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Synthesis and Antibacterial Study of4-(2-Aminoethyl) morpholine Derivatives

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ABSTRACT

Because of broad spectrum of biological activities bysulfamoyl group, a series of 4-(2-(*N*-(2-chlorobenzyl/4-bromobenzyl)arylsulfamoyl)ethyl)morpholine, **6a-d/7a-d**, have been synthesized from4-(2-aminoethyl)morpholine (**1**). First step includes the synthesis of4-(2-(arylsulfamoyl)ethyl)morpholine, **3a-d**,by reaction of(**1)**andarylsulfonyl chlorides, **2a-d**, in water under definite pH control by 10% Na_2CO_3. In the second step,the molecules **3a-d** were converted to **6a-d** and **7a-d**on reaction with 2-chlorobenzyl chloride (**4**) and 4-bromobenzyl bromide(**5**), respectively, in DMF in the presence of NaH. UsingIR,[1]H-NMR and EI-MS spectral records, the proposed molecular structures were verified.The antibacterial activity results showed good inhibitory action against all the bacterial strains of gram-bacteria with a few exceptions like*B. subtilis*.

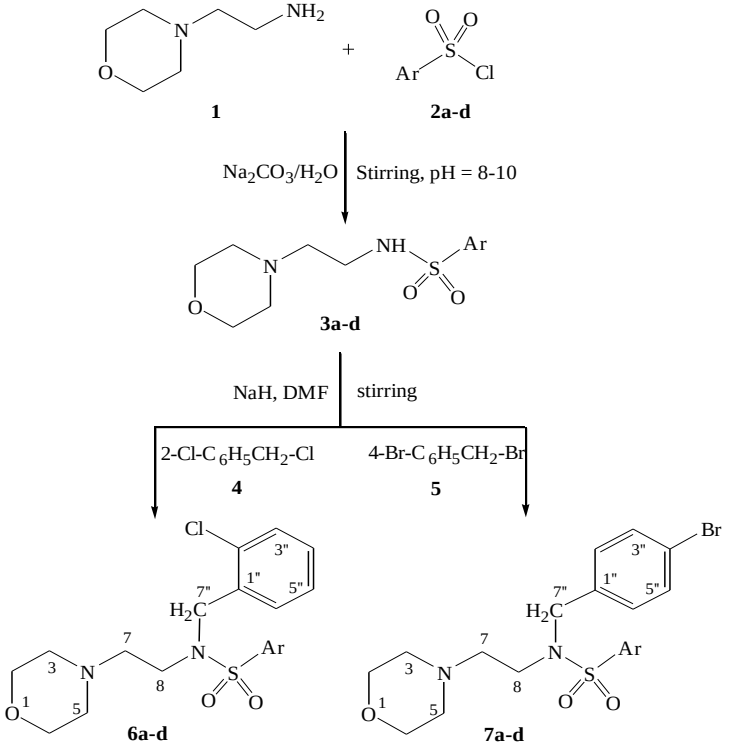
Keywords: 4-(2-Aminoethyl) morpholine, antibacterial activity, sulfonamides.

1. INTRODUCTION

The biological active compounds in medicinal chemistry have been found to possess substituted sulfamoyl group and their wide use owes to simplicity of synthesis and ease of access to reagents required[1-8]. Such compounds have been foundpotent to histone deacetylase (HDAC)[9]andcell cycle disruption in G1 phase in their anticancer action[10]. These molecules are bacteriostatic in nature andso in use for various infections like urinary-tract infection[11-13]. Theirbacteriostatic action is because ofstructural similaritywith 4-aminobenzoic acid (PABA),required by bacteria duringfolic acid synthesis, the main activator of bacterial growth[2-13].

The antimicrobial action of sulfamoyl bearing molecules prompted us to synthesize such type of molecules.In protraction of our projects[14-18] for inauguration of potent molecules against certain diseases, a series of molecules,**6a-d/7a-d**, has been synthesized and evaluated forantibacterial activity.

2. RESULTS AND DISCUSSION



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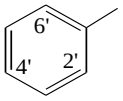
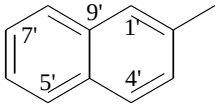
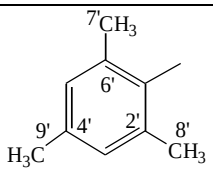
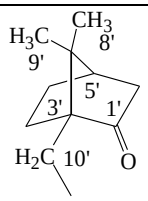
Compound	R	Compound	R
2a,3a,6a,7a		**2c,3c,6c,7c**	
2b,3b,6b,7b		**2d,3d,6d,7d**	

Scheme 1: *N*-aralkyl substituted derivatives of 4-(2-(arylsulfamoyl)ethyl) morpholine

The applied reaction steps to synthesize the target molecules from 4-(2-aminoethyl) morpholine (**1**) are sketched in scheme 1. The detailed reaction procedures, reaction conditions and results of spectral analysis are elaborated in experimental section.

2.1 *Chemistry*

The molecules **3a-d** were acquired through filtration from acidic aqueous medium after coupling4-(2-aminoethyl)morpholine(**1**) with arylsulfonyl chlorides (**2a-d**) through nucleophilic substitution in basic aqueous medium. The molecules **6a-d** and **7a-d** were collected through filtration or solvent extraction after reaction of **3a-d** with 2-chlorobenzyl chloride (**4**) and 4-bromobenzyl bromide (**5**), respectively, in a polar aprotic solvent using NaH as an activator.The halogenated electrophiles have been employed because of enhanced potential of halogenated molecules[19].

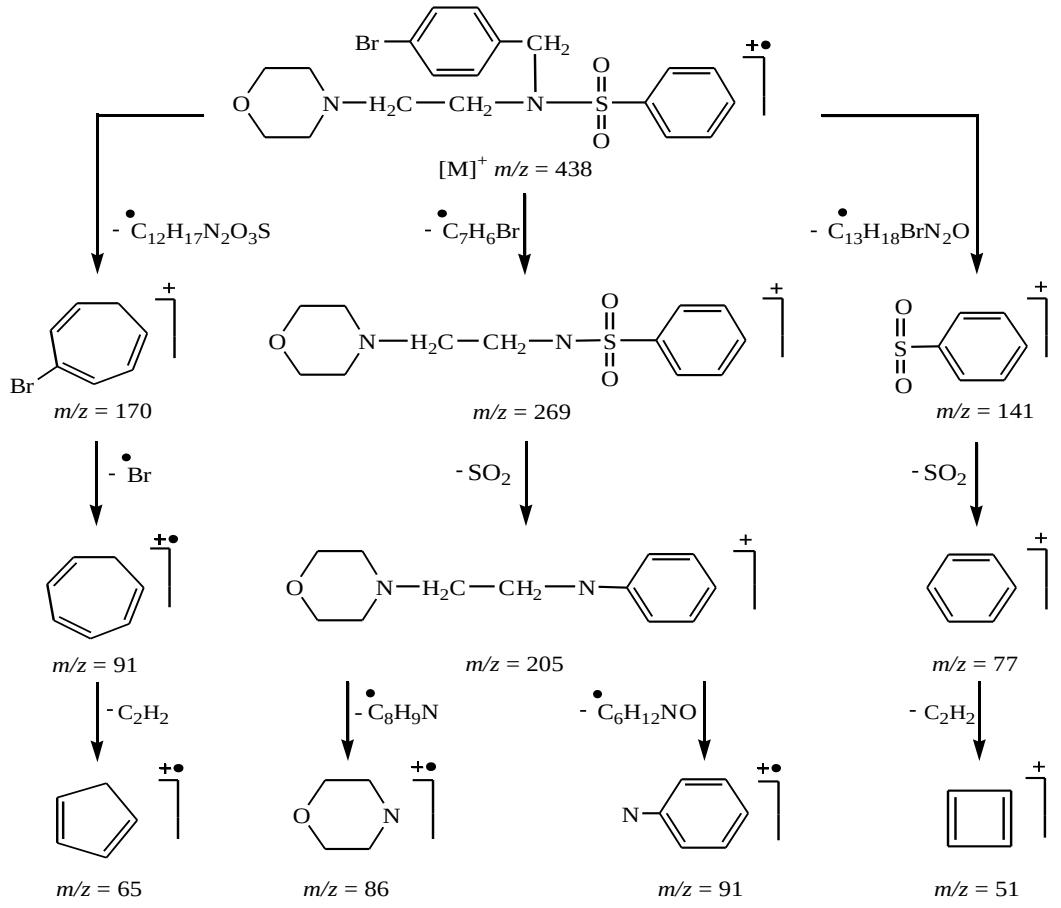


Fig.1: Mass fragmentation pattern of 4-(2-(*N*-(4-Bromobenzyl) phenylsulfamoyl)ethyl) morpholine (**7a**)

The compound **3a** was extracted from reaction mixture by chloroform as reddish brown sticky solid. EIMS showed $[M]^+$ peak at *m/z* 270 for$C_{12}H_{18}N_2O_3S$ with seven resonating peaks in ^{1}H-NMR spectrum for seventeen protons, omitting the peak of acidic proton of sulfamoyl group. The specific absorption bands (cm^{-1}) were 3325 (N-H) and 1367 (S=O) for sulfamoyl group in IR spectrum. The two prominent fragments in EIMS appeared at *m/z* 141 for benzenesulfonyl cation and 129 for 2-(Morpholin-4-yl)ethylamino cation. A fragmentation pattern for assistance is drawn in figure 1 for the molecule, **7a**. In ^{1}H-NMR spectrum, three signals resonated for five aromatic protons at δ 7.85 ppm (as doublet with *o*-coupling of 7.6 Hz and double integration), 7.53 ppm (as triplet with *o*-coupling of 7.2 Hz and

single integration) and 7.46ppm (as triplet with *o*-coupling of 7.2 Hz and double integration). Four signals appeared for twelve aliphatic protons at δ 3.73 ppm (as triplet with small coupling of 4.8 Hz and integration for four protons of morpholine ring adjacent toits oxygen), 3.10 ppm (as triplet with vicinal proton coupling of 7.2 Hz and double integration for methylene protons adjacent to nitrogen of morpholine), 2.57 ppm (as triplet with vicinal proton coupling of 7.2 Hz and double integration for methylene protons adjacent to nitrogen of sulfamoyl group) and 2.47 ppm (as triplet with small coupling of 4.8 Hz and integration for four protons of morpholine ring adjacent to its nitrogen).The cumulative discussion justified **3a** as 4-(2-(phenylsulfamoyl)ethyl)morpholine. Likewise discussion supported the other synthesized molecules of this series.

2.2 *Antibacterial activity*

The parent and target molecules were evaluated for their antibacterial activity with reference of ciprofloxacin against certain strains of gram bacteria.The inhibition activity was tabulated as %age inhibition and MIC values (Table **1** and Table **2**).

Table.1: %age inhibition values of antibacterial activity

	%AGE INHIBITION				
Compound	**S. typhi (-)**	**E. coli (-)**	**P. aeruginosa (-)**	**B. subtilis (+)**	**S. aureus (+)**
3a	69.28±1.17	68.77±2.68	68.45±2.25	60.95±5.00	70.58±2.68
3b	71.17±3.61	65.91±2.27	72.00±0.30	37.90±3.50	71.84±5.00
3c	80.67±3.00	78.45±2.45	81.90±3.30	37.55±2.25	70.63±2.21
3d	71.28±0.72	70.09±1.27	78.10±1.30	56.05±1.55	60.74±0.63
6a	81.14±2.16	67.19±1.74	67.15±3.15	51.75±3.65	69.12±2.58
6b	77.72±0.28	77.91±1.45	77.90±1.00	62.50±4.50	73.84±4.05
6c	78.61±0.61	76.82±0.64	70.85±0.35	62.80±5.00	71.58±1.16
6d	70.69±2.50	68.19±3.06	72.01±2.04	57.21±3.43	62.17±1.03
7a	79.53±4.81	64.16±2.79	51.24±2.65	66.21±2.80	41.04±1.21
7b	75.39±0.06	77.23±1.32	76.45±1.35	45.05±3.05	67.37±0.95
7c	77.41±2.75	76.72±3.69	78.36±2.95	36.82±1.51	73.36±4.60
7d	70.56±2.55	71.90±4.76	76.32±2.05	61.36±2.98	63.42±1.38
Ciprofloxacin	**91.54±1.56**	**90.98±0.83**	**91.04±2.15**	**89.20±1.11**	**92.20±1.37**

Table.2: MIC values of antibacterial activity

	MIC				
Compound	***S. typhi (-)***	***E. coli (-)***	***P. aeruginosa (-)***	***B. subtilis (+)***	***S. aureus (+)***
3a	13.67±4.11	13.81±3.20	10.97±1.11	11.99±5.00	11.73±3.51
3b	10.68±1.22	13.81±2.20	15.73±4.00	-	10.43±1.62
3c	9.83±2.22	11.59±4.60	11.86±2.67	-	11.25±0.54
3d	10.77±1.33	10.73±2.80	11.30±1.33	13.31±2.09	10.36±1.68
6a	11.23±1.07	13.34±3.01	16.04±3.40	17.33±2.84	15.09±1.53
6b	10.28±5.00	8.47±1.20	12.59±2.89	16.96±1.09	10.40±1.44
6c	8.75±1.56	8.70±1.60	13.75±1.22	12.21±1.45	10.44±1.27
6d	13.87±2.84	15.76±2.76	12.18±3.89	15.61±3.50	12.63±2.18
7a	16.09±3.12	14.79±3.20	13.43±4.04	-	16.05±4.18
7b	11.29±3.22	11.85±2.00	11.50±5.00	-	13.35±3.92
7c	12.42±1.87	13.82±5.16	12.06±4.13	-	14.99±1.05
7d	14.11±2.92	13.08±1.73	13.61±3.80	15.81±4.19	14.39±2.83
Ciprofloxacin	**8.24±1.87**	**7.98±1.33**	**8.03±1.54**	**7.63±1.95**	**8.00±0.54**

NOTE: Minimum inhibitory concentration (MIC) was measured with suitable dilutions (5-30 µg/ well) and results were calculated using EZ-Fit Perrella Scientific Inc. Amherst USA software

The MIC values suggested the least inhibition *B. subtilis* by these molecules. The compounds of series **3** and **7** exhibited minimum inhibition and that of **6** exhibited maximum activity against *B. subtilis*. *S. typhi*, the negative bacterial strain, was best inhibited by **3c** and **6c** having MIC values of 9.83±2.22 and 8.75±1.56 µM, respectively, with reference to 8.24±1.87 µM. *E. coli* was best screened by **6b** and **6c** with MIC values of 8.47±1.20 and 8.70±1.60 µM, respectively, in comparison of 7.98±1.33 µM. P. *aeruginosa* was screened efficiently by**3a**, **3c**, **3d**and **7b**.The molecules, **3c**, **6c** and **7c**, remained the most efficient and that might be because of naphthyl group present in these molecules.

3. CONCLUSION

The compounds bearing sulfamoyl group were synthesized and supported by spectral data.The synthesis of compounds was aidedby antibacterial activity evaluation for inhibition of growth of bacterial strains listed as gram bacteria. The molecules bearing naphthyl moiety have been found to be valuable inhibitors and these might be assistive in drug discovery pathwayunder development by pharmacists.

4. EXPERIMENTAL

4.1 *General*

The analytical grade solvents were purchased through local suppliers.Allthe chemicals employed for synthesis of target molecules were of synthetic grade and purchased from Alfa Aesar and Sigma Aldrich. The reaction completion and final purification of synthesized molecules was found out by TLC equippedby silica gel G-25,visualized at 254 nm and run in ethyl acetate and *n*-hexane. Melting points were noted by thermometer through Griffin-George apparatus using an open capillary tube. EI-MS spectra were recorded by JMS-HX-110 spectrometer, IR spectra in KBrby Jasco-320-A spectrophotometer andproton NMR spectra in $CHCl_3$-d_1 by Bruker spectrometer working at 400 MHz.The δ-values are in ppmand referenced to TMS.*J*-values are in Hz.

4.2 *General method for preparation of 4-(2-(arylsulfamoyl)ethyl)morpholine (3a-d)*

4-(2-Aminoethyl)morpholine (**1**, 0.018mol) was mixed with 16 mL distilled water in a 100 mL round bottom flask and stirred.During stirring, arylsulfonyl chlorides (**2a-d**, 0.018 mol) were introduced by parts and stirred for further 3-4 hours. The decrement in pH because of HCl produced was hinderedby neutralizationthrough 15% aqueous Na_2CO_3 solution. The pH was maintained at 8-10.The reaction was supervised through TLC till completion.A few drops of concentratedHCl were added on shaking to set the pH of 5-6 and left for precipitation.The settled solid wasfiltered, rinsedbyexcess water and dried.

4.2.1 *4-(2-(Phenylsulfamoyl)ethyl)morpholine(3a)*

Reddish brown sticky solid; Yield: 70%; Mol. formula: $C_{12}H_{18}N_2O_3S$; Mol. weight: 270 gmol^{-1}; IR (KBr, ν_{max}/cm^{-1}): 3325 (N-H), 3024 (Ar C-H), 1574 (Ar C=C), 1367 (S=O);^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ 7.85 (d, *J* = 7.6 Hz, 2H, H-2', H-6'), 7.53 (t, *J* = 7.2 Hz, 1H, H-4'), 7.46 (t, *J* = 7.2 Hz, 2H, H-3', H-5'), 3.73 (t, *J* = 4.8 Hz, 4H, H-2, H-6), 3.10 (t, *J* = 7.2 Hz, 2H, H-7), 2.57 (t, *J* = 7.2 Hz, 2H, H-8), 2.47 (t, *J* = 4.8 Hz, 4H, H-3, H-5); EIMS (*m/z*): 270 $[M]^+$, 206 $[C_{12}H_{18}N_2O]^+$, 141 $[C_6H_5SO_2]^+$, 129 $[C_6H_{13}N_2O]^+$, 101 $[C_4H_9N_2O]^+$.

4.2.2 *4-(2-((2,4,6-Trimethylphenyl)sulfamoyl)ethyl)morpholine(3b)*

Light brown amorphous solid; Yield: 79%; M. P.: 76-78 ^{o}C; Mol. formula: $C_{15}H_{24}N_2O_3S$; Mol. weight: 312 gmol^{-1}; IR (KBr, ν_{max}/cm^{-1}): 3337 (N-H), 3056 (Ar C-H), 1567 (Ar C=C), 1352 (S=O);^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ 7.82 (s, 2H, H-3', H-5'), 3.83 (t, *J* = 4.8 Hz, 4H, H-2, H-6), 3.19 (t, *J* = 7.2 Hz, 2H, H-7), 2.64 (t, *J* = 7.2 Hz, 2H, H-8), 2.59 (t, *J* = 4.8 Hz, 4H, H-3, H-5), 2.55 (s, 6H, CH_3-2', CH_3-6'), 2.26 (s, 3H, CH_3-4'); EIMS (*m/z*): 312 $[M]^+$, 248 $[C_{15}H_{24}N_2O]^+$, 183 $[(CH_3)_3C_6H_3SO_2]^+$, 129 $[C_6H_{13}N_2O]^+$, 119 $[(CH_3)_3C_6H_3]^+$, 101 $[C_4H_9N_2O]^+$.

4.2.3 *4-(2-(Naphthalen-2-ylsulfamoyl)ethyl)morpholine (3c)*

White amorphous solid; Yield: 77%; M. P.: 84-86 ^{o}C; Mol. formula: $C_{16}H_{20}N_2O_3S$; Mol. weight: 320 gmol^{-1}; IR (KBr, ν_{max}/cm^{-1}): 3343 (N-H), 3029 (Ar C-H), 1587 (Ar C=C), 1389 (S=O);^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ 8.59 (d, *J* = 0.8 Hz, 1H, H-1'), 8.04 (d, *J* = 8.8 Hz, 1H, H-8'), 8.02 (d, *J* = 7.6 Hz, 1H, H-4'), 7.98 (dd, *J* = 8.8, 1.6 Hz, 1H, H-5'), 7.95 (d, *J* = 9.6 Hz, 1H, H-3'), 7.73 (td, *J* = 8.0, 0.8 Hz, 1H, H-7'), 7.67 (td, *J* = 8.4, 1.2 Hz, 1H, H-6'), 3.86 (t, *J* = 4.8 Hz, 4H, H-2, H-6), 3.21 (t, *J* = 7.2 Hz, 2H, H-7), 2.67 (t, *J* = 7.2 Hz, 2H, H-8), 2.61 (t, *J* = 4.8 Hz, 4H, H-3, H-5); EIMS (*m/z*): 320 $[M]^+$, 256 $[C_{16}H_{20}N_2O]^+$, 191 $[C_{10}H_7SO_2]^+$, 129 $[C_6H_{13}N_2O]^+$, 127 $[C_{10}H_7]^+$, 102 $[C_8H_6]^+$, 101 $[C_4H_9N_2O]^+$.

4.2.4 *4-(2-(Camphor-10-ylsulfamoyl)ethyl)morpholine (3d)*

Orange yellow liquid; Yield: 69%; Mol. formula: $C_{16}H_{28}N_2O_4S$; Mol. weight: 344 gmol^{-1}; IR (KBr, ν_{max}/cm^{-1}): 3332 (N-H), 1718 (ketone C=O),1361 (S=O);^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ 3.68 (t, *J* = 4.4 Hz, 4H, H-2, H-6), 3.45 (d, *J* = 15.2 Hz, 1H, H_a-10'), 3.32-3.21 (m, 1H, H_{eq}-6'), 2.89 (d, *J* = 15.2 Hz, 1H, H_b-10'), 2.58-2.53 (m, 1H, H_{ax}-6'), 2.51 (t, *J* = 7.2 Hz, 2H, H-7), 2.36 (t, *J* = 7.2 Hz, 2H, H-8), 2.33-2.26 (m, 1H, H_{eq}-4'), 2.09 (t, *J* = 4.8 Hz, 4H, H-3, H-5), 2.02-1.99
(m, 2H, H_{ax}-4', H_{ax}-5'), 1.86-1.80 (m, 1H, H_{eq}-3'), 1.45-1.38 (m, 1H, H_{ax}-3'), 1.02 (s, 3H, CH_3-9'), 0.86 (s, 3H, CH_3-8'); EIMS (*m/z*): 344 $[M]^+$, 280 $[C_{16}H_{28}N_2O_2]^+$, 215 $[C_{10}H_{15}OSO_2]^+$, 151 $[C_{10}H_{15}O]^+$, 129 $[C_6H_{13}N_2O]^+$, 101 $[C_4H_9N_2O]^+$.

4.3 *General method for preparation of 4-(2-(N-(aralkyl)arylsulfamoyl)ethyl)morpholine(6a-d, 7a-d)*

The synthesized parent molecules**3a-d**(0.011mol)weremixed and stirredwith8 mL DMFand 0.011 molNaHfor 0.75 hour in a 50 mL RB flask. During stirring,aralkyl halides(**4-5**,0.011mol) were introducedandstirred for further5-6 hours. The reaction progress and completion wereensuredby TLC.Excess cold distilled water was added and formed target molecules were filtered or extracted through solvent.

4.3.1 *4-(2-(N-(2-Chlorobenzyl)phenylsulfamoyl)ethyl)morpholine(6a)*

Light brown sticky solid; Yield: 71%; Mol. formula: $C_{19}H_{23}ClN_2O_3S$; Mol. weight: 394 gmol^{-1}; IR (KBr, ν_{max}/cm^{-1}): 3047 (Ar C-H), 1585 (Ar C=C), 1384 (S=O), 707 (C-Cl);^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ 7.83 (d, *J* = 7.6 Hz, 1H, H-3''), 7.71 (d, *J* = 8.0 Hz, 2H, H-2', H-6'), 7.63 (t, *J* = 7.6 Hz, 1H, H-4'), 7.51 (td, *J* = 8.0, 1.6 Hz, 1H, H-4''), 7.42 (t, *J* = 7.6 Hz, 1H, H-5''), 7.34 (t, *J* = 7.6 Hz, 2H, H-3', H-5'), 7.21 (d, *J* = 7.2 Hz, 1H, H-6''), 4.31 (s, 2H, H-7''), 3.89 (t, *J* = 4.8 Hz, 4H, H-2, H-6), 3.23 (t, *J* = 7.2 Hz, 2H, H-7), 2.57 (t, *J* = 7.2 Hz, 2H, H-8), 2.52 (t, *J* = 4.8 Hz, 4H, H-3, H-5);

EIMS (*m/z*): 396 $[M+2]^+$, 394 $[M]^+$, 205 $[C_{12}H_{17}N_2O]^+$, 141 $[C_6H_5SO_2]^+$, 129 $[C_6H_{13}N_2O]^+$, 125 $[C_7H_6Cl]^+$, 101 $[C_4H_9N_2O]^+$.

4.3.2 ***4-(2-(N-(2-Chlorobenzyl)-2,4,6-trimethylphenylsulfamoyl)ethyl)morpholine(6b)***
Yellow liquid; Yield: 76%; Mol. formula: $C_{22}H_{29}ClN_2O_3S$; Mol. weight: 436 gmol^{-1}; IR (KBr, ν_{max}/cm^{-1}): 3066 (Ar C-H), 1563 (Ar C=C), 1354 (S=O), 695 (C-Cl);^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ 7.97 (d, *J* = 7.6 Hz, 1H, H-3"), 7.94-7.88 (m, 2H, H-4", H-5"), 7.83 (d, *J* = 8.0 Hz, 1H, H-6"), 7.79 (s, 2H, H-3', H-5'), 4.36 (s, 2H, H-7"), 3.91 (t, *J* = 4.8 Hz, 4H, H-2, H-6), 3.28 (t, *J* = 7.2 Hz, 2H, H-7), 2.72 (t, *J* = 7.2 Hz, 2H, H-8), 2.61 (t, *J* = 4.8 Hz, 4H, H-3, H-5), 2.47 (s, 6H, CH_3-2', CH_3-6'), 2.29 (s, 3H, CH_3-4'); EIMS (*m/z*): 438 $[M+2]^+$, 436 $[M]^+$, 247 $[C_{15}H_{23}N_2O]^+$, 183 $[(CH_3)_3C_6H_3SO_2]^+$, 129 $[C_6H_{13}N_2O]^+$, 125 $[C_7H_6Cl]^+$,101 $[C_4H_9N_2O]^+$.

4.3.3 ***4-(2-(N-(2-Chlorobenzyl)naphthalen-2-ylsulfamoyl)ethyl)morpholine(6c)***
Light yellow liquid; Yield: 74%; Mol. formula: $C_{23}H_{25}ClN_2O_3S$; Mol. weight: 444 gmol^{-1}; IR (KBr, ν_{max}/cm^{-1}): 3039 (Ar C-H), 1583 (Ar C=C), 1387 (S=O), 701 (C-Cl);^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ 8.71 (d, *J* = 1.6 Hz, 1H, H-1'), 8.06 (d, *J* = 8.0 Hz, 1H, H-8'), 8.02 (d, *J* = 7.6 Hz, 1H, H-4'), 7.98 (d, *J* = 8.4 Hz, 1H, H-5'), 7.93 (d, *J* = 8.4 Hz, 1H, H-3'), 7.85 (t, *J* = 8.4 Hz, 1H, H-7'), 7.78 (d, *J* = 8.0 Hz, 1H, H-3"), 7.66 (t, *J* = 8.4 Hz, 1H, H-6'), 7.64 (t, *J* = 7.6 Hz, 1H, H-4"), 7.43 (t, *J* = 8.0 Hz, 1H, H-5"), 7.20 (br.s, 1H, H-6"), 4.37 (s, 2H, H-7"), 3.84 (t, *J* = 4.8 Hz, 4H, H-2, H-6), 3.25 (t, *J* = 7.2 Hz, 2H, H-7), 2.77 (t, *J* = 7.2 Hz, 2H, H-8), 2.66 (t, *J* = 4.8 Hz, 4H, H-3, H-5); EIMS (*m/z*): 446 $[M+2]^+$, 444 $[M]^+$, 255 $[C_{16}H_{19}N_2O]^+$, 191 $[C_{10}H_7SO_2]^+$, 129 $[C_6H_{13}N_2O]^+$, 127 $[C_{10}H_7]^+$, 125 $[C_7H_6Cl]^+$, 101 $[C_4H_9N_2O]^+$.

4.3.4 ***4-(2-(N-(2-Chlorobenzyl)camphor-10-ylsulfamoyl)ethyl)morpholine(6d)***
Light yellow liquid; Yield: 81%; Mol. formula: $C_{23}H_{33}ClN_2O_4S$; Mol. weight: 469 gmol^{-1}; IR (KBr, ν_{max}/cm^{-1}): 3043 (Ar C-H), 1722 (ketone C=O), 1592 (Ar C=C), 1374 (S=O), 698 (C-Cl);^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ 7.83 (d, *J* = 7.6 Hz, 1H, H-3"), 7.74 (t, *J* = 8.0 Hz, 1H, H-4"), 7.69 (d, *J* = 8.0 Hz, 1H, H-5"), 7.63 (d, *J* = 8.4 Hz, 1H, H-6"), 4.38 (s, 2H, H-7"), 3.64 (t, *J* = 4.4 Hz, 4H, H-2, H-6), 3.43 (d, *J* = 14.4 Hz, 1H, H_a-10'), 3.38-3.33 (m, 1H, H_{eq}-6'), 2.87 (d, *J* = 14.4 Hz, 1H, H_b-10'), 2.67-2.62 (m, 1H, H_{ax}-6'), 2.55 (t, *J* = 7.2 Hz, 2H, H-7), 2.33 (t, *J* = 7.2 Hz, 2H, H-8), 2.35-2.31 (m, 1H, H_{eq}-4'), 2.17 (t, *J* = 4.8 Hz, 4H, H-3, H-5), 2.10-2.06 (m, 2H, H_{ax}-4', H_{ax}-5'), 1.87-1.83 (m, 1H, H_{eq}-3'), 1.46-1.41 (m, 1H, H_{ax}-3'), 1.07 (s, 3H, CH_3-9'), 0.91 (s, 3H, CH_3-8'); EIMS (*m/z*): 471 $[M+2]^+$, 469 $[M]^+$, 279 $[C_{16}H_{27}N_2O_2]^+$, 215 $[C_{10}H_{15}OSO_2]^+$, 151 $[C_{10}H_{15}O]^+$, 129 $[C_6H_{13}N_2O]^+$, 125 $[C_7H_6Cl]^+$, 101 $[C_4H_9N_2O]^+$.

4.3.5 ***4-(2-(N-(4-Bromobenzyl)phenylsulfamoyl)ethyl)morpholine(7a)***
Dark brown sticky solid; Yield: 76%; Mol. formula: $C_{19}H_{23}BrN_2O_3S$; Mol. weight: 438 gmol^{-1}; IR (KBr, ν_{max}/cm^{-1}): 3014 (Ar C-H), 1577 (Ar C=C), 1383 (S=O), 674 (C-Br);^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ 7.69 (d, *J* = 8.4 Hz, 2H, H-2', H-6'), 7.58 (t, *J* = 7.6 Hz, 1H, H-4'), 7.50 (d, *J* = 8.0 Hz, 2H, H-3", H-5"), 7.43 (t, *J* = 7.6 Hz, 2H, H-3', H-5'), 7.19 (d, *J* = 7.6 Hz, 2H, H-2", H-6"), 4.27 (s, 2H, H-7"), 3.87 (t, *J* = 4.8 Hz, 4H, H-2, H-6), 3.19 (t, *J* = 7.2 Hz, 2H, H-7), 2.56 (t, *J* = 7.2 Hz, 2H, H-8), 2.49 (t, *J* = 4.8 Hz, 4H, H-3, H-5); EIMS (*m/z*): 440 $[M+2]^+$, 438 $[M]^+$, 205 $[C_{12}H_{17}N_2O]^+$, 170 $[C_7H_6Br]^+$, 141 $[C_6H_5SO_2]^+$, 129 $[C_6H_{13}N_2O]^+$, 101 $[C_4H_9N_2O]^+$.

4.3.6 ***4-(2-(N-(4-Bromobenzyl)-2,4,6-trimethylphenylsulfamoyl)ethyl)morpholine(7b)***
Yellow amorphous solid; Yield: 76%; M. P.: 80-82 ^{o}C; Mol. formula: $C_{22}H_{29}BrN_2O_3S$; Mol. weight: 480 gmol^{-1}; IR (KBr, ν_{max}/cm^{-1}): 3068 (Ar C-H), 1565 (Ar C=C), 1354 (S=O), 673 (C-Br);^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ 7.87 (d, *J* = 8.0 Hz, 2H, H-3", H-5"), 7.83 (d, *J* = 8.0 Hz, 2H, H-2", H-6"), 7.80 (s, 2H, H-3', H-5'), 4.34 (s, 2H, H-7"), 3.92 (t, *J* = 4.8 Hz, 4H, H-2, H-6), 3.30 (t, *J* = 7.2 Hz, 2H, H-7), 2.67 (t, *J* = 7.2 Hz, 2H, H-8), 2.62 (t, *J* = 4.8 Hz, 4H, H-3, H-5), 2.44 (s, 6H, CH_3-2', CH_3-6'), 2.25 (s, 3H, CH_3-4'); EIMS (*m/z*): 482 $[M+2]^+$, 480 $[M]^+$, 247 $[C_{15}H_{23}N_2O]^+$, 183 $[(CH_3)_3C_6H_3SO_2]^+$, 170 $[C_7H_6Br]^+$, 129 $[C_6H_{13}N_2O]^+$,101 $[C_4H_9N_2O]^+$.

4.3.7 ***4-(2-(N-(4-Bromobenzyl)naphthalen-2-ylsulfamoyl)ethyl)morpholine(7c)***
Yellow sticky solid; Yield: 78%; Mol. formula: $C_{23}H_{25}BrN_2O_3S$; Mol. weight: 488 gmol^{-1}; IR (KBr, ν_{max}/cm^{-1}): 3037 (Ar C-H), 1583 (Ar C=C), 1382 (S=O), 639 (C-Br);^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ 8.70 (d, *J* = 1.2 Hz, 1H, H-1'), 8.04 (d, *J* = 8.0 Hz, 1H, H-8'), 8.01 (d, *J* = 8.0 Hz, 1H, H-4'), 7.97 (d, *J* = 8.0 Hz, 1H, H-5'), 7.94 (d, *J* = 8.0 Hz, 1H, H-3'), 7.86 (t, *J* = 8.4 Hz, 1H, H-7'), 7.76 (d, *J* = 8.4 Hz, 2H, H-3", H-5"), 7.65 (t, *J* = 8.0 Hz, 1H, H-6'), 7.47 (d, *J* = 8.4 Hz, 1H, H-2", H-6"), 4.36 (s, 2H, H-7"), 3.85 (t, *J* = 4.8 Hz, 4H, H-2, H-6), 3.23 (t, *J* = 7.2 Hz, 2H, H-7), 2.79 (t, *J* = 7.2 Hz, 2H, H-8), 2.68 (t, *J* = 4.8 Hz, 4H, H-3, H-5); EIMS (*m/z*): 490 $[M+2]^+$, 488 $[M]^+$, 255 $[C_{16}H_{19}N_2O]^+$, 191 $[C_{10}H_7SO_2]^+$,129 $[C_6H_{13}N_2O]^+$, 101 $[C_4H_9N_2O]^+$.

4.3.8 ***4-(2-(N-(4-Bromobenzyl)camphor-10-ylsulfamoyl)ethyl)morpholine(7d)***
Light brown sticky solid; Yield: 77%; Mol. formula: $C_{23}H_{33}BrN_2O_4S$; Mol. weight: 512 gmol^{-1}; IR (KBr, ν_{max}/cm^{-1}): 3037 (Ar C-H), 1721 (ketone C=O), 1591 (Ar C=C), 1364 (S=O), 651 (C-Br);^{1}H-NMR ($CDCl_3$, 400 MHz, ppm): δ 7.73 (d, *J* = 8.0 Hz, 2H, H-3", H-5"), 7.18 (d, *J* = 8.4 Hz, 2H, H-2", H-6"), 4.35 (s, 2H, H-7"), 3.63 (t, *J* = 4.4 Hz, 4H, H-2, H-6), 3.44 (d, *J* = 14.8 Hz, 1H, H_a-10'), 3.36-3.32 (m, 1H, H_{eq}-6'), 2.84 (d, *J* = 14.8 Hz, 1H, H_b-10'), 2.69-2.65 (m, 1H, H_{ax}-6'), 2.53 (t, *J* = 7.2 Hz, 2H, H-7), 2.37 (t, *J* = 7.2 Hz, 2H, H-8), 2.40-2.36 (m, 1H, H_{eq}-4'), 2.21 (t, *J* = 4.8 Hz, 4H, H-3, H-5), 2.09-2.04 (m, 2H, H_{ax}-4', H_{ax}-5'), 1.91-1.88 (m, 1H, H_{eq}-3'), 1.48-1.44 (m, 1H, H_{ax}-3'), 1.03 (s, 3H, CH_3-9'),

0.88 (s, 3H, CH_3-8'); EIMS (*m/z*): 514 $[M+2]^+$, 512 $[M]^+$, 279 $[C_{16}H_{27}N_2O_2]^+$, 215 $[C_{10}H_{15}OSO_2]^+$, 170 $[C_7H_6Br]^+$,129 $[C_6H_{13}N_2O]^+$, 101 $[C_4H_9N_2O]^+$.

4.4 ***Antibacterial activity assay***

The target molecules were evaluated for their inhibition against bacterial strains of gram-bacteriathroughthe reported method[20,21].

4.5 ***Statistical analysis***

All the results of %age inhibition and MIC values were performed in triplicate and statistically analyzed by ME 2010. The findings are written as mean± SEM in tables (1 & 2).

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