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**Research Article**

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# *SYNTHESIS AND CHARACTERIZATION OF 5-ARYL-1,3,4-OXADIAZOLE-2(3H)THIONE DERIVATIVES*

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***ABSTRACT***

1,3,4-oxadiazoles represent a class of heterocyclic five membered compounds it contain two nitrogen and one oxygen of great importance in Pharmaceutical chemistry. This nucleus show four isomeric forms 1,2,4-oxadiazole,1,3,4-oxadiazole, 1,2,5-oxadiazole, and 1,2,3-oxadiazole. This nucleus has various biological activity such as antioxidant, antimicrobial, antifungal, antitumor, antidepressant, anticancer, analgesic etc. have been reported. A series of 1,3,4-oxadiazoles-2(3*H*)thione derivative has been synthesized in four steps and the derivative were characterized by FTIR spectral analysis. This article explain the different biological activities associated with 1,3,4-oxadiazole five membered ring are useful for researchers across the world working on this nucleus.

## *INTRODUCTION*

Heterocyclic compounds having great effects in treatments of diseases studies, for this reasons chemists advantage for those compounds, they develop a wider ranges of products interests. As a result of studies and facts, those kinds of compounds become greater in quality over a period time and clearly gives proofs of producing a good results health and treatments. Compounds contain N and O are very active compounds due to their important act in practical uses in studies of preparation of drugs and medicine scientific study of living things and analytical fields [1]. 1,3,4-Oxadiazoles are an important class of heterocyclic compounds with broad spectrum of biological activities. Substituted 1,3,4-oxadiazoles have revealed antibacterial, anti-mycobacterial, antifungal, anti-inflammatory, analgesic, anticonvulsant and anticancer properties [2]. Oxadiazole is considered to be resultant from furan by replacement of two methane (–CH=) groups by two pyridine type nitrogen atoms (–N=). Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles [3]

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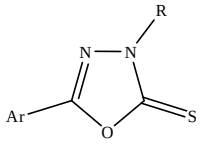
## OXADIAZOLES

**Nucleus**

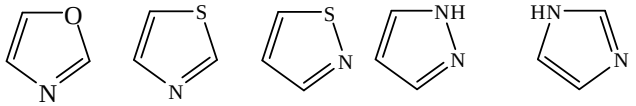


**5-aryl-1,3,4-oxadiazole-2(3*H*)thione derivatives**

Oxadiazole ring has been shown to impart anti-inflammatory properties in compounds designed as orally-active nonulcerogenic agents1 or in products formulated as analogs of fenamates for the inhibition of cyclooxygenase and 5-lipooxygenase. Pharmacological screening of several 2-(acetylamino)-5-alkyl-1,3,4-oxadiazoles revealed their spasmolytic and potent hypotensive action.2,5-Disubstituted 1,3,4-oxadiazole derivatives were shown to be promising hypoglycemic agents able to reduce the level of blood glucose when administered at an oral dose of 100mg/kg. A structure–activity relationship study towards the inhibition of monoamine oxidase A involved a series of tricyclics bearing oxadiazole moieties [4].

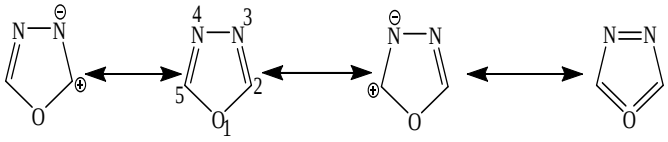
**Chemistry**

The group of five-membered aromatic heterocycles is much larger than that of the six-membered heterocycles. This is because one of the atoms in the ring need only be divalent and so more heteroatoms can be incorporated into neutral five-membered rings [5].



Oxazole Thiazole Isothiazole 1H-Pyrazole 1H-Imidazole

1,3,4-oxadiazole is pseudo heteroatom ring containing three heteroatom represented by following canonical forms [6].



**Oxadiazole**

Nitrogen heterocycles play an important role in the drug discovery scenario. The nitrogenated cores commonly occur as fragments in the structure of most drugs with varied ring sizes; aromatic and nonaromatic rings; fused and bicyclic rings.Oxadiazoles are heterocyclic compounds composed by two atoms of carbon, two atoms of nitrogen and one atom of oxygen. They were firstly discovered in 1884 by Tiemann and Krüger, then named furo[ab]diazoles. Oxadiazoles can be isosterically compared with furan, but the replacement of two methine groups (-CH=) by two $sp^2$ nitrogen (-N=) reduces their aromaticity so that some of their isomers are electronically comparable to conjugated diene systems. Oxadiazoles can be found in four different isomeric structures [7].

1,2,3-oxadiazole 1,2,4-oxadiazole 1,2,5-oxadiazole 1,3,4-oxadiazole

**Properties of Oxadiazole**

| | | |
|---|---|---|
| Molecular formula | : | $C_2H_2N_2O$ |
| Molecular weight | : | 70.05 |
| Physical state | : | liquid |
| Boiling point | : | 150 °C |

**Structure**

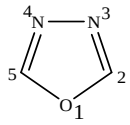
1,3,4 oxadiazole (1) is a thermally stable neutral aromatic molecule, only the isomer not containing oxygen-nitrogen bond and exists in two partially reduced form; 2,3 dihydro- 1,3,4-oxadiazole (2) and 2,5 dihydro 1,3,4- oxadiazole (3) depending on position of double bond. The completely reduced form of 1,3,4- oxadiazole is designated as 2,3,4,5- tetrahydro- 1,3,4-oxadiazole (4) [8].

(1) (2) (3) (4)

1,3,4-oxadiazole ring is symmetrical and planer with the following structural parameters.

**Bond Length (Å)**

$N_3$-$N_4$ = 1.399
$C_2$-$N_3$ = 1.297
$N_4$-$C_5$ = 1.297
O-$C_2$ = 1.348
O-$C_5$ = 1.348



[1,3,4]Oxadiazole

**Bond angle (°)**

$C_2$-O-$C_5$ = 102.0
O-$C_2$-N = 113.4
$C_2$-$N_3$-$N_4$ = 105.6
$N_3$-$N_4$-$N_5$ = 105.6
O-$C_5$-$C_4$ = 113.4

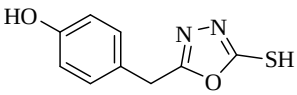
1,3,4–Oxadiazole is an aromatic, molecule with resonance energy 167.4 kJ/mol. The bond lengths in the 1,3,–Oxadiazole reflect π-electron delocalization. However the C=N bond lengths are very close to that in acyclic compound (1.27 Å) and therefore indicate some dienic character in 1,3,4-oxadiazole.

## BIOLOGICAL ACTIVITY OF 1,3,4-OXADIAZOLS

Heterocyclic compounds containing the five-membered oxadiazole nucleus possess a diversity of useful biological effects. 1,3,4-Oxadiazole are important because of their versatile biological actions [9].

**Anti-inflammatory activity**

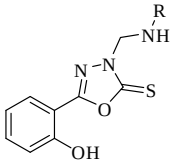
Amir, M. *et al.* synthesized a series of 1,3,4-oxadiazole derivatives **(I)** of 4-hydroxyphenyl acetic acid and evaluated for their anti-inflammatory activity by carrageenan induced rat paw edema method. The compounds, which showed good anti-inflammatory activity [10].



**(I)**

**Anti-cancer activity**

Aboraia, S.A. *et al.* synthesized a series of 5-(2-hydroxylphenyl)-3-substtuted-2,3-dihhydro-1,3,4-oxadiazole-2-thione derivative **(II)** and 13 of them were selected by the national cancer institute(NCI) and evaluated for their *in-vitro* anticancer activity [11].

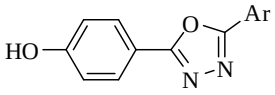


**(II)**

R=$C_6H_4$(2Cl), $C_6H_4$(3Cl), $C_6H_4$(4Cl), $C_6H_5$, $C_6H_5$($3CH_3$), $C_6H_5$($4CH_3$), $C_6H_5$($OCH_3$),etc.

**Antimicrobial activity**

Nagalakshmi, G. *et al.* synthesized 2,5-disubstituted-1,3,4-oxadiazoles **(III)** by the condensation of 4-hydroxybenzohydrazide with various aromatic acids in presence of phosphorus oxychloride. The structures of the newly synthesized compounds were established on the basis of elemental analysis, UV, IR and $^1$H NMR spectral data. The synthesized compounds were screened for their *in-vitro* strong antibacterial activity [12].

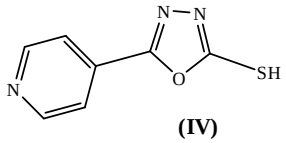


**(III)**

Ar= $C_6H_5$, 4-$NH_2C_6H_4$, $C_5H_4N$ etc.

**Antitubercular activity**

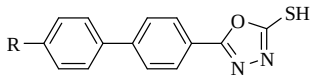
Dewangan, D. *et al.* Due to the interesting activity of 2,5-disubstituted 1,3,4-oxadiazole (**IV**) as biological agent's considerable attention has been focused on this class. The pharmaceutical importance of these compounds lies in the fact that they can be effectively utilizing as antibacterial, antitubercular and insecticidal agents [13].



**(IV)**

**Analgesic activity**

Ramprasad, G.C. *et al.* synthesized a series of biphenyl-1,3,4-oxadiazoles namely 5-[substituted-(1,10-biphenyl)-3-yl]-1,3 ,4-oxadiazole-2 (3H)-thiones **(V)** and its S-alkyl derivatives by multi step organic synthesis involving Suzuki-Miyaura coupling using palladium catalyst. The synthesized compounds were characterized by $^1$H NMR, $^{13}$C NMR, $^{19}$F NMR, IR and LCMS spectroscopic properties. They were tested for their antimicrobial and analgesic activities. Some of them showed significant activity [14].

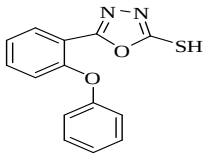


**(V)**

R= 5-F, 2-$OCH_3$, 2-F, 3-Cl, etc

**Anticonvulsant activity**

Almasirad *et al.* synthesized a series of 5-[2-(phenylthio) phenyl]-1,3,4-oxadiazole **(VI)**, derivatives. Compounds were evaluated *in- vivo* for their anticonvulsant and muscle relaxant activities [15].



**(VI)**

## *MATERIAL AND METHODS*

The studies on various analogues of substituted 5-aryl-1,3,4-oxadiazole 2(3*H*)thione derivatives for the treatment of inflammation has led to the discovery of a large number of compounds. The chemicals required were obtained from Hi-media Chem. Ltd, SD-Fine Ltd. and Sigma Aldrich Pvt. Ltd and were used as such.

Melting points were determined using open capillary tube melting point apparatus and are uncorrected. Reaction progress was monitored by performing thin layer chromatography on silica gel G plates, using iodine vapors and UV chamber as visualizing agents. After physical characterization, the compounds were subjected to spectral analysis. Proton nuclear magnetic resonance spectra were recorded on Bruker WM-300 (at 300 MHz) spectrometer and chemical shifts were reported in

parts per million (δ value) taking TMS (δ 0 ppm for $^1$H NMR) as an internal standard. Coupling constant given in Hertz. Mass spectra were recorded on a JEOL- SX-102 instrument using ESI. Infrared spectra were taken on Shimadzu 8400 spectrometer and values expressed in $cm^{-1}$.

**SYNTHESES OF ANALOUGES**

**Procedure for the synthesis of methyl benzoate**

A mixture of (30.03g, 0.246 mol) of benzoic acid **(Ia)**, (2.5mol) of abs. methanol and 2.7 mL of conc. sulphuric acid was gently refluxed for 4hrs. Excess of alcohol was distilled off. Sodium bicarbonate was added till all free acid was removed. The product was filtered and washed with water to obtain the methyl benzoate **(Ib)**. Purity was confirmed by thin layer chromatography using methanol: chloroform (0.5:9.5) [16].

**Procedure for the synthesis of benzohydrazide**

The mixture of methyl benzoate (**Ib)** (14.75mL, 0.1 mol) and hydrazine hydrate (10mL, 0.2 mol) was refluxed in absolute alcohol (50mL) for 8hrs. The excess solvent was then distilled off under vacuum pressure and the concentrated solution was quenched in to ice cold water. The separated solid was filtered, washed and dried. The crude product benzohydrazides (**Ic)** was recrystallized from ethanol. Purity was confirmed by thin layer chromatography using methanol: chloroform (3:7) [17].

**Procedure for the synthesis of 5-phenyl 1,3,4-oxadiazole 2(3*H*)thione**

A mixture of benzohydrazide **(Ic)** (6.8g, 0.05 mol), potassium hydroxide (2.8g, 0.05 mol), carbon disulfide (16.33mL, 0.17 mol), and ethanol (70mL) was heated under reflux. Ethanol was distilled off under reduced pressure and the residue was dissolved in water and then acidified with dilute hydrochloric acid (10%). The resulting precipitate was filtered and washed with water dried, and recrystallized from ethanol to obtain the product 5-phenyl 1,3,4-oxadiazole 2(3*H*)thione **(Id)**. Purity was confirmed by thin layer chromatography using methanol: chloroform (2:8) [18].

**Procedure for the synthesis of 1-[5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2*H*)- yl) ethanone**

5-Phenyl-1,3,4-oxadiazole-2(3*H*)thione **(Id)** (7.83g, 0.044mol) was taken in a 100mL RBF fitted with a reflux condenser. To this a mixture of acetyl chloride (8.66mL, 0.1mol) and glacial acetic acid (9.48mL, 0.15mol) was added. The reaction mixture was refluxed for about 40minutes and then poured in to 100mL cold water, contained in a 500ml beaker with vigorous stirring. Crude crystals of 1-(5-phenyl-2-thioxo- 1,3,4-oxadiazol-3(2*H*)-yl) ethanone **(IdA)** separated out as solid were filtered and washed with cold water, and dried. Purity was confirmed by thin layer chromatography using methanol: chloroform (1: 9) [19]

**Procedure for the synthesis of phenyl [5-phenyl-2-thioxo-1,3,4-oxadiazol- 3(2*H*)-yl] methanone**

5-Phenyl-1,3,4-oxadiazole-2(3*H*)thione **(Id)** (7.83g, 0.044mol) was taken in a 100mL RBF fitted with a reflux condenser. To this a mixture of benzoyl bromide (26.63mL, 0.1mol) and glacial acetic acid (9.48mL, 0.15mol) was added. The reaction mixture was refluxed for about 40minutes and then poured in to 100mL cold water, contained in a 500ml beaker with vigorous stirring. Crude crystals of 1-[5- phenyl [5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl] methanone **(IdB)** separated out as solid were filtered and washed with cold water, and dried. Purity was confirmed by thin layer chromatography using methanol: chloroform (1: 9).

**Procedure for the synthesis of 2-chloromethyl benzoate**

A mixture of (37.51g, 0.246 mol) of 2-chlorobenzoic acid **(IIa)**, (2.5mol) of abs. methanol and 2.7 mL of conc. sulphuric acid was gently refluxed for 4hrs. Excess of alcohol was distilled off. Sodium bicarbonate was added till all free acid was removed. The product was filtered and washed with water to obtain the 2-cloromethyl benzoate **(IIb)**. Purity was confirmed by thin layer chromatography using methanol: chloroform (0.5:9.5).

**Procedure for the synthesis of 2-chlorobenzohydrazide**

The mixture of 2-chloromethyl benzoate (**IIb)** (20.3mL, 0.1 mol) and hydrazine hydrate (10mL, 0.2 mol) was refluxed in absolute alcohol (50 mL) for 8hrs. The excess solvent was then distilled off under vacuum pressure and the concentrated solution was quenched in to ice cold water. The separated solid was filtered, washed and dried. The crude product 2-chlorobenzohydrazides (**IIc)** was recrystallized from ethanol. Purity was confirmed by thin layer chromatography using methanol: chloroform (3:7).

**Procedure for the synthesis of 5-(2-chlorophenyl)-1,3,4-oxadiazole 2(3*H*)thione**

A mixture of 2-chlorobenzohydrazide **(IIc)** (8.53g, 0.05 mol), potassium hydroxide (2.8g, 0.05 mol), carbon disulfide (16.33mL, 0.17 mol), and ethanol (70mL) was heated under reflux. Ethanol was distilled off under reduced pressure and the residue was dissolved in water and then acidified with dilute hydrochloric acid (10%). The resulting precipitate was filtered and washed with water dried, and recrystallized from ethanol to obtain the product 5-(2-chlorophenyl)-1,3,4-oxadiazole

2(3*H*)thione **(IId)**. Purity was confirmed by thin layer chromatography using methanol: chloroform (2:8).

**Procedure for the synthesis of 1-(5-(2-chlorophenyl)-2-thioxo-1,3,4- oxadiazol-3(2*H*)-yl) ethanone**

5-(2-chlorophenyl)-1,3,4-oxadiazole 2(3*H*)thione **(IId)** (9.33g, 0.044mol) was taken in a 100mL RBF fitted with a reflux condenser. To this a mixture of acetyl chloride (8.66mL, 0.1mol) and glacial acetic acid (9.48mL, 0.15mol) was added. The reaction mixture was refluxed for about 40minutes and then poured in to 100mL cold water, contained in a 500ml beaker with vigorous stirring. Crude crystals of 1-(5-(2- chlorophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl) ethanone **(IdA)** separated out as solid were filtered and washed with cold water, and dried. Purity was confirmed by thin layer chromatography using methanol: chloroform (1: 9).

**Procedure for the synthesis of 1-(5-(2-chlorophenyl)-2-thioxo-1,3,4- oxadiazol-3(2*H*)-yl) (phenyl)methanone**

5-(2-chlorophenyl)-1,3,4-oxadiazole 2(3*H*)thione **(IId)** (9.33g, 0.044mol) was taken in a 100mL RBF fitted with a reflux condenser. To this a mixture of benzoyl bromide (26.63mL, 0.1mol) and glacial acetic acid (9.48mL, 0.15mol) was added. The reaction mixture was refluxed for about 40minutes and then poured in to 100mL cold water, contained in a 500ml beaker with vigorous stirring. Crude crystals of 1-(5-(2- chlorophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl) (phenyl)methanone **(IIdB)** separated out as solid were filtered and washed with cold water, and dried. Purity was confirmed by thin layer chromatography using methanol: chloroform (1: 9).

**Procedure for the synthesis of 5-(pyridin-3-yl)-1,3,4-oxadiazole- 2(3*H*)thione**

A mixture of isoniazide **(IIIc)** (6.85g, 0.05 mol), potassium hydroxide (2.8g, 0.05 mol), carbon disulfide (16.33mL, 0.17 mol), and ethanol (70mL) was heated under reflux. Ethanol was distilled off under reduced pressure and the residue was dissolved in water and then acidified with dilute hydrochloric acid (10%). The resulting precipitate was filtered and washed with water dried, and recrystallized from ethanol to obtain the product 5-(pyridin-3-yl)-1,3,4-oxadiazole-2(3*H*)thione **(IIId)**. Purity was confirmed by thin layer chromatography using methanol: chloroform (2:8).

**Procedure for the synthesis of 1-[5-(pyridi-3-yl)-2-thioxo-1,3,4-oxadiazol- 3(2*H*)-yl]ethanone**

5-(pyridin-3-yl)-1,3,4-oxadiazole-2(3*H*)thione **(IIId)** (7.87g, 0.044mol) was taken in a 100mL RBF fitted with a reflux condenser. To this a mixture of acetyl chloride (8.66mL, 0.1mol) and glacial acetic acid (9.48mL, 0.15mol) was added. The reaction mixture was refluxed for about 40minutes and then poured in to 100mL cold water, contained in a 500ml beaker with vigorous stirring. 1-[5-(pyridi-3-yl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl]ethanone **(IIIdA)** separated out as solid were filtered and washed with cold water, and dried. Purity was confirmed by thin layer chromatography using methanol: chloroform (1: 9).

**Procedure for the synthesis of phenyl-[5-(pyridin-3-yl)-2-thioxo-1,3,4- oxadiazol-3(2*H*)-yl]methanone**

5-(pyridin-3-yl)-1,3,4-oxadiazole-2(3*H*)thione **(IIId)** (7.87g, 0.044mol) was taken in a 100mL RBF fitted with a reflux condenser. To this a mixture of acetyl chloride (8.66mL, 0.1mol) and glacial acetic acid (9.48mL, 0.15mol) was added. The reaction mixture was refluxed for about 40minutes and then poured in to 100mL cold water, contained in a 500ml beaker with vigorous stirring. Crude crystals of phenyl-(5- (pyridin-3-yl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl)methanone **(IIIdB)** separated out as solid were filtered and washed with cold water, and dried. Purity was confirmed by thin layer chromatography using methanol: chloroform (1: 9).

**Procedure for the synthesis of 4-chloromethyl benzoate**

A mixture of (37.51g, 0.246 mol) of 4-chorobenzoic acid **(IVa)**, 2.5mol) of abs. methanol and 2.7 mL of conc. sulphuric acid was gently refluxed for 4hrs. Excess of alcohol was distilled off. Sodium bicarbonate was added till all free acid was removed. The product was filtered and washed with water to obtain the methyl 4- chloromethyl benzoate **(IVb)**. Purity was confirmed by thin layer chromatography using methanol: chloroform (0.5:9.5).

**Procedure for the syntheses of 4-chlorobenzohydrazide**

The mixture of 4-chloromethyl benzoate (**IVb)** (17.69mL, 0.1mol) and hydrazine hydrate (10mL, 0.2mol) was refluxed in absolute alcohol (50 mL) for 8hrs. The excess solvent was then distilled off under vacuum pressure and the concentrated solution was quenched in to ice cold water. The separated solid was filtered, washed and dried. The crude product 2-chlorobenzohydrazides (**IVc)** was recrystallized from ethanol. Purity was confirmed by thin layer chromatography using methanol: chloroform (3:7).

**Procedure for the synthesis of 5-(4-chlorophenyl)-1,3,4-oxadiazole 2(3*H*)thione**

A mixture of 4-clorobenzohydrazide **(IVc)** (8.53g, 0.05 mol), potassium hydroxide (2.8g, 0.05 mol), carbon disulfide (16.33mL, 0.17 mol), and ethanol (70mL) was heated under

reflux. Ethanol was distilled off under reduced pressure and the residue was dissolved in water and then acidified with dilute hydrochloric acid (10%). The resulting precipitate was filtered and washed with water dried, and recrystallized from ethanol to obtain the product 5-(4-chlorophenyl)-1,3,4-oxadiazole 2(3*H*)thione **(IVd)**. Purity was confirmed by thin layer chromatography using methanol: chloroform (2:8).

**Procedure for the synthesis of 1-(5-(4-chlorophenyl)-2-thioxo-1,3,4- oxadiazol-3(2*H*)-yl)ethanone**

5-(4-chlorophenyl)-1,3,4-oxadiazole 2(3*H*)thione **(IVd)** (9.33g, 0.044mol) was taken in a 100mL RBF fitted with a reflux condenser. To this a mixture of acetyl chloride (8.66mL, 0.1mol) and glacial acetic acid (9.48mL, 0.15mol) was added. The reaction mixture was refluxed for about 40minutes and then poured in to 100mL cold water, contained in a 500ml beaker with vigorous stirring. Crude crystals of 1-[5-(4- chlorophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl]ethanone **(IVdA)** separated out as solid were filtered and washed with cold water, and dried. Purity was confirmed by thin layer chromatography using methanol: chloroform (1: 9).

**Procedure for the synthesis of (5-(4-chlorophenyl)-2-thioxo-1,3,4- oxadiazol-3(2*H*)-yl)(phenyl)methanone**

5-(4-chlorophenyl)-1,3,4-oxadiazole 2(3*H*)thione **(IVd)** (9.33g, 0.044mol) was taken in a 100mL RBF fitted with a reflux condenser. To this a mixture of acetyl chloride (8.66mL, 0.1mol) and glacial acetic acid (9.48mL, 0.15mol) was added. The reaction mixture was refluxed for about 40minutes and then poured in to 100mL cold water, contained in a 500ml beaker with vigorous stirring. Crude crystals of (5-(4-chlorophenyl)-2-thioxo- 1,3,4-oxadiazol-3(2*H*)-yl)(phenyl)methanone **(IVdA)** separated out as solid were filtered and washed with cold water, and dried. Purity was confirmed by thin layer chromatography using methanol: chloroform (1: 9).

**Procedure for the synthesis of methyl 4-nitrobenzoate**

A mixture of (41.1g, 0.246 mol) of methyl 4-nitrobenzoic acid **(Va)**, (2.5mol) of abs. methanol and 2.7 mL of conc. sulphuric acid was gently refluxed for 4hrs. Excess of alcohol was distilled off. Sodium bicarbonate was added till all free acid was removed. The product was filtered and washed with water to obtain the methyl 4- nitobenzoate **(Vb)**. Purity was confirmed by thin layer chromatography using methanol: chloroform (0.5:9.5).

**Procedure for the syntheses of 4-nirobenzohydrazide**

The mixture of methyl 4-nitrobenzoate (**Vb)** (18.12mL, 0.1mol) and hydrazine hydrate (10mL, 0.2mol) was refluxed in absolute alcohol (50 mL) for 8hrs. The excess solvent was then distilled off under vacuum pressure and the concentrated solution was quenched in to ice cold water. The separated solid was filtered, washed and dried. The crude product 4-nitrobenzohydrazides (**Vc)** was recrystallized from ethanol. Purity was confirmed by thin layer chromatography using methanol: chloroform (3:7).

**Procedure for the synthesis of 5-(4-nitrophenyl)-1,3,4-oxadiazole 2(3*H*)thione**

A mixture of 4-nitrobenzohydrazide **(Vc)** (9.05g, 0.05 mol), potassium hydroxide (2.8g, 0.05 mol), carbon disulfide (16.33mL, 0.17 mol), and ethanol (70mL) was heated under reflux. Ethanol was distilled off under reduced pressure and the residue was dissolved in water and then acidified with dilute hydrochloric acid (10%). The resulting precipitate was filtered and washed with water dried, and recrystallized from ethanol to obtain the product 5-(4-nitrophenyl)-1,3,4-oxadiazole 2(3*H*)thione **(Vd)**. Purity was confirmed by thin layer chromatography using methanol: chloroform (2:8).

**Procedure for the synthesis of 1-(5-(4-nitrophenyl)-2-thioxo-1,3,4- oxadiazol-3(2*H*)-yl) ethanone**

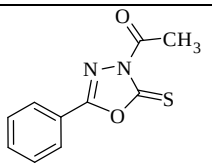
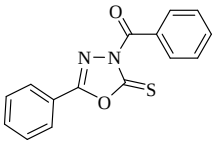
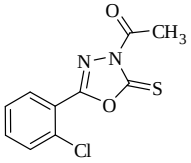
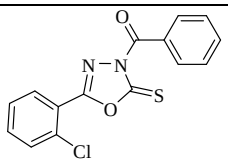
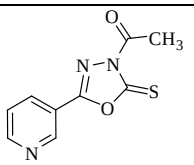
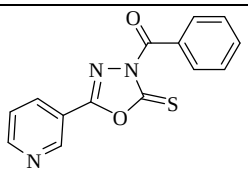
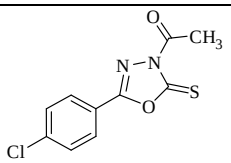
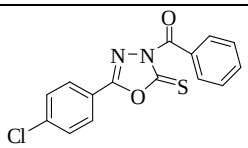
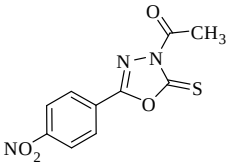
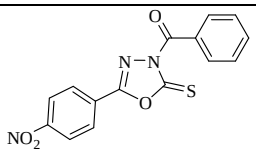
5-(4-nitrophenyl)-1,3,4-oxadiazole 2(3*H*)thione **(Vd)** (9.81g, 0.044mol) was taken in a 100mL RBF fitted with a reflux condenser. To this a mixture of acetyl chloride (8.66mL, 0.1mol) and glacial acetic acid (9.48mL, 0.15mol) was added. The reaction mixture was refluxed for about 40minutes and then poured in to 100mL cold water, contained in a 500ml beaker with vigorous stirring. Crude crystals of 1-(5-(4- nitrophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl) ethanone **(VdA)** separated out as solid were filtered and washed with cold water, and dried. Purity was confirmed by thin layer chromatography using methanol: chloroform (1: 9).

**Procedure for the synthesis of (5-(4-nitrophenyl)-2-thioxo-1,3,4- oxadiazol-3(2*H*)-yl) (phenyl)methanone**

5-(4-nitrophenyl)-1,3,4-oxadiazole 2(3*H*)thione **(Vd)** (9.81g, 0.044mol) was taken in a 100mL RBF fitted with a reflux condenser. To this a mixture of benzoyl bromide (26.63mL, 0.1mol) and glacial acetic acid (9.48mL, 0.15mol) was added. The reaction mixture was refluxed for about 40minutes and then poured in to 100mL cold water, contained in a 500ml beaker with vigorous stirring. Crude crystals of (5-(4- nitrophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl) (phenyl)methanone **(VdA)** separated out as solid were filtered and washed with cold water, and dried. Purity was confirmed by thin layer chromatography using methanol: chloroform (1: 9).

**Synthesized Compounds**

**Table 1 Name, structure and molecular formula of lead compounds**

| S. No. | Compounds code | Name | Structure | Molecular formula |
|---|---|---|---|---|
| **1.** | **IdA** | 1-(5-phenyl-2-thioxo 1,3,4-oxadiazol-3(2*H*)-yl) ethanone |  | $C_{10}H_8N_2O_2S$ |
| **2.** | **IdB** | Phenyl(5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2*H*)-y) methanone |  | $C_{15}H_{10}N_2O_2S$ |
| **3.** | **IIdA** | 1-(5-(2-chlorophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl)ethanone |  | $C_{10}H_7ClN_2O_2S$ |
| **4.** | **IIdB** | (5-(2-chlorophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl) (phenyl)methanone |  | $C_{15}H_9ClN_2O_2S$ |
| **5.** | **IIIdA** | 1-[5-(pyridi-3-yl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl]ethanone |  | $C_9H_7N_3O_2S$ |
| **6.** | **IIIdB** | Phenyl-[5-(pyridin-3-yl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl]methanone |  | $C_{14}H_9N_3O_2S$ |
| **7.** | **IVdA** | 1-[5-(4-chlorophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl]ethanone |  | $C_{10}H_7ClN_2O_2S$ |
| **8.** | **IVdB** | [5-(4-chlorophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl](phenyl)methanone |  | $C_{15}H_9ClN_2O_2S$ |
| **9.** | **VdA** | 1-[5-(4-nitrophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl] ethanone |  | $C_{10}H_7N_3O_4S$ |
| **10.** | **VdB** | [5-(4-nitrophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl] (phenyl)methanone |  | $C_{15}H_9N_3O_4S$ |

## CHARACTERIZATION

### Physical characterization

A total of ten compounds were synthesized as analogues of 5-aryl-1,3,4-oxadiazole. Physical characterization was carried out on the basis of thin layer chromatography (TLC), melting range, colour and solubility. The physicochemical data of compounds is summarized as follows.

| Compounds code | Colour | State | Solubility | M.P. & B.P. (°C) | $R_f$ value | %Yield |
|---|---|---|---|---|---|---|
| (Ib) | Off White | Liquid | Chloroform | 199 | 0.78 | 62.96 |
| (Ic) | Off White | Solid | Ethanol | 123 | 0.62 | 72.86 |
| (Id) | Orange | Solid | Ethanol | 111 | 0.52 | 51.52 |
| A) | Off White | Solid | Ethanol | 136 | 0.71 | 68.10 |
| (IdB) | Light Brown | Solid | Chloroform | 99 | 0.76 | 76.83 |
| (IIb) | Off White | Liquid | Ethanol | 226 | 0.83 | 85.52 |
| (IIc) | Yellow | Solid | Ethanol | 131 | 0.61 | 79.41 |
| (IId) | Light Brown | Solid | Ethanol | 145 | 0.57 | 61.52 |
| (IIdA) | Off White | Solid | Ethanol | 102 | 0.73 | 66.90 |
| (IIdB) | White | Solid | Chloroform | 87 | 0.72 | 74.50 |
| (IId) | Yellow | Solid | Ethanol | 271 | 0.58 | 43.39 |
| (IIIdA) | Dark Yellow | Solid | Ethanol | 144 | 0.74 | 70.90 |
| (IIIdB) | Light Brown | Solid | Ethanol | 89 | 0.57 | 80.10 |
| (IVb) | Off White | Solid | Ethanol | 123 | 0.77 | 65.29 |
| (IVc) | Off White | Solid | Ethanol | 157 | 0.68 | 58.52 |
| (IVd) | White | Solid | Ethanol | 167 | 0.45 | 58.85 |
| (IVdA) | Yellow | Solid | Ethanol | 145 | 0.79 | 68.24 |
| (IVdB) | Off White | Solid | Chloroform | 79 | 0.68 | 78.25 |
| (Vb) | Light Yellow | Solid | Ethanol | 109 | 0.77 | 81.20 |
| (Vc) | Light Orange | Solid | Ethanol | 146 | 0.69 | 57.25 |
| (Vd) | Orange | Solid | Ethanol | 230 | 0.63 | 56.25 |
| (VdA) | Brown | Solid | Ethanol | 135 | 0.54 | 77.10 |
| (VdB) | Light Brown | Solid | Ethanol | 81 | 0.62 | 79.50 |

*M.P. & B.P.= Melting and boiling Point, $R_f$= Retention factor*

### Spectral studies of compounds

After physical characterization, the compounds were subjected to spectral analysis. FT-IR spectra were taken on Shimadzu 8400 spectrometer and values expressed in cm-[1]

**Spectral data of compounds 1-[5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl] ethanone IdA**

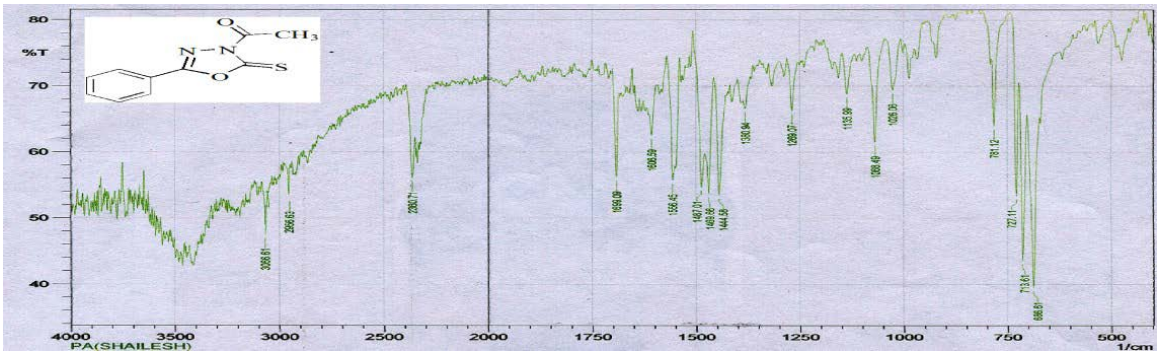



**Fig. 1a) IR spectrum of compound IdA**

**Spectral data of compounds phenyl [5-phenyl-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl] methanone IdB**

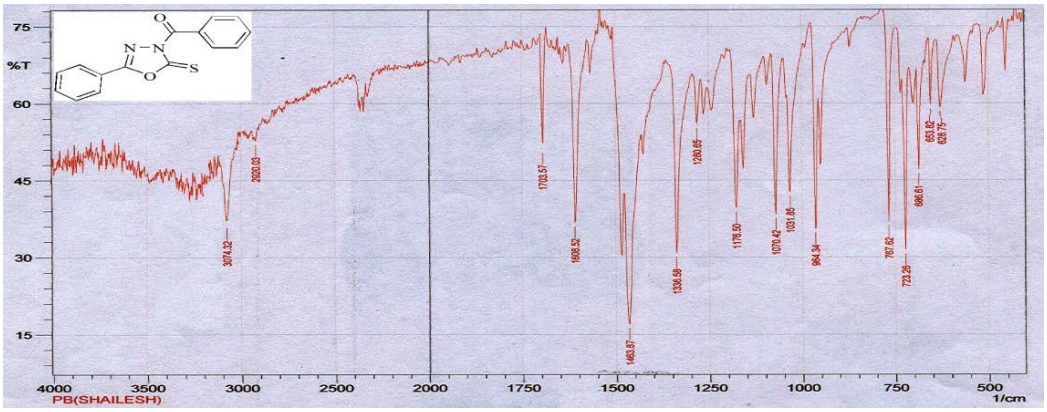



**Fig. 1 b) IR spectrum of compound IdB**

**Spectral data of compounds 1-[5-(2-chlorophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl] ethanone IIdA**

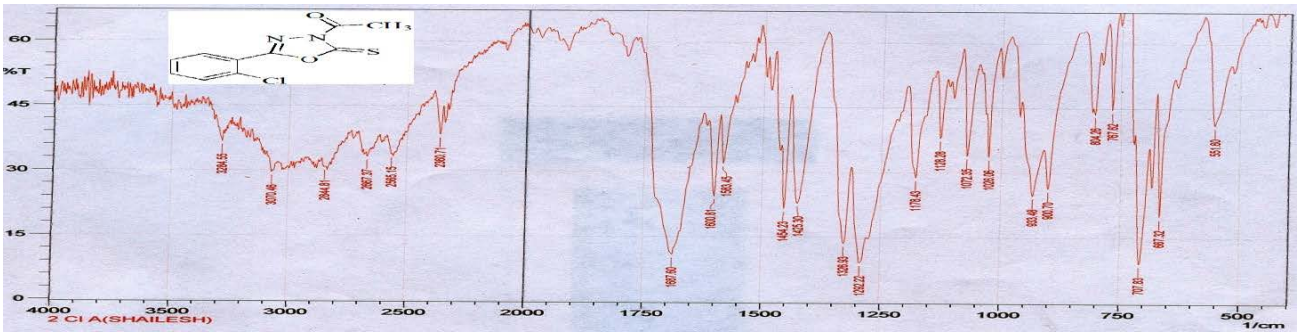



**Fig. 1 c) IR spectrum of compound IIdA**

**Spectral data of compounds 1-[5-(2-chlorophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl] (phenyl)methanone IIdB**

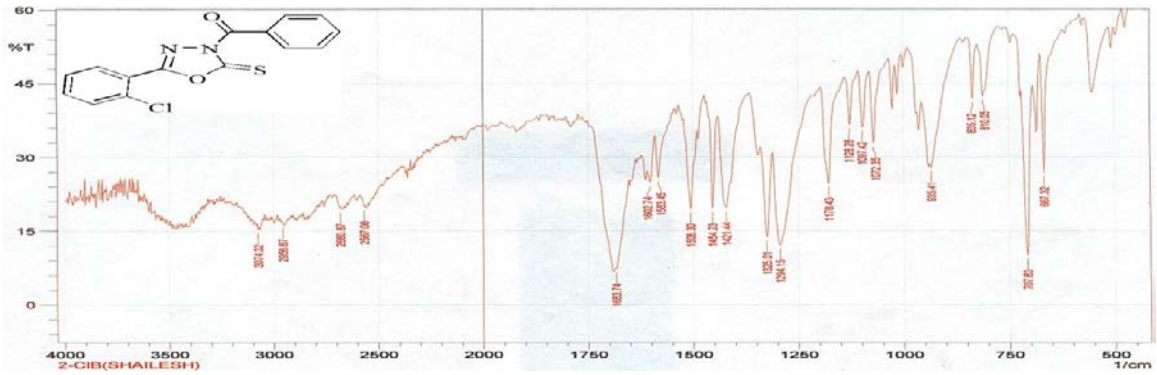



**Fig. 1 d) IR spectrum of compound IIdB**

**Spectral data of compounds 1-[5-(pyridi-3-yl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl]ethanone IIIdA**

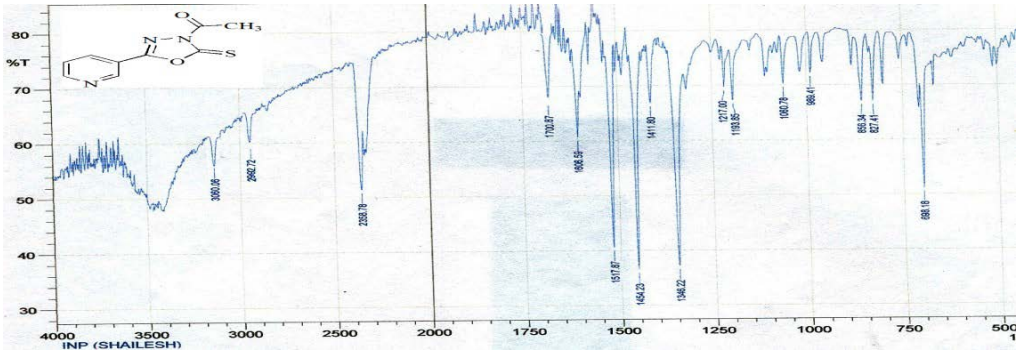



**Fig. 1 e) IR spectrum of compound IIIdA**

**Spectral data of compounds phenyl-[5-(pyridi-3-yl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl]methanone IIIdB**

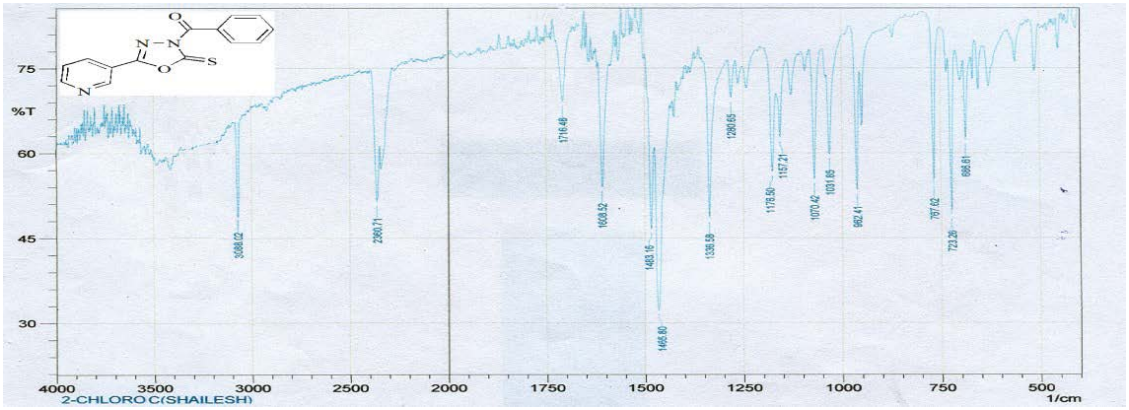



**Fig. 1 f) IR spectrum of compound IIIdB**

**Spectral data of compounds 1-[5-(4-chlorophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl]ethanone IVdA**

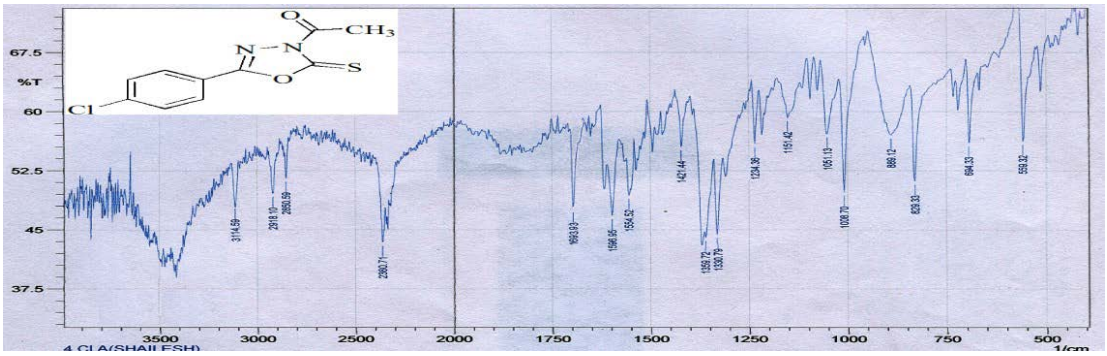



**Fig. 1 g) IR spectrum of compound IVdA**

**Spectral data of compounds [5-(4-chlorophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl](phenyl)methanone IVdB**

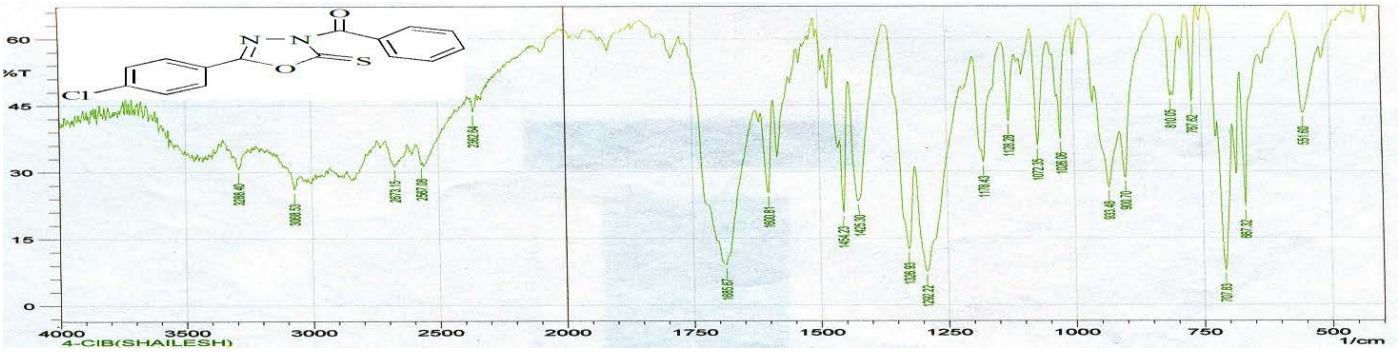



**Fig. 1 h) IR spectrum of compound IVdB**

**Spectral data of compounds 1-[5-(4-nitrophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl] ethanone VdA**

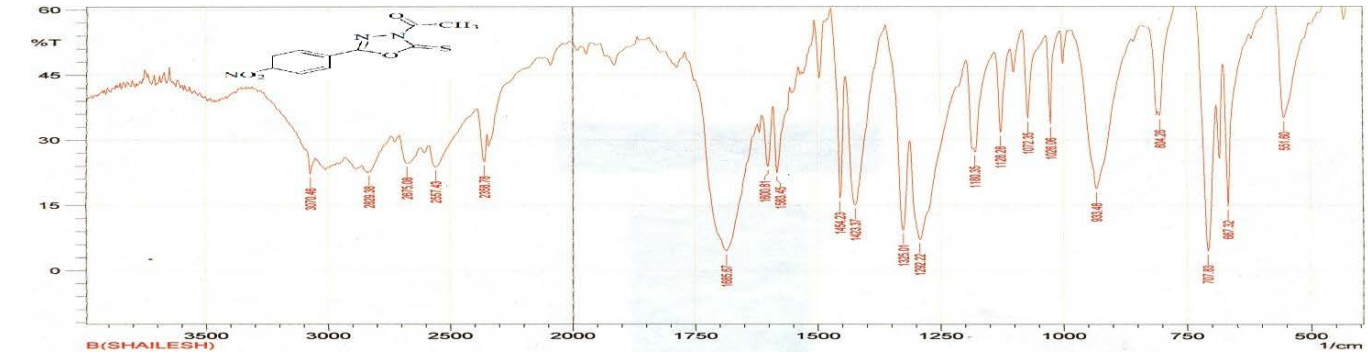



**Fig. 1 i) IR spectrum of compound VdA**

**Spectral data of compounds 1-[5-(4-nitrophenyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl] ethanone VdB**

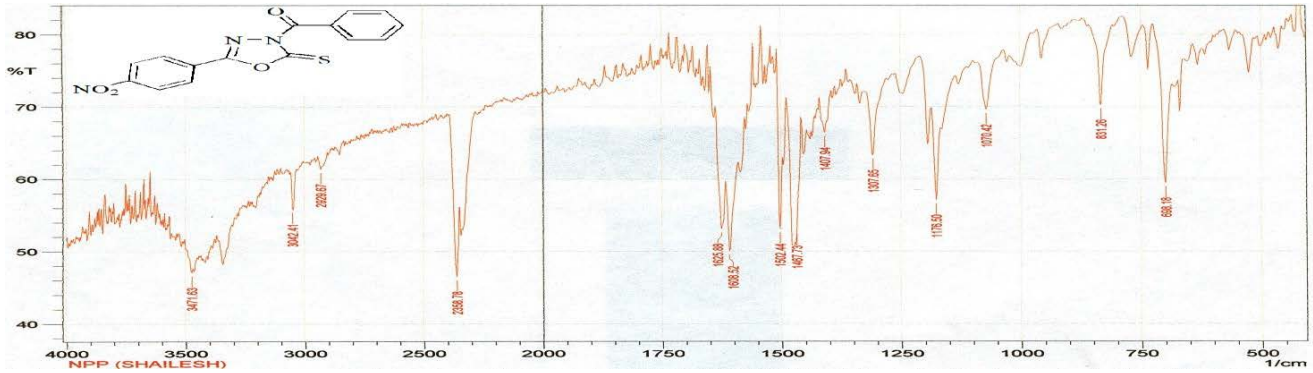



**Fig. 1 j) IR spectrum of compound VdA**

A total of ten derivatives of 1,3,4-oxadiazole **(IdA, IdB, IIdA, IIdB, IIIdA, IIIdB, IVdA, IVdB, VdA & VdB).** In the present study, different 1,3,4-oxadiazole derivatives were synthesized in four steps: Aromatic esters were obtained from esterification of aromatic acids which were further reacted with hydrazine hydrate (99%) to get benzohydrazides. Now these benzohydrazides were cyclized with carbondisulphide and potassium hydroxide to get 5-aryl-1,3,4-oxadiazole-2(3*H*)thiones which were further benzoylated/acylated to get the title compounds.

Physical characterization was carried out on the basis of thin layer chromatography, colour, solubility and melting point. Melting points was determined in open capillaries apparatus and are uncorrected. After physical characterization, the compounds were subjected to spectral analysis by infrared, mass and nuclear magnetic resonance spectroscopy.

FT-IR spectra were taken on Shimadzu 8400 spectrometer and values are expressed in $cm^{-1}$. IR spectra showed characteristic absorption peaks ($cm^{-1}$) ketone C=O stretching range of (1725-1705), thio C=S range of (1375-1140) and aromatic C=C-H stretching range of (3150-3050)

## *CONCLUSION*

On the basis of literature survey, various derivatives of 5-aryl 1,3,4-oxadiazole-2(3H)thione derivatives were synthesized and characterized. The summary of the work is described below.

In the present work ten derivatives of 5-aryl-1,3,4-oxadiazole-2(3H)thione **IdA, IdB, IIdA, IIdB, IIIdA, IIIdB, IVdA, IVdB, VdA and VdB** were synthesized by a four step reaction.

Step1: In the first step esterification of substituted aromatic acid takes place and aromatic ester form.

Step2: In the second step aromatic ester react with hydrazine hydrate (99%) to form substituted benzohydrate.

Step3: In the third step cylization of substituted benzohydrate takes place and form 5-aryl-1,3,4-oxadiazole-2(3H)thione.

Step4: In the last step acylation takes place and form 5-aryl-1,3,4-oxadiazole-2(3H)thione derivatives.

Physical characterization was carried out on the basis of thin layer chromatography, colour, solubility and melting point. Melting point was determined in open capillaries and is uncorrected. After physical characterization, the compounds were subjected to spectral analysis by Infrared, Mass, Nuclear Magnetic Resonance spectroscopy and elemental analysis.

FT-IR spectra were taken on Shimadzu 700 spectrometer and values are expressed in $cm^{-1}$. IR Spectra showed characteristic absorption peaks ($cm^{-1}$) of in first step ester C=O at 1726 for compound **(IVb)**, 1718 for compound **(Vb)**, in second step amide C=O amine N-H at 1676, 3425 for compound **(Ic)**, 1645, 3286 for compound **(IIc)**, 1631, 3303 for compound **(IIIc)**, 1662, 3309 for compound **(IVc)**, 1654, 3251 for compound **(Vc)**, in third step imine C=N stretching, thio C=S, C-O-C, amine N-H at 1550, 1269, 1070, 3427 for compound **(Id)**, 1544, 1336, 1033, 3288 for compound **(IId)**, 1618, 1234, 1147, 3467 for compound **(IIId)**, 1410, 1282, 1176, 3441 for compound **(IVd)**, 1512, 1307, 1172, 3360 for compound **(Vd)**, and in final step ketone C=O 1699 for compound **(IdA)**, 1703 for compound **(IdB)**, 1687 for compound **(IIdA)**, 1683 for compound **(IIdB)** 1700 for compound **(IIIdA)**, 1716 for compound **(IIIdB)**, 1693 for compound **(IVdA)** 1685 for compound **(IVdB)**, 1685 for compound **(VdA)**, 1625 for compound **(VdB)**.

Molecular modification of a promising lead compound is a major line of approach in search for new drug as the structural modification has a direct influence on the activity of compounds.

In conclusion, above derivatives can be screened for diverse biological activities such as antioxidant, antimicrobial, antifungal, antitumor, antidepressant, anticancer, analgesic etc. In addition, a large number of 5-aryl-1,3,4-oxadiazole-2(3*H*)thione derivatives can be synthesized with substitution of different aromatic acid at 5th position and substitution of different alkyl and acyl group at 2nd position

***FINANCIAL ASSISTANCE***
Nil

***CONFLICT OF INTEREST***
The authors declare no conflict of interest.

***AUTHOR CONTRIBUTION***
Shailesh Pathak performed all experimental work in the laboratory. Sharad Sharma contributed in literature survey and preparation of manuscript. Vinay Pathak contributed in designing of experiment and review of manuscript before final submission. Mahesh Prasad contributed by conceptualizing the work, designing the experiment and guiding each and every step of manuscript submission and publication.

***REFERENCES***
[1] Saaid FH, Dawood SJ, Marbeen BH. Synthesis and Characterization of 1,3,4- oxadiazole Derivatives using an Ultrasonic Technique. *Al-Mustansiriyah Journal of Science*, **29(2)**, 101-105 (2018).

[2] Manjunatha K, Poojari B, Lobo LP, Fernandes J, Kumari N. Synthesis and biological evaluation of some 1,3,4-oxadiazole derivatives. *European Journal of Medicinal Chemistry*, **45(11)**, 5225-33 (2010)

[3] Bala S, Kamboj S, Kajal A, Saini V. and Prasad DN. 1,3,4-Oxadiazole Derivatives: Synthesis, Characterization, Antimicrobial Potential, and Computational Studies. *Bio Med Research International*, **18** (2014)

[4] Roman G, Agache Costel, Manciulea I, Comaniţa E. and Dumitrescu L. Synthesis of new mannich bases derived from 5-phenyl-1,3,4-oxadiazole-2-thione and investigation of the conformational isomers of dimethyl 5-(5-phenyl-2-thioxo-1,3,4-oxadiazole-3-methylamino)isophthalate. *Revue Roumaine de Chimie*, **52(12)**, 1103–1110 (2007)

[5] Gilchrist TL. *Heterocyclic chemistry*, 3th Ed.; Dorling Kindersley(India) Pvt. Ltd., pp. 12-13. (2007)

[6] Kulkarni VS, Lele1 MD, Gavitre BB, Patil MD, Bobe KR. and Gaikwad DT. Oxadiazole: a new profile of biological activities. *International Journal of Drug Formulation & Research*, **1(3)**, 134-166 (2010)

[7] Paulo PS, Vitor SS, Marco EFL. 1,2,4- and 1,3,4-Oxadiazoles as Scaffolds in the Development of Antiparasitic Agents. *J. Braz. Chem. Soc*. **29**, 3 (2018)

[8] Shukla C, Srivastava S. Biologically active oxadiazole. *Journal of Drug Delivery & Therapeutics*. **5(6)**, 8-13 (2015)

[9] Musmade DS, Pattan SR. and Manjunath SY. Oxadiazole a nucleus with versatile biological behavior. *IJPC*, **05(01)**, 11-20 (2015)

[10] Amir M, Shikha K. Synthesis and anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities of some new 2-[(2,6-dichloroanilino)phenyl]acetic acid derivative. *Eur. J. Med. Chem*., **39**, 535-545 (2004)

[11] Aboraia AS, Abdel-Rahman HM, Mahfouz NM, EL-Gendy MA. Novel 5-(2-hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives: Promising anticancer agents. *Bioorg. Med. Chem.*, **14**, 1236–1246 (2006)

[12] Nagalakshmi G. Synthesis, antimicrobial and antiinflammatory activity of 2,5-disubstituted-1,3,4-oxadiazoles. *Indian J Pharm Sci*, **70(1)**, 49-55 **(**2008)

[13] Dewangan D, Pandey A, Sivakumar T, Rajavel R, Dubey RD. Synthesis of some Novel 2, 5- Disubstituted 1, 3, 4-Oxadiazole and its Analgesic, Anti-Inflammatory, Anti-Bacterial and Anti-Tubercular Activity. *Int. J. of Chem Tech Research*, **2(3),** 1397-1412 (2010)

[14] Ramaprasad GC, Kalluraya B, Kumar BS, Hunnur RK. Synthesis and biological property of some novel 1,3,4-oxadiazoles. *Eur. J. Med. Chem*., **45**, 4587-4593 (2010)

[15] Almasirada A. *et al*. Synthesis, Anticonvulsant and Muscle Relaxant Activities of Substituted 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole. *Acta Chim. Slov*. **317(54)**, 317–324 (2007)