ANTICONVULSANT PSYCHOPHARMACOLOGICAL AND SOME OTHER PROPERTIES OF QUINAZOLONES

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The importance of pyrimidine nucleus in the metabolism of neurone is well recognised. Several compounds which are intimately concerned with the essential life processes of the neurones such as vitamins, coenzymes and both RNA and DNA of the mitochondria and of the nuclei contain pyrimidine moiety. It is not surprising that quite a large number of central nervous system depressants are derived from this ring system. It has been shown (12,20) amongst quinazolones studied that certain 3-aryl-6-alkyl possessed central nervous system depressant action. It was found (4) that compound 3-phenyl-quinazol-4-one was equal to acetylsalicylic acid as far as antipyretic action in febrile rats was concerned. Quinazol-4-ones have been found to have potent hypnotic (9, 8), antipyretic and hypothermic (14) anticonvulsant and antiepileptic (10, 1 and 13) properties.

The present study deals with seventeen 4 (3H)-quinazolone compounds as far as their anticonvulsant (Table I), analgesic and hypothermic properties are concerned. Since the compound, 2 : 6-dimethyl-3-0-tolyl 4 (3H)-quinazolone (QZL-9) was found to be the most potent anticonvulsant in this series a detailed study was done, with particular reference to its sedative-hypnotic action, hypnotic potentiation properties, effect on spontaneous motor activity, haemodynamic studies and behavioral studies. Its ED_{50} both against electroshock and Leptazol induced convulsions and the oral LD_{50} in rats was also determined.

METHODS AND MATERIALS

The compounds (QZL) were insoluble in water, they were administered orally except otherwise mentioned as 5% gum acacia suspension so that 1 ml contained the dose/gm of body wt. The compounds were administered in doses of 200 mg and 300 mg/kg unless otherwise stated. Gum acacia 5% solution was used as control.

I. *Anticonvulsant activity* :—Three groups of 10 rats each were used for each dose of the compounds. The anticonvulsant properties were studied by two assay techniques. Before and after the administration of drugs each animal was examined for neurotoxicity tests (17).

(a) *Modification of maximal electroshock seizure pattern test* :—Convulsions were induced by means of convulsometer by using corneal electrodes with current strength of 150 mA for 0.3 sec. (11). Only those animals were selected which exhibited extension of the hind limbs with supramaximal shock. The shock was delivered 2 hours after drug administration and the desired end point of the drug for protection was abolition of the hind leg extension. Two control groups were used. One was given phenytoin sodium 30 mg/kg orally and the other was given only 5% gum acacia.

(b) *Leptazol threshold test* —Leptazol convulsions were induced in the rat by giving leptazol 80 mg/kg in the loose subcutaneous tissue of the back. Two control groups were employed ; one was given only 5% gum acacia and while the other 500 mg/kg Troxidone.

II. *Analgesic activity* :—It was studied by means of radiant heat method (6). Troxidone 500 mg/kg was used as control. The analgesic activity was assessed before the administration of drug and after ½ hour, 1 hour and 1½ hours of drug administration.

III. *Hypothermic activity* ;—Any change in body temperature was observed in rats by noting the rectal temperature before and after drug administration alongwith the control groups.

IV. *Spontaneous motor activity* :—The effect on spontaneous motor activity in normal and amphetamine stimulated rats (amphetamine sulphate 2 mg/kg I. P. 1 hour and 45 minutes after drug administration) was studied on spring tambour mounted activity cage. QZL-9 was given in doses of 100, 150 and 200 mg/kg. The control groups received chlorpromazine in doses of 1, 2, and 3 mg/kg and Troxidone in doses of 200, 300 and 500 mg/kg.

V. *Hypnotic activity* :—Hypnotic activity of QZL-9 was studied in albino rats in doses of 100, 150 and 200 mg/kg. Two control groups were taken ; one was given phenobarbitone sodium 80 mg/kg orally while the other received only 5% gum acacia. Animals were observed for eight hours for any sedation or hypnosis.

VI. *Hypnotic potentiation activity* :—Rats weighing between 40-60 gm were divided into four groups of 10 each. Three doses of QZL-9, i.e., 100, 150 and 200 mg were studied using fresh animals each time. The control groups were given gum acacia only. Pentobarbitone sodium was injected 35 mg/kg I.P., 1 hour and 45 minutes after drug administration and the sleeping time was noted.

VII. *Behavioral studies* :—Behavioral studies were performed by two techniques to study the Conditioned Avoidance Response (CAR).

(a) *Cooks pole climbing apparatus* :—The animals were divided into six groups of 10 rats each. Three doses of QZL-9, viz., 100, 150 and 200 mg/kg were given orally. Chlorpromazine in doses of 1, 2.5 and 5 mg/kg was given I. P. Each group was given one dose only. Prior testing of the animals before giving drug served as their own control. The effect of QZL-9 was seen after 2 hours while that of chlorpromazine was seen after 30 minutes. Before each experiment the CAR was reinforced in trained rats 4-5 times to ensure good response throughout the experiment.

(b) *Skinner's pigeon box* :—This was used for studies on behaviour of pecking performance in pigeons depending on the schedule of reward. The technique employed was the same as used by Skinner and his co-workers (16, 7). Skinner's pigeon box modified by Peter, B. Dews was used. The pigeons were trained on fixed ratio (FR) 64 (reward after 64 pecks) and fixed interval (FI) 5 minutes (reward on first peck after every 5 minutes).

The effect of QZL-9 was compared with phenobarbitone sodium. Multiple schedule was used. The trained pigeon was placed in the completely darkened box and

One dose per group and each experiment was repeated five times using.

after 15 minutes it was put to standard run. The standard run consisted of the following sequence, FR, FI, FR, 2FI, 8FR, FI and 2FR. The record of the normal pigeons were taken. Three pigeons were given three different doses of QZL-9 ; one was given 100 mg/kg, the other 150 mg/kg while the third 200 mg/kg orally. The fourth pigeon was given phenobarbitone sodium 20 mg/kg intramuscularly. The pigeons were then put on standard run, 2 hours, 6 hours and 24 hours after drug administration. Record taken before the administration of drug served as control.

VIII. *Haemodynamic Experiments* :—(a) *Effect on isolated frog heart and rabbit heart* :—After recording the normal tracings, the effect of QZL-9 was seen in doses of 2.5, 5, 10 and 20 mg i/v.

(b) *Effect on blood pressure and respiration* :—The effect of QZL-9 in doses of 2.5, 5 and 10 mg/kg was studied on dog blood pressure and respiration both before and after atropine (2 mg/kg i/v.), Synopen (5 mg/kg i/v) and Ansolysen (2.5 mg/kg i/v).

IX. *Acute Toxicity studies of QZL-9* —Acute toxicity studies were conducted in rats. Nine different doses varying between 1.75 gm and 4 gm/kg were employed orally and LD_{50} was calculated (18).

RESULTS

I. *Anticonvulsant activity* : (a) *Modification of the maximal electroshock seizure pattern test* :—The results of assay of seventeen compounds are given in Table I. QZL-2 (2-Methyl-3-p-bromo-phenyl-4 (3H)-quinazolone) was used by Bianchi and David (1). Out of compounds tested, QZL-9 (2 : 6-dimethyl-3-o-tolyl) was found to be the most active. It showed 80% protection in dose of 200 mg/kg, while with dose of 300 mg/kg it exhibited 90% protection. QZL-11 though showed 100% protection with dose of 300 mg/kg it was found to be neurotoxic. The animals were markedly sedated, the righting reflex was absent and there was flaccidity of the voluntary muscles. With phenytoin sodium there was 90% protection in dose of 80 mg/kg orally.

(b) *Leptazol threshold test* :—The results are summarised in Table I. QZL-9 showed 75% protection with 200 mg/kg and 80% protection with 300 mg/kg, (protection means no convulsions lasting for period of 5 seconds or more ; tremulousness or hyper activity was not taken into account). With Troxidone there was 90% protection with 500 mg/kg.

The ED_{50} of QZL-9 against maximal electroshock seizure pattern test was 135 mg/kg orally while that of phenytoin sodium was 28.18 mg/kg orally. The ED_{50} against leptazol induced convulsions was 150 mg/kg, while that of Troxidone was 200 mg/kg orally.

II. *Analgesic activity* :—None out of 17 quinazolone compounds tested showed any analgesic activity.

III. *Hypothermic activity* —No hypothermic activity was seen with any of the 4 (3H) quinazolones tested.

TABLE I

Anticonvulsant activity of 4 (3H)-quinazolones against electroshock and Leptazol-induced convulsions

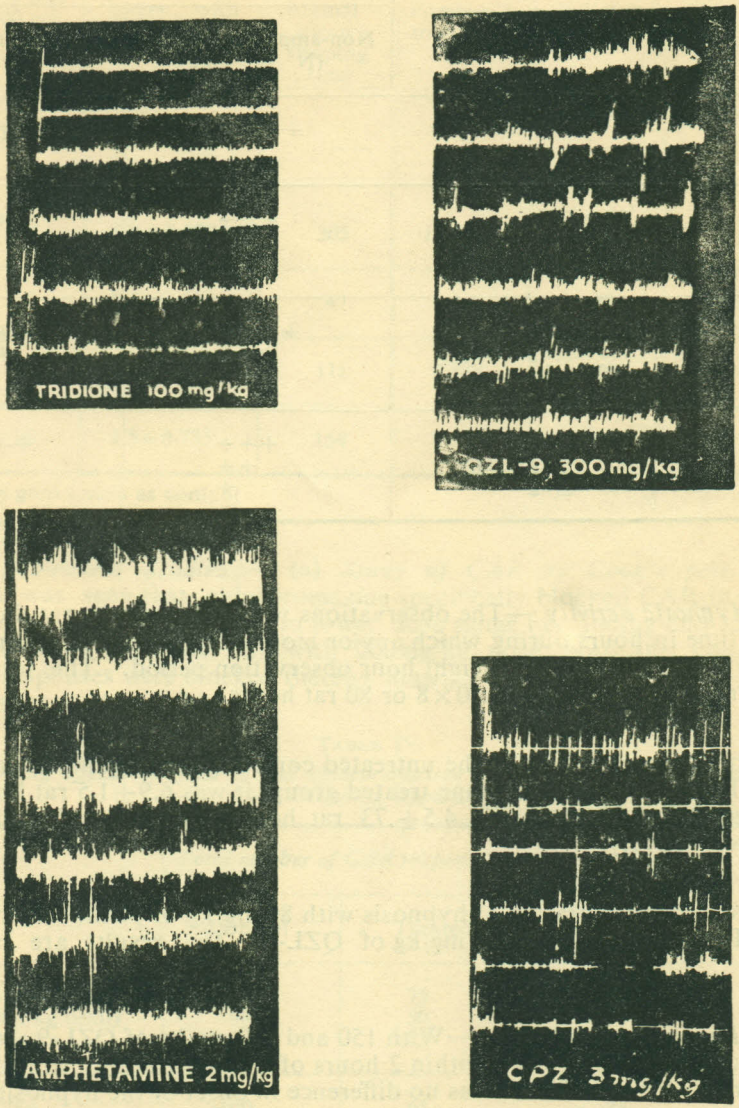
S. No. (1)	Chemical name & code No. (2)	Protection against Maximal Electroshock Seizure Pattern Test.		Protection against Leptazol induced convulsions	
		Dose 200 mg/kg Percentage protected. (3)	Dose 300 mg/kg Percentage protected (4)	Dose 200 mg/kg Percentage protected (5)	Dose 300 mg/kg Percentage protected (6)
1.	2-Methyl-3-p-bromo-phenyl-4(3H)-quinazolone (QZL-2) (B.D.H.-1880)	80(10)	90(10)	80(10)	80(10)
2.	2-Styryl-3-p-bromo-phenyl-6-bromo 4 (3)-quinazolone (QZL-3).	Nil(10)	20(10)	20(20)	25(20)
3.	2-p-Methoxystyryl-3-p-bromo-phenyl-6-bromo-4(3H)-quinazolone (QZL-4)	20(10)	30(10)	Nil(10)	25(20)
4.	2-styryl-3-phenyl-6- bromo-4 (3H)-quinazolone (QZL-5)	50(20)	60(20)	20(20)	40(10)
5.	2-Methyl-3-phenetyl-6:8-dibromo-4 (3H)-quinazolone (QZL-8)	40(10)	40(10)	Nil(10)	Nil(10)
6.	2:6-Dimethyl-3-o-tolyl-4 (3H)-quinazolone (QZL-9)	80(30)	90(30)	75(40)	80(40)
7.	2:6-Dimethyl-3-p-phenetyl-4 (3H)-quinazolone (QZL-10)	10(10)	20(10)	50(20)	50(20)
8.	2:6-Dimethyl-3-o-anisyl-4 (3H)-quinazolone (QZL-11)	*70(20)	*100(20)	20(60)	15(60)
9.	2:6-Dimethyl-3-p-chloro-phenyl-4 (3H)-quinazolone (QZL-12)	30(10)	40(10)	20(20)	25(20)
10.	2-Methyl-3-p-anisyl-6:8-dibromo-4 (3H) quinazolone (QZL-13)	40(10)	60(20)	30(10)	30(10)
11.	2-Methyl-3-p-chloro-phenyl-6:8-dibromo-4 (3H) -quinazolone (QZL-14)	65(20)	75(20)	20(10)	20(10)
12.	2:6 Dimethyl-3-p-anisyl-4 (3H)-quinazolone (QZL-16)	25(20)	40(20)	Nil(10)	20(10)
13.	2-Methyl-3-o-anisyl-6:8-dibromo-4 (3H)-quinazolone (QZL-17)	25(20)	30(20)	Nil(10)	20(10)
14.	2-Methyl-3-p-chloro-phenyl-6-chloro-4 (3H)-quinazolone (QZL-19)	50(20)	50(20)	25(20)	60(20)
15.	2-Methyl-3-phenyl-6-chloro-4 (3H)-quinazolone (QZL-20)	50(20)	50(20)	Nil(10)	Nil(10)
16.	2-Methyl-3-p-chlorophenyl-6-chloro-8-bromo-4 (3H)-quinazolone (QZL-23)	10(10)	20(10)	Nil(10)	10(10)
17.	2-Methyl-3-phenyl-6-chloro-8-bromo-4 (3H)-quinazolone (QZL-24)	10(10)	20(10)	Nil(10)	20(10)
18.	Troxidone (500 mg/kg)	—	—	90(90)	—
19.	Phenytoin sodium (80 mg/kg)	90(120)	—	—	—
20.	Gum acacia 5%	Nil(120)	—	—	—

Figures in Parenthesis indicate the number of animals employed.

*Marked sedation.

IV. *Spontaneous motor activity*:—There was reduction in spontaneous motor activity of both normal and amphetamine stimulated rats after treatment with QZL-9,

but it was much less than that seen with Troxidone and chlorpromazine. The results are summarized in Table II and Fig. 1.



EFFECTS OF QZL-9 CHLORPROMAZINE AND TRIDIONE. ON AMPHETAMINE STIMULATED RATS .

Fig. 1

TABLE II

Effect of QZL-9, Chlorpromazine and Troxidone on normal and amphetamine stimulated rats

Drug	Dose	Spontaneous Motor Activity (SMA)	
		Non-amphetamine rats (N = 6/gp)	Amphetamine stimulated rats (N=6/gp)
Control (Gum Acacia)	.....	++++	++++++
CPZ	1 mg/kg 2 mg/kg I.P. 3 mg/kg	+++ ++ +	++++++ +++ ++
QZL-9	100 mg/kg 150 mg/kg orally 300 mg/kg	++++ +++ ++	++++++ ++++ +++
Troxidone	100 mg/kg 400 mg/kg orally 500 mg/kg	+++ ++ +	++++++ +++ ++

V. *Hypnotic activity* :—The observations were taken as the rat hour units, i.e., the period of time in hours during which any/or more members of a group of ten rats manifested hypnotic effect over an eight hour observation period. The total observation period for a group of 10 rats being 10×8 or 80 rat hours.

The mean sleeping time in the untreated control group (gum acacia treated) was 1.70 ± 0.6 rat hours, in phenobarbitone treated group, it was 6.9 ± 1.5 rat hours and with QZL-9. it was 2.5 ± 0.82, $3.6 \pm .80$, $4.5 \pm .73$ rat hours with 100, 150 and 200 mg/kg body weight respectively.

It was seen that duration of hypnosis with 80 mg/kg of phenobarbitone is significantly more ($P < .001$) than with 200 mg/kg of QZL-9. The results are summarized in Table III.

VI. *Hypnotic potentiation* :—With 150 and 200 mg/kg of QZL-9 the animals were sedated but did not go off to sleep within 2 hours of administration, while with 100 mg/kg there was no sedation. There was no difference in onset of the hypnosis with QZL-9 and pentobarbitone treated rats as compared to control groups treated with pentobarbitone and gum acacia. As regards duration of sleep there was increase of 55%, 84% and 110% with doses of 100, 150 and 200 mg/kg of QZL-9 and pentobarbitone over that of pentobarbitone alone.

TABLE III

Hypnotic activity of QZL—9 and phenobarbitone

(Room temperature 30°C to 32°C)

Drug	Dose mg/ 100 gm	Mean sleeping time in rat hours with standard deviation	Percent increase over normal mean sleeping time	't' test as compared to control	P Value	't' as compared to phenobarbital	P^1 Value
Control	5% gum acacia	1.7±0.612	.....	.....			
Phenobarbitone	8	6.9± 1.500	305	14.444	<.001		
QZL-9	10	2.5± .821	47	5.000	<.001	14.5	<.001
QZL-9	15	3.6±1.314	111	3.888	<.001	5.3	<.001
QZL-9	20	4.5±0.735	164	9.333	<.001	12	<.001

P—Taking gum acacia as control

P^1—Taking phenobarbital as control

VII. *Behavioral Studies* :— (a) *Study of CAR by Cook's pole climbing apparatus* :— It was seen that chlorpromazine specifically blocked CAR in doses of 1mg, 2.5mg and 5 mg/kg I.P. With QZL-9 in lower dose range i.e., 100mg and 150mg/kg there was partial blockade of CAR but with 200mg/kg dose both the conditioned and unconditioned responses were blocked thereby showing incapactiation of motor functions. Results are summarized in Table IV.

TABLE IV

Table showing effects of QZL—9 and chlorpromazine on CAR as determined by Cook's Pole Climbing apparatus

Drug	Dose	*Total number of CAR responses*		*Percentage of conditioned* avoidance response	*Percentage blockade of unconditioned* response
		Control	Treated		
QZL—9	100 mg/kg	95	75	25	Nil
	150 mg/kg orally	98	50	50	10%
	200 mg/kg	98	35	95	85%
Chlorpromazine	1 mg/kg	100	65	35	Nil
	2.5 mg/kg I.P.	96	35	65	Nil
	5 mg/kg	98	10	90	Nil

TABLE V

Table showing effects of QZL—9 and phenobarbitone on pecking performance of pigeons

Drug	Dose mg/kg body wt.	2 hrs. after drug administration			6 hrs. after drug administration			24 hrs. after drug administration		
		Fixed ratio (Time)	Fixed interval		Fixed ratio	Fixed interval		Fixed ratio	Fixed interval	
			Initial pause	No. of pecks		Initial pause	No. of pecks		Initial pause	No of pecks
Control	——	1 min 4 secs	44 secs	212	——	——	——	——	—	—
Phenobarbitone	20 mg/kg	1 min 52 secs	2 secs	120	Normal 1 min 42 secs	16 secs	168	Normal 1 min 38 secs	38 secs	204
Control	——	1 min 8 secs	50 secs	220	——	——	——	——	—	—
QZL-9	100 mg/kg	1 min 10 secs	32 secs	195	1 min 20 secs	43 secs	216	——	—	—
Control	——	1 min 1 sec	40 secs	215	——	——	——	——	—	—
QZL-9	150 mg/kg	1 min 20 secs	21 secs	172	1 min 4 secs	36 secs	208	——	—	—
Control	——	1 min 8 secs	45 secs	195	——	——	——	——	—	—
QZL-9	200 mg/kg	1 min 48 secs	5 secs	105	1 min 12 secs	20 secs	164	1 min 36 secs	42 secs	202

(b) *Studies of behaviour of pecking performance in pigeons depending on the schedule of reward :—* Results are summarized in Table V.

(i) *Comparison of QZL-9 with control :—* With 100mg/kg of QZL-9 after 2 hours there was no change in ratio performance but the interval performance was slightly disturbed i.e., the initial pause was less and the total number of pecks were reduced from 220 to 195 and after 6 hours of QZL-9 administration, interval performance also came back to normal. With 150 mg/kg ratio performance was disturbed i.e., mean time taken for fixed ratio was increased from 1 min 1 sec to 1 min 20 sec. Interval performance was also disturbed, the initial pause was reduced from 40 to 21 sec and the total number of pecks made were reduced from 215 to 172. After six hours both ratio and interval performance reverted back to normal. With 200mg/kg ratio performance was markedly disturbed, the pecks made were irregular and the mean time taken for fixed ratio was more. In control group it was 1 min 8 sec, while after drug administration it was 1 min 48 sec. The interval performance was also profoundly disturbed. The initial pause was lost, pecking was irregular throughout the whole interval and the total number of pecks made in 5 minutes interval were reduced from 195 to 105, Six hours later, ratio performance came back to normal while interval performance was still disturbed. After 24 hrs. both fixed ratio and fixed interval performances came back to normal.

(ii) *Comparison of phenobarbitone with control :—* In case of phenobarbitone 20mg/kg, 2 hrs. later it was seen that fixed ratio performance was disturbed. There were irregular pecks and the speed of pecking was slow so that mean time taken for one fixed ratio was more as compared to its own control. In control it was 1 min. 52 sec. The fixed interval performance was markedly disturbed. The initial pause was lost, the bird pecked irregularly throughout the whole fixed interval and the total number of pecks made in 5 minutes were also reduced from 212 to 120.

Six hrs. after phenobarbitone, ratio performance was normal while interval performance was still disturbed. After 24 hrs. both ratio and interval performance came back to normal.

(iii) *Comparison of QZL-9 with phenobarbitone treated pigeons* :— It was seen that pigeons treated with 200mg/kg of QZL-9 orally showed same effects both on fixed ratio and fixed interval as shown by pigeons treated with 20mg/kg of phenobarbitone given intramuscularly. The lower doses of QZL-9 were found to be less effective. It is concluded that action of QZL-9 is more of sedative one than that of tranquillizer.

VIII *Haemodynamic experiments :—* (a) *Effect on isolated heart :—* QZL-9 depressed the tone, rate and amplitude of contraction of both in frog and rabbit heart. In rabbit heart there was diminution in coronary flow with higher doses.

(b) *Effect on blood Pressure and respiration in dog*:— The mean percentage fall was 32.6, which lasted only for 1 min. and 20 sec. There was also slight bradycardia (21%) and a slight stimulant effect on respiration. There was no qualitative or quantitative change in the nature of fall after administration of atropine, synopen or ansolysen suggesting that probably hypotension is due to direct depressant effect of QZL-9 on heart.

IX. *Acute toxicity studies of QZL-9 :—* The deaths were observed for 24 hrs. only. The deaths were mostly due to depression of central nervous system and respiratory failure. The LD_{50} was found to be 2.75gm/kg orally,

DISCUSSION

In the present study, QZL-9 was found to be the most active as far as anticonvulsant activity is concerned and the least toxic compound. It was effective both against electroshock and chemoshock thus resembling phenobarbitone, phenurone and Mysoline in its anticonvulsant spectrum.

Overlapping of the anticonvulsant and the hypnotic activities is a great limitation in the use of potential antiepileptics. Although many anticonvulsants do possess hypnotic action, the two properties are separable and have been resolved in a number of compounds like phenytoin sodium and 5-phenylbutyl barbituric acid. Some central nervous system depressants, on the other hand, do not possess any significant anticonvulsant activity. Reserpine inspite of its being a powerful central nervous system depressant, is not effective against both electroshock or chemoshocks (5), rather it facilitates, although it protects rats against audiogenic seizures (15,18).

QZL-9 was found to be much less sedative than phenobarbitone and from this point of view QZL-9 should prove to be a promising compound. The effect of QZL-9 on spontaneous motor activity differed from other drugs of barbiturate group (3) that hexabarbitone, pentothal and amobarbitone produce hyperactivity in small and subtoxic doses, marked reduction in toxic doses and hypnosis at a higher dose i.e. less than LD_{50}. QZL-9 reduced the spontaneous motor activity unlike barbiturates as a function of the dose without any hyperactivity or loss of righting reflex. Moreover, it was observed in case of QZL-9 that though the animals were less active yet the exploratory behaviour was not lost as with non-tranquillizing drugs like phenobarbitone, which do not have any effect on exploratory behaviour of mice (2). The behavioral studies indicate that QZL-9 resembles sedatives more than tranquillizers.

SUMMARY

I. Seventeen 4 (3H) quinazolone compounds have been screened for their anticonvulsant, analgesic and hypothermic properties and none has been found to have any analgesic or hypothermic properties.

II. QZL-9 was found to be the most potent and least toxic of the series as regards its anticonvulsant properties. Its ED_{50} against electroshock seizure pattern test was 135mg/kg orally while against Leptazol convulsions it was 150mg/kg orally. Its LD_{50} was 2.66gm/kg orally.

III. The compound reduced the spontaneous motor activity in normal and amphetamine stimulated rats but less than Troxidone and chlorpromazine.

IV. The compound was found to have less sedative hypnotic and hypnotic potentiating properties than phenobarbitone.

V. It blocks both conditioned and unconditioned responses due to motor incapacitation, as tested by Cook's pole climbing test, and also resembles phenobarbitone when tested no pecking performance in pigeons.

VI. QZL-9 produces transient hypotension due to cardiac depressant action.

ACKNOWLEDGEMENT

We are grateful to Mr. M. S. Dhatt, Assistant Director, National Institute of Communicable Diseases, Delhi, who has synthesised these compounds for us.

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