Sulfamethoxazole: Molecular Docking and Crystal Structure Prediction

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Abstract

The conformational stability of sulfonamide derivatives was examined in the active site of Dihydropteroate synthase enzyme. The best docked conformer was identified via molecular docking approach. Possible stable packing of best docked conformer was predicted and evaluated from the intermolecular interactions. Further, the interactions of stable conformer with the active site residue was characterized by charge density analysis based on Bader's Quantum Theory of Atoms in Molecule.

1. Introduction

Sulfonamides are extensively used as antibiotic drugs [1] for treating the infections triggered by fungi and protozoa. However, there exist a non-antibiotic sulfonamides [2], wherein they have been deployed for treating diabetes. In general, these drugs were used widely for treating the infections in urinary tract caused by bacteria *Escherichia Coli* (E.Coli). Some eukaryotic and prokaryotic cells needs sulfonamide drugs to synthesis folates which are essential in the production of purines and glycine, by employing the Dihydropteroate synthase (DHPS) enzyme [3]. The Sulfonamide varieties targets DHPS, which causes the inhibition of cell growth and cell death through folate cofactor depletion. There have been a variety of sulfonamide drugs reported which can treat the diseases in urinary tract along with they are considered as frontline treatment for pneumonia observed in AIDS patients [4].

The present study focus the conformational stability of 24 variants of sulfonamide drugs in the active site of DHPS enzyme. The stable packing of best docked drug was predicted through *ab initio* methods [5] and the intermolecular interaction of the inhibitor molecule in the active site of DHPS enzyme was analyzed. Further, the charge density analysis has been carried out via Bader's Quantum Theory of Atoms in Molecule (QTAIM) [6], to characterize the bonds.

2. Materials And Methods

Molecular docking

The coordinates of all the 24 ligands were obtained from the reported crystal structures. The crystal structure of DHPS in complex form [1AJ0] was obtained from the Protein data bank. Protein Preparation Wizard tool [7] was used for preparing the enzyme and prior to the docking study, the water molecules and ions were removed from the complex. Ligprep Module [8] was incorporated for preparing all the ligands and Induced Fit docking approach [9] was employed for the docking process. Among the 24 ligands, the sulfamethoxazole (SMA), [Fig. 1] was found to have a best docking score and this lowest energy complex was considered for further analysis. The docking score values of all the ligands were listed in the Table 1. The intermolecular interactions between SMA and DHPS were visualized by Maestro [10] and PyMol [11].

Table 1
Induce Fit docking score values of SMA-DHPS complex

Sulfonamide Derivatives	docking score	glide gscore	glide emodel	glide energy	Prime Energy	IFD Score
Sulfamethoxazole (SMA)	-6.637	-6.637	-72.265	-48.437	-11611.1	-587.19
4-amino-N-(3,4-dichlorophenyl)-benzene-sulfonamide	-5.883	-5.883	-62.86	-47.028	-11594.3	-585.6
4-amino-N-(4-ethylphenyl)-benzene-sulfonamide	-6.609	-6.609	-65.867	-45.794	-11565.6	-584.89
4-amino-N-(2,5-dichlorophenyl)-benzene-sulfonamide	-6.127	-6.127	-59.189	-42.607	-11574.6	-584.86
4-amino-N-(4-nitrophenyl)-benzene sulfonamide	-6.105	-6.105	-59.353	-45.175	-11573.8	-584.8
4-amino-N-(2-bromo-4-nitrophenyl)-benzene-sulfonamide	-5.688	-5.688	-61.634	-46.654	-11580.4	-584.71
4-amino-N-(5-chloro-2-methylphenyl)benzene-sulfonamide	-6.122	-6.122	-53.777	-41.655	-11567.9	-584.52
4-amino-N-(4-methoxyphenyl)-benzene-sulfonamide	-5.682	-5.682	-55.148	-41.373	-11574.5	-584.41
4-amino-N-(4-chlorophenyl)-benzene-sulfonamide	-5.688	-5.688	-61.644	-46.274	-11573.6	-584.37
4-amino-N-(3,4-dimethyl-5-isoxazolyl)-benzene-sulfonamide	-6.436	-6.436	-73.446	-49.414	-11558.4	-584.36
N-(4-nitrophenyl)-benzene-sulfonamide	-5.636	-5.636	-58.85	-44.383	-11542.7	-582.77
N-(2-nitrophenyl)-benzene-sulfonamide	-5.415	-5.415	-50.652	-38.341	-11536.8	-582.25
N-(4-chlorophenyl)-benzene-sulfonamide	-5.532	-5.532	-48.872	-37.656	-11527.7	-581.92
N-(2,5-dibromophenyl)-benzene-sulfonamide	-5.059	-5.059	-53.576	-42.832	-11522.8	-581.2
N-phenyl-benzene-sulfonamide	-5.613	-5.613	-55.69	-41.78	-11504.2	-580.82
N-(2-chloro-3-pyridinyl)-benzene-sulfonamide	-5.425	-5.425	-53.847	-41.617	-11499.5	-580.4
N-(2,3-dichlorophenyl)-benzene-sulfonamide	-5.282	-5.282	-47.633	-37.704	-11500	-580.28
N-(2-chlorophenyl)-benzene sulfonamide	-5.321	-5.321	-46.664	-36.793	-11498.3	-580.23

Crystal structure prediction

Initially, the selected ligand was optimized with B3LYP/6-31g(d) [12] method and the dense packing was searched among the most common occurring 31 space groups using MOLPAK package [13]. The searching method was done by orienting the central molecule from -90° to +90° in the interval of 10°. The repetition of this procedure leads to have 6859 hypothetical structures. These starting structures have undergone a lattice minimization using DMACRYS algorithm [14] which implements the repulsion-dispersion potential field. Further, the electrostatic and intermolecular interactions can be well defined from the multipoles obtained from GDMA algorithm [15].

3. Results And Discussion

SMA-DHPS complex

The DHPS enzyme having 282 residues, is folded into eight α -helix stacked around the outside of nine β -strands. The assessment of the binding affinity of SMA against the active site residues of DHPS was done by molecular docking approach [16]. The binding pocket of DHPS comprises hydrophobic and electrostatic regions framed by ARG63, LYS221, ARG255, THR62, ASP185, PHE190 and PRO64 residues. Moreover, the ligand interaction with protein was predominantly stabilized by 10 number of hydrogen bonds. The NH, NH₂ and SO₂ groups dominates most of the H-bond interactions with residues. The complete list of interactions in SMA-DHPS complex was tabulated in Table 2. Figure 2 pose both the 2D and 3D ligand interaction with protein.

Table 2
Ligand-Protein Interactions

Interactions	Distance [Å]	Type
ARG63:HE ... SMA:O1	2.782	Hydrogen Bond
ARG63:HH21 ... SMA:O1	1.962	Hydrogen Bond
LYS221:HZ1 ... SMA:O2	2.047	Hydrogen Bond
ARG255:HH12 ... SMA:O1	2.283	Hydrogen Bond
ARG255:HH22 ... SMA:O1	2.680	Hydrogen Bond
SMA:H1 ... THR62:OG1	1.908	Hydrogen Bond
SMA:H7 ... ASP185:OD2	1.889	Hydrogen Bond
LYS221:HE3 ... SMA:O2	3.072	Hydrogen Bond
LYS221:HE3 ... SMA:N3	3.021	Hydrogen Bond
LYS221:HZ2 ... SMA:N3	2.252	Hydrogen Bond
LYS221:HZ2 ... SMA	2.716	Hydrogen Bond;Electrostatic [Pi...Cation;Pi...Donor Hydrogen Bond]
ARG255:NH1 ... SMA	3.644	Electrostatic [Pi...Cation]
SMA ... PHE190	3.617	Hydrophobic [Pi...Pi Stacked]
PHE190 ... SMA	5.224	Hydrophobic [Pi...Pi T...shaped]
SMC10 ... PRO64	4.829	Hydrophobic [Alkyl]
PHE190 ... SMC10	4.029	Hydrophobic [Pi...Alkyl]
SMA ... ARG63	4.835	Hydrophobic [Pi...Alkyl]

Structure close to real and hydrogen bonding interactions

Table 3 depicts the list of lattice minimized crystal structure of SMA molecule encountered for different space groups and they are ranked on basis of energy. From this table, it was clear that the structure, DD, with -126.7 Kj/mol reflects the experimental structure [17] well and the packing is stable at C2/c spacegroup of monoclinic system, which is highly correlated with the reported X-ray structure [exp]. Figure 3 shows the dense crystal energy landscape with the generated optimized crystal structures together with the minimised experimental SMA structure within the region from -97 to -153 kJ mol⁻¹. The thermodynamic stability of predicted structure [DD] was further confirmed from their strong H-bond interactions [Table 4] and the same was compared well with that of real structure. Moreover, the individual contribution of atoms in the H-bonding interactions was well exploited from the 2D fingerprint plot of Hirshfeld surface (HS) [Figure 4] using Crystal Explorer package [18].

Table 3
List of Predicted crystal structures together with reproduced experimental structure (Exp)

ID	Sp _g	U _{lattice} kJ/mol	a (Å)	b (Å)	c (Å)	ALPHA	BETA	GAMMA	Volume	density (g/cm ³)
AK	P2 ₁ /c	-152.66	13.59	5.45	15.84	90.00	103.99	90.00	1137.65	1.48
AI	P21/c	-152.65	13.59	5.45	15.84	90.00	104.00	90.00	1137.68	1.48
AH	P21	-151.41	8.77	5.38	14.07	90.00	68.49	90.00	617.51	1.36
FC	P21/c	-150.84	14.71	5.23	16.80	90.00	113.04	90.00	1188.10	1.42
CA	P-1	-148.97	8.16	5.58	13.54	89.53	102.10	75.26	581.52	1.45
FA	P21/c	-146.68	8.16	26.85	5.60	90.00	105.55	90.00	1181.96	1.42
AM	P21/c	-146.47	8.37	20.27	7.04	90.00	101.78	90.00	1168.04	1.44
BF	Pm	-146.23	14.22	15.45	5.28	90.00	90.00	90.00	1159.96	1.45
AV	Pna2 ₁	-146.18	14.22	15.46	5.28	90.00	90.00	90.00	1160.26	1.45
Exp	C2/c	-145.91	15.70	5.54	26.93	90.00	90.74	90.00	2343.54	1.44
DD	C2/c	-145.91	15.70	5.54	26.93	90.00	90.71	90.00	2343.62	1.44
DC	C2/c	-145.90	15.70	5.54	26.94	90.00	90.70	90.00	2343.78	1.44
DE	C2/c	-145.88	15.70	5.54	26.94	90.00	90.67	90.00	2343.81	1.44
AB	P-1	-144.14	8.99	6.92	13.35	96.03	128.04	78.29	640.93	1.31
CB	Pbca	-143.66	5.53	15.83	27.49	90.00	90.00	90.00	2406.54	1.40
CC	Pbca	-143.64	5.53	15.83	27.49	90.00	90.00	90.00	2406.56	1.40
AZ	P2 ₁ 2 ₁ 2 ₁	-136.30	12.52	11.09	9.01	90.00	90.00	90.00	1251.26	1.34
CE	Pbcn	-135.10	18.50	6.87	18.74	90.00	90.00	90.00	2381.63	1.41
CD	P2 ₁ /c	-135.07	18.51	6.87	18.74	90.00	90.00	90.00	2381.80	1.41
AP	P2 ₁ 2 ₁ 2	-132.22	13.97	13.60	6.29	90.00	90.00	90.00	1195.31	1.41
AY	Pca2 ₁	-132.12	15.39	8.42	10.01	90.00	90.00	90.00	1297.60	1.30
BH	Pca2 ₁	-132.06	15.43	8.41	10.01	90.00	90.00	90.00	1299.21	1.29
DB	C2	-129.49	15.05	7.76	14.00	90.00	58.04	90.00	1386.71	1.21
AQ	P212121	-127.21	8.89	13.23	10.13	90.00	90.00	90.00	1190.10	1.41
AS	Pna2 ₁	-124.39	14.15	16.10	5.48	90.00	90.00	90.00	1249.55	1.35
BB	P1	-117.17	25.80	8.68	5.66	90.00	90.00	90.00	1267.41	1.33
BA	P2 ₁ 2 ₁ 2	-116.93	25.78	8.69	5.66	90.00	90.00	90.00	1267.65	1.33
BD	Pna21	-113.57	14.71	8.42	10.75	90.00	90.00	90.00	1330.59	1.26
AA	P1	-104.01	8.84	5.50	11.94	125.71	56.00	137.22	310.79	1.35
AF	P2 ₁	-100.70	10.39	7.00	9.09	90.00	111.89	90.00	612.95	1.37

ID	Spg	U _{lattice} kJ/mol	a (Å)	b (Å)	c (Å)	ALPHA	BETA	GAMMA	Volume	density (g/cm ³)
DA	Cc	-97.04	10.08	12.79	13.08	90.00	122.32	90.00	1424.46	1.18
AU	Pna2 ₁	-96.08	13.61	5.35	17.94	90.00	90.00	90.00	1304.98	1.29

Table 4
Intermolecular interactions for predicted (DD) and experimental (EXP) crystal structures.

H-Bond	Donor...Acceptor [Å]	Donor-H.....Acceptor [°]
	DD/EXP	DD/EXP
N1-H1...O2	3.5/3.2	164/165
N2-H4...S1	3.3/-	107/-
N2-H4...O2	3.0/-	134/-
N2-H7...O1	2.9/3.3	126/141
N2-H4...O1	3.5/3.3	128/163
C5-H5...O1	3.4/3.6	144/145
C8-H8...N3	3.3/3.2	131/158
C10-H10...O3	3.5/3.7	166/152
C10-H10...N3	3.5/-	142/-
C10-H9...N3	3.6/3.6	142/137

The maximum contact contribution towards the total HS surface is identified from O...H/H...O interactions with 30.8% and 32.8% for both predicted and experimental crystal structure. These were originated by NH₂ groups interacted with oxygen atoms of SO₂ group [N2-H4...O1, N2-H4...O2, N2-H7...O1], CH of aniline ring and NH group with oxygen atoms of SO₂ [C5-H5...O1, N1-H1...O2] and methyl group with oxygen of isoxazole ring [C10-H10...O3]. These were highlighted by sharp spikes at short distance in the fingerprint plot. Next to this, H...H contacts contributes with 28.9% (predicted) and 27.8% (Exp) with least distance, d(H6,H9) of 2.56Å for predicted crystal structure and the equivalent distance in the experimental structure is 2.83Å. The least contribution is calculated for N...H/H...N interactions involved in isoxazole ring [C8-H8...N3, C10-H9...N3 and C10-H10...N3] and the corresponding percentage values for predicted and experimental crystal structures were 15.8% and 13.6% respectively. These interaction contributions was well established from contact enrichment ratio and %contacts listed in Table 5.

Table 5
Nature of intermolecular contacts on the Hirshfeld surface by chemical types

DD							EXP						
atom	H	C	N	O	S	HC	atom	H	C	N	O	S	HC
Surf%	14.38	23.59	9.89	14.97	2.73	34.45	Surf%	14.6	23.46	9.87	14.78	2.73	34.56
H	1.25						H	1.28					
C	1.26	5.42					C	1.21	5.43				%contacts
N	0.87	1.26	0.41	%contacts			N	0.84	1.25	0.43			
O	14.38	4.44	0.16	0.21			O	14.36	4.4	0.16	0.22		
S	2.47	0.06	0.63	0	0		S	2.59	0.04	0.57	0	0	
HC	7.23	27.13	14.56	9.51	2.26	6.47	HC	7.19	27.27	14.41	9.42	2.38	6.55
E							E						
H	0.61						H	0.62					
C	0.2	1.07		Enrichment			C	0.19	1.07			Enrichment	
N	0.33	0.31	0.5				N	0.32	0.31	0.53			
O	3.46	0.68	0.06	0.1			O	3.47	0.68	0.06	0.11		
S	3.17	0.05	1.28	0	0		S	3.23	0.03	1.13	0	0	
HC	0.68	1.63	2.15	0.89	1.13	0.48	HC	0.68	1.64	2.15	0.89	1.16	0.48

Energy between molecular pairs

The symmetric molecules of SMA crystal structure of both real and predicted structures were stacked in antiparallel and framed the ribbon pattern [Figure 5]. This orientation was predominantly stabilized by N2-H7...O1 and N2-H4...O2 H-bond interactions. The energies of all interactions between the molecular pairs are listed in Table 6 for both predicted and real crystal structures and the values were found to be coherent. Five molecular pairs were identified with significant intermolecular energy, E_{tot} ranges from -23.3 to -38.3 Kcal/mol. First molecular pair is framed from the N2-H4...S1, N2-H4...O2 and N2-H7...O1, H-bond interactions with total energy of -39.4 Kcal/mol [real] and -38.3 Kcal/mol [DD]. This molecular pair is highly stabilized from 27% of electrostatic and 71% of dispersion energies. 50% contribution of these energies was found for the second molecular pair stabled from N1-H1...O2 interaction with E_{tot} values were -32.1 Kcal/mol and -38.2 Kcal/mol for predicted and real crystal structures respectively. The third molecular pair contradict with the previous one, as 71% of electrostatic and 29% of dispersion energies contribute towards the total energy for the interaction N2-H4...O1 and C5-H5...O1. The average E_{tot} values for the fourth and fifth molecular pairs were 31 Kcal/mol [real] and 25 Kcal/mol [DD], with 37% and 63% contributions of electrostatic and dispersion energies. On the whole, it was noted that molecular packing is highly stabilized by dispersion energies in both real and predicted crystal structures.

Table 6
Energy components (kJ/mol) for predicted DD structure (first line) and experimental (EXP) (second line) between the molecular pairs

Symm.operator	Centroid Distance	E_col	E_pol	E_dis	E_rep	E_tot
x+1/2, y+1/2, z	8.33	-33.2	-6.1	-14.4	39.4	-27.9
	8.49	-14.2	-4.4	-9.6	10	-20.4
-x, y, -z+1/2	13.25	2.4	-0.8	-3.7	1.1	-0.6
	12.75	0.7	-1.2	-6	3.8	-3
-x+1/2, y+1/2, -z+1/2	8.74	-12	-2	-19.8	13.1	-23.3
	8.22	-16.7	-2.4	-24.3	15.8	-30.8
x, y, z	5.54	-16.6	-6.7	-28.9	25	-32.1
	5.48	-27.9	-9.1	-31.1	40.7	-38.2
-x, -y, -z	7.80	-10.8	-2.5	-28.7	18.5	-26.9
	7.17	-10.9	-3.6	-28.9	13.8	-30.9
-x+1/2, -y+1/2, -z	6.48	-13.1	-5	-41.2	24.5	-38.3
	6.65	-12.6	-3.5	-44	23.9	-39.4
-x, -y, -z	8.12	4.2	-0.7	-9	0.8	-3.4
	7.82	3.2	-1.2	-14.5	5.3	-7

Closed Shell interactions in active and crystal phase

The strength of the intermolecular interactions between ligand and protein was validated from the electron density analysis using QTAIM approach [19]. In SMA-DHPS complex, the electron density and Laplacian of electron density of all possible H-bond interactions [Table 7] were listed in Table 6. It is clearly revealed that among the interactions, NH group of SMA ligand makes strong binding with the oxygen atom of THR62 residue with the energy value of -27.9 Kj/mol.

Table 7
Topological properties of closed shell interactions of SMA in active site.

Bonds	$\rho(r)$ $e\text{\AA}^{-3}$	$\Delta 2\rho(r)$ $e\text{\AA}^{-5}$	V(r) Kj/mol	G(r) Kj/mol	H(r) Kj/mol	E_inter Kj/mol
H1...THR62:OG1	0.20	1.8	-55.8	52.4	-3.3	-27.9
H7...ASP185:OD2	0.18	1.9	-52.1	52.5	0.4	-26.1
O1...ARG63:HH21	0.16	1.7	-46.4	46.3	0.0	-23.2
O2....LYS221:HZ1	0.14	1.5	-41.8	41.4	-0.5	-20.9
O1...ARG255:HH12	0.10	1.2	-28.8	30.3	1.5	-14.4
N3...LYS221:HZ2	0.11	1.2	-28.7	30.2	1.5	-14.3
O1...ARG255:HH22	0.04	0.6	-10.4	13.3	2.9	-5.2
O1...ARG63:HE	0.03	0.5	-8.0	10.7	2.7	-4.0

Moreover, the similar analysis was carried out for SMA molecule in solid state from the search of (3,-1) type of critical point [6] and the corresponding topological values were listed in Table 8. The impact of N-H...O interactions; N2-H4...O1, N2-H4...O2, N2-H7...O1 and N1-H1...O2, in packing stability was well defined from their interaction energies and the values are -4.12 Kcal/mol, -4.10 Kcal/mol and -1.41 Kcal/mol respectively.

Table 8
Topological properties of closed shell interactions of SMA in solid state.

Bonds	$\rho(r)$ $\text{e}\text{\AA}^{-3}$	$\Delta 2\rho(r)$ $\text{e}\text{\AA}^{-5}$	$V(r)$ Kcal/mol	$G(r)$ Kcal/mol	$H(r)$ Kcal/mol	E_{inter} Kcal/mol
C1-S1	1.41	-10.04	-129.90	32.26	-97.64	-64.95
C1-C2	2.08	-19.73	-252.98	62.27	-190.71	-126.49
C2-C3	2.13	-20.67	-265.57	65.50	-200.06	-132.78
C3-C4	2.07	-20.09	-248.60	58.91	-189.69	-124.30
C4-C5	2.07	-20.10	-249.23	59.19	-190.04	-124.61
C5-C6	2.13	-20.68	-265.22	65.30	-199.92	-132.61
C6-C1	2.08	-19.76	-253.34	62.35	-190.99	-126.67
C4-N2	2.10	-24.32	-412.43	127.05	-285.38	-206.22
S1-N1	1.43	-11.20	-225.96	76.53	-149.43	-112.98
N1-C7	2.03	-23.56	-364.76	105.70	-259.06	-182.38
C7-N3	2.49	-24.21	-635.14	238.77	-396.37	-317.57
N3-O3	2.09	-8.18	-313.44	130.08	-183.36	-156.72
O3-C9	1.98	-2.85	-548.57	265.02	-283.55	-274.28
C9-C8	2.25	-22.85	-309.54	80.39	-229.15	-154.77
C8-C7	1.99	-18.34	-237.86	59.22	-178.64	-118.93
C9-C10	1.78	-15.88	-183.62	40.11	-143.51	-91.81
H4...O2	0.11	1.31	-8.23	8.39	0.16	-4.12
H7...O1	0.11	1.36	-8.20	8.53	0.33	-4.10
H1...O2	0.04	0.61	-2.83	3.39	0.56	-1.41

Electrostatic potential of predicted structures

The polar characteristics of SMA molecule was established from molecular electrostatic potential (MESP) [20] by evaluating the positive, V_{smax} and negative extrema, V_{smmin} potentials on the molecular surface. The negative potential of the ligand in the active site was enhanced due to the interactions with the residues ARG63, LYS221, ARG255, THR62 and ASP185 [Fig. 6]. The donar and acceptor sites in the predicted structures were well identified from strong positive V_{smmax} potential values for the atoms 106.02 Kcal/mol and strong negative extrema, V_{smmin} for the atoms 123.40 Kcal/mol. Moreover, these values were in good agreement with those calculated for real crystal structure.

The electrostatic energy was calculated from the electron density multipolar model and the values are listed in the Table 9 and futher it is computed that E_{elec} and U_{lattice}

Table 9
Electrostatic energies of
predicted and experimental
crystal structures.

ID	E _{elect} [Kcal/mol]
AK	-143.5
AI	-141.7
AH	-143.8
FC	-198.7
CA	-149.4
FA	-95.0
AM	-189.4
BF	-151.1
AV	-154.5
Exp	-253.7
DD	-253.8
DC	-252.5
DE	-253.4
AB	-162.0
CB	-116.6
CC	-115.2
AZ	-214.1
CE	-117.1
CD	-115.9
AP	-142.0
AY	-152.3
BH	-150.4
DB	-324.1
AQ	-159.6
AS	-160.5
BB	-70.0
BA	-68.4
BD	-81.5
AA	-79.4
AF	-98.6
DA	-169.0

ID	E _{elect} [Kcal/mol]
AU	-87.8

values are correlated by 17%.

Further, the correlation coefficient C_{VV} [Fig. 7] between interior and exterior potential was calculated for both experimental and predicted structures, which reveals the complementarity of inner and outer potential. In the experimental crystal structure, the polar hydrogen atoms were lies on the regions of the highest inner potential and the oxygen atoms are at the origin of the electronegative areas. The similar trend was noted for predicted crystal structure. Among the predicted structures, DB has the highest E_{elec} energy and thus have additional H-bond network when compared with experimental and DD crystal structures. In DB, the hydrogen atom of NH_2 forms six H-bonds with the atoms O1, O3, N2 and N3. The C_{VV} correlation for DB structure is -0.41%, whereas the equivalent values for experimental and DD crystal structures was -0.12%. Percentage of actual contacts in the real and predicted crystal packings is shown in the figure 8.

4. Conclusion

The stable conformer of sulfamethoxzole was established from the various types of interactions with the amino acid residues ARG63, LYS221, ARG255, THR62, ASP185, PHE190 and PRO64 residues. The major contribution was resulted from 10 number of hydrogen bonds framed by NH , NH_2 and SO_2 groups of ligand with amino acid residues. The more stable packing were predicted and ranked the hypothetical structures based on the energy. From the energy landscape it was determined that structure DD of spacegroup C2/c was highly resembled with experimental structure with lattice energy of -126.7 KJ/mol. In both predicted and experimental crystal structure, the majority contact contribution towards the total HS surface is predicted from $O...H/H...O$ interactions with 30.8% and 32.8% respectively. The closed shell interactions between the stable ligand and active site residues were characterized by QTAIM theory.

Declarations

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*Code availability

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*Authors' contributions

S.No	Author Name	Contribution
1	Arputharaj David Stephen	Carried out all necessary literature survey and other CSP calculations
2	Rajasekaran Meenashi	Carried out the docking analysis
3	Mehboobali Pannipara	Carried out the Interaction energy calculations
4	Abdullah Godran Al-Sehemi	Carried out the bond topological analysis
5	Mohamed Mustafa Abdul Rahman	Carried out the basic interpretations and language corrections

References

- [1] C. Capasso, C.T. Supuran, Sulfa and trimethoprim-like drugs-antimetabolites acting as carbonic anhydrase, dihydropteroate synthase and dihydrofolate reductase inhibitors, *J. Enzyme Inhib. Med. Chem.* (2014). doi:10.3109/14756366.2013.787422.
- [2] B.L. Strom, R. Schinnar, A.J. Apter, D.J. Margolis, E. Lautenbach, S. Hennessy, W.B. Bilker, D. Pettitt, Absence of Cross-Reactivity between Sulfonamide Antibiotics and Sulfonamide Nonantibiotics, *N. Engl. J. Med.* 349 (2003) 1628–1635. doi:10.1056/NEJMoa022963.
- [3] D. Fernández-Villa, M.R. Aguilar, L. Rojo, Folic acid antagonists: Antimicrobial and immunomodulating mechanisms and applications, *Int. J. Mol. Sci.* 20 (2019) 1–30. doi:10.3390/ijms20204996.
- [4] W.T. Hughes, J. Killmar, Monodrug efficacies of sulfonamides in prophylaxis for *Pneumocystis carinii* pneumonia, *Antimicrob. Agents Chemother.* 40 (1996) 962–965. doi:10.1128/aac.40.4.962.
- [5] D. Chivian, T. Robertson, R. Bonneau, D. Baker, Ab Initio Methods, in: *Struct. Bioinforma.*, 2005. doi:10.1002/0471721204.ch27.
- [6] P.S.V. Kumar, V. Raghavendra, V. Subramanian, Bader's Theory of Atoms in Molecules (AIM) and its Applications to Chemical Bonding, *J. Chem. Sci.* 128 (2016) 1527–1536. doi:10.1007/s12039-016-1172-3.
- [7] G. Madhavi Sastry, M. Adzhigirey, T. Day, R. Annabhimoju, W. Sherman, Protein and ligand preparation: Parameters, protocols, and influence on virtual screening enrichments, *J. Comput. Aided. Mol. Des.* (2013). doi:10.1007/s10822-013-9644-8.
- [8] Schrödinger, LigPrep | Schrödinger, Schrödinger Release 2018-1. (2018).
- [9] W. Sherman, T. Day, M.P. Jacobson, R.A. Friesner, R. Farid, Novel procedure for modeling ligand/receptor induced fit effects, *J. Med. Chem.* (2006). doi:10.1021/jm050540c.
- [10] Schrödinger, Maestro | Schrödinger, Schrödinger Release 2018-1. (2018).
- [11] W.L. DeLano, The PyMOL Molecular Graphics System, Version 1.1, Schrödinger LLC. (2002). doi:10.1038/hr.2014.17.
- [12] A.D. Becke, Density-functional thermochemistry. III. The role of exact exchange, *J. Chem. Phys.* 98 (1993) 5648–5652. doi:10.1063/1.464913.

- [13] J.R. Holden, Z.Y. Du, H.L. Ammon, Prediction of Possible Crystal-Structures for C-Containing, H-Containing, N-Containing, O-Containing and F-Containing Organic-Compounds, *J. Comput. Chem.* (1993).
- [14] S.L. Price, M. Leslie, G.W.A. Welch, M. Habgood, L.S. Price, P.G. Karamertzanis, G.M. Day, Modelling organic crystal structures using distributed multipole and polarizability-based model intermolecular potentials, *Phys. Chem. Chem. Phys.* (2010). doi:10.1039/c004164e.
- [15] A.J. Stone, Distributed multipole analysis: Stability for large basis sets, *J. Chem. Theory Comput.* 1 (2005) 1128–1132. doi:10.1021/ct050190+.
- [16] G.M. Morris, M. Lim-Wilby, Molecular docking, *Methods Mol. Biol.* (2008). doi:10.1007/978-1-59745-177-2_19.
- [17] G.L. Perlovich, A.M. Ryzhakov, V. V. Tkachev, L.K. Hansen, O.A. Raevsky, Sulfonamide molecular crystals: Structure, sublimation thermodynamic characteristics, molecular packing, hydrogen bonds networks, *Cryst. Growth Des.* 13 (2013) 4002–4016. doi:10.1021/cg400666v.
- [18] M.A. Spackman, J.J. McKinnon, Fingerprinting intermolecular interactions in molecular crystals, *CrystEngComm.* (2002). doi:10.1039/b203191b.
- [19] J. Pilmé, E. Renault, F. Bassal, M. Amaouch, G. Montavon, N. Galland, QTAIM analysis in the context of quasirelativistic quantum calculations, *J. Chem. Theory Comput.* 10 (2014) 4830–4841. doi:10.1021/ct500762n.
- [20] J.S. Murray, P. Politzer, Statistical analysis of the molecular surface electrostatic potential: An approach to describing noncovalent interactions in condensed phases, *J. Mol. Struct. THEOCHEM.* (1998). doi:10.1016/S0166-1280(97)00162-0.

Figures

Figure 1

Sulfamethoxazole.

Figure 2

The SMA-DHPS complex showing (a) 2D and (b) 3D intermolecular interactions.

Figure 3

Energy landscape of predicted crystal structures along with the minimized experimental structure.

Figure 4

Fingerprint plot showing the percentage of contact contribution towards the total HS surface for both (a) predicted and (b) Exp crystal structures.

Figure 5

Packing pattern in the unit cell of (a) Predicted and (b) Experimental crystal structures.

Figure 6

Electrostatic potential maps. Blue dots: Positive potential; Red dots: Negative potential

Figure 7

Scatterplot of inner and outer electrostatic potential V on the Hirshfeld surface for crystal structures (a) DD, (b) EXP and (c) DB. The contacts donated by oxygen and by the hydrogen atom Hc from the inner molecule are highlighted in red and blue color, respectively.

Figure 8

Percentage of actual contacts in the real and predicted crystal packings