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Synthesis, Characterization and Anti Microbial Activity of 1- (1-Bengyl – 2 – Oxo –1, 2 – Dihydro – 3 H – Pyrrolo Pyridin -3 – Ylidine] – 2 – (Substituted Amino) Acetohydrazide

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Abstract:
A convenient method has been developed for the conversion of azaindoles into Azaisatin derivatives into excellent yields. In recent yeras, 7-azaisatin has received considerable interest in view of their potential relationship to pharmacologically important azaindoles and azaisatin.
Objective: Synthesis and evaluation of Anti microbial activity of some novel 7- azaisatin derivatives.
Methods: 1-[- benzyl-2 – oxo – 1, 2 –dihydro – 3H-Pyrrolo pyridin – 3 – ylidine] – 2 – (substituted amino) acetohydrazide was synthesized by condensation of chloro acetyl – 2– [1 – benzyl – 2 – oxo – 1, 2 – dihydro -3H – pyrrolo [2, 3 – b] pyridine – 3 – ylidene] hydrazine (v) with various secondary amines the compound (v) was synthesized by reacting reacting with chloroacetyl chloride with – 1 bengzyl 7 – azaisatin hydrazone (IV) which was prepared by treating 1-benzy1 azaisatin (III) with hydrazine hydrate. Oxidation of 1-benzyl azaindole by using N-bromo succinamide gives 1-benzyl azaisatin (III) The chemical structure of the synthesized compounds was confirmed by means of IR, 'HNMR, and Mass spectral analysis. The title compounds were screened for Anti microbial activity by tail immersion method in Rats.
Result: The results of Anti microbial activity showed that most of the compounds exhibited significant activity.
Conclusion: Novel Schiff bases of 7-azaisatin were prepared characterized by spectral data and screened for Anti microbial activity by tail immersion method.

Key words: 7-zaindole, 7-zaisatin, Anti microbial activity

I. INTRODUCTION:

7-azaindole (1H-pyrrolo (2, 3 b) pyridine) nucleus is present only in a few natural products such as alkaloids Never theless, 7-azaindole derivatives have attracted much attention due to their physicochemical and pharmacological properties. 7-azaisatin ring system consists of pyrrole ring fused with pyridine ring. It is also evident from the literature that azaisatins are also biologically active and found to have various pharmacological activities like the 7-azaindole mucleus has proven to be an interesting and impoetant model for synthesizing its different analogues for number of purposes[1-4]. Different azaindole derivative compounds have been reported for antibacterial[5], cytotoxic activity[6] Anti microbial[7], hypotensive activity[8]. Recently reported one pot synthesis of 1-alkyl – 7 azaisatins via 1-alkyl 7-azaindole[9] Bacterial infections often produce pain and inflammation. In normal practice, two groups of agents (chemotherapeutic, Anti microbial and anti-inflammatory) are prescribed simultaneously. Isatin, a heterocyclic compound was identified in animals as a major component of the endogenous monoamine oxidase inhibitor. Isatin derivatives have gained unique importance due to the broad spectrum of pharmacological activities are reflected by their use as anti-microbial[11] Anti microbial[12] anti-inflammatory[13] and anti-convulsant[14-15]. 7 - Azaisatin was first obtained by treatment of 7-azaoxindole with nitrous acid to give its 3-oxime, followed by hydrolysis of the oxime[16]. Another route for the preparation of 7-azaisatin from 7-azaindole in five steps with difficulty was reported by Parrick and coworker[17] in 1989. The aim of the present work is to explore the some novel 7-azaisatin derivatives as potential Anti microbial agents

2. MATERIALS AND METHODS

The melting points were recoreded in open capillary tubes using toshniwal melting point apparatus and are uncorrected.IR spectra were recorded in Kbr on FTIR Brucker spectrophotometer and frequencies are expressed in cm1. Purity of compounds was checked by thin llayer chromatography on silica Gel precoated plates. The 1HNMR spectra were recorded on Brucker DPX-400MHz spectrometer using CDCL3 and DMSO as solvent. Chemical shift values are reported as values in ppm relative to TMS as internal standard.

2.1 CHEMICALS

All the chemicals used were of analytical grade only.7-azaindole, Dimethyl sulphoxide, Benzyl chloride purchased from Merck chemicals private Limited. Hyderabad, India.N-Bromo succinamide, Hydrazine hydrate, Chloroacetylchloride, various secondary amines, purchased from Bhargavi Enterprises, Warangal, India.

2.2 CHEMISTRY:

The compounds were synthesized by conventional methods and

also methods developed in our laboratory General reactions were monitored by TLC using precoated silicagel (GF-245) and were visualized under ultraviolet light. 1-benzyl 1H-pyrrolo [2, 3-b] pyridine was synthesized by the method available in the literature [10] the synthetic strategies adopted to obtain target compounds are depited in figure 1.

2.3 Synthesis of 1-benzyl-1H-pyrrolo [2, 3-b] pyridine-II
Taken potassium hydroxide (6.5gm) was added to dimethyl sulfoxide (50ml)in a 250ml of round bottom flask and stirred for 5min.7-Azaindole(2.93gm)was added and stirred an additional 45min.The reaction was placed in icebath, then benzylchloride(3.55gm,5.05ml)was added and reaction was again stirred for 45min.Water(50ml)was added and the reaction was partitioned with ether(100ml3X) The ether phases were combined back extracted with water(100ml3X)and taken to dryness.,. Completion of the reaction was monitored by TLC.

2.4 Synthesis of 1-benzyl-1H-pyrrolo [2, 3-b] pyridine-2, 3-dione-III
Taken 1gm of N-benzyl 7-azaindole, and added 1.8gm of NBS N-bromo succinamide and 40ml Dimethylsulfoxide the reaction mixture was stirred at 60^0C for 6 hours. After completion of the 6hours again stirring under reduced pressure at 80^0C for 20 hrs. Completion of the reaction was monitored by TLC

2.5 Synthesis of (Z)- 1-benzyl -3-hydrazone- -1H-pyrrolo[2,3-b]pyridine-2(3H)-one-:IV In a cleaned, dry round bottom flask placed 80ml of absolute alcohol and equimolar quantities of compound (III) and hydrazine hydrate followed by addition of two drops of glacial acetic acid. Refluxed for about 2hrs, during heating period itself. The crystals of compound (IV) started separating out. Then the reaction mixture was cooled to room temperature and poured on crushed ice with stirring. After standing for 1hr the product separated was filtered washed several times with small portion of cold water and dried. Completion of the reaction was monitored by TLC

2.6 Synthesis of (Z)-N- (1-benzy1-1, 2-dihydro-2-oxopyrrolo [2,3-b]pyridine-3- ylidene)-2-chloro acetohyd razide: V
An appropriate 7-Azaisatin hydrazone (0.01 mol) was heated under reflux with chloroacetyl chloride (0.01 mol) in dry acetone under anhydrous conditions using calcium chloride guard tube for 2hrs. The product thus formed was filtered and washed with small portions of acetone to remove any unreacted chloroacetyl chloride. It was purified by recry stallization with ethanol.

2.7 Synthesis of (Z)-N-(1-benzy1-1, 2-dihydro-2-oxopyrrolo [2,3-b]pyridine-3-ylidene)- 2– chloroaceto hydrazide derivatives: VI
An appropriate (V) compound was heated under reflux with various secondary amines (0.01 mol) in dry acetone under anhydrous condition using calcium chloride guard tube for 2hrs. The product thus formed was filtered and washed with small portions of acetone to remove any unreacted secondary amines it was purified by recrystallization with ethanol.

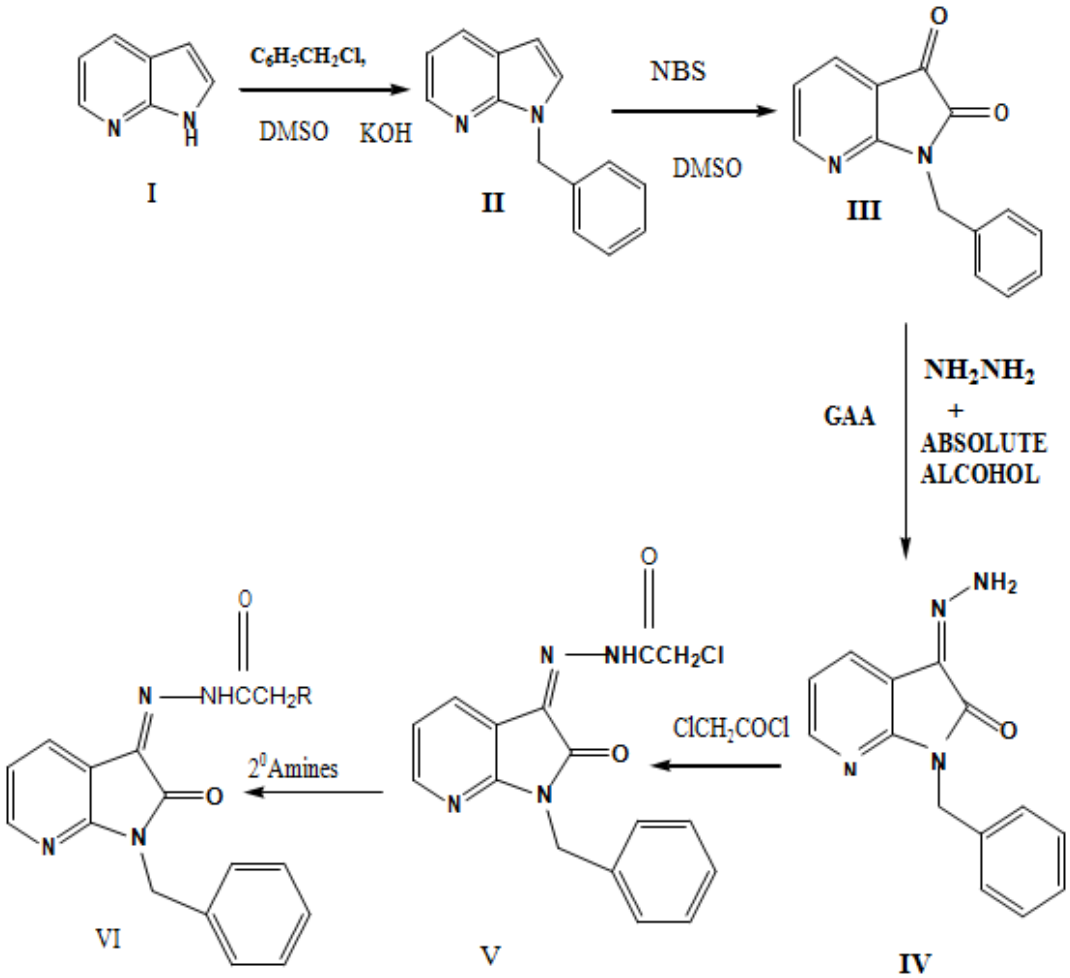

Figure.1. Experimental Scheme – I for the synthesis of 1-[1' –benzy1-2' –oxo-1', 2' –dihydro-3' H-pyrrolo pyridine -3' –ylidine]-2-(substituted amino) aceto hydrazide.

Table.1. Physical date of 1-[1' –benzy1-2' –oxo-1', 2' –dihydro-3' H-pyrrolo pyridine -3'–ylidine]-2-(substituted amino) aceto hydrazide (VI a-e).

Compound	Various Secondary Amines	Molecular formula	Molecular weight	Percent age % yield	Melting Point °C	Rf Value(solvent system used ethyl acetate:chloro form
VIa	Dimethylamino	$C_{18}H_{19}N_5O_2$	337	71	125	0.70
VIb	Diethylamino	$C_{20}H_{23}N_5O_2$	367	85	130	0.63
VIc	Maarpholino	$C_{20}H_{17}N_5O_2$	375	67	185	0.69
VId	Piperidino	$C_{21}H_{18}N_5O_2$	371	79	145	0.50
VIe	Piperizino	$C_{20}H_{17}N_6O_2$	373	78	155	0.72

3. BIOLOGICAL ACTIVITY

Antibacterial test was performed at the Department of Microbiology, Balaji Institution of Pharmaceutical Sciences, and Warangal.

MINIMUM INHIBITORY CONCENTRATION

- The newly synthesized compounds were screened for antibacterial activity studies at a concentration of 200µg/ml, 100µg/m). 50µg/m/ 25µg/ml. 12.5µg/ml using dimethyl form amide as a control against gram positive (Bacillus subtilis) and gram Negative (E.coli P.Vulgaries) bacteria. The antibacterial activity of the test compounds was compared with standard. The antibacterial studies of 7 azaisatins derivatives were carried out against a battery of microorganisms:
- The antibacterial activity of the test compounds was assayed systematically against '4' different strains of bacteria ie *Ecoli, P.Vulgaries,* and *B.Subtilis S.aureus (* ie '2' gram -ve and '2' gram +ve) by serial dilution method.
- Generally, the antibacterial activity of a compound is expressed in terms of its ability to inhibit the growth of bacteria in nutrient broth or agar by Minimum inhibitory concentration method. The bacterial inhibition can be measured by '2' methods: one is serial dilution method and the other is diffusion method. Serial dilution method is useful for the qualitative detection tests.

Preparation of Nutrient Broth:

2.6gm of Nutrient broth dissolved in 200ml of distill water.

Preparation of test solution:

The entire test compounds equivalent to concentration of 200 µg/ml, 100µg/ml and 50µg/ml 25µg/ml,12.5µg/mlwere prepared by dissolving in dimethylformamide.

Preparation of standard solution:

Weight equivalent to concentration of 200µg/ml, 100µg/ ml and 50µg/ml 25µg/ml, 12.5µg/ml was prepared by dissolving Ampicillin in sterile water.

Preparation of Nutrient broth tubes:

Sterilized media was cooled to 40°c and 0.5 ml of in o culum for 100m1 of media was added. The flasks were shaken gently to avoid formation of air bubbles..

MINIMUM INHIBITORY CONCENTRATION

- Desired amounts of test solution i.e. 200 µg/ml, 100µg/ml and 50µg/ml 25µg/ ml, 12.5µg/ ml of each concentration of test compounds and 200µg/ml,100µg/ml and 50µg/ml 25µg/ml,12.5µg/ml of standard sample were added into each tube with the help of a micropipette.
- Tubes were kept undisturbed for at least 2hrs at room temperature to allow proper diffusion of the test and standard solution into the nutrient broth medium.
- Incubation of the tubes at 37± 1°c for 24hrs

Table .2. Antimicrobial Screening

Compounds	Antibacterial activity Zone of inhibition (mm)			
	B.subtilis	E.coli	P.vulgaris	S.aureus
VIa	25 µg	50 µg	25 µg	50 µg
VIb	50 µg	12.5 µg	25 µg	25 µg
VIc	25 µg	50 µg	25 µg	50 µg
VId	50 µg	25 µg	12.5 µg	25 µg
VIe	25 µg	50 µg	25 µg	12.5 µg
Ampicillin	25 µg	12.5 µg	50 µg	25 µg
Streptomycin	12.5 µg	25 µg	12.5 µg	25 µg

DISCUSSION

ANTIBACTERIAL ACTIVITY:

At all the titled compounds (VIa-VIe) were evaluated for in vitro antimicrobial activity against pathogenic microorganisms by serial dilution method. All the compounds exhibited mild to moderate antibacterial activity against all the microbes tested at the concentrations of 200µg/ml, 100µg/ml and 50µg/ml,25µg/ml,12.5µg/ml. It could be evidenced from the results of present investigation that all test compounds are comparable with standard i.e., Ampicillin in their antibacterial activity.

4. CONCLUSION

From the above results, it has been observed that the schiffbases of azaisatin VId. Displayed more Anti microbial activity the signiticant activity is attributed to the presence of 7-azaisatin nucleus.

5. ACKNOWLEDGEMENT

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6. CONFLICT OF INTEREST

We do not have any conflict of interest with any one

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