ORIGINAL ARTICLE

QSAR Modeling, Docking, Scaffold Study, Synthesis and Characterization of Novel Sulfonamides Tested Against *E. coli* and *Bacillus subtilis*

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ABSTRACT

Context: High proportion of antibiotic resistance is increasing in bacteria. **Aim:** Designing and synthesizing novel sulphonamides as anti-bacterial. **Settings and Design:** Standard drug design process. **Methods and Materials:** ANN-QSAR model, docking studies, applicability domain (Williams plot), distance mapping, HOMO, LUMO surface study, mapped density surface study, NMR (1H and C-13), IR, MASS, CHNS, Kirby-Bauer's disk diffusion method were used. **Statistical analysis used:** Fraction of variance (r^2), Cross-Validation Test (q^2), Standard deviation (s), r^2-q^2 < 0.3, Quality Factor (Q), Fischer Statistics (F) and Y-Randomization Test were used as a part of this study. **Results:** Most active compound of the series was 4-[(3-Methoxy-phenylamino)-methyl]-benzenesulfonamide found against *E. coli*. **Conclusions:** Novel designed and synthesized sulfonamides act as potential anti-bacterials.

Key words: Drug design, QSAR, docking, scaffold, sulfonamide, antibacterial

Key message: Derivatives of Benzenesulfonamides acts as potential anti-bacterials and proper drug design process and *in-silico* studies makes the study feasible, accurate and time saving process.

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INTRODUCTION

Several sulfonamides have been studied and found to possess interesting biological activities such as anticonvulsant,[1-5] antitubercular[6,7] and antimicrobial.[8,9] Out of these activities, in the present study, antimicrobial activity has been considered. In all regions of the world, the high proportion of antibiotic resistance is increasing in bacteria that cause common infections as blood stream infections, pneumonia and urinary tract infections etc. About 9.0% of MDR-TB cases have found with extensive drug resistant. To overcome the problems of drug resistance for antimicrobial activity, there is substantial need to develop new potential leads. Sulfonamide derivatives have also found to be with a wide range for antimicrobial activity.[10] Now a day 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 best example. Multi-drug resistance has created another problem to work with. This type of problem could be observed in continents like Europe, Asia and America with vancomycin resistance.[11-18] The above mentioned problems and others like these promoted us to contribute hands a little towards solving the problems.

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.[19] The mode of action of sulphonamide drugs is inhibition of metabolic processes. They interfere with folic acid synthesis by preventing addition of para-aminobenzoic acid into the folic acid molecule through competing for enzyme dihydropteroate synthetase, which catalyzes an enzyme in the biosynthesis of tetrahydrofolate and then nucleotides.[5]

In this study, we synthesized novel antibacterial compounds tested against *E. coli* and *Bacillus subtilis*. All the designed and synthesized compounds were initially screened via two tier screening system consisting of QSAR model and docking studies.

The following criteria has been designed and adopted in this research and development:

SUBJECTS AND METHODS

Preparation of 2D structures of novel designed molecules

The 2D structure construction, energy minimization and geometry optimization of the designed sulfonamide derivatives were carried out by using ChemDraw Ultra 7.0 and Chem3D Pro 7.0 (CambridgeSoft Corporation, 100 CambridgePark Drive, Cambridge MA, 02140 USA) on an Intel(R) Core(TM)2 Duo Central Processing Unit T6670 @ 2.20 GHz and 4.00 GB of RAM, running the Windows 7 Home Basic, 64-bit compatible operating system. The energy minimization was carried out to minimum RMS Gradient of 0.100, with step interval of 2.0 Fs and frame interval of 10 Fs.

Model preparation

Bioactivity values and information about 2D structure of sulfonamide analogues were taken from literature. Log1/C is a variable that comprises the bioactivity parameter for the QSAR model. In order to calculate the molecular descriptors, PaDEL descriptor software, which incorporate CDK library for descriptor calculation has been used after optimizing the sulfonamide analogues. For the development of QSAR model, Artificial Neural Network (ANN) has been employed and all were validated through statistics.[20-28]

Descriptor selection

The selection of descriptors among the calculated descriptors for the Artificial Neural Network (ANN) is based on the correlation matrix. This matrix is analyzed for the least correlated descriptors.[20-28]

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Statistical parameters

In the QSAR model, number of data points is denoted as n, squared correlation coefficient as r^2 (fraction of variance), cross-validated r^2 is denoted as q^2. Other parameters includes are r^2-q^2<0.3, root mean square deviation (RMSD), variance and Fischer statistics is denoted by F.[20-28]

Model validation

The QSAR model validation was carried with statistical analysis and with internal validation.[20-28]

Artificial Neural Network (ANN)

To produce a complex system, simple elements may be gathered. [29] Networks are the concept for achieving this. There are too many different types of networks, but they all are characterized by some components: a set of nodes, and connections between nodes.

These are used to model a wide range of phenomena in physics, computer science, pharmacy, biochemistry, sociology, ethology, mathematics, economics, telecommunications, and many other areas. This is because many systems can be seen as a network such that chemical molecule, proteins, computers, communities, etc.

One type of network assumes the nodes as 'artificial neurons'. These are known as artificial neural networks (ANNs). An artificial neuron is a computational model simulates the natural neurons. Natural neurons receive signals from synapses located on the dendrites or membrane of the neuron. When the signals received a minimum required amount, the neuron is activated and emits a signal through the axon and so on.

Applicability domain of model

Williams plot

Williams plot was used to judge the applicability domain of model. It has been defined by Leverage value and Standardized residual values.

Scaffold studies

These studies have been performed with the help of ArgusLab 4.0.1, in which we gone through distance mapping, molecular orbital surface and ESP-mapped density surface studies.

Docking studies

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.[20-28]

Docking procedures allows virtually screening a data-base of compounds and predict the strongest binder based on various scoring functions.[20-28]

Receptor

Bacillus subtilis lipase A, *E. coli* primosomal protein.

Docking tool

Docking has been performed with AutoDock Vina (PyRx-Python Prescription 0.8) 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.[20-28]

For performing docking, all receptors have been downloaded from NCBI website with PDB ID 1R4Z (*Bacillus subtilis* lipase A), 2CCZ (*E. coli* primosomal protein), all the designed ligands have been docked with protein (receptor) with AutoDock Vina (PyRx-Python Prescription 0.8) software having its default settings.

Synthesis and spectral characterization

All the chemicals and solvents, purchased from Merck (India), Spectrochem (India), Sigma-Aldrich (India), Himedia (India) and S. D. Fine (India) were used without further purification. Thin layer chromatographic analysis of compounds was performed on silica gel G coated glass plates. The adsorbent silica gel G was coated to a thickness of about 0.3 mm on previously cleaned TLC plates of 20 × 5 cm using conventional spreader. The plates were placed in hot air oven at 105°C for 30 min. The solutions of compounds were applied as a spot on the activated plate about 2 cm above from the lower edge. The mobile phases were selected according to the polarity of compounds.

Melting points were determined by using open capillary melting point apparatus and are reported uncorrected. FT-IR spectra (KBr) were recorded on a Perkin-Elmer Spectrometer BX-II spectrophotometer. The ^{1}H-NMR spectra were recorded on Bruker 400 MHz and C-13 NMR were recorded on 100 MHz High Resolution NMR spectrometer. Chemical shifts were reported in ppm (δ) and signals were described as singlet (s), doublet (d), triplet (t) and multiplet (m). The mass spectra were recorded on a Waters Micro-Mass ZQ 2000 mass spectrometer. A elemental analysis of compounds have also been performed on a vario EL III CHNS elemental analyzer for estimating percentage purity.

Synthesis of substituted 4-amino-benzenesulfonamides

For the synthesis of an appropriate amide, the (2-Chloro-substituted)-substituted benzene (0.009 mol) dissolved in 20 ml. of dry acetone was added dropwise 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 was stirred for about 12 hour at room temperature and then the solvent was evaporated under reduced pressure. The residue was dissolved 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 were combined and extracted with ethyl acetate. The ethyl acetate extracts were combined, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Further, the dried products have been purified by subjecting it with ethanol: petroleum ether (1:3) mixture to give white to off white pure crystalline powder.[5]

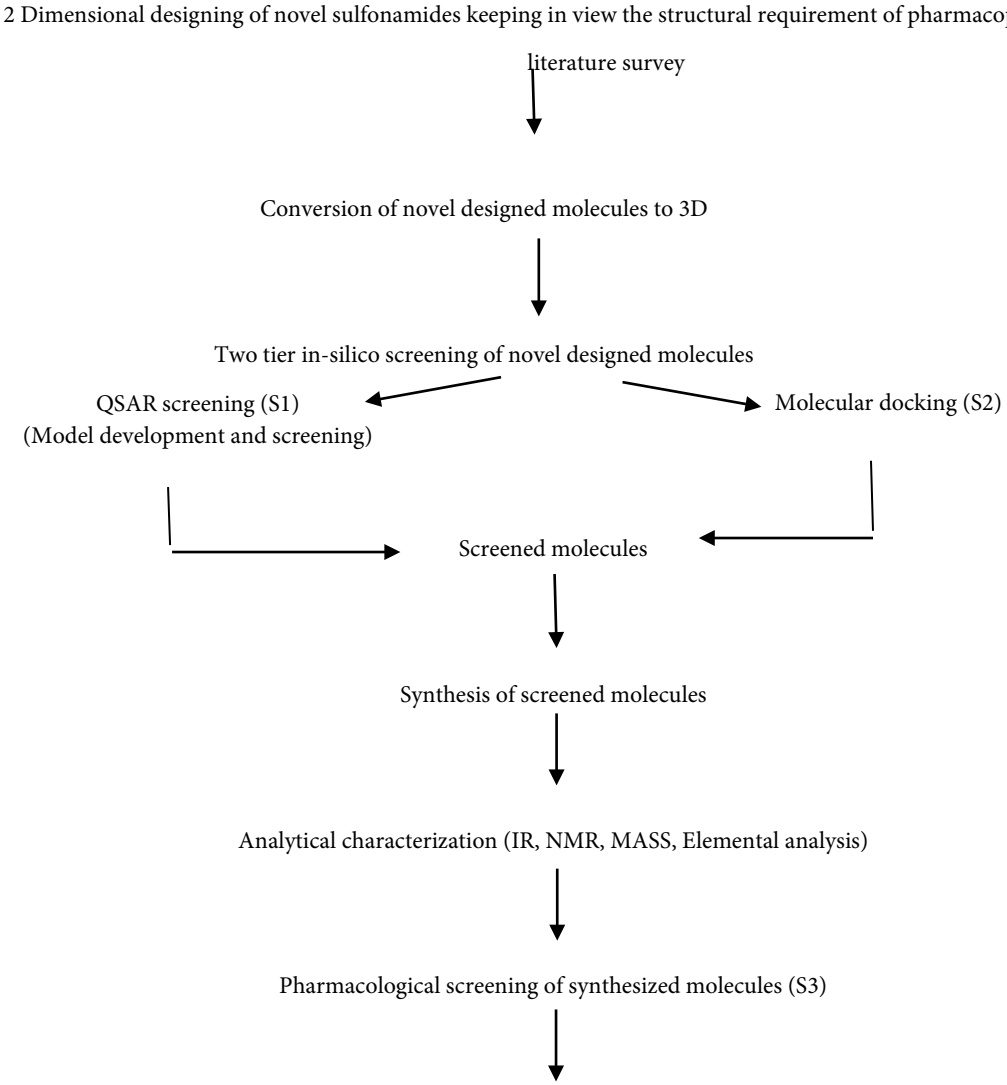
Antibacterial screening

Media

Mueller Hinton Media with the formula of Acid hydrolysate of casein 17.5 gm/lt., beef extract 2 gm/lt., starch 1.5 gm/lt. and agar 17.0 gm/lt. with pH of around 7.[30-34]

Kirby-Bauer's disk diffusion method

Antibacterial screening of synthesized compounds has been performed by Kirby-Bauer's disk diffusion method, which was also recommended by NCCLS (National Committee for Clinical Laboratory Standards). [30-34]



RESULTS AND DISCUSSION

Artificial Neural Network (ANN) model

As earlier described that artificial neurons describes as input neurons/nodes, here 3 input nodes are used which corresponds to descriptors used, which are Eccentric Connectivity index (ECI); Lipo-affinity Index (LAI) and AlogP. There are 3 hidden nodes are used along with one output node [Scheme 1]. Optimized value of learning rate is 0.05 as amounts the weights and momentum applied to the weights are 0.2. The 2D structure of sulphonamide derivatives from which the QSAR model have been developed is shown in Figure 1 and data given in Table 1, QSAR-ANN model was developed where number of data point (n) is 25 and number of descriptors used are 3.

Validation of QSAR model

A quantitative assessment of model robustness has been performed through model validation. All the statistical results of model validation have been given in Table 2.

Statistical analysis

(1) n/p ratio: n/p= ≥ 4, where n is the number of data points and p is the number of descriptors used in the QSAR model. The model obeys the condition.

(2) Fraction of variance (r^2): The value of fraction of variance may vary between 0 (means model without explanatory power) and 1 (means perfect model). QSAR model having $r^2>0.6$ will only be considered for validation.

(3) Cross-Validation Test (q^2): A QSAR model must have $q^2>0.5$ for the predictive ability.

(4) Standard deviation (s): The smaller s value is always required for the predictive QSAR model.

(6) $r^2-q^2<0.3$: The difference between r^2 and q^2 should never be exceeding by 0.3. A large difference suggests the following: presence of outliers, over-fitted model, and presence of irrelevant variables in data.

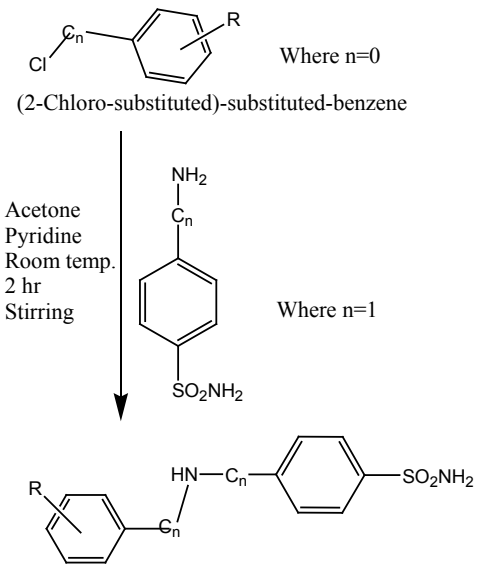
(7) Quality Factor (Q): Over fitting and chance correlation, due to excess number of descriptors, can be detected by Q value. Positive value for this QSAR model suggests its high predictive power and lack of over fitting.

(8) Fischer Statistics (F): The F value of QSAR model was compared with their literature value at 95% level.

Internal validation

Y-Randomization Test: To establish the QSAR model robustness, this technique is being used widely. For this test, the dependent variable

Scheme 1: Synthetic scheme of substituted 4-aminomethyl-benzenesulfonamide from (2-Chloro-substituted)-substituted benzene



	Compound no.
R= *p*-NH_2	8
R= *p*-OCH_3	10
R= *m*-OCH_3	11
R= *o*-OCH_3	12
R= *m*-NH_2	13
R= *o*-NH_2	14
R= *m*-$COCH_3$	15
R= *o*-$COCH_3$	16

Table 1: log1/C values and descriptors of sulphonamide derivatives used to derive QSAR model

Training set	Observed log1/C	AlogP	ECI	LAI
1	4.35	0.0623	325	5.0764
2	4.45	-0.2073	260	4.0409
3	4.35	0.0431	294	4.4324
4	4.47	-0.2073	304	3.9765
5	4.66	0.7377	262	4.2386
6	4.46	0.7377	243	4.2519
7	4.6	0.7377	245	4.2478
8	4.8	0.0431	321	4.4250
9	4.8	-0.2073	279	4.0021
10	4.89	0.66	262	3.6797
11	4.89	0.744	262	3.6550
12	4.99	0.744	243	3.5094
13	4.95	0.5738	262	3.7559
14	5.6	0.5046	298	3.0092
15	6	0.5046	325	2.9494
16	4.32	1.1841	260	4.4875
17	4.8	1.1064	260	3.9342
18	4.8	1.1064	258	3.9074
19	5.4	1.0287	279	3.2765
20	5.55	1.0287	262	3.3275
21	5.1	0.1614	294	3.7230
22	5.55	0.951	340	3.2527
23	5.41	0.951	311	3.3990
24	5.64	0.9573	340	2.3351
25	5.32	1.4071	391	6.4116

Table 2: Statistical results of model validation

	n/p (≥ 4)	r^2	q^2	r^2-q^2<0.3	RMSD	Q	Variance	F
ANN	8.33	0.8567	0.5707	0.2719	0.1765	2.04	0.211	41.84

vector is randomly shuffled, and a new QSAR model is developed using the unchanged independent variable. This process was repeated for five times. The values r^2<0.6 in Y-randomization test confirm the robustness of this QSAR model.[20] The statistical data of r^2 for randomized five runs are given in Table 3. An ANN curve of observed values and predicted values of log1/C for sulphonamide derivatives is shown in Figure 2 and predicted values are given in Table 4.

Applicability domain check for model

Williams plot

Applicability domain (Figure 3) of model was defined by Leverage value (H_{max} value=0.48 ANN model) and Standardized residual values (± 0.5572 for ANN model). All the data points exist in applicability domain for the model.

Screening of novel designed compounds via QSAR model developed

All the designed and synthesized compounds have been filtered with the developed ANN QSAR model and their log1/C values have been predicted and is given in Table 5.

Scaffold study

This section has been comprises for studying essential structural requirements of designing sulphonamides as antibiotics. In this context, we studied distance mapping, molecular orbital surface and ESP-mapped density surface.

Distance mapping of scaffold designed

Distance mapping of both training set and test set have been calculated and listed in Tables 6 and 7. This distance map comprises of distance among hydrogen bond acceptors (HBA1 and HBA2) and hydrogen bond donors (HBD). The minimum, maximum range and average distance have been shown in Table 8. Distance map of scaffold designed has been shown in Figure 4.

Molecular orbital surface of scaffold designed

Molecular orbital surface containing both type i.e., HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) have been shown in Figures 5 and 6.

ESP-mapped density surface of scaffold designed

The electrostatic potential has been mapped in the form of density surface, shown in the Figure 7.

Prediction of ADME property and other essentials

A computational study for prediction of ADME properties of novel

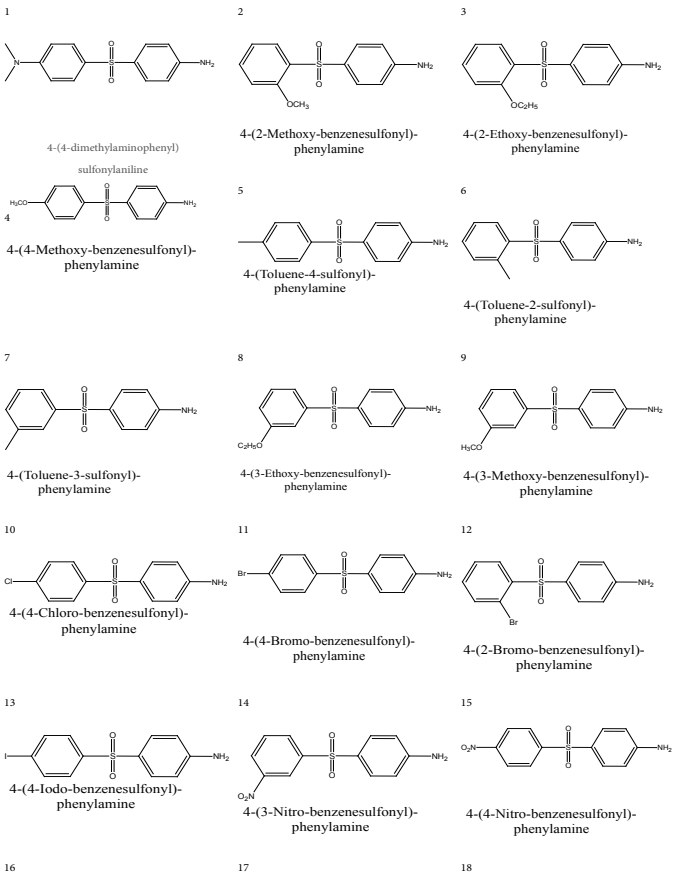


Figure 1: Structures of sulphonamide derivatives for developing the QSAR model

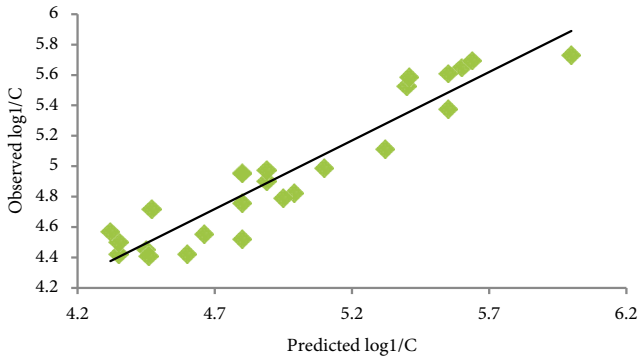


Figure 2: A plot of observed values and predicted values of log1/C for sulphonamide derivatives (ANN)

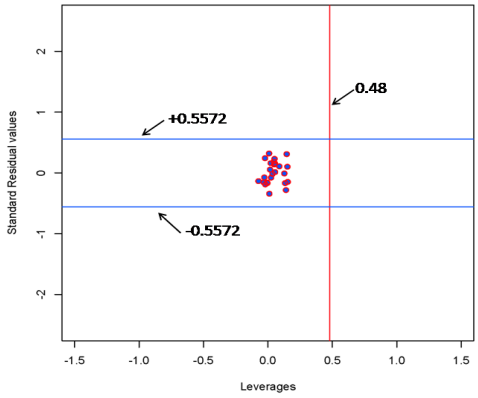


Figure 3: Williams plot for ANN model showing all the training set within the applicability domain

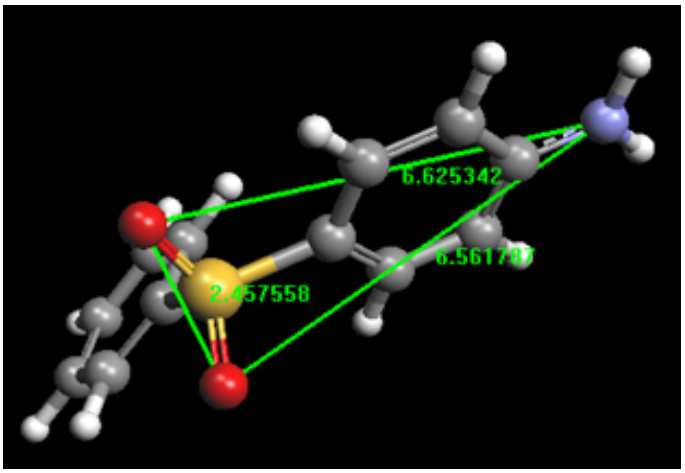


Figure 4: Distance map of scaffold designed

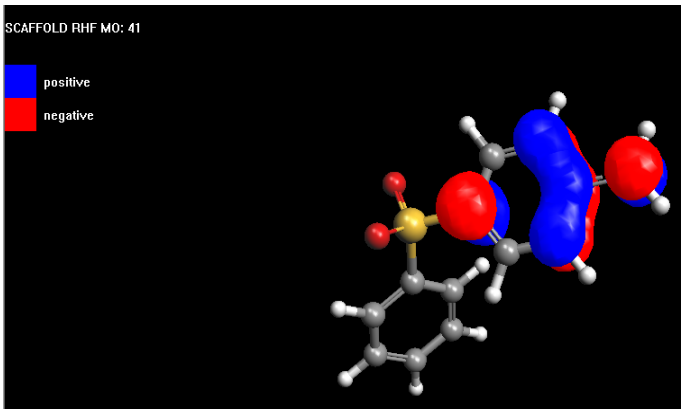


Figure 5: HOMO (Highest Occupied Molecular Orbital) surface of scaffold designed

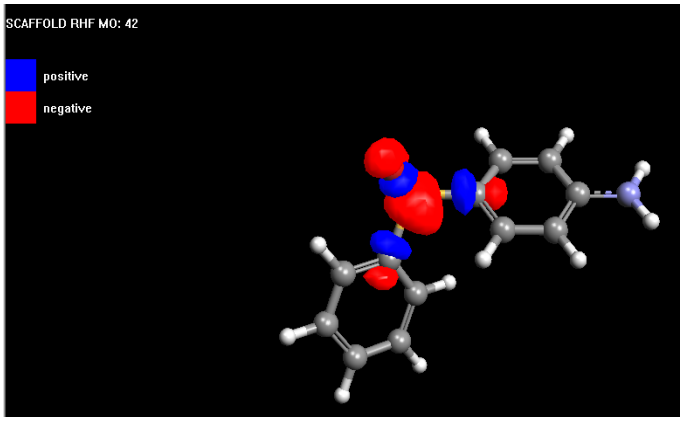


Figure 6: LUMO (Lowest Unoccupied Molecular Orbital) surface of scaffold designed

designed compounds was performed (Table 9). Topological polar surface area (TPSA), i.e., surface belonging to polar atoms, is a descriptor that was shown to correlate well with passive molecular transport through membranes and, therefore, allows prediction of transport properties of drugs in the intestines.[34]

Docking

Docking study of different proteins were performed with the designed inhibitors is given in Table 10 and number of hydrogen bonds and binding pattern such as element, type of bond, atom number and residue at binding site were evaluated.

On docking analysis, designed compound 8 has been found to be

Table 3: Y-Randomization test results for ANN-QSAR model

Training set	Shuffled observed log1/C				
	Run 1	Run 2	Run 3	Run 4	Run 5
1	6	6	4.35	6	4.35
2	4.45	4.45	4.45	4.45	4.45
3	4.35	5.55	5.55	5.55	5.32
4	4.47	4.47	4.47	4.47	4.47
5	4.66	4.66	4.66	4.66	4.66
6	4.46	4.46	4.46	4.46	4.46
7	4.6	4.6	4.6	4.6	4.6
8	4.8	4.8	4.8	4.8	4.8
9	4.8	4.8	4.8	4.89	4.8
10	4.89	4.89	4.89	4.8	4.89
11	4.89	4.89	4.89	4.89	4.89
12	4.99	4.99	4.99	4.99	4.99
13	4.95	4.95	4.95	4.95	4.95
14	5.6	5.6	5.6	5.6	5.6
15	4.35	4.35	4.35	4.35	4.35
16	4.32	4.32	4.32	4.32	4.32
17	4.8	4.8	4.8	4.8	4.8
18	4.8	4.8	4.8	4.8	4.8
19	5.4	5.4	5.4	5.4	5.4
20	5.55	5.55	5.55	5.55	5.55
21	5.1	5.1	5.1	5.1	5.1
22	5.55	4.35	6	4.35	6
23	5.41	5.41	5.41	5.41	5.41
24	5.64	5.64	5.64	5.64	5.64
25	5.32	5.32	5.32	5.32	5.55
r^2	0.3701	0.1942	0.4670	0.1902	0.4790

Table 4: Predicted log1/C and there residuals obtained from non-linear model (ANN)

Compound S. No.	Observed	log 1/C	
		Predicted	Residuals
1	4.35	4.498	-0.148
2	4.45	4.349	0.101
3	4.35	4.519	-0.169
4	4.47	4.753	-0.283
5	4.66	4.429	0.231
6	4.46	4.447	0.013
7	4.6	4.447	0.153
8	4.8	4.81	-0.01
9	4.8	4.492	0.308
10	4.89	4.907	-0.017
11	4.89	4.969	-0.079
12	4.99	4.831	0.159
13	4.95	4.812	0.138
14	5.6	5.546	0.054
15	6	5.681	0.319
16	4.32	4.663	-0.343
17	4.8	4.967	-0.167
18	4.8	4.96	-0.16
19	5.4	5.475	-0.075
20	5.55	5.309	0.241
21	5.1	4.993	0.107
22	5.55	5.707	-0.157
23	5.41	5.6	-0.19
24	5.64	5.776	-0.136
25	5.32	5.134	0.186

strongly docked with 2CCZ as compared to 1R4Z, with 6 hydrogen bonds and binding affinity of -6.2 Kcal/mol. On residue study Ala94, Ser55, Asn59, Glu38, Gln37 and Arg4 were found to be significant. On the account of ligand nitrogen atom is significant in binding with donor bonds, whereas significant element in receptor is oxygen.

On docking analysis, designed compound 10 has been found to be strongly docked with 2CCZ as compared to 1R4Z, with 5 hydrogen bonds and binding affinity of -6.6 Kcal/mol. On residue study Lys88 and Ser88 were found to be significant. On the account of ligand oxygen atom is significant in binding with acceptor bonds, whereas significant element in receptor is nitrogen.

On docking analysis, designed compound 11 has been found to be strongly docked with 2CCZ as compared to 1R4Z, with 3 hydrogen bonds and binding affinity of -7 Kcal/mol. On residue study Ser55, Glu58 and His93 were found to be significant. On the account of ligand oxygen atom is significant in binding with donor bonds, whereas significant element in receptor is nitrogen.

On docking analysis, designed compound 12 has been found to be strongly docked with 1R4Z as compared to 2CCZ, with 3 hydrogen bonds and binding affinity of -6.1 Kcal/mol. On residue study Ala38, Lys23 and Leu36 were found to be significant. On the account of ligand nitrogen atom is significant in binding with donor bonds, whereas significant element in receptor is oxygen.

On docking analysis, designed compound 13 has been found to be strongly docked with 2CCZ as compared to 1R4Z, with 5 hydrogen bonds and binding affinity of -6.5 Kcal/mol. On residue study Asn59, Gln37, Glu38, Glu58 and Arg4 were found to be significant. On the account of ligand nitrogen atom is significant in binding with donor bonds, whereas significant element in receptor is oxygen.

On docking analysis, designed compound 14 has been found to be strongly docked with 2CCZ as compared to 1R4Z, with 6 hydrogen bonds and binding affinity of -6.3 Kcal/mol. On residue study Ser79, His93, Lys89, Met90 and Arg44 were found to be significant. On the account of ligand nitrogen atom is significant in binding with donor bonds, whereas significant element in receptor is oxygen.

On docking analysis, designed compound 15 has been found to be strongly docked with 2CCZ as compared to 1R4Z, with 5 hydrogen bonds and binding affinity of -6.9 Kcal/mol. On residue study Ser79, His93, Lys89 and Arg44 were found to be significant. On the account of ligand nitrogen atom is significant in binding with donor bonds, whereas significant element in receptor is oxygen.

On docking analysis, designed compound 16 has been found to be strongly docked with 2CCZ as compared to 1R4Z, with 4 hydrogen bonds and binding affinity of -6.6 Kcal/mol. On residue study Ala94, Ser55, Asn59, Glu38, Gln37 and Arg4 were found to be significant. On the account of ligand nitrogen atom is significant in binding with donor bonds, whereas significant element in receptor is oxygen. Figure 8 shows the docking images of all novel compounds with proteins 1R4Z and 2CCZ.

Compound characterization

After synthesizing the designed compounds, they were treated for physical data like percentage yield, retention factor (R_f), melting point and elemental data (CHNS analysis). The physical and elemental data of the compounds are reported in Table 11.

Spectral characterization of synthesized substituted 4-aminomethyl-benzenesulfonamide

Compound number 8: 4-[(4-Amino-phenylamino)-methyl]-

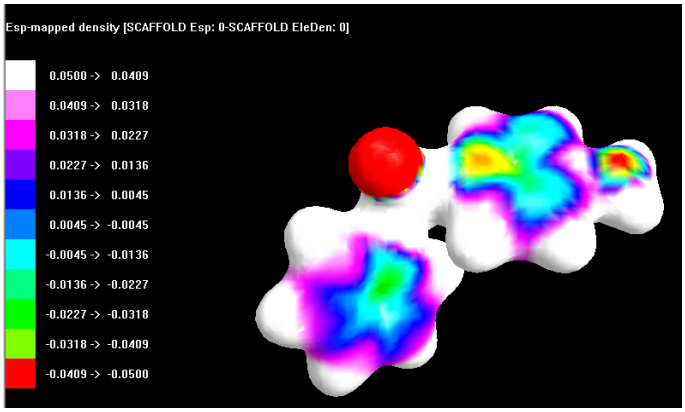


Figure 7: ESP-mapped density surface of scaffold designed

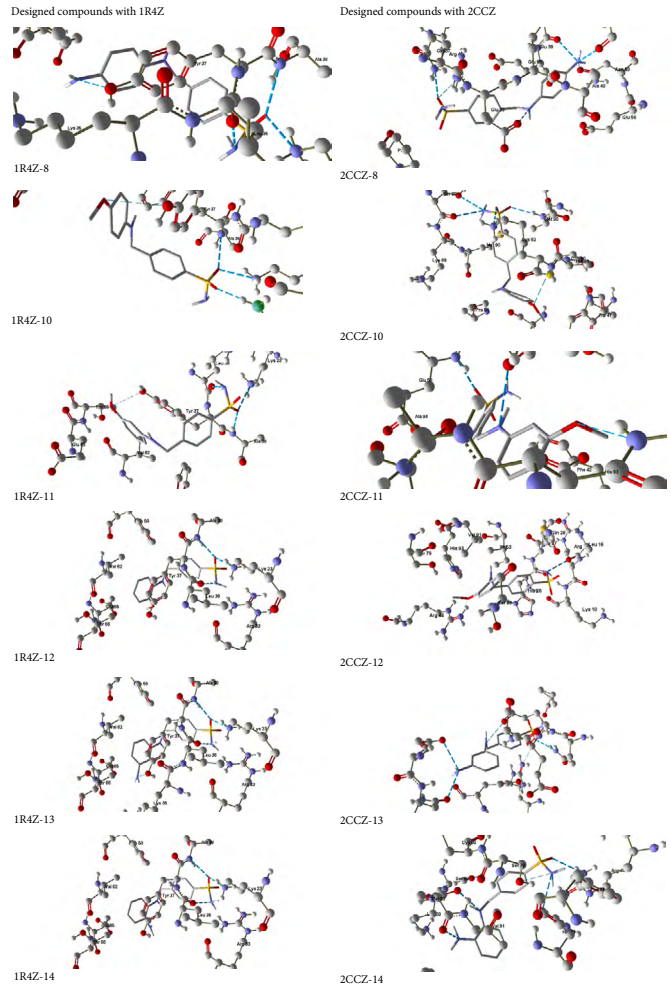


Figure 8: Docked images of designed molecules 8, 10, 11, 12, 13, 14, 15 and 16 with 1R4Z and 2CCZ

benzenesulfonamide

^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 4.43(s, 1H of -NH_2 of C16); 4.83(d, 2H of C11); 5.64(s, Ar-H of C18); 5.74(s, Ar-H of C17); 6.34(s, Ar-H of C14); 6.46(s, Ar-H of C15); 6.84(s, Ar-H of C1); 6.88(s, Ar-H of C3); 6.97(d, Ar-H of C6); 7.24(s, Ar-H of C4); 7.47(m, 2H of -SO_2NH_2); 7.86(m, 1H of -NH_2 of C16); 7.86(m, 1H of >NH). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 45.98(s, C11); 115.94(m, C14, C18); 117.81(m, C15, C17); 125.77(m, C1, C3); 125.86(m, C4, C6); 139.47(s, C16); 139.75(s, C13); 143.22(d, C5); 143.64(d, C2). IR (KBr, cm^{-1}, υ): 1169.96, 758.31. MS (m/z, %): (277.08, M^+, 95).

Compound number 10: 4-[(4-Methoxy-phenylamino)-methyl]-benzenesulfonamide

^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 3.81(m, 3H of -OCH_3); 4.29(s, 1H of C11); 4.49(s, 1H of C11); 6.53(m, Ar-H of C14 and Ar-H of C18); 6.76(m, Ar-H of C15 and Ar-H of C17); 6.84(d, Ar-H of C3); 7.20(d, Ar-H of C4); 7.24(d, Ar-H of C6); 7.47(m, 2H of -SO_2NH_2); 7.59(s, Ar-H of C1); 7.85(s, 1H of >NH). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 45.98(s, C11); 56.04(s, C of –OCH_3); 113.58(m, C14, C18); 115.51(m, C15, C17); 125.77(m, C1, C3); 125.86(m, C4, C6); 141.13(s, C13); 143.22(d, C5); 143.34(d, C2); 151.54(s, C16). IR (KBr, cm^{-1}, υ): 1044.18, 904.95. MS (m/z, %): (292.08, M^+, 75)

Compound number 11: 4-[(3-Methoxy-phenylamino)-methyl]-benzenesulfonamide

^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 3.82(m, 3H of -OCH3); 4.37(s, 1H of C11); 4.49(s, 1H of C11); 6.20(s, Ar-H of C18); 6.23(d, Ar-H of C14); 6.29(d, Ar-H of C16); 6.84(s, Ar-H of C3); 7.11(s, Ar-H of C15); 7.20(d, Ar-H of C4); 7.24(d, Ar-H of C6); 7.47(m, 2H of -SO_2NH_2); 7.59(s, Ar-H of C1); 7.85(s, 1H of >NH). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 46.86(s, C11); 56.04(s, C of -OCH_3); 100.19(s, C18); 103.25(s, C16); 106.66(s, C14); 125.73(m, C1, C3); 125.83(m, C4 and C6); 129.63(s, C15); 143.04(s, C5); 143.43(s, C2); 148.73(s, C13); 160.92(s, C17). IR (KBr, cm-1, υ): 1300.52, 900.36. MS (m/z, %): (292.08, M^+, 100).

Compound number12: 4-[(2-Methoxy-phenylamino)-methyl]-benzenesulfonamide

^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 3.80(m, 3H of -OCH_3); 4.47(d, 1H of C11); 4.49(d, 1H of C11); 6.52(s, Ar-H of C14); 6.61(d, Ar-H of C16); 6.73(d, Ar-H of C17); 6.78(s, Ar-H of C15); 6.83(s, Ar-H of C3); 7.19(s, Ar-H of C4); 7.24(s, Ar-H of C6); 7.58(t, Ar-H of C1); 7.58(t, 2H of -NH_2); 7.83(s, 1H of >NH). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 45.86(s, C11); 56.79(s, C of -OCH_3); 112.12(s, C17); 114.22(s, C14); 118.75(s, C16); 121.18(s, C15); 125.77(m, C1 and C3); 125.86(m, C4 and C6); 138.77(s, C13); 143.22(d, C5); 143.34(d, C2); 146.25(s, C18). IR (KBr, cm^{-1}, υ): 1090.58, 835.34. MS (m/z, %): (292.08, M^+, 95).

Compound number13: 4-[(3-Amino-phenylamino)-methyl]-benzenesulfonamide

^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 4.43(s, 1H of -NH_2 of C17); 4.79(s, 1H of C11); 4.94(s, 1H of C11); 5.42(s, Ar-H of C18); 5.51(s, Ar-H of C16); 5.99(s, Ar-H of C14); 6.67(s, Ar-H of C15); 6.84(d, Ar-H of C1); 6.88(d, Ar-H of C3); 7.11(s, Ar-H of C6); 7.24(s, Ar-H of C4); 7.47(m, 2H of -SO_2NH_2); 7.86(m, 1H of –NH_2 of C17); 7.86(m, 1H of >NH). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 45.98(s, C11); 98.41(s, C18); 104.07(s, C14); 107.48(s, C16); 125.77(m, C1 and C3); 125.86(m, C4 and C6); 130.99(s, C15); 143.22(d, C5); 143.34(d, C2); 149.19(d, C13); 149.37(d, C17). IR (KBr, cm^{-1}, υ): 1054.94, 901.09. MS (m/z, %): (277.08, M^+, 95).

Compound number 14: 4-[(2-Amino-phenylamino)-methyl]-benzenesulfonamide

^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 4.43(s, 1H of –NH_2 of C18); 4.84, 4.85(d, 2H of C11); 5.81(d, Ar-H of C17); 5.82(d, Ar-H of C16); 6.35(s, Ar-H of C14); 6.52(s, Ar-H of C15); 6.84(d, Ar-H of C1); 6.88(d, Ar-H of C3); 7.09(s, Ar-H of C6); 7.24(s, Ar-H of C4); 7.47(m, 2H of –SO_2NH_2); 7.86(m, 1H of –NH_2 of C18); 7.86(m, 1H of >NH). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 45.86(s, C11); 115.90(s, C17); 116.46(s, C14); 119.03(s, C15); 120.34(s, C16); 125.77(m, C1 and C3); 125.86(m, C4 and C6); 134.46(s, C13); 137.67(s, C18); 143.22(d, C5); 143.34(d, C2). IR (KBr, cm^{-1}, υ): 1629.81. MS (m/z, %): (277.08, M^+, 95).

Compound number 15: 4-[(3-Acetyl-phenylamino)-methyl]-benzenesulfonamide

Table 5: Descriptors and predicted log1/C of novel designed compounds

Compound no.	Predicted log1/C	AlogP	ECI	LAI
8	3.819	-0.8244	370	3.8194
10	4.562	-0.1263	418	4.5623
11	4.564	-0.1263	391	4.5642
12	4.562	-0.1263	366	4.5617
13	3.825	-0.8244	347	3.8251
14	3.83	-0.8244	345	3.8300
15	4.396	-0.0772	414	4.3964
16	4.394	-0.0772	387	4.3939

Table 6: Distance map between HBA1-HBD, HBA2-HBD and HBA1-HBA2 for training set

S. No.	HBA1-HBD (Å)	HBA2-HBD (Å)	HBA1-HBA2 (Å)
1	6.62803	6.56688	2.45652
2	6.57332	6.62425	2.45417
3	6.55496	6.63307	2.45086
4	6.62574	6.5521	2.45626
5	6.62027	6.55362	2.45674
6	6.55724	6.62817	2.45185
7	6.7114	6.72042	2.46729
8	6.54888	6.60897	2.45761
9	6.55025	6.60325	2.45682
10	6.62917	6.56248	2.45793
11	6.62529	6.56011	2.45806
12	6.54163	6.62678	2.4512
13	6.62562	6.5563	2.45827
14	6.62041	6.59774	2.4616
15	6.62723	6.5604	2.45734
16	6.54946	6.62836	2.45089
17	6.56331	6.63026	2.45284
18	6.48596	6.63669	2.45654
19	6.63247	6.56366	2.45875
20	6.63251	6.5686	2.45879
21	6.5732	6.62648	2.45519
22	6.54522	6.62858	2.45308
23	6.48356	6.67556	2.44276
24	6.53785	6.64127	2.45184
25	6.52012	6.65779	2.44983

Table 7: Distance map between HBA1-HBD, HBA2-HBD and HBA1-HBA2 for test set

S. No.	HBA1-HBD (Å)	HBA2-HBD (Å)	HBA1-HBA2 (Å)
1	7.57607	7.44564	2.4551
2	7.43469	7.61495	2.45481
3	7.34103	7.50357	2.56242
4	7.2518	7.72762	2.45635
5	7.56757	7.44689	2.45505
6	7.44443	7.57644	2.45495
7	7.44651	7.57549	2.45527
8	7.3998	7.69448	2.45425

Table 8: Comparing training set and test data for maximum, minimum and average distances between HBA1-HBD, HBA2-HBD and HBA1-HBA2

	Training set (Å)			Test set (Å)		
	Min.	Max.	Avg.	Min.	Max.	Avg.
HBA_1-HBD	6.48356	6.7114	6.582524	7.2518	7.57607	7.4327375
HBA_2-HBD	6.67556	6.72042	6.6084716	7.44564	7.72762	7.573135
HBA_1-HBA_2	2.44276	2.46729	2.4553212	2.45425	2.56242	2.468525

Table 9: Calculated descriptive properties of novel synthesized compounds for drug likeness property. TPSA-Topological Polar Surface Area; E-max-Electrotopological state (Maximum)

Compound no.	Lipinski Failures	TPSA	E-max	No. of rotating bonds
8	0	106.59	11.2538	4
10	0	89.8	11.2823	5
11	0	89.8	11.2904	5
12	0	89.8	11.3008	5
13	0	106.59	11.2574	4
14	0	106.59	11.2619	4
15	0	97.64	11.3109	5
16	0	97.64	11.5168	5

^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 2.54(m, 3H of C20); 4.38, 4.48(s, 2H of C11); 6.74(s, Ar-H of C14); 6.84(s, Ar-H of C3); 7.11(s, Ar-H of C18); 7.18(d, Ar-H of C16); 7.20(d, Ar-H of C4); 7.24(d, Ar-H of C6); 7.26(d, Ar-H of C15); 7.47(m, 2H of $-SO_2NH_2$); 7.59(s, Ar-H of C1); 7.86(s, 1H of >NH). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 27.79(s, C20 of $-COCH_3$); 45.98(s, C11); 114.57(s, C18); 120.10(s, C14); 121.04(s, C16); 125.77(m, C1 and C3); 125.86(m, C4 and C6); 128.74(s, C15); 138.25(s, C17); 143.22(d, C5); 143.34(d, C2); 148.34(s, C13); 197.18(s, C19 of $-COCH_3$). IR (KBr, cm^{-1}, υ): 782.58. MS (m/z, %): (304.08, M^+, 75).

Compound number 16: 4-[(2-Acetyl-phenylamino)-methyl]-benzenesulfonamide

^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 2.54(m, 3H of C21); 4.49, 5.17(s, 2H of C11); 6.68(s, Ar-H of C14); 6.78(s, Ar-H of C16); 6.83(s, Ar-H of C3); 7.19(s, Ar-H of C4); 7.24(d, Ar-H of C6); 7.29(d, Ar-H of C15); 7.59(s, Ar-H of C1); 7.65(t, 1H of C17); 7.66(m, 2H of $-SO_2NH_2$); 7.84(s, 1H of >NH). C13 NMR (CDCl3, 100 MHz, δ in ppm): 28.28(s, C21 of $-COCH_3$); 45.86(s, C11); 114.69(s, C14); 116.76(s, C16); 124.57(s, C18); 125.77(m, C1 and C3); 125.86(m, C4 and C6); 130.21(s, C17); 132.66(s, C15); 143.22(d, C5); 143.34(d, C2); 147.67(s, C13); 201.78(s, C19 of –COCH3). IR (KBr, cm^{-1}, υ): 1174.85, 775.40. MS (m/z, %): (304.08, M^+, 67).

PHARMACOLOGICAL EVALUATION- ANTIBACTERIAL SCREENING

Synthesized compounds were tested against *Bacillus subtilis* (ATCC 6633), *E. coli* (ATCC 25922). The concentration of novel synthesized compounds and standard drug sulfafurazole was 250 mcg/disc. One of the synthesized compounds (compound number 11) is found potent against *E. coli* and compound number 15 was found potent against *Bacillus subtilis*. Against *E. coli* few of compounds named compound number 8, 10, 13, 14 and 15 were found with moderate anti-bacterial activity [Table 12].

CONCLUSION

A series of substituted 4-aminomethyl-benzenesulfonamide were designed and synthesized and evaluated for anti-bacterial activity. A proper drug development process has been followed such as 2 Dimensional designing of novel sulfonamides keeping in view the structural requirement, conversion of novel designed molecules to 3D, Two tier in-silico screening of novel designed molecules (QSAR screening and Molecular docking) and synthesis of screened molecules. Compound number 11 was found significant against *E. coli* which emerged as a lead in the series and compound number 15 was found significant against *Bacillus subtilis*. Further, compound number 8, 10, 13 and 14 came out as a potential candidate for further investigation. Furthermore, no compound violated the Lipinski's rule, making them

Table 10: Docking analysis of synthesized compound

Ligand (Comp. no.)	Recept.	Affinity Kcal/mol	H-bonds	H- Binding Ligand			H- Binding Receptor			
				Elem.	At. ID.	Type	Res.	Elem.	At.ID.	Type
8	1R4Z	-6.2	4	N	15	Donor	Tyr 37	O	270	Both
				N	21	Donor	Leu 36	O	254	Acceptor
				O	19	Acceptor	Lys 23	N	150	Donor
				O	19	Acceptor	Ala 38	N	271	Donor
	2CCZ	-6.8	6	15	N	Donor	Ala94	O	729	Acceptor
				15	N	Donor	Ser55	O	443	Acceptor
				15	N	Donor	Asn59	O	475	Acceptor
				7	N	Donor	Glu38	O	325	Acceptor
				20	O	Acceptor	Gln37	N	317	Donor
				20	O	Acceptor	Arg4	N	55	Donor
10	1R4Z	-6	4	N	15	Acceptor	Tyr 37	O	270	Both
				O	19	Acceptor	Lys 23	N	150	Donor
				O	19	Acceptor	Ala 38	N	271	Donor
				O	18	Acceptor	Arg 33	N	232	Donor
	2CCZ	-6.6	5	O	15	Acceptor	Lys 82	N	646	Donor
				N	20	Donor	Ser 88	O	681	Acceptor
				N	20	Donor	Ser 88	O	683	Both
				O	19	Acceptor	Lys 82	N	654	Donor
				O	18	Acceptor	Met 90	N	704	Donor
11	1R4Z	-6.4	4	O	18	Acceptor	Lys 23	N	150	Donor
				O	18	Acceptor	Ala 38	N	271	Donor
				N	20	Donor	Leu 36	O	254	Acceptor
				O	15	Acceptor	Tyr 37	O	270	Both
	2CCZ	-7	3	N	07	Donor	Ser 55	O	456	Acceptor
				O	18	Acceptor	Glu 58	N	473	Donor
				O	15	Acceptor	His 93	N	730	Donor
12	1R4Z	-6.1	3	O	18	Acceptor	Ala 38	N	271	Donor
				O	18	Acceptor	Lys 23	N	150	Donor
				N	20	Donor	Leu 36	O	254	Acceptor
	2CCZ	-6.1	2	N	20	Donor	Leu 16	O	149	Acceptor
				O	15	Acceptor	Arg 44	N	359	Donor
13	1R4Z	-6.3	4	O	19	Acceptor	Ala 38	N	271	Donor
				O	19	Acceptor	Lys 23	N	150	Donor
				N	21	Donor	Leu 36	O	254	Acceptor
	2CCZ	-6.5	5	N	15	Donor	Tyr 37	O	270	Both
				N	15	Donor	Asn 59	O	475	Acceptor
				N	15	Donor	Glu 58	O	468	Acceptor
				O	20	Acceptor	Gln 37	N	317	Donor
				O	20	Acceptor	Arg 4	N	55	Donor
14	1R4Z	-6.2	3	N	07	Donor	Glu 38	O	325	Acceptor
				O	19	Acceptor	Ala 38	N	271	Donor
				O	19	Acceptor	Lys 23	N	150	Donor
	2CCZ	-6.3	6	N	21	Donor	Leu 36	O	254	Acceptor
				O	20	Acceptor	Arg 44	N	358	Donor
				O	20	Acceptor	Arg 44	N	359	Donor
				N	21	Donor	Ser 79	O	634	Both
				N	21	Donor	His 93	N	733	Acceptor
				N	07	Donor	Lys 89	O	698	Acceptor
15	1R4Z	-6.8	4	N	15	Donor	Met 90	O	707	Acceptor
				O	19	Acceptor	Ala 38	N	271	Donor
				O	19	Acceptor	Lys 23	N	150	Donor
				N	21	Donor	Leu 36	O	254	Acceptor
	2CCZ	-6.9	5	O	17	Acceptor	Tyr 37	O	270	Both
				O	20	Acceptor	Arg 44	N	358	Donor
				O	20	Acceptor	Arg 44	N	359	Donor
				N	21	Donor	Ser 79	O	634	Both
				N	21	Donor	His 93	N	733	Acceptor
				N	07	Donor	Lys 89	O	698	Acceptor

16	1R4Z	-6.2	4	N	21	Donor	Asp72	O	546	Acceptor
				N	21	Donor	Leu173	O	1293	Acceptor
				O	19	Acceptor	Asn 98	N	736	Donor
				O	16	Acceptor	Asn 4	N	10	Donor
	2CCZ	-6.6	4	N	21	Donor	Ser 88	O	681	Acceptor
				N	21	Donor	Ser 88	O	683	Both
				O	20	Acceptor	Lys 82	N	654	Donor
				O	19	Acceptor	Met 90	N	704	Donor

Table 11: Physical and elemental data of all the synthesized compounds

Comp.	Molecular formula (MW)	Yield (%)	MP (0C)	Elemental analysis (%):Found (Calculated)				% purity	Rf
				C	H	N	S		
8	C13H15N3O2S (277.34)	88.42	215-216	56.01 (56.30)	4.98 (5.45)	14.05 (15.15)	11.14 (11.56)	97.42	0.40
10	C14H16N2O3S (292.35)	68.22	209-210	56.81 (57.52)	4.99 (5.52)	9.42 (9.58)	10.00 (10.97)	97.16	0.42
11	C14H16N2O3S (292.35)	67.80	184-185	57.05 (57.52)	5.10 (5.52)	9.50 (9.58)	10.88 (10.97)	98.72	0.43
12	C14H16N2O3S (292.35)	62.00	180-181	57.10 (57.52)	5.04 (5.52)	9.48 (9.58)	10.02 (10.97)	97.88	0.49
13	C13H15N3O2S (277.34)	85.88	190-191	56.09 (56.30)	4.93 (5.45)	14.87 (15.15)	11.01 (11.56)	98.23	0.48
14	C13H15N3O2S (277.34)	80.02	185-186	56.02 (56.30)	4.92 (5.45)	15.01 (15.15)	11.32 (11.56)	98.65	0.52
15	C15H16N2O3S (304.36)	82.44	194-195	58.09 (59.19)	5.10 (5.30)	9.17 (9.20)	9.28 (10.54)	96.92	0.45
16	C15H16N2O3S (304.36)	78.80	190-191	58.97 (59.19)	5.02 (5.30)	9.01 (9.20)	9.99 (10.54)	98.52	0.57

Table 12: Antibacterial activity of novel synthesized compounds

	Inhibition zone (mm)	
Compound	Gram negative - *E. coli*	Gram positive - *Bacillus subtilis*
8 (250 mcg)	21	15
10 (250 mcg)	21	14
11 (250 mcg)	23	16
12 (250 mcg)	19	15
13 (250 mcg)	21	16
14 (250 mcg)	21	16
15 (250 mcg)	21	18
16 (250 mcg)	20	15
Sulfafurazole (250 mcg)	21	18

potentially promising agents as anti-bacterial. However, further studies need to be carried out to ascertain the precise mechanism of action of anti-bacterial activity of these compounds.

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