Synthesis and Biological Evaluation of Some Novel Chromene-2-one Derivatives for Antihelmintic Activity

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Abstract: Various Chromene -2- one derivatives (1a-1f) were synthesized and evaluated for antihelmintic activity on adult Indian earthworm (*Pheritima posthuma*) at various concentrations (15, 30, 60 mg/ml). All synthesized compounds showed a significant (P<0.05) dose dependant action and inhibition of spontaneous motility (paralysis) and death of earthworms. Compound 1f showed comparable antihelmintic effect to that of standard drug Albendazole.

Kev Words: Antihelmintic activity, *Pheritima posthuma*, Chromene-2-one, Paralysis.

Introduction:

Helminthic infestations are now being recognized as a cause of chronic ill health and sluggishness amongst the children. More than half of the population in the world suffers from worm infestations of one or other. Helminthes also affect domestic animals and livestock causing considerable economic loss.[1]

Chromene-2-one & its derivatives are known to possess diverse biological activities such as antibacterial[2], antifungal[3], antineoplastic[4], antitubercular[5] & anthelmintic[6]. In this direction our efforts were devoted to synthesize some novel Chromene-2-one derivatives that would be beneficial to treat helminthic infestations.

Materials and Methods:

Synthetic part

In present work all synthetic reactions were monitored by TLC. All the synthesized compounds (1a-1f) were characterized by analytical and spectroscopic methods. Melting points (Table-1) were determined on Veego melting point apparatus, model no-MPI by open capillary method and are uncorrected. The FTIR spectra (Table-1) were recorded on Jasco FTIR instrument model no-5300, using KBr pellets. ^{1}H-NMR spectra (Table-2) were recorded on BRUKER AVANCE II 400 NMR spectrometer at 400 MHz, for which $CDCl_3$ was used as solvent and TMS as internal standard.

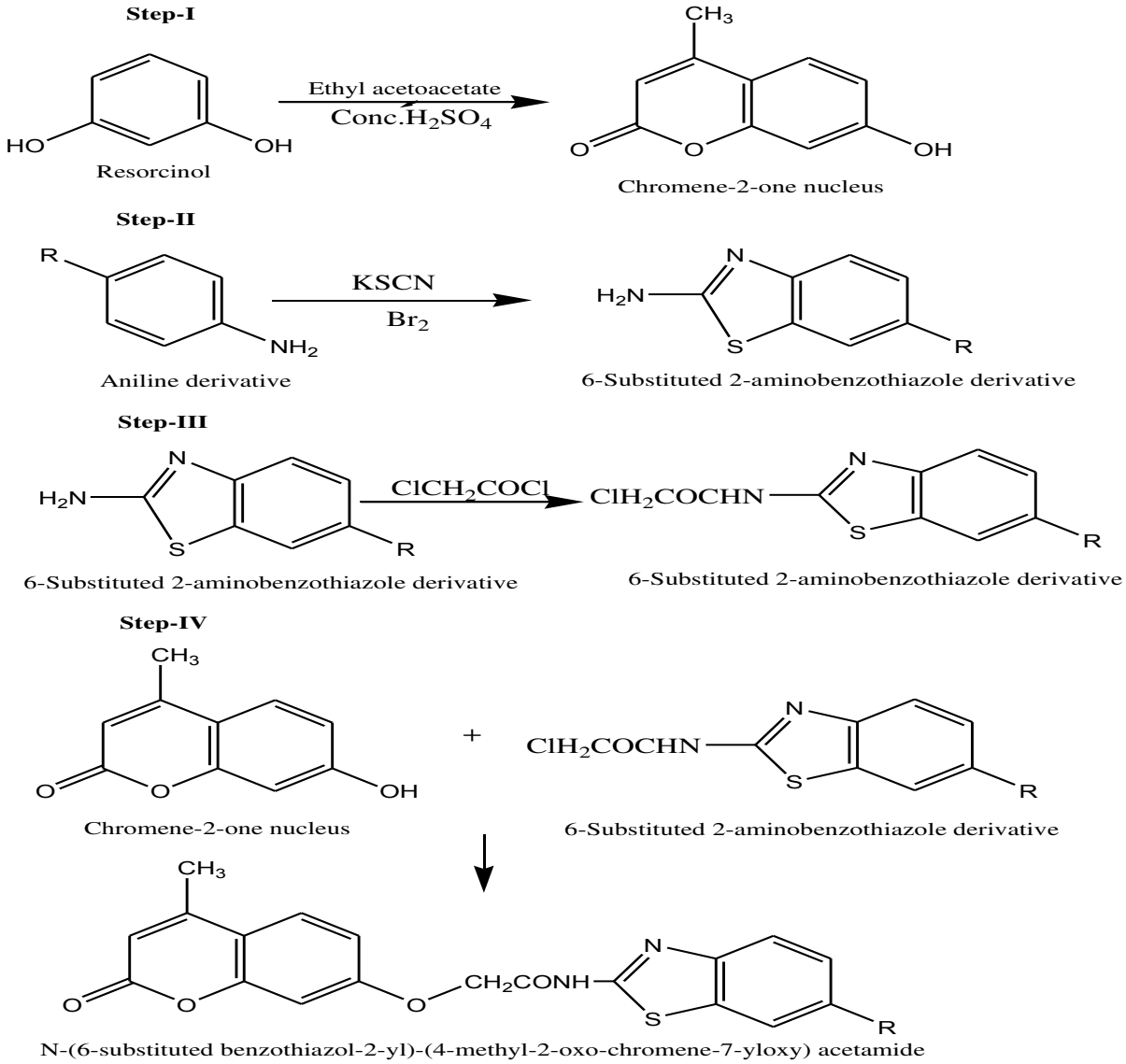
General procedure for synthesis of Chromene-2-one nucleus, (step-I)

The method of Pechmann and Duisburg was followed for the synthesis of Chromeme-2-one nucleus[7].

General procedure for synthesis of 6-Substituted 2-aminobenzothiazole derivatives,(step-II)

0.06 moles of aniline derivative & 0.06 moles of potassium thiocyanate were added to 150 ml of glacial acetic acid (previously cooled to 5°C). The mixture was placed in freezing mixture of ice & salt and mechanically stirred, while bromine (0.02 moles of bromine in 10 ml glacial acetic acid) was added from a dropping funnel at such a rate that temperature does not rise beyond 0-5°C. After addition of bromine (105 min), the solution was stirred for an additional 2 hours at 0-10°C. The residue was filtered and dissolved in hot water (150 ml). The solution was filtered and filtrate was neutralized with ammonia solution to pH 6.0. The precipitate was collected and crystallized with ethanol[8].

Figure 1: Scheme of synthesis



General procedure for synthesis of 6-Substituted (1'-chloroacetyl)-2-aminobenzothiazole derivatives, (step-III)

To a stirred solution of 6-substituted 2-aminobenzothiazole (0.05 moles) and triethylamine (0.05 moles) in dry benzene (50 ml), chloroacetyl chloride (0.05 moles) was added drop wise to an ice-cold condition. The reaction mixture was stirred for about 6 hours and the separated amine hydro Chloride was filtered off. The filtrate was refluxed on a water-bath for about 4 hr, concentrated at reduced pressure and the separated solid was purified over the column of silica gel using chloroform as an eluant. The product was crystallized from ethanol[9].

General procedure for synthesis of N-(6-substituted benzothiazol-2-yl)-(4-methyl-2-oxo-chromene-7-yloxy) acetamide derivatives (1a-1f), (step-IV)

0.01 mole of chromene-2-one nucleus and 0.01 mole of 6-Substituted (1'-chloroacetyl)-2-aminobenzothiazole derivatives were added to round bottom flask containing 30 ml of acetonitrile. 0.01 mole of anhydrous potassium carbonate was added to reaction mixture and refluxed for 38 hours, then solvent was removed under vacuum and residue was dissolved in dichloromethane. Dichloromethane layer was washed with water to remove potassium carbonate and then washed with 5% w/v sodium hydroxide solution to remove the unreacted material. Dichloromethane layer was again washed with water and then anhydrous sodium sulphate was added to remove water and this layer was kept overnight to collect crude product which was crystallized from ethanol.

Table-1: Physicochemical parameters and IR spectral data of synthesized compounds (1a-1f)

Compound	-R	Yield (%)	M.P. (°C)	R_f value	IR (KBr disc, cm^{-1})
1a	-H	57	124	0.458	1742, 3060, 1575, 3120, 1610
1b	-Br	53	134	0.523	1740, 3085, 1564, 3130, 1624
1c	-Cl	44	128	0.621	1740, 3060, 1566, 3135, 1635, 762
1d	-F	53	138	0.592	1744, 3068, 1570, 3132, 1640, 1195
1e	$-OCH_3$	48	116	0.487	1742, 3065, 1560, 3140, 1640, 1242
1f	$-OC_2H_5$	50	122	0.436	1739, 3070, 1572, 3128, 1644, 1246

*(Benzene: Ethyl acetate: 3:2)

Table-2: ^{1}H-NMR spectral data

Compound	^{1}H-NMR (δ, 400MHz, $CDCl_3$)
1a	δ 6.53 (t, Benzene (-CH)), δ 7.16 (t, Benzene (-CH)), δ 5.90 (t, Benzene (-CH)), δ 1.71 (d, $-CH_3$), δ 8.1 (s, -NH), δ 4.80 (d, Methylene-CH_2), δ 7.52 (m, Benzothiazole (-CH)), δ 8.12 (m, Benzothiazole (-CH)), δ 8.22 (m, Benzothiazole (-CH))
1b	δ 6.53 (t, Benzene (-CH)), δ 7.14 (t, Benzene (-CH)), δ 5.95 (t, Benzene (-CH)), δ 1.74 (d, $-CH_3$), δ 8.1 (s, -NH), δ 4.84 (d, Methylene-CH_2), δ 7.70 (m, Benzothiazole (-CH)), δ 8.10 (m, Benzothiazole (-CH)), δ 8.29 (m, Benzothiazole (-CH))
1c	δ 6.54 (t, Benzene (-CH)), δ 7.16 (t, Benzene (-CH)), δ 5.92 (t, Benzene (-CH)), δ 1.71 (d, $-CH_3$), δ 8.0 (s, -NH), δ 4.82 (d, Methylene-CH_2), δ 7.56 (m, Benzothiazole (-CH)), δ 8.11 (m, Benzothiazole (-CH)), δ 8.20 (m, Benzothiazole (-CH))
1d	δ 6.53 (t, Benzene (-CH)), δ 7.16 (t, Benzene (-CH)), δ 5.90 (t, Benzene (-CH)), δ 1.71 (d, $-CH_3$), δ 8.1 (s, -NH), δ 4.80 (d, Methylene-CH_2), δ 7.82 (m, Benzothiazole (-CH)), δ 7.24 (m, Benzothiazole (-CH)), δ 8.2 (m, Benzothiazole (-CH))
1e	δ 6.56 (t, Benzene (-CH)), δ 7.15 (t, Benzene (-CH)), δ 5.93 (t, Benzene (-CH)), δ 1.71 (d, $-CH_3$), δ 8.1 (s, -NH), δ 4.83 (d, Methylene-CH_2), δ 7.62 (m, Benzothiazole (-CH)), δ 7.06 (m, Benzothiazole (-CH)), δ 8.12 (m, Benzothiazole (-CH)), δ 3.71 (d, $-OCH_3$)
1f	δ 6.53 (t, Benzene (-CH)), δ 7.16 (t, Benzene (-CH)), δ 5.90 (t, Benzene (-CH)), δ 1.71 (d, $-CH_3$), δ 8.1 (s, -NH), δ 4.80 (d, Methylene-CH_2), δ 7.64 (m, Benzothiazole (-CH)), δ 8.10 (m, Benzothiazole (-CH)), δ 8.23 (m, Benzothiazole (-CH)), δ 1.33 (s, Ethoxy-CH_3), δ 3.88 (d, Ethoxy-CH_2)

Pharmacological Evaluation:

Animals

Indian adult earthworms, *Pheritima posthuma*, resemble both anatomically and physiologically to the intestinal roundworm parasites of human beings hence these were used to study antihelmintic activity.[10,11,12] The earthworms of 3-6 cm in length and 0.1-0.3 cm in width were used for all experimental protocols. The earthworms collected from the moist soil of the campus of Madhav University (Rajasthan), India and were washed with normal saline to remove the faecal matter.

Evaluation of Antihelmintic activity:

The antihelmintic activity was evaluated on adult Indian earthworm. The earthworms were divided into twenty two groups; each group containing six earthworms. The group first served as control which was treated with vehicle (5% DMF in normal saline). The second, third & fourth groups served as standard which were treated with Albendazole at various concentrations (15, 30, 60 mg/ml). The fifth to twenty second groups were served as test which were treated with all synthesized compounds (1a-1f) at various concentrations (15, 30, 60 mg/ml) respectively. The time taken by worms to paralysis and death was observed. Time for paralysis was noted when no movement could be observed with a slight pin prick method. Death was ascertained by applying external stimuli which stimulate and induce movements in worms as well as fade of the body color was noted.

Statistical analysis:

Results obtained in the present investigation were expressed as mean SEM. The data were analyzed using Student's t-test and results were considered significant when $P<0.05$.

Results and discussion:

All synthesized compounds produced a significant antihelmintic activity in dose dependent manner. Results are shown in Table-1.

Summary and conclusion:

At lower concentrations (15 & 30 mg/ml), all synthesized compounds produced paralysis as well as death but the time taken for these actions were found to be more than the time taken by standard drug. But at higher concentration (60 mg/ml), all synthesized compounds demonstrated paralysis as well as death of worms in a less time as compared to albendazole. Among all synthesized compounds compound 1f showed comparable effect to that of standard drug Albendazole.

Table-1: Effect of synthesized Chromene-2-one derivatives on *Pheritima posthuma*

Groups	Concentration (mg/ml)	Time taken (minutes)	
		For paralysis	For death
Control	5% DMF in normal saline	-	-
Albendazole	15	30.46±0.04	62.44±0.06
	30	24.32±0.04	50.44±0.03
	60	20.14±0.02	40.12±0.02
Compound 1a	15	44.26±0.03	78.36±0.05
	30	36.16±0.02	70.24±0.03
	60	20.06±0.04	39.52±0.02
Compound 1b	15	40.44±0.03	75.54±0.04
	30	35.52±0.02	68.50±0.05
	60	19.52±0.05	40.04±0.05
Compound 1c	15	38.56±0.02	77.24±0.03
	30	29.40±0.03	70.22±0.04
	60	20.04±0.04	39.52±0.02
Compound 1d	15	40.53±0.03	72.24±0.05
	30	34.50±0.02	66.45±0.04
	60	19.50±0.06	39.46±0.02
Compound 1e	15	39.10±0.04	74.40±0.04
	30	30.46±0.02	68.22±0.05
	60	19.46±0.03	39.42±0.03
Compound 1f	15	34.14±0.05	65.15±0.02
	30	24.45±0.04	52.44±0.05
	60	18.32±0.02	36.18±0.04

Values are mean ±SEM, $P<0.05$

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