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Synthesis, characterization and biological activities of 2,5-disubstituted 1,3,4–oxadiazoles

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ABSTRACT

*A series of 2,5–disubstituted 1,3,4-oxadiazoles **5a-k** have been synthesized by the condensation of p-phenyl sulphonyl benzohydrazide with various aromatic acids in the presence of phosphorous oxy chloride. The structure of compounds was analyzed by IR, H^1 NMR and mass spectral data. The compounds **5a-k** were screened for antibacterial activity against Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pyogene and antifungal activity against Aspergillus Niger, Helminthosporium oryzae using disc diffusion method. Some of the compounds showed prominent activity against bacteria and fungi.*

Key Words: 1,3,4-oxadiazole, antibacterial activity, antifungal activity.

INTRODUCTION

Five membered heterocyclic compounds possess interesting biological activity. Among them the compounds bearing 1,3,4-oxadiazole nucleus have wide applications in medicinal chemistry. These compounds also have been reported to have significant anti-inflammatory [1], antifungal [2], antibacterial [3], antiviral [4], and anticancer [5] activities. Heterocyclic compounds like fluconazole [6, 7], itraconazole [8], ravuconazole [9], voriconazole [10, 11] and posaconazole [12], were used as therapeutically important medicines. The biological studies on sulphones indicate that they can be used in chemotherapy and agriculture, Ex: sulphones like chlorothiazide and hydrochlorothiazide were used as diuretics. Sulphonal, trional and tetranal were used as sedatives and hypnotics. Dapsone [13] was used as potential drug against leprosy and it is also proved to be a potent prophylactic agent.

Bis (p-aminophenyl) sulphone is having chemotherapeutic activity & high anti-bacterial activity, its activity is hundred times as active as sulphonilamide. The N, N′-diacetyl and N,N′-digalactoside derivatives of bis (p-aminophenyl) sulphones have been found to be useful as

therapeutic agents, similar to the sulphonamides. Promine, [sodium bis (p-aminophenyl) sulphones- N′, N′- bis (glucosesulphonate)], diazone [disodium formaldehyde sulphonate bis (p-aminophenyl) sulphone] were found to be effective tuberculostatic agents.

Based on these observations the present study reports the synthesis of a series of 2, 5-disubstituted 1, 3, 4-oxadiazole and their antibacterial and antifungal activities.

MATERIALS AND METHODS

Melting points were determined on mel temp apparatus in open capillary method and were uncorrected. The IR spectra were recorded using potassium bromide on a Perkin Elmer-FTIR spectrum 100 spectrophotometer. Proton NMR spectra were recorded on Bruker spectrophometer (400 MHz) in dueterated chloroform using TMS as internal standard. Mass spectra were recorded on LC-MSD Trap-SL 2010A-Shimadzu. The starting compounds Phenyl p-tolyl sulfone(**1**), p-phenyl sulfonyl benzoic acid (**2**), methyl p-phenyl sulfonyl benzoate (**3**) and p-phenyl sulfonyl benzohydrazide (**4**) were prepared by the known procedures.

Synthesis of Phenyl p-tolyl Sulfone (1)

In a 100 ml round bottomed flask 10 gm of P-toluene sulphonyl chloride (0.05mole), 10 ml of benzene (0.1 mole) were added and 10.45 gm aluminum chloride (0.0786 mole) is added in small portions and the contents of the flask were refluxed on water bath, stirred for 3hrs at temperature of 70^0c. The completion of the reaction was monitored on silica gel G coated T L C plates using ethyl acetate and petroleum ether (1:1) as an eluent and observed under U V light.

After 3 hrs the mixture, is cooled to low temperature by cooling in ice and slowly added to a mixture of 10 ml of Con. HCl and 30 gm of ice contained in a beaker. After one day the mixture is thoroughly washed with water and hot water for 10 to 15 times, The crystals were separated, washed with little water and extracted with ether and ether is evaporated to get crystals. This was recrystallised in ethanol.

Yield: 85%, M.P: 124-126 ^{0}C. FTIR (KBr): 3064.27 (Ar-H str), 1308.14 (SO_2 Asym str), 1157.86 (SO_2 Sym str), 687.40(C-S-C str); ^{1}H NMR (DMSO) : δ 7.3-7.90 (m, 9H, Ar C-H), 2.35 (s, 3H, -CH_3). MS (m/z%) : 232.06 (M^+), 233.06 (M^++1).

Synthesis of p-phenyl sulfonyl benzoic acid (2)

5gm of Phenyl P-tolyl sulphone (0.02155 mole) and tert butyl alcohol (10 ml) are warmed to 80 ^{0}C, then a solution of potassium permanganate(4 gm) in water (10ml), pre warmed to 80^0c, is added at such a rate that the mixture boils continuously. The permanganate solution is added in portions of 10 ml from a dropping funnel, then the mixture is boiled for a further 15 mts after which the manganese oxides are filtered from the hot mixture. These are well washed with water and the filtrate is evaporated in a vaccum, the solution potassium salt of carboxylic acid obtained is acidified at 60 ^{0}C by con. HCl and then cooled to 20^0C. solid separated is collected, recrystallized from alcohol.

Yield: 90, M.P: 277-279 ^{0}C. FTIR (KBr): 3366.02 (O-H str), 3064.85 (ArC-Hstr), 1694.21(C=O str), 1399.12(SO_2 Asym str), 1159.60 (SO_2 Sym str), 684.62 (C-S-C str).

^{1}H NMR (DMSO): δ7.3-8.30 (m, 9H, Ar C-H), 11.0 (s, 1H, -OH). MS(m/z%): 262.03(M^+), 263.03 (M^++1).

Synthesis of methyl p-phenyl sulfonyl benzoate (3)

In a 50 ml round bottomed flask a mixture of 10 gm p-phenyl sulfonyl benzoic acid **2** (0.037 mole), 50 ml methanol and 3 ml of con. sulphuric acid were refluxed on steam bath for 8-10 hrs. The completion of the reaction was monitored on silica gel G coated T L C plates using ethyl acetate and petroleum ether (1:1) as an eluent and observed under U V light. The contents of the flask were cooled, evaporated and solid product was obtained. The product is taken in a separating funnel and extracted with ether, the ethereal solution was washed with sodium hydrogen carbonate solution until effervescence ceases, then with water, the aqueous layer was removed and ethereal solution was dried over sodium sulphate, evaporated to get solid product, recrystallized from ethanol.

Yield: 90%, M.P: 147-149 ^{0}C. FTIR (KBr): 3094.47 (Ar C-H str), 1726.50(C=O str), 1324.94 (SO_2 Asym str), 1157.98 (SO_2 Sym str), 686.32 (C-S-Cstr); ^{1}H NMR (DMSO): δ 7.3-8.14 (m, 9H,Ar C-H), 3.88 (s, 3H, -CH_3). MS (m/z%): 276.05 (M^+), 277.05 (M^+ +1).

Synthesis of p-phenyl sulfonyl benzohydrazide (4)

A mixture of 5 gm ester **3** (0.01 mole) and 1 ml hydrazine hydrate (0.02 mole) in ethanol was heated under reflux for 6 hrs. The completion of the reaction was monitored on silica gel G coated T L C plates using ethyl acetate and petroleum ether (1:1) as an eluent and observed under U V light. The reaction mixture was cooled and the solid separated was collected by filtration, dried over sodium sulphate and recrystallized from methanol.

Yield: 57%, M.P: 204-205 ^{0}C. FTIR(KBr) : 3345.76 (NH2), 3284.20 (NH), 3064.85 (Ar C-H str),1671.72(C=O str), 1308.48 (SO_2 Asym str), 1156.45 (SO_2 Sym str), 685.41 (C-S-C str). ^{1}H NMR (DMSO)**:** δ 7.3-8.12 (m, 9H, Ar C-H), 8.0(s, 1H, -CONH), 2.0 (s, 2H, -NH_2). MS(m/z%): 248.05 (M^+), 249.05 (M^++1).

General method for the synthesis of 2, 5 –disubstituted 1,3,4-oxadiazoles 5a-k

An equimolar mixture of compound **4** and appropriate aromatic acids in 10 ml of phosphorous oxy chloride was heated under reflux for 5-6 hrs. The excess phosphorous oxy chloride was removed under reduced pressure and the residue was poured on to crushed ice. The resulting precipitate was filtered, washed with saturated sodium bicarbonate solution and then with water, dried, recrystallized from ethanol.

Synthesis of 2- (4-nitrophenyl-5-(4- phenylsulphonyl phenyl) 1,3,4-oxadiazole 5a

Yield: 80%, M.P: 260-263 ^{0}C. FTIR(KBr) : 3070.36 (Ar C-H str), 1603.14 (C=N str), 1071.93 (C-O-C str), 687.75(C-S-C str), 1542.63 (NO_2 Asym str), 1406.92 (NO_2 Sym str), 1341.17 (SO_2 Asym str), 1160.36 (SO_2 Sym str). ^{1}H NMR (DMSO): δ 7.03-8.49 (m, 13H,Ar C-H). MS (m/z%): 408.03 (M^+ +1).

Synthesis of 2-(3,4-dinitrophenyl)-5-(4-phenylsulphonyl phenyl)1,3,4-oxadiazole 5b

Yield: 85%, M.P: 220-224 ^{0}C. FTIR(KBR) : 3095.88 (Ar C-H str), 1597.77 (C=N str), 1011.92 (C-O-C str), 685.41 (C-S-C str), 1538.10 (NO_2 Asym str), 1406.92 (NO_2 Sym str),

1345.73 (SO_2 Asym str), 1160.88 (SO_2 Sym str). ^{1}H NMR (DMSO): δ 7.65-9.32 (m, 12H, Ar C-H). MS (m/z%) : 453.02 (M^+ +1).

Synthesis of 2-(2-mercaptophenyl)-5-(4-phenylsulphonyl phenyl) 1,3,4-oxadiazole 5c

Yield: 87%, M.P: 96-99 ^{0}C. FTIR (KBr): 3092.32 (Ar C-H str), 1666.51 (C=N str), 1071.02 (C-O-C str), 687.20 (C-S-C str), 1320.38 (SO_2 Asym str), 1105.86 (SO_2 Sym str). ^{1}H NMR (DMSO): δ 6.95-8.33 (m, 13H, ArC-H), 5.00 (s, 1H, Ar-OH). MS (m/z%): 394.47(M^+).

Synthesis of 2-(4-methoxyphenyl-5-(4-phenylsulphonyl phenyl) 1,3,4-oxadiazole 5d

Yield: 78%, M.P: 217-219 ^{0}C. FTIR (KBr) : 3066.30 (Ar C-H str), 1611.35(C=N str), 1079.47 (C-O-C str), 685.75 (C-S-C str), 1320.19 (SO_2 Asym str), 1109.22 (SO_2 Sym str). ^{1}H NMR (DMSO): δ 7.17-8.34 (m, 13H, ArC-H), 3.87 (s,3H,-CH_3). MS (m/z%): 393.02 (M^+ +1).

Synthesis of 2-benzyl- 5-(4-phenylsulphonyl phenyl) 1,3,4-oxadiazole 5e

Yield: 88%, M.P: 80-83 ^{0}C. FTIR(KBr): 3029.66(Ar C-H str), 1645.20(C=N str), 651.76 (C-S-C str), 1156.66(SO_2 Sym str). ^{1}H NMR (DMSO): δ 7.21-8.15 (m, 14H, ArC-H), 3.53(s, 2H, -CH_2). MS (m/z%) : 376.04 (M^+).

Synthesis of 2-phenyl- 5-(4-phenylsulphonyl phenyl) 1,3,4-oxadiazole 5f

Yield: 9o%, M.P: 136-139 ^{0}C. FTIR(KBR) : 3061.43 (Ar C-H str), 1606.72(C=N str), 1069.98(C-O-C str), 688.25(C-S-C str), 1321.52(SO_2 Asym str), 1157.34(SO_2 Sym str). ^{1}H NMR (DMSO): δ 7.41-8.36(m, 14H, ArC-H). MS (m/z%) : 363.03 (M^+ +1).

Synthesis of 2-styryl- 5-(4-phenylsulphonyl phenyl) 1,3,4-oxadiazole 5g

Yield: 78%, M.P: 76-79 ^{0}C. FTIR (KBr) : 3037.62 (Ar C-H str), 1606.19 (C=N str), 1050.55 (C-O-C str), 1354.55 (SO_2 Asym str), 1174.09 (SO_2 Sym str), 661.56 (C-S-C str). ^{1}H NMR (DMSO): δ 7.32-8.36 (m, 14H, Ar C-H, 2H, =C-H). MS (m/z%): 389.03(M^+ +1).

Synthesis of 2-(4-methoxybenzyl)-5-(4-phenylsulphonyl phenyl) 1,3,4-oxadiazole 5h

Yield: 80%, M.P: 287-290 ^{0}C. FTIR (KBR): 3092.32(Ar C-H str), 1608.31(C=N str), 1016.73(C-O-C str), 687.67(C-S-C str), 1291.16(SO_2 Asym str), 1106.26(SO_2 Sym str). ^{1}H NMR (DMSO): δ 7.26-8.29 (m, 13H, ArC-H), 3.73(s, 3H, -CH_3), 3.81(s, 2H, -CH_2). MS (m/z%): 407.10 (M^+ +1).

Synthesis of 2-(2,5-dichloro phenoxy methyl)-5-(4-phenylsulphonyl phenyl) 1,3,4 oxadiazole 5i

Yield: 85%, M.P: 98-102 ^{0}C. FTIR (KBR): 3065.08 (Ar C-H str), 1631.65(C=N str), 1070.67 (C-O-C str), 687.09 (C-S-C str), 1307.48 (SO_2 Asym str), 1105.97 (SO_2 Sym str). ^{1}H NMR (DMSO): δ 7.34-8.29 (m, 12H, ArC-H), 5.20(s, 2H, -CH_2). MS (m/z%) : 461.97(M^++1).

Synthesis of 2-(2-hydroxy phenyl)-5-(4-phenylsulphonyl phenyl) 1,3,4-oxadiazole 5j

Yield: 75%, M.P: 64-66 ^{0}C. FTIR (KBr): 3400.73 (O-H str), 3064.19 (Ar C-H str), 1600.09(C=N str), 1069.27 (C-O-C str), 687.40 (C-S-C str), 1308.69 (SO_2 Asym str), 1160.72 (SO_2 Sym str). ^{1}H NMR (DMSO): δ 7.02-8.36 (m, 13H, ArC-H), 4.30 (s, 1H, Ar-OH). MS (m/z%): 378.07 (M^+).

Synthesis of 2-(1-phenyl-1-hydroxymethyl)-5-(4-phenylsulphonyl phenyl) 1,3,4-oxadiazole 5k

Yield: 80%, M.P: 289-292 ^{0}C. FTIR (KBR): 3430.42 (O-H str), 3061.80 (Ar C-H str), 1660.05 (C=N str), 1071.14 (C-O-C str), 686.05 (C-S-C str), 1320.43 (SO_2 Asym str), 1156.73(SO_2 Sym str).^{1}H NMR (DMSO): δ 7.26-8.29 (m, 14H, ArC-H), 3.48 (s,1H,-CH), 2.39 (s,1H,-OH). MS (m/z%): 392.08 (M^+).

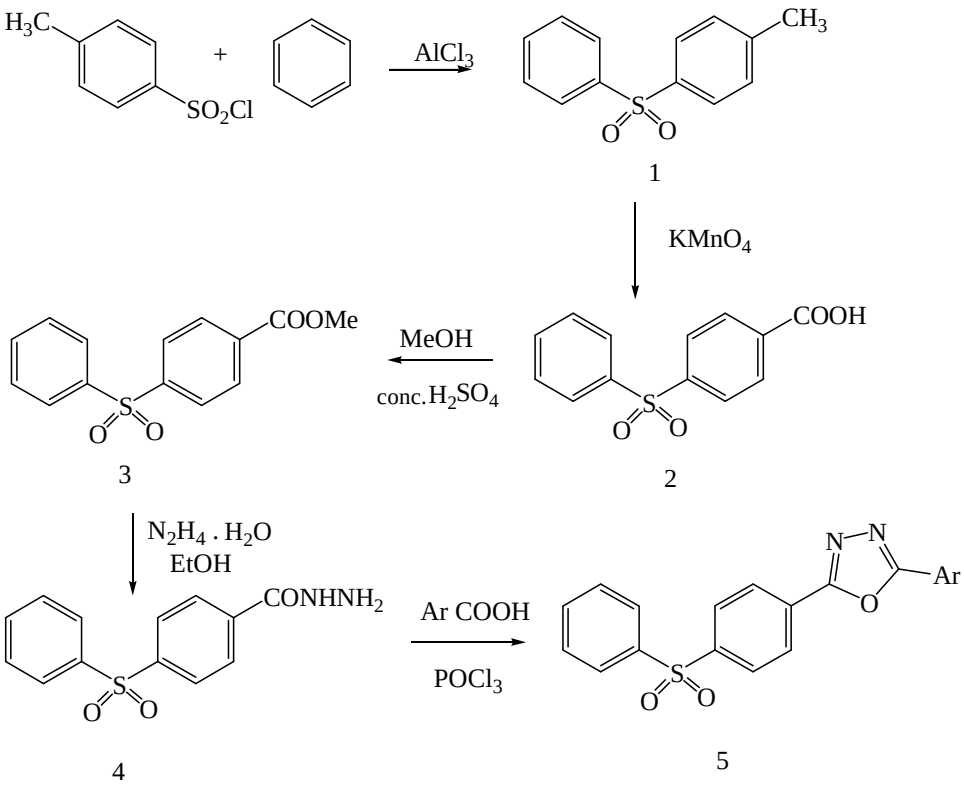
RESULTS AND DISCUSSION

Compounds were synthesized as per the Scheme-1. Phenyl P-tolyl sulphone (1) prepared from p-toluene sulphonyl chloride with benzene by friedel-crafts reaction in presence of aluminium chloride. Phenyl p-tolyl sulphone (**1**) on oxidation with potassium permanganate gave Phenyl sulphonyl benzoic acid (**2**). This on esterification with methanol in presence of conc. H_2SO_4 followed by reaction with hydrazine hydrate resulted P-Phenyl sulphonyl Benzoate (**3**) and p-phenyl sulphonyl benzohydrazide (**4**) respectively. The acid hydrazide 4 on condensation with various aromatic acids 4-nitrobenzoicacid, 3,4-dinitrobenzoicacid, thiosalicylicacid, p-anisicacid, phenylaceticacid, benzoicacid, cinnamicacid, 4-methoxyphenylaceticacid, 2,5-dichlorophenoxyaceticacid, salicylicacid, mandelicacid in the presence of phosphorus oxy chloride yielded 2, 5-disubstituted 1, 3, 4-oxadiazoles **5a-k**. The structures of the synthesized compounds were confirmed by their IR, NMR and Mass spectral analysis.

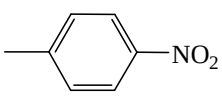
The IR spectra of oxadiazole 5a exhibited intense bands at 1603 and 1072 cm^{-1} conforming the presence of C=N & C-O-C groups respectively. ^{1}H NMR showed multiplets corresponding to Ar C-H grouping, conforming the structure of the oxadiazole **5a**. Similarly, oxadiazoles **5b-k** were conformed.

Table-1

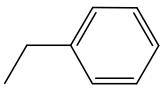
Compound No.	Zone of Inhibition (mm)			
	Escherichia coli	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Streptococcus pyogene*
5a	11	12	13	11
5b	12	15	12	12
5c	14	13	13	17
5d	14	16	17	16
5e	13	15	15	16
5f	13	12	15	12
5g	12	13	13	11
5h	13	12	14	13
5i	14	12	11	11
5j	14	13	14	15
5k	12	13	14	11
Ciprofloxacin	17	21	21	23



A r =



5a



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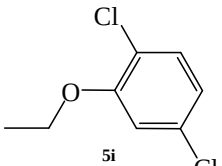

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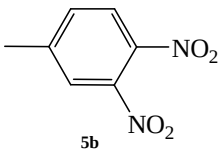
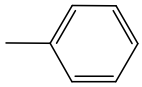


5b



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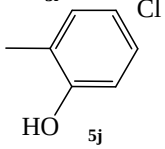

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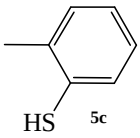
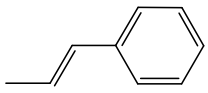
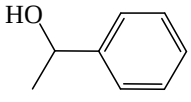


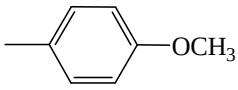
5c



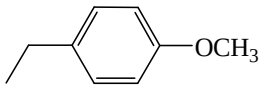
5g



5k



5d



5h

Scheme-1

Table-2

Compound No.	Zone of Inhibition (mm)	
	Aspergillus niger	*Helminthosporium oryzae*
5a	13	11
5b	12	11
5c	-	-
5d	12	09
5e	08	08
5f	09	11
5g	09	10
5h	12	12
4i	10	11
5j	11	07
5k	09	08
Griseofulvin	15	14

Biological activity

The compounds 5a-k were screened for antibacterial activity against Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pyogene and antifungal activity against two organisms viz. Aspergillus Niger and Helminthosporium oryzae in dimethyl sulfoxide (DMSO) using disc diffusion method, the results are represented in Table-1 and 2. The compounds 5c, 5d, 5e, 5f and 5j were effective towards antibacterial activity, the compounds 5c,5e,5j was more effective towards Streptococcus pyogene, and the compounds 5d,5f was more effective towards Staphylococcus aureus.

The compounds 5a, 5b, 5d, 5f, 5h and 5i were effective towards antifungal activity, the compounds 5a, 5b, 5d were more effective towards Aspergillus Niger, and the compounds 5f, 5h, 5i were more effective towards Helminthosporium oryzae.

CONCLUSION

Some new disubstituted 1,3,4-oxadiazoles have been synthesized from p-phenyl sulfonyl benzohydrazide (**4**). The Structures of these compounds were determined from IR, NMR and Mass spectral data. The antibacterial and antifungal activities of synthesized compounds, compared with those of the standard reference compound were investigated using different micro-organisms**.** The compounds having benzyl group and electron donating substituents showed enhanced activity.

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