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Synthesis, characterization and antioxidant activity of some 1,3,4-oxadiazoles carrying 4-(methylsulfonyl)benzyl moiety

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ABSTRACTS

*A series of new 2-[4-(alkylsulfonyl) benzyl]-5-substituted-1,3,4-oxadiazole **(6a-l)** have been synthesized from 4-(alkyl thio) phenyl actetonitrile (**1**) through a multi step reaction sequence. The structures of new compounds were established on the basis of their elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. All the synthesized compounds were screened for their antioxidant activity.*

Key words 1,3,4-Oxadaiazoles, antioxidant activity.

INTRODUCTION

In the family of heterocyclic compounds, nitrogen containing heterocycles with an oxygen atom are considered to be an important class of compounds in medicinal chemistry because of their interesting diversified biological application. During the past few years, considerable evidence has been accumulated that demonstrates the efficacy of 1,3,4-oxadiazoles. The substituted oxadiazoles serve both as biomimetic and reactive pharamacophores and many are key elements with potential biological activities [1-3] such as antitubercular [4], antimalarial [5], insecticidal [6], antiperipheral vasomotility [7], CNS stimulant, antiinflammatory [8], hypotensive [9], insecticidal [10], bactericidal [11], hypoglycemic [12], anticonvulsive[13], analgesic [14], muscle relaxant [15,16], herbicidal [17] and fungicidal activity [18], anti-cancer[19].

MATERIALS AND METHODS

Melting points were determined by the open capillary method and are uncorrected. The IR

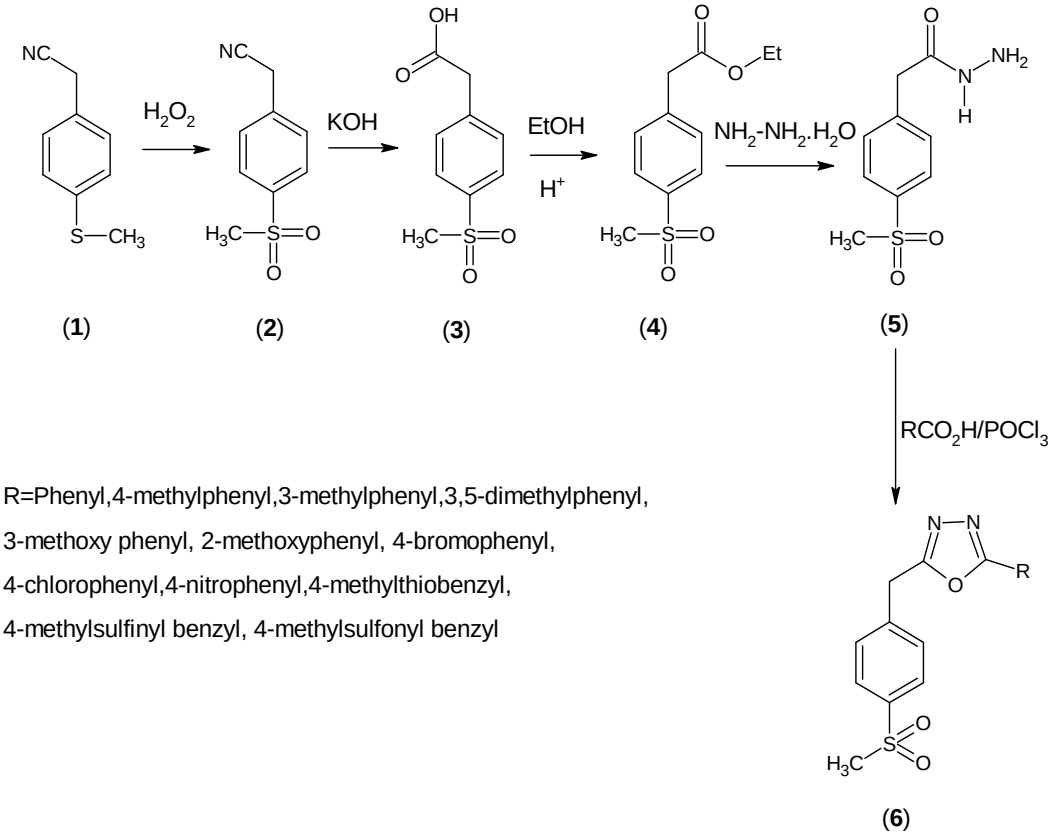
spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 4100 type A spectrophotometer. ^{1}H NMR and ^{13}C spectra were recorded on a Varian 400 MHz NMR spectrometer/Perkin-Elmer EM300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on a MDS SCIEX/API 4000 spectrophotometer. Elemental analyses were carried out using Flash EA 1112 Series, CHNSO Analyzer (Thermo). The progress of the reaction was monitored by thin layer chromatography (TLC) on pre-coated silica gel G plates.

Materials

All the reagents and solvents are from spectrochem and Aldrich and they were used as received without further purification.

Experimental methods

The reaction sequences employed for the synthesis of title compounds is shown in **Scheme I**. The 4-methyl thio phenyl acetonitril (**1**) is oxidized to 4-(methyl sulfonyl) phenyl acetonitril (**2**). This on hydrolysis (**3**) followed by esterification (**4**) and treatment with hydrazine hydrate gave acid hydrazides (**5**). The reaction of the acid hydrazide with various aromatic carboxylic acids in presence of phosphorous oxychloride afforded the title compounds 2-[4-(methylsulfonyl) benzyl]-5-substituted-1,3,4-oxadiazoles (**6a-l**). All the compounds were characterized by analytical and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR and Mass) data. The characterization data of the newly synthesized compounds are given in **Table I**.



Scheme I Formation of 1,3,4-oxadiazole

Table I Characterization data of 1,3,4-oxadiazoles (6a-l)

Comp	R	Mol Formula	Mol wt	M.P (°C)	Yield (%)	Elemental analysis % Calculated (found)		
						C	H	N
6a	C_6H_5	$C_{16}H_{14}N_2O_3S$	314.35	179-180	83	61.13 (61.15)	4.49 (4.45)	8.91 (8.9)
6b	4-CH_3-C_6H_4	$C_{17}H_{16}N_2O_3S$	328.38	126-128	82	62.18 (62.15)	4.91 (4.88)	8.53 (8.5)
6c	3-CH_3-C_6H_4	$C_{17}H_{16}N_2O_3S$	328.38	109-110	80	62.18 (62.15)	4.91 (4.88)	8.53 (8.5)
6d	3,5-$(CH_3)_2$-C_6H_3	$C_{18}H_{18}N_2O_3S$	342.41	158-160	89	63.14 (63.1)	5.3 (5.28)	8.18 (8.15)
6e	3-OCH_3-C_6H_4	$C_{17}H_{16}N_2O_4S$	344.38	114-115	78	59.29 (59.27)	4.68 (4.66)	8.13 (8.1)
6f	2-OCH_3-C_6H_4	$C_{17}H_{16}N_2O_4S$	344.38	112-113	78	59.29 (59.26)	4.68 (4.65)	8.13 (8.11)
6g	4-Br-C_6H_4	$C_{16}H_{13}BrN_2O_3S$	393.25	158-160	86	48.87 (48.88)	3.33 (3.33)	7.12 (7.10)
6h	4-Cl-C_6H_4	$C16H_{13}ClN2O3S$	348.8	123-126	85	55.09 (55.05)	3.76 (3.77)	11.69 (11.7)
6i	4-NO_2-C_6H_4	$C_{16}H_{13}N_3O_5S$	359.36	168-170	80	53.48 (53.44)	3.65 (3.63)	11.69 (11.69)
6j	4-S-CH_3-C_6H_4-CH_2-	$C_{24}H_{22}N_2O_3S$	450.57	178-180	81	63.98 (63.95)	4.92 (4.9)	6.22 (6.2)
6k	4-SO(CH_3)-C_6H_4-CH_2-	$C_{24}H_{22}N_2O_4S$	466.57	195-196	89	61.78 (61.75)	4.75 (4.95)	6 (5.99)
6l	4-SO_2(CH_3)-C_6H_4-CH_2-	$C_{24}H_{22}N_2O_5S$	482.57	200-203	80	59.73 (59.7)	4.6 (4.55)	5.81 (5.8)

*Preparation of 4-(methylsulfonyl)phenyl acetonitrile (**2**) from 4-methylthiophenylacetonitriel (**1**)*
4-methylthiophenylacetonitrile (**1**) (0.1 mole) was dissolved in 3 volume of acetic acid and cooled to 5 °C. To the reaction mixture 0.02 mole of sodium tungstate was added followed by 0.2 mole of 30% hydrogen peroxide which was diluted in 1.2 volume of acetic acid and water mixture (in 2:1 ratio). After the addition of hydrogen peroxide solution, the temperature of the reaction mixture was slowly brought to RT. The completion of reaction was monitored by TLC. The solid precipitated was filtered and washed with water until the pH of the fitrate was neutral. The product was dried at 65 °C for 10-12 h. The product was recrystallized from methanol.

Colourless solid (92 %). mp 120-124 °C. IR (KBr, γ/cm^{-1}): 2255 (CN), 3075 (Ar-H), 2995, 2895 (C-H), 1315 (S=O), 1145 (S=O**).** ^{1}H NMR (400 mHz, CD_3OD): δ ppm, 3.10 (s, 3H, CH_3), 3.75 (s, 2H, CH_2), 7.55-7.57 (d, 2H, Ar-H, *J= 8.0)*, 7.88-7.90 (d, 2H, Ar-H, *J= 8.0)*. MS (m/z, %): 195(M^+).

*Preparation of 4-(methylsulfonyl)phenyl aceticacid (**3**) from 4-(methylsulfonyl)phenyl actonitrile (**2**)*
4- (Methylsulphonyl)phenyl acetonitrile (0.1 mole) was taken in 5 volume of water. To this potassium hydroxide (0.25 mole) was added and heated to 98 °C. The reaction mass was refluxed for 2 h. The completion of reaction was monitored by TLC. The reaction was cooled to 25-28 °C. The impurities were removed by Toluene wash. The aq layer was acidified to pH=2 using Conc HCl. The solid thus precipitated was filtered and washed with water until the filtrate was neutral. The product was dried at 65 °C for 10-12 h. The product was recrystallized from methanol.

Colourless solid (95 %). mp 142-144° C. IR (KBr, γ/cm^{-1}): 3450 (O-H), 3056 (Ar-H), 2941, 2898 (C-H), 1694 (C=O), 1310 (S=O)**,** 1245 (C-O), 1140 (S=O**)**. ^{1}H NMR (δ ppm, CD3OD, 400 mHz): 3.11 (3H, s, CH_3), 3.76 (2H, s, CH_2), 7.54-7.56 (2H, d, Ar-H, *J= 8.0)*, 7.89-7.91 (2H, d, Ar-H, *J= 8.0)*. ^{13}C NMR: δ ppm, 40.164, 43.06, 127.139, 130.33, 139.176, 141.29, 172.91. DEPT: δ ppm, CH_3: 43.06, CH_2: -40.16, 127.14, 130.32. MS (m/z, %): 215(M^+).

*Preparation of ethyl 4-(methylsulfonyl) phenyl acetate (**4**)*
The above esters were prepared by refluxing 4-(methylsulfonyl)phenyl aceticacid in excess absolute ethanol in the presence of few drops of conc. sulfuric acid. After the reaction ethanol was distilled off, the ester was extracted to Ethyl acetate and concentrated. The compounds after usual workup were obtained as low melting white solids.

IR (KBr, γ/cm^{-1}): 3072 (Ar-H), 2980 (C-H), 1694 (C=O), 1493 (C-O-C), 1310 (S=O)**,** 1245 (C-O), 1140 (S=O**)**.

*Preparation of 4-(methylsulfonyl/sulfinyl) acetohydrazide (**5**)*
A mixture of ethyl- 4-(methylsulfonyl)phenyl acetate **(4)** (0.1mol), hydrazine hydrate (0.15 mol) and 20ml of ethanol was refluxed on an oil bath for 10 h. The excess solvent was then distilled off under reduced pressure and the concentrated solution was quenched to ice cold water. The solid separated was filtered, washed and dried. The crude product was purified by recrystallization from ethanol.

Colourless solid (89 %); mp 118-120°C. IR (KBr, γ/cm^{-1}): 3286 (NH_2/NH), 3012 (Ar-H), 2989, 2885 (C-H), 1644 (C=O), 1315 (S=O)**,** 1243 (C-O), 1142 (S=O**)**.

*General Procedure for the Preparation of 2-[4-(methylsulfonyl)benzyl]-5-substituted-1,3,4-oxadiazole **(6a-l)***
A mixture of 2-[4-methylsulphonylphenyl] acetohydrazide **(5)** (1mmol), aromatic acid (1 mmol), and phosphorous oxy chloride (5 ml) was refluxed for 2-3h. The reaction mixture was gradually poured into crushed ice with stirring and neutralized with solid sodium bicarbonate. The aqueous layer was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate, and finally distilled under reduced pressure to remove the solvent. The resulting solid was recrystallized using ethanol.

*2-(4-methylphenyl)-5-[4-(methylsulfonyl)benzyl]-1,3,4-oxadiazole (**6b**)*
IR: (KBr: γ/cm^{-1}): 3021 (Ar-H), 2998, 2895 (C-H), 1694 (C=N), 1514(C=C), 1298 (S=O), 1253 (C-O-C), 1132 (S=O**)**. 1H NMR (δ ppm, $CDCl_3$, 400 MHz): 3.10 (3H, s, SCH3), 4.52 (2H, s, CH2), 7.62-7.64 (2H, d, 4-methylphenyl, *J* = 8.0), 7.82-7.84 (2H , d, 4-methylphenyl, *J* = 8.0), 8.22-8.24 (2H, d, 4-(methylsulphonyl)phenyl, *J* = 8.0), 8.37-8.39 (2H, d, 4-(methylsulphonyl) phenyl, *J* = 8.0). ^{13}C NMR: δ ppm, 31.79, 44.47, 124.47, 127.85, 128.32, 128.26, 129.35, 129.99, 139.52, 140.30, 149.55, 163.80, 165.19. DEPT : CH and CH_3 : δ ppm, 44.47, 124.47, 127.85, 128.32, 129.99, CH_2 : -31.79.

*2-(3-methoxyphenyl)-5-[4-(methylsulfonyl)benzyl]-1,3,4-oxadiazole (**6e**)*
IR: (KBr: γ/cm^{-1}): 3000 (Ar-H), 2989, 2890 (C-H), 1693 (C=N), 1491 (C=C), 1308 (S=O), 1240(C-O-C), 1135 (S=O**)**. 1H NMR (δ ppm, $CDCl_3$, 400 MHz): 3.053 (3H, s, SCH3), 3.87 (3H,

s, OCH3), 4.38 (2H, s, CH2), 7.06-7.08 (1H, d, 3-methoxy phenyl, *J* = 8.0), 7.37-7.41 (1H, t, 3-methoxyphenyl, *J* = 8.0), 7.54-7.55 (1H, d, 3-methoxyphenyl, *J* = 8.0), 7.67 (1H, s, 3-methoxy phenyl), 7.70-7.72 (2H, d, 4-(methyl sulphonyl)phenyl, *J* = 8.0), 7.94-7.96 (2H, d, 4-(methyl sulphonyl)phenyl, *J* = 8.0). ^{13}C NMR: δ ppm, 31.79, 44.52, 55.54, 111.64, 118.27, 119.23, 124.67, 128.14, 129.93, 130.25, 140.04, 159.97, 164.01, 165.42; DEPT : CH and CH_3 : δ ppm, 44.52, 55.54, 111.63,118.27, 119.23, 128.14, 129.93, 130.25, CH_2: - 31.79. MS: 345.1 m/z, (M^+).

2-(2-methoxyphenyl)-5-[4-(methylsulfonyl)benzyl]-1,3,4-oxadiazole ***(6f)***
IR: (KBr: γ/cm^{-1}): 3020 (Ar-H), 2989, 2877 (C-H), 1694 (C=N), 1493 (C=C), 1310 (S=O), 1243(C-O-C), 1136 (S=O**)**. 1H NMR (δ ppm, $CDCl_3$, 400 MHz,): 3.055 (3H, s, SCH3), 3.90 (3H, s, OCH3), 4.39 (2H, s, CH2), 7.07-7.09 (1H, d, 2-methoxyphenyl, *J* = 8.0), 7.38-7.42 (1H, t, 2-methoxyphenyl, *J* = 8.0), 7.55-7.59 (1H, t, 2-methoxyphenyl, *J* = 8.0), 7.68-7.70 (1H, d, 2-methoxyphenyl, *J* = 8.0), 7.73-7.75 (2H, d, 4-(methylsulphonyl)phenyl, *J* = 8.0), 7.95-7.97 (2H, d, 4-(methylsulphonyl)phenyl, *J* = 8.0). ^{13}C NMR: δ ppm, 31.80, 44.55, 55.56, 112.63, 119.18, 120.25, 125.80, 128.55, 131.01, 131.25, 141.14, 160.3, 164.53, 165.62. DEPT : CH and CH_3 : δ ppm, 44.55, 55.56, 112.63, 119.181, 128.55, 131.02, 131.25, CH_2: -31.80. MS: 345.1, m/z, (M^+).

2-(4-Bromo phenyl)-5-[4-(methylsulfonyl)benzyl]-1,3,4-oxadiazole ***(6g)***
IR: (KBr: γ/cm^{-1}): 3000 (Ar-H), 2985, 2885 (C-H), 1692 (C=N), 1495 (C=C), 1312 (S=O), 1243(C-O-C), 1138 (S=O**)**. 1H NMR (δ ppm, $CDCl_3$, 400 MHz): 3.028 (3H, s, SCH3), 4.35 (2H, s, CH2), 7.54-7.56 (2H, d, 4-Bromophenyl, *J* = 8.0), 7.60-7.65 (2H , d, 4- Bromophenyl, *J* = 8.0), 7.92-7.94 (2H, d, 4-(methylsulphonyl)phenyl, *J* = 8.0), 7.97-7.99 (2H, d, 4-(methyl sulphonyl)phenyl, *J* = 8.0).

2-[4-(methylsulfonyl)benzyl]-5-(4-nitrophenyl)-1,3,4-oxadiazole ***(6i)***
IR: (KBr: γ/cm^{-1}): 3015 (Ar-H), 2995, 2888 (C-H), 1695 (C=N), 1482(C=C), 1300 (S=O), 1235(C-O-C), 1130 (S=O**)**. 1H NMR (δ ppm, $CDCl_3$, 400 MHz): 3.06 (3H, s, SCH3), 4.43 (2H, s, CH2), 7.59-7.61 (2H, d, 4-Nitrophenyl, *J* = 8.0), 7.96-7.98 (2H , d, 4-Nitrophenyl, *J* = 8.0), 8.20-8.22 (2H, d, 4-(methylsulphonyl)phenyl, *J* = 8.0), 8.35-8.37 (2H, d, 4-(methylsulphonyl) phenyl, *J* = 8.0). ^{13}C NMR: δ ppm, 31.78, 44.47, 124.417, 127.85, 128.12, 128.23, 129.03, 129.98, 139.49, 140.28, 149.68, 163.75, 165.14. DEPT : CH and CH_3 : δ ppm, 44.45, 124.40, 127.84, 128.22, 129.98, CH_2 : δ, -31.77.

RESULTS AND DISCUSSION

Antioxidant activity

DPPH radical-scavenging assay

The antioxidant activity of the compounds **(6a-l**) and the standard (Rutin) were assessed on the basis of radical scavenging effect of the stable DPPH (1,1-Diphenyl-2-picrylhydrazyl) free radical, with minor modification of the method of Germano *et. al.*, [20]. The test samples and the Rutin (Std) were dissolved in methanol, aliquots (0.5 mL) were mixed with 3 mL of a 39.4 µg/mL methanolic solution of DPPH. The mixture was shaken vigorously and then kept in the dark for 30 min at room temperature. The decrease in absorbance of the resulting solution was measured at 517 nm with a spectrophotometer (Shimadzu UV-1601). All tests were performed in

triplicate and the results were expressed as mean ±S.D. The inhibition percentage (% I) of the DPPH radical was calculated according to the following formula

$$I\% = \frac{A_{C(0)} - A_{A(t)}}{A_{C(0)}} \times 100$$

where $A_{C(0)}$ is the absorbance of the control DPPH solution at ***t***=0 min and $A_{A(t)}$ is the absorbance after addition of test samples at t=30 min. The concentration of the compound required to reduce the absorbance of DPPH control solution by 50% (IC_{50}) was calculated.

The **Table II** contains the antioxidant activity data of the compounds **(6a-l)**. The antioxidant activity study revealed that all the compounds tested showed moderate anti oxidant activities. Structure and biological activity relationship of the title compounds showed that the presence of 4-Bromophenyl, 4-Chlor phenyl and 3,5-dimethylphenyl groups at C-5 position of oxadiazole ring are responsible for increased antioxidant activity compared to other derivatives in newly synthesized compounds.

Table II Antioxidant (DPPH Scavenging) activity data of 1,3,4-oxadiazoles (6a-l)

Compounds	**IC_{50} (µg/mL)**
Rutin (std)	5.80 ±2.08
6a	>200
6b	>200
6c	>200
6d	193.08±0.05
6e	>200
6f	>200
6g	199.04±0.06
6h	193.08±0.08
6i	>200
6j	>200
6k	>200
6l	>200

The structure of 2-[4-(Methylsulfonyl)phenyl]acetonitrile (**2**) was confirmed by single crystal X-ray study [21] and is given in **Figure I** and **Figure II** and the crystal data is given in **Table III** and **Table IV.**

Figure I The molecular structure of 2-[4-(Methylsulfonyl)phenyl]acetonitrile (2) showing 30% probability displacement ellipsoids for non-H atoms and the atom-numbering scheme.

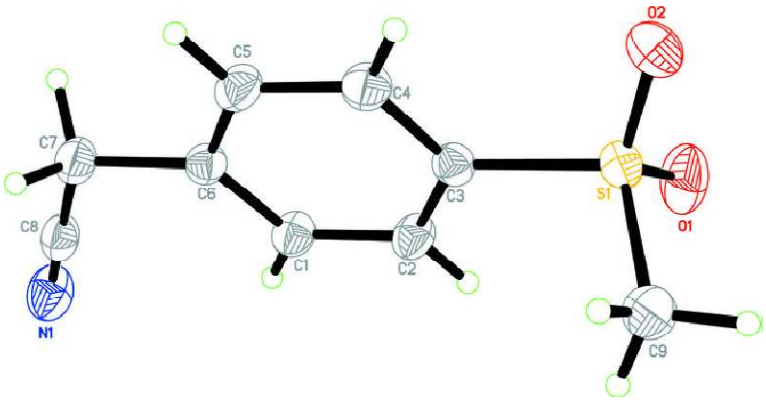


Figure II The crystal structure of 2-[4-(Methylsulfonyl)phenyl]acetonitrile (2) viewed along the *c* axis. H atoms not involved in hydrogen bonds (dashed lines) have been omitted for clarity.

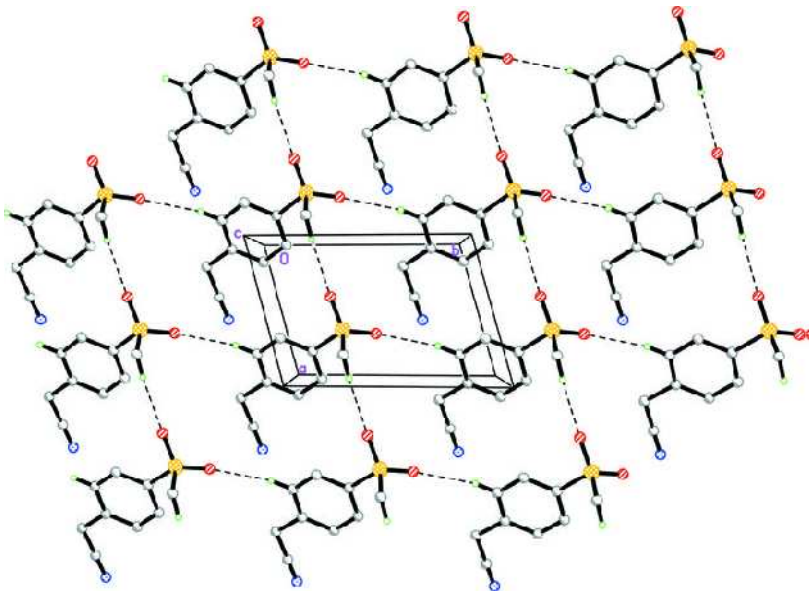


Table III Crystal data of 2-[4-(Methylsulfonyl)phenyl] acetonitrile (2)

$C_9H_9NO_2S$	$F(000) = 204$
$Mr = 195.23$	$Dx = 1.390$ Mg m^{-3}
Triclinic P_1	Melting point: 120-124°C
Hall symbol: P 2ac 2ab	Mo $K\alpha$ radiation, $\lambda = 0.71073$A°
$a = 5.559$ (1) A°	Cell parameters from 4240 reflections
$b = 8.094$ (2) A°	$\theta = 2.6–33°$
$c = 10.90$ (3) A°	$\mu = 0.31$ mm^{-1}
$V = 466.6$ (3) A°^{3}	Block, colourless
$Z = 2$	0.51 × 0.28 × 0.14 mm
$T = 296$ K	

Table IV Data collection of 2-[4-(Methylsulfonyl)phenyl] acetonitrile (2)

Bruker SMART APEXII CCD area-detector diffractometer	1826 independent reflections
Radiation source: sealed tube	3620 reflections with $I > 2\sigma(I)$
Graphite	Rint = 0.023
ω and φ scans	θmax = 26°, θmin = 1.9°
Absorption correction: ψ scan (*SADABS*; Bruker, 2009)	$h = -6 \rightarrow 6$
Tmin = 0.810, Tmax = 0.957	$k = -9 \rightarrow 9$
5970 measured reflections	$l = -13 \rightarrow 13$

CONCLUSION

Series of novel substituted derivatives of 1,3,4-oxadiazoles were synthesized in reasonably good yields. They were characterized by ^{1}H NMR, ^{13}C NMR, mass spectrometry, IR studies and elemental analyses. All the newly synthesized compounds were studied for antioxidant activity.

The antioxidant activity study revealed that the oxadiazoles containing 4-Bromo phenyl, 4-Chloro phenyl and 3,5-di methyl phenyl at C-5 position of oxadiazole ring have better result as compared to the standard drug.

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