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SYNTHESIS AND PHARMACOLOGICAL TESTING OF SOME NEW DERIVATIVES OF 2,4-(1H,3H)-QUINAZOLINEDIONE (PART II)*

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سبق تشييد عدد كبير من الإسترات المختلفة من نواة الكينازولين دايون ودراستها أقربازينيا فوجد أن لها فاعلية عالية جدا كمنومات ومضادات التشنجات العصبية وذلك بمقارنتها بمادة الفينوباربيتون.

فى هذا البحث تم تصميم وتشييد ثلاث وأربعون مركبا جديدا من الإسترات المختلفة من مشتقات نواة الكينازولين دايون وذلك للحصول على مركبات لها فاعلية أعلى مما سبق تشييده.

وبدراسة هذه الإسترات أقربازينيا وجد أن أى تغيير فى مجموعة الإستر الموجودة فى الموضع-٣ لنواة الكينازولين دايون يؤدى إلى تقليل الفاعلية وكذلك إدخال مجموعة الميثيل فى الموضع رقم (٦) لمجموعة البنزين يعطى مركبات لها فاعلية عالية أو متساوية لما سبق تخليقه وإدخال البرومين فى الموضع-٦ من البنزين يعطى مركبات عديمة الفاعلية.

تم التعرف على هذه المركبات بالتحليل العنصرى للمركبات وكذلك الأشعة تحت الحمراء والرنين النووى المغناطيسى وكذلك مطياف الكتلة.

A variety of 2,4 (1H, 3H) quinazolinediones were converted into the corresponding potassium salts, and then allowed to react with some halogen-containing compounds. The structures of the derivatives thus prepared, were confirmed by elemental, IR, ^{1}H-NMR and MS spectral data. Testing for anticonvulsant and hypnotic activities in frogs is also presented.

INTRODUCTION

Certain derivatives of 2,4 (1H, 3H) quinazolinediones have been reported to exhibit sedative, tranquilizing, anticonvulsant and hypnotic activities[1-7]. Consequently, it was decided to prepare 2,4 (1H, 3H) quinazoline-diones (III, VII-XI) bearing variable substituents at the 1,3 and 6 positions for possible pharmacological screening in an attempt to study the structure-activity relationship.

EXPERIMENTAL

Melting points were taken on a Griffen melting points apparatus and are uncorrected. Microanalyses were performed at the Central Laboratory, Faculty of Science, Ain Shams University. IR spectra were recorded on a Buck Scientific 500 IR Spectrophotometer using KBr disc. ^{1}H-NMR spectra were recorded on a Bruker 200 MHz NMR Spectrometer at the Central Laboratory, Faculty of Science, Ain Shams University. MS spectra were recorded at the Microanalytical Center, Faculty of Science, Cairo University, Cairo, Egypt.

According to reported procedures, the following intermediates were prepared: Alkyl chloroacetates[8], N-alkyl[9] and N-acylanthranilic acids[10-12], 5-bromo-N-substituted anthranilic acid[13-14], 2,4-(1H, 3H)-quinazolinedione[15], 6-substituted 2,4-(1H, 3H)-quinazoline-diones[16], 1,6-disubstituted 2,4-(1H, 3H)-quinazoline-diones[16-20], potassium salts of certain 1-substituted 2,4-(1H, 3H)-quinazolinediones[5,7]. 1-Substituted-3 (2-hydroxyethyl) 2,4 (1H, 3H)-quinazolinediones[21-23].

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Potassium salts of 2,4-(1H, 3H) quinazolinediones

General procedure

A solution of the appropriate quinazolinedione (I or V) (0.01 mol) in absolute ethanol was treated with alcoholic potassium hydroxide solution (0.02 mol and 0.01 mol respectively). The mixture was stirred for 30 minutes at room temperature and left for further 30 minutes. The potassium salts (II) and (VI) were precipitated, filtered, washed several times with absolute ethanol and then dried.

m.p. (°C): > 300.

Yield: almost quantitative.

1,3-Bis (alkoxycarbonylmethyl)-6-methyl-2,4 (1H, 3H) quinazolinedione (III)(a-e)

A mixture of dipotassium salt (II) (0.01 mole) and the suitable alkyl chloroacetes (0.02 mole) in DMF (20 ml) was heated on a water bath for two hours. The reaction mixture was cooled, poured into ice-cold water (200 ml), whereupon the crude ester precipitated, filtered and finally recrystallized from ethanol (Table 1).

1-Benzyl and 1-benzoyl-3-(alkoxycarbonylmethyl)-6-bromo-2,4 (1H, 3H) quinazolinediones (VII)(a-j)

A mixture of equimolar quantities of the appropriate potassium salt (VI) (0.01 mole) and the suitable alkyl chloroacetates (0.01 mole) in DMF (20 ml) was heated on a water bath for two hours. The reaction mixture was cooled, poured into cold water, the precipitated ester was filtered and then crystallized from ethanol (Tabel 1).

1-Alkyl-3-substituted 2,4 (1H, 3H)-quinazolinediones (IX)(a-j)

A mixture of equimolar quantities of 1-alky-3-(2-hydroxyethyl)-quinazolinedione (VIII) and the appropriate acyl halide (0.01 mole) was heated in absolute ethanol (20 ml) for two hours on a water bath. The reaction mixture was cooled, poured into water, filtered and then crystallized from ethanol (Table 1).

Ethyl 4-(1-substituted-quinazolin-2,4-dion-3-yl) crotonate (X) and ethyl 6-(1-substituted-quinazolin-2,4-dion-3-yl) hexanoate (XI)

A mixture of the potassium salts (V) (0.01 mole) and ethyl 4-chlorocrotonate (0.01 mole) or ethyl 6-chlorohexanoate (0.01 mole) was heated in DMF (20 ml) on a water bath for 3 hours. The reaction mixture was then cooled, poured into cold water. The solid produced was filtered then crystallized from ethanol to afford the new target esters (X) or (XI) respectively (Table 1).

For the preparation of these new compounds, scheme (I) was adopted.

Structures of all new derivatives of 2,4 (1H, 3H)-quinazolinedione (III, VII-XI) were substantiated from elemental (Table 1) and spectral data (Table 2).

RESULTS AND DISCUSSION

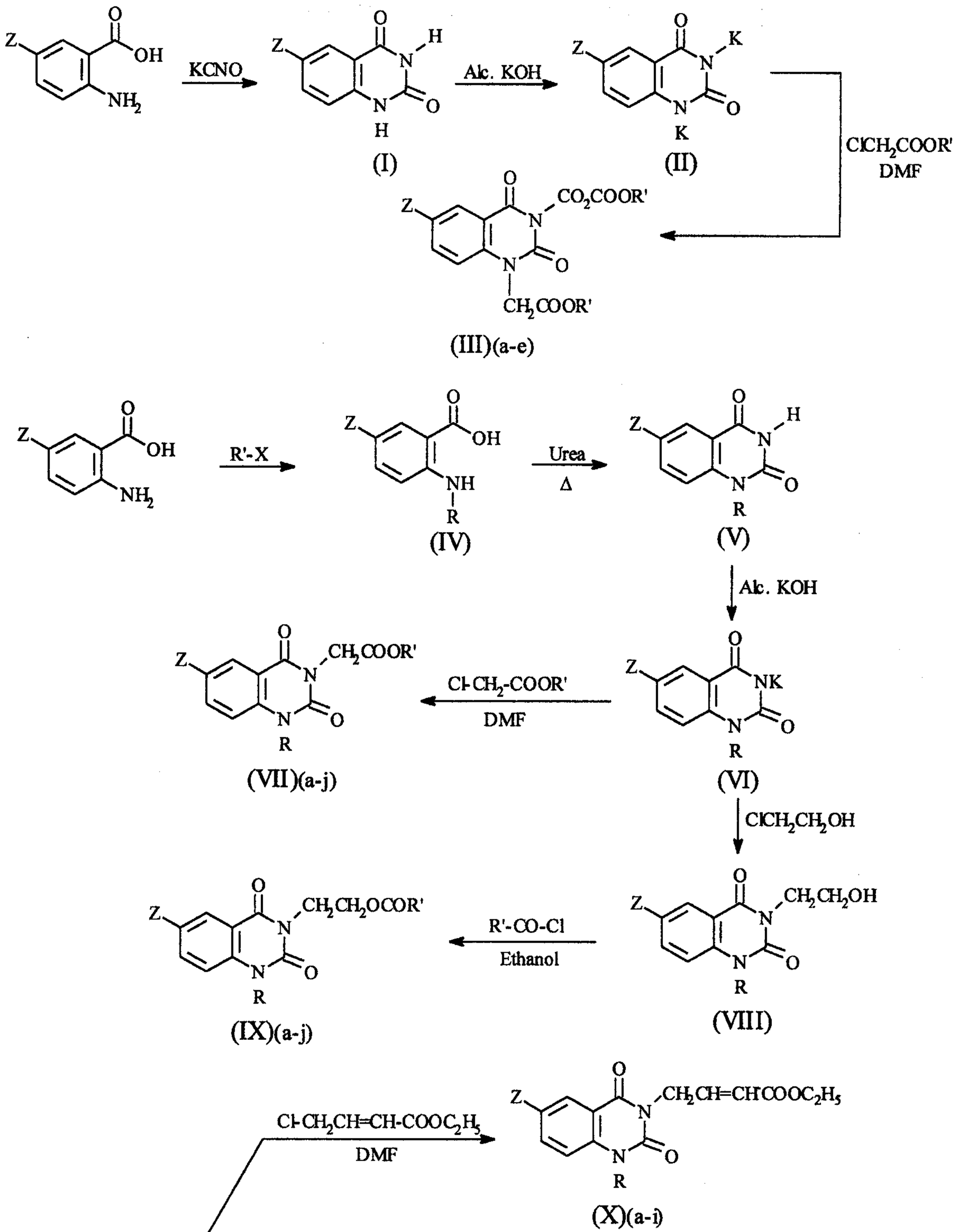
5-Methylanthranilic acid was converted into 6-methyl-2,4-(1H, 3H) quinazolinedione (I), the potassium salt (II) of which was allowed to react with alkyl chloroacetates to obtain the final compounds (III). Other pathways for the synthesis of 1,3,6-trisubstituted 2,4-(1H, 3H) quinazolinediones were followed starting with 5-substituted anthranilic acid, which was initially N-alkylated for N-acylated, then reacted with urea to produce the 1,6-disubstituted 2,4 (1H, 3H) quinazolinediones (V), the latter potassium salts (VI) reacted with alkyl chloroacetates to afford VII. Elongation of the side chain at the 3-position of the 2,4 (1H, 3H) quinazolinedione ring system was attempted by allowing (VI) to react with ß-chloroethanol to get the ß-hydroxyethyl derivatives (VIII), which were finally esterified with acyl halides into the target products (IX). Furthermore, in the same broad line, the potassium salts (VI) were allowed to react with ethyl chlorocrotonate and ethyl ώ-chlorohexanoate whereupon the respective esters (X and XI) were obtained in good yields.

Pharmacological testing

1- Hypnotic activity

Hypnotic activity of the new compounds was primarily determined in frogs by the

Scheme I



(I) (II) (III)(a-e) (IV) (V) (VI) (VII)(a-j) (VIII) (IX)(a-j) (X)(a-i) (XI)(a-i)

Table 1: 1,3,6-trisubstituted 2,4 (1H,3H) quinazolinedione derivatives.

Comp. No.	Z	R	R'	M.P °C	Yield %	Molecular formula	M.wt.	Analysis Calcd./found		
								C%	H%	N%
III-a	CH_3	-	CH_3	90-1	76	$C_{15}H_{16}N_2O_6$	320	56.25 56.30	5.00 5.10	8.75 8.60
b	CH_3	-	C_2H_5	88-9	77	$C_{17}H_{20}N_2O_6$	348	58.62 58.60	5.74 5.60	8.04 8.10
c	CH_3	-	C_3H_7(n)	70-1	45	$C_{19}H_{24}N_2O_6$	376	60.63 60.60	6.38 6.40	7.44 7.40
d	CH_3	-	C_3H_7(iso)	105	72	$C_{19}H_{24}N_2O_6$	376	60.63 60.50	6.38 6.30	7.44 7.60
e	CH_3	-	C_4H_9(n)	68-9	62	$C_{21}H_{28}N_2O_6$	404	62.37 62.20	6.93 6.80	6.93 7.00
VII-a	Br	$C_6H_5CH_2$	CH_3	110	42	$C_{18}H_{15}BrN_2O_4$	403	53.59 53.70	3.72 3.80	6.94 6.90
b	Br	$C_6H_5CH_2$	C_2H_5	125-6	44	$C_{19}H_{17}BrN_2O_4$	417	54.67 54.70	4.07 4.00	6.71 6.90
c	Br	$C_6H_5CH_2$	C_3H_7(n)	112	45	$C_{20}H_{19}BrN_2O_4$	431	55.68 56.00	4.40 3.80	6.49 6.40
d	Br	$C_6H_5CH_2$	C_3H_7(iso)	143-4	67	$C_{20}H_{19}BrN_2O_4$	431	55.68 55.70	4.40 4.00	6.49 6.70
e	Br	$C_6H_5CH_2$	C_4H_9(n)	75	52	$C_{21}H_{21}BrN_2O_4$	445	56.62 57.00	4.71 4.40	6.29 6.30
f	Br	C_6H_5CO	CH_3	130	53	$C_{18}H_{13}BrN_2O_5$	417	51.79 51.80	3.11 3.20	6.71 6.70
g	Br	C_6H_5CO	C_2H_5	112-3	65	$C_{19}H_{15}BrN_2O_5$	431	52.90 53.00	3.48 3.30	6.49 6.50
h	Br	C_6H_5CO	C_3H_7(n)	115-6	45	$C_{20}H_{17}BrN_2O_5$	445	53.93 54.00	3.82 3.80	6.29 6.50
i	Br	C_6H_5CO	C_3H_7(iso)	125-6	55	$C_{20}H_{17}BrN_2O_5$	445	53.93 53.60	3.82 3.50	6.29 6.00
j	Br	C_6H_5CO	C_4H_9(n)	95	85	$C_{21}H_{19}BrN_2O_5$	459	54.90 55.00	4.13 4.00	6.10 6.30
IX-a	H	C_2H_5	CH_3	97	70	$C_{14}H_{16}N_2O_4$	276	60.86 60.76	5.79 5.80	10.14 10.00
b	H	C_6H_5	C_2H_5	100	80	$C_{19}H_{18}N_2O_4$	338	67.45 67.80	5.32 5.30	8.28 8.30
c	H	C_6H_5	$C_2H_5CH_2$	75-6	77	$C_{20}H_{20}N_2O_4$	352	68.18 68.30	5.68 5.50	7.95 7.60

Table 1: Continued

Comp. No.	Z	R	R'	M.P °C	Yield %	Molecular formula	M.wt.	Analysis Calcd./found		
								C%	H%	N%
d	H	C_2H_5	C_6H_4-Cl(p)	135	90	$C_{19}H_{17}ClN_2O_4$	372.5	61.20 61.30	4.56 4.50	7.51 7.30
e	H	C_2H_5	C_6H_4-NO_2(p)	220	85	$C_{19}H_{17}N_3O_6$	383	59.53 59.60	4.43 4.50	10.90 11.00
f	H	$CH_2CH=CH_2$	CH_3	70-1	82	$C_{15}H_{16}N_2O_4$	288	62.50 62.50	5.55 5.30	9.72 10.00
g	H	$CH_2CH=CH_2$	C_6H_5	110	55	$C_{20}H_{18}N_2O_4$	350	68.57 68.70	5.14 5.00	8.00 7.90
h	H	$CH_2CH=CH_2$	$C_6H_5CH_2$	90-1	45	$C_{21}H_{20}N_2O_4$	364	69.23 69.00	5.49 5.50	7.69 8.00
i	H	$CH_2CH=CH_2$	C_6H_4-Cl(p)	175	76	$C_{20}H_{17}ClN_2O_4$	384.5	62.41 62.25	4.42 4.42	7.28 7.00
j	H	$CH_2CH=CH_2$	C_6H_4-NO_2(p)	200	50	$C_{20}H_{17}N_3O_6$	395	60.75 61.00	4.30 4.00	10.63 10.60
X-a	H	CH_3	-	50	76	$C_{15}H_{16}N_2O_4$	288	62.50 62.50	5.55 5.50	9.72 9.50
b	H	C_2H_5	-	80-1	69	$C_{16}H_{18}N_2O_4$	302	63.57 63.40	5.96 6.00	9.27 9.00
c	H	C_3H_7(n)	-	61-1	75	$C_{17}H_{20}N_2O_4$	316	64.55 64.50	6.32 6.30	8.86 9.00
d	H	$CH_2CH=CH_2$	-	55	76	$C_{17}H_{18}N_2O_4$	314	64.96 65.00	5.73 6.00	8.91 9.00
e	H	C_4H_9(n)	-	75-6	80	$C_{18}H_{22}N_2O_4$	330	65.45 65.40	6.66 6.50	8.48 8.50
f	H	C_6H_{11}	-	100-1	75	$C_{20}H_{24}N_2O_4$	356	67.41 67.40	6.74 6.50	7.88 7.80
g	H	$C_6H_5CH_2$	-	70	85	$C_{21}H_{20}N_2O_4$	364	69.23 69.00	5.49 5.50	7.69 8.00
h	H	C_6H_5CO	-	65	92	$C_{21}H_{18}N_2O_5$	378	66.66 60.50	4.76 4.50	7.40 7.30
i	H	C_6H_5	-	154-5	87	$C_{20}H_{18}N_2O_4$	350	68.57 68.60	5.14 5.00	8.00 8.00

Table 1: Continued

Comp. No.	Z	R	R'	M.P °C	Yield %	Molecular formula	M.wt.	Analysis Calcd./found		
								C%	H%	N%
XI-a	H	CH_3	-	70	65	$C_{17}H_{22}N_2O_4$	318	64.15 64.00	6.91 7.00	8.80 9.00
b	H	C_2H_5	-	45	62	$C_{18}H_{24}N_2O_4$	332	65.06 65.00	7.22 7.50	8.43 8.40
c	H	C_3H_7(n)	-	60	76	$C_{19}H_{26}N_2O_4$	346	65.89 66.00	7.51 7.60	8.09 8.00
d	H	$CH_2CH=CH_2$	-	65	83	$C_{19}H_{24}N_2O_4$	344	66.27 66.50	6.97 7.00	8.13 8.00
e	H	C_4H_9(n)	-	65	60	$C_{20}H_{28}N_2O_4$	360	66.66 66.00	7.77 8.00	7.77 7.50
f	H	C_6H_{11}	-	120-1	70	$C_{22}H_{30}N_2O_4$	386	68.39 68.30	7.77 5.50	7.25 7.30
g	H	$C_6H_5CH_2$	-	65	75	$C_{23}H_{26}N_2O_4$	394	70.05 70.00	6.59 6.80	7.10 7.00
h	H	C_6H_5CO	-	57	80	$C_{23}H_{24}N_2O_4$	408	67.64 67.50	5.88 6.00	6.86 7.00
i	H	C_6H_5	-	61	65	$C_{22}H_{24}N_2O_4$	380	69.47 69.50	6.31 6.20	7.36 7.20

righting reflex method using phenobarbitone as a reference drug[24]. Groups of six frogs were injected in the dorsal lymph sac with the test compounds or phenobarbitone in three graded doses. The animals were observed until loss of righting reflex and for further three hours later. The animal was considered asleep, if it showed loss of righting reflex during 60 minutes. The percentage of hypnotic response was calculated for each dose. The results of hypnotic activity are shown in Table (3).

2- The anticonvulsant activity

For evaluation of the anticonvulsant activity, the method of soaji-Echaqueod Lim was used[25]. Frogs (Bufo-Regularis from Egypt) were used as experimental animals. Phenobarbitone sodium was used as a reference compound. Pentylenetetrazol was used as a convulsion inducer. The test compounds were suspended in water (water for injection) by the aid of few drops of Tween-80, phenobarbitone sodium and pentylenetetrazol were dissolved in water (water for injection) containing few drops of the same suspending agent. Frogs weighing 15-30 gm were randomly arranged in groups each 6 animals. Each of three graded doses of the test compounds as well as phenobarbitone were injected in the dorsal lymph sac of a group of animals. Forty-five minutes later,a convulsive dose of pentylenetetrazol (320 mg/kg) was injected in each animal. The animals were observed for further one hour for the occurrence of an episode of tonic convulsion. Animal not exhibited such convulsion during the observation time were considered protected, the results of anticonvulsant activity are shown in Table (4).

Table 2: Spectral data of the new compounds (III, VII-XI).

Comp. No.	Spectral data IR (cm^{-1}), ^{1}HNMR (δ, ppm), Mass (m/z, %)
III-a	**IR**: 1765, 1745 (CO of the esters at positions 1 and 3), 1715 (CO at position-4), 1675 (CO at position-2 of the quinazoinedione ring system).
III-b	**^{1}HNMR**: 1.22 (2t, 6H, 2-CH_2-$\underline{CH_3}$), 1.5 (s, 3H, -CH_3), 4.2 (2q, 4H, 2-$\underline{CH_2}$-CH_3), 4.75 (s, 2H, N-CH2-CO at position-1), 4.90 (s, 2H, N-CH_2-CO at position-3), 7.30-8.50 (m, 4H, aromatic protons).
VII-b	**IR**: 1749 (CO of the ester), 1700 (CO at position-4), 1660 (CO at position-2 of the quinazolinedione ring system). **^{1}HNMR**: 1.39 (t, 3H, CH_2-$\underline{CH_3}$), 3.91 (q, 2H, $\underline{CH_2}$-CH_3), 4.98 (s, 2H, N-CH_2-CO), 5.44 (s, 2H, N-$\underline{CH_2}$-C_6H_5), 7.30-8.50 (m, 8H, aromatic protons).
IX-a	**IR**: 1715 (CO of the OCO-CH_3 group), 1700 (CO at position-4), 1650 (CO at position-4), 1650 (CO at position-2 of the quinazolinedione ring system). **MS**: 276 ($C_{14}H_{16}N_2O_4$, 12.52, M^+), 252 ($C_{12}H_{16}N_2O_4$, 100, Base peak), 217 ($C_{12}H_{13}N_2O_2$, 50.44), 190 ($C_{10}H_{10}N_2O_2$, 59.44), 189 ($C_{10}H_9N_2O_2$, 30.80), 162 ($C_8H_6N_2O_2$, 40.00), 132 ($C_7H_4N_2O$, 15.1)
X-b	**IR**: 2990-2875 (CH stretching of the aliphatic side chain at position-3), 1745 (CO of the ester), 1700 (CO at position-4), 1660 (CO at position-2 of the quinazolinedione ring system. **^{1}HNMR**: 1.30 (t, 3H, CH_2-$\underline{CH_3}$), 4.00-4.2 (m, 1H (allylic system),CH_2-$\underline{CH}$-CH_2-), 4.8 (q, $\underline{CH_2}$-CH_3), 5.10-5.30 (2d, 4H, N-$\underline{CH_2}$-CH=and=CH-$\underline{CH_2}$-CO), 7.30-8.50 (m, 9H, aromatic protons).
XI-b	**IR**: 2995-2800 (CH_2 stretching of the aliphatic side chain at position-3), 1740 (CO of the ester) 1700 (CO at position-4) 1650 (CO at position-2 of the quinazolinedione ring system. **^{1}HNMR**: 1.20 (t, 3H, CH_2-$\underline{CH_3}$), 1.30-1.60 (m, 2H, -CH_2-$\underline{CH_2}$-CH_2), 2.35 (t, 2H, -CH_2-CH_2-CO), 3.70 (s, 3H, N-$\underline{CH_3}$), 4.10-4.40 (m, 4H, CO-$\underline{CH_2}$-CH_3 and N-CH_2), 7.30-8.3 (m, 4H, aromatic protons).

Table 3: Hypnotic activity of 2,4(1H,3H) quinazolinedione derivatives.

Comp. No.	Dose mg/kg	Protection %	Onset Time Min.	ED_{50}	Relative Potency	Comp. No.	Dose mg/kg	Protection %	Onset Time Min.	ED_{50}	Relative Potency
IIIa	50 100 150	33.3 66.6 100	20	75	2.6	XId	50 100 150	33.3 50 100	30	94	2.1
b	50 100 150	33.3 66.6 100	20	75	2.6	e	100 200 300	33.3 66.6 100	30	150	1.33
c	50 100 150	33.3 50 100	20	43	4.6	f	200 300 400	33.3 50 100	45	273	0.72
d	25 50 100	26.6 50 100	25	43	4.6	g	100 200 300	33.3 66.6 100	45	150	1.33
e	50 100 150	33.3 66.6 100	30	75	2.6	h	200 300 400	33.3 66.6 100	45	250	0.8
XIa	100 200 300	33.3 66.6 100	40	150	1.33	i	50 100 200	33.3 50 100	25	94	2.1
b	100 200 300	33.3 66.6 100	40	150	1.33	p*	150 250 300	33.3 66.6 100	35	200	1.00
c	100 200 300	33.3 50 100	30	150	1.33						

* Phenobarbitone.

Table 4: Anticonvulsant activity of 2,4(1H,3H) quinazolinedione derivatives.

Comp. No.	Dose mg/kg	Protection %	ED_{50}	Relative Potency	Comp. No.	Dose mg/kg	Protection %	ED_{50}	Relative Potency
IIIa	50 100 175	50 66.6 100	50	1.8	XId	150 300 400	33.3 66.6 100	225	0.4
b	50 100 150	16.6 50 100	100	0.9	e	150 300 400	33.3 66.6 100	225	0.4
c	50 100 150	33.3 66.6 100	75	1.2	g	200 300 400	33.3 50 100	275	0.36
d	25 50 100	33.3 66.6 100	40	2.2	i	150 250 350	33.3 66.6 100	200	0.5
e	50 100 150	33.3 66.6 100	75	1.2	p*	75 125 200	33.3 66.6 100	100	1.0
XIa	200 300 400	33.3 50 100	27.5	0.36					
b	150 250 350	33.3 66.6 100	200	0.50					
c	150 300 400	16.6 50 100	275	0.36					

* Phenobarbitone.

Structure activity relationship

From the results of the pharmacological testing (Tables 3 and 4), it has been shown that the introduction of an electron repelling methyl group at the 6-position of the 2,4-(1H, 3H)-quinazolinedione ring system has no influence on the pharmacological activity. On the other hand, substitution of this CH3 group at the 6-position by an electron withdrawing bromide atom practically inhibited the pharmacological activity of the original compounds. Furthermore, insertion of a propionate, crotonate, or hexonate esters at the 3-position through elongation of the side chain was found to decrease the anti-convulsant and hypnotic activities relative to our previous results concerning the Ethyl 1-ethyl- and 1-benzyl-2,4-(1H, 3H) quinazolinedion-3-yl acetate[5,7], which has been proved to be the most potent anticonvulsant and hypnotic compounds out of these series.

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