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Original article

Synthesis of novel triheterocyclic thiazoles as anti-inflammatory and analgesic agents

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Abstract

Triheterocyclic thiazoles containing coumarin and carbostyril (1-aza coumarin) have been synthesized by the reaction of the *in situ* generated 4-thioureidomethyl carbostyril and 3-bromoacetyl coumarins. The new compounds have been tested for their *in vivo* analgesic and anti-inflammatory activities. Qualitative SAR studies indicate that, the chloro substitution at C-7 in carbostyril and 6,8-dibromo substitution in the coumarin ring enhance anti-inflammatory activity. These compounds were also found to provide significant protection against acetic acid writhing in animal models. All the compounds have been characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry.

Keywords: Triheterocyclic thiazoles; *In vivo* analgesic; Anti-inflammatory activities; Ulcerogenic

1. Introduction

Coumarins and carbostyrils (1-aza coumarin) with diverse structural features and versatile biological properties such as anti-microbial, anti-cancer, anti-inflammatory and anti-HIV activities have been recently reviewed [1]. Linkage of various heterocycles at C-4 position in 2-arylamino thiazoles has resulted in novel molecular matrices which were associated with anti-neoplastic activity [2]. Number of 2,4-disubstituted thiazoles [3], imidazolyl thiazoles [4], and pyrazolyl thiazoles [5] have been recognized as potent anti-inflammatory and analgesic agents. Synthesis of many 3-substituted biheterocyclic coumarins with thiazoles and fused thiazoles possessing anti-microbial and anti-inflammatory agents has been reported from our laboratory [6–8]. In view of our earlier observation on the anti-inflammatory activity associated with 4-substituted carbostyrils [9] it was thought of interest to synthesize some triheterocycles containing coumarin and 1-aza coumarins (carbostyrils) linked to thiazole moiety.

2. Chemistry

The sequence of the reactions employed for the construction of triheterocyclic molecular library is outlined in Scheme 1. 4-Bromomethyl carbostyrils (**1–3**) were synthesized by bromination of acetoacetanilides and cyclising the intermediate ω-bromo acetoacetanilides in sulphuric acid [10]. They were converted to 4-aminomethyl carbostyril hydrochlorides (**4–6**) by the acid hydrolysis of their hexamine adducts, which were prepared by the reaction of compounds (**1–3**) with hexamethylenetetramine. Corresponding thioureas (**7–9**) were easily generated *in situ* by the reaction of compounds (**4–6**) with potassium thiocyanate in dry methanol. 3-Acetyl coumarins (**13–15**) were synthesized by the reaction of salicylaldehydes (**10–12**) with ethylacetoacetate in the presence of catalytic amount of piperidine at room temperature. These were

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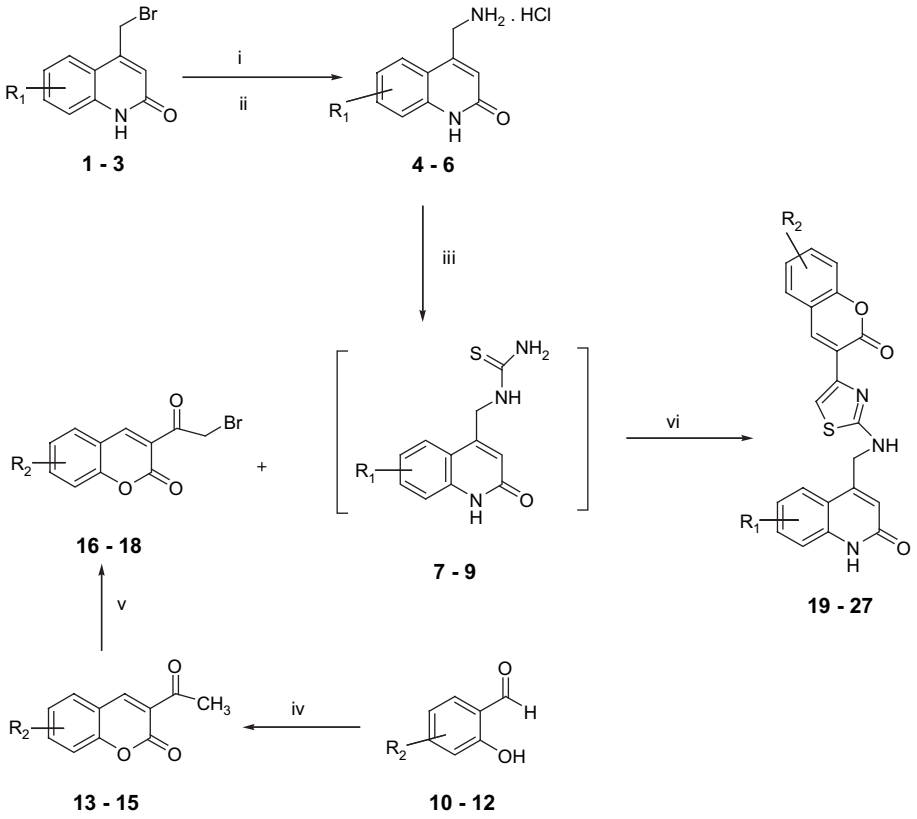

R_1 = 6-Cl, 7-Cl, 8-CH_3 ; R_2 = H, 6' - Br, 6' 8' - dibromo .

Scheme 1. Synthesis of tryheteroaryl thiazoles. Reagents and conditions: (i) Hexamine, ab. EtOH, reflux; (ii) conc. HCl, ab. EtOH, heat; (iii) KCNS, ab. MeOH, reflux; (iv) E.A.A, piperidine, stirr at R.T.; (v) liq. Br_2, dry $CHCl_3$, stirr, reflux. (vi). ab. MeOH, reflux.

brominated according to the method of Koelsh [11] to obtain the corresponding 3-bromoacetyl coumarins (**16**–**18**) [12]. Title compounds (**19**–**27**) were obtained by the reaction of synthons (**7**–**9**) and coumarins (**16**–**18**) representing the double electrophile and double nucleophile approach for five membered heterocycles. Thiazole formation in refluxing methanol was indicated by a stable canary yellow colour of the reaction mixture and was found to be complete (TLC) in about 3–4 h. The separated products were in a free base form and no hydrobromides were isolated in accordance with earlier observations [13]. The reactions are outlined in Scheme 1 and the compounds synthesized are given in Table 1. Structures of all the newly synthesized compounds are well supported by spectral data such as IR, NMR, mass and elemental analysis.

3. Results and discussion

3.1. Acute toxicity studies

It is found that, all the compounds have shown good safety profile till the highest dose. No mortality of animals observed even after 24 h.

3.2. Analgesic activity

Abdominal constriction response induced by acetic acid is sensitive procedure to establish efficacy of peripherally acting analgesics. Intraperitonial administration of acetic acid causes increase in the level of PGE2 and PGF 2α [14]. Amongst the tested compounds, **22** and **26** significantly inhibited the acetic acid induced writhing (up to 88% and 78%, respectively) and other compounds (**23**–**25**) in the range of 64–35% as compare to the standard. Thus compounds **22** and **26** appear to possess significant peripheral anti-nociceptive activity. The analgesic

Table 1
List of triheteroaryl thiazoles synthesized (**19**–**27**)

Compound	R_1	R_2
19	6-Cl	H
20	7-Cl	H
21	8-CH_3	H
22	6-Cl	6′-Br
23	7-Cl	6′-Br
24	8-CH_3	6′-Br
25	6-Cl	6′,8′-Br
26	7-Cl	6′,8′-Br
27	8-CH_3	6′,8′-Br

activity was expressed as percentage of protection, the results of which are summarized in Table 2.

3.3. Anti-inflammatory activity

Inhibition of formalin induced paw oedema in rats is one of the most acceptable test procedures to evaluate anti-inflammatory agents [15,16]. Anti-inflammatory activity exhibited by the compounds may be attributed to the inhibition of cycloxygenase enzyme, which plays a vital role in inflammation process [17]. The standard used for the present anti-inflammatory activity testing is phenyl butazone. The test compounds were found to be slow acting anti-inflammatory agents. Hence the results after 3 h for compounds (**19**–**27**) were not encouraging. But the same compounds after 4 h till 8th hour showed significant increase in the activity. Compound **26** has shown inhibition, comparable with the standard at the 8th hour. The same compound after 4th hour shows 69% inhibition. Almost all compounds show increased activity at the 8th hour. This is depicted in Fig. 1. Hence the compounds (**22**–**27**) seem to be more effective as slow acting anti-inflammatory agents. The results indicating the percentage inhibition of inflammation at various time intervals have been summarized in Table 3.

4. Experimental

4.1. Chemistry

The melting points were determined by open capillaries on a Buchi apparatus and are uncorrected. The IR spectra were recorded on a Nicolet-Impact-410 FT-IR spectrometer, using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300F, 300 MHz, spectrometer in $CDCl_3$ using TMS as an internal standard and the values are expressed in δ (ppm). The mass spectra were recorded using FAB-MS (Indian Institute of Technology, Bombay). The elemental analysis was carried out using Heraus CHN rapid analyzer. All the new compounds gave C, H and N analysis within ±0.4% of the theoretical values. All the chemicals purchased were of analytical reagent grade, and were used without further purification unless otherwise stated.

Table 2
Analgesic activities of the test compounds

Compound	No. of. writhes	Percentage of protection
22	05.01 ± 0.73*	88.89
23	15.83 ± 1.24*	64.94
24	06.16 ± 0.60*	35.05
25	13.33 ± 0.95*	48.70
26	09.83 ± 0.79*	78.22
27	06.50 ± 0.56*	62.73
Control	45.16 ± 0.90	
Standard	08.33 ± 0.42	81.56

Values are expressed as mean ± SEM. *$P < 0.001$ Vs control. Note: For both the screened activities the results were analyzed by using one way ANOVA ($F = 76.782$) followed by Turkey's multiple comparative test. 'P' values of $P < 0.05$, $P < 0.01$ and $P < 0.001$ were considered statistically significant.

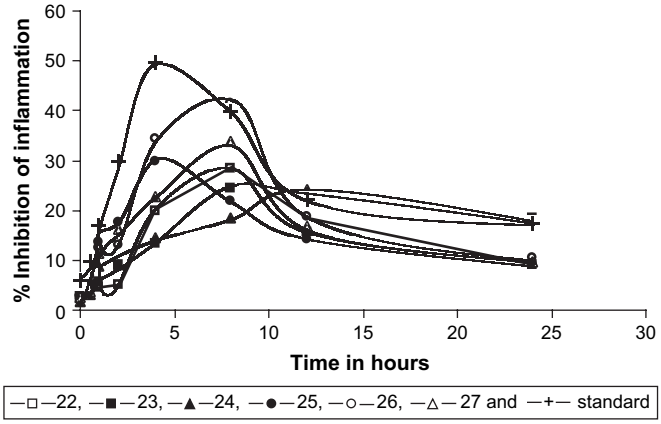

Fig. 1.

4.1.1. Preparation of triheterocycles (*19*–*27*) (general procedure)

A mixture of substituted 4-aminomethylcarbostyrilhydrochloride (**4**–**6**) (3.00 mmol) and potassium thiocyanate (6.00 mmol) in dry methanol (20 ml) was refluxed on a water bath for 4 h. After cooling, the separated salt of potassium sulfate was filtered, to the filtrate, 3-bromoacetylcoumarin (**16**–**18**) (3.00 mmol) was added and the reaction mixture was refluxed on a water bath for 4 h, and left overnight. A yellow colored solid obtained was filtered, washed with excess of cold water, dried and crystallized from suitable solvent.

4.1.2. 4-{[4-(2-Oxo-2H-chromen-3-yl)-thiazol-2-ylamino]-methyl}-6-chloro-1H-quinoline-2-one (*19*)

Yellow solid (methanol); yield: 74%; m.p. 152–154 °C; FAB-MS: 436 (M + 1); IR (KBr): $\nu_{C=O}$1657 cm^{-1} (amide), $\nu_{C=O}$1720 cm^{-1} (lactone), $\nu_{C=N}$1611 cm^{-1}, ν_{NH}3429 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 4.05 (s, 1H, C4-CH_2–N*H*), 4.77 (s, 2H, C4-CH_2), 7.32–8.18 (m, 10H, Ar-H), 8.78 (s, 1H, N*H*CO); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 174.6, 161.4, 159.8, 155.9, 153.2, 150.8, 142.3, 139.6, 136.8, 132.1, 131.4, 128.6, 125.9, 124.8, 124.4, 122.6, 122.1, 120.8, 118.6, 110.9, 108.6, 58.98. Anal. calc. for $C_{22}H_{14}ClN_3O_3S$ (%): C, 60.62; H, 3.24; N, 9.64; found (%): C, 60.32; H, 3.62; N, 9.80.

4.1.3. 4-{[4-(2-Oxo-2H-chromen-3-yl)-thiazol-2-ylamino]-methyl}-7-chloro-1H-quinoline-2-one (*20*)

Pale yellow solid (methanol); yield: 78%; m.p. 144–146 °C; FAB-MS: 436 (M + 1); IR (KBr): $\nu_{C=O}$1659 cm^{-1} (amide), $\nu_{C=O}$1720 cm^{-1} (lactone), $\nu_{C=N}$1607 cm^{-1}, ν_{NH}3438 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 4.13 (s, 1H, C4-CH_2–N*H*), 4.70 (s, 2H, C4-CH_2), 7.30–8.15 (m, 10H, Ar-H), 8.76 (s, 1H, N*H*CO); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 174.8, 162.6, 160.8, 156.6, 153.8, 151.1, 142.4, 138.8, 136.6, 132.4, 131.8, 129.6, 125.4, 125.1, 124.6, 122.8, 122.1, 120.6, 119.2, 110.0, 109.1, 60.3. Anal. calc. for $C_{22}H_{14}ClN_3O_3S$ (%): C, 60.62; H, 3.24; N, 9.64; found (%): C, 60.28; H, 3.54; N, 9.72.

Table 3
Anti-inflammatory activities of the test compounds

Compound	% Inhibition of inflammation							
	0 h	0.5 h	1 h	2 h	4 h	8 h	12 h	24 h
22	3.03	4.11	4.42	5.26	19.83	28.57	15.55	9.08
23	2.40	5.26	5.80	9.09	13.27	24.48	23.17	18.40
24	1.60	3.12	8.76	9.19	14.52	18.52	24.08	16.85
25	2.85	6.75	13.75	17.75	29.83	21.85	14.36	9.35
26	2.89	3.27	12.56	13.04	34.53	41.47	18.73	10.58
27	2.65	3.65	11.27	16.34	22.73	33.73	16.73	9.78
Standard	5.97	9.76	17.08	29.89	49.89	39.71	22.17	17.45

*4.1.4. 4-{[4-(2-Oxo-2H-chromen-3-yl)-thiazol-2-ylamino]-methyl}-8-methyl-1H-quinoline-2-one (**21**)*

Brown solid (ethanol + dioxan); yield: 70%; m.p. 158–160 °C; FAB-MS: 416 (M + 1); IR (KBr): $\nu_{C=O}$1668 cm^{-1} (amide), $\nu_{C=O}$1719 cm^{-1} (lactone), $\nu_{C=N}$1608 cm^{-1}, ν_{NH}3410 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.48 (s, 3H, C8-CH_3), 4.06 (s, 1H, C4-CH_2–N*H*), 4.58 (s, 2H, C4-CH_2), 7.35–8.48 (m, 10H, Ar-H), 8.80 (s, 1H, N*H*CO); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 174.3, 161.3, 159.7, 156.6, 153.8, 150.7, 141.8, 139.6, 136.4, 132.2, 131.4, 129.7, 128.1, 125.6, 124.1, 123.9, 122.7, 120.6, 118.4, 111.2, 108.7, 60.2, 18.4. Anal. calc. for $C_{23}H_{17}N_3O_3S$ (%): C, 66.49; H, 4.12; N, 10.11; found (%): C, 66.80; H, 4.38; N, 9.80.

*4.1.5. 4-{[4-(6-Bromo-2-oxo-2H-chromen-3-yl)-thiazol-2-ylamino]-methyl}-6-chlorol-1H-quinoline-2-one (**22**)*

Yellow solid (methanol); yield: 82%; m.p. 148–150 °C; FAB-MS: 515 (M + 1); IR (KBr): $\nu_{C=O}$1672 cm^{-1} (amide), $\nu_{C=O}$1721 cm^{-1} (lactone), $\nu_{C=N}$1610 cm^{-1}, ν_{NH}3439 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 4.18 (s, 1H, C4-CH_2–N*H*), 4.68 (s, 2H, C4-CH_2), 7.32–8.48 (m, 9H, Ar-H), 8.75 (s, 1H, N*H*CO); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 173.8, 161.8, 159.4, 155.3, 153.8, 150.7, 142.4, 139.6, 136.2, 132.2, 131.4, 128.7, 125.7, 124.9, 124.1, 122.7, 122.2, 120.4, 119.2, 111.2, 108.9, 60.4. Anal. calc. for $C_{22}H_{13}ClBrN_3O_3S$ (%): C, 51.33; H, 2.55; N, 8.16; found (%): C, 51.08; H, 2.20; N, 8.60.

*4.1.6. 4-{[4-(6-Bromo-2-oxo-2H-chromen-3-yl)-thiazol-2-ylamino]-methyl}-7-chloro-1H-quinoline-2-one (**23**)*

Yellow solid (ethanol + dioxan); yield: 78%; m.p. 155–157 °C; FAB-MS: 515 (M + 1); IR (KBr): $\nu_{C=O}$1652 cm^{-1} (amide), $\nu_{C=O}$1733 cm^{-1} (lactone), $\nu_{C=N}$1605 cm^{-1}, ν_{NH} 3422 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 4.10 (s, 1H, C4-CH_2–N*H*), 4.66 (s, 2H, C4-CH_2), 7.29–8.48 (m, 9H, Ar-H), 8.76 (s, 1H, N*H*CO); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 174.1, 161.7, 159.8, 155.8, 153.4, 150.8, 142.1, 139.7, 136.7, 132.4, 131.8, 128.4, 125.7, 125.1, 124.4, 122.8, 122.1, 120.6, 118.8, 111.8, 109.3, 60.1. Anal. calc. for $C_{22}H_{13}ClBrN_3O_3S$ (%): C, 51.33; H, 2.55; N, 8.16; found (%): C, 51.10; H, 2.31; N, 8.24.

*4.1.7. 4-{[4-(6-Bromo-2-oxo-2H-chromen-3-yl)-thiazol-2-ylamino]-methyl}-8-methyl-1H-quinoline-2-one (**24**)*

Yellow solid (methanol); yield: 78%; m.p. 150–152 °C; FAB-MS: 495 (M + 1); IR (KBr): $\nu_{C=O}$1678 cm^{-1} (amide), $\nu_{C=O}$1730 cm^{-1} (lactone), $\nu_{C=N}$1610 cm^{-1}, ν_{NH}3411 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.45 (s, 3H, C8-CH_3), 3.96 (s, 1H, C4-CH_2–N*H*), 4.51 (s, 2H, C4-CH_2), 7.32–8.10 (m, 9H, Ar-H), 8.80 (s, 1H, N*H*CO); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 174.6, 160.9, 159.8, 156.7, 153.8, 151.1, 149.8, 141.2, 139.8, 131.4, 131.1, 129.7, 128.9, 125.7, 124.6, 123.4, 122.8, 120.7, 118.8, 110.8, 109.2, 60.4, 18.8. Anal. calc. for $C_{23}H_{16}BrN_3O_3S$ (%): C, 55.88; H, 3.26; N, 8.50; found (%): C, 55.50; H, 3.06; N, 8.21.

*4.1.8. 4-{[4-(6,8-Dibromo-2-oxo-2H-chromen-3-yl)-thiazol-2-ylamino]-methyl}-6-chloro-1H-quinoline-2-one (**25**)*

Pale yellow solid (ethanol + dioxan); yield: 80%; m.p. 158–160 °C; FAB-MS: 594 (M + 1); IR (KBr): $\nu_{C=O}$1662 cm^{-1} (amide), $\nu_{C=O}$1722 cm^{-1} (lactone), $\nu_{C=N}$1616 cm^{-1}, ν_{NH}3419 cm^{-1}; ^{1}H NMR (300 MHz,$CDCl_3$, δ ppm): 4.10 (s, 1H, C4-CH_2–N*H*), 4.68 (s, 2H, C4-CH_2), 7.38–8.20 (m, 8H, Ar-H), 8.76 (s, 1H, N*H*CO); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 174.2, 162.1, 159.8, 155.4, 153.3, 150.8, 142.2, 140.1, 136.6, 132.8, 131.2, 128.7, 125.6, 124.4, 122.8, 122.6, 122.1, 120.7, 118.1, 111.4, 108.7, 61.1. Anal. calc. for $C_{22}H_{12}Br_2ClN_3O_3S$ (%): C, 44.51; H, 2.04; N, 7.08; found (%): C, 44.22; H, 2.01; N, 6.88.

*4.1.9. 4-{[4-(6,8-Dibromo-2-oxo-2H-chromen-3-yl)-thiazol-2-ylamino]-methyl}-7-chloro-1H-quinoline-2-one (**26**)*

Yellow solid (methanol); yield: 75%; m.p. 148–150 °C; FAB-MS: 594 (M + 1); IR (KBr): $\nu_{C=O}$1655 cm^{-1} (amide), $\nu_{C=O}$1720 cm^{-1} (lactone), $\nu_{C=N}$1615 cm^{-1}, ν_{NH}3416 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 4.16 (s, 1H, C4-CH_2–N*H*), 4.66 (s, 2H, C4-CH_2), 7.38–8.20 (m, 8H, Ar-H), 8.79 (s, 1H, N*H*CO); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 174.6, 162.0, 159.8, 155.8, 153.3, 150.7, 142.3, 139.8, 138.0, 136.8, 132.6, 131.4, 129.0, 125.8, 124.8, 122.7, 122.1, 120.8, 118.7, 111.2, 108.9, 60.4. Anal. calc. for $C_{22}H_{12}Br_2ClN_3O_3S$ (%): C, 44.51; H, 2.04; N, 7.08; found (%): C, 44.12; H, 1.92; N, 6.96.

*4.1.10. 4-{[4-(6,8-Dibromo-2-oxo-2H-chromen-3-yl)-thiazol-2-ylamino]-methyl}-8-methyl-1H-quinoline-2-one (**27**)*

Pale yellow solid (ethanol); yield: 74%; m.p. 147–149 °C; FAB-MS: 574 (M + 1); IR (KBr): $\nu_{C=O}$1672 cm^{-1} (amide), $\nu_{C=O}$1723 cm^{-1} (lactone), $\nu_{C=N}$1618 cm^{-1}, ν_{NH}3409 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.52 (s, 3H, C8-CH_3), 4.12 (s, 1H, C4-CH_2–N*H*), 4.70 (s, 2H, C4-CH_2), 7.40–8.22

(m, 8H, Ar-H), 8.82 (s, 1H, N*H*CO); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 174.8, 161.0, 160.1, 156.8, 153.4, 151.2, 149.6, 141.8, 139.6, 131.5, 131.0, 129.8, 128.6, 125.6, 124.8, 123.9, 122.4, 120.3, 118.7, 111.3, 109.6, 61.2, 18.4. Anal. calc. for $C_{23}H_{15}Br_2N_3O_3S$ (%): C, 48.19; H, 2.64; N, 7.33; found (%): C, 47.90; H, 2.20; N, 7.06.

4.2. Pharmacology

4.2.1. Acute toxicity studies

The acute toxicity for all test compounds was carried out in albino mice weighing 20–25 g [18] which were fasted overnight. The dosage was varied 1000–100 mg kg^{-1} body weight. The animals were observed for 24 h for any signs of acute toxicity such as increased or decreased motor activity, tremors, convulsion, sedation, lacrimation etc. No mortality of the animals was observed even after 24 h. Hence the LD_{50} cut off value of the test compounds was fixed as 1000 mg kg^{-1}. So that 100 mg kg^{-1} i.e., 1/10 of cut off value was taken as screening dose for the evaluation of anti-inflammatory and analgesic activity.

4.2.2. Analgesic activity

The analgesic activity of test compounds was carried out *in vivo* by acetic acid induced writhing method [14]. Albino mice of either sex were divided into control, standard and different test groups of six mice each (20–25 g). Control group received 2 ml kg^{-1} of 2% aqueous gum acacia, p.o. standard was treated with aspirin at a dose level of 100 mg kg^{-1} and test compounds were administered p.o. at dose level of 100 mg kg^{-1} body weights in 2% aqueous gum acacia. One hour after the administration, all the groups received acetic acid (0.6% v/v in distilled water) i.p. at dose level of 1 ml/100 g, 10 min after i.p. injection of acetic acid solution, the number of writhes per animal was recorded for 20 min. The analgesic activity was expressed as percentage of protection, the results of which are given in Table 2.

4.2.3. Anti-inflammatory activity

The anti-inflammatory activity of the test compounds was carried out by formalin induced rat paw oedema inhibition method according to winter et al. [15,16] by employing 3.5% of formalin as the phlogistic agent. All the test compounds were administered intraperitoneally as suspensions in 2% CMC, 30 min before the injection of the phlogistic agent, at dose level of 100 mg kg^{-1} body weights. Phenyl butazone was used as a standard at a dose level of 150 mg kg^{-1} body weight. The groups of six albino rats of either sex were used in each experiment. Plain CMC (2%) was served as a control. The paw oedema volume was measured with the help of plethysmograph by mercury displacement method at 0 h (immediately after injection of formalin). Then the oedema volume was observed at 0.5, 1, 2, 3, 4, 8, 12 and 24 h. The results are depicted in Table 3.

5. Conclusion

It can be seen that amongst the test compounds substitution at position 7 of the carbostyril increases both analgesic and anti-inflammatory activities and 6,8-dibromo substitutions on coumarin favors higher analgesic and anti-inflammatory activity. In general, test compounds are non-toxic up to 1000 mg kg^{-1} body weights of the animals. And show reasonable anti-inflammation activity and clearly very good analgesic activity. It is important to note that these are slow acting anti-inflammation agents, which can be easily degradable in the metabolic system after 24 h. Further studies are required to establish their exact mechanism of action.

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