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Polycyclic compounds by sunlight exposure of the drug rosuvastatin in water

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Abstract

Irradiation of rosuvastatin in water by sunlight or UV lamp (Pyrex) affords cyclic compounds. The main photo-induced reaction is cyclization of the drug to give diastereomeric dihydrobenzoquinazolines. Products derived from side-chain loss were also isolated in the irradiation mixture, and characterized as dihydrobenzoquinazoline and benzoquinazoline derivatives by spectroscopic means. Photoproducts structure elucidation and mechanistic hypothesis are reported.

Keywords: Rosuvastatin; Dihydrobenzoquinazolines; Benzoquinazolines; Photocyclization; Photoxidation

1. Introduction

Rosuvastatin sodium is a statin of new generation that acts as lipid-lowering agent and is widely used in the prevention of cardiovascular events. It works as inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme which catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. This pharmaceutical product is widely prescribed in Europe and in the USA [1,2].

Rosuvastatin presents a *p*-fluorophenyl, a pyrimidinic ring and an unsaturated functionalized side-chain, necessary for the interaction with the active site of the enzyme.

Nowadays, pharmaceuticals and personal care products (PPCPs) are receiving considerable attention as emerging pollutants of the aquatic ecosystem [3]. The continuous introduction of these chemicals in the aquatic environment has been evidenced by the detection of a large number of PPCPs in surface waters in many countries [4,5]. A lot of articles in environmental chemistry reported the occurrence of these compounds, but data on the fate of pharmaceuticals in water are still limited. The large quantities utilized and the bioactive properties of drugs call for a deeper insight on their fate in the environment. Once in water, these chemicals can undergo hydrolytic and photochemical transformations leading to different compounds [6–9]. In such cases the analytical and eco-toxicological investigations should be addressed also to these transformation compounds.

In this context, in a recent work, we have investigated the photochemical behaviour of atorvastatin in water [10]. The data show that the drug is not stable when irradiated by sunlight giving rise to several photoproducts.

In this work the photochemical transformation processes of rosuvastatin in water have been investigated. Here we report the structure elucidation of the transformation products.

2. Experimental

2.1. Chemicals

Rosuvastatin sodium was obtained from KEMPROTEC Limited. This product was used without further treatment. Solutions and suspensions of drugs were prepared using Milli-Q water. All other solvents were of HPLC grade.

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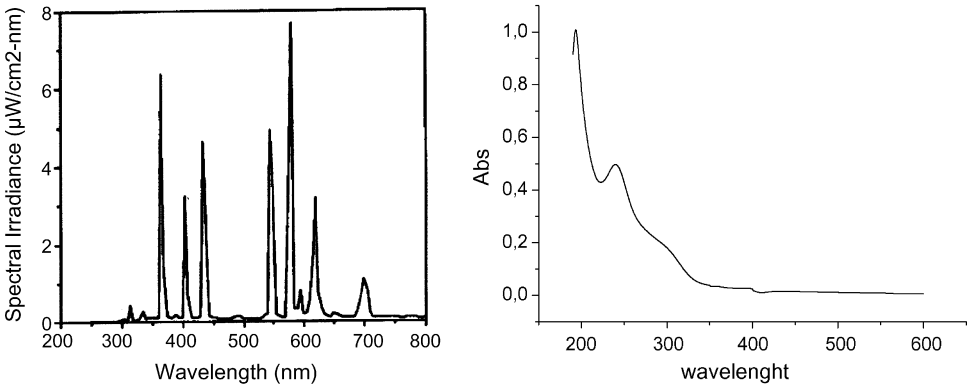

Fig. 1. Emission spectrum Hg lamp and UV spectrum of rosuvastatin in water.

2.2. General procedures

HPLC experiments were carried out on an Agilent 1100 HPLC system equipped with an UV detector, the column used was a RP-18 column (Prodigy Prep ODS, 10 μm, 250 mm × 10 mm). Nuclear magnetic resonance (NMR) spectra were recorded at 500 MHz for [^{1}H] and 125 MHz for [^{13}C] on a Fourier Transform NMR Varian 500 Unity Inova spectrometer and at 400 MHz for [^{1}H] and 100 MHz for [^{13}C] on a Bruker AC 400 spectrometer. The carbon multiplicity was evidenced by DEPT experiments. The proton couplings were evidenced by ^{1}H–^{1}H COSY experiments. The heteronuclear chemical shift correlations were determined by HMQC and HMBC pulse sequences. ^{1}H–^{1}H proximities through space within a molecule were determined by NOESY. UV/vis spectra were recorded in CH_3OH on a Perkin-Elmer Lambda 7 spectrophotometer. Low resolution electron impact mass spectra were obtained operating at 70 eV on a GC–MS (QP-5050A Shimadzu). IR spectra were recorded in CH_2Cl_2 on a Nicolet 5700 FT-IR spectrometer. Analytical TLC was performed on precoated Merck aluminium sheet (DC-Alufolien Kielselgel 60 F_{254}, 0.2 mm) or RP-18 F_{254} plates with 0.2 mm film thickness. The spots were visualized by UV light or by spraying with H_2SO_4–AcOH–H_2O (1:20:4). The plates were then heated for 5 min at 110 °C. Prep. TLC was performed on a Merck Kiesegel 60 F_{254} plates, with 0.5 or 1 mm film thickness.

2.3. Experimental procedure

2.3.1. Rosuvastatin irradiation experiments

Rosuvastatin calcium is slightly soluble in water. Experiments in the dark were conducted on solution (10^{-5} M) or dispersion of the drug (80 ppm) in pure water and in buffered water pH 7 with NaH_2PO_4/Na_2HPO_4.

The preparations were kept in the dark for 1, 4 and 7 days, then the water was concentrated, dissolved with CH_2Cl_2 and filtered on Millex; the residue was analyzed by TLC and ^{1}H NMR.

Solutions of rosuvastatin (10^{-5} M) were exposed to sunlight in water for 4 days on January in Naples in open Pyrex flasks.

Other irradiation experiments were conducted with a photoreactor equipped with a 500 W mercury vapor lamp (Helios Italquarz, emission spectrum shown in Fig. 1), through a Pyrex filter, for 8 h in open Pyrex tube at room temperature under stirring at a distance of 15 cm from the lamp.

A dispersion of rosuvastatin calcium (40 mg in 500 ml of water) was exposed to sunlight for 4 days, the irradiation mixture was dried under vacuum and separated by silica gel TLC-chromatography eluting with CH_2Cl_2/MeOH (95:5) with drops of AcOH (two runs) to obtain three main fractions.

Fraction 1 (5%) was a mixture of polar products in which aromatic functions were absent, fraction 2 (45%) was a diastereomeric mixture and fraction 3 (50%) contained two apolar products.

Separation of the diastereomeric mixture **2** was performed on RP-18 HPLC column eluting with MeOH/H_2O (0.2% HCOOH) (7:3) to obtain pure isomers **2a** (6 mg, 15%) and **2b** (7 mg, 17%).

Two compounds, **3** (12 mg, 30%) and **4** (4 mg, 10%), from fraction 3 were separated by silica gel TLC-chromatography eluting with hexane/CH_2Cl_2 (8:2) (five runs).

2.3.2. Compound *1*

White powder; UV spectrum shown in Fig. 1. ν_{max}($CHCl_3$) 3688, 3612, 3300, 2971, 1596, 1547, 1378 cm^{-1}. ^{1}H and ^{13}C NMR data are listed in Tables 1 and 2.

2.3.3. Compound *2a*

White powder; UV λ_{max} (CH_3OH) nm: 314 (log ε 3.8). ν_{max}($CHCl_3$) 3686, 3602, 3056, 2928, 1724, 1612, 1558, 1383 cm^{-1}; EI-MS (as methyl ester) *m/z* (%): 463 (10), 445 (5), 384 (65), 366 (37), 348 (100). Anal. calcd for $C_{22}H_{28}FN_3O_6S$: C, 54.88, H, 5.82, F, 3.95, N, 8.73. Found: C, 55.00, H, 5.75, F, 3.99, N, 8.77. ^{1}H and ^{13}C NMR data are listed in Tables 1 and 2.

2.3.4. Compound *2b*

White powder; UV λ_{max} (CH_3OH) nm: 312 (log ε 3.8). ν_{max}($CHCl_3$) 3686, 3599, 3056, 2928, 1724, 1612, 1558, 1420, 1383 cm^{-1}; EI-MS (as methyl ester) *m/z* (%): 463 (10), 445 (5), 384 (65), 366 (37), 348 (100). Anal. calcd for $C_{22}H_{28}FN_3O_6S$: C, 54.88, H, 5.82, F, 3.95, N, 8.73. Found: C, 54.92, H, 5.70, F, 3.92, N, 8.73. ^{1}H and ^{13}C NMR data are listed in Tables 1 and 2.