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Face-to-Face Stacking in Sulfonamide Based Bis-ethylene Bridged Heteroaromatic Dimers

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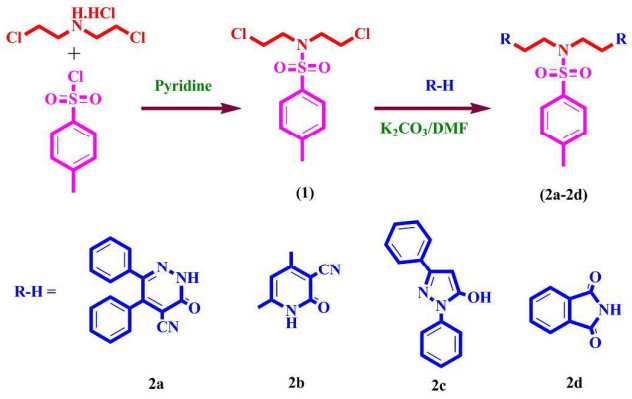
Four sulfonamide based bis-ethylene bridged heteroaromatic dimers were syntheasized for their structural and conformational analysis. Interestingly, all models showed intramolecular offset face-to-face stacking between tosyl and heteroaromatic system in their solid state conformation. ^{1}H NMR in solutions revealed that conformations were not for off than the solid state stacked geometry. However, gaseous state optimizations of different conformers divulged that crystal structures were the lowest energy conformers.

INTRODUCTION

Due to versatile nature of noncovalent interactions, their study at the molecular level is being considered vital in the field of biology, chemistry and in nanotechnology.[1-8] Further, crystal engineering has unveiled various complex phenomenon by employing the concept of supramolecular synthons.[9-13] As the matter concerning to the stacking phenomenon between arene moieties in biological system, these are fundamentally important to study the crystal packing of smaller system having the relating moieties.[14-17] Instead of mere role of π···π interaction to stabilize the face-to-face stacking, some other weak interactions have also been reported for the similar phenomenon.[18-19] Although, such stacking phenomenon are frequent in donor-acceptor type complexes.[20]

Literature reveals that solid state stacking prefered the edge-to-face interaction in small aromatic hydrocarbon.[21-23] However, this edge-to-face orientation has been contrasted with the crystal packing of heteroaromatics where there is a preference for the face-to-face arrangement.[24-26] Periodically, various models have been synthesized for progressive study of stacking phenomenon as well as their conformational stability.[18,26-29] Due to presence of sulphone moiety in various drouges[30-33], their solis, solution and gaseous state conformational study is of interest for the pharmaceuticals and medicinal chemists.[34-36] Further, sulphonamide group has also been use to manipulate the conformation of amino acid backbone into peptides[37-38] and thus structural analysis of bis-ethylene are importent.[39]

The present study deals with the synthesis of heteroaromatic dimers (**2a-2d**) on N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide (**1**) backbone (**Scheme 1**). The heteroaromatic molecules that are selected for the synthesis of modeled compounds **2a-2d** are generally been used for the synthesis of biologically active compounds or pro-drugs.[40-42] Our aim for selection of different heteroaromatic molecules is to know the nature of interactions with tosyl group in their solid, solution and gaseous state.



Scheme 1: Synthesis of compounds **2a**, **2b**, **2c** and **2d**.

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EXPERIMENTAL SECTION

General Methods. All reactions were performed in ordinary conditions at ambient temperature, and reagents were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on JEOL AL300 FT-NMR spectrometer (300 MHz). TMS was used as internal reference, and chemical shift values were expressed in ppm units.

Synthesis: Heteroaromatic molecules and compound **1** were synthesized according to literature procedure.[43-46]

Synthesis of compounds (2a-2d): In a 100 ml round- bottom flask, hetero-aromatic compounds (3.4mmol) were dissolved in minimum amount of dry DMF and to that anhydrous potassium carbonate (3.4mmol) was added and reaction mixture was stirred for 30 minutes. Subsequently, compound **1** (1.7 mmol) was added to the reaction mixture and stirring was continued for next 15-20 h. Completions of the reaction were monitored with TLC. After completion of reactions DMF was removed in vacuo. The obtained crude products were purified by column chromatography.

*N,N-bis(2-(5-cyano-6-oxo-3,4-diphenylpyridazin-1(6H)-yl)ethyl)-4-methylbenzenesulfonamide (**2a**)* M.P. 153-157 ^{0}C; Yield: 0.56g (79%); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, CH_3), 3.92-3.96 (t, 4H, -NCH_2), 4.54-4.57 (t, 4H, -NCH_2), 7.10-4.41 (m, 22 H, ArH), 7.62-7.65 (d, 2H, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 21.5, 45.3, 50.4, 113.2, 113.5, 126.9, 128.2, 128.6, 129.0, 129.2, 129.9, 130.4, 132.3, 134.2 136.7, 143.7, 151.2, 156.9.

*N,N-bis(2-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2H)-yl)ethyl)-4-methylbenzenesulfonamide (**2b**)* M.P. 231-234 ^{0}C; Yield: 0.73g (83%); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 6H, CH_3), 2.42 (s, 3H, CH_3), 2.49 (s, 6H, CH_3), 3.47-3.52 (t, 4H, -NCH_2) 4.20-4.25 (t, 4H, -NCH_2) 6.033 (s, 2H, CH), 7.27-7.30 (d, 2H, ArH), 7.65-7.68 (d, 2H, ArH); ^{13}CNMR (75 MHz, $CDCl_3$): δ 20.4, 43.3, 45.4, 99.2, 109.6, 115.9, 126.9, 129.9, 135.8, 143.7, 152.5, 158.7, 160.5.

*N,N-bis(2-((1,3-diphenyl-1H-pyrazol-5-yl)oxy)ethyl)-4-methylbenzenesulfonamide (**2c**):* M.P. 164-168 ^{0}C; Yield: 0.6g (81%); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 6H, CH_3), 3.57-3.61 (t, 4H, -NCH_2), 4.22-4.25 (t, 4H, -OCH_2), 5.88 (s, 2H, -CH), 7.18-7.24 (t, 4H, ArH), 7.30- 7.42(m, 12H, ArH), 7.62-7.65 (d, 4H, ArH), 7.79-7.82 (d, 4H, ArH); ^{13}CNMR (75 MHz, $CDCl_3$): δ 21.4, 48.7, 70.7, 83.9, 84.0, 122.4, 122.6, 125.4, 126.5, 126.9, 128.1, 128.6, 128.8, 130.0, 133.2, 136.0, 138.4, 144.0, 150.6,154.3.

*N,N-bis(2-(1,3-dioxoisoindolin-2-yl)ethyl)-4-methylbenzenesulfonamide (**2d**):* M.P. 220-224 ^{0}C; Yield: 0.75 g (85%); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, CH_3), 3.31-3.35 (t, 4H, -NCH_2), 3.74-3.76 (q, 4H, -NCH_2), 7.06-7.09 (d, 4H, ArH), 7.62-7.64 (d, 4H, ArH); 7.70-7.80 (m, 4H, Ar-H), ^{13}CNMR (75 MHz, $CDCl_3$): δ 21.3, 33.1, 44.4, 35.1, 123.2, 126.8, 129.4, 132.0, 133.9, 137.0, 142.9, 168.00.

X-ray Crystallography: Single-crystal X-ray data, space groups, unit cell dimensions, and intensity data for compounds **2a**, **2b**, **2c**, and **2d** were collected with an Oxford Diffraction X-calibur CCD diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å). The structures were determined by direct methods using SHELXS-97 and refined on F^2 by a full-matrix least-squares technique using SHELXL-97.[47] Non-hydrogen atoms were refined anisotropically and hydrogen atoms were geometrically fixed with thermal parameters equivalent to 1.2 times that of the atom to which they are bonded. Molecular graphics, ORTEP diagrams and packing diagrams (Fig. S1-S4) for all compounds were prepared using Mercurry version 3.1.[48] PLATON was used for the analysis of bond lengths, bond angles, and other geometrical parameters. Crystallographic details of compounds **2a**, **2b**, **2c**, and **2d** have been summarized in Table 1.

Theoretical Study. In order to investigate the conformational stability in gaseous state, single point and optimized energies have been calculated using the DFT-D method equipped in Gaussian 09.[49]

RESULTS AND DISCUSSION

X-ray crystallography evidences:

In this section we shall discuss about crystallographic evidences of compound **2a**-**2d** (Fig. 1), particularly the intramolecular interactions that stabilized the stacked conformation. Although, molecular packing of all the compounds are stabilized by intermolecular C–H···O, C–H···N, and C–H···π interactions except compound **2b** and **2d** that are further stabilized by π···π interactions (table S1). Yet, the molecular conformation is mainly controlled by intramolecular interactions. Compound **2a** crystallized in monoclinic crystal system with $P2_1/c$ space group having two molecules in asymmetric unit cell along with a strained ether molecule. Due to poor diffraction quality, crystals diffracted extremely weakly and possessed many disorders. The occupational disorders were modeled. The twinned and statically disordered crystals were obtained due to faster crystallization in highly volatile solvent (i.e. diethyl ether). In the crystal lattice, intramolecular π···π stacking between one of the pyridazinone and the tosyl ring shows 3.79 Å in one molecule and 3.75 Å in other molecule. Further, the stacked conformation is stabilized by C–H···π interaction that is formed between methyl hydrogen of tosyl group and phenyl ring attached with pyridazinone. Compound **2b** crystallized in triclinic crystal system with *P*-1 space group. The intramolecular π···π stacking distance between pyridone and the tosyl ring is 3.73 Å that is shorter than that in compound **2a**. Furthermore, there is no intramolecular C–H···π interaction to stabilize the conformation. Subsequently, compound **2c** crystallized in monoclinic crystal system with $P2_1/n$ space group. The intramolecular π···π stacking distance between pyrazole and the tosyl ring is 3.57 Å that is shorter than that in compound **2a** and **2b**. Additionally, the stacked conformation is stabilized by C–H···π interaction that is formed between one of the

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Table 1: Crystallographic data of compounds **2a**, **2b**, **2c** and **2d**

crystal data	**compound 2a**	**compound 2b**	**compound 2c**	**compound 2d**
emp formula	$2(C_{45}H_{35}N_7O_4S).C_3H_7O.CH_3$	$C_{27}H_{29}N_5O_4S$	$C_{41}H_{37}N_5O_4S$	$C_{27}H_{23}N_3O_6S$
formula wt	1613.84	519.61	695.82	517.54
CCDC no.	1427105	1024187	1024186	1024188
crystal system	Monoclinic	Triclinic	Monoclinic	Monoclinic
space group	$P2_1/c$	P-1	$P2_1/n$	$P2_1/n$
T (K)	293 (2)	293 (2)	293 (2)	293 (2)
a (Å)	9.8236(5)	7.2941(9)	16.2384(11)	15.8185(17)
b (Å)	27.0693(15)	7.3475(10)	7.5985(5)	7.3892(7)
c (Å)	32.9799(19)	25.047(3)	29.120(2)	21.053(2)
α (deg)	90.00	85.954(10)	90.00	90.00
β (deg)	94.074(5)	85.943(10)	94.364(6)	92.893(10)
γ (deg)	90.00	82.508(11)	90.00	90.00
Z	4	2	4	4
volume ($Å^3$)	8747.8(8)	1325.0(3)	3582.6(4)	2457.7 (4)
D_{calc} (g cm^{-3})	1.225	1.302	1.290	1.399
F (000)	3384	548	1464	1080.0
measured reflns	40599	13122	17773	11728
indep reflns	17951	4991	8128	6666
theta range (deg)	28.9°- 3.0°	29.1°- 3.2°	29.3°- 3.3°	29.2°- 2.9°
GOF on F^2	1.00	1.04	1.02	1.01
μ (mm^{-1})	0.13	0.16	0.14	0.18
R_{int}	0.070	0.031	0.046	0.035
R-factor (%)	11.2	7.9	7.4	5.9
wR2	0.392	0.242	0.211	0.148

m-hydrogen of tosyl group and the phenyl ring attached with nitrogen atom of pyrazole ring. Finally, compound **2d** crystallized in monoclinic crystal system with $P2_1/n$ space group. The intramolecular π···π stacking distance between five membered ring of phthalimide and the tosyl ring is 3.60 Å that is shorter than that in compound **2a** and **2b** while little greater than in compound **2c**. There is no intramolecular C–H···π interaction in **2d** to stabilize the π···π stacking. The careful observation towards π···π stacking inferred that stacking is stronger in five membered heteroaromatic and tosyl ring in compare to six menbered heteroaromatic.

Face to face stacking is the phenomenon, where one aromatic ring is directly over the opposing ring. The heteroaromatic rings selected in this study have bulkier substituents, which affects π···π stacking due to steric repulsion. Therefore, the only solution to minimise repulsion is to increase both centroid separation and offset of the contiguous rings.[50] Table 2 shows the centroid separation (Cg···Cg) and offset between the contiguous rings. The offset

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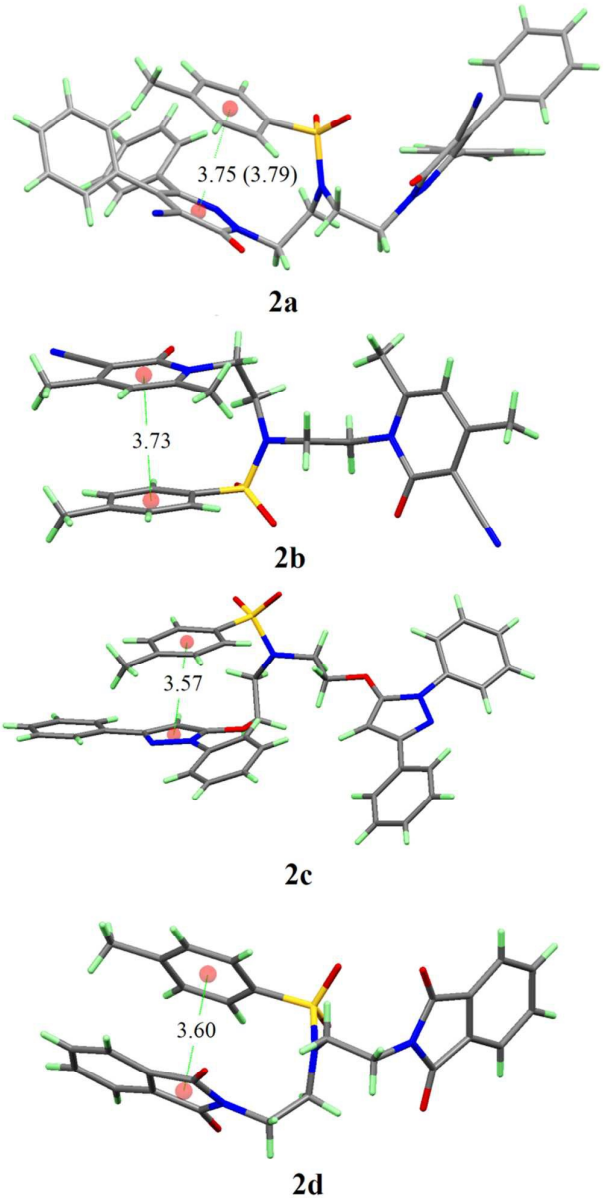

Fig. 1 Structure of compounds **2a-2d** showing face to face stacking.

Table 2. Geometric parameters of intramolecular π···π interactions between tosyl ring and heteroaromatic rings.

Compounds	Cg···Cg[a]/Å	α[b]/°	Cg···plane/Å	Offset/Å
2a[c]	3.795 (3.752)	9.91 (11.12)	3.554 (3.564)	0.241 (0.188)
2b	3.735	2.77	3.605	0.13
2c	3.573	5.49	3.500	0.073
2d	3.604	9.09	3.562	0.042

[a]Cg = centre of gravity of the aromatic ring. [b]α = angle between planes of two aromatic rings. [c]values in bracket are of second molecule in asymmetric unit of **2a**.

values reveal that the contiguous rings in compound **2c** and **2d** are very close to face to face manner with offset of 0.073 and 0.042 Å, respectively, where as **2a** and **2b** shows offset of 0.241 (0.188) and 0.13 Å, respectively. Consequently, these parameters reveal that intramolecular aromatic stacking interaction observed in the modeled compounds is in offset face-to-face manner.[51]

Solution phase NMR evidences:

For our great delight, methyl protons at the tosyl ring helped us to determine the probable geometry in the solutions through ^{1}H NMR. Since molecular rotations in solutions are very fast at room temperature and may exist in several conformers, yet, the equilibrium would be greater toward stable conformation. The high field shifting of methyl protons

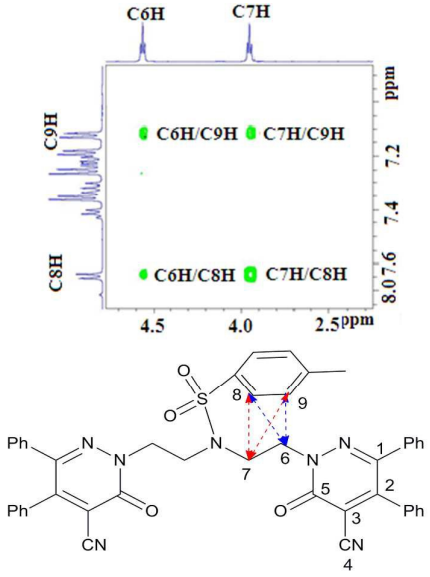

Fig. 2 The structure and Partial 2D NOESY spectra of Compound **2a** showing characteristic NOEs. The dipolar couplings are indicated with red and blue arrows.

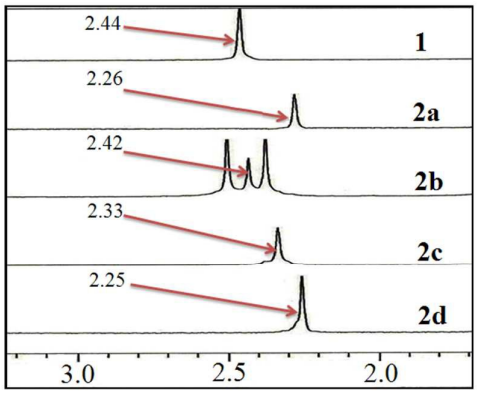

Fig. 3: The comparisons of shifting of methyl proton of tosyl moiety in compound **1** and compounds **2a-2d** in its ^{1}HNMR spectra.

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in compounds 2a-2d in compare to compound 1 reveals that methyl protons are anisotropically shielded. To resolve this outcome, 2D NOESY was performed on compound 2a. NOE excerpts reveal that the molecule is relaxed in comparison to the solid state structure. The characteristic inter-residual NOEs interactions show that both o- and m-protons are interacting with methylene protons of the linker (Fig. 2). However, p-methyl protons of tosyl group lying near to the heteroaromatic ring and could be expected in vicinity of anisotropic ring current. The extent of shielding of p-methyl protons has been calculated in reference to the chemical shift value in compound 1. The relative chemical shifts are -0.18, -0.02, -0.11 and -0.19 ppm in compound 2a, 2b, 2c and 2d, respectively. Consequently, compound 2d shows highest shielding among all, and has been anticipated due to planer and larger delocalization of electrons over phthalimide ring. However, in compound 2b it is only -0.02 ppm that can be expected due to absence of phenyl rings on pyridone ring while heteroaromatic rings in compound **2a** and **2c** contain two phenyl rings and displayed the significant relative chemical shifts (Fig. 3).

Computational Studies:

To probe the conformational stability in gaseous state, single point energy of crystal structures, and optimized energies of several possible conformers of each molecule were calculated at the ωB97X-D/6-31G (d, p) level of theory.[52-53] The ωB97X-D method is known to describe both exchange and dispersion corrections reasonably well. Furthermore, it correctly described both bond changes and weak interactions. Among all conformers (Fig. 4), crystal structure optimization showed lowest energy in all molecules (i.e. **2a1** = -1767933.77, **2b1** = -1266736.56, **2c1** = -1604386.24 and **2d1** = -1290188.00 kcal/mol) that is shown in table 3. It was expected that π···π stacking between phenyl ring of sulfone moiety and heterocyclic ring of other moiety was due to geometrical constraint and lattice forces (table S2). Fortunately the optimization showed the persistence of solid state geometry in molecule **2a**, **2c** and **2d**, it revealed that these molecules felt no force of conformational deformation during crystallization. However, optimization showed flipping through C_{11}-C_{12} bond in one of the pyridone ring of the molecule **2b** that changed the conformation from *anti* (crystal structure) to *gauch* (optimized structure i.e. **2b1**) without affecting the stacked moieties. The energy of other two conformers of molecule **2b** (i.e. **2b2** and **2b3**) were 7.74 kcal/mol and 6.53 kcal/mol higher than **2b1**, respectively. Conformer **2b3** was obtained by rotating the sulfone ring through 180˚ on N-S bond of conformer **2b2**. Consequently, conformer **2b2** was stabilized by four C-H···O interactions while **2b3** showed three C-H···O interactions. Optimized energy of molecule **2a** (**2a1** in fig. 4) was 8.60 kcal/mol lower than conformer **2a2** while 15.94 kcal/mol than **2a3**. The stability of conformer **2a2** was due to extensive intramolecular C-H···O, C-H···N and C-H···π interactions while conform **2a3** showed only two C-H···O interactions. Molecule **2c** was optimization in four different conformers including crystal structure geometry. Among all conformers, energy of **2c4** was very close to optimized structure of the crystal (i.e. 5.13 kcal/mol higher than **2c1**). The geometry of **2c1** was stabilized by one π···π interaction, **2c2** by one C-H···O interaction, **2c3** by one π···π interaction and **2c4** by four C-H···π interactions. Interestingly, **2d** formed two enantiomers (**2d2** and **2d3**) of equal energy (10.26 kcal/mol) while tosyl ring was rotated through 180˚ on N-S bond. Both conformers were stabilized by two C-H···O interactions, however, optimized crystal structure showed one C-H···O and one π···π interaction.

Table 3: Single point[§] and optimized energy[§§] of compounds **2a, 2b, 2c** and **2d** at ωB97X-D/6-31G (d, p) level of theory.

Compound name	Energy (kcal/mol)
2a-sp[§]	-1767464.62
2a1[§§]	-1767933.77
2a2	-1767925.17
2a3	-1767917.83
2b-sp[§]	-1266440.44
2b1[§§]	-1266736.56
2b2	-1266728.82
2b3	-1266730.03
2c-sp[§]	-1603917.43
2c1[§§]	-1604386.24
2c2	-1604370.99
2c3	-1604376.77
2c4	-1604381.11
2d-sp[§]	-1290245.61
2d1[§§]	-1290188.00
2d2	-1290177.73
2d3	-1290177.73

CONCLUSION

In brief it can be concluded that the structural analysis of four sulfonamide based bis-ethylene bridged heteriaromatic dimers **2a-2d** were carried out through single crystal X-ray diffraction, ^{1}H NMR and density functional theory. Single crystal X-ray structures of each compound (i.e. **2a**, **2b**, **2c** and **2d**) showed stacked geometry between tosyl ring and one of the heteroaromatic rings. However, NMR studies in solutions revealed the relaxed geometry than the solid state but gave the evidences of imminent geometry by chemical shifts of *p*-methyl protons of tosyl group. Further, gaseous state optimizations in various conformation revealed that solid state geometry was the most stable one. Addition to all these, the most spectacular result is that tosyl ring formed stacked structure with structurally varied heteroaromatic rings in bis-ethylene bridges dimers which is a important ramifications for designing the sulfone based drugs and macromolecules.

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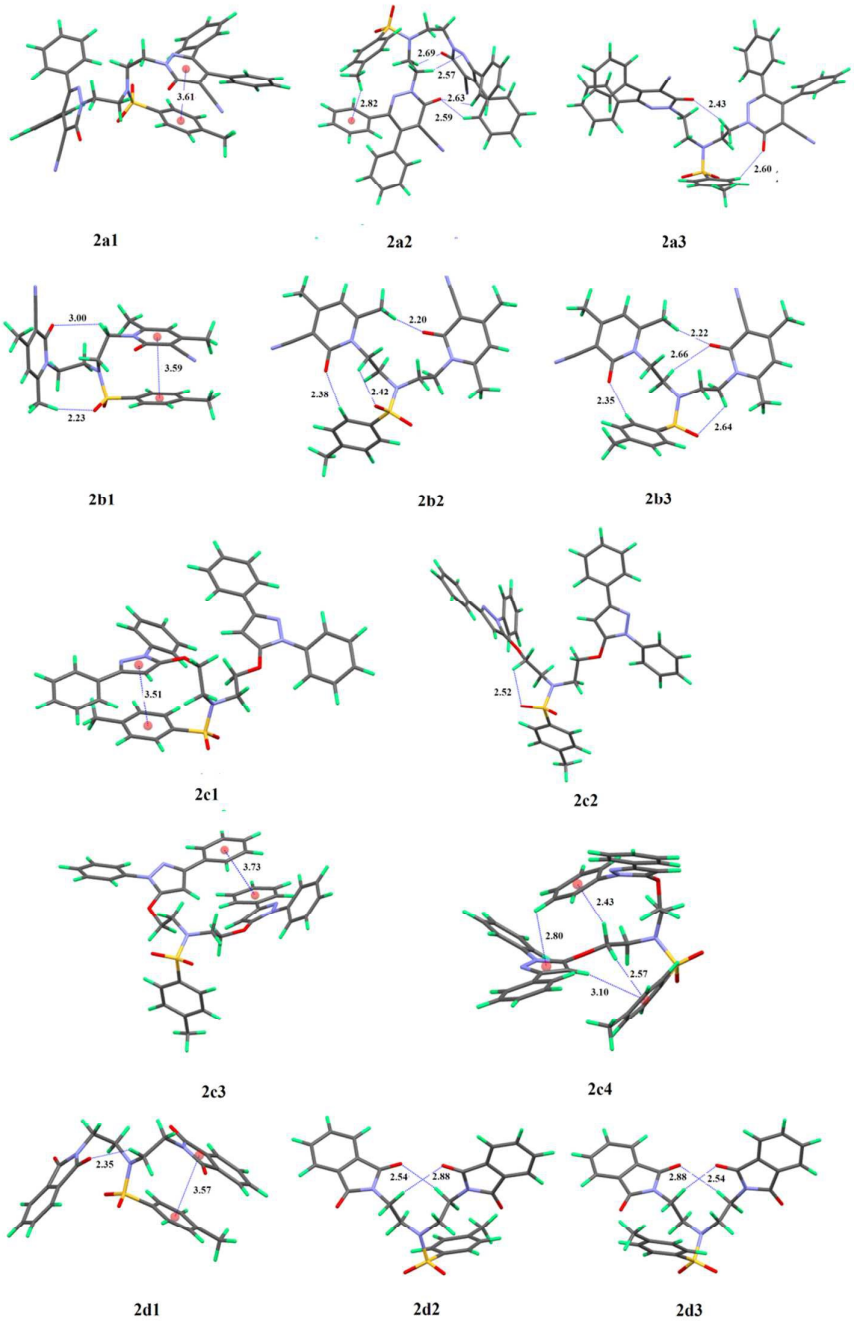

Fig 4 Optimized and other possible low energy conformers for compounds **2a**, **2b**, **2c** and **2d**. Only flexible interactions are shown in the figure.

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Face-to-Face Stacking in Sulfonamide Based Bis-ethylene Bridged Heteroaromatic Dimers

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Abstract: Four sulfonamide based bis-ethylene bridged heteroaromatic dimers were syntheasized for their structural and conformational analysis. Interestingly, all models showed intramolecular offset face-to-face stacking between tosyl and heteroaromatic system in their solid state conformation. ^{1}H NMR in solutions revealed that conformations were not for off than the solid state stacked geometry. However, gaseous state optimizations of different conformers divulged that crystal structures were the lowest energy conformers.