Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular Structure 837 (2007) 252–256
Journal of MOLECULAR STRUCTURE
www.elsevier.com/locate/molstruc

Absolute configuration and structural features of R207910, a novel anti-tuberculosis agent

S. Petit *, G. Coquerel, C. Meyer, J. Guillemont

Sciences et Méthodes Séparatives, UPRES EA 3233 IRCOF, University of Rouen, Rue Tesnière, F-76821 Mont Saint Aignan Cedex, France
Johnson & Johnson Pharmaceutical Research and Development, Campus de Maigremont-BP615, F-27106 Val de Reuil Cedex, France

Received 6 September 2006; received in revised form 31 October 2006; accepted 1 November 2006
Available online 8 December 2006

Abstract

In the structure of R207910 ((1*R*,2*S*)-1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol, $C_{32}H_{31}BrN_2O_2$), the two independent molecules of the asymmetric unit present similar conformations. They are related to each other by a local pseudo-binary axis whose orientation does not correspond to a defined crystallographic direction of the orthorhombic unit cell, giving rise to an unusual type of supersymmetry. Infinite molecular chains are generated by two types of weak intermolecular contacts: Br–Br interactions and π-stacking. The role of these weak contacts and of (CH–π) interactions in the structural cohesion is highlighted, and their possible incidence on supersymmetry is envisaged.

Keywords: Pseudosymmetry; Crystal packing; Weak interactions; Absolute configuration

1. Introduction

Tuberculosis (TB), an infection of *Mycobacterium tuberculosis*, still remains the leading cause of worldwide death among infectious diseases. According to current estimates of the World Health Organization [1], one third of the world's population is infected and millions of people die every year. The current standard regimen of izoniazid, rifampin, and pyrazinamid requires 6–8 months of daily treatment. Patients failures to complete the therapy was responsible for the emergence of multidrug-resistant (MDR-TB) tuberculosis [2]. Consequently, there is an urgent need to discover new drug candidates able to reduce the treatment time and allowing to treat multidrug-resistant patients [3].

Recently, Johnson & Johnson Pharmaceutical Research and Development has discovered the Diarylquinoline class (DARQ) that is highly potent against *M. tuberculosis* and working by a novel mechanism of action. The DARQ compound R207910 ((1*R*,2*S*)-1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol, Fig. 1, see numbering in Fig. 2) blocks the ATP synthase enzyme, depleting the main energy source that mycobacteria use to grow. R207910 is the most promising candidate of the DARQ class, exhibiting a submicromolar minimum inhibitory concentration (MIC) against both *M. tuberculosis* and MDR-TB strains of *M. tuberculosis* [4]. The complete structural characterization of this lead compound in the DARQ family is therefore a key step for a deeper understanding of its mechanism of action, and structural data were used as a validation step of a combined NMR-molecular modelling study aiming at better understanding the conformational behaviour of R207910 in solution [5]. X-ray diffraction analysis was also required for the determination of its absolute configuration. Beyond the study of conformational features, the structural investigations reported here revealed that the crystal packing presents an unusual combination of intermolecular interactions and an interesting case of supersymmetry.

* Corresponding author. Tel.: +33 2 35 52 24 28; fax: +33 2 35 52 29 59.
E-mail address: samuel.petit@univ-rouen.fr (S. Petit).

0022-2860/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.molstruc.2006.11.001

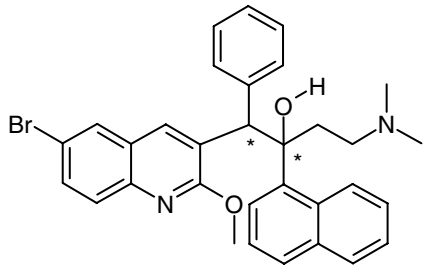

Fig. 1. Chemical diagram of R207910.

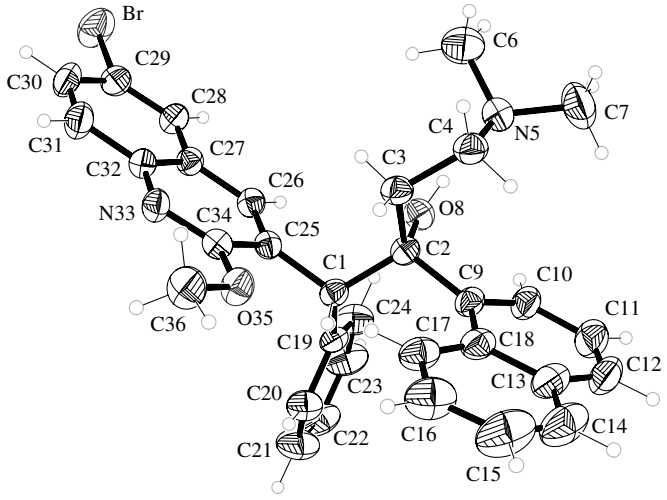

Fig. 2. Atom labelling and displacement ellipsoids at the 30% probability level for molecule A of R207910. Hydrogen atoms appear as small circles with an arbitrary radius.

2. Experimental

Using a sample of R207910 provided by Johnson & Johnson PRD, single crystals suitable for X-ray diffraction measurements could be prepared by slow evaporation at room temperature of saturated solutions obtained in acetonitrile or with solvent mixtures such as ethanol/acetonitrile (20/80) and ethanol/diisopropyl ether (40/60). A colourless tablet-shaped particle collected from the latter solvent mixture was mounted on a glass fibre for structural analysis.

Diffracted intensities were measured using a Bruker SMART APEX diffractometer equipped with a CCD area detector. Cell refinement and data reduction were performed with *SAINT-Plus* [6], and the *SHELXTL* program [7] was used to solve and to refine the structure. After data collection and reduction, no merge of Friedel pairs was performed in view to determine the absolute configurations. During the last refinement steps, several residual peaks corresponding unambiguously to hydrogen atom positions could be identified. However, in order to improve the molecular geometry, only hydrogen atoms bonded to C1, C3, C4 and O8 atoms were localized from Fourier maps. All other H atom positions were calculated from expected bond lengths and angles, and only torsion angles of methyl groups (C6, C7 and C36) were further refined.

For description of structural features and measurement of geometric data, the molecular modelling softwares Cerius^2 [8] and Sybyl [9] were used.

3. Results and discussion

R207910 crystallizes in the orthorhombic system with two independent molecules (denoted A and B) in the asymmetric unit, and therefore belongs to the structural class $P2_12_12_1$, $Z = 8(1^2)$ [10]. The satisfactory accuracy of the structure determination can be assessed from the refinement parameters given with crystal data (Table 1), and from the thermal displacement ellipsoids shown in Fig. 2 for molecule A (molecule B presents similar ellipsoids, see comparison in Table 2). Due to the presence of a bromine atom, the anomalous scattering effects could be used to determine unambiguously (see Flack factor) the absolute configuration of the two chiral carbons as R for (C1) and S for (C2).

Table 1
Crystal data, collection and refinement parameters for R207910[a]

Formula	$C_{32}H_{31}BrN_2O_2$	Crystal size (mm)	$0.94 \times 0.75 \times 0.25$
Molecular weight	555.50	$D_{calc.}$ (Mg m^{-3})	1.311
Crystal system	Orthorhombic	Radiation (Å)	0.71073 (Mo K_α)
Space group	$P2_12_12_1$	μ (mm^{-1})	1.49
Z	8	Crystal habit	Colourless tablet
a (Å)	11.2357(7)	θ range (°)	1.9–26.4
b (Å)	13.7607(9)	h	$-14 \rightarrow 14$
c (Å)	36.411(2)	k	$-17 \rightarrow 17$
V (Å^3)	5629.5 (6)	l	$-44 \rightarrow 45$
Measured reflections	45107	R_{int}	0.039
Independent reflections	11501	Goodness of fit (S)	0.83
Reflections [$I > 2\sigma(I)$]	6352	R_1 [$I > 2\sigma(I)$]	0.036
Refined parameters	681	$wR_2(I)$	0.078
Flack factor	−0.002(5)	$\Delta\rho_{max}/\Delta\rho_{min}$ (e Å^{-1})	0.45/−0.26
Friedel pairs	5108		

[a] CCDC 619587 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).