Asian Journal of Chemistry Vol. 16, No. (2) (2004), 872–876

Synthesis and Evaluation of Some Substituted 2-Arylamino Coumarinyl Thiazoles as Potential NSAIDs

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

Substituted 2′-arylamino-4′-(3-coumarinyl) thiazoles (**5a–j**) and 2′-arylamino-4′-(6-bromo-3-coumarinyl) thiazoles (**5k–v**) were synthesized by the condensation of respective 3-bromoacetyl-coumarins with thiourea and substituted phenylthioureas. Finally the compounds were characterized by spectral data and screened for their analgesic and anti-inflammatory activities. Some of these compounds exhibited promising activity.

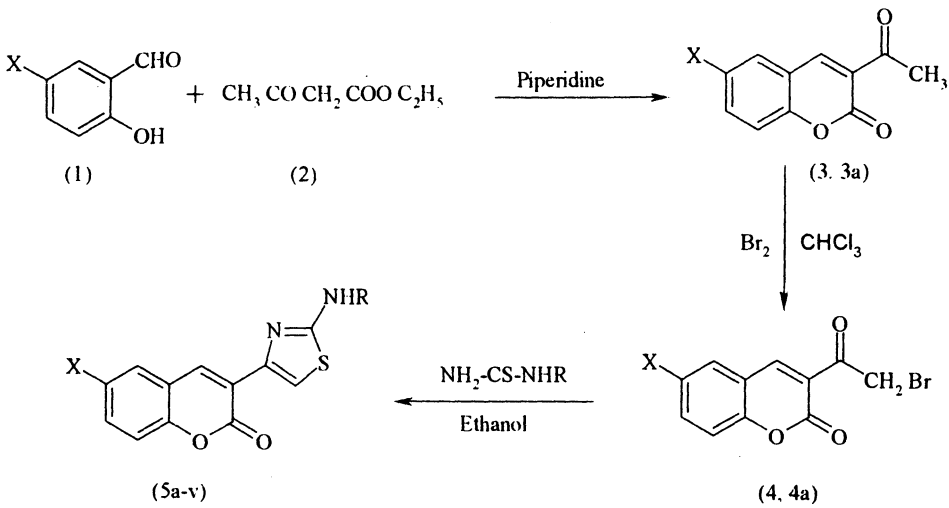
Key Words: Synthesis, Coumarin, Thiazole, Characterization, Analgesic and anti-inflammatory activity.

INTRODUCTION

The quest for a more reliable and suitable drug is always fascinating and challenging. A number of drugs containing simple heterocyclic or a combination of different heterocyclic moieties have been in use these days. Coumarins have been reported for their diverse biological activities like anticoagulant, HIV protease inhibition[1], antibacterial[2], analgesic[3] and anti-inflammatory[4] activities. Thiazoles[5] have also been reported for their analgesic and anti-inflammatory activities. In the present study, it is envisaged to combine coumarin nucleus with thiazole ring system to yield compounds having better analgesic and anti-inflammatory activity.

EXPERIMENTAL

All the reactants and solvents were of synthetic reagent grade. Melting points were determined on a Buchi apparatus in glass capillary tubes and were found uncorrected. The purity of the synthesized compounds including intermediate was checked by thin layer chromatography (TLC) and the chromatogram was developed using a mixture of ethylacetate : *n*-hexane (2 : 5). All the compounds were characterized by IR spectra (KBr), in the range of 4000–500 cm^{-1} on Shimadzu 8700. Few of the compounds were characterized by ^{1}H-NMR spectra in deuteriated chloroform solution on AMX (400 MHz) spectrophotometer and mass spectra were recorded on Joel JMS DX 303 mass spectrophotometer. Elemental analyses were within ±0.4% of their calculated values. The physical data of the synthesized compounds are given in Table-1.



Scheme - 1

3-Acetyl-6-bromocoumarin (3a)

To a cooled suspension of mixture of 5-bromosalicylaldehyde (100.5 g, 0.5 mol) and ethylacetoacetate (65 g, 0.5 mol) piperidine (10 g) was added with shaking. The mixture was then maintained at freezing temperature for 2–3 h. The yellow coloured lumps which separated out were broken in cold ethanol, filtered and crystallized from hot glacial acetic acid to give needle-shaped crystals of **(3a)**. Yield 126 g (94%), m.p. 220°C.

Compound **(3)** was also synthesized by following the above method.

The formation of acetyl coumarins was confirmed by the difference in m.p., R_f values and specific IR (cm^{-1}) peaks at 3045 ν(ArC—H), 1730 ν(lactone —C=O), 1700 ν(—C=O), 1610, 1549 ν(ArC=C), 1230 ν(—C—O—), 838, 766 ν(ArC—H), 563 ν(ArC—Br).

^1H NMR **3**: = 8.52 (s, 1 H, arom.), 7.64–7.65 (m, 2H, arom), 7.27–7.40 (m, 2H, arom.), 2.74 (s, 3H, $—CH_3$).

3-Bromoacetyl-6-bromocoumarin (4a)

To a solution of 3-acetyl-6-bromocoumarin (66.5 g, 0.25 mol) in alcohol free chloroform (200 mL), bromine (39.5 g, 0.25 mol) in chloroform (25 mL) was added with intermittent shaking and warming. The mixture was heated for fifteen minutes on a water bath, cooled and filtered. The solid was washed with ether and crystallized from acetic acid to yield **(4a)**. Yield 74.0 g (80%), m.p. 205°C.

Compound **4** was also synthesized in a similar manner.

The formation of bromoacetyl coumarins was confirmed by the difference in m.p., R_f values and specific IR (cm^{-1}) peaks at 3051 ν(ArC—H), 1731 ν(lactone C=O), 1689 ν(—C=O), 1609, 1546 ν(ArC=C), 1228 ν(—C—O—), 836, 770 ν(ArC—H), 557 ν(ArC—Br).

2′-Amino-4′-(6-bromo-3-coumarinyl) thiazole (5k)

When a suspension of compound **(4a)** (34.4 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 deposits were removed, washed with ethanol and 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 (cm^{-1}) peaks at 3424, 3300 ν(—NH_2), 3058 ν(ArC—H), 1720 ν(lactone C=O), 1627 ν(—NH_2 def.), 1602, 1536, 1475 ν(ArC=C), 1375 ν(—C—N—), 1245 ν(—C—O—), 818, 783 ν(ArC—H), 603 ν(ArC—Br).

^{1}H NMR 8.42 (s, 1 H, 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: m/z 322 (M^+, 19), 324 (M^+, +2, 20), 296 (5), 252 (4), 149 (7), 137 (11), 123 (9), 109 (10), 95 (15), 81 (45), 69 (100), 57 (40), 43 (40).

2′-(3″-Methylphenylamino)-4′-(6-Bromo-3-coumarinyl) thiazole (5r)

A suspension of 3-bromoacetyl-6-bromocoumarin **(4a)** (34.4 g, 0.1 mol) and 3-methylphenyl thiourea[6] (16.6 g, 0.1 mol) in amyl alcohol (175 mL) was refluxed for 1 h. The solid separated was filtered, dried and crystallized from aqueous dimethyl sulphoxide to yield pale yellow coloured crystals of **(5r)**. Yield 28.4 g (69%), m.p. 234°C.

The other compounds reported in Table-1 were prepared in the same manner.

The formation of compounds **5(a–v)** were confirmed by the difference in m.p., R_f values and specific IR (cm^{-1}) peaks between 3215–3180 ν(—NH—), 3058 ν(Ar—H), 1735–1716 ν(—C=O), 1450–1600 ν(arom —C=C—) and 1H NMR spectra as follows:

5r: = 8.4 (s, 1H, —NH—), 7.9–6.9 (m, 9H, arom.), 2.4 (s, 3H, —CH_3),

5m: = 8.5 (s, 1H, —NH—), 8.2–7.0 (m, 9H, arom.),

5q: = 8.4 (s, 1H, —NH—), 7.8–6.9 (m, 9H, arom), 2.3 (s, 3H, —CH_3).

Mass spectral data is shown below:

5c: MS: m/z 354 (M^+, 65), 319 (100), 291 (8), 184 (7), 172 (12), 145 (21) 125 (4), 102 (24), 90 (19), 63 (22).

5j: MS: m/z 338 (M^+), 323 (5), 305 (6), 265 (3), 228 (2), 203 (6), 172 (12), 145 (18), 131 (8), 115 (10), 102 (26), 95 (20), 83 (15), 57 (20).

Analgesic activity

The analgesic activity of the synthesized compounds was determined by acetic acid-induced abdominal constriction method[7]. Each compound was suspended in 0.5% aqueous carboxymethylcellulose and given orally to mice at 100 mg kg^{-1} dose; 1 h after administration, pain was induced by intraperitoneal injection of a 1% solution of acetic acid at a dose of 10 μL g^{-1}. The control group received carboxymethylcellulose 1 h. before injection of acetic acid. Each animal was placed in a separate cage 5 min after acetic acid injection and the number of abdominal constrictions per animal was recorded during the following 10 min period. Diclofenac sodium was used as the standard at the dose of 7.14 mg

kg^{-1} body weight and administered according to the test protocol. Results of the analgesic activity test are given as the percentage inhibition of abdominal constriction in Table-1

TABLE-1
PHYSICAL DATA AND PHARMACOLOGICAL ACTIVITIES OF COMPOUNDS (5a–v)

Compd.	X	R	m.p. (°C)	Yield (%)	% Anti-inflammatory activity	Analgesic activity (%)
3	H	—	118	96	—	—
3a	Br	—	220	94	—	—
4	H	—	162	77	—	—
4a	Br	—	205	80	—	—
5a	H	H	223	78	28.47	08.61
5b	H	C_6H_5	204	77	56.80	30.18
5c	H	2-ClC_6H_4	282	67	49.60	68.56
5d	H	3-ClC_6H_4	248	66	41.59	50.94
5e	H	4-ClC_6H_4	225	76	46.93	60.37
5f	H	2-$CH_3C_6H_4$	248	58	37.00	39.01
5g	H	3-$CH_3C_6H_4$	215	72	48.52	18.26
5h	H	4-$CH_3C_6H_4$	233	75	43.00	46.56
5i	H	4-BrC_6H_4	229	65	47.25	71.69
5j	H	4-FC_6H_4	222	64	52.06	56.60
5k	Br	H	211	81	46.96	06.95
5l	Br	C_6H_5	180	76	44.83	31.47
5m	Br	2-ClC_6H_4	198	59	49.42	57.88
5n	Br	3-ClC_6H_4	285	58	48.37	51.69
5p	Br	4-ClC_6H_4	190	77	50.53	49.05
5q	Br	2-$CH_3C_6H_4$	265	65	48.35	66.67
5r	Br	3-$CH_3C_6H_4$	234	69	49.52	21.29
5s	Br	4-$CH_3C_6H_4$	194	72	59.86	19.50
5t	Br	4-BrC_6H_4	280	63	52.14	47.16
5u	Br	4-FC_6H_4	282	68	54.20	64.15
5v	Br	4-$NO_2C_6H_4$	190	64	39.06	50.00
Std.	Ibuprofen				74.00	—
Std.	Diclofenac sodium				—	72.98

Anti-inflammatory activity

The anti-inflammatory activity of the synthesized compounds was determined by the carrageenan induced rat hind paw oedema method[8]. The test compounds **5a–v** were suspended in 0.5% aqueous carboxymethylcellulose and given orally to rats at the dose of 100 mg kg^{-1} dose, 1 h after administration; a 1% suspension

of carrageenan (Sigma Co.) in 0.9% w/v saline was prepared 12 h before each experiment. Acute oedema was induced in the right hind paw of rats by injecting 0.1 mL of 1% suspension of carrageenan. The left paw was injected with 0.1 mL 0.9% w/v saline and served as a control. Carrageenan was injected under the planter region of the right hind paw, and the volume was measured using a plethysmometer at 0, 30, 60, 120, 180 and 240 min after carrageenan administration. Inflammation was expressed as the percentage inhibition in paw volume. Ibuprofen was used as the standard and administered according to the test protocol. Results of the anti-inflammatory activity test are given as the percentage inhibition of paw volume in Table-1

RESULTS AND DISCUSSION

Out of twenty-one compounds screened for analgesic and anti-inflammatory activities, compounds such as **5c, 5e, 5i, 5q** and **5u** showed good analgesic activity (68.56, 60.37, 71.69, 66.67 and 64.15% respectively) when compared with that of the standard diclofenac sodium (72.98%). Compounds **5b, 5j, 5s, 5t** and **5u** showed significant anti-inflammatory activity (56.80, 52.06, 59.86, 52.14 and 54.20% respectively) when compared to that of ibuprofen as standard (74.00%). Other compounds were found to possess moderate analgesic and anti-inflammatory activities. Among all the test samples, only **5u**, which is *p*-fluoro derivative of substituted coumarin, showed both analgesic and anti-inflammatory activity at 64.15 and 54.20% respectively.

ACKNOWLEDGEMENTS

The authors are thankful to Prof B.G. Shivananda, Principal, Al-Ameen College of Pharmacy, Bangalore for facilities and to Prof. S. Asokan, Department of Instrumentation, Indian Institute of Science, Bangalore for ^{1}H NMR and mass spectra.

REFERENCE

1. P.J. Tummino, D. Ferguson and D. Hupe, *Biochem. Biophys. Res. Comm.*, **201**, 290 (1994).
2. Eur. Pat. Appl. Ep 816353 A2 (1998).
3. *Chem. Abstr.*, **89**, 109099c (1978).
4. K.N. Venugopala and B.S. Jayashree, *Indian J. Heterocyclic Chem.*, **12**, 307 (2003).
5. B.R. Shridar, M. Jogibhukta, L.C. Vishwakarma, P. P. Joshi, G. Narayana, P.P. Singh, C.S. Rao and A.Y. Jannakar, *Indian. J. Chem.*, **23B**, 445 (1984).
6. B.D. Irwin and F.B. Dainy, *J. Am. Chem. Soc.*, **56**, 1408 (1934).
7. K. Gyires and Z. Torma, *Arch. Int. Pharmacodyn.*, **267**, 131 (1984).
8. C.A. Winter, G.A. Risley and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **3**, 544 (1962).

(*Received*: 26 July 2003; *Accepted*: 12 December 2003) AJC-3285