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Biological activity, structural characterization and crystal packing of chromane-carboxylate derivatives

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Abstract: We report here the crystal and molecular structure of a new chromane-derivative, namely isopropyl(2R*,3S*,4S*)-4-(benzo[d]thiazol-2-ylamino)-2-hydroxy-2-ethylchromane-3-carboxylate (I), $C_{21}H_{22}N_2O_4S$, which crystallizes as racemate in the space group *C*2/c. Its structure has been solved using X-ray diffraction data obtained at low temperature (100(2) K). In this compound, the chromane moiety consists of a benzene ring fused with a six-membered heterocyclic ring which adopts a distorted half-chair conformation. The molecules are linked by a combination of O—H···N and N—H···O hydrogen bonds, resulting in a two-dimensional network which helps stabilizing the crystal structure of the compound (I). Dihedral angle between the chromane and benzothiazol rings is 80.6(1)°.

Keywords: carboxylates, crystal structure, chromane, hydrogen bonding

Introduction

Chromanes (dihydrobenzopyranes) are ubiquitously found in numerous biologically active natural products. Molecules containing a chromane skeleton exhibit a broad range of bioactivities, such as antiviral, antitumor, antimicrobial, sex pheromone, and those of the central nervous system activity (Ellis & Lockhart, 2007; Horton et al., 2003). Among the rich variety of natural prenylated molecules, chromane derivatives, with an extra dihydropyrano ring, represent a family of compounds endowed with most interesting properties (Nicolaou et al., 2000). All these derivatives are generally characterized by low cellular toxicity and good membrane permeability, properties that make them ideal drug template compounds. Some of these derivatives have been shown to inhibit mycobacterial growth (Prado et al., 2007), as promising therapeutic agents for AIDS (Ma et al., 2008) and possesing antitumoral activity (Tanaka et al., 2004; Zou et al., 2005). Recently, the use of chromane derivatives as therapeutic agents in the treatment of cancer and cell proliferative disorders has also been reported (Kwak et al., 2010; Pecchio et al., 2006). Based on these data, the development of novel chromane-like molecules with potentially high biological activity for the design of new drugs or as molecular building blocks for chemical synthesis is a compelling target for pharmaceutical applications. Chromane carboxylates, especially those with quaternary carbons, with multiple applications have been pursued heavily by the pharmaceutical industry. They were seen as leukotriene D4 (LTD4) inhibitors for the treatment of allergic reactions and inflammatory conditions; as peroxisome proliferator activated receptor (PPAR) agonists for treatment of type 2 diabetes and for their antioxidants/antiarrythmic (Lang et al., 2003) activity.

Chromanones are found to exhibit strong activity in inhibiting *in vitro* cell growth of human tumor cells (Lampronti et al., 2003). Many chromanone derivatives are versatile intermediates for the synthesis of natural products such as brazillin, hematoxylin, riparіochromene, clausenin, calonlide A and inophylum B (Koojiman et al.,1984; Ellis et al., 1997; Chenera et al., 1993). It has been suggested that they have significant activity against human immunodeficiency virus type I (HIV-1) (Hussain & Amir, 1986). Chromanone heterocycles have also attracted much attention owing to their important pharmacological properties (Ellis et al., 1977).

Also benzothiazole derivatives possess antitumour properties (Jin et al., 2006; Mortimer et al., 2006; Akhtar et al., 2008). The precise mechanism of

action for these selectively acting compounds has not yet been identified (O'Brien et al., 2003; Choi et al., 2006). It has been postulated that benzothiazoles are metabolized to as-yet unidentified reactive species, which then form DNA adducts causing cancer cell death. The knowledge of geometric parameters, primary sites available for noncovalent interactions, charge distribution, stereoelectronic properties and conformational flexibility is helpful in the determination of the drug molecular interaction mechanisms.

Based on these facts, we report here the crystal structure of compound (I) (Fig. 1), which crystallizes in the centrosymetric monoclinic space group *C*2/c as racemic mixtures (RSS, SRR).

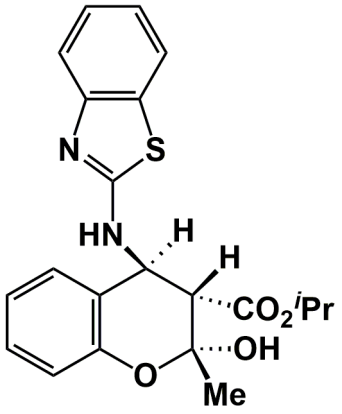

Fig. 1. Molecular structure of compound (I).

Experimental

Compound (I), isopropyl(2R*,3S*,4S*)-4-(benzo[d] thiazol-2-ylamino)-2-hydroxy-2-ethylchromane-3-carboxylate, was prepared according to a standard protocol described in literature (Světlík et al., 2014).

Refinement

Refinement of F^2 against all reflections. The weighted *R*-factor, *wR*, and goodness of fit, S, are based on F^2, conventional *R*-factors, *R*, are based on F with F set to zero for negative F^2. The threshold expression of $F^2 > 2s(F^2)$ is used only to calculate *R*-factors(gt) *etc.* and is not relevant to the choice of reflections for the refinement. *R*-factors based on F^2 are statistically about twice as high as those based on F, and R-factors based on all data are even higher. All H atoms were positioned with idealized geometry using a constrained riding model with C—H distances in the range of 0.95—0.98 Å, N—H = 0.88 Å and O—H = 0.84 Å. The U_{iso}(H) values were set to 1.2 U_{eq}(C-aromatic). Friedel pairs were merged.

Data collection

Crystal data and conditions of data collection and refinement are reported in Tab. 1. CrysAlis CCD (Oxford Diffraction, 2009); cell refinement: CrysAlis RED (Oxford Diffraction, 2009); data reduction: CrysAlis RED (Oxford Diffraction, 2009); program(s) used to solve structure: SHELXS97 (Sheldrick, 2008); program(s) used to refine structure: SHELXL97 (Sheldrick, 2008); molecular graphics: DIAMOND (Brandenburg, 2001);

Tab. 1. Experimental details.

Empirical formula	$C_{21}H_{22}N_2O_4S$
Formula weight	M_r = 398.48
Temperature	100(2) K
Wavelength	λ = 0.71073 Å, MoK_α radiation
Crystal system, space group	Monoclinic, *C*2/*c*
Unit cell dimensions	a = 20.810(1) Å
	b = 9.866(1) Å
	c = 20.671(1) Å
	α = 90 °
	β = 108.75(1) °
	γ = 90 °
Volume	V = 4018.8(5) $Å^3$
Z, Calculated density	8, 1.317 Mg/m^3
Crystal size	0.40 × 0.20 × 0.25 mm
Reflections collected/unique	80176 /4104;
	3767 reflections with I > 2σ(I)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4104/0/256
Goodness-of-fit on F^2	S = 1.04
Final R indices [I > 2sigma(I)]	R1 = 0.034, wR2 = 0.093
Largest diff. peak and hole	0.23 and –0.25 $e.A^{-3}$
Monochromator	Graphite

Tab. 2. Selected geometric parameters: bond lengths [Å].

C1—N1	1.304(1)	C12—C16	1.389(2)
C1—N2	1.344(1)	C13—O2	1.395(2)
C1—S1	1.756(1)	C13—O1	1.434(2)
C2—C3	1.382(2)	C13—C17	1.512(2)
C2—C6	1.392(2)	C13—C14	1.544(2)
C3—C4	1.381(2)	C14—C18	1.513(2)
C4—C5	1.382(2)	C15—C16	1.391(2)
C5—C7	1.388(2)	C16—O1	1.375(2)
C6—N1	1.395(2)	C18—O4	1.206(2)
C6—C7	1.396(2)	C18—O3	1.330(2)
C7—S1	1.750(1)	C19—O3	1.469(2)
C8—N2	1.452(1)	C19—C20	1.501(3)
C8—C15	1.511(2)	C19—C21	1.505(3)
C8—C14	1.527(2)	C10—C11	1.380(3)
C9—C10	1.379(2)	C11—C12	1.371(3)
C9—C15	1.392(2)	C12—C16	1.389(2)

Tab. 3. Selected geometric parameters: bond angles [°].

N1—C1—N2	122.4(1)	C17—C13—C14	113.0(1)
N1—C1—S1	116.0(1)	C18—C14—C8	109.3(1)
N2—C1—S1	121.6(1)	C18—C14—C13	111.0(1)
C3—C2—C6	118.8(1)	C8—C14—C13	110.0(1)
C2—C6—N1	125.2(1)	O1—C16—C12	116.3(1)
C2—C6—C7	119.4(1)	O1—C16—C15	123.1(1)
N1—C6—C7	115.4(1)	O4—C18—O3	124.2(1)
C5—C7—S1	128.9(1)	O4—C18—C14	123.9(1)
C6—C7—S1	109.5(1)	O3—C18—C14	111.8(1)
N2—C8—C15	112.0(1)	O3—C19—C20	105.4(2)
N2—C8—C14	108.5(1)	O3—C19—C21	108.9(2)
O2—C13—O1	108.4(1)	C1—N1—C6	110.5(1)
O2—C13—C17	113.3(1)	C1—N2—C8	126.9(1)
O1—C13—C17	105.1(1)	C16—O1—C13	117.8(1)
O2—C13—C14	108.3(1)	C18—O3—C19	117.2 (1)
O1—C13—C14	108.5(1)	C7—S1—C1	88.6(1)

Tab. 4. Hydrogen-bond geometry (Å, º).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O2—H2W···N1^{i}	0.84	1.97	2.777(1)	160(2)
N2—H2A···O2^{ii}	0.88	2.54	3.157(2)	128(2)
N2—H2A···O4^{ii}	0.88	2.20	3.008(1)	152(2)

Symmetry codes: (i) 3/2 – x; –1/2 + y; 3/2 – z; (ii) 3/2 – x; 1/2 + y; 3/2 – z

software used to prepare material for publication: enCIFer (Allen et al., 2004) and PLATON (Spek, 2009), WinGX (Farrugia, 1999).

Results and Discussion

Molecular geometry and the atom numbering scheme of the title compound are shown in Fig. 2. Crystal packing of the title compound is shown in Fig. 3. Geometric parameters are provided in Tabs. 2 and 3. The expected stereochemistry of atoms C13, C14, C8 was confirmed as R, S, S.

Conformation of the dihydropyran ring in the chroman moiety is close to that of a distorted half-chair, also called a sofa conformation with the Cremer-Pople puckering amplitude Q_T = 0.501(1) Å, θ = 48.4(2)º and φ = 96.9(2)º (Cremer, Pople, 1975). Calculation of the least-squares plane shows that thees rings are puckered in such a manner that the five atoms (O1, C13, C8, C15 and C16) of the dihydropyran ring are coplanar, while atom C14 is deviates by 0.656(2) Å from the mean plane. The chromane and benzothiazol fragments are nearly orthogonal to each other, dihedral angle between the least-squares planes of these fragments ring is 80.6(1)º. In compound (I), atom N2 is sp^2-hybridized, as evidenced by the sum of the valence angles around them (359.9 °). These data are consistent with the conjugation of the lone-pair electrons on the nitrogen atom with the adjacent carbonyl, similarly as observed for amides. In the nine-membered benzothiazol ring, non-H atoms do not deviate markedly from coplanarity; the maximum deviation

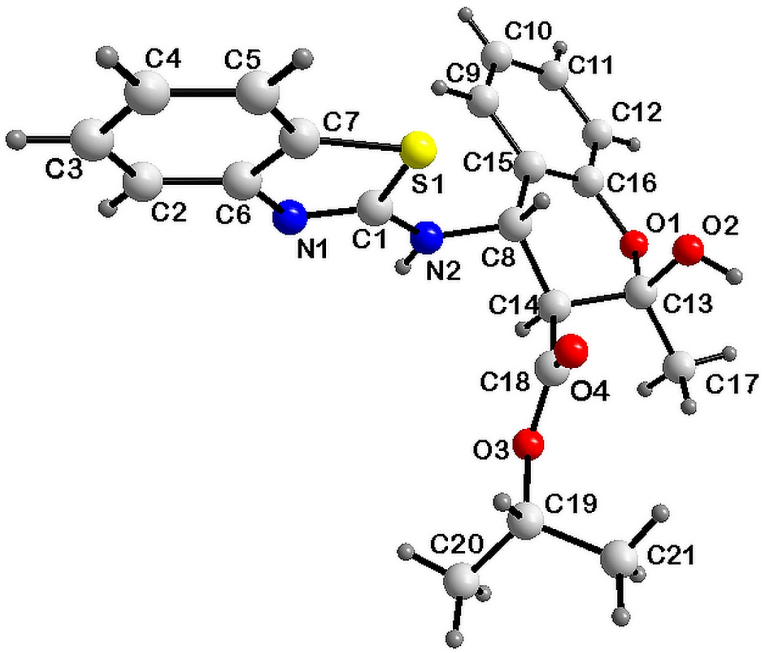

Fig. 2. Molecular structure of compound (I) showing the atom labelling scheme. Displacement ellipsoids are drawn at the 50 % probability level (Brandenburg, 2001).

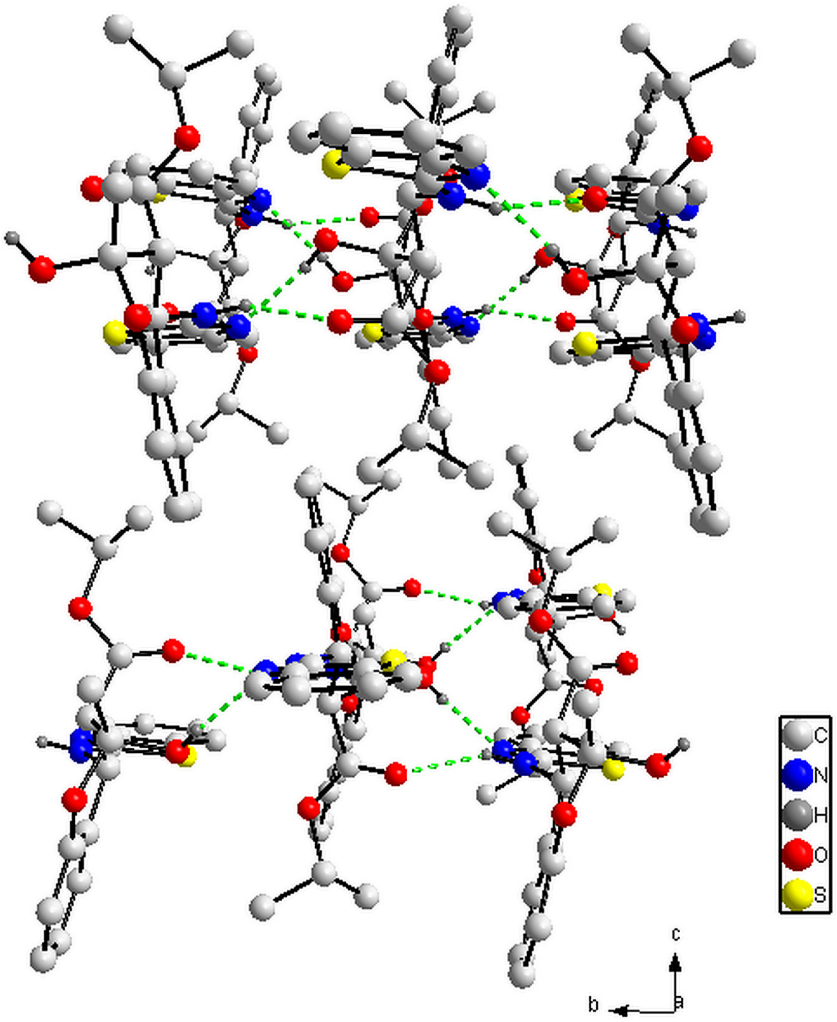

Fig. 3. Part of the crystal structure of (I) showing the formation of hydrogen bond sheets parallel to [010]. Green dashed lines indicate hydrogen bonds. For the sake of clarity, H atoms not involved in the motif shown have been omitted.

from the mean plane of these atoms is exhibited by atom C1[– 0.026 (2) Å].

There are a number of strong and weak intermolecular hydrogen bonds within the crystal structure of (I); their geometric parameters are given in Table 4. The combination of strong intermolecular O2—H2W···N1^{i} [symmetry code: (i) 3/2 – x; –1/2 + y; 3/2 – z] and N2—H2A···O4^{ii} [symmetry code: (ii) 3/2 – x; 1/2 + y; 3/2 – z] hydrogen bonds link into infinite sheets of molecules along the b axis, and generate the $R_2^2(10)$ graph-set motif (Bernstein et al., 1995) (Fig. 3).

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