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Original Article

Synthesis and in vivo analgesic and anti-inflammatory activity of some bi heterocyclic coumarin derivatives

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Abstract

Sets of coumarinyl ethers having chromone, benzofuranyl and 4-hydroxy coumarins (**4**, **5**, **6**) were prepared and tested for analgesic and antiinflammatory activity. The 4-(4′-acetyl-3′-hydroxy-phenoxymethyl)-coumarin **3** were synthesised by the reaction of 4-bromo methyl coumarin with 2, 4-dihydroxy acetophenones, were found to less active. Further compound **3** having the ortho hydroxy moiety was cyclised to chromones **4** and benzofurans **5** were found to enhance the analgesic and anti-inflammatory activity. The cyclisation to 4-hydroxy coumarin **6** was found to be reducing the anti-inflammatory and analgesic activity in this series. These newly synthesized compounds were found to produce less toxicity and less ulcerogenic effects.

Keywords: Benzofuranyl ether; Coumarinyl ether; Chromonyl ether; Anti-inflammatory activity

1. Introduction

4-aryloxy methyl and heteroaryl coumarin derivatives are known for the anti-inflammatory activity [1–3]. Previously we have reported that vanallinyl ethers of 4-bromomethyl coumarins can exhibit good anti-inflammatory activity and low acute toxicity [4].

As the extension of our interest for the search of new heterocyclic moieties as potent anti-inflammatory agents and at the same time they are devoid of side effects like ulcerogenic activity, we have synthesized series of o-alkylated coumarin derivatives. Here we aimed to synthesise series of heterocyclic moieties like benzofuran, chromone and 4-hydroxy coumarin, which were linked to coumarin moiety at 4th position by ether linkage. These coumarinyl ethers were investigated for analgesic and anti-inflammatory activity.

2. Chemistry

According to our previous reports [5,6], the anti-inflammatory activity of ethers of 4-bromomethyl coumarins, can be significantly modified by using different aryl systems. Here we have modified the aryl moieties to heterocyclic moieties like chromone, benzofuran and coumarin ring and these were synthesized for further SAR investigation. 4-(Bromomethyl) coumarins **1** were synthesised by the Pechmann cyclization of phenols with 4-bromoethyl acetoacetate [7]. The 4-bromomethyl coumarin was reacted with 2, 4-dihydroxy acetophenone gave corresponding 4-(4′-acetyl-3′-hydroxy-phenoxy methyl) coumarin **3a-d.** The reaction of the **3a–d** undergone Kostanecki synthesis [8] using sodium acetate and acetic anhydride gave the corresponding chromonyl ethers **4a-d** The benzofuranyl ethers **5a-d** were obtained by the treatment of phenacyl bromide with corresponding 4-(4′-acetyl-3′-hydroxy-phenoxy methyl)-coumarin [9] (Scheme 1). The 4-hydroxy coumarinyl ethers were synthesized by the reaction of **3a-d** with diethyl carbonate and sodium using Boyd method of synthesis [10]. The compound **6a** was also prepared by other route using 4, 7-dihydroxy cou-

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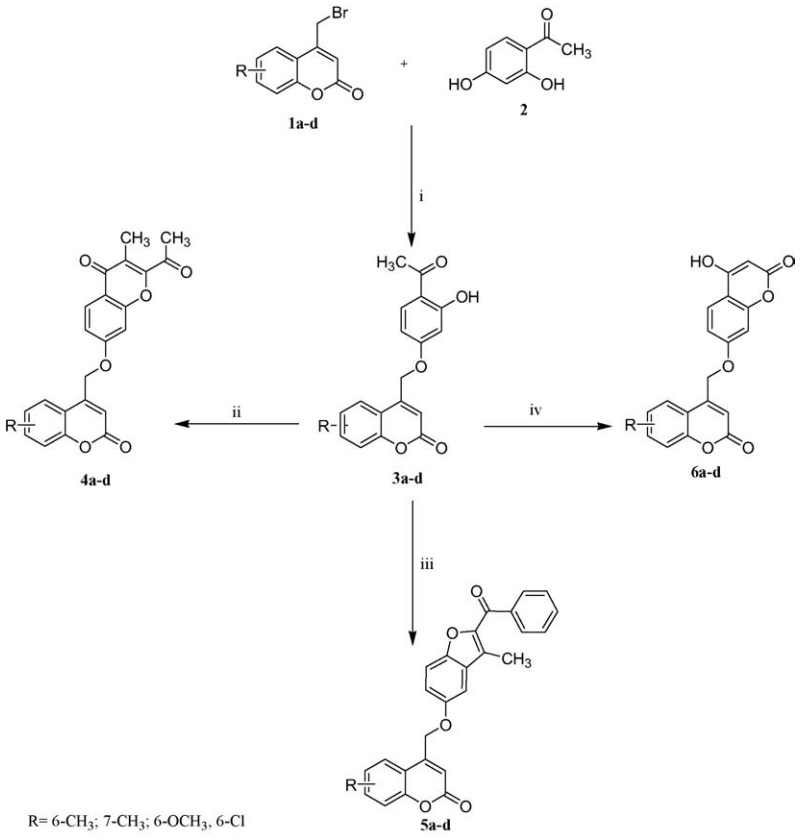


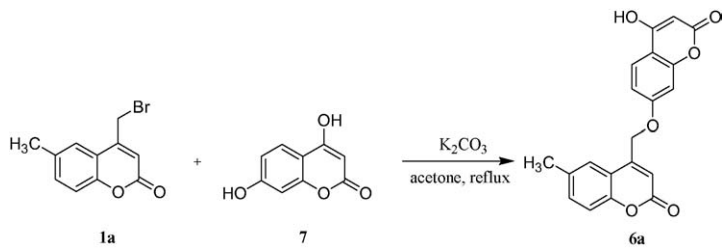
Scheme 1. Synthesis of coumarinyl ethers.

marin with 4-bromomethylcoumarin in the presence of K_2CO_3 in dry acetone under stirring conditions. (Scheme 2). The required 4,7-dihydroxy coumarins were prepared from resorcinol using known method [11].

Postulated structures of the newly synthesized compounds **3a-d 4a-d, 5a-d** and **6a-d** are in agreement with their IR, ^{1}H NMR spectral and elemental analysis data.

In the IR spectrum of compound **3a**, (R = 6-CH_3) exhibited prominent bands around 1709 1648 and 3042 cm^{-1}due to carbonyl lactone of coumarin, carbonyl of acetophenone and OH stretching vibrations respectively. The lower stretching of OH and carbonyl of acetophenone were observed due to the intramolecular hydrogen bonding between OH and $COCH_3$.

In the ^{1}HNMR spectrum the two sharp singlets at δ 2.49 and 2.67 are due to 6-CH_3 and $COCH_3$ protons respectively. The OH proton observed at down field region at δ 12.87. The compound **4a, 5a** and **6a** (R = 6-CH_3) showed the absence of OH stretching in IR at 3000-3400 cm^{-1}and absence in ^{1}H NMR at δ 12-13. This means the free OH present in the 4th position has undergone cyclisation to afford chromone, benzofuran respectively. However the compound **6** showed presence of OH the IR spectrum at 3444 cm^{-1}, which is due to the presence of 4-hydroxy moiety. The absence of peak in the down field region at δ 12-13 and presence of an additional peak is observed at δ 5.50 due the OH of 4-hydroxycoumarin in the NMR spectrum. The compound **4a** (R = 6-CH3) showed three peak the IR region at 1720, 1648 and



Scheme 2. Synthesis of 6a using 4,7-dihydroxy acetophenome.

Table 1
R and ^{1}H NMR data of the compounds of 3a-6d

Sl. No	Compd	R	$\nu_{C=0}$ cm^{-1}	ν_{0H} cm^{-1}	Chemical Shift (δH) 300 MHz
1	3a	6-CH_3	1709, 1648	3042	2.49(s, 3H, 6-CH_3), 2.54(s, 3H, $COCH_3$), 5.02(s, 2H, CH_2O), 6.63(s, 1H, C_3-H), 7.6 (s, 1H, C_5-H), 7.2 (d, 1H, C_7-H, J = 8.1 Hz), 7.4 (d, 1H, C_8-H, J=8.4 Hz), 7.54(d, 2H, J = 7.2 Hz), 6.9 (d, 2H, J = 7.4 Hz), 6.54 (s, 1H) 12.87 (s, 1H OH), D2O exchanged.
2	3b	5,6-Benzo	1722, 1640	3056	2.54(s, 3H, $COCH_3$), 5.09(s, 2H, CH_2O), 6.54 (s, 1H, C_3-H), 6.92-7.88(m, 9H Ar-H), 12.76(s, 1H, OH), D2O exchanged..
3	3c	6-OCH_3	1715, 1646	3022	2.60(s, 3H, $COCH_3$), 3.62 (s, 3H, OCH_3), 5.20(s, 2H, CH_2O), 6.68(s, 1H, C_3-H), 7.56 (s, 1H, C_5-H), 7.26 (d, 1H, C_7-H, J = 8.1 Hz), 7.44 (d, 1H, C_8-H, J = 8.2 Hz), 7.49(d, 2H, J = 7.2 Hz), 6.86 (d, 2H, J = 7.2 Hz), 6.54 (s, 1H), 12.85(s, 1H, OH),(exchanged with D2O)
4	3d	6-Cl	1715 1662	3074	2.62(s, 3H, $COCH_3$), 5.47(s, 2H, CH_2O), 6.67(s, 1H, C_3-H), 7.18 (s, 1H, C_5-H), 7.11(d, 1H, C_7-H, J = 8.3 Hz), 7.15 (d, 1H, C_8-H, J = 8.4 Hz), 7.44(d, 2H, J = 7.2 Hz), 7.04 (d, 2H, J = 7.4 Hz), 6.52 (s, 1H), 12.75(s, 1H, OH),(exchanged with D2O)
5	4a	6-CH_3	1720 1633, 1648	----	2.39(s, 3H, CH_3 of chromone), 2.45(s, 3H, CH_3 of coumarin), 2.54(s, 3H, $COCH_3$), 5.26(s, 2H, CH_2O), 6.43(s, 1H, C_3-H), 7.46 (s, 1H, C_5-H), 7.18 (d, 1H, C_7-H, J = 7.9 Hz), 7.43 (d, 1H, C_8-H, J = 8.0 Hz), 7.39(d, 2H, J = 7.1 Hz), 6.88 (d, 2H, J = 7.2 Hz), 6.47 (s, 1H),
6	4b	5,6-Benzo	1714 1650, 1645	----	2.38(s, 3H, CH_3 of chromone), 2.59(s, 3H, $COCH_3$), 5.24(s, 2H, CH_2O), 6.22(1H, C_3-H), 7.09-7.69(m, 9H,Ar-H)
7	4c	6-OCH_3	1718, 1642, 1644	----	2.42(s, 3H, CH_3 of chromone), 2.54(s, 3H, $COCH_3$), 3.64(s, 3H, OCH_3), 5.3(s, 2H, CH_2O), 6.62(s, 1H, C_3-H), 7.38 (s, 1H, C_5-H), 7.08 (d, 1H, C_7-H, J = 7.8 Hz), 7.39 (d, 1H, C_8-H, J = 7.8 Hz), 7.34(d, 2H, J = 7.0 Hz), 6.88 (d, 2H, J = 7.0 Hz), 6.56 (s, 1H)
8	4d	6-Cl	1724, 1644, 1666	----	2.35(s, 3H, CH_3 of chromone), 2.54(s, 3H, $COCH_3$), 5.25(s, 2H, CH_2O), 6.34(s, 1H, C_3-H), 7.55 (s, 1H, C_5-H), 7.24 (d, 1H, C_7-H, J = 7.9 Hz), 7.37 (d, 1H, C_8-H, J = 7.90 Hz), 7.34(d, 2H, J = 7.0 Hz), 6.92 (d, 2H, J = 7.2 Hz), 6.53 (s, 1H).
9	5a	6-CH_3	1711, 1670	----	2.44(s, 3H, 6-CH_3), 2.33(s, 3H, CH_3), 5.26(s, 2H, CH_2O), 6.56(s, 1H, C_3-H)), 7.18-7.79 (m, 11H, Ar-H).
10	5b	5,6-Benzo	1725, 1674	----	2.38(s, 3H, CH_3), 5.22(s, 2H, CH_2O), 6.66(s, 1H, C_3-H)), 7.01-7.95 (m, 15H, Ar-H).
11	5c	6-OCH_3	1738, 1673	----	2.38(s, 3H, CH_3), 3.62(s, 3H, OCH_3), 5.21(s, 2H, CH_2O), 6.52(s, 1H, C_3-H)), 7.24-7.68 (m, 11H, Ar-H).
12	5d	6-Cl	1715, 1678	----	2.48(s, 3H, CH_3), 5.31(s, 2H, CH_2O), 6.68(s, 1H, C_3-H)), 7.24-8.01(m, 11H, Ar-H).
13	6a	6-CH_3	1720, 1711	3444(br)	2.44(s, 3H, 6-CH_3), 5.26(s, 2H, CH_2O), 5.50 (s, 1H,OH), 6.06(s, 1H, C_3-H)), 6.66(s, 1H, C_3-H)), , 7.59 (s,1H, C_5-H), 7.24 (d, 1H, C_7-H, J = 8.4 Hz), 7.27 (d, 1H, C_8-H, J = 8.40 Hz), 6.94(d, 2H, J = 7.6 Hz), 7.78(d, 2H, J = 7.6 Hz) 6.84 (s, 1H).
14	6b	5,6-Benzo	1714, 1702	3423(br)	5.22(s, 2H, CH_2O), 5.89(s, 1H, C_3-H)), 5.52 (s, 1H,OH), 6.56(s, 1H, C_3-H)), 6.84-8.01(m, 10H, Ar-H).
15	6c	6-OCH_3	1722, 1708	3420(br)	3.66(s, 3H, OCH_3), 5.21(s, 2H, CH_2O), 5.42 (s, 1H,OH), 6.02(s, 1H, C_3-H)), 6.72(s, 1H, C_3-H)), 7.79 (s, 1H, C_5-H), 7.31 (d, 1H, C_7-H, J = 8.4 Hz), 7.34 (d, 1H, C_8-H, J = 8.4 Hz), 6.92(d, 2H, J = 7.6 Hz), 7.83(d, 2H, J = 7.4 Hz) 6.89 (s, 1H).
16	6d	6-Cl	1722, 1702	3428(br)	5.24(s, 2H, CH_2O), 5.48 (s, 1H,OH), 6.1(s, 1H, C_3-H)), 6.62(s, 1H, C_3-H)), 7.59 (s, 1H, C_5-H), 7.44 (d, 1H, C_7-H, J = 8.5 Hz), 7.46 (d, 1H, C_8-H, J = 8.6 Hz), 6.99(d, 2H, J = 7.4 Hz), 7.88(d, 2H, J = 7.4 Hz) 7.1 (s, 1H).

1633 cm^{-1} assingened as lactone carbonyl of coumarin, lactone carbonyl of chromone and carbonyl of $COCH_3$.The NMR spectra showed the presence of three singlets at δ 2.33, 2.45 and 2.54 are due to the methyl of chromone, coumarin and $COCH_3$ respectively indicating the formation of 3- acylated product. It is worthy to note that the addition of equimolar quanity of acetic anhydride the reaction does not precede instead the addition of excess amount of the acetic anhydride forms the acylated chromone. The IR spectrum of compound **6a** showed the two stretching bands at 1720 and 1702 cm^{-1} due the carbonyl stretching of two coumarin moieties. The OH stretching is observed as broad band at 3444 cm^{-1}. The NMR spectrum showed the presence of two C_3-H of coumarin at 6.06 and 6.66, the OH proton observed as singlet at δ 5.50 (Table 1).

3. Experimental

3.1. Chemistry

Melting points are uncorrected and were recorded on a Buchi instrument using open capillaries. IR spectra were recorded on Nicolet impact spectrometer using KBr pellets

and ^{1}H NMR spectra were recorded on Bruker 300 MHz in $CDCl_3$+$DMSOd_6$ with TMS as an internal standard. Chemical shifts (δ) are reported in ppm, coupling constants (J) are given in Hz. All new compounds were analysed for C, H and the results were in an acceptable range. The 4-bromethyl coumarin was synthesized by the known methods [7].

*3.1.1. 4-(4'-Acetyl-3'-hydroxy-phenoxy methyl)-coumarin**(3a-d)***

To a mixture of 0.00395 mol of 4-bromomethyl coumarin **1** and 0.004 mol (0.56gms) of 2,4 dihydroxy acetophenone **2** and 0.5gms of K_2CO_3 were stirred at room temperature in 25 ml of dry acetone for 12 hours. The reaction mixture was evaporated to remove acetone and added to 100 ml of H_2O. The obtained precipitate was washed with dilute HCl, filtered, dried and recrystallised from dioxane and ethanol mixture (1:1) (Table 2).

*3.1.2. 2-Acetyl-3-methyl-6-(coumarin-4'-yl methoxy)-chromen-4-one **(4a-d)***

A mixture of substituted 4-(4′-acetyl-3′-hydroxy-phenoxy-methyl)-coumarin **(3a-d)** 0.004 mol was heated with 1gm of sodium acetate and 2 ml of acetic anhydride at 150-160 °C for 4 hours. The reaction mixture was left overnight and added to crushed ice. The separated precipitate was washed with dilute ethanol, filtered and recrystallised from ethanol (Table 2).

*3.1.3. 4-(2'-Benzoyl-3'-methyl-benzofuran-5'-yloxymethyl)-coumarin **(5a-d)***

A mixture of substituted 4-(4′-acetyl-3′-hydroxy-phenoxy-methyl)-coumarin **(3a-d)** 0.004 mol and phenacyl bromide (0.006 mol) was refluxed with K_2CO_3 (0.5gms) in dry acetone (20 ml) for 10 hours. The reaction mixture was poured in to crushed ice, the precipitate obtained was filtered, washed with dilute HCl, dried and recrystallised from dioxane (Table 2).

*3.1.4. 4-hydroxy 7-[(coumarin 4′-yl) oxy methyl] coumarin **(6a-d)***

A mixture of substituted 4-(4′-acetyl-3′-hydroxy-phenoxymethyl)-coumarin **(3a-d)** 0.004 mol and molecular sodium (1gms) was warmed in the presence of diethyl carbonate in steam bath for 30 minutes. When the vigorous reaction was ceased sufficient methyl alcohol was added to decompose the excess of sodium followed by diethyl ether (150-200 ml). The sodium salt was extracted with water (50x3), and the water layer wad acidified with dilute hydrochloric acid afford 4-hydroxy coumarin derivative. The residue was filtered, washed with 10% sodium bicarbonate solution, dried and recrystallised from methanol (Table 2).

Table 2
Experimental, data for compounds 3a-6d

Compound No	R	Formula	Yield (%)	Melting point(°C)
3a	6-CH_3	$C_{19}H_{16}O_5$	92	262
3b	5,6-Benzo	$C_{22}H_{16}O_5$	94	218
3c	6-OCH_3	$C_{19}H_{16}O_6$	88	228
3d	6-Cl	$C_{18}H_{13}ClO_5$	84	258
4a	6-CH_3	$C_{23}H_{18}O_6$	78	204
4b	5,6-Benzo	$C_{26}H_{18}O_6$	76	236
4c	6-OCH_3	$C_{23}H_{18}O_7$	77	248
4d	6-Cl	$C_{22}H_{15}ClO_6$	74	212
5a	6-CH_3	$C_{28}H_{20}O_5$	72	206
5b	5,6-Benzo	$C_{31}H_{20}O_5$	70	184
5c	6-OCH_3	$C_{28}H_{20}O_6$	72	208
5d	6-Cl	$C_{27}H_{17}ClO_5$	68	198
6a	6-CH_3	$C_{20}H_{14}O_6$	77	188
6b	5,6-Benzo	$C_{23}H_{14}O_6$	76	204
6c	6-OCH_3	$C_{20}H_{14}O_7$	72	236
6d	6-Cl	$C_{19}H_{11}ClO_6$	70	210

Method B: A mixture of 4,7-dihydroxy coumarin (0.004 mol) and 4-bromomethyl coumarin (0.004 mol) were stirred with anhydrous potassium carbonate in dry acetone for about 12 hours. The reaction mixture was dried and the residue was added to crushed ice, neutralized with dilute HCl and extracted with ethyl acetate.

3.2. Pharmacology

Albino rats of both sexes (150-200 g) and albino mice of either sex (18–22 g) were used. The animals were allowed food and water ad libitum. They were housed in cages at 18–20 °C with a 12 h light/dark cycle and relative humidity of 55–60%. The animals were randomly allocated into groups at the beginning of all the experiments. All test compounds and the reference drugs were administered orally suspended in 0.5% carboxy methylcellulose solution. The data for activity and toxicity were evaluated statistically using Student's *t*-test. A level of $P < 0.05$ was adopted for the test of significance.

3.2.1. Carrageenin test

Carrageenin-induced hind-paw edema in rats was produced by the method of Winter et al. [12]. Carrageenin solution (1.0% in sterile 0.9% NaCl solution) in a volume of 0.1 ml was injected subcutaneously into the subplantar region of the right hind paw 1 hour after the administration of the test compound. Control animals received only 0.5% carboxymethylcellulose solution. Right hind-paw volume was measured with an glass plethysmometer coupled to a peristaltic pump, immediately before and 3 hours after the carrageenin injection. The increase of results was matched with that of control rats. Each experiment was made with five groups of rats, 6 animals each (the 1st one was control).

3.2.2. Analgesic activity

The analgesic activity was determined in vivo by using abdominal constriction test induced by acetic acid 0.6% (0.1 ml/10 g) in mice [13]. Albino mice of both sexes (18-22gm) were used. Compounds were administered orally (1 mg/Kg) and 10 mg/kg) as a suspension in 5% carbethoxy methylcellulose (vehicle). Indomethacin (10 mg/kg) was used as the standard drug under same conditions.

Acetic acid solution was administered i.p. one hour after administration of the compounds **3a-6d**. Ten minutes after i.p. injection of the acetic acid solution, the number of constrictions per animal was recorded for 20 min. Control animals received on equal volume of vehicle. Analgesic activity was expressed as percentage of inhibition of constrictions when compared with the vehicle control group.

Table 3
In vivo Pharmacological data of compounds 3a-6d

Comp.	Analgesic activity Acetic acid writhing test % Protection		Antiinflammatory activity Carrageenin rat paw oedema % Inhibition 100 mg/kg	Ulcerogenic score (400 mg/kg)	Acute toxicity Approximate toxicity- LD_{50} (mg/kg)	
	1 mg/kg	10 mg/kg			i.p.	p.o
3a	15	28	26	10	> 800	> 1000
3b	18	34*	28	15	> 800	> 1000
3c	18	42*	32*	18	> 800	> 1000
3d	20	44*	35*	25	> 800	> 1000
4a	24	48*	44*	34	> 700	> 1000
4b	23	52*	44*	33	> 700	> 1000
4c	30	55*	48*	37	> 700	> 1000
4d	32*	58*	52*	46	> 700	> 1000
5a	28	55*	55*	44	> 700	> 1000
5b	26	57*	54*	28	> 700	> 1000
5c	31*	58*	59*	40	> 700	> 1000
5d	32*	60*	62*	22	> 700	> 1000
6a	15	24	25	32	> 800	> 1000
6b	17	22	23	43	> 800	> 1000
6c	15	25	31*	22	>800	> 1000
6d	18	28	34*	28	> 800	> 1000
Indomethacin	55*		62[a]*	278[b]*	~15	~25

Oral administration for all test compounds, *$P < 0.05$, Student's r-test versus controls.
[a] Indomethacin: 10 mg/kg.
[b] Indomethacin 2 x 10 mg/kg.

3.2.3. Acute toxicity

The tests of acute toxicity of the compounds were done on mice fasted for 24 h, water ad libitum. Groups of six mice were treated per orally and i.p. with the test compound at various dose levels. The animals were watched for mortality and symptoms until 8th day [14].

3.2.4. Ulcerogenic activity

Compounds showed low or no harmful effects on the stomach at the tested dose of 400 mg/kg p.o., when administered twice at a 2 h interval in fasted rats. Indomethacin, at lower doses, produced serious gastric ulcers in all animals.

4. Results and discussion

Anti-inflammatory activity was studied using Carrageenin induced paw edema in rats. The inhibition of edema was evaluated by the comparison of paw volume measured with an plethysmometer coupled to a peristaltic pump, immediately before and 3 h after the injection of carrageenin. Obtained data are given as an arithmetical means of measurements (Table 3). Indomethacin was used as a reference drugs. Only compound **6a, 6b 3a** and **3b** possess week anti-inflammatory and analgesic activity. Compounds **3c**, **3d**, **6c** and **6d** possess the less anti-inflammatory activity comparable with that of Indomethacin. **4a, 4b** and **4c** possess the moderately to good anti-inflammatory activity. Compounds **4d**, **5a, 5b, 5c** and **5d** are showed significantly activity compared to the Indomethacin. The difference of anti-inflammatory activity of synthesized compounds was too small to make any founded conclusions about the influence of any substituent. However the methoxy and chloro substitution in the coumarin ring has increased the activity in all cases. In spite of our previous results [4] and prognosis, the O-alkylated heteroaryl compounds were enhanced their activity. The activity of **3a–d** and their heterocyclic derivatives enhances the both anti-inflammatory and analgesic activity. The influence of methyl substitution at 6th position and the benzo at 5, 6-possition of coumarin ring found to be less active compare to the 6- methoxy and 6-Chloro coumarin ring. The activity **4d, 5d** and **6d** was a higher compared to their analogs **3d.** The **3c, 4c, 5c** and **6c** are less active compare to the **3d, 4d, 5d** and **6d,** all these are chloro substituted derivatives of coumarin. Among these chloro substitution at 6th position of coumarin ring the **6d** 4-hydroxy coumarinyl ether was found to be less active. The benzofuranyl ethers **5a-d** were showed significant activity indicating the benzofuranyl ethers are more potent compare to the other heterocycles like chromone or 4-hydroxy coumarin. The results indicate the changing the aromatic nucleus to heterocyclic moiety found to enhance the analgesic and anti-inflammatory activity. However the 4-hydroxy coumarinyl derivatives were found to be exceptional to this. The acute toxicity (LD50) of all the compounds showed the less than acute toxicity than that of Indomethacin (Table 3).

5. Conclusion

The new series of heterocyclic ethers were synthesized. The analgesic and anti-inflammatory activity of these compounds were comparable with the standard drug used. The benzofuranyl ethers of coumarins were found to be most active amongst all the compounds. The Chloro and methoxy substitution in coumarin ring found to increase the activity.

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