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Designing, Proposed Synthesis and Docking Analysis of Novel Sulfonamide Derivatives as Antimicrobial Agents

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Abstract Substituted N-acetyl-4-amino-benzenesulfonamide derivatives were designed using ChemDraw Ultra 7.0 and energy minimization of derivatives was achieved with Chem3D Pro of ChemOffice suit, keeping in view the structural requirements of pharmacophore. Their proposed synthesis along with *in-silico* study (docking analysis) in favor of antimicrobial activity has been shown in this work with the possible mechanism of reaction. Docking studies were carried out to study the binding properties of drugs with molecular targets with the help of AutoDock Vina (Python-Prescription 0.8). Titled compounds (CS, DPS, SRS and TS) exhibited good binding properties with molecular target pseudomonas aeruginosa exotoxin A in Lamarckian genetic algorithm based flexible docking studies.

Keywords: *sulfonamide derivatives, proposed synthesis, antimicrobial, molecular docking*

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1. Introduction

With serious mortality and morbidity results, drug resistance against bacteria have emerges with public health problem all over the world. The case of penicillin resistance worldwide could be considered as one of the example. Additionally, multi-drug resistance has created another problem to work with. This type of problem could be observed in Europe, Asia and America with vancomycin resistance [1-8]. The above mentioned problems and so many others like these promoted us to contribute hands a little towards solving the problems by proposing synthesis and screening a series of sulfonamide derivatives.

Mode of action of sulfonamide drugs observed so far is inhibition of carbonic anhydrase against a wide range of bacteria. The substituted ring of benzenesulfonamide containing $-SO_2NH_2$ groups act by binding or coordination of the $-SO_2NH^-$ anion to the Zn^{2+} of the enzyme, mimicking the bicarbonate anion in the transition state [9]. The mode of action of antimetabolite sulfa drugs is the inhibition of dihydropteroate synthetase, which catalyzes an enzyme in the biosynthesis of tetrahydrofolate and then nucleotides [10].

In the same way, we have screened (*in-silico* screening) the designed compounds against Pseudomonas aeruginosa exotoxin A by the means of docking studies.

The Pseudomonas exotoxin A is an exotoxin produced by *Pseudomonas aeruginosa*. It inhibits elongation factor-2. It does so by ADP-ribosylation of EF2 (eukaryotic elongation factor-2). This then causes the elongation of polypeptides to cease.

2. Material and Methods

The chemical structures of the derivatives were drawn using ChemDraw Ultra 7.0 and energy minimization of derivatives was achieved with Chem3D Pro of ChemOffice suit for taking energy of each molecule up to its lowest energy state (highest stability).

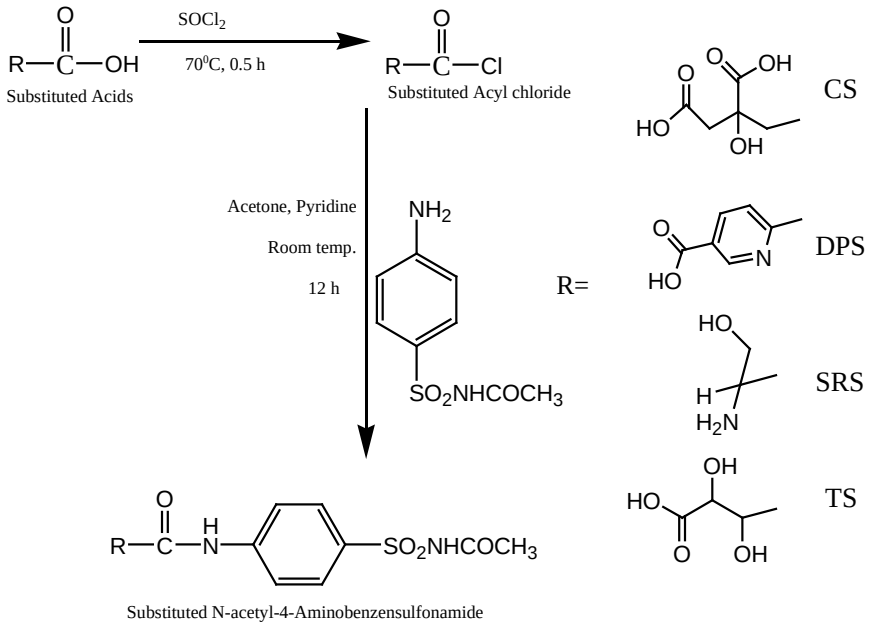
2.1. Proposed Synthesis of Substituted Acyl Chlorides

Substituted acid (0.1 mol) and thionyl chloride (0.4 mol) should place in a 250 ml flask equipped with a magnetic stirrer bar and a condenser with a drying tube. The reaction mixture should stir and heated in a 70°C oil bath. After 0.5 hours, the reaction mixture would allow cooling at room temperature with opened flask; this facilitates the evaporation of remaining thionyl chloride and lefts acyl chloride in the flask [11,12].

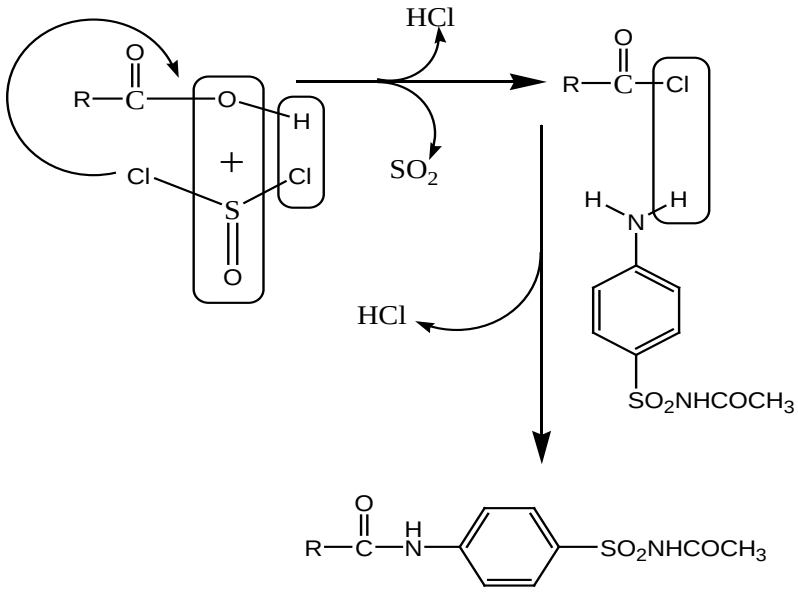
2.2. Proposed Synthesis of Substituted N-acetyl-4-amino-benzenesulfonamide

For the synthesis of an appropriate amide, the substituted acyl chloride (0.009 mol) of an individual acid dissolved in 20 ml. of dry acetone would added drop wise to a stirred solution of aromatic aminosulfonamide (0.0092 mol) and pyridine (0.0091mol) in 50 ml. of dry acetone. After addition, the reaction mixture would stir for about 12 hour at room temperature and then the solvent should evaporate under reduced pressure. The residue should then dissolve in 100 ml. ethyl acetate and the

organic phase washed three times with 20 ml. of distilled water. Then 10% HCl solution was added until pH 1 was reached, and the organic phase was separated from the aqueous phase and washed three times with brine. The aqueous solutions should combine and extracted with ethyl acetate. The ethyl acetate extracts were combined, dried over $MgSO_4$, filtered and evaporated under reduced pressure [11,12].



Scheme 1. Proposed synthetic scheme of substituted N-acetyl-4-amino-benzenesulfonamide from substituted acids (CS, DPS, SRS, TS)



Mechanism 1. Proposed mechanism of reaction

2.3. *In-silico* Studies

2.3.1. Docking Studies

2.3.1.1. Docking

Molecular docking techniques are used in modern drug design to help understand drug–receptor interaction. It has been shown in the literature that these computational procedures can strongly support and help the design of new, more potent drugs by revealing the mechanism of drug–receptor interaction. Rational drug design helps to facilitate and speedup the drug designing process, which involves variety of methods to identify novel compound, out of them one method is the docking of the drug molecule with the receptor. The therapeutic action of the clinical drug will be effective when the biochemical pathway of the enzyme can be exploited. Docking procedures allows virtually screening a data-base of compounds and predict the strongest binder based on various scoring functions [13-18].

2.3.1.2. Receptor

Pseudomonas aeruginosa exotoxin A.

2.3.1.3. Docking Tool

Here docking has been performed with AutoDock docking software. It is virtual screening software for computational drug discovery that can be used to screen libraries of compounds against potential drug targets. It enables medicinal chemists to run virtual screening form

any platform and helps users in every steps of this process from data preparation to job submission and analysis of the results [13-18].

For performing docking, receptor has been downloaded from NCBI website with PDB ID 1IKQ (Pseudomonas aeruginosa exotoxin A), then designed ligand has been docked with protein (receptor) with AutoDock software having its default settings.

3. Results and Discussion

3.1. Docking Study of N-acetyl-4-amino-benzenesulfonamide Derivatives and Standard Drug Taken Norfloxacin (CID_4539)

Docking study of protein was performed with the designed inhibitors and standard drug taken is given in Table 1 & Table 2 and number of hydrogen bonds & binding pattern such as element, type of bond, atom number and residue at binding site were evaluated.

Table 1. Docking analysis of designed compounds

Ligand	Receptor	Affinity Kcal/mol	H-bonds	H-binding ligand			H-binding receptor			
				Elem.	At.ID	Type	Res.	Elem.	At.ID	Type
CS	1IKO	-7.5	6	O	10	Both	ARG 458	N	3515	Donor
				O	09	Acceptor	ARG 458	N	3514	Donor
				O	14	Acceptor	GLN 458	N	3728	Donor
				N	01	Donor	GLY 441	O	3387	Acceptor
				O	15	Both	TYR 481	O	3689	Acceptor
				N	26	Donor	ILE 471	O	3623	Acceptor
DPS		-7.7	5	O	12	Acceptor	ARG 458	N	3515	Donor
				N	13	Donor	SER 459	O	3519	Acceptor
				O	25	Both	TYR 470	O	3611	Acceptor
				O	25	Both	TRY 439	O	3365	Acceptor
				O	25	Both	ALA 472	N	3628	Donor
SRS		-6.7	5	N	11	Donor	GLY 441	O	3387	Acceptor
				N	11	Donor	THR 442	O	3393	Both
				O	15	Both	THR 442	O	3393	Both
				O	15	Both	HIS 440	N	3383	Acceptor
				N	20	Donor	ILE 471	O	3623	Acceptor
TS		-7.3	11	N	13	Donor	TYR 394	O	3008	Acceptor
				O	02	Acceptor	SER 188	O	1416	Both
				O	02	Acceptor	AGR 186	N	1396	Donor
				O	24	Both	ASP 217	O	1651	Acceptor
				O	24	Both	LYS 194	N	1463	Donor
				O	24	Both	ASN 215	O	1627	Acceptor
				O	22	Both	ASP 217	O	1651	Acceptor
				O	19	Acceptor	LYS 194	N	1463	Donor
				O	20	Both	ASN 215	O	1627	Acceptor
				O	20	Both	ASN 215	O	1632	Acceptor
				O	20	Both	ASP 217	O	1650	Acceptor

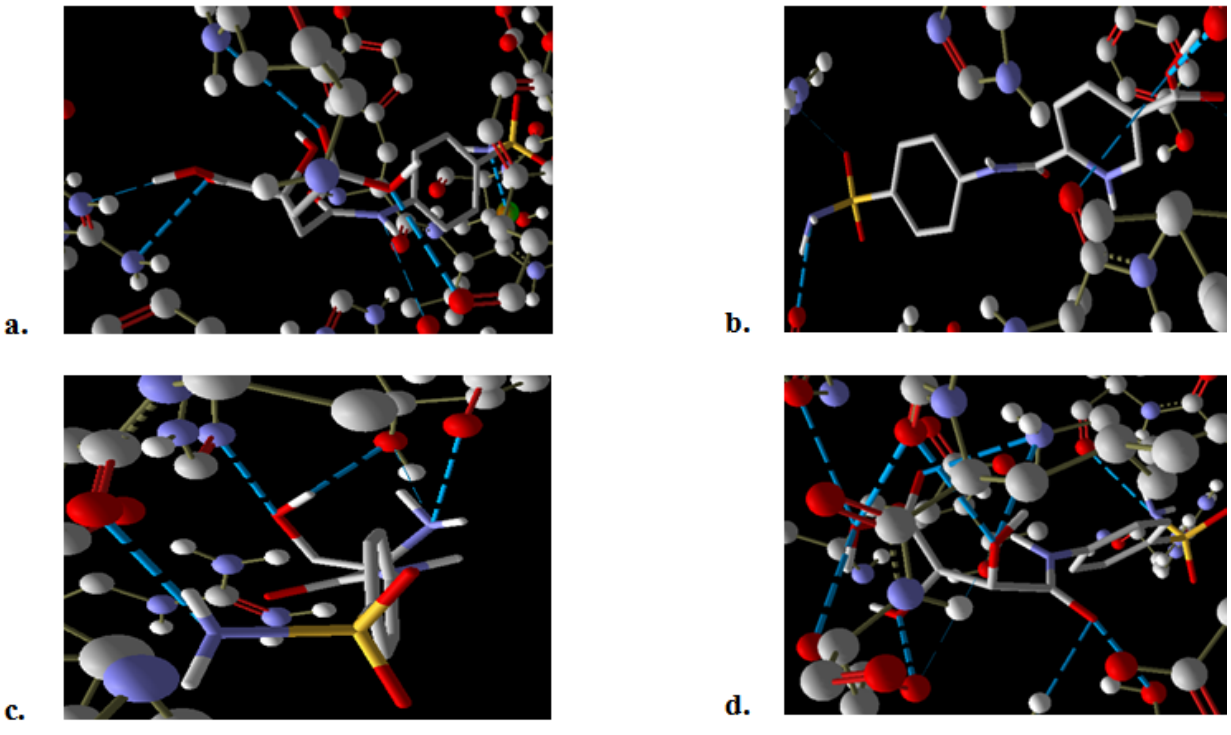


Figure 1. Docked photographs of (a) CS, (b) DPS, (c) SRS, (d) TS with protein 1IKQ

On docking analysis, designed compound TS have been found to be strongly docked with the protein 1IKQ in order to study its inhibition activity. When it is docked with the protein PDB ID- 1IKQ, it forms 11 hydrogen bonds with binding affinity of -7.3 Kcal/mol. On residue study, the amino acids TYR 394, SER 188, ARG 186, ASP 217, LYS 194 and ASN 215 were found to be significant. While other novel designed molecules CS, DPS and SRS shows moderate binding pattern with -7.5 Kcal/mol, -7.7 Kcal/mol, -6.7 Kcal/mol and 6, 5, 5 hydrogen bonds respectively. Their docking images have been shown in Figure 1.

Table 2. Docking analysis of Norfloxacin (CID_4539)

Ligand	Receptor	Affinity Kcal/mol	H-bonds	H- Binding Ligand			H- Binding Receptor			
				Elem.	At. ID.	Type	Res.	Elem.	At.ID.	Type
CID_4539	1IKQ	-8.1	4	O	23	Both	GLN 212	O	1604	Acceptor
				O	23	Both	GLU 399	O	3048	Acceptor
				O	22	Acceptor	TYR 206	O	1554	Both
				O	22	Acceptor	GLN 212	N	1605	Donor

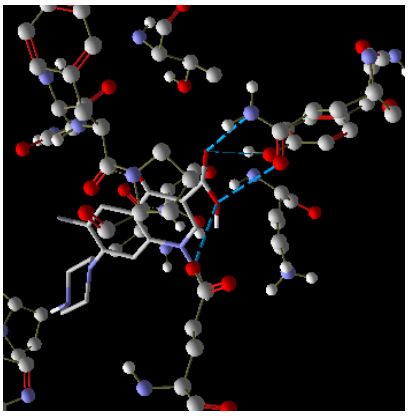


Figure 2. Docked photographs of Norfloxacin (CID_4539) with protein 1IKQ

On docking analysis, the standard drug CID_4539 has been found to be strongly docked with the protein 1IKQ in order to study its inhibition activity. When it is docked with the protein PDB ID- 1IKQ, it forms 4 hydrogen bonds with binding affinity of -8.1 Kcal/mol. On residue study, the amino acids TYR 206, GLN 212, GLU 399, TYR 206 and GLN 212 were found to be significant. Its docking image has been shown in Figure 2.

3.2. Comparison of Docking Results of Novel Designed Molecules with the Standard Drug CID_4539

On docking analysis, the docked poses of DPS, CS and SRS do not superimpose with standard drug molecule which can be clearly seen in Figure 3, but the docking analysis shows that they are nicely docked with protein rather in the catalytic domain, it means it binds in the allosteric site and there is possibility of making it antimicrobial.

On docking analysis of TS, it is clearly observed that this is only the molecule out of four which intercalate with the binding domain of the standard drug taken. (see Figure 3).

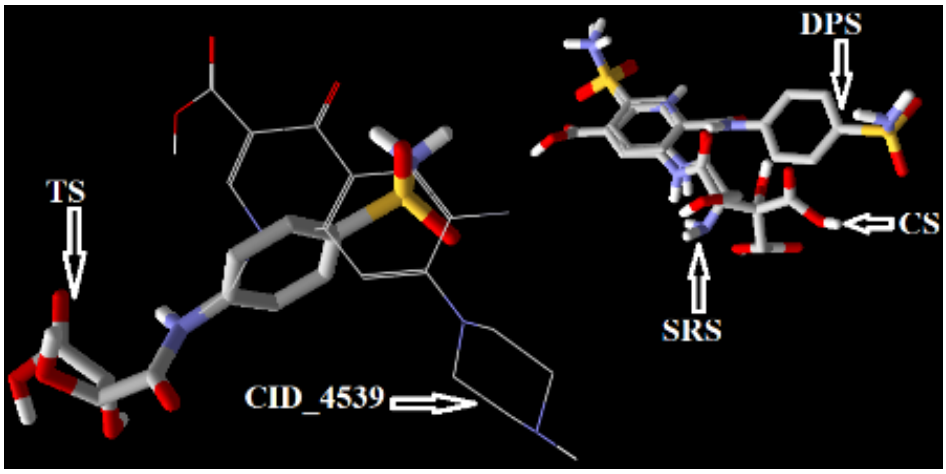


Figure 3. Comparative docking poses of novel designed molecules (showing with stick model) along with standard drug CID_4539 (showing with wireframe model)

4. Conclusion

In the present work, a synthetic procedure has been proposed for the synthesis of novel sulfonamide derivatives based on previous works keeping in view the structural requirement of the compound with antimicrobial activity. For, targeting the above problem we designed compounds and evaluated them with docking studies.

In order to obtain substituted acyl chlorides, substituted acids could be treated with thionyl chloride and then substituted acyl chloride could be treated with aminosulfonamides in the presence of pyridine for obtaining the substituted N-acetyl-4-amino-benzenesulfonamides.

The docking result of standard drug taken CID_4539 (Norfloxacin) correlates well with the performance of compound TS in docking study. Hence, it could be concluded that molecular target responsible for the antimicrobial activity of substituted N-acetyl-4-amino-

benzenesulfonamides may be pseudomonas aeruginosa exotoxin A. Although a proper synthesis, their analytical characterization and systemic biochemical study of novel designed molecules is necessary to confirm the findings.

On comparing the chemical structure of novel designed N-acetyl-4-amino-benzenesulfonamides derivatives with chemical structure of Norfloxacin (1-ethyl-6-fluoro-4-oxo-7-piperazin-1-yl-1H-quinoline-3-carboxylic acid), it is concluded that a phenyl ring and a free carboxylic functionality are essential pharmacophoric requirements in designing a pseudomonas aeruginosa exotoxin A inhibitor.

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