I J C R
International Journal of Chemical Research
ISSN: 0975-3699 & E-ISSN: 0975–9131, Vol. 3, Issue 3, 2011, pp-99-104
Available online at http://www.bioinfo.in/contents.php?id=23

# SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF VARIOUS *N*-SUBSTITUTED DERIVATIVES OF SULFONAMIDES

**AZIZ-UR-REHMAN[1,*] WAJEEHA TANVEER[1], MUHAMMAD ATHAR ABBASI[1], SUMBAL AFROZ[1], KHALID MOHAMMED KHAN[2], MUHAMMAD ASHRAF[3], AND IFTIKHAR AFZAL[3]**

[1]Department of Chemistry, Government College University, Lahore-54000, Pakistan.
[2]HEJ Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi-75270, Pakistan.
[3]Department of Pharmacy, Faculty of Pharmacy and Alternative Medicine, The Islamia University of Bahawalpur, Bahawalpur-63100, Pakistan.
*Corresponding Author E-mail: azizryk@yahoo.com Tel: (+92)-42-111000010 Ext.449.

Received: September 29, 2011; Accepted: October 21, 2011

**Abstract-** In the present study, a series of *N*-substituted sulfonamides have been synthesized. The reaction of benzene sulfonyl chloride (**1)** with *O*-anisidine (**2)** yielded *N*-(2-methoxyphenyl) benzenesulfonamide (**3)**, which on bromination with bromine in the presence of acetic acid gave *N*-(4,5-dibromo-2-methoxyphenyl)benzenesulfonamide (**6)**. The two products (**3**) and (**6**) further on treatment with alkyl halides/acyl halide in the presence of sodium hydride yielded thirteen different *N*-substituted sulfonamides. The compounds were characterized by IR, EIMS and $^1$H-NMR and screened against acetyl cholinesterase, butyryl cholinesterase and lipoxygenase enzymes. The results revealed that *N*-butyl-*N*-(4, 5-dibromo-2-methoxyphenyl)benzene sulfonamide (**6d**) and *N*-pentyl-*N*-(4,5-dibromo-2-methoxy phenyl)benzenesulfonamide (**6e**) exhibited good inhibitory potential against lipoxygenase.
**Key words-** *O*-anisodine, Sulfonamide, butyryl cholinesterase, lipoxygenase and $^1$H-NMR

## Introduction

Sulfonamides containing group $–SO_2NH-$ is a present in many pharmacologically active compounds [1]. Sulfonamides are considered as an important group of drugs which are used widely as antimicrobial, high ceiling diuretics, ant thyroid and anti-inflammatory agents [2]. The mechanism through which sulfonamides perform its function is to inhibit the conversion of *p*-amino benzoic acid, thus creating hurdle in utilization of *p*-amino benzoic acid for bacteria in folic acid synthesis which leads to formation of purine and DNA [3]. Many infectious diseases caused by Gram-negative and Gram-positive bacteria are also cured by widely used sulfonamides [4]. These compounds also find their wide application as antitumor, anticancer and anti-viral agent because they have been reported to inhibit cancer cell growth and to cease tumor invasion [2]. Although excessive use of other antibiotics has ceased the usefulness of different sulfonamides, even then these clinically active compounds have therapeutically important place [4]. Sulfonamides are also ruling as most widely used second veterinary medicine [3]. Some derivatives of sulfonamides are extensively used for gastrointestinal and urinary tract infections because of their ease of administration and non-interaction with defense mechanism of host [5]. All these findings encouraged us to explore the synthesis of different *N*-substituted sulfonamides derived from *o*-anisidine with improved and different biological activity.

In lipoxygenase type-1 (LOX, EC 1.13.11.12), the iron is present in the divalent state and is oxidized to the catalytically active $Fe^{3+}$ by the reaction product 15-hydroperoxy-eicosatetraenoic acid (15-HPETE) and leukotrienes from arachidonic acid as a substrate, and 13- hydroperoxy-octadecadienoic acid (13-HPODE) from linoleic acid as a substrate [6,7]. Leukotrienes are important biologically active mediators in a variety of inflammatory events. It has been found that these LOX products play a key role in variety of disorders such as bronchial asthma, inflammation [8, 9].

In this work, we report various *N*-substituted derivatives of *o*-anisidine. First, a parent sulfonamide *N*-(2-methoxyphenyl) benzenesulfonamide **(3**) was prepared by reacting benzene sulfonyl chloride with *o*-anisidine in basic media at room temperature in excellent yield. Further bromination of **3** yielded *N*-(4, 5-dibromo-2-methoxyphenyl)benzene sulfonamide (**6**). Simple stirring gave the desired compounds that were further processed to obtain different *N*-substituted sulfonamides.

Literature survey revealed that minor modification in the structure of compound can result in qualitative as well as quantitative changes in the activity, which prompted us to carry out the synthesis of various sulfonamide derivatives of *o*-anisidine and to study their structure-

activity relationship; these were screened against AChE, BChE and lipoxygenase (LOX) and were found active against LOX.

## Materials and Methods

### General

TLC was performed on pre-coated silica gel G-25-$UV_{254}$ plates. Detection was carried out at 254 nm, and by ceric sulphate reagent. Purity was checked on TLC with different solvent systems using ethyl acetate and *n*-hexane giving single spot. The IR spectra were recorded in KBr on a Jasco-320-A spectrophotometer (wave number in $cm^{-1}$). $^1H$ NMR spectra were recorded in $CDCl_3$ on a Bruker spectrometers operating at 400 MHz. Chemical shifts are given in ppm. Mass spectra (EIMS) were measured on Finnigan MAT-112 instrument. EI-MS were recorded in were recorded on a JMS-HX-110 spectrometer, with a data system. The melting points were recorded on a Griffin & George melting point apparatus by open capillary tube and were uncorrected.

### Procedure for the synthesis of sulfonamide in aqueous medium

A mixture of benzenesulfonyl chloride (10.0 mmol; 1.3 mL) and *O*-anisidine (10.0 mmol; 2.6 mL) was suspended in 50 mL water. The pH of the suspension was adjusted and was maintained at 10.0 by adding basic aqueous solution of a $Na_2CO_3$ at room temperature. The reaction mixture was stirred and monitored with TLC for the completion of reaction. Then concentrated HCl was added slowly to adjust the pH to 2.0. The precipitates were collected by filtration, washed with distilled water and dried to afford the title compound **3**. The product was dissolved in ethanol and re-crystallized by slow evaporation of the solvent, to generate off white crystalline solid of *N*-(2-methoxyphenyl) benzenesulfonamide. Yield 94%.

### Bromination of *N*-(2-methoxyphenyl) benzenesulfonamide (3)

2g of compound **3** was dissolved in 15 mL of glacial acetic acid. The bromine liquid (2 mL) was added gradually in the reaction mixture for the bromination of **3**. The reaction mixture was stirred at room temperature for at least 2 hours and the completion of reaction was monitored by TLC. The product was filtered, washed with distilled water and dried to afford light orange precipitates of *N*-(4, 5-dibromo-2-methoxyphenyl)benzenesulfonamide (**6**). Yield 92%.

### General procedure for the synthesis of *N*-alkyl substituted sulfonamides in DMF

The calculated amount of **3** or **6** (0.1 mmol) was taken in a round bottomed flask (50 mL), then dimethyl formamide DMF (10 mL) was added to dissolve it followed by the addition of sodium hydride (0.1 mmol) to the mixture. The mixture was stirred for 30 minutes at room temperature and then slowly added the alkyl halide/acyl halide to the mixture and the solution was further stirred for three hours. The progress of reaction was monitored *via* TLC till single spot. The product was precipitated by adding water. It was filtered, washed with water and crystallized from aqueous methanol.

### Acetylcholinesterase assay

The AChE inhibition activity was performed according to the method with slight modifications. Total volume of the reaction mixture was 100 µL. It contained 60 µL $Na_2HPO_4$ buffer with concentration of 50 mM and pH 7.7. Ten µL test compound (0.5 mM $well^{-1}$) was added, followed by the addition of 10 µL (0.005 unit $well^{-1}$) enzyme. The contents were mixed and pre-read at 405 nm. Then contents were pre-incubated for 10 min at 37ºC. The reaction was initiated by the addition of 10 µL of 0.5 mM $well^{-1}$ substrate (acetylthiocholine iodide), followed by the addition of 10 µL DTNB (0.5 mM $well^{-1}$). After 15 min of incubation at 37ºC, absorbance was measured at 405 nm. Synergy HT (BioTek, USA) 96-well plate reader was used in all experiments. All experiments were carried out with their respective controls in triplicate. Eserine (0.5 mM $well^{-1}$) was used as a positive control. The percent inhibition was calculated by the help of following equation [10].

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

### Butyrylcholinesterase assay

The BChE inhibition activity was performed according to the method with slight modifications. Total volume of the reaction mixture was 100 µL containing 60 µL, $Na_2HPO_4$ buffer, 50 mM and pH 7.7. Ten µL test compound 0.5 mM $well^{-1}$, followed by the addition of 10 µL (0.5 unit $well^{-1}$) BChE. The contents were mixed and pre-read at 405 nm and then pre-incubated for 10 mins at 37ºC. The reaction was initiated by the addition of 10 µL of 0.5 mM $well^{-1}$ substrate (butyrylthiocholine bromide) followed by the addition of 10 µL DTNB, 0.5 mM $well^{-1}$. After 15 min of incubation at 37ºC, absorbance was measured at 405 nm. Synergy HT (BioTek, USA) 96-well plate reader was used in all experiments. All experiments were carried out with their respective controls in triplicate. Eserine (0.5 mM $well^{-1}$) was used as positive control. The percent inhibition was calculated by the help of following equation [10].

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

$IC_{50}$ values (concentration at which there is 50% enzyme inhibition) of compounds were calculated using EZ–Fit Enzyme kinetics software (Perella Scientific Inc. Amherst, USA).

### Lipoxygenase assay

Lipoxygenase activity was assayed according to the reported method [11-13] but with slight modifications. A total volume of 200 µL assay mixture contained 150 µL

sodium phosphate buffer (100 mM, pH 8.0), 10 µL test compound and 15µL purified lipoxygenase enzyme (Sigma, USA). The contents were mixed and pre-read at 234 nm and preincubated for 10 minutes at 25°C. The reaction was initiated by addition of 25 µL substrate solution. The change in absorbance was observed after 6 min at 234 nm. Synergy HT (BioTek, USA) 96-well plate reader was used in all experiments. All reactions were performed in triplicates. The positive and negative controls were included in the assay. Quercetin (0.5 mM well$^{-1}$) was used as a positive control. The percentage inhibition was calculated by formula given below.

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

**_N_-(2-methoxyphenyl)benzenesulfonamide (3)**

Off white crystalline solid, yield 94%. IR (KBr): $\nu_{max}$: 3430 (N-H), 3056 (Ar-H), 1341 (-$SO_2$-NH-), 1258 (Ar-O-R); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 7.66 (dd, $J$ = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.53 (br t, $J$ = 7.2 Hz, 1H, H-4'), 7.51 (br t, $J$ = 7.2 Hz, 2H, H-3', H-5'), 7.42 (ddd, $J$ = 1.6, 7.6, 8.0 Hz, 1H, H-4), 7.02 (dd, $J$ = 1.6, 8.0 Hz, 1H, H-6), 6.88 (ddd, $J$ = 1.2, 7.6, 8.0 Hz, 1H, H-5), 6.70 (dd, $J$ = 1.2, 8.0 Hz, 1H, H-3) and 3.32 (s, 3H, -$OCH_3$); EIMS: $m/z$ 263 $[M]^+$, 248 $[M\text{-}CH_3]^+$, 232 $[M\text{-}OCH_3]^+$, 199 $[M\text{-}SO_2]^+$, 122 $[M\text{-}C_6H_5SO_2]^+$, 141 $[C_6H_5SO_2]^+$

**_N_-Methyl-_N_-(2-methoxyphenyl) benzene sulfonamide (5a)**

White amorphous powder, yield 89%. IR (KBr): $\nu_{max}$: 3466 (N-R), 3040 (Ar-H), 1344 (-$SO_2$-NR-), 1279 (Ar-O-R); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 7.65 (dd, $J$ = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.53 (br t, $J$ = 7.2 Hz, 1H, H-4'), 7.52 (br t, $J$ = 7.2 Hz, 2H, H-3', H-5'), 7.42 (ddd, $J$ = 1.6, 7.6, 8.0 Hz, 1H, H-4), 7.02 (ddd, $J$ = 1.2, 7.6, 8.0 Hz, 1H, H-5), 6.70 (dd, $J$ = 1.6, 8.0 Hz, 1H, H-3), 6.88 (dd, $J$ = 1.6, 8.0 Hz, 1H, H-6), 3.32 (s, 3H,-$OCH_3$) and 3.18 (s, 3H, H-1"); EIMS: $m/z$ 277 $[M]^+$, 262 $[M\text{-}CH_3]^+$, 246 $[M\text{-}OCH_3]^+$, 213 $[M\text{-}SO_2]^+$, 136 $[M\text{-}C_6H_5SO_2]^+$, 141 $[C_6H_5SO_2]^+$.

**_N_-Ethyl-_N_-(2-methoxyphenyl) benzene sulfonamide (5b)**

Mustard needle like crystals, yield 82%. IR (KBr): $\nu_{max}$: 3460 (N-R), 3041 (Ar-H), 1348 (-$SO_2$-NR-), 1268 (Ar-O-R); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 7.67 (dd, $J$ = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.53 (br t, $J$ = 7.2, 1H, H-4'), 7.50 (br t, $J$ = 7.2 Hz, 2H, H-3', H-5'), 7.41 (ddd, $J$ = 1.6, 7.6, 8.0 Hz, 1H, H-4), 7.02 (ddd, $J$ = 1.2, 7.6, 8.0 Hz, 1H, H-5), 6.88 (dd, $J$ = 1.6, 8.0 Hz, 1H, H-3), 6.70 (dd, $J$ = 1.6, 8.0 Hz, 1H, H-6), 3.63 (br s, 2H, $CH_2$-1"), 3.32 (s, 3H,-$OCH_3$) and 1.03 (t, 3H, $CH_3$-2"); EIMS: $m/z$ 291$[M]^+$, 276 $[M\text{-}CH_3]^+$, 260 $[M\text{-}OCH_3]^+$, 230 $[M\text{-}SO_2]^+$, 150 $[M\text{-}C_6H_5SO_2]^+$, 141 $[C_6H_5SO_2]^+$.

**_N_-Iso-propyl-_N_-(2-methoxyphenyl) benzene sulfonamide (5c)**

Off white Amorphous powder, yield 74%. IR (KBr): $\nu_{max}$: 3468 (N-R), 3048 (Ar-H), 1341 (-$SO_2$-NR-), 1261 (Ar-O-R); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 7.66 (dd, $J$ = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.53 (br t, $J$ = 7.2, 1H, H-4'), 7.50 (br t, $J$ = 7.2 Hz, 2H, H-3', H-5'), 7.46 (ddd, $J$ = 1.6, 7.6, 8.0 Hz, 1H, H-4), 7.01 (ddd, $J$ = 1.2, 7.6, 8.0 Hz, 1H, H-5), 6.82 (dd, $J$ = 1.6, 8.0 Hz, 1H, H-3), 6.72 (dd, $J$ = 1.6, 8.0 Hz, 1H, H-6), 4.50 (m, 1H, H-1"), 3.31 (s, 3H,-$OCH_3$) and 1.01 (d, 6H, $CH_3$-2", $CH_3$-3"); EIMS: $m/z$ 305 $[M]^+$, 290 $[M\text{-}CH_3]^+$, 274 $[M\text{-}OCH_3]^+$, 241 $[M\text{-}SO_2]^+$, 164 $[M\text{-}C_6H_5SO_2]^+$, 141 $[C_6H_5SO_2]^+$.

**_N_-Butyl-_N_-(2-methoxyphenyl) benzene sulfonamide (5d)**

Rust greasy liquid. yield 69%. IR (KBr): $\nu_{max}$: 3468 (N-R), 3048 (Ar-H), 1341 (-$SO_2$-NR-), 1261 (Ar-O-R); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 7.71 (dd, $J$ = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.55 (br t, $J$ = 7.2, 1H, H-4'), 7.52 (br t, $J$ = 7.2 Hz, 2H, H-3', H-5'), 7.47 (ddd, $J$ = 1.6, 7.6, 8.0 Hz, 1H, H-4), 7.03 (ddd, $J$ = 1.2, 7.6, 8.0 Hz, 1H, H-5), 6.84 (dd, $J$ = 1.6, 8.0 Hz, 1H, H-3), 6.71 (dd, $J$ = 1.6, 8.0 Hz, 1H, H-6), 3.30 (s, 3H,-$OCH_3$), 2.74 (t, $J$ = 7.0, 2H, $CH_2$-1"), 1.48 (m, 2H, $CH_2$-2"), 1.27 (m, 2H, $CH_2$-3") and 0.88 (t, $J$ = 7.5, 3H, $CH_3$-4"); EIMS: $m/z$ 319 $[M]^+$, 304 $[M\text{-}CH_3]^+$, 288 $[M\text{-}OCH_3]^+$, 255 $[M\text{-}SO_2]^+$, 178 $[M\text{-}C_6H_5SO_2]^+$, 141$[C_6H_5SO_2]^+$.

**_N_-Pentyl-_N_-(2-methoxyphenyl) benzene sulfonamide (5e)**

Rust greasy liquid. yield 73%. IR (KBr): $\nu_{max}$: 3461 (N-R), 3041 (Ar-H), 1347 (-$SO_2$-NR-), 1267 (Ar-O-R); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 7.73 (dd, $J$ = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.54 (br t, $J$ = 7.2, 1H, H-4'), 7.51 (br t, $J$ = 7.2 Hz, 2H, H-3', H-5'), 7.45 (ddd, $J$ = 1.6, 7.6, 8.0 Hz, 1H, H-4), 7.01 (ddd, $J$ = 1.2, 7.6, 8.0 Hz, 1H, H-5), 6.81 (dd, $J$ = 1.6, 8.0 Hz, 1H, H-3), 6.72 (dd, $J$ = 1.6, 8.0 Hz, 1H, H-6), 3.31 (s, 3H,-$OCH_3$), 2.74 (t, $J$ = 7.0, 2H, $CH_2$-1"), 1.49 (m, 2H, $CH_2$-2"), 1.26 (m, 4H, $CH_2$-3", $CH_2$-4") and 0.85 (t, $J$ = 7.5, 3H, $CH_3$-5"); EIMS: $m/z$ 333 $[M]^+$, 318 $[M\text{-}CH_3]^+$, 302 $[M\text{-}OCH_3]^+$, 269 $[M\text{-}SO_2]^+$, 192 $[M\text{-}C_6H_5SO_2]^+$, 141 $[C_6H_5SO_2]^+$.

**_N_-Allyl-_N_-(2-methoxyphenyl) benzene sulfonamide (5f)**

Rust sticky liquid. yield 65%. IR (KBr): $\nu_{max}$: 3460 (N-R), 3040 (Ar-H), 1345 (-$SO_2$-NR-), 1267 (Ar-O-R); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 7.76 (dd, $J$ = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.56 (br t, $J$ = 7.2, 1H, H-4'), 7.54 (br t, $J$ = 7.2 Hz, 2H, H-3', H-5'), 7.47 (ddd, $J$ = 1.6, 7.6, 8.0 Hz, 1H, H-4), 7.04 (ddd, $J$ = 1.2, 7.6, 8.0 Hz, 1H, H-5), 6.85 (dd, $J$ = 1.6, 8.0 Hz, 1H, H-3), 6.76 (dd, $J$ = 1.6, 8.0 Hz, 1H, H-6), 5.61 (m, 1H, H-2"), 5.17 (dd, $J$ =1.6, 17.3 Hz, 1H, $H_b$-3"), 5.13 (dd , $J$ =1.2, 10 Hz, 1H, $H_a$-3"), 3.79 (d, $J$ = 6.5 Hz, 2H, $CH_2$-1") and 3.32 (s, 3H,-$OCH_3$); EIMS: $m/z$ 303 $[M]^+$, 288 $[M\text{-}CH_3]^+$, 272 $[M\text{-}OCH_3]^+$, 239 $[M\text{-}SO_2]^+$, 162 $[M\text{-}C_6H_5SO_2]^+$, 141$[C_6H_5SO_2]^+$.

**_N_-Acetyl-_N_-(2-methoxyphenyl) benzene sulfonamide (5g)**

Off white powder. yield 71%. IR (KBr): $\nu_{max}$: 3458 (N-R), 3039 (Ar-H), 1338 (-$SO_2$-NR-), 1262 (Ar-O-R); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 7.71 (dd, $J$ = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.52 (br t, $J$ = 7.2, 1H, H-4'), 7.51 (br t, $J$ = 7.2 Hz,

2H, H-3', H-5'), 7.46 (ddd, *J* = 1.6, 7.6, 8.0 Hz, 1H, H-4), 7.01 (ddd, *J* = 1.2, 7.6, 8.0 Hz, 1H, H-5), 6.81 (dd, *J* = 1.6, 8.0 Hz, 1H, H-3), 6.73 (dd, *J* = 1.6, 8.0 Hz, 1H, H-6), 3.30 (s, 3H,-$OCH_3$) and 1.40 (t, 3H, $CH_3$-1''); EIMS: *m/z* 305 $[M]^+$, 290 $[M\text{-}CH_3]^+$, 374 $[M\text{-}OCH_3]^+$, 239 $[M\text{-}SO_2]^+$, 164 $[M\text{-}C_6H_5SO_2]^+$, 141 $[C_6H_5SO_2]^+$.

**_N_-Benzyl-_N_-(2-methoxyphenyl) benzene sulfonamide (5h)**

Brown cubic crystals. yield 80%. IR (KBr): $\nu_{max}$: 3465 (N-R), 3045 (Ar-H), 1342 (-$SO_2$-NR-), 1263 (Ar-O-R); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 7.70 (dd, *J* = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.51 (br t, *J* = 7.2, 1H, H-4'), 7.49 (br t, *J* = 7.2 Hz, 2H, H-3', H-5'), 7.43 (ddd, *J* = 1.6, 7.6, 8.0 Hz, 1H, H-4), 6.98 (ddd, *J* = 1.2, 7.6, 8.0 Hz, 1H, H-5), 6.97-6.92 (m, 5H, H-2'' to H-6''), 6.80 (dd, *J* = 1.6, 8.0 Hz, 1H, H-3), 6.70 (dd, *J* = 1.6, 8.0 Hz, 1H, H-6), 4.67 (s, 2H, $CH_2$-7'') and 3.30 (s, 3H,-$OCH_3$); EIMS: *m/z* 353 $[M]^+$, 338 $[M\text{-}CH_3]^+$, 322 $[M\text{-}OCH_3]^+$, 289 $[M\text{-}SO_2]^+$, 212 $[M\text{-}C_6H_5SO_2]^+$, 141 $[C_6H_5SO_2]^+$.

***N*-(4, 5-dibromo-2-methoxyphenyl) benzenesulfonamide (6)**

Light orange colored powder, yield 92%. IR (KBr): $\nu_{max}$: 3428 (N-H), 3462 (N-R), 3037 (Ar-H), 1336 (-$SO_2$-NR-), 1260 (Ar-O-R); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 7.71 (dd, *J* = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.56 (br t, *J* = 7.6, 1H, H-4'), 7.47 (br t, *J* = 7.6 Hz, 2H, H-3', H-5'), 7.25 (s, 1H, H-6), 6.93 (s,1H, H-3) and 3.36 (s, 3H, -$OCH_3$); EIMS: *m/z* 421 $[M]^+$, 406 $[M\text{-}CH_3]^+$, 490 $[M\text{-}OCH_3]^+$, 357 $[M\text{-}SO_2]^+$, 279 $[M\text{-}C_6H_5SO_2]^+$, 141$[C_6H_5SO_2]^+$.

***N*-Ethyl-*N*-(4, 5-dibromo-2-methoxyphenyl) benzenesulfonamide (6b)**

White needle like crystals. yield 85%. IR (KBr): $\nu_{max}$: 3462 (N-R), 3037 (Ar-H), 1336 (-$SO_2$-NR-), 1260 (Ar-O-R); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 7.68 (dd, *J* = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.53 (br t, *J* = 7.6 Hz, 1H, H-4'), 7.46 (s, 1H, H-6), 7.42 (br t, *J* = 7.6 Hz, 2H, H-3', H-5'), 7.01 (s,1H, $CH_3$-3), 3.58 (q, 2H, $CH_2$-1'') 3.36 (s, 3H, -$OCH_3$) and 1.03 (t, *J* = 7.0, 3H, $CH_3$-2''); EIMS: *m/z* 449 $[M]^+$, 434 $[M\text{-}CH_3]^+$, 418 $[M\text{-}OCH_3]^+$, 385 $[M\text{-}SO_2]^+$, 307 $[M\text{-}C_6H_5SO_2]^+$, 141$[C_6H_5SO_2]^+$.

***N*-Butyl-*N*-(4, 5-dibromo-2-methoxyphenyl) benzenesulfonamide (7d)**

Mustard needle like crystals. yield 78%. IR (KBr): $\nu_{max}$: 3460 (N-R), 3038 (Ar-H), 1330 (-$SO_2$-NR-), 1265 (Ar-O-R); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 7.66 (dd, *J* = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.53 (br t, *J* = 7.6 Hz, 1H, H-4'), 7.46 (s, 1H, H-6), 7.42 (br t, *J* = 7.6 Hz, 2H, H-3', H-5'), 7.00 (s,1H, H-3), 3.49 (br s, 2H, $CH_2$-1''), 3.34 (s, 3H, -$OCH_3$), 1.35 (m, 2H, $CH_2$-2''), 1.27 (m, 2H, $CH_2$-3'') and 0.84 (t, *J* = 7.5, 3H, $CH_3$-4''); EIMS: *m/z* 477 $[M]^+$, 462 $[M\text{-}CH_3]^+$, 446 $[M\text{-}OCH_3]^+$, 413 $[M\text{-}SO_2]^+$, 336 $[M\text{-}C_6H_5SO_2]^+$, 141 $[C_6H_5SO_2]^+$.

***N*-Pentyl-*N*-(4, 5-dibromo-2-methoxyphenyl) benzenesulfonamide (6e)**

Rust needle like crystals. yield 82%. IR (KBr): $\nu_{max}$: 3463 (N-R), 3035 (Ar-H), 1328 (-$SO_2$-NR-), 1259 (Ar-O-R); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 7.64 (dd, *J* = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.53 (br t, *J* = 7.6 Hz, 1H, H-4'), 7.45 (s, 1H, H-6), 7.40 (br t, *J* = 7.6 Hz, 2H, H-3', H-5'), 7.00 (s,1H, H-3), 3.48 (br s, 2H, $CH_2$-1''), 3.34 (s, 3H, -$OCH_3$), 1.38 (m, 2H, $CH_2$-2''), 1.25 (m, 2H, $CH_2$-3''), 1.23 (m, 2H, $CH_2$-4'') and 0.82 (t, *J* = 7.5 Hz, 3H, $CH_3$-5''); EIMS: *m/z* 491 $[M]^+$, 476 $[M\text{-}CH_3]^+$, 460 $[M\text{-}OCH_3]^+$, 427 $[M\text{-}SO_2]^+$, 350 $[M\text{-}C_6H_5SO_2]^+$, 141 $[C_6H_5SO_2]^+$.

***N*-Benzyl-*N*- (4,5-dibromo-2-methoxyphenyl)benzene sulfonamide (6h)**

Rust cubic crystals. yield 87%. IR (KBr): $\nu_{max}$: 3461 (N-R), 3032 (Ar-H), 1334 (-$SO_2$-NR-), 1263 (Ar-O-R); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 7.62 (dd, *J* = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.51 (br t, *J* = 7.6 Hz, 1H, H-4'), 7.44 (s, 1H, H-6), 7.39 (br t, *J* = 7.6 Hz, 2H, H-3', H-5'), 7.01 (s,1H, H-3), 6.96-6.90 (m, 5H, H-2''' to H-6'''), 4.65 (s, 2H, $CH_2$-7'') and 3.33 (s, 3H, -$OCH_3$); EIMS: *m/z* 511 $[M]^+$, 496 $[M\text{-}CH_3]^+$, 480 $[M\text{-}OCH_3]^+$, 447 $[M\text{-}SO_2]^+$, 370 $[M\text{-}C_6H_5SO_2]^+$, 141 $[C_6H_5SO_2]^+$.

***N*-(2-Bromoethyl-*N*-(4,5-dibromo-2-methoxyphenyl)benzenesulfonamide (6i)**

Mustard needle like crystals. yield 80%. IR (KBr): $\nu_{max}$: 3462 (N-R), 3035 (Ar-H), 1332 (-$SO_2$-NR-), 1263 (Ar-O-R); $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ 7.64 (dd, *J* = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.58 (s, 1H, H-6), 7.55 (br t, *J* = 7.6 Hz, 1H, H-4'), 7.45 (br t, *J* = 7.6 Hz, 2H, H-3', H-5'), 7.00 (s,1H, H-3), 3.83 (br s, 2H, $CH_2$-1''), 3.40 (t, *J* = 7.5, 2H, $CH_2$-2'') and 3.30 (s, 3H, -$OCH_3$); EIMS: *m/z* 528 $[M]^+$, 513 $[M\text{-}CH_3]^+$, 497 $[M\text{-}OCH_3]^+$, 464 $[M\text{-}SO_2]^+$, 386 $[M\text{-}C_6H_5SO_2]^+$, 141 $[C_6H_5SO_2]^+$.

**Results and Discussion**

Compound **3** was synthesized as off white crystalline solid. The molecular formula $C_{13}H_{12}NO_3S$ was established by HR-MS showing molecular ion peak at *m/z* 263.3164 (calcd. for $C_{13}H_{12}NO_3S$, 263.3131). The IR spectrum revealed the presence of methoxy group (1258 $cm^{-1}$), a sulfonyl group (1341 $cm^{-1}$) and –NH- group (3430 $cm^{-1}$) in the molecule. The EIMS gave distinct peak at *m/z* 199 after the removal of sulfony group and further fragment ion peak was observed at *m/z* 232 which showed the presence of methoxy groups in the molecule. In the aromatic region of the $^1$H-NMR spectrum of **3,** signals appeared at $\delta$ 7.66 (dd, *J* = 7.2, 1.2 Hz, 2H, H-2', H-6'), 7.53 (br t, *J* = 7.2 Hz, 1H, H-4') and 7.51 (br t, *J* = 7.2 Hz, 2H, H-3', H-5'). Due to downfield shift, these protons were assigned to mono-substituted ring bearing sulfonyl group and the signals appearing at $\delta$ 7.42 (ddd, *J* = 1.6, 7.6, 8.0 Hz, 1H, H-4), 7.02 (dd, *J* = 1.6, 8.0 Hz, 1H, H-6), 6.88 (ddd, *J* = 1.2, 7.6, 8.0 Hz, 1H, H-5) and 6.70 (dd, *J* = 1.2, 8.0 Hz, 1H, H-3) were assigned to the protons of disubstituted ring. In the aliphatic region, a singlet was appeared at δ 3.32 corresponding to the methoxy group present in the molecule. On the basis of these evidences the structure

of **3** was assigned as *N*-(2-methoxyphenyl)benzenesulfonamide.

Similarly on the basis of structural evidences from IR, EIMS, and $^1$H-NMR, the structures of other derivatives were elucidated as described in experimental section.

The screening of these sulfonamide derivatives against acetyl cholinesterase, butyryl cholinesterase and lipoxygenase enzymes revealed that they were inactive against acetyl cholinesterase (AchE) but exhibited good inhibitory potential against lipoxygenase as it was evident from their $IC_{50}$ values (Table 1). Among these, *N*-butyl-*N*-(4,5-dibromo-2-methoxyphenyl)benzenesulfonamide (**6d**) and *N*-pentyl-*N*-(4,5-dibromo-2-methoxy phenyl)benzenesulfonamide (**6e**) were found to be the good inhibitors having $IC_{50}$ value of 90.81 ± 0.91and 78.65 ± 0.85 µmoles respectively, relative to baicalein, a reference standard with $IC_{50}$ value of 22.4 ± 1.3 µmoles, probably due to the substitution of butyl and pentyl group respectively in these molecules. The screening against butyryl cholinesterase enzyme revealed that only two compounds, namely, *N*-isopropyl-*N*-(2-methoxy phenyl)benzenesulfonamide (**5c**) and *N*-benzyl-*N*-(2-methoxyphenyl)benzenesulfonamide (**5h**) exhibited inhibitory potential, however all other compounds were inactive.

## References


[1] Remko M. and Lieth C.W.V.D. (2004) *Bioorgan. Med. Chem.*, 12(20), 5395-5403.

[2] El-Sayed N.S., El-Bendary E.R., El-Ashry S.M. and El- Kerdawy M.M.(2011) *Eur. J. Med. Chem*.,46(9), 3714-3720.

[3] Garcia-Galan M.J., Diaz-Cruz M.S. and Barcelo D. (2008) *Trends Anal. Chem*., 27(11), 1008-1022.

[4] Perlovich G. L., Strakhova N. N., Kazachenko V. P., Volkova T.V., Tkachev V. V., Schaper K.J. and Raevsk O.A. (2008) *Int. J. Pharm.,*349, 300-313.

[5] Gadad A.K., Mahajanshetti C.S., Nimbalkars S. and Raichurkar A.(2000) *Eur. J. Med. Chem*., 35(9), 853-857.

[6] Clapp H. C., Banerjee A. and Rotenberg S. A. (1985) *J. Biochem.,* 24,1826-1830.

[7] Kemal C., Louis-Flemberg P., Krupinski-Olsen R. and Shorter A. L. (1987) *J. Biochem*., 26, 7064-7072.

[8] Steinhilber D. (1999) *Curr. Med. Chem*., 6, 71-85.

[9] Alitonou G. A., Avlessi F., Sohounhloue D. K., Agnaniet H., Bessiere J. M. and Menut C. (2006) *Int. J. Aromatherap*.,16, 37-41.

[10] Ellman G. L., Courtney K. D., Andres V. and Featherstone R. M. (1961) *Bio. Pharm*., 7, 88-95.

[11] Baylac S. and Racine P. (2003) *Int. J. Aromatherap*., 13,138-142.

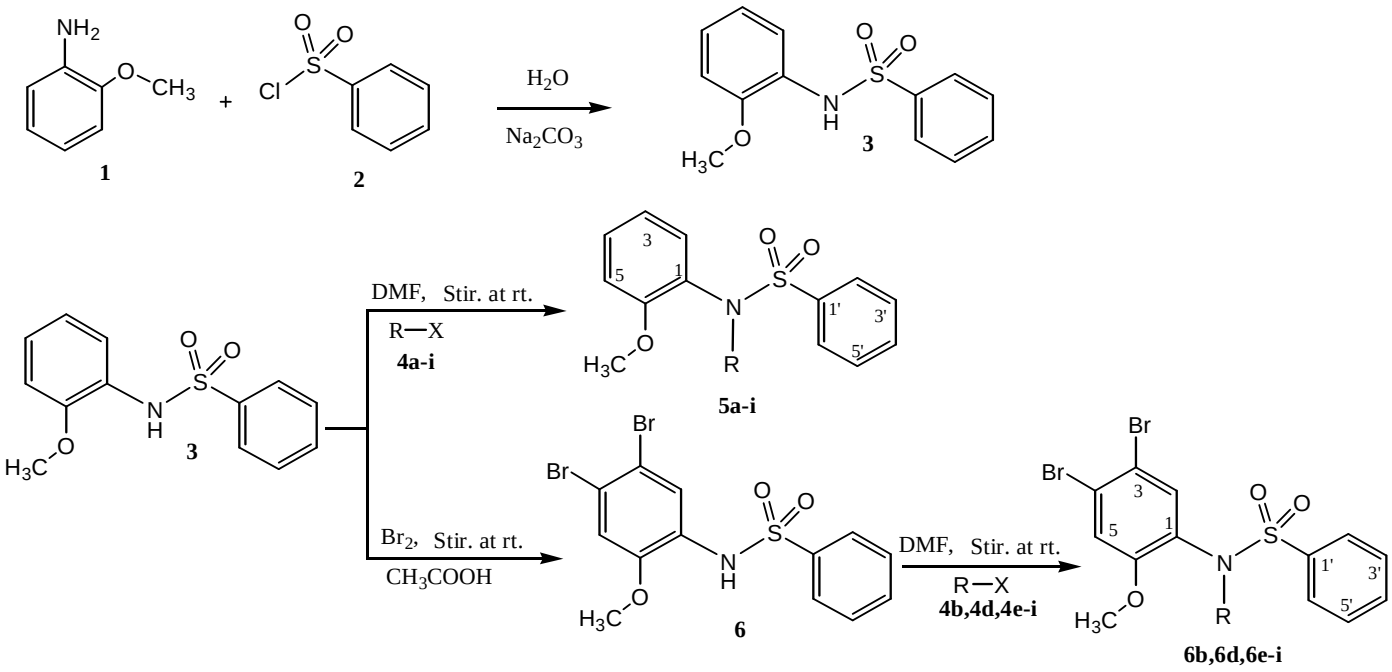
[12] Tappel A. L. (1953) *Arch. Biochem. Biophys.,* 44(2), 378–395.

[13] Evans A. T. (1987) *Bio. Pharm.,* 1987; 36: 2035-2037.


*Table 1- Evaluation of biological activities of the compounds (n=3, mean±sem).*

| Sample No. | DPPH | | AChE | | BChE | | LOX | |
|---|---|---|---|---|---|---|---|---|
| | (%) at 0.5 mM | ($IC_{50}$) µmoles | (%) at 0.5mM | ($IC_{50}$) µmoles | (%) at 0.5mM | ($IC_{50}$) µmoles | (%) at 0.5Mm | ($IC_{50}$) µmoles |
| **3** | 68.65±0.59 | <500 | 8.09±0.87 | Nil | 26.83±0.99 | Nil | 37.72±0.75 | Nil |
| **3a** | 68.50±0.78 | <500 | 30.31±0.95 | Nil | 51.89±0.87 | <500 | 40.84±0.81 | Nil |
| **3b** | 67.37±0.75 | <500 | 8.21±0.83 | Nil | 52.52±0.91 | <500 | 43.71±1.12 | Nil |
| **3c** | 64.17±0.91 | <500 | 28.02±1.01 | Nil | 73.69±1.11 | 175.25±0.85 | 77.60±0.99 | 119.59±0.85 |
| **3d** | 44.80±0.84 | Nil | 50.97±0.93 | <500 | 45.07±1.01 | Nil | 75.21±0.93 | 128.27±0.85 |
| **3e** | 39.73±1.02 | Nil | 26.43±0.85 | Nil | 31.76±0.89 | Nil | 73.77±0.89 | 139.81±0.85 |
| **3f** | 59.76±0.93 | <500 | 41.30±0.92 | Nil | 54.30±0.94 | <500 | 84.79±0.97 | 97.64±0.59 |
| **3g** | 71.51±0.76 | 138.87±0.88 | 8.70±0.97 | Nil | 24.63±0.84 | Nil | 40.12±0.93 | Nil |
| **3h** | 87.59±0.87 | 99.36±0.99 | 55.68±0.99 | <500 | 71.07±0.93 | 187.41±0.94 | 55.33±0.95 | <500 |
| **6** | 51.39±0.99 | <500 | 11.47±0.89 | Nil | 11.22±0.91 | Nil | 36.77±0.75 | Nil |
| **6b** | 44.80±0.85 | Nil | 32.49±0.81 | Nil | 29.35±0.96 | Nil | 10.18±1.12 | 190.81±0.99 |
| **6d** | 78.28±0.74 | 148.12±0.89 | 62.92±0.94 | 289.12±0.91 | 28.30±1.11 | Nil | 50.54±0.93 | 90.81±0.91 |
| **6e** | 69.91±0.93 | 259.51±0.95 | 44.93±0.95 | Nil | 32.39±0.99 | Nil | 80.12±0.84 | 78.65±0.85 |
| **6h** | 52.42±0.88 | <500 | 35.87±0.95 | Nil | 32.81±0.99 | Nil | 14.25±0.81 | Nil |
| **6i** | 38.69±0.96 | Nil | 18.72±0.88 | Nil | 37.95±0.89 | Nil | 38.08±0.99 | Nil |
| **Control** | Quercetin | 16.96±0.14 | Eserine | 0.04±0.001 | Eserine | 0.85±0.001 | Baicalein | 22.4±1.3 |

Note: DPPH = 1,1-diphenyl-2-picrylhydrazyl radical




| Compound | R | Compound | R |
|---|---|---|---|
| **5a** | $-CH_3$ (1") | **6b** | $-CH_2-CH_3$ (1", 2") |
| **5b** | $-CH_2-CH_3$ (1", 2") | **6d** | $-CH_2-CH_2-CH_2-CH_3$ (1", 2", 3", 4") |
| **5c** | $-CH(CH_3)_2$ (2", 1", 3") | **6e** | $-CH_2-CH_2-CH_2-CH_2-CH_3$ (1", 2", 3", 4", 5") |
| **5d** | $-CH_2-CH_2-CH_2-CH_3$ (1", 2", 3", 4") | **6h** | $-CH_2-C_6H_5$ (7", 1", 3", 5") |
| **5e** | $-CH_2-CH_2-CH_2-CH_2-CH_3$ (1", 2", 3", 4", 5") | **6i** | $-CH_2-CH_2-Br$ (1", 2") |
| **5f** | $-CH_2-CH=CH_2$ (1", 2", 3"; $H_a$, $H_b$) | | |
| **5g** | $-C(=O)-CH_3$ (1") | | |
| **5h** | $-CH_2-C_6H_5$ (7", 1", 3", 5") | | |