Arch. Pharm. (Weinheim) *316*, 431–434 (1983)

Synthesis of Some New 2-(Phenoxyacetylthio)-3-aryl-6-bromo- or -6,8-dibromoquinazoline-4(3*H*)-ones a Possible AChE Inhibitors

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Eingegangen am 8. April 1982

Sixteen new 2-(phenoxyacetylthio)-3-aryl-6-bromo- or -6,8-dibromoquinazolones were synthesized by condensation of various phenoxyacetyl chlorides with mercaptoquinazolones. Their inhibitory properties towards choline esterase and their bactericidal activities were studied *in vitro*. Nine of the compounds exhibited (> 50 %) choline esterase inhibition, whereas the antibacterial screening showed moderate results.

Synthese einiger neuer 2-(Phenoxyacetylthio)-3-aryl-6-brom- oder 6,8-dibromchinazolin-4(3*H*)one als potentielle Acetylcholinesterase-Hemmer

Die Synthese von 16 neuen 2-(Phenoxyacetylthio)-3-aryl-6-brom- oder 6,8-dibrom-chinazolonen durch Kondensation verschiedener Phenoxyacetylchloride mit Mercaptochinazolonen wird beschrieben. Ihre cholinesterasehemmende Wirkung und antibakterielle Aktivität wurden *in vitro* geprüft. 9 Verbindungen zeigten starke Cholinesterasehemmung, aber nur mäßige antibakterielle Wirkung.

The multifacet biological properties of 4 (3*H*)-quinazolones which include insecticidal[1,2] and bactericidal[3] activities are well known. In addition, some of the quinazolone derivatives[4,5] have been shown to possess antiacetylcholinesterase activity. In continuation of our earlier studies[6–8] on the synthesis of substituted quinazolone derivatives as potential antiacetylcholinesterase agents, it was considered reasonable to synthesize the title quinazolones which are reported in this communication and to study their potential AChE inhibitor activities.

The authors express their sincere thanks to the Head, Department of Chemistry, Lucknow University, India for providing necessary facilities, to Director, C.D.R.I., Lucknow, India for micro analysis and I.R. Spectroscopy of the compounds and one of us (*K.H.*) is grateful to U.G.C. for the award of J.R.F.

Experimental

MP: open capillaries (uncorr.). *I.R. spectra*: Perkin-Elmer 137 spectrophotometer. *TLC* on silica gel G plates.

0365–6233/83/0505–0431 $ 02.50/0

2-Mercapto-3-aryl-6-or 6,8-dibromo-4-(3H) quinazolones **1**

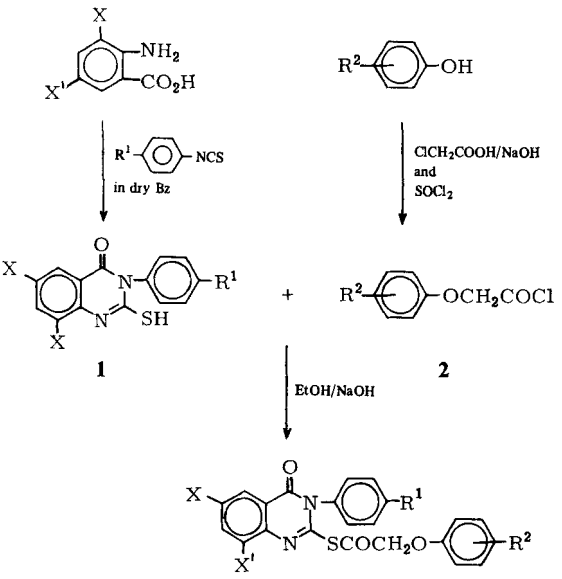
prepared by the known method of *Bhargava* and *Chaurasia*[9,10].

4-Substituted phenoxyacetylchlorides **2**

These were prepared by refluxing 0.01 mole of substituted phenoxyacetic acids[11,12] with minimum quantity of thionyl chloride for about 4 h. Excess thionyl chloride then was distilled off under reduced pressure.

6- or 6,8-Dibromo-2(phenoxyacetylthio)-3-aryl-4(3H)quinazolones **3–18**

4.25 g (0.01 mole) **1** was suspended in 30 ml of warm ethanol and 0.4 g of sodium hydroxide and the solution stirred until a clear solution was obtained. To this 1.84 g (0.01 mole) **2** was added and heated under reflux for 6 h. Finally it was cooled and poured in ice water, the solid thus separated was washed with cold water and recrystallised from ethanol.



3 -18

Biochemical Studies

Acetylcholinesterase inhibitory activity

It was determined following the method of *Parmar* et al.[4]

Homogenate preparation

Adult albino rats weighing about 100–200 g were killed by decapitation. Brain was quickly removed and washed with chilled 0.25 N-sucrose. Tissue was homogenised in sucrose in cold. The homogenate was diluted with sucrose so that 1,0 ml of this preparation was equivalent to 100 mg of fresh tissue i.e. 1 % (w/v) of fresh tissue.

Determination of acetylcholinesterase activity

The reaction mixture in a final vol. of 2.0 ml contained 1 ml of 0.5M-phosphate buffer pH 7.4, 0.2 ml of 3.5N-NaCl, 0.2 ml 0.015 M-acetylthiocholine and 0.4 ml of enzyme preparation and a suitable amount of water. The reaction was started by the addition of substrate after 10 min of preincubation at 37 °C. After incubation for 15 min the reaction was stopped by addition of 0.5 ml of trichloroacetic acid. Simultaneously control experiments were carried out in which all the constituents were the same as described above except the substrate which was added after the addition of trichloroacetic acid. Tubes were chilled and centrifuged at 700 g for 15 min. Aliquot of the supernatent was taken out. The thiocholine content was determined as given below.

2 ml of saturated sodium chloride, 0.4 ml of sodium carbonate/sodium cyanide and 0.4 ml of sodium nitroprusside solution was taken in a cuvette, to this 0.20 ml of clear supernatent of the reaction mixture was added and the optical density was measured after 30 sec at 520 nm. The difference in optical density of the control and the experiment corresponds to the enzyme activity. Propylene glycol was used as solvent.

Table 1: *Physical constants of quinazolone derivatives* **3–18**

Compound No.	R^1	R^2	X	X′	m.p. °C	Yield %	Molecular formula	N Calc.	N Found	AChE inhibition* %
3	H	4-Cl	H	H	282	65	$C_{22}H_{15}N_2O_3SCl$	6.6	6.3	25
4	H	2-Cl	H	H	266	55	$C_{22}H_{15}N_2O_3SCl$	6.6	6.5	55
5	H	2-CH_3	H	H	251	60	$C_{23}H_{18}N_2O_3S$	6.9	6.9	70
6	H	4-CH_3	H	H	260	65	$C_{23}H_{18}N_2O_3S$	6.9	6.8	60
7	Br	4-Cl	H	Br	244	60	$C_{22}H_{13}N_2O_3SBr_2Cl$	4.8	4.7	70
8	Br	2-Cl	H	Br	275	62	$C_{22}H_{13}N_2O_3SBr_2Cl$	4.8	4.8	85
9	Br	2-CH_3	H	Br	290	70	$C_{23}H_{16}N_2O_3SBr_2$	5.0	4.9	90
10	Br	4-CH_3	H	Br	273	65	$C_{23}H_{16}N_2O_3SBr_2$	5.0	4.9	90
11	CH_3	4-CH_3	H	Br	297	51	$C_{24}H_{19}N_2O_3SBr$	5.6	5.6	70
12	CH_3	4-Cl	H	Br	290	45	$C_{23}H_{16}N_2O_3SBrCl$	5.4	5.4	0
13	CH_3	2-Cl	H	Br	272	50	$C_{23}H_{16}N_2O_3SBrCl$	5.4	5.4	0
14	CH_3	2-CH_3	H	Br	290	55	$C_{24}H_{19}N_2O_3SBr$	5.7	5.6	90
15	Cl	2-CH_3	Br	Br	232	58	$C_{23}H_{15}N_2O_3SBr_2Cl$	4.7	4.4	10
16	Cl	2-Cl	Br	Br	243	60	$C_{22}H_{12}N_2O_3SBr_2Cl_2$	4.6	4.9	10
17	Cl	4-Cl	Br	Br	204	65	$C_{22}H_{12}N_2O_3SBr_2Cl_2$	4.2	4.8	0
18	Cl	4-CH_3	Br	Br	198	67	$C_{23}H_{15}N_2O_3SBr_2Cl$	4.7	4.7	0

* The values are mean of two separate experiments.

4: IR (KBr) vmax = 1730 (acyclic CO) 1650 (α, β unsaturated (O) 1620 (C=N) 1260 cm^{-1} (CH_2O=C).

9: IR(KBr) vmax = 1710 (acyclic CO) 1660 (α, β unsaturated CO) 1620 (C=C 1270 cm^{-1} (CH_2O=C).

Results

It is evident from the table 1 that half of the compounds showed more than 60 % inhibition at the concentration 10^{-3}M. Compounds substituted with a bromo atom in the 3-aryl-ring coupled with an electron donating group in the phenyl ring of the phenoxy

acetyl group showed the maximum inhibition **(7, 8 and 10)**. Further it is interesting to note that the introduction of a second bromo atom in the quinazolone nucleus turned out to be unfavourable and produced compounds totally devoid of enzyme inhibitory action.

Antibacterial activity

All the compounds reported in Table 1 were assayed *in vitro* against different bacteria, namely Bacillus pumilus, Bacillus subtilis, Bacillus cereus and Staphylococcus aureus using the agar plate technique[13]. Tetracycline was used as control in all the four cases. All the compounds tested showed only marginal interaction with all the micro-organisms used. Further the study of antibacterial screening showed no correlation between bacterial action and acetylcholinesterase inhibition.

Table 2: *Antibacterial activity*
Mean area inhibition after 24 hr

No.	B.pumilus	B.subtilis	B.cereus	S.aureus	No.	B.pumilus	B.subtilis	B.cereus	S.aureus
1	–	–	–	–	9	–	–	+	–
2	+	–	+	–	10	+	+	–	–
3	–	+	–	+	11	+	–	–	–
4	–	++	–	–	12	–	–	–	–
5	–	+	–	+	13	++	+++	+++	+
6	–	–	–	–	14	+	++	+++	+
7	+	–	+	–	15	–	+	+++	–
8	+	–	++	++	16	–	–	++	–

– = No inhibition; + = Zone size 6–8 mm; ++ = Zone size 8–12 mm; +++ = Zone size greater than 12 mm.

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