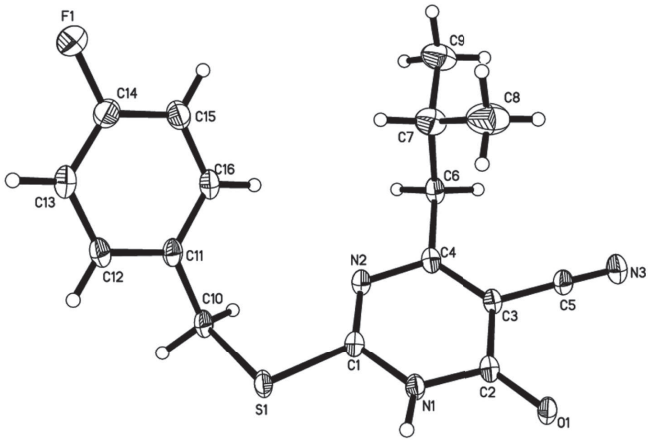
Open Access

Ali A. El-Emam, Hazem A. Ghabbour*, Omar A. Al-Deeb, Mohammed S. M. Abdelbaky and Santiago García-Granda

Crystal structure of 2-[(4-fluorobenzyl)sulfanyl]-4-(2-methylpropyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile, $C_{16}H_{16}FN_3OS$



DOI 10.1515/ncrs-2015-0123
Received November 20, 2015; accepted January 7, 2016; available online January 30, 2016

Abstract

$C_{16}H_{16}FN_3OS$, triclinic, $P\bar{1}$ (no. 2), $a = 5.6885(3)$ Å, $b = 9.4378(4)$ Å, $c = 15.0736(7)$ Å, $\alpha = 84.037(4)°$, $\beta = 81.442(4)°$, $\gamma = 74.271(4)°$, $V = 768.56(7)$ Å^3, $Z = 2$, $R_{gt}(F) = 0.0518$, $wR_{ref}(F^2) = 0.1430$, $T = 100$ K.

CCDC no.: 1405607

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

Ali A. El-Emam and Omar A. Al-Deeb: Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O.Box 2457, Riaydh 11451, Saudi Arabia

Mohammed S. M. Abdelbaky and Santiago García-Granda: Departamento de Química Física y Analítica, Facultad de Química, Universidad de Oviedo – CINN, C/ Julian Clavería, 8, 33006 Oviedo, (Asturias), Spain

Table 1: Data collection and handling.

Crystal:	Colourless, prism, size 0.0508×0.0622×0.4616 mm
Wavelength:	CuK_α radiation (1.5418 Å)
μ:	20.14 cm^{-1}
Diffractometer, scan mode:	Xcalibur, Ruby, Gemini, ω scans
$2\theta_{max}$:	141.36°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	11233, 2940
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\,\sigma(I_{obs})$, 2544
$N(param)_{refined}$:	199
Programs:	CrysAlis [18], SHELX [19]

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

Atom	Site	x	y	z	U_{iso}
H(1)	2*i*	0.4381	0.6334	0.5251	0.026
H(13)	2*i*	−0.4737	1.2318	0.8092	0.035
H(12)	2*i*	−0.2578	1.1887	0.6676	0.030
H(6A)	2*i*	0.9096	0.8271	0.7583	0.030
H(6B)	2*i*	1.0731	0.6639	0.7605	0.030
H(16)	2*i*	0.3620	1.0019	0.7788	0.032
H(10A)	2*i*	0.3864	1.0708	0.6198	0.029
H(10B)	2*i*	0.1497	1.1572	0.5771	0.029
H(15)	2*i*	0.1479	1.0477	0.9204	0.038
H(7)	2*i*	0.5987	0.7620	0.8599	0.046
H(9A)	2*i*	0.9170	0.8135	0.9222	0.069
H(9B)	2*i*	1.0533	0.6451	0.9280	0.069
H(9C)	2*i*	0.8003	0.7030	0.9872	0.069
H(8A)	2*i*	0.6347	0.5257	0.8186	0.084
H(8B)	2*i*	0.6248	0.5259	0.9231	0.084
H(8C)	2*i*	0.8769	0.4663	0.8637	0.084

Source of material

4-Fluorobenzyl chloride (1.45 g, 0.01 mol) and anhydrous potassium carbonate (1.38 g, 0.01 mol) were added to a solution of 6-(2-methylpropyl)-2-thiouracil-5-carbonitrile (2.09 g, 0.01 mol) in *N*,*N*-dimethylformamide (10 mL) and the mixture was stirred at room temperature for 12 hours. Water (15 mL) was gradually added and the mixture was stirred

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*	0.2170(1)	0.90545(6)	0.56345(4)	0.0213(3)	0.0169(3)	0.0320(3)	0.0027(2)	−0.0085(2)	−0.0033(2)
O(1)	2*i*	0.7895(3)	0.4171(2)	0.5397(1)	0.0205(8)	0.0153(7)	0.0312(8)	−0.0002(6)	−0.0056(6)	−0.0036(6)
N(1)	2*i*	0.5314(3)	0.6460(2)	0.5619(1)	0.0189(9)	0.0167(9)	0.028(1)	−0.0004(7)	−0.0077(7)	−0.0031(7)
F(1)	2*i*	−0.3080(3)	1.1698(2)	0.9594(1)	0.0371(9)	0.054(1)	0.0331(8)	0.0011(7)	0.0015(6)	−0.0048(7)
N(2)	2*i*	0.5880(3)	0.8033(2)	0.6637(1)	0.0197(9)	0.0167(9)	0.029(1)	−0.0010(7)	−0.0038(7)	−0.0022(7)
N(3)	2*i*	1.2865(4)	0.3801(2)	0.6700(2)	0.024(1)	0.021(1)	0.040(1)	−0.0016(8)	−0.0078(8)	−0.0001(8)
C(5)	2*i*	1.1004(4)	0.4611(2)	0.6592(2)	0.023(1)	0.017(1)	0.028(1)	−0.0039(9)	−0.0045(9)	−0.0013(8)
C(3)	2*i*	0.8740(4)	0.5667(2)	0.6426(2)	0.018(1)	0.017(1)	0.027(1)	−0.0012(8)	−0.0046(8)	0.0001(8)
C(1)	2*i*	0.4714(4)	0.7753(2)	0.6021(2)	0.018(1)	0.017(1)	0.027(1)	−0.0022(8)	−0.0014(8)	−0.0015(8)
C(2)	2*i*	0.7375(4)	0.5334(2)	0.5781(2)	0.017(1)	0.016(1)	0.027(1)	−0.0021(8)	−0.0019(8)	0.0010(8)
C(4)	2*i*	0.7908(4)	0.6957(2)	0.6862(2)	0.019(1)	0.017(1)	0.027(1)	−0.0030(8)	−0.0017(8)	0.0011(8)
C(13)	2*i*	−0.3059(4)	1.1861(3)	0.8025(2)	0.020(1)	0.024(1)	0.040(1)	−0.0007(9)	−0.003(1)	−0.004(1)
C(12)	2*i*	−0.1764(4)	1.1600(2)	0.7183(2)	0.023(1)	0.017(1)	0.035(1)	−0.0023(9)	−0.0091(9)	0.0000(9)
C(6)	2*i*	0.9050(4)	0.7245(2)	0.7633(2)	0.022(1)	0.018(1)	0.034(1)	−0.0021(8)	−0.0075(9)	−0.0009(9)
C(11)	2*i*	0.0752(4)	1.0910(2)	0.7083(2)	0.023(1)	0.013(1)	0.033(1)	−0.0029(8)	−0.0049(9)	−0.0024(8)
C(16)	2*i*	0.1945(4)	1.0486(2)	0.7849(2)	0.021(1)	0.019(1)	0.038(1)	−0.0005(9)	−0.0070(9)	−0.0032(9)
C(14)	2*i*	−0.1813(5)	1.1430(3)	0.8763(2)	0.031(1)	0.029(1)	0.031(1)	−0.004(1)	−0.000(1)	−0.004(1)
C(10)	2*i*	0.2172(4)	1.0720(2)	0.6161(2)	0.024(1)	0.015(1)	0.033(1)	−0.0007(8)	−0.0059(9)	−0.0002(9)
C(15)	2*i*	0.0678(5)	1.0750(3)	0.8694(2)	0.031(1)	0.027(1)	0.035(1)	−0.001(1)	−0.011(1)	−0.003(1)
C(7)	2*i*	0.7607(5)	0.6908(3)	0.8553(2)	0.042(2)	0.042(2)	0.033(1)	−0.013(1)	−0.008(1)	−0.001(1)
C(9)	2*i*	0.8953(6)	0.7153(4)	0.9301(2)	0.062(2)	0.050(2)	0.033(2)	−0.023(2)	−0.014(1)	0.002(1)
C(8)	2*i*	0.7207(7)	0.5384(4)	0.8661(2)	0.078(2)	0.060(2)	0.039(2)	−0.037(2)	−0.004(2)	0.002(1)

for additional 30 minutes. The precipitated crude product was filtered, washed with water, dried, and crystallized from aqueous ethanol to yield 2.29 g (72%) of the title compound. M.p. 481–483 K. Colourless prismatic single crystals were obtained by slow evaporation of an ethanolic solution at room temperature. ^{1}H NMR (DMSO-d_6, 500.13 MHz): δ 0.92 (d, 6H, CH_3, $J = 6.0$ Hz), 2.14 (m, 1H, CH), 2.55 (d, 2H, C***H***$_2$CH, $J = 6.0$ Hz), 4.46 (s, 2H, CH_2S), 7.12–7.16 (m, 2H, Ar—H), 7.45–7.47 (m, 2H, Ar—H), 13.70 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125.76 MHz): δ 22.6 (CH_3), 28.0 (CH), 33.7 (CH_2S), 45.4 (***C***H_2CH), 96.2 (C-5), 115.5 (CN), 115.8, 131.4, 133.5, 162.9 (Ar—C), 161.0 (C-6), 165.9 (C = O), 174.0 (C-4); ESI-MS, *m/z* (rel. int.): 316.2 (M—H, 100)$^-$.

Discussion

Various pyrimidine non-nucleoside analogues have been developed as potent chemotherapeutic agents with anticancer, antiviral, antifungal and antibacterial activities. Non-nucleoside pyrimidine-based analogues have emerged as useful therapies against human immunodeficiency viruses (HIV) [1–4], hepatitis B viruses (HBV) [5], herpes simplex viruses (HSV) [6, 7], varicella-zoster virus (VZV) [8] and influenza viruses [9]. A large number of pyrimidine-based antimetabolites are currently used as potent and selective anticancer activity [10–12]. In addition, marked antibacterial and antifungal activities were observed for several pyrimidine-5-carbonitrile derivatives [13–17]. Here, we report the crystal structure of the recently synthesized [16] title compound ($C_{16}H_{16}FN_3OS$).

The crystal structure of the title compound contains one molecule in the asymmetric unit. With respect to the pyrimidinyl ring, (C1/N1/C2/C3/C4/N2), the fluorobenzene ring (C11—C16) form dihedral angle of 51.2 (1)°. The molecular packing is stabilized by one intermolecular hydrogen bond where O1 acts as hydrogen bond acceptor and the NH group (N1) is the hydrogen bond donor. The H···O distance of the N1—H1···O1 hydrogen bond is 1.91(1) Å and the angle is 169.7(1)°.

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. PRG-1436–23. We also acknowledge the financial support from Spanish Ministerio de Economía y Competitividad (MINECO-13-MAT2013–40950-R, FPI grant BES-2011–046948 to MSM-A).

References

1. 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.
2. 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.
3. 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.
4. 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(3H)-ones as potent HIV-1 NNRTIs. Bioorg. Med. Chem. **17** (2009) 7749–7754.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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(3H)-pyrimidinone, and uridine derivatives as potent and selective inhibitors of parainfluenza 1 (Sendai) virus. J. Med. Chem. **44** (2001) 4554–4562.
10. 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.
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. 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.
13. 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.
14. 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.
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. CrysAlis CCD, CrysAlis RED and associated programs: Oxford Diffraction. Oxford Diffraction Ltd, Abingdon, England, 2006.
19. Sheldrick, G. M.: A short history of SHELX. Acta Cryst. **A64** (2008) 112–122.