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Microwave-assisted Expeditious Synthesis and Anti-microbial Evaluation of Novel Heterocyclic derivatives of Sulfonamides

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ABSTRACT
*An eco-friendly method of synthesis of substituted-1, 3, 4-oxadiazol-2-yl-benzenesulfonamides through reflexion of a mixture of an appropriate (4-aminophenyl)-5-substituted-1,3,4-oxadiazole (**1**), Et_3N, an appropriate sulfonyl chloride (**2**) in CH_3Cl and catalytic amount of DMAP [4-(N, N-dimethyl-amino) pyridine] in neat and solvent-free conditions under microwave irradiation has been developed. The synthesized compounds were characterized by microanalyses, IR and ^1H & ^{13}C NMR spectral studies. These compounds were evaluated for their antimicrobial activity against certain bacteria and fungi and found that all have shown moderate antimicrobial activity.*

Key words: *Heterocyclic sulfonamides, anti-microbial activity, microwave irradiation, Multicomponent reaction.*

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I. INTRODUCTION

The molecular structures of compounds have the significant impact on their biological activity. Heterocyclic compounds have gained greater importance in recent years as they are present in many compounds that exhibit biological activities [1]. The pharmaceutical community has been interested in heterocyclic compounds, particularly those with five and six members, for their therapeutic properties for years. Polyfunctionalized heterocyclic compounds containing nitrogen, sulphur, and oxygen as heteroatoms play important roles in the drug discovery process [2-3]. Heterocyclic sulfonamides have occupied an important place in the drug industry and brought a lot of attention over the several decades because of their wide pharmaceutical and nonpharmaceutical and other uses. Since the usefulness of the exploration of heterocyclic derivatives of sulfonamides, as therapeutic agents, several thousands of substituted derivatives were synthesised and proved to be effective against several pathogenic microorganisms and beneficial in improving various physiological disorders [4].

The development of environmentally friendly goods and procedures for the synthesis of bioactive heterocyclic compounds is being pursued due to concerns about climate change, limited natural resources, human and animal health issues, and other related issues. Microwave irradiation is a potential alternative to the traditional method of synthesizing heterocycles. Microwave irradiation is a clean, efficient, and economical technology [5-8]. It has considerably simplified work up, reduced cost, short reaction time. Due to these advantages, there is an increasing interest in the use of MWI for synthesizing heterocycles [9-11].

As a part of our research projects to synthesize new bioactive compounds [12-14], the present article describes the environmentally benign approach using microwave-promoted expeditious synthesis, characterization, and *in vitro* biological screening of some novel substituted-1, 3, 4-oxadiazol-2-yl-benzenesulfonamides.

II. EXPERIMENTAL

Materials & Methods:

All the chemicals and solvents used in this research project were of analytical grade and were obtained from Sigma Aldrich, and Spectrochem Pvt Ltd. All the investigated compounds were analysed satisfactorily for C, H and N using Carl-Ebra 1106 Elemental Analyser in the micro-analytical laboratory. The Shimadzu UV-Vis-160A spectrophotometer (wavelength 200-1100 nm) was used for obtaining the electronic spectra of the

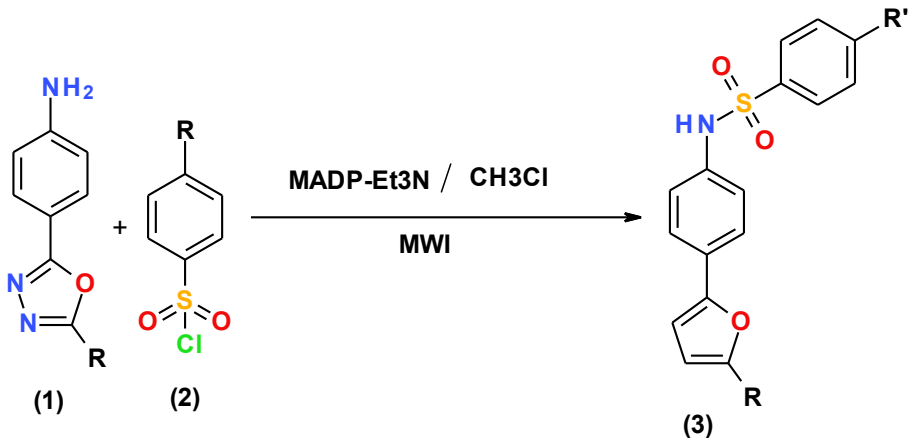
undertaken compounds (in DMSO at 10^{-3} M). The infrared spectra of the synthesized compounds were recorded (using KBr or $CHCl_3$) on Shimadzu 8400-S FT-IR spectrophotometer in the wavelength range of 4000-400 cm^{-1}. The NMR Varian-Mercury 400 MHz spectrometer was used for recording the ^1H NMR & ^{13}C NMR spectra of the compounds in DMSO-d_6 using tetramethyl silane (TMS) as an internal standard. The chemical shift was measured in ppm on the δ scale and the coupling constants were measured in Hertz.

A modified microwave oven model 2001 ETB with rotating tray and a power source 230V, microwave energy output 800 W and microwave frequency 2450 MHz was used for the microwave promoted synthesis of the investigated compounds. The progress of the synthetic reactions was monitored by performing TLC where TLC sheets precoated with UV fluorescent silica gel, Merck 60 F254 that was visualized by UV lamp.

Microwave-Promoted Synthesis of 4-Substituted-N[4-(5-substitutedphenyl)-1,3,4-oxadiazol-2-yl)phenyl] benzene sulfonamides

A mixture of an appropriate (4-aminophenyl)-5-substituted-1,3,4-oxadiazole (**1**), Et_3N, an appropriate sulfonyl chloride (**2**) in CH_3Cl and catalytic amount of DMAP [4-(N, N-dimethyl-amino) pyridine] initially stirred and then mixture was refluxed in a microwave oven for 12-20 minutes. The cooled reaction mixture was washed with dilute HCl, brine and water. The excess solvent was distilled off and the residue was recrystallized from aqueous ethanol (35%). The resultant sulfonamides (**3**) were obtained after drying over anhydrous sodium sulfate and reaction was monitored by TLC (**scheme-1**) and their identification was confirmed by IR, NMR spectra and the melting point.

All the synthesized products are listed in **table-1** and the spectral characterization data for synthesized compounds are presented in **table-2.**



Scheme-1: *Microwave-assisted expeditious synthesis of 4-Substituted-N-[4-(5-ubstitutedphenyl)-1,3,4-oxadiazol-2-yl)phenyl] benzenesulfonamides*

Table-1: Physical and analytical data of the synthesized compounds

Compound	R	R'	MP (in K)	Mol. Formula (Mol. wt.)	Analytical results % Found (calc.)			
					H	C	N	S
I	CH_3	Phenyl	460	$C_{21}H_{17}N_3O_3S$ (391.4 amu)	4.3 (4.4)	64.4 (64.0)	10.7 (10.5)	8.2 (8.3)
III	CH_3	4-Methyl phenyl	467	$C_{22}H_{19}N_3O_3S$ (405.5 amu)	4.7 (4.7)	65.2 (65.0)	10.4 (10.5)	7.9 (8.2)
III	CH_3	4-Methoxy phenyl	471	$C_{22}H_{19}N_3O_4S$ (421.5 amu)	4.5 (4.6)	62.7 (62.8)	9.9 (10.0)	7.6 (7.8)
IV	CH_3	3,4,5-Trimethoxy phenyl	458	$C_{24}H_{23}N_3O_6S$ (481.3 amu)	4.8 (5.0)	59.8 (60.0)	8.7 (8.9)	6.6 (6.8)
V	CH_3	3-Chloro phenyl	451	$C_{21}H_{16}N_3O_3SCl$ (425.9 amu)	3.8 (3.7)	59.2 (59.4)	9.8 (9.9)	7.5 (7.7)
VI	CH_3	4-Chloro phenyl	460	$C_{21}H_{16}N_3O_3SCl$ (425.9 amu)	3.8 (3.7)	59.2 (59.4)	9.8 (9.9)	7.5 (7.7)
VII	CH_3	2-Bromo phenyl	441	$C_{21}H_{16}N_3O_3SBr$ (470.3 amu)	3.4 (3.5)	56.6 (56.5)	8.9 (9.0)	6.8 (6.9)

In comparison to the common conventional method, the microwave-promoted synthetic approach requires short time and produced better yield (about 65-76%) of the product. The reaction completion time of the product using conventional method and green chemical approach are presented in **table-3** for comparison.

Table-2: Spectral characterization data of synthesized compounds

Compound	IR Bands {KBr, cm^{-1}}	^{1}H-NMR (DMSO-d_6) {δ-ppm}	^{13}C-NMR {δ-ppm}	UV (λ_{max} CH_3OH, nm)
I	3285(NH), 3089 (CH-Ar), 1605 (C=N), 1372, 1157 (SO_2).	2.37(s,3H, NH_3); 7.12 (d, J = 8.0Hz, 2H, ArH); 7.52-7.66 (m, 7H, ArH); 7.78 (d, J = 8.0 Hz, 2H, ArH); 7.91 (d, J = 8.2 Hz, 2H, ArH); 10.56 {s-(br), 1H, NH}	21.1, 119.2, 124.4, 124.8, 126.0, 127.2, 127.4, 128.2, 129.0, 131.5, 135.2, 135.7, 136.1, 141.8, 163.0, 164.1	298 236
II	3265 (NH); 1590 (C=N); 1380, 1150 (SO_2)	2.44 (s,3H, CH_3-Ar), 2.84 (s, 3H, CH_3-Ar), 7.25 (d, 2H, J = 8.1Hz, ArH), 7.43 (d, 2H, J = 8.1 Hz, ArH); 7.49 (d, 2H, J = 8.1 Hz, ArH); 7.81 (d, 2H, J = 8.1 Hz, ArH); 8.06 (d, 2H, J = 7.9 Hz, ArH); 8.20 (d, 2H, J = 7.9 Hz, ArH); 10.54{s(br), 1H, NH}	119.4, 120.2, 124.3, 124.9, 126.0, 126.8, 127.2, 128.2, 128.8, 131.6, 135.2, 136.4, 142.0, 162.8, 164.5	299 233
III	3298 (NH); 1598 (C=N); 1377, 1165 (SO_2)	2.45 (s,3H, CH_3-Ar); 3.91 (s, 3H, OCH3); 5.75 (s, 1H =, NH); 7.25 (d, J = 8.0 Hz, 2H, ArH); 7.42 (s, 2H, ArH); 7.50 (d, J = 8.0 Hz, 2H, ArH); 7.86 (d, J = 8.1 Hz, 2H, ArH); 8.16 (d, J = 8.1 Hz, 2H, ArH); 8.23 (d, J = 8.1 Hz, 2H, ArH); 10.84{s(br), 1H, NH}	115.12, 115.84, 122.37, 122.69. 127.26, 128.47, 129.40, 129.63, 135.99, 136.49, 144.00, 157.87, 164.61, 164.73,	292 236
IV	3266 (NH) 1587 (C=N); 1351, 1162 (SO_2)	2.50 (s,3H, CH_3-Ar); 3.88 (s, 6H, OCH_3); 3.90 (s, 3H, OCH_3); 7.31 (d, J = 8.1Hz, 2H, ArH); 7.51-7.66 (m, 4H, ArH); 7.78 (d, J = 8.1Hz, 2H, ArH); 8.10 (d, J = 8.0Hz, 2H, ArH); 10.91{s(br), 1H, NH}	26.4, 65.5, 109.4, 123.5, 130.3, 133.2, 133.4, 135.3, 140.7, 1416, 145.6, 150.9, 158.7, 168.9	359 239
V	3289 (NH); 3065(Ar-CH); 1592 (C=N); 1379, 1159 (SO_2)	2.49 (s,3H, Ar-CH_3); 7.34 (d, J = 7.5Hz, 4H, ArH); 7.79 (d, J = 7.9Hz, 2H, ArH); 7.91-8.05 (m, 6H, ArH); 10.89{s(br), 1H, NH}	21.7, 121.4, 125.9, 128.1, 131.9, 132.5, 138.5, 142.9, 163.2, 164.7,	291 235
VI	3266 (NH); 3091 (Ar-CH); 1592 (C=N); 1375, 1166 (SO_2)	2.48 (s, 3H, CH_3) 7.32(d, J = 8.1 Hz, 2H ArH) 7.76(d, J = 8.1 Hz, 2H ArH) 7.79(d, J = 8.1 Hz, 2H ArH) 7.81-7.90 (m, 4H, Ar-H) 11.14 {s (br), 1H, NH} 8.13 (d, J = 8.1 Hz, 2H, ArH).	21.0, 123.0, 127.1, 127.2, 128.8, 129.2, 131.5, 131.8, 135.7, 136.9, 162.7, 165.5	293 237
VII	3286 (NH); 3061 (Ar-CH); 1582 (C=N); 1341, 1157 (SO_2)	2.38 (s, 3H, CH_3) 6.98(d, J = 8.0 Hz, 2H ArH) 7.32(d, J = 8.4 Hz, 2H ArH) 7.79(d, J = 8.4 Hz, 2H ArH) 7.72-7.55 (m, 5H, Ar-H) 10.82 {s (br), 1H, NH} 8.11 (d, J = 8.0 Hz, 1H, ArH).	21.55, 118.75, 122.37, 122.84, 126.61, 127.26, 128.19, 129.40, 129.63, 130.30, 130.66, 132.55, 135.99, 136.49, 144.00, 164.33, 164.61	288 233

Table-3: Comparative results of conventional and Microwave methods of the investigated Compounds (I-VII)

Compounds	Period of synthesis		Percentage yield (%)	
	CM	MWI	CM	MWI
I	6 hrs.	12 min.	58	73
II	7 hrs.	15 min.	61	72
III	6 hrs.	13 min.	54	69
IV	5 hrs.	11 min.	53	68
V	7 hrs.	14 min.	57	72
VI	8 hrs.	15 min.	45	65
VII	5hrs.	7 min.	62	76

CM =Conventional Method; MWI = Microwave irradiation

Antimicrobial activity: Zone of Inhibition & Minimum Inhibitory Concentration (MIC)

The newly green synthesized heterocyclic compounds 1,3,4-oxadaizle sulfonamides, were tested for the following activities:

A. Anti-Fungal Activity and
B. Anti-Bacterial Activity

The antimicrobial activities (anti-bacterial & anti-fungal) of the newly green synthesized heterocyclic compounds 1,3,4-oxadaizle sulfonamides were investigated using the agar cup-plate method [15-16]. The antibacterial screening was performed for two gram-positive bacteria (*S. aureus* & *S. pyogenes*) and one gram-negative bacteria (*E. coli*.) using nutrient agar broth as test media and antifungal screening was done against two fungi (*A. niger* & *C. albicans*) using the potato dextrose agar as test media. Chloramphenicol and Nystatin were used as references for antibacterial and antifungal activities respectively. The experimental observations/results are presented in table-4.

Table-4: *Average zone of inhibition against tested microorganisms*

Compound		**Zone of inhibition in mm (SEM)**				
		Gram-positive bacteria		**Gram-negative bacteria**	**Fungi**	
	Concentration (µg/10µl)	***S. aureus***	***S. pyogenes***	***E. coli***	***A. niger***	***C. albicans***
Chloramphenicol	30	10	12	12	-	-
Nystatin	30	-	-	-	12	10
I	50	9	10	7	24	34
	100	16	15	13	30	42
II	50	7	10	8	25	36
	100	14	18	15	29	45
III	50	11	12	8	25	37
	100	19	21	15	38	44
IV	50	10	9	7	24	31
	100	15	16	12	32	43
V	50	8	10	7	17	18
	100	14	18	13	25	30
VI	50	11	12	8	18	24
	100	19	20	17	26	37
VII	50	10	9	7	19	16
	100	18	16	15	22	26

III. RESULTS & DISCUSSION

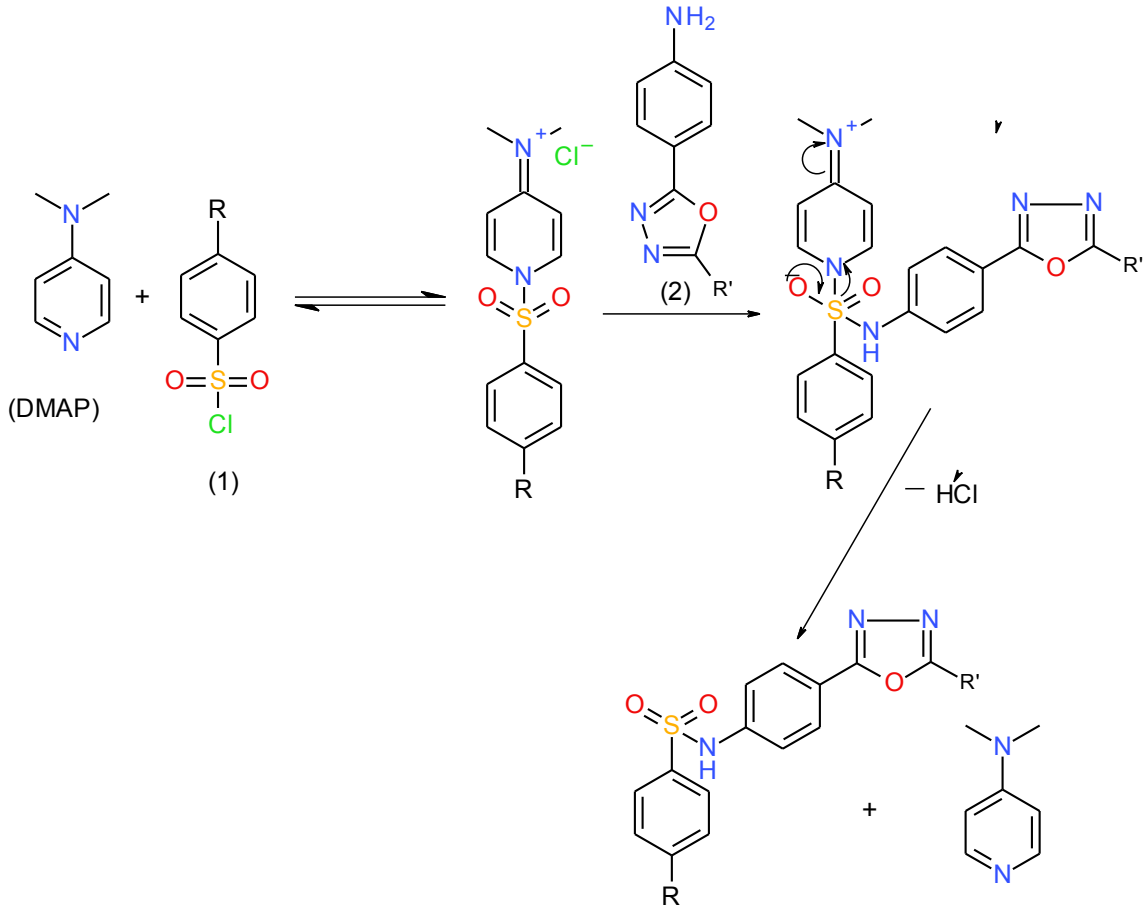
Multicomponent reactions (MCRs) are an advanced class of organic reactions which allow for the easy, fast, and efficient synthesis of chemical diversity in just one assembly step [17-19]. We followed the principle of MCRs for the synthesis of a series of new bioactive substituted-1,3,4-oxadaizle sulfonamides of pharmaceutical interest were synthesized by applying eco-friendly microwave-assisted synthetic approach by reflexion of appropriate (4-aminophenyl)-5-substituted-1,3,4-oxadiazole (**1**), Et_3N, an appropriate sulfonyl chloride (**2**) in CH_3Cl and catalytic amount of DMAP [4-(N, N-dimethyl-amino) pyridine] catalyst [20] in clean and green conditions. This procedure accomplished with excellent yield in the shortest period in compare to the conventional methods.

The literature survey established that the catalytic efficiency of DMAP [4-(N,N-dimethyl-amino)pyridine] is due to the substituted pyridinium ion, steric effects, the donor ability of the amine substituents, and good nucleophilic character of DMAP additionally affect the reactivity of DMAP. The proposed mechanism of the catalytic efficiency of DMAP is being presented here in sufonylation reactions (scheme-2). Since the used catalyst (DMAP) was recycled by simple filtration and may be used repeatedly. That is why this catalyst is known as green catalyst. Thus, the present synthesis complies with the principle of environmentally benign or sustainable or green chemistry.

TLC was used to monitor the overall progress of the synthetic reaction and the synthesized compounds were characterized by their IR & NMR spectral analyses. The formation of products, I-VII was confirmed using both ^{1}H NMR & ^{13}C NMR spectroscopy.

In the IR spectra of the investigated compounds, the characteristic NH absorption was observed between 3317-3112 cm^{-1}. The sulfonamide group showed characteristic absorption bands between 1376-1351 cm^{-1} which were assigned to SO_2 group.

The ^{1}H NMR spectra of the compounds exhibited a broad singlet at 11.21-10.51 ppm attributed to NH of the sulfonyl group. The ^{13}C NMR spectra of the compounds showed characteristics signals of C_2 and C_5 of the oxadiazole unit between 169-159 ppm along with the C atoms of the phenyl rings in the usual range [21] .



Scheme-2: *Proposed mechanism on catalytic efficiency of DMAP in sulfonylation reaction*

The results of the assessment of the antibacterial and antifungal activity were based on measurement of the diameter of inhibition zone formed around the well and show that the zone of inhibition increased with the increasing of concentration of the tested compounds as shown in table-4. From the results, at concentration 50/100µg/ml, all the investigated compounds showed less activity against gram positive bacterium (*Staphylococcus aureus),* and (*Streptococcus pyogenes*). But all tested compounds showed moderate to good activity against gram negative bacteria (*E. coli)*. Furthermore, the results revealed that all the tested compounds showed significant activity against all type of fungi tested in all the concentrations used in comparable to the standard (Nystatin). At concentration 20/50µg/ml, all compounds showed moderate to good activity against (*Aspergillus niger)* while all showed low to moderate activity against (*Candida albicans*).

IV. CONCLUSIONS

An easy, efficient, clean, and environmentally benign method for the synthesis of seven bioactive substituted-1,3,4-oxadaizle sulfonamides from various synthons through multicomponent reaction under microwave irradiation with excellent yields and high purity of the desired products has been developed. The results were compared with conventional methods for their yields and reaction time. The synthesized compounds were characterised by the micro-analytical elemental method, IR, and NMR (^{1}H & ^{13}C) spectral analysis. All the synthesized compounds were evaluated for their antibacterial and antifungal activities and it was found that all were active and comparatively efficient.

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