METHOD OF PREPARING MARIBAVIR

TECHNICAL FIELD OF INVENTION

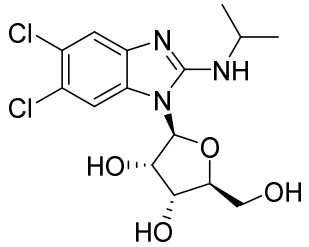
[0001] The present invention relates to compounds useful as antivirals, pharmaceutical compositions thereof, and methods of making said compounds and compositions.

BACKGROUND

[0002] Cytomegalovirus (CMV) is a member of the herpes virus family. Human cytomegalovirus (HCMV) infection is common, with serologic evidence of prior infection in 40% to 100% of various adult populations. However, serious HCMV disease occurs almost exclusively in individuals with compromised or immature immune systems. Cytomegalovirus remains a significant problem for patients undergoing various types of transplants that are associated with the use of potent immunosuppressive chemotherapy, including hematopoietic stem cell transplants (HSCTs) and solid organ transplants (SOTs).

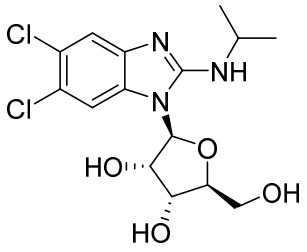
SUMMARY

[0003] Maribavir is a benzimidazole riboside, and is an orally available antiviral medication against CMV. Maribavir is also known under its trade name LIVTENCITY™. Maribavir ((2S,3S,4R,5S)-2-(5,6-dichloro-2-(isopropylamino)-1H-benzo[d]imidazol-1-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol), a compound having the chemical structure:

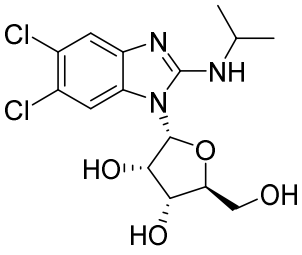


is a potent and orally bioavailable antiviral for the treatment of CMV infection and disease in transplant recipients. Transplant recipients are at significant risk of CMV infection.

[0003a] In one aspect, the disclosure provides a composition comprising maribavir and Compound 4,



maribavir



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wherein Compound 4 is present in an amount of 0.1% w/w or less relative to maribavir.

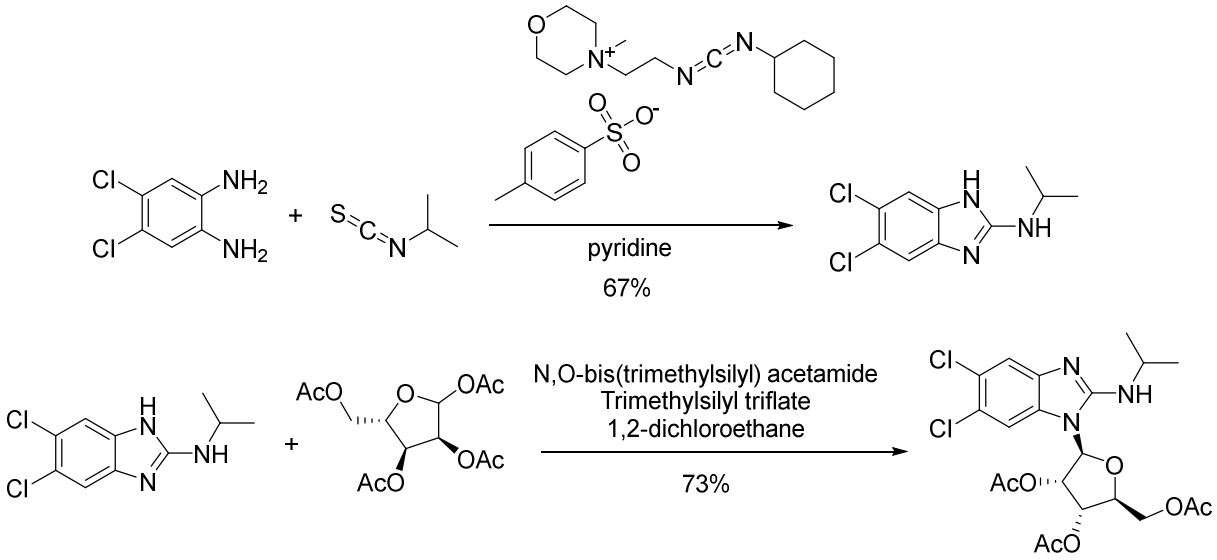
[0003b] In one aspect, the disclosure provides a pharmaceutical composition comprising a composition as disclosed herein and one or more pharmaceutically acceptable excipients.

[0004] The synthesis of maribavir is described in Examples 1, 2, and 5 of US 6,077,832 (the '832 patent). This synthesis, depicted in Scheme 1 below, consists of three chemical transformation steps with a combined yield of about 27%.

’083 publication also discloses a two-step process for providing 2-bromo-5,6-dichlorobenzimidazole.

[0008] US 6,617,315 (the ’315 patent) discloses an alternative route: synthesis of 2-(alkylamino)-1H-benzimidazoles using 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimde metho-*p*-toluenesulfonate as a desulfurizing agent; coupling 2-(alkylamino)-1H-benzimidazoles with 1,2,3,5-tri-O-acetyl-ribofuranose; and deprotection of 2-(alkylamino)-1-(2,3,5-tri-O-acetyl-beta-L-ribofuranosyl-1H-benzimidazoles. *See* General Procedures I, II, and III at columns 27-28 of the ’315 patent. Specifically, the ’315 patent discloses the synthesis of the acetyl-protected intermediate in Scheme 3 at Examples 24 and 25:

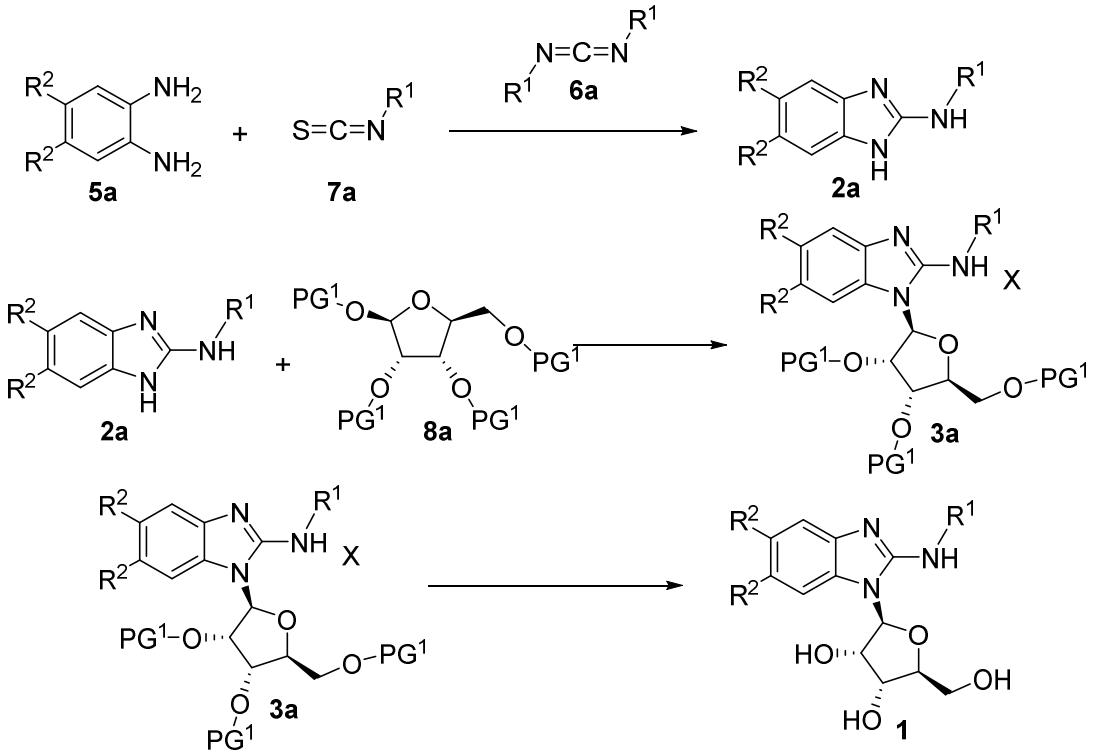
Scheme 3



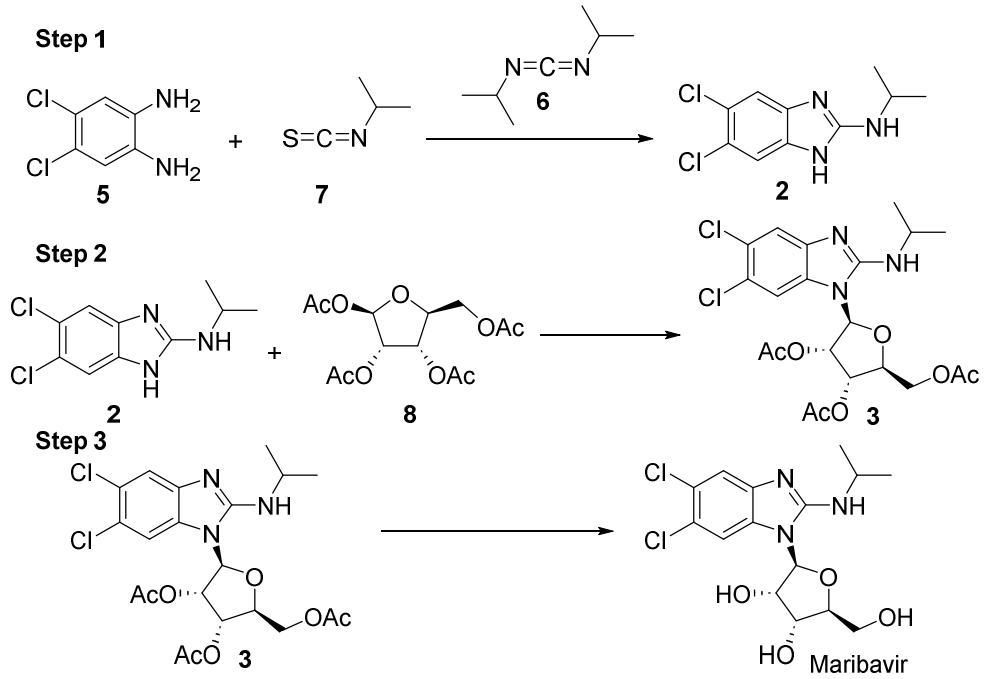
[0009] These two-steps have a combined yield of about 49%. Notably, the ’315 patent does not exemplify deacetylation of 5,6-dichloro-2-(isopropylamino)-1-(2,3,5-tri-O-acetyl-betal-L-ribofuranosyl)-1H-benzimidazole to afford maribavir. While the synthesis disclosed in the ’315 patent appears to be a marked improvement over the syntheses described in the ’832 patent and the ’083 publication, the yield of maribavir is still expected to be below 49% (e.g., 37% when assuming 75% yield for deacetylation as exemplified in the ’832 patent and the ’083 publication).

[0010] Accordingly, in some examples, the present disclosure encompasses the recognition that the synthesis of maribavir can be modified to increase the overall yield. In some examples, maribavir, or a pharmaceutically acceptable salt thereof, is prepared according to Scheme 4 or Scheme 5, set forth below:

Scheme 4



Scheme 5



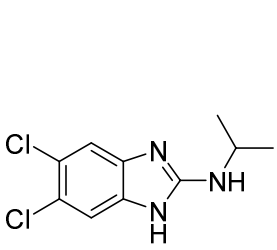
[0011] In some examples, the present disclosure provides an improved synthesis of maribavir in Scheme 5 with overall yields of at least 45%. It will be appreciated that the physical

and/or chemical properties of certain intermediate compounds (e.g., compounds **2**-**3** or **5**-**8**), solvents and/or reagents, as well as reaction conditions may contribute to the overall yield of maribavir and/or help control impurities, particularly when scaling-up the synthesis.

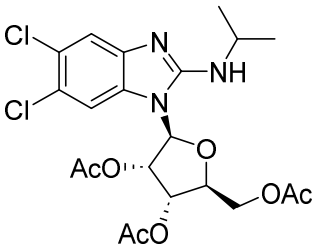
[0012] Additionally or alternatively, the present disclosure also provides the recognition that maribavir of acceptable quality is important to be properly milled and formulated into a tablet. For example, in some examples, a particular polymorphic form of maribavir (e.g., Form VI as disclosed in US 6,482,939) is desired, free of other crystal forms, solvates, or hydrates. In some examples, the present disclosure provides methods of preparing maribavir in a particular polymorphic form (e.g., Form VI as disclosed in US 6,482,939), free of other crystal forms, solvates, or hydrates. Additionally or alternatively, in some examples, the particular size distribution of maribavir is important for tablet manufacture. In some examples, the present disclosure provides methods of preparing maribavir with particular particle size distributions that are amenable for milling and formulating into a tablet. Additionally or alternatively, in some examples, the particular size distribution of maribavir is important for manufacturing an oral solid formulation. In some examples, the present disclosure provides methods of preparing maribavir with particular particle size distributions that are amenable for formulating into an oral solid formulation. Additionally or alternatively, in some examples, the particular size distribution of maribavir may affect bioavailability of maribavir. In some examples, the present disclosure provides a solid oral formulation comprising maribavir polymorphic Form VI having particular particle size distributions (e.g., d(50) is between about about 50 and about 400 μm). In some examples, the present disclosure provides methods of crystallization of maribavir polymorphic Form VI having particular particle size distributions (e.g., d(50) is between about about 50 and about 400 μm).

[0013] Additionally or alternatively, the present disclosure provides the recognition that minimizing certain impurities is important when manufacturing a drug product. For example, impurity profiles should be consistent to maintain consistency of efficacy and minimize potential adverse effects. In some examples, where synthesis of a drug product consists of multiple steps, it will be appreciated that impurities formed in an early step may be carried through subsequent steps to form additional impurities. Therefore, reducing impurities at each step in the synthesis of maribavir (e.g., Steps 1, 2, or 3) is important to maintain consistency in the manufactured drug product.

[0014] Accordingly, in some examples, the present disclosure provides compositions comprising maribavir, or a pharmaceutically acceptable salt thereof, and methods of preparing the same. In some examples, provided compositions comprise maribavir and one or more compounds selected from:

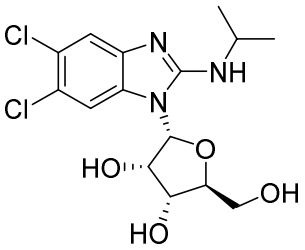


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or



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or pharmaceutically acceptable salts thereof.

[0015] In some examples, provided compositions are prepared according to methods disclosed herein (e.g., Steps 1-3). In some examples, provided composition comprise at least 90%, 95%, 99%, 99.5%, or 99.9% by weight of maribavir. In some examples, provided composition comprise maribavir substantially free of impurities. As used herein, the term "substantially free of impurities" means that the composition or compound contains no significant amount of extraneous matter. Such extraneous matter may include starting materials, residual solvents, or other impurities that may result from the preparation of, and/or isolation of maribavir. In some examples, provided compositions comprise maribavir, or a pharmaceutically acceptable salt thereof, and compound **2**, **3**, and/or **4** in an amount of less than 0.10% (w/w HPLC), relative to maribavir. In some examples, provided compositions comprise maribavir, or a pharmaceutically acceptable salt thereof, and compound **2**, **3**, and/or **4** in an amount of less than 0.10% (w/w HPLC), relative to maribavir. In some examples, provided compositions comprise maribavir, or a pharmaceutically acceptable salt thereof, and compound **2**, **3**, and/or **4** in an amount of less than 0.10% (a/a HPLC), relative to maribavir. In some examples, provided compositions comprise maribavir, or a pharmaceutically acceptable salt thereof, and compound **2**, **3**, and/or **4** in an amount not detectable by HPLC. In some examples, provided compositions comprise maribavir as Form VI, as described in US 6,482,939. In some examples, provided compositions comprise at least 90%, 95%, 99%, 99.5%, or 99.9% by weight of Form VI maribavir. In some examples, provided compositions comprise maribavir substantially free of other polymorphic forms, e.g., as described in US 6,482,939, US 8,546,344, or US 11,130,777. US

8,546,344, or US 11,130,777. In some examples, provided compositions comprise maribavir having a particular size distribution as defined and described herein. Impurities (e.g., intermediates, enantiomeric impurities) would potentially impact drug substance and drug product quality and may represent a risk to the drug product safety. There is a possible impact to patient safety if certain impurities are present in quantities above qualified limits. There are unknown risks to drug product safety for unknown impurities.

BRIEF DESCRIPTION OF THE DRAWING

[0016] Figure 1 displays a plot of Compound **2** purity as a function of input quality, after filtration of the recrystallized Compound **2** (i.e., before the wash steps).

[0017] Figure 2 depicts a plot of Compound **2** (HPLC purity) versus Recrystallization Temperature and Observed Crystallization Temperature (H = high temperature wherein T > 90 °C & L = low temperature wherein T < 40 °C).

[0018] Figure 3 depicts an Interval Plot of Compound **2** versus Recrystallization Temp. The pooled standard deviation is used to calculate the intervals.

[0019] Figure 4 depicts a Contour Plot of Compound **2** purity examining the effects of Recrystallization Temperature and Observed Crystallization Temperature

DETAILED DESCRIPTION

Definitions

[0020] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0021] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely