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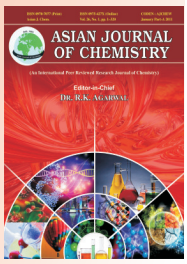

Synthesis of Biologically Active *N*-Benzyl-*N*-[(3,4-methylenedioxyphenyl)methyl]arylsulfonamides

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A new series of *N*-benzyl-*N*-[(3,4-methylenedioxyphenyl)methyl]arylsulfonamides (**5a-f**) was synthesized by using (3,4-methylenedioxyphenyl)methylamine (**1**). Compound **1** on reaction with arylsulfonyl chlorides (**2a-f**) in a weak basic aqueous medium gave *N*-[(3,4-methylenedioxyphenyl)methyl]arylsulfonamides (**3a-f**), which were converted to target molecules **5a-f**, by the reaction of **3a-f** with electrophile, benzyl chloride (**4**) in the presence of LiH and *N,N*-dimethylformamide. All the synthesized molecules were characterized by IR, ^{1}H NMR and EIMS. Further, all the molecules were screened for the antibacterial activity and showed moderately good inhibition activity.

Keywords: (3,4-Methylenedioxyphenyl)methylamine, Antibacterial activity, Arylsulfonyl chlorides.

INTRODUCTION

All the sulfonamides bear sulfamoyl group in common and have significance in medicinal chemistry due to their biological activities. These are extensively employed as the carbonic anhydrase inhibitors; anticancer, antiinflammatory, antiviral agents; antimicrobial drugs and antitumor drugs, plausibly because of reasonable cost, decremented toxicity and incremented activities[1-5]. The sulfonamides have been evaluated for a number of biological activities including antibacterial activities[6,7]. The benzodioxol moiety has much significance in the field of biological active compounds. The various natural products like narciclasine, lycoricidine and pancratistatin bear benzodioxole moiety and have been employed for anticancer *etc*. Some other drugs like the antidepressant including paroxetine, escitalopram *etc.* also possess this moiety[8,9].

In continuation of our previous work[10-13], the synthesis and biological screening of new *N*-benzyl-*N*-[(3,4-methylenedioxyphenyl)methyl]arylsulfonamides compounds with an objective to detect the antimicrobial activity of the synthesized compounds. This is crucial as the need of hour is to inaugurate new potent molecules with great resistance against the existing microbes. This encouraged us to develop new effective molecules and the effort remained productive in this regard.

EXPERIMENTAL

Purity of the synthesized molecules was analyzed by thin layer chromatography (TLC) using EtOAc and *n*-hexane as solvent systems, followed by visualization under UV at 254 nm. Melting points of all compounds were recorded on a Griffin-George melting point apparatus by open capillary tube and were uncorrected. Infrared spectra were recorded in KBr pellet method on a Jasco-320-A spectrophotometer. ^{1}H NMR spectra were recorded in $CHCl_3$ (deuterated) on a Bruker spectrometer at 400 MHz along with chemical shift in δ-values, tetramethylsilane as reference standard and the coupling constants (J) in Hz. Mass spectra (EIMS) were recorded on a JMS-HX-110 spectrometer.

Synthesis of *N*-[(3,4-methylenedioxy-phenyl)methyl]-arylsulfonamides (3a-f): (3,4-Methylene-dioxyphenyl)methylamine (0.01 mol; 1) was suspended in 50 mL water using 200 mL round bottom flask. The pH of reaction mixture was maintained 9-10 by using aqueous Na_2CO_3 solution. Different arylsulfonyl chlorides (0.01 mol; **2a-f**) were added into the flask along with stirring. The reaction mass was kept on stirring for 2-3 h and checked by TLC till the single spot. At the completion of reaction, dil. HCl (2.0-3.0 mL) was added slowly to make the pH slightly acidic. The reaction mixture was kept undisturbed for 0-5 min and then shaken to get the precipitates.

Synthesis of *N*-benzyl-*N*-[(3,4-methylenedioxyphenyl)-methyl]arylsulfonamides (5a-f): Compounds **3a-f** (0.01 mol) was homogeneously dissolved in 10 mL *N,N*-dimethyl formamide in a 100 mL round bottom flask along with the addition of lithium hydride (0.01 mol) at room temperature. The reaction mixture were stirred for 30-45 min and then the electrophile; benzyl chloride (0.01 mol; 4) was added to get the target mole-

cules **5a-f**, after stirring for 3-4 h. After completion of reaction as per single spot on TLC, the reaction mixture was quenched with ice cold water (150 mL). The formed precipitates were filtered, washed with distilled water and dried to yield the corresponding products **5a-f**.

***N*-Benzyl-*N*-[(3,4-methylenedioxyphenyl)methyl]-benzenesulfonamide (5a):** Dark grey amorphous solid; Yield: 83 %; m.p.: 84-86 °C; m.f.: $C_{21}H_{19}NO_4S$; Mol. Mass: 381 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3067 (Ar C-H), 1608 (Ar C=C), 1346 (S=O), 1239 (C-O); ^1H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.82 (d, *J* = 8.0 Hz, 2H, H-2', H-6'), 7.52 (t, *J* = 8.0 Hz, 1H, H-4'), 7.49 (t, *J* = 8.0 Hz, 2H, H-3', H-5'), 7.17-7.10 (m, 5H, H-2" to H-6"), 6.68 (d, *J* = 7.6 Hz, 1H, H-6), 6.65 (s, 1H, H-2), 6.61 (d, *J* = 7.6 Hz, 1H, H-5), 5.90 (s, 2H, H-8), 4.07 (s, 2H, H-7), 3.85 (s, 2H, H-7"); EIMS (*m/z*): 381 $[M]^+$, 150 $[C_8H_8NO_2]^+$, 141 $[C_6H_5SO_2]^+$, 135 $[C_8H_7O_2]^+$, 121 $[C_7H_5O_2]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

***N*-Benzyl-*N*-[(3,4-methylenedioxyphenyl)methyl]-2,4,6-trimethylbenzene sulfonamide (5b):** White amorphous solid; Yield: 87 %; m.p.: 108-110 °C; m.f.: $C_{24}H_{25}NO_4S$; Mol. Mass: 423 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3086 (Ar C-H), 1613 (Ar C=C), 1378 (S=O), 1251 (C-O); ^1H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.21-7.15 (m, 5H, H-2" to H-6"), 6.89 (s, 2H, H-3', H-5'), 6.70 (s, 1H, H-2), 6.66 (d, *J* = 7.6 Hz, 1H, H-6), 6.62 (d, *J* = 7.6 Hz, 1H, H-5), 5.90 (s, 2H, H-8), 4.15 (s, 2H, H-7), 3.39 (s, 2H, H-7"), 2.59 (s, 6H, CH_3-7', CH_3-8'), 2.18 (s, 3H, CH_3-9'); EIMS (*m/z*): 423 $[M]^+$, 183 $[C_9H_{11}SO_2]^+$, 150 $[C_8H_8NO_2]^+$, 135 $[C_8H_7O_2]^+$, 121 $[C_7H_5O_2]^+$, 119 $[C_9H_{11}]^+$, 91 $[C_7H_7]^+$, 74 $[C_6H_2]^+$, 65 $[C_5H_5]^+$.

***N*-Benzyl-*N*-[(3,4-methylenedioxyphenyl)methyl]-2,4-dinitrobenzenesulfonamide (5c):** Light brown sticky solid; Yield: 83 %; m.f.: $C_{21}H_{17}N_3O_8S$; Mol. Mass: 471 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3083 (Ar C-H), 1601 (Ar C=C), 1356 (S=O), 1253 (C-O); ^1H NMR ($CDCl_3$, 400 MHz, δ/ppm): 8.49 (d, *J* = 2.0 Hz, 1H, H-3'), 8.37 (dd, *J* = 8.0, 2.4 Hz, 1H, H-5'), 8.21 (d, *J* = 8.4 Hz, 1H, H-6'), 7.29-7.25 (m, 5H, H-2" to H-6"), 6.73 (d, *J* = 8.4 Hz, 1H, H-6), 6.69 (s, 1H, H-2), 6.67 (d, *J* = 8.0 Hz, 1H, H-5), 5.86 (s, 2H, H-8), 4.31 (s, 2H, H-7), 3.39 (s, 2H, H-7"); EIMS (*m/z*): 381 $[M]^+$, 231 $[C_6H_3N_2O_4SO_2]^+$, 167 $[C_6H_3N_2O_4]^+$, 150 $[C_8H_8NO_2]^+$, 135 $[C_8H_7O_2]^+$, 121 $[C_7H_5O_2]^+$, 91 $[C_7H_7]^+$, 75 $[C_6H_3]^+$, 65 $[C_5H_5]^+$.

***N*-Benzyl-*N*-[(3,4-methylenedioxyphenyl)methyl]-2-naphthalenesulfonamide (5d):** White crystalline solid; Yield: 79 %; m.p.: 114-116 °C; m.f.: $C_{25}H_{21}NO_4S$; Mol. Mass: 431 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3029 (Ar C-H), 1616 (Ar C=C), 1343 (S=O), 1237 (C-O); ^1H NMR ($CDCl_3$, 400 MHz, δ/ppm): 8.38 (s, 1H, H-8'), 7.95 (d, *J* = 8.4 Hz, 1H, H-3'), 7.90 (d, *J* = 8.4 Hz, 1H, H-2'), 7.80 (dd, *J* = 8.4, 1.6 Hz, 1H, H-4'), 7.73 (dd, *J* = 8.4, 1.6 Hz, 1H, H-7'), 7.64 (t, *J* = 8.0 Hz, 1H, H-6'), 7.60 (t, *J* = 7.6 Hz, 1H, H-5'), 7.19-7.10 (m, 5H, H-2" to H-6"), 6.64 (d, *J* = 7.2 Hz, 1H, H-6), 6.62 (d, *J* = 3.2 Hz, 1H, H-2), 6.58 (d, *J* = 7.2 Hz, 1H, H-5), 5.82 (s, 2H, H-8), 4.06 (s, 2H, H-7), 3.46 (s, 2H, H-7"); EIMS (*m/z*): 431 $[M]^+$, 191 $[C_{10}H_7SO_2]^+$, 150 $[C_8H_8NO_2]^+$, 135 $[C_8H_7O_2]^+$, 127 $[C_{10}H_7]^+$, 121 $[C_7H_5O_2]^+$, 102 $[C_8H_6]^+$, 91 $[C_7H_7]^+$, 65 $[C_5H_5]^+$.

***N*-Benzyl-*N*-[(3,4-methylenedioxyphenyl)methyl]-1-phenylmethanesulfonamide (5e):** Cream white amorphous solid; Yield: 89 %; m.p.: 88-90 °C; m.f.: $C_{22}H_{21}NO_4S$; Mol. Mass: 395 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3079 (Ar C-H), 1611 (Ar C=C), 1345 (S=O), 1234 (C-O); ^1H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.36-7.23 (m, 10H, H-2' to H-6' & H-2" to H-6"), 6.72 (d, *J* = 8.4 Hz, 1H, H-6), 6.69 (s, 1H, H-2), 6.66 (d, *J* = 8.0 Hz, 1H, H-5), 5.93 (s, 2H, H-8), 4.15 (s, 2H, H-7'), 4.10 (s, 2H, H-7), 3.96 (s, 2H, H-7"); EIMS (*m/z*): 395 $[M]^+$, 155 $[C_7H_7SO_2]^+$, 150 $[C_8H_8NO_2]^+$, 135 $[C_8H_7O_2]^+$, 121 $[C_7H_5O_2]^+$, 91 $[C_7H_7]^+$, 65 $[C_5H_5]^+$.

***N*-Benzyl-*N*-[(3,4-methylenedioxyphenyl)methyl]-1-[(1R,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]-methanesulfonamide (5f):** Light grey amorphous solid; Yield: 79 %; m.p.: 114-116 °C; m.f.: $C_{25}H_{29}NO_5S$; Mol. Mass: 455 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3075 (Ar C-H), 1604 (Ar C=C), 1386 (S=O), 1232 (C-O); ^1H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.22-7.17 (m, 5H, H-2" to H-6"), 6.71 (s, 1H, H-2), 6.67 (d, *J* = 8.0 Hz, 1H, H-6), 6.63 (d, *J* = 8.0 Hz, 1H, H-5), 5.85 (s, 2H, H-8), 4.25 (s, 2H, H-7), 3.40 (s, 2H, H-7"), 3.13 (s, 2H, H-10'), 2.35-2.30 (m, 2H, H-3'), 2.11-2.06 (m, 2H, H-6'), 1.99-1.93 (m, 2H, H-4'), 1.49-1.45 (m, 1H, H-5'), 0.91 (s, 6H, CH_3-8', CH_3-9'); EIMS (*m/z*): 455 $[M]^+$, 215 $[C_{10}H_{15}OSO_2]^+$, 151 $[C_{10}H_{15}O]^+$, 150 $[C_8H_8NO_2]^+$, 135 $[C_8H_7O_2]^+$, 121 $[C_7H_5O_2]^+$, 91 $[C_7H_7]^+$, 65 $[C_5H_5]^+$.

Antibacterial activity: Determination of the antibacterial activity was based on the principle that microbial cell number or microbial growth was directly related to the log phase of growth with increase in absorbance of broth medium[14,15]. The clinically isolated two Gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and three Gram-negative (*Salmonella typhi*, *Escherichia coli* and *Pseudomonas aeruginosa*) bacteria were stored on stock culture agar medium. 20 µg test samples with dilution by suited solvents and 180 µL overnight maintained fresh bacterial culture with suited dilution with fresh nutrient broth were mixed. The initial absorbance was crucially between 0.12-0.19 at 540 nm. The incubation was processed at 37 °C for 16-24 h with lid on the micro plate. The absorbance was measured at 540 nm using micro plate reader before and after incubation and the difference was noted as an index of bacterial growth. The per cent inhibition was calculated using the formula: Inhibition (%) = 100-(Abs of test sample/Abs of control) × 100

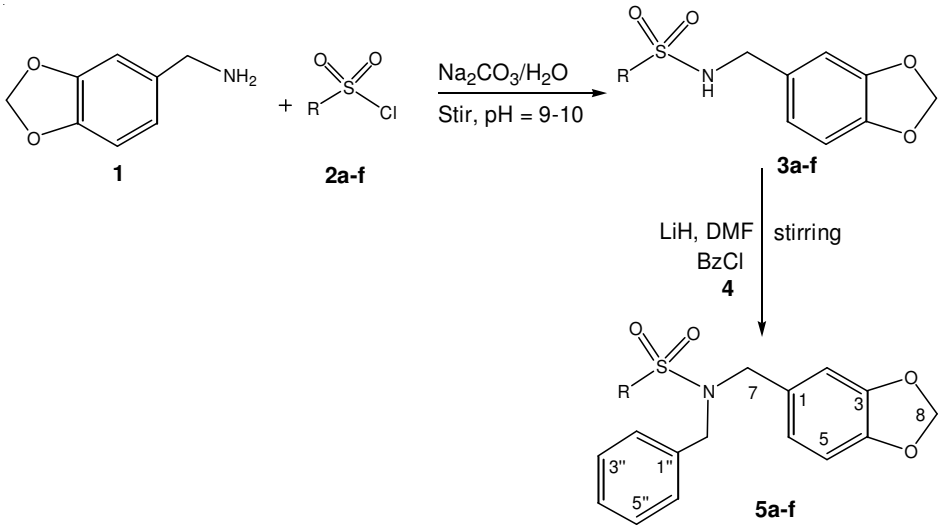
Results are mean of triplicate (n = 3, ± sem). Ciprofloxacin was employed as standard. Minimum inhibitory concentration (MIC) was measured with suitable dilutions (5-30 µg/well) and results were calculated using EZ-Fit Perrella Scientific Inc. Amherst USA software and data was expressed as MIC.

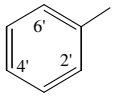
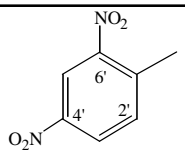
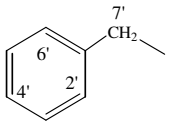
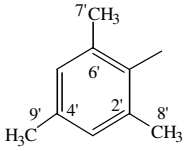
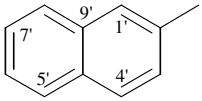
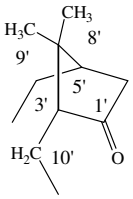
Statistical analysis: All the measurements were done in triplicate and statistical analysis was performed by Microsoft Excel 2010. Results are presented as mean ± sem.

RESULTS AND DISCUSSION

A new series of *N*-benzyl-*N*-[(3,4-methylenedioxyphenyl)-methyl]arylsulfonamides (**5a-f**) was synthesized according to the protocol sketched in **Scheme-I**.

The parent molecules, *N*-[(3,4-methylenedioxyphenyl)-methyl]arylsulfonamides (**3a-f**) were synthesized by reacting (3,4-methylenedioxyphenyl)methylamine (**1**) with arylsulfonyl chlorides (**2a-f**) under basic pH control in an aqueous medium. The products were separated after acidification by dil. HCl.



Compd.	R	Compd.	R	Compd.	R
5a		**5c**		**5e**	
5b		**5d**		**5f**	

Scheme-I: Synthesis of *N*-benzyl-*N*-[(3,4-methylenedioxyphenyl)methyl]arylsulfonamides

The parent molecules were further treated with the electrophile, benzyl chloride (**4**) to synthesize the product, **5a-f** in the presence of NaH as weak base and in a polar aprotic solvent using DMF. The molecule **5a** showed the $[M]^+$ peak at *m/z* 381 and the prominent peaks were appeared at *m/z* 141 for phenylsulfonyl cation, at *m/z* 77 for phenyl cation after the loss of SO_2 and at *m/z* 135 for the (3,4-methylenedioxyphenyl)-methyl cation, in EI-MS spectrum. The IR spectrum showed absorption bands at 3067, 1608 and 1346 cm^{-1} due to Ar-C-H (aromatic C-H stretching), Ar-C=C (aromatic C=C stretching), -SO_2 (stretching of sulfonyl group), respectively. In the ^{1}H NMR spectrum, the signals resonating at δ 6.68 (d, *J* = 7.6 Hz, 1H, H-6), 6.65 (s, 1H, H-2), 6.61 (d, *J* = 7.6 Hz, 1H, H-5) and 5.90 (s, 2H, H-8) confirmed the presence of tri-substituted aromatic ring. The three signals resonating at δ 7.82 (d, *J* = 8.0 Hz, 2H, H-2', H-6'), 7.52 (t, *J* = 8.0 Hz, 1H, H-4') and 7.49 (t, *J* = 8.0 Hz, 2H, H-3', H-5'), confirmed the phenyl ring attached to the withdrawing sulfonyl group. A multiplet of five protons was appeared in the aromatic region at δ 7.17-7.10 (m, 5H, H-2" to H-6") which showed the presence of mono-substituted aromatic ring. In the aliphatic region, three signals were appeared at δ 5.90 (s, 2H), 4.07 (s, 2H,) and 3.85 (s, 2H,) which corresponding to the H-8, H-7 and H-7" methylene protons, respectively. On the basis of above data, the structure of the molecule is *N*-benzyl-*N*-[(3,4-methylenedioxy-phenyl)methyl]-benzenesulfonamide. In the same way, the structures of other synthesized compounds were corroborated by ^{1}H NMR, IR and mass spectral data as described in experimental section.

Antibacterial activity: The results of antibacterial study of the synthesized compounds are listed in Tables 1 and 2 as their percentage inhibition and MIC values respectively. The series of synthesized molecules has been shown to be potentially active against the five bacterial strains of Gram-bacteria. Among the Gram-negative bacterial strains, the molecules **8f** showed the most potential activity (with MIC value 10.77 ± 1.88 μM) relative to the reference standard, ciprofloxacin (with MIC value of 9.42 ± 1.09 μM) against *Salmonella typhi*. Among the Gram-positive bacterial strains, the molecules **8f** showed the significant activity against *Staphylococcus aureus*. Almost the whole series remained active against all the bacterial strains, credibly, because of the heterocyclic moiety attached to the sulfamoyl group.

Conclusion

The projected structures of the synthesized compounds are well supported by spectroscopic data. The newly synthesized compounds showed varying degree of antibacterial activity.

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TABLE-1
PERCENTAGE INHIBITION OF ANTIBACTERIAL ACTIVITY

Compound	Percentage inhibition				
	S. typhi (-)	*E. coli* (-)	*P. aeroginosa* (-)	*B. subtilis* (+)	*S. aureus* (+)
8a	68.33 ± 1.22	75.37 ± 0.84	58.26 ± 5.00	51.95 ± 5.00	40.05 ± 1.68
8b	52.28 ± 4.61	68.95 ± 4.74	47.17 ± 3.43	49.14 ± 1.50	49.23 ± 1.28
8c	63.88 ± 0.47	82.06 ± 2.31	63.04 ± 3.88	56.50 ± 3.50	57.45 ± 0.35
8d	59.78 ± 2.22	53.26 ± 5.00	54.87 ± 1.83	39.59 ± 5.00	56.89 ± 2.81
8e	47.67 ± 1.89	61.42 ± 0.37	56.96 ± 3.39	40.45 ± 1.82	35.00 ± 2.35
8f	72.22 ± 3.33	68.11 ± 1.26	57.83 ± 5.00	49.50 ± 5.00	64.18 ± 11.73
Ciprofloxacin	91.19 ± 2.10	90.44 ± 1.23	92.00 ± 2.76	89.98 ± 2.07	92.21 ± 1.59

TABLE-2
MIC OF ANTIBACTERIAL ACTIVITY

Compound	MIC				
	S. typhi (-)	*E. coli* (-)	*P. aeroginosa* (-)	*B. subtilis* (+)	*S. aureus* (+)
8a	11.49 ± 2.32	12.82 ± 2.16	15.85 ± 1.31	19.17 ± 4.69	-
8b	15.68 ± 1.65	13.19 ± 3.33	-	-	-
8c	11.35 ± 5.00	10.20 ± 1.94	13.17 ± 2.58	15.92 ± 3.17	15.45 ± 1.50
8d	15.02 ± 3.98	16.82 ± 2.23	18.32 ± 1.55	-	15.00 ± 3.21
8e	-	16.81 ± 1.43	18.75 ± 3.23	-	-
8f	10.77 ± 1.88	12.69 ± 2.56	15.62 ± 1.14	-	14.55 ± 2.09
Ciprofloxacin	9.42 ± 1.09	8.02 ± 2.17	8.11 ± 1.32	8.88 ± 2.00	9.23 ± 1.87

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, and data was expressed as MIC

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