Synthesis and Pharmacological Evaluation of 3-propyl-2-substitutedamino-3*H*-quinazolin-4-ones as Analgesic and Anti-Inflammatory Agents

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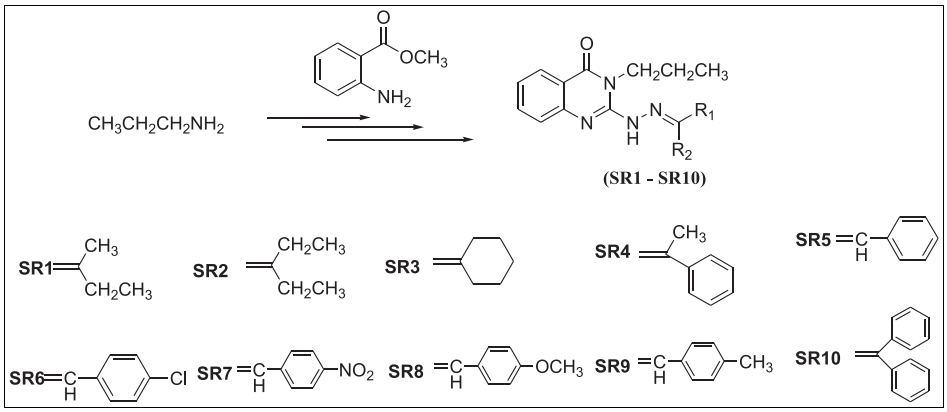

A variety of novel 3-propyl-2-substitutedamino-quinazolin-4(3*H*)-ones were synthesized by reacting the amino group of 2-hydrazino-3-propyl quinazolin-4(3*H*)-one with a variety of aldehydes and ketones. The starting material 2-hydrazino-3-propyl quinazolin-4(3*H*)-one was synthesized from propylamine. The title compounds were investigated for analgesic and anti-inflammatory activities. The compound 2-(1-ethylpropylidene-hydrazino)-3-propyl-quinazolin-4(3*H*)-one **(SR2)** emerged as the most active compound of the series, and it is more potent in its analgesic and anti-inflammatory activities when compared with the reference standard diclofenac sodium.

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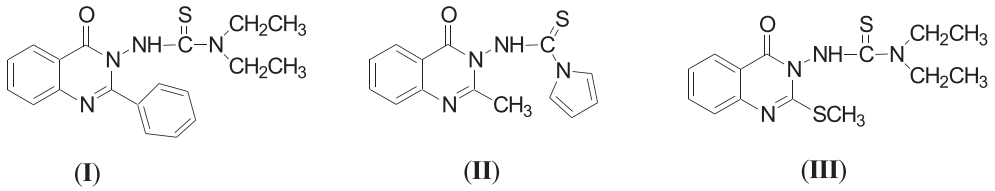
INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for the treatment of acute and chronic inflammation, pain, and fever. The most of NSAIDs act via inhibition of cyclooxygenase, thus preventing prostaglandin biosynthesis. However, this mechanism of action is also responsible for their main undesirable effects, gastrointestinal ulceration, and, less frequently, nephrotoxicity. The increase in hospitalization and deaths due to gastrointestinal-related disorders parallels the increased use of NSAIDs. Therefore, the discovery of a new safer anti-inflammatory drugs represents a challenging goal for such a research area [1–4]. On our going medicinal chemistry research program, we found that quinazolines and condensed quinazolines exhibit potent central nervous system activities including analgesic, anti-inflammatory [5], and anticonvulsant behavior [6]. Quinazolin-4(3*H*)-ones with 2,3-substitution are reported to possess significant analgesic, anti-inflammatory [7,8], and anticonvulsant activities [9]. Earlier, we have documented some lead 2-phenyl-3-substituted quinazolines [10] [Fig. 1(I)], 2-methyl-3-substituted quinazolines [11] [Fig. 1(II)], 2-methylthio-3-substituted quinazaolines [12] [Fig. 1(III)], and 2,3-disubstituted quinazolines [13] that exhibited good analgesic and anti-inflammatory properties. The present work is an extension of our ongoing efforts toward the development and identification of new molecules for analgesic and anti-inflammatory activities. With this background in the present study, we have synthesized a series of 3-propyl-2-substitutedamino-3*H*-quinazolin-4-ones (Scheme 1). The synthesized compounds were tested for their analgesic and anti-inflammatory activities.

RESULT AND DISCUSSION

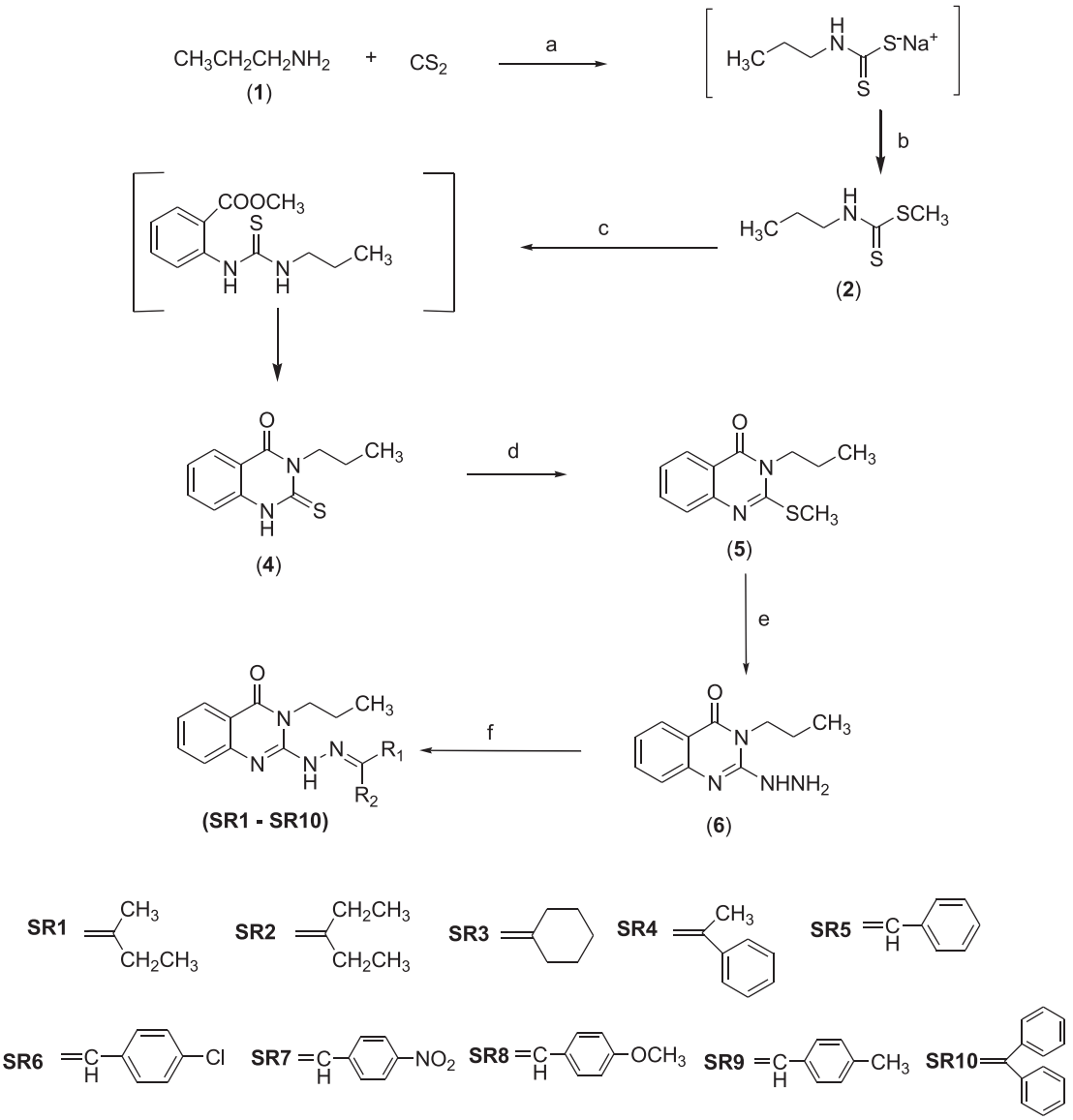
The key intermediate 3-propyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **4** was prepared by reacting ethyl amine **(1)** with carbon disulphide and sodium hydroxide in dimethyl sulfoxide to give sodium dithiocarbamate, which was methylated with dimethyl sulfate to afford the dithiocarbamic acid methyl ester **(2)**. Compound **2** on reflux with methyl anthranilate **(3)** in ethanol yielded the desired 3-propyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **(4)** via the thiourea intermediate in good yield (86%). It was confirmed by infrared (IR) spectra of compound **4** show intense peaks at 3242 cm^{-1} for cyclic thiourea (NH),



(**I**) (**II**) (**III**)

Figure 1. Lead molecules of quinazolin-4-ones.

Scheme 1. Synthesis of 3-propyl-2-substituted amino-3*H*-quinazolin-4-ones.



Reagents and conditions: (a) DMSO, rt, 30 min; (b) $(CH_3)_2SO_4$, 5-10°C, 2 h; (c) Methyl anthranilate (**3**), K_2CO_3, Ethanol reflux for 24 h; (d) 2% alcoholic NaOH, $(CH_3)_2SO_4$, rt, 1 h; (e) NH_2NH_2, K_2CO_3, Ethanol reflux for 30 h; (f) $(R_2R_1)CO$; gla.CH_3COOH reflux, 30-36 h.

1666 cm^{-1} for carbonyl (C = O), and 1218 cm^{-1} for thioxo (C = S) stretching. ^{1}H-NMR spectra of **4** showed a multiplet around δ 1.0–2.0 and 7.6–7.8 for ethyl (5H) protons and aromatic (4H) protons, respectively and a singlet at δ 10.26 indicating the presence of NH. Data from the elemental analyses have been found to be in conformity with the

assigned structure. Further, the molecular ion recorded in the mass spectra is also in agreement with the molecular weight of the compound.

The 2-methysulfanyl-3-propyl-3*H*-quinazolin-4-one **(5)** was obtained by dissolving **4** in 2% alcoholic sodium hydroxide solution and methylation by dimethyl sulfate at room temperature stirring. The infrared (IR) spectra of compound **5** showed disappearance of NH and C = S stretching signals of cyclic thiourea. It showed a peak for carbonyl (C = O) stretching at 1682 cm^{-1}. The ^{1}H-nuclear magnetic resonance (NMR) spectra of compound **5** showed singlets due to SCH_3, at δ 2.91, multiplet around 7.11–7.32 for aromatic (4H) protons, respectively. Data from the elemental analyses and molecular ion recorded in the mass spectra further confirmed the assigned structure.

Nucleophilic displacement of methylthio group of **5** with hydrazine hydrate was carried out using ethanol as solvent to afford 2-hydrazino-3-propyl-3*H*-quinazolin-4-one **(6)**. The long duration of reaction (29 h) required might be because of the presence of propyl group at position **3**. The formation of **6** was confirmed by the ^{1}H-NMR spectra showed singlets at δ 4.65 and 8.51 due to NH_2 and NH, respectively; a multiplet at δ 1.04–2.05 and 7.36–7.62 for ethyl (5H) protons and aromatic (4H) protons, respectively. The NH and NH_2 signals at 3310 and 3226 cm^{-1} are appeared in the IR spectra. It also showed a peak for carbonyl (C = O) at 1680 cm^{-1}. Data from the elemental analyses have been found to be in conformity with the assigned structure. Further, the molecular ion recorded in the mass spectra is also in agreement with the molecular weight of the compound.

The title compounds 3-propyl-2-substitutedamino-3*H*-quinazolin-4-ones **(SR1–SR10)** were obtained by the condensation of amino group of 3-propyl-2-hydrazino-3*H*-quinazolin-4-one **(6)** with a variety of aldehydes and ketones. The formation of title product is indicated by the disappearance of peak due to NH_2 of the starting material in IR and ^{1}H-NMR spectrum of all the compounds **SR1–SR10**. The IR ^{1}H-NMR spectra of these compounds showed the presence of peaks due to ($N = CR_1R_2$) carbonyl (C = O), NH, and Aryl groups. The mass spectra of the title compounds showed molecular ion peaks corresponding to their molecular formula. In the mass spectra of compounds **SR1–SR10**, a common peak at m/z 144 corresponding to quinazolin-4-one moiety appeared. The M^++2 peaks was observed in the spectra of compound **SR6** confirming the presence of a chlorine atom in the compounds. The relative intensities of these M^++2 peaks in comparison with M^+ peaks were in the ratio of 1:3. Elemental (C, H, N) analysis satisfactorily confirmed elemental composition and purity of the synthesized compounds.

Analgesic activity. Evaluation of analgesic activity was performed by the tail-flick technique [14,15] using Wistar albino mice. The results of analgesic testing indicate that the test compounds exhibited moderate analgesic activity at 30 min of reaction time and an increase in activity at 1 h, which reached a peak level at 2 h. Decline in activity was observed at 3 h (Table 1). Compound **SR1** with 1-methylpropylidene substituent showed good activity; with the increased lipophilicity (1-ethylpropylidene group, compound **SR2**) showed increase in activity. Replacement of C-2 alkyl chain with a cycloalkyl group and an aralkyl group (compounds **SR3** and **SR4**, respectively) leads to retention of similar potency. Placement of aryl group at the N-3 position (compounds **SR5**, **SR8**, **SR9**, and **SR10**) results in decreasing the activity. Placement of electron withdrawing group at N-3 aryl ring (compounds **SR6**, **SR7**) leads to further decrease of activity. Compound 2-(1-ethylpropylidene)-hydrazino-3-propyl-quinazolin-4(3*H*)-one **(SR2)** emerged as the most active analgesic agent, and it is moderately more potent when compared with the reference standard diclofenac.

Anti-inflammatory activity. Anti-inflammatory activity was evaluated by the Carrageenan-induced paw edema test in rats [16]. The anti-inflammatory activity data (Table 2) indicated that all the test compounds protected rats from Carrageenan-induced inflammation moderately at 30 min of reaction time with increased activity at 1 h that reached a peak level at 2 h. Decline in activity was observed at 3 h. The compound 2-(1-ethylpropylidene)-hydrazino-3-propyl-quinazolin-4(3*H*)-one **(SR2)** showed the most potent anti-inflammatory activity of the series and it is more potent when compared to the reference standard diclofenac sodium.

CONCLUSION

In our earlier studies [10–13], we observed that the presence of alkyl groups exhibited more analgesic and anti-inflammatory activities over aryl groups at the N-3 position. Hence, in the C-2 position also, we made a substitution in such a way to increase lipophilicity of the molecule. The placement of such a group enhanced the analgesic and anti-inflammatory activities. With this background, synthesis of new series of 3-propyl-2-substituted amino-quinazolin-4(3*H*)-ones **(SR1–SR10)** have been described. The title compounds have exhibited promising analgesic and anti-inflammatory activities when tested using the model tail-flick technique on Wistar albino mice and Carrageenan-induced paw edema test in rats, respectively. Among the series, compound 2-(1-ethylpropylidene)-hydrazino-3-propyl-quinazolin-4(3*H*)-one **(SR2)** was found to be the most active compound of the series, and it is more potent in its analgesic and anti-inflammatory activities when compared with the reference standard diclofenac sodium. Hence, this compound could therefore serve as a lead molecule for further modification to obtain a clinically useful novel class of analgesic and anti-inflammatory agents.

Table 1

Analgesic activity of synthesized compounds (SR1-SR10).

		Percent analgesic activity			
Compound code	Dose (mg/kg)	30 min	1 h	2 h	3 h
SR1	5	26.55 ± 3.16^{c}	32.68 ± 4.18^{c}	36.76 ± 4.91^{c}	20.44 ± 2.73^{b}
	10	40.04 ± 3.09^{c}	50.03 ± 3.68^{c}	52.03 ± 3.09^{c}	34.05 ± 2.67^{c}
	20	52.03 ± 3.09^{c}	62.02 ± 1.99^{c}	68.02 ± 3.99^{c}	42.04 ± 3.68^{c}
SR2	5	35.30 ± 2.63^{c}	39.22 ± 3.61^{c}	43.14 ± 4.72^{c}	29.71 ± 2.81^{c}
	10	46.04 ± 2.68^{c}	52.03 ± 4.37^{c}	62.02 ± 4.81^{c}	36.05 ± 2.52^{c}
	20	53.08 ± 2.04^{c}	65.32 ± 3.76^{c}	71.44 ± 2.58^{c}	42.88 ± 2.58^{c}
SR3	5	26.05 ± 4.81^{c}	32.05 ± 5.05^{c}	38.05 ± 4.81^{c}	20.06 ± 2.53^{b}
	10	40.04 ± 4.37^{c}	48.04 ± 5.05^{c}	52.03 ± 3.09^{c}	34.05 ± 4.09^{c}
	20	50.98 ± 3.61^{c}	60.81 ± 2.49^{c}	68.63 ± 3.92^{c}	41.18 ± 4.29^{c}
SR4	5	26.06 ± 2.00^{c}	30.05 ± 3.68^{c}	36.05 ± 2.52^{c}	19.73 ± 2.65^{c}
	10	42.88 ± 2.58^{c}	46.96 ± 2.58^{c}	49.00 ± 2.04^{c}	30.64 ± 2.58^{c}
	20	47.06 ± 2.63^{c}	58.82 ± 2.63^{c}	62.74 ± 3.61^{c}	39.22 ± 3.61^{c}
SR5	5	25.49 ± 2.48^{c}	31.37 ± 4.72^{c}	31.37 ± 3.61^{c}	19.60 ± 1.96^{c}
	10	37.80 ± 3.31^{c}	46.96 ± 2.58^{c}	49.00 ± 3.76^{c}	28.60 ± 3.76^{c}
	20	47.06 ± 2.63^{c}	58.82 ± 2.63^{c}	62.74 ± 3.61^{c}	39.22 ± 3.61^{c}
SR6	5	21.56 ± 2.48^{c}	25.49 ± 2.48^{c}	31.37 ± 1.96^{c}	17.64 ± 3.03^{c}
	10	33.33 ± 2.48^{c}	35.28 ± 2.62^{c}	43.14 ± 3.61^{c}	25.49 ± 3.92^{c}
	20	41.18 ± 4.29^{c}	47.06 ± 4.01^{c}	47.06 ± 4.01^{c}	37.26 ± 2.48^{c}
SR7	5	25.49 ± 3.92^{c}	29.41 ± 3.03^{c}	39.22 ± 3.61^{c}	21.56 ± 2.48^{c}
	10	32.68 ± 4.18^{c}	38.80 ± 4.46^{c}	44.92 ± 4.18^{c}	28.60 ± 3.76^{c}
	20	44.92 ± 6.12^{c}	51.04 ± 5.47^{c}	53.08 ± 3.76^{c}	38.80 ± 4.46^{c}
SR8	5	25.49 ± 3.92^{c}	31.37 ± 4.72^{c}	39.22 ± 4.72^{c}	19.60 ± 3.61^{a}
	10	37.26 ± 3.92^{c}	43.14 ± 5.61^{c}	45.10 ± 4.96^{c}	29.41 ± 4.29^{c}
	20	46.04 ± 5.99^{c}	56.03 ± 5.92^{c}	60.02 ± 5.05^{c}	38.05 ± 3.68^{c}
SR9	5	22.48 ± 2.58^{c}	26.56 ± 4.46^{c}	34.72 ± 4.08^{c}	18.40 ± 2.58^{b}
	10	36.05 ± 2.52^{c}	42.04 ± 3.68^{c}	44.04 ± 3.99^{c}	28.05 ± 4.37^{c}
	20	42.04 ± 3.68^{c}	56.03 ± 3.99^{c}	58.02 ± 4.09^{c}	36.05 ± 2.52^{c}
SR10	5	22.48 ± 2.58^{b}	28.60 ± 3.76^{c}	30.64 ± 5.16^{c}	18.40 ± 4.08^{a}
	10	33.33 ± 3.92^{c}	37.26 ± 2.48^{c}	45.10 ± 3.92^{c}	31.37 ± 3.61^{c}
	20	45.10 ± 4.96^{c}	50.98 ± 4.96^{c}	56.86 ± 4.96^{c}	37.26 ± 2.48^{c}
Control		1.852 ± 1.85^{Ns}	5.787 ± 2.59^{Ns}	7.870 ± 2.50^{Ns}	3.935 ± 2.49^{Ns}
Std	5	21.76 ± 2.20^{c}	31.48 ± 2.62^{c}	35.42 ± 4.41^{c}	17.59 ± 2.52^{b}
	10	35.18 ± 3.89^{c}	42.82 ± 5.20^{c}	48.61 ± 5.83^{c}	29.17 ± 3.42^{c}
	20	48.15 ± 4.47^{c}	58.33 ± 4.40^{c}	62.04 ± 3.54^{c}	37.96 ± 3.54^{c}

NS, Not significant. Data expressed as mean ± standard error of the mean from six different experiments carried out in duplicate. Significance levels $^{a}p < 0.05$, $^{b}p < 0.01$, and $^{c}p < 0.001$ as compared with the respective control.

EXPERIMENTAL

Melting points (mp) were taken in open capillaries on Thomas Hoover melting point apparatus (Thomas Hoover, Philadelphia, PA) and are uncorrected. The IR spectra were recorded in film or in potassium bromide disks on a Perkin-Elmer 398 spectrometer (Bio Engineering, Wald, Switzerland). The ^{1}H NMR spectra were recorded on a DPX-300 MHz Bruker FT-NMR spectrometer (Pacific Northwest, Richland, WA). The chemical shifts were reported as parts per million (δ ppm) tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a JEOL-SX-102 instrument (Maspec, Tokyo, Japan) using fast atom bombardment (FAB positive). Elemental analysis was performed on a Perkin-Elmer 2400 CHN analyzer (Bio Engineering, Wald, Switzerland). and values were within the acceptable limits of the calculated values (± 0.4%). Spectral data (IR, NMR and mass spectra) confirmed the structures of the synthesized compounds; the purity of these compounds was ascertained by microanalysis. Elemental (C, H, N) analysis indicated that the calculated and observed values were within the acceptable limits (± 0.4%). The progress of the reaction was monitored on ready made silica gel plates (Merck Whitehouse Station, NJ) using chloroform/methanol (9:1) as a solvent system. Iodine was used as a developing agent. All chemicals and reagents used in the synthesis were obtained from Aldrich (Sigma-Aldrich, Spruce St. St. Louis, MO), or Spectrochem Pvt.Ltd (Mumbai, India) and were used without further purification.

***3-propyl-2-thioxo-2,3-dihydro-1H*-quinazolin-4-one (4)**. A solution of propyl amine (1.31 g, 0.02 mol) in dimethyl sulfoxide (10 mL) was stirred vigorously. To this was added carbon disulphide (1.6 mL) and aqueous sodium hydroxide (1.2 mL of 20 *M* solution) dropwise during 30 min with stirring. Dimethyl sulfate (2.5 g, 0.02 mol) was then added gradually keeping the reaction mixture in freezing mixture with stirring, and the stirring was continued for further 2 h. The reaction mixture was then poured into ice water and the solid obtained was filtered, washed with water, dried, and recrystallized from ethanol.

Table 2

Anti-inflammatory activity of synthesized compounds (**SR1–SR10**)

Compound code	Dose (mg/kg)	Percent protection			
		30 min	1 h	2 h	3 h
SR1	5	26.31 ± 6.37^{b}	34.92 ± 5.52^{c}	39.29 ± 2.38^{c}	24.49 ± 2.91^{b}
	10	28.94 ± 9.48^{b}	52.77 ± 5.84^{c}	55.14 ± 1.70^{c}	40.47 ± 2.41^{c}
	20	53.40 ± 4.14^{c}	63.04 ± 1.34^{c}	68.89 ± 1.44^{c}	42.08 ± 4.13^{c}
SR2	5	36.05 ± 10.12^{b}	42.46 ± 7.15^{c}	44.93 ± 3.99^{c}	29.92 ± 1.46^{a}
	10	44.73 ± 1.17^{c}	56.74 ± 2.70^{c}	57.58 ± 1.98^{c}	42.09 ± 0.68^{c}
	20	54.38 ± 4.64^{c}	63.88 ± 1.88^{c}	69.11 ± 1.73^{c}	46.19 ± 1.97^{c}
SR3	5	27.19 ± 9.35^{a}	33.32 ± 6.05^{b}	36.01 ± 4.08^{c}	20.97 ± 1.38^{a}
	10	42.10 ± 3.84^{c}	47.78 ± 3.92^{c}	49.16 ± 2.10^{c}	41.11 ± 3.19^{c}
	20	53.50 ± 9.25^{c}	61.57 ± 6.27^{c}	62.69 ± 3.46^{c}	46.19 ± 2.24^{c}
SR4	5	28.06 ± 6.32^{c}	28.57 ± 4.47^{c}	32.11 ± 1.32^{c}	19.21 ± 2.306^{b}
	10	33.33 ± 11.90^{a}	37.69 ± 7.66^{b}	42.92 ± 5.19^{b}	30.65 ± 2.07^{a}
	20	50.87 ± 11.9^{c}	45.23 ± 7.11^{c}	49.16 ± 2.71^{c}	32.43 ± 3.22^{a}
SR5	5	29.82 ± 10.93^{a}	29.36 ± 7.23^{a}	33.07 ± 2.04^{b}	20.09 ± 1.74^{a}
	10	41.23 ± 14.47^{a}	42.45 ± 10.11^{a}	44.05 ± 5.34^{b}	31.38 ± 3.83^{a}
	20	42.98 ± 12.99^{c}	54.76 ± 2.94^{c}	57.14 ± 3.51^{c}	41.06 ± 3.64^{b}
SR6	5	21.92 ± 9.15^{a}	24.20 ± 15.02^{a}	26.69 ± 4.17^{a}	17.46 ± 1.65^{a}
	10	25.43 ± 7.24^{a}	31.35 ± 6.88^{c}	34.27 ± 5.01^{c}	24.50 ± 4.63^{a}
	20	39.47 ± 13.57^{b}	40.47 ± 9.91^{b}	42.49 ± 6.68^{b}	31.38 ± 3.78^{a}
SR7	5	25.44 ± 9.64^{c}	28.96 ± 6.54^{c}	30.71 ± 3.64^{c}	21.36 ± 1.97^{b}
	10	35.96 ± 12.19^{a}	33.33 ± 8.06^{a}	38.70 ± 5.78^{b}	22.58 ± 1.89^{a}
	20	43.86 ± 11.98^{b}	40.47 ± 9.91^{b}	42.49 ± 6.68^{b}	31.38 ± 3.78^{a}
SR8	5	26.31 ± 8.80^{a}	28.57 ± 5.46^{b}	30.70 ± 4.83^{b}	19.67 ± 1.94^{a}
	10	28.94 ± 8.34^{a}	35.71 ± 9.17^{b}	41.15 ± 5.62^{c}	28.01 ± 3.42^{a}
	20	39.47 ± 12.14^{b}	39.28 ± 7.89^{b}	50.81 ± 3.50^{c}	32.26 ± 2.42^{a}
SR9	5	23.68 ± 6.19^{b}	30.95 ± 6.30^{c}	34.70 ± 3.96^{c}	22.38 ± 2.65^{a}
	10	33.33 ± 12.05^{b}	35.31 ± 3.81^{b}	38.71 ± 3.36^{b}	25.81 ± 3.02^{a}
	20	47.40 ± 10.53^{c}	47.22 ± 7.41^{c}	50.38 ± 4.86^{c}	35.64 ± 3.50^{b}
SR10	5	23.80 ± 7.49^{a}	28.17 ± 7.41^{a}	30.69 ± 3.15^{a}	17.91 ± 2.41^{a}
	10	27.19 ± 8.85^{a}	34.52 ± 7.08^{b}	44.92 ± 5.98^{c}	23.46 ± 2.77^{a}
	20	31.57 ± 11.21^{a}	44.84 ± 5.91^{c}	49.38 ± 4.01^{c}	30.80 ± 3.62^{a}
Std	5	16.66 ± 4.38^{a}	24.20 ± 5.47^{b}	30.66 ± 4.68^{c}	20.17 ± 1.82^{b}
	10	32.45 ± 9.83^{b}	36.50 ± 4.33^{c}	43.78 ± 3.69^{c}	33.04 ± 2.97^{b}
	20	41.22 ± 8.74^{c}	54.36 ± 6.06^{c}	65.11 ± 4.49^{c}	47.22 ± 8.06^{c}

Data expressed as mean ± standard error of the mean from six different experiments carried out in duplicate. Significance levels $^{a}p < 0.05$, $^{b}p < 0.01$, and $^{c}p < 0.001$ as compared with the respective control.

The methyl anthranilate **(3)** (1.5 g, 0.01 mol) and the previously prepared *N*-(propyl) methyl dithiocarbamic acid (0.01 mol) were dissolved in ethanol (20 mL). To this, anhydrous potassium carbonate (100 mg) was added and refluxed for 24 h. The reaction mixture was cooled in ice, and the solid separated was filtered and purified by dissolving in 10% alcoholic sodium hydroxide solution and reprecipitating by the treatment with dilute hydrocholoric acid. The solid obtained was filtered, washed with water, and dried. It was recrystallized from ethanol to afford **(4)**. Yield = 86%, mp 283–285°C; IR (KBr) cm^{-1}: 3242 (NH), 1666 (C = O), 1218 (C = S); ^{1}H-NMR ($CDCl_3$) δ: 0.82–0.89 (t, 3H, $CH_2CH_2CH_3$), 1.25–1.28 (m, 2H, $CH_2CH_2CH_3$), 1.72–1.73 (t, 2H, $CH_2CH_2CH_3$), 6.64–6.66 (m, 2H, Ar-H), 7.74–7.88 (m, 2H, Ar-H), 10.26 (br s, 1H, NH, D_2O Exchangeable); mass spectrometry (MS) (m/z): 220 (M^+); *Anal*. Calcd for $C_{11}H_{12}N_2OS$: C, 60.05%; H, 5.49%; N, 12.73%. Found: C, 60.21%; H, 5.42%; N, 12.70%.

***2-methylsulfanyl-3-propyl-3H*-quinazolin-4-one (5)**. The 3-propyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **(4)** (0.01 mol) was dissolved in 40 mL of 2% alcoholic sodium hydroxide solution. To this dimethyl sulfate (0.01 mol) was added dropwise with stirring. The stirring was continued for 1 h; the reaction mixture was then poured into ice water. The solid obtained was filtered, washed with water, dried, and recrystallized from ethanol. Yield = 89%, mp 180–181°C; IR (KBr) cm^{-1}: 1682 (C = O), 1603 (C = N); ^{1}H-NMR ($CDCl_3$) δ: 0.95–0.99 (t, 3H, $CH_2CH_2CH_3$), 1.72–1.74 (m, 2H, $CH_2CH_2CH_3$), 2.65–2.70 (t, 2H, $CH_2CH_2CH_3$), 2.91 (s, 3H, SCH_3), 6.64–6.66 (m, 2H, Ar-H), 7.74–7.75 (m, 2H, Ar-H), 7.87–7.88 (m, 2H, Ar-H); MS (m/z): 234 (M^+); *Anal*. Calcd for $C_{12}H_{14}N_2OS$: C, 61.59%; H, 6.02%; N, 11.97%. Found: C, 61.53%; H, 6.05%; N, 11.92%.

***2-hydrazino-3-propyl-3H*-quinazolin-4-one (6)**. The 2-methylsulfanyl-3-propyl-3*H*-quinazolin-4-one **(5)** (0.01 mol) was dissolved in ethanol (25 mL). To this hydrazine hydrate (99%, 0.1 mol) and anhydrous potassium carbonate (100 mg) were added and refluxed for 29 h. The reaction mixture was cooled and poured into ice water. The solid so obtained was filtered, washed with water, dried, and recrystallized from chloroform: benzene (25:75) mixture. Yield = 78%, mp 202–204°C; IR (KBr) cm^{-1}: 3310, 3226 (NH NH_2), 1680 (C = O), 1610 (C = N); ^{1}H-NMR ($CDCl_3$): δ 0.91–0.99 (t, 3H, $CH_2CH_2CH_3$), 1.68–1.79 (m, 2H, $CH_2CH_2CH_3$), 2.68–2.74 (t, 2H, $CH_2CH_2CH_3$), 4.65 (br s, 2H, NH_2 D_2O Exchangeable), 7.74 (s, 1H, Ar-H), 7.76 (d, J = 7.5 Hz, 1H, Ar-H),

7.87–7.88 (m, 2H, Ar-H), 8.51 (br s, 1H, NH D_2O Exchangeable); MS (m/z): 218 (M^+); *Anal*. Calcd for $C_{11}H_{14}N_4O$: C, 60.60%; H, 6.47%; N, 25.70%. Found: C, 60.63%; H, 6.49%; N, 25.78%.

***2-(1-methylpropylidene-hydrazino)-3-propyl--3H*-quinazolin-4-one (SR1)**. A mixture of 2-hydrazino-3-propyl-3*H*-quinazolin-4-one **(6)** (0.004 mol) and ethyl methyl ketone (0.004 mol) in glacial acetic acid was refluxed for 34 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol. Yield = 78%, mp 213–14°C; IR (KBr) cm^{-1}: 3340 (NH), 1670 (C = O), 1619 (C = N); ^{1}H-NMR ($CDCl_3$): δ 0.98–1.04 (t, 3H, $CH_2CH_2CH_3$), 1.23–1.24 (m, 2H, CH_2CH_3), 1.61–69 (t, 2H, $CH_2CH_2CH_3$), 1.70–1.72 (t, 3H, CH_2CH_3), 2.48 (s, 3H, CH_3), 2.81–2.96 (m, 2H, $CH_2CH_2CH_3$), 7.31 (s, 1H, Ar-H), 7.44 (d, J = 7.5 Hz, 1H, Ar-H), 7.46–7.48 (m, 2H, Ar-H), 10.86 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 272 (M^+); *Anal*. Calcd for $C_{15}H_{20}N_4O$: C, 66.15%; H, 7.40%; N, 20.57%. Found: C, 66.11%; H, 7.43%; N, 20.64%.

***2-(1-ethyl propylidene-hydrazino)-3-propyl-3H*-quinazolin-4-one (SR2)**. A mixture of 2-hydrazino-3-propyl-3*H*-quinazolin-4-one **(6)** (0.004 mol) and diethyl ketone (0.004 mol) in glacial acetic acid was refluxed for 34 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol. Yield = 74%, mp 228–229 °C; IR (KBr) cm^{-1}: 3311 (NH), 1680 (C = O), 1608 (C = N); ^{1}H-NMR ($CDCl_3$): δ 1.04–1.10 (t, 3H, $CH_2CH_2CH_3$), 1.15–1.21 (t, 2H, $CH_2CH_2CH_3$), 1.37–1.43 (m, 6H, $(CH_2CH_3)_2$), 1.78–1.90 (m, 4H, $(CH_2CH_3)_2$), 2.83–2.90 (m, 2H, $CH_2CH_2CH_3$), 7.48 (s, 1H, Ar-H), 7.51 (d, J = 7.5 Hz, 1H, Ar-H), 7.62 (s, 1H, Ar-H), 7.68 (d, J = 8.0 Hz, 1H, Ar-H), 9.03 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 286 (M^+); *Anal*. Calcd for $C_{16}H_{22}N_4O$: C, 67.10%; H, 7.74%; N, 19.56%. Found: C, 67.13%; H, 7.72%; N, 19.51%.

***2-(cyclohexylidene-hydrazino)-3-propyl-3H*-quinazolin-4-one (SR3)**. A mixture of 2-hydrazino-3-propyl-3*H*-quinazolin-4-one **(6)** (0.004 mol) and cyclohexanone (0.004 mol) in glacial acetic acid was refluxed for 31 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol. Yield = 78%, mp 230–231°C; IR (KBr) cm^{-1}: 3250 (NH), 1685 (C = O), 1610 (C = N); ^{1}H-NMR ($CDCl_3$): δ 1.10–1.22 (t, 3H, $CH_2CH_2CH_3$), 1.29–1.86 (m, 10H, CH_2 cyclohexyl), 1.93–2.07 (t, 2H, $CH_2CH_2CH_3$), 2.41–2.49 (m, 2H, $CH_2CH_2CH_3$), 7.38 (s, 1H, Ar-H), 7.48 (d, J = 7.5 Hz, 1H, Ar-H), 7.52 (s, 1H, Ar-H), 7.99 (d, J = 8.0 Hz, 1H, Ar-H), 9.32 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 298 (M^+); *Anal*. Calcd for $C_{17}H_{22}N_4O$: C, 68.43%; H, 7.43%; N, 18.77%. Found: C, 68.49%; H, 7.47%; N, 18.74%.

***2-(N-1-phenylethylidene-hydrazino)-3-propyl-3H*-quinazolin-4-one (SR4)**. A mixture of 2-hydrazino-3-propyl-3*H*-quinazolin-4-one **(6)** (0.004 mol) and acetophenone (0.004 mol) in glacial acetic acid was refluxed for 30 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol. Yield = 74%, mp 223–225°C; IR (KBr) cm^{-1}: 3290 (NH), 1680 (C = O), 1608 (C = N); ^{1}H-NMR ($CDCl_3$): δ 0.95–1.06 (t, 3H, $CH_2CH_2CH_3$), 1.45–1.56 (t, 2H, $CH_2CH_2CH_3$), 1.94 (s, 3H, CH_3), 2.31–2.39 (m, 2H, $CH_2CH_2CH_3$), 7.34–7.36 (m, 2H, Ar-H), 7.38 (s, 1H, Ar-H), 7.41 (d, J = 2.5 Hz, 1H, Ar-H), 7.52 (s, 1H, Ar-H), 7.64 (d, J = 8.0 Hz, 2H, Ar-H), 8.01 (d, J = 8.0 Hz, 2H, Ar-H), 9.04 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 320 (M^+); *Anal*. Calcd for $C_{19}H_{20}N_4O$: C, 71.22%; H, 6.29%; N, 17.48%. Found: C, 71.28%; H, 6.27%; N, 17.49%.

***2-(benzylidene-hydrazino)-3-propyl-3H*-quinazolin-4-one (SR5)**. A mixture of 2-hydrazino-3-propyl-3*H*-quinazolin-4-one **(6)** (0.004 mol) and benzaldehyde (0.004 mol) in glacial acetic acid was refluxed for 31 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol. Yield = 73%, mp 251–252°C; IR (KBr) cm^{-1}: 3360 (NH), 1693 (C = O), 1608 (C = N); ^{1}H-NMR ($CDCl_3$): δ 1.21–1.34 (t, 3H, $CH_2CH_2CH_3$), 1.42–1.49 (m, 2H, $CH_2CH_2CH_3$), 2.34–2.87 (t, 2H, $CH_2CH_2CH_3$), 6.00 (s, 1H, CH), 7.32–7.34 (m, 2H, Ar-H), 7.36 (s, 1H, Ar-H), 7.43 (d, J = 2.5 Hz, 1H, Ar-H), 7.54 (s, 1H, Ar-H), 7.62 (d, J = 8.0 Hz, 2H, Ar-H), 8.23 (d, J = 8.0 Hz, 2H, Ar-H), 9.01 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 306 (M^+); *Anal*. Calcd for $C_{18}H_{18}N_4O$: C, 70.56%; H, 5.92%, N, 18.28%. Found: C, 70.51%; H, 5.95%; N, 18.37%.

***2-(N-(4-chloro-benzylidene-hydrazino)-3-propyl-3H*-quinazolin-4-one (SR6)**. A mixture of 2-hydrazino-3-propyl-3*H*-quinazolin-4-one **(6)** (0.004 mol) and 4-chlorobenzaldehyde (0.004 mol) in glacial acetic acid was refluxed for 33 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol. Yield = 79% yield, mp 223–224°C; IR (KBr) cm^{-1}: 3260 (NH), 1682 (C = O), 1610 (C = N); ^{1}H-NMR ($CDCl_3$): δ 1.11–1.21 (t, 3H, $CH_2CH_2CH_3$), 1.61–1.70 (m, 2H, $CH_2CH_2CH_3$), 2.51-2.64 (t, 2H, $CH_2CH_2CH_3$), 6.01 (s, 1H, CH), 7.34 (s, 1H, Ar-H), 7.38 (s, 1H, Ar-H), 7.44 (d, J = 2.5 Hz, 1H, Ar-H), 7.54 (s, 1H, Ar-H), 7.67 (d, J = 8.0 Hz, 2H, Ar-H), 8.01 (d, J = 8.0 Hz, 2H, Ar-H), 9.21 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 341 (M^+); *Anal*. Calcd for $C_{18}H_{17}N_4OCl$: C, 63.43%; H, 5.02%; N, 16.43%. Found: C, 63.40%; H, 5.06%; N, 16.35%.

***2-(N-(4-nitro-benzylidene-hydrazino))-3-propyl-3H*-quinazolin-4-one (SR7)**. A mixture of 2-hydrazino-3-propyl-3*H*-quinazolin-4-one **(6)** (0.004 mol) and 4-nitrobenzaldehyde (0.004 mol) in glacial acetic acid was refluxed for 34 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol. Yield = 78%, mp 252–254°C; IR (KBr) cm^{-1}: 3221 (NH), 1690 (C = O), 1608 (C = N); ^{1}H-NMR ($CDCl_3$): δ 1.08-1.16 (t, 3H, $CH_2CH_2CH_3$), 1.63–1.71 (m, 2H, $CH_2CH_2CH_3$), 2.62-2.64 (t, 2H, $CH_2CH_2CH_3$), 6.03 (s, 1H, CH), 7.24 (s, 1H, Ar-H), 7.32 (s, 1H, Ar-H), 7.47 (d, J = 2.5 Hz, 1H, Ar-H), 7.57 (s, 1H, Ar-H), 7.69 (d, J = 8.0 Hz, 2H, Ar-H), 8.05 (d, J = 8.0 Hz, 2H, Ar-H), 8.83 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 351 (M^+); *Anal*. Calcd for $C_{18}H_{17}N_5O_3$: C, 61.53%; H, 4.87%; N, 19.93%. Found: C, 61.56%; H, 4.84%; N, 19.90%.

***2-(N-(4-methoxy-benzylidene-hydrazino))-3-propyl-3H*-quinazolin-4-one (SR8)**. A mixture of 2-hydrazino-3-propyl-3*H*-quinazolin-4-one **(6)** (0.004 mol) and 4-methoxybenzaldehyde (0.004 mol) in glacial acetic acid was refluxed for 32 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol. Yield = 74%, mp 235–236°C; IR (KBr) cm^{-1}: 3319 (NH), 1684 (C = O), 1602 (C = N); ^{1}H-NMR ($CDCl_3$): δ 1.06-1.16 (t, 3H, $CH_2CH_2CH_3$), 1.51–1.62 (m, 2H, $CH_2CH_2CH_3$), 2.10–2.23 (t, 2H, $CH_2CH_2CH_3$), 3.12 (s, 3H, OCH_3), 6.10 (s, 1H, CH), 7.54 (s, 1H, Ar-H), 7.56 (s, 1H, Ar-H), 7.64 (d, J = 2.5 Hz, 1H, Ar-H), 7.68 (s, 1H, Ar-H), 7.70 (d, J = 8.0 Hz, 2H, Ar-H), 8.04 (d, J = 8.0 Hz, 2H, Ar-H), 9.51 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 336 (M^+); *Anal*. Calcd for $C_{19}H_{20}N_4O_2$: C, 67.83%; H, 5.99%; N, 16.65%. Found: C, 67.86%; H, 5.95%; N, 16.60%.

***2-(N-(4-methyl-benzylidene-hydrazino)-3-propyl-3H*-quinazolin-4-one (SR9)**. A mixture of 2-hydrazino-3-propyl-3*H*-quinazolin-4-one **(6)** (0.004 mol) and 4-methylbenzaldehyde (0.004 mol) in glacial acetic acid was refluxed for 30 h. The reaction mixture was poured into ice water. The solid obtained was

recrystallized from ethanol. Yield = 78%, mp 279–280°C; IR (KBr) cm^{-1}: 3285 (NH), 1685 (C = O), 1612 (C = N); ^{1}H-NMR ($CDCl_3$): δ 1.08-1.16 (t, 3H, $CH_2CH_2CH_3$), 1.82–1.96 (m, 2H, $CH_2CH_2CH_3$), 2.62–2.68 (t, 2H, $CH_2CH_2CH_3$), 2.90 (s, 3H, CH_3), 6.05 (s, 1H, CH), 7.44 (s, 1H, Ar-H), 7.48 (s, 1H, Ar-H), 7.52 (d, J = 2.5 Hz, 1H, Ar-H), 7.54 (s, 1H, Ar-H), 7.67 (d, J = 8.0 Hz, 2H, Ar-H), 8.12 (d, J = 8.0 Hz, 2H, Ar-H), 9.62 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 320 (M^+); *Anal*. Calcd for $C_{19}H_{20}N_4O$: C, 71.22%; H, 6.29%; N, 17.48%. Found: C, 71.23%; H, 6.26%; N, 17.42%.

***2-(N-phenyl-benzylidene-hydrazino)-3-propyl-3H*-quinazolin-4-one (SR10)**. A mixture of 2-hydrazino-3-propyl-3*H*-quinazolin-4-one **(6)** (0.004 mol) and diphenyl ketone (0.004 mol) in glacial acetic acid was refluxed for 36 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol. Yield = 78%, mp 282–283°C; IR (KBr) cm^{-1}: 3268 (NH), 1685 (C = O), 1605 (C = N); ^{1}H-NMR ($CDCl_3$): δ 1.02-1.08 (t, 3H, $CH_2CH_2CH_3$), 1.32–1.41 (m, 2H, $CH_2CH_2CH_3$), 2.56–2.68 (t, 2H, $CH_2CH_2CH_3$), 6.03 (s, 1H, CH), 7.44 (s, 1H, Ar-H), 7.46–7.47 (m, 2H, ArH), 7.48 (s, 1H, Ar-H), 7.52 (d, J = 2.5 Hz, 1H, Ar-H), 7.50 (d, J = 7.5 Hz, 2H, Ar-H), 7.54 (s, 1H, Ar-H), 7.67 (d, J = 8.0 Hz, 2H, Ar-H), 8.12 (d, J = 8.0 Hz, 2H, Ar-H), 8.24 (d, J = 8.0 Hz, 2H, Ar-H), 9.06 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 382 (M^+); *Anal*. Calcd for $C_{24}H_{22}N_4O$: C, 75.37%; H, 5.79%; N, 14.64%. Found: C, 75.32%; H, 5.73%; N, 14.61%.

Pharmacology. The synthesized compounds were evaluated for analgesic and anti-inflammatory activities. Student *t*-test was performed to ascertain the significance of all the exhibited activities. The test compounds and the standard drugs were administered in the form of a suspension (1% carboxy methyl cellulose as a vehicle) by oral route. Each group consisted of six animals. The animals were maintained in colony cages at 25 ± 2°C, relative humidity of 45–55%, under a 12 h light and dark cycle; they were fed standard animal feed. All the animals were acclimatized for a week before use. The Institutional Animal Ethics committee approved the protocol adopted for the experimentation of animals.

Analgesic activity. Test for analgesic activity was performed by tail-flick technique [14,15] using Wistar albino mice (25–35 g) of either sex selected by random sampling technique. Diclofenac sodium at a dose level of 5, 10, and 20 mg/kg was administered orally as reference drug for comparison. The test compounds at three dose levels (5, 10, 20 mg/kg) were administered orally. The reaction time was recorded at 30 min, 1, 2, and 3 h after the treatment, and cut-off time was 10 s. The percent analgesic activity was calculated by the following formula,

$$\mathrm{PAA} = \left[\frac{T_2 - T_1}{10 - T_1}\right] X\ 100$$

where T_1 is the reaction time (s) before treatment, and T_2 is the reaction time (s) after treatment.

Anti-inflammatory activity. Anti-inflammatory activity was evaluated by Carrageenan-induced paw edema test in rats [16]. Diclofenac sodium 5, 10 and 20 mg/kg was administered as a standard drug for comparison. The test compounds were administered at three dose levels (5, 10 and 20 mg/kg). The paw volumes were measured using the mercury displacement technique with the help of a plethysmograph immediately before and 30 min, 1, 2, and 3 h after Carrageenan injection. The percent inhibition of paw edema was calculated using the following formula

$$\text{Percent inhibition I} = 100[1 - (a - x)/(b - y)]$$

Where x is the mean paw volume of rats before the administration of Carrageenan and test compounds or reference compound (test group), a is the mean paw volume of rats after the administration of Carrageenan in the test group (drug treated), b is the mean paw volume of rats after the administration of Carrageenan in the control group, y is the mean paw volume of rats before the administration of Carrageenan in the control group.

Statistical analysis. Statistical analysis of the biological activity of the synthesized compounds on animals was evaluated using a one-way analysis of variance. In all cases, post hoc comparisons of the means of individual groups were performed using Tukey's test. A significance level of $p < 0.05$ denoted significance in all cases. All values are expressed as mean ± standard deviation. For statistical analysis, we have used GraphPad Prism 3.0 version. (GraphPad Prism 3.0 version, GraphPad Software, Inc.11452 El Camino Real, #215, San Diego, CA 92130 USA).

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