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Synthesis, Characterization and Analgesic 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 Analgesic 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 were confirmed by means of IR, 'HNMR, and Mass spectral analysis. The title compounds were screened for analgesic activity by tail immersion method in Rats.
Result: The results of analgesic 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 analgesic activity by tail immersion method.

Key words: 7-zaindole, 7-zaisatin, Analgesic 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] analgesic[7], hypotensive activity[8]. Recently reported one pot synthesis of 1-alkyl – 7 azaisatins via 1-alkyl 7-azaindole[9]Bacterial infections often produces pain and inflammation. In normal practice, two group of agents (chemotherapeutic, analgesic 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] analgesic[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 analgesic agents

II. 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.

Synthesis of 1-benzyl-1H-pyrrolo [2, 3-b] pyridine-II

Taken potassium hydroxide (6.5gm)was added to dimethylsulfoxide (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 ice bath, then benzyl chloride(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.

2.3 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

2.4 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

2.5 Synthesis of (Z)-N-(1-benzy1-1, 2-dihydro-2-oxopyrrolo [2,3-b]pyridine-3-ylidene)-2-chloroaceto hydra zide: 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 recrystallization with ethanol.

2.6 Synthesis of (Z)-N-(1-benzy1-1, 2-dihydro-2-oxopyrrolo [2,3-b]pyridine-3- ylidene)- 2 – chloroacetohy drazide 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.

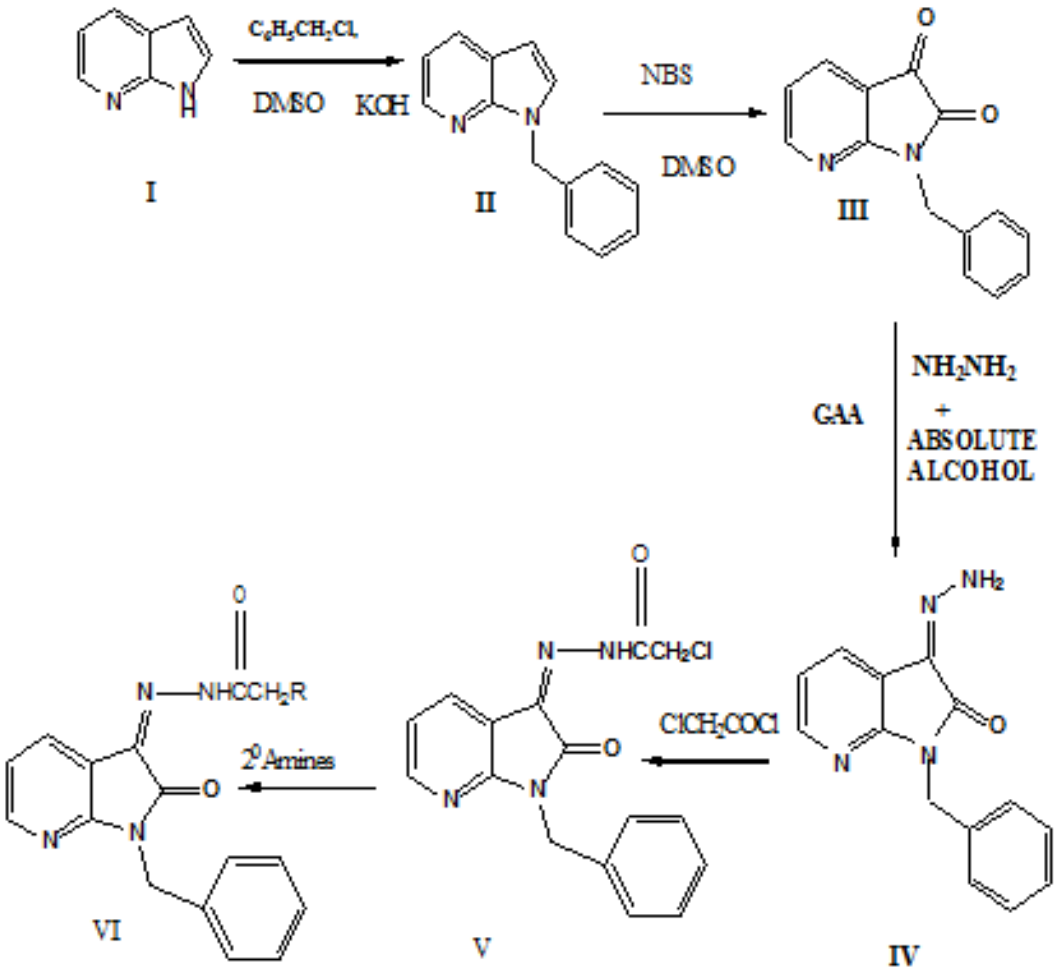

Figure. 1. Experimental Scheme – I for the synthesis of 1-[1' –benzy1-2' –oxo-1', 2' –dihydro-3' H-pyrrolo pyridine -3' –ylidine]-2-(substituted amino) aceto hydrazide.

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

Compound	Various Secondary Amines	Molecular formula	Molecular weight	Percentage % yield	Melti ng 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

2.7 Analgesic activity by tail immersion method in Rats:
All the protocols of animal experiments have been sanctioned by the institutional Animal & Ethics committee (IAEC) Reference No. 1694 /PO/a/CPCSEA Analgesic activity was evaluated by tail immersion method in Rats. In the tail immersion method the lower 5cm portion of the healthy wistar rat tail was marked and immersed in a cup of freshly filled water of 550c. The reaction time was determined before ral feeding of the drug & test compounds which recorded as o min reacding. After the drug administration, the reactions were recorded at 15min, 30min, 45min, 60min. The mean reaction time was recorded for each group and compared with control the percentage analgesic activity was calculate using the following formula.

PAA = [(T2 – T1) / T2] X 100
Where,
T1 is the reaction time (in sec) before treatment T2 is the eaction time (in sec) after treatment PAA is the percentage analgesic activity

Table.2. Analgesic activity of 1-[1' –benzy1-2' –oxo-1', 2' –dihydro-3' H-pyrrolo pyridine -3' –ylidine]- 2-(substituted amino) acetohydrazide (VI a-e) by tail immersion method

TREATMENT	DOSE mg/kg	BASAL REACTION TIME	REACTION TIME IN SECS (%Analgesic activity)			
			15Min	30Min	45Min	60Min
Normal Saline	0.1ml	2.20+0.04	2.22+0.12	2.18+0.05	2.23+0.08	2.19+0.02
Penta Zocine	30	2.28+0.23	2.35+0.03 (2.97)	6.72+0.20 (66.07)	7.29+0.15 (68.72)	4+0.32** (73.61)
Via	50	2.18+0.11	2.26+0.22 (3.53)	2.54+0.25 (14.17)	3.27+0.14 (33.33)	49+0.09* (37.53)
VIa	100	2.24+0.24	2.34+0.14 (4.27)	2.64+0.07 (15.15)	3.33+0.22 (33)	60+0.16* (37.77)
Vib	50	2.23+0.16	2.32+0.23 (3.87)	2.60+0.11 (14.23)	3.17+0.34 (29.65)	56+0.03* (37.35)
VIb	100	2.20+0.09	2.31+0.03 (4.76)	2.65+0.05 (16.98)	3.30+0.13 (33.33)	72+0.21* (40.86)
Vic	50	2.25+0.25	2.32+0.27 (3)	2.80+0.26 (19.64)	4.36+0.14 (48.39)	33+0.07* (53.41)
Vic	100	2.19+0.14	2.32+0.08 (5.60)	3.26+0.04 (32.82)	5.70+0.28 (61.57)	52+0.13* (70.87)
Vid	50	2.26+0.03	2.33+0.02 (3)	2.82+0.07 (19.85)	3.97+0.14 (43.07)	64+0.20* (51.29)
Vid	100	2.23+0.04	2.35+0.16 (5.10)	3.40+0.02 (34.41)	6.05+0.20 (62.47)	0+0.05** (68.59)
Vie	50	2.21+0.01	2.28+0.09 (3.07)	2.52+0.16 (12.30)	2.97+0.13 (25.58)	49+0.26* (36.67)
TREATMENT	**DOSE mg/kg**	**BASAL REACTION**	**REACTION TIME IN SECS (%Analgesic activity)**			

Values are expressed as Mean ± SEM for 2 animals in each group.
****P<0.01, *P<0.05 When compared with control.**

3. RESULTS & DISCUSSION

Statistical Analysis: Values are expressed as mean ± standard deviation & statistical analysis was carried out by one way ANOVA P < 0.01 is considered us significant A new series of 7-azaisatin derivatives have been synthesized and screened for analgesic activity by tail immersion method in Rats. The results of analgesic activity are presented in the table -2. From the results it was observed that the compounds VId displayed significant activity the percentage of tail immersion volume in rats was recorded as 73.61 for pentazocine and 68.59 VId respectively at the dose of 100mg/kg wt the other compounds VIb, VIc 40.86, 70.87 showed percentage analgesic activity respectively. The remaining compound VIa VIe 37.53, 36.67 exhibited very low percentage analgesic activity. When compared to the standard drug. The compounds were purified by recrystallization from suitable solvents. The completion of the reactions was cheeked by TLC. The synthesized derivatives exhibited significant analgesic activity.

4. CONCLUSION

From the above results, it has been observed that the

schiffbases of fazaisatin VId. Displayed more analgesic activity the signiticant activity is attributed to the presence of 7-azaisatin nucleus.

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6. CONFLICT OF INTEREST:

We do not have any conflict of interest with any one

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