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# SYNTHEISIS AND EVALUATION OF ANTIFUNGAL ACTIVITY OF NOVEL INDOLE DERIVATIVES

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## ABSTRACT

Novel Mannich bases of indole were synthesized by using a series of secondary amines and formaldehyde in presence of ethanol with magnetic stirring for 4-6 hours in cold condition. The structures of these compounds were established on the basis of spectral data. The final compounds were screened for antifungal activity against *Candida albicans* using cup- plate method. Ketoconazole was used as standard drug.

**Key words** : Indole, Secondary amines, Antifungal.

## INTRODUCTION

In recent years, with the increasing instances of systemic mycosis and the realization of fungal diseases becoming fatal, there has been renewed interest in synthesis of new antifungal agents. Since there are fewer new drugs available and there is an ever increasing threat of microbial drug resistance, it is becoming more and more essential to devote attention to mycology and more importantly to synthesize drugs with higher potency and low toxicity[1].

Indole derivatives had been a topic of substantial research interest and continued to be one of the most active areas of heterocyclic chemistry, particularly due to their natural occurrence and pharmacological activities[2]. indole derivatives also occur widely in many natural products such as those from plants[3], fungi[4] and marine organisms[5]. The present research work describes the synthesis and antifungal evaluation of novel indole derivatives.

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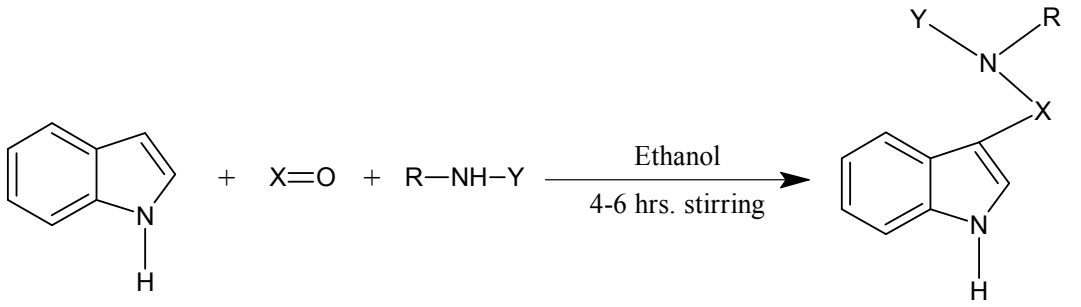
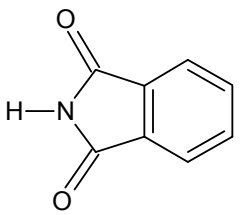
## EXPERIMENTAL

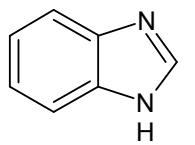
**Scheme : Synthesis of mannich bases of indole[6]**



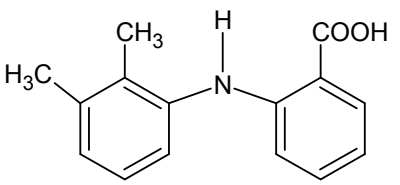

**a[1]** **d[1]**



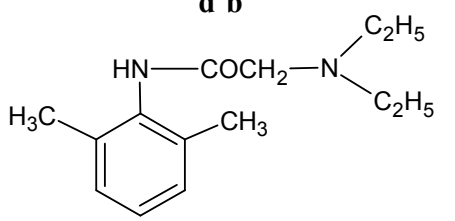
**d[1]a**



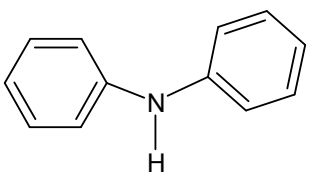
**d[1]b**



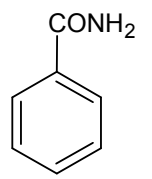
**d[1]c**



**d[1]d**



**d[1]e**



**d[1]f**

Equimolar quantities (0.01 mol) of indole and secondary amines and formaldehyde

were dissolved in ethanol and stirred for 4-6 hrs. in cold condition. The content was kept over night in the freezer. The product obtained was dried, filtered and recrystallised from alcohol.

## Evaluation of antifungal activity[7]

The antifungal activity was determined by cup-plate method[8]. The in vitro antifungal activity was carried out against 24 h culture of *Candida albicans.* The compounds were tested at concentration 0.001 mol/mL in dimethyl formamide against *Candida albicans*. Ketoconazole (0.001 mol/mL) was used as standard for comparison of antifungal activity. The zone of inhibition was compared with the standard drug after 24 h of incubation at 72 h at 25º C for antifungal activity. The results are reported in Table 1

**Table 1. Physico-chemical data and activity of compounds**

| Comp. | Mol. formula | Mol. Wt. | M. P. (ºC) | Yield (%) | $R_f$ Value | Zone of inhibition (mm)* |
|---|---|---|---|---|---|---|
| **d[1]a** | $C_{17}H_{12}N_2O_2$ | 276 | 89-92 | 65 | 0.49 | 20 |
| **d[1]b** | $C_{16}H_{13}N_3$ | 247 | 80 – 82 | 72 | 0.39 | 15 |
| **d[1]c** | $C_{24}H_{22}N_2O_2$ | 370 | 92 – 94 | 75 | 0.60 | 11 |
| **d[1]d** | $C_{23}H_{29}N_3O$ | 363 | 69 – 71 | 74 | 0.54 | 18 |
| **d[1]e** | $C_{29}H_{27}N_2$ | 403 | 120 – 122 | 73 | 0.53 | 11 |
| **d[1]f** | $C_{24}H_{23}N_3O$ | 369 | 83 – 85 | 62 | 0.55 | 14 |
| Standard | Ketoconazole | - | - | - | - | 22 |

* Including diameter of the well, control is DMF (0.1% solution in distilled water) and it did not show any activity

## Spectral studies[9]

Melting points were determined by open ended capillary tube method. Purity of compounds was checked on silica Gel TLC plates. IR spectra were recorded on Shimadzu 4000 FTIR Spectrophotometer using KBr disc method. $^1$H NMR spectra were recorded on Bruker AMX-4000 $CDCl_3$ - d[3] as internal standard.

## Spectral data

**d[1]a** : IR (KB r) $cm^{-1}$ : 3447 (NH str.), 2980 (Ar-CH), 1604 (C = O str.), $^1$H NMR

(δ ppm) : 7.12-7.89 (Ar. H, 8H), 5.25 (1H, S, NH), 6.95 (1H, S, CH), 4.25 (2H, T, $CH_2$)

**$d^1$b :** IR (KBr) $cm^{-1}$ : 3252 (NH str.), 1457 ($CH_2$ str.), 3050 (Ar. CH str.), 740 (Ar Disubstituted str.)

**$d^1$c :** IR (KBr) $cm^{-1}$ : 3242 (NH str.), 1452 ($CH_2$ str.), 1699.17 (Aryl COOH), 1328 (Ar. tº-amine), 746 (. Ar Disubstituted str.), $^1$H NMR (δ ppm) : 6.73 (1H, T, NH), 9.1 (1H, S, OH), 4.25 (1H, S, $CH_2$), 7.03-8.06 (Ar. H, 12H).

**$d^1$d :** IR (KBr) $cm^{-1}$ : 3329 (NH str.), 3029 (Ar. CH str.), 1647 (C=O str.), 1457 $CH_3$ str.), 1309 (Ar. $t^0$ - amine str.)

**$d^1$e :** IR (KBr) $cm^{-1}$ : 3399 (NH str.), 3056 (Ar. CH), 1338 (Ar tº-amine), 688 Ar. m substituted), 747 (Ar. Disubstituted).

**$d^1$f** : IR (KBr) $cm^{-1}$ : 3367 (NH str.), 3064 (Ar-CH), 1700 (Aryl COOH), 1652 (C=O), 1354 (Ar. 2º - amide), 770.51 (Ar. m substituted); $^1$H NMR (δ ppm) : 1.75 (6H, S, $CH_3$), 6.12 (1H, S, CH), 7.26-7.84 (14H, M, Ar. H)

## RESULTS AND DISCUSSION

Novel Mannich bases were synthesized by Mannich Reaction and spectral data were analyzed by $^1$H NMR and FT-IR spectrophotometer. The title compounds synthesized were evaluated for antifungal activity by cup plate method. Few compounds have shown maximum antifungal activity. Compounds **$d^1$a, $d^1$b** and **$d^1$d** have showed maximum antifungal activity. Compounds **$d^1$c**, **$d^1$e** and **$d^1$f** have showed less significant antifungal activity. Ketoconazole was used as standard.

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