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ABACAVIR

Active Pharmaceutical Ingredient

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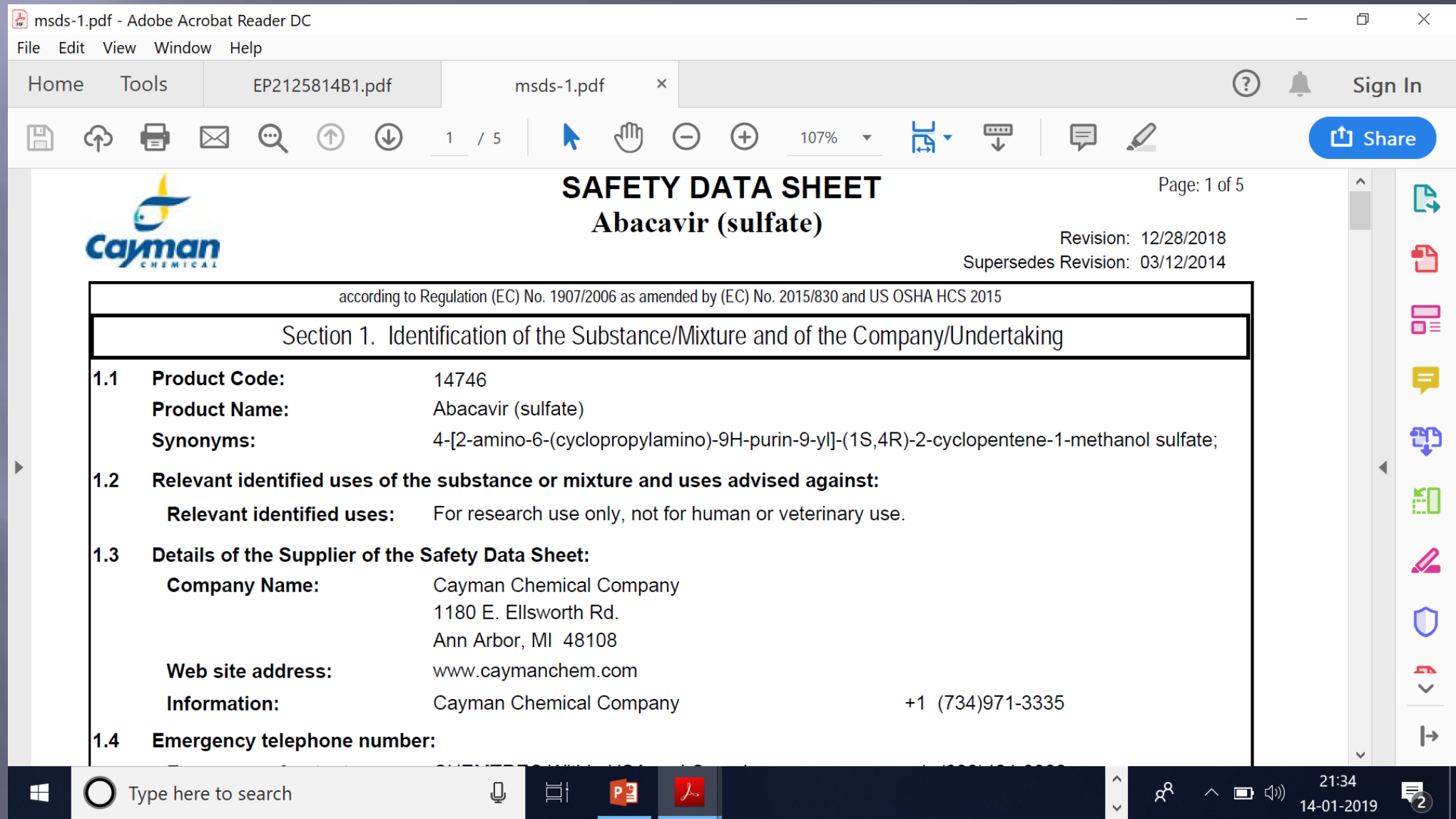
The chemical classification of abacavir is Nucleoside Analog.

- Abacavir (ABC) is a powerful nucleoside analog reverse transcriptase inhibitor (NRTI) used to treat HIV and AIDS. Chemically, it is a synthetic carbocyclic nucleoside and is the enantiomer with 1S, 4R absolute configuration on the cyclopentene ring. In vivo, abacavir sulfate dissociates to its free base, abacavir.
  - The combination HIV medicines abacavir/lamivudine [brand name: Epzicom], abacavir/lamivudine/zidovudine [brand name: Trizivir], and abacavir/dolutegravir/lamivudine [brand name: Triumeq] also contain abacavir
    - Abacavir is in the NRTI class of medications, which work by blocking reverse transcriptase, an enzyme needed for HIV virus replication. Within the NRTI class, abacavir is a carbocyclic nucleoside. Abacavir was patented in 1988 and approved for use in the United States in 1998
      - Lamivudine (Epivir-HBV) is used to treat hepatitis B infection. Lamivudine is in a class of medications called nucleoside reverse transcriptase inhibitors (NRTIs)
        - It works by decreasing the amount of HIV and hepatitis B in the blood.

Manufacturing plant

Company, Product & SDS



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ABSTRACT

A general and efficient synthesis of carbocyclic and hexenopyranosyl nucleosides has been developed. Abacavir and its derivatives as well as hexenopyranosyl nucleoside analogues have been prepared by this sequence. All compounds were purified by column chromatography and were characterized by IR, ^{1}H NMR, ^{13}C NMR and by mass spectral analyses.

INTRODUCTION

Abacavir is a reverse transcriptase inhibitor used for treatment of HIV. Emerging drug-resistant virus strains and toxicity are major problems in antiviral chemotherapy. The presence of impurities, even in small amounts, may influence the quality and safety of the medicine. Impurity profiling (identification and quantification) is now receiving important acute attention from regulatory authorities. The different pharmacopoeias, such as the European Pharmacopoeia (EP), British Pharmacopoeia (BP), and the United States Pharmacopoeia (USP), are slowly incorporating limits to allowable levels of impurities present in the APIs or formulations. The International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances.[**7**] products.[**8**] and residual solvents.[**9**] Impurity and API reference standards are in good demand for both regulatory authorities and pharmaceutical companies. A number of recent articles [10–12] have described a designed approach and guidance for isolating and identifying process related impurities and degradation products using spectral and analytical techniques.

The important step in impurity profiling is the synthesis of the material (impurity standard) with the proposed structure. The synthesized material with the proposed structure is useful for analytical method development and validation. In this perspective, the present paper reports the synthesis and characterization of two potential impurities of Abacavir, *viz.*, Abacavir tert-butyl (**8**) and O-Pyrimidine (**12**) derivative. These impurities were listed in United States Pharmacopeia and to the best of our knowledge until now the synthesis of these impurities has not been reported in the literature.

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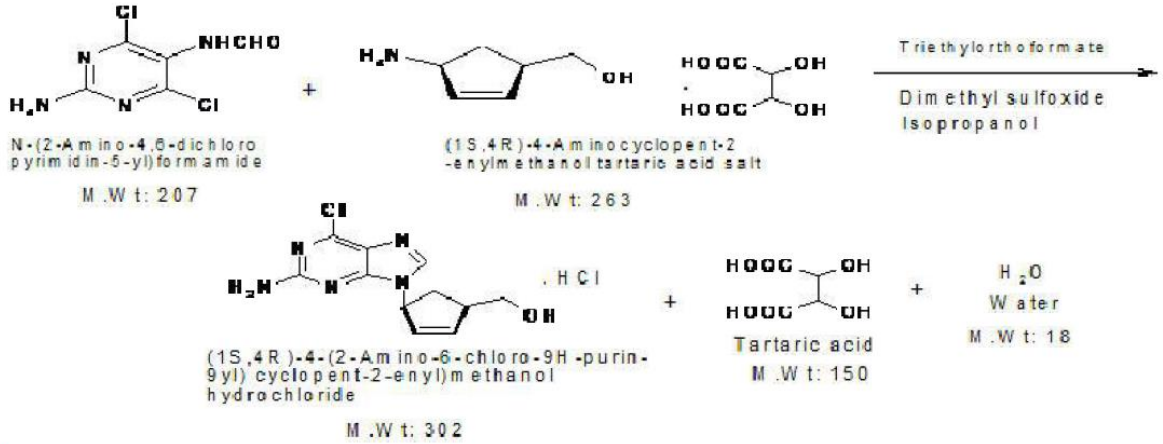
2.1.6 Process Description of Abacavir Sulfate

Reaction Scheme

STAGE-I



STAGE-II

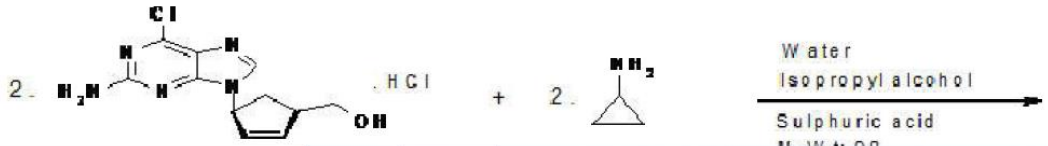


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Table 2.9 Material Balance for Abacavir Sulfate

Stage I

Input	Quantity (Kg/day)	Output	Quantity (Kg/day)	Remarks
N-(2-Amino-4,6-dichloro pyrimidin-5-yl)formamide	4.5	Stage I Product	6.2	To Stage-II
(1S,4R)-4-Aminocyclopent-2 -enylmethanol tartaric acid	5.7	Tartaric Acid	3.1	To Waste water
Triethylorthoformate(TEOF)	10	Water	0.4	To wastewater
Dimethyl sulfoxide(DMSO)	5	IPA Recovered	9.7	Recovery & reuse
Isopropanol(IPA)	10	IPA Loss	0.2	Fugitive loss
Water	30	IPA to Waste Water	0.1	To wastewater
		IPA to Residue	0.1	Solvent in residue
		TEOF Recovered	9.8	Recovery & reuse
		TEOF Loss	0.1	Fugitive loss
		TEOF to Waste Water	0.05	To wastewater
		TEOF to Residue	0.06	Solvent in residue
		DMSO Recovered	5	Recovery & reuse
		DMSO Loss	0.05	Fugitive loss
		DMSO to Waste Water	0.05	To wastewater

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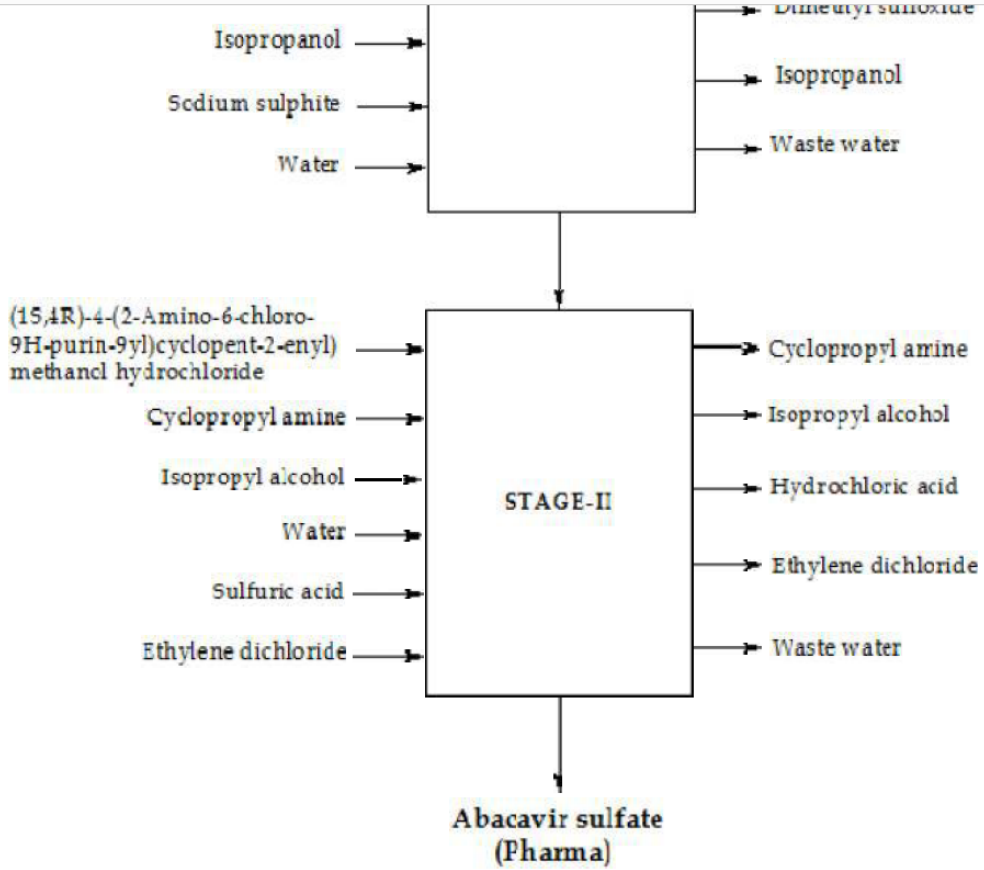

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solution was evaporated and the syrup was dissolved in hot isopropanol (120ml). This mixture was cooled to 0-2 °C and the resulting slurry filtered off. The solid was dried under vacuum at 30 °C. There was obtained 10.97g (73%) of (-)-N-{6-(cyclopropylamino)-9-[(1 R,4S)-4-(hydroxymethyl)cyclopent-2-enyl]-9H-purin-2-yl}isobutyramide as a white powder. HPLC analysis: 95.0% + 3.8% Abacavir.

Example 3: Preparation of abacavir hemisulfate

[0029] N-{6-(cyclopropylamino)-9-[(1 R,4S)-4-(hydroxymethyl)cyclopent-2-enyl]-9H-purin-2-yl}isobutyramide (6.56 g, 18.40 mmol) was slurried in a mixture of isopropanol (32.8 ml) and 10% solution of NaOH (36.1 ml, 92.0 mmol). The mixture was refluxed for 1 h. The resulting solution was cooled to 20-25 °C and tert-butyl methyl ether (32.8 ml) was added. The layers were separated and H_2SO_4 96% (0.61 ml, 11.03 mmol) was added dropwise to the organic layer. This mixture was cooled to 0-5 °C and the resulting slurry filtered off. The solid was dried under vacuum at 40 °C. Abacavir hemisulfate (5.98 g, 97%) was obtained as a white powder.

Example 4: Preparation of abacavir hemisulfate

[0030] N-{6-(cyclopropylamino)-9-[(1 R,4S)-4-(hydroxymethyl)cyclopent-2-enyl]-9H-purin-2-yl)}isobutyramide (6.56 g, 18.40 mmol) was slurried in a mixture of isopropanol (32.8 ml) and 10% solution of NaOH (36.1 ml, 92.0 mmol). The mixture was refluxed for 1 h. The resulting solution was cooled to 20-25 °C and toluene (32.8 ml) was added. The layers were separated and H_2SO_4 96% (0.61 ml, 11.03 mmol) was added dropwise to the organic layer. This mixture was cooled to 0-5 °C and the resulting slurry filtered off. The solid was dried under vacuum at 40 °C. Abacavir hemisulfate (5.42 g, 88%) was obtained as a white powder.

Example 5: Preparation of abacavir

[0031] N-{6-(cyclopropylamino)-9-[(1 R,4S)-4-(hydroxymethyl)cyclopent-2-enyl]-9H-purin-2-yl}isobutyramide (1.0 g, 2.80 mmol) was slurried in a mixture of isopropanol (2 ml) and 10% solution of NaOH (1.1 ml, 2.80 mmol). The mixture

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