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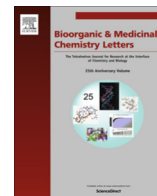
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## Synthesis, anticonvulsant activity and molecular modeling study of some new hydrazinecarbothioamide, benzenesulfonohydrazide, and phenacylacetohydrazide analogues of 4(3H)-quinazolinone <sup>☆</sup>



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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<sub>A</sub> receptor. The studied quinazoline analogues could be considered as useful templates for future development and further derivatization.

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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.<sup>1</sup> 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.<sup>2</sup> Literature survey reveals that natural quinazolinones and their synthetic analogues possess a variety of pharmacological activities, including antitumor,<sup>3–5</sup> CNS depressant,<sup>6</sup> antimicrobial,<sup>7,8</sup> and muscle relaxant activities.<sup>9,11</sup>

Methaqualone (**1**) is an important landmark in the field of synthetic anticonvulsant,<sup>12</sup> 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.<sup>13,14</sup> 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<sub>50</sub>) that are less than or only slightly higher than the ED<sub>50</sub> values. Consequently, the protective index (PI) corresponding to TD<sub>50</sub>/ED<sub>50</sub> is too low.<sup>15,16</sup> Modification of the 2-methyl group of **1** by some other chemical moiety yielded structural analogues with potent anticonvulsant activity.<sup>17</sup> 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<sub>50</sub> 73.1 mg/kg), which showed a 100% protection against PTZ induced clonic convulsion (Chart 1).<sup>18–20</sup>

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,<sup>2,10</sup> 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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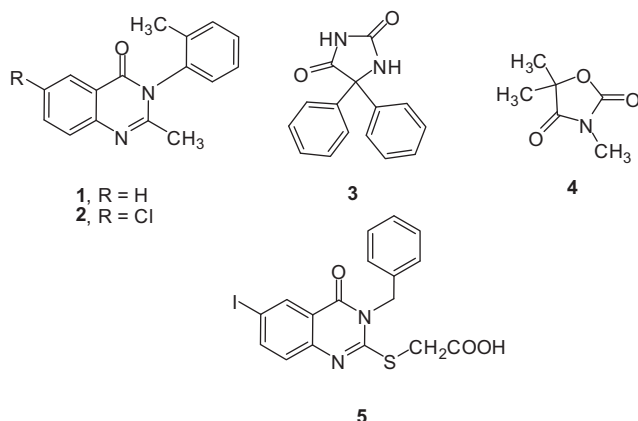


Chart 1. Structures of some literature anticonvulsants.

to explore the influence of both phenyl or benzyl substituent at position 3- of the quinazolinone nucleus, in addition to the electronic effect of the electron withdrawing Cl group at position 6- and two adjacent electron donating OCH<sub>3</sub> 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<sub>50</sub>), median sedative (TD<sub>50</sub>), and median lethal (LD<sub>50</sub>) 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.<sup>21</sup>

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(3H)-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.<sup>22</sup> The obtained products were methylated using CH<sub>3</sub>I/K<sub>2</sub>CO<sub>3</sub> 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-acetohydrazide 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-acetohydrazide 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, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. <sup>1</sup>H 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. <sup>1</sup>H 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<sup>-1</sup>. <sup>1</sup>H NMR spectrum of compounds **26–29** showed two singlets at 9–10 and 12 ppm due to two NH<sub>2</sub> and NH protons, respectively. <sup>1</sup>H 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<sup>+</sup> 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<sub>2</sub>Ph singlet protons at around 5 ppm. The phenylacetohydrazide derivatives **57–62** and their benzyl isosteres showed characteristic peaks at their expected values. <sup>13</sup>C NMR spectral analysis was in accordance with proposed structures. <sup>13</sup>C NMR spectra of **73** as an example revealed the presence of C=O, quinazolinone, N=CH,

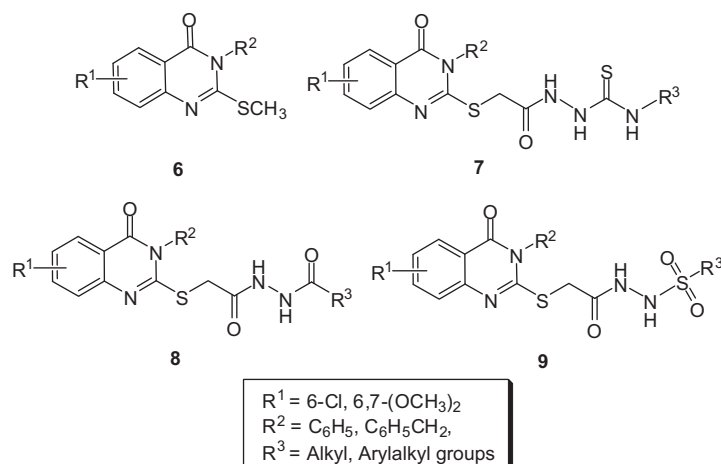
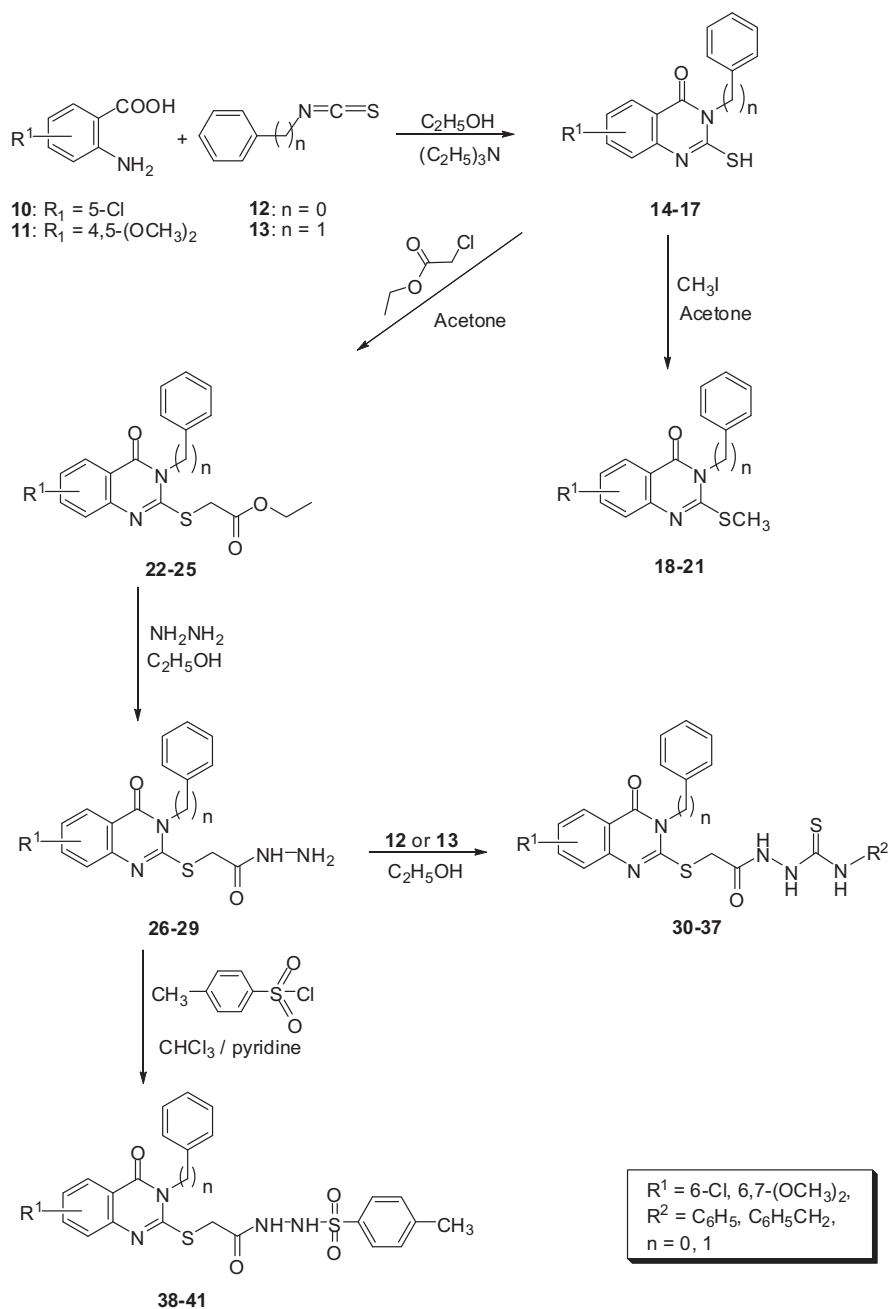


Chart 2. Structures of the proposed target compounds.



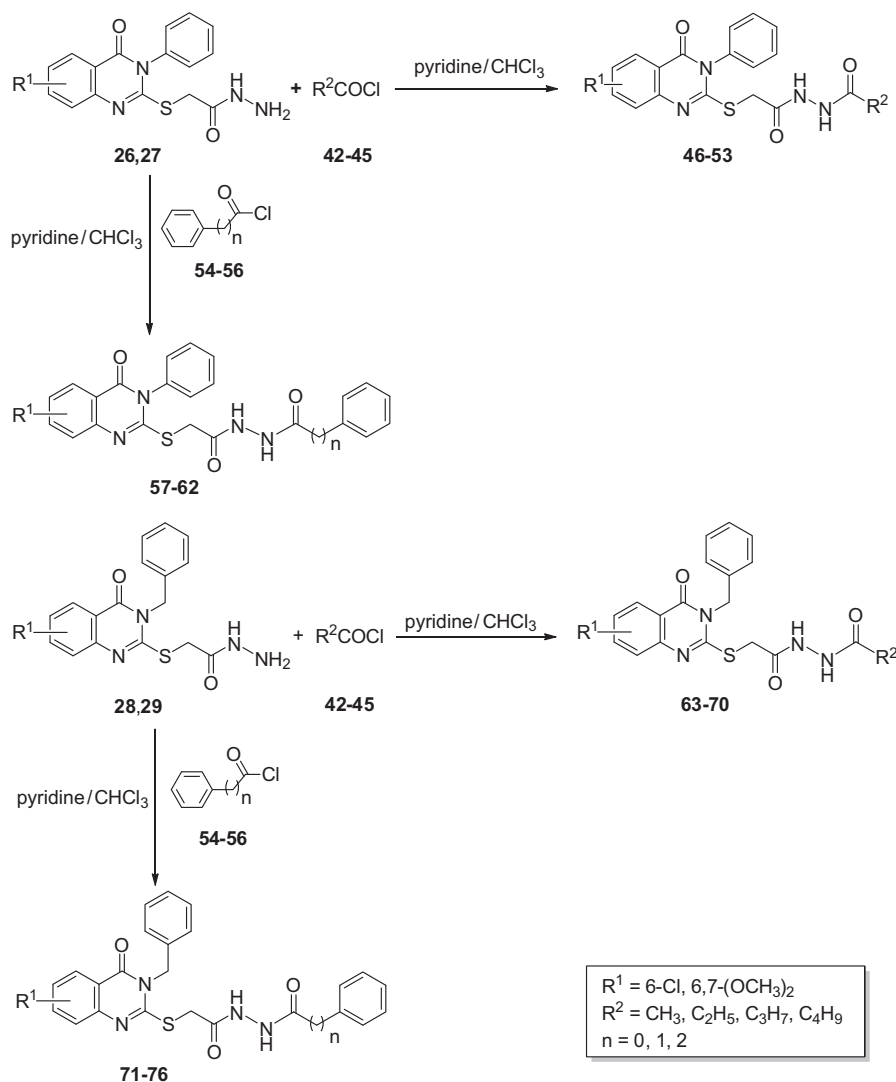
**Scheme 1.** Synthesis of the target compounds **18–41**.

and  $\text{SCH}_2$  carbon atoms resonating as double singlet at approximately 170.5–165.9 and 160.5–157.5, 156.81–156.40, 141.5–146.1 and 34.6–35.2 and 39.6–39.8 ppm.

A typical anticonvulsant agent can prevent the convulsion episodes caused by convulsion-inducing material such as pentylenetetrazole (PTZ) and picrotoxin which can be used to evaluate the potency of any alleged anticonvulsant agents.<sup>23,24</sup> In the present investigation, test compounds were injected and animals were monitored to register the onset of the first tonic convulsion; the frequency of convulsions till death; and the time of death following the injection of the convulsant. During the 20 min pre-treating time, the animals were followed carefully and any change of behavior was noted. Compounds **18–76** were injected at doses of 25–200 mg/kg, ip pentylenetetrazole (PTZ) was used at dose level of 100 mg/kg, ip, 20 min after the test compounds. This dose was

found to be the minimum dose that induced 100% clonic convulsion. Sodium valproate was used as positive control at dose level of 200 mg/kg (1.38 mmole/kg) ip.

Pentylenetetrazole (PTZ) induced clonic convulsions within 1.6 min. frequency of convulsions was every 2.0 min and animal died in 4.0 min. Any compound able to prevent such episodes or delayed this time pattern in varying magnitude will be considered to possess an anticonvulsant activity.<sup>25–27</sup> Compound **21** proved to be lethal at dose of 150 mg/kg ip and non-effective at lower doses while compound **22** proved to devoid any anticonvulsant activity. Compound **63** protected the animals prolonging the death time by 303%. Compounds **47** and **73** prolonged the convulsion onset time by more than 600% ( $P < 0.001$ ,  $N = 4$ ). The order of the test compounds in prolonging the convulsion onset time was **47** > **73** > **68** = **35** > **75** = **46** > **71** (Table 3). The order of the test

Scheme 2. Synthesis of the target compounds **46–53** and **57–76**.

compounds in reducing the frequency of convulsions by more than 80% were **49** = **57** > **48** > **36** = **68** = **76** ( $P < 0.01$ ,  $N = 4$ ); while the order of compounds in prolonging the death time by more than 300% were **47** > **19** > **63** ( $P < 0.001$ ,  $N = 4$ ). Compounds prolonged the death time by more than 200% found to be in the following order **73** > **46** = **68** ( $P < 0.001$ ,  $N = 4$ ). Compounds **47**, **63** and **68** ( $P < 0.001$ ,  $N = 4$ ) succeeded in prolonging the onset time, the death time and reduced the frequency of PTZ induced convulsions.

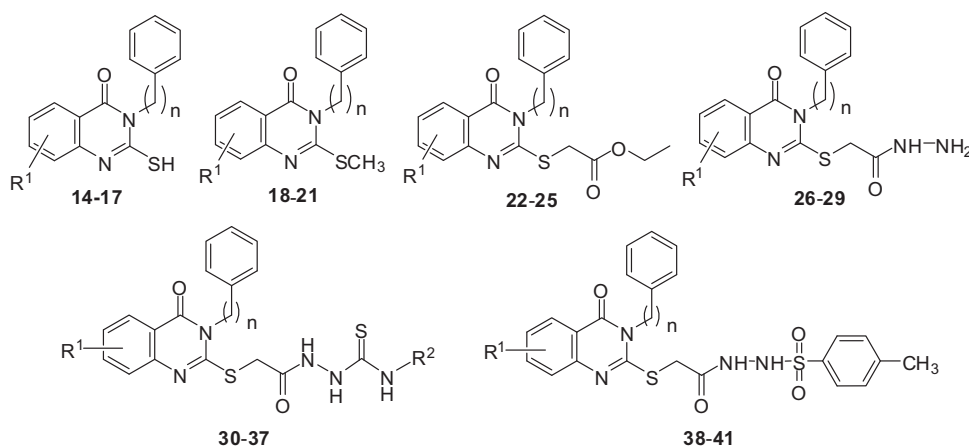
Picrotoxin is a chloride channel blocker producing hyperpolarization and clonic convulsions. Compounds protect the animals against picrotoxin-induced convulsions; act as GABA<sub>A</sub> receptor agonist by increasing chloride influx via brain chloride channels. Picrotoxin model will help to find out the mode of action of an anti-convulsant agent.<sup>22</sup> Picrotoxin (10 mg/kg, ip) induced clonic convulsions within 6.75 min; frequency of convulsions was 36 per 10 min and animal died in 12 min. Any compound was able to prevent such episodes or delayed this time pattern in varying magnitude will be considered to possess an anticonvulsant activity. Compounds **18**, **19**, **30**, **31**, **34**, **38–41**, **47–49**, **57–59**, **64**, **66**, **67**, **69–72**, **74**, **76** proved to be inactive in this test indicating that they act through a mechanism other than GABA<sub>A</sub> receptor agonism. Compounds **20**, **37** and **63** significantly prolonged the onset time for convulsions and the death time and decreased the frequency

of picrotoxin induced convulsions. The order in prolonging the onset time for convulsions was **37** > **63** > **20** ( $P < 0.01$ ,  $N = 4$ ). Three compounds (**75** > **20** = **36**) significantly decreased the frequency of convulsions by >89%. Two potent compounds (**65** > **63**) prolonged the death time significantly. In general, the order of the test compounds in decreasing the frequency of picrotoxin induced convulsions was: **75** > **20** = **36** > **68** > **37** > **65** = **63** > **35** > **24**, (Table 4). Compound **63** (0.36 mmole/kg), proved to be active in both pentylenetetrazole and picrotoxin test models suggesting that its anticonvulsant activity might be through GABA<sub>A</sub> receptor agonist mode of action; while compound **65** (0.33 mmole/kg), was the only active compound against picrotoxin-induced convulsion.

In general, compounds **47**, **63**, **68** and **73** proved to be the most active compounds in this study with remarkable 100% protection against PTZ induced convulsions as compared with the standard drug sodium valproate (Table 5). It is worth mentioning that compounds **47** (0.12 mmole/kg), **63** (0.36 mmole/kg), **68** (0.33 mmole/kg) and **73** (0.29 mmole/kg) proved to be almost 10, 4, 4, and 5 fold more active, than the used positive control sodium valproate (1.38 mmole/kg), respectively.

Structure activity correlation of the obtained results allowed the withdrawal of some valuable pharmacophoric information

**Table 1**  
Physicochemical properties of the synthesized compounds **14–41**



Compound	R <sup>1</sup>	R <sup>2</sup>	n	Solvent	Yield %	MP (°C)	Molecular formula <sup>a</sup>
<b>14</b>	6-Cl	—	0	EtOH	38	261–3	C <sub>14</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>2</sub> S
<b>15</b>	6,7-OCH <sub>3</sub>	—	0	—	—	—	Ref. 32
<b>16</b>	6-Cl	—	1	EtOH	48	190–2	C <sub>15</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>2</sub> S
<b>17</b>	6,7-OCH <sub>3</sub>	—	1	EtOH/CHCl <sub>3</sub>	64	222–4	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> S
<b>18</b>	6-Cl	—	0	EtOH/CHCl <sub>3</sub>	83	148–50	C <sub>15</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>2</sub> S
<b>19</b>	6,7-OCH <sub>3</sub>	—	0	EtOH/CHCl <sub>3</sub>	98	173–5	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> S
<b>20</b>	6-Cl	—	1	EtOH/CHCl <sub>3</sub>	45	96–8	C <sub>16</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub> S
<b>21</b>	6,7-OCH <sub>3</sub>	—	1	EtOH/CHCl <sub>3</sub>	42	194–6	C <sub>18</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> S
<b>22</b>	6-Cl	—	0	CH <sub>3</sub> COCH <sub>3</sub>	70	85–7	C <sub>18</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>3</sub> S
<b>23</b>	6,7-OCH <sub>3</sub>	—	0	CH <sub>3</sub> COCH <sub>3</sub>	87	145–6	C <sub>20</sub> H <sub>20</sub> N <sub>2</sub> O <sub>5</sub> S
<b>24</b>	6-Cl	—	1	CH <sub>3</sub> COCH <sub>3</sub>	90	73–5	C <sub>19</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>3</sub> S
<b>25</b>	6,7-OCH <sub>3</sub>	—	1	CH <sub>3</sub> COCH <sub>3</sub>	98	104–5	C <sub>21</sub> H <sub>22</sub> N <sub>2</sub> O <sub>5</sub> S
<b>26</b>	6-Cl	—	0	CHCl <sub>3</sub>	81	181–3	C <sub>16</sub> H <sub>13</sub> ClN <sub>4</sub> O <sub>2</sub> S
<b>27</b>	6,7-OCH <sub>3</sub>	—	0	CHCl <sub>3</sub>	10	166–8	C <sub>18</sub> H <sub>18</sub> N <sub>4</sub> O <sub>4</sub> S
<b>28</b>	6-Cl	—	1	CHCl <sub>3</sub>	89	151–2	C <sub>17</sub> H <sub>15</sub> ClN <sub>4</sub> O <sub>2</sub> S
<b>29</b>	6,7-OCH <sub>3</sub>	—	1	CHCl <sub>3</sub>	79	170–2	C <sub>19</sub> H <sub>20</sub> N <sub>4</sub> O <sub>4</sub> S
<b>30</b>	6-Cl	Ph	0	EtOH/CHCl <sub>3</sub>	79	170–1	C <sub>23</sub> H <sub>18</sub> ClN <sub>5</sub> O <sub>2</sub> S <sub>2</sub>
<b>31</b>	6-Cl	Bn	0	EtOH/CHCl <sub>3</sub>	98	155–6	C <sub>24</sub> H <sub>20</sub> ClN <sub>5</sub> O <sub>2</sub> S <sub>2</sub>
<b>32</b>	6,7-OCH <sub>3</sub>	Ph	0	EtOH/CHCl <sub>3</sub>	44	175–7	C <sub>25</sub> H <sub>23</sub> N <sub>5</sub> O <sub>4</sub> S <sub>2</sub>
<b>33</b>	6,7-OCH <sub>3</sub>	Bn	0	EtOH/CHCl <sub>3</sub>	25	180–1	C <sub>26</sub> H <sub>25</sub> N <sub>5</sub> O <sub>4</sub> S <sub>2</sub>
<b>34</b>	6-Cl	Ph	1	EtOH/CHCl <sub>3</sub>	68	150–1	C <sub>24</sub> H <sub>20</sub> ClN <sub>5</sub> O <sub>2</sub> S <sub>2</sub>
<b>35</b>	6-Cl	Bn	1	EtOH/CHCl <sub>3</sub>	19	164–6	C <sub>25</sub> H <sub>22</sub> ClN <sub>5</sub> O <sub>2</sub> S <sub>2</sub>
<b>36</b>	6,7-OCH <sub>3</sub>	Ph	1	EtOH/CHCl <sub>3</sub>	57	164–6	C <sub>26</sub> H <sub>25</sub> N <sub>5</sub> O <sub>4</sub> S <sub>2</sub>
<b>37</b>	6,7-OCH <sub>3</sub>	Bn	1	EtOH/CHCl <sub>3</sub>	55	152–4	C <sub>27</sub> H <sub>27</sub> N <sub>5</sub> O <sub>4</sub> S <sub>2</sub>
<b>38</b>	6-Cl	—	0	MeOH/CHCl <sub>3</sub>	29	210–1	C <sub>23</sub> H <sub>19</sub> ClN <sub>4</sub> O <sub>4</sub> S <sub>2</sub>
<b>39</b>	6,7-OCH <sub>3</sub>	—	0	MeOH/CHCl <sub>3</sub>	30	200–2	C <sub>25</sub> H <sub>24</sub> N <sub>4</sub> O <sub>6</sub> S <sub>2</sub>
<b>40</b>	6-Cl	—	1	MeOH/CHCl <sub>3</sub>	36	197–8	C <sub>24</sub> H <sub>21</sub> ClN <sub>4</sub> O <sub>4</sub> S <sub>2</sub>
<b>41</b>	6,7-OCH <sub>3</sub>	—	1	MeOH/CHCl <sub>3</sub>	71	196–8	C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O <sub>6</sub> S <sub>2</sub>

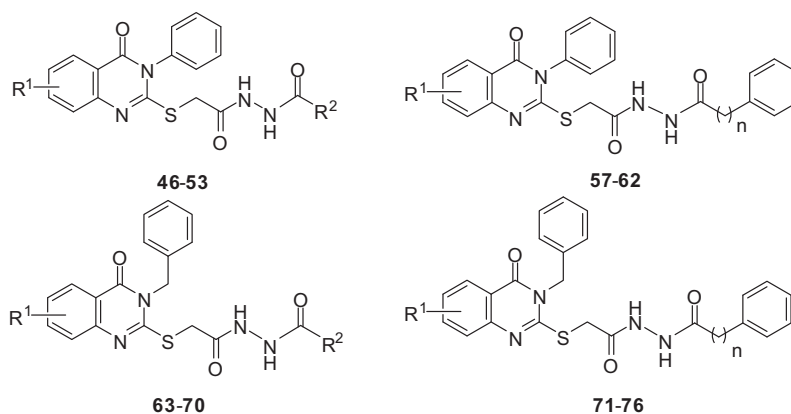
<sup>a</sup> Compounds analyzed for C,H,N; results were within  $\pm 0.4\%$  of the theoretical values for the given formulae.

about the anticonvulsant drug design of this class of compounds. Four series of compounds were studied in the present investigation, namely: 6-chloro-2-(substituted-thio)-3-phenyl-quinazolin-4(3H)-one series; 6-chloro-2-(substituted-thio)-3-benzyl-quinazolin-4(3H)-one series; 6,7-dimethoxy-2-(substituted-thio)-3-phenyl-quinazolin-4(3H)-one series; and 6,7-dimethoxy-2-(substituted-thio)-3-benzyl-quinazolin-4(3H)-one series. Regarding the 6-chloro-3-phenyl-series, methylation of the 2-mercapto function of **14** produced the methylthio analogue **18** which prolonged PTZ-induced convulsion onset time in experimental animal by 114%, while alkylation of **14** with ethyl chloroacetate produced the biologically inactive ester **22**. Hydrazinolysis of **22** produced the inactive hydrazone analogue **26**. Reacting **26** with benzyl isothiocyanate produced the active compound **31** which regained the activity of **18** prolonging PTZ induced convulsion onset time by 114%. Reaction of the hydrazone **26** with 4-toluene sulfonyl chloride produced **38** with diminished activity into 43%. Acylation of the hydrazone moiety of **26** with aliphatic acid chlorides of various alkyl

lengths or aromatic acid chlorides produced active anticonvulsant agents of various magnitudes. Acylation using acetyl chloride produced **46** with increased potency (186%), while acylation using propionyl chloride produced **47**, one of the most active compounds in this investigation (1471%). Acylation with acid chloride of longer length such as butyryl chloride or acid chloride of branched alkyl chain as 2-methylbutanoyl chloride produced **48** and **49** with reduced activity (43% and 114%, respectively). Acylation with aryl-alkyl acids of various lengths as benzoic, phenyl acetic and dihydrocinnamic acids produced compounds **57**, **58** and **59** with anticonvulsant activity (114%, 43%, 43%, respectively) which decreased by the increase of the acid alkyl chain length. It is proved that short chain aliphatic acid acylation of the hydrazone **26** favors the activity rather than the aryl-alkyl acids acylation. Regarding the 6-chloro-3-benzyl-series, replacement of the 3-phenyl moiety of **31** by 3-benzyl group produced **35** with four fold increases in activity (471%). The same was also applicable in case of **46** producing **63** which prevented the convulsion episodes by 100%; **57**



**Table 2**  
Physicochemical properties of the synthesized target compounds **46–53**, **57–76**



Compound	R <sup>1</sup>	R <sup>2</sup>	n	Solvent	Yield %	MP (°C)	Molecular formulae <sup>a</sup>
<b>46</b>	6-Cl	CH <sub>3</sub>	—	MeOH	77	87–9	C <sub>18</sub> H <sub>15</sub> ClN <sub>4</sub> O <sub>3</sub> S
<b>47</b>	6-Cl	C <sub>2</sub> H <sub>5</sub>	—	MeOH	55	128–30	C <sub>19</sub> H <sub>17</sub> ClN <sub>4</sub> O <sub>3</sub> S
<b>48</b>	6-Cl	C <sub>3</sub> H <sub>7</sub>	—	CHCl <sub>3</sub>	38	164–6	C <sub>20</sub> H <sub>19</sub> ClN <sub>4</sub> O <sub>3</sub> S
<b>49</b>	6-Cl	C <sub>4</sub> H <sub>9</sub>	—	EtOH/CHCl <sub>3</sub>	51	175–7	C <sub>21</sub> H <sub>21</sub> ClN <sub>4</sub> O <sub>3</sub> S
<b>50</b>	6,7-OCH <sub>3</sub>	CH <sub>3</sub>	—	MeOH	43	209–10	C <sub>20</sub> H <sub>20</sub> N <sub>4</sub> O <sub>5</sub> S
<b>51</b>	6,7-OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	—	EtOH	68	211–2	C <sub>21</sub> H <sub>22</sub> N <sub>4</sub> O <sub>5</sub> S
<b>52</b>	6,7-OCH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	—	EtOH	25	205–6	C <sub>22</sub> H <sub>24</sub> N <sub>4</sub> O <sub>5</sub> S
<b>53</b>	6,7-OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub>	—	EtOH	33	218–9	C <sub>23</sub> H <sub>26</sub> N <sub>4</sub> O <sub>5</sub> S
<b>57</b>	6-Cl	—	0	MeOH	98	131–3	C <sub>23</sub> H <sub>17</sub> ClN <sub>4</sub> O <sub>3</sub> S
<b>58</b>	6-Cl	—	1	DMF/CHCl <sub>3</sub>	69	199–201	C <sub>24</sub> H <sub>19</sub> ClN <sub>4</sub> O <sub>3</sub> S
<b>59</b>	6-Cl	—	2	MeOH/CHCl <sub>3</sub>	30	206–8	C <sub>25</sub> H <sub>21</sub> ClN <sub>4</sub> O <sub>3</sub> S
<b>60</b>	6,7-OCH <sub>3</sub>	—	0	EtOH/CHCl <sub>3</sub>	37	221–2	C <sub>25</sub> H <sub>22</sub> N <sub>4</sub> O <sub>5</sub> S
<b>61</b>	6,7-OCH <sub>3</sub>	—	1	MeOH/CHCl <sub>3</sub>	24	206–7	C <sub>26</sub> H <sub>24</sub> N <sub>4</sub> O <sub>5</sub> S
<b>62</b>	6,7-OCH <sub>3</sub>	—	2	MeOH/CHCl <sub>3</sub>	28	204–5	C <sub>27</sub> H <sub>26</sub> N <sub>4</sub> O <sub>5</sub> S
<b>63</b>	6-Cl	CH <sub>3</sub>	—	CHCl <sub>3</sub>	73	206–7	C <sub>19</sub> H <sub>17</sub> ClN <sub>4</sub> O <sub>3</sub> S
<b>64</b>	6-Cl	C <sub>2</sub> H <sub>5</sub>	—	CHCl <sub>3</sub>	87	188–90	C <sub>20</sub> H <sub>19</sub> ClN <sub>4</sub> O <sub>3</sub> S
<b>65</b>	6-Cl	C <sub>3</sub> H <sub>7</sub>	—	MeOH/CHCl <sub>3</sub>	66	185–7	C <sub>21</sub> H <sub>21</sub> ClN <sub>4</sub> O <sub>3</sub> S
<b>66</b>	6-Cl	C <sub>4</sub> H <sub>9</sub>	—	DMF/CHCl <sub>3</sub>	58	214–5	C <sub>22</sub> H <sub>23</sub> ClN <sub>4</sub> O <sub>3</sub> S
<b>67</b>	6,7-OCH <sub>3</sub>	CH <sub>3</sub>	—	MeOH/CHCl <sub>3</sub>	85	210–1	C <sub>21</sub> H <sub>22</sub> N <sub>4</sub> O <sub>5</sub> S
<b>68</b>	6,7-OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	—	EtOH/CHCl <sub>3</sub>	96	197–9	C <sub>22</sub> H <sub>24</sub> N <sub>4</sub> O <sub>5</sub> S
<b>69</b>	6,7-OCH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	—	EtOH/CHCl <sub>3</sub>	98	203–5	C <sub>23</sub> H <sub>26</sub> N <sub>4</sub> O <sub>5</sub> S
<b>70</b>	6,7-OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub>	—	EtOH/CHCl <sub>3</sub>	62	214–6	C <sub>24</sub> H <sub>28</sub> N <sub>4</sub> O <sub>5</sub> S
<b>71</b>	6-Cl	—	0	MeOH/CHCl <sub>3</sub>	74	196–8	C <sub>24</sub> H <sub>19</sub> ClN <sub>4</sub> O <sub>3</sub> S
<b>72</b>	6-Cl	—	1	CHCl <sub>3</sub>	67	200–2	C <sub>25</sub> H <sub>21</sub> ClN <sub>4</sub> O <sub>3</sub> S
<b>73</b>	6-Cl	—	2	CHCl <sub>3</sub>	68	199–1	C <sub>26</sub> H <sub>23</sub> ClN <sub>4</sub> O <sub>3</sub> S
<b>74</b>	6,7-OCH <sub>3</sub>	—	0	EtOH/CHCl <sub>3</sub>	88	116–8	C <sub>26</sub> H <sub>24</sub> N <sub>4</sub> O <sub>5</sub> S
<b>75</b>	6,7-OCH <sub>3</sub>	—	1	MeOH/CHCl <sub>3</sub>	86	147–9	C <sub>27</sub> H <sub>26</sub> N <sub>4</sub> O <sub>5</sub> S
<b>76</b>	6,7-OCH <sub>3</sub>	—	2	MeOH	78	212–4	C <sub>28</sub> H <sub>28</sub> N <sub>4</sub> O <sub>5</sub> S

<sup>a</sup> Compounds analyzed for C,H,N; results were within  $\pm 0.4\%$  of the theoretical values for the given formulae.

producing **71** with modest increase in the anticonvulsant activity and **59** producing **73** with remarkable increase of activity by almost 16 fold. The series of 6,7-dimethoxy-3-phenyl showed the lowest anticonvulsant activity in this study represented by **19** and **24**. In the 6,7-dimethoxy-3-benzyl-series, the presence of 3-benzyl moiety brought the inactive 3-phenyl counterpart into the active side as exemplified by compounds **36**, **68**, **75** and **76** which prolonged PTZ induced convulsion onset time in experimental animal by 150%, 471%, 186% and 114%, respectively. In general, 6-chloro function proved to enhance the anticonvulsant activity of the synthesized quinazolin-4(3H)-one more than the 6,7-dimethoxy group. Also, 3-phenyl moiety at the synthesized quinazolin-4(3H)-one proved to contribute to the anticonvulsant potency as well as safety more than the 3-benzyl function.

The binding study of compound **68** as an example representing the most active compounds into GABA<sub>A</sub> receptor binding site where the diazepam bound GABA<sub>A</sub> receptor homology model was used where only the extracellular domains of the structures with PDB codes 2BG9 and 2QC1 were considered,<sup>28</sup> for possible revealing of the mode of action was quite interesting. The

orientation of compound **68** inside the benzodiazepine (BZD)-binding site of GABA<sub>A</sub> receptor was examined by a flexible docking experiment using MOE software. The docking was performed using the Alpha Triangle placement method.<sup>29–31</sup> Diazepam was used as a reference ligand for validation purpose. The important amino acid interacting with **68** were displayed in Figure 1a, where hydrogen bonding interaction between the carbonyl amide functions with Thr56 amino acid by 90%; the methoxy group oxygen and Gln119 by 30% was observed. The aligned binding conformations of **68** at the binding site revealed a clear quite well binding preference as seen in Figure 1b. The best conformation for **68** showed interaction binding energy of  $-15.46$  kcal/mol possessing a similar binding mode of diazepam in the homology model pocket of GABA<sub>A</sub> receptor (RMSD: 0.17 Å). This finding supports the hypothesis that **68** exert its anticonvulsant activity as GABA<sub>A</sub> agonist.

To probe similarity between the 3D structures of the most active compounds **73** and diazepam, MOE/MMFF94 flexible alignment using systematic conformational search<sup>32–34</sup> was employed to automatically generate superposition of **73** with minimal user bias.<sup>35</sup> 200 conformers of the compound were generated and

**Table 3**Effect of compounds **18–20**, **24**, **31**, **34–38**, **40**, **41**, **46–49**, **57–59** and **63–76** on PTZ-induced convulsions in mice

Compound	Dose		% prolongation of convulsion onset time	% decrease in convulsion frequency	% delay of death time
	(mmole/kg)	(mg/kg)			
<b>18</b>	0.50	150	114 ± 6	0.0	44 ± 5
<b>19</b>	0.45	150	35 ± 4	0.0	461 ± 11
<b>20</b>	0.47	150	114 ± 4	61 ± 3	5 ± 1
<b>22</b>	0.40	150	0.0	0.0	0.0
<b>24</b>	0.38	150	0.0	0.0	0.0
<b>31</b>	0.30	150	114 ± 9	0.0	145 ± 8
<b>34</b>	0.30	150	0.0	0.0	0.0
<b>35</b>	0.29	150	471 ± 15	61 ± 5	101 ± 7
<b>36</b>	0.28	150	150 ± 6	81 ± 4	5 ± 1
<b>37</b>	0.27	150	43 ± 5	38 ± 6	32 ± 4
<b>38</b>	0.29	150	43 ± 4	48 ± 6	40 ± 3
<b>40</b>	0.28	150	43 ± 6	74 ± 3	47 ± 4
<b>41</b>	0.27	150	43 ± 4	0.0	0.0
<b>46</b>	0.37	150	186 ± 11	48 ± 3	216 ± 12
<b>47</b>	0.12	50	1471 ± 29	74 ± 5	636 ± 12
<b>48</b>	0.34	150	43 ± 4	82 ± 6	75 ± 4
<b>49</b>	0.32	150	114 ± 5	87 ± 6	47 ± 4
<b>57</b>	0.32	150	114 ± 2	87 ± 6	0.0
<b>58</b>	0.10	50	43 ± 3	0.0	0.0
<b>59</b>	0.30	150	43 ± 6	0.0	0.0
<b>63</b>	0.36	150	No convulsions	—	303 ± 17
<b>64</b>	0.35	150	43 ± 5	74 ± 6	0.0
<b>65</b>	0.33	150	78 ± 5	61 ± 6	14 ± 3
<b>66</b>	0.32	150	0.0	0.0	0.0
<b>67</b>	0.34	150	0.0	0.0	0.0
<b>68</b>	0.33	150	471 ± 13	81 ± 9	216 ± 10
<b>69</b>	0.32	150	114 ± 6	0.0	58 ± 8
<b>70</b>	0.30	150	0.0	0.0	0.0
<b>71</b>	0.31	150	185 ± 11	23 ± 3	75 ± 4
<b>72</b>	0.30	150	43 ± 4	61 ± 5	47 ± 2
<b>73</b>	0.29	150	685 ± 21	74 ± 4	254 ± 9
<b>74</b>	0.30	150	0.0	0.0	0.0
<b>75</b>	0.29	150	186 ± 11	68 ± 7	58 ± 6
<b>76</b>	0.28	150	114 ± 5	81 ± 6	0.0

**Table 4**Effect of compounds **20**, **24**, **35–37**, **63**, **65**, **68** and **75** on picrotoxin-induced convulsions in mice

Compound	Dose		% prolongation of convulsion onset time	% decrease in convulsion frequency	% delay of death time
	(mmole/kg)	(mg/kg)			
<b>20</b>	0.47	150	36 ± 4	91 ± 6	0.0
<b>24</b>	0.38	150	5 ± 1	25 ± 4	17 ± 3
<b>35</b>	0.29	150	15 ± 2	39 ± 4	25
<b>36</b>	0.28	150	4 ± 1	89 ± 6	25
<b>37</b>	0.27	150	78 ± 6	66 ± 4	22 ± 3
<b>63</b>	0.36	150	63 ± 6	60 ± 4	50 ± 3
<b>65</b>	0.33	150	0.0	61 ± 5	61 ± 4
<b>68</b>	0.33	150	11 ± 2	79 ± 9	8 ± 2
<b>75</b>	0.29	150	18 ± 3	97 ± 11	17 ± 2

**Table 5**ED<sub>50</sub>, TD<sub>50</sub>, PI, LD<sub>50</sub> and TI for **47**, **63**, **68** and **73**

Compound <sup>a</sup>	Dose		% protection	ED <sub>50</sub> <sup>b</sup> (mg/kg)	TD <sub>50</sub> <sup>b</sup> (mg/kg)	PI <sup>c</sup>	LD <sub>50</sub> <sup>d</sup> (mmole/kg)	TI <sup>e</sup>
	(mmole/kg)	(mg/kg)						
<b>47</b>	0.12	50	100	11.79	100.3	8.5	290.3	24.6
<b>63</b>	0.36	150	100	24.75	215.3	8.7	239.6	9.7
<b>68</b>	0.33	150	100	32.7	134.1	4.1	167.5	5.1
<b>73</b>	0.29	150	100	29.5	135.7	4.6	290.3	9.8
Sodium Valproate	1.13	50	100	189	470	2.4	985	5.2

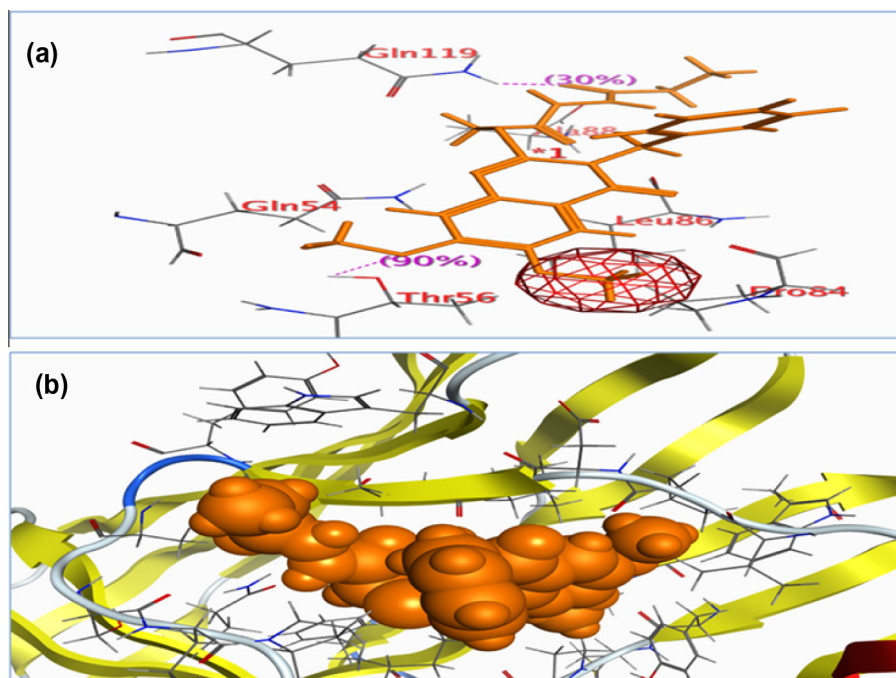
<sup>a</sup> Each dose of selected compounds was tested using 4 animals and the percentage of animals protected was recorded and the anticonvulsant activity was calculated.<sup>b</sup> ED<sub>50</sub> and TD<sub>50</sub>: median effective and median sedative doses, respectively.<sup>c</sup> PI: protective index = TD<sub>50</sub>/ED<sub>50</sub>.<sup>d</sup> LD<sub>50</sub>: median lethal dose.<sup>e</sup> TI: therapeutic index = LD<sub>50</sub>/ED<sub>50</sub>.

minimized with a distance-dependant dielectric model. A low energy set of 100 was selected for further analysis. The top scoring alignment of both the least strain energy and the best alignment score is shown in Figure 2. Compound **73** and diazepam align fairly well (Fig. 2a), while the least active compound **22** showed a distinct different pattern with dramatic alignment deviation from that of diazepam (Fig. 2b).

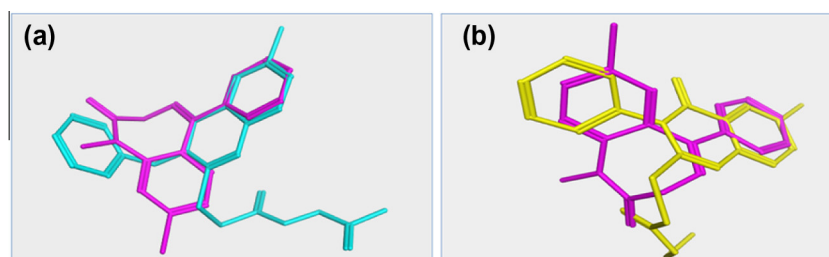
The atomic-level details of the structure of pharmaceutically relevant receptors are not available; in such cases, 3D superposition of putative ligands can be used to deduce specific structural requirements for biological activity.<sup>35,36</sup> Structure superposition of the most active compounds **47**, **63**, and **73** with specified mark points (Fig. 3) such as *N*-1 of the quinazoline nucleus, the phenyl ring substituent, *N*-3 of the quinazoline nucleus, 2-*S*-linkage directly attached to quinazoline moiety, NH at side chain and the  $\pi$ -system represented by aryl group of the quinazoline core, align fairly well with almost complete superposition of the quinazoline rings (0.40 Å). This superposition provides possible existence of a region on the receptor suited for specific recognition of the aforementioned selected features. This hypothesis is ascertained by biological results which strongly suggest that these chosen mark points could be used as a pharmacophore model for further anti-convulsant compounds. The features responsible for the remarkable anticonvulsant activity of **47** were employed for surface map of its lowest energy conformer to examine the similarity or the dissimilarity in the conformational properties of its molecule surface in comparison to the surface mapping of the reference compound diazepam. Compound **47** (Fig. 4) showed hydrophilic region, hydrogen bond acceptor–donor, region located on the 4-carbonyl, *N*-1 and non-polar area located on the aryl moiety attached to the quinazoline core distributed on both sides of the aryl parts; which are generally having a common feature, with the surface mapping distribution of diazepam (Fig. 4b). Such results indicated the structure mapping similarity and hence biological resemblance between **47** and diazepam. Moreover the results provided further support that the investigated compounds might exert their anti-convulsant action as GABA<sub>A</sub> agonist.

Oral bioavailability plays an important role in the development of bioactive molecules into therapeutic agents. Many potential therapeutic agents fail to reach the clinic because of their unfavorable absorption, distribution, metabolism, elimination and toxic (ADMET) factors.<sup>37</sup> Therefore, a computational study for the ADMET properties prediction of the most active anticonvulsants **47**, **63**, **68**, and **73** was performed for the determination of topological polar surface area (TPSA), and the ‘rule of five’ formulated by Lipinski for activity prediction of an orally administered drug,<sup>38</sup> if it has no more than one violation of the following rules: Clog $P$  <5; number of hydrogen bond donors sites ≤5; number of hydrogen bond acceptor sites ≤10; molecular weight <500; number of rotatable bonds <5. In addition, the total polar surface area

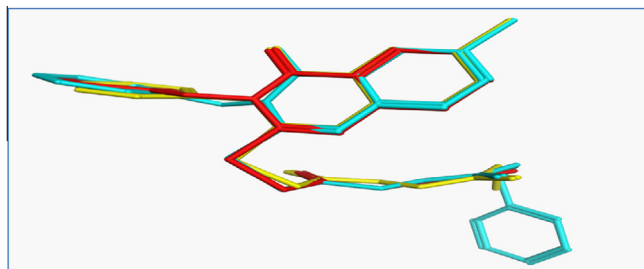




**Figure 1.** (a) The binding mode and interaction of **68** (orange) with amino acids residues in diazepam-binding pocket of GABA<sub>A</sub> receptor. (b) The aligned conformation of the most active compound **68** (space filled) occupying diazepam-binding pocket of GABA<sub>A</sub> receptor.

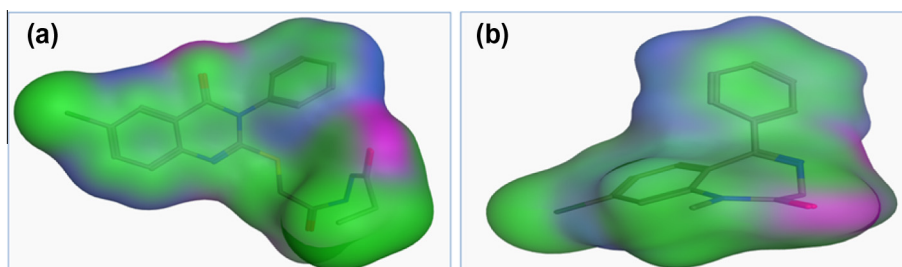


**Figure 2.** (a) Flexible alignment of the most active compound **73** (cyan), and diazepam (pink). (b) Flexible alignment of the least active compound **22** (yellow) and diazepam (pink).



**Figure 3.** Superposition of the most active compounds **47** (in yellow), **63** (in red), and **73** (in cyan) with specified mark points.

(TPSA) is another key property linked to drug bioavailability; the passively absorbed molecules with TPSA >140 have low oral bioavailability.<sup>31</sup> All calculated descriptors were obtained using the MOE package, and the results are listed in Table 6. The obtained results revealed that the molecular weight was <500, except for compound **73** (507.014), ClogP <5, hydrogen bond acceptor <10 and hydrogen bond donors <5 which fulfill Lipinski's rule. Also, the percent absorption of all tested compounds proposed a higher bioavailability with total surface area with <140. Lip.V molecules should have less than 2 violations; all of the tested compounds applied no violations except compound **73** had only one violation.

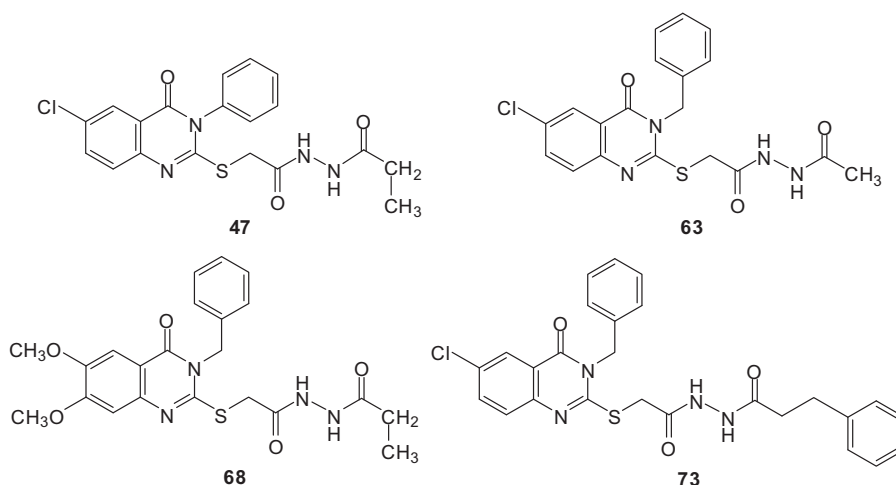


**Figure 4.** (a) Surface map for the most active compound **47** in pocket side. (b) Surface map for Diazepam. Pink: hydrogen bond, blue: mild polar, green: hydrophobic areas.

**Table 6**ADMET properties prediction parameters of compounds **47**, **63**, **68** and **73**

Compound	Mwt	TPSA	LogP	Lip.don	Lip.acc	Lip.V
<b>47</b>	416.889	90.87	3.2785	2	7	0
<b>63</b>	416.889	90.87	3.1504	2	7	0
<b>68</b>	456.523	109.33	2.9043	2	9	0
<b>73</b>	507.014	90.83	4.76327	2	7	1

Mwt: molecular weight, TPSA: polar surface area, LogP: calculated lipophilicity, Lip.don: number of hydrogen bond donors, Lip.acc: number of hydrogen bond acceptors, Lip.V: number of violations of Lipinski rule.

**Figure 5.** Structures of the most active anticonvulsant agents **47**, **63**, **68** and **73**.

Since compounds **47**, **63**, **68** and **73** has a highly anticonvulsant activity, and from the data above, it could be suggested that they could be used as good orally absorbed agents with diminished toxicity.

In conclusion, compounds **47**, **63** and **68** ( $P < 0.001$ ,  $N = 4$ ) succeeded in prolonging the onset time, the death time and reduced the frequency of PTZ induced convulsions. Compounds **37** and **63** significantly prolonged the onset time for convulsions and the death time and decreased the frequency of picrotoxin induced convulsions. Compounds **47**, **63**, **68** and **73** (Fig. 5) proved to be the most active compounds in this study against PTZ induced convulsions. It is worth mentioning that compound **47** (0.12 mmole/kg), **63** (0.36 mmole/kg), **68** (0.33 mmole/kg) and **73** (0.29 mmole/kg) proved to be almost 10, 4, 4, and 5 fold more active, respectively, than the used positive control sodium valproate (1.38 mmole/kg). Compound **63** (0.36 mmole/kg), showed 100% protection against PTZ-induced convulsions in addition to 63% protection against picrotoxin-induced convulsions suggesting that it might act directly as GABA<sub>A</sub> receptor agonist or indirectly by increasing GABA synthesis or its release as a brain inhibitory neurotransmitter. Structure activity correlation of the obtained results revealed that, 6-chloro function proved to enhance the anticonvulsant activity of the synthesized quinazolin-4(3H)-one more than the 6,7-dimethoxy group. Also, the 3-phenyl moiety at quinazolin-4(3H)-one proved to contribute to the anticonvulsant potency as well as safety more than the 3-benzyl function. Molecular modeling studies revealed that the investigated compounds bind to the benzodiazepine (BZD)-binding site of GABA<sub>A</sub> receptor through hydrogen bonding with Thr56 and Gln119 amino acids. Superposition among the active compounds provides evidence that chosen mark points: N-1 of the quinazoline nucleus, the phenyl ring substituent, N-3 of the quinazoline nucleus, 2-S-linkage directly attached to quinazoline moiety, NH at side chain and the  $\pi$ -system

represented by aryl group of the quinazoline core could be used as a pharmacophore model for anticonvulsant activity. ADMET study suggested that the obtained active compounds can be used as good orally absorbed anticonvulsant agents with expected diminished toxicity. Further binding affinity studies to GABA<sub>A</sub> receptor will be quite informative. The studied quinazoline analogues could be considered as useful templates for future development and further derivatization or modification to obtain more potent anticonvulsant compounds.

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bmcl.2015.02.025>.

### References and notes

- Ben-Menachem, E.; Gabbai, A.; Hufnagel, A.; Maia, J.; Almeida, L.; Soares-da-Silva, P. *Epilepsy Res.* **2010**, *89*, 278.
- Laddha, S.; Bhatnagar, S. Novel fused quinazolines: Further studies on the anticonvulsant activity of 1,2,9,11-tetrasubstituted-7H-thieno[2',3':4,5]pyrimido[6,1-b]-quinazolin-7-one and 1,3,10,12-tetrasubstituted-8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one. The 13th International Conference on Synthetic Organic Chemistry (ECSOC-13) 2009.
- Al-Rashood, S.; Aboldahab, I.; Nagi, M.; Abouzeid, L.; Abdel-aziz, A.; Abdel-Hamide, S.; Youssef, K.; Al-Obaid, A.; El-Subbagh, H. *Bioorg. Med. Chem.* **2006**, *14*, 8608.
- Al-Obaid, A.; Abdel-Hamide, S.; El-Kashef, H.; Abdel-Aziz, A.; El-Azab, A.; Al-Khamees, H.; El-Subbagh, H. *Eur. J. Med. Chem.* **2009**, *44*, 2379.

5. Al-Omary, F.; Abou-Zeid, L.; Nagi, M.; Habib, E.; Abdel-Aziz, A.; El-Azab, A.; Abdel-Hamide, S.; Al-Omar, M.; Al-Obaid, A.; El-Subbagh, H. *Bioorg. Med. Chem.* **2010**, *18*, 2849.
6. Kashaw, S.; Gupta, V.; Kashaw, V.; Mishra, P.; Stables, J.; Jain, N. *Med. Chem. Res.* **2010**, *19*, 250.
7. Al-Omar, M.; Abdel-Hamide, S.; Al-Khamees, H.; El-Subbagh, H. *Saudi Pharm. J.* **2004**, *12*, 63.
8. Mathew, J.; Dinakaran, V.; Kaur, N.; Srinivasan, K. *Pharmacologyonline* **2008**, *2*, 618.
9. Kashaw, S.; Kashaw, V.; Mishra, P.; Jain, N.; Stables, J. *Med. Chem. Res.* **2010**, *20*(6), 738.
10. Kashaw, S.; Gupta, V.; Kashaw, V.; Mishra, P.; Stables, J.; Jain, N. *Med. Chem. Res.* **2010**, *19*, 250.
11. Kadi, A.; El-Azab, A.; Alafeefy, A.; Abdel-Hamide, S. *Az. J. Pharm. Sci.* **2006**, *34*, 147.
12. Gujral, M.; Saeen, K.; Kohli, R. *Ind. J. Med. Res.* **1957**, *45*, 207.
13. Salimath, R.; Patel, S.; Shah, N. *J. Ind. Chem. Soc.* **1964**, *33*, 140.
14. Bhaduri, A.; Khanna, N.; Dhar, M. *Ind. J. Chem.* **1964**, *2*, 159.
15. Barthwal, J.; Tandon, S.; Agarwal, V.; Dixit, K.; Parmar, S. *J. Pharm. Sci.* **1973**, *62*, 613.
16. Wolfe, J.; Rathman, T.; Slevi, M. *J. Med. Chem.* **1990**, *33*, 161.
17. Jatava, V.; Mishra, P.; Kashaw, S.; Stables, J. *Eur. J. Med. Chem.* **2008**, *43*, 135.
18. Abdel-Hamide, S.; El-Obeid, E.; Al-Majed, A.; Al-Kashef, H.; El-Subbagh, H. *Med. Chem. Res.* **2001**, *10*, 378.
19. El-Subbagh, H. I.; Hassan, G. S.; El-Azab, A. S.; Abdel-Aziz, A. A.-M.; Kadi, A. A.; Al-Obaid, A. M.; Al-Shabanah, O. A.; Sayed-Ahmed, M. M. *Eur. J. Med. Chem.* **2011**, *46*, 5567.
20. El-Azab, A. S.; Abdel-Hamide, S. G.; Sayed-Ahmed, M. M.; Hassan, G. S.; El-Hadiyah, T. M.; Al-Shabanah, O. A.; Al-Deeb, O. A.; El-Subbagh, H. I. *Med. Chem. Res.* **2013**, *22*, 2815.
21. Huda S. A. Al-Salem, Hussein I. El-Subbagh, Kamal E. H. El-Taher, Gehan H. Hegazy, Abdulrahman M. Al-Obaid. Quinazolinone analogues for use as anticonvulsant agents. European Patent, EP 2 740 727 A1, June 2014.
22. Li, Z.; Huang, H.; Sun, H.; Jiang, H.; Liu, H. *J. Comb. Chem.* **2008**, *10*, 484.
23. White, H.; Woodhead, J.; Franklin, M.; Swinyard, E.; Wolf, H. In *Antiepileptic Drugs*; Levy, R. H., Mattson, R. H., Meldrum, B. S., Eds., 4th ed.; Raven: New York, 1995; pp 99–121.
24. Ulrich, R.; Miller, J. *Percept Psychophys.* **2004**, *66*, 517.
25. Khanna, N.; Garg, A.; Sharma, K.; Khosla, R. *Indian J. Clin. Biochem.* **1997**, *12*, 86.
26. Ankica, V.; Joranovic, M.; Nincovic, M.; Maksimovic, M.; Boskovic, B. *Acta Vet.* **2003**, *53*, 103.
27. Chakrabarti, A.; Saini, H.; Garg, S. *J. Pharm. Pharmacol.* **1997**, *49*, 812.
28. Richter, L.; De Graaf, C.; Sieghart, W.; Varagic, Z.; Mrzinger, M.; Pde Esch, I. J.; Ecker, G. F.; Ernst, M. *Nat. Chem. Biol.* **2012**, *8*, 455.
29. Kearsley, S.; Smith, G. M. *Tetrahedron Comput. Methodol.* **1990**, *3*, 615.
30. Profeta, S.; Allinger, N. L. *J. Am. Chem. Soc.* **1907**, *1985*, 107.
31. Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.
32. Profeta, S.; Allinger, N. L. *J. Am. Chem. Soc.* **1985**, *107*, 1907.
33. Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz, K. M., Jr.; Ferguson, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 5179.
34. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
35. Labute, P.; Williams, C.; Feher, M.; Sourial, E.; Schmidt, J. M. *J. Med. Chem.* **2001**, *44*, 1483.
36. Mihic, S. J.; Whiting, P. J.; Klein, R. L.; Wafford, K. A.; Harris, R. A. *J. Biol. Chem.* **1994**, *269*, 32768.
37. Zhao, Y.; Abraham, M. H.; Lee, J.; Hersey, A.; Luscombe, N. C.; Beck, G.; Sherborne, B.; Cooper, I. *Pharm. Res.* **2002**, *19*, 1446.
38. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug. Delivery Rev.* **1997**, *23*, 3.