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Synthetic and Antibacterial Profiling of 4-Methyl-N-(2-Morpholinoethyl) Benzene Sulfonamide

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ABSTRACT

Morpholine sulphonamide (4-Methyl-N-(2-morpholinoethyl) benzene sulfonamide) and their derivatives were synthesized. 2-morpholinoethylamine reacted with 4-Methyl benzene sulphonyl chloride in the presence of 10% Na_2CO_3 to form the product 4-Methyl-N-(2-morpholinoethyl) benzene sulfonamide. Derivatives of Morpholine sulfonamides was formed by reaction of above formed product using different organic halides. LiH taken as base and DMF was used as solvent. Biological activity of synthesized compound examined by using different strains of bacteria including *Streptococcus faecalis, Escherichia Coli, S. typhi, Staphylococcus aureus, Pseudomonas aeruginosa.* Some compounds exhibit antibacterial activity. The compounds 3Ac and 3Ad showed outstanding antibacterial activity against *Pseudomonas aeruginosa (-)* while compound 3Ab showed anti-*E. coli* activities. Synthesized compounds characterization was done by ^{1}H-NMR, Mass spectrometry & IR spectroscopy.

Keywords: 4-Methyl-N-(2-morpholinoethyl) benzene, morpholine, benzene sulphonyl chloride, sulphonamide derivatives.

1. INTRODUCTION

Sulfonamides have the -SO_2NH- group and are found in a wide range of pharmacologically active chemicals[1]. Sulfonamides were the initial medicinal compounds that had wide applications as chemotherapeutic drugs. Other uses of sulphonamide include antibacterial and antiprotozoal [2]. Free amino group in sulphonamide is responsible for its derivatization which causes sulfonamide to have a large application [3]. The need for new antibacterial drugs remains important in pharmaceutical chemistry. The sulphonamide group is found largely in antimicrobial agents. Sulphonamide stop the synthesis of folic acid in bacteria by targeting the enzyme dihydropteroate synthase (DHS) which is the important enzyme in

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catalyzing folic acid formation in bacteria [4]. Sulphonamide shows activity including anti-inflammatory, hypoglycemic activity and antiplatelet working. Some sulphonamide also act as carbonic anhydrase inhibitor [5]. Sulphonamide shows different pharmacokinetics properties because of their high lipid solubility as compared to other antimicrobial drugs [6]. Sulfonamides are antibiotics that are frequently require for fungi, and worms diseases [7]. Sulfonamides which are antibiotic are derived from the sulfanilamide and they have attached substituent to N_1 position and aromatic amine at position of N_4 [8]. The structure of sulfonamide possesses effective amino group and sulfonyl group. This can be used to prepare compounds that showed excellent antifungal activity [9]. Sulphonamide groups found as protease inhibitors in HIV and HCV [10]. Various drugs that possess this sulpha group have large uses in the field of medication include Sulfacetamide sodium[11], sulfadiazine [12] and sulfamethoxazole [13]. Morpholine is a liquid in its natural physical state. It smells like fish or ammonia. The chief uses of Morpholine includes cleanser color, solvent, rusting preventive, corrector, elastomer activator, and boilers steam component. [14]. Morpholine is a unique abundant nitrogen-containing heterocyclic compound found usage in pharmacological centres. "Morpholine (C_4H_9NO, 1,4-tetrahydro-oxazine)"is an aromatic six-membered heterocyclic molecule with both ether as well as amine functional groups. It is a practically strong base having pKa of 8.7, that is commonly employed as a precursor in numerous organic product synthesis. [15]. Morpholine comprising drugs are used extensively for the cure of cancer because these drugs have little or no adversarial effects. These have chief role in the treatment of cancer related to central nervous system. Principal target is the enzyme kinase which is used for regulatory mechanism of cell entitled as phosphotidylinositrol 3-kinase [16]. The rising number of scientific periodicals and review papers reveals how the morpholine ring has apprehended the attention of a significant portion of the pharmacological production for synthesis of molecules with a prevalent range of various biological functions. In pharmaceutical industry, morpholine sulfonamide derivatives have been utilized as cytotoxic drugs, antibacterial, and relievers. Antimicrobial mediators known as sulfonamides are broadly used against damage persuaded by various bacteria, as well as fungi and worms [7].

Since no work has been performed so far in this field so we are going to form a novel series of morpholine sulphonamide derivatives. Our research will let us easily manipulate the basic structure of morpholine sulphonamide derivatives and these compounds characterized by using elemental analysis and spectroscopic methods like mass spectrometry, IR and ^{1}H-NMR.

2.EXPERIMENTAL

2.1. General

All the chemical used 2-morpholinoethanamine, benzene sulphonyl chloride was purchased from Sigma Aldrich. Quality of formed compounds was estimated by thin layer chromatography and this technique was employed to note the work progress by use of different solvents ratio. Methanol

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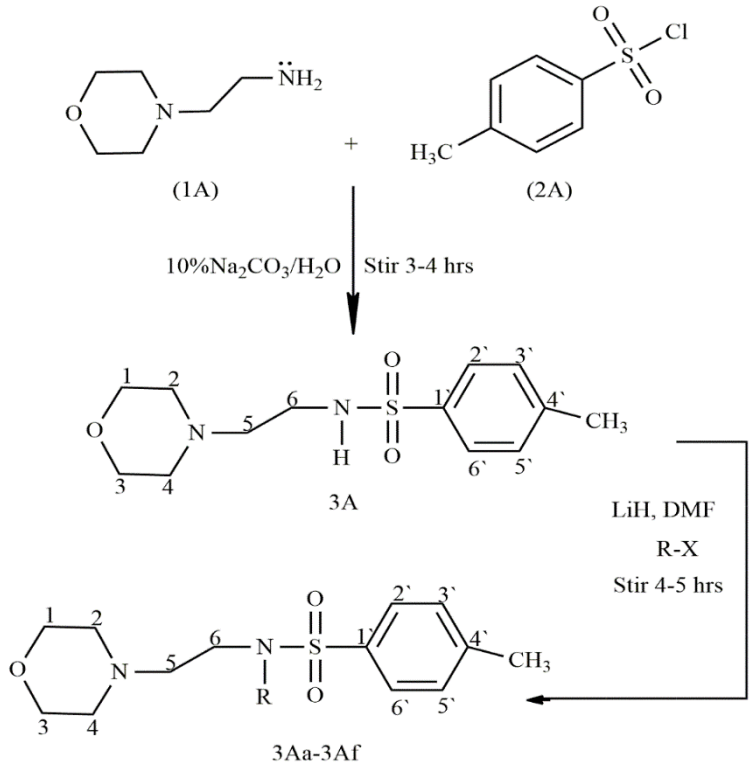

Scheme-1: Synthesis of parent compound (4-Methyl-N-(2-morpholinoethyl) benzene sulfonamide)

and n-hexane as solvents with changing concentration (1:3). Ceric sulphate solution was applied for improved visualization to check TLC plates by using UV light at 356 nm. Gallenkamp method was employed for determining the melting points of all formed compounds. The proton-NMR spectra was taken at 400MHz using $CDCl_3$ as solvent. The IR spectrum is produced in KBr pellet by using Thermo scientific NICOLET IS10 spectrophotometer.

2.2. General method for the formation of (4-Methyl-N-(2-morpholinoethyl) benzene sulfonamide) (3A)

1.2 g (0.00921 mol) of 2-morpholinoethanamine taken in flask. And then other reagent 4-methylbenzene-1-sulfonyl Chloride (0.00921 mol) also measured and take in the same flask. The pH (9-10) of the reaction mixture was accomplished by adding of 10% aqueous solution of the sodium carbonate (Na_2CO_3) at room temperature. For a reaction to take place as planned, stirring must continue for 3–4 hours. To observe how the working reaction was developing, a TLC plate was used. In order to obtain the parent compound (3A), the product was collected after precipitate filtration and washed with ether or water.

2.2.1. 4-Methyl-N-(2-morpholinoethyl) benzene sulfonamide (3A)

Molecular Formula: $C_{13}H_{20}N_2O_3S$, Molecular Weight: 284.37 $gmol^{-1}$, yield 78%, m.p 127, IR stretching (KBR, ν_{max}/cm): 1150 (C-N), 3323 (N-H), 1098 (C-O-C), 1585 (C=C), 1375

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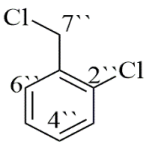
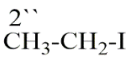
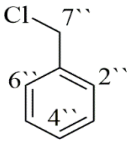
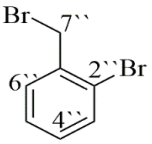
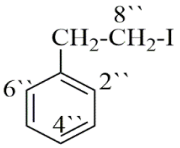
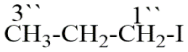
(S=O); ^{1}H NMR chemical shift (400 MHz, CDCl3, ppm): δ 3.67 (t, *J* = 11.88 Hz, 4H, H-1 & H-3), 2.36 (t, *J* = 8.97 Hz, 4H, H-2 & H-4), 2.52 (t, *J* = 2.67 Hz, 2H, H-5), 3.21 (t, *J* = 2.68Hz, 2H, H-6), 7.74 (d, *J* = 8.07 Hz, 2H, H-2` & H-6`), 7.76 (d, *J* = 8.05 Hz, 2H, H-3` & H-5`), 2.34 (s, 3H, H-4`); EI-MS: m/z, 286.38 $[M+2]^+$, 284.37 $[M]^+$, 91.37 $[M-C_6H_{13}N_2O_3S]^+$, 15.04 $[M-C_{12}H_{17}N_2O_3S]^+$, 129.18 $[M-C_7H_7O_2S]^+$, 170.2 $[M-C_6H_{12}NO]^+$, 193.11 $[M-C_7H_7]^+$

2.3. General approach to N-alkyl/aralkyl substituted derivatives synthesis (3Aa to 3Af)

0.5g (0.00175mol) of parent substance (3A) was weighed and taken in flask to make solution. After this different reagents of organic halides (0.00175 mol) were taken in flasks containing the parent compound. These reactions were proceeded using LiH base (0.005g) and DMF as solvent (5ml). Then reaction undergoes continual stirring for 3-4hrs to proceed further. The development of reaction was examined by the employment of TLC plates with a range of varying concentration of solvents. This reaction produces precipitates that undergoes filtration and then collected, washed with water to achieve synthesized compounds **(3Aa to 3Af).**

R-x=different alkyl halide/ aralkyl for synthesis of parent 4-Methyl-N-(2-morpholinoethyl) benzene sulfonamide derivatives

Compd. No.	R-X	Compd. No.	R-X
(3Aa)		(3Ad)	
(3Ab)		(3Ae)	
(3Ac)		(3Af)	

2.3.1. N-(2-chlorobenzyl)-4-Methyl-N-(2-morpholinoethyl) benzenesulfonamide (3Aa):

Mol. Formula: $C_{20}H_{25}ClN_2O_3S$, M.Weight: 408.94 $gmol^{-1}$,yield 80%, m.p 255, IR stretching (KBR, ν_{max}/cm): 1371 (S=O), 1095 (C-O-C), 1580 (C=C), 1142 (stretching of C-N) ; ^{1}H-

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NMR (400 MHz, CDCl3): δ (ppm) 3.7 (t, *J* = 12.02 Hz, 4H, H-1 & H-3), 2.59 (t, *J* = 9.67 Hz, 4H, H-2 & H-4), 2.39 (t, *J* = 2.67 Hz, 2H, H-5), 3.26 (t, *J* = 2.68 Hz, 2H, H-6), 7.72 (d, *J* = 8.06 Hz, 2H, H-2` & H-6`), 7.78 (d, *J* = 8.05 Hz, 2H, H-3` & H-5`), 2.33 (s, 3H, H-4`), 8.17 (d, *J* = 7.86 Hz, 1H, H-3``), 7.25 (t, *J* = 7.87 Hz, 1H, H-4``), 7.20 (t, *J* = 8.86 Hz, 1H, H-5``), 7.68 (d, *J* = 8.10 Hz, 1H, H-6``), 4.42 (s, 2H, H-7``) ; EI-MS: m/z 410.09 $[M+2]^+$, 408.01 $[M]^+$, 155.16 $[M-C13H18\ ClN2O]^+$, 373.03 $[M-Cl]^+$

2.3.2. N-benzyl-4-Methyl-N-(2-morpholinoethyl) benzenesulfonamide (3Ab):

Molecular Formula: $C_{20}H_{26}N_2O_3S$, M.Wgt : 374.50 $gmol^{-1}$, yield 76%, m.p 213, IR (stretching) (KBR, ν_{max}/cm): 1094 (C-O-C), 1140 (C-N), 1579 (C=C), 1367 (S=O); ^{1}H-NMR (chemical shift) (400 MHz, CDCl3, ppm): δ 3.59 (t, *J* = 11.99 Hz, 4H, H-1 & H-3), 3.03 (t, *J* = 10.24 Hz, 4H, H-2 & H-4), 2.50 (t, *J* = 2.67 Hz, 2H, H-5), 3.26 (t, *J* = 2.68 Hz, 2H, H-6), 7.44 (d, *J* = 8.04 Hz, 2H, H-2` & H-6`), 7.41 (d, *J* = 8.06 Hz, 2H, H-3` & H-5`), 2.36 (s, 3H, H-4`), 7.23 (d, *J* = 7.98 Hz, 2H, H-2`` & H-6``), 7.43 (t, *J* = 7.91 Hz, 2H, H-3`` & H-5``), 7.26 (t, *J* = 7.75 Hz, 1H, H-4``), 4.41 (s, 2H, H-7``); EI-MS: m/z, 376.02 $[M+2]^+$, 374.13 $[M]^+$, 283.10 $[M-C_7H_7]^+$, 155.17 $[M-C_{13}H_{19}N_2O]^+$

2.3.3. 4-Methyl-N-(2-morpholinoethyl)-N-phenylethylbenzenesulfonamide (3Ac):

M. Formula: $C_{19}H_{24}N_2O_3S$, Molecular Weight: 360.47 $gmol^{-1}$, yield 82%, m.p 244 °C, IR stretching (KBR, ν_{max}/cm): 1577 (C=C), 1094 (C-O-C), 1369 (S=O), 1141 (C-N) ; ^{1}H NMR (400 MHz, CDCl3, ppm): δ 3.61 (t, *J* = 11.89 Hz, 4H, H-1 & H-3), 3.08 (t, *J* = 10.26 Hz, 4H, H-2 & H-4), 2.41 (t, *J* = 2.61 Hz, 2H, H-5), 3.28 (t, *J* = 2.69 Hz, 2H, H-6), 7.50 (d, *J* = 8.1 Hz, 2H, H-2` & H-6`), 7.43 (d, *J* = 8.07 Hz, 2H, H-3` & H-5`), 2.10 (s, 3H, H-4`), 7.2 (d, *J* = 7.25 Hz, 2H, H-2`` & H-6``), 7.39 (t, *J* = 7.99 Hz, 2H,H-3``& H-5``), 7.27 (t, *J* = 7.78 Hz, 1H, H-4``), 2.69 (t, *J* = 7.77 Hz, 2H, H-7``), 3.49 (t, *J* = 7.78 Hz, 2H, H-8``); EI-MS: m/z 362.30 $[M+2]^+$, 360.1 $[M]^+$, 269.06 $[M-C_7H_7]^+$, 155.15 $[M-C_{12}H_{17}N_2O]^+$

2.3.4. N-ethyl-4-Methyl-N-(2-morpholinoethyl) benzenesulfonamide (3Ad):

M.F: C15H24N2O3S, M.wt: 312.43 $gmol^{-1}$, yield 83%, m.p 130.7, IR (KBR, ν_{max}/cm): 1097 (C-O-C), 1366 (S=O), 1147 (C-N), 1581 (C=C); ^{1}H NMR, chemical shift, (400 MHz, CDCl3 , ppm): δ 3.69 (t, *J* = 11.98 Hz, 4H, H-1 & H-3), 2.52 (t, *J* = 9.87 Hz, 4H, H-2 & H-4), 3.85 (t, *J* = 2.67 Hz, 2H, H-5), 3.29 (t, *J* = 2.69 Hz, 2H, H-6), 7.40 (d, *J* = 8.07 Hz, 2H, H-2` & H-6`), 7.43 (t, *J* = 8.08 Hz, 2H, H-3` & H-5`), 2.32 (m, *J* = 7.01 Hz, 3H, H-1``), 2.01 (t, *J* = 8.0 Hz, 3H, H-2``); EI-MS: m/z 314.04 $[M+2]^+$, 312.13 $[M]^+$, 221.09 $[M-C_7H_7]^+$, 155.11 $[M-C_8H_{17}N_2O_3S]^+$

2.3.5. N-(2-bromobenzyl)-4-Methyl-N-(2-morpholinoethyl) benzenesulfonamide (3Ae):

Molecular Formula: $C_{20}H_{25}BrN_2O_3S$, M.W: 453.39 $gmol^{-1}$, m.p 285.7, yield 78%, IR , Stretching, (KBR, ν_{max}/cm): 1143 (C-N), 1090 (C-O-C), 1571 (C=C), 1365 (S=O) ; ^{1}H NMR (400 MHz, CDCl3, ppm): δ 3.61 (t, *J* = 12.04 Hz, 4H, H-1 & H-3), 2.5 (t, *J* = 9.7 Hz, 4H, H-2 & H-4), 2.79 (t, *J* = 2.64 Hz, 2H, H-5), 3.25 (t, *J* = 2.68 Hz, 2H, H-6), 7.41 (d, *J* = 7.99 Hz, 2H, H-2` & H-6`), 7.76 (d, *J* = 8.05 Hz, 2H, H-3` & H-5`), 2.34 (s, 3H, -CH3), 7.12 (d, *J* =7.86 Hz, 1H, H-3``), 7.27 (t, *J* = 7.87 Hz, 1H, H-4``), 7.15 (t, *J* = 7.86 Hz, 1H, H-5``), 7.48

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(d, *J* = 8.10 Hz, 1H, H-6``), 4.42 (s, 2H, H-7``); EI-MS: m/z 455.1 $[M+2]^+$, 453.05 $[M]^+$, 373.01 $[M-Br]^+$, 363.17 $[M-C_7H_7]^+$

2.3.6. 4-Methyl-N-(2-morpholinoethyl)-N-propylbenzenesulfonamide (3Af):

Mol.For: $C_{16}H_{26}N_2O_3S$, Molecular Weight: 326.45 $gmol^{-1}$, yield 74%, m.p 142, IR stretching (KBR, ν_{max}/cm): 1142 (C-N), 1525 (C=C), 1363 (S=O), 1088 (C-O-C),; ^{1}H NMR Che.Shift (400 MHz, CDCl3, ppm): δ 3.65 (t , *J* = 12.02 Hz, 4H, H-1 & H-3), 2.36 (t, *J* = 9.67 Hz, 4H, H-2 & H-4), 2.39 (t, *J* = 2.67 Hz, 2H, H-5), 3.26 (t, *J* = 2.68 Hz, 2H, H-6), 7.46 (d, *J* = 8.08 Hz, 2H, H-2` & H-6`), 7.84 (d, *J* = 8.05 Hz, 2H, H-3` & H-5`), 2.34 (s, 3H, -CH3), 3.0 (t, *J* = 8.1 Hz, 2H, H-1``), 1.46 (m, *J* = 7.14 Hz, 2H, H-2``), 0.90 (t, *J* = 7.13 Hz, 3H, H-3``); EI-MS: m/z 328.21 $[M+2]^+$, 326.10 $[M]^+$, 235.01 $[M-C_7H_7]^+$, 155.09 $[M-C_9H_{19}N_2O]^+$

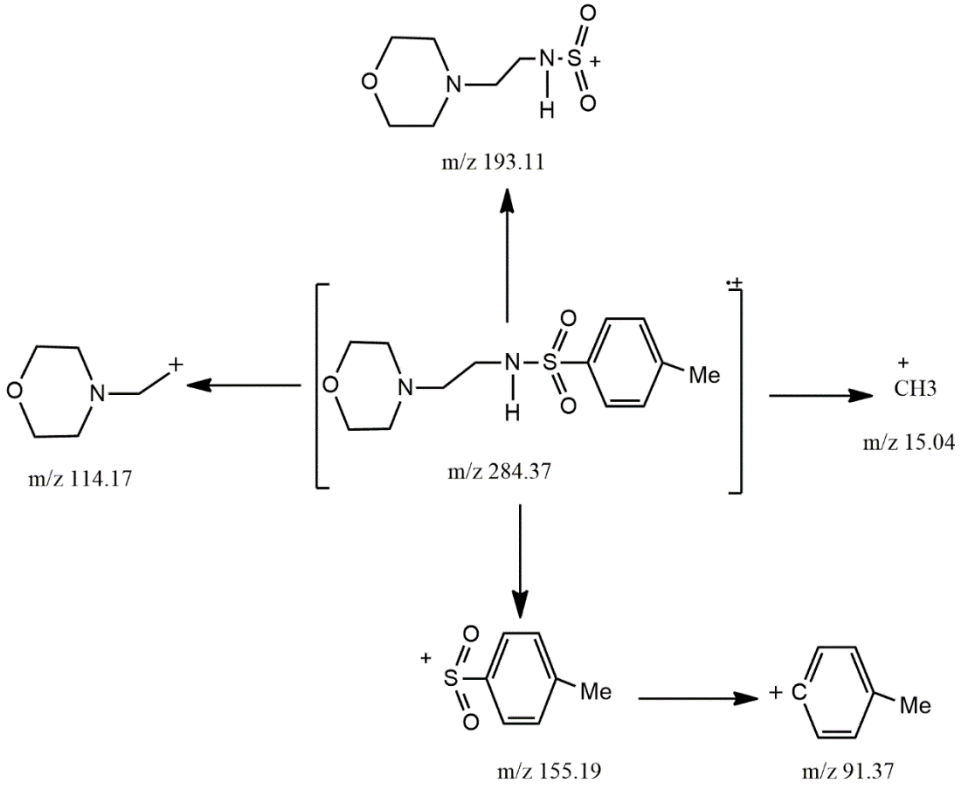

Fig.01: EI-MS Fragments of parent Compound 3A

2.4. Antibacterial assay

The broth dilution method was utilized for computing the MIC value of test solution in accordance with the CLSI 2012 standard organization. The dilution of cell cultures was done by using serial dilution until they ensured 2X 10^4 cells per milliliter of culture. The extent of cells was calculated by means of a hemocytometer. 2 milliliters of Muller Hinton agar broth were added into tubes alongside 100 µl of cell culture. At that point, 100 µl of different antibiotic concentrations (6.25, 12.5, 25.0, 50.0, and 100 mg/ml) were added into each test tube. Growth control was used in concurrence with every experiment. Anaerobic jars were used to incubate separately test tube for 48 hours. Afterward the period of incubation, at 600

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nm the optical density was calculated. Lowermost sample concentration that reserved 20% of the test organisms from developing was recognized as MIC. Subsequent equation was used for finding the percentage of bacterial inhibitions:
Inhibition Percentage: (Control OD − (Sample OD/Control OD)) × 100.

Compounds	***Escherichla coli (-)* ATCC 10536**		***Pseudomomas aeruglnosa (-)* ATCC 14502**		***Streptococcus faecalis (+)* ATCC 10541**		***Staphylococcus aureus(+)PS* ATCC 6538 p**		***S. typhi(-)***	
	%) Inhibition	**MIC**	**%) Inhibition**	**MIC**	**%) Inhibition**	**MIC**	**%) Inhibition**	**MIC**	**%) Inhibition**	**MIC**
3A	75.65 ±1.99	10.2 ± 2.10	80.1± 41.80	12.55 ± 2.35	68.03 ±1.67	13.50± 3.06	64.25± 3.07	13.40±5.3	64.61 ±2.57	16.14±1.16
3Aa	69.92 ±2.90	15.2 ±1.31	71.15 ±1.30	14.36 ± 1.67	50.61 ±3.72	17.53± 3.45	63.86± 2.69	21.59± 2.01	73.45 ±5.15	17.14± 2.01
3Ab	67.42 ±1.69	9.40 ± 1.45	70.13 ± 2.25	16.03 ± 1.70	61.01 ±1.32	16.13± 2.12	57.30± 2.14	>500	53.01 ±2.00	18.01±2.92
3Ac	67.37 ±2.1	17.10± 1.86	64.91 ± 1.30	11.28 ± 3.05	53.17 ±3.61	14.67 ±5.62	53.01± 1.90	14.21± 2.81	70.54 ±5.45	19.03±4.36
3Ad	67.37 ±1.74	9.41 ± 1.26	52.22 ± 2.15	11.28 ± 1.10	60.73 ±0.78	54.11 ±2.06	66.77± 2.08	15.55± 5.56	65.65 ±5.31	17.36±4.95
3Ae	65.57 ±1.52	>500	50.10 ± 1.96	20.66 ± 3.01	45.45 ±1.48	55.65± 3.50	52.19± 1.0	9.46 ±5.89	40.61 ±3.30	67.54± 5.76
3Af	51.84 ±3.00	>500	50.55 ±2.11	11.04 ±4.13	60.37 ±2.44	66.66± 3.60	39.19 2.23	46.79±3.24	75.60 ±0.46	11.88±4.0
Ciprofloxacin	80.14 ±2.0	0.625±2.	80.14 ±2.11	0.625 ±1.84	80.24 ±2.01	91.14± 0.02	1.26±0.11	1.25 ±1.10	8.14± 2.10	1.25±2.01

3. RESULTS AND DISCUSSION

Subsequent recommendations of the CLSI. Synthetic compounds antibacterial activities were assessed against *Pseudomonas aeruginosa (-)* ATCC 14502, *Escherichia coli (-)* ATCC

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10536, *Staphylococcus aureus (+)* PS ATCC 6538 p, *Streptococcus faecalis (+)* ATCC 10541 and *S. typhi (-)* using ciprofloxacin as reference antibacterial mediator. Against *Pseudomonas aeruginosa (-)* compounds 3Ac and 3Ad showed outstanding antibacterial activities with zones of inhibition comparable to standard medication (MIC 11.28). Compound 3Ab showed anti-*E. coli* activities when compared to the zone of inhibition caused by the reference drug ciprofloxacin (MIC 9.40), while compound 3Ae and 3Af not displayed antibacterial action (MIC > 500). All other compounds were moderately effective against different strain in question. Anti-bacterial action of each substance against *S. typhi* fluctuated from reasonable to low. Compounds 3Aa (MIC 17.14± 2.01), 3Ab (MIC 18.01±2.92), and 3Ad (MIC 17.36±4.95) revealed modest activity against *S. typhi*. Compound 3Ae (MIC 9.46±5.89) displayed tremendous activity contrary to the *Staphylococcus aureus* while 3Ab (MIC >500) demonstrated reduced activity. Table-2 shows the values of MIC and inhibition zone.

The parent compound 4-methyl-N-(2-morpholinoethyl) benzene sulfonamide was created by reaction of 2-morpholinoethanamine with 4-methylbenzene-1-sulfonyl Chloride. Molecules structural confirmation was supported by by means of spectral techniques alike ^{1}H-NMR, EI-MS and IR. EI-MS primarily used to resolve the molecular formulaof each compound. In EI-MS distinguished peak of molecular ion existed at m/z 284.37. However the other peaks at 114.17 were indicated the occurrence of Morpholine moity and 155.01 owed to the removel of NH-moity. IR spectra of this compound reside of different bands that supported the existence of functional groups in this molecule. Stretching of S=O functional group appeared at 1375 cm^{-1}. But stretching of N-H and ether (C-O-C) were found at 3323 cm^{-1} and 1098 cm^{-1} respectively. Similarly IR spectra demonstrated the distinguished band for C=C aromatic ring stretching at 1585 cm^{-1} and C-N stretching frequency happend in spectra at 1150 cm^{-1}. All these bands confirmed the occurrence of these groups in parent molecule. ^{1}H-NMR spectrum of this compound presented sinals at chemical shift δ (ppm) 7.74 (d, J = 8.07 Hz, 2H, H-2` & H-6`) and 7.76 (d, J = 8.05 Hz, 2H, H-3` & H-5`) appeared downfield owing to the electron extracting effect of sulfonyl group on the aromatic ring and signals at δ (ppm) 2.34 (s, 3H, H-4`) occured due to methyl group in the ring. The upfield signals at **δ** (ppm) 3.67 (t, J = 11.88 Hz, 4H, H-1 & H-3) and 2.36 (t, J = 8.97 Hz, 4H, H-2 & H-4) designated the occurrence of heterocylic morpholine ring in the molecular structure. Signals that displayed at 2.52 (t, J = 2.67 Hz, 2H, H-5) and 3.21 (t, J = 2.68Hz, 2H, H-6) in spectra of aliphatic region, upfield shift confirmed the presence of ethyl group of morpholine attached to sulfonamide nitrogen group. So, the name 4-methyl-N-(2-morpholinoethyl) benzene sulfonamide was given to parent comppund.

4. CONCLUSION

The synthesized parent compound and derivatives were obtained in equitable yields and were structurally proved by spectral investigation. The antibacterial activity assessment rendered them strong to moderate inhibitors. Out all synthesized derivatives, compounds 3Ac and 3Ad showed outstanding antibacterial activity against *Pseudomonas aeruginosa (-)* while compound 3Ab showed anti-*E. coli* activities. The prepared compound **(3A)** and their derivatives **3Aa-3Af** would be used as greatest pharmacological mediators for several clinical sectors.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

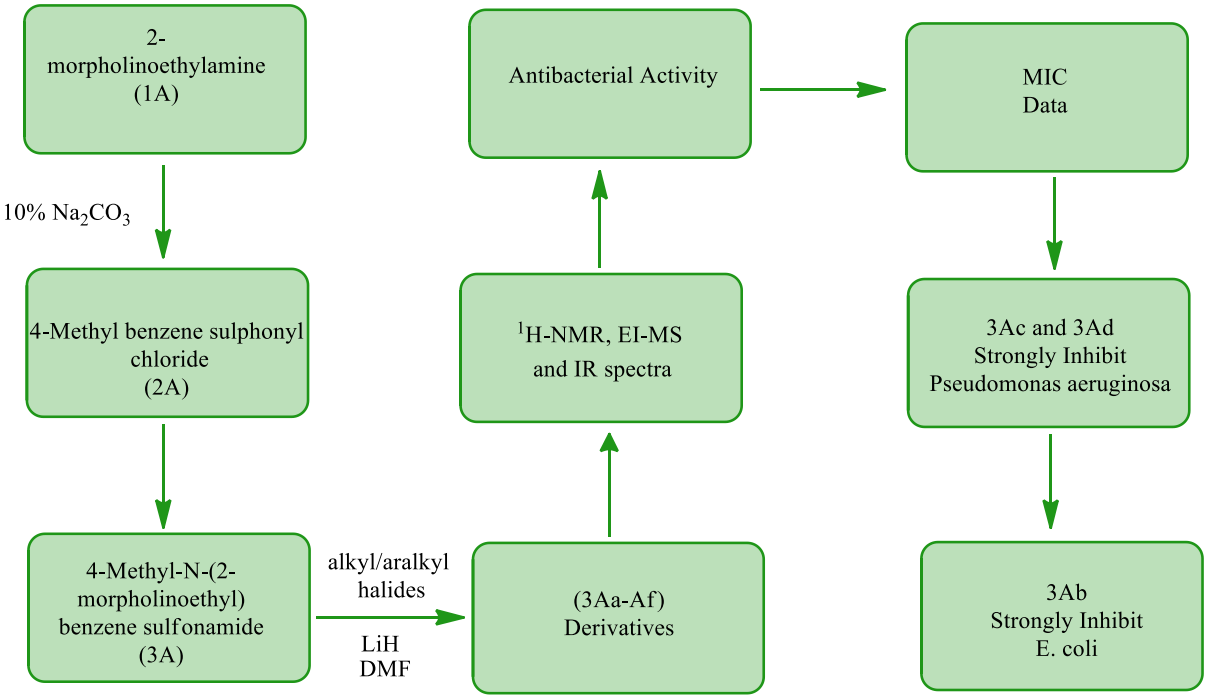
FUNDING DETAILS

This study did not get any financial provision.

CONFLICTS OF INTEREST

No authors have reported any competing interest.

Graphical Abstract



Graphical Representation of Abstract

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