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Design and synthesis of some new derivatives of 3*H*-quinazolin-4-one with promising anticonvulsant activity

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A new series of 3-substituted (methyl, ethyl or phenyl)-3*H*-quinazolin-4-one derivatives (**4a-l**) were synthesized through condensation reaction of their potassium salts (**3a-l**) with methyl, ethyl and phenylisocyanate. The newly synthesized derivatives (**4a-l**) were evaluated for anticonvulsant activity. It was found that these compounds showed the highest anticonvulsant activity at low doses (50–100 mg kg^{-1}), whereas at doses over 100 mg kg^{-1} they showed a stimulant effect on the central nervous system that even potentiated the effect of the convulsive agent, pentylenetetrazole, in mice. A series of halogenated derivatives, 3-methyl, 3-ethyl and 3-phenyl-6-mono and 6,8-disubstituted-3*H*-quinazolin-4-one derivatives (**4m-z**) was also synthesized and evaluated for anticonvulsant activity. Reduced anticonvulsant activity was recorded. Phenobarbitone sodium was used as a reference drug.

Keywords: 3*H*-quinazolin-4-one derivatives, synthesis, anticonvulsant activity

The search for new antiepileptic drugs with reduced toxicity and lower side-effects is continuous (1). 3*H*-Quinazolin-4-one represents a very good nucleus for preparation of some new sedative/hypnotic and anticonvulsant agents, since such a heterocyclic system possesses the pharmacophoric moiety (2). From the literature survey it was found that the 3*H*-quinazolin-4-one has been reported to possess different pharmacological effects, namely sedative-hypnotic (3, 4) and anticonvulsant ones (5–10). El-Helby *et al*. (11) synthesized some new derivatives of substituted 2-sulfanyl-3*H*-quinazolin-4-one (A). Some of them showed promising anticonvulsant effects. In the present work, we have synthesized some new derivatives of substituted 2-sulfanyl quinazolinones with another biological isoster, as shown in formula (B), hoping to obtain safer, more effective, non-hypnotic anticonvulsant agents with reduced side-effects:

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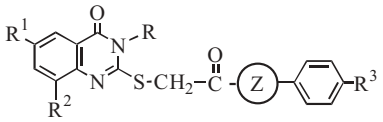


A

Z: NH
R: C_6H_5
R^1, R^2: H or Br
R^3: substituent

B

Z: O
R: CH_3, C_2H_5 or C_6H_5
R^1, R^2: H or halogen
R^3: not substituted or substituted by aromatic or cyclohexyl nucleus

EXPERIMENTAL

All melting points are uncorrected and were determined in the open capillary tube using the Griffin (UK) melting point apparatus. IR spectra were recorded in KBr discs on Bruker FT-ir Vector 22 (Germany). ^{1}H NMR spectra were determined on a Varian EM 390 (90 MHz) NMR spectrometer (Germany) in DMSO-d_6 using TMS as internal standard. Elemental analyses were performed with a CHN Analyzer at the Microanalytical Center (Cairo University, Cairo, Egypt).

5-Chloroanthranilic acid (12), 3,5-dichloroanthranilic acid (12), 5-bromo-anthranilic acid (13), 3,5-dibromoanthranilic acid (13), 5-iodoanthranilic acid (14), 3-methyl, 3-ethyl or 3-phenyl-6,8-disubstituted or not substituted 2-sulfanyl-3*H*-quinazolin-4-ones (15) and chloroacetic acid esters (16) were prepared according to the reported procedures.

*Potassium salts of newly synthesized compounds of 2-sulfanyl-3*H*-quinazolin-4-one (**3a-l**).* – Equimolar amounts (0.01 mol) of the appropriate 3*H*-quinazolin-4-one (**2a-l**) and potassium hydroxide were dissolved separately in absolute ethanol (50 mL). The alcoholic KOH solution was added dropwise into the alcoholic solution of substituted 2-sulfanyl-3*H*-quinazolin-4-one (**2a-l**) under stirring at room temperature for 30 min. The precipitated potassium salts of substituted 2-sulfanyl-3*H*-quinazolin-4-one (**3a-l**) were filtered off washed several times with absolute ethanol and dried (m.p. > 300 °C, yield: almost quantitative).

*2-Sulfanyl-3*H*-quinazolin-4-one derivatives (**4a-z**).* – Equimolar amounts (0.01 mol) of the appropriate potassium salts of 2-sulfanyl-3*H*-quinazolin-4-ones (**3a-l**) (Table I) and the appropriate substituted chloroacetic acid ester were allowed to react in DMF (20 mL) for 4 h. The reaction mixture was cooled, poured onto ice-cooled water (200 mL) and the precipitate so obtained was filtered off, dried and crystallized from ethanol.

The structures of these compounds were confirmed by elemental analyses (Table I), IR and ^{1}H NHR spectral data (Table II).

Pharmacology

Some compounds were tested for their anticonvulsant activity against pentylenetetrazole induced convulsions in mice according to the method reported by Turner (17).

Table I. Physical and analytical data of the newly synthesized compounds ***4a-z***

Comp. No.	R	R^1	R^2	R^3	M.p. (°C)	Yield (%)	Molecular formula (M_r)	Elemental analysis(%) Calc./found		
								C	H	N
4a	CH_3	H	H		150–151	70	$C_{17}H_{14}N_2O_3S$ (326.27)	62.56 62.10	4.32 4.50	8.58 9.00
4b	CH_3	H	H		135–136	75	$C_{18}H_{16}N_2O_3S$ (340.40)	63.51 63.40	4.74 4.80	8.23 8.00
4c	CH_3	H	H		165–166	71	$C_{21}H_{16}N_2O_3S$ (376.43)	67.00 67.00	4.28 4.00	7.44 7.50
4d	CH_3	H	H		120–121	77	$C_{17}H_{20}N_2O_3S$ (332.42)	61.42 61.50	6.06 6..00	8.43 8.40
4e	C_2H_5	H	H		135–136	75	$C_{18}H_{16}N_2O_3S$ (340.40)	63.51 63.70	4.74 4.90	8.23 7.90
4f	C_2H_5	H	H		145–146	73	$C_{19}H_{18}N_2O_3S$ (354.42)	64.39 64.60	5.12 5.10	7.90 8.00
4g	C_2H_5	H	H		165–166	72	$C_{22}H_{18}N_2O_3S$ (390.46)	67.67 67.50	4.66 5.00	7.17 7.20

Table I. Continued

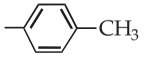
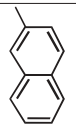
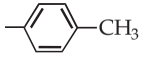
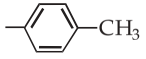
Comp. No.	R	R^1	R^2	R^3	M.p. (°C)	Yield (%)	Molecular formula (M_r)	Elemental analysis(%) Calc./found		
								C	H	N
4h	C_2H_5	H	H		165–166	72	$C_{18}H_{22}N_2O_3S$ (346.44)	62.40 62.50	6.40 6.70	8.09 8.20
4i	C_6H_5	H	H		175–176	81	$C_{22}H_{16}N_2O_3S$ (388.44)	68.02 68.10	4.15 4.20	7.21 7.50
4j	C_6H_5	H	H		185–186	82	$C_{23}H_{18}N_2O_3S$ (402.47)	68.64 68.90	4.51 4.40	6.96 7.20
4k	C_6H_5	H	H		160–161	72	$C_{26}H_{18}N_2O_3S$ (438.50)	71.22 71.50	4.14 3.90	6.39 6.90
4l	C_6H_5	H	H		125–126	70	$C_{22}H_{22}N_2O_3S$ (394.49)	66.98 66.90	5.62 6.00	7.10 7.50
4m	CH_3	Br	H		138–139	77	$C_{17}H_{13}BrN_2O_3S$ (405.27)	50.38 50.50	3.23 3.10	6.91 6.50
4n	CH_3	Br	H		110–111	80	$C_{17}H_{19}BrN_2O_3S$ (411.31)	49.64 50.00	4.66 5.00	6.81 7.00
4o	CH_3	I	H		223–224	75	$C_{17}H_{13}IN_2O_3S$ (452.27)	45.15 45.00	2.90 3.00	6.19 6.50
4p	C_2H_5	Br	H		110–111	77	$C_{19}H_{17}BrN_2O_3S$ (433.32)	52.66 52.60	3.95 4.00	6.46 6.50
4q	C_2H_5	Cl	Cl		160–161	91	$C_{18}H_{14}Cl_2N_2O_3S$ (409.29)	52.82 52.50	3.45 3.40	6.84 7.00
4r	C_2H_5	Cl	Cl		167–168	92	$C_{19}H_{14}Cl_2N_2O_3S$ (423.31)	53.91 54.30	3.81 3.50	6.62 7.00

Table I. Continued

Comp. No.	R	R^1	R^2	R^3	M.p. (°C)	Yield (%)	Molecular formula (M_r)	Elemental analysis(%) Calc./found		
								C	H	N
4s	C_2H_5	I	H		120–121	85	$C_{18}H_{15}IN_2O_3S$ (466.29)	46.36 46.70	3.24 3.50	6.01 6.20
4t	C_2H_5	I	H		130–131	85	$C_{19}H_{17}IN_2O_3S$ (480.32)	47.51 47.60	3.57 3.70	5.83 6.00
4u	C_6H_5	Cl	H		162–163	82	$C_{22}H_{15}ClN_2O_3S$ (422.88)	62.48 62.50	3.58 3.70	6.62 7.00
4v	C_6H_5	Cl	H		170–171	81	$C_{23}H_{17}ClN_2O_3S$ (436.91)	63.23 63.30	3.92 4.00	6.41 6.70
4w	C_6H_5	Br	H		152–153	82	$C_{22}H_{15}BrN_2O_3S$ (467.34)	56.54 56.80	3.24 3.20	5.99 6.00
4x	C_6H_5	Br	H		178–179	82	$C_{23}H_{17}BrN_2O_3S$ (481.36)	57.39 57.50	3.56 3.60	5.82 6.00
4y	C_6H_5	Br	Br		195–196	77	$C_{22}H_{14}Br_2N_2O_3S$ (546.23)	48.37 48.00	2.58 2.30	5.13 5.60
4z	C_6H_5	Br	Br		205–206	70	$C_{23}H_{16}Br_2N_2O_3S$ (560.26)	49.31 49.60	2.88 3.00	5.00 5.40

Table II. IR (cm^{-1}) and ^1H NMR (δ, ppm) of some of the synthesized compounds

Comp. No.	Spectral data	
4a	^{1}H NMR	3.80 (s, 3H, NCH_3), 4.50 (s, 2H, SCH_2CO), 7.20–8.60 (m, 9H, ArH)
4b	^{1}H NMR	2.35 (s, 3H, $C_6H_5CH_3$–*p*), 3.65 (s, 3H, NCH_3), 4.25 (s, 2H, SCH_2CO), 6.80–8.35 (m, 8H, ArH)
4c	^{1}H NMR	3.70 (s, 3H, NCH_3), 4.60 (s, 2H, SCH_2CO), 7.30–8.60 (m, 11H, ArH)
4d	^{1}H NMR	1.40–1.80 (m, 11H, aliphatic protons of cyclohexyl group), 3.95 (s, 3H, NCH_3), 4.50 (m, 1H, cyclohexyl protons), 4.80 (s, 2H, SCH_2CO), 7.40–8.80 (m, 4H, ArH)
4e	^{1}H NMR	1.35 (t, 3H, CH_2CH_3), 4.20 (q, 2H, CH_2CH_3), 5.00 (s, 2H, SCH_2CO), 7.40–8.70 (s, 9H, ArH)
4f	IR	2917 (CH aliph.), 1769 (ester CO), 1682 (CO of quinazolinone moiety), 1555 (N=CHS) of sulfanyl quinazolinone)
	^{1}HNMR	1.30 (t, 3H, CH_2CH_3), 2.00 (s, 3H, $C_6H_5CH_3$–*p*), 4.30 (q, 2H, CH_2CH_3), 5.00 (s, 2H, SCH_2CO)
4g	^{1}H NMR	1.35 (t, 3H, CH_2CH_3), 4.20 (q, 2H, CH_2CH_3), 4.50 (s, 2H, SCH_2CO), 7.30–8.40 (m, 11H, ArH)
4h	^{1}H NMR	1.20–1.40 (m, 10H, aliphatic protons of cyclohexyl group), 1.60 (t, 3H, CH_2CH_3), 4.40 (q, 2H, CH_2CH_3), 4.70 (m, 1H, aliphatic protons of cyclohexyl group), 5.00 (s, 2H, SCH_2CO), 7.20–8.60 (s, 4H, ArH)
4i	^{1}H NMR	5.00 (s, 2H, SCH_2CO), 6.90–8.80 (m, 14H, ArH)
4j	^{1}H NMR	2.35 (s, 3H, $C_6H_5CH_3$–*p*), 4.80 (s, 2H, SCH_2CO), 7.20–8.20 (m, 13H, ArH)
4k	^{1}H NMR	4.35 (s, 2H, SCH_2CO), 7.40–8.40 (m, 16H, ArH)
4l	^{1}H NMR	1.20–1.80 (m, 10H, cyclohexyl protons), 4.60 (m, 1H of the cyclohexyl proton), 4.80 (s, 2H, SCH_2CO), 7.20–8.80 (m, 9H, ArH)
4m	^{1}H NMR	4.00 (s, 3H, NCH_3), 4.60 (s, 2H, SCH_2CO), 7.60–8.80 (m, 8H, ArH)
4n	^{1}H NMR	1.20–1.80 (m, 10H, cyclohexyl group), 3.50 (s, 3H, NCH_3), 4.20 (s, 2H, SCH_2), 4.70 (m, 1H, of cyclohexyl group), 7.341–7.384 (d, 1H at C_8 of quinazolinone), J = 0.043, 7.928–7.960 (d, 1H, at C_7 of quinazolinone), J = 0.032, 8.15 (s, 1H at C_5 of quinazolinone)
4o	^{1}H NMR	3.80 (s, 3H, NCH_3), 4.40 (s, 2H, SCH_2CO), 7.20–8.20 (s, 8H, ArH)
4p	^{1}H NMR	1.30 (t, 3H, CH_2CH_3), 2.30 (s, 3H, $C_6H_5CH_3$–*p*), 4.20 (q, 2H, NCH_2CH_3), 4.50 (s, 2H, SCH_2CO), 7.04–7.07 [2d, 2H, at C_2 and C_6 of phenoxy group), J = 0.333, 7.26–7.30 (2d, 2H, of C_3 and C_5 of phenoxy group), J = 0.033, 7.50–7.54 (d,1H, ArH, at C_8 of quinazolinone moiety), J = 0.043, 8.02–8.06 (d, 1H, ArH, at C_7 of quinazolinone moiety), J = 0.0432, 8.24 (s, 1H, ArH at C_5 of quinazolinone moiety)

Table II. Continued

Comp. No.	Spectral data	
4q	^{1}H NMR	1.30 (t, 3H, NCH_2CH_3), 4.20 (q, 2H, NCH_2CH_3), 4.50 (s, 2H, SCH_2CO), 7.10–7.50 (m, 5H, ArH of phenoxy group), 7.90 (s, 1H, ArH at C_5 of quinazolinone moiety), 8.10 (s, 1H, ArH at C_7 of quinazolinone moiety
4r	^{1}H NMR	1.30 (t, 3H, $NCHCH_3$), 2.30 (s, 3H, ($C_6H_5CH_3$–*p*), 4.10 (q, 2H, NCH_2CH_3), 4.50 (s, 2H, SCH_2CO), 6.99–7.00 (2d, 2H, ArH at C_2 and C_6 of phenoxy group), J = 0.010, 7.18–7.21 (2d, 2H, ArH at C_3 and C_5 of phenoxy group), J = 0.035, 7.98 (s, 1H, ArH at C_5 of quinazolinone), 8.09 (s, 1H, ArH, at C_7 of quinazolinone)
4s	^{1}H NMR	1.45 (t, 3H, NCH_2CH_3), 4.20 (s, 2H, SCH_2CO), 4.80 (q, 2H, CH_2CH_3), 6.90–8.40 (m, 8H, ArH)
4t	^{1}H NMR	1.30 (t, 3H, NCH_2CH_3), 2.30 (s, 3H, $C_6H_5CH_3$–*p*), 4.10 (q, 2H, NCH_2CH_3), 4.40 (s, 2H, SCH_2CO), 6.975–6.985 (2d, 2H, ArH of *p*–substituted phenoxy group), J = 0.010, 7.17–7.22 (2d, 2H, Ar–H of the *p*–substituted phenoxy group), J = 0.043, 7.25–7.30 (d, 1H, ArH at C_8 of quinazolinone group), J = 0.043, 8.10–8.11 (d, 1H, ArH, at C_7 of quinazolinone group), J = 0.0011, 8.34 (s, 1H, ArH at C_5 of quinazolinone
4u	^{1}H NMR	4.90 (s, 2H, SCH_2CO), 7.10–8.60 (m, 14H, ArH)
4v	IR ^{1}H NMR	2835 (CH of aliph.), 1766 (ester CO), 1689 (CO of the ring), 1547 (N=CH–S) 2.40 (s, 3H, $C_6H_5CH_3$–*p*), 5.00 (s, 2H, SCH_2CO), 7.40–8.40 (m, 13H, ArH)
4w	^{1}H NMR	5.00 (s, 2H, SCH_2CO), 6.80–8.60 (m, 14H, ArH)
4x	^{1}H NMR	2.3 (s, 3H, $C_6H_3CH_3$–*p*), 4.30 (s, 2H, SCH_2CO), 7.10–8.20 (m, 12H, ArH)
4y	^{1}H NMR	4.00 (s, 2H, SCH_2CO), 7.00–8.20 (m, 12H, ArH)
4z	^{1}H NMR	2.35 (s, 3H, $C_6H_5CH_3$–*p*), 4.90 (s, 2H, SCH_2CO), 6.80–8.40 (m, 13H, ArH)

Swiss albino male mice, weighing 20–25 g, were obtained from an animal facility (Al-Azhar University, Cairo, Egypt). Mice were housed in stainless steel wire-floored cages without any stressful stimuli. Room temperature was kept at 23 ± 2 °C. Animals were fed standard laboratory chow (El-Nasr Co., Abou-Zabal, Egypt) and tap water *ad libitum*. Mice were randomly arranged in different groups, 6 in each. Test compounds were suspended in Tween 80 (0.2%) (Sigma, USA) and were given *i.p.* in doses ranging from 50–100 mg kg^{-1} body mass. Dosing volume was 0.2 ml per 20 g. Phenobarbitone sodium (Sigma) was dissolved in water in 2% concentration and used as a reference standard and it was given *i.p.* in doses of 3.25, 6.5 and 12.5 mg kg^{-1}. Pentylenetetrazole (PTZ, Sigma) was dissolved in water in 2% concentration and was given *i.p.* in a dose of 100 mg kg^{-1} one hour after the test compounds or phenobarbitone sodium. The animals were observed for convulsions. Animals that showed no convulsion within one hour after PTZ injection were considered to be protected.

Table III. The anticonvulsant effect of some of the tested compounds

Comp. No.	Dose (mmol kg^{-1})	Protection (%)	ED_{50} (mmol kg^{-1})	Relative potency
4a	15.00 22.50 30.00	50 66.6 100	13.5	0.19
4b	14.60 21.90 29.20	50 66.6 100	14.6	0.17
4c	13.30 19.95 26.60	50.0 66.6 83.3	12.7	0.20
4d	15.00 22.50 30.00	50.0 66.6 66.5	15.0	0.17
4e	14.60 21.90 29.20	50 66.6 83.3	14.0	0.02
4f	14.11 21.17 28.22	50.3 66.6 83.3	14.1	0.18
4g	12.80 19.20 25.60	50.0 63.6 100	14.1	0.18
4h	14.43 21.65 28.86	66.6 66.6 100	15.9	0.16
4i	12.87 19.31 25.74	33.3 66.5 100	8.4	0.30
4j	12.42 18.63 24.84	33.3 50 100	8.2	0.31
4k	11.40 17.10 22.80	65.5 66.6 83.3	15.4	0.16
4l	12.67 19.00 25.34	50.0 66.6 66.6	15.2	0.17
4m	12.33 18.50 24.66	100 66.6 50	23.9	0.11
4p	11.54 17.31 23.08	100 66.6 50	22.4	0.11

Table III. Continued

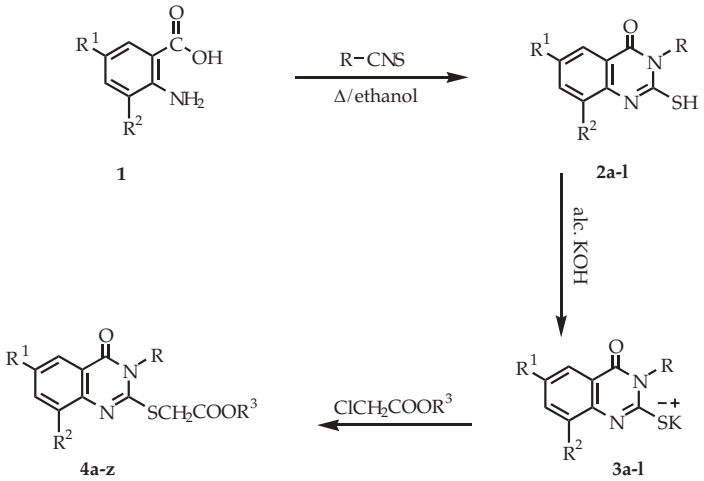
Comp. No.	Dose (mmol kg^{-1})	Protection (%)	ED_{50} (mmol kg^{-1})	Relative potency
4r	11.80 17.70 23.60	100 83.3 50	22.4	0.11
4t	10.41 15.62 20.82	8.3 83.3 50	16.7	0.16
4v	11.44 17.16 22.88	100 66.6 50	20.3	0.12
4x	10.39 15.59 20.48	100 66.6 50	20.2	0.13
4z	8.92 13.38 17.84	100 66.6 50	17.3	0.14
Phenobarbitone	1.40 2.80 5.38	33.3 50 100	2.5	1

ED_{50} – effective dose that protects 50% of the animals.
Relative potency – ED_{50} (phenobarbitone)/ED_{50} (tested compound)

RESULTS AND DISCUSSION

The starting derivatives of aromatic acid (12–14), 2-[3-alkyl phenyl-6,8-disubstituted] sulfanyl-3*H*-quinonlin-4-one (**2a-l**) (15) and esters of chloroacetic acid (16) were prepared according to the reported procedures. The potassium salts of 2-(3-alkyl/phenyl--6,8-disubstituted) sulfanyl-3*H*-quinolin-4-ones (**3a-l**) were prepared by dissolving compounds (**2a-l**) in absolute ethanol. In the reaction of compounds (**3a-l**) with substituted esters of chloroacetic acid in DMF, the substituted 2-sulfanyl-3*H*-quinazolin-4-one derivatives (**4a-z**) were afforded (Scheme I). The IR spectra of compounds **4a-z** are characterized by the appearance of ester carbonyl bands ranging from 1780 to 1766 cm^{-1}. The ^1H NMR spectra of compounds **4a-z** are characterized by the presence of a singlet signal (δ 4.30–5.20 ppm) which may be attributed to two protons of methylene group SCH_2COOR^3 of all compounds.

The anticonvulsant effect of the test compounds, compared to that of phenobarbitone sodium, showed that all test compounds exhibited anticonvulsant effect. Compounds **4i** and **4j** exhibited the highest anticonvulsant effect with anticovulsant potency relative to phenobarbitone sodium of 0.30 and 0.31, respectively, whereas compound **4e** exhibited the lowest relative potency of 0.02.



R: CH_3, C_2H_5 and C_6H_5

R^1, R^2: H, Br, Cl

R^3: not substituted or substituted by aromatic or cyclohexyl nucleus

Scheme I

It may be assumed that the introduction of the ester moiety instead of the amide moiety as reported by El-Helby *et al.* (11), increases the anticonvulsant activity of 2-sulfanyl-3*H*-quinazolin-4-one derivatives by 10 times. Substitution at N-3 position of 3*H*--quinazolin-4-one nucleus by CH_3 and C_6H_5 increases the anticonvulsant effect while substitution by C_2H_5 decreases the anticonvulsant effect. Halogenation of the benzene ring of 3*H*-quinazolin-4-one nucleus generally reduces the anticonvulsant effect, but a dose over 100 mg kg^{-1} made the compounds have a CNS stimulant effect and potentiate the effect of PTZ. The alcoholic residue in acetic acid ester did not affect the activity.

CONCLUSIONS

The newly synthesized compounds showed promising anticonvulsant activity against PTZ-induced convulsions in mice. The ester moiety and the N-3 substituents of the 2-sulfanyl-3*H*-quinazolin-4-one seem to be essential for anticonvulsant activity.

REFERENCES

1. E. A. Swinyard and J. H. Woodhead, *Anticonvulsant*, in *Antiepileptic Drugs*, 2nd ed. (Eds. D. M. Woodburgg, J. K. Penny and C. E. Pippenger), Raven Press, New York 1982, pp. 11–126.
2. M. J. Kornet, T. Varia and W. Beaven, Synthesis and anticonvulsant activity of 3-amino 4-(3H) quinazolinones, *J. Heterocycl. Chem.* **20** (1983) 1553–1555.
3. J. Tani, Y. Yamada, T. Toine, T. Ochiai, R. Ishida and I. Inoue, Studies on biologically active halogenated compounds. Synthesis and central nervous system depressant activity of 2-(fluoromethyl)-3-aryl-4(3H)-quinazolinone derivatives, *J. Med. Chem.* **22** (1979) 95–99.
4. M. El-Sayed and B. Abdel-Fattah, Synthesis and CNS depressant activity of quinazolinone derivatives, *Bull. Fac. Pharm. Cairo Univ.* **15** (1976) 273–283.
5. A. A. El-Helby, S. E. Brakat and S. G. Abdel Hamide, Synthesis and anticonvulsant activity of some new derivatives of quinazolinones, *Az. J. Pharm. Sci.* **23** (1999) 25–34.
6. A. E. El-Hakim, A. A. El-Helby and S. G. Abdel Hamide, Synthesis and biological activity of 1,3-disubstituted quinazoline-2,4-diones, *Az. J. Pharm. Sci.* **14** (1994) 156–163.
7. A. E. Osman and S. E. Barakat, Synthesis of some new 4(3H) quinazolinone derivatives as potential anticonvulsants, *Saudi Pharm. J.* **2** (1994) 21–31.
8. M. J. Kornet, Synthesis and anticonvulsant activity of 3-amino 2,4(1H,3H) quinazolinone, *Eur. J. Med. Chem.* **21** (1986) 529–536.
9. S. G. Abdel-Hamide, H. A. El-Obeid, A. A. Al-Majed, H. A. El-Kashef and H. I. El-Subbaagh, Synthesis and anticonvulsant activity of some new 4-oxo-3*H*-quinazoline analogs, *Med. Chem. Res.* **10** (2001) 378–389.
10. M. A. Aziza, M. K. Ibrahim and A. A. El-Helby, Synthesis of novel substituted mercaptoquinazolinones of expected anticonvulsant activity, *Az. J. Pharm Sci.* **14** (1994) 296–304.
11. A. A. El-Helby, S. G. Abdel Hamide and A. E. El-Hakim, Design and synthesis of some new derivatives of substituted-2-mercaptoquinazolinones for anticonvulsant activity, *Az. J. Pharm. Sci.* **15** (1995) 1–13.
12. M. M. Endicott, B. W. Alden and M. L. Sherrill, Quinazoline derivatives: The synthesis of 4-(3'--diethylaminopropoxy)-6-chloroquinazoline, *J. Am. Chem. Soc.* **68** (1946) 1303–1309.
13. A. S. Wheeler and W. M. Oates, The bromination of anthranilic acid, *J. Am. Chem. Soc.* **32** (1910) 770–773.
14. M. T. Bogert and W. F. Hand, The halogenation of anthranilic acid, *J. Am. Chem. Soc.* **27** (1905) 1476–1478.
15. G. R. Dave, G. S. Mewada and G. C. Amin, 2-Mercapto-3-substituted phenylquinazo-4-one, *J. Indian Chem. Soc.* **37** (1950) 595–597.
16. C. R. Hauser, The preparation of chloroacetic acid esters, *Org. Synth.* **24** (1944) 19–22.
17. R. A. Turner, *Anti-epileptic Drugs*, in *Screening Methods in Pharmacology*, 15nd ed. (Ed. R. A. Turner), Academic Press, New York 1965, pp. 165–172.

S A Ž E T A K

Sinteza novih derivata 3*H*-kinazolin-4-ona s potencijalnim antikonvulzivnim djelovanjem

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Serija 3-supstituiranih (metil, etil ili fenil) derivata 3*H*-kinazolin-4-ona (**4a-l**) sintetizirana je kondenzacijom njihovih soli (**3a-l**) s metil, etil i fenilizocijanatom. Ispitano je antikonvulzivno djelovanje produkata **4a-l**. Ti spojevi djeluju snažno antikonvulzivno u niskim dozama od 50 do 100 mg kg^{-1}, a u dozama većim od 100 mg kg^{-1} djeluju stimulirajuće na središnji živčani sustav i čak povećavaju konvulzivni učinak pentilentetrazola u miševa. Osim toga, sintetizirana je i ispitana na antikonvulzivno djelovanje serija halogeniranih derivata 3-metil, 3-etil i 3-fenil-6-mono i 6,8-disupstituiranih 3*H*-kinazolin-4--on derivata (**4m–z**). Ti spojevi posjeduju slabije antikonvulzivno djelovanje. Kao referentni lijek upotrebljen je fenobarbiton natrij.

Ključne riječi: derivati 3*H*-kinazolin-4-ona, sinteza, antikonvulzivno djelovanje

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