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ORIGINAL PAPER

Synthesis and anticonvulsant evaluation of some novel 4(3*H*)-quinazolinones

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Abstract A series of novel quinazoline derivatives, methaqualone analogs, were synthesized, evaluated for their anticonvulsant activity against electrically and chemically (pentylenetetrazole, picrotoxin, and strychnine) induced seizures and compared with the standard drugs methaqualone and sodium valproate. 3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yl propanoate, benzenesulfonate, and 4-nitrobenzenesulfonate as well as 2-methyl-3-(2-methylphenyl)-8-methoxy-4(3H)-quinazolinone and 2-[3,4-dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]acetic acid hydrazide were found to be the most potent compounds of this series accompanied with relatively low neurotoxicity and low toxicity in the median lethal dose test as compared with the reference drugs.

Keywords Methaqualone · Thiadiazol · Triazole · Neurotoxicity

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Introduction

Epilepsy is one of the most common neurological disorders, affecting about 1% of the world's population. Many efforts devoted in recent years to the development of novel therapeutics have resulted in the availability of several newer drugs as promising anticonvulsants [1, 2]. However, the currently available anticonvulsants are effective in reducing the severity and number of seizures in less than 70% of patients. Moreover, their usage is associated with numerous undesirable side effects [3–6]. Therefore, the continued search for safer and more effective anticonvulsants is urgently necessary.

One of the most frequently encountered heterocycles in medicinal chemistry is 4(3*H*)-quinazolinone, which has diverse pharmacological activities, such as anti-tumor [7, 8], anti-inflammatory [9], anticonvulsant [10, 11] and anti-microbial activities [12, 13]. A literature survey revealed that the presence of a methyl group at position 2 and a substituted aromatic ring at position 3 are necessary requirements for the CNS depression and anticonvulsant activities of compounds such as methaqualone, etaqualone, mecloqualone, mebroqualone, and afloqualone. Figure 1 represents the similarities between the reported CNS active quinazolinone agents and our designed compounds.

Etaqualone and mecloqualone are analogues of methaqualone, which were developed and marketed mainly in France, and some other European countries as sedative hypnotic for the treatment of insomnia [14–16]. Methylmethaqualone and mebroqualone presumably have similar sedative and hypnotic properties to its parent compound, whereas afloqualone has sedative and muscle relaxant effects [17, 18]. Despite the therapeutic benefits of these drugs, there is strong circumstantial evidence that these drugs can cause photosensitization as a side

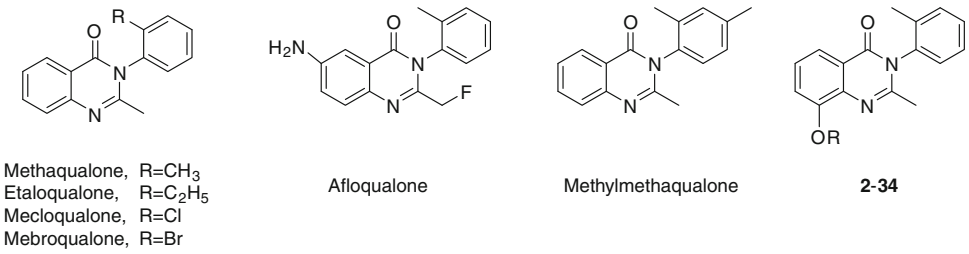


Fig. 1 Reported and designed quinazolinones as CNS active agents

effect that can cause skin problems such as dermatitis [19, 20].

In our laboratory, much research effort focuses on synthesizing quinazoline derivatives with substituted moieties possessing high lipid solubility in the hope of developing potent and safe new effective compounds [21, 22]. Herein, a new series of methaqualone analogues possessing carbonyloxy, sulfonyloxy, acetamidoxy, alkoxy, acetonitriloxy, benzyloxy, ethylacetoxy, acetohydrazino, hydrazincarboxamido, hydrazincarbothioamido, 1,2,4-triazol-3-yl, and 1,3,4-thiadiazol-2-yl moieties at position 8 were designed, synthesized, and investigated for anticonvulsant activity. The chosen substituted moieties were known to increase the lipid solubility [21]. Therefore, the objective of the current study was to synthesize and investigate if the substituents at position 8 could enhance the anticonvulsant activity of methaqualone with lower neurotoxicity in mice, a mammalian model.

Results and discussions

Chemistry

Synthesis of 8-hydroxy-2-methyl-3-(2-methylphenyl)-4(3*H*)-quinazolinone (**3**) as a first key intermediate was done by the reaction of 3-hydroxyanthranilic acid with acetic anhydride followed by treatment with *o*-toludine in anhydrous pyridine to afford 8-acetyloxy-2-methyl-3-(2-methylphenyl)-4(3*H*)-quinazolinone (**2**). The latter compound was subjected to catalytic hydrolysis by the reaction with potassium carbonate in methanol to give compound **3** in 70% overall yield.

Compound **3** was reacted with various acid chlorides (benzoyl chloride, *p*-chlorobenzoyl chloride, *p*-tolyl chloride, thiophen-2-carbonyl chloride, and propionyl chloride) in anhydrous pyridine at room temperature to obtain 8-(substituted carbonyloxy)-4(3*H*)-quinazolinones **4**–**8**. Also, **3** was reacted with various substituted phenylsulfonyl chlorides in anhydrous pyridine to afford 8-(substituted phenylsulfonyloxy)-4(3*H*)-quinazolinones **9**–**12** in 88–94% yield (Scheme 1).

Compound **3** was heated with various chloroacetanilides in anhydrous acetone in the presence of potassium carbonate to give 8-(substituted acetamido)-4(3*H*)-quinazolinones **13**–**18** in 90–96% yield. Moreover, reaction of **3** with various halides (methyl iodide, ethyl iodide, benzyl chloride, *p*-nitrobenzyl chloride, and chloroacetonitrile) in acetone in the presence of potassium carbonate at room temperature gave the corresponding 8-(substituted methoxy)-4(3*H*)-quinazolinones **19**–**23** in 80–92% yield (Scheme 2).

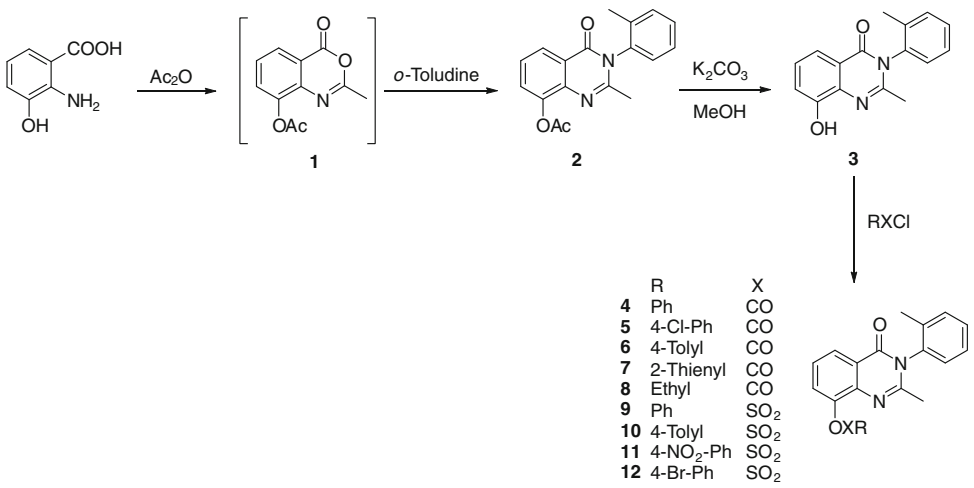
On the other hand, 8-hydroxymethaqualone **3** was reacted with ethyl bromoacetate in dry acetone in the presence of potassium carbonate at room temperature to afford a quantitative yield of ethyl 2-[3,4-dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]acetate (**24**), which was treated with hydrazine hydrate in ethanol at room temperature to furnish 2-[3,4-dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]acetic acid hydrazide (**25**) as a second key intermediate in 90% yield.

Acid hydrazide **25** was reacted with *p*-chlorophenyl isocyanate in ethanol at room temperature to produce 2-[3,4-dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]acetic acid 2-[(4-chlorophenyl)aminocarbonyl]-hydrazide (**26**) in 88% yield. Reaction of **25** with various isothiocyanates in ethanol at room temperature produced 2-[3,4-dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]acetic acid 2-[(substituted amino)thioxomethyl]hydrazides **27**–**29** in 88, 84, and 90% yield, respectively.

Compounds **27**–**29** were cyclized according to the reported procedure [23] to the corresponding 8-[(4-substituted 5-mercapto-4*H*-1,2,4-triazol-3-yl)methoxy]-2-methyl-3-(2-methylphenyl)-4(3*H*)-quinazolinones **30**–**32** by boiling in ethanol containing triethylamine. An attempt to cyclize compound **26** under the same reaction conditions failed. Compounds **30**–**32** were also obtained in another pathway on treatment of **25** with various isothiocyanates in boiling ethanol containing triethylamine in 86, 85, and 88% yield, respectively.

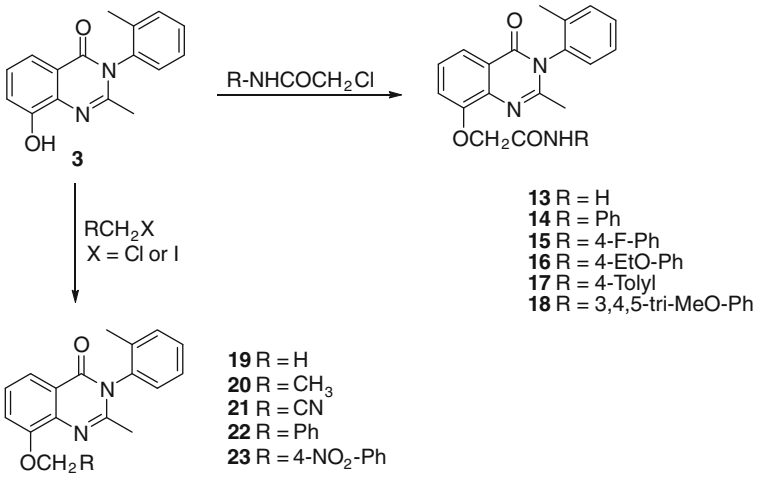
The acid dehydrative cyclization of compounds **27** and **28** by using concentrated H_2SO_4 at room temperature yielded 8-[(5-amino-1,3,4-thiadiazol-2-yl)methoxy]-2-methyl-3-(2-methylphenyl)-4(3*H*)-quinazolinone (**33**) and 2-methyl-3-(2-methylphenyl)-8-[(5-phenylamino-1,3,4-thiadiazol-2-yl)methoxy]-4(3*H*)-quinazolinone (**34**) in 62 and 68% yield, respectively (Scheme 3).

Scheme 1



	R	X
4	Ph	CO
5	4-Cl-Ph	CO
6	4-Tolyl	CO
7	2-Thienyl	CO
8	Ethyl	CO
9	Ph	SO_2
10	4-Tolyl	SO_2
11	4-NO_2-Ph	SO_2
12	4-Br-Ph	SO_2

Scheme 2



13 R = H
14 R = Ph
15 R = 4-F-Ph
16 R = 4-EtO-Ph
17 R = 4-Tolyl
18 R = 3,4,5-tri-MeO-Ph

19 R = H
20 R = CH_3
21 R = CN
22 R = Ph
23 R = 4-NO_2-Ph

Pharmacology

The anticonvulsant activity and the acute neurotoxicity of the newly synthesized compounds were evaluated by the use of standard techniques [24, 25]. The preliminary screening was performed at 0.5 mmol/kg of all synthesized compounds **2**–**34** by use of pentylenetetrazole (PTZ), picrotoxin, strychnine induced and maximal electroshock seizure (MES) model of seizures. The MES test is associated with the electrical induction of the seizure, whereas PTZ, picrotoxin, and strychnine methods involve a chemical induction to generate the convulsion [26].

The initial anticonvulsant evaluation showed that many of these compounds are inactive; however, compounds **8**, **9**, **11**, **13**, **15**, **18**, **19**, **25**, and **29** were active against PTZ at 0.5 mmol/kg, among which compounds **8**, **9**, **11**, **19**, and **25** presented 100% protection, while compounds **13**, **15**, **18**, and **29** presented 50% protection (Table 1). Compounds **8** and **19** appear unique among these anticonvulsants in their ability to antagonize picrotoxin-induced seizures at a dose of 0.5 mmol/kg. Compound **19** possessed 100% protection, while compound **8** presented 50% protection. Compounds **8**, **9**, **19**, and **25** exhibited anticonvulsant activity against MES-induced seizure at the dose of 0.5 mmol/kg. The most active of these compounds were **8** and **19,** which presented 100% protection. The remaining two compounds **9** and **25** exhibited an anti-MES effect by only 50%. Nevertheless, none of all synthesized compounds exhibited any potency towards anti-strychnine activity at the same dose levels.

As a result of preliminary screening, the most active compounds **8**, **9**, **11**, **19**, and **25** were subjected to further investigations at different doses for quantification of their anticonvulsant activity (indicated by ED_{50}) and neurotoxicity (indicated by TD_{50}) in mice (Table 2). The selected compounds **8**, **9**, **11**, **19**, and **25** exhibited anticonvulsant activity against PTZ-induced seizure with ED_{50} values of 0.3, 0.24, 0.22, 0.36, and 0.29 mmol/kg, respectively. Methaqualone and valproate were used as reference drugs, and these compounds produced ED_{50} values of 1.4 and 4.8 mmol/kg, respectively. Interestingly, the ED_{50} values of the selected compounds were found to be smaller

Scheme 3

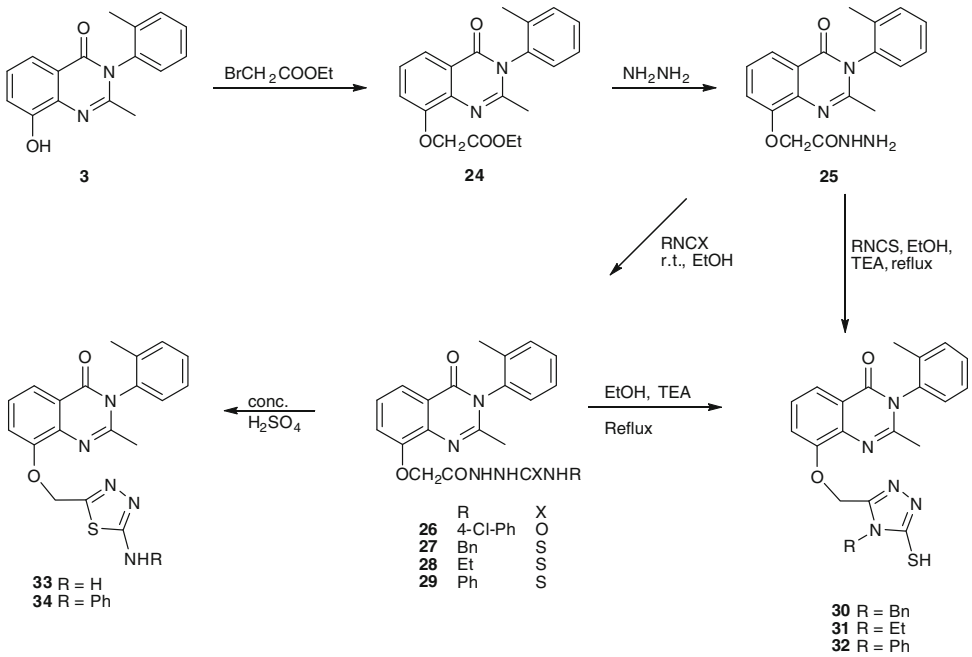


Table 1 Preliminary anticonvulsant activity of the synthesized compounds (0.5 mmol/kg), valproate (1.5 mmol/kg), and methaqualone (1.4 mmol/kg)

Compound	PTZ/% of protection	Strychnine/% of protection	Picrotoxin/% of protection	MES/% of protection
Valproate	100	100	100	100
Methaqualone	100	0	50	100
8	100	0	50	100
9	100	0	0	50
11	100	0	0	50
13	50	0	0	0
15	50	0	0	0
18	50	0	0	0
19	100	0	100	100
25	100	0	0	50
29	50	0	0	0

PTZ pentylenetetrazol, *MES* maximal electroshock test

compared to the reference anticonvulsant drugs at molar doses.

The protective index (ED_{50}/TD_{50}) is considered to be an index representing the margin of safety and tolerability between anticonvulsant doses and doses of anticonvulsant drugs exerting acute adverse effects (e.g., sedation, motor coordination impairment, ataxia, or other neurotoxic manifestations) [27]. Evaluation of the acute adverse effect profile (TD_{50}) of compounds **8**, **9**, **11**, **19**, and **25** revealed that these agents exerted a low neurological deficit (Table 2). The protective index values of the selected compounds were higher than the reference drugs and ranged from 1.2 to 3.9 as compared to 1.14 for methaqualone and 2.0 for valproate. It is obvious that the protective index values for these selected compounds revealed an exceptional difference between the doses producing neurotoxic action (TD_{50}) and those exerting anti-PTZ (ED_{50}) actions in mice. The present results are in agreement with the results of the anticonvulsant study of 2-substituted 3-aryl-4(3*H*)-quinazolinones in mice by Wolfe et al. [28]. Wolfe and colleagues reported that a series of 4(3*H*)-quinazolinones possessing 3-(*o*-tolyl) and 3-(*o*-chlorophenyl) groups showed good protection against MES- and PTZ-induced seizures combined with relatively low neurotoxicity after i.p. administration of 4(3*H*)-quinazolinones in mice.

Compounds **8**, **9**, **11**, **19**, and **25** revealed LD_{50} values of 2.79, 1.97, 2.66, 2.89, and 2.96 with therapeutic index (LD_{50}/ED_{50}) values ranging from 8 to 12.1. It is worthwhile to note that the therapeutic index of the selected

Table 2 Comparison of the anticonvulsant activity (ED_{50}), acute neurotoxic effects (TD_{50}), median lethal dose (LD_{50}), therapeutic and protective indexes of the most promising anticonvulsant synthesized compounds, valproate, and methaqualone in mice

Compound	ED_{50} (mmol kg^{-1})	TD_{50} (mmol kg^{-1})	LD_{50} (mmol kg^{-1})	Therapeutic index	Protective index
Valproate	4.8	9.6	11.9	2.48	2.00
Methaqualone	1.40	1.60	2.00	1.40	1.14
8	0.3	0.97	2.79	9.3	3.2
9	0.24	0.94	1.97	8.2	3.9
11	0.22	0.27	2.66	12.1	1.2
19	0.36	0.89	2.89	8.0	2.4
25	0.29	0.79	2.96	10.2	2.7

ED_{50} median effective dose providing anticonvulsant protection in 50% of mice against pentylenetetrazole (PTZ)-induced seizures, *TD_{50}* median toxic dose producing minimal neurological toxicity in 50% of mice subjected to the chimney test, *LD_{50}* median lethal dose that causes 50% mortality in mice. *Therapeutic index* LD_{50}/ED_{50}, *protective index* TD_{50}/ED_{50}

compounds was found to be much higher as compared to the reference anticonvulsant drugs at molar doses (Table 2). However, compounds **9**, **11**, and **25** showed slight sedative activity 5 min after injection with a duration range from 5 to 15 min at doses close to those required for anticonvulsant activity.

The results of the seizure induction screening methods in the current study showed that several new methaqualone analogues were effective in controlling the seizures induced by PTZ, picrotoxin, and MES, but failed to control those induced by strychnine. This effect is similar to that of 4(3*H*)-quinazolinones, which have anticonvulsant effects on seizures induced by MES and PTZ and are ineffective against strychnine-induced seizures in mice [28]. It has been reported that the convulsants induce seizures by inhibiting γ-aminobutyric acid (GABA) neurotransmission (such as PTZ) and $GABA_A$-antagonist (such as picrotoxin), or directly antagonizes the inhibitory spinal reflexes of glycine (such as strychnine) [29–31]. Generally, in the MES test, one can determine the anti-seizure effects of agents or drugs that suppress tonic-clonic seizures and, to a certain extent, partial convulsions in humans [27]. Because of their partial effectiveness, it is difficult to report that our synthesized compounds had anticonvulsant effects via influencing glycine neurotransmission. However, most of our new compounds can control the seizures induced by PTZ, picrotoxin, and MES. This might suggest that these compounds exhibit a broad spectrum of anticonvulsant activity in animal models of partial and generalized epilepsy via GABA activation. In addition, a more detailed study on the GABA pathways, $GABA_A$ receptors, and the neurotransmitter levels might be interesting and provide more insights for the anticonvulsant effects of these new methaqualone analogues against convulsant-induced seizures, which will be considered extensively in our future study. However, at present several of the newly synthesized methaqualone analogues have relatively potent anticonvulsant effects combined with relatively low neurotoxicity.

In conclusion, new derivatives of 4(3*H*)-quinazolinones were synthesized and evaluated for their anticonvulsant activity in mice. The results of this study demonstrated that 8-substituted-4(3*H*)-quinazolinone derivatives possess a good anticonvulsant activity; especially compounds **8**, **9**, **11**, **19**, and **25** showed better anticonvulsant activity and much lower toxicity than the benchmark marketed drugs valproate and methaqualone. In addition, compounds **8** and **19** demonstrated potent antagonistic activity against seizures induced by PTZ, picrotoxin, and MES, but failed to control those induced by strychnine. These experiments suggested that compounds **8** and **19** possess a broad spectrum of anticonvulsant activity in animal models of partial and generalized epilepsy via GABA activation.

Structure activity relationship

Considering the pharmacological results of all newly synthesized compounds, it can be shown that compounds having phenylsulfonyl, aliphatic alkanoyl, or methyl fragments at position 8 possess a significant anticonvulsant activity, such as compounds **8**, **9**, **11**, and **19**. Presence of a nitro group at the aromatic ring of benzenesulfonyl enhances the activity compared with a methyl group, for example, compounds **9**, **10**, and **11**, which indicated the requirement of a small electron deficient group on the benzenesulfonyl moiety. Moreover, a propionyl moiety at position 8 greatly increases the anticonvulsant activity when compared with the aryl moieties such as compounds **4**–**8**. Compound **25** was more potent as compared to its ester form **24** and cyclized fragments **32** or **34**, which indicated the requirement of a small hydrogen bond-rich group at position 8 of the aromatic ring. The obtained new findings indicate that further investigations of structural

features are required for anticonvulsant activity and probably the pharmacokinetic profile of these compounds.

Experimental

Melting points (corrected) were recorded on a Barnstead 9100 Electrothermal melting apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ on a Bruker 500 MHz instrument using TMS as internal standard (chemical shifts: δ in ppm). Mass spectra were recorded on a Shimadzu PQ-5000 GC-MS apparatus. Solvent evaporation was performed under reduced pressure using a Buchan Rotatory Evaporator unless otherwise stated. TLC was performed on precoated silica gel plates (60-F254, 0.2 mm) manufactured by E.M. Sciences, Inc. (CH_2Cl_2-EtOH 10:1), and shortwave UV (254 nm) was used to detect the UV absorbing compounds.

8-Acetyloxy-2-methyl-3-(2-methylphenyl)-4(3H)-quinazolinone (**2**, $C_{18}H1_6N_2O_3$)

3-Hydroxyanthranilic acid (20 mmol, 3.08 g) was refluxed with 50 cm^3 acetic anhydride for 3 h. The reaction mixture was cooled, filtered, washed with petroleum ether, and dried to yield 8-acetyloxy-2-methyl-4*H*-3,1-benzoxazin-4-one (**1**) as an a gummy compound, which was used in the next step without further purification.

A mixture of 2.19 g benzoxazinone **1** (10 mmol) and 1.18 g *o*-toludine (11 mmol) in 30 cm^3 pyridine was heated under reflux for 8 h. The reaction mixture was cooled, the solvent was removed under reduced pressure, and the residue was triturated with water and filtered. The solid obtained was dried and chromatographed ($CHCl_3$). Yield 93%; m.p.: 130–132 °C; ^{1}H NMR ($CDCl_3$): $\delta = 8.10$ (d, 1H, $J = 7.5$ Hz), 7.68 (d, 1H, $J = 7.5$ Hz), 7.42 (d, 1H, $J = 7.5$ Hz), 7.36–7.25 (m, 3H), 7.07 (d, 1H, $J = 7.0$ Hz), 2.35 (s, 3H), 2.10 (s, 3H), 2.03 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 17.3$, 20.8, 24.3, 122.4, 124.7, 124.9, 125.8, 126.3, 127.2, 129.7, 131.5, 135.4, 136.7, 140.6, 145.9, 154.8, 161.1, 169.4 ppm; MS (70 eV): $m/z = 308$.

8-Hydroxy-2-methyl-3-(2-methylphenyl)-4(3H)-quinazolinone (**3**)

A mixture of 3.08 g 4(3*H*)-quinazolinone **2** (10 mmol) and 1.52 g anhydrous potassium carbonate (11 mmol) in 50 cm^3 methanol was stirred at room temperature for 6 h. The reaction mixture was filtered, the solvent was removed under reduced pressure, and the solid obtained was dried and chromatographed ($CHCl_3$). Yield 70%; m.p.: 162–164 °C, Ref. [32] m.p.: 149.5 °C.

*General procedure for the synthesis of compounds **4–8***

A mixture of 532 mg 8-hydroxymethaqualone (**3**, 2 mmol) and the appropriate benzoyl chloride (2.1 mmol) in 10 cm^3 pyridine was stirred at room temperature for 10–12 h. The solvent was removed under reduced pressure, and the residue was triturated with water and filtered. The solid obtained was dried and recrystallized.

3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yl benzoate (**4**, $C_{23}H_{18}N_2O_3$)

Yield 94%; m.p.: 165–167 °C; ^{1}H NMR ($CDCl_3$): $\delta = 8.21$ (d, 2H, $J = 7.5$ Hz), 8.09 (d, 1H, $J = 8.0$ Hz), 7.82 (d, 1H, $J = 8.0$ Hz), 7.78 (t, 1H, $J = 7.5$ Hz), 7.65–7.58 (m, 3H), 7.46–7.38 (m, 4H), 2.04 (s, 3H), 1.99 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 17.3$, 24.5, 122.3, 124.7, 127.0, 127.9, 128.2, 128.8, 129.3, 129.5, 129.9, 130.4, 131.6, 134.5, 135.5, 137.1, 140.9, 146.2, 155.5, 160.7, 165.0 ppm; MS (70 eV): $m/z = 370$.

3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yl 4-chlorobenzoate (**5**, $C_{23}H_{17}ClN_2O_3$)

Yield 95%; m.p.: 220–222 °C (EtOH); ^{1}H NMR ($CDCl_3$): $\delta = 8.27$–8.08 (m, 3H), 7.61 (d, 1H, $J = 7.5$ Hz), 7.55–7.37 (m, 6H), 7.15 (d, 1H, $J = 7.5$ Hz), 2.14 (s, 3H), 2.11 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 17.4$, 24.3, 122.5, 125.1, 126.4, 127.1, 127.7, 129.0, 129.4, 131.6, 131.8, 135.4, 136.7, 140.2, 141.4, 146.0, 154.9, 161.1, 164.4 ppm; MS (70 eV): $m/z = 404$, 406 (M + 2).

3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yl 4-methylbenzoate (**6**, $C_{24}H_{20}N_2O_3$)

Yield 95%; m.p.: 192–194 °C (EtOH); ^{1}H NMR ($CDCl_3$): $\delta = 8.25$–8.22 (m, 3H), 7.64 (d, 1H, $J = 7.5$ Hz), 7.52 (t, 1H, $J = 7.5$ Hz), 7.43–7.28 (m, 5H), 7.15 (d, 1H, $J = 7.5$ Hz), 2.49 (s, 3H), 2.15 (s, 3H), 2.11 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 17.4$, 21.8, 24.3, 120.7, 124.9, 126.4, 126.7, 127.4, 127.6, 127.9, 129.3, 129.6, 130.5, 131.5, 135.4, 136.8, 141.0, 144.5, 146.3, 154.7, 161.2, 165.3 ppm; MS (70 eV): $m/z = 384$.

3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yl thiophene-2-carboxylate

(**7**, $C_{21}H_{16}N_2O_3S$)

Yield 94%; m.p.: 184–186 °C (EtOH); ^{1}H NMR ($CDCl_3$): $\delta = 8.24$ (d, 1H, $J = 7.5$ Hz), 8.10 (d, 1H, $J = 3.5$ Hz), 7.71 (d, 1H, $J = 5.0$ Hz), 7.65 (d, 1H, $J = 8.0$ Hz), 7.50 (t, 1H, $J = 8.0$ Hz), 7.40–7.36 (m, 3H), 7.22 (t, 1H, $J = 8.5$ Hz), 7.15 (d, 1H, $J = 7.0$ Hz), 2.14 (s, 3H), 2.13 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 17.4$, 24.3, 122.4, 125.1, 126.4, 127.4, 127.7, 127.9, 128.1, 129.6, 131.9, 132.6, 133.7, 135.0, 135.4, 136.8, 141.0, 145.8, 154.9, 160.5, 161.1 ppm; MS (70 eV): $m/z = 376$.

3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yl propanoate (**8**, $C_{19}H_{18}N_2O_3$)
Yield 88%; m.p.: 98–100 °C (EtOH); ^{1}H NMR ($CDCl_3$): $\delta = 8.17$ (d, 1H, $J = 7.5$ Hz), 7.50–7.35 (m, 5H), 7.14 (d, 1H, $J = 7.0$ Hz), 2.76 (q, 2H, $J = 7.5$ Hz), 2.16 (s, 3H), 2.12 (s, 3H), 1.36 (t, 3H, $J = 7.5$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 9.3$, 17.4, 24.3, 27.5, 122.3, 124.7, 126.3, 127.2, 127.7, 127.9, 129.6, 131.5, 135.3, 136.7, 140.7, 146.1, 154.7, 161.1, 173.0 ppm; MS (70 eV): $m/z = 325$ (M + 3).

*General procedure for the synthesis of compounds **9–12***

A mixture of 532 mg 8-hydroxymethaqualone (**3**, 2 mmol) and the appropriate benzenesulfonyl chloride (2.1 mmol) in 15 cm^3 pyridine was stirred at room temperature for 10–12 h. The solvent was removed under reduced pressure, and the residue was triturated with water and filtered. The solid obtained was dried and recrystallized.

3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yl benzenesulfonate (**9**, $C_{22}H_{18}N_2O_4S$)
Yield 91%; m.p.: 165–167 °C (EtOH); ^{1}H NMR ($CDCl_3$): $\delta = 8.19$ (d, 1H, $J = 7.0$ Hz), 7.97 (d, 2H, $J = 7.0$ Hz), 7.72–7.62 (m, 2H), 7.51–7.27 (m, 6H), 7.07 (d, 1H, $J = 7.0$ Hz), 2.00 (s, 3H), 1.96 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 17.20$, 23.8, 122.5, 126.2, 126.3, 127.7, 127.8, 128.7, 128.8, 129.0, 129.7, 131.6, 134.0, 135.1, 136.3, 136.4, 141.1, 143.9, 155.0, 160.6 ppm; MS (70 eV): $m/z = 405$ (M − 1).

3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yl 4-methylbenzenesulfonate (**10**, $C_{23}H_{20}N_2O_4S$)
Yield 93%; m.p.: 182–184 °C (EtOH); ^{1}H NMR ($CDCl_3$): $\delta = 8.19$ (d, 1H, $J = 8.0$ Hz), 7.85 (d, 2H, $J = 8.0$ Hz), 7.69 (d, 1H, $J = 8.0$ Hz), 7.46–7.37 (m, 4H), 7.29 (d, 2H, $J = 8.0$ Hz), 7.08 (d, 1H, $J = 7.5$ Hz), 2.43 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 17.1$, 21.7, 23.8, 100.0, 122.5, 126.1, 126.3, 127.7, 128.7, 129.0, 129.3, 129.7, 131.6, 133.2, 135.1, 136.4, 141.2, 144.0, 145.1, 154.8, 160.7 ppm; MS (70 eV): $m/z = 419$ (M − 1).

3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yl 4-nitrobenzenesulfonate (**11**, $C_{22}H_{17}N_3O_6S$)
Yield 93%; m.p.: 142–144 °C (EtOH); ^{1}H NMR ($CDCl_3$): $\delta = 8.33$ (d, 2H, $J = 8.5$ Hz), 8.21 (d, 3H, $J = 8.5$ Hz), 7.74 (d, 1H, $J = 7.5$ Hz), 7.48 (t, 1H, $J = 8.0$ Hz), 7.41–7.34 (m, 3H), 7.06 (d, 1H, $J = 7.5$ Hz), 1.99 (s, 3H), 1.91 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 17.1$, 23.7, 122.7, 123.7, 126.5, 126.7, 127.7, 127.8, 128.8, 129.8, 130.6, 131.6, 135.0, 136.2, 140.8, 141.9, 143.5, 151.0, 155.4, 160.4 ppm; MS (70 eV): $m/z = 451$.

3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yl 4-bromobenzenesulfonate (**12**, $C_{22}H_{17}BrN_2O_4S$)
Yield 93%; m.p.: 178–180 °C (EtOH); ^{1}H NMR ($CDCl_3$): $\delta = 8.21$ (d, 1H, $J = 8.0$ Hz), 7.80–7.75 (m, 3H), 7.62 (d, 2H, $J = 9.0$ Hz), 7.48–7.36 (m, 4H), 7.10 (d, 1H, $J = 6.5$ Hz), 2.05 (s, 3H), 1.95 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 17.2$, 23.7, 122.5, 126.4, 127.7, 129.1, 129.3, 129.8, 130.6, 131.6, 132.0, 135.0, 135.1, 136.3, 140.9, 143.6, 155.0, 160.5 ppm; MS (70 eV): $m/z = 484$, 486 (M + 2).

*General procedure for the synthesis of compounds **13–17***

A mixture of 532 mg 8-hydroxymethaqualone (**3**, 2 mmol) and the appropriate chloroacetanilide (2.1 mmol) in 15 cm^3 acetone containing 415 mg anhydrous potassium carbonate (3 mmol) was heated under reflux for 10–12 h. The reaction mixture was filtered while hot, the solvent was removed under reduced pressure, and the solid obtained was dried and recrystallized.

2-[3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]acetamide (**13**, $C_{18}H_{17}N_3O_3$)
Yield 94%; m.p.: 119–121 °C (EtOH); ^{1}H NMR ($CDCl_3$): $\delta = 8.02$ (s, 1H), 7.90 (d, 1H, $J = 8.0$ Hz), 7.44–7.38 (m, 4H), 7.30 (t, 1H, $J = 7.5$ Hz), 7.16 (d, 1H, $J = 7.5$ Hz), 6.39 (s, 1H), 4.72 (s, 2H), 2.21 (s, 3H), 2.12 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 17.3$, 24.0, 70.1, 119.2, 120.9, 122.2, 127.0, 127.7, 127.8, 129.8, 131.6, 135.5, 136.5, 138.9, 152.7, 154.5, 161.1, 171.6 ppm; MS (70 eV): $m/z = 323$.

2-[3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]-N-phenylacetamide (**14**, $C_{24}H_{21}N_3O_3$)
Yield 93%; yellow oil; ^{1}H NMR ($CDCl_3$): $\delta = 9.74$ (s, 1H, exchangeable), 7.95 (d, 1H, $J = 7.0$ Hz), 7.61–7.38 (m, 7H), 7.03–6.89 (m, 3H), 4.81 (s, 2H), 2.23 (s, 3H), 2.15 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 17.3$, 24.3, 70.1, 115.5, 115.7, 120.1, 121.5, 122.3, 126.6, 127.8, 129.8, 131.8, 133.7, 135.1, 136.5, 139.1, 152.5, 154.8, 158.6, 160.3, 161.0, 165.8 ppm; MS (70 eV): $m/z = 398$ (M − 1).

2-[3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]-N-(4-fluorophenyl)acetamide (**15**, $C_{24}H_{20}FN_3O_3$)
Yield 92%; m.p.: 157–159 °C (EtOH); ^{1}H NMR ($CDCl_3$): $\delta = 9.91$ (s, 1H, exchangeable), 8.01 (d, 1H, $J = 7.0$ Hz), 7.61–7.38 (m, 7H), 7.17 (d, 1H, $J = 7.5$ Hz), 7.04–7.00 (m, 2H), 4.85 (s, 2H), 2.25 (s, 3H), 2.13 (s, 3H) ppm; ^{13}C

NMR ($CDCl_3$): δ = 17.3, 24.2, 71.1, 115.4, 115.7, 120.3, 121.5, 122.3, 126.9, 127.8, 129.8, 131.7, 133.4, 135.2, 136.5, 139.1, 152.8, 154.8, 158.6, 160.6, 161.0, 166.8 ppm; MS (70 eV): m/z = 416 (M − 1).

2-[3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]-N-(4-ethoxyphenyl)acetamide (**16**, $C_{26}H_{25}N_3O_4$)
Yield 96%; m.p.: 126–128 °C (EtOH); ^{1}H NMR ($CDCl_3$): δ = 9.84 (s, 1H, exchangeable), 8.00 (d, 1H, J = 7.5 Hz), 7.52 (d, 2H, J = 8.5 Hz), 7.46-7.37 (m, 5H), 7.16 (d, 1H, J = 7.5 Hz), 6.86 (d, 2H, J = 8.5 Hz), 4.83 (s, 2H), 4.01 (q, 2H, J = 7.0 Hz), 2.23 (s, 3H), 2.12 (s, 3H), 1.39 (t, 3H, J = 7.0 Hz) ppm; ^{13}C NMR ($CDCl_3$): δ = 14.8, 17.6, 24.1, 63.7, 71.1, 114.8, 120.1, 121.2, 122.2, 122.3, 127.1, 127.7, 127.8, 129.8, 130.4, 131.6, 135.2, 136.6, 139.1, 152.9, 154.7, 156.1, 161.0, 166.5 ppm; MS (70 eV): m/z = 443.

2-[3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]-N-(4-methylphenyl)acetamide (**17**, $C_{25}H_{23}N_3O_3$)
Yield 95%; m.p.: 174–176 °C (EtOH); ^{1}H NMR ($CDCl_3$): δ = 9.71 (s, 1H, exchangeable), 8.01 (d, 1H, J = 7.0 Hz), 7.51–7.40 (m, 7H), 7.19–7.14 (m, 3H), 4.86 (s, 2H), 2.33 (s, 3H), 2.26 (s, 3H), 2.14 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): δ = 17.4, 20.9, 24.3, 71.3, 120.2, 120.5, 121.4, 122.3, 127.0, 127.8, 127.9, 129.5, 129.8, 130.4, 131.6, 134.4, 134.8, 135.2, 136.6, 139.3, 153.0, 154.7, 161.0, 166.7 ppm; MS (70 eV): m/z = 413 (M − 1).

2-[3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]-N-(3,4,5-trimethoxyphenyl)-acetamide (**18**, $C_{27}H_{27}N_3O_6$)
Yield 92%; m.p.: 112–114 °C (EtOH); ^{1}H NMR ($CDCl_3$): δ = 9.69 (s, 1H, exchangeable), 7.92 (d, 1H, J = 7.5 Hz), 7.39–7.28 (m, 5H), 7.10 (d, 1H, J = 7.5 Hz), 6.91 (s, 2H), 4.76 (s, 2H), 3.77 (s, 9H), 2.18 (s, 3H), 2.06 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): δ = 17.3, 24.2, 54.0, 56.2, 60.9, 70.9, 120.0, 121.1, 122.2, 126.5, 127.0, 129.8, 130.4, 131.6, 133.2, 133.4, 135.1, 135.2, 136.5, 139.0, 152.7, 153.3, 154.5, 161.0, 164.0, 166.6 ppm; MS (70 eV): m/z = 491 (M + 2).

General procedure for the synthesis of compounds ***19–23***

A mixture of 532 mg 8-hydroxymethaqualone (**3**, 2 mmol) and the appropriate alkyl halides, aryl halides, or chloroacetonitrile (2.1 mmol) in 15 cm^3 acetone containing 415 mg anhydrous potassium carbonate (3 mmol) was heated under reflux for 10–12 h. The reaction mixture was filtered while hot, the solvent was removed under reduced pressure, and the solid obtained was dried and recrystallized.

2-Methyl-3-(2-methylphenyl)-8-methoxy-4(3H)-quinazolinone (**19**)
Yield 90%; m.p.: 166–168 °C (AcOH), Ref. [33] m.p.: 166–167 °C.

8-Ethoxy-2-methyl-3-(2-methylphenyl)-4(3H)-quinazolinone (**20**, $C_{18}H_{18}N_2O_2$)
Yield 92%; m.p.: 148–150 °C (AcOH); ^{1}H NMR (DMSO-d_6): δ = 7.64 (d, 1H, J = 7.5 Hz), 7.44-7.33 (m, 6H), 4.18 (q, 2H, J = 7.0 Hz), 2.07 (s, 3H), 2.00 (s, 3H), 1.41 (t, 3H, J = 7.0 Hz) ppm; ^{13}C NMR (DMSO-d_6): δ = 15.1, 17.3, 24.0, 64.7, 116.7, 117.7, 121.9, 127.3, 128.8, 129.7, 131.5, 135.4, 137.4, 138.5, 153.1, 153.8, 161.1 ppm; MS (70 eV): m/z = 294.

2-[3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]acetonitrile (**21**, $C_{18}H_{15}N_3O_2$)
Yield 88%; m.p.: 216–218 °C (AcOH); ^{1}H NMR (DMSO-d_6): δ = 7.81–7.37 (m, 7H), 5.38 (s, 2H), 2.08 (s, 3H), 2.01 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6): δ = 17.3, 24.1, 55.4, 117.0, 119.0, 120.6, 122.4, 127.0, 127.9, 128.8, 129.8, 131.5, 135.5, 137.2, 139.0, 151.5, 154.4, 160.8 ppm; MS (70 eV): m/z = 305.

8-Benzyloxy-2-methyl-3-(2-methylphenyl)-4(3H)-quinazolinone (**22**, $C_{23}H_{20}N_2O_2$)
Yield 86%; m.p.: 176–178 °C (AcOH); ^{1}H NMR ($CDCl_3$): δ = 7.89 (d, 1H, J = 8.0 Hz), 7.53 (d, 2H, J = 7.0 Hz), 7.41–7.31 (m, 7H), 7.22 (d, 1H, J = 8.0 Hz), 7.17 (d, 1H, J = 7.5 Hz), 5.40 (s, 2H), 2.27 (s, 3H), 2.15 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): δ = 17.4, 24.3, 71.3, 117.1, 119.0, 122.1, 126.6, 127.0, 127.6, 127.9, 128.0, 128.6, 129.5, 131.5, 135.3, 136.8, 137.0, 138.8, 153.3, 153.6, 161.5 ppm; MS (70 eV): m/z = 356.

2-Methyl-3-(2-methylphenyl)-8-(4-nitrobenzyloxy)-4(3H)-quinazolinone (**23**, $C_{23}H_{19}N_3O_4$)
Yield 80%; m.p.: 140–142 °C (AcOH); ^{1}H NMR ($CDCl_3$): δ = 8.25 (d, 2H, J = 8.5 Hz), 7.91 (d, 1H, J = 8.0 Hz), 7.71 (d, 2H, J = 8.0 Hz), 7.41–7.32 (m, 4H), 7.17 (d, 2H, J = 7.5 Hz), 5.47 (s, 2H), 2.26 (s, 3H), 2.14 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): δ = 17.4, 24.3, 70.2, 117.2, 119.8, 122.3, 123.9, 126.6, 127.5, 127.7, 127.8, 129.6, 131.6, 135.3, 136.8, 138.9, 144.3, 147.6, 152.6, 154.0, 161.3 ppm; MS (70 eV): m/z = 401.

Ethyl 2-[3,4-dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]acetate (**24**, $C_{20}H_{20}N_2O_4$)
A mixture of 2.66 g 8-hydroxymethaqualone (**3**, 10 mmol), 1.84 g ethyl bromoacetate (11 mmol), and 1.66 g anhydrous potassium carbonate (12 mmol) in 100 cm^3 dry acetone was stirred at room temperature for 6 h. The reaction mixture was filtered, the solvent was removed

under reduced pressure, and the solid obtained was dried and recrystallized from ethanol. Yield 80%; m.p.: 100–102 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.84$ (d, 1H, $J = 7.0$ Hz), 7.32–7.26 (m, 4H), 7.09 (d, 3H, $J = 7.0$ Hz), 4.85 (s, 2H), 4.20 (q, 2H, $J = 7.5$ Hz), 2.16 (s, 3H), 2.04 (s, 3H), 1.21 (t, 3H, $J = 7.5$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.0$, 17.2, 24.7, 61.0, 66.7, 119.9, 120.1, 122.0, 126.4, 127.4, 127.9, 129.5, 131.4, 135.2, 136.8, 138.3, 150.8, 153.7, 161.2, 169.0 ppm; MS (70 eV): $m/z = 352$.

2-[3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]acetic acid hydrazide
(**25**, $C_{18}H_{18}N_4O_3$)
A mixture of 3.52 g ester **3** (10 mmol) and 750 mg hydrazine hydrate (15 mmol) in 50 cm^3 absolute ethanol was stirred at room temperature for 8 h. The reaction mixture was filtered and dried. Yield 90%; m.p.: 116–118 °C; ^{1}H NMR ($CDCl_3$): $\delta = 9.88$ (s, 1H, exchangeable), 7.98 (d, 1H, $J = 7.5$ Hz), 7.44–7.32 (m, 4H), 7.33 (d, 1H, $J = 7.5$ Hz), 7.16 (d, 1H, $J = 7.5$ Hz), 4.79 (s, 2H), 3.97 (s, 1H, exchangeable), 2.62 (s, 1H, exchangeable), 2.26 (s, 3H), 2.13 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 17.3$, 24.0, 71.0, 120.5, 121.4, 122.2, 127.0, 127.7, 127.8, 129.8, 131.6, 135.2, 136.5, 139.2, 153.0, 154.9, 161.0, 168.8 ppm; MS (70 eV): $m/z = 338$.

2-[3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]acetic acid 2-[(4-chlorophenyl)aminocarbonyl]hydrazide
(**26**, $C_{25}H_{22}ClN_5O_4$)
A mixture of 676 mg acid hydrazide **25** (2.0 mmol) and 323 mg *p*-chlorophenylisocyanate (2.0 mmol) in 20 cm^3 absolute ethanol containing 405 mg TEA (4 mmol) was refluxed for 10 h. The reaction mixture was allowed to cool, the solvent was removed under reduced pressure, and the solid obtained was dried and recrystallized from acetic acid. Yield 88%; m.p.: 134–136 °C; ^{1}H NMR (DMSO-d_6): $\delta = 10.38$ (s, 1H, exchangeable), 8.98 (s, 1H, exchangeable), 8.27 (s, 1H, exchangeable), 7.86 (m, 1H), 7.50–7.29 (m, 10H), 4.87 (s, 2H), 2.10 (s, 3H), 2.02 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 17.2$, 24.0, 68.9, 119.4, 119.5, 119.6, 120.6, 122.0, 126.1, 127.3, 127.9, 128.7, 128.9, 129.8, 131.6, 135.4, 137.2, 138.9, 139.0, 153.4, 154.1, 155.6, 161.0, 167.3, 168.3 ppm; MS (70 eV): $m/z = 491$.

General procedure for the synthesis of compounds ***27–29***

A mixture of 676 mg acid hydrazide **25** (2.0 mmol) and appropriate isothiocyanate (2.0 mmol) in 20 cm^3 absolute ethanol was stirred at room temperature for 9–12 h. The solvent was removed under reduced pressure, and the solid obtained was dried and recrystallized.

2-[3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]acetic acid 2-[(benzylamino)thioxomethyl]hydrazide
(**27**, $C_{26}H_{25}N_5O_3S$)
Yield 88%; m.p.: 127–129 °C (AcOH); ^{1}H NMR (DMSO-d_6): $\delta = 10.38$ (s, 1H, exchangeable), 9.46 (s, 1H, exchangeable), 8.64 (s, 1H, exchangeable), 7.74 (d, 1H, $J = 7.0$ Hz), 7.46-7.22 (m, 11H), 4.86 (s, 2H), 4.76 (s, 2H), 2.09 (s, 3H), 2.02 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 17.3$, 24.0, 47.2, 68.6, 119.4, 122.0, 126.9, 127.1, 127.2, 127.4, 128.5, 128.8, 129.3, 129.8, 131.6, 135.5, 137.2, 138.9, 139.6, 153.5, 153.9, 161.0, 168.2, 182.8 ppm; MS (70 eV): $m/z = 487$.

2-[3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]acetic acid 2-[(ethylamino)thioxomethyl]hydrazide
(**28**, $C_{21}H_{23}N_5O_3S$)
Yield 84%; m.p.: 122–124 °C (AcOH); ^{1}H NMR (DMSO-d_6): $\delta = 10.25$ (s, 1H, exchangeable), 9.24 (s, 1H, exchangeable), 8.06 (s, 1H, exchangeable), 7.75–7.35 (m, 7H), 4.84 (s, 2H), 3.47 (q, 2H, $J = 7.0$ Hz), 2.09 (s, 3H), 2.03 (s, 3H), 1.05 (t, 3H, $J = 7.0$ Hz) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 14.9$, 17.3, 24.0, 39.0, 68.6, 119.3, 122.0, 127.2, 137.3, 127.9, 128.8, 129.8, 131.6, 135.5, 137.2, 138.9, 135.5, 153.8, 161.0, 167.3, 181.9 ppm; MS (70 eV): $m/z = 426$ (M + 1).

2-[3,4-Dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy]acetic acid 2-[(phenylamino)thioxomethyl]hydrazide
(**29**, $C_{25}H_{23}N_5O_3S$)
Yield 90%; m.p.: 150–152 °C (AcOH); ^{1}H NMR (DMSO-d_6): $\delta = 10.53$ (s, 1H, exchangeable), 9.72 (s, 1H, exchangeable), 7.76 (d, 1H, $J = 7.5$ Hz), 7.52–7.35 (m, 10H), 7.18 (d, 1H, $J = 6.5$ Hz), 4.90 (s, 2H), 3.46 (s, 1H, exchangeable), 2.10 (s, 3H), 2.02 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 17.3$, 24.0, 68.8, 119.5, 122.1, 125.6, 126.9, 127.2, 127.9, 128.6, 129.8, 131.6, 135.5, 137.2, 138.9, 139.5, 153.6, 153.9, 161.0, 168.0, 181.6 ppm; MS (70 eV): $m/z = 472$ (M − 1).

General procedures for the synthesis of compounds ***30–32***

Method A: A mixture of 676 mg acid hydrazide **25** (2.0 mmol) and appropriate isothiocyanate (2.0 mmol) in 20 cm^3 absolute ethanol containing 405 mg TEA (4 mmol) was refluxed for 10–12 h. The reaction mixture was allowed to cool, the solvent was removed under reduced pressure, and the solid obtained was dried and recrystallized.

Method B: *N*-Substituted hydrazinecarbothioamide **27–29** (1.0 mmol) was refluxed in 20 cm^3 absolute ethanol

in the presence of 203 mg TEA (1.5 mmol) for 6–8 h. The reaction mixture was allowed to cool, the solvent was removed under reduced pressure, and the solid obtained was dried and recrystallized.

8-[(4-Benzyl-5-mercapto-4H-1,2,4-triazol-3-yl)methoxy]-2-methyl-3-(2-methylphenyl)-4(3H)-quinazolinone (**30**, $C_{26}H_{23}N_5O_2S$)
Yield 86%; m.p.: 258-260 °C (AcOH); ^{1}H NMR (DMSO-d_6): $\delta = 14.04$ (s, 1H, exchangeable), 7.75 (d, 1H, $J = 5.5$ Hz), 7.54–7.27 (m, 11H), 5.46 (s, 2H), 5.24 (s, 2H), 2.06 (s, 3H), 2.03 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 17.3$, 24.2, 46.8, 63.2, 119.3, 122.2, 123.5, 127.1, 127.8, 127.9, 128.1, 128.8, 129.0, 129.8, 131.5, 136.8, 138.1, 140.2, 148.4, 154.0, 160.9, 169.4, 201.2 ppm; MS (70 eV): $m/z = 471$ (M + 2).

8-[(4-Ethyl-5-mercapto-4H-1,2,4-triazol-3-yl)methoxy]-2-methyl-3-(2-methylphenyl)-4(3H)-quinazolinone (**31**, $C_{21}H_{21}N_5O_2S$)
Yield 85%; m.p.: 269–271 °C (AcOH); ^{1}H NMR (DMSO-d_6): $\delta = 13.86$ (s, 1H, exchangeable), 7.76 (d, 1H, $J = 6.5$ Hz), 7.61 (d, 1H, $J = 6.5$ Hz), 7.48–7.36 (m, 5H), 5.40 (s, 2H), 4.16 (q, 2H, $J = 6.5$ Hz), 2.05 (s, 3H), 2.01 (s, 3H), 1.40 (t, 3H, $J = 6.5$ Hz) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 13.7$, 17.3, 24.0, 39.0, 62.1, 119.1, 119.8, 122.1, 127.1, 127.9, 128.8, 129.8, 131.5, 135.4, 137.2, 139.1, 148.3, 152.5, 153.9, 161.0, 167.8 ppm; MS (70 eV): $m/z = 407$.

2-Methyl-3-(2-methylphenyl)-8-[(4-phenyl-5-mercapto-4H-1,2,4-triazol-3-yl)methoxy]-4(3H)-quinazolinone (**32**, $C_{25}H_{21}N_5O_2S$)
Yield 88%; m.p.: 147–149 °C (AcOH); ^{1}H NMR ($CDCl_3$): $\delta = 11.33$ (s, 1H, exchangeable), 8.00 (d, 1H, $J = 8.0$ Hz), 7.41–7.11 (m, 11H), 4.82 (s, 2H), 2.26 (s, 3H), 2.09 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 17.4$, 23.9, 71.4, 121.4, 121.9, 122.2, 124.4, 126.2, 127.1, 127.7, 127.8, 129.0, 129.8, 131.6, 135.3, 136.4, 137.6, 139.3, 152.9, 155.3, 161.0, 168.2, 180.8 ppm; MS (70 eV): $m/z = 456$ (M + 1).

*General procedure for the synthesis of compounds **33** and **34***

A mixture of carbothioamide **27** or **29** (2 mmol) and 5 cm^3 conc. H_2SO_4 was stirred at room temperature for 12 h. The reaction mixture was neutralized with $KHCO_3$, filtered, washed with water, dried, and recrystallized.

8-[(5-Amino-1,3,4-thiadiazol-2-yl)methoxy]-2-methyl-3-(2-methylphenyl)-4(3H)-quinazolinone (**33**, $C_{19}H_{17}N_5O_2S$)
Yield 62%; m.p.: 244–246 °C (AcOH); ^{1}H NMR (DMSO-d_6): $\delta = 7.73$ (d, 1H, $J = 7.5$ Hz), 7.56 (d, 1H, $J = 7.5$ Hz), 7.44–7.32 (m, 5H), 5.49 (s, 2H), 3.38 (s, 2H, exchangeable), 2.09 (s, 3H), 2.03 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 17.3$, 24.1, 66.1, 118.8, 119.3, 122.2, 127.1, 127.9, 128.8, 129.8, 131.5, 135.5, 137.3, 139.0, 152.8, 153.8, 154.4, 161.0, 170.5 ppm; MS (70 eV): $m/z = 381$ (M + 2).

2-Methyl-3-(2-methylphenyl)-8-[(5-phenylamino-1,3,4-thiadiazol-2-yl)methoxy]-4(3H)-quinazolinone (**34**, $C_{25}H_{21}N_5O_2S$)
Yield 68%; m.p.: 292–294 °C (AcOH); ^{1}H NMR (DMSO-d_6): $\delta = 10.51$ (s, 1H, exchangeable), 7.77–7.12 (m, 12H), 5.61 (s, 2H), 2.11 (s, 3H), 2.03 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 17.3$, 24.1, 66.3, 116.9, 119.3, 119.6, 122.2, 127.1, 127.8, 128.8, 129.8, 131.5, 135.5, 137.3, 139.1, 141.0, 142.6, 152.8, 153.8, 153.9, 156.3, 161.0, 165.9 ppm; MS (70 eV): $m/z = 455$.

Pharmacology

Animals and treatment

Adult male white Swiss albino mice weighing 20–25 g (10–12 weeks old) were obtained from the Experimental Animal Care Center, College of Pharmacy, King Saud University. The animals were maintained under standard conditions of humidity, temperature (25 ± 2 °C), and light (12 h light/12 h dark). They were fed with a standard mice pellet diet and had free access to water. All animal experimentation described in the article was conducted in accord with accepted standards of humane animal care in accordance with the King Saud University guidelines and the legal requirements in the Kingdom of Saudi Arabia. Each treatment group and vehicle control group consisted of ten animals.

Anticonvulsant activity

The anticonvulsant activity of all synthesized compounds was evaluated by four models, namely pentylentetrazole (PTZ), picrotoxin, strychnine, and maximal electroshock (MES) models [26]. The test compounds were dissolved in 10% DMSO and injected intraperitoneally (i.p.) at a dose of 0.5 mmol/kg 30 min before seizure induction. Sodium valproate (1.5 mmol/kg) and methaqualone (1.4 mmol/kg) were used as reference drugs [34, 35]. In the MES test, seizures were elicited with a 75-Hz alternating current of 99 mA intensity in mice. The current was applied via ear electrodes for 2 s. Protection against the spread of MES-induced seizures was defined as the abolition of the hind leg and tonic maximal extension component of the seizure [36]. The PTZ test was carried out by the i.p. injection of a convulsant dose of PTZ (100 mg/kg). Seizures and tonic-clonic convulsions, hypnosis, and death were recorded. As with PTZ, the chemo-convulsants picrotoxin and strychnine were administered i.p. to mice in a dose eliciting convulsions in 100% of control mice. The doses needed

were 8 and 1.5 mg/kg, respectively. With picrotoxin, suppression of clonic-tonic episodes and death were used as the endpoints. With strychnine, animals not experiencing any tonic seizure components were counted as being protected. Five of the most promising compounds (**8**, **9**, **11**, **19**, and **25**) at different doses were further evaluated in the PTZ model to determine their protective and therapeutic indexes. Groups of ten mice each were given a range of i.p. doses of the selected drug until at least four points were established in the range of 10–90% seizure protection or minimal observed neurotoxicity. From the plots of these data, the respective ED_{50} and TD_{50} values, slopes of the regression line, and the standard error were calculated using a computer program based on the method described by Finney [37]. The dose of tested compounds that prevented 50% of the treated animals from PTZ-induced clonic convulsion was calculated (ED_{50}). Observation time with all convulsants was 60 min for convulsions and death. The animals that showed no convulsion within 1 h after convulsive drug administration were considered to be protected [38].

Neurological toxicity

The acute neurotoxicity of the selected compounds was evaluated in mice using the chimney test [39]. Here, motor impairment was indicated by the inability of the mice to climb backward up the tube within 30 s. Tested animals were given an i.p. injection of the selected compounds in various doses 30 min before the test. The neurotoxic effects of the tested compounds were expressed as their median toxic doses (TD_{50} values), representing the doses at which the investigated compounds impaired motor coordination in 50% of the animals.

Protective and therapeutic indexes

The protective index for the selected compounds was calculated by dividing the TD_{50} value, as determined in the chimney test, by the respective ED_{50} value, as determined in the PTZ test. The protective index is considered to be an index representing the margin of safety and tolerability between ED_{50} and TD_{50} [27]. The median lethal dose (LD_{50}), the dose of the selected compounds that causes 50% mortality in mice, was determined from dose-response curves with at least four doses by the method of Litchfield and Wilcoxon [40]. The therapeutic index, the ratio of the dose producing toxicity in 50% of animals to the dose needed to produce the desired 50% therapeutic response, was then calculated.

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