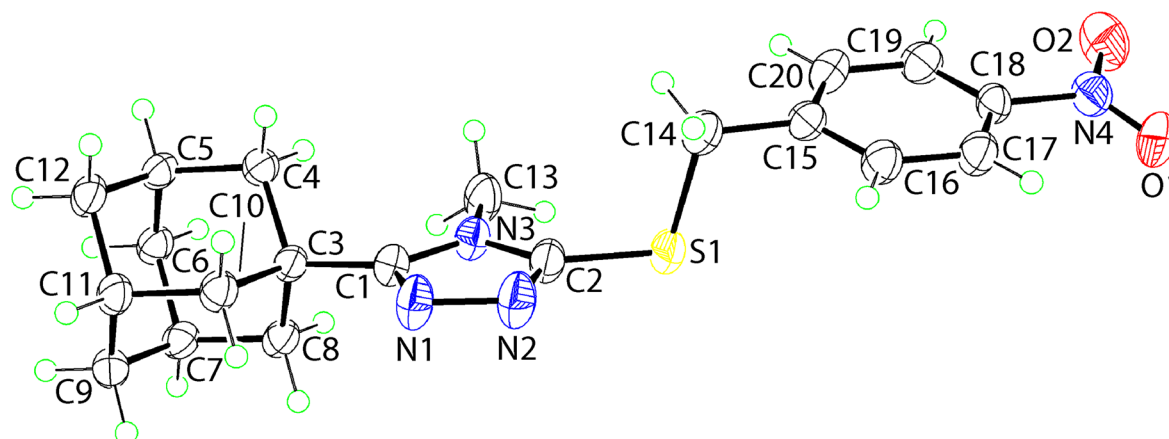


Lamya H. Al-Wahaibi, Mohammed S. M. Abdelbaky, Santiago Garcia-Granda,  
Edward R. T. Tiekink and Ali A. El-Emam\*

# Crystal structure of 3-(adamantan-1-yl)-4-methyl-5-[[4-(nitrophenyl)methyl]sulfanyl]-4H-1,2,4-triazole, $C_{20}H_{24}N_4O_2S$



<https://doi.org/10.1515/ncrs-2022-0392>

Received July 14, 2022; accepted July 19, 2022;

published online September 7, 2022

## Abstract

$C_{20}H_{24}N_4O_2S$ , monoclinic,  $C2/c$  (no. 15),  $a = 28.5901(10)$  Å,  $b = 6.4383(4)$  Å,  $c = 20.060(1)$  Å,  $\beta = 99.682(4)^\circ$ ,  $V = 3639.9(3)$  Å<sup>3</sup>,  $Z = 8$ ,  $R_{gt}(F) = 0.0557$ ,  $wR_{ref}(F^2) = 0.1514$ ,  $T = 150$  K.

CCDC no.: 2203657

**Table 1:** Data collection and handling.

|                                                                            |                                                            |
|----------------------------------------------------------------------------|------------------------------------------------------------|
| Crystal:                                                                   | Colourless prism                                           |
| Size:                                                                      | $0.18 \times 0.08 \times 0.06$ mm                          |
| Wavelength:                                                                | Cu $K\alpha$ radiation (1.54184 Å)                         |
| $\mu$ :                                                                    | $1.78 \text{ mm}^{-1}$                                     |
| Diffractometer, scan mode:                                                 | Xcalibur, $\omega$                                         |
| $\theta_{\max}$ , completeness:                                            | $75.8^\circ$ , >99%                                        |
| $N(hkl)_{\text{measured}}$ , $N(hkl)_{\text{unique}}$ , $R_{\text{int}}$ : | 16,466, 3726, 0.094                                        |
| Criterion for $I_{\text{obs}}$ , $N(hkl)_{\text{gt}}$ :                    | $I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$ , 2330         |
| $N(\text{param})_{\text{refined}}$ :                                       | 245                                                        |
| Programs:                                                                  | CrysAlis <sup>PRO</sup> [1], SHELX [2, 3], WinGX/ORTEP [4] |

\*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, Department of Chemistry, College of Sciences, Princess Nourah bint Abdulrahman University, Riyadh, 11671, Saudi Arabia, E-mail: lhalwahaibi@pnu.edu.sa

Mohammed S. M. Abdelbaky and Santiago Garcia-Granda, Department of Physical and Analytical Chemistry, Faculty of Chemistry, Oviedo University – CINN, Oviedo, 33006, Spain, E-mail: saidmohammed.uo@uniovi.es (M.S.M. Abdelbaky), sgg@uniovi.es (S. Garcia-Granda)

Edward R. T. Tiekink, Research Centre for Crystalline Materials, School of Medical and Life Sciences, Sunway University, Bandar Sunway, 47500, Selangor Darul Ehsan, Malaysia, E-mail: edwardt@sunway.edu.my

The molecular 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

To a solution of 5-(adamantan-1-yl)-4-methyl-4H-1,2,4-triazole-3-thiol [5] (1.25 g, 5.0 mmol) in DMF (10 mL), 4-nitrobenzyl chloride (1.08 g, 5.0 mmol) and anhydrous potassium carbonate (0.69 g, 5 mmol) were added; the mixture was then stirred at room temperature for 8 h. After this, ice-cold water (10 mL) was added to the reaction

**Table 2:** Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å<sup>2</sup>).

| Atom | x            | y            | z            | <i>U</i> <sub>iso</sub> */ <i>U</i> <sub>eq</sub> |
|------|--------------|--------------|--------------|---------------------------------------------------|
| S1   | 0.42766 (3)  | 0.30733 (16) | 0.68614 (4)  | 0.0418 (3)                                        |
| O1   | 0.53920 (9)  | 0.7788 (5)   | 0.98621 (14) | 0.0587 (8)                                        |
| O2   | 0.52822 (10) | 1.0658 (5)   | 0.93034 (14) | 0.0590 (8)                                        |
| N1   | 0.33771 (10) | −0.0530 (5)  | 0.57618 (13) | 0.0421 (7)                                        |
| N2   | 0.36515 (11) | 0.0031 (5)   | 0.63718 (14) | 0.0465 (8)                                        |
| N3   | 0.37213 (8)  | 0.2435 (4)   | 0.56105 (13) | 0.0336 (6)                                        |
| N4   | 0.52057 (9)  | 0.8800 (5)   | 0.93738 (15) | 0.0422 (7)                                        |
| C1   | 0.34254 (10) | 0.0918 (5)   | 0.53107 (15) | 0.0315 (7)                                        |
| C2   | 0.38512 (10) | 0.1800 (6)   | 0.62679 (15) | 0.0360 (8)                                        |
| C3   | 0.32083 (10) | 0.0738 (5)   | 0.45725 (14) | 0.0271 (6)                                        |
| C4   | 0.29333 (10) | 0.2690 (5)   | 0.42840 (15) | 0.0293 (7)                                        |
| H4A  | 0.268038     | 0.300134     | 0.455099     | 0.035*                                            |
| H4B  | 0.315172     | 0.389336     | 0.432052     | 0.035*                                            |
| C5   | 0.27119 (10) | 0.2354 (5)   | 0.35415 (15) | 0.0314 (7)                                        |
| H5   | 0.253704     | 0.363681     | 0.336292     | 0.038*                                            |
| C6   | 0.31046 (10) | 0.1901 (5)   | 0.31286 (15) | 0.0323 (7)                                        |
| H6A  | 0.332693     | 0.309005     | 0.316063     | 0.039*                                            |
| H6B  | 0.296430     | 0.170365     | 0.264695     | 0.039*                                            |
| C7   | 0.33727 (10) | −0.0068 (5)  | 0.34022 (15) | 0.0310 (7)                                        |
| H7   | 0.362769     | −0.036683    | 0.313019     | 0.037*                                            |
| C8   | 0.35982 (10) | 0.0247 (5)   | 0.41457 (15) | 0.0319 (7)                                        |
| H8A  | 0.382847     | 0.140705     | 0.418213     | 0.038*                                            |
| H8B  | 0.377117     | −0.102573    | 0.431997     | 0.038*                                            |
| C9   | 0.30278 (10) | −0.1896 (5)  | 0.33431 (15) | 0.0335 (7)                                        |
| H9A  | 0.319950     | −0.317638    | 0.351308     | 0.040*                                            |
| H9B  | 0.288646     | −0.211691    | 0.286306     | 0.040*                                            |
| C10  | 0.28578 (10) | −0.1110 (5)  | 0.44985 (15) | 0.0319 (7)                                        |
| H10A | 0.302774     | −0.238652    | 0.467633     | 0.038*                                            |
| H10B | 0.260439     | −0.083809    | 0.476812     | 0.038*                                            |
| C11  | 0.26358 (10) | −0.1440 (5)  | 0.37571 (15) | 0.0322 (7)                                        |
| H11  | 0.241077     | −0.263907    | 0.372130     | 0.039*                                            |
| C12  | 0.23666 (10) | 0.0526 (5)   | 0.34851 (16) | 0.0338 (7)                                        |
| H12A | 0.221975     | 0.031871     | 0.300654     | 0.041*                                            |
| H12B | 0.211094     | 0.082046     | 0.374889     | 0.041*                                            |
| C13  | 0.38872 (12) | 0.4329 (6)   | 0.53311 (18) | 0.0436 (9)                                        |
| H13A | 0.418684     | 0.476551     | 0.560731     | 0.065*                                            |
| H13B | 0.364956     | 0.542582     | 0.533101     | 0.065*                                            |
| H13C | 0.393692     | 0.407107     | 0.486661     | 0.065*                                            |
| C14  | 0.39039 (10) | 0.4716 (6)   | 0.73011 (17) | 0.0387 (8)                                        |
| H14A | 0.372873     | 0.574265     | 0.698623     | 0.046*                                            |
| H14B | 0.367201     | 0.386281     | 0.749522     | 0.046*                                            |
| C15  | 0.42390 (10) | 0.5799 (6)   | 0.78545 (16) | 0.0347 (7)                                        |
| C16  | 0.44075 (11) | 0.4790 (6)   | 0.84613 (16) | 0.0364 (8)                                        |
| H16  | 0.430261     | 0.342067     | 0.853324     | 0.044*                                            |
| C17  | 0.47270 (10) | 0.5762 (6)   | 0.89623 (16) | 0.0380 (8)                                        |
| H17  | 0.484404     | 0.507332     | 0.937555     | 0.046*                                            |
| C18  | 0.48700 (10) | 0.7756 (5)   | 0.88441 (16) | 0.0330 (7)                                        |
| C19  | 0.47070 (11) | 0.8812 (6)   | 0.82517 (17) | 0.0378 (8)                                        |
| H19  | 0.480956     | 1.018943     | 0.818596     | 0.045*                                            |
| C20  | 0.43898 (10) | 0.7814 (6)   | 0.77548 (17) | 0.0389 (8)                                        |
| H20  | 0.427447     | 0.851266     | 0.734265     | 0.047*                                            |

mixture with continuous stirring for 1 h. The precipitated crude product was filtered, washed with cold water, dried and crystallised from aqueous ethanol to yield 1.71 g (89%) of the title compound as colourless prisms. **M. pt:** 443–445 K (uncorrected). **Anal. Calcd.** for C<sub>20</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>S: C, 62.48; H, 6.29; N, 14.57; S, 8.34%. Found: C, 62.44; H, 6.31; N, 14.53; S, 8.32%. **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 700.17 MHz): δ 1.78 (s, 6H, adamantane-H), 1.98–2.02 (m, 9H, adamantane-H), 3.32 (s, 3H, CH<sub>3</sub>), 4.35 (s, 2H, benzylic CH<sub>2</sub>), 7.36 (d, 2H, Ar–H, *J* = 8.5 Hz), 8.01 (d, 2H, Ar–H, *J* = 8.5 Hz). **<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 176.08 MHz): δ 33.25 (CH<sub>3</sub>), 28.0, 35.14, 37.16, 40.60 (adamantane-C), 36.30 (benzylic-CH<sub>2</sub>), 122.84, 130.30, 142.53, 146.02 (Ar–C), 149.64, 161.26 (triazole-C). Single crystals for X-ray diffraction were obtained by slow evaporation of a solution of the title compound in ethanol:chloroform (2:1, v/v) held at room temperature.

## Experimental details

The C-bound H atoms were geometrically placed (C–H = 0.95–1.00 Å) and refined as riding with *U*<sub>iso</sub> (H) = 1.2–1.5 *U*<sub>eq</sub> (C).

## Comment

Considerable attention has been devoted to adamantane-based derivatives owing to their diverse chemotherapeutic activities [6–8]. For example, several adamantane-linked 1,2,4-triazole derivatives have been identified as efficient therapies for the treatment of type 2 diabetes and obesity through the inhibition of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) [9, 10]. In an extension of on-going interest in the structural studies and potential biological applications of adamantane-linked 1,2,4-triazoles [11, 12], herein the crystal and molecular structures of the title compound, a potential 11β-HSD1 inhibitor [5], are described.

The molecular structure of (I) is shown in the figure (50% probability ellipsoids). The central 1,2,4-triazolyl ring is planar with a r.m.s. deviation for the five atoms being 0.004 Å with maximum deviations of ±0.003 Å noted for the N1 and C1 atoms. The C1–N1 and C2–N2 bond lengths of 1.323 (4) and 1.306 (4) Å, respectively, are experimentally equivalent, and systematically shorter than the C1–N3

and C2–N3 bond lengths of 1.364(4) and 1.371(4) Å, respectively, which are also experimentally the same. In connection with the last mentioned bonds, which are shorter than their standard single bond values, the decrease in the N1–N2 bond length [1.386(4) Å] is suggestive of substantial delocalisation of  $\pi$ -electron density in the five-membered ring. The adamantan-1-yl group is appended at the C1-position with the S-bound [(4-nitrophenyl)methyl]sulfanyl substituent connected at the C2-position. A significant kink is apparent in the molecule, at the S–CH<sub>2</sub>– link, as seen in the C2–S1–C14 [101.77(14)°] and C15–C14–S1 [105.8(2)°] bond angles although the four atoms are co-planar: the C2–S1–C14–C15 torsion angle = 176.9(2)°. As expected, the C2–S1 bond length of 1.756(3) Å, i.e. involving the ring-carbon atom, is shorter than the C14–S1 bond of 1.830(3) Å, involving the methylene-carbon atom. Despite the kink in the molecule, the aromatic residues are close to parallel with the dihedral angle between them being 11.21(17)°. Finally, the nitro group is twisted out of the plane of the phenyl ring it is connected to, as reflected in the O1–N4–C18–C17 torsion angle of 9.1(4)°.

The most closely related structure in the crystallographic literature available for comparison is the derivative with a nitrogen-bound phenyl group instead of a nitrogen-bound methyl group [12]. Here, the crucial central C<sub>ring</sub>–S–C<sub>methylene</sub>–C<sub>phenyl</sub> torsion angle is 84.3(3)° resulting in an orthogonal relationship between the triazolyl and phenyl rings. Similar conformations were noted in the 4-fluorophenyl (83.1(3)°) and 4-chlorophenyl (79.06(13)°) analogues. Presumably this change of conformation in these three molecules arises as a result of the steric congestion due to the nitrogen-bound phenyl rings [12]. However, other influences come into play as in the two other nitrogen-bound methyl derivatives, quite distinct conformations are apparent. Thus, in the 4-chloro species, a very similar conformation is noted as for the title compound (torsion angle = 179.32(14)°) [11]. In the parent compound with an unsubstituted phenyl ring [13], the torsion angle of 163.3(2)° resembles that in the title compound, yet a more open conformation was noted as manifested in the dihedral angle of 51.42(8)° between the rings; the second independent molecule comprising the asymmetric-unit suffered from positional disorder but presented an analogous conformation.

In the absence of conventional hydrogen bonding, C–H $\cdots$ O, C–H $\cdots$ N and nitro-O $\cdots\pi$  interactions come to the fore in the molecular packing of (I). Thus, methyl-C–H $\cdots$ O (nitro) [C13–H13a $\cdots$ O1<sup>i</sup>: H13a $\cdots$ O1<sup>i</sup> = 2.55 Å, C13a $\cdots$ O1<sup>i</sup> = 3.103(5) Å with angle at H13a = 116° for symmetry operation (i): 1 – x, y,

3/2 – z], phenyl-C–H $\cdots$ O (nitro) C17–H17 $\cdots$ O1<sup>ii</sup>: H17 $\cdots$ O1<sup>ii</sup> = 2.56 Å, C17 $\cdots$ O1<sup>ii</sup> = 3.342(5) Å with angle at H17 = 140° for (ii): 1 – x, 1 – y, 2 – z] and phenyl-C–H $\cdots$ N (triazolyl) C20–H20 $\cdots$ N2<sup>iii</sup>: H20 $\cdots$ N2<sup>iii</sup> = 2.60 Å, C20 $\cdots$ N2<sup>iii</sup> = 3.496(4) Å with angle at H20 = 158° for (iii): x, 1 + y, z] interactions occur at separations within the respective sum of the van der Waals radii [14]. The prominent role of the nitro-O atoms in the molecular packing is emphasised by the presence of a nitro-O $\cdots\pi$ (triazolyl) interaction [N4–O2 $\cdots$ Cg (N1–N3, C1, C2)<sup>iv</sup>: O2 $\cdots$ Cg (N1–N3, C1, C2)<sup>iv</sup> = 3.259(3) Å with angle at O2 = 105.1(2)° for (iv): 1 – x, 1 + y, 3/2 – z]. The nitro-O atom approaches the triazole ring in a side-on fashion with the closest O2 $\cdots$ C2 contact being short at 2.991(4) Å. The aforementioned contacts occur within layers that stack along the *a*-axis with the adamantan-1-yl residues projecting to either side. There are no directional interactions between layers.

A recent study on organotin compounds of adamantanyl-substituted carboxylates indicated very high contributions to the calculated Hirshfeld surfaces by H $\cdots$ H contacts owing to the relatively large volume occupied by these substituents [15]. Thus, analogous calculations were conducted for the title compound employing standard methods [16] and Crystal Explorer 17.5 [17]. The present analysis indeed showed H $\cdots$ H surface contacts contributed 50.9% to all contacts, despite the identified interactions giving rise to the described supramolecular layer. The next major contributions were due to N $\cdots$ H/H $\cdots$ N [13.6%], O $\cdots$ H/H $\cdots$ O [12.0%] and C $\cdots$ H/H $\cdots$ C [10.4%] contacts. After these, the only significant contacts to the Hirshfeld surface were from S $\cdots$ H/H $\cdots$ S [4.1%], O $\cdots$ N/N $\cdots$ O [2.2%], then O $\cdots$ C/C $\cdots$ O and S $\cdots$ C/C $\cdots$ S contacts, each contributing 1.7%.

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

**Research funding:** Princess Nourah bint Abdulrahman University Researchers Supporting Project No. PNURSP2022R3, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia.

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

## References

1. Rigaku Oxford Diffraction. CRYSAUS<sup>PRO</sup>; Rigaku Corporation: Oxford, UK, 2015.
2. Sheldrick G. M. SHELXT – Integrated space-group and crystal-structure determination. *Acta Crystallogr.* 2015, *A71*, 3–8.
3. Sheldrick G. M. Crystal structure refinement with SHELXL. *Acta Crystallogr.* 2015, *C71*, 3–8.

4. Farrugia L. J. WinGX and ORTEP for Windows: an update. *J. Appl. Crystallogr.* 2012, 45, 849–854.
5. El-Emam A. A., Ibrahim T. M. Synthesis and anti-inflammatory and analgesic activity of some 3-(1-adamantyl)-4-substituted-5-mercapto-1,2,4-triazoles. *Arzneim. Forsch.* 1991, 41, 1260–1264.
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. Olson S., Aster S. D., Brown K., Carbin L., Graham D. W., Hermanowski-Vosatka A., LeGrand C. B., Mundt S. S., Robbins M. A., Schaeffer J. M., Slossberg L. H., Szymonifka M. J., Thieringer R., Wright S. D., Balkovec J. M. Adamantyl triazoles as selective inhibitors of 11 $\beta$ -hydroxysteroid dehydrogenase type 1. *Bioorg. Med. Chem. Lett.* 2005, 15, 4359–4362.
10. Joharapurkar A., Dhanesha N., Shah G., Kharul R., Jain M. 11 $\beta$ -Hydroxysteroid dehydrogenase type 1: potential therapeutic target for metabolic syndrome. *Pharmacol. Rep.* 2012, 64, 1055–1065.
11. Al-Wahaibi L. H., Joubert J., Blacque O., Al-Shaalan N. H., El-Emam A. A. Crystal structure, Hirshfeld surface analysis and DFT studies of 5-(adamantan-1-yl)-3-[(4-chlorobenzyl)sulfanyl]-4-methyl-4H-1,2,4-triazole, a potential 11 $\beta$ -HSD1 inhibitor. *Sci. Rep.* 2019, 9, 19745.
12. Osman D. A., Macías M. A., Al-Wahaibi L. H., Al-Shaalan N. H., Zondagh L. S., Joubert J., Garcia-Granda S., El-Emam A. A. Structural insights and docking analysis of adamantane-linked 1,2,4-triazole derivatives as potential 11 $\beta$ -HSD1 inhibitors. *Molecules* 2021, 26, 5335.
13. Al-Abdullah E. S., El-Emam A. A., Ghabbour H. A., Chantapromma S., Fun H.-K. 5-(Adamantan-1-yl)-3-(benzylsulfanyl)-4-methyl-4H-1,2,4-triazole. *Acta Crystallogr.* 2012, E68, o2427–o2428.
14. Spek A. L. *checkCIF* validation ALERTS: what they mean and how to respond. *Acta Crystallogr.* 2020, E76, 1–11.
15. Basu Baul T. S., Manne R., Duthie A., Liew L. Y., Chew J., Lee S. M., Tiekink E. R. T. Synthesis, structural and in vitro biological evaluation of diamondoid-decorated lipophilic organotin(IV) derivatives. *J. Organomet. Chem.* 2021, 941, 121802.
16. Tan S. L., Jotani M. M., Tiekink E. R. T. Utilizing Hirshfeld surface calculations, non-covalent interaction (NCI) plots and the calculation of interaction energies in the analysis of molecular packing. *Acta Crystallogr.* 2019, E75, 308–318.
17. Spackman P. R., Turner M. J., McKinnon J. J., Wolff S. K., Grimwood D. J., Jayatilaka D., Spackman M. A. CrystalExplorer: a program for Hirshfeld surface analysis, visualization and quantitative analysis of molecular crystals. *J. Appl. Crystallogr.* 2021, 54, 1006–1011.