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Research Article

SYNTHESIS, CHARACTERIZATION AND ANTHELMINTIC ACTIVTY OF NOVEL SCHIFF'S BASE DERIVATIVES

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ABSTRACT

*The research envisaged in the present study is the synthesis and evaluation of novel Schiff's bases derivatives for anthelmintic activity. The title compounds were synthesized in a good yield. The synthesized Compounds 5a-5h was characterized by FT-IR, LC-MASS and ^{1}H NMR data and evaluated for their antimicrobial and anthelmintic activities by standard protocol available in literature. All the compounds were subjected for anthelmintic screening, among this series of compounds **5g and 5e** showed high activity against.*

Keywords: *Isatin and its derivatives, Thiocarbohydrazide, Aniline, Chloroacetil Chloride, Anthelmintic activities.*

INTRODUCTION

Heterocyclic compounds containing a ring made up, in addition to carbon atoms, other elements (heteroatoms), most often nitrogen, oxygen, and sulfur, and less frequently phosphorus, boron, and silicon. The primary amine reacted with carbonyl compound to give Schiff base [1-3].

The novel isatine Schiff bases nucleus, which is a useful structure for research and development of new pharmaceutical molecules, has received much attention in last decade. novel isatine Schiff bases are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities. Owing to the immense importance and varied by bioactivities exhibited by isatine Schiff bases, efforts have been made from time to time to generate libraries of these compounds and screened them for potential biological activities.

Due to their antimicrobial activities, new novel isatine Schiff bases have been synthesized and investigated for medical applications [4, 5]. Numerous attempts have been made to develop new structural prototypes to search for more effective antimicrobials. The novel isatine Schiff bases still remains one of the most versatile classes of compounds against microbes and, therefore are useful substructures for further molecular exploration. The exhibit a range of biological activities. [6]

MATERIALS AND METHODS [7-9]

The synthesized compounds were screened for anthelmentic activities. Fourier Transform IR spectrometer (model Shimadzu 8700) in the range of 400-4000 cm^{-1} Using KBr pellets and values are reported in cm^{-1} and the spectra were interpreted. ^{1}H-NMR spectra were recorded on DPX-200 MHz NMR spectrometer using DMSO-d_6 and chemical shifts (δ) are reported in parts per million down field from internal reference Tetramethylsilane (TMS) and the Spectra were interpreted. Mass spectra were recorded on Mass spectrophotometer (model Shimadzu) by LC- MS and the spectra were interpreted. Precoated Silica gel G plates were used to monitor the progress of reaction as well as to check the purity of the compounds **:** n-Hexane : Chloroform : ethylacetate (6:3:1).

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General procedures:

Steps 1: Synthesis of isonitrosoaceto-P-toluidine from P-toluidine:

9 gm of Chloral hydrate was taken into the round bottom flask and dissolved in 120 ml water. To that 13 gm of sodium sulphate, a solution of 5.4 gm of p-toluidine in 30 ml of water containing 5.12 gm of concentrated hydrochloric acid (4.34 ml) to dissolve the amine and solution of 11 gm of hydroxylamine hydrochloride in 50 ml of water were added. Flask was then heated vigorously until the reaction was completed. After it, the solution containing beaker was cooled in running water followed by the filtration of reminder crystallized product with suction pump and air dried.

Step 2: Synthesis of 5-Methyl Isatin from isonitrosoaceto- P-toluidine:

18.4 gm of concentrated sulphuric acid (10.0 ml) was warmed to 50^{0}C and 2.5 gm of dry isonitrosoaceto-p-toluidine was added in such a rate so as to keep the temperature between 60-70^{0}C but not higher. External cooling was applied at this stage so that the reaction could be carried out more rapidly after the addition of isonitroso compound was finished. The solution was heated to 80^{0}C and kept at this temperature for about 10 min to complete the reaction. Then the reaction mixture was cooled to room temperature and poured it into ten times its volume of cracked ice. After standing for 90 mint, the final product was filtered with suction pump followed by washing with cold water to remove sulphuric acid and dried in air.m.p:135-137^{0}C.(Lit m.p: 136-138^{0}C).

Step III: N-Benzyl indole 2, 3- dione (N-Benzyl Isatin):

In the round bottomed flask take indole-2,3-dione (Isatin) 0.8gm (3.37mM) and equimolar quantity of benzyl chloride i.e. 6.5ml (3.7mM), mix with 20ml of DMF and to this mixture add 2gm of K_2CO_3. After gentle mixing of this reaction mixture, reflux for 2 hr, cool and pour to 100 ml of ice cold water. The resultant orange red ppt. collected wash with water and dried and recrystallized from acetonitrile m.p:134-136^{0}C (Lit m.p:133-134^{0}C).

Step IV: Synthesis of Thiocarbohydrazide: *[10-13]*

Carbon disulphide (13ml, 0.22mol) was added drop wise under stirring to a mixture of 85% hydrazine hydrate (24ml) and water (75ml), then stirring was continued for 30min at room temperature. The reaction temperature was then rapidly raised to 100-110^{0}c. After refluxing for 2hrs, the reaction mixture was cooled in an ice-bath and filtered. The residue was washed with ethanol and followed by ether, then recrystallized from water to afford pure thiocarbohydrazide crystals. (Lit m.p:170-172^{0}C).

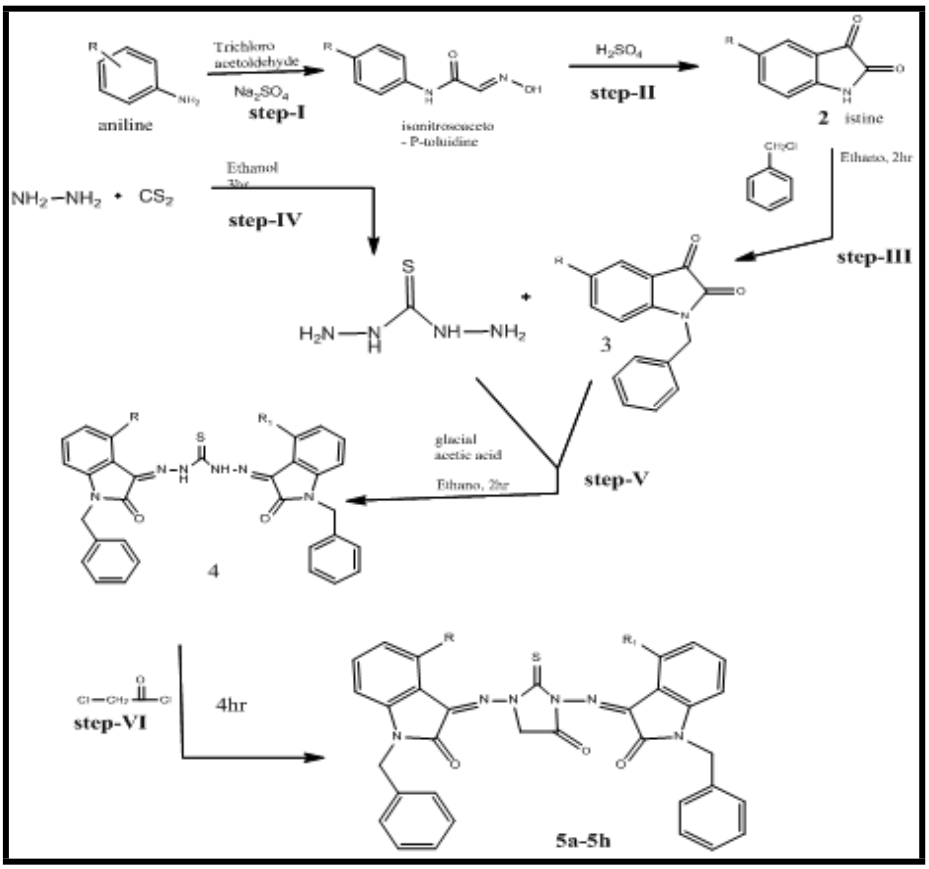
Step V: Synthesis of Schiff's Bases:

Compound 3 (0.01 mol) was taken in a mixture of thiocarbazide (0.01 mol) and glacial acetic acid (5 mL) and Ethanol 30ml, then the reaction mixture was refluxing for 2hrs. The progress of the reaction was monitored by TLC (Hexane:EtoAc 1:4). The reaction mixture was cooled to room temperature. A solid was obtained, which was filtered off and washed with hexane and recrystallized from methanol to give crystalline solid.

Step IV: Synthesis of Some Novel 3,3'-((4-oxo-2-thioxoimidazol idine-1,3-diyl) bis (azanylylidene)) bis(1-benzylindolin-2-one):

The Compound 4 (0.01 mol) obtained above was dissolved in 30ml of ethanol to which an equimolar (0.01 mol) amount of Chloroacetyl chloride was added with refluxing for 4h. The reaction mixture was cooled to room temperature. A solid was obtained, which was filtered off and washed with hexane and recrystallized from methanol to give crystalline solid.

Scheme of synthesis:



R, R_1 = H, -NO_2, -CH_3, -Cl

5a-IR Cm^{-1} (KBr): 3103(-CH *Str*, benzene), 2956(-CH_3 *Str*), 2775(-CH_2 *Str*), 1696 (C=O *Str*), 1586 (C=N *Str*), 1375(C-N *Str*), 1255(C=S *Str*). ***^{1}H-NMR (DMSO δ ppm):*** 8.10(2H, -CH_2.thioxoimidazolidine), 7.92-6.84 (17H, Ar-H), 2.32 (2H,-CH_2). 1.912 (3H, -CH_3). ***Mass (EI-MS):*** 603(M+1, 100%), 601(M-1).

5b-IR Cm^{-1} (KBr): 3058(-CH *Str*, benzene), 282(-CH_2 *Str*), 1705 (C=O *Str*), 1578 (C=N *Str*), 1390(C-N *Str*), 1298(C=S *Str*), 1080(C-Cl *Str*). ***^{1}H-NMR (DMSO δ ppm):*** 8.07(2H, -CH_2.thioxoimidazolidine), 7.80-6.68 (17H, Ar-H), 2.86 (2H,-CH_2). ***Mass (EI-MS):*** 619(M+1, 100%), 617(M-1).

5c-IR Cm^{-1} (KBr): 3123(-CH *Str*, benzene), 289(-CH_3 *Str*), 2792(-CH_2 *Str*), 1720 (C=O *Str*), 1598 (C=N *Str*), 1402(C-N *Str*), 1298(C=S *Str*). 1076(C-Cl *Str*). ***^{1}H-NMR (DMSO δ ppm):*** 8.34(2H, -CH_2.thioxoimidazolidine), 8.03-6.67 (16H, Ar-H), 3.23 (2H,-CH_2), 2.01(3H, -CH_3). ***Mass (EI-MS):*** 633(M+1, 100%), 631(M-1).

5d-IR Cm^{-1} (KBr): 3086(-CH *Str*, benzene), 2698(-CH_2 *Str*), 1703 (C=O *Str*), 1623(-NO_2 *Str*), 1567 (C=N *Str*), 1382(C-N *Str*) 1289(C=S *Str*). ***^{1}H-NMR (DMSO δ ppm):*** 8.10(2H, -CH_2.thioxoimidazolidine), 7.92-6.84 (17H, Ar-H), 2.32 (2H,-CH_2). ***Mass (EI-MS):*** 630(M+1, 100%), 628(M-1).

5e-IR Cm^{-1} (KBr): 3112(-CH *Str*, benzene), 2805(-CH_2 *Str*), 1716 (C=O *Str*), 1645(-NO_2 *Str*),1572 (C=N *Str*), 1402(C-N *Str*), 1268(C=S *Str*). ***^{1}H-NMR (DMSO δ ppm):*** 8.32(2H, -CH_2.thioxoimidazolidine), 8.02-6.64 (16H, Ar-H), 2.87 (2H,-CH_2). ***Mass (EI-MS):*** 675(M+1, 100%), 673(M-1).

5f-IR Cm^{-1} (KBr): 3106(-CH *Str*, benzene), 2968(-CH_3 *Str*), 2786(-CH_2 *Str*), 1699 (C=O *Str*), 1584 (C=N *Str*), 1390(C-N *Str*), 1272(C=S *Str*). ***^{1}H-NMR (DMSO δ ppm):*** 8.34(2H, -CH_2.thioxoimidazolidine), 8.02-6.65 (16H, Ar-H), 2.86 (2H,-CH_2). 2.05 (6H, -CH_3). ***Mass (EI-MS):*** 613(M+1, 100%), 611(M-1).

5g-IR Cm^{-1} (KBr): 3123(-CH *Str*, benzene), 2739(-CH_2 *Str*), 1701 (C=O *Str*), 1592 (C=N *Str*), 1383(C-N *Str*), 1293(C=S *Str*), 1068(C-Cl *Str*). ***^{1}H-NMR (DMSO δ ppm):*** 8.14(2H, -CH_2.thioxoimidazolidine), 7.99-6.45 (16H, Ar-H), 2.38 (2H,-CH_2). ***Mass (EI-MS):*** 653(M+1, 100%), 651(M-1).

5h-IR Cm^{-1} (KBr): 3046(-CH *Str*, benzene), 2795(-CH_2 *Str*), 1703(C=O *Str*), 1548(C=N *Str*), 1389(C-N *Str*), 1268(C=S *Str*). ***^{1}H-NMR (DMSO δ ppm):*** 8.10(2H, -CH_2.thioxoimidazolidine), 7.92-6.84 (17H, Ar-H), 2.32 (2H,-CH_2). 1.912 (3H, -CH_3). ***Mass (EI-MS):*** 603(M+1, 100%), 601(M-1).

Anthelmintic activity: [14-15]

The synthesized compounds are screened for anthelminthic 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 (**Figure 1, 2**). 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.2.**

RESULTS AND DISCUSSION

Synthesis:

The characterization data of all compounds **5a-5h** are given the experimental section. All the synthesized compounds gave satisfactory analysis for the proposed structures, which were confirmed on the basis of their elemental analysis by FT-IR, LC-MASS, ^{1}H NMR data. The present work which involve reaction between Amine or p-methy aniline with Chloralhydrate and hydraxilamine and Con.sulphuric acide to get Isatin or 5-methyl isatin which on reaction with thiocarbohydrazide to get intermediates schiff's bases , which on rection with chloroacetyl chloride to give respective title compounds. The synthesized compounds were screened for anthelmentic activities.

Spectroscopy:

The structures of all the newly synthesized compounds were characterized as **5a-5h** on the basis of satisfactory analytical and spectral data including IR, LC-MASS, ^{1}H NMR data. The IR spectra of the compound **5a** Novel 3,3'-((4-oxo-2-thioxoimidazolidine-1,3-diyl) bis (azanylylidene)) bis(1-benzylindolin-2-one) show characteristic absorption bands at 3103(-CH *Str*, benzene), 2956(-CH_3 *Str*), 2775(-CH_2 *Str*), 1696 (C=O *Str*), 1586 (C=N *Str*), 1375(C-N *Str*), 1255(C=S *Str*) groups respectively. The ^{1}H NMR spectra of **(5a)** 3,3'-((4-oxo-2-thioxoimidazolidine-1,3-diyl) bis (azanylylidene)) bis(1-benzylindolin-2-one) 8.10(2H, -CH_2.thioxoimidazolidine), 7.92-6.84 (17H, Ar-H), 2.32 (2H,-CH_2). 1.912 (3H, -CH_3) assigned to the each particular set of protons. The molecular ion peak in their mass spectra was **m/z =** 603(M+1, 100%), 601(M-1) peaks identified respectively.

Table No. 1: Physical data of (5a-5h)

Code	R	R_1	Mol. Formula	Mol. wt (g.mol^{-1})	M.P (^{0}C)
5a	H	-CH_3	$C_{34}H_{30}N_6O_3S$	602	138-140
5b	H	-Cl	$C_{33}H_{23}N_6O_3SCl$	618	208-210
5c	-Cl	-CH_3	$C_{34}H_{25}N_6O_3SCl$	632	198-200
5d	H	-NO_2	$C_{33}H_{23}N_7O_5S$	629	118-120
5e	-NO_2	-NO_2	$C_{33}H_{28}N_8O_7S$	674	208-210
5f	- CH_3	CH_3	$C_{35}H_{28}N_6O_3S$	612	158-160
5g	-Cl	-Cl	$C_{33}H_{22}N_6O_3SCl_2$	652	225-228
5h	H	H	$C_{33}H_{27}N_6O_3S$	584	142-144

Anthelmintic activity:

The synthesised compounds (5a-5h) were evaluated for anthelmintic activity on Indian earthworms (*Pheretima posthuma*). All compounds showed anthelmintic activity is shown in table. Among the compounds tested all the compounds were showed significant paralytic time of earthworms, compared to standard drug albendazole at 0.1%, 0.2% and 0.5% concentrations of compounds. A closer inspiration of data from this table indicated that compound **5g** and **5e** having more activity and compounds **5b,5c** and **5d** showed moderate activity. After all, the synthesized compounds in overall estimation confirm the better activity against *peritima posthuma.*

Table No. 2: Antihelmintic activity of Novel Benimidazole 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	18	14	10	44	34	26
3	5a	25	22	20	60	50	42
4	5b	20	19	17	53	49	45
5	5c	23	19	16	56	45	47
6	5d	25	20	19	48	40	30
7	5e	19	20	14	51	39	32
8	5f	28	25	21	49	52	58
9	5g	22	18	15	50	42	44
10	5h	32	25	20	46	37	28

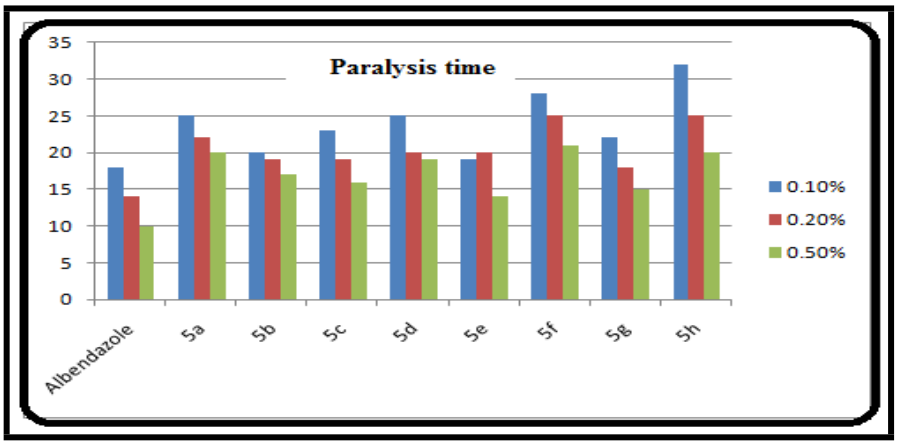


Fig. 1: Graphical representation of anthelmentic activity of compounds (5a-5h) - Paralysis time (min)

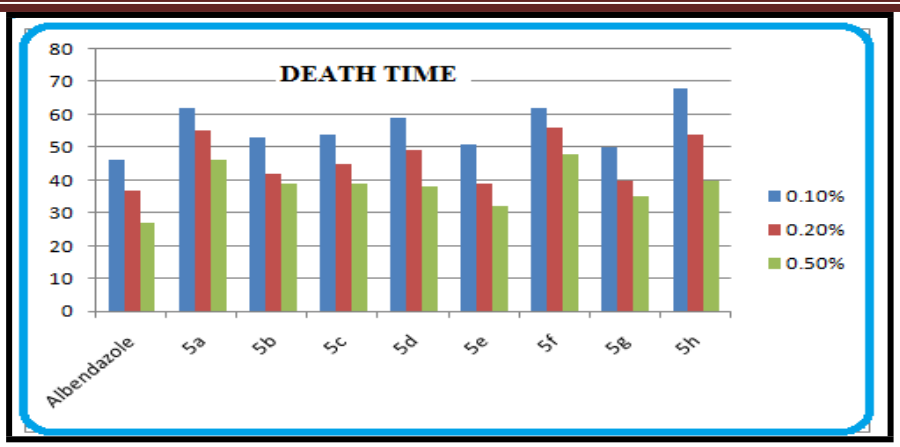


Fig. 2: Graphical representation of anthelmentic activity of compounds (5a-5h) - Death time(min)

Fig. 3: Photographs of various Novel Schiff's Bases derivatives – Anthelmintic activity

CONCLUSION

The objective of the present work was to synthesize, purify, characterize and evaluate the biological activity of various Novel Schiff's Bases derivatives. The yield of the synthesized compound was found to be in the range from 60-87 %. In conclusion, the present study highlights the importance of various Novel Schiff's Bases derivatives having various heterocyclic moiety features responsible for the anthelmintic activities and may serve as a lead molecule for further modification to obtain clinically useful novel entities.

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