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SYNTHESIS, CHARACTERIZATION AND ANTHELMINTIC ACTIVITY OF NOVEL ISATIN SUBSTITUTED IMIDAZOLINE DERIVATIVES

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ABSTRACT

Novel Isatin substituted Imidazole derivatives have been synthesized and screened for anthelmintic activity. Literature revealed that vast majority of Isatin and imidazole compounds are known to possess pharmacologically proven therapeutic potentials. Isatine substituted 5-Oxo-imidazoline derivatives were synthesized from 1,3-oxazole-5-ones which were synthesized from the benzoyl glycine by Erlynmayer synthesis. These 5-oxazoline compounds upon condensation with isatine semicarbazide, it formed isatine substituted 5-oxo-imidazoline derivatives (**3a-3j**). All compounds have been characterised using IR, 1H NMR and Mass spectral data and have been evaluated for their antmelmintic activity and Albendazole was used as a standard drug.

Keywords: Isatin**,** benzoyl glycine, benzaldehyde, acetic anhydride, anthelmintic activity.

INTRODUCTION

The heterocyclic nitrogen compounds like Imidazoline derivatives have a vital role in synthetic drugs and biological processes Medicinal chemistry involves the identification, synthesis and development of new chemical entities suitable for therapeutic use. It also includes the study of existing drugs, their biological properties, and their quantitative structure-activity relationships (QSAR). Isatin is an important structure of class having wide variety of interesting biological activities such as anti-viral, anti-oxidant, antiproliferative, antimicrobial and antifungal activities [3]. There are many research reports about 5-imidazolinone ring system especially in the applications of herbicides and as precursors to amino acids. There is still much interest in investigating these compounds for their many applications such as anthelmintic activities.

EXPERIMENTAL

Melting points were determined in open capillaries, using Toshniwal melting point apparatus, expressed in ^{o}C and are uncorrected. The IR spectra of the compounds were recorded on thermo Nicolet Nexus 670S series, FT-IR spectrometer using KBr disc. ^{1}H NMR was scanned on Avance-400 MHz instrument. Chemical shifts are expressed in δ (ppm) relative to TMS as an internal standard using DMSO-d_6 *as* solvent. Mass spectra's were recorded on a LC-MSD-Trap-SL. The purity of the compounds was checked on silica gel-coated aluminum sheets (Merck, 1.005554, silica gel HF254–361, Type 60, 0.25 mm, Darmstadt, Germany) by thin-layer chromatography (TLC). TLC was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapour or by irradiation with ultraviolet light (short wave length, 254 nm). Column chromatography was performed by using Qualigen's silica gel for column chromatography (60–120 mesh).

General synthesis: Isatine substituted 5-Oxo-imidazoline derivatives were synthesized from 1,3-oxazole-5-ones which were synthesized from the benzoyl glycine by Erlynmayer synthesis. These 5-oxazoline compounds upon condensation with isatine semicarbazide, it formed isatine substituted 5-oxo-imidazoline derivatives. The procedures used in the synthesis of title compounds is as follows.

Step 1: Synthesis of 4-substituted benzylidene-2-phenyl-1,3-oxazol-5-one: In a 250 ml conical flask equipped with a reflux condenser a mixture of benzaldehyde (1.01ml, 0.01mol), benzoyl glycine (1.82g, 0.01 mol), acetic anhydride (2.85ml, 0.03mol) and anhydrous sodium acetate (0.82g, 0.01 mol) was placed and heated on an electric hot plate with constant shaking. As soon as the mixture has liquefied completely, transfer the flask to a water bath and heat for 2 hours. Cool and then add 20 ml of ethanol slowly to the contents of the flask, allow the mixture to stand overnight, filter the crystalline product with solution, wash with 5 ml of ice cold alcohol and then finally wash with 5 ml of boiling water, dry at 100 ^{0}C. Different 5-oxazolone derivatives were synthesized by using different aldehydes.

Step 1I: Synthesis of Isatine thiosemicarbone: Equimolar quantities (0.01mol) of Isatin or substituted Isatin and Thiosemicarbazide were dissolved in warm ethanol and glacial acetic acid (1:1%, 30ml). The reaction mixture was refluxed for 3hrs and then kept in refizerator for overnight. The resultant solid was filtered, dried and recrystallized from suitable solvent to afford compounds.

Step III: 4-Benzylidene-5-oxo-2-phenyl-imidazolidine-1-carbothioic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide(3a-3j): A mixture of equimolar quantities of Isatine thiosemicarbone (0.01mol) and 2-phenyl-4-(benzylidene)-5-oxazolinone (0.01mol) was refluxed in pyridine for 7-8 h. One KOH pellet was added to this mixture. The progress of the reaction was monitored by TLC. After completion of the reaction resulting mass was poured into crushed ice and neutralised with dil. HCl. Precipitate was filtered, dried and the product was recrystallized form methanol. Different isatine substituted 5-oxo-imidazoline derivatives were prepared by using different 5-oxazolone derivatives. 4-Benzylidene-5-oxo-2-phenyl-4,5-dihydro-imidazole-1-carbothioic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide (**3a**). **IR (ῡ, cm^{-1}):** 3423(-NH *Str*, Indole), 3025(-CH *Str*, benzene), 2902(-CH *Str*, aliphatic), 1723(C=O *Str*), 1534(C=N *Str*), 1345(C-N *Str*), 1232(C=S *Str*), 1076(N-N *Str*), **1H NMR (DMSO δ ppm):** 11.23(1H,-NH in indole), 8.54-7.67(14H, Ar-H), 6.21(1H, benzylidene-H), 5.87(1H, -NH), **Mass (EI-MS)**: 452(M+1, 100%), 474(M+Na, 60%),4-(4-Methyl-benzylidene)-5-oxo-2-phenyl-4,5-dihydro-imidazole-1-carbothioic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide**(3b): IR (ῡ Cm^{-1}**3401(-NH *Str*, Indole), 3101(-CH *Str*, benzene), 2920(-CH *Str*, aliphatic), 1698(C=O *Str*), 1515(C=N *Str*), 1332(C-N *Str*), 1268(C=S *Str*), 1022(N-N *Str*), **1H NMR (DMSO δ ppm**11.13(1H,-NH in indole), 8.012-7.55(13H, Ar-H), 6.56(1H, benzylidene-H), 5.50(1H, -NH), 3.49-3.42(3H, -CH_3), M**ass (EI-MS)**: 466(M+1, 100%), 498(M+Na, 70**%).** 4-(4-Chloro-benzylidene)-5-oxo-2-phenyl-4,5-dihydro-imidazole-1-carbothioic acid (5-chloro-2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide**(3i) IR (ῡ, cm^{-1}):** 3407(-NH *Str*, Indole), 3100(-CH *Str*, benzene), 2903(-CH *Str*, aliphatic), 1732(C=O *Str*), 1576(C=N *Str*), 1354(C-N *St)r*, 1212(C=S *Str*), 1112(N-N *Str*), 1021(C-Cl *Str*), **1H NMR (DMSO δ ppm):** 2.37(1H, Indole), 8.56-7.47(12H, Ar-H), 6.23(1H, benzylidene-H), 5.34(1H, -NH), **Mass (EI-MS)**: 521(M+1, 100%), 543(M+Na, 65%).

BIOLOGICAL EVALUATION
ANTHELMINTIC ACTIVITY

All the synthesized compounds were screened for *in vitro* anthelmintic activity [6] was carried out on earthworms. Anthelmintics are drugs that are used to treat infections with parasitic worms.

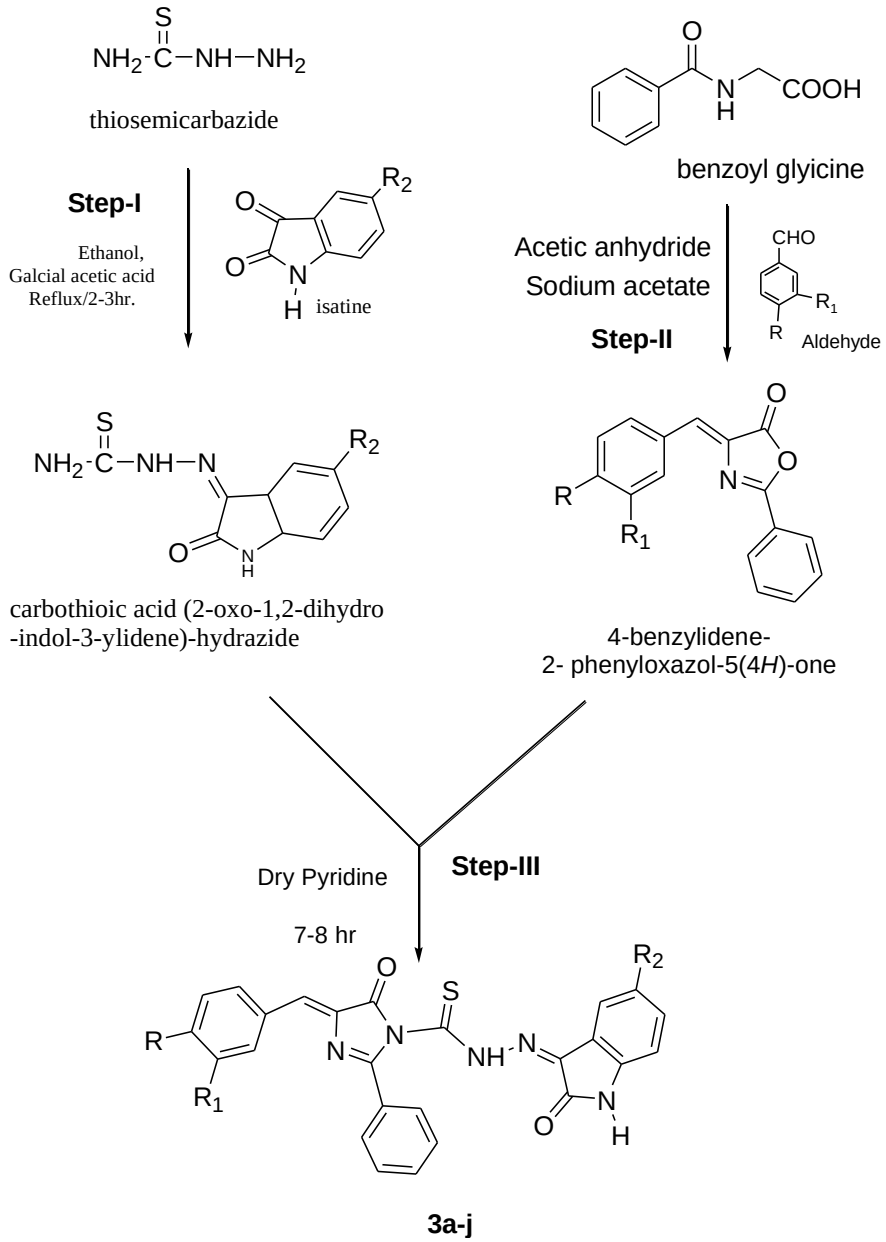
Procedure: The synthesized compounds are screened for anti-helminthic activity by using Earth worms. Six earthworms of nearly equal size were placed in standard drug solution and test compound's solutions at room temperature. Normal saline used as control. The standard drug and test compounds were dissolved in minimum quantity of dimethyl sulfoxide (DMSO) and adjusted the volume up to 10 ml with normal saline solution to get the concentration of 0.1% w/v, 0.2 % w/v and 0.5% w/v. Albendazole was used as a standard drug. The compounds were evaluated by the time taken for complete paralysis and death of earthworms. The mean lethal time for each test compound was recorded and compared with standard drug. The time taken by worms to become motionless was noted as paralysis time. To ascertain the death of the motionless worms were frequently applied with external stimuli, which stimulate and induce movement in the worms, if alive. The mean lethal time and paralysis time of the earthworms for different test compounds and standard drug are tabulated in **Table No.1**

RESULTS AND DISCUSSIONS

All the synthesized compounds (**3a-j**) were purified by successive recrystallisation using methanol. The structure of the new compounds prepared during the present investigation were authentically established by their melting point, IR, NMR and Mass spectral data. All the test compounds have anthelmenitic activity and comparable with standard Albendazole.

CONCLUSION

In the present study, a series of 4-(4-Methyl-benzylidene)-5-oxo-2-phenyl-imidazolidine-1-carbothioic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazidewere synthesized according to the above mentioned procedures by conventional methods as mentioned in the scheme by the condensation of isatine substituted 5-oxazolone derivatives and evaluated for their possible anthelmintic activitiesIn conclusion, the present study reveals that the imidazole and Isatine substituted ring present in the synthesized compounds is responsible for the anthelmintic activities and may serve as a lead molecule for further modifications to obtain clinically useful novel entities.



3a-j

R= -H, -OCH_3, -Cl, -NO_2, -CH_3, **R_1** = H, -OCH_3 **R_2** = H, -Cl

Scheme-I

Table 1.Antihelmintic activity of novel isatin substituted Imidazoline derivatives

S.No.	Name	Time in minutes					
		For paralysis			For death		
		% Concentration			% Concentration		
		0.1	0.2	0.5	0.1	0.2	0.5
1	Control	-	-	-	-	-	-
2	Albendazole	15	12	8	44	34	26
3	3a	28	26	18	58	59	49
4	3b	20	18	17	55	49	40
5	3c	16	17	15	49	42	32
6	3d	22	22	18	53	59	61
7	3e	20	23	20	41	56	59
8	3f	20	19	17	52	58	60
9	3g	17	14	10	47	37	29
10	3h	18	15	12	48	40	31
11	3i	16	13	9	46	36	28
12	3j	17	15	12	48	37	30

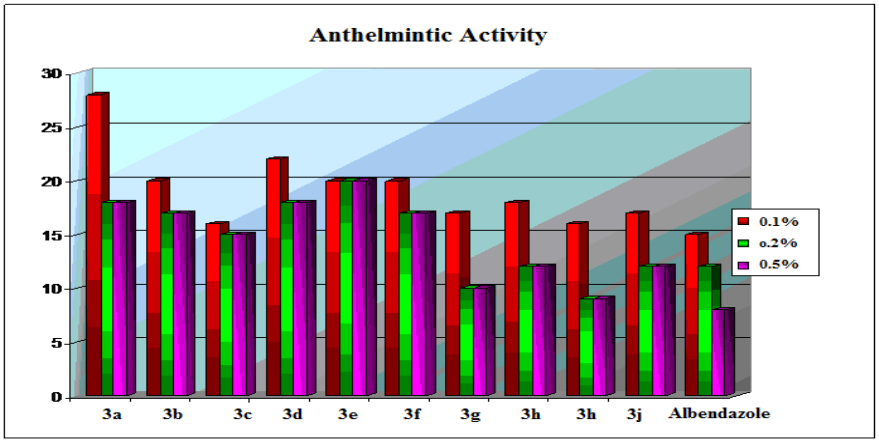


Figure 1: Graphical representation of anthelmentic activity of compounds (**3a-j**) – Paralysis time (min).

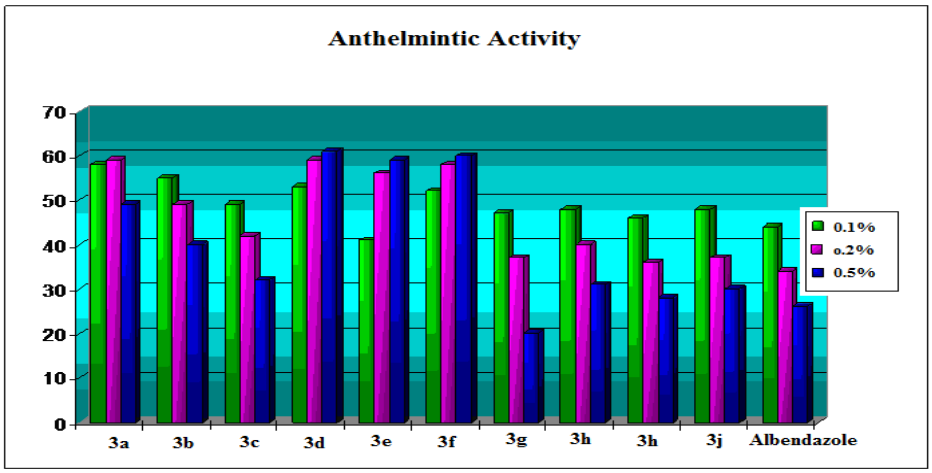


Figure 2: Graphical representation of anthelmentic activity of compounds (**3a-j**) - Death time(min)

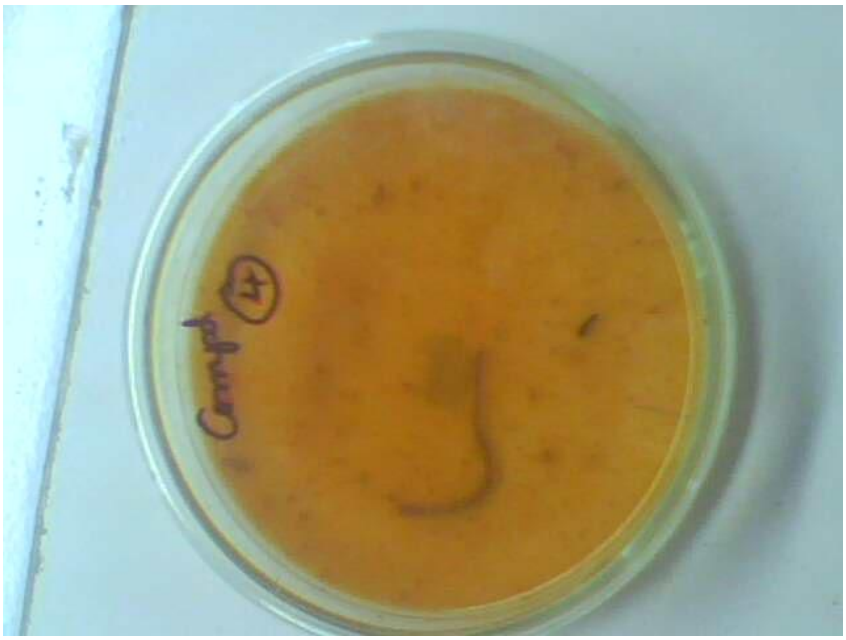


Fig.2: Photographs of various Novel Isatin substituted Imidazoline derivatives–Anthelmintic activities.

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