

SYNTHESIS AND ANTHELMINTIC ACTIVITY OF 3-(2-HYDRAZINO BENZOTHIAZOLES)-SUBSTITUTED INDOLE-2-ONE

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ABSTRACT

Benzothiazoles and Isatins have emerged as structurally novel anthelmintics. Therefore various 3-(2-hydrazino benzothiazoles)-substituted Indole-2-one, were synthesized by condensation of various 2-hydrazino benzothiazole, 2-hydrazino 1,4-thiazine and 2-acid hydrazide benzothiazoles with different substituted Indole -2,3-diones (Isatins). The structures of the synthesized compounds (A₁₋₆)(B₁₋₆)(C₁₋₆) were characterized by FTIR, ¹HNMR and elemental analysis. All the synthesized compounds were screened for anthelmintic activity by using Indian adult earthworms (*pheretima postuma*). The compounds A_{4,5}, B₄, C₄ have showed good paralytic time, compared to standard albendazole drug.

KEYWORDS: Isonitrosoacetanilides, Isatins, Benzothiazoles, Earthworms, Anthelmintic activity.

INTRODUCTION

The search for anthelmintic compounds with a more selective activity and lower toxicity continues to be an area of investigation in medicinal chemistry. The chemical diversity and various mechanisms of action of anthelmintics make it difficult to find a common way of identifying new drugs. Compounds containing a hydrazinobenzothiazole, hydrazinobenzothiazine and Isatin component have shown a broad spectrum of chemotherapeutic properties including antimicrobial,^{1,2} antiviral^{3,4}, anthelmintic⁵, analgesics⁶, antiinflammatory⁷ and anticytotoxic^{8,9} activities of substituted indoles.

In view of our program to develop novel anthelmintic agents it was decided to synthesize various 3-(2-hydrazino benzothiazoles)-substituted Indole-2-one by condensation of substituted Isatins with different 2-hydrazino benzothiazoles (Scheme 1). The chemical structures of the synthesized compounds were confirmed on the basis of their spectral data (FTIR, ¹HNMR and elemental analysis) and the purity was ascertained by TLC analysis. The details of the synthesis and biological results are presented herein.

MATERIALS AND METHODS

All the chemicals and solvents were obtained from commercial and purified using standard procedures wherever required. Melting points were taken by open

capillary method and were uncorrected. The reactions were monitored by thin layer chromatography on silica gel G plates (Merck silica – 60F₂₅₄) and the final products were purified by recrystallization from absolute ethanol. The structure of all the newly synthesized compounds were confirmed by FTIR (Recorded on a FTIR-8400S spectrophotometer, shimadzu), ¹HNMR recorded on Bruker NMR spectrometer in deuterium substituted DMSO form using TMS as internal standard) all exchange able protons were confirmed by addition of D₂O and elemental analysis (C, H & N) using Perkin-Elmer model 240C.

General procedure for synthesis of Isonitrosoacetanilide-I (part-I)

In a 5 lit round bottomed flask were placed chloral hydrate (0.54 mol) and 1200ml of water. To this solution, were then added crystallized sodium sulphate (1300g) followed by a solution of an appropriate aromatic amine (0.5mol) in 300ml of water concentrated hydrochloric acid (0.52mol). Finally a solution of hydroxylamine hydrochloride (1.58mol) in 500ml of water was added. The contents of flask were heated over a wire gange by a mecker burner so that vigorous boiling begins in bout 45min. During the heating period itself the crystals of isonitroso acetaminilide started separating out on cooling under the current of water the entire product

was solidified. It was filter under suction, air dried and purified by recrystallization from alcohol.

Synthesis of Indole-2,3-diones (Isatines): (II)

In a one-liter round bottomed flask place a sulphuric acid 326ml was warmed to 50⁰C which is fitted with an efficient mechanical stirrer and to this finely powdered an appropriate isonitroso acetanilide (0.46mol) was added at such a rate so as to maintain the temperature between 60⁰C to 70⁰C. Then external cooling was applied at this stage so that the reaction could be carried out more rapidly. After the addition of isonitroso acetanilide compound was completed, the temperature of the solution was raised to 80⁰c and maintained at that temperature for 10 minutes to complete the reaction. Then the reaction mixture was cooled at room temperature and which is poured on crushed ice (2.5kg) while stirring. After standing for about half an hour the crude isatin separated, it is filtered and washed with cold water, to remove traces of sulphuric acid and dried. It was purified by recrystallization from methanol.

General procedure for the synthesis of 3-(2-hydrazino benzothiazole/2-hydrozino-1,4-benzothiazine/2-carbonyl hydrazine benzothiazole) - substituted Indole-2-one¹⁰. (A₁₋₆, B₁₋₆, C₁₋₆) (Part-II)

Equimolar quantities of 2-Hydrazino benzothiazoles and different substituted indole -2,3-diones were added to a mixture of 4 ml of dry pyridine and 20 ml of acetic anhydride and the mixture was refluxed for 2 hrs. then the reaction mixture was poured into ice water and solid obtained was filtered by recrystallization from ethanol to give title compounds (A₁₋₆, B₁₋₆, C₁₋₆) as shown physical data in table no 1.

Anthelmintic Activity^{11,12}

The synthesized compounds by scheme I were screened for anthelmintic activity by using earthworms. Six Indian adult earth worms (*Pheretima Postama*) of nearly equal size 5-8 cm in length and 0.2-0.3 cm in width were placed in standard drug solution and test compound solutions at room temperature. Normal saline was used as a control. The standard drug and test compounds were dissolved un minimum quantity of dimethylformamide (DMF) and adjusted the volume upto 15ml with normal saline to get the concentration of 0.1% w/v, 0.2% w/v and 0.5% w/v. Albendazole was used as standard drug, the compounds were evaluated for the time taken for complete paralysis and death of earth worms. 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 motionless worms, they were frequently applied with external stimuli, which stimulate

and induce movement in the worms, if alive. The mean lethal time and paralysis time of earthworms for different test compounds and standard drug were tabulated in tables 2.

Spectral Data

3-(2-hydrazino benzothiazole)-indolin-2-one(A)

IR (KBr)v(cm⁻¹); 3425.82(NH);2669.93(Ar-H);1593.80(CO);1499.21(C=C);1258.61(N-N=C);695.58(CS);

¹H-NMR(CDCl₃):δ7.55-8.21(4CH-benzothiazole); δ6.97-11.92(NH-hydrazide) ;δ6.82-7.36(CH-benzylidenium); δ8.12-11.24(NH-sec.amide)

3-(2-hydrazino -1,4-benzothiazine)-indolin-2-one(B)

IR (KBr)v(cm⁻¹); 3338.75(NH);2980.56(Ar-CH);1646.35(CO);1501.06(N-N=C); 1453.77(C=C);689.12(CS);

¹H-NMR(CDCl₃):δ6.92-7.66(benzothiazine); δ7.02-7.34(NH-hydrazide) ;δ6.89-7.82(CH-benzylidenium); δ8.23-10.92(NH-sec.amide)

3-(2-carbonyl hydrazino benzothiazole)-indolin-2-one(C)

IR (KBr)v(cm⁻¹); 3421.03(NH);2964.45(Ar-CH);1691.69(CO);1596.25(N-N=C); 1445.98(C=C);691.53(CS);

¹H-NMR(CDCl₃):δ7.30-8.36(CH-benzothiazole); δ6.82-10.98(NH-hydrazide) ;δ7.02-7.38(CH-benzylidenium); δ8.00-11.28(NH-sec.amide)

RESULT & DISCUSSION

The Anthelmintic activity of all eighteen compounds by scheme I was carried out using adult earth worms. The compounds A₄₋₅, B₄, C₄, have showed good paralytic time, where as compounds A₆, B₅₋₆, C₅₋₆, have showed moderate paralytic time on earthworms compared to standard albendazole drug at 0.1%, 0.2% and 0.5% concentration of the test compounds.

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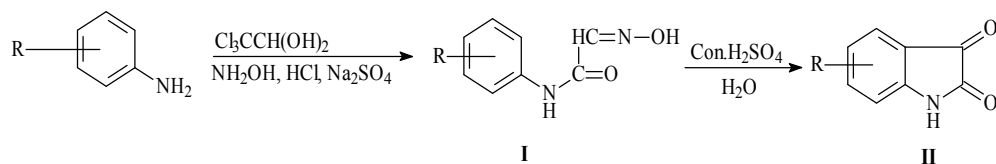
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Table 1: ANALYTICAL DATA FOR THE SYNTHESIZED COMPOUNDS

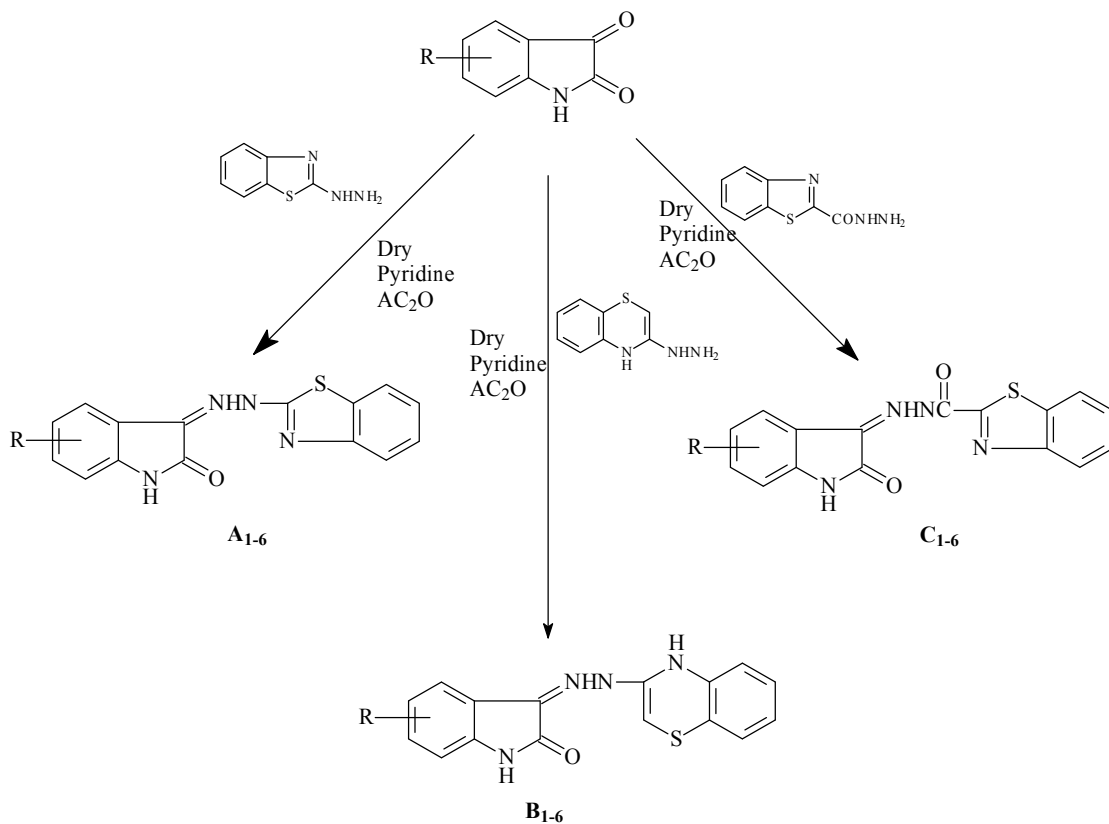
S.No	Comp	Molecular Formula	m.p° C	% yield	Mol.wt	% Calculated		
						C	H	N
01	A ₁	C ₁₅ H ₁₀ N ₄ OS	217	75	294.32	61.21	3.42	19.03
02	A ₂	C ₁₆ H ₁₀ N ₄ O ₃ S	220	87	338.33	56.80	2.97	16.56
03	A ₃	C ₁₆ H ₂ N ₄ OS	210	78	308.33	62.32	3.92	18.16
04	A ₄	C ₁₅ H ₉ CLN ₄ OS	206	84	328.76	54.80	2.75	17.04
05	A ₅	C ₁₅ H ₉ N ₅ OS	190	73	339.32	53.09	2.67	20.63
06	A ₆	C ₁₅ H ₉ BrN ₄ OS	228	79	364.22	49.46	2.49	15.38
07	B ₁	C ₁₆ H ₁₂ N ₄ OS	218	80	308.33	62.27	3.92	18.16
08	B ₂	C ₁₇ H ₁₂ N ₄ O ₃ S	222	81	320.34	63.73	3.77	17.48
09	B ₃	C ₁₇ H ₁₄ N ₄ OS	213	73	322.38	63.33	4.37	17.37
10	B ₄	C ₁₆ H ₁₁ CLN ₄ OS	202	69	342.80	56.06	3.23	16.34
11	B ₅	C ₁₆ H ₁₁ N ₅ O ₃ S	192	68	353.33	54.38	3.13	19.81
12	B ₆	C ₁₆ H ₁₁ BrN ₄ OS	226	71	377.44	50.91	2.93	14.84
13	C ₁	C ₁₆ H ₁₀ N ₄ O ₂ S	219	66	332.34	57.82	3.03	16.85
14	C ₂	C ₁₇ H ₁₀ N ₄ O ₄ S	221	68	366.34	55.73	2.75	15.29
15	C ₃	C ₁₇ H ₁₂ N ₄ O ₂ S	190	71	336.36	60.70	3.59	16.65
16	C ₄	C ₁₆ H ₉ N ₄ ClO ₂ S	210	74	356.78	52.53	2.54	15.70
17	C ₅	C ₁₆ H ₉ N ₅ O ₄ S	196	80	367.33	52.31	2.46	19.06
18	C ₆	C ₁₆ H ₉ N ₄ BrO ₂ S	224	82	392.23	48.99	2.29	14.28

SCHEME

Part - I



Part - II



R = -H, -5-COOH, 5-CH₃, 5-Cl, 5-NO₂, -5-Br

Table 2: ANTHELMINTIC ACTIVITY OF SYNTHESIZED COMPOUNDS

S.No	Compound	Concentration % W/V	Time in Minutes Mean \pm SD	
			For Paralysis	For Death
	Control	0.8	-	-
	Standard	0.1	54 \pm 0.52	76 \pm 0.39
		0.2	49 \pm 0.29	68 \pm 0.24
		0.5	0.6 \pm 0.63	52 \pm 0.16
1	A ₁	0.1	61 \pm 0.28	169 \pm 0.20
		0.2	59 \pm 0.24	146 \pm 0.35
		0.5	64 \pm 0.43	142 \pm 0.45
2	A ₂	0.1	57 \pm 0.37	143 \pm 0.28
		0.2	47 \pm 0.46	138 \pm 0.45
		0.5	49 \pm 0.39	127 \pm 0.32
3	A ₃	0.1	61 \pm 0.41	171 \pm 0.63
		0.2	58 \pm 0.26	175 \pm 0.14
		0.5	54 \pm 0.63	146 \pm 0.35
4	A ₄	0.1	57 \pm 0.28	149 \pm 0.35
		0.2	48 \pm 0.31	151 \pm 0.92
		0.5	37 \pm 0.82	139 \pm 0.21
5	A ₅	0.1	48 \pm 0.59	152 \pm 0.32
		0.2	43 \pm 0.26	138 \pm 0.61
		0.5	32 \pm 0.51	126 \pm 0.19
6	A ₆	0.1	57 \pm 0.43	161 \pm 0.32
		0.2	56 \pm 0.45	153 \pm 0.29
		0.5	42 \pm 0.38	134 \pm 0.28
7	B ₁	0.1	53 \pm 0.29	172 \pm 0.38
		0.2	62 \pm 0.33	158 \pm 0.19
		0.5	57 \pm 0.37	148 \pm 0.43
8	B ₂	0.1	64 \pm 0.44	168 \pm 0.38
		0.2	60 \pm 0.52	163 \pm 0.41
		0.5	58 \pm 0.53	148 \pm 0.28
9	B ₃	0.1	68 \pm 0.41	169 \pm 0.36
		0.2	65 \pm 0.62	152 \pm 0.18
		0.5	58 \pm 0.28	142 \pm 0.35
10	B ₄	0.1	49 \pm 0.58	149 \pm 0.34
		0.2	46 \pm 0.42	142 \pm 0.42
		0.5	35 \pm 0.34	133 \pm 0.42
11	B ₅	0.1	62 \pm 0.32	168 \pm 0.26
		0.2	59 \pm 0.28	172 \pm 0.51
		0.5	56 \pm 0.38	148 \pm 0.36
12	B ₆	0.1	67 \pm 0.16	162 \pm 0.21
		0.2	65 \pm 0.52	148 \pm 0.26
		0.5	59 \pm 0.28	142 \pm 0.36
13	C1	0.1	58 \pm 0.13	173 \pm 0.38
		0.2	63 \pm 0.26	156 \pm 0.16
		0.5	51 \pm 0.32	146 \pm 0.36
14	C2	0.1	73 \pm 0.42	178 \pm 0.21
		0.2	67 \pm 0.16	179 \pm 0.17
		0.5	60 \pm 0.20	158 \pm 0.09
15	C3	0.1	68 \pm 0.14	181 \pm 0.23
		0.2	64 \pm 0.24	162 \pm 0.22
		0.5	59 \pm 0.13	147 \pm 0.33
16	C4	0.1	44 \pm 0.51	138 \pm 0.31
		0.2	39 \pm 0.52	132 \pm 0.42
		0.5	36 \pm 0.25	128 \pm 0.36
17	C5	0.1	56 \pm 0.30	172 \pm 0.41
		0.2	54 \pm 0.28	161 \pm 0.52
		0.5	40 \pm 0.42	154 \pm 0.32
18	C6	0.1	52 \pm 0.34	163 \pm 0.24
		0.2	48 \pm 0.32	152 \pm 0.36
		0.5	41 \pm 0.61	146 \pm 0.22
		0.2	73 \pm 0.19	195 \pm 0.22
		0.5	71 \pm 0.32	187 \pm 0.10