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Synthesis and pharmacological investigation of some novel 2,3-disubstituted quinazolin-4(3*H*)-ones as analgesic and antiinflammatory agents

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A series of novel 2-substituted quinazolin-4(3*H*)-ones have been synthesized by condensing the aromatic primary amine of 2-substituted quinazolines with different aldehydes and ketones. The synthesized compounds were confirmed by their spectral data (IR, NMR and MS) and the purity was ascertained by elemental analysis. When these compounds were evaluated for analgesic and antiinflammatory activities, compounds **I**–**VIII** exhibited more potent analgesic activity than diclofenac sodium, while the compounds **IV**, **V**, **VI** and **VII** exhibited more potent antiinflammatory activity than diclofenac sodium. The activity values were found to be significant as compared to those of controls.

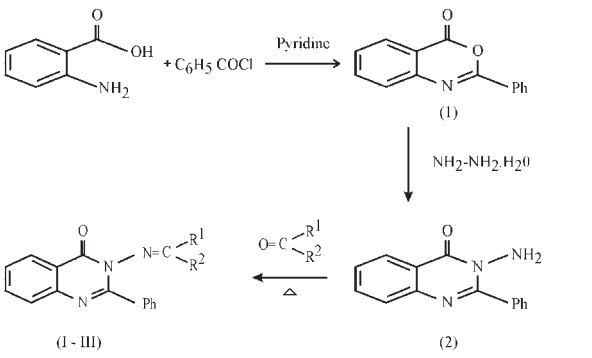
1. Introduction

Quinazolines and condensed quinazolines show a wide range of biological activities which include analgesic and antiinflammatory [1, 2], as well as antibacterial [3, 4], antiviral [5, 6], antihistaminic [7, 8], antihypertensive [9, 10], anticancer [11] and antiepileptic [12] activities. Some Schiff bases possess potent analgesic and antiinflammatory activities [13]. In view of these facts and as a continuation of our previous efforts [14], in the present study it was envisaged that the pharmacophore possessing Schiff bases of quinazoline could be of advantage.

2. Investigations, results and discussion

The title compounds 2,3-disubstituted quinazolin-4(3*H*) ones were prepared by condensing the aromatic primary amino group of 2-substituted quinazolines with different aldehydes and ketones. The starting materials 2-substituted-3-amino-quinazolines were synthesized as represented in Schemes 1 and 2. All compounds (Table 1) gave satisfactory elemental analyses. IR, ^{1}H NMR and MS were consistent with the assigned structures. The title compounds were screened for analgesic and antiinflammatory activity.

Scheme 1



Scheme 2

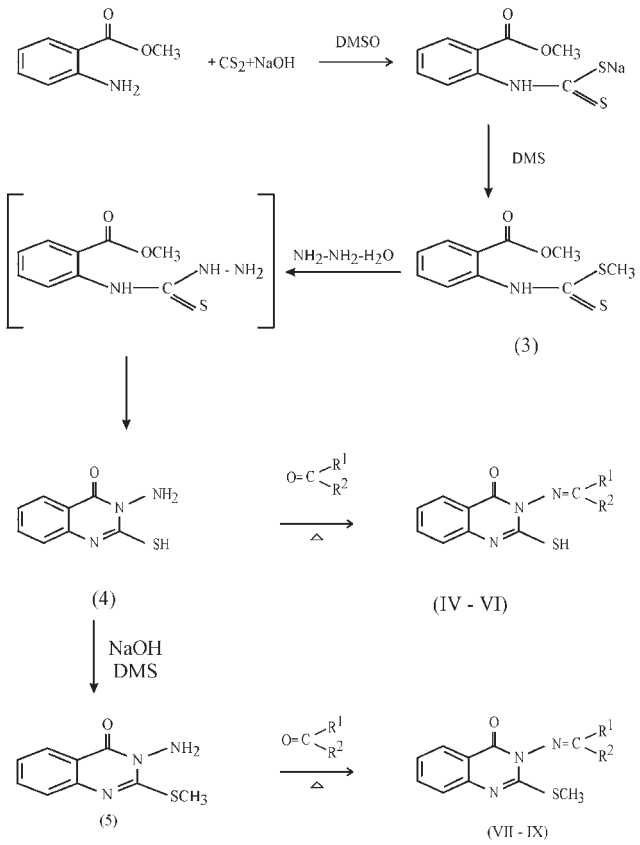
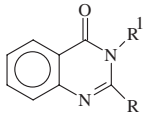
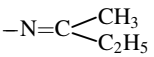
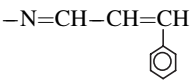
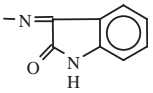
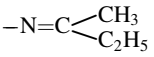
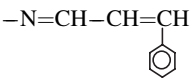
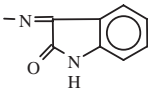
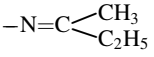
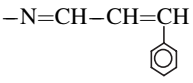
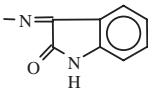


Table 1: Characterization data for 2,3-disubstituted quinazolin -4(3*H*)-ones



Compd.	R	R^1	Mol. Formula (Mol. Wt)*	Yield (%)	M.p. (°C)	Rf $CHCl_3 : CH_3OH$ (9.8 : 0.2)
I	C_6H_5		$C_{18}H_{17}N_3O$ (291)	75	192–194	0.73
II	C_6H_5		$C_{23}H_{17}N_3O$ (351)	71	252–254	0.88
III	C_6H_5		$C_{22}H_{14}N_4O_2$ (366)	76	172–174	0.56
IV	SH		$C_{12}H_{13}N_3OS$ (247)	72	310–312	0.48
V	SH		$C_{17}H_{13}N_3OS$ (307)	69	220–222	0.85
VI	SH		$C_{16}H_{10}N_4O_2S$ (322)	73	>320	0.63
VII	SCH_3		$C_{13}H_{15}N_3OS$ (261)	81	142–143	0.76
VIII	SCH_3		$C_{18}H_{15}N_3OS$ (321)	72	130–132	0.79
IX	SCH_3		$C_{17}H_{12}N_4O_2S$ (336)	77	218–220	0.60

*Molecular weight determination by mass spectra

All the synthesized compounds were tested for analgesic activity by the tail flick method at 10 mg/kg and 20 mg/kg. The percentages of analgesic activity of test compounds and reference standard diclofenac sodium are shown in Table 2. All test compounds exhibited potent analgesic activity. When compared to diclofenac sodium, the compounds **I**–**VIII** were more potent, while compound **IX** is only comparably potent. Compound **VII** was found to be the most active analgesic agent.

All the synthesized compounds were tested for their anti-inflammatory activity by carrageenan-induced paw oedema test in rats at 10 mg/kg and 20 mg/kg. The percentages of protection of test compounds and reference standard are shown in Table 3. All the test compounds exhibited potent antiinflammatory activity. When compared to diclofenac sodium, compounds **IV**, **V**, **VI**, and **VII** were more potent, while compounds **I**, **II**, **III**, **VIII** and **IX** are only comparably potent. Compound **VII** was found to be the most active antiinflammatory agent. Given the good analgesic and antiinflammatory activities, compound **VII** could serve as a lead molecule in this series for further studies to obtain a clinically useful agent.

3. Experimental

3.1. Chemistry

Melting points were in open capillary tubes on a Thomas Hoover apparatus and were uncorrected. IR spectra were recorded on Perkin Elmer – 841 Grating spectrometer in KBr. ^{1}H NMR spectra were recorded on a varian EM-360 spectrometer (300 MHz), TMS as the internal reference. Mass spectra on Varian Atlas CH-7 mass spectrometer at 70 eV. Elemental analyses were performed on a Carlo Erba 1108.

3.1.1. 2-Phenyl-3,1-benzoxazin-4-one (**1**)

To a solution of anthranilic acid (0.1 mol), dissolved in pyridine (60 ml), benzoyl chloride (0.2 mol) was added. The mixture was stirred for 0.5 h followed by treatment with 5% sodium bicarbonate (15 ml). The separated solid was crystallized from ethanol. Yield: 80%; m.p. 120 °C; IR (KBr): 3350 (NH), 1680 (C=O), 1620 cm^{-1} (C=N); NMR ($CDCl_3$) (δ ppm): 6.8–7.5 (m, 9 H, ArH); MS (m/z) 223 ($M^{+\bullet}$).
$C_{14}H_9N_2O$

3.1.2. 3-Amino-2-phenylquinazolin-4(3H)-one (**2**)

A mixture of **1** (0.05 mol) and hydrazine hydrate (0.05 mol) in ethanol was refluxed for 3 h and cooled. The separated solid was recrystallized from ethanol. Yield: 85%, m.p. 196 °C; IR (KBr): 3320, 3300 (NH_2), 1680 (C=O) 1620 (C=N), 1600 cm^{-1} (C=C); NMR ($CDCl_3$) (δ ppm): 4.5 (s, 2 H, NH_2), 6.7–7.4 (m, 9 H, ArH); MS (m/z) 237 ($M^{+\bullet}$).
$C_{14}H_{11}N_3O$

3.1.3. 3-Amino-2-mercaptoquinazolin- 4(3H)-one (**4**)

To a vigorously stirred solution of methylanthranilate (0.02 mol) in dimethylsulfoxide (10 ml) at room temperature, carbondisulphide (0.026 mol) and aqueous NaOH (1.2 ml; 20 mol solution) were added dropwise simultaneously during 30 min, and was stirred for further 30 min. Then dimethyl sulphate (0.02 mol) was added dropwise under cooling with an ice bath. Stirring was continued for 3 h, the mixture was poured into water, and then it was extracted with chloroform. The solvent was removed by distillation under reduced pressure. Crude methyl *N*-(2-methoxycarbonylphenyl)dithiocarbamate (**3**) so obtained was used for further reaction without

Table 2: Analgesic activity of compounds I–IX

Compd.	Percentage Analgesic activity							
	10 mg/kg				20 mg/kg			
	30 min	1st h	2nd h	3rd h	30 min	1st h	2nd h	3rd h
I	126.00 ± 0.43^{++}	138.00 ± 0.37^{+++}	132.00 ± 0.30^{+++}	123.00 ± 0.38^{++}	200.00 ± 0.41^{++}	210.00 ± 0.36^{+++}	220.00 ± 0.29^{+++}	120.00 ± 0.41^{+}
II	142.20 ± 2.40^{+}	150.57 ± 1.28^{+}	172.16 ± 1.26^{++}	118.66 ± 0.78^{++}	214.28 ± 2.63^{+}	257.14 ± 1.08^{+}	271.42 ± 1.04^{++}	178.57 ± 0.72^{++}
III	146.20 ± 0.34^{++}	196.06 ± 0.36^{++}	220.00 ± 0.73^{+++}	138.00 ± 0.23^{++}	233.33 ± 0.29^{++}	300.00 ± 0.29^{++}	350.00 ± 0.75^{+++}	216.66 ± 0.25^{++}
IV	152.66 ± 0.23^{+++}	190.02 ± 0.58^{++}	232.00 ± 0.62^{++}	168.05 ± 0.22^{+++}	250.00 ± 0.25^{+++}	300.00 ± 0.5^{+++}	366.66 ± 0.65^{+++}	250.00 ± 0.25^{+++}
V	172.00 ± 0.31^{+++}	230.00 ± 0.62^{+++}	270.00 ± 0.2^{+++}	170.00 ± 0.28^{+++}	280.00 ± 0.29^{+++}	360.00 ± 0.65^{+++}	400.00 ± 0^{+++}	280.00 ± 0.29^{+++}
VI	220.44 ± 0.47^{+++}	256.33 ± 0.70^{+++}	286.33 ± 0.82^{+++}	158.05 ± 0.40^{+++}	319.44 ± 0.48^{+++}	383.33 ± 0.71^{+++}	405.55 ± 0.87^{+++}	233.33 ± 0.48^{+++}
VII	242.00 ± 0.25^{+++}	260.55 ± 0.60^{+++}	280.00 ± 0.65^{+++}	170.00 ± 0.42^{++}	315.00 ± 0.29^{+++}	380.00 ± 0.65^{+++}	400.00 ± 0.71^{+++}	260.00 ± 0.48^{++}
VIII	160.76 ± 0.60^{+++}	240.54 ± 0.68^{+++}	255.33 ± 0.40^{+++}	135.35 ± 0.58^{++}	253.84 ± 0.65^{++}	317.30 ± 0.75^{+++}	330.76 ± 0.46^{+++}	211.54 ± 0.65^{++}
IX	88.89 ± 0.22^{++}	99.98 ± 0.55^{+}	115.15 ± 0.25^{++}	90.00 ± 0.38^{+}	122.80 ± 0.25^{+}	157.89 ± 0.65^{+}	192.98 ± 0.29^{++}	140.35 ± 0.41^{+}
Control	4.41 ± 0.61	3.39 ± 0.52	1.13 ± 0.29	2.12 ± 0.42	4.41 ± 0.61	3.39 ± 0.52	1.13 ± 0.29	2.12 ± 0.42
Diclofinac	102.33 ± 0.62^{++}	136.00 ± 0.26^{+++}	148.12 ± 0.75^{+++}	88.39 ± 0.78^{+}	173.33 ± 0.65^{++}	200.00 ± 0.29^{+++}	226.66 ± 0.82^{+++}	120.00 ± 0.85^{+}

$^{+}$ denotes significant differences from control at $P \leq 0.05$

Table 3: Antiinflammatory activity of compounds I–IX

Compd.	Percentage Protection							
	10 mg/kg				20 mg/kg			
	30 min	1st hr	2nd hr	3rd hr	30 min	1st hr	2nd hr	3rd hr
I	24.42 ± 0.36^{++}	25.30 ± 0.35^{+++}	30.42 ± 0.30^{+++}	24.48 ± 0.38^{+}	30.17 ± 0.39^{++}	33.78 ± 0.38^{+++}	37.42 ± 0.30^{+++}	29.30 ± 0.41^{+}
II	24.78 ± 2.55^{+}	28.45 ± 1.02^{+}	31.48 ± 1.06^{++}	22.18 ± 0.70^{++}	32.45 ± 2.60^{+}	39.17 ± 1.06^{+}	39.18 ± 1.02^{++}	31.48 ± 0.75^{++}
III	22.47 ± 0.30^{++}	26.77 ± 0.29^{++}	29.31 ± 0.70^{+++}	24.42 ± 0.25^{++}	29.47 ± 0.29^{++}	36.18 ± 0.32^{++}	38.13 ± 0.70^{+++}	31.42 ± 0.25^{++}
IV	25.44 ± 0.28^{+++}	34.77 ± 0.50^{+++}	42.44 ± 0.58^{+++}	29.17 ± 0.26^{+++}	36.19 ± 0.25^{+++}	45.77 ± 0.55^{+++}	54.31 ± 0.62^{+++}	37.44 ± 0.23^{+++}
V	27.19 ± 0.26^{+++}	39.78 ± 0.58^{+++}	44.17 ± 0.13^{+++}	28.18 ± 0.29^{+++}	37.44 ± 0.28^{+++}	50.17 ± 0.60^{+++}	55.78 ± 0.1^{+++}	34.83 ± 0.27^{+++}
VI	33.85 ± 0.42^{+++}	32.12 ± 0.58^{+++}	38.79 ± 0.82^{+++}	23.87 ± 0.42^{+++}	39.19 ± 0.46^{+++}	41.12 ± 0.70^{+++}	49.85 ± 0.85^{+++}	32.17 ± 0.45^{+++}
VII	40.78 ± 0.27^{+++}	36.14 ± 0.60^{+++}	43.79 ± 0.68^{+++}	24.33 ± 0.65^{+++}	54.51 ± 0.28^{+++}	46.11 ± 0.62^{+++}	52.79 ± 0.71^{+++}	31.18 ± 0.46^{++}
VIII	26.17 ± 0.25^{+}	28.76 ± 0.58^{++}	26.87 ± 0.40^{+++}	23.78 ± 0.58^{+}	31.17 ± 0.65^{++}	35.78 ± 0.73^{+++}	38.15 ± 0.45^{+++}	34.33 ± 0.63^{++}
IX	20.14 ± 0.20^{+}	28.87 ± 0.58^{++}	30.11 ± 0.30^{+}	20.33 ± 0.35^{+}	29.19 ± 0.24^{+}	40.14 ± 0.63^{++}	41.87 ± 0.27^{++}	31.11 ± 0.40^{+}
Control	4.15 ± 0.60	4.19 ± 0.48	3.31 ± 0.27	2.47 ± 0.40	4.15 ± 0.60	4.19 ± 0.48	3.31 ± 0.27	2.47 ± 0.40
Diclofenac	24.26 ± 0.62^{++}	27.76 ± 0.26^{+++}	34.47 ± 0.75^{+++}	22.78 ± 0.80^{+}	35.15 ± 0.66^{++}	42.44 ± 0.28^{+++}	49.18 ± 0.80^{+++}	33.19 ± 0.86^{+}

$^{+}$ denotes significant differences from control at $P \leq 0.05$

purification. Hydrazine hydrate (0.2 mol) was added dropwise under stirring at 0 °C. Stirring was continued for 1.5 h at 50 °C and the reaction mixture was poured into ice water. The solid so obtained was filtered, washed with water, dried and crystallized from dimethylformamide and ethanol. Yield 90%; m.p. 236–237 °C; IR (KBr): 3300, 3220, (NH_2), 2990 (CH), 2560 (SH), 1680, cm^{-1} (C=O); ^1H NMR ($CDCl_3$) (δ ppm) 3.21 (s, 1 H, SH, D_2O exch.), 5.12 (s, 2 H, NH_2, D_2O exch.), 7.14 (m, 4 H, Ar-H); MS (m/z): 193 ($M^{+\bullet}$).
$C_8H_7N_3OS$

3.1.4. 3-Amino-2-methylthio quinazolin-4(3H)-one (**5**)

A solution of **4** (0.01 mol) in NaOH (10 ml, 10% w/v) was obtained by warming on a water bath. The solution was filtered in warm condition, cooled and treated with dimethylsulphate (0.01 mol) under constant stirring for 12 h. The solid so obtained was filtered, washed with cold water, dried and recrystallized from chloroform. Yield 90%; m.p. 155–157 °C; IR (KBr): 3400, 3200 (NH_2), 1680 (C=O), 1640 (C=N), 1600 cm^{-1} (C=C). ^1H NMR (DMSO-d_6) (δ ppm): 2.51 (s, 3 H, SCH_3), 6.6 (s, 2 H, NH_2, D_2O exch.), 7.5–7.8 (m, 4 H, Ar-H); MS (m/z): 207 ($M^{+\bullet}$).
$C_9H_9N_3OS$

3.1.5. 2-Phenyl-3-(2-butylidene)quinazolin-4(3H)-one (**I**)

A mixture of **2** (0.005 mol) and ethyl-methylketone (0.005 mol) in 25 ml of methanol and 1 ml of glacial acetic acid was refluxed for 17 h and cooled. The separated solid was crystallized from benzene and methanol. IR (KBr): 1680 (C=O), 1590 (C=N), 1560 (C=C), 1260 (C−N), 770, 700 cm^{-1} (C-H). ^1H NMR ($CDCl_3$) (δ ppm) 1.2–1.4 (t, 3 H, CH_2-CH_3), 1.5–1.6 (s, 3 H, CH_3), 4–4.4 (q, 2 H, CH_2-CH_3), 7.4–7.8 (m, 5 H, Ar-H), 8.1–8.3 (m, 4 H, Ar-H).
Compounds **II** and **III** were synthesized similarly using cinnamaldehyde and isatin, resp.

3.1.6. 2-Mercapto-3-(1-phenyl-3-propylidene)quinazolin-4(3H)-one (**V**)

A mixture of **4** (0.005 mol) and cinnamaldehyde (0.005 mol) in dimethylformamide and 2 ml acetic anhydride was refluxed for 17 h and cooled. The mixture was poured into methanol, the solid so obtained was crystallized from dimethyl formamide. IR (KBr): 3050, 2900 (Ar−CH), 2580 (S−H) 1680 (C=O), 1600 (C=C), 1440 (ring C=N), 700 (C−S), 750 cm^{-1} (C−H). ^1H NMR ($CDCl_3$) (δ ppm): 3.2–3.3 (s, 1 H, SH D_2O exch.), 4.9–5.1 (d, 1 H, $-CH-CH=CH-C_6H_5$), 5.7–5.9 (2 m, 1 H, $-CH-CH=CH-C_6H_5$), 6.4–6.6 (d, 1 H, $-CH-CH=CH-C_6H_5$), 7.4–7.8 (m, 5 H, Ar-H), 8.2–8.5 (m, 4 H, Ar-H).
Similarly compounds **IV** and **VI** were synthesized using ethyl-methylketone and isatin, resp.

3.1.7. 2-Methylthio-3-(2-butylidene)quinazolin-4(3H)-one (**VII**)

A mixture of **4** (0.005 mol) and ethyl-methylketone (0.005 mol) in acetic acid was refluxed for 24 h. The mixture was poured into water. The solid so obtained was crystallized from methanol. IR (KBr): 2900, 2420, 2280, (Ar-CH), 1660 (C=O), 1530 (C=N), 1300 (ring C=C), 680 cm^{-1} (C-S). ^1H NMR ($CDCl_3$) (δ ppm): 1.2–1.5 (t, 3 H, CH_2-CH_3), 1.6–1.7 (s, 3 H, CH_3), 4.1–4.4 (q, 2 H, CH_2-CH_3) 2.6–2.7 (s, 3 H, SCH_3), 8.1–8.4 (m, 4 H, Ar-H).
Compounds **VIII** and **IX** were synthesized similarly using cinnamaldehyde and isatin, resp.

3.2. Analgesic activity

Test for analgesic activity was performed by tail flick technique [15, 16] using mice. Animals were divided into groups each consisting of six animals. Test compounds and standard diclofenac sodium were administered orally at doses of 10 and 20 mg/kg as aqueous suspension in 1% sodium carboxymethyl-cellulose (Na CMC), while the control group was fed with the same volume of 1% Na CMC. The reaction time was recorded at 30 min, 1, 2 and 3 h after the treatment. The percentage of analgesic activity (PAA) was calculated with the following formula.

$$PAA = (T_2/T_1) \times 100$$

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

3.3. Antiinflammatory activity

Antiinflammatory activity was measured by carrageenan-induced paw oedema test in rats [17]. Animals were divided into groups each consisting of six animals. Test compounds and standard diclofenac sodium were administered orally at doses of 10 and 20 mg/kg as aqueous suspension in 1% Na CMC, while the control group was fed with the same volume of 1% Na CMC. 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 percentage of paw oedema inhibition was calculated using the following formula.

$$\text{Percentage inhibition I} = 100\left(1 - \frac{(a - x)}{(b - y)}\right)$$

where x = the mean paw volume of rats before the administration of carrageenan and test compounds or standard compound; a stands for mean paw volume of rats after the administration of carrageenan in the control group; b is the mean paw volume of rats before the administration of carrageenan in the control group. y is the mean paw volume of rats after the administration of carrageenan in the control group.

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