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POSSIBLE CNS DEPRESSANT EFFECTS OF SOME NEWLY SYNTHESIZED QUINAZOLINONE DERIVATIVES

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ABSTRACT

In the present investigation, five recently synthesized derivatives (designated as compounds I,II,III,IV and V) of 2,3-disubstituted 4 (3H)-quinazolinone (I) were evaluated for their CNS depressant activites in mice. In the course of this study, all compounds were suspended in a 5% suspension of gum acacia in water and were injected i.p. with the test compound in a dose level of 60 mg/kg.

All tested compounds were found to decrease spontaneous locomotor activity of mice. Only compound IV was found to potentiate pentobarbitone induced hypnosis. Regarding the effect on the skeletal muscle activity, quinazolinone derivatives II and III led to motor incoordination in 40% of mice. Out of the five tested compounds, compounds I, II and IV resulted in an increase in the mean survival time of strychnine-injected mice and a greater protection against death in these animals. However, the anticonvulsant effects exerted by quinazolinones was less efficient than those produced by phenobarbitone.

In conclusion, quinazolinone compounds II and IV are more likely to be the most potent as CNS depressant compounds, whereas compound V appears to be the least efficient one.

INTRODUCTION

The pharmacologic activities of the quinazoline ring system have received an extensive research work in the second half of this century. This ring system is present in some physiologically active compounds such as vasicine alkaloid, fibrifugine and arbortine antimalarials. Some 3-substitued 2-alkyl-4 (3H)- quinazolinones were proved to have bactericidal activity[1]. Other derivatives demonstrated tuberculostatic activity[2,3]. Different 2-alkyl 3-aryl-4 (3H)- quinazolinones displayed sedative hypnotic properties [4,5]. Methaqualone (Quaalude, Sopor) 2-methyl-3-(0-Tolyl)4 (3H)- quinazolinone was used successfully as a potent nonbarbiturate sedative hypnotic drug. In addition, 2-methyl-3-(p-bromophenyl)-4 (3H)- quinazolinone was found to possess anticonvulsant effects quantitatively similar to that of the most potent drugs[6]. Furthermore, potent anticonvulsant properties were exhibited by some 2-acyloxmethyl-3-aryl-4 (3H)-quniazolinones[7].

In the light of these results, El-Sherif et al[9] have conducted the synthesis of certain new 3-aryl-2 (1-p nitrophenyl 1,3-dihydroxy-2 propylamino)-methyl-4(3H)-quinazolinones (1). Six of these compounds, carrying p-tolyl and p-bromophenyl at position, 3, were studied by El-Koussi[8] for their effect on the CNS. The author showed that four of the investigated compounds possess potent CNS effects; as sedative hypnotics, muscle relaxants or as anticonvulsants.

In an attempt to extend their previous work, El-Sherif et al[10] have synthesized a new series of quinazolinone compounds (2,3-disubstitued-4 (3H-quinazolinones (I). In the present study, five of these quinazolinones were selected and evaluated for their central effects in mice. The possible relationship between the chemical structure of these compounds and their effects on spontaneous locomotor activity, pentobarbitone hypnosis, motor coordination as well as strychnine-induced convulsions was studied.

MATERIAL AND METHODS

Animals and drugs :

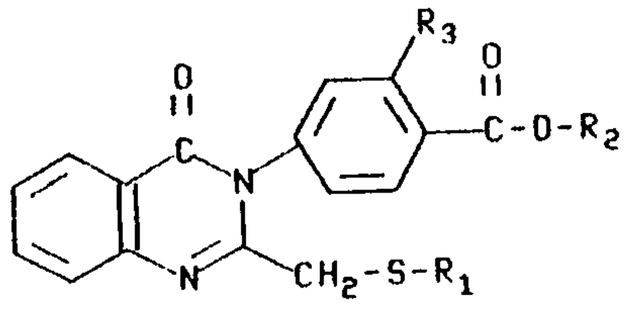
Adult albino mice, of either sex, weighing 18-22 gm were supplied locally. Standard drugs employed in the present investigation were pentobarbitone sodium (BDH), phenobarbitone sodium (El-Nasr Co.) and strychnine hydrochloride (CID Co.).

Quinazolinone compounds investigated in this study were prepared at the Department of Pharmaceutical Chemistry,Faculty of Pharmacy, Assiut University. In addition, the structure of these compounds was confirmed by elementary analysis, U.V. and I.R. spectrometry (El-Sherif, et al[10]).

The chemical structure and molecular formula of the five quinazolinones to be investigated are shown in Table (1).

Because of the water insolubility of the tested quinazolinones, these derivatives as weil as the standard drugs used in this study were suspended in 5% aqueous suspension of gum acacia. Control nice were treated in the same way with the proper volumes of 5% suspension of gum acacia.

Table 1 : Chemical Structure and Molecular Formulae of the 5 quinazolinones to be investigated.



2,3-Disubstituted-4(3H)-quinazolinones (I).

Quinazolinone derivatives	Substituen R_1	R_2	R_3	Molecular formulae
I	$-CH_2-COOH$	$-C_2H_5$	--	$C_{20}H_{18}N_2O_5S$
II	$-CH_2-CH_2-COOH$	$-C_2H_5$	-H	$C_{21}H_{20}N_2O_5S$
III	-CH -COOH	$-C_2H_5$	-H	$C_{21}H_{20}N_2O_5S$
IV	$-Ch_2-COOH$	$-CH_3$	-OH	$C_{19}H_{16}N_2O_6S$
V	$-Ch_2-CH_2-cooh$	$-CH_3$	-OH	$C_{20}H_{18}N_2O_5S$

1-Measurement of the spontaneous locomotor activity :

Mice were allowed free access of food and water. The spontaneous locomotor activity (SLA) of these animals was measured over a 30-min period[11]. Measurements of SLA was usually carried out at 9.00 A.M. to 1.00 P.M. An activity cage (Cat. No. 7400 UGO Basile, Biological Ressearch Apparatus, 21025 Canerio, Varese, Italy.) was used, the floor of which is made up of 30 evenly spaced stainless steel bars. As the animal moves, it links or disconnects one or more of the active bars with earth resulting in random configurations that are concerted into pulses. The latter can be recorded at the preset intervals by a print-out counter.

Mice were placed singly in the activity cage and their SLA was recorded 5 min before i.p. administration of the new drugs (control SLA). Following their injection, quinazolinones in a dose of 60 mg/kg were allowed to exert their effect over a period of 30 min. The mean percentage change in SLA of mice recorded over this period was calculated for each compound.

2-Potentiation of pentobarbital hypnosis:

Modification of pentobarbital sleeping time by the tested quinazolinones was determined in mice[21]. The mean sleeping time of pentobarbital was firstly determined in a group of 20 mice following i.p. injection of this drug. Loss and restoration of the righting reflex were taken as the onset and termination of pentobarbital action respectively[13]. The investigated compounds were intraperitoneally injected in a dose of 60 mg/kg into groups of at least 10 mice. Thirty min later, these animals received pentobarbitone sodium (30 mg/kg, i.p.) and the mean sleeping time was again calculated. The student's "t" test[14] was used to analyse statistically the data concerning the effect of the screened compounds on the sleeping time of pentobarbitone.

3-Rotarod motor coordination test:

Quinazolinone derivatives in a dose of 60 mg/kg were intraperitoneally injected into groups of 10 mice. The ability of animals to remain on a rotating rod for 15 sec without falling was determined at 10-min. intervals over a peroid of 2 hours after the i.p. administration of the new quinazolinones[15]. Each experiment is composed of 3 trials conducted at 1-min. intervals. Control experiments were carried out using mice injected with a solution of gum acacia.

4-Anticonvulsant properties :

Anticonvulsant actions of the new quinazolinone chemicals were evaluated against strychnine-induced convulsions in mice. In this set of experiments, phenobarbitone sodium was used as a reference anticonvulsant drug. The test quinazolinones (60 mg/kg i.p.) were administered into groups of 10 mice. Thirty min. later animals were allowed to receive an i.p. injection of strychnine hydrochloride (2 mg/kg). The number of animals protected against convulsions and lethality produced by strychnine was calculated for each group[16]. To serve as a control, 20 mice were intraperitoneally injected with gum acacia at volumes comparable to those used to suspend quinazolinones. After 30 min. these animals were injected with the challenging dose of strychnine hydrochloride (2 mg/kg, i.p.) and the number of convulsive and dead animals was computed.

RESULTS AND DISCUSSION

It is noteworthy that a great attention has been paid to the quinazoline ring present in several physiologically active compounds. A vast number of activities have been reported for many quinazoline derivatives. Among these activities are the bactericidal, tuberculostatic[2,3] and the antibacterial effects[3]. Besides, CNS depressant activities such as analgesic, antipyretic and antiinflammatory effects[4] as well as sedative hypnotic[4,5] and anticonvulsant properties[5] have been reported.

It should also be recalled that various 2,3 disubstituted quinazolinones were reported to possess CNS depressant properties [4,5,17,18]. Methaqualone is the only drug of the quinazolinone group which is marketed as a sedative-hypnotic. Methaqualone abuse as a spree drug[19,20] has led to several attempts aiming at the discovery of more potent and safe quinazolinone derivatives[4,5,5,7].

In 1979, El-Sherif et al[9] synthesized 33 new derivatives of 2,3-disubstituted-4 (3H)-quinazolinones. Six of these compounds were screened for their CNS activities by El-Koussi[8]. In this study El-Koussi demonstrated CNS depressant properties for 4 quinazolinone compounds.

Recently, El-Sherif et al[10] extended their previous studies and synthesized 60 new derivatives of the quinazolinone group (2,3-disubstituted -4(3H)-quinazolinones (I)).

In the present investigation, an attenpt was undertaken to evaluate the possible CNS depressant effects of 5 derivatives, of these quinazolinones which are structurally related to methaqualone and other potent quinazolinone CNS depressant compounds[16,17].

Possible CNS Depressant Effects of some Newly Synthesized Quinazolinone Derivatives

Preliminary experiments were firstly conducted to reveal the influence of one dose level (60 mg/kg) of the investigated quinazolinone compounds on the behaviour of mice. As illustrated in Fig. (1), the 5 tested quinazolinones seem to possess CNS depressant activity. All tested compounds led to a significant decrease in the mean percentage change of the spontaneous locomotor activity (SLA) of mice during the 30-min period of the experiment. There were decreases in SLA by 88.00, 85.74, 81.18, 81.83 and 84.84% for compounds I,II,III,IV and V respectively. In control mice, the recorded fall in SLA was amounting to 60.61%.

With the exception of compound IV, all the investigated quinazolinone compounds in a dose level of 60 mg/kg showed no potentiation of pentobarbital-induced hypnosis (Fig. 2). The recorded sleeping times of pentobarbital in compound IV-treated and control mice were 78 and 50 min respectively. In other words, compound IV was able to prolong the sleeping time of pentobarbital by a value of 28 min. However, this compound did not elicit any change in the onset of pentobarbital action.

As has been reported by Sheth et al[12], the potentiation of the sleeping time of barbiturates by a test drug is more possibly correlated to its CNS depressant action provided that barbiturate excretion via the kidney is not affected by the test drug. Accordingly, a more potent CNS depressant effects can be essentially related to compound IV which was able to significantly prolong the hypnotic effect obtained by pentobarbital sodium in mice.

A correlation between the potentiation of pentobarbital hypnosis and the different substitutions on the phenyl ring of quinazolinones (as is the case with compound IV) can not be ruled out. The inability of other quinazolinones (I,II,III and V) to potentiate the hypnotic action of pentobarbital may be linked to both the lack of hydroxyl group at R_3 and the existence of a longer side chain at R_1 and R_2.

In view of the aforementioned results, the 5 quinazolinones were subjected to further screening tests for their muscle relaxant and anticonvulsant properties. The rotarod test is looked upon by many authors as a specific screening test[15,21,22]. Out of the 5 tested quinazolinone compounds used in a dose of 60 mg/kg, only 2 compounds (II and III) demonstrated a reasonable degree of muscle relaxation (Fig. 3) as measured by the rotarod motor coordination test. The muscle relaxant properties of these 2 compounds were recorded 10-min. following their administration and throughout the 2-hours period of experimentation. This effect was observed only in 40% of the tested animals.

Relating muscle incoordination to the structure of these different quinazolinone derivatives might indicate that the absence of hydroxyl group at R_3 is necessary for muscle relaxation. In addition, the presence of ethoxy group at R_3 as well as the propionic acid substituent (with sulfur atom) at R_1 may be required for such an activity. On the other hand, compounds having hydroxyl group at R_3 and methoxy group at R_2 showed no muscle relaxant effects.

The last set of experiments comprised evaluation of anticonvulsant properties of the quinazolinones against strychnine induced convulsions. All mice injected with strychnine hydrochloride (2 mg/kg, i.p.) showed the typical strychnine convulsions which were usually followed by death. As it is evident from Table (2) the mean survival time of strychnine-treated mice was found to be 5.8 min. with a resultant percentage protection (against death) of zero. As a standard anticonvulsant drug, phenobarbitone (60 mg/kg, i.p.) protected 84% animals against mortality with a concomittant increase in the mean survival time of about 18.00 min.

Table 2 : Anticonvulsant Activity of Quinazolinone Compounds (60 mg/kg, i.p.) Against Strychnine (2 mg/kg,i.p.) Induced Convulsions in Mice.

Treatment	Number of animals	Dead/ Surviving	Mean survival (min)+S.E.	Percentage Protection
Control	10	10/Zero	5.8+0.27	Zero %
Phenobarbital	6	1/5	18.0+0.00*	84 %
Comp. I	6	2/4	10.5+0.22*	66 %
Comp. II	6	2/4	12.5+0.20*	66 %
Comp III	6	6/Zero	4.67+0.41	Zero %
Comp. IV	6	3/3	11.0+1.03*	50 %
Comp. V	6	6/Zero	4.67+0.22	Zero %

* Significant difference at $P < 0.05$

Phenobarbital (60 mg/kg, i.p.) was used as a reference anticonvulsant drug.

With the exception of compounds III and V, the other quinazolinone derivatives showed an effective anticonvulsant action. Quinazolinones I,II and IV brought about a prolongation in the mean survival time of mice to 10.5, 12.5 and 11.0 min. respectively. Concerning the protection against strychnine-induced lethality, compounds I,II and IV were found to increase this protection by values of 66,66 and 50% respectively.

However, the anticonvulsant action displayed by quinazolinones I,II and IV was not superior than that of phenobarbitone although the tested compounds were used in the same dose as that of phenobarbitone. Quinazolinones I,II and IV were not as effective as phenobarbitone both in protecting mice against strychnine-induced mortality and in prolonging the mean survival time of these animals. The anticonvulsant action of quinazolinones was not always correlating with their sedative activity since compound IV was the only quinazolinone which combined both potent sedative and anticonvulsant properties.

It could be concluded from this study that quinazolinones II and IV are the most effective CNS depressants whereas compound V is the least potent one.

It should be emphasized that this study is a preliminary one pointing out the possible sedative and anticonvulsant properties of the investigated quinazolinone derivatives. Besides, it is necessary that these compounds should be subjected to more through screening tests and toxicological studies.

Possible CNS Depressant Effects of some Newly Synthesized Quinazolinone Derivatives

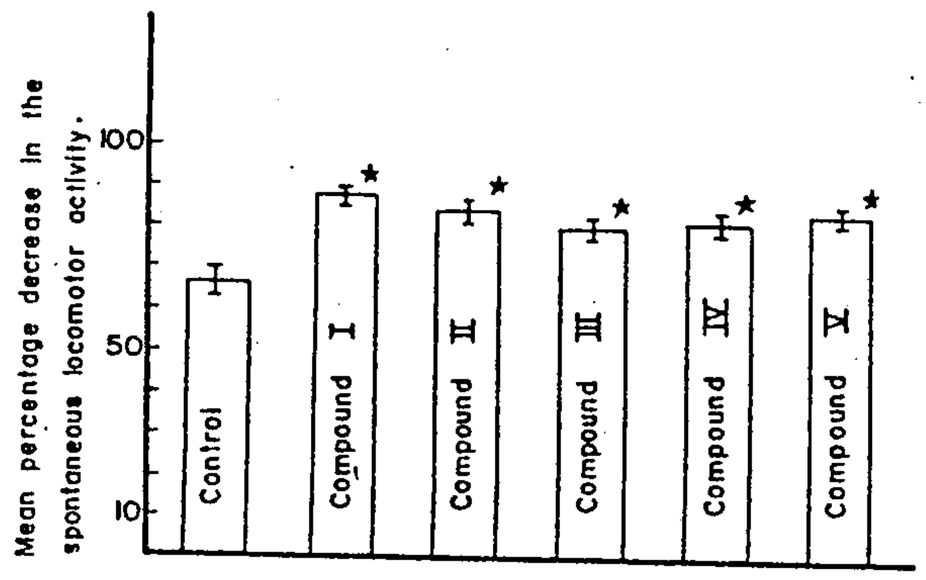


Fig.(1): Mean percentage decrease in the spontaneous locomotor activity of mice following i.p. adminstration of quinazolinone derivatives (60 mg/Kg).
(*) Significant increase from control at $P < 0.05$.

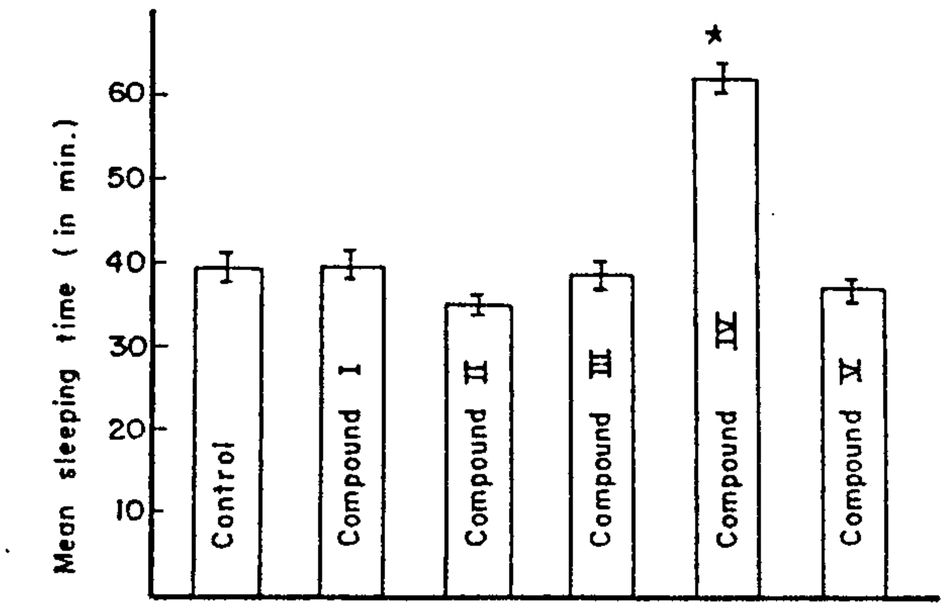


Fig.(2): Effect of i.p. injection of quinazolinone compounds (60 mg/Kg) on the sleeping time of pentobarbital sodium (30 mg/Kg) in mice.
Number of animals in control group = 20
Number of animals in drug-treated group = 10
(*) Significant increase from the control at $P < 0.05$.

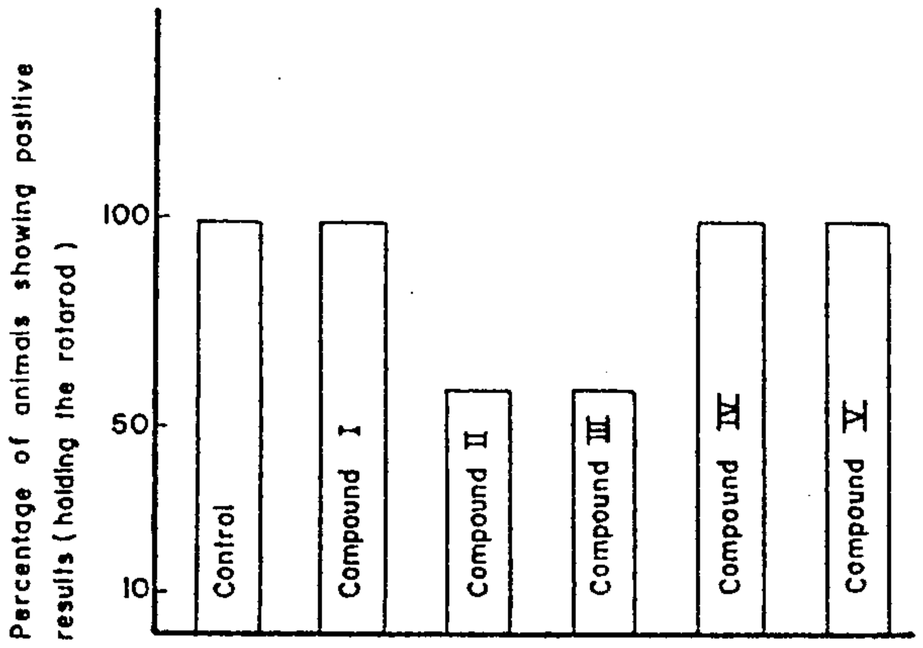


Fig.(3): Percentage of animals showing muscle relation following i.p. injection of quinazoline derivatives (n=10).

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التأثيرات المثبطة للجهاز العصبى المركزى لبعض مشتقات الكينازولينون المخلقة حديثا

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فى هذه الدراسة تم تقييم خمسة مركبات مخلقة حديثا (اشير اليها بارقام ١،٢،٣،٤،٥) من العائلة الكيميائية المسماه بالكينازولينون ، هذه المركبات درست من حيث تأثيراتها المثبطة للجهاز العصبى المركزى فى الفئران ٠

المركبات التى استخدمت فى هذه الدراسة شحيحة الذوبان فى الماء ، لذلك فان هذه المواد تم تعليقها فى معلق صمغى تركيزه ٥ / وقد تم حقن كل هذه المشتقات داخل الغشاء البريتونى فى حرعة مقدارها ٦٠ / محم / كحم من جسم الحيوان ٠

لقد وجد ان كل هذه المركبات لها القدرة على انقاص النشاط الحركى الذاتى للفئران كما وجد ان مركب رقم ٤ هو المركب الوحيد الذى يستطيع اطالة المفعول المنوم لمادة الفينوباربيتون ٠

اما فيما يتعلق بمفعول المركبات التى تم دراستها على العضلات الهيكلية فانه امكن التوصل الى ان مركبات ٢ ، ٣ تستطيع ان تؤدى الى حدوث نوع من انواع عدم التوافق الحركى فى حوالى ٤٠ / من مجموعات الحيوانات المستخدمة فى هذا البحث ٠

ولقد توصلنا ايضا الى ان المركبات ١ ،٢ ، ٤ ،تستطيع ان تزيد من متوسط البقاء على قيد الحياة للحيوانات المعرضة للتشنجات التى تم احداثها باستخدام مادة الستركنين ، كما ان نسبة الحيوانات التى تموت تحت تاثير مادة الستركنين قد تقل بدرجة ملحوظة عند حقن الحيوانات بالمركبات ١،٢،٤، الا ان تأثير هذه المواد المانع لحدوث التشنجات لم يكن له نفس درجة الفاعلية لمادة الفينوباربيتون ٠

من هذه الدراسة نستطيع ان نستنبط ان المركبين ٢ ،٤ من بين الخمس مواد التى استخدمت فى هذه الدراسة هى اكثر المواد فاعلية من حيث تثبيطها للجهاز العصبى المركزى كما ان المركب رقم ٤ هو على ما يبدو انه اقل هذه المواد فاعلية ٠

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