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Quinazolinones as Potential Anti-inflammatory Agents

RITU TYAGI, BHAWNA GOEL, V.K. SRIVASTAVA AND A. KUMAR*
Department of Pharmacology,
L.L.R.M. Medical College, Meerut-250004 (U.P.)

2-Methyl-3-arylidenamino-4 (3H)-quinazolinones (Ia-Ie) on cyclocondensation with thiolactic acid and diazomethane are converted into thiazolidinyl quinazolinones (IIa-IIe) and triazolidinyl quinazolinones (IIIa-IIIe) respectively. Their structures have been delineated by IR, ^{1}HNMR and mass spectroscopy. The compounds were evaluated for anti-inflammatory activity.

VARIOUS quinazolinone derivatives are reported to possess broad spectrum biological activities that include cardiovascular[1], anthelmentic[2], antiparkinsonian[3,4] and anti-inflammatory[5]. This prompted us to synthesize newer 2,3 disubstituted quinazolinone derivatives with a view to develop new molecules with better anti-inflammatory activity. The most active compound, 2-Methyl-3-[5'-(2,6-dichlorophenyl)-Δ^2-triazolinyl]-4 (3H)-quinazolinone (IIIa) was compared with phenylbutazone, with reference to the anti-inflammatory potency (ED_{50}) and ulcerogenic liabilities. The CVS and CNS effects and toxicity of this compound have also been investigated.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. The purity of the compounds was checked by TLC using silica gel G. IR spectra (KBr) were recorded on a Parkin-Elmer 137 spectrophotometer and PMR spectra ($CDCl_3$/$DMSOd_6$) on a varian A 90D using TMS as an internal standard. Mass spectra were recorded on a JMSD 3000 instrument with JMS 2000 data system.

2-Methyl-3 (substituted arylidene)-4 (3H) quinazolinones (Ia-Ie)

A mixture of 2-Methyl-3-amino-quinazolinone (0.01 mol) and substituted benzaldehyde (0.01 mol) were dissolved in absolute ethanol (50 ml) in the presence of few drops of glacial acetic acid. The reaction mixture was refluxed for 8 h and poured into water and the resultant solid was washed with petroleum ether and recrystallized from an appropriate solvent. Compound Ia, IR (ϑmax), 1710 (CO), 1620 (C=N) cm^{-1}; $CDCl_3$ δ 8.15-7.20 (m, 7H, ArH), 8.60 (s, 1H, N=CH), 2.25 (s, 3H, CH_3-Ar); $[M]^+$ m/z 322.

*For Correspondence

2-Methyl-3-[4'-oxo-5'-methyl)-thiazolidinyl]-4 (3H)-quinazolinones (IIa-IIe) :

To a cooled mixture of Ia-Ie (0.01 mol) and triethylamine (0.02 mol) in dry DMF (50 ml), thiolactic acid (0.02 mol) was added dropwise with stirring at ambient temperature and the mixture was kept for 3 days at room temperature and refluxed for 12 h. The reaction mixture was filtered and the filterate concentrated and poured into crushed ice. The resulting solid was recrystallized from an appropriate solvent. Compound IIa, IR (ϑmax), 1710 (CO), 1590 (C-N), 1760 (C=O of β-lactam ring) cm^{-1}; $DMSOd_6$ δ 8.30-7.10 (m, 7H, ArH), 6.65 (s, 1H, Ar-CH)5.50 (q, 1H, CH_3 CH of thialactam ring), 4.45 (d, 3H, CH_3 CH of thialactam ring), 2.30 (s, 3H, CH_3-Ar) (ppm) $[M]^+$ m/z 420.

2-Methyl-3 [5' (substituted phenyl)-Δ^2-triazolinyl]-4 (3H) quinazolinones

A solution of Ia-Ie (0.01 mol) in dry THF was treated with excess of dry and ethereal diazomethane. The reaction mixture was maintained below 15° during which fresh

Table - I : Physical and analytical data of 2-Methyl-3 (substituted arylidine)-4(3H) quinazolinones (Ia-Ie) and 2-Methyl-3 [4'-oxo-5' methyl)-thiazolidinyl]-4(3H)-quinazolinones (IIa-IIE)

Compound No.	R	MP°C	Molecular Formula*
Ia	2,6-Cl_2	285	$C_{16}H_{11}N_3OCl_2$
Ib	2,4-Cl_2	260	$C_{16}H_{11}N_3OCl_2$
Ic	2-F	225	$C_{16}H_{12}N_3OF$
Id	4-F	215	$C_{16}H_{12}N_3OF$
Ie	2-Cl	195	$C_{16}H_{12}N_3OCl$
IIa	2,6-Cl_2	263	$C_{19}H_{15}N_3O_2SCl_2$
IIb	2,4-Cl_2	271	$C_{19}H_{15}N_3O_2SCl_2$
IIc	2-F	248	$C_{19}H_{16}N_3O_2SF$
IId	4-F	251	$C_{19}H_{16}N_3O_2SF$
IIe	2-Cl	243	$C_{19}H_{16}N_3O_2SCl$
IIIa	2,6-Cl_2	202	$C_{17}H_{13}N_5OCl_2$
IIIb	2,4-Cl_2	216	$C_{17}H_{13}N_5OCl_2$
IIIc	2-F	269	$C_{17}H_{14}N_5OF$
IIId	4-F	191	$C_{17}H_{14}N_5OF$
IIIe	2-Cl	187	$C_{17}H_{14}N_5OCl$

* C, H and N analysis is within the limit (±0.4%)

amount of ethereal diazomethane was added. The ether was then evaporated and the resulting solid was washed with petroleum ether (b.p. 40-60°) and recrystallized from appropriate solvents, compound IIIa, IR (υ max) 1720 (CO), 1520 (N-N), 1429 (N=N) cm^{-1}; $CDCl_3$ δ 8.30-7.75 (m, 7H, ArH), 2.27 (s, 3H, $C\underline{H}_3$), 6.45 (t, 1H, C<u>H</u> of triazoline ring), 5.9 (d, 2<u>H</u> of triazoline ring) (ppm) $[M]^+$ m/z 374.

Pharmacological Studies :

The compound were screened for anti-inflammatory, ulceregenic potentiality and behavioural effects in rats. Rats of either sex weighing between 100-200 g were selected and inflammation was induced in their paw by the method of Winter *et al.* (1962)[6]. The compounds were pretreated one hour before the induction of inflammation to assess their effect on inflammation. The ulcerogenic potential of these compounds was determined by the method of Verma *et al.* (1984)[7]. Anaesthetized cats were selected to observe the effect of the compound on blood pressure according to the method of Kumar et al. (1985)[1]. For changes in behavioural parameters the rats were observed for locomotor activity, hind limb weakness, head-drop, loss of righting reflex and reactivity to sensory stimuli after the administration of these compounds. After 24 h mortality was also noted following the method of Smith (1950)[8].

RESULTS

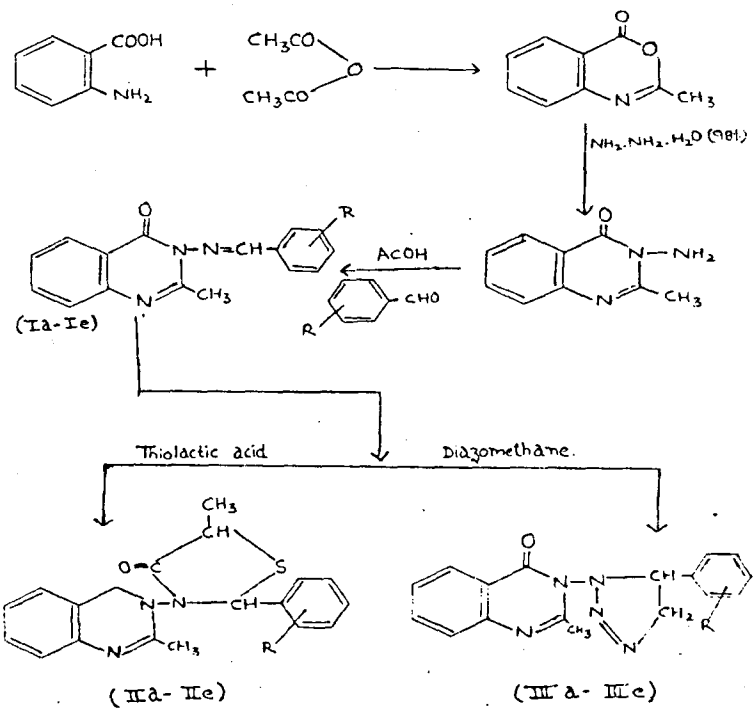
Newly synthesized compounds were evaluated for anti-inflammatory activity on carrageenan-induced rat paw oedema. All compounds were tested at a dose of 50 mg/

Table-2 : Anti-inflammatory activity of 2-Methyl-3-[5'-(substituted phenyl) -Δ^2-triazolinyl]-4 (3H) quinazolinones (IIIa-IIIe)

Compound No.	R	Dose mg/kg p.o.	% Anti-inflammatory activity	ALD_{50}
IIIa	2,6-Cl_2	25	16.6*	
		50	39.8*	>2000
		100	51.2*	
IIIb	2,4-Cl_2	50	32.6*	>1000
IIIc	2-F	50	30.6*	>1000
IIId	4-F	50	28.2*	>1000
IIIe	2-Cl	50	25.1*	>1000
Phenylbutazone		25	26.98*	
		50	34.65*	
		100	48.6*	

* $P < 0.05$

SCHEME



kg p.o. Arylidenamino quinazolinones (Ia-Ie), the first stage compounds have elicited mild anti-inflammatory activity of varying degree (9.4-15.7% inhibition of oedema). Thiazolidinyl quinazolinones IIa-IIe (second stage compounds), exhibited moderate percent (20.4 to 26.7) inhibition of oedema. However, these compounds (Ia-Ie and IIe-IIe) did not show statistically significant anti-inflammatory activity.

On the contrary, triazolinyl quinazolinones IIIa-IIIe, in general, have shown potent activity (table-2). Moreover, the compound IIIa exhibited most potent activity (39.8% inhibition of rat paw oedema at 50 mg/kg dose). Being the most potent compound it was further studied in detail to establish a dose response relationship (25, 50 and 100 mg/kg oral) and was also compared with standard drug phenylbutazone (PBZ). Both drugs showed approximately equal anti-inflammatory activity (ED_{50} of compound IIIa = 96.4 mg/kg and ED_{50} of phenylbutazone is 100 mg/kg oral).

Graded doses of compound IIIa and the standard drug were injected intraperitonially to rats and incidence of ulceration was determined. The compound IIIa had much less ulcerogenic liability as compared to phenylbutazone UD_{50} = 199.5 mg/kg i.p., UD_{50} of PBz = 66.6 mg/kg i.p.

This compound has no significant effect on the cardiovascular system of the cat at a dose of 1.25 and 2.5 mg/kg i.v. However at a dose of 5 mg/kg i.v. it induced a transient fall of 15 mm Hg in blood pressure.

Compound IIIa was given orally in a dose of 500, 1000, 1500, 2000 mg/kg in rats. Doses upto 1500 mg/kg did not show any change in gross behaviour but in the highest dose it however induced mild retardation of of locomotor activities without hypnosis or muscular weakness.

The LD_{50} of compounds could not be determined as no animal died upto the maximum dose tested (>2000 mg/kg p.o.).

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