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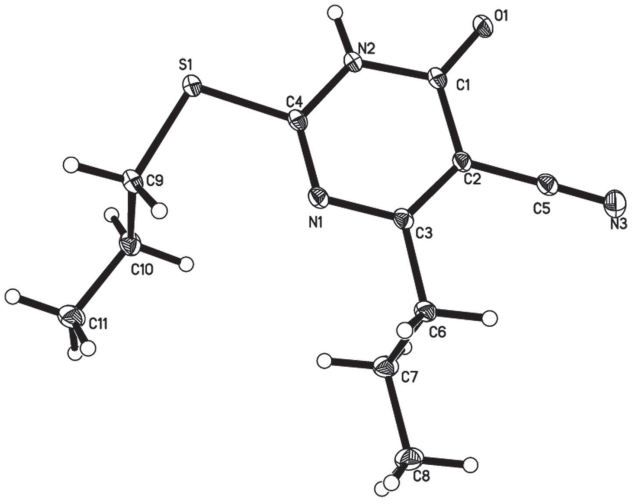
Abdul-Malek S. Al-Tamimi, Hazem A. Ghabbour* and Ali A. El-Emam

Crystal structure of 6-oxo-4-propyl-2-(propylthio)-1,6-dihydropyrimidine-5-carbonitrile, $C_{11}H_{15}N_3OS$



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Abstract

$C_{11}H_{15}N_3OS$, triclinic, $P\bar{1}$ (no. 2), $a = 4.6579(2)$ Å, $b = 9.6316(5)$ Å, $c = 13.6654(7)$ Å, $\alpha = 87.982(2)°$, $\beta = 87.330(2)°$, $\gamma = 78.403(2)°$, $V = 599.69(5)$ Å^3, $Z = 2$, $R_{gt}(F) = 0.0450$, $wR_{ref}(F^2) = 0.128$, $T = 100$ K.

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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.

***Corresponding author: Hazem A. Ghabbour,** Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O.Box 2457, Riaydh 11451, Saudi Arabia, e-mail: ghabbourh@yahoo.com; and Department of Medicinal Chemistry, Faculty of Pharmacy, University of Mansoura, Mansoura 35516, Egypt
Abdul-Malek S. Al-Tamimi: Department of Pharmaceutical Chemistry, College of Pharmacy, Prince Sattam bin Abdulaziz University, Alkharj 11942, Saudi Arabia
Ali A. El-Emam: Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O.Box 2457, Riaydh 11451, Saudi Arabia

Table 1: Data collection and handling.

Crystal:	Colourless, block, size 0.18×0.25×0.48 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	2.53 cm^{-1}
Diffractometer, scan mode:	Bruker APEX-II D8 venture, φ and ω scans
$2\theta_{max}$:	66.38°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	30731, 4565
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\,\sigma(I_{obs})$, 3906
$N(param)_{refined}$:	151
Programs:	SHELX [19], Bruker programs [20]

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

Atom	Site	x	y	z	U_{iso}
H(6A)	2*i*	0.7445	0.1658	0.4203	0.020
H(6B)	2*i*	0.4557	0.0995	0.4326	0.020
H(7A)	2*i*	0.4528	0.3912	0.3789	0.025
H(7B)	2*i*	0.1628	0.3253	0.3889	0.025
H(8A)	2*i*	0.2219	0.4458	0.5332	0.039
H(8B)	2*i*	0.5294	0.3402	0.5491	0.039
H(8C)	2*i*	0.2312	0.2814	0.5580	0.039
H(9A)	2*i*	1.1096	0.3689	0.1937	0.019
H(9B)	2*i*	1.1949	0.4579	0.0998	0.019
H(10A)	2*i*	0.6368	0.5092	0.2034	0.022
H(10B)	2*i*	0.6965	0.5909	0.1027	0.022
H(11A)	2*i*	0.7499	0.7280	0.2405	0.037
H(11B)	2*i*	1.0509	0.6921	0.1766	0.037
H(11C)	2*i*	1.0108	0.6047	0.2764	0.037
H(1N2)	2*i*	0.632(4)	0.090(2)	0.029(2)	0.040(5)

Source of material

To a solution of 6-propyl-2-thiouracil-5-carbonitrile (1.95 g, 0.01 mol) in *N*,*N*-dimethylformamide (DMF) (8 mL), 1-bromopropane (1.23 g, 0.01 mol) and anhydrous potassium carbonate (1.38 g, 0.01 mol) were added and the mixture was stirred at room temperature for 12 h. Water (10 mL) was then gradually added and the mixture was stirred for further 10 min and allowed to stand for 1 h. The precipitated crude product was filtered, washed with cold water, dried and crystallized from aqueous ethanol to yield 1.54 g (65%) of

Table 3: 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*	0.92108(6)	0.29522(3)	0.05407(2)	0.0199(1)	0.0128(1)	0.0162(1)	−0.00635(9)	0.00095(9)	−0.00037(9)
O(1)	2*i*	0.3415(2)	−0.07114(8)	0.10536(6)	0.0268(4)	0.0169(4)	0.0180(4)	−0.0118(3)	−0.0012(3)	−0.0024(3)
N(1)	2*i*	0.7260(2)	0.21810(9)	0.23138(7)	0.0165(4)	0.0104(3)	0.0160(4)	−0.0026(3)	−0.0016(3)	−0.0005(3)
N(2)	2*i*	0.6207(2)	0.09815(9)	0.09428(7)	0.0170(4)	0.0122(4)	0.0152(4)	−0.0057(3)	0.0001(3)	−0.0015(3)
N(3)	2*i*	0.1192(2)	−0.1021(1)	0.35935(8)	0.0262(5)	0.0196(4)	0.0254(5)	−0.0076(4)	0.0018(4)	0.0018(4)
C(1)	2*i*	0.4574(2)	0.0142(1)	0.14710(8)	0.0151(4)	0.0100(4)	0.0174(4)	−0.0024(3)	−0.0011(3)	−0.0002(3)
C(2)	2*i*	0.4343(2)	0.0389(1)	0.25060(7)	0.0148(4)	0.0096(4)	0.0157(4)	−0.0018(3)	0.0002(3)	−0.0005(3)
C(3)	2*i*	0.5703(2)	0.1384(1)	0.28932(8)	0.0153(4)	0.0086(4)	0.0159(4)	−0.0002(3)	−0.0012(3)	−0.0001(3)
C(4)	2*i*	0.7417(2)	0.1964(1)	0.13722(8)	0.0128(4)	0.0091(4)	0.0172(4)	−0.0013(3)	−0.0013(3)	−0.0004(3)
C(5)	2*i*	0.2623(2)	−0.0405(1)	0.31073(8)	0.0180(5)	0.0116(4)	0.0182(5)	−0.0015(3)	−0.0012(4)	−0.0014(3)
C(6)	2*i*	0.5458(2)	0.1713(1)	0.39577(8)	0.0238(5)	0.0116(4)	0.0145(4)	−0.0028(3)	−0.0016(4)	−0.0008(3)
C(7)	2*i*	0.3607(3)	0.3190(1)	0.41438(8)	0.0269(5)	0.0150(5)	0.0176(5)	0.0005(4)	0.0003(4)	−0.0024(4)
C(8)	2*i*	0.3334(3)	0.3493(1)	0.52337(9)	0.0358(7)	0.0208(5)	0.0188(5)	−0.0014(5)	0.0035(5)	−0.0046(4)
C(9)	2*i*	1.0327(2)	0.4202(1)	0.13338(8)	0.0159(4)	0.0125(4)	0.0197(5)	−0.0043(3)	−0.0017(3)	−0.0006(3)
C(10)	2*i*	0.7891(2)	0.5444(1)	0.16233(9)	0.0190(5)	0.0124(4)	0.0234(5)	−0.0022(3)	0.0007(4)	0.0001(4)
C(11)	2*i*	0.9111(3)	0.6519(1)	0.21904(9)	0.0357(6)	0.0157(5)	0.0232(6)	−0.0051(4)	0.0013(5)	−0.0048(4)

the title compound ($C_{11}H_{15}N_3OS$) as colourless block crystals. M.P.: 404–406 K. Single crystals suitable for X-ray diffraction were obtained by slow evaporation of an ethanolic solution at room temperature. ^{1}H NMR (DMSO-d_6, 500.13 MHz): δ 0.98–1.02 (m, 6H, CH_3), 1.68–1.76 (m, 2H, C***H***$_2$CH$_3$), 1.92–2.08 (m, 4H, CH_2), 3.06 (t, 2H, CH_2S, $J = 6.8$ Hz), 12.68 (s, 1H, HN). ^{13}C NMR (DMSO-d_6, 125.76 MHz): 12.83 (CH_3), 14.03 (CH_3), 19.25 (CH_2), 25.35 (CH_2), 29.30 (CH_2S), 34.95 (CH_2), 99.15 (C-5), 114.50 (CN), 161.0 (C-2), 165.34 (C = O), 175.44 (C-4). ESI-MS, *m/z*: 236.2 $(M-H)^-$.

Experimental details

Cell refinement and data reduction were carried out by Bruker SAINT and SHELXS-97 [19, 20]. All hydrogen atoms were idealized and refined using a riding model (AFIX 23 or AFIX 137 option of the SHELX-2008 program [19]) except the nitrogen bonded H atom, which was refined freely.

Discussion

Pyrimidine and pyrimidine-related non-nucleoside derivatives occupy a distinct and unique position in the field of chemotherapy. The chemotherapeutic efficacy of pyrimidine derivatives is related to their ability to inhibit vital enzymes responsible for DNA biosynthesis as dihydrofolate reductase (DHFR), thymidylate synthetase (TSase), thymidine phosphorylase (TPase) and reverse transcriptase (RTase). Non-nucleoside pyrimidine-based derivatives have long been known as potent anticancer drugs [1–4]. Large array of pyrimidine-based analogues have emerged as useful therapies against human immunodeficiency viruses (HIV) [5–8], hepatitis B viruses (HBV) [9], herpes simplex viruses (HSV) [10, 11], influenza viruses [12] and varicella-zoster virus (VZV) [13]. Moreover, several pyrimidine derivatives were reported to display antibacterial [14–17] and antifungal [18] activities. Taking into consideration the diverse chemotherapeutic properties of pyrimidine-5-carbonitrile derivatives, we report herein the synthesis and the crystal structure of the title compound.

The asymmetric unit of the title structure contains only one molecule. The molecule is composed of a dihydropyrimidine ring attached to a propyl, sulfanylpropyl, cyano group and an oxygen atom. The molecular packing in the crystal structure is stabilized *via* one intermolecular hydrogen bond, of which O1 acts as the hydrogen bond acceptor and the NH group (N2) acts as the hydrogen bond donor. The distance of the interactions between N2—H1N2···O1 is 2.7438(13) Å and the angle is 179.00(3)°. Two symmetry related hydrogen bonds connect pairs of adjacent molecules to dimers.

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References

1. Ghoshal, K.; Jacob, S. T.: An alternative molecular mechanism of action of 5-fluorouracil, a potent anticancer drug. Biochem. Pharmacol. **53** (1997) 1569–1575.
2. 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.
3. Matsushita, S.; Nitanda, T.; Furukawa, T.; Sumizawa, T.; Tani, A.; Nishimoto, K.; Akiba, S.; Miyadera, K.; Fukushima, M.; Yamada, Y.; Yoshida, H.; Kanzaki, T.; Akiyama, S.: The effect of a thymidine phosphorylase inhibitor on angiogenesis and apoptosis in tumors. Cancer Res. **59** (1999) 1911–1916.

4. Klein, R. S.; Lenzi, M.; Lim, T. H.; Hotchkiss, K. A.; Wilson, P.; Schwartz, E. L.: Novel 6-substituted uracil analogs as inhibitors of the angiogenic actions of thymidine phosphorylase. Biochem. Pharmacol. **62** (2001) 1257–1263.
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 virus type 1. Antiviral Chem. Chemother. **4** (1993) 361–368.
6. Andries, K.; Azijn, H.; Thielemans, T.; Ludovici, D.; Kukla, M.; Heeres, J.; Janssen, P.; De Corte, B.; Vingerhoets, J.; Pauwels, R.; de Béthune, M. -P.: TMC125, a novel next-generation nonnucleoside reverse transcriptase inhibitor active against nonnucleoside reverse transcriptase inhibitor-resistant human immunodeficiency virus type 1. Antimicrob. Agents Chemother. **48** (2004) 4680–4686.
7. Summa, V.; Petrocchi, A.; Bonelli, F.; Crescenzi, B.; Donghi, M.; Ferrara, M.; Fiore, F.; Gardelli, C.; Paz, O. G.; Hazuda, D. J.; Jones, P.; Kinzel, O.; Laufer, R.; Monteagudo, E.; Muraglia, E.; Nizi, E.; Orvieto, F.; Pace, P.; Pescatore, G.; Scarpelli, R.; Stillmock, K.; Witmer, M. V.; Rowley, M.: Discovery of raltegravir, a potent, selective orally bioavailable HIV-Integrase inhibitor for the treatment of HIV-AIDS infection. J. Med. Chem. **51** (2008) 5843–5855.
8. Yu, M.; Liu, X.; Li, Z.; Liu, S.; Pannecouque, C.; De Clercq, E.: Synthesis and biological evaluation of novel 2-(substituted phenylaminocarbonylmethylthio)-6- (2,6-dichlorobenzyl)-pyrimidin-4(3*H*)-ones as potent HIV-1 NNRTIs. Bioorg. Med. Chem. **17** (2009) 7749–7754.
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. 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.
11. Skorobogatyi, M. V.; Ustinov, A. V.; Stepanova, I. A.; Pchelintseva, A. A.; Petrunina, A. L.; Andronova, V. L.; Galegov, G. A.; Malakhov, A. D.; Korshun, V. A.: 5-Arylethynyl-2-deoxyuridines, compounds active against HSV-1. Org. Biomol. Chem. **4** (2006) 1091–1096.
12. Saladino, R.; Crestini, C.; Palamara, A. T.; Danti, M. C.; Manetti, F.; Corelli, F.; Garaci, E.; Botta, M.: Synthesis, biological evaluation, and pharmacophore generation of uracil, 4(3*H*)-pyrimidinone, and uridine derivatives as potent and selective inhibitors of parainfluenza 1 (Sendai) virus. J. Med. Chem. **44** (2001) 4554–4562.
13. Onishi, T.; Mukai, C.; Nakagawa, R.; Sekiyama, T.; Aoki, M.; Suzuki, K.; Nakazawa, H.; Ono, N.; Ohmura, Y.; Iwayama, S.; Okunishi, M.; Tsuji, T.: Synthesis and antiviral activity of novel anti-VZV 5-substituted uracil nucleosides with a cyclopropane sugar moiety. J. Med. Chem. **43** (2000) 278–282.
14. Agarwal, N.; Srivastava, P.; Raghuwanshi, S. K.; Upadhyay, D. N.; Sinha, S.; Shukla, P. K.; Ram, V. J.: Chloropyrimidines as a new class of antimicrobial agents. Bioorg. Med. Chem. **10** (2002) 869–874.
15. 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.
16. 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.
17. Al-Abdullah, E. S.; Al-Turkistani, A. A.; Al-Deeb, O. A.; El-Brollosy, N. R.; Habib, E. E.; El-Emam, A. A.: Pyrimidine-5-carbonitriles II: synthesis and antimicrobial activity of novel 6-alkyl-2,4-disubstituted pyrimidine-5-carbonitriles. Drug Res. **64** (2014) 31–39.
18. Agarwal, N.; Raghuwanshi, S. K.; Upadhyay, D. N.; Shukla, P. K.; Ram, V. J.: Suitably functionalised pyrimidines as potential antimycotic agents. Bioorg. Med. Chem. Lett. **10** (2000) 703–706.
19. Sheldrick, G. M.: A short history of SHELX. Acta Crystallogr. **A64** (2008) 112–122.
20. Brucker. APEX2, SAINT and SADABS. Brucker AXS Inc., Madison, WI, USA, 2009.