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# PRIVILEDGED SYNTHESIS OF PYRAZOLE-[1, 3, 4] THIADIAZOL-[1, 3, 4] OXADIAZOLE-2-THIONE DERIVATIVES

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**ABSTRACT**

*The titled compound was synthesized by using mixture of oxadiazole-2-thione and substituted 5-phenyl- 1, 3, 4-thiadiazole-2-amine to react with formaldehyde in methanol. And the synthesized compound was screened for their biological activities against microorganism viz. E.coli, B.subtilis, S.aureus, Candida ablicans and Aspergillus niger.*

**KEYWORDS : Oxadiazole-2-thione, 5-phenyl- 1, 3, 4-thiadiazole-2-amine, E.coli, B.subtilis, S.aureus, Candida ablicans and Aspergillus niger.**

## INTRODUCTION

Pyrazoles are five member ring heterocyclic compounds, have some structural features with two nitrogen atoms in adjacent position and are also called as Azoles [1]. Recently Pyrazole derivatives have been found in nature [1], β-[1-pyrazolyl]alanine was isolated from the seeds of water melons [Citurllus lanatus]. The best described property of almost every group of pyrazoles is in the treatment of inflammation and inflammation associated disorders, such as arthritis [2]. Pyrazole derivatives are the subject of many research studies due to their widespread potential biological activities such as antimicrobial [3], antiviral [4], antitumor [5-6], antihistaminic [7], antidepressant [8], insecticides [9] and fungicides [9].

Substituted 1, 3, 4-oxadiazoles are of considerable pharmaceutical and biological interest [10]. They have been shown to possess muscle relaxant, antimitotic, analgesic, anti-inflammatory [11], anticonvulsive [12], diuretic and anti-emetic properties [13]. They also possess tranquilizing,

antitubercular, hypoglycemic, herbicidal, antiviral [14], amoebicidal, insecticidal, hypnotic and sedative activities. 2-Amino-5[2-(phenylthio) phenyl]-1, 3, 4-oxadiazole was synthesized from 2-(Phenylthio) benzoic acid hydrazide in dioxane sodium bicarbonate and cyanogene bromide [15].

During recent years there has been intense investigation of different classes of thiadiazole compounds, many of which known to possess interesting biological properties such as antimicrobial [16], antituberculosis [17], anti-inflammatory [18-20], anticonvulsants [21-22], antihypertensive [23-24], antioxidant [25], anticancer [26-28] and antifungal[29] activity.

## EXPERIMENTAL

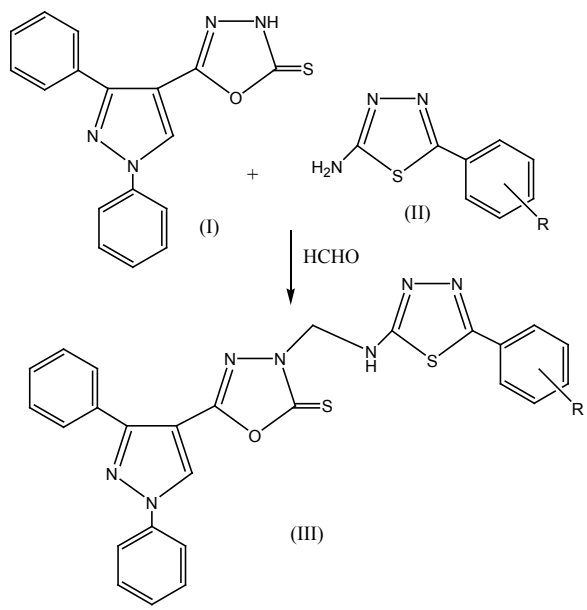
### GENERAL

All chemicals were used as received without further purification. NMR spectra were recorded on a Bruker Advance DPX-400400 FT spectrometer (400 MHz for $^1$H NMR, 100 MHz for $^{13}$C) using $CDCl_3$ as solvent and TMS as an internal reference. Mass spectra were recorded on a JEOL SX-102 (FAB) mass spectrometer at 70 eV. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyzer. Silica gel-G was used for TLC. Melting points were determined by open glass capillary method and are uncorrected.

### III. Synthesis of 5 - (1, 3-Diphenyl- 1H- Pyrazol- 4- yl) -3- [(s-phenyl- [1, 3, 4] thiadiazol -2- ylamino) -methyl] -3H- [1, 3, 4] oxadiazole -2- thione

A methanolic solution of I [30] (0.001mole) was charged into a three neck flask equipped with a stirred and dropping funnel. The solution was stirred to dissolve it completely. To this methanolic solution, formaldehyde (37%) was added dropwise during 15-20 minutes. The resulting mixture was stirred during half an hour to complete reaction of formaldehyde. To this reaction mixture, the methanolic solution of II[31] (0.001mol) was added dropwise with stirring in about half an hour at 30 ° C temperature and refluxed for two hour at 65-70 °C. It was allowed to cool and poured in ice water. The solid obtained was filtered off washed thoroughly with hot water and air dried.

**Scheme 1**:




**Characterization of the synthesized compounds Compound III (a-g):**

**Compound III (a)**

Yield: 90 %; m.p: 112°C; $^1$H NMR (400 MHz, $CDCl_3$/TMS) δ :7.30-7.38 (m, 5H, ArH), 8.2 (s, 1H, -CH=), 7.9 (m, 5H, ArH), 4.33 (s, 2H, -$CH_2$-), 4.5 (s, 1H, -NH-), 7.17-7.32 (m, 5H, ArH); $^{13}$CNMR (100MHz, $CDCl_3$ / TMS) δ:158.8, 157.2, 155.7, 139.9, 136.7, 136.5, 129.9, 129.7, 128.8, 127.5, 126.0, 118.8, 106.5, 68.7 ; EIMS: (m/z): 509.11 (M+). Anal. calcd. For $C_{26}H_{19}N_7OS_2$ C: 61.28 , H: 3.76 , N: 19.24 , 0: 3.14, S: 12.58 %

**Compound III (b)**

Yield: 89 %; m.p: 98°C; $^1$H NMR (400 MHz, $CDCl_3$/TMS) δ :7.18-7.30 (m, 5H, ArH), 8.6 (s, 1H, -CH=), 7.1 (m, 5H, ArH), 4.45 (s, 2H, -$CH_2$-), 4.7 (s, 1H, -NH-), 7.23-6.52 (m, 4H, ArH), 4.0 (s, 2H, -$NH_2$); $^{13}$CNMR (100MHz, $CDCl_3$ / TMS) δ:158.0, 157.0, 155.0, 146.7, 139.7, 136.8, 129.4, 129.2, 128.3, 127.8, 127.3, 126.5, 126.2, 118.3, 115.6, 106.0, 68.2; EIMS: (m/z): 524.12 (M+). Anal. calcd. For $C_{26}H_{20}N_8OS_2$ C: 59.52 , H: 3.84 , N: 21.36 , 0: 3.05, S: 12.22 %

**Compound III (c)**

Yield: 84 %; m.p: 85°C; $^1$H NMR (400 MHz, $CDCl_3$/TMS) δ :7.28-7.52 (m, 5H, ArH), 8.8 (s, 1H, -CH=), 7.6 (m, 5H, ArH), 4.48 (s, 2H, -$CH_2$-), 4.2 (s, 1H, -NH-), 7.12-7.36 (m, 4H, ArH), 2.39 (s, 3H, -$CH_3$); $^{13}$CNMR (100MHz, $CDCl_3$ / TMS) δ:158.4, 157.6, 155.4, 139.9,137.3, 136.3, 133.7, 129.9, 129.2, 129.1, 128.8, 127.4, 126.9, 126.4, 118.7, 106.8, 68.9, 20.9; EIMS: (m/z): 523.12 (M+). Anal. calcd. For $C_{27}H_{21}N_7OS_2$ C: 61.93 , H: 4.04 , N: 18.72 , 0: 3.06, S: 12.25 %

**Compound III (d)**

Yield: 90 %; m.p: 105°C; $^1$H NMR (400 MHz, $CDCl_3$/TMS) δ :7.22-7.37 (m, 5H, ArH), 7.6 (s, 1H, -CH=), 7.1 (m, 5H, ArH), 4.42 (s, 2H, -$CH_2$-), 4.7 (s, 1H, -NH-), 6.79-7.31 (m, 4H, ArH), 5.0 (s, 1H, -OH); $^{13}$CNMR (100MHz, $CDCl_3$ / TMS) δ:158.7, 157.9, 157.3, 155.5, 139.4, 136.2, 129.3, 129.0, 128.5, 128.4, 127.1, 126.9, 118.3, 116.2, 106.5, 68.5; EIMS: (m/z): 525.10 (M+). Anal. calcd. For $C_{26}H_{19}N_7O_2S_2$ C: 59.41 , H: 3.64 , N: 18.65 , 0: 6.09, S: 12.20 %

**Compound III (e)**

Yield: 82 %; m.p: 92°C; $^1$H NMR (400 MHz, $CDCl_3$/TMS) δ :7.18-7.40 (m, 5H, ArH), 8.2 (s, 1H, -CH=), 7.7 (m, 5H, ArH), 4.46 (s, 2H, -$CH_2$-), 4.3 (s, 1H, -NH-), 6.83-7.37 (m, 4H, ArH), 3.79 (s, 3H, -$OCH_3$); $^{13}$CNMR (100MHz, $CDCl_3$ / TMS) δ:162.0, 158.2, 157.6, 155.2, 139.7, 136.9, 129.7, 129.2, 128.8, 128.5, 128.0, 127.5, 126.6, 118.1, 114.6, 106.3, 68.2, 56.0; EIMS: (m/z): 539.12 (M+). Anal. calcd. For $C_{27}H_{21}N_7O_2S_2$ C: 60.09 , H: 3.92 , N: 18.17 , 0: 5.93, S: 11.88 %

**Compound III (f)**

Yield: 96 %; m.p: 118°C; $^1$H NMR (400 MHz, $CDCl_3$/TMS) δ :7.25-7.45 (m, 5H, ArH), 8.0 (s, 1H, -CH=), 7.3 (m, 5H, ArH), 4.44 (s, 2H, -$CH_2$-), 4.9 (s, 1H, -NH-), 7.37-7.49 (m, 4H, ArH); $^{13}$CNMR (100MHz, $CDCl_3$ / TMS) δ:158.9, 157.9, 155.6, 139.5, 136.5, 135.5, 132.3, 129.7, 129.4, 129.0, 128.7, 127.0, 126.0, 123.1, 118.8, 106.6, 68.9 ; EIMS: (m/z): 589.02 (M+). Anal. calcd. For $C_{26}H_{18}BrN_7OS_2$ C: 53.06 , H: 3.08 , Br: 13.58, N: 16.66 , 0: 2.72, S: 10.90 %

**Table 1: Temperature optimization**

| Entry | Temperature(°C) | Reaction Time(hrs) | Product yield (%) |
|---|---|---|---|
| 1 | Below 30 °C | - | - |
| 2 | 30-40 °C | - | - |
| 3 | 40-50 °C | 20 | 33 |
| 4 | 50-60 °C | 15 | 62 |
| 5 | 65-70 [c] | 2 | 90 |

As the results from **table 1,** it was revealed that the yield of the product was found to be excellent when the reaction mixture was maintained to reflux at 65-70 °.

**Antimicrobial Activity:**

Antibacterial activity[32-33] study was carried out by cup-plate agar diffusion method using nutrient agar. The compounds were tested *in-vitro* for their antibacterial activity against microorganism viz. *E.coli, B.subtilis and S.aureus.*

Antifungal activity [32-33] study was carried out by cup-plate agar diffusion method using nutrient agar. Fungal culture were made in the Sabouraud-Dextrose agar and the incubated at 37°C for 18-24hrs. The concentration was 200µ/mL. Compounds were tested *in-vitro* for their antibacterial activity against microorganism viz. *Candida ablicans* and *Aspergillus niger*. Standard drugs Ciprofloxacin and Griseofulvin were used.

**Table 2 : Antimicrobial activity of compounds (IIIa-f)**

| Compd. | Minimal bactericidal conc. µg/ml | | | Minimal fungicidal conc. µg/ml | |
|---|---|---|---|---|---|
| | E.coli | B.subtilis | S.aureus | C.ablicans | A.niger |
| IIIa | 19 | 16 | 12 | 16 | 16 |
| IIIb | 22 | 18 | 17 | 19 | 17 |
| IIIc | 14 | 12 | 12 | 15 | 15 |
| IIId | 23 | 19 | 20 | 22 | 18 |
| IIIe | 19 | 17 | 17 | 18 | 17 |
| IIIf | 16 | 15 | 16 | 17 | 16 |
| Ciprofloxacin | 28 | 24 | 26 | - | - |
| Griseofulvin | - | - | - | 28 | 26 |

## III. RESULTS AND DISCUSSION

To overcome the resistance to antibacterial agents since last three decades promotes us to synthesize such a biologically active compound as second nitrogen in the five-membered ring also influences the antibacterial or pharmacokinetic properties. And the synthesized compounds were screened for their *in vitro* antibacterial and antifungal activity. Some of the derivatives showed moderate to excellent activity.

## IV. CONCLUSION

A series of novel 1, 3, 4-Thiadiazole-1, 3, 4-oxadiazole-2-thione derivatives were synthesized and the structures of the entire compounds were confirmed by recording by their1H NMR, and 13C NMR spectra. In conclusion, we feel that the preliminary All the synthesized compounds was screened for their *in vitro* antibacterial and antifungal activity. The screening studies have demonstrated that the newly synthesized compounds exhibit promising antibacterial and antifungal properties.

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