Synthesis, Structure Elucidation and Biological Screening of *N*-(4-((6-methoxy-8-quinoline-yl) amine) pentyl) benzene sulfonamide Derivatives

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ABSTRACT

A new series of *N*-substituted derivatives of primaquine sulfonamide *N*-(4-((6-methoxy-8-quinoline-yl) amine) pentyl) benzene sulfonamide (3S) has been synthesized. Antibacterial activity of these compounds was screened out against different bacterial strains. *N*-(4-((6-methoxyquinolin-8-yl) pentane-1,4diamine (1S) was used as precursor to synthesize *N*-alkyl/aralkyl-*N*-(4-((6-methoxy-8-quinoline-yl) amine) pentyl) benzene sulfonamide derivatives 3S-a to 3S-f. Compound (1S) was reacted with aryl sulfonyl chloride (2S) in the presence of 10% aqueous solution of Na_2CO_3 to synthesize ***N*-(4-((6-methoxy-8-quinoline-yl) amine) pentyl) benzene sulfonamide (3S)**. The molecule 3S was further treated with alkyl/aralkyl halides (4). The structure of synthesized molecules was confirmed by using IR, ^{1}H-NMR, and EIMS spectroscopy. The antibacterial % age inhabitation these compounds proved them strong to moderate inhibitors relative to standard Ciprofloxacin.

Keywords: *N*-(4-((6-methoxyquinolin-8-yl) pentane-1, 4 diamine, antibacterial activity, aryl sulfonylchloride

1. INTRODUCTION

Sulfa medicines have contributed to the discovery and use of numerous potent antibacterial infections in vivo but not in vitro. Most sulfa medications function as an antimetabolite to PABA, which stops bacterial proliferation [1]. Sulfonamides were the first antimicrobial compounds or drugs which act on selective bacteria and can be used analytically [2]. Sulfonamides constrain the bacterial enzyme, dihydropteroate, which is answerable for PABA

integration into dihydro-folic acid, which is the instant pioneer of folic acid [3]. Sulfonamides are amide derivatives of sulfonic acid [4], contain a SO_2NH_2 fraction in their structure, they suppress bacterial growth. It destroys bacteria that cause illnesses, by preventing the bacterial cell's ability to produce folate. Sulfonamides are used in the pharmaceutical industry and these are used to cure infections occurred by bacteria, viruses, and fungi [5]. Sulfonamides as medicines act as bacteriostatic and inhibit the growth of bacteria [6]. SO_2NH_2 functionalities presence made sulfonamide a medicinally important compound. Sulfonamides are drugs used as medicines due to their antimicrobial, antibiotic, antifungal, anticonvulsant [7], anti-inflammatory [8], antitumor [9], and hypothyroidism and are also inhibitors for HIV protease [9].

In order to maintain good activity, the occurrence of a p-amino benzene sulfonyl radical is essential and all consequent consideration practically was attentive to N^1-substituents [10]. Common sulfa medications having sulfamoyl functionalities include sulfa quinoxaline, sulfamethoxazole, silver sulfadiazine [11], celecoxib [12], sulfisoxazole [13], and glipizide are commercially available drugs. These sulfonamide-based drugs are orally absorbed quickly [14]and subcutaneously absorbed slowly [15].

Literature survey shows that no work has so far been carried out on the synthesis of primaquine sulfonate amide derivatives therefore in the context of medicinal importance of sulfonamide derivatives, we have made an attempt for the synthesis, antibacterial activity and structure elucidation of primaquine sulfonamide derivatives by using **IR, ^{1}H-NMR and EIMS spectroscopy.**

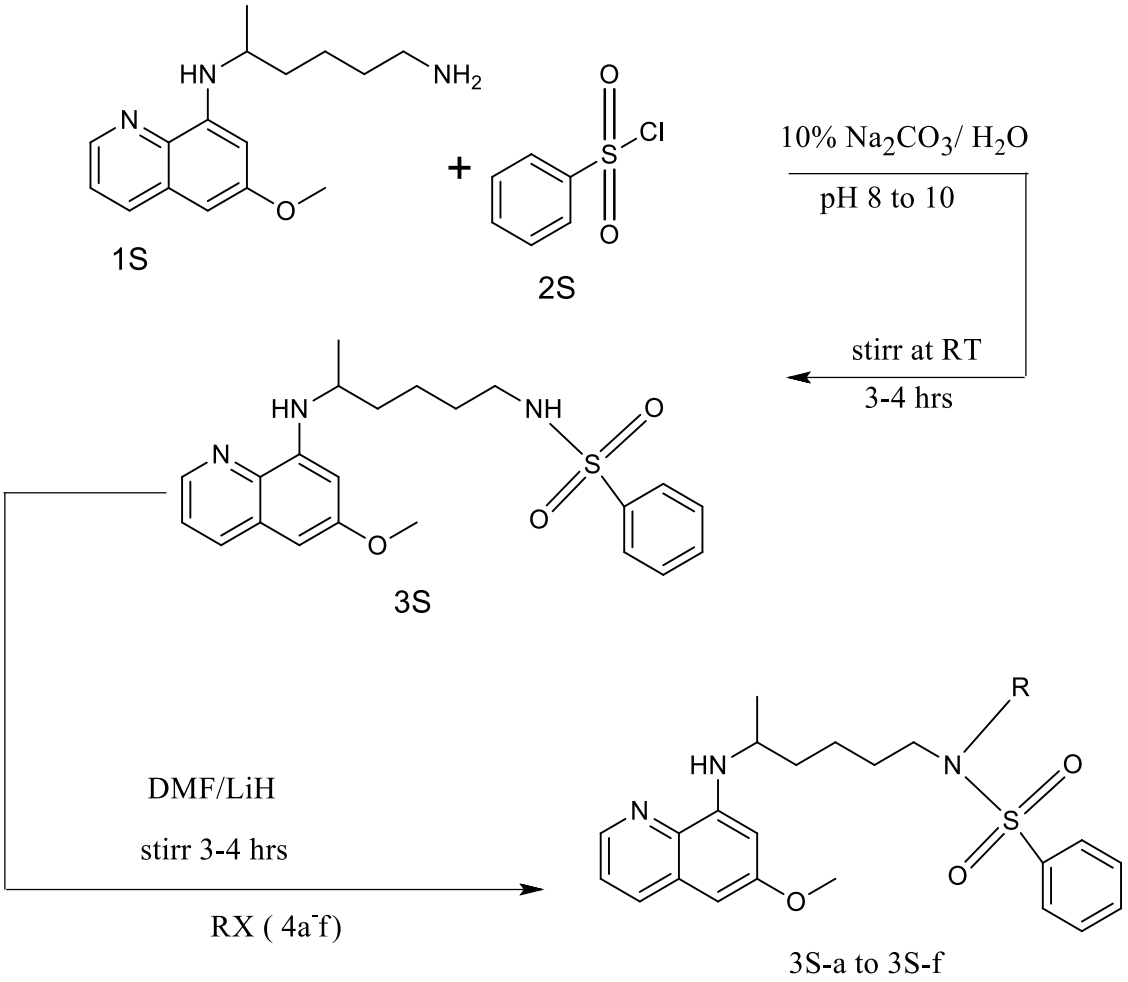
2. EXPERIMENTAL

2.1 General

Chemical reagents used *N*-(4-((6-methoxyquinolin-8-yl) pentane-1,4diamine, benzene sulfonyl chloride and alkyl/aralkyl halides were purchased from Sigma Aldrich. The purity of the synthesized compounds was confirmed by using **Thin Layer Chromatography (TLC)** was subjected to evaluate work progress in the presence of solvents methanol and n-hexane in 1:3 ratio and UV-254 was used for visualization. Gallen Kamp was used to determine the melting point of the synthesized compounds. FTIR of these compounds was achieved by the use of MIDAC M 2000 model of spectrometer. The ^{1}H-NMR spectroscopy was done by using the $CDCl_3$ solvents and the apparatus was run at 400M*Hz* at room temperature.

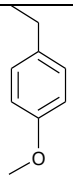
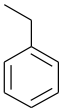
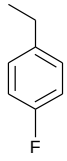
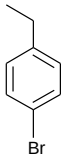
2.2 General procedure for the synthesis of N-alkyl/aralkyl-*N*-(4-((6-methoxy-8-quinoline-yl) amine) pentyl) benzene sulfonamide (3S)

1.5 g (0.00894 mol) of *N*-(4-((6-methoxyquinolin-8-yl) pentane-1,4diamine was measured in 100 ml round bottom flask and then (0.00894 mol) aryl sulfonyl chloride was added in this flask. After this the flask was set to stir for 3-4 hours. The reaction media was basified by the addition of 5 ml Na_2CO_3 (8-10%). The reaction was continued until single spot. To maintain the pH hydrochloric acid was used and pH was maintained 5-6. The product obtained was then washed and dried for future use.



Scheme 1: Outline scheme for the synthesis of N-alkyl/aralyl-*N*-(4-((6-methoxy-8-quinoline-yl) amine) pentyl) benzene sulfonamide

Table 1: different alkyl/aryl/aralkyl (4a-f)

Compd. No.	-R	Compd. No.	-R
(3S-a)	$-CH_2-CH_3$ (4a)	**(3S-d)**	 (4d)
(3S-b)	 (4b)	**(3S-e)**	 (4e)
(3S-c)	 (4c)	**(3S-f)**	$-CH_2-CH_2-CH_3$ (4f)

2.2.1 *N*-(4-((6-methoxy-8-quinoline-yl) amine) pentyl) benzene sulfonamide

light brown powdery, mol formula. $C_{21}H_{25}N_3O_3S$, mol. Weight 399.5gmol^{-1}, yield 77%, IR (KBR, ν_{max}cm^{-1}): 1008 (C-O), 1109 (C-N), 1370 (S=O), 1371 (-OCH_3), 1540 (C=C aromatic), 1558 (C-H), 3435 (N-H stretching), ^{1}H-NMR (400M*Hz*, $CDCl_3$): (ppm) 7.74 (t, *J* = 7.61.0 *Hz*, 2H, H-2, H-6,), 8.71 d, *J* = 8.81 *Hz*, H, H-4,), 7.86 (d, *J* = 7.26 , 2H, H-3, H-5), .6.66 (q, J = 7.68 *Hz*, 2H, H-4, H-6), 7.56 (t, *J* = 7.29 *Hz*, 2H, H-3, H-5), 8.25 (q, *J* = 8.1 *Hz*, 2H, H-7), 7.86 (t, J = 7.26 *Hz*, 2H, H-1), 7.62 (t, *J* = 7.26 *Hz*, 3H, CH_3-8), 7.71 (q, *J* = 7.26 *Hz*, H-3, 4-CH_3), EI-MS *(m/z)* $[M]^+$=399, $[C_6H_6]^+$ = 78, $[C_6H_5SO_2]^+$= 141$[C_{10}H_9NO]^+$=159, $[C_{10}H_{10}ON_2]^+$ = 201, $[C_6H_{21}N_2O]^+$ =259.

2.3 General procedure for the synthesis of alkyl/aryl/aralkyl-N--(4-((6-methoxy-8-quinoline-yl) amine) pentyl) benzene sulfonamide (3S-a to 3S-f)

The compound (3S) was 0.5 g (0.001148 mol) measured and taken in round bottom flask of 50 ml. 5 ml dimethyl formamide (DMF) was added to act as reaction media solvent. To start the reaction LiH (0.004 g) was added in the flask. Then the electrophiles (0.001148 mol) of alkyl/aryl/aralkyl were added to the flask. The flask was stand to stir for 5-6 hours. TLC of the compound was done until single spot obtained. Then the precipitate was washed with water and was further used.

2.3.1 *N*-(4-((6-methoxy-8-quinoline-yl) amine) pentyl)-*N*-ethyl) benzene sulfonamide (3S-a)

Brown powder, Mol. formula $C_{23}H_{29}N_3O_3S$, mol. weight 425.5gmol^{-1}, yield 77% IR (KBR, ν_{max}cm^{-1}): 1000 (C-O), 1155 (C-N), 1410 (S=O), 1510 (C=C aromatic), 1375 (-OCH_3), 3435 (N-H stretching), ^{1}H-NMR (400M*Hz*, $CDCl_3$) (ppm) 8.71 (d, *J* = 8.81, 2H, H-3, H-5,), 6.66 t, *J* = 7.68 , 1H, H-5,), 7.56 (d, *J* = 7.26 , 2H, H-4, H-3), 6.56 (t, *J* = 7.61 , 2H, H-5, H-4), 8.25 (t, *J* =8.00 , 2H, H-5, H-4), 7.86 (q, *J* = 7.26 Hz, 2H, H-7), 7.71 (d, *J* = 7.26 , 2H, H-2'), 3.16 (d, *J* = 1.37 , 2H, CH_3-4), 2.79 (d, *J* = 1.50 , 2H, CH_3-8) EI-MS *(m/z)*: $[M]^+$=428, $[C_6H_6]^+$ = 78, $[C_6H_5SO_2]^+$= 141 $[C_{10}H_9NO]^+$ =159, $[C_{15}H_{21}NO_2]^+$ =287, $[C_{10}H_{10}ON_2]^+$ = 201, $[C_{21}H_{25}N_3O_3S]^+$ =399

2.3.2 *N*-(4-((6-methoxy-8-quinoline-yl) amine) pentyl)-*N*-ethylphenyl) benzene sulfonamide (3S-b)

Light brown, mol. formula $C_{29}H_{33}N_3O_3S$, mol. weight 503.65gmol^{-1}, yield 75%, IR (KBR, ν_{max}cm^{-1}): 1000 (C-O), 1155 (C-N), 1375 (-OCH_3), 1510 (C=C aromatic), 1558 (C-H), 3321 (N-H stretching) ^{1}H-NMR (400M*Hz*, $CDCl_3$ (ppm) 8.71 (d, *J* = 8.81, 2H, H-5, H-4,), 6.66 (d, *J* = 7.60 , 2H, H-6), 7.56 (d, *J* = 7.26 , 2H, H-5, H-4), 8.25 (d, *J* = 8.00 , 2H, H-3, H-4), 7.23 (t, *J* =7.26, 2H, H-5, H-4), 7.62 (q, *J* = 7.26 *Hz*, 2H, H-7), 7.33 (t, *J* = 7.26 , 2H, H-2'), 3.83 (t, *J* = 0.86 , 2H, CH3-4), 4.42 (d, *J* = 1.37 , 2H, CH3-8), EI-MS *(m/z)* $[M]^+$= 503, , $[C_6H_6]^+$ = 78, $[C_6H_5SO_2]^+$= 141, $[C_{10}H_9NO]^+$=159, $[C_{10}H_{10}ON_2]^+$ = 201, $[C_{23}H_{29}N_3O]^+$ =363, $[C_{21}H_{25}N_3O_3S]^+$ =399

2.3.3 *N*-(4-((6-methoxy-8-quinoline-yl) amine) pentyl)-*N*-(4-bromoethylphenyl) benzene sulfonamide (3S-c)

brown green, mol. formula $C_{29}H_{32}BrN_3SO_3$, mol. weight 582.5gmol^{-1}, yield 81%, IR (KBR, ν_{max}cm^{-1}): 1000 (C-O), 1375 (-OCH_3), 1510 (C=C aromatic), 1569 (S=O), 2891 (C-H), 3317 (N-H stretching) , ^{1}H-NMR (400M*Hz*, $CDCl_3$) (ppm) 8.71 (d, *J* = 8.81 *Hz*, 2H, H-3, H-4,), 7.85 (t, *J* = 7.26 *Hz*, 3H, H-4,), 7.86 (t, *J* = 7.26 Hz, 1H, H-3, H-6), 6.66 (d, *J* = 7.68 Hz,

2H, H-4, H-6), 7.76 (d, *J* = 7.26 Hz, 1H, H-4, H-6), 6.56 (q, *J* = 7.61 *Hz*, 1H, H-5), 8.25 (q, *J* = 7.1 *Hz*, 1H, H-3`), 7.12 (t, *J* = 7.26 *Hz*, 3H, CH_3-7), 1.48 (t, *J* = 1.37 *Hz*, 2H, CH_3-6) , EI-MS *(m/z)* $[M]^+$ = 582, $[C_6H_6]^+$ = 78, $[C_6H_5O_2S]^+$= 141, $[C_{10}H_9NO]^+$=159, $[C_{10}H_{10}ON_2]^+$ = 201, $[C_{21}H_{25}N_3O_3S]^+$ =399, $[C_{23}H_{28}N_3OBr]^+$ =442

2.3.4 *N*-(4-((6-methoxy-8-quinoline-yl) amine) pentyl)-*N*-(4-methoxy-1-ethyl) phenylbenzene sulfonamide (3S-d)

Chocolate brown, mol. formula $C_{30}H_{35}N_3O_4S$, mol. weight 555.68gmol^{-1}, yield 82% IR (KBR, ν_{max}cm^{-1}): 1059 (C-O), 1155 (C-N), 1459 (S=O), 1593 (C=C aromatic),1765 (-OCH_3), 3315 (N-H stretching), ^{1}H-NMR (400M*Hz*, $CDCl_3$) (ppm) 8.71 (d, *J* = 8.81 *Hz*, 2H, H-2, H-6,), 7.86 (t, *J* = 7.26 *Hz*, 1H, H-4,), 6.66 (t, *J* = 7.68 *Hz*, 2H, H-3, H-5), 6.87 (d, *J* = 7.26 *Hz*, 2H, H-2, H-6), 7.56 (d, *J* = 7.26 *Hz*, 2H, H-3, H-5), 8.25 (q, *J* = 8.00 *Hz*, 2H, H-7), 7.86 (q, *J* = 7.26 Hz, 2H, H-1), 6.87 (t, *J* = 7.26 *Hz*, 3H, CH_3-8), 1.25 (t, *J* = 0.86 *Hz*, 3H, CH_3-4), EIMS *(m/z)*: $[M]^+$= 555, , $[C_6H_6]^+$ = 78, $[C_6H_5SO_2]^+$= 141, $[C_{10}H_9NO]^+$=159, $[C_{10}H_{10}ON_2]^+$ = 201, $[C_{24}H_{31}N_3O_2]^+$ = 393, $[C_{21}H_{25}N_3O_3S]^+$ =399.

2.3.5 N-(4-((6-methoxy-8-quinoline-yl) amine) pentyl)-*N*-(4-flouro-1-ethyl) phenylbenzene sulfonamide (3S-e)

Yellowish green, mol. formula C_{29} H_{32} FN_3SO_3, molecular weight 521.64gmol^{-1}, yield 85%, IR (KBR, ν_{max}cm^{-1}): 1115 (C-O) 1587 (C=C aromatic), 1770 (-OCH_3), 2810 (C-H), 3350 (N-H stretching), ^{1}H-NMR (400M*Hz*, $CDCl_3$)) (ppm) 8.71 (d, *J* = 8.81 *Hz*, 2H, H-5, H-6,), 6.66 (t, *J* = 7.68 *Hz*, 1H, H-5,), 8.25 (t, *J* = 8.00 *Hz*, 1H, H-3, H-4), 7.86 (t, *J* = 7.26 *Hz*, H-3, H-6), 7.12 (d, *J* = 7.26 *Hz*, 2H, H-3, H-5), 7.62 (q, *J* = 7.26 *Hz*, 2H, H-7), 7.71 (q, *J* = 7.26 *Hz*, 2H, H-5), 3.83 (t, *J* = 0.86 *Hz*, 3H, CH3-8), 4.42 (d, *J* = 1.37 *Hz*, 3H, CH3-4), EI-MS *(m/z)*: $[M]^+$ = 521, $[C_6H_6]^+$ = 78, $[C_6H_5SO_2]^+$= 141, $[C_{10}H_9NO]^+$=159, $[C_{10}H_{10}ON_2]^+$ = 201, $[C_{23}H_{28}N_3OF]^+$ = 381, , $[C_{21}H_{25}N_3O_3S]^+$ =399

2.3.6 *N*-(4-((6-methoxy-8-quinoline-yl) amine) pentyl)-*N*-propyl) benzene sulfonamide (3S-f)

light orange powder, molecular formula $C_{24}H_{31}N_3O_3S$, mol. weight 441.58gmol^{-1}, yield 82%, IR (KBR, ν_{max}cm^{-1}):, 1107(C-O), 1365 (-OCH_3), 1155 (C-N), 1570 (C=C aromatic), 2888 (C-H), 3410 (N-H stretching), ^{1}H-NMR (400M*Hz*, $CDCl_3$) (ppm) 8.71 (d, *J* = 8.81 *Hz*, H-2, H-4,

H-5,), 7.86 (t, *J* = 7.26 *Hz*, 2H, H-5,), 7.56 (t, *J* = 7.26 *Hz*, 1H, H-3, H-4), 7.86 (d, *J* = 7.26 *Hz*, 2H, H-2, H-6), 7.62 (d, *J* = 7.26 *Hz*, 2H, H-3, H-5), 7.71 (q, *J* = 7.26 *Hz*, 2H, H-7), 3.83 (q, *J* = 0.86 *Hz*, 2H, H-5), 2.79 (t, *J* = 1.50 *Hz*, 3H, CH_3-8), 1.25 (t, *J* = 0.86 *Hz*, 3H, CH_3-4), EI-MS *(m/z)* $[M]^+$= 521, $[C_6H_6]^+$= 78, $[C_6H_5SO_2]^+$= 141 $[C_{10}H_9NO]^+$=159, $[C_{10}H_{10}ON_2]^+$ = 201, $[C_{18}H_{27}N_3O]^+$ = 381, , $[C_{21}H_{25}N_3O_3S]^+$ =399

Table 1. 1: Antibacterial activity MIC & inhibition values

Compound	***E. coli (-) P. aeruginosa (-) B. subtilis (+) S. aureus (+) S. typhi (-)***									
	%) Inhibition	**MIC**	**%) Inhibition**	**MIC**	**%) Inhibition**	**MIC**	**%) Inhibition**	**MIC**	**%) Inhibition**	**MIC**
3S	76.65±1.99	11.2 ± 2.10	81.1± 41.80	13.55 ± 2.35	68.01 ±1.67	13.50 ±3.05	64.25 ± 3.05	13.40 ±5.2	64.60 ±2.57	16.15 ±1.16
3S-a	69.93±2.90	10.28± 1.45	71.16 ±1.30	14.36 ± 1.67	50.61 ±3.72	17.53 ± 3.45	63.86 ±2.69	15.59 ± 2.0	73.45 ±5.15	20.14 ± 2.0
3S-b	67.40±1.69	14.13± 1.23	70.11 ± 2.25	13.01 ± 1.70	60.01 ±1.32	15.13 ± 2.12	58.30 ±2.14	12.95 ±4.45	53.01 ±2.0	19.01 ±2.91
3S-c	67.35±2.1	17.1 ± 1.86	64.90 ± 1.30	12.18 ± 3.07	53.17 ±3.60	14.68 ±5.62	53.01 ± 1.91	14.20 ± 2.81	70.55 ±5.45	19.03 ±4.35
3S-d	67.37±1.73	10.41± 1.27	52.21 ± 2.15	16.01 ± 1.10	60.74 ±0.78	54.10 ±2.06	66.77 ± 2.09	60.55 ± 5.55	65.65 ±5.30	15.37 ±4.95

3S-e	65.57±1.53	11.93± 2.95	50.10 ± 1.95	20.66 ± 3.00	45.45 ±1.47	55.64 ± 3.50	52.18 ±1.0	67.55 ± 5.76	40.60 ±3.30	12.45 ±5.89
3S-f	51.84±3.0	16.64± 5.5	50.55 ±2.10	11.03 ±4.13	60.36 ±2.44	66.67 ±3.60	39.18 2.23	46.79 ±3.23	75.60 ±0.45	11.89 ±4.0
Ciprofloxacin	80.14±2.0	80± 2.31	80.14 ±2.11	91.15 ±1.84	80.24 ±2.01	91.14 ±0.02	90.04 ±0.11	90.44 ±1.10	8.14± 2.10	91.24 ±2.01

2.4 Antibacterial activity

The role of antibacterial activity depends on the growth rate logarithm. The cell number of microbes depend on the growth rate logarithm. This growth rate logarithm relies on the broth medium absorbance. As one increase others also increase along with it. And at the end when logarithm of growth rate and broth absorbance medium increase, microbial cell number also increases.

2.5 Statistical analysis

Microsoft excel 2010 was used for the triplicate and statistical analysis of calculations and measurements. The results are triplicates (n=4±SEM). Ciprofloxacin as a standard drug was in this study. 5-30 micro gram/well was used for the dilution and at this dilution minimum inhibitory concentration was measured.

3. RESULTS AND DISCUSSIONS

A scheme is given with reagents and conditions for the synthesis of parent compound and its derivatives. The antibacterial activity of all the derivatives was done against gram positive and negative bacteria. Ciprofloxacin was used as standard in this analysis.

3.1 Chemistry

The parent compound (3S) was synthesized by the condensation of benzene sulfonyl chloride and N-(4-((6-methoxyquinolin-8-yl) pentane-1,4diamine. Confirmation of all the structures was done by the ^{1}HMNR, IR, and EI-MS spectral techniques. This characterization supported in the confirmation of compound 3S. Spectral peak [M^{+}] in EI-MS at m/z 399 exhibited ion. Two *m/z* 159 and at *m/z* 141 peaks emerged when benzene sulfonyl was removed from the compound. Different functional groups were confirmed by IR spectrum showing the presence of N-H group 3435, 1540 (C=C aromatic), 1371 (-OCH_3), 1279 (N-H bending), 1109 (C-N), 3435 (N-H stretching), 1159 (S=O), 1008 (C-O), 1558 (C-H). The signals of ^{1}H-NMR were emerged at (ppm) 7.74 (t, *J*=2 *Hz*, H-2,2H, H-6) for benzyl group attached to sulfamoyl moiety while the meta and para sites in the ring for the three protons showing signals at 8.71 *Hz* (d, *J*= 8.81 Hz, H, H-4) and 7.86(d, *J*= 7.26 *Hz*, 2H, H-3, H-5) shown quinoline existence in the structure. This downfield shift was due to the presence of amide groups. Neighboring methyl groups shown peaks at 7.62 (t, *J* =7.26 *Hz*, H-3, CH_3-8). This structure was named as N-(4-((6-methoxy-8-quinoline-yl) amine) pentyl) benzene sulfonamide.

3.2 Antibacterial activity (in *vitro*)

Antibacterial assay was reported for the 5-gram positive bacterium and is given in the table. In this antibacterial assay Ciprofloxacin as, standard drug was under use. All compounds were tested had shown strong to medium activity against the bacterial strains which were under observations. Compounds 3S-a & 3S-f had shown strong antibacterial activity against the *Salmonella typhi*. The tested compound 4a was not active against *Staphylococcus aureus* and *Pseudomonas auregina*. But the compound 4e was active against all bacterium strains such as *Escherichia coli, Staphylococcus aureus, Pseudomonas auregina and Bacillus subtilis* with minimum inhibition concentration values of 9.43±1.00 micro-M, 13.50±1.67, 11.2±2.10 and 10.28±1.45 as compared to standard values of MIC which are 8.91±1.65, 9.01±0.11, 8.1±0.34 and 8.39±1.02 respectively. This compound shows medium inhibition for the *Salmonella typhi*. And this was found to be resistant against all other gram bacterium.

4. CONCLUSION

The spectral analysis of all the synthesized compounds was done and the compounds were obtained in reasonable yields. Anti-bacterial activity of these derivatives rendered then strong to moderate inhibitors. Among the synthesized compounds, the compound 4e was active against all bacterium strains

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