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Synthesis, anticonvulsant activity and molecular modeling study of some new hydrazinecarbothioamide, benzenesulfonohydrazide, and phenacylacetohydrazide analogues of 4(3*H*)-quinazolinone ☆

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ABSTRACT

A new series of quinazoline analogues was designed and synthesized to get the target compounds **18**–**21**, **30**–**41**, **46**–**53**, and **57**–**76**. The Obtained compounds were evaluated for their anticonvulsant activity using PTZ and picrotoxin convulsive models. Compounds **47**, **63**, **68** and **73** proved to be the most active compounds in this study with a remarkable 100% protection against PTZ induced convulsions. Compounds **47**, **63**, **68** and **73** proved to be 10, 4, 4, and 5 fold more active, respectively than the used positive control sodium valproate. Structure activity correlation concluded valuable pharmacophoric information which confirmed by molecular modeling studies. Molecular docking study of **68** suggested its agonistic behavior toward $GABA_A$ receptor. The studied quinazoline analogues could be considered as useful templates for future development and further derivatization.

Despite the broad and growing array of antiepileptic drugs (AEDs) available for treatment, approximately 30% of epileptic patients have inadequate seizure control and a further 25% suffer from significant adverse effects.[1] Thus there is an ongoing need to develop more AEDs that are effective and endowed with improved safety profile. Recently, a number of fused pyrimidine derivatives became known as potential drug molecules against various types of diseases. One of the most important compound families are quinazolinones which are the building blocks for approximately 150 naturally occurring alkaloids and drugs.[2] Literature survey reveals that natural quinazolinones and their synthetic analogues possess a variety of pharmacological activities, including antitumor,[3–5] CNS depressant,[6] antimicrobial,[7,8] and muscle relaxant activities.[9,11]

Methaqualone (**1**) is an important landmark in the field of synthetic anticonvulant,[12] and its 6-chloro analogue **2** which proved to possess marked anticonvulsant action, 1.5 times more potent than phenytoin sodium (**3**) against electroshock induced convulsions and 10 times more potent than troxidone (**4**) against pentylenetetrazol induced seizures.[13,14] Several quinazolinones related to **1** have been synthesized and tested; a persistent problem arises from the fact that nearly every derivative exhibited neurotoxicity values (TD_{50}) that are less than or only slightly higher than the ED_{50} values. Consequently, the protective index (PI) corresponding to TD_{50}/ED_{50} is too low.[15,16] Modification of the 2-methyl group of **1** by some other chemical moiety yielded structural analogues with potent anticonvulsant activity.[17] In continuation to our previous efforts, recently some new quinazoline analogues that possess remarkable anticonvulsant activity were prepared in our laboratory such as **5**, (ED_{50} 73.1 mg/kg), which showed a 100% protection against PTZ induced clonic convulsion (Chart 1).[18–20]

Based on the previous mentioned considerations, bearing in mind the inherited anticonvulsant potency of quinazoline nuclei, the CNS activity enhancement of the thioacetic acid hydrazide, and the potentiating effect of alkoxy functions and halogens to the anticonvulsant activity,[2,10] the combination of all these features in one structure to produce derivatives **6**–**9** was rationalized, (Chart 2). A new series of quinazoline analogues were synthesized

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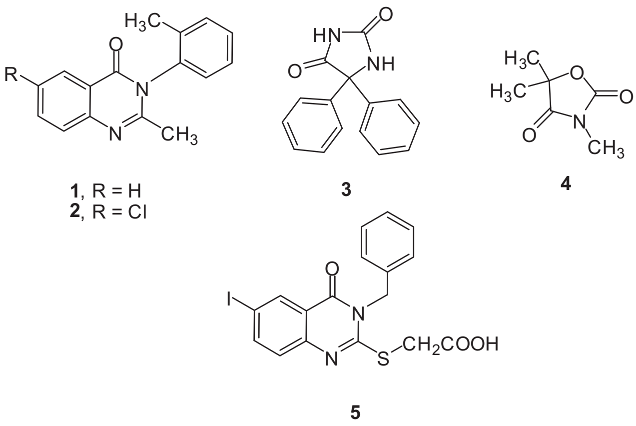
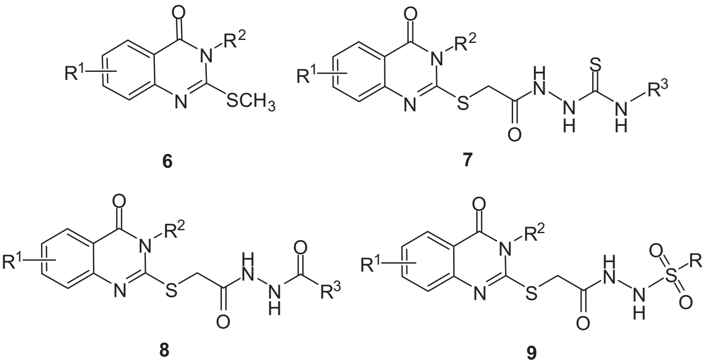


Chart 1. Structures of some literature anticonvulsants.

to explore the influence of both phenyl or benzyl substituent at position 3- of the quinazoline nucleus, in addition to the electronic effect of the electron withdrawing Cl group at position 6- and two adjacent electron donating OCH_3 groups at positions 6- and 7- on the anticonvulsant activity and hence the deduction of structure activity relationship (SAR). Biological evaluation of the new synthesized anticonvulsant compounds **18–21**, **30–41**, **46–53**, and **57–76** were performed using different convulsive models, as well as the determination of the median effective (ED_{50}), median sedative (TD_{50}), and median lethal (LD_{50}) doses; protective index (PI), and therapeutic index (TI) of the proven active compounds. Molecular modeling study was employed to explain the reasons behind the obtained remarkable anticonvulsant potency, which allowed the filling for a European Patent.[21]

The synthetic strategy for the preparation of the target compounds **18–21**, **30–41**, **46–53**, **57–76** were illustrated in Schemes 1 and 2. The 2-mercapto-3-(phenyl or benzyl)-quinazolin-4(3*H*)one derivatives **14–17** were prepared by the reaction of the substituted-anthranilic acid **10** and **11** with phenyl-isothiocyanate (**12**) or benzyl-isothiocyanate (**13**) in ethanol in the presence of catalytic amount of triethylamine to give the 3-phenyl (**14**, **15**), and the 3-benzyl (**16**, **17**) derivatives, respectively. Compound **15** was previously reported.[22] The obtained products were methylated using CH_3I/K_2CO_3 to give the 2-(methylthio)-analogues **18–21**, or treated with ethyl 2-chloroacetate to yield the 3-substituted-quinazolin-2-yl-thioacetates **22–25**. The latter products were reacted with hydrazine hydrate in ethanol to afford the 2-acetohydrazide derivatives **26–29**. Compounds **26–29** were further reacted with the isothiocyanate derivatives **12** or **13** to obtain the target compounds **30–37**. On the other hand, the target compounds **38–41** were obtained by stirring the acetohydrazide derivatives **26–29** with 4-toluene sulfonylchloride in chloroform at room temperature (Scheme 1, Table 1). The 3-phenyl-aceto hydrazide analogues **26** and **27** were acylated by the use of chloroformic solution of aliphatic acid chlorides namely; acetyl, propionyl, butyryl, and 2-methylbutanoyl chlorides (**42–45**) to afford the target compounds **46–53**; or aromatic acid chlorides namely; benzoyl, 2-phenylacetyl, and dihydrocinnamoyl chlorides (**54–56**) to give the target compounds **57–62** in presence of catalytic amount of pyridine. Similarly, the 3-benzyl-aceto hydrazide analogues **28** and **29** were also acylated using the same aliphatic and aromatic acid chlorides to afford the targets **63–76**, (Scheme 2, Table 2). Structure elucidation of the synthesized compounds was determined using IR spectroscopy, Mass spectrometry, ^1H and ^{13}C NMR spectroscopy. ^1H NMR spectra of compounds **14–16** showed singlet proton of SH at 2 position of quinazolinone at around 4–5 ppm. Moreover, the mass spectrum of **16** showed a molecular ion peak at 303. The methylated products **18–21** showed a characteristic singlet at 2.5 for methyl group. ^1H NMR spectra of compounds **22–25** adopted the appearance of significant characteristic triplet and quartet peaks for ethyl group. The IR spectrum of compounds **24**, revealed the existence of stretching absorption of carbonyl ester at around 1730 cm^{-1}. ^1H NMR spectrum of compounds **26–29** showed two singlets at 9–10 and 12 ppm due to two NH_2 and NH protons, respectively. ^1H NMR spectrum of compounds **30–37** showed three deuterium oxide-exchangeable singlets at expected chemical shifts attributed to three NH protons, while the toluene sulfonyl derivatives **38–41** showed the peaks of two singlets at 7 and 10 ppm due to two NH protons, indicating the existence of the compound in the hydrazono form in addition to 3 singlet protons at around 2 ppm referred to methyl group. The mass spectrum of target compounds showed the molecular ion at m/z (%) M^+ and M+2. The target compounds **46–53** showed characteristic singlets of 2 NH protons along with phenyl multiplet protons and different alkyl chain at far upper field while their benzyl counterparts' compounds **63–70** spectra were confirmed by the formation of additional CH_2Ph singlet protons at around 5 ppm. The phenacylacetohydrazide derivatives **57–62** and their benzyl isosteres showed characteristic peaks at their expected values. ^{13}C NMR spectral analysis was in accordance with proposed structures. ^{13}C NMR spectra of **73** as an example revealed the presence of C=O, quinazoline, N=CH,



R^1 = 6-Cl, 6,7-$(OCH_3)_2$
R^2 = C_6H_5, $C_6H_5CH_2$,
R^3 = Alkyl, Arylalkyl groups

Chart 2. Structures of the proposed target compounds.