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Synthesis, Analysis of H-bonding Interactions, Molecular Docking Studies and Biological Activity Investigations of Molecular Salt formed between the Drug Sulfathiazole and *p*-Toluenesulfonic acid

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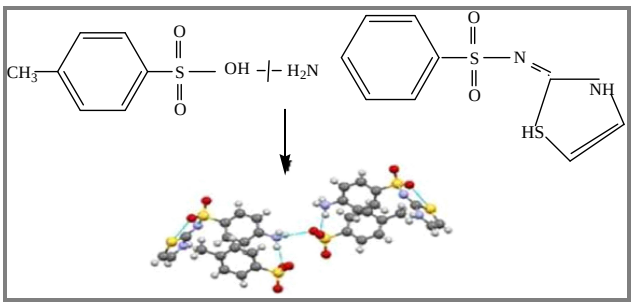
ABSTRACT

The drug sulfathiazole known to be a proton acceptor interacts with p-toluenesulfonic acid by abstracting the proton and forms a molecular salt through hydrogen bonding interactions. The molecular structure has been studied by single crystal X-ray diffraction studies and the asymmetric unit is found to contain two protonated sulfathiazole cations bonded to two p-toluene sulfonate anions. N-H···O hydrogen bonds are formed between -SO_3 group of p-toluenesulfonic acid and -NH_2 of sulfathiazole. The crystal packing is stabilized by N-H···N intramolecular hydrogen bonds in sulfathiazole and secondary H-bonds C-H···C. The new adduct is found to possess a greater antibacterial and antifungal activities compared to sulfathiazole and the activities are comparable to the standard drugs used as control. Further, the molecular docking studies compounded the bioactive nature of the molecular salt formed.

Graphical Abstract



Molecular salt formed between *p*-toluenesulfonic acid and sulfathazole

Keywords: Molecular salts, Multiple H-bonding, Molecular docking studies, Biological activity.

INTRODUCTION

Sulfa drugs were amongst the first clinically used antibacterial agents [1]. The importance of modifying the basic units of the active moieties in attempts of their usage against new bacterial strains

and the bacteria that have developed resistance to the sulfa drugs has been acknowledged [**2-4**]. Sulfa drugs are chemotherapeutic agents which are derivatives of *p*-amino benzene sulfonamide, commonly known as sulphanilamide, due to the presence of sulfonamide group ($-SO_2NH_2$). Sulfa drugs are the first compounds used to prevent and treat bacterial and microbial infections [**1, 5**]. The antimicrobial activity of these drugs is believed to be due to the structural resemblance between sulfanilamide group and *p*-amino benzoic acid where the sulpha drug blocks folic acid synthesis in bacteria, thereby causing cell death [**6, 7**]. In many sulpha drugs like sulfamethazine, sulphadiazine, sulphamerazine, sulphamethoxazole, the basic structural unit [$-SO_2NH-$] acts as an important toxophoric function [**8**]. One of the strategies is to modify the transportation properties without significantly modifying the original unit. This can be achieved by forming supramolecular entities via diversified hydrogen-bond connectivities associated with the drug molecule which is relatively direct and cost effective. Crystal engineering has gained interest in the pharmaceutical field as it has been shown that the stability, solubility, mechanical and pharmaceutical properties of new crystal forms (solvates, salts, molecular complexes, co-crystals, polymorphs) are improved when compared to pure APIs [**9, 10**]. It is interesting to investigate how novel solid forms of sulfa drugs with both hydrogen-bond donor and acceptor groups can be used to develop new crystal forms and how intermolecular interactions between drug molecule and conformer dictate their therapeutic efficacy. An efficient way of investigating the basic reconstitution of a molecule is to allow it to crystallize. Generating polymorphs, salts and co-crystals of the molecule provide a direct means to carry out this trial. Co-crystal/Salt forms of sulfathiazole that is a weak base (p*Ka* = 7.2) with several acids are reported in the literature [**10**]. In view of the importance of improving the pharmacological and pharmacokinetic properties of the selected drug, sulfathiazole, the present investigations are carried out to develop molecular salt of sulfathiazole and *p*-toluenesulfonic acid and to study its antibacterial and antifungal activities.

The paper describes the preparation of the molecular salt of sulfathiazole with *p*-toluenesulfonic acid, investigation of its molecular structure through single crystal X-ray diffraction studies, evaluation of antibacterial and antifungal activities and also the molecular docking studies.

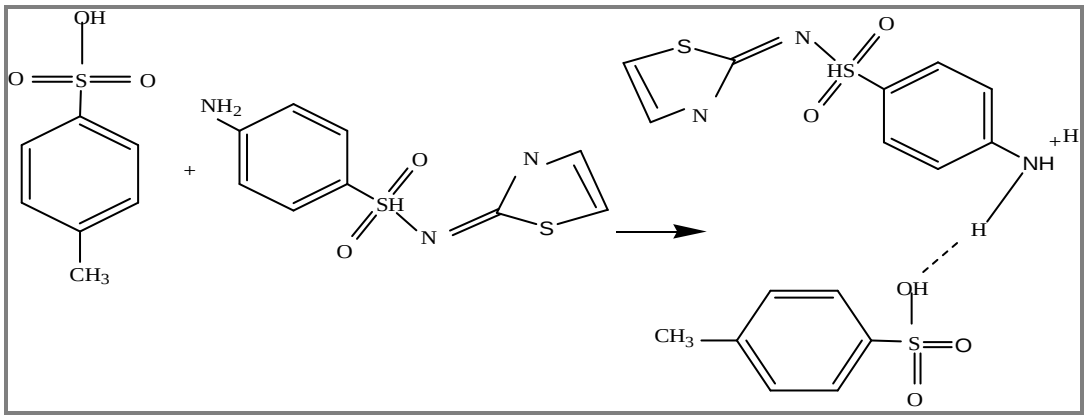
MATERIALS AND METHODS

All reagents and solvents were used as obtained from the supplier and recrystallized/redistilled as necessary. The UV-Vis spectra were recorded in methanol solution on Shimadzu UV-Vis spectrophotometer model 2401 PC. Single crystal X-ray diffraction data of the compound were collected on Crysalis CCD xcalibur, Eos(Nova) oxford diffractometer with X-ray generator operating at 50 kV and 1 mA, using Mo Kα radiation (λ=0.7107 Å). The structure was solved and refined using SHELX97 module in the program WinGX [**11-13**]. The molecular diagrams were generated using ORTEP-3 and the packing diagrams were generated using Mercury 2.3 [**14**]. The geometric calculations were carried out by PARST 95 and PLATON [**15**]. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined from 29035 reflections for the compound. Anisotropic displacement parameters were included for all non-hydrogen atoms. The hydrogen atoms attached to nitrogen and oxygen atoms were located in a difference density map and refined isotopically. All other H atoms were positioned geometrically and treated as riding on their parent C atoms. The crystal data for the compound are listed in table 2. Further, details of X-ray structure determination are deposited at the CCDC (deposition number CCDC 1020342). DNA binding domain preparation was done using AUTODOCK 4.2 tools. The autodock tools package version 1.4.6 was employed to generate the docking input files. All the nonpolar hydrogens were merged and the water molecules were removed. For the docking, a grid spacing of 0.375 Å and 60×60×60 number of points was used. Before docking all water molecules were removed from the protein structure followed by addition of hydrogen atoms to receptor and merging non-polar hydrogens. Receptor protein was assigned by Kollman united atom charges and solvation parameters while saponin ligands were assigned by Gasteiger charge. Rigid roots were also

assigned to the ligand and five bonds were made rotatable. Modeled three dimensional structure of Sulfathiazole-2 and the structure of the ligand were converted to PDBQT format.

RESULTS AND DISCUSSION

Synthesis: The title compound was prepared by treating sulfathiazole with *p*-toluenesulfonic acid in aqueous solution (Scheme 1) in 1:1 molar ratio. The crystals were harvested from the solution after 10 days and suitable crystal for single-crystal X-ray diffraction study was chosen using a polarizing microscope.



Scheme 1. Preparation of p-Toluenesulfonic Acid-Sulfathiazole proton transfer complex.

The molecular salt with molecular formula $C_{16}H_{17}N_3O_5S_3$ is analyzed for (%) C- 44.76 (44.95), H -3.92 (4.01), N-9.64 (9.83), S-21.98 (22.50). The calculated values are presented in parentheses.

Spectrophotometric Investigations of Supramolecular Interactions between Sulfathiazole and p-Toluene sulfonic acid: The drug sulfathiazole is a good proton acceptor and readily forms molecular salts. *p*-Toluenesulfonic acid is a strong monobasic acid with pKa value of 1.34. It is known to form co-crystals/salts with many acceptors and hence it is selected for studying the formation of supramolecular entity with sulfathiazole and thereby modifying the solubility and pharmacokinetic properties of the drug. The spectrophotometric titrations give a confirmative indication of such interactions. *p*-Toluenesulfonic acid exhibits one distinct absorption at 221.4 nm corresponding to $\pi \rightarrow \pi^*$ transition. Sulfathiazole exhibits three transitions at 289.4, 260.8 and 204.00 nm. The spectral characteristics of the mixtures of sulfathiazole and *p*-toluenesulfonic acid are presented in the table 1 and the titration curves are shown in figure 1.

Table 1. Spectrophotometric titration data of sulfathiazole ($1x10^{-4}$ *M* – 1.0 mL*)* with *p*-toluene sulfonic acid ($1x10^{-4}$ *M)* (Total volume = 5.0 mL)

S.No.	S Vol. of PTSA	O.D at 284.4 nm	O.D at 260.8 nm	O.D at 204.0 nm
1	0	0.691	0.527	0.657
2	0.5	0.636	0.482	0.680
3	1	0.665	0.512	0.726
4	1.5	0.695	0.539	0.833
5	2	0.782	0.605	0.954
6	2.5	1.268	0.969,	1.275

The spectra of sulfathiazole–*p*-toluenesulfonic acid mixtures show a distinct change in the spectrum of *p*-toluenesulfonic acid. The absorption at 221.4 nm shows a hypsochromic (blue) shift and completely merges with or masked by the absorptions of the sulfathiazole indicating the formation of a molecular complex. The mixtures for investigating the host-guest interactions were prepared by

mixing the solutions ($1x10^{-4}$M) of sulfathiazole and *p*-toluenesulfonic acid. Varying volumes of *p*-toluenesulfonic acid solution (0.0 to 2.5 mL) are added to a fixed volume of sulfathiazole (1.0 mL) and equilibrated at the experimental temperature. The absorptivities of the mixtures are measured. The optical densities of pure sulfathiazole solution at 289.40 nm (0.691); 260.8 nm (0.527): 204.0 nm (0.657) increased with increase in concentration of *p*-toluenesulfonic acid. These changes in the spectra and absorptivities indicate the formation of molecular complex between sulfathiazole and *p*-toluenesulfonic acid. To get complete details of the molecular interactions between the proton donor nd the acceptor and formation of the molecular crystal, X-ray diffraction studies using a suitable single crystal were taken up. Slow evaporation of solution containing sulfathiazole and *p*-toluenesulfonic acid in 1:1 ratio, resulted in needle shaped crystals over a period of 10 days.

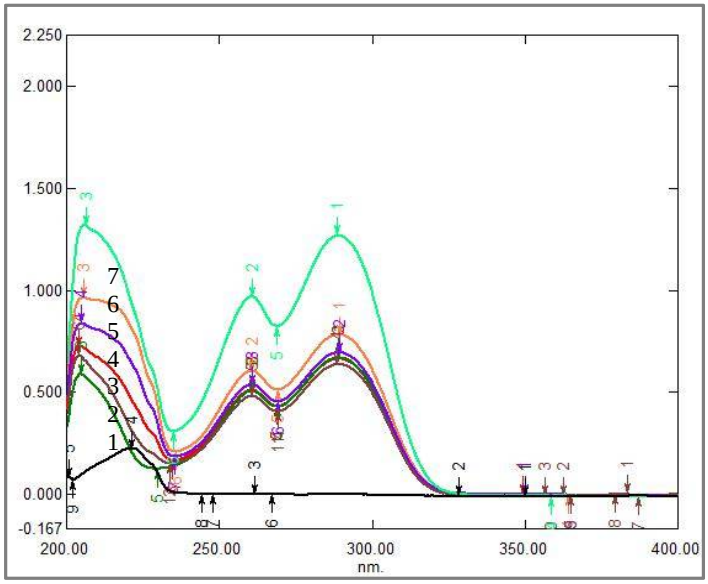


Figure 1. The electronic spectra of p-toluenesulfonic acid (1); sulfathiazole (2) and Sulfathiazole [1 mL] + p-toluenesulfonic acid 0.5 mL, (3); + 1.0 mL (4); + 1.5 mL (5); + 2.0 mL (6); + 2.5 mL (7)

Single crystal X-ray diffraction analysis: The structure of the title compound has been determined by single crystal X-ray diffraction analysis. X-ray diffraction intensities were collected at 296.15 K using Bruker APEX-II CCD diffractometer, graphite monochromated MoKα radiation of wavelength 0.71073 Å. The cell refinement and data reductions are performed using SAINT programme. In total, 7069 reflections have been collected for hkl ranging $-7 \leq h \leq 7$, $-17 \leq k \leq 18$ and $-24 \leq l \leq 25$, out of which 5424 reflections found to satisfy the criteria $I \geq 2u(I)$ and used for further structure solution and refinement purpose. The structure was solved with the olex2 using charge flipping and refined with the Shel XL refinement package using Gauss-Newton minimization. Mercury program is used for molecular graphics. All non-hydrogen atoms are refined anisotropically. The structure is refined to R = 0.0380 and R = 0.0536 for all data, Goodness of fit S = 1.048. Highest and lowest electron density peaks 'Dq' are 0.361 and -0.430 $eÅ^{-3}$ respectively. Preliminary crystallographic data and details of the data collection along with structure refinement parameters are listed in table 2.

The molecular salt crystallizes in triclinic *P-1* space group, while the sulfathiazole crystallizes in monoclinic *P21/c* space group [**16**]. Sulfathiazole was reported to be existing in imide tautomeric form (C–N bond lengths of 1.323(4) and 1.340(5) Å, a partial double bond) with two molecules in the asymmetric unit (Z=2). The four molecules form two independent dimmers through H-bonds, NH-N and NH--OS. The asymmetric unit of molecular salt consists of four pairs of host and guest ions (*viz.* $C_9H_{10}N_3O_2S_2^+$ $C_7H_7O_3S^-$) bonded to each other through H-bonds. In addition to the protonation of sulfathiazole $–NH_2$ group and forming a supramolecular structure through H-bonding a few conspicuous changes have been observed in the structure of sulfathiazole. The sulfathiazole in the

molecular salt is also found to be in the imide tautomeric form with C–N bond lengths of 1.329 Å and 1.337 Å.

Table 2. Crystal data and structure refinement parameters

Empirical formula	C33H34N5O10S6	Empirical formula	C33H34N5O10S6
Formula weight	855.01	m/mm^{-1}	0.441
Temperature/K	296.15	F(000)	888
Crystal system	triclinic	Crystal size/mm^3	0.38 × 0.26 × 0.18
Space group	*P-1*	2Θ range for data collection	2.8 to 52°
a/Å	5.9835(7)	Index ranges	$-7 \le h \le 7, -17 \le k \le 18, -24 \le l \le 25$
b/Å	14.6389(18)	Reflections collected	27312
c/Å	20.927(3)	Independent reflections	7069[R(int) = 0.0408]
α/°	85.217(6)	Data/restraints/parameters	7069/0/491
β/°	89.842(6)	Goodness-of-fit on F^2	1.048
γ/°	89.910(6)	Final R indexes [I>=2σ (I)]	R1 = 0.0380, wR2 =0.0941
Volume/$Å^3$	1826.7(4)	Final R indexes [all data]	R1 = 0.0536, wR2 =0.1008
Z	2	Largest diff. peak/hole/ e $Å^{-3}$	0.36/-0.43

The H of *p*-toluene sulfonic acid group is positioned on the amine nitrogen atom of sulfathiazole in the cation. The noticeable change is that the two H atoms of amine group (N1– H1 and N1–H2: 0.8782 and 0.8493 Å) of sulfathiazole become equidistant in the molecular salt with N–H distance of 0.890 Å. The CAr–NH_3^+ bond lengths in the supramolecular entity are longer (N5–C1-1.466 Å) and N5-C29-1.469(3) Å) than literature values for non-protonated amine (C–NH_2) group found in sulfathiazole, C1–N1 bond length (1.4010 Å). The S–O bond lengths of sulfonate anion in the molecular salt in the range of 1.443 to 1.470 Å are in the same range of the S–O bond lengths in other sulfonate anions [**17**]. The supramolecular interactions through H-bonds between the donor and acceptor are presented in table 3. The three dimensional supramolecular framework is shown in Figure 4.

Table 3. Hydrogen-Bond lengths (Å) and angles (°)

S.No.	D—H··· A	D—H	H···A	D···A	D—H···A
1	N3-H3…O7	0.86	2.605	3.04	112.50
2	N1-H1C…O5	0.89	1.977	2.84	164.03
3	N1-H1A…O3	0.89	1.89	2.75	161.47
4	N1-H1B…N2	0.89	2.05	2.90	159.81
5	N5-H5A…O8	0.89	1.900	2.76	161.88
6	N5-H5C…O6	0.89	1.982	2.84	163.21
7	N5-H5B…N4	0.89	2.048	2.90	159.94
8	N31-H31···O4	0.86	2.610	3.04	112.17

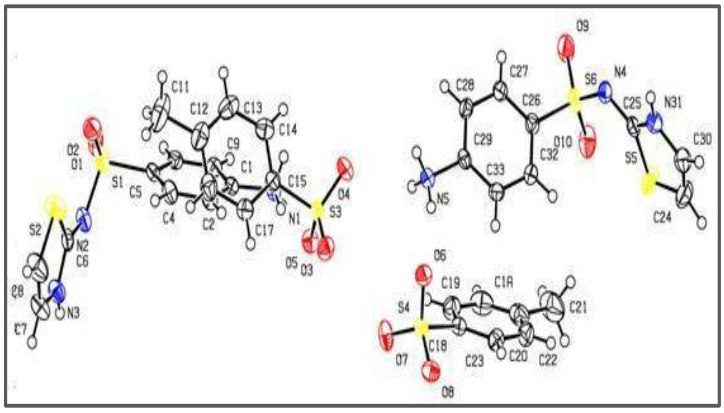


Figure 2. The ORTEP view of the p-Toluenesulfonic Acid-Sulfathiazole proton transfer complex showing atomic labelling scheme and 50 % probability level displacement ellipsoids.

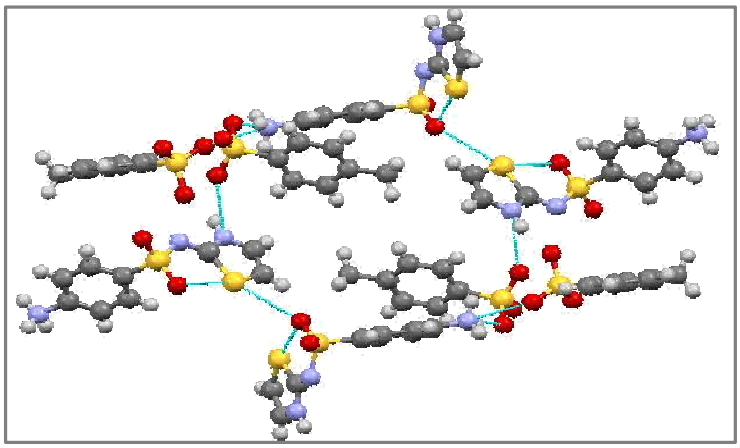


Figure 3. The crystal packing of the p-Toluenesulfonic Acid-Sulfathiazole proton transfer complex, hydrogen bonds are shown as dashed lines.

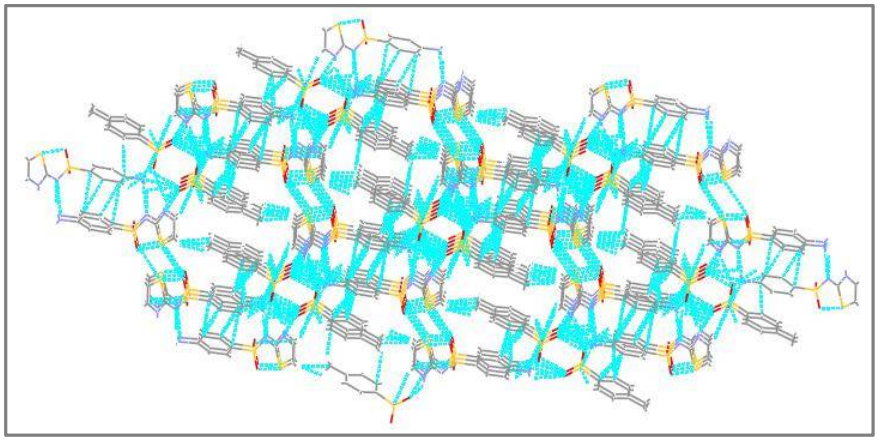


Figure 4. A view along the b axis of the crystal packing of the p-Toluenesulfonic Acid-Sulfathiazole proton transfer complex showing the three dimensional supramolecular framework, Hydrogen bonds are shown as dashed lines.

APPLICATIONS

Sulfathiazole-p-Toluenesulfonic Acid Molecular Crystal–Antibacterial activity: The antibacterial activity of the synthesized sulfathiazole compound was performed by adopting cup plate method. Freshly prepared liquid agar medium (35 mL Petri dish^{-1}) was poured into the Petri dishes and 200 µL of standardized culture (99 mL Nutrient broth media + 1 mL culture) of organism was spread on each Petri dish by L-shaped spreader with a borer (5 mm). Three bores were made on each plate. The compounds were diluted with dimethyl sulfoxide (DMSO). The Petri dishes were kept aseptically for 4 to 5 h for diffusion of the sample. After the completion of diffusion period, all Petri dishes were kept for incubation at 37°C for 24 h. After 24 h the zone of inhibition was observed for compound against four (2 Gram positive and 2 Gram negative) microorganisms, namely *Staphylococcus aureus*, *Micrococcus luteus*, *Escherichia coli* and *Klebsiella pneumoniae*. In vitro antimicrobial activities were measured from the diameter of clear inhibition zones (mm) caused by samples against the same bacteria and under the identical experimental conditions. In order to clarify role of DMSO, sulfathiazole [2] and sulfathiazole-*p*-toluenesulfonic acid salt in the biological screening, separate studies were carried out with the solutions alone of DMSO, sulfathiazole, and the salt. The results are given in table 4. DMSO was used as a control.

The preliminary screening for antibacterial activity of sulfathiazole derivative was determined against two gram positive (*Staphylococcus aureus & Micrococcus luteus)* and two gram negative *(Escherichia coli and Klebsiella pneumonia)* bacterial strains and compared with sulfathiazole and also with the standard antibacterial drugs ampicillin and chloramphenical. The results obtained indicate that the bacterial growth was inhibited in presence of synthesized sulfathiazole salt equally with the standard drugs. It is important to mention that the bacterial growth of same strains was not inhibited by sulfathiazole with the same rate as that of the synthesized compound.

Table 4. Antibacterial Activity of compound

Gram-positive bacteria	Compound	Sulfathiazole	Ampicillin	Chloramphenicol
S. aureus	16	6	22	19
M. luteus	20	8	21	20
		Gram-negative bacteria		
E. coli	21	8	20	21
K. pneumonia	16	7	19	23

Antifungal activity: The antifungal activity of the synthesized substituted sulfathiazole compound was performed by adopting cup plate method. The Sabouraud agar medium (dextrose 4%, peptone 1%, agar 1.5%) was used for antifungal activity. The medium was prepared and sterilized in an autoclave at 15 Psi for 15 min. Then, it was poured in sterilized Petri plates, aseptically. The fungal strains *Candida albicans* and *Cryptococcus neoformans* were inoculated on the surface of petriplates separately after 2 h of pouring the agar media, when the media sets on Petri plates the cups (diameter 6 mm) were made in the Sabouraud agar medium using sterilized cup borer under aseptic conditions. 0.1 mL of each standard and test (10 mg mL^{-1}) prepared by dissolving it in DMSO was added into cups. The Petri plates were incubated at 28 ± 2°C for 48 h. Fungal growth and zone of inhibition (in mm) was recorded and compared with standard drug, fluconazole. The results are presented in table 5.

Table 5. Antifungal Activity of compound

Fungal Species	Compound	Sulfatiazole	fluconazole
C.albicans	16	7	22
C.neoformans	20	6	21

Molecular Docking Study of Sulfathiazole-2 against Pdb Id-1YET: The newly synthesized sulfathiazole salt showed potential activity against Gram+ve and Gram-ve bacteria predominantly against *E. coli*, the Gram-ve bacterium, with a clear inhibition zone of 20 mm. This is important because *E. coli* is known to develop resistance quickly against antibacterial drugs. Earlier to the activity assays, computational studies involving molecular docking were undertaken to investigate structural and functional basis of antibacterial activity of our newly synthesized sulfathiazole derivative with *p*-toluene sulfonic acid. Docking simulation was done using Autodockvina suite as molecular-docking tool in Windows operating system, cygwin interface was used to launch autodockvina. The default optimization parameter lamarckian Genetic Algorithm was used with a population size of 20 dockings. Autodock 4.2 tools generated 10 possible binding conformations, i.e. 10 runs for each docking by using Genetic Algorithm (GA-LS) searches. A default protocol constituting a maximum number of 2.5 x 105 energy evaluations, a maximum number of 2.7 x 10^4 generations and an initial population of 150 randomly placed individuals were applied. Mutation rate of 0.02 and crossover rate of 0.8 were used. The grid box used for specifying the search space was set at 60 × 60 × 60 centre on of 1YET with a default grid point spacing of 0.375 Å. Autogrid was used to obtain pre-calculated grid maps. Most suitable conformation was chosen based on lowest docked energy after completion of docking. Selected conformations were analyzed using Pymol software.

The structures of the compounds used for docking were constructed using Marvin sketch tool of ChemAxon software. From the assessment of molecules, it was observed that the ligand molecule cucumarioside showed better Molecular docking study of the salt of the cation sulfathiazole and *p*-toluenesulfonate anion against (PDB 1YET) binding domain. Based on the results of molecular docking, the bioactive compound showed significant binding energy (-6.4 kcal mol^{-1}) with 1YET receptor as shown in figure 5. The binding energy and antimicrobial activity have shown good correlation, and is therefore considered as a potential bioactive compound.

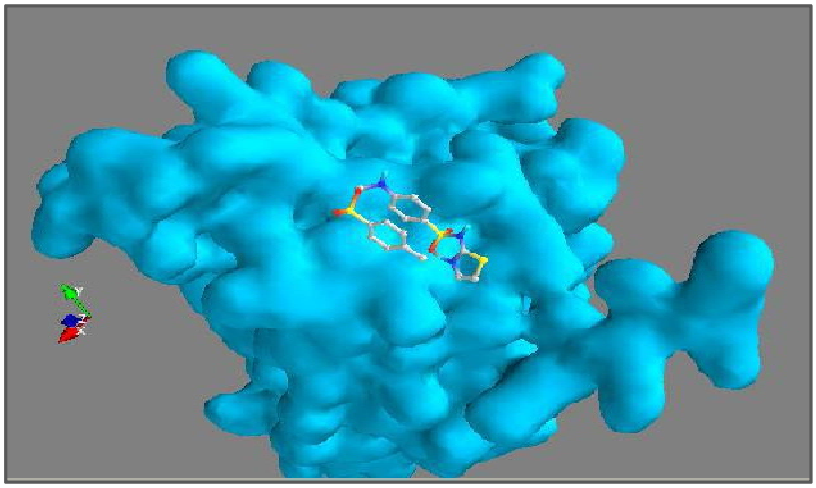


Figure 5. Docking interaction of 1YET receptor with the title compound.

CONCLUSION

The sulfathiazole was found to have many side effects and a good number of safer antibiotics have been developed. Modifying the pharmacokinetic and pharmacological properties of the drug molecules and minimizing the toxicity has been the subject of importance and greater activity. Developing supramolecular entities between a drug API and a suitable donor or acceptor has been recognized as one of the successful method to achieve the same. Our attempt to prepare the supramolecular entity of sulfathiazole (acceptor) and *p*-toluenesulfonic acid (donor) resulted in crystalline molecular salt. The title compound crystallized in triclinic space group1. The intra- and inter-molecular H-bonds stabilized the structure. The salt was assayed for its biological activity against selected bacteria (*Staphylococcus aureus and Micrococcus luteus* - grampositive and two gram negative bacteria *Escherichia coli and Klebsiella pneumonia*) and fungi *Candida albicans* and *Cryptococcus neoformans*. The activity of the compound is found to be better than the API sulfathiazole and comparable to the standard controls used to study the antibacterial and antifungal activity.

Supplementary Material: CCDC 1020342 contains the supplementary crystallographic data for the compound. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/ retrieving. html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (0044) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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