydroxyalkanyl, hydroxyalkenyl, hydroxylalkynyl, alkanyl alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aminoalkanyl, aminoalkenyl or aminoalkynyl

R``` independently represents H or alkanyl

R^2 is H or OR^6, NHR^7, NR^7OR^7;
or R^2 together with the nitrogen atom which is attached to R^8 forms a 5 to 7 membered, preferably 5 or 6 membered heteroyclic ring wherein R^2 is $-[CH_2]_s$ and R^8 is absent;

R^3 is H, alkanyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, alkanyloxy, alkenyloxy, alkynyloxy, -O-aryl; -O-cycloalkyl, -O-heterocycloalkyl, halogen, aminoalkanyl, aminoalkenyl, aminoalkynyl, alkanylamino, alkenylamino, alkynylamino, hydroxylamino, hydroxylalkanyl, hydroxylalkenyl, hydroxylalkynyl, haloalkanyloxy, haloalkenyloxy, haloalkynyloxy, heteroaryl, alkanylthio, alkenylthio, alkynylthio, -S-aryl; -S-cycloalkyl, -S-heterocycloalkyl, aralkyl, haloalkanyl, haloalkenyl or haloalkynyl;

R^4 is H, alkanyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

R^5 is H, OH, alkanyloxy, alkenyloxy, alkynyloxy, O-aryl, alkanyl, alkenyl, alkynyl or aryl;

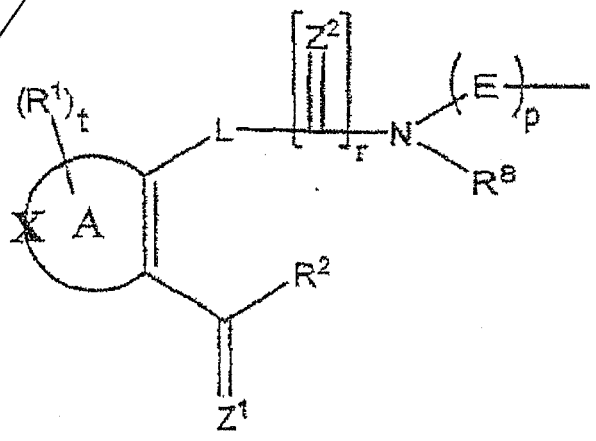
R^6 is H, alkanyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, alkanyloxyalkanyl, alkanyloxyalkenyl, alkanyloxyalkynyl, alkenyloxyalkanyl, alkenyloxyalkenyl, alkenyloxyalkynyl, alkynyloxyalkanyl, alkynyloxyalkenyl, alkynyloxyalkynyl, acylalkanyl, (acyloxy)alkanyl, (acyloxy)alkenyl, (acyloxy)alkynyl acyl, non-symmetrical (acyloxy)alkanyldiester, non-symmetrical (acyloxy)alkenyldiester, non-symmetrical (acyloxy)alkynyldiester, or dialkanylphosphate, dialkenylphosphate or dialkynylphosphate;

R^7 is H, OH, alkanyl, alkenyl, alkynyl, aryl, alkanyloxy, alkenyloxy, alkynyloxy, -O-aryl, cycloalkyl, heterocycloalkyl, or -O-cycloalkyl, -O-heterocycloalkyl;

R^8 is hydrogen, alkanyl, alkenyl or alkynyl;

E is an alkanyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl or cycloalkyl group or a fused bi-or tricyclic ring system wherein one phenyl ring is fused to one or two monocyclic cycloalkyl or heterocycloalkyl rings or one bicyclic cycloalkyl or heterocycloalkyl ring, or wherein two phenyl rings are fused to a monocyclic cycloalkyl or heterocycloalkyl ring, wherein monocyclic and bicyclic cycloalkyl and heterocycloalkyl rings are as defined herein, and wherein all of the aforementioned groups may optionally be substituted by one or more substituents R`

Y is hydrogen, halogen, haloalkanyl, haloalkenyl, haloalkynyl, haloalkanyloxy, haloalkenyloxy, haloalkynyloxy, alkanyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl or cycloalkyl group or a fused bi-or tricyclic ring system wherein one phenyl ring is fused to one or two monocyclic cycloalkyl or heterocycloalkyl rings or one bicyclic cycloalkyl or heterocycloalkyl ring, or wherein two phenyl rings are fused to a monocyclic cycloalkyl or heterocycloalkyl ring, and wherein all of the aforementioned groups may optionally be substituted by one or more substituents R`, or Y is



wherein R^1, X, A, Z^1, Z^2, R^8, R^2, E and p are as defined herein;

m is 0 or 1;
n is 0 or 1;
p is 0 or 1;
q is 0 or 1;
r is 0 or 1;
s is 0 to 2; and
t is 0 to 3.

2. The use of a dihydroorotate-dehydrogenase inhibitor according to claim 1, wherein the dihydroorotate-dehydrogenase inhibitor has a half-maximal inhibitory concentration (IC_{50}) of 50 nM or less for the inhibition of dihydroorotate-dehydrogenase or less in an *in vitro* assay and a half-maximal effective concentration (EC_{50}) of 200 nM or less for inhibition of viruses in an *in vitro* assay.

3. The use of a dihydroorotate-dehydrogenase inhibitor according to any of claims 1 to 2, wherein the dihydroorotate-dehydrogenase inhibitor has a solubility in water of 10 µg/mL or greater and/or an absolute oral availability (F) of 30% or greater.

4. Use of a pharmaceutical composition comprising a compound as defined in any of claims 1 to 3 in free form or in the form of a pharmaceutically acceptable salt or physiologically functional derivative,
wherein in said physiologically functional derivative one or more of the chemical groups of the compound of the general formula (I) are modified by a modification selected from the group comprising ester, phosphate or sulfate derivatives of hydroxyl groups; ester or amide derivatives of carboxylic groups; and imine, amide or urea derivatives of amino groups,
and a pharmaceutically acceptable diluent or carrier in the manufacture of a medicament for the treatment or amelioration of a disease or medical condition caused by a viral infection.

5. The use of a compound according to any of claims 1 to 3 or a composition according to claim 4 wherein the disease or indication is selected from the group comprising transplant rejection.

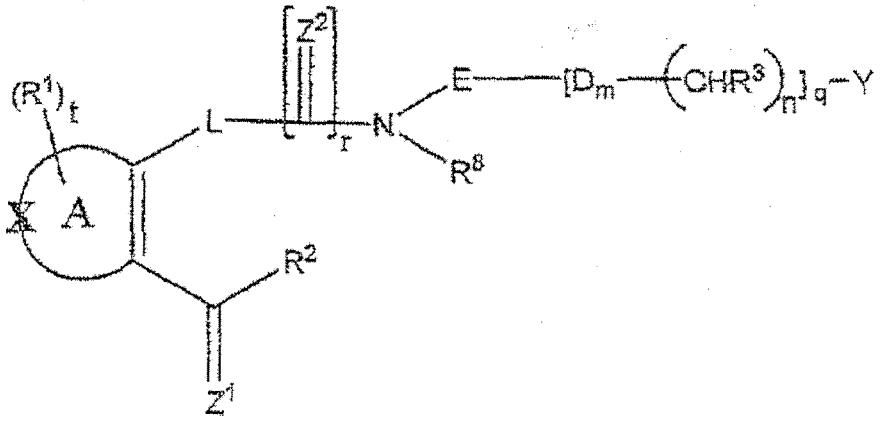
CLAIMS

1. The use of a dihydroorotate-dehydrogenase inhibitor in the manufacture of a medicament for treatment or amelioration of a disease or medical condition caused by a viral infection by a virus selected from the group comprising Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Hepatitis B Virus (HBV), and Influenza, BK-Polyomavirus (BKV), Human Cytomegaly Virus (HCMV), Rift Valley Fever Virus (RVFV), Norovirus (NV), Lassa Virus (LV), Ebolavirus (EBOV), West Nile Virus (WNV), Dengue Virus (DV), Human Respiratory Syncytial Virus (RSV), Yellow fever virus (YFV),

wherein the dihydroorotate-dehydrogenase inhibitor is a compound of the general formula (I) or a physiologically functional derivative,

wherein in said physiologically functional derivative one or more of the chemical groups of the compound of the general formula (I) are modified by a modification selected from the group comprising ester, phosphate or sulfate derivatives of hydroxyl groups; an ester or amide derivatives of carboxylic groups; and imine, amide or urea derivatives of amino groups,

or a pharmacologically tolerable salt thereof,



(Formula I)

wherein

A is furan, thiophene, phenyl, cyclopentenyl, cyclopentadienyl, pyridyl or dihydrothiophene;

L is a single bond;

D is O, or S;

Z^1 is O;

Z^2 is O;

R' independently represents H, -CO_2R", -CONR"R", -CR"O, -SO_2-NR", -NR"-CO-haloalkanyl, -haloalkenyl, -haloalkynyl, -NO_2, -NR"-SO_2-haloalkanyl, -haloalkenyl, -haloalkynyl, -NR"-SO_2-alkanyl, -NR"-SO_2-alkenyl, -NR"-SO_2-alkynyl, -SO_2-alkanyl, -SO_2-alkenyl, -SO_2-alkynyl, -NR"-CO-alkanyl, -NR"-CO-alkenyl, -NR"-CO-alkynyl, -CN, alkanyl, alkenyl. alkynyl. cycloalkyl, heterocycloalkyl, aminoalkanyl , aminoalkenyl, aminoalkynyl, alkanylamino. alkenylamino, alkynylamino, alkanyloxy, alkenyloxy. alkynyloxy, cycloalkyloxy, -OH, -SH, alkanylthio, alkenylthio, alkynylthio, hydroxyalkanyl, hydroxyalkenyl, hydroxyalkynyl, hydroxyalkanylamino, hydroxyalkenylamino, hydroxyalkynylamino, halogen, haloalkanyl, haloalkenyl, haloalkynyl, haloalkanyloxy, haloalkenyloxy, haloalkynyloxy, aryl, aralkyl or heteroaryl;

R" independently represents hydrogen, haloalkanyl, haloalkenyl, haloalkynyl, hydroxyalkanyl. hydroxyalkenyl, hydroxyalkynyl, alkanyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aminoalkanyl, aminoalkenyl or aminoalkynyl;

R"' independently represents H or alkanyl;

R^2 is OR^6,

R^3 is H,

R^6 is H,

R^8 is hydrogen,

E is phenyl or pyridyl, each of which is optionally substituted by one or more substituents R';

Y is phenyl, which is optionally substituted by one or more substituents R';

m is 1;

n is 1;

q is 0 or 1;

r is 1; and

t is 0.

2. The use according to claim 1, wherein in the compound of formula (I), L = single bond, Z^1 = O, Z^2 = O, r = 1, q = 0, t = 1, R^2 = OH, R^8 = H, and E is phenylene which is either unsubstituted or substituted with Cl, F and/or CF_3, OCH_3, OCH2CH_3, or OCF_3, and Y is phenyl which is either unsubstituted or substituted with CI, F and/or CF_3, OCH_3, OCH_2CH_3, or OCF_3, and A is thiophene, R^1 = H.

3. The use according to claim 1, wherein the compound of formula (I) is:
3-(2,3,5,6-tetrafluoro-3′-trifluoromethoxy-biphenyl-4-ylcarbamoyl)-thiophene-2-carboxylic acid;
4-(2′-chloro-3,5-difluoro-biphenyl-4-ylcarbamoyl)-2,5-dihydro-thiophene-3-carboxylic acid;
2-[3-chloro-4-(2-chloro-6-fluoro-benzyloxy)-phenylcarbamoyl]-cyclopent-1-enecarboxylic acid;
2-(2,3,5,6-Tetrafluoro-3′-trifluoromethoxy-biphenyl-4-ylcarbamoyl)-cyclopent-1-enecarboxylic acid;
2-[4-(2-chloro-6-fluoro-benzyloxy)-3-fluoro-phenylcarbamoyl]-cyclopent-1-enecarboxylic acid;
2-(3-fluoro-3′-methoxy-biphenyl-4-ylcarbamoyl)-cyclopent-1-enecarboxylic acid;
2-(3-biphenyl-4-ylureido)benzoic acid;
2-(2,3,5,6-tetrafluoro-3′-methoxybiphenyl-4-ylcarbamoyl)furan-3-carboxylic acid;
4-(3′-ethoxy-3,5-difluorobiphenyl-4-ylcarbamoyl)thiophene-3-carboxylic acid;
2-(2,3,5,6-tetrafluoro-3′-methoxybiphenyl-4-ylcarbamoyl)cyclopent-1-enecarboxylic acid;
2-(2,3,5,6-tetrafluoro-2′-methoxybiphenyl-4-ylcarbamoyl)cyclopent-1-enecarboxylic acid;
2-(3,5-difluoro-3′-(trifluoromethoxy)biphenyl-4-ylcarbamoyl)cyclopent-1-enecarboxylic acid;
3-hydroxy-2-(2,3,5,6-tetrafluoro-3′-(trifluoromethoxy)biphenyl-4-ylcarbamoyl)cyclopent-1-enecarboxylic acid;
2-(2-chloro-4′-methoxybiphenyl-4-ylcarbamoyl)cyclopent-1-enecarboxylic acid;
4-(3,5-difluoro-3′-(trifluoromethoxy)biphenyl-4-ylcarbamoyl)thiophene-3-carboxylic acid;
5-(4-(2-chloro-6-fluorobenzyloxy)-3-fluorophenylcarbamoyl)cyclopenta-1,4-dienecarboxylic acid;
3-(3,5-difluoro-3′-(trifluoromethoxy)biphenyl-4-ylcarbamoyl)thiophene-2-carboxylic acid;
2-(3-fluoro-3′-methoxybiphenyl-4-ylamino)nicotinic acid;
2-(3,5-difluoro-3′-methoxybiphenyl-4-ylamino)nicotinic acid;
5-cyclopropyl-2-(5-methyl-6-(3-(trifluoromethoxy)phenyl)pyridin-3-ylamino)benzoic acid;
2-[4-(2-chloro-6-fluoro-benzyloxy)-3-fluoro-phenylcarbamoyl]-cyclopent-1-enecarboxylic acid;
2-[3,5-dichloro-4-(2-chloro-6-fluoro-benzyloxy)-phenylcarbamoyl]-cyclopent-1-enecarboxylic acid;
2-(2-chloro-4′-dimethylamino-biphenyl-4-ylcarbamoyl)-cyclopent-1-enecarboxylic acid;
3-(3-fluoro-3′-methoxy-biphenyl-4-ylcarbamoyl)-thiophene-2-carboxylic acid; or
4-(2,3,5,6-tetrafluoro-3′-trifluoromethoxy-biphenyl-4-ylcarbamoyl)-2,5-dihydro-thiophene-3-carboxylic acid.

4. The use according to claim 1, wherein the compound of formula (I) is 3-(2,3,5,6-tetrafluoro-3′-trifluoromethoxy-biphenyl-4-ylcarbamoyl)-thiophene-2-carboxylic acid.