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Synthesis and Antiinflammatory Activity of 2-[5'-(4-Pyridinyl)-1',2',3'-oxadiazol-2-yl-thiomethyl]-3-substituted-aryl-6-substituted-quinazolin-4-ones

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In present study, a novel series of quinazolin-4-ones derivatives *viz.*, 2-methyl-3-substituted aryl-6-substituted quinazolin-4-ones (**4-18**), 2-bromomethyl-3-substitutedaryl-6-substuted quinazolin-4-ones (**19-33**), 2-[5'-(4-pyridinyl)-1',3',4'-oxadiazol-2'-yl-thiomethyl]-3-substituted aryl-6-substituted quinazolin-4-ones (**34-48**) have been synthesized. The structures of all these newly synthesized compounds were confirmed by their analytical and spectral data. The compounds were evaluated for their antiinflammatory activity. Compound **43** showed maximum antiinflammatory (36.25 %) activity at the dose of 50 mg/kg p.o.

Key Words: Quinazolin-4-ones, 1',3',4'-Oxadiazoles, Antiinflammatory activity.

INTRODUCTION

Quinazolinone derivatives have been found to possess potent wide spectrum of activities like antibacterial[1,2], anticonvulsant[3-5] and antiinflammatory[6-10]. It is also reported that substitution of halo group at 6th[8] and 8th[6] position in this nucleus enhances its antiinflammatory action. A large number of oxadiazoles[11-15] are reported to possess potent antiinflammatory activity. This prompted us to syntheses a new series of quinazolinone derivatives by incorporating the oxadiazole moiety at 2nd position of the quinazolinone nucleus. The structures of all compounds have been evaluated by elemental analysis and spectral analysis (IR, ^{1}H NMR and mass spectrometry). All the compounds have been screened for their antiinflammatory activity.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. Analytical data of C, H, N were with in ± 0.4 % of the theoretical values. IR spectra (cm^{-1}) were recorded on Beckman-Acculab 10 spectrophotometer. ^{1}H NMR spectra were determined in $CHCl_3$ on Brucker 300-FT instrument.

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Synthesys of compounds

5-Bromoanthranilic acid and 5-iodoanthranilic acid: These compounds were prepared according to reported methods by Wheeler *et al.*[16] and Klemme *et al.*[17], respectively.

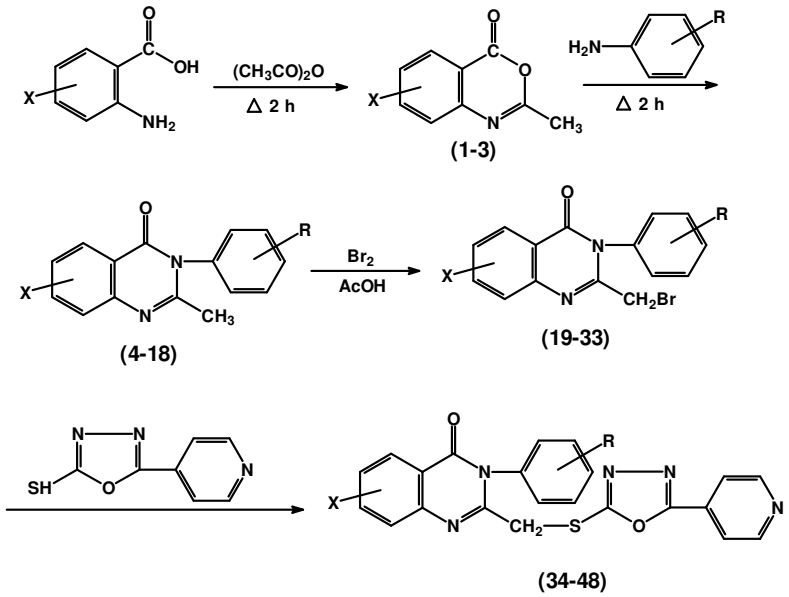
2-Methyl-6-substituted benzoxazin-4-one (1-3): These compounds were synthesized by known method[18].

A mixture of substituted anthranilic acid (0.19 mol) and acetic anhydride (142 mL, 99 %, 1.5 mol) was heated under reflux for 2 h. The excess of acetic anhydride was then distilled off under reduced pressure, on cooling the flask the residue solidified. The benzoxazinone was dissolved in hot dry ethyl acetate and the filtrate was treated with *n*-hexane just to remove turbidity and chilled in a ice bath and was dried *in vacuo* over calcium chloride.

2-Methyl-3-substituted aryl-6-substituted quinazolin-4-ones (4-18): A mixture of **1-3** (0.01 mol) and substituted aniline (0.01 mol) were heated on a free flame for 10-20 min. On cooling a jelly like mass was obtained. The analytical data of the compounds are given in Table-1. Compound **8**: m.p. 97 ºC, yield 55 %, m.f. $C_{16}H_{14}N_2O_2$, IR (KBr, ν_{max}, cm^{-1}): 1525 (C-N), 1460 (C-C of aromatic ring), 1580 (C=N), 1695 (C=O), 3020 (C-H aromatic), 2810-2930 (aliphatic C-H). ^{1}H NMR ($CDCl_3$) δ in ppm : 2.27 (s, 3H, CH_3), 3.41 (s, 3H, OCH_3), 7.26-7.90 (m, 8H, Ar-H): MS: m/z 266 $[M]^+$.

2-Bromomethyl-3-substituted aryl-6-substituted quinazolin-4-ones (19-33): Compounds (**19-33**) were synthesized by adding a solution of bromine (0.02 mol) in acetic acid dropwise with constant stirring in the cold solution of compounds (**4-18**) (0.01 mol). The reaction mixture was further stirred for 4 h. The solvent was distilled off and the residue thus obtained was washed with petroleum ether (40-60 ºC). The analytical data of the compounds are given in Table-1. Compound **23**: m.p. 141 ºC, yield 55 %, molecular formula $C_{16}H_{13}N_2O_2Br$, IR (KBr, ν_{max}, cm^{-1}): 1525 (C-N), 1465 (C-C of aromatic ring), 1580 (C=N), 1695 (C=O), 3025 (C-H aromatic), 765 (C-Br). ^{1}H NMR ($CDCl_3$) δ in ppm : 3.40 (s, 3H, OCH_3), 2.89, (s, 2H, CH_2Br), 7.36-8.36 (m, 8H, Ar-H): MS: m/z 345 $[M]^+$.

2-[5'-(4-pyridinyl)-1',3',4'-oxadiazol-2'-ylthiomethyl]-3-substituted aryl-6-substituted quinazolin-4-ones (34-48): The solutions of (**19-33**) (0.03 mol) in pyridine (80 mL) and 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiol (0.03 mol) were refluxed for 3 h. The contents were then poured onto crushed ice and solid masses were obtained (**Scheme-I**). The analytical data of the compounds are given in Table-1. Compound **38**: m.p. 163 ºC, yield 55 %, m.f. $C_{23}H_{17}N_5O_3S$. IR (KBr, ν_{max}, cm^{-1}): 1180 (C-O-C), 1525 (C-N), 1460 (C-C of aromatic ring), 1575 (C=N), 1690 (C=O), 1640, 1615, 1570, 1415, (ring str. of oxadiazole nucleus), 1065 (C-O str. of oxadiazole nucleus), 1270 (N-N). ^{1}H NMR ($CDCl_3$) δ in ppm: 2.75 (s, 2H, CH_2), 3.42 (s, 3H, OCH_3), 8.01-8.70 (4H, pyridinyl ring). 7.26-8.33 (m, 8H, Ar-H): MS: m/z 443 $[M]^+$.



Scheme-I

Pharmacological evaluation: The experiments were performed with albino rats of the Charles-Foster strain of either sex, excluding pregnant females, of 70 to 95 d weighing 60 to 160 g. Acute toxicity was tested in albino mice (120-125 g). Food (chaw pallet) and water was given to the animals *ad libitum*. The test compounds were dissolved in propylene glycol. Phenylbutazone drug was used as reference drug.

Antiinflammatory activity: Antiinflammatory activity performed by carrageenan-induced paw oedema test in rats was done by following the procedure of Winter *et al.*[19]. The rats were divided into three groups (control, drugs treated and standard drugs) of six animals each. A freshly prepared suspension of carrageenan (1 % in 0.9 % saline), 0.05 mL was injected under the planter aponeurosis of the right hind paw of each rat. The compound and standard drug were administered orally to the animals of drug treated groups and the standard drug group, respectively, 1h before the carrageenan injection. The paw volume of each rat was measured before 1 and after 3 h of carrageenan treatment with the help of a plethysmo-meter. The percent antiinflammatory activity was calculated according to the formula given below.

$$\text{Percentage of inhibition of oedema} = (1 - V_t/V_c) \times 100$$

where V_t and V_c are paw volume of rats of the treated and control group, respectively. Results obtained were statistically analyzed.

Acute toxity: Approximate lethal dose (ALD_{50}) of all the compounds were investigated by the method of Smith[20].

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS **4-48**

Compd.	X	R	m.p. (ºC)	Recrystalliation solvent	Yield (%)	m.f.	Found (Calcd.) (%)		
							C	H	N
4	H	H	85	Ethanol	70	$C_{15}H_{12}N_2O$	76.40 (76.27)	5.16 (5.08)	11.92 (11.86)
5	H	2-Cl	83	Methanol	65	$C_{15}H_{11}N_2OCl$	66.78 (66.54)	4.01 (4.07)	10.43 (10.35)
6	H	4-Cl	86	Ethanol	70	$C_{15}H_{11}N_2OCl$	66.70 (66.54)	4.10 (4.07)	10.46 (10.35)
7	H	2-OCH_3	91	Methanol	85	$C_{16}H_{14}N_2O_2$	72.38 (72.18)	5.34 (5.26)	10.58 (10.53)
8	H	4-OCH_3	97	Ethanol	55	$C_{16}H_{14}N_2O_2$	72.41 (72.18)	5.32 (5.26)	10.62 (10.53)
9	6-I	H	137	Ethanol	50	$C_{15}H_{11}N_2OI$	49.50 (49.72)	3.18 (3.04)	7.96 (7.73)
10	6-I	2-Cl	156	Ethanol	50	$C_{15}H_{10}N_2OClI$	45.54 (45.40)	2.43 (3.52)	7.18 (7.06)
11	6-I	4-Cl	164	Ethanol	68	$C_{15}H_{10}N_2OClI$	45.61 (45.40)	2.61 (2.52)	7.23 (7.06)
12	6-I	2-OCH_3	180	Methanol	55	$C_{16}H_{13}N_2O_2I$	49.21 (48.98)	3.28 (3.32)	7.32 (7.14)
13	6-I	4-OCH_3	186	Ethanol	65	$C_{16}H_{13}N_2O_2I$	49.18 (48.98)	3.23 (3.32)	7.29 (7.14)
14	6-Br	H	123	Benzene	56	$C_{15}H_{11}N_2OBr$	57.26 (57.14)	3.23 (3.49)	8.94 (8.89)
15	6-Br	2-Cl	142	Ethanol	45	$C_{15}H_{10}N_2OBrCl$	51.78 (51.50)	2.69 (2.86)	8.07 (8.01)
16	6-Br	4-Cl	149	DMF/water	55	$C_{15}H_{10}N_2OBrCl$	57.81 (51.50)	2.71 (2.86)	8.05 (8.01)
17	6-Br	2-OCH_3	171	Ethanol	60	$C_{16}H_{13}N_2O_2Br$	55.36 (55.56)	5.58 (3.77)	8.32 (8.12)
18	6-Br	4-OCH_3	178	DMF	65	$C_{16}H_{13}N_2O_2Br$	55.41 (55.56)	5.54 (3.77)	8.29 (8.12)
19	H	H	98	Ethanol	65	$C_{15}H_{11}N_2OBr$	57.42 (57.14)	3.65 (3.49)	9.02 (8.89)
20	H	2-Cl	147	Ethanol	70	$C_{15}H_{10}N_2OBrCl$	51.63 (51.50)	2.72 (2.86)	8.08 (8.01)
21	H	4-Cl	152	Acetic acid	62	$C_{15}H_{10}N_2OBrCl$	51.65 (51.50)	2.69 (2.86)	8.03 (8.01)
22	H	2-OCH_3	134	Acetone/Pet. Ether	68	$C_{16}H_{13}N_2O_2Br$	55.79 (55.65)	3.82 (3.77)	8.22 (8.12)
23	H	4-OCH_3	141	Ethanol	55	$C_{16}H_{13}N_2O_2Br$	55.81 (55.65)	3.81 (3.77)	8.25 (8.12)
24	6-I	H	142	Methanol	66	$C_{15}H_{10}N_2OBrI$	40.26 (40.82)	2.19 (2.27)	6.16 (6.35)
25	6-I	2-Cl	163	Methanol	54	$C_{15}H_9N_2OBrClI$	38.01 (37.85)	2.08 (1.89)	5.67 (5.89)

Compd.	X	R	m.p. (ºC)	Recrystalliation solvent	Yield (%)	m.f.	Found (Calcd.) (%)		
							C	H	N
26	6-I	4-Cl	167	DMF/water	60	$C_{15}H_9N_2OBrClI$	37.96 (37.85)	2.10 (1.89)	5.63 (5.89)
27	6-I	2-OCH_3	208	Rectified Spirit	65	$C_{16}H_{12}N_2O_2BrI$	41.98 (40.76)	2.88 (2.55)	6.09 (5.94)
28	6-I	4-OCH_3	222	Ethanol	50	$C_{16}H_{12}N_2O_2BrI$	41.93 (40.76)	2.79 (2.55)	6.13 (5.94)
29	6-Br	H	95	Benzene	58	$C_{15}H_{10}N_2OBr_2$	57.33 (57.14)	3.64 (3.49)	9.03 (8.89)
30	6-Br	2-Cl	148	Methanol	52	$C_{15}H_9N_2OBr_2Cl$	51.68 (51.50)	2.79 (2.86)	8.10 (8.01)
31	6-Br	4-Cl	155	Ethanol	65	$C_{15}H_9N_2OBr_2Cl$	51.63 (51.50)	2.71 (2.86)	8.07 (8.01)
32	6-Br	2-OCH_3	210	DMF/water	57	$C_{16}H_{12}N_2O_2Br_2$	55.83 (55.56)	3.81 (3.77)	8.24 (8.12)
33	6-Br	4-OCH_3	216	Ethanol	54	$C_{16}H_{12}N_2O_2Br_2$	55.79 (55.56)	3.83 (3.77)	8.21 (8.12)
34	H	H	112	Ethanol	50	$C_{22}H_{15}N_5O_2S$	63.81 (63.92)	3.59 (3.63)	16.99 (16.94)
35	H	2-Cl	178	Ethanol	45	$C_{22}H_{14}N_5O_2SCl$	59.08 (58.99)	3.08 (3.13)	15.59 (15.64)
36	H	4-Cl	284	Methanol	40	$C_{22}H_{14}N_5O_2SCl$	58.77 (58.99)	3.16 (3.13)	15.57 (15.64)
37	H	2-OCH_3	155	Benzene	38	$C_{23}H_{17}N_5O_3S$	62.51 (62.30)	3.79 (3.84)	15.83 (15.80)
38	H	4-OCH_3	163	DMF	55	$C_{23}H_{17}N_5O_3S$	62.44 (62.30)	3.87 (3.84)	15.85 (15.80)
39	6-I	H	189	Ethanol	56	$C_{22}H_{14}N_5O_2IS$	48.69 (48.98)	2.64 (2.60)	12.92 (12.99)
40	6-I	2-Cl	197	Acetic acid	44	$C_{22}H_{13}N_5O_2IClS$	46.18 (46.03)	2.29 (2.27)	12.23 (12.21)
41	6-I	4-Cl	215	Methanol	51	$C_{22}H_{13}N_5O_2IClS$	46.15 (46.03)	2.25 (2.27)	12.25 (12.21)
42	6-I	2-OCH_3	221	Methanol	52	$C_{23}H_{16}N_5O_3IS$	48.40 (48.51)	2.86 (2.81)	12.33 (12.30)
43	6-I	4-OCH_3	227	Acetone	57	$C_{23}H_{16}N_5O_3IS$	46.48 (48.51)	2.83 (2.81)	12.31 (12.30)
44	6-Br	H	135	Ethanol	58	$C_{22}H_{14}N_5O_2BrS$	55.78 (55.66)	2.81 (2.85)	14.19 (14.23)
45	6-Br	2-Cl	185	Ethanol	49	$C_{22}H_{13}N_5O_2BrClS$	50.05 (50.14)	2.41 (2.47)	13.35 (13.29)
46	6-Br	4-Cl	198	Benzene	52	$C_{22}H_{13}N_5O_2BrClS$	50.23 (50.14)	2.44 (2.47)	13.35 (13.29)
47	6-Br	2-OCH_3	217	DMF	46	$C_{23}H_{16}N_5O_3BrS$	52.85 (52.87)	3.14 (3.06)	13.34 (13.41)
48	6-Br	4-OCH_3	223	Acetic acid	50	$C_{23}H_{16}N_5O_3BrS$	52.92 (52.87)	3.12 (3.06)	13.38 (13.41)

RESULTS AND DISCUSSION

All newly synthesized quinazolinones (**19-48**) have shown antiinflammatory activity of varying degree from 12.45 to 36.25 % and biological results are given in Table-2. All compounds of this series have been evaluated for their antiinflammatory activity against carrageenan induced rat hind

TABLE-2
ANTIINFLAMMATORY ACTIVITY OF TITLED COMPOUNDS (**19-48**)

Compd.* no.	X	R	Dose mg/kg p.o.	%Decrease in paw oedema antiinfammatory activity
19	H	H	50	12.45
20	H	2-Cl	50	18.79
21	H	4-Cl	50	17.55
22	H	2-OCH_3	50	15.56
23	H	4-OCH_3	50	14.78
24	6-I	H	50	14.50
25	6-I	2-Cl	50	19.97
26	6-I	4-Cl	50	18.25
27	6-I	2-OCH_3	50	17.67
28	6-I	4-OCH_3	50	16.88
29	6-Br	H	50	16.35
30	6-Br	2-Cl	50	21.27
31	6-Br	4-Cl	50	20.57
32	6-Br	2-OCH_3	50	19.48
33	6-Br	4-OCH_3	50	18.75
34	H	H	50	22.25
35	H	2-Cl	50	24.72
36	H	4-Cl	50	23.25
37	H	2-OCH_3	50	21.35
38	H	4-OCH_3	50	20.98
39	6-I	H	50	25.23
40	6-I	2-Cl	50	27.24
41	6-I	4-Cl	50	26.45
42	6-I	2-OCH_3	50	26.68
			25	17.20
43	6-I	4-OCH_3	50	36.25
			100	69.21
44	6-Br	H	50	25.67
45	6-Br	2-Cl	50	24.75
46	6-Br	4-Cl	50	24.95
47	6-Br	2-OCH_3	50	27.33
48	6-Br	4-OCH_3	50	26.59
			25	18.30
Phenylbutazone	-	-	50	36.80
			100	64.50

*ALD_{50} values of all compounds were found to be >1000 mg/kg p.o.

paw oedema test at a dose of 50 mg/kg per oral. The compounds (**19-33**) have shown modulate antiinflammatory activity (12.45-21.27 %). Further oxadiazole substituted compounds (**34-48**) have shown better antiinflammatory (21.35-36.25 %) activity than compounds (**19-33**) at the dose of 50 mg/kg p.o. Among these, compound **43** have shown most potent activity, which showed 36.25 % inhibition of oedema. This compound elicited almost equal activity like the standard drug phenylbutazone (36.8 % inhibition at 50 mg/kg p.o.).This compound was further screened for antiinflammatory activity at three graded doses that is 25, 50 and 100 mg/kg p.o. Interestingly, this compound showed better antiinflammatory activity than the standard drug at the dose of 100 mg/kg p.o.

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