Original Article

DESIGN AND MOLECULAR DOCKING OF SULFONAMIDE DERIVATIVES

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ABSTRACT

Objective: Sulfonamides are a sulfa-related group of antibiotics, which are used to treat bacterial infections and some fungal infections. Some sulfonamides are also devoid of antibacterial activity, such as thiazide diuretics, etc. In this study, an effort was made to find out some novel and potent Sulfonamide derivatives as diuretic agents.

Methods: Here, 30 three-dimensional sulphonamides are designed and docking simulation with PDB ID 1AZM which was downloaded from www. rcsb. org. All the molecules were also screened through a preliminary property filter (Molinspiration Property Calculator).

Results: Among the 30 different molecules designed, 5 molecules were found to have a very good affinity towards the target protein.

Conclusion: These molecular properties define if a molecule can be orally active in our body.

Keywords: Docking, Sulphonamide, SAR

INTRODUCTION

Molecular docking is an attractive scaffold to understand drug biomolecular interactions for the rational drug design and discovery, as well as in the mechanistic study by placing a molecule (ligand) into the preferred binding site of the target-specific region of the DNA/protein (receptor) mainly in a non-covalent fashion to form a stable complex of potential efficacy and more specificity. The information obtained from the docking technique can be used to suggest the binding energy, free energy, and stability of complexes. At present, a docking technique is utilized to predict the tentative binding parameters of the ligand-receptor complex. The main objective of molecular docking is to attain a ligand-receptor complex with optimized conformation and to possess less binding free energy [1, 2].

A sulfonamide is a functional group (a part of a molecule) that is the basis of several groups of drugs, which are called sulphonamides, sulfa drugs, or sulpha drugs. The original antibacterial sulfonamides are synthetic (non-antibiotic) antimicrobial agents that contain the sulfonamide group. Some sulfonamides are also devoid of antibacterial activity, e. g., the anticonvulsant sultiame. The sulfonylureas and thiazide diuretics are newer drug groups based upon the antibacterial sulphonamides [3].
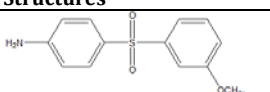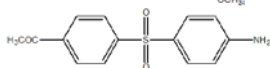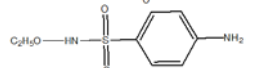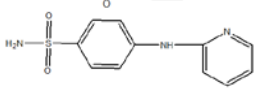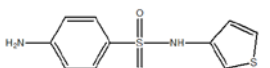
The discovery of sulphonamide diuretic i. e, thiazide diuretics in 1957-58 was the beginning of a new era in the treatment of edema and hypertension. In general, diuretics such as carbonic anhydrase inhibitors, thiazides, and loop diuretics are sulfonamide compounds. Loop diuretics are considered safer and high ceiling diuretics. Their efficacy has a linear relationship with their doses, to the contrary of thiazides which are low-ceiling diuretics. These properties can be attributed to the reason that the sulphonamide derivative shows diuretic activity [4, 5].

Thiazides are sulfonamide-related organic acids that are secreted into the proximal tubule by an organic secretory mechanism.

MATERIALS AND METHODS

The various kind of software which are used. Marvin sketch is used to design 2D and 3D structures of molecules as described in table 1. Molinspiration property calculatorb is used to determine the physicochemical property predictions. Arguslab It is used for docking study of the designed molecule.
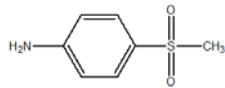
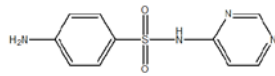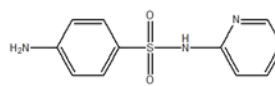## Table 1: Molecule and the structure

Molecule	Structures
S1A	
S1B	
S1C	
S1D	
S1E	
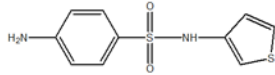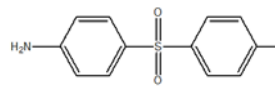
S1F	
S1G	
S1H	
S1I	
S1J	
S1K	
S1L	
S1M	
S1N	
S1O	
S1P	
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S1T	
S1U	
S1V	
S1W	
S1X	
S1Y	
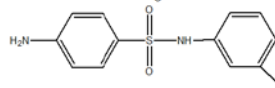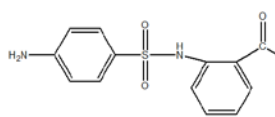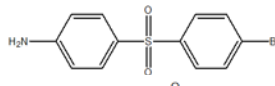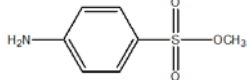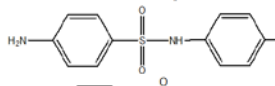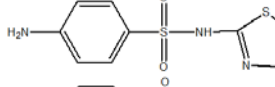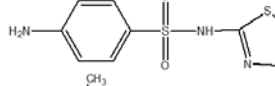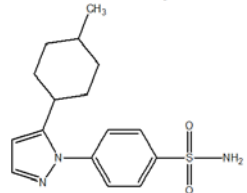
S1Z

S1Zi

S1Zii

S1Ziii

S1Ziv
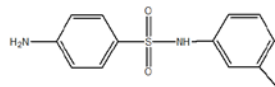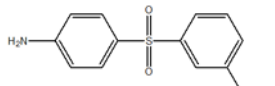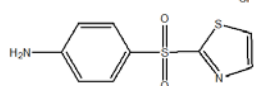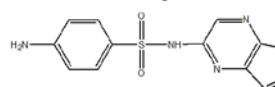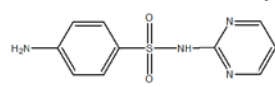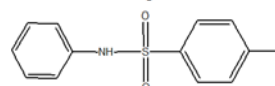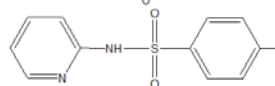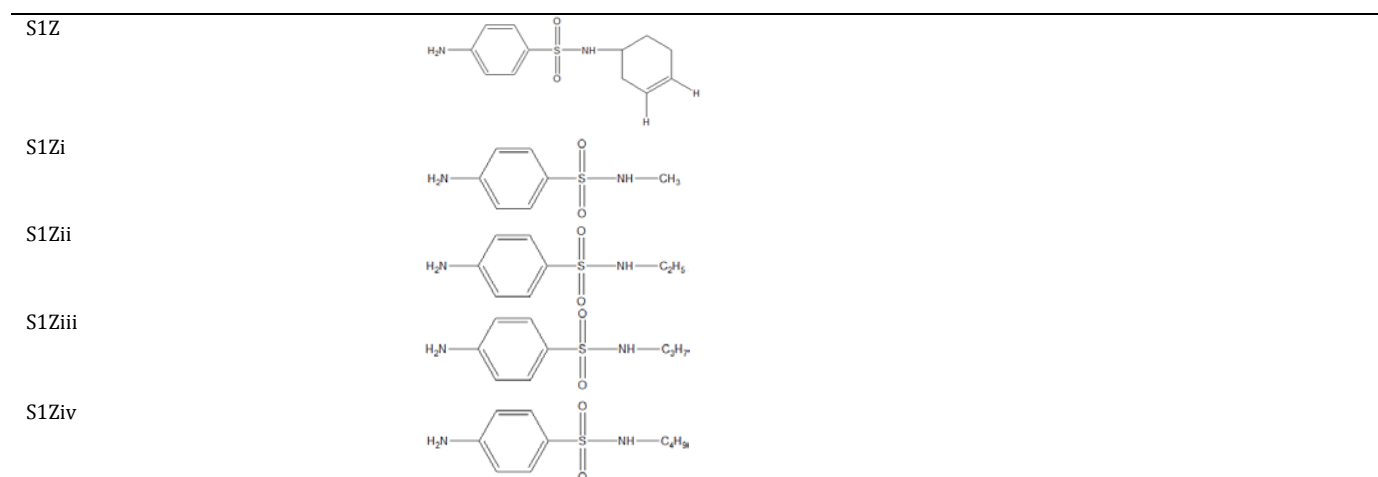
Lipinski's rule of five also known as Pfizer's rule of five or simply the Rule of five (RO5) is a rule of thumb to evaluate drug-likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans [6, 7]. Here in the present study, a java-based online platform (molinspiration property calculator) was used to calculate the molecular properties like lipophilicity (miLogP), Total Polar Surface Area (TPSA), No of atoms, Molecular Weight(MW), No. of Oxygen and Nitrogen, No. of OH and NH, and the number of rotatable bonds were predicted.

Table 2: Predicted physicochemical properties of designed molecules

| Molecule	mi LogP	No. of atoms	M. W.	No. of O and N	No. of OH and NH	No. of violations
S1A	1.67	19	273.31	4	2	0
S1B	1.51	20	285.32	4	2	0
S1C	0.20	15	226.26	5	3	0
S1D	1.72	17	249.29	5	3	0
S1E	1.37	16	254.34	4	3	0
S1F	0.92	16	238.27	5	3	0
S1G	-0.34	12	181.22	3	2	0
S1H	-0.02	17	250.28	6	3	0
S1I	1.62	18	257.31	3	2	0
S1J	2.53	17	267.74	3	2	0
S1K	1.71	20	293.30	7	3	0
S1L	1.52	19	276.32	5	3	0
S1M	2.67	17	312.19	3	2	0
S1N	0.06	13	197.22	4	2	0
S1O	1.74	20	293.30	7	3	0
S1P	0.38	16	257.34	5	3	0
S1Q	0.85	18	263.32	5	5	0
S1R	2.04	23	329.43	5	2	0
S1S	1.98	20	287.34	5	4	0
S1T	2.51	17	267.74	3	2	0
S1U	1.07	15	240.31	4	2	0
S1V	1.26	20	288.33	6	3	0
S1W	-0.20	18	265.30	7	5	0
S1X	1.78	17	248.31	4	3	0
S1Y	0.88	17	249.29	5	3	0
S1Z	1.50	17	252.34	4	3	0
S1Zi	-0.14	13	196.23	4	3	0
S1Zii	0.24	14	210.26	4	3	0
S1Ziii	0.51	15	224.28	4	3	0
S1Ziv	0.78	16	238.31	4	3	0

Cut off values: miLogP: 5, TPSA: 400 c Å, MW: 500 Dalton, No of O, N: 10, No of OH, NH: 5, Volume: 800 c Å.

Receptor preparation and washing

A structure of sulfonamide drug complexed with human carbonic anhydrase I (PDB entry code: 1AZM) was obtained from a protein data bank provided by www. rcsb. org. Water molecules were removed and ligand and cofactors were allowed to retain. Protein was cleaned to remove any extra conformation and the binding site was analyzed. Finally, the protein was prepared according to the requirements of the docking protocol [8].

Structures of the designed ligands were prepared by the Marvin sketch tool as supported by Sanjeevani online program [9]. Then the 3D structures of the ligands were imported to the Arguslab workplace and energy minimization was done by adding hydrogens and CharmM forcefield. Further possible ligand conformations were generated by considering an *in silico* PH of 7-7.4 [10, 11].

Docking

Prepared Ligand was then docked at the active site of the enzyme protein using dock a ligand protocol keeping full flexibility of both the ligand and the protein [12, 13]. A greed consideration of 0.4 Å was applied while docking and the binding energy of the best pose were recorded [14]. Further binding pose of the ligand was refined and the number of hydrogen bonds formed and the amino acid responsible for individual hydrogen bonds was determined [15, 16].

Table 3: Binding energy of docked molecules

| Molecule	(-) Binding energy kcal/mol
S1A	9.85
S1P	9.32
S1H	9.10
S1F	9.09
S1K	9.04
S1W	9.02
S1N	8.90
S1C	8.87
S1G	8.80
S1M	8.79
S1I	.70
S1J	8.69
S1T	8.69
S1B	8.55
S1Z	8.53
S1X	8.50
S1Y	8.49
S1Zi	8.44
S1Zii	8.33
S1Q	8.32
S1Ziv	8.24
S1E	8.24
S1S	8.05
S1U	8.02
S1Ziii	7.79
S1D	7.28
S1L	–
S1O	–
S1R	–
S1V	–

RESULTS AND DISCUSSION

The present study results in a systematic and rational plan of work that was carried out to overcome the different problems of the classical approach of drug discovery. Among the 30 different molecules designed, 5 molecules were found to have a very good affinity towards the target protein as shown in fig. 1 to fig. 5. The binding pose of the 5 probable active molecules is depicted below.
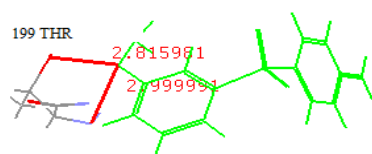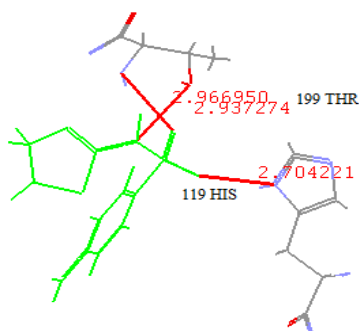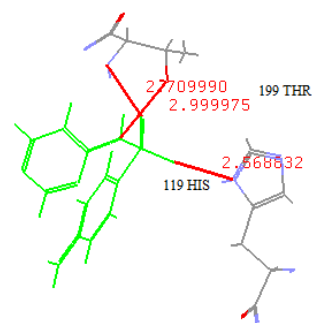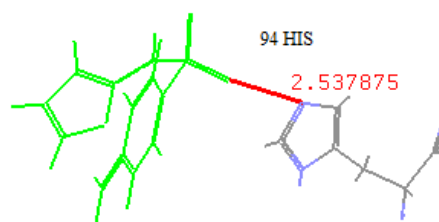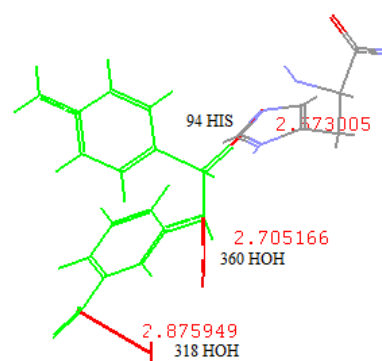

Fig. 1: Binding pose of S1A

Fig. 2: Binding pose of S1P

Fig. 3: Binding pose of S1H

Fig. 4: Binding pose of S1F

Fig. 5: Binding pose of S1K

CONCLUSION

In the present study, an effort was made to find out some novel and potent sulfonamide derivatives as diuretic agents. Arguslab, a free to user software was used to dock the designed molecules at the enzyme active site. The three-dimensional enzyme (Carbonic anhydrase I) with PDB ID 1AZM was downloaded from https://www. rcsb. org and used for the docking studies. All the molecules were also screened through a preliminary property filter (Molinspiration Property Calculator), where certain molecular properties like Molecular Weight, LogP value, No of Hydrogen Bond Donor, No of Hydrogen Bond Acceptor, TPSA, and No of Atoms were calculated. These molecular properties define if a molecule can be orally active in our body.

Out of 30 designed molecules, five designed molecules viz. S1A, S1P, S1H, S1F, and S1K were found to be active and can be used for further studies.

ACKNOWLEDGEMENT

Conflict of Interest: No conflict of Interest

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