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SYNTHESIS AND ANTICONVULSANT ACTIVITY OF 1,3-DISUBSTITUTED 2,4(1H,3H)QUINAZOLINEDIONE

Abdel Ghany Ali El-Helby

Pharmaceutical Chemistry Department, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt

تم فى هذا البحث تشييد مركبات جديدة من نواة الكينازولين دايون وذلك عن طريق عمل ملح الصوديوم ثم تكثيفه مع خلات كلوروالأيثيل والبروبيل والكلوروأسيتانليد وقد أمكن عمل الهيدرازيدات من الإسترات الناتجة وتفعيلها مع بعض الألدهيدات وكذلك تكثيفها مع بعض الأنهيدريدات. وتم إثبات التركيب البنائى لجميع المركبات عن طريق التحليل الدقى لعناصر المركبات والأشعة دون الحمراء والرنين النووى المغناطيسى ومطياف الكتلة وقد تم أختبار بعض المركبات الجديدة كمضادات للشنجات العصبية على الفئران مستعملا مادة الفينوباربيتون صوديوم كمرجع فوجد أن لها فاعلية ضعيفة وذلك نتيجة تغيير مجموعة الأستر الى الوضع ١ من الكينازولين دايون مقارنة بالفاعلية العالية عندما كانت مجموعة الأسترات فى الوضع ٣ فى الأبحاث السابقة.

Some new 2,4(1H,3H)-quinazolinedione were synthesized and characterized by elemental analysis, IR, ^{1}HNMR and Ms spectral data. Pharmacological evaluation of some of the synthesized compounds as anticonvulsants showed that they displayed weak anticonvulsant activity relative to phenobarbitone sodium as reference drug.

INTRODUCTION

The quinazolinedione derivatives have been reported to exhibit different pharmacological activities such as: hypnotic, anticonvulsant,[1,2] analgesic,[3,4] antiinflammatory,[5] antimicrobial,[6-8] antitubercular,[9] serotoin reuptake inhibition,[10] matrix metalloproteinase (MMP) inhibitors[11] and puromycin-sensitive aminopeptidase inhibitors.[12] In 1986, Ossman *et al.*[13] synthesized some new derivatives of 1,3-disubstituted quinazolinedione which showed hypnotic and anticonvulsant activities. El-Helby[14,15] synthesized some 1,3-disubstituted quinazolinediones and evaluated their anticonvulsant and hypnotic effects. The ester group of all of the synthesized compounds[13-15] is the pharmacophoric[14,15] group which is present at the 3-position of the quinazolinedione. In the present work, the ester group was inserted into position 1 to study its effect on the expected anticonvulsant activity. The present work was performed according Schemes 1 and 2.

EXPERIMENTAL

All melting points were carried out on a Geriffin melting point apparatus and are uncorrected. Elemental analyses were performed on CHN analyzer at the Microanalytical unit, Cairo University, Cairo, Egypt. The IR spectra were recorded on a Pye Unicam SP-1000 IR spectrophotometer at Microanalytical Unit., Cairo University. ^{1}HNMR were recorded on a Joel 200 MHz spectrophotometer at Faculty of Science, Cairo, University, Cairo, Egypt. and Inova 400 Cosy-Chem. buffalo edu. at the Natural Science Complexes, Buffalo, USA. Chemical shifts are given as δvalues relative to TMS as internal standard. Mass spectra were performed on Hewlett Packard 5988 (70 ev) spectrometer at the Microanalytical Unit, Cairo, University.

The following intermediates were prepared according to reported procedures which include methyl 2-(3-ethyl and 3-phenylureido) benzoate[16] **II;$_{1,2}$**, 3-ethyl and 3-phenyl-2,4-(1H,3H) quinazolinediones[16] **III;$_{1,2}$** and the sodium salts of 3-ethyl and 3-phenyl-2,4-(1H,3H) quinazolinediones **IV;$_{1,2}$**.[17]

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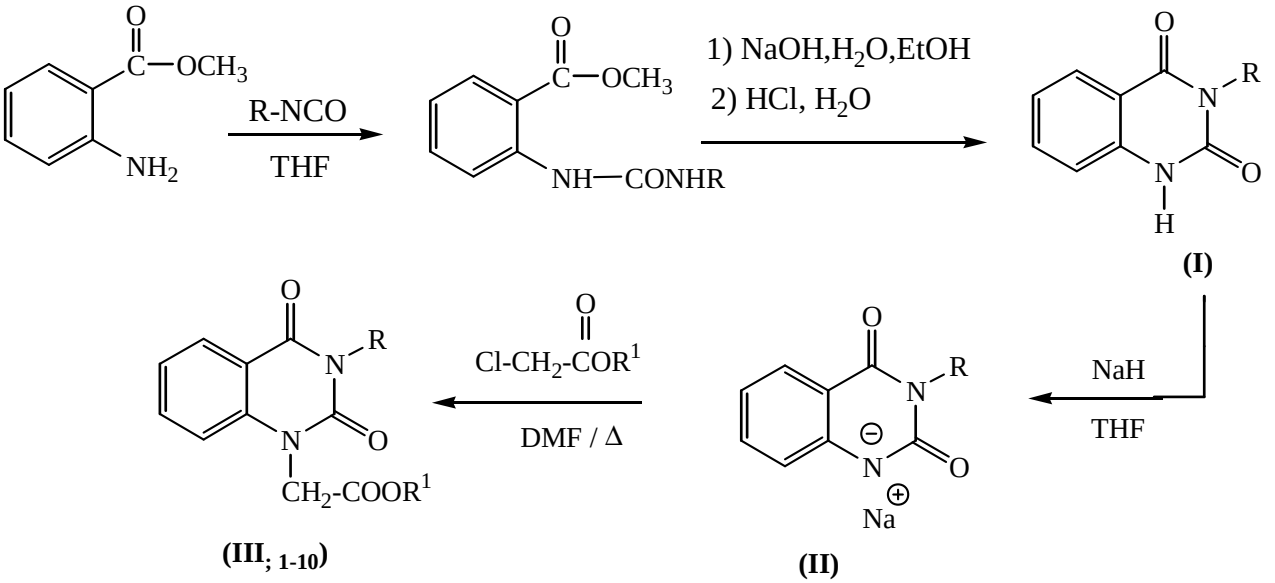
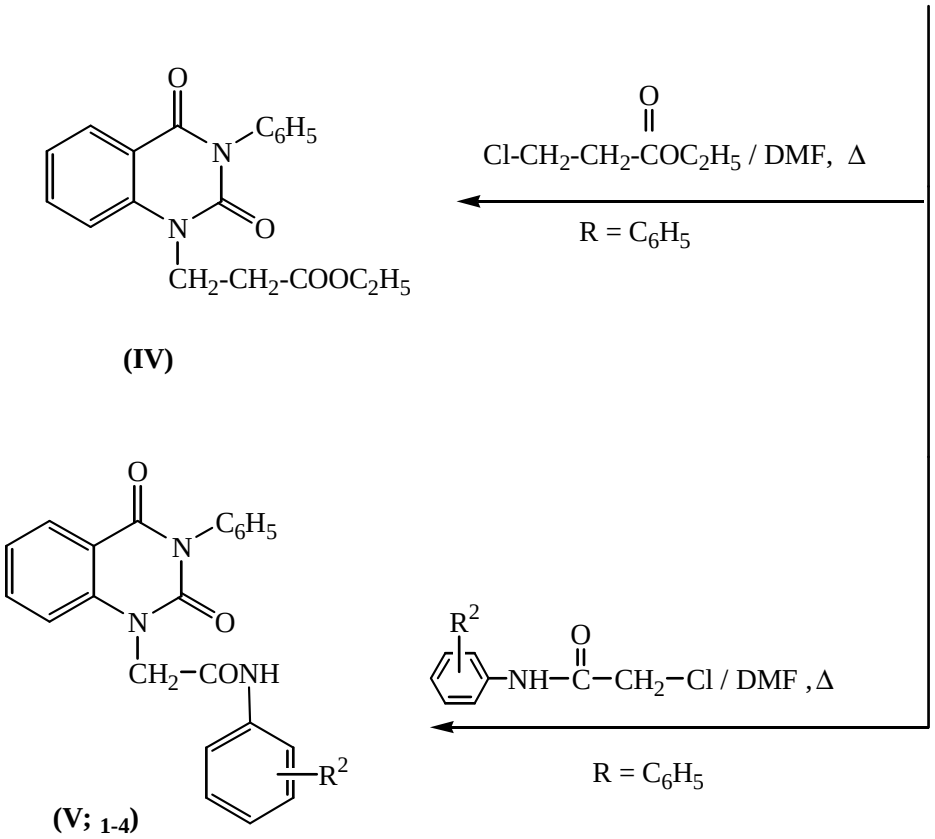


(I) **(II)** **(III; 1-10)**

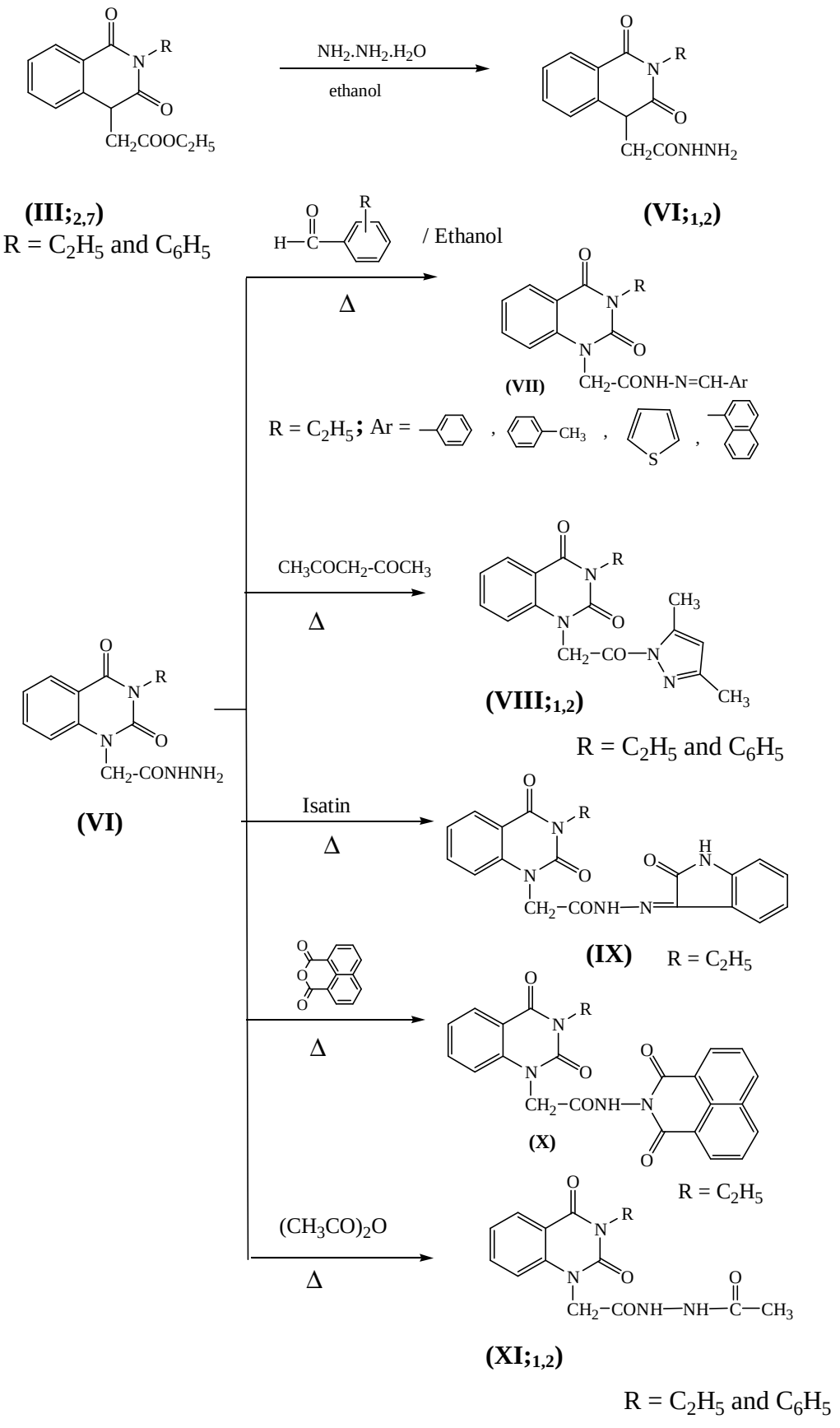
R = C_2H_5 and C_6H_5

R^1= CH_3,C_2H_5,C_3H_7(n), C_3H_7(iso) and C_4H_9(iso)



(IV) **(V; 1-4)**

Scheme 1


NH2.NH2.H2O
ethanol
(III;2,7)
R = C2H5 and C6H5
(VI;1,2)
/ Ethanol
Δ
(VII)
CH2-CONH-N=CH-Ar
R = C2H5; Ar =
CH3COCH2-COCH3
(VIII;1,2)
R = C2H5 and C6H5
(VI)
CH2-CONHNH2
Isatin
(IX)
R = C2H5
(X)
R = C2H5
(CH3CO)2O
(XI;1,2)
R = C2H5 and C6H5

Scheme 2

Alkyl 3-ethyl/3-phenyl-2,4-(1H,3H)-quinazolinedione-1-yl acetates III;$_{1\text{-}10}$

The sodium salts **II;$_{1,2}$**, 2.12 g, 2.6 g (0.01 mole) and alkyl chloroacetates 1.09 g (0.01 mole) in dimethylformamide (20 ml) were heated on water-bath for 3 hrs. The reaction mixture was poured onto ice-cold water and stirred for 30 min. The solid obtained was filtered and crystallized from ethanol (Table 1).

Ethyl 3-[3-phenyl-2,4-(1H,3H)-quinazolinedione-1-yl] propionate IV

Was prepared by interaction of the sodium salt **II;$_2$**, 2.6 g (0.01 mole) and ethyl chloropropionate 1.37 g (0.01 mole) in DMF as mentioned above (Table 1).

1-Arylaminocarbonylmethyl-3-ethyl/3-phenyl-2,4-(1H,3H)-quinazolinediones V;$_{1\text{-}4}$

Were prepared by interaction of the sodium salt **II;$_2$**, 2.6 g (0.01 mole) and chloroacetanilides 1.66 g (0.01 mole) in DMF as mentioned above (Table 2).

3-Ethyl/3-phenyl-2,4-(1H,3H)-quinazolinedione-1-yl acetic acid hydrazides VI;$_{1,2}$

A mixture of ethyl [3-ethyl and 3-phenyl)-2,4-(1H, 3H)-quinazoinedione] acetate **III;$_{2,7}$**, 2.48 g (0.01 mole) and hydrazine hydrate 5 ml (0.1 mole) in ethanol (20 ml) was stirred and heated at 70° for 2 hrs, then cooled. The solid obtained was filtered, washed with water and crystallized from ethanol (Table 2).

1-(Arylidenehydrazinocarbonylmethyl)-3-ethyl-2,4-(1H,3H)-quinazolindione VII;$_{1\text{-}4}$

A mixture of 1-[(3-ethyl)-2,4-(1H,3H)-quinazolinedione] acetic acid hydrazide **VI;$_1$** 2.62 g (0.01 mole) and the appropriate aldehydes (0.01 mole) in absolute ethanol (20 ml) was heated under reflux for 3 hrs. The mixture was cooled, poured onto water and the solid obtained was crystallized from ethanol (Table 2).

1-(3,5-Dimethylpyrazol-1-yl) carbonylmethyl-3-ethyl / 3-phenyl-2,4(1H,3H)-quinazolinedione VIII;$_{1,2}$

A mixture of 1-[(3-ethyl-3-phenyl)-2,4-(1H,3H)-quinazolinedione] acetic acid hydrazide **VI;$_{1,2}$**, 2.62 g and 3.1 g (0.01 mole) and acetylacetone 2 ml (0.02 mole) was heated under reflux for 2 hrs. The reaction mixture was cooled and stirred well for 15 min. until a solid mass was separated. The solid was filtered, dried and crystallized from aqueous ethanol **VIII;$_1$**, m.p 187°, yield 2.28 g (70%),**VIII;$_2$** m.p 205°, yield 2.81 g (75%).

Analysis for **VIII;$_1$** $C_{17}H_{18}N_4O_3$, M.wt. 326.30.

	C%	H%	N%
Calcd.	62.57	5.56	17.16
Found	62.43	5.60	16.70

Analysis for **VIII;$_2$** $C_{21}H_{18}N_4O_3$, M.wt 374.39.

	C%	H%	N%
Calcd.	67.37	4.85	14.96
Found.	67.23	4.99	1 4.89

1-(Isatin hydrazoinocarbonylmethyl)-3-ethyl-2,4-(1H,3H)-quinazolinedione IX

A mixture of **VI;$_1$**, 2.62 g (0.01 mole) and isatin 1.47 g (0.01 mole) was heated under reflux for 12 hrs in 1,4-dioxane (50 ml). The reaction mixture was concentrated and the product obtained was filtered and crystallized from ethanol m.p 290°, yield 2.94 g (75%).

Analysis for **IX** $C_{20}H_{17}N_5O_4$, M. wt 391.38

	C%	H%	N%
Calcd.	61.38	4.38	17.89
Found	61.48	4.37	17.83.

1-(1,8-Naphthalimidoaminocarbonylmethyl)-3-ethyl-2,4-(1H,3H)-quinazolinedione X

A mixture of **VI;$_1$** 2.62 g (0.01 mole) and 1,8-naphthalic anhydride 1.98 g (0.01 mole) was heated under reflux for 4 hrs in absolute ethanol (50 ml). The reaction mixture was distilled under reduced pressure to evaporate the solvent. The solid obtained was crystallized from ethanol, m.p 295-6°, yield 2.7 g (61%).

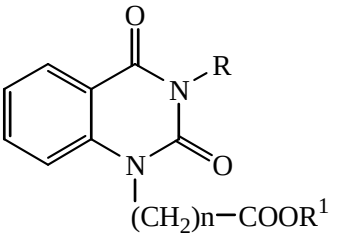
Analysis for **X** $C_{24}H_{18}N_4O_5$, M. wt 442.42

	C%	H%	N%
Calcd.	65.15	4.10	12.65
Found.	65.50	5.47	12.61

1-(Acetylaminocarbamoylmethyl)-3-ethyl and phenyl-2,4(1H,3H)-quinazolinedione XI;$_{1,2}$

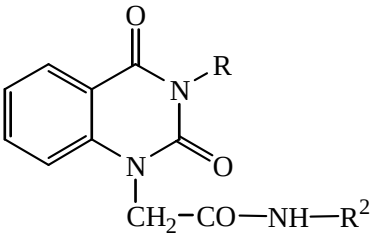
A mixture of the acetic acid hydrazide **VI;$_{1,2}$** 2.62 g and 3.1 g (0.01 mole) and acetic anhydride (20 ml) was heated under reflux overnight. Acetic anhydride was then distilled

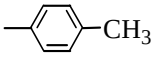
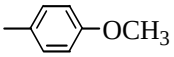
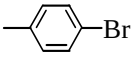
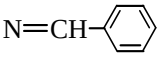
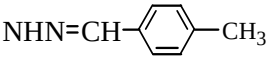
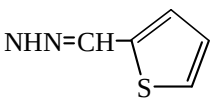
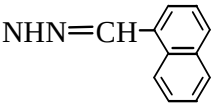
Table 1: Physical properties of 2, 4 (1H, 3H) quinazolinediones, **III_{1-10}**.



Comp. No.	R	R^1	n	Yield %	M.P, °	M. Formula M.Wt	Analyses		
							%	Calc.	Found
III_1	C_2H_5	CH_3	1	81	160-1	$C_{13}H_{14}N_2O_4$ 262.26	C H N	59.54 5.38 10.68	59.84 5.51 10.24
III_2	C_2H_5	C_2H_5	1	80	90-1	$C_{14}H_{16}N_2O_4$ 276.29	C H N	60.86 5.84 10.14	60.71 5.64 10.10
III_3	C_2H_5	C_3H_7 (n)	1	78	135-6	$C_{15}H_{18}N_2O_4$ 290.31	C H N	62.06 6.25 9.65	61.99 5.72 9.59
III_4	C_2H_5	C_3H_7 (iso)	1	80	110-2	$C_{15}H_{18}N_2O_4$ 290.31	C H N	62.06 6.25 9.65	61.63 5.67 9.61
III_5	C_2H_5	C_4H_9 (iso)	1	69	125-6	$C_{16}H_{20}N_2O_4$ 304.34	C H N	63.14 6.62 9.20	62.20 6.67 9.15
III_6	C_6H_5	CH_3	1	75	160-1	$C_{17}H_{14}N_2O_4$ 310.30	C H N	65.80 4.55 9.03	65.76 4.34 8.94
III_7	C_6H_5	C_2H_5	1	77	165-6	$C_{18}H_{16}N_2O_4$ 324.33	C H N	66.66 4.97 8.64	66.43 4.86 8.77
III_8	C_6H_5	C_3H_7 (n)	1	65	141-3	$C_{19}H_{18}N_2O_4$ 338.36	C H N	67.44 5.36 8.28	67.39 5.45 8.22
III_9	C_6H_5	C_3H_7 (iso)	1	67	155-6	$C_{19}H_{18}N_2O_4$ 338.36	C H N	67.44 5.36 8.28	67.44 5.08 7.90
III_{10}	C_6H_5	C_4H_9 (iso)	1	61	115-6	$C_{20}H_{20}N_2O_4$ 352.38	C H N	68.07 5.72 7.95	67.73 5.63 7.62
IV	C_6H_5	C_2H_5	2	63	145-7	$C_{19}H_{18}N_2O_4$ 338.36	C H N	67.44 5.36 8.28	67.35 5.24 8.22

Table 2: Physical properties of 2, 4 (1H, 3H) quinazolinediones, **V-VII**.



Comp. No.	R	R^2	Yield %	M.P, °	M. Formula M.Wt	Alaysis		
						%	Calc.	Found
V_1	C_6H_5		72	280-1	$C_{22}H_{17}N_3O_3$ 371.39	C H N	71.15 4.61 11.31	70.95 5.05 11.20
V_2	C_6H_5		71	300-2	$C_{23}H_{19}N_3O_3$ 385.42	C H N	71.67 4.97 10.90	71.61 5.02 10.90
V_3	C_6H_5		75	250-2	$C_{23}H_{19}N_3O_4$ 401.41	C H N	68.82 4.77 10.47	68.54 4.65 10.65
V_4	C_6H_5		79	280-2	$C_{22}H_{16}BrN_4O_3$ 450.28	C H N	58.68 3.58 9.33	58.84 3.70 9.29
VI_1	C_2H_5	$-NH_2$	85	225-6	$C_{12}H_{14}N_4O_3$ 262.26	C H N	54.96 5.38 21.36	54.73 5.11 21.32
VI_2	C_6H_5	$-NH_2$	87	250-2	$C_{16}H_{14}N_4O_3$ 310.31	C H N	61.93 4.55 18.06	61.61 4.69 17.95
VII_1	C_2H_5		85	285-6	$C_{19}H_{18}N_4O_3$ 350.37	C H N	65.13 5.18 15.99	65.19 5.14 16.13
VII_2	C_2H_5		75	275-6	$C_{20}H_{20}N_4O_4$ 364.40	C H N	65.92 5.53 15.38	65.76 5.30 15.42
VII_3	C_2H_5		72	255-7	$C_{17}H_{16}N_4O_3S$ 356.36	C H N	57.24 4.52 15.71	57.36 4.51 16.02
VII_4	C_2H_5		63	295-6	$C_{23}H_{20}N_4O_3$ 400.43	C H N	68.99 5.03 13.99	69.19 5.37 13.89

under reduced pressure. The reaction mixture was cooled and the solid obtained was crystallized from ethanol. **XI;$_1$**, m.p= 260° yield 2.13 g (70%) and **XI;$_2$**, m.p 285° yield 2.11 g (65%).

Analysis for **XI;$_1$** $C_{14}H_{16}N_4O_4$, M.wt 304.36,

	C%	H%	N%
Calcd.	55.25	5.30	18.42
Found.	54.60	5.42	18.03

Analysis for **XI;$_2$** $C_{18}H_{16}N_4O_4$, M.wt 352.35

	C%	H%	N%
Calcd.	61.36	4.57	15.90
Found.	61.62	4.11	15.90

RESULTS AND DISCUSSION

Reaction of methyl anthranilate with ethyl and phenyl isocyanate in THF gave methyl 2-(3-ethyl and 3-phenylureido) benzoate[16] which upon treatment with aqueous solution of 10% NaOH in ethanol and stirring over night at room temperature then acidified with HCl, the 3-ethyl and 3-phenyl-2,4-(1H,3H) quinazolinediones[16] **I;$_{1,2}$** were obtained. The latter when treated with NaH in THF afforded the corresponding sodium salt **II;$_{1,2}$** in good yields[17] which upon reaction with alkyl chloroacetates or propionates afforded the alkyl 1-[3-ethyl and 3-phenyl-2,4-(1H,3H)-quinazolinedione] acetates **III;$_{1-10}$** and ethyl 1-[3-phenyl-2,4-(1H,3H)-quinazolinedione] propionate **IV**. The IR spectra of compounds **III;$_{1-10}$** are characterized by the appearance of an ester carbonyl band at 1726-1716 cm^{-1}, the carbonyl bands of quinazolinediones nucleus appeared at 1658 cm^{-1} and 1606 cm^{-1}, ^{1}HNMR spectra of these compounds were characterized by the presence of a deshielded methylene group at δ 4.87-5.02 ppm. Reaction of the sodium salt **II;$_2$** with chloroacetanilides in DMF afforded 1-arylaminocarbonylmethyl-3-phenyl-2,4(1H,3H)-quinazolinediones **V;$_{1-4}$**. The ^{1}HNMR spectra of these compounds showed singlet of 2H due to metylene group at δ 4.86-5.02 ppm and another singlet of 1H due to NH group at δ 8.00-10.35 ppm. Hydrazinolysis of the ester compounds **III;$_{2,7}$** in ethyl acohol by heating for 30 min. afforded the acetic acid hydrazids **VI;$_{1,2}$**. The IR spectra of such compounds revealed the amide NH stretching at 3210, 3330 cm^{-1}. IR, ^{1}HNMR and Ms of these compounds are presented in Table (3). Reaction of the hydrazides **VI;$_{1,2}$** with the appropriate aromatic aldehydes in ethanol gave the arylidenes **VII;$_{1-4}$**. The IR spectra of such compounds showed bands at 3293 cm^{-1}, 1694 cm^{-1}, 1671 cm^{-1} for NH and carbonyl absorption bands respectively. ^{1}HNMR spectra are characterized by the presence of deshielded-CH_2- group which ranged from δ 5.33-5.35 ppm. The pyrazole derivatives **VIII;$_{1,2}$** was obtained from the reaction of acetylacetone with the acetic acid hydrazides **VII;$_{1,2}$** in ethanol. The ^{1}HNMR spectrum of compound **VIII;$_1$** showed two singlet signals of two methyl groups at C_3 and C_5 of the pyrazole ring at δ 2.28 and δ 2.51 ppm. The singlet signal of the pyrazole proton at 4-position appeared at 6.31 ppm, the singlet of 2H of methylene group at δ 5.69 ppm. The mass spectrum of compound **VIII;$_2$** was recorded in Table (3). Reaction of the acetic acid hydrazide **VI;$_{1,2}$** with isatin and naphthalic anhydride in ethanol afforded compounds **IX** and **X** respectively. The mass spectra of these compounds are showed in Table (3). Reaction of the hydrazide **VI;$_{1,2}$** with acetic anhydride afforded the acetyl derivatives **XI;$_{1,2}$**. The IR spectra of these compounds showed strong bands at 3202 or 3207cm^{-1}, 1708-1711 cm^{-1} for NH and carbonyl absorption respectively. The ^{1}HNMR of the compounds **XI;$_{1,2}$** showed the two singlet signals of the two NH protons at δ 9.88 and δ 10.20 ppm for the compound **XI;$_1$** and at δ 9.88 and at δ 10.19 ppm for the compound **XI;$_2$**.

Pharmacological testing

The anticonvulsant activity[18,19]

The method reported by Soaje-Echague and Lim[18] was adopted to assess the anticonvulsant activity of the tested compounds and the reference drug in mice.

Thus each of three graded doses for each tested compound as well as for phenobarbitone was injected intraperitoneal to a group of animals. One hour later, the animals were injected subcutaneously with a dose of 100 mg/kg of pentylentetrazole. The animals were observed for further one hour. The animal that showed no clonic seizures during a 60-minute

Table 3: Spectral data of the new compounds (**III-XI**).

No.	IR (cm^{-1}), ^{1}HNMR (δ, ppm), Mass (m/z, %), J (Hz)	
III$_1$	IR	2964 (CH aliphatic), 1734 (carbonyl of ester), 1676, 1608 (two carbonyls of quinazolinedione nucleus)
	^{1}HNMR $CDCl_3$	1.29 (t, 3H, -CH_2-$\underline{CH_3}$, J= 7.08 Hz), 4.16 (q, 2H, $\underline{CH_2}$-CH_3, J= 7.02 Hz), 3.79 (s, 3H, OCH_3), 4.91 (s, 2H, N-CH_2-CO), 6.95 (d, 1H, aromatic proton at C_8, J= 8.32 Hz), 7.26 (t, 1H, aromatic proton at C_6, J= 7.48 Hz), 7.63 (t, 1H, aromatic proton at C_7, J= 7.34 Hz), 8.26 (d, 1H, aromatic proton at C_5, J= 6.42 Hz).
III$_2$	IR	2964 (CH aliphatic), 1732 (carbonyl of ester), 1702, 1656 (two carbonyls of quinazolinedione nucleus)
	^{1}HNMR $CDCl_3$	1.30 (doublet of triplet, 6H, $2CH_3$), 4.23 (doublet of quartet, 4H, $2CH_2$), 4.90 (s, 2H, -N-CH_2), 6.95 (d, 1H, aromatic proton at C_8, J= 8.54 Hz), 7.27 (t, 1H, aromatic proton at C_6, J= 7.34 Hz), 7.65 (t 1H, aromatic proton at C_7, J= 1.78 Hz), 8.29 (d, 1H, aromatic proton at C_5, J= 6.38 Hz).
III$_3$	IR	2972 (CH aliphatic), 1732 (carbonyl of ester), 1702, 1656 (two carbonyls of quinazolinedione nucleus)
	^{1}HNMR $CDCl_3$	0.90 (t, 3H, OCH_2-CH_2-CH_3, J= 5.06 Hz), 1.29 (t, 3H, N_CH_2-CH_3, J= 5.06 Hz), 1.66 (q, 2H, $OCH_2CH_2CH_3$, J= 5.06 Hz), 4.16 (m, 4H, N-CH_2CH_3 and OCH_2-CH_2), 4.91 (s, 2H, N-CH_2COO), 6.95 (d, 1H, aromatic at C_8, J= 8.00 Hz), 7.26 (t, 2H, aromatic C_6, J= 6.06 Hz), 7.64 (t, 1H, aromatic at C_7, J= 1.20 Hz), 8.26 (d, 1H, aromatic C_5, J= 5.20 Hz).
III$_4$	IR	2972 (CH aliphatic), 1732 (carbonyl of ester), 1702, 1656 (two carbonyls of quinazolinedione nucleus)
	^{1}HNMR $CDCl_3$	1.33-1.24 (m, 9H, $2CH_3$ of CH ($\underline{CH_3}$)$_2$ and CH_3 of C_2H_5), 4.19 (q, 2H, N-CH-CH_3), 4.87 (s, 2H, N-CH_2-CO), 5.10 (m, 1H of $\underline{CH}$-(CH_3)$_2$), 6.95 (d, 1H, aromatic proton at C_8, J= 6.24 Hz), 7.29 (t, 1H, aromatic proton at C_6, J= 8.24 Hz), 7.63 (t 1H, aromatic proton at C_7, J= 7.20 Hz), 8.26 (d, 1H, aromatic proton at C_5, J= 6.54 Hz).
III$_5$	IR	2966 (CH aliphatic), 1732 (carbonyl of ester), 1702, 1654 (two carbonyls of quinazolinedione nucleus)
	^{1}HNMR $CDCl_3$	0.88 (d, 6H, of –CH ($\underline{CH_3}$)$_2$, J= 5.60 Hz), 1.29 (t, 3H, N-CH_2-$\underline{CH_3}$, J= 5.60 Hz), 1.91 (m, 1H, -$\underline{CH}$ (CH_3)$_2$), 3.97 (d, 2H, -N-CH_2CO, J= 5.60 Hz), 4.17 (q, 2H, N-$\underline{CH_2}$-CH_3, J= 5.60 Hz), 4.92 (s, 2H, -COO$\underline{CH_2}$)., 6.97 (d, 1H, aromatic at C_8, J= 6.80 Hz), 7.26 (t, 1H, aromatic at C_6, J= 1.20 Hz), 7.63 (t, 1H, aromatic at C_7, J= 6.00 Hz), 8.26 (d, 1H, aromatic at C_5, J= 6.04 Hz).
III$_6$	IR	3068 (CH aliphatic), 1728 (carbonyl of ester), 1662, 1602 (two carbonyls of quinazolinedione nucleus)
	^{1}HNMR $CDCl_3$	3.90 (s, 3H, OCH_3), 4.95 (s, 2H, N-CH_2CO), 7.01-8.31 (M, 9H, aromatic protons).
III$_7$	^{1}HNMR $CDCl_3$	1.29 (t, 3H, OCH_2-$\underline{CH_3}$, J= 7.16 Hz), 4.27 (q, 2H, $\underline{OCH_2}$-CH_3, J= 7.12 Hz), 4.93 (s, 2H, N-CH_2CO), 7.01-8.30 (m, 9H, aromatic protons)
III$_8$	^{1}HNMR (Acetone-d_6)	0.89 (t, 3H, CH_3, J= 5.20 Hz), 1.65 (m, 2H, CH_2-CH_2-$\underline{CH_3}$), 4.12 (t, 2H, $\underline{OCH_2}$, J= 5.60 Hz), 5.02 (s, 2H, N-CH_2CO), 7.32-8.17 (m, 9H, aromatic protons)
III$_9$	IR	2972 (CH aliphatic), 1730 (carbonyl of ester), 1710, 1668 (two carbonyls of quinazolinedione nucleus)
	^{1}HNMR $CDCl_3$	1.28 (d, 6H, CH ($\underline{CH_3}$)$_2$, J= 6.24 Hz), 4.90 (s, 2H, N-CH_2CO), 5.18 (m, 1H, $\underline{CH}$ (CH_3)$_2$), 7.00-8.30 (m, 9H, aromatic protons).

Table 3: Continued.

No.	IR (cm^{-1}), ^{1}HNMR (δ, ppm), Mass (m/z, %), J (Hz)	
III$_{10}$	IR	2970 (CH aliphatic), 1738 (carbonyl of ester), 1712, 1666 (two carbonyls of quinazolinedione nucleus)
	^{1}HNMR Acetone	0.89 (d, 6H, CH ($\underline{CH_3}$)$_2$, J= 6.80 Hz), 1.92 (m, 1H, $\underline{CH}$ (CH_3)$_2$), 3.95 (d, 2H, COO$\underline{CH_2}$-CH (CH_3)$_2$, J= 4.80 Hz), 5.03 (s, 2H, N$\underline{CH_2}$CO), 7.32-8.17 (m, 9H, aromatic protons).
IV	IR	2972 (CH aliphatic), 1734 (carbonyl of ester), 1710, 1668 (two carbonyls of quinazolinedione nucleus)
	^{1}HNMR $CDCl_3$	1.25 (t, 3H, OCH_2-$\underline{CH_3}$, J= 7.06 Hz), 4.18 (q, 2H, $\underline{OCH_2}$-CH_3, J= 7.12 Hz), 2.80 (t, 2H, N-$\underline{CH_2}CH_2$, J= 7.82 Hz), 4.48 (t, 2H, -$CH_2\underline{CH_2}$CO, J= 7.62 Hz), 7.26-8.31 (m, 10H, aromatic protons) and $CDCl_3$ protons.
V$_1$	IR	3272 (NH amidic), 1710 (amidic carbonyl) 1662, 1602 (two carbonyl of quinazolinedione nucleus)
	^{1}HNMR DMSO-d_6	5.01 (s, 2H, N-CH_2CO), 7.04-8.14 (m, 14H, aromatic protons), 10.35 (s, 1H, NH).
V$_2$	^{1}HNMR $CDCl_3$	2.29 (s, 3H, p-CH_3), 4.87 (s, 2H, N-CH_2CO), 7.09-8.28 (m, 15H, 12, aromatic protons, NH and $CDCl_3$).
	Ms	M/z 385 (M+, $C_{23}H_{19}N_3O_3$, 5.84%), 2.79 ($C_{16}H_{11}N_2O_3$, 56.60%), 132 (C_8H_6NO, 100% base)
V$_3$	^{1}HNMR $CDCl_3$	3.77 (s, 3H, p-OCH_3), 4.86 (s, 2H, N-CH_2CO), 6.65-8.33 (m, 15H, 12 aromatic protons, NH and $CDCl_3$).
V$_4$	IR	3272 (NH aliphatic), 3286 (NH, amidic), 1710 (amidic carbonyl), 1664, 1608 (two ketonic carbonyl of quinazolinedione nucleus)
	Ms	M/z 451, 499 (M, M^{+2}, 1.37, 1.30% respectively), 279 (M 96.21%), 132 (C_8H_6NO, 100% base)
VI$_1$	IR	3328 (NH amidic), 3294 (NH_2), 1700, 1666 and 1608 (carbonyl groups)
	^{1}HNMR $CDCl_3$	1.29 (t, 3H, -CH_2-$\underline{CH_3}$, J= 6.00 Hz), 4.17 (q, 2H, $\underline{CH_2}$-CH_3, J= 6.00 Hz), 3.89 (s, 2H, NH_2), 4.76 (s, 2H, NCH_2CO), 7.30 (t, 1H, aromatic at C_8, J= 9.60Hz), 7.36 (d, 1H, aromatic at C_6, J= 6.80 Hz), 7.49 (s, 1H, NH), 7.69 (t, 1H, aromatic at C_7, J= 1.20 Hz), 8.25 (d, 1H, aromatic at C_5, J= 5.20 Hz).
	Ms	M/z 262 (M^+, $C_{12}H_{14}N_4O_3$, 1.09%), 231 ($C_{12}H_{11}N_2O_3$, 42.9%), 203 ($C_{11}H_{11}N_2O_2$, 20.35), 132 (C_8H_6NO, 100% base)
VI2	1HNMR CDCl3	3.80 (s, 2H, NH2), 4.93 (s, 2H, NCH2CO), 7.04-8.29 (m, 11H, 9 aromatic protons, 1H for NH and CDCl3).
	Ms	M/z 310 (M+, C16H14N4O3, 0.9%), 279 (C16H11N2O3, 38.21%), 132 (C8H6NO, 100% base).
VII1	IR	3194 (NH amidic), 1736 (amidic carbonyl), 1676, 1608 (two ketonic carbonyls of quinazolinedione nucleus)
	Ms	M/z 350 (M+, C19H16N4O3, 1.34 %), 231 (C12H11N2O3, 57.26%), 132 (C8H6NO, 100% base)
VII2	IR	3061 (CH aliphatic), 1713, 1667, 1607 (carbonyls of quinazolinedione and CH2CO)
	1HNMR DMSO-d6	1.19 (t, 3H, CH2-CH3, J= 5.60 Hz), 2.36 (s, 3H, p-CH3), 4.02 (q, 2H, CH2-CH3, J= 5.60 Hz), 5.33 (s, 2H, N-CH2CO), 7.25-8.21 (m, 9H, aromatic protons (8) and N= CH-Ph), 11.69 (s, 1H, NH)
VII3	IR	3331 (NH), 3079 (CH aliphatic), 1713, 1660, 1603 (carbonyls of quinazolinedione and amide side chain)
	Ms	M/z 356 (M+, C17H16N4O3S, 1.84%), 132 (C8H6NO, 70.10%), 69 (base, 100%).

Table 3: Continued.

No.	IR (cm^{-1}), ^{1}HNMR (δ, ppm), Mass (m/z, %), J (Hz)	
VII_4	IR Ms	3219 (NH), 2922 (CH aliphatic), 1703, 1666, 1906 (carbonyls of quinazolinedione and amide side chain). M/z 400 (M^+, $C_{23}H_{20}N_4O_3$, 3.65 %), M/e 231 (, $C_{12}H_{11}N_2O_3$, 46.08 %), M/e 132 (C_8H_6NO, 100% base).
$VIII_1$	^{1}HNMR DMSO-d_6	1.18 (t, 3H, CH_2-$\underline{CH_3}$, J= 13.28Hz), 2.28 (s, 3H, CH_3 at 3-position of pyrazole group), 2.51 (s, 3H, CH_3 at 5-position of pyrazole group), 4.02 (q, 2H, CH_2CH_3, J= 7.02 Hz), 5.69 (s, 2H, NCH_2CO), 6.31 (s, 1H, CH at C_4 of pyrazole ring).
$VIII_2$	IR Ms	3061 (CH aliphaatic). 1713, 1667, 1607 (carbonyls of quinazolinedione and CH_2CO). M/z 374 (M^+, $C_{21}H_{18}N_4O_3$, 0.9%), 278 (M^{-1}, $C_{16}H_{11}N_2O_3$, 100 base), M/e, 132 (C_8H_6NO, 43.1% base).
IX	IR Ms	3253 (NH), 2973 (CH aliphatic), 1691, 1651, 1616 (carbonyls of quinazolinedione and isatine group) M/z 391 (M^+, $C_{20}H_{17}N_5O_4$, 0.7%), 231 ($C_{12}H_{11}N_2O_3$, 95.5%) 132 (C_8H_6NO, 100% base)
X	IR Ms	3307 (NH), 1705 (CONH), 1668, 1608, 1586 (carbonyls of quinazoline-dione and diphenimide groups) M/z 442 (M^+, $C_{24}H_{18}N_4O_5$, 1.6%), 231 ($C_{12}H_{11}N_2O_3$, 97.1%), 132 (C_8H_6NO, 100% base)
XI_1	IR NMR DMSO-d_6	3202 (NH), 3058 (CH aliphatic), 1708, 1671, 1608 (carbonyls of quinazoli-nedione and amide moiety). 1.18 (t, 3H, N-CH_2-$\underline{CH_3}$, J= 1.46 Hz), 1.85 (s, 3H, $COCH_3$), 4.01 (q, 2H, N-CH_2CH_3, J= 5.42 Hz), 4.85 (s, 2H, N-CH_2CO), 7.21-8.10 (m, 4H, aromatic protons), 9.89 (s, 1H, CONH), 10.20 (s, 1H, NHCO)
XI_2	IR NMR DMSO-d_6	3207 (NH), 3059 (CH aliphatic), 1711, 1667, 1612 (carbonyl of quinazoline-dione and amide moiety) 1.76 (s, 3H, $NHCOCH_3$), 4.87 (s, 2H, N-CH_2CO), 7.30-8.12 (m, 9H, aromatic protons), 9.88 (s, 1H, CONH), 10.19 (s, 1H, $NHCOCH_3$).

period was considered protected against pentylenetetrazole-induced convulsion. The number of protected animals in each group was recorded. The percent of protection as well as the medium effective dose (ED_{50}) and the reltative potency of the tested compounds to the reference drug were calculated as presented in Table 4.

Conclusion

From the data recorded in Table (4), it was shown that most of the tested compounds exhibited low effect as anticonvulsant compared with phenobarbitone as shown in Fig. (1). The lower effect is due to the change of the position of ester moiety from 3-position into the 1-position of 2,4(1H,3H) quinazolinedione when comparing with compounds containing ester moiety at 3-position.[3,13-15]

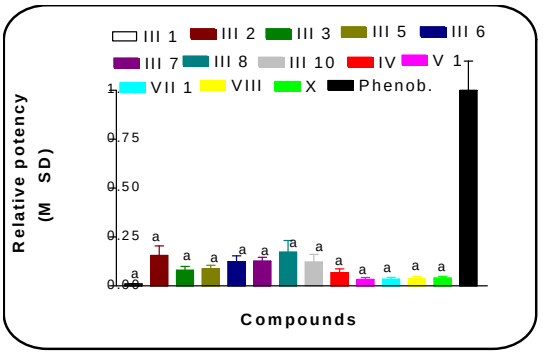


Fig. 1: Anticonvulsant activity of tested compounds against Phenobarbital as standard drug on mice

- Data were represented as mean ± standard deviation (M ± SD).
- Statistical analysis were carried out using instat 2 soft ware program, one way analysis of variance (ANOVA) test was used as statistical test followed by Tukey-Kramer as post ANOVA test for comparison between groups.
- a: indicates significant different from Phenobarbiton sodium at $p < 0.001$.

Table 4: Anticonvulsant effect of some of the synthesized compounds and phenobarbitone sodium as reference compound.

Comp. No	Dose mg/kg	No. of mice Injected	No. of mice protected	Protection %	ED_{50} Mg/kg mmol/L	Relative potency X±SD
III_1	50 100 150	6 6 6	2 5 6	33.3 83.3 100	66.7 (0.254)	0.01 ± 0.01^a
III_2	50 100 150	6 6 6	3 5 6	50 83.3 100	44.5 (0.161)	0.155 ± 0.05^a
III_3	50 100 150	6 6 6	1 4 6	16.6 66.6 100	86.7 (0.298)	0.08 ± 0.02^a
III_5	50 100 150	6 6 6	1 4 6	16.6 83.3 100	86.7 (0.284)	0.088 ± 0.017^a
III_6	50 75 125	6 6 6	2 4 6	33.3 66.6 100	63.9 (0.205)	$0.124 \pm .0.03^a$
III_7	50 75 125	6 6 6	2 4 6	33.3 66.6 100	63.9 (0.198)	0.126 ± 0.028^a
III_8	50 75 125	6 6 6	2 5 6	33.3 83.3 100	55.9 (0.145)	0.172 ± 0.06^a
III_{10}	50 75 125	6 6 6	1 4 6	16.6 66.6 100	72.77 (0.206)	0.121 ± 0.04^a
IV	100 150 200	6 6 6	2 4 6	33.3 66.6 100	125.3 (0.37)	0.067 ± 0.02^a
V_1	200 300 400	6 6 6	1 4 6	16.6 66.6 100	273.5 (0.736)	0.033 ± 0.01^a
VII_1	200 300 400	6 6 6	1 4 6	16.6 66.6 100	273.5 (0.731)	0.034 ± 0.01^a
$VIII_1$	200 300 400	6 6 6	2 5 6	33.3 83.3 100	233.43 (0.666)	0.037 ± 0.01^a
X	200 300 400	6 6 6	1 4 6	16.6 66.6 100	273.5 (0.618)	0.04 ± 0.009^a
Phenob.	3.25 6.25 12.50	6 6 6	2 3 6	33.33 50 150	6.25 (0.025)	1 ± 0.15

$$\text{Relative potency} = \frac{\text{ED50 of S.}}{\text{ED50 of T.}}$$

a: Indicate significant deferent from Phenobarbiton sodium at $p < 0.001$.

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REFERENCES

1- M. A. Aziza, F. M. Salama, M. A. Amin and A.G.A. El-Helby, Az. J. Pharm. Sci, 9, 63-74 (1992).
2- S. E. S. Barakat, M. A. El-Zahabi and M. F. Radowan, Az. J. Pharm. Sci, 23, 36-45 (1999).
3- A. A. El-Helby, S. E. S. Barakat and S. G. Abdel Hamide, Az. J. Pharm. Sci., 23, 25-34(1999).
4- M. El-Sadek, M. M. Baraka, S. M. Mostafa and M. Kh. Soltan, Egypt. J. Pharm. Sci., 44 (1), 87-99 (2003).
5- M. Y. Ebeid, M. A. S. Amin, El-Sayed S. Barakat, M. K. Ibrahim, A. G. A. El-Helby and H. M. Saker, Saudi Pharm. J., 6 (2) (1998).
6- S. M. Mosaad, K. I. Mohammed, M. A. Ahmed and S. G. Abdel-Hamid, Pakistan J. Biol. Sci., 7 (7), 1268 (2004).
7- S. M. Mosaad, K. I. Mohammed, M. A. Ahmed and S. G. Abdel-Hamid, J. Biol. Sci., 4 (4), 504-509 (2004).
8- M. A. Al-Omar, S. G. Abdel-Hamide, H. A. Al-Khamees and H. I. El-Subbagh , Saudi Pharm. J., 12 (2), 63-71 (2004).
9- S. M. Mosaad, K. I. Mohammed, M. A. Ahmed and S. G. Abdel-Hamide, J. Appl. Sci., 4 (2), 302-307 (2004).
10- T. W. Butler, A. F. J. Fliri, R. J. Gallaschun, B. P. Jones and J. A. Ragan, Eur, Pat,. Appl. Epl, 083, 178 (Cl. Co7D 498104). 14 Mar 2001, Us. Appl. Pv, 151, 725, 31, 1999 (Eng) Through C. A. Vol. 134, 222727s (2001).
11- J. Heinicke, U. Klausmeier, C. Arkona and S. leistner, Ger.; DE 10,101, 324. (Cl. Co7D239/96) 13 Dec. 2001 Appl. 10, 101, 324, 13 Jan., 2001, 8 pp (Ger). Through C. A. 138, 20086n (2002).
12- H. Kakuta, A. Tanatani, K. Nagasawa and Y. Hashimoto, Chem. Pharm. Bull., 51 (11), 1273-1282 (2003).
13- A. R E. N. Ossman, A. G. N. Osman and A. G. A. El-Helby, Bull. Pharm. Sci., Assiut Univ., 9 (1) 105 (1986).
14- A. G. A. El-Helby, Bull. Pharm. Sci., Assiut Univ., 118 (2), 69-78 (1995).
15- A. G. A. El-Helby, Egypt J. Pharm. Sci., 36 (1-6), 287-296 (1995).
16- E. P. Papadopoulos and C. D. Torres, J. Heterocyclic Chem., 19, 269 (1982).
17- N. P. Peet and S. Sunder, J. Org. Chem., 40, 13, 1909-1914 (1975).
18- E. Soaje-Echaque and R. K. S. Lim, J. Pharmacol. Exp. Ther., 138, 224 (1962).
19- R. A. Turner, "Screening Methods in Pharmacology", Academic Press, INC London LTD, London, New York, 1955, pp.(a) 69 (b)164.