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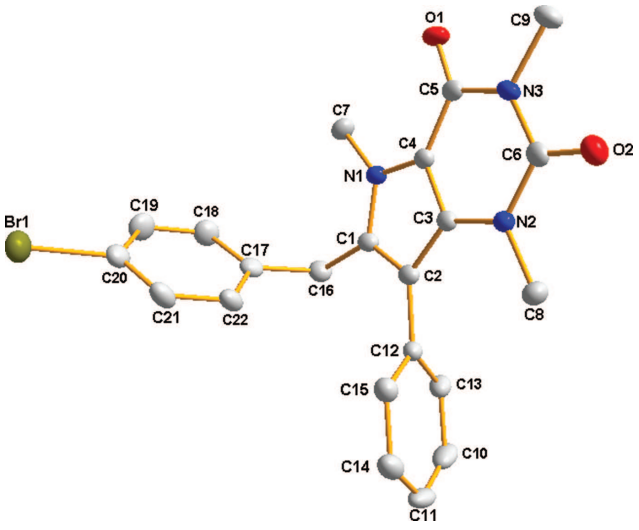
The crystal structure of 6-(4-bromobenzyl)-1,3,5-trimethyl-7-phenyl-1,5-dihydro-2*H*-pyrrolo[3,2-d] pyrimidine-2,4(3*H*)-dione, $C_{22}H_{20}BrN_3O_2$



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Abstract

$C_{22}H_{20}BrN_3O_2$, monoclinic, $P2_1/c$ (no. 14), $a = 15.889(12)$ Å, $b = 16.332(13)$ Å, $c = 7.324(5)$ Å, $\beta = 94.985(5)$, $V = 1893(2)$ Å^3, $Z = 4$, $R_{gt}(F) = 0.0295$, $wR_{ref}(F^2) = 0.0790$, $T = 100(2)$ K.

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The asymmetric unit of the title crystal structure is shown in the figure. Hydrogen atoms are omitted for clarity. 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

To a stirred solution of 1,3-dimethyl-5-(methylamino) uracil (169 mg, 1 mmol) in CH_3CN (2 mL) was added 1-(4-bromophenyl)-3-phenyl propargylic alcohol (344 mg, 1.2 mmol, 1.2 eq.) at room temperature under a nitrogen atmosphere. After stirring for ca. 5 min $Al(OTf)_3$ (47 mg, 0.1 mmol, 0.1 eq.), used as catalyst, was added and the reaction mixture heated to reflux for ca. 2 h. Upon completion (monitored by TLC) the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was extracted with dichloromethane (3×25 mL), the organic phases combined, washed with brine (4×25 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product purified by flash column chromatography using *n*-hexane-ethyl acetate mixture (8:1) to yield the title compound (370 mg, 85%). Crystallization from *n*-hexane and ethyl acetate yielded grey needle-shaped crystals. **Mp** 178–180 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 2.99 (s, 3H), 3.32 (s, 3H), 3.70 (s, 2H), 3.74 (s, 3H), 6.76 (d, 2H, $J = 9.0$ Hz), 7.12–7.17 (m, 2H), 7.24–7.29 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 27.9, 29.7, 32.4, 33.2, 110.4, 111.1, 120.5, 128.0, 128.4, 129.4, 131.5, 131.9, 132.2, 133.5, 136.5, 138.3, 152.0, 156.0. **HRMS (ESI)** calcd for $C_{22}H_{20}BrN_3O_2Na$ $(M + Na)^+$ 460.0637; found 460.0636.

Table 1: Data collection and handling.

Crystal:	Needle, colorless
Size:	$0.58 \times 0.21 \times 0.16$ mm
Wavelength:	Mo $K\alpha$ radiation (0.71069 Å)
μ:	2.19 mm^{-1}
Diffractometer, scan mode:	Bruker APEX-II, φ and ω-scans
θ_{max}, completeness:	50°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	72106, 4558, 0.055
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 3788
$N(param)_{refined}$:	257
Programs:	Bruker programs [1], SHELX [2], DIAMOND [3]

Experimental details

The aromatic H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms, with C—H = 0.95 and 0.98 Å and $U_{iso}(H) = 1.5\ U_{eq}(C)$ and $1.2\ U_{eq}(C)$, respectively. The placement of the H atoms of the methyl group was that of an idealised methyl group according

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
Br1	0.87269(2)	0.12325(2)	0.45364(3)	0.03384(8)
N1	1.22507(9)	0.21902(8)	−0.04103(18)	0.0190(3)
N2	1.41962(9)	0.15349(9)	0.1866(2)	0.0198(3)
N3	1.42448(9)	0.29810(8)	0.1879(2)	0.0214(3)
O1	1.31760(9)	0.37807(7)	0.05439(18)	0.0263(3)
O2	1.53312(8)	0.22176(8)	0.32185(18)	0.0291(3)
C1	1.21240(11)	0.13636(10)	−0.0528(2)	0.0194(3)
C2	1.28148(11)	0.09527(10)	0.0320(2)	0.0193(3)
C3	1.33920(10)	0.15749(10)	0.0978(2)	0.0180(3)
C4	1.30319(10)	0.23279(10)	0.0516(2)	0.0186(3)
C5	1.34481(11)	0.30914(10)	0.0931(2)	0.0205(3)
C6	1.46360(11)	0.22377(10)	0.2375(2)	0.0216(3)
C7	1.16553(11)	0.28248(11)	−0.1075(2)	0.0235(4)
H7A	1.1416	0.2687	−0.2315	0.035*
H7B	1.1949	0.3352	−0.1098	0.035*
H7C	1.1200	0.2863	−0.0258	0.035*
C8	1.46049(11)	0.07487(11)	0.2326(3)	0.0255(4)
H8A	1.4362	0.0511	0.3390	0.038*
H8B	1.5212	0.0834	0.2615	0.038*
H8C	1.4514	0.0375	0.1280	0.038*
C9	1.47477(12)	0.37172(10)	0.2365(3)	0.0280(4)
H9A	1.5034	0.3652	0.3597	0.042*
H9B	1.4375	0.4196	0.2343	0.042*
H9C	1.5169	0.3794	0.1480	0.042*
C10	1.30899(12)	−0.12650(12)	−0.0957(3)	0.0340(5)
H10	1.3169	−0.1579	−0.2021	0.041*
C11	1.30637(12)	−0.16487(11)	0.0711(3)	0.0363(5)
H11	1.3125	−0.2226	0.0796	0.044*
C12	1.28952(10)	0.00488(10)	0.0471(2)	0.0205(3)
C13	1.30005(11)	−0.04174(11)	−0.1088(3)	0.0260(4)
H13	1.3011	−0.0156	−0.2245	0.031*
C14	1.29485(12)	−0.11938(11)	0.2268(3)	0.0338(4)
H14	1.2927	−0.1461	0.3415	0.041*
C15	1.28645(11)	−0.03478(11)	0.2155(3)	0.0269(4)
H15	1.2786	−0.0038	0.3225	0.032*
C16	1.13021(11)	0.10044(11)	−0.1334(2)	0.0239(4)
H16A	1.1393	0.0428	−0.1688	0.029*
H16B	1.1102	0.1312	−0.2453	0.029*
C17	1.06334(11)	0.10373(10)	0.0022(2)	0.0218(3)
C18	0.98923(12)	0.14876(12)	−0.0298(3)	0.0285(4)
H18	0.9782	0.1765	−0.1433	0.034*
C19	0.93089(12)	0.15402(13)	0.1007(3)	0.0310(4)
H19	0.8800	0.1841	0.0762	0.037*
C20	0.94843(11)	0.11474(11)	0.2667(3)	0.0251(4)
C21	1.02109(11)	0.06872(11)	0.3015(3)	0.0275(4)
H21	1.0322	0.0414	0.4156	0.033*
C22	1.07732(11)	0.06286(11)	0.1688(3)	0.0255(4)
H22	1.1266	0.0302	0.1916	0.031*

to the electron-density map (AFIX 123 option of the SHELX system [2]). The highest peak is 0.41 e·Å^{-3} and the deepest hole is −0.49 e·Å^{-3}

Discussion

The presented scaffold represents a family of alkaloids which potentially translate to be a derivative of xanthines. It is known that the strategic substitutions on the amine nitrogen or the core itself could potentially impact towards a different pharmacological behaviour of the compound. As a result these compounds become selective towards different Adenosine Receptor (ARs) antagonists as perceived with OT-7999 studied for the treatment of glaucoma [4]. Moreover, these heterocycles have proved to be very important prospects in medicinal chemistry and organic synthesis in prompting extensive research on these pyrrole and pyrimidine-containing compounds [5, 6]. They have been found to exhibit active pharmacological properties such as antibacterial [7], antimicrobial [8], antitumor [8, 9], antimalarial [10], immunosuppressant [11], anti-oxidant [12] and anti-inflammatory [13] activities. To some extent, these pymiridine and pyrrole segments combined, signalled to also exhibit biological activities [14–16]. It is of these aforementioned statements, that the synthesis of these xanthine based derivatives, from easily accessible precursors, are of paramount importance.

There is one molecule in the asymmetric unit of the title structure (*cf*. the figure). The crystal structure is stabilized by very weak intra-molecular interactions between O1 and O2, respectively, with hydrogen atoms from neighbouring methyl groups. The atom O1 undergoes bifurcation with two hydrogens from C7 and C9 methyl groups. The core xanthine molecule in the asymmetric unit conforms in a way that is about 8° off from sitting perpendicular to the substituted bromo-benzyl moiety. As a result, the molecule itself hinders any inter-molecular interactions due to the observed steric hindrance (with a dihedral angle of almost perpendicular planes amounting to 81.9°).

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References

1. Bruker, SAINT-Plus (Version 7.12), Bruker AXS Inc., Madison, WI, USA (2004).
2. Sheldrick, G. M.: A short history of SHELX. Acta Crystallogr. **A64** (2008) 112–122.
3. Brandenbug, K.; Putz, H.: DIAMOND. Visual Crystal Structure Information System. Version 3.0c. Crystal Impact GbR, Bonn, Germany (2005).
4. Jacobson, K. A.: Introduction to adenosine receptors as therapeutic targets. Springer Berlin Heidelberg **193** (2009) 13–16.
5. Bean, G. P.: Chemistry of heterocyclic compounds, pyrroles. Jones R. A., Ed. John Wiley & Sons, Inc., New York (1990) 105–294.
6. Gilchrist, T. L.: Synthesis of aromatic heterocycles. J. Chem. Soc. Perkin Trans. **1** (1998) 615–628.

7. Paliwal, P. K.; Jetti, S. R.; Jain, S.: Green approach towards the facile synthesis of dihydropyrano(c)chromene and pyrano [2,3-d]pyrimidine derivatives and their biological evaluation. Med. Chem. Res. **22** (2013) 2984–2990.
8. El-Kalyoubi, S.; Agili, F.: A novel synthesis of fused uracils: indenopyrimidopyridazines, pyrimidopyridazines, and pyrazolopyrimidines for antimicrobial and antitumor evalution. Molecules **21** (2016) 1714.
9. El-Kalyoubi, S.; Fayed, E.: Synthesis and evaluation of antitumour activities of novel fused tri-and tetracyclic uracil derivatives. J. Chem. Res. **40** (2016) 771–777.
10. Mital, A.; Murugesan, D.; Kaiser, M.; Yeates, C.; Gilbert, I. H.: Discovery and optimisation studies of antimalarial phenotypic hits. Eur. J. Med. Chem. **103** (2015) 530–538.
11. Murray, C. M.; Hutchinson, R.; Bantick, J. R.; Belfield, G. P.; Benjamin, A. D.; Brazma, D.; Bundick, R. V.; Cook, I. D.; Craggs, R. I.; Edwards, S.; Evans, L. R.; Harrison, R.; Holness, E.; Jackson, A. P.; Jackson, C. G.; Kingston, L. P.; Perry, M. W. D.; Ross, A. R. J.; Rugman, P. A.; Sidhu, S. S.; Sullivan, M.; Taylor-Fishwick, D. A.; Walker, P. C.; Whitehead, Y. M.; Wilkinson, D. J.; Wright, A.; Donald, D. K.: Monocarboxylate transporter MCT1 is a target for immunosuppression. Nat. Chem. Biol. **1** (2005) 371–376.
12. Yousefi, A.; Yousefi, R.; Panahi, F.; Sarikhani, S.; Zolghadr, A. R.; Bahaoddini, A.; Khalafi-Nezhad, A.: Novel curcumin-based pyrano[2,3-d]pyrimidine anti-oxidant inhibitors for α-amylase and α-glucosidase: Implications for their pleiotropic effects against diabetes complications. Int. J. Biol. Macromol. **78** (2015) 46–55.
13. Choi, Y. H.; Shin, E. M.; Kim, Y. S.; Cai, X. F.; Lee, J. J.; Kim, H. P.: Anti-inflammatory principles from the fruits of evodia rutaecarpa and their cellular action mechanisms. Arch. Pharm. Res. **29** (2006) 293–297.
14. Singh, P.; Kaur, J.; Singh, G.; Bhatti, R.: Triblock Conjugates: identification of a highly potent antiinflammatory agent. J. Med. Chem. **58** (2015) 5989–6001.
15. Gupta, P. K.; Nassiri, M. R.; Coleman, L. A.; Wotring, L. L.; Drach, J. C.; Townsend, L. B.: Synthesis, cytotoxicity, and antiviral activity of certain 7-[(2-hydroxyethoxy)methyl]pyrrolo [2,3-d]pyrimidine nucleosides related to toyocamycin and sangivamycin. J. Med. Chem. **32** (1989) 1420–1425.
16. Suresh, T.; Nandha kumar R.; Mohan, P. S.: Synthesis and antibacterial activities of 1,2,3,4,6,7,8,9-octahydro-1,3,7,9-tetraphenyl 5-pyrrolo-2,4,6,8-tetraoxo-10*H*, 5*H* pyrido[2,3-d; 6,5-d′] dipyrimidine. Heterocycl. Commun. **9** (2011) 203–208.