Crystal Structure and Hirshfeld Surface Analysis of 3,5,5-trimethyl-1-tosyl-4,5-dihydro-1*H*-pyrazole

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Abstract – Pyrazoles are widely used as the starting material of many compounds due to their important biological and pharmacological properties, such as antibacterial, anticancer, antifungal, anti-inflammatory, antidepressant, antioxidant activity, and antiviral agents. In this study, we report crystal structure of the title compound containing a pyrazole ring, $C_{13}H_{18}N_2O_2S$. The title compound which consists of a pyrazole ring linked to a phenyl ring crystallizes in the monoclinic space group P21/c with one molecule in the asymmetric unit. The unit cell parameters are a=8.6192 (9) Å, b=9.4478 (6) Å, c=16.8410 (19) Å, $\alpha = \gamma = 90°$, $\beta = 98.692$ (9)° and Z=4. In the crystal, the phenyl and pyrazole rings subtend at a dihedral angle of 81.23 (10)°. The packing of the title compound features aromatic $\pi - \pi$ stacking. These weak $\pi \cdots \pi$ interactions in the compound form a layer structure parallel to the *ab* plane. In addition, Hirshfeld surface analysis was carried out to investigate the location of atoms with the potential to form hydrogen bonds and the numerical ratio of these interactions of the $C_{13}H_{18}N_2O_2S$ compound. The results obtained showed that the most important contributions in crystal packing are due to the interactions of H···H (60.5%), O···H (20.4%), C···H (10.7%) and N···H (6.5%).

Keywords – Crystal structure, Pyrazole, Tosyl, π stacking, Hirshfeld Surface Analysis.

I. INTRODUCTION

Appropriate organization of atoms or groups in the structures of compounds synthesized in drug discovery and development studies is used for the development of new treatment methods in the field of pharmacy and medicine, causing different pharmacological effects [1].

A tosyl group usually derived from the compound 4-toluenesulfonyl chloride, forming esters and amides of toluenesulfonic acid; is often used as a protecting group for alcohols and amines in organic synthesis reactions. Structures in which two aryl rings are substituted at adjacent positions of the pyrazole ring, which are strategically important in interaction with the biological target, are referred to as vicinal diaryl pyrazoles. A wide variety of therapeutically effective compounds containing a vicinal diaryl heterocyclic ring with a broad spectrum of biological activity have been reported in the literature [2]. Among the heterocyclic compounds, vicinal diaryl pyrazoles represent the chemical class in which many drugs with clinical potential are found. Drug or drug candidate molecules carrying this heterocyclic chemical framework cover a wide range of pharmacological activities such as NSAIDs (non-steroidal anti-inflammatory drugs), anticancer, antidepressant, antiviral and antioxidants. Especially in studies on the development of anticancer drug candidates, it is seen that there is a close relationship between compounds carrying the vicinal diaryl pyrazole ring system and anticancer activity [3-6].

To understand the structural properties of compounds that are characterized as privileged structures in terms of medicinal chemistry and have pharmacological importance, the determination of their chemical structures can be made by the X-ray diffraction method. In addition, it is possible to obtain the full three-dimensional shape of the functional groups in the compound and to determine where and how the atoms in the compound are bonded with this method. In this study, the crystal structure of the compound, 3,5,5-trimethyl-1-tosyl-4,5-dihydro-1*H*-pyrazole, $C_{13}H_{18}N_2O_2S$, which has a significant anticancer effect, was elucidated. Hirshfeld surface analysis was also done to obtain more detailed information about the structure.

Table 1. Experimental details of $C_{13}H_{18}N_2O_2S$.

Chemical formula	$C_{13}H_{18}N_2O_2S$
Mr	266.35
Temperature	296(2)
Wavelength	0.71073
Crystal System, Space Group	Monoclinic, $P2_1/c$
a, b, c (Å)	8.6192(9); 9.4478(6); 16.8410(19)
α, β, γ	90; 98.692(9); 90
Cell Volume, V	1355.7(2)
Radiation type	Mo K\a
μ (mm^{-1})	0.24
Data collection Diffractometer	STOE IPDS 2 Diffractometer
Absorption correction	integration
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	5761, 2823, 1840
No. of parameters	163
F(000)	568
Crystal Size	0.53 x 0.46 x 0.37
Z	4
Theta range for data collection	2.4-26.8
Limiting Indices	$-10 \leq h \leq 10$, $-10 \leq k \leq 11$, $-19 \leq l \leq 21$
R_{int}	0.047
$wR(F^2)$, S	0.139, 0.90
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e/Å^3)	0.27, −0.35

II. MATERIALS AND METHOD

Single crystal X-ray data for $C_{13}H_{18}N_2O_2S$ were collected with a STOE IPDS 2 [7] diffractometer. It was collected at 296 K room temperature using Mo Kα rays with a wavelength of λ=0.71073 Å. The crystallographic data of $C_{13}H_{18}N_2O_2S$ is shown in Table 1. The crystal structure of the compound $C_{13}H_{18}N_2O_2S$ was solved using direct methods using the crystal structure solution program SHELXT [8] and anisotropically refined using SHELXL 2018 [9]. In addition, WinGX [10] package programs were used for crystal structure determination. Hirshfeld surface [11] and fingerprint plots were calculated using CrystalExplorer17 [12].

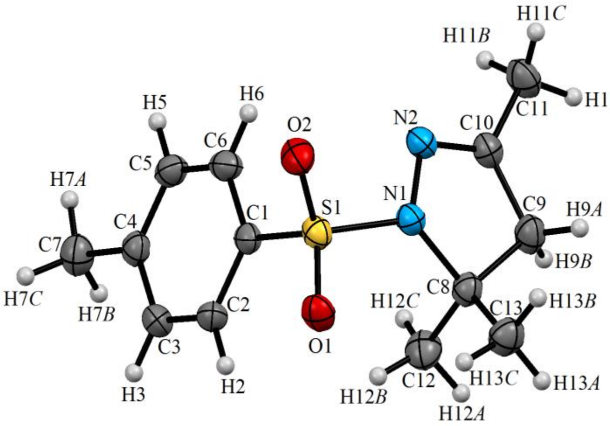

Fig. 1 Crystal structure of $C_{13}H_{18}N_2O_2S$.

III. RESULTS AND DISCUSSION

A. *The Crystal Structure of $C_{13}H_{18}N_2O_2S$*

ORTEP representation of the $C_{13}H_{18}N_2O_2S$ compound with atomic number is as in Fig. 1. The displacement ellipsoids of the atoms other than the H atoms of the molecule shown in Figure 2 are drawn with 30% probability. Parameters related to the molecule, data collection, structure solution and purification information are given in Table 1. It has been determined that a single crystal of the compound crystallizes in the monoclinic $P2_1/c$ space group, and there are four molecules in its unit cell.

The phenyl ring is oriented at a 81.23 (10)° dihedral angle with respect to the 3-methyl-1H-pyrazole ring. C2–C3–C4–C5, C8–C9–C10–C11, C10–C9–C8–Cl2, C10–C9–C8–Cl3 and C2–C1–S1–N1 torsion angles are -1.1 (4), -174.3 (2), 101.0 (2), -133.5 (2), and 107.3 (2)°. In this study, all bond and angle values of the $C_{13}H_{18}N_2O_2S$ compound are within normal values and are consistent. The selected bond length, bond angle and torsion angle values of the compound are given in Table 2.

The packing of the title compound features aromatic π–π stacking. These weak π···π

($Cg2\cdots Cg2$) interactions in the compound form a layer structure parallel to the *ab* plane. Here, *Cg*2 is the centroid of the C1–C6 phenyl ring.

The bond length of the sulfonyl (S=O) group in the structure was determined as 1.432 (2) Å. However, the bond lengths for the C1−S1 and N1−S1 groups in the molecular centres observed between the phenyl ring and the 3-methyl-1H-pyrazole ring for the studied molecule were determined as 1.763 (3) and 1.644 (2) Å, respectively.

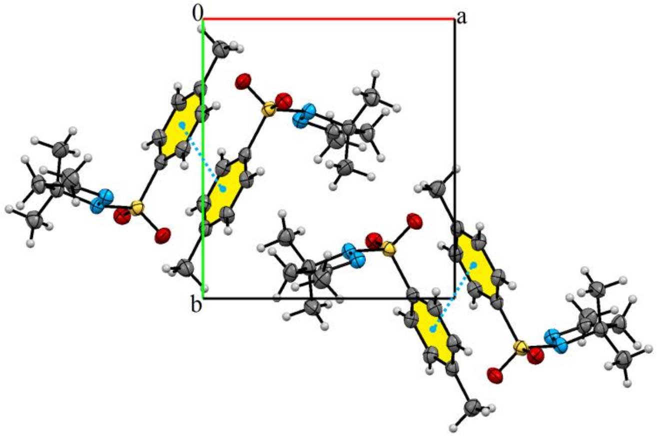

Fig. 2 Crystal packing of $C_{13}H_{18}N_2O_2S$.

Table 2. Some selected bond distances and angles.

Bond	X-ray	Angle	X-ray
S1−O1	1.432(2)	O1−S1−O2	119.97(12)
S2−O2	1.432(2)	N1−S1−O1	104.88(10)
S1−N1	1.644(2)	N1−S1−O2	106.17(10)
S1−C1	1.763(3)	C1−S1−O1	108.76(11)
N1−N2	1.425(2)	C1−S1−O2	107.08(11)
C8−N1	1.519(3)	N1−N2−S1	113.43(14)
C10−N2	1.280(3)	N1−N2−C10	107.32(18)
C4−C7	1.502(4)	C5−C4−C7	121.5(2)
C10−C11	1.493(3)	C9−C10−C11	123.3(2)

B. *The Hirshfeld Surface Analysis*

Hirshfeld surface analysis was carried out to investigate the location of atoms with the potential to form hydrogen bonds and the numerical ratio of these interactions of the $C_{13}H_{18}N_2O_2S$ compound. Crystal Explorer 17.5 program was used to generate the Hirshfeld surface and two-dimensional fingerprint graphics (Figures 4 and 5) using atomic coordinates.

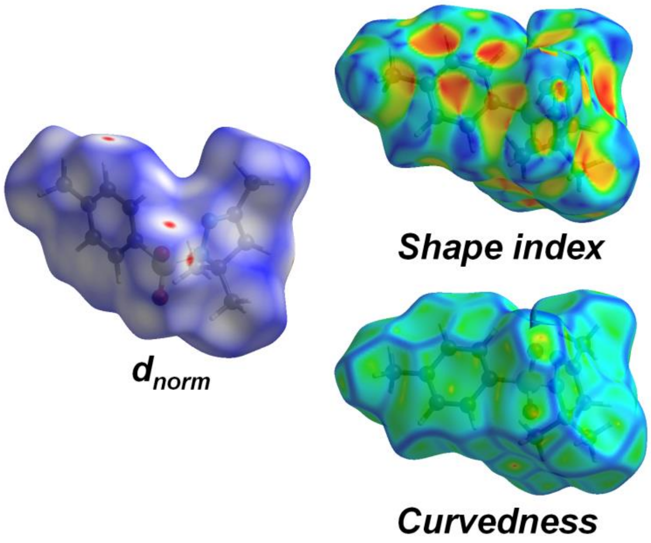

Fig. 3 Hirshfeld surfaces of $C_{13}H_{18}N_2O_2S$.

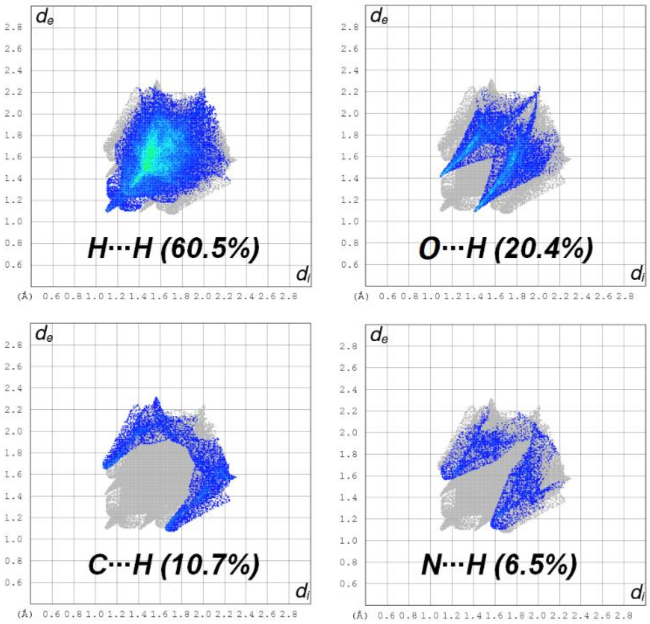

Fig. 4 Two-dimensional fingerprint of $C_{13}H_{18}N_2O_2S$.

Hirshfeld surface analysis is a method that examines intermolecular interactions. These surfaces are used to visualize Van der Waals distances and also to determine interaction points between molecules. Hirshfeld surface maps include d_{norm}, d_i, d_e, shape and curvature indices, and the most basic surface map can be visualized with d_{norm}. As seen in Fig. 3, with the exception of the red dots, the overall surface mapped on the d_{norm} is covered in white and blue colors, indicating that the distances between the contact atoms in the intermolecular contacts are almost the same or longer than the sum of the Van der Waals radii. The green planes seen on the benzene ring on the curvedness surface indicate closer regions on the surface and correspond to π···π interactions. H···H (60.5%), O···H (20.4), C···H (10.7%) and N···H (6.5%) interactions were confirmed in the two-dimensional fingerprint maps shown in Fig. 4, respectively. The relative contributions of the interatomic contacts to the Hirshfeld surface are given in Fig. 5.

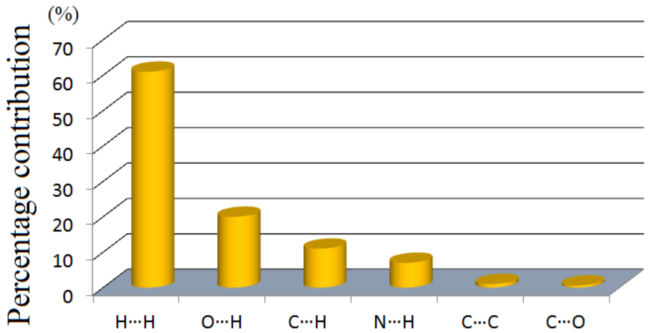

Fig. 5 The percentage contribution of the interactions in $C_{13}H_{18}N_2O_2S$.

IV. CONCLUSION

In this study, the crystal structure of $C_{13}H_{18}N_2O_2S$ compound was elucidated by using the data collected by the single crystal X-ray diffraction method. The compound $C_{13}H_{18}N_2O_2S$ crystallized in the monoclinic $P2_1/c$ space group. Hirshfeld surface analysis of the compound $C_{13}H_{18}N_2O_2S$ was carried out to investigate the position of atoms with the potential to form hydrogen bonds and the rate of these interactions. As a result of the research, the most important contributions for the crystal package were H···H (60.5%), O···H (20.4%), C···H (10.7%), and N···H (6.5%). It has been determined that the least contribution comes from C···C (1.1%) and C···O (0.6%). The molecules are linked by π-π interactions to contribute to stabilizing the molecular packaging. Molecular packing of $C_{13}H_{18}N_2O_2S$ compound was observed as π-π stacking interactions in the *c*-axis.

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