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Synthesis and Antimicrobial Evaluation of Novel Sulfonyl and Amide Coupling Derivatives

Chandrakant D Pawar[1]*, Dattatraya N Pansare[1] and Devanand B Shinde[2]

[1]Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra, India

[2]Shivaji University, Vidyanagar, Kolhapur, Maharashtra, India

***Corresponding Author:** Chandrakant D Pawar, Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra, India.

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Abstract

A series of molecules containing sulfonamide coupling and amide coupling structure were designed and synthesized. The structures of the synthesized compounds were elucidated and confirmed by Proton Nuclear Magnetic Resonance and Carbon 13 Nuclear Magnetic Resonance, Mass spectrum and the purity was checked through High Performance Liquid Chromatography analysis. All synthesized compounds (4a-4u) were tested for their antimicrobial activity (minimum inhibitory concentration) against a series of strains of *Bacillus subtilis*, *Staphylococcus aureus* and *Escherichia coli* for antibacterial activity and against the strains of *Candida albicans*, *Aspergillus flavus* and *Aspergillus niger* for antifungal activity respectively. The results of the antimicrobial screening data revealed that most of the tested compounds showed moderate to good microbial inhibitions.

Keywords: *Sulfonamide; Amide; Antibacterial Activity; Antifungal Activity*

Introduction

The fused ring nucleus having sulfonamide and amide coupling is an important component for a huge spectrum of therapeutic agents, including anticancer, antiproliferative, antimalarial, antifungal and antibacterial agents [1-5]. The Sulfonamide acts as matrix metalloproteinase inhibitors it is an important pharmacophore and its coupling with other rings could furnish new biologically active compounds [6]. In recent times, the applications of amide coupled with naphthoyl rings were found to show antimicrobial agents and biofilm inhibitors [7]. The compounds like some esters and amide coupled compounds acts as anti-inflammatory drugs as cyclooxygenase-2-inhibitors [8]. Some sulfonamide acts as antimalarial [9]. The sulfonamide coupled with pyrimidine shows antimicrobial and anticancer activities [10]. Inhibitors of 5-Lipoxygenase [11], *Yersinia enterocolitica* opH tyrosine phosphatase inhibitors [12], antimalassezia [13], antiamoebic and antimalarial activities [14], inhibiter of phosphodiesterase type [4,15] antihypertensive [16]. Some sulfonamides linked compounds acts as hepatitis-C virus as nonstructural protein 3 protease inhibitors [17].

The sulfonamide coupled with thiourea shows anti-inflammatory and anti-microbial activities [18]. Some dihydropyrazole sulfonamide derivatives as potential COX-1/COX-2 inhibitors [19]. Literature revealed some chromone-based sulfonamide derivatives sows carbonic anhydrase inhibition and cytotoxic activity [20], Some heterocyclic sulfonamides acts as sphingosine 1-phosphate receptor 1 (S1P1) antagonists [21].

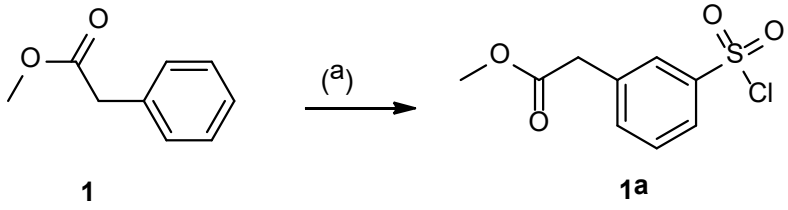
After extensive literature search, it was observed that, different coupling of sulfonamide and amide compounds shows different activities like carbonic anhydrase inhibitors [22], Anti-mycobacterial [23], some sulfonamides acts as sphingosine-1-phosphate (S1P1) receptor [24]. 11-β hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors for the treatment of metabolic disorders [25], sulfonamide-1,2,4-triazoles, 1,3,4-thiadiazoles and 1,3,4-oxadiazoles, as potential antibacterial and antifungal agents [26]. A close report of compounds having sulfonamide and amide linkage in combinations derivatives are showing selectively SIRT-2 inhibitors activity [27].

Our research group previously reported synthesis, characterization and antimicrobial evaluation of derivatives of thiazole, piperidine and thiazolidinone [28], here, we wish to mention the development of novel sulfonyl and amide coupling derivatives scaffold in one framework. The synthetic methods adopted for the preparation of the title compounds 4a-u care depicted in the schemes presented below.

Material and Method

From above references, it is clear that sulfonamide and amide coupled with different group compounds shows considerable varied activity. All above references indicates that the chances of potent antimicrobial activity of the containing sulfonamide and amide coupled compound increases considerably. So, we have synthesized compounds having sulfonamide and amide compounds which coupled at Meta positions of benzene to each other. Study shows that these compounds show good antimicrobial activity. We have also developed simplified reaction conditions for all the steps so we can avoid costly reagents, tedious purifications, and all the synthesized compounds shows have good purity also. We herein report the synthesis of new substituted sulfonamide and amide coupled derivatives (Scheme 6) with the aim of investigating their antimicrobial activity. The synthetic methods adopted for the preparation of the title compounds (4a-4u) [29] care depicted in the schemes presented below [29].

From above (Scheme 1, Table 1) here we have optimized the condition for aromatic chlorosulfonation in the presence of ester group. The reactivity changes according to the equivalent of chlorosulfonic acid used. We have carried out 10 different combinations and optimized the reaction condition which reduces the efforts of tedious work up and purifications of intermediate for first time. For all the reactions, we have kept time constant. It is confirmed that when we use neat excess of chlorosulfonic acid without solvent there is 60% formation of required product (entry 10), then we have used excess chlorosulfonic acid with DCM then yield is 40% (entry 9). From above these two conditions it is clear that we have to use chlorosulfonic acid in equivalents along with in neat and in DCM solvent conditions.



Scheme 1: *Screening of model reaction methyl 2-(3-(chlorosulfonyl)phenyl)acetate (1a). Reaction condition (a): Sulfonyl chloride (1.1 equiv to excess), solvent, temperature 0°C-rt.*

The varied results are shown in table 1. The (entries 1, 2, 3 and 4) shows there is formation product along with side products, the yields are 30% to 55 %. When we consider (entries 5, 6, 7 and 8) the yields are increasing from 40% to 80% when we used equivalent amount of chlorosulfonic acid. Mainly there is formation of product and less side products in (entries 5 to 8). But in (entries 1 to 4) there is formation of multiple spots on TLC, but in entries 5 to 8 the TLC profile much more promising. The yields are isolated yields after series

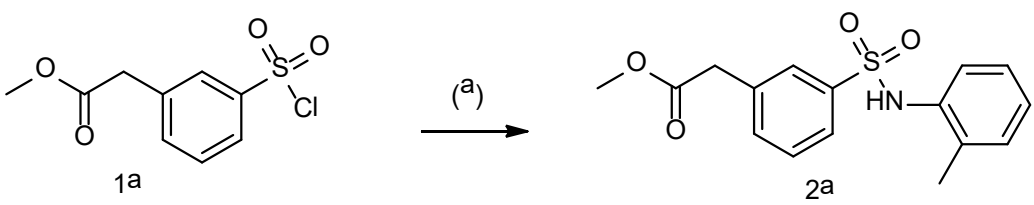
of reactions optimization and the condition 8 works (entry 8) well for given compound. By using this method, the work up is easy we have to evaporate reaction mixture under reduced pressure and obtained gummy material which is washed with excess of hexane and it is crystallized from 20% ethyl acetate: hexane mixture to obtain white solid which is used further for sulfonamide coupling reaction. In entries 1 to 4 the side product is 4-substituted sulfonyl chloride compound obtained along with polar junk material, which required purification by column chromatography so the yields are less, but in latter case purification not required; pure compound obtained by crystallization which is not possible in earlier entries, the gummy material remains as such.

Entry	$ClSO_3H$	Solvent	Time (h)	Yield[a] (%)
1	(3 equiv)	Neat	1	45
2	(2 equiv)	Neat	1	40
3	(1.5 equiv)	Neat	1	55
4	(1.1 equiv)	Neat	1	30
5	(3 equiv)	DCM	1	60
6	(2 equiv)	DCM	1	60
7	(1.5 equiv)	DCM	1	70
8	(1.1 equiv)	DCM	1	80
9	(Excess)	DCM	1	40
10	(Excess)	Neat	1	60

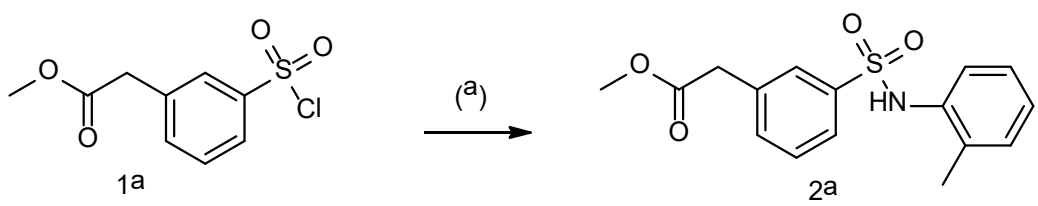
Table 1: *Screening of mole equiv, solvents, time of compound (1a).*

[a]Isolated yield, sulfonyl chloride (2 equiv)

In scheme 2 and scheme 3 first we have optimized the reaction solvent and base, from initial screening we have finalized DCM as the solvent and pyridine as the base that we have tabulated in table 2. From table 2 it is confirmed that when we used equivalents of pyridine and DCM the yield is 90% table 3 entries 5.



Scheme 2: *Screening of model reaction methyl 2-(3-(N-(o-tolyl)sulfamoyl)phenyl)acetate (2a). Reaction condition (a): 2-methyl aniline, bases, solvents, temperature 00C-rt, time 6-16h.*



Scheme 3: *Screening of model reaction methyl 2-(3-(N-(o-tolyl)sulfamoyl)phenyl)acetate (2a). Reaction condition (a): 2-methyl aniline, pyridine (1 equiv to excess), DCM, temperature 00C-rt, time 6-16h.*

Entry	Base	Solvent	Time (h)	Yield[a] (%)
1	TEA (2 equiv)	DCM	16	45
2	DIPEA (2 equiv)	DCM	16	30
3	DMAP (2 equiv)	DCM	16	55
4	2,6-Leutidine (2 equiv)	DCM	16	30
5	Pyridine (1.5 equiv)	DCM	6	70
6	DMAP (2 equiv)	THF	16	60
7	2,6-Leutidine (2 equiv)	THF	12	25
8	DIPEA (2 equiv)	THF	16	40
9	TEA (2 equiv)	THF	16	40
10	Pyridine (1.5 equiv)	THF	6	60

Table 2: *Screening of bases, solvents, time of compound (2a).*

[a]Isolated yield, sulfonyl comound (1 equiv), substituted amine (1 equiv)

There are many reports for the formations of sulfonamide so initially we have screened different bases by taking DCM and THF as solvents. In entry 5 with 2.5 equiv. of pyridine and in DCM the yield is 70 % from entries 1 to 4 the yield ranges from 30% to 60 %, in entries 6 to 10.

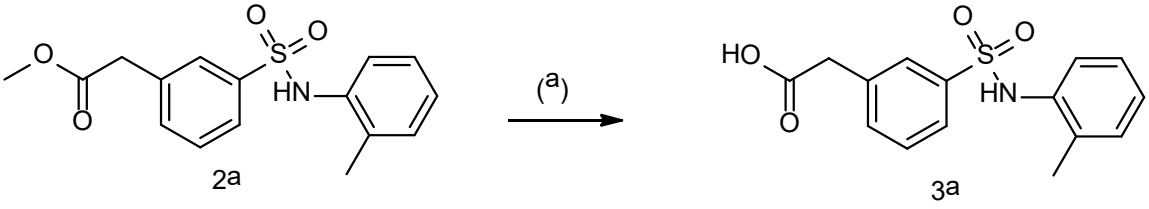
The yield is 25% to 60 % also the reaction time for all entries is from 6 to 16h. Time monitored on the bases on consumption of starting material. We have faced isolation problem in all the cases extraction needed for all the examples and obtained compounds are not cleaner so need to modify the yields from entry 5 and also optimize work up condition so that we have to avoid rigorous extractions. In table 3 we have varied the equivalents of pyridine and we have come to conclude that if we use equivalent volumes of pyridine along with DCM solvent then yield is 90% (entry 5). We have used pyridine so most of the examples we have treated the reaction mass with cold 2N aq. HCl and stirred reaction mass for 30 min., the solid precipitates out in most of cases which is filtered and washed it with cold diethyl ether and cold pentane, all the intermediates obtained are white solids. Most of examples the yield of solid is 70% to 80% further we have extracted the aqueous layer with DCM and evaporated it to obtained the remaining solids then yield increases up to 80% to 90% in all the intermediates.

Entry	Base(Pyridine)	Solvent	Time (h)	Yield[a] (%)
1	Pyridine (1 equiv)	DCM	16	45
2	Pyridine (1.5 equiv)	DCM	16	60
3	Pyridine (2 equiv)	DCM	10	65
4	Pyridine (5 equiv)	DCM	8	70
5	Pyridine (excess)	DCM	6	90

Table 3: *Screening of base mole equiv., and time of compound (2a).*

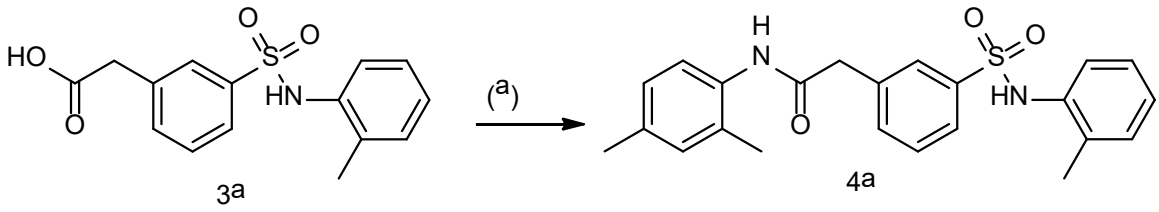
[a]Isolated yield, sulfonyl comound (1 equiv), substituted amine (1.5 equiv)

For scheme 4 we have used excess of lithium hydroxide 5 equiv. we have modified the reaction work up condition, by giving back wash in basic condition and later acidifying it to get desired product with required purity and no column purification is required all the acids obtained are enough pure to used further for next amide coupling with different amines. All intermediates gives yield up to 80% to 85 % in most of cased and all the compounds obtain as white solids.



Scheme 4: *Screening of model reaction 2-(3-(N-(o-tolyl)sulfamoyl)phenyl)acetic acid (3a). Reaction condition (a): Li(OH), THF, EtOH, H_2O, rt.*

Scheme 5 we have screened different coupling reagents and bases and solvents it is concluded that when we use EDCI (1.5 equiv) along with DIPEA (2.5 equiv) in DCM the yields is 90 % last entry. We have varied different coupling reagents, different bases, different reaction time in DMF and DCM (Table 4). We have done series of peptide coupling relations using HATU, along with triethyl amine and DIPEA the yields are in between 50% to 55 %. With PyBoP used triethyl amine and DIPEA again yields are in 47% to 50%. With most commonly conditions EDCI and HOBt using triethyl amine and DIPEA in DCM and DMF solvents the yields are in the range of 50% to 70%.

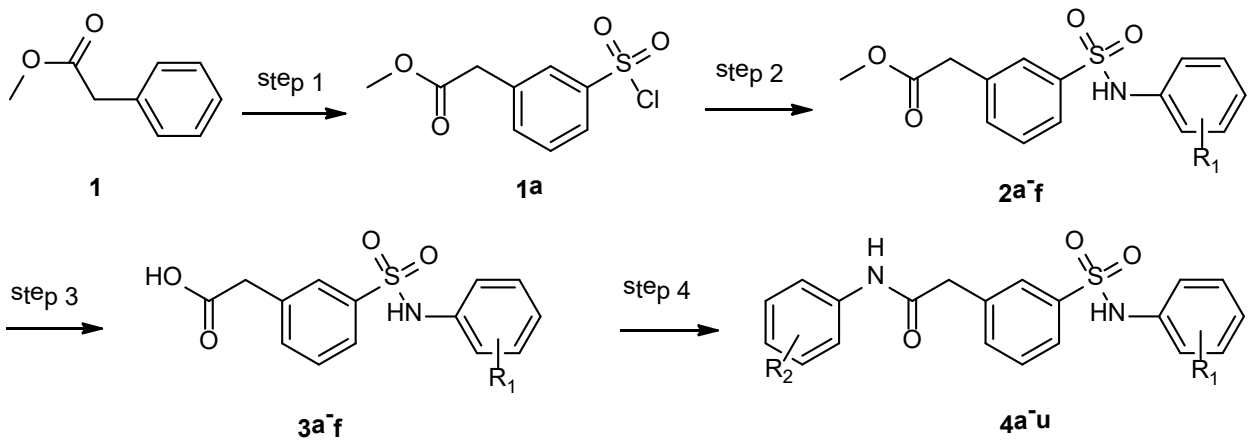


Scheme 5: *Screening of model reaction N-(2,4-dimethylphenyl)-2-(3-(N-(o-tolyl)sulfamoyl)phenyl)acetamide (4a): Reaction condition (a): 2,4-dimethyl aniline, coupling reagent, bases, solvents, time, rt.*

Coupling Reagent	Base	Solvent	Time (h)	Yield (%)
HATU (1.1 equiv)	TEA (1,2 equiv)	DMF	16	55
	DIPEA (1.2 equiv)			50
PyBOP (1.1 equiv)	TEA (1,2 equiv)	THF	16	47
	DIPEA (1.2 equiv)			50
EDCI (1.5 equiv) HOBt (1.5 equiv)	TEA (2.5 equiv.)	DMF	16	60
EDCI (1.5 equiv) HOBt (1.5 equiv)	DIPEA (2.5 equiv)	DMF	12	70
EDCI (1.5 equiv)	TEA (4 equiv)	DMF	16	76
HOBt (1.5 equiv)	DIPEA (4 equiv)			65
T3P (1.2 equiv)	TEA (2.5 equiv)	DCM	12	50
	DIPEA (2.5equiv)			60
EDCI (1.5 equiv)	DIPEA (2.5 equiv)	DCM	12	90
Acid (1equiv) and amine (1.5 equiv)				

Table 4: *Optimization of reaction condition for amide formation of compound (4a).*

In all above examples the aqueous work up required, the reagents are costly and in all the cases the yield obtained after column purifications. But, the condition in entry 10, requires the extraction, and later on washing with 2N aq. HCl washing to obtain 70% to 80 % pure product. Which was washed with 5% DCM and Hexane, cold diethyl ether and cold pentane gives the desired compounds with 95% and above purity and yield is also 90% in most of synthesized compounds. We have optimized all the 4 steps, no need of column chromatography, no costly reagents required, no prep purification required. All obtained compounds are with 95% and above purity. From above data, we decided to synthesis of N-(Substituted phenyl)-2-(3-substituted) sulfamoyl) phenyl) acetamide derivatives (4a-4u) (Scheme 6).



	R_1	R_2		R_1	R_2
4a	2-CH_3	2,4-CH_3	**4l**	2-CH_3-CH_2	4-$C(CH_3)_3$
4b	2-CH_3-CH_2	2,4-CH_3	**4m**	2-CF_3	2-$C(CH_3)_3$
4c	2-CF_3	2,4-CH_3	**4n**	2-$C(CH_3)_3$	2-$C(CH_3)_3$
4d	2-$C(CH_3)_3$	2,4-CH_3	**4o**	Indoline	2-$C(CH_3)_3$
4e	Indoline	2,4-CH_3	**4p**	2,4-CH_3	2-CH_3
4f	2-CH_3	2-CH_3, 4-Cl	**4q**	2,4-CH_3	2-CH_3-CH_2
4g	2-CH_3-CH_2	2-CH_3, 4-Cl	**4r**	2,4-CH_3	2-OCH_3
4h	2-CF_3	2-CH_3, 4-Cl	**4s**	2-CH_3,4-$C(CH_3)_3$	2-CH_3
4i	2-$C(CH_3)_3$	2-CH_3, 4-Cl	**4t**	2-CH_3,4-$C(CH_3)_3$	2-CH_3-CH_2
4j	Indoline	2-CH_3, 4-Cl	**4u**	2-CH_3,4-$C(CH_3)_3$	2-OCH_3
4k	2-CH_3	4-$C(CH_3)_3$			

Scheme 6: *Synthesis of N-(Substituted phenyl)-2-(3-substituted) sulfamoyl) phenyl) acetamide derivatives (4a-4u). Reagents and conditions: (step 1) sulfonyl chloride, DCM 0°C-rt; (step 2) substituted amine, pyridine, DCM, 00C-rt; (step 3) Li(OH), THF, EtOH, H2O, rt; (step 4) substituted amine, EDCI, DIPEA, DCM, rt.*

Antimicrobial activity data

All the synthesized compounds were screened for in vitro antimicrobial activity. The antibacterial activity was evaluated against different bacterial strains such as *Staphylococcus aureus* (NCIM-2901), *Bacillus subtilis* (NCIM-2063) and *Escherichia coli* (NCIM-2256). Minimum inhibitory concentration (MIC, µg/mL) of antibacterial activity was determined using broth dilution methods per CLSI guidelines [30-35]. Levofloxacin was used as a standard drug for the comparison of antibacterial activity. Fluconazole and miconazole were used as standard drugs for the comparison of antifungal activity. Dimethyl sulfoxide was used as solvent control. From the antimicrobial data, it is observed that all the newly synthesized compounds shows good to moderate level of antibacterial and antifungal activity. The antimicrobial activity data reveals that compounds (4a, 4b, 4f, 4g, 4k, 4p, 4r and 4t) are found to be most active and potent as antimicrobial agents among the series.

From the antimicrobial activity data (Table 5), it is clearly observed that many of the synthesized compounds were shows prominent antimicrobial activity. Some compounds were narrow spectrum active against only one fungal and bacterial strain while some of them were found to be a broad spectrum active against both fungal and bacterial strains. Amongst series the compounds (4a, 4b, 4f, 4g, 4k, 4p, 4r and 4t) were found to broad spectrum molecule, they were active against all tested bacteria strains and fungus.

Compounds	MIC values[a] (µg/ml)					
	B. subtilis	***E. coli***	***S. aureus***	***C. Albicans***	***A. Flavus***	***A. Niger***
4a	32	53	28	72	53	50
4b	28	28	38	25	12.5	12.5
4c	45	90	100	65	90	90
4d	36	63	52	80	60	40
4e	30	32	28	28	13.5	13.5
4f	32	29	33	43	26	26
4g	35	60	30	100	50	50
4h	40	100	100	75	100	100
4i	35	60	50	100	50	50
4j	45	60	100	75	100	100
4k	35	50	70	75	25	25
4l	45	60	100	75	100	100
4m	35	50	70	75	50	50
4n	42	90	100	65	90	90
4o	36	63	52	80	60	40
4p	32	50	60	30	28	80
4q	31	37	23	25	16	15
4r	30	38	32	50	27	27
4s	35	60	50	100	50	50
4t	35	29	30	25	14	15
4u	35	50	70	75	50	50
Levofloxacin	28	28	27	-	-	-
Fluconazole	-	-	-	38	24	24
Miconazole	-	-	-	12.5	12.5	12.5

Table 5: *Antimicrobial activity of the synthesized compounds (4a-u).*

[a]Values are the average of three readings.

The compound (4b) was more potent than standard drugs Levofloxacin against *B. subtilis* with MIC 29 µg/mL. The MIC value of this group of molecules, remaining bacterial and fungal strains are in the range of 12.5 - 38 µg/mL. The fungal strain, *A. flavus* and *A. niger* shows higher level of resistance MIC 12.5 µg/mL.

The antimicrobial activity data reveals that among the synthesized compounds 4a,4f, 4g, 4k, and 4p are found to be most active and potent antimicrobial agents among the series when compared with the standard drugs Levofloxacin, Fluconazole and Miconazole against *B. subtilis* with MIC 29 µg/mL. The MIC value of this group of molecules, remaining bacterial and fungal strains are in the range of 12.5 - 50 µg/mL. The fungal strain, *A. flavus* and *A. niger* shows higher level of resistance MIC 12.5 µg/mL.

The compound 4c, 4d, 4h, 4i, 4j, 4l, 4m, and 4n shown reduced antimicrobial and antifungal MIC values are in the range of 45 to 100 µg/mL of all the antimicrobial stains. The compounds 4e, 4r, 4q, 4o, 4s and 4u shows intermediate antibacterial and antifungal activity in the range of MIC 35 to 75 µg/mL for all the stains for all antimicrobial and antifungal activity. Finally compounds 4a, 4b, 4f, 4g, 4k, and 4p shows higher antifungal activity when tested on the fungal strains. The structure-activity relationship of the series can be explained as follows: The molecules gave increased antimicrobial activity due to the presence of methyl group on sulfonamide ring and 2, 4-dimethyl groups on amide ring in 4a. The activity was further found to be increased when there was the presence of methyl group on sulfonamide ring and 2-methyl-4-chloro groups on amide ring in 4f, also same results obtained with 2-methyl sulfonamide and 4-tertbutyl group on amide ring in 4k because electron donating group. Antimicrobial activity increases with presence of methyl group on amide and 2,4-dimethyl group on sulfonamide ring in 4p. Also same types of results obtained when methyl group of sulfonamide ring is replaced with ethyl group there is increase in antimicrobial activity observed in compounds 4b and 4g. Compounds containing groups like triflouromethyl group on sulfonamide and 2, 4-dimethyl, 2-methyl-4-chloro, 4-tertbutyl, groups on amide ring shows decrease in antimicrobial activity in 4c, 4h, 4m. Same results are obtained when 2-tertbutyl group is present on sulfonamide ring along with 2, 4-dimethyl, 2-methyl-4-chloro, 4-tertbutyl , groups on amide ring shows decrease in antimicrobial activity in 4d, 4i, 4n. The presence of indolin on sulfonamide along with 2-methyl-4-chloro decreases the antimicrobial activity, also same results obtained for 2-ethyl group on sulfonamide and 4-tert butyl group on amide in 4j and 4l. Indolin substitution on sulfonamide along with 2,4-dimethyl and 4-tertbutyl substitution of amide shows moderate antimicrobial activity in 4e and 4o. Compound having 2-methyl on amide and 2-methyl-4-tertbutyl on sulfonamide also shows moderate antimicrobial activity 4s. Compounds having ethyl on amide ring and 2,4-dimethyl and 2-methyl-4-tertbutyl on sulfonamide shows moderate activity in 4q and 4t, along with compounds having 2-methoxy on amide ring and 2,4-dimethyl and 2-methyl-4-tertbutyl on sulfonamide shows moderate activity in 4r but better activity of compound 4t. From all above antimicrobial data, it is proved that there is decreases in antimicrobial activity for remaining examples on sulfonamide ring as triflouromethyl group 4c, 2-tertbutyl group 4d and indanone ring 4j the activity decreases due to bulky group which creates steric hindrance. In all these 6 types of amide coupled compounds the activity because of 2-methyl-4-chloro amide compound is great in examples 4f, 4g, are having promising activity. But for 4h, 4i, and 4j there is decrease in activity. From above values the chloro containing ring is showing promising activity then it is the methoxy, methyl and later ethyl and tertbutyl in last for amide ring compounds.

From the all above studies it is confirmed that the activity of sulfonamide and amide coupled compounds changes weather groups attached are different as seen in example like 4a and 4p. The dimethyl group is attached to sulfonamide ring or amide ring is having methyl group and vice in example 4p the activity change for different group.

Conclusion

By using this methodology, a series of molecules containing sulfonamide coupling and amide coupling structure were designed and synthesized. We have developed simple and continent method for the synthesis of some sulfonamide coupling and amide coupling derivatives by simple reaction steps. No costly reagents are required, no any pre-purification is needed and all the compounds synthesized were obtained in good yields. The mild reaction conditions, shorter reaction time and promising antimicrobial activity. The compounds (4a, 4b, 4f, 4g, 4k, 4p, 4r and 4t) are shows better antimicrobial activity of the present method.

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Experimental Section

All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification. The major chemicals were purchased from Sigma Aldrich and Avra labs. The development of reactions was monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F254 aluminum sheets, visualized by UV light. IR spectra were recorded on a FT-IR (Bruker). Melting points were recorded on SRS Optimelt, melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a 500 MHz Varian NMR spectrometer. The ^{13}C were recorded on a 100 MHz Varian NMR spectrometer. The chemical shifts are reported as NMR spectra δ_{ppm} units. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer.

Spectral Data

N-(2,4-dimethylphenyl)-2-(3-(N-(o-tolyl)sulfamoyl)phenyl)acetamide (4a)

White Solid, LC-MS *m/z* (%): 409 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.054 (s, 1H), 9.701 (s, 1H), 8.26 (s, 1H), 8.22 (d, *J*=7.6 Hz, 1H), 7.814 (d, *J*=8 Hz, 1H), 7.7 (d, *J*=8 Hz, 1H), 7.180-7.138 (m, 2H), 7.1-7.085 (m, 3H), 7.018 (d, *J*=8.4 Hz, 1H), 6.951-6.928 (m, 1H), 3.5 (s, 2H), 2.284 (s, 3H), 2.159 (s, 3H), 2.027 (s, 3H). HPLC-98.25% RT-5.68 min. ^{13}C NMR ($CDCl_3$, 100 MH_Z): 17.65, 17.79, 20.54, 40.5, 126.09, 126.38, 126.40, 126.43, 126.58, 129.23, 129.42, 130.82, 130.89, 131.38, 133.42, 133.62, 134.27, 134.65, 135.40, 135.41, 135.45, 141.09, 163.93.

N-(2,4-dimethylphenyl)-2-(3-(N-(2-ethylphenyl)sulfamoyl)phenyl)acetamide (4b)

White Solid, LC-MS *m/z* (%): 423 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.063 (s, 1H), 9.705 (s, 1H), 8.274 (s, 1H), 8.226 (d, *J*=8 Hz, 1H), 7.842 (d, *J*=8 Hz, 1H), 7.714 (t, *J*=7.6 Hz, 1H), 7.219-7.138 (m, 3H), 7.088-7.011 (m, 3H), 6.858 (d, *J*=8 Hz, 1H), 3.5 (s, 2H), 2.53 (s, 2H), 2.285 (s, 3H), 2.161 (s, 3H), 0.968 (t, *J*=7.2 Hz, 3H). HPLC-99.53% RT-9.21 min. ^{13}C NMR ($CDCl_3$, 100 MH_Z): 14.39, 17.80, 20.57, 23.18, 40.5, 126.15, 126.23, 126.62, 126.63, 126.66, 126.99, 129.08, 129.34, 129.46, 130.93, 131.36, 133.44, 133.67, 133.88, 135.46, 140.52, 141.13, 164.0.

N-(2,4-dimethylphenyl)-2-(3-(N-(2-(triflouromethyl)phenyl)sulfamoyl)phenyl)acetamide (4c)

White Solid, LC-MS *m/z* (%): 463 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.163 (s, 1H), 10.103 (s, 1H), 8.369 (s, 1H), 8.269 (d, *J*=7.2 Hz, 1H), 7.964 (d, *J*=7.6 Hz, 1H), 7.79-7.719 (m, 2H), 7.588 (t, *J*=8 Hz, 1H), 7.495 (t, *J*=7.8 Hz, 1H), 7.18 (d, *J*=8 Hz, 1H), 7.091 (s, 1H), 7.031 (t, J=8 Hz, 2H), 3.5 (s, 2H), 2.285 (s, 3H), 2.173 (s, 3H). HPLC-96.65%RT-4.89 min.^{13}C NMR ($CDCl_3$, 100 MH_Z): 17.74, 20.51, 40.5, 124.55, 126.07, 126.55, 127.08, 127.09, 127.54, 128.58, 128.59, 129.23, 129.57, 130.86, 131.51, 133.29, 133.39, 133.59, 133.88, 135.36, 135.51,163.87.

N-(2,4-dimethylphenyl)-2-(3-(N-(2-(tert-butyl)phenyl)sulfamoyl)phenyl)acetamide (4d)

Off White Solid, LC-MS *m/z* (%): 451 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.121 (s, 1H), 9.49 (s, 1H), 8.46 (s, 1H), 8.287 (d, *J*=7.6 Hz, 1H), 8.046 (d, *J*=8 Hz, 1H), 7.815 (t, *J*=8 Hz, 1H), 7.44(d, *J*=8 Hz, 1H), 7.229-7.188 (m, 2H), 7.097 (s, 1H), 7.039-6.993 (m, 2H), 6.456 (d, *J*=7.6 Hz, 1H), 3.5 (s, 2H), 2.288 (s, 3H), 2.195 (s, 3H), 1.435 (s, 9H). HPLC-97.99% RT-5.09 min.^{13}C NMR ($CDCl_3$, 100 MH_Z): 14.34, 17.63, 30.12, 34.24, 40.5, 112.12, 115.12, 118.42, 121.13, 122.12, 122.27, 124.12, 125.74, 126.14, 127.34, 127.85, 129.10, 129.85, 131.2, 135,42, 137.35, 139.80, 140.56, 141.52, 164.12.

N-(2,4-dimethylphenyl)-2-(3-(indolin-1-ylsulfonyl)phenyl)acetamide (4e)

Off White Solid, LC-MS *m/z* (%): 421 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.105 (s, 1H), 8.387 (s, 1H), 8.241 (d, *J*=7.2 Hz, 1H), 8,070 (d, *J*=8 Hz, 1H), 7.765 (t, *J*=8 Hz, 1H), 7.248 (s, 4H), 7.188 (d, *J*=8 Hz, 1H), 7.036 (s, 1H), 7.026 (d, *J*=8 Hz, 1H), 4.636 (s, 4H), 3.5 (s, 2H), 2.286 (s, 3H), 2.17 (s, 3H). HPLC-93.70% RT-7.58 min.^{13}C NMR ($CDCl_3$, 100 MH_Z): 14.34, 17.63, 26.72, 42.80, 40.5, 112.12, 115.12, 118.42, 121.13, 122.12, 122.27, 124.12, 125.74, 126.14, 127.34, 127.85, 129.10, 129.85, 131.2, 135,42, 137.35, 139.80, 140.56, 141.52, 164.12.

N-(4-chloro-2-methylphenyl)-2-(3-(N-(o-tolyl)sulfamoyl)phenyl)acetamide (4f)

White Solid, LC-MS *m/z* (%): 429 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.178 (s, 1H), 9.714 (s, 1H), 8.258 (s, 1H), 8.221 (d, *J*=7.6 Hz, 1H), 7.834 (d, *J*=8 Hz, 1H), 7.716 (d, *J*=8 Hz, 1H), 7.384-7.345 (m, 2H), 7.294-7.268 (m, 1H), 7.161-7.139 (m, 1H), 7.1-7.077(m, 2 H), 6.950-6.928 (m, 1H), 3.5 (s, 2H), 2.208 (s, 3H), 2.028 (s, 3H). HPLC-97.54% RT-5.84 min. ^{13}C NMR ($CDCl_3$, 100 MH_Z): 14.34, 17.63, 40.5, 125.63, 126.03, 126.12, 126.29, 126.71, 126.84, 128.2, 129.01, 129.37, 129.53, 129.94, 130.31, 131.43, 133.87, 135.11, 136.24, 140.41, 141.16, 165.03.

N-(4-chloro-2-methylphenyl)-2-(3-(N-(2-ethylphenyl)sulfamoyl)phenyl)acetamide (4g)

White Solid, LC-MS *m/z* (%): 443 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.18 (s, 1H), 9.71 (s, 1H), 8.27 (s, 1H), 8.226 (d, *J*=7.6 Hz, 1H), 7.863 (d, *J*=8 Hz, 1H), 7.731 (t, *J*=8 Hz, 1H), 7.379-7.295 (m, 2H), 7.29-7.274 (m, 1H), 7.202 (t, *J*=8 Hz, 1H), 7.159 (t, *J*=8 Hz, 1H),7.07 (t, *J*=8 Hz, 1H) 6.858 (d, *J*=7.6 Hz, 1H), 3.5 (s, 2H), 2.499 (s, 3H), 2.21 (s, 3H), 0.969 (t, *J*=7.2 Hz, 3H). HPLC-95.85% RT-6.59 min. ^{13}C NMR ($CDCl_3$, 100 MH_Z): 14.35, 17.66, 23.14, 40.5, 125.94, 126.14, 126.18, 126.21, 126.61, 126.93, 128.19, 129.04, 129.47, 129.51, 129.92, 130.21, 131.44, 133.83, 135.09, 136.21, 140.21, 141.14, 164.03.

N-(4-chloro-2-methylphenyl)-2-(3-(N-(2-(triflouromethyl)phenyl)sulfamoyl)phenyl)acetamide (4h)

White Solid, LC-MS *m/z* (%): 483 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.208 (s, 1H), 10.162 (s, 1H), 8.367 (s, 1H), 8.261 (d, *J*=7.2 Hz, 1H), 7.981 (d, *J*=7.6 Hz, 1H), 7.78 (t, *J*=7.6 Hz, 1H), 7.727 (t, *J*=7.2 Hz, 1H), 7.579 (t, *J*=8 Hz, 1H), 7.455 (t, *J*=8 Hz, 1H), 7.384 (s, 1H), 7.357 (s, 1H), 7.301-7.275 (m, 1H), 7.056 (d, *J*=8 Hz, 1H), 3.5 (s, 2H), 2.226 (s, 3H). HPLC-99.19%RT-4.78 min. ^{13}C NMR ($CDCl_3$, 100 MH_Z): 14.36, 40.5, 115.25, 126.43, 126.07, 126.28, 126.70, 126.83, 128.19, 129.23, 129.47, 129.76, 130.71, 130.91, 132.5, 133.62, 134.8, 135.12, 135.63, 140.41, 164.32.

N-(4-chloro-2-methylphenyl)-2-(3-(N-(2-(tert-butyl)phenyl)sulfamoyl)phenyl)acetamide (4i)

Off White Solid, LC-MS *m/z* (%): 471 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.234 (s, 1H), 9.489 (s, 1H), 8.461 (s, 1H), 8.288 (d, *J*=7.2 Hz, 1H), 8,066 (d, *J*=7.6 Hz, 1H), 7.831 (t, *J*=8 Hz, 1H), 7.443 (d, *J*=8 Hz, 1H), 7.396-7.375 (m, 2H), 7.297 (d, *J*=8.8 Hz, 1H), 7.211 (d, *J*=8 Hz, 1H), 7.012 (t, *J*=8 Hz, 1H), 6.463 (d, *J*=8 Hz, 1H) 3.5 (s, 2H), 2.247 (s, 3H), 1.435 (s, 9H). HPLC-99.33% RT-6.18 min. ^{13}C NMR ($CDCl_3$, 100 MH_Z): 14.42, 31.57, 31.6, 40.5, 125.64, 126.04, 126.12, 126.30, 126.73, 126.83, 128.21, 129.12, 129.35, 129.54, 129.91, 130.30, 131.42, 133.85, 135.12, 136.24, 140.41, 141.12, 165.01.

N-(4-chloro-2-methylphenyl)-2-(3-(indolin-1-ylsulfonyl)phenyl)acetamide (4j)

Off White Solid, LC-MS *m/z* (%): 442 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.201 (s, 1H), 8.388 (s, 1H), 8.242 (d, *J*=8 Hz, 1H), 8,070 (d, *J*=8 Hz, 1H), 7.776 (t, *J*=8 Hz, 1H), 7.386-7.365 (m, 2H), 7.312-7.240 (m, 5H), 4.638 (s, 4H), 3.5 (s, 2H), 2.221 (s, 3H).HPLC-99.70% RT-7.63 min. ^{13}C NMR ($CDCl_3$, 100 MH_Z): 14.42, 26.32, 40.2, 40.5, 115.12, 117.15, 125.43, 126.02, 126.32, 126.21, 126.61, 126.93, 128.14, 128.23, 128.93, 129.23, 129.54, 129.9, 130.32, 131.46, 133.92, 135.12, 136.42, 140.48, 142.12, 164.32.

(4-(tert-butyl)phenyl)-2-(3-(N-(o-tolyl)sulfamoyl)phenyl)acetamide (4k)

White Solid, LC-MS *m/z* (%): 437 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.414 (s, 1H), 9.707 (s, 1H), 8.252 (s, 1H), 8.198 (d, *J*=7.6 Hz, 1H), 7.794 (d, *J*=8 Hz, 1H), 7.694 (t, *J*=7.6 Hz, 1H), 7.646 (d, *J*=8.4 Hz, 2H), 7.362 (d, *J*=8.4 Hz, 2H), 7.147-7.099 (m , 1H), 7.085-7.063 (m, 2H), 6.921-6.899 (m, 1H), 3.5 (s, 2H), 2.011 (s, 3H), 1.266 (s, 3H). HPLC-99.25% RT-7.20 min. ^{13}C NMR ($CDCl_3$, 100 MH_Z): 14.34, 26.72, 42.80, 40.5, 112.12, 115.12, 118.42, 121.13, 122.12, 122.27, 124.12, 125.74, 126.14, 127.34, 127.85, 129.10, 129.85, 131.2, 135,42, 137.35, 139.80, 140.56, 141.52, 164.12.

N-(4-(tert-butyl)phenyl)-2-(3-(N-(2-ethylphenyl)sulfamoyl)phenyl)acetamide (4l)

White Solid, LC-MS *m/z* (%): 451 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.418 (s, 1H), 9.709 (s, 1H), 8.262 (s, 1H), 8.201 (d, *J*=7.6 Hz, 1H), 7.826 (d, *J*=8 Hz, 1H), 7.708 (t, *J*=8 Hz, 1H), 7.651 (d, *J*=8.4 Hz, 2H), 7.363 (d, *J*=8.4 Hz, 2H), 7.204-7.186 (m , 1H), 7.118 (t, *J*=8 Hz, 1H), 7.065 (t, *J*=8 Hz, 1H), 6.18 (d, *J*=7.6 Hz, 1H), 3.5 (s, 2H),), 2.49 (s, 2H), 1.266 (s, 9H), 0.955 (t, *J*=7.2 Hz, 3H).HPLC-96.1% RT-7.81 min. ^{13}C NMR ($CDCl_3$, 100 MH_Z): 14.39, 23.18, 31.17, 34.05, 40.5, 120.30, 125.25, 126.06, 126.17, 126.18, 126.57, 126.92, 129.05, 129.34, 129.35, 131.43, 133.85, 135.82, 136.22, 140.52, 141.13, 146.37, 163.84.

N-(-(tert-butyl)phenyl)-2-(3-(N-(2-(triflouromethyl)phenyl)sulfamoyl)phenyl)acetamide (4m)

White Solid, LC-MS *m/z* (%): 491 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.435 (s, 1H), 10.152 (s, 1H), 8.358 (s, 1H), 8.229 (t, *J*=8 Hz, 1H), 7.959 (d, *J*=7.6 Hz, 1H), 7.757 (d, *J*=8 Hz, 1H), 7.674 (d, *J*=8.8 Hz, 3H), 7.549(d, *J*=7.6 Hz, 1H), 7.381 (d, *J*=8.8 Hz, 3H), 7.045 (d, *J*=8 Hz, 1H), 1.248 (s, 9H). HPLC-99.65%RT-5.17 min.^{13}C NMR ($CDCl_3$, 100 MH_Z): 30.12, 30.13, 34.24, 34.25, 40.5, 112.12, 115.12, 118.42, 121.13, 122.12, 122.27, 124.12, 125.74, 126.14, 127.34, 127.85, 129.10, 129.85, 131.2, 135,42, 137.35, 139.80, 140.56, 141.52, 164.12.

N-(tert-butyl)phenyl)-2-(3-(N-(2-(tert-butyl)phenyl)sulfamoyl)phenyl)acetamide (4n)

Off White Solid, LC-MS *m/z* (%): 479 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.480 (s, 1H), 9.489 (s, 1H), 8.459 (s, 1H), 8.274 (d, *J*=7.6 Hz, 1H), 8,055 (d, *J*=7.6 Hz, 1H), 7.824 (t, *J*=8 Hz, 1H), 7.691 (d, *J*=8.4 Hz, 2H), 7.44 (d, *J*=8 Hz, 1H), 7.389 (d, *J*=8 Hz, 2H), 7.303 (d, *J*=8.4 Hz, 1H), 7.002 (t, *J*=7.2 Hz, 1H), 6.438(d, *J*=7.2 Hz, 1H) 3.5 (s, 2H), 1.389 (s, 9H), 1.286 (s, 9H). HPLC-98.11% RT-8.12 min.^{13}C NMR ($CDCl_3$, 100 MH_Z): 26.71, 26.72, 40.5, 42.80, 42.81, 112.12, 115.12, 118.42, 121.13, 122.12, 122.27, 124.12, 125.74, 126.14, 127.34, 127.85, 129.10, 129.85, 131.2, 135,42, 137.35, 139.80, 140.56, 141.52, 164.12.

N-(tert-butyl)phenyl)-2-(3-(indolin-1-ylsulfonyl)phenyl)acetamide (4o):

Off White Solid, LC-MS m/z (%): 449 (M+H). 1H NMR (400 MHz, DMSO-d6) δ 10.443 (s, 1H), 8.372 (s, 1H), 8.231 (d, J=7.2 Hz, 1H), 8,069 (d, J=8 Hz, 1H), 7.77 (t, J=8 Hz, 1H), 7.663 (d, J=8 Hz, 2H), 7.382 (d, J=8 Hz, 2H), 7.246 (s, 4H), 4.607 (s, 4H), 3.5 (s, 2H), 1.282 (s, 9H). HPLC-97.99% RT-8.42 min.13C NMR (CDCl3, 100 MHZ): 26.72, 30.13, 34.24, 40.5, 42.80, 112.12, 115.12, 118.42, 121.13, 122.12, 122.27, 124.12, 125.74, 126.14, 127.34, 127.85, 129.10, 129.85, 131.2, 135,42, 137.35, 139.80, 140.56, 141.52, 164.12.

N-(2-methylphenyl)-2-(3-(N-(2,4-dimethylphenyl)sulfamoyl)phenyl)acetamide (4p)

White Solid, LC-MS *m/z* (%): 409 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.136 (s, 1H), 9.58 (s, 1H), 8.246 (s, 1H), 8.228 (d, *J*=8 Hz, 1H), 7.807 (d, *J*=8 Hz, 1H), 7.709 (t, *J*=8 Hz, 1H), 7.319-7.1274 (m, 2H), 7.242-7.166 (m, 2H), 6,963 (s, 1H), 6.888 (d, *J*=8 Hz, 1H), 6.787 (d, *J*=8 Hz, 1H), 3.5 (s, 2H), 2.205 (s, 3H), 2.196 (s, 3H), 1.978 (s, 3H). HPLC-99.26% RT-6.37 min. ^{13}C NMR ($CDCl_3$, 100 MH_Z): 17.75, 17.79, 20.64, 40.5, 126.19, 126.38, 126.40, 126.43, 126.68, 129.23, 129.52, 130.82, 130.90, 131.38, 133.42, 133.62, 134.27, 134.60, 135.40, 135.51, 135.45, 141.29, 163.83.

N-(2-ethylphenyl)-2-(3-(N-(2,4-dimethylphenyl)sulfamoyl)phenyl)acetamide (4q)

White Solid, LC-MS *m/z* (%): 423 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.131 (s, 1H), 9.582 (s, 1H), 8.241 (s, 1H), 8.22 (d, *J*=8 Hz, 1H), 7.809 (d, *J*=8 Hz, 1H), 7.71 (t, *J*=8 Hz, 1H), 7.318-7.227 (m, 4H), 6.961 (s, 1H), 6.886 (d, *J*=8 Hz, 1H),6.792 (d, *J*=8 Hz, 1H) 3.5 (s, 2H), 2.677 (q, *J*=15.2 Hz, 8 Hz , 2H), 2.196 (s, 3H), 1.977 (s, 3H), 1.111 (t, *J*=7.2 Hz, 3H). HPLC-99.07% RT-6.71 min. ^{13}C NMR ($CDCl_3$, 100 MH_Z): 14.38, 17.81, 20.67, 23.28, 40.5, 126.15, 126.23, 126.62, 126.63, 126.68, 126.99, 129.18, 129.34, 129.46, 130.94, 131.36, 133.44, 133.57, 133.78, 135.56, 140.22, 141.33, 164.05.

N-(2-methoylphenyl)-2-(3-(N-(2,4-dimethylphenyl)sulfamoyl)phenyl)acetamide (4r)

White Solid, LC-MS *m/z* (%): 425 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.75 (s, 1H), 9.591 (s, 1H), 8.24 (s, 1H), 8.202 (d, *J*=8 Hz, 1H), 7.772 (d, *J*=8 Hz, 1H), 7.698-7.642 (q, *J*=14.8 Hz,7.2 Hz, 2H), 7.202 (t, *J*=8.4 Hz, 1H), 7.103 (d, *J*=7.2 Hz, 1H), 6,981-6.95 (m, 2H), 6.872 (d, *J*=8.4 Hz, 1H), 6.765 (d, *J*=7.6 Hz, 1H), 3.5 (s, 2H), 3.808(s, 3H), 2.179 (s, 3H), 1.972 (s, 3H). HPLC-99.17% RT-6.56 min. ^{13}C NMR ($CDCl_3$, 100 MH_Z): 17.99, 18.08, 40.5, 55.67, 112.54, 120.18, 123.17, 125.17, 126, 126.29, 126.30, 126.34, 127.62, 129.3, 129.47, 131.44, 132.95, 133.85, 135.45, 141.62, 148.75, 151.88, 163.83.

N-(2-methylphenyl)-2-(3-(N-(2-methyl-4-tert-butylphenyl)sulfamoyl)phenyl)acetamide (4s)

White Solid, LC-MS *m/z* (%): 451 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.14 (s, 1H), 9.623 (s, 1H), 8.271 (s, 1H), 8.232 (d, *J*=7.2 Hz, 1H), 7.876 (d, *J*=7.6 Hz, 1H), 7.73 (d, *J*=7,6 Hz, 1H), 7.293 (d, *J*=8.4 Hz, 2H), 7.237-7.162 (m, 3H), 7.085 (d, *J*=8.4 Hz, 1H), 6.830 (d, *J*=8.4 Hz, 1H), 3.5 (s, 2H), 2.209 (s, 3H), 2.049 (s, 3H), 1.21 (s, 9H). HPLC-98.67% RT-7.43 min. ^{13}C NMR ($CDCl_3$, 100 MH_Z): 14.39, 17.98, 31.08, 34.02, 40.5, 111.66, 120.19, 123.27, 125.17, 126.13, 126.29, 126.32, 126.34, 127.74, 129.3, 129.49, 131.44, 131.95, 133.88, 135.35, 141.46, 148.98, 151.78, 163.80.

N-(2-ethylphenyl)-2-(3-(N-(2-methyl-4-tert-butylphenyl)sulfamoyl)phenyl)acetamide (4t)

White Solid, LC-MS *m/z* (%): 465 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.141 (s, 1H), 9.63 (s, 1H), 8.274 (s, 1H), 8.228 (d, *J*=7.6 Hz, 1H), 7.887 (d, *J*=7.6 Hz, 1H), 7.731 (t, *J*=8 Hz, 1H), 7.318-7.226 (m, 4H), 7.162 (s, 1H), 7.9 (d, *J*=8.4 Hz, 1H),6.835 (d, *J*=8.4 Hz, 1H) 3.5 (s, 2H), 2.62-2.499 (q, *J*=15.2 Hz, 8 Hz , 2H), 2.049 (s, 3H), 1.21 (s, 9H), 1.111 (t, *J*=7.2 Hz, 3H). HPLC-98.86% RT-7.7 min. ^{13}C NMR ($CDCl_3$, 100 MH_Z): 14.39, 17.98, 31.08, 34.02, 40.5, 111.56, 120.19, 123.17, 125.17, 126.03, 126.29, 126.32, 126.34, 127.64, 129.3, 129.49, 131.24, 131.95, 133.85, 135.35, 141.42, 148.88, 151.78, 163.83.

N-(2-methoylphenyl)-2-(3-(N-(2-methyl-4-tert-butylphenyl)sulfamoyl)phenyl)acetamide (4u)

White Solid, LC-MS *m/z* (%): 467 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.756 (s, 1H), 9.632 (s, 1H), 8.263 (s, 1H), 8.204 (d, *J*=6.8 Hz, 1H), 7.38 (d, *J*=8 Hz, 1H), 7.717-7.640 (m, 2H), 7.201 (t, *J*=7.6 Hz, 1H), 7.148 (s, 1H), 7.101-7.07 (m, 2H), 6.959 (t, *J*=7.6 Hz, 1H), 6.806 (t, *J*=7.6 Hz, 1H), 3.5 (s, 2H), 3.805 (s, 3H), 2.04 (s, 3H), 1.91 (s, 9H). HPLC-98.8% RT-7.65 min. ^{13}C NMR ($CDCl_3$, 100 MH_Z): 17.99, 31.08, 34.02, 40.5, 55.67, 111.54, 120.18, 123.17, 125.07, 126, 126.29, 126.30, 126.34, 127.62, 129.3, 129.47, 131.24, 131.95, 133.75, 135.35, 141.42, 148.95, 151.98, 163.73.

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36. General experimental procedure for the synthesis of compound 4a-4u

Step-1: Preparation of 2-(3-chlorosulfonylphenyl)acetate (1) To a stirred solution of methyl 2-phenylacetate (40g 266 mmol) in DCM (100 mL). RM was cooled to 0°C and Chloro sulfonic acid (34g 293 mmol) was added drop wise followed by stirring at room temperature for 1 h. The reaction was monitored by LCMS and TLC after completion of reaction evaporate reaction mixture under reduced pressure and obtained gummy material is washed with excess of hexane and it is crystalized from 20% ethyl acetate: hexane mixture to obtain white solid as 2-(3-chlorosulfonylphenyl)acetate (1) which is used further for sulfonamide coupling reaction Yield 54 g (81%).

Step-2: Preparation of 2a-2f

To a stirred solution of 2-(3-chlorosulfonylphenyl)acetate (1) (1 equiv) in DCM (10 times) was added Pyridine (10 times) the mixture was stirred at rt for 15 min. RM was cooled to 0^0C and substituted amine (1.5 equiv) was added drop wise followed by stirring at rt for 6h. The reaction was monitored by TLC and LCMS after completion of reaction poured reaction mass on cold 2N aqueous HCl and stirrd it for 30 min. The precipitation formed in RM. Filtered the obtained solid and washed it with excess of water and cold diethyl ether and cold pentane to obtain all compounds as white solids. For filtrate extracted with DCM twice. The organic layer was washed with brine solution organic layer was evaporated under reduced pressure to get desired products as white solids. But in most of cases solid compound yields are in 70-80%. Yield 80 - 90%

Step-3: preparation of 3a-3f

To a stirred solution of compound 3 (1 equiv) in THF (10 times) added Ethanol (4 times) and water (2 times) finally added lithium hydroxide (5 equiv) and stirred reaction mixture for 8 h. Progress reaction was monitored by TLC and LCMS. After the completion of reaction evaporate reaction mixture under reduced pressure to obtained gummy material. Added 10 ml of water in it and extracted it with diethyl ether (10 ml). Collected aqueous layer and adjust its PH to 4 by using 6N aqueous HCl. Precipitation occurs stirred it for 30 min. Filtered the obtained solid and wash it with excess of water cold diethyl ether (10 ml) and cold pentane (10 ml) to obtain desired compounds as white solids. Yield- 80%

Step-4: Preparation of 4a-4u

The acid (1 equiv.) was treated with EDCI (1.5 equiv) DIPEA (2.5 equiv) in DCM. Then added amine (1.5 equiv) and stirred RM at room temperature for 8 h. The reaction was monitored by TLC. Added 15 ml of cold water and stirred for 20 min. Then extracted it with 20 ml of DCM. Collected organic layer wash it with 1N aqueous HCl and washed with brine (10 Ml). Evaporate the organic layer to obtain compound with 70 to 80% purity of compounds 4a to 4z. Purification done by washing with 5:95% of DCM: hexane. Obtained solid washed with cold diethyl ether (20 ml) and cold pentane (20 ml) to obtain compounds 4a-4z as white solids. Yield 80-90%

Step-2: Scheme 2 preparation of 2a

To a stirred solution of 2-(3-chlorosulfonylphenyl)acetate (1) (5 g 20.1 mmol) in DCM (10 ml) was added Pyridine (10 ml) the mixture was stirred at rt for 15 min. RM was cooled to 0^0 C and 2-methyl aniline (3.228 g 30.16 mmol) was added drop wise followed by stirring at rt for 6 h. The reaction was monitored by TLC and LCMS after completion of reaction poured reaction mass on cold 2N aqueous HCl (20 ml) and stirred RM it for 30 min. Precipitation formed in RM. Filtered the obtained solid and wash it with excess of water and cold diethyl ether (25 ml) and cold pentane (25 ml) to obtain compound 2a as white solid. Yield- 5.8 g (90 %)

Step-3: Preparation of 3a

To a stirred solution of compound 2a (3g 9.40 mmol) in THF (15 ml) added Ethanol (7 ml) and water (3 ml) finally added lithium hydroxide (0.677g 28.2 mmol) and stirred reaction mixture for 8h. Progress reaction was monitored by TLC and LCMS. After the completion of reaction evaporate reaction mixture under reduced pressure to obtain gummy material. Added 10 ml of water in it and extracted it with diethyl ether (10 ml). Collected aqueous layer and adjust its PH to 4 by using 6N aqueous HCl. Precipitation occurs stirred it for 30 min. Filtered the obtained solid and wash it with excess of water cold diethyl ether (20 ml) and cold pentane (20 ml) to obtain desired compounds 3a as white solids. Yield 2.5 g (87 %)

Step-4: N-(24-dimethylphenyl)-2-(3-(tolyl)sulfamoyl)phenyl)acetamide (4a)

The acid 3a (0.2 g 0.65 mmol) was treated with EDCI (0.188 g 0.98 mmol) DIPEA (0.34 ml 1.96 mmol) in DCM (10 ml). Then added amine (0.238 g 1.96 mmol) and stirred RM at room temperature for 8 h. The reaction was monitored by TLC. Added 15 ml of cold water and stirred for 20 min. Then extracted it with 20 ml of DCM. Collected organic layer wash it with 1N aqueous HCl and washed

with brine (10 ml). To evaporate the organic layer to obtained the compound with 80% purity 4a.

Purification done by washing with 5:95% of DCM: hexane. Obtained solid washed with cold diethyl ether (20 ml) and cold pentane (20 ml) to obtain compounds 4a as white solids.

Yield 0.245 g (91 %).

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