# Synthesis, Spectral Characterization, Docking Studies and QSAR Screening of 4-amino-benzenesulfonamides/N-acetyl 4-amino-benzenesulfonamide Derivatives as Antimicrobial Agents

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**Abstract:** A series of substituted 4-amino-benzenesulfonamides / N-acetyl-4-amino-benzenesulfonamide were designed & synthesized keeping in view the structural requirements of pharmacophore and were evaluated for *in-silico* antimicrobial activity. For establishing the structure, spectral characterization like FT-IR, 1H NMR, GC-MS and elemental analysis (CHNS) has been performed. The antimicrobial activity of the titled compounds was assessed using *in-silico* studies (QSAR screening and Docking). It was carried out for the prediction of pharmacokinetic properties and to study the binding properties of drugs with molecular targets. Titled compounds exhibited good binding properties with molecular target. It could be concluded that molecular target responsible for the antimicrobial activity of substituted 4-amino-benzenesulfonamides / N-acetyl-4-amino-benzenesulfonamides may be pseudomonas aeruginosa exotoxin A.

**Keywords:** Sulfonamide, *in-silico* studies, statistics, quantitative structure activity relationship.

## 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 synthesizing 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, Bacillus subtilis lipase A, E-coli primosomal protein, heterodimeric hexaprenyl diphosphate synthase, Staphylococcus aureus metallopeptidase and Bacillus subtilis Lon protease.

In this study, the designed sulfonamide derivatives were synthesized, characterized and screened (*in-silico* screening with docking and QSAR study) against antimicrobial activity.

## EXPERIMENTAL

### Material and Methods

#### *Synthesis and Spectral Characterization*

All the chemicals and solvents, purchased from Merck (India), Spectrochem (India), Sigma-Aldrich (India), Himedia (India) and S. D. Fine 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 20x5 cm using conventional spreader. The plates were placed in hot air oven at $105^o$ 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 High Resolution NMR spectrometer using TMS as

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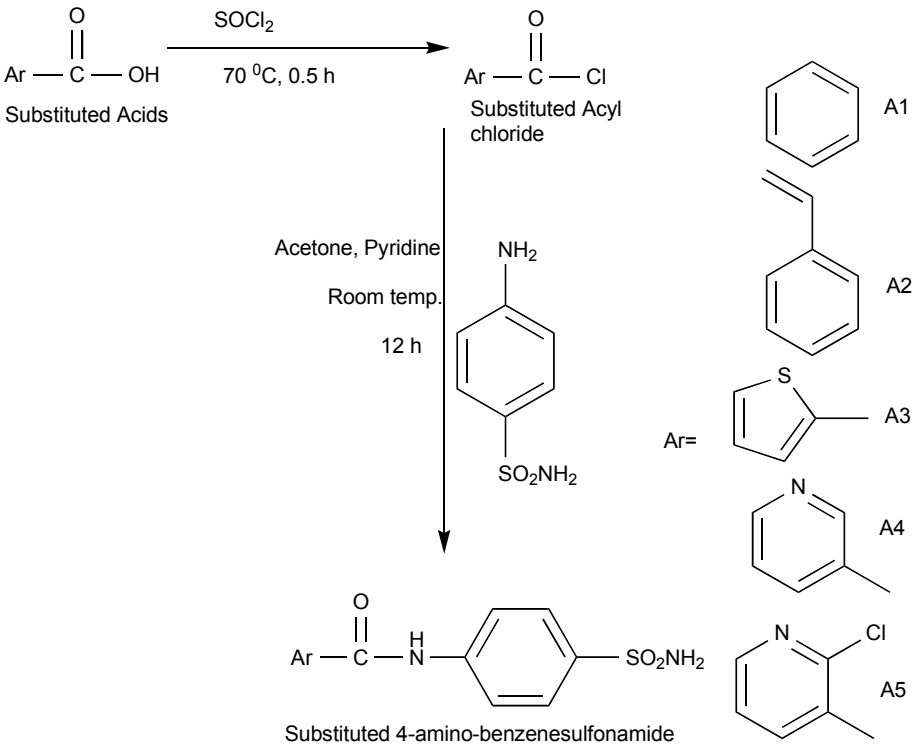



**Scheme 1:** Synthetic scheme of substituted 4-amino-benzenesulfonamide from substituted acids (A1, A2, A3, A4, A5).

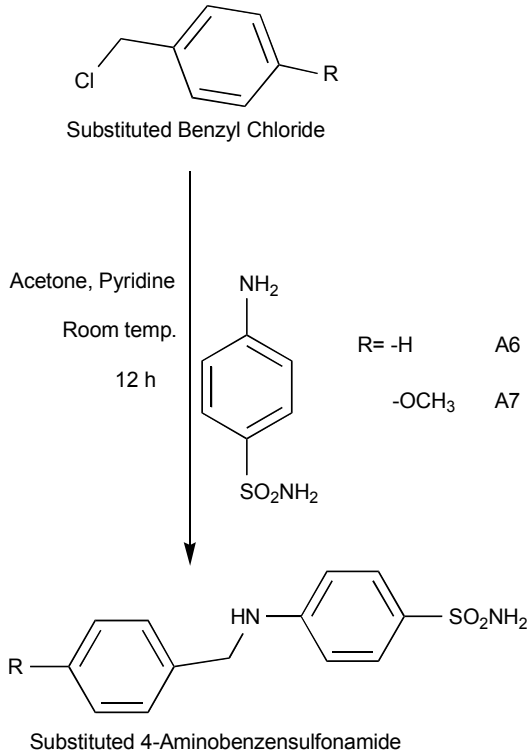
an internal standard. Chemical shifts were reported in ppm (δ) and signals were described as singlet (s), doublet (d), triplet (t) and multiplet (m). The mass spectra were recorded on a Waters Micro-Mass ZQ 2000 mass spectrometer.

### *Synthesis of Substituted Acyl Chlorides*

Substituted acid (0.1 mol) and thionyl chloride (0.4 mol) were placed in a 250 ml flask equipped with a magnetic stirrer bar and a condenser with a drying tube. The reaction mixture was stirred and heated in a $70^0$ C oil bath. After 0.5 hours, the reaction mixture was allowed to cool at room temperature with opened flask; this facilitates the evaporation of remaining thionyl chloride and lefts acyl chloride in the flask [11, 12].

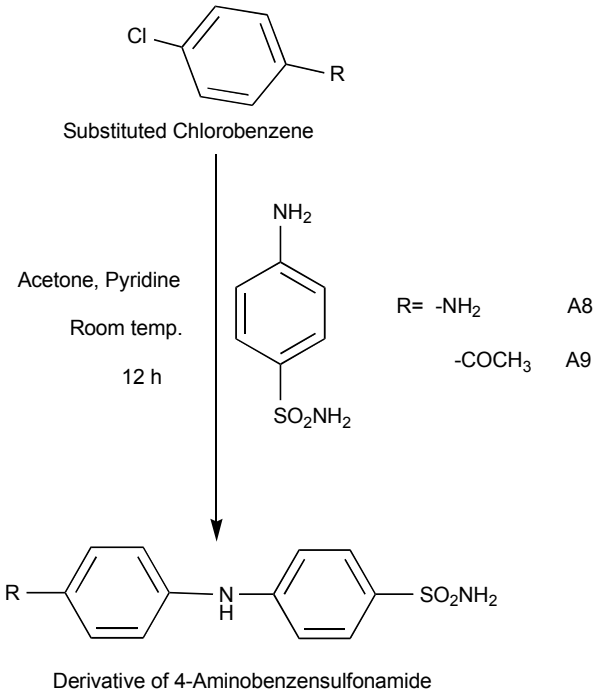
### *Synthesis of Substituted 4-amino-benzenesulfonamides/N-acetyl-4-amino-benzenesulfonamide*

For the synthesis of an appropriate amide, the substituted acyl chloride/substituted benzyl chloride (0.009 mol) of an individual acid dissolved in 20 ml. of dry acetone was added dropwise to a stirred solution of suitable 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.




**Scheme 2:** Synthetic scheme of substituted 4-amino-benzenesulfonamide from substituted benzyl chloride (A6, A7).

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 crystals [11, 12].




**Scheme 3:** Synthetic scheme of substituted 4-amino-benzenesulfonamide from substituted chlorobenzene (A8, A9).

## *In-Silico* Studies

### *Docking Studies*

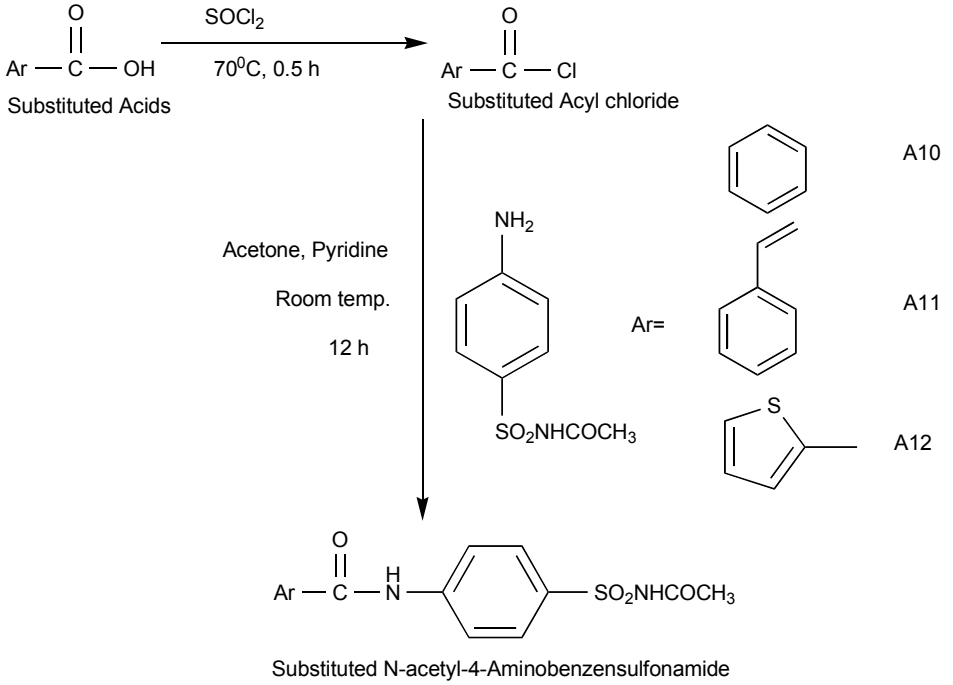
Docking

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 [13-18].

Docking procedures allows virtually screening a data-base of compounds and predict the strongest binder based on various scoring functions [13-18].

Receptor

Pseudomonas aeruginosa exotoxin A, Bacillus subtilis lipase A, E-coli primosomal protein, heterodimeric hexaprenyl diphosphate synthase, Staphylococcus aureus metallopeptidase and Bacillus subtilis Lon protease.




**Scheme 4:** Synthetic scheme of substituted N-acetyl-4-amino-benzenesulfonamide from substituted acids (A10, A11, A12).

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, all receptors have been downloaded from NCBI website with PDB ID 1IKQ (Pseudomonas aeruginosa exotoxin A), 1R4Z (Bacillus subtilis lipase A), 2CCZ (E-coli primosomal protein), 3AQB (heterodimeric hexaprenyl diphosphate synthase), 3KHX (Staphylococcus aureus metallopeptidase) and 3M65 (Bacillus subtilis Lon protease), all the designed ligands have been docked with protein (receptor) with AutoDock software having its default settings.

**QSAR Studies**

***QSAR***

QSAR (quantitative structure-activity relationship) includes all statistical methods, by which biological activities (most often expressed by logarithms of equipotent molar activities) are related with structural elements, physicochemical properties or fields [19-26].

Classical QSAR analyses consider only 2D structures. Their main field of application is in substituent variation of a common scaffold.

3D-QSAR analysis has a much broader scope. It starts from 3D structures and correlates biological activities with 3D property fields.

Basic requirements in QSAR studies are-

- all analogs belong to a congeneric series
- all analogs exert the same mechanism of action
- all analogs bind in a comparable manner
- the effects of isosteric replacement can be predicted
- binding affinity is correlated to interaction energies
- biological activities are correlated to binding affinity

**Molecular Descriptors**

Molecular descriptors can be defined as a numerical representation of chemical information encoded within a molecular structure *via* mathematical procedure. Type of QSAR is based on the dimensionality of molecular descriptors used:

0D- These are descriptors derived from molecular formula e.g. molecular weight, number and type of atoms etc.

1D- A substructure list representation of a molecule can be considered as a one-dimensional (1D) molecular representation and consists of a list of molecular fragments (e.g. functional groups, rings, bonds, substituents etc.).

2D- A molecular graph contains topological or two dimensional (2D) information. It describes how the atoms are bonded in a molecule, both the type of bonding and the interaction of particular atoms (e.g. total path count, molecular connectivity indices etc.).

3D- These are calculated starting from a geometrical or 3D representation of a molecule. These descriptors include molecular surface, molecular volume and other geometrical properties. There are different types of 3D descriptors e.g. electronic, steric, shape etc.

**Model Preparation**

All the 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, multiple linear regressions have been employed and all were validated through statistics [19-26].

**Modeling Parameters and Structure Optimization**

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

**Table 1: Physical and Elemental Data of all the Synthesized Compounds**

| Comp. | Molecular formula (MW) | Yield (%) [$R_f$] | MP ($^0$C) | Elemental analysis (%) : Found (Calculated) | | | |
|---|---|---|---|---|---|---|---|
| | | | | C | H | N | S |
| A1 | $C_{13}H_{12}N_2O_3S$ (276.306) | 68.75 [0.4] | 205-208 | 56.42 (56.50) | 3.260 (4.377) | 10.13 (10.14) | 11.16 (11.60) |
| A2 | $C_{15}H_{14}N_2O_3S$ (302.342) | 71.92 [0.84] | 220-222 | 59.44 (59.58) | 1.922 (4.667) | 9.224 (9.267) | 10.63 (10.60) |
| A3 | $C_{11}H_{10}N_2O_3S_2$ (282.41) | 56.73 [0.63] | 210-212 | 39.89 (46.77) | 0.969 (3.569) | 8.540 (9.921) | 19.16 (22.73) |
| A4 | $C_{12}H_{11}N_3O_3S$ (277.052) | 10.47 [0.34] | 211-212 | 45.42 (51.98) | 2.08 (4.00) | 14.18 (15.16) | 10.80 (11.54) |
| A5 | $C_{12}H_{10}ClN_3O_3S$ (311.013) | 86.18 [0.8] | 230-231 | 46.15 (46.23) | 2.90 (3.24) | 13.25 (13.49) | 10.03 (10.26) |
| A6 | $C_{13}H_{14}N_2O_2S$ (262.077) | 23.04 [0.24] | 170-172 | 59.48 (59.52) | 4.80 (5.38) | 10.10 (10.69) | 11.92 (12.20) |
| A7 | $C_{14}H_{16}N_2O_3S$ (292.088) | 41.98 [0.16] | 180-182 | 57.21 (57.52) | 3.90 (5.52) | 9.20 (9.59) | 10.02 (10.95) |
| A8 | $C_{12}H_{13}N_3O_2S$ (263.072) | 93.42 [0.46] | 208-210 | 54.34 (54.74) | 3.52 (4.98) | 15.41 (15.97) | 11.92 (12.15) |
| A9 | $C_{14}H_{14}N_2O_3S$ (290.072) | 84.88 [0.25] | 216-218 | 57.36 (57.92) | 2.98 (4.86) | 9.42 (9.65) | 10.87 (11.02) |
| A10 | $C_{15}H_{14}N_2O_4S$ (318.067) | 29.21 [0.18] | 250-252 | 55.99 (56.59) | 3.98 (4.44) | 8.72 (8.81) | 9.92 (10.05) |
| A11 | $C_{17}H_{16}N_2O_4S$ (344.083) | 62.18 [0.66] | 265-266 | 59.12 (59.29) | 3.23 (4.69) | 8.11 (8.14) | 9.10 (9.29) |
| A12 | $C_{13}H_{12}N_2O_4S_2$ (324.023) | 33.95 [0.2] | 225-227 | 47.92 (48.14) | 2.65 (3.73) | 8.21 (8.64) | 19.04 2(19.73) |

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.

### QSAR Screening

All the designed 4-amino-benzenesulfonamides / N-acetyl-4-amino-benzenesulfonamide derivatives have been passed through the model (given below) after determining the descriptors used in model. Descriptors used are AlogP, Eccentric connectivity index (ECI) and Lipo-affinity index (LAI) for calculating *log1/C*.

### Descriptor Selection

The selection of descriptors among the calculated descriptors for the multiple linear regression analysis is based on the correlation matrix. This matrix is prepared and analyzed for the least correlated descriptors [19-26].

### 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 $q^2$, s is standard deviation. Q is quality factor, where *Q = r/s* (here r is correlation coefficient and s is standard deviation). Fischer statistics is denoted by F [19-26].

### Model Validation

The QSAR model validation was carried with statistical analysis and with internal validation [19-26].

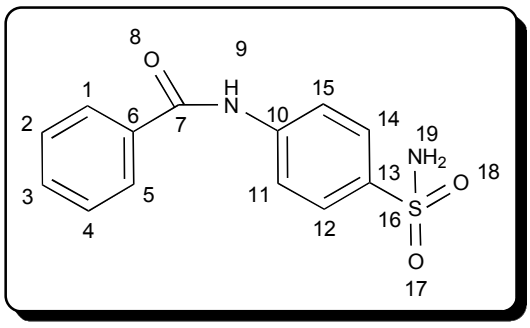
## RESULTS AND DISCUSSION

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 synthesized compounds are reported in Table **1**.

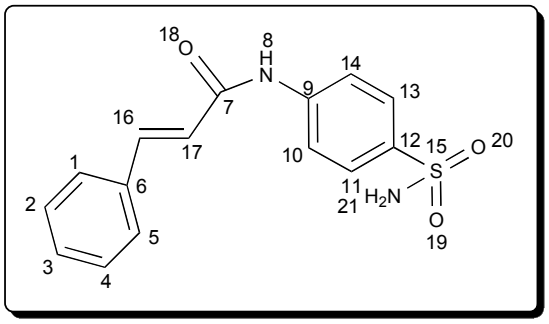
### Spectral Characterization of Synthesized Substituted 4-amino-benzenesulfonamides/*N*-acetyl-4-amino-benzenesulfonamide Derivatives

#### *N-(4-Sulfamoyl-phenyl)-benzamide (A1)*



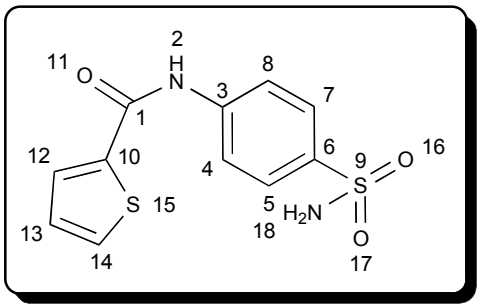

IR (KBr, $cm^{-1}$, υ): 3340.53 (-$NH_2$-); 3250.94 (-NH-); 1659.10 (>C=O); 1397.80(-$SO_2$-). $^1$H NMR (DMSO, 400 MHz, δ in ppm): 7.286(s, 2H, -$NH_2$); 7.548-7.580(d, 2H, Ar-H of C12 and C14); 7.616-7.648(t, 1H, Ar-H of C3); 7.809-7.826(t, 2H, Ar-H of C2 and C4); 7.958-7.994 (d, 4H, Ar-H of C1, C5, C11 and C15); 10.564(s, 1H, >NH). MS (m/z, %): 277.30 ($M^+$ +1, 95).

***3-Phenyl-N-(4-sulfamoyl-phenyl)-acrylamide (A2)***



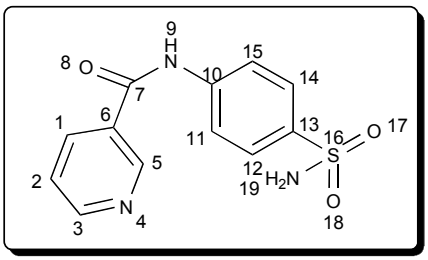
IR (KBr, $cm^{-1}$, υ): 3359.69(-$NH_2$-); 3182.61(-NH-); 1674.59(>C=O); 1400.63(-$SO_2$-). $^1$H NMR (DMSO, 400 MHz, δ in ppm): 7.271(s, 2H, -$NH_2$); 2.5-3.3(d, 2H, C16 and C17); 7.489-7.492(d, 2H, Ar-H of C11 and C13); 7.631-7.663(t, 1H, Ar-H of C3); 7.791-7.809(t, 2H, Ar-H of C2 and C4); 7.857-7.875(d, 4H, Ar-H of C1, C5, C10 and C14); 10.551(s, 1H, >NH). MS (m/z, %): 303.70 ($M^+$ +1, 100).

***Thiophene-2-carboxylic acid (4-sulfamoyl-phenyl)-amide (A3)***



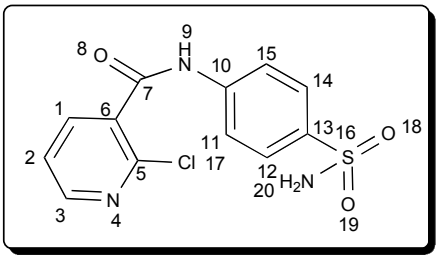
IR (KBr, $cm^{-1}$, υ): 3375.09(-$NH_2$-); 3275.82(-NH-); 1650.90(>C=O); 1408.75(-$SO_2$-). $^1$H NMR (DMSO, 400 MHz, δ in ppm): 7.289(s, 2H, -$NH_2$); 7.248-7.265(d, 1H, Thiophene-H of C14); 7.804-7.822(t, 1H, Ar-H of C13 ); 7.907-7.947(d, 4H, Ar-H of C4, C5, C7 and C8); 8.132-8.141(d, 2H, Thiophene-H of C12); 10.603(s, 1H, >NH). MS (m/z, %): 283.71 ($M^+$ +1, 100).

***N-(4-Sulfamoyl-phenyl)-nicotinamide (A4)***



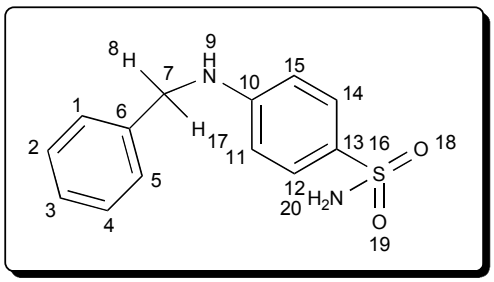
IR (KBr, $cm^{-1}$, υ): 3345.93 (-$NH_2$-); 3230.94 (-NH-); 1659.19 (>C=O); 1390.70(-$SO_2$-). $^1$H NMR (DMSO, 400 MHz, δ in ppm): 7.279(s, 2H, -$NH_2$); 7.568-7.590(d, 2H, Ar-H of C12 and C14); 7.656-7.688(d, 1H, Ar-H of C3); 7.819-7.836(t, 2H, Ar-H of C2); 7.918-7.924 (d, 3H, Ar-H of C1, C11 and C15); 7.89(s, 1H, Ar-H of C5); 10.584(s, 1H, >NH). MS (m/z, %): 278.10 ($M^+$ +1, 88).

***2-Chloro-N-(4-sulfamoyl-phenyl)-nicotinamide (A5)***



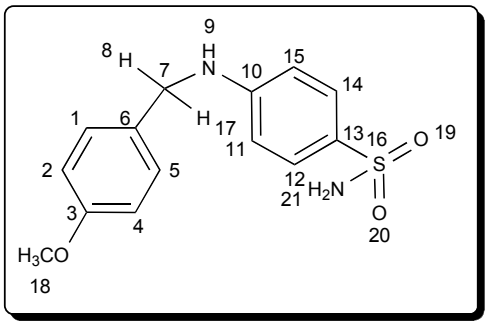
IR (KBr, $cm^{-1}$, υ): 700.10(>C-Cl), 3348.83 (-$NH_2$-); 3238.94 (-NH-); 1657.19 (>C=O); 1390.70(-$SO_2$-). $^1$H NMR (DMSO, 400 MHz, δ in ppm): 7.299(s, 2H, -$NH_2$); 7.588-7.593(d, 2H, Ar-H of C12 and C14); 7.686-7.689(d, 1H, Ar-H of C3); 7.820-7.836(t, 2H, Ar-H of C2); 7.928-7.929(d, 3H, Ar-H of C1, C11 and C15); 10.594(s, 1H, >NH). MS (m/z, %): 311.80 ($M^+$ +1, 90).

***4-Benzylamino-benzenesulfonamide (A6)***



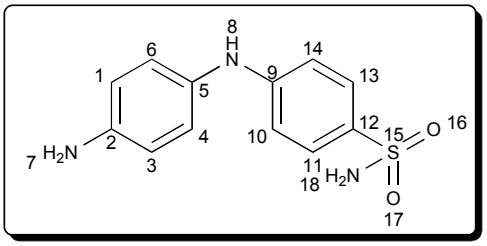
IR (KBr, $cm^{-1}$, υ): 3340.53 (-$NH_2$-); 3250.94 (-NH-); 1397.80(-$SO_2$-); 1465.76(>C-H). $^1$H NMR (DMSO, 400 MHz, δ in ppm): 1.343(d, 2H of C7); 7.306(s, 2H, -$NH_2$); 7.558-7.590(d, 2H, Ar-H of C12 and C14); 7.626-7.638(t, 1H, Ar-H of C3); 7.819-7.827(t, 2H, Ar-H of C2 and C4); 7.918-7.904(d, 4H, Ar-H of C1, C5, C11 and C15); 10.563(s, 1H, >NH). MS (m/z, %): 263.30 ($M^+$ +1, 95).

***4-(4-Methoxy-benzylamino)-benzenesulfonamide (A7)***



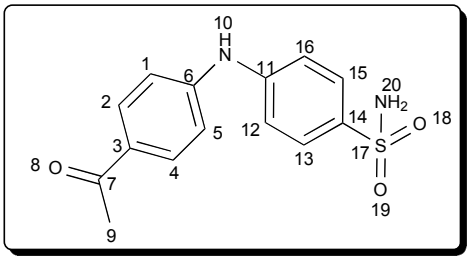
IR (KBr, $cm^{-1}$, υ): 3340.53 (-$NH_2$-); 3250.94 (-NH-); 1397.80(-$SO_2$-); 1315.87(>C-O-); 1465.76(>C-H). $^1$H NMR (DMSO, 400 MHz, δ in ppm): 0.899(s, 3H, -$CH_3$); 1.383(d, 2H of C7); 7.316(s, 2H, -$NH_2$); 7.508-7.510(d, 2H, Ar-H of C12 and C14); 7.828-7.829(d, 2H, Ar-H of C2 and C4); 7.910-7.914(d, 4H, Ar-H of C1, C5, C11 and C15); 10.523(s, 1H, >NH). MS (m/z, %): 293.10 ($M^+$ +1, 90).

***4-(4-Amino-phenylamino)-benzenesulfonamide (A8)***



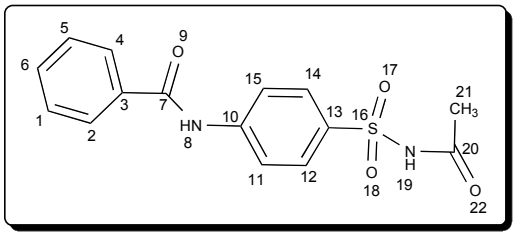
IR (KBr, $cm^{-1}$, υ): 3337.23(-$NH_2$- of C2); 3342.83 (-$NH_2$-); 3190.84 (-NH-); 1679.10 (>C=O); 1387.90 (-$SO_2$-). $^1$H NMR (DMSO, 400 MHz, δ in ppm): 6.986(s, 2H, -$NH_2$); 7.236(s, 2H, -$NH_2$); 7.498-7.550(d, 2H, Ar-H of C11 and C13); 7.819-7.829(d, 2H, Ar-H of C1 and C3); 7.928-7.964 (d, 4H, Ar-H of C4, C6, C10 and C14); 10.524(s, 1H, >NH). MS (m/z, %): 264.80 ($M^+$ +1, 89).

***4-(4-Acetyl-phenylamino)-benzenesulfonamide (A9)***



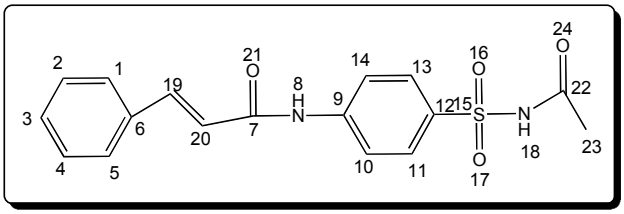
IR (KBr, $cm^{-1}$, υ): 3348.83 (-$NH_2$-); 3193.84 (-NH-); 1639.70 (>C=O); 1392.90(-$SO_2$-). $^1$H NMR (DMSO, 400 MHz, δ in ppm): 0.909(s, 3H of C9); 7.256(s, 2H, -$NH_2$); 7.428-7.510(d, 2H, Ar-H of C13 and C15); 7.839-7.859(d, 2H, Ar-H of C2 and C4); 7.978-7.994 (d, 4H, Ar-H of C1, C5, C12 and C16); 10.584(s, 1H, >NH). MS (m/z, %): 291.30 ($M^+$ +1, 98).

***N-(4-Acetylsulfamoyl-phenyl)-benzamide (A10)***



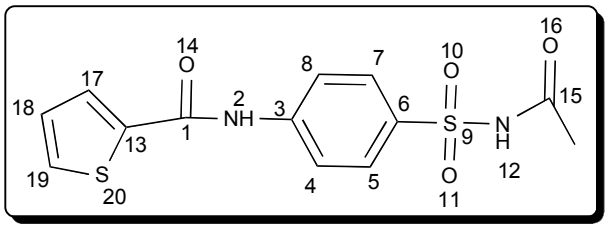
IR (KBr, $cm^{-1}$, υ): 3245.53, 3250.94 (-NH-); 1678.30, 1659.10 (>C=O); 1396.50(-$SO_2$-). $^1$H NMR (DMSO, 400 MHz, δ in ppm): 0.919(s, 3H, -$CH_3$); 7.512-7.530(d, 2H, Ar-H of C12 and C14); 7.596-7.628(t, 1H, Ar-H of C6); 7.839-7.846(t, 2H, Ar-H of C1 and C5); 7.908-7.954 (d, 4H, Ar-H of C2, C4, C11 and C15); 10.497, 10.527(s, 1H, >NH). MS (m/z, %): 319.90 ($M^+$ +1, 70).

***N-(4-Acetylsulfamoyl-phenyl)-3-phenyl-acrylamide (A11)***



IR (KBr, $cm^{-1}$, υ): 3188.98, 3181.61(-NH-); 1681.09, 1678.59(>C=O); 1420.63(-$SO_2$-). $^1$H NMR (DMSO, 400 MHz, δ in ppm): 0.917(s, 3H, -$CH_3$); 2.518-3.398(d, 2H, C19 and C20); 7.479-7.482(d, 2H, Ar-H of C11 and C13); 7.611-7.623(t, 1H, Ar-H of C3); 7.781-7.701(t, 2H, Ar-H of C2 and C4); 7.859-7.870(d, 4H, Ar-H of C1, C5, C10 and C14); 10.534, 10.550(s, 1H, >NH). MS (m/z, %): 345.70 ($M^+$ +1, 94).

***Thiophene-2-carboxylic acid (4-acetylsulfamoyl-phenyl)-amide (A12)***



IR (KBr, $cm^{-1}$, υ): 3252.83, 3277.80(-NH-); 1659.07, 1654.90(>C=O); 1408.75(-$SO_2$-). $^1$H NMR (DMSO, 400 MHz, δ in ppm): 0.927(s, 3H, -$CH_3$); 7.247-7.255(d, 1H, Thiophene-H of C19); 7.807-7.820(t, 1H, Ar-H of C18); 7.937-7.949(d, 4H, Ar-H of C4, C5, C7 and C8); 8.134-8.142(d, 2H, Thiophene-H of C17); 10.567, 10.603(s, 1H, >NH). MS (m/z, %): 325.81 ($M^+$ +1, 100).

**Docking study of 4-amino-benzenesulfonamides/N-acetyl-4-amino-benzenesulfonamide derivatives and standard drug taken Norfloxacin (CID_4539)**

Docking study of different proteins were performed with the designed inhibitors and standard drug taken is given in Tables **2** to **14** and number of hydrogen bonds & binding pattern such as element, type of bond, atom number and residue at binding site were evaluated.

**Table 2: Docking Analysis of Synthesized Compound A1**

| Ligand | Receptor | Affinity Kcal/mol | H-bonds | H- Binding Ligand | | | H- Binding Receptor | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Elem. | At. ID. | Type | Res. | Elem. | At.ID. | Type |
| A1 | 1IKQ | -7.6 | 4 | O | 18 | Acceptor | THR 271 | O | 2083 | Both |
| | | | | O | 17 | Acceptor | THR 271 | O | 2083 | Both |
| | | | | O | 08 | Acceptor | TRP 187 | N | 1397 | Donor |
| | | | | O | 08 | Acceptor | SER 188 | N | 1411 | Donor |
| | 1R4Z | -6 | 5 | N | 19 | Donor | LEU 173 | O | 1293 | Acceptor |
| | | | | N | 19 | Donor | ASP 72 | O | 546 | Acceptor |
| | | | | O | 18 | Acceptor | ASN 4 | N | 17 | Donor |
| | | | | O | 17 | Acceptor | ASN 98 | N | 736 | Donor |
| | | | | O | 08 | Acceptor | HIS 3 | N | 0 | Donor |
| | 2CCZ | -6.1 | 3 | O | 17 | Acceptor | SER 88 | O | 683 | Both |
| | | | | N | 19 | Donor | SER 88 | O | 683 | Both |
| | | | | N | 19 | Donor | SER 88 | O | 681 | Acceptor |
| | 3AQB | -7.5 | 0 | - | - | - | - | - | - | - |
| | 3KHX | -6.4 | 5 | N | 19 | Donor | ASP 311 | O | 2350 | Acceptor |
| | | | | N | 19 | Donor | ASP 311 | O | 2351 | Acceptor |
| | | | | N | 19 | Donor | PRO 273 | O | 2052 | Acceptor |
| | | | | N | 19 | Donor | GLY 276 | O | 2073 | Acceptor |
| | | | | O | 17 | Acceptor | ASN 278 | N | 2081 | Donor |
| | 3M65 | -6.8 | 3 | N | 19 | Donor | LEU 171 | O | 1325 | Acceptor |
| | | | | N | 19 | Donor | SER 169 | O | 1309 | Acceptor |
| | | | | O | 08 | Acceptor | SER 147 | N | 1146 | Donor |

On docking analysis, designed compound A1 has been found to be strongly docked with the protein 1IKQ when binding with 6 different proteins have been observed 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 -7.6 Kcal/mol. On residue study, the amino acids THR 271, TRP 187 and SER 188 were found to be significant. On the account of ligand here oxygen atom is significant in the binding with the type of binding found with acceptor bonds, whereas significant elements in receptor binding are oxygen and nitrogen both.

On docking analysis, designed compound A2 has been also found to be strongly docked with the protein 1IKQ when binding with 6 different proteins have been observed 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 -8.4 Kcal/mol. On residue study, the amino acids THR 271, TRP 187, GLU 270 and ARG 274 were found to be significant. On the account of ligand here oxygen and nitrogen both atoms are significant in the binding, the type of binding found with acceptor bonds, whereas significant elements in receptor binding are oxygen and nitrogen both.

On docking analysis, designed compound A3 has been also found to be strongly docked with the protein 1IKQ when binding with 6 different proteins have been observed 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 -7.2 Kcal/mol. On residue study, the amino acids THR 271, TRP 187 and SER 188 were found to be significant. On the account of ligand here oxygen atom is significant in the binding with the type of binding found with acceptor bonds, whereas significant elements in receptor binding are oxygen and nitrogen both.

On docking analysis, designed compound A4 has been also found to be strongly docked with the protein 1IKQ when binding with 6 different proteins have been observed in order to study its inhibition activity. When it is docked with the protein PDB ID- 1IKQ, it forms 5 hydrogen bonds with binding affinity of -7.8 Kcal/mol.

**Table 3: Docking Analysis of Synthesized Compound A2**

| Ligand | Receptor | Affinity Kcal/mol | H-bonds | H- Binding Ligand | | | H- Binding Receptor | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Elem. | At. ID. | Type | Res. | Elem. | At.ID. | Type |
| A2 | 1IKQ | -8.4 | 4 | O | 19 | Acceptor | THR 271 | O | 2083 | Both |
| | | | | O | 20 | Acceptor | ARG 274 | N | 2112 | Donor |
| | | | | N | 21 | Donor | GLU 270 | O | 2076 | Acceptor |
| | | | | O | 08 | Acceptor | TRP 187 | N | 1397 | Donor |
| | 1R4Z | -6.3 | 4 | N | 21 | Donor | LEU 173 | O | 1293 | Acceptor |
| | | | | N | 21 | Donor | ASP 72 | O | 546 | Acceptor |
| | | | | O | 19 | Acceptor | ASN 98 | N | 736 | Donor |
| | | | | O | 20 | Acceptor | ASN 4 | N | 17 | Donor |
| | 2CCZ | -6.5 | 3 | O | 08 | Acceptor | GLN 49 | N | 394 | Donor |
| | | | | O | 19 | Acceptor | LYS 89 | N | 692 | Donor |
| | | | | O | 20 | Acceptor | ARG 13 | N | 119 | Donor |
| | 3AQB | -7.5 | 0 | - | - | - | - | - | - | - |
| | 3KHX | -6.8 | 5 | N | 21 | Donor | ASP 311 | O | 2350 | Acceptor |
| | | | | N | 21 | Donor | ASP 311 | O | 2351 | Acceptor |
| | | | | N | 21 | Donor | PRO 273 | O | 2052 | Acceptor |
| | | | | N | 21 | Donor | GLY 276 | O | 2073 | Acceptor |
| | | | | O | 19 | Acceptor | ASN 278 | N | 2081 | Donor |
| | 3M65 | -7.2 | 2 | N | 06 | Donor | THR 150 | O | 1171 | Both |
| | | | | O | 08 | Acceptor | THR 150 | O | 1171 | Both |

**Table 4: Docking Analysis of Synthesized Compound A3**

| Ligand | Receptor | Affinity Kcal/mol | H-bonds | H- Binding Ligand | | | H- Binding Receptor | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Elem. | At. ID. | Type | Res. | Elem. | At.ID. | Type |
| A3 | 1IKQ | -7.2 | 4 | O | 08 | Acceptor | TRP 187 | N | 1397 | Donor |
| | | | | O | 08 | Acceptor | SER 188 | N | 1411 | Donor |
| | | | | O | 17 | Acceptor | THR 271 | O | 2083 | Both |
| | | | | O | 16 | Acceptor | THR 271 | O | 2083 | Both |
| | 1R4Z | -6 | 5 | N | 18 | Donor | LEU 173 | O | 1293 | Acceptor |
| | | | | N | 18 | Donor | ASP 72 | O | 546 | Acceptor |
| | | | | O | 08 | Acceptor | HIS 3 | N | 0 | Donor |
| | | | | O | 17 | Acceptor | ASN 4 | N | 17 | Donor |
| | | | | O | 16 | Acceptor | ASN 98 | N | 736 | Donor |
| | 2CCZ | -5.8 | 3 | N | 18 | Donor | SER 88 | O | 681 | Acceptor |
| | | | | N | 18 | Donor | SER 88 | O | 683 | Both |
| | | | | O | 16 | Acceptor | SER 88 | O | 683 | Both |
| | 3AQB | -6.9 | 2 | N | 06 | Donor | ASP 152 | O | 1180 | Acceptor |
| | | | | O | 17 | Acceptor | SER 159 | O | 1243 | Both |
| | 3KHX | -5.8 | 5 | N | 18 | Donor | ASP 311 | O | 2350 | Acceptor |
| | | | | N | 18 | Donor | ASP 311 | O | 2351 | Acceptor |
| | | | | N | 18 | Donor | PRO 273 | O | 2052 | Acceptor |
| | | | | N | 18 | Donor | GLY 276 | O | 2073 | Acceptor |
| | | | | O | 16 | Acceptor | ASN 278 | N | 2081 | Donor |
| | 3M65 | -6.5 | 3 | O | 17 | Acceptor | THR 150 | O | 1171 | Both |
| | | | | O | 17 | Acceptor | HIS 170 | N | 1318 | Donor |
| | | | | N | 18 | Donor | HIS 170 | O | 1315 | Acceptor |

**Table 5: Docking Analysis of Synthesized Compound A4**

| Ligand | Receptor | Affinity Kcal/mol | H-bonds | H- Binding Ligand | | | H- Binding Receptor | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Elem. | At. ID. | Type | Res. | Elem. | At.ID. | Type |
| A4 | 1IKQ | -7.8 | 5 | N | 20 | Donor | THR 134 | O | 1035 | Both |
| | | | | N | 20 | Donor | GLU 270 | O | 2077 | Acceptor |
| | | | | N | 14 | Donor | SER 188 | O | 1414 | Acceptor |
| | | | | O | 19 | Acceptor | GLU 270 | N | 2069 | Donor |
| | | | | N | 06 | Donor | GLU 391 | O | 2984 | Acceptor |
| | 1R4Z | -6.2 | 2 | O | 08 | Acceptor | HIS 3 | N | 0 | Donor |
| | | | | N | 14 | Donor | LEU 173 | O | 1293 | Acceptor |
| | 2CCZ | -5.9 | 0 | - | - | - | - | - | - | - |
| | 3AQB | -7.3 | 0 | - | - | - | - | - | - | - |
| | 3KHX | -6.4 | 2 | N | 14 | Donor | THR 398 | O | 2966 | Acceptor |
| | | | | O | 08 | Acceptor | THR 398 | O | 2968 | Both |
| | 3M65 | -6.8 | 3 | O | 19 | Acceptor | THR 150 | O | 1171 | Both |
| | | | | O | 19 | Acceptor | HIS 170 | N | 1318 | Donor |
| | | | | N | 20 | Donor | HIS 170 | O | 1315 | Acceptor |

**Table 6: Docking Analysis of Synthesized Compound A5**

| Ligand | Receptor | Affinity Kcal/mol | H-bonds | H- Binding Ligand | | | H- Binding Receptor | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Elem. | At. ID. | Type | Res. | Elem. | At.ID. | Type |
| A5 | 1IKQ | -7.4 | 6 | O | 19 | Acceptor | SER 192 | O | 1450 | Both |
| | | | | O | 19 | Acceptor | GLY 193 | N | 1451 | Donor |
| | | | | O | 19 | Acceptor | LYS 194 | N | 1455 | Donor |
| | | | | N | 21 | Donor | THR 371 | O | 2858 | Both |
| | | | | O | 08 | Acceptor | THR 396 | O | 3029 | Both |
| | | | | O | 20 | Acceptor | TYR 206 | O | 1554 | Both |
| | 1R4Z | -6.4 | 6 | N | 06 | Donor | ASN 174 | O | 1301 | Acceptor |
| | | | | O | 20 | Acceptor | ASN 4 | N | 10 | Donor |
| | | | | O | 19 | Acceptor | ASN 98 | N | 736 | Donor |
| | | | | O | 19 | Acceptor | ASN 4 | N | 17 | Donor |
| | | | | N | 21 | Donor | ASP 72 | O | 546 | Acceptor |
| | | | | N | 21 | Donor | LEU 173 | O | 1293 | Acceptor |
| | 2CCZ | -6 | 1 | N | 21 | Donor | GLN 49 | O | 410 | Acceptor |
| | 3AQB | -7.6 | 0 | - | - | - | - | - | - | - |
| | 3KHX | -6.9 | 0 | - | - | - | - | - | - | - |
| | 3M65 | -6.7 | 3 | N | 21 | Donor | LEU 171 | O | 1325 | Acceptor |
| | | | | N | 21 | Donor | SER 169 | O | 1309 | Acceptor |
| | | | | O | 08 | Acceptor | SER 147 | N | 1146 | Donor |

On residue study, the amino acids THR 234, GLU 270, GLU 391 and SER 188 were found to be significant. On the account of ligand here nitogen atom is significant in the binding, the type of binding found with donor bonds, whereas significant elements in receptor binding are oxygen.

**Table 7: Docking Analysis of Synthesized Compound A6**

| Ligand | Receptor | Affinity Kcal/mol | H-bonds | H- Binding Ligand | | | H- Binding Receptor | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Elem. | At. ID. | Type | Res. | Elem. | At.ID. | Type |
| A6 | 1IKQ | -7.6 | 3 | N | 18 | Donor | SER 188 | O | 1416 | Both |
| | | | | N | 18 | Donor | SER 188 | O | 1414 | Acceptor |
| | | | | O | 16 | Acceptor | SER 188 | O | 1416 | Both |
| | 1R4Z | -5.8 | 5 | O | 16 | Acceptor | ASN 98 | N | 736 | Donor |
| | | | | O | 16 | Acceptor | ASN 4 | N | 17 | Donor |
| | | | | N | 18 | Donor | ASP 72 | O | 546 | Acceptor |
| | | | | N | 18 | Donor | LEU 173 | O | 1293 | Acceptor |
| | | | | O | 17 | Acceptor | ASN 4 | N | 10 | Donor |
| | 2CCZ | -6 | 1 | O | 17 | Acceptor | CYS 80 | S | 640 | Donor |
| | 3AQB | -7.6 | 0 | - | - | - | - | - | - | - |
| | 3KHX | -6.4 | 0 | - | - | - | - | - | - | - |
| | 3M65 | -6.2 | 2 | N | 18 | Donor | GLU 208 | O | 1630 | Acceptor |
| | | | | N | 18 | Donor | LEU 205 | O | 1605 | Acceptor |

**Table 8: Docking Analysis of Synthesized Compound A7**

| Ligand | Receptor | Affinity Kcal/mol | H-bonds | H- Binding Ligand | | | H- Binding Receptor | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Elem. | At. ID. | Type | Res. | Elem. | At.ID. | Type |
| A7 | 1IKQ | -7.5 | 8 | O | 18 | Acceptor | LYS 114 | N | 869 | Donor |
| | | | | O | 18 | Acceptor | HIS 246 | N | 1894 | Donor |
| | | | | O | 18 | Acceptor | THR 134 | O | 1035 | Both |
| | | | | N | 20 | Donor | GLU 270 | O | 2077 | Acceptor |
| | | | | N | 20 | Donor | THR 134 | O | 1035 | Both |
| | | | | O | 15 | Acceptor | SER 188 | O | 1416 | Both |
| | | | | N | 06 | Donor | HIS 262 | N | 2015 | Acceptor |
| | | | | N | 06 | Donor | GLU 391 | O | 2984 | Acceptor |
| | 1R4Z | -6.2 | 0 | - | - | - | - | - | - | - |
| | 2CCZ | -6.1 | 2 | O | 19 | Acceptor | LYS 82 | N | 654 | Donor |
| | | | | O | 18 | Acceptor | MET 90 | N | 704 | Donor |
| | 3AQB | -7.3 | 3 | N | 20 | Donor | VAL 158 | O | 1234 | Acceptor |
| | | | | O | 19 | Acceptor | TYR 156 | O | 1223 | Both |
| | | | | O | 18 | Acceptor | TYR 156 | O | 1223 | Both |
| | 3KHX | -6.4 | 2 | O | 19 | Acceptor | ASN 309 | N | 2330 | Donor |
| | | | | N | 20 | Donor | ASP 311 | O | 2350 | Acceptor |
| | 3M65 | -6.6 | 1 | O | 15 | Acceptor | SER 147 | O | 1151 | Both |

On docking analysis, designed compound A5 has been found to be strongly docked with the protein 1IKQ when binding with 6 different proteins have been observed in order to study its inhibition activity. When it is docked with the protein PDB ID- 1IKQ, it forms 6 hydrogen bonds with binding affinity of -7.4 Kcal/mol. On residue study, the amino acids SER 192, GLY 193, LYS 194, THR 371, THR 396 and TYR 206 were found to be significant. On the account of ligand here oxygen atom is significant in the binding, the type of binding

**Table 9: Docking Analysis of Synthesized Compound A8**

| Ligand | Receptor | Affinity Kcal/mol | H-bonds | H- Binding Ligand | | | H- Binding Receptor | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Elem. | At. ID. | Type | Res. | Elem. | At.ID. | Type |
| A8 | 1IKQ | -7.3 | 4 | N | 14 | Donor | THR 134 | O | 1035 | Both |
| | | | | N | 20 | Donor | SER 188 | O | 1414 | Acceptor |
| | | | | N | 20 | Donor | SER 188 | O | 1416 | Both |
| | | | | O | 18 | Acceptor | SER 188 | O | 1416 | Both |
| | 1R4Z | -6.3 | 5 | O | 18 | Acceptor | ASN 4 | N | 17 | Donor |
| | | | | O | 18 | Acceptor | ASN 98 | N | 736 | Donor |
| | | | | N | 20 | Donor | LEU 173 | O | 1293 | Acceptor |
| | | | | N | 20 | Donor | ASP 72 | O | 546 | Acceptor |
| | | | | O | 19 | Acceptor | ASN 4 | N | 10 | Donor |
| | 2CCZ | -6 | 1 | N | 20 | Donor | GLN 49 | O | 410 | Acceptor |
| | 3AQB | -7.6 | 3 | N | 20 | Donor | VAL 158 | O | 1234 | Acceptor |
| | | | | O | 19 | Acceptor | TYR 156 | O | 1223 | Both |
| | | | | O | 18 | Acceptor | TYR 156 | O | 1223 | Both |
| | 3KHX | -6.8 | 0 | - | - | - | - | - | - | - |
| | 3M65 | -6.1 | 3 | N | 14 | Donor | HIS 170 | O | 1315 | Acceptor |
| | | | | N | 20 | Donor | SER 143 | O | 1119 | Both |
| | | | | O | 18 | Acceptor | TYR 139 | O | 1088 | Both |

found with acceptor bonds, whereas significant elements in receptor binding are oxygen and nitrogen both.

On docking analysis, designed compound A6 has been found to be strongly docked with the protein 1IKQ when binding with 6 different proteins have been observed in order to study its inhibition activity. When it is docked with the protein PDB ID- 1IKQ, it forms 3 hydrogen bonds with binding affinity of -7.6 Kcal/mol. On residue study, the amino acid SER 188 was found to be significant. On the account of ligand here nitrogen atom is significant in the binding, the type of binding found with donor bonds, whereas significant elements in receptor binding are oxygen.

On docking analysis, designed compound A7 has been found to be strongly docked with the protein 1IKQ when binding with 6 different proteins have been observed in order to study its inhibition activity. When it is docked with the protein PDB ID- 1IKQ, it forms 8 hydrogen bonds with binding affinity of -7.5 Kcal/mol. On residue study, the amino acids LYS 114, HIS 246, THR 134, GLU 270, HIS 262, GLU 391 and SER 188 were found to be significant. On the account of ligand here oxygen and nitrogen atoms are significant in the binding, the type of binding found with acceptor and donor bonds, whereas significant elements in receptor binding are oxygen and nitrogen both.

On docking analysis, designed compound A8 has been found to be strongly docked with the protein 3AQB when binding with 6 different proteins have been observed in order to study its inhibition activity. When it is docked with the protein PDB ID- 3AQB, it forms 3 hydrogen bonds with binding affinity of -7.6 Kcal/mol. On residue study, the amino acids VAL 158 and TYR 156 were found to be significant. On the account of ligand here oxygen atom is significant in the binding, the type of binding found with acceptor bonds, whereas significant elements in receptor binding are oxygen.

On docking analysis, designed compound A9 has been found to be strongly docked with the protein 3AQB when binding with 6 different proteins have been observed in order to study its inhibition activity. When it is docked with the protein PDB ID- 3AQB, it forms 3 hydrogen bonds with binding affinity of -8.2 Kcal/mol. On residue study, the amino acids VAL 158 and TYR 156 were found to be significant. On the account of ligand here oxygen atom is significant in the binding, the type of binding found with acceptor bonds, whereas significant elements in receptor binding are oxygen.

**Table 10: Docking Analysis of Synthesized Compound A9**

| Ligand | Receptor | Affinity Kcal/mol | H-bonds | H- Binding Ligand | | | H- Binding Receptor | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Elem. | At. ID. | Type | Res. | Elem. | At.ID. | Type |
| A9 | 1IKQ | -8 | 4 | O | 18 | Acceptor | SER 188 | O | 1416 | Both |
| | | | | N | 20 | Donor | SER 188 | O | 1416 | Both |
| | | | | N | 20 | Donor | SER 188 | O | 1414 | Acceptor |
| | | | | O | 15 | Acceptor | THR 134 | O | 1035 | Both |
| | 1R4Z | -6.2 | 1 | N | 20 | Donor | GLY 30 | O | 202 | Acceptor |
| | 2CCZ | -6.5 | 2 | O | 19 | Acceptor | CYS 80 | S | 640 | Donor |
| | | | | O | 19 | Acceptor | HIS 81 | N | 641 | Donor |
| | 3AQB | -8.2 | 3 | O | 19 | Acceptor | TYR 156 | O | 1223 | Both |
| | | | | O | 18 | Acceptor | TYR 156 | O | 1223 | Both |
| | | | | N | 20 | Donor | VAL 158 | O | 1234 | Acceptor |
| | 3KHX | -6.6 | 1 | O | 15 | Acceptor | THR 358 | O | 2968 | Both |
| | 3M65 | -6.5 | 2 | O | 18 | Acceptor | LYS 178 | N | 1387 | Donor |
| | | | | N | 20 | Donor | SER 169 | O | 1309 | Acceptor |

**Table 11: Docking Analysis of Synthesized Compound A10**

| Ligand | Receptor | Affinity Kcal/mol | H-bonds | H- Binding Ligand | | | H- Binding Receptor | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Elem. | At. ID. | Type | Res. | Elem. | At.ID. | Type |
| A-10 | 1IKQ | -9 | 5 | N | 19 | Donor | SER 188 | O | 1416 | Both |
| | | | | O | 22 | Acceptor | SER 188 | O | 1416 | Both |
| | | | | O | 22 | Acceptor | SER 192 | O | 1450 | Both |
| | | | | N | 06 | Donor | ALA 191 | O | 1443 | Acceptor |
| | | | | O | 08 | Acceptor | LEU 269 | N | 2061 | Donor |
| | 1R4Z | -7.1 | 1 | N | 06 | Donor | GLY 30 | O | 202 | Acceptor |
| | 2CCZ | -7 | 1 | O | 08 | Acceptor | LYS 82 | N | 654 | Donor |
| | 3AQB | -8.7 | 0 | - | - | - | - | - | - | - |
| | 3KHX | -7.1 | 1 | O | 17 | Acceptor | THR 398 | O | 2968 | Both |
| | 3M65 | -7.2 | 1 | N | 19 | Donor | HIS 170 | O | 1315 | Acceptor |

On docking analysis, designed compound A10 has been also found to be strongly docked with the protein 1IKQ when binding with 6 different proteins have been observed in order to study its inhibition activity. When it is docked with the protein PDB ID- 1IKQ, it forms 5 hydrogen bonds with binding affinity of -9 Kcal/mol. On residue study, the amino acids SER 188, SER 192, ALA 191 and LEU 269 were found to be significant. On the account of ligand here oxygen atom is significant in the binding, the type of binding found with acceptor bonds, whereas significant elements in receptor binding are oxygen.

On docking analysis, designed compound A11 has been found to be strongly docked with the protein 1IKQ when binding with 6 different proteins have been observed in order to study its inhibition activity. When it is docked with the protein PDB ID- 1IKQ, it forms 5 hydrogen bonds with binding affinity of -9.4 Kcal/mol. On residue study, the amino acids SER 188, SER 369, ALA 191 and ASN 393 were found to be significant. On the account of ligand here oxygen atom is significant in the binding, the type of binding found with acceptor bonds, whereas significant elements in receptor binding are oxygen.

On docking analysis, designed compound A12 has been found to be strongly docked with the protein 3M65 when binding with 6 different proteins have been

**Table 12: Docking Analysis of Synthesized Compound A11**

| Ligand | Receptor | Affinity Kcal/mol | H-bonds | H- Binding Ligand | | | H- Binding Receptor | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Elem. | At. ID. | Type | Res. | Elem. | At.ID. | Type |
| A-11 | 1IKQ | -9.4 | 5 | O | 19 | Acceptor | SER 369 | O | 2844 | Both |
| | | | | O | 24 | Acceptor | SER 369 | O | 2844 | Both |
| | | | | O | 08 | Acceptor | SER 188 | O | 1416 | Both |
| | | | | O | 19 | Acceptor | ASN 393 | N | 3004 | Donor |
| | | | | N | 21 | Donor | ALA 191 | O | 1443 | Acceptor |
| | 1R4Z | -7 | 0 | - | - | - | - | - | - | - |
| | 2CCZ | -6.9 | 2 | O | 19 | Acceptor | LYS 82 | N | 654 | Donor |
| | | | | O | 20 | Acceptor | MET 90 | N | 704 | Donor |
| | 3AQB | -8.7 | 0 | - | - | - | - | - | - | - |
| | 3KHX | -6.9 | 3 | O | 08 | Acceptor | ASN 278 | N | 2100 | Donor |
| | | | | N | 06 | Donor | ASN 331 | O | 2453 | Acceptor |
| | | | | O | 19 | Acceptor | THR 329 | O | 2438 | Both |
| | 3M65 | -7.5 | 2 | O | 08 | Acceptor | THR 150 | O | 1171 | Both |
| | | | | N | 06 | Donor | THR 150 | O | 1171 | Both |

**Table 13: Docking Analysis of Synthesized Compound A12**

| Ligand | Receptor | Affinity Kcal/mol | H-bonds | H- Binding Ligand | | | H- Binding Receptor | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Elem. | At. ID. | Type | Res. | Elem. | At.ID. | Type |
| A-12 | 1IKQ | -7.8 | 3 | O | 21 | Acceptor | SER 369 | O | 2844 | Both |
| | | | | O | 16 | Acceptor | SER 369 | O | 2844 | Both |
| | | | | O | 08 | Acceptor | SER 188 | O | 1416 | Both |
| | 1R4Z | -6.2 | 2 | O | 21 | Acceptor | ASN 4 | N | 17 | Donor |
| | | | | O | 17 | Acceptor | HIS 3 | N | 0 | Donor |
| | 2CCZ | -6.4 | 1 | O | 21 | Acceptor | LYS 82 | N | 654 | Donor |
| | 3AQB | -7.6 | 0 | - | - | - | - | - | - | - |
| | 3KHX | -6.5 | 1 | O | 08 | Acceptor | THR 398 | O | 2968 | Both |
| | 3M65 | -7 | 5 | O | 21 | Acceptor | TYR 139 | O | 1088 | Both |
| | | | | O | 16 | Acceptor | TYR 139 | O | 1088 | Both |
| | | | | O | 16 | Acceptor | SER 143 | O | 1119 | Both |
| | | | | O | 08 | Acceptor | THR 150 | O | 1171 | Both |
| | | | | O | 08 | Acceptor | HIS 170 | N | 1318 | Donor |

observed in order to study its inhibition activity. When it is docked with the protein PDB ID- 3M65, it forms 5 hydrogen bonds with binding affinity of -7 Kcal/mol. On residue study, the amino acids TYR 139, SER 143, THR 150 and HIS 170 were found to be significant. On the account of ligand here oxygen atom is significant in the binding, the type of binding found with acceptor bonds, whereas significant elements in receptor binding are oxygen.

On docking analysis, the standard drug CID_4539 has been found to be strongly docked with the protein 1IKQ when binding with 6 different proteins have been observed 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. On the account of ligand here oxygen atom

**Table 14: 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 |
| | 1R4Z | -6.2 | 1 | O | 23 | Both | GLN 29 | O | 193 | Acceptor |
| | 2CCZ | -6.1 | 0 | - | - | - | - | - | - | - |
| | 3AQB | -7.3 | 0 | - | - | - | - | - | - | - |
| | 3KHX | -6.3 | 0 | - | - | - | - | - | - | - |
| | 3M65 | -7.4 | 2 | O | 22 | Acceptor | THR 150 | O | 1171 | Both |
| | | | | O | 23 | Both | HIS 170 | O | 1315 | Acceptor |

is significant in the binding, the type of binding found with both acceptor and donor bonds, whereas significant elements in receptor binding are oxygen.

### Validation of QSAR Model

The 2D structure of sulphonamide derivatives from which the QSAR model has been developed is shown in Figure **1**. From the data in Table **15**, QSAR equation was developed where number of data point (n) is 25 and number of descriptors used are 3. The derived QSAR model is given below. Here 95% confidence intervals are given in parantheses.

*log1/C* = (4.192476)(0.8976384) + (0.3564435)(AlogP) (0.220396) + (0.0073582)(ECI)(0.0028634) + (-0.4004489) (LAI)(0.1360423)

A comparison (multiple linear regression curve) of observed values and predicted values of *log1/C* for sulphonamide derivatives used for development of QSAR equation is shown in Figure **2**.

A quantitative assessment of model robustness has been performed through model validation. All the statistical results of model validation have been given in Table **16**.

### 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. The value for this QSAR model is 0.765.

***(3)*** ***Cross-Validation Test ($q^2$)*:** A QSAR model must have $q^2 > 0.5$ for the predictive ability. The value of $q^2$ for this QSAR model is 0.7784.

***(4)*** ***Standard deviation (s)*:** The smaller s value is always required for the predictive QSAR model. The value of s for this QSAR model is 0.4.

***(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. The value of $r^2$-$q^2$ for this QSAR model is -0.013.

***(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. The F value of this QSAR model is 19.36 (where $F > F_{lit}$) suggests that the QSAR model is statistically significant at 95% level.

### Evaluation of Designed Compounds (A1-A12) from QSAR Model Developed

All the designed and synthesized compounds have been filtered with the developed QSAR model and their log1/C values have been predicted which is given in Table **17**.

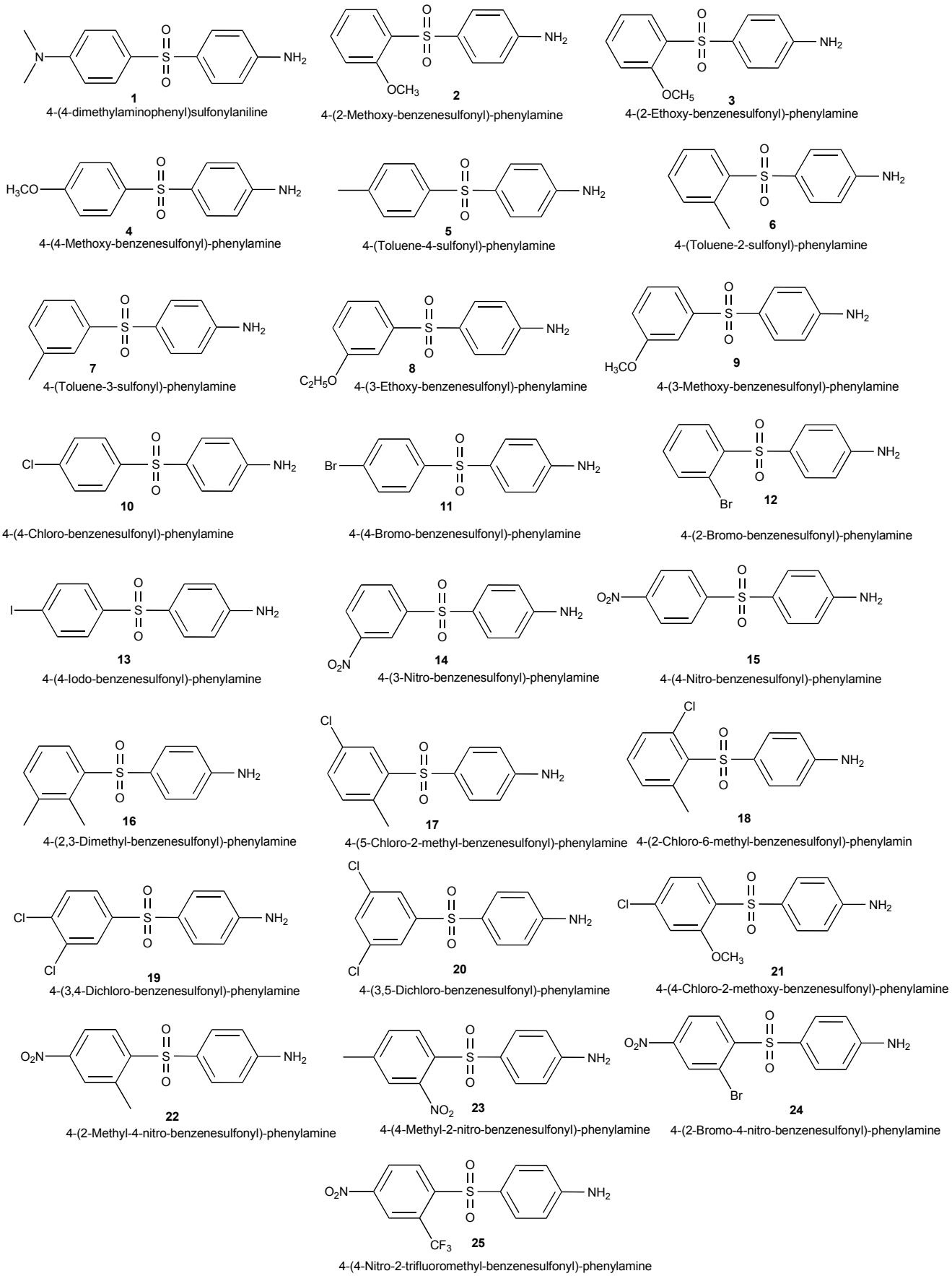



**Figure 1:** Structures of sulphonamide derivatives for developing the QSAR model.

**Table 15: log1/C Values and Descriptors of Sulphonamide Derivatives Used to Derive QSAR Equation**

| Compound S. No. | log1/C | | | AlogP | ECI | LAI |
|---|---|---|---|---|---|---|
| | Observed | Predicted | Difference | | | |
| 1 | 4.35 | 4.57 | -0.22 | 0.0623 | 325 | 5.0764 |
| 2 | 4.45 | 4.41 | 0.04 | -0.2073 | 260 | 4.0409 |
| 3 | 4.35 | 4.59 | -0.24 | 0.0431 | 294 | 4.4324 |
| 4 | 4.47 | 4.76 | -0.29 | -0.2073 | 304 | 3.9765 |
| 5 | 4.66 | 4.68 | -0.02 | 0.7377 | 262 | 4.2386 |
| 6 | 4.46 | 4.54 | -0.08 | 0.7377 | 243 | 4.2519 |
| 7 | 4.6 | 4.55 | 0.05 | 0.7377 | 245 | 4.2478 |
| 8 | 4.8 | 4.79 | 0.01 | 0.0431 | 321 | 4.4250 |
| 9 | 4.8 | 4.56 | 0.24 | -0.2073 | 279 | 4.0021 |
| 10 | 4.89 | 4.88 | 0.01 | 0.66 | 262 | 3.6797 |
| 11 | 4.89 | 4.92 | -0.03 | 0.744 | 262 | 3.6550 |
| 12 | 4.99 | 4.84 | 0.15 | 0.744 | 243 | 3.5094 |
| 13 | 4.95 | 4.82 | 0.13 | 0.5738 | 262 | 3.7559 |
| 14 | 5.6 | 5.36 | 0.24 | 0.5046 | 298 | 3.0092 |
| 15 | 6 | 5.58 | 0.42 | 0.5046 | 325 | 2.9494 |
| 16 | 4.32 | 4.73 | -0.41 | 1.1841 | 260 | 4.4875 |
| 17 | 4.8 | 4.92 | -0.12 | 1.1064 | 260 | 3.9342 |
| 18 | 4.8 | 4.92 | -0.12 | 1.1064 | 258 | 3.9074 |
| 19 | 5.4 | 5.30 | 0.1 | 1.0287 | 279 | 3.2765 |
| 20 | 5.55 | 5.15 | 0.4 | 1.0287 | 262 | 3.3275 |
| 21 | 5.1 | 4.92 | 0.18 | 0.1614 | 294 | 3.7230 |
| 22 | 5.55 | 5.73 | -0.18 | 0.951 | 340 | 3.2527 |
| 23 | 5.41 | 5.45 | -0.04 | 0.951 | 311 | 3.3990 |
| 24 | 5.64 | 6.10 | -0.46 | 0.9573 | 340 | 2.3351 |
| 25 | 5.32 | 5.00 | 0.32 | 1.4071 | 391 | 6.4116 |

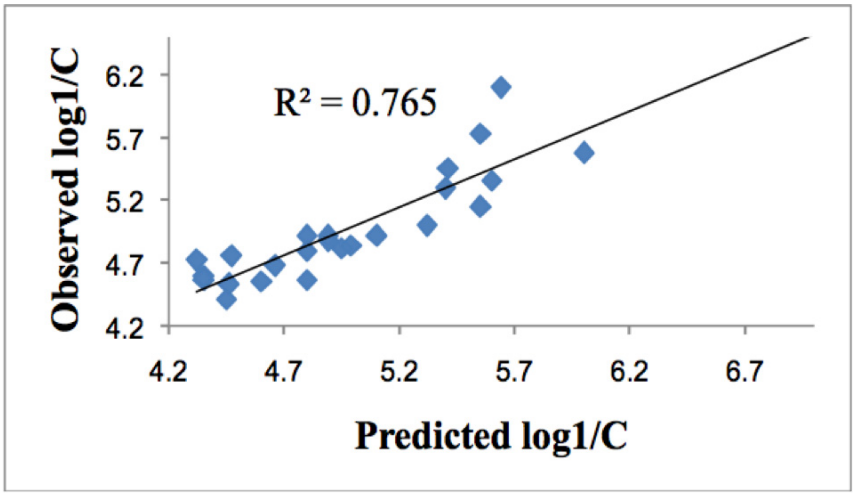



**Figure 2:** A plot of observed values and predicted values of log1/C for sulphonamide derivatives.

**Table 16: Statistical Results of Model Validation**

| n/p(>=4) | $r^2$ | $q^2$ | $r^2$-$q^2$ < 0.3 | RMSD | Q | variance | F |
|---|---|---|---|---|---|---|---|
| 8.33 | 0.765 | 0.7784 | -0.013 | 0.0451 | 1.97 | 0.0607 | 19.36 |

**Table 17: Descriptors and Predicted log1/C Values of Designed Compounds**

| Compound S. No. | Predicted log1/C | AlogP | ECI | LAI |
|---|---|---|---|---|
| A1 | 3.442427 | -4.1763 | 341 | 0 |
| A2 | 3.442073 | -4.2087 | 445 | 0 |
| A3 | 3.528493 | -3.5416 | 298 | -0.68119 |
| A4 | 3.436394 | -4.2531 | 341 | 0 |
| A5 | 3.480161 | -3.5988 | 360 | 0.147473 |
| A6 | 3.450361 | -3.8366 | 326 | 0.338429 |
| A7 | 3.429939 | -3.6508 | 418 | 1.016806 |
| A8 | 3.362193 | -5.192 | 320 | 0 |
| A9 | 3.416152 | -4.07 | 387 | 0.653385 |
| A10 | 3.432445 | -3.9882 | 455 | 0.498572 |
| A11 | 3.432425 | -4.0206 | 574 | 0.498234 |
| A12 | 3.519576 | -3.3535 | 405 | -0.20488 |

An *in-silico* evaluation have been performed which include the QSAR and docking studies. On QSAR study the predicted bioactivity values (*log1/C*) were found between 3.362193 and 3.528493. On the other hand, docking studies showed three proteins which significantly inhibited by the designed compounds , which are 1IKQ- Pseudomonas aeruginosa exotoxin A (inhibited by compounds A1, A2, A3, A4, A5, A6, A7, A10 and A11), 3AQB- heterodimeric hexaprenyl diphosphate synthase (inhibited by compounds A8 and A9) and 3M65- Bacillus subtilis Lon protease (inhibited by compound A12).

## CONCLUSION

In order to obtain substituted acyl chlorides, substituted acids were treated with thionyl chloride and then substituted acyl chloride/substituted benzyl chloride/substituted chlorobenzene were treated with aminosulfonamides in the presence of pyridine for obtaining the substituted 4-amino-benzenesulfonamides/N-acetyl-4-amino-benzenesulfonamides. The structures of synthesized compounds were confirmed by physical, analytical and elemental analysis.

The docking result of standard drug taken CID_4539 (Norfloxacin) correlates well with the performance of compounds A1, A2, A3, A4, A5, A6, A7, A10 and A11 in docking study. Hence, it could be concluded that molecular target responsible for the antimicrobial activity of substituted 4-amino-benzenesulfonamides/N-acetyl-4-amino-benzenesulfonamides may be pseudomonas aeruginosa exotoxin A. The other remaining proteins 1R4Z- Bacillus subtilis lipase A, 2CCZ- E-coli primosomal protein and 3KHX- Staphylococcus aureus metallopeptidase also showed prominent inhibition by the designed molecules. Although a systemic biochemical study of synthesized compounds is necessary to confirm the findings.

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