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Synthesis and Characterization of Schiff Bases of 2′-Amino-4′-(6-chloro-3-coumarinyl)thiazole as Potential NSAIDs

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Some of the Schiff bases of aminothiazolylchlorocoumarin are synthesized by the reaction between 2′-amino-4′-(6-chloro-3-coumarinyl)thiazole and substituted aromatic aldehydes. The former is obtained by cyclization of 3-bromoacetyl-6-chlorocoumarin and thiourea. The resulting compounds are characterized by spectral data and evaluated for their analgesic and anti-inflammatory activity by acetic acid induced abdominal constriction method and carrageenan induced rat hind paw oedema method respectively. Few of the compounds have shown interesting biological activity based on the presence of certain functional groups.

Key Words: Synthesis, Coumarin, Thiazole, Schiff bases, Analgesic, Antiinflammatory activity.

INTRODUCTION

The coumarin nucleus has been a seat of diverse biological properties through its innumerable derivatives. Compounds containing the benzopyran moiety are endowed with anti-inflammatory property[1]; thiazole and coumarin derivatives[2,3] have been associated with diverse pharmacological activities such as antibiotic, anti-inflammatory, schistosomicidal and fungicidal properties. Several coumarin derivatives[4] reported in the literature were found to possess CNS depressant, hypnotic, sedative, diuretic, analgesic and antitubercular activities. The potent antibiotics like novobiocin, coumaromycin and charteusin are coumarin derivatives. It was envisaged that incorporation of thiazolyl heterosystem in a coumarin nucleus may contribute to the enhanced biological activity. With this in view, herein the synthesis and biological activity of the title compounds **3, 4a–n** and **5** have been reported.

EXPERIMENTAL

Melting points were determined in open capillaries and are found uncorrected. IR spectra were recorded on Fourier transform IR spectrophotometer model Shimadzu 8700 using KBr disc method, ^{1}H NMR spectra were recorded on

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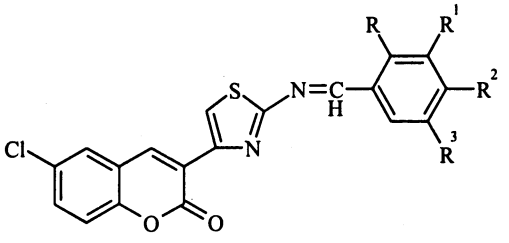
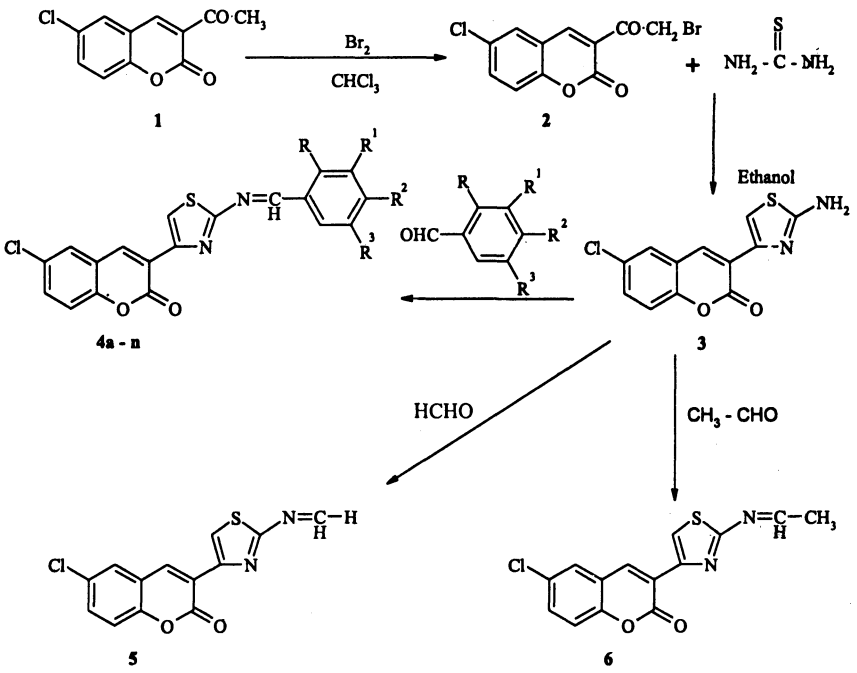
AMX-400 liquid state NMR spectrometer in $CDCl_3$ using tetramethyl silane as an internal standard and mass spectra was recorded on JEOL JMS DX303 mass spectrometer with electron impact ionization at 70 eV. The purity of the products was determined by thin layer chromatography using several solvent systems of different polarity. The compounds were analyzed for C, H and N analysis and the values were found within ±0.4% of the calculated values. Reaction time and physical data of the products are reported in Table-1.

TABLE-1
PHYSICAL DATA AND PHARMACOLOGICAL ACTIVITY OF SCHIFF BASES OF 2'-AMINO-4'-(6-CHLORO-3-COUMARINYL) THIAZOLE



Compd.	R	R^1	R^2	R^3	Yield (%)	m.p. (°C)	Reaction time (min)	Analgesic activity (%)	Anti-inflammatory activity (%)
3	—	—	—	—	88	235	—	40.30	46.23
4a	H	H	Cl	H	59	291	120	56.55	78.49
4b	H	H	H	H	73	251	120	46.20	53.76
4c	OH	H	H	H	62	289	120	51.17	78.49
4d	H	H	NO_2	H	68	282	120	50.60	61.29
4e	OCH_3	OCH_3	OCH_3	H	69	221	120	64.90	64.51
4f	H	OCH_3	OCH_3	H	68	217	100	59.30	59.26
4g	H	OCH_3	H	H	66	276	100	47.50	58.72
4h	OCH_3	H	H	H	70	204	80	54.15	60.21
4i	H	H	$N(CH_3)_2$	H	78	218	120	44.80	64.51
4j	NO_2	H	H	H	65	262	110	54.15	40.91
4k	H	NO_2	H	H	67	289	90	53.10	35.48
4l	H	H	NO_2	H	68	269	100	49.40	57.26
4m	H	Cl	H	H	63	231	70	40.72	60.21
4n	Cl	H	H	H	67	247	90	47.32	64.51
5	—	—	—	—	67	218	100	23.10	53.76
6	—	—	—	—	61	211	120	30.00	56.98
Standard		Acetylsalicylic acid						31.05	—
Standard		Ibuprofen						—	89.24

The synthesis of 2'-amino-4'-(6-chloro-3-coumarinyl) thiazole **(3)** was achieved by cyclization of 3-bromoacetyl-6-chlorocoumarin **(2)** with thiourea in absolute ethanol medium and the resulting compounds **4a–m, 5** and **6** were obtained by refluxing compound **3** and different aromatic aldehydes, formaldehyde and acetaldehyde respectively in absolute ethanol with different time intervals. The synthetic route is shown in **Scheme-1.**



Scheme-1

3-Acetyl-6-chlorocoumarin (1)

A mixture of 5-chlorosalicylaldehyde (111 g, 0.5 mol) and ethylacetoacetate (65 g, 0.5 mol) was taken in a conical flask, stirred and cooled. To this mixture piperidine (10 g) was added with shaking. The mixture was then maintained at freezing temperature for 2–3 h and then a yellow coloured solid mass separated out. The lumps were broken in cold ethanol and filtered. The solid was washed with cold ethanol and dried which gave 119 g (75%) of 3-acetyl-6-chlorocoumarin. The product was recrystallized from hot glacial acetic acid, which yielded needle-shaped crystals, m.p. 219°C. IR (KBr, cm^{-1}): 3049 ν(ArC—H), 1727 ν(lactone C=O), 1704 ν(—C=O), 1608, 1546 ν(ArC=C), 1226 ν(—C—O—), 833, 764 ν(ArC—H), 564 ν(ArC—Br).

3-Bromoacetyl-6-chlorocoumarin (2)

To a solution of compound **1** (55.5 g, 0.25 mol) in 200 mL of alcohol free chloroform, bromine (39.5 g, 0.25 mol) was added in 25 mL of chloroform, with intermittent shaking. The mixture was warmed to decompose an addition product. The mixture was heated for 15 min on a water bath to expel most of the hydrogen

bromide, cooled and filtered. The solid on washing with ether gave 68.0 g (91%) of almost pure product, which on crystallization from acetic acid gave colourless needles, m.p. 221°C. IR (KBr, cm^{-1}): 3046 ν(ArC—H), 1726 ν(lactone —C=O), 1685 ν(—C=O), 1608, 1544 ν(ArC=C), 1227 ν(—C—O—), 831, 772 ν(ArC—H), 556 ν(ArC—Br).

2′-Amino-4′-(6-chloro-3-coumarinyl)thiazole (3)

When a suspension of compound **1** (27.8 g, 0.1 mol) in hot ethanol (175 mL) was treated with thiourea (7.6 g, 0.1 mol), a mild exothermic reaction took place, giving a clear solution that soon deposited crystals. The deposit was removed, washed with ethanol and then boiled with water containing sodium acetate which yielded 23 g (88%) of 2′-amino-4′-(6-chloro-3-coumarinyl)thiazole and the product obtained was recrystallized with ethanol, m.p. 235°C. IR (KBr, cm^{-1}): 3398, 3305 ν(—NH_2), 3058 ν(ArC—H), 1710 ν(lactone —C=O), 1633 ν(—NH_2 def.), 1377 ν(—C—N—), 1245 ν(—C—O—), 719 ν(Ar—Cl). ^1H NMR: 8.42 (s, 1H, hetero Ar—H). 7.80 (s, 1H, hetero Ar—H), 7.53 (d, 1H, Ar—H), 7.47 (dd, 1H, Ar—H), 7.42 (d, 1H, Ar—H), 4.98 (s, 2H, NH_2). MS m/z: 278 (M^+), 250, 236, 208, 179, 164, 145, 111, 99 and 87.

2′-(4″-Chlorophenyl azomethine)-4′-(6-chloro-3-coumarinyl)thiazole (4a)

Compound **3** (2.0 g, 0.005 mol), 4-chlorobenzaldehyde (0.7 g, 0.005 mol) and ethanol (25 mL) were taken in a 100 mL round bottom flask and refluxed at 70°C for 2 h. The reaction medium was cooled and filtered; the product obtained was recrystallized from aqueous dimethylsulfoxide. Yield 59%, m.p. 291°C. Similar procedure was used to synthesize the other Schiff bases (**4b–n**) and crystallization was done using absolute ethanol and aqueous dimethylsulfoxide. IR (KBr, cm^{-1}): 3051 ν(ArC—H), 1732 ν(lactone —C=O), 1595 ν(—N=CH—), 1562, 1483 ν(ArC=C), 1367 ν(—C—N—), 1251 ν(—C—O—), 879, 817 ν(ArC—H), 785 ν(ArC—Cl). ^1H NMR: 9–9.2 (s, 1H, —N=CH—), 8.6–8.8 (s, 1H, hetero Ar—H), 8.4–8.6 (s, 1H, hetero Ar—H), 7.8–8.0 (d, 2H, Ar—H), 7.4–7.6 (s, 1H, Ar—H), 7.4–7.6 (d, 1H, Ar—H), 7.2–7.4 (d, 2H, Ar—H), 7.0–7.2 (d, 1H, Ar—H).

The newly synthesized compounds were screened for their analgesic activity by acetic acid induced writhing method in mice[5, 6] using acetylsalicylic acid as standard and anti-inflammatory activity by carrageenan induced rat hind paw oedema method[7, 8] using Ibuprofen as standard.

RESULTS AND DISCUSSION

Results of the analgesic activity of the test compounds are given as the percentage inhibition of abdominal constriction as shown in Table-1. Compounds such as **4e, 4f, 4a** and **4h 4j, 4k** and **4d** were found active and their analgesic activity was greater than aspirin. It was clear from our study that electron withdrawing groups substituted on the aromatic ring significantly increased their analgesic activity as shown in Table-1 and a donating group like methyl suppressed the activity. However, the Schiff bases of aliphatic aldehydes such as formaldehyde and acetaldehyde showed reduced activity.

Results of the anti-inflammatory activity of test compounds are given as the percentage inhibition of paw volume as shown in Table-1. Test compounds such as **4a** and **4c** having chloro group at fourth position and hydroxy group at second position were almost as potent as ibuprofen whereas compounds such as **4e, 4i, 4n, 4d, 4h** and **4m** exhibited lower antiinflammatory activity. Electron withdrawing groups substituted on the aromatic ring significantly decreased their anti-inflammatory activity as shown in Table-1 when compared with the standard ibuprofen.

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