Crystal and electronic structure, N—H⋯N and C—H⋯O interactions in novel spiro-[chroman-chromene]-carboxylate

Viktor Vrábel[a], Július Sivý[b], Ľubomír Švorc[a], Jan Světlík[c], Šafař Peter[d]

[a]*Institute of Analytical Chemistry, Faculty of Chemical and Food Technology, Slovak Technical University, Radlinského 9, SK-812 37 Bratislava, Slovak Republic*
[b]*Institute of Mathematics and Physics, Faculty of Mechanical Engineering, Slovak University of Technology, Námestie slobody 17, SK-812 31 Bratislava, Slovak Republic*
[c]*Department of Pharmaceutical Analysis and Nuclear Pharmacy, Faculty of Pharmacy, Comenius University, Odbojárov 10, Bratislava, SK-83232, Slovak Republic*
[d]*Institute of Organic Chemistry, Catalysis and Petrochemistry, Faculty of Chemical and Food Technology, Slovak Technical University, Radlinského 9, SK-812 37 Bratislava, Slovak Republic*

viktor.vrabel@stuba.sk

Abstract: We report here the structure of new spiro-derivative, namely methyl (2R,4R)-4-(5-methylthiazol-2-ylamino)spiro[chroman-2,2'-chromene]-3'-carboxylate, $C_{23}H_{20}N_2O_4S$, which crystallizes as racemate in the space group P-1. In this compound, the chromanone 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 N—H⋯N hydrogen bonds and weak C—H⋯O, C—H⋯S, C—H⋯π, inter- and intra-molecular interactions resulting in a two-dimensional network in the crystal structure.

Keywords: carboxylates, crystal structure, spiro chroman-chromene, hydrogen bonding

Introduction

Among the rich variety of natural prenylated molecules, chromane and chromene derivatives with an extra pyrano or dihydropyrano ring represent a family of compounds endowed with most interesting properties (Nicolaou et al., 2000). All these molecules are generally characterized by low cellular toxicity and good membrane permeability, properties that make them ideal drug template compounds. Some of these molecules have been proved to inhibit mycobacterial growth (Prado et al., 2007), to be promising therapeutic agents for AIDS (Ma et al., 2008) and to posses 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. So far, most of such active compounds have been obtained as natural products via direct isolation mainly from higher plants (Ribeiro et al., 2008; Odejinmi et al., 2005). Heterocyclic spiropyrans of different series are substances which potentially possess photochromic properties as a result of reversible opening-closing reactions of

the pyran ring under light (Bertleson, 1971; Durr, 1990; Minkin, 2004). Based on these facts, crystal and electronic structure of the title compound (Fig. 1), which crystallizes in the centrosymmetric triclinic space group P-1 as racemic mixtures (RR, SS), is reported.
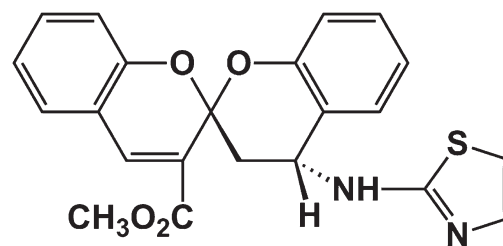

Fig. 1. Molecular structure of the title compound.

Experimental

The title compound, methyl (2R,4R)-4-(5-methyl-thiazol-2-ylamino)spiro[chroman-2,2'-chromene]-3'-carboxylate, was prepared according to a standard protocol described in literature (Světlík et al., 2014).

Refinement

Refinement of F^2 was done against all reflections. The weighted *R*-factor, wR^2, and the 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. 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 larger. All H atoms were positioned with idealized geometry using a constrained riding model with C—H distances in the range of 0.93—0.98 Å and N—H = 0.86 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); software used to prepare material for publication: enCIFer (Allen et al., 2004) and PLATON (Spek, 2009), WinGX (Farrugia, 1999).

Tab. 1. Experimental details.

Empirical formula	$C_{23}H_{20}N_2O_4S$
Formula weight	M_r = 420.47
Temperature	298(2) K
Wavelength	λ = 0.71073 Å , MoK$_\alpha$ radiation
Crystal system, space group	Triclinic, *P*-1
Unit cell dimensions	a = 8.449(3) Å
	b = 9.450(1) Å
	c = 13.816(1) Å
	α = 99.21(1)°
	β = 92.55(2)°
	γ = 105.16(2)°
Volume	V = 1046.6(4) Å^3
Z, Calculated density	2, 1.334 Mg/m^3
Crystal size	0.45 × 0.20 × 0.15 mm
Reflections collected/unique	13557/4265; 3469 reflections with I > 2σ(I)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4265/0/273
Goodness-of-fit on F^2	S = 1.01
Final *R* indices [I > 2sigma(I)]	R1 = 0.039, wR^2 = 0.111
Largest diff. peak and hole	0.17 and –0.20 e.A^{-3}
Monochromator	Graphite

Tab. 2. Selected geometric parameter: bond length [Å].

C1—O1	1.425(2)	C3—N1	1.451(2)
C1—O2	1.426(2)	C18—N2	1.298(2)
C9—O1	1.385(2)	C18—N1	1.350(2)
C17—O2	1.376(2)	C18—S1	1.744(2)
C22—O3	1.205(2)	C19—N2	1.384(2)
C22—O4	1.335(2)	C20—S1	1.740(2)
C23—O4	1.429(3)	C19—C20	1.330(3)

Tab. 3. Selected geometric parameter: bond angle [°].

O1—C1—O2	108.6(1)	O1—C9—C8	115.2(1)
O1—C1—C2	110.9(1)	O1—C9—C4	123.5(1)
O2—C1—C2	104.5(1)	C9—O1—C1	117.1(1)
O1—C1—C10	104.8(1)	O4—C22—C10	111.9(2)
O2—C1—C10	111.5(1)	N2—C18—N1	122.9(1)
O3—C22—O4	122.5(2)	N2—C18—S1	114.2(1)
O3—C22—C10	125.5(2)	N1—C18—S1	122.9(1)
O4—C22—C10	111.9(2)	C20—C19—N2	118.4(2)
C16—C17—O2	118.4(1)	C19—C20—S1	108.1(1)
O2—C17—C12	119.9(2)	C21—C20—S1	121.9(2)
O3—C22—O4	122.5(2)	C18—N1—C3	125.3(1)
O3—C22—C10	125.5(2)	C18—N2—C19	109.7(1)

Tab. 4. Values of net charges at individual atoms and Wiberg bonding indices, I_w, in (I).

Atom	Charge, q	Bond	I_w
C1	–0.046	C1—C2	0.972
C2	–0.080	C2—C3	0.993
C3	–0.085	C3—C4	0.994
C4	–0.098	C4—C5	0.976
C5	–0.252	C6—C7	0.973
C6	0.055	C7—C8A	1.602
C7	–0.336	C8A—C9A	1.272
C8A	–0.110	C9A—C10A	1.629
C9A	–0.118	N1—C1	0.970
C10A	–0.278	N1—C5	1.142
C11	0.348	N1—C6	0.959
N1	0.011	O1—C5	1.739
O1	–0.399	O2—C11	1.073
O2	–0.261	O3—C11	1.827
O3	–0.361	S1A—C7	1.159
S1A	0.403	S1A—C10A	1.183

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

Tab. 5. Hydrogen-bond geometry (Å, °).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N1—H1$\cdots$N2^{i}	0.86	2.16	2.996(2)	164.2
C2—H2B$\cdots$O3	0.97	2.33	2.951(2)	121.1
C11—H11$\cdots$O4	0.93	2.36	2.691(3)	100.7
C3—H3$\cdots$S1	0.98	2.66	3.156(2)	112.0
C15—H15$\cdots$Cg1^{ii}	0.93	2.69	3.580(3)	160.0
C23—H23A$\cdots$Cg2^{iii}	0.93	2.62	3.538(3)	159.0

Symmetry codes: (i) $-x+1$, $-y+2$, $-z+2$; (ii) $-x+2$, $-y+2$, $-z+1$; (iii) $-x+1$, $-y+1$, $-z+1$.

Fig. 3. Geometric parameters are listed in Tabs. 2 and 3. Electron structure of the title compound was calculated by the semi-empirical quantum chemistry method PM3, (Stewart, 2012). Net charges on individual atoms and values of the Wiberg bond indices I_w (Wiberg, 1968) are given in Tab. 4. The expected stereochemistry of atoms C1 and C3 was confirmed as R, R.

Conformation of the dihydropyran ring in the chroman moiety is close to that of a distorted half-chair, also called a sofa conformation with a Cremer-Pople puckering amplitude $Q_T = 0.488(2)$ Å, $\theta = 52.2(2)°$ and $\varphi = 102.0(2)°$ (Cremer, Pople, 1975). Atom C2 is at the apex and deviates by $-0.647(2)$ Å from the mean plane passing through the other atoms (C1, O1, C9, C4 and C3) of the ring. The 2-chromane and 2'-chromene fragments are nearly orthogonal to each other, [the dihedral angle between the least-squares planes of the pyran and dihydropyran ring is 86.8(1)°]. In the compound, atom N1 is sp^2-hybridized, as evidenced by the sum of the valence angles around them (360.1°). These data are consistent with the conjugation of the lone-pair electrons on the nitrogen atom with the adjacent carbonyl, similarly to the observed for amides. Planar thiazole ring bridged by the dihydropyran ring are nearly perpendicular to each other; the relevant dihedral angles are 89.3(1)°. The six-membered spiropyran ring is in an envelope conformation, atom O2 is at the apex and deviates by $-0.382(1)$ Å from the mean plane.

Calculation of the electronic structure provided several indices which characterize the distribution of electron density in the molecule and the multiplicity of atomic bonds. The net charges give a picture of the distribution of electron density in the molecule and the values of the Wiberg bond indices enable estimation of the multiplicity of individual atomic bonds. Evaluation of the experimental interactions of the structure in the solid phase showed that the intra- and intermolecular interactions are the most important in the carboxylate part of the molecule primarily between the intramolecular O3 oxygen and the H2A hydrogen in the compound. It follows from the calculations that atom O3 carries quite a large negative charge (–0.587), while atom H2A has a positive charge (0.218). Charge distribution in the thiazole rings indicates that the positive charge are localized at the sulfur S1 and carbon C18 atoms (0.249) and (0.262) (see Tab. 4). This charge distribution and the spatial arrangement (geometry) of the molecule govern its biological activity and are important for the overall stabilization of the crystal structure. From the Wiberg index values follows that bond C22 = O3 is not purely double but that π-electrons are also delocalized in the carboxylate moiety. Values of the Wiberg indices for bonds S1—C18, $I_w = 1.122$ and S1—C20, $I_w = 1.104$, have the character of partial single or conjugated bonds. Other bonds of the 2-chromane and 2'-chromene fragments have the character of single and conjugated bonds (Tab. 4). Results of these calculations are in good agreement with the experimental values of bond lengths found by X-ray structure analysis. There are a number of strong and weak intra- and intermolecular contacts, together with C—H$\cdots\pi$ contacts within the crystal structure (Tab. 5). In (I), a pair of N1—H1$\cdots$N2^{i} and N2$\cdots$H1—N1^{i} [N$\cdots$N = 2.996(2) Å; symmetry code: (i) 1 – x, –y, –z,] hydrogen bonds connect the two symmetric molecules into cyclic dimers with an $R^2_2(8)$ graph-set motif (Bernstein et al., 1995) (Fig. 3). One molecule of the dimer has an R, R configuration of its stereogenic centre and the other has an S, S configuration, which resulted in inversion-related pairs of the molecules. The acceptor N atoms are part of the amine groups of the respective molecules. In the compound, intramolecular hydrogen bonds between neighboring carboxylate O atoms and pyrane and dihydropyrane hydrogen atoms (C—H$\cdots$O) were observed; their geometric parameters are given in Tab. 5. There are two further intermolecular C—H$\cdots\pi$(arene) hydrogen bonds in (**I**). The molecules are linked into an extensive network in which every molecule acts as both, a hydrogen-bond donor and an acceptor, and the supramolecular assembly takes the form of infinite two-dimensional sheets: H$\cdots$Cg1 (Cg1 is the centroid of the C4 — C9 ben-
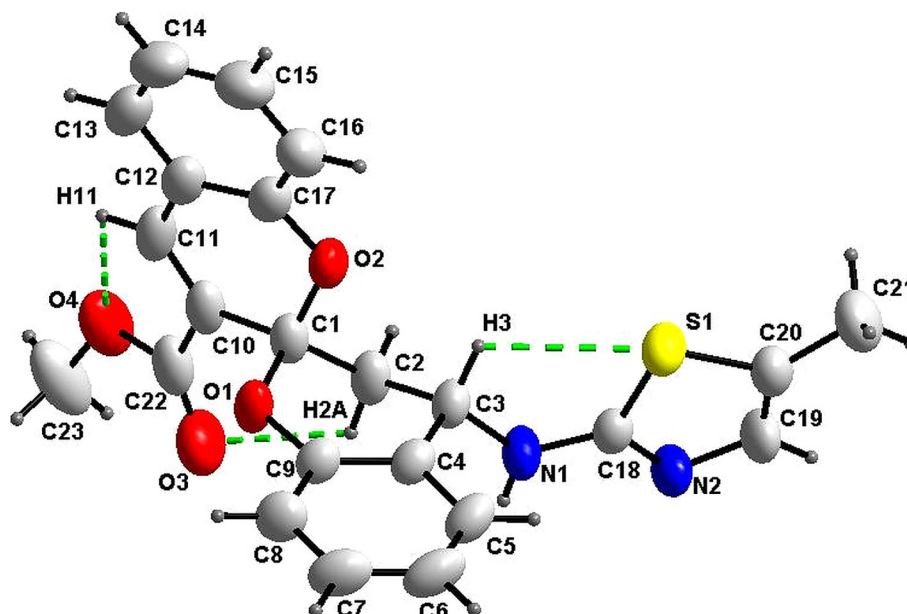
Fig. 2. Molecular structure of the title compound showing the atom labelling scheme. Displacement ellipsoids are drawn at the 50 % probability level (Brandenburg, 2001). The intramolecular hydrogen interaction is shown as a dashed line.
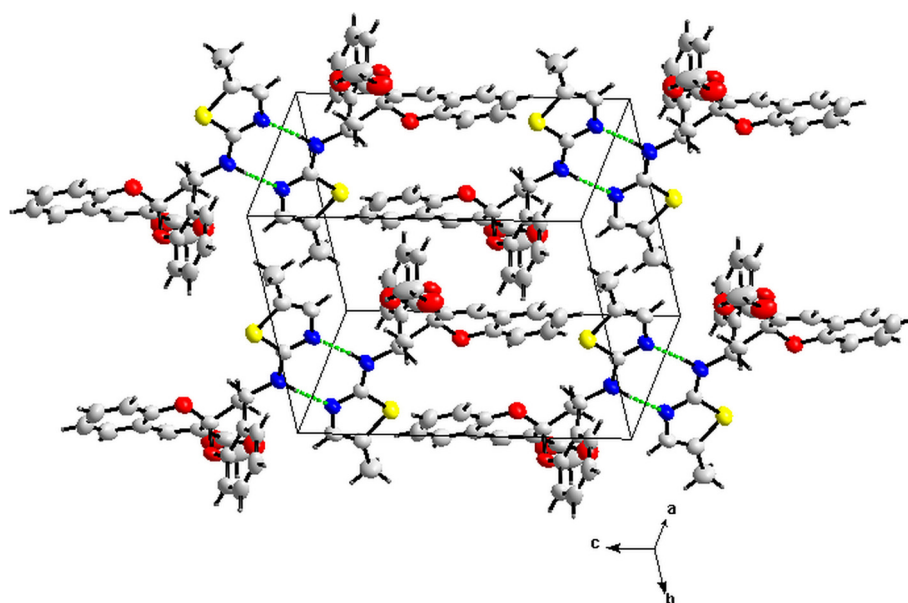

Fig. 3. Stereoview of a part of the crystal structure of the title compound showing the formation of a hydrogen-bonded dimer. Green dashed lines indicate hydrogen bonds.

zene ring) and H · · · *Cg*2 (*Cg*2 is the centroid of the C12 − C17 phenyl ring) (see Tab. 5).

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