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# Synthesis, Characterization and Antimicrobial Activity of Novel Coumarin-fused Tetracycline Pyrazolo[3,4-b]pyridines

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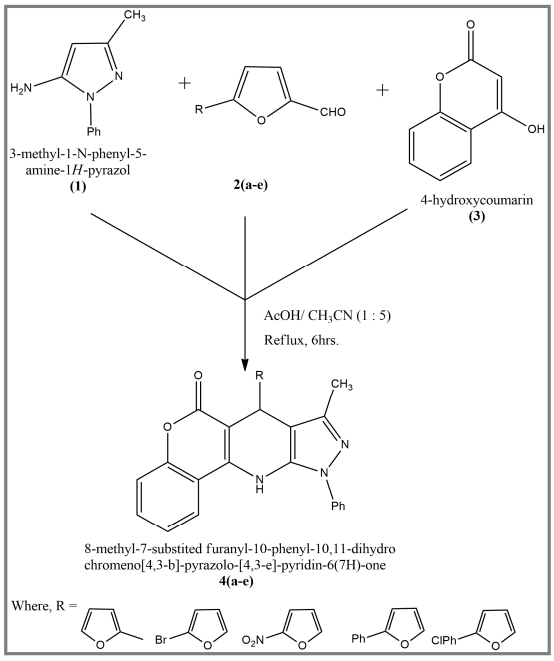
## ABSTRACT

*The three component reaction for the synthesis of coumarin-fused tetracycline system from 3-methyl-1-N-phenyl-5-amine pyrazole (1), 2-furaldehyde derivatives (2a-e) and 4-hydroxy coumarin (3) is presented. In acetonitrile /acetic acid solvent system yield 8-methyl-7-substited furanyl-10-phenyl-10,11-dihydrochromeno[4,3-b]-pyrazolo-[4,3-e]- pyridin-6(7H)-one 4(a-e) derivatives. All the 4a-e derivatives were characterized duly. The antifungal activities of all the derivatives were also monitored against plant pathogens.*

## Graphical Abstract

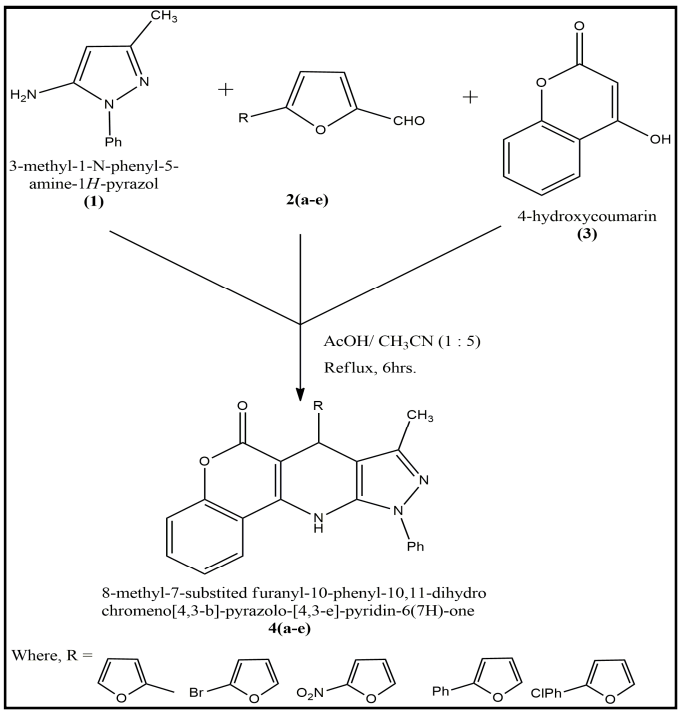



Tetracyclo coumarino pyrazolo-pyridine derivatives

**Keywords:** Coumarin-fused tetracycline system, 3-Methyl-1-phenyl-1H-pyrazol-5-amine, 4-hydroxy coumarin, Characterization, Antifungal activities.

## INTRODUCTION

Nitrogen containing heterocyclic compounds are backbone of drug design and play an important role in bio-chemical reaction [**1-3**]. Among them Pyrazolo[3,4-b]pyridine skeleton have proven to be interesting classes of heterocycles due to diverse biological properties including antitubercular, antibacterial and antioxidant activities [**4-7**]. Pyrazolo [3,4-b] pyridine exhibit a broad variety of biological activities, like antimicrobial, insecticidal, anti-inflammatory, antineoplastic, anticonvulsant, antiparasitic, anti-fungal activities [**8-15**]. Thus in continuous of our previous research work [**16**], it was thought to synthesized this type of fuse molecules. The present communication deals with the synthetic approach shown in scheme 1.




**Scheme 1.** Tetracyclo coumarino pyrazolo-pyridine derivatives.

## MATERIALS AND METHODS

All the chemicals were used laboratory grade. The methods in [**17**] were followed for the synthesis of 3-Methyl-1-N-phenyl-5-amine-1H-pyrazol (1).

$^{1}$HNMR spectra were recorded on a Bruker (400 MHz) spectrometer. Deuterated DMSO was used as a solvent. The IR spectra of all compounds were taken in KBr pellets on a Nicolet 400D spectrometer. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046. All the compounds were checked for their purity by TLC. The characterization data of all these compounds are given in table 1.

Antifungal activity of all the samples was monitored against various fungi, following the method reported in literature [**18**]. The antifungal activities of the series of compounds 4(a-e) were shown in table 2.

Synthesis of 8-methyl-7-substited furanyl-10-phenyl-10,11-dihydro chromeno [4,3-b]-pyrazolo-[4,3-e]- pyridin- 6(7H)- one 4(a-e):A mixture of 3-Methyl-1-phenyl-1H-pyrazol-5-amine (1) (1 mmol), 2-furaldehyde (1 mmol) and 4-hydroxy coumarin (3) (1 mmol) in acetic acid (25 mL) and in

the presence of acetonitrile (1.5 mL) was heated under reflux for 5-6 h. The reaction mixture was poured into crushed ice (30 mL) and the solid obtained was collected by filtration, washed with water and recrystallized from Ethyl alcohol give pure 4(a-e). The details are given in table 1.

**Table 1.** Physical and Analytical Data of the Compounds Synthesized 4(a-e)

| Comp. No. | Molecular Formula | M.P.* °C | Elemental Analysis | | |
|---|---|---|---|---|---|
| | | | C% | H% | N% |
| | | | Calcd. (Found) | Calcd. (Found) | Calcd. (Found) |
| **4a** | $C_{24}H_{17}N_3O_3$ (395) | 174-175 | 72.90 (72.8) | 4.33 (4.3) | 10.63 (10.6) |
| **4b** | $C_{24}H_{16}N_3O_3Br$ (474) | 170-171 | 60.77 (60.7) | 3.40 (3.3) | 8.86 (8.8) |
| **4c** | $C_{24}H_{16}N_4O_5$ (440) | 168-169 | 65.45 (65.4) | 3.66 (3.6) | 12.72 (12.7) |
| **4d** | $C_{30}H_{21}N_3O_3$ (471) | 163-164 | 76.42 (76.4) | 4.49 (4.4) | 8.91 (8.8) |
| **4e** | $C_{30}H_{20}N_3O_3Cl$ (505.5) | 175-176 | 71.22 (71.2) | 3.98 (3.9) | 8.31 (8.3) |

***Uncorrected LC*-MS data for **4a**:396.8, **4d**: 473.2

## RESULTS AND DISCUSSION

Here, it accomplished synthesis of pyrazolo[3,4-b]pyridine derivatives**4(a-e)** in which the multi component reactions of 3-methyl-1-N-phenyl-5-amine pyrazol(1), 2-furaldehyde derivatives (2a-e) and 4-hydroxycoumarin (3) were carried out in acetic acid (as shown in scheme 1).

The structures of **4(a-e)** were confirmed by elemental analysis and IR spectra showing an absorption bands at 3030-3080 $cm^{-1}$(C-H of Ar), 1120$cm^{-1}$(C-N), 1080 (-Cl), 1555, 1375(-$NO_2$), 2960, 1370$cm^{-1}$(-$CH_3$), 690$cm^{-1}$ (C-Br), 750-800 $cm^{-1}$ (C=N), 1755(CO), 1180-1200 $cm^{-1}$ (C-O). $^1$H NMR(400MHz, DMSO-$d_6$, δ/*ppm*): 8.92(s,1H,N-H), 5.1(s,1H,C-H of pyridine ring), 2.08 (s,3H,$CH_3$), **(4a):** 8.35-7.42 (m, 9H, Ar-H), 6.10-7.62(m,3H,furan ring); **(4b)**: 8.35-7.42 (m, 9H, Ar-H), 6.45-7.62 (d, 2H, furan ring); **(4c)**: 8.35-7.42 (m,9H,Ar-H), 6.44-7.62(d,H,furan ring); **(4d)**: 8.35-7.42 (m,14H, Ar-H), 6.43-7.62(d,3H,furan ring), 8.25-7.42(m,9H,Ar-H); **(4e)**: 8.35-7.42 (m,14H,Ar-H), 6.44-7.62(d,3H,furan ring), 8.32-7.42 (m, 9H, Ar-H). The C, H, N analysis data of all compounds are presented in table 1.

**Table 2.** Antifungal Activity of Compounds 4(a-e)

| Comp. No. | Zone of inhibition of fungus at 1000 ppm (%) | | | |
|---|---|---|---|---|
| | *Aspergillus niger* | *Botryodiplodia theobromae* | *Nigrospora sp* | *Fusarium oxysporum* |
| **4a** | 64 | 59 | 61 | 65 |
| **4b** | 77 | 74 | 76 | 78 |
| **4c** | 65 | 60 | 66 | 64 |
| **4d** | 68 | 64 | 71 | 69 |
| **4e** | 74 | 70 | 74 | 76 |

All the elemental and spectral features suggest that the data are consistent with the predicted structure shown in scheme 1. The LC-MS of selected compounds shows the peak of $M^+$ ion which is consistent of their molecular weight. All these facts confirm the structures 4(a-e).

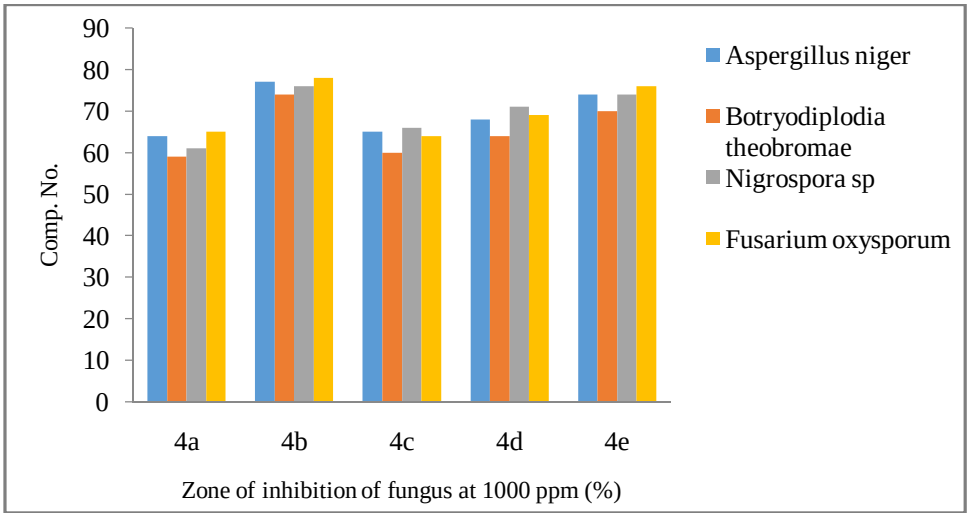



**Figure 1.** Antifungal Activity of Compounds 4(a-e).

The examination of antibacterial activity data reveals that all compounds toxic against microbes and the compounds **4b** and **4e** found more active against the gram-positive and gram-negative bacteria. The results show that the compounds are good toxic for microbes.

## APPLICATION

Synthesis compounds have very good antifungal activity for tested microbes. So the compounds can be used as vegetable and garden fungicide. Having structural functionally the compounds can also form metal complexes. The compound can also applicable for metal corrosion inhibition.

## CONCLUSION

Multicomponent synthesis of tetracycline fused coumarino-pyrazolo-pyridin derivatives was performed. The fused tetracyclo heterocycles have characterized and assigned their structures. The antifungal activity of all the compound is found to be very good.

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