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LETTER TO THE EDITOR

EVALUATION OF SOME 1,2,4–DITHIAZOLIDINES AS ANTICONVULSANT AGENTS IN WISTAR RATS

Sir,

(Received on July 5, 1991)

In our previous studies we have reported the CNS activities of the synthesised heterocyclic ring compounds (1,2). Certain phenylurethanes of pyrazolidinols and piperidazinols have moderate anticonvulsant activity (3). Some 2–(N–substituted glycylamino)–methylthiazoles and (1–phenyl–1–hydroxyethyl) azoles have been found to possess, anticonvulsant and anxiolytic activities (4,5). A series of 5–aryl–2, 4–dihydro-3H–1, 2, 4–triazol–3–ones also exhibited anticonvulsant activity (6). In view of these facts a series of 1,2,4–dithiazolidines were prepared and evaluated for their anticonvulsant activity in rats.

The 1,2,4–dithiazolidines were prepared by condensing S-benzylisothiourea with cyclohexylisothiocyanate to give Isodithiobiuret which upon bromination oxidised to corresponding dithiazolidines. The identity of the compounds were confirmed by elemental analysis and IR spectra.

The anticonvulsant activities were determined by maximal electroshock seizure (MES) and subcutaneous seizure test in rats.

(i) *MES test :* Anticonvulsant activity as evaluated by MES test of of Toman et al (7). Groups of ten adult wistar rats (100-120 g) were prescreened 24th before by applying supramaximal electroshock of 150 mA intensity of 0.2 sec via corneal electrodes using a Technocovulsiometer. A drop of 0.9% saline was instilled on the eye of the rat prior to application of electrodes to ensure electrical contact. Only those rats showing hind limb tonic extensor response were selected and control study done with the vehicle solution (propylene glycol) in which the compounds were dissolved, showed no significant change in seizure response.

5, and 25 mg/kg of the test compounds were administered i.p. in propylene glycol and after an hour the rats were again given electroshock. Abolition of the hind limb tonic extension component of the seizure was defined as the protection in MES test. The results were compared with activity shown by clinically useful anticonvulsants such as phenytoin (5 mg/kg, i.p.) and phenobarbitone (20 mg/kg, i.p.).

(ii) Chemoshock seizure Test : The animals were divided into control and treated groups. The control group of animals were injected either saline (0.5 ml) or propylene glycol (0.5 ml). The other group of animals received test drugs in propylene glycol. Forty five minutes later, both control and treated group of animals received s.c. injection of either chemical convulsants, 4.0 mg/kg of strychnine (IDPL) or 4.5 mg/kg of picrotoxin (SISCO Research Lab) and were observed for convulsions for 30 min (8). Protection was defined as the failure to observe a single episode of clonic spasm of at least 5-sec duration (Threshold). The statistical analysis was done by Chi-square test.

In MES test of the ten compounds (NS–1–10) screened, it was observed that the parent compound (NS–1) was completely ineffective in having anticonvulsant activity. Whereas substitution with o-Chloro, o-methoxy, p-methoxy, p-ethoxy, p-bromo groups, compounds (NS-4, NS-7, NS-8, NS-9, NS-10) showed insignificant anticonvulsant activity at 25 mg/kg, i.p. These compounds displayed potencies lesser than that of standard drugs, phenytoin (5 mg/kg, i.p) ($P<0.05$) and phenobarbitone (20 mg/kg, i.p) ($P<0.001$). In chemoshock test, the compounds (NS-2, NS-3, NS-5, NS-6) gave protection to only some extent at 25 mg/kg, i.p. whereas these compounds (NS-2, NS-5) and (NS-3, NS-6) showed significant activity at 50 mg/kg. i.p. in strychnine and picrotoxin seizure test respectively (Table I).

The ability of the compounds to antagonize maximal electroshock seizures showed that they may be acting through the inhibitory transmitter gamma-amino butyric acid (GABA) in the brain of the rats (9). Since convulsant action of strychnine is due to interference with the postsynaptic inhibition that is mediated by glycine (10) therefore the compounds (NS-2, NS-5) which significantly blocked strychnine seizures may be predicted to act on the postsynaptic receptors of the brain and the inability of these compounds to block picrotoxin seizures indicates that blocking of presynaptic inhibition mediated by GABA is not involved. Since picrotoxin blocks presynaptic inhibition in CNS and antagonizes the inhibitory transmitter GABA (10), the compounds (NS-3, NS-6) which gave significant protection against picrotixin seizures may be acting on the presynaptic receptors of the brain.

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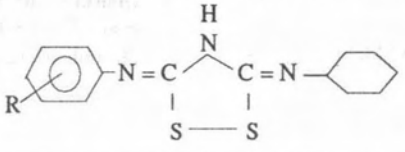
TABLE I: Anticonvulsant activity of 1,2,4-dithiazolidines



Compd. No.	*R*	*Dose mg/kg*	*Percentage protection*		
			Electroshock	*Chemoshock*	
			MES	*Strychnine*	*Picrotoxin*
NS-1	H	25	0	–	–
NS–2	m-CH_3	25	60*	20	0
		5	20	60*	–
		50	–	5	20
NS–3	p-CH_3	25	60*	0	40
		5	40	–	–
		50	–	50	60*
NS-4	o-Cl	25	20	–	–
NS–5	m–Cl	25	60*	20	0
		5	40	–	–
		50	–	60*	40
NS–6	p–Cl	25	70**	0	20
		5	50	–	–
		50	–	30	70**
NS–7	o-OCH_3	25	20	–	–
NS–8	p–OCH_3	25	40	–	–
NS-9	p–OC_2H_5	25	40	–	–
NS–10	p–Br	25	20	–	–
Phenytoin		5	60*	–	–
Phenobarbitone		20	100***		

n= 10; propylene glycol or saline (control) = 0% protection, *P<0.05, **P<0.01, ***P<0.001.

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REFERENCES

1. Pandeya SN, Kumar S, Siddiqui N. Synthesis and Biological activities of 1,2,4–thiadiazolines. *Indian Drug* 1983 : 24; 1–5.

2. Pandeya SN, Jain AK, Siddiqui N. Synthesis of series of new thiobiurets, triazines and thiadiazolines and their anticonvulsant activity. *Acta Pharm Turcica* 1989: 31; 67-76.

3. Kornet MJ. Phenylurethanes of pyrazolidinols and piperidazinols as anticonvulsants. *J Heterocycl Chem* 1990: 27: 2125–2127.

4. Bachir M. Lemoine J, De AA, Hauziaux P, Danree B. Synthesis and anticonvulsant activity of some 2–(N–substituted glycylamino)–4–methylthiazoles. *Eur J Med Chem* 1990: 25; 71-74.

5. Kottmann H, Kirsch R, Stechl J. Preparation of (1-phenyl-1-hydroxyethyl) azoles as anticonvulsant and anxiolytics. *Chem Abstr* 1991: 114; 102004 u.

6. Kane JM, Baron BM, Dudley MW, Sorensen SM, Staeger MA, Miller FP. 2,4–Dihydro-3H-1, 2,4–triazol-3-ones as anticonvulsant agents. *J Med Chem* 1990: 33; 2772-2777.

7. Toman JEP, Swinyard EA, Goodman LS. Properties of maximal seizures, and their alteration by anticonvulsant drugs and other agents. *J Neurophysiol* 1946: 9; 231-240.

8. Everett GM, Richards RK. Comparative anticonvulsant action of 3,5,5-trimethyloxazolidine-2, 4-dione- (tridione), dilantin and phenobarbital. *J Pharmacol Exp Ther* 1944: 81; 402-407.

9. Bowman WC, Rand MJ. Central control of muscle activity: Drugs used in spasticity, Parkinsonian and epilepsy. "Text book of Pharmacology". 2nd Edn. Blackwell Scientific Publications, Oxford, 1982: p. 1830-1831.

10. Franz DN. Central nervous system stimulants. "Goodman and Gilman's The Pharmacological Basis of Therapeutics". Gilman AG, Goodman LS. Rall TW, Murad F. (ed.), 7th Edn. Macmillan Publishing Co., New York 1980: p. 582-584.