and J were found to be active against all the test bacteria and fungi , except *K. pneumoniae* and *P. crysogenum*. It is noteworthy that among the identified alkaloids, compounds H-J exhibited substantial activity against the bacteria as compared to fungi, except of lasocarpine-N-oxide which exhibited no activity. It is concluded that the alkaloids isolated from chloroform fraction has increased activity as against petroleum ether.

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Microwave Assisted Synthesis of New Bioactive 1, 3,4-Thiadiazolyl Substituted 1, 3,4-Oxadiazoles

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A series of new 2- [5'- methyl-1, 3,4-thiadiazolyl] -5-aryl-1,3,4-oxadiazoles have been synthesised by the reaction of 5-methyl-1, 3,4-thiadiazolyl-2-thioacetic acid hydrazide with appropriate aromatic acids in $SoCl^2$ under microwave irradiation in open vessels using a domestic microwave oven as compared to the conventional method. The reaction rate has been improved tremendously. These oxadiazoles have shown promising antifungal activity against *A. niger* and *A. Flavous*

1 3, 4-Oxadiazoles have been extensively investigated by the organic chemists due to their close association with various types of biological activities[1-3]. In addition, 1,3, 4-thiadiazoles are potent antibacterial antifungal and antiviral agents[4-6]. Recently, accelerating the rate of a wide range of chemical reactions using microwave dielectric heating technique has become a field of wide interest[7-10].

In view of the importance of 1,3,4-oxadiazoles as potential pharmacological agents, substantial reduction in reaction time under microwave irradiation is of interest to us to prepare the title compounds starting from 2-mercapto-5-methyl-1,3,4-thiadiazole which is a side chain at c-3 position of an antibiotic drug cefazolin sodium[11].

Melting points were taken on Thomas Hoover apparatus and are uncorrected. The IR spectra (υ_{max} in cm^{-1}) of the synthesised compounds were recorded on 1710 Perkin Elmer FTIR Spectrophotometer using KBr discs and ^1H NMR on FT NMR Hitachi R-600 using TMS as internal reference (Chemical Shifts in δppm). 2-Mercapto-5-methyl-1, 3,4-thiadiazole (1) was purchased from Aldrich Chemical Co.

Table 1 : Spectral Data of Compounds (4a-h)

Compd. No.	M.P. (°C)	IR (υ,cm^{-1})	^{1}H NMR (δ, ppm) ($CDCl_3$ + DMSO-d_6)	Reaction time Method A(h)	Reaction time Method B(min)	% Yield Method A	% Yield Method B
4a	134-136	1580, 1350(NO_2), 1270, 1040(COC), 1650 (C=N)	2.70(s, 3H,5'-CH_3), 4.60(s,2H, SCH_2, 7.0-7.8(m, 4H, Ar-H).	6.5	6.0	73	85
4b	147-150	1280, 1025 (COC), 1655 (C=N)	2.40(s, 3H, 4-CH_3), 2.70 (s, 3H,5'-CH_3), 4.55(s, 2H,SCH_2), 6.9-7.4(m, 4H, Ar-H)	8.0	7.0	62	73
4c	167-170	1250, 1035(COC), 1655(C=N)	2.70(s, 3H,5'-CH_3), 3.80(s, 3H,4-OCH_3), 4.50(s, 2H, SCH_2), 7.0-7.7(m, 4H, Ar-H).	6.5	6.0	70	83
4d	172-175	1240, 1030 (COC), 1640 (C=N)	1.40 (t,3H,OCH_2CH_3), 2.70(s, 3H, 5'-CH_3), 4.20(q, 2H, OCH_2CH_3), 4.50 (s, 2H, SCH_2),6.8-7.4(m, 4H, Ar-H).	7.0	6.5	71	84
4e	138-140	1240, 1050 (COC), 1650(C=N)	2.70(s,3H,5'-CH_3), 4.50(s,2H,SCH_2), 6.9-7.5(m, 4H, Ar-H).	7.5	6.5	68	77
4f	162-165	1570, 1350(NO_2), 1275, 1040 (COC), 1640 (C=N)	2.70(s, 3H, 5'-CH_3), 4.50 (s,2H, SCH_2), 7.0-7.6(m,4H, Ar-H).	7.0	6.5	70	80
4g	145-147	1260, 1030 (COC), 1650 (C=N)	2.70(s, 3H,5'-CH_3), 4.50(s,2H, SCH_2), 6.8-7.4(m,3H, Ar-H).	7.5	7.0	65	75
4h	140-142	1590, 1360(NO_2), 1265, 1040 (COC), 1640 (C=N).	2.70(s,3H,5'-CH_3), 4.60(s, 2H, SCH_2), 6.9-7.8(m,3H, Ar-H).	6.0	6.0	75	88

Table-2 : Antifungal Activities of Compounds (4a-h)

Compd. No.	R	Inhibition of *A. niger* 25 ug/ml	50ug/ml	Inhibition of *A. flavous* 25 ug/ml	50 ug/ml
4a	4-NO_2	+	+	-	-
4b	4-CH_3	+++	+++	+++	+++
4c	4-OCH_3	++	++	++	++
4d	4-OC_2H_5	+	++	+	++
4e	3-Cl	++	++	++	++
4f	3-NO_2	+	+	-	-
4g	2-Cl	+++	+++	+++	+++
4h	3,5$(NO_2)_2$	-	-	-	-
Reference	Salicylic acid	+++	++++	+++	++++

(-) Not Measurable Activity, + 3-9 mm, ++ 10-12 mm, +++ 13-16 mm, ++++ 16-20 mm

Ethyl [5-methyl-1,3,4-thiadiazolyl-2-thio] acetate (2) was prepared according to the literature method[10]. 5-methyl-1,3,4- thiadiazolyl-2-thioacetic acid hydrazide (3) was prepared according to the literature method[10].

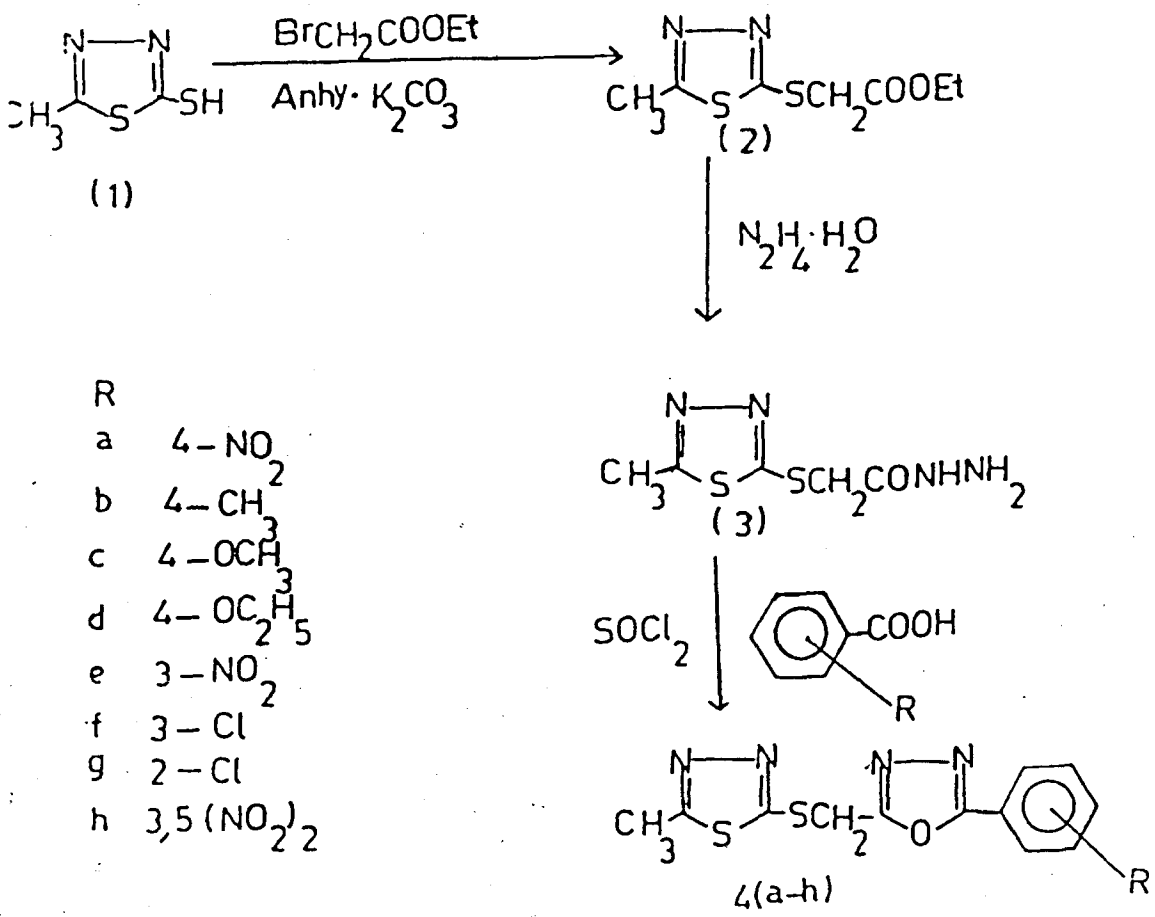
5- [5'-Methyl-1,3, 4-thiadiazolyl-2'-thiomethyl]-2-(substituted phenyl)-1, 3,4-oxadiazoles (4) was synthesized using two methods, method A and method B.

In method A, a mixture of compound 3 (2g, 0.01 mol) and an appropriate aromatic acid (1.6g, 0.01 mole) in $SoCl_2$ 15 ml was refluxed for 6-8h. After distilling of excess of $SOCl_2$, the residual mass was poured over crushed ice and neutralised with 10% $NaHCO_3$ solution. The solid thus separated was filtered washed thoroughly with water and sodium bicarbonate solution. It was recrystallised from chloroform + DMSO (1:1).

In method B, appropriate acid (1.0g, 0.01 mol) was dissolved in $SOCl_2$ 8 ml. To this, compound 3 (0.8 mg 0,01 mol) was added and subjected to microwave irradiation for 6 to 7 minutes. After distilling of excess of $SOCl_2$, the residual mass was worked up as described in method A. Physical and spectral data are given in table 1.

2-Mercapto-5-methyl-1,3,4-thiadiazole (1) on reaction with ethyl bromoacetate in dry acetone in the presence of anhydrous K_2CO_3 afforded ethyl (5-methyl-1,3,4-thiadiazolyl-2-thio) acetate (2). The IR spectrum of compound (2) showed absorption bands at 1740 Cm^{-1} and at 1280 and 1070 cm^{-1} which were assigned to -$\overset{o}{\overset{\|}{C}}$-and -c-o-c respectively. The ester (2) on hydrazinolysis with hydrazine hydrate yielded 5'-methyl-1,3,4-thiadiazolyl-2-thio acetic acid hydrazide (3) which showed absorption bands in the region at 3400-3250 cm^{-1} due to -NH_2 and -NH- stretching vibrations. Cyclisation of compound (3) with different substituted aromatic acids in the presence of $SOCl_2$ on refluxing or under microwave irradiation gave the corresponding 2-[5'-methyl-1,3,4-thiadiazolyl] -5-aryl-1,3,4-oxadiazoles (4a-h) in good yields. This was confirmed by the disappearence of C=O, NH_2 and -NH- stretching vibrations. The absence of signals in the ^1H NMR for the NH and NH_2 protons supported the structure.

All the synthesised compounds were screened for antifungal activity against the fungi *A. niger* and *A. flavous* by paper disc diffusion method [12]. The zone of inhibition was measured in millimeters. The antifungal activity of the test compounds were compared with the standard salicylic acid[13], DMF was used as solvent. Results of the antifungal screening (table-2) showed that most of the compounds displayed significant antifungal activity against *A. niger* and *A. flavous*. However compounds 4b and 4g displayed enhanced antifungal activity.



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