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# Synthesis and Antifungal Activity of Some 3-[3-(5-Nitro)indolyl]-5-(4-substituted phenyl)isoxazoline and Isothiazoline Derivatives

MUKESH KUMAR AHIRWAR*, RAHUL BARDIA and S.P. SHRIVASTAVA
*Department of Chemistry, Dr. H.S. Gour University, Sagar-470 003, India*
*E-mail: mukesh_phd @yahoo.co.in*

1-[3-(-5-nitro)indolyl]-3-substituted phenyl-2-ene-propanones **3(a-i)** were react with ethanol, hydroxylamine hydrochloride and aqueous NaOH to give 3-[3-(5-nitro)indolyl]-5-substituted phenyl isoxazolines **4(a-i)**. Isoxazolines **4(a-i)** was refluxed with phosphorous pentasulphide in pyridine to give 3-[3-(5-nitro)indolyl]-5-substituted phenyl isothiazolines **5(a-i)**. All the synthesized isoxazoline and isothiazoline were screened for antifungal activity.

**Key Words: Isoxazoline, Isothiazoline, Indole, Antifungal activity.**

## INTRODUCTION

Synthesis of isoxazoline derivative remains a main focus of medicinal chemists, due to their diverse pharmacological activity. Isoxazoline derivatives have been reported to possess antifungal[1,2], antibacterial[3], anticonvulsant[4], antiinflammatory[5], antiviral[6] and analgesic activity[7]. We have synthesized indole based isoxazoline and isothiazoline and screened for antifungal activity.

## EXPERIMENTAL

The melting points were determined in open capillaries with an electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT-IR -8400 spectrometer and $^1$H NMR spectra on Bruker spectrometer (300 Mz) using TMS as an internal standard. All chemical shift values were recorded as δ (ppm).

**Step-I: Synthesis of 5-nitro-3-acetyl indole (2):** To a solution of 5-nitro indole (0.01 mol) in $CHCl_3$ (dry 20 mL) acetyl chloride (0.02 mol) was added twice at 0.5 ºC with constant stirring. The reaction mixture was stirred for 2 h on magnetic stirrer and excess of solvent was distilled off and precipitate was poured into ice water. The resulting solid was filtered and washed with water and recrystallized from methanol.

Infrared of compound **2**: 3450 cm$^{-1}$ N-H str. of indole, 3025 cm$^{-1}$ Ar-H str. of indole 2930 cm$^{-1}$, 1680 >C=O str., 1475 cm$^{-1}$ O←N=O str.; $^1$H NMR of compound **2**: $CDCl_3$ in δ ppm): 8.67 singlet -NH- of indole, 6.34 unsym. multiplet- (4H of indole), 2.46 singlet (3H of $CH_3$).

**Step-II: Synthesis of 1-[3-(5-nitro)indolyl]-3-substituted phenyl 2-ene-propanone 3(a-i):** To a solution of compound 5-nitro-3-acetyl indole (0.01 mol) in methanol (25 mL) the aromatic aldehydes (0.01 mol) were added in presence of 30 % NaOH solution (10 mL) at 0 ºC. The reaction mixture was stirred for 6 h at room temperature and poured into ice water. The resulting solid was washed several times with water and recrystallized from methanol.

IR of compound **3a**: 3460 $cm^{-1}$ -NH- str. of indole, 3028 $cm^{-1}$ Ar-H str. of indole, 2628 $cm^{-1}$ C=C-H str., 1675 $cm^{-1}$ >C=O str., 1485 $cm^{-1}$ O←N=O str., 826 $cm^{-1}$ Ar-H for '*ortho*' substituted. $^1$H NMR of compound **3a**: ($CDCl_3$ in δ ppm): 8-69 singlet (NH of indole), 6.36 unsym. multiplet-(4H of indole), 2.89 singlet (1H; -CO-CH=), 1.78 singlet (1H; =CH-Ar), 7.43 unsym. multiplet (4H;- ('*ortho*' disubstituted benzene).

**Step-III: Synthesis of 3-[3-(5-nitro)indolyl]-5- substituted phenyl isoxazolines 4(a-i):** To an ethanolic solution of compound **3(a-i)** (0.01 mol), hydroxyl amine hydrochloride (0.02 mol) and KOH (30 % 20 mL) was added in presence of few drop of acetic acid as catalyst the reaction mixture was refluxed for 7-8 h. The solution as concentrated and cooled and a few drops of petroleum ether were added to give solid product which were recrystallized from benzene. The physical data of the synthesized compounds are given in Table-1.

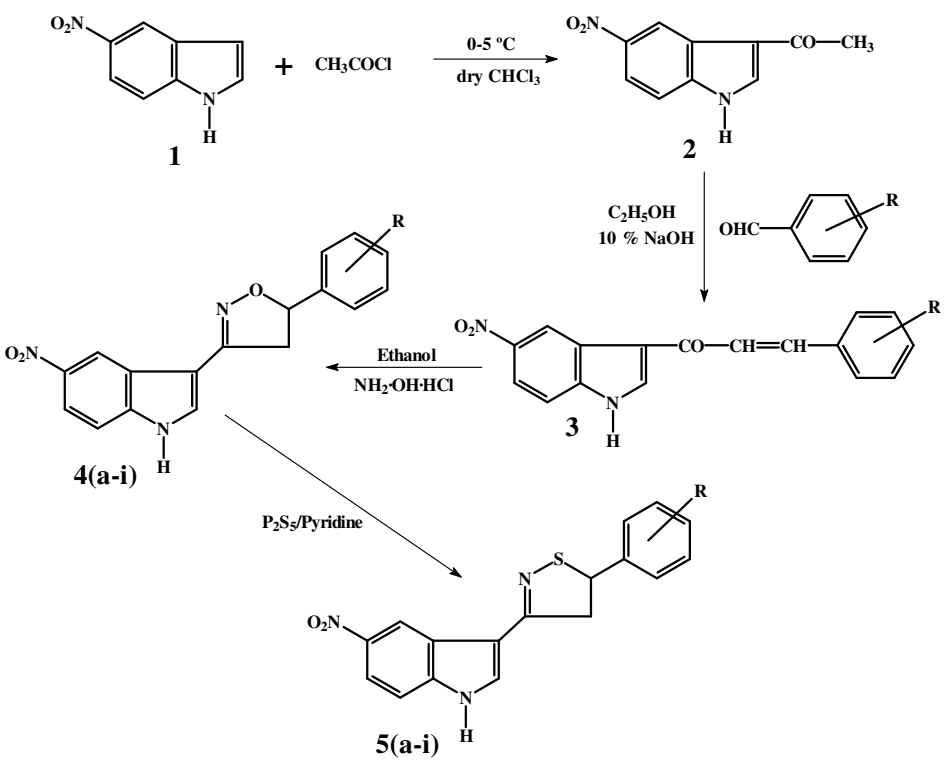
TABLE-1
PHYSICAL DATA OF ISOXAZOLINE DERIVATIVES **4(a-i)**

| Compd. | m.f. | Yield (%) | m.p. (ºC) | Elemental analysis (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | C | | H | | N | |
| | | | | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| **4a** | $C_{17}H_{12}N_3O_3Cl$ | 67 | 148 | 59.75 | 59.71 | 3.53 | 3.49 | 12.96 | 12.93 |
| **4b** | $C_{17}H_{12}N_3O_3Cl$ | 75 | 176 | 59.75 | 59.72 | 3.53 | 3.48 | 12.96 | 12.91 |
| **4c** | $C_{17}H_{12}N_3O_3Cl$ | 61 | 158 | 59.75 | 59.69 | 3.53 | 3.47 | 12.96 | 12.92 |
| **4d** | $C_{17}H_{12}N_4O_5$ | 74 | 186 | 57.96 | 57.93 | 3.43 | 3.39 | 15.96 | 15.94 |
| **4e** | $C_{17}H_{12}N_4O_5$ | 67 | 209 | 57.96 | 57.93 | 3.43 | 3.37 | 15.96 | 15.93 |
| **4f** | $C_{17}H_{12}N_4O_5$ | 63 | 192 | 57.96 | 57.92 | 3.43 | 3.35 | 15.96 | 15.92 |
| **4g** | $C_{17}H_{13}N_3O_4$ | 71 | 178 | 63.16 | 63.12 | 4.05 | 4.02 | 12.99 | 12.95 |
| **4h** | $C_{17}H_{13}N_3O_4$ | 67 | 205 | 63.16 | 63.11 | 4.05 | 4.01 | 12.99 | 12.96 |
| **4i** | $C_{17}H_{13}N_3O_4$ | 69 | 196 | 63.16 | 63.12 | 4.05 | 4.03 | 12.99 | 12.96 |

IR of compound **4a**: 3466 $cm^{-1}$ (NH of indole, 3029 $cm^{-1}$ Ar-H of indole, 2410 $cm^{-1}$ C=N str. isoxazoline,1436 $cm^{-1}$ O←N=O- str. of $NO_2$ group, 2840 and 2834 $cm^{-1}$ C-H str. of $CH_2$ of isoxazoline, 825 $cm^{-1}$ ('*ortho*' disubstituted benzene ring). $^1$H NMR of compound **4a** ($CDCl_3$ in δ ppm): 8.64 singlet (-NH- of indole), 6.24 unsym. multiplet (4H of indole), 2.48 triplet (1H; isoxazoline $C_5$-H), 2.32 doublet( 2H; isoxazoline $C_4$-$H_2$), 7.36 unsym. multiplet (4H- "o" disubstituted benzene ring).

**Step-IV: Synthesis of 3-[3-(5-nitro)indolyl]-5-substituted phenyl isothiazolines 5(a-i)[8]:** A mixture of compound **4(a-i)** (0.01 mol) and phosphorous pentasulphide (0.01 mol) in pyridine (20 mL) was refluxed on sand bath for 2 h

cooled and diluted with water. The solid separated was filtered, wash with water and crystallized from ethanol (**Scheme-I**). The physical data of the synthesized compounds are given in Table-2.




**Scheme-I**

TABLE-2
PHYSICAL DATA OF ISOTHIAZOLINE DERIVATIVES **5(a-i)**

| Compd. | m.f. | Yield (%) | m.p. (ºC) | Elemental analysis (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | C | | H | | N | |
| | | | | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| **5a** | $C_{17}H_{12}N_3SO_2Cl$ | 62 | 154 | 57.06 | 57.02 | 3.38 | 3.34 | 11.74 | 11.71 |
| **5b** | $C_{17}H_{12}N_3SO_2Cl$ | 72 | 187 | 57.06 | 57.01 | 3.38 | 3.35 | 11.74 | 11.71 |
| **5c** | $C_{17}H_{12}N_3SO_2Cl$ | 58 | 167 | 57.06 | 57.04 | 3.38 | 3.35 | 11.74 | 11.69 |
| **5d** | $C_{17}H_{12}N_4SO_4$ | 67 | 198 | 55.43 | 55.39 | 3.28 | 3.26 | 15.21 | 15.18 |
| **5e** | $C_{17}H_{12}N_4SO_4$ | 75 | 220 | 55.43 | 55.40 | 3.28 | 3.24 | 15.21 | 15.16 |
| **5f** | $C_{17}H_{12}N_4SO_4$ | 68 | 216 | 55.43 | 55.38 | 3.28 | 3.27 | 15.21 | 15.17 |
| **5g** | $C_{17}H_{13}N_3O_3S$ | 58 | 198 | 60.17 | 60.14 | 3.86 | 3.83 | 12.01 | 11.98 |
| **5h** | $C_{17}H_{13}N_3O_3S$ | 62 | 217 | 60.17 | 60.11 | 3.86 | 3.83 | 12.01 | 11.99 |
| **5i** | $C_{17}H_{13}N_3O_3S$ | 59 | 214 | 60.17 | 60.15 | 3.86 | 3.82 | 12.01 | 11.97 |

IR of compound **5a**: 3468 $cm^{-1}$ N-H str. of indole, 3026 $cm^{-1}$ Ar-H str. of indole, 2456 $cm^{-1}$ C=N- str. of isothiazoline, 1437 $cm^{-1}$ O←N=O str. of $NO_2$ group 2852-2845 $cm^{-1}$ C-H str. of $CH_2$ of isothiazoline, 821 $cm^{-1}$ ("*ortho*" disubstituted benzene ring). $^1H$ NMR of compound **5a** ($CDCl_3$ in δ ppm): 8.65 singlet (-N-H of indole), 6.43 unsym. multiplet (4H of indole), 2.43 triplet (1H; isothiazoline $C_5$-H), 2.29 doublet (2H; isothiazoline $C_4$-$H_2$), 7.45 unsym. multiplet (4H- "*ortho*" disubstituted benzene ring).

## RESULTS AND DISCUSSION

In the synthesis of compound **2** to compound **3**; >C=O *str.* 1680 $cm^{-1}$ shift to 1675 $cm^{-1}$ indicate that conjugation was present in compound **3**. On going from **3a** to **4a**, band at 1675 $cm^{-1}$ was absent and new *str.* band at 2410 $cm^{-1}$ indicate the formation of isoxazoline ring and **4a** to **5a**; 2410 $cm^{-1}$ band shift to 2456 $cm^{-1}$ indicate that isothiazoline ring will be formed. Same observation reflected by NMR spectrum of **2**, **3a**, **4a** and **5a** (shift of δ ppm number of equivalent proton sets; and its multiplicity).

Antifugal activity correlation show that shifting of Cl group "*ortho* to *para*" increased activity in isoxazoline ring (**4a-4c**); $NO_2$ group more potent as compound of Cl group, showed maximum activity at "*meta*" position (**4e**); but -OH group show less activity as compaired to Cl and $NO_2$ group and show maximum activity at "*meta*" position (**4h**).

But on going through the result of (**4a-i** to **5a-i**) (replacement of "O" by "S") overall increased the antifungal activity and substituent effect were same but enhanced.

**Antifungal activity:** Filter paper disc diffusion plate method[9] was used for evaluating antifungal activity of synthesized compounds **4(a-i)** and **5(a-i)** and related data were given in Table-3.

TABLE-3
ANTIFUNGAL ACTIVITY OF THE SYNTHESIZED
**4(a-i)** AND **5(a-i)** AGAINST VARIOUS FUNGI

| Compd. | *C. albicans* | Penicillin SP | *A. niger* |
|---|---|---|---|
| **4a(5a)** | - (±) | - (±) | (±)± |
| **4b(5b)** | ± (±) | ± (+) | + (+) |
| **4c(5c)** | + (++) | ++ (++) | ++ (++) |
| **4d(5d)** | + (+) | - (+) | - (+) |
| **4e(5e)** | ++ (++) | ± (+) | ± (+) |
| **4f(5f)** | ± (++) | + (++) | ++ (+) |
| **4g(5g)** | - (+) | - (-) | - (++) |
| **4h(5h)** | + (+) | ± (+) | - (+) |
| **4i(5i)** | ±(+) | + (+) | ± (+) |

Concentration = 50 µg/disc; (-) = Inactive (heavy colony); (++) = Strongly active (no fungal colony); Standard drugs = Gentamycin (no fungal colony); (+) = Moderately active (one colony); Incubation = 72 h at 35 ºC; (±) = Active (two colonies).

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