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Synthesis and X-ray structural studies of the dextro-rotatory enantiomer of methyl α-5(4,5,6,7-tetrahydro(3,2-*c*)thieno pyridyl) (2-chlorophenyl)-acetate isopropylsulfate

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Abstract

This study resolves conflicting data on a particular salt of the enantiomer of methyl α-5(4,5,6,7-tetrahydro(3,2-*c*)thieno pyridyl) (2-chlorophenyl)-acetate (S(+)clopidogrel). The title compound, $(C_{16}H_{17}ClNO_2S)^+$ $(C_3H_7O_4S)^-$, was obtained and successfully characterized by X-ray diffraction, NMR, TG/DSC/MS. This salt previously reported in the literature as a 2-propanol solvate of the hydrogensulfate salt appears to be actually an isopropylsulfate salt.

Keywords: Clopidogrel; Polymorphism; Solvates; Chirality; Crystal structure

1. Introduction

The importance of polymorphism and solvate formation in the crystallization of organic compounds has an increasing impact in the pharmaceutical sector because they may have very different physical, chemical and biological properties [1]. Polymorphism is defined as the possibility of at least two crystalline arrangements for the same molecules [2]. A solvate is a crystalline material that contains solvent molecules within the crystal structure [3]. Two solvates of the same compound with identical solvent molecules and the same stoichiometry can also exist in different crystal structures. They are then called ''polymorphs of a solvate'' [4]. Every polymorph and solvate is a unique phase having its own physical and chemical properties. Solubility, melting point (when it exists), density, hygroscopicity, color, hardness, or dissolution rate, etc., depend on the nature of the crystalline phase and may have important effect on the processing of drug substances into drug products [3]. Therefore, when an industrial application is at stake, patents can become an issue for the pharmaceutical companies. In this article, we will focus our attention on the dextro-rotatory enantiomer of methyl α- 5(4,5,6,7-tetrahydro(3,2-*c*) thieno pyridyl) (2-chlorophenyl)-acetate (hereafter, S(+)clopidogrel). This compound can be crystallized by using clopidogrel salts as the S(+)clopidogrel hydrogensulfate (hereafter, salt 1) (Fig. 1), which is commercialized as PLAVIX® [5]. Two polymorphic forms of salt 1 are already described in the literature [6]. In 2003, a patent from TEVA Pharmaceuticals Inc. (USA) disclosed four new crystalline forms of salt 1 which are claimed to be ''solvates or polymorphs'' [7]. One year later, another patent from Dinamite Dipharma S.p.A. (Italy) has appropriated TEVA's invention by claiming that these new crystalline forms are, in fact, new salts and not solvates, nor polymorphs of salt 1 [8].

In order to establish the genuine identity of these new compounds, a study has been launched more particularly on the system composed of S(+)clopidogrel, 2-propanol and sulfuric acid. The investigations led to the synthesis

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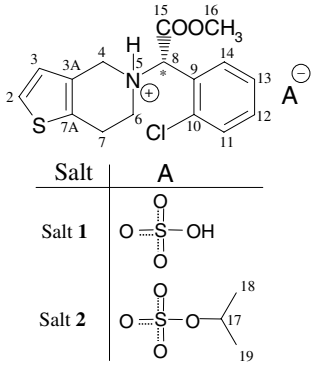

Fig. 1. Sulfate salts of the dextro-rotatory enantiomer of methyl α-5(4,5,6,7-tetrahydro(3,2-*c*)thieno pyridyl) (2-chlorophenyl)-acetate (S(+)clopidogrel).

of S(+)clopidogrel isopropylsulfate (hereafter, salt 2) (Fig. 1). The synthesis as well as the analyses by X-ray diffraction, differential scanning calorimetry and nuclear magnetic resonance are described in this paper.

2. Experimental

2.1. Differential scanning calorimetry (DSC) coupled to thermogravimetric (TG) and mass spectroscopy (MS) analysis

Differential scanning calorimetry (DSC) was made on a Setaram 141 with a heating rate of 5 °C/min. DSC coupled to the thermogravimetric (TG) analysis was performed on a TG/DSC NETZSCH STA 409 PC/PG instrument. Samples (15–20 mg) were put in a 30 μl open aluminum crucible and melted under a heating rate of 2 °C/min. N_2 purging gas was used. DSC coupled to TG and mass spectroscopy (MS) analysis was performed on a DSC/TG/MS 111 Setaram instrument.

2.2. Crystal structure determination

A suitable single crystal was obtained from a saturated solution of salt 2 in DMF at room temperature by a lowering of temperature to 4 °C. Single crystals were isolated and stuck on a glass fiber. Data collection was performed on a Bruker Smart Apex diffractometer at room temperature. Three sets of exposures (1800 frames) were recorded, corresponding to three ω scans, for three different values of ϕ. Unit cell parameters and orientation matrix were determined by means of SMART Software [9]. Intensities were integrated, corrected for Lorentz, polarization and absorption and unit cell parameters were refined by means of SAINT + Software [10]. Space group determination and structure solution were achieved by means of the direct methods and refined with SHELXTL package [11]. Anisotropic displacement parameters were refined for non-hydrogen atoms. Hydrogen atom positions were calculated except for N(5)–H(5) which was located from subsequent difference Fourier synthesis and refined isotropically.

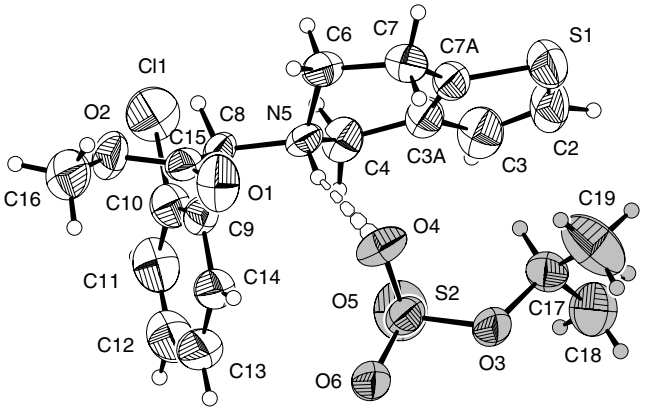

Fig. 2. ORTEP drawing of the asymmetric unit of salt 2 with the numbering scheme. The isopropylsulfate anion is represented with 50% probability grey ellipsoids. The clopidogrel cation is represented with 50% probability white ellipsoids. Hydrogen atoms are represented with an arbitrary radius. The N(5)–H(5)...O(4) hydrogen bond is drawn in dashed line.

2.3. X-ray powder diffraction

Crystalline solid phases were analyzed at room temperature by means of X-ray powder diffraction (XRPD) on a Siemens D5005 apparatus (θ-θ set, fixed slits 1.6 mm) with CuKα radiation (1.54056 Å) (Ni Kβ filter) under 40 kV and

Table 1
Crystal, X-ray data collection and refinement parameters for salt 2

Formula	$(C_{16}H_{17}ClNO_2S)^+$ $(C_3H_7O_4S)^-$
Molecular weight (g mol^{-1})	461.96
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Z	4
Temperature (K)	296(2)
$F(000)$	968
Crystal size (mm)	$0.3 \times 0.05 \times 0.05$
a (Å)	8.267(1)
b (Å)	13.211(1)
c (Å)	20.083(3)
V (Å^3)	2193(1)
μ(MoKα_1) (mm^{-1})	0.399
Calculated density (g cm^{-3})	1.399
θ range	1.85–26.40
Number of reflections	16,706
No. of unique reflections	4485
No. of reflections obsd ($I > 2\sigma(I)$)	2190
Parameters refined	269
R(all) ($I > 2\sigma(I)$)	0.0811(0.0387)
R_w(all)	0.0817
Goodness of fit (all)	0.733
Diff. Fourier residues (e$^-$ Å^{-3}) Max/Min	0.205/−0.259
Flack parameter	0.07(7)

$R = \sum\|F_O| - |F_C\|/\sum|F_O|$, $R_w = [\sum w(F_O^2 - F_C^2)^2 / \sum w(F_O^2)^2]^{1/2}$.