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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis, and biological evaluation studies of novel quinazolinone derivatives as anticonvulsant agents

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Abstract In view of their expected anticonvulsant activity, some novel derivatives of 6,8-diiodo-2-methyl-3-substituted-quinazolin-4(3H)-ones (**4**–**14**) were synthesized, evaluated for their anticonvulsant activity by the maximal electroshock-induced seizure and subcutaneous pentylenetetrazole tests. The neurotoxicity was assessed using rotorod test. All the tested compounds showed considerable anticonvulsant activity in at least one of the anticonvulsant tests. Compounds **5**, **6**, and **8** proved to be the most potent compounds of this series with relatively low neurotoxicity and low toxicity in the median lethal dose test when compared with the reference drugs. The obtained results showed that the most potent compounds could be useful as a template for future design, optimization, and investigation to produce more active analogs.

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Introduction

Epilepsy is ubiquitous disease characterized by recurrent seizures and inflicts >60 million people worldwide according to epidemiological studies (Leppik, 1994). Every year ~250,000 new cases are added to this figure. About 28–30 % of epilepsy patients have a multidrug resistance and develop refractory epilepsy (RE). This particular refractoriness is now attributed to overexpression and upregulation of p-glycoprotein in brain, leading to impaired access of antiepileptic drugs to CNS targets. These findings were documented in both human as well as in experimental models of RE after the biological examination of brain capillary endothelial cells from cerebral cortex biopsies from normal and drug-resistant epileptic patients (Chen *et al*., 2007).

Despite the development of several new anticonvulsants, the treatment of epilepsy remains still inadequate and the patients suffer from many side effects like neurotoxicity, depression, and other CNS disorders. Therefore, it is necessary to search for safer and more effective anticonvulsants (French, 1999).

The sedative-hypnotic (neurotoxicity) properties of 4(3H)-quinazolinone are well documented (Jatav *et al*., 2008). A literature survey revealed that the presence of aromatic or aliphatic group at position 2 and a substituted aromatic ring at position 3 are essential requirements for CNS activities of quinazolinone moiety predominantly anticonvulsant properties (Nagwa *et al*., 2011). 2-Methyl-3-O-tolyl 4(3H)-quinazolinone (methaqualone) is an important landmark in the field of synthetic anticonvulsant and prototype

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sedative-hypnotic containing quinazolinone ring system (Wolfe *et al*., 1990). Many quinazolinones structurally related to compound methaqualone were synthesized and biologically tested for their anticonvulsant activity. None of those compounds are clinically used (Aziza, 1997) because of the fact that, nearly every derivative tested in combined neurotoxicity and anticonvulsant screenings exhibited neurotoxicity values (TD_{50}'s) that are less than or only slightly higher than the effective doses (ED_{50}'s) consequently, the protective index (PI) corresponding to (TD_{50}/ED_{50}) is too low (Zappalà *et al*., 2003).

Results and discussion

Rationale and structure-based design

Various reported facts were analyzed before the chemical synthesis of our target compounds. First fact was: modifications at second and third positions of methaqualone have led to the generation of many CNS active agents as afaqualone and mecloqualone. Mecloqualone was found to possess a significant anticonvulsant action 1.5 times more potent than phenytoin against MES-induced convulsions and ten times more potent than troxidone against PTZ-induced seizures (Zappalà *et al*., 2003). Second fact explained that substitution of the quinazolinone ring with halogens or electron rich group at 6th or 8th positions greatly enhanced the anticonvulsant activity as in compound (A) which has been reported to posses better activity, longer duration and lower toxicity than phenytoin and ethosuximide (Saravanan *et al*., 2012). Figure (1) represents the structural similarities and pharmacophoric features of some reported anticonvulsants quinazolinones and our designed compounds. Based on the previously mentioned facts, it appeared to us that considerable promise for discovering of new anticonvulsants might be found through the synthesis of structural analogs of these compounds.

Figure (1) showed that structure of the title compounds **(4–14)** fulfilled all the pharmacophoric structural requirements. These requirements include: the presence of quinazolin-4(3H)-one moiety as hydrophobic portion, N as electron donor system, the presence of carbonyl group and another hydrophobic distal aryl ring responsible for controlling the pharmacokinetic properties of the antiepileptic activity.

The present study was carried out to prepare the target compounds as hybrid molecules. These molecules formed of quinazolinone ring system joined with aromatic amine derivatives. The target compounds were also designed to contain different substituents with different electronic environments to study the SAR of these compounds and the effect of each substituent on their anticonvulsant activity. Quinazolinone moiety joined with aromatic unit through an aliphatic linker (CH_2) to form group of novel compounds maintaining basic features of the lead structure methaqualone. All the target compounds contain iodine. Iodine was selected because it has received considerable attention in organic synthesis due to its high tolerance to air and moisture, low-cost, nontoxic nature, and ready availability (Laznicek *et al*., 1985; Wang *et al*., 2003). The presence of iodine at 6th and 8th positions increases the lipophilicity of the molecules, the hydrophobic surface of contact the absorption and the distribution (Ugale *et al*., 2012). This study was carried out in hope of developing potent, safe, new and effective anticonvulsant agents with low dose-related toxicity and without idiosyncratic side effects.

Chemistry

The synthetic strategy to prepare the target compounds (**4–14**) is depicted in Scheme 1: it includes two simple reactions, first one is acetylation/benzoylation followed by ring closure reaction for 2-amino-3,5-diiodobenzoic acid (**1**) when refluxed with acetic anhydride for 1 h, converted to benzoxazinone. This reaction afforded quantitative yield of 6,8-diiodo-2-methyl-4H-benzo[d][1,3]oxazin-4-one (**2**). Second reaction is a nucleophilic displacement reaction for the oxygen of benzoxazinone with the nitrogen of amino group upon treating with substituted aromatic amines. These amines were selected following a second manual method of the Hansch approach to drug design suggested by Topliss (1977). Hansch approach is a procedure in which an initial small group of compounds are selected, tested, and ordered according to potency.

The title compounds were designed to contain unsubstituted, monosubstituted, and disubstituted aromatic ring with different kinds of halogens and other hydrophobic and hydrophilic groups of different electronic environment either electronic rich or electronic deficient groups to study SAR of these compounds and compare the differences in their anticonvulsant activity. The second reaction was done by refluxing compound (**2**) with the appropriate aromatic amine in dry conditions for 6 h to give target compounds of 6,8-diiodo-2-methyl-3-substituted-quinazolin-4(3H)-one (**4–14**).

Biological screening

The anticonvulsant activity of the target compounds were evaluated by the use of standard techniques (Krall *et al*., 1968; Yogeeswari *et al*., 2005), while the acute neurotoxicity was done according to the method described by

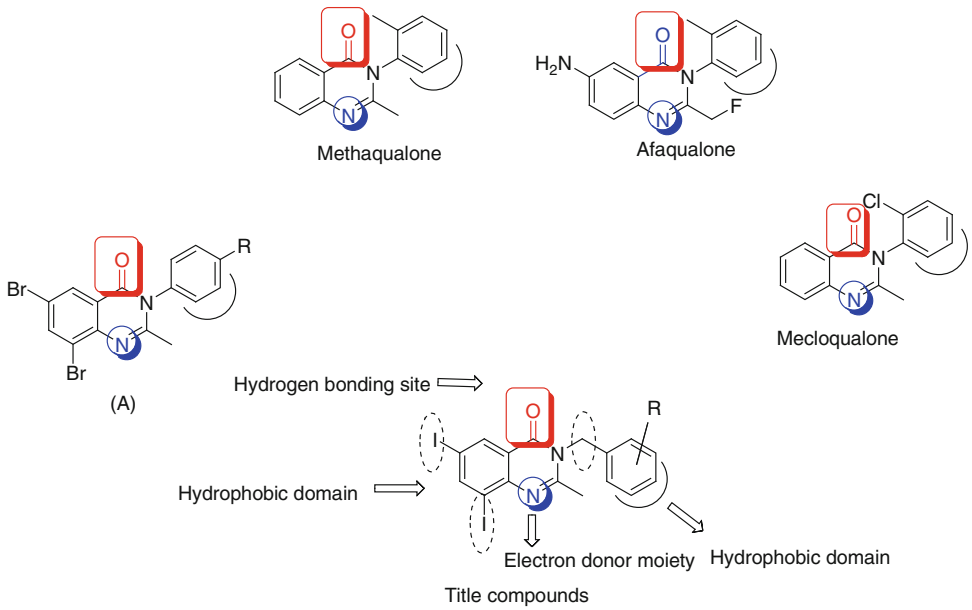
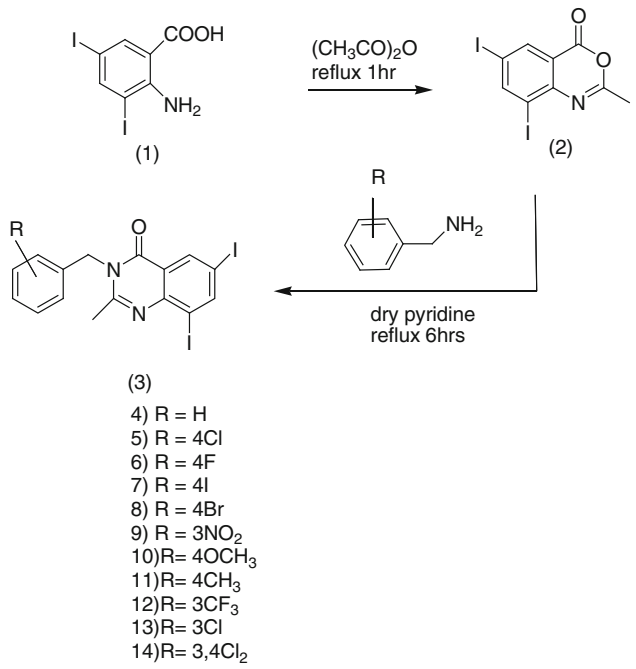


Fig. 1 Structural similarities and pharmacophoric features of reported and designed quinazolinones (**4–14**) as anticonvulsants



Scheme 1 Synthesis of target compounds **4–14**

Dunham and Miya (1957). The preliminary screening was performed at 0.5 mmol/kg of all synthesized compounds (**4–14**) by chemical induction of the convulsions using of pentylenetetrazole (PTZ) and electrical induction of convulsions using maximal electroshock (MES) models of seizures (Crivori *et al*., 2000). The MES model has served to identify the anticonvulsants that are functionally similar to phenytoin. Activity in this model seems highly predictive of the ability of those anticonvulsants to protect against generalized tonic–clonic seizures. The scPTZ model has been proven to be a good predictor of clinical efficacy against generalized spike-wave epilepsies which are known as the absence seizures. Thus, the MES and scPTZ screens have become the most widely employed seizure models for initial identification of candidate anticonvulsants (Rogawski, 2006). The initial anticonvulsant evaluation showed that all of the target compounds were active in mice i.p. against PTZ at 0.5 mmol/kg, among which compounds **5**, **6**, **8**, **9**, and **13** showed 100 % protection, compounds **4**, **7**, **10,** and **14** showed 66 % protection while compounds **11** and **12** showed 50 % protection. For the MES test, compounds **5**, **6**, and **8** showed 100 % protection, compounds **7**, **9**, **13**, and **14** showed 66 % protection, compound **4** showed 50 % protection while compounds **10**, **11,** and **12** presented 33 % protection. The results explained in Table (1).

From the result of preliminary screening, the most active compounds **5**, **6**, and **8** were subjected to further investigations in mice i.p. at different doses for quantification of their anticonvulsant activity which indicated by the effective dose causing protection for 50 % of mice (ED_{50}) and neurotoxicity which indicated by median toxic dose producing minimal neurological toxicity in 50 % of mice (TD_{50}).

As demonstrated in Table (2), the selected compounds **5**, **6**, and **8** exhibited anticonvulsant activity against PTZ-induced seizure with (ED_{50}) values of 150, 160, and 138 mg/kg, respectively. Methaqualone and valproate were used as reference drugs produced (ED_{50}) values of 200 and 300 mg/kg, respectively. The (ED_{50}) values of the selected compounds were found to be smaller than the reference anticonvulsant drugs at molar doses. The protective index (PI) = (TD_{50}/ED_{50}) is defined to be an index representing the margin of safety and tolerability between

Table 1 Preliminary anticonvulsant activity of the newly synthesized compounds and C log P values of the most potent compounds, comparing compounds (0.5 mmol/kg), methaqualone (0.8 mmol/kg), and valproate (1.8 mmol/kg)

Compound	PTZ (% protection)	MES (% protection)	C log P
4	66	50	–
5	100	100	6.03844
6	100	100	5.88844
7	66	66	–
8	100	100	5.31844
9	100	66	–
10	66	33	–
11	50	33	–
12	50	33	–
13	100	66	–
14	66	66	–
21	66	66	3.777
22	66	66	4.91335
23	100	66	6.26531
Methaqualone	100	100	3.64597
Valproate	100	100	2.76

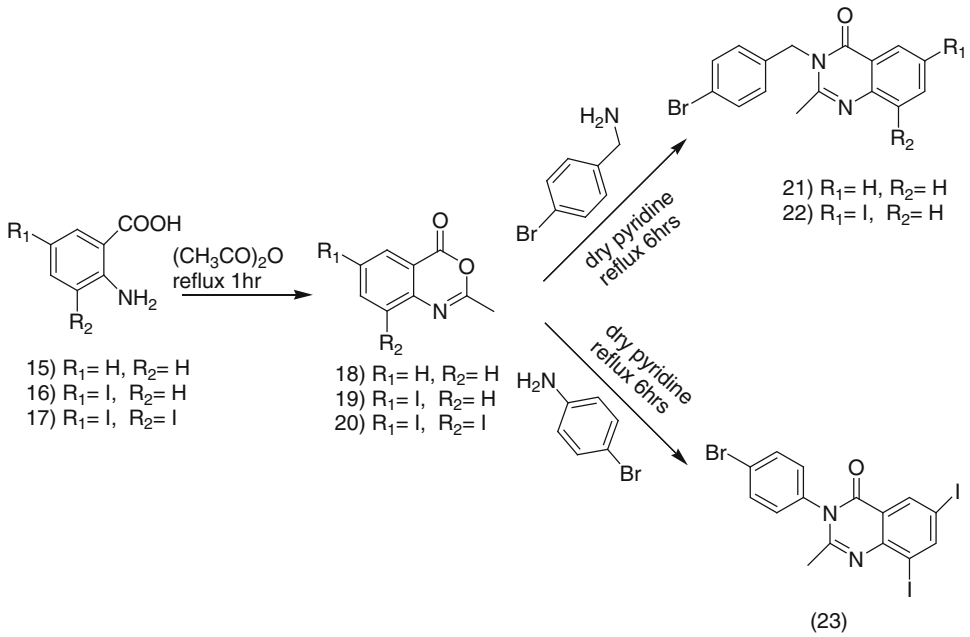
anticonvulsant doses and doses of anticonvulsant drugs exerting acute adverse effects like sedation, motor coordination impairment, ataxia, or any other neurotoxic manifestations (Loscher and Nolting, 1991). The most potent compounds **5**, **6**, and **8** had (TD_{50}) values of 280, 360, and 330 mg/kg. These values revealed that these agents exerted low neurological disorders. From the results of ED_{50} and TD_{50}, compounds **5**, **6,** and **8** had (PI) values of 1.87, 2.25, and 2.39, which means that compounds **6** and **8** had higher (PI) values than the reference drugs methaqualone and valproate as shown in Table (2). The present results are implying high safety margin of the synthesized compounds when compared with the reference drugs. The therapeutic index (TI) = (LD_{50}/ED_{50}) is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes death in mice (Zappalà *et al*., 2003). Compounds **5**, **6**, and **8** had (LD_{50}) values of 600, 420, and 565 mg/kg with (TI) values of 4, 2.62, and 4.09. It is worthwhile to note that (TI) values of the most potent compounds **6** and **8** were found to be higher than that of the reference anticonvulsant drugs as shown in Table (2). The results of the anticonvulsion screening methods in the present study showed that some new quinazolinones were effective in controlling the seizures induced by PTZ and MES. From the MES test, one can suggest that the anti-seizure effects of agents or drugs that suppress tonic–clonic seizures through raising seizure's threshold and/or possessing the ability to prevent the spread of seizure discharge throughout neuronal tissues (Dunham and Miya, 1957).

Concerning their partial effectiveness, our newly synthesized compounds can control the seizures induced by PTZ and MES indicating that these compounds exhibited a broad spectrum of anticonvulsant activity in animal models of partial and generalized epilepsy. The high lipid solubility of the target compounds might account for their good activity, in addition, more detailed study on the GABA pathways, neurotransmitter levels and MDR of our newly synthesized compounds might be interesting and might provide us with more insights for the anticonvulsant effects of the newly synthesized quinazolinones which will be considered extensively in our future study. However, at present, some of our newly synthesized compounds have relatively significant anticonvulsant effects combined with relatively low neurotoxicity. Structure activity relationship (SAR) studies indicated that different substitution on the aromatic ring, exerted varied anticonvulsant activities. The electronic nature of the substituent group attached to the aromatic ring led to a significant variation in anticonvulsant activity. From the data shown above, it is clear that the presence of electron withdrawing group at aromatic ring enhanced the activity when compared to unsubstituted or electron donating group in the phenyl ring. For example, electronic withdrawing groups (mainly bromo substitution) enhanced the anticonvulsant activity whereas non-bromo analogs showed less activity and the order of analogs activity was monobromo analog (**8**) > monochloro analog (**5**) > monofluoro analog (**6**) > monochloro and mononitro analogs (**13**, **9**) > monoiodo and dichloro analogs (**7**, **14**) > unsubstituted analog (**4**) > monomethoxy analog (**10**) > monomethyl and trifluromethyl analogs (**11**, **12**).

Table 2 ED_{50}, TD_{50}, LD_{50}, therapeutic index (TI) and protective index (PI) for the most active compounds 5, 6, and 8 compared to reference drugs methaqualone and valproate

Compound	ED_{50} (mg/kg)	TD_{50} (mg/kg)	LD_{50} (mg/kg)	Therapeutic index (TI)	Protective index (PI)
5	150	280	600	4	1.87
6	160	360	420	2.62	2.25
8	138	330	565	4.09	2.39
Methaqualone	200	400	500	2.5	2
Valproate	300	450	500	1.66	1.5

Scheme 2 Synthesis of the comparing compounds **(21–23)**



From the structure of newly synthesized compounds, we can notice that there are two major differences between them and the related lead structure methaquolane, first difference is substitution at 6th and 8th position with diiodo substituent and second difference is the presence of (CH_2) linker between aromatic moiety and quinazolinone moiety. For practical assessment of these two differences and for determination the role of them, the highest potent compound (**8**) which was selected for further investigations and quantitative study of target compounds and had best ED_{50}, was synthesized again with unsubstituted quinazolinone moiety (compound **21**), monoiodo substitution (compound **22**) and without (CH_2) linker (compound **23**) as shown in Scheme (2).

All of the comparing compounds were tested the same way under the same conditions of testing target compounds to measure their anticonvulsant activity and compare it to that of the target compounds. The initial anticonvulsant evaluation of these three compounds showed that compounds **21** and **22** were active against PTZ and MES at 0.5 mmol/kg and they presented 66 % protection against chemical and electrical convulsants while compound **23** presented 100 % protection in PTZ and 66 % in MES at 0.5 mmol/kg. The initial activity of these compounds were less than that of the title compounds which indicated and confirmed the role of diiodo substitution and (CH_2) linker in enhancement the activity of our target compounds as anticonvulsant agents.

C log P correlation

As a trial for interpretation the correlation between chemical structure of compounds **5**, **6**, **8**, **21**, **22**, and **23** with their biological activity, an attempted correlation of anticonvulsant activity with C log P data were calcd. for measurement the lipophilicity factor which could be attributed in their anticonvulsant activity. For antiepileptic agents to be effective, they have to cross the blood brain barrier (BBB) (Crivori *et al*., 2000). Crossing the brain is therefore a crucial step in developing effective drug therapies for treatment of neurological disorders. Lipophilic substances are able to permeate into the brain interstitium in a relatively easy way (Bhaduri *et al*., 1964). Determination of brain-blood partitioning in vitro is difficult, time-consuming, expensive, not always available and not suitable to screen a large collection of new chemicals. Therefore, an alternative method was used based on computerized models (Cambridge software). So, the C log P values were calcd. for some compounds to reflect the overall lipophilicity of these compounds and compare between them. It is postulated that a C log P value of at least 2.0 is required by a specific compound to cross the BBB (Shank *et al*., 2000). The C log P data for all selected anticonvulsant compounds (**5**, **6**, **8**, **21**, **22**, and **23**) explained in Table (1) and ranged from 3.777 to 6.26531. All the compounds were found to have C log P values above 2 which required for effective penetration in the brain. It is worthwhile to note that the C log P values for compounds **5**, **6,** and **8** which had higher potency were higher than that of the other two compounds **21** and **22** which might explain the significant variation in their biological activity in correlation with their lipophilicity. While compound **23** had higher C log P value than other compounds and had no correlation with the lipophilicity factor. Interestingly, the values of C log P for the selected potent compounds agree with their potency levels, compound (**8**)

which had the highest activity, had also highest C log P value (6.03844), while compound 5 which had the medium activity, had medium C log P value (5.88844) and compound (**9**) had lowest C log P value as its activity (5.31844). In general, it was found that compounds having more C log P values having higher potency as anticonvulsant agents.

Experimental

General

All chemicals used for synthesis were purchased from (Sigma-Aldrich). All m.p. were measured on a Griffin melting point apparatus (Griffin) and were uncorrected. The Infrared spectra were recorded as KBr disks on a Nicolet IR 200 (Thermo Fisher Scientific).^{1}HNMR and ^{13}C NMR was recorded in DMSO-d_6 and/or $CDCl_3$ on a Jeol 500 MHz instrument using TMS as internal standard (chemical shifts in d ppm). MS were obtained on a JEOL-SX-102 instrument using electron impact ionization. Solvent evaporation was done under reduced pressure using Buchi rotary evaporator. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 240C analyzer (Perkin-Elmer). All compounds were within ± 0.4 % of the theoretical values. The elemental analyses indicated that purity of the synthesized compounds was above 99.6 %.

6,8-Diiodo-2-methyl-4H-benzo[d][1,3]oxazin-4-one (**2**)

It was prepared by refluxing (3.88 g, 0.01 mol) of 2-amino-3,5-diiodobenzoic acid (1) with appropriate amount of acetic anhydride for 1 h. The residue obtained was evaporated tell complete dryness, left to cool, washed with petroleum ether many times, collected, filtered, and dried well in the absence of moisture.

Yield 85 %, mp: 245–247 °C; ^{1}HNMR (DMSO-d_6): δ 1.21(s, 3H, CH_3) 7.21–8.19 (m, 2H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 24, 90, 118, 138, 149, 150, 154, 158.Anal. Calcd. For $C_9H_5I_2NO_2$ (412.84): C, 26.18; H, 1.22; N, 3.39. Found C, 26.32; H, 1.01; N, 3.74. MS (EI) *m/z* 412.8 [M+1].

General method for preparation of test compounds (**4–14**)

They were prepared in a conical flask by mixing (0.01 mol, 4.13 g) of compound (2) with the appropriate amount (0.01 mol) of aromatic amine derivatives in 100 ml dry pyridine, refluxed for 6 h, cooled then treated with few amount of 10 % hydrochloric acid and poured on crushed ice. The obtained crystals collected by filtration and recrystallized from ethanol or glacial acetic acid. The method used for the preparation and isolation of the compounds gave materials of good purity, as evidenced by their spectral analyses and by thin layer chromatography. All m.p. were above 300 °C.

3-Benzyl-6,8-diiodo-2-methylquinazolin-4(3H)-one (**4**)

Yield 73 %, ^{1}HNMR (DMSO-d_6): δ 1.05 (s, 3H, CH_3), 4.91 (s, 2H, CH_2), 6.96–8.17 (m, 7H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 21, 41, 82, 91, 122, 124., 125, 127, 128, 132, 145, 149, 155, 157, 164. Anal. Calcd. for $C_{16}H_{12}I_2N_2O$ (501.9): C, 38.27; H, 2.41; N, 5.58. Found C, 38.51; H, 2.61; N, 5.39. MS (EI) *m/z* 502.9 [M+1].

3-(4-Chlorobenzyl)-6,8-diiodo-2-methylquinazolin-4(3H)-one (**5**)

Yield 70 %, ^{1}HNMR (DMSO-d_6): δ 2.34 (s, 3H, CH_3), 4.69 (s, 2H, CH_2), 7.01–8.23 (m, 6H, Ar–H). ^{13}C NMR (DMSO-*d*6): δ 21, 44, 82, 93, 123, 126., 127, 128, 129, 132, 135, 153, 155, 162. Anal. Calcd. for $C_{16}H_{11}ClI_2N_2O$ (535.86): C, 35.82; H, 2.07; N, 5.22. Found C, 35.61; H, 2.31; N, 5.17. MS (EI) *m/z* 536.8 [M+1].

3-(4-Florobenzyl)-6,8-diiodo-2-methylquinazolin-4(3H)-one (**6**)

Yield 68 %, ^{1}HNMR (DMSO-d_6): δ 2.43 (s, 3H, CH_3), 4.87 (s, 2H, CH_2), 7.11–8.43 (m, 6H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 21, 44, 82, 94, 110, 117, 123, 126, 134, 142, 153, 156, 160, 164. Anal. Calcd. for $C_{16}H_{11}FI_2N_2O$ (519.89): C, 36.95; H, 2.13; N, 5.39. Found C, 36.71; H, 2.37; N, 5.54. MS (EI) *m/z* 520.8 [M+1].

6,8-Diiodo3-(4-iodobenzyl)-2-methylquinazolin-4(3H)-one (**7**)

Yield 65 %, ^{1}HNMR (DMSO-*d*6): δ 2.49 (s, 3H, CH_3), 4.72 (s, 2H, CH_2), 7.08–8.23 (m, 6H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 21, 45, 82, 93, 96, 126, 134, 138, 139, 140, 146, 153, 156, 164. Anal. Calcd. for $C_{16}H_{11}I_3N_2O$ (627.8): C, 30.60; H, 1.77; N, 4.46. Found C, 36.42; H, 1.93; N, 4.57. MS (EI) *m/z* 628.8 [M+1].

3-(4-Bromobenzyl)-6,8-diiodo-2-methylquinazolin-4(3H)-one (**8**)

Yield 62 %, ^{1}HNMR (DMSO-d_6): δ 2.34 (s, 3H, CH_3), 4.86 (s, 2H, CH_2), 7.01–8.23 (m, 6H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 21, 44, 82, 93, 123, 127, 128, 129, 132, 135, 138, 153, 155, 162. Anal. Calcd. for $C_{16}H_{11}BrI_2N_2O$ (579.81): C, 33.08; H, 1.91; N, 4.82. Found C, 32.96; H, 2.01; N, 5.11. MS (EI) *m/z* 580.8 [M+1].

*6,8-Diiodo3-(3-nitrobenzyl)-2-methylquinazolin-4(3H)-one (**9**)*

Yield 58 %, ^{1}HNMR (DMSO-d_6): δ 2.46 (s, 3H, CH_3), 4.92 (s, 2H, CH_2), 7.14–8.41 (m, 6H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 24, 45, 84, 98, 120, 123, 128, 129, 132, 137, 143, 145, 148, 152, 158, 164. Anal. Calcd. for $C_{16}H_{11}I_2N_3O_3$ (546.89): C, 35.13; H, 2.03; N, 7.68. Found C, 35.41; H, 2.24; N, 7.57. MS (EI) *m/z* 547.8 [M+1].

*6,8-Diiodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3H)-one (**10**)*

Yield 60 %, ^{1}HNMR (DMSO-d_6): δ 2.31 (s, 3H, CH_3), 3.28 (s, 3H, OCH_3), 4.51 (s, 2H, CH_2), 7.11–8.33 (m, 6H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 23, 46, 58, 85, 96, 114, 122, 130, 137, 143, 149, 156, 158, 162, 164. Anal. Calcd. for $C_{17}H_{14}I_2N_2O_2$ (531.91): C, 38.37; H, 2.65; N, 5.26. Found C, 38.21; H, 2.81; N, 5.19. MS (EI) *m/z* 532.9 [M+1].

*6,8-Diiodo-2-methyl-3-(4-methylbenzyl)quinazolin-4(3H)-one (**11**)*

Yield 65 %, ^{1}HNM R (DMSO-d_6): δ 2.16 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.67 (s, 2H, CH_2), 7.09–8.24 (m, 6H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 21, 23, 47, 85, 96, 124, 129, 130, 133, 135, 138, 149, 154, 157, 162. Anal. Calcd. for $C_{17}H_{14}I_2N_2O$ (515.91): C, 39.56; H, 2.73; N, 5.43. Found C, 39.71; H, 2.89; N, 5.61. MS (EI) *m/z* 516.9 [M+1].

*6,8-Diiodo-2-methyl-3-(3-trifluoromethyl)benzyl) quinazolin-4(3H)-one (**12**)*

Yield 55 %, ^{1}HNMR (DMSO-d_6): δ 2.34 (s, 3H, CH_3), 4.78 (s, 2H, CH_2), 7.19–8.31 (m, 6H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 24, 48, 86, 98, 122, 124, 126, 128, 129, 132, 134, 138, 138, 149, 156, 158, 164. Anal. Calcd. for $C_{17}H_{11}F_3I_2N_2O$ (569.89): C, 35.82; H, 1.94; N, 4.91. Found C, 35.63; H, 2.21; N, 5.22. MS (EI) *m/z* 570.9 [M+1].

*3-(3-Chlorobenzyl)-6,8-diiodo-2-methylquinazolin-4(3H)-one (**13**)*

Yield 68 %, ^{1}HNMR (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 4.63 (s, 2H, CH_2), 7.06–8.41 (m, 6H, Ar–H). ^{13}C NMR (DMSO-d_6): 2 δ 1, 43, 84, 92, 122, 124, 126, 128, 129, 129, 132, 135, 152, 155, 161. Anal. Calcd. for $C_{16}H_{11}ClI_2N_2O$ (535.86): C, 35.82; H, 2.07; N, 5.22. Found C, 35.57; H, 2.28; N, 5.41. MS (EI) *m/z* 536.8 [M+1].

*3-(3,4-Dichlorobenzyl)-6,8-diiodo-2-methylquinazolin-4(3H)-one (**14**)*

Yield 61 %, ^{1}HNMR (DMSO-d_6): δ 2.19 (s, 3H, CH_3), 4.72 (s, 2H, CH_2), 6.93–8.01 (m, 5H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 24, 36, 88, 98, 125, 129, 129, 132, 132, 136, 138, 145, 149, 156, 158, 165. Anal. Calcd. for $C_{16}H_{10}Cl_2I_2N_2O$ (569.83): C, 33.66; H, 1.77; N, 4.91. Found C, 33.87; H, 1.92; N, 5.04. MS (EI) *m/z* 570.8 [M+1].

*3-(4-Bromobenzyl)-2-methylquinazolin-4(3H)-one (**21**)*

Yield 68 %, ^{1}HNMR (DMSO-d_6): δ 2.21 (s, 3H, CH_3), 4.68 (s, 2H, CH_2), 7.03–7.98 (m, 8H, Ar–H). ^{13}C NMR (DMSO-d_6): 2 δ 4, 46, 121, 123, 124, 127, 128, 130, 132, 136, 145, 149, 158, 164. Anal. Calcd. for $C_{16}H_{13}BrN_2O$ (328.02): C, 58.38; H, 3.98; N, 8.51. Found C, 58.55; H, 4.21; N, 8.37. MS (EI) *m/z* 329 [M+1].

*3-(4-Bromobenzyl)-6-iodo-2-methylquinazolin-4(3H)-one (**22**)*

Yield 64 %, ^{1}HNMR (DMSO-d_6): δ 2.19 (s, 3H, CH_3), 4.53 (s, 2H, CH_2), 7.13–8.24 (m, 7H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 24, 48, 96, 122, 127, 128, 132, 134, 137, 142, 146, 148, 158, 163. Anal. Calcd. for $C_{16}H_{12}BrIN_2O$ (453.92): C, 42.23; H, 2.66; N, 6.16. Found C, 42.51; H, 2.81; N, 6.34. MS (EI) *m/z* 454.9 [M+1].

*3-(4-Bromophenyl)-6,8-diiodo-2-methylquinazolin-4(3H)-one (**23**)*

Yield 60 %, ^{1}HNMR (DMSO-*d*6): δ 2.27 (s, 3H, CH_3), 7.23–8.31 (m, 6H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 24, 87, 121, 126, 128, 136, 138, 138, 149, 154, 158, 162. Anal. Calcd. for $C_{15}H_9BrI_2N_2O$ (565.8): C, 31.78; H, 1.60; N, 4.94. Found C, 31.91; H, 1.89; N, 5.19. MS (EI) *m/z* 566.8 [M+1].

Pharmacological tests

Adult male white Swiss albino mice weighing 20–30 g (10–12 weeks old) were obtained from Experimental Animal Care Centre, King Abdul-Aziz University. The animals were maintained under standard conditions of humidity, temperature (23 ± 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. The protocol adopted for the testing of animals was approved by Institutional Animal Ethics Committee (approval No: 409/432). All the trials

were carried out according to the respective internationally valid guidelines. Each test group and vehicle control group included six animals.The anticonvulsant activities of all title compounds were evaluated by two models, pentylentetrazole (PTZ), and maximal electroshock (MES) models according to the reported procedures (Vogel and Vogel, 2002). The test compounds were dissolved 10 % DMSO and injected i.p. at dose of 0.5 mmol/kg 30 min before seizures induction. Methaqualone (0.8 mmol/kg) and sodium valproate (1.8 mmol/kg) were used as reference drugs. In the MES test, the electrical stimulus produced from electroconvulsiometer was 50 mA, 60 Hz. The current was applied for 0.2 s via auricular electrodes. Protection against the spread of MES-induced seizures identified by the abolition of the hind leg and tonic maximal extension component of the seizure (Woodbury and Davenport, 1952). The PTZ test was performed by the i.p. injection of a convulsing dose of PTZ (100 mg/kg). Seizures and tonic–clonic convulsions, hypnosis and death were recorded. The highest potent compounds **5**, **6,** and **8** were further evaluated at different doses in PTZ model to determine their protective and therapeutic indexes. Groups of 6 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, (ED_{50}) was determined, slopes of the regression line and the standard error were calcd. using a computer program based on the method described by Finney (1971). The animals considered to be protected if showed no convulsion within 1 h after convulsive drug administration (Everett and Richards, 1952). Neurological toxicity (NT) was determined by rotrod test in mice using the method reported by Dunham and Miya (1957). In brief, group of animals (mice) were trained to balance on a rotating rod (3 cm diameter and 6 rpm speed) and they allowed three attempts to remain on the rotating rod for 20 s. The trained animals were treated with the tested compounds at a various dose levels by i.p. administration. The tested compounds considered to be neurotoxic at a particular dose level if the trained animal showed lack of Rolling Roller Performance. The trained animals were tested in this manner at 30 min and 4 h after the drug administration and then the neurotoxic effect was recorded in terms of median toxic dose (TD_{50}). The protective index was determined from the equation ($PI = TD_{50}/ED_{50}$). The median lethal dose (LD_{50}), the dose that causes 50 % mortality in mice was determined from dose-response curves with at least four doses according to the reported method by Litchfield and Wilcoxon (1949). Therapeutic index was determined from the equation ($TI = LD_{50}/ED_{50}$).

Conclusions

New derivatives of 4(3H)-quinazolinones were synthesized and evaluated for their anticonvulsant activity and acute neurotoxicity in mice. The results of this study demonstrated that some 6,8-diiodo-2-methyl-3-substituted-4(3H)-quinazolinones derivatives possess a good anticonvulsant activity, specially, compounds **5**, **6**, and **8** showed better anticonvulsant activity and much lower toxicity compared with the reference drugs. The obtained results showed that compounds **5**, **6,** and **8** could be useful as a template for future design, optimization, and investigation to produce more active analogs.

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