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Synthesis and Characterization of Schiff Bases of Aminothiazolylbromo Coumarin for Their Analgesic and Anti-inflammatory Activity

K.N. VENUGOPALA* and B.S. JAYASHREE
Department of Pharmaceutical Chemistry, Al-Ameen College of Pharmacy
Near Lalbagh Main Gate, Hosur Road, Bangalore-560 027, India

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

Key Words: Synthesis, Coumarin, Thiazole, Schiff bases, Analgesic and Anti-inflammatory activity.

INTRODUCTION

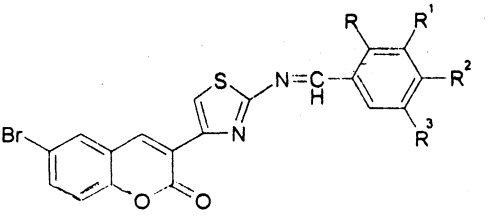
The coumarin nucleus has been a seat of diverse biological properties through its innumerable derivatives. Compounds containing the benzopyran moiety are endowed with anti-inflammatory property[1], thiazole and coumarin derivatives[2] have been associated with diverse pharmacological activities such as antibiotic, anti-inflammatory, schistosomicidal and fungicidal properties. Several coumarin derivatives[3] 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. We envisaged that the incorporation of thiazolyl heterosystem in a coumarin nucleus may impart enhanced biological activity to the resulting compounds. With this in view, the synthesis and biological activity of the title compounds have been reported (**4a–m**).

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 AMX-400 liquid state NMR spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard and mass spectra were recorded on Jeol JMS DX303 mass

spectrometer with electron impact ionization (EII) 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-BROMO-3-COUMARINYL) THIAZOLE

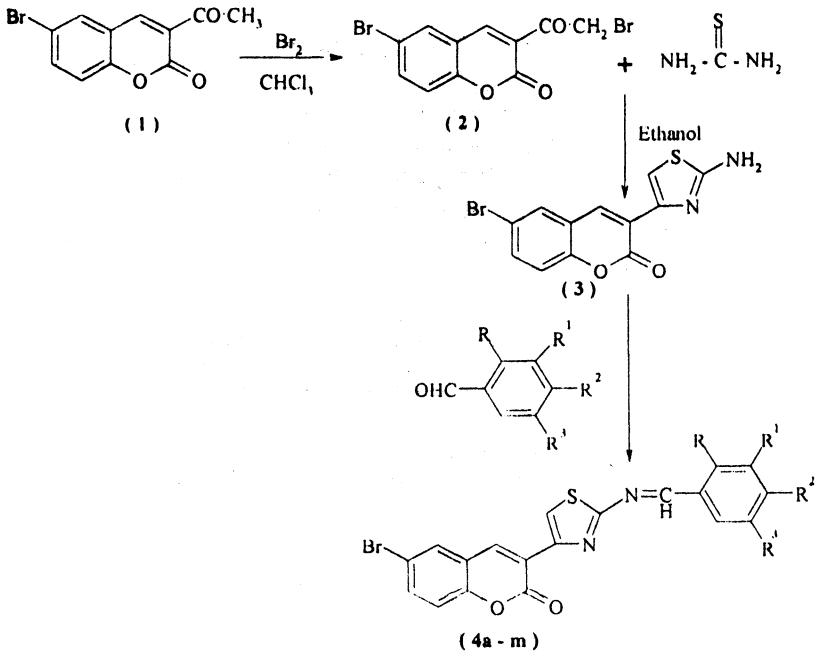


Comp.	R	R^1	R^2	R^3	Yield (%)	m.p. (°C)	Reaction time (min)	Analgesic activity (%)	Anti-inflammatory activity (%)
4a	H	H	Cl	H	62	255	120	39.86	51.38
4b	H	OCH_3	OCH_3	OCH_3	71	234	90	37.76	60.22
4c	NO_2	H	H	H	58	243	120	35.21	50.01
4d	H	NO_2	H	H	60	256	120	34.95	49.17
4e	H	OCH_3	OH	H	66	235	150	34.35	47.62
4f	OH	H	H	Br	66	276	90	39.86	51.38
4g	H	H	$N(CH_3)_2$	H	69	180	120	39.15	51.38
4h	CH_3	H	H	H	64	218	120	37.76	50.22
4i	OH	H	H	H	68	224	60	37.14	52.04
4j	OCH_3	H	H	H	62	150	120	37.76	49.17
4k	H	H	H	H	78	225	90	37.36	42.54
4l	H	OCH_3	OCH_3	H	67	214	120	39.15	58.01
4m	H	H	NO_2	H	64	264	120	32.15	48.04
Standard		Acetylsalicylic acid						37.45	—
Standard		Phenylbutazone						—	45.30

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

3-Acetyl-6-bromocoumarin (1)

A mixture of 5-bromosalicylaldehyde (100.5 g, 0.5 mol) and ethylacetoacetate (65 g, 0.5 mol) were taken in a conical flask, stirred and cooled. To this mixture 10



Scheme-1

g of piperidine 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 126 g (94%) of 3-acetyl-6-bromocoumarin. The product was recrystallized from hot glacial acetic acid, which yielded needle-shaped crystals (m.p. 220°C). The formation of this compound was confirmed by the difference in m.p. R_f values and IR peaks at 3045 cm^{-1} ν(ArC—H), 1730 cm^{-1} ν(lactone C=O), 1610, 1549 cm^{-1} ν(ArC=C), 1230 cm^{-1} ν(C—O), 838, 766 cm^{-1} ν(ArC—H), 563 cm^{-1} ν(ArC—Br).

3-Bromoacetyl-6-bromocoumarin (2)

To a solution of compound **1** (66.5 g, 0.25 mol) in 200 mL of alcohol free chloroform, bromine (39.5 g, 0.25 mol) was added to 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 74.0 g (80%) of almost pure product, which on crystallization from acetic acid gave colourless needles (m.p. 205°C). The formation of this compound was confirmed by the difference in m.p. R_f values and IR peaks at 3051 cm^{-1} ν(ArC—H), 1731 cm^{-1} ν(lactone C=O), 1609, 1546 cm^{-1} ν(ArC=C), 1228 cm^{-1} ν(C—O), 836, 770 cm^{-1} ν(ArC—H), 557 cm^{-1} ν(ArC—Br).

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

When a suspension of compound **2** (34.4 g, 0.1 mol) in 175 mL of hot ethanol

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 26 g (81%) of 2′-amino-4′-(6-bromo-3-coumarinyl) thiazole and the product obtained was recrystallized with ethanol m.p. 255°C. The formation of this compound was confirmed by the difference in m.p. R_f values and IR peaks at 3424, 3300 cm^{-1} ν(—NH_2), 3058 cm^{-1} ν(ArC—H), 1720 cm^{-1} ν(lactone C=O), 1627 cm^{-1} ν(—NH_2 def.), 1602, 1536, 1475 cm^{-1} ν(ArC=C), 1375 cm^{-1} ν(C—N), 1245 cm^{-1} ν(C—O), 818, 783 cm^{-1} ν(ArC—H), 603 cm^{-1} ν(ArC—Br).

^{1}H-NMR δ(ppm): 8.42 (s, 1H, hetero Ar—H), 7.80 (s, 1H, hetero Ar—H), 7.69 (d, 1H, Ar—H), 7.58 (dd, 1H, Ar—H), 7.23 (d, 1H, Ar—H), 4.99 (s, 2H, NH_2)

MS : Molecular ion peak at m/e 322 (M + 1), 324 (M + 2) and base peak at m/e 69.

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

Compound **3** (0.006 mol), 4-chlorobenzaldehyde (0.007 mol) and 25 mL ethanol 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 (DMSO). Yield 62%, m.p. 255°C. Similar procedure was used to synthesize the other schiff bases (**4b–m**) and crystallization was done using absolute ethanol and aqueous DMSO. The formations of the compounds were confirmed by the m.p. R_f values and presence of specific IR peaks at 3042 cm^{-1} ν(ArC—H), 1735 cm^{-1} ν(lactone C=O), 1676 cm^{-1} ν(N=CH), 1606, 1548 cm^{-1} ν(ArC=C), 1355 cm^{-1} ν(C—N), 1231 cm^{-1} ν(C—O), 835, 769 cm^{-1} ν(ArC—H), 744 cm^{-1} ν(ArC—Cl), 558 cm^{-1} ν(ArC—Br).

^{1}H NMR δ (ppm) : 8.98 (s, 1H, methine, N=CH), 8.73 (s, 1H, hetero AR—H), 8.42 (s, 1H, hetero Ar—H), 7.97 (d, 2H, Ar—H), 7.75 (d, 1H, Ar—H), 7.65 (dd, 1H, Ar—H), 7.51 (d, 2H, Ar—H), 7.27 (d, 1H, Ar—H).

MS: Molecular ion peak at m/z 445 and base peak at m/e 196.

Evaluation of pharmacological activity

The newly synthesized compounds were screened for analgesic activity by acetic acid induced writhing method in mice[4, 5] using acetylsalicylic acid as standard and anti-inflammatory activity by carrageenan induced rat hind paw oedema method[6, 7] using phenylbutazone as standard.

RESULTS AND DISCUSSION

Results of the analgesic activity test are given as the percentage inhibition of abdominal constriction in Table-1. Compounds **4c, 4d** and **4e** exhibited lower analgesic activity, Compounds **4b, 4h, 4i, 4j** and **4k** were almost equipotent and compounds **4a, 4f, 4g** and ***4l*** were found to possess higher activity than aspirin. Functional groups like 4-chloro, 2-hydroxy and 5-bromo, 4-dimethyl amino on phenyl ring enhanced analgesic activity. Groups like 3-methoxy and 4-hydroxy, nitro groups at 2nd, 3rd and 4th position on phenyl ring suppressed analgesic activity when compared with that of the standard aspirin.

Results of the anti-inflammatory activity test are given as the percentage inhibition of paw volume in Table-1. Compound **4k**, which is an unsubstituted phenyl derivative, exihibited lower anti-inflammatory activity. Compounds **4d, 4e** and **4j** were almost as potent and compounds **4a, 4b, 4c, 4f, 4g, 4h, 4i** and ***4l*** showed higher anti-inflammatory activity when compared with that of standard phenylbutazone. From the activity of the test compounds **4j, *4l*** and **4b**, it is observed that the introduction of bulky groups such as methoxy on phenyl ring increases the anti-inflammatory activity by 49.17, 58.01 and 60.22% respectively.

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