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Synthesis of some new 2-(3-methyl-7-substituted-2-oxoquinoxalinyl)-5-(aryl)-1,3,4-oxadiazoles as potential non-steroidal anti-inflammatory and analgesic agents

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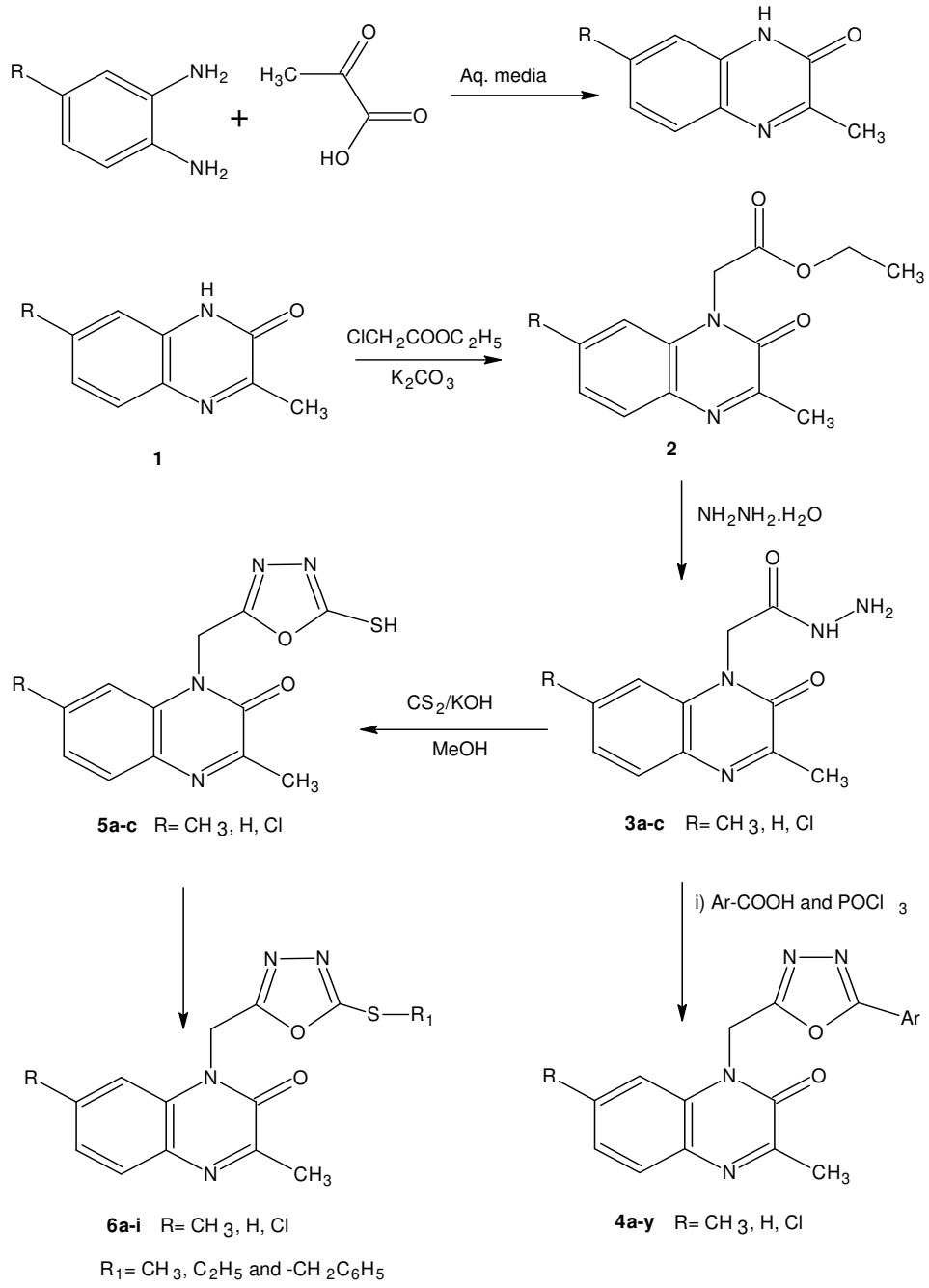
Ethyl (3-methyl-7-substituted-2-oxoquinoxalin-1(2*H*)-yl) acetates **2a-c** are prepared by the condensation of ethyl chloroacetate with 3-methyl-7-substituted quinoxalin-2(1*H*)-ones **1a-c**. The reaction of **2a-c** with hydrazine hydrate furnished 2-(3-methyl-7-substituted-2-oxoquinoxalin-1(2*H*)-yl) acetohydrazides **3a-c**, which on cyclisation with substituted aromatic carboxylic acids in the presence of phosphorous oxychloride give 3-methyl-7-substituted-1-[(5-aryl-1,3,4-oxadiazol-2-yl)methyl]quinoxalin-2(1*H*)-ones **4a-y**. Further, the compounds **3a-c** on cyclisation with carbon disulphide in methanolic potassium hydroxide yielded 1-[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]-3-methyl-7-substituted quinoxalin-2(1*H*)-ones **5a-c**. Finally, the compounds **5a-c** are converted to 3-methyl-7-substituted-1-{[5-(alkylsulfanyl)-1,3,4-oxadiazol-2-yl]methyl}quinoxalin-2(1*H*)-ones **6a-i** by reacting them with different alkyl halides. The newly synthesized compounds have been characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data and elemental analysis. Selected compounds are screened for *in vivo* anti-inflammatory and analgesic activity. Few of them exhibited promising activity.

Keywords: Quinoxaline, 1,3,4-oxadiazoles, alkyl halides, anti-inflammatory, analgesic activity

Derivatives of 1,3,4-oxadiazole constitute an important family of heterocyclic compounds[1]. Since many of them display a remarkable biological activity[2, 3] and find wide usage as dyes, photosensitive electrical materials, polymer precursors, stabilizers, their synthesis, and transformations have received great attention for a long time. Particularly, the 2-aryl-5-substituted-1,3,4-oxadiazoles have been reported to show antibacterial[4], antifungal[5,6], analgesic, anti-inflammatory[7,] and hypoglycemic activities. Similarly, a number of quinoxaline derivatives have been shown to possess a variety of pharmacological properties like antibacterial[8], antifungal[9], anti-tuberculosis[10], antitumor,[11] analgesic, antiviral[12], and anti-inflammatory[13], and hence quinoxaline is found to be an important structural feature in some synthetic drugs. Keeping this in view, it was thought worth-while to design the synthesis of title compounds wherein the biologically active quinoxaline is linked to potent 1,3,4-oxadiazole moiety, through methylene bridge. The present communication reports the multistep synthesis of hitherto unknown 3-methyl-7-substituted-1-{[5-(aryl)-1,3,4-oxadiazol-2-yl]methyl}-quinoxalin-2(1*H*)-ones **4a-y**, 1-[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]-3-methyl-7-substituted quino-xalin-2(1*H*)-ones **5a-c** and 3-methyl-7-sustituted-1-{[5-(alkylsulfanyl)-1,3,4-oxadiazol-2-yl]methyl}quin-oxalin-2(1*H*)-ones **6a-i** and evaluation of their anti-inflammatory and analgesic activities.

Results and Discussion

The target compounds were synthesized according to the representative **Scheme I**. The required starting material, 3,7-dimethylquinoxalin-2(1*H*)-one **1a** was prepared in good yield by condensation of 3,4-diaminotoluene with pyruvic acid at acidic *p*H. The reaction of **1a** with ethyl chloroacetate, in the presence of potassium carbonate under refluxing condition yielded ethyl (3,7-dimethyl-2-oxoquino-xalin-1(2*H*)-yl)acetate **2a**, which on reaction with hydrazine hydrate in methanol at 65^{o}C gave 2-(3,7-dimethyl-2-oxoquinoxalin-1(2*H*)-yl)acetohydrazide **3a**. The compound **3a** was reacted with different aromatic carboxylic acid in the presence of phosphorous



Scheme I

oxychloride give the title compounds 3,7-dimethyl-1-[(5-substituted phenyl-1,3,4-oxadiazol-2-yl)methyl]-quinoxalin-2(1*H*)-one **4a-h**. The hydrazide **3a**, on refluxing with carbon disulphide and potassium hydroxide in methanol was converted to 1-[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]-3,7-dimethyl-quinoxalin-2(1*H*)-one **5a** in good yield. Finally, the compound **5a** was conveniently alkylated by condensing it with different alkyl halides to give 3,7-dimethyl-1-{[5-(alkylsulfanyl)-1,3,4-oxadiazol-2-yl]-methyl}quinoxalin-2(1*H*)-ones **6a-c**. Similarly the compounds **4i-y** and **6d-i** were prepared in good yield.

The structural assignments to the new compounds were based on their elemental analysis and IR, ^{1}H NMR, ^{13}C NMR and mass spectra. The formation of 3,7-dimethylquinoxalin-2(1*H*)-one **1a** was confirmed by its ^{1}H NMR and IR spectra. FTIR spectrum of it showed absorption bands at 3224, 1680, 1544 cm^{-1} owing to -NH, >C=O, and >C-C< groups respectively. Further, ^{1}H NMR spectrum of **1a** showed two sharp

singlets at δ 2.37 and δ 2.50 indicating the presence of two methyl groups. The appearance of two doublets at δ 7.15 and δ 7.27 was due to two aromatic protons of quinoxaline and two singlets at δ 7.48 and 7.55 were due to –NH group and an aromatic proton of quinoxaline ring respectively. In the mass spectrum, it revealed molecular ion peak at *m/z* 175 (100%), which matches with its molecular formula $C_{10}H_{10}N_2O$. The synthesis of **2a** from **1a** was confirmed by recording its NMR and IR spectra. A quartet at 4.24 and a triplet at 1.30 clearly indicate the incorporation of ester. Further, the formation of **3a** was confirmed by its IR and ^1H NMR spectral data. Its FTIR spectrum showed strong peaks at 3340 and 1620 cm^{-1} indicating the presence of -$NHNH_2$ and >C=O groups respectively, while its ^1H NMR spectrum showed a broad peak at δ 2.74 and a sharp peak at 8.60 confirming the presence of –$NHNH_2$ group. The mass spectrum of it showed a molecular ion peak at *m/z* 247 (50%), which matches with its molecular formula $C_{12}H_{14}N_2O_2$.

Formation of oxadiazoles from **3a** was confirmed by IR, ^1H NMR, ^{13}C NMR and mass spectral studies. In IR spectrum of compound **4a** the typical absorption bands due to carbonyl and $NHNH_2$ group of hydrazide **3a** were absent. The absorption bands corresponding to C=N stretching of oxadiazole ring were seen at 1611-1602 cm^{-1}. Further the mass spectrum of **4a** showed a molecular ion peak at *m/z* 347 (100%), which is in agreement with its molecular formula $C_{20}H_{18}N_4O_2$. In FTIR spectrum of **5a**, weak absorption band due to SH functional group was found at 2355 cm^{-1} and the typical absorption bands due to carbonyl and $NHNH_2$ group of hydrazide **3a** were absent. In IR spectrum of the alkylated products **6a** this band was absent. Absorption bands at 700-703 and 1258-1268 cm^{-1} were attributed to C-S-C and C=S functional group in compound **5a.** Physical and elemental analysis data of **4a-y** and **6a-i** are listed in **Tables I** and **II** respectively.

The anti-inflammatory activity of the compounds **4a-y** and **6a-i** were evaluated by carrageenan-induced paw edema method. The compounds were tested at 50 mg/kg dose and the results were compared with that of indomethacin as a reference drug. The results are summarized in **Table-III**. Few of the compounds showed good inhibition against carrageenan-induced edema in rats. The results of anti-inflammatory screening are in the range of 20.83 to 63.33%, whereas standard drug indomethacin showed an activity of 63.33% after 4 hr. Compounds **4a**, **4g**, **6a** and **6b** displayed good anti-inflammatory activity. It was observed that amongst the tested compounds **4a-y**, oxadiazole containing 7-methyl quinoxaline **4a** was found to exhibit higher activity (63.33%) than that of unsubstituted quinoxaline. It can be concluded that the presence of methyl group on position 7 of quinoxaline moiety and methoxy substitution to phenyl ring enhanced the activity considerably. The increased hydrophobic nature due to the presence of methyl group and electron releasing nature of methoxy group substituted at phenyl moiety in the structure may be responsible for the higher activity

The results of analgesic activity of resulting compounds **4a-y** and **6a-i** were evaluated by hot-plate method which is a well-established method of testing the analgesic activity of the compounds. The standard drug pethidine showed analgesic activity in the model used. The compounds **4a**, **4g**, **4o**, **4q** and **4w** displayed good analgesic activity which is comparable with the standard. Whereas rest of the tested compounds did not show analgesic activity in the model used. The preliminary results show that the introduction of electron donating substituents such as 4-OCH_3 (**4a**, **4q**), 3,4,5-$(OCH_3)_3$ (**4g**, **4o**, **4w**) in the aromatic ring significantly increases the analgesic activity. It is interesting to note that the compounds **4a** and **4g** manifested both anti-inflammatory and analgesic activities.

Anti-inflammatory activity results of the compounds showed good correlation with their analgesic activity. As seen in **Table-III**, the same derivatives **4a** and **4g** exhibited at 50 mg/kg as potent anti-inflammatory activity as indomethacin. R.Viniegra *et al.*[14] reported that edema produced by carrageenan is a biphasic event and the inhibitory effects of agents which act on the first stage of the carrageenan-induced hind paw inflammation are due to the inhibition of the chemical mediators such as histamine, serotonin and bradykinin, while the second stage of the edema may be related to the arachidonic acid metabolites since it is inhibited by pethidine, indomethacin and other cyclooxygenase inhibitors. As seen in **Table III**, the tested compounds exhibited considerable anti-inflammatory activity both in the first and second phases of edema and the activity did not show a significant increase in the second phase of the edema indicating that these compounds might exert their anti-inflammatory activities through the mechanisms that involve the inhibition of chemical mediators such as histamine and serotonin only. This explains the potent analgesic and anti-inflammatory activities of **4a** and **4g**.

Table I — Characterization data of compounds **4a-y**

Compd	Ar	Mole. formula	Mole. weight	m.p. (°C) / Crystal-lization solvent	Yield (%)	Analysis % Found (Calcd)		
						C	H	N
4a	$4(OCH_3)C_6H_4$	$C_{20}H_{18}N_4O_3$	362	$CHCl_3$ / 148-50	65	66.25 (66.29	4.95 4.97	11.58 11.60)
4b	$4(CH_3)C_6H_4$	$C_{20}H_{18}N_4O_2$	346	$CHCl_3$ / 148-50	67	69.29 (69.36	5.09 5.20	13.88 13.87)
4c	$3,5(Cl_2)C_6H_3$	$C_{19}H_{14}Cl_2N_4O_2$	401	$CHCl_3$ / 188-89	75	56.85 (56.80	3.49 3.45	13.96 14.02)
4d	$3(NH_2)C_6H_4$	$C_{19}H_{17}N_5O_2$	347	$CHCl_3$ / 228-30	64	65.70 (65.72	4.89 4.87	20.17 20.20)
4e	$4(NO_2)C_6H_4$	$C_{19}H_{15}N_5O_4$	377	$CHCl_3$ / 160-62	78	60.47 (60.45	5.95 5.98	16.80 16.82)
4f	$3,5(NO_2)_2C_6H_3$	$C_{19}H_{14}N_6O_6$	422	DMF / 196-98	75	54.12 (54.02	3.30 3.31	19.92 19.90)
4g	$3,4,5(OCH_3)_3C_6H_2$	$C_{22}H_{22}N_4O_5$	422	$CHCl_3$ / 136-38	62	62.55 (62.51	5.21 5.16	13.27 13.25)
4h	Quinoline	$C_{22}H_{17}N_5O_2$	383	DMF / 240-41	68	68.92 (68.90	4.43 4.55	18.30 18.25)
4i	$4(OCH_3)C_6H_4$	$C_{19}H_{16}N_4O_3$	348	$CHCl_3$ / 156-58	73	65.54 (65.51	4.60 4.59	16.13 16.09)
4j	$4(CH_3)C_6H_4$	$C_{19}H_{16}N_4O_2$	332	$CHCl_3$ / 145-47	73	68.67 (68.62	4.81 4.75	16.80 16.90)
4k	$3,5(Cl_2)_2C_6H_3$	$C_{18}H_{12}Cl_2N_4O_2$	387	DMF / 150-52	78	55.81 (55.75	3.10 3.14	14.47 14.53)
4l	$3(NH_2)C_6H_4$	$C_{18}H_{15}N_5O_2$	333	$CHCl_3$ / 303-05	61	64.86 (64.82	4.50 4.40	21.02 21.08)
4m	$3(NO_2)C_6H_4$	$C_{18}H_{13}N_5O_4$	363	$CHCl_3$ / 270-72	70	59.50 (59.45	3.58 3.50	19.28 19.35)
4n	$3,5(NO_2)_2C_6H_3$	$C_{18}H_{12}N_6O_6$	408	DMF / 298-300	78	52.90 (52.94	2.98 2.94	20.64 20.58)
4o	$3,4,5(OCH_3)_3C_6H_2$	$C_{21}H_{20}N_4O_5$	408	$CHCl_3$ / 146-48	65	61.76 (61.74	4.90 4.85	13.72 13.70)
4p	C_6H_5	$C_{18}H_{14}N_4O_2$	318	$CHCl_3$ / 180-82		67.76 (67.92	4.32 4.40	17.55 17.61)
4q	$4(OCH_3)C_6H_4$	$C_{19}H_{15}ClN_4O_3$	382.8	$CHCl_3$ / 148-50	71	59.52 (59.56	3.96 3.91	14.63 14.62)
4r	$4(CH_3)C_6H_4$	$C_{19}H_{15}ClN_4O_2$	366.8	$CHCl_3$ / 160-61	71	62.12 (62.08	4.08 4.12	15.25 15.32)
4s	$3,5(Cl_2)_2C_6H_3$	$C_{18}H_{11}Cl_3N_4O_2$	421	DMF / 130-32	82	51.32 (51.30	2.43 2.61	13.06 13.30)
4t	$3(NH_2)C_6H_4$	$C_{18}H_{14}ClN_5O_2$	367	$CHCl_3$ / 305-07	70	58.80 (58.85	3.76 3.81	19.10 19.07)
4u	$3(NO_2)C_6H_4$	$C_{18}H_{12}ClN_5O_4$	397	$CHCl_3$ / 120-22	72	54.38 (54.40	3.00 3.02	17.65 17.63)
4v	$3,5(NO_2)_2C_6H_3$	$C_{18}H_{11}ClN_6O_6$	443	DMF / 160-62	82	48.80 (48.75	2.43 2.48	18.94 18.96)
4w	$3,4,5(OCH_3)_3C_6H_2$	$C_{21}H_{19}ClN_4O_5$	443	$CHCl_3$ / 138-40	68	56.85 (56.88	4.26 4.28	12.60 12.64)
4x	Quinoline	$C_{21}H_{14}ClN_5O_2$	404	DMF / 290-92	69	62.35 (62.37	3.42 3.46	17.34 17.32)
4y	C_6H_5	$C_{18}H_{13}ClN_4O_2$	352.7	$CHCl_3$ / 130-32	74	61.35 (61.24	3.64 3.68	15.91 15.87)

Table II — Characterization data of compounds **6a-i**

Compd	R_1	Mole. formula	Mole. weight	m.p (°C) / Crystal-lization solvent	Yield (%)	Analysis % Found (Calcd)		
						C	H	N
6a	$-CH_3$	$C_{14}H_{14}N_4O_2S$	302	$CHCl_3$/ 120-22	75	55.60 (55.62	4.65 4.63	18.50 18.54)
6b	$-C_2H_5$	$C_{15}H_{16}N_4O_2S$	316	$CHCl_3$/ 176-78	80	56.90 (56.96	5.02 5.06	17.74 17.72)
6c	$-CH_2C_6H_5$	$C_{20}H_{18}N_4O_2S$	378	DMF / 288-90	69	63.46 (63.49	4.78 4.76	14.80 14.81)
6d	$-CH_3$	$C_{13}H_{12}N_4O_2S$	288	$CHCl_3$/ 110-12	78	54.18 (54.16	4.20 4.16	19.42 19.44)
6e	$-C_2H_5$	$C_{14}H_{14}N_4O_2S$	302	$CHCl_3$/ 136-38	79	55.60 (55.62	4.65 4.63	18.53 18.54)
6f	$-CH_2C_6H_5$	$C_{19}H_{16}N_4O_2S$	364	DMF/ > 300	65	62.60 (62.63	4.45 4.39	15.44 15.38)
6g	$-CH_3$	$C_{13}H_{11}ClN_4O_2S$	323	$CHCl_3$/ 150-52	81	48.20 (48.29	3.28 3.40	17.20 17.33)
6h	$-C_2H_5$	$C_{14}H_{13}ClN_4O_2S$	337	$CHCl_3$/ 132-34	78	49.76 (49.85	3.72 3.85	16.67 16.61)
6i	$-CH_2C_6H_5$	$C_{19}H_{15}ClN_4O_2S$	399	DMF/ > 300	70	57.06 (57.14	3.70 3.75	14.10 14.03)

Table III — Anti-inflammatory and analgesic activity of compounds **4a-y** and **6a-i**

Sl.No	Compd (50mg/kg, p.o)	Anti-inflammatory activity		Analgesic activity Time of reaction to pain stimulus at time (hr) [s] ± SEM		
		Increase in paw volume in mL	% inhibition of inflammation	0	1	3
1	2% Gum acacia (control)	1.2	—	—	—	—
2	Indomethacin (2 mg/kg)	0.44	63.33	—	—	—
3	Control (10mL/kg)	—	—	9.1	8.6	9.4
4	Pethidine (5 mg/kg)	—	—	8.9	16.4	13.8
5	**4a**	0.44	63.33	7.8	12.7	12.3
6	**4b**	0.58	51.66	7.8	10.3	8.2
7	**4c**	1.3	-8.33	8.4	8.1	7.9
8	**4d**	0.72	40.00	8.0	8.8	7.6
9	**4g**	0.47	60.83	7.9	11.9	12.5
10	**4i**	0.82	31.66	7.8	10.6	8.4
11	**4j**	0.95	20.83	7.4	8.3	7.9
12	**4l**	0.90	25.00	6.9	8.9	9.3
13	**4o**	0.49	59.16	7.6	12.5	12.3
14	**4q**	0.52	56.66	7.8	12.0	12.1
15	**4r**	0.50	58.33	8.6	10.1	10.2
16	**4w**	0.70	41.66	8.0	12.1	12.2
17	**6a**	0.48	60.00	8.4	8.1	9.4
18	**6b**	0.47	60.83	8.6	8.1	7.9
19	**6d**	0.62	48.33	8.1	10.3	9.5
20	**6h**	0.56	53.33	7.4	8.1	8.6

Experimental Section

Materials and Methods

Melting points were determined by open capillary and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. ^{1}H NMR spectra were recorded on Perkin-Elmer EM-390 (300 MHz) and Bruker WH-200 (400 MHz) spectrometers using TMS as an internal standard. ^{13}C NMR spectra were obtained on a Perkin-Elmer (Model RB-12, 100MHz) spectrometer. All chemical shifts are reported in ppm downfield from tetramethylsilane. The mass spectra were recorded on a Jeol JMS-D 300 mass spectrometer (FAB) operating at 70 eV. Elemental analysis was performed on a Flash E A 112 Thermo Electron Corporation CHNS analyzer. The purity of the compounds was checked by TLC on Merck silica gel 60 F_{254} precoated sheets using hexane and ethyl acetate 4:1. Starting materials were purchased from Aldrich Chemical Company or Spectrochem Chemical Company and used without further purification. All solvents were of analytical grade and freshly distilled prior to use.

3,7-Dimethylquinoxalin-2(1*H*)-one 1a

A mixture of 3,4-diamino toluene (12.21 g, 100 mmole) in aq. HCl (20%, 100 mL) and sodium pyruvate (12.2 g, 110 mmole) in aq. HCl (20%, 100 mL) was stirred at 40°C for 4 hr. Progress of the reaction was evidenced by the formation of thick solid and it was monitored by TLC (ethyl acetate/hexane, 1:1). After the completion of the reaction, the solid product separated was filtered, washed with water (2 × 50 mL) and dried. The crude product was purified by dissolving in hot aq. NaOH (5% w/v, 50 mL), followed by neutralization with acetic acid to a *p*H of 6.0 at 10°C. Finally, the isolated product was recrystalized from methylisobutylketone, to give 14.0 g (80%), pale yellow crystals, m.p. 245-46°C. IR (KBr, cm^{-1}): 3232 (NH), 1630.7 (C=O), 1578, 1530, 1389, 1358, 1378, 978, 834, 620 (Ar-H); MS (*m/z*, %): 175(M+1, 100), 174(M$^+$, 30), 154(10), 120(10), 107(20), 89(20), 77(10); ^{1}H NMR (DMSO-d_6): δ 7.55 (s, 1H, CH), 7.48 (s, 1H, NH), 7.27 (d, 1H, *J* = 8.8 Hz), 7.15 (d, 1H, *J* = 8.0 Hz), 2.50 (s, 3H, CH_3), 2.37 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): 20.18 (CH_3), 20.92 (CH_3), 118.72, 125.17, 125.83, 131.91, 135.04, 136.23 (aromatic carbons), 161.39 (N=C-CH_3), 166.96 (C=O); Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.96; H, 5.74; N, 16.09. Found: C, 68.93; H, 5.70; N, 16.10%. Similarly, the compounds **1b-c** were prepared.

1c: m.p. 240-41°C. IR (KBr, cm^{-1}): 3240 (NH), 1637 (C=O), 1580, 1389, 1351, 978, 834, 620 (Ar-H); MS (*m/z*, %): 195(M+1, 100), 194(M$^+$, 80), 120(10), 107(20), 89(20); ^{1}H NMR (DMSO-d_6): δ 7.81 (s, 1H, CH), 7.29 (d, 1H, *J* = 8.4 Hz), 7.17 (d, 1H, *J* = 8.4 Hz), 2.50 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): 20.62 (CH_3), 115.77, 125.31 126.32, 133.99, 136.67, (aromatic carbons), 161.43 (N=C-CH_3), 166.90 (C=O); Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 55.49; H, 3.59; N, 14.38. Found: C, 55.50; H, 3.70; N, 14.45%.

Ethyl (3,7-dimethyl-2-oxoquinoxalin-1(2*H*)-yl)acetate 2a

A mixture of **1a** (25 g, 143.6 mmole), ethyl chloroacetate (21 g, 172 mmole) and potassium carbonate (24 g, 174 mmole) were refluxed in 75 mL of acetone for 4 hr. Progress of the reaction was monitored by TLC (ethyl acetate/hexane, 1:1). After removal of acetone under reduced pressure, the residue was added to chilled water (500 mL), acidified with acetic acid. The solid separated was filtered, washed with water and finally crystallized from ethyl acetate to give 19.5 g (78%) brown solid. m.p. 98-100°C. IR (KBr, cm^{-1}): 1745 (C=O ester), 1548, 1398, 976, 889, 731 (Ar-H); MS (*m/z*, %): 261(M+1, 100), 260(M$^+$, 40), 232(10), 202(10), 107(20), 89(20), 77(10); ^{1}H NMR (DMSO-d_6): δ 7.25 (s, 1H, CH), 6.93 (d, 1H, CH, *J* = 8.6 Hz), 6.61 (d, 1H, *J* = 8.6 Hz), 5.01 (s, 2H, CH_2), 4.24 (q, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 1.27-1.30 (t, 3H, CH_3); ^{13}C NMR (DMSO-d_6): 14.00 (CH_3), 20.60 (CH_3), 21.85 (CH_3), 48.09 (CH_2), 59.37 (CH_2), 118.92, 122.94, 123.18, 133.49, 134.37, 137.40 (aromatic carbons), 162.24 (N=C-CH_3), 164.62 (C=O), 169.35 (C=O). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.61; H, 6.15; N, 10.76. Found: C, 64.58; H, 6.12; N, 10.88%. Compounds **2b** and **2c** were prepared following the general procedure.

2b: m.p. 128-30°C, Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.41; H, 5.69; N, 11.38. Found: C, 63.38; H, 5.71; N, 11.52%.

2c: Biege coloured solid. m.p. 110-12°C. IR (KBr, cm^{-1}): 1748 (C=O ester), 1548, 1398, 1365, 976, 889, 720 (Ar-H); MS (*m/z*, %): 281(M+1, 100), 280(M$^+$, 80), 235(50), 234(10), 207(30), 179(75), 119(20); ^{1}H NMR (DMSO-d_6): δ 7.47 (s, 1H, CH), 7.33 (d, 1H, CH, *J* = 8.5 Hz), 7.08 (d, 1H, *J* = 8.5 Hz), 5.04 (s, 2H, CH_2), 4.30 (q, 2H, CH_2), 2.45 (s, 3H, CH_3), 1.28-1.32 (t, 3H, CH_3); ^{13}C NMR (DMSO-d_6): 14.06 (CH_3), 20.62 (CH_3), 48.13 (CH_2), 59.37 (CH_2), 116.25,

122.83, 125.00, 132.45, 134.59, 134.84 (aromatic carbons), 162.24 (N=C-CH_3), 164.60 (C=O), 169.40 (C=O); Anal. Calcd. for $C_{13}H_{13}ClN_2O_3$: C, 55.57; H, 4.63; N, 9.97. Found: C, 55.56; H, 4.60; N, 10.06%.

2-(3,7-dimethyl-2-oxoquinoxalin-1(2*H*)-yl)acetohydrazide 3a

A mixture of **2a**, (19.0 g, 73.07 mmole) and hydrazine hydrate (100%, 3.5 g, 109.6 mmole) in methanol (75 mL) was refluxed for 6 hr. The reaction-mixture was then kept in deep-freezer overnight. The precipitated product was filtered off, washed with methanol (25 mL) and recrystalized from water/DMF mixture to give beige colored solid, 15.2 g (80%), m.p. 228-29°C. IR (KBr, cm^{-1}): 3336 ($NHNH_2$), 3046 (aromatic C-H), 1620 (C=O), 1560, 1365, 1320, 975, 891, 735, 620 (Ar-H); MS (*m/z*, %): 247(M+1, 100), 246(M^+, 80), 215(60), 187(20), 177(20), 161(100), 120(20), 107(25); ^{1}H NMR (DMSO-d_6): δ 7.25 (s, 1H, CH), 7.12 (d, 1H, CH, *J* = 8.8 Hz), 6.53 (d, 1H, *J* = 8.8 Hz), 6.22 (bs, 1H, $NHNH_2$), 4.96 (s, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.46 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): 20.60 (CH_3), 21.85 (CH_3), 48.93 (CH_2), 118.86, 123.03, 123.21, 133.42, 135.20, 137.25 (aromatic carbons), 159.93 (N=C-CH_3), 164.92 (C=O), 170.07 (C=O). Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.69; N, 22.76. Found: C, 58.60; H, 5.70; N, 22.67%. Synthesis of **3b** and **3c** was done according to the general procedure.

3b: m.p., 198-200°C; Anal. Calcd. for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.17; N, 24.13. Found: C, 56.90; H, 5.15; N, 24.20%.

3c: m.p. 212-14°C; IR (KBr, cm^{-1}): 3342 ($NHNH_2$), 3049 (aromatic C-H), 1635 (C=O), 1558, 1320, 980, 878, 735, 624 (Ar-H); MS (*m/z*, %): 267(M+1, 100), 266(M^+, 60), 231(30), 177(20), 120(10), 107(20); ^{1}H NMR (DMSO-d_6): δ 7.51 (d, 1H, CH, *J* = 8.5 Hz), 7.45 (s, 1H, CH,), 6.98 (d, 1H, *J* = 8.5 Hz), 6.26 (bs, 1H, $NHNH_2$), 5.02 (s, 2H, CH_2), 2.48 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6): 20.60 (CH_3), 48.93 (CH_2), 116.18 122.68, 125.27, 132.30, 134.78, 135.41 (aromatic carbons), 159.90 (N=C-CH_3), 164.94 (C=O), 170.10 (C=O). Anal. Calcd for $C_{11}H_{11}ClN_4O_2$: C, 49.53; H, 4.12; N, 21.01. Found: C, 49.51; H, 4.10; N, 21.08%.

3,7-dimethyl-1-[(5-aryl-1,3,4-oxadiazol-2-yl)methyl]quinoxalin-2(1*H*)-one 4a-y

General procedure: A mixture of an equimolar quantity of hydrazide **3a** (0.0082 mole) and substituted aromatic carboxylic acid (0.0085 mole) in 10 mL of phosphorous oxychloride was refluxed for 8 hr. The mass was then poured carefully to ice-cold water, neutralized with sodium bicarbonate. The resulting solid was filtered and recrystalized from appropriate solvent to give **4a-y**.

4a: IR (KBr, cm^{-1}): 3079 (C-H str.), 1607-1461 (C=N, C=C str.), 1422 (CH_2 bend.), 1261 (C-O-C str.), 839, 720; MS (*m/z*, %): 363(M+1, 100), 362(M^+, 20), 307(20), 227(10), 159(10), 107(20); ^{1}H NMR (DMSO- d_6): δ 7.97-7.99 (d, 2H), 7.51 (d, 1H, CH, *J* = 8.5 Hz), 7.45 (s, 1H, CH,), 7.10-7.13 (d, 2H), 6.98 (d, 1H, *J* = 8.5 Hz), 5.02 (s, 2H, CH_2), 3.91 (s, 3H, OCH_3), 2.62 (s, 3H, CH_3), 2.48 (s, 3H, CH_3).

4b: IR (KBr, cm^{-1}): 3081 (C-H str.), 1611-1458 (C=N, C=C str.), 1428 (CH_2 bend.), 1247 (C-O-C str.), 833, 747; MS (*m/z*, %) : 347(M+1, 100), 346(M^+, 60), 227(10), 159(10), 107(20).

4c: IR (KBr, cm^{-1}): 3083 (C-H str.), 1619-1469 (C=N, C=C str.), 1424 (CH_2 bend.), 1244 (C-O-C str.), 838, 741; MS (*m/z*, %): 401(M^+, 80), 391(30), 307(10), 215(80), 173(10), 120(20), 91(20); ^{1}H NMR ($CDCl_3$) : δ 7.94-7.98 (d, 2H), 7.53 (d, 1H, CH, *J* = 8.5 Hz), 7.47 (s, 1H, CH,), 7.12-7.15 (d, 2H), 7.02 (d, 1H, *J* = 8.5 Hz), 5.08 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 2.58 (s,3H, CH_3), 2.48 (s, 3H, CH_3).

4f: IR (KBr, cm^{-1}): 3071 (C-H str.), 1608-1487 (C=N, C=C str.), 1409 (CH_2 bend.), 1250 (C-O-C str.), 840, 731; MS (*m/z*, %): 423(M^+, 50), 422(10), 307(20), 215(30), 167(10), 120(20), 91(30).

4i: IR (KBr, cm^{-1}): 3068 (C-H str.), 1600-1450 (C=N, C=C str.), 1412 (CH_2 bend.), 1254 (C-O-C str.), 839, 708; ^{1}H NMR (DMSO-d_6): δ 7.87 (d, 1H, CH, *J* = 6.64 Hz), 7.51 (t, 1H, *J* = 7.2 Hz), 7.37 (d, 1H), 7.32 (t, 1H, CH, *J* = 8.5 Hz), 6.73-6.70 (dd, 2H, CH), 6.67-6.64 (dd, 2H), 5.02 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 2.48 (s, 3H, CH_3).

4j: IR (KBr, cm^{-1}): 3079 (C-H str.), 1607-1461 (C=N, C=C str.), 1422 (CH_2 bend.), 1261 (C-O-C str.), 839, 720; MS (*m/z*, %): 363(M+1, 100), 362(M^+, 20), 307(20), 227(10), 159(10), 107(20); ^{1}H NMR (DMSO-d_6): δ 7.92 (d, 1H, CH, *J* = 6.64 Hz), 7.54-7.50 (t, 1H, *J* = 7.2 Hz), 7.43-7.41 (d, 1H), 7.34-7.36 (t, 1H, CH, *J* = 8.5 Hz), 6.73-6.70 (dd, 2H, CH), 6.67-6.64 (dd, 2H) 5.42 (s, 2H, CH_2), 2.59 (s, 3H, CH_3), 2.46 (s, 3H, CH_3).

4k: IR (KBr, cm^{-1}): 3084 (C-H str.), 1618-1484 (C=N, C=C str.), 1435 (CH_2 bend.), 1270 (C-O-C str.), 850, 731; MS (*m/z*, %): 387(M^+, 40), 337(20), 324(10), 225(50), 201(50), 173(100), 149(60), 91(45).

4m: IR (KBr, cm^{-1}): 3079 (C-H str.), 1607-1461 (C=N, C=C str.), 1422 (CH_2 bend.), 1261 (C-O-C str.), 839, 720; MS (*m/z*, %): 364(M+1, 80), 363(M^+, 20), 307(50), 201(20), 176(10), 107(20).

4p: IR (KBr, cm^{-1}): 3083 (C-H str.), 1619-1469 (C=N, C=C str.), 1424 (CH_2 bend.), 1244 (C-O-C str.), 838, 741; MS (*m/z*, %): 319(M+1, 60), 318(M^+, 20), 307(70), 279(10), 167(20), 120(20), 89(30); ^{1}H NMR ($CDCl_3$): δ 7.89-7.87 (d, 1H), 7.76-7.73 (t, 1H), 7.64-7.62 (d, 1H), 7.58-7.56 (t, 1H), 7-48-7.45 (dd, 2H), 7.30-7.26 (t, 1H), 7.21-7.17 (t, 2H), 5.78 (s, 2H, CH_2), 2.66 (s, 3H, CH_3).

4q: IR (KBr, cm^{-1}): 3086 (C-H str.), 1618-1458 (C=N, C=C str.), 1420 (CH_2 bend.), 1237 (C-O-C str.), 842, 750; ^{1}H NMR (DMSO-d_6): δ 7.92 (d, 2H), 7.54 (d, 1H, CH, *J* = 8.5 Hz), 7.45 (s, 1H, CH), 6.98 (d, 1H, *J* = 8.5 Hz), 7.19 (d, 2H), 4.98 (s, 2H), 3.78 (s, 3H, OCH_3), 2.46 (s, 3H, CH_3).

4r: IR (KBr, cm^{-1}): 3080 (C-H str.), 1618-1458 (C=N, C=C str.), 1426 (CH_2 bend.), 1238 (C-O-C str.), 842; MS (*m/z*, %): 367(M^+ 1, 100), 366(M+, 60), 345(10), 273(10), 245(20), 223(50), 195(20), 105(60), 91(40).

4y: IR (KBr, cm^{-1}) 3074 (C-H str.), 1610-1434 (C=N, C=C str.), 1408 (CH_2 bend.), 1225 (C-O-C str.), 832, 738; MS (*m/z*, %): 353(M^+ 1, 100), 352(M+, 20), 345(10), 273(10), 253(20), 223(50), 195(20), 165(10), 105(60); ^{1}H NMR (DMSO-d_6): δ 7.86 6.62 (complex multiplate, 8H) 5.02 (s, 2H, CH_2), 2.58 (s, 3H, CH_3).

1-[(5-Mercapto-1,3,4-oxadiazol-2-yl)methyl]-3,7-dimethylquinoxalin-2(1*H*)-one 5a

General procedure: The compound **3a** (0.04 mole) was mixed with potassium hydroxide (0.10 mole) dissolved in methanol (50 mL) and the resulting mixture was cooled to 0°C. To this mixture distilled carbon disulfide (0.048 mole) was added slowly while stirring and it was slowly heated to reflux and reflux was continued till the evolution of hydrogen sulphide gas ceased completely (5 hr). Progress of the reaction was monitored by TLC (ethyl acetate/hexane, 2:3). When the reaction was complete, the solvent was removed by vacuum distillation to give a white solid, which was dissolved in water and acidified with acetic acid at 0-5°C. The separated product was filtered, washed with water and dried. It was recrystalized from chloroform.

5a: m.p. 240-42°C; IR (KBr, cm^{-1}): 3040 (C-H str.), 2352 (SH str), 1595-1468 (C=N, C=C str), 1444 (CH_2 bend.), 860, 703; ^{1}H NMR ($CDCl_3$): δ 11.94 (s, 1H, NH / SH), 7.70 (d, 1H, CH, *J* = 8.12 Hz), 7.18 (d, 1H, *J* = 8.2 Hz), 7.06 (s, 1H, CH), 5.49 (s, 2H, CH_2), 2.63 (s, 3H, CH_3), 2.45 (s, 3H, CH_3). Similarly compounds **5b** and **5c** were prepared.

5b: m.p. 218-20°C; IR (KBr, cm^{-1}): 3048 (C-H str.), 2358 (SH str.), 1596-1472 (C=N, C=C str.), 1435 (CH_2 bend.), 837, 787, 701; ^{1}H NMR ($CDCl_3$): δ 10.98 (s, 1H, NH / SH), 7.83 (d, 1H, CH, *J* = 6.64 Hz), 7.59 (d, 1H, *J* = 7.2 Hz), 7.37 (q, 2H), 5.55 (s, 2H, CH_2), 2.67 (s, 3H, CH_3).

5c: m.p. 230-34°C; IR (KBr, cm^{-1}): 3041 (C-H str.), 2355 (SH str.), 1595-1468 (C=N, C=C str.), 1435 (CH_2 bend.), 787 (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ 11.24 (s, 1H, NH / SH), 7.51 (d, 1H, CH, *J* = 8.5 Hz), 7.45 (s, 1H, CH,), 6.98 (d, 1H, *J* = 8.5 Hz), 5.02 (s, 2H, CH_2), 2.48 (s, 3H, CH_3).

General procedure for alkylation 6a-i: To a mixture of 5-substituted-1,3,4-oxadiazole-2-thiol (0.01 mole) in water (20 mL) containing KOH (0.011 mole), alkyl halide (0.01 mole) in methanol (10 mL) was added drop-wise. The contents were stirred at RT for 8 hr. The solid separated was filtered, washed with water and recrystalized from appropriate solvent to give the title compound.

6a: IR (KBr, cm^{-1}): 3065 (C-H str), 1594-1471 (C=N, C=C str), 1401 (CH_2 bend.), 828, 735; ^{1}H NMR ($CDCl_3$): δ 7.70 (d, 1H, CH, *J* = 8.12 Hz), 7.24 (s, 1H), 7.18 (d, 1H, CH, *J* = 7.0 Hz), 5.66 (s, 2H, -CH_2), 2.68 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.47 (s, 3H, CH_3).

6b: IR (KBr, cm^{-1}): 3069 (C-H str.), 1590-1474 (C=N, C=C str.), 1408 (CH_2 bend.), 836, 730; ^{1}H NMR ($CDCl_3$): δ 7.70 (d, 1H, CH, *J* = 8.12 Hz), 7.24 (s, 1H), 7.17 (d, 1H, CH, *J* = 7.28 Hz), 5.66 (s, 2H, -CH_2), 3.25 (q, 3H, CH_2), 2.59 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 1.45 (t, 3H, CH_3).

6c: IR (KBr, cm^{-1}): 3061 (C-H str.), 1591-1473 (C=N, C=C str.), 1407 (CH_2 bend.), 700 (Ar-H str.); ^{1}H NMR (DMSO-d_6): δ 7.82 (d, 1H, CH, *J* = 8.12 Hz), 7.68 (d, 1H, *J* = 8.2 Hz), 7.53 (s, 1H, CH), 7.27-7.38 (m, 5H, Ar-H), 4.47 (s, 2H, -CH_2), 4.34 (s, 2H, -CH_2-Ar), 2.60 (s, 3H, CH_3), 2.46 (s, 3H, CH_3).

6d: IR (KBr, cm^{-1}): 3062 (C-H str.), 1588-1461 (C=N, C=C str.), 1410 (CH_2 bend.), 710 (Ar-H str.); ^{1}H NMR ($CDCl_3$): δ 7.76 (d, 1H, CH, *J* = 6.76 Hz), 7.46-7.42 (m, 2H), 7.40 (d, 1H, CH, *J* = 5.92 Hz), 5.61 (s, 2H, -CH_2), 2.60 (s, 3H, CH_3), 2.56 (s, 3H, CH_3).

6e: IR (KBr, cm^{-1}): 3056 (C-H str.), 1598-1473 (C=N, C=C str.), 1414 (CH_2 bend.), 706 (Ar-H str.); ^{1}H NMR ($CDCl_3$): δ 7.50 (d, 1H, CH, *J* = 7.48 Hz),

7.54-7.45 (m, 2H), 7.36 (d, 1H, CH, J = 5.92 Hz), 5.72 (s, 2H, -CH_2), 3.25 (q, 2H, -CH_2), 2.68 (s, 3H, CH_3), 1.65 (t, 3H, CH_3).

6g: IR (KBr, cm^{-1}): 3059 (C-H str.), 1602-1496 (C=N, C=C str.), 1410 (CH_2 bend.), 836, 720; ^{1}H NMR ($CDCl_3$): δ 7.70 (d, 1H, CH, J = 8.12 Hz), 7.24 (s, 1H), 7.18 (d, 1H, CH, J = 7.0 Hz), 5.66 (s, 2H, -CH_2), 2.68 (s, 3H, CH_3), 2.56 (s, 3H, CH_3).

Biological activity

Anti-inflammatory activity

Carrageenan induced rat paw edema method[15] was employed for evaluating the anti-inflammatory activity of the compounds.

Wistar albino rats of either sex weighing 180-250 g were used for the experiments. They were housed in clean polypropylene cages and kept under RT (25 ± 2°C) relative humidity 60-70% in a 12:12 hr natural light-dark cycle. The animals were given standard laboratory food and water. Food was withdrawn 12 hr before and during experimental hr.

The animals were divided into several groups of six each. The control group received 2% gum acacia suspension orally, while the other groups received different drug treatment as detailed below. One hr after oral administration of the drug, acute inflammation was produced by sub plantar injection of 0.1 mL of 1% suspension of carrageenan with 2% gum acacia in normal saline, in the right hind paw of the rats. A mark was applied on the leg at the malleolus to facilitate subsequent readings. The paw volume was measured plethysmometrically (Ugo Basile, Italy) at 0, 2 and 4 hr after the carrageenan injection. The difference between 0 hr and subsequent readings was taken as the volume of the edema and the percentage anti-inflammatory activity was calculated by applying Newbould formula[16]. Indomethacin 1.5 mg/kg p.o suspended in 25 gum acacia was used as the standard drug. The results of anti-inflammatory studies are shown in **Table III**.

Analgesic activity

Animals: Male albino mice (18-26 g) were used for analgesia test. The animals were housed and fed in a laboratory kept at constant temperature of 22°C under standard conditions (12:12 h light-dark cycle, standard diet, tap water). Each experimental group consisted of 6 animals/dose and all the animals were used only once.

Hot plate test

The hot plate test was conducted according to the procedure described by Eddy and Leimbach[17]. In this test, reaction of mice to painful stimulus was measured. Mice were placed on the metal plate heated to 55 ± 0.4°C and covered with a glass cylinder (25 cm high, 15 cm in diameter). The time(s) elapsing to the first pain response (licking or jumping) was determined by a stop-watch and then recorded as response latency, prior to and 60, 180 min following the administration of the investigated compounds. All test compounds were given orally. Pethidine 5 mg/kg was used as standard drug, intraperitoneally. The results of analgesics studies are shown in **Table III**.

Conclusion

This study reports the successful synthesis of the hitherto unknown title compounds in good yields and evaluation of anti-inflammatory and analgesic activities by carrageenan induced rat paw edema method and hot plate method respectively. The investigation of anti-inflammatory and analgesic activity revealed that many compounds showed moderate level of anti-inflammatory and analgesic properties. Few of them, particularly compounds containing methyl and methoxy groups showed good anti-inflammatory and analgesic activity which is comparable to that of standards.

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