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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Novel 4(3*H*)-quinazolinone analogs: synthesis and anticonvulsant activity

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Abstract A new series of quinazoline analogs was designed, synthesized, and evaluated for their anticonvulsant activity. Compounds **6**, **12**, **21**, **36**, **37**, and **38** showed 70–100 % protection against PTZ-induced seizures acting as $GABA_A$ receptor agonists. Compound *N*-(3,4,5,6-tetrachlorophthalimido)-2-[(3-phenyl-4-oxo-6-methyl-3*H*-quinazolin-2-yl)-thio]acetamide (**12**) representing the moderate active compounds and 2-[6-iodo-4-oxo-2-(thiophen-2-yl)-quinazolin-3(4*H*)-yl]-isoindoline-1,3-dione (**38**) representing the remarkably active compounds in this stud, showed ED_{50} values of 457 and 251 mg/kg; TD_{50} values of 562 and 447 mg/kg; PI values of 1.22 and 1.78, LD_{50} values of 1,288 and 1,380 mg/kg, and TI values of 2.82 and 5.50, respectively. Compound **38** proved to be almost twofold more active than the standard drug sodium valproate.

Keywords Synthesis · 4(3*H*)-Quinazolinones · Anticonvulsant activity

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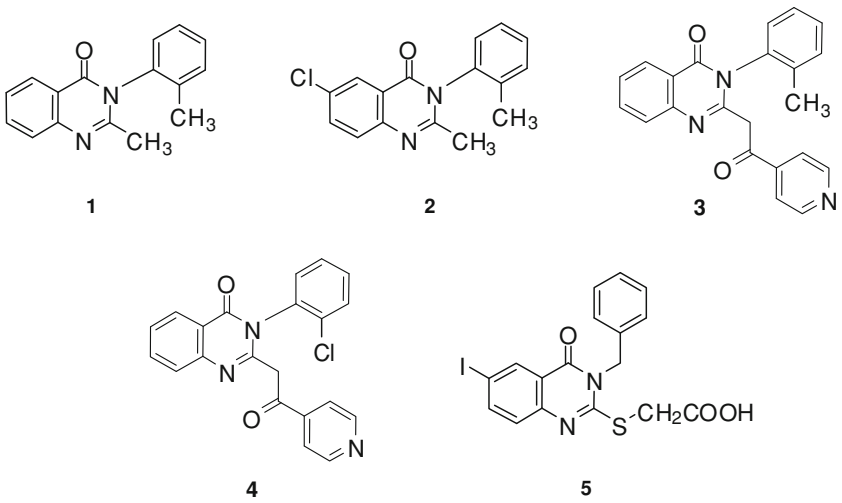
Introduction

Methaqualone (**1**) as a quinazoline analog is an important landmark in the field of synthetic anticonvulsants; its 6-chloro analog (**2**) found to possess marked anticonvulsant potency, which is 1.5 times more potent than phenytoin sodium against electroshock-induced convulsions and 10 times more active than troxidone against pentylenetetrazol (PTZ)-induced seizures (Armarego, 1963; Bhaduri *et al*., 1964; Salimath *et al*., 1956), Chart 1. In spite of the fact that literally hundreds of quinazolinones related to compound **1** have been synthesized and tested for their anticonvulsant activity, none of those drugs are currently in use. A persistent problem with those compounds arises from the fact that nearly every derivative tested exhibited neurotoxicity values (TD_{50}'s) which are less or slightly higher than the effective doses (ED_{50}'s), (Barthwal *et al*., 1973). Consequently, the protective index (PI) corresponding to TD_{50}/ED_{50} is too low. The discovery of 3-tolyl-4(3*H*)-quinazolinones, which possessed an adequate separation between the anticonvulsant and the sedative properties, inspired the synthesis of a series of 2-[2-oxo-2-(4-pyridyl)-ethyl]-3-aryl-4(3*H*)-quinazolinones (**3**, **4**) with a single *ortho* substituent. Compounds **3** and **4** showed remarkable protection against maximal electroshock and subcutaneous metrazol-induced seizures, Chart 1 (Wolfe *et al*., 1990).

The present study is a continuation to the previous efforts aiming to locate novel synthetic anticonvulsant lead

Chart 1 Structures of literature cited anticonvulsants



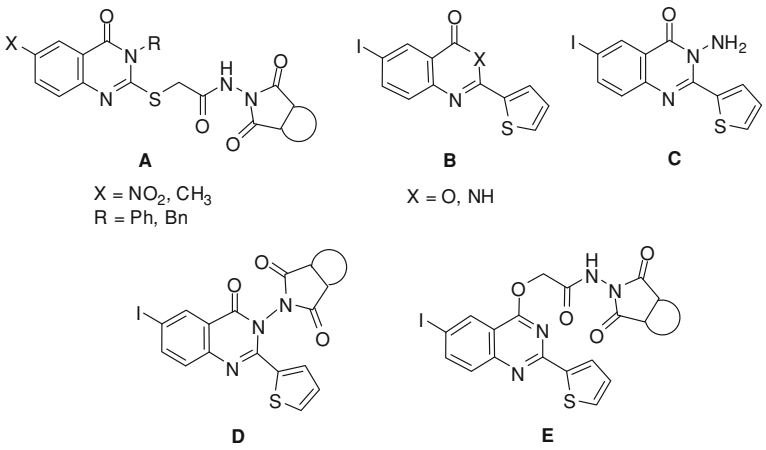
compound(s) (Löscher and Nau, 1985; Swinyard *et al*., 1986; Archana and Kumar, 2002; Welch *et al*., 2001). Some new quinazoline analogs prepared in our laboratory possessed remarkable anticonvulsant activity, showing 100 % protection against PTZ-induced clonic convulsion (Elmazar *et al*., 1993; El-Subbagh *et al*., 2011; Abdel-Hamide *et al*., 2001), such as 6-iodo-3-benzyl-4-oxo-3*H*-quinazoline-2-thioacetic acid (**5**, ED_{50} 73.1 mg/kg). Based on these considerations, new series of quinazoline analogs is designed to accommodate thioacetic acid hydrazide at C-2, which then used to produce cyclic-imines. Phenyl or benzyl moiety was introduced to position 3- and electron donating CH_3 group or electron withdrawing NO_2 group to position 6- to investigate their electronic effect on activity (**A**). Another new series is designed to accommodate sulfur-containing aryl moiety, such as thiophone at position 2-(**B**), and either oxygen or nitrogen connected to a free amino group to position 3-(**C**). The 3-amino function was then used to produce the cyclic-imines **D**. Meanwhile, the 2-thioacetic acid hydrazide moiety of **A** was moved to position 4- and used to synthesize the cyclic-imines **E**, Chart 2. These structure alterations, and modifications, are known to contribute to the anticonvulsant activity of the quinazoline nucleus (Armarego, 1963; Bhaduri *et al*., 1964; Salimath *et al*., 1956; Barthwal *et al*., 1973; Wolfe *et al*., 1990). Such structural alteration is expected to enhance the anticonvulsant potency and produce compounds with reasonable protective index (PI).

Results and discussion

Chemistry

2-(Ethoxycarbonyl-methylthio)-3-phenyl-4-oxo-6-methyl-(3*H*)-quinazoline (**7**) was prepared by reacting 2-mercapto-6-methyl-3-phenyl-4-oxo-(3*H*)-quinazoline (**6**) with ethyl bromoacetate in boiling acetone. Upon refluxing compound **7** with hydrazine hydrate in boiling ethanol, a mixture of two unexpected products were obtained, namely 2-hydrazinyl-6-methyl-3-phenyl-quinazolin-4(3*H*)-one (**8**) and 2-hydrazinyl-6-methyl-quinazolin-4(3*H*)-one (**9**), which were separated by the use of column chromatography (20 % EtOH/Hexane). As an attempt to circumvent this problem and to avoid getting these unexpected products and reach the target intermediate **10**, compound **7** was stirred at room temperature for a long period of time with hydrazine hydrate. This attempt ended up with fruition and 2-(6-methyl-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl-thio)aceto-hydrazide (**10**) was obtained in good yield and considerable purity. Compound **10** was reacted with substituted phathalic anhydride or 1,8-naphthalic anhydride in acetic acid to give *N*-(substituted-phthalimido)-2-(3-phenyl-4-oxo-6-methyl-3*H*-quinazolin-2-yl)thioacetamide (**11**–**13**) and *N*-(1,8-naphthalimido)-2-(3-phenyl-4-oxo-6-methyl-3*H*-quinazolin-2-yl)thioacetamide (**14**) (Scheme 1; Table 1). Upon treating **10** with other anhydrides, such as succinic, malic and tetrahydro-phathalic anhydrides under the same condition, the starting material **10** was always recovered unreacted. Unfortunately, when more drastic condition was employed, such as fusion, the starting material 2-mercapto-6-methyl-3-phenyl-quinazolin-4(3*H*)-one (**6**) was obtained with the elimination of the 2-thioacetohydrazide moiety, Scheme 1. 2-Mercapto-6-methyl-3-benzyl-4-oxo-quina-zoline (**15**) was alkylated with ethylbromoacetate to produce the thioalkyl ester **16**. Interaction of the latter compound with hydrazine hydrate in absolute ethanol led to the formation of the acetic acid hydrazide analog **17**. The acid hydrazide **17** was allowed to react with substituted phthalic, 1,8-naphthalic, and succinic anhydrides in boiling acetic acid to give 1-substituted phthalimido, 1,8-naphthalimido, and succinimido analogs **18**–**22** (Scheme 2, Table 1). The same behavior noticed with the hydrazide **10** toward the used anhydrides also occurred to hydrazide **17** affording either the starting material **15** or the isolation of **17**

Chart 2 General structures of the new designed anticonvulsants

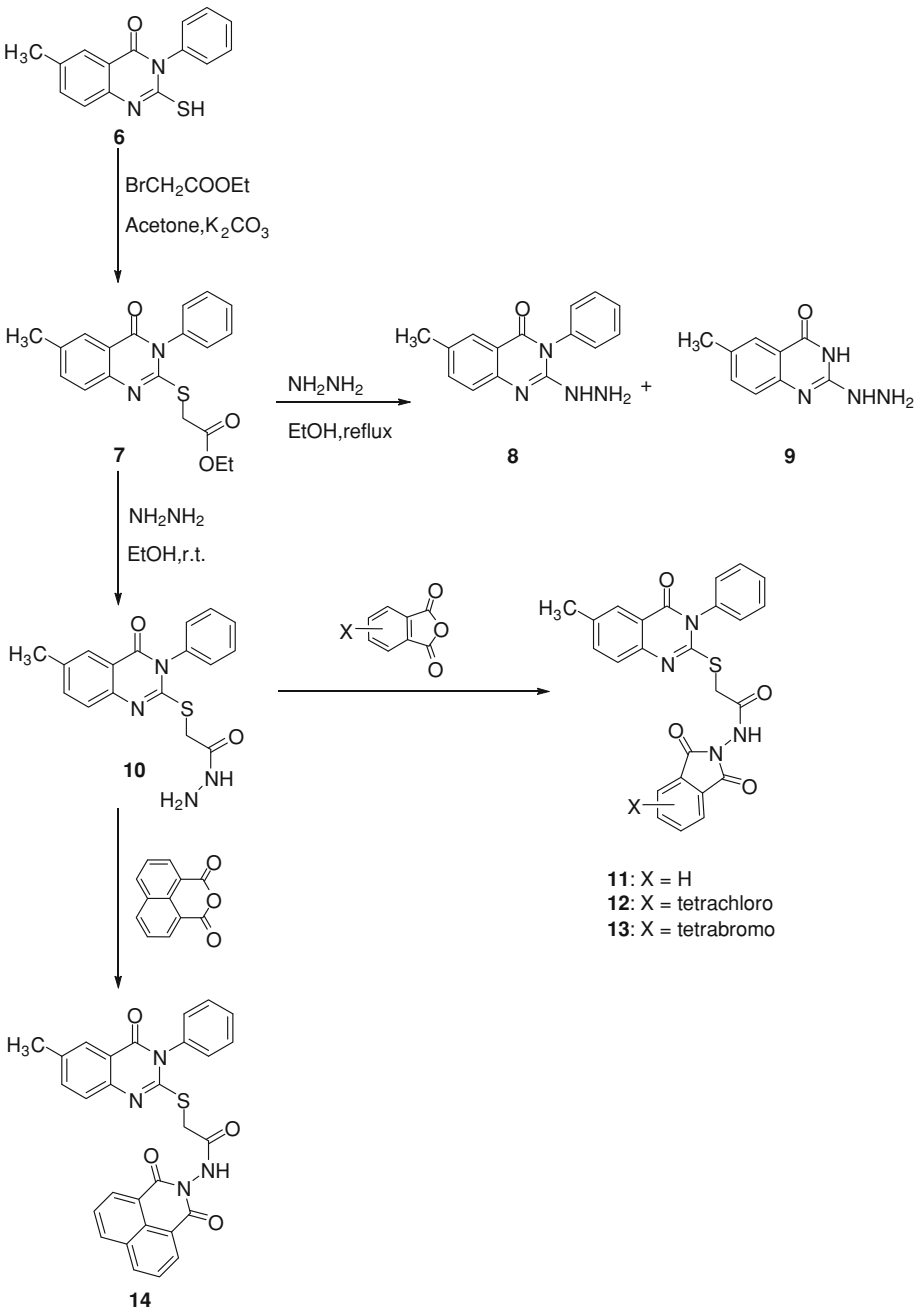


upon work up unreacted. The 2-sulfhydryl function of **23** and **24** was alkylated with ethylbromoacetate to afford the thioalkyl ester analogs **25** and **26**, respectively. Attempts to prepare the corresponding acid hydrazides **27** and **28** failed; instead, the starting materials **23** and **24** were retrieved or the corresponding 2-hydrazino analogs **29** and **30** were obtained depending on the amount of hydrazine hydrate used and the duration of reaction under reflux. It seems that the strong electron withdrawing effect of the 6-NO_2 group facilitates the cleavage of the alkyl side chain or the replacement of the sulfur side chain attached to the 2- position of the quinazoline nucleus to give the hydrazine analogs **29** and **30**. Reaction of the 2-hydrazino analog **30** with 1,8-naphthalic anhydride in boiling acetic acid afforded the corresponding cyclic-imide analog **31** (Scheme 3; Table 1). The key benzoxazone intermediate **35** was prepared by the reaction of 2-iodoanthranilic acid **32** with 2-thiophenecarbonyl chloride **33** to obtain the amide **34**, which was refluxed in acetic anhydride to afford compound **35**. Condensation of **35** with hydrazine hydrate afforded 3-amino derivative **36**. Compound **36** was reacted with benzoyl chloride in pyridine to afford the benzamide analog **37** also with various anhydrides in acetic acid to afford the corresponding compounds **38–40**, respectively (Scheme 4; Table 1). The intermediate **35** was heated under reflux with formamide to afford 2-(2-thieno)-6-iodo-3,4-dihydroquinazolin-4-one (**42**). Alkylation of the latter compound with ethyl bromoacetate in boiling acetone affords the *O*-alkyl derivative **43**. Interaction of **43** with hydrazine hydrate in absolute ethanol at room temperature led to the formation of hydrazide derivative **44**. The reaction of compound **44** with substituted phthalic anhydrides or 1,8-naphthalic anhydride affords substituted phthalimido and naphthalimido analogs **45–48** (Scheme 4, Table 1). The same behavior of **10** and **17** toward succinic, malic, and tetrahydro-phathalic anhydrides was also observed in the case of the hydrazide **44** affording either the starting material **42** or the isolation of **44** upon work up, unreacted.

Anticonvulsant screening

Four animal models were adopted to evaluate the anticonvulsant potency, namely: pentylenetetrazole (PTZ)-, maximal electroshock (MES)-, picrotoxin (Pic)-, and bicuculline (Bic)-induced convulsions. The anticonvulsant activities of the new synthesized compounds against pentylenetetrazole (PTZ)-induced seizures are shown in Table 2. PTZ (85 mg/kg, s.c.) was given 30 min after the administration of each of the tested compounds (1.5 mmol, i.p.). Only six compounds (**6**, **12**, **21**, **36**, **37**, and **38**) resulted in 70–100 % protection against PTZ-induced seizures. On the other hand, ten compounds showed minimal (30 %) protection against PTZ-induced convulsions. Two compounds (**10** and **17**) produced 100 % mortality within 4–7 min before the administration of PTZ. The remaining 21 compounds showed no anticonvulsant activity against PTZ-induced seizures. Compounds **12**, **21,** and **38** produced 70, 30, and 30 % protection against MES-induced tonic extension seizure, respectively (Table 2). These findings suggest that those compounds possess the ability to prevent the spread of seizure discharge throughout neuronal tissues and to raise seizure threshold. Compounds **6**, **36**, and **37** proved to be inactive in such test. Picrotoxin is a chloride channel blocker producing depolarization and clonic convulsions. All the tested compounds produced 80–100 % protection against picrotoxin-induced convulsions suggesting that those compounds may act as $GABA_A$ receptor agonist by increasing chloride influx via brain chloride channels (Table 2). Bicuculline is a $GABA_A$ receptor blocker inducing clonic convulsions. All the tested compounds produced 100 % protection against bicuculline-induced convulsions suggesting that the active compounds may act directly as $GABA_A$ receptor agonist or indirectly by increasing GABA synthesis or its release as a brain inhibitory neurotransmitter (Table 2). A dose response curve for the moderately active compounds **12** and the remarkably active anticonvulsant agents **38** was

Scheme 1 Synthetic route for the preparation of the target compounds **11**–**14**



performed along with the median effective (ED_{50}), median sedative (TD_{50}), protective index (PI), and the acute toxicity determination (LD_{50}). Results are shown in Table 3. Compounds **12** and **38** showed ED_{50} values of 457 and 251 mg/kg, TD_{50} values of 562 and 447 mg/kg, PI (95 % CL) values of 1.22 and 1.78, LD_{50} (95 % CL) values of 1,288 and 1,380 mg/kg, and TI (95 % CL) values of 2.82 and 5.50, respectively. Compound **38** proved to be almost twofold more active than the standard drug sodium valproate.

Structure activity correlations

In the present study, structure activity correlations of the obtained results revealed that the anticonvulsant activity is embedded in the designed quinazolines. The starting material 2-mercapto-6-methyl-3-phenyl-4-oxo-(3*H*)-quinazoline (**6**) showed 70 % protection against PTZ-induced convulsions. Replacement of the 3-phenyl of **6** by 3-benzyl function produced compound **15** with total loss of activity. In the 3-phenyl series, the replacement of the 2-sulfhydryl

Table 1 Physicochemical properties of the synthesized compounds

Compd.	Solvent	Yield	MP (°C)	Molecular formula
7	EtOH	75	130–35	$C_{19}H_{18}N_2O_3S$
8	EtOH	50	174–5	$C_{15}H_{14}N_4O$
9	EtOH	60	198–9	$C_9H_{10}N_4O$
10	EtOH	60	287–90	$C_{17}H_{16}N_4O_2S$
11	AcOH	65	189–91	$C_{25}H_{18}N_4O_4S$
12	AcOH	50	254–5	$C_{25}H_{14}Cl_4N_4O_4S$
13	AcOH	45	293–4	$C_{25}H_{14}Br_4N_4O_4S$
14	AcOH	53	182–4	$C_{29}H_{20}N_4O_3S$
16	EtOH	69	153–5	$C_{20}H_{20}N_2O_3S$
17	Dioxane	50	>300	$C_{18}H_{18}N_4O_2S$
18	AcOH	35	144–45	$C_{26}H_{20}N_4O_4S$
19	AcOH	60	253–5	$C_{26}H_{16}Cl_4N_4O_4S$
20	AcOH	50	247–8	$C_{26}H_{16}Br_4N_4O_4S$
21	AcOH	35	>300	$C_{30}H_{22}N_4O_4S$
22	AcOH	39	>300	$C_{22}H_{20}N_4O_4S$
25	EtOH	75	174–5	$C_{18}H_{15}N_3O_5S$
26	EtOH	69	165–6	$C_{19}H_{17}N_3O_5S$
29	EtOH-benzene	60	193–5	$C_{14}H_{11}N_5O_3$
30	EtOH-benzene	65	202–4	$C_{15}H_{13}N_5O_3$
31	AcOH	38	271–3	$C_{27}H_{17}N_5O_5$
38	AcOH	43	237–39	$C_{20}H_{10}IN_3O_3S$
39	AcOH	65	197–96	$C_{20}H_6Cl_4IN_3O_3S$
40	AcOH	70	299–300	$C_{20}H_6Br_4IN_3O_3S$
41	AcOH	69	190–92	$C_{24}H_{12}IN_3O_3S$
45	AcOH	77	178–80	$C_{20}H_{13}IN_4O_3S$
46	AcOH	48	>300	$C_{22}H_9Cl_4IN_4O_4S$
47	AcOH	32	>300	$C_{22}H_9Br_4IN_4O_4S$
48	AcOH	42	285–6	$C_{26}H_{15}IN_4O_4S$

function of **6** by *N*-(tetrachloro-phthalimido)-2-thioacetamide moiety preserved the anticonvulsant activity (compound **12** with its 70 % protection against PTZ-induced convulsions), while its replacement with *N*-(1,8-naphthalimido)-2-thioacetamide led to **14** with total loss of activity. The contrary was observed in the 3-benzyl series, compound **21** with its *N*-(1,8-naphthalimido)-2-thioacetamide showed 70 % protection against PTZ-induced convulsions, while its *N*-tetrachloro-phthalimido analogs **19** and **20** showed no sign of anticonvulsant activity. Replacing the phthalimido or naphthalimido nucleus by succinimide retained some of the activity as shown in compound **22** with 30 % protection against PTZ-induced convulsions. Replacement of the 6-CH_3 function of the quinazoline ring by 6-NO_2 produced the inactive analog **31**, which implies that electron donating functions favor the activity rather than electron withdrawing moieties. In the 6-iodo-2-thieno-quinazoline series, three compounds proved to be the most active anticonvulsants in the present investigation (**36**, **37**, and **38**). The 3-amino analog **36** showed 100 % protection against PTZ-induced convulsions. Benzoylation of the 3-amino function of **36** gave the benzamido analog **37** with preserved magnitude of activity. The introduction of phthalimido function at position 3- produced **38** with 100 % protection. Increasing the bulkiness of the substituents at position, 3- such as the tetrachloro- and tetrabromo-phthalimido analogs **39** and **40** as well as 1,8-naphthalimido analog **41,** produced inactive compounds. Moving such substituents to position 4- of the quinazoline nucleus, to be connected through ether linkage, produced compounds **45**–**48**, which were devoid of any anticonvulsant activity.

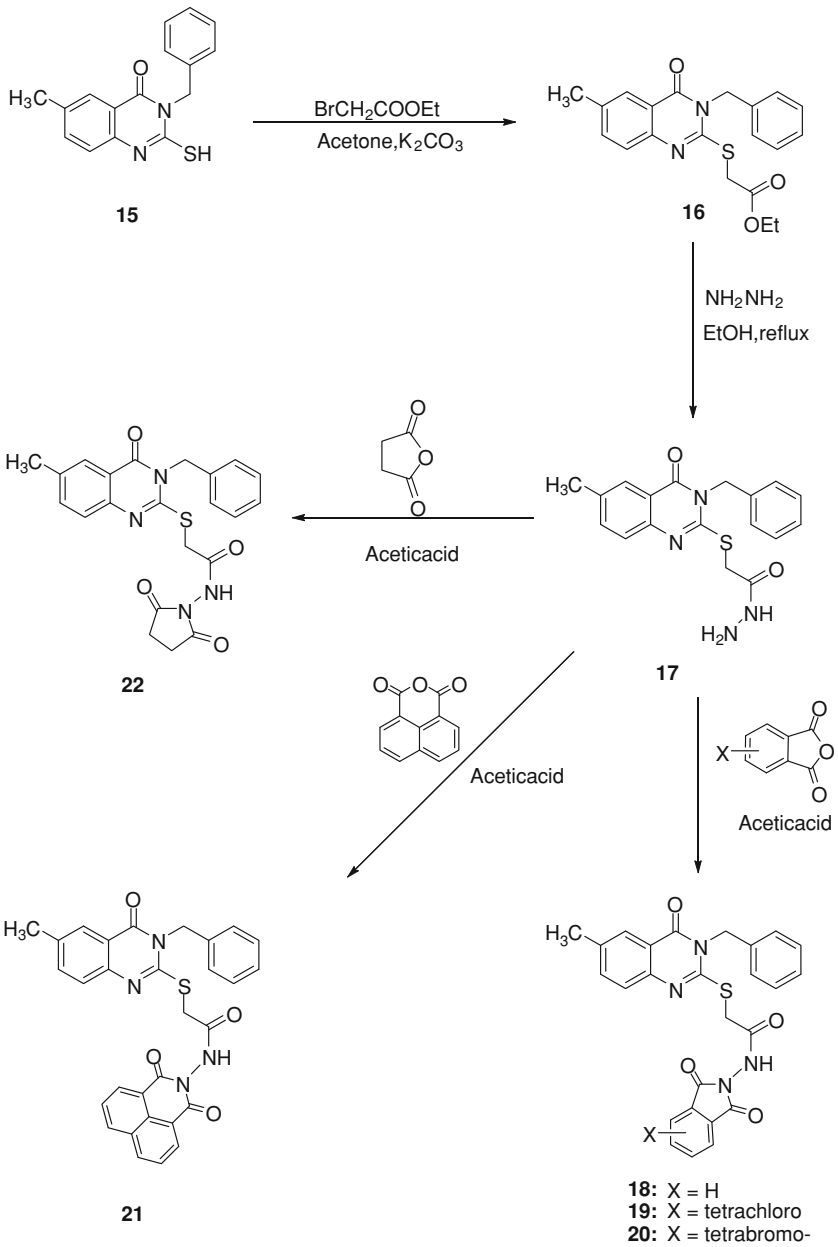
Conclusion

The present study netted three compounds with 100 % protection against PTZ-induced seizures which are 3-amino-6-iodo-2-(thiophen-2-yl)-quinazolin-4(3*H*)-one (**36**), *N*-[6-iodo-4-oxo-2-(thiophen-2-yl)quinazolin-3(4*H*)-yl]-benzamide (**37**), and 2-[6-iodo-4-oxo-2-(thiophen-2-yl)-quinazolin-3(4*H*)-yl]-isoindoline-1,3-dione (**38**), Chart 3. Those compounds possess the ability to prevent the spread of seizure discharge throughout neuronal tissues and to raise seizure threshold. Those compounds proved to act as $GABA_A$ receptor agonist by increasing chloride influx via brain chloride channels or by increasing GABA synthesis and its release as a brain inhibitory neurotransmitter. The protective index (PI) of **38** proved to be 1.78 which insured an adequate separation between the anticonvulsant activity and the sedation property. Structure activity correlation of the investigated quinazolines proved that the electron-donating 6-CH_3 function contribute to the anticonvulsant activity rather than the electron-withdrawing 6-NO_2 group. The 3-phenyl moiety contributes to the activity rather than the 3-benzyl function; the 2-thioacetamido moiety proved important for activity. In the 3-phenyl series, phthalimido-2-thioacetamide group preserved the anticonvulsant potency rather than the 1,8-naphthalimido-2-thioacetamide function; the opposite was noticed in the 3-benzyl series where 1,8-naphthalimido-2-thioacetamide preserved the potency rather than the phthalimido-2-thioacetamide function. The obtained active compounds could be used as lead template for future investigation and derivatization.

Experimental

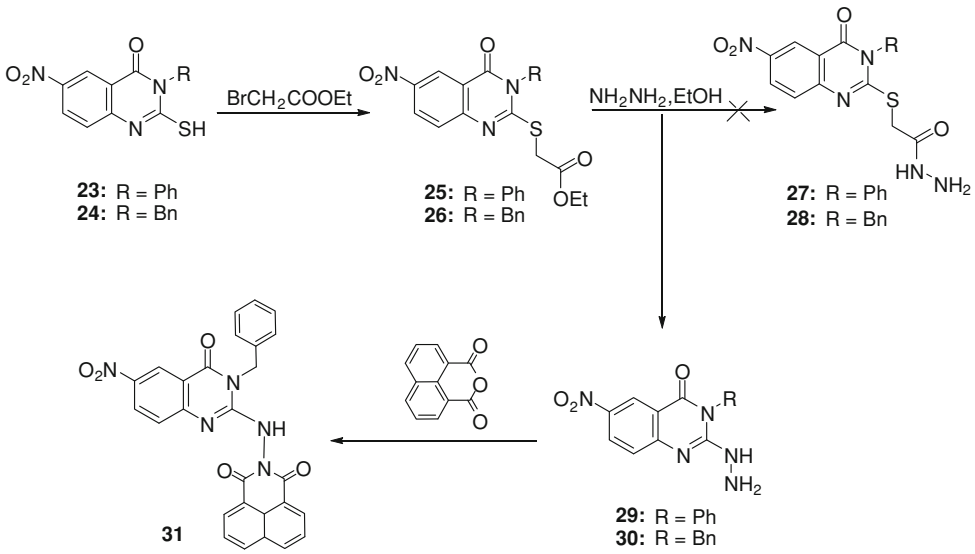
Unless otherwise specified, all chemicals were of commercial grade, used without further purification and were obtained from Aldrich Chemical Co. (Milwaukee, WI, USA). Solvents used for work ups were dried over $MgSO_4$, filtered, and removed on a rotary evaporator. Elemental

Scheme 2 Synthetic route for the preparation of the target compounds **18–22**



analyses were performed at College of Pharmacy, Central Laboratory, King Saud University. IR spectra (KBr) were measured using a Mattson 5000 FT-IR Spectrophotometer (ν cm^{-1}). Mass spectral (MS) data were obtained on a Shimadzu GC/MS QP 5000 apparatus. ^{1}H and ^{13}C NMR spectra obtained at 400 and 100 MHz on a JEOL instrument, respectively, using TMS as internal standard. Thin layer and flash chromatography were performed using E. Merck Silica gel (230–400 mesh). Preparative thin layer chromatography was performed on Harrison model 7924 A chromatotron using Analtech silica gel GF rotors. Compounds **6**, **15**, **23**, **24**, **34–37**, and **42–44** were prepared according to reported procedures (Al-Obaid *et al*., 2009; Al-Omar *et al*., 2004; Al-Rashood *et al*., 2006; Al-Omary *et al*., 2010). Male Swiss albino mice (SWR) weighing 25–30 g, were obtained from the Animal Care Center, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia, and were housed in metabolic cages under controlled environmental conditions (25 °C and a 12 h light/dark cycle). Animals had free access to pulverized standard rat pellet food and tap water unless otherwise indicated. The protocol of this study has been approved by Research Ethics Committee of College of Pharmacy, King Saud University, Riyadh, Kingdom of Saudi Arabia.

Scheme 3 Synthetic route for the preparation of the target compound **31**



Chemistry

*2-(Ethoxycarbonylmethyl)-thio-3-phenyl-4-oxo-6-methyl-3H-quinazoline (**7**)*

A mixture of 2-mercapto-3-phenyl-4-oxo-6-methyl-3*H*-quinazoline (**6**, 2.68 g, 0.01 mol), ethylbromoacetate (2.51 g, 0.015 mol), and anhydrous potassium carbonate (2.0 g) in dry acetone (50 ml) was heated under reflux for 12 h. The reaction mixture was filtered while hot and the filtrate was concentrated *in vacuo* to give the crude product, which was crystallized from ethanol (Table 1). IR (KBr, ν cm^{-1}): 1,741 and 1,693 (2 C=O). ^{1}H NMR ($CDCl_3$): δ 1.32 (t, 3H, $J = 7$ Hz, CH_3CH_2O), 2.49 (s, 3H, CH_3), 3.9 (s, 2H, S–CH_2CO), 4.25 (q, 2H, $J = 7$ Hz, CH_3CH_2), 7.37–7.39 (m, 2H, Ar–H), 7.48 (d, 1H, $J = 8.5$ Hz, Ar–H), 7.55–7.58 (m, 4H, Ar–H), 8.04 (s, 1H, Ar–H).

*2-Hydrazinyl-6-methyl-3-phenyl-quinazolin-4(3H)-one (**8**) and 2-Hydrazinyl-6-methyl-quinazolin-4(3H)-one (**9**)*

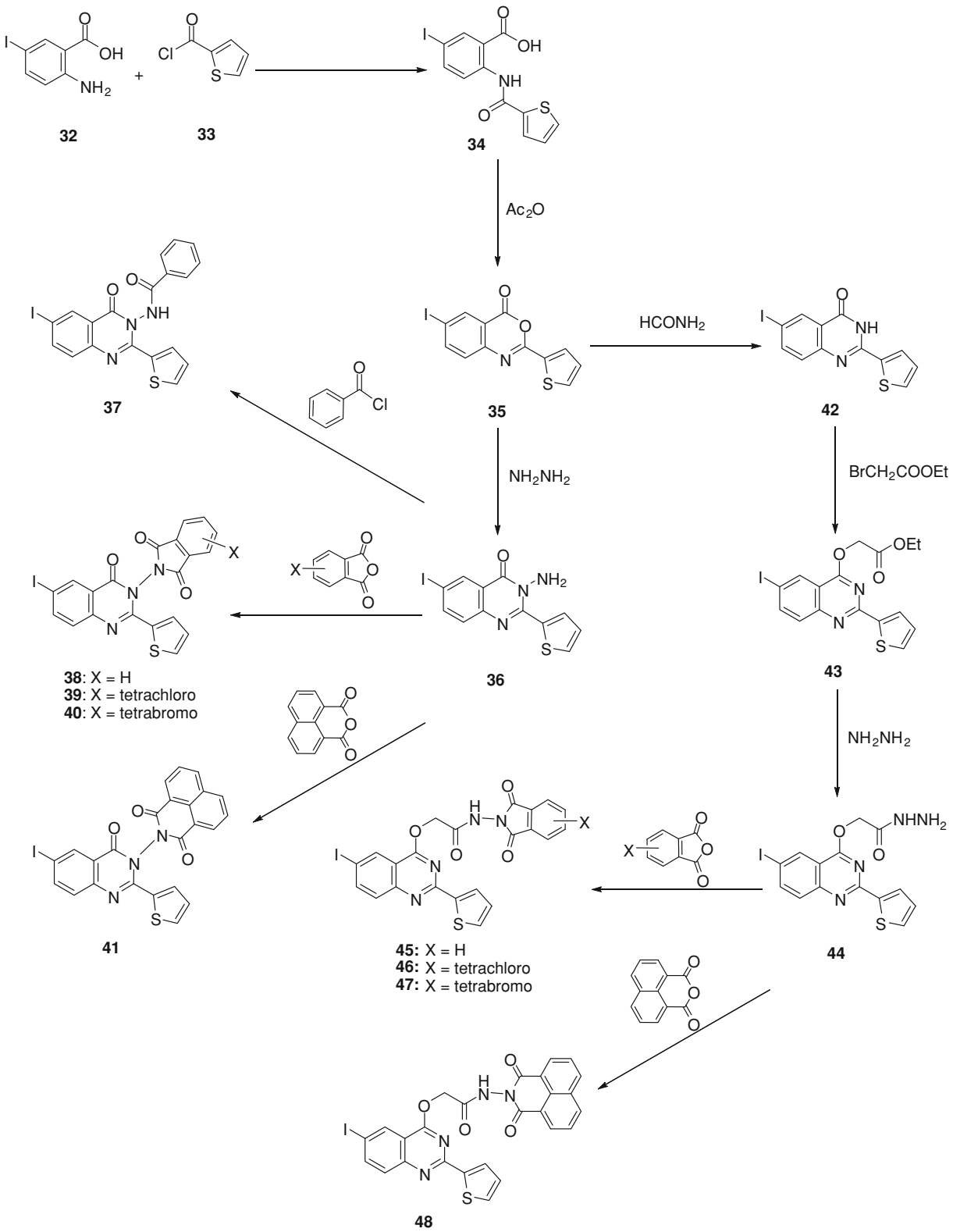
A solution of 2-(ethoxycarbonylmethyl)-thio-3-phenyl-4-oxo-6-methyl-3*H*-quinazoline (**7**, 3.0 g, 0.01 mol) and hydrazine hydrate (85 %, 3 ml) in ethanol (30 ml) was heated under reflux for 1 h. The obtained solid was filtered, dried, and chromatographed (silica gel, 100 g, elution with EtOAc-Hexan 1:8 v/v) to give compounds **8** and **9**. ^{1}H NMR, (DMSO-d_6) **8**: δ 8.54 (s, 1H, NH, D_2O exchangeable), 7.81 (s, 1H, Ar–H), 7.78 (d,2H, $J = 8.0$ Hz, Ar–H), 7.42–7,035 (m, 4H, Ar–H), 7.11 (t, 1H, $J = 7.0$ Hz, Ar–H), 4.63 (s, 2H, NH_2, D_2O exchangeable), 2.38 (s, 3H, CH_3). ^{13}C NMR: 20.9, 117.2, 119.7, 123.3, 125.5, 125.8, 128.9, 133.0, 136.0, 138.2, 145.8, 146.0, 162.0. **9**: δ 8.09 (s, 1H, NH, D_2O exchangeable), 7.72 (s, 1H, Ar–H), 7.42 (d, 1H, $J = 8.0$ Hz, Ar–H), 7.24 (d, 1H, $J = 8.0$ Hz, Ar–H), 5.41 (s, 2H, NH_2, D_2O exchangeable), 4.36 (s, 1H, NH, D_2O exchangeable), 2.34 (s, 3H, CH_3). ^{13}C NMR: 20.9, 116.7, 124.8, 125.8, 131.2, 135.8, 146.9, 152.6, 161.3.

*2-(6-Methyl-4-oxo-3-phenyl-3,4-dihydro-quinazolin-2-yl-thio)acetohydrazide (**10**)*

A solution of 2-(ethoxycarbonylmethyl)thio-3-phenyl-4-oxo-6-methyl-3*H*-quinazo-line (**7**, 3.5 g, 0.01 mol) and hydrazine hydrate (85 %, 3 ml) in ethanol (30 ml) was stirred at room temperature for 7 days. The obtained solid was filtered and dried to give compound **10**. IR (KBr, ν cm^{-1}): 1,741 and 1,693 (C=O). ^{1}H NMR, (DMSO-d_6): δ 9.32 (s, 1H, NH, D_2O exchangeable), 7.78 (s, 1H, Ar–H), 7.65(d, 1H, $J = 8.0$ Hz, Ar–H), 7.57–7.53 (m, 4H, Ar–H), 7.45 (d, 2H, $J = 5.0$ Hz, Ar–H), 4.31(s, 2H, NH_2, D_2O exchangeable), 3.85 (s, 2H, CH_2), 2.43 (s, 3H, CH_3). ^{13}C NMR: 21.2, 34.9, 119.7, 126.3, 126.4, 129.9, 130.4, 136.0, 136.5, 145.8, 156.1, 156.8, 161.1, 166.7, 171.3.

*N-(Substituted-phthalimido)-2-[(3-phenyl-4-oxo-6-methyl-3H-quinazolin-2-yl)-thio]acet amide (**11–13**) and N,N-(1,8-naphthalimido)-2-[(3-phenyl-4-oxy-6-methyl-3H-quinazolin-2-yl)-thio]acetamide (**14**)*

A mixture of **10** (1.7 g, 0.005 mol) and the appropriate anhydride (0.007 mol) was heated under reflux for 18 h. The formed precipitate was filtered while hot, dried, and crystallized from acetic acid (Table 1). **11**: IR (KBr, ν cm^{-1}): 3,242 (CONH), 1731, 1699 (2 C=O). ^{1}H NMR, (DMSO-d_6), δ 2.44 (s, 3H, CH_3), 4.11 (s, 2H, SCH_2CO), 7.47–814 (m, 12H, Ar–H), 11.04 (s, 1H, CONH). **12**: IR



Scheme 4 Synthetic route for the preparation of the target compounds **37–48**

(KBr, ν cm^{-1}): 3,446 (NH), 1787, 1756, 1636 (3 C=O). ^1H NMR, (DMSO-d_6), δ 2.45 (s, 3H, CH_3), 4.11 (s, 2H, SCH_2CO), 7.46–7.56 (m, 2H, Ar–H), 7.59–7.61 (m, 4H, Ar–H), 7.71 (s, 1H), 11.28 (s, 1H, CONH, exchangeable). MS: (M-$C_8Cl_4NO_2$) $m/z = 326$ (4.35 %), M-$C_8Cl_4HNO_2$, $m/z = 311$ (7.4 %), M-$C_9Cl_4HN_2O_3$, $m/z = 283$ (6.4 %),

Table 2 Potential anticonvulsant activity of the newly synthesized compounds at dose of 1.5 mmol each, against PTZ, MES, and Pic and Bic-induced clonic convulsions

Compd.	% Protection[a]			
	PTZ[b]	MES[c]	Pic[d]	Bic[e]
6	70	0.0	80	100
12	70	70	70	100
21	70	30	80	100
22	30	nt	nt	nt
24	30	nt	nt	nt
29	30	nt	nt	nt
31	30	nt	nt	nt
36	100	0.0	100	100
37	100	0.0	80	100
38	100	30	100	100
40	30	nt	nt	nt
43	30	nt	nt	nt
44	30	nt	nt	nt
45	30	nt	nt	nt
46	30	nt	nt	nt
47	30	nt	nt	nt
Sod. valproate	100	100	100	100

[a] Compounds **10** and **17** showed 100 % mortality

[b] Compounds **7**,**10**, **11**, **13**–**20**, **23**, **25**, **26**, **30**, **34**, **35**, **39**, **41**,**42**, and **48** showed no anticonvulsant activity against PTZ-induced convulsions

[c] *MES* maximal electroshock test, was applied 30 min after the administration of each compound

[d] *Pic* picrotoxin (3.15 mg/kg, s.c.) was given 30 min after the administration of each compound

[e] *Bic* bicuculline (2.7 mg/kg, s.c.) was given 30 min after the administration of each compound

M-$C_{10}Cl_4H_3N_2O_3$, $m/z = 269$ (8 %), M-$C_{10}Cl_4H_3N_2O_3S$, $m/z = 237$ (7.6 %). **13**: ^{1}H NMR, (DMSO-d_6): δ 11.16 (s, 1H, NH, D_2O exchangeable), 7.89 (s, 1H, Ar–H), 7.59–7.46 (m, 7H, Ar–H), 4.12 (s, 2H, CH_2), 2.45 (s, 3H, CH_3). ^{13}C NMR: 21.2, 34.4, 119.7, 121.7, 126.2, 126.8, 129.4, 129.9, 130.0, 130.5, 136.2, 136.5, 137.9, 145.7, 155.5, 161.1, 161.4, 167.1. **14**: IR (KBr, ν cm^{-1}): 3,251 (CONH), 1740, 1687 (2 C=O). ^{1}H NMR, (DMSO-d_6), δ 2.46 (s, 3H, CH_3), 4.21 (s, 2H, SCH_2CO), 7.47–7.49 (m, 2H, Ar–H), 7.61 (d, 3H, Ar–H), 7.73–7.78 (m, 2H, Ar–H), 7.89–7.93 (m, 3H, Ar–H), 8.58 (d, 4H, Ar–H), 11.11 (s, 1H, CONH).

*2-(Ethoxycarbonylmethyl)thio-3-benzyl-4-oxo-6-methyl-3H-quinazoline (**16**)*

A mixture of 2-mercapto-3-benzyl-4-oxo-6-methyl-3*H*-quinazoline (**15**, 2.82 g, 0.01 mol), ethylbromoacetate (2.51 g, 0.015 mol), and anhydrous potassium carbonate (2.0 g) in dry acetone (50 ml) was heated under reflux for 18 h. The reaction mixture was filtered while hot, and the filtrate was concentrated *in vacuo* to give the crude product which was crystallized from ethanol (Table 1). ^{1}H NMR ($CDCl_3$), δ 1.88 (t, 3H, $J = 7$ Hz, CH_3CH_2O), 2.43 (s, 3H, CH_3), 4.08 (s, 2H, SCH_2CO), 4.12 (q, 3H, $J = 7$ Hz), 5.33 (s, 2H, CH_2Ph), 7.28 (t, 2H, $J = 7$ Hz, Ar–H), 7.33–7.38 (m, 2H, Ar–H), 7.68 (d, 1H, $J = 8.5$ Hz), 7.8–8.5 (m, 3H, Ar–H).

*2-[(3-Benzyl)-4-oxo-6-methyl-3H-quinazolin-2-yl)-thio]acetyl hydrazide (**17**)*

A solution of the ester **16** (3.68 g, 0.01 mol) and hydrazine hydrate (85 %, 3 ml) in ethanol (40 ml) was heated under reflux for 2 h. The obtained solid was filtered, dried, and recrystallized from dioxane (Table 1). ^{1}H NMR (DMSO-d_6): δ 2.44 (s, 3H, CH_3), 3.93 (s, 2H, SCH_2CO), 4.31 (b, 2H, NH_2), 5.34 (s, 2H, CH_2Ph), 7.27–7.40 (m, 4H, Ar–H), 7.58 (d, 1H, $J = 8$ Hz, Ar–H), 7.81–7.84 (m, 1H, Ar–H), 8.16 (d, 1H, $J = 8$ Hz, Ar–H), 9.37 (s, 1H, CONH).

*N-(Substituted phthalimido)-2-[(3-benzyl-4-oxo-6-methyl-3H-quinazolin-2-yl)thio]-acetamide (**18**–**20**), N,N-(1,8-naphthalimido)-2-[(3-benzyl-4-oxo-6-methyl-3H-quinazolin-2-yl)-thio]acetamide (**21**) and N-(succinamido)-2-[(3-benzyl-4-oxo-6-methyl-3H-quinazolin-2-yl)-thio]acetamide (**22**)*

A mixture of compound **17** (1.77 g, 0.005 mol) and appropriate anhydride (0.007 mol) and fused sodium acetate (1.0 g) in glacial acetic acid (30 ml) was heated under reflux for 18 h. The formed precipitate was filtered while hot, dried, and crystallized from acetic acid (Table 1). ^{1}H NMR(DMSO-d_6): **18**: δ 2.45 (s, 3H, CH_3), 4.22 (s, 2H, SCH_2CO), 5.34 (s, 2H, CH_2Ph), 7.28–7.32 (m, 4H, Ar–H), 7.69–7.54 (m, 4H, Ar–H), 8.06 (d, 2H, $J = 2$ Hz, Ar–H), 8.12 (d, 2H, $J = 2$ Hz, Ar–H), 11.03 (s, 1H, CONH). **19**: δ 2.50 (s, 3H, CH_3), 4.25 (s, 2H, SCH_2CO), 5.35 (s, 2H, CH_2Ph), 7.29–7.34 (m, 4H, Ar–H), 7.50 (t, 1H, $J = 7$ Hz, Ar–H), 7.9 (d, 1H, $J = 7.5$ Hz, Ar–H), 7.66 (d, 1H, $J = 7.5$ Hz, Ar–H), 8.12 (d, 1H, $J = 7.5$ Hz, Ar–H), 11.07 (bs, 1H, NHCO). **20**: δ 2.50 (s, 3H, CH_3), 4.25 (s, 2H, SCH_2CO), 5.35 (s, 2H, CH_2Ph), 7.28–7.36 (m, 5H, Ar–H), 7.50 (t, 1H, $J = 7.5$ Hz, Ar–H), 7.9–7.97 (m, 2H, Ar–H and NH), 8.18 (d, 1H, $J = 8$ Hz, Ar–H). **21**: IR (KBr, ν cm^{-1}): 3,424 (NH), 1785, 1772, 1668 (3 C=O), Ms: m/z 534 (20 %). **22**: δ 2.45 (s, 3H, CH_3), 2.89 (s, 4H, $COCH_2CO$), 3.98 (s, 2H, SCH_2CO), 5.78 (s, 2H, CH_2Ph), 7.2–8.1 (m, 8H, Ar–H), 11.76 (s, 1H, NH).

Table 3 Dose response curve, ED_{50}, TD_{50}, PI, LD_{50}, and TI for compounds **12** and **38**

Compd.[a]	Dose (mmol/kg)	Dose (mg/kg)	% PTZ	% Chim[b]	% MES[c]	% Pic[d]	% Bic[e]	ED_{50}^{f} (mg/kg)	TD_{50}^{f} (mg/kg)	PI[g]	LD_{50} (mg/kg)	TI[h]
12	1.5	912	70	100	70	70	100	457 (363–575)	562 (447–708)	1.22	1,288 (920–1,803)	2.82
	0.75	456	50	30	10	50	70					
	0.37	228	30	0.0	0.0	20	10					
	0.18	114	0.0	0.0	0.0	0.0	0.0					
38	1.5	748	100	80	30	100	100	251 (200–316)	447 (355–562)	1.78	1,380 (1,030–1,849)	5.50
	0.75	374	70	30	0.0	50	40					
	0.37	187	30	30	0.0	50	10					
	0.18	94	0.0	0.0	0.0	20	0.0					

[a] Each dose of selected compounds was tested using 10 animals and the percentage of animals protected was recorded and the anticonvulsant activity was calculated

[b] *Chim* chimney test, was applied 15, and 25 min after the administration of each compound

[c] *MES* maximal electroshock test, was applied 30 min after the administration of each compound

[d] *Pic* picrotoxin (3.15 mg/kg, s.c.) was given 30 min after the administration of each compound

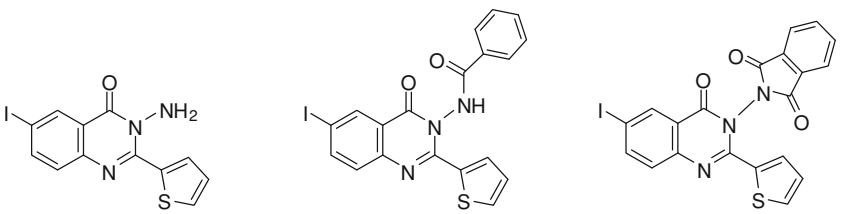
[e] *Bic* bicuculline (2.7 mg/kg, s.c.) was given 30 min after the administration of each compound

[f] ED_{50} and TD_{50}: median effective and median sedative doses, respectively

[g] *PI* protective index = TD_{50}/ED_{50}

[h] *TI* Therapeutic index = LD_{50}/ED_{50}

Chart 3 List of structures of the active anticonvulsant agents



*2-(Ethoxycarbonylmethyl)-thio-3-phenyl-4-oxo-6-nitro-3H-quinazoline (**25**) and 2-(ethoxy carbonylmethyl)-thio-3-benzyl-4-oxo-6-nitro-3H-quinazoline (**26**)*

A mixture of 2-mercapto-3-phenyl-4-oxo-6-nitro-3*H*-quinazoline **23** or 2-mercapto-3-benzyl-4-oxo-6-nitro-3*H*-quinazoline **24** (0.01 mol), ethylbromoacetate (2.51 g, 0.015 mol) and anhydrous potassium carbonate (2.0 g) in dry acetone (50 ml) was heated under reflux for 12 h. Solvents were evaporated and the obtained residue was recrystallized from the appropriate solvent (Table 1). **25**: IR (KBr, ν cm^{-1}): 1724, 1701 (2 C=O), ^{1}H NMR(DMSO-d_6): δ 1.31 (t, 3H, J = 7 Hz, OCH_2CH_3), 3.95 (s, 2H, SCH_2CO), 4.2 (q, 2H, J = 7 Hz, OCH_2CH_3), 7.38–7.4 (m, 2H, Ar–H), 7.61 (t, 3H, J = 3 Hz, Ar–H), 7.69 (d, 1H, J = 9 Hz, Ar–H), 8.51–8.54 (dd, 1H, J = 2.5 Hz, Ar–H), 9.09 (d, 1H, J = 2.5 Hz, Ar–H), **26**: IR (KBr, ν cm^{-1}): 3,087 (CH), 1730, 1683 (2 C=O). ^{1}H NMR (DMSO-d_6): δ 1.29 (t, 3H, J = 8 Hz, OCH_2CH_3), 3.97 (s, 2H, SCH_2CO), 4.16 (q, 2H, J = 8 Hz, OCH_2CH_3), 5.23 (s, 2H, CH_2Ph), 7.16–7.31 (m, 6H, Ar–H), 8.22 (m, 1H, Ar–H), 8.61 (s, 1H, Ar–H).

*2-Hydrazino-6-nitro-3-phenyl-4-oxo-3H-quinazoline (**29**) and 2-hydrazino-6-nitro-3-benzyl-4-oxo-3H-quinazoline (**30**)*

A mixture of **25** or **26** (0.01 mol) and hydrazine hydrate (0.03 mol) in ethanol (40 ml) was heated under reflux for 1 h. The reaction mixture was cooled; the obtained solid was filtered and recrystallized from ethanol–benzene (Table 1). ^{1}H NMR (DMSO-d_6), **29**: δ 3.36 (s, 2H, $NHNH_2$), 7.5–7.6 (m, 1H, Ar–H), 7.7 (t, 1H, J = 7.5 Hz, Ar–H), 7.84 (t, 1H, J = 7 Hz, Ar–H), 8.09–8.18 (dd, 1H, J = 8 Hz, Ar–H), 8.28 (d, 1H, J = 7.5 Hz, Ar–H), 8.78 (d, 1H, J = 3.5 Hz, Ar–H), 8.87 (s, 1H, Ar–H), 9.09 (s, 1H, Ar–H), 12.36 (s, 1H, $NHNH_2$), **30**: δ 3.34 (brs, 2H, $NHNH_2$), 5.22 (s, 2H, CH_2Ph), 7.16–7.32 (m, 7H, Ar–H, and $NHNH_2$), 8.22–8.24 (m, 1H, Ar–H), 8.61 (s, 1H, Ar–H).

*2-(1,8-Naphthalimidoamino)-6-nitro-3-benzyl-4-oxo-3H-quinazoline (**31**)*

Equimolar amounts of compound **30** and 1,8-naphthalic anhydride (10.01 mol) was refluxed in acetic acid (30 ml) and fused sodium acetate (2.0 g) for 24 h. The reaction mixture was concentrated to its half volume and filtered while hot. The resulting solid was crystallized from acetic acid (Table 1). (DMSO-d_6): δ 5.48 (s, 2H, CH_2Ph), 7.36–7.93 (m, 8H, Ar–H), 8.52–8.62 (m, 6H, Ar–H), 11.2 (s, 1H, NH).

*6-Iodo-2-thieno-3-substituted phthalimido-4-(3H)-quinazolinone (**38–40**) and 6-iodo-2-thieno-3-naphthalimido-4-(3H)-quinazolinone (**41**)*

A mixture of compound **36** (3.69 g, 0.01 mol) and appropriate anhydride (0.015 mol) and fused sodium acetate (1.0 g) in acetic acid (30 ml) was heated under reflux for 6 h. The formed precipitate was filtered while hot, dried, and crystallized from acetic acid (Table 1). **38**: ^{1}H NMR; (DMSO-d_6), δ 7.17–7.23 (m, 1H), 7.50 (d, 1H, J = 8 Hz thiophene-H), 7.61 (d, 1H, J = 8.5 Hz thiophene-H), 7.87–8.27 (m, 6H, thiophene-H), 8.39 (d, 1H, J = 8.0 Hz, Ar–H). I.R. 1799, 1751, 1700 (3 C=O). ^{13}C NMR: 92.3, 122.3, 128.5, 129.5, 130.3, 132.8, 134.3, 135.2, 137.2, 145.4, 146.5, 149.0, 150.6, 158.5, 164.7, 170.2. **39**: IR (KBr, ν cm^{-1}): 1797, 1702, 1645 (3 C=O). ^{1}H NMR; (DMSO-d_6), δ 7.18-7.19 (m, 1H, thiophene-H), 7.62 (d, 1H, J = 2.5 thiophene-H), 7.89–7.91 (m, 1H, thiophene-H), 8.01–8.05 (m, 1H, Ar–H), 8.33 (d, 1H, J = 9 Hz, Ar–H), 8.37-8.39 (m, 1H, Ar–H). ^{13}C NMR: 94.0, 120.8, 126.3, 129.7, 130.3, 130.7, 133.0, 133.2, 134.5, 135.6, 141.4, 145.7, 146.1, 148.5, 165.9, 160.7. **40**: IR (KBr, ν cm^{-1}): 1769, 1751, 1693 (3 C=O). ^{1}H NMR; (DMSO-d_6), δ 7.23–7.24 (m, 1H, thiophene-H), 7.47 (d, 1H, J = 8.5 Hz, thiophene-H), 7.89–7.9 (m, 1H, thiophene-H), 8.07-8.09 (m, 1H, Ar–H), 8.38–8.39 (m, 1H, Ar–H), 8.42–8.43 (m, 1H, Ar–H), ^{13}C NMR: 93.4, 122.8, 124.8, 128.4, 129.8, 131.3, 133.3, 134.5, 135.3, 144.4, 145.2, 146.4, 150.3, 157.3, 158.5, 172.5. **41**: δ 7.22–7.23 (m, 1H, Ar–H), 7.46 (m, 1H, J = 8.5 Hz, thiophene-H). 7.89–7.94 (m, 3H, thiophene-H and Ar–H), 8.07–8.09 (dd, 1H, J = 2, 7 Hz, Ar–H), 8.38–8.39 (m, 1H, Ar–H), 8.42–8.43 (m, 1H, Ar–H), 8.53–8.57 (m, 4H, Ar–H).

*N-(1-Substituted-phthalimido)-2-[(2-thieno-6-iodo-quinazolin-4-yl)oxo]acetamide (**45–47**) and naphthalimido-2-[(2-thieno-6-iodo-quinazolin-4-yl)oxo]acetamide (**48**)*

A mixture of 2-(6-iodo-2-(thiophen-2-yl)quinqzolin-4-yloxy)acetohydrazide (**44**, 4.26 g, 0.01 mol), the appropriate anhydride (1.5 g, 0.01 mol) in acetic acid (30 ml) was heated under reflux for 18 h. The formed precipitate was filtered while hot, dried and crystallized (Table 1). **45**: ^{1}H NMR (DMSO-d_6): δ 4.76 (s, 2H, OCH_2CO), 7.26–7.27 (m, 1H, thiophene-H), 7.70 (d, 1H, J = 8.5 Hz, thiophene-H), 7.84 (d, 1H, 8.5 Hz, thiophene-H), 7.83-7.99 (m, 4H, Ar–H), 8.18–8.22 (m, 2H, Ar–H), 8.65 (d, 1H, J = 1.5 Hz, Ar–H), 11.03 (s, 1H, NHCO). **46**: IR (KBr, ν cm^{-1}): 3,246 (NH), 1802, 1758, 1654 (3 C=O). ^{1}H NMR (DMSO-d_6): δ 5.43 (s, 2H, OCH_2CO), 7.25 (s, 1H, Ar–H), 7.69 (d, 1H, J = 8.5 Hz, thiophene-H), 7.83 (d, 1H, J = 3.5 Hz, thiophene-H), 8.16–8.21 (m, 2H, Ar–H), 8.61 (s, 1H, Ar–H), 12.00 (s, 1H, NHCO, exchangeable). ^{13}C NMR: 64.4, 116.3, 126.6, 128.9, 129.4, 129.5, 131.0, 132.0, 132.6, 139.7, 143.5, 150.8, 161.0, 164.5, 167.0. **47**: IR (KBr, ν cm^{-1}): 3,212 (NH), 1791, 1751, 1654 (3 C=O). ^{1}H NMR (DMSO-d_6): δ 5.43 (s, 2H, OCH_2CO), 7.25 (s, 1H), 7.69 (d, 1H, J = 8.5 Hz, thiophene-H), 7.82–8.21 (m, 2H), 8.62 (s, 1H, Ar–H), 11.34 (s, 1H, NHCO, exchangeable). ^{13}C NMR: 64.4, 92.5, 116.3, 121.8, 128.9, 129.4, 129.5, 131.0, 132.0, 132.6, 138.0, 143.0, 143.5, 150.8, 156.6, 161.3, 164.5, 166.9. **48**: ^{1}H NMR (DMSO-d_6): δ 5.46 (s, 2H, OCH_2CO), 7.70–8.70 (m, 12H, Ar–H), 11.25 (s, 1H, NHCO, exchangeable). ^{13}C NMR: 64.6, 119.5, 122.1, 127.9, 128.0, 130.2, 132.0, 132.1, 132.7, 133.0, 135.8, 135.9, 143.5, 150.9, 156.6, 161.2, 162.1, 164.0, 166.4, 172.4.

Anticonvulsant screening

The test compounds were freshly dissolved in 99 % DMSO. In a preliminary screening, compounds were used at dose level of 1.5 mol/kg, i.p. Pentylene-tetrazole (PTZ) was freshly dissolved in 0.9 % NaCl and used at dose level of 85 mg/kg, s.c. This dose was found to be the minimum dose which induced 100 % clonic convulsion. Picrotoxin (Pic) was freshly dissolved in 1 ml 0.1 N warmed HCl and the final volume was made up with 0.9 % NaCl. It has been used at dose level of 3.15 mg/kg sc and was given 30 min after the test compounds. Bicuculline (Bic) was freshly dissolved in 1 ml 0.1 N warmed HCl and the final volume was made up with 0.9 % NaCl. It has been used at dose level of 2.7 mg/kg s.c. and was given 30 min after the test compounds. Sodium valproate was freshly dissolved in 0.9 % NaCl and used at a dose level of 200 mg/kg (1.38 mmol/kg) s.c., 30 min after the test compounds.

Pentylenetetrazole (PTZ)-induced convulsion

Pentylenetetrazole seizure threshold test is one of the well-known chemical tests used to evaluate the potential anti-convulsant activity of the tested compounds according to White *et al.*, 1995. Each compound was tested in 10 mice and was given i.p. at dose level of 1.5 mmol. 30 min later, animals received PTZ (85 mg/kg, s.c.) and observed for 30 min. A single 5-s episode of clonic spasms was taken as

a threshold seizure. Compounds **6**, **12**, **21**, **36**, **37**, and **38** produced 100 % protection against PTZ-induced seizures. Those active compounds were further tested against maximal electroshock seizure (MES), picrotoxin, and bicuculline-induced clonic convulsions to explore the involvement of GABA receptors in their anticonvulsant activity.

Effect of tested compounds against the maximal electroshock (MES)-induced convulsion

The MES is one of the electrical tests used to evaluate anticonvulsant activity according to White *et al*., 1995. MES that induced 100 % maximal seizures was found to be 50 mA alternating current of 100 Hz frequency for 0.2 s, using ECT UNIT (model number 7801, UGO Basile, Varese, Italy). 1.5 mmol of the tested compounds (**6**, **12**, **21**, **36**, **37**, and **38**), which produced 100 % protection against PTZ-induced seizures, were injected i.p. 30 min later, mice were restrained by hand and subjected to electric shock through their ears, and released immediately following electrical stimulation to permit observation of the maximal seizure. The maximal seizure typically consists of a short period of initial tonic flexion and a prolonged period of tonic extension (especially the hind limb). Protection was defined as the complete absence of hind limb tonic extension.

Effect of tested compounds against picrotoxin (Pic)-induced convulsion

1.5 mmol of each compounds (**6**, **12**, **21**, **36**, **37**, and **38**), which produced 100 % protection against PTZ-induced seizures, were injected i.p. in 10 mice. 30 min later, animals were injected s.c. with Pic (3.15 mg/kg) and observed for 30 min and the percentage protection against convulsive seizures for each compound was calculated White *et al*., 1995.

Effect of tested compounds against bicuculline (Bic)-induced convulsion

1.5 mmol of each compounds (**6**, **12**, **21**, **36**, **37**, and **38**), which produced 100 % protection against PTZ-induced seizures, were injected i.p. in 10 mice. 30 min later, animals were injected s.c. with Bic (2.7 mg/kg) and observed for 30 min and the percentage protection against convulsive seizures for each compound was calculated White *et al*., 1995.

Minimal neurotoxicity (chimney test)

At 15 and 25 min after i.p. administration of each compounds **12** and **38** (1.5 mmol), the inability of mice to climb up backwards in a glass tube of 25-cm length and 3-cm inner diameter within 30 s was recorded and taken as a measure of neurologic deficits. Normal mice climb up in 5–10 s. (Cheymol *et al*., 1961; Buckley and Dorato, 2009).

Determination of LD_{50} and dose–response curve

Several doses of compounds **12** and **38** which produced 70–100 % protection against MES, Pic, and Bic-induced convulsion were used to construct a dose–response curve. Also, LD_{50} for compounds **12** and **38** was determined by the Spearman–Karber method in which the doses were selected at equal logarithmic intervals White *et al*., 1995.

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