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RESEARCH ARTICLE

Design, molecular docking, synthesis, characterization, biological activity evaluation (against MES model), *in-silico* biological activity spectrum (PASS analysis), toxicological and predicted oral rat LD_{50} studies of novel sulphonamide derivatives

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BACKGROUND: Among the reported potential agents to treat the epilepsy, sulphonamides are important and their significance cannot be ignored. A series of substituted 4-amino-benzene sulfonamides were designed, keeping in view the structural requirement of pharmacophore.
METHODS: Lipinski rule of five has been calculated; failure to Lipinski rule was not observed. Docking was performed through AutoDock Vina. Molecules have been screened out through docking. Compounds were synthesized and characterized through IR, ^{1}HNMR, ^{13}C NMR, Mass and elemental analysis. The anticonvulsant activity of the synthesized compounds was assessed using the Maximal Electroshock Seizure (MES) model. *In-silico* biological activity spectrum, toxicological studies, predicted oral rats LD50 were performed.
RESULTS: Docking studies showed good interaction with lyase (Oxo-acid) - human carbonic anhydrase-I (1AZM). The *in-silico* studies proved them to be with good drug-likeness properties, especially 4-(3-Acetyl-phenylamino)-methyl)-benzenesulfonamide (2g). These results revealed that the synthesized compounds **(1a-1c, 2a-2q)** exhibited promising anticonvulsant effect against MES model for inhibition of Lyase- Human Carbonic Anhydrase-I.
CONCLUSION: After investigating all the results, the compound 4-(3-Acetyl-phenylamino)-methyl)-benzenesulfonamide (2g) is found to be best in the series. A comparatively good activity of compound **2g** suggests us that sulphonamide can be leads to further optimization for building potent and chemically diversified anti-convulsant agents.

Keywords anticonvulsant, sulfonamide, docking, *in-silico* studies

Introduction

Epilepsy is one of the serious disorders with no age, sex, geographical, social class or racial boundaries. Epilepsy imposes a large economic burden on health care systems of countries. There is also a hidden burden associated with stigma and discrimination against the patient and even their family in the community, workplace, and home. In general, the patients with epilepsy suffer severe emotional distress, behavioral disorders and extreme social isolation (Satischandra et al., 2005).

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Epilepsy is usually associated with recurrent seizures. The word “epilepsy” is derived from Latin and Greek words for “seizure” or “to seize upon.” This implies that epilepsy is an ancient disorder; indeed, in all civilizations it can be traced as far back as medical records exist. In fact, epilepsy is a disorder that can occur in all mammalian species, probably more frequently as brains have become more complex. Epilepsy is also remarkably uniformly distributed around the world. There are no racial, geographical or social class boundaries. It occurs in both sexes, at all ages, especially in childhood, adolescence and increasingly in aging populations (Reynolds, 2002).

Among the reported potential agents to treat the epilepsy, sulphonamides are important and their significance cannot be ignored. Sulphonamides are of high attention for various pharmacological importance, as it is reported for chiefly

anticonvulsant (Masereel et al., 2002; Thiary et al., 2008), antitubercular (Price et al., 1952; Vannada et al., 2006) and antimicrobial activities.(Perrin et al., 1937; Heidi et al., 2005) For all these activities, the sulphonamide derivatives are reported with multiple scaffolds such as Sulfonamides incorporating Valproyl derivatives, Sulfamates, Sulfamides, Thiazolidin derivatives, Aminobenzamides, Beta-Ketosulfonamide etc.(Perrin et al., 1937; Price et al., 1952; Masereel et al., 2002; Heidi et al., 2005; Vannada et al., 2006; Thiary et al., 2008).

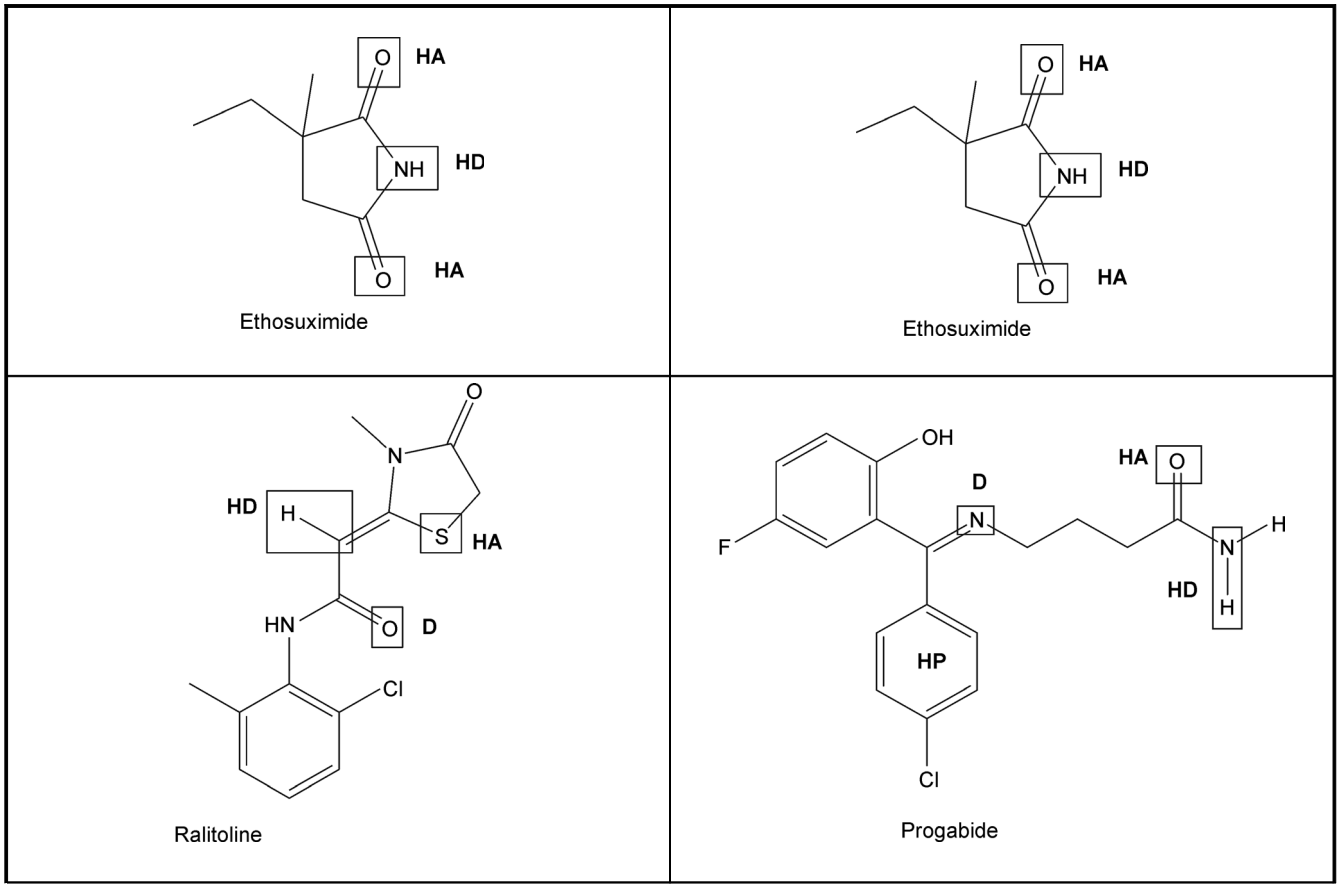
Being inspired from the previous developments, there is always an enthusiasm to design of novel sulphonamide with many scaffolds and to evaluate their possible pharmacological properties as well as mechanism of action. These novel designs will support for future drug developments for multiple diseases in human health care. There is always a chance to get a potential compound on hit and trial basis for design. Beyond this, at present multi-disciplinary protocols are being suggested to screen the designed-only compounds through computational methods to get the possibility of pharmacological importance of compounds prior to their synthesis and *in-vitro* experiments. Sequential computational procedures include: (i) Collection of information about scaffolds, linkers and side-groups for possible novel compound; (ii) Structural designing of location specific derivative combinations with one or more scaffold; (iii) Virtual-screening of activity of designed compounds through structure-activity-relationship (SAR) models; (vi) Ligand-protein docking studies of designed compounds; (v) Toxicity estimation of designed compound and (vi) Evaluation of possible pharmacological properties designed compounds.

Material and methods

Designing of molecules

Identification of pharmacophoric groups was done from the structures of well known anticonvulsants. The structures of well known anticonvulsants and identified pharmacophore are presented in Table 1 (Barbara, 2003; Tripathi et al., 2012). The essential structural features which could be responsible for an interaction with the active site were a hydrophobic (HP) unit, an electron donor (D) group, and a hydrogen donor/acceptor (HD / HA) unit.

Table 1 Pharmacophoric pattern of well-known anticonvulsants



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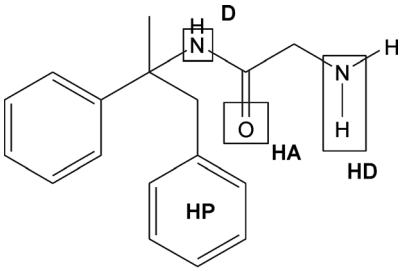
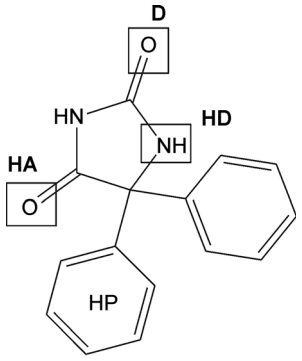
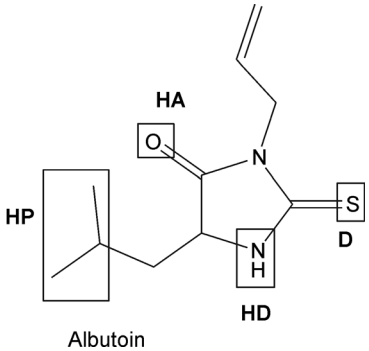


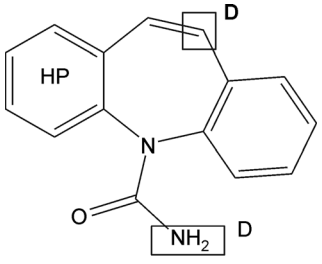
Remacemide



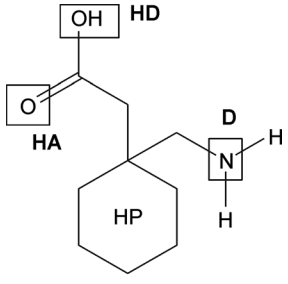
Phenytoin



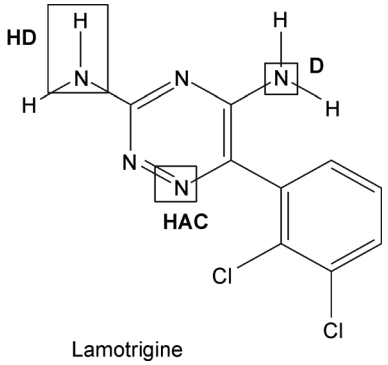
Albutoin



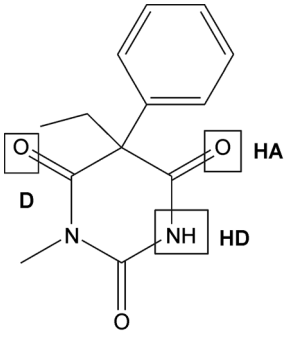
Carbamazepine



Gabapentin

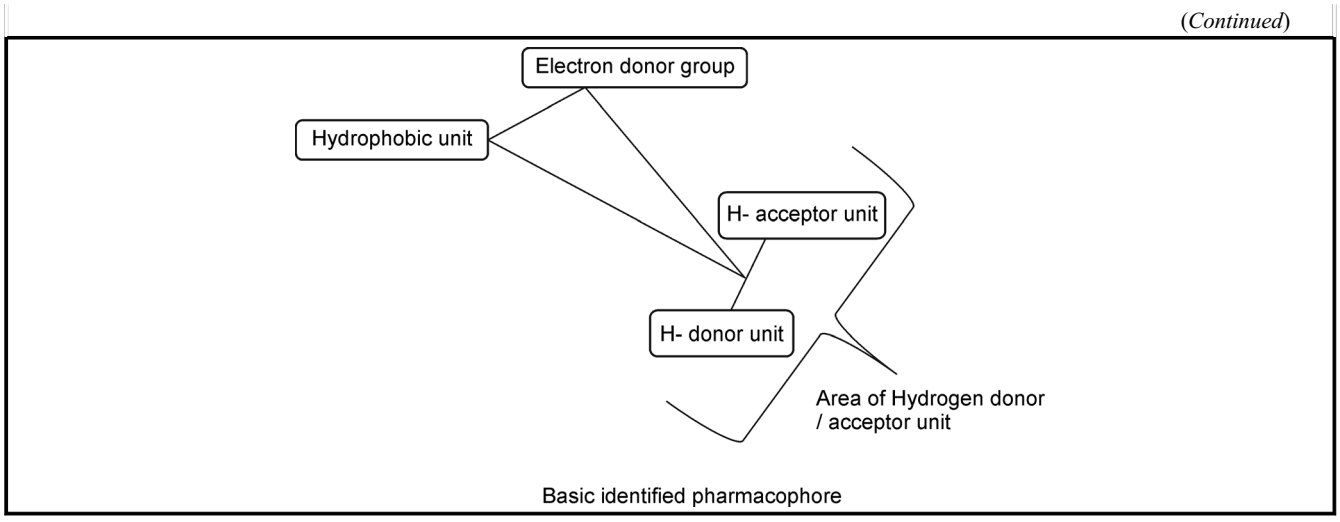


Lamotrigine



Methylphenobarbital

(*Continued*)



Docking studies

Docking tool

Docking was performed with AutoDock Vina (PyRx-Python Prescription 0.8) docking software (Trott and Olson, 2010) . 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 (Reynolds et al., 2010).

Receptor

Lyase (Oxo-acid) - Human Carbonic Anhydrase-I.

Experimental

Chemistry

All the chemicals and solvents, purchased from Merck (India), Spectrochem (India), Sigma-Aldrich (India), Hi-Media (India) and S. D. Fine (India) were used without further purification. Thin layer chromatographic (TLC) 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^2 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. The ^{1}H-NMR spectra were recorded on Avance-III, Bruker, 400 MHz High Resolution NMR spectrometer and C13-NMR were recorded with Avance-III, Bruker, 100 MHz. Signals were described as singlet (s), doublet (d), triplet (t) and multiplet (m). FT-IR spectra (KBr) were recorded on a Perkin-Elmer Spectrometer BX-II spectrophotometer. The mass spectra were recorded on a Waters Micro-Mass ZQ 2000 mass spectrometer.

Synthetic schemes

Mechanism of reaction

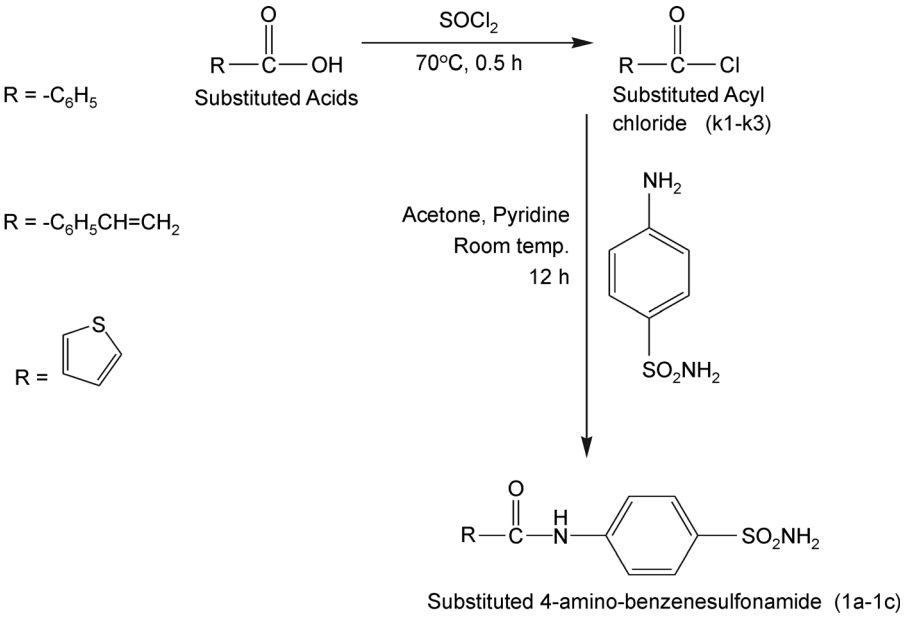
A reaction mechanism of given schemes has been depicted in Fig. 3.

Synthesis of substituted acyl chlorides

The compounds **(k1-k3)** were synthesized as shown in scheme 1. Substituted acid (0.1 mol) and thionyl chloride (0.4 mol) were placed in a 250 ml flask equipped with a magnetic stirrer bead and a condenser with a drying tube. The reaction mixture was heated at 70°C in an oil bath and product obtained (Naama et al., 2010) .

Synthesis of substituted 4-amino-benzenesulfonamides

Further, for the synthesis of an appropriate amide **(1a-1c, 2a-2q)**, substituted acyl chloride / substituted benzyl chloride / substituted chlorobenzene (0.009 mol) of an individual acid dissolved in 20 ml. of dry acetone was added drop wise to a stirred solution of suitable aminosulfonamide (0.0092 mol) and pyridine (0.0091mol) in 50 ml. of dry acetone (Scheme 2). After addition, the reaction mixture was stirred for about 12 h 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 (3×20 ml). 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 (3×50 ml). The ethyl acetate



Scheme 1. Synthetic scheme of substituted 4-amino-benzenesulfonamide from substituted acids **(1a-1c)**

extracts were combined and dried over $MgSO_4$ and product obtained **(1a-1c, 2a-2q)** was filtered and evaporated under reduced pressure (Naama et al., 2010) .

Pharmacology

Anticonvulsant activity

Animals

Rats of weight (125–160 g) were used to study the effect of test drug on MES induced seizures via "Electro convulsometer." Female animals were excluded because of the fact that estrus cycle influences the seizure threshold. The protocol for animal based experiments was approved by Institutional Animal Ethical Committee, IFTM University, Moradabad (Resolution no. 2015/837ac/PhD/04) as per guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA, India). Animals were housed in polypropylene cages with dust free rice husk as a bedding material under laboratory condition with controlled environment of temperature 25±2°C, humidity (60%±10%) and 12 h light/dark cycle as per CPCSEA guidelines. They were provided with balanced food and water, before subjecting them to experimentation, the animals were given a week's time to get acclimatized with the laboratory conditions. The animals were fasted overnight before the experiment.

The synthesized compounds were suspended in 0.5% methyl cellulose and the test compound was usually manipulated with a mortar pestle to help preparation of suspension. In the preliminary screening by MES, each compound was administered, at dose level of 100 mg/kg (oral) and anticonvulsant and neurotoxicity was assessed at 30 min and 2 h intervals after administration with different groups at each time interval having same species of animals.

The Maximal electroshock seizure (MES) model or maximal seizure pattern test

In the MES test, an electrical stimulus of 0.2 s in duration (150 mA in rat at 60Hz) is delivered via trans-auricular electrodes. Rats are tested at time intervals between 30 min. and 2h following a standard dose of 100 mg/kg (oral). Abolition of the hind limb tonic extensor component indicates the test compound's ability to inhibit MES-induced seizure spread. Control animals were also treated with the same MES procedure as of the test animals. Different behavioral phases under MES model including Flexion (legs in particular are bent), Extensor (arms and legs being flung outwards), Clonus (sustained rhythmical jerking) and Stupor (reduced level of consciousness) were also recorded for their duration of action (second) so that a reduction in duration of phases can be observed as an additional parameter for MES.

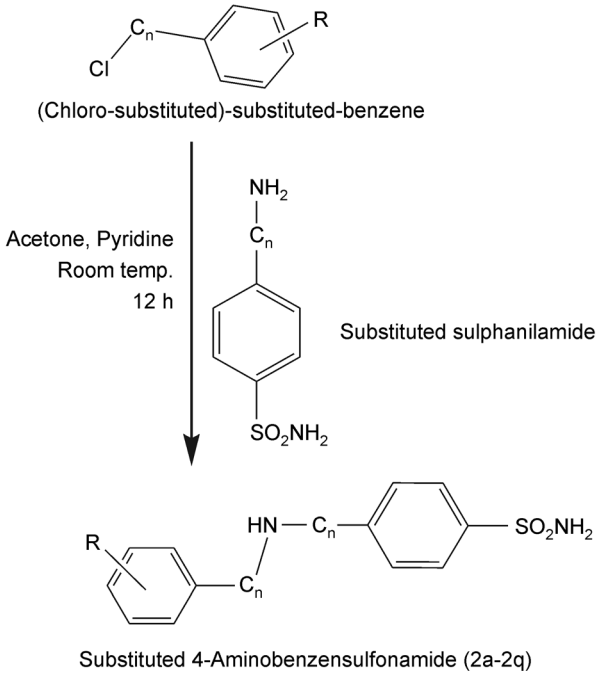
Minimal neurotoxicity

For minimal toxicity, 3 assessments i.e. rota rod test positional sense test, and gait and stance test were used.

Toxicity induced by a compound is detected in rats using the standard rota rod test. Untreated control rats, when placed on a 6 r/min. Rotation rod can maintain their equilibrium for a prolonged period of time. Neurological impairment can be demonstrated by the inability of a mouse to maintain equilibrium for one minute in each of three successive trials.

Rats are examined for behavioral toxicity by the positional sense test and a gait and stance test. In the positional sense test, one hind leg is gently lowered over the edge of a table,

Comp. No.	R	n for (Chlorosubstituted)-substituted benzene	n for substituted Sulphanilamide
2a	*p*-NH_2	0	1
2b	*p*-$COCH_3$	0	1
2c	*m*-OCH_3	0	1
2d	*o*-OCH_3	0	1
2e	*m*-NH_2	0	1
2f	*o*-NH_2	0	1
2g	*m*-$COCH_3$	0	1
2h	*p*-NH_2	1	1
2i	*m*-NH_2	1	1
2j	*p*-$COCH_3$	1	1
2k	*m*-$COCH_3$	1	1
2l	*p*-NH_2	2	2
2m	*m*-NH_2	2	2
2n	*o*-NH_2	2	2
2o	*p*-OCH_3	2	2
2p	*m*-OCH_3	2	2
2q	*m*-OCH_3	2	2



Scheme 2. Synthetic scheme of substituted 4-amino-benzenesulfonamide from (Chloro-substituted)-substituted benzene **(2a-2q)**

whereupon the rat, experiencing neurological deficit, will fail to lift its leg quickly back to a normal position. In the gait and stance test, neurotoxicity is indicated by a circular or zigzag gait, ataxia, abnormal spread of the legs, abnormal posture, tremor, hyperactivity, lack of exploratory behavior and stupor. Neurotoxicity tests have been carried with a dose of 100 mg/kg bodyweight at 30 min. and at 4 h from dose administration.

In-silico studies

In-silico biological activity spectrum

The biological activity spectrum of a chemical compound is the set of different types of biological activity that reflect the results of the compound's interaction with various biological entities. Biological activity is defined qualitatively (“yes”/ ”none”) suggesting that the biological activity spectrum represents the “intrinsic” property of a substance depending only on its structure and physical-chemical characteristics.

PASS (Prediction of Activity Spectra for Substances)(Filimonov et al., 1995) is a software product designed as a tool for evaluating the general biological potential of an organic drug like molecule. PASS provides simultaneous predictions of many types of biological activity based on the structure of organic compounds. Thus, we have used PASS to estimate the biological activity profiles for virtual molecules.

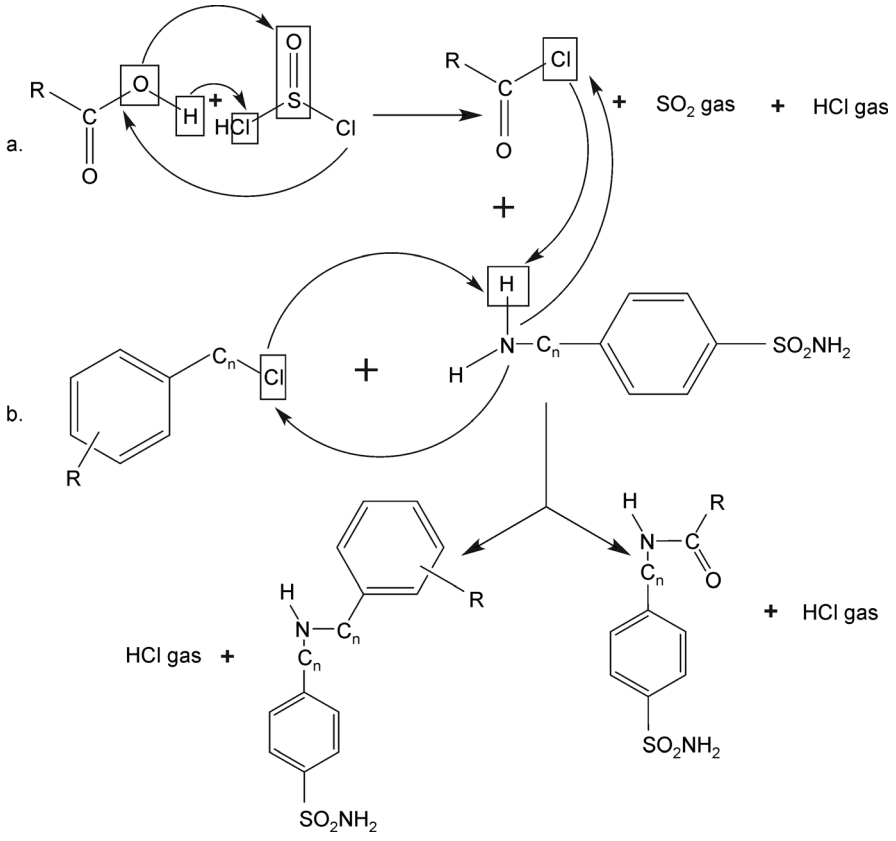


Figure 3 Common reaction mechanism of schemes employed.

Probability "to be active" estimates the chance that the studied compound is belonging to the sub-class of active compounds (resembles the structures of molecules, which are the most typical in a sub-set of "actives" in PASS training set).

Predictive toxicology

Mutagenicity

It's a capacity to induce mutation, as it said in genetics, a mutagen is a physical or chemical agent that changes the genetic material, usually DNA, of an organism and thus increases the frequency of mutations above the natural background level.

Irritants

Irritants are chemicals that cause reversible skin damage (unlike corrosion, which is irreversible). Clinical signs of irritation include the development of a rash, inflammation, swelling, scaling, and abnormal tissue growth in the affected area.

In-silico mutagenicity and skin irritancy studies

The Ames laboratory test was developed in the 1970s by Bruce Ames, Professor of Biochemistry at UC-Berkeley, as a fast and sensitive assay of the ability of a chemical compound or mixture to induce mutations in DNA.

Ames *in-silico* test was performed for finding probability of being mutagenic and skin irritant with the help of trial version of Discovery Studio 3.5 using TOPKAT® (Toxicity Prediction by Komputer Assisted Technology)(Venkatapathy et al., 2004) and freely available version of TEST 4.2.1 (Toxicity Estimation Software Tool) (US EPA, 2016) using Consensus method.

Predicted Oral rat LD50

Lethal dose (LD50) is the amount of an ingested chemical substance that kills 50 percent to test animal. It is expressed in mg/kg, or milligrams of substance per kilogram of body-weight. Commonly it is known as lethal doses.

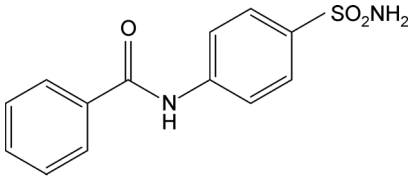
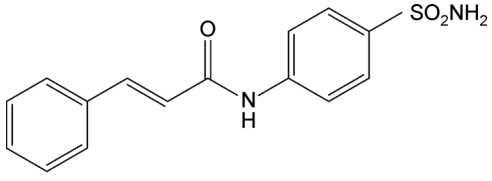
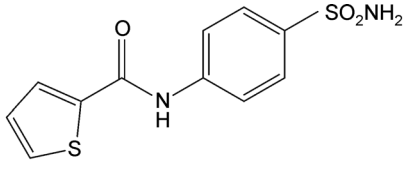
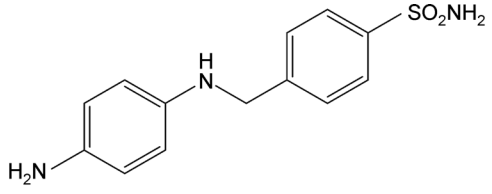
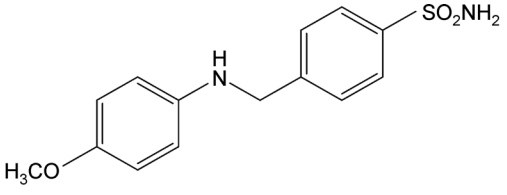
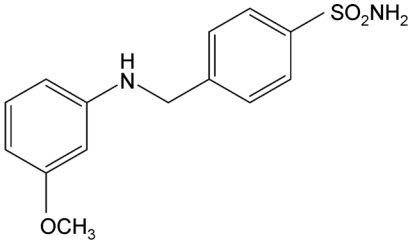
Predicted oral rat LD50 has been calculated with help of freely available version of TEST 4.2.1 (Toxicity Estimation Software Tool) (US EPA, 2016) using Consensus method.

Results and discussion

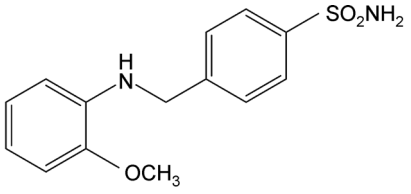
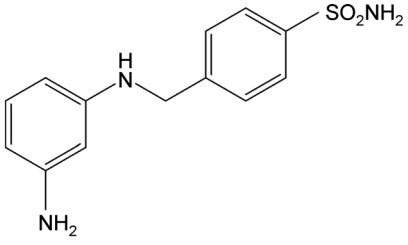
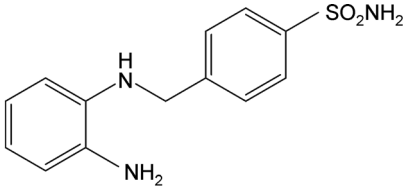
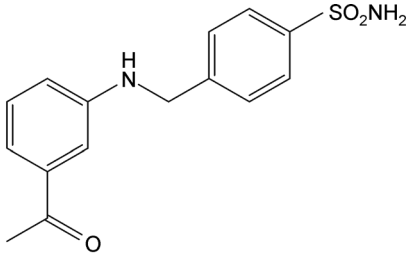
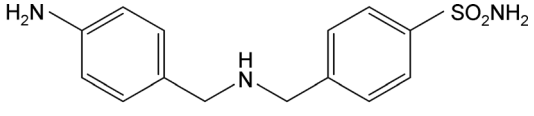
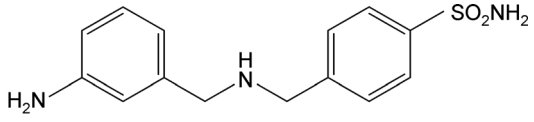
Designed molecules

A list of designed molecules have been shown in Table 2.

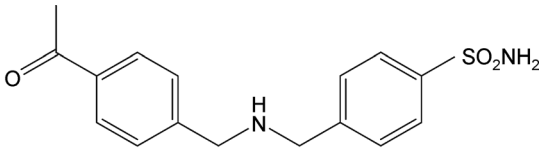
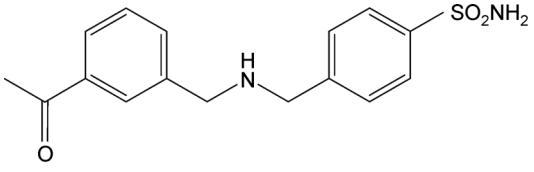
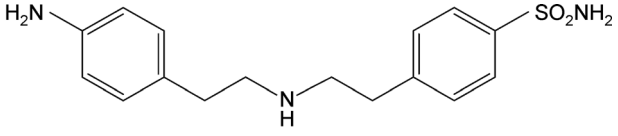
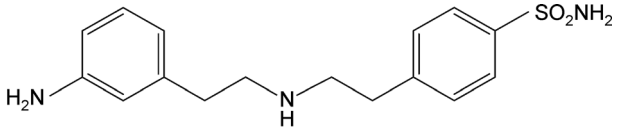
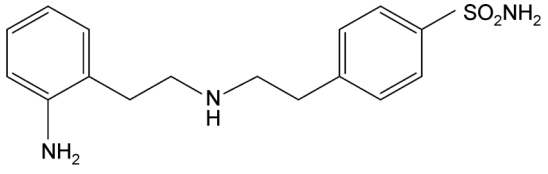
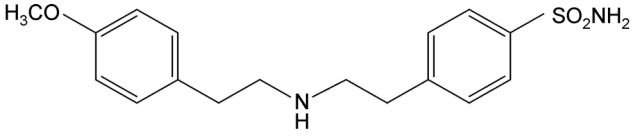
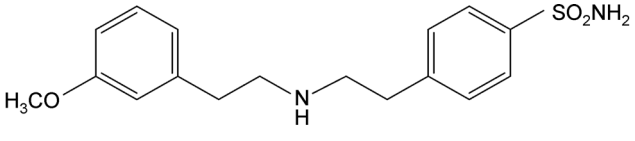
Table 2 Designed molecules

Compound	Structure
1a	 *N*-(4-Sulfamoyl-phenyl)-benzamide
1b	 3-Phenyl-*N*-(4-sulfamoyl-phenyl)-acrylamide
1c	 Thiophene-2-carboxylic acid (4-sulfamoyl-phenyl)-amide
2a	 4-[(4-Amino-phenylamino)-methyl]-benzenesulfonamide
2b	 4-[(4-Methoxy-phenylamino)-methyl]-benzenesulfonamide
2c	 4-[(3-Methoxy-phenylamino)-methyl]-benzenesulfonamide

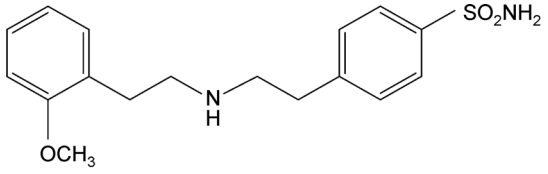
(*Continued*)

Compound	Structure
2d	 4-[(2-Methoxy-phenylamino)-methyl]-benzenesulfonamide
2e	 4-[(3-Amino-phenylamino)-methyl]-benzenesulfonamide
2f	 4-[(2-Amino-phenylamino)-methyl]-benzenesulfonamide
2g	 4-[(3-Acetyl-phenylamino)-methyl]-benzenesulfonamide
2h	 4-[(4-Amino-benzylamino)-methyl]-benzenesulfonamide
2i	 4-[(3-Amino-benzylamino)-methyl]-benzenesulfonamide

(*Continued*)

Compound	Structure
2j	 4-[(4-Acetyl-benzylamino)-methyl]-benzenesulfonamide
2k	 4-[(3-Acetyl-benzylamino)-methyl]-benzenesulfonamide
2l	 4-{2-[2-(4-Amino-phenyl)-ethylamino]-ethyl}-benzenesulfonamide
2m	 4-{2-[2-(3-Amino-phenyl)-ethylamino]-ethyl}-benzenesulfonamide
2n	 4-{2-[2-(2-Amino-phenyl)-ethylamino]-ethyl}-benzenesulfonamide
2o	 4-{2-[2-(4-Methoxy-phenyl)-ethylamino]-ethyl}-benzenesulfonamide
2p	 4-{2-[2-(3-Methoxy-phenyl)-ethylamino]-ethyl}-benzenesulfonamide

(*Continued*)

Compound	Structure
2q	 4-{2-[2-(2-Methoxy-phenyl)-ethylamino]-ethyl}-benzenesulfonamide

Lipinski rule of five

An initial descriptor calculation has also performed in order to observe designed compounds with its drug ability property (Lipinski Rule of Five). (Table 3).

Lipinski rule of five (Leeson, 2012) helps in distinguishing between drug like and non drug like molecules. It predicts high probability of success or failure due to drug likeness for molecules complying with 2 or more of the following rules-

- Molecular mass less than 500 Dalton
- High lipophilicity (AlogP less than 5)
- Less than 5 hydrogen bond donors (nHBD)
- Less than 10 hydrogen bond acceptors (nHBA)
- Molar refractivity (MR) should be between 40 and 130
- This filter helps in early preclinical development and could help avoid costly late-stage preclinical and clinical failures.

None of the designed molecules are found to be Lipinski failure. Hence, it implies that all the 20 designed compounds have the drug ability properties / drug likeness properties. So, it may be concluded that all these designed molecules may proceed for further screening.

Docking

For performing docking, all receptors have been downloaded from NCBI website with PDB ID 1AZM (Lyase- Human Carbonic Anhydrase-I), all the designed ligands have been docked with protein (receptor) with AutoDock Vina (PyRx-Python Prescription 0.8) (Trott and Olson, 2010) software having its default settings.

Docking study of different proteins were performed with the designed inhibitors is given in Table 4, Fig. 4; number of hydrogen bonds and binding pattern such as element, type of bond, atom number and residue at binding site were evaluated.

Table 3 Descriptors of Lipinski Rule of Five

Comp.	Molec. mass	AlogP	nHBD	nHBA	MR	Lipinski failure
1a	276.0569	0.1463	2	5	77.93	0
1b	302.0725	0.5074	2	5	88.1735	0
1c	282.0133	–0.5031	2	5	75.1944	0
2a	277.0885	–0.8244	2	5	82.0505	0
2b	292.0882	–0.1263	2	5	85.1442	0
2c	292.0882	–0.1263	2	5	85.1442	0
2d	292.0882	–0.1263	2	5	85.1442	0
2e	277.0885	–0.8244	2	5	82.0505	0
2f	277.0885	–0.8244	2	5	82.0505	0
2g	304.0882	–0.0772	2	5	88.051	0
2h	291.1041	–0.5616	2	5	86.2149	0
2i	291.1041	–0.5616	2	5	86.2149	0
2j	318.1038	0.1856	2	5	92.2154	0
2k	318.1038	0.1856	2	5	92.2154	0
2l	319.1354	0.00254	3	5	95.1185	0
2m	319.1354	0.00254	3	5	95.1185	0
2n	319.1354	0.00254	3	5	95.1185	0
2o	334.1351	0.419515	2	5	98.2122	0
2p	334.1351	0.419515	2	5	98.2122	0
2q	334.1351	0.419515	2	5	98.2122	0

Table 4 Docking results of all the compounds with receptor 1AZM

Ligand	Affinity kcal/mol	H-bond	H- binding ligand			H- binding receptor			
			Elem	At. ID	Type	Residue	Elem	At.ID	Type
1a	−7.7	6	O	19	Acceptor	Thr199	N	196	Donor
			O	19	Acceptor	Thr199	O	201	Both
			N	20	Donor	Thr199	O	201	Both
			N	20	Donor	His96	N	94	Acceptor
			N	20	Donor	His94	N	82	Acceptor
			O	18	Acceptor	His119	N	113	Donor
1b	−7.7	7	O	21	Acceptor	Thr199	N	196	Donor
			O	21	Acceptor	Thr199	O	201	Both
			N	22	Donor	Thr199	O	201	Both
			N	22	Donor	His96	N	94	Acceptor
			N	22	Donor	His94	N	82	Acceptor
			O	20	Acceptor	His119	N	113	Donor
			O	9	Acceptor	Gln92	N	69	Donor
1c	−7.2	7	O	18	Acceptor	Thr199	N	196	Donor
			O	18	Acceptor	Thr199	O	201	Both
			N	19	Donor	Thr199	O	201	Both
			N	19	Donor	His96	N	94	Acceptor
			N	19	Donor	His94	N	82	Acceptor
			O	17	Acceptor	His119	N	113	Donor
			O	9	Acceptor	Gln92	N	69	Donor
2a	−7.3	6	O	21	Acceptor	Thr199	N	196	Donor
			O	21	Acceptor	Thr199	O	201	Both
			N	22	Donor	Thr199	O	201	Both
			N	22	Donor	His96	N	94	Acceptor
			N	22	Donor	His94	N	82	Acceptor
			O	20	Acceptor	His119	N	113	Donor
2b	−7.3	6	O	20	Acceptor	Thr199	N	196	Donor
			O	20	Acceptor	Thr199	O	201	Both
			N	21	Donor	Thr199	O	201	Both
			N	21	Donor	His96	N	94	Acceptor
			N	21	Donor	His94	N	82	Acceptor
			O	19	Acceptor	His119	N	113	Donor
2c	−7.3	6	O	20	Acceptor	Thr199	N	196	Donor
			O	20	Acceptor	Thr199	O	201	Both
			N	21	Donor	Thr199	O	201	Both
			N	21	Donor	His96	N	94	Acceptor
			N	21	Donor	His94	N	82	Acceptor
			O	19	Acceptor	His119	N	113	Donor
2d	−7.3	6	O	20	Acceptor	Thr199	N	196	Donor
			O	20	Acceptor	Thr199	O	201	Both
			N	21	Donor	Thr199	O	201	Both
			N	21	Donor	His96	N	94	Acceptor
			N	21	Donor	His94	N	82	Acceptor
			O	19	Acceptor	His119	N	113	Donor
2e	−7.3	6	O	21	Acceptor	Thr199	N	196	Donor
			O	21	Acceptor	Thr199	O	201	Both
			N	22	Donor	Thr199	O	201	Both
			N	22	Donor	His96	N	94	Acceptor
			N	22	Donor	His94	N	82	Acceptor
			O	20	Acceptor	His119	N	113	Donor

(*Continued*)

Ligand	Affinity kcal/mol	H-bond	H- binding ligand			H- binding receptor			
			Elem	At. ID	Type	Residue	Elem	At.ID	Type
2f	−7.2	6	O	21	Acceptor	Thr199	N	196	Donor
			O	21	Acceptor	Thr199	O	201	Both
			N	22	Donor	Thr199	O	201	Both
			N	22	Donor	His96	N	94	Acceptor
			N	22	Donor	His94	N	82	Acceptor
			O	20	Acceptor	His119	N	113	Donor
2g	−7.4	6	O	21	Acceptor	Thr199	N	196	Donor
			O	21	Acceptor	Thr199	O	201	Both
			N	22	Donor	Thr199	O	201	Both
			N	22	Donor	His96	N	94	Acceptor
			N	22	Donor	His94	N	82	Acceptor
			O	20	Acceptor	His119	N	113	Donor
2h	−7.2	6	O	10	Acceptor	Thr199	N	196	Donor
			O	10	Acceptor	Thr199	O	201	Both
			N	11	Donor	Thr199	O	201	Both
			N	11	Donor	His96	N	94	Acceptor
			N	11	Donor	His94	N	82	Acceptor
			O	9	Acceptor	His119	N	113	Donor
2i	−7.2	6	O	10	Acceptor	Thr199	N	196	Donor
			O	10	Acceptor	Thr199	O	201	Both
			N	11	Donor	Thr199	O	201	Both
			N	11	Donor	His96	N	94	Acceptor
			N	11	Donor	His94	N	82	Acceptor
			O	9	Acceptor	His119	N	113	Donor
2j	−7.4	6	O	10	Acceptor	Thr199	N	196	Donor
			O	10	Acceptor	Thr199	O	201	Both
			N	11	Donor	Thr199	O	201	Both
			N	11	Donor	His96	N	94	Acceptor
			N	11	Donor	His94	N	82	Acceptor
			O	9	Acceptor	His119	N	113	Donor
2k	−7.4	6	O	10	Acceptor	Thr199	N	196	Donor
			O	10	Acceptor	Thr199	O	201	Both
			N	11	Donor	Thr199	O	201	Both
			N	11	Donor	His96	N	94	Acceptor
			N	11	Donor	His94	N	82	Acceptor
			O	9	Acceptor	His119	N	113	Donor
2l	−7.0	6	O	11	Acceptor	Thr199	N	196	Donor
			O	11	Acceptor	Thr199	O	201	Both
			N	12	Donor	Thr199	O	201	Both
			N	12	Donor	His96	N	94	Acceptor
			N	12	Donor	His94	N	82	Acceptor
			O	10	Acceptor	His119	N	113	Donor
2m	−6.5	6	O	11	Acceptor	Thr199	N	196	Donor
			O	11	Acceptor	Thr199	O	201	Both
			N	12	Donor	Thr199	O	201	Both
			N	12	Donor	His96	N	94	Acceptor
			N	12	Donor	His94	N	82	Acceptor
			O	10	Acceptor	His119	N	113	Donor

(*Continued*)

Ligand	Affinity kcal/mol	H-bond	H- binding ligand			H- binding receptor			
			Elem	At. ID	Type	Residue	Elem	At.ID	Type
2n	−6.6	7	O	11	Acceptor	Thr199	N	196	Donor
			O	11	Acceptor	Thr199	O	201	Both
			N	12	Donor	Thr199	O	201	Both
			N	12	Donor	His96	N	94	Acceptor
			N	12	Donor	His94	N	82	Acceptor
			O	10	Acceptor	His119	N	113	Donor
			N	25	Donor	Pro201	O	220	Acceptor
2o	−7.0	6	O	10	Acceptor	Thr199	N	196	Donor
			O	10	Acceptor	Thr199	O	201	Both
			N	11	Donor	Thr199	O	201	Both
			N	11	Donor	His96	N	94	Acceptor
			N	11	Donor	His94	N	82	Acceptor
			O	9	Acceptor	His119	N	113	Donor
2p	−6.8	6	O	10	Acceptor	Thr199	N	196	Donor
			O	10	Acceptor	Thr199	O	201	Both
			N	11	Donor	Thr199	O	201	Both
			N	11	Donor	His96	N	94	Acceptor
			N	11	Donor	His94	N	82	Acceptor
			O	9	Acceptor	His119	N	113	Donor
2q	−6.7	5	O	10	Acceptor	Thr199	N	196	Donor
			O	10	Acceptor	Thr199	O	201	Both
			N	11	Donor	Thr199	O	201	Both
			N	11	Donor	His96	N	94	Acceptor
			N	11	Donor	His94	N	82	Acceptor
Zonisamide	−6.3	6	N	14	Donor	Thr199	O	201	Both
			N	14	Donor	His96	N	94	Acceptor
			N	14	Donor	His92	N	82	Acceptor
			O	13	Acceptor	Thr199	O	201	Both
			O	18	Acceptor	Thr199	N	196	Donor
			O	12	Acceptor	His119	N	113	Donor
Acetazolmide	−6.4	5	N	15	Donor	His94	N	82	Acceptor
			N	15	Donor	His96	N	94	Acceptor
			N	15	Donor	Thr199	O	201	Both
			O	14	Acceptor	Thr199	O	201	Both
			O	14	Acceptor	Thr199	N	196	Donor

On docking analysis, designed compound 1a has been found to be strongly docked with 1AZM with 6 hydrogen bonds and binding affinity of –7.7 kcal/mol. On residue study Thr199, His96 and His94 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 also nitrogen.

The designed compound 1b has been found to be strongly docked with 1AZM with 7 hydrogen bonds and binding affinity of –7.7 kcal/mol. On residue study Thr199, His96, Gln92 and His119 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.

The designed compound 1c has been found to be strongly docked with 1AZM with 7 hydrogen bonds and binding affinity of –7.2 kcal/mol. On residue study Thr199, His96, His119, Gln92 and His94 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 also nitrogen.

Upon, analyzing the findings of docking, the designed compound 2a has been found to be strongly docked with 1AZM with 6 hydrogen bonds and binding affinity of –7.3 Kcal/mol. On residue study Thr199, His96, His119 and His94 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 also nitrogen.

On docking analysis, designed compound 2b, 2c, 2d and 2e has been found to be strongly docked with 1AZM with 6 hydrogen bonds and binding affinity of –7.3 kcal/mol. On residue study Thr199, His96, His119 and His94 were found to

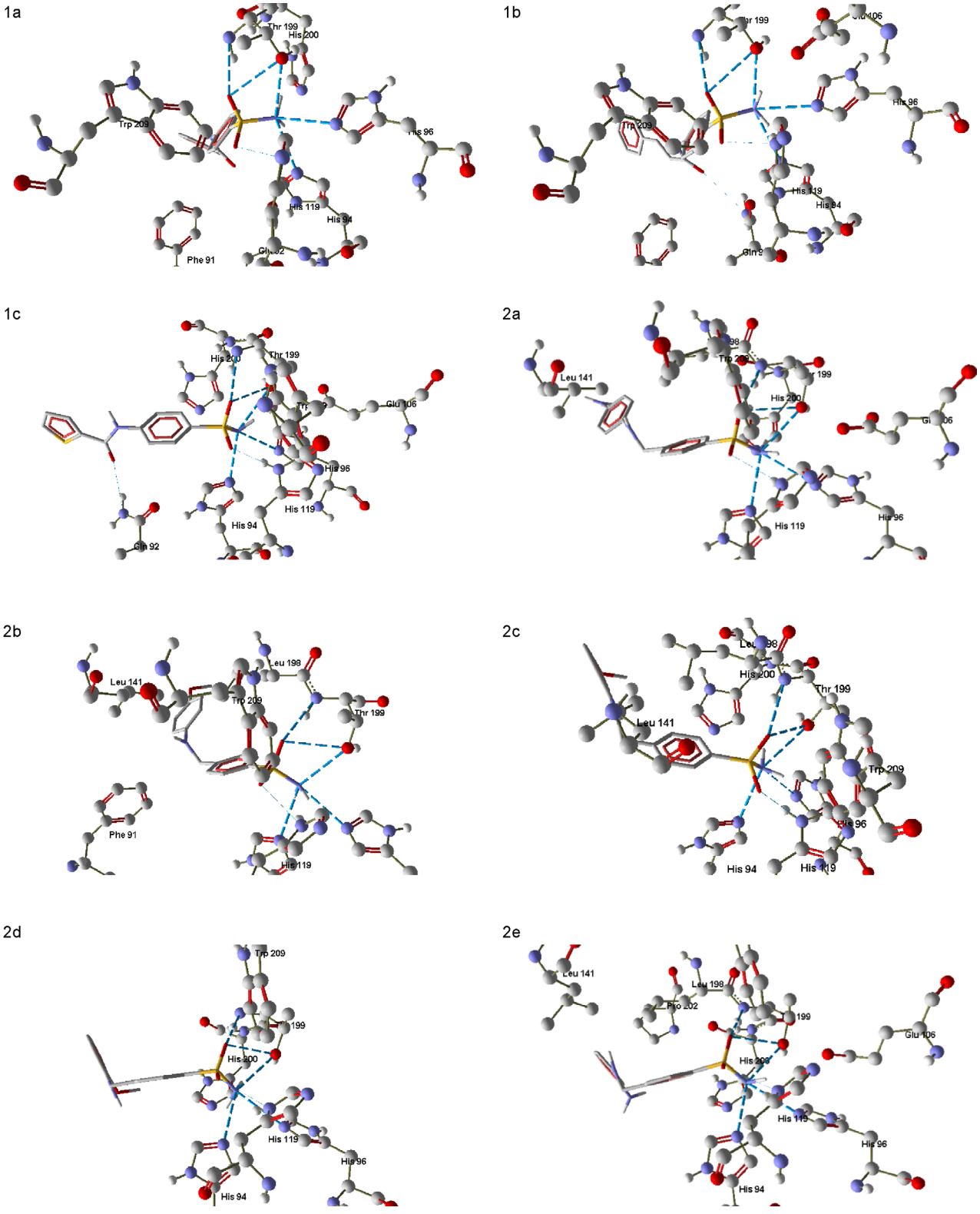
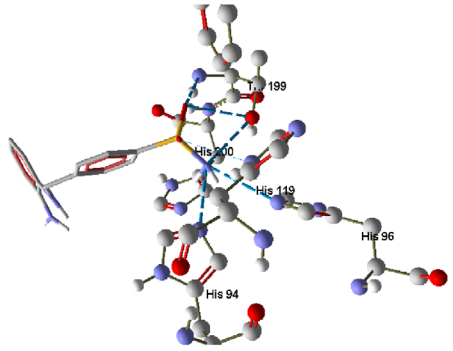
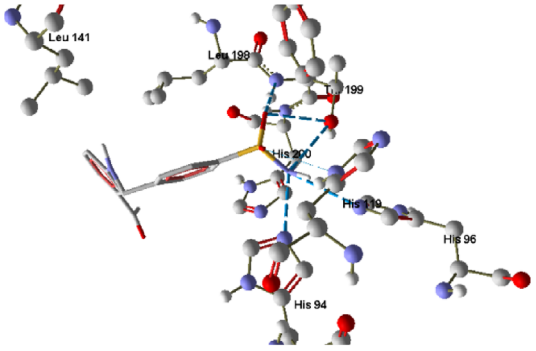


Figure 4 Docked images of designed molecules 1a, 1b, 1c, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2l, 2m, 2n, 2o, 2p and 2q with 1AZM

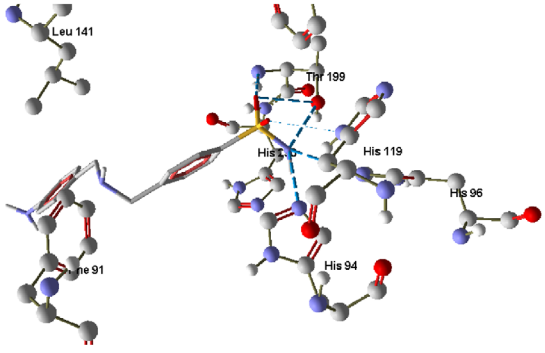
2f



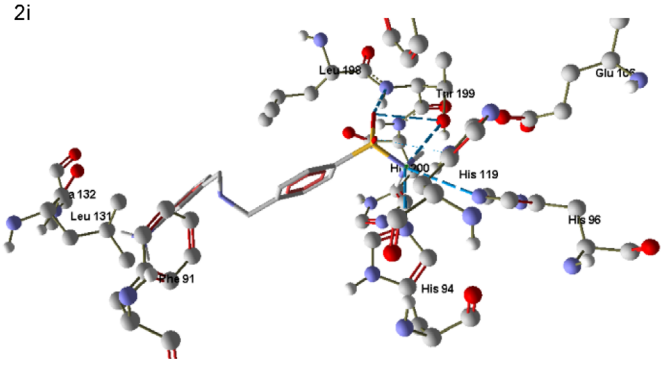
2g



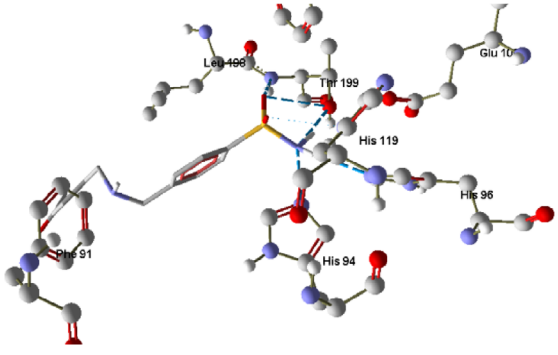
2h



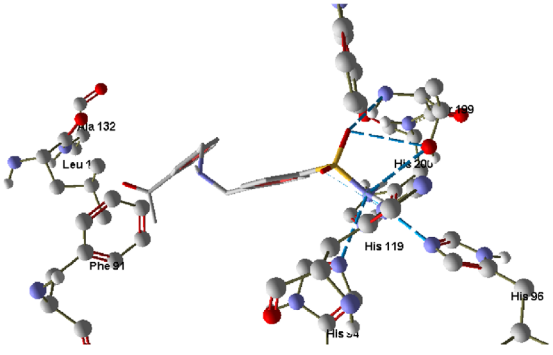
2i



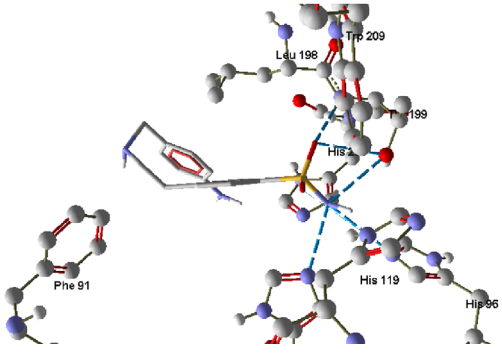
2j



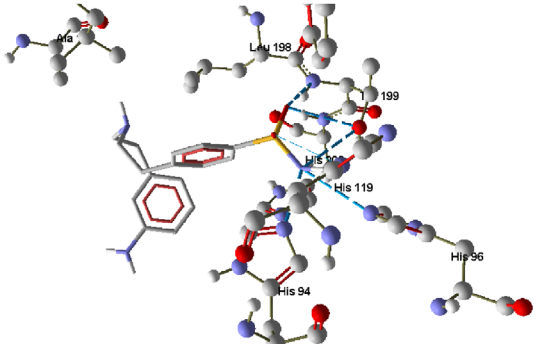
2k



2l



2m



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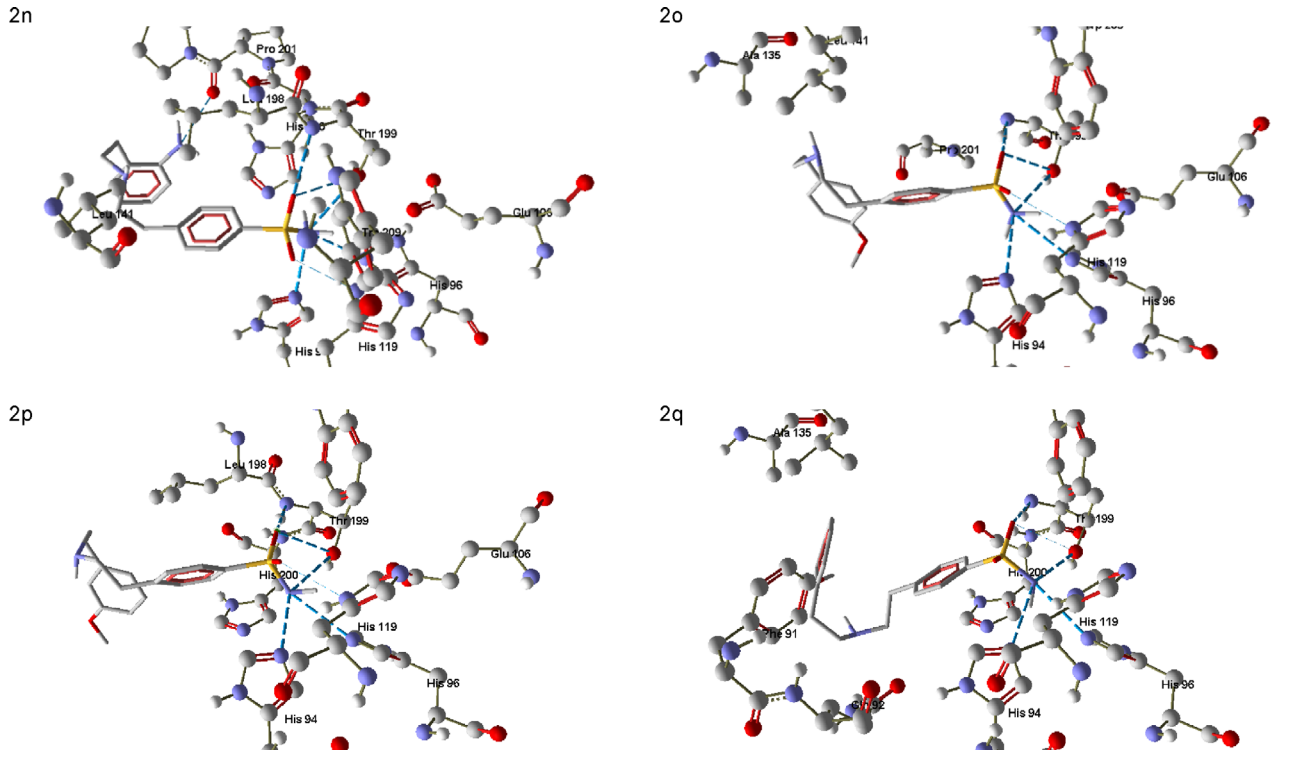


(Continued)

be significant. On the account of ligand oxygen atom is significant in binding with donor bonds, whereas significant element in receptor is nitrogen.

Further, the designed compound 2f has been found to be strongly docked with 1AZM with 6 hydrogen bonds and binding affinity of –7.2 kcal/mol. On residue study Thr199, His96, His119 and His94 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 2g has been found to be strongly docked with 1AZM with 6 hydrogen bonds and binding affinity of –7.4 kcal/mol. On residue study Thr199, His96, His119 and His94 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 2h, 2i, 2j, 2k, 2l and 2m has been found to be strongly docked with 1AZM with 6 hydrogen bonds and binding affinity of –7.2, –7.2, –7.4, –7.4, –7.0 and –6.5 kcal/mol respectively. On residue study Thr199, His96, His119 and His94 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.

The docking analysis revealed that designed compound 2n has been found to be strongly docked with 1AZM with 7 hydrogen bonds and binding affinity of –6.6 kcal/mol. On residue study Thr199, His96, His119, Pro201 and His94 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.

The designed compound 2o, 2p and 2q has been found to be strongly docked with 1AZM with 6, 6 and 5 hydrogen bonds and binding affinity of –7.0, –6.8 and –6.7 kcal/mol respectively. On residue study Thr199, His96, His119 and His94 were found to be significant.

Experimental

Compound characterization

After synthesizing the designed compounds, percentage yield, retention factor (R_f), melting point and elemental analysis (CHNS analysis) were performed.

The findings of physical and elemental data of the compounds are reported in Table 5.

Spectral characterization of synthesized substituted 4-amino-benzenesulfonamides

Compound No. 1a. *N*-(4-Sulfamoyl-phenyl)-benzamide

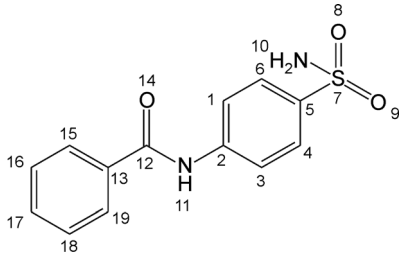
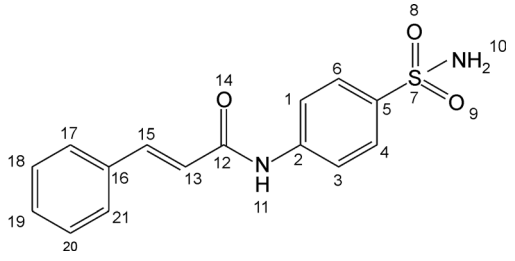


Table 5 Physical and elemental data of all the synthesized compounds

Comp.	Molecular formula (MW)	Yield (%)	MP (°C)	Elemental analysis (%): Found (Calculated)				% purity	R_f
				C	H	N	S		
1a	$C_{13}H_{12}N_2O_3S$ (276.056)	68.75	205-208	56.42 (56.50)	3.260 (4.37)	10.13 (10.14)	11.16 (11.60)	98.00	0.42
1b	$C_{15}H_{14}N_2O_3S$ (302.072)	71.92	220-222	59.44 (59.58)	1.922 (4.66)	9.224 (9.26)	10.63 (10.60)	96.55	0.80
1c	$C_{11}H_{10}N_2O_3S_2$ (282.013)	56.73	210-212	39.89 (46.77)	0.969 (3.56)	8.540 (9.92)	19.16 (22.73)	82.59	0.63
2a	$C_{13}H_{15}N_3O_2S$ (277.088)	88.42	215-217	56.01 (56.30)	4.98 (5.45)	14.05 (15.15)	11.14 (11.56)	97.42	0.39
2b	$C_{14}H_{16}N_2O_3S$ (292.088)	68.22	209-211	56.81 (57.52)	4.99 (5.52)	9.42 (9.58)	10.00 (10.97)	97.16	0.41
2c	$C_{14}H_{16}N_2O_3S$ (292.088)	67.80	184-186	57.05 (57.52)	5.10 (5.52)	9.50 (9.58)	10.88 (10.97)	98.72	0.43
2d	$C_{14}H_{16}N_2O_3S$ (292.088)	62.00	180-182	57.10 (57.52)	5.04 (5.52)	9.48 (9.58)	10.02 (10.97)	97.88	0.49
2e	$C_{13}H_{15}N_3O_2S$ (277.088)	85.88	190-192	56.09 (56.30)	4.93 (5.45)	14.87 (15.15)	11.01 (11.56)	98.23	0.48
2f	$C_{13}H_{15}N_3O_2S$ (277.088)	80.02	185-187	56.02 (56.30)	4.92 (5.45)	15.01 (15.15)	11.32 (11.56)	98.65	0.52
2g	$C_{15}H_{16}N_2O_3S$ (304.088)	82.44	194-197	58.09 (59.19)	5.10 (5.30)	9.17 (9.20)	9.28 (10.54)	96.92	0.45
2h	$C_{14}H_{17}N_3O_2S$ (291.104)	88.33	198-200	56.87 (57.71)	4.98 (5.88)	14.02 (14.42)	10.31 (11.00)	96.82	0.51
2i	$C_{14}H_{17}N_3O_2S$ (291.104)	86.53	200-202	56.76 (57.71)	5.06 (5.88)	13.82 (14.42)	10.32 (11.00)	96.57	0.47
2j	$C_{16}H_{18}N_2O_3S$ (318.103)	61.21	197-200	59.62 (60.36)	4.94 (5.70)	8.13 (8.80)	9.89 (10.07)	97.23	0.58
2k	$C_{16}H_{18}N_2O_3S$ (318.103)	60.54	188-190	60.05 (60.36)	4.38 (5.70)	8.13 (8.80)	9.22 (10.07)	96.29	0.38
2l	$C_{16}H_{21}N_3O_2S$ (319.135)	89.12	204-206	59.01 (60.16)	4.32 (6.63)	11.32 (13.16)	8.98 (10.04)	92.93	0.53
2m	$C_{16}H_{21}N_3O_2S$ (319.135)	86.78	203-205	59.41 (60.16)	5.41 (6.63)	12.33 (13.16)	9.07 (10.04)	95.81	0.33
2n	$C_{16}H_{21}N_3O_2S$ (319.135)	81.89	187-189	58.97 (60.16)	6.41 (6.63)	12.84 (13.16)	9.65 (10.04)	97.64	0.50
2o	$C_{17}H_{22}N_2O_3S$ (334.135)	61.22	206-208	60.22 (61.05)	5.44 (6.63)	7.96 (8.38)	8.95 (9.59)	96.40	0.36
2p	$C_{17}H_{22}N_2O_3S$ (334.135)	60.22	183-185	60.86 (61.05)	5.78 (6.63)	8.02 (8.38)	9.01 (9.59)	97.68	0.40
2q	$C_{17}H_{22}N_2O_3S$ (334.135)	59.35	196-198	57.88 (61.05)	4.53 (6.63)	7.31 (8.38)	8.98 (9.59)	91.88	0.61

IR (KBr, cm^{-1}, υ): 3108.2 (Aromatic-H); 1695.1 (>C=O); 1582.8 (C-C in ring); 1317.1 (S=O); 1011.5(>NH); 833.6(-NH_2). ^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 7.04(d, H, Ar-H of C3); 7.07(s, H, >NH); 7.26(d, H, Ar-H of C4); 7.27(d, 2H, -NH_2); 7.44 (t, 2H, Ar-H of C16 and C18); 7.49(t, 1H, Ar-H of C17); 7.81(d, H, Ar-H of C1); 7.87(d, 2H, Ar-H of C15 and C19); 8.67(d, H, Ar-H of C6). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 121.33(m, C1 and 3); 128.10(m, C4, C6); 128.27(m, C15, C19); 128.59(m, C16, C18); 131.77(s, C17); 135.04(s, C3); 140.08(s, C5); 141.86(s, C2); 167.77(s, C12). MS (m/z, %): 276.30 (M^+, 20).

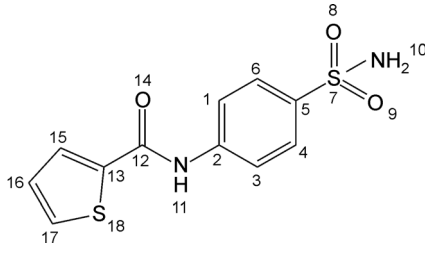
Compound No. 1b. 3-Phenyl-*N*-(4-sulfamoyl-phenyl)-acrylamide



IR (KBr, cm^{-1}, υ): 3029.4(Aromatic-H); 1688.4(>CO); 1585.2(C-C in ring); 1304.3(S=O); 1066.7(>NH); 823(C=C); 714.6(-NH_2). ^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm):

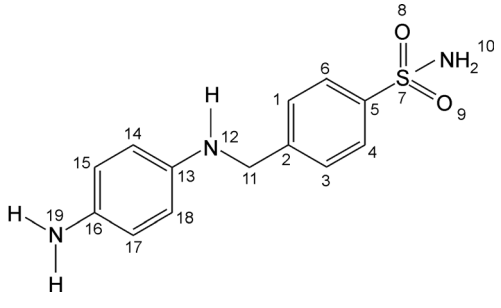
6.82(d, H, C13); 7.04(d, H, Ar-H of C3); 7.06(s, H, > NH); 7.18 (t H, Ar-H of C19); 7.24(d, 2H, -NH_2 and t, 2H of C18 and C20); 7.26(d, H, Ar-H of C4); 7.32(d, 2H, Ar-H of C17 and C21); 7.70(d H, C15); 7.81(d, H, Ar-H of C1); 8.66(d, H, Ar-H of C6). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 117.66 (s, C13); 120.86(m, C1 and C3); 127.99(m, C4, C6); 128.10 (m, C17, C21); 129.03(m, C18, C20); 129.48(s, C19); 135.22 (s, C16); 139.82(s, C5); 141.09(s, C15); 142.55(s, C2); 166.66(s, C12). MS (m/z, %): 302.34 (M^+, 30).

Compound No. 1c. Thiophene-2-carboxylic acid (4-sulfamoyl-phenyl)-amide



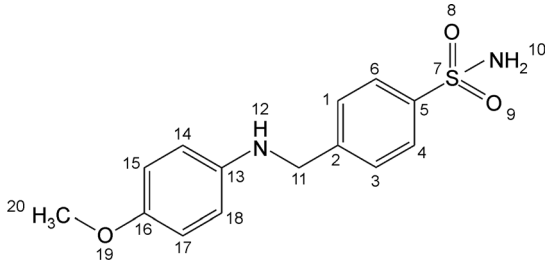
IR (KBr, cm^{-1}, υ): 3059.4(Aromatic-H); 1696.9(-CONH-in 5 membered ring); 1411.8(C-C in ring); 1300.5(S = O); 705(-NH_2). ^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 7.03(d, H, Ar-H of C3); 7.06(s, H, > NH); 7.11(t, H, Thiophene-H of C16); 7.25(d, H, Ar-H of C4); 7.36(d, 2H, -NH_2); 7.58(d, H, Thiophene-H of C17); 7.81(d, H, Ar-H of C1); 7.84(d, H, Thiophene-H of C15); 8.68(d, H, Ar-H of C6). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 121.35(m, C1 and C3); 127.68 (s, C16); 128.10(m, C4 and C6); 128.42(s, C15); 132.26(m, C13 and C17); 140.08(s, C5); 141.86(s, C2); 156.64(s, C12). MS (m/z, %): 282.41 (M^+, 10).

Compound No. 2a. 4-((4-Amino-phenylamino)-methyl)-benzenesulfonamide



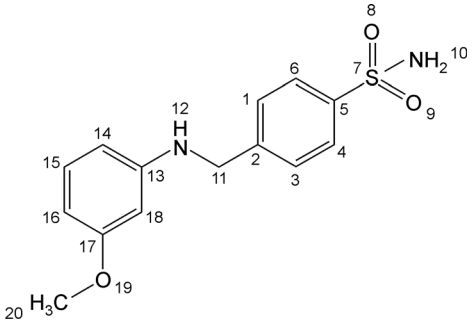
IR (KBr, cm^{-1}, υ): 1446.9 (C-C in ring); 1312.1(S = O); 1055.8(> NH); 817.1(-NH_2). ^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 4.43(d, 1H of-NH_2 of C16); 4.83(d, 2H of C11); 5.64 (d, Ar-H of C18); 5.74(d, Ar-H of C17); 6.34(d, Ar-H of C14); 6.46(d, Ar-H of C15); 6.84(d, Ar-H of C1); 6.88(d, Ar-H of C3); 6.97(d, Ar-H of C6); 7.24(d, Ar-H of C4); 7.47(d, 2H of-SO_2NH_2); 7.86(d, 1H of-NH_2 of C16); 7.86(d, 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). MS (m/z, %):(277.08, M^+, 95)

Compound No. 2b. 4-((4-Methoxy-phenylamino)-methyl)-benzenesulfonamide



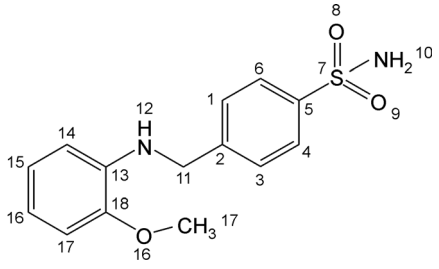
IR (KBr, cm^{-1}, υ): 1639.5(-NH_2); 1460.5(C-C in ring); 1378.6(-CH_3); 1318.2(S = O); 1121.2(> NH). ^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 3.81(t, 3H of –OCH_3); 4.29 (d, 1H of C11); 4.49(d, 1H of C11); 6.53(d, Ar-H of C14 and Ar-H of C18); 6.76(d, Ar-H of C15 and Ar-H of C17); 6.84(d, Ar-H of C3); 7.20(d, Ar-H of C4); 7.24(d, Ar-H of C6); 7.47 (d, 2H of –SO_2NH_2); 7.59(d, Ar-H of C1); 7.85(t, 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). MS (m/z, %): (292.35, M^+, 75)

Compound No. 2c. 4-((3-Methoxy-phenylamino)-methyl)-benzenesulfonamide



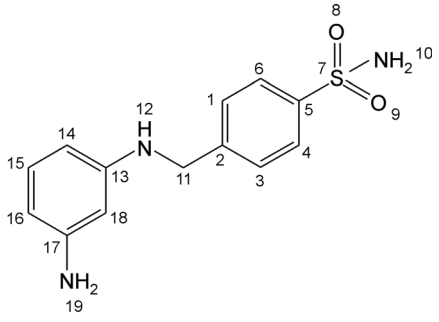
IR (KBr, cm^{-1}, υ): 1450.2(C-C in ring); 1387.3(S = O); 1242.1(Ar-O-R); 1023.8(> NH); 754.7(-NH_2). ^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 3.82(t, 3H of –OCH_3); 4.37 (d, 1H of C11); 4.49(d, 1H of C11); 6.20(s, Ar-H of C18); 6.23(d, Ar-H of C14); 6.29(d, Ar-H of C16); 6.84(d, Ar-H of C3); 7.11(t, Ar-H of C15); 7.20(d, Ar-H of C4); 7.24(d, Ar-H of C6); 7.47(d, 2H of –SO_2NH_2); 7.59(d, Ar-H of C1); 7.85 (d, 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). MS (m/z, %): (292.35, M^+, 100)

Compound No. 2d. 4-((2-Methoxy-phenylamino)-methyl)-benzenesulfonamide



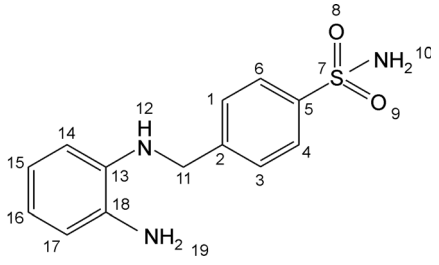
IR (KBr, cm^{-1}, υ): 2926(> CH_2); 1599.9(C-C in ring); 1382.6(S = O); 1238.1(Ar-O-R); 1072.2(> NH); 686.2(-NH_2). ^1H NMR ($CDCl_3$, 400 MHz, δ in ppm): 3.80(t, 3H of –OCH_3); 4.47(d, 1H of C11); 4.49(d, 1H of C11); 6.52(d, Ar-H of C14); 6.61(t, Ar-H of C16); 6.73(d, Ar-H of C17); 6.78(t, Ar-H of C15); 6.83(d Ar-H of C3); 7.19(d, Ar-H of C4); 7.24(d, Ar-H of C6); 7.58(d, Ar-H of C1); 7.58(d, 2H of –NH_2); 7.83(t, 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). MS (m/z, %): (292.35, M^+, 95).

Compound No. 2e. 4-((3-Amino-phenylamino)-methyl)-benzenesulfonamide



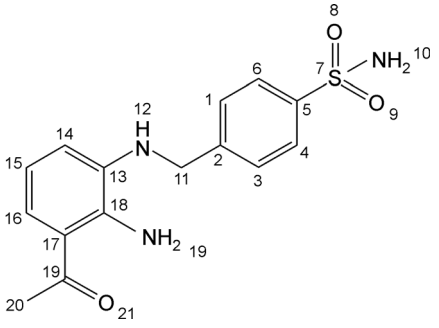
IR (KBr, cm^{-1}, υ): 2920.6(> CH_2); 1404.3(C-C in ring); 1332.3(S = O); 1040.1(> NH); 682.2(-NH_2). ^1H NMR ($CDCl_3$, 400 MHz, δ in ppm): 4.43(d, 1H of –NH_2 of C17); 4.79(d, 1H of C11); 4.94(d, 1H of C11); 5.42(s, Ar-H of C18); 5.51(d, Ar-H of C16); 5.99(d, Ar-H of C14); 6.67(t, Ar-H of C15); 6.84(d, Ar-H of C1); 6.88(d, Ar-H of C3); 7.11(d, Ar-H of C6); 7.24(d, Ar-H of C4); 7.47(d, 2H of –SO_2NH_2); 7.86 (d, 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). MS (m/z, %): (277.34, M^+, 95).

Compound No. 2f. 4-((2-Amino-phenylamino)-methyl)-benzenesulfonamide



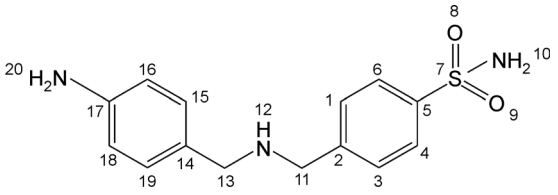
IR (KBr, cm^{-1}, υ): 2852.9(> CH_2); 1577.1(C-C in ring); 1411.1(S = O); 1040.1(> NH); 719.4(-NH_2). ^1H NMR ($CDCl_3$, 400 MHz, δ in ppm): 4.43(d, 1H of –NH_2 of C18); 4.84, 4.85(d, 2H of C11); 5.81(d, Ar-H of C17); 5.82(t, Ar-H of C16); 6.35(d, Ar-H of C14); 6.52(t, Ar-H of C15); 6.84(d, Ar-H of C1); 6.88(d, Ar-H of C3); 7.09(d, Ar-H of C6); 7.24 (d, Ar-H of C4); 7.47(d, 2H of –SO_2NH_2); 7.86(d, 1H of –NH_2 of C18); 7.86(d, 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). MS (m/z, %): (277.34, M^+, 95).

Compound No. 2g. 4-((3-Acetyl-phenylamino)-methyl)-benzenesulfonamide



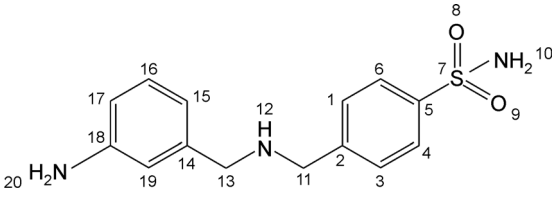
IR (KBr, cm^{-1}, υ): 2920.1(-CH_3); 2851.9(> CH_2); 1731.6 (> CO); 1588.5(C-C in ring); 1372.7(S = O); 1034.8(> NH); 722.4(-NH_2). ^1H NMR ($CDCl_3$, 400 MHz, δ in ppm): 2.54(t, 3H of C20); 4.38, 4.48(d, 2H of C11); 6.74(d, Ar-H of C14); 6.84(d, Ar-H of C3); 7.11(s, Ar-H of C18); 7.18(d, Ar-H of C16); 7.20(d, Ar-H of C4); 7.24(d, Ar-H of C6); 7.26(t, Ar-H of C15); 7.47(d, 2H of –SO_2NH_2); 7.59(d, Ar-H of C1); 7.86 (d, 1H of > NH). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 27.79(s, C20 of –COCH3); 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 –$COCH_3$). MS (m/z, %): (304.36, M^+, 75)

Compound No. 2h. 4-((4-Amino-benzylamino)-methyl)-benzenesulfonamide



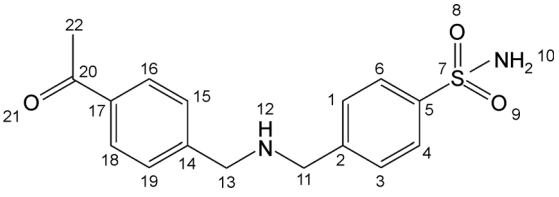
IR (KBr, cm^{-1}, υ): 3086.7(Ar-H); 2851.6(> CH_2); 1465.9 (C-C in ring); 1348.3(S = O); 1025.8(> NH); 731.1(-NH_2). ^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 3.95(d, 2H of C11); 4.36(d, 1H of C13); 4.41(d, 1H of –NH_2); 4.46(d, 1H of C13); 5.94(d, Ar-H of C18); 6.31(d, Ar-H of C19); 6.57(d, Ar-H of C6); 6.68(d, Ar-H of C16); 6.78(d, Ar-H of C3); 6.83(d, Ar-H of C1); 6.94(d, Ar-H of C15); 7.14(d, Ar-H of C4); 7.42(d, 2H of –SO_2NH_2); 7.80(t, H of > NH). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 52.74(m, C11 and C13); 114.50(m, C16 and C18); 125.69(m, C1 and C3); 126.33(m, C4 and C6); 126.75 (s, C14); 128.38(m, C15 and C19); 143.38(s, C17); 143.62(s, C5); 144.12(s, C2). MS (m/z, %): (291.37, M^+, 10).

Compound No. 2i. 4-((3-Amino-benzylamino)-methyl)-benzenesulfonamide



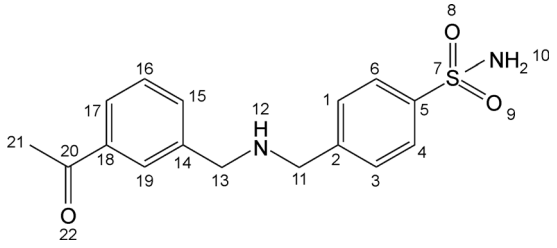
IR (KBr, cm^{-1}, υ): 2851.7(> CH_2); 1463.4(C-C in ring); 1356.8(S = O); 1037.4(> NH); 722.3(-NH_2). ^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 4(d, 2H of C11); 4.42(d, 1H of –NH_2); 4.48(d, 1H of C13); 4.57(d, 1H of C13); 5.95(d, Ar-H of C17); 5.99(s, Ar-H of C19); 6.57(d, Ar-H of C6); 6.66(d, Ar-H of C15); 6.75(d, Ar-H of C3); 6.83(d, Ar-H of C1); 6.97(d, Ar-H of C16); 7.11(d, Ar-H, C4); 7.33(d, 2H of –SO_2NH_2); 7.78(t, H of > NH). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 52.74(s, C11); 53.07(s, C13); 114.78(s, C19); 115.04(s, C17); 117.87(s, C15); 125.69(m, C1 and C3); 126.33(m, C4 and C6); 129.09(s, C16); 141.11(s, C14); 143.62(d, C5); 143.72(d, C18); 144.12(s, C2). MS (m/z, %): (291.37, M^+, 60).

Compound No. 2j. 4-((4-Acetyl-benzylamino)-methyl)-benzenesulfonamide



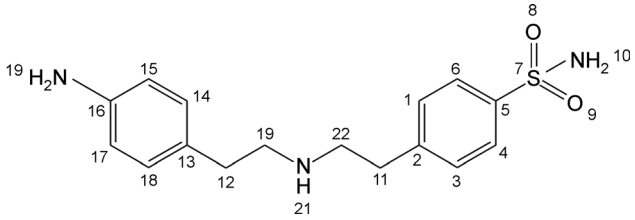
IR (KBr, cm^{-1}, υ): 3067.2(Ar-H); 2936.4(> CH_2); 1687.7 (> CO); 1588.4(C-C in ring); 1349.5(S = O); 1037.7(> NH); 730.8(-NH_2). ^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 2.54(t, 3H of C22); 2.83, 3.47(d, 1H of C11); 3.96(d, 1H of C11); 4.01(d, H of C13); 6.84(d, Ar-H of C3); 7.11(d, Ar-H of C6); 7.19(d, Ar-H of C4); 7.32(d, 2H of –SO_2NH_2); 7.39(d, 1H of C15, C19); 7.57(d, Ar-H of C1); 7.77(m, H of > NH); 7.81(d, 1H of C16, C18). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 27.79(s, C22); 52.74(m, C11 and C13); 125.69(m, C1 and C3); 126.33(m, C4 and C6); 126.91(m, C16 and C18); 127.92 (m, C15 and C19); 137.89(s, C17); 143.62(s, C5); 144.12(s, C2); 146.33(s, C14); 196.96(s, C20). MS (m/z, %): (318.39, M^+, 40).

Compound No. 2k. 4-((3-Acetyl-benzylamino)-methyl)-benzenesulfonamide



IR (KBr, cm^{-1}, υ): 3014.2(Ar-H); 2955.2(-CH_3); 2923.3(-CH_2); 1685.9(> CO); 1427.4(C-C in ring); 1390.7(S = O); 1092.6(> NH); 710.8(-NH_2). ^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 2.56(t, 3H of C21); 2.83, 3.48(d, 1H of C11); 3.97(d, 1H of C11); 4.01(d, 2H of C13); 6.84(d, Ar-H of C3); 7.11(d, Ar-H of C6); 7.20(d, Ar-H of C4); 7.36(d, 2H of –SO_2NH_2); 7.40(t, 1H of C16); 7.43(d, Ar-H of C15); 7.58(d, Ar-H of C1); 7.74(d, Ar-H of C17); 7.81(m, H of > NH); 7.87(s, Ar-H of C19). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 27.79(s, C21); 52.74(s, C11); 53.07(s, C13); 124.71(s, C19); 125.69 (m, C1 and C3); 126.33(m, C4 and C6); 127.94(s, C17); 128.62(s, C16); 129.86(s, C15); 135.08(s, C18); 140.31(s, C14); 143.62(s, C5); 144.12(s, C2); 197.18(s, C20). MS (m/z, %): (318.39, M^+, 30).

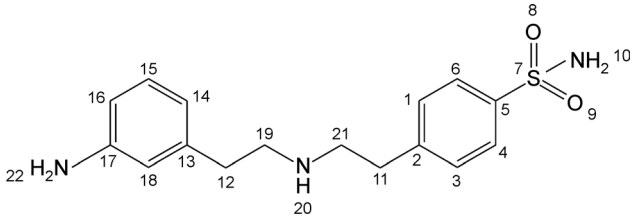
Compound No. 2l. 4-{2-(2-(4-Amino-phenyl)-ethyl}-benzenesulfonamide



IR (KBr, cm^{-1}, υ): 3112.4(Ar-H); 2943.9(> CH_2); 1464(C-C in ring); 1424.2(S = O); 1178.5(> NH); 836.5(-NH_2). ^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 2.70(d, 1H of C11); 2.74 (m, 1H of C20); 2.97(m, 1H of C20, C22); 3.20(t, 2H of C12);

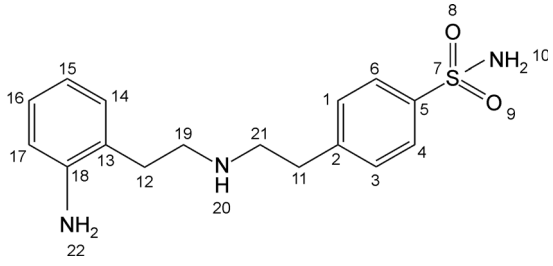
3.37(d, H of C11); 4.43(m, H of > NH); 5.92(d, Ar-H of C15, C17); 6.14(d, Ar-H of C18); 6.45(d, Ar-H, C-3); 6.77(d, Ar-H, C1); 6.80(d, Ar-H, C6), 6.84(d, Ar-H, C-4); 6.97(d, Ar-H, C-14); 7.37(d, 2H of $–SO_2NH_2$); 7.82(d, 2H of-NH_2). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 34.74(m, C11 and C12); 50.32(m, C20 and C22); 113.90(m, C15 and C17); 126.05(m, C1 and C3); 129.02(m, C4 and C6); 129.70(m, C14 and C18); 129.87(m, C13); 142.75(s, C2); 145.07(s, C16); 145.56(s, C5). MS (m/z, %): (319.42, M^+,

Compound No. 2m. 4-{2-(2-(3-Amino-pheyl)-ethylamino)-ethyl}-benzenesulfonamide



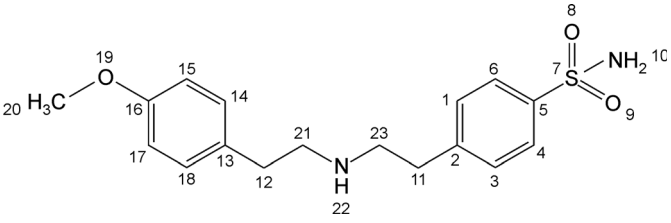
IR (KBr, cm^{-1}, υ): 3074.2(Ar-H), 2923.9(> CH_2); 1453(C-C in ring); 1377.4(S = O); 1102.3(> NH); 801.7(-NH_2). ^1H NMR ($CDCl_3$, 400 MHz, δ in ppm): 2.73(d, 1H of C11); 2.97 (m, 2H of C19); 3.05(m, 2H of C21); 3.29(t, 1H of C12); 3.39 (d, 1H of C11); 3.39(t, 1H of C12); 4.44(d, 1H of $–NH_2$); 5.74 (d, Ar-H of C16); 6.20(t, Ar-H, C15); 6.45(d, Ar-H, C3); 6.57 (d, Ar-H, C14); 6.78(d, Ar-H, C1); 6.83(d, Ar-H, C6); 6.84(d, Ar-H of C4); 7.37(d, 2H of $–SO_2NH_2$); 7.81(m, 1H of-NH_2, 1H of > NH). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 34.74 (d, C11); 34.85(d, C12); 50.32(m, C19 and C21); 115.54(s, C16); 117(s, C18); 117.21(s, C14); 126.05(m, C1 and C3); 129.06(m, C4 and C6); 129.43(s, C15); 140.21(s, C13); 142.75(s, C2); 145.46(s, C5); 145.72(s, C17). MS (m/z, %): (319.42, M^+, 45).

Compound No. 2n.4-{2-(2-(2-Amino-phenyl)-ethylamino)-ethyl}-benzenesulfonamide



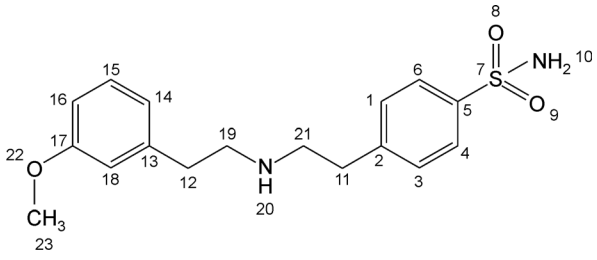
IR (KBr, cm^{-1}, υ): 3074.2(Ar-H); 2023.9(> CH_2); 1569.2 (C-C in ring); 1416.4(S = O); 1097.1(> NH); 807.5(-NH_2). ^1H NMR ($CDCl_3$, 400 MHz, δ in ppm): 2.66(d, 1H of C11); 2.97(m, 2H of C19); 3.08(m, 2H of C21); 3.32(t, 1H of C12); 3.37(t, 1H of C11); 3.37(d, 1H of C12); 4.45(d, 2H of $–NH_2$); 5.41(d, Ar-H of C17); 5.92(t, Ar-H of C15); 6.11(t, Ar-H, C16); 6.45(d, Ar-H, C3); 6.75(d, Ar-H, C6); 6.78(d, Ar-H, C1); 6.84(d, Ar-H, C4); 6.87(d, Ar-H of C14); 7.37(d, 2H of $–SO_2NH_2$); 7.80(m,1H of > NH). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 32.28(s, C12); 34.74(s, C11); 49.75(s, C19); 50.32(s, C21); 115.20(s, C17); 119.80(s, C15); 125.33(s, C13); 126.05(m, C1 and C3); 127.33(s, C16); 128.76(s, C14); 129.02(m, C4 and C6); 142.75(s, C2); 144.85(s, C18); 145.46 (s,C5). MS (m/z, %): (319.42, M^+, 50).

Compound No. 2o. 4-{2-(2-(4-Methoxy-phenyl)-ethylamino)-ethyl}-benzenesulfonamide



IR (KBr, cm^{-1}, υ): 2923.9(> CH_2); 1426.4(C-C in ring); 1368.1(S = O); 1248.3(Ar-O-R); 1046(> NH); 897.1(-NH_2). ^1H NMR ($CDCl_3$, 400 MHz, δ in ppm): 2.71(d, 1H of C11 and 1H of C12); 2.74(d, 1H of C11); 2.75(m, 2H of C21); 2.96(m, 1H of C21 and 1H of C23); 3.39(d, 1H of C12); 3.65 (t, 1H of 20); 3.81(m, 2H of C20); 6.43(d, Ar-H of C18); 6.78 (d, Ar-H of C3); 6.84(d, Ar-H, C6); 6.86(d, Ar-H, C15); 6.91 (d, Ar-H, C17); 7.10(d, Ar-H, C14); 7.17(d, Ar-H, C4); 7.36 (d, 2H of $–SO_2NH_2$); 7.52(d, Ar-H of C1); 7.81(m, 1H of > NH). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 43.74(m, C11 and C12); 50.32(m, C21 and C23); 56.04(s, C20); 114.74 (m, C15 and C17); 126.05(m, C1 and C3); 129.02(m, C4 and C6); 129.59(m, C14 and C18); 131.58(s, C13); 142.75(s, C2); 145.46(s, C5); 157.48(s, C16). MS (m/z, %): (334.43, M^+, 20).

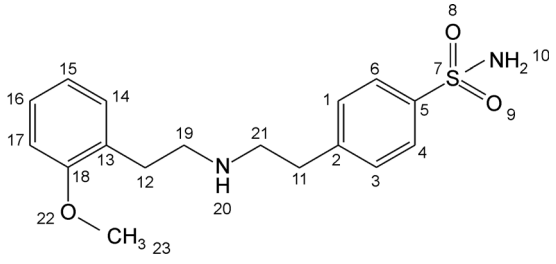
Compound No. 2p. 4-{2-(2-(3-Methoxy-phenyl)-ethylamino)-ethyl}-benzenesulfonamide



IR (KBr, cm^{-1}, υ): 2923.3(> CH_2); 1426.6(C-C in ring); 1365(S = O); 1225.1(Ar-O-R); 1046.2(> NH); 897.4(-NH_2). ^1H NMR ($CDCl_3$, 400 MHz, δ in ppm): 2.73(t, 1H of C11 and 1H of C12); 2.75(m, 1H of C19); 2.97(m, 1H of C19 and 1H of C21); 3.34(t, 1H of C12); 3.81(t, 3H of C23); 6.0(d, Ar-H of C18); 6.75(d, Ar-H of C16); 6.78(d, Ar-H, C3); 6.84(d, Ar-H, C6); 6.92(d, Ar-H, C14); 7.13(t, Ar-H, C15); 7.17(d, Ar-H,

C4); 7.37(d, 2H of $–SO_2NH_2$); 7.52(d, Ar-H of C1); 7.81(m, 1H of > NH). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 34.74 (d, C11); 34.85(d, C12); 50.32(m, C19 and C21); 56.04(s, C23); 112.33(s, C16); 115.20(s, C18); 121.30(s, C14); 126.05 (m, C1 and C3); 128.94(t, C15); 129.02(t, C4 and C6); 141.34 (s, C13); 142.75(s, C2); 145.46(s, C5); 159.44(s, C17). MS (m/z, %): (334.43, M^+, 5).

Compound No. 2q. 4-{2-(2-(2-Methoxy-phenyl)-ethylamino)-ethyl}-benzenesulfonamide



IR (KBr, cm^{-1}, υ): 2924.1(> CH_2); 1459.3(C-C in ring); 1371.1(S = O); 1249.2(Ar-O-R); 1044.5(> NH); 896.2(-NH_2). ^1H NMR ($CDCl_3$, 400 MHz, δ in ppm): 2.73(t, 1H of C11 and 1H of C12); 2.74(m, 1H of C19); 2.97(m, 2H of C21); 2.98(m, 1H of C19); 3.39(t, 1H of C12); 3.81(t, 3H of C23); 6.09(d, Ar-H of C17); 6.77(d, Ar-H, C3); 6.84(d, Ar-H, C6); 6.96(t, Ar-H, C15); 7.07(t, Ar-H, C16); 7.11(d, Ar-H, C14); 7.17(d, Ar-H of C4); 7.37(d, 2H of $–SO_2NH_2$); 7.52(d, Ar-H of C1); 7.81(m, 1H of > NH). C13 NMR ($CDCl_3$, 100 MHz, δ in ppm): 30.54(s, C12); 34.74(s, C11); 49.75(s, C19); 50.32(s, C21); 56.79(s, C23); 112.82(s, C17); 121.58(s, C15); 126.05(m, C1 and C3); 126.67(s, C16); 129.02(m, C4 and C6); 129.03(m, C13); 129.55(s, C14); 142.75(s, C2); 145.46 (s, C5); 158.74(s, C18). MS (m/z, %): (334.43, M^+, 5).

Pharmacology

Anticonvulsant activity and neurotoxicity of substituted-4-amino-benzenesulfonamides

A maximal electroshock seizure test has been performed with an electrical stimulus of 0.2 s in duration (150 mA in rat at 60Hz) is delivered via trans-auricular electrodes. Animals were tested at 30 min and 2 h following doses of 100 mg/kg of test compound. Rats are tested at time intervals between 30 min. and 2h following a standard dose of 100 mg/kg. Abolition of the hind limb tonic extensor component indicates the test compound's ability to inhibit MES-induced seizure spread. It was observed that no animal has got neurotoxicity during a period of 30 min. to 4 h.

MES activity and neurotoxicity studies are given in Table 6 and their various phase activities has been given in Table 7

In-silico studies

In-silico biological activity spectrum

Probability to be active of designed screened compounds

Table 6 Anticonvulsant (MES) activity and neurotoxicity of synthesized compounds

Comp.	Dose (mg/kg)	Oral administration to rat [a]			
		30 min[c]	2 h[c]	Neurotox.[b]	
				30 min	4 h
1a	100	4/6	6/6	0/4	0/4
1b	100	5/6	6/6	0/4	0/4
1c	100	3/6	5/6	0/4	0/4
2a	100	3/6	4/6	0/4	0/4
2b	100	3/6	4/6	0/4	0/4
2c	100	2/6	4/6	0/4	0/4
2d	100	3/6	4/6	0/4	0/4
2e	100	3/6	5/6	0/4	0/4
2f	100	4/6	4/6	0/4	0/4
2g	100	6/6	6/6	0/4	0/4
2h	100	4/6	5/6	0/4	0/4
2i	100	5/6	5/6	0/4	0/4
2j	100	4/6	5/6	0/4	0/4
2k	100	5/6	6/6	0/4	0/4
2l	100	2/6	3/6	0/4	0/4
2m	100	2/6	4/6	0/4	0/4
2n	100	2/6	3/6	0/4	0/4
2o	100	4/6	6/6	0/4	0/4
2p	100	2/6	3/6	0/4	0/4
2q	100	2/6	3/6	0/4	0/4
Acetazola-mide	100	6/6	6/6	0/4	0/4

against carbonic anhydrase have been calculated with the help of PASS and shown in Table 8.

In-silico Mutagenicity and skin irritancy studies

Ames *In-silico* test results have been shown in Table 9.

Table 7 Anticonvulsant effect on all phases of MES model

Compound	Time taken (s)$^{+}$			
	Flexion	Extensor	Clonus	Stupor
1a	1.68±0.09***	2.78±0.07***	1.78±0.07 ***	7.1±0.24***
1b	2.18±0.07 ***	3.28±0.07 ***	2.38±0.06***	7.1±0.20***
1c	3.99±0.06 **	4.31±0.08 ***	10.50±0.18 ***	10.88±0.11 ***
2a	4.3±0.08 ^{ns}	4.9±0.16 ***	11.20±0.18 ***	11.18±0.21***
2b	3.36±0.06 ***	4.04±0.13***	7.65±0.12 ***	9.65±0.22 ***
2c	4.31±0.07^{ns}	4.94±0.20 ***	10.71±0.15 ***	10.64±0.12 ***
2d	4.16±0.10 ^{ns}	5.1±0.12 ***	11.21±0.16***	11.26±0.14 ***
2e	4.10±0.09 *	4.76±0.18 ***	10.98±0.20 ***	11.17±0.20***
2f	4.48±0.11 ^{ns}	4.79±0.23 ***	11.1±0.25 ***	11.6±0.18***
2g	1.74±0.12 ***	1.88±0.07***	1.99±0.13***	6.64±0.14***
2h	4.435±0.14 ^{ns}	4.8±0.21***	10.77±0.23***	11.11±0.22***
2i	4.32±0.14 ^{ns}	4.8±0.17 ***	10.83±0.22***	11.5±0.27 ***
2j	4.18±0.11 ^{ns}	4.78±0.26 ***	10.85±0.26 ***	11.40±0.22***
2k	1.76±0.17 ***	3.07±0.16 ***	1.88±0.14 ***	6.70±0.24 ***
2l	7.91±0.18***	8.14±0.22***	12.73±0.62***	96.96±0.28 ***
2m	8.07±0.17 ***	7.44±0.22 ***	13.72±0.17 ***	97.79±0.33 ***
2n	7.88±0.25 ***	7.97±0.25***	14.06±0.18***	96.98±0.30***
2o	1.93±0.16 ***	2.8±0.13 ***	2.2±0.29***	7.05±0.23***
2p	7.62±0.22 ***	7.89±0.17 ***	13.69±0.26***	98.62±0.12***
2q	8.23±0.27***	8.35±0.19***	13.79±0.22***	98.16±0.12***
Acetazolamide	2.01±0.13***	0±0.26 ***	2.8±0.31***	2.6±0.21***
Control: HPMC 5% w/v	4.5±0.30	18.7±0.97	15.06±0.97	13.1±0.89

TWO WAY ANOVA followed by Bonferroni test.***$P < 0.001$ significant; ns = not significant

Table 8 Biological activity Spectrum against Carbonic anhydrase (Probability to be active)

Comp.	CA I inhibitor	CA II inhibitor	CA IV inhibitor	CA IX inhibitor	CA V inhibitor	CA VII inhibitor	CA XII inhibitor	CA XIV inhibitor
1a	0.180	0.186	0.104	0.180	0.440	0.220	0.140	0.101
1b	0.050	0.128	0.032	0.108	0.262	0.188	0.090	0.105
1c	0.040	0.252	0.093	0.111	0.118	0.172	0.086	0.073
2a	0.161	0.193	0.102	0.195	0.424	0.206	0.135	0.067
2b	0.034	0.074	0.020	0.084	0.107	0.150	0.070	0.068
2c	0.025	0.054	0.015	0.060	0.090	0.136	0.060	0.058
2d	0.021	0.041	0.013	0.063	0.080	0.140	0.063	0.063
2e	0.117	0.157	0.072	0.162	0.343	0.186	0.108	0.058
2f	0.068	0.085	0.042	0.152	0.230	0.181	0.100	0.063
2g	0.027	0.051	0.014	0.056	0.104	0.135	0.060	0.051
2h	0.179	0.291	0.139	0.197	0.399	0.205	0.142	0.064
2i	0.145	0.249	0.112	0.166	0.374	0.184	0.113	0.056
2j	0.034	0.104	0.020	0.090	0.096	0.158	0.081	0.065
2k	0.025	0.083	0.016	0.062	0.087	0.141	0.068	0.062
2l	0.225	0.284	0.163	0.169	0.411	0.198	0.151	0.058
2m	0.201	0.242	0.127	0.142	0.384	0.179	0.123	0.050
2n	0.149	0.167	0.088	0.119	0.255	0.168	0.107	0.050
2o	0.073	0.111	0.036	0.080	0.096	0.157	0.091	0.066
2p	0.043	0.086	0.022	0.059	0.038	0.081	0.142	0.076
2q	0.033	0.073	0.019	0.054	0.086	0.142	0.076	0.064

Table 9 Probability and current status to be mutagenic and skin irritant of designed screened compound

Comp.	Mutagenicity		Skin irritancy		Method employed
	Probability	Status	Probability	Status	
1a	0.020	Non-Mutagen	0.043	Non-irritant	Consensus
1b	0.020	Non-Mutagen	0.012	Non-irritant	Consensus
1c	0.300	Non-Mutagen	0.025	Non-irritant	Consensus
2a	0.398	Non-Mutagen	0.058	Non-irritant	TOPKAT®
2b	0.366	Non-Mutagen	0.014	Non-irritant	TOPKAT®
2c	0.349	Non-Mutagen	0.187	Non-irritant	TOPKAT®
2d	0.418	Non-Mutagen	0.524	Non-irritant	TOPKAT®
2e	0.450	Non-Mutagen	0.011	Non-irritant	TOPKAT®
2f	0.468	Non-Mutagen	0.570	Non-irritant	TOPKAT®
2g	0.330	Non-Mutagen	0.162	Non-irritant	TOPKAT®
2h	0.575	Non-Mutagen	0.662	Non-irritant	TOPKAT®
2i	0.551	Non-Mutagen	0.597	Non-irritant	TOPKAT®
2j	0.314	Non-Mutagen	0.947	Non-irritant	TOPKAT®
2k	0.354	Non-Mutagen	0.910	Non-irritant	TOPKAT®
2l	0.537	Non-Mutagen	0.481	Non-irritant	TOPKAT®
2m	0.459	Non-Mutagen	0.360	Non-irritant	TOPKAT®
2n	0.494	Non-Mutagen	0.314	Non-irritant	TOPKAT®
2o	0.325	Non-Mutagen	0.908	Non-irritant	TOPKAT®
2p	0.255	Non-Mutagen	0.728	Non-irritant	TOPKAT®
2q	0.170	Non-Mutagen	0.543	Non-irritant	Consensus

The model used in Ames *In-silico* test matches the predicted value with the experimental values used in modeling of software, depending upon them if probability comes 1 then the designed molecules may act as mutagenic.

Predicted oral rat LD_{50}

Predicted oral rat LD_{50} of screened compound is presented in Table 10, where it is converted to g/kg instead of mg/kg.

Table 10 Predicted oral rat LD_{50}

Compound	Oral rat LD_{50} (g/kg)
1a	5.27
1b	4.33
1c	0.810
2a	2.87
2b	4.15
2c	4.59
2d	4.54
2e	3.27
2f	5.13
2g	2.66
2h	3.12
2i	3.25
2j	2.82
2k	2.66
2l	2.71
2m	2.99
2n	3.21
2o	1.71
2p	4.27
2q	2.92

Possible mechanism of action of synthesized sulfonamide derivatives

Literature shows that variety of isoforms of Carbonic anhydrase is responsible as anticonvulsant target (17) . Sulfonamides are the most important class of Carbonic Anhydrase Inhibitors (CAIs).(Wood, 1942; Supuran, 2008; Thiary et al., 2008)

The inhibition and activation of CAs are well-understood processes: most types of classical inhibitors bind to the metal center (De Simone et al., 2009) .

CO_2, bicarbonate, and protons are essential molecules/ions in many important physiologic processes in all life kingdoms (Bacteria, Archaea, and Eukarya), throughout the tree of life, and for this reason, relatively high amounts of CAs are present in different tissues/cell compartments of most investigated organisms (Wood, 1942; Supuran, 2008) .

In many organisms, CAs enzymes are involved in crucial physiologic processes connected with respiration and transport of CO_2/bicarbonate, pH and CO_2 homeostasis, electrolyte secretion in a variety of tissues/organs, biosynthetic reactions (e.g. gluconeogenesis, lipogenesis, and ureagenesis), bone resorption, calcification, tumorigenicity and many

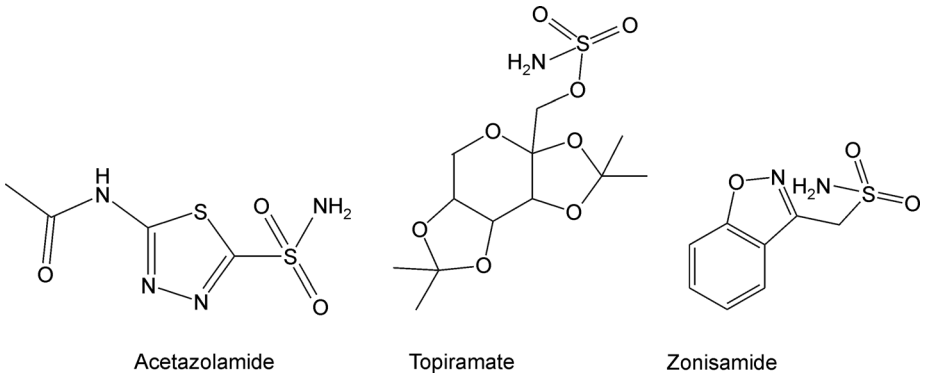


Figure 5 Carbonic anhydrase inhibitors.

other physiologic or pathologic processes (thoroughly studied in vertebrates). In algae, plants, and some bacteria they play an important role in photosynthesis and other biosynthetic reactions.(Capasso and Supuran, 2005) Many such enzymes from vertebrates, nematodes, fungi, protozoa and bacteria are well-known drug targets (Supuran, 2008).

Carbonic anhydrase inhibition as anticonvulsant effect

One potential factor that may contribute to seizure is the modification of the environmental pH (alkalosis increases the neuronal excitability) (Thiry et al., 2007) . The pH buffering of the extracellular and intracellular spaces is mainly carried out by the CO_2 / HCO_3 buffer. The ratio of these two species is regulated by the activity of the carbonic anhydrase which catalyzes the reversible conversion of CO_2 and H_2O into H^+ and HCO_3^- (Zimmerman et al., 2004) . Acetazolamide, Topiramate and Zonisamide (Fig. 5) are a well known Carbonic anhydrase inhibitors as anticonvulsants.

These drugs act by blocking sodium and calcium channels, which leads to the suppression of neuronal hypersynchronization.

Conclusion

In conclusion, we have described the designing, synthesis, biological evaluation, computational studies and *in-silico* evaluation of synthesized compounds as anticonvulsant agents. The designed compounds were successfully and well characterized by analytical and spectral data. Docking studies showed good interaction with lyase (Oxo-acid) - human carbonic anhydrase-I (1AZM). The *in-silico* studies proved them to be with good drug-likeness properties. *In-silico* studies proved them with promising results, especially 4-(3-acetyl-phenylamino)-methyl)-benzenesulfonamide (2g), however, further clinical studies need to be carried to re-confirm and proved the findings. These results revealed that the synthesized compounds **(1a-1c, 2a-2q)** exhibited promising anticonvulsant effect against MES model for inhibition of Lyase- Human Carbonic Anhydrase-I. A comparatively good activity of compound **2g** suggests us that sulphonamide can be leads to further optimized for building potent and chemically diversified anti-convulsant agents.

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Author's contribution

Ajeet conceptualized overall study design and carried synthesis, biological studies, analyzed and interpreted data. Dr. Arvind Kumar and Dr. Arun Kumar Mishra analyzed and revised the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Permission was sought from Institutional Animal Ethics Committee, IFTM University, India for carrying biological studies (Animal studies) under Registration No. 837/ac/04/CPCSEA and Resolution No. 2015/837ac/PhD/04.

Conflicts of interest

None conflict of interest declared.

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