Molecular Crystals and Liquid Crystals

ISSN: 1542-1406 (Print) 1563-5287 (Online) Journal homepage: https://www.tandfonline.com/loi/gmcl20

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To cite this article: S. Naveen, S. B. Benaka Prasad, H. R. Manjunath, C. S. Ananda Kumar, K. S. Rangappa, N. K. Lokanath & M. A. Sridhar (2015) Synthesis, Characterization, Crystal, and Molecular Structure Studies of [1-(3,5-Dimethyl-2,3-dihydro-isoxazole-4-sulfonyl)-piperidin-4-yl}-diphenyl-methanol, Molecular Crystals and Liquid Crystals, 616:1, 143-150, DOI: 10.1080/07315171.2014.964791

To link to this article: https://doi.org/10.1080/07315171.2014.964791

Mol. Crys. and Liq. Crys., Vol. 616: pp. 143–150, 2015

ISSN: 1542-1406 print/1563-5287 online
DOI: 10.1080/07315171.2014.964791

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Synthesis, Characterization, Crystal, and Molecular Structure Studies of [1-(3,5-Dimethyl-2,3-dihydro-isoxazole-4-sulfonyl)-piperidin-4-yl}-diphenyl-methanol

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The title compound [1-(3,5-Dimethyl-2,3-dihydro-isoxazole-4-sulfonyl)-piperidin-4-yl)-diphenyl-methanol was synthesized and the product obtained was characterized by spectroscopic techniques and finally the structure was confirmed by X-ray diffraction studies. The compound crystallizes in the monoclinic crystal system with the space group $P2_1/c$ and with unit cell parameters $a = 8.5280(6)$ Å, $b = 25.223(4)$ Å, $c = 10.7060(17)$ Å, $\beta = 99.879(8)^\circ$, and $Z = 4$. The structure reveals that the piperidine ring is in chair conformation. The geometry around the S atom is distorted tetrahedral. The structure exhibits both inter- and intramolecular hydrogen bonds of the type O—H···N and C—H···O.

Keywords Distorted tetrahedron; hydrogen bond; piperidine; X-ray diffraction

1. Introduction

Despite major breakthroughs in many areas of modern medicine over past 100 years, the successful treatment of cancer remains a significant challenge at the start of the 21st century. Because it is difficult to discover novel agents that selectively kill tumor cells or inhibit

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their proliferation without the general toxicity, the use of traditional cancer chemotherapy is still very limited. Antiproliferative and cytotoxic drugs play a major role in cancer chemotherapy, whether used alone or in combination with other treatment modalities such as surgery, radiation, and biological therapy. In the past 50 years, the mass screening of either synthetic derivatives or natural products has led to the discovery of the currently utilized anticancer drugs.

Cancer is a serious pathology and a substantial number of new antineoplastic agents have been discovered. Considerable insight has been gained into the mechanisms by which many of these compounds affect cellular growth and this knowledge has been used to design new chemotherapeutic drugs [1–3]. Currently, combined anticancer therapies or multiacting drugs are clinically preferred to traditional cytotoxic treatment, with the aim of overcoming resistance and toxicity drawbacks. These events often prevent successful treatment and are responsible for reduced survival times [4,5].

The accentuated interest in the piperidine class of opiate analgesics continues to be expressed in the pharmaceutical community and biological properties of these agents have been the subject of ongoing investigations [6]. The piperidine scaffold has wide-ranging in its therapeutic uses as it is ubiquitously found in drugs. It is a key structural component of successful anti-Parkinson's drugs [7] and displays antipsychotic [8], antiviral [9], metabolic [10], antimicrobial [11,12], antidepressants [13], acetylcholinesterase [14], antimalarial [15], and anticonvulsant activity [16,17]. Compounds containing amide bond can alter the chemical properties, disposition, and biological activities of drugs [18]. Amides are currently used as antidepressants, anti-inflammatory agents, antimalarial agents, antipsychotic agents, antiviral agents, steroids, and general anesthetics [19].

2. Experimental

2.1. Preparation of [1-(3,5-Dimethyl-2,3-dihydro-isoxazole-4-sulfonyl)-piperidin-4-yl)-diphenyl-methanol

A solution of diphenyl-(piperidin-4-yl)-methanol (0.5 g, 1.77 mmol) in dry dichloromethane was taken and cooled to 0°C–5°C in an ice bath. Triethyl amine (0.537 g, 5.31 mmol) was added to the cold mixture and stirred for 10 min, then 3,5-dimethyl-2,3-dihydro-isoxazole-4-sulfonyl chloride (0.349 g, 1.77 mmol) was added. The mixture was allowed to room temperature under stirring for 5–6 hr. The reaction mixture was monitored by TLC. Upon completion, the solvent was removed under reduced pressure and residue was taken in water and extracted with ethyl acetate. The organic layer was washed with 10% ammonium chloride solution and finally water wash was given to organic layer and dried with anhydrous sodium sulphate. The solvent was evaporated to get crude product which was purified by column chromatography over silica gel (60–120 mesh) using hexane:ethyl acetate (8:2) as an eluent. The obtained pure compound was dissolved in ethyl acetate. After 4–5 days, white crystals developed due to the slow evaporation of solvent. The method employed for synthesis is shown in Fig. 1.

^{1}H NMR (DMSO, 400 MHz) δ: 7.47 (m, 4H, Ar-H), 7.23 (m, 4H, Ar-H), 7.09 (t, 2H, Ar-H), 3.1 (d, 2H, -CH_2), 3.61 (d, 2H, -CH_2), 2.68 (t, 2H, -CH_2), 2.62 (s, 3H, -CH_3), 2.56 (s, 3H, -CH_3), 2.4 (m, 1H, -CH), 2.31 (s, 2H, -CH_2), 2.2 (s, 1H, -OH).

IR (KBr, cm^{-1}): 3515, 1470, 1376, 1356, 1276.

MS (ESI) *m/z*: 427.00 ($M + H^+$).

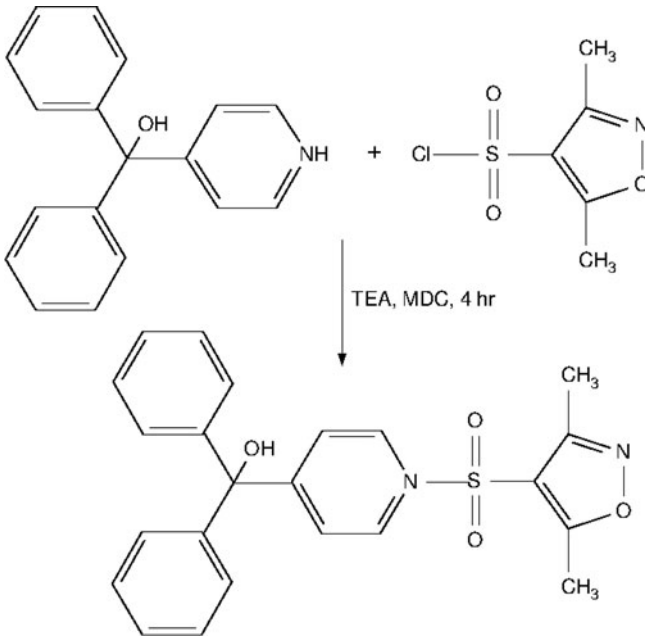

Figure 1. Reaction scheme of the title compound.

Anal. calcd. for $C_{23}H_{26}N_2O_4S$ (in%): C-64.77, H-6.14, N-6.57, S-7.52. Found C-64.75, H-6.10, N-6.53, S-7.48.

2.2. Crystal Structure Determination

A single crystal of the title compound with dimensions of 0.27 × 0.23 × 0.20 mm was chosen for X-ray diffraction study. The data were collected on a DIPLabo Image Plate diffractometer equipped with a normal focus, 3 kW sealed X-ray source (graphite-monochromated MoK_α). The crystal to detector distance was fixed at 120 mm with a detector area 441 × 240 mm. Thirty six frames of data were collected at room temperature by the oscillation method. Each exposure of the image plate was set to a period of 400 sec. Successive frames were scanned in steps of 5° per minute with an oscillation range of 5°. Image processing and data reduction were done using Denzo [20]. The reflections were merged with scalepack. All of the frames could be indexed using a primitive monoclinic lattice. The structure was solved by direct methods using SHELXS-97. All of the non-hydrogen atoms were revealed in the first Fourier map itself. The structure was refined by a full-matrix least-squares method with anisotropic temperature factors for non-hydrogen atoms using SHELXL-97. The hydrogen atoms were fixed at chemically acceptable positions and were allowed to ride on their parent atoms. The residuals finally converged to 0.0710. The details of the crystal structure and data refinement are given in Table 1. The selected bond lengths and bond angles of the non-hydrogen atoms are given Table 2. Figure 2 represents the ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

Table 1. Crystal data and structure refinement

Parameter	Value
CCDC deposit no.	711047
Empirical formula	$C_{23}H_{26}N_2O_4S$
Formula weight	426.52
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	$a = 8.5280(6)$ Å
	$b = 25.223(4)$ Å
	$c = 10.7060(17)$ Å
	$\beta = 99.879(8)^\circ$
Volume	2268.7(5) Å^3
Z, Calculated density	4, 1.249 Mg/m^3
Absorption coefficient	0.173 mm^{-1}
$F_{(000)}$	904
Crystal size	0.27 × 0.23 × 0.20 mm
Theta range for data collection	2.09° to 25.02°
Limiting indices	$-9 \leq h \leq 9$, $-30 \leq k \leq 28$, $-10 \leq l \leq 10$
Reflections collected/unique	5046/3108 [R(int) = 0.0276]
Refinement method	Full-matrix least squares on F^2
Data/restraints/parameters	3108/0/274
Goodness-of-fit on F^2	1.068
Final R indices [$I>2\sigma(I)$]	$R1 = 0.0710$, $wR2 = 0.2137$
R indices (all data)	$R1 = 0.0929$, $wR2 = 0.2420$
Largest diff. peak and hole	0.350 and −0.334 e. Å^{-3}

Table 2. Selected bond lengths and angles (Å, º)

N1-C6	1.474(5)
N1-C2	1.446(2)
N1-S7	1.610(3)
S7-O8	1.425(3)
S7-O9	1.426(3)
S7-C10	1.739(4)
O12-N13	1.405(5)
C6-N1-C2	112.7(3)
C6-N1-S7	120.4(2)
C2-N1-S7	118.2(2)
O8-S7-N1	120.1(2)
O8-S7-N1	107.3(2)
O9-S7-N1	106.8(2)
O9-S7-C10	107.4(2)
O8-S7-C10	105.7(2)
N1-S7-C10	109.3(2)

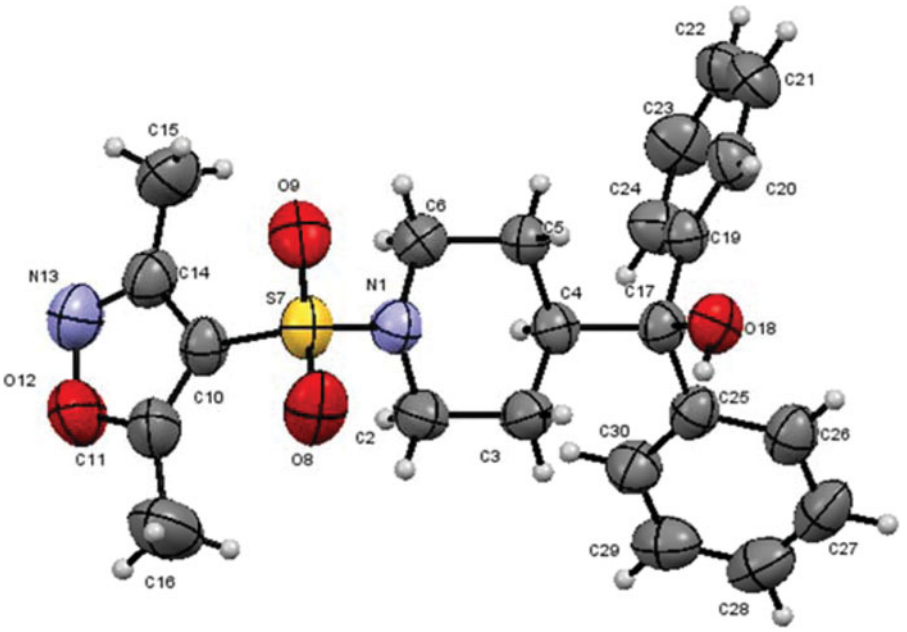

Figure 2. ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability.

3. Results and Discussion

A study of torsion angles, asymmetric parameters, and least-square plane calculations reveals that the piperidine ring adopts a chair conformation with the atoms N1 and C4 deviating – 0.240(4) Å and 0.241(4) Å respectively from the Cremer and Pople plane [21] defined by the atoms C2/C3/C5/C6. This is confirmed by the puckering parameters $Q = 0.5882(43)$ Å, $\theta = 180(44)^\circ$, and $\phi = 289(91)^\circ$. The bonds N1-S7 and C4-C17 make an angle of 82.1(2)° and 72.9(2)°, respectively, with the Cremer and Pople plane of the piperidine ring and thus are in equatorial plane of the piperidine ring. The isoxazole ring is planar within the experimental limits. The dihedral angle between the least-squares plane of the piperidine ring and isoxazole ring bridged by the sulfonyl group is 63.2(3)° which differs from the value of 49.80(1)° reported earlier [22]. The piperidine ring makes and angle of 80.5(2)° and 53.4(2)° with the two phenyl rings [C19-C24] and [C25-C30], respectively. The dihedral angle between the two phenyl rings bridged by the carbon atom is 84.32(2)°. The steric hindrance caused by the bulky sulfonyl group is more than the steric effects caused by the dimethylphenyl ring which are attached on either side of the piperidine ring. This is evident from the bond angle values of 112.7(3)° and 108.2(3)° for C6-N1-C2 and C3-C4-C5, respectively.

The geometry around the S atom is distorted from regular tetrahedron, with the largest deviation observed for the O-S-O [O9-S7-O8 = 120.1(2)°] and O-S-N angle [O9-S7-N1 = 107.43(19)°]. This widening of the angles is due to the repulsive interactions between the S = O bonds and the nonbonded interactions involving the two S-O bonds and the varied steric hindrance of the substituents. The structure thus has less steric interference. The S = O bond distance lies within the expected range of 1.60-1.69 Å. The value of bond angle for N1-S7-C10 is 109.3(2)° which is comparable with the ideal tetrahedral value of 109.47° is attributed to the Thorpe-Ingold effect [23]. The sulfonyl O atoms, O8 and O9

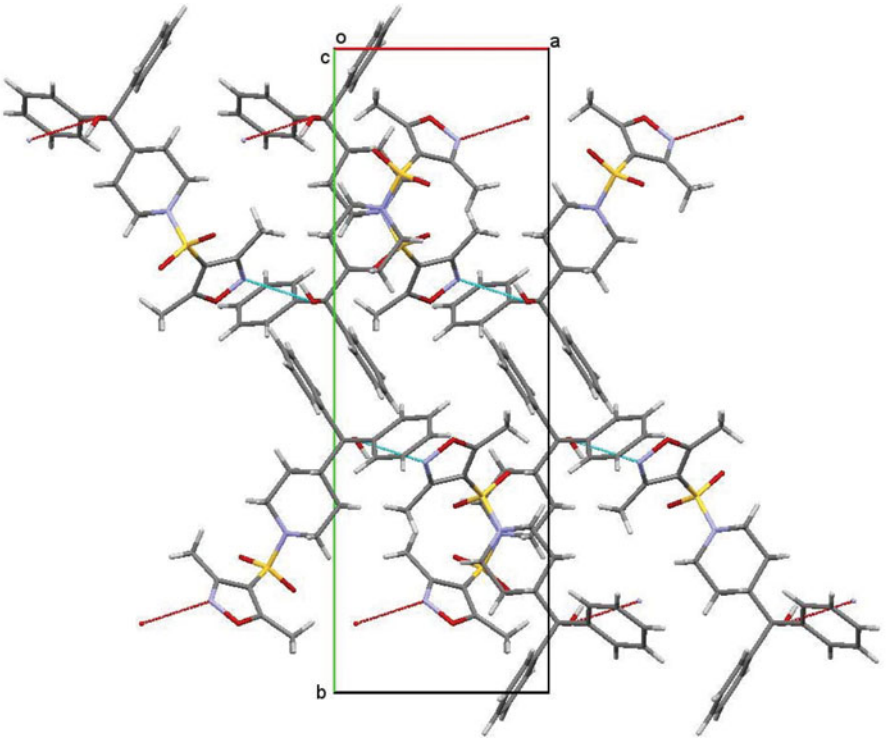

Figure 3. Packing diagram of the molecule down the *c*-axis. The dashed lines indicate the hydrogen bonds.

adopts *–synclinal* and *+synclinal* conformations, respectively, as indicated by the torsion angle values of −35.7(4)° and 49.1(4)° for C6-N1-S-O9 and C2-N1-S7-O8, respectively. The structure exhibits both inter- and intramolecular hydrogen bonds of the type O—H···N which play a vital role in stabilizing the crystal structure. The intermolecular hydrogen bond O18—H18···N13 has a length of 2.986(5) Å and an angle of 130° with symmetry code $-1 + x$, $^1/_2 - y$, $-^1/_2 + z$. The packing of the molecules when viewed down along the *c* axis as shown in Fig. 3 indicates that the molecule exhibits layered stacking and are interlinked by the intermolecular hydrogen bond to form a 1D chain.

4. Conclusion

The title compound [1-(3,5-Dimethyl-2,3-dihydro-isoxazole-4-sulfonyl)-piperidin-4-yl)-diphenyl-methanol was synthesized and characterized by means of ^{1}H NMR, FT-IR spectroscopic data. The molecular structure of the compound was determined by single crystal X-ray diffraction technique. The crystal structure of the title compound reveals that the piperidine ring adopts a chair conformation and the structure has a less steric interference.

Funding

The authors are grateful to the University of Mysore and Department of Science and Technology, Government of India for the financial assistance under the project SP/I2/FOO/93.

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