



# INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND DEVELOPMENT (IJPRD)

Platform for Pharmaceutical Researches & Innovative Ideas  
www.ijprd.com

## SYNTHESIS AND FUNGICIDICITY OF 2-ARYL -6, 7-DIFLUOROPHENYL-1,3,4-OXADIAZOLO (3,2-a) (1,3,5)- TRIAZINE-5-(6H,7H)-THIONES AS FUNGICIDES

Kiran Mishra<sup>1\*</sup>,  
P.S.Bedi<sup>1</sup>, Abdul Wahab<sup>2</sup>

<sup>1</sup>Department of Chemistry, M.M.University, Solan (H.P.)

<sup>2</sup>Department of Chemistry, S. N. P. G. College, Azamgarh (U.P.)

### ABSTRACT

oxadiazolo compounds are bicyclic compounds In present study 2-Aryl-6,7-difluoro phenyl-1,3,4-oxadiazolo (3,2-a) (1,3,5)-triazine-5-(6H,7H)-thiones (2a-j) have been synthesized by the cyclo addition of para- fluorophenyl 4 –fluoro phenyl isothiocynate and 2-(4-fluorobenzylidene ) from (1a-j) 2-amino -5-phenyl-1,3,4-oxadiazole in dry toluene all the synthesized compounds were well characterized by their elemental analysis and spectral data. The synthesized compounds have been screened for their antifungal activity against *Phytophthora infestans* and *Colletotrichum falcatum*. Results showed that maximum antifungal activity was shown by the compounds 2b, 2c, 2g and 2h. These compounds showed 99%, 98%, 99% and 97% inhibition of *phytophthora infestans* and 97%, 96%, 98% and 97% *Colletotrichum falcatum* at 1000ppm respectively.

### Correspondence to Author



**Kiran Mishra**

Associate Professor  
Department of Chemistry,  
M.M.University, Solan (H.P.)  
India.

### Email

drmishrakiran@gmail.com

### Key Words

Fungitoxicity, Oxadiazole,  
Triazine, Thiones

## INTRODUCTION

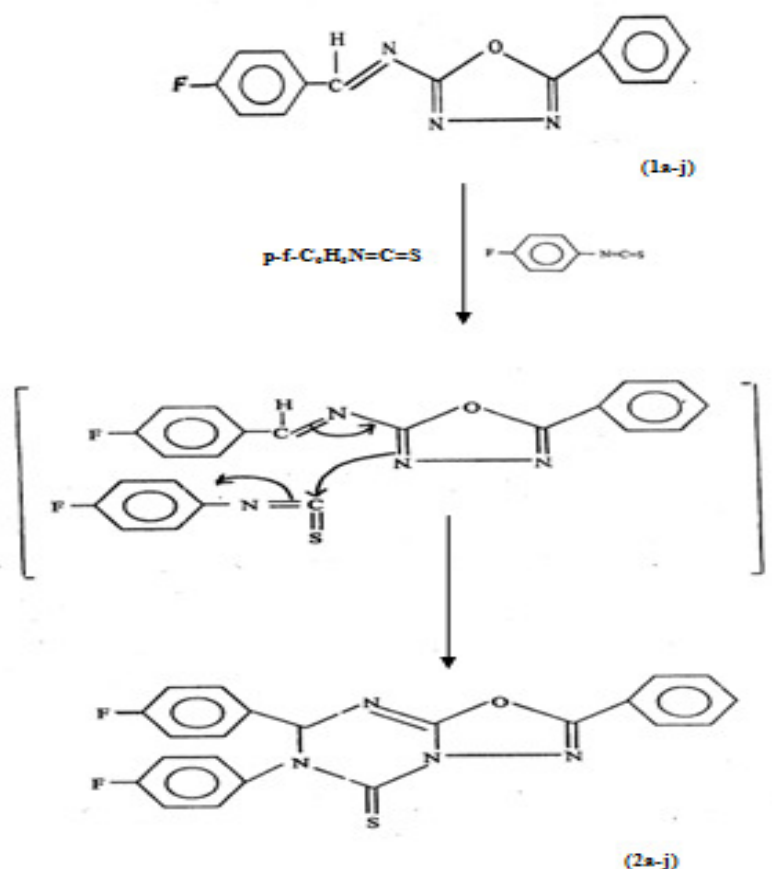
Several 1,3,4-oxadiazole derivatives are known to exhibit various type of useful biological activities including herbicidal [1-2], fungicidal [3-7], bactericidal [8-9], insecticidal [10-14] etc. possibly toxophoric importance of which have been well stressed in many pesticides [15-19].

Many types of 1,3,5-triazine derivatives have significance in agriculture as herbicides and fungicides of these, Simanize (1) [2-chloro-4,6-bis (ethyl amino) -1,3,5-triazine], Atrazine [2-chloro -4-ethylamino-6-isopropylamino -1,3, 5-triazine], Prometryne [2-methylthio-4,6-bis (isopropyl amino)-1,3,5-triazine], Ametryne [2-Methylthio-4-ethylamino-6-(isopropylamino)-1,3,5-triazine], Dyrene [2,4-dichloro-6-(2-chloroanilino)-1,3,5-triazine] and Methoprotryne [2-Methylthio-4-isopropylamino-6(3-

methoxypropylamino)-1,3,5-triazine] are more outstanding. This importance of 1,3,4-oxadiazole derivatives and 1,3,5-triazine derivatives have prompted us to synthesize. Some novel title compounds (2a-j). Thus antifungal activity of synthesize compounds have been screened against fungi *phythophthora infestans* and *colletotrichum falcatom*.

## EXPERIMENTAL

Melting points were taken in an open capillary tubes and are uncorrected. The IR spectra were recorded in KBr on Perkin-Elmer-720 spectrophotometer (fig.1). The  $^1\text{H}$ NMR spectra were recorded in  $\text{CDCl}_3$  on Varian A-60D spectrophotometer (fig.2). The chemical shifts are recorded in ppm downfield from TMS, which are used as an internal standard.



= replaced by following groups in compound (a-j)

- (a) C<sub>6</sub>H<sub>5</sub> (b) 2-ClC<sub>6</sub>H<sub>4</sub> (c) 4- ClC<sub>6</sub>H<sub>4</sub> (d) 2-oCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>  
 (e) 4- oCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>  
 (f) C<sub>6</sub>H<sub>5</sub> (g) 2-ClC<sub>6</sub>H<sub>4</sub> (h) 2-oCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub> (i) 2-oCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>  
 (j) 4- oCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>

### Synthesis of compounds (2a-j)

#### 2-(4-fluorobenzylidene amino)-5-phenyl-1, 3, 4-oxadiazole (1a-j).

A mixture of 2-amino-5-phenyl-1,3,4-oxadiazole 0.02mol and 4-fluorobenzaldehyde 0.02mol in absolute ethanol was refluxed for 4 hrs. and filtered while hot. The filtrate upon cooling furnished the desired product which was recrystallized from ethanol as yellowish needles. All the prepared compounds well agreed with their antifungal data.

#### 7-(4-Fluorophenyl-6,7-dihydro-2-phenyl-6-fluorophenyl)-1,3,4-oxadiazolo(3,2-a)-s-triazine-5-thione (2a-j).

A mixture of 2-(4-fluorobenzylidene) amino -5-phenyl-1,3,4-oxadiazole 0.01mol and 4-fluorophenyl isothiocyanate 0.01mol) was refluxed in dry toluene for 6 hrs. and the solvent was distilled off under reduced pressure. The residue thus obtained was washed with small amounts of ethanol followed by water and the product was recrystallised from ethanol was shining yellowish needles. Yield, melting point, molecular formula and elemental analysis of this as well as that of the other compounds of this class are recorded in table-1. The IR (KBr), <sup>1</sup>H-NMR (CDCl<sub>3</sub>+DMSO-d<sub>6</sub>) spectra of the two representative compounds are also given table -1.

**Table-1:** Yield, melting point, molecular formula and elemental analysis of 7-(4- Fluorophenyl-6,7-dihydro-2-phenyl-6-fluorophenyl)-1,3,4-oxadiazolo(3,2-a)-s-triazine-5-thione (2a-j).

Comp. No.	Ar	Yield %	M.P (°C)	Molecular Formula	Found (Calcd.)%		
					C	N	S
2a	C <sub>6</sub> H <sub>5</sub>	76	236	C <sub>12</sub> H <sub>14</sub> F <sub>2</sub> N <sub>4</sub> OS	62.85(62.83)	13.33(13.34)	07.61(07.60)
2b	2-ClC <sub>6</sub> H <sub>4</sub>	80	250	C <sub>22</sub> H <sub>13</sub> ClF <sub>2</sub> N <sub>4</sub> OS	58.14(58.11)	13.33(13.34)	07.04(07.60)
2c	4- ClC <sub>6</sub> H <sub>4</sub>	70	240	C <sub>22</sub> H <sub>13</sub> ClF <sub>2</sub> N <sub>4</sub> O <sub>2</sub> S	58.14(58.16)	13.33(13.34)	07.04(07.03)
2d	2-oCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	75	185	C <sub>23</sub> H <sub>16</sub> F <sub>2</sub> N <sub>4</sub> O <sub>2</sub> S	61.33(61.30)	13.33(13.34)	07.11(07.14)
2e	4- oCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	78	242	C <sub>23</sub> H <sub>16</sub> F <sub>2</sub> N <sub>4</sub> O <sub>2</sub> S	61.33(61.35)	13.33(13.34)	07.11(07.10)
2f	C <sub>6</sub> H <sub>5</sub>	74	235	C <sub>22</sub> H <sub>14</sub> F <sub>2</sub> N <sub>4</sub> OS	62.85(62.86)	13.33(13.31)	07.61(07.63)
2g	2-ClC <sub>6</sub> H <sub>4</sub>	78	248	C <sub>22</sub> H <sub>13</sub> ClF <sub>2</sub> N <sub>4</sub> OS	58.14(58.15)	12.33(12.35)	07.04(07.03)
2h	4- ClC <sub>6</sub> H <sub>4</sub>	73	240	C <sub>22</sub> H <sub>13</sub> ClF <sub>2</sub> N <sub>4</sub> OS	58.14(58.17)	12.33(12.32)	07.04(07.07)
2i	2-oCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	76	189	C <sub>23</sub> H <sub>16</sub> F <sub>2</sub> N <sub>4</sub> O <sub>2</sub> S	61.33(61.31)	13.34(12.45)	07.11(07.12)
2j	4- oCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	72	240	C <sub>23</sub> H <sub>16</sub> F <sub>2</sub> N <sub>4</sub> O <sub>2</sub> S	61.33(61.37)	12.44(12.42)	07.11(07.09)

#### Antifungal activity :

The compounds(2a-j) were screened for their antifungal activity against *Phytophthora infestans* and *colletotrichum falcatum* by known method at the three concentrations Viz., 1000, 100, 10 ppm. The screening data of compounds are listed in Table-2. Results were compared with commercial fungicide DithaneM-45 tested under similar conditions. The percentage inhibition has been calculated by the formula -

$$\% \text{ of inhibition} = \frac{(C-T)}{C} \times 100$$

Where C and T are diameter (in mm) of fungus colony in control and treated plates respectively.

#### RESULTS AND DISCUSSION

The 2-Aryl-6,7-difluorophenyl-1,3,4-oxadiazolo (3,2-a) (1,3,5)-triazine-5-(6H,7H)-thiones compounds were screened against *phytophthora infestans* and

*colletotrichum falcatum* for antifungal activity and their screening data have been summarized in table-2. Perusal of the screening results indicates that all the tested compounds (2a-j) inhibited more than 65% growth of the both the test fungi at 1000ppm concentrations of these,

**Table- 2 :** Antifungal activity of compounds (2a-j) and Dithane M-45

the most active compounds 2b and 2g exhibited the fungicidal activity almost equivalent to that of Dithane M-45 at 1000ppm concentrations, and inhibited 40-44% growth of the fungal species even at 10ppm concentrations.

Comp. No.	Ar	Average % inhibition after 96 hours					
		Phytophthora infestans			Colletotrichum falcatum		
		1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm
2a	C <sub>6</sub> H <sub>5</sub>	66	37	20	65	35	19
2b	2-ClC <sub>6</sub> H <sub>4</sub>	99	58	40	97	53	40
2c	4- ClC <sub>6</sub> H <sub>4</sub>	98	56	38	96	52	40
2d	2-oCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	72	43	30	74	45	33
2e	4- CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	67	39	23	68	41	24
2f	C <sub>6</sub> H <sub>5</sub>	71	42	30	69	39	26
2g	2-ClC <sub>6</sub> H <sub>4</sub>	99	65	44	98	63	43
2h	4- ClC <sub>6</sub> H <sub>4</sub>	97	60	41	97	60	39
2i	2-oCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	71	42	29	72	43	31
2j	4-oCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	69	40	24	70	42	26
Dithane M-45		100	80	66	100	85	68

The introduction of nitro group to furan ring in the N-Arylidene-2-bromo-5-methoxybenzoyl-hydrazine molecular formula C<sub>13</sub>H<sub>10</sub>BrN<sub>2</sub>O and substitution of alkyl group (R) with m-ClC<sub>6</sub>H<sub>4</sub>- in 3-Substitutedaminomethyl-5-(2-bromo-5-methoxyphenyl)-1,3,4-oxadiazoline-2-thiones show the maximum antibacterial activity against *Staph.aureus* strain[20]. The results of the present study are in consequence with these observations that the introduction of chloro substituted phenyl ring in the compound enhances its antimicrobial activity.

Antibacterial activity of the compound [1,3,4]oxadiazolo[3,2a][1,3,5]triazine-5-one was studied [21]. The substitution of R group by p-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> and another alkyl group R' replaced by phenyl ring, molecular formula C<sub>16</sub>H<sub>9</sub>N<sub>5</sub>O<sub>4</sub>, substitution of R group with p-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub> and R' replaced by methyl group having molecular formula is C<sub>12</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub> and again substitution

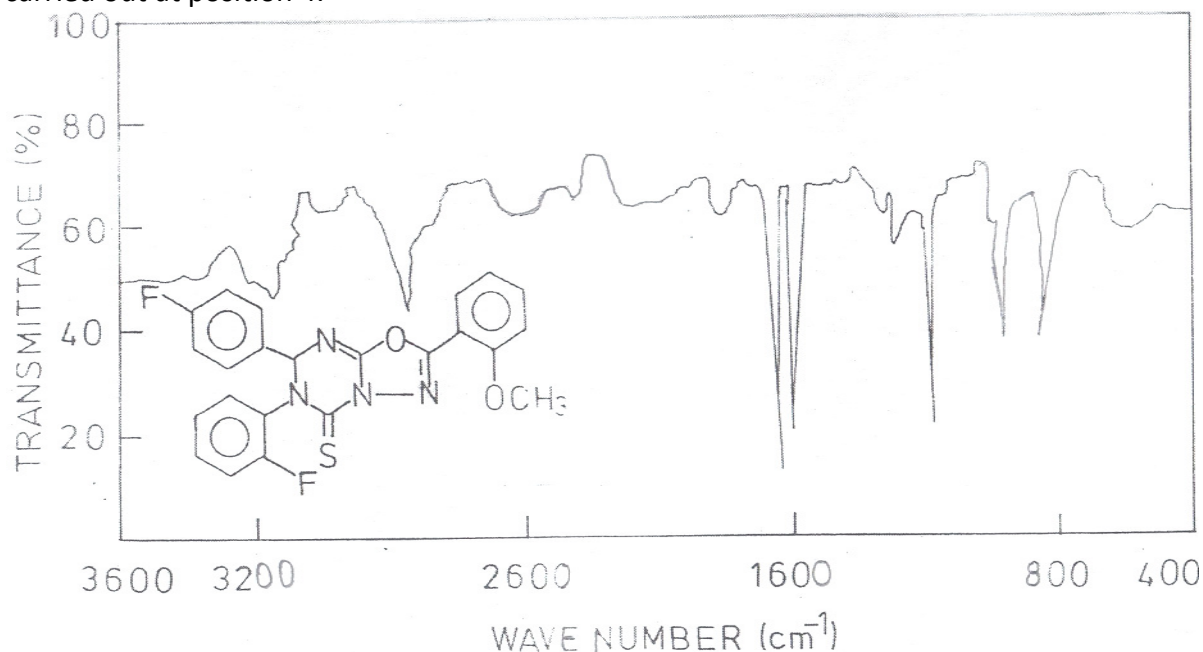
of R by p-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub> and R' replaced by ethyl group molecular formula C<sub>13</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub> had shown the maximum antibacterial activity against *B.subtilis* & *E.coli*. The compound [1,3,4]oxadiazolo[3,2a][1,3,5]triazine-5-thione and their antibacterial activity was also studied [21]. The results revealed that the substitution of R group with p-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> and another alkyl group R' replaced by phenyl ring and having the molecular formula C<sub>16</sub>H<sub>9</sub>N<sub>5</sub>O<sub>3</sub>S, substitution of R group with p-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub> and R' was replaced by methyl group having the molecular formula C<sub>12</sub>H<sub>10</sub>N<sub>4</sub>OS and again if R is substituted by p-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub> and R' was replaced by ethyl group having the molecular formula C<sub>13</sub>H<sub>12</sub>N<sub>4</sub>OS had shown the maximum antibacterial activity against *B.subtilis*.

In the present study it was observed that the introduction of chlorophenyl group in place of aryl group attached to the heterocyclic ring of 1,3,4-

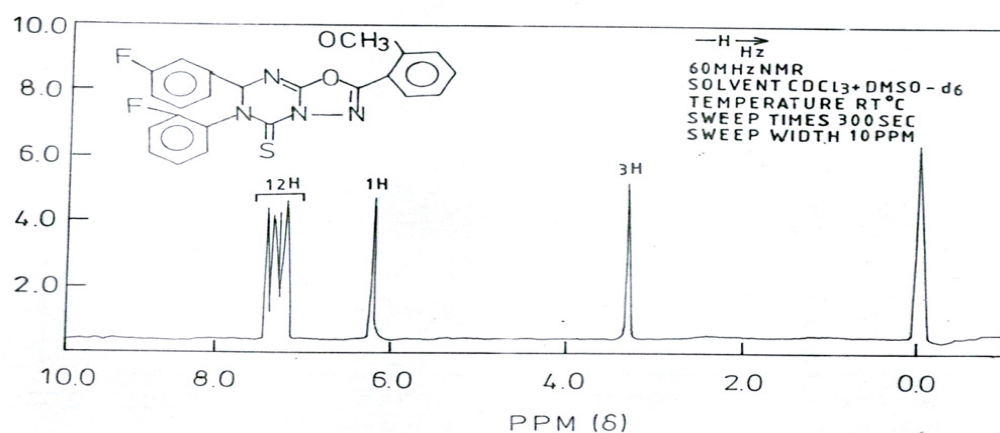
oxadiazole increases the antifungal activity of the compound. If the substitution is made at position 2 of the heterocyclic ring it showed 99%, 58% and 40% antifungal activity at 1000,100 and 10 ppm concentration respectively followed by the 98%, 56% and 38% at 1000,100 and 10 ppm respectively if the substitution is carried out at position 4.

#### ACKNOWLEDGEMENT

The authors are very grateful to the Director, CDRI, Lucknow for providing elemental, spectral data and to the Director, IARI, New Delhi for antifungal activity data.



**Fig.1** : IR (KBr): 1605, 1635 (>C=N), 1190 (>C=S)  $\text{cm}^{-1}$



**Fig.2** :  $^1\text{H-NMR}$  ( $\text{CDCl}_3 + \text{DMSO-d}_6$ )  $\delta$  : 3.75 (3H, s,  $\text{OCH}_3$ ), 6.74, 7.48-7.98 (12H, m, Ar-H)

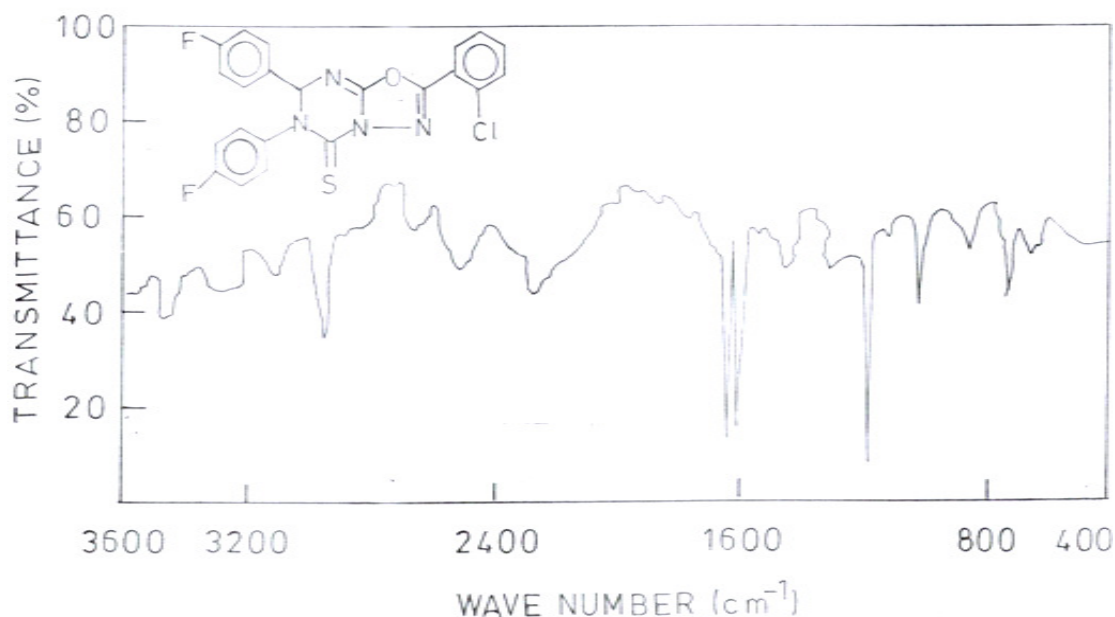


Fig.3 : IR (KBr): 1610, 1640 (>C=N, 1195 (>C=S)  $\text{cm}^{-1}$

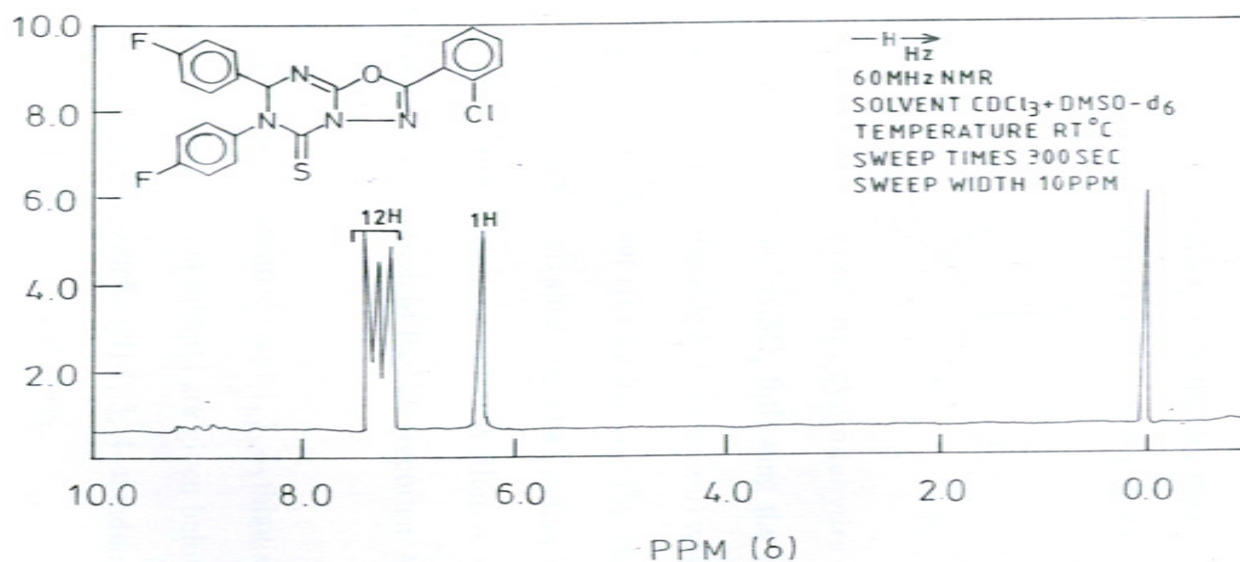


Fig.4 :  $^1\text{H-NMR}$  ( $\text{CDCl}_3+\text{DMSO-d}_6$ )  $\delta$  : 7.42-7.96, (12H, m, Ar-H)

## REFERENCES

1. C. G. Krespan and W.J. Middleton, *Fluorine Chem. Rev.* 1967, 1,145.
2. F. F. Deong, P. 256, Reinhold Publishing corporation, New york, 1956.
3. R.S. Elias, M.C. Shephard; B.k. Shell and J. Stubbs, *Nature*, 1968, 219,1160.
4. K. E. Weinke, J. J. Lauber, B. W. Greenwald and F. A. Preiser.. 5<sup>th</sup> *Brit. Insect. Fungic. Conf.*1969, 2, 340-346.

5. R.Filler, Y. Koboyashi, Kodansha and Elsevier biomedical: amsterdam,1983.
6. B. Von schmeling and M. Kulka, *Science*, 1966,152,659.
7. Giri, S.; Singh, H; Yadav, L.D.S.;Kahre, R.K. *J. Ind. Chem. Soc.* 1978, 55,168.
8. Sengupta, A.K.; Bajaj,O.P.; Chandura,U.J. *J. Ind. Chem. Soc.* 1978, 55, 962.

9. K. Rathwell and R.L. Wain, *Ann. Appl. Biol*, 1963, 51,161.
10. S. Singh, L.D.S. Yadav and H. Singh, *Indian J. Chem.*, 1981,20B, 518.
11. M. S. Gibson, *Tetrahedron*, 1962, 18,1377.
12. F. Hoggarth, *J.chem. Soc.*, 1949, 1918-1923.
13. L. A. Summers, *Tetrahedron*, 1976, 32,615.
14. Ramarakhyuani and R.S. Shukla, *J.Indian Chem. Soc.*, 1980, 57(8),856-57.
15. Singh, H.; Yadav, L.D.S.; Battacharya, B.K.J. *J. Ind. Chem. Soc.* 1979, 56, 1013.
16. Ram, V.J.; Vlietinck, A.J. *J. Hetrocycl. Chem.* 1988, 25, 253.
17. Yang, G.F., LiuZM, Qing XH. *Chinese Chemical Letters*, 2001,12(10), 877-880.
18. Jumat S, Nadia S, Ayad H, Hiba IEY. *J. of Applied Sciences Research*, 2010, 6(7), 866-870.
19. Selvakumar Kanthiah; Anandarajgopal Kalusalingam; Rajamanickam Velayutham; Ajaykumar Thankakan Vimala; Jesindha Beyatricks. *Intnl. J. of Pharm. Sci. Rev. and Res.*2011, 6(1), 64-67.
20. A.A. EL-EMAM *J.Chem. Soc.* 1987,9(1),87-92.
21. Ravidash Deshmukh *Intnl. J. of Res. In Pharm. And Biomedical Sci.* 2011,2(1),215-219.

\*\*\*\*\*