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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Design, molecular docking and synthesis of some novel 4-acetyl-1-substituted-3,4-dihydroquinoxalin-2(1*H*)-one derivatives for anticonvulsant evaluation as AMPA-receptor antagonists

**Abdel-Ghany A. El-Helby[1] · Rezk R. A. Ayyad[1,2] · Khaled El-Adl[1] · Helmy Sakr[1] · Ashraf A. Abd-Elrahman[1] · Ibrahim H. Eissa[1] · Alaa Elwan[1]**

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**Abstract** A new series of 4-acetyl-1-substituted-3,4-dihydroquinoxalin-2(1*H*)-ones (**2–13**) were designed and synthesized in order to evaluate their AMPA-receptor antagonism as a potential mode of anticonvulsant activity. The structure of the synthesized compounds was confirmed by elemental analysis and spectral data (IR, $^{1}$HNMR, $^{13}$CNMR and Mass). The molecular design was performed for all the synthesized compounds to predict their binding affinity to AMPA-receptor in order to rationalize their anticonvulsant activity in a qualitative way. The data obtained from the molecular modeling was strongly correlated with that obtained from the biological screening which revealed that; compounds $12_b$, 13, $12_a$ and $7_a$ showed the highest binding affinities toward AMPA-receptor and also showed the highest anticonvulsant activities against pentylenetetrazole -induced seizures in experimental mice. The relative potencies of these compounds were 1.66, 1.66, 1.61 and 0.82 respectively, in comparing to diazepam.

**Keywords** Quinoxaline · Molecular docking · AMPA antagonists · Anticonvulsant agents

## Introduction

Extensive studies have been conducted on quinoxaline derivatives to possess central nervous system (CNS) depressant action (Rogawski 2006; Wagle et al. 2009; Ibrahim et al. 2013; Elkaeed et al. 2014) with potent AMPA receptor antagonist activity, which in some cases inhibit AMPA-induced lethal convulsions in mice (Jin et al. 2003; Jin and Gouaux 2003; Traynelis et al. 2010).

The quinoxalinedione derivatives are one of the most important chemical classes of competitive AMPA receptor antagonists. A great number of them have made it possible to test the importance of AMPA receptors in different disease models. However, early pharmacological studies have been hampered by the lack of potent and selective compounds. CNQX (**I**) (Fig. 1) was, among the quinoxalinedione series, the first potent and selective AMPA receptor antagonist to be discovered (Rogawski 2013; Catarzi et al. 2007). CNQX (**I**) and DNQX (**II**) showed to be useful in developing and understanding of the pharmacology of AMPA receptor. However, these compounds also have activity at the Gly/NMDA binding site, thus lacking sufficient selectivity to be really useful tools for the characterization of the AMPA receptors. Subsequently, NBQX (**III**) was demonstrated to have improved AMPA receptor selectivity with respect to CNQX and thus, it was used as the antagonist of choice in many "in vitro" and "in vivo" models (Catarzi et al. 2007). Moreover, the clinical development of NBQX was prevented by its low-water solubility at physiological pH (Faust et al. 2009). On the contrary, YM90K (**IV**) showed to be systemically active, but it has a short "in vivo" duration of action (Catarzi et al., 2007).

In fact, most simple quinoxalinedione derivatives showed limited water solubility which restricted efforts to formulate acceptable parenteral solutions. With this

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✉ Khaled El-Adl
eladlkhaled74@yahoo.com

[1] Pharmaceutical Chemistry Department, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt

[2] Pharmaceutical Chemistry Department, Faculty of Pharmacy, Delta University, Gamasa, Dakahlia, Egypt

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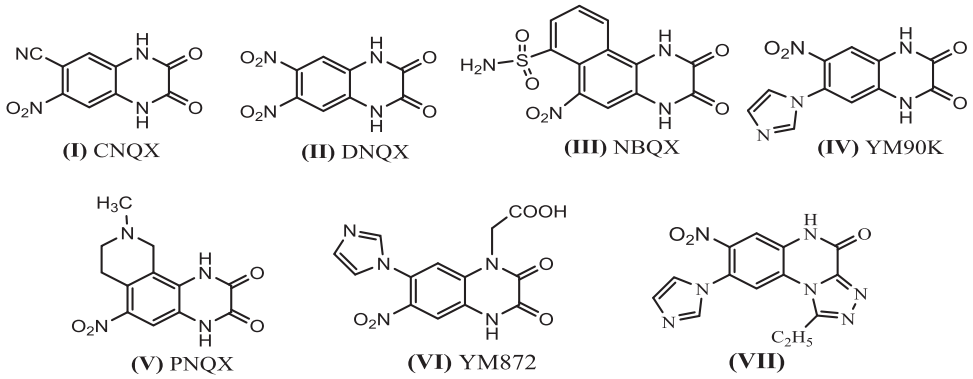



**Fig. 1** Reported quinoxalines as potent AMPA receptor antagonists

problem to solve, new compounds such as PNQX (**V**) and YM872 (**VI**) were prepared as possible AMPA receptor antagonist candidates. Unfortunately, PNQX showed low water solubility at physiological pH. YM872 is a very water-soluble AMPA antagonist due to the presence of a hydrophilic acetic acid side chain (Catarzi et al. 2007).

Taking YM90K as lead compound, compound **VII** (1-ethyl-8-(1*H*-imidazol-1-yl)-7-nitro-[1,2,4]triazolo[4,3-a] quinoxalin-4(5*H*)-one) was designed through replacement of the oxygen atom, of the 2,3-dione moiety, at C-3 with a bioisosteric nitrogen atom as a constituent of the fused heterocyclic ring at C3-N4. This modifications exhibited high-AMPA affinity and selectivity versus the Gly/NMDA site (Catarzi et al. 2007).

On the other hand, it has been reported that a lot of compounds containing, ester (Ibrahim et al. 2015), amide (El-Adl 2011), hydrazide (Ibrahim et al. 2013), pyrazole, oxadiazole, semicarbazide, thiosemicarbazide, phthalimide (El-Helby et al. 2009; Ibrahim et al. 2015), isatin, and/or Schiff's base (Alswah et al. 2013; Bayoumi et al. 2012; Elhelby et al. 2011) moieties possessed good anticonvulsant activity.

Based on that, it was decided to synthesize the title compounds as hybrid molecules formed of quinoxaline nucleus joined with the previously mentioned moieties in hope of developing potent and safe new effective anticonvulsant agents. The hybrid of these pharmacophoric features are designed to have different linkers at N-1 in order to act as a supplementary interaction point which reinforce the binding with the AMPA receptor which may improve selectivity and binding affinity of our target compounds toward AMPA receptor and overcome water solubility problems.

## Results and discussion

### Rationale and structure-based design

**YM872 (VI)** is a very water-soluble AMPA antagonist due to the presence of a hydrophilic acetic acid side chain. This structural modification made it possible to overcome the solubility problems.

In addition, compound **VII** is the most potent 1,2,4-triazolo[4,3-a]quinoxalin-4-one derivative with high-AMPA affinity and selectivity (Catarzi et al. 2007).

Taking compounds **YM872 (VI)** and **(VII)** as lead compounds, our target quinoxaline-2-one derivatives were designed as hybrids to maintain the basic features of N-1 substituted lead compound **YM872** and, at the same time, the basic features of N-4 substituted lead compound **VII**.

Figure 2 represents the structure similarities and pharmacophoric features of the lead compounds **YM872** and **(VII)** and our designed compounds. It also shows that structure of our designed final compounds fulfilled all the pharmacophoric structural requirements. These requirements include: the presence of quinoxalin-2-one moiety as hydrophobic domain, the carboxylic acid (C=OO) moiety at N-1 of **YM872** was replaced by bioisosteric (C=ON or C=NO) moieties as linkers in most derivatives to maintain the same hydrogen bonding sites. As a result, our designed derivatives maintained the improved AMPA receptor binding affinities of the lead compound **VI**.

On the other hand, the nitrogen atom at position-2 of compound **VII** was replaced by a bioisosteric oxygen atom and the N atom at position-3 of the fused heterocyclic ring was removed to obtain N-4 acetyl derivatives. As a result the oxygen atom of the acetyl group in our derivatives formed hydrogen bond with the same amino acid residue *Tyrosine220, while Proline89* formed hydrogen bond with N-4 of compound **VI**.

Moreover, the presence of (un)substituted distal moieties (e.g. ester, alkyl, cyclohexyl, phenyl, oxadiazole etc) as another hydrophobic domain attached to the N-1 atom through different linkers was responsible for controlling the pharmacokinetic properties of the anticonvulsant activity.

The present study was carried out to prepare the target compounds as hybrid molecules. These molecules formed of quinoxaline-2-one ring system joined with the acetyl group at 4-position and different substituents at position-1 with different electronic environments to study the SAR of

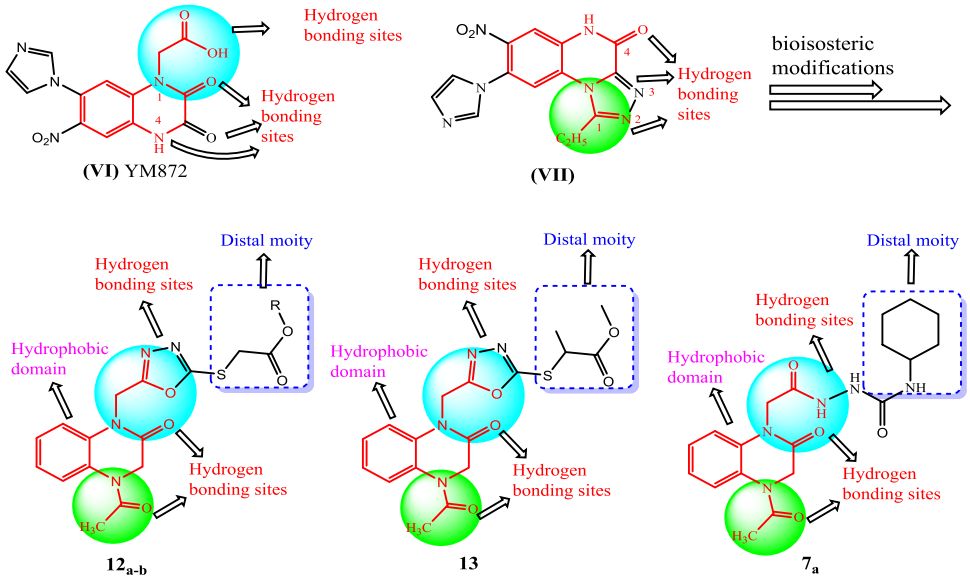



**Fig. 2** Structural similarities and pharmacophoric features of reported potent AMPA antagonists and our designed compounds specially $\mathbf{12_{a–b}}$, **13** and $\mathbf{7_a}$ as anticonvulsants

these compounds and the effect of each substituent on their anticonvulsant activity.

## Chemistry

The synthetic strategy for preparation of the target compounds (**2–13**) is depicted in Schemes 1–3. The title compounds were synthesized starting with ortho-phenylenediamine by its reaction with 2-chloroacetic acid to afford 3,4-dihydroquinoxalin-2(1*H*)-one (**1**), following the reported procedure, which was then treated with acetyl chloride and/or chloroacetyl chloride (Bonuga et al. 2013) to afford the corresponding N-4 acetyl derivatives ($\mathbf{2_{a–b}}$) respectively. The obtained acetyl derivative $\mathbf{2_a}$ was refluxed with ethyl chloroacetate to afford the corresponding ethyl ester (**3**). Heating the ethyl ester (**3**) with hydrazine hydrate furnished the corresponding acid hydrazide (**4**). On the other hand, the reaction of chloroacetyl derivative $\mathbf{2_b}$ with the appropriate aromatic amine, namely aniline, 4-bromoaniline and/or 4-methylaniline resulted in the corresponding derivatives ($\mathbf{5_{a–c}}$) respectively (Scheme 1).

Stirring of the acid hydrazide (**4**) with benzoyl chloride yielded the corresponding benzoyl derivative (**6**). Heating of acid hydrazide (**4**) with the appropriate isocyanates and/or isothiocyanates under reflux afforded the corresponding semicarbazide $\mathbf{7_{a–b}}$ and thiosemicarbazide $\mathbf{8_{a–b}}$ derivatives respectively. Condensation of the acid hydrazide (**4**) with the appropriate aldehyde, namly benzaldehyde, 2-chlorobenzaldehyde and/or 2-methoxybenzaldehyde resulted in the corresponding Schiff's bases $\mathbf{9_{a–c}}$ respectively (Scheme 2).

The acid hydrazide (**4**) underwent cyclization by reaction with acetic anhydride and/or carbon disulfide to afford the corresponding 5-methyloxadiazole (**10**) and/or 5-sulfanyloxadiazole (**11**) derivatives respectively. Treatment of 5-sulfanyloxadiazole derivative (**11**) with the appropriate alkyl 2-chloroacetate and/or methyl chloropropionate yielded the corresponding ester derivatives ($\mathbf{12_{a–b}}$) and (**13**) respectively (Scheme 3).

## Docking studies

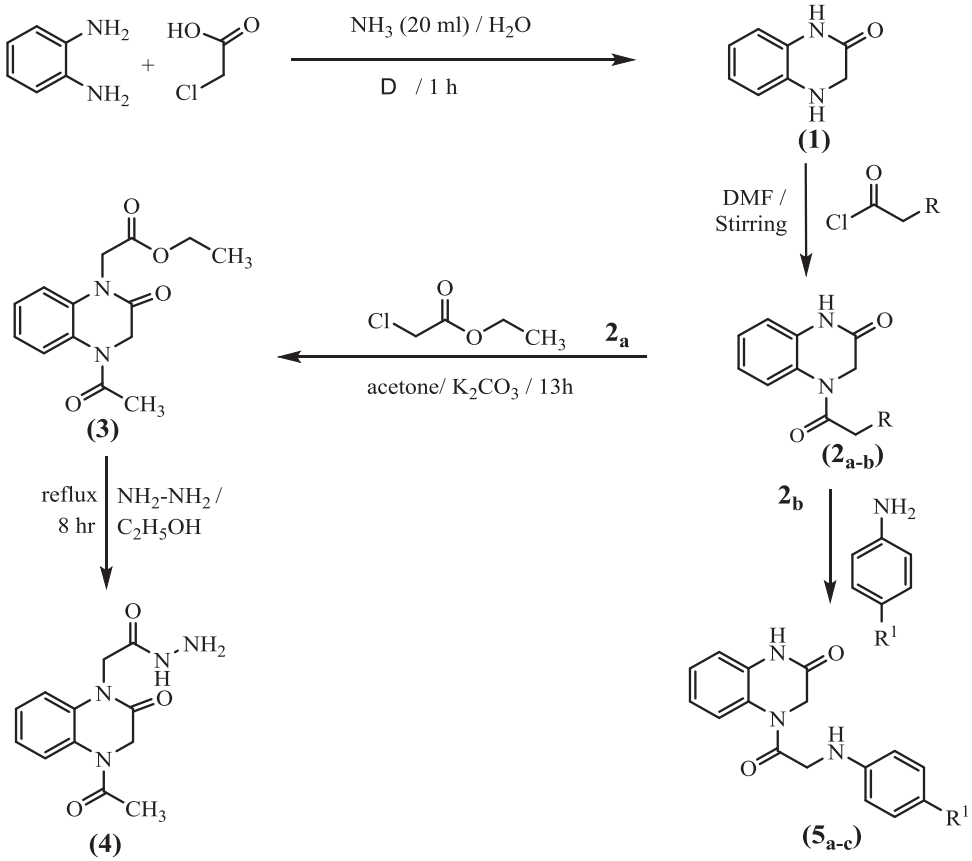
In the present work, all modeling experiments were performed using Molsoft software. Each experiment used AMPA (Loscher and Rogawski 2002) downloaded from the Brookhaven Protein Databank (http://www.rcsb.org/pdb/explore/explore.do?structureId=1FTL).

The obtained results indicated that all studied ligands have similar position and orientation inside the putative binding site of AMPA receptor (PDB code 1FTL) which reveals a large space bounded by a membrane-binding domain which serves as entry channel for substrate to the active site (Fig. 3). In addition, the affinity of any small molecule can be considered as a unique tool in the field of drug design.

There is a relationship between the affinity of organic molecules and the free energy of binding (Baum et al. 2009; Englert et al. 2010; Ibrahim et al. 2015). This relationship can contribute in prediction and interpretation of the activity of the organic compounds toward the specific target protein. The obtained results of the free energy of binding (ΔG) explained that most of these compounds had good binding affinity toward the receptor and the computed values reflected the overall trend (Table 1).

The proposed binding mode of **YM872** revealed affinity value of −70.63 kcal/mol and 7 H-bonds. The carboxylate group at position-1 formed 1 H-bond with *Threonine143* (–O atom) with a distance of 2.92 Å. The carbonyl group at

**Scheme 1** Synthetic route for preparation of the target compounds **2–6**




2) a) R= H b) R= Cl

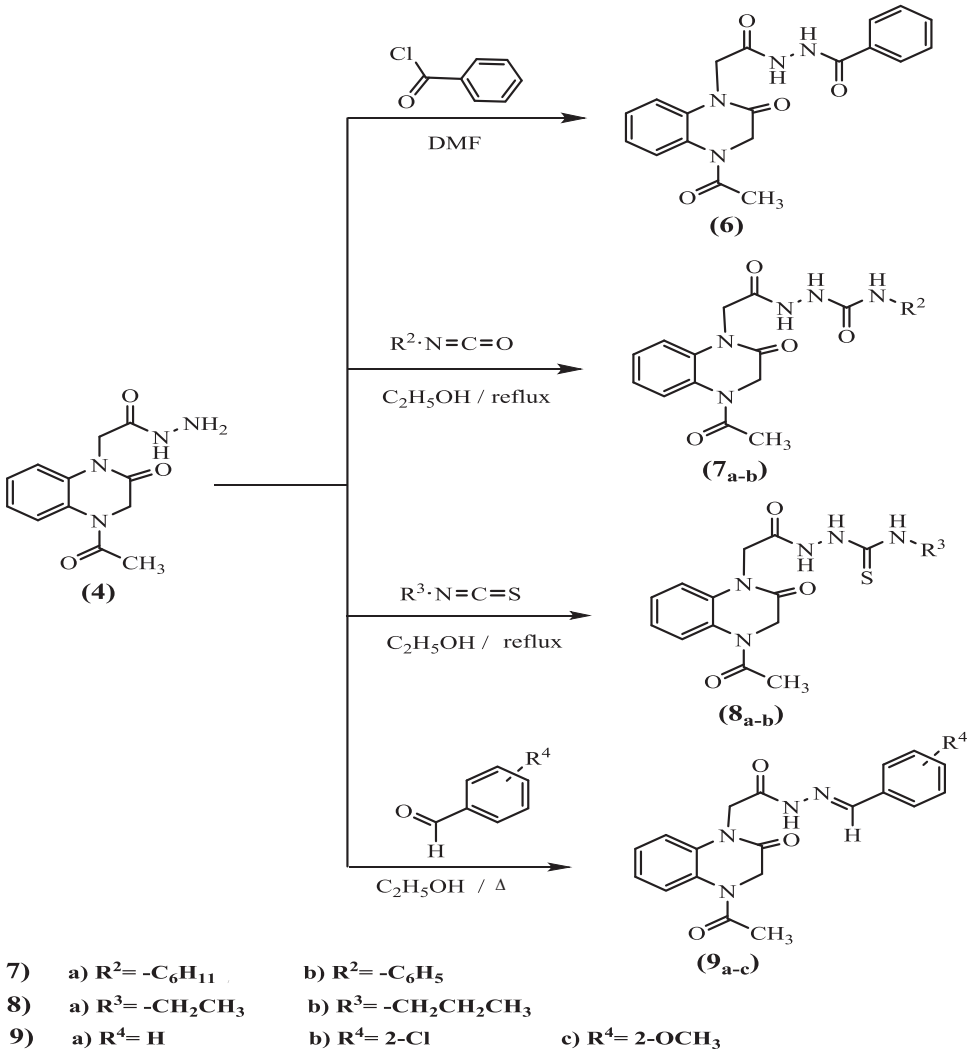
5) a) $R^1$= H b) $R^1$= Br c) $R^1$= $CH_3$

position-2 formed one H-bond with *Arginine96* (–NH group) with a distance of 1.95 Å and another H-bond with *Threonine91* (–OH group) with a distance of 2.70 Å. The other carbonyl group at position-3 was stabilized by formation of 1 H-bond with *Arginine96* (–NH group) with a distance of 1.68 Å and 1 H-bond with *Threonine91* (–NH group) with a distance of 1.55 Å. NH group at position-4 formed 1 H-bond with *proline89* (–O atom) with a distance of 1.71 Å. The imidazole moiety at position-7 formed one H-bond with *Threonine174* (–OH group) with a distance of 1.77 Å and occupied the hydrophobic pocket formed by *Threonine174, Leucine192, Glutamate193* and *Methionine196*. The quinoxaline nucleus occupied the hydrophobic pocket formed by *Lysine60, Tyrosine61, Arginine96, Threonine91*, *proline89, Lysine218, Tyrosine220, Glutamate193, Serine142* and *Threonine143* (Fig. 4).

The proposed binding mode of **compound VII** is virtually the same as that of **YM872** which revealed affinity value of −67.74 kcal/mol and 6 H-bonds. The N atom at position-2 of the fused triazole group formed one H-bond with *Threonine91* (–NH group) with a distance of 1.33 Å and the other N atom at position-3 of the fused triazole group formed 2 H-bonds with *Arginine96* (–NH groups) with distances of 1.83 and 2.07 Å. The carbonyl group formed 1 H-bond with *Arginine96* (–NH group) with a distance of 2.07 Å. The nitro group formed 1 H-bond with *Threonine174* (–OH group) with a distance of 1.54 Å. The imidazole moiety at position-8 formed one H-bond with *Tyrosine16* (–OH group) with a distance of 1.83 Å and occupied the hydrophobic pocket formed by *Tyrosine61, proline89, Tyrosine220, Tyrosine16, Glutamate193* and *Methionine196*. The ethyl group at position-1 occupied the hydrophobic pocket formed by *Threonine91, Lysine218, Tyrosine220* and *proline89*. The quinoxaline nucleus occupied the hydrophobic pocket formed by *Lysine60, Tyrosine61, Arginine96, Threonine91*, *proline89, Lysine218, Tyrosine220, Glutamate193, Serine142* and *Threonine143* (Fig. 5).

The proposed binding mode of **compound $12_b$** is virtually the same as that of **YM872** and **compounds VII** which revealed affinity value of −89.86 kcal/mol and 7 H-bonds. The two nitrogen atoms of the distal oxadiazole linker moiety at position-1 formed 2 H-bonds with

**Scheme 2** Synthetic route for preparation of the target compounds **6–9$_{a–c}$**




*Serine142* (–NH groups) with distances of 1.31 and 2.41 Å. The carbonyl group of the ester moiety formed 1 H-bond with *Threonine143* (–OH group) with a distance of 2.10 Å and the oxygen atom formed another H-bond with *Threonine174* (–OH group) with a distance of 2.95 Å. The carbonyl group at position-2 formed 2 H-bonds with *Arginine96* (–NH groups) with distances of 1.58 and 2.16 Å. The carbonyl group of acetyl moiety at position-4 formed 1 H-bond with *Tyrosine220* (–OH group) with a distance of 1.82 Å. The oxadiazole moiety occupied the hydrophobic pocket formed by *Threonine143, Serine142, Lysine218* and *Lysine60*. The ethyl group of the distal ester moiety occupied the hydrophobic pocket formed by *Threonine174, Leucine192, Glutamate193* and *Methionine196*. The methyl group of acetyl moiety at position-4 occupied the hydrophobic pocket formed by *Tyrosine61, Threonine91, Tyrosine220,* and *proline89*. The quinoxaline nucleus occupied the hydrophobic pocket formed by *Lysine60, Tyrosine61, Arginine96, Threonine91*, *proline89, Lysine218, Tyrosine220, Glutamate193, Serine142* and *Threonine143* (Fig. 6). These interactions of compound 12$_{\mathbf{b}}$ may explain the highest anticonvulsant activity.

The proposed binding mode of **compound 13** is virtually the same as that of **12$_{\mathbf{b}}$** which revealed affinity value of −86.09 kcal/mol and 7 H-bonds. The two nitrogen atoms of the distal oxadiazole linker moiety at position-1 formed 2 H-bonds with *Serine142* (–NH groups) with distances of 1.47 and 2.67 Å. The carbonyl group of the ester moiety formed 1 H-bond with *Threonine143* (–OH group) with a distance of 1.84 Å and the oxygen atom formed another H-bond with *Threonine174* (–OH group) with a distance of 2.98 Å. The carbonyl group at position-2 formed 2 H-bonds with *Arginine96* (–NH groups) with distances of 1.56 and 2.08 Å. The carbonyl group of acetyl moiety at position-4 formed 1 H-bond with *Tyrosine220* (–OH group) with a distance of 1.75 Å. The oxadiazole moiety occupied the

**Scheme 3** Synthetic route for preparation of the target compounds **10–14**

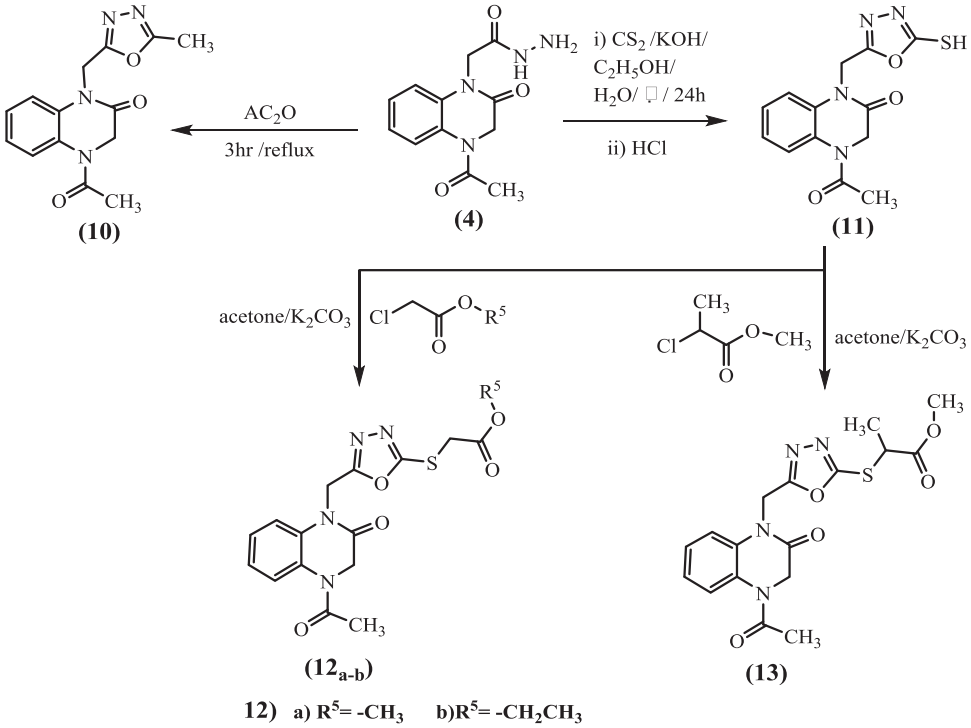
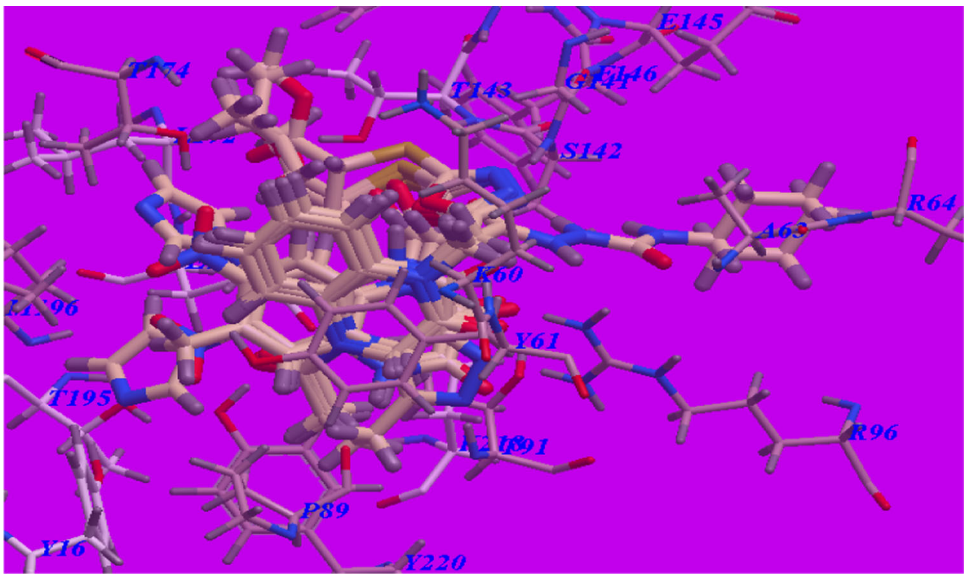



**Fig. 3** Superimposition of some docked compounds inside the binding pocket of 1FTL




hydrophobic pocket formed by *Threonine143, Serine142, Lysine218* and *Lysine60*. The methyl group of the distal ester moiety occupied the hydrophobic pocket formed by *Threonine174, Leucine192* and *Glutamate193*. The methyl group of acetyl moiety at position-4 occupied the hydrophobic pocket formed by *Tyrosine61, Threonine91, Tyrosine220,* and *proline89*. The quinoxaline nucleus occupied the hydrophobic pocket formed by *Lysine60, Tyrosine61, Arginine96, Threonine91*, *proline89, Lysine218, Tyrosine220, Glutamate193, Serine142* and *Threonine143* (Fig. 7). These interactions of compound **13** may explain the high anticonvulsant activity.

The proposed binding mode of **compound $12_a$** is virtually the same as that of $\mathbf{12_b}$ which revealed affinity value of –82.12 kcal/mol and 5 H-bonds. The two nitrogen atoms of the distal oxadiazole linker moiety at position-1 formed 2 H-bonds with *Serine142* (–NH groups) with distances of 1.51 and 2.50 Å. The carbonyl group at position-2 formed 2 H-bonds with *Arginine96* (–NH groups) with distances of 1.68 and 2.16 Å. The carbonyl group of acetyl moiety at

**Table 1** The calculated ΔG (free energy of binding) and binding affinities for the ligands (ΔG in Kcal/mole)

| Compound | ΔG (kcal $mol^{-1}$) | Compound | ΔG (kcal $mol^{-1}$) |
|---|---|---|---|
| $\mathbf{2_a}$ | −48.39 | $\mathbf{8_b}$ | −75.38 |
| $\mathbf{2_b}$ | −45.59 | $\mathbf{9_a}$ | −75.29 |
| **3** | −64.03 | $\mathbf{9_b}$ | −72.97 |
| **4** | −55.10 | $\mathbf{9_c}$ | −76.91 |
| $\mathbf{5_a}$ | −65.06 | **10** | −65.29 |
| $\mathbf{5_b}$ | −59.54 | **11** | −64.87 |
| $\mathbf{5_c}$ | −67.61 | $\mathbf{12_a}$ | −82.42 |
| **6** | −68.19 | $\mathbf{12_b}$ | −89.86 |
| $\mathbf{7_a}$ | −81.02 | **13** | −86.09 |
| $\mathbf{7_b}$ | −76.88 | **YM872 (VI)** | −70.63 |
| $\mathbf{8_a}$ | −75.31 | **Comp. (VII)** | −67.45 |

position-4 formed 1 H-bond with *Tyrosine220* (–OH group) with a distance of 1.67 Å. The oxadiazole moiety occupied the hydrophobic pocket formed by *Threonine143, Serine142, Lysine218* and *Lysine60*. The methyl group of the distal ester moiety occupied the hydrophobic pocket formed by *Threonine174, Leucine192* and *Glutamate193*. The methyl group of acetyl moiety at position-4 occupied the hydrophobic pocket formed by *Tyrosine61, Threonine91, Tyrosine220,* and *proline89*. The quinoxaline nucleus occupied the hydrophobic pocket formed by *Lysine60, Tyrosine61, Arginine96, Threonine91, proline89, Lysine218, Tyrosine220, Glutamate193, Serine142* and *Threonine143* (Fig. 8). These interactions of compound $\mathbf{12_a}$ may explain the high anticonvulsant activity.

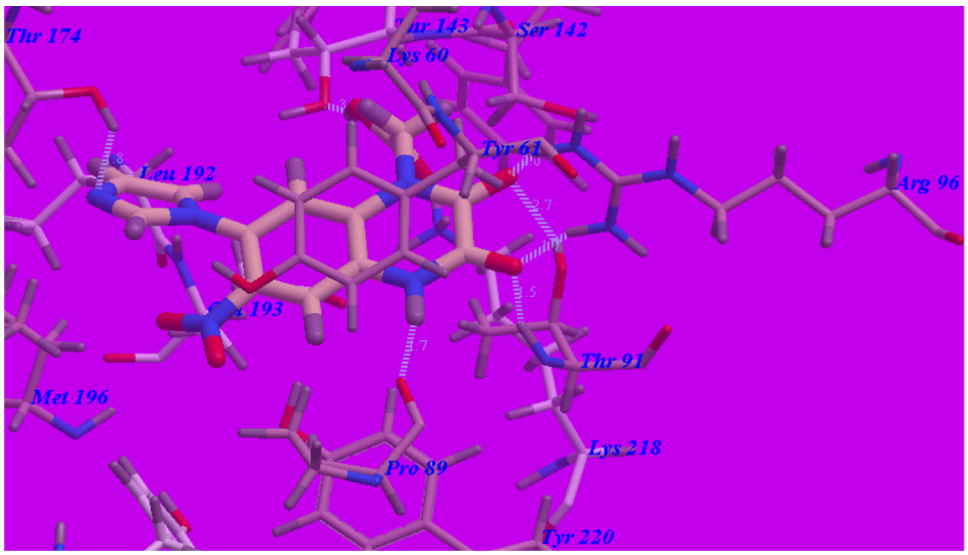



**Fig. 4** Predicted binding mode for **YM872** with 1FTL

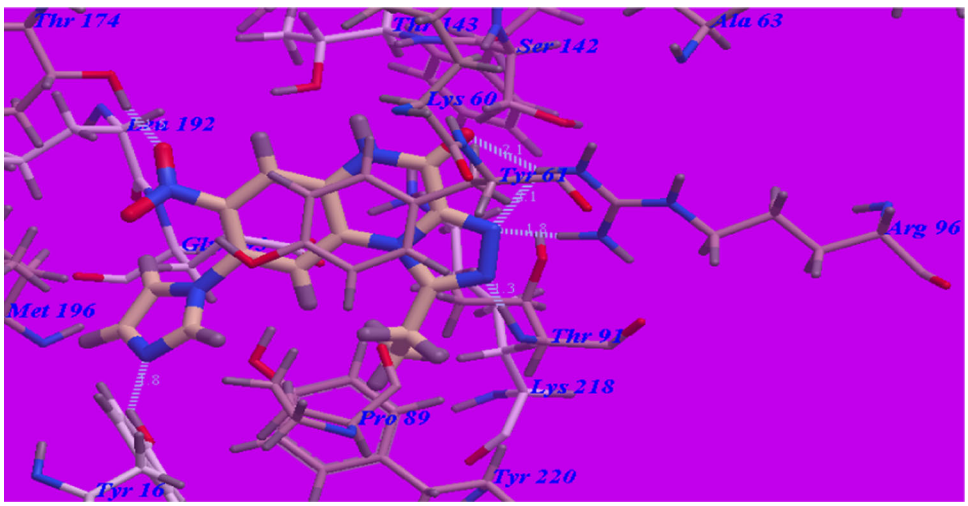



**Fig. 5** Predicted binding mode for VII with 1FTL

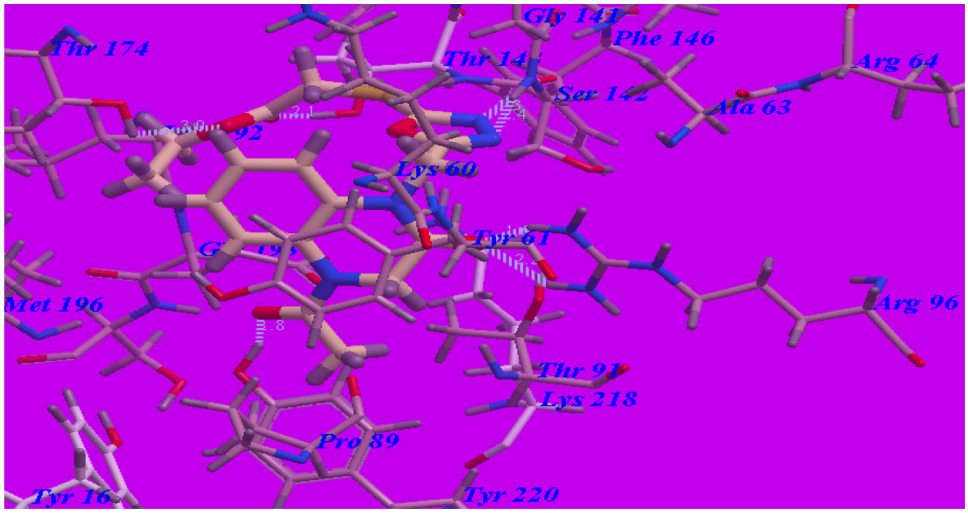



**Fig. 6** Predicted binding mode for $\mathbf{12_b}$ with 1FTL

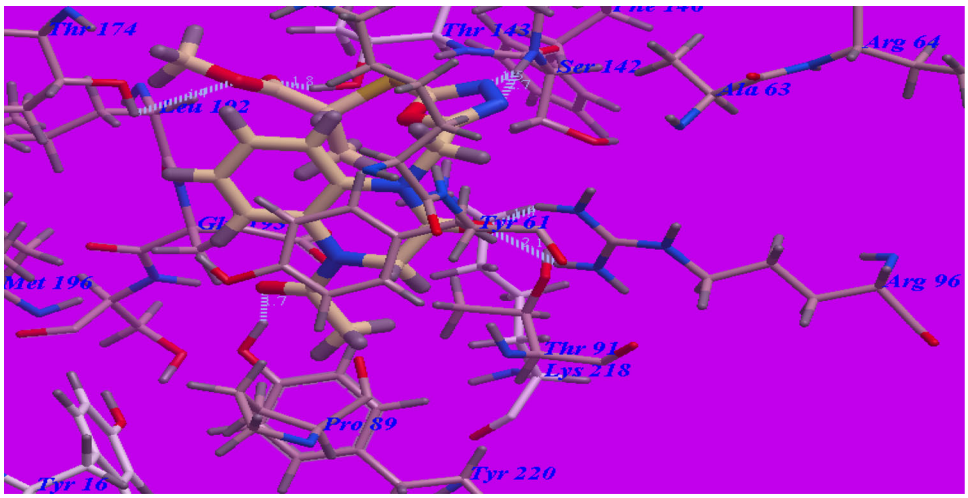



**Fig. 7** Predicted binding mode for **13** with 1FTL

## Biological screening

In the present study, thirteen compounds of the newly synthesized quinoxaline derivatives were selected to be screened in vivo for their anticonvulsant activity against pentylenetetrazole-induced convulsions in mice following a reported procedure (Vogel 2008). Thirteen groups of six 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. From the plots of these data, ($ED_{50}$) was determined. The results were compared with diazepam as a standard anticonvulsant drug. Most of the tested compounds showed good anticonvulsant activities. The tested compounds exhibited relative anticonvulsant potencies ranged from 0.37 to 1.66 of diazepam. Compounds $\mathbf{12_b}$, **13**, $\mathbf{12_a}$ and $\mathbf{7_a}$ showed the highest anticonvulsant activities in experimental mice with relative potencies of 1.66, 1.66, 1.61 and 0.82 respectively. Compounds $\mathbf{9_a}$ **and** $\mathbf{9_b}$ exhibited the lowest relative potencies of 0.37 and 0.41 respectively. Compound $\mathbf{8_a}$ exhibited relative potency of 50 % of diazepam. Other compounds exhibited relative potencies higher than 50 % of diazepam (Fig. 9). Compounds $\mathbf{12_a}$, $\mathbf{12_b}$ and **13** caused 100 % protection in a dose of 500 mcg/kg body weight. While compounds $\mathbf{5_a}$, $\mathbf{7_b}$ and $\mathbf{8_b}$ caused 100 % protection in a dose of 1000 mcg/kg body weight. Compounds $\mathbf{5_b}$, $\mathbf{5_c}$, $\mathbf{7_a}$, $\mathbf{8_a}$, $\mathbf{9_a}$, $\mathbf{9_b}$ and $\mathbf{9_c}$ caused 83.33 % protection at the same dose Table 2). Compounds $\mathbf{12_a}$, $\mathbf{12_b}$ and **13** caused 50 % protection in a dose of 125 mcg/kg body weight while the remaining compounds showed 50 % protection at higher doses. The percent of protection per each dose as well as the medium effective dose ($ED_{50}$), the dose which makes 50 % protection of animals, was calculated using INSTAT 2 program (ICS, Philadelphia, PA, USA).

Structure activity relationship (SAR) studies indicated that different substitution on the quinoxaline ring exerted varied anticonvulsant activity. Substitution at 1-position showed higher activities than those at 4-position. The electronic nature of the substituent group attached to

quinoxaline ring led to a significant variation in the anticonvulsant activity. From the structure of the substituted compounds at 4-position, the presence of lipophilic electron releasing group ($CH_3$ at $5_c$) attached to phenyl moiety slightly increased the activity when compared to the unsubstituted phenyl at **$5_a$**. While the presence of highly lipophilic electron deficient group (Br at **$5_b$**) attached to phenyl moiety decreased the activity. From the structure of the substituted compounds at 1-position and the data shown in Table 2 we can divide these tested compounds into four groups. The first group is substituted semicarbazide derivatives **$7_a$** and **$7_b$**. In this group, the presence of lipophilic electron releasing group (cyclohehyl ring at **$7_a$**) attached to semicarbazide moiety enhanced the activity when compared to the electron withdrawing phenyl group at **$7_b$**. The second group is substituted thiosemicarbazide derivatives **$8_a$** and **$8_b$**. The propyl group at **$8_b$** produced slightly increased activity in spite of high difference in lipophilicity. The third group is Schiff's bases **$9_a$, $9_b$** and **$9_c$**. Among these compounds, **$9_c$** with electron releasing group (2-$OCH_3$) exhibited higher activity than **$9_b$** with electron deficient group (2-Cl), which exhibited lower activity. The fourth group is 1,3,4 Oxadiazole-5-sulfanyl ester derivatives **$12_a$**, **$12_b$** and **13**. The ethyl acetate derivative **$12_b$** and methyl propionate derivative **13** showed the same highest activity. It was noticed that, the two derivatives also have nearly the same lipophilicity. The methyl acetate derivative **$12_a$** produced slightly decreased activity in spite of high difference in lipophilicity.

## C log P correlation

As a trial for interpretation of the correlation between chemical structure of compounds **$5_a$**, **$5_b$**, **$5_c$**, **$7_a$**, **$7_b$**, **$8_a$**, **$8_b$**, **$9_a$**, **$9_b$**, **$9_c$**, **$12_a$**, **$12_b$** and **13** and their biological activity, an attempted correlation of anticonvulsant activity with C log P data was calculated for the measurement of the lipophilicity factor which could be attributed in their anticonvulsant activity. Determination of lipid-water 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. So, the C log P values were calculated for some derivatives to reflect the overall lipophilicity of these compounds and compared. The C log P data for all selected anticonvulsant compounds were explained in Table 2 ranging from 0.07 to 3.01. C log P for **diazepam**, **YM872** (**VI**) and **VII** were calculated and were found to be 2.74, 0.89 and 0.65 respectively. It is worthwhile to note that the C log P values for compounds **$12_b$**, **13** and **$12_a$** which had higher potency were found to be 0.50, 0.49 and 0.12 respectively. It is noted that, C log P values for compounds **$12_b$**, **13** and **$12_a$** were found to be less than that for compounds **YM872** (**VI**) and **VII**. This indicated that, the water solubility of our designed compounds, **$12_b$**, **13** and **$12_a$** were higher than that of the reference ligands **YM872** (**VI**) and **VII**. The improved aqueous solubility may explain the higher affinity and selectivity towards AMPA receptor.

In spite of compound **$5_b$** have lower anticonvulsant potency than compounds **$5_a$** and **$5_c$**, it had higher C log P value and had no correlation with the lipophilicity factor while compounds **$7_a$** had higher C log P values than **$7_b$** (1.06 and 0.85 respectively) and had good correlation with the lipophilicity factor. Interestingly, the values of C log P for compounds **$8_a$** and **$8_b$** were 0.07 and 0.57 respectively and had no significant effect on biological activity. Moreover compounds **$9_a$**, **$9_b$**, and **$9_c$** showed C log P values of 1.71, 2.34 and 1.72 and relative potencies of 0.37, 0.41 and 0.80 respectively and also had no correlation of the lipophilicity factor with their potency levels.

## Conclusion

The molecular design was performed to assess the binding mode of the proposed compounds with AMPA receptor. The data obtained from the docking studies showed that; all the synthesized derivatives have considerable high affinity towards the AMPA receptor in comparing to **YM872 (VI)** and **(VII)** as reference ligands. The data obtained from the biological screening fitted with that obtained from the molecular modeling. All the tested compounds showed variable anticonvulsant activities. Their potencies range from 0.37 to 1.66 of that of diazepam. Compounds $12_b$, 13, $12_a$ and $7_a$ showed the highest anticonvulsant activities in experimental mice with anticonvulsant potencies of 1.66, 1.66, 1.61 and 0.82 respectively in comparing to diazepam as a reference drug. C log P values for compounds **$12_b$**, **13** and **$12_a$** were found to be less than that for compounds **YM872** (**VI**) and **VII**. This indicated that, the water solubility of our designed compounds, **$12_b$**, **13** and **$12_a$** were higher than that of the reference ligands which may explain the higher affinity and selectivity towards AMPA receptor.

The obtained results showed that, the most active compounds could be useful as a template for future design, optimization, adaptation and investigation to produce more potent and selective AMPA receptor antagonists with good physicochemical properties and higher anticonvulsant analogs.

## Experimental

### Chemistry

All melting points were carried out by open capillary method on a Gallen kamp Melting point apparatus at faculty

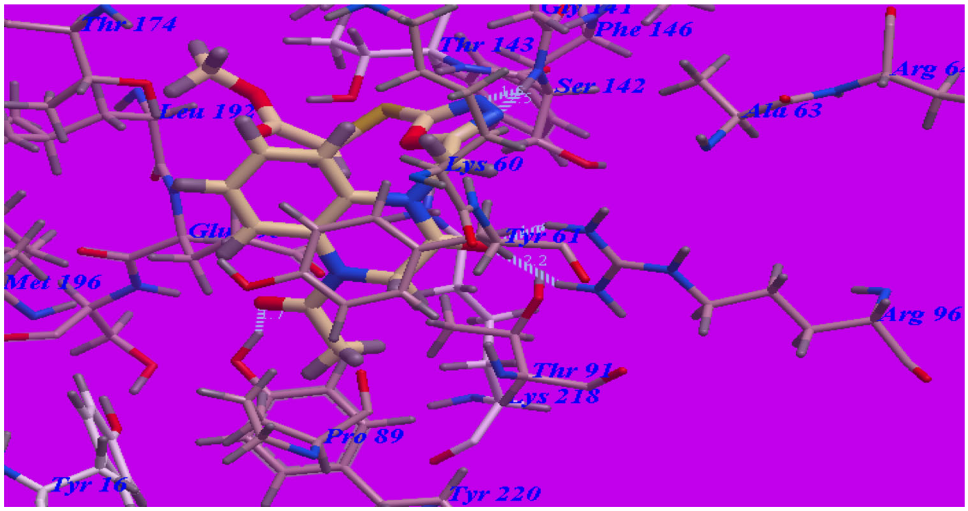



**Fig. 8** Predicted binding mode for $\mathbf{12_a}$ with 1FTL

of pharmacy Al-Azhar University and were uncorrected. The infrared spectra were recorded on pye Unicam SP 1000 IR spectrophotometer at Pharmaceutical analytical Unit, Faculty of Pharmacy, Al-Azhar University using potassium bromide disk technique. Proton magnetic resonance $^1$HNMR spectra were recorded on a Bruker 400 MHZ-NMR spectrometer at Microanalytical Center, Zagazig University—Zagazig. $^{13}$CNMR spectra were recorded on an Agilent 400 MHZ-NMR spectrometer at and Chemical Laboratory—Ministry of Defense—Cairo. TMS was used as internal standard and chemical shifts were measured in δ scale (ppm). The mass spectra were carried out on Direct Probe Controller Inlet part to Single Quadropole mass analyzer in Thermo Scientific GCMS model ISQ LT using Thermo X-Calibur software at the Regional Center for Mycology and Biotechnology, Al-Azhar University. Elemental analyses (C, H, N) were performed on a CHN analyzer at Regional Center for Mycology and Biotechnology, Al-Azhar University. All compounds were within ±0.4 of the theoretical values. The reactions were monitored by thin-layer chromatography (TLC) using TLC sheets precoated with UV fluorescent silica gel Merck 60 F254 plates and were visualized using UV lamp and different solvents as mobile phases.

3,4-Dihydroquinoxalin-2(1*H*)-one (1) and 4-(2-chloroacetyl)-3,4-dihydroquinoxalin-2(1*H*)-one ($2_b$) were obtained according to the reported procedures (Bonuga et al. 2013).

*4-Acetyl-3,4-dihydroquinoxalin-2(1*H*)-one ($2_a$)*

Acetyl chloride (7.85 g, 0.1 mol) was added dropwise to the stirred solution of 3,4-dihydro-quinoxalin-2(1*H*)-one 2 (14.8 g, 0.1 mol) in dry DMF (100 ml) in the presence of potassium carbonate (13.8 g, 0.1 mol) using ice-bath. After addition, the solution was stirred at room temperature for 1 h. The contents of the reaction flask were then poured slowly into water with continuous stirring and the resulting precipitate was filtered, washed with water, dried and crystallized from ethanol to obtain the target compound ($\mathbf{2_a}$).

Yield, 80 %; m.p.: 165–168 °C. Analysis for $C_{10}H_{10}N_2O_2$ (m.w. 190); calcd.: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.31; H, 5.36; N, 14.89. IR (KBr, $cm^{-1}$): 3192 (NH), 3072 (C–H aromatic), 2992 (C–H aliphatic), 1672 (2C=O amidic overlapped). $^1$HNMR (DMSO, d6-400 MHz, ppm): 2.17 (s, 3H, $CH_3$ acetyl), 4.32 (s, 2H, $CH_2$ quinoxaline), 7.03 (m, 2H, H-6 and H-8 quinox.), 7.19 (m, 1 H, H-7 quinox.), 7.48 (d, 1H, H-5 quinox. $J = 7.6\ Hz$), 10.68 (s, 1H, NH) ($D_2O$ exchangeable). $^{13}$CNMR (DMSO-$d_6$, 400 MHz): $\delta = 169.13$ (C, $CH_3CO$), 166.64 (C, C-2), 133.44 (C, C-8′), 129.45 (C, C-4′), 127.09 (CH, C-5), 125.03 (2CH, C-6, C-7), 123.15 (CH, C-8), 45.92 ($CH_2$, C-3), 22.12 ($CH_3$, $CH_3CO$). MS (m/z): 190 ($M^+$, 35 %), 148 (82 %), 119 (100 %, base beak).

*Ethyl 2-(4-acetyl-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl) acetate (**3**)*

A mixture of 4-acetyl-3,4-dihydroquinoxalin-2(1*H*)-one ($\mathbf{2_a}$) (6.70 g, 0.03 mol) and ethyl chloroacetate (3.68 g, 0.03 mol) in dry acetone (30 ml) in the presence of anhydrous $K_2CO_3$ (8.28 g, 0.06 mol) was refluxed for 13 h while stirring. The reaction mixture was filtered, the solvent was evaporated and the resulting product was collected by filtration and re-crystallized from ethanol to give the target compound (**3**).

Yield, 80 %; m.p.: 73-–75 °C. Analysis for $C_{14}H_{16}N_2O_4$ (m.w. 276); calcd.: C, 60.86; H, 5.84; N, 10.14. Found: C, 61.02; H, 5.89; N, 10.31. IR (KBr, $cm^{-1}$): 3072 (C–H aromatic), 2990 (C–H aliphatic), 1741 (C=O ester), 1676 (2C=O amidic overlapped). $^1$HNMR (DMSO-$d_6$, ppm):

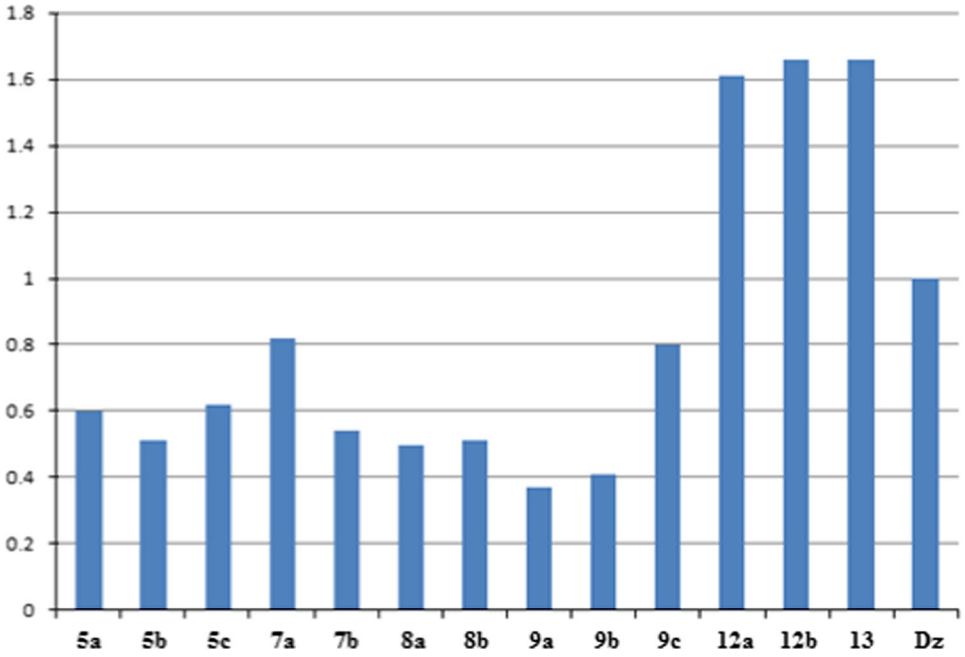



**Fig. 9** Relative potencies of the tested compounds and diazepam

1.19 (t, 3H, $CH_2CH_3$, $J = 7.2$ Hz), 2.16 (s, 3H, $CH_3$ acetyl), 4.15 (q, 2H, $CH_2CH_3$, $J = 7.2$ Hz), 4.46 (s, 2H, $CH_2$ quinox.), 4.69 (s, 2H, $NCH_2$), 7.16 (m, 2H, H-6 and H-7 quinox.), 7.29 (d, 1H, H-8 quinox. $J = 7.6$ Hz), 7.56 (d, 1H, H-5 quinox. $J = 7.6$ Hz). $^{13}$CNMR (DMSO-$d_6$, 400 MHz): $\delta = 169.12$ (2C, $CH_3CO$, COO), 166.65 (C, C-2), 133.43 (C, C-8′), 129.45 (C, C-4′), 125.05 (CH, C-6), 123.16 (CH, C-7), 116.61 (2CH, C-5,C-8), 59.69 ($CH_2$, $OCH_2$), 45.95 ($CH_2$, C-3), 42.93 ($CH_2$, $NCH_2$), 22.14 ($CH_3$, $CH_3CO$), 11.27 ($CH_3$, $CH_2CH_3$).

*2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl) acetohydrazide (**4**)*

A mixture of the ester (**3**) (2.76 g, 0.01 mol) and hydrazine hydrate (10 ml, 50 %) in ethanol (50 ml) was stirred well and refluxed for 8 h. The reaction mixture was cooled and the solid produced was collected by filtration, washed with water, dried and re-crystallized from ethanol.

Yield, 80 %; m.p.: 230–231 °C. Analysis for $C_{12}H_{14}N_4O_3$ (m.w. 262); calcd.: C, 54.96; H, 5.38; N, 21.36. Found: C, 55.12; H, 5.43; N, 21.49. IR (KBr, $cm^{-1}$): 3299, 3229 ($NH–NH_2$), 3044 (C–H aromatic), 2930 (C–H aliphatic), 1672 (3C=O amidic overlapped). $^1$HNMR (DMSO-$d_6$, ppm): 2.16 (s, 3H, $CH_3$ acetyl), 4.26 (s, 2H, $NH_2$) ($D_2O$ exchangeable), 4.45 (s, 2H, $NCH_2$), 4.46 (s, 2H, $CH_2$ quinox.), 7.00–7.04 (m, 1H, H-6 quinox.), 7.11–7.15 (m, 1H, H-7 quinox.), 7.25–7.28 (d, 1H, H-8 quinox. $J = 8$ Hz), 7.53 (d, 1H, H-5 quinox. $J = 8$ Hz), 9.30 (s, 1H, NH) ($D_2O$ exchangeable). $^{13}$CNMR (DMSO-$d_6$, 400 MHz): $\delta =$ 169.34 (C, $CH_3CO$), 166.71 (2C, CONH, C-2), 154.65 (C, C-8′), 149.80 (C, C-4′), 124.89 (CH, C-6), 123.29 (CH, C-7), 118.34 (CH, C-5), 116.47 (CH, C-8), 44.17 ($2CH_2$, C-3, $NCH_2$), 22.31 ($CH_3$, $CH_3CO$). MS (*m*/*z*): 263 ($M^+$+1, 1.03 %), 262 ($M^+$, 4.72 %), 231 (43 %), 190 (1.8 %), 147 (6 %), 133 (100 %, base beak).

*4-(2-(4-Substitutedphenylamino)acetyl)-3,4-dihydroquinoxalin-2(1*H*)-one (**5**$_{a–c}$)*

General method To a stirred solution of compound 4-(2-chloroacetyl)-3,4-dihydroquinoxalin-2(1*H*)-one (**2**$_b$) (0.45 g, 0.002 mol) and $NaHCO_3$ (0.34 g, 0.004 mol) in 2-propanol (15 ml), the appropriate aromatic amine namely, aniline, 4-bromoaniline and/or 4-methylaniline (0.002 mol) was added followed by potassium iodide (20 mol%). The reaction mixture was refluxed for12 h, cooled to room temperature and filtered to remove the inorganic salts. The solvent was evaporated and the resulting precipitate was re-crystallized from ethanol to get the corresponding derivatives (**5**$_{a–c}$), respectively**.**

*4-(2-Phenylaminoacetyl)-3,4-dihydroquinoxalin-2(1*H*)-one (**5**$_a$)*

Yield, 70 %; m.p.: 220–222 °C. Analysis for $C_{16}H_{15}N_3O_2$ (m.w. 281); calcd.: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.52; H, 5.44; N, 15.12. IR (KBr, $cm^{-1}$): 3192, 3131 (2NH), 3063 (C–H aromatic), 2996 (C–H aliphatic), 1679 (2C=O amidic overlapped). $^1$HNMR (DMSO-$d_6$, ppm): 4.08 (s, 2H, $CH_2$ acetyl), 4.38 (s, 2H, $CH_2$ quinox.),

**Table 2** Anticonvulsant activity of the selected compounds

| Test comp. | Dose (mcg/kg) | No. of protected animal | Protection (%) | $ED_{50}$ (mcg/kg) | M.w | $ED_{50}$ (mmol/kg) | Relative potency | C log P |
|---|---|---|---|---|---|---|---|---|
| **$5_a$** | 250 | 3 | 50.00 | | | | | |
| | 500 | 5 | 83.33 | 250 | 281 | 0.89 | 0.60 | 2.20 |
| | 1000 | 6 | 100.00 | | | | | |
| **$5_b$** | 250 | 2 | 33.33 | | | | | |
| | 500 | 4 | 66.67 | 375 | 360 | 1.04 | 0.51 | 3.01 |
| | 1000 | 5 | 83.33 | | | | | |
| **$5_c$** | 250 | 3 | 50.00 | | | | | |
| | 500 | 4 | 66.67 | 250 | 295 | 0.85 | 0.62 | 2.65 |
| | 1000 | 5 | 83.33 | | | | | |
| **$7_a$** | 250 | 3 | 50.00 | | | | | |
| | 500 | 4 | 66.67 | 250 | 387 | 0.65 | 0.82 | 1.06 |
| | 1000 | 5 | 83.33 | | | | | |
| **$7_b$** | 250 | 2 | 33.33 | | | | | |
| | 500 | 5 | 83.33 | 375 | 381 | 0.98 | 0.54 | 0.85 |
| | 1000 | 6 | 100.00 | | | | | |
| **$8_a$** | 250 | 2 | 33.33 | | | | | |
| | 500 | 4 | 66.67 | 375 | 349 | 1.07 | 0.50 | 0.07 |
| | 1000 | 5 | 83.33 | | | | | |
| **$8_b$** | 250 | 2 | 33.33 | | | | | |
| | 500 | 5 | 83.33 | 375 | 363 | 1.03 | 0.51 | 0.57 |
| | 1000 | 6 | 100.00 | | | | | |
| **$9_a$** | 250 | 1 | 16.67 | | | | | |
| | 500 | 3 | 50.00 | 500 | 350 | 1.43 | 0.37 | 1.71 |
| | 1000 | 5 | 83.33 | | | | | |
| **$9_b$** | 250 | 1 | 16.67 | | | | | |
| | 500 | 3 | 50.00 | 500 | 384 | 1.30 | 0.41 | 2.34 |
| | 1000 | 5 | 83.33 | | | | | |
| **$9_c$** | 250 | 3 | 50.00 | | | | | |
| | 500 | 4 | 66.67 | 250 | 380 | 0.66 | 0.80 | 1.72 |
| | 1000 | 5 | 83.33 | | | | | |
| **$12_a$** | 250 | 5 | 83.33 | | | | | |
| | 500 | 6 | 100.00 | 125 | 376 | 0.33 | 1.61 | 0.12 |
| | 1000 | 6 | 100.00 | | | | | |
| **$12_b$** | 250 | 5 | 83.33 | | | | | |
| | 500 | 6 | 100.00 | 125 | 390 | 0.32 | 1.66 | 0.50 |
| | 1000 | 6 | 100.00 | | | | | |
| **13** | 250 | 5 | 83.33 | | | | | |
| | 500 | 6 | 100.00 | 125 | 390 | 0.32 | 1.66 | 0.49 |
| | 1000 | 6 | 100.00 | | | | | |
| **Diazepam** | 75 | 1 | 16.67 | | | | | |
| | 150 | 3 | 50 | 150 | 284.5 | 0.53 | 1.00 | 2.74 |
| | 300 | 6 | 100 | | | | | |

5.75 (s, 1H, NH-phenyl) ($D_2O$ exchangeable), 6.46 (m, 1H, H-4 phenyl), 6.53 (m, 2H, H-2 and H-6 phenyl), 7.02 (m, 2H, H-6 and H-8 quinox.), 7.06 (m, 2H, H-3 and H-5 phenyl), 7.22 (m, 1 H, H-7 quinox.), 7.58 (d, 1H, H-5 quinox. $J = 7.6$ Hz), 10.71 (s, 1H, NH quinox.) ($D_2O$ exchangeable).

*4-(2-(4-Bromophenylamino)acetyl)-3,4-dihydroquinoxalin-2(1H)-one (**5b**)*

Yield, 80 %; m.p.: 295–297 °C. Analysis for $C_{16}H_{14}BrN_3O_2$ (m.w. 360); calcd.: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.49; H, 7.05; N, 14.01. IR (KBr, $cm^{-1}$): 3196, 3135 (2NH), 3057 (C–H aromatic), 2916 (C–H aliphatic), 1654 (2C=O amidic overlapped. $^{13}$CNMR (DMSO-$d_6$, 400 MHz): $\delta = 168.66$ (C, C-2), 167.41 (C, CON), 143.36 (C, $C_6H_4$ (C-1)), 140.40 (C, C-8′), 133.43 (C, C-4′), 132.04 (C, 2CH, $C_6H_4$ (C-3, C-5)), 131.70 (CH, C-5), 130.34 (2CH, C-6, C-7), 127.29 (CH, C-8), 123.31 (CH, C-6), 116.78 (2CH, $C_6H_4$ (C-2, C-6)), 44.75 ($CH_2$, $NHCH_2$), 44.28 ($CH_2$, C-3). MS (*m/z*): 362 ($M^{+2}$, 8.33 %), 360 ($M^+$, 9.74 %), 207 (68.84 %), 147 (5.00 %), 133 (54.90 %), 87 (100 %, base beak).

*4-(2-(4-Tolylamino)acetyl)-3,4-dihydroquinoxalin-2(1H)-one (**5c**)*

Yield, 85 %; m.p.: 230–232 °C. Analysis for $C_{17}H_{17}N_3O_2$ (m.w. 295); calcd.: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.28; H, 5.87; N, 14.35. IR (KBr, $cm^{-1}$): 3196, 3143 (2NH), 3066 (C–H aromatic), 2916 (C–H aliphatic), 1685 (2C=O amidic overlapped). $^1$HNMR (DMSO-$d_6$, ppm): 2.13 (s, 3H, $CH_3$), 4.06 (s, 2H, $CH_2$ acetyl), 4.37 (s, 2H, $CH_2$ quinox.), 5.56 (s, 1H, NH-phenyl) ($D_2O$ exchangeable), 6.43 (d, 2H, H-2 and H-6 phenyl, $J = 7.6$ Hz), 6.85 (m, 2H, H-6 and H-8 quinox.), 7.06 (m, 2H, H-3 and H-5 phenyl), 7.21 (m, 1 H, H-7 quinox.), 7.63 (d, 1H, H-5 quinox. $J = 8$ Hz), 10.70 (s, 1H, NH quinox.) ($D_2O$ exchangeable). $^{13}$CNMR (DMSO-$d_6$, 400 MHz): $\delta = 170.16$ (C, C-2), 168.02 (C, NCO), 146.27 (2C, C-8′, C-4′), 144.27 (C, $C_6H_4$ (C-1)), 129.68 (2CH, $C_6H_4$ (C-3, C-5)), 126.53 (C, $C_6H_4$ (C-4)), 125.11 (CH, C-6), 124.54 (CH, C-7), 116.80 (CH, C-5), 112.83 (3CH, C-8, $C_6H_4$ (C-2, C-6) ), 45.95 ($CH_2$, $NHCH_2$), 40.58 ($CH_2$, C-3), 20.50 ($CH_3$, $C_6H_4$(4-$CH_3$)).

N′*-(2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl) acetyl)benzohydrazide (**6**)*

Benzoyl chloride (0.14 g, 0.001 mol) was added dropwise to the stirred solution of the acid hydrazide (**4**) (0.26 g, 0.001 mol) in dry DMF (30 ml) in the presence of potassium carbonate (0.14 g, 0.001 mol) using ice-bath. After addition, the solution was stirred at room temperature for 1 h. The contents of the reaction flask were then poured slowly into water with continuous stirring and the resulting precipitate was filtered, washed with water, dried and crystallized from ethanol to obtain compound (**6**).

Yield, 70 %; m.p.: 290–292 °C. Analysis for $C_{19}H_{18}N_4O_4$ (m.w. 366); calcd.: C, 62.29; H, 4.95; N, 15.29. Found: C, 62.43; H, 4.98; N, 15.51. IR (KBr, $cm^{-1}$): 3465 (NH), 3069 (C–H aromatic), 2930 (C–H aliphatic), 1650 (4C=O overlapped). $^{13}$CNMR (DMSO-$d_6$, 400 MHz): $\delta = 169.34$ (C, $CH_2CONH$), 168.21 (C, $CH_3CO$), 167.43 (C, NHCOPh), 163.67 (C, C-2), 147.37 (2C, C-8′, C-4′), 144.27 (2C, $C_6H_4$ (C-1, CH-4)), 129.07 (2CH, $C_6H_4$ (C-3, C-5)), 128.97 (2CH, $C_6H_4$ (C-2, C-6)), 127.06 (CH, C-6), 124.88 (CH, C-7), 116.75 (CH, C-5), 114.74 (CH, C-8), 55.74 ($CH_2$, C-3), 44.23 ($CH_2$, $NCH_2$), 22.21 ($CH_3$, $CH_3CO$). MS (*m/z*): 366 ($M^+$, 1.41 %), 189 (4.5 %), 77 (100 %, base beak).

*2-(2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl) acetyl)-*N*-substituted-hydrazine-1-carboxamide (**7a–b**)*

General method A mixture of the acid hydrazide (**4**) (0.26 g, 0.001 mol) and the appropriate isocyanate namely cyclohexyl and/or phenyl isocyanate (0.0015 mol) was refluxed in ethanol (25 ml) for 2 h. the reaction mixture was cooled and the formed solid was filtered and re-crystallized from ethanol to obtain compounds (**7a–b**) respectively.

*2-(2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl) acetyl)-*N*-cyclohexylhydrazine-1-carboxamide (**7a**)*

Yield, 70 %; m.p.: 255–257 °C. Analysis for $C_{19}H_{25}N_5O_4$ (m.w. 387); calcd.: C, 58.90; H, 6.50; N, 18.08. Found: C, 59.08; H, 6.57; N, 18.22. IR (KBr, $cm^{-1}$): 3240, 3110 (3NH overlapped), 3058 (C–H aromatic), 2930 (C–H aliphatic), 1669 (4C=O overlapped). $^1$HNMR (DMSO-$d_6$, $\delta$, ppm): 1.21–1.26 (m, 4H, C-3 and C-5 cyclohexyl), 1.52–1.55 (m, 2H, C-4 cyclohexyl), 1.63–1.72 (m, 4H, C-2 and C-6 cyclohexyl), 2.16 (s, 3H, $CH_3$ acetyl), 3.34–3.36 (m, 1H, cyclohexyl), 4.45 (s, 2H, N–$CH_2$), 4.54 (s, 2H, $CH_2$ quinox.), 6.07 (s, 1H, CONH-cyclohexyl) ($D_2O$ exchangeable), 7.12 (m, 1H, H-6 quinox.), 7.16 (m, 1H, H-7 quinox.), 7.25 (d, 1H, H-8 quinox. $J = 8$ Hz), 7.54 (d, 1H, H-5 quinox. $J = 8$ *Hz*), 7.72 (s, 1H, CONHNHCO) ($D_2O$ exchangeable), 9.82 (s, 1H, CONHNHCO) ($D_2O$ exchangeable). $^{13}$CNMR (DMSO-$d_6$, 400 MHz): $\delta = 169.31$ (C, $CH_3CO$), 167.32 (2C, CONH, C-2), 157.54 (C, NHCONH), 155.84 (C, C-8′), 154.73 (C, C-4′), 124.88 (CH, C-6), 123.67 (CH, C-7), 118.43 (CH, C-5), 116.73 (CH, C-8), 48.48 ($CH_2$, C-3), 44.16 ($CH_2$, $NCH_2$), 33.38 (CH, $C_6H_{11}$), 25.76 ($2CH_2$, $C_6H_{11}$(C-2,6)), 25.08 ($3CH_2$, $C_6H_{11}$(C-3,4,5)), 22.25 ($CH_3$, $CH_3CO$).

*2-(2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl) acetyl)-*N*-phenylhydrazine-1-carboxamide (**7b**)*

Yield, 85 %; m.p.: 270–272 °C. Analysis for $C_{19}H_{19}N_5O_4$ (m.w. 381); calcd.: C, 59.84; H, 5.02; N, 18.36. Found: C, 59.98; H, 5.09; N, 18.57. IR (KBr, $cm^{-1}$): 3288, 3110 (3NH

overlapped), 3061 (C–H aromatic), 2930 (C–H aliphatic), 1667 (4C=O overlapped). $^1$HNMR (DMSO-$d_6$, $\delta$, ppm): 2.16 (s, 3H, $CH_3$ acetyl), 3.83 (s, 2H, N–$CH_2$), 4.57 (s, 2H, $CH_2$ quinox.), 6.70 (m, 1H, H-4 phenyl), 6.85 (m, 2H, H-3 and H-5 phenyl), 6.96 (m, 2H, H-2 and H-6 phenyl), 7.25 (m, 2H, H-6 and H-7 quinox.), 7.46 (m, 2 H, H-5 and H-8 quinox.), 8.17 (s, 1H, CONH-phenyl) ($D_2O$ exchangeable), 8.66 (s, 1H, CONHNHCO) ($D_2O$ exchangeable), 10.02 (s, 1H, CONHNHCO) ($D_2O$ exchangeable).

*2-(2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl) acetyl)*-N-*substituted-hydrazine-1-carbothioamide (**8$_{a–b}$**)*

General method A mixture of the acid hydrazide (**4**) (0.26 g, 0.001 mol) and the appropriate isothiocyanate namely ethyl and/or propyl isothiocyanate (0.0015 mol) was refluxed in ethanol (25 ml) for 2 h. the reaction mixture was cooled and the formed solid was filtered and re-crystallized from ethanol to obtain compounds (**8$_{a–b}$**) respectively.

*2-(2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl) acetyl)*-N-*ethylhydrazine-1-carbothioamide (**8$_a$**)*

Yield, 70 %; m.p.: 195–196 °C. Analysis for $C_{15}H_{19}N_5O_3S$ (m.w. 349); calcd.: C, 51.56; H, 5.48; N, 20.04. Found: C, 51.73; H, 5.46; N, 20.19. IR (KBr, $cm^{-1}$): 3253, 3110 (3NH overlapped), 3058 (C–H aromatic), 2972 (C–H aliphatic), 1668 (4C=O overlapped). $^1$HNMR (DMSO-$d_6$, $\delta$, ppm): 1.08 (t, 3H, $CH_2CH_3$, $J = 6.8$ Hz), 2.16 (s, 3H, $CH_3$ acetyl), 3.47 (q, 2H, $CH_2CH_3$, $J = 6.8$ Hz), 4.46 (s, 2H, N–$CH_2$), 4.62 (s, 2H, $CH_2$ quinox.), 7.16 (m, 2H, H-6 and H-7 quinox.), 7.26 (d, H, H-8 quinox. $J = 7.2$ Hz), 7.54 (d, H, H-5 quinox. $J = 7.6$ Hz), 7.88 (s, 1H, CSNH–$CH_2CH_3$) ($D_2O$ exchangeable), 9.26 (s, 1H, NHNHCSNH) ($D_2O$ exchangeable), 10.11 (s, 1H, NHNHCSNH) ($D_2O$ exchangeable). $^{13}$CNMR (DMSO-$d_6$, 400 MHz): $\delta = 167.26$ (C, $CH_3CO$), 166.45 (C, CONH), 164.06 (C, C-2), 155.34 (C, CS), 154.73 (C, C-8′), 150.30 (C, C-4′), 124.91 (CH, C-6), 124.14 (CH, C-7), 116.84 (CH, C-5), 115.62 (CH, C-8), 44.11 ($2CH_2$, C-3, $NCH_2$), 37.76 ($CH_2$, $NHCH_2$), 22.24 ($CH_3$, $CH_3CO$), 14.74 ($CH_3$, $CH_2CH_3$).

*2-(2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl) acetyl)*-N-*propylhydrazine-1-carbothioamide (**8$_b$**)*

Yield, 70 %; m.p.: 200–202 °C. Analysis for $C_{16}H_{21}N_5O_3S$ (m.w. 363); calcd.: C, 52.88; H, 5.82; N, 19.27. Found: C, 53.12; H, 5.89; N, 19.45. IR (KBr, $cm^{-1}$): 3253, 3110 (3NH overlapped), 3058 (C–H aromatic), 2972 (C–H aliphatic), 1668 (3C=O overlapped). $^1$HNMR (DMSO-$d_6$, $\delta$, ppm): 0.85 (t, 3H, $CH_2CH_2CH_3$, $J = 7.2$ Hz), 1.50 (m, 2H, $CH_2CH_2CH_3$), 2.16 (s, 3H, $CH_3$ acetyl), 3.39 (t, 2H, $CH_2CH_2CH_3$, $J = 7.2$ Hz), 4.46 (s, 2H, N–$CH_2$), 4.61 (s, 2H, $CH_2$ quinox.), 7.16 (m, 2H, H-6 and H-7 quinox.), 7.25 (d, H, H-8 quinox. $J = 7.2$ Hz), 7.54 (d, H, H-5 quinox. $J = 7.6$ Hz), 7.87 (s, 1H, CSNH–$CH_2CH_2$ $CH_3$) ($D_2O$ exchangeable), 9.26 (s, 1H, NHNHCSNH) ($D_2O$ exchangeable), 10.11 (s, 1H, NHNHCSNH) ($D_2O$ exchangeable).

*2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)*-N ′*-substitutedbenzylideneacetohydrazide (**9$_{a–c}$**)*

General method Equimolar amounts of (**4**) (0.52 g, 0.002 mol) and the appropriate aromatic aldehyde namely, benzaldehyde, 2-chlorobenzaldehyde and/or 2-methoxy benzaldehyde (0.002 mol) were refluxed in ethanol (25 ml) for 4 h. The mixture was cooled and the formed solid was filtered and re-crystallized from ethanol to furnish the corresponding compounds **9$_{a–c}$,** respectively.

*2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)*-N ′*-benzylideneacetohydrazide (**9$_a$**)*

Yield, 80 %; m.p.: 250–252 °C. Analysis for $C_{19}H_{18}N_4O_3$ (m.w. 350); calcd.: C, 65.13; H, 5.18; N, 15.99. Found: C, 65.32; H, 5.26; N, 16.13. $^1$HNMR (DMSO-$d_6$, $\delta$, ppm): 2.17 (s, 3H, $CH_3$ acetyl), 4.47 (s, 2H, $CH_2$ quinox.), 5.06 (s, 2H, N–$CH_2$), 7.12 (m, 2H, H-3 and H-5 phenyl), 7.16 (m, 1H, H-4 phenyl), 7.27 (m, 2H, H-2 and H-6 phenyl), 7.45 (m, 2H, H-6 and H-7 quinox.), 7.71 (m, 2H, H-5 and H-8 quinox.), 8.05 (s, 1H, N=CH), 11.70 (s, 1H, NH) ($D_2O$ exchangeable).

*2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)*-N′-*(2-chlorobenzylidene)acetohydrazide (**9$_b$**)*

Yield, 70 %; m.p.: 255–256 °C. Analysis for $C_{19}H_{17}ClN_4O_3$ (m.w. 384.5); calcd.: C, 59.30; H, 4.45; N, 14.56. Found: C, 59.53; H, 4.49; N, 14.67. IR (KBr, $cm^{-1}$): 3210 (NH), 3082 (C–H aromatic), 2994 (C–H aliphatic), 1691, 1647 (3C=O overlapped). $^1$HNMR (DMSO-$d_6$, $\delta$, ppm): 2.17 (s, 3H, $CH_3$ acetyl), 4.47 (s, 2H, $CH_2$ quinox.), 5.07 (s, 2H, N–$CH_2$), 7.13 (m, 2H, H-3 and H-5 phenyl), 7.26 (m, 1H, H-4 phenyl), 7.41–7.43 (d, 1H, H-6 phenyl, $J = 8.4$ Hz), 7.46 (m, 1H, H-7 quinox.), 7.53 (m, 1H, H-6 quinox.), 7.92–7.94 (d, 1H, H-8 quinox. $J = 8$ Hz), 8.03–8.05 (d, 1H, H-5 quinox. $J = 8$ Hz), 8.43 (s, 1H, N=CH), 11.90 (s, 1H, NH) ($D_2O$ exchangeable). $^{13}$CNMR (DMSO-$d_6$, 400 MHz): $\delta = 169.33$ (C, $CH_3CO$), 168.67 (C, CONH), 164.18 (C, C-2), 143.36 (C, C-8′), 140.40 (C, C-4′), 133.60 (C, C–Cl), 131.80 (CH, N=CH), 130.35 (C, $C_6H_4$ (C-1)), 128.11 (CH, $C_6H_4$ (C-6)), 128.02 (CH, $C_6H_4$ (C-4)), 127.45 (2CH, $C_6H_4$ (C-3, C-5)), 124.91 (CH, C-6), 123.32 (CH, C-7), 116.79

(2CH, C-5, C-8), 44.75 ($CH_2$, $NCH_2$), 44.29 ($CH_2$, C-3), 22.21 ($CH_3$, $CH_3CO$).

*2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)-N′-(2-methoxybenzylidene)acetohydrazide (**$9_c$**)*

Yield, 86 %; m.p.: 263–265 °C. Analysis for $C_{20}H_{20}N_4O_4$ (m.w. 380); calcd.: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.24; H, 5.37; N, 14.89. IR (KBr, $cm^{-1}$): 3182 (NH), 3055 (C–H aromatic), 2940 (C–H aliphatic), 1675 (3C=O overlapped). $^{13}$CNMR (DMSO-$d_6$, 400 MHz): $\delta = 169.34$ (C, $CH_3CO$), 168.21 (C, CONH), 163.67 (C, C-2), 147.36 (C, $C_6H_4$ (C-2)), 144.27 (2C, C-8′, C-4′), 129.14 (2CH, $C_6H_4$ (C-4, C-6)), 129.07 (CH, N=CH), 128.97 (CH, $C_6H_4$ (C-5)), 127.06 (C, $C_6H_4$ (C-1)), 124.88 (CH, C-6), 123.24 (CH, C-7), 116.75 (CH, C-5), 114.76 (CH, C-8), 114.74 (CH, $C_6H_4$ (C-3)), 55.74 ($CH_3$, $OCH_3$), 44.60 ($CH_2$, C-3), 44.23 ($CH_2$, $NCH_2$), 22.21 ($CH_3$, $CH_3CO$). MS (*m/z*): 380 ($M^+$, 37.32 %), 231 (21.00 %), 177 (75.50 %), 133 (100 %, base beak).

*4-Acetyl-1-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)-3,4-dihydroquinoxalin-2(1H)-one (**10**)*

The acid hydrazide (**4**) (0.52 g, 0.002 mol) was refluxed with acetic anhydride (5 ml) for 3 h. The reaction mixture was allowed to attain room temperature, and then poured carefully onto an ice-water (100 ml). The formed precipitate was filtered and crystallized from ethanol to give the target compound (**10**).

Yield, 75 %; m.p.: 270–272 °C. Analysis for $C_{14}H_{14}N_4O_3$ (m.w. 286); calcd.: C, 58.74; H, 4.93; N, 19.57. Found: C, 59.01; H, 5.02; N, 19.72. IR (KBr, $cm^{-1}$): 3012 (C–H aromatic), 2963 (C–H aliphatic), 1676 (2C=O amidic overlapped). $^1$HNMR (DMSO-$d_6$, ppm): 2.17 (s, 3H, $CH_3$ acetyl), 2.33 (s, 3H, $CH_3$), 4.47 (s, 2H, $CH_2$ quinox.), 5.14 (s, 2H, $CH_2$), 7.01 (m, 1 H, H-7 quinox.), 7.14–7.18 (m, 1 H, H-6 quinox.), 7.25–7.27 (d, 1H, H-5 quinox. $J = 8$ Hz), 7.56–7.58 (d, 1H, H-8quinox. $J = 8$ Hz).

*4-Acetyl-1-((5-sulfanyl-1,3,4-oxadiazol-2-yl)methyl)-3,4-dihydroquinoxalin-2(1H)-one (**11**)*

The acid hydrazide (**4**) (2.62 g, 0.01 mol) was dissolved in a solution of potassium hydroxide (0.56 g, 0.01 mol) in ethanol/water mixture (20:2 ml). Carbon disulphide (0.76 g, 0.01 mol) was then added while stirring, and the reaction mixture was refluxed for 18 h. The reaction mixture was concentrated, cooled to room temperature and acidified with diluted hydrochloric acid. The obtained solid was filtered, washed with water and re-crystallized from ethanol to produce compound **(11)**.

Yield, 90 %; m.p.: 246–248 °C. Analysis for $C_{13}H_{12}N_4O_3S$ (m.w. 304); calcd.: C, 51.31; H, 3.97; N, 18.41. Found: C, 51.53; H, 3.93; N, 18.67. IR (KBr, $cm^{-1}$): 3068 (C–H aromatic), 2913 (C–H aliphatic), 2590 (SH), 1684, 1621 (2 C=O amide). $^1$HNMR (DMSO-$d_6$, $\delta$, ppm): 2.16 (s, 3H, $CH_3$ acetyl), 4.50 (s, 2H, $CH_2$ quinox.), 5.23 (s, 2H, N–$CH_2$), 7.19 (m, 1 H, H-7 quinox.), 7.31 (m, 1 H, H-6 quinox.), 7.42 (d, 1H, H-5 quinox.), 7.57 (d, 1H, H-8quinox.), 14.57 (s, 1H, SH) ($D_2O$ exchangeable). $^{13}$CNMR (DMSO-$d_6$, 400 MHz): $\delta = 169.37$ (2C, $CH_3CO$, C-2), 159.84 (2C, $CN_2$, CSH), 154.27 (C, C-8′), 150.36 (C, C-4′), 130.37 (CH, C-6), 127.18 (CH, C-7), 116.82 (CH, C-5), 115.33 (CH, C-8), 37.85 (2$CH_2$, C-3, $NCH_2$), 22.23 ($CH_3$, $CH_3CO$).

*Alkyl 2-((5-((4-acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl)-1,3,4-oxadiazol-2-yl)sulfanyl)acetate (**$12_{a–b}$**)*

General method A mixture of **11** (0.61 g, 0.002 mol) and the appropriate alkyl chloroacetate, namely methyl chloroacetate and/or ethyl chloroacetate (0.002 mol) in dry acetone (50 ml) in the presence of anhydrous $K_2CO_3$ (0.83 g, 0.006 mol) was refluxed for 13 h while stirring. The reaction mixture was filtered, the solvent was evaporated and the resulting product was collected by filtration and re-crystallized from ethanol to furnish the corresponding ester derivatives (**$12_{a–b}$**) respectively.

*Methyl 2-((5-((4-acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl)-1,3,4-oxadiazol-2-yl)sulfanyl)acetate (**$12_a$**)*

Yield, 82 %; m.p.: 140–142 °C. Analysis for $C_{16}H_{16}N_4O_5S$ (m. w. 376); calcd.: C, 51.06; H, 4.28; N, 14.89. Found: C, 51.30; H, 4.32; N, 15.03. IR (KBr, $cm^{-1}$): 3068 (C–H aromatic), 2986 (C–H aliphatic), 1731 (C=O ester), 1660 (2C=O amide). $^1$HNMR (DMSO-$d_6$, $\delta$, ppm): 1.14 (s, 3H, $CH_3$ ester), 2.16 (s, 3H, $CH_3$ acetyl), 4.06 (s, 2H, $SCH_2$), 4.15 (s, 2H, $CH_2$ quinox.), 5.72 (s, 2H, N–$CH_2$), 7.43–7.89 (m, 4H, aromatic protons).

*Ethyl 2-((5-((4-acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl)-1,3,4-oxadiazol-2-yl)sulfanyl)acetate (**$12_b$**)*

Yield, 85 %; m.p.: 145–147 °C. Analysis for $C_{17}H_{18}N_4O_5S$ (m. w. 390); calcd.: C, 52.30; H, 4.65; N, 14.35. Found: C, 52.47; H, 4.71; N, 14.49. IR (KBr, $cm^{-1}$): 2999 (C–H aromatic), 2950 (C–H aliphatic), 1728 (C=O ester), 1660 (2C=O amide). $^1$HNMR (DMSO-$d_6$, $\delta$, ppm): 1.09 (t, 3H, $CH_2CH_3$, $J = 6.8$ Hz), 2.16 (s, 3H, $CH_3$ acetyl), 4.02 (q, 2H, $CH_2CH_3$, $J = 6.8$ Hz), 4.04 (s, 2H, $SCH_2$), 4.09 (s, 2H, $CH_2$ quinox.), 5.68 (s, 2H, N–$CH_2$), 7.43 (m, H, H-7 quinox.), 7.65 (m, 2H, H-5 and H-6 quinox.), 7.88 (d, H, H-8 quinox.

$J = 7.6$ Hz). MS (*m/z*): 390 ($M^+$, 0.71 %), 332 (26.87 %), 227 (100 %, base beak). $^{13}$CNMR (DMSO-$d_6$, 400 MHz): $\delta$ = 169.35 (C, COO), 166.87 (C, $CH_3CO$), 165.97 (C, C-2), 154.69 (2C, $CN_2$, CS), 150.55 (2C, C-4′, C-8′), 131.42 (CH, C-8), 130.12 (CH, C-5), 124.87 (CH, C-6), 123.94 (CH, C-7), 59.69 ($CH_2$, $CH_2CH_3$), 45.34 ($CH_2$, $NCH_2$), 44.65 ($CH_2$, C-3), 31.54 ($CH_2$, $SCH_2$), 22.28 ($CH_3$, $CH_3CO$), 14.08 ($CH_3$, $CH_3CH_2$).

*Methyl 2-((5-((4-acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl)-1,3,4-oxadiazol-2-yl)sulfanyl)propionate (**13**)*

General method A mixture of **12** (0.61 g, 0.002 mol) and methyl chloropropionate (0.61 g, 0.002 mol) in dry acetone (50 ml) in the presence of anhydrous $K_2CO_3$ (0.83 g, 0.006 mol) was refluxed for 12 h while stirring. The reaction mixture was filtered, the solvent was evaporated and the resulting product was collected by filtration and re-crystallized from ethanol to furnish the corresponding methyl ester derivative (**13**). Yield, 80 %; m.p.: 154–156 °C. Analysis for $C_{17}H_{18}N_4O_5S$ (m. w. 390); calcd.: C, 52.30; H, 4.65; N, 14.35. Found: C, 52.43; H, 4.70; N, 14.52. IR (KBr, $cm^{-1}$): 3020 (C–H aromatic), 2980 (C–H aliphatic), 1730 (C=O ester), 1660 (2 C=O amide). $^{13}$CNMR (DMSO-$d_6$, 400 MHz): $\delta = 178.27$ (C, COO), 169.37 (C, $CH_3CO$), 167.18 (C, C-2), 160 (2C, $CN_2$, CS), 154.27 (C, C-8′), 150.36 (C, C-4′), 125.17 (CH, C-8), 124.25 (CH, C-5), 116.82 (CH, C-6), 115.33 (CH, C-7), 56.47 ($CH_3$, $OCH_3$), 45.83 (CH, CHOO), 37.85 ($2CH_2$, C-3, $NCH_2$), 22.22 ($CH_3$, $CH_3CO$), 19.00 ($CH_3$, $CH_3CHCOO$). MS (*m/z*): 390 ($M^+$, 1.89 %), 235 (22.90 %), 199 (20.22 %), 148 (21.87 %), 45 (100 %, base beak).

*Docking studies*

In the present work, all the target compounds were subjected to docking study to explore their binding mode to AMPA-receptor. All modeling experiments were performed using molsoft program which provides a unique set of tools for the modeling of protein/ligand interactions. It predicts how small flexible molecule such as substrates or drug candidates bind to a protein of known 3D structure represented by grid interaction potentials (http://www.molsoft.com/icm_pro.html). Each experiment used the biological target AMPA-receptor downloaded from the Brookhaven Protein Databank (http://www.rcsb.org/pdb/explore/explore.do?structureId=1FTL). In order to qualify the docking results in terms of accuracy of the predicted binding conformations in comparison with the experimental procedure, the reported AMPA-receptor antagonist drugs (**YM872 (VI)** and **(VII)**) were used as reference ligands. The docking study has been conducted to predict the binding mode and to rationalize the observed biological activity.

## Anticonvulsant screening

The animal studies were undertaken with approval from the Ethics Committee (approval # 23PD/3/12/8R) of Al-Azhar University, Nasr City, Cairo, Egypt. All the trials were carried out according to the respective internationally guidelines. Swiss albino adult male mice, weighing 20–25 g, were used as experimental animals. They were obtained from an animal facility (Animal house, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Al-Azhar University). Mice were housed in stainless steel wire-floored cages without any stressful stimuli. Animals were kept under well-ventilated conditions at room temperature (25–30 °C). They were fed on an adequate standard laboratory chow (El-Nasr Co., Abou-Zabal, Egypt) and allowed to acclimatize with free access to food and water for 24 h period before testing except during the short time they were removed from the cages for testing. Albino mice were randomly arranged in groups, each of six animals. Diazepam (Sigma-Aldrich Chemical Co, Milwaukee, WI, USA) was used as a reference drug for comparison. Pentylenetetrazole (Sigma-Aldrich Chemical Co, Milwaukee, WI, USA) was used to induce convulsions in the experimental animals.

The selected derivatives of the newly synthesized compounds were suspended in normal saline using Tween 80 (2 %) and were given intraperitoneally (*i.p.*) in doses ranging from 250–1000 mcg/kg animal weight using the same dosing volume of 0.2 ml per 20 g. The chosen dose was based on preliminary experimental work. Pentylenetetrazole (PTZ, Sigma) was dissolved in normal saline in 2 % concentration and was given intraperitoneally (i.p.) in a dose of 60 mg/kg body weight (dose that could induce convulsions in at least 80 % of the animals without death during the following 24 h). Diazepam was suspended in normal saline using Tween 80 (2 %) and was i.p. given in doses of 75, 150 and 300 mcg/kg using the same dosing volume. All drugs were freshly prepared to the desired concentration just before use.

Groups of six mice were administered the graded doses of the test compounds intraperitoneally. Control animals received an equal volume of saline (10 ml/kg). After one hour, the animals were subcutaneously injected with the convulsive dose of pentylenetetrazole (60 mg/kg). The criterion of anticonvulsant activity is complete protection against convulsions of any kind. Observations were made at least 60 minutes after the administration of pentylenetetrazole. Doses that gave full protection against the induced convulsions and that which exhibited 50 % protection in addition to the relative potencies of the test compounds to diazepam were recorded.

The percentage protection per each dose and the $ED_{50}$ of each compound (in mcg/kg and millimole/kg) were calculated and presented in (Table 2). Finally the relative potencies of the test compounds compared to Diazepam were calculated and used for comparison among compounds under test as shown in (Table 2).

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interests.

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