

Synthesis and x-ray crystallographic studies of azatricyclo-sulfonamide derivatives

Azatricyclo and its derivatives occupy an important position in medicinal and pesticide chemistry with having a wide range of bioactivities such as antimicrobial, anticancer, anti-inflammatory, antibacterial, antifungal and antitumor activities. Similarly, the sulfonamide groups were proved to possess various biological properties such as antimicrobial, antifungal, anticancer, anti-inflammatory, antitubercular and antiviral agents as well as HIV protease inhibitors. In view of these biological and medicinal importances, X-ray crystallographic studies for the azatricyclo sulfonamide derivatives have been carried out. The structures were solved by direct methods and refinement was carried out using least squares procedures. The detailed information on the molecular conformation in the solid state, IUPAC name and chemical diagram of the compounds are reported.

Lakshminarayanan Karthik¹, Jagadeesan Ganapathy², Pennathur Gautam² & Gunasekaran Krishnasamy*¹

¹CAS in Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai-600025, India

²Centre for Biotechnology, Anna University, Chennai-600025, India

*Author for correspondence: gunaunom@gmail.com

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Introduction

In the field of medicinal and pesticide chemistry, azatricyclo and its derivatives plays an important role by possessing various bioactivities such as antimicrobial, anticancer, anti-inflammatory, antibacterial, antifungal and antitumor activities. Similarly, the sulfonamide groups are reported to possess numerous biological properties such as antimicrobial [1,2], antifungal [3], anticancer [4,5], anti-inflammatory [6], and as well as HIV protease inhibitors [7]. Also some sulfonamides derivatives are well recognized as antimetabolite [8] and good cytotoxic against breast cancer cells [9].

Sulfonamides were the first effective chemotherapeutic agents to be utilized efficiently to prevent and cure the bacterial infection in human beings [10-13]. Recently, some sulfonamide derivatives were screened for their antioxidant activity. In addition, sulfonamides have shown carbonic anhydrase inhibition [14], COX-2 inhibition [15] and selective 5-HT receptor antagonist [16] activity. Based on the above mentioned facts, the combination of azatricyclo-sulfonamide system results in novel heterocycles which are biologically active compounds, especially as anticancer and anti-

HIV agents [17]. In view of these biological and medicinal importances of the azatricyclo derivatives, X-ray crystallographic studies for the four azatricyclo derivatives have been carried out to obtain detailed information on the molecular conformation in the solid state.

Material and methods

Synthesis

N-allylated amino aldehyde were added with hydroxylamine (NH₂OH.HCl) in the presence of 50% sodium hydroxide and produces the required aldoxime. On further treatment of aldoxime derivative (without isolation) with N-Chlorosuccinimide (NCS) and (Triethylamine) Et₃N in the presence of carbon tetra chloride (CCl₄) at room temperature over a period of 6H successfully provided the anticipated tricyclic tetrahydro isoxazoloquinoline.

Intensity data collection

X-ray diffraction intensity data were collected for all the four compounds on Bruker Kappa APEXII area-detector diffractometer [18] at the Indian Institute of Technology (IIT), Chennai equipped with graphite mono-chromated MoK α ($\lambda=0.7103$ Å) radiation and CCD detector. Crystals were cut to suitable size and mounted on a glass fiber using cyanoacrylate adhesive.

The unit cell parameters were determined from 36 frames (0.5° phi-scan) measured from three different crystallographic zones and using the technique of difference vectors. The intensity data were collected with an average four-fold redundancy per reflection and optimum resolution (0.75Å). The intensity data collection, frames integration, Lp and decay correction were done using SAINT-NT (version 6.0) software. Empirical absorption correction (multi-scan) is performed using SADABS [18] program. The cell parameters and other data processing statistics of the compounds are given in the result section whereas the 2-D chemical diagram along with the IUPAC name are provided in the **SUPPLEMENTARY FILE**.

Results and Discussion

Structure solution and refinement

Crystal structures were solved by direct methods using SHELXS-97. The residual factors (RE) calculated based on the point atom model are 0.202, 0.210, 0.230 and 0.231, respectively for compounds I, II, III and IV. The structures were refined by the full-matrix least-squares method using SHELXL-97. All the non-hydrogen atoms were first refined isotropically and then with anisotropic displacement parameters for compound I, II, III and IV respectively. For compounds I-IV, the positions of all the hydrogen atoms were fixed by geometry and these atoms were treated by ride on their parent C atoms, with aromatic C-H distances of 0.93Å and methyl C-H distances of 0.96Å with $U_{iso}(H)=1.5U_{eq}(C)$ for methyl H and $1.2U_{eq}(N,C)$ for other H atoms. The refinement converged to a final R-factor of 0.048 for compound I, 0.049 for compound II, 0.050 for compound III and 0.045 for compound IV (**TABLE 1**). All the four compounds have been deposited in Cambridge Structural Database (CSD) and obtained CCDC number for compound I is 1488162, compound II is 1488163, compound III is 1488176 and compound IV is 1488177.

Crystal structure of compound I

In compound I, the azatricyclo ring (C1-C9/C10/N1/N2/O3) is essentially in planar system expect for the atoms C1 and C9 which are deviated with maximum root mean square (rms) deviation of 0.337 (1) Å and -0.366 (1) Å respectively. The azatricyclo ring are almost perpendicular to the chloro phenyl ring (C11-C16, CL) which forms the dihedral angles of 86.87 (1)°. The bond length of the atom S1-O1, S1-O2, S1-C17, and S1-N1 distances are 1.422 (2) Å, 1.427 (2) Å, 1.761 (2) Å and 1.656

(2) Å respectively. These values are comparable with similar structures [19,20]. As a result of the electron-withdrawing character of the phenylsulfonyl group, the N-C sp² bond lengths, viz. N1-C8 [1.430 (3) Å] and N1-C9 [1.476 (3) Å] are longer than the mean value of 1.355 (1) Å reported for N atoms with planar configurations [21]. It has been observed that S atom exhibits significant deviation from that of a regular tetrahedron, with the largest deviation being O-S-O [O1-S1-O2=120.46 (1)°] whereas O-S-N deviates by angle [O1-S1-N1=108.96 (1)°]. The widening of the angles may be due to repulsive interactions between the two short S=O bonds, similar to what is observed in related structures [22]. The sum of bond angles around N1 is 357.76 (2)° which indicate that the pyridine ring is in accordance with sp² hybridization [23]. In the azatricyclic ring, six membered pyridine ring (C1-C3/C8/N1/C9) adopts a sofa conformation while five membered oxazole ring (C1/C2/N2/O3/C10) adopts an envelope conformation with respect to its puckering parameters [24] for pyridine ring as $q_2=0.386(4)$ Å, $\Phi_2=-47.35(1)^\circ$ and for oxazole as $q_2=0.251(1)$ Å, $\Phi_2=147.01(1)^\circ$. It can be further confirmed from the least-square planes analysis that the atom C9 of pyridine and C1 of oxazole ring are found to be deviated by maximum deviation of -0.366 (1) Å and 0.377(1) Å respectively. Crystal packing of the compound is stabilized by C6-H6...N2 inter molecular hydrogen bond interactions (**FIGURES 1A and 1B; TABLE 2**).

Crystal structure of compound II

In compound II, the azatricyclo ring (C1-C9/C10/N1/N2/O5) system is essentially planar expect the atoms C1 and C2 are deviated with a maximum rms deviation of -0.357 (1) Å and 0.310 (1) Å respectively. The azatricyclo ring are almost perpendicular to the chloro phenyl ring (C11-C16, CL) which forms the dihedral angles of 86.09 (1)°. The bond length of the atom S1-O1, S1-O2, S1-C17, and S1-N1 distances are 1.425 (2) Å, 1.426 (2) Å, 1.759 (3) Å and 1.650 (2) Å respectively. These values are comparable with the previously reported structures [20]. As a result of the electron-withdrawing character of the phenylsulfonyl group, the N-C sp² bond lengths, viz. N1-C2 [1.468 (4) Å] and N1-C3 [1.435 (4) Å] are longer than the mean value of 1.355 (1) Å reported for N atoms with planar configurations [21]. As observed in compound I, the S atom in compound II also exhibits significant deviation from that of a regular tetrahedron, with the largest deviation being O-S-O [O1-

S1-O2=120.13 (2)°] while O-S-N [O1-S1-N1] is deviated by an angle of 106.29 (1)°. The widening of the angles may be due to repulsive interactions between the two short S=O bonds, similar to what is observed in related structures [22]. The sum of bond angles around N1 is 356.55 (2)° which indicates that the pyridine ring is in accordance with sp² hybridization [23]. As for the azatricyclic ring of compound II, the six membered pyridine ring (C1/C2/N1/C3/C8/C9) and five membered oxazole ring (C1/C9/N2/O5/C10) adopts sofa and

envelop conformation respectively with respect to its puckering parameters [24] for pyridine ring as $q_2=0.342$ (3) Å, $\Phi_2=54.53$ (1)° and for oxazole as $q_2=0.274$ (6) Å, $\Phi_2=-34.14$ (1)°. The least-square planes analysis further confirms that C2 atom of pyridine and C1 atom of oxazole ring are found to be deviated by maximum deviation of 0.310 (1) Å and -0.357 (1) Å respectively. Crystal packing of the compound is stabilized by C6-H6...O3 inter molecular hydrogen bond interactions (FIGURES 2A and 2B; TABLE 2).

Table 1. Crystal data for compounds I, II, III and IV.

Parameters	I	II
Empirical formula	C ₂₅ H ₂₁ ClN ₂ O ₅ S	C ₂₅ H ₂₁ ClN ₂ O ₅ S
Formula weight	496.95	496.95
Temperature	293(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic
Space group	P21/c	P21/n
Unit cell dimensions	a=11.179 (6) Å b=18.835 (1) Å c=12.137 (7) Å β=114.599 (2)°	a=9.3900 (6) Å b=22.333 (17) Å c=11.1068 (9) Å β=99.643 (2)°
Volume	2323.7 (2) Å ³	2296.4 (3) Å ³
Z, Calculated density	4, 1.421 mg/m ³	4, 1.437 mg/m ³
Absorption coefficient	0.295 mm ⁻¹	0.298 mm ⁻¹
F(000)	1032	1032
Crystal size (mm)	0.25 × 0.20 × 0.20	0.20 × 0.25 × 0.20
θ range for data collection	2 to 30.48°	1.82 to 27.93°
Limiting indices	-15 ≤ h ≤ 15 -26 ≤ k ≤ 26 -16 ≤ l ≤ 17	-12 ≤ h ≤ 11 -29 ≤ k ≤ 29 -14 ≤ l ≤ 14
Reflections collected/unique	48042/6492 [Rint=0.038]	30812/5514 [Rint=0.068]
Completeness to theta	100%	100%
Refinement method	Full-matrix least-squares on F2	Full-matrix least-squares on F2
Data/restraints/parameters	6492/0/307	5514/0/307
Goodness-of-fit on F2	0.917	0.776
Final R indices [I>2σ(I)]	R1=0.0481	R1=0.0497
R indices (all data)	wR2=0.1152 R1=0.0943 wR2=0.1489	wR2=0.1448 R1=0.1248 wR2=0.2190
Largest diff. peak and hole	0.304 and -0.370 e.Å ⁻³	0.376 and -0.454 e.Å ⁻³

Parameters	III	IV
Empirical formula	C ₂₅ H ₂₁ Cl ₂ N ₂ O ₅ S	C ₂₇ H ₂₅ N ₃ O ₃ S
Formula weight	531.39	471.56
Temperature	293(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic
Space group	P21/c	Cc
Unit cell dimensions	a=17.0689 (17) Å b=11.9646 (11) Å c=24.353 (3) Å β=104.665 (3)°	a=15.9500 (8) Å b=14.9091 (8) Å c=10.6610 (5) Å β=106.551 (2)°
Volume	4811.5 (8) Å ³	1986.1 (3) Å ³
Z, Calculated density	8, 1.467 mg/m ³	4, 1.289 mg/m ³
Absorption coefficient	0.397 mm ⁻¹	0.167 mm ⁻¹
F(000)	2192	992
Crystal size (mm)	0.25 × 0.20 × 0.20	0.20 × 0.25 × 0.20
θ range for data collection	1.23 to 24.15°	2.47 to 31.57°
Limiting indices	-19 ≤ h ≤ 19 -13 ≤ k ≤ 13 -26 ≤ l ≤ 27	-23 ≤ h ≤ 23 -21 ≤ k ≤ 21 -15 ≤ l ≤ 13
Reflections collected/unique	38647/7635 [Rint=0.048]	24506/7062 [Rint=0.029]
Completeness to theta	99.4%	93.0%
Refinement method	Full-matrix least-squares on F ²	Full-matrix least-squares on F ²
Data/restraints/parameters	7635/0/631	7062/2/307
Goodness-of-fit on F ²	1.01	0.997
Final R indices [I>2σ(I)]	R1=0.0508	R1=0.0454
R indices (all data)	wR2=0.1320 R1=0.0910 wR2=0.1684	wR2=0.1010 R1=0.0904 wR2=0.1240
Largest diff. peak and hole	0.284 and -0.334 e.Å ⁻³	0.218 and -0.300 e.Å ⁻³

Crystal structure of compound III

In the title compound III, it consists of two molecules (A and B) in the asymmetric unit. Molecule A of azatricyclo ring (C1A-C9A/C10A/N1A/N2A/O3A) system is essentially planar except the atoms C1A and C2A are deviated with a maximum rms deviation of 0.338 (1) Å and -0.377 (1) Å respectively. Similarly molecule B of azatricyclic ring, the atom C1B and C9B are deviated with a maximum rms deviation of 0.338 (1) Å and -0.368 (1) Å respectively. The azatricyclo ring of molecule (A & B) are almost perpendicular to the dichloro phenyl ring which

forms the dihedral angles of 81.72 (1)° for molecule A and 75.50 (1)° for molecule B. In case of the bond length of atoms, distances between S1A-O1A, S1A-O2A, S1A-C17A and S1A-N1A in molecule A are 1.423 (3) Å, 1.431 (3) Å, 1.756 (4) Å and 1.648 (3) Å respectively while the distances between S1B-O1B, S1B-O2B, S1B-C17B and S1B-N1B in molecule B are 1.427 (3) Å, 1.427 (3) Å, 1.746 (4) Å and 1.651 (3) Å respectively. These values are comparable with the previously reported structures [20]. As a result of the electron-withdrawing character of the phenylsulfonyl group, the N-C sp² bond

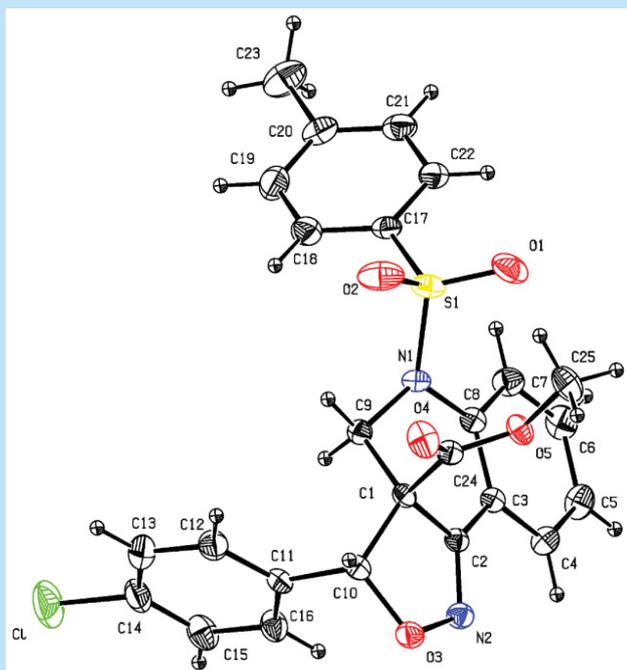


Figure 1A. The ORTEP plot of compound I with the atom numbering scheme. Displacement ellipsoids are drawn at 30% probability level.

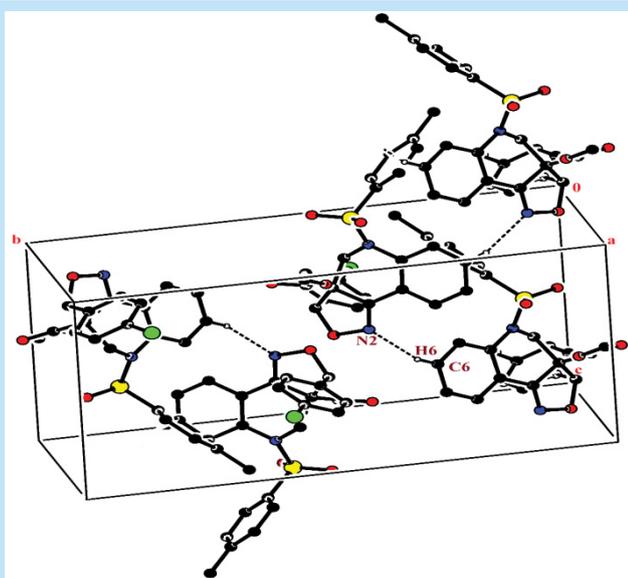


Figure 1B. Portion of the molecular packing viewed down the a-axis for compound I.

Table 2. Hydrogen bond interactions for compounds I-IV [\AA and $^\circ$].

Compounds	D-H...A	D-H	H...A	D...A	D-H...A
I	C6-H6...N2i	0.930(1)	2.492(1)	3.379(1)	159
II	C6-H6...O3 i	0.930(1)	2.472(1)	3.365(1)	157
III	C19A-H19A...O4Ai	0.930(1)	2.580(1)	3.505(4)	173
	C19B-H19B...O4Bii	0.930(1)	2.530(1)	3.446(3)	169
IV	C10-H10...O2i	0.980(1)	2.332(1)	3.228(1)	152
	C15-H15...O1iii	0.930(2)	2.515(1)	3.346(1)	149

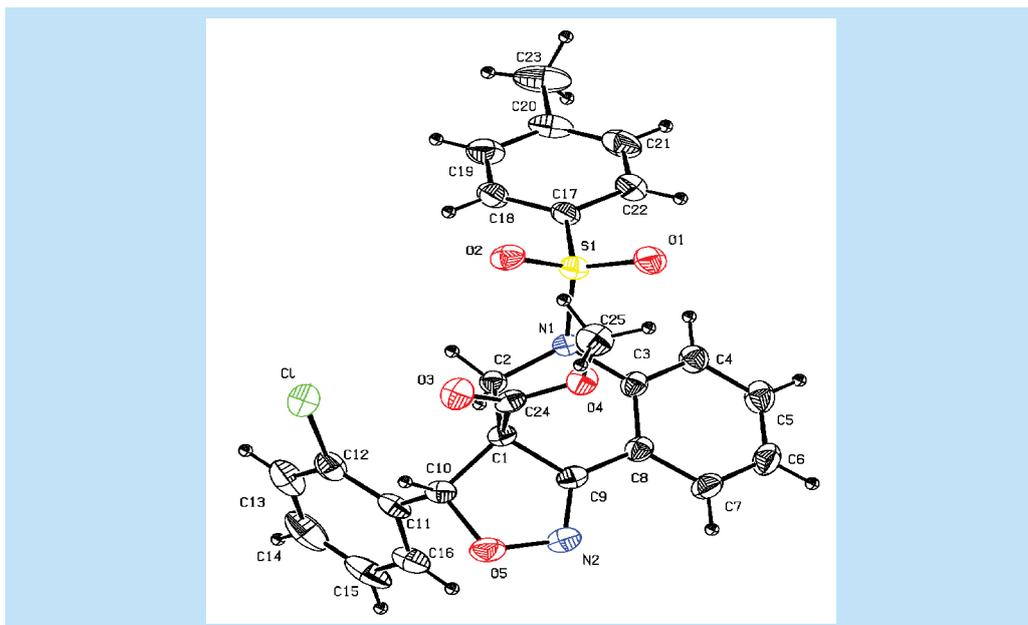


Figure 2A. The ORTEP plot of compound II with the atom numbering scheme. Displacement ellipsoids are drawn at 30% probability level.

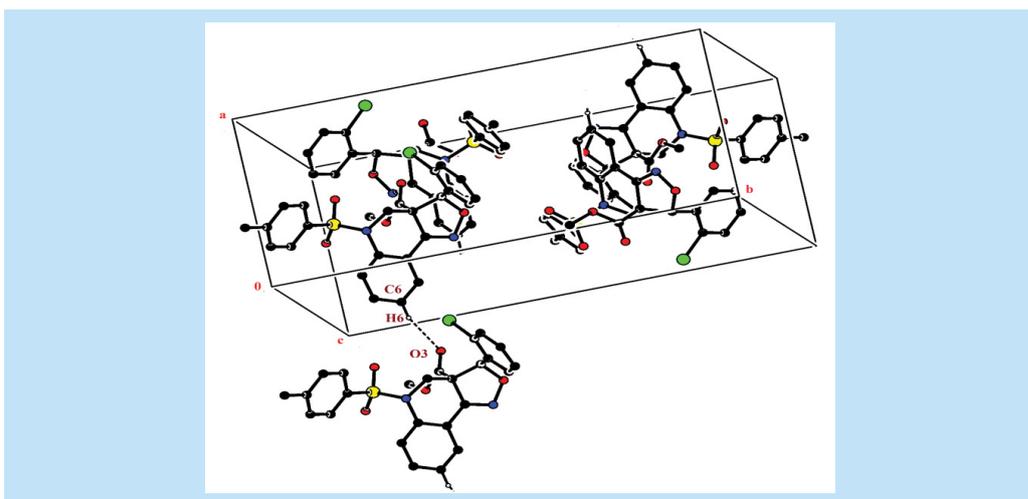


Figure 2B. Portion of the molecular packing viewed down the c-axis for compound II.

lengths, viz. N1A-C2A [1.479 (5) Å], N1A-C3A [1.432 (5) Å], N1B-C9B [1.479 (4) Å] and N1B-C8B [1.431 (5) Å] are longer than the mean value of 1.355 (1) Å reported for N atoms with planar configurations [21]. The S atom also exhibits significant deviation from that of a regular tetrahedron, with the largest deviation being O-S-O where [O1A-S1A-O2A] of molecule A is around 118.6 (2)° and [O1B-S1B-O2B] of molecule B is around 118.2 (2)°.

As observed in the compounds I and II, O-S-N is deviated by angles [O1A-S1A-N1A] with 108.04 (1)° for molecule A and [O1B-S1B-N1B] with 107.89 (2)° for molecule B. The widening of the angles may be due to repulsive interactions between the two short S=O bonds,

similar to what is observed in related structures [22]. The sum of bond angles around N1A is 359.3 (1)° and N1B is 359.1 (1)° which indicate that the molecule (A&B) of pyridine ring is in accordance with sp^2 hybridization [23].

For the azatricyclo ring in molecule (A&B), six membered pyridine ring of molecule A (C1A/C2A/N1A/C3A/C8A/C9A) and molecule B (C1B/C2B/N1B/C3B/C8B/C9B) adopts sofa conformation whereas five membered oxazole ring of molecule A (C1A/C2A/N2A/O3A/C10A) and molecule B (C1B/C9B/N2B/O5B/C10B) adopts envelop conformation with respect to its puckering parameters [24] as follows. For the pyridine ring of molecule A, $q_2=0.278$ (3) Å, $\Phi_2=146.89$ (1)° and molecule B $q_2=0.381$

(1) Å, $\Phi_2=128.95$ (1) $^\circ$ whereas for the oxazole of molecule A, $q_2=0.278$ (3) Å, $\Phi_2=146.89$ (1) $^\circ$ and molecule B $q_2=0.278$ (1) Å, $\Phi_2=69.64$ (1) $^\circ$. Crystal packing of the compound is stabilized by C19A-H19A...O4A and C19B-H19B...O4B inter molecular hydrogen bond interactions (FIGURES 3A and 3B; TABLE 2).

Crystal structure of compound IV

In compound IV, the azatricyclo ring (C1-C9/C10/N1/N2/O3) system is essentially planar except the atoms C8 and C10 are deviated with maximum rms deviation of -0.368 (1) Å and 0.338 (1) Å respectively. The azatricyclo ring are almost perpendicular to the methyl phenyl ring (C20-C25) which forms the dihedral angles of 87.74 (1) $^\circ$ similarly on other side of dimethyl phenyl (C11-C16) ring tilted with respect to the

azatricyclic ring which forms the dihedral angle of 36.46 (1) $^\circ$. The bond length of the atom S1-O1, S1-O2, S1-C20, and S1-N1 distances are 1.414 (2) Å, 1.427 (1) Å, 1.753 (3) Å and 1.647 (2) Å. These values are comparable with similar structures. As a result of the electron-withdrawing character of the phenyl sulfonyl group, the N-C sp^2 bond lengths, viz. N1-C8 [1.429 (3) Å] and N1-C9 [1.463 (3) Å] are longer than the mean value of 1.355 (1) Å reported for N atoms with planar configurations [21].

In addition to this, it was observed that S atom exhibits significant deviation from that of a regular tetrahedron, with the largest deviation being O-S-O [O1-S1-O2=119.44 (2) $^\circ$] and O-S-N deviates by angles [O1-S1-N1=108.57 (1) $^\circ$]. The widening of the angles may be due to repulsive

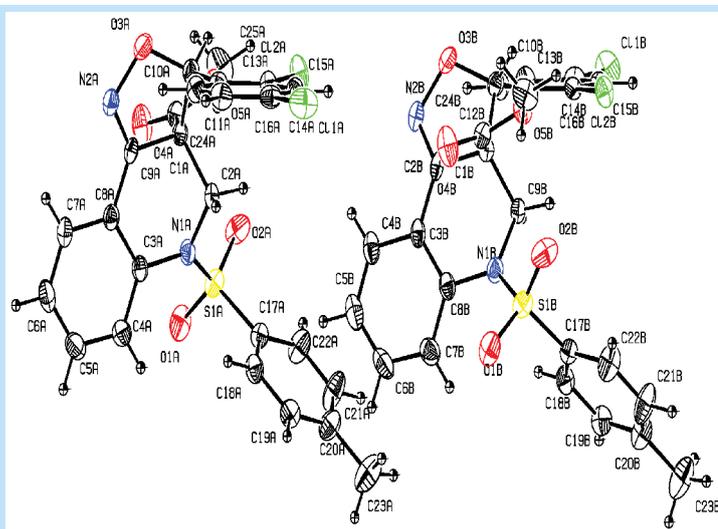


Figure 3A. The ORTEP plot of compound III with the atom numbering scheme. Displacement ellipsoids are drawn at 30% probability level.

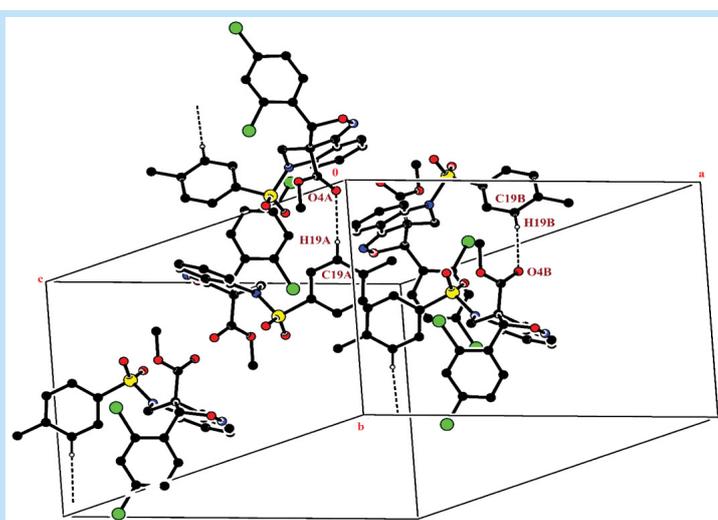


Figure 3B. Portion of the molecular packing viewed down the c-axis for compound III.

interactions between the two short S=O bonds, similar to what is observed in related structures [22]. The sum of bond angles around N1 is 359.89 (1)° which indicate that the pyridine ring is in accordance with sp² hybridization [23]. In the azatricyclic ring, six membered pyridine ring (C1-C3/C8/N1/C9) adopts sofa conformation and five membered oxazole ring (C1/C2/N2/O3/C10) adopts envelop conformation with respect to its puckering parameters (24) for pyridine ring as $q_2=0.369$ (3) Å, $\Phi_2=-38.65$ (1)° and for oxazole as $q_2=0.238$ (8) Å, $\Phi_2=143.53$ (1)°. From the least-square planes analysis it can be confirmed further that the atom C8 of pyridine and C10 of oxazole ring are deviated

by maximum deviation of -0.368 (1) Å and 0.338 (1) Å respectively. Crystal packing of the compound is stabilized by C10-H10...O2 and C15-H15...O1 inter molecular hydrogen bond interactions (FIGURES 4A and 4B; TABLE 2).

Conclusion

The azatricyclo derivatives were crystallized and structure determination was carried out using X-ray diffraction. All the crystals were diffracted well and intensity statistics found agreeable with crystallographic standards. The structures were solved by direct methods using SHELXS and refinement was carried out using (SHELXL) least squares procedures. All the four compounds

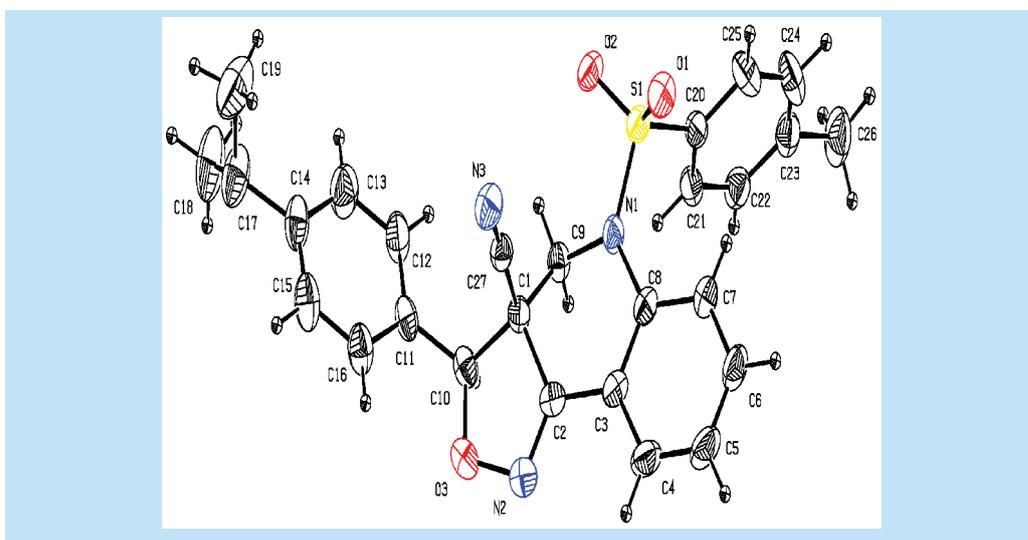


Figure 4A. The ORTEP plot of compound IV with the atom numbering scheme. Displacement ellipsoids are drawn at 30% probability level.

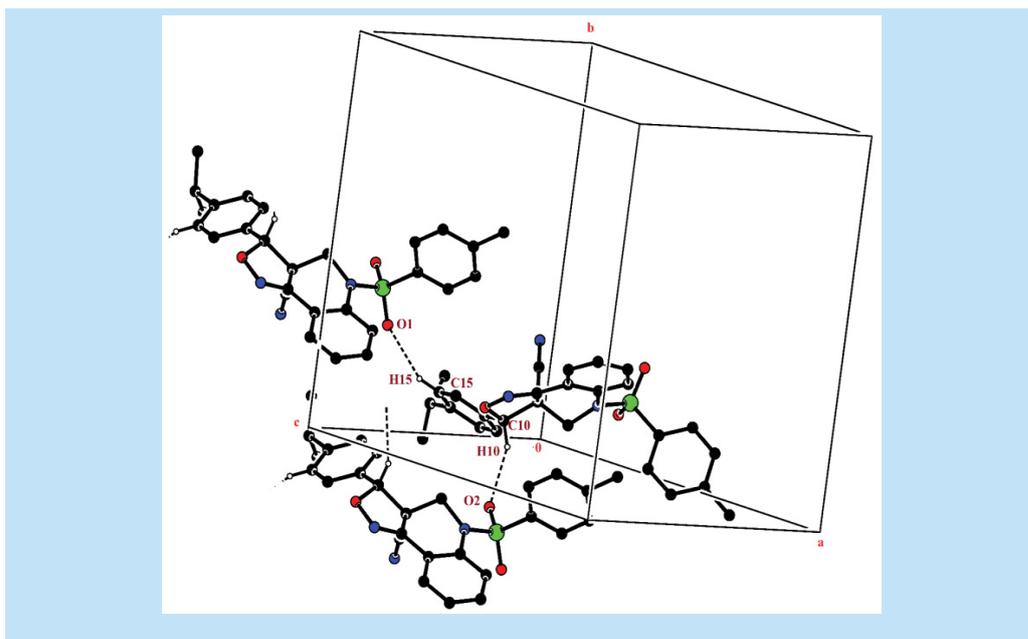


Figure 4B. Portion of the molecular packing viewed down the a-axis for compound IV.

were deposited in the Cambridge Structural Database (CSD). In future, all these compounds can play a role in aiding Structure Based Drug Design (SBDD) where their inhibitory activity will be carried out through *in silico* as well as *in vivo* studies against the suitable protein targets. Further optimizations will be employed to increase their inhibitory potency and be utilized in combating many dreadful diseases.

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