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SYNTHESIS AND ANTICONVULSANT ACTIVITY OF SOME N-SUBSTITUTED-N'- (2-METHYL-4-OXOQUINAZOLIN-3-YL) OXAMIDES

A M. Abdel-Alim, S.A. Hussein, H.I. El-Bitar* and R.A. Abdel-Aal*.

Department of Pharmaceutical Chemistry, Faculty of Pharmacy and *Department of Pharmacology, Faculty of Medicine. Assiut University, Assiut, Egypt

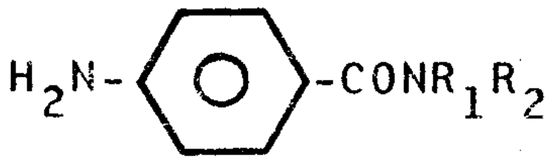
ABSTRACT

Fourteen new oxamides were synthesized by amidation of ethyl N-(2-methyl-4-oxoquinazolin-3-yl) oxamate with the appropriate amines. Preliminary anticonvulsant activity of five oxamides was evaluated, Correlation of activity with structure of the test compounds is also discussed .

INTRODUCTION

Numerous compounds are reported each year as having anticonvulsant properties[1]. These compounds represent a diverse chemical grouping. Structurally, some of the simplest compounds possessing anticonvulsant properties are the carboxylic acids and their amides e.g. valproic acid and its amide[2-4] as well as some amides of substituted benzoic and cinnamic acids[4,5] The local anesthetic amide, lidocaine has been shown to suppress the electroencephalogenic manifestation of epileptic seizures in cats[6].

Recently, a series of 4-aminobenzamides (I) were evaluated for anticonvulsant effects in mice[7].



(I)

It has been observed that 4-amino-N-amylbenzamide was the most potent against maximal electroshock seizures, while the 4-amino-N-cyclohexylbenzamide showed the greatest protective index. The introduction of a second aromatic ring produced more potent compounds , thus I (R_1 = CH (CH_3) C_6H_5, R_2 = H) showed the highest level of activity[7]. In addition, some quinazolinones are known as sedative-hypnotic drugs[8-10] along with their potent anticonvulsant activies[11-13]. On the other hand, oxamic acid derivatives are known to possess a wide range of biological activities which can be summarized in the following:

1 - Ambenonium chloride (Mytelase)[14-17] is an oxamide which is official in the USP XX as anticholinesterase drug with more potent actions than those of neostigmine and pyridostigmine and with longer duration of action. It is especially used in the treatment of myasthenia gravis in patients, who can't tolerate the above drugs. The drug is safe and just have the same side effects as those of other anticholinesterases.

2- Oxapyrine; N-methyl-N'-(4-antripyryl) oxamide has been successfully passed clinical trials to be applied in medicinal practice in USSR as a safe non-narcotic analgesic agent, since it exhibits 3-4 times the activity of amidopyrine and far less toxic[18,19].

3- Many oxamic acid amides and hydrazides proved promising antibacterial activity similar to those of chloramphenicol and sulfacetamide sodium[20,21]. Others showed more potent hypoglycemic effect and less toxicity than tolbutamide[22,23].

4- Recently, new series of oxamic and oxanilic acid derivatives were found to be potent, orally active and quite non-toxic antiallergic agents[24,25].

5- Different biological investigations revealed that incorporation of the oxalyl moiety in the structure of biologically active compounds greatly lowered their toxicity without marked inhibition of the activity[26,27].

Therefore, searching for new oxamides is worthy to be structurally modified and biologically tested and thus the present work aims at the synthesis of some N-subtituted-N'-(2-methyl-4-oxoquinazolin-3-yl) oxamides (V) to be evaluated for their possible anticonvulsant activity. In previous works, we reported the CNS depressant, analgesic and antiinflammatory effects of some N,N'-oxanilamides[28,29]. Thus, we expect that combination of both quinazolinyl and oxalyl moieties in an amide structure may augment the anticonvulsant activity and may suppress the toxicity[26,27].

Concerning the metabolism of oxamides, unfortunately no data are available even about the official ambenonium chloride[14-17]. Nevertheless, the proposed oxamides (V), as other amides[30], need a long time to be hydrolysed (metabolised) to the toxic free oxalic acid. Most probably (V) can pass other metabolic pathways e.g. hydroxylation of the substituent R and also hydroxylation of the CH_3 at position 2 in the same fashion as methaqualone[31]. The hydroxylated metabolites may be rapidly excreted before hydrolysis of oxamides to oxalic acid.

EXPERIMENTAL

All melting points are uncorrected. Microanalyses were done at the unit of microanalysis, National Research Center, Dokki, Cairo. IR spectra were run on a Pye Unicam SP 1000 Infrared spectrophotometer in KBr discs. ^{1}H NMR spectrum of ester (IV) was determined on a Varian T-60 spectrometer, while the other spectra of oxamides (V) were taken on an NT-200 instrument using TMS as an internal standard. The starting materials; acetanthranil (II)[32] and 3- amino-2-methyl-4(3H)-quinazolinone (III)[33] were prepared according to conventional methods. Anticonvulsant activity was determined by the electroshock method using an electroshock apparatus ECT unit 7801 (UGO Basile, 21025 Comerio- Varese, Italy).

Ethyl N-(2-methyl-4-oxoquinazolin-3-yl) oxamate (IV)

To a cooled 8 ml of ethyl oxalyl chloride, 8.75 g (0.05 mole) of finely powdered amine (III) were added gradually while stirring under anhydrous conditions. When the vigorous reaction has been subsided, the mixture was further stirred for 2 hr under reflux on a sand bath at 140^{o}C. Excess ethyl oxalyl chloride was distilled on a rotavapour, where a yellowish brown residue was obtained. The product was cooled, suspended in water and neutralized to pH 6-7 by the cautious addition of a 10% solution of sodium carbonate. The precipitate was filtered, washed with water, dried and crystallized from aqueous ethanol. M.P. 238-40^{o}C, yield 12.6 g (91.6%). Anal. Calc. for $C_{13}H_{13}N_3O_4$: C, 56.73; H, 4.73; N, 15.27 Found: C, 57.31; H, 4.91, N, 15.13. IR (KBr); 3305 (NH), 1745-1730 (COCOOET), 1700 (quinazol. C=O) and 1290 Cm^{-1} (C-O) in addition to the characteristic skeletal vibrations of the quinazolinone nucleus at 1650, 1560 and 1500 Cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.6-7.4 (m, 4H, aromatic protons), 4.65 (q, 2H, OCH_2), 2.1 (s, 3H, CH_3), 1.42 (t, 3H, CH_3). The NH shows up as a broad bump at δ 10.75 which disappeared after addition of D_2O.

Synthesis and Anticonvulsant Activity of some N-Substituted -N'- (2-methyl-4-Oxoquinazolin-3-yl) Oxamides.

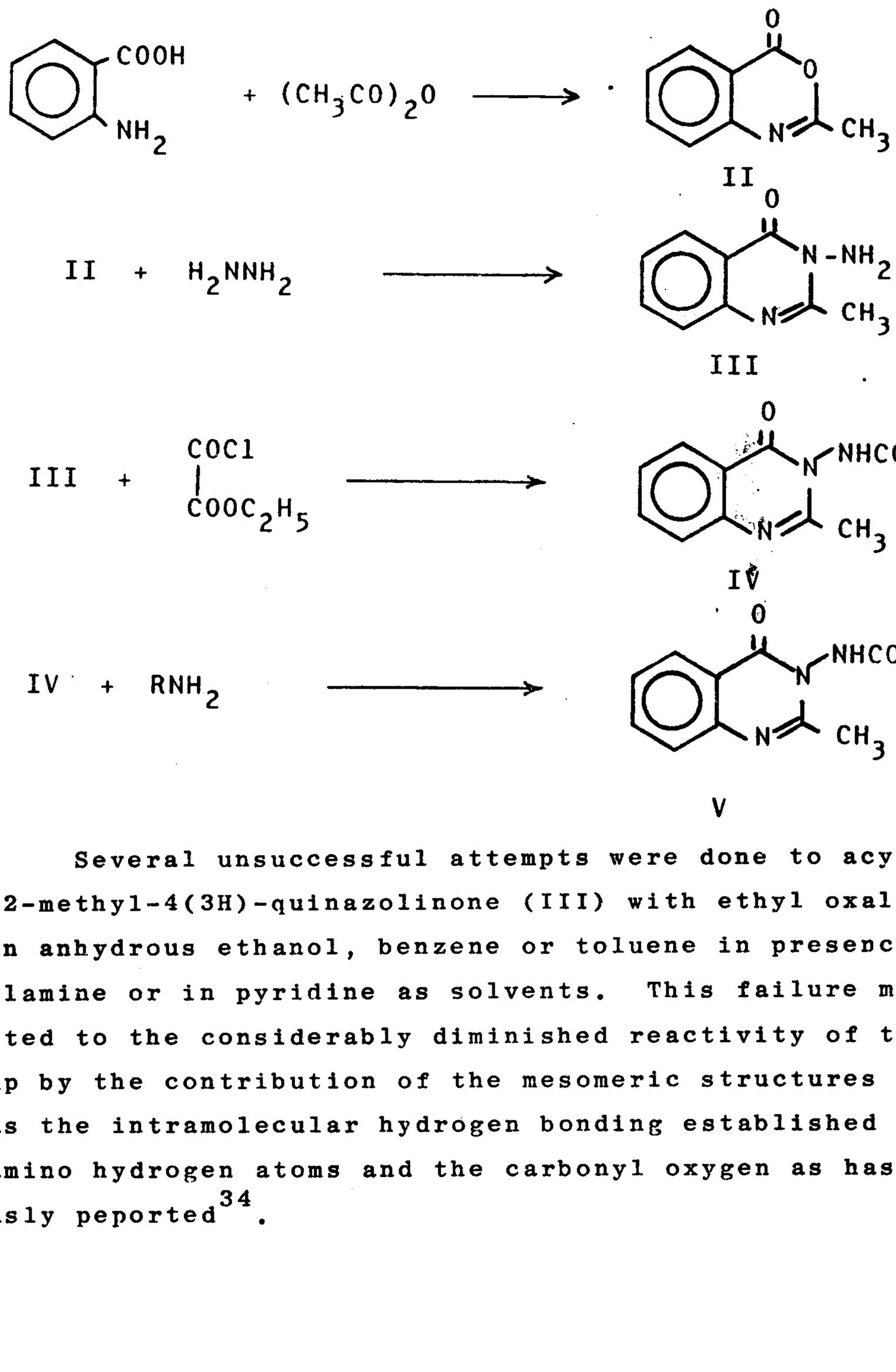
General method for synthesis of N-substituted-N'-(2-methyl-4-oxoquinazolin-3-yl) Oxamides (Va-n)

To the solution of 2.75 g (0.01 mole) of ester (IV) in 30 ml of a mixture of DMF and ethanol (1:5), the appropriate amine (0.012 mole) was dropped while stirring. A yellowish to orange colouration was developed and the reaction mixture was further stirred at the ambient temperature for 2 hr. For oxamides (Vl-n), the reaction mixture was refluxed for 3 hr.

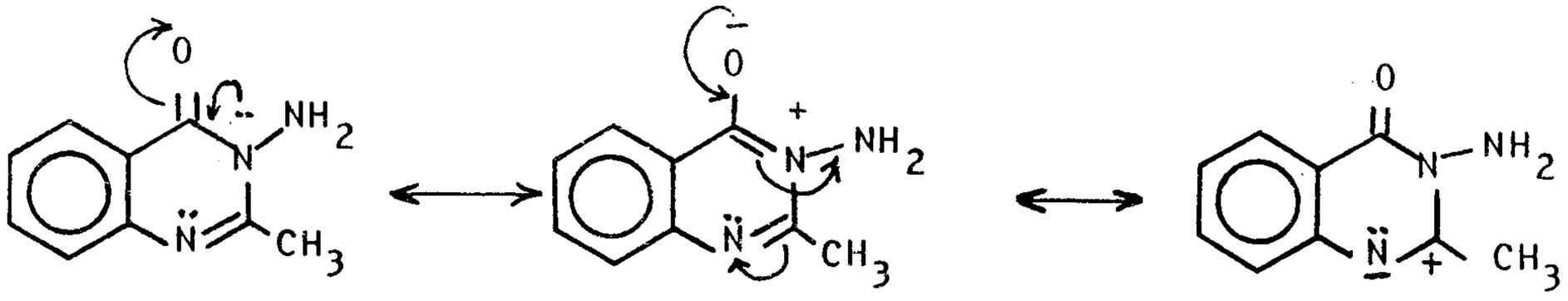
Most of the solvent was distilled under vacuum. The residue was triturated with 10% acetic acid and the precipitate filtered, washed thoroughly with water and crystallized (Table 1). IR spectra (KBr): 3290 (NH), 1685 (quinazol.C=O), 1635 (CONH) and 1300 Cm^{-1} (C-O) in addition to the skeletal vibrations of the quinazolinone nucleus at 1620, 1600, 1550 and 1500 $C\,m^{-1}$. NMR spectrum of Vb(DMSO-d_6) δ: 8.65- 7.20 (m, 4H, aromatic protons), 4.6(q, 2H, CH_2), 2.1 (s, 3H, CH_3), 1.44 (t, 3H, CH_3). Vd (DMSO-d_6) δ : 8.4-7.4 (m, 4H, aromatic protons), 4.4 (septet, 1H, CH), 2.1 (s, 3H, CH_3), 1.4 (d, 6H, 2 CH_3) Both spectra showed broad singlets at δ 12.3 and 12.15 corresponding to 2 NH groups which completely disappeared after addition of D_2O.

SYNTHESIS AND DISCUSSION

The proposed oxamides (V) were prepared according to the following scheme:



Several unsuccessful attempts were done to acylate 3-amino -2-methyl-4(3H)-quinazolinone (III) with ethyl oxalyl chloride in anhydrous ethanol, benzene or toluene in presence of triethylamine or in pyridine as solvents. This failure may be attributed to the considerably diminished reactivity of the amino group by the contribution of the mesomeric structures (VI) as well as the intramolecular hydrogen bonding established between the amino hydrogen atoms and the carbonyl oxygen as has been previously peported[34].



VI

Nevertheless, synthesis of ester (IV) was afforded in higher yield (96.6%) upon acylation of (III) with the acid chloride without addition of any diluent. Structure of the ester was confirmed by microanalysis, IR and NMR spectroscopy.

Synthesis of oxamides (V) was accomplished by amidation of ester (IV) with aliphatic amines at the ambient temperature. We noticed that, interaction of the ester with the different isomers of threo-2-amino-1-(p-nitrophenyl)-1,3- propanediol under reflux conditions improved both yields and purity of the desired oxamides (VI-n). Structures of the oxamides were confirmed by microanalysis, IR and some representative NMR spectroscopy.

Pharmacological Screening

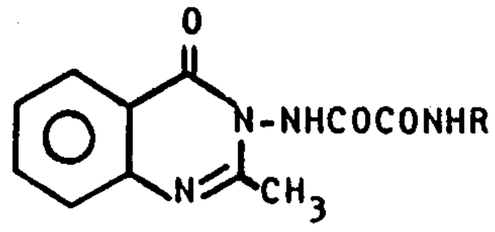
Preliminary anticonvulsant evaluation of five oxamides(Vc, d,f,g & J, Table 1) in comparison to Diazepam® (Hoffman La Roche) was conducted at five dose levels by the electroshock method[35]. All tests were done with adult albino mice (20-30 g) of either sex. 0.4% suspensions of all test compounds (V) were prepared in 1% aqueous solution of carboxymethylcellulose (CMC). Five different dose levels of each compound or the standard drug (diazepam) were injected intraperitoneallv, at 60 min prior to testing, into groups of mice each of 10 animals. Besides, another group of mice served as a control and was dosed intraperitoneally with 1 ml of the CMC solution prior to testing as above. Initial 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 electroshock via the ear electrodes using a 60 cycle alternating current of 20-mA intensity delivered for 0.1 s. For each of the tested oxamides (V) and diazepam, the dose producing protection in 50% animals (ED_{50} and the 95% fiducial limits) was calculated by the graphical method of Litchfield and Wilcoxon[36]. Results are listed in Table 2.

The above data indicate that anticonvulsant activity of oxamides V is dependant upon the size of the substituent R on the N atom of the oxamide structure (Table 1). Thus, anticonvulsant activity decreases as the bulk of R increases (c.f;Vc, g & j). In addition, comparison of anticonvulsant activity of the isomers (Vc) and (Vd) shows that branching of R (C_3H_7) seems to be crucial for anticonvulsant activity. This may be attributed to the facile hydroxylation of the isopropyl substituent (R) in oxamide (Vd) to the corresponding propanediol to simulate, to certain extent, some 2,2-disubstituted-1,3-propanediols of reported potent anticonvulsant effectiveness[37,38]. Additional pharmacological and toxicological studies on Vd are currently being conducted.

Synthesis and Anticonvulsant Activity of Some N-Substituted -N'-(2-Methyl-4-Oxoquinazolin-3-yl) Oxamides.

Table 1. N-Substituted - N'-(2-methyl-4-oxoquinazolin-3-yl)oxamides (V)



V	R	M.P. °C	Yield %	Molecular formula*	Microanalysis: Calc./Found %C	%H	%N
a	CH_3	255-6	63	$C_{12}H_{12}N_4O_3$	55.38	4.61	21.54
					55.12	4.70	21.32
b	C_2H_5	223-4	60	$C_{13}H_{14}N_4O_3$	56.93	5.11	20.44
					57.00	5.18	20.38
c	$n\text{-}C_3H_7$	338-9	88	$C_{14}H_{16}N_4O_3$	58.33	5.55	19.44
					58.42	5.62	19.00
d	$iso\text{-}C_3H_7$	338-9	92	$C_{14}H_{16}N_4O_3$	58.33	5.55	19.44
					58.01	5.85	19.02
e	$n\text{-}C_4H_9$	293-4	73	$C_{15}H_{18}N_4O_3$	59.60	5.96	18.54
					59.24	6.10	18.42
f	$iso\text{-}C_4H_9$	298-9	78	$C_{15}H_{18}N_4O_3$	59.60	5.96	18.54
					59.35	6.08	18.61
g	$n\text{-}C_5H_{11}$	298-9	94	$C_{16}H_{20}N_4O_3$	60.76	6.33	17.72
					61.00	6.52	17.55
h	CH_2CH_2OH	198-9	58	$C_{13}H_{14}N_4O_4$	53.79	4.83	19.31
					53.55	5.00	19.01
i	$CH_2\text{-}CH{=}CH_2$	335-7	69	$C_{14}H_{14}N_4O_3$	58.74	4.89	19.58
					58.60	5.02	19.37
j	C_6H_{11}	281-3	87	$C_{17}H_{20}N_4O_3$	62.19	6.09	17.07
					62.04	6.20	16.88
k	$CH_2C_6H_5$	> 360	83	$C_{18}H_{16}N_4O_3$	64.28	4.76	16.66
					63.92	4.93	16.43
l	$-CH(HO)CHC_6H_4NO_2\text{-}p$ (D) CH_2OH	180-1	51	$C_{20}H_{19}N_5O_7$			
m	$-CH(HO)CHC_6H_4NO_2\text{-}p$ (L) CH_2OH	198-9	56	$C_{20}H_{19}N_5O_7$	54.42	4.31	15.87
					53.98	4.56	15.73
n	$-CH(HO)CHC_6H_4NO_2\text{-}p$ (DL) CH_2OH	180-1	60	$C_{20}H_{19}N_5O_7$			

* Oxamides Va,b were recrystallized from ethanol, Vd,e - from a mixture of ethanol, DMF & H_2O (2:1:1), Vh,j - from aqueous ethanol, while the rest compounds were recrystallized from aqueous DMF.

Table 2. Median Effective (anticonvulsant) Doses ED_{50} of Oxamides V in Comparison to Diazepam

Compound	ED_{50} (mg / Kg) and its fiducial limits
Vc	120 (75.00-144.00)
Vd	52 (29.37-92.04).
Vf	150 (86.95-258.75).
Vg	150 (86.95-258.75).
Vj	160 (95.32-268.80).
Diazepam	1.25(0.525-2.95).

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تخليق بعض مشتقات الاوكس اميدات ذات الفاعليه المضادة للتشنجات العصبيـــــــة

عبدالعليم محمد عبدالعليم ، سميحه عبدالرحمن حسين،حسين اسماعيل البيطار*

ورأفت عبدالبديع عبدالعال*

قسم الكيمياء الصيدلية بكلية الصيدلة ، * وقسم الاقربازين بكلية الطب ،

جامعة اسيوط - اسيوط - مصـــــــر

تم فى هذا البحث تحضير اربعة عشر اميدا جديدا بتفاعل ايثيل ن - (٢ - ميثيل -٤ - اوكسى كينازولين -٣ - ايل) اوكسامات مع الامينـــــات المناسبة . ولقد تاكدت صحة التركيب البنائى للاميدات والاستر بواســطة التحليل الدقى للعناصر ، الاشعة تحت الحمراء واشعة الرنين النـــــووى المغناطيسى .

تم تقييم الفاعليه المضادة للتشنجات العصبية لخمسة مركبـــــات بصفة مبدئية ونوقشت العلاقة بين التركيب البنائى للمركبات المختبـــرة وفاعليتها الفارماكولوجيه .

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