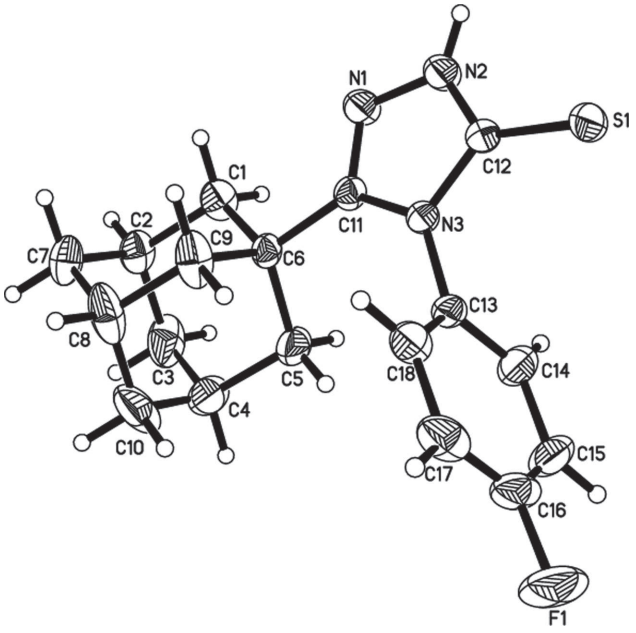
Open Access

Mona M. Al-Shehri, Tilal Elsaman, Ebtehal S. Al-Abdullah, Hazem A. Ghabbour and Ali A. El-Emam*

Crystal structure of 3-(adamantan-1-yl)-4-(4-fluorophenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione, $C_{18}H_{20}FN_3S$



DOI 10.1515/ncrs-2016-0309
Received October 6, 2016; accepted March 15, 2017; available online April 1, 2017

Abstract

$C_{18}H_{20}FN_3S$, triclinic, $P\bar{1}$, $a = 7.3884(4)$ Å, $b = 10.0741(6)$ Å, $c = 12.6533(8)$ Å, $\alpha = 69.209(2)°$, $\beta = 73.778(2)°$, $\gamma = 72.638(2)°$, $V = 824.33(8)$ Å^3, $Z = 2$, $R_{gt}(F) = 0.0480$, $wR_{ref}(F^2) = 0.1351$, $T = 296(2)$ K.

CCDC no.: 1507728

Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	0.47 × 0.21 × 0.17 mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ:	2.1 cm^{-1}
Diffractometer, scan mode:	Bruker APEX-II, φ and ω
$2\theta_{max}$, completeness:	55°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	38531, 3785, 0.057
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 2741
$N(param)_{refined}$:	212
Programs:	SHELX [24, 25], Bruker programs [26]

The crystal structure is shown in the figure. Tables 1 and 2 contain details on crystal structure and measurement conditions and a list of the atoms including atomic coordinates and displacement parameters.

Source of material

4-Fluorophenyl isothiocyanate (1.53 g, 0.01 mol) was added to a solution of adamantane-1-carbohydrazide (1.94 g, 0.01 mol), in ethanol (10 mL), and the mixture was heated under reflux with stirring for one hour. The solvent was then distilled off *in vacuo*; an aqueous sodium hydroxide solution (10%, 15 mL) was added to the residue and the mixture was heated under reflux for two hours then filtered hot. On cooling, the mixture was acidified with hydrochloric acid (*p*H 1–2) and the precipitated crude product was filtered, washed with water, dried and crystallized from aqueous ethanol to yield 3.03 g (92%) of the title compound ($C_{18}H_{20}FN_3S$) as

***Corresponding author: Ali A. El-Emam,** Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P. O. Box 2457, Riyadh 11451, Saudi Arabia, e-mail: elemam5@hotmail.com
Mona M. Al-Shehri and Ebtehal S. Al-Abdullah: Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P. O. Box 2457, Riyadh 11451, Saudi Arabia
Tilal Elsaman: Department of Pharmaceutical Chemistry, Omdurman Islamic University, Khartoum, Sudan
Hazem A. Ghabbour: Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P. O. Box 2457, Riyadh 11451, Saudi Arabia; and Department of Medicinal Chemistry, Faculty of Pharmacy, University of Mansoura, Mansoura 35516, Egypt

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

Atom	x	y	z	U_{iso}*/U_{eq}
S1	−0.01552(8)	0.59470(6)	0.14514(5)	0.04636(19)
F1	0.3030(3)	0.6663(2)	0.50902(18)	0.1032(7)
N1	0.4015(2)	0.28424(18)	0.06263(15)	0.0394(4)
N2	0.2347(3)	0.38967(19)	0.05035(16)	0.0414(4)
N3	0.3230(2)	0.40237(16)	0.19199(13)	0.0303(3)
C1	0.7369(3)	0.0947(2)	0.11679(18)	0.0429(5)
H1A	0.6495	0.0456	0.1049	0.051*
H1B	0.7871	0.1590	0.0411	0.051*
C2	0.9053(3)	−0.0196(2)	0.16708(19)	0.0435(5)
H2A	0.9776	−0.0776	0.1124	0.052*
C3	1.0395(3)	0.0557(3)	0.1828(3)	0.0659(8)
H3A	1.0901	0.1209	0.1076	0.079*
H3B	1.1504	−0.0174	0.2136	0.079*
C4	0.9291(4)	0.1440(3)	0.2664(3)	0.0780(10)
H4A	1.0183	0.1920	0.2792	0.094*
C5	0.7609(3)	0.2606(2)	0.2165(3)	0.0573(7)
H5A	0.6907	0.3192	0.2699	0.069*
H5B	0.8116	0.3267	0.1418	0.069*
C6	0.6237(3)	0.18627(19)	0.19914(16)	0.0306(4)
C7	0.8276(3)	−0.1201(2)	0.2804(2)	0.0501(6)
H7A	0.9357	−0.1946	0.3132	0.060*
H7B	0.7421	−0.1706	0.2685	0.060*
C8	0.7150(4)	−0.0324(3)	0.3632(2)	0.0631(8)
H8A	0.6637	−0.0992	0.4385	0.076*
C9	0.5461(3)	0.0824(2)	0.31396(19)	0.0515(6)
H9A	0.4721	0.1379	0.3691	0.062*
H9B	0.4581	0.0341	0.3019	0.062*
C10	0.8472(5)	0.0417(3)	0.3820(3)	0.0911(12)
H10A	0.9546	−0.0322	0.4159	0.109*
H10B	0.7749	0.0985	0.4365	0.109*
C11	0.4548(3)	0.29277(19)	0.14938(16)	0.0308(4)
C12	0.1802(3)	0.4624(2)	0.12725(17)	0.0336(4)
C13	0.3284(3)	0.4647(2)	0.27702(16)	0.0315(4)
C14	0.4012(3)	0.5876(2)	0.2401(2)	0.0448(5)
H14A	0.4556	0.6258	0.1612	0.054*
C15	0.3937(4)	0.6551(3)	0.3205(3)	0.0611(7)
H15A	0.4439	0.7397	0.2979	0.073*
C16	0.3123(4)	0.5967(3)	0.4329(3)	0.0590(7)
C17	0.2403(3)	0.4758(3)	0.4709(2)	0.0552(6)
H17A	0.1875	0.4376	0.5501	0.066*
C18	0.2460(3)	0.4094(2)	0.39095(18)	0.0413(5)
H18A	0.1932	0.3258	0.4145	0.050*
H1N2	0.173(3)	0.397(3)	0.000(2)	0.050(7)*

fine transparent block crystals. M.P.: > 573 K. Single crystals were obtained by slow evaporation of a solution of the title compound in EtOH/$CHCl_3$ (1:2) at room temperature. **^{1}H-NMR** ($CDCl_3$, 500.13 MHz): δ 1.55–1.69 (m, 6H, adamantane-H), 1.86 (s, 3H, adamantane-H), 1.96 (s, 6H, adamantane-H), 7.24–7.32 (m, 4H, Ar—H), 11.89 (br. s, 1H, NH). **^{13}C-NMR** ($CDCl_3$, 125.76 MHz): δ 27.85, 35.14, 36.72, 38.85 (adamantane-C), 118.22, 127.16, 132.51, 137.99 (Ar—C), 158.17 (triazole C = N), 171.11 (triazole C = S). EI-MS *m/z* (Rel. Int.): 329 (M^+, 100).

Experimental details

Carbon-bound hydrogen atoms were placed in calculated positions and were included in the refinement using the riding model approximation, with U_{iso}(H) set to 1.2U_{eq}(C). The position and U_{iso} of the nitrogen-bound hydrogen atom was freely refined.

Discussion

Various adamantane-based drugs have long been known as efficient medications for the control of several diseases [1, 2]. Amantadine [3–5], rimantadine [6] and tromantadine [7] are currently used as efficient antiviral drugs. Moreover, adamantane derivatives were also reported to exhibit marked anti-HIV [8–10], antibacterial [11–13], antimalarial [14], hypoglycemic [15, 16], anti-inflammatory [17, 18], and anticancer [19] activities. 1,2,4-Triazole derivatives were reported to possess significant anti-inflammatory [20, 21] and antibacterial [22] activities. The title compound was prepared as an adamantane-triazole hybrid derivative as potential bioactive agent [23]. The asymmetric unit of the title compound contains one independent molecule. Pairs of molecules pack in the crystal structure *via* one strong classical intermolecular hydrogen bond N2—H1N2···S1^{i}. The D···A and H···A distances are 3.252(2) and 2.40(2) Å, respectively, and the D-H···A angle is 176(3)°. Symmetry code: (i) $-x, -y+1, -z$.

Acknowledgements: The authors would like to extend their sincere appreciation to the Deanship of Scientific Research at King Saud University for funding this work through the Research Group Project No. RG-1435-062.

References

1. Liu, J.; Obando, D.; Liao, V.; Lifa, T.; Codd, R.: The many faces of the adamantyl group in drug design. Eur. J. Med. Chem. **46** (2011) 1949–1963.
2. Lamoureux, G.; Artavia, G.: Use of the adamantane structure in medicinal chemistry. Curr. Med. Chem. **17** (2010) 2967–2978.
3. Davies, W. L.; Grunnert, R. R.; Haff, R. F.; McGahen, J. W.; Neumeyer, E. M.; Paulshock, M.; Watts, J. C.; Wood, T. R.; Hermann, E. C.; Hoffmann, C. E.: Antiviral activity of 1-adamantamine (amantadine). Science **144** (1964) 862–863.
4. Togo, Y.; Hornick, R. B.; Dawkins, A. T.: Studies on induced influenza in man. I. Double blind studies designed to assess prophylactic efficacy of amantadine hydrochloride against A2/Rockville/1/65 strain. J. Am. Med. Assoc. **203** (1968) 1089–1094.
5. Wendel, H. A.; Snyder, M. T.; Pell, S.: Trial of amantadine in epidemic influenza. Clin. Pharmacol. Therap. **7** (1966) 38–43.
6. Hayden, F. G.; Gwaltney, J. M. I.; Van, C. R. L.; Adams, K. F.; Giordani, B.: Comparative toxicity of amantadine hydrochloride and rimantadine hydrochloride in healthy adults. Antimicrob. Agents Chemother. **19** (1981) 226–233.

7. Rabinovich, S.; Baldini, J. T.; Bannister, R.: Treatment of influenza. The therapeutic efficacy of rimantadine HCl in a naturally occurring influenza A2 outbreak. Am. J. Med. Sci. **257** (1969) 328–335.
8. Van Derpoorten, K.; Balzarini, J.; De Clercq, E.; Poupaert, J. H.: Anti-HIV activity of *N*-1-adamantyl-4-aminophthalimide. Biomed. Pharmacother. **51** (1997) 464–468.
9. El-Emam, A. A.; Al-Deeb, O. A.; Al-Omar, M. A.; 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. **12** (2004) 5107–5113.
10. Balzarini, J.; Orzeszko, B.; Mauri, J. K.; Orzeszko, A.: Synthesis and anti-HIV studies of 2-adamantyl-substituted thiazolidin-4-ones. Eur. J. Med. Chem. **42** (2007) 993–1003.
11. Scherman, M. S.; North, E. J.; Jones, V.; Hess, T. N.; Grzegorzewicz, A. E.; Kasagami, T.; Kim, I. H.; Merzlikin, O.; Lenaerts, A. J.; Lee, R. E.; Jackson, M.; Morisseau, C.; McNeil, M. R.: Screening a library of 1600 adamantyl ureas for anti-Mycobacterium tuberculosis activity *in vitro* and for better physical chemical properties for bioavailability. Bioorg. Med. Chem. **20** (2012) 3255–3262.
12. El-Emam, A. A.; Al-Tamimi, A.-M. S.; Al-Omar, M. A.; Al-Rashood, K. A.; Habib, E. E.: Synthesis and antimicrobial activity of novel 5-(1-adamantyl)-2-aminomethyl-4-substituted-1,2,4-triazoline-3-thiones. Eur. J. Med. Chem. **68** (2013) 96–102.
13. Protopopova, M.; Hanrahan, C.; Nikonenko, B.; Samala, R.; Chen, P.; Gearhart, J.; Einck, L.; Nacy, C. A.: Identification of a new antitubercular drug candidate, SQ109, from a combinatorial library of 1,2-ethylenediamines. J. Antimicrob. Chemother. **56** (2005) 968–974.
14. Wang, X.; Dong, Y.; Wittlin, S.; Charman, S. A.; Chiu, F. C. K.; Chollet, J.; Katneni, K.; Mannila, J.; Morizzi, J.; Ryan, E.; Scheurer, C.; Steuten, J.; Tomas, J. S.; Snyder, C.; Vennerstrom, J. L.: Comparative antimalarial activities and ADME profiles of ozonides (1,2,4-trioxolanes) OZ277, OZ439, and their 1,2-dioxolane, 1,2,4-trioxane, and 1,2,4,5-tetraoxane isosteres. J. Med. Chem. **56** (2013) 2547–2555.
15. Villhauer, E. B.; Brinkman, J. A.; Naderi, G. B.; Burkey, B. F.; Dunning, B. E.; Prasad, K.; Mangold, B. L.; Russell, M. E.; Hughes, T. E.: 1-(3-Hydroxy-1-adamantyl)aminoacetyl-2-cyano-(*S*)-pyrrolidine: a potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitor with antihyperglycemic properties. J. Med. Chem. **46** (2003) 2774–2789.
16. Augeri, D. J.; Robl, J. A.; Betebenner, D. A.; Magnin, D. R.; Khanna, A.; Robertson, J. G.; Wang, A.; Simpkins, L. M.; Taunk, P.; Huang, Q.; Han, S.; Abboa-Offei, B.; Cap, M.; Xin, L.; Tao, L.; Tozzo, E.; Welzel, G. E.; Egan, D. M.; Marcinkeviciene, J.; Chang, S. Y.; Biller, S. A.; Kirby, M. S.; Parker, R. A.; Hamann, L. G.: Discovery and preclinical profile of saxagliptin (BMS-477118): A highly potent, long-acting, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. J. Med. Chem. **48** (2005) 5025–5037.
17. El-Emam, A. A.; Ibrahim, T. M.: Synthesis, anti-inflammatory and analgesic activity of certain 3-(1-adamantyl)-4-substituted-5-mercapto-1,2,4-triazole derivatives. Arzneim.-Forsch. **41** (1991) 1260–1264.
18. Kouatly, O.; Geronikaki, A.; Kamoutsis, C.; Hadjipavlou-Litina, D.; Eleftheriou, P.: Adamantane derivatives of thiazolyl-*N*-substituted amide, as possible non-steroidal anti-inflammatory agents. Eur. J. Med. Chem. **44** (2009) 1198–1204.
19. Sun, S. Y.; Yue, P.; Chen, X.; Hong, W. K.; Lotan, R.: The synthetic retinoid CD437 selectively induces apoptosis in human lung cancer cells while sparing normal human lung epithelial cells. Cancer Res. **62** (2002) 2430–2436.
20. Navidpour, L.; Shafaroodi, H.; Abdi, K.; Amini, M.; Ghahremani, M. H.; Dehpour, A. R.; Shafiee, A.: Design, synthesis, and biological evaluation of substituted 3-alkylthio-4,5-diaryl-4*H*-1,2,4-triazoles as selective COX-2 inhibitors. Bioorg. Med. Chem. **14** (2006) 2507–2517.
21. Tozkoparan, B.; Küpeli, E.; Ye silada, E.; Ertan, M.: Preparation of 5-aryl-3-alkylthio-l,2,4-triazoles and corresponding sulfones with anti-inflammatory-analgesic activity. Bioorg. Med. Chem. **15** (2007) 1808–1814.
22. Almajan, G. L.; Barbuceanu, S. -F.; Almajan, E.; Draghici, C.; Saramet, G.: Synthesis, characterization and antibacterial activity of some triazole Mannich bases carrying diphenylsulfone moieties. Eur. J. Med. Chem. **44** (2009) 3083–3089.
23. Al-Deeb, O. A.; Al-Omar, M. A.; El-Brollosy, N. R.; Habib, E. E.; Ibrahim, T. M.; El-Emam, A. A.: Synthesis, antimicrobial, and anti-inflammatory activities of novel 2-[3-(1-adamantyl)-4-substituted-5-thioxo-1,2,4-triazolin-1-yl]acetic acids, 2-[3-(1-adamantyl)-4-substituted-5-thioxo-1,2,4-triazolin-1-yl]propionic acids and related derivatives. Arzneim.-Forsch. **56** (2006) 40–47.
24. Sheldrick, G. M.: A short history of SHELX. Acta Crystallogr. **A64** (2008) 112–122.
25. Sheldrick, G. M.: Crystal structure refinement with SHELXL. Acta Crystallogr. **C71** (2015), 3–8.
26. Brucker. APEX2, SAINT and SADABS. Brucker AXS Inc., Madison, Wisconsin, USA, (2009).