

Synthesis and Antibacterial Study of 4-(2-Aminoethyl) morpholine Derivatives

*Aziz-ur-Rehman, ¹Y. Masih, M. A. Abbasi, S. Z. Siddiqui, ¹T. Hussain and S. Rasool

*Department of Chemistry, Government College University, Lahore-54000, Pakistan.

¹Department of Chemistry, Minhaj University, Lahore, Pakistan.

E-mail: azizryk@yahoo.com

ABSTRACT

Because of broad spectrum of biological activities by sulfamoyl group, a series of 4-(2-(*N*-(2-chlorobenzyl/4-bromobenzyl) arylsulfamoyl)ethyl) morpholine, **6a-d/ 7a-d**, have been synthesized from 4-(2-aminoethyl) morpholine (**1**). First step includes the synthesis of 4-(2-(aryl-sulfamoyl)ethyl) morpholine, **3a-d**, by reaction of (**1**) and arylsulfonyl chlorides, **2a-d**, in water under definite pH control by 10% Na₂CO₃. 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. Using IR, ¹H-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*.

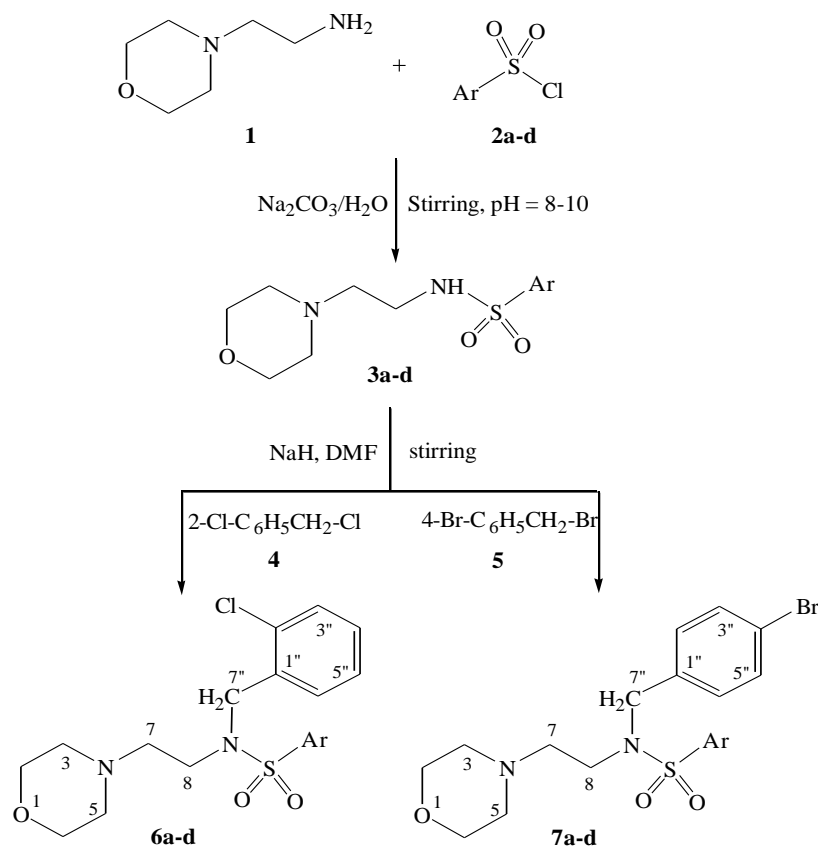
Keywords: 4-(2-Aminoethyl) morpholine, antibacterial activity, sulfonamides.

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 required¹⁻⁸. Such compounds have been found potent to histone deacetylase (HDAC)⁹ and cell cycle disruption in G1 phase in their anticancer action¹⁰. These molecules are bacteriostatic in nature and so in use for various infections like urinary-tract infection¹¹⁻¹³. Their bacteriostatic action is because of structural similarity with 4-aminobenzoic acid (PABA), required by bacteria during folic acid synthesis, the main activator of bacterial growth²⁻¹³.

The antimicrobial action of sulfamoyl bearing molecules prompted us to synthesize such type of molecules. In protraction of our projects¹⁴⁻¹⁸ for inauguration of potent molecules against certain diseases, a series of molecules, **6a-d/7a-d**, has been synthesized and evaluated for antibacterial activity.

2. RESULTS AND DISCUSSION



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 coupling 4-(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 molecules¹⁹.

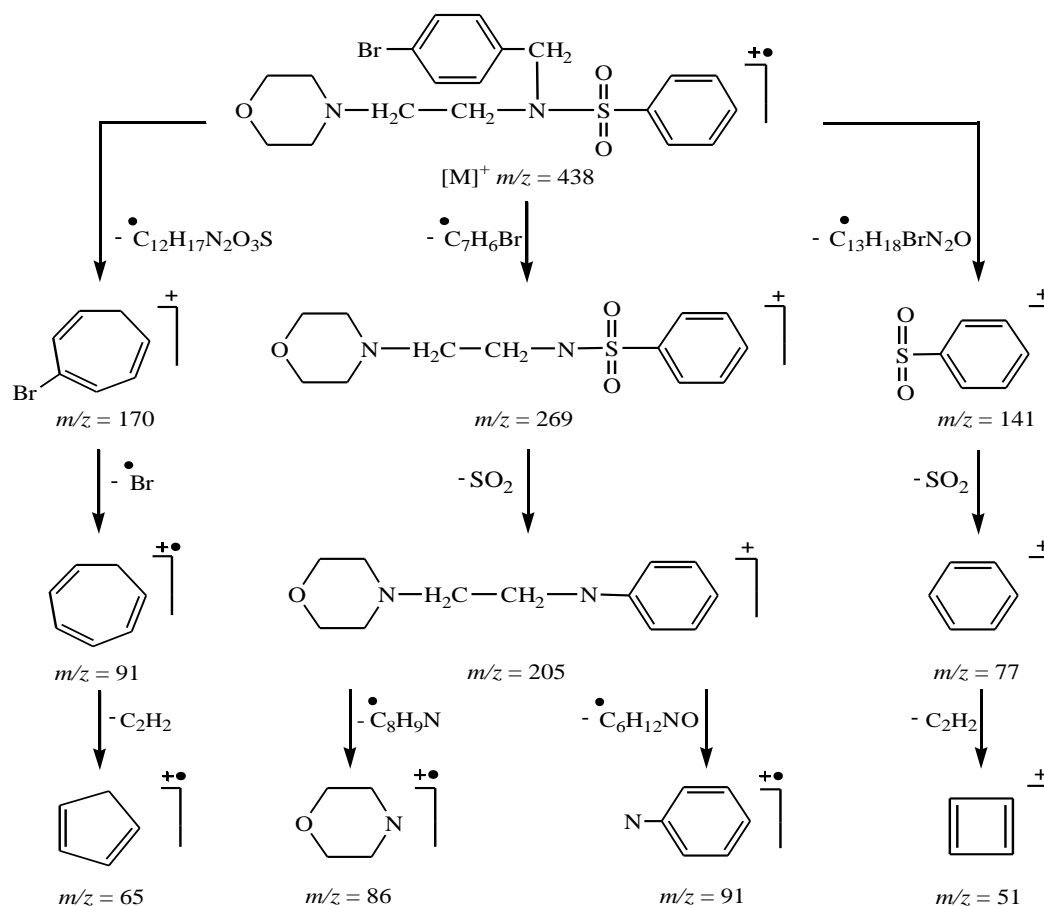


Fig.1: Mass fragmentation pattern of 4-(2-(N-(4-Bromobenzyl) phenylsulfamoyl)ethyl) morpholine (7a)

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 1H -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 1H -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 7.46 ppm (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 to its 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	<i>S. typhi</i> (-)	<i>E. coli</i> (-)	<i>P. aeruginosa</i> (-)	<i>B. subtilis</i> (+)	<i>S. aureus</i> (+)
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	<i>S. typhi</i> (-)	<i>E. coli</i> (-)	<i>P. aeruginosa</i> (-)	<i>B. subtilis</i> (+)	<i>S. aureus</i> (+)
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 aided by 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 pathway under development by pharmacists.

4. EXPERIMENTAL

4.1 General

The analytical grade solvents were purchased through local suppliers. All the 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 equipped by 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 KBr by Jasco-320-A spectrophotometer and proton NMR spectra in CHCl_3-d_1 by Bruker spectrometer working at 400 MHz. The δ -values are in ppm and 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 hindered by neutralization through 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 concentrated HCl

were added on shaking to set the pH of 5-6 and left for precipitation. The settled solid was filtered, rinsed by excess 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); 1H -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 °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); 1H -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 °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); 1H -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); 1H -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, CH₃-9'), 0.86 (s, 3H, CH₃-8'); EIMS (*m/z*): 344 [M]⁺, 280 [C₁₆H₂₈N₂O₂]⁺, 215 [C₁₀H₁₅OSO₂]⁺, 151 [C₁₀H₁₅O]⁺, 129 [C₆H₁₃N₂O]⁺, 101 [C₄H₉N₂O]⁺.

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) were mixed and stirred with 8 mL DMF and 0.011 mol NaH for 0.75 hour in a 50 mL RB flask. During stirring, *aralkyl* halides (**4-5**, 0.011 mol) were introduced and stirred for further 5-6 hours. The reaction progress and completion were ensured by 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: C₁₉H₂₃ClN₂O₃S; Mol. weight: 394 gmol⁻¹; IR (KBr, *v*_{max}/cm⁻¹): 3047 (Ar C-H), 1585 (Ar C=C), 1384 (S=O), 707 (C-Cl); ¹H-NMR (CDCl₃, 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 [C₁₂H₁₇N₂O]⁺, 141 [C₆H₅SO₂]⁺, 129 [C₆H₁₃N₂O]⁺, 125 [C₇H₆Cl]⁺, 101 [C₄H₉N₂O]⁺.

4.3.2 4-(2-(*N*-(2-Chlorobenzyl)-2,4,6-trimethylphenylsulfamoyl)ethyl)morpholine(6b)

Yellow liquid; Yield: 76%; Mol. formula: C₂₂H₂₉ClN₂O₃S; Mol. weight: 436 gmol⁻¹; IR (KBr, *v*_{max}/cm⁻¹): 3066 (Ar C-H), 1563 (Ar C=C), 1354 (S=O), 695 (C-Cl); ¹H-NMR (CDCl₃, 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, CH₃-2', CH₃-6'), 2.29 (s, 3H, CH₃-4'); EIMS (*m/z*): 438 [M+2]⁺, 436 [M]⁺, 247 [C₁₅H₂₃N₂O]⁺, 183 [(CH₃)₃C₆H₃SO₂]⁺, 129 [C₆H₁₃N₂O]⁺, 125 [C₇H₆Cl]⁺, 101 [C₄H₉N₂O]⁺.

4.3.3 4-(2-(*N*-(2-Chlorobenzyl)naphthalen-2-ylsulfamoyl)ethyl)morpholine(6c)

Light yellow liquid; Yield: 74%; Mol. formula: C₂₃H₂₅ClN₂O₃S; Mol. weight: 444 gmol⁻¹; IR (KBr, *v*_{max}/cm⁻¹): 3039 (Ar C-H), 1583 (Ar C=C), 1387 (S=O), 701 (C-Cl); ¹H-NMR (CDCl₃, 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); 1H -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, CH₃-9'), 0.91 (s, 3H, CH₃-8'); 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); 1H -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 °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); 1H -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,

CH₃-2', CH₃-6'), 2.25 (s, 3H, CH₃-4'); EIMS (*m/z*): 482 [M+2]⁺, 480 [M]⁺, 247 [C₁₅H₂₃N₂O]⁺, 183 [(CH₃)₃C₆H₃SO₂]⁺, 170 [C₇H₆Br]⁺, 129 [C₆H₁₃N₂O]⁺, 101 [C₄H₉N₂O]⁺.

4.3.7 4-(2-(N-(4-Bromobenzyl)naphthalen-2-ylsulfamoyl)ethyl)morpholine(7c)

Yellow sticky solid; Yield: 78%; Mol. formula: C₂₃H₂₅BrN₂O₃S; 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); ¹H-NMR (CDCl₃, 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 [C₁₆H₁₉N₂O]⁺, 191 [C₁₀H₇SO₂]⁺, 129 [C₆H₁₃N₂O]⁺, 101 [C₄H₉N₂O]⁺.

4.3.8 4-(2-(N-(4-Bromobenzyl)camphor-10-ylsulfamoyl)ethyl)morpholine(7d)

Light brown sticky solid; Yield: 77%; Mol. formula: C₂₃H₃₃BrN₂O₄S; 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); ¹H-NMR (CDCl₃, 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, CH₃-9'), 0.88 (s, 3H, CH₃-8'); EIMS (*m/z*): 514 [M+2]⁺, 512 [M]⁺, 279 [C₁₆H₂₇N₂O₂]⁺, 215 [C₁₀H₁₅OSO₂]⁺, 170 [C₇H₆Br]⁺, 129 [C₆H₁₃N₂O]⁺, 101 [C₄H₉N₂O]⁺.

4.4 Antibacterial activity assay

The target molecules were evaluated for their inhibition against bacterial strains of gram-bacteria through the 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).

5. REFERENCES

1. Ozbek, N., Katircioglu, H., Karacan, N., Baykal, T., *Bioorg. Med. Chem.* (2007), 15, 5105.

2. Alsughayer, A., Elassar, A. Z. A., Mustafa, S., Al-Sagheer, F., *J. Biomater. Nanobiotechnol.* (2011), 2, 144.
3. Kumar, S., Niranjana, M. S., Chaluvareju, K. C., Jamakhandi, C. M., Kadadevar, D., *J. Curr. Pharmaceut. Res.* (2010), 1, 39.
4. Baskin, J. M., Wang, Z., *Tetrahedron Lett.* (2002), 43, 8479.
5. Shi, F., Tse, M. K., Zhou, S., Pohl, M. M., Radnik, J., Huebner, S., Jaehnisch, K., Brueckner, A., Beller, M., *J. Am. Chem. Soc.* (2009), 131, 1775.
6. Sondhi, S. M., Dwivedi, A. D., Singh, J., Gupta, P. P., *Indian J. Chem.*(2010), 49B, 1076.
7. Cami, G. E., Arellano, R. D., Del, M. C., Fustero, S., Pedregosa, J. C., *J. Argent. Chem. Soc.* (2006), 94, 5.
8. Argyropoulou, I., Geronikaki, A., Vicini, P., Zani, F., *Arkivoc.* (2009), 6, 89.
9. Seikwan, O., Moon, H. I., Son, H. H., Jung, J. C., *Molecules* (2007), 12, 1125.
10. Al-Said, M. S., Ghorab, M. M., Al-Dosari, M. S., Hamed, M. M., *Eur. J. Med. Chem.* (2011), 46, 201.
11. Wang, Z., Kai, Z., Beier, R. C., Shen, J., Yang, X., *Int. J. Mol. Sci.*(2012), 13, 6334.
12. Vaid, F. H. M., Aminuddin, M., Mehmood, K., *Pak. J. Pharm. Sci.* (2004), 17, 77.
13. Thakur, A., Thakur, M., Khadikar, P. V., *Arkivoc.*(2006), 14, 87.
14. Khalid, H., Aziz-ur-Rehman, Abbasi, M. A., Khan, K. M., *Int. J. Pharm. Pharm. Sci.*(2012), 4, 443.
15. Aziz-ur-Rehman, Afroz, S., Abbasi, M. A., Tanveer, W., Khan, K. M., Ashraf, M., Afzal, I., Ambreen, N., *Pak. J. Pharm. Sci.* (2012), 25, 809.
16. Aziz-ur-Rehman, Tanveer, W., Abbasi, M. A., Afroz, S., Khan, K. M., Ashraf, M., Afzal, I., Ambreen, N., *Int. J. Chem. Res.* (2011), 3, 99.
17. Aziz-ur-Rehman, Rasool, S., Abbasi, M. A., Khan, K. M., Ashraf, M., Afzal, I., *Asian J. Pharm. Bio. Res.* (2012), 2, 100.
18. Aziz-ur-Rehman, Awais-ur-Rehman, Abbasi, M. A., Khalid, H., Dar, P., Khan, K. M., *Asian J. Pharm. Hea. Sci* (2012), 2, 384.
19. Liu, J., Wu, F., Chen, L., Zhao, L., Zhao, Z., Wang, M., Lei, S., *Food Chem.* (2012), 135, 2872.
20. Kaspady, M., Narayanaswamy, V. K., Raju, M., Rao, G. K., *Lett. Drug Des. Discov.* (2009), 6, 21.
21. Yang, C., Zang, Y., Jacob, M. R., Khan, S. I., Zhang, Y., Li, X., *Antimicrob. Agents Ch.* (2006), 50, 1710.