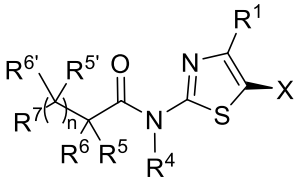
Enantiomers of Substituted Thiazoles as Antiviral Compounds

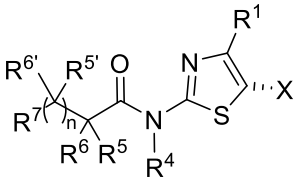
SUMMARY OF THE INVENTION

The present invention relates to novel antiviral compounds with specific stereoconfiguration, especially to specific novel enantiomers, to a process for their preparation and to their use as medicaments, in particular as antiviral medicaments.

In one aspect, there is provided compounds according to the Formula (**Ia**) and/or (**Ib**):

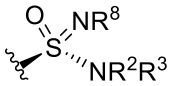
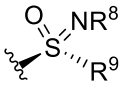

(Ia)

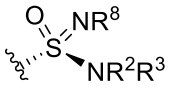
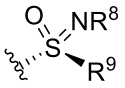
or


(Ib)

wherein

X is selected from


and

, or


and

, respectively;

R^1 is selected from H, halogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, hydroxy-C_{1-6}-alkyl, C_{3-6}-cycloalkyl, halo-C_{3-6}-cycloalkyl, -O-C_{1-6}-alkyl, -O-halo-C_{1-6}-alkyl and -NH-C_{1-6}-alkyl,

R^2 is selected from H, -CN, -NO_2, C_{1-10}-alkyl, C_{2-10}-alkenyl, C_{2-10}-alkynyl, C_{0-10}-alkylene-C_{3-10}-cycloalkyl, C_{0-10}-alkylene-C_{3-10}-heterocycloalkyl, C_{0-10}-alkylene-(5- to 10-membered heteroaryl), C_{0-10}-alkylene-(6- to 10-membered aryl), C_{0-10}-alkylene-(6- to 10-membered heteroaryl), C_{0-10}-alkylene-OR^{11}, C_{0-10}-alkylene-CO_2R^{11}, C_{0-10}-alkylene-$C(=O)NR^{11}R^{12}$, C_{0-10}-alkylene-$C(=S)NR^{11}R^{12}$, C_{0-10}-alkylene-$C(=O)NR^{11}SO_2R^{13}$, C_{0-10}-alkylene-$C(=S)NR^{11}SO_2R^{11}$, C_{0-10}-alkylene-$C(=O)R^{11}$, C_{0-10}-alkylene-$C(=S)R^{11}$, C_{0-10}-alkylene-SR^{11}, C_{0-10}-alkylene-SO_xR^{13}, C_{0-10}-alkylene-SO_3R^{11}, C_{0-10}-alkylene-$SO_2NR^{11}R^{12}$, C_{0-10}-alkylene-$NR^{11}C(=O)R^{11}$, C_{0-10}-alkylene-$NR^{11}C(=S)R^{11}$, C_{0-10}-alkylene-$NR^{11}SO_2R^{13}$, C_{0-10}-alkylene-$NR^{11}C(=O)NR^{11}R^{12}$, C_{0-10}-alkylene-$NR^{11}C(=S)NR^{11}R^{12}$, C_{0-10}-alkylene-$NR^{11}SO_2NR^{11}R^{12}$, C_{0-10}-alkylene-$NR^{11}R^{12}$, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of oxo, CN, -NO_2, OR^{11}, O-C_{2-6}-alkylene-OR^{11}, C_{1-6}-

alkyl, halo-C_{1-6}-alkyl, halogen, CO_2R^{11}, $C(=O)NR^{11}R^{12}$, $C(=O)NR^{11}SO_2R^{11}$, $C(=O)R^{11}$, SR^{11}, SO_xR^{11}, SO_3R^{11}, $P(=O)(OR^{11})_2$, $SO_2NR^{11}R^{12}$, $NR^{11}C(=O)R^{11}$, $NR^{11}SO_2R^{13}$, $NR^{11}C(=O)NR^{11}R^{12}$, $NR^{11}SO_2NR^{11}R^{12}$, C_{3-10}-cycloalkyl, O-C_{3-10}-cycloalkyl, C_{3-10}-heterocycloalkyl, O-C_{3-10}-heterocycloalkyl and $NR^{11}R^{12}$,

R^3 is selected from H, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, -O-C_{1-6}-alkyl, -O-halo-C_{1-6}-alkyl, C_{3-6}-cycloalkyl and C_{3-6}-heterocycloalkyl, wherein alkyl, cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 5 substituents independently selected from halogen, -CN, OH, oxo, C_{1-3}-alkyl, halo-C_{1-3}-alkyl, O-C_{1-3}-alkyl, O-halo-C_{1-3}-alkyl, SO_2-C_{1-3}-alkyl, CO_2H;

or R^2 and R^3 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms, wherein 1 or 2 carbon atoms can be replaced by heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, $-NO_2$, OH, oxo, C_{1-3}-alkyl, halo-C_{1-3}-alkyl, O-C_{1-3}-alkyl, O-halo-C_{1-3}-alkyl, SO_2-C_{1-3}-alkyl, CO_2H;

R^4 is selected from H, C_{1-6}-alkyl, C_{1-6}-acyl, C_{2-6}-alkenyl, C_{3-8}-cycloalkyl and C_{3-8}-heterocycloalkyl, wherein alkyl, acyl, alkenyl, cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 5 substituents independently selected from halogen, -CN, OH, oxo, C_{1-3}-alkyl, halo-C_{1-3}-alkyl, O-C_{1-3}-alkyl, O-halo-C_{1-3}-alkyl;

R^5 and R^6 and $R^{5'}$ and $R^{6'}$ are independently selected from H, halogen, C_{1-6}-alkyl, NH_2, NHC_{1-6}-alkyl, $N(C_{1-6}$-alkyl$)_2$, C_{0-6}-alkylene-$C(=O)NH_2$;

or R^5 and R^6 and $R^{5'}$ and $R^{6'}$ independently when taken together with the carbon to which they are attached complete a 3- to 8-membered ring containing carbon atoms, wherein 1 or 2 carbon atoms can be replaced by heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, $-NO_2$, OH, oxo, C_{1-3}-alkyl, halo-C_{1-3}-alkyl, O-C_{1-3}-alkyl, O-halo-C_{1-3}-alkyl, SO_2-C_{1-3}-alkyl, CO_2H,

or R^5 and $R^{5'}$ and R^6 and $R^{6'}$ independently when taken together with the two adjacent carbon to which they are attached complete a 3- to 8-membered ring containing carbon atoms wherein 1 or 2 carbon atoms can be replaced by heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, $-NO_2$, OH, oxo, C_{1-3}-alkyl, halo-C_{1-3}-alkyl, O-C_{1-3}-alkyl, O-halo-C_{1-3}-alkyl, SO_2-C_{1-3}-alkyl, CO_2H,

R^7 is selected from a 6-membered aryl and 5- or 6-membered heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, -CN, $-NO_2$, OH, C_{1-6}-alkyl, O-C_{1-6}-alkyl, C_{3-6}-cycloalkyl, O-C_{3-6}-cycloalkyl, C_{3-}

$_6$-heterocycloalkyl, O-C_{3-6}-heterocycloalkyl, SO_y-C_{1-6}-alkyl, CO_2H, C(=O)O-C_{1-6}-alkyl, 6- to 10-membered aryl, 5- or 10-membered heteroaryl, O-(6- to 10-membered aryl) and O-(5- or 10-membered heteroaryl), wherein

alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 5 substituents independently selected from halogen, -CN, $-NO_2$, OH, R^{13}, OR^{13}, CO_2R^{11}, $NR^{11}R^{12}$, $C(=O)R^{11}$, $C(=S)R^{11}$, $C(=O)NR^{11}R^{12}$, $NR^{11}C(=O)NR^{11}R^{12}$, $NR^{11}C(=O)OR^{13}$, $OC(=O)NR^{11}R^{12}$, $C(=S)NR^{11}R^{12}$, $NR^{11}C(=S)NR^{11}R^{12}$, $NR^{11}C(=S)OR^{13}$, $OC(=S)NR^{11}R^{12}$; SO_y-C_{1-6}-alkyl, SO_y-halo-C_{1-6}-alkyl, SR^{11}, SO_xR^{13}, SO_3R^{11}, $SO_2NR^{11}R^{12}$, $NR^{11}SO_2R^{13}$, $NR^{11}SO_2NR^{11}R^{12}$,

R^8 is selected from H, -CN, $-NO_2$, C_{1-10}-alkyl, C_{2-10}-alkenyl, C_{2-10}-alkynyl, C_{0-10}-alkylene-C_{3-10}-cycloalkyl, C_{0-10}-alkylene-C_{3-10}-heterocycloalkyl, C_{0-10}-alkylene-(5 to 10-membered heteroaryl), C_{0-10}-alkylene-(6 to 10-membered aryl), C_{0-10}-alkylene-(6 to 10-membered heteroaryl), C_{0-10}-alkylene-OR^{11}, C_{0-10}-alkylene-CO_2R^{11}, C_{0-10}-alkylene-$C(=O)NR^{11}R^{12}$, C_{0-10}-alkylene-$C(=S)NR^{11}R^{12}$, C_{0-10}-alkylene-$C(=O)NR^{11}SO_2R^{13}$, C_{0-10}-alkylene-$C(=S)NR^{11}SO_2R^{11}$, C_{0-10}-alkylene-$C(=O)R^{11}$, C_{0-10}-alkylene-$C(=S)R^{11}$, C_{0-10}-alkylene-SR^{11}, C_{0-10}-alkylene-SO_x-R^{13}, C_{0-10}-alkylene-SO_3R^{11}, C_{0-10}-alkylene-$SO_2NR^{11}R^{12}$, C_{0-10}-alkylene-$NR^{11}C(=O)R^{11}$, C_{0-10}-alkylene-$NR^{11}C(=S)R^{11}$, C_{0-10}-alkylene-$NR^{11}SO_2R^{11}$, C_{0-10}-alkylene-$NR^{11}C(=O)NR^{11}R^{12}$, C_{0-10}-alkylene-$NR^{11}C(=S)NR^{11}R^{12}$, C_{0-10}-alkylene-NR^{11}-SO_2-$NR^{11}R^{12}$, C_{0-10}-alkylene-$NR^{11}R^{12}$, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of oxo, CN, $-NO_2$, OR^{11}, O-C_{2-6}-alkylene-OR^{11}, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, halogen, CO_2R^{11}, $CONR^{11}R^{12}$, $CONR^{11}SO_2R^{11}$, COR^{11}, SO_xR^{11}, SO_3H, $PO(OH)_2$, $SO_2NR^{11}R^{12}$, $NR^{11}COR^{11}$, $NR^{11}SO_2R^{11}$, NR^{11}-CO-$NR^{11}R^{12}$, NR^{11}-SO_2-$NR^{11}R^{12}$, C_{3-10}-cycloalkyl, O-C_{3-10}-cycloalkyl, C_{3-10}-heterocycloalkyl, O-C_{3-10}-heterocycloalkyl and $NR^{11}R^{12}$,

R^9 is selected from C_{1-10}-alkyl, C_{2-10}-alkenyl, C_{2-10}-alkynyl, C_{0-10}-alkylene-C_{3-10}-cycloalkyl, C_{0-10}-alkylene-C_{3-10}-heterocycloalkyl, C_{0-10}-alkylene-(5- to 10-membered heteroaryl), C_{0-10}-alkylene-(6- to 10-membered aryl), C_{0-10}-alkylene-(6- to 10-membered heteroaryl), C_{0-10}-alkylene-OR^{11}, C_{0-10}-alkylene-CO_2R^{11}, C_{0-10}-alkylene-$C(=O)NR^{11}R^{12}$, C_{0-10}-alkylene-$C(=S)NR^{11}R^{12}$, C_{0-10}-alkylene-$C(=O)NR^{11}SO_2R^{13}$, C_{0-10}-alkylene-$C(=S)NR^{11}SO_2R^{11}$, C_{0-10}-alkylene-$C(=O)R^{11}$, C_{0-10}-alkylene-$C(=S)R^{11}$, C_{0-10}-alkylene-SR^{11}, C_{0-10}-alkylene-SO_xR^{13}, C_{0-10}-alkylene-SO_3R^{11}, C_{0-10}-alkylene-$SO_2NR^{11}R^{12}$, C_{0-10}-alkylene-$NR^{11}C(=O)R^{11}$, C_{0-10}-alkylene-$NR^{11}C(=S)R^{11}$, C_{0-10}-alkylene-$NR^{11}SO_2R^{13}$, C_{0-10}-alkylene-$NR^{11}C(=O)NR^{11}R^{12}$, C_{0-10}-alkylene-$NR^{11}C(=S)NR^{11}R^{12}$, C_{0-10}-alkylene-$NR^{11}SO_2NR^{11}R^{12}$, C_{0-10}-alkylene-$NR^{11}R^{12}$, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from the

group consisting of oxo, CN, $-NO_2$, OR^{11}, $O-C_{2-6}$-alkylene-OR^{11}, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, halogen, CO_2R^{11}, $C(=O)NR^{11}R^{12}$, $C(=O)NR^{11}SO_2R^{11}$, $C(=O)R^{11}$, SR^{11}, SO_xR^{11}, SO_3R^{11}, $P(=O)(OR^{11})_2$, $SO_2NR^{11}R^{12}$, $NR^{11}C(=O)R^{11}$, $NR^{11}SO_2R^{13}$, $NR^{11}C(=O)NR^{11}R^{12}$, $NR^{11}SO_2NR^{11}R^{12}$, C_{3-10}-cycloalkyl, $O-C_{3-10}$-cycloalkyl, C_{3-10}-heterocycloalkyl, $O-C_{3-10}$-heterocycloalkyl and $NR^{11}R^{12}$,

R^{11} is independently selected from H, C_{1-6}-alkyl, C_{0-6}-alkylene-C_{3-10}-cycloalkyl and C_{0-6}-alkylene-C_{3-10}-heterocycloalkyl, wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, -CN, OH, oxo, C_{1-3}-alkyl, halo-C_{1-3}-alkyl, $O-C_{1-3}$-alkyl, O-halo-C_{1-3}-alkyl, NH_2, $NH(C_{1-3}$-alkyl), $N(C_{1-3}$-alkyl)$_2$, C_{3-6}-heterocycloalkyl, C_{3-6}-cycloalkyl, SO_2-NHC_{1-3}-alkyl, SO_2-$N(C_{1-3}$-alkyl)$_2$ and SO_2-C_{1-3}-alkyl, wherein cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, OH, oxo, CH_3, CHF_2 and CF_3,

R^{12} is independently selected from H, C_{1-6}-alkyl, halo-C_{1-6}-alkyl and C_{3-6}-cycloalkyl,

or R^{11} and R^{12} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms, wherein 1 or 2 carbon atoms can be replaced by heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, $-NO_2$, OH, oxo, C_{1-3}-alkyl, halo-C_{1-3}-alkyl, $O-C_{1-3}$-alkyl, O-halo-C_{1-3}-alkyl, SO_2-C_{1-3}-alkyl, CO_2H;

R^{13} is independently selected from C_{1-6}-alkyl, C_{0-6}-alkylene-C_{3-10}-cycloalkyl and C_{0-6}-alkylene-C_{3-10}-heterocycloalkyl, wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, -CN, OH, oxo, C_{1-3}-alkyl, halo-C_{1-3}-alkyl, $O-C_{1-3}$-alkyl, O-halo-C_{1-3}-alkyl, NH_2, $NH(C_{1-3}$-alkyl), $N(C_{1-3}$-alkyl)$_2$, C_{3-6}-heterocycloalkyl, C_{3-6}-cycloalkyl, SO_2-NHC_{1-3}-alkyl, SO_2-$N(C_{1-3}$-alkyl)$_2$ and SO_2-C_{1-3}-alkyl, wherein cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, OH, oxo, CH_3, CHF_2 and CF_3,

n is selected from 0 and 1,

x is independently selected from 1 and 2,

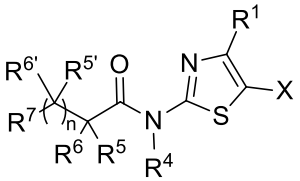
y is independently selected from 0, 1 and 2,

and wherein R^1 can be connected to one residue selected from R^2, R^3, R^8, R^9, R^{10} or R^{12} to form a 5 to 8-membered heterocycle, which is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, $-NO_2$, OH, oxo, C_{1-3}-alkyl, halo-C_{1-3}-alkyl, $O-C_{1-3}$-alkyl, O-halo-C_{1-3}-alkyl, SO_2-C_{1-3}-alkyl, CO_2H;

or a tautomer, N-oxide, solvate and pharmaceutically acceptable salt thereof, and wherein for any of R^1 to R^{13} the term heterocycloalkyl represents a saturated or partially unsaturated 3- to 10-membered ring containing 1, 2 or 3 heteroatoms independently selected from N, O, and S and the term heteroaryl represents a 5- to 10-membered mono- or bicyclic heteroaromatic ring system containing 1 to 5 heteroatoms independently selected from N, O, and S.

In another aspect there is provided a process for preparing the compounds according to Formula (**Ia**) or (**Ib**) as described on, the process comprising the steps of:

a) providing a mixture comprising the compounds of the Formulae (**Ia**) and (**Ib**), such mixture being represented by the general Formula (**I**):



(I)

, and

b) separating and isolating the compounds of the Formula (**Ia**) or (**Ib**) using HPLC on a chiral column;

wherein in the Formula (**I**) the substituents have the meaning as defined herein.

In another aspect, there is provided a compound as described herein or obtaineable by a process as described herein for use as an antiviral drug.

In yet another aspect, there is provided process for preparing the compounds according to Formula (Ia) or (Ib) as described herein by stereoselective synthesis.

In a further aspect, there is provided a use of a compound as described herein or obtainable by a process described herein in the preparation of a medicament for the treatment or prophylaxis of a disease or disorder caused by herpes viruses.

In another aspect, there is provided a use of a compound as described herein or obtainable by a process described herein in the preparation of a medicament for the treatment or prophylaxis of a disease or disorder caused by wild type or genetically engineered herpes viruses which nucleic acids encode a helicase and/or primase and the herpes virus is susceptible to said compounds based on the helicase and/or primase mechanism of action.

In yet another aspect, thereis provided a use of a compound as described herein or obtainable by a process described herein in the preparation of a medicament for the treatment or prophylaxis of neurodegenerative diseases caused by herpes viruses, including Alzheimer's disease.

In a further aspect, there is provided a use of a compound as described herein or obtainable by a process described herein in the preparation of a medicament for the treatment and prophylaxis of herpes infections, including herpes simplex infections, in patients displaying herpes labialis, herpes genitalis and herpes-related keratitis, in patients displaying Alzheimer's disease, encephalitis, pneumonia, hepatitis or viral shedding; in patients with a suppressed immune system, including AIDS patients, cancer patients, patients having a genetic or inherited immunodeficiency, transpant patients; in new-born children and infants; in herpes-positive patients, in particular herpes-simplex-positive patients, for suppressing recurrence or viral shedding (suppression therapy); patients, in particular in herpes-positive patients, in particular herpes-simplex-positive patients, who are resistant to nucleosidic antiviral therapy such as acyclovir, penciclovir, famciclovir, ganciclovir, valacyclovir and/or foscarnet or cidofovir

In a further aspect, there is provided a pharmaceutical composition having antiviral activity comprising one or more of the compounds as described herein or obtainable by a process described herein, and at least one pharmaceutically acceptable carrier and/or excipient and/or at least one further substance having antiviral activity or having immune modulating activity and being effective in treating a disease or disorder caused by herpes viruses

INTRODUCTION

The pandemic of viral infections has plagued humanity since ancient times, causing muco-cutaneous infection such as herpes labialis and herpes genitalis. Disease symptoms often interfere with everyday activities and occasionally HSV infections are the cause of life-threatening (encephalitis) or sight-impairing disease (keratitis), especially in neonates, elderly and the immunocompromised patient population such as transplant or cancer patients or patients with an inherited immunodeficiency syndrome or disease. After infection the alpha herpesviridae persist for life in neurons of the host in a latent form, periodically reactivating and often resulting in significant psychosocial distress for the patient. Currently no cure is available.

So far, vaccines, interleukins, interferones, therapeutic proteins, antibodies, immunomodulators and small- molecule drugs with specific or non-specific modes of action either lacked efficacy or

the required safety profile to replace the nucleosidic drugs acyclovir, valacyclovir and famciclovir as the first choice of treatment.

The known thiazolylamides are the most potent drugs in development today. These antiviral agents act by a novel mechanism of action and display low resistance rates *in vitro* and superior efficacy in animal models compared to nucleosidic drugs, however, development is hampered by off target carbonic anhydrase activity and an unusual pharmacokinetic profile.

This patent application discloses new antiviral compounds lacking (or at least with significantly reduced) carbonic anhydrase activity, showing an improved solubility and a suitable pharmacokinetic profile for use as a medicament.

PRIOR ART

2-Aminothiazol-5-sulfonamides are known from the publication C. Ziegler et al., *J. Org. Chem.* **1960**:25,1454. Moreover, the German Offenlegungsschrift 2101640 describes *N*-thiazol-2-yl-amides and -ureas having herbicidal action.

WO97/24343 relates to phenylthiazole derivates having anti-herpes virus properties.

WO99/42455 likewise relates to phenylthiazole derivates having anti-herpes virus properties.

WO99/47507 relates to 1,3,4-thiadiazoles derivates having anti-herpes virus properties.