

Diastereomeric aminoalcohol and aminoether salts of 2-[(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetic acid and their use for enantiomeric separation

The present invention relates to aminoalcohol and aminoether salts of 2-[(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetic acid, a method of producing those and a method for enantiomeric separation. The invention further relates to methods of preparation of 2-[(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetic acid (“Letermovir”) or salts or solvates thereof via enantiomeric separation from a mixture comprising 2-[(4R)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetic acid (“R-Enantiomer”) and Letermovir or salts or solvates or solvates of salts or co-crystals or solvates of co-crystals or salts of co-crystals or solvates of salts of co-crystals thereof.

Background of the invention

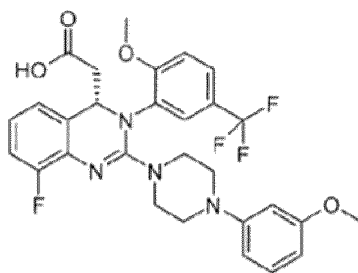
Cytomegalovirus (CMV) is a common opportunistic infection that causes significant morbidity and preventable mortality after solid-organ and allogeneic hematopoietic stem cell transplantation.

Human Cytomegalovirus is a species of virus that belongs to the viral family known as *Herpesviridae* or herpes viruses. It is typically abbreviated as HCMV and is alternatively known as human herpesvirus-5 (HHV-5). Within *Herpesviridae*, HCMV belongs to the *Betaherpesvirinae* subfamily, which also includes cytomegaloviruses from other mammals.

Letermovir is known as a highly active drug for addressing HCMV infection and extensively described in *Lischka et al., In Vitro and In Vivo Activities of the Novel Anticytomegalovirus Compound Letermovir. Antimicrob. Agents Chemother.* 2010, 54: p.1290–1297, and *Kaul et al., First report of successful treatment of multidrug-resistant cytomegalovirus disease with the novel anti-CMV compound Letermovir. Am. J. Transplant.* 2011, 11:1079-1084; as well as *Marschall et al., In Vitro Evaluation of the*

Activities of the Novel Anticytomegalovirus Compound Letermovir against Herpesviruses and Other Human Pathogenic Viruses. Antimicrob. Agents Chemother. 2012, 56:1135-1137.

The precise chemical name of Letermovir is 2-[(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetic acid, which has the structure as depicted below:



Letermovir was developed by the applicant as an antiviral agent, in particular for prophylaxis of the human cytomegalovirus (HCMV) in human transplant patients. The synthesis of Letermovir is disclosed in WO 2006/133822 and WO 2004/096778.

Salts of Letermovir are described in WO 2013/127971. Particularly, some solvates of sodium and calcium salts of Letermovir have been prepared in crystalline and amorphous form. In case of the sodium salt of Letermovir, mixed alcohol water solvates, such as methanol or ethanol hydrates were obtained (example 1 of WO 2013/127971). The trihydrate of sodium salt of Letermovir is described in WO 2021/170874 and the monohydrate form is disclosed in WO 2021/170879. A potassium salt of Letermovir and its solvates are described in WO 2021/170882. The tosylate and besylate salts of Letermovir and their preparation is disclosed in WO 2013/127968.

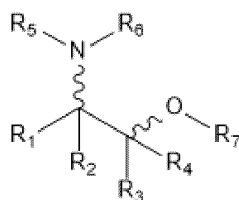
For preparation of enantiomerically pure Letermovir there is an inevitable need to separate enantiomers in one of the synthesis steps. In WO 2004/096778 the enantiomers are separated by preparative HPLC on a chiral column. In WO 2006/133822 enantiomeric separation of one of the synthesis intermediates via crystallization with (2S,3S)-2,3-bis[(4-methylbenzoyl)oxy]succinic acid is described.

There remains a need, however, for a robust method of enantiomeric separation of the synthesis end-product 2-[(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetic acid, regardless of its synthesis method. It has been surprisingly discovered that the 4R- and 4S-enantiomers of 2-[(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetic acid can be efficiently separated via formation of the diastereomeric salts of aminoalcohols and aminoethers with very high enantiomeric purity. A particular advantage is that the synthesis end-product can be directly converted to Letermovir or the desired salt or solvate form thereof. A further advantage is that the method of the present invention is easily scalable for real manufacturing.

Description of the invention

The first aspect of the present invention relates to a method for producing 2-[(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl] acetic acid (“Letermovir”) or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, comprising the steps:

- i) providing a mixture comprising Letermovir and 2-[(4R)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl] acetic acid (“R-Enantiomer”) or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;
- ii) contacting said mixture with an enantiomerically enriched compound of Formula (I)



(I)

wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I),

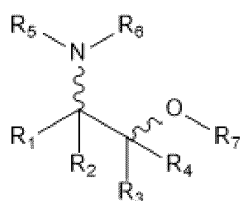
iii-1) separating the Letemovir salt of the compound of Formula (I);

iv-1) converting the Letemovir salt of the compound of Formula (I) into Letemovir or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof; and optionally

v-1) isolating Letemovir or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof.

Another aspect of the present invention relates to a method for producing a Letemovir salt of a compound of Formula (I), comprising the steps:

- i) providing a mixture comprising Letemovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;
- ii) contacting said mixture with an enantiomerically enriched compound of Formula (I)



(I)

wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

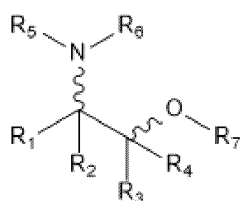
wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I);

iii-1) separating the Letemovir salt of the compound of Formula (I).

Another aspect of the present invention relates to a method for producing an R-Enantiomer salt of a compound of Formula (I), comprising the steps:

- i) providing a mixture comprising Letemovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;
- ii) contacting said mixture with an enantiomerically enriched compound of Formula (I)



(I)

wherein

R_1 and R_2 each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R_3 and R_4 each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R_5 and R_6 each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R_7 is H or C₁-C₆-alkyl,

wherein R_1 and R_3 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R_1 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R_3 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R_1 and R_5 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

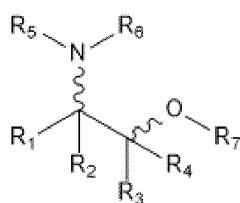
wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I);

iii-2) separating the R-Enantiomer salt of the compound of Formula (I).

Another aspect of the present invention relates to a method for enantiomeric separation of a mixture comprising Letemovir and R-Enantiomer comprising the steps:

- i) providing a mixture comprising Letemovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;
- ii) contacting said mixture with an enantiomerically enriched compound of Formula (I)



(I)

wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinoliny and methoxyquinoliny,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I),

iii-1) separating the Letemovir salt of the compound of Formula (I);

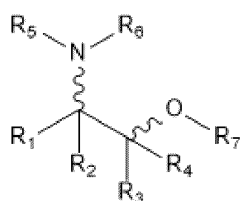
iv-1) transferring the Letemovir salt of the compound of Formula (I) into the compound of Formula (I) and Letemovir and optionally

v-1) isolating Letemovir.

Another aspect of the present invention relates to a method for enantiomeric separation of a mixture comprising Letemovir and R-Enantiomer comprising the steps:

i) providing a mixture comprising Letemovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;

ii) contacting said mixture with an enantiomerically enriched compound of Formula (I)



(I)

wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R_5 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C_3 - C_6 -heterocyclic ring,

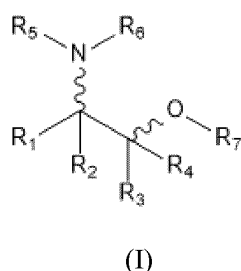
thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I);

iii-2) separating the R-Enantiomer salt of the compound of Formula (I);

iv-2) transferring the R-Enantiomer salt of the compound of Formula (I) into the compound of Formula (I) and R-Enantiomer; and optionally

v-2) isolating R-Enantiomer.

Another aspect of the present invention relates to use of a compound of Formula (I) for producing Letemovir or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, wherein the compound of Formula (I) is



wherein

R_1 and R_2 each is independently selected from the group consisting of H, C_1 - C_6 -alkyl, phenyl, methoxyphenyl, benzyl and CH_2OH ,

R_3 and R_4 each is independently selected from the group consisting of H, C_1 - C_6 -alkyl, phenyl, benzyl, 4-nitrophenyl, quinoliny and methoxyquinoliny,

R_5 and R_6 each is independently selected from the group consisting of H, C_1 - C_6 -alkyl and C_3 - C_5 -cycloalkyl,

R_7 is H or C_1 - C_6 -alkyl,

wherein R_1 and R_3 , together with the atoms to which they are attached, are optionally connected to form a C_3 - C_6 -carbocyclic ring,

wherein R_1 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C_3 - C_6 -oxocyclic ring,

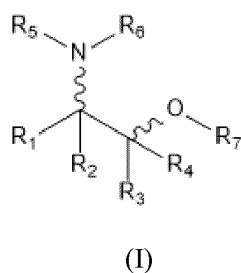
wherein R_3 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C_3 - C_6 -oxocyclic ring,

wherein R_1 and R_5 , together with the atoms to which they are attached, are optionally connected to form a C_3 - C_6 -heterocyclic ring or to form a C_5 - C_8 -heterobicyclic system, wherein said C_3 - C_6 -heterocyclic ring or said C_5 - C_8 -heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C_1 - C_6 -alkyl or C_1 - C_6 -alkenyl,

wherein R_5 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C_3 - C_6 -heterocyclic ring,

in particular by the method as described in the present invention.

Another aspect of the present invention relates to use of a compound of Formula (I) for producing R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, wherein the compound of Formula (I) is



wherein

R_1 and R_2 each is independently selected from the group consisting of H, C_1 - C_6 -alkyl, phenyl, methoxyphenyl, benzyl and CH_2OH ,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

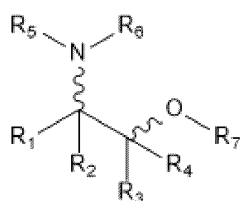
wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

in particular by the method as described in the present invention.

Another aspect of the present invention relates to use of a compound of Formula (I) for enantiomeric separation of a mixture comprising Letemovir and R-Enantiomer, or salts thereof or solvates thereof or solvates of salts thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, wherein the compound of Formula (I) is



(I)

wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

in particular by the method as described in the present invention.

Another aspect of the present invention relates to aminoalcohol and aminoether salts of Letemovir and R-Enantiomer, in particular those specifically described in the present invention.

It has been surprisingly discovered that the 4R- and 4S-enantiomers of 2-[(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetic acid can be efficiently separated via formation of the diastereomeric salts of enantiomerically enriched aminoalcohols and aminoethers. In particular, diastereomeric aminoalcohol/aminoether salts of enantiomeric pairs have different solubilities, which can be used for efficient separation via selective crystallization so that one diastereomeric salt precipitates out of the solution, whereas the second diastereomeric salt remains in a solution or vice versa. The selectivity can be controlled by the stereoisomeric configuration of the chiral agent. This stereoisomeric configuration has a good match with the Cahn–Ingold–Prelog nomenclature. For example, the S/S and R/R enantiomeric pairs of Letemovir and the R-Enantiomer with 1,2-aminoalcohols are commonly significantly less soluble than their respective diastereomers (R/S and S/R). It has been surprisingly discovered that the enantiomeric purity of the obtained diastereomeric salts, which can be easily converted to respectively Letemovir, R-Enantiomer or salts or solvates or co-crystals thereof, is very high and enantiomeric excess of more than 95% can be achieved.

Detailed description

It is noted that the term “comprising” also encompasses the meaning “consisting of”, e.g., a group of members comprising said members also encompasses a group of members consisting only of these members.

As used herein, the terms “Letermovir” or “4S-Enantiomer” refer to 2-[(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetic acid.

As used herein, the terms “R-Enantiomer” or “4R-Enantiomer” refer to 2-[(4R)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl]acetic acid.

As used herein, the term “Letermovir salt of the compound of Formula (I)” refers to an electrically neutral chemical compound, consisting of positively charged cations and negatively charged anions. In one example, Letermovir salt of the compound of Formula (I) consists of positively charged Letermovir cations and negatively charged anions of the compound of Formula (I). In another example, Letermovir salt of the compound of Formula (I) consists of negatively charged Letermovir anions and positively charged cations of the compound of Formula (I).

As used herein, the term “R-Enantiomer salt of the compound of Formula (I)” refers to an electrically neutral chemical compound, consisting of positively charged cations and negatively charged anions. In one example, R-Enantiomer salt of the compound of Formula (I) consists of positively charged R-Enantiomer cations and negatively charged anions of the compound of Formula (I). In another example, R-Enantiomer salt of the compound of Formula (I) consists of negatively charged R-Enantiomer anions and positively charged cations of the compound of Formula (I).

As used herein, the terms “S/S”, “R/R”, “S/R” and “R/S” with respect to enantiomeric pairs of Letermovir and the R-Enantiomer with chiral 1,2-aminoalcohols or 1,2-aminoethers refer to diastereomeric salts, in which the first letter indicates the stereometric configuration of Letermovir or the R-Enantiomer and second letter indicates the stereometric configuration of chiral 1,2-aminoalcohols or 1,2-aminoethers. For example, “S/S” salt refers to Letermovir salt with an S chiral 1,2-aminoalcohol or 1,2-aminoether. “R/R” salt refers to R-Enantiomer salt with an S chiral 1,2-aminoalcohol or 1,2-aminoether. “S/R” salt refers to Letermovir salt with an R chiral 1,2-aminoalcohol or 1,2-aminoether. “R/S” salt refers to R-Enantiomer salt with an S chiral 1,2-aminoalcohol or 1,2-aminoether.

As used herein, the term “transferring” with respect to the Letermovir salt of the compound of Formula (I) or the R-Enantiomer salt of the compound of Formula (I) refers to the process of converting said salt consisting of positively charged cations and negatively charged anions into the neutral compound of Formula (I) and the neutral Letermovir or the neutral R-Enantiomer, respectively.

As used herein, the term “enantiomerically pure” or “enantiomerically enriched” means a composition that comprises one stereoisomer of a compound, in particular an aminoalcohol or an aminoether, and is substantially free of other stereoisomers of that compound. In certain embodiments as used herein, a composition with an enantiomeric excess (“ee”) of at least 80%, preferably at least 85%, more preferably at least 90%, even more preferably at least 95%, most preferred at least 99% is enantiomerically enriched.

The term "room temperature" as used herein, is synonymous to the term "standard room temperature" and refers to a temperature in the range of from 19°C to 26°C.

For example, "cooled down to room temperature" means "cooled down to a temperature in the range of from 19°C to 26°C".

As used herein, the term “crystal” refers to any three-dimensional ordered array of molecules that diffracts X-rays.

The term "polymorph" refers to a particular crystal form (i.e. structure of crystal lattice) of a compound, in particular Letermovir or a salt, or a solvate, or a solvate of a salt thereof that can exist in more than one crystal form in the solid state.

As used herein, the term “solvates” refers to those forms of a compound, in particular, Letermovir or R-Enantiomer, which form a complex through coordination with solvent molecules. Hydrates are a special form of solvates in which the coordination takes place with water. The term “solvates” includes also solvates of salts, unless otherwise specified.

As used herein, the term “salt” refers to derivatives of the disclosed compounds wherein the parent compound, in particular Letermovir, is modified by converting an existing acid or base moiety to its salt form. Examples of salts include but are not limited to mineral or

organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Particular examples include sodium, potassium, calcium, besylate and tosylate salts as well as the salts of aminoalcohols and aminoethers described herein. The salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods, in particular those as described in WO 2013/127971, WO 2013/127968, WO 2021/170874, WO 2021/170879 or WO 2021/170882.

As used herein, the term "co-crystal" refers to crystalline materials composed of two or more different molecular and/or ionic compounds in the same crystal lattice excluding solvents so that at least two of them are associated by non-ionic and noncovalent bonds.

Within the scope of the present invention the terms "obtained by" and "obtainable by" have the same meaning and are used interchangeably.

As used herein the term "solvent" refers to a liquid or a mixture of liquids which is suitable for dissolving or solvating a component or material described herein. According to the methods of the present invention, a solvent is selected from the group consisting of ketones, such as acetone, methyl ethyl ketone, cyclohexanone, 4-methylcyclohexanone, 4-methyl-2-pentanone or 3-pentanone; alkanes, such as pentane, hexane, heptane or isooctane; cycloalkanes, such as cyclohexane or cyclopentane; aromatic solvents, such as chlorobenzene, 1,2-dichlorobenzene, cumene, toluene or xylenes; esters such as ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, ethyl propionate, methyl propionate, isoamyl propionate, isobutyl propionate, hexyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, cyclohexyl butyrate, benzyl butyrate, isobutyl formate, ethyl formate, ethyl formate, isopropyl formate, butyl formate, pentyl formate, diethylene glycol monoethyl ether acetate and ethylene glycol diacetate; ethers, such as diisopropyl ether, cyclopentyl methyl ether, butyl ether, diethoxymethane, anisole, ethylene glycol dimethyl ether, diethylene glycol diethyl ether or dimethoxyethane; alcohols such as ethanol, methanol, 2-butanol, isopropanol, n-butanol, diethylene glycol, isobutanol, isopentanol or *tert*-butanol; nitriles, such as acetonitrile; carbonates, such as dimethyl carbonate or diethyl carbonate; and water, or mixtures thereof. According to the methods of the present invention, preferably the solvent is selected from the group consisting of acetonitrile,

ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof. According to the methods of the present invention, more preferably the solvent is selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, or mixtures thereof. According to the methods of the present invention, most preferred the solvent is pentyl acetate, ethyl butyrate, propyl butyrate or mixtures thereof.

As used herein the term “antisolvent” refers to a liquid, which reduces the solubility of Letemovir in a solvent. In one embodiment, the solvent is selected from the group consisting of acetic acid, formic acid, triethylamine, ethyl acetate, butyl acetate, methyl acetate, isobutyl acetate, propyl acetate, isopropyl acetate, ethyl formate, isopropanol, 1-propanol, n-pentanol, ethanol, methanol, n-butanol, 2-butanol, 2-methyl-1propanol, 3-methyl-1-butanol, *tert*-butanol, cyclohexanone, acetone, methyl ethyl ketone, 3-pentanone, methyl butyl ketone, methyl isobutyl ketone, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, 2-ethoxyethanol, 2-methoxyethanol, ethyleneglycol, formamide, N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, nitromethane, pyridine, sulfolane, tetralin, 1,2-dichloroethane, dichloromethane, 1,1,2-trichloroethane, 1,1,1-trichloroethane, chloroform, chlorobenzene, toluene, cumene, xylenes, anisole, acetonitrile, N-methyl pyrrolidone, dimethyl carbonate, pentyl acetate, or mixtures thereof, and the antisolvent is selected from the group consisting of n-heptane, pentane, n-octane, diisopropyl ether, cyclohexane, hexane, methylcyclohexane, *tert*-butyl methyl ether, methyl *tert*-butyl ether ethyl ether, cyclopentyl methyl ether, and water, or mixtures thereof. In one embodiment, the solvent is selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethyl carbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-

pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, 3-methyl-1-butanol, N,N-dimethylformamide, and xylenes, or mixtures thereof, and the antisolvent is selected from the group consisting of cyclohexane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether, water and n-heptane, or mixtures thereof. In one embodiment, the solvent is selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethyl carbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, and xylenes, or mixtures thereof, and the antisolvent is selected from the group consisting of cyclohexane, diisopropyl ether, water and n-heptane, or mixtures thereof. In a preferred embodiment the solvent is selected from the group consisting of acetone, acetonitrile, ethyl acetate, ethanol, isopropanol, methanol, methyl ethyl ketone, tetrahydrofuran, dioxane, toluene, 3-methyl-1-butanol, *tert*-butanol, N,N-dimethylformamide and dichloromethane or mixtures thereof, and the antisolvent is selected from the group consisting of n-heptane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether and water, or mixtures thereof. In a more preferred embodiment, the solvent is acetone or acetonitrile and the antisolvent is water.

As used herein, the term “seeding” refers to a procedure in which a small quantity of crystals (known as seeds) is added in order to promote and control crystallization in a given supersaturated solution. In the particular case of the enantiomeric resolution of the racemate, the added crystals are those of the less soluble diastereomeric salt of the chiral agent and Letermovir (or R-Enantiomer).

As used herein the term “contacting” with respect to two materials refers to the addition of the first material to the second material or the addition of the second material to the first material. In particular, the term “contacting” refers to the addition of a solid to a solvent or the addition of a solvent to a solid.

As used herein, the term “racemic” or “racemate” means about 50%±5% of one enantiomer and about 50%±5% of the other enantiomer relative to all chiral centers in the molecule.

As used herein the term "alkyl" by itself or as part of another substituent refers to a radical of alkane having the number of carbon atoms designated (i.e. C₁-C₆-alkyl means one to six carbon atoms, C₁-C₅-alkyl means one to five carbon atoms, C₁-C₄-alkyl means one to four carbon atoms, C₁-C₃-alkyl means one to three carbon atoms) and includes straight and branched chains. Non-limiting examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, pentyl, neopentyl, and hexyl. For the avoidance of doubt where two alkyl moieties are present in a group, the alkyl moieties may be the same or different.

As used herein the term "alkenyl" by itself or as part of another substituent refers to an alkyl group containing one or more carbon-carbon double bonds, wherein the position of the double bond may vary along the carbon chain. Examples of alkenyl groups include ethylenyl (-CH=CH₂) and propenyl (-CH₂-CH=CH₂).

As used herein the term "cycloalkyl" refers to a monocyclic nonaromatic group wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. In one embodiment, the cycloalkyl group is saturated or partially unsaturated. In one embodiment, cycloalkyl groups include groups having 3 to 5 ring atoms (C₃-C₅-cycloalkyl), such as cyclopropyl, cyclobutyl or cyclopentyl.

As used herein, the term "oxocyclic ring" refers to a monocyclic nonaromatic group, wherein one of the atoms forming the ring is oxygen and each of the remaining atoms forming the ring is a carbon atom. In one embodiment the oxocyclic ring has 3 to 7 ring carbon atoms (C₃-C₇-oxocyclic ring), preferably 3 to 6 carbon atoms (C₃-C₆-oxocyclic ring). Illustrative examples include, but are not limited to tetrahydrofuran, tetrahydropyran and oxepane.

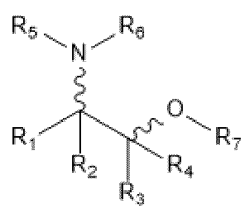
As used herein, the term "methoxyphenyl" refers to a phenyl group, which is substituted with one or more, in particular, one, two or three methoxy groups, e.g. -Ph-OCH₃. Similarly, the term "methoxyquinolinyl" refers to a quinolinyl group, which is substituted with one or more, in particular, one, two or three methoxy groups.

As used herein, the term "quinolinyl" refers to a radical derived from quinoline, i.e. an aromatic heterocycle, characterized by a double-ring structure composed of a benzene and a pyridine ring fused at two adjacent carbon atoms.

As used herein, the term “quinine” refers to (R)-[(2S,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol.

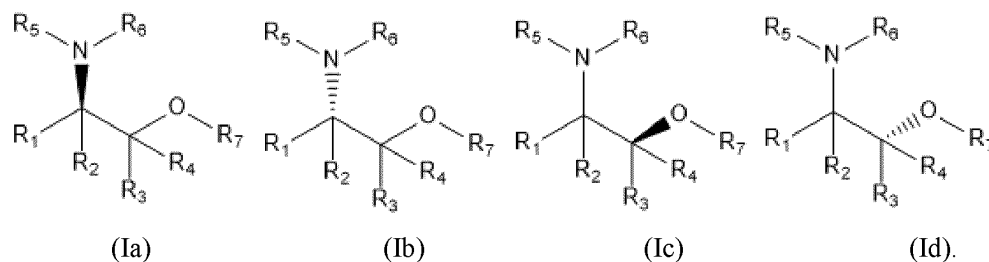
As used herein, the term “quinidine” refers to (S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol.

As used herein, a wavy bond in a Markush formula denotes at least one chiral center, which is either in the R- or S-configuration. For example, the compound of Formula (I)



(I)

encompasses the following structures (Ia)-(Id):



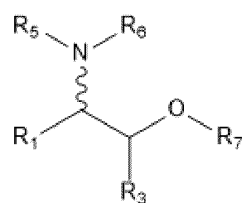
(Ia)

(Ib)

(Ic)

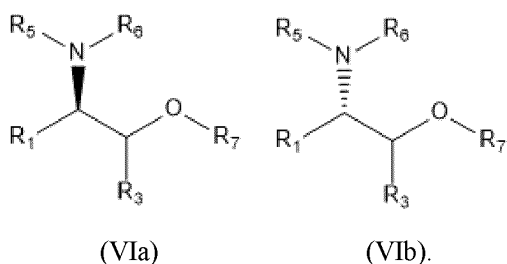
(Id)

Analogously, the compound of Formula (VI)

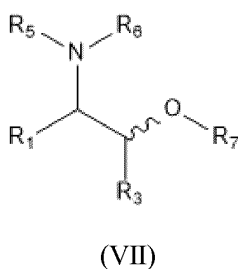


(VI)

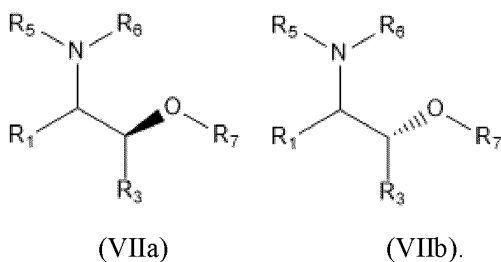
encompasses the following structures (VIa) and (VIb):



Analogously, the compound of Formula (VII)



encompasses the following structures (VIIa) and (VIIb):

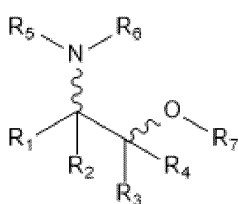


If not specified otherwise, particular embodiments of the present invention refer to any method for producing Letemovir, any method for producing an aminoalcohol/aminoether salt of Letemovir, any method for producing an aminoalcohol/aminoether salt of R-Enantiomer or any method for enantiomeric separation disclosed herein.

The first aspect of the present invention relates to a method for producing 2-{(4S)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid (“Letemovir”) or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or

a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, comprising the steps:

- i) providing a mixture comprising Letemovir and 2-[(4R)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl] acetic acid (“R-Enantiomer”) or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;
- ii) contacting said mixture with an enantiomerically enriched compound of Formula (I)



(I)

wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I),

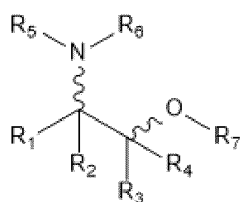
iii-1) separating the Letemovir salt of the compound of Formula (I);

iv-1) converting the Letemovir salt of the compound of Formula (I) into Letemovir or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof; and optionally

v-1) isolating Letemovir or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof.

In one embodiment, the present invention relates to a method for producing 2-{(4S)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid ("Letemovir") or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, comprising the steps:

- i) providing a mixture comprising Letemovir and 2-{{(4R)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}} acetic acid (“R-Enantiomer”) or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;
- ii) contacting said mixture with an enantiomerically enriched compound of Formula (I)



(I)

wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I),

iii-1) separating the Letemovir salt of the compound of Formula (I);

iv-1) converting the Letemovir salt of the compound of Formula (I) into Letemovir or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof; and optionally

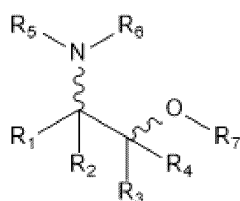
v-1) isolating Letemovir or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof.

In one embodiment of said method for producing Letemovir said Letemovir is in an amorphous state and said method further comprises precipitation of Letemovir obtained in step iv-1) or v-1) from a solvent selected from the group consisting of acetic acid, formic acid, triethylamine, ethyl acetate, butyl acetate, methyl acetate, isobutyl acetate, propyl acetate, isopropyl acetate, ethyl formate, isopropanol, 1-propanol, n-pentanol, ethanol, methanol, n-butanol, 2-butanol, 2-methyl-1propanol, 3-methyl-1-butanol, *tert*-butanol, cyclohexanone, acetone, methyl ethyl ketone, 3-pentanone, methyl butyl ketone, methyl isobutyl ketone, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, 2-ethoxyethanol, 2-methoxyethanol, ethyleneglycol, formamide, N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, nitromethane, pyridine, sulfolane, tetralin, 1,2-dichloroethane, dichloromethane, 1,1,2-trichloroethane, 1,1,1-trichloroethane, chloroform, chlorobenzene, toluene, cumene, xylenes, anisole, acetonitrile, N-methyl pyrrolidone, dimethyl carbonate, pentyl acetate, or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, pentane, n-octane, diisopropyl ether, cyclohexane, hexane, methylcyclohexane, *tert*-butyl methyl ether, ethyl ether,

cyclopentyl methyl ether, and water, or mixtures thereof, preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethylcarbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, 3-methyl-1-butanol, N,N-dimethylformamide and xylenes, or mixtures thereof, by an antisolvent selected from the group consisting of cyclohexane, diisopropyl ether, water, *tert*-butyl methyl ether, ethyl ether, and n-heptane, or mixtures thereof, more preferably from a solvent is selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethyl carbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, and xylenes, or mixtures thereof, and the antisolvent is selected from the group consisting of cyclohexane, diisopropyl ether, water and n-heptane, or mixtures thereof, even more preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, ethanol, isopropanol, methanol, methyl ethyl ketone, tetrahydrofuran, dioxane, toluene, 3-methyl-1-butanol, *tert*-butanol, N,N-dimethylformamide and dichloromethane or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether and water, or mixtures thereof, most preferred from a water miscible solvent acetone or acetonitrile into excess stirred water, to obtain amorphous Letermovir, followed by isolation via filtration or centrifugation, e.g. by the method as described in Example 3b in WO 2014/202737 and in Example 6A in WO 2013/127971.

Another aspect of the present invention relates to a method for producing a Letermovir salt of a compound of Formula (I), comprising the steps:

- i) providing a mixture comprising Letermovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;
- ii) contacting said mixture with an enantiomerically enriched compound of Formula (I)



(I)

wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring ,

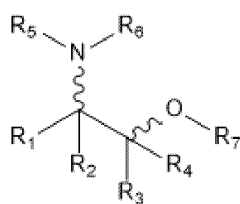
thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I);

iii-1) separating the Letemovir salt of the compound of Formula (I).

In one embodiment the present invention relates to a method for producing a Letemovir salt of a compound of Formula (I), comprising the steps:

i) providing a mixture comprising Letemovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;

ii) contacting said mixture with an enantiomerically enriched compound of Formula (I)



(I)

wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinoliny and methoxyquinoliny,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring ,

thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I);

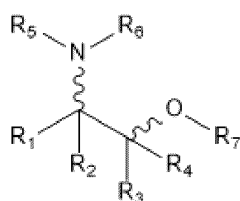
iii-1) separating the Letemovir salt of the compound of Formula (I).

In one embodiment, said Letemovir salt of a compound of Formula (I) in step iii-1) is isolated in a form of a precipitate, in particular by filtration or centrifugation.

In one embodiment, said Letemovir salt of a compound of Formula (I) in step iii-1) is isolated in a form of a mother liquor, in particular by filtration or centrifugation, optionally followed by evaporation of the mother liquor.

Another aspect of the present invention relates to a method for producing an R-Enantiomer salt of a compound of Formula (I), comprising the steps:

- i) providing a mixture comprising Letemovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;
- ii) contacting said mixture with an enantiomerically enriched compound of Formula (I)



(I)

wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R_5 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C_3 - C_6 -heterocyclic ring,

thereby producing a Letermovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I);

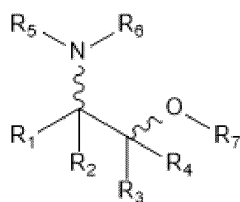
iii-2) separating the R-Enantiomer salt of the compound of Formula (I).

In one embodiment, said R-Enantiomer salt of a compound of Formula (I) in step iii-2) is isolated in a form of a precipitate, in particular by filtration or centrifugation.

In one embodiment, said R-Enantiomer salt of a compound of Formula (I) in step iii-2) is isolated in a form of a mother liquor, in particular by filtration or centrifugation, optionally followed by evaporation of the mother liquor.

Another aspect of the present invention relates to a method for enantiomeric separation of a mixture comprising Letermovir and R-Enantiomer comprising the steps:

- i) providing a mixture comprising Letermovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;
- ii) contacting said mixture with an enantiomerically enriched compound of Formula (I)



(I)

wherein

R_1 and R_2 each is independently selected from the group consisting of H, C_1 - C_6 -alkyl, phenyl, methoxyphenyl, benzyl and CH_2OH ,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I),

iii-1) separating the Letemovir salt of the compound of Formula (I);

iv-1) transferring the Letemovir salt of the compound of Formula (I) into the compound of Formula (I) and Letemovir and optionally

v-1) isolating Letemovir.

In one embodiment, said Letermovir in step v-1) is isolated in a form of a precipitate, in particular by filtration or centrifugation.

In one embodiment, said Letermovir in step v-1) is isolated in a form of a mother liquor, in particular by filtration or centrifugation, optionally followed by evaporation of the mother liquor.

In one embodiment, said method for enantiomeric separation further comprises precipitation of Letermovir obtained in step iv-1) or v-1) from a solvent selected from the group consisting of acetic acid, formic acid, triethylamine, ethyl acetate, butyl acetate, methyl acetate, isobutyl acetate, propyl acetate, isopropyl acetate, ethyl formate, isopropanol, 1-propanol, n-pentanol, ethanol, methanol, n-butanol, 2-butanol, 2-methyl-1-propanol, 3-methyl-1-butanol, *tert*-butanol, cyclohexanone, acetone, methyl ethyl ketone, 3-pentanone, methyl butyl ketone, methyl isobutyl ketone, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, 2-ethoxyethanol, 2-methoxyethanol, ethyleneglycol, formamide, N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, nitromethane, pyridine, sulfolane, tetralin, 1,2-dichloroethane, dichloromethane, 1,1,2-trichloroethane, 1,1,1-trichloroethane, chloroform, chlorobenzene, toluene, cumene, xylenes, anisole, acetonitrile, N-methyl pyrrolidone, dimethyl carbonate, pentyl acetate, or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, pentane, n-octane, diisopropyl ether, cyclohexane, hexane, methylcyclohexane, *tert*-butyl methyl ether, ethyl ether, cyclopentyl methyl ether, and water, or mixtures thereof, preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethylcarbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, 3-methyl-1-butanol, N,N-dimethylformamide and xylenes, or mixtures thereof, by an antisolvent selected from the group consisting of cyclohexane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether, water and n-heptane, or mixtures thereof, more preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethyl carbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol,

isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, tert-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, and xylenes, or mixtures thereof, and the antisolvent is selected from the group consisting of cyclohexane, diisopropyl ether, water and n-heptane, or mixtures thereof, even more preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, ethanol, isopropanol, methanol, methyl ethyl ketone, tetrahydrofuran, dioxane, toluene, 3-methyl-1-butanol, *tert*-butanol, N,N-dimethylformamide and dichloromethane or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether and water, or mixtures thereof, most preferred from a water miscible solvent acetone or acetonitrile into excess stirred water, to obtain amorphous Letemovir, followed by isolation via filtration or centrifugation.

In one embodiment, said method for enantiomeric separation of a mixture comprising Letemovir and R-Enantiomer further comprises the steps:

vi-1) isolating the R-Enantiomer salt of the compound of Formula (I);

vii-1) transferring the R-Enantiomer salt of the compound of Formula (I) into the compound of Formula (I) and R-Enantiomer; and optionally

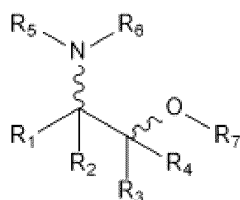
viii-1) isolating R-Enantiomer.

In one embodiment, said R-Enantiomer in step viii-1) is isolated in a form of a precipitate, in particular by filtration or centrifugation.

In one embodiment, said R-Enantiomer in step viii-1) is isolated in a form of a mother liquor, in particular by filtration or centrifugation, optionally followed by evaporation of the mother liquor.

Another aspect of the present invention relates to a method for enantiomeric separation of a mixture comprising Letemovir and R-Enantiomer comprising the steps:

- i) providing a mixture comprising Letemovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;
- ii) contacting said mixture with an enantiomerically enriched compound of Formula (I)



(I)

wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system,

wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I);

iii-2) separating the R-Enantiomer salt of the compound of Formula (I);

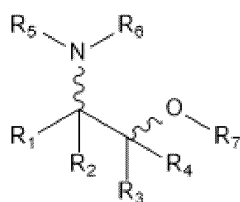
iv-2) transferring the R-Enantiomer salt of the compound of Formula (I) into the compound of Formula (I) and R-Enantiomer; and optionally

v-2) isolating R-Enantiomer.

In one embodiment, the present invention relates to a method for enantiomeric separation of a mixture comprising Letemovir and R-Enantiomer comprising the steps:

i) providing a mixture comprising Letemovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;

ii) contacting said mixture with an enantiomerically enriched compound of Formula (I)



(I)

wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I);

iii-2) separating the R-Enantiomer salt of the compound of Formula (I);

iv-2) transferring the R-Enantiomer salt of the compound of Formula (I) into the compound of Formula (I) and R-Enantiomer; and optionally

v-2) isolating R-Enantiomer.

In one embodiment, said R-Enantiomer in step v-2) is isolated in a form of a precipitate, in particular by filtration or centrifugation.

In one embodiment, said R-Enantiomer in step v-2) is isolated in a form of a mother liquor, in particular by filtration or centrifugation, optionally followed by evaporation of the mother liquor.

In one embodiment, said method for enantiomeric separation of a mixture comprising Letermovir and R-Enantiomer further comprises the steps:

vi-2) isolating the Letermovir salt of the compound of Formula (I);

vii-2) transferring the Letermovir salt of the compound of Formula (I) into the compound of Formula (I) and Letermovir; and optionally

viii-2) isolating Letermovir.

In one embodiment, said Letermovir in step viii-2) is isolated in a form of a precipitate, in particular by filtration or centrifugation.

In one embodiment, said Letermovir in step viii-2) is isolated in a form of a mother liquor, in particular by filtration or centrifugation, optionally followed by evaporation of the mother liquor.

In one embodiment, said method for enantiomeric separation further comprises precipitation of Letermovir obtained in step vii-2) or viii-2) from a solvent selected from the group consisting of acetic acid, formic acid, triethylamine, ethyl acetate, butyl acetate, methyl acetate, isobutyl acetate, propyl acetate, isopropyl acetate, ethyl formate, isopropanol, 1-propanol, n-pentanol, ethanol, methanol, n-butanol, 2-butanol, 2-methyl-1-propanol, 3-methyl-1-butanol, *tert*-butanol, cyclohexanone, acetone, methyl ethyl ketone, 3-pentanone, methyl butyl ketone, methyl isobutyl ketone, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, 2-ethoxyethanol, 2-methoxyethanol, ethyleneglycol, formamide, N,N-dimethylacetamide, N,N-dimethylformamide, dimethyl sulfoxide, nitromethane, pyridine, sulfolane, tetralin, 1,2-dichloroethane, dichloromethane, 1,1,2-trichloroethane, 1,1,1-trichloroethane, chloroform, chlorobenzene, toluene, cumene,

xylenes, anisole, acetonitrile, N-methyl pyrrolidone, dimethyl carbonate, pentyl acetate, or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, pentane, n-octane, diisopropyl ether, cyclohexane, hexane, methylcyclohexane, *tert*-butyl methyl ether, ethyl ether, cyclopentyl methyl ether, and water, or mixtures thereof, preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethylcarbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, 3-methyl-1-butanol, N,N-dimethylformamide and xylenes, or mixtures thereof, by an antisolvent selected from the group consisting of cyclohexane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether, water and n-heptane, or mixtures thereof, more preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethyl carbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, and xylenes, or mixtures thereof, and the antisolvent is selected from the group consisting of cyclohexane, diisopropyl ether, water and n-heptane, or mixtures thereof, even more preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, ethanol, isopropanol, methanol, methyl ethyl ketone, tetrahydrofuran, dioxane, toluene, 3-methyl-1-butanol, *tert*-butanol, N,N-dimethylformamide and dichloromethane or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether and water, or mixtures thereof, most preferred from a water miscible solvent acetone or acetonitrile into excess stirred water, to obtain amorphous Letermovir, followed by isolation via filtration or centrifugation.

In one embodiment of said method for producing Letermovir or a salt thereof or a solvate thereof or a salt of solvate thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, the method for producing a Letermovir salt or an R-Enantiomer salt of a compound of Formula (I) or said method for enantiomeric separation step (ii) is carried out in a solid state. In one

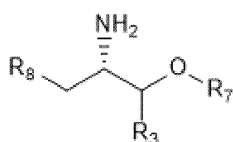
embodiment step (ii) is carried without a solvent. In one embodiment step (ii) is conducted by means of mixing a mixture comprising Letermovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof with the compound of formula (I) in a solid state and grinding in a ball mill.

In one embodiment, step ii) is carried out in a solid state and separating the Letermovir salt of the compound of Formula (I) in step iii-1) is conducted by means of dissolving the R-Enantiomer salt of the compound of Formula (I) in a solvent selected from the group consisting of ketones, such as acetone, methyl ethyl ketone, cyclohexanone, 4-methylcyclohexanone, 4-methyl-2-pentanone or 3-pentanone; alkanes, such as pentane, hexane, heptane or isooctane; cycloalkanes, such as cyclohexane or cyclopentane; aromatic solvents, such as chlorobenzene, 1,2-dichlorobenzene, cumene, toluene or xylenes; esters such as ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, ethyl propionate, methyl propionate, isoamyl propionate, isobutyl propionate, hexyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, cyclohexyl butyrate, benzyl butyrate, isobutyl formate, ethyl formate, ethyl formate, isopropyl formate, butyl formate, pentyl formate, diethylene glycol monoethyl ether acetate and ethylene glycol diacetate; ethers, such as diisopropyl ether, cyclopentyl methyl ether, butyl ether, diethoxymethane, anisole, ethylene glycol dimethyl ether, diethylene glycol diethyl ether or dimethoxyethane; alcohols such as ethanol, methanol, 2-butanol, isopropanol, n-butanol, diethylene glycol, isobutanol, isopentanol or *tert*-butanol; nitriles, such as acetonitrile; and carbonates, such as dimethyl carbonate or diethyl carbonate; or mixtures thereof, preferably selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, and isolating the solid phase comprising the Letermovir salt of the compound of Formula (I).

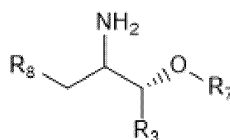
In one embodiment, step ii) is carried out in a solid state and separating the Letermovir salt of the compound of Formula (I) in step iii-1) is conducted by means of dissolving the

R-Enantiomer salt of the compound of Formula (I) in a solvent selected from the group consisting of isopropanol, acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate isobutyl acetate and pentyl acetate, or mixtures thereof, preferably selected from the group consisting of ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate isobutyl acetate and pentyl acetate, or mixtures thereof, more preferably selected from the group consisting of pentyl acetate, ethyl butyrate, propyl butyrate or mixtures thereof, and isolating the solid phase comprising the Letermovir salt of the compound of Formula (I).

In one embodiment, step ii) is carried out in a solid state and separating the Letermovir salt of the compound of Formula (I) in step iii-1) is conducted by means of dissolving the R-Enantiomer salt of the compound of Formula (I) in a solvent selected from the group consisting of isopropanol, acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate isobutyl acetate and pentyl acetate, or mixtures thereof, preferably selected from the group consisting of ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate isobutyl acetate and pentyl acetate, or mixtures thereof, more preferably selected from the group consisting of pentyl acetate, ethyl butyrate, propyl butyrate or mixtures thereof, and isolating the solid phase comprising the Letermovir salt of the compound of Formula (I), wherein the compound of Formula (I) is a compound of Formula (II) or (III)



(II)



(III)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

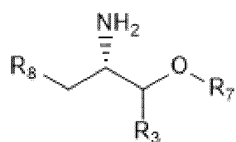
R₇ is H or C₁-C₃-alkyl,

R₈ is selected from the group consisting of H, OH, methyl or ethyl,

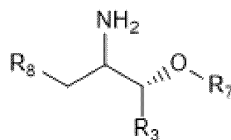
wherein R_7 and R_8 , together with the atoms to which they are attached, are optionally connected to form a C_3 - C_6 -oxocyclic ring,

wherein R_3 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C_3 - C_6 -oxocyclic ring.

In one embodiment, step ii) is carried out in a solid state and separating the Letermovir salt of the compound of Formula (I) in step iii-1) is conducted by means of dissolving the R-Enantiomer salt of the compound of Formula (I) in a solvent selected from the group consisting of isopropanol, acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate isobutyl acetate and pentyl acetate, or mixtures thereof, preferably selected from the group consisting of ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate isobutyl acetate and pentyl acetate, or mixtures thereof, more preferably selected from the group consisting of pentyl acetate, ethyl butyrate, propyl butyrate or mixtures thereof, and isolating the liquid phase comprising the R-Enantiomer salt of the compound of Formula (I), wherein the compound of Formula (I) is a compound of Formula (II) or (III)



(II)



(III)

wherein

R_3 is selected from the group consisting of H, C_1 - C_3 -alkyl and phenyl,

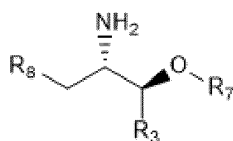
R_7 is H or C_1 - C_3 -alkyl,

R_8 is selected from the group consisting of H, OH, methyl or ethyl,

wherein R_7 and R_8 , together with the atoms to which they are attached, are optionally connected to form a C_3 - C_6 -oxocyclic ring,

wherein R_3 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C_3 - C_6 -oxocyclic ring.

In a preferred embodiment, the compound of Formula (II) is a compound of Formula (IIa)



(IIa)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl, and phenyl,

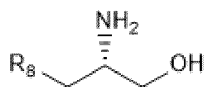
R₇ is H or C₁-C₃-alkyl,

R₈ is H or OH,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a tetrahydrofuran ring.

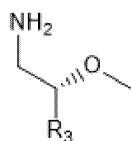
In another preferred embodiment, the compound of Formula (II) is a compound of Formula (IIb)



(IIb)

wherein R₈ is H, methyl or ethyl.

In another preferred embodiment, the compound of Formula (III) is a compound of Formula (IIIa)

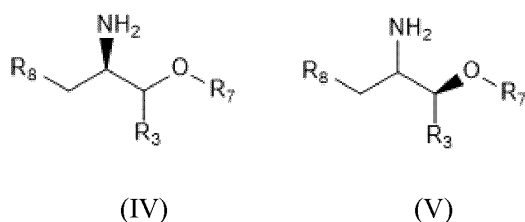


(IIIa)

wherein R₃ is H, CH₂OH or methyl.

In one embodiment, step ii) is carried out in a solid state and separating the Letemovir salt of the compound of Formula (I) in step iii-1) is conducted by means of dissolving the

Letermovir salt of the compound of Formula (I) in a solvent selected from the group consisting of isopropanol, acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate isobutyl acetate and pentyl acetate, or mixtures thereof, preferably selected from the group consisting of ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate isobutyl acetate and pentyl acetate, or mixtures thereof, more preferably selected from the group consisting of pentyl acetate, ethyl butyrate, propyl butyrate or mixtures thereof, and isolating the solid phase comprising the R-Enantiomer salt of the compound of Formula (I), wherein the compound of Formula (I) is a compound of Formula (IV) or (V)



wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

R₇ is H or C₁-C₃-alkyl,

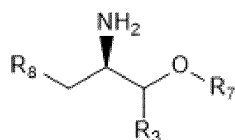
R₈ is selected from the group consisting of H, OH, methyl or ethyl,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

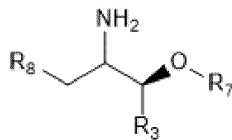
wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring.

In one embodiment, step ii) is carried out in a solid state and separating the Letermovir salt of the compound of Formula (I) in step iii-1) is conducted by means of dissolving the Letermovir salt of the compound of Formula (I) in a solvent selected from the group consisting of isopropanol, acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate isobutyl acetate and pentyl acetate, or mixtures thereof, preferably selected from the group consisting of ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate isobutyl acetate and pentyl acetate, or mixtures

thereof, more preferably selected from the group consisting of pentyl acetate, ethyl butyrate, propyl butyrate or mixtures thereof, and isolating the liquid phase comprising the Letermovir salt of the compound of Formula (I), wherein the compound of Formula (I) is a compound of Formula (IV) or (V)



(IV)



(V)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

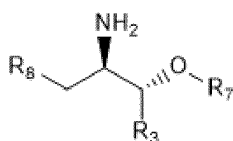
R₇ is H or C₁-C₃-alkyl,

R₈ is selected from the group consisting of H, OH, methyl or ethyl,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring.

In a preferred embodiment, the compound of Formula (IV) is a compound of Formula (IVa)



(IVa)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl, and phenyl,

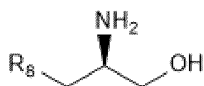
R₇ is H or C₁-C₃-alkyl,

R₈ is H or OH,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a tetrahydrofuran ring.

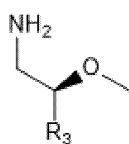
In another preferred embodiment, the compound of Formula (IV) is a compound of Formula (IVb)



(IVb)

wherein R₈ is H, methyl, or ethyl.

In another preferred embodiment, the compound of Formula (V) is a compound of Formula (Va)



(Va)

wherein R₃ is H, CH₂OH or methyl.

In one embodiment, step ii) is carried out in a solid state according to any of the preceding embodiments and said method further comprises precipitation of Letemovir obtained in step iv-1) or v-1) from a solvent selected from the group consisting of acetic acid, formic acid, triethylamine, ethyl acetate, butyl acetate, methyl acetate, isobutyl acetate, propyl acetate, isopropyl acetate, ethyl formate, isopropanol, 1-propanol, n-pentanol, ethanol, methanol, n-butanol, 2-butanol, 2-methyl-1propanol, 3-methyl-1-butanol, *tert*-butanol, cyclohexanone, acetone, methyl ethyl ketone, 3-pentanone, methyl butyl ketone, methyl isobutyl ketone, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, 2-ethoxyethanol, 2-methoxyethanol, ethyleneglycol, formamide, N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, nitromethane, pyridine, sulfolane, tetralin, 1,2-dichloroethane, dichloromethane, 1,1,2-trichloroethane, 1,1,1-trichloroethane, chloroform, chlorobenzene, toluene, cumene, xylenes, anisole, acetonitrile, N-methyl

pyrrolidone, dimethyl carbonate, pentyl acetate, or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, pentane, n-octane, diisopropyl ether, cyclohexane, hexane, methylcyclohexane, *tert*-butyl methyl ether, ethyl ether, cyclopentyl methyl ether, and water, or mixtures thereof, preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethylcarbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, 3-methyl-1-butanol, N,N-dimethylformamide and xylenes, or mixtures thereof, by an antisolvent selected from the group consisting of cyclohexane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether, water and n-heptane, or mixtures thereof, more preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethyl carbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, and xylenes, or mixtures thereof, and the antisolvent is selected from the group consisting of cyclohexane, diisopropyl ether, water and n-heptane, or mixtures thereof, even more preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, ethanol, isopropanol, methanol, methyl ethyl ketone, tetrahydrofuran, dioxane, toluene, 3-methyl-1-butanol, *tert*-butanol, N,N-dimethylformamide and dichloromethane or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether and water, or mixtures thereof, most preferred from a water miscible solvent acetone or acetonitrile into excess stirred water, to obtain amorphous Letermovir, followed by isolation via filtration or centrifugation.

In one embodiment of said method for producing Letermovir or a salt thereof or a solvate thereof or a salt of solvate thereof, the method for producing a Letermovir salt or an R-Enantiomer salt of a compound of Formula (I) or said method for enantiomeric separation step (ii) is carried out in a liquid phase. In one embodiment, step (ii) is carried out in presence of a solvent selected from the group consisting of ketones, such as acetone, methyl ethyl ketone, cyclohexanone, 4-methylcyclohexanone, 4-methyl-2-pentanone or

3-pentanone; alkanes, such as pentane, hexane, heptane or isooctane; cycloalkanes, such as cyclohexane or cyclopentane; aromatic solvents, such as chlorobenzene, 1,2-dichlorobenzene, cumene, toluene or xylenes; esters such as ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, ethyl propionate, methyl propionate, isoamyl propionate, isobutyl propionate, hexyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, cyclohexyl butyrate, benzyl butyrate, isobutyl formate, ethyl formate, ethyl formate, isopropyl formate, butyl formate, pentyl formate, diethylene glycol monoethyl ether acetate and ethylene glycol diacetate; ethers, such as diisopropyl ether, cyclopentyl methyl ether, butyl ether, diethoxymethane, anisole, ethylene glycol dimethyl ether, diethylene glycol diethyl ether or dimethoxyethane; alcohols such as ethanol, methanol, 2-butanol, isopropanol, n-butanol, diethylene glycol, isobutanol, isopentanol or *tert*-butanol; nitriles, such as acetonitrile; and carbonates, such as dimethyl carbonate or diethyl carbonate; or mixtures thereof, preferably selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof.

In one embodiment, the mixture comprising Letermovir or R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof is provided in a solid phase and the compound of Formula (I) is provided in a form of a solution in a solvent selected from the group consisting of ketones, such as acetone, methyl ethyl ketone, cyclohexanone, 4-methylcyclohexanone, 4-methyl-2-pentanone or 3-pentanone; alkanes, such as pentane, hexane, heptane or isooctane; cycloalkanes, such as cyclohexane or cyclopentane; aromatic solvents, such as chlorobenzene, 1,2-dichlorobenzene, cumene, toluene or xylenes; esters such as ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, ethyl propionate, methyl propionate, isoamyl propionate, isobutyl propionate, hexyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, cyclohexyl butyrate, benzyl butyrate, isobutyl formate, ethyl formate, ethyl

formate, isopropyl formate, butyl formate, pentyl formate, diethylene glycol monoethyl ether acetate and ethylene glycol diacetate; ethers, such as diisopropyl ether, cyclopentyl methyl ether, butyl ether, diethoxymethane, anisole, ethylene glycol dimethyl ether, diethylene glycol diethyl ether or dimethoxyethane; alcohols such as ethanol, methanol, 2-butanol, isopropanol, n-butanol, diethylene glycol, isobutanol, isopentanol or *tert*-butanol; nitriles, such as acetonitrile; and carbonates, such as dimethyl carbonate or diethyl carbonate; or mixtures thereof, preferably selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof.

In one embodiment, the mixture comprising Letermovir or R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof is provided in a form of a solution in a solvent selected from the group consisting of ketones, such as acetone, methyl ethyl ketone, cyclohexanone, 4-methylcyclohexanone, 4-methyl-2-pentanone or 3-pentanone; alkanes, such as pentane, hexane, heptane or isooctane; cycloalkanes, such as cyclohexane or cyclopentane; aromatic solvents, such as chlorobenzene, 1,2-dichlorobenzene, cumene, toluene or xylenes; esters such as ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, ethyl propionate, methyl propionate, isoamyl propionate, isobutyl propionate, hexyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, cyclohexyl butyrate, benzyl butyrate, isobutyl formate, ethyl formate, ethyl formate, isopropyl formate, butyl formate, pentyl formate, diethylene glycol monoethyl ether acetate and ethylene glycol diacetate; ethers, such as diisopropyl ether, cyclopentyl methyl ether, butyl ether, diethoxymethane, anisole, ethylene glycol dimethyl ether, diethylene glycol diethyl ether or dimethoxyethane; alcohols such as ethanol, methanol, 2-butanol, isopropanol, n-butanol, diethylene glycol, isobutanol, isopentanol or *tert*-butanol; nitriles, such as acetonitrile; and carbonates, such as dimethyl carbonate or diethyl carbonate; or mixtures thereof, preferably selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate,

butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, and the compound of Formula (I) is provided in a solid state.

In one embodiment, step ii) is carried out in a liquid state according to any of the preceding embodiments and said method further comprises precipitation of Letermovir obtained in step iv-1) or v-1) from a solvent selected from the group consisting of acetic acid, formic acid, triethylamine, ethyl acetate, butyl acetate, methyl acetate, isobutyl acetate, propyl acetate, isopropyl acetate, ethyl formate, isopropanol, 1-propanol, n-pentanol, ethanol, methanol, n-butanol, 2-butanol, 2-methyl-1-propanol, 3-methyl-1-butanol, *tert*-butanol, cyclohexanone, acetone, methyl ethyl ketone, 3-pentanone, methyl butyl ketone, methyl isobutyl ketone, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, 2-ethoxyethanol, 2-methoxyethanol, ethylene glycol, formamide, N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, nitromethane, pyridine, sulfolane, tetralin, 1,2-dichloroethane, dichloromethane, 1,1,2-trichloroethane, 1,1,1-trichloroethane, chloroform, chlorobenzene, toluene, cumene, xylenes, anisole, acetonitrile, N-methyl pyrrolidone, dimethyl carbonate, pentyl acetate, or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, pentane, n-octane, diisopropyl ether, cyclohexane, hexane, methylcyclohexane, *tert*-butyl methyl ether, ethyl ether, cyclopentyl methyl ether, and water, or mixtures thereof, preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethylcarbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, 3-methyl-1-butanol, N,N-dimethylformamide and xylenes, or mixtures thereof, by an antisolvent selected from the group consisting of cyclohexane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether, water and n-heptane, or mixtures thereof, more preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethyl carbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane,

dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, and xylenes, or mixtures thereof, and the antisolvent is selected from the group consisting of cyclohexane, diisopropyl ether, water and *n*-heptane, or mixtures thereof, even more preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, ethanol, isopropanol, methanol, methyl ethyl ketone, tetrahydrofuran, dioxane, toluene, 3-methyl-1-butanol, *tert*-butanol, *N,N*-dimethylformamide and dichloromethane or mixtures thereof, by an antisolvent selected from the group consisting of *n*-heptane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether and water, or mixtures thereof, most preferred from a water miscible solvent acetone or acetonitrile into excess stirred water, to obtain amorphous Letemovir, followed by isolation via filtration or centrifugation.

A mixture comprising Letemovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof provided in step i), in particular the racemate, may be present in different forms, such as crystalline or amorphous free acid form, or a salt thereof, a solvate thereof or a solvate of salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, e.g. those described in WO 2013/127971, WO 2013/127968, WO 2021/170874, WO 2021/170879 or WO 2021/170882. The crystalline form may be present in different polymorph and co-crystal forms. Polymorphs are different crystalline forms of the same compound which may have substantially different physicochemical properties, such as solubility, stability, and bioavailability.

Different methods for examination of polymorphs can be used. Such methods include microscopy, IR-spectroscopy, Raman spectroscopy, Solid-state NMR, TGA, DSC, PXRD, PDF, SCXRD, Electron Diffraction and other techniques. A combination of different techniques can be applied. In particular, PXRD is a powerful technique for examination of polymorphs. X-rays are reflected from crystals only when the angle between the beam and the planes in the crystal satisfies the Bragg condition. There is an infinite number of possible planes in the crystal. Each molecular repetition gives a unique set of reflections and, therefore, generates a unique pattern, which can be recorded as a spectrum.

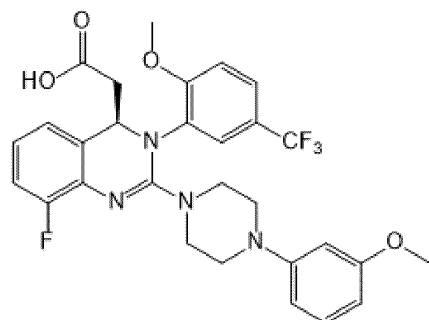
In one embodiment, a mixture comprising Letermovir and R-Enantiomer, in particular the racemate, is provided in step i) in free acid form.

In one embodiment, a mixture comprising Letermovir and R-Enantiomer, in particular the racemate, is provided in step i) by means of the following steps:

- a) reacting R-Enantiomer with a C₁-C₂-alcohol in the presence of an acid to obtain an ester of R-Enantiomer, and
- b) treating the ester of R-Enantiomer obtained in step a) with a base to obtain a mixture comprising Letermovir and R-Enantiomer.

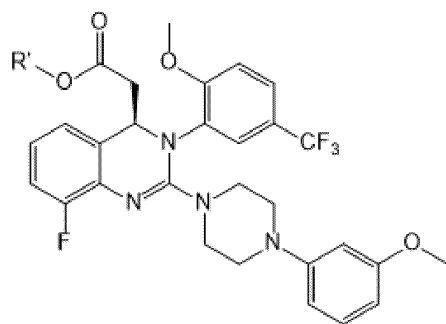
In one embodiment, a mixture comprising Letermovir and R-Enantiomer, in particular the racemate, is provided in step i) by means of the following steps:

- a) reacting R-Enantiomer of Formula (VIII)



Formula (VIII)

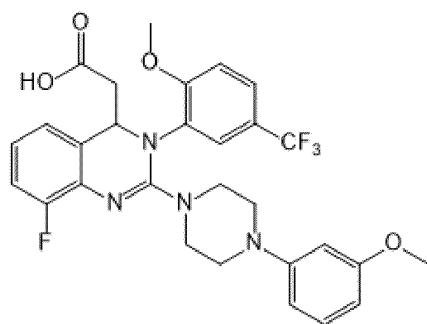
with a C₁-C₂-alcohol in the presence of an acid to obtain an ester of R-Enantiomer of Formula (IX)



Formula (IX)

wherein R' is methyl or ethyl, and

- b) treating the ester of R-Enantiomer of Formula (IX) obtained in step a) with a base to obtain a mixture comprising Letemovir and R-Enantiomer of Formula (X)



Formula (X).

In one embodiment said C₁-C₂-alcohol in step a) is methanol.

In one embodiment said C₁-C₂-alcohol in step a) is ethanol.

In one embodiment, R-Enantiomer is dissolved in said C₁-C₂-alcohol in step a), wherein the concentration of R-Enantiomer in said C₁-C₂-alcohol is in the range of from 0.05 M to 0.3 M, preferably from 0.1 to 0.2 M.

In one embodiment said acid in step a) is selected from the group consisting of sulfuric acid, hydrochloric acid, perchloric acid, nitric acid, a sulfonic acid, such as methanesulfonic acid (MsOH), p-toluenesulfonic acid (TsOH) or trifluoromethanesulfonic acid (TfOH), and a Lewis acid, such as FeCl₃, TiO(acac)₂, Sc(OTf)₂, or mixtures thereof. In a preferred embodiment said acid in step a) is selected

from the group consisting of sulfuric acid, hydrochloric acid, perchloric acid and nitric acid, or mixtures thereof. In a more preferred embodiment said acid in step a) is sulfuric acid.

In one embodiment said acid in step a) is added in an amount of from 0.5 to 2.0 equivalents, preferably from 1.0 to 1.5 equivalents with respect to R-Enantiomer.

In one embodiment, said acid in step a) is selected from the group consisting of sulfuric acid, hydrochloric acid, perchloric acid and nitric acid, wherein said acid is added in an amount of from 1.0 to 1.5 equivalents, preferably from 1.1 to 1.3 equivalents with respect to R-Enantiomer.

In one embodiment, said acid in step a) is a Lewis acid, such as FeCl_3 , $\text{TiO}(\text{acac})_2$, $\text{Sc}(\text{OTf})_2$, or mixtures thereof, wherein said acid is added in an amount of from 1.0 to 1.2 equivalents, preferably 1.0 to 1.1 equivalents with respect to R-Enantiomer.

In one embodiment, step a) is conducted at a temperature in the range of from 60 to 110 °C.

In one embodiment, step a) is conducted for at least 1 hour. In one embodiment, step a) is conducted for 1 to 96 hours, preferably for 15 to 20 hours.

In one embodiment, in step a) R-Enantiomer reacts with methanol in the presence of sulfuric acid to obtain a methyl ester of R-Enantiomer, preferably at a temperature in the range of from 60 to 110 °C.

In one embodiment said base in step b) is selected from the group consisting of alkali hydroxides, alkali earth metal hydroxides, alkoxides, 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) and DBU – 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU). In a preferred embodiment said base in step b) is selected from the group consisting of alkali hydroxides, such as LiOH, NaOH, KOH, CsOH, alkali earth metal hydroxides, such as $\text{Ca}(\text{OH})_2$, $\text{Sr}(\text{OH})_2$, $\text{Ba}(\text{OH})_2$, and alkoxides, such as lithium ethoxide (EtOLi), sodium ethoxide (EtONa), potassium ethoxide (EtOK), lithium isopropoxide (iPrOLi), sodium isopropoxide (iPrONa), potassium isopropoxide (iPrOK), lithium tert-butoxide (tBuOLi),

sodium tert-butoxide (tBuONa) and potassium tert-butoxide (tBuOK). In a more preferred embodiment said base in step b) is potassium tert-butoxide (tBuOK) or potassium hydroxide (KOH).

In one embodiment said base in step b) is added in an amount of 1 to 5 equivalents, preferably 1.5 to 4.0 equivalents with respect to the ester of R-Enantiomer.

In one embodiment, step b) is conducted in a polar aprotic solvent, such as acetonitrile (ACN), dimethylformamide (DMF), 2-methyltetrahydrofuran (2-MeTHF), propionitrile, 1,4-dioxane, chlorobenzene, methyl tert-butyl ether (MTBE), N-methyl-2-pyrrolidone (NMP) or tetrahydrofuran (THF). In one embodiment step b) is conducted in a polar aprotic solvent selected from the group consisting of dimethylformamide, propionitrile and acetonitrile.

In one embodiment, step b) is conducted at a temperature in the range of from 20 to 110 °C, preferably from 40 to 60 °C.

In one embodiment, step b) is conducted for at least 10 minutes, preferably for at least 30 minutes. In one embodiment, step b) is conducted for 10 minutes to 96 hours, preferably from 1.5 to 15 hours.

In one embodiment, step b) is followed by a step of adding an aqueous solution, such as water.

In one embodiment converting the Letermovir salt of a compound of Formula (I) in step iv-1) is conducted by means of transferring said salt into the compound of Formula (I) and Letermovir, which can be in turn converted to a salt or a solvate or a solvate of salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, in particular by methods as described in WO 2013/127971, WO 2013/127968, WO 2021/170874, WO 2021/170879 or WO 2021/170882. The R-Enantiomer salt of a compound of Formula (I) can be converted in a similar way.

In one embodiment, said transferring of the Letermovir salt of a compound of Formula (I) is conducted by treating a solution of said salt with an aqueous solution with a pH of from 1 to 4, wherein Letermovir in said salt acts as an acid.

In one embodiment, said transferring of the R-Enantiomer salt of a compound of Formula (I) is conducted by treating a solution of said salt with an aqueous solution with a pH of from 1 to 4, wherein R-Enantiomer in said salt acts as an acid.

In one embodiment, said transferring of the Letermovir salt of a compound of Formula (I) is conducted by treating a solution of said salt with an aqueous solution with a pH of from 8 to 12, wherein Letermovir in said salt acts as a base.

In one embodiment, said transferring of the R-Enantiomer salt of a compound of Formula (I) is conducted by treating a solution of said salt with an aqueous solution with a pH of from 8 to 12, wherein R-Enantiomer in said salt acts as a base.

In one embodiment, the ratio of Letermovir to R-Enantiomer in said mixture is in the range of from 10:90 to 90:10, preferably from 20:80 to 80:20, more preferably from 30:70 to 70:30, even more preferably from 40:60 to 60:40, most preferred from 45:55 to 55:45. In a preferred embodiment, said mixture is racemic 2-{{(4R,S)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}} acetic acid or a salt thereof, or a solvate thereof, or a salt of a solvate thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof.

In a more preferred embodiment said mixture is racemic 2-{{(4R,S)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}} acetic acid.

In one embodiment, step (ii) is carried out in presence of a solvent selected from the group consisting of ketones, such as acetone, methyl ethyl ketone, cyclohexanone, 4-methylcyclohexanone, 4-methyl-2-pentanone or 3-pentanone; alkanes, such as pentane, hexane, heptane or isooctane; cycloalkanes, such as cyclohexane or cyclopentane; aromatic solvents, such as chlorobenzene, 1,2-dichlorobenzene, cumene, toluene or xylenes; esters such as ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate,

butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, ethyl propionate, methyl propionate, isoamyl propionate, isobutyl propionate, hexyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, cyclohexyl butyrate, benzyl butyrate, isobutyl formate, ethyl formate, ethyl formate, isopropyl formate, butyl formate, pentyl formate, diethylene glycol monoethyl ether acetate and ethylene glycol diacetate; ethers, such as diisopropyl ether, cyclopentyl methyl ether, butyl ether, diethoxymethane, anisole, ethylene glycol dimethyl ether, diethylene glycol diethyl ether or dimethoxyethane; alcohols such as ethanol, methanol, 2-butanol, isopropanol, n-butanol, diethylene glycol, isobutanol, isopentanol or *tert*-butanol; nitriles, such as acetonitrile; and carbonates, such as dimethyl carbonate or diethyl carbonate; or mixtures thereof, preferably selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, more preferably selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, or mixtures thereof, most preferred from the group consisting of pentyl acetate, ethyl butyrate and propyl butyrate or mixtures thereof.

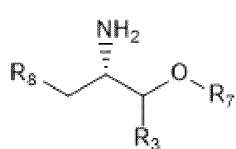
In one embodiment, said separating in step iii-1) or iii-2) comprises seeding by means of adding between 0.1% and a 10% of crystals, preferably between 0.1% and 5% of crystals, more preferably between 0.1% and 1% of crystals of the less soluble diastereomeric pure salt (prepared beforehand), referred to the total amount of the dissolved solid, to a supersaturated solution of the Letermovir salt of the compound of Formula (I) and an R-Enantiomer of the compound of Formula (I). Depending on the behavior of the formed diastereomeric salts, the temperature and time at which the crystal seeds are added may differ. In one embodiment the seeding is performed having the dissolution at a temperature between 90°C and 0°C. In one embodiment the seeds are added from 1 minute after reaching the seeding temperature ($t=1$ min) to 5 hours after reaching the seeding temperature.

In the enantiomeric resolution, the seeding process is particularly effective in promoting the crystallization of the less soluble diastereomeric salt, which may crystallize in a much more controlled fashion improving the yield and providing a better crystallization selectivity with a higher degree of crystallinity and a higher enantiomeric excess in a shorter process time, compared to the resolution without the seeding process.

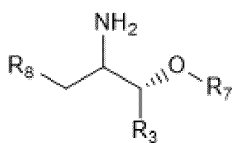
In one embodiment, said compound of Formula (I) produces in step ii) diastereomeric salts of Letermovir and R-Enantiomer, which have essentially different solubilities, such as at least 1.1 times, preferably at least 1.2 times, more preferably at least 1.5 times, yet more preferably at least 2 times, yet more preferably at least 2.5 times, most preferred 3.5 times lower in a solvent selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, preferably selected from the group consisting of pentyl acetate, ethyl butyrate and propyl butyrate or mixtures thereof. In one embodiment, diastereomeric salts of Letermovir and R-Enantiomer have from 1.1 to 5 times different solubilities, preferably from 1.5 to 5 times different solubilities, more preferably from 2.5 to 5 times different solubilities, in particular, from 3.5 to 5 times different solubilities.

In one embodiment, the Letermovir salt of a compound of Formula (I) in step ii) has essentially lower solubility than the R-Enantiomer salt of a compound of Formula (I), such as at least 1.1 times lower, preferably at least 1.2 times lower, more preferably at least 1.5 times lower, yet more preferably at least 2 times lower, yet more preferably at least 2.5 times lower, most preferred 3.5 times lower in a solvent selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, preferably selected from

the group consisting of pentyl acetate, ethyl butyrate and propyl butyrate or mixtures thereof. In one embodiment, the Letermovir salt of a compound of Formula (I) in step ii) has from 1.1 to 5 times lower solubility, preferably from 1.5 to 5 times lower solubility, more preferably from 2.5 to 5 times lower solubility, in particular, from 3.5 to 5 times lower solubility than the R-Enantiomer salt of a compound of Formula (I). In a preferred embodiment, said Letermovir salt of a compound of Formula (I) is separated from said solvent as a precipitate, preferably by filtration or centrifugation. In yet another preferred embodiment, said R-Enantiomer salt of a compound of Formula (I) is separated from said solvent as a mother liquor, preferably by filtration or centrifugation. In a preferred embodiment the compound of Formula (I) is a compound of Formula (II) or (III)



(II)



(III)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

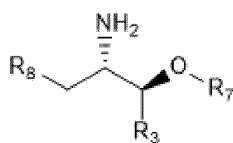
R₇ is H or C₁-C₃-alkyl,

R₈ is selected from the group consisting of H, OH, methyl or ethyl,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring.

In a more preferred embodiment, the compound of Formula (II) is a compound of Formula (IIa)



(IIa)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

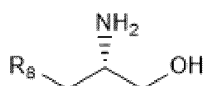
R₇ is H or C₁-C₃-alkyl,

R₈ is H or OH,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a tetrahydrofuran ring.

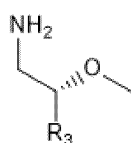
In another more preferred embodiment, the compound of Formula (II) is a compound of Formula (IIb)



(IIb)

wherein R₈ is H, methyl or ethyl.

In another more preferred embodiment, the compound of Formula (III) is a compound of Formula (IIIa)

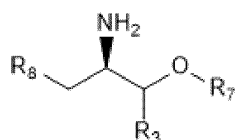


(IIIa)

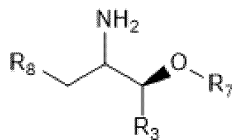
wherein R₃ is H, CH₂OH or methyl.

In one embodiment, the R-Enantiomer salt of a compound of Formula (I) in step ii) has essentially lower solubility than the Letemovir salt of a compound of Formula (I), such as at least 1.1 times lower, preferably at least 1.2 times lower, more preferably at least 1.5 times lower, yet more preferably at least 2 times lower, yet more preferably at least 2.5

times lower, most preferred 3.5 times lower solubility in a solvent selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, preferably selected from the group consisting of pentyl acetate, ethyl butyrate and propyl butyrate or mixtures thereof. In one embodiment, the R-Enantiomer salt of a compound of Formula (I) in step ii) has from 1.1 to 5 times lower solubility, preferably from 1.5 to 5 times lower solubility, more preferably from 2.5 to 5 times lower solubility, in particular from 3.5 to 5 times lower solubility, than the Letermovir salt of a compound of Formula (I). In a preferred embodiment, said R-Enantiomer salt of a compound of Formula (I) is separated from said solvent as a precipitate, preferably by filtration or centrifugation. In yet another preferred embodiment, said Letermovir salt of a compound of Formula (I) is separated from said solvent as a mother liquor, preferably by filtration or centrifugation. In a preferred embodiment the compound of Formula (I) is a compound of Formula (IV) or (V)



(IV)



(V)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

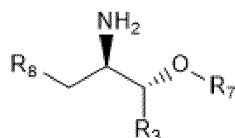
R₇ is H or C₁-C₃-alkyl,

R₈ is selected from the group consisting of H, OH, methyl or ethyl,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring.

In a more preferred embodiment, the compound of Formula (IV) is a compound of Formula (IVa)



(IVa)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

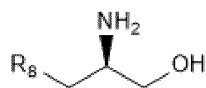
R₇ is H or C₁-C₃-alkyl,

R₈ is H or OH,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a tetrahydrofuran ring.

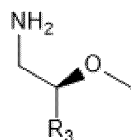
In another more preferred embodiment, the compound of Formula (IV) is a compound of Formula (IVb)



(IVb)

wherein R₈ is H, methyl or ethyl.

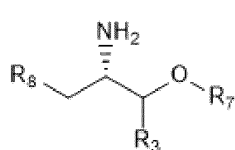
In another more preferred embodiment, the compound of Formula (V) is a compound of Formula (Va)



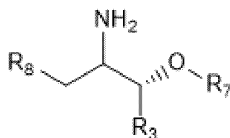
(Va)

wherein R₃ is H, CH₂OH or methyl.

In one embodiment of said method for producing Letermovir or a salt thereof or a solvate thereof or a salt of solvate thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, the method for producing a Letermovir salt or an R-Enantiomer salt of a compound of Formula (I) or said method for enantiomeric separation the compound of Formula (I) is a compound of Formula (II) or (III)



(II)



(III)

wherein

R_3 is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

R_7 is H or C₁-C₃-alkyl,

R_8 is selected from the group consisting of H, OH, methyl or ethyl,

wherein R_7 and R_8 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

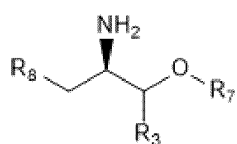
wherein R_3 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein step iii-1) comprises isolating the solid phase comprising the Letermovir salt of the compound of Formula (II) or (III).

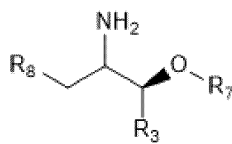
In a preferred embodiment of said method, the compound of Formula (I) is a compound of Formula (II) or (III) as defined above and step (ii) is carried out in a liquid phase in presence of a solvent selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether,

cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, preferably selected from the group consisting of pentyl acetate, ethyl butyrate and propyl butyrate or mixtures thereof.

In one embodiment of said method for producing Letermovir or a salt thereof or a solvate thereof or a salt of solvate thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, the method for producing a Letermovir salt or an R-Enantiomer salt of a compound of Formula (I) or said method for enantiomeric separation the compound of Formula (I) is a compound of Formula (IV) or (V)



(IV)



(V)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

R₇ is H or C₁-C₃-alkyl,

R₈ is selected from the group consisting of H, OH, methyl or ethyl,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

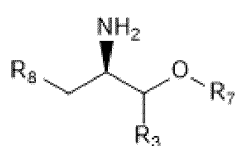
wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein step iii-1) comprises isolating the liquid phase comprising the Letermovir salt of the compound of Formula (IV) or (V).

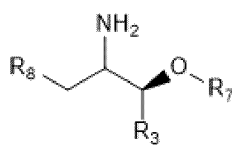
In a preferred embodiment of said method, the compound of Formula (I) is a compound of Formula (IV) or (V) as defined above and step (ii) is carried out in a liquid phase in presence of a solvent selected from the group consisting of acetonitrile, ethyl acetate,

methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, preferably selected from the group consisting of pentyl acetate, ethyl butyrate and propyl butyrate or mixtures thereof.

In one embodiment of said method for producing Letemovir or a salt thereof or a solvate thereof or a salt of solvate thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, the method for producing a Letemovir salt or an R-Enantiomer salt of a compound of Formula (I) or said method for enantiomeric separation the compound of Formula (I) is a compound of Formula (IV) or (V)



(IV)



(V)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

R₇ is H or C₁-C₃-alkyl,

R₈ is selected from the group consisting of H, OH, methyl or ethyl,

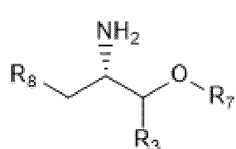
wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

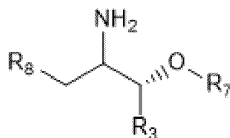
wherein step iii-2) comprises isolating the solid phase comprising the R-Enantiomer salt of the compound of Formula (IV) or (V).

In a preferred embodiment of said method, the compound of Formula (I) is a compound of Formula (IV) or (V) as defined above and step (ii) is carried out in a liquid phase in presence of a solvent selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, preferably selected from the group consisting of pentyl acetate, ethyl butyrate and propyl butyrate or mixtures thereof.

In one embodiment of said method for producing Letermovir or a salt thereof or a solvate thereof or a salt of solvate thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, the method for producing a Letermovir salt or an R-Enantiomer salt of a compound of Formula (I) or said method for enantiomeric separation the compound of Formula (I) is a compound of Formula (II) or (III)



(II)



(III)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

R₇ is H or C₁-C₃-alkyl,

R₈ is selected from the group consisting of H, OH, methyl or ethyl,

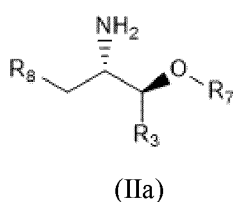
wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein step iii-2) comprises isolating the liquid phase comprising the R-Enantiomer salt of the compound of Formula (II) or (III).

In a preferred embodiment of said method, the compound of Formula (I) is a compound of Formula (II) or (III) as defined above and step (ii) is carried out in a liquid phase in presence of a solvent selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, preferably selected from the group consisting of pentyl acetate, ethyl butyrate and propyl butyrate or mixtures thereof.

In a preferred embodiment, the compound of Formula (II) is a compound of Formula (IIa)



wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

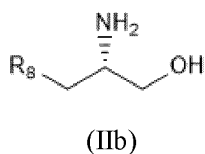
R₇ is H or C₁-C₃-alkyl,

R₈ is H or OH,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

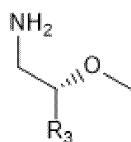
wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a tetrahydrofuran ring.

In another preferred embodiment, the compound of Formula (II) is a compound of Formula (IIb)



wherein R_8 is H, methyl or ethyl.

In another preferred embodiment, the compound of Formula (III) is a compound of Formula (IIIa)

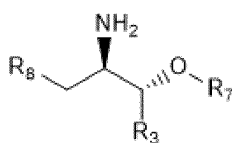


(IIIa)

wherein R_3 is H, CH_2OH or methyl.

In a more preferred embodiment of said method, the compound of Formula (II) is a compound of Formula (IIa) or (IIb) and the compound of Formula (III) is a compound of Formula (IIIa) as defined above and step (ii) is carried out in a liquid phase in presence of a solvent selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, preferably selected from the group consisting of pentyl acetate, ethyl butyrate and propyl butyrate or mixtures thereof.

In a more preferred embodiment, the compound of Formula (IV) is a compound of Formula (IVa)



(IVa)

wherein

R_3 is selected from the group consisting of H, C_1 - C_3 -alkyl and phenyl,

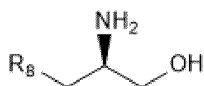
R_7 is H or C_1 - C_3 -alkyl,

R_8 is H or OH,

wherein R_7 and R_8 , together with the atoms to which they are attached, are optionally connected to form a C_3 - C_6 -oxocyclic ring, and

wherein R_3 and R_7 , together with the atoms to which they are attached, are optionally connected to form a tetrahydrofuran ring.

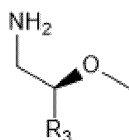
In another more preferred embodiment, the compound of Formula (IV) is a compound of Formula (IVb)



(IVb)

wherein R_8 is H, methyl or ethyl.

In another more preferred embodiment, the compound of Formula (V) is a compound of Formula (Va)



(Va)

wherein R_3 is H, CH_2OH or methyl.

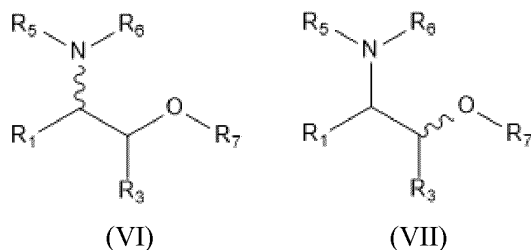
In a more preferred embodiment of said method, the compound of Formula (IV) is a compound of Formula (IVa) or (IVb) and the compound of Formula (V) is a compound of Formula (Va) as defined above and step (ii) is carried out in a liquid phase in presence of a solvent selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, preferably selected from the group consisting of pentyl acetate, ethyl butyrate and propyl butyrate or mixtures thereof.

In one embodiment of said method for producing Letermovir or a salt thereof or a solvate thereof or a salt of solvate thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, the method for producing a Letermovir salt or an R-Enantiomer salt of a compound of Formula (I) or said method for enantiomeric separation, said method further comprises adding the compound of Formula (II) or (III) as defined above, to said mother liquor comprising said Letermovir salt of a compound of Formula (I) followed by isolating the precipitate comprising the Letermovir salt of the compound of Formula (II) or (III). In a preferred embodiment the compound of Formula (II) is a compound of Formula (IIa) or (IIb) as defined above. In another preferred embodiment the compound of Formula (III) is a compound of Formula (IIIa) as defined above.

In another embodiment of said method for producing Letermovir or a salt thereof or a solvate thereof or a salt of solvate thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, the method for producing a Letermovir salt or an R-Enantiomer salt of a compound of Formula (I) or said method for enantiomeric separation, said method further comprises adding the compound of Formula (IV) or (V) as defined above, to said mother liquor comprising said R-Enantiomer salt of a compound of Formula (I) followed by isolating the precipitate comprising the R-Enantiomer salt of the compound of Formula (IV) or (V). In a preferred embodiment the compound of Formula (IV) is a compound of Formula (IVa) or (IVb) as defined above. In another preferred embodiment the compound of Formula (V) is a compound of Formula (Va) as defined above.

In one embodiment, the enantiomeric purity of the compound of Formula (I) is at least 80% ee, preferably at least 85% ee, more preferably at least 90% ee, more preferably at least 95% ee, more preferably at least 98% ee, most preferred at least 99% ee.

In one embodiment of said method for producing Letermovir or a salt thereof or a solvate thereof or a salt of solvate thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, the method for producing a Letermovir salt or an R-Enantiomer salt of a compound of Formula (I) or said method for enantiomeric separation the compound of Formula (I) is a compound of Formula (VI) or (VII)



wherein

R_1 is selected from the group consisting of H, C₁-C₃-alkyl and CH₂OH,

R_3 is selected from the group consisting of H, C₁-C₃-alkyl, phenyl and 4-nitrophenyl,

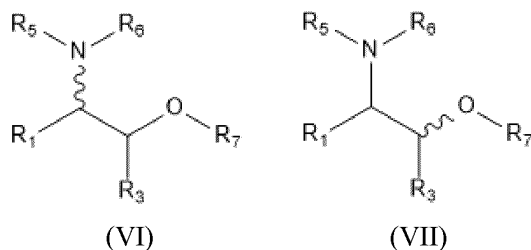
R_5 and R_6 each is independently selected from the group consisting of H and C₁-C₃-alkyl, preferably each is H,

R_7 is H or C₁-C₃-alkyl,

wherein R_1 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₇-oxocyclic ring, and

wherein R_3 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring.

In one embodiment of said method for producing Letemovir or a salt thereof or a solvate thereof or a salt of solvate thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, the method for producing a Letemovir salt or an R-Enantiomer salt of a compound of Formula (I) or said method for enantiomeric separation the compound of Formula (I) is a compound of Formula (VI) or (VII)



wherein

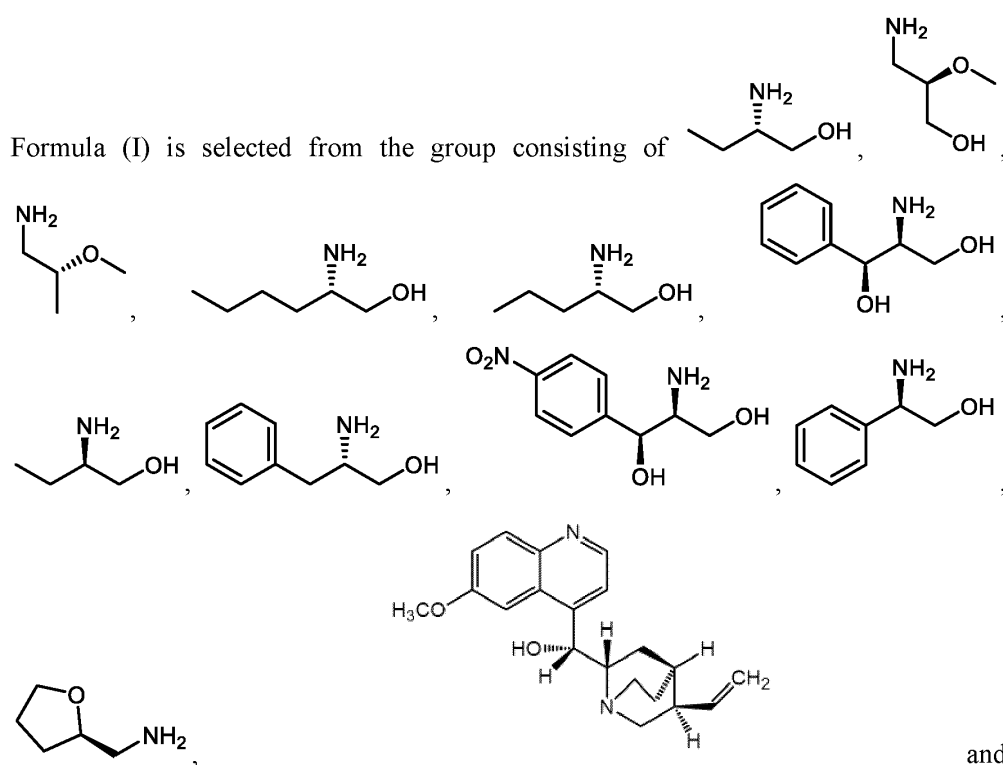
R₁ is selected from the group consisting of H, C₁-C₃-alkyl and CH₂OH,
R₃ is selected from the group consisting of H, C₁-C₃-alkyl, phenyl and 4-nitrophenyl,
R₅ and R₆ each is independently selected from the group consisting of H and C₁-C₃-alkyl, preferably each is H,
R₇ is H or C₁-C₃-alkyl,
wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₇-oxocyclic ring,
wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring and
wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl, such as 5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl.

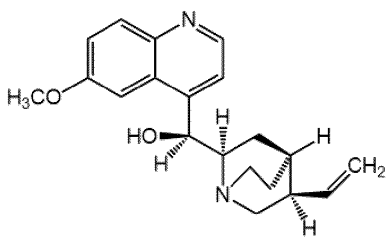
In a preferred embodiment of said method, the compound of Formula (I) is a compound of Formula (VI) or (VII) as defined above and step (ii) is carried out in a liquid phase in presence of a solvent selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, preferably selected from the group consisting of pentyl acetate, ethyl butyrate and propyl butyrate or mixtures thereof.

In one embodiment of said method for producing Letemovir or a salt thereof or a solvate thereof or a salt of solvate thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, the method for producing a Letemovir salt or an R-Enantiomer salt of a compound of Formula (I) or said method for enantiomeric separation the compound of Formula (I), the compound of Formula (I) is selected from the group consisting of (S)-(+)-2-Amino-1-butanol, (2R)-3-amino-2-methoxy-propan-1-ol, (R)-2-Methoxypropan-1-amine, (S)-(+)-2-Amino-1-

hexanol, (S)-(+)-2-Amino-1-pentanol, (R)-(-)-2-Amino-1-butanol, L-Phenylalaninol, (1S,2S)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol, (R)-(-)-2-Phenylglycinol, (R)-(Tetrahydrofuran-2-yl)methanamine, and (1S,2S)-2-amino-1-phenylpropane-1,3-diol, preferably (S)-(+)-2-Amino-1-butanol, (2R)-3-amino-2-methoxy-propan-1-ol, (R)-2-Methoxypropan-1-amine, (S)-(+)-2-Amino-1-hexanol, (S)-(+)-2-Amino-1-pentanol, (1S,2S)-2-amino-1-phenylpropane-1,3-diol, (R)-[(2S,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinine) and (S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinidine).

In one embodiment of said method for producing Letemovir or a salt thereof or a solvate thereof or a salt of solvate thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, the method for producing a Letemovir salt or an R-Enantiomer salt of a compound of Formula (I) or said method for enantiomeric separation the compound of Formula (I), the compound of



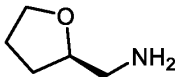
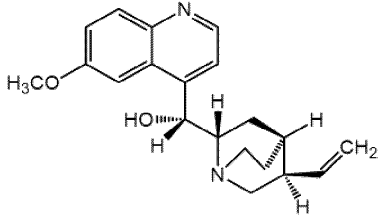
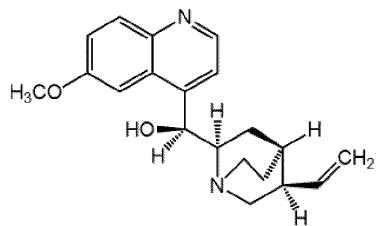


, as also depicted with the respective nomenclature in

Table 1:

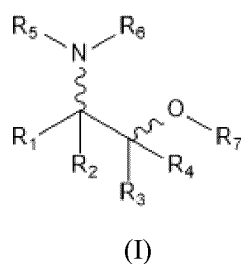
Table 1

Structure	Nomenclature
	(S)-(+)-2-Amino-1-butanol
	(2R)-3-amino-2-methoxy-propan-1-ol
	(R)-2-methoxypropan-1-amine
	(S)-(+)-2-amino-1-hexanol
	(S)-(+)-2-amino-1-pentanol
	(1S,2S)-2-amino-1-phenylpropane-1,3-diol
	(R)-(-)-2-Amino-1-butanol
	L-Phenylalaninol
	(1S,2S)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol
	(R)-(-)-2-Phenylglycinol

	(R)-(Tetrahydrofuran-2-yl)methanamine
	(R)-[(2S,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl]-(6-methoxyquinolin-4-yl)methanol (quinine)
	(S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl]-(6-methoxyquinolin-4-yl)methanol (quinidine)

In one embodiment, the compound of Formula (I) is (S)-(+)-2-Amino-1-butanol and the solvent is pentyl acetate.

Another aspect of the present invention relates to use of a compound of Formula (I) for producing Letemovir or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, wherein the compound of Formula (I) is



wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

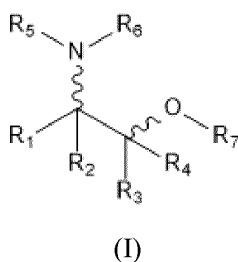
wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

in particular by the method as described in the present invention.

Another aspect of the present invention relates to use of a compound of Formula (I) for producing R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, wherein the compound of Formula (I) is



wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

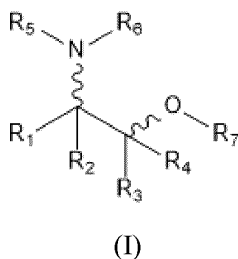
wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

in particular by the method as described in the present invention.

Another aspect of the present invention relates to use of a compound of Formula (I) for enantiomeric separation of a mixture comprising Letemovir and R-Enantiomer, or salts

thereof or solvates thereof or solvates of salts thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, wherein the compound of Formula (I) is



wherein

R_1 and R_2 each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R_3 and R_4 each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinoliny and methoxyquinoliny,

R_5 and R_6 each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R_7 is H or C₁-C₆-alkyl,

wherein R_1 and R_3 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R_1 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R_3 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

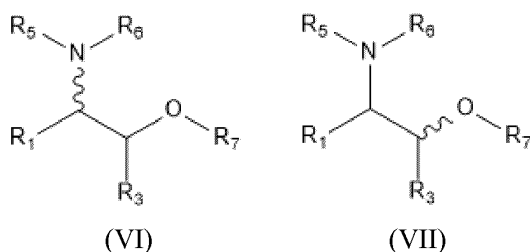
wherein R_1 and R_5 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally

substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

in particular by the method as described in the present invention.

In one embodiment of said use, the compound of Formula (I) is a compound of Formula (VI) or (VII)



wherein

R₁ is selected from the group consisting of H, C₁-C₃-alkyl and CH₂OH,

R₃ is selected from the group consisting of H, C₁-C₃-alkyl, phenyl and 4-nitrophenyl,

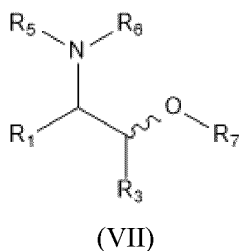
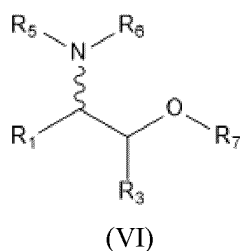
R₅ and R₆ each is independently selected from the group consisting of H and C₁-C₃-alkyl, preferably each is H,

R₇ is H or C₁-C₃-alkyl,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₇-oxocyclic ring, and

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring.

In one embodiment of said use, the compound of Formula (I) is a compound of Formula (VI) or (VII)



wherein

R₁ is selected from the group consisting of H, C₁-C₃-alkyl and CH₂OH,

R₃ is selected from the group consisting of H, C₁-C₃-alkyl, phenyl and 4-nitrophenyl,

R₅ and R₆ each is independently selected from the group consisting of H and C₁-C₃-alkyl, preferably each is H,

R₇ is H or C₁-C₃-alkyl,

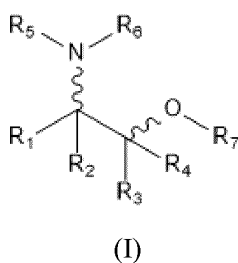
wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₇-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system,

wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl, such as 5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl.

In one aspect, the present invention refers to an R-Enantiomer salt of a compound of Formula (I)



wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

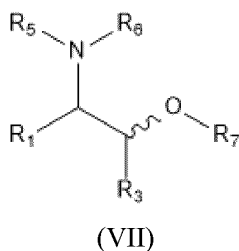
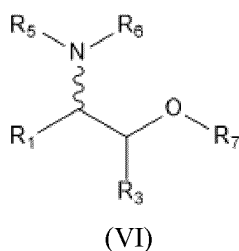
wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring.

In one embodiment, the present invention refers to an R-Enantiomer salt of a compound of Formula (I), wherein the compound of Formula (I) is a compound of Formula (VI) or (VII)



wherein

R₁ is selected from the group consisting of H, C₁-C₃-alkyl and CH₂OH,

R₃ is selected from the group consisting of H, C₁-C₃-alkyl, phenyl and 4-nitrophenyl,

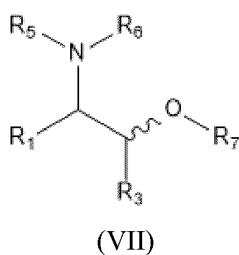
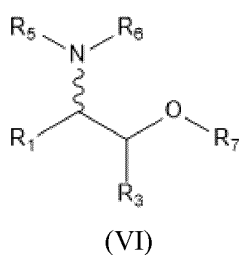
R₅ and R₆ each is independently selected from the group consisting of H and C₁-C₃-alkyl,

R₇ is H or C₁-C₃-alkyl,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₇-oxocyclic ring, and

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring.

In one embodiment, the present invention refers to an R-Enantiomer salt of a compound of Formula (I), wherein the compound of Formula (I) is a compound of Formula (VI) or (VII)



wherein

R₁ is selected from the group consisting of H, C₁-C₃-alkyl and CH₂OH,

R₃ is selected from the group consisting of H, C₁-C₃-alkyl, phenyl and 4-nitrophenyl,

R₅ and R₆ each is independently selected from the group consisting of H and C₁-C₃-alkyl,

R₇ is H or C₁-C₃-alkyl,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₇-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring and

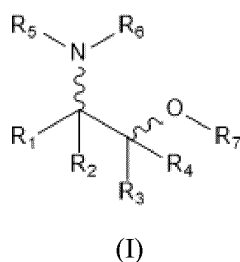
wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system,

wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl, such as 5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl.

In one embodiment, the present invention refers to an R-Enantiomer salt of a compound of Formula (I), wherein said salt is (R)-1-hydroxy-2-methoxypropan-3-aminium salt of 2-{(4R)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.0, 9.2, 12.0, 15.2, 17.5, 18.6, 20.4, 21.3, 21.8 and 26.0 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

In one embodiment, the present invention refers to an R-Enantiomer salt of a compound of Formula (I), wherein said salt is (R)-[(2S,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinine) salt of 2-{(4R)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 5.1, 9.9, 13.3, 13.5, 15.4, 15.7, 16.0, 16.8, 17.2, 18.0, 18.7, 19.1, 20.4, 21.4 and 22.6 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

In one aspect, the present invention refers to a Letermovir salt of a compound of Formula (I),



wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

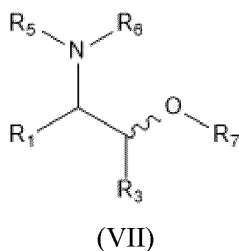
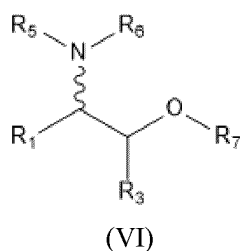
wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring.

In one embodiment, the present invention refers to a Letermovir salt of a compound of Formula (I), wherein the compound of Formula (I) is a compound of Formula (VI) or (VII)



wherein

R₁ is selected from the group consisting of H, C₁-C₃-alkyl and CH₂OH,

R₃ is selected from the group consisting of H, C₁-C₃-alkyl, phenyl and 4-nitrophenyl,

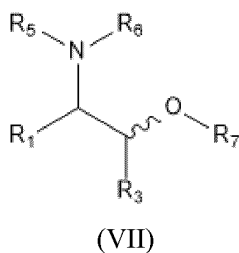
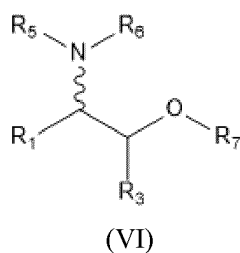
R₅ and R₆ each is independently selected from the group consisting of H and C₁-C₃-alkyl,

R₇ is H or C₁-C₃-alkyl,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₇-oxocyclic ring, and

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring.

In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein the compound of Formula (I) is a compound of Formula (VI) or (VII)



wherein

R₁ is selected from the group consisting of H, C₁-C₃-alkyl and CH₂OH,

R₃ is selected from the group consisting of H, C₁-C₃-alkyl, phenyl and 4-nitrophenyl,

R₅ and R₆ each is independently selected from the group consisting of H and C₁-C₃-alkyl,

R₇ is H or C₁-C₃-alkyl,

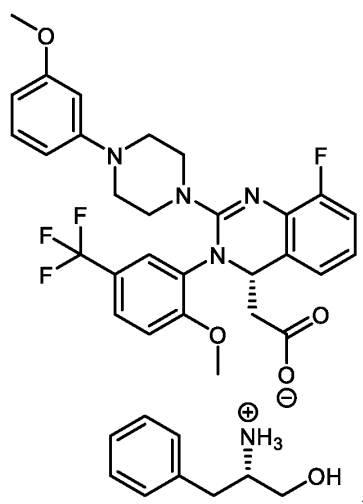
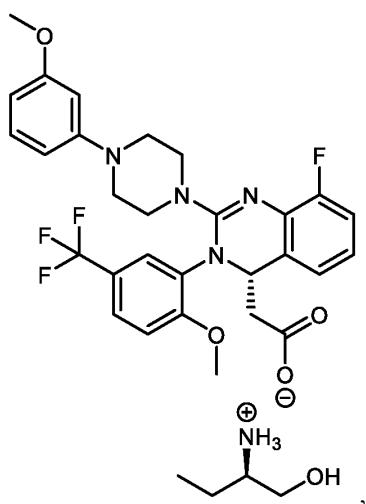
wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₇-oxocyclic ring,

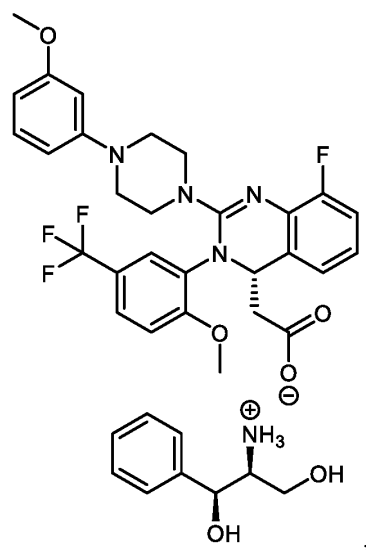
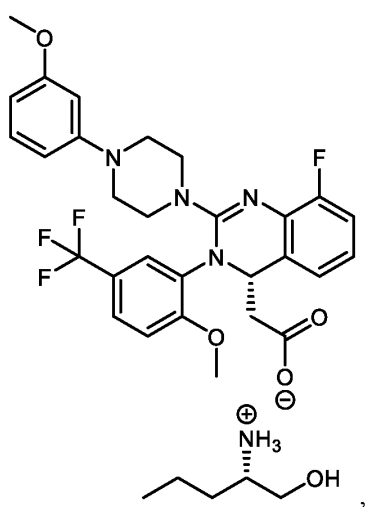
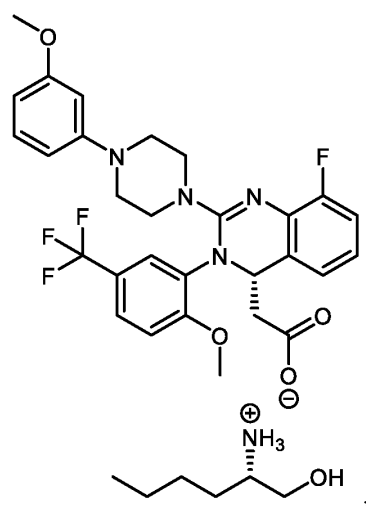
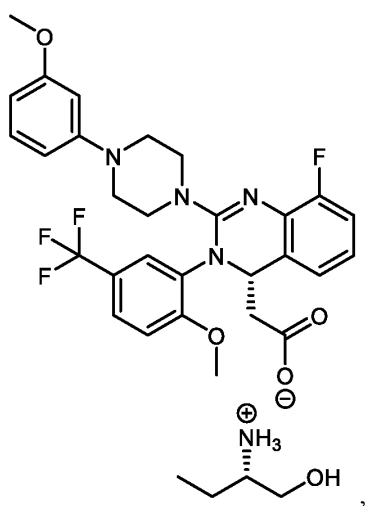
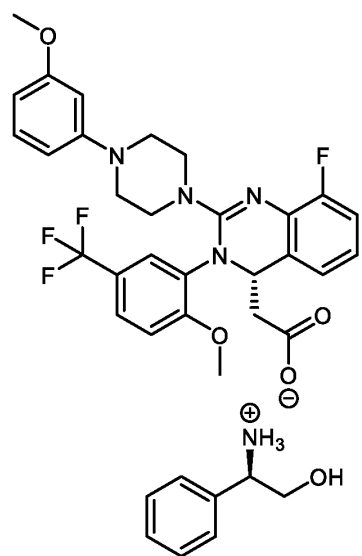
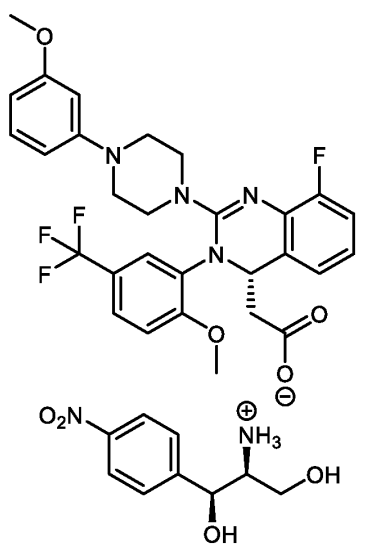
wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

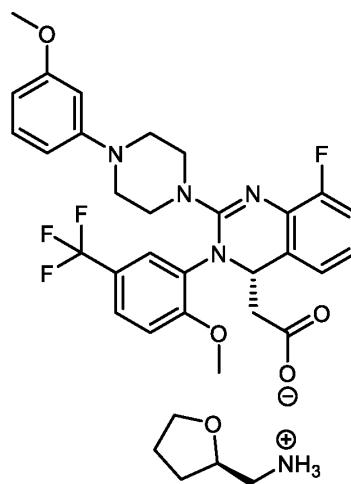
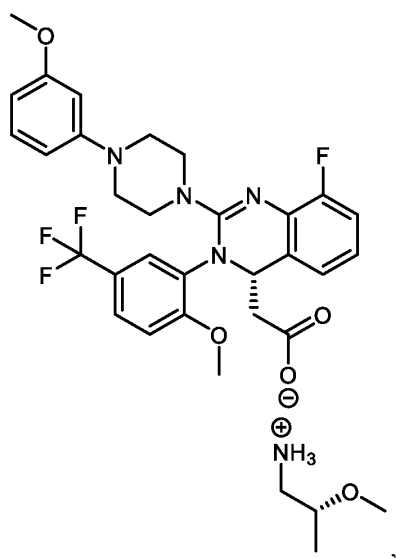
wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl, such as 5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl.

In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein the compound of Formula (I) is selected from the group consisting of (R)-(-)-2-Amino-1-butanol, L-Phenylalaninol, (1S,2S)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol, (R)-(-)-2-Phenylglycinol, (S)-(+)-2-Amino-1-butanol, (S)-(+)-2-Amino-1-hexanol, (S)-(+)-2-Amino-1-pentanol, (1S,2S)-2-amino-1-phenyl-propane-1,3-diol, (R)-2-Methoxypropan-1-amine, (R)-(Tetrahydrofuran-2-yl)methanamine, (S)-(+)-1-Amino-2-propanol, (S)-(+)-Leucinol and (S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinidine).

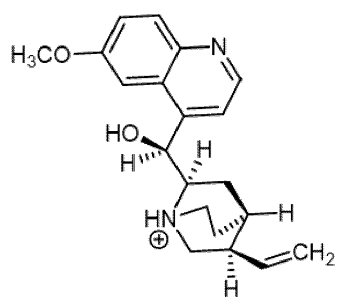
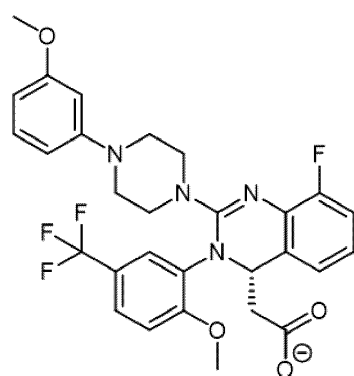
In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein said salt is selected from the group consisting of







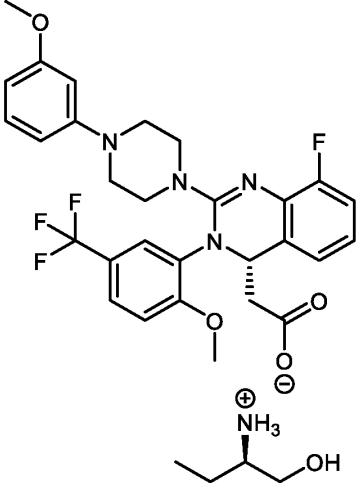
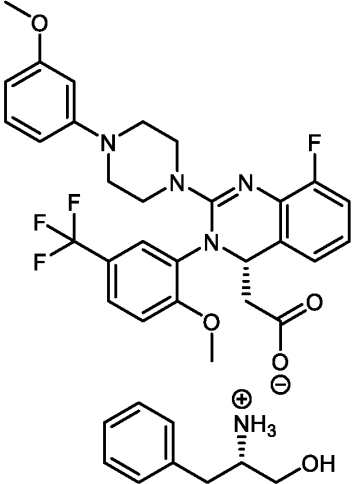
and

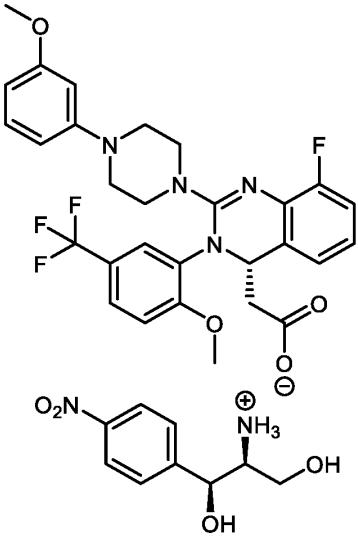
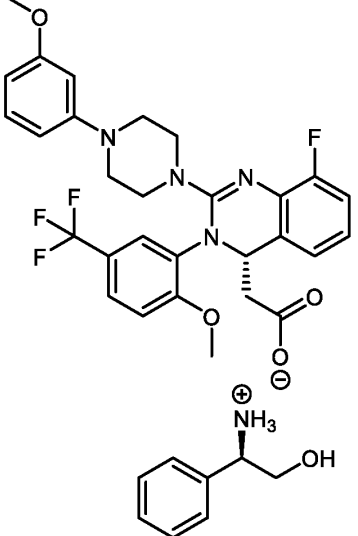
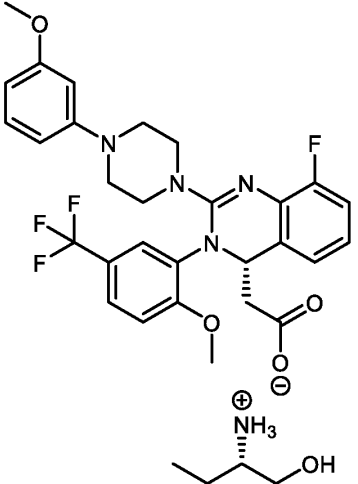


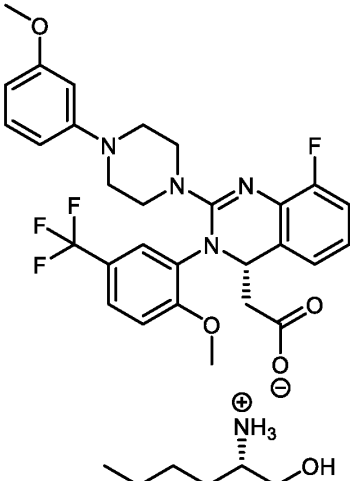
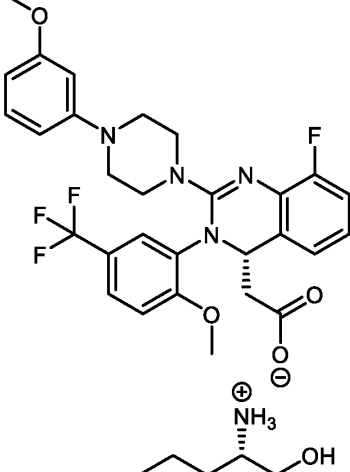
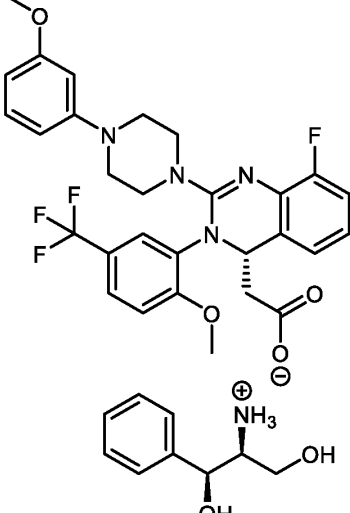
, as also depicted with the

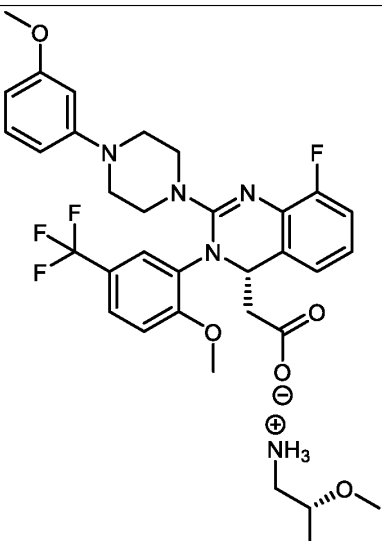
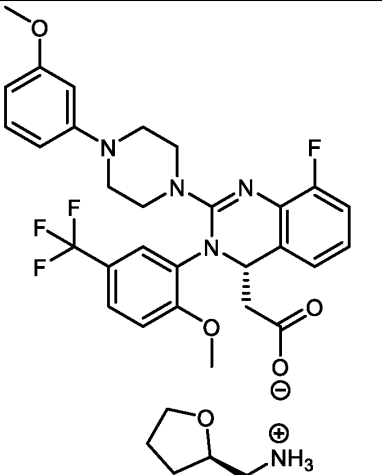
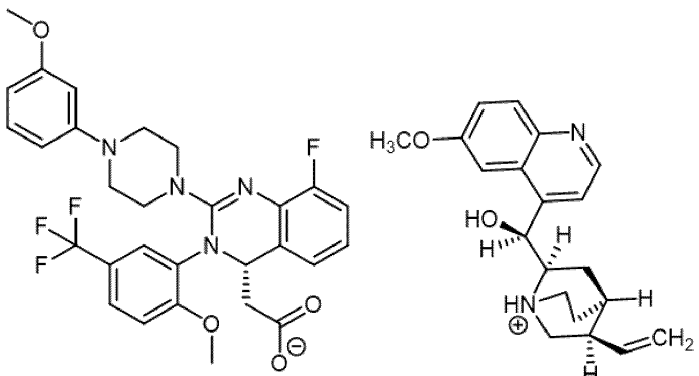
respective nomenclature in Table 2:

Table 2

Structure	Nomenclature
	(R)-1-hydroxybutan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1)
	(S)-1-hydroxy-3-phenylpropan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1)

	(1S,2S)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1)
	(R)-2-hydroxy-1-phenylethan-1-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1)
	(S)-1-hydroxybutan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1)

	(S)-1-hydroxyhexan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1)
	(S)-1-hydroxypentan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1)
	(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1)

	(R)-2-methoxypropan-1-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1)
	(R)-(tetrahydrofuran-2-yl)methanaminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1)
	(S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinidine) salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1)

In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein said salt is (R)-1-hydroxybutan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-

dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.1, 8.9, 12.3, 15.3, 16.8, 17.6, 17.9, 20.6, 21.4 and 22.4 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein said salt is (S)-1-hydroxy-3-phenylpropan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 5.4, 5.8, 14.3, 14.8, 15.2, 17.8, 18.4, 19.1, 19.5, 19.9, 21.4, 21.8 and 22.2 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein said salt is (1S,2S)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 5.8, 8.9, 11.7, 14.4, 17.5, 19.2, 19.8, 20.8 and 21.2 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein said salt is (R)-2-hydroxy-1-phenylethan-1-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 5.6, 5.9, 11.8, 14.5, 15.4, 16.9, 17.5, 18.2, 19.4, 20.5, 21.1 and 21.6 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein said salt is (S)-1-hydroxybutan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.1, 8.9, 12.3, 15.2, 17.6,

17.9, 20.6 and 22.3 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein said salt is (S)-1-hydroxyhexan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.2, 9.9, 12.4, 13.2, 14.6, 16.6, 18.2, 18.8, 19.8, 20.3, 22.6 and 23.9 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein said salt is (S)-1-hydroxypentan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.3, 9.9, 12.7, 13.3, 14.8, 16.5, 18.4, 18.8, 20.5, 23.0 and 24.2 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein said salt is (1S,2S)-1,3-dihydroxy-1-phenylpropan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 5.7, 5.8, 9.3, 11.7, 14.5, 15.3, 18.6, 19.4, 20.6 and 21.1 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein said salt is (R)-2-methoxypropan-1-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.0, 9.3, 12.0, 15.2, 17.5, 18.8, 20.4, 21.7 and 25.9 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein said salt is (R)-(tetrahydrofuran-2-yl)methanaminium salt of 2-{(4S)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.0, 9.3, 12.0, 15.2, 17.5, 18.7, 20.4 and 21.8 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein said salt is (S)-1-hydroxybutan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.0, 9.3, 12.1, 15.3, 18.6, 19.0, 20.6, 21.9 and 22.3 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein said salt is (2S)-1-hydroxy-4-methylpentan-2-aminium salt of 2-{(4S)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.3, 9.8, 13.3, 16.2, 18.6, 20.5 and 23.0 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

In one embodiment, the present invention refers to a Letemovir salt of a compound of Formula (I), wherein said salt is (S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinidine) salt of 2-{(4S)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 4.2, 9.4, 13.4, 14.2, 14.4, 16.5, 16.7, 17.4, 17.7, 18.3, 18.5, 18.8, 19.6, 22.2 and 23.9 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

In one aspect, the present invention further relates to Letemovir or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof which is obtainable by the method disclosed herein.

In one aspect, the present invention further relates to a Letemovir or R-Enantiomer salt of a compound of Formula (I) which is obtainable by a method disclosed herein.

Abbreviations

h	hour(s)
DSC	differential scanning calorimetry
DVS	dynamic vapour sorption
eq	equivalent
HPLC	high pressure liquid chromatography
min	minutes
NMR	nuclear magnetic resonance
TGA	thermogravimetric analysis
PXRD	powder X-ray diffraction
3D-ED	electron diffraction
UPC2	UltraPerformance Convergence Chromatography

Description of the figures

Figure 1 shows PXRD analyses of the obtained salts with Letemovir and the R-Enantiomer with both 2-Amino-1-butanol enantiomers.

Figure 2a shows PXRD of the Letemovir / (R)-(-)-2-Amino-1-butanol salt.

Figure 2b shows TGA (above) and DSC (below) of the Letemovir / (R)-(-)-2-Amino-1-butanol salt.

Figure 2c shows DVS of the Letemovir / (R)-(-)-2-Amino-1-butanol salt.

Figure 3a shows PXRD of the Letemovir / L-Phenylalaninol salt Phase 1.

Figure 3b shows TGA (above) and DSC (below) of the Letemovir / L-Phenylalaninol salt Phase 1.

Figure 3c shows DVS of the Letemovir / L-Phenylalaninol salt Phase 1.

Figure 3d shows PXRD of the Letermovir / L-Phenylalaninol salt Phase 2.

Figure 4a shows PXRD of the Letermovir / (1S,2S)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol salt.

Figure 4b shows TGA (above) and DSC (below) of the Letermovir / (1S,2S)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol salt.

Figure 4c shows DVS of the Letermovir / (1S,2S)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol salt.

Figure 5a shows PXRD of the Letermovir / (R)-(-)-2-Phenylglycinol salt.

Figure 5b shows TGA (above) and DSC (below) of the Letermovir / (R)-(-)-2-Phenylglycinol salt.

Figure 5c shows DVS of the Letermovir / (R)-(-)-2-Phenylglycinol salt.

Figure 6a shows PXRD of the Letermovir / (S)-(+)-2-Amino-1-butanol salt.

Figure 6b shows ¹H-NMR spectrum of Letermovir / (S)-(+)-2-Amino-1-butanol salt.

Figure 6c shows TGA (above) and DSC (below) of Letermovir / (S)-(+)-2-Amino-1-butanol salt.

Figure 6d shows SCXRD of Letermovir / (S)-(+)-2-Amino-1-butanol salt.

Figure 7a shows PXRD of the Letermovir / (S)-(+)-2-Amino-1-hexanol salt.

Figure 7b shows ¹H-NMR spectrum of the Letermovir / (S)-(+)-2-Amino-1-hexanol salt.

Figure 7c shows TGA (above) and DSC (below) of the Letermovir / (S)-(+)-2-Amino-1-hexanol salt.

Figure 8a shows PXRD of the Letermovir / (S)-(+)-2-Amino-1-pentanol salt.

Figure 9a shows PXRD of the Letermovir / (1S,2S)-2-amino-1-phenyl-propane-1,3-diol salt.

Figure 10a shows PXRD of the R-Enantiomer / (2R)-3-amino-2-methoxy-propan-1-ol salt.

Figure 10b shows ¹H-NMR spectrum of the R-Enantiomer / (2R)-3-amino-2-methoxy-propan-1-ol salt.

Figure 10c shows TGA (above) and DSC (below) of the R-Enantiomer / (2R)-3-amino-2-methoxy-propan-1-ol salt.

Figure 10d shows SCXRD of the R-Enantiomer / (2R)-3-amino-2-methoxy-propan-1-ol salt.

Figure 11a shows PXRD of the Letermovir / (R)-2-Methoxypropan-1-amine salt.

Figure 11b shows ¹H-NMR spectrum of the Letermovir / (R)-2-Methoxypropan-1-amine salt.

Figure 11c shows TGA (above) and DSC (below) of the Letemovir / (R)-2-Methoxypropan-1-amine salt.

Figure 11d shows SCXRD of the Letemovir / (R)-2-Methoxypropan-1-amine salt.

Figure 12a shows PXRD of the Letemovir / (R)-(Tetrahydrofuran-2-yl)methanamine salt.

Figure 12b shows TGA (above) and DSC (below) of the Letemovir / (R)-(Tetrahydrofuran-2-yl)methanamine salt.

Figure 12c shows SCXRD of the Letemovir / (R)-(Tetrahydrofuran-2-yl)methanamine salt.

Figure 13 shows PXRD of the R-Enantiomer / (R)-(-)-2-Amino-1-butanol salt.

Figure 14 shows PXRD of the R-Enantiomer / (S)-(+)-2-Amino-1-butanol salt.

Figure 15 shows PXRD of the R-Enantiomer / (R)-(-)-2-Phenylglycinol salt.

Figure 16 shows PXRD of the R-Enantiomer / (R)-(-)-2-Amino-1-hexanol salt.

Figure 17 shows PXRD of the R-Enantiomer / (R)-(-)-2-Amino-1-pentanol salt.

Figure 18 shows PXRD of the R-Enantiomer / (R)-(-)-2-Amino-1-propanol salt.

Figure 19 shows PXRD of the R-Enantiomer / (R)-(-)-1-Amino-2-propanol salt.

Figure 20 shows PXRD of the Letemovir / (S)-(+)-1-Amino-2-propanol salt.

Figure 21 shows PXRD of the R-Enantiomer / (R)-(-)-Leucinol salt.

Figure 22 shows PXRD of the Letemovir / (S)-(+)-Leucinol salt.

Figure 23a shows PXRD of the R-Enantiomer / Quinine salt.

Figure 23b shows ¹H-NMR spectrum of the R-Enantiomer / Quinine salt.

Figure 23c shows TGA (above) and DSC (below) of the R-Enantiomer / Quinine salt.

Figure 24a shows PXRD of the Letemovir / Quinidine salt.

Figure 24b shows ¹H-NMR spectrum of the Letemovir / Quinidine salt.

Figure 24c shows TGA (above) and DSC (below) of the Letemovir / Quinidine salt.

Figure 25 shows PXRD of amorphous Letemovir obtained in Example 2.10.

Figure 26a shows PXRD of the racemic tosylate salt.

Figure 26b shows TGA (above) and DSC (below) of the racemic tosylate salt.

Figure 26c shows DVS of the racemic tosylate salt.

Figure 27a shows PXRD of the racemic calcium salt.

Figure 27b shows TGA (above) and DSC (below) of the racemic calcium salt.

Figure 27c shows DVS of the racemic calcium salt.

Figure 28a shows PXRD of the racemate diphenylurea co-crystal.

Figure 28b shows TGA (above) and DSC (below) of the racemate diphenylurea co-crystal.

Figure 28c shows DVS of the racemate diphenylurea co-crystal.

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skilled in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skilled in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLES

Methods and equipment

Powder X-Ray Diffraction analysis (PXRD): Approximately 20 mg of sample were prepared in standard sample holders using two foils of polyacetate. The samples were analysed without further manipulation. Powder diffraction patterns were acquired on a D8 Advance Series 2Theta/Theta powder diffraction system using $\text{Cu}_{K\alpha 1}$ -radiation (1.54060 Å) in transmission geometry. The system was equipped with a VÅNTEC-1 single photon counting PSD, a Germanium monochromator, a ninety positions autochanger sample stage, fixed divergence slits and a radial soller. The generator intensity for the generation of the X-ray beam is set to 40 mA and 40 kV. Programs used: Data collection with DIFFRAC plus XRD Commander V.2.5.1, and evaluation with High Score Plus 4.9 (Malvern Panalytical). The samples were measured at room temperature in a 0.5 to 1 hour measurement in a range from 4 to 40° in 2θ using an angular step of 0.049° and a time per step of 2787 s.

Proton nuclear magnetic resonance spectroscopy (¹H-NMR): Proton nuclear magnetic resonance analyses were recorded in deuterated DMSO ($\text{DMSO-}d_6$) in a Bruker Avance 400 Ultrashield NMR spectrometer. Spectra were acquired solving 8 to 10 mg of sample in 0.6 mL of deuterated solvent.

Differential scanning calorimetry analysis (DSC): Approximately 1 to 4 mg of sample were weighed (using a MX5 Mettler Toledo microbalance) into 40 µL aluminium crucibles with a pinhole lid. DSC analyses were recorded in a Mettler Toledo DSC822e

calorimeter. Programs used: Data collection and evaluation with software STARe. The samples were heated under dry nitrogen (flow rate: 50 mL/min) at 10°C/min from 30 to 300°C.

Thermogravimetric analysis (TGA): Approximately 1 to 10 mg of sample were weighed (using a MX5 Mettler Toledo microbalance) into 40 µL aluminium crucibles with a pinhole lid. Thermogravimetric analyses were recorded in a Mettler Toledo TGA/DSC 3+ with a balance XP1 type. Programs used:

Data collection and evaluation with software STARe. The samples were heated under dry nitrogen (flow rate: 10 mL/min) at 10°C/min from 30 to 300°C.

Dynamic Vapour Sorption (DVS): Approximately 10 to 20 mg of sample were weighed into 150 µL platinum crucibles without lid. The experiments were performed in a Mettler Toledo TGA / DSC 1 LF instrument equipped with a LF SDTA FRS2 sensor and coupled with a Modular Humidity Generator MHG 32. Data collection and evaluation was done with STARe software.

UltraPerformance Convergence Chromatography (UPC2): The enantiomeric excess (%ee) was determined by means of chiral Ultra Performance Convergence Chromatography (UPC2) using two methodologies. The method parameters are available in Table 3:

Table 3: UPC methodologies

	Methodology 1	Methodology 2
Column	Trefoil CEL2 Column 2.5 µm, 2.1 mm x 50 mm	Chiral Pak IC-3 Column 3 µm, 4.6 mm x 100 mm
Mobile Phase	CO ₂ - Methanol + 0,3% Formic acid (85:15)	CO ₂ - Methanol + 0,1% Diethylamine (85:15)
Elution Rate	2 mL/min	3 mL/min
Injector Volume	1 µL	2 µL
Detector	DAD (210 to 360) nm / Selected wavelength: 255 nm	DAD (210 to 360) nm / Selected wavelength: 255 nm
Column Temp.	40°C	35°C
Run Time	7 min, R-Enantiomer and Letermovir peaks appear at	9 min, R-Enantiomer and Letermovir peaks appear at

	around 3.30 and 5.10 min, respectively	around 5.46 and 6.78 min, respectively
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Electron diffraction (3D-ED)

Sample preparation: The sample was gently grinded using two glass slides and prepared on a standard copper-graphite grid (Cu200J from JEOL) by lightly contacting the grid with the pulverized sample and removing the excess amount by shaking.

For the room temperature (RT) measurements: The grid with the sample was mounted on a JEOL standard sample holder.

For the low temperature samples: The grid with the sample was cryo-prepared on an ELSA sample holder and using the cryo-preparation stage from GATAN. The measurements were performed at 100 K (LT).

Device: The sample was measured on a XtalLAB Synergy-ED from Rigaku-JEOL provided with a HyPix-ED detector and a LiB6 200 kV electron source (200 kV, 101.20 μ A) using shutterless operation. Wavelength: 0.0251 Å. Total dose: 5.508×10^{-1} e/A², condenser strength 3, Magnification diffraction: 50 cm, IL1 projection focus: hex 51C1 (21185), CL 10 μ m, SA 100 μ m, distance (camera length): 644 mm, scan width: 0.25° and exposure time 0.25 s.

Accessories: ELSA (GATAN) sample holder and sample preparation stage for preparation and measurement of samples at low temperatures.

Software: CrysAlisPro 43.98a (Rigaku), Olex2 Version 1.5-ac6 (Olex2 v1.5-ac6-012 © OlexSys Ltd. 2004 – 2023).

Single Crystal X-Ray Diffraction (SCXRD)

Crystal selection was made using a Zeiss stereomicroscope using polarized light and prepared under inert conditions immersed in perfluoropolyether as protecting oil for manipulation. Crystal structure determination was carried out using a Rigaku diffractometer equipped with a Pilatus 200K area detector, a Rigaku MicroMax-007HF microfocus rotating anode with MoK α radiation, Confocal Max Flux optics and an Oxford Cryosystems low temperature device Cryostream 700 plus ($T = -173^\circ\text{C}$). Full-sphere data collection was used with ω and ϕ scans. *Programs used:* Data collection and reduction with CrysAlisPro (Rigaku OD, 2015). $V/60\text{A}$ and absorption correction with Scale3

Abspack scaling algorithm (CrysAlisPro 1.171.39.12b (Rigaku OD, 2015)). Crystal structure solution was achieved using the computer program SHELXT (Sheldrick, G.M. *Acta Cryst.* **2015** A71, 3-8.) and visualized using the program SHELXL (C.B. Huebschle, G.M. Sheldrick & B. Dittrich; *J.Appl.Cryst.*, **2011** 44, 1281-1284). Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F_0^2 using all measured intensities was carried out using the program SHELXL 2015 (SHELXL; Sheldrick, G.M. *Acta Cryst.*, **2015** A71, 3-8.). All non-hydrogen atoms were refined including anisotropic displacement parameters.

Example 1. Preparation of pure chiral salts of Letemovir and R-Enantiomer with chiral aminoalcohols.

Experimental procedure: A suspension / solution of Letemovir or the R-Enantiomer and the respective chiral agent at 75°C was prepared. The suspensions were stirred for 1 to 2 hours, then cooled down to room temperature and stirred for 15 hours. The obtained solid was filtered off, washed with the respective solvent and dried under vacuum.

Table 4 shows the salts that were prepared with 1,2-aminoalcohol derivatives and the solvents used. In the case of 2-Amino-1-butanol, all the possible stereoisomers (S/S, R/R, S/R and R/S) were successfully prepared and compared. PXRD analyses are available in Figure 1.

Table 4: Preparation of pure chiral salts of 1,2-aminoalcohol derivatives

Aminoalcohol	Prepared pure chiral Salts	Solvents used
(R)-(-)-2-Amino-1-butanol	Letemovir R-Enantiomer	<i>Diisopropylether</i>
(S)-(+)-2-Amino-1-butanol	Letemovir R-Enantiomer	<i>Diisopropylether, Isobutyl Acetate</i>
(R)-(-)-2-Amino-1-pentanol	R-Enantiomer	<i>Pentyl acetate</i>
(S)-(+)-2-Amino-1-pentanol	Letemovir	<i>Pentyl acetate</i>
(R)-(-)-2-Amino-1-propanol	R-Enantiomer	<i>Pentyl acetate</i>
(R)-(-)-1-Amino-2-propanol	R-Enantiomer	<i>Pentyl acetate</i>
(S)-(+)-1-Amino-2-propanol	Letemovir	<i>Pentyl acetate</i>
(R)-(-)-2-Amino-1-hexanol	R-Enantiomer	<i>Pentyl acetate</i>
(S)-(+)-2-Amino-1-hexanol	Letemovir	<i>Pentyl acetate</i>

(1S,2S)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol	Letermovir R-Enantiomer	<i>Isopropanol, Pentyl acetate</i>
L-Phenylalaninol	Letermovir R-Enantiomer	<i>Diisopropylether, Pentyl acetate</i>
(R)-(-)-2-Phenylglycinol	Letermovir R-Enantiomer	<i>Isopropanol, Pentyl acetate</i>
(1S,2S)-2-amino-1-phenylpropane-1,3-diol	Letermovir	<i>Pentyl acetate</i>
(2R)-3-amino-2-methoxypropan-1-ol	R-Enantiomer	<i>Pentyl acetate</i>
(R)-2-Methoxypropan-1-amine	Letermovir	<i>Pentyl acetate</i>
(R)-(Tetrahydrofuran-2-yl)methanamine	Letermovir	<i>Pentyl acetate</i>
(R)-(-)-Leucinol	R-Enantiomer	<i>Pentyl acetate</i>
(S)-(+)-Leucinol	Letermovir	<i>Pentyl acetate</i>
(R)-/[(2S,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinine)	R-Enantiomer	<i>Pentyl acetate</i>
(S)-/[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinidine)	Letermovir	<i>Pentyl acetate</i>

It must be noted that the results that afford R/R and S/R salts are equivalent (but mirrored) to those affording S/S and R/S salts. That means, if a specific chiral agent (*S*) provides Letermovir, the same chiral agent (*R*) will provide the R-Enantiomer. Thus, all the results with *R* chiral agents can be translated to the *S* chiral agents but inverting the chirality of the enantiomer obtained.

Characterization of the obtained salts

Letermovir / (R)-(-)-2-Amino-1-butanol salt

Table 5: Characterization of Letermovir / (R)-(-)-2-Amino-1-butanol salt

Analysis	Results	Figure
Powder X-Ray Diffraction	Crystalline phase, high crystallinity.	2a
Thermal Analyses	DSC: Wide endotherm (onset 58°C). Endotherm (onset 130°C) TGA: Loss of 2.7% mass between 40 and 140°C	2b
Dynamic Vapour Sorption	2.50% weight increase from 10 to 80% RH 0.85% weight increase from 10 to 20% RH 0.86% weight increase from 20 to 30% RH	2c

	0.13% weight increase from 30 to 70% RH 0.51% weight increase from 70 to 80% RH PXRD pattern (end of experiment): Almost identical to the initial solid.	
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Table 6: Peak List for the PXRD analysis of the Letemovir / (R)-(-)-2-Amino-1-butanol salt

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]
5.99	14.76	71.0
9.07	9.75	50.3
10.42	8.49	4.2
10.88	8.13	12.3
12.04	7.35	40.5
12.45	7.11	10.7
15.11	5.86	77.6
15.97	5.55	20.2
16.28	5.44	15.5
17.17	5.16	23.8
17.38	5.10	29.8
18.22	4.87	57.6
18.71	4.74	6.5
19.19	4.63	12.2
19.39	4.58	16.5
20.33	4.37	90.0
20.99	4.23	30.0
21.23	4.18	18.7
21.85	4.07	100.0
22.74	3.91	8.5
22.91	3.88	8.4
24.49	3.63	12.8
25.09	3.55	8.2
25.99	3.43	34.5
26.50	3.36	21.1
26.72	3.34	14.6
27.27	3.27	13.5
27.88	3.20	5.1
28.73	3.11	7.7
29.41	3.04	3.0
30.13	2.97	4.9
30.52	2.93	5.2
31.36	2.85	4.6
32.37	2.77	2.6
34.06	2.63	2.5

34.25	2.62	1.8
34.74	2.58	1.6
35.90	2.50	2.2
36.39	2.47	1.2
37.04	2.43	2.8
37.34	2.41	1.8
37.50	2.40	1.5
38.00	2.37	2.6
38.43	2.34	2.0
39.03	2.31	1.7
39.57	2.28	1.0
40.52	2.23	1.0

Letermovir / L-Phenylalaninol salt Phase 1

Table 7: Characterization of Letermovir / L-Phenylalaninol salt Phase 1

Analysis	Results	Figure
Powder X-Ray Diffraction	Crystalline phase.	3a
Thermal Analyses	TGA: Loss of 2.62% mass between 50 and 130°C DSC: Wide endotherm (onset 77°C). Sharp endotherm (onset 129°C)	3b
Dynamic Vapour Sorption	2.43% weight increase from 10 to 80% RH 1.23% weight increase from 10 to 70% RH 3.13% weight increase from 80 to 90% RH PXRD pattern (end of experiment): Almost identical to the initial solid.	3c

Table 8: Peak List for the PXRD analysis of the Letermovir / L-Phenylalaninol salt Phase 1

Pos.[°2θ]	d-spacing [Å]	Rel. Int. [%]
5.39	16.39	77.82
5.83	15.16	55.95
6.04	14.62	27.31
8.86	9.98	22.66
9.16	9.65	20.72
9.48	9.33	20.85
9.84	8.99	6.81
10.83	8.17	12.79
11.25	7.87	5.76

11.69	7.57	11.53
11.91	7.43	15.63
12.11	7.31	12.02
12.56	7.05	12.95
14.27	6.21	29.61
14.81	5.98	55.49
15.23	5.82	49.73
16.29	5.44	31.18
17.07	5.20	35.6
17.78	4.99	73.72
18.38	4.83	64.47
18.71	4.74	53.92
19.05	4.66	84.82
19.45	4.56	100
19.92	4.46	95.63
20.20	4.40	67.5
20.55	4.32	54.1
21.39	4.15	55.96
21.78	4.08	56.27
22.21	4.00	51.85
22.56	3.94	30.09
23.14	3.84	30.43
23.45	3.79	29.89
24.40	3.65	25.57
24.85	3.58	24.49
25.37	3.51	25.16
25.78	3.46	20.84
26.20	3.40	20.13
26.75	3.33	31.97
27.36	3.26	11.63
27.70	3.22	8.73
28.33	3.15	13.44
28.76	3.10	8.46
29.40	3.04	8.25
30.37	2.94	9.32
30.84	2.90	6.61
31.72	2.82	5.91
32.17	2.78	3.95
33.14	2.70	2.12
33.57	2.67	1.9
34.29	2.62	2.48
35.30	2.54	2.03
37.10	2.42	4.08
37.76	2.38	3.37
38.16	2.36	3.74
39.95	2.26	1.88

Letermovir / L-Phenylalaninol salt Phase 2**Table 9:** Characterization of Letermovir / L-Phenylalaninol salt Phase 2

Analysis	Results	Figure
Powder X-Ray Diffraction	Crystalline phase.	3d

Table 10: Peak List for the PXRD analysis of the Letermovir / L-Phenylalaninol salt Phase 2

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]
5.38	16.44	23.7
5.69	15.54	85.7
6.05	14.61	3.3
9.11	9.71	33.4
9.48	9.33	2.9
9.87	8.96	8.3
10.26	8.62	1.1
10.74	8.24	8.9
11.41	7.75	36.1
12.17	7.27	10.6
12.55	7.05	1.5
14.61	6.06	35.1
15.13	5.86	32.7
15.74	5.63	8.1
16.30	5.44	3.7
16.74	5.30	8.8
17.10	5.18	6.2
17.34	5.11	10.8
17.59	5.04	10.2
17.75	5.00	10.9
18.30	4.85	66.6
18.62	4.76	17.3
19.04	4.66	14.5
19.47	4.56	59.7
19.87	4.47	27.9
20.32	4.37	23.7
20.67	4.30	100.0
21.45	4.14	8.5
21.78	4.08	12.0

22.25	4.00	11.1
22.95	3.88	14.9
23.36	3.81	17.4
24.42	3.65	5.3
24.76	3.60	10.6
25.07	3.55	27.0
25.45	3.50	16.5
26.35	3.38	15.6
26.76	3.33	6.1
27.37	3.26	8.7
27.95	3.19	3.3
28.28	3.16	3.2
28.88	3.09	6.7
29.49	3.03	7.3
29.75	3.00	6.3
29.95	2.98	5.2
30.87	2.90	4.0
31.74	2.82	1.0
32.20	2.78	3.1
33.01	2.71	1.5
33.37	2.69	1.5
33.96	2.64	2.3
34.59	2.59	1.7
38.38	2.35	1.1

Letermovir / (1S,2S)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol salt

Table 11: Characterization of Letermovir / (1S,2S)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol salt

Analysis	Results	Figure
Powder X-Ray Diffraction	Crystalline phase.	4a
Thermal Analyses	DSC Three consecutive endotherms (onset 96°C). Wide endotherm (onset 187°C) TGA Loss of 2.7% mass between 40 and 120°C	4b
Dynamic Vapour Sorption	18.96% weight increase from 10 to 80% RH 4.44% weight increase from 10 to 40% RH 7.07% weight increase from 40 to 70% RH 7.08% weight increase from 70 to 80% RH 24.02% weight increase from 80 to 90% RH PXRD pattern (end of experiment): Almost identical to the initial solid.	4c

Table 12: Peak List for the PXRD analysis of the Letemovir / (1S,2S)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol salt

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]
5.80	15.24	100
8.94	9.89	30.76
9.38	9.43	18.16
10.02	8.83	10.06
10.59	8.35	18.05
10.76	8.22	17.59
11.48	7.71	24.93
11.72	7.55	37.32
12.38	7.15	0.95
12.74	6.95	10.9
13.08	6.77	13.24
14.35	6.17	40.38
14.82	5.98	17.72
15.18	5.84	7.83
15.53	5.71	22.73
16.18	5.48	5.79
16.66	5.32	2.13
16.96	5.23	6.5
17.46	5.08	32.6
17.95	4.94	20.06
18.54	4.79	14.29
18.84	4.71	30.13
19.21	4.62	45.38
19.78	4.49	52.88
20.16	4.40	18.37
20.43	4.35	32.41
20.84	4.26	64.84
21.20	4.19	75.22
21.83	4.07	19.27
22.18	4.01	12.51
22.44	3.96	3.72
22.65	3.93	2.68
23.17	3.84	12.42
23.46	3.79	19.83
23.67	3.76	13.7
24.24	3.67	7.71
24.54	3.63	11.63

24.88	3.58	10.5
25.34	3.51	28.15
25.77	3.46	22.23
26.53	3.36	8.77
26.88	3.32	20.95
27.46	3.25	6.75
27.78	3.21	3.23
28.00	3.19	4.83
28.53	3.13	10.25
28.93	3.09	9.65
29.38	3.04	4.66
29.80	3.00	2.44
30.33	2.95	7.68
30.71	2.91	1.36
31.36	2.85	5.6
32.03	2.79	3.02
32.38	2.76	5.07
32.96	2.72	5.58
33.77	2.65	1.3
34.22	2.62	1.11
34.49	2.60	2.56
34.76	2.58	0.09
35.50	2.53	2.86
35.78	2.51	1.93
36.11	2.49	0.81
36.31	2.47	1.35
36.61	2.45	3.07
36.80	2.44	2.28
37.35	2.41	0.81
37.78	2.38	0.68
38.16	2.36	3.17
38.44	2.34	2.2
38.76	2.32	3.22
39.08	2.31	2.28
39.76	2.27	1.63

Letermovir / (R)-(-)-2-Phenylglycinol

Table 13: Characterization of the Letermovir / (R)-(-)-2-Phenylglycinol salt

Analysis	Results	Figure
Powder X-Ray Diffraction	Crystalline phase.	5a
Thermal Analyses	DSC: Wide endotherm (onset 77°C). Sharp endotherm (onset 129°C) TGA: Loss of 2.62% mass between 50 and 130°C	5b
Dynamic Vapour Sorption	1.52% weight increase from 10 to 80% RH 1.30% weight increase from 80 to 90% RH PXRD pattern (end of experiment): Almost identical to the initial solid.	5c

Table 14: Peak List for the PXRD analysis of the Letermovir / (R)-(-)-2-Phenylglycinol salt

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]
5.62	15.73	98.92
5.86	15.09	100
8.44	10.47	9.07
9.04	9.79	13.39
9.26	9.55	15.27
9.90	8.93	4.34
10.62	8.33	3.75
11.29	7.84	13.57
11.78	7.51	24.67
12.15	7.29	0.53
12.61	7.02	2.54
14.05	6.31	17.8
14.47	6.12	32.23
15.04	5.89	18.03
15.37	5.77	27.57
15.82	5.60	10.79
16.29	5.44	15
16.85	5.26	26.9
17.52	5.06	22.19
18.16	4.89	36.26
18.58	4.77	38.83
19.15	4.63	29.19
19.43	4.57	35.16
19.92	4.46	28.33
20.50	4.33	55.96
21.09	4.21	44.37
21.58	4.12	35

22.19	4.01	9.21
22.71	3.92	13.56
23.77	3.74	18.47
24.41	3.65	11.9
25.01	3.56	11.48
25.33	3.52	14.2
25.68	3.47	14.66
26.17	3.41	13.86
26.99	3.30	9.11
27.41	3.25	5.07
28.29	3.15	7.11
29.18	3.06	3.74
29.73	3.01	2.11
30.42	2.94	3.98
31.16	2.87	2.82
31.85	2.81	1.51
33.48	2.68	1.09
34.20	2.62	0.97
35.06	2.56	0.52
35.64	2.52	1.27
35.95	2.50	1.79
37.97	2.37	1.46
39.18	2.30	1.25

Letermovir / (*S*)-(+)-2-Amino-1-butanol salt

Table 15: Characterization of the Letermovir / (*S*)-2-Amino-1-butanol salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	6a
¹ H – NMR	1:1 ratio Letermovir – Chiral Agent	6b
Thermal Analyses	TGA Loss of 1.0% mass between 45 to 90°C Loss of 9.3% mass between 115 to 225°C Decomposition at ca. 270°C DSC Wide endotherm (onset at 32°C) Sharp endotherm (onset at 160°C).	6c
SCXRD	The compound crystallizes in the rhombohedral space group R3. The asymmetric unit contains one molecule of Letermovir in its anionic form, one molecule of the <i>S</i> -(+)-2-Amino-1-butanol in its cationic form and 0.4 molecules of water. In the main molecule the CF ₃ -group is disordered in four orientations. The crystals	6d

	of Letermovir / <i>S</i> -(+)-2-Amino-1-butanol salt are formed in a 40 % ratio by a hydrate and a 60 % ratio by a non-hydrated form. Both forms are overlapped showing in the structure as a disordered model. The structure is of excellent quality with a R1 value of 4.3 %.	
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Table 16: Peak List for the PXRD analysis of the Letermovir / (*S*)-2-Amino-1-butanol salt

Pos.[°2θ]	d-spacing [Å]	Rel. Int. [%]			
6.13	14.42	47.8	30.13	2.97	3.4
8.92	9.92	35.7	30.56	2.93	2.4
10.63	8.32	6.3	30.77	2.91	2.6
10.84	8.16	13.3	31.12	2.87	6.9
12.31	7.19	44.3	31.84	2.81	1.5
15.23	5.82	68.0	32.44	2.76	1.3
16.44	5.39	19.2	32.66	2.74	3.6
16.81	5.27	22.5	33.01	2.71	4.1
17.57	5.05	28.3	33.57	2.67	1.0
17.92	4.95	53.3	33.87	2.65	0.9
18.52	4.79	4.3	34.79	2.58	2.4
18.96	4.68	7.0	35.04	2.56	1.2
19.65	4.52	8.0	35.37	2.54	2.8
20.60	4.31	69.2	35.77	2.51	1.9
20.90	4.25	19.4	36.17	2.48	1.4
21.43	4.15	23.2	36.55	2.46	2.9
21.81	4.08	5.9	37.01	2.43	3.2
22.32	3.98	100.0	37.63	2.39	1.4
22.68	3.92	14.6	38.11	2.36	3.0
23.26	3.82	5.7	38.45	2.34	2.2
24.34	3.66	1.4	38.72	2.33	1.9
24.84	3.58	6.1	39.20	2.30	3.2
25.13	3.54	5.6	39.93	2.26	0.6
25.54	3.49	5.2	40.19	2.24	0.6
25.90	3.44	13.8			
26.41	3.38	22.4			
27.07	3.29	22.4			
27.38	3.26	18.0			
27.75	3.22	1.1			
28.48	3.13	6.4			
28.78	3.10	6.7			
29.24	3.05	5.8			
29.82	3.00	9.7			

Table 17: Crystal data and structure refinement for the Letermovir / S-(+)-2-Amino-1-butanol salt

Identification code	mo_P11901SMBPAT20_0m
Empirical formula	C ₃₃ H _{39.8} F _{4.03} N ₅ O _{5.4}
Formula weight	669.40
Temperature/K	99.97
Crystal system	trigonal
Space group	R3
a/Å	28.339(3)
b/Å	28.339(3)
c/Å	10.758(3)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	120
Volume/Å ³	7482(2)
Z	9
$\rho_{\text{calc}}/\text{cm}^3$	1.337
μ/mm^{-1}	0.106
F(000)	3170.0
Crystal size/mm ³	0.6 × 0.3 × 0.3
Radiation	MoK α ($\lambda = 0.71073$)
2 θ range for data collection/ $^\circ$	2.874 to 63.064
Index ranges	-41 ≤ h ≤ 35, -41 ≤ k ≤ 36, -15 ≤ l ≤ 13
Reflections collected	27091
Independent reflections	9711 [$R_{\text{int}} = 0.0645$, $R_{\text{sigma}} = 0.0631$]
Data/restraints/parameters	9711/179/575
Goodness-of-fit on F ²	1.018
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0432$, $wR_2 = 0.1116$
Final R indexes [all data]	$R_1 = 0.0474$, $wR_2 = 0.1143$
Largest diff. peak/hole / e Å ⁻³	0.35/-0.31
Flack parameter	-0.1(4)

Letermovir / (S)-(+)-2-Amino-1-hexanol salt

Table 18: Characterization of the Letermovir / (S)-2-Amino-1-hexanol salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	7a
¹ H – NMR	1:1 ratio Letermovir – Chiral Agent	7b

Thermal Analyses	TGA Loss of 1.0% mass between 45 to 95°C Loss of 9.3% mass between 115 to 220°C Decomposition at ca. 270°C DSC Wide endotherm (onset at 32°C) Sharp endotherm (onset at 160°C).	7c
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Table 19: Peak List for the PXRD analysis of the Letemovir / (*S*)-2-Amino-1-hexanol salt

Pos.[°2θ]	d-spacing [Å]	Rel. Int. [%]			
6.18	14.30	42.5	36.15	2.49	2.8
9.87	8.97	56.3	36.56	2.46	3.6
10.75	8.23	11.5	36.94	2.43	2.1
12.43	7.12	17.2	37.31	2.41	2.5
13.23	6.69	27.5	38.23	2.35	2.4
14.63	6.05	20.5	38.57	2.33	4.1
16.60	5.34	50.7	38.79	2.32	5.1
18.21	4.87	48.5	39.34	2.29	1.2
18.83	4.71	100.0			
19.84	4.47	21.4			
20.26	4.38	39.3			
21.65	4.11	1.8			
22.56	3.94	79.9			
23.01	3.87	8.7			
23.85	3.73	32.9			
24.35	3.66	3.8			
25.06	3.55	2.1			
25.64	3.47	13.9			
26.39	3.38	11.6			
26.70	3.34	9.4			
27.38	3.26	17.8			
28.48	3.13	9.7			
29.85	2.99	10.9			
31.50	2.84	3.9			
31.96	2.80	0.6			
32.46	2.76	2.2			
33.03	2.71	4.6			
33.35	2.69	1.4			
33.64	2.66	3.8			
34.31	2.61	3.8			
35.14	2.55	0.8			
35.43	2.53	1.9			

Letermovir / (S)-(+)-2-Amino-1-pentanol salt

Table 20: Characterization of the Letermovir / (S)-2-Amino-1-pentanol salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	8a

Table 21: Peak List for the PXRD analysis of the Letermovir / (S)-2-Amino-1-pentanol salt

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]			
6.30	14.04	41.3	33.40	2.68	5.0
9.87	8.96	62.0	33.97	2.64	0.9
10.95	8.08	10.5	34.57	2.59	1.4
12.65	7.00	16.5	34.87	2.57	3.2
13.34	6.64	31.3	35.26	2.55	2.0
14.78	5.99	24.9	35.80	2.51	0.4
16.50	5.37	49.9	36.43	2.47	5.9
16.81	5.27	10.2	37.52	2.40	3.0
18.44	4.81	42.9	38.18	2.36	2.7
18.81	4.72	100.0	38.74	2.32	5.8
19.86	4.47	19.9	39.26	2.29	5.5
20.54	4.32	42.4			
22.04	4.03	1.5			
22.97	3.87	61.3			
23.35	3.81	6.8			
23.82	3.74	8.8			
24.21	3.68	28.6			
25.50	3.49	17.2			
26.30	3.39	13.5			
26.65	3.35	9.0			
26.93	3.31	7.6			
27.85	3.20	10.8			
28.57	3.12	10.1			
28.91	3.09	7.3			
29.31	3.05	3.4			
29.98	2.98	4.0			
30.33	2.95	11.1			
31.43	2.85	0.5			
32.03	2.79	3.3			
32.74	2.74	6.5			

Letermovir / (1*S*,2*S*)-2-amino-1-phenyl-propane-1,3-diol salt

Table 22: Characterization of the Letermovir / (1*S*,2*S*)-2-amino-1-phenyl-propane-1,3-diol salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	9a

Table 23: Peak List for the PXRD analysis of the Letermovir / (1*S*,2*S*)-2-amino-1-phenyl-propane-1,3-diol salt

Pos.[°2θ]	d-spacing [Å]	Rel. Int. [%]
5.65	15.63	100.0
5.84	15.13	78.2
8.61	10.27	9.1
9.27	9.54	13.8
9.89	8.95	2.7
10.67	8.29	1.7
11.33	7.81	12.6
11.71	7.55	17.1
12.61	7.02	2.2
14.27	6.21	21.4
14.49	6.11	23.1
15.07	5.88	20.0
15.33	5.78	23.8
15.68	5.65	12.3
16.30	5.44	11.1
17.09	5.19	19.8
17.35	5.11	23.4
18.33	4.84	31.0
18.63	4.76	36.6
19.36	4.58	41.3
19.98	4.44	24.0
20.56	4.32	48.6
21.09	4.21	38.6
21.43	4.15	29.7
22.85	3.89	10.0
23.70	3.75	14.0
24.22	3.68	12.7
25.43	3.50	13.7
26.28	3.39	13.4
28.41	3.14	5.3
30.65	2.92	3.0
32.07	2.79	1.0

34.00	2.64	0.9
36.12	2.49	0.6
37.78	2.38	1.2
39.12	2.30	0.8

R-Enantiomer / (2R)-3-amino-2-methoxy-propan-1-ol salt

Table 24: Characterization of the R-Enantiomer / (2R)-3-amino-2-methoxy-propan-1-ol salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	10a
¹ H – NMR	1:1 ratio Letemovir – Chiral Agent	10b
Thermal Analyses	TGA Loss of 2.5% mass between 45 to 146°C Loss of 7.5% mass between 146 to 225°C Decomposition at ca. 270°C DSC Broad endotherm (onset at 120°C)	10c
SCXRD	This compound crystallizes in the rhombohedral space group R3. The asymmetric unit contains one molecule of Letemovir in its anionic form, one molecule of the (2R)-3-amino-2-methoxy-propan-1-ol in its cationic form and one molecule of water. In the main molecule the CF ₃ -group is disordered in three orientations and the carboxylate and one of the ether groups are disordered in two orientations. The (2R)-3-amino-2-methoxy-propan-1-ol cation and the water molecule are disordered in two orientations. The structure is of good quality with a R1 value of 5.7 %	10d

Table 25: Crystal data and structure refinement for the R-Enantiomer / (2R)-3-amino-2-methoxy-propan-1-ol salt

Identification code	mo_P11901RMPPAT12_0m
Empirical formula	C ₃₃ H ₄₁ F ₄ N ₅ O ₇
Formula weight	695.71
Temperature/K	100.00
Crystal system	trigonal
Space group	R3
a/Å	29.0050(12)
b/Å	29.0050(12)

c/Å	10.2875(8)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	120
Volume/Å ³	7495.2(9)
Z	9
$\rho_{\text{calc}}/\text{g/cm}^3$	1.387
μ/mm^{-1}	0.112
F(000)	3294.0
Crystal size/mm ³	0.5 × 0.3 × 0.2
Radiation	MoK α ($\lambda = 0.71073$)
2 θ range for data collection/ $^\circ$	2.808 to 55.142
Index ranges	-37 ≤ h ≤ 31, -34 ≤ k ≤ 37, -13 ≤ l ≤ 13
Reflections collected	31148
Independent reflections	7420 [$R_{\text{int}} = 0.0952$, $R_{\text{sigma}} = 0.0695$]
Data/restraints/parameters	7420/245/629
Goodness-of-fit on F^2	1.036
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0566$, $wR_2 = 0.1483$
Final R indexes [all data]	$R_1 = 0.0684$, $wR_2 = 0.1572$
Largest diff. peak/hole / e Å ⁻³	0.35/-0.37
Flack parameter	-0.6(5)

Table 26: Peak List for the PXRD analysis of the R-Enantiomer / (2*R*)-3-amino-2-methoxy-propan-1-ol salt

Pos.[2θ]	d-spacing [Å]	Rel. Int. [%]
6.00	14.74	42.1
9.22	9.59	39.5
10.42	8.49	9.5
11.02	8.03	4.1
12.04	7.35	35.3
12.57	7.04	13.6
15.21	5.83	65.9
15.96	5.55	12.2
16.37	5.42	7.1
17.47	5.08	39.8
18.12	4.90	5.3
18.55	4.78	100.0
19.49	4.55	19.0
20.38	4.36	89.0
20.96	4.24	16.3
21.30	4.17	30.6

21.83	4.07	90.6
22.19	4.01	2.2
22.99	3.87	8.3
24.25	3.67	4.3
24.53	3.63	10.4
25.32	3.52	9.5
26.02	3.42	52.7
26.46	3.37	20.4
26.65	3.35	21.8
27.46	3.25	17.2
27.99	3.19	7.5
28.78	3.10	9.6
29.41	3.04	1.6
30.07	2.97	5.5
30.57	2.92	10.9
31.29	2.86	3.8
31.82	2.81	4.8
32.27	2.77	1.2
32.52	2.75	2.8
33.12	2.71	0.4
33.55	2.67	2.6
34.02	2.64	3.7
34.77	2.58	2.5
34.96	2.57	3.9
35.35	2.54	1.7
35.86	2.50	4.6
36.41	2.47	0.7
36.73	2.45	1.4
37.10	2.42	3.8
37.37	2.41	4.3
38.13	2.36	4.2
38.41	2.34	5.6
39.05	2.31	0.4
39.65	2.27	3.8
40.14	2.25	2.8
40.47	2.23	0.9

Letermovir / (R)-2-Methoxypropan-1-amine salt**Table 27:** Characterization of the Letermovir / (R)-2-Methoxypropan-1-amine salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	11a
¹ H – NMR	1:1 ratio Letermovir – Chiral Agent	11b
Thermal Analyses	TGA Loss of 2.8% mass between 75 to 135°C Loss of 8.2% mass between 135 to 225°C DSC Broad endotherm (onset at 89°C) Decomposition at ca. 270°C	11c
SCXRD	This compound crystallizes in the chiral trigonal space group P3 ₂ . The asymmetric unit contains three independent molecules of Letermovir in its anionic form, three independent molecules of the (R)-2-Methoxypropan-1-amine in its cationic form and three molecules of water. In the main molecule the CF ₃ -groups are disordered in different orientations and in one case the ether group is disordered in two orientations. Two of the (R)-2-Methoxypropan-1-amine cations are also disordered in two orientations. The structure is of good quality with a R1 value of 6.4 %.	11d

Table 28: Peak List for the PXRD analysis of the Letermovir / (R)-2-Methoxypropan-1-amine salt

Pos.[°2θ]	d-spacing [Å]	Rel. Int. [%]
5.97	14.81	26.06
9.33	9.47	30.79
10.37	8.53	10.48
11.10	7.97	3.24
11.98	7.39	29.18
12.62	7.02	13.25
15.22	5.82	54.54
15.88	5.58	18
16.37	5.42	4.51
17.45	5.08	37.28
17.76	4.99	8.55
18.03	4.92	3.27

18.76	4.73	59.6
19.42	4.57	8.01
19.71	4.51	8.59
20.35	4.37	82.84
20.85	4.26	9.9
21.22	4.19	10.58
21.71	4.09	100
22.32	3.98	2.3
22.89	3.89	5.65
23.14	3.84	4.88
24.12	3.69	3.52
24.45	3.64	10.68
25.42	3.50	6.36
25.92	3.44	35.89
26.33	3.38	15.72
26.63	3.35	8.21
26.96	3.31	12.67
27.53	3.24	16.09
28.30	3.15	2.46
28.64	3.12	4.65
28.90	3.09	2.34
29.30	3.05	1.98
29.93	2.99	2.15
30.29	2.95	5.14
30.84	2.90	7
31.18	2.87	1.12
31.76	2.82	1.15
32.05	2.79	3.25
32.53	2.75	2.32
33.12	2.70	0.14
33.82	2.65	6.05
34.33	2.61	0.73
34.63	2.59	1.41
35.44	2.53	2.87
35.71	2.51	1.86
35.97	2.50	1.88
36.53	2.46	1.61
36.78	2.44	1.25
37.06	2.43	1.05
37.55	2.40	5.84
38.06	2.36	2.76
38.55	2.34	5.72
38.97	2.31	0.55
39.54	2.28	0.6
40.04	2.25	3.39

Table 29: Crystal data and structure refinement for the Letermovir / (*R*)-2-Methoxypropan-1-amine

Identification code	mo_P11905RMAPAT_0m
Empirical formula	C ₉₉ H ₁₂₅ F ₁₂ N ₁₅ O ₁₈
Formula weight	2041.13
Temperature/K	99.90
Crystal system	trigonal
Space group	P3 ₂
a/Å	29.0840(13)
b/Å	29.0840(13)
c/Å	10.1157(8)
α/°	90
β/°	90
γ/°	120
Volume/Å ³	7410.3(9)
Z	3
ρ _{calc} /g/cm ³	1.372
μ/mm ⁻¹	0.110
F(000)	3228.0
Crystal size/mm ³	0.3 × 0.1 × 0.1
Radiation	MoKα (λ = 0.71073)
2θ range for data collection/°	1.616 to 50.792
Index ranges	-35 ≤ h ≤ 23, -32 ≤ k ≤ 27, -12 ≤ l ≤ 12
Reflections collected	41121
Independent reflections	17513 [R _{int} = 0.0842, R _{sigma} = 0.1214]
Data/restraints/parameters	17513/251/1504
Goodness-of-fit on F ²	1.028
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0636, wR ₂ = 0.1522
Final R indexes [all data]	R ₁ = 0.0884, wR ₂ = 0.1708
Largest diff. peak/hole / e Å ⁻³	0.50/-0.38
Flack parameter	-0.3(6)

Letermovir / (*R*)-(Tetrahydrofuran-2-yl)methanamine salt

Table 30: Characterization of the Letermovir / (*R*)-(Tetrahydrofuran-2-yl)methanamine salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	12a
Thermal Analyses	TGA Loss of 2.6% mass between 85 to 120°C Loss of 9.9% mass between 120 to 224°C	12b

	Decomposition at ca. 265°C (onset). DSC Broad endotherm (onset at 92°C)	
SCXRD	This compound crystallizes in the chiral trigonal space group $P3_2$. The asymmetric unit contains three independent molecules of Letermovir in its anionic form, three independent molecules of the (<i>R</i>)-(Tetrahydrofuran-2-yl)methanamine in its cationic form and three molecules of water. In the main molecule the CF ₃ -groups are disordered in three orientations. The structure is of good quality with a R1 value of 6.4 %.	12c

Table 31: Peak List for the PXRD analysis of the Letermovir / (*R*)-(Tetrahydrofuran-2-yl)methanamine salt

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]
5.99	14.76	22.8
9.32	9.49	31.0
10.40	8.51	11.6
11.09	7.98	2.8
12.02	7.36	26.0
12.62	7.01	15.7
15.24	5.81	47.2
15.93	5.56	15.2
16.37	5.41	2.6
17.47	5.08	31.1
17.73	5.00	14.1
18.08	4.91	5.3
18.73	4.74	100.0
19.44	4.57	5.4
19.68	4.51	12.9
20.39	4.36	74.5
20.91	4.25	8.3
21.26	4.18	8.9
21.46	4.14	15.2
21.78	4.08	99.1
22.92	3.88	6.5
23.14	3.84	8.9
24.20	3.68	4.4
24.51	3.63	9.4
25.42	3.50	7.4
25.98	3.43	24.7
26.41	3.38	17.4
26.67	3.34	9.3

26.91	3.31	21.8
27.55	3.24	14.7
28.26	3.16	6.4
28.73	3.11	6.6
28.91	3.09	5.8
29.37	3.04	3.3
30.01	2.98	2.6
30.38	2.94	4.4
30.81	2.90	11.3
31.24	2.86	1.5
32.03	2.79	3.7
32.56	2.75	2.4
33.93	2.64	4.6
34.72	2.58	1.6
35.37	2.54	5.4
35.86	2.50	2.1
36.44	2.47	1.2
36.90	2.44	1.1
37.19	2.42	1.4
37.52	2.40	4.8
37.92	2.37	2.9
38.55	2.34	5.7
40.00	2.25	3.2
40.46	2.23	2.0

Table 32: Crystal data and structure refinement for the Letemovir / (R)-(Tetrahydrofuran-2-yl)methanamine salt

Identification code	mo_P11905TFFPAT_b_0m
Empirical formula	C ₁₀₂ H ₁₂₃ F ₁₂ N ₁₅ O ₁₈
Formula weight	2075.15
Temperature/K	100.21
Crystal system	trigonal
Space group	P3 ₂
a/Å	29.057(3)
b/Å	29.057(3)
c/Å	10.1236(17)
α /°	90
β /°	90
γ /°	120
Volume/Å ³	7402.3(18)
Z	3
$\rho_{\text{calc}}/\text{cm}^3$	1.397
μ/mm^{-1}	0.111

F(000)	3276.0
Crystal size/mm ³	0.3 × 0.1 × 0.1
Radiation	MoK α (λ = 0.71073)
2 θ range for data collection/°	1.618 to 55.072
Index ranges	-35 ≤ h ≤ 37, -29 ≤ k ≤ 37, -13 ≤ l ≤ 12
Reflections collected	44214
Independent reflections	21453 [R_{int} = 0.0819, R_{sigma} = 0.1241]
Data/restraints/parameters	21453/493/1504
Goodness-of-fit on F^2	0.981
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0640, wR_2 = 0.1551
Final R indexes [all data]	R_1 = 0.0933, wR_2 = 0.1745
Largest diff. peak/hole / e Å ⁻³	0.56/-0.34
Flack parameter	0.2(5)

R-Enantiomer / (R)-(-)-2-Amino-1-butanol salt

Table 33: Characterization of the R-Enantiomer / (R)-(-)-2-Amino-1-butanol salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	13

Table 34: Peak List for the PXRD analysis of the R-Enantiomer / (R)-(-)-2-Amino-1-butanol salt

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]
6.14	14.38	46.7
8.92	9.91	33.7
10.85	8.15	13.2
12.32	7.18	42.8
12.52	7.07	12.7
15.25	5.81	66.5
16.35	5.42	20.6
16.81	5.27	21.1
17.59	5.04	28.1
17.92	4.95	53.1
18.55	4.78	4.9
18.97	4.68	7.2
19.66	4.52	7.1
20.62	4.31	67.8
20.92	4.25	19.5
21.46	4.14	22.1
21.82	4.07	5.8
22.34	3.98	100.0

22.70	3.92	13.9
23.28	3.82	6.1
24.35	3.66	1.5
24.75	3.60	5.0
24.90	3.58	5.5
25.15	3.54	5.7
25.54	3.49	5.0
25.91	3.44	13.5
26.43	3.37	22.1
27.09	3.29	21.7
27.40	3.26	18.0
27.76	3.21	1.2
28.51	3.13	6.5
28.80	3.10	6.4
29.27	3.05	5.8
29.82	3.00	9.2
30.16	2.96	3.5
30.59	2.92	2.5
30.80	2.90	2.5
31.14	2.87	6.4
31.88	2.81	1.6
32.48	2.76	1.4
32.69	2.74	3.5
33.03	2.71	3.8
33.90	2.64	1.1
34.83	2.58	2.5
35.07	2.56	1.2
35.39	2.54	2.8
35.72	2.51	2.1
36.21	2.48	1.4
36.58	2.46	3.0
36.87	2.44	3.1
37.05	2.43	2.9
37.67	2.39	1.5
38.13	2.36	3.0
38.48	2.34	2.6
38.76	2.32	1.9
39.24	2.29	3.5

R-Enantiomer / (S)-(+)-2-Amino-1-butanol salt

Table 35: Characterization of the R-Enantiomer / (S)-(+)-2-Amino-1-butanol salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	14

Table 36: Peak List for the PXRD analysis of the R-Enantiomer / (S)-(+)-2-Amino-1-butanol salt

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]
5.98	14.79	98.5
8.81	10.03	41.6
9.11	9.71	100.0
9.45	9.36	11.7
10.41	8.49	7.2
10.93	8.10	14.7
12.03	7.36	41.9
12.48	7.10	14.8
12.88	6.87	2.1
13.47	6.57	1.4
15.13	5.86	86.0
15.94	5.56	18.9
16.30	5.44	18.6
17.30	5.13	60.2
17.75	5.00	26.4
18.31	4.85	91.4
18.85	4.70	18.5
19.33	4.59	26.6
20.32	4.37	85.8
20.94	4.24	29.6
21.19	4.19	38.6
21.82	4.07	92.3
22.29	3.99	19.1
22.88	3.89	12.1
23.42	3.80	7.2
24.48	3.64	17.4
25.14	3.54	12.7
25.51	3.49	13.0
25.92	3.44	35.7
26.19	3.40	21.4
26.68	3.34	23.9
27.26	3.27	15.1
27.64	3.23	11.5
27.89	3.20	8.5
28.73	3.11	10.6
29.32	3.05	4.7
29.94	2.98	6.7
30.30	2.95	7.0
30.53	2.93	4.7
31.55	2.84	3.9
32.34	2.77	1.3
33.51	2.67	1.2
34.00	2.64	1.5
34.43	2.60	2.9
34.78	2.58	2.9

35.19	2.55	1.4
35.87	2.50	3.3
36.56	2.46	3.0
37.78	2.38	3.9
39.15	2.30	2.8

R-Enantiomer / (R)-(-)-2-Phenylglycinol salt

Table 37: Characterization of the R-Enantiomer / (R)-(-)-2-Phenylglycinol salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	15

Table 38: Peak List for the PXRD analysis of the R-Enantiomer / (R)-(-)-2-Phenylglycinol salt

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]
5.83	15.16	72.5
6.75	13.10	1.1
9.20	9.62	36.6
10.13	8.74	4.2
10.38	8.52	1.8
10.91	8.11	10.3
11.71	7.56	28.8
12.39	7.15	17.8
14.52	6.10	4.4
14.92	5.94	49.7
15.52	5.71	16.4
16.04	5.53	12.6
17.09	5.19	18.1
17.52	5.06	14.5
17.75	5.00	6.0
18.16	4.88	24.8
18.48	4.80	52.0
19.01	4.67	13.1
19.40	4.58	13.6
19.92	4.46	74.7
20.37	4.36	11.3
20.77	4.28	21.7
21.21	4.19	100.0
21.95	4.05	3.5
22.40	3.97	10.9
22.73	3.91	8.8
23.25	3.83	6.7
23.57	3.77	7.9
23.92	3.72	14.6
24.56	3.63	3.5

24.95	3.57	7.3
25.35	3.51	18.1
25.71	3.47	25.8
26.05	3.42	13.7
26.59	3.35	5.7
27.03	3.30	13.0
27.46	3.25	11.5
28.01	3.19	4.9
28.72	3.11	4.5
29.28	3.05	4.4
29.58	3.02	4.0
29.96	2.98	4.0
30.42	2.94	3.9
31.11	2.87	2.3
31.69	2.82	2.8
32.25	2.78	1.8
33.04	2.71	5.2
33.82	2.65	1.1
34.92	2.57	2.4
35.49	2.53	1.7
35.98	2.50	3.0
36.94	2.43	1.3
37.20	2.42	2.4
37.49	2.40	1.1
38.00	2.37	3.1
39.38	2.29	1.5
39.96	2.26	1.0

R-Enantiomer / (R)-(-)-2-Amino-1-hexanol salt

Table 39: Characterization of the R-Enantiomer / (R)-(-)-2-Amino-1-hexanol salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	16

Table 40: Peak List for the PXRD analysis of the R-Enantiomer / (R)-(-)-2-Amino-1-hexanol salt

Pos.[°2θ]	d-spacing [Å]	Rel. Int. [%]
6.20	14.26	41.7
9.87	8.96	57.3
10.76	8.22	11.7
12.44	7.12	18.2

13.24	6.69	28.7
14.64	6.05	22.1
16.61	5.34	49.6
18.21	4.87	52.8
18.83	4.71	100.0
19.84	4.47	22.6
20.26	4.38	43.1
21.64	4.11	2.5
22.55	3.94	81.1
23.00	3.87	9.6
23.85	3.73	34.3
24.33	3.66	4.3
25.04	3.56	2.4
25.63	3.48	13.8
26.23	3.40	8.2
26.41	3.38	11.9
26.68	3.34	9.6
27.37	3.26	17.5
28.44	3.14	9.6
29.82	3.00	10.6
31.49	2.84	3.7
32.44	2.76	2.0
33.00	2.71	4.5
33.36	2.69	1.4
33.61	2.67	3.9
34.27	2.62	4.3
35.40	2.54	1.9
36.15	2.49	2.9
36.55	2.46	3.6
36.93	2.43	2.2
37.28	2.41	2.5
38.21	2.36	2.4
38.76	2.32	5.2
39.35	2.29	1.2
39.66	2.27	4.0
40.35	2.24	5.1

R-Enantiomer / (R)-(-)-2-Amino-1-pentanol salt

Table 41: Characterization of the R-Enantiomer / (R)-(-)-2-Amino-1-pentanol salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	17

Table 42: Peak List for the PXRD analysis of the R-Enantiomer / (R)-(-)-2-Amino-1-pentanol salt

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]
6.32	14.00	42.8
9.88	8.95	64.1
10.96	8.07	11.1
12.67	6.99	18.9
13.36	6.63	32.9
14.79	5.99	28.2
16.50	5.37	46.0
16.80	5.28	11.5
17.92	4.95	1.0
18.46	4.81	47.2
18.81	4.72	100.0
19.07	4.65	11.2
19.86	4.47	20.3
20.55	4.32	46.3
22.05	4.03	1.7
22.74	3.91	24.5
22.97	3.87	67.1
23.36	3.81	7.1
23.81	3.74	7.8
24.23	3.67	29.4
24.50	3.63	3.8
25.49	3.49	15.2
26.29	3.39	12.3
26.66	3.34	8.8
26.92	3.31	7.3
27.67	3.22	8.5
27.87	3.20	10.1
28.57	3.12	9.4
28.92	3.09	7.4
29.32	3.05	3.4
30.00	2.98	3.9
30.33	2.95	11.6
31.89	2.81	1.7
32.07	2.79	2.8
32.73	2.74	6.0
33.00	2.71	1.3
33.39	2.68	4.4
34.26	2.62	0.1
34.58	2.59	1.5
34.88	2.57	3.5
35.23	2.55	1.8
36.42	2.47	6.0
37.54	2.40	3.1
38.16	2.36	2.7
38.72	2.33	5.6

39.26	2.29	5.3
40.36	2.23	6.3

R-Enantiomer / (R)-(-)-2-Amino-1-propanol salt

Table 43: Characterization of the R-Enantiomer / (R)-(-)-2-Amino-1-propanol salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	18

Table 44: Peak List for the PXRD analysis of the R-Enantiomer / (R)-(-)-2-Amino-1-propanol salt

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]
6.11	14.46	46.1
9.33	9.48	66.2
10.60	8.34	4.0
11.17	7.92	24.1
11.68	7.58	1.1
12.27	7.21	52.6
12.75	6.94	15.9
15.45	5.74	80.6
16.26	5.45	21.3
16.64	5.33	37.4
17.73	5.00	65.5
18.74	4.73	100.0
19.76	4.49	19.5
20.73	4.28	86.2
21.35	4.16	28.1
21.61	4.11	31.5
22.24	4.00	95.0
23.32	3.81	10.4
24.71	3.60	5.0
24.96	3.57	9.2
25.36	3.51	1.9
25.69	3.47	7.3
26.47	3.37	44.1
26.89	3.32	25.1
27.21	3.28	17.3
27.87	3.20	19.2
28.29	3.15	11.6
28.97	3.08	2.1

29.27	3.05	15.9
29.95	2.98	2.5
30.59	2.92	2.4
30.95	2.89	9.8
31.86	2.81	2.2
32.19	2.78	6.4
32.47	2.76	2.1
33.07	2.71	4.4
34.01	2.64	1.8
34.27	2.62	1.4
34.61	2.59	5.4
35.28	2.54	6.3
35.95	2.50	2.1
36.53	2.46	4.6
37.48	2.40	3.3
37.95	2.37	3.8
38.56	2.33	3.5
38.98	2.31	6.5
39.57	2.28	1.0
39.75	2.27	1.1
40.11	2.25	6.7

R-Enantiomer / (R)-(-)-1-Amino-2-propanol salt

Table 45: Characterization of the R-Enantiomer / (R)-(-)-1-Amino-2-propanol salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	19

Table 46: Peak List for the PXRD analysis of the R-Enantiomer / (R)-(-)-1-Amino-2-propanol salt

Pos.[°2θ]	d-spacing [Å]	Rel. Int. [%]
6.01	14.69	59.2
9.26	9.55	41.0
9.44	9.37	21.7
10.35	8.55	1.8
10.62	8.33	2.1
11.03	8.03	10.9
11.28	7.85	7.7
12.06	7.34	31.7
12.34	7.17	16.4

12.57	7.04	12.7
12.95	6.84	4.2
15.32	5.79	65.8
15.88	5.58	7.8
16.25	5.46	20.8
16.40	5.41	15.6
16.88	5.25	6.9
17.41	5.09	26.1
17.76	4.99	17.4
18.06	4.91	16.9
18.61	4.77	52.0
18.96	4.68	29.4
19.50	4.55	11.1
19.84	4.47	8.7
20.58	4.31	100.0
20.86	4.26	10.8
21.35	4.16	28.2
21.91	4.06	48.4
22.35	3.98	39.6
22.69	3.92	4.1
22.95	3.87	4.0
23.31	3.82	6.6
23.92	3.72	1.3
24.19	3.68	2.4
24.59	3.62	5.2
24.89	3.58	4.7
25.35	3.51	3.9
25.87	3.44	7.9
26.19	3.40	25.4
26.75	3.33	26.1
27.08	3.29	10.7
27.56	3.24	14.8
27.92	3.20	7.0
28.70	3.11	10.2
29.38	3.04	2.0
29.71	3.01	4.2
30.19	2.96	2.3
30.58	2.92	6.3
31.34	2.85	2.1
31.84	2.81	2.2
32.12	2.79	2.1
32.42	2.76	2.4
32.76	2.73	2.4
33.55	2.67	0.9
34.08	2.63	2.3
34.91	2.57	1.6
35.27	2.54	3.4

36.22	2.48	1.9
36.74	2.45	1.5
37.07	2.43	1.5
37.38	2.41	1.5
37.66	2.39	2.2
38.11	2.36	1.9
38.50	2.34	4.4
38.94	2.31	2.9
39.28	2.29	1.3
39.63	2.27	2.2
40.23	2.24	2.3

Letermovir / (S)-(+)-1-Amino-2-propanol salt

Table 47: Characterization of the Letermovir / (S)-(+)-1-Amino-2-propanol salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	20

Table 48: Peak List for the PXRD analysis of the Letermovir / (S)-(+)-1-Amino-2-propanol salt

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]
4.04	21.89	11.4
6.02	14.69	66.6
9.27	9.54	57.0
10.35	8.55	1.3
11.04	8.01	12.9
11.25	7.87	8.9
12.05	7.35	32.1
12.57	7.04	13.8
12.96	6.83	4.3
15.34	5.78	72.4
15.87	5.59	6.8
16.30	5.44	20.8
16.86	5.26	6.2
17.39	5.10	26.5
17.73	5.00	23.9
18.07	4.91	15.7
18.61	4.77	64.6
18.96	4.68	33.7

19.49	4.55	11.7
19.84	4.48	9.8
20.57	4.32	100.0
21.29	4.17	31.1
21.85	4.07	58.2
22.34	3.98	38.3
22.99	3.87	5.2
23.32	3.81	6.8
24.20	3.68	2.3
24.56	3.63	6.2
24.86	3.58	4.9
25.35	3.51	5.0
25.85	3.45	8.0
26.23	3.40	27.7
26.74	3.33	28.4
27.08	3.29	12.7
27.55	3.24	15.5
28.70	3.11	11.9
29.36	3.04	2.5
29.71	3.01	4.4
30.17	2.96	2.2
30.58	2.92	7.8
31.40	2.85	2.0
31.80	2.81	2.6
32.14	2.78	2.3
32.41	2.76	3.1
32.75	2.73	2.1
33.59	2.67	1.1
34.08	2.63	2.1
34.87	2.57	1.2
35.28	2.54	4.3
35.74	2.51	1.2
36.20	2.48	2.0
36.74	2.45	1.5
37.09	2.42	1.9
37.66	2.39	3.0
38.16	2.36	2.6
38.49	2.34	4.9
38.95	2.31	3.3
39.30	2.29	1.2

R-Enantiomer / (R)-(-)-Leucinol salt

Table 49: Characterization of the R-Enantiomer / (R)-(-)-Leucinol salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	21

Table 50: Peak List for the PXRD analysis of the R-Enantiomer / (R)-(-)-Leucinol salt

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]
6.33	13.97	53.3
9.78	9.04	57.3
10.99	8.05	10.2
12.70	6.97	17.8
13.29	6.66	37.3
14.75	6.01	31.1
16.24	5.46	44.3
16.84	5.26	9.3
18.42	4.82	64.4
18.59	4.77	100.0
19.12	4.64	12.4
19.66	4.52	19.4
20.54	4.32	55.5
22.59	3.94	29.3
23.03	3.86	84.7
23.37	3.81	16.4
24.24	3.67	28.6
25.11	3.55	11.5
25.60	3.48	1.7
25.92	3.44	10.6
26.70	3.34	11.9
27.57	3.24	10.1
27.93	3.19	10.5
28.24	3.16	9.1
28.95	3.08	8.7
29.40	3.04	3.9
29.70	3.01	5.3
30.37	2.94	16.1
31.82	2.81	2.3
32.18	2.78	8.0
32.84	2.73	4.0
33.11	2.71	3.6
34.34	2.61	2.1
34.72	2.58	2.0
34.93	2.57	3.9
35.95	2.50	4.9
36.75	2.45	1.4
37.36	2.41	5.2

37.71	2.39	3.5
38.28	2.35	6.4
38.52	2.34	4.3
39.11	2.30	4.1
39.61	2.28	2.2
39.95	2.26	3.4
40.18	2.24	2.8

Letermovir / (S)-(+)-Leucinol salt

Table 51: Characterization of the Letermovir / (S)-(+)-Leucinol salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	22

Table 52: Peak List for the PXRD analysis of the Letermovir / (S)-(+)-Leucinol salt

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]
6.32	14.00	45.2
9.77	9.05	52.4
10.98	8.06	8.7
12.69	6.97	14.7
13.29	6.66	33.0
14.74	6.01	26.3
16.24	5.46	46.4
16.83	5.27	7.5
18.58	4.77	100.0
19.11	4.64	10.3
19.66	4.52	17.9
20.54	4.32	46.1
22.10	4.02	1.2
22.58	3.94	27.0
23.02	3.86	69.3
23.39	3.80	15.1
24.24	3.67	26.1
25.11	3.55	11.8
25.93	3.44	11.1
26.72	3.34	11.3
27.57	3.24	9.8
27.93	3.19	9.6
28.25	3.16	9.8
28.95	3.08	7.8
29.39	3.04	3.5

29.72	3.01	5.6
30.37	2.94	14.3
31.80	2.81	2.3
32.19	2.78	8.6
32.84	2.73	4.7
33.13	2.70	3.2
34.35	2.61	1.8
34.95	2.57	3.4
35.95	2.50	5.1
36.76	2.45	1.5
37.37	2.41	5.1
37.73	2.38	3.4
38.28	2.35	6.1
38.55	2.34	5.0
39.11	2.30	3.4

R-Enantiomer / (*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinine) salt

Table 53: Characterization of the *R*-Enantiomer / (*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinine) salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	23a
¹ H – NMR	1:1 ratio <i>R</i> -Enantiomer – Chiral Agent	23b
Thermal Analyses	TGA Loss of 1.2% mass between 37 and 90 °C Loss of 1.5% mass between 90 and 145 °C Decomposition with onset at 261 °C DSC Wide endotherm, onset at 37 °C Wide endotherm, onset at 90 °C	23c

Table 54: Peak List for the PXRD analysis of the *R*-Enantiomer / (*R*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinine) salt

Pos.[°2θ]	d-spacing [Å]	Rel. Int. [%]
5,1	17,23	21,5
7,1	12,44	2,7

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]
8,4	10,55	6,4
8,8	10,00	14,5
9,9	8,93	90,4
10,3	8,59	25,1
10,9	8,10	16,9
11,5	7,72	21,7
11,8	7,52	5,3
12,1	7,33	17,3
12,3	7,22	13,9
13,3	6,66	42,3
13,5	6,54	57,4
14,3	6,22	19,1
14,8	6,00	2,1
15,0	5,89	3,1
15,4	5,75	45,4
15,7	5,64	50,1
16,0	5,53	64,8
16,4	5,42	23,2
16,7	5,32	18,4
16,8	5,26	65,6
17,2	5,17	55,3
17,4	5,11	32,9
17,7	5,00	13,4
18,0	4,92	31,9
18,2	4,87	14,6
18,7	4,76	100,0
19,1	4,65	79,8
19,3	4,60	23,2
19,6	4,52	14,3
19,9	4,46	26,4
20,2	4,38	10,6
20,4	4,34	69,1
20,6	4,30	6,5
21,0	4,23	6,6
21,4	4,15	55,0
21,8	4,09	25,5
22,1	4,03	13,9
22,2	3,99	10,6
22,6	3,93	51,9
22,9	3,89	9,2
23,4	3,81	21,9
23,6	3,76	10,4
23,9	3,73	18,4
24,4	3,65	7,5
24,7	3,61	7,1
24,9	3,58	8,2
25,1	3,54	9,2
25,6	3,48	20,0
25,9	3,43	6,5
26,1	3,41	7,3
26,4	3,38	19,4
26,8	3,33	8,5
27,3	3,26	7,2
27,9	3,20	7,1

Pos.[°2θ]	d-spacing [Å]	Rel. Int. [%]
28,2	3,16	9,3
28,6	3,12	12,2
29,0	3,08	7,5
29,3	3,04	2,4
29,5	3,03	4,3
29,7	3,00	5,1
30,0	2,98	9,1
30,4	2,94	13,3
30,7	2,92	3,2
31,3	2,86	4,3
31,7	2,82	4,7
32,0	2,79	7,8
32,5	2,76	10,7
33,1	2,71	3,2
33,4	2,68	6,5
33,7	2,66	1,3
34,3	2,62	3,7
34,9	2,57	4,9
35,1	2,55	4,9
35,4	2,54	5,2
35,8	2,51	2,9
36,0	2,49	1,8
36,4	2,47	2,3
36,6	2,45	6,0
37,1	2,42	1,8
37,4	2,41	5,4
37,9	2,38	1,0
38,1	2,36	1,7
38,5	2,34	1,4
38,9	2,32	3,4
39,2	2,30	2,9
39,5	2,28	3,0
40,0	2,26	1,4

Letermovir / (S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinidine) salt

Table 55: Characterization of the Letermovir / (S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinidine) salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	24a
¹ H – NMR	1:1 ratio <u>Letermovir</u> – Chiral Agent	24b
Thermal Analyses	TGA Loss of 1.9% mass between 37 and 96 °C	24c

	Loss of 4.9% mass between 96 and 204 °C Decomposition with onset at 256 °C DSC Wide endotherm, onset at 48 °C	
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Table 56: Peak List for the PXRD analysis of the Letermovir / (*S*)-[(2*R*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinidine) salt

Pos.[°2θ]	d-spacing [Å]	Rel. Int. [%]
4,2	21,24	46,5
7,4	11,97	7,2
8,2	10,75	17,7
8,6	10,23	27,7
9,4	9,44	49,6
11,0	8,06	11,8
11,2	7,90	16,6
11,8	7,52	10,5
12,6	7,00	24,2
13,4	6,60	45,1
13,8	6,41	20,3
14,2	6,23	100,0
14,4	6,15	69,3
14,8	5,97	14,4
15,2	5,83	13,2
15,6	5,70	8,6
16,5	5,37	45,0
16,7	5,31	53,0
17,1	5,20	29,7
17,4	5,11	45,1
17,7	5,02	43,9
18,3	4,85	43,8
18,5	4,78	46,3
18,8	4,72	71,1
19,0	4,66	23,2
19,3	4,59	23,5
19,6	4,53	56,4
20,2	4,40	27,8
20,5	4,34	12,6
20,8	4,27	27,2
21,1	4,21	19,4
21,5	4,13	31,4
22,2	4,00	58,9
23,0	3,87	26,0
23,5	3,78	25,3
23,7	3,75	36,7
23,9	3,72	55,1
24,5	3,63	24,1
24,9	3,58	33,3
25,2	3,53	12,5
25,5	3,50	6,1

Pos.[°2 θ]	d-spacing [Å]	Rel. Int. [%]
26,0	3,43	1,7
26,4	3,38	28,6
26,7	3,34	17,5
27,4	3,25	6,8
27,9	3,20	2,1
28,7	3,12	18,6
29,3	3,05	9,0
29,6	3,02	3,3
29,9	2,98	5,3
30,3	2,95	14,0
30,7	2,91	2,2
31,1	2,87	10,7
31,3	2,85	4,6
31,9	2,81	4,5
32,3	2,77	9,4
32,9	2,72	1,2
33,5	2,68	6,2
33,7	2,66	7,7
34,1	2,63	5,6
34,6	2,60	12,2
35,0	2,56	3,4
35,1	2,55	4,4
35,5	2,53	3,1
35,7	2,51	3,7
35,9	2,50	4,4
36,3	2,47	0,7
36,9	2,44	1,7
37,2	2,42	3,7
37,8	2,38	4,3
38,1	2,36	3,8
38,7	2,33	1,2
39,0	2,31	1,5
39,3	2,29	1,3
39,6	2,28	1,2

Solubility assessment

Solubility assessments in isobutyl acetate showed that the S/S and R/R enantiomeric pairs of Letemovir and R-Enantiomer with 1,2-aminoalcohols are surprisingly significantly less soluble than their respective diastereomers (R/S and S/R). This suggests that chiral aminoalcohols may be especially suited for enantiomeric resolution via selective crystallization.

Example 2. Enantiomeric resolution

General procedures for the enantiomeric resolution

Procedure 1: Direct enantiomeric resolution

A 200 to 700 mg/mL (500 mg/mL) solution/suspension of the racemic 2-{(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid, or a basic or an acidic salt thereof, or a solvate thereof or a solvate of a salt thereof, or a co-crystal thereof, or a solvate of a co-crystal thereof, or a co-crystals of a salt thereof, or a solvate of a co-crystal of a salt thereof is prepared in the respective solvent at 40 to 100°C (85°C). Then, 0.5 to 10 eq (preferably 1.1 eq if the free racemate or a co-crystal or a solvate of the racemate is used; 2 eq if an acidic or basic salt of the racemate is used) of the aminoalcohol or the aminoether are added directly or as a 50 to 400 mg/mL solution (150 mg/mL) in the respective solvent. When an acidic salt of the racemate is used, additional 0.5 to 1.5 eq of a non-chiral base (e.g. triethylamine, isopropylamine, butylamine or diethylamine) may be added. The obtained solution/suspension is cooled down to 25 to 85°C (75°C). At this point, the solution/suspension may be seeded with the pure less soluble diastereomeric salt. 1 to 10 temperature cycles of heating and cooling may be applied at this stage.

The solution/suspension is then stirred for 0.5 to 4 hours (2 hours) and allowed to cool down to room temperature for 3 to 24 hours (4 hours) whilst stirring. The obtained solid (Letermovir salt) is filtered off, washed with the respective solvent and dried under vacuum (2 to 20 mbar) for 5 to 48 hours (15 hours).

Procedure 2: Inverse enantiomeric resolution

A 200 to 700 mg/mL (500 mg/mL) solution/suspension of the racemic 2-{(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid or a basic or an acidic salt thereof, or a solvate thereof or a solvate of a salt thereof, or a co-crystal thereof, or a solvate of a co-crystal thereof,

or a co-crystals of a salt thereof, or a solvate of a co-crystal of a salt thereof is prepared in the respective solvent at 40 to 100°C (85°C). Then, 0.5 to 10 eq (preferably 1.1 eq if the free racemate or a co-crystal or a solvate of the racemate is used; 2 eq if an acidic or basic salt of the racemate is used) of the aminoalcohol or the aminoether are added directly or as a 50 to 400 mg/mL solution (150 mg/mL) in the respective solvent. The obtained solution/suspension is cooled down to 25 to 85°C (75°C). At this point, the solution/suspension may be seeded with the pure less soluble diastereomeric salt. The solution/suspension is then stirred for 0.5 to 4 hours and allowed to cool down to room temperature for 5 to 24 hours (15 hours) whilst stirring.

The solid (R-Enantiomer salt) is then separated by filtration and the solution (enriched with Letermovir) is subjected to a work-up, which can be either work-up 1 or work-up 2:

Work-up 1: The aminoalcohol or the aminoether of the solution is extracted with an acetate buffer (pH 3 to 4). The aqueous phase is discarded. The organic phase is washed 1 to 3 times with water. Procedure 1 is applied to the resulting Letermovir enriched solution.

Work-up 2: Procedure 1 is directly applied without removing the aminoalcohol or the aminoether.

Cooling: Whilst stirring, lowering the temperature of the solution/suspension at a rate of 0.1 to 20°C/min

Heating: Whilst stirring, raising the temperature of the solution/suspension at a rate of 0.1 to 20°C/min

Temperature Cycle: Heating followed by a Cooling procedure, or vice versa. The cycles can be repeated, and the temperature ranges modified in each cycle. The temperature ranges may be between 90°C and 0°C.

Procedure 3: Release of the Letermovir free base from the chiral salt

The chiral salt of Letermovir or the R-Enantiomer was dissolved in dichloromethane (concentration: 100 to 500 mg/mL) and extracted 1 to 5 times with < 0.1 M acetate buffer (pH = 3 to 4). The organic phase was then evaporated under reduced pressure, and the white foamy residue was dissolved in acetone (final concentration: 100 to 500 mg/mL) and precipitated via addition of water (final ratio: 1:5 – 1:20 acetone/water). The suspension was stirred for 15 to 60 hours, filtered off and then dried under vacuum, affording a white solid.

Procedure 4: Solid-state enantiomeric resolution

The racemic 2-{{(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}} acetic acid or a basic or an acidic salt thereof, or a solvate thereof or a solvate of a salt thereof, or a co-crystal thereof, or a solvate of a co-crystal thereof, or a co-crystals of a salt thereof, or a solvate of a co-crystal of a salt thereof and 1 to 10 equivalents of the respective chiral agent were mixed and grinded in a ball mill (5

to 120 minutes, frequency 5 to 30 s⁻¹). A catalytic amount of a given solvent, such as ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate isobutyl acetate, acetonitrile, isopropanol or pentyl acetate may be added (1 to 100 µL) before the grinding procedure.

The obtained solids were suspended in ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate isobutyl acetate or pentyl acetate (preferably pentyl acetate, final concentration ca. 100 to 500 mg/mL, stirred for 0.5 to 15 hours at room temperature, filtered off, washed 1 to 3 times with pentyl acetate and dried under vacuum.

Procedure 5: Letemovir free base release (liquid-liquid extraction)

The chiral salt of Letemovir or the R-Enantiomer was dissolved in dichloromethane (concentration: 100 - 500 mg/mL) and extracted 1 to 5 times with < 0.1 M acetate buffer (pH 3 to 4). The organic phase was then evaporated under reduced pressure to afford Letemovir as a foamy, resinous solid.

Procedure 6: Precipitation of amorphous Letemovir

Direct antisolvent addition:

The Letemovir free base was dissolved in a solvent or solvent mixture (concentration 100 – 1000 mg/mL). Then, 1 to 20 volumes, preferably 5 to 10 volumes, of an antisolvent or antisolvent mixture were added. The obtained suspension was stirred for 3 to 60 hours, preferably ca 15 hours. The obtained off-white solid was filtered off and dried under vacuum (3 to 100 mBar, 40 to 70°C, 2 to 15 hours).

Inverse antisolvent addition:

To 2 to 20 volumes of a given antisolvent, a solution of Letemovir in a given solvent (concentration 400 - 1200 mg / mL, preferably 800 mg/mL), was slowly added whilst stirring (controlled addition via syringe pump). The suspension was stirred for 3 to 60 hours, preferably 15 hours, filtered off and dried under vacuum (3 to 100 mBar, 40 to 70°C, 2 to 15 hours).

The results of the experiments are summarized in Tables 57 and 58.

Table 57: Selection of solvent and antisolvent pairs which afford amorphous Letermovir.

Solvent	Antisolvent
Ethyl acetate	<i>n</i> -Heptane (direct addition)
Isopropanol	
<i>tert</i> -Butyl alcohol	
Methyl ethyl ketone (MEK)	
Tetrahydrofuran	
1,4-Dioxane	
Dichloromethane	
Toluene	
Acetonitrile	
Acetone	<i>n</i> -Heptane (inverse addition)
Toluene	Diisopropylether (direct addition)
Ethyl Acetate	Diisopropylether (inverse addition)
Dichloromethane	Water (direct addition)
Isopropanol	
Ethanol	
Methanol	
<i>tert</i> -butanol	
Acetone	
Tetrahydrofuran	
N,N-Dimethylformamide	Water (inverse addition)
Methyl ethyl ketone (MEK)	
1,4-Dioxane	
Acetonitrile	

The amorphous nature of the obtained product was confirmed by PXRD for all the performed experiments. The PXRD data is in all cases identical and matches the PXRD pattern as depicted in Figure 25.

Table 58: Selection of results using 1,2-aminoalcohols and 1,2-aminoethers.

Yields are expressed with respect to the racemate (maximum yield for a perfect resolution through crystallization of one enantiomer: 50%). % ee values may refer to an excess of the R-Enantiomer (**R**) or to an excess of Letermovir (**Let**).

Aminoalcohol/Aminoether	Solvent	Reaction	Seeded? Reaction time	Yield	% ee
(<i>R</i>)-(-)-2-Amino-1-pentanol	Pentyl acetate	0.25 g racemate 1 eq base	Yes 15h reaction	35%	91 (<i>R</i>)

		1 mL solvent			
(1 <i>S</i> ,2 <i>S</i>)-2-amino-1-(4-nitrophenyl)-propane-1,3-diol	Pentyl acetate	0.25 g racemate 1 eq base 1 mL solvent	Yes 15h reaction	14%	95 (Let)
(<i>R</i>)-(-)-2-Amino-1-butanol	Acetonitrile	1 g racemate 1 eq base 2 mL solvent	Yes 15h reaction	9%	>99 (<i>R</i>)
(S)-(+)-2-Amino-1-butanol	Ethyl acetate	3.2 g racemate 1 eq base 9 mL solvent	Yes 48h reaction	37%	96 (Let)
	Butyl acetate	1 g racemate 1 eq base 3 mL solvent	Yes 15h reaction	38%	96 (Let)
	Isobutyl acetate	1 g racemate 1 eq base 3 mL solvent	Yes 15h reaction	35%	96 (Let)
	Diethylene glycol monoethyl ether acetate	0.5 g racemate 1 eq base 1.5 mL solvent	Yes 15h reaction	29%	93 (Let)
	Methyl propionate	0.5 g racemate 1 eq base 1.5 mL solvent	Yes 15h reaction	27%	94 (Let)
	Propyl butyrate	0.5 g racemate 1 eq base 1.5 mL solvent	Yes 15h reaction	38%	92 (Let)
	Benzyl butyrate	0.5 g racemate 1 eq base 1.5 mL solvent	Yes 15h reaction	38%	90 (Let)
	Ethyl butyrate	0.5 g racemate 1 eq base 1.5 mL solvent	Yes 15h reaction	38%	95 (Let)
		0.5 g racemate 1 eq base 2.5 mL solvent	Yes 15h reaction	35%	99 (Let)
		2.5 g racemate	Yes	39%	97 (Let)

		1.1 eq base 7 mL solvent	6h reaction		
	Pentyl acetate	0.25 g racemate 1 eq base 1 mL solvent	Yes 15h reaction	45%	90 (Let)
		0.5 g racemate 1 eq base 1.5 mL solvent	Yes 15h reaction	39%	95 (Let)
		1 g racemate 1 eq base 3 mL solvent	Yes 15h reaction	42%	95 (Let)
		0.5 g racemate 1 eq base 2.5 mL solvent	Yes 15h reaction	35%	>99 (Let)
		1 g racemate 1.5 eq base 2 mL solvent	Yes 5h reaction	36%	97 (Let)
		10 g racemate 1.1 eq base 25 mL solvent	Yes 5h reaction	42%	88 (Let)
		10 g racemate 1.1 eq base 35 mL solvent	Yes 5h reaction	38%	89 (Let)
		2.5 g racemate 1.1 eq base 7 mL solvent	Yes 6h reaction	37%	96 (Let)
(2 <i>R</i>)-3-amino-2-methoxy- propan-1-ol	Pentyl acetate	1 g racemate 1.1 eq base 4 mL solvent	Yes 90h reaction	37%	>99 (<i>R</i>)
		2 g racemate 1.1 eq base 6 mL solvent	Yes 6h reaction	40%	>99 (<i>R</i>)
(<i>S</i>)-2-Methoxypropan-1- amine	Pentyl acetate	1 g racemate 1.1 eq chiral agent 3 mL solvent	Yes 6h reaction	36%	>99 (<i>R</i>)
(<i>R</i>)-[(2 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-5-ethenyl- 1-azabicyclo[2.2.2]octan-2- yl](6-methoxyquinolin-4- yl)methanol (quinine)	Pentyl acetate	1 g racemate 1.1 eq chiral agent 3 mL solvent	Yes 15h reaction	32%	84 (<i>R</i>)

(S)-[(2 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinidine)	Pentyl acetate	3 g racemate 1.1 eq chiral agent 6 mL solvent	Yes 15h reaction	24%	86 (Let)
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Example 2.1: (S)-(+)-2-Amino-1-butanol / butyl acetate (90 hours)

Experimental procedure: A 160 mg/mL solution of (S)-(+)-2-Amino-1-butanol in butyl acetate (80 mg in 0.5 mL) was added over 1 eq of a 500 mg/mL solution (500 mg in 1 mL) of the racemic 2-[(4*R*,*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl] acetic acid in butyl acetate at 75°C. The solution was seeded with Letemovir / (S)-(+)-2-Amino-1-butanol salt, then stirred for 1 hour and allowed to cool down for 90 hours whilst stirring. The obtained solid was filtered off, washed with butyl acetate (0.5 mL, twice) and dried under vacuum overnight (2 to 3 mBar, 50°C). 242 mg of crystalline Letemovir / (S)-(+)-2-Amino-1-butanol salt were obtained (42% with respect to the racemate, enantiomeric excess: 79%).

Example 2.2: (S)-(+)-2-Amino-1-butanol / pentyl acetate (15 hours)

Experimental procedure: A 160 mg/mL solution of (S)-(+)-2-Amino-1-butanol in pentyl acetate (80 mg in 0.5 mL) was added over 1 eq of a 500 mg/mL solution (500 mg in 1 mL) of the racemic 2-[(4*R*,*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl] acetic acid in pentyl acetate at 85°C. The solution was cooled down to 70 to 80°C and seeded with Letemovir / (S)-(+)-2-Amino-1-butanol salt, then stirred for 1 hour and allowed to cool down for 15 hours whilst stirring. The obtained solid was filtered off, washed with pentyl acetate (0.5 mL, twice) and dried under vacuum overnight (2 to 3 mBar, 50°C). 225 mg of crystalline Letemovir / (S)-(+)-2-Amino-1-butanol salt were obtained (39% with respect to the racemate, enantiomeric excess: 95%).

Example 2.3: (R)-(-)-2-Amino-1-pentanol / pentyl acetate (15 hours)

Experimental procedure: An 80 mg/mL solution of (R)-2-Amino-1-pentanol in pentyl acetate (40 mg in 0.5 mL) was added over 1 eq of a 500 mg/mL solution (250 mg in 0.5 mL) of the racemic 2-[(4*R*,*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl] acetic acid in pentyl acetate at 85°C. The solution was cooled down to 50°C and seeded with pure R-Enantiomer / (R)-2-Amino-1-

pentanol salt, then stirred for 1 hour and allowed to cool down for 15 hours whilst stirring. The obtained solid was filtered off, washed with pentyl acetate (0.5 mL) and dried under vacuum overnight (2 to 3 mBar, 50°C). 87 mg of crystalline R-Enantiomer / (R)-2-Amino-1-pentanol salt were obtained (30% with respect to the racemate, enantiomeric excess: 94%).

Example 2.4: Inverse resolution. 1) (R)-(-)-2-Amino-1-butanol, 2) (S)-(+)-2-Amino-1-butanol / pentyl acetate

Experimental procedure: The racemic 2-{(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid (1 g) and 1 eq of (R)-(-)-2-Amino-1-butanol (160 mg) were dissolved in pentyl acetate at 85°C (concentration of the racemate 200 mg/mL). The solution was cooled down to 75°C and seeded with the R-Enantiomer / (R)-(-)-2-Amino-1-butanol salt.

The suspension was cooled down to 65°C, then heated up to 85°C and finally cooled down to room temperature and slurried for 15 hours.

The suspension was filtered off and washed with pentyl acetate (0.5 mL, twice). 441 mg of the R-Enantiomer / (R)-(-)-2-Amino-1-butanol salt were obtained (38% with respect to the racemate, enantiomeric excess: >95%).

The mother liquor was extracted with 10 mL of HCl 0.15 M, then washed with 10 mL of water and dried with CaCl₂. The resulting yellow solution was then reacted with 78 mg of (S)-(+)-2-Amino-1-butanol salt (1 eq with respect to the theoretical remaining Letemovir in solution), seeded at room temperature with Letemovir / (S)-(+)-2-Amino-1-butanol salt and allowed to slurry overnight.

The suspension was filtered off and washed with pentyl acetate (0.5 mL, twice). 100 mg of Letemovir / (S)-(+)-2-Amino-1-butanol salt were obtained (18% with respect to the racemate, enantiomeric excess: 94%).

Example 2.5: (S)-(+)-2-Amino-1-butanol / pentyl acetate (heating-cooling cycles, 24 hours)

Experimental procedure: The racemic 2-{(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid (1 g) and 1 eq of (S)-(+)-2-Amino-1-butanol were dissolved in 3 mL of pentyl acetate at 85°C. The solution was cooled down to 70°C and seeded with Letemovir / (S)-(+)-2-Amino-1-butanol salt, then subjected to the following heating-cooling cycles:

- 1st Cycle: Heating to 85°C, then cooling down to 30 to 35°C (ca. 1 hour).
- 2nd Cycle: Heating to 85°C, then cooling down to 30 to 35°C (ca. 1 hour).

- 3rd Cycle: Heating to 85°C, then cooling down to 30 to 35°C and slurry overnight (ca. 15 hours).
- 4th Cycle: Heating to 85°C, then cooling down to 30 to 35°C (ca. 1 hour).
- 5th Cycle: Heating to 85°C, then cooling down to 30 to 35°C (ca. 1 hour).

The obtained solid was filtered off, washed with pentyl acetate (0.5 mL, twice) and dried under vacuum (2 to 3 mBar, 50°C, 15 hours). 457 mg of crystalline Letemovir / (S)-(+)-2-Amino-1-butanol salt were obtained (40% with respect to the racemate; enantiomeric excess: 95%).

Example 2.6: (S)-2-Methoxypropan-1-amine / pentyl acetate (cooling-heating cycle, 6 hours)

Experimental procedure: The racemic 2-{(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid (1 g) and 1.1 eq of (S)-2-Methoxypropan-1-amine were dissolved in 3 mL of pentyl acetate at 90°C (concentration of the racemate: 333 mg/mL).

The solution was cooled down to 60 to 70°C, seeded with the R-Enantiomer / (S)-2-Methoxypropan-1-amine salt, cooled down to 35°C, then subjected to one heating-cooling cycle (heating to 60 to 70°C, followed by cooling to room temperature). The solution was stirred for 3 hours, filtered off, washed with pentyl acetate (0.5 mL, three times) and dried under vacuum overnight. 416 mg of crystalline Letemovir / (S)-2-Methoxypropan-1-amine salt were obtained (36% with respect to the racemate; enantiomeric excess: 99%).

Example 2.7: (S)-(+)-2-Amino-1-butanol salt / pentyl acetate (solid state enantiomeric resolution).

Experimental procedure: The racemic 2-{(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid (100 mg) and 1.1 eq of (S)-(+)-2-Amino-1-butanol (20 mg) were grinded in a ball mill for 15 minutes at a 15 s⁻¹ frequency. A catalytic amount (ca. 50 µL) of pentyl acetate was added to the mixture before the grinding procedure (LAG: liquid assisted grinding).

The obtained resinous residue was then suspended in 0.2 mL of pentyl acetate and stirred for 1 hour at room temperature. The solvent was decanted, and the resulting white powder was washed with 0.2 mL of pentyl acetate. Ca. 30 mg of solid of crystalline Letemovir / (S)-(+)-2-

Amino-1-butanol salt were obtained (25% with respect to the racemate; enantiomeric excess: 81%).

Example 2.8: (R)-2-Methoxypropan-1-amine salt / pentyl acetate (solid state enantiomeric resolution)

Experimental procedure: The racemic 2-{(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid (100 mg) and 1.1 eq of (R)-2-Methoxypropan-1-amine (18 mg) were grinded in a ball mill for 15 minutes at a 15 s⁻¹ frequency. A catalytic amount (ca. 50 µL) of pentyl acetate was added to the mixture before the grinding procedure (LAG: liquid assisted grinding).

The obtained resinous residue was then suspended in 0.2 mL of pentyl acetate and stirred for 1 hour at room temperature. The solvent was decanted, and the resulting white powder was washed with 0.2 mL of pentyl acetate. Ca. 30 mg of solid of crystalline Letemovir / (R)-2-Methoxypropan-1-amine salt were obtained (25% with respect to the racemate; enantiomeric excess: 75%).

Example 2.9: Letemovir Free Base release from the Letemovir / (S)-(+)-2-Amino-1-butanol salt (liquid - liquid extraction)

Experimental procedure: The Letemovir / (S)-(+)-2-Amino-1-butanol salt (1.5 g) was dissolved in 15 mL of dichloromethane. The organic phase was extracted twice with 20 mL of an acetate buffer (pH = 4), and the aqueous phase was extracted once with 20 mL of dichloromethane. The organic solution was evaporated to dryness in a rotary evaporator, affording 1.38 g (>99% yield) of Letemovir free base as a foamy, resinous solid.

Example 2.10: Letemovir Free Base precipitation

Experimental procedure: The Letemovir free base (150 mg) was dissolved in 0.5 mL of acetone. 5 mL of water were added (1:10 acetone/water ratio). The obtained suspension was stirred for 15 hours. The obtained off-white solid was filtered off and dried under vacuum (3 to 5 mBar, 40°C, 15 hours). 128 mg of solid Letemovir free base (85% yield) were obtained. PXRD confirmed the amorphous nature of the obtained solid product (see Figure 25).

Example 2.11: (S)-(+)-2-Amino-1-butanol salt / ethyl acetate (solid state enantiomeric resolution)

Experimental procedure: The racemic 2-{(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid (200 mg) and 1 eq of (*S*)-(+)-2-Amino-1-butanol were grinded in a ball mill for 60 minutes at a 30 s⁻¹ frequency. A catalytic amount (ca. 50 µL) of ethyl acetate was added to the mixture before the grinding procedure (LAG: liquid assisted grinding).

The obtained mixture was then suspended in 0.5 mL of pentyl acetate and stirred for 30 minutes at room temperature. The resulting suspension was filtered off and washed with 0.5 mL of pentyl acetate, affording ca. 75 mg of crystalline Letemovir / (*S*)-(+)-2-Amino-1-butanol salt (yield: 29% with respect to the racemate, enantiomeric excess: 84%).

Example 2.12: (*S*)-(+)-2-Amino-1-butanol salt / acetonitrile (solid state enantiomeric resolution)

Experimental procedure: The racemic 2-{(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid (200 mg) and 1 eq of (*S*)-(+)-2-Amino-1-butanol were grinded in a ball mill for 60 minutes at a 30 s⁻¹ frequency. A catalytic amount (ca. 50 µL) of acetonitrile was added to the mixture before the grinding procedure (LAG: liquid assisted grinding).

The obtained mixture was then suspended in 0.5 mL of pentyl acetate and stirred for 30 minutes at room temperature. The resulting suspension was filtered off and washed with 0.5 mL of pentyl acetate, affording ca. 70 mg of crystalline Letemovir / (*S*)-(+)-2-Amino-1-butanol salt (yield: 25% with respect to the racemate, enantiomeric excess: 84%).

Example 2.13: Quinine / pentyl acetate (15 hours)

Experimental procedure: 0.6 g of quinine and 1 g of the racemic 2-{(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid were dissolved in 3 mL of pentyl acetate at 90 °C. The solution was cooled down to 40 °C, then seeded with R Enantiomer / quinine salt, then stirred for 2 hours and allowed to cool down for 15 hours whilst stirring. The obtained solid was filtered off, washed with pentyl acetate (0.2 mL, twice) and dried under vacuum overnight (3 to 6 mBar, 50 °C). 500 mg of crystalline R-Enantiomer / quinine salt were obtained (yield: 32% with respect to the racemate, enantiomeric excess: 84%).

Example 2.14: Quinidine / pentyl acetate (15 hours)

Experimental procedure: 1.7 g of quinidine and 3 g of the racemic 2-{(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid were dissolved in 6 mL of pentyl acetate at 85 °C. The solution was cooled down to 40 °C, then seeded with Letemovir / quinidine salt, then stirred for 5 hours and allowed to cool down for 15 hours whilst stirring. The obtained solid was filtered off, washed with pentyl acetate (1 mL, thrice) and dried under vacuum (3 to 6 mBar, 50 °C, 4 hours). 1.10 g of crystalline Letemovir / quinidine salt were obtained (yield: 24% with respect to the racemate, enantiomeric excess: 86%).

Example 2.15: Enantiomeric resolution of a Racemate Tosylate salt

Experimental procedure: 0.15 g of the racemic 2-{(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate tosylate salt (characterization is provided in Table 59) and 2.1 eq of (S)-(+)-2-Amino-1-butanol (20 mg) were dissolved in 0.5 mL of pentyl acetate at 85 °C. The solution was cooled down to room temperature, then seeded with Letemovir / (S)-(+)-2-Amino-1-butanol salt, then allowed to cool down for 15 hours whilst stirring. The obtained suspension was filtered off, affording ca. 50 mg crystalline Letemovir / (S)-(+)-2-Amino-1-butanol salt (yield: 30% with respect to the racemate, enantiomeric excess: 91%).

Table 59: Characterization of the Racemic Tosylate salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	26a
Thermal Analyses	TGA Decomposition with an onset at ca. 276 °C DSC Endotherm (fusion) with an onset at 164 °C	26b
Dynamic Vapour Sorption	1.4 % water gain between 10 and 80% RH. 3.3 % water gain between 10 and 90% RH. Slightly different phase after experiment (PXRD).	26c

Example 2.16: Enantiomeric resolution of a Racemate Calcium salt

Experimental procedure: 0.15 g of the racemic 2-{(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate calcium salt (characterization is provided in Table 60) and 1.1

eq of (S)-(+)-2-Amino-1-butanol (20 mg) were dissolved in 0.5 mL of pentyl acetate at 85 °C. The solution was cooled down to room temperature, then seeded with Letermovir calcium salt, then stirred for 5 hours and allowed to cool down for 15 hours whilst stirring. The solution was allowed to partially evaporate under air, affording ca. 50 mg of crystalline Letermovir of (S)-(+)-2-Amino-1-butanol salt (yield: 30% with respect to the racemate, enantiomeric excess: 92%).

Table 60: Characterization of the Racemic Calcium salt

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	27a
Thermal Analyses	TGA 5.7 % mass loss between 39 and 140 °C 2.4 % mass loss between 140 and 187 °C Decomposition with an onset at ca. 260 °C DSC Broad endotherm with an onset at 61 °C Broad endotherms with an onset at 133 °C Broad exotherm with an onset at 204 °C	27b
Dynamic Vapour Sorption	4.9 % water gain between 10 and 80% RH 14.2 % water gain between 10 and 90% RH Similar phase after experiment (PXRD)	27c

Example 2.17: Enantiomeric resolution of a Racemate Diphenylurea co-crystal

Experimental procedure: 0.15 g of the racemic 2-[(4R,S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl] acetic acid diphenylurea co-crystal (characterization is provided in Table 61) and 1.1 eq of (S)-(+)-2-Amino-1-butanol (20 mg) were suspended in 0.5 mL of pentyl acetate at 85 °C. The suspension was cooled down to room temperature, then seeded with Letermovir / (S)-(+)-2-Amino-1-butanol salt, then allowed to cool down for 15 hours whilst stirring. The obtained suspension was filtered off, affording ca. 40 mg crystalline Letermovir / (S)-(+)-2-Amino-1-butanol salt mixed with excess diphenyl urea (enantiomeric excess > 99%).

Table 61: Characterization of the Racemate Diphenylurea co-crystal

Analyses	Result	Figure
Powder X-Ray Diffraction	Crystalline phase	28a

Thermal Analyses	TGA Decomposition with an onset at ca. 214 °C DSC Endotherm (fusion) with an onset at 171 °C	28b
Dynamic Vapour Sorption	0.1 % water gain between 10 and 80% RH 0.7 % water gain between 10 and 90% RH Similar phase after experiment (PXRD)	28c

Example 2.18: Esterification of the R-Enantiomer

Experimental procedure: To a solution of R-Enantiomer (531 mg, 1 eq, 927 μ mol) in MeOH (6.72 mL), sulfuric acid (126 mg, 76.9 μ L, 96% wt, 1.33 eq, 1.23 mmol) was added. The reaction mixture was stirred at 80 °C for 20 hours. The reaction was cooled down to room temperature and concentrated under vacuo. The resulting residue was dissolved in DCM and extracted with NaHCO₃ saturated aqueous solution. The aqueous phase was extracted with DCM. The combined organic fractions were dried with Na₂SO₄, filtered and concentrated under vacuo to obtain the methyl ester of the R-Enantiomer (602 mg, 1.03 mmol, 111%) as a white solid. Yield higher than 100% due to the presence of solvent (DCM) in the crude.

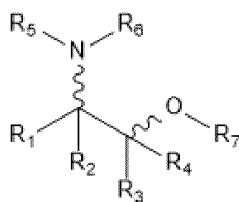
Example 2.19: Epimerization of the methyl ester of the R-Enantiomer with *t*BuOK

Experimental procedure: The methyl ester of the R-Enantiomer (600 mg, 1 eq, 1.02 mmol) was added in a tube, followed by *t*BuOK (4.1 eq) and acetonitrile (2.56 mL). The reaction mixture was stirred at 50 °C for 2 hours. Then, water (2.40 g, 2.40 mL, 130 eq, 133 mmol) was added and the reaction was stirred at 50 °C for another 2 hours. The reaction was cooled down, concentrated under vacuo and acidified (pH = 4) with an acetate buffer solution (0.1 M, 70 mL) at pH = 4. The resulting suspension was extracted with DCM (3 x 50 mL) and concentrated under vacuo to obtain a mixture of the R-Enantiomer and Letermovir (470 mg). The mixture was dissolved in acetone (1.2 mL, 390 mg/mL). Then, water (15.6 mL, 26.0 vol.) was added via a syringe pump in 1 hour (0.26 mL/min) with vigorous stirring. The suspension was left stirring at room temperature for 15 hours. The suspension was filtered under vacuo and the flask was washed with water (3.0 mL, thrice). The resulting solid was dried under vacuo to obtain the enantiomeric mixture of R-Enantiomer and Letermovir (421.5 mg, 736.2 μ mol, 72.0%) as a white solid. The ee was measured via UPLC and it was determined to be 11.0%, with slight excess of the R-Enantiomer. With the above context, the following consecutively numbered embodiments provide further specific aspects of the invention:

1. A method for producing 2-{(4S)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid (“Letermovir”) or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, comprising the steps:

i) providing a mixture comprising Letermovir and 2-{(4R)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid (“R-Enantiomer”) or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;

ii) contacting said mixture with an enantiomerically enriched compound of Formula (I)



(I)

wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring,

thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I),

iii-1) separating the Letemovir salt of the compound of Formula (I);

iv-1) converting the Letemovir salt of the compound of Formula (I) into Letemovir or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof; and optionally

v-1) isolating Letemovir or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof.

2. The method for producing Letemovir according to embodiment 1, wherein said Letemovir is in an amorphous state and wherein said method further comprises precipitation of Letemovir obtained in step iv-1) or v-1) from a solvent selected from the group consisting of acetic acid, formic acid, triethylamine, ethyl acetate, butyl acetate, methyl acetate, isobutyl acetate, propyl acetate, isopropyl acetate, ethyl formate, isopropanol, 1-propanol, n-pentanol, ethanol, methanol, n-butanol, 2-butanol, 2-methyl-1propanol, 3-methyl-1-butanol, *tert*-butanol, cyclohexanone, acetone, methyl ethyl ketone, 3-pentanone, methyl butyl ketone, methyl isobutyl ketone, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, 2-ethoxyethanol, 2-methoxyethanol, ethyleneglycol, formamide, N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, nitromethane, pyridine, sulfolane, tetralin, 1,2-dichloroethane, dichloromethane, 1,1,2-trichloroethane, 1,1,1-trichloroethane, chloroform, chlorobenzene, toluene, cumene, xylenes, anisole, acetonitrile, N-methyl pyrrolidone, dimethyl carbonate, pentyl acetate, or mixtures thereof, by an antisolvent selected from the group

consisting of n-heptane, pentane, n-octane, diisopropyl ether, cyclohexane, hexane, methylcyclohexane, *tert*-butyl methyl ether, ethyl ether, cyclopentyl methyl ether, and water, or mixtures thereof, preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethylcarbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, 3-methyl-1-butanol, N,N-dimethylformamide and xylenes, or mixtures thereof, by an antisolvent selected from the group consisting of cyclohexane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether, water and n-heptane, or mixtures thereof, more preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethyl carbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, and xylenes, or mixtures thereof, and the antisolvent is selected from the group consisting of cyclohexane, diisopropyl ether, water and n-heptane, or mixtures thereof, even more preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, ethanol, isopropanol, methanol, methyl ethyl ketone, tetrahydrofuran, dioxane, toluene, 3-methyl-1-butanol, *tert*-butanol, N,N-dimethylformamide and dichloromethane or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether and water, or mixtures thereof, most preferred from a water miscible solvent acetone or acetonitrile into excess stirred water, to obtain amorphous Letemovir, followed by isolation via filtration or centrifugation.

3. A method for producing a Letemovir salt of a compound of Formula (I), comprising the steps:

- i) providing a mixture comprising Letemovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;
- ii) contacting said mixture with an enantiomerically enriched compound of Formula (I), thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I);

iii-1) separating the Letermovir salt of the compound of Formula (I),

wherein the compound of Formula (I) is as defined in embodiment 1.

4. A method for enantiomeric separation of a mixture comprising Letermovir and R-Enantiomer, comprising the steps:

i) providing a mixture comprising Letermovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;

ii) contacting said mixture with an enantiomerically enriched compound of Formula (I), thereby producing a Letermovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I),

iii-1) separating the Letermovir salt of the compound of Formula (I);

iv-1) transferring the Letermovir salt of the compound of Formula (I) into the compound of Formula (I) and Letermovir and optionally

v-1) isolating Letermovir,

wherein the compound of Formula (I) is as defined in embodiment 1.

5. The method for enantiomeric separation of a mixture comprising Letermovir and R-Enantiomer according to embodiment 4, further comprising the steps:

vi-1) isolating the R-Enantiomer salt of the compound of Formula (I);

vii-1) transferring the R-Enantiomer salt of the compound of Formula (I) into the compound of Formula (I) and R-Enantiomer; and optionally

viii-1) isolating R-Enantiomer,

wherein the compound of Formula (I) is as defined in embodiment 1.

6. A method for enantiomeric separation of a mixture comprising Letermovir and R-Enantiomer, comprising the steps:

i) providing a mixture comprising Letemovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;

ii) contacting said mixture with an enantiomerically enriched compound of Formula (I), thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I);

iii-2) separating the R-Enantiomer salt of the compound of Formula (I);

iv-2) transferring the R-Enantiomer salt of the compound of Formula (I) into the compound of Formula (I) and R-Enantiomer; and optionally

v-2) isolating R-Enantiomer,

wherein the compound of Formula (I) is as defined in embodiment 1.

7. The method for enantiomeric separation of a mixture comprising Letemovir and R-Enantiomer according to embodiment 6, further comprising the steps:

vi-2) isolating the Letemovir salt of the compound of Formula (I);

vii-2) transferring the Letemovir salt of the compound of Formula (I) into the compound of Formula (I) and Letemovir; and optionally

viii-2) isolating Letemovir.

8. The method according to any of embodiments 4, 5 or 7, wherein said method further comprises precipitation of Letemovir obtained in step iv-1), v-1), vii-2) or viii-2) from a solvent selected from the group consisting of acetic acid, formic acid, triethylamine, ethyl acetate, butyl acetate, methyl acetate, isobutyl acetate, propyl acetate, isopropyl acetate, ethyl formate, isopropanol, 1-propanol, n-pentanol, ethanol, methanol, n-butanol, 2-butanol, 2-methyl-1-propanol, 3-methyl-1-butanol, *tert*-butanol, cyclohexanone, acetone, methyl ethyl ketone, 3-pentanone, methyl butyl ketone, methyl isobutyl ketone, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, 2-ethoxyethanol, 2-methoxyethanol, ethyleneglycol, formamide, N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, nitromethane, pyridine, sulfolane, tetralin, 1,2-dichloroethane, dichloromethane, 1,1,2-trichloroethane, 1,1,1-

trichloroethane, chloroform, chlorobenzene, toluene, cumene, xylenes, anisole, acetonitrile, N-methyl pyrrolidone, dimethyl carbonate, pentyl acetate, or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, pentane, n-octane, diisopropyl ether, cyclohexane, hexane, methylcyclohexane, *tert*-butyl methyl ether, ethyl ether, cyclopentyl methyl ether, and water, or mixtures thereof, preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethylcarbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, 3-methyl-1-butanol, N,N-dimethylformamide and xylenes, or mixtures thereof, by an antisolvent selected from the group consisting of cyclohexane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether, water and n-heptane, or mixtures thereof, more preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethyl carbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, and xylenes, or mixtures thereof, and the antisolvent is selected from the group consisting of cyclohexane, diisopropyl ether, water and n-heptane, or mixtures thereof, even more preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, ethanol, isopropanol, methanol, methyl ethyl ketone, tetrahydrofuran, dioxane, toluene, 3-methyl-1-butanol, *tert*-butanol, N,N-dimethylformamide and dichloromethane or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether and water, or mixtures thereof, most preferred from a water miscible solvent acetone or acetonitrile into excess stirred water, to obtain amorphous Letermovir, followed by isolation via filtration or centrifugation.

9. The method according to any of embodiments 1 to 8, wherein step ii) is carried out in a solid state.

10. The method according to embodiments 1 to 5, wherein step ii) is carried out in a solid state and separating the Letermovir salt of the compound of Formula (I) in step iii-1) is conducted by means of dissolving the R-Enantiomer salt of the compound of Formula (I) in a solvent selected from the group consisting of ketones, such as acetone, methyl ethyl ketone,

cyclohexanone, 4-methylcyclohexanone, 4-methyl-2-pentanone or 3-pentanone; alkanes, such as pentane, hexane, heptane or isooctane; cycloalkanes, such as cyclohexane or cyclopentane; aromatic solvents, such as chlorobenzene, 1,2-dichlorobenzene, cumene, toluene or xylenes; esters such as ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, ethyl propionate, methyl propionate, isoamyl propionate, isobutyl propionate, hexyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, cyclohexyl butyrate, benzyl butyrate, isobutyl formate, ethyl formate, ethyl formate, isopropyl formate, butyl formate, pentyl formate, diethylene glycol monoethyl ether acetate and ethylene glycol diacetate; ethers, such as diisopropyl ether, cyclopentyl methyl ether, butyl ether, diethoxymethane, anisole, ethylene glycol dimethyl ether, diethylene glycol diethyl ether or dimethoxyethane; alcohols such as ethanol, methanol, 2-butanol, isopropanol, n-butanol, diethylene glycol, isobutanol, isopentanol or *tert*-butanol; nitriles, such as acetonitrile; and carbonates, such as dimethyl carbonate or diethyl carbonate; or mixtures thereof, preferably selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, and isolating the solid phase comprising the Letermovir salt of the compound of Formula (I).

11. The method according to embodiments 1 to 5, wherein step ii) is carried out in a solid state and separating the Letermovir salt of the compound of Formula (I) in step iii-1) is conducted by means of dissolving the Letermovir salt of the compound of Formula (I) in a solvent selected from the group consisting of ketones, such as acetone, methyl ethyl ketone, cyclohexanone, 4-methylcyclohexanone, 4-methyl-2-pentanone or 3-pentanone; alkanes, such as pentane, hexane, heptane or isooctane; cycloalkanes, such as cyclohexane or cyclopentane; aromatic solvents, such as chlorobenzene, 1,2-dichlorobenzene, cumene, toluene or xylenes; esters such as ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, ethyl propionate, methyl propionate, isoamyl propionate, isobutyl propionate, hexyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, cyclohexyl butyrate, benzyl butyrate, isobutyl formate, ethyl formate, ethyl formate, isopropyl formate, butyl formate, pentyl formate, diethylene glycol monoethyl ether acetate and ethylene glycol diacetate; ethers, such as diisopropyl ether, cyclopentyl methyl ether, butyl ether,

diethoxymethane, anisole, ethylene glycol dimethyl ether, diethylene glycol diethyl ether or dimethoxyethane; alcohols such as ethanol, methanol, 2-butanol, isopropanol, n-butanol, diethylene glycol, isobutanol, isopentanol or *tert*-butanol; nitriles, such as acetonitrile; and carbonates, such as dimethyl carbonate or diethyl carbonate; or mixtures thereof, preferably selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, and isolating the solid phase comprising the R-Enantiomer salt of the compound of Formula (I).

12. The method according to any of embodiments 1 to 8, wherein step ii) is carried out in a liquid phase.

13. The method according to any of embodiments 1 to 12, wherein the ratio of Letermovir to R-Enantiomer in said mixture in step i) is in the range of from 10:90 to 90:10, preferably from 20:80 to 80:20, more preferably from 30:70 to 70:30, even more preferably from 40:60 to 60:40, most preferred from 45:55 to 55:45.

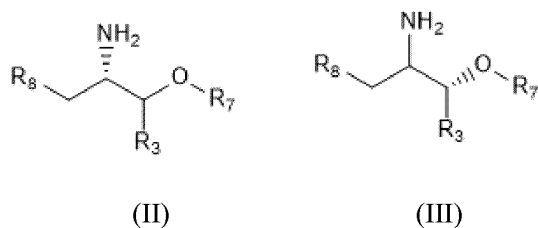
14. The method according to any of embodiments 1 to 13, wherein said mixture in step i) is racemic 2-{(4R,S)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid or a salt thereof, or a solvate thereof, or a salt of a solvate thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof.

15. The method according to any of embodiments 1 to 8 and 12, wherein step (ii) is carried out in presence of a solvent selected from the group consisting of ketones, such as acetone, methyl ethyl ketone, cyclohexanone, 4-methylcyclohexanone, 4-methyl-2-pentanone or 3-pentanone; alkanes, such as pentane, hexane, heptane or isooctane; cycloalkanes, such as cyclohexane or cyclopentane; aromatic solvents, such as chlorobenzene, 1,2-dichlorobenzene, cumene, toluene or xylenes; esters such as ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, ethyl propionate, methyl propionate, isoamyl propionate, isobutyl propionate, hexyl propionate, ethyl butyrate, propyl

butyrate, amyl butyrate, cyclohexyl butyrate, benzyl butyrate, isobutyl formate, ethyl formate, ethyl formate, isopropyl formate, butyl formate, pentyl formate, diethylene glycol monoethyl ether acetate and ethylene glycol diacetate; ethers, such as diisopropyl ether, cyclopentyl methyl ether, butyl ether, diethoxymethane, anisole, ethylene glycol dimethyl ether, diethylene glycol diethyl ether or dimethoxyethane; alcohols such as ethanol, methanol, 2-butanol, isopropanol, n-butanol, diethylene glycol, isobutanol, isopentanol or *tert*-butanol; nitriles, such as acetonitrile; and carbonates, such as dimethyl carbonate or diethyl carbonate; or mixtures thereof, preferably selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof.

16. The method according to any of embodiments 1 to 15, wherein the enantiomeric purity of said compound of Formula (I) is at least 80% ee, preferably at least 85% ee, more preferably at least 90% ee, more preferably at least 95% ee, more preferably at least 98% ee, most preferred at least 99% ee.

17. The method according to any of embodiments 1 to 5, wherein the compound of Formula (I) is a compound of formula (II) or (III)



wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

R₇ is H or C₁-C₃-alkyl,

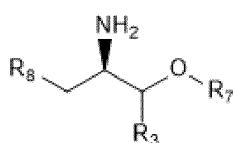
R₈ is selected from the group consisting of H, OH, methyl or ethyl,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

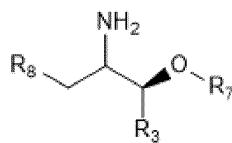
wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein step iii-1) comprises isolating the solid phase comprising the Letemovir salt of the compound of Formula (II) or (III).

18. The method according to any of embodiments 1 to 5, wherein the compound of Formula (I) is a compound of formula (IV) or (V)



(IV)



(V)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

R₇ is H or C₁-C₃-alkyl,

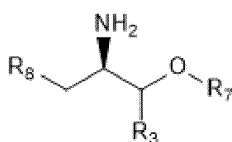
R₈ is selected from the group consisting of H, OH, methyl or ethyl,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

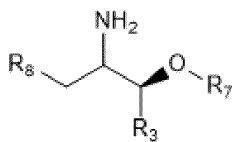
wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein step iii-1) comprises isolating the liquid phase comprising the Letemovir salt of the compound of Formula (IV) or (V).

19. The method according to embodiment 6 or 7, wherein the compound of Formula (I) is a compound of formula (IV) or (V)



(IV)



(V)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

R₇ is H or C₁-C₃-alkyl,

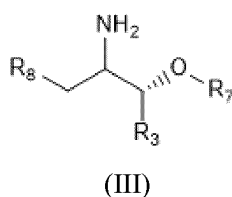
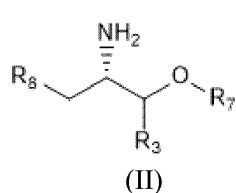
R₈ is selected from the group consisting of H, OH, methyl or ethyl,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein step iii-2) comprises isolating the solid phase comprising the R-Enantiomer salt of the compound of Formula (IV) or (V).

20. The method according to embodiment 6 or 7, wherein the compound of Formula (I) is a compound of formula (II) or (III)



wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

R₇ is H or C₁-C₃-alkyl,

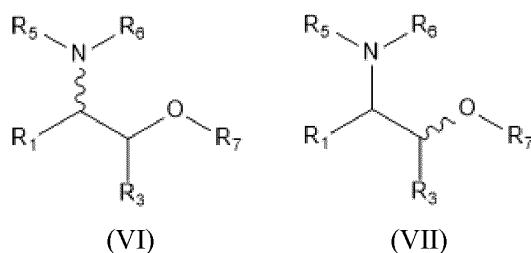
R₈ is selected from the group consisting of H, OH, methyl or ethyl,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein step iii-2) comprises isolating the liquid phase comprising the R-Enantiomer salt of the compound of Formula (II) or (III).

21. The method according to any of embodiments 1 to 16, wherein the compound of Formula (I) is a compound of formula (VI) or (VII)



wherein

R₁ is selected from the group consisting of H, C₁-C₃-alkyl and CH₂OH,

R₃ is selected from the group consisting of H, C₁-C₃-alkyl, phenyl and 4-nitrophenyl,

R₅ and R₆ each is independently selected from the group consisting of H and C₁-C₃-alkyl,

R₇ is H or C₁-C₃-alkyl,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₇-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

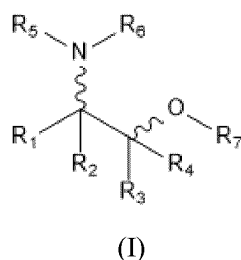
wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl, such as 5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl.

22. The method according to embodiment 21, wherein R₅ and R₆ each is H.

23. The method according to embodiment 21, wherein the compound of Formula (I) is selected from the group consisting of (S)-(+)-2-Amino-1-butanol, (2R)-3-amino-2-methoxypropan-1-ol, (R)-2-Methoxypropan-1-amine, (S)-(+)-2-Amino-1-hexanol, (S)-(+)-2-Amino-1-pentanol, (R)-(-)-2-Amino-1-butanol, L-Phenylalaninol, (1S,2S)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol, (R)-(-)-2-Phenylglycinol, (R)-(Tetrahydrofuran-2-yl)methanamine and (1S,2S)-2-amino-1-phenylpropane-1,3-diol, preferably (S)-(+)-2-Amino-1-butanol, (2R)-3-amino-2-methoxypropan-1-ol, (R)-2-Methoxypropan-1-amine, (S)-(+)-2-Amino-1-hexanol, (S)-(+)-2-Amino-1-pentanol, (1S,2S)-2-amino-1-phenylpropane-1,3-diol, (R)-[(2S,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinine) and (S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinidine).

28. Use of a compound of Formula (I) for enantiomeric separation of a mixture comprising Letemovir and R-Enantiomer, wherein the compound of Formula (I) is defined as in embodiment 4.

29. An R-Enantiomer salt of a compound of Formula (I)



wherein

R_1 and R_2 each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R_3 and R_4 each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl

R_5 and R_6 each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R_7 is H or C₁-C₆-alkyl,

wherein R_1 and R_3 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

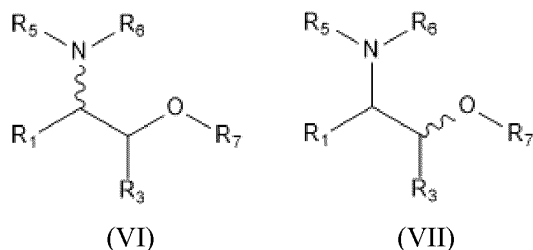
wherein R_1 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R_3 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R_1 and R_5 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R_5 and R_7 , together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring.

30. The R-Enantiomer salt of a compound of Formula (I) according to embodiment 29, wherein the compound of Formula (I) is a compound of Formula (VI) or (VII)



wherein

R₁ is selected from the group consisting of H, C₁-C₃-alkyl and CH₂OH,

R₃ is selected from the group consisting of H, C₁-C₃-alkyl, phenyl and 4-nitrophenyl,

R₅ and R₆ each is independently selected from the group consisting of H and C₁-C₃-alkyl,

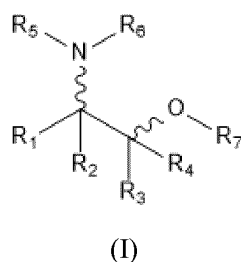
R₇ is H or C₁-C₃-alkyl,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₇-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl, such as such as 5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl.

31. A Letemovir salt of a compound of Formula (I),



wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

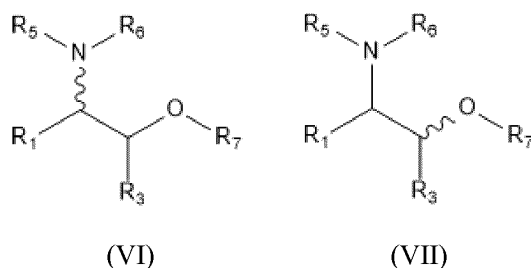
wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring.

32. The Letermovir salt of a compound of Formula (I) according to embodiment 31, wherein the compound of Formula (I) is a compound of Formula (VI) or (VII)



wherein

R₁ is selected from the group consisting of H, C₁-C₃-alkyl and CH₂OH,

R₃ is selected from the group consisting of H, C₁-C₃-alkyl, phenyl and 4-nitrophenyl,

R₅ and R₆ each is independently selected from the group consisting of H and C₁-C₃-alkyl,

R₇ is H or C₁-C₃-alkyl,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₇-oxocyclic ring,

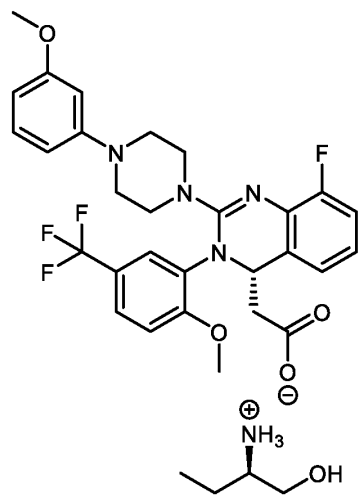
wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl, such as such as 5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl.

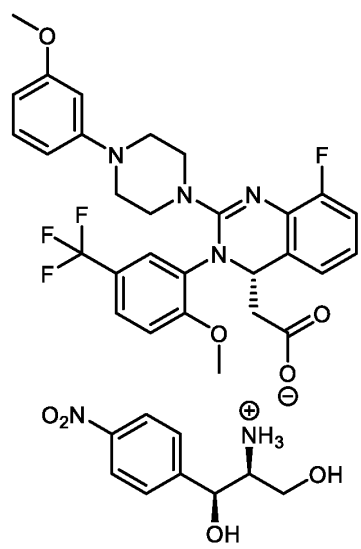
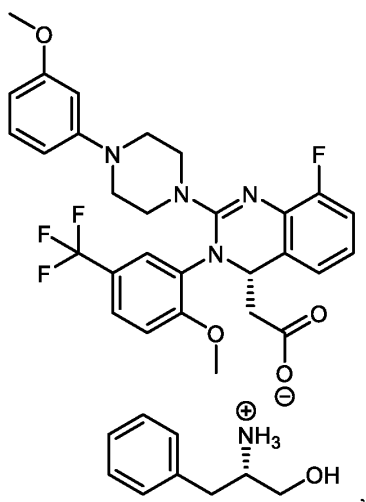
33. The Letemovir salt of a compound of Formula (I) according to embodiment 32, wherein said salt is selected from the group consisting of (R)-1-hydroxybutan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (S)-1-hydroxy-3-phenylpropan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (1S,2S)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (R)-2-hydroxy-1-phenylethan-1-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (S)-1-hydroxybutan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (S)-1-hydroxyhexan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (S)-1-hydroxypentan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (1S,2S)-1,3-dihydroxy-1-phenylpropan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (R)-2-methoxypropan-1-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (R)-(tetrahydrofuran-2-yl)methanaminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and (S)-[(2R,4S,5R)-5-ethenyl-1-

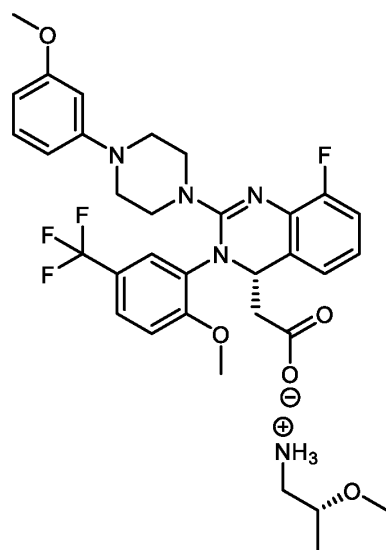
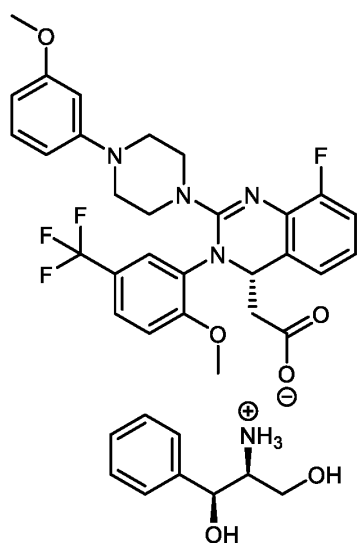
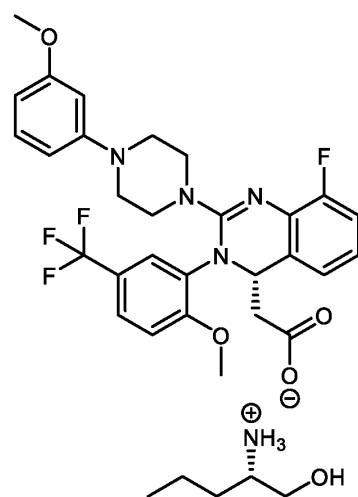
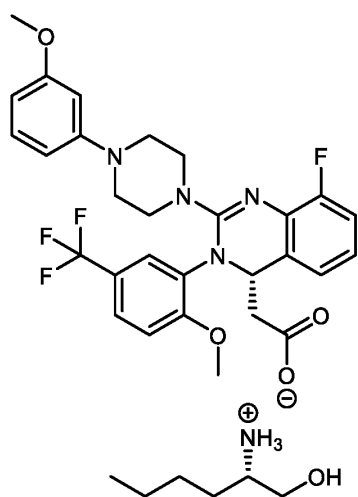
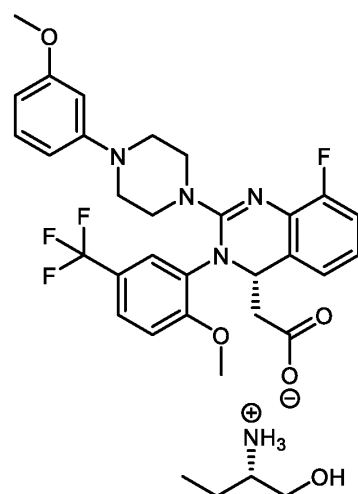
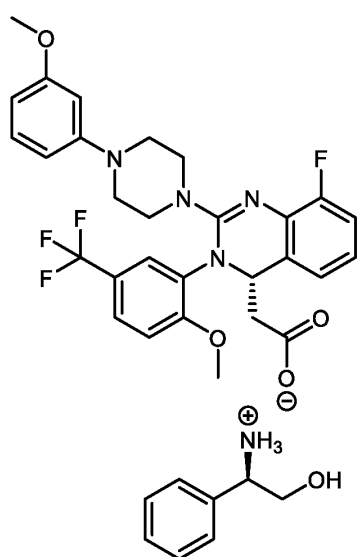
azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinidine) salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1).

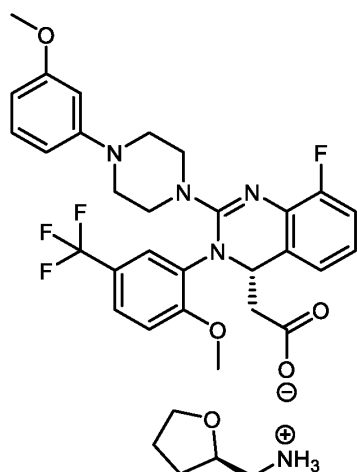
34. The Letemovir salt of a compound of Formula (I) according to embodiment 32, wherein



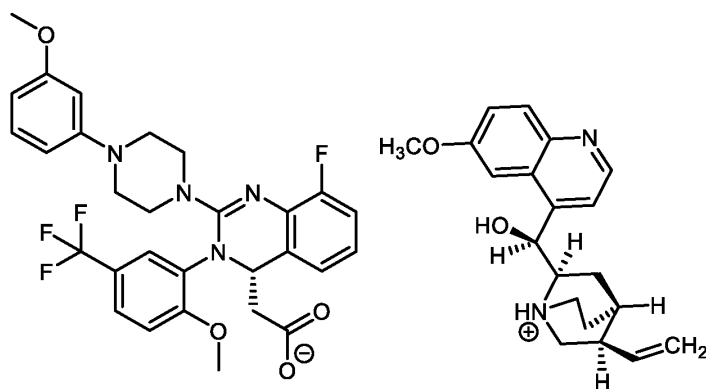
said salt is selected from the group consisting of







and



35. The Letermovir salt of a compound of Formula (I) according to embodiment 32, wherein said salt is (R)-1-hydroxybutan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.1, 8.9, 12.3, 15.3, 16.8, 17.9, 20.6, 21.4 and 22.4 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

36. The Letermovir salt of a compound of Formula (I) according to embodiment 32, wherein said salt is (S)-1-hydroxy-3-phenylpropan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 5.4, 5.8, 14.3, 14.8, 15.2, 17.8, 18.4, 19.1, 19.5, 19.9, 21.4, 21.8 and 22.2 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

37. The Letermovir salt of a compound of Formula (I) according to embodiment 32, wherein said salt is (1S,2S)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 5.8, 8.9, 11.7, 14.4, 17.5, 19.2, 19.8, 20.8 and 21.2 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

38. The Letermovir salt of a compound of Formula (I) according to embodiment 32, wherein said salt is (R)-2-hydroxy-1-phenylethan-1-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 5.6, 5.9, 11.8, 14.5, 15.4, 16.9, 17.5, 18.2, 19.4, 20.5, 21.1 and 21.6 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

39. The Letermovir salt of a compound of Formula (I) according to embodiment 32, wherein said salt is (S)-1-hydroxybutan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.1, 8.9, 12.3, 15.2, 17.6, 17.9, 20.6 and 22.3 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

40. The Letermovir salt of a compound of Formula (I) according to embodiment 32, wherein said salt is (S)-1-hydroxyhexan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.2, 9.9, 12.4, 13.2, 14.6, 16.6, 18.2, 18.8, 19.8, 20.3, 22.6 and 23.9 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

41. The Letermovir salt of a compound of Formula (I) according to embodiment 32, wherein said salt is (S)-1-hydroxypentan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-

dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.3, 9.9, 12.7, 13.3, 14.8, 16.5, 18.4, 18.8, 20.5, 23.0 and 24.2 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

42. The Letermovir salt of a compound of Formula (I) according to embodiment 32, wherein said salt is (1S,2S)-1,3-dihydroxy-1-phenylpropan-2-aminium salt of 2-{(4S)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 5.7, 5.8, 9.3, 11.7, 14.5, 15.3, 18.6, 19.4, 20.6 and 21.1 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

43. The Letermovir salt of a compound of Formula (I) according to embodiment 32, wherein said salt is (R)-2-methoxypropan-1-aminium salt of 2-{(4S)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.0, 9.3, 12.0, 15.2, 17.5, 18.8, 20.4, 21.7 and 25.9 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

44. The Letermovir salt of a compound of Formula (I) according to embodiment 32, wherein said salt (R)-(tetrahydrofuran-2-yl)methanaminium salt of 2-{(4S)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.0, 9.3, 12.0, 15.2, 17.5, 18.7, 20.4 and 21.8 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

45. The R-Enantiomer salt of a compound of Formula (I) according to embodiment 30, wherein said salt is (R)-1-hydroxy-2-methoxypropan-3-aminium salt of 2-{(4R)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 6.0, 9.2, 12.0, 15.2, 17.5, 18.6, 20.4, 21.3, 21.8 and 26.0 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

46. The Letermovir salt of a compound of Formula (I) according to embodiment 32, wherein said salt is (S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinidine) salt of 2-[(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl] acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 4.2, 9.4, 13.4, 14.2, 14.4, 16.5, 16.7, 17.4, 17.7, 18.3, 18.5, 18.8, 19.6, 22.2 and 23.9 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

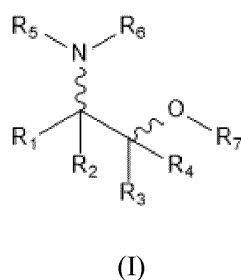
47. The R-Enantiomer salt of a compound of Formula (I) according to embodiment 30, wherein said salt is (R)-[(2S,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinine) salt of 2-[(4R)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl] acetate (1:1) and said salt is characterized by having an X-ray diffraction pattern which comprises 2-theta angle values of: 5.1, 9.9, 13.3, 13.5, 15.4, 15.7, 16.0, 16.8, 17.2, 18.0, 18.7, 19.1, 20.4, 21.4 and 22.6 degrees, and said 2-theta angle values have a normal deviation of $\pm 0.1^\circ$.

CLAIMS

1. A method for producing 2-{(4S)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid (“Letermovir”) or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof, comprising the steps:

i) providing a mixture comprising Letermovir and 2-{(4R)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid (“R-Enantiomer”) or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;

ii) contacting said mixture with an enantiomerically enriched compound of Formula (I)



wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl,

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

wherein R₁ and R₇ together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇ together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring, thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I),

iii-1) separating the Letemovir salt of the compound of Formula (I);

iv-1) converting the Letemovir salt of the compound of Formula (I) into Letemovir or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof; and optionally

v-1) isolating Letemovir or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof.

2. The method for producing Letemovir according to claim 1, wherein said Letemovir is in an amorphous state and wherein said method further comprises precipitation of Letemovir obtained in step iv-1) or v-1) from a solvent selected from the group consisting of acetic acid, formic acid, triethylamine, ethyl acetate, butyl acetate, methyl acetate, isobutyl acetate, propyl acetate, isopropyl acetate, ethyl formate, isopropanol, 1-propanol, n-pentanol, ethanol, methanol, n-butanol, 2-butanol, 2-methyl-1propanol, 3-methyl-1-butanol, tert-butanol, cyclohexanone, acetone, methyl ethyl ketone, 3-pentanone, methyl butyl ketone, methyl isobutyl ketone, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, 2-ethoxyethanol, 2-methoxyethanol, ethyleneglycol, formamide, N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, nitromethane, pyridine, sulfolane, tetralin, 1,2-dichloroethane, dichloromethane, 1,1,2-trichloroethane, 1,1,1-trichloroethane, chloroform,

chlorobenzene, toluene, cumene, xylenes, anisole, acetonitrile, N-methyl pyrrolidone, dimethyl carbonate, pentyl acetate, or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, pentane, n-octane, diisopropyl ether, cyclohexane, hexane, methylcyclohexane, tert-butyl methyl ether, ethyl ether, cyclopentyl methyl ether, and water, or mixtures thereof, preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethylcarbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, 3-methyl-1-butanol, N,N-dimethylformamide and xylenes, or mixtures thereof, by an antisolvent selected from the group cyclohexane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether, pentane, n-octane, water and n-heptane, or mixtures thereof, more preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, ethanol, isopropanol, methanol, methyl ethyl ketone, tetrahydrofuran, dioxane, toluene, 3-methyl-1-butanol, *tert*-butanol, N,N-dimethylformamide and dichloromethane or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether and water, or mixtures thereof, even more preferably from a water miscible solvent acetone or acetonitrile into excess stirred water, to obtain amorphous Letemovir, followed by isolation via filtration or centrifugation.

3. A method for producing a Letemovir salt of a compound of Formula (I), comprising the steps:

i) providing a mixture comprising Letemovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;

ii) contacting said mixture with an enantiomerically enriched compound of Formula (I), thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I);

iii-1) separating the Letemovir salt of the compound of Formula (I), wherein the compound of Formula (I) is as defined in claim 1.

4. A method for enantiomeric separation of a mixture comprising Letermovir and R-Enantiomer, comprising the steps:

i) providing a mixture comprising Letermovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;

ii) contacting said mixture with an enantiomerically enriched compound of Formula (I), thereby producing a Letermovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I),

iii-1) separating the Letermovir salt of the compound of Formula (I);

iv-1) transferring the Letermovir salt of the compound of Formula (I) into the compound of Formula (I) and Letermovir and optionally

v-1) isolating Letermovir,

wherein the compound of Formula (I) is as defined in claim 1.

5. The method for enantiomeric separation of a mixture comprising Letermovir and R-Enantiomer according to claim 4, further comprising the steps:

vi-1) isolating the R-Enantiomer salt of the compound of Formula (I);

vii-1) transferring the R-Enantiomer salt of the compound of Formula (I) into the compound of Formula (I) and R-Enantiomer; and optionally

viii-1) isolating R-Enantiomer,

wherein the compound of Formula (I) is as defined in claim 1.

6. A method for enantiomeric separation of a mixture comprising Letermovir and R-Enantiomer, comprising the steps:

i) providing a mixture comprising Letemovir and R-Enantiomer or a salt thereof or a solvate thereof or a solvate of a salt thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof;

ii) contacting said mixture with an enantiomerically enriched compound of Formula (I), thereby producing a Letemovir salt of the compound of Formula (I) and an R-Enantiomer salt of the compound of Formula (I);

iii-2) separating the R-Enantiomer salt of the compound of Formula (I);

iv-2) transferring the R-Enantiomer salt of the compound of Formula (I) into the compound of Formula (I) and R-Enantiomer; and optionally

v-2) isolating R-Enantiomer,

wherein the compound of Formula (I) is as defined in claim 1.

7. The method for enantiomeric separation of a mixture comprising Letemovir and R-Enantiomer according to claim 6, further comprising the steps:

vi-2) isolating the Letemovir salt of the compound of Formula (I);

vii-2) transferring the Letemovir salt of the compound of Formula (I) into the compound of Formula (I) and Letemovir; and optionally

viii-2) isolating Letemovir.

8. The method according to any of claims 4, 5 or 7, wherein said method further comprises precipitation of Letemovir obtained in step iv-1), v-1), vii-2) or viii-2) from a solvent selected from the group consisting of acetic acid, formic acid, triethylamine, ethyl acetate, butyl acetate, methyl acetate, isobutyl acetate, propyl acetate, isopropyl acetate, ethyl formate, isopropanol, 1-propanol, n-pentanol, ethanol, methanol, n-butanol, 2-butanol, 2-methyl-1propanol, 3-methyl-1-butanol, tert-butanol, cyclohexanone, acetone, methyl ethyl ketone, 3-pentanone, methyl butyl ketone, methyl isobutyl ketone, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, 2-ethoxyethanol, 2-methoxyethanol, ethyleneglycol, formamide, N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide, nitromethane, pyridine, sulfolane, tetralin, 1,2-

dichloroethane, dichloromethane, 1,1,2-trichloroethane, 1,1,1-trichloroethane, chloroform, chlorobenzene, toluene, cumene, xylenes, anisole, acetonitrile, N-methyl pyrrolidone, dimethyl carbonate, pentyl acetate, or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, pentane, n-octane, diisopropyl ether, cyclohexane, hexane, methylcyclohexane, tert-butyl methyl ether, ethyl ether, cyclopentyl methyl ether, and water, or mixtures thereof, preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, isobutyl acetate, isopropyl acetate, propyl acetate, butyl acetate, dimethylcarbonate, chlorobenzene, chloroform, 1,2-dichloroethane, dichloromethane, dioxane, ethanol, ethyl formate, isobutanol, isopropanol, methyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methanol, nitromethane, 3-pentanone, 1-propanol, *tert*-butanol, 1,1,1-trichloroethane, tetrahydrofuran, toluene, 3-methyl-1-butanol, N,N-dimethylformamide and xylenes, or mixtures thereof, by an antisolvent selected from the group consisting of cyclohexane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether, pentane, n-octane, water and n-heptane, or mixtures thereof, more preferably from a solvent selected from the group consisting of acetone, acetonitrile, ethyl acetate, ethanol, isopropanol, methanol, methyl ethyl ketone, tetrahydrofuran, dioxane, toluene, 3-methyl-1-butanol, *tert*-butanol, N,N-dimethylformamide and dichloromethane or mixtures thereof, by an antisolvent selected from the group consisting of n-heptane, diisopropyl ether, *tert*-butyl methyl ether, ethyl ether and water, or mixtures thereof, even more preferably from a water miscible solvent acetone or acetonitrile into excess stirred water, to obtain amorphous Letermovir, followed by isolation via filtration or centrifugation.

9. The method according to any of claims 1 to 8, wherein step ii) is carried out in a solid state.

10. The method according to claims 1 to 5, wherein step ii) is carried out in a solid state and separating the Letermovir salt of the compound of Formula (I) in step iii-1) is conducted by means of dissolving the R-Enantiomer salt of the compound of Formula (I) in a solvent selected from the group consisting of ketones, such as acetone, methyl ethyl ketone, cyclohexanone, 4-methylcyclohexanone, 4-methyl-2-pentanone or 3-pentanone; alkanes, such as pentane, hexane, heptane or isooctane; cycloalkanes, such as cyclohexane or cyclopentane; aromatic solvents, such as chlorobenzene, 1,2-dichlorobenzene, cumene, toluene or xylenes; esters such as ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, ethyl propionate, methyl propionate, isoamyl propionate, isobutyl propionate, hexyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate,

cyclohexyl butyrate, benzyl butyrate, isobutyl formate, ethyl formate, ethyl formate, isopropyl formate, butyl formate, pentyl formate, diethylene glycol monoethyl ether acetate and ethylene glycol diacetate; ethers, such as diisopropyl ether, cyclopentyl methyl ether, butyl ether, diethoxymethane, anisole, ethylene glycol dimethyl ether, diethylene glycol diethyl ether or dimethoxyethane; alcohols such as ethanol, methanol, 2-butanol, isopropanol, n-butanol, diethylene glycol, isobutanol, isopentanol or *tert*-butanol; nitriles, such as acetonitrile; and carbonates, such as dimethyl carbonate or diethyl carbonate; or mixtures thereof, preferably selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, and isolating the solid phase comprising the Letermovir salt of the compound of Formula (I).

11. The method according to claims 1 to 5, wherein step ii) is carried out in a solid state and separating the Letermovir salt of the compound of Formula (I) in step iii-1) is conducted by means of dissolving the Letermovir salt of the compound of Formula (I) in a solvent selected from the group consisting of ketones, such as acetone, methyl ethyl ketone, cyclohexanone, 4-methylcyclohexanone, 4-methyl-2-pentanone or 3-pentanone; alkanes, such as pentane, hexane, heptane or isooctane; cycloalkanes, such as cyclohexane or cyclopentane; aromatic solvents, such as chlorobenzene, 1,2-dichlorobenzene, cumene, toluene or xylenes; esters such as ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, ethyl propionate, methyl propionate, isoamyl propionate, isobutyl propionate, hexyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, cyclohexyl butyrate, benzyl butyrate, isobutyl formate, ethyl formate, ethyl formate, isopropyl formate, butyl formate, pentyl formate, diethylene glycol monoethyl ether acetate and ethylene glycol diacetate; ethers, such as diisopropyl ether, cyclopentyl methyl ether, butyl ether, diethoxymethane, anisole, ethylene glycol dimethyl ether, diethylene glycol diethyl ether or dimethoxyethane; alcohols such as ethanol, methanol, 2-butanol, isopropanol, n-butanol, diethylene glycol, isobutanol, isopentanol or *tert*-butanol; nitriles, such as acetonitrile; and carbonates, such as dimethyl carbonate or diethyl carbonate; or mixtures thereof, preferably selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl

propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof, and isolating the solid phase comprising the R-Enantiomer salt of the compound of Formula (I).

12. The method according to any of claims 1 to 8, wherein step ii) is carried out in a liquid phase.

13. The method according to any of claims 1 to 12, wherein the ratio of Letemovir to R-Enantiomer in said mixture in step i) is in the range of from 10:90 to 90:10, preferably from 20:80 to 80:20, more preferably from 30:70 to 70:30, even more preferably from 40:60 to 60:40, most preferred from 45:55 to 55:45.

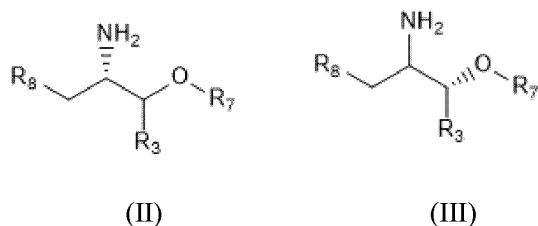
14. The method according to any of claims 1 to 13, wherein said mixture of step i) is racemic 2-{(4R,S)8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetic acid or a salt thereof, or a solvate thereof, or a salt of a solvate thereof or a co-crystal thereof or a solvate of a co-crystal thereof or a salt of a co-crystal thereof or a solvate of a salt of a co-crystal thereof.

15. The method according to any of claims 1 to 8 and 12, wherein step (ii) is carried out in presence of a solvent selected from the group consisting of ketones, such as acetone, methyl ethyl ketone, cyclohexanone, 4-methylcyclohexanone, 4-methyl-2-pentanone or 3-pentanone; alkanes, such as pentane, hexane, heptane or isooctane; cycloalkanes, such as cyclohexane or cyclopentane; aromatic solvents, such as chlorobenzene, 1,2-dichlorobenzene, cumene, toluene or xylenes; esters such as ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, ethyl propionate, methyl propionate, isoamyl propionate, isobutyl propionate, hexyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, cyclohexyl butyrate, benzyl butyrate, isobutyl formate, ethyl formate, ethyl formate, isopropyl formate, butyl formate, pentyl formate, diethylene glycol monoethyl ether acetate and ethylene glycol diacetate; ethers, such as diisopropyl ether, cyclopentyl methyl ether, butyl ether, diethoxymethane, anisole, ethylene glycol dimethyl ether, diethylene glycol diethyl ether or dimethoxyethane; alcohols such as ethanol, methanol, 2-butanol, isopropanol, n-butanol, diethylene glycol, isobutanol, isopentanol or *tert*-butanol; nitriles, such as

acetonitrile; and carbonates, such as dimethyl carbonate or diethyl carbonate; or mixtures thereof, preferably selected from the group consisting of acetonitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, isoamyl propionate, isobutyl propionate, ethyl butyrate, propyl butyrate, amyl butyrate, isoamyl butyrate, diethylene glycol monoethyl ether acetate, ethylene glycol diacetate, cyclohexyl butyrate, benzyl butyrate, diisopropylether, cyclopentyl methyl ether, cumene, isopropanol, 2-butanol, acetonitrile and dimethylcarbonate or mixtures thereof.

16. The method according to any of claims 1 to 15, wherein the enantiomeric purity of said compound of Formula (I) is at least 80% ee, preferably at least 85% ee, more preferably at least 90% ee, more preferably at least 95% ee, more preferably at least 98% ee, most preferred at least 99% ee.

17. The method according to any of claims 1 to 5, wherein the compound of Formula (I) is a compound of formula (II) or (III)



wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

R₇ is H or C₁-C₃-alkyl,

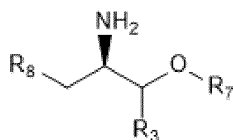
R₈ is selected from the group consisting of H, OH, methyl or ethyl,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

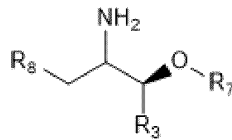
wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein step iii-1) comprises isolating the solid phase comprising the Letermovir salt of the compound of Formula (II) or (III).

18. The method according to any of claims 1 to 5, wherein the compound of Formula (I) is a compound of formula (IV) or (V)



(IV)



(V)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

R₇ is H or C₁-C₃-alkyl,

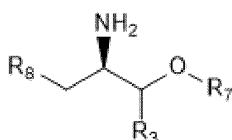
R₈ is selected from the group consisting of H, OH, methyl or ethyl,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

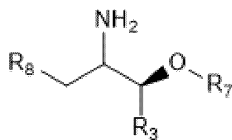
wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein step iii-1) comprises isolating the liquid phase comprising the Letermovir salt of the compound of Formula (IV) or (V).

19. The method according to any of claims 6 or 7, wherein the compound of Formula (I) is a compound of formula (IV) or (V)



(IV)



(V)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

R₇ is H or C₁-C₃-alkyl,

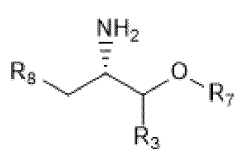
R₈ is selected from the group consisting of H, OH, methyl or ethyl,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

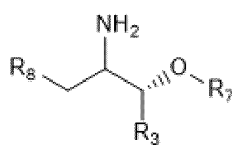
wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein step iii-2) comprises isolating the solid phase comprising the R-Enantiomer salt of the compound of Formula (IV) or (V).

20. The method according to claims 6 or 7, wherein the compound of Formula (I) is a compound of formula (II) or (III)



(II)



(III)

wherein

R₃ is selected from the group consisting of H, C₁-C₃-alkyl and phenyl,

R₇ is H or C₁-C₃-alkyl,

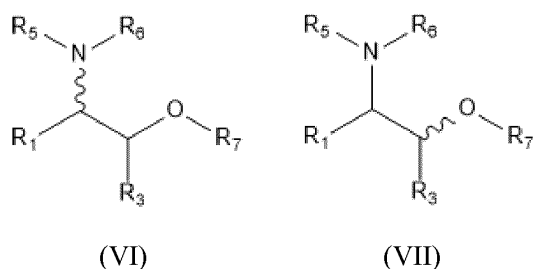
R₈ is selected from the group consisting of H, OH, methyl or ethyl,

wherein R₇ and R₈, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein step iii-2) comprises isolating the liquid phase comprising the R-Enantiomer salt of the compound of Formula (II) or (III).

21. The method according to any of claims 1 to 16, wherein the compound of Formula (I) is a compound of formula (VI) or (VII)



wherein

R₁ is selected from the group consisting of H, C₁-C₃-alkyl and CH₂OH,

R₃ is selected from the group consisting of H, C₁-C₃-alkyl, phenyl and 4-nitrophenyl,

R₅ and R₆ each is independently selected from the group consisting of H and C₁-C₃-alkyl,

R₇ is H or C₁-C₃-alkyl,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₇-oxocyclic ring,

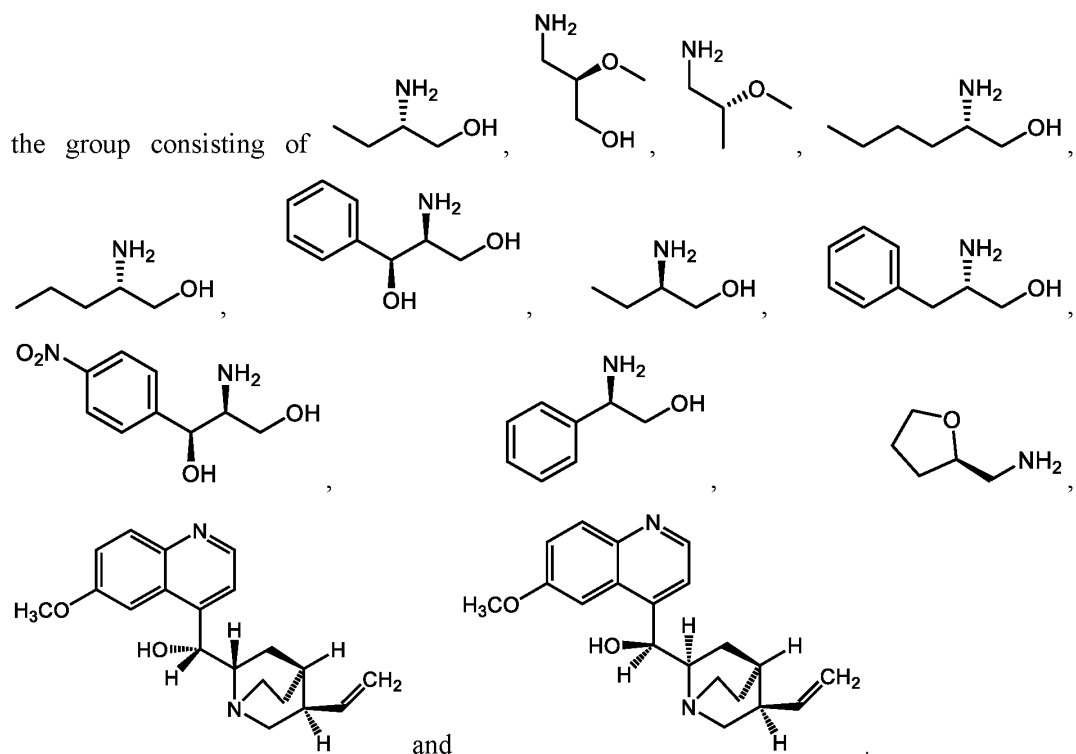
wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl.

22. The method according to claim 21, wherein R₅ and R₆ each is H.

23. The method according to claim 21, wherein the compound of Formula (I) is selected from the group consisting of (S)-(+)-2-Amino-1-butanol, (2R)-3-amino-2-methoxy-propan-1-ol, (R)-2-Methoxypropan-1-amine, (S)-(+)-2-Amino-1-hexanol, (S)-(+)-2-Amino-1-pentanol, (R)-(-)-2-Amino-1-butanol, L-Phenylalaninol, (1S,2S)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol, (R)-(-)-2-Phenylglycinol, (R)-(Tetrahydrofuran-2-yl)methanamine, (1S,2S)-2-amino-1-phenylpropane-1,3-diol, (R)-[(2S,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinine) and (S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol (quinidine).

24. The method according to claim 21, wherein the compound of Formula (I) is selected from



25. The method according to claim 23, wherein the compound of Formula (I) is (S)-(+)-2-Amino-1-butanol and the solvent is pentyl acetate.

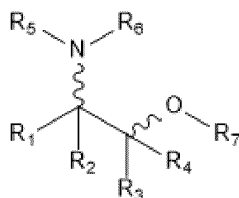
26. The method according to any of claims 1 to 25, wherein said mixture in step i) is the mixture comprising Letemovir and R-Enantiomer, in particular the racemate, which is provided in step i) by means of the following steps:

- a) reacting R-Enantiomer with a C₁-C₂-alcohol in the presence of an acid to obtain an ester of R-Enantiomer, and
- b) treating the ester of R-Enantiomer obtained in step a) with a base to obtain a mixture comprising Letermovir and R-Enantiomer.

27. Use of a compound of Formula (I) for producing Letemovir, wherein the compound of Formula (I) is defined as in claim 1.

28. Use of a compound of Formula (I) for enantiomeric separation of a mixture comprising Letemovir and R-Enantiomer, wherein the compound of Formula (I) is defined as in claim 4.

29. An R-Enantiomer salt of a compound of Formula (I)



(I)

wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinolinyl and methoxyquinolinyl

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

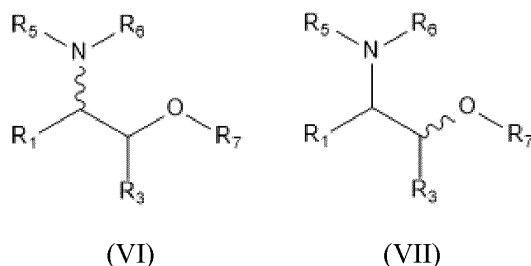
wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring.

30. The R-Enantiomer salt of a compound of Formula (I) according to claim 29, wherein the compound of Formula (I) is a compound of Formula (VI) or (VII)



wherein

R₁ is selected from the group consisting of H, C₁-C₃-alkyl and CH₂OH,

R₃ is selected from the group consisting of H, C₁-C₃-alkyl, phenyl and 4-nitrophenyl,

R₅ and R₆ each is independently selected from the group consisting of H and C₁-C₃-alkyl,

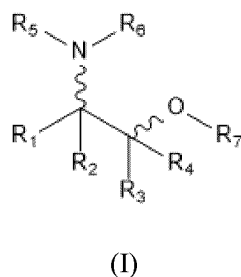
R₇ is H or C₁-C₃-alkyl,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₇-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl.

31. A Letemovir salt of a compound of Formula (I),



wherein

R₁ and R₂ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, methoxyphenyl, benzyl and CH₂OH,

R₃ and R₄ each is independently selected from the group consisting of H, C₁-C₆-alkyl, phenyl, benzyl, 4-nitrophenyl, quinoliny and methoxyquinoliny

R₅ and R₆ each is independently selected from the group consisting of H, C₁-C₆-alkyl and C₃-C₅-cycloalkyl,

R₇ is H or C₁-C₆-alkyl,

wherein R₁ and R₃, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-carbocyclic ring,

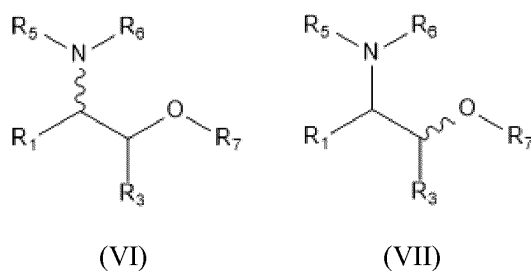
wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring,

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl,

wherein R₅ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring.

32. The Letermovir salt of a compound of Formula (I) according to claim 31, wherein the compound of Formula (I) is a compound of Formula (VI) or (VII)



wherein

R₁ is selected from the group consisting of H, C₁-C₃-alkyl and CH₂OH,

R₃ is selected from the group consisting of H, C₁-C₃-alkyl, phenyl and 4-nitrophenyl,

R₅ and R₆ each is independently selected from the group consisting of H and C₁-C₃-alkyl,

R₇ is H or C₁-C₃-alkyl,

wherein R₁ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₇-oxocyclic ring,

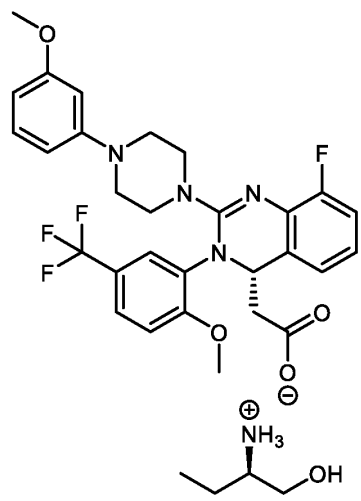
wherein R₃ and R₇, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-oxocyclic ring, and

wherein R₁ and R₅, together with the atoms to which they are attached, are optionally connected to form a C₃-C₆-heterocyclic ring or to form a C₅-C₈-heterobicyclic system, wherein said C₃-C₆-heterocyclic ring or said C₅-C₈-heterobicyclic system is optionally substituted with 1, 2 or 3 groups independently selected from C₁-C₆-alkyl or C₁-C₆-alkenyl.

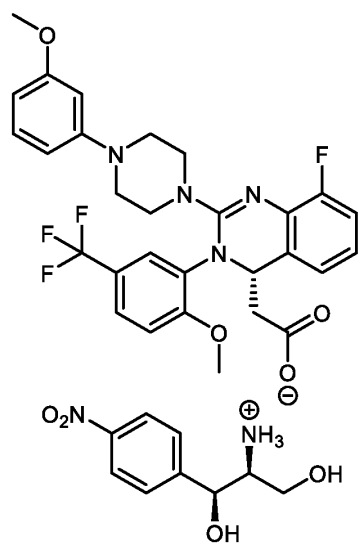
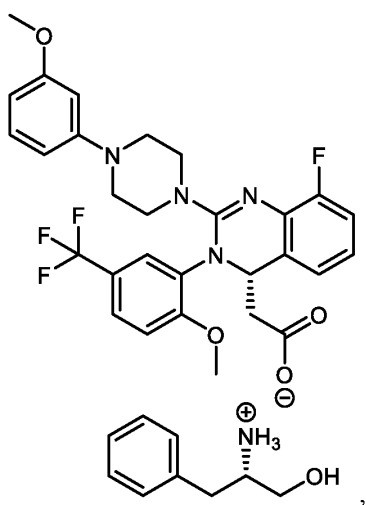
33. The Letermovir salt of a compound of Formula (I) according to claim 32, wherein said salt is selected from the group consisting of (R)-1-hydroxybutan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (S)-1-hydroxy-3-phenylpropan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (1S,2S)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (R)-2-hydroxy-1-phenylethan-1-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (S)-1-hydroxybutan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (S)-1-hydroxyhexan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (S)-1-hydroxypentan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (1S,2S)-1,3-dihydroxy-1-phenylpropan-2-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (R)-2-methoxypropan-1-aminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1), (R)-(tetrahydrofuran-2-yl)methanaminium salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1) and (S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methanol

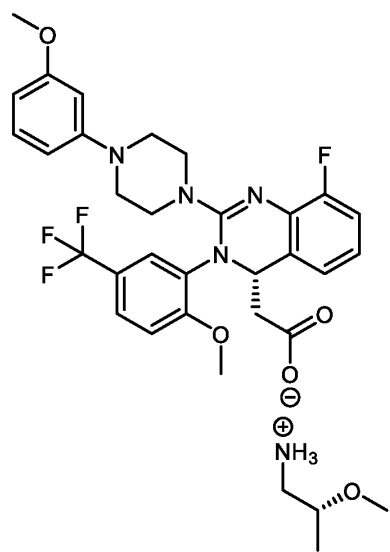
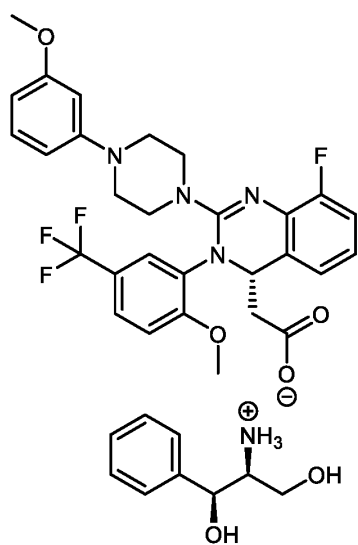
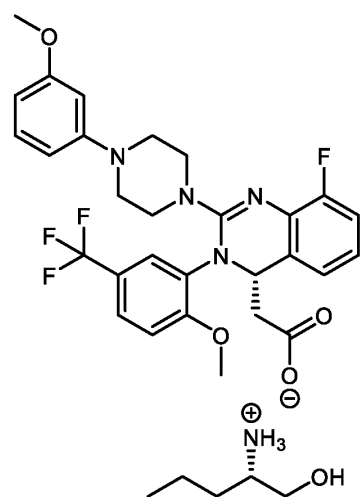
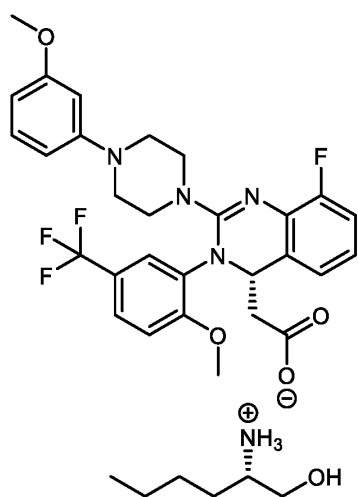
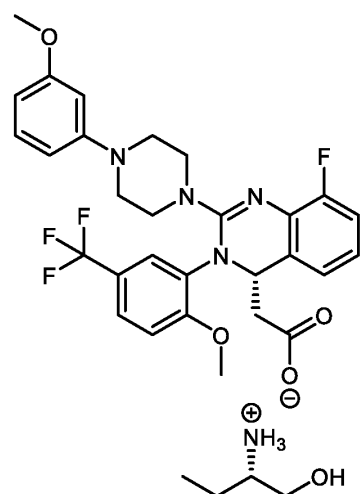
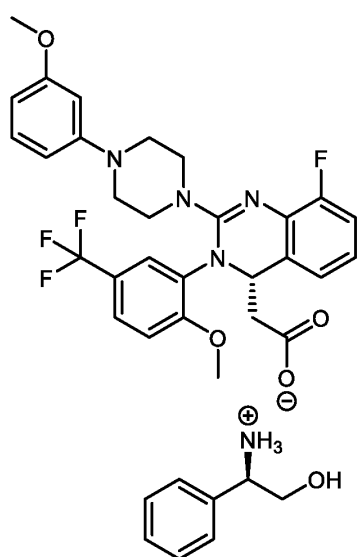
(quinidine) salt of 2-{(4S)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl} acetate (1:1).

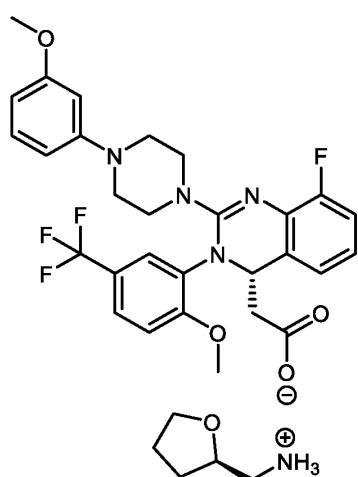
34. The Letermovir salt of a compound of Formula (I) according to claim 32, wherein said salt



is selected from the group consisting of







and

