METHOD OF PREPARING MARIBAVIR

TECHNICAL FIELD OF INVENTION

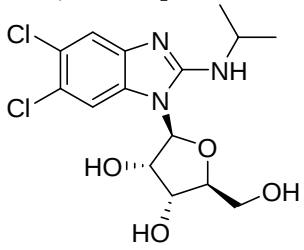
[0001] The present invention relates to compounds useful as antivirals, pharmaceutical compositions thereof, and methods of making said compounds and compositions.

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).

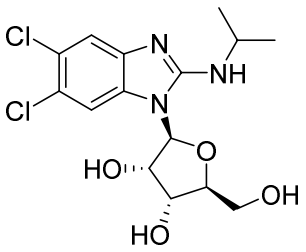
SUMMARY

[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:

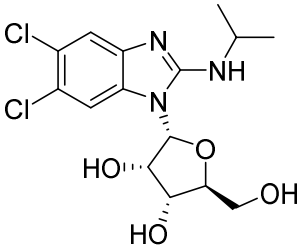


is a potent and orally bioavailable antiviral for the treatment of CMV infection and disease in transplant recipients. Transplant recipients are at significant risk of CMV infection.

[0003a] In one aspect, the disclosure provides a composition comprising maribavir, or a pharmaceutically acceptable salt thereof, and Compound 4, or a pharmaceutically acceptable salt thereof,



maribavir



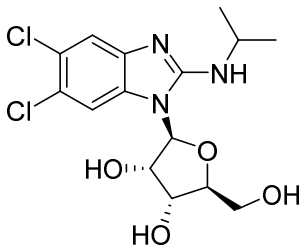
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comprising less than or equal to 0.1% w/w of Compound 4 relative to maribavir.

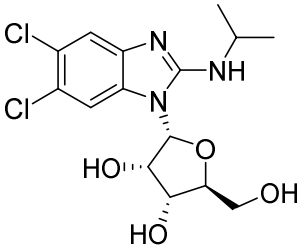
[0004] The synthesis of maribavir is described in Examples 1, 2, and 5 of US 6,077,832 (the '832 patent). This synthesis, depicted in Scheme 1 below, consists of three chemical transformation steps with a combined yield of about 27%.

CLAIMS

1. A composition comprising maribavir, or a pharmaceutically acceptable salt thereof, and Compound 4, or a pharmaceutically acceptable salt thereof,



maribavir



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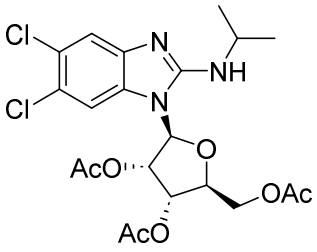
comprising less than or equal to 0.1% w/w of Compound 4 relative to maribavir.

2. The composition of claim 1, comprising 0.01- 0.10% w/w of Compound 4 relative to maribavir.

3. The composition of claim 1, comprising less than or equal to 0.05% w/w of Compound 4 relative to maribavir.

4. The composition of claim 2, comprising 0.02-0.05% w/w of Compound 4 relative to maribavir.

5. The composition of any one of claims 1-4, further comprising Compound 3, or a pharmaceutically acceptable salt thereof,



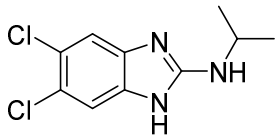
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comprising less than or equal to 0.1% w/w of Compound 3 relative to maribavir.

6. The composition of claim 5, comprising 0.01-0.1% w/w of Compound 3 relative to maribavir.

7. The composition of claim 6, comprising 0.02-0.05% w/w of Compound 3 relative to maribavir.

8. The composition of any one of claims 1-7, further comprising Compound 2, or a pharmaceutically acceptable salt thereof,



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comprising less than or equal to 0.1% w/w of Compound 2 relative to maribavir.

9. The composition of claim 8, comprising 0.01-0.10% w/w of Compound 2 relative to maribavir.

10. The composition of claim 9, comprising 0.01-0.05% w/w of Compound 2 relative to maribavir.

11. The composition of any one of claims 1-10, further comprising D-maribavir, comprising 0.01-0.5% w/w of D-maribavir.

12. The composition of any one of claims 1-11, wherein the maribavir has a particle size distribution (PSD) of d(50) of between 170 and 350 µm.

13. The composition of claim 12, wherein the d(50) is between 170 and 226 µm.

14. The composition of claim 12, wherein the d(50) is between 227 and 280 µm.

15. The composition of claim 12, wherein the d(50) is between 281 and 336 µm.

16. The composition of any one of claims 1-15, further comprising a pharmaceutically acceptable excipient.