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Ultrasound assisted synthesis, molecular docking and antimicrobial activities of some aryl sulfonamides

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A series of aryl sulfonamides have been synthesised with more than 70% yield using ultrasound assisted condensation of aryl sulfonyl chloride and aryl amines in the presence of ferric chloride-bentonite in ethanol medium. The synthesised sulfonamides have been characterized from their physical constants, infrared and NMR spectroscopic data. In this synthetic method, the effect of catalyst and solvents on the yields have been studied. The molecular docking analysis of these sulfonamides have been investigated by finding protein-ligand interaction and binding affinities. Antimicrobial activities of these sulfonamides have been studied against selected microbes.

Keywords: Aryl sulfonamides, Ultrasound assisted synthesis, Ferric chloride-bentonite, Molecular docking, Antimicrobial activities

Now-a-days ultrasound assisted synthetic methodology plays an important role for organic building blocks[1-4]. This technique makes it possible to synthesise a large number of organic molecules in a simple, clean, rapid, efficient, pollution less and economic manner[4]. Chemists and Scientists employed various methods for the synthesis of sulfonamides such as microwave irradiation[4,5], solvent-free synthesis[6,7], sonication[2-4], and aqueous medium techniques[8,9]. In these methods numerous catalysts were employed for the synthesis of sulfonamides such as Lewis's acids and bases[10,11], Pd, Ru and Cu metals[12-14], oxides of Mg and Cu[15,16], nano-ZnO particles[17], DABCO[18], Iodine-TBHP[19], beta-Cyclodextrin[20], Cu/Zeolite[4], Fly-ash:H_3PO_4[3], potassium phthalate[2] and CsF-Celite[20]. Several synthetic methods have been developed for the synthesis of sulfonamides such as chlorosulfonylatio13, rearrangement of sulfonimidate[14], transformations[21], monosulfonylation[22] and cyclization[23]. Tsai *et al.*, reported the novel route for the synthesis of N-tosylhydrazones in the presence of DABSCO catalyst[24]. Lee *et al.* have synthesis five different sulfonamides from sulfonate ester resin and various amines in THF medium[25]. Some aliphatic sulfonamides[26] were synthesised from sulfonyl fluoride in the presence of triethyl amine. Various aryl sulfonamides were synthesised from hetero aryl thiols, disulfides, thiols, aryl halides and sulfur-di-oxides, and polyboronic acid with tosyl azides[27-29]. Dineshkumar *et al.*, reported the microwave assisted synthesis of more than 70% yields of mesalazine based sulfonamides[4]. Synthesis and spectral QSAR study of 3-(substituted phenylsulfonamido) benzoic acids were reported by Dinesh kumar and Thirunarayanan[3]. Mokhtar and his team reported the efficient synthetic route for the synthesis of various sulfonamides from various amines and sulfonyl chlorides under sonication technique[30]. Recently potassium phthalate and fly-ash-Phosphoric acid catalysed ultrasound assisted synthesis and antimicrobial activities of some sulfonamide acids and difluoro-sulfonamides are visible in the literature[2-4]. Sulfonamides are the most common antibiotics worldwide and these come in the medical field since 1968 (Ref. 31). In front sulfonamides are mainly used to treat the urinary tract, as well as upper airway infections[32]. These medicines have stayed popular because they are well tolerated by patients, and they are relatively cheap[33]. Sulphonamides possess numerous biological activities such as antimicrobial[2-4,34], antitumour[35], anti-carbonic-anhydrase[36], anti-malarial[37],

anti-HIV[38], antiretro-viral[39], anti-convulsant[40], anti-inflammatory[41], insulin releasing[42], anti-dandruff[43], Alzheimer's[44], Diuric[45], hypoglycemic[46], anti-thyroid[47] and protease inhibitions[48]. Also, sulfonamides are widely employed as synthons for the synthesis of various bio-active organic substances such as sulpha drugs, dyes and metal complexes[49-51]. According to the literature survey, there is no report available for the synthesis, molecular docking and biological activities of some sulfonamides including 5-substituted phenylsulfamide isophthalic acid derivatives. Hence, the authors employed Ultrasound assisted ferric chloride-bentonite catalyzed condensation method for the synthesis of some aryl sulfonamides, evaluation of molecular docking and biological activities.

Results and Discussion

The authors synthesised some series of aryl sulfonamides using ultrasound assisted ferric chloride-bentonite catalysed condensation of aryl sulfonyl chloride and aryl amines. In this synthesis equal molar volume of aryl sulfonyl chloride and aryl amines and 0.3 mg of ferric chloride-bentonite catalyst were used in the ethanol medium. During the reaction 0.1 mL of triethylamine was added to neutralize the formation of hydrochloride. This reaction follows well known simple condensation by the nucleophilic attack of phenyl sulfoxide cation followed by lose of proton and elimination of hydrochloride affords the sulfonamide derivatives. The proposed possible reaction mechanism was illustrated in Scheme 1.

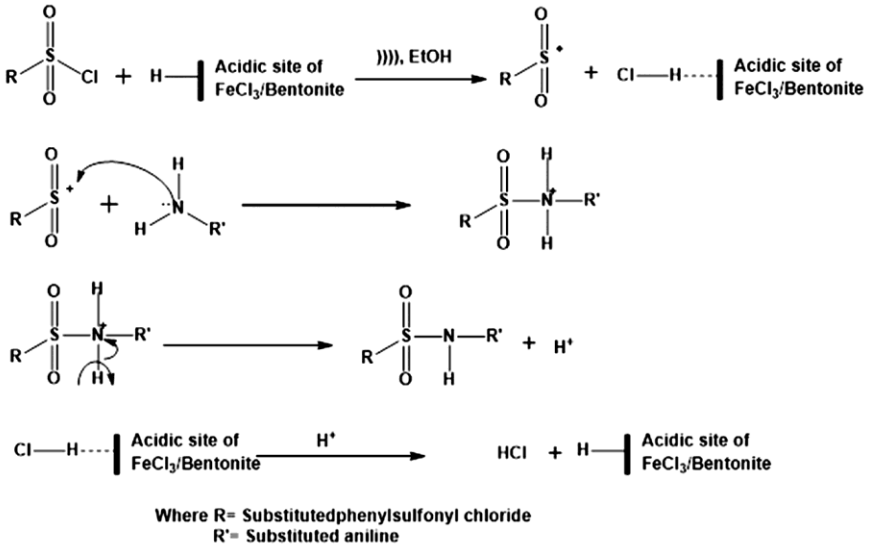
First step consists of the formation aryl sulfoxide cation by abstraction of chloride ion on the acidic site of catalyst. Second step is the nucleophilic attack of aryl sulfoxide by amine to from the positive charge on the amine nitrogen atom. Then it loses proton to afforded the sulfonamide. The proton combined with chloride ion to form hydrogen chloride and the catalyst was regenerated. Synthesised sulfonamides from this method were analysed with their physical constants and spectroscopic data. These data are well agreed with the data published in earlier for reported compounds.

Effect of catalyst

In this condensation, sulfonamides which have electron releasing groups gave higher yield than with electron withdrawing groups. Further we investigated the effect of catalyst on the synthesis of sulfonamide **5a** by increasing the catalyst from 0.05 to 4 mg. The obtained yields of the condensation are 35 to 76%. The optimum quantity of the catalyst was 0.3 mg. Beyond this quantity of the catalyst added, there is no increases in the yield. This is illustrated in Fig. 1. The obtained yield of sulfonamides is shown in Table 1.

Effect of solvent

Similarly, the authors studied the effect of solvents on the synthesis of sulfonamides by conventional heating method with various solvents such as acetonitrile, dichloromethane, dioxane, ethanol, methanol, n-propanol and tetrahydrofuran. Among these solvents, we found that the ethanol solvent gave



Scheme 1 — Ultrasound irradiated ferric chloride-bentonite catalyst assisted synthesis of sulfonamides

more yield than other solvents. Lowest yield was obtained in dioxane solvent. In general, the electron donating substituents yields higher percentage of products than electron-withdrawing substituents in all solvents medium. The high electronegative fluorine substituted aldehyde gave lesser yields than parent and electron donating substituent methoxy group. The effect of solvent on this condensation was presented in Table 2.

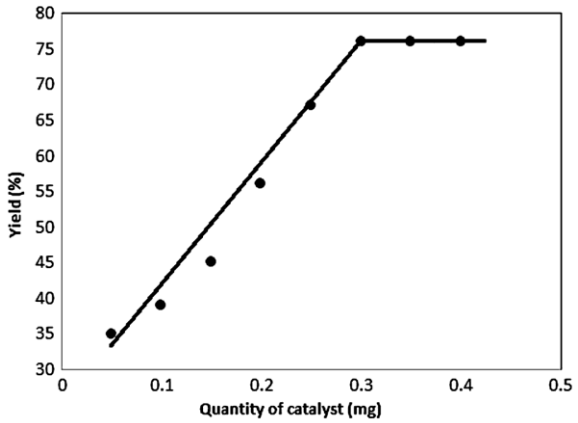


Fig. 1 — Effect of catalyst on the synthesis of sulfonamide **5a**

Molecular docking study

The docking analysis of the 2-Hydroxy-5-(substituted phenylsulfonamido) benzoic acids as ligands to protein active sites were carried out by Auto dock 4 for determining the binding energies of the compounds. The designed compounds were docked towards the Topoisomerase II inhibitors (5GWK)[52,53]. The compound 2-Hydroxy-5-(4-nitrophenylsulfonamido) benzoic acid **1i** shows good affinity to the receptor. The compound **1i** has highest binding energy when compared to other compounds. The results are listed out in Table 3.

Molecular docking method showed very exciting results of designed ligands. Results pointed out that binding of all designed ligands displayed binding energy values with receptor protein 5GWK ranging from (–3.99 to –5.4). The docking receptor Topoisomerase II inhibitors (5GWK) with newly synthesized ligands showed well organized bonds with one or more amino acids in the receptor pocket. The active compound consisted of Amino acid residues are ASN B:1126, ILE A: 1074, LYS B:1071, LYS B:1075, PRO A:1123, SER A:1121 (Asparagine,

Table 1 — Effect of catalyst loading

Qty. of catalyst (mg)	0.05	1	1.5	2	2.5	3	3.5	4
Yield (%)	35	38	48	56	66	76	76	76

Table 2 — Influence of solvents on the synthesis of 5-(substituted phenyl sulfonamido)isophthalic acids

Compd	Solvents→ X ↓	ACN	DCM	DO	EtOH	MeOH	*n*-Prop	THF
5a	H	54	52	39	76	62	51	55
5b	4-Br	50	53	36	72	60	48	55
5c	4-Cl	50	55	36	72	61	48	56
5d	2-F	53	54	35	70	60	49	55
5e	4-F	53	50	35	74	63	44	55
5f	4-OCH_3	58	56	42	76	66	53	58
5g	4-CH_3	55	55	41	75	64	52	56
5h	2-NO_2	55	52	36	71	63	46	51
5i	4-NO_2	58	53	33	72	63	46	52

CAN: Acetonitrile; DCM: Dichloromethane; DO: Dioxane; EtOH: Ethanol; MeOH: Methanol; *n*-Prop: *n*-Propanol; THF: Tetrahydrofuran

Table 3 — The results of molecular docking analysis of 2-hydroxy-5-(phenylsulfonamido) benzoic acids **1a-i**

Compd	Subst	PDB ID	Binding Energy ΔG (Kcal/mol)	Grid X-Y-Z Coordinates
1a	H	5GWK	–3.99	60, 80, 60
1b	4-Br	5GWK	–4.6	60, 80, 60
1c	4-Cl	5GWK	–4.64	60, 80, 60
1d	2-F	5GWK	–5.09	60, 80, 60
1e	4-F	5GWK	–4.38	60, 80, 60
1f	4-OCH_3	5GWK	–4.32	60, 80, 60
1g	4-CH_3	5GWK	–4.1	60, 80, 60
1h	2-NO_2	5GWK	–4.56	60, 80, 60
1i	4-NO_2	5GWK	–5.4	60, 80, 60

Isoleucine, Lysine, Proline, Serine) and also displays the docking mode of compound **1i** with all three important interactions like hydrogen bonding, hydrophobic interaction and the Vander Waals forces interactions. The binding energies for **1i** were found to be –5.4, which is the highest values in the series of synthesized compounds and compared to other compounds. This docking binding energy might be due to the presence of nitro group substitution. The 2D and 3D image of highest binding energies of compound shown in Fig. 2.

The results of docking analysis of the ligands 3-(substituted phenylsulfonamido) benzoic acids **2a-i** were done with Topoisomerase II inhibitors (5GWK). The compound 3-(4-nitrophenylsulfonamido benzoic acid) **2i** showed good affinity to the receptor. Also, this compound has highest binding energy when compared to other compounds. The results are listed out in the Table 4.

Molecular docking method showed very exciting results of designed ligands. Results pointed out that binding of all designed ligands displayed binding energy values with receptor protein 5GWK ranging from (–4.93 to –6.49). The docking receptor Topoisomerase II inhibitors (5GWK) with newly synthesized ligands showed well organized bonds with one or more amino acids in the receptor pocket. The active **2i** consisted of Amino acid residues are ASN B:583, ASN B:604, LYS B:582, LYS B:607 (Asparagine, Lysine) and also displays the docking mode of compound **2i** with all three important interactions like hydrogen bonding, hydrophobic interaction and the Vander Waals forces interactions. The binding energies for **2i** were found to be –6.49, which is the highest values in the series of synthesized compounds and compared to other compounds. This docking binding energy might be due to the presence of methyl group substitution. The 2D and 3D image of highest binding energies of compound **2i** shown in Fig. 3.

The docking analysis of the ligands 4-(substituted phenylsulfonamido) benzoic acids **3a-i** to protein active sites were carried out by Auto dock 4 for determining the binding energies of the compounds. The designed compounds were docked towards the Topoisomerase II inhibitors (5GWK). The compound

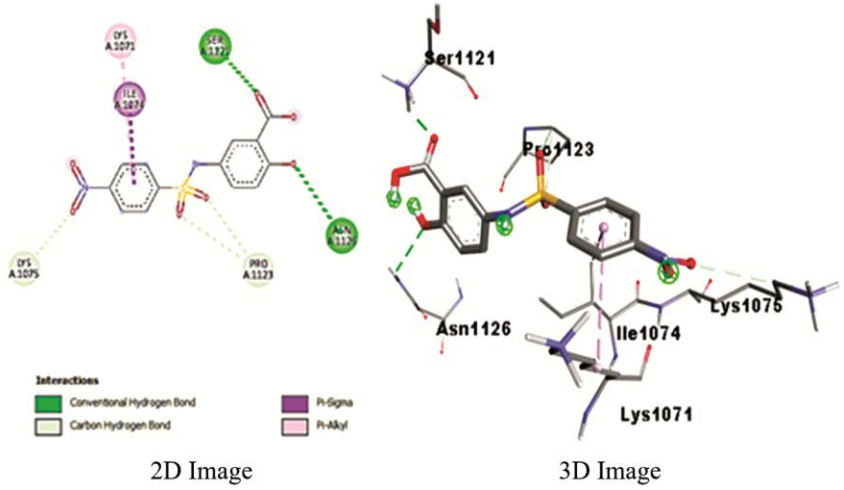


Fig. 2 — The 2D and 3D image of highest binding energies of compound 2-hydroxy-5-(4-nitrophenylsulfonamido) benzoic acid **1i**

Table 4 — The results of molecular docking analysis of 3-(phenylsulfonamido) benzoic acids **2a-i**

Compd	Subst	PDB ID	Binding Energy ΔG (Kcal/mol)	Grid X-Y-Z Coordinates
2a	H	5GWK	–5.49	60, 80, 60
2b	4-Br	5GWK	–4.87	60, 80, 60
2c	4-Cl	5GWK	–5.48	60, 80, 60
2d	2-F	5GWK	–5.15	60, 80, 60
2e	4-F	5GWK	–4.93	60, 80, 60
2f	4-OCH_3	5GWK	–5.1	60, 80, 60
2g	4-CH_3	5GWK	–5.56	60, 80, 60
2h	2-NO_2	5GWK	–5.22	60, 80, 60
2i	4-NO_2	5GWK	–5.92	60, 80, 60

4-(4-methoxyphenylsulfonamido) benzoic acid **3f** showed good affinity to the receptor. The compound **3f** has highest binding energy when compared to other compounds. The results are listed out in Table 5.

Molecular docking method showed very exciting results of designed ligands. Results pointed out that binding of all designed ligands displayed binding energy values with receptor protein 5GWK ranging from (–4.87 to –5.92). The docking receptor Topoisomerase II inhibitors (5GWK) with newly synthesized ligands showed well organized bonds with one or more amino acids in the receptor pocket. The active **3f** consisted of Amino acid residues are ARG B:958, ASN B:917, ASP B:956, LYS B:971, THR B:919, TYR B:960, VAL B:969 (Arginine, Asparagine, Aspartic acid, Lysine, Threonine, Tyrosine, Valine) and also displays the docking mode of compound **3f** with all three important interactions like hydrogen bonding, hydrophobic interaction and the Vander Waals forces interactions. The binding energies for **3f** were found to be –5.92, which is the highest values in the series of synthesized compounds and compared to other compounds. This docking binding energy might be due to the presence of nitro group substitution. The 2D and 3D image of highest binding energies of compound **3f** shown in Fig. 4.

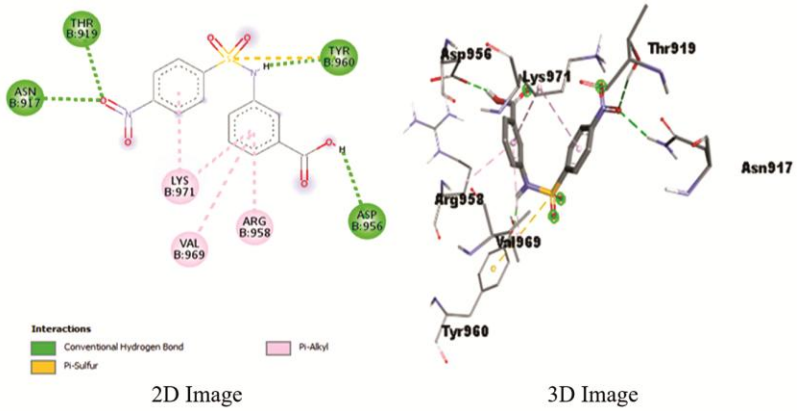


Fig. 3 — The 2D and 3D image of highest binding energies of compound 3-(4-nitrophenylsulfonamido) benzoic acid **2i**

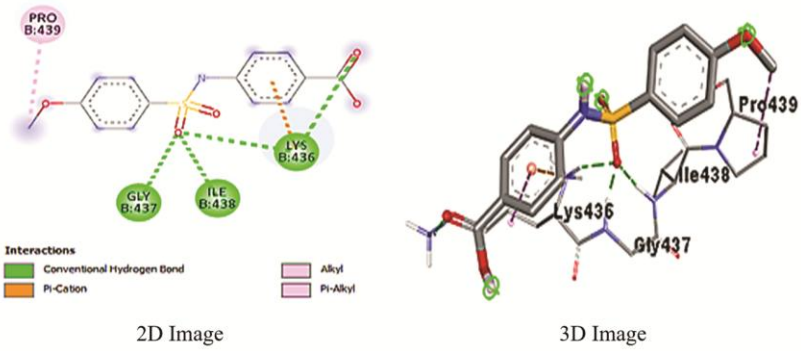


Fig. 4 — The 2D and 3D image of highest binding energies of compound 3-(4-methoxyphenylsulfonamido) benzoic acid **3f**

Table 5 — The results of molecular docking analysis of 3-(phenylsulfonamido) benzoic acids **3a-i**

Compd	Subst	PDB ID	Binding Energy ΔG (Kcal/mol)	Grid X-Y-Z Coordinates
3a	H	5GWK	–4.59	60, 80, 60
3b	4-Br	5GWK	–5.39	60, 80, 60
3c	4-Cl	5GWK	–4.45	60, 80, 60
3d	2-F	5GWK	–4.76	60, 80, 60
3e	4-F	5GWK	–4.65	60, 80, 60
3f	4-OCH_3	5GWK	–5.46	60, 80, 60
3g	4-CH_3	5GWK	–4.83	60, 80, 60
3h	2-NO_2	5GWK	–5.07	60, 80, 60
3i	4-NO_2	5GWK	–5.08	60, 80, 60

The docking analysis of the ligands 2,4-(Difluoro phenyl)(substituted benzene sulfonamides **4a-i** to protein active sites were carried out by Auto dock 4 for determining the binding energies of the compounds. The designed compounds were docked towards the Topoisomerase II inhibitors (5GWK). The compound 2,4-(Difluorophenyl)(4-nitrophenylsulfonamide **4i** showed good affinity to the receptor. The compound **4i** has highest binding energy when compared to other compounds. The results are listed out in Table 6.

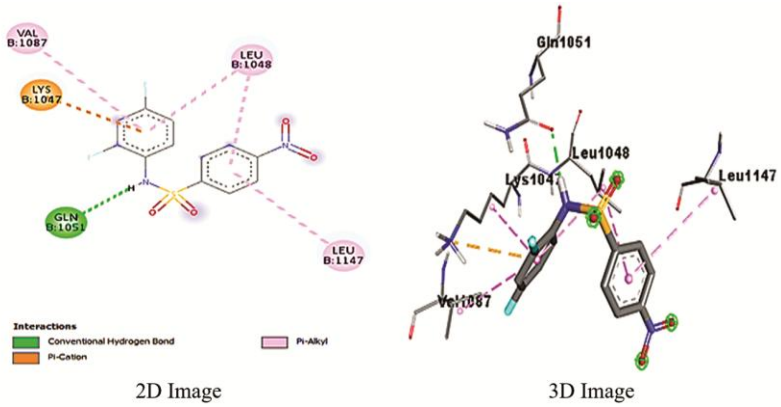
Molecular docking method showed very exciting results of designed ligands. Results pointed out that binding of all designed ligands displayed binding energy values with receptor protein 5GWK ranging from (–4.45 to –5.46). The docking receptor Topoisomerase II inhibitors (5GWK) with newly synthesized ligands showed well organized bonds with one or more amino acids in the receptor pocket. The active **4i** consisted of Amino acid residues are GLY B:437, ILE B: 438, LYS B:436, PRO B:439 (Glycine, Isoleucine, Lysine, Proline) and also displays the docking mode of compound **4i** with all three important interactions like hydrogen bonding, hydrophobic interaction and the Vander Waals forces interactions. The binding energies for **4i** were found to be –5.46, which is the highest values in the series of synthesized compounds and compared to other compounds. This docking binding energy might be due to the presence of methoxy group substitution. The 2D and 3D image of highest binding energies of compound **4i** shown in Fig. 5.

The docking analysis of the ligands 5-(Substituted phenylsulfonamido)isophthalic acids **5a-i** to protein active sites were carried out by Auto dock 4 for determining the binding energies of the compounds. The designed compounds were docked towards the Topoisomerase II inhibitors (5GWK). The compound 5-(4-methyl phenyl sulfonamido) isophthalic acid **5g** showed good affinity to the receptor. The compound **5g** has highest binding energy when compared to other compounds. The results are listed out in Table 7.

Molecular docking method showed very exciting results of designed ligands. Results pointed out that binding of all designed ligands displayed binding energy values with receptor protein 5GWK ranging from (–4.46 to –5.08). The docking receptor Topoisomerase II inhibitors (5GWK) with newly synthesized ligands showed well organized bonds with one or more amino acids in the receptor pocket. The active **5g** consisted of Amino acid residues are

Table 6 — The results of molecular docking analysis of 2,4-(difluoro phenyl)(substituted benzene sulfonamides **4a-i**

Compd	Subst	PDB ID	Binding Energy ΔG (Kcal/mol)	Grid X-Y-Z Coordinates
4a	H	5GWK	–4.56	60, 80, 60
4b	4-Br	5GWK	–5.04	60, 80, 60
4c	4-Cl	5GWK	–4.82	60, 80, 60
4d	2-F	5GWK	–4.46	60, 80, 60
4e	4-F	5GWK	–4.92	60, 80, 60
4f	4-OCH_3	5GWK	–4.54	60, 80, 60
4g	4-CH_3	5GWK	–4.74	60, 80, 60
4h	2-NO_2	5GWK	–4.73	60, 80, 60
4i	4-NO_2	5GWK	–5.08	60, 80, 60



2D Image 3D Image

Fig. 5 — The 2D and 3D image of highest binding energies of compound 2,4-(difluoro phenyl)(4-nitrophenylsulfonamide **4i**

Table 7 — The results of molecular docking analysis of 5-(substituted phenylsulfonamido) isophthalic acids **5a-i**

Compd	Subst	PDB ID	Binding Energy ΔG (Kcal/mol)	Grid X-Y-Z Coordinates
5a	H	5GWK	–5.58	60, 80, 60
5b	4-Br	5GWK	–6.45	60, 80, 60
5c	4-Cl	5GWK	–5.21	60, 80, 60
5d	2-F	5GWK	–4.93	60, 80, 60
5e	4-F	5GWK	–6.33	60, 80, 60
5f	4-OCH_3	5GWK	–5.88	60, 80, 60
5g	4-CH_3	5GWK	–6.49	60, 80, 60
5h	2-NO_2	5GWK	–5.18	60, 80, 60
5i	4-NO_2	5GWK	–5.52	60, 80, 60

Table 8 — Antibacterial activities of 5-(substituted phenyl sulfonamido)isophthalic acid

Compd	Substituent	Zone of inhibition (mm)			
		Gram-positive		Gram-negative	
		Micrococcus luteus	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*
5a	H	9	8	–	13
5b	4-Br	8	9	–	7
5c	4-Cl	–	6	12	–
5d	2-F	–	6	10	6
5e	4-F	–	11	6	–
5f	4-OCH_3	6	–	12	11
5g	4-CH_3	6	12	7	10
5h	2-NO_2	–	10	9	7
5i	4-NO_2	7	10	9	7
Standard	Ampicillin	17	17	18	18
Control	DMSO	–	–	–	–

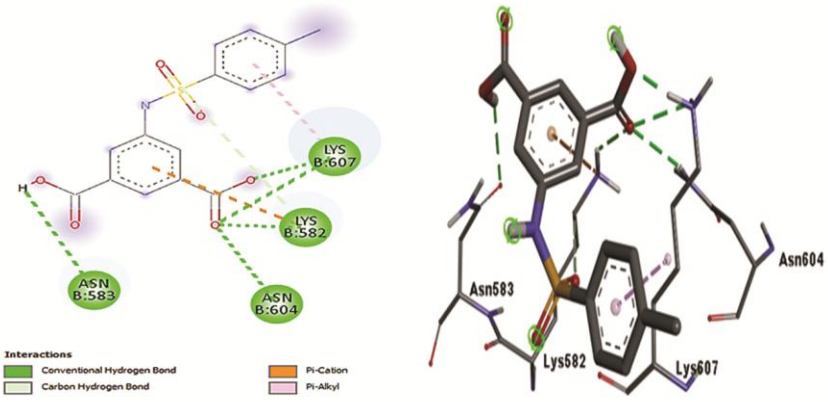


Fig. 6 — The 2D and 3D image of highest binding energies of compound 5-(4-methyl phenyl sulfonamido) isophthalic acid **5g**

GLN B:1051, LEU B:1048, LEU B:1147, LYS B:1047, VAL B:1087 (Glutamine, Leucine, Lysine, Valine) and also displays the docking mode of compound **5g** with all three important interactions like hydrogen bonding, hydrophobic interaction and the Vander Waals forces interactions. The binding energy for compound **5g** were found to be –5.08, which is the highest values in the series of synthesized compounds and compared to other compounds. This docking binding energy might be due to the presence of nitro group substitution. The 2D and 3D image of highest binding energies of compound **5g** shown in Fig. 6.

Antimicrobial activities

Antibacterial activity

The antibacterial activities of all synthesized 5-(substituted phenyl sulfonamido) isophthalic acid compounds **5a-i** are presented in Fig. 7 and the zone of inhibition[54-61] values are indicated in Table 8. The corresponding clustered column graph appears in

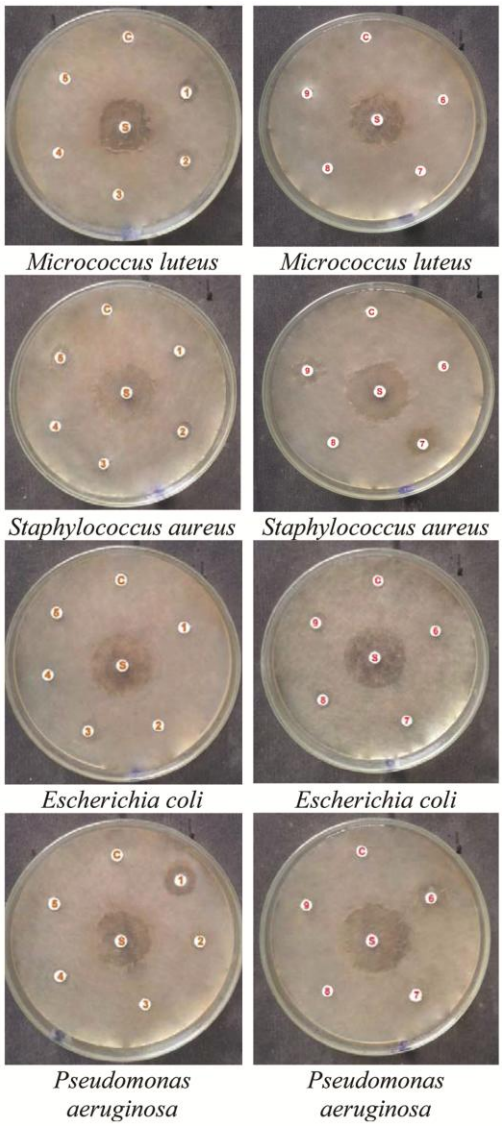


Fig. 7 — Antibacterial activities (petri-dishes) of 5-(substituted phenylsulfonamido)isophthalic acid compounds (Series B). C – Standard drug (Ampicillin)

Fig. 8. The parent substituent (H) shows satisfactory antibacterial activity, the substituents 4-Br, 4-OCH_3, 4-CH_3 and 4-NO_2 have shown least activity. Here the inductive effects of the substituents and hyper conjugation of methyl groups enhance the antibacterial activity. and the other substituted (4-Cl, 2-F, 4-F and 2-NO_2) compounds have no antibacterial activity against *Micrococcus luteus*. This is due to the electronegativity of fluorine atoms inability of inductive effects of chlorine and nitro groups unable to predict the antibacterial activity.

The sulfonamides with 4-Br, 4-F, 4-CH_3, 2-NO_2 and 4-NO_2 substituents have shown satisfactory antibacterial activity, the substituents Parent, 4-Cl

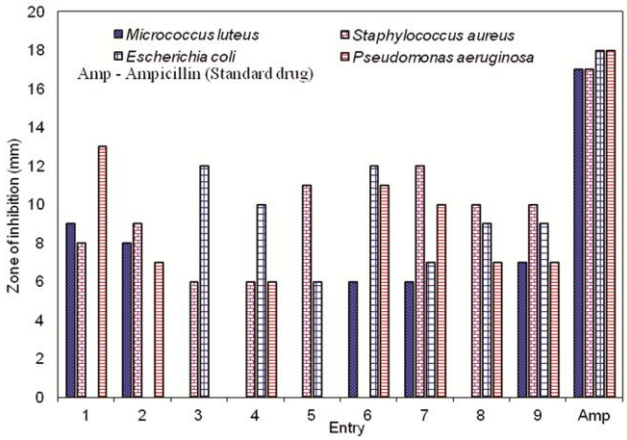


Fig. 8 — Antibacterial activities (clustered column chart) of 5-(phenyl sulfonamido)isophthalic acid

and 2-F have shown least activity and the 4-OCH_3 substituted compounds have no antibacterial activity against *Staphylococcus aureus*. Here the inductive effect of chloride and electronegative character of fluorine atoms are reduced the antibacterial activity. The inability of inductive effect of methoxy group affects the antibacterial activity

The substituents in the sulfonamides such as 4-Cl, 4-OCH_3, 2-F, 2-NO_2 and 4-NO_2 substituent shows satisfactory antibacterial activity, the substituents 4-F and 4-CH_3 have shown least activity. Here the inductive effect, electonegatity of fluorine and hypercojugative effect of methyl groups were inducts the antibacterial activity. The other substituted compounds (H and 4-Br) have no antibacterial activity against *Escherichia coli*. This is due to the inability of inductive effect to show the activity.

Sulfonamides with parent, 4-OCH_3 and 4-CH_3 substituents have shown satisfactory antibacterial activity. Here the inductive and hypercojugative effects inducts the antibacterial activity. Due to the inability of inductive effects and electronegativity of fluorine substituents (4-Br, 2-F, 2-NO_2 and 4-NO_2) were reduced to least level of the antibacterial activity. The other substituted compounds (4-Cl, 4-F) have no antibacterial activity against *Pseudomonas aeruginosa*. This is due to absence of inductive and electronegativity of substituents for showing the antibacterial activity.

Antifungal activities

The antifungal activity of 5-(substituted phenylsulfonamido) isophthalic acid compounds in series **B** is shown in Fig. 9 and the zone of

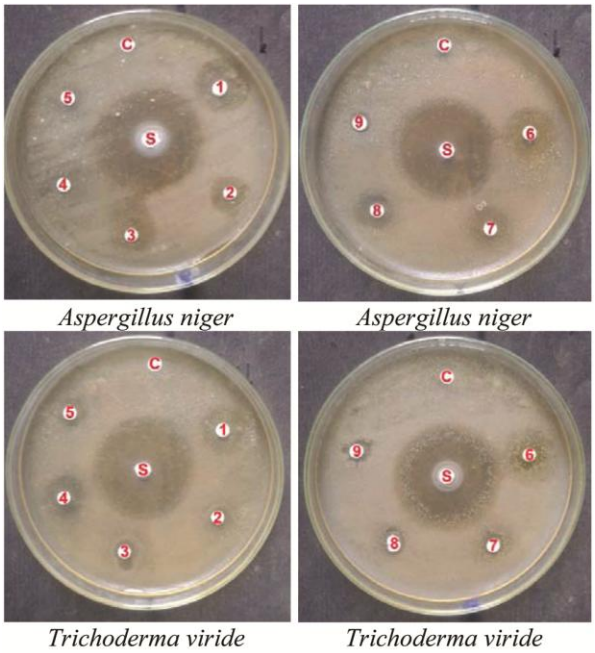


Fig. 9 — Antifungal activities of 5-(substituted phenyl sulfonamido) isophthalic acid compounds C – Standard drug (Miconazole)

Table 9 — Antifungal activities of 5-(substituted phenyl sulfonamido) isophthalic acids

Entry	Subs.	Zone of inhibition (mm)	
		Aspergillus niger	*Trichoderma viride*
5a	H	15	14
5b	4-Br	10	7
5c	4-Cl	11	8
5d	2-F	13	13
5e	4-F	8	7
5f	4-OCH_3	15	14
5g	4-CH_3	11	8
5h	2-NO_2	10	8
5i	4-NO_2	8	8
Standard	Miconazole	22	22
Control	DMSO	–	–

inhibition[62-75] values are given in Table 9. The corresponding clustered column chart is shown in Fig. 10. The 5-(substituted phenylsulfonamido) isophthalic acid compounds with Parent, and 4-OCH_3 substituents have shown good antifungal activity. The well operates of inductive effect of the substituents parent and methoxy groups. The compounds with 4-Br, 4-Cl and 2-NO_2 substituents shows satisfactory antifungal activity. Here the inductive effects of the substituents enhance the antifungal activity. The other substituted compounds (2- and 4-F, 4-CH_3 and 4-NO_2 have shown least antifungal activity against *Aspergillus niger*. This due to the electronegativity of fluorine atom, inductive and hypercojugative effect of

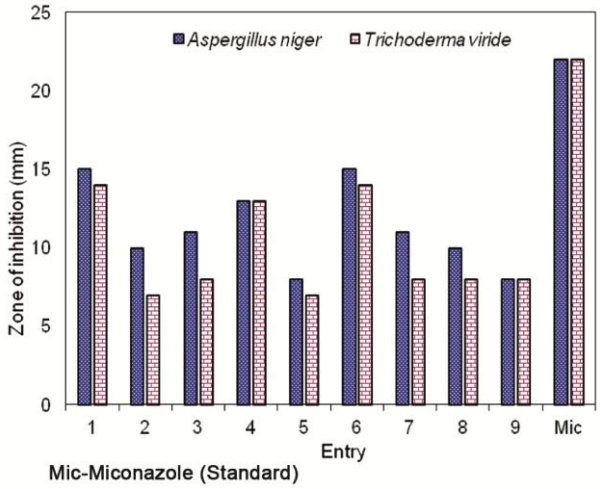


Fig. 10 — Antifungal activities (clustered column chart) of 5-(substituted phenyl sulfonamido)isophthalic acid compounds

methyl groups unable to shows the antifungal activity.

The 5-(substituted phenylsulfonamido) isophthalic acid compounds with Parent, and 4-OCH_3 substituents have shown good antifungal activity due to well transmittance of the inductive effect enhances the antifungal activity. The compounds with 4-Cl substituent have shown satisfactory antifungal activity. The other substituted compounds (2-F, 4-F, 4-Br, 4-CH_3, 2- and 4-NO_2) have shown least antifungal activity against *Trichoderma viride*. This is due to the absence of inductive effect, electronegativity of fluorine atoms and hyper conjugative effect of ethyl groups unable to show the antifungal activity.

Experimental Section

Material and Methods

The chemicals needed for the synthesis were obtained from Sigma-Aldrich. The melting points of all the synthesized compounds were determined in open glass capillaries by means of the Mettler FP51 melting point device and are uncorrected. Infrared spectra of all compounds have been captured in Avatar-300 Thermo Nicolet Fourier Transform Infrared Spectrophotometer using KBr discs with a frequency range of 4000-400 cm^{-1}. NMR spectra for all compounds were recorded on the Bruker AV 400 spectrometer operated at 400 MHz. Bruker AV 500 spectrometer operated at 500 MHz was used for ^{1}H NMR spectra and 125 MHz for ^{13}C NMR spectra in $CDCl_3$ solvent utilizing TMS as an internal standard. Elementary analysis was performed with a Perkin-Elmer 240 CHN analyzer. Mass spectra of all

compounds were recorded in the Varian-Saturn 2200 GC-MS spectrometer by means of the electronic impact technique (70 eV) and the FAB technique in chemical ionization mode. The chemicals, namely nutrient broth, Mueller-Hinton Agar, potato dextrose agar, tween-80 solution and other necessary materials for microbial studies were obtained from Himedia, Mumbai.

Experimental procedure for the synthesis of sulfonamides

Equimolar concentration of substituted benzenesulfonylchloride (1 mmol), substituted anilines (1 mmol), ferric chloride-bentonite[76] (0.3 mg) catalyst and 20 mL of ethanol were taken in a 100 mL conical flask, mixed thoroughly and closed. This mixture was subjected to ultrasonication for 13-24 min in a sonicator (Citizen Ultrasound Sonictor, 5 L, 120 W, HF 90 W, 40 kHz, 220-240 V, AC/50 Hz (Scheme 2). In this reaction 0.1 mL of triethylamine was added to neutralize the formation of HCl. The completion of the reaction was monitored by TLC. The product obtained was washed with *n*-hexane and the catalyst separated with methanol by filtration and dried in order to obtain the solid. Their physical constants, yields and time of the reactions are presented in Table 10.

The assigned IR, ^{1}H and ^{13}C NMR spectroscopic data of synthesised 5-(substitutedphenylsulfonamido) isophthalic acids are summarized as follows.

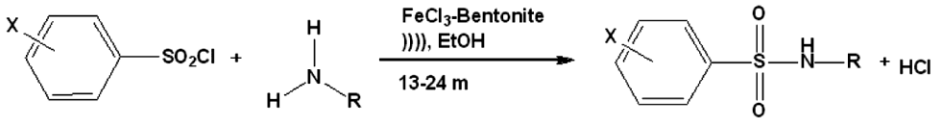
5-(Phenylsulfonamido)isophthalic acid, 5a: Colourless solid. IR (KBr): 3219.3(NH), 1693.4(CO), 1326.3 (SOsym), 1162 cm^{-1} (SOasym); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.851(s, 1H, NH), 12.362(s, 1H, COOH), 7.501-8.140(m, 7H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.47 (CO), 124.73-138.68(Ar-C). Anal. Calcd for $C_{13}H_{11}NO_5S$: C, 53.24; H, 3.78; N, 4.78. Found: C, 53.26; H, 3.76; N, 4.72%. Mol. Wt.: 293.30; MS: *m/z* 293 [M^+].

5-((4-Bromophenyl)sulfonamido)isophthalic acid, 5b: Colourless solid. IR (KBr): 3264.7(NH), 1697.3(CO), 1342.9 (SOsym), 1157.3 cm^{-1} (SOasym); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.864(s, 1H, NH), 12.358(s, 1H, COOH), 7.525-8.104(m, 6H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.43 (CO), 126.24–137.36 (Ar-C). Anal. Calcd for $C_{14}H_{10}BrNO_6S$: C, 42.02; H, 2.52; N, 3.50. Found: C, 42.09; H, 2.47; N, 3.51%. Mol. Wt.: 400; MS: *m/z* 400 [M^+], 402 [M^{2+}].

5-((4-Chlorophenyl)sulfonamido)isophthalic acid, 5c: Colourless solid. IR (KBr): 3269.1(NH), 1695.6(CO), 1342.4 (SOsym), 1158.1 cm^{-1} (SOasym); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.807 (s, 1H, NH), 12.301(s, 1H, COOH), 7.429-7.981(m, 6H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.44 (CO), 124.96 -137.71(Ar-C). Anal. Calcd for $C_{14}H_{10}ClNO_6S$: C, 47.27; H, 2.83; N, 3.94. Found: C 47.16, H 2.89, N 3.85%. Mol. Wt.: 355; MS: *m/z* 355 [M^+], 357 [M^{2+}].

5-((2-Fluorophenyl)sulfonamido)isophthalic acid, 5d: Colourless solid. IR (KBr): 3252.3(NH), 1696.8(CO), 1341.9 (SOsym), 1170.2 cm^{-1} (SOasym); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.807(s, 1H, NH), 11.123(s, 1H, COOH), 7.250-7.834(m, 6H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.43 (CO), 127.12-139.65(Ar-C). Anal. Calcd for $C_{14}H_{10}FNO_6S$: C, 49.56; H, 2.83; N, 3.94. Found: C, 49.58; H, 2.92; N, 4.05%. Mol. Wt.: 339; MS: *m/z* 339 [M^+], 341 [M^{2+}].

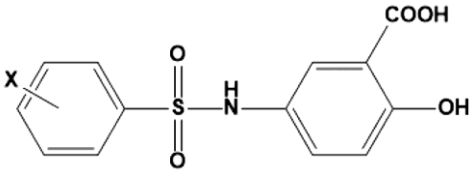
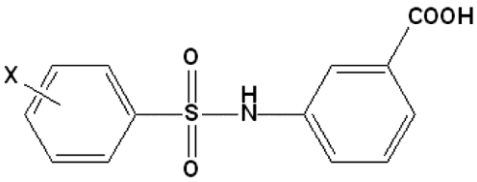
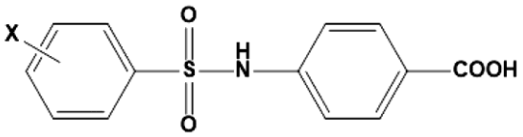
5-((4-Fluorophenyl)sulfonamido)isophthalic acid, 5e: Colourless solid. IR (KBr): 3261.5(NH), 1692.7(CO), 1324.9 (SOsym), 1169.0 cm^{-1} (SOasym); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.807 (s, 1H, NH), 10.932(s, 1H, COOH), 7.262-7.694(m, 6H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.39 (CO), 124.31 - 138.26(Ar-C). Anal. Calcd for $C_{14}H_{10}$



Series 1: X= Substituents; R= 4-Hydroxy-3-phenyl carboxylic acid; Compounds; 1a-1i
Series 2: X= Substituents; R= Phenyl-3- carboxylic acid; Compounds; 2a-2i
Series 3: X= Substituents; R= Phenyl-4- carboxylic acid; Compounds; 3a-3i
Series 4: X= Substituents; R= 2,4-Difluorophenyl; Compounds; 4a-4i
Series 5: X= Substituents; R=Phenyl-3,5-dicarboxylic acid; Compounds; 5a-5i

Scheme 2 — Ultrasound assisted ferric chloride-bentonite catalysed synthesis of substituted phenyl sulphonamides

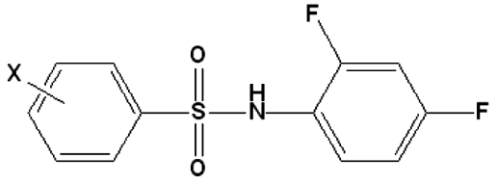
Table 10 — The physical constants, yield, and time for the synthesized sulfonamides

Compd	X	R	Time (min)	Yield (%)	m.p. (°C)
		Series 1: 2-Hydroxy-5(substituted phenylsulfonamido) benzoic acids			
					
1a	H	4-Hydroxyphenyl-3-carboxylic acid	15	72	276-277 (276)[4]
1b	4-Br	,,	14	70	303-305 (305)[4]
1c	4-Cl	,,	15	71	310-311(310)[4]
1d	2-F	,,	18	70	278-280(277-281)[4]
1e	4-F	,,	19	72	292-293(291-293)[4]
1f	4-OCH_3	,,	13	76	301-302(301)[4]
1g	4-CH_3	,,	14	75	282-283(282)[4]
1h	2-NO_2	,,	20	73	314-314(314)[4]
1i	4-NO_2	,,	22	74	320-321(318-320)[4]
		Series 2: 3-(substituted phenylsulfonamido)benzoic acids			
					
2a	H	Phenyl-3-carboxylic acid	15	76	236-237(235-237)[3]
2b	4-Br	,,	13	73	286-288(289)[3]
2c	4-Cl	,,	14	74	270-272 (271)[3]
2d	2-F	,,	20	71	274-275(272-275)[3]
2e	4-F	,,	19	73	229-271(268-270)[3]
2f	4-OCH_3	,,	13	77	262-263(260-262)[3]
2g	4-CH_3	,,	16	76	271-273(270-273)[3]
2h	2-NO_2	,,	21	74	279-280(278-279)[3]
2i	4-NO_2	,,	23	72	283-284(280-283)[3]
		Series 3: 4-(substituted phenylsulfonamido)benzoic acids			
					
3a	H	Phenyl-4-carboxylic acid	14	75	276-277(276)[76]
3b	4-Br	,,	14	74	293-294(292-293)[76]
3c	4-Cl	,,	15	74	286-287(285-287)[76]
3d	2-F	,,	18	70	268-269(267-268)[76]
3e	4-F	,,	20	71	271-273(270-272)[76]
3f	4-OCH_3	,,	14	78	280-281(278-281)[76]
3g	4-CH_3	,,	15	76	266-268(265-267)[76]
3h	2-NO_2	,,	20	73	279-280(280-282)[76]
3i	4-NO_2	,,	18	71	276-277(275-276)[76]

(*Contd*.)

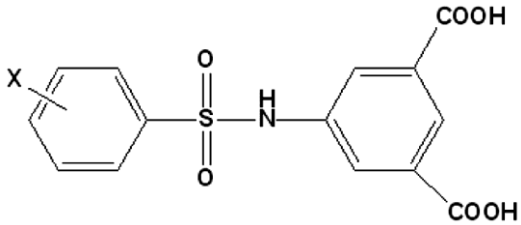
Table 10 — The physical constants, yield, and time for the synthesized sulfonamides (*Contd*.)

Series 4: 2,4-(Difluoro phenyl)(substituted benzene sulfonamides



4a	H	2,4-Difluorophenyl	18	74	164-165(163-165)[2]
4b	4-Br	,,	17	71	186-187(184-186)[2]
4c	4-Cl	,,	16	72	190-191(189-191)[2]
4d	2-F	,,	22	70	168-170(167-169)[2]
4e	4-F	,,	23	70	173-174(171-173)[2]
4f	4-OCH_3	,,	17	76	184-185(182-185)[2]
4g	4-CH_3	,,	19	75	175-176(172-174)[2]
4h	2-NO_2	,,	20	71	178-180(176-179)[2]
4i	4-NO_2	,,	22	70	181-183(180-182)[2]

Series 5: 5-(Substituted phenylsulfonamido)isophthalic acids



5a	H	Phenyl-3,5-dicarboxylic acid	14	75	276-277
5b	4-Br	,,	15	73	309-312
5c	4-Cl	,,	16	72	311-312
5d	2-F	,,	18	70	266-270
5e	4-F	,,	19	70	285-288
5f	4-OCH_3	,,	15	77	287-290
5g	4-CH_3	,,	14	76	268-270
5h	2-NO_2	,,	20	72	294-296
5i	4-NO_2	,,	22	70	306-308

FNO_6S: C, 49.56; H, 2.83; N, 3.94. Found: C, 49.56; H, 2.83; N 3.94. Found: C 49.49, H 2.92, N 4.08%. Mol. Wt.: 339; MS: *m/z* 339 [M^+], 341 [M^{2+}].

5-((4-Methoxyphenyl)sulfonamido)isophthalic acid, 5f: Colourless solid. IR (KBr): 3239.4(NH), 1694.4(CO), 1342.2 (SOsym), 1158.8 cm^{-1} (SOasym), 1449.4(C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.807(s, 1H, NH), 11.897(s, 1H, COOH), 7.541-7.803(m, 6H, Ar-H), 3.276(s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.53 (CO), 124.72 -138.38(Ar-C), 63.26(OCH_3). Anal. Calcd for $C_{15}H_{13}NO_7S$: C, 51.28; H, 3.73; N, 3.99. Found: C, 51.22; H, 3.67; N, 3.92%. Mol. Wt.: 351; MS: *m/z* 351 [M^+].

5-((4-Methylphenyl)sulfonamido)isophthalic acid, 5g: Colourless solid. IR (KBr): 3249.3(NH), 1696.2(CO), 1322.0 (SOsym), 1160.9 cm^{-1} (SOasym); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.662(s, 1H, NH), 11.652(s, 1H, COOH), 7.724-7.891(m, 6H, Ar-H), 2.121(s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.45 (CO), 122.63-139.21(Ar-C), 23.78(CH_3). Anal. Calcd for $C_{15}H_{13}NO_6S$: C, 53.73; H, 3.91; N, 4.18. Found: C, 53.71; H, 3.89; N, 4.15%. Mol. Wt.: 335; MS: *m/z* 335 [M^+].

5-((2-Nitrophenyl)sulfonamido)isophthalic acid, 5h: Colourless solid. IR (KBr): 3288.0(NH), 1717.0(CO), 1347.2 (SOsym), 1175.1 cm^{-1} (SOasym); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.252(s, 1H, NH), 12.365(s, 1H, COOH), 7.436-7.924(m, 6H,

Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.38(CO), 124.96-139.91(Ar-C). Anal. Calcd for $C_{14}H_{10}N_2O_8S$: C, 45.91; H, 2.75; N, 7.65. Found: C, 45.89; H, 2.71; N, 7.62%. Mol. Wt.: 366; MS: *m/z* 366 [M^+].

5-((4-Nitrophenyl)sulfonamido)isophthalic acid, 5i: Colourless solid. IR (KBr): 3252.2(NH), 1692.8(CO), 1345.4 (SOsym), 1161.5 cm^{-1} (SOasym); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.981(s, 1H, NH), 12.409(s, 1H, COOH), 7.652-7.915(m, 6H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.48(CO), 124.95-139.81(Ar-C). Anal. Calcd for $C_{14}H_{10}N_2O_8S$: C, 45.91; H, 2.75; N, 7.65. Found: C, 45.93; H, 2.72; N, 7.61%. Mol. Wt.: 366; MS: *m/z* 366 [M^+].

Molecular docking Evaluation

Auto dock vina 4 was used to run docking tests on sulfonamide derivatives. The Protein Data Bank (PDB) was used to get the crystal structure of enzyme protein receptor (PDB ID: 5GWK)[52,53]. The Protein Data Bank (PDB) supplied the crystal structure of the protein receptor, which was served in this work. The ligand structures were prepared in the CDX format by using Chem Draw ultra-version 8.0. Chem Draw 3D was used to convert the prepared ligand in CDX format into PDB format. Next, a PDBQT file was prepared and grid box size and centre were fixed. Kollman charges and polar hydrogen atoms were added to the protein structure of 5GWK. The grid size was set at 60, 80, 60 (x, y, and z) points respectively. This file was fixed and saved in PDBQT format. Ligand binding affinities were noted as negative Gibbs free energy (ΔG) scores (kcal/mol). The post docking analysis was identified with Discovery studio, which shows the binding sites, hydrogen-bonding interactions, hydrophobic interactions, and bond distances.

Measurement of antibacterial sensitivity assay

Antibacterial sensitivity test was carried out using the Kirby-Bauer disc diffusion Technique[77]. Within each petri plate, approximately 0.5 mL of the test bacterial sample was evenly distributed over the solidified Mueller-Hinton agar with a sterile glass spreader. Next, the disk of 5 mm diameter composed of Whatman No. 1 filter paper soaked with the solution of the compound was placed on the medium using sterile pliers. To prevent the collection of water droplets, the plates were incubated upside down for 24 h at 37°C. The plates were examined after 24 h, and the diameters of the zones of inhibition were measured. By repeating the same procedure three times, duplicate results were recorded.

Measurement of antifungal sensitivity assay

The Kirby-Bauer[77] disc diffusion technique was used to test antifungal sensitivity. The PDA medium was prepared and sterilized in the same manner as described above. A Petri-plate with 1 mL of the fungal species was already filled with the solution (ear bearing heating condition). To ensure uniform spreading of the species, the plate was rotated clockwise and counter clockwise. In 1 mL of DMSO solvent, 15 mg of sulfonamides were dissolved and used as test solution. A solidification period of 24 hours was allowed for the medium. After visual inspection, the diameter values of the inhibition zones were measured. The same procedure was repeated three times to obtain triple results.

Conclusions

More than 70% of yields of five series of aryl sulfonamides were synthesised using ultrasound irradiated $FeCl_3$-Bentonite catalysed condensation of various substituted phenyl sulfonyl chloride and amines. In this condensation the effect of catalyst and solvent were investigated. In this condensation optimized catalyst quantity is 0.35mg. Highest yields was obtained in ethanol medium. Synthesised sulfonamides were characterized using physical constants and spectroscopic data. These data ate supported for the formation of sulfonamides. The results of molecular docking study the sulfonamide compounds 2-Hydroxy-5-(4-nitrophenylsulfonamido) benzoic acid **1i**, 3-(4-nitrophenylsulfonamido benzoic acid) **2i**, 4-(4-methoxyphenylsulfonamido) benzoic acid **3f**, 2,4-(Difluoro phenyl)(4-nitrophenyl sulfonamide **4i** and 5-(4-methyl phenyl sulfonamido) isophthalic acid **5g** shows good affinity to the receptor. The antimicrobial activity of 5-(substituted phenylsulfonamido) isophthalic acid compounds **5a-i**, the parent substituent (H) shows satisfactory antibacterial activity and the substituents 4-Br, 4-OCH_3, 4-CH_3 and 4-NO_2 have shown least activity against *Micrococcus luteus* strain. The sulfonamides with 4-Br, 4-F, 4-CH_3, 2-NO_2 and 4-NO_2 substituents have shown satisfactory antibacterial activity against *Staphylococcus aureus*. The substituents in the sulfonamides such as 4-Cl, 4-OCH_3, 2-F, 2-NO_2 and 4-NO_2 substituent shows satisfactory antibacterial activity against *Escherichia coli*. Sulfonamides with parent, 4-OCH_3 and 4-CH_3 substituents have shown

satisfactory antibacterial activity *Pseudomonas aeruginosa* strain. The Parent, and 4-OCH_3 substituents have shown good antifungal activity against *Aspergillus niger* and *Trichoderma viride* stains.

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