Pak. J. Chem. 5(1): 23-29, 2015 Full Paper
ISSN (Print): 2220-2625
ISSN (Online): 2222-307X DOI: 10.15228/2015.v05.i01.p04

Synthetic *N*-Alkyl/aralkyl-4-methyl-*N*-(naphthalen-1-yl)benzenesulfonamides as Potent Antibacterial Agents

[*]M. A. Abbasi, S. Manzoor, Aziz-ur-Rehman, S. Z. Siddiqui, [1]I. Ahmad, [1]R. Malik, [2]M. Ashraf
[2]Qurat-ul-Ain and [3,4]S. A. A. Shah
[*]Department of Chemistry, Government College University, Lahore, Pakistan.
[1]Department of Pharmacy, The Islamia University of Bahawalpur, Pakistan.
[2]Department of Biochemistry and Biotechnology, The Islamia University of Bahawalpur, Bahawalpur, Pakistan.
[3]Faculty of Pharmacy, Universiti Teknologi MARA, Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor Darul Ehsan, Malaysia.
[4]Atta-ur-Rahman Institute for Natural Products Discovery (AuRIns), Level 9, FF3, Universiti Teknologi MARA, Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor Darul Ehsan, Malaysia.
E-mail: [*]atrabbasi@yahoo.com; abbasi@gcu.edu.pk

ABSTRACT
The current research effort involved the reaction of napthalen-1-amine (1) with 4-methylbenzenesulfonyl chloride (2) under dynamic pH control at 9-10, maintained with 10% aqueous Na_2CO_3 to obtain 4-methyl-*N*-(naphthalen-1-yl) benzenesulfonamide (3). The parent molecule 3 was further substituted at *N*-atom with alkyl/aralkyl halides (4a-f) in polar aprotic solvent; *N*,*N*-dimethylformamide, and lithium hydride which acts as a base, to achieve *N*-alkyl/aralkyl-4-methyl-*N*-(naphthalen-1-yl)benzenesulfonamides (5a-f). All the synthesized compounds were structurally elucidated by IR, ^{1}H-NMR and EIMS spectral techniques. All the derivatives were further screened for antibacterial and anti-enzymatic potential against various bacterial strains and enzymes, respectively, and were found to be potent antibacterial agents and moderate to weak enzyme inhibitors.

Keywords: 4-Methyl-*N*-(naphthalen-1-yl) benzenesulfonamide, Spectral analysis, Antibacterial and Anti-enzymatic Analysis.

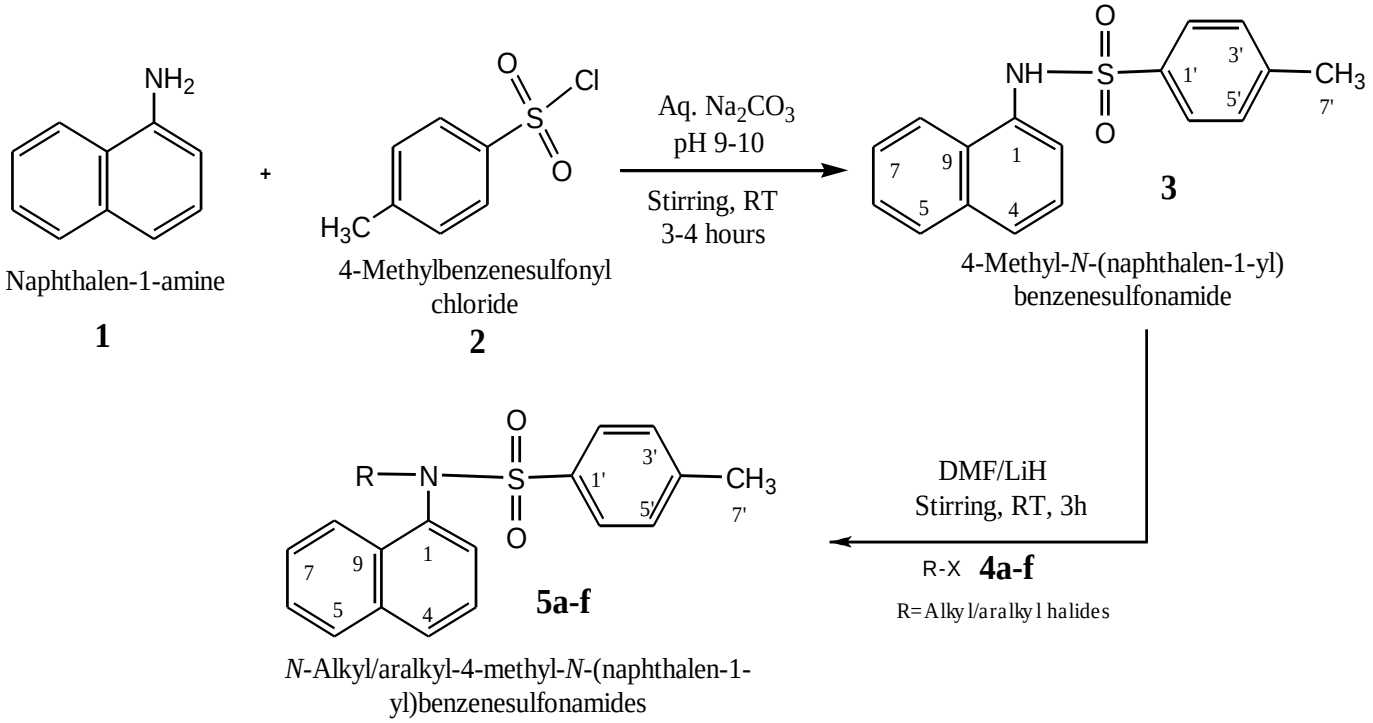
1. INTRODUCTION
Sulfonamides are biologically active amide derivative of sulfonic acid having general formula RSO_2NH-. They are mostly used as bacteriostatic to inhibit the growth of gram positive and gram negative bacteria[1-4]. They play important role in pharmaceutical industry and function as anticonvulsant, antiviral, antifungal agents and enzyme inhibitors. Aryl sulfonamides are used against tumor cell lines. Clinically sulfonamides are mostly used to cure various types of gastrointestinal and urinary infections. They act as anticancer agents and inhibitors of carbonic anhydrase which is the root cause for cancer[5-6]. 1-Napthylamine belongs to a class of benzo-fused aromatic compound. The driving force in the generation of sulfonamides is the affinity of nitrogen atom of amine for sulfonyl group of sulfonyl halide and hence is the most commonly employed method for their synthesis[7].

On the basis of aforesaid evidences documented in literature and in continuation of our research efforts[8-11], we synthesized various *N*-alkyl/aralkyl-4-methyl-*N*-(naphthalen-1-yl)benzenesulfonamides (5a-f) by reacting 4-methyl-*N*-(naphthalen-1-yl)benzenesulfonamide (3) in DMF/LiH with different alkyl/aralkyl sulfonyl chlorides, 4a-f. It was evident that amalgamation of different electrophiles with sulfonamide moiety can results in improved bioactivity of compounds which were later found to be in concordance with the biological evaluation results of synthesized derivatives against different bacterial strains and enzymes. Moreover, the structure-activity relationship was also established.

2. RESULTS AND DISCUSSION
2.1 *Chemistry*
A series of *N*-alkyl/aralyl-4-methyl-*N*-(naphthalen-1-yl)benzenesulfonamides was synthesized by reaction of napthalene-1-amine (1) with 4-methylbenzene-1-sulfonyl chloride (2) at room temperature in aqueous alkaline media at pH 9-10 to yield 4-methyl-*N*-(naphthalen-1-yl)benzenesulfonamide (3) which was further treated with alkyl/aralkyl halides, 4a-f, to obtain *N*-alkyl/aralkyl-4-methyl-*N*-(naphthalen-1-yl)benzenesulfonamides (5a-f) as illustrated in Scheme 1 and Table 1. Compound, 5a, was obtained as dark purple amorphous powder having molecular formula, $C_{20}H_{21}NO_2S$, which was established by counting number of protons in ^{1}H-NMR spectrum and appearance of molecular ion peak at *m/z* 339 $[M]^+$. The signals in aromatic region appeared at δ 8.20 (d, J = 8.4 Hz, 1H, H-8), 7.90-7.84 (m, 2H, H-5 & H-6), 7.76 (d, J = 6.4 Hz, 2H, H-2' & H-6'), 7.74 (d, J = 6.4 Hz, 1H, H-4), 7.59 (t, J = 6.4 Hz, 1H, H-3), 7.50 (d, J =8.8 Hz , 1H, H-2), 7.48 (d, J = 8.4 Hz, 2H, H-3' & H-5'), 7.40-7.31 (m, 1H, H-7) confirmed the presence of naphthyl ring and 1,4-disubstituted phenyl ring. A singlet at δ 2.30 having an integration of three protons was assigned to CH_3-7' group positioned at 4-position in 1,4-disubstituted phenyl ring. A multiplet integrated for one proton at δ 4.50-3.33 (H-2") and a doublet resonated at δ 0.93 (J = 6.8 Hz) having integration of six protons (CH_3-1" & CH_3-3') was in agreement with the substitution of 2-propyl group at nitrogen atom of the parent sulfonamide core.

*Corresponding Author Received 16th September 2015, Accepted 23rd February 2015

Similarly, on the basis of spectral evidences, the structures of other derivatives were confirmed and their spectral data has been described in experimental section. Mass fragmentation pattern of compound 5f is sketched in Figure 1.



Scheme-1: *Synthesis of N-alkyl/aralkyl-4-methyl-N-(naphthalen-1-yl)benzenesulfonamides* (5a-f)

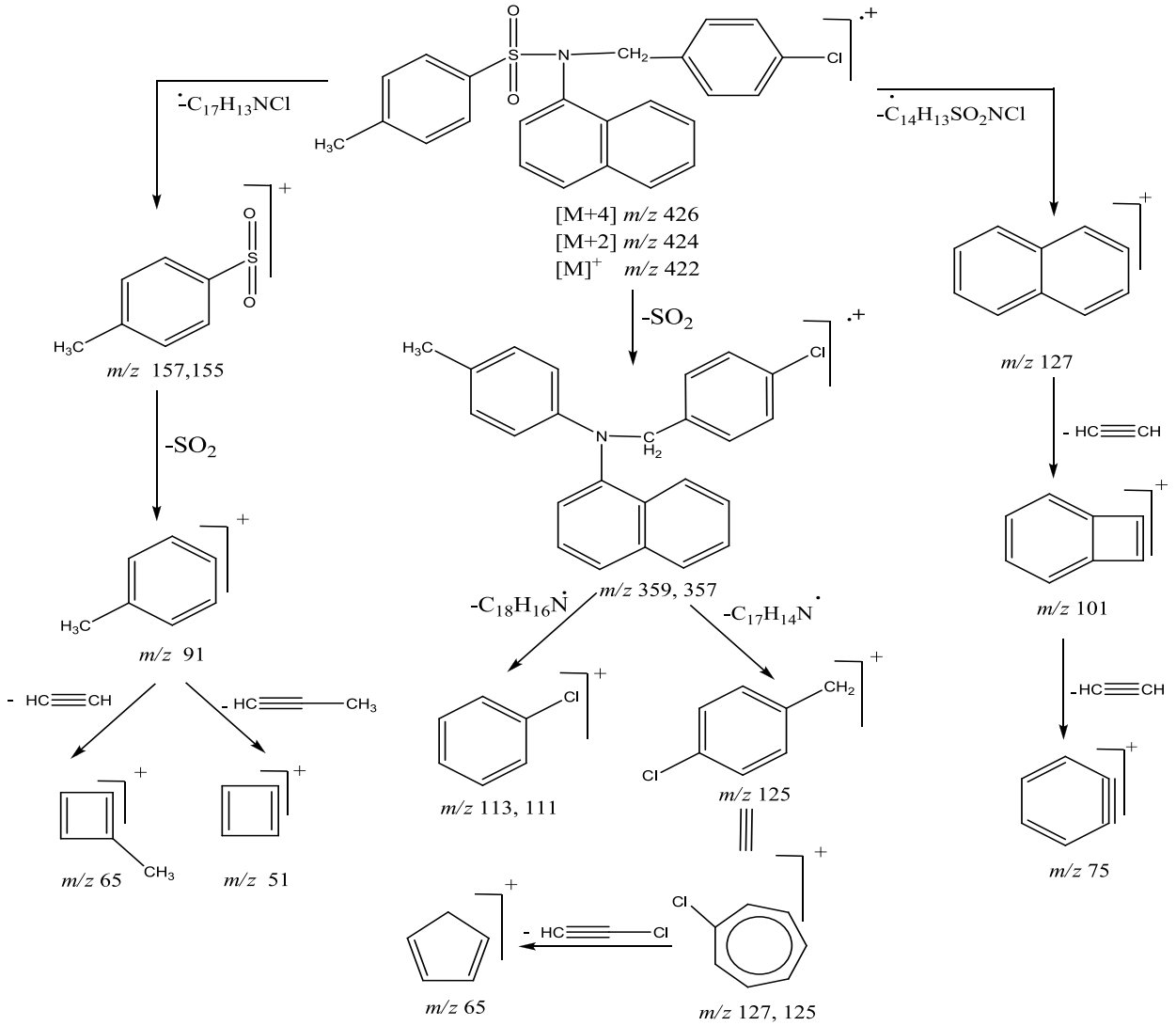
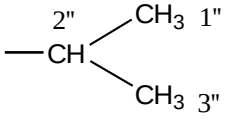
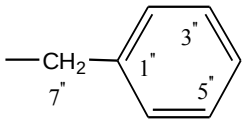
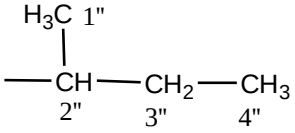
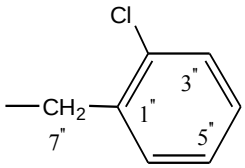
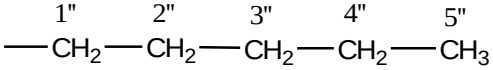
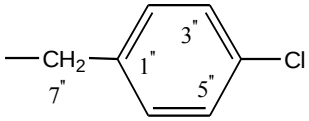


Fig-1: Mass fragmentation pattern of *N*-(4-Chlorobenzyl)-4-methyl-*N*-(naphthalen-1-yl)benzenesulfonamide (5f)

Table-1: List of various alkyl/aralkyl groups utilized in synthesis of 5a-f.

Codes	-R	Codes	-R
5a		5d	
5b		5e	
5c		5f	

2.2 *Anti-bacterial potential*

The screening of the *N*-alkyl/aralkyl-4-methyl-*N*-(naphthalen-1-yl) benzenesulfonamides (5a-f) was carried out against various gram-positive and gram-negative bacterial strains which demonstrated excellent to good activity as evident from their % age inhibition and MIC values mentioned in Table 2 & Table 3, respectively. Amongst all these synthesized molecules, 5d displayed excellent MIC values against both gram-positive (*B. subtilis*: 11.33±0.91 & *S. aureus*: 9.26±0.45 µg/well) and gram-negative bacterial strains (*S. typhi*: 11.25±0.68, *P. aureginosa*: 10.61±0.58 & *E. coli*: 12.48±0.39 µg/well). Its antibacterial potential was almost close to that of reference standard, Ciprofloxacin. The better inhibitory action of this molecule might be attributed to the attachment of benzyl moiety at the at nitrogen atom of the parent sulfonamide core.

Table-2: Antibacterial activity (% age inhibition) of *N*-alkyl/aralkyl-4-methyl-*N*-(naphthalen-1-yl)benzenesulfonamides (5a-f).

Codes	*S. typhi (-)*	*P. aeruginosa (-)*	*E. coli (-)*	*B. subtilis (+)*	*S. aureus (+)*
3	43.75±1.25	47.80±0.30	47.25±0.85	39.09±0.50	47.73±0.90
5a	68.50±2.13	62.56±0.35	71.29±0.95	66.00±0.65	74.69±1.43
5b	44.25±1.44	64.31±0.20	51.86±0.67	52.14±2.00	60.66±1.58
5c	60.88±1.22	43.51±0.20	64.86±1.73	39.14±0.90	67.40±0.53
5d	74.13±0.38	59.44±0.25	73.71±0.75	71.86±0.57	79.58±0.63
5e	64.63±0.87	87.38±0.25	63.29±0.68	63.86±1.02	69.95±2.81
5f	36.75±1.72	78.31±0.87	12.43±1.05	33.00±1.60	47.94±1.00
Ciprofloxacin	91.21±0.22	92.00±0.23	90.63±0.12	91.98±0.04	91.38±0.01

Table-3: Antibacterial activity (MIC µg/well) of *N*-alkyl/aralkyl-4-methyl-*N*-(naphthalen-1-yl)benzenesulfonamides (5a-f).

Codes	*S. typhi (-)*	*P. aeruginosa (-)*	*E. coli (-)*	*B. subtilis (+)*	*S. aureus(+)*
3	-	-	-	-	-
5a	12.60±0.89	11.62±0.93	11.60±0.23	18.38±0.58	14.62±0.33
5b	-	13.93±1.00	17.61±0.54	18.38±0.58	14.62±0.33
5c	14.64±0.60	-	14.23±0.86	-	12.38±0.82
5d	11.25±0.68	10.61±0.58	12.48±0.39	11.33±0.91	9.26±0.45
5e	12.13±1.06	14.82±0.22	14.83±0.67	14.61±0.49	12.60±0.53
5f	-	12.25±0.79	-	-	-
Ciprofloxacin	7.83±0.78	7.98±0.89	8.01±0.12	7.22±0.67	8.10±1.54

Note: Minimum Inhibition concentration was measured with suitable dilutions (5-30 µg/well) and results were calculated using EZ-fit Perrella Scientific Inc. Amherts USA Software.

2.3 *Anti-enzymatic analysis*

The anti-enzymatic analysis was carried out against acetyl and butyrylcholinesterases and lipoxygenase enzymes. The IC_{50} values showed that the synthesized sulfonamides overall displayed moderate to weak inhibitory actions. Compound 5c showed relatively better inhibition against AChE having value of 88.50±0.15 µM. Similarly, compound 5b and 5c against BChE displayed reasonable inhibition having IC_{50} values of 41.23±0.11 ad 51.35±0.12 µM, respectively. The inhibitory action of 5b and 5c might be due to the substitution of butan-2-yl and pentyl groups, respectively, at the parent sulfonamide nucleus. The other compounds did not show significant activities as compared to reference standards Eserine in case of cholinesterases and Baicalein in case of lipoxygenase enzyme (Table 4).

Table-4: Anti-enzymatic analysis of *N*-alkyl/aralkyl-4-methyl-*N*-(naphthalen-1-yl)-benzenesulfonamides (5a-f).

Codes	AChE		BChE		LOX	
	Inhibition (%) 0.5 mM	IC_{50} (µM)	Inhibition (%) 0.5 mM	IC_{50} (µM)	Inhibition (%) 0.5 mM	IC_{50} (µM)
3	96.00±0.85	221.60±0.16	95.15±0.36	41.62±0.13	88.43±0.34	43.08±0.16
5a	96.31±0.45	155.70±0.17	99.81±0.65	118.51±0.15	51.21±0.34	477.43±1.24
5b	94.23±0.73	329.70±0.36	94.00±0.49	47.23±0.11	63.55±0.71	341.36±0.58
5c	98.54±0.55	88.50±0.15	95.51±0.32	51.35±0.12	63.62±0.55	239.13±0.69
5d	93.70±0.56	219.60±0.18	92.85±0.37	64.18±0.19	50.09±0.49	498.92±1.74
5e	30.73±0.31	-	32.86±0.22	-	64.63±0.41	380.31±0.53
5f	86.77±0.35	227.30±0.19	69.54±0.74	375.23±0.28	68.37±0.23	215.67±0.90
Control	Eserine	0.85±0.001	Eserine	0.04±0.001	Baicalein	22.41±1.3

3. EXPERIMENTAL

3.1 *Measurements*

The chemicals utilized in research work were purchased from sigma Aldrich/Fluka and were used as such. Purity of all synthesized compounds was checked by thin layer chromatography (TLC) on plates coated with silica gel G-25-UV254 using different percentages of ethyl acetate and *n*–hexane. The IR spectra were taken in KBr on a Jasco-320-A spectrophotometer (wave number in cm^{-1}). ^1H NMR spectra were recorded in DMSO-d_6 on a Bruker spectrometer operating at 400 MHz. The chemical shifts (δ) and coupling constant (*J*) are given in ppm (parts per million) and Hz (Hertz), respectively. Melting points were recorded on a Griffin and George melting point apparatus by open capillary tube and were found to be uncorrected. Mass spectra (EIMS) were measured on Finnigan MAT-112 instrument along with data system.

3.2 *Synthesis of 4-methyl-N-(naphthalen-1-yl)benzenesulfonamide* (3)

Napthalene-1-amine (0.5 g; 0.0034 mol; 1) was suspended in 25 ml distilled water in a 250 ml round-bottomed flask. The pH of suspension was adjusted till 9 with 10 % aqueous Na_2CO_3. 4-Methylbenzenesulfonyl chloride (0.6 g; 0.0034 mol; 2) was gradually added in the reaction mixture and was further stirred for 2 hours at room temperature. After completion of reaction, which was monitored by TLC till single spot, the product was precipitated by adding few drops of conc. HCl till pH 2. The precipitates were filtered, washed with distilled water and air-dried to obtain 4-methyl-*N*-(naphthalen-1-yl)benzenesulfonamide (3) as purple colored solid.

3.3 *Synthesis of N-alkyl/aralkyl-4-methyl-N-(naphthalen-1-yl)benzenesulfonamides* (5a-f)

4-Methyl-*N*-(naphthalen-1-yl)benzenesulfonamide (0.2 g; 0.1 mmol; 3) was solubilized in 10 ml *N*,*N*-dimethylformamide along with (0.1 mmol) of lithium hydride. The reaction mixture was allowed to stir for half an hour at room temperature after which alkyl/aralkyl halides, 4a-f, were added to reaction mixture and was additionally stirred for 3 hours. After reaction completion, the precipitates of product were obtained by addition of cold distilled water, filtered and air-dried to afford respective *N*-alkyl/aralkyl-4-methyl-*N*-(naphthalen-1-yl)benzenesulfonamides (5a-f).

3.4 *Antibacterial assay*

Antibacterial activity was carried out in 96-wells microplates under aseptic conditions. The principle involved is that microbial cell number increases as the microbial growth proceeds in a log phase of growth which finally results in increased absorbance of broth medium[12,13]. Four gram-negative (*Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa* and *Salmonella typhi*) and two gram-positive bacteria (*Bacillus subtilis, Staphylococcus aureus*) (clinical isolate) were incorporated in the study. The organisms were maintained on stock culture agar medium. Test samples in appropriate solvents and dilutions were pipetted out into wells (20 µg $well^{-1}$). Overnight maintained fresh bacterial culture after suitable dilution with fresh nutrient broth was poured into wells (180 µL). The initial absorbance of the culture was firmly maintained between 0.12-0.19 at 540 nm. The incubation was completed for 16-24 h at 37 ^oC with lid on micro plate and absorbance was measured at 540 nm using micro plate reader. Before and after incubation, the difference was noted as an index of bacterial growth. The percent inhibition was calculated using the formula:

$$\text{Inhibition } \% = \frac{X - Y}{X} \times 100$$

Where, X = Absorbance in control with bacterial culture
Y = Absorbance in test sample.

Results are mean of triplicate (n = 3, ± SEM). Ciprofloxacin was taken as standard. MIC was measured with suitable dilutions (5-30 µg $well^{-1}$) and results were calculated using EZ-Fit5 Perrella Scientific Inc. Amherst USA software.

3.5 *Cholinesterase assays*

The AChE and BChE inhibitory assays were performed by the reported method[14,15] with minor modifications. 100 µL volume was made by 60 µL Na_2HPO_4 buffer (50 mM; pH 7.7), 10 µL test compound (0.5 mM well^{-1}) and 10 µL (0.005 unit well^{-1}) enzyme. These 100 µL assay volume was mixed together. After that its reading was taken at 405 nm followed by pre-incubation for 10 min at 37 ºC. The initiation of reaction was performed by the 10 µL of 0.5 mM well^{-1} substrate (acetylthiocholine iodide for AChE and butyrylthiocholine chloride for BChE) followed by 10 µL DTNB (0.5 mM well^{-1}). After incubating for 15 min at 37 ºC, Again absorbance was taken at 450 nm. All conducted tests were performed in three folds with the particular controls. Eserine (0.5 mM well^{-1}) was employed as a positive control. The %age inhibition was accounted as:

$$\text{Inhibition} \quad \% \quad = \frac{Control - Test}{Control} \times 100$$

By using EZ–Fit Enzyme kinetics software (Perella Scientific Inc. Amherst, USA), IC_{50} values of compounds were intended, it is the concentration at which there is 50 % of enzyme is inhibited.

3.6 *Lipoxygenase assay*

Lipoxygenase activity was assayed using the reported method[16-17] with some modifications. 200 µL assay mixture was prepared from 150 µL Na_3PO_4 buffer (100 mM; pH 8.0), 10 µL test compound and 15 µL enzyme followed by mixing, pre reading (at 234 nm) and pre incubation (10 minutes at 25 °C). Reaction was started at 25 µL of substrate concentration, followed by absorbance at 234 nm repeated after every 6 min. All readings were taken thrice using positive and negative controls. Bailcain (0.5 mM well^{-1}) was used as a positive control. The % age inhibition was work out by the similar method as given for cholinesterase assays.

4. SPECTRAL ANALYSIS

4.1 *4-Methyl-N-(naphthalen-1-yl)benzenesulfonamide* (3)

Dark purple amorphous Solid; Yield: 72 %; m.p.: 176 ˚C; Molecular Formula: $C_{17}H_{15}NO_2S$; Molecular Mass: 297 gmol^{-1}; IR (KBr, cm^{-1}): ν_{max}: 3500 (N-H stretching), 3046 (C-H stretching of aromatic ring), 2978 (-CH_2 stretching), 1635 (C=C stretching of aromatic ring), 1385 (-SO_2 stretching), 1152; ^{1}H-NMR (DMSO-d_6, 400 MHz, ppm): δ 8.21 (br.d, *J* = 7.4 Hz, 1H, H-8), 7.82 (br.d, *J* = 7.4 Hz, 1H, H-5), 7.76 (d, *J* = 8.4 Hz, 2H, H-2' & H-6'), 7.52 (m, 2H, H-6 & H-7), 7.48 (t, *J* = 8.0 Hz, 1H, H-3), 7.31 (d, *J* = 6.4 Hz, 1H, H-2), 6.66 (d, *J* = 8.4 Hz, 2H, H-3' & H-5'), 2.3 (s, 3H, CH_3-7'); EI-MS (*m/z*): 297 $[M]^+$, 233 $[C_{17}H_{15}N]^+$, 208 $[C_{10}H_{10}NO_2S]^+$, 196 $[C_9H_{10}NO_2S]^+$, 170 $[C_7H_8NO_2S]^+$, 155 $[C_7H_7O_2S]^+$, 142 $[C_{10}H_8N]^+$, 127 $[C_{10}H_7]^+$, 91 $[C_7H_7]^+$.

4.2 *N-(Propan-2-yl)-4-Methyl-N-(naphthalen-1-yl)benzenesulfonamide* (5a)

Move Sticky Solid; Yield: 65 %; Molecular Formula: $C_{20}H_{21}NO_2S$; Molecular Mass: 339 gmol^{-1}; IR (KBr, cm^{-1}): ν_{max}: 3449 (N-H stretching), 3047 (C-H stretching of aromatic ring), 2979 (-CH_2 stretching), 1636 (C=C stretching of aromatic ring), 1383 (-SO_2 stretching); ^{1}H-NMR (DMSO-d_6, 400 MHz, ppm): δ 8.20 (br.d, *J* = 7.2 Hz, 1H, H-8), 7.84 (br.d, *J* = 7.4 Hz, 1H, H-5), 7.78 (d, *J* = 8.4 Hz, 2H, H-2' & H-6'), 7.76-7.74 (m, 2H, H-6 & H-7),7.72 (br.d, *J* = 6.4 Hz, 1H, H-4), 7.59 (br.t, *J* = 6.4 Hz, 1H, H-3), 7.50 (br.d, *J* = 8.8 Hz, 1H, H-2), 7.48 (d, *J* = 8.4 Hz, 2H, H-3' & H-5'), 4.50-3.33 (m, 1H, H-2"), 2.30 (s, 3H, CH_3-7'), 0.93 (d, *J* = 6.8 Hz, 6H, CH_3-1" & CH_3-3"); EI-MS (*m/z*): 341 $[M+2]^+$ $(C_{20}H_{21}NO_2S+2)^{\cdot+}$, 339 $[M]^+$ $(C_{20}H_{21}NO_2S)^{\cdot+}$, 275 $[C_{20}H_{21}N]^{\cdot+}$, 157 $[C_7H_7O_2S+2]^+$, 155 $[C_7H_7O_2S]^+$, 127 $[C_{10}H_7]^+$, 101 $[C_8H_5]^+$, 91 $[C_7H_7]^+$, 75 $[C_6H_4]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$, 43 $[C_3H_7]^+$, 41 $[C_3H_5]^+$.

4.3 *N-(Butan-2-yl)-4-Methyl-N-(naphthalen-1-yl)benzenesulfonamide* (5b)

Purple Sticky Solid; Yield: 52 %; Molecular Formula: $C_{21}H_{23}NO_2S$; Molecular Mass: 353 gmol^{-1}; IR (KBr, cm^{-1}): ν_{max}: 3345 (N-H stretching), 3049 (C-H stretching of aromatic ring), 2975 (-CH_2 stretching), 1639 (C=C stretching of aromatic ring), 1383 (-SO_2 stretching); ^{1}H-NMR (DMSO-d_6, 400 MHz, ppm): δ 8.20 (br.d, *J* = 7.6 Hz, 1H, H-8), 7.80 (br.d, *J* = 7.6 Hz, 1H, H-5), 7.78 (d, *J* = 7.2 Hz, 2H, H-2' & H-6'), 7.74-7.72 (m, 2H, H-6 & H-7), 7.64 (br.d, *J* = 7.2 Hz, 1H, H-4), 7.38 (br.t, *J* = 8.0 Hz, 1H, H-3), 7.01 (d, *J* = 7.2 Hz, 2H, H-3' & H-5'), 6.96 (br.d, *J* = 7.6 Hz, 1H, H-2), 4.40-4.34 (m, 1H, H-2"), 2.3 (s, 3H, CH_3-7'), 1.57-1.54 (m, 2H, CH_2-3"), 1.04 (d, *J* = 6.8 Hz, 3H, CH_3-1"), 0.84 (t, *J* = 7.2 Hz, 3H, CH_3-4"); EI-MS (*m/z*): 355 $[M+2]^+$ $(C_{21}H_{23}NO_2S+2)^{\cdot+}$, 355 $[M]^+$ $(C_{21}H_{23}NO_2S)^{\cdot+}$, 289 $[C_{21}H_{23}N]^{\cdot+}$, 157 $[C_7H_7O_2S+2]^+$, 155 $[C_7H_7O_2S]^+$, 127 $[C_{10}H_7]^+$, 101 $[C_8H_5]^+$, 91 $[C_7H_7]^+$, 75 $[C_6H_4]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$, 57 $[C_4H_9]^+$, 41 $[C_3H_5]^+$, 29 $[C_2H_5]^+$.

4.4 *N-(Pentan-1-yl)-4-Methyl-N-(naphthalen-1-yl)benzenesulfonamide* (5c)

Purple Sticky Solid; Yield: 71 %; Molecular Formula: $C_{22}H_{25}NO_2S$; Molecular Mass: 367 gmol^{-1}; ν_{max}: 3248 (N-H stretching), 3045 (C-H stretching of aromatic ring), 2979 (-CH_2 stretching), 1640 (C=C stretching of aromatic ring), 1385 (-SO_2 stretching); ^{1}H-NMR (DMSO-d_6, 400 MHz, ppm): δ 8.18 (br.d, *J* = 7.2 Hz, 1H, H-8), 7.84 (br.d, *J* = 7.2 Hz, 1H, H-5), 7.80 (d, *J* = 7.6 Hz, 2H, H-2' & H-6'), 7.76-7.74 (m, 2H, H-6 & H-7), 7.66 (br.d, *J* = 7.4 Hz, 1H, H-4), 7.35 (br.t, *J* = 8.0 Hz, 1H, H-3), 6.98 (d, *J* = 7.6 Hz, 2H, H-3' & H-5'), 6.94 (br.d, *J* = 7.6 Hz, 1H, H-2), 3.63 (t, *J* =

7.6 Hz, 2H, CH_2-1"), 2.3 (s, 3H, CH_3-7'), 1.20-1.11 (m, 6H, CH_2-2" to CH_2-4"), 0.85 (t, *J* = 6.4 Hz, 3H, CH_3-5"); EI-MS (*m/z*): 369 $[M+2]^+$ $(C_{22}H_{25}NO_2S+2)^{\cdot+}$, 367 $[M]^+$ $(C_{22}H_{25}NO_2S)^{\cdot+}$, 303 $[C_{22}H_{25}N]^{\cdot+}$, 157 $[C_7H_7O_2S+2]^+$, 155 $[C_7H_7O_2S]^+$, 127 $[C_{10}H_7]^+$, 101 $[C_8H_5]^+$, 91 $[C_7H_7]^+$, 75 $[C_6H_4]^+$, 71 $[C_5H_{11}]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$, 43 $[C_3H_7]^+$, 41 $[C_3H_5]^+$.

4.5 *N-(Benzyl)-4-methyl-N-(naphthalen-1-yl)benzenesulfonamide* (5d)

Dark Purple Sticky Solid; Yield: 67 %; Molecular Formula: $C_{24}H_{21}NO_2S$; Molecular Mass: 387 $gmol^{-1}$; ν_{max}: 3354 (N-H stretching), 3056 (C-H stretching of aromatic ring), 2967 (-CH_2 stretching), 1649 (C=C stretching of aromatic ring), 1390 (-SO_2 stretching); ^{1}H-NMR (DMSO-d_6, 400 MHz, ppm): δ 8.02 (br.d, *J* = 7.2 Hz, 1H, H-8), 7.84 (br.d, *J* = 7.2 Hz, 1H, H-5), 7.80 (d, *J* = 7.8 Hz, 2H, H-2' & H-6'), 7.58-7.54 (m, 2H, H-6 & H-7), 7.44 (br.d, *J* = 7.4 Hz, 1H, H-4), 7.28-7.26 (m, 2H, H-2 & H-3), 7.23 (br.t, *J* = 7.0 Hz, 2H, H-3" & H-5"), 7.21 (br.t, *J* = 8.5 Hz, 1H, H-4"), 7.17 (br.d, *J* = 8.0 Hz, 2H, H-2" & H-6"), 6.80 (d, *J* = 7.8 Hz, 2H, H-3' & H-5'), 4.93 (s, 2H, CH_2-7"), 2.3 (s, 3H, CH_3-7'); EI-MS (*m/z*): 389 $[M+2]^+$ $(C_{24}H_{21}NO_2S)^{\cdot+}$, 387 $[M]^+$ $(C_{24}H_{21}NO_2S)^{\cdot+}$, 323 $[C_{24}H_{21}N]^{\cdot+}$, 157 $[C_7H_7O_2S+2]^+$, 155 $[C_7H_7O_2S]^+$, 127 $[C_{10}H_7]^+$, 101 $[C_8H_5]^+$, 91 $[C_7H_7]^+$, 75 $[C_6H_4]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

4.6 *N-(2-Chlorobenzyl)-4-methyl-N-(naphthalen-1-yl)benzenesulfonamide* (5e)

Dark Purple Sticky Solid; Yield: 53 %; Molecular Formula: $C_{24}H_{20}ClNO_2S$; Molecular Mass: 421 $gmol^{-1}$; ν_{max}: 3356 (N-H stretching), 3040 (C-H stretching of aromatic ring), 2989 (-CH_2 stretching), 1645 (C=C stretching of aromatic ring), 1382 (-SO_2 stretching); ^{1}H-NMR (DMSO-d_6, 400 MHz, ppm): δ 8.04 (br.d, *J* = 7.6 Hz, 1H, H-8), 7.80 (br.d, *J* = 7.4 Hz, 1H, H-5), 7.78 (d, *J* = 8.0 Hz, 2H, H-2' & H-6'), 7.62-7.60 (m, 2H, H-6 & H-7), 7.42 (br.d, *J* = 7.4 Hz, 1H, H-4), 7.32 (br.d, *J* = 7.0 Hz, 1H, H-3"), 7.28-7.24 (m, 2H, H-2 & H-3), 7.20 (br.d, *J* = 7.4 Hz, 1H, H-6"), 7.12-7.10 (m, 2H, H-4" & H-5"), 6.81 (d, *J* = 8.0 Hz, 2H, H-3' & H-5'), 4.50 (s, 2H, CH_2-7"), 2.3 (s, 3H, CH_3-7'); EI-MS (*m/z*): 425 [M+4 $(C_{24}H_{20}ClNO_2S)]^{\cdot+}$, 423 [M+2 $(C_{24}H_{20}ClNO_2S)]^{\cdot+}$, 421 [M $(C_{24}H_{20}ClNO_2S)]^{\cdot+}$, 359 $[C_{24}H_{20}ClN+2]^{\cdot+}$, 357 $[C_{24}H_{20}ClN]^{\cdot+}$, 157 $[C_7H_7O_2S+2]^+$, 155 $[C_7H_7O_2S]^+$, 127 $[C_7H_6Cl+2]^+$, 125 $[C_7H_6Cl]^+$, 113 $[C_6H_5Cl+2]^+$, 111 $[C_6H_5Cl]^+$, 101 $[C_8H_5]^+$, 91 $[C_7H_7]^+$, 75 $[C_6H_4]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

4.7 *N-(4-Chlorobenzyl)-4-methyl-N-(naphthalen-1-yl)benzenesulfonamide* (5f)

Dark Purple Sticky Solid; Yield: 64 %; Molecular Formula: $C_{24}H_{20}ClNO_2S$; Molecular Mass: 421 $gmol^{-1}$; ν_{max}: 3305 (N-H stretching), 3049 (C-H stretching of aromatic ring), 2943 (-CH_2 stretching), 1642 (C=C stretching of aromatic ring), 1388 (-SO_2 stretching); ^{1}H-NMR (DMSO-d_6, 400 MHz, ppm): δ 8.08 (br.d, *J* = 7.2 Hz, 1H, H-8), 7.82 (br.d, *J* = 7.2 Hz, 1H, H-5), 7.76 (d, *J* = 7.8 Hz, 2H, H-2' & H-6'), 7.64-7.62 (m, 2H, H-6 & H-7), 7.54 (d, *J* = 8.2 Hz, 2H, H-3" & H-5"), 7.44 (br.d, *J* = 7.2 Hz, 1H, H-4), 7.26-7.24 (m, 2H, H-2 & H-3), 7.02 (d, *J* = 8.2 Hz, 2H, H-2" & H-6"), 6.72 (d, *J* = 7.8 Hz, 2H, H-3' & H-5'), 4.74 (s, 2H, CH_2-7"), 2.3 (s, 3H, CH_3-7'); EI-MS (*m/z*): 425 $[M+4]^+$ $(C_{24}H_{20}ClNO_2S+4)^{\cdot+}$, 423 $[M+2]^+$ $(C_{24}H_{20}ClNO_2S+2)^{\cdot+}$, 421 $[M]^+$ $(C_{24}H_{20}ClNO_2S)^{\cdot+}$, 359 $[C_{24}H_{20}ClN+2]^{\cdot+}$, 357 $[C_{24}H_{20}ClN]^{\cdot+}$, 157 $[C_7H_7O_2S+2]^+$, 155 $[C_7H_7O_2S]^+$, 127 $[C_7H_6Cl+2]^+$, 125 $[C_7H_6Cl]^+$, 113 $[C_6H_5Cl+2]^+$, 111 $[C_6H_5Cl]^+$, 101 $[C_8H_5]^+$, 91 $[C_7H_7]^+$, 75 $[C_6H_4]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

5. CONCLUSION

A series of *N*-alkyl/aralkyl-4-methyl-*N*-(naphthalen-1-yl)-benzenesulfonamides (5a-f), was synthesized by reaction of different alkyl/aralkyl halides with 4-methyl-*N*-(naphthalen-1-yl)-benzenesulfonamide (3) in polar aprotic solvent in the presence of base; LiH under stirring at room temperature. The *N*-substituted sulfonamides were structurally confirmed by modern spectral techniques. The studied molecules displayed tremendous antibacterial activity against gram-negative and gram-positive strains and also showed moderate to weaker inhibition against cholinesterases and lipoxygenase enzymes. Hence the synthesized molecules could be utilized as suitable therapeutic agents for the treatment of different bacterial diseases.

6. REFERENCES

1. Omar, F. A., Mahfouz, N. M., Rahman, M. A., Eur. J. Med. Chem., **(1996)**, 31, 819, http://dx.doi.org/10.1016/0223-5234(96)83976-6.
2. Baylac, S., Racine, P., Int. J. Aromatherap., **(2003)**, 13, 138, http://dx.doi.org/10.1016/S0962-4562(03)00083-3.
3. Yang, C. R., Zang, Y., Jacob, M. R., Khan, S. I., Zhang, Y. J., Li, X. C., Antimicrob. Agents Chemother., **(2006)**, 50, 1710, http://dx.doi.org/10.1128/AAC.50.5.1710-1714.2006.
4. Aneja, R., Vangapandu, S. N., Lopus, M., Viswesarappa, V. G., Dhiman, N., Verma, A., Chandra, R., Panda, D., Joshi, H. C., Biochem. Pharmacol., **(2006)**, 72, 415, http://dx.doi.org/10.1016/j.bcp.2006.05.004.
5. Bhardwaj, N., Saraf, S. K., Sharma, P., Kumar, P., Eur. J. Chem., **(2009)**, 6, 1133.
6. Ebrahimi, S., Eur. J. Med. Chem., **(2010)**, 1, 322, http://dx.doi.org/10.5155/eurjchem.1.4.322-324.65.
7. Chong-Ren, Yang, Zang, Jacob, Y., Khan, M. R., Zhang, S. I., Li, X. C., Antimicrob. Agents Chemother., **(2006)**, 50, 1710.

8. Abbasi, M. A., Aziz-ur-Rehman, Qureshi, M. Z., Khan, F. M., Khan, K. M., Ashraf, M., Afzal, I., Braz. J. Pharm. Sci., **(2013)**, 49, 127, http://dx.doi.org/10.1590/S1984-82502013000100014.
9. Abbasi, M.A., Raza, N., Aziz-ur-Rehman, Rasool, S., Khan, K.M., Ashraf, M., Alam, U., Nasar, R., World J. Pharm. Sci., **(2014)**, 2, 161.
10. Abbasi, M. A., Ahmad, S., Aziz-ur-Rehman, Rasool, S., Khan, K. M., Ashraf, M., Nasar, R., Ismail, T., Trop. J. Pharm. Res., **(2014)**, 13, 739, http://dx.doi.org/10.4314/tjpr.v13i5.13.
11. Abbasi, M. A., Saeed, A., Aziz-ur-Rehman, Khan, K. M., Ashraf, M., Ejaz, S. A., Iran. J. Pharm. Res., **(2014)**, 13, 87.
12. Kaspday, M. V., Narayanaswamy, K., Raju, M., Rao, G. K., Lett. Drug Des. Discov., **(2009)**, 6, 21, http://dx.doi.org/10.2174/157018009787158481.
13. Jamil, H., Haq, I. U., Mirza, B., Qayyum, H., Ann. Clin. Microb. Antimicrob., **(2012)**, 11, 11, http://dx.doi.org/10.1186/1476-0711-11-11.
14. Ozbek, N., Katircioglu, H., Karacan, N., Baykal, T., Bioorg. Med. Chem., **(2007)**, 15, 5105, http://dx.doi.org/10.1016/j.bmc.2007.05.037.
15. Ellman, G. L., Courtney, K. D., Andres, V., Featherstone, R. M., Biochem. Pharmacol., **(1961)**, 7, 88, http://dx.doi.org/10.1016/0006-2952(61)90145-9.
16. Clapp, C. H., Banerjee, A., Rotenberg, S. A., Biochem., **(1985)**, 24, 1826, http://dx.doi.org/10.1021/bi00329a004.
17. Kemal, C., Louis-Flemberg, P., Krupinski-Olsen, R., Shorter, A. L., Biochem., **(1987)**, 26, 7064, http://dx.doi.org/10.1021/bi00396a031.