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Synthesis of isomeric naphthofuranyl coumarins as anti-inflammatory and analgesic agents

Naazneen Yaragatti[a], Netravati Khanapurmath[b] & Manohar V Kulkarni*[b]

[a] P. G. Department of Studies in General Chemistry, Karnatak Science College, Dharwad 580 003, India

[b] Department of Studies in Chemistry, Karnatak University, Pavatenagar, Dharwad 580 003, India

E-mail: manohar274@gmail.com

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A two-step synthetic scheme has been employed for the synthesis of 4-naphtho [2, 1-b] furan-2-yl-chromen-2-ones/4-(3-alkoxy-naphtho-[2,3-b]furan-2-yl)-chromen-2-ones(angular/linear naphthofuranyl coumarins). The reactions have been monitored by TLC and structures of the intermediates and the target compounds have been ascertained by IR, NMR and mass spectral data. Both the isomeric naphthofuranyl coumarins have been found to exhibit anti-inflammatory activity comparable to asprin but when tested for analgesic activity, angularly fused naphthofuranyl coumarins show better activity comparable to asprin whereas linear naphthofuranyl coumarins are less active.

Keywords: Naphthofuranyl, coumarin, anti-inflammatory, analgesic activity, angular/linear naphthofuranyl coumarins

Oxygen containing heterocycles such as coumarins and naphtho[b]furans are structural components of a large number of biologically active natural and synthetic compounds. Coumarins are naturally occurring δ-lactones occurring extensively in the plant kingdom. Their application in the field of medicinal chemistry[1,2], in the study of bio-chemical mechanisms[3] and in the design of fluorescent probes[4] has attracted researchers in these areas. Coumarin derivatives with different heterocyclic moieties linked at position C-4 are well known for their biological properties[5-7] and industrial applicability[8-10]. Coumarin linked to furan and benzofuran at C_4 exhibited antibacterial[11] and anti-inflammatory[12] activities (Figure 1).

Regio-isomeric naphtho[2,1-b]- and [2,3-b]-furans are also present in many biologically important natural products[13]. Naphthofuran derivatives exhibit various biological activities such as antimicrobial[14], anti-inflammatory[15], analgesic[16], anthelmintic[17], genotoxic[18] and anticancer[19] activities (Figure 1). The broad spectrum of therapeutic values of coumarin and naphthofuran ring system prompted us to synthesize the title compounds and screen them for analgesic and anti-inflammatory activities. Although a lot of synthetic methodologies for the synthesis naphtho[b]furans have been reported in the literature[20], the development of new approaches to their syntheses, employing efficient routes is currently a popular research area[21,22].

Results and Discussion

Synthesis and characterization

In view of the above mentioned important biological properties of 4-heterocyclic coumarins and 2-heteroaryl naphthofurans, it was thought worthwhile to synthesize isomeric naphtho furanyl coumarins and study its biological properties. The sequences of reactions are presented in Scheme I and Scheme II. The required 4-bromomethyl coumarins were prepared by the reported method[23]. 2-Hydroxy-1-naphthaldehyde was used as a commercial sample and 2-hydroxy 3-naphthoic esters were prepared using alcohol and conc. H_2SO_4 from 2-hydroxy-3-naphthoic acid.

Reaction of 4-bromomethyl coumarins (**1**) with equimolar proportions of 2-hydroxy-1-naphthaldehyde (**2**) resulted in a facile nucleophilic displacement at room temperature resulting in the formation of the ethers (**3**). In the next step, under refluxing conditions in ethanol and in the presence of K_2CO_3, ethers (**3**) underwent an intramolecular carbanion addition followed by dehydration leading to the formation of 4-2' naphtho[2,1-b]furanyl coumarins (**4**). Extension of this methodology to the esters of 2-hydroxy-3-naphthoic acid (**5**) lead to the formation of 3-alkoxy 4-2'-naphtho [2,3-b]furanyl coumarins (**6**).

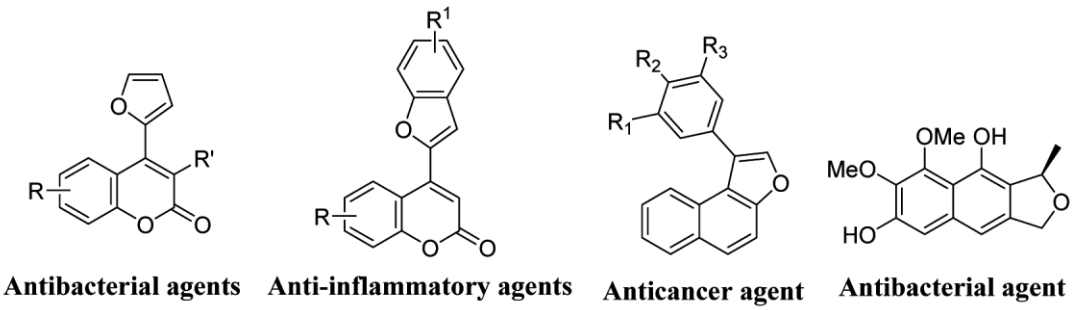
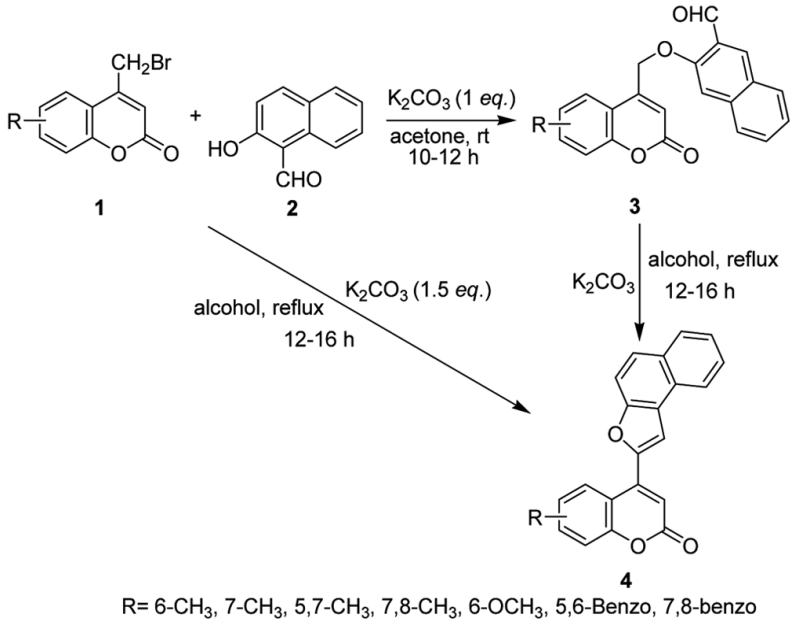
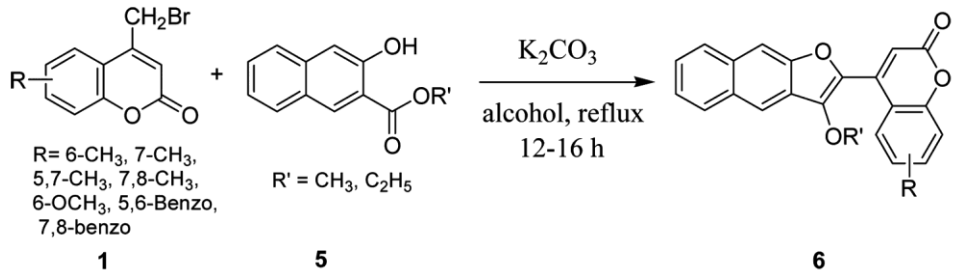


Figure 1 — Biologically active Coumarins and Naphthofurans



Scheme I — Synthesis of 4-naphtho [2, 1-b] furan-2-yl-chromen-2-ones (**4a**-**g**)



Scheme II — Synthesis of 4-(3-alkoxy-naphtho [2, 3-b] furan-2-yl) chromen-2-ones (**6a**-**g**)

Intermediacy of the naphthofuranol **(P)** is supported by our earlier work[24] wherein coumarin linked dihydro-benzofuranols have been isolated (Figure 2). In case of ester **5** elimination of water takes place rather than alcohol which looks more favorable, thus yields **6**. Formation of these compounds is supported by the spectral methods employed for their characterization.

IR spectrum of 6-methyl-4-naphtho [2, 1-b] furan-2-yl-chromen-2-one, **(4a)** exhibited lactone carbonyl at 1716 cm^{-1}. ^1H NMR spectrum exhibited six doublets at 8.22, 8.05, 7.99, 7.87, 7.74 and 7.21 ppm correspond to Ar-H of Coumarin and naphthyl moieties. Two triplets at 7.56 and 7.67 ppm correspond to Ar-H of naphthyl moiety. Three singlets at 7.84, 7.26 (merged with solvent peak) and

6.86 ppm correspond to Coumarin-C_5-H, furan C_3-H and Coumarin-C_3-H respectively. The ESI mass spectrum exhibited a peak at 327.2 (M+H) which confirmed the formation of **4a** (R= -CH_3).

IR spectrum in the case of 4-(3-Methoxy-naphtho [2,3-b] furan-2-yl)-6-methyl-chromen-2-one, **(6a**) exhibited the lactone carbonyl at 1711 cm^{-1}. ^1H NMR exhibited singlets at 7.77 and 6.90 ppm corresponding to coumarin C_5 and C_3 protons. Methyl and methoxy protons appeared at 2.51 and 3.85 ppm as singlet each. Four doublets at 8.24, 8.00, 7.88 and 7.59 ppm correspond to Ar-H of Coumarin and naphthyl moieties. 2 triplets at 7.42 and 7.33 ppm correspond to Ar-H of naphthyl moiety. Two singlets at 8.08 and 7.68 correspond to Naphthyl C_1 and C_4-H. ESI mass spectrum exhibited a peak at 357 (M+H) confirmed the formation of (R and R'= -CH_3).

Biological Evaluation

Anti-inflammatory activity by carrageenan induced rat paw edema and analgesic activity by rat caudal immersion in hot water were carried out simultaneously in same group of animals[25]. Measurement of paw edema volume followed by reaction to thermal stimuli (tail withdrawal) in seconds were recorded at 0, 0.5 h, 1 h, 2 h, 3 h, 4 h, 5 h and 6 h, after injection of carrageenan. Percentage inhibition of paw edema and percentage of analgesia for test drugs as well as for standards are presented in Table I and Table II. Results obtained were analyzed by one-way ANOVA followed by Dunnet's multiple comparison tests.

Anti-inflammatory activity of naphthofuranyl coumarins derivatives are shown in Table I and Figure 3 and it was observed that at 2 hr compounds **(4c), (4d), (4e), (4f), (6a), (6f)** significantly (P<0.01) inhibited the carrageenan induced ratpaw edema (42.85%, 50%, 50%, 42.85%, 42.85% and 42.85%) at the dose of 150 mg/kg b.w. by oral (p. o) route, when compared with control group.

Analgesic activity of naphthofuranyl coumarins derivatives are shown in Table II and Figure 4, it was observed that at 3 hr naphthofuranyl coumarins derivatives (compounds **4c, 4d, 4e and 4f)** significantly (P< 0.01) inhibited the threshold pain (113.64%, 126.11%, 127.89% and 98.51%) of rat by tail immersion at the dose 150 mg/kg b.w. by oral (p. o) route, when compared with control group.

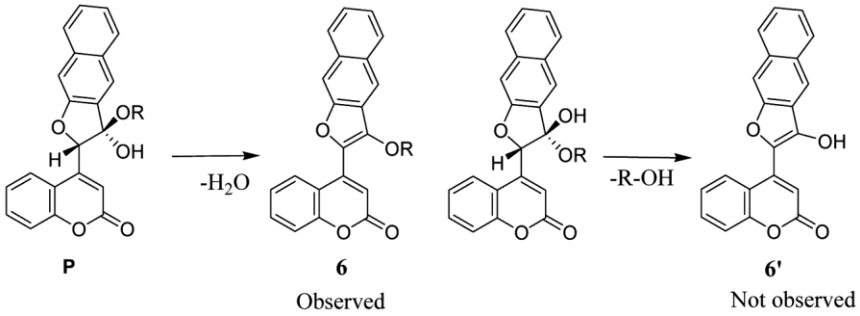


Figure 2 — Plausible Mechanism for the formation of Naphthofuranyl coumarins

Table I — Percentage inhibition of paw edema by naphthofuranyl coumarins in carrageenan induced paw edema model

Groups	R	R'	% inhibition of paw edema at different time intervals							
			0 h	0.5 h	1 h	2 h	3 h	4 h	5 h	6 h
Aspirin			0	37.5	45.454	57.142	58.333	50	50	57.142
4a	6-CH_3	H	0	12.5	27.272	35.714	33.333	30	25	28.571
4b	7-CH_3	H	0	25	27.272	35.714	33.333	30	25	14.285
4c	5,7-CH_3	H	0	25	27.272	42.857	41.666	40	25	28.571
4d	7,8-CH_3	H	0	37.5	45.454	50	41.666	40	37.5	28.571
4e	6-OCH_3	H	0	25	45.454	50	50	40	37.5	42.857
4f	5,6-benzo	H	0	12.5	18.181	42.857	41.666	40	37.5	28.571
6a	6-CH_3	OCH_3	0	25	36.363	42.857	41.666	40	37.5	28.571
6b	7-CH_3	OCH_3	0	25	27.272	28.571	25	30	25	28.571
6f	6-CH_3	OC_2H_5	0	25	36.363	42.857	33.333	40	25	28.571
6g	7,8-CH_3	OC_2H_5	0	25	27.272	28.571	25	30	25	14.285

Table II — Percentage inhibition of pain threshold by naphthofuranyl coumarins in tail immersion model

Groups	% Inhibition of pain threshold							
	0 hr	30 min	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr
Aspirin	42.116	58.571	89.887	128.783	131.666	80.562	77.749	67.836
4a	17.49	47.857	57.752	89.614	76.333	43.734	50.895	56.432
4b	18.574	38.809	45.617	86.943	102.333	74.424	37.595	59.356
4c	1.9438	42.619	78.651	113.649	106.666	56.010	58.567	56.725
4d	19.222	48.333	85.842	126.112	104.666	80.306	47.314	68.713
4e	31.749	52.142	79.550	127.893	115	74.168	50.639	69.883
4f	15.550	7.857	9.438	98.516	67.666	52.941	41.687	57.017
6a	6.2634	24.523	19.550	79.525	77.666	15.601	62.659	68.713
6b	5.1835	25.952	26.966	72.997	60	25.575	24.296	43.859
6f	12.742	23.571	24.719	72.997	65.333	15.601	52.941	40.058
6g	11.447	32.857	39.101	58.456	48.666	25.575	47.058	52.631

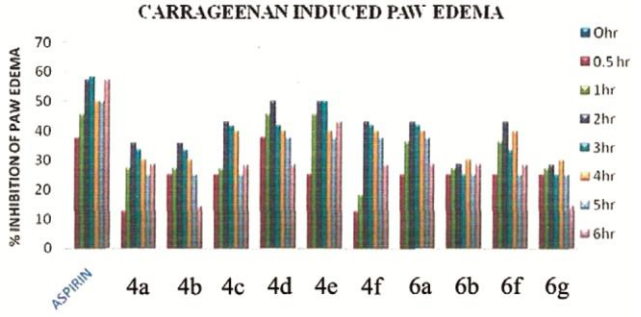


Figure 3 — Effect of naphthofuranyl coumarins derivatives on carrageenan induced paw edema model

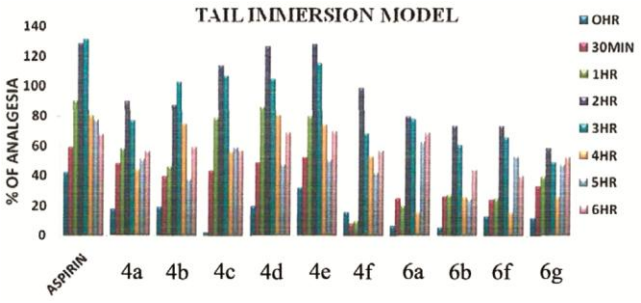


Figure 4 — Effect of naphthofuranyl coumarin derivatives on Tail immersion model

Experimental Section

Melting points were determined by open capillary method and are uncorrected. Thin layer chromatography (TLC) was performed using silica-gel GF254 plates. IR spectra (KBr disc) were recorded on a Nicolet-5700 FT-IR spectrophotometer. Bruker 300 MHz spectrometer was used to record ^{1}H- and ^{13}C-NMRin $CDCl_3$.Mass spectra were recorded using LCMS- MPS-SCIEX-API-2000 and GCMS-QP2010SD Shimadzu. Heraus CHN rapid analyser has been used for elemental analysis. Unless stated otherwise, chemicals were all purchased from commercial sources and used without treatment.

General procedure for the preparation of 2-hydroxy-naphthalene-1-carboxylic acid methyl and ethyl esters

A mixture of 2-hydroxy 1-naphthaldehyde (18.8 g, 0.1 mol) and 50 mL of absolute methanol/ ethanol is taken in a round bottom flask and stirred for about 10 min at room temperature. 5 mL of conc. H_2SO_4 is added drop wise to the reaction mixture with stirring and allowed to stir for another 10 min., followed by reflux on water bath temperature for about 8-10 h. The viscous reaction mixture allowed to cool at room temperature, shining crystals separates out, filtered and washed with alcohol and dried. Compound crystallized from alcohol.

General procedure for the preparation of isomeric naphthofuranyl coumarins (4a-4g, 6a-6g)

To a dry 100 mL flask equipped with a stir bar was added substituted 4-bromo methyl coumarins (0.004 mol), 2-hydroxy 1-naphthaldehyde/2-hydroxy-naphthalene-3-carboxylic acid methyl/ethyl esters (0.004 mol), anhydrous K_2CO_3 (0.82 g, 0.006 mol) and absolute ethanol (30 mL). The reaction mixture was stirred for 15 min at room temperature, followed by reflux for 12-16 h. Reaction on completion, as monitored on TLC, alcohol was concentrated and the solution was poured onto crushed ice. The crude solid obtained was filtered, washed with dil. HCl, then with water and finally with minimum amount of alcohol and crystallized from alcohol. All synthesized compounds have been characterized by ^{1}H NMR, ^{13}C NMR and MS.

Characterization data for the compounds 4(a-g) and 6(a-g)

6-Methyl-4-naphtho [2,1-b] furan-2-yl-chromen-2-one (4a): Yield: 0.93 g (72%).mp 172-176 ^{o}C. FT-IR (KBr, cm^{-1})1716.^{1}H NMR (300 MHz, $CDCl_3$) δ:8.22 (d, 2H, *J*= 9 Hz), 8.03 (q, 2H, *J* = 9 Hz), 7.89-7.84 (m, 2H, Ar-H), 7.74 (d,1H, *J*= 9 Hz), 7.67 (t, 1H, *J*= 9 Hz), 7.57 (d,1H, *J*= 9 Hz), 7.21(d, 1H, *J*= 6 Hz), 6.86 (s,1H, C3-H of coum.),2.45 (s, 6H, 2CH_3 of coum.). MS (ESI+) *m/ z* =327 (M+H). Anal. calc. for $C_{22}H_{14}O_3$: C, 80.97; H, 4.32. Found C, 80.88; H, 4.60.

7-Methyl-4-naphtho [2,1-b] furan-2-yl-chromen-2-one (4b): Yield:0.91 g (70%). Mp 187-188 ^{o}C. FT-IR (KBr, cm^{-1}) 1716. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.22 (dd, 2H, *J*= 9 Hz), 8.00 (d, 1H, *J*= 6 Hz), 7.88 (d, 2H, *J*= 9 Hz), 7.74 (d, 1H, *J*= 9 Hz),7.68 (t, 1H, *J*= 9 Hz), 7.57(t, 1H, *J*= 9 Hz), 7.23 (m, 2H,), 6.87 (s, 1H, C3-H of coum.), 2.51 (s, 3H, CH_3 of coum.). MS (ESI+) *m/ z* = 327 (M+H). Anal. calc. for $C_{22}H_{14}O_3$:C, 80.97; H, 4.32. Found C, 80.80; H, 4.42.

5,7-Dimethyl-4-naphtho [2,1-b] furan-2-yl-chromen-2-one (4c): Yield: 0.92 g (68%).mp180-184 ^{o}C.FT-IR (KBr, cm^{-1}) 1719. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.20 (s, 1H, *J*= 9 Hz), 8.04 (q, 2H, *J*=9 Hz), 7.86-7.82 (m, 2H), 7.76 (d, 1H, *J*= 9 Hz),7.68 (1H, *J*=9 Hz),7.82 (d, 1H, *J*= 6 Hz), 7.26-7.20 (m, 1H), 6.86 (s, 1H, C3-H of coum.), 2.47 (s, 6H, 2CH_3 of coum.). MS (ESI+) *m/ z*= 341 (M+H). Anal. Calc. for $C_{23}H_{16}O_3$: C, 81.16; H, 4.74. Found C, 81.20; H, 4.19.

7,8-Dimethyl-4-naphtho [2,1-b] furan-2-yl-chromen-2-one (4d):Yield:1.00 g (74%). mp 190-192 ^{o}C.FT- IR (KBr, cm^{-1}) 1718. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.22 (s, 1H, *J*= 9 Hz), 8.02 (q, 2H, *J*=9 Hz), 7.89-7.85 (m, 2H), 7.74 (d, 1H, *J*= 9 Hz),7.67 (1H, *J*=9 Hz),7.88 (d, 1H, *J*= 6 Hz), 7.23-7.20 (m, 1H), 6.85 (s, 1H, C3-H of coum.), 2.44 (s, 6H, 2CH_3 of coum.). MS (ESI+) *m/ z*= 341(M+H). Anal. Calc. for $C_{23}H_{16}O_3$: C, 81.16; H, 4.74. Found C, 81.44; H, 4.20.

6-Methoxy-4-naphtho [2,1-b] furan-2-yl-chromen-2-one (4e): Yield:0.96 g (70%).mp 200^{o}C. FT- IR (KBr, cm^{-1}) 1720. ^{1}H NMR (300 MHz, $CDCl_3$) δ:8.22 (d, 1H, *J*=6 Hz), 8.00 (d,1H, *J*= 6 Hz), 7.90-7.82 (m, 3H), 7.75 (d, 1H, *J*= 9 Hz), 7.68 (t, 1H, *J*= 9 Hz), 7.57 (t, 1H, *J*=9 Hz),7.38 (d, 1H, *J*=9 Hz), 7.22 (d, 1H, *J* = 9 Hz), 6.92 (s,1H, C3-H), 3.92 (s, 3H, OCH_3 of coum.). MS (ESI+) *m/ z* = 343 (M+H). Anal. Calc. for $C_{22}H_{14}O_4$ C, 77.18; H, 4.12. Found C, 77.44; H, 4.26.

1-Naphtho [2,1-b] furan-2-yl-benzo[f]chromen-3-one (4f): Yield:0.98 g (68%). m.p 202-204 ^{o}C.FT-IR (KBr, cm^{-1}) 1721. ^{1}H NMR (300 MHz, $CDCl_3$) δ:8.38-7.22 (m,13H), 6.85 (s, 1H, C3-H of coum.). MS (ESI+) *m/z*= 363 (M+H). Anal. Calc. for $C_{25}H_{14}O_3$ C, 82.86; H, 3.89. Found C, 82.72; H, 3.66.

4-Naphtho [2,1-b] furan-2-yl-benzo[h]chromen-2-one (4g): Yield:0.93 g (65%). mp 216-218 ^{o}C. FT-IR (KBr, cm^{-1}) 1720.^{1}H NMR (300 MHz, $CDCl_3$) δ:8.35-7.20 (m,13H), 6.84 (s, 1H, C3-H of coum.). MS (ESI+) *m/z*= 363 (M+H). Anal. Calc. for $C_{25}H_{14}O_3$ C, 82.86; H, 3.89. Found C, 82.30; H, 3.36.

4-(3-Methoxy-naphtho [2,3-b] furan-2-yl)-6-methyl-chromen-2-one (6a): Yield:0.99 g (70%). mp 216-219 ^{o}C. FT- IR (KBr, cm^{-1}) 1711. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.26-7.27 (m, 9H), 6.90 (s, 1H, C3-H of coum.), 3.85 (s, 3H, OCH_3 of coum.), 2.51 (s, 3H, CH_3 of coum.). MS (ESI+) *m/ z* = 357 (M+H). Anal. Calc. for$C_{23}H_{16}O_4$: C, 77.52; H, 4.53. Found C, 77.30; H, 4.36.

4-(3-Methoxy-naphtho [2,3-b] furan-2-yl)-7-methyl-chromen-2-one (6b): Yield:0.96 g (68%). mp 224-225 ^{o}C. FT- IR (KBr, cm^{-1}) 1714.^{1}H NM R (300 MHz, $CDCl_3$) δ: 8.24-7.22 (m, 9H), 6.84 (s, 1H, C3-H of coum.), 3.86 (s, 3H, OCH_3 of coum.), 2.47 (s, 3H, CH_3 of coum.). MS (ESI+) *m/ z*=357 (M+H). Anal. Calc. for$C_{23}H_{16}O_4$: C, 77.52; H, 4.53. Found C, 77.42; H, 4.20.

4-(3-Methoxy-naphtho [2,3-b] furan-2-yl)-7, 8-dimethyl-chromen-2-one (6c): Yield:1.04g (70%). mp230-232 ^{o}C. FT- IR (KBr, cm^{-1}) 1716. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.20-7.20 (m, 8H), 6.86 (s, 1H, C3-H of coum.),3.88 (s, 3H, OCH_3 of coum.), 2.47 (s, 6H, 2CH_3 of coum.). MS (ESI+) *m/ z* = 371(M+H). Anal. Calc. for $C_{24}H_{18}O_4$: C, 77.82; H, 4.90. Found C, 77.89; H, 4.20.

1-(3-Methoxy-naphtho [2,3-b] furan-2-yl)-benzo[f]chromen-3-one (6d): Yield:0.99 g (63%). mp242-248 ^{o}C. FT- IR (KBr, cm^{-1}) 1715. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.24-7.19 (m, 12H), 6.84 (s, 1H, C3-H of coum.), 3.90 (s, 3H, OCH_3 of coum.). MS

(ESI+) *m/ z*= 393(M+H). Anal. Calc. for$C_{26}H_{16}O_4$: C, 79.58; H, 4.11. Found C, 79.42; H, 4.20.

4-(3-Methoxy-naphtho [2, 3-b] furan-2-yl)-benzo [h]chromen-2-one (6e): Yield: 0.94 g (60%). mp250-252 ^oC.FT- IR (KBr, cm^{-1}) 1714. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.28-7.20 (m, 12H), 6.85 (s, 1H, C3-H of coum.), 3.90 (s, 3H, OCH_3 of coum.). MS (ESI+) *m/ z* = 393(M+H). Anal. Calc. for $C_{26}H_{16}O_4$: C, 79.58; H, 4.11. Found C, 79.42; H, 4.20.

4-(3-Ethoxy-naphtho [2, 3-b] furan-2-yl)-6-methyl-chromen-2-one (6f): Yield:1.02 g (69%). mp252-255^oC.FT- IR (KBr, cm^{-1}) 1717.^1H NMR (300 MHz, $CDCl_3$) δ:8.25-7.24 (m, 9H), 6.84 (s, 1H, C3-H of coum.),4.48 (q, *J*= 9.0 Hz, 2H, OCH_2), 1.47 (t, *J*= 9.0 Hz, 3H, CH_3), 2.45 (s, 3H, CH_3 of coum.). MS (ESI+) *m/ z* = 371(M+H). Anal. Calc. for$C_{24}H_{18}O_4$: C, 77.82; H, 4.90. Found: C, 77.02; H, 4.36.

4-(3-Ethoxy-naphtho [2, 3-b] furan-2-yl)-7, 8-dimethyl-chromen-2-one (6g): Yield: 1.04 g (68%). mp 257-260 ^oC.FT-IR (KBr, cm^{-1}) 1718. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.22-7.19 (m, 8H), 6.85 (s, 1H, C3-H of coum.), 4.47 (q, *J*= 9.0 Hz, 2H, OCH_2), 1.47 (t, *J*= 9.0 Hz, 3H, CH_3), 2.44 (s, 6H, $2CH_3$ of coum.). MS (ESI+) *m/ z* = 385 (M+H). Anal. Calc. for $C_{25}H_{20}O_4$ C, 78.11; H, 5.24. Found: C, 78.36; H, 5.72.

Biological Evaluation

Animals

Albino Wistar rats (170-220 g) and Swiss albino mice (20-25 g) of either sex were used in the study. The inbred colonies of rats were purchased from Venkateshwara enterprises, Bangalore. They were acclimatized to controlled conditions of temperature (23 ± 2 ^oC), 30-70% humidity and 12 hr light-dark cycles. The animals were randomized into experimental and control groups and housed four each in sanitized polypropylene cages containing sterile paddy husk as bedding. They had free assessed to standard pellets as basal diet and water *ad libitum*. All the studies conducted were approved by Institutional Animal Ethical Committee (IAEC), SET's College of Pharmacy, Dharwad, Karnataka (REG. No. 112/1999/CPCSEA). According to prescribed guidelines of committee for the purpose of Control and Supervision of Experiments in Animals (CPCSEA), Government of India.

Conclusions

(i) Naphthofuranyl coumarins have been synthesized in two regioisomeric forms using similar synthetic protocol.
(ii) This methodology is adoptable for any allylic and benzylic type of halides to get regioisomeric naphthofurans.
(iii) Both the regioisomeric forms of naphthofuranyl coumarins showed good anti-inflammatory and analgesic activities but less than standard Asprin.
(iv) Angular naphthofuranyl coumarins exhibited better analgesic activity than linear naphthofuranyl coumarins.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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