Dihydroorotate - Dehydrogenase Inhibitors~~Anti-Inflammatory Agents~~ as Virostatic Compounds

Description

The present invention relates to compounds that have been described as anti-inflammatory, immunomodulatory and antiproliferatory agents and surprisingly show virostatic activities. In particular the invention refers to the use of compounds which inhibit dihydroorotate dehydrogenase (DHODH), for the treatment and prevention of viral diseases, in particular HCMV, HIV, HCV, HBV, and influenza.

Viral infections are usually treated with substances targeting viral proteins, e.g. influenza is treated with M2-membrane protein inhibitors (adamantin and rimantadin) or neuraminidase inhibitors (oseltamivir and zanamivir); HIV is treated with HIV protease inhibitors, reverse transcriptase inhibitors (nucleoside and non-nucleoside analoga), fusion inhibitors (blocking the viral transmembrane protein gp41) or cell entry inhibitors; HCV is treated by a combination of ribavirin and interferone alpha, where ribavirin as a nucleoside analogue inhibits the viral polymerase, and interferone alpha activates the host immune system; HBV is treated with pegylated interferone alpha and/or nucleoside or nucleotide analoga.

However, treatment of these viral diseases is not satisfactory due to the high mutation rate of viruses and the thus resulting lack of efficacy of presently known medications. Moreover, severe side effects caused by interaction with host factors or by incompatibility of treatments for patients who are infected with two or several different viruses occur regularly. In view of the viruses' abilities to quickly adapt to new selection pressures caused by substances targeting viral proteins, new treatment options for viral diseases are urgently required. A new approach to circumvent the selection pressure on viruses and thus avoid the generation of resistences is the targeting of host cell factors vital for the viral replication cycle.

The active metabolite of leflunomide, a DHODH inhibitor with a completely different structure has been discussed and tested lately in several viral infection models as well as in infected patients (Gabriel T. Meister, dissertation Ohio State University 2005; Chong et al. Am. J. Transplant 2006 6(1): 69-75), however, anti-viral activity is largely attributed to the inhibition of protein kinases which results in inhibition of phosphorylation of viral proteins. Moreover, administration of uridine in viral plaque assays did not affect the reduction of viral loads in a cytomegalovirus (CMV) model; an inhibitor exerting its activity by the inhibition of DHODH, however, according to the above-cited publications would be expected to lose its inhibitory potential when the assay is supplemented with uridine.

The compounds to which this invention relates have been described as DHODH inhibitors before (WO 03/006425, WO 04/056746, WO 04/056797, WO04056747, WO 08/077639, WO 09/021696), and the treatment of diseases caused by viral infections has been mentioned.

The pathogenity of viruses heavily relies on host cell machinery for replication, leading to a high need of nucleobase building blocks due to the high replication rate of the viruses. It has now been found unexpectedly, that the inhibition of DHODH, which leads to an inhibition of the *de novo* biosyntheses of pyrimidines can be exploited to suppress the replication of certain viruses.

Summary

Here we disclose that the use of substances according to formula I is particularly advantageous for the treatment of diseases caused by the following viruses:

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), Yellow fever virus (YFV), Human Respiratory Syncytial Virus (RSV).

Thus, in particular, the subject of the present disclosure~~invention~~ comprises the following embodiments~~aspects~~:

r is 0 or 1;

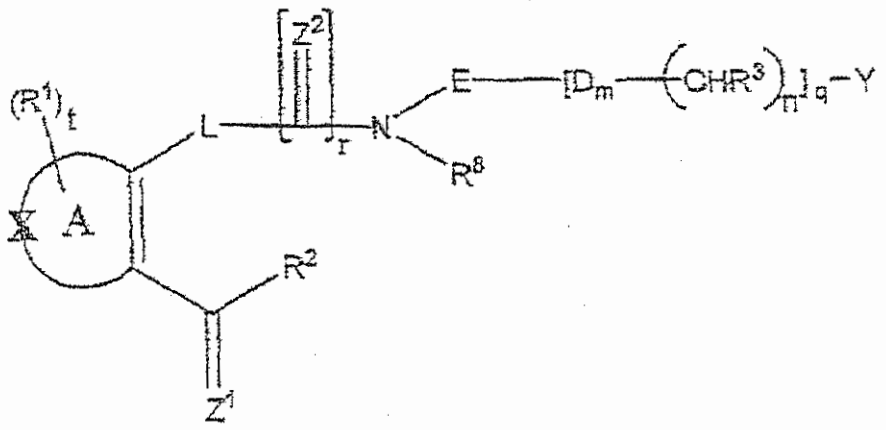
s is 0 to 2; and

t is 0 to 3.

6. A pharmaceutical composition comprising a compound as defined in any of aspects 1 to 5 in free form or in the form of a pharmaceutically acceptable salt or physiologically functional derivative and a pharmaceutically acceptable diluent or carrier for use in the treatment or amelioration of a disease or medical condition caused by a viral infection.

7. A compound according to any of aspects 1 to 5 or a composition according to aspect 6 wherein the disease or indication is selected from the group comprising transplant rejection.

In an aspect, there is provided 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;

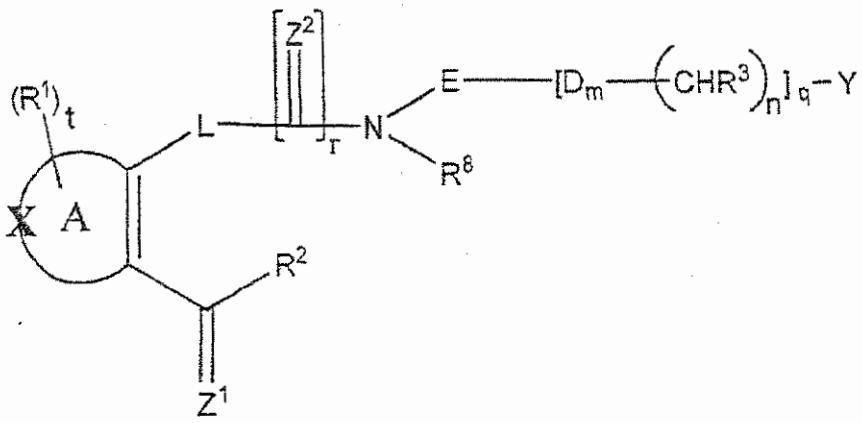
R'" independently represents H or alkanyl;

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.

Detailed Description

Compounds of Formula (I) comprise the following substances:

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;