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Anticonvulsant and some neuropharmacological properties of 2-methyl-3-*o*-tolyl-6-chloro-4(3*H*)-quinazolone and related compounds

V. L. MEHTA AND C. L. MALHOTRA

Three 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolone derivatives and five 3-*p*-bromophenyl-4(3*H*)-quinazolone derivatives were screened for oral anticonvulsant, analgesic and hypothermic properties. The anticonvulsant properties were assessed using a modified maximal electroshock seizure test and the leptazol threshold test. 2-Methyl-3-*o*-tolyl-6-chloro-4(3*H*)-quinazolone, being the compound with the greatest anticonvulsant action, was examined in more detail. It is about 1½ times more potent than phenytoin sodium against electroshock induced convulsions, and its potency ratio with phenobarbitone is 1·2 to 1. Against leptazol-induced convulsions, it is 10 times more potent than troxidone. Its sedative-hypnotic properties are much less than those of phenobarbitone sodium and it also has a much weaker potentiating action on phenobarbitone-induced hypnosis. There is no reduction in the spontaneous motor activity of normal and amphetamine-stimulated rats at its ED50 dose level. None of the compounds possesses any analgesic or hypothermic properties.

SOME quinazol-4-one derivatives possess potent hypnotic and other neuropharmacological properties (Gujral, Saxena & Tiwari, 1955; Gujral, Kohli & Saxena, 1955). As some hypnotic drugs and their chemical congeners possess anticonvulsant activity, Gujral, Saxena & Tiwari (1957) screened some of the quinazol-4-one compounds for anticonvulsant action and found 2-methyl-3-*o*-tolyl-quinazol-4-one (QZ-2) quite potent against electroshock and leptazol-induced convulsions. Bianchi & David (1960) screened a series of 2,3-disubstituted quinazolones and found 2-methyl-3-*p*-bromophenyl quinazolone (BDH-1880) to be the most potent as an anticonvulsant in the same tests.

We have synthesised some 4(3*H*)-quinazolones and examined them for their anticonvulsant, hypothermic and analgesic actions. The chemical structure of the compounds is given in Table 1. As the compound 2-methyl-3-*o*-tolyl-6-chloro-4(3*H*)-quinazolone (compound No. 8) possessed marked anticonvulsant action, it was examined in greater detail for its anticonvulsant action, sedative hypnotic properties, hypnotic potentiation action and its effects on spontaneous motor activity. Its ED50, LD50 and therapeutic indices for anticonvulsant action were also calculated. Troxidone, phenytoin sodium and phenobarbitone sodium were reference standards. The compound No. 8 was synthesised by Salimath, Patel & Shah (1956). It crystallises from dilute ethanol in colourless granules, m.p. 167°, is soluble in ethanol but insoluble in water *M* 284·5; the molecular formula is $C_{16}H_{13}ClN_2O$.

Experimental

The compounds were administered in 5% gum acacia such that the dose/g body weight was contained in 1 ml; control groups received 5% gum acacia only. Drugs were given orally to rats of 80–120 g weight, and injected intraperitoneally in mice of 15–25 g. Animals were allowed

From the Department of Pharmacology and Therapeutics, Lady Hardinge Medical College, New Delhi, India.

free access to food and water, except during experiments, because starvation modifies the supramaximal-electroshock seizure pattern test by prolonging the tonic-extensor component, and reduces the threshold for minimal electroshock seizure (Davenport & Davenport, 1948).

Anticonvulsant activity. The anticonvulsant activity of the quinazolones was assayed by a modificd maximal electroshock seizure test in normal albino rats, using corneal electrodes with current strength of 150 mA for 0·3 sec (Harned & others, 1953) and also by protection of albino rats against leptazol-induced convulsions (Swinyard, Brown & Goodman, 1952).

The compounds were administered orally in doses of 200 and 300 mg/kg, except compound No. 8 which was given in doses ranging from 5–300 mg/kg. In the electroshock test, convulsions were induced by convulsometer before the drug, to assess the positive response, and also 2 hr after the drug when the abolition of the hind leg extensor component was taken as the end-point. Leptazol convulsions were induced in rats by injecting 80 mg/kg in the loose subcutaneous tissue of the back 1 hr 50 min after giving the test drug.

Analgesic effect. The rat tail radiant heat method of Davies, Raventos & Walpole (1946) was used and the effect of drugs was noted at 30 min intervals for 2 hr. after the compounds in 200 and 300 mg/kg doses.

Hypothermic effect. Any change in body temperature in rats was observed by noting the rectal temperature 30 min before, and at 30 min intervals for 2 hr after the compounds in 200 and 300 mg/kg doses.

Neurological toxicity. This was studied before and after administration of the drug by neurotoxicity tests outlined by Swinyard & others (1952).

The preliminary screening showed compound No. 8 to be the most potent of the compounds examined; it therefore received further attention.

Sedative-hypnotic properties. The hypnotic activity of compound No. 8 was assessed in 10 albino mice. Three doses, 5, 10 and 20 mg/kg, were given intraperitoneally. Two control groups of 10 animals were also used; one was given phenobarbitone 5, 10 and 20 mg/kg and the other 5% gum acacia alone. The mice were observed for loss of righting reflex for 8 hr. Results were calculated in mice hr units.

Hypnotic potentiation activity. Compound No. 8 and phenobarbitone were given in doses of 5, 10 and 20 mg/kg intraperitoneally to groups of animals and another group was given 5% gum acacia. Pentobarbitone sodium was injected 30 mg/kg intraperitoneally 30 min after drug administration and the sleeping time of compound No. 8-treated group was compared with that of the phenobarbitone- and gum acacia-treated groups.

Spontaneous motor activity. The effect on spontaneous motor activity of compound No. 8 and phenobarbitone was examined in groups of albino rats in doses of 20, 40, 80 and 160 mg/kg. Each dose was given to five animals and the effect was assessed before and 2 hr after the drug.

The effect of drugs on amphetamine-stimulated rats was similarly studied. Amphetamine sulphate was given, 2 mg/kg intraperitoneally, 2 hr 45 min after drug administration.

Acute toxicity studies. Acute toxicity studies of compound No. 8 were made in rats, eight doses being used. The drug was administered orally and the animals were observed for 48 hr. The LD50 value was calculated by the method of Litchfield & Wilcoxon (1949).

Results

ANTICONVULSANT ACTIVITY

Modification of the supramaximal seizure pattern test. The results of assay of the eight compounds are summarised in Table 1. Of these, compound No. 8 was the most potent. According to the Litchfield & Wilcoxon method, the oral ED50 of compound No. 8 was 18 mg/kg (27·9–11·6); that of phenytoin sodium was 28 and phenobarbitone 22 mg/kg.

TABLE 1. ANTICONVULSANT ACTIVITY OF 4(3H)-QUINAZOLONES AGAINST ELECTRO-SHOCK AND LEPTAZOL INDUCED CONVULSIONS

Compound No.	Protection against maximal electro-shock seizure pattern test				Protection against leptazol-induced convulsion			
	Dose 200 mg/kg		Dose 300 mg/kg		Dose 200 mg/kg		Dose 300 mg/kg	
	No. of rats used	Protection %	No. of rats used	Protection %	No. of rats used	Protection %	No. of rats used	Protection %
2-Methyl-3-*p*-bromophenyl-6-bromo-4(3*H*)-quinazolone (1)	20	10	20	10	20	20	20	25
2-Methyl-3-*p*-bromophenyl-6,8-dibromo-4(3*H*)-quinazolone (2)	10	Nil	10	30	10	Nil	10	20
2,6-Dimethyl-3-*p*-bromophenyl-4(3*H*)-quinazolone (3)	10	Nil	10	20	10	Nil	10	40
2-Methyl-3-*p*-bromophenyl-6-chloro-4(3*H*)-quinazolone (4)	10	10	20	40	10	20	10	40
2-Methyl-3-*p*-bromophenyl-6-chloro-8-bromo-4(3*H*)-quinazolone (5)	10	Nil	10	20	10	Nil	10	30
2-Methyl-3-*o*-tolyl-6,8-dibromo-4(3*H*)-quinazolone (6)	10	Nil	10	20	10	Nil	10	20
2-Methyl-3-*o*-tolyl-6-chloro-8-bromo-4(3*H*)-quinazolone (7)	20	65	20	75	30	70	30	70
2-Methyl-3-*o*-tolyl-6-chloro-4(3*H*)-quinazolone (8)	30	100	30	100	40	80	40	90
Dilantin sodium 80 mg/kg	30	90	—	—	—	—	—	—
Troxidone 500 mg/kg	—	—	—	—	30	90	—	—

Leptazol threshold test. Results are given in Table 1. Compound No. 8 was found to be the most potent; its oral ED50 was 23 mg/kg (11–48) while that of troxidone was 200 mg/kg.

Analgesic and hypothermic activity. Of the eight compounds tested, none was found to have any analgesic or hypothermic activity.

Sedative-hypnotic properties. The mean sleeping time in the untreated control groups (gum acacia treated rats) was 21 mice-hr units and with

the approximate ED50 dose of compound No. 8 and phenobarbitone (about 20 mg/kg in both instances) it was 34 mice-hr units and 50·8 mice-hr units respectively.

Hypnotic potentiation. The mean onset of hypnosis with phenobarbitone treated rats was 1 hr 15 min, and with compound No. 8 it was 14 min. Other data are in Table 2.

TABLE 2. HYPNOTIC POTENTIATING EFFECT OF COMPOUND NO. 8 AND PHENOBARBITONE ON PENTOBARBITONE-INDUCED HYPNOSIS. ROOM TEMPERATURE, 28°

Drug administered intraperitoneally mg/kg	Pentobarbitone sodium intraperitoneally mg/kg	Mean sleeping time in min	Potentiation %	P value compared with phenobarbitone
Compound No. 8				
5	30	38 ± 3·5	58	
10	30	45·5 ± 5·4	90	<0·05>0·001
20	30	53 ± 7·0	121	<0·05>0·001
Phenobarbitone				
5	30	48·5 ± 5·2	102	
10	30	62·5 ± 6·8	160	
20	30	68·5 ± 9·2	185	
Gum acacia 5%	30	24 ± 2·2	—	

Spontaneous motor activity. There was no reduction in spontaneous motor activity of normal and amphetamine-stimulated rats at doses of 20 and 40 mg/kg orally with compound No. 8. A reduction produced by this compound at a dose of 160 mg/kg was about the same as that produced by 40 mg/kg of phenobarbitone orally, both in normal and amphetamine stimulated rats.

The experimental results indicate that compound No. 8 is a compound with some promise, being more active than phenobarbitone without the drawback of sedative-hypnotic effect. Its LD50 is 6 g/kg. The therapeutic index is above 250.

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