Synthesis and Anticonvulsant Activity of Acetylenic Quinazolinone Derivatives

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Summary

Acetylenic derivatives of quinazolinones and quinazolinediones were synthesized and evaluated for their anticonvulsant activity. Most compounds displayed seizure-antagonizing activity in the maximal electroshock test (MES test) in most cases associated with little or no acute neurotoxicity determined in the rotorod test. Only three compounds exhibited significant activity in the seizure threshold test with subcutaneous pentylenetetrazole (scMet test). Based on the ED_{50} in the MES test, 1,3-bis-(prop-2-ynyl)-quinazoline-2,4-(1*H*,3*H*)-dione (**9a**) was about ten-fold less active than phenytoin or carbamazepine but about as active as mesuximide.

Introduction

Worldwide, approximately 40–50 million people (about 0.5–1% of the population) suffer from epilepsy, a symptom of excessive temporary neuronal discharge, characterized by discrete recurrent episodes, in which there is a disturbance of movement, sensation, behavior, perception, and/or consciousness [1]. 20–30% of the patients have seizures that are resistant to the available medical therapies. This fact warrants the search for new anticonvulsant drugs.

Quinazolinones are a large class of active chemical compounds exhibiting a broad spectrum of biological activities in animals as well as in humans [2,3]. The effects of 4-(3*H*)-quinazolinones on the central nervous system have been well documented especially for the 3-aryl derivatives. The prototype of this series is 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone, the sedative drug methaqualone. In this context numerous derivatives, especially 2-substituted quinazolinones, have been investigated for their anticonvulsant activity [2,3]. Quinazolinediones have also been studied [4,5].

Acetylenic derivatives of quinazolinones and quinazolinediones have been synthesized previously [6–9] but their pharmacological potential has not been fully evaluated. The propargyl group has also been used to modify the anticonvulsant properties of hydantoins [10] a well known class of anticonvulsants. Moreover, allyl substituted quinazolinediones displayed anticonvulsant activity [4]. The present study was conducted in order to evaluate the anticonvulsant activity of acetylenic quinazolinones and quinazolinediones.

Results and Discussion

Chemistry

The acetylenic derivatives of the quinazolinones were synthesized according to general procedures as outlined in Scheme 1. *N*-Alkylation of the quinazolinones **1a**–**g** with propargyl bromide in dimethylformamide in the presence of potassium carbonate at room temperature yielded the 2-substituted quinazolinones **2a**–**g**. In the case of the phenyl and trifluoromethyl derivatives **2b** and **2c**, respectively, *O*-alkylation occurred as a side reaction. This is in agreement with an earlier study on the synthesis of acetylenic quinazolinones [6] reporting a ratio of 36:64 and 10:90 for the *N*-propargyl and *O*-propargyl derivatives of the phenyl and trifluoromethyl compound by gas chromatography. No *O*-alkylation was observed for the benzyl derivative [6]. When isolated by column chromatography we found a ratio of 32:68 for both sets of compounds **2b**/**3b** and **2c**/**3c**. Compounds **6a** and **6b** were prepared by ring opening of isatoic acid anhydride with 2-propyn-1-ylamine and 2-methyl-3-butyn-2-ylamine, respectively, to the corresponding 2-amino benzamides **5a** and **5b** followed by cyclization with triethylorthoformate.

The mono- and dialkylated quinazolinediones **8a** and **9a**, and **8b** and **9b**, respectively, were prepared by *N*-alkylation of quinazolindiones **7a** and **7b** with propargyl bromide using sodium hydroxide in methanol-water (1:1). No attempt was made to synthesize the mono and dialkylated derivatives specifically but the resulting mixture of the mono- and dialkylated products was separated by alkaline extraction of the monoalkylated derivatives. The assignment of all structures was established on the basis of IR, ^{1}H- and ^{13}C-NMR, mass spectrometry, and microanalysis.

Pharmacology

The compounds were tested for anticonvulsant activity according to standard procedures [11] which included the maximal electroshock seizure test (MES test) and the seizure threshold test with subcutaneous pentylenetetrazole (scMet test). The acute neurological toxicity was determined in the rotorod test. The results of the screening in mice is summarized in Table 1. The intermediate 2-aminobenzamides **5a** and **5b** were included as the anticonvulsant activity of 2- and 4-aminobenzamides has been reported [12-14]. However, only **5a** displayed an effect in the MES test at a dose of 100 mg/kg.

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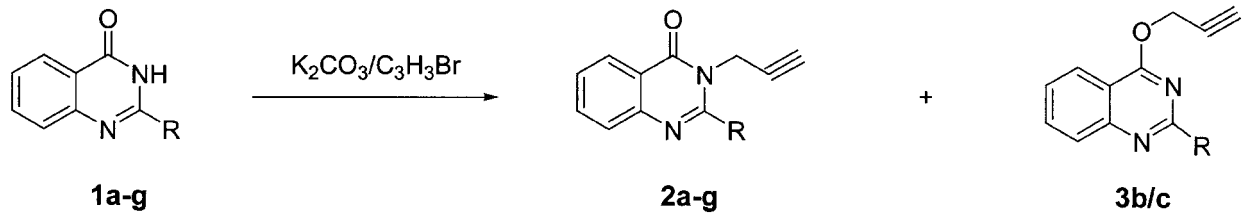
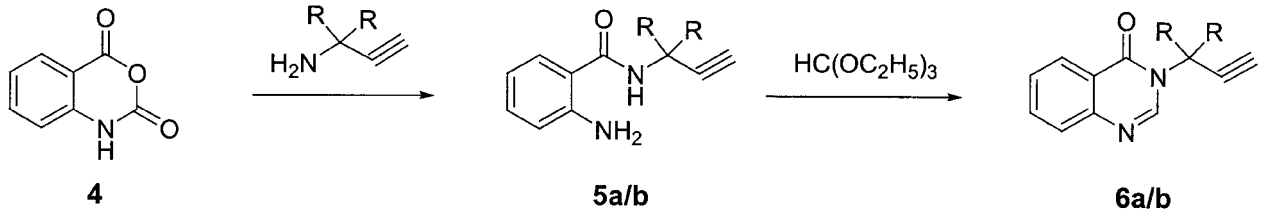
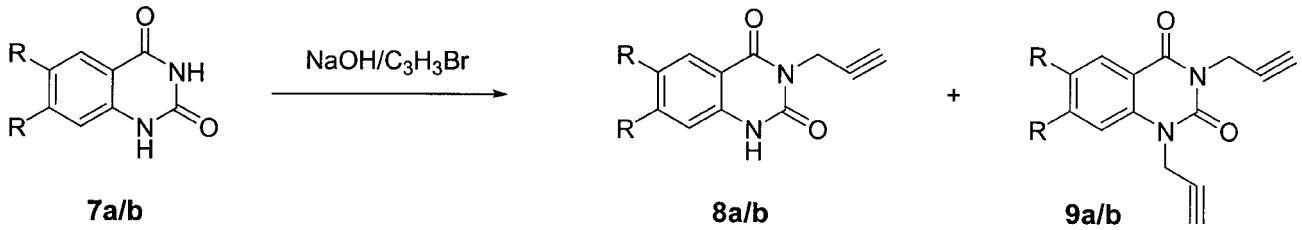


	R
a	CH_3
b	CF_3
c	C_6H_5
d	$CH_2C_6H_5$
e	$(CH_2)_3COCH_3$
f	$(CH_2)_3CH(OH)CH_3$
g	$CONH_2$



	R
a	H
b	CH_3



	R
a	H
b	OCH_3

Scheme 1

Table 1. Anticonvulsant activity in the MES test and the ScMet test and toxicity in the rotorod test of quinazolinones following intraperitoneal administration to mice. The numbers are expressed as animals protected/animals tested.

		MES		ScMet		Toxicity		
Cmpnd	Dose [mg/kg]	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	Class [a)]
2a	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	3/3	0/3	2/5	0/1	1/8	0/4	
	300	1/1	1/1	–	–	4/4	2/2	
2b	30	0/1	0/1	0/1	0/1	0/4	0/2	2
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	1/1	0/1	0/1	0/1	0/4	2/2	
2c	30	0/1	0/1	0/1	1/1	0/4	0/2	2
	100	0/3	0/3	1/5	0/1	1/8	0/4	
	300	0/1	1/1	3/5	1/1	0/4	2/2	
2d	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	3/3	0/3	0/1	0/1	1/8	0/4	
	300	1/1	1/1	1/1	0/1	4/4	2/2	
2e	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	1/3	0/3	0/1	0/1	0/8	0/4	
	300	1/1	1/1	0/1	0/1	4/4	0/2	
2f	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	3/3	0/3	0/1	0/1	2/8	0/4	
	300	1/1	1/1	1/1	0/1	4/4	0/2	
2g	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	1/3	1/3	0/1	0/1	0/8	0/4	
	300	1/1	1/1	0/1	0/1	1/4	0/2	
3b	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	0/3	1/3	0/1	0/1	0/8	0/4	
	300	0/1	1/1	0/1	0/1	0/4	0/2	
3c	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
5a	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	1/3	0/3	0/1	0/1	0/8	0/4	
	300	1/1	0/1	0/1	0/1	3/4	0/2	
5b	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	1/4	0/2	
6a	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
6b	30	0/1	0/1	0/1	0/1	0/4	0/2	2
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	1/1	0/1	1/1	0/1	4/4	0/2	
8a	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	2/3	0/3	0/1	0/1	0/8	0/4	
	300	1/1	1/1	0/1	0/1	4/4	0/2	
8b	30	0/1	0/1	0/1	0/1	0/4	0/2	2
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	1/1	0/1	0/1	0/4	0/2	
9a	30	0/1	0/1	0/1	0/1	0/4	0/2	2
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	1/1	1/1	0/1	0/1	0/4	0/2	
9b	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	0/3	2/3	0/1	0/1	0/8	0/4	
	300	0/1	1/1	0/1	0/1	0/4	0/2	

[a)] Classification according to reference [11]. Class 1, active at ≤ 100 mg/kg; class 2, active at 300 mg/kg; class 3, inactive.

Table 2. Median effective dose (ED_{50}), median toxic dose (TD_{50}) and protective index (PI) of **9a** and standard anticonvulsant drugs after intraperitoneal administration to mice. The values are expressed in μmol/kg; 95% confidence intervals are given in brackets. The time of testing at the time of peak effect is listed in square brackets.

Compound	ED_{50} (MES)	TD_{50} (rotorod)	PI (TD_{50}/ED_{50})
9a	364 (299–431)	> 1680	> 4.6
	[1 h]	[1 h]	
phenytoin [a)]	37.7 (32.2–41.2)	260 (208–286)	6.9
	[2 h]	[2 h]	
mesuximide [a)]	375 (310–440)	925 (780–1160)	2.5
	[0.5 h]	[0.5 h]	
carbamazepine [a)]	37.3 (23.1–59.7)	303 (194–570)	8.1
	[0.25 h]	[0.25 h]	

[a)] Data from reference [11]; for better comparison the data given in [11] on a mg/kg basis were converted to μmol/kg.

Generally, most quinazolinone derivatives exhibited activity in the MES test while a seizure antagonizing effect in the scMet test was only observed for **2a**, **2c**, **2d**, and **2f**. However, none of the compounds exhibited significant activity at the lowest concentration tested. The quinazolinones **6a** and **6b** which bear no substituent in position 2 displayed no activity or only a low activity. In contrast, most 2-substituted derivatives displayed activity in the MES test at a dose of 100 mg/kg. This is in accordance with structure activity relationships which revealed a higher activity of 2-substituted quinazolinones compared to the unsubstituted compounds [3]. Interestingly, the *O*-alkylated derivative **3b** is more active than the corresponding quinazolinone **2b**. All quinazolinediones showed activity in the MES test. Most compounds showed no acute neurotoxicity in the rotorod test.

Compound **9a** was selected for quantitative evaluation. The median effective dose (ED_{50}) in the MES test and the median neurotoxic dose (TD_{50}) in the rotorod test of **9a** and the anticonvulsant drugs phenytoin, carbamazepine and mesuximide are summarized in Table 2. Based on the ED_{50} in the MES test, **9a** is about ten-fold less active than phenytoin or carbamazepine but about as active as mesuximide. **9a** did not display significant acute neurotoxicity up to a dose of 240 mg/kg (1.68 mmol/kg), resulting in a protective index (PI = TD_{50}/ED_{50}) of at least 4.6 which is comparable to the approved drugs.

In conclusion, acetylenic quinazolinone derivatives were synthesized and their anticonvulsant activity has been evaluated. In agreement with other studies [2–5] *bis-N*-alkylated quinazolinones might represent interesting structures for the development of antiepileptic drugs.

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Experimental

General

Mp: Kofler melting point apparatus, uncorrected.– IR: Perkin-Elmer 457.– NMR: Varian Gemini 200 (TMS), ^{1}H: 200 MHz, ^{13}C: 50 MHz.– MS Varian MAT 44S, EI: 70 eV, source temp. 200 °C. TLC: Pre-coated silica gel plates Merck (F_{254}).– Column chromatography: Silica gel Merck Si-60 (70–230 mesh). 2-Methyl-4(3*H*)-quinazolinone (**1a**), isatoic acid anhydride (**4**) and the quinazolinediones **7a** and **7b** were from Aldrich Chemical Co. (Deisenhofen, Germany). The remaining quinazolinones were synthesized from *ortho*-anthranilamide according to the literature: **1b** [15], **1c** [16], **1d** [16], **1e** [17], **1f** [17] and **1g** [18].

General Procedure for the Synthesis of 2-Substituted Quinazolinones

Propargyl bromide (6.0 mmol) was added to a stirred suspension of 5 mmol of the appropriate quinazolinone **1a**–**g** and 60 mmol potassium carbonate in 10 ml dry *N*,*N*-dimethylformamide. The reaction mixture was stirred at room temperature till TLC (6–8 h) indicated the complete disappearance of the quinazolinone. The reaction mixture was poured into 100 ml brine/ethyl acetate (1:1) and the aqueous phase was extracted with ethyl acetate. The combined organic phase was dried and evaporated in vacuo to give a crude product which was further purified by column chromatography (dichloromethane to dichloromethane/ethyl acetate 6:1).

*3-Prop-2-ynyl-2-methyl-quinazolin-4(3H)-one (***2a***)*

Yield 0.69 g (70%), mp 91–92 °C (CH_2Cl_2/hexane) (Ref.[8] 91–93 C). IR (KBr): ν (cm^{-1}) = 3200 (C≡CH), 2100 (C≡C), 1680 (C=O). ^{1}H NMR ($CDCl_3$): δ = 2.35 (t, *J* = 2.5 Hz, 1H, 3′-H), 2.75 (s, 3H, 2-CH_3), 4.91 (d, *J* = 2.5 Hz, 2H, 1′-H), 7.44 (ddd, *J* = 1.4, 7.4, 8.2 Hz, 1H, 6-H), 7.62 (dd, *J* = 1.4, 8.2 Hz, 1H, 8-H), 7.73 (ddd, *J* = 1.5, 7.1, 8.3 Hz, 1H, 7-H), 9.24 (dd, *J* = 1.5, 8.3 Hz, 1H, 5-H). ^{13}C NMR ($CDCl_3$): δ = 22.8, 33.1, 72.7, 77.6, 120.5, 126.8, 127.0, 127.2, 134.8, 147.5 154.0, 161.6. MS: *m/z* = 198 [M^+] (100), 197 [M^+–1] (88), 183 (22), 169 (36), 156 (6), 143 (10), 129 (14), 117 (10), 102 (14), 90 (14), 76 (16).

*3-Prop-2-ynyl-2-trifluoromethyl-quinazolin-4-(3H)-one (***2b***)*

Yield 0.38 g (30%), mp 97–98 °C (CH_2Cl_2/*n*-hexane). IR (KBr): ν (cm^{-1}) = 3200 (C≡C), 2100 (C≡CH), 1680 (C=O). ^{1}H NMR ($CDCl_3$): δ = 2.28 (t, *J* = 2.2 Hz, 1H, 3′-H), 4.93 (d, *J* = 2.2 Hz, 2H, 1′-H), 7.60–7.65 (ddd, *J* = 2.3, 7.7, 8.1 Hz, 1H, 6-H), 7.80–7.85 (m, 2H, 5-H, 7-H), 8.34 (d, *J* = 7.8 Hz, 1H, 8-H). ^{13}C NMR ($CDCl_3$): δ = 34.6, 35.5, 72.9, 77.5, 117.4, 122.2, 127.8, 129.1, 130.1, 135.7, 145.2, 161.1. MS: *m/z* = 252 [M^+] (90), 223 (8), 210 (18), 183 (10), 155 (22), 129 (64), 102 (75), 90 (100), 69 (74), 51 (41). $C_{12}H_7N_2OF_3$ (252.20): Calc. C 57.15 H 2.80 N 11.11; found C 57.10 H 2.76 N 11.00.

*4-Prop-2-ynoxy-2-trifluoromethyl-quinazoline (***3b***)*

Yield 0.82 g (65%), mp 99–100 °C (CH_2Cl_2/*n*-hexane). IR (KBr): ν (cm^{-1}) = 3000, 1630, 1600. ^{1}H NMR ($CDCl_3$): δ = 2.56 (t, *J* = 2.3 Hz, 1H, 3′-H), 5.27 (d, *J* = 2.3 Hz, 2H, 1′-H), 7.68 (t, *J* = 7.4 Hz, 1H, 7-H), 7.92 (t, *J* = 7.4 Hz, 1H, 6-H), 8.06 (d, *J* = 8.4 Hz, 1H, 5-H), 8.25 (d, *J* = 8.1 Hz, 1H, 8-H). ^{13}C NMR ($CDCl_3$): δ = 2.56 (t, *J* = 2.3 Hz, 1H, 3′-H), 5.27 (d, *J* = 2.3 Hz, 2H, 1′-H), 7.68 (t, *J* = 7.4 Hz, 1H, 7-H), 7.92 (t, *J* = 7.4 Hz, 1H, 6-H), 8.06 (d, *J* = 8.4 Hz, 1H, 8-H), 8.25 (d, *J* = 8.1 Hz, 1H, 5-H). ^{13}C NMR ($CDCl_3$): δ = 55.8, 76.4, 77.6, 116.8, 118.7, 124.2, 129.1, 129.6, 135.3,150.9, 167.4. MS: *m/z* = 252 [M^+] (82), 233 (7), 210 (19), 198 (13), 155 (15), 129 (100), 116 (14), 102 (85), 90 (98), 76 (73), 63 (73), 51 (30). $C_{12}H_7N_2OF_3$ (252.20): Calc. C 57.15 H 2.80 N 11.11; found C 56.90 H 2.90 N 11.21.

*3-Prop-2-ynyl-2-phenyl-quinazolin-4(3H)-one (**2c**)*

Yield 0.34 g (26%), mp 171–172 °C (CH_2Cl_2/*n*-hexane) (Ref.[6] 176–177 °C). IR (KBr): ν (cm^{-1}) = 3215 (C≡C), 2100 (C≡CH), 1670 (C=O), 1600. ^{1}H NMR ($CDCl_3$): δ = 2.31 (t, *J* = 2.4 Hz, 1H, 3′-H), 4.65 (d, *J* = 2.4 Hz, 2H, 1′-H), 7.48–7.53 (m, 4H, Ar-H), 7.70–7.76 (m, 4H, Ar-H), 8.33 (d, *J* = 7.6 Hz, 1H, Ar-H). ^{13}C NMR ($CDCl_3$): δ = 34.6, 72.6, 77.4, 118.8, 124.4, 126.4, 128.2, 129.4, 130.2, 134.8, 137.8, 152.4, 159.8, 166.4. MS: *m/z* = 261 [M^++1] (12), 260 [M^+] (99), 259 [M^+–1] (100), 231 (35), 204 (7), 179 (10), 152 (6), 128 (9), 115 (15), 102 (33), 90 (35), 76 (58), 51 (39). $C_{17}H_{12}N_2O$ (260.30).

*4-Prop-2-ynoxy-2-phenyl-quinazoline (**3c**)*

Yield 0.72 g (55%), mp 127–128 °C (CH_2Cl_2/*n*-hexane) (Ref.[6] 135–137 °C). IR (KBr): ν (cm^{-1}) = 3200 (C≡C), 2995 (CH), 2115 (C≡CH), 1640 (C=O). ^{1}H NMR ($CDCl_3$): δ = 2.55 (t, *J* = 2.2 Hz, 1H, 3′-H), 5.32 (d, *J* = 2.1 Hz, 2H, 1′-H), 7.49–7.52 (m, 4H, Ar-H), 7.8 (t, *J* = 7.9 Hz, 1H, Ar-H), 8,0 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.18 (d, *J* = 8.1 Hz, 1H, Ar-H), 8.59 (d, *J* = 7.8 Hz, 2H, Ar-H). ^{13}C NMR ($CDCl_3$): δ = 54.2, 75.1, 78.2, 114.9, 123.4, 126.6, 127.9, 128.4, 128.5, 130.6, 133.8, 137.8, 151.9, 159.6, 165.5. MS: *m/z* = 260 [M^+] (34), 259 [M^+–1] (100), 231 (6), 205 (6), 151 (5), 119 (6), 103 (34), 90 (88), 77 (56), 63 (59), 54 (40).

*3-Prop-2-ynyl-2-benzyl-quinazolin-4(3H)-one (**2d**)*

Yield 1.23 g (90%), mp 99–99.5 °C (CH_2Cl_2/*n*-hexane) (Ref.[6] 102–104 °C). IR (KBr): ν (cm^{-1}) = 3210 (C≡CH), 2100 (C≡C), 1690 (C=O), 1600. ^{1}H NMR ($CDCl_3$): δ = 2.23 (t, *J* = 2.4 Hz, 1H, 3′-H), 4.36 (s, 2H, CH_2ph), 4.68 (d, *J* = 2.4 Hz, 2H, 1′-H), 7.17–7.36 (m, 5H, Ar-H), 7.42 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.62–7.68 (m, 2H, Ar-H), 8.20 (d, *J* = 8.0 Hz, 1H, Ar-H). ^{13}C NMR ($CDCl_3$): δ = 32.4, 42.1, 72.6, 77.7, 120.4, 126.9, 127.0, 127.2, 127.5, 128.2, 129.2, 134.6, 134.86, 147.0, 154.5, 161.6. MS: *m/z* = 274 [M^+] (58), 273 [M^+–1] (88), 235 (5), 197 (9), 167 (6), 130 (9), 128 (18), 116 (26), 102 (33), 91 (100), 77 (50), 65 (90).

*3-Prop-2-ynyl-2-penta-2-olyl-quinazolin-4(3H)-one (**2e**)*

Yield 9.87 g (65%), mp 109–110 °C (*n*-pentane). IR (KBr): ν (cm^{-1}) = 3405 (OH), 3250 (C≡CH), 2100 (C≡C), 1670 (C=O), 1600. ^{1}H NMR ($CDCl_3$): δ = 1.15–1.25 (d, *J* = 6.7 Hz, 3H, CH_3), 1.55–1.70 (q, *J* = 6.7 Hz, 2H, 3″-H), 1.95–2.18 (m, 2H, 4″-H), 2.30 (t, *J* = 2.4 Hz, 1H, 3′-H), 2.90–3.10 (t, *J* = 7.0 Hz, 2H, 5″-H), 3.80–3.95 (m, 1H, 2″-H), 4.95 (d, *J* = 2.4 Hz, 2H, 1′-H), 7.44–7.52 (ddd, *J* = 1.2, 7.2, 8.0 Hz, 1H, 8-H), 7.50–7.82 (m, 2H, 6-H, 7-H), 8.24–8.32 (dd, *J* = 1.2, 8.0 Hz, 1H, 5-H). ^{13}C NMR ($CDCl_3$): δ = 22.3, 23.7, 38.6, 67.3, 72.6, 77.9, 120.3, 126.8, 126.9, 127.1, 134.6, 146.9, 156.2, 161.5. MS: *m/z* = 269 [M^+–1] (1), 253 [M^+–OH] (38) 225 (7), 211 (33), 198 (49), 197 (100), 169 (11), 130 (5), 115 (5), 92 (5), 77 (6). $C_{16}H_{18}N_2O_2$ (270.33): Calc. C 71.09 H 6.71 N 10.36; found C 71.02 H 6.58 N 10.30.

*3-Prop-2-ynyl-2-penta-2-onyl-quinazolin-4(3H)-one (**2f**)*

Yield 1.02 g (80%), mp 88–89 °C (CH_2Cl_2/*n*-hexane). IR (KBr): ν (cm^{-1}) = 3200 (C≡CH), 2960 (Ar-H), 2100 (C≡C), 1740, 1685 (C=O), 1600. ^{1}H NMR ($CDCl_3$): δ = 2.14 (s, 3H, CH_3), 2.18–2.22(m, 2H, CH_2), 2.26 (s, 1H, 3′-H), 2.62–2.69 (t, *J* = 6.7 Hz, 2H, 3″-H), 2.91–3.98 (t, *J* = 7.3 Hz, 2H, 4″-H), 4.96 (s, 2H, 1′-H), 7.41 (t, *J* = 7.0 Hz, 1H, 8-H), 759 (d, *J* = 7.8 Hz, 1H, 6-H), 7.66 (t, *J* = 7.0 Hz, 1H, 7-H), 8.20 (d, *J* = 7.8 Hz, 1H, 5-H). ^{13}C NMR ($CDCl_3$): δ = 21.0, 30.5, 32.9, 42.7, 72.9, 110.0, 120.7, 127.1, 127.4, 134.9, 147.4, 155.9, 161.9, 208.8. MS: *m/z* = 254 [M^+] (2), 253 [M^+–1] (3), 225 (28), 211 (18), 198 (86), 197 (100), 184 (8), 169 (13), 142 (3), 130 (4), 115 (4). $C_{16}H_{16}N_2O_2$ (268.32): Calc. C 71.62 H 4.51 N 10.44; found C 71.56 H 4.60 N 10.50.

*3-Prop-2-ynyl-quinazolin-4(3H)-one Carboxamide (**2g**)*

Yield 0.85 g (75%), mp 203–205 °C (ethyl acetate/*n*-hexane). IR (KBr): ν (cm^{-1}) = 3415, 3395 (NH_2), 1680, 1670 (C=O). ^{1}H NMR (DMSO-d_6): δ = 3.30 (t, *J* = 2.3 Hz, 1H, 3′-H), 5.05 (d, *J* = 2.4 Hz, 2H, 1′-H), 7.58–7.69 (ddd, *J* = 1.4, 7.2, 8.0 Hz, 1H, 8-H), 7.70–7.78 (dd, *J* = 1.2, 8.2 Hz, 1H, 6-H), 7.86–7.96 (ddd, *J* = 1.5, 7.4, 8.2 Hz, 1H, 7-H), 8.14–8.24 (dd, *J* = 1.6, 8.0 Hz, 5-H), 8.18 (s, 1H, $CONH_2$), 8.46 (s, 1H, $CONH_2$). ^{13}C NMR (DMSO-d_6): δ = 33.1, 74.6, 78.6, 120.9, 126.4, 127.5, 128.3, 135.1, 145.8, 148.6, 159.9, 163.1. MS: *m/z* = 227 [M^+] (100), 199 (7), 184 (60), 155 (16), 146 (9), 129 (20), 102 (16), 90 (11). $C_{12}H_9N_3O_2$ (227.22): Calc. C 63.43 H 3.99 N 18.49; found C 63.20, H 3.84 N 18.40.

*2-Amino-N-prop-2-ynyl-benzamide (**5a**)*

1.65 g propargylamine (30 mmol) in 20 ml DMF were added slowly to a solution of 3.3 g isatoic acid anhydride (20 mmol) in 20 ml DMF at 40–50 °C and maintained at this temperature for 3 h. The reaction mixture was pored into 200 ml water adjusted to pH 9 with NaOH. The precipitated was filtered, washed with water, dried and recrystallized. Yield 3.1 g (89%), mp 100–101 °C (CH_2Cl_2/*n*-hexane) (Ref.[19] 99–100.5 °C). IR (KBr) 3480, 3300 (NH_2, NH), 1660. ^{1}H NMR ($CDCl_3$): δ = 2.24 (t, *J* = 2.5 Hz, 1H, 3′-H), 4.18 (dd, *J* = 2.5 Hz, 2H, 1′-H), 5.56 (brs, 2H, NH_2), 6.35 (brs, 1H, NH), 6.63 (t, *J* = 7.8 Hz, 1H, 5-H), 6.70 (d, *J* = 8.2 Hz, 1H, 3-H), 7.23 (ddd, *J* = 1.6, 7.2, 8.3 Hz, 1H, 4-H), 7.33 (dd, *J* = 1.5, 7.8 Hz, 1H, 6-H). ^{13}C NMR ($CDCl_3$): δ = 29.5, 71.9, 80.0, 115.5, 117.0, 117.7, 127.6, 133.1, 149.4, 169.3. MS: *m/z* = 174 [M^+] (52), 145 (10), 130 (8), 120 (100), 105 (3), 92 (74), 77 (2), 65 (52).

*2-Amino-N-(1,1-dimethylprop-2-ynyl)-benzamide (**5b**)*

2.5 g 1,1-Dimethyl-2-propynylamine (30 mmol) and 3.3 g isatoic acid anhydride (20 mmol) were treated as described for **5a**. Yield 2.6 g (65%), mp 122–123 °C (CH_2Cl_2/*n*-hexane) (Ref.[20] 121–123 °C). IR (KBr): ν (cm^{-1}) = 3490 (NH) 3380, 3300 (NH_2), 1640, 1610. ^{1}H NMR ($CDCl_3$): δ = 1.73 (s, 6H, 2×CH_3), 2.38 (s, 1H, 3′-H), 5.34 (brs, 2H, NH_2), 6.13 (brs, 1H, NH), 6.61 (t, *J* = 7.9 Hz, 1H, 5-H), 6.65 (d, *J* = 8.2 Hz, 1H, 3-H), 7.20 (ddd, *J* = 1.2, 7.4, 7.9 Hz, 1H, 4-H), 7.79 (dd, *J* = 1.6, 7.8 Hz, 6-H). ^{13}C NMR ($CDCl_3$): δ = 29.3, 48.0, 70.0, 87.4, 116.5, 116.9, 117.7, 127.6, 132.6, 149.4, 169.3. MS: *m/z* = 202 [M^+] (54), 174 (10), 136 (16), 119 (100), 105 (32), 92 (51), 65 (45).

*3-Prop-2-ynyl-quinazolin-4(3H)-one (**6a**)*

1.7 g **5a** (10 mmol), 1 g acetic acid (17 mmol) and 1.6 g triethyl orthoformate (11 mmol) in 30 ml EtOH were refluxed for 4 h. Upon concentration in vacuo and addition of 5% aqueous NaOH to pH 8 the mixture was extracted with CH_2Cl_2. The organic phase was dried over $NaSO_4$, evaporated under reduced pressure and the residue was recrystallized from MeOH to yield 1.55 g (85%) of **6a**. Mp 115–116 °C (MeOH) (Ref.[8] 115–116 °C) IR (KBr) ν (cm^{-1}) = 3210 (C≡CH), 2110 (C≡C), 1660. ^{1}H NMR ($CDCl_3$): δ = 2.50 (t, *J* = 2.5 Hz, 1H, 3′-H), 4.83 (d, *J* = 2.4 Hz, 2H, 1′-H), 7.52 (ddd, *J* = 1.9, 6.3, 7.8 Hz, 1H, 6-H), 7.74 (s, 1H, 2-H), 7.77 (dd, *J* = 1.8, 8.0 Hz, 1H, 8-H), 8.27–8.32 (m, 2H, 5-H, 7-H). ^{13}C NMR ($CDCl_3$): δ = 35.2, 75.2, 77.8, 121.9, 126.8, 127.9, 128.1, 134.8, 145.6, 148.4, 160.8. MS: *m/z* = 180 [M^+] (100), 155 (30), 142 (8), 129 (42), 116 (6), 102 (34), 90 (14), 76 (34), 63 (20), 51 (20).

*3-(1,1-Dimethylprop-2-ynyl)-quinazolin-4(3H)-one (**6b**)*

2.0 g **5b** (10 mmol) were treated as described for **6a**. Yield 1.2 g (56%), mp 98–99 °C (Ref.[8] 97–99 °C). IR (KBr): ν (cm^{-1}) = 3240 (C≡CH), 2100 (C≡C), 1660. ^{1}H NMR ($CDCl_3$): δ = 2.10 (s, 6H, 2×CH_3), 2.96 (s, 1H, 3′-H), 7.44–7.58 (ddd, *J* = 1.9, 6.3, 8.2 Hz, 1H, 6-H), 7.60–7.78 (m, 2H, 7-H, 8-H), 8.30 (ddd, *J* = 1.3,7.1, 7.9 Hz, 1H, 5-H), 8.96 (s, 1H, 2-H). ^{13}C NMR ($CDCl_3$): δ = 28.5, 58.4, 77.9, 84.7, 127.1, 127.3, 127.5, 127.6, 134.6, 145.1, 148.0, 162.1. MS: *m/z* = 212 [M^+] (58), 197 (14), 183 (8), 169 (10), 146 (100), 131 (8), 118 (28), 102 (16), 90 (26), 69 (26).

General Procedure for the Synthesis of Quinazoline-2,4-diones

6.0 mmol sodium hydroxide were added to 6.0 mmol of the quinazolinediones **7a** or **7b** in 30 ml 50% methanol and stirred at room temperature for 30 min. 0.7 mmol 3-bromo-prop-1-yne was added and the reaction mixture was refluxed for 6 hours. After cooling to room temperature, 40 ml of 0.7 M sodium hydroxide were added and stirred for 15 min to remove the monoalkylated product. The dialkylated product was filtered and dried. Precipitation of the monoalkylated product was carried out by adjusting the filtrate to pH 5 with 0.1 M HCl. The precipitate was filtered and dried. The compounds were further purified by column chromatography (CH_2Cl_2).

*3-Prop-2-ynyl-quinazoline-2,4-(1H)-dione (**8a**)*

Yield 0.86 g (60%), mp 240–241 °C (EtOH) (Ref.[19] 239–240.5 °C). IR (KBr) ν (cm^{-1}) = 3310 (NH), 1705, 1680, 1640, 1290, 700. ^{1}H NMR (DMSO-d_6): δ = 3.10 (t, *J* = 2.4 Hz, 1H, 3′-H), 4.65 (d, *J* = 2.4 Hz, 2H, 1′-H), 7.21 (d, *J* = 7.9 Hz, 1H, 8-H), 7.42 (t, *J* = 8.0 Hz, 1H, 6-H), 7.67 (ddd, *J* = 1.4, 7.6, 7.9 Hz, 1H, 7-H), 7.98 (dd, *J* = 1.6, 7.9 Hz, 1H, 5-H). ^{13}C NMR (DMSO-d_6): δ = 29.3, 72.7, 79.2, 113.6, 115.3, 122.8, 127.5, 135.4, 139.5, 149.0, 161.3. MS: *m/z* = 200 [M^+] (100), 171 (16), 158 (10), 146 (76), 130 (26), 119 (46), 104 (6), 92 (64), 76 (12), 64 (36), 51 (18).

*1,3-Bis-(prop-2-ynyl)-quinazoline-2,4-(1H,3H)-dione (**9a**)*

Yield 0.45 g (32%), mp 168–170 °C (ethanol) (Ref.[7] 169–171 °C). IR (KBr): ν (cm^{-1}) = 3270, 2120 (C≡CH) 1697, 1650. ^{1}H NMR ($CDCl_3$): δ = 2.21 (t, J = 2.5 Hz, 1H, 3′-H), 2.31 (t, *J* = 2.5 Hz, 1H, 3″-H), 4.88 (d, *J* = 2.5 Hz, 2H, 1′-H), 4.97 (d, *J* = 2.5 Hz, 2H, 1″-H), 7.20–7.50 (m, 2H, 6-H, 7-H), 7.71–7.86 (ddd, *J* = 1.5, 7.5, 8.0 Hz, 8-H), 8.30–8.38 (dd, *J* = 1.6, 7.9 Hz, 1H, 5-H). ^{13}C NMR ($CDCl_3$): δ = 30.9, 33.2, 70.7, 73.2, 77.4, 78.1, 114.0, 115.5, 123.4, 129.3, 135.3, 138.9, 149.8, 160.7. MS: *m/z* = 239 [M^++1] (12), 238 [M^+] (8), 237 [M^+–1] (12), 199 [M^+–C_3H_3] (100), 172 (10), 156 (26), 146 (20), 129 (20), 102 (34).

6,7-Dimethoxy-3-prop-2-ynyl-quinazoline-2,4-(3H)-dione **(8b)**

Yield 0.68 (50%), mp 289–290 °C (EtOH). IR (KBr): ν (cm^{-1}) = 3340 cm^{-1} (NH), 1680, 1640 (C=O). ^{1}H NMR (CF_3 COOH/$CDCl_3$): δ = 2.24 (t, *J* = 2.4 Hz, 1H, 3′-H), 3.99 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.88 (d, *J* = 2.4 Hz, 2H, 1′-H), 6.70 (s, 1H, 8-H), 7.59 (s, 1H, 5-H), 10.36 (brs, 1H, NH). ^{13}C NMR (CF_3 COOD): δ = 31.4, 56.7, 56.8, 72.3, 98.1, 106.7, 108.6, 112.6, 134.8, 147.3, 152.7, 157.2, 163.0. MS: *m/z* = 260 [M^+] (100), 222 (84), 207 (56), 190 (20), 164 (94), 150 (12), 136 (67), 120 (14), 108 (30), 77 (16). $C_{13}H_{12}N_2O_4$ (260.25) calc. C 60.00 H 4.65 N 10.76. Found C 59.94 H 4.62 N 10.66.

*1,3-Bis-(prop-2-ynyl)-6,7-dimethoxy-quinazoline-2,4-(1H,3H)-dione (**9b**)*

Yield 0.73 g (40%), mp 226–227 °C (EtOH) (Ref.[9] 225–227 °C). IR (KBr): ν (cm^{-1}) = 3265, 2125 (C≡CH), 1690, 1662 (C=O). ^{1}H NMR ($CDCl_3$): δ = 2.22 (t, *J* = 2.4 Hz, 1H, 3′-H), 2.32 (t, *J* = 2.4 Hz, 1H, 3″-H), 3.92 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.86 (d, *J* = 2.4 Hz, 2H, 1′-H), 4.96 (d, *J* = 2.4 Hz, 2H, 1″-H), 6.85 (s, 1H, 8-H), 7.63 (s, 1H, 5-H). ^{13}C NMR ($CDCl_3$): δ = 30.9, 32.4, 56.2, 70.6, 73.8, 77.4, 78.4, 97.2, 108.2, 109.1, 134.6, 146.0, 150.2, 155.7, 160.2. MS: *m/z* = 299 [M^++1] (20), 298 [M^+] (100), 297 [M^+–1] (21), 260 (9), 259 [M^+–C_3H_3] (50), 216 (10), 202 (15), 186 (16), 146 (16).

Pharmacology

Anticonvulsant testing was provided by the Antiepileptic Drug Development Program, Epilepsy Branch, Division of Convulsive, Developmental and Neuromuscular Disorders, National Institutes of Health, according to standard procedures [11] and included the MES test and the seizure scMet test. In the MES test, an electrical stimulus of 50 mA was delivered for 0.2 s via corneal electrodes to male CF1 mice at 30 min and 4 h after the administration of the compounds. Blockade of the tonic extension of the hind limbs was considered protection against seizures. For the scMet test a convulsant dose of 85 mg/kg of pentylenetetrazole dissolved in saline was injected in a loose fold of skin on the back of the neck and the animals were isolated and observed for 30 min. Absence of clonic spasms for at least 5 s indicated the elevation of the pentylenetetrazole-induced seizure threshold. The acute neurological toxicity was determined in the rotorod test where the animal was placed on a rod rotating at 6 rpm. Neurological deficiency was indicated by inability to maintain equilibrium for 1 min in each of 3 trials. For all these evaluations the compounds were dissolved or suspended in 0.5% aqueous methyl cellulose.

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