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PHARMACOLOGICAL EVALUATION OF SOME OXAMIDE DERIVATIVES ON CEREBRAL ACTIVITY

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ABSTRACT

The present study was adopted in an attempt to evaluate the anticonvulsant and central depressant activity of five N-substituted-N-(2-methyl-4-oxoquinazolin-3-yl) oxamides. The anticonvulsant activity was determined against both electroshock and pentyleneterazole induced seizures in mice. The CNS deperessant activity was indicated by measuring their effect on the spontaneous motor activity of mice using the activity cage apparatus.

Diazepam was used in these experiments as a reference drug for comparative purpose. Results of the present study revealed that most of the compounds in question possess variable degrees of anticonvulsant and CNS depressant activity and the compound N-Isopropyl-N-(2-methyl-4-oxoquinazolin-3-yl) oxamide displayed the greatest response. Intraperitoneal injection of this compound into rabbits has not led to any remarkable changes in the ECG, blood pressure or respiration However on weight basis the magnitude of diazepam response is greater than any of the tested compunds.

INTRODUCTION

In the pharmacotherapy of convulsive seizures phenobarbitone and phenytion were among the first drugs to be used[1,2]. Subsequently numerous compounds of diverse chemical structure were employed for their anticonvulsant properties. Benzodiazepines[3], valproic acid[4], and some amides of both cinnamic acid and benzoic

acid derivatives[5,5] are representative of these compounds. However, none of the currently used drugs satisfies the criteria of being ideal because of their side effects and lack of selectivity[7]. Moreover, Bruni in 1980 pointed out that with the drugs available complete seizures control can be achieved only in 60% of epileptic cases[8]. Consequently, there is still a need of new anticonvulsants with more selective action and fewer side effects Quinozolinones which are known as sedative hyponotics[9,10,11], exhibit also potent anticonvulsant activities[12,13]. Besides the anticonvulsant activity of a series of 4-aminobenzamides has been recently demonstrated in mice[14].

In the Department of Pharmaceutical Chemistry of our University a series of n-substituted, N'-(2-methyl-4-Oxaquinazolin-3-yl) oxamides (V) were synthetized[15] and it is the goal of our work to assess the anticonvulsant and CNS depressant activity of such compounds.

EXPERIMENTAL

Materials:

Compounds under investigation were obtained from Department of Pharmaceutical Chemistry, Assiut University[15] and their chemical structures are listed in Table (1). Other chemicals used include: Diazepam (Hoffman-La Roche) and Pentylenetetrazole (Knoll CO.).

Animals Used:

Adult albino mice (20-30 gm) and rabbits (1½ - 2½ Hg) of either sex were used in this study. They are allowed food and drink before experiments.

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I- Evaluation of Anticonvulsant Activity:

Compounds were tested for their anticonvulsant activity in comparison to diazepam by measuring their ability to protect the mice against convulsive seizures induced by both electrical stimulation[16] and systemic administration of pentylenetetrazole[17].

Suspensions (0.4%) of all tested compounds were prepared in 1% aqueous solution of carboxymethyl cellulose (CMC) which is inert and devoid of any anticonvulsant activity. Groups of 10 mice were housed in plastic cages. Experiments were done consistently at the same hours during day time.

A) The electroshock method: (MES)

In performing this test five different dose levels of each compound (40, 60,80,100 and 120 mg/kg) or the standard drug diazepam (0.2.0.3,0.4,0.5 and 0.6 mg/Kg) were injected intraperitoneally (I.P) into groups of mice 10 animals each. The injections were carried out one hour prior to testing. In addition, another group of mice served as control and was injected I.P. with 1 ml. of CMC. Anticonvulsant activity was determined by measuring the ability of the test compound to abolish the hind limbs tonic extensor component of seizures induced in mice by electrical stimulation via the ear electrodes of the electroconvulsive apparatus (UGO, Basile, Italy). In evaluating the results the dose producing protection in 50% of animals (ED_{50}) and its 95% fiducial limits was calculated by the graphical method of litchfield and Wilcoxon[18].

B) Pentylenetetrazole-induced seizures: (PTZ)

Groups of mice each of ten animals were injected I.P. with graded dose levels of each of the compounds in question (60,80,100,120 and 140 mg/Kg) or diazepam.(0.2,0.3,0.4,0.5 and 0.6 mg/Kg). A control group which received 1 ml of CMC was tested at the same time. One hour following each medication, all groups were injected subcutanceously with pentylenetetrazole (100 mg/Kg). The animals were observed for 30 minutes for the development of seizures. The number of mice protected in each group was recorded and the medium effective (ED_{50}) anticonvulsant does of the tested compound with its 95% fiducial limits was calculated.

2- Evaluation of the CNS depressant activity:

The CNS depressant activity of the compounds under investigation was evaluated by measuring their effects on the spontaneous motor activity of mice[19]. The activity cage apparatus (UGO, Basile, Italy) in which the bridges "broken" by the animals paws are converted into pulses that are summed up by an electronic counter and printed, was employed for this purpose. Each of the tested oxamides was injected I.P. into group of 6 mice each in a dose level of 100 mg/Kg. Besides, two groups served as control, one was saline, treated and the other was injected with 1 ml of CMC solution. In addition, another group was injected I.P. with 2 mg/Kg of diazepam for standardization. The test was carried out by placing each mouse in the activity cage and a 5 minutes count was taken before and 30,60,90 and 120 minutes after drug treatment. The percentage decrease in the normal spontaneous activity was determined and compared with the control group.

3- Evaluation of cardiovascular and respiratory effects of the most effective compound:

Six rabbits were anaesthetized with urethane (1.6 gm/Kg) and the arterial blood pressure was recorded via the carotid artery which was cannulated and connected to a Bourdon blood pressure transducer and an amplifier of 6 channels physiograph E & M. The depth and rate of respiration were recorded by fixing two needle electrodes across the chest of the rabbit and connected to an impedance pneumograph transducer and an amplifier of the physiograph. Electrocardiographic changes were simultaneously monitored by means of "Cardiwrite ECG" using standard lead II. The compound in question was injected I.P. in a dose of 100 mg/Kg and the changes in blood pressure, respiration and ECG were recorded before and buring a period of 2 hours following injection.

RESULTS AND DISCUSSION

The foregoing results revealed that the oxamides in question exibit remarkable anticonvulsant activity against PTZ/ and MES/ induced-seizures. It can be seen that, the activities were greater

against MES than PTZ induced seizures as evidenced by the low ED 50 for MES as compared to that for PTZ (Table 2). In contrast, the ED 50 of diazepam for PTZ (1.05 mg/Kg) is relatively low as compared to that for MES (1.25 mg/Kg). Although the data obtained from experimental studies are not necessarily reproducible in man, it was reported that clinical aspects of generalized seizures are highly correlated with PTZ induced seizures. Likewise, partial seizures in human correlate with seizures elicited by MES[20].

Nevertheless, a tentative correlation can be observed between the substituent (R) in the N atom of the oxamide structure (Table 1) and the anticonvulsant activity against MES-induced seizures. Thus, the anticonvulsant activity decreases as the bulk of R increase (Vf, Vg,Vj). In addition the ED 50 of the two isomers N-propyle(Vc) and N-isopropyle (Vd) was 120 mg/Kg and 52 mg/Kg respectively which might indicate that the branches of R (C_3H_7) is optimun for anticonvulsant activity. In contrast, no consistent relationship was observed between the chemical structure of the investigated oxamides and their anticonvulsant activity against PTZ-induced seizures. Generally, the tested oxamides can be seen to resemble the currently available anticonvulsant agents diazepam, carbamazepine and phenytion in the involvement of -HN-C-moiety in their chemical structures[7].

It is also evident from these ED 50 values that compound Vd is a most potent oxamides against both types of induced seizures. It is of interest to notice that the structures of compound Vd and the anticonvulsant drug valproic acid share the isopropyl moiety[7].

In studying the effect of the investigated compounds on the locomotor system, a significant reduction in the spontaneous motor activity of mice was observed following the injection of each of the oxamides and diazepam (Table 3). This might reflect the action of these compounds on the various levels of the CNS responsible for initiation and coordination of locomotion[21]. In previous works the CNS depressant effects of some N,N'-oxanilamides were reported[22,23].

Thus we expect that combination of both quinazolinyl and oxalyl moieties in an amide structures may augment the CNS depressant activity and might be responsible for the anticonvulsant properties. The general pattern of response obtained with CNS depressant activity of the investigated compounds shows a positive response as that of anticonvulsant activity. Further work is required to localize the site of action of the tested compounds and to identify their possible mechanism of action in comparison with other known anticonvulsant drugs.

The marked noticeable anticonvulsant activity of the isopropyl substituent of oxamide (Vd) and its ability to depress the spontaneous motor activity led us to extend our study to test the different cardiovascular and respiratory effects of this compound. Results revealed that administration of a relatively large dose of this compound was devoid of any remarkable cardiovascular or respiratory responses (Fig. 1) which generally might indicate its relatively safety. Trials were made to determine the LD 50 of compound Vd in mice, but when a high dose of 300 mg/Kg was used only two out of ten animals were dead. The inavailability of sufficient amount of the drug as well as its insolubility in water even in the presence of solubilizing agents hindered the estimation of the LD_{50} of the compound. However, the low incidence of mortality of two animals out of ten may indicate the relatively low toxicity of this compound. Recommendation of this compound for clinical trials demands a more thorough pharmacological and toxicological studies.

Acknowledgment:

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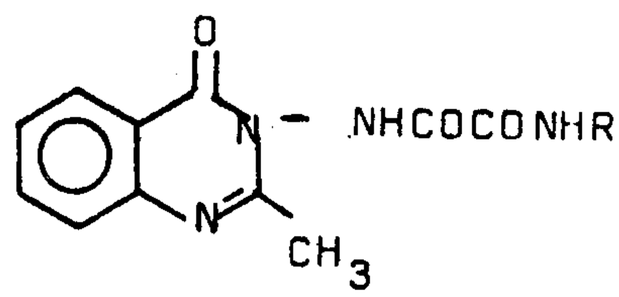
Table 1: Chemical structure of the five oxamide derivatives under investigation.



Compound	R
Vc	-. CH_2-CH_2CH_3
Vd	-CH(CH_3)(CH_3)
Vf	-CH_2-CH_2CH_2-CH_3
Vg	CH_2-$CH_2CH_2CH_2CH_3$
Vj	

Table (2): Medium effective doses (ED_{50}) of oxamides (V) and diazepam (DP) reflecting their anticonvulsant activity against maximal electrical shock (MES) and pentylenetetrazole (PTZ) in mice.

Compound	ED_{50}(mg/kg) and its fiducial limits	
	MES	PTZ
Vc	120(75-144)	190 (131-94-273.0)
Vd	52(29.37-92.04)	160 (91.16-280.8)
Vf	150 86.95-258.75	200 (120.48-332)
Vg	150(86.95-258.75)	250 (171.58-364.25)
Vj	160(95.2-268)	180 (113.56-285.3)
Dp	1.25(0.525-2.95)	1.05(0.5-2.1)

Table (3): Effect of oxamides (100 mg/Kg) and diazepam (Dp)(2 mg/Kg) on the spontaneous motor activity of mice.

Compound	% decrease in spontaneous motor activity of mice after			
	30'	60'	90'	120'
Saline	31.14±2.68	55.13±2.68	62.8 ±2.68	63.54±2.88
CMC	32.11±2.17	54.25±1.44	63.87±1.20	63.89±1.27
Vc	29.15±1.71	62.47±2.74*	72.53±2.71*	77.37±4.28*
Vd	46.99±2.1*	68.74±4.10*	78.04±3.74*	77.35±3.13*
Vf	29.86+2.55	54.54+3.23	71.06+1.08*	74.27+2.44*
Vg	41.02±2.80*	70.45±3.38*	80.28±2.58*	78.71±3.13*
Vj	40.34±3.05	68.11±8.11	82.16±2.10*	78.40±1.87*
Dp	55.05±1.83*	82.25±3.25*	86.89±3.38*	83.68±2.54*

Data represent mean ±S.E. of 6 observations.

* Significant result at $P<0.05$.

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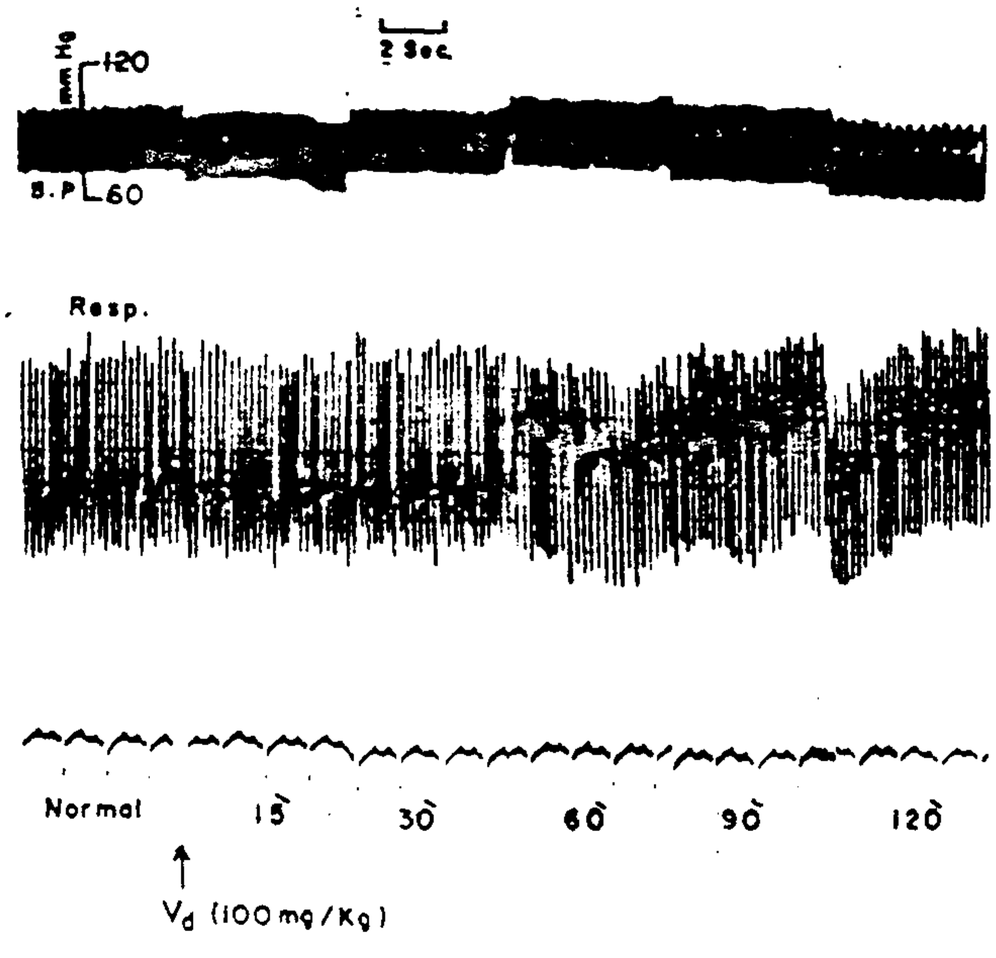

Effect of compound Vd (100 mg/Kg) on blood pressure, respiration and ECG of rabbits. Number below the record indicate time in minutes after administration.

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التقييم الفارماكولوجى لبعض مشتقات الاوكس اميدات على الانشطه المخيه

حسين اسماعيل البيطار و رأفت عبد البديع عبد العال
قسم الفارماكولوجى ـ كليه الطب ـ جامعه اسيوط ـ مصر

لقد أوضحت نتائج هذه الدراسة فاعلية هذه المركبات بدرجات متفاوته ضد التشنجات العصبية التى أمكن احداثها كهربائيا وكيميائيا فى فيران التجارب كما تبين أيضا أن لها تأثير مثبط على الجهاز العصبى المركزى .

وقد تم مقارنة هذه التأثيرات لتلك المركبات بعقار الديازيبام كما تم أيضا مناقشة العلاقه بين التأثير الفارماكولوجى لهذه المركبات وتركيبها الكيميائى .

وعند حقن أكثر تلك المركبات فاعلية فى الارانب لم ينتج عنه أى تأثيرات ملحوظه على حركة التنفس أو ضغط الدم أو رسام القلب الكهربائى .

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