Synthesis and Anticonvulsant Properties of Some Novel Quinazolone-thiosemicarbazone and 4-Thiazolidone Derivatives

Synthese und antikonvulsive Eigenschaften einiger neuer Chinazolinon-thiosemicarbazon- und 4-Thiazolidon- Derivate

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Diverse biological activities have been found in compounds having a quinazolinone ring system[1]. A large number of 4(3*H*)-quinazolinones, in particular those possessing 2-alkyl-3-aryl[2], 2,3-dialkyl[3], and 2-alkyl-3-amino[4] substitution, have been evaluated for pharmacological activity.

On the other hand, thiazolidone derivatives are reported to have anesthetic[5], anticonvulsant[6], and hypnotic[7] activity.

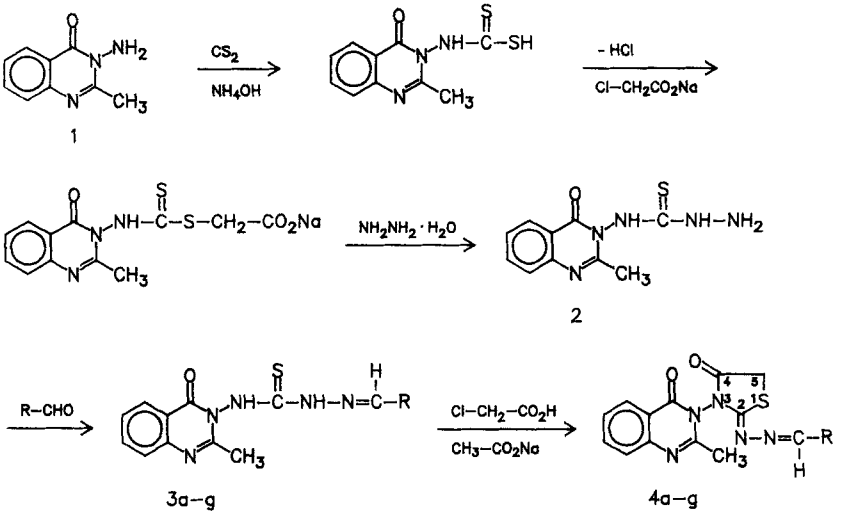
These observations promoted the synthesis of 4-(2-methyl-4(3*H*)-quinazolinon-3-yl)-1-substituted-3-thiosemicarbazones **3a-g** and 3-(2-methyl-4(3*H*)-quinazolinon-3-yl)-4-oxo-thiazolin-2-yl-substituted hydrazones **4a-g** to evaluate their anticonvulsant activity.

The designed thiosemicarbazones **3a-g** and thiazolidones **4a-g** were prepared according to the scheme (*vide supra*).

The reaction of 2-methyl-3-amino-4(3*H*)-quinazolinone (**1**)[8] with CS_2/NH_3 following the method of *Kumar* et al.[9] yield the pertinent dithiocarbamate. This compound on treatment with an aqueous solution of the sodium salt of monochloroacetic acid and followed by condensation with hydrazine hydrate gave 4-(2-methyl-4(3*H*)-quinazolinon-3-yl)-3-thiosemicarbazide (**2**).

The reaction of **2** with different aldehydes formed (4-(3*H*)-quinazolinon-3-yl)-1-substituted-3-thiosemicarbazones **3a-g**.

Cyclization of **3** with monochloroacetic acid in the presence of fused sodium acetate gave the corresponding 3-(2-methyl-4-(3*H*)-quinazolinon-3-yl)-4-oxo-thiazolin-2-yl-substituted hydrazones **4a-4g**.



1 2 3a–g 4a–g

Comp. No.	3a, 4a	3b, 4b	3c, 4c	3d, 4d,
R	4–ClC_6H_4	2–OHC_6H_4	3–OCH_6H_4	2–$OCH_3C_6H_4$
Comp. No.	3e, 4e	3f, 4f,	3g, 4g	
R	4–$OCH_3C_6H_4$	2–$NO_2C_6H_4$	3–$NO_2C_6H_4$	

Pharmacology

Anticonvulsant Activity

According to table 3, anticonvulsant activities ranging from 75 to 20% protection were exhibited by the test compounds. **4a** was able to inhibit the induction of tonic extension completely, though clonic convulsions occured rarely.

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In contrast, **4e** showed a weak protection against pentetrazol induced seizures.

The anticonvulsant properties of the substances parallel their ability to protect against death in pentetrazol treated animals during a 24 h period. The results indicate that the substitution of position 2 of the 4-thiazolidone ring by a =N-N=CHR moiety influence the activity according the following decreasing order: **4a, 4b, 4c, 4f, 4d, 4g, 4e.**

Here, lipophilicity can play an important role. When doses higher than 100 mg/kg were given all of the animals show some signs of toxicity such as tremors.

Experimental Part

Melting points: open glass capillaries, uncorrected. - Microanalysis: Faculty of Science, University of Cairo. - IR spectra: KBr; Beckman-IR-4210 spectrophotometer. - ^{1}H-NMR spectra: DMSO-d_6, TMS as internal standard, 60 MHz, Varian T60 (chemical shifts in δ (ppm)).

4-(2-Methyl-4(3H)-quinazolinon-3-yl)-3-thiosemicarbazide(**2**)

To an ethanolic solution of 2-methyl-3-amino-4-(3H)-quinazoline (**1**) (0.25 mole) was slowly added 40 ml of conc. NH_3/H_2O. The mixture was cooled below 30°C and CS_2 (15 ml) was added dropwise during 15 min. After 1 h an aqueous solution of sodium salt on monochloroacetic acid (0.25 mole) was added, followed by hydrazine hydrate (0.25 mole, 80%). The mixture was cooled overnight in a refrigerator and the crude thiosemicarbazide which separated was filtered and recrystallized from ethanol, mp 180-182 °C; yield 75%. - IR: 3230-3200 (NH); 1650 (C = O) and 1460; 1170 cm^{-1} (C = S). - $C_{10}H_{11}NO_5S$ (257) Calcd. C 48.1 H 4.4 N 28.1 Found C 48.5 H 4.6 N 28.5.

4-(2-Methyl-4-(3H)-quinazolinon-3-yl)-1-substituted-3-thiosemicarbazones **3a-g**

Equimolar quantities of thiosemicarbazide **2** (0.05 mole) and the appropriate aldehyde (0.05 mole) in 100 ml of ethanol were refluxed for 2 h. The mixture was concentrated under reduced pressure and the solid mass which separated on cooling was recrystallized from ethanol. Physical properties and yields: table 1. - IR: 3250-3160 (NH); 1670-1650 (C = O); 1460; 1170 cm^{-1} (C = S). - ^{1}H-NMR (DMSO-d_6): 2.40 (s; 3H, CH_3), 6.95 (s; 1H, -N=CH-), 7.15-8.50 (m; 4H, Ar-H), 10.5 and 11.2 (2s; 2H, NH).

3-(2-Methyl-4(3H)-quinazolinon-3-yl)-4-oxo-thiazolin-2-yl-substituted hydrazones **4a-g**

A mixture of the proper thiosemicarbazone **3a-g** (0.01 mole), monochloroacetic acid (0.01 mole) and fused sodium acetate (0.015 mole) in 15 ml of glacial acetic acid was refluxed for 6 h. The mixture was poured into ice-cold water and stored overnight in a refrigerator. The crude product which separated was washed with water, dried and recrystallized from ethanol. Physical properties and yields: table 2. - IR: 1745 - 1730 (C=O, thiazolidinone); 1680 - 1660 (C=O, quinazolinone); 1595 - 1575 cm^{-1} (C=N); no NH bands. - ^{1}H-NMR (DMSO-d_6): 2.40 (s; 3H, CH_3), 4.15 (s; 2H, CH_2), 7.05 (s; 1H, -N=CH-) and 7.35-8.40 (m, 4H, Ar-H).

Pharmacology

Anticonvulsant Activity

Swiss albino mice (25-30 g) of either sex were used. The compounds were suspended in 5% aqueous suspension of gum acacia. 4 h after i.p. administration at a dose of 100 mg/kg to a group of 10 mice, 90 mg/kg of pentetrazol were given i.p. This dose causes convulsions within 10 min after administration and produces 100% mortality within 24 h. Animals

Table 1: Physical data of (4-(2-Methyl-4(3*H*)-quinazolinon-3-yl)-1-substituted-3-thiosemicarbazones **3a-g**

Compound No.	R	Yield	Mp °C	Molecular Formula	Analysis % C	H	N
3a	4-ClC$_6$H$_4$	75	247	$C_{17}H_{14}ClN_5OS$	54.9	3.76	18.8
					54.6	3.40	18.9
3b	2-OH-C$_6$H$_4$	80	210	$C_{17}H_{15}N_5O_2S$	57.8	4.24	19.8
					57.5	4.64	19.6
3c	3-OH-C$_6$H$_4$	78	233	$C_{17}H_{15}N_5O_2S$	57.8	4.24	19.8
					57.4	4.50	19.9
3d	2-OCH$_3$-C$_6$H$_4$	50	217	$C_{18}H_{17}N_5O_2S$	58.8	4.63	19.1
					58.7	4.42	19.0
3e	4-OCH$_3$-C$_6$H$_4$	77	163	$C_{18}H_{17}N_5O_2S$	58.8	4.63	19.1
					58.4	4.70	19.2
3f	2-O$_2$N-C$_6$H$_4$	72	158	$C_{17}H_{14}N_6O_3S$	53.4	3.66	22.0
					53.2	3.40	21.7
3g	3-O$_2$N-C$_6$H$_4$	76	212	$C_{17}H_{14}N_6O_3S$	53.4	3.66	22.0
					53.7	3.90	21.8

Table 2: Physical Data of 3-(2-Methyl-4(3*H*)-quinazolinon-3-yl)-4-oxo-thiazolin-2-yl-substituted hydrazones **4a-g**

Compound No.	R	Yield	Mp °C	Molecular Formula	Analysis % C	H	N
4a	4-Cl-C_6H_4	63	204	$C_{19}H_{14}ClN_5O_2S$	55.4	3.40	17.0
					55.1	3.00	17.0
4b	2-OH-C_6H_4	50	240	$C_{19}H_{15}N_5O_3S$	58.0	3.81	17.8
					58.0	3.70	17.8
4c	3-OH-C_6H_4	60	225	$C_{19}H_{15}N_5O_3S$	58.0	3.81	17.8
					58.1	3.60	17.9
4d	2-OCH_3-C_6H_4	70	200	$C_{20}H_{17}N_5O_3S$	58.9	4.17	17.2
					58.7	4.0	17.0
4e	4-OCH_3-C_6H_4	60	180	$C_{20}H_{17}N_5O_3S$	58.9	4.17	17.2
					58.6	4.0	17.0
4f	2-O_2N-C_6H_4	50	196	$C_{19}H_{14}N_6O_4S$	54.0	3.31	19.9
					54.0	3.30	19.9
4g	3-O_2N-C_6H_4	40	212	$C_{19}H_{14}N_6O_4S$	54.0	3.31	19.9
					54.1	3.20	19.8

Table 3: Anticonvulsant Activity of **4a-g** at 100 mg/kg.

Compounds	Protection %
4a	75
4b	60
4c	50
4d	40
4e	20
4f	45
4g	35

devoid of a threshold convulsion were considered protected. The mortality within 24 h was recorded. A threshold convulsion is the episode of clonic spasm that persisted for a minimum of 5 sec.

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