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Journal of Molecular Structure



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Supramolecular architecture in sulfonylurea, sulfonyldiurea and sulfonyltriurea drugs: Synthesis, X-ray structure and Hirshfeld surface analysis



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ARTICLE INFO

Article history: Received 4 November 2020 Revised 2 February 2021 Accepted 16 February 2021 Available online 23 February 2021

Keywords: Sulfonylurea Sulfonyldiurea Sulfonyltriurea Crystal structure Hirshfeld surface 2D fingerprint plot analysis

ABSTRACT

Sulfonylureas provide a useful motif for carrying donor and acceptor sites capable of hydrogen bonding. These are a prominent class of therapeutic agents in the pharmaceutical industry. However, the use of aryl sulfonyl oligomers in drug discovery, supramolecular chemistry and crystal engineering are unexplored. This motivated us to design, synthesize and understand the structural features of aryl sulfonylurea oligomers (n = 1-3). Here, we report the synthesis and spectroscopic characterization details such as ¹H NMR, ¹³C NMR, mass spectrometry and single-crystal X-ray diffraction analysis for three sulfonylurea oligomer derivatives. Further, the molecular packing analysis of three derivatives reveals the significance of N–H…O and C–H…O intra and intermolecular hydrogen bonding. These hydrogen bonding contacts enable the sulfonylurea derivatives to form 2D framework/architecture. We quantify various intermolecular interactions in these derivatives by Hirshfeld analysis and 2D fingerprint plots. We have performed *in-silico* docking studies against *Plasmodium falciparum (Pf)* prolyl-tRNA synthetase (ProRS) to rationalize the binding affinity of title compounds.

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1. Introduction

Weak non-covalent interactions such as hydrogen bonding [1], metal-ligand coordination [2], π - π stacking [3], hydrophobic, ionic, and van der Waals forces [4] enable mobility in biological structures and are the energetic cornerstones for biomolecular interaction [5]. These interactions form the basis of critical processes occurring in living systems. Biomolecular interactions have provided inspiration for the design of synthetic supramolecular constructs with diverse applications [5-7]. Most drug-receptor interactions in medicinal chemistry operate in a supramolecular framework. Materials based on supramolecular design find application in a variety of domains such as drug delivery, imaging, diagnostic methods and regenerative medicine [8]. In crystal engineering, the supramolecular chemist aims to design and control packing arrangements to obtain specific crystal size, shape and crystalline form with specific properties [5, 9]. Crystal engineering now encompasses many aspects of solid-state intermolecular interactions, rationalisation and control of structures, as well as the synthesis of distinctive molecular building blocks and crystalline materials. Engineered crystals

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may be broadly categorized into components of analysis and synthesis. Crystal engineering also provides an effective route to improving solubility, dissolution rates and bioavailability of poorly soluble drugs [10]. Active pharmaceutical ingredients (APIs) are extremely valuable materials and pharmaceutical co-crystallization plays a significant role in API formulation in the context of drug development and delivery [11]. Crystalline API's are preferred owing to their ease of isolation, rejection of impurities inherent to the crystallization process and the physico-chemical stability afforded by crystalline solid state [12]. API's can exist in several polymorphic, solvated and/or hydrated forms and they provide an opportunity in pharmaceutical research to scrutinize and identify the stability of different polymorphs of each potential new drug [12-14].

Bioisosteric replacement approach is widely used in medicinal chemistry and in the drug discovery process to attenuate the toxicity and/or improve the pharmacokinetic profile of biologically active molecules [15]. Sulfonylurea is one such group, used as a surrogate for amides, ureas, thioureas, nitrosoureas, carbamates, and sulfonamides in the bioisosteric replacement process [16]. Sulfonylureas are an eminent class of oral antidiabetic agents widely used for the management of Type 2 diabetes mellitus (T2DM) [17]. These compounds exert their hypoglycaemic effects by stimulating insulin secretion from the pancreatic β -cell and have been successfully used to treat non-insulin dependent diabetes mellitus [17, 18].

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 $\label{eq:structure} \begin{array}{l} \textbf{Fig. 1.} Structure of (\textbf{A}) \ N-((4-methoxyphenyl) carbamoyl)-4-methylbenzenesulfonamide (\textbf{B}) \ N-(((4-methoxyphenyl) carbamoyl)-4-methylbenzenesulfonamide (\textbf{C}) \ N-(((4-methoxyphenyl) carbamoyl) carbamoyl)-4-methylbenzenesulfonamide. \end{array}$

Literature reports have described a range of other medicinal applications of sulfonylureas such as zinc metalloenzyme modulators [19], human carbonic anhydrase II inhibitor [20], inhibitor of interleukin (IL)–1 β activity [21, 22], anticancer activity [23-25], 5lipoxygenase inhibitors [26] and antimicrobial agents [27, 28]. The presence of donor and acceptor moieties in sulfonylurea groups facilitates their participation in various non-covalent interactions especially hydrogen bonding (N-H...O). Such interactions can contribute to crystal packing, stability of polymorphs and solvatomorphs, and co-crystallization. Accordingly, synthetic methodology and structural properties of sulfonylureas has attracted attention for several years. As part of our work we have reported the synthesis of oligometric sulfonylurea products (n = 1 and 3) and highlighted their biological applications [29]. Based on their applicability as a unique scaffold in medicinal chemistry, we were motivated to learning more about the structural details of the molecules. In this work, we report the comparative analysis of structural properties and packing features in three sulfonylurea derivatives, namely sulfonylurea (A), sulfonyldiurea (B) and sulfonyltriurea (C) molecules (Fig. 1). Also, we have generated Hirshfeld surface and 2D fingerprint plots for these three derivatives to assess the applicable molecular interactions and their contribution towards overall crystal packing.

The distinctive structural differences between A, B, and C led us to explore their effects on a specific protein target. We based our preliminary investigation on the well-known anti-malarial sulfonylurea molecule glyburide. Malaria continues to affect public health worldwide and remain dominant in resource-poor tropical and subtropical regions [30, 31]. Resistance of antiparasitic drugs demands the development of new classes of cost-effective antimalarial drugs [31-33]. Plasmodium falciparum (Pf) prolyl-tRNA synthetase (ProRS) has been recognized as one of the few chemicalgenetically validated drug targets for malaria [31, 34]. While several drugs have been developed for the treatment of malaria, the search for suitable inhibitors of Pf ProRS continues to persist. In particular, halofuginone and its analogues are associated with toxicity related to Homo sapiens (Hs) ProRS inhibition [31, 35, 36]. Recently, Hewitt and co-workers have developed glyburide and TCMDC-124506 as selective allosteric inhibitors of prolyl-tRNA synthetase with IC_{50} values 34 μM and 74 μM respectively [31]. In search of new scaffolds for Pf ProRS, we have performed in silico docking studies for comparing sulfonylurea, sulfonyldiurea and sulfonyltriurea. Our results show that these sulfonylurea oligomers offer promising potential for the development of a new class allosteric inhibitor of Pf ProRS.

2. Experimental section

2.1. Materials and methods

Chemicals were procured from Sigma Aldrich or Merck or Alfa Aesar. Solvents were obtained from Merck Chemicals or SDFCL or FINAR and were used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded on a 500 MHz Bruker Instrument using tetramethylsilane (TMS) as an internal reference. Chemical shifts were measured in ppm (δ) relative to TMS (0.00 ppm). Coupling constants (*J*) are reported in Hertz (Hz). Multiplicity of resonance peaks are indicated as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Mass spectra were measured by LC-MS on a Waters SYNAPT-G2S-S using the electrospray ionization technique. Progress of the reactions was monitored by thin-layer chromatography (TLC) analysis on silica gel plates.

2.2. General procedure for the synthesis of sulfonylurea (A) and sulfonyltriurea (C)

Compounds A and C were synthesized according to the reported method [37]. Briefly, sulfonyl chloride (2.4 mmol) was stirred in pyridine (5.0 mmol) for 5 min. The resulting solution was added to a mixture of sodium cyanate (3.9 mmol) in acetonitrile (10 mL) and allowed to stir at room temperature for 4 h. Aniline derivatives (4.4 mmol) were added to the reaction mixture and stirred for another 1 h at the same temperature. The resulting reaction mixture was poured on crushed ice-cold water and acidified with dilute HCl (pH 5–6). The aqueous layer was extracted with ethyl acetate and was washed with brine and dried over anhydrous sodium sulphate (Na₂SO₄). The ethyl acetate layer was purified by flash column chromatography using ethyl acetate and hexane as mobile phase. *N*-((4-methoxyphenyl)carbamoyl)–4-methylbenzenesulfonamide



The title compound was synthesized as described above and obtained as white solid powder, yield 48%, ¹H NMR (DMSO-d₆, 500 MHz): δ 8.62 (s, 1H, NH), 7.84 (d, 2H, *J* = 8), 7.40 (d, 2H, *J* = 8), 7.25 (d, 2H, *J* = 8.5), 6.83 (d, 2H, *J* = 9), 3.69 (s, 3H, OCH₃), 2.39 (s, 3H, CH₃); ¹³C NMR (DMSO-d₆, 126 MHz): δ 155.65, 150.63, 143.84, 138.27, 131.72, 129.80, 127.82, 121.20, 114.40, 55.64, 21.49; MS (ESI): m/z calculated: 321.0904 [M + H]⁺ and observed: 321.0903 [M + H]⁺.

N-((((4-methoxyphenyl)carbamoyl)carbamoyl)-4methylbenzenesulfonamide (C)

The title compound was synthesized as described above and obtained as white solid powder, yield 24%, ¹H NMR (DMSO-d₆, 500 MHz): δ 10.01 (s, 1H, NH), 9.84 (s, 1H, NH), 9.51 (s, 1H, NH), 7.87 (d, 2H, *J* = 8), 7.44 (d, 2H, *J* = 8), 7.37(d, 2H, *J* = 8.5), 6.91 (d, 2H, *J* = 9), 3.73 (s, 3H, OCH₃), 2.41 (s, 3H, CH₃); ¹³C NMR (DMSO-d₆, 126 MHz): δ 156.25, 152.31, 151.01, 150.07, 144.64, 137.07, 130.73, 129.99, 128.18, 121.99, 114.57, 55.69, 21.53; MS (ESI): m/z calculated: 407.1020 [M + H]⁺ and observed: 407.1027 [M + H]⁺.

2.3. General procedure for the synthesis of sulfonyldiurea (B)

A mixture of sulfonyl isocyanate (1.5 mmol) and N-monosubstituted urea (1 mmol) was taken in a dry round bottom flask and refluxed at 100 $^\circ$ C for 60 min. The progress of the

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Table 1

X-ray diffraction data collection, refinement and structure solution details for compound A, B and C.

Data collection parameters	Compound A	Compound B	Compound C
Chemical formula	$C_{30}H_{32}N_4O_8S_2$	C ₁₆ H ₁₇ N ₃ O ₅ S	C ₁₇ H ₁₈ N ₄ O ₆ S
Molecular weight	640.72	363.38	406.41
Crystal system, space group	Triclinic, P-1	Orthorhombic, Pbca	Monoclinic, P2 ₁
Temperature (K)	273	293	273
a, b, c (Å)	9.7390 (14), 9.8883 (14), 16.541 (3)	10.208 (2), 15.865 (3), 21.164 (4)	5.177 (2), 30.656 (12), 5.909 (2)
α, β, γ (°)	96.557 (5), 90.077 (4), 100.361 (4)	90, 90, 90	90, 101.73 (2), 90
V (Å ³)	1556.3 (4)	3427.5 (11)	918.2 (6)
Ζ	2	8	2
Radiation type	Μο Κα	Μο Κα	Μο Κα
μ (mm–1)	0.23	0.22	0.22
Crystal size (mm)	$0.20\times0.10\times0.10$	$0.28\times0.06\times0.03$	$0.26\times0.18\times0.03$
Diffractometer	Bruker D8-Quest	Bruker D8-Quest	Bruker D8-Quest
No. of measured, independent and	19,961, 7826, 3771	19,801, 4385, 2529	8876, 6138, 4683
observed $[I > 2\sigma(I)]$ reflections			
R _{int}	0.064	0.091	0.028
$(\sin \theta / \lambda)_{max} (Å^{-1})$	0.673	0.675	0.781
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.061, 0.207, 0.97	0.073, 0.184, 1.06	0.045, 0.146, 0.88
No. of reflections	7826	4385	6138
No. of parameters	401	236	267
$\Delta ho_{ m max}$, $\Delta ho_{ m min}$ (e Å $^{-3}$)	0.45, -0.39	0.20, -0.30	0.19, -0.25
CCDC	2,026,187	2,026,188	2,026,189

Table 2

Hydrogen-bond geometry (Å, °) in compound A, B and C.

Compound A					
$D - H \bullet \bullet \bullet A$	D—H (Å)	H●●●A(Å)	D•••A (Å)	$D-H\bullet \bullet \bullet A(\circ)$	
N1−H1●●O2A	0.86	1.97	2.826 (3)	170.5	
N2-H2•••03A	0.86	2.08	2.910 (3)	161.8	
N1A-H1A•••02 ⁱ	0.86	2.05	2.867 (3)	158.9	
N2A-H2AB•••O3 ⁱ	0.86	2.08	2.865 (3)	151.9	
C2A-H2AA01 ⁱⁱ	0.93	2.64	3.286 (4)	126.8	
Symmetry codes: (i) $x - 1$, y , z ii) 1- x , 1- y , - z [Symmetry codes are taken from Res file after commanding HTAB in SHELX].					
Compound B					
$D-H \bullet \bullet \bullet A$	<i>D</i> —Н (Å)	H∙••A (Å)	D•••A (Å)	D−H•••A(°)	
N1−H1•••04	0.73 (3)	1.97 (3)	2.568 (4)	139 (3)	
N2−H2•••O2 ⁱ	0.86	2.09	2.921 (3)	161.7	
N3−H4•••O2 ⁱ	0.81 (4)	2.50 (3)	3.315 (4)	136 (3)	
N3−H4•••O3 ⁱ	0.81 (4)	2.40 (4)	3.116 (4)	149 (3)	
Symmetry codes: (i) $x + \frac{1}{2}, -y + \frac{1}{2}, -z + 1$					
Compound C					
$D-H \bullet \bullet \bullet A$	D—H (Å)	H∙∙•A (Å)	D •••A (Å)	<i>D</i> −H•••A(°)	
N5−H1•••O2 ⁱ	0.87 (5)	2.08 (5)	2.927 (4)	165 (5)	
N3−H4•••O3	0.85 (4)	2.00 (4)	2.694 (3)	138 (3)	
N3−H4•••04 ⁱⁱ	0.85 (4)	2.62 (4)	3.184 (4)	125 (3)	
N4−H4A•••O3 ⁱ	0.86	2.63	3.177 (4)	122.5	
N4−H4A•••O5 ⁱⁱⁱ	0.86	2.35	3.067 (4)	141.5	
N2-H5•••04	0.91 (6)	1.90 (6)	2.624 (4)	135 (5)	
N2−H5•••05 ⁱ	0.91 (6)	2.58 (5)	3.180 (4)	124 (4)	
C16-H16●●O4 ^{iv}	0.93	2.34	3.165 (5)	147.2	

Symmetry codes: (i) x + 1, y, z; (ii) x - 1, y, z; (iii) x + 1, y, z + 1; (iv) x - 1, y, z - 1.

reaction was monitored using TLC. After completion of reaction, the reaction mixture was allowed to cool to room temperature and resulting white solid residue was further purified by flash chromatography to afford desired compound B.

N-(((4-methoxyphenyl)carbamoyl)carbamoyl)-4-

methylbenzenesulfonamide (B)

The title compound was synthesized as described above and obtained as white solid powder, yield 72%, ¹H NMR (DMSO-d₆, 500 MHz): δ 9.30 (s, 1H, NH), 9.20 (s, 1H, NH), 7.88 (d, 2H, *J* = 8.5), 7.46 (d, 2H, *J* = 8), 7.34(d, 2H, *J* = 9), 6.89 (d, 2H, *J* = 9), 3.73 (s, 3H, OCH₃), 2.42 (s, 3H, CH₃); ¹³C NMR (DMSO-d6, 126 MHz): δ 156.27, 151.63, 150.46, 144.89, 136.77, 130.62, 130.13, 128.14, 122.16, 114.53, 55.69, 21.56; MS (ESI): m/z calculated: 364.0962 [M + H]⁺ and observed: 364.0957 [M + H]⁺.

2.4. Crystallization condition

We used slow solvent evaporation method to harvest all the crystals at room temperature. Each compound was dissolved in minimum amount of acetone followed by addition of a suitable amount of hexane before allowing for solvent evaporation in a dust-free environment. Good quality crystals were subjected to single-crystal X-ray diffraction analysis (Tables 1 and 2).

2.5. SCXRD data collection, structure solution and refinement

Suitable crystals were picked for data collection. The details of data collection and structure refinement are summarized in Tables 1 and 2. Single crystal X-ray diffraction data for the good



Scheme 1. General synthetic scheme for the synthesis of sulfonylurea and sulfonyltriurea (A) and Sulfonyldiurea (B).

quality crystals were recorded on a Bruker D8-Quest diffractometer with a PHOTON detector equipped with a Mo K α (λ = 0.71073 Å) source. The atomic structure was solved by direct methods with SHELXS-97 and refined by the full matrix least square methods on F² utilizing the SHELXL-2014. All the non-hydrogen atoms were refined anisotropically. All hydrogens were placed in geometrically idealized positions and constructed to ride on their parent N or C atoms, with N–H = 0.86 Å, C–H = 0.93 Å and Uiso(H) = 1.2 Ueq(N,C), for the aromatic and amine hydrogens, and with C–C–H = 0.96 Å and Uiso(H) = 1.5 Ueq(C) for methyl H atoms. Bruker SHELXTL was used to generate molecular graphics and Mercury CSD 4.0.0 was used to generate packing diagrams.

2.6. Hirshfeld surface and 2D fingerprint plot analysis

The molecular packing of aryl sulfonylurea oligomers was studied by employing the Hirshfeld surface (HS) and 2D Fingerprint plot analysis using Crystal Explorer 3.1 software [38, 39]. The crystallographic information (CIF) files were used as input file to generate Hirshfeld surfaces. The HS was mapped over curvedness, shape index, and d_{norm} were studied for all three compounds [40]. On d_{norm} surface was mapped using red-white-blue colour scheme: Where red, white, blue regions represent closer, exactly equal and longer contacts than the sum of van der Waals radii. Shape index and curvedness were generated to examine $\pi \dots \pi$ interactions in the three derivatives. 2D fingerprint plots were used to represent the relative contribution of each contact towards overall crystal packing.

2.7. Molecular docking studies

Crystal structure of prolyl-tRNA synthetase from plasmodium falciparum in complex with glyburide (PDB ID: 5IFU) was acquired from the Protein Data Bank (PDB, https://www.rcsb.org/). The prolyl-tRNA synthetase enzyme was prepared and minimized using the protein preparation wizard tool of Glide software (Schrödinger, LLC, New York, NY, USA) applying OPLS- 2005 force field. Molecule Builder tool of Maestro 9.8 was used to prepare designed molecules and glyburide, then all the ligands were minimized using LigPrep module of Schrödinger suite applying force field OPLS-2005. Finally, we carried out Glide extra precision (XP) docking of sulfonylurea oligomer derivatives into the active site of the enzyme prolyl-tRNA synthetase. Standard parameters and protocol as included in Glide was followed during protein and ligand preparation and docking studies.

3. Results and discussion

3.1. Chemical synthesis

Sulfonylurea and sulfonyltriurea were synthesized according to reported method [30] from commercially available sulfonyl chloride and amines at room temperature (Scheme 1, A). Sulfonyldiurea was synthesized from corresponding N-monosubstituted urea and p-Toluenesulfonyl isocyanate at 100 °C (Scheme 1, B).

3.2. Crystal structure and molecular packing

Molecular structure of N-((4-methoxyphenyl)carbamoyl)-4methylbenzenesulfonamide (A)

Sulfonylureas are known to readily self-assemble to homodimers. A "head to-head" hydrogen bonding pattern of diaryl sulfonylurea molecule has been reported by Kim and coworkers [41]. They observed that "head to-head" pattern of sulfonylurea affords a better crystal packing based on suitable π - π interactions and steric effects. We observed a similar pattern of "head to-head" arrangement of sulfonylurea-A. Thirunahari and coworkers have reported crystal polymorphism of the anti-diabetic drug Tolbutamide (TB) [42]. They have observed that TB crystallizes in four polymorphic forms, which differ in their mode of packing and in molecular conformation. However, they exhibit a similar hydrogen bonding synthon namely the urea tape motif. The crystal structure of A was solved and refined in triclinic space group P –1. ORTEP diagram for compound-A with the atom labelling is shown in Fig. 2. The asymmetric unit of N-((4-methoxyphenyl)carbamoyl)-4-methylbenzenesulfonamide (compound-A) contains two independent molecules (molecule 1 and 1A) connected via a pair of N-H...O hydrogen bonds (graphs set notation: $R_2^2(10)$). Compound-A exists in L- conformation, where the 4-methoxy phenyl ring is in parallel orientation with torsional angle of -179.5° (C8-N2-C7-N1) with respect to sulfonylurea motif while the 4-methyl phenyl group is in perpendicular orientation 60.9° (C1-S1-N1-C7) with respect to sulfonylurea motif. The sulfonylurea motif in molecule 1 and 1A was found to be in planar conformation with torsional angles of -174.6° (S1-N1-C7-N2) and 175.4°(S002-N1A-C7A-N2A) respectively.

The molecular packing in compound A is primarily stabilized by intermolecular N–H...O hydrogen bonds involving the sulfonylurea motif (Fig. 3). These interactions extended along a single direction forming a 1D framework. Further, crystal packing is also stabilized by weak C3-H3...O1A and C2A-H2AA...O1 hydrogen bonding interactions between 4-methyl phenyl ring and sulfonyl oxygen of neighbouring molecule. These interactions extended along ac plane and contributing in formation of the 2D framework in compound A.



Fig. 2. ORTEP diagram of compound-**A** with displacement ellipsoids drawn at the 50% probability. Hydrogen bonding is represented as dotted lines.

N-(((4-methoxyphenyl)carbamoyl)carbamoyl)–4methylbenzenesulfonamide (B)

The crystal structure of sulfonyldiurea (B) was solved and refined in orthorhombic space group *Pbca*. ORTEP diagram for the compound-B with the atom labelling is shown in Fig. 4. The asymmetric unit of compound-B contains one molecule. Compound B exits in L-conformation where 4-methoxy phenyl ring is in a parallel orientation with torsional angle of -175.8° (C10-N3-C8-N2) with respect to sulfonyldiurea motif while the 4-methyl phenyl ring is in orientation -63.2° (C1-S1-N1-C7) with respect to sulfonyldiurea motif. Compound-B forms one intramolecular hydrogen bond through the N-H...O route (graphs set notation: S₁¹(6)).

The molecular packing in compound-B is mainly stabilized by intermolecular N–H…O hydrogen bonds involving the sulfonyldiurea motif. We observed a six membered ring motif stabilized through N1-H1...O4 intramolecular hydrogen bonds (graph set representation of intramolecular hydrogen bonding: $S_1^{-1}(6)$). Another six membered motif was observed through N2-H2...O2





Fig. 4. ORTEP diagram of compound-**B** with displacement ellipsoids drawn at the 50% probability. Intramolecular hydrogen bonding is represented as dotted lines (graph set representation of intramolecular hydrogen bonding: $S_1^{-1}(6)$).

and N3-H4...O2 intermolecular hydrogen bonding (graph set representation of intermolecular hydrogen bonding: $R_2^{1}(6)$) between sulfonyl oxygen and sulfonyldiurea motif from neighbouring molecule (Fig. 5).

N-((((4-methoxyphenyl)carbamoyl)carbamoyl)carbamoyl)-4methylbenzenesulfonamide (C)

The crystal structure of sulfonyltriurea (C) was solved and refined in monoclinic space group P_{2_1} . ORTEP diagram for compound-C with the atom labelling is shown in Fig. 6. Compound C exists in L- conformation, where 4-methoxy phenyl ring is in a parallel orientation with torsional angle of -172.2° (C13-N2-C12-N3) with respect to sulfonylurea motif and 4-methyl phenyl group is in perpendicular orientation 63.0° (C1-S1-N5-C10) with respect to the sulfonylurea motif. Compound C forms one intramolecular hydrogen bonding through N–H...O interaction (graphs set notation: $S_1^{-1}(6)$).

Compound-C is also stabilized primarily by intermolecular N–H...O hydrogen bonding involving sulfonyltriurea motif. A pair of intramolecular hydrogen-bonding motif through N3-H4...O3 (graph set representation of intramolecular hydrogen bonding: $S_1^{1}(6)$) and N2-H5...O4 interactions (graph set representation of intramolecular hydrogen bonding: $S_1^{1}(6)$) plays a crucial role in inducing planarity in sulfonyltriurea. We also observed six membered hydrogen-bonding ring motifs through N3-H4...O4 and N4-H4A...O3 (graph set representations of intermolecular hydrogen



Fig. 3. Crystal packing diagram of compound-A, viewed down along crystallographic 'b' axis. N-H...O and C-H...O interactions are highlighted as dotted line with atom labelling.



Fig. 5. Crystal packing diagram of compound-B, viewed down along crystallographic 'a' axis.



Fig. 6. ORTEP diagram of compound-C with displacement ellipsoids drawn at the 50% probability. Intramolecular hydrogen bonding is represented as dotted lines (graph set representation of intramolecular hydrogen bonding: $S_1^{-1}(6)$).

bonding: $R_2^2(10)$ and $R_2^2(6)$ respectively) interactions between two neighboring sulfonyltriurea units.

Further, crystal packing is stabilized by C16-H16...O4 hydrogen bonds between 4-methoxy phenyl ring and the carbonyl oxygen of sulfonyltriurea from the neighboring molecule (Fig. 7). These interactions extended along bc plane giving 2D hydrogen bonding framework.

The C-S bond lengths in sulfonylurea (C1-S1), sulfonyldiurea (C1-S1) and sulfonyltriurea (C1-S1) are 1.763 (3), 1.748 (3), and 1.760 (4) Å respectively, which indicates that C-S bond lengths are

somewhat shorter than typical C-S single bond length (C-S: 1.82 Å) [43]. The S-N bond lengths in sulfonylurea (S1-N1), sulfonyldiurea (S1-N1) and sulfonyltriurea (S1-N5) are 1.646 (3), 1.631(3), 1.666 (3) respectively. The S-O bond lengths in sulfonylurea (S1-O1 and S1-O2), sulfonyldiurea (S1-O1 and S1-O2) and sulfonyltriurea (S1-O1 and S1-O2) are 1.422 (2) and 1.426 (2), 1.426 (2) and 1.425 (2), 1.418 (3) and 1.437 (2) respectively. The C-O bond length in sulfonylurea (C7-O3) is 1.225 (4). The C-O bond lengths in sulfonyldiurea (C7-O3 and C8-O4) are 1.212 (4) and 1.224 (4) respectively. The C-O bond lengths in sulfonyltriurea (C10-O3, C11-O4 and C12-O5) are 1.215 (3), 1.228 (4), 1.217 (4) respectively.

3.3. Hirshfeld surface and fingerprint plot analysis

Hirshfeld surface was generated for three compounds and enabled scrutiny of various intermolecular contacts in crystal packing (Fig. 8). The d_{norm}, shape index and curvedness were mapped in the range of -0.602 to -1.590, -1.00 to 1.00, and -4.00 to 0.40, respectively, for all the compounds. Deep red spots on the d_{norm} surface of A, B and C indicates the prominent feature of N–H...O (1.97–2.08 Å) intermolecular interaction integral to the sulfony-lurea motif.

In compound C, apart from N–H…O interactions, additional weak C–H…O interaction on the d_{norm} surface was also visualized as light red spots. Further, to understand the effect of number of urea motif on π … π interaction, we examined the shape index and curvedness of sulfonylurea oligomeric products. The shape index of compound A and B showed no sign of complementary blue and red triangles on the Hirshfeld surface, confirming the absence of π … π (C…C) interactions in these two derivatives. Interestingly, in sulfonyltriurea, shape index showed complementary blue and red spots over urea and aryl groups. Further, curvedness of compound C showed flat region in the same area, confirming the presence of weak π … π stacking.

Additionally, two-dimensional (2D) fingerprint plots were generated using d_e versus d_i values from Hirshfeld surface (Fig. 9). It is understood that H...H, O...H, and C...H, contacts are playing prominent role in molecular packing [44-48]. The O...H/H...O contact are represented as a pair of sharp spikes with minimum di + de values of \approx 1.95 Å in sulfonylurea oligomers (A, B and C). This confirms the presence of strong O...H/H...O hydrogen bonding in sulfonylurea oligomeric products.

Further, C...H/H...C interactions appear as chicken wing-shaped structure with minimum di + de values of \approx 2.85, 3.15 and 2.95 Å in A, B and C respectively, have its place to weak and medium hydrogen bonding. The relative contribution of O...H, N...H, and C...H, interactions in sulfonylurea derivatives were also studied from 2D intercontacts.



Fig. 7. a) Crystal packing diagram of compound-C, viewed down along crystallographic 'a' axis; b) highlighting C-H...O and N-H...O interactions.



Fig. 8. Hirshfeld surface of sulfonylurea oligomers (compound A, B and C) mapped over d_{norm}, shape index and curvedness.



Fig. 9. 2D fingerprint plots for the compound A, B and C.



Fig. 10. Relative contribution of all non-covalent interaction in crystal packing of compound A, B and C.

Due to its dimeric nature, compound A showed a slightly higher percentage of H...H (40.5%) contacts when compared to compound B (40%) and C (37.8%) (Fig. 10). Compound A also showed a higher percentage of C...H contact (23.1%) as compared to compounds B and C having lower contributions of the similar contacts 14.9% and 16.9%, respectively. On the other hand, compound B showed a greater percentage of O...H contact (32.3%) as compared to compound A and C having lower contributions of the similar contacts 29.7% and 30.3%, respectively.

Further, compound B has maximum C...C contact contribution of 4.1% followed by 2.7% and 1.8% for compound A and C, respectively. On the other hand, compound C showed a higher percentage of C...O contact (4.3%) as compared to compound A and B having lower contributions of the similar contacts 1.5% and 3.1%, respectively. Comparable N...H contacts of 2.3%, 2% and 1.9% were observed for compounds A, B and C, respectively.

Table 3

Docking scores of sulfonylurea-oligomer compounds.





Fig. 11. 2D binding interactions of design compound 6 (A) Sulfonylurea (SU), (B) Sulfonyldiurea (SDU), (C) Sulfonyltriurea (STU) and (D) glyburide. Hydrogen bonding interactions are shown as purple coloured dotted arrows.

3.4. Molecular docking

The binding interactions and binding affinity of sulfonylurea oligomers towards prolyl-tRNA synthetase were evaluated by in silico molecular docking studies. One of the well-known sulfonylurea molecules, glyburide motivated us to screen sulfonylurea oligomer compounds against prolyl-tRNA synthetase through in silico studies. Glyburide has been reported to be absent from the enzyme active site and instead preferring to bind at allosteric site of prolyl-tRNA synthetase [31]. The urea unit (-NH-CO-NH) of glyburide was observed to form hydrogen bonds to Glu404 and Tyr266. It formed hydrophobic interactions with surrounding residues Tyr266, Arg514, Tyr746, Ser263, and Asn470. The sulfoxide group (-SO₂-) of glyburide molecule was found to form a weak hydrogen bond with Arg514. Glide docking scores of selected compounds are represented in Table 3. The molecules used comprise substitutions at two phenyl rings that are mainly responsible for their inhibitory activity. 2D binding interactions and 3D binding poses of sulfonylurea oligomeric compounds in the active site of Pf prolyl-tRNA synthetase are shown in figure Fig. 11 and Fig 12 respectively. Molecules A, B and C formed similar pattern of hydrogen bonding interactions with important amino acid residues such as Glu404, Tyr266, Arg514 and Thr402. These compounds also shared most of the important residues that glyburide shared in the allosteric site of *Pf* prolyl-tRNA synthetase. The docking scores of A, B and C with *Pf*prolyl-tRNA synthetase are similar with one another and to the glyburide. Interestingly, substitution patterns on the sulfonylurea oligomeric compounds clearly influences their binding with the enzyme. In particular, the docking scores of sulfonyltriureas of two designs 11 and 12 appear quite promising for their potential inhibitory activity. Our *in silico* studies suggest that sulfonylurea oligomers can be explored for the optimization and development of potential lead candidates against *Plasmodium falciparum (Pf)* prolyl-tRNA synthetase.

3.5. Conclusions

In summary, sulfonylurea, sulfonyldiurea and sulfonyltriurea derivatives have been successfully synthesized and characterized using spectroscopic methods and SCXRD. Our study identifies that



Fig. 12. Superimposed binding poses of designed compounds 9 (A) and 5 (B). Hydrogen bonding interactions are shown in dotted red lines. Sulfonylurea, sulfonyldiurea, sulfonyltriurea and glyburide molecules are represented in red, plum, orange and green colours respectively. Amino acid residues and compounds are shown in stick and, ball and stick representations respectively.

compound A crystallizes as the Triclinic with space group P - 1, compound B crystallizes as Orthorhombic, with space group P bca and compound C crystallizes as the Monoclinic, with space group P 21. Asymmetric unit of compound A contains two independent molecules (molecule 1 and 1a) connected via pair of N-H...O hydrogen bonds (graphs set notation: $R_2^2(10)$). On the other hand, the asymmetric unit of compound B and C contains one molecule. Compound B and C are stabilized by intramolecular N-H...O and C-H...O interactions. The molecular packing in compound A, B and C is mainly stabilized by intermolecular N-H...O and C-H...O hydrogen bonds. The relative contribution of intermolecular H...H, C...H, N...H, C...C, and C...O contacts in all three compounds are highlighted in the Hirshfeld surface and 2D decomposition plots. This study clearly demonstrates that sulfonylurea, sulfonyldiurea and sulfonyltriurea serves as a useful hydrogen bonding motif with multiple donor and acceptor sites that could be applied in crystal engineering and supramolecular chemistry of sulfonylurea-based drug molecules. Molecular docking studies suggest that sulfonylurea oligomers can be explored for the design and development of potent allosteric inhibitor of Plasmodium falciparum (Pf) prolyltRNA synthetase.

Credit author statement

Amarjyoti Das Mahapatra: Conceptualization, Methodology, Investigation, Data curation, Writing-Original draft preparation, Visualization. Althaf Shaik: Conceptualization, Methodology, Investigation, Data curation, Writing-Original draft preparation. Vijay Thiruvenkatam: Conceptualization, Methodology, Writing-Reviewing and Editing, Visualization, Supervision. Bhaskar Datta: Conceptualization, Methodology, Data curation, Writing-Reviewing and Editing, Visualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

B.D. is grateful to CSIR for financial support through grant no. 02(0342)/18/EMR-II. We acknowledge DST-FIST Department of Science and Technology, India for Single Crystal X-ray Diffraction Facility provided at IIT Gandhinagar (Project no. SR/FST/CSI-277/2016) and for the Schrodinger Suite for molecular modelling and docking purposes.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2021.130158.

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