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# Synthesis and Antifungal Activity of Isatin-3-semicarbazone

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Isatin-3-semicarbazone and substituted isatin-3-semicarbazone were synthesized and their antifungal activity was screened. It was observed that the semicarbazones showed inhibitory activity at 100-500 µg/mL.

**Key Words: Isatin-3-semicarbazone, Antibacterial activity.**

## INTRODUCTION

Since the 1970's, there has been a steady increase in the incidence of serious secondary systemic fungal infections. One of the factor aiding the spread of fungal disease has been the wide spread use of broad-spectrum antibiotics, which eliminate or decrease the non-pathogenic bacterial populations that normally compete with fungi. Another has been the increased number of individuals with reduced immune responses caused by the acquired immuno-deficiency syndrome (AIDS) or by the action of immunosuppresant drugs or cancer chemotherapy agents. This has led to an increased prevalance of opportunistic infections *i.e.*, infections with fungi that rarely cause disease in healthy individuals.

Majority in the World, the commonest systemic fungal infections are blastomycosis, histoplasmosis, coccidiomycosis and *para*-coccidiomycosis; these are primary infections *i.e.*, they are not secondary to reduced immunological function or altered commensal microorganisms[1-3].

The need for better clinical agents has emerged because of the increasing detection of systemic mycosis in patients suffering from debilitating diseases such as in neoplasias. Systemic mycosis has been found in 61 % of patient dying with acute leukemia, in 45 % deaths in renal transplant recipients and 75 % of AIDS patients[4]. The compounds synthesized in this study with isatin moiety could very well be new chemical entities as antifungal agents and so the compounds were tested for antifungal activity[5,6].

Isatin, also named indoline-2, 3-dione, is a bright coloured compound with a long history and a broad range of pharmacological actions. Chemically, isatin may be characterised as lactam of *o*-amino-benzoylformic acid. It possesses both amide group and a keto group.

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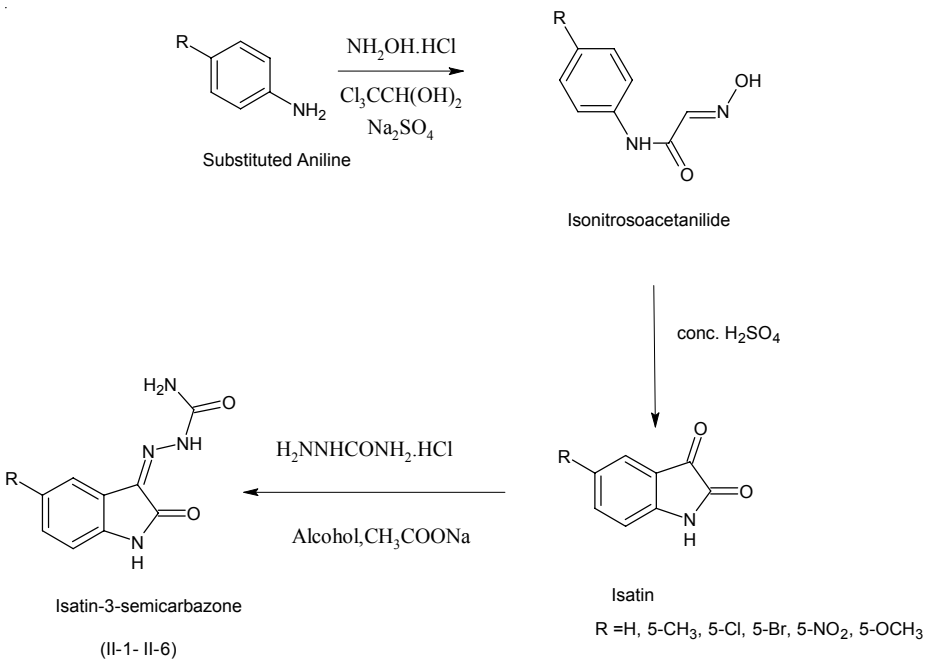
## EXPERIMENTAL

Melting points were taken by Open Capillary method and are uncorrected. UV Spectra were recorded on a Jasco 7800UV/Visible spectrophotometer and IR spectra on a Jasco 5800 FT-IR using KBr discs.The $^1$H NMR spectra were recorded on a Jeol FX-90Q spectrophotometer in DMSO-$d_6$ or $CDCl_3$ with TMS as an internal standard. Elemental analysis were determined with Perkin-Elmer model 240 analyzer. The purity of the compounds was confirmed by thin layer chromatography using silica gel plates and different solvent systems. Isatin was purchased from Ward, Blenkinsop & Co. Ltd.

A mixture of semicarbazide hydrochloride (0.1 mol, 11.1 g) and sodium acetate (0.15 mol, 12.3 g) was dissolved in 100 mL of water. To this isatin (0.1 mol, 14.7 g) dissolved in 150 mL of alcohol was added and the whole mixture stirred for 10-15 min. It was warmed on a water-bath to dissolve the contents and then cooled in ice when a yellow precipitate was obtained (**Scheme-I**). It was filtered, dried and recrystallized with alcohol, m.p. 270 °C, yield 61.0 %. Similarly, 5-subsituted isatin-3-semicarbazones were prepared from corresponding isatin (Table-1).

**Spectral data:** UV ($\lambda_{max}$ MeOH): 400; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3550-3400s (N-H), 1730s ($CONH_2$), 1710m (C=O), 1690m (amide C=O), 1680s (C=N); $^1$H NMR (DMSO-$d_6$, δ ppm): 7.0 (s, 2H, $CONH_2$) 7.2-7.5 (m, 4H, aromatic), 8.2 (d, 1H, NH, indole), 10.5 (s, 1H, =NNH $D_2O$ exchangeable).




**Scheme-I:** Synthesis of isatin-3-semicarbazone (**II-1**) and substituted isatin-3-semicarbazones (**II-2-6**)

TABLE-1
CHARACTERIZATION DATA OF 5-SUBSTITUTED ISATIN-3-SEMICARBAZONES

| Compd. No. (m.f.) | R | m.p. (ºC) / Yield (%) | Analysis % | | $R_f$ value | IR (KBr, $\nu_{max}$, $cm^{-1}$) |
|---|---|---|---|---|---|---|
| | | | Calcd. | Found | | |
| II-2 ($C_9H_7ClN_4O_2$) | 5-Cl | 210 (62) | C: 45.29 H: 2.95 N: 23.48 | C: 45.35 H: 2.68 N: 23.32 | 0.71 | 3550-3400m (NH stretch), 1720s (C=O), 1680s (C=N), 550m (C-Cl) |
| II-3 ($C_{10}H_{10}N_4O_2$) | 5-$CH_3$ | 245 (69) | C: 56.03 H: 4.61 N: 25.68 | C: 55.42 H: 4.83 N: 25.74 | 0.73 | 3400s (NH stretch), 1720s (C=O), 1685m (C=N) |
| II-4 ($C_9H_7BrN_4O_2$) | 5-Br | 205 (68) | C: 38.18 H: 2.49 N: 19.79 | C: 38.23 H: 2.31 N: 19.83 | 0.68 | 3450-3400m (NH stretch), 1750s (C=O), 1680s (C=N), 1400m (aromatic) |
| II-5 ($C_9H_7N_5O_4$) | 5-$NO_2$ | 160 (67) | C: 43.37 H: 2.83 N: 28.11 | C: 43.62 H: 2.57 N: 28.28 | 0.38 | 3420, 3340, 1725m (C=O), 1680s (C=N), 1500s (aromatic) |
| II-6 ($C_{10}H_{10}N_4O_3$) | 5-$OCH_3$ | 215 (54) | C: 51.27 H: 4.30 N: 23.92 | C: 51.53 H: 4.51 N: 23.85 | 0.62 | 3400s (NH stretch), 1720s (C=O), 1670m (C=N), 1570s (aromatic) |

## Antifungal activity[6-8]

**Culture media:** Sabouraud glucose agar (SGA) medium was used. Glucose (4 g), agar agar (2.0 g) and peptone (1.0 g) were dissolved in 100 mL of distilled water and pH was adjusted to 6-8 using acid or alkali. The medium was sterilized in an autoclave at 15 lbs per sq. inch for 15 min.

**Preparation of test samples:** Each test sample (0.5 mg) was dissolved in 5 mL of DMF (100 mg/mL) with warming to form the stock solution. From each stock sample, 1 mL was poured into each sterile test tube.

**Tube slant culture method:** Sabouraud glucose agar (SGA) medium was melted, cooled to 45-50 ºC and poured 1 mL each into test tubes containing 1 mL of test samples to make the final concentration of test samples 100 mg/mL. The contents were mixed well without formation of any air bubbles. The cotton plugged test tubes were then kept at an angle of 30 ºC and media were allowed to solidify to form slants.

In the aseptic UV chamber, the slants were inoculated with a platinum loopful of the fungi from stock culture so that fungi were just embedded into the slant and also spread over the surface of the slant. The inoculated slants were then in incubated at 37 ºC in an incubator and growth of fungi studied after 45 h and 7 d. The growth of fungi in the slant was compared for the test samples against the control group[7,8].

## RESULTS AND DISCUSSION

The antifungal activity of isatin-3-semicarbazones (**II-1** to **II-6**) were investigated against *Candida albicans* and *Aspergillus niger* at different concentrations and the semicarbazones showed inhibitory activity at 100-500 µg/mL. The antifungal activity

exhibited by these compounds is not very encouraging. The isatin-3-semicarbazone (**II-1**) was found to be active at the concentration used. Among the semicarbazones, the 5-chloro (**II-2**) and 5-bromo (**II-4**) showed a zone of inhibition of 1.6 and 2.2 cm (Table-2).

TABLE-2
ANTIFUNGAL ACTIVITY OF ISATIN-3-SEMICARBAZONES

| Bacteria | II-I | II-2 | II-3 | II-4 | II-5 | II-6 |
|---|---|---|---|---|---|---|
| *Candida albican* | + | + | – | + | – | – |
| *Aspergillus niger* | + | – | – | – | – | – |

Concentration = 100 mg/mL for II-1; 500 mg/mL for II-2 to II-6
+ = Inhibition; – = no inhibition; ± = Weak inhibition.

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