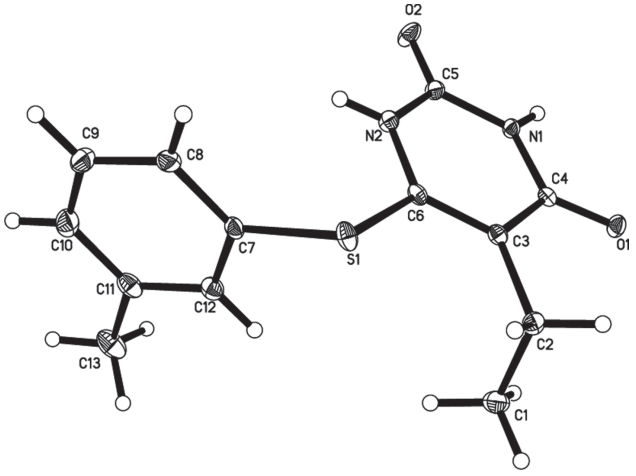
Open Access

Reem I. Al-Wabli, Hazem A. Ghabbour, Siham Lahsasni, Ebtehal S. Al-Abdullah and Ali A. El-Emam*

Crystal structure of 5-ethyl-6-[(3-methylphenyl) sulfanyl]pyrimidine-2,4(1*H*,3*H*)-dione, $C_{13}H_{14}N_2O_2S$



DOI 10.1515/ncrs-2015-0207
Received December 18, 2015; accepted February 8, 2016; available online February 26, 2016

Abstract

$C_{13}H_{14}N_2O_2S$, triclinic, $P\bar{1}$ (no. 2), $a = 4.8885(2)$ Å, $b = 10.3414(5)$ Å, $c = 12.6056(6)$ Å, $\alpha = 95.162(2)°$, $\beta = 97.487(1)°$, $\gamma = 101.494°$, $V = 614.73(5)$ Å^3, $Z = 2$, $R_{gt}(F) = 0.0507$, $wR_{ref}(F^2) = 0.1149$, $T = 100$ K.

CCDC no.: 1422422

The crystal structure is shown in the figure. Tables 1–3 contain details of the measurement method and a list of the atoms including atomic coordinates and displacement parameters.

Table 1: Data collection and handling.

Crystal:	Colourless, needle, size $0.041 \times 0.125 \times 0.789$ mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	2.58 cm^{-1}
Diffractometer, scan mode:	Bruker APEX-II D8 venture, φ and ω scans
$2\theta_{max}$:	66.39°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	34863, 4704
$N(param)_{refined}$:	173
Programs:	SHELX [16], Bruker programs [17]

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

Atom	Site	*x*	*y*	*z*	U_{iso}
H(1A)	2*i*	0.7206	0.0336	0.8976	0.030
H(1B)	2*i*	0.4402	0.0635	0.8329	0.030
H(1C)	2*i*	0.7034	0.1830	0.8788	0.030
H(2A)	2*i*	0.9739	0.1015	0.7559	0.017
H(2B)	2*i*	0.7174	−0.0221	0.7119	0.017
H(8A)	2*i*	1.3085	0.6147	0.6737	0.021
H(9A)	2*i*	1.2738	0.8305	0.7354	0.027
H(10A)	2*i*	1.0003	0.8643	0.8680	0.027
H(12A)	2*i*	0.7837	0.4677	0.8797	0.019
H(13A)	2*i*	0.7400	0.6462	1.0358	0.038
H(13B)	2*i*	0.4861	0.6583	0.9459	0.038
H(13C)	2*i*	0.7178	0.7881	0.9984	0.038
H(1N2)	2*i*	0.703(5)	0.439(2)	0.575(2)	0.037(6)
H(1N1)	2*i*	0.108(5)	0.135(2)	0.484(2)	0.029(5)

Source of material

6-Chloro-5-ethyluracil (1.75 g, 0.01 mol) and *m*-thiocresol (1.24 g, 0.01 mol) were added to a solution of potassium hydroxide (0.56 g, 0.01 mol), in ethanol (50 mL), and the mixture was heated under reflux for four hours. The solvent was then evaporated *in vaccuo* and the residue was treated with water (200 mL), filtered, washed with cold water, dried and crystallized from aqueous ethanol to yield 1.99 g (76%) of the title compound as colourless needles. M.P.: 452–454 K. Crystals suitable for X-ray diffraction were obtained by slow

***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
Reem I. Al-Wabli, Hazem A. Ghabbour, Ebtehal S. Al-Abdullah and Ali A. El-Emam: Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O.Box 2457, Riyadh 11451, Saudi Arabia
Siham Lahsasni: Department of Chemistry, College of Sciences, King Saud University, Riyadh, 11451, Saudi Arabia

Table 3: Fractional coordinates and atomic displacement parameters (Å^2).

Atom	Site	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S(1)	2*i*	1.09014(7)	0.35958(4)	0.72973(3)	0.0096(2)	0.0150(2)	0.0179(2)	0.0024(1)	−0.0026(1)	−0.0043(1)
O(1)	2*i*	0.2631(2)	−0.02499(9)	0.59015(8)	0.0144(5)	0.0105(5)	0.0172(5)	0.0003(4)	0.0004(4)	0.0015(4)
O(2)	2*i*	0.2623(2)	0.3684(1)	0.45650(9)	0.0206(5)	0.0151(5)	0.0220(6)	−0.0023(4)	−0.0079(4)	0.0081(4)
N(1)	2*i*	0.2697(2)	0.1718(1)	0.52333(9)	0.0104(5)	0.0106(5)	0.0119(5)	−0.0002(4)	−0.0021(4)	0.0000(4)
N(2)	2*i*	0.6357(2)	0.3547(1)	0.5810(1)	0.0103(5)	0.0111(5)	0.0145(6)	−0.0014(4)	−0.0010(4)	0.0019(4)
C(1)	2*i*	0.6468(3)	0.0898(2)	0.8472(1)	0.0233(8)	0.0224(7)	0.0150(7)	0.0070(6)	0.0019(6)	0.0036(6)
C(2)	2*i*	0.7655(3)	0.0729(1)	0.7416(1)	0.0141(6)	0.0142(6)	0.0155(6)	0.0056(5)	0.0002(5)	0.0019(5)
C(3)	2*i*	0.6476(3)	0.1537(1)	0.6602(1)	0.0097(6)	0.0129(6)	0.0107(6)	0.0028(5)	0.0006(4)	−0.0006(5)
C(4)	2*i*	0.3855(3)	0.0920(1)	0.5902(1)	0.0108(6)	0.0122(6)	0.0097(6)	0.0027(5)	0.0014(4)	−0.0007(5)
C(5)	2*i*	0.3814(3)	0.3033(1)	0.5164(1)	0.0124(6)	0.0126(6)	0.0119(6)	−0.0011(5)	−0.0002(5)	0.0017(5)
C(6)	2*i*	0.7613(3)	0.2828(1)	0.6525(1)	0.0087(5)	0.0132(6)	0.0105(6)	0.0020(5)	0.0003(4)	−0.0020(5)
C(7)	2*i*	1.0460(3)	0.5220(1)	0.7706(1)	0.0130(6)	0.0123(6)	0.0117(6)	0.0016(5)	−0.0026(5)	−0.0012(5)
C(8)	2*i*	1.1950(3)	0.6289(2)	0.7276(1)	0.0180(7)	0.0190(7)	0.0127(6)	−0.0012(5)	−0.0009(5)	0.0029(5)
C(9)	2*i*	1.1750(4)	0.7565(2)	0.7645(1)	0.0272(8)	0.0170(7)	0.0199(7)	−0.0014(6)	−0.0034(6)	0.0066(6)
C(10)	2*i*	1.0114(3)	0.7762(2)	0.8435(1)	0.0254(8)	0.0155(7)	0.0234(8)	0.0061(6)	−0.0059(6)	0.0014(6)
C(11)	2*i*	0.8622(3)	0.6705(2)	0.8882(1)	0.0150(6)	0.0236(7)	0.0153(7)	0.0068(6)	−0.0033(5)	−0.0019(6)
C(12)	2*i*	0.8821(3)	0.5417(2)	0.8506(1)	0.0123(6)	0.0177(7)	0.0147(6)	0.0014(5)	0.0003(5)	0.0004(5)
C(13)	2*i*	0.6862(4)	0.6927(2)	0.9746(1)	0.0228(8)	0.0336(9)	0.0208(8)	0.0119(7)	0.0011(6)	−0.0056(7)

evaporation of an ethanolic solution at room temperature. ^{1}H NMR (DMSO-d_6, 250 MHz): δ 0.95 (t, 3H, CH_2CH_3, $J = 7.4$ Hz), 2.31 (s, 3H, CH_3), 2.45 (q, 2H, CH_2CH_3, $J = 7.4$ Hz), 7.23–7.48 (m, 4H, Ar-H), 10.82 (s, 1H, NH), 11.22 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ 13.61 (CH_2CH_3), 19.74 (CH_2CH_3), 20.73 (CH_3), 118.63 (Pyrimidine C-5), 126.97, 127.52, 128.20, 129.16, 130.66, 138.82 (Ar—C), 142.83 (Pyrimidine C-2), 150.48 (Pyrimidine C-6), 163.03 (Pyrimidine C-4). ESI-MS, *m/z*: 261.2 $(M\text{-}H)^-$.

Experimental details

Cell refinement and data reduction were carried out by Bruker SAINT and SHELXS-97 [16, 17]. The nitrogen bonded hydrogen atoms were refined freely; all others were idealizes and refined using a riding model (AFIX43, AFIX23 or AFIX137 option of the SHELX program [16].

Discussion

The pyrimidine-2,4(1*H*,3*H*-dione (uracil) nucleus is a major pharmacophore in many chemotherapeutic agents. The chemotherapeutic efficacy of pyrimidine-related derivatives is related to their ability to inhibit vital enzymes responsible for DNA biosynthesis including dihydrofolate reductase (DHFR), thymidylate synthetase (TSase), thymidine phosphorylase (TPase) and reverse transcriptase (RTase). 1-[2-(Hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) and its derivatives have long been known for their potent activity against human immunodeficiency viruses (HIV) [1–7]. In addition, numerous pyrimidine-related derivatives displayed marked activities against herpes simplex viruses (HSV) [8], and hepatitis B viruses (HBV) [9]. Moreover, potent anticancer [10, 11] and antimicrobial activities [12–15] were observed among several pyrimidine-2,4-dione derivatives. In the present investigation, we report the crystal structure of the title compound, which was proved to exhibit marked anti-HIV-1 activity [7].

The asymmetric unit of the crystal structure of title compound contains one molecule. There are two aromatic ring systems in title molecule: the tolyl ring (C7—C12) and the pyrimidine ring (C3/C4/N1/C5/N2/C6) attached to the sulphur atoms. The of these rings planes are almost perpendicular and make a dihedral angle of 88.94(3)°. The molecules packing in the crystal structure is stabilized *via* three intermolecular hydrogen bonds, of which the O1 and O2 act as hydrogen bond acceptors and N1, N2 and C9 act as hydrogen bond donors. The distance of the interactions between the N2—H1N2$\cdots$O2^{i}, N1—H1N1$\cdots$O1^{ii} and C9—H9A$\cdots$O1^{iii} are 2.04(2), 2.00(2) and 2.47 Å, respectively, and the angles are 163(2), 169.7(19) and 146.0°, respectively. Symmetry codes: (i) -*x*+1, -*y*+1, -*z*+1; (ii) -*x*, -*y*, -*z*+1; (iii) *x*+1, *y*+1, *z*.

Acknowledgment: This research project was supported by a grant from the 'Research Center of the Female Scientific and Medical Colleges', Deanship of Scientific Research, King Saud University.

References

1. Hopkins, A. L.; Ren, J.; Esnouf, R. M.; Willcox, B. E.; Jones, E. Y.; Ross, C.; Miyasaka, T.; Walker, R. T.; Tanaka, H.; Stammers, D. K.; Staurt, D. I.: Complexes of HIV-1 reverse transcriptase with Inhibitors of the HEPT Series reveal conformational changes relevant to the design of potent non-nucleoside inhibitors. J. Med. Chem. **39** (1996) 1589–1600.

2. Miyasaka, T.; Tanaka, H.; Baba, M.; Hayakawa, H.; Walker, R. T.; Balzarini, J.; De Clercq, E.: A novel lead for specific anti-HIV-1 agents 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine. J. Med. Chem. **32** (1989) 2507–2509.
3. Pontikis, R.; Benhida, R.; Aubertin, A. H.; Grieson, D. S.; Monneret, C.: Synthesis and anti-HIV activity of novel N-1 side chain-modified analogs of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT). J. Med. Chem. **40** (1997) 1845–1854.
4. Lu, X.; Chen, Y.; Guo, Y.; Liu, Z.; Shi, Y.; Xu, Y.; Wang, X.; Zhang, Z.; Liu, J.: The design and synthesis of *N*-1-alkylated-5-aminoaryalkylsubstituted-6-methyluracils as potential non-nucleoside HIV-1 RT inhibitors. Bioorg. Med. Chem. **15** (2007) 7399–7407.
5. Artico, M.; Massa, S.; Mai, A.; Marongiu, M. E.; Piras, G.; Tramontino, E.; La Colla, P.: 3,4-Dihydro-2-alkyloxy-6-benzyl-4-oxoypyrimidines (DABOs): a new class of specific inhibitors of human immunodeficiency vitus type 1. Antiviral Chem. Chemother. **4** (1993) 361–368.
6. El-Emam, A. A.; Massoud, M. A.; El-Bendary, E. R.; El-Sayed, M. A.: Synthesis of certain 6-substituted uracils and related derivatives as potential antiviral agents. Bull. Kor. Chem. Soc. **25** (2004) 991–996.
7. El-Emam, A. A.; Nasr, M. N. A.; Pedersen, E. B.; Fouad, T.; Nielsen, C.: Synthesis of certain 6-(arylthio)uracils as potential antiviral agents. Phosphorus, Sulfur Silicon Relat. Elem. **174** (2001) 25–35.
8. Russ, P.; Schelling, P.; Scapozza, L.; Folkers, G.; De Clercq, E.; Marquez, V. E.: Synthesis and biological evaluation of 5-substituted derivatives of the potent antiherpes agent (north)-methanocarbathymine. J. Med. Chem. **46** (2003) 5045–5054.
9. Semaine, W.; Johar, M., Tyrrell, D. L. J.; Kumar, R.; Agrawal, B.: Inhibition of hepatitis B virus (HBV) replication by pyrimidines bearing an acyclic moiety:Effect on wild-type and mutant HBV. J. Med. Chem. **49** (2006) 2049–2054.
10. Al-Safarjalani, O. N.; Zhou, X.; Rais, R. H.; Shi, J.; Schinazi, R. F.; Naguib, F. N. M.; El Kouni, M. H.: 5-(Phenylthio)acyclouridine: a powerful enhancer of oral uridine bioavailability: relevance to chemotherapy with 5-fluorouracil and other uridine rescue regimens. Cancer Chemother. Pharmacol. **55** (2005) 541–551.
11. Ghoshal, K.; Jacob, S. T.: An alternative molecular mechanism of action of 5-fluorouracil, a potent anticancer drug. Biochem. Pharmacol. **53** (1997) 1569–1575.
12. Periti, P.: Evolution of bacterial dihydrofolate reductase inhibitors. J. Antimicrob. Chemother. **36** (1995) 887–890.
13. Sincak, C. A.: Iclaprim, a novel diaminopyrimidine for the treatment of resistant Gram-positive infections. Ann Pharmacother. **43** (2009) 1107–1114.
14. Al-Abdullah, E. S.; Al-Obaid, A. M.; Al-Deeb, O. A.; Habib, E. E.; El-Emam, A. A.: Synthesis of novel 6-phenyl-2,4-disubstituted pyrimidine-5-carbonitriles as potential antimicrobial agents. Eur. J. Med. Chem. **46** (2011) 4642–4647.
15. Al-Deeb, O. A.; Al-Turkistani, A. A.; Al-Abdullah, E. S.; El-Brollosy, N. R.; Habib, E. E.; El-Emam, A. A.: Pyrimidine-5-carbonitriles – part III: Synthesis and antimicrobial activity of novel 6-(2-substituted propyl)-2,4-disubstituted pyrimidine-5-carbonitriles. Heterocycl. Commun. **19** (2013) 411–419.
16. Sheldrick, G. M.: A short history of SHELX. Acta Crystallogr. **A64** (2008) 112–122.
17. Brucker. APEX2, SAINT and SADABS. Brucker AXS Inc., Madison, Wisconsin, USA, 2009.