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# SYNTHESIS, CHARACTERAZION AND EVALUATION OF NOVEL INDOLE DERIVATIVES

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## ABSTRACT

*A series of para substituted-2-(1H-pyrrolo[2,3-b] pyridin-3-yl carbonyl) hydrazinecarbothioamide (III) derivatives were synthesized by treating 1H-pyrrolo[2,3-b] pyridine-3-carboxylic acid with thionyl chloride followed by reaction with para substituted aryl thiosemicarbazides. IR, $^1$H NMR spectral data are confirming the synthesis of para substituted-2-(1H-pyrrolo[2,3-b] pyridin-3-yl carbonyl) hydrazinecarbothioamide (III) derivatives. The synthesized compounds were evaluated for their antifungal and antioxidant activities, among the series chloro-substituted derivatives were showed potent but all the compounds showed mild to moderate activities, all the compounds are less potent than standard.*

## KEY WORDS

*para substituted-2-(1H-pyrrolo[2,3-b] pyridin-3-yl carbonyl) hydrazine carbothioamide, antifungal activity, antioxidant activity.*

## INTRODUCTION

Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. Indole is a popular component of fragrances and the precursor to many pharmaceuticals. Indoles are probably the most widely distributed heterocyclic compounds in nature. Tryptophan is an essential amino acid and as such is a constituent of most proteins; it also serves as a biosynthetic precursor for a wide variety of tryptamine, a neurotransmitter 5-HydroxyTryptamine (serotonin), indole-, and 2,3-dihydroindole-containing secondary metabolites. Substituted indoles, azaindole group was considered as a potential surrogate for the indole core, thus providing a distinct series of therapeutic agents with varied pharmacological activities. The (mono)-azaindoles, trivially named pyrrolopyridines, where a carbon of the six-membered ring has been replaced by nitrogen either at 4- or 7- positions, are of theoretical interest as prototypes of bicyclic systems comprising an electron-rich ring fused to an electron poor ring. The simple systems do not occur in nature, but polycyclic compounds, such as the variolins have been isolated from sponges. Simple azaindoles have been isolated from coal tar and the oxidative degradation of carboline alkaloids. They have elicited significant interest in medicinal chemistry as isosteres of indoles, Azaindoles show the typical reactivity of both component systems but to a reduced and varying degree, with reduced electron density in the five-membered ring and increased electron density in the six-membered ring particularly as components of azatryptamine analogues and even as di-deazapurines.

## EXPERIMENTAL

**General Procedure for the Synthesis of 1H-Pyrrolo[2,3-b] pyridino-3-carbonyl chloride (II)[1]**

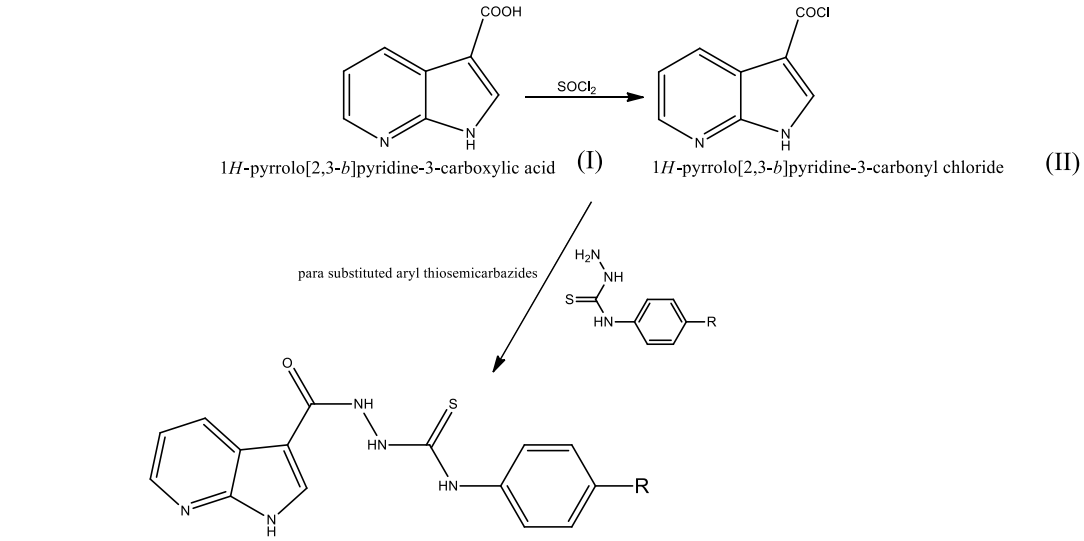
4.0 grams of 1H-Pyrrolo[2,3-b] pyridino-3-carboxylic acid (I) was dissolved in 70ml of chloroform in a RB flask with sttiring. Thionylchloride (4.03ml) was added to the reaction mixture at room temperature in dropwise

manner. Reflux the reaction mixture for three hours. Cool the reaction mixture and distilled off the excess thionylchloride.

**General Procedure for the Synthesis of para substituted 2(1H-pyrrolo[2,3-b] pyridine-3-carbonyl-N(p-tolyl) hydrozine carbothiamide) (III)[2]**

The cyclocondesation reaction of compounds (II) with para-substituted aryl thio semicarbazide were carried out in a molar ratio of 1:1, using pure methonol as solvent.the reactions were monitorted by TLC and the most satisfactory reaction time and reaction temperature were found to be 24h at 20-25°C.

**SCHEME - I**




***N*-phenyl-2-(1*H*-pyrrolo[2,3-*b*] pyridin-3-ylcarbonyl) hydrazinecarbothioamide ($III_a$):**

Mol.formula: $C_{15}H_{13}N_5OS$; mp: 205-210°C;

**IR (KBr, $cm^{-1}$):** 3320 (NH str), 2928 (Ar-CH str), 1650 & 1568 (Ar-C=C str), 1675 (C=O str).

**$^1$H NMR ($CDCl_3$,δ ppm):** 3.90 (br, s, 1H, NH of ring), 4.02 (br, s, 2H, NH-S-NH), 6.32 (s, 1H, =CH), 7.25-7.68 (m, 8H, Ar-H), 8.01 (s, br, 1H, NH-C=O).

***N*-(4-chlorophenyl)-2-(1*H*-pyrrolo[2,3-*b*] pyridin-3-ylcarbonyl) hydrazinecarbothioamide ($III_b$):**

Mol.formula: $C_{15}H_{12}ClN_5OS$; mp: 220-225°C;

**IR (KBr, $cm^{-1}$):** 3310 (NH str), 2932 (Ar-CH str), 1655& 1570 (Ar-C=C str), 1685 (C=O str), 720 (C-Cl str).

**$^1$H NMR ($CDCl_3$,δ ppm):** 3.85 (br, s, 1H, NH of ring), 4.06 (br, s, 2H, NH-S-NH), 6.32 (s, 1H, =CH), 7.35-7.78 (m, 7H, Ar-H), 8.05 (s, br, 1H, NH-C=O).

***N*-(4-fluorophenyl)-2-(1*H*-pyrrolo[2,3-*b*] pyridin-3-ylcarbonyl) hydrazinecarbothioamide ($III_c$):**

Mol.formula: $C_{15}H_{12}FN_5OS$; mp: 245-250°C;

**IR (KBr, $cm^{-1}$):** 3320 (NH str), 2940 (Ar-CH str), 1665& 1550 (Ar-C=C str), 1670 (C=O str), 620 (C-F str).

**$^1$H NMR ($CDCl_3$,δ ppm):** 3.65 (br, s, 1H, NH of ring), 4.01 (br, s, 2H, NH-S-NH), 6.40 (s, 1H, =CH), 7.25-7.39 (m, 7H, Ar-H), 8.09 (s, br, 1H, NH-C=O).

***N*-(4-hydroxyphenyl)-2-(1*H*-pyrrolo[2,3-*b*] pyridin-3-ylcarbonyl) hydrazinecarbothioamide ($III_d$):**

Mol.formula: $C_{15}H_{13}N_5O_2S$; mp: 265-270°C;

**IR (KBr, $cm^{-1}$):** 3320 (NH str), 3215 (br, OH str)2940 (Ar-CH str), 1665& 1550 (Ar-C=C str), 1670 (C=O str).

**$^1$H NMR ($CDCl_3$,δ ppm):** 3.65 (br, s, 1H, NH of ring), 4.01 (br, s, 2H, NH-S-NH), 5.05 (1H, OH)6.40 (s, 1H, =CH), 7.25-7.39 (m, 7H, Ar-H), 8.09 (s, br, 1H, NH-C=O).

***N*-(4-bromophenyl)-2-(1*H*-pyrrolo[2,3-*b*] pyridin-3-ylcarbonyl) hydrazinecarbothioamide ($III_e$):**

Mol.formula: $C_{15}H_{12}BrN_5OS$; mp: 250-255°C;

**IR (KBr, $cm^{-1}$):** 3330 (NH str), 3220 (br, OH str), 2945 (Ar-CH str), 1655& 1560 (Ar-C=C str), 1675 (C=O str), 660 (C-Br, str).

**$^1$H NMR ($CDCl_3$,δ ppm):** 3.65 (br, s, 1H, NH of ring), 4.01 (br, s, 2H, NH-S-NH), 5.05 (1H, OH)6.40 (s, 1H, =CH), 7.25-7.39 (m, 7H, Ar-H), 8.09 (s, br, 1H, NH-C=O).

**ANTIFUNGAL ACTIVITY [3]**

The test compounds were screened for antifungal activity using sabouraud dextrose agar medium.The organisms used are *Asperigillus niger, Candida albicans, Malassezia furfur.*

**Preparation of sabouraud dextrose agar medium**

Media was prepared by dissolving 40grams dextrose,12grams peptone in100ml distilled water and pH was adjusted to 5.6 ± 0.2 using 0.1 N sodium hydroxide.Then 15g agar was added and allowed to dissolve by heating on water bath.The prepared media was sterilized by autoclaving at 15lb/$in^2$ for 20 minutes.

**Method**

Different concentrations (25, 50, 75, 100, 125, 150, 175, 200 µg/ml) from the entire test compounds (IIIa-e) were prepared stock solition which is prepared by dissoving 10mg/10ml of DMSO.

Antifungal activity data: MIC (µg/ml) of compounds IIIa-e were presented in Table 1.

| CODE | R | MIC (µg/ml) | | |
|---|---|---|---|---|
| | | *M.furfur* | A.niger | C.albicans |
| IIIa | -H | 200 | 175 | 180 |
| IIIb | -Cl | 125 | 100 | 90 |
| IIIc | -F | 150 | 125 | 175 |
| IIId | -OH | 125 | 175 | 150 |
| IIIe | -Br | 180 | 175 | 145 |
| Std | Fluconazole | 8 | 10 | 20 |

**ANTIOXIDANT ACTIVITY [4]**

**DPPH Method**

Two 1ml of 0.135mM DPPH prepared in methanol was mixed with 1ml of test compounds ranging from 20-100µg/ml.The reaction mixture was vortexed thoroughly and left in dark at room temperature for 30min.The absorbannce was measured spectrophotometrically at 517nm.The scavenging ability of the test compounds was calculated using the standard equation.

The % inhibition and $IC_{50}$ values were given in Table 2.

**Table 2: Antioxidant activity of synthesized compounds (IIIa-e) by DPPH method**

| CODE | R | % Inhibition | | | | | $IC_{50}$ (µg/ml) | $IC_{50}$ (µm) | $IC_{50}$ (nm) |
|---|---|---|---|---|---|---|---|---|---|
| | | 20 | 40 | 60 | 80 | 100 | | | |
| IIIa | -H | 22.23 | 25.24 | 28.63 | 35.04 | 40.64 | 107.44 | 0.37 | 374 |
| IIIb | -Cl | 18.33 | 21.83 | 22.33 | 27.14 | 32.77 | 35.26 | 0.23 | 230 |
| IIIc | -F | 37.03 | 42.44 | 47.15 | 54.52 | 58.29 | 70.41 | 0.19 | 189 |
| IIId | -OH | 51.83 | 55.24 | 62.67 | 72.35 | 76.68 | 51.35 | 0.17 | 168 |
| IIIe | -Br | 59.26 | 72.35 | 79.74 | 82.44 | 85.26 | 45.33 | 0.13 | 134 |

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