

Lamya H. Al-Wahaibi, Olivier Blacque, Nora H. Al-Shaalan, Edward R. T. Tiekink and Ali A. El-Emam*

Crystal structure of 2-([5-(adamantan-2-yl)-2-sulfanylidene-1,3,4-oxadiazolidin-3-yl]methyl)amino)benzonitrile, C₂₀H₂₂N₄OS

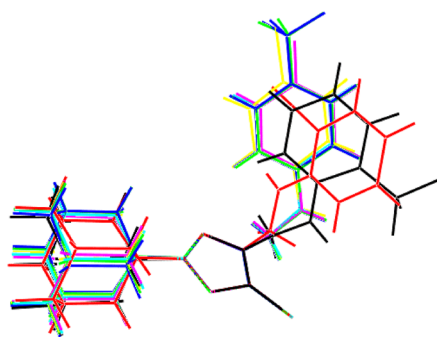
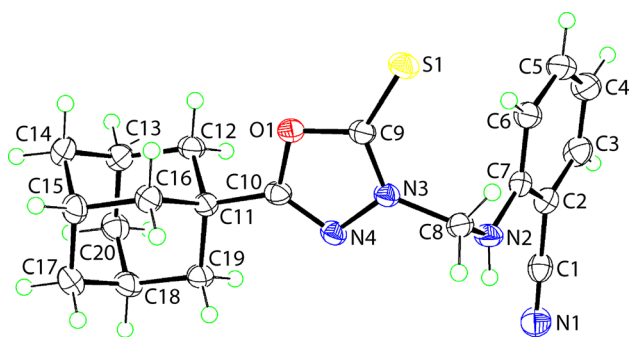


Table 1: Data collection and handling.

Crystal:	Colourless plate
Size:	0.19 × 0.10 × 0.02 mm
Wavelength:	Cu Kα radiation (1.54184 Å)
μ:	1.70 mm ⁻¹
Diffractometer, scan mode:	XtaLAB Synergy, ω
θ _{max} , completeness:	74.6°, >99%
N(hkl) _{measured} , N(hkl) _{unique} , R _{int} :	24,423, 24,423
Criterion for I _{obs} , N(hkl) _{gt} :	I _{obs} > 2 σ(I _{obs}), 19,275
N(param) _{refined} :	239
Programs:	CRYSLIS ^{PRO} [1], SHELX [2, 3], OLEX2 [4]

Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Source of material

2-Aminobenzonitrile (0.59 g, 5.0 mmol) and 37% formaldehyde solution (0.5 mL) were added to a solution of 5-(adamantan-1-yl)-1,3,4-oxadiazole-2(3H)-thione [5] (1.18 g, 0.5 mmol) in ethanol (10 mL). The mixture was stirred at room temperature for 2 h and allowed to stand overnight. The precipitated crude product was filtered, washed with water, dried and crystallized from aqueous ethanol to yield 1.37 g (75%) of the title compound as colourless plates. M.pt: 447–449 K (uncorrected). **IR** ν (cm⁻¹): 3374 (NH), 3021 (aromatic CH), 2911, 2850 (aliphatic CH), 2210 (CN), 1266 (C–O–C). **¹H NMR** (CDCl₃, 250 MHz): δ 1.72 (q, 6H, adamantane–H), 1.96 (s, 6H, adamantane–H), 2.10 (s, 3H, adamantane–H), 5.50 (d, 2H, NCH₂N), 5.77 (t, 1H, NH), 6.86 (t, 1H, Ar–H), 7.31 (d, 1H, Ar–H), 7.47–7.51 (m, 2H, Ar–H). **¹³C NMR** (CDCl₃, 62.9 MHz): δ 27.41, 34.55, 36.03, 39.02 (adamantane–C), 56.94 (NCH₂N), 97.77 (CN), 112.72, 117.13, 119.35, 132.94, 134.50, 147.06 (Ar–C), 168.66 (oxadiazole C5), 176.94 (C=S). **EI–MS** m/z (Rel. Int.): 366 (M⁺, 8), 236 (100), 176 (29), 135 (97), 131 (58), 102 (42). Suitable single crystals for X-ray diffraction were obtained by slow evaporation of a solution of the title compound in ethanol:chloroform (1:1, v/v) held at room temperature.

<https://doi.org/10.1515/ncrs-2022-0511>

Received November 2, 2022; accepted December 5, 2022; published online December 19, 2022

Abstract

C₂₀H₂₂N₄OS, triclinic, *P* $\bar{1}$ (no. 2), *a* = 6.8528(3) Å, *b* = 11.3498(5) Å, *c* = 13.3896(9) Å, α = 114.083(5)°, β = 104.326(4)°, γ = 90.369(3)°, *V* = 914.38(9) Å³, *Z* = 2, *R*_{gt}(*F*) = 0.0844, *wR*_{ref}(*F*²) = 0.2217, *T* = 160 K.

CCDC no.: 2216322

*Corresponding author: Ali A. El-Emam, Department of Medicinal Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt, E-mail: elemam@mans.edu.eg. <https://orcid.org/0000-0002-9325-9497>

Lamya H. Al-Wahaibi and Nora H. Al-Shaalan, Department of Chemistry, College of Sciences, Princess Nourah bint Abdulrahman University, Riyadh 11671, Saudi Arabia

Olivier Blacque, Department of Chemistry, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland

Edward R. T. Tiekink, Research Centre for Crystalline Materials, School of Medical and Life Sciences, Sunway University, 47500 Bandar Sunway, Selangor Darul Ehsan, Malaysia

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²).

Atom	x	y	z	<i>U</i> _{iso} */ <i>U</i> _{eq}
C1	0.3603 (6)	0.8333 (3)	0.6742 (3)	0.0283 (8)
C2	0.5068 (6)	0.7458 (3)	0.6457 (3)	0.0278 (8)
C3	0.5088 (7)	0.6359 (4)	0.6694 (4)	0.0350 (10)
H3	0.410156	0.619318	0.702435	0.042*
C4	0.6509 (8)	0.5528 (4)	0.6455 (4)	0.0372 (10)
H4	0.652854	0.479596	0.662962	0.045*
C5	0.7932 (7)	0.5761 (3)	0.5951 (4)	0.0340 (9)
H5	0.892182	0.518273	0.578294	0.041*
C6	0.7923 (6)	0.6827 (3)	0.5691 (3)	0.0292 (8)
H6	0.888634	0.696007	0.533294	0.035*
C7	0.6515 (6)	0.7703 (3)	0.5950 (3)	0.0248 (8)
C8	0.7895 (6)	0.9163 (3)	0.5261 (3)	0.0254 (8)
H8A	0.925414	0.896205	0.556915	0.031*
H8B	0.798008	1.011363	0.549199	0.031*
C9	0.8366 (6)	0.7691 (3)	0.3337 (3)	0.0233 (8)
C10	0.5462 (6)	0.7960 (3)	0.2346 (3)	0.0243 (8)
C11	0.3895 (6)	0.7742 (3)	0.1280 (3)	0.0235 (7)
C12	0.3016 (6)	0.6287 (3)	0.0660 (3)	0.0263 (8)
H12A	0.412221	0.574220	0.050279	0.032*
H12B	0.237979	0.604900	0.115127	0.032*
C13	0.1439 (6)	0.6038 (3)	−0.0454 (3)	0.0293 (8)
H13	0.088109	0.509684	−0.085046	0.035*
C14	0.2442 (7)	0.6392 (4)	−0.1220 (3)	0.0322 (9)
H14A	0.355671	0.585673	−0.138316	0.039*
H14B	0.143235	0.621426	−0.195166	0.039*
C15	0.3283 (7)	0.7839 (4)	−0.0614 (4)	0.0307 (9)
H15	0.392055	0.807313	−0.111492	0.037*
C16	0.4882 (6)	0.8091 (3)	0.0495 (3)	0.0272 (8)
H16A	0.546063	0.901778	0.088068	0.033*
H16B	0.599666	0.755638	0.033004	0.033*
C17	0.1557 (7)	0.8665 (4)	−0.0363 (4)	0.0339 (9)
H17A	0.052801	0.850609	−0.108288	0.041*
H17B	0.209495	0.959864	0.001956	0.041*
C18	0.0579 (6)	0.8306 (4)	0.0408 (4)	0.0310 (9)
H18	−0.054954	0.884468	0.057081	0.037*
C19	0.2158 (6)	0.8569 (3)	0.1524 (3)	0.0267 (8)
H19A	0.152323	0.835019	0.202494	0.032*
H19B	0.269868	0.950240	0.191907	0.032*
C20	−0.0282 (6)	0.6860 (4)	−0.0208 (4)	0.0321 (9)
H20A	−0.094507	0.662140	0.027267	0.038*
H20B	−0.131178	0.669578	−0.093000	0.038*
N1	0.2453 (6)	0.9064 (3)	0.6983 (3)	0.0366 (8)
N2	0.6479 (5)	0.8798 (3)	0.5738 (3)	0.0275 (7)
H2	0.566 (6)	0.934 (3)	0.598 (4)	0.031 (11)*
N3	0.7322 (5)	0.8487 (3)	0.4011 (3)	0.0233 (7)
N4	0.5488 (5)	0.8661 (3)	0.3387 (3)	0.0242 (7)
O1	0.7161 (4)	0.7336 (2)	0.2254 (2)	0.0262 (6)
S1	1.06010 (15)	0.71962 (8)	0.36407 (9)	0.0295 (3)

Experimental details

The C-bound H atoms were geometrically placed (C–H = 0.95–1.00 Å) and refined as riding with $U_{iso}(H) = 1.2U_{eq}(C)$.

The N-bound H atom was located in a difference map and refined with N–H = 0.87 ± 0.01 Å. The crystal was refined as a two-component twin. The diffraction intensities were integrated according to a merohedral twin law: component two is rotated by 180° around [0.00 −0.00 1.00] in reciprocal space or [0.40 0.40 0.82] in direct space with respect to component one. The maximum and minimum residual electron density peaks of 1.29 and 0.29 e Å^{−3}, respectively, were located 0.02 and 0.90 Å from the S1 and C8 atoms, respectively.

Comment

Adamantane derivatives have long been known for their diverse chemotherapeutic activities [6–8]. In addition, the 1,3,4-oxadiazole heterocycle represents an important scaffold in many chemotherapeutic agents [9, 10]. It was in this context that the title hybrid adamantanyl/oxadiazolidin-3-yl derivative, **1**, was synthesised and its crystal and molecular structures studied.

The molecular structure of **1** is shown in the upper view of the figure (50% probability ellipsoids). The molecule is constructed about a strictly planar oxadiazolidin-3-yl ring appended at the N3 position by the methylene-bound substituent and at the C10 position by the adamantan-2-yl group. The substituted phenyl ring occupies a position almost perpendicular to the five-membered ring [dihedral angle = 72.2(2)°] so the molecule has the shape of the letter L. The amine–N–H and phenyl–nitrile groups project to the same side of the molecule as does the non-substituted ring-nitrogen atom. Within the five-membered ring, the short C10–N4 bond length [1.288(5) Å] as well as standard C9–N3 [1.343(5) Å] and C9, C10–O1 [1.368(5) & 1.373(5) Å] bond lengths are suggestive of limited delocalisation of π -electron density over ring.

There are five literature precedents for **1**. Referring to the overlay diagram shown in the lower view of the figure, the molecule of **1** is shown in red; the molecules have been overlapped so the S, O and unsubstituted N atoms of the oxadiazolidin-3-yl fragment are coincident. The parent compound [11; aquamarine] and 4-fluorophenyl [12; pink], 4-chlorophenyl [13; yellow], 2-trifluoromethyl [14; black] and recently reported 4-trifluoromethyl [15; two independent molecules: green and blue] derivatives present very similar structural features with the exception of the relative orientations of the five- and six-membered rings. For example, the dihedral angle between the rings in the parent molecule, 2-trifluoromethyl derivative and **1** are 50.26(7), 66.80(6) and 72.2(2)°, respectively.

The most prominent intermolecular contact in the crystal of **1** is an amine–N–H...N(oxadiazolidin-3-yl)

hydrogen bond $[N2-H2...N4^i: H2...N4^i = 2.30(4) \text{ \AA}, N2...N4^i = 3.095(5) \text{ \AA}$ with angle at H2 = $156(4)^\circ$ for symmetry operation (i): $1 - x, 2 - y, 1 - z]$ within a centrosymmetric aggregate and leading to a 10-membered synthon with the shape of an extended chair. The dimeric aggregates stack in columns along the a-axis with methylene-C-H...N(nitrile) $[C8-H8a...N1^{ii}: H8a...N1^{ii} = 2.48 \text{ \AA}, C8...N1^{ii} = 3.426(6) \text{ \AA}$ with angle at H8a = 159° for (ii) $1 + x, y, z]$ and methylene-C-H...S(thione) $[C8-H8b...S1^{iii}: H8b...S1^{iii} = 2.85 \text{ \AA}, C8...S1^{iii} = 3.813(4) \text{ \AA}$ with angle at H8b = 164° for (iii) $2 - x, 2 - y, 1 - z]$ contacts between them. Columns are connected into layers in the ab-plane by $\pi(\text{phenyl})... \pi(\text{phenyl})$ $[Cg(C2-C7)...Cg(C2-C7)^{iv} = 3.865(2) \text{ \AA}$; slippage = $1.76 \text{ \AA}$ for (iv): $1 - x, 2 - y, 1 - z]$ contacts between centrosymmetrically related rings. The adamantan-2-yl groups project to either side of the supramolecular layer and inter-digitate along the c-axis with neighbouring layers.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: Deanship of Scientific Research at Princess Nourah bint Abdulrahman University through the Research Group Program (Grant No. RGP-1442-0010-5).

Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

References

1. Rigaku Oxford Diffraction. CRYALIS^{PRO}; Rigaku Corporation: Oxford, UK, 2019.
2. Sheldrick G. M. A short history of SHELX. *Acta Crystallogr.* 2008, A64, 112–122.
3. Sheldrick G. M. Crystal structure refinement with SHELXL. *Acta Crystallogr.* 2015, C71, 3–8.
4. Dolomanov O. V., Bourhis L. J., Gildea R. J., Howard J. A. K., Puschmann H. OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* 2009, 42, 339–341.
5. El-Emam A. A., Al-Deeb O. A., Al-Omar M., Lehmann J. Synthesis, antimicrobial, and anti-HIV-1 activity of certain 5-(1-adamantyl)-2-substituted thio-1,3,4-oxadiazoles and 5-(1-adamantyl)-3-substituted aminomethyl-1,3,4-oxadiazoline-2-thiones. *Bioorg. Med. Chem.* 2004, 12, 5107–5013.
6. Spilovska K., Zemek F., Korabecny J., Nepovimova E., Soukup O., Windisch M., Kuca K. Adamantane – a lead structure for drugs in clinical practice. *Curr. Med. Chem.* 2016, 23, 3245–3266.
7. Wanka L., Iqbal K., Schreiner P. R. The lipophilic bullet hits the targets: medicinal chemistry of adamantane derivatives. *Chem. Rev.* 2013, 113, 3516–3604.
8. Liu J., Obando D., Liao V., Lifa T., Codd R. The many faces of the adamantyl group in drug design. *Eur. J. Med. Chem.* 2011, 46, 1949–1963.
9. Vaidya A., Pathak D., Shah K. 1,3,4-Oxadiazole and its derivatives: a review on recent progress in anticancer activities. *Chem. Biol. Drug Des.* 2021, 97, 572–591.
10. Glomb T., Świhatek P. Antimicrobial activity of 1,3,4-oxadiazole derivatives. *Int. J. Mol. Sci.* 2021, 22, 6979.
11. Al-Tamimi A.-M. S., Al-Deeb O. A., El-Emam A. A., Ng S. W., Tiekink E. R. T. 5-(Adamantan-1-yl)-3-anilinomethyl-2,3-dihydro-1,3,4-oxadiazole-2-thione. *Acta Crystallogr.* 2013, E69, o729.
12. Al-Tamimi A.-M. S., Alafeefy A. M., El-Emam A. A., Ng S. W., Tiekink E. R. T. 5-(Adamantan-1-yl)-3-[(4-fluoroanilino)methyl]-2,3-dihydro-1,3,4-oxadiazole-2-thione. *Acta Crystallogr.* 2013, E69, o730.
13. Al-Alshaikh M. A., Ghabbour H. A., Al-Tamimi A.-M. S., Abdelbaky M. S. M., Garcia-Granda S., El-Emam A. A. Crystal structure of 5-(adamantan-1-yl)-3-[(4-chloroanilino)methyl]-2,3-dihydro-1,3,4-oxadiazole-2-thione, $C_{19}H_{22}ClN_3OS$. *Z. Kristallogr. N. Cryst. Struct.* 2016, 231, 301–303.
14. Al-Wabli R. I., El-Emam N. A., Ghabbour H. A., Haress N. G., El-Emam A. A. Crystal structure of 5-(adamantan-1-yl)-3-[(2-trifluoromethylanilino)methyl]-2,3-dihydro-1,3,4-oxadiazole-2-thione, $C_{20}H_{22}F_3N_3OS$. *Z. Kristallogr. N. Cryst. Struct.* 2016, 231, 815–817.
15. Al-Wahaibi L. H., Ghabbour H. A., Al-Omary F. A. M., Tiekink E. R. T., El-Emam A. A. Crystal structure of 5-(adamantan-1-yl)-3-[(4-trifluoromethylanilino)methyl]-2,3-dihydro-1,3,4-oxadiazole-2-thione, $C_{20}H_{22}F_3N_3OS$. *Z. Kristallogr. N. Cryst. Struct.* 2022, 235, 587–591.