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Synthesis, Characterization and Anthelmentic Screening of 1-(Substituted Benzylidene)-5-(5-Chloro-2-Oxoindolin-3-Ylidene) Thiocarbonohydrazide Derivatives

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ABSTRACT: In the current research a series of 1-(substituted benzylidene)-5-(5-chloro-2-oxoindolin-3-ylidene) thiocarbonohydrazide **(5a-g)** were designed and synthesized. All the synthesized compounds were tested against earth worms for anthelmintic activity. The reference medicine of choice was albendazole. The structural conformation of compounds was done by IR, NMR and Mass spectroscopy technique's. spectra were of good intensity.
From all the synthesized compounds **(5a-g)** compound **5e** and **5f** were found to be most potent tested for anthelmintic activity, with reference to albendazole as standard drug.

KEYWORDS: Thiocarbohydrazide, Isatin, Albendazole, Anthelmentic.

I. INTRODUCTION

[1].The most common sickness worldwide, soil-transmitted helminth infections, strike the poorest and most neglected communities, according to the WHO report 2022. They are dispersed by eggs found in human faeces, which contaminate the soil in filthy areas. [2-3].The three primary types of worms that infect people are Ascaris lumbricoides (round warm) trichuris trichiura (whipworms) Necator americanus and Ancylostoma duodenale (hookworms,). Due to their shared diagnostic requirements and therapeutic responses, many STH species are typically treated together.

[4-6].Over 1.5 billion individuals, or 24% of the world's population, have helminth diseases that are spread via soil. Tropical and subtropical regions are commonly infected, with sub-Saharan Africa, the Americas, China, and East Asia having the highest rates of infection. Children who live in places where these parasites are frequently transmitted more than 267 million preschoolers and more than 568 million school-age kids need treatment and prevention measures. Over 600 million individuals are thought to be infected with S. stercoralis worldwide, however because this parasite is also spread in unsanitary places, its geographic range overlaps with that of another helminthiasis that is spread through the soil.

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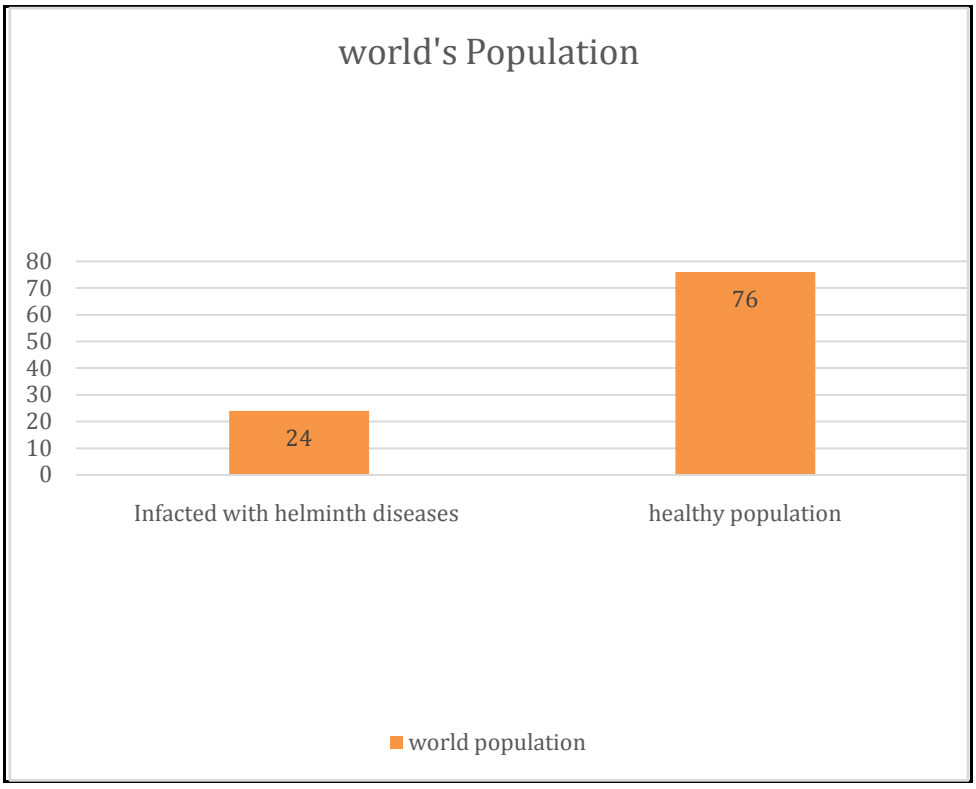
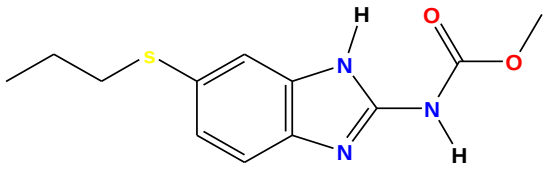
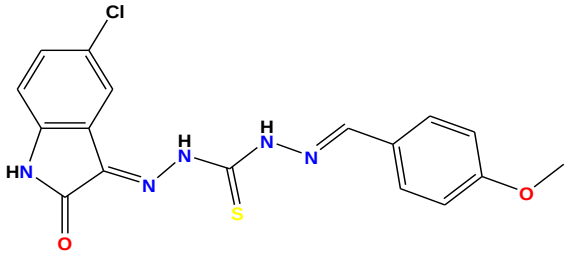


Anthelmentics are the agents which are used to treat parasitic worms after they cause infections in human. [7-10].As the upper graph suggest that a huge population of world is suffering from the parasitic infection so the drug discover for these parasitic infection causing agents should be done.



Albendazole



5e

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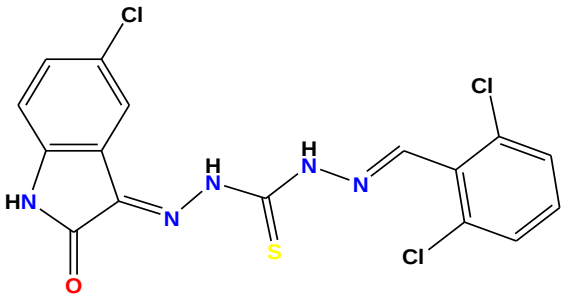
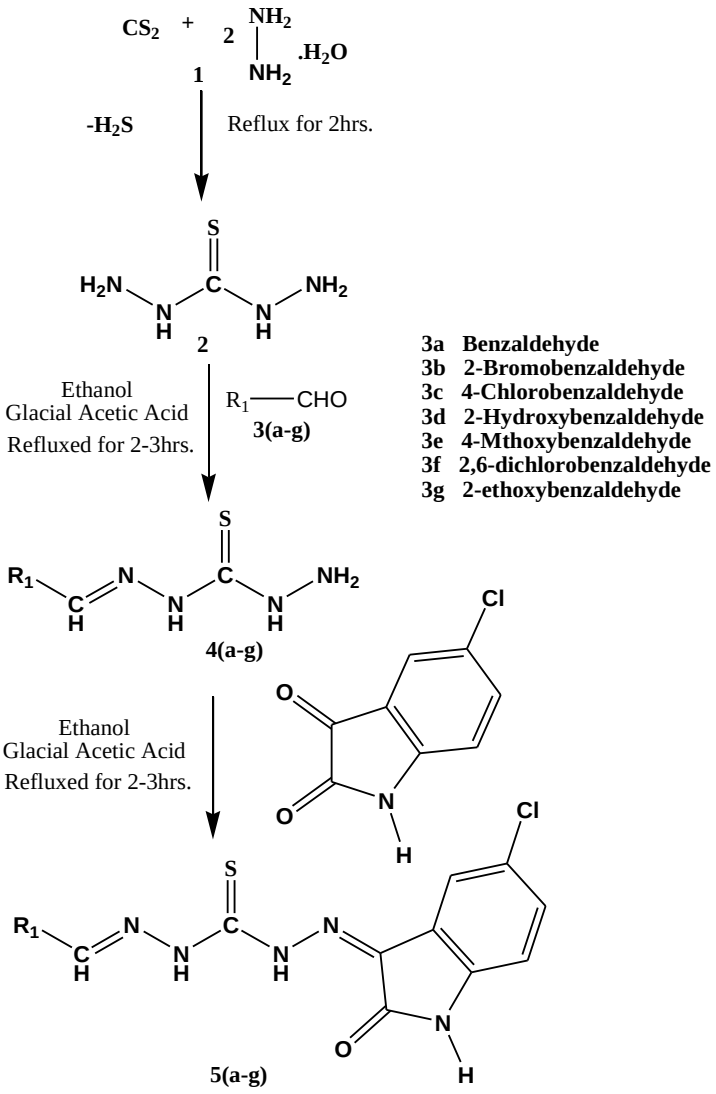


5f

[11-15].Schiff base show wide spectrum on pharmacological screening such as antiviral, anticancer, antibacterial, ant tubercular, antiviral, anti-inflammatory, antioxidant and anthelmintic, also it shows good activity as anti-HIV etc.

Scheme



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II. EXPERIMENTATION

MATERIAL AND METHOD

A. SYNTHESIS OF THIOCARBO-HYDRAZIDE.

[16-17]A mixture of hydrazine hydrate 85% (24ml) and water (75ml) was prepared into this, a 13 ml solution of carbon disulphide (0.22mol) was transferred drop by drop with continuous starring for 3o minutes. Then the reaction mixture was refluxed for 2hrs at 100-110^{0}C. After refluxing the reaction mixture for 2hrs it is was cooled on ice bath and the precipitate was filtered. The precipitate was filtered, washed with ethanol and ether and recrystallized with water to get pure crystals of thiocarbohydrazide.

B. SYNTHESIS OF 1-(SUBSTITUTED BENZYLIDENE)THIOCARBONOHYDRAZIDE (4a-g)

[18-19].In a mixture of glacial acetic acid (5ml), ethanol (30ml) trihydrocarbohydrazides and substituted benzaldehydes were dissolved in equimolar quantities (0.01). The reaction mixture was refluxed for 2-3hrs. After refluxing the reaction mixture was cooled and left overnight in refrigerator. The precipitate was filtered, and recrystallized by suitable solvent.

Table 2: Physicochemical properties of compounds (4a-g)

Compound code.	R	Molecular Formula	Molecular weight	% Yield	R_f Value
4a	Benzaldehyde	$C_8H_{10}N_4S$	194.2	57	0.67
4b	2-Bromobenzaldehyde	$C_8H_9BrN_4S$	273.1	63	0.61
4c	4-Chlorobenzaldehyde	$C_8H_{10}ClN_4S$	228.0	59	0.51
4d	2-Hydroxybenzaldehyde	$C_8H_{10}N_4OS$	210.2	65	0.65
4e	4-Mthoxybenzaldehyde	$C_9H_{12}N_4OS$	224.2	62	0.73
4f	2,6-dichlorobenzaldehyde	$C_8H_8Cl_2N_4S$	263.1	67	0.83
4g	2-ethoxybenzaldehyde	$C_{11}H_{14}N_4OS$	250.3	64	0.68

C. Synthesis Of 1-(Substituted Benzylidene)-5-(5-Chloro-2-Oxoindolin-3-Ylidene) Thiocarbonohydrazide. (5a-g)

[19-20].In glacial acetic acid and warm ethanol in a ratio of 1:1 (30 ml), 5-chloro-2-oxoindolin-3-ylidene (0.01mol) and 1-(substituted benzylidene)thiocarbonohydrazide **(4a-j)** were dissolved in the same molar ratio. The reaction mixture was then refluxed for another 3–4 hours. The reaction mixture was cooled after refluxing and kept in the refrigerator for the night. The precipitate was filtered, and a suitable solvent was used to recrystallize it.

Table 3: Physicochemical properties of compounds (5a-g)

Compound code	R	Molecular Formula	Molecular weight	% Yield	R_f Value	m.p (^{0}C)
5a	Benzaldehyde	$C_{16}H_{12}ClN_5OS$	357	79	0.54	142-143
5b	2-Bromobenzaldehyde	$C_{16}H_{11}BrClN_5OS$	436	48	0.61	153-154
5c	4-	$C_{16}H_{11}Cl_2N_5OS$	392	53	0.52	160-161

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	Chlorobenzaldehyde					
5d	2-Hydroxybenzaldehyde	$C_{16}H_{12}ClN_5O_2S$	373	74	0.49	175-176
5e	4-Mthoxybenzaldehyde	$C_{17}H_{14}ClN_5O_2S$	387	64	0.55	149-150
5f	2,6-dichlorobenzaldehyde	$C_{16}H_{10}Cl_3N_5OS$	426	43	0.59	164-165
5g	2-ethoxybenzaldehyde	$C_{18}H_{16}ClN_5OS$	385	77	0.49	168-169

1-benzylidene-5-(5-chloro-2-oxoindolin-3-ylidene) thiocarbonohydrazide. (5a)
Yield: 79%, m.p: 142-143^{0}C; IR Spectra [KBr; cm^{-1}]: 3112 (N-H), 1709 (C=O), 1662 (N=C), 1599 (N-CH), 1260 (C=S), 708 (C-Cl). ^{1}H-NMR Spectra (300 MHz; DMSO-d_6/ppm): 13.8 (s, 1H, N-H), 12.9 (s, 1H, N-H) 10.1 (s, 1H, indole N-H) 8.32 (s, 1H, C=NH) 8.23-6.87 (m, 8H, Ar-H). EIMS (m/z): 357.8 [M]$^{+1}$.

1-(2-bromobenzylidene)-5-(5-chloro-2-oxoindolin-3-ylidene) thiocarbonohydrazide. (5b)
Yield: 48%, m.p: 153-154^{0}C; IR Spectra [KBr; cm^{-1}]: 3176 (N-H), 1724 (C=O), 1642 (N=C), 1574 (N-CH), 1254 (C=S), 711 (C-Cl). ^{1}H-NMR Spectra (300 MHz; DMSO-d_6/ppm): 13.1 (s, 1H, N-H), 12.7 (s, 1H, N-H) 9.9 (s, 1H, indole N-H) 8.12 (s, 1H, C=NH) 8.27-6.87 (m, 7H, Ar-H). EIMS (m/z): 436.7 [M]$^{+1}$.

1-(4-chlorobenzylidene)-5-(5-chloro-2-oxoindolin-3-ylidene) thiocarbonohydrazide. (5c)
Yield: 53%, m.p: 160-161^{0}C; IR Spectra [KBr; cm^{-1}]: 3153 (N-H), 1744 (C=O), 1671 (N=C), 1604 (N-CH), 1262 (C=S), 706 (C-Cl). ^{1}H-NMR Spectra (300 MHz; DMSO-d_6/ppm): 12.8 (s, 1H, N-H), 11.4 (s, 1H, N-H) 9.8 (s, 1H, indole N-H) 8.34 (s, 1H, C=NH) 8.01-6.22 (m, 7H, Ar-H). EIMS (m/z): 393.0 [M]$^{+1}$.

1-(2-hydroxybenzylidene)-5-(5-chloro-2-oxoindolin-3-ylidene) thiocarbonohydrazide. (5d)
Yield: 74%, m.p: 175-176^{0}C; IR Spectra [KBr; cm^{-1}]: 3188 (N-H), 1756 (C=O), 1667 (N=C), 1541 (N-CH), 1272 (C=S), 710 (C-Cl). ^{1}H-NMR Spectra (300 MHz; DMSO-d_6/ppm): 13.7 (s, 1H, N-H), 12.4 (s, 1H, N-H) 10.7 (s, 1H, indole N-H) 8.49 (s, 1H, C=NH) 7.99-6.27 (m, 7H, Ar-H) 5.44 (s, 1H, O-H). EIMS (m/z): 375.8 [M]$^{+1}$.

1-(4-methoxybenzylidene)-5-(5-chloro-2-oxoindolin-3-ylidene) thiocarbonohydrazide. (5e)
Yield: 64%, m.p: 149-150^{0}C; IR Spectra [KBr; cm^{-1}]: 3232 (N-H), 1722 (C=O), 1655 (N=C), 1576 (N-CH), 1207 (C=S), 709 (C-Cl). ^{1}H-NMR Spectra (300 MHz; DMSO-d_6/ppm): 13.4 (s, 1H, N-H), 12.4 (s, 1H, N-H) 10.3 (s, 1H, indole N-H) 8.44 (s, 1H, C=NH) 8.11-6.67 (m, 7H, Ar-H) 4.12 (m. 3H, -OCH_3). EIMS (m/z): 389.0 [M]$^{+1}$.

1-(2,6-dichlorobenzylidene)-5-(5-chloro-2-oxoindolin-3-ylidene) thiocarbonohydrazide.(5f)
Yield: 43%, m.p: 164-165^{0}C; IR Spectra [KBr; cm^{-1}]: 3162 (N-H), 1767 (C=O), 1669 (N=C), 1582 (N-CH), 1302 (C=S), 719 (C-Cl). ^{1}H-NMR Spectra (300 MHz; DMSO-d_6/ppm): 13.9 (s, 1H, N-H), 12.8 (s, 1H, N-H) 9.7 (s, 1H, indole N-H) 8.31 (s, 1H, C=NH) 8.07-6.39 (m, 6H, Ar-H). EIMS (m/z): 426.9 [M]$^{+1}$.

1-(2-ethyoxlbenzylidene)-5-(5-chloro-2-oxoindolin-3-ylidene) thiocarbonohydrazide. (5g)
Yield: 77%, m.p: 169-170^{0}C; IR Spectra [KBr; cm^{-1}]: 3211 (N-H), 1710 (C=O), 1663 (N=C), 1569 (N-CH), 1309 (C=S), 716 (C-Cl). ^{1}H-NMR Spectra (300 MHz; DMSO-d_6/ppm): 12.6 (s, 1H, N-H), 11.9 (s, 1H, N-H) 10.5 (s, 1H, indole N-H) 8.19 (s, 1H, C=NH) 8.17-6.67 (m, 7H, Ar-H) 3.59 (m, 2H, CH_2) 1.32 (m. 3H, CH_3). EIMS (m/z): 387.0 [M]$^{+1}$.

PHARMACOLOGICAL SCREENING

ANTHELMINTIC ACTIVITY

[21-23].All the newly synthesized compounds were evaluated for anthelmintic activity against albendazole using earth warms. All the earth warms were distributed into three man groups (Test, Standard and Control) all the groups contain three earth warms nearly having equal size. All the test was performed at room temperature.

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The test and standard compounds were dissolved in very little amount of DMSO and then the volume was make adjusted to 10ml with normal saline. The test and standard solution was prepared in the concentration of 0.1%, 0.2%, 0.5 % w/v. For control group normal saline was used. The time was recorded for bothe the phases of study i.e. paralysis and Death of earth warms.

III. RESULTS

CHEMISTRY

Compound with exocyclic and end cyclic Sulphur atom shows good therapeutic window on pharmacological screening. All the compounds were synthesized according to the Scheme-I via condensation of thiocarbohydrazide with different substituted aldehydes and at last Schiff bases were formed using 5-chloro isatin.

All the compounds were synthesized as per scheme, firstly thiocarbohydrazide were synthesized by reacting carbon disulphide with mixture of hydrazine hydrate and water, then thiocarbohydrazide was again reacted with substituted aromatic benzaldehyde to give 1-(substituted benzylidene) thiocarbonohydrazide **(2a-g).** Further these intermediate is reacted with 5-chloroisatin to get 1-(substituted benzylidene)-5-(5-chloro-2-oxoindolin-3-ylidene) thiocarbon-hydrazide. **(3a-g)** target compounds.

IR spectra of isatin derivatives (3a-g) reported an intense peak at 3112-3232 region of due to N-H stretch, an C=O stretch occurs between 1767-1709 shows the presence of oxygen in the structure, the C=S peak was observed at 1254-1309. At 706-719 region the C-Cl peak was recorded shows the presence of chlorine group in the structure.

^{1}H-NMR spectra of final compounds (3a-g) shows a multiple singlet peak at different regions due to presence of four different N-H groups at different position in the structure. As three N-H groups present in the sight chains, were reported there NMR values, first N-H singlet starching between 13.9-12.6, second N-H stretching 12.9-11.4, third N-H stretching 8.49-8.12. 4th NH group is present in isatins structure its starching was recorded between 10.7-9.7, and multiple aromatic proton were recorded at 8.77-6.22. also the presence of –OH group was recorded at 5.44. The presence of groups like –OCH_3 was confirmed by shiff value at 4.12 and –CH_3 at 1.32.

BIOLOGICAL EVALUATION

ANTHELMINTIC ACTIVITY

The anthelmintic evaluation shows that benzaldehyde ring attached with methoxy group at fourth position and two chlorine group at 2 and 6 position shows significant activity. Highest activity was produced by compound 3e having methoxy group at 4th position and compound 3f having chloro group at 2nd and 6th position. On the other hand, compound 3c has shown moderate Anthelmintic effect. The anthelmintic activity induced that synthesized compounds having –OCH_3 and Cl substitutions shows highest anthelmintic activity. However compound 3e and 3f shows excellent activity.

Table 4: Anthelmintic activity of compounds (5a-g)

S. No.	Name	Time in minutes (mean ± sem)					
		For paralysis			For death		
		% concentration			% concentration		
		0.1	0.2	0.5	0.1	0.2	0.5
1	Control	-	-	-	-	-	-
2	Albendazole	49±0.46	44±0.18	38±0.43	68±0.34	62±0.24	53±0.16
3	5a	79±0.31	73±0.19	68±0.16	195±0.22	187±0.22	179±0.17
4	5b	75±0.22	71±0.43	63±0.19	189±0.15	181±0.34	170±0.26
5	5c	48±0.24	45±0.34	43±0.36	142±0.18	138±0.14	134±0.34
6	5d	68±0.15	65±0.35	60±0.24	180±0.15	173±0.17	164±0.16
7	**5e**	**40±0.41**	**38±0.25**	**30±0.15**	**135±0.13**	**130±0.24**	**118±0.38**
8	**5f**	**48±0.36**	**44±0.49**	**39±0.25**	**145±0.38**	**137±0.19**	**124±0.24**
9	5g	63±0.42	60±0.19	57±0.35	172±0.28	169±0.34	162±0.34

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IV. CONCLUSION

During this anthelmintic experiment it was found that 5-chloroistain along with substituted benzaldehydes shows good anthelmintic activity. Among all the synthesized compounds compound 1-(4-methoxybenzylidene)-5-(5-chloro-2-oxoindolin-3-ylidene) thiocarbonohydrazide **(5e)** and 1-(2,6-dichlorobenzylidene)-5-(5-chloro-2-oxoindolin-3-ylidene) thiocarbonohydrazide **(5f)** has expressed good anthelmintic activity. From the above data it is clear that, Schiff bases can serve as a lead analogue for future modification to archived further novel entities.

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