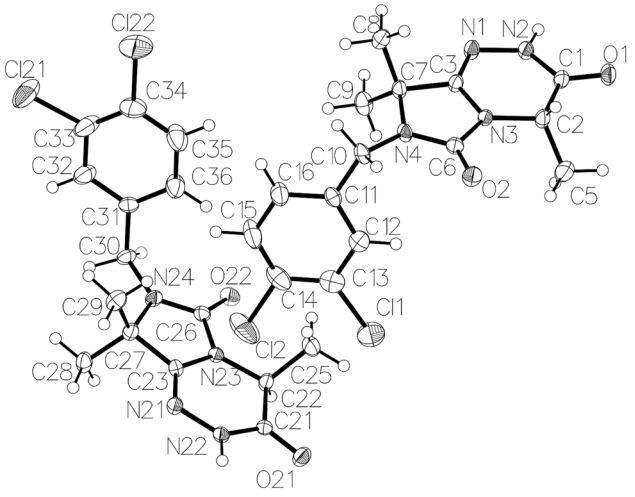
Nikolay T. Tzvetkov*, Martina I. Peeva, Ivanka Tsakovska, Luigi Milella, Ilza Pajeva and Hans-Georg Stammler

The crystal structure of (4*SR*)-7-(3,4-dichlorobenzyl)-4,8,8-trimethyl-7,8-dihydroimidazo[5,1*c*][1,2,4]triazine-3,6(2*H*,4*H*)-dione, $C_{15}H_{16}Cl_2N_4O_2$



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Abstract

$C_{15}H_{16}Cl_2N_4O_2$, monoclinic, $P2_1/c$ (no. 14), a = 26.2014(7) Å, b = 7.59320(10) Å, c = 17.9766(4) Å, β = 109.217(3)°, V = 3377.20(14) Å^3, Z = 8, $R_{gt}(F)$ = 0.0503, $wR_{ref}(F^2)$ = 0.1411, T = 100.0(1) K.

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Table 1: Data collection and handling.

Crystal:	Colorless plate
Size:	0.17 × 0.07 × 0.02 mm
Wavelength:	Cu *K*α radiation (1.54184 Å)
μ:	3.59 mm^{-1}
Diffractometer, scan mode:	SuperNova, ω
θ_{max}, completeness:	76.4°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	51,349, 8782, 0.044
Criterion for I_{obs}, $N(hkl)_{gt}$:	I_{obs} > 2 σ(I_{obs}), 7282
$N(param)_{refined}$:	441
Programs:	CrysAlis^{PRO} [1], Olex2 [2], SHELX [3, 4]

The asymmetric unit of the title crystal structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Source of material

The title compound has been obtained *via* a five-step synthetic procedure using an intramolecular N1–C5 heterocondensation of [3-(3,4-dichlorobenzyl)-4,4-dimethyl-2-oxo-5-thioxoimidazolidin-1-yl]propionic acid ethyl ester with a large excess of hydrazine hydrate (20 equiv.) in dry ethanol as last step [5]. The mixture was stirred under reflux for then hours in the presence of freshly activated molecular sieve 4 Å under argon atmosphere. In a typical condensation reaction 10.0 mg molecular sieve was used for the conversion of 1.00 mmol starting material. After evaporation, the crude product was purified by column chromatography on silica gel (dichloromethane/methanol, 95:5, R_f = 0.49) followed by RP-HPLC (methanol/water, 70:30) to give a pure product as a white solid. Colorless flaky-like crystals suitable for X-ray structure analysis were

***Corresponding author: Nikolay T. Tzvetkov**, Institute of Molecular Biology, "Roumen Tsanev", Bulgarian Academy of Sciences, Acad. G. Bonchev Str., Bl. 21, Sofia 1113, Bulgaria,
E-mail: ntzvetkov@bio21.bas.bg. https://orcid.org/0000-0002-8482-0481
Martina I. Peeva, Institute of Molecular Biology "Roumen Tsanev", Bulgarian Academy of Sciences, Acad. G. Bonchev Str., Bl. 21, Sofia 1113, Bulgaria
Ivanka Tsakovska and Ilza Pajeva, Department of QSAR and Molecular Modelling, Institute of Biophysics and Biomedical Engineering, Bulgarian Academy of Sciences, Acad. G. Bonchev Str., Bl. 105, Sofia 1113, Bulgaria. https://orcid.org/0000-0003-1389-1685 (I. Tsakovska). https://orcid.org/0000-0001-5412-1586 (I. Pajeva)
Luigi Milella, Department of Science, University of Basilicata, via dell'Ateneo Lucano 10, 85100 Potenza, Italy; and Spinoff Bioactiplant, University of Basilicata, via dell'Ateneo Lucano 10, 85100 Potenza, Italy. https://orcid.org/0000-0002-5874-1237
Hans-Georg Stammler, Department of Chemistry, University of Bielefeld, Universitätsstrasse 25, D-33615 Bielefeld, Germany

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
Cl1[a]	0.24064 (6)	0.8803 (2)	0.54017 (9)	0.0601 (4)
Cl2	0.20413 (4)	0.90910 (16)	0.34773 (7)	0.0618 (3)
Cl3[b]	0.28647 (10)	0.7416 (4)	0.25871 (12)	0.0443 (7)
O1	0.44535 (10)	0.0447 (3)	0.86184 (11)	0.0312 (4)
O2	0.44157 (10)	0.6376 (2)	0.70472 (12)	0.0339 (5)
N1	0.42112 (10)	0.0409 (3)	0.65427 (12)	0.0232 (4)
N2	0.42767 (10)	−0.0051 (3)	0.73251 (12)	0.0230 (4)
H2	0.424750	−0.117917	0.741555	0.028*
N3	0.42918 (9)	0.3351 (3)	0.69885 (11)	0.0197 (4)
N4	0.42162 (9)	0.4782 (3)	0.58863 (12)	0.0207 (4)
C1	0.43787 (12)	0.1021 (3)	0.79549 (15)	0.0233 (5)
C2	0.44052 (15)	0.3005 (3)	0.78324 (15)	0.0312 (6)
H2A	0.478422	0.339455	0.811589	0.037*
C3	0.42210 (10)	0.2057 (3)	0.64346 (13)	0.0190 (5)
C5	0.4042 (2)	0.3985 (5)	0.8177 (2)	0.0532 (11)
H5A	0.405546	0.524576	0.806851	0.080*
H5B	0.416149	0.379461	0.874826	0.080*
H5C	0.367050	0.355768	0.794188	0.080*
C6	0.43151 (11)	0.4997 (3)	0.66679 (14)	0.0223 (5)
C7	0.41816 (11)	0.2906 (3)	0.56517 (14)	0.0206 (5)
C8	0.46718 (12)	0.2348 (4)	0.54158 (15)	0.0257 (5)
H8A	0.466340	0.296842	0.493392	0.039*
H8B	0.465855	0.107456	0.532216	0.039*
H8C	0.500565	0.264517	0.584107	0.039*
C9	0.36532 (12)	0.2479 (4)	0.50024 (16)	0.0289 (6)
H9A	0.334832	0.285889	0.516487	0.043*
H9B	0.362981	0.120590	0.490631	0.043*
H9C	0.364153	0.309595	0.451837	0.043*
C10	0.42311 (11)	0.6247 (3)	0.53679 (15)	0.0241 (5)
H10A	0.441900	0.585872	0.500031	0.029*
H10B	0.444481	0.721855	0.569064	0.029*
C11	0.36803 (11)	0.6939 (3)	0.48958 (15)	0.0229 (5)
C12	0.33246 (12)	0.7516 (4)	0.52757 (16)	0.0273 (5)
H12	0.342715	0.745747	0.583353	0.033*
C13	0.28240 (13)	0.8172 (4)	0.4842 (2)	0.0356 (6)
H13[b]	0.258358	0.857075	0.510283	0.043*
C14	0.26701 (13)	0.8252 (4)	0.4026 (2)	0.0387 (7)
C15	0.30212 (14)	0.7692 (6)	0.36474 (19)	0.0434 (8)
H15[a]	0.291907	0.776254	0.308987	0.052*
C16	0.35204 (13)	0.7031 (4)	0.40802 (17)	0.0331 (6)
H16	0.375880	0.663203	0.381616	0.040*
Cl21[a]	0.20841 (6)	0.1885 (3)	−0.03351 (8)	0.0585 (4)
Cl22	0.29098 (4)	0.0819 (2)	0.13548 (7)	0.0710 (3)
Cl24[b]	0.27097 (9)	0.2646 (4)	0.29263 (13)	0.0441 (7)
O21	0.05460 (9)	0.9722 (2)	0.41383 (11)	0.0274 (4)
O22	0.05551 (9)	0.3798 (2)	0.26042 (11)	0.0276 (4)
N21	0.07745 (9)	0.9750 (3)	0.22835 (12)	0.0200 (4)
N22	0.07060 (9)	1.0221 (3)	0.30005 (12)	0.0196 (4)
H22	0.071980	1.135487	0.310705	0.024*
N23	0.06836 (9)	0.6815 (2)	0.26527 (12)	0.0187 (4)
N24	0.07511 (9)	0.5362 (3)	0.16239 (12)	0.0208 (4)
C21	0.06214 (10)	0.9141 (3)	0.35464 (13)	0.0194 (5)
C22	0.06107 (12)	0.7159 (3)	0.34149 (14)	0.0241 (5)
H22A	0.024752	0.670534	0.339216	0.029*
C23	0.07601 (10)	0.8096 (3)	0.21674 (13)	0.0178 (4)
C25	0.10347 (15)	0.6249 (4)	0.40855 (17)	0.0362 (7)
H25A	0.101788	0.497557	0.399094	0.054*
H25B	0.096774	0.649356	0.458058	0.054*
H25C	0.139361	0.668682	0.411983	0.054*
C26	0.06558 (11)	0.5152 (3)	0.23124 (14)	0.0199 (5)
C27	0.08086 (11)	0.7232 (3)	0.14327 (14)	0.0210 (5)
C28	0.03465 (12)	0.7830 (3)	0.07122 (14)	0.0262 (5)
H28A	0.037428	0.724005	0.024214	0.039*
H28B	0.036674	0.910765	0.065095	0.039*
H28C	0.000080	0.752614	0.077968	0.039*
C29	0.13579 (12)	0.7594 (4)	0.13373 (16)	0.0274 (5)
H29A	0.164632	0.720584	0.181144	0.041*
H29B	0.139521	0.885887	0.126022	0.041*
H29C	0.138408	0.694855	0.087914	0.041*
C30	0.07418 (11)	0.3899 (3)	0.10984 (14)	0.0221 (5)
H30A	0.056105	0.428730	0.054858	0.026*
H30B	0.052269	0.293496	0.120934	0.026*
C31	0.12956 (11)	0.3184 (3)	0.11694 (15)	0.0216 (5)
C32	0.14193 (13)	0.2777 (4)	0.05010 (18)	0.0342 (6)
H32	0.116201	0.300355	−0.000279	0.041*
C33	0.19119 (14)	0.2046 (5)	0.0555 (2)	0.0432 (8)
H33[b]	0.198910	0.174851	0.008941	0.052*
C34	0.22937 (13)	0.1745 (5)	0.1285 (2)	0.0385 (7)
C35	0.21756 (15)	0.2155 (7)	0.1953 (2)	0.0534 (10)
H35[a]	0.243745	0.195419	0.245533	0.064*
C36	0.16758 (13)	0.2861 (6)	0.18997 (19)	0.0429 (8)
H36	0.159494	0.312315	0.236556	0.052*

[a]Occupancy: 0.670 (2), [b]Occupancy: 0.330 (2).

obtained after recrystallization from methanol and crystallization over a period of several days at 268–270 K (m.p. 468–469 K).

Experimental details

A single crystal of the title compound was examined on a Rigaku Supernova diffractometer [1] using Cu-Ka (λ = 1.54184 Å) radiation. The crystal was kept at 100.0(1) K during data collection. Using Olex2 [2], the structure was solved with the ShelXT [3] structure solution program using Intrinsic Phasing and refined with the ShelXL [4] refinement package using Least Squares minimization. Positional disorder of one chlorine atom with ratio 67:33 can be obtained at each of the two molecules inside the asymmetric unit, which is shown in the figure. Displacement ellipsoids are drawn at the 50% probability level, only the major occupied part of the disorder is shown. Hydrogen atoms were taken into account using a riding model. The crystal was pseudomerohedrically twinned with ratio 65:35, transformation matrix: 1.0000 0.0003 −0.0000 0.0000 −0.9999 0.0000 −0.9618 −0.0003 −1.0001.

Comment

The title structure was prepared following our previous procedure for regioselective synthesis of drug-like small molecules incorporating an imidazo[1,2,4]triazine-3,6-dione framework [5, 6]. There are several biologically active compounds and natural products comprising a condensed heterobicyclic 1,2,4-triazine scaffold [7]. The large variety of biological effects include antimicrobial [8], antiinflammatory [9], neuroprotective [10], and anticancer [11] properties. The racemic compound crystallizes centrosymmetrically and the asymmetric unit contains two independent molecules, which show different orientation of the chlorine atoms Cl1 and Cl3 (for molecule No. 1) and Cl21 and Cl23 (for molecule No. 2), respectively, in position *meta* of the benzyl moiety. Both molecules showed positional disorder of the chlorine atoms around the C10–C11 and C30–C31 bonds, representing a rotameric mixture in a 2:1 ratio. The crystal structure contains eight molecules per unit cell. The enantiomeric molecules show an antiparallel orientation in the crystal packing. All intramolecular bond lengths are normal. The significant shorter N1–N2 (1.404(3) Å) and N21–N22 (1.405(3) Å) bonds indicate the localization of the double bond of the corresponding six-membered rings. The imidazo[1,2,4] trazine unit in all molecules is almost planar. The methyl group is connected to the imidazotriazine basic structure in the corresponding asymmetric centers C2 and C21 and it is *cis* to the benzyl substituent in the positions N4 and N24 of the respective molecule No. 1 and No. 2. The main imidazotriazine core in both molecules is almost planar including followed atoms for molecule No. 1: N1, N2, N3, N4, C1, C2, C3, C6, C7, C10, O1, O2, and for molecule No. 2: N21, N22, N23, N24, C21, C22, C23, C26, C27, C30, O21, O22. The benzyl substituent forms a second planar moiety consisting of C10, C11, C12, C13, C14, C15, C16 for molecule No. 1, and C30, C31, C32, C33, C34, C35, C36 for molecule No. 2. The tilt angle between the main imidazotriazine planes and the second planar arrangement are 71.7(0)° for molecule No. 1 and 75.0(2)° for molecule No. 2. The benzyl and the imidazotriazine moiety form a bond angle of N4–C10–C11 = 113.8(2)° for molecule No. 1 and N24–C30–C31 = 114.1(2)° for molecule No. 2, respectively.

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