STUDIES ON THE NEUROPHARMACOLOGICAL ACTIONS OF SOME NEWER SUBSTITUTED TETRAZOLES AND QUINAZOLONES

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Summary : Pharmacoligical screening of substituted tetrazoles and quinazolones exhibited CNS depressant and stimulant activities. These compounds were also tested for their anticonvulsant, anti-reserpine and monoamine oxidase inhibitory activities.

Key words : tetrazole, quinazolone, CNS, SMA, anti-reserpine, MAO, anticonvulsant activities

INTRODUCTION

In our previous communication (12, 13), we have reported the synthesis of various substituted tetrazoles and quinazolones. The present paper deals with their psychotropic activity. The significance of methaqualone and pentamethylene tetrazole in the functioning of CNS has in recent years aroused great interest in search of quinazolone and tetrazole derivatives. It was observed that these nuclei exhibited anticonvulsant (3, 5, 7, 8), monoamine oxidase (10) and CNS activities (4). Furthermore diverse variety of CNS activities have been associated with these moieties. Thus it was worthwhile to investigate the effect of these substituted tetrazoles and quinazolones on the CNS. We incorporated substituted phenoxymethyl group at position 2 and 2'-pyridyl and 2'-thiazolyl substituents at position 3 in quinazolone nucleus. Amido groupt at α and amino group at β–position was introduced in the tetrazole moiety.

MATERIAL AND METHODS

Acute toxicity: Acute toxicity was performed in mice of either sex. LD_{50} values were determined by the conventional procedure (9).

Gross behaviour activity: Gross behaviour activity was determined according to

the scheme outlined by Irwin (6). The test compounds were given 100 *mg/kg* ip in 5% aqueous suspension of gum acacia.

Spontaneous motor activity (SMA): The method described by Dews (2) was used for determining SMA. Adult male, albino mice weighing 20–25 *g* were used. Experiments were performed in dark quiet room maintained at 20–24°C. To minimise the effect of diurnal variation on SMA, the test were performed at the same time each day. The compounds were injected in groups of 5 mice and placed for 10 min later on runaway. Counts per 5 mice were recorded every 10 min for 90 min (nine counts). Control SMA records in 10 mice injected with a matching volume of 0.9% saline ip were similarly taken.

Pentylenetetrazole–induced convulsion: Pentylenetetrazole seizure (1) were induced in mice of either sex weighing 20–30 *g*. The mice were divided into groups of 10, keeping the group weights as equal as possible. Each compound was suspended in 5% aqueous gum acacia to give a concentration of 0.5%. The compounds were injected ip in a group of 10 animals at a dose of 100 *mg/kg*. Four hr after the administration of compounds, the mice were injected with pentylenetetrazole (90 *mg/kg*, sc). This dose of pentylenetetrazole has been shown not only to produce convulsion in almost all untreated mice but also to produced 100% mortality during 24 hr. The mice were then observed for 60 min for seizures and those not shwoing convulsions during 60 min were considered protected. The number of animals protected in each group was recorded and the anticonvulsant activity of ccmpound was represented as percent protection. The mortality was observed after 24 hr.

Anti–reserpine activity: Anti–reserpine activity was measured in mice according to the method of Randall and Bagdoren (11).

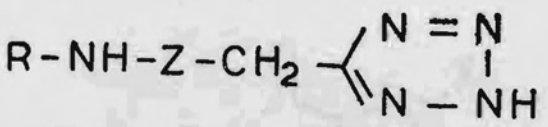
Monoamine oxidase activity (MAO): Monoamine oxidase activity was determined (14) in adult male rats weighing 100–150 *g*. One animal was used for each compound in each experiment. Benzylamine hydrochloride (0.1 M) was used as substrate. They were killed by decapitation. Brain were quickly removed and homoginized in ice cold 0.25 M sucrose solution to give 10% (w/v) brain homogenate. The reaction mixture in a final volume of 2 *ml* consisted of 0.4 *ml* phosphate buffer (pH 7.2, 0.5M), 0.2 *ml* of 10% homogenizer and 0.1 *ml* benzylamine. The various compounds were dissolved in propylene glycol (100%) and used at a final concentration of 1×10^{-3} M. The compounds under assay were incubated for 10 min at 37°C with brain homogenate before the addition of benzylamine. The reaction mixture was further incuabated for 30 min at 37°C (after the addition of substrate). The enzymatic reaction was stopped by the

addition of 1 *ml* of 10% perchloric acid and the precipetated protein was removed by centrifugation. The absorbance of alequot was measured at 250 *nm*. The percentage inhibition was calculated frcm decrease in optimal density.

RESULTS

Acute toxicity: The LD_{50} values of the compounds were high (Tables I and II).

TABLE I Pharmacological and biolcgical properties of 5-substituted tetrazoles.



Compound	*R*	*LD*50±S.E. (mg/kg, ip)*	*MAO inhibition**% mean±SEM*	*Anticonvulsant pentylenetetrazole–induced seizures*	
				protection%	*mortality%*
			Z=>C=O		
1	*p*–tolyl	825	44 ±0.3162	40	60
2	*o*–tolyl	825	46.4±0.3873	40	50
3	α–naphthyl	>1000	46.4±0.2236	20	60
4	*p*–chlorophenyl	681±73	50 ±0.5467	20	70
5	*p*–nitrophenyl	1000	60 ±0.3873	20	60
			Z=>CH_2		
6	*p*–tolyl	1000	54.9±0.158	40	50
7	phenyl	>1000	56.2±0.4183	50	40
8	*p*–anisyl	825	68.4±0 4183	50	50
9	*m*–tolyl	<1000		40	60
10	*p*–bromophenyl	875		30	60

* Mortality observed 24 hr after the drug observation.

**All compounds were used at a final concentration of 1×10^{-3} M

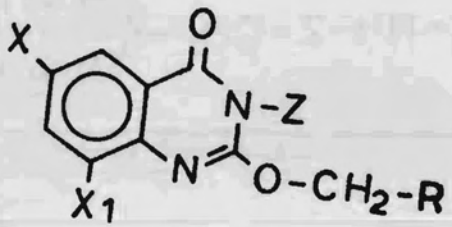
Gross behaviour activity: All the compounds in tetrazole series exhibited CNS depressant action while quinazolone derivatives produced both CNS depressant and stimulant actions.

Spontaneous motor activity (SMA): It was observed that compounds of tetrazole series ranging from 1-10 reduced the SMA by 57.3, 32.6, 37.2, 31.1, 33.0, 44.3, 21.1, 29.6, 36.2 and 27.4% respectively. Quinazolone derivatives numbring from 1,2,3,5,6,10 and 11 also reduced the SMA by 33.2, 26.6, 56.3, 24.8, 44.3 and 31.1% respectively. In con-

trast 4, 7, 8, 9 and 12 of quinazolone series increased the SMA by 27.4, 26.7, 15.11, 23.1 and 31.2% respectively.

Pentylenetetrazole-induced convulsion: All tetrazole and quinazolone at a dose of 100 *mg/kg*, ip exhibited anticonvulsant activity, which ranged from 20–50% and 30-70% respectively against pentylenetetrazole-induced seizure. Compounds 7 and 8 in the tetrazole the series exhibited higher (50%) activity. Maximum protection in the quinazolone series was observed with compound 12 (Table II).

TABLE II. Pharmacological and biological properties of 2,3-disubstituted quinazolones.



Compound	R	LD*50±S.E. (mg/kg, ip)	MAO inhibition**% mean±SEM	Anticonvulsant pentylenetetrazole-induced seizures protection%	mortality%
			X=X1, Z=2'-thiazolyl		
1	*p*-nitrophenyl	>1000	56.4±0.2739	60	40
2	*p*-tolyl	215±51	65.8±0.5837	40	30
3	*p*-anisyl	825	———	40	60
			X=X1, Z=2'-pyridyl		
4	phenyl	825	———	60	40
			X=bromo, X1=H, Z=2'-thiazolyl		
5	*p*-anisyl	825	58.2±0.3535	30	70
6	*p*-nitrophenyl	>1000	23.2±0.3535	60	40
			X=bromo, X1=H, Z=2'-pyridyl		
7	*p*-anisyl	1000	62.8±0.4472	50	50
			X=iodo, X1=H, Z=2'-pyridyl		
8	phenyl	825	58.4±0.3868	60	30
9	*p*-tolyl	925	60.2±0.3162	50	30
			X=X1=bromo, Z=2'-thiazolyl		
10	*p*-nitrophenyl	1000	———	60	40
11	phenyl	1000	———	60	40
			X=X1=bromo, Z=2'-pyridyl		
12	*p*-nitrophenyl	681±69	35.2±0.2739	70	30

*Mortality observed 24 hr after the drug administration.

**All compounds were used at a final concentration of 1×10^{-3} M.

Anti-reserpine activity: None of the compound showed anti-reserpine activity.

Monoamine oxidase activity (MAO): The MAO inhibitor activity of substituted tetrazole and quinazolone compounds using brain homogenate during oxidative deamination of benzylamine is shown in Tables I and II. Compound 8 produced maximum (68.4±0.4183%) inhibition in the tetrazole series and compound 2 exhibited higher inhibition (65.8±0.5837%) in the quinazolone series.

DISCUSSION

All the substituted tetrazoles and quinazolones exhibited high LD_{50} values suggesting their low toxicity.

Data on the anticonvulsant and MAO suggested that anisyl and phenyl group at position R in tetrazole moiety increased the activity (Compounds 7, 8). Nitrophenyl and bromophenyl group at the same position reduced anticonvulsant activity (Compounds 5, 10), while the nitrophenyl group enhanced the MAO inhibitory activity (Compound 5).

Protection value against pentylenetetrazole–induced seizures suggested that nitrophenyl group at position 2 and pyridyl group at position 3 in quinazolone nucleus induced higher anticonvulsant activity (Compound 12), while tolyl and anisyl groups at position 2 and thiazolyl group at position 3, led to lower degree of anticonvulsant activity (Compound 2, 3, 5). Introduction of tolyl and anisyl group at position 2, increased the MAO inhibitor activity (Compounds 2, 5, 7, 9) and nitrophenyl group (Compounds 1,6,12) reduced the activity.

These observation suggest that tolyl and anisyl groups increase the anticonvulsant and MAO inhibitory activity in the tetrazole series whereas these groups reduce the anticonvulsant activity in quinazolone series. Further, nitrophenyl group enhanced the anticonvulsant activity in the quinazolone rather than the tetrazole series and reduced MAO inhibitory activity only in the quinazolone series.

No such co–relationship has been estiblished earlier between MAO and anticonvulsant activity in these moieties.

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