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Synthesis and Evaluation of Antibacterial Activity of Novel Azaindole Derivatives

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ABSTRACT: *Azaindoles are an important class of nitrogen containing heterocyclics and were identified as the most active and potent classes of compounds with wide range of biological and pharmacological activities. They were extensively used as pharmaceuticals. Although the number of drugs are available in the market even though the search for new molecules is ever demanding. In present work various Azaindoles were synthesized and characterized using physical and spectral data. Finally, the Azaindole derivatives were screened for their In vitro antibacterial activity. Some of the molecules exhibited very good potency when compared with respective standards. The approach is very challenging and was found difficult to get a molecule with potency. Even though, the present molecules were provided novel leads against gram +ve and gram –ve bacteria.*

Keywords*: Azaindoles, antibacterial, gram +ve, gram –ve, heterocyclics, potent.*

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I. Introduction

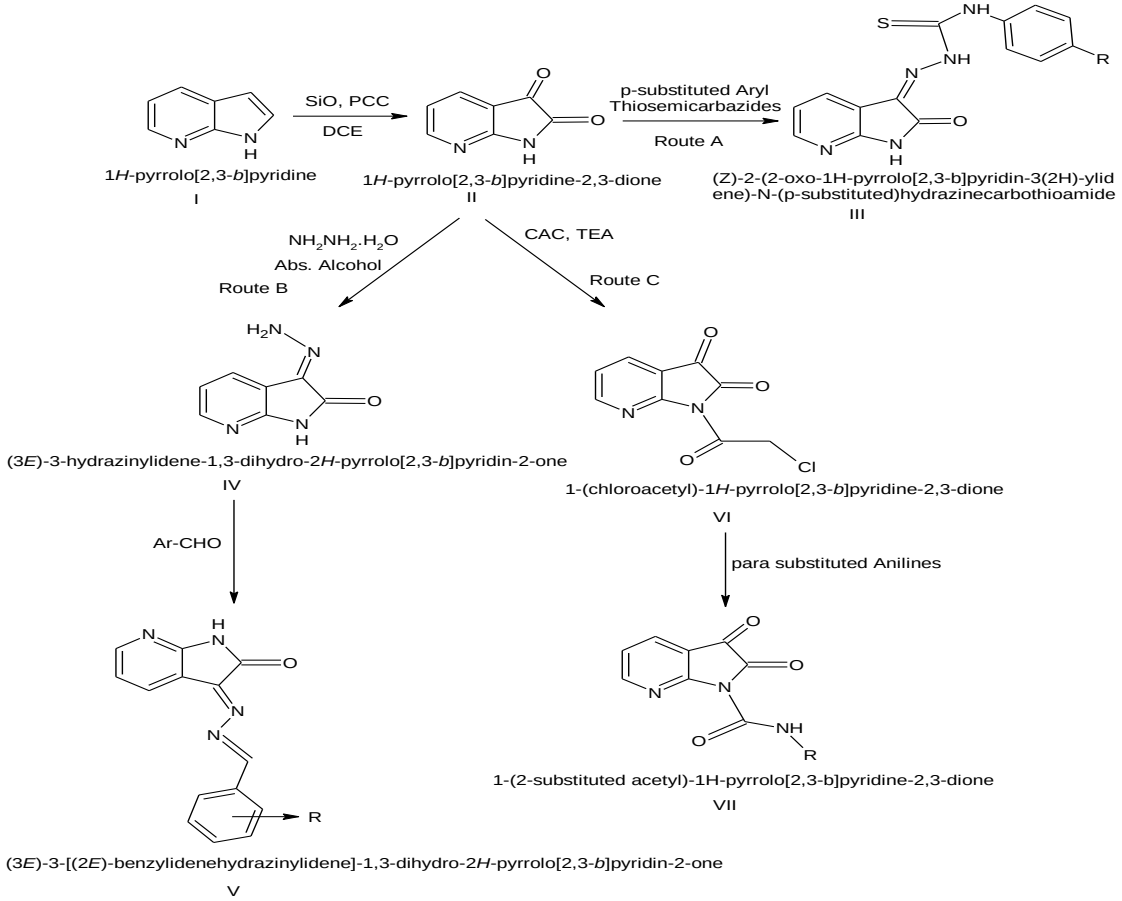
Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. Indole is a popular component of fragrances and the precursor to many pharmaceuticals. Compounds that contain an indole ring are called indoles. 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-, 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 The (mono)-azaindoles, trivially named pyrrolopyridines, where a carbon of the six-membered ring has been replaced by nitrogen either at 4- or 7- positions , are of theoretical interest as protoypes of bicyclic systems comprising an electron-rich ring fused to an electron poor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.

Azaindole derivatives are under investigation as potential narcotic agonists, PPARɣ modulators, antitumor, antiparasitic, cytotoxic, selective B-Raf inhibitors, DP1 receptor antagonists, selective ATP-competitive inhibitors of mammalian target of rapamycin (mTOR) etc. In view of biological significance of azaindole moiety, it is yet to be explored synthetically and biologically with several other important heterocyclic systems.

Azaindoles have fueled considerable synthetic interest due to their physicochemical and pharmacological properties primarily as bioisostere of an indole or purine moiety. Substitution of the C–7 position of indole by sp^2-hybridized nitrogen provides a skeleton containing a hydrogen–bond donor and acceptor in a rigid three–atom arrangement. Although naturally occurring 7-azaindoles are relatively scarce compared to indoles, 7-azaindole (1H-pyrrolo[2,3-b]pyridine) nucleus is present only in a few natural products such as alkaloids from the variolin family.

Antibiotics are one of the most important medications in treating bacterial infections and have greatly benefited the health-related quality of human life since their introduction. However, over the past few decades, these health benefits are under threat as many commonly used antibiotics have become less potent and less effective against certain diseases not only because many of them produce toxic reactions, but also due to incidence of drug-resistant bacteria. It is essential to investigate novel drugs with lesser resistance. Drugs derived from natural sources play a important role in the prevention and treatment of diseases. In many developing countries, traditional medicine is one of the primary healthcare systems [1,2]. The emergence and spread of multidrug resistant (MDR) bacterial pathogens have substantially threatened the current antibacterial therapy [3]. Even though pharmacological industries have produced a number of new antibiotics in the last three decades; resistance to these drugs by microorganisms has increased. Indoles are the class of compounds which can exhibit significant antibacterial activity. Various methods can be employed to perform antibacterial activity among which cup-plate method can be employed conveniently to investigate antibacterial activity.

Scheme



II. Experimental

2.1 Synthesis and characterization of Z–2-(2-oxo–1H–pyrrolo[2,3-b] pyridin–3(2H)–ylidene)–N–(p–substituted) hydrazine carbothioamide [Route A][4].

The synthesis of title compound has been executed as outlined in Scheme.

2.1.1: Synthesis of 1H–pyrrolo[2,3-b]pyridine-2,3-diones: Pyridinium chlorochromate (PCC) (0.25 mol) was ground with silica gel (5.37g, 70-230 mesh) and it was transferred to RB flask containing of dichloroethane (DCE) (400ml). To the resulting orange suspension, 1H-pyrrolo[2,3-b]pyridine (I) (0.1 mol) in dichloroethane (DCE) (50 ml) was added while stirring at room temperature. To this $AlCl_3$ (15% W/W with respect to the 1H–pyrrolo[2,3-b] pyridine) was added and the completion of the reaction was monitored by TLC. The usual workup of the reaction was carried out. The resultant solid was purified by recrystallization with n-hexane, ethyl acetate (4.1) mixture. [Sriram Rekulapally et al., 2012].

2.1.2: Synthesis of Z–2–(2-oxo-1H–pyrrolo[2,3-b]pyridin–3(2H)–ylidene–N(1-substituted hydrazine carbothioamide [III a-e][5].

Each of the five para substituted aryl thiosemicarbazides have been undergo condensation with 1H–pyrrolo[2,3-b]pyridine–2,3–dione [II] yielded (Z)–2–(2–oxo–1H–pyrrolo[2,3-b]pyridine–3(2H)-ylidene–N(p–

substituted)hydrazine carbothioamide [III a-e]. The progress of the reaction has been monitored by TLC. The usual workup of the reaction has been resulted in a single product.

To present one of such reactions, in specific and in detail, 1H–pyrrolo–[2,3-b]pyridine-2,3-dione (II) has been reacted with p–chlorophenylthiosemicarbazide in methanol. The product obtained has been purified by recrystallization from appropriate solvent to a colorless crystalline solid with a yield 85%.

Its IR Spectrum (KBr, Cm-^{1}) has been found to show the following absorptions: 3328 (NH, str), 2920 (Ar–CH, str), 1686 and 1586 (Ar C=C, str), 720 (C-Cl, str).

^{1}H NMR Spectrum of the compound [in $CDCl_3$ 300 MHz , δ PPM] revealed the following characteristic proton signals:

3.74 (br, s, IH, NH of ring); 4.80 (br, s, IH, =N–NH); 5.02 (br, s, 1H, =S–NH)

7.42 – 8.02 [m, 7H, Ar–H + pyrrolo–pyridine).

Mass Spectrum [ESI, positive] of the compound has been recorded its molecular ion [M^+] at m/z 331 equal to its mass (Mol.Wt).

CHN analyses Calcd. for $C_{14}H_{10}ClN_5OS$; C, 54.29, H, 4.25, N, 21.11;

Found ; C, 54.21, H, 4,21, N, 21.09.

Based on the data recorded, the resultant compound has been characterized as (Z)–2–(2-oxo-1H–pyrrolo[2,3-b]pyridine–3(2H)–ylidene–N(p-chlorophenyl) hydrazine carbothioamide [IIIb].

2.1.3: Synthesis and characterization of (E)–3–hydrzone IH–pyrrolo[2,3-b] pyridine–2(3H)ones; [Route B][6].

The synthesis of title compound has been designed, and executed as per scheme.

2.1.3.1: Synthesis of (E)–3–hydrazono –IH–pyrrolo[2,3-b]pyridin–2(3H)–ones [Route B ; IV][7].

The synthesis of compounds IV has been synthesized as per the procedure described in section 2.1.

2.1.3.2: Synthesis of (E)–3-(E)–substituted benzylidenehydrazono)–1H-pyrrolo[2,3-b]pyridine–2(3H)ones [Route B ; V a-h] ;

The synthesis of title compounds [V a-h] are characterized by their analytical and spectral [IR, ^{1}HNMR and Mass] data.

For the purpose of screening, present compounds are classified in to the following groups:

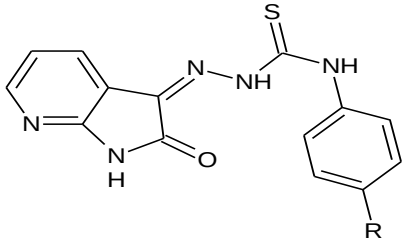
Series-I:(Z)-2-(2-oxo-IH–pyrrolo[2,3-b]pyridine-3(2H)-ylidene-N-(p– substituted)hydrazine carbothioamides.

Series-II:(E)-3-[(E)-substituted benzlidene hydrazone)–IH-pyrrolo[2,3-b]pyridin –2(3H)-ones.

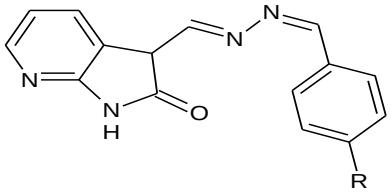
Series-III:1-(2-substituted acetyl)1-H-pyrrolo[2,3-b]pyridine-2,3-diones.

All the new azaindole derivatives **(Series I to III)** have been subjected to the antimicrobial test by appropriate standard experimental method.

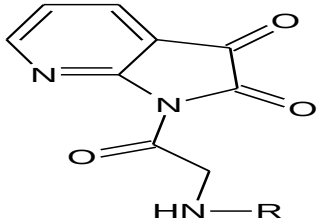
Series of New Azaindoles for Biological and Pharmacological Activities



Series-I R= H, Cl, F, OH, Br



Series-II R= H, CH_3, Cl, F, NH_2, OH, $N(CH_3)_2$, OCH_3



Series-III R= H, CH_3, Cl, F, NH_2, OH, $N(CH_3)_2$, OCH_3

2.2 Antibacterial Activity by Cup-Plate Method [8]:

The antibacterial activity of synthesized compounds was conducted against two grams–positive bacteria viz., *Bacillus thermophilus* and *Staphylococcus aureus* and two gram–negative bacteria viz., *Klebsiella pneumoniae* and *Salmonella paratyphi A* by using cup–plate method.

III. Results And Discussions

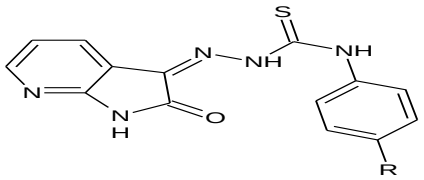
The antibacterial activity of **Series I,** Compounds (Z)-2-(2-oxo-IH–pyrrolo[2,3-b]pyridine-3(2H)-ylidene-N-(p–substituted)hydrazine carbothioamides as presented in **Table 1A** is discussed here. Only two compounds of the series; **III_b** (R=Cl) and **III_C** (R=F) are shown to be active against both gram +ve and gram –ve bacteria tested and the potency is comparable with standard Ciprofloxacin. Compound **III_a** (R=H) is inactive against selective organism i.e.; *K. pneumoniae*. However the compounds tested among the series are mild to moderate inhibitory activity.

Table 1B depicts the antibacterial activity of **Series II**. Its perusal conveys the information that three of the test compounds **V_c** (R=Cl), **V_d** (R=F) and **V_g** (R=$N(CH_3)_2$) are relatively more active against *B. thermophilus, S. aureus, K. pneumoniae, S. paratyphi A* and the inhibitory activity is comparable with that of reference Ciprofloxacin. However compounds **V_a** (R=H) and **V_h** (R=OCH_3) are inactive against *S. paratyphi A.* Selectively compound **V_e** (R= NH_2) is equipotent against *B. thermophilus* and *S. aureus*. Rest of the compounds among the series possess mild to moderate inhibitory activity.

Table 1C presents the antibacterial activity of **Series III,** 1-(2-substituted acetyl)1-H-pyrrolo[2,3-b]pyridine-2,3-diones. Among all the compounds, the **VII_d** (R=4-Cl Anilino) and **VII_h** (4-OMe anilino) are active against both gram +ve and gram –ve bacteria. Compounds VII_d (4-Cl Anilino), **VII_e** (4-F Anilino), **VII_k** (2-F Anilino) and **VII_a** (R=guanidine) are selectively against **B. thermophilus**. VII_d (4-Cl Anilino), VII_h (4-OMe Anilino) and VII_j (2-Cl Anilino) are active against *S. aureus***.** Compounds: **VII_a** (R=Guanidine) and **VII_j** (2-Cl Anilino) are equipotent against *K. pneumoniae***.** However compounds VII_d (2-Br Anilino) and VII_m (2-OMe Anilino) are not active against *S. aureus* and *S. paratyphi A* respectively. The rest of the compounds are found to show mild to moderate inhibitory activity.

Table 1A

Antibacterial activity of (Z)-2-(2-oxo-IH–pyrrolo[2,3-b]pyridine-3(2H)-ylidene-N-(psubstituted)hydrazine carbothioamides [III_{a-e}; Series III].

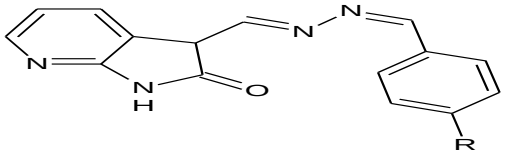


Compound	R	Gram +ve		Gram –ve	
		Bacillus thermophilus	Staphylococcus aureus	Klebsiella pneumoniae	Salmonella paratyphi A
III_a	-H	2	3	NA	2
III_b	-Cl	**12**	**10**	**9**	**12**
III_c	-F	**10**	**11**	**7**	**8**
III_d	-OH	6	3	5	7
III_e	-Br	3	1	2	2
Ciprofloxacin 10µg/cup		18	20	16	18

(Concentration of the test compound: 200 µg/cup; zone of inhibition in mm; NA: No Activity)

Table 1B

Antibacterial activity of (E)-3-[(E)-substituted benzlidene hydrazone)–IH-pyrrolo[2,3-b]pyridin–2(3H)-ones [V_{a-h}; Series IV].

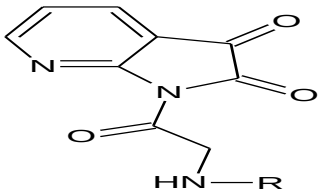


Compound	R	Gram +ve		Gram –ve	
		Bacillus thermophilus	Staphylococcus aureus	Klebsiella pneumoniae	Salmonella paratyphi A
V_a	-H	3	3	2	1

V_b	$-CH_3$	2	3	4	3
V_c	-Cl	**12**	**10**	**13**	**11**
V_d	-F	**11**	**8**	**7**	**12**
V_e	$-NH_2$	7	7	6	6
V_f	-OH	3	4	2	1
V_g	$-N(CH_3)_2$	**10**	**9**	**8**	7
V_h	$-OCH_3$	4	2	5	-
Ciprofloxacin 10µg/cup		18	20	16	18

(Concentration of the test compound: 200 µg/cup; zone of inhibition in mm)

Table 1C
Antibacterial activity of 1-(2-substituted acetyl)1-H-pyrrolo[2,3-b]pyridine-2,3-diones (VII_{a-m}; Series V).



Compound	R	Gram +ve		Gram –ve	
		Bacillus thermophilus	**Staphylococcus aureus**	**Klebsiella pneumoniae**	**Salmonella paratyphi A**
VII_a	Guanidino	9	8	12	8
VII_b	Sulphainlanido	8	7	7	10
VII_c	Anilino	5	6	6	9
VII_d	4-Cl-Aninilo	**12**	**10**	**8**	**13**
VII_e	4-F-Anilino	10	9	4	7
VII_f	4-Br-Anilino	5	3	6	5
VII_g	4-Me-Anilino	8	8	6	3
VII_h	4-OMe-Anilino	**8**	**13**	**9**	**11**
VII_i	2-Me-Anilino	5	9	6	8
VII_j	2-Cl-Anilino	6	10	12	7
VII_k	2-F-Anilino	9	8	7	7
VII_l	2-Br-Anilino	3	-	9	5
VII_m	2-OMe-Anilino	5	4	8	-
Ciprofloxacin 10µg/cup		**18**	**20**	**16**	**18**

(Concentration of the test compound: 200 µg/cup; zone of inhibition in mm)

IV. Conclusion

Azaindoles are an important class of nitrogen containing heterocyclics and were identified as the most active and potent classes of compounds with wide range of biological and pharmacological activities. They were extensively used as pharmaceuticals. Although the number of drugs are available in the market even though the search for new molecules is ever demanding.

Various Azaindoles were synthesized and characterized using physical and spectral data. Finally, the Azaindole derivatives screened for their possible antibacterial activity. Some of the molecules exhibited very good potency when compared with respective standards.

The approach is very challenging and was found difficult to get a molecule with potency. Even though, the present molecules were provided novel leads against both gram +ve and gram –ve bacteria and also insights into structural features required to be considered while designing the molecules with Azaindole core structures for antibacterial studies.

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