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Short Note

5-[(3-Fluorophenyl)(2-hydroxy-6-oxocyclohex-1-en-1-yl)methyl]-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione

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Abstract: 5-[(3-Fluorophenyl)(2-hydroxy-6-oxocyclohex-1-en-1-yl)-methyl]-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **3** was synthesized via a multicomponent reaction. The Aldol–Michael addition reactions of *N*,*N*-dimethylbarbituric acid, cyclohexane-1,3-dione, and 3-fluorobenzaldehyde in aqueous solution gave the product in high yield. The molecular structure of the compound was confirmed by spectroscopic methods and X-ray crystallography. The title compound ($C_{19}H_{19}FN_2O_5 \cdot H_2O$) crystallizes in the Monoclinic form, $P2_1/c$, a = 7.8630 (5) Å, b = 20.0308 (13) Å, c = 11.3987 (8) Å, β = 104.274 (3)°, V = 1739.9 (2)° Å^3, Z = 4, R_{int} = 0.117, $wR(F^2)$ = 0.124, T = 100 K.

Keywords: Barbituric acid; Pyrimidine; Green chemistry

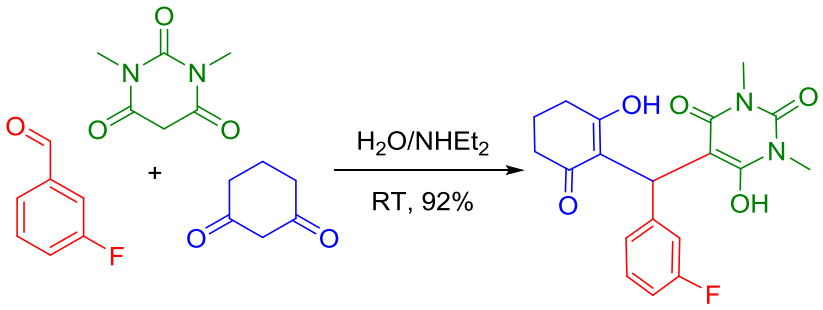
1. Introduction

The barbituric acid skeleton represents an important structural motif that is embodied in a number of pharmaceutical agents with activities including anti-osteoporosis [1–3], anticonvulsant [4,5], urease inhibition [6,7], sedation, anesthesia [8,9], hypnosis [10], anti-oxidant [11], radio-sensitization, tyrosinase or alpha-glucosidase inhibition [12,13], anti-bacterial [14], anti-fungal [14], anti-cancer [14], and anxiolytic effects [3]. Many of these representatives are in clinical use as hypnotic and anti-inflammatory drugs; for example, sodium pentothal, phenobarbital, veronal, seconal, and bucolome [8,9]. We have synthesized a new pyrimidine derivative through a tandem Aldol–Michael reaction in aqueous medium. The desired compound was characterized by spectroscopic techniques and by X-ray single crystal analysis.

2. Results

The title compound 5-[(3-fluorophenyl)(2-hydroxy-6-oxocyclohex-1-en-1-yl)-methyl]-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione was synthesized following a reported procedure by Barakat et al. [15] (Scheme 1). The chemical reagents and solvents used in this study are commercially available. This reaction proceeds efficiently at room temperature (RT) in water and it is mediated by $NHEt_2$. The structure of the synthesized compound was characterized using spectroscopic techniques like IR,

^{1}H-, and ^{13}C-NMR, GCMS, and elemental analysis. A suitable single crystal was grown in a mixture of dichloromethane/ethanol/diethyl ether and was used for X-ray diffraction analysis.



Scheme 1. Synthesis of the target compound.

3. Discussion

Single-Crystal X-Ray Diffraction Study

The structure of 5-[(3-fluorophenyl)(2-hydroxy-6-oxocyclohex-1-en-1-yl)-methyl]-6-hydroxy-1,3-dimethyl-pyrimidine-2,4(1*H*,3*H*)-dione was confirmed by X-ray crystal structure analysis. The features of the structure refinements, crystallographic data, and conditions retained for the intensity data collection are given in Table 1. The bond angles and interatomic distances are listed in Table 2 [16,17]. COD ID 3000079 contains the supplementary crystallographic data for this paper.

In the unit cell (Figure 1), the title compound was crystallized with one molecule of water as a solvent, which forms strong hydrogen bonds with O1, O2, and O4. The F atom shows disorder over two positions, with site occupancies of 0.773 (4) and 0.227 (4). The 6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione ring (C1/N1/C3/N2/C5/C6) was found to adopt nearly dihedral angles with the 2,6-dihydroxycyclohex-1-en ring (C8–C13) and 3-fluorophenyl ring (C14–C19) as 64.56 (5) and 68.38 (3)°, respectively. On the other hand, the 2,6-dihydroxycyclohex-1-en ring forms a dihedral angle of 46.90 (5)° with the 3-fluorophenyl ring. The title compound having bond lengths of C5=C6 and C8=C9 are 1.369 (4) and 1.373 (4) Å, respectively, and these are typical carbon carbon double bonds. In the crystal structure, molecules are linked via a network of intermolecular hydrogen bonds (Table 3, Figure 2).

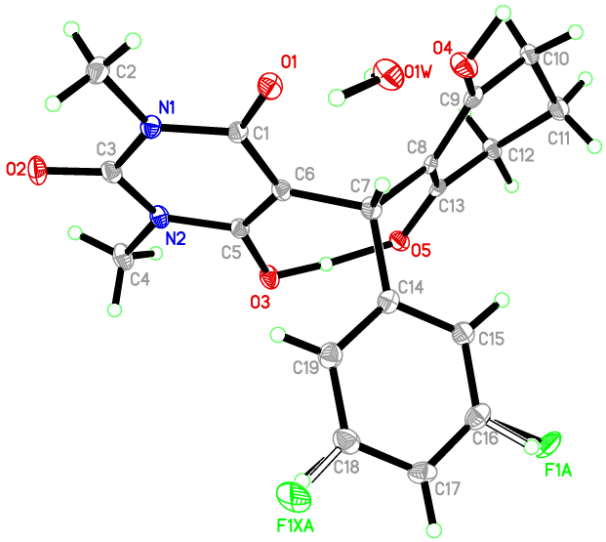


Figure 1. The molecular structure of the target compound showing 40% probability displacement ellipsoids for non-H atoms.

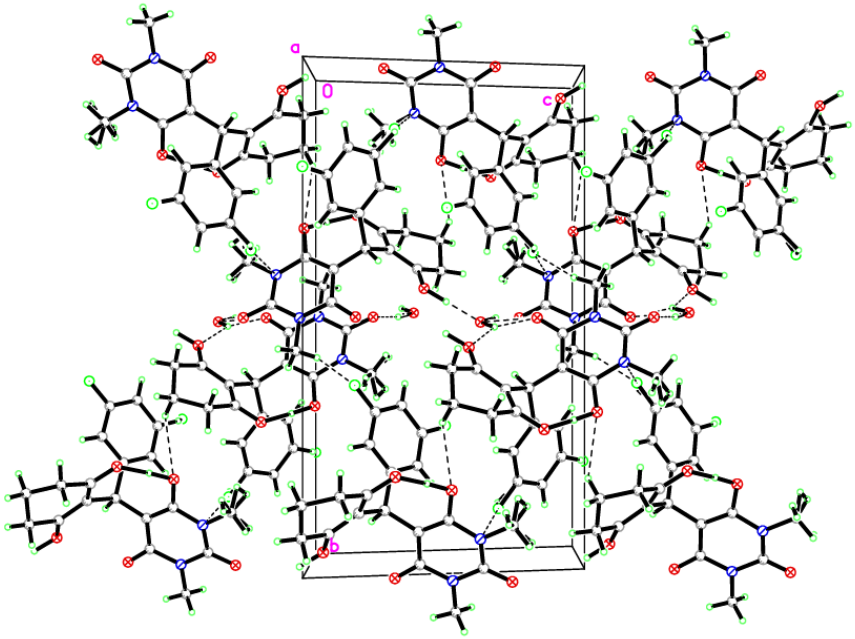


Figure 2. H-bonding network in the crystal structure of the title compound viewed as 3D network; dotted lines indicate intermolecular interactions.

Table 1. Crystal data, data collection, and refinement.

Crystal Data	
Chemical formula	$C_{19}H_{19}FN_2O_5 \cdot H_2O$
Mr	392.38
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	100 K
a, b, c (Å)	7.8630 (5), 20.0308 (13), 11.3987 (8)
β (°)	104.274 (3)
V (Å^3)	1739.9 (2)
Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.12
Crystal size (mm)	0.34 × 0.22 × 0.09
Data Collection	
Diffractometer	D8 Venture area detector
Absorption correction	multi-scan, SADABS V2014/3
No. of measured, independent, and observed [I > 2σ(I)] reflections	18454, 3070, 1995
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.594
R_{int}	0.117
Refinement	
R[$F^2 > 2\sigma(F^2)$], $wR(F^2)$, S	0.055, 0.124, 1.05
No. of reflections	3070
No. of parameters	288
No. of restraints	2
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$(\Delta/\sigma)_{max}$	1.208
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.28, −0.27

Table 2. Selected geometric parameters (Å, °).

F1–C16	1.344 (4)	N1–C1	1.411 (4)
F1X–C18	1.268 (16)	N1–C2	1.465 (4)
O1–C1	1.243 (4)	N1–C3	1.370 (4)
O2–C3	1.229 (4)	N2–C4	1.470 (4)
O3–C5	1.306 (4)	N2–C5	1.388 (4)
O4–C9	1.324 (4)	N2–C3	1.374 (4)
O5–C13	1.257 (4)		
C2–N1–C3	116.9 (2)	O3–C5–C6	125.3 (3)
C1–N1–C3	124.3 (3)	O3–C5–N2	113.0 (3)
C1–N1–C2	118.7 (2)	N2–C5–C6	121.7 (3)
C3–N2–C4	118.5 (2)	O4–C9–C10	116.9 (3)
C3–N2–C5	121.9 (3)	O4–C9–C8	119.6 (3)
C4–N2–C5	119.4 (2)	O5–C13–C12	116.2 (3)
O1–C1–N1	117.7 (3)	O5–C13–C8	122.7 (3)
O1–C1–C6	125.3 (3)	F1–C16–C15	117.8 (3)
N1–C1–C6	117.0 (3)	F1–C16–C17	118.4 (3)
O2–C3–N2	121.3 (3)	F1X–C18–C17	114.7 (9)
N1–C3–N2	116.2 (3)	F1X–C18–C19	124.3 (9)
O2–C3–N1	122.5 (3)		

Table 3. Hydrogen-bond geometry (Å, °).

D*–H···*A	***D*–H**	**H···*A***	***D*···*A***	***D*–H···*A***
O1W–H2OW···O2 [i]	1.09 (6)	1.74 (6)	2.815 (3)	171 (5)
O3–H1O3···O5	1.02 (4)	1.44 (4)	2.454 (3)	175 (4)
O4–H1O4···O1W [ii]	1.01 (4)	1.62 (4)	2.622 (3)	173 (4)
O1W–H1OW···O1 [iii]	1.00 (3)	1.92 (5)	2.754 (3)	138 (4)
O1W–H1OW···O4 [iii]	1.00 (3)	2.34 (4)	3.051 (3)	127 (4)
C2–H2A···F1 [iv]	0.9600	2.4000	3.300 (4)	156.00
C11–H11B···O3 [v]	0.9700	2.5400	3.288 (4)	133.00

Symmetry codes: (i) $x, -y + 1/2, z + 3/2$; (ii) $x, -y + 1/2, z-1/2$; (iii) $-x, y-1/2, -z + 3/2$; (iv) $-x, y + 1/2, -z + 1/2$; (v) $x, -y + 1/2, z + 1/2$.

4. Materials and Methods

4.1. General

The chemicals were purchased from Aldrich (Riedstraße, Germany) and Fluka (Buchs, Switzerland), and were used without further purification, unless otherwise stated. The IR spectrum was measured for a KBr pellet on a Nicolet 6700 FT-IR spectrophotometer (Thermo Fisher Scientific, Madison, WI, USA).The NMR spectra were recorded on a Jeol-400 NMR spectrometer (Tokyo, Japan). ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) were recorded in deuterated dimethylsulfoxide (DMSO-d_6). Chemical shifts (δ) are reported in ppm and *J* -coupling constants are given in Hz. Mass spectrometric analysis was conducted by using ESI mode on an AGILENT Technologies 6410–triple quad LC/MS instrument (Santa Clara, CA, USA). Elemental analysis was carried out on a Perkin Elmer 2400 Elemental Analyzer, CHN mode (Waltham, MA, USA). X-ray crystal structure analysis was performed on a Bruker APEX-II D8 Venture area diffractometer (Bruker AXS GmbH, Karlsruhe, Germany).

4.2. Synthesis of 5-[(3-Fluorophenyl)(2-hydroxy-6-oxocyclohex-1-en-1-yl)-methyl]-6-hydroxy-1,3-dimethyl-pyrimidine-2,4(1H,3H)-dione

A mixture of 1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1.0 mmol), cyclohexane-1,3-dione (1.0 mmol), and 3-fluorobenzaldehyde (1.0 mmol) in 2.0 mL of H_2O was charged into a 10 mL round bottom flask mediated by diethylamine (1.0 mmol). The reaction mixture was stirred at room

temperature for 24 h, until TLC (Merck Silica Gel 60 F–254; eluent: 30% EtOAc/n-hexane) showed that the reactants were completely consumed. After completion of the reaction, the solid product was collected by filtration and dried. The compound was obtained as white crystals by crystallization using a mixture of (CH_2Cl_2/EtOH/Et_2O).

White crystalline compound; Yield 92%, m.p.: 113–115 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.21 (t, J = 7.3 Hz, 1H, Ph), 6.91 (s, 1H, Ph), 6.83 (d, J = 7.3 Hz, 2H, Ph), 5.90 (s, 1H, benzyl-H), 3.16 (m, 2H, CH_2), 2.97 (s, 6H, CH_3), 2.20 (t, J = 7.3 Hz, 2H, CH_2), 1.75 (t, J = 7.3 Hz, 2H, CH_2); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 191.7, 168.1, 167.7, 152.2, 143.8, 129.2, 124.6, 114.9, 112.5, 112.0, 51.9, 42.1, 31.8, 28.0, 20.2; IR (KBr, cm^{-1}) ν_{max} = 3155, 2928, 1660, 1550, 1256; Anal. calcd. for $C_{19}H_{19}FN_2O_5$: C, 60.96; H, 5.12; N, 7.48; Found: C, 60.97; H, 5.11; N, 7.50]; LC/MS (ESI, m/z): [M + 1], found 375.37, $C_{19}H_{19}FN_2O_5$: 374.37.

5. Conclusions

A new barbituric acid derivative was synthesized via a green protocol. The molecular structure of the synthesized compound was investigated by spectroscopic tools and X-ray single crystal diffraction technique.

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Author Contributions: A.B. and A.M.A conceived and designed the experiments; S.A. performed the experiments; M.S.I. and M.A. analyzed the data; H.A.G. carried out the X-ray single crystal; A.B. contributed reagents/materials/analysis tools; A.B. wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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