



SYNTHESIS AND X-RAY STRUCTURE OF 2-AMINO-4-(4-FLUOROPHENYL)-7,7-DIMETHYL-5-OXO-5,6,7,8-TETRAHYDRO-4H-CHROMENE-3-CARBONITRILE

Dalbir Kour,^[a] D. R. Patil,^[b] Madhukar B. Deshmukh,^[b] Vivek K. Gupta^[a] and Rajni Kant^{[a]*}

Keywords: Crystal structure; direct methods; conformations; C-H...O, N-H...N and N-H...O intra- and intermolecular interactions; crystallographic dimers; substituted tetrahydro-4H-chromene-3-carbonitrile

The title compound, 2-amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (C₂₁H₂₄FN₃O₃), crystallizes in the monoclinic space group C2/c with unit cell parameters: a=31.342(3), b=9.3481(9), c=15.9051(11) Å, β=118.687(9)°, Z=8. The crystal structure was solved by direct methods and refined by full-matrix least-squares procedures to a final R-value of 0.0588 for 2776 observed reflections. The fused cyclohexene and pyran rings adopt sofa and boat conformations, respectively. The four essentially planar atoms (C1/C2/C5/C6) of pyran ring (maximum deviation = 0.0878 Å for C2) form a dihedral angle of 87.85(7)° with the benzene ring and is almost coplanar with the mean plane of the cyclohexene ring [dihedral angle = 7.23(7)°]. In the crystal, molecules are connected into inversion dimers via pairs of N-H...N hydrogen bonds and these dimers are further linked by N-H...O hydrogen bonds into a two-dimensional network.

* Corresponding Authors

Fax: +91 191 243 2051

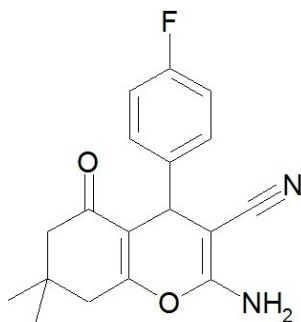
E-Mail: rkvc.paper1@gmail.com

[a] X-ray Crystallography Laboratory, Post-Graduate Department of Physics & Electronics, University of Jammu, Jammu Tawi - 180 006, India.

[b] Department of Chemistry, Shivaji University, Kolhapur - 416 004 (MS), India.

Introduction

In recent years, polyfunctionalized 4H-pyrans and their derivatives have been the subject of significant interest for the synthetic community and have been widely recognized as versatile scaffolds with diverse biological activities.¹⁻⁴ These are often used in cosmetics, pigments and are utilized as potentially biodegradable agrochemicals.^{5,6} 4H-Pyran derivatives are also potential calcium channel antagonists⁷ which are structurally similar to biologically active 1,4-dihydropyridines. Furthermore, these compounds can be employed as pigments, photoactive materials and used as biodegradable agrochemicals.⁸ Hence, investigation of the structural features of biologically relevant tetrahydrobenzo[b]pyran derivatives is of both scientific and practical interest. The present investigation is a continuation of our work⁹ that includes synthesis and structural studies of a polyfunctionalized substituted pyran derivative (**1**).



Scheme 1. Structure of the compound **1**.

Experimental

Synthesis

In a 50 ml round bottom flask charged with 1mmole of dimedone, 1 mmole of 4-fluorobenzaldehyde and 1 mmol of malononitrile. Then 5 ml of aqueous ethanol (1:1) and 25 mol % of NH₄Cl was added and the reaction mixture stirred at 30-45 min. at 50-55 °C. The reaction was monitored by TLC. After completion of reaction, the reaction mixture poured on crushed ice and stir well. The solid precipitated was filtered and recrystallized in ethanol to afford pure product. M.P.: 205-207 °C, Yield: 84 %. ¹H NMR (300 MHz, DMSO-d₆): δ 1.26(s, 3H, CH₃), 1.35(s, 3H, CH₃), 2.38-2.46(m, 2H, CH₂), 2.71(s, 2H, CH₂), 4.57(s, 1H, CH), 6.18-6.23(d, 2H, NH₂), 7.17-7.23(m, 2H, Ar-H), 7.42-7.47(m, 2H, Ar-H).

Crystal structure determination and refinement

The X-ray intensity data of a well defined crystal (0.30 x 0.20 x 0.10 mm) were collected at room temperature (293 K) by using a CCD area-detector diffractometer (*X'calibur system – Oxford diffraction, 2010*) which is equipped with graphite monochromated MoKα radiation (λ=0.71073 Å). The cell dimensions were determined by the least-squares fit of angular settings of 2901 reflections in the θ range 3.85 to 28.27°. A total number of 8432 reflections were collected of which 2776 reflections were treated as observed (*I* > 2σ(*I*)). Data were corrected for Lorentz, polarization and absorption factors.

The structure was solved by direct methods using SHELXS97.¹⁰ All non-hydrogen atoms of the molecule were located from the E-map. Full-matrix least-squares refinement was carried out by using SHELXL97 software.¹⁰ The geometry of the molecule is determined by PLATON.¹¹ All the hydrogen atoms were positioned geometrically and were treated as riding on their parent C/N atoms, with C-H distances of 0.93–0.98 Å and N-H distance of 0.88-0.89 Å;

and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C/N})$, except for the methyl groups where $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$. The final refinement cycles yielded an R-factor of 0.0588 ($wR(F^2)=0.1424$) for the observed data. The residual electron density ranges from -0.253 to $0.191 \text{ e}\text{\AA}^{-3}$.

Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4). The crystallographic data are summarized in Table 1. CCDC-963179 contains the supplementary crystallographic data for this paper.

Results and discussion

An ORTEP view of the title compound with atomic labeling is shown in Figure 1.¹² In the crystal structure, it is observed that structure unit contains a substituted 5,6,7,8-tetrahydro-4H-chromene, a benzene ring and a DMF solvent.

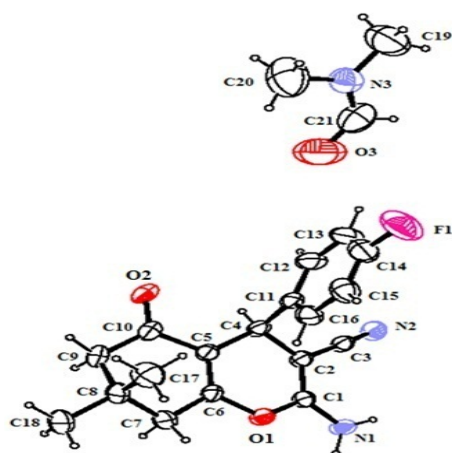


Figure 1. ORTEP view of the molecule with displacement ellipsoids drawn at the 50 % probability level. H atoms are shown as small spheres of arbitrary radii.

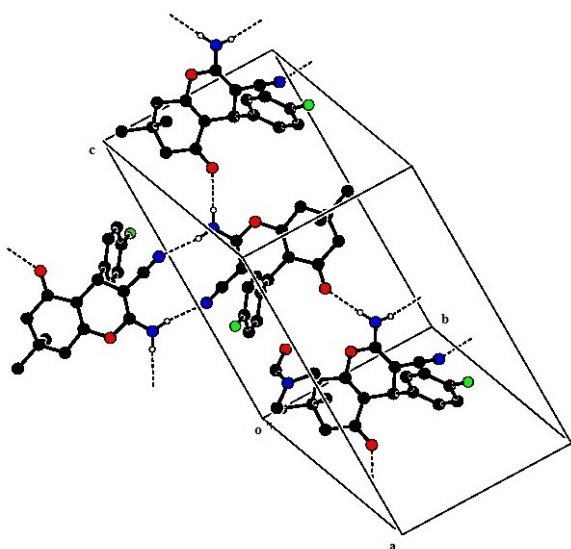


Figure 2. The packing arrangement of molecules in the unit cell box. The dashed lines show intermolecular N-H...O and N-H...N hydrogen bonds.

Table 1. Crystal data and other experimental details for **1**.

CCDC	963179
Crystal description	White block
Crystal size	0.30x 0.20 x 0.10
Empirical Formula	$\text{C}_{21}\text{H}_{24}\text{FN}_3\text{O}_3$
Formula weight (g mol^{-1})	385.43
Radiation, Wavelength (\AA)	Mo $K\alpha$, 0.71073
Unit cell dimensions	$a = 31.342(3)$, $b = 9.3481(9)$, $c = 15.9051(11) \text{ \AA}$, $\beta = 118.687(9)^\circ$
Crystal system, Space group	monoclinic, C 2/c
Unit cell volume (\AA^3)	4088.0(6)
No. of molecules per unit cell, Z	8
No. of parameters refined	265
Absorption coefficient (mm^{-1})	0.091
F(000)	816
θ range for entire data collection ($^\circ$)	$3.87 < \theta < 26.00$
Limiting indices	$-38 \leq h \leq 38$, $-11 \leq k \leq 10$, $-18 \leq l \leq 19$
Reflections collected / unique	8432/3998
Reflections observed ($I > 2\sigma(I)$)	2776
Final R-factor	0.0588
$wR(F^2)$	0.1424
R_{int}	0.0478
R_{sigma}	0.0532
Goodness-of-fit	1.016
$(\Delta / \sigma)_{\text{max}}$	0.001
Final residual electron density ($\text{e}\text{\AA}^{-3}$)	$-0.253 < \Delta\rho < 0.191$

The geometry of the molecule was calculated using the PLATON¹¹ and PARST¹³ software. All bond lengths and angles are normal and correspond to those observed in related structures^{14,15} (Table 2).

Table 2. Selected bond lengths (\AA) and angles ($^\circ$) for non hydrogen atoms (e.s.d.'s are given in parentheses) for **1**.

Bond lengths		Bond angles	
F1- C14	1.359(3)	C1- O1- C6	118.9(1)
O1- C1	1.371(2)	N1- C1- C2	128.0(2)
O1- C6	1.380(2)	N1- C1- O1	110.6(2)
O2- C10	1.227(2)	C2- C1- O1	121.4(2)
N1- C1	1.332(3)	N2- C3- C2	177.8(2)
N2- C3	1.144(3)	C5- C6- O1	122.7(2)
O3- C21	1.246(4)	O1- C6- C7	111.4(2)
N3- C21	1.307(4)	O2- C10- C5	119.9(2)
N3- C20	1.427(4)	O2- C10- C9	122.1(2)
N3- C19	1.427(4)	C13- C14- F1	118.8(3)
		F1- C14- C15	118.8(3)
		C21- N3- C20	122.3(3)
		C21- N3- C19	119.5(3)
		C20- N3- C19	118.1(3)
		O3- C21- N3	123.5(4)

The cyclohexene ring (C5/C6/C7/C8/C9/C10) and pyran ring (O1/C1/C2/C4/C5/C6) exhibit *sofa* and *boat* conformations, respectively, with asymmetry parameters ($\Delta\text{Cs}(C5)=9.236$ and $\Delta\text{Cs}(C4)=2.453$, $\Delta\text{Cs}(C5-C6)=10.94$).¹⁶

Table 3. Geometry of intra- and intermolecular hydrogen bonds for **1**.

D-H...A	D-H (Å)	H...A (Å)	D...A (Å)	θ [D-H...A(°)]	Symmetry code
C19-H19C...O3	0.96	2.295	2.704	105	
N1-H11...N2	0.89	2.502	2.898	170(3)	-x,-y,-z+1
N1-H22...O2	0.88	2.049	2.934	178	x,-y+1,+z+1/2

The four essentially planar atoms (C1/C2/C5/C6) of pyran ring (maximum deviation=0.0878 Å for C2) form a dihedral angle of 87.85(7)° with the benzene ring and is almost coplanar with the mean plane of the cyclohexene ring [dihedral angle=7.23(7)°]. The nitrile group is typical [N≡C=1.144(3) Å] and the double bonds C10=O2 and C21=O3 are confirmed by their respective distances of 1.227(2) and 1.246 (4) Å. These distances are larger than the standard value for carbonyl group [1.192 Å] and this lengthening could be due to the strong intermolecular interactions.

Both H-atoms of the NH₂ group are involved in the formation of N1-H22...O2 and N1-H11...N2 intermolecular hydrogen bonds. In the crystal, molecules are connected into dimers via N1-H11...N2 hydrogen bonds generating an R₂²(12) graph-set motif¹⁷ and these dimers are further connected by N1-H22...O2 (Table 3) hydrogen bonds into a two-dimensional network (Fig. 2).

Acknowledgements

One of the authors (Rajni Kant) acknowledges the Department of Science & Technology for single crystal X-ray diffractometer as a National Facility under Project No. SR/S2/CMP-47/2003.

References

- Zamocka, J., Misikova, E., Durinda, J., *J. Prep.*, **1991**, *46*, 610.
- Wang, J. L., Liu, D., Zhang, Z. J., Shan, S., Han, X., Srinivasula, S. M., Croce, C. M., Alnemri, E. S., Huang, Z., *Proc. Natl. Acad. Sci. USA*, **2000**, *97*, 7124.
- Hatakeyama, S., Ochi, N., Numata, H., Takano, S., *J. Chem. Soc. Chem. Commun.*, **1988**, *17*, 1202.
- González, R., Martín, N., Seoane, C., Marco, J. L., Albert, A., Cano, F. H., *Tetrahedron Lett.*, **1992**, *33*, 3809.
- Morinaka, Y., Takahashi, K., *Japanese Patent JP52017498*, **1977**.
- Hafez, E. A. A., Elnagdi, M. H., Elagamey, A. G. A., El-Taweel, F. M. A. A., *Heterocycles*, **1987**, *26*, 903.
- Suañez, M., Salfrañ, E., Verdecia, Y., Ochoa, E., Alba, L., Martín, N., Martínez, R., Quinteiro, M., Seoane, C., Novoa, H., Bleton, N., Peeters, O. M., De Ranter, C., *Tetrahedron*, **2002**, *58*, 953.
- Fotouhi, L., Heravi, M. M., Fatehi, A., Bakhtiari, K., *Tetrahedron Lett.*, **2007**, *48*, 5379.
- Kant, R., Gupta, V. K., Kapoor, K., Patil, D. R., Chandam, D. R., Deshmukh, M. B., *Acta Cryst.*, **2013**, *E69*, o417.
- Sheldrick, G. M., *Acta Cryst.*, **2008**, *A64*, 112.
- Spek, A. L., *Acta Cryst.*, **2009**, *D65*, 148.
- Farrugia, L. J., *J. Appl. Cryst.*, **2012**, *45*, 849.
- Nardelli, M., *J. Appl. Cryst.*, **1995**, *28*, 659.
- Wang, X., *Acta Cryst.*, **2011**, *E67*, o832.
- Anthal, S., Brahmachari, G., Laskar, S., Banerjee, B., Kant, R., Gupta, V. K., *Acta Cryst.*, **2012**, *E68*, o2592.
- Duax, W.L., Norton, D. A., *Atlas of Steroid Structures*, New York: Plenum Press, **1975**, 1.
- Bernstein, J., Davis, R. E., Shimon, L., Chang, N.-L., *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 1555.

Received: 26.12.2013.
Accepted: 19.01.2014.