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Journal of Pharmaceutical and Biomedical Analysis 43 (2007) 1573–1575
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Short communication

Isolation and characterisation of a phenolic impurity in a commercial sample of duloxetine

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Received 27 July 2006; received in revised form 15 November 2006; accepted 20 November 2006
Available online 18 December 2006

Abstract

A phenolic impurity of duloxetine hydrochloride was isolated and characterised (MS, NMR, X-ray-analysis).

Keywords: Duloxetine; Impurity; Isolation; Structural characterisation; Mitsunobu

1. Introduction

Duloxetine (**1**) (Fig. 1) is a selective serotonin and norepinephrine reuptake inhibitor and it has been approved for the treatment of major depressive disorder and for the management of diabetic peripheral neuropathic pain. The drug is believed to potentiate serotonergic and noradrenergic activity in the central nervous system. The hydrochloride salt of the (*S*) enantiomer was introduced as a therapeutic agent under the trade name of Cymbalta® (Eli Lilly).

We had in our hands a sample of the active pharmaceutical ingredient (*S*)-**1** hydrochloride whose synthetic history was unknown. We noticed the presence of a phenolic impurity (5%, ^{1}H NMR) that we could isolate by extraction with a 20% sodium hydroxide solution. We now wish to report on the structural characterisation of this impurity [1].

2. Experimental

2.1. Chemicals

Cyclohexane, hydrogen chloride and sodium hydroxide were obtained from Sigma–Aldrich (Milano, Italy). Ethyl acetate and sodium sulphate were obtained from Carlo Erba Reagenti (Milano, Italy).

2.2. Instrumentation

Positive ion ESI-MS was performed on Esquire 3000 plus ion-trap mass spectrometer (Bruker Daltonik, Bremen, Germany) equipped with an ESI source. Sample solutions were introduced into the ion source at a flow rate 4 l m^{-1}, capillary voltage 3.8 kV, drying gas temperature 250 °C, drying gas flow rate 5 l m^{-1} and nebulizer pressure 14 psi. Nitrogen was used as both nebulizing gas and drying gas.

The ESI spectrum was acquired on a Bruker Esquire 3000 plus instrument. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DMX instrument at 305 K. The hydrogen and carbon chemical shifts are referred to the internal tetramethylsilane (TMS). The coupling constants are expressed in Hertz.

2.3. Isolation of the impurity *2·HCl* *[3-(4-hydroxynaphthalen-1-yl)-N-methyl-3-(thiophen-2-yl) propan-1-aminium chloride]*

The hydrochloride salt of duloxetine was suspended in cyclohexane and treated with a 20% sodium hydroxide solution. The aqueous phase was separated, neutralised and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in ether and the solution was saturated with $HCl_{(g)}$, to afford **2·HCl** as a white solid, which was crystallized from methanol.

ESI *m/z*: 298 (M^+(**2**) +1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H, OH), 8.82 (br s, 2H, NH2+), 8.18 (dd, 1H, J = 8.4

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doi:10.1016/j.jpba.2006.11.026

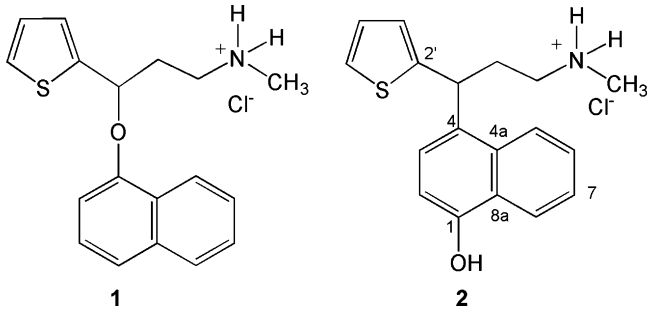

Fig. 1. Structure of duloxetine hydrochloride and of its impurity.

and 1.1 Hz, H8- or H5-naphthalene), 8.13 (d, 1H, $J = 8.4$ Hz, H5- or H8-naphthalene), 7.47 (m, 2H, H6 and H7 naphthalene), 7.34 (d, 1H, $J = 7.7$ Hz, H3-naphthalene), 7.30 (dd, $J = 5.1$ and 1.1 Hz, H5-thiophene), 7.05 (d, 1H, $J = 3.3$ Hz, H3-thiophene), 6.93 (dd, 1H, $J = 5.1$ and 3.3Hz, H4-thiophene), 6.90 (d, 1H, $J = 8.0$ Hz, H2-naphthalene), 5.10 (t, 1H, $J = 7.7$ Hz, CHCH2), 2.87 (m, 2H, CH2N), 2.52 (s, 3H, CH3N), 2.47 (m, 2H, CHCH2). ^{13}C NMR (DMSO-d_6): 152.4 (C_1), 148.8 ($C_{2'}$), 132.0 (C_{4a} or C_4), 129.1 (C_4 or C_{4a}), 126.6 ($C_{4'}$), 126.2 (C_6 or C_7), 125.0 (C_{8a}), 124.4 ($C_{3'}$), 124.3 (C_3), 124.2 (C_7 or C_6), 124.1 ($C_{5'}$), 123.2 (C_8 or C_5), 122.6 (C_5 or C_8), 107.2 (C_2), 46.9 (NCH_2), 37.7 (CH), 32.6 (CH_2), 32.2 (NCH_3).

X-ray analysis: compound **2·HCl** crystallizes in the monoclinic system, space group $P2_1/n$, with cell data: $a = 10.026(1)$, $b = 16.860(2)$, $c = 10.747(1)$ Å, $\beta = 106.35(1)$, $V = 1743.2(3)$ Å^3, $Z = 4$, $D_c = 1.272$ g cm^{-3}, $F(0\,0\,0) = 704$. Intensities data were collected, at room temperature, on a Siemens P4 diffractometer with graphite monochromated Cu Kα radiation ($\lambda = 1.54179$ Å), using $\theta/2\theta$ scan technique, voltage 40 kV, current 40 mA. Unit cell parameters were determined using 84 reflections in the range $14.8 \leq 2\theta \leq 69.6°$. A total of 5637 reflections (2830 unique, $R_{int} = 0.1628$) were collected up to 130° in 2θ and index range: $-10 \leq h \geq 11$, $-19 \leq k \geq 19$, $-12 \leq l \geq 12$. Three standard reflections, monitored every 100 reflections, showed no intensity decay. No empirical adsorption correction was applied.

The structure was solved by direct method using SIR97 program [2] which revealed the position of all non-H atoms. The refinement was carried out on F^2 by full-matrix least-squares procedure with SHELXL97 [3] for 242 parameters, with anisotropic temperature factors for non-H atoms. The final stage converged to $R = 0.0597$ ($R_w = 0.153$) for 1509 observed reflections, with $I \geq 2\sigma(I)$, and $R = 0.0735$ ($R_w = 0.167$) for all reflections after merging the equivalents.

3. Results and discussion

The ESI mass spectrum (positive ions) of **2·HCl** highlighted that the impurity had the same molecular mass as duloxetine hydrochloride, thus showing **2** to be an isomer of **1**.

The diagnostic signal of the proton NMR spectrum was found to be a triplet at 5.10 ppm, attributed to the CH linked to the thiophene ring. This signal resulted to be shifted to higher fields than the corresponding proton in the duloxetine hydrochloride spectrum (6.19 ppm). This information, combined with the lack of an aromatic hydrogen, led to the hypothesis of a migration of the thienylpropylamino chain onto the naphthalene ring, giving rise to a new C–C bond and to the formation of a free phenolic group. X-ray analysis allowed us to confirm our hypothesis and to ascertain that the new C–C bond had been established with the carbon atom in para position respect to the OH group.

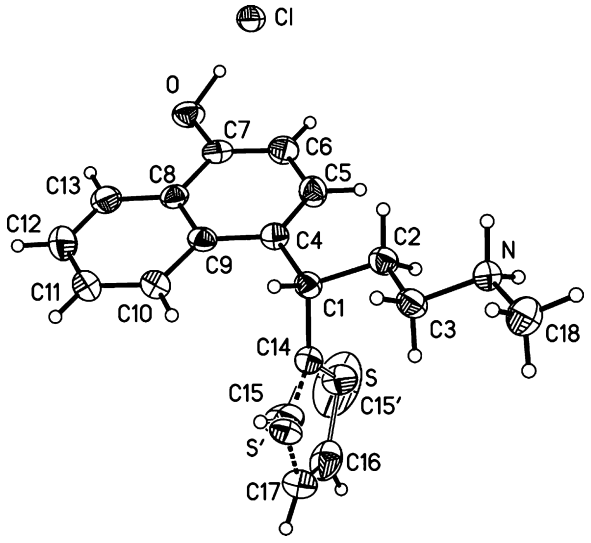

Fig. 2. X-ray structure of impurity **2·HCl**.

Crystallographic analysis determined the molecular geometry of the compound in the solid state. The molecular structure is shown in Fig. 2 and the molecular conformation is illustrated by the selected geometrical parameters reported in Table 1. The

Table 1
Selected geometrical parameters

Bond length (Å)	
O–C7	1.370(4)
N–C3	1.478(4)
N–C18	1.485(4)
S–C14	1.631(8)
S–C17	1.604(4)
Bond angles (°)	
C6–C7–O	123.4(3)
C14–S–C17	96.6(2)
C3–N–C18	114.3(3)
Torsion angles (°)	
C4–C1–C2–C3	167.4(2)
C1–C2–C3–N	−176.6(3)
C2–C3–N–C18	179.6(3)
C5–C4–C1–C2	18.0(4)
C5–C4–C1–C14	−108.0(3)
C4–C1–C14–S	52.7(4)

Hydrogen-bonding geometry (Å, °)

D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
N–H(1N)···Cl#1	0.88(4)	2.27(4)	3.149(3)	175(3)
N–H(2N)···Cl#2	0.96(4)	2.15(4)	3.110(3)	178(3)
O–H(1O)···Cl	1.11(5)	1.96(5)	3.028(3)	162(4)

Symmetry transformations used to generate equivalent atoms: #1, $x-1, y, z$; #2, $-x, -y, -z+2$.

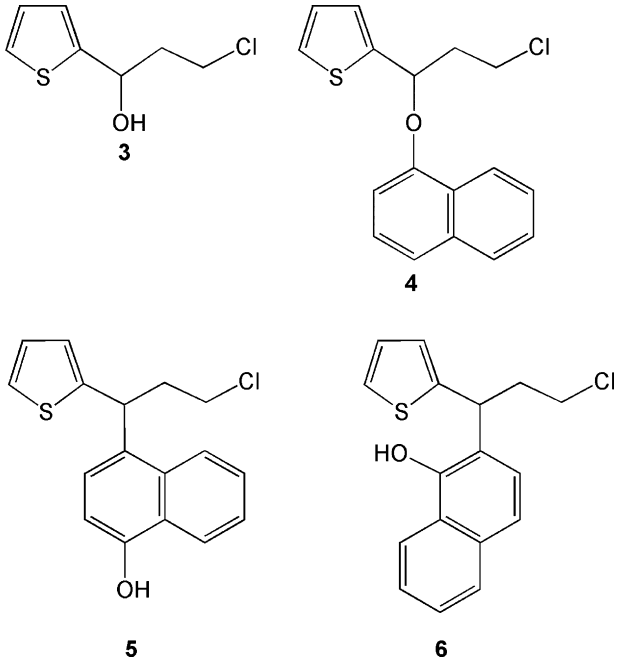

Fig. 3. Structures from ref. [4].

thiophene ring was found to be affected by disorder: within the ring the S and C15 atoms share alternatively the same positions with site occupation factors of about 40 and 60%, respectively. In the crystal, intermolecular short contacts between the hydroxyl and amino H atoms and the Cl atoms give rise to double chains of molecules extending along the *a* axis.

A search in the literature allowed us to find the following information. In 1995, Wheeler and Kuo (Eli Lilly) described [4] that when (*R*)-chloro derivative **3** (Fig. 3) was treated with 1-naphthol under Mitsunobu conditions, a complex mixture of aryl ether **4** and of *ortho*- and *para*-C-alkylated naphthol derivatives **5** and **6** was obtained. The formation of these unusual reaction products **5** and **6** can be tentatively attributed to the ambidentate nature of the nucleophile naphthol, rather than to the occurrence of a rearrangement of naphthyl ether **4**. As a matter of fact, this kind of rearrangement, the so-called photo Claisen reaction, is known to occur under irradiation via a radical mechanism [5]. The presence of impurity **2** in the commercial sample of duloxetine might be related to a side reaction of a Mitsunobu procedure, eventually employed in its preparation.[1]

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[1] One of the reviewers of the work suggested us another hypothesis. He had experimental evidence in his hands that if one attempts a simple elimination reaction in the presence of HCl and THF on structures that are closely related to duloxetine, the same rearrangement, leading to a phenolic compound, takes place as a side reaction.