Quinazolinones, 13.Comm.[1]

Synthesis of 3-[2-(2,3-Dihydro-5-phenyl-4-substituted-3H-1,2,4-triazole-3-thione-2-yl)-acetylamino]-2-methyl-4(3H)-quinazolinones and their pharmacological activities

Servet Büyüktimkin, Nadir Büyüktimkin, and Osman Özdemir

Faculty of Pharmacy, University of Istanbul, Beyazit 34452 Istanbul, Turkey

Sevim Rollas

Faculty of Pharmacy, University of Marmara, Nisantasi 80200 Istanbul, Turkey

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Some 2-methyl-3-triazole-substituted-4(3H)-quinazolinones **3a-f** were prepared and tested for their H_1- and H_2- antihistaminic activities. In addition these compounds are central nervous system depressants and anticonvulsants. **3e** shows highly significant decrease of locomotor activity.

Chinazolinone, 13.Mitt.: Synthese und pharmakologische Wirksamkeiten einiger 3-[2-(2,3-Dihydro-5-phenyl-4-substituierter-3H-1,2,4-triazol-3-thion-2-yl)-acetylamino]-2-methyl-4(3H)-chinazolinone

Es wurden einige 2-Methyl-3-triazol-substituierte-4(3H)-chinazolinone **3a-f** dargestellt und deren H_1- und H_2- antihistaminische Wirksamkeiten geprüft. Außerdem wirken diese Verbindungen zentral dämpfend und antikonvulsiv. Insbesondere **3e** zeigt eine signifikante Verringerung der Spontanmotilität.

Quinazolinones possess a wide range of biological activities especially on the central nervous system[2-8]. It was also proven that they also exhibit antiviral, antibacterial[7], antifungal[9], antiallergic[10], antitumor[11], and hypoglycemic[12] properties. Recently they have been reported to have pronounced coronary vasodilatator and cardiac[13] and H_1-,H_2-antagonist activities[14,15].

These observations together with our earlier work on 4(3H)-quinazolinones[5] prompted us to undertake the synthesis of some new quinazolinones derivatives containing different 1,2,4-triazole-3-thione groups which are claimed to have some H_2-antagonistic and anticonvulsant activities[16-18]. The compounds have been evaluated for anticonvulsant, sedative, hypnotic, H_1 and H_2 activities.

Synthesis

3-(2-Chloracetylamino)-2-methyl-4(3H)-quinazolinone **1**[5] was used as starting material. Different 2,3-dihydro-5-phenyl-3H-1,2,4-triazole-3-thiones **2a-f** were prepared according to[19]. Treatment of **1** with the equivalent amount of **2a-f** in boiling dry benzene resulted in the formation of the desired compounds **3a-f** (Scheme).

The structure of the compounds were identified by elementary analyses, UV-, IR-(Table 1) and for a representative example **3f** by ^{1}H-NMR-spectra and by mass spectrometry. Theoretically thione [**3a-f**] and thiol [4] structures are possible. The UV spectra of **2a-f** show that in ethanol the thiol form is preferred. But **3a-f** exhibit UV absorption maxima near 202, 250 and 300 nm. These data are similar with the findings of *Kubota* and *Uda*[20] for the thione structure. According to these authors thiols absorb at 235 and 283 nm, our findings show that here the thiol form can be eliminated. IR spectra in the solid state – besides characteristic 4(3H)-quinazolinone and secondary amide signals[1] – exhibit peaks at 1210-1290 cm^{-1} attributed to the C=S group[21] (Table 1). – The ^{1}H-NMR-spectrum of **3f** displays: at 2.5 ppm a singlet for 2-CH_3, at 2.65-3.5 and 3.5-3.95 ppm two triplets for the -CH_2-CH_2- moiety, at 3.95-4.02 ppm a doublet for the -CO-CH_2 group, at 7.04-8.5 ppm a multiplet for 4 aromatic protons and at 11.35 ppm a singlet for the secondary amide proton exchangeable with D_2O. Other spectrometric data will be reported elsewhere.

Pharmacology

H_1 and H_2 activities

Some of the compounds possess weak H_1 and H_2 activities. **3b** and **3e** were devoid of any H_2 agonistic activity on the guinea-pig atrium. Also on the guinea-pig ileum **3e** was found to be inactive, but it proved to be a non-competitive H_1 antagonist. Highest H_2 antagonist activity was exhibited by **3f**. Finally pD_2 values were in the range of 4.15 and pA_2 values were situated between 4.38 and 5.02. Low activity of the substances may be due to their relatively low solubility in water.

Sedative, spontaneous locomotor and anticonvulsant activities

All of the tested compounds show distinct activities in different degrees. With a i.p. dose of 100 mg/kg all of the

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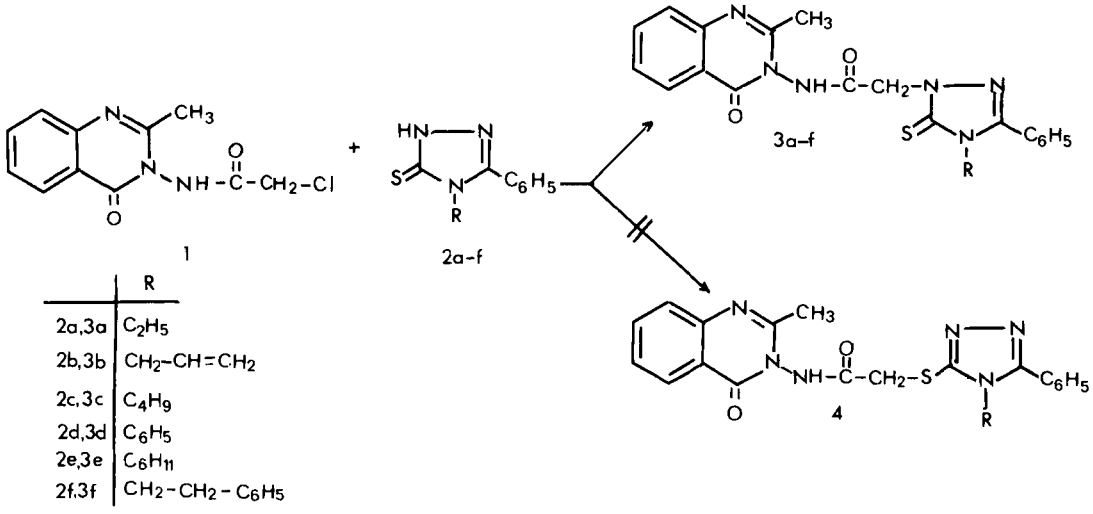

compounds show a remarkable decrease of spontaneous locomotor activity. A maximal inhibition was observed with **3e** which had highest R_{Mo} value (Table 2). Activity was decreased according to the following order: **3e > 3f > 3d > 3a > 3b > 3c** .

As it is evident form table 3 anticonvulsant activities ranging from 60% to nil protection were exhibited by the test compounds. **3f** was able to inhibit the induction of tonic extension completely, though clonic convulsions occurred rarely. In contrast **3c** did not show any 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. Generally the mice which did not show occurence of seizures for the next 60 min were protected against death. The results indicate that the substitution of position 4 of the triazole nucleus influences the activity according to the following order: **3f > 3e > 3d > 3a > 3b > 3c** . Here lipophilicity can play an important role. Maximum protecting activity was observed with compound **3f**. When doses higher than 100 mg/kg were given all of the animals show some signs of toxicity such as tremors.

As a result the substances exhibit relatively weak H_1 and H_2 activities and moderate anticonvulsant and remarkable locomotor activity decreasing properties.

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Experimental Part

Mp.: Büchi apparatus according to Dr. Tottoli (uncorrected). – UV-spectra: Carl Zeiss PMQ II spectrophotometer (Methanol). – IR spectra: Perkin-Elmer 1420 spectrophotometer (KBr). – ^{1}H-NMR-spectra: Bruker WP 60, 60 MHz spectrometer ($CDCl_3$,DMSO-d_6); – MS: Varian Mat CH 7A spectrometer at an electron energy of 70eV. – Elementary analysis: Perkin-Elmer-analyzer 240C.

2,3-Dihydro-4-phenethyl-5-phenyl-3H-1,2,4-triazole-3-thione (**2f**)

2f was prepared according to lit.[19]. The crude product was crystallized from ethanol (yield 65%). Mp. 107-108 °C. -$C_{16}H_{15}N_3S$ (281.4) calcd. C 68.3 H 5.37 N 14.93 found C 68.05 H 5.4 N 15.22. –UV: λ max= 201; 256 nm. –IR: 1615; 1565; 1500; 1280 cm^{-1}. -^{1}H-NMR δ (ppm) ($CDCl_3$)= 2.65-3.35 (t; J=6Hz, 2H, -CH_2-C_6H_5), 4.0-4.50(t; J=11Hz, N-CH_2-), 6.82-7.65 (m; 10H, Ar-H), 8.28 (s; 1H, NH).

General procedure for the synthesis of 3-[2-(2,3-dihydro-5-phenyl-4-substituted-3H-1,2,4-triazole-3-thione-2-yl)-acetylamino]-2-methyl-4(3H)-quinazolinones **3a-f**

10 mmol of **1** and 10 mmol of **2a-f** each were dissolved in 50 ml dry benzene and refluxed for 5 h. The solution was evaporated under vacuo. The remaining solid was neutralized with 5% aqueous $NaHCO_3$ solution and filtered. As **3a, 3b, 3c** and **3f** are highly soluble in $NaHCO_3$ solutions, their filtrates were acidified and additionally extracted with chloroform. The org. phase was evaporated in vacuo. The final solids were crystallized from appropriate solvents.

Pharmacology

Swiss Albino mice weighing 20-25 g of either sex were used for the experiments. The compounds were suspended in 5% aqueous suspension of gum acacia with the use of an ultrasonic bath (15 min). The suspensions were given intraperitoneally.

Gross observation

Groups of 10 mice were used for compounds. 50 mg/kg of **3a-3f** were given to each group. The behaviour and signs of toxicity were observed in detail for 180 min. The results thus obtained were useful as criteria for screening of CNS activities.

Anticonvulsant activity

Four hours after i.p. administration of the test compounds to a group of 10 mice, 90 mg/kg of pentetrazol was given i.p. This dose of pentetrazol causes convulsions within 10 min after administration and produces 100% mortality within 24 h. The mice were observed for the next 60 min for occurrence of seizures. An episode of clonic spasm that persisted for a minimum of 5 sec was considered as threshold convulsion. Transient intermittent jerks and tremulousness were not counted. Animals devoid of a threshold convulsion were considered protected. The mortality within 24 h was also recorded.

Spontaneous locomotor activity

The spontaneous locomotor activity in mice was measured using an activity cage (Ugo Basile, Model 7400 Comerio-Varese, Italy) coupled to a

Table 1. Physical Constants and Analytical Data

Compound	Mp.(°C) (Recryst.sol.)[a] yield (%)	Mol.formula (Mol.Wt.)	Analysis calcd./found C	H	N	UV(λmax) nm			IR cm^{-1} C=O	C=S	MS m/z (rel.Int)
3a	184-185 (B)	$C_{21}H_{20}N_6SO_2$	60.0	4.78	20.0	202	223	251	1686;1567	1262	420
	75	(420.5)	60.1	4.88	20.1	259sh	302	313			(37)
3b	170-172 (B)	$C_{22}H_{19}N_6SO_2$	61.2	4.40	19.5	203	223	249sh	1691;1565	1262	431
	69	(431.5)	60.9	4.87	19.0	259sh	302	313sh			(6)
3c	149-150 (B)	$C_{23}H_{23}N_6SO_2$	61.7	5.18	18.8	203	223	250	1691;1567	1264	447
	62	(447.5)	62.1	4.87	19.0	259sh	302	312sh			(62)
3d	153-155 (A)	$C_{25}H_{19}N_6SO_2$	57.5	4.90	16.1	202	221	260	1695;1550	1268	467
	87	(467.5)	57.1	4.54	16.1	300	311				(84)
3e	241-242 (B,C)	$C_{25}H_{25}N_6SO_2$	63.4	5.32	17.7	202	222	250	1691;1568	1266	473
	85	$\cdot 1/2H_2O$									
		(482.6)	63.0	5.72	18.1	258sh	301	312sh			(23)
3f	169-171 (B)	$C_{27}H_{24}N_6SO_2$	65.3	4.87	16.9	203	223	250sh	1692;1567	1261	496
	58	(496.6)	65.4	5.03	16.8	259sh	302	313sh			(2.5)

[a] A=ethanol, B=isopropanol, C=benzene

Table 2. R_{M_0} values of **3a-f**

Compounds	R_{M_0}
3a	0.7753
3b	1.5293
3c	0.9296
3d	1.4836
3e	1.7495
3f	1.7125

Table 3. Anticonvulsant activity of **3a-f** at 50 mg/kg

Compounds	Protection (%)
3a	15
3b	10
3c	nil
3d	25
3e	40
3f	60

printing counter. This was done under identical conditions at the same time of the day in a temperature controlled (20 ± 2 °C), sound proof room. Control animals as well as those given test substances as groups of 5 mice each were placed into the cage at least 15 min before recording of the locomotor activity; thus during the actual measurement of running activity the contribution of exploratory activity to the total count was kept to a minimum. The values in results have been calculated from 20 min counts of groups of 5 animals each during 240 min. The results were compared with those of control groups.

H_1 activity

The substances have been dissolved in ethanol with the addition of few drops of N HCl. H_1 activity has been determined at the guinea-pig ileum as described by *Schunack*[22].

H_2 activity

Guinea-pigs of either sex were killed by a blow on the head. The heart was removed rapidly. Right atria were attached to a tissue holder. H_2 activity has been determined according to *Schunack*[23,24].

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