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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Quinoxalin-2(1*H*)-one derived AMPA-receptor antagonists: Design, synthesis, molecular docking and anticonvulsant activity

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Abstract A new series of 4-acetyl-1-substituted-3,4-dihydroquinoxalin-2(1*H*)-ones (**3–14**) were designed and synthesized in order to evaluate their α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptor antagonism as a proposed mode of their anticonvulsant activity. The structure of the synthesized compounds was confirmed by elemental analysis and spectral data (infrared, ^{1}H nuclear magnetic resonance (NMR), ^{13}CNMR, and mass). The molecular design was performed for all synthesized compounds to predict their binding affinity towards AMPA-receptor in order to rationalize their anticonvulsant activity in a qualitative way and explain the possible interactions that might take place between the tested derivatives and AMPA receptor in comparing to compounds **III** and YM872 in order to obtain the anticonvulsant effect. The data obtained from the molecular modeling was strongly correlated with that obtained from the biological screening which revealed that; compounds $\mathbf{14_b}$, $\mathbf{14_a}$, and $\mathbf{13_b}$ 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 1.89, 1.83, and 1.51 respectively, in comparing to diazepam.

Keywords Quinoxaline · Molecular docking · AMPA antagonists · Anticonvulsant agents

Introduction

A quarter century of research and studies in in vitro preparations and animal models revealed the potential utility of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors as a target for seizure protection (Rogawski 2013). In the near future, the most important clinical application for the AMPA receptor antagonists will probably be as neuroprotectant in neurodegenerative diseases, such as epilepsy, for the treatment of patients not responding to current therapies (Catarzi et al. 2007).

Competitive AMPA receptor antagonists were first reported in 1988, and the systemically active NBQX(**I**) was first shown to have useful therapeutic effects in animal models of neurological disease in 1990 (Azam et al. 2013). Since then, quinoxaline template was represented as the backbone of various competitive AMPA receptor antagonists belonging to different classes which had been developed in order to increase potency, selectivity, water solubility and also to prolong the "in vivo" action (Catarzi et al. 2007). However, early pharmacological studies have been hampered by the lack of potent and selective compounds. NBQX(**I**) was recognized as selective AMPA receptor antagonist. It was used as the antagonist of choice in many "in vitro" and "in vivo" models. Moreover, the clinical development of NBQX was prevented by its low-water solubility at physiological pH (Azam et al. 2013; Faust et al. 2009). On the contrary, YM90K(**II**) showed to be systemically active, but it has a short "in vivo" duration of action (Catarzi et al. 2007) (Fig. 1).

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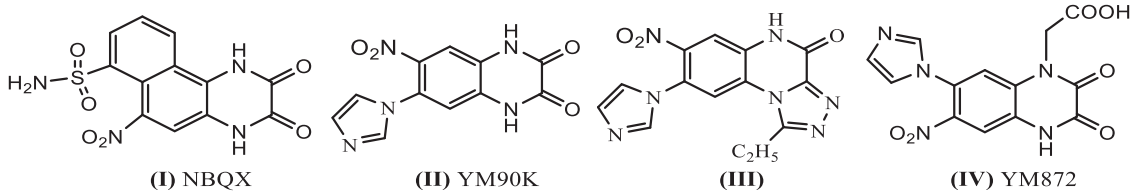


Fig. 1 Reported compounds as potent AMPA receptor antagonists

Taking YM90K as lead compound, compound(**III**) (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). In fact, most simple quinoxalinedione derivatives showed limited water solubility which restricted efforts to formulate acceptable parenteral solutions. With this problem to solve, YM872(**IV**) was prepared as possible AMPA receptor antagonist candidate. YM872 is a very water-soluble AMPA antagonist due to the presence of a hydrophilic acetic acid side chain (Azam et al. 2013).

On the other hand, esters (Ibrahim et al. 2015), amides (El-Adl 2011), hydrazides (Ibrahim et al. 2013), pyridazines (Dong et al. 2015), pyrazoles, oxadiazoles (Ibrahim et al. 2015; El-Helby et al. 2009), isatin, and/or Schiff's bases (Alswah et al. 2013; Bayoumi et al. 2012; El-Hhelby et al. 2011, 2016) moieties are other important pharmacodynamic moieties which when incorporated into different heterocyclic templates, have been reported to possess potent anticonvulsant activity.

Based on the above observations and in continuation of our anticonvulsant work, it was of interest to synthesize a novel series of quinoxaline derivatives with structure modifications involving incorporation of the above mentioned moieties as a trial to obtain more 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

Compound **III** is the most potent 1,2,4-triazolo[4,3-a]quinoxalin-4-one derivative with high-AMPA affinity and selectivity. In addition, **YM872**(**IV**) 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.

Taking compounds(**III**) and **YM872**(**IV**) 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 **III**.

Figure 2 represents the structure similarities and pharmacophoric features of the lead compounds **YM872** and (**III**) 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 **IV**.

On the other hand, the nitrogen atom at position-2 of compound **III** 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.

Moreover, the presence of (un)substituted distal moieties (e.g., alkyl, phenyl, thiazole, pyrazole 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 these compounds and the effect of each substituent on their anticonvulsant activity.

Chemistry

The synthetic strategy for preparation of the target compounds ($\mathbf{3_{a–c}}$–$\mathbf{14_{a–b}}$) is depicted in Schemes 1–3. The title compounds were synthesized starting with ortho-phenylenediamine by its reaction with 2-chloroacetic acid according to the reported procedure (Bonuga et al. 2013) to

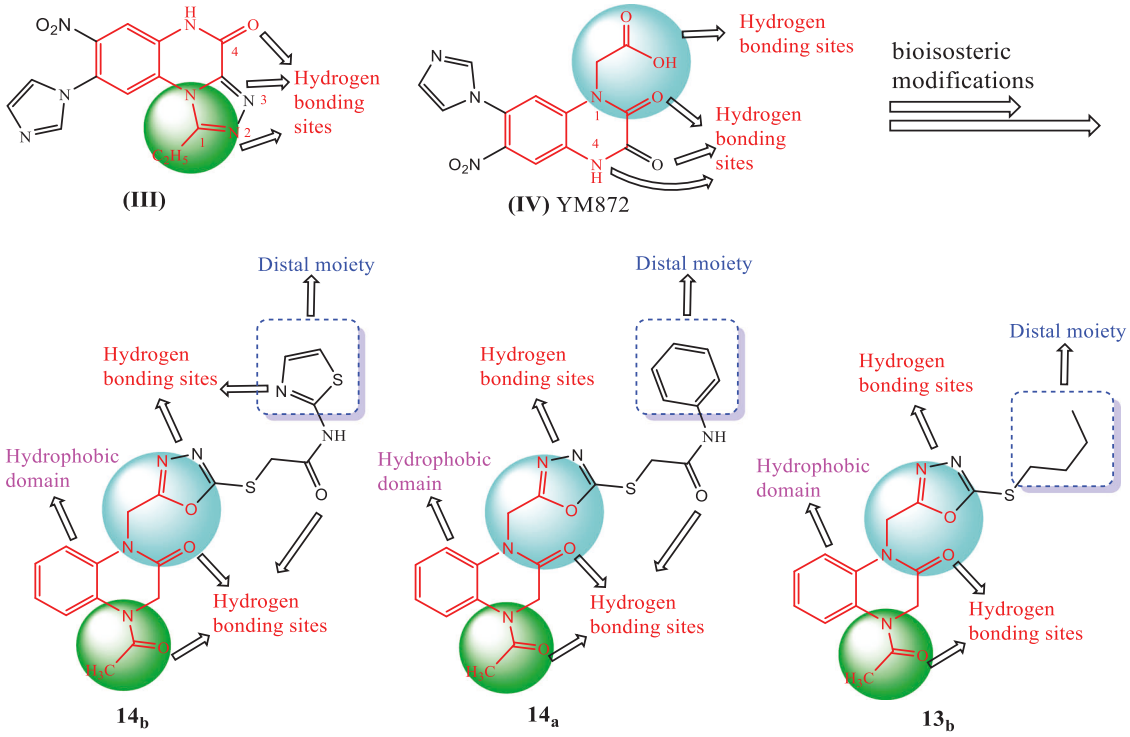


Fig. 2 Structural similarities and pharmacophoric features of reported potent AMPA antagonists and our designed compounds specially $\mathbf{14_b}$, $\mathbf{14_a}$ and $\mathbf{13_b}$ as anticonvulsants

afford 3,4-dihydroquinoxalin-2(1*H*)-one **1**, which was then treated with acetyl chloride to afford the corresponding N-4 acetyl derivatives **2**. The obtained acetyl derivative **2** was refluxed with alkyl bromide and/or ethyl chloroacetate to afford the corresponding alkyl derivatives $\mathbf{3_{a\text{-}c}}$ and/or ethyl ester **4** respectively. Heating the ethyl ester **4** with the appropriate amine, namely methyl amine, butyl amine and/or phenylmethyl amine, furnished the corresponding amide derivatives $\mathbf{5_{a–c}}$ respectively. The ethyl ester **4** was refluxed with hydrazine hydrate to obtain the corresponding acid hydrazide **6** (Scheme 1).

Stirring of the acid hydrazide **6** with chloroacetyl chloride afforded the corresponding 2-chloroacetyl derivative **7**, which underwent cyclization by heating under reflux to produce the corresponding tetrahydropyridazine-3,6-dione derivative **8**. While cyclization of **6** with acetyl acetone yielded the corresponding pyrazole derivatives **9**. On the other hand, condensation of the acid hydrazide **6** with isatin and/or different aldehydes afforded the corresponding 2-oxoindoline **10** and/or Schiff's bases $\mathbf{11_{a–d}}$ respectively (Scheme 2).

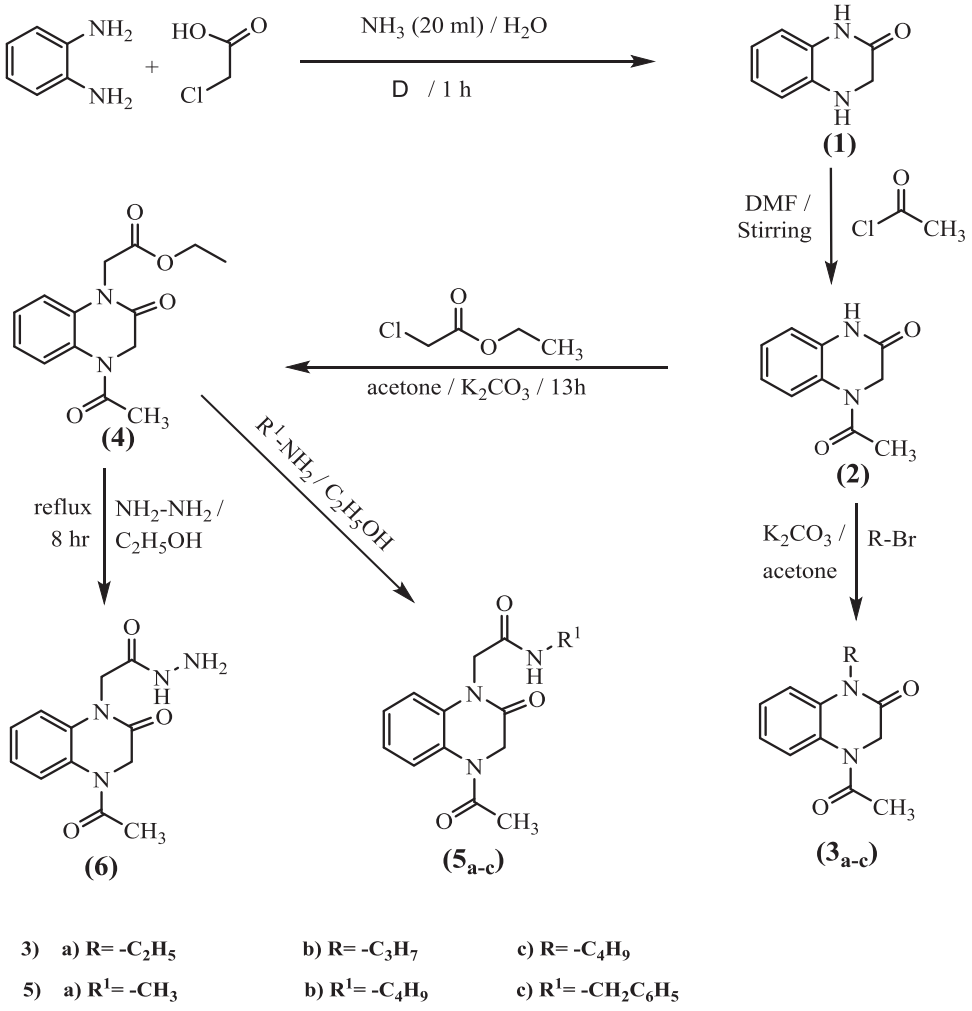
The acid hydrazide **6** underwent another cyclization by reaction with carbon disulfide to afford the corresponding 5-sulfanyloxadiazole derivative **12**, which was then reacted with the appropriate alkyl bromide and/or chloroacetamide to obtain the corresponding S-alkyl $\mathbf{13_{a–b}}$ and/or amide derivatives $\mathbf{14_{a–b}}$ respectively (Scheme 3).

Docking studies

All modeling experiments were performed using Molsoft program. Molsoft is a suit of automated docking tools, which allows flexible ligand docking at physiological PH (7.365). Molsoft predicts how small molecules, such as substrates or drug candidates bind to a receptor of known 3D structure. Each experiment used AMPA complexes with Ligand downloaded from the Brookhaven Protein Databank. The protein was prepared for docking by removing water molecules automatically and addition of polar hydrogens to the protein atoms. The protein active site was defined by placing a grid over the center of co-crystallized ligand. Before a protein is ready for docking simulations, all the necessary grid maps were calculated prior to docking. The compounds were drawn as a 3D structure and their energies were minimized. The ligand was extracted from the binding site and the compounds discussed herein were docked into the active site.

The aim of this work was to study the crystal structure of AMPA receptor and to rationalize the obtained biological data and explain the possible interactions that might take place between the tested derivatives and AMPA receptor in comparing to compounds III and **YM872** in order to obtain the anticonvulsant effect. In the present work, all modeling experiments were performed using Molsoft software. Each experiment used AMPA (Loscher and Rogawski 2002)

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



downloaded from the Brookhaven Protein Databank (http://www.rcsb.org/pdb/explore/explore.do?structureId=1FTL).

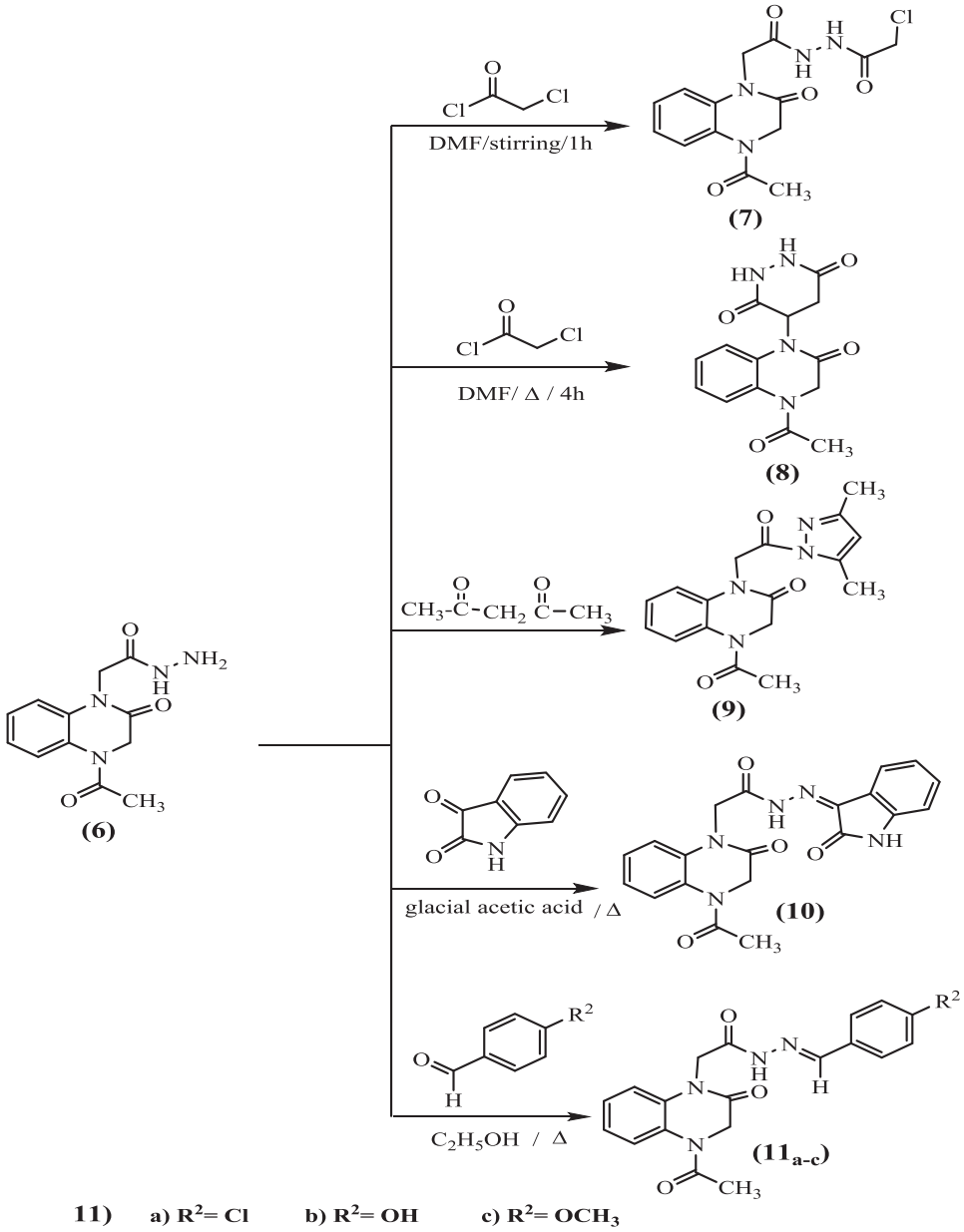
The obtained results indicated that all studied ligands have virtually the same position and orientation inside the putative binding active site of AMPA receptor (PDB code 1FTL) which reveals a large space bounded by a membrane-binding domain which serves as entry channel for substrate to the active 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 (Amin et al. 2010; 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 Diazepam revealed affinity value of −62.60 kcal/mol and 2 H-bonds. The carbonyl group at position-2 formed two H-bond with with *Arginine96* (–NH groups) with distances of 1.81 and 2.21 Å. The phenyl group at position-5 occupied the hydrophobic pocket formed by *Tyrosine61*, *Serine142 Threonine143*, *Threonine174*, and *Leucine192*. The methyl group at position-1 occupied the hydrophobic pocket formed by *proline89*, *Threonine91*, *Lysine218*, and *Tyrosine220*. The benzodiazepine nucleus occupied the hydrophobic pocket formed by *Lysine60*, *Tyrosine61*, *Arginine96*, *Threonine91*, *proline89*, *Lysine218*, *Tyrosine220*, *Leucine192*, and *Methionine196* (Fig. 4).

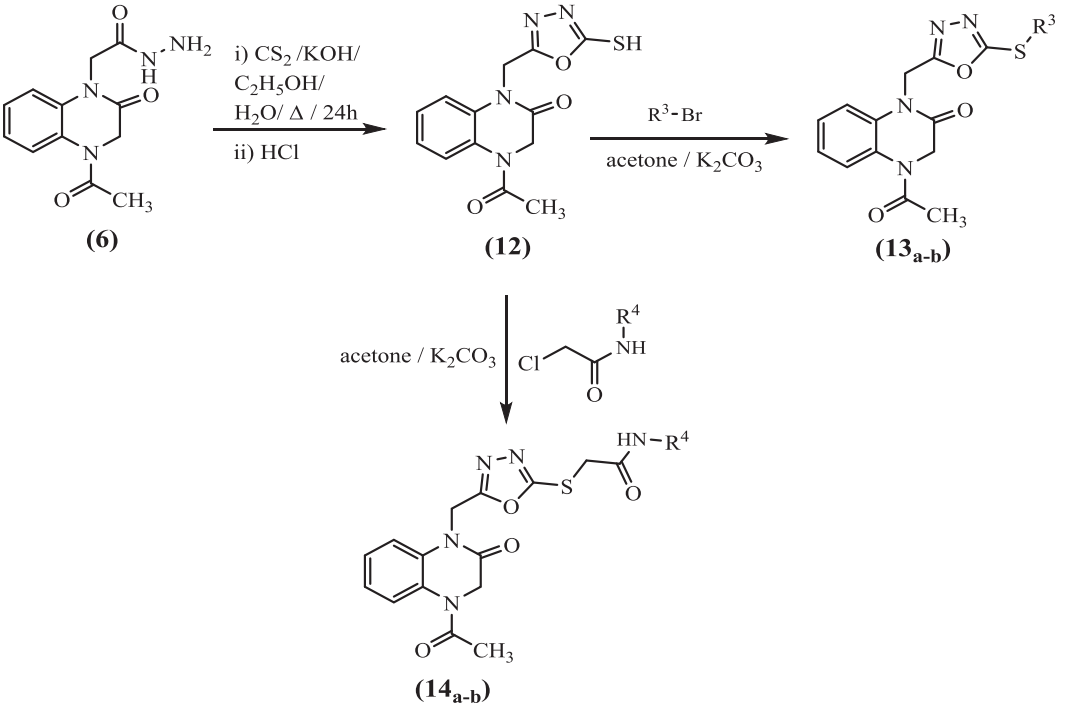
The proposed binding mode of compound **III** revealed affinity value of −67.74 kcal/mol and 6 H-bonds. The N atom at position-2 of the fused triazole group formed one H-bond with *Threonine91* (–NH group) with a distance of 1.33 Å and the other N atom at position-3 of the fused triazole group formed 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.

Scheme 2 Synthetic route for preparation of the target compounds **7–11$_{a–c}$**



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 **YM872** is virtually the same as that of compound **III** which 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 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



13) a) $R^3 = -C_2H_5$ b) $R^3 = -C_4H_9$
14) a) $R^4 = -C_6H_5$ b) R^4 = -Thiazol-2-yl

Scheme 3 Synthetic route for preparation of the target compounds **12–14$_{a–b}$**

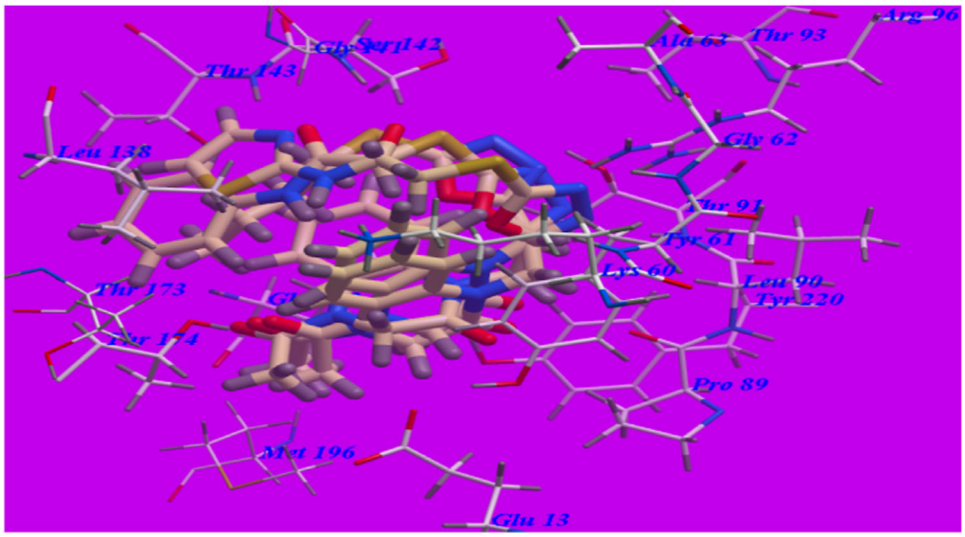


Fig. 3 Superimposition of some docked compounds inside the binding pocket of 1FTL

Methionine196. The quinoxaline nucleus occupied the hydrophobic pocket formed by *Lysine60*, *Tyrosine61*, *Arginine96*, *Threonine91*, *proline89*, *Lysine218*, *Tyrosine220*, *Glutamate193*, *Serine142*, and *Threonine143* (Fig. 6).

The proposed binding mode of compound **14$_b$** is virtually the same as that of compounds **III** and **YM872** which revealed affinity value of −90.51 kcal/mol and 11 H-bonds. The nitrogen atom (N3) of the oxadiazole linker moiety at position-1 formed 2 H-bonds with *Arginine96* (–NH groups) with distances of 2.06 and 2.07 Å. The other nitrogen atom (N4) formed 2 H-bonds with *Arginine96* (–NH groups) with a distance of 2.64 Å and *Glycine62* (–NH groups) with a distance of 2.27 Å. The carbonyl group of the amide linker moiety formed 1 H-bond with *Lysine60* (–NH group) with a distance of 1.34 Å and the N

atom of the distal thiazole moiety formed 2 H-bonds with *Lysine60* (–NH groups) with distances of 2.19 and 2.39 Å. The carbonyl group at position-2 was stabilized by formation of 2 H-bonds with *Arginine96* (–NH groups) with distances of 1.60 and 1.88 Å and one H-bond with *Threonine91* (–OH group) with a distance of 2.97 Å. The carbonyl group of acetyl moiety at position-4 formed 1 H-bond with *Tyrosine220* (–OH group) with a distance of 2.22 Å.

The distal thiazole moiety occupied the hydrophobic pocket formed by *Isoleucine11*, *Glutamate13*, *Glycine59*, *Lysine60*, *Tyrosine61*, and *Threonine173*. The oxadiazole moiety occupied the hydrophobic pocket formed by *Tyrosine61*, *Glycine62*, *Alanine63*, *Leucine93*, and *Glycine141*. The methyl group of acetyl moiety at position-4 occupied the hydrophobic pocket formed by *proline89*, *Leucine90*, *Threonine91*, and *Tyrosine220*. The quinoxaline nucleus occupied the hydrophobic pocket formed by *Glutamate13*, *Tyrosine61*, *Threonine91*, *Leucine138*, *Glutamate193*, and *Methionine196* (Fig. 7). These interactions of compound $\mathbf{14_b}$ may explain the highest anticonvulsant activity.

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})
2	−48.39	**10**	−75.79
$\mathbf{3_a}$	−51.60	$\mathbf{11_a}$	−74.36
$\mathbf{3_b}$	−59.37	$\mathbf{11_b}$	−74.95
$\mathbf{3_c}$	−61.55	$\mathbf{11_c}$	−80.79
4	−64.03	**12**	−64.87
$\mathbf{5_a}$	−60.47	$\mathbf{13_a}$	−74.57
$\mathbf{5_b}$	−73.15	$\mathbf{13_b}$	−82.30
$\mathbf{5_c}$	−80.75	$\mathbf{14_a}$	−89.64
6	−55.10	$\mathbf{14_b}$	−90.51
7	−61.35	**YM872(VI)**	−70.63
8	−45.57	Comp.(**VII**)	−67.45
9	−78.89	Diazepam	−62.60

The proposed binding mode of compound $\mathbf{14_a}$ is virtually the same as that of compound $\mathbf{14_b}$ which revealed affinity value of −89.64 kcal/mol and 11 H-bonds. The nitrogen atom (N3) of the oxadiazole linker moiety at position-1 was stabilized by formation of 2 H-bonds with *Arginine96* (–NH groups) with distances of 2.06 and 2.73 Å and 2 H-bonds with *Threonine91* (–NH and –OH groups) with distances of 2.48 and 2.79 Å respectively. The other nitrogen atom (N4) was also stabilized by formation of 3 H-bonds with *Arginine96* (–NH groups) with distances of 2.20 and 2.53 Å and *Threonine91* (–OH group) with a distance of 2.24 Å respectively. The carbonyl group of the amide linker moiety formed 2 H-bond with *Serine142* and *Threonine143*, (–NH groups) with distances of 2.09 and 2.33 Å respectively. The carbonyl group at position-2 formed 1 H-bond with *Tyrosine220* (–OH group) with a distance of 2.35 Å. The carbonyl group of acetyl moiety at position-4 formed 1 H-bond with *Threonine174* (–OH group) with a distance of 1.52 Å.

The distal phenyl moiety occupied the hydrophobic pocket formed by *Leucine138*, *Threonine143*, *Threonine174*, and *Glutamate193*. The oxadiazole moiety occupied the hydrophobic pocket formed by *Tyrosine61*, *Glycine62*, *Alanine63*, *Leucine93*, and *Serine142*. The methyl group of acetyl moiety at position-4 occupied the hydrophobic pocket formed by *Glutamate13*, *Threonine174*, *Glutamate193,* and *Methionine196*. The quinoxaline nucleus occupied the hydrophobic pocket formed by *Glutamate13*, *Tyrosine61*, *proline89*, *Leucine138*, *Glutamate193*, and *Methionine196* (Fig. 8). These interactions of compound $\mathbf{14_a}$ may explain the high anticonvulsant activity.

The proposed binding mode of compound $\mathbf{13_b}$ is virtually the same as that of compounds $\mathbf{14_{a\text{-}b}}$ which revealed

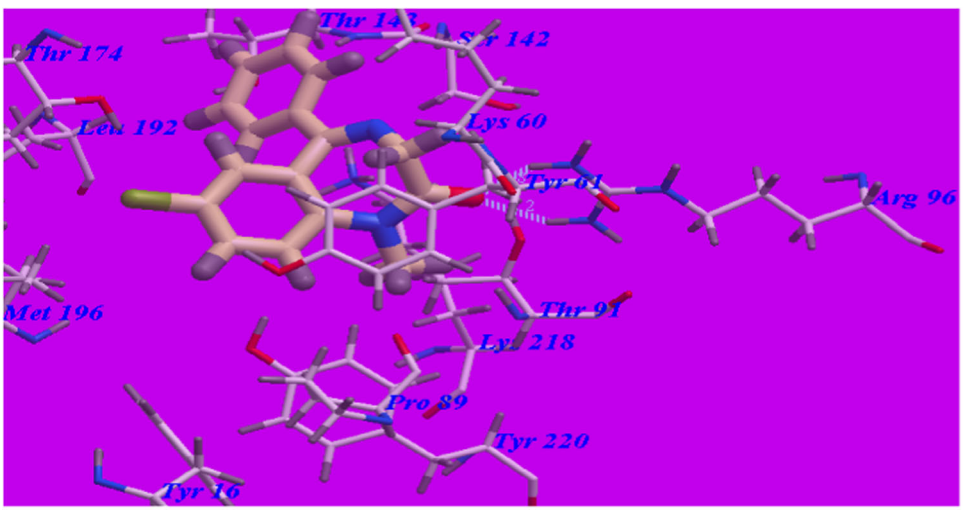


Fig. 4 Predicted binding mode for diazepam with 1FTL

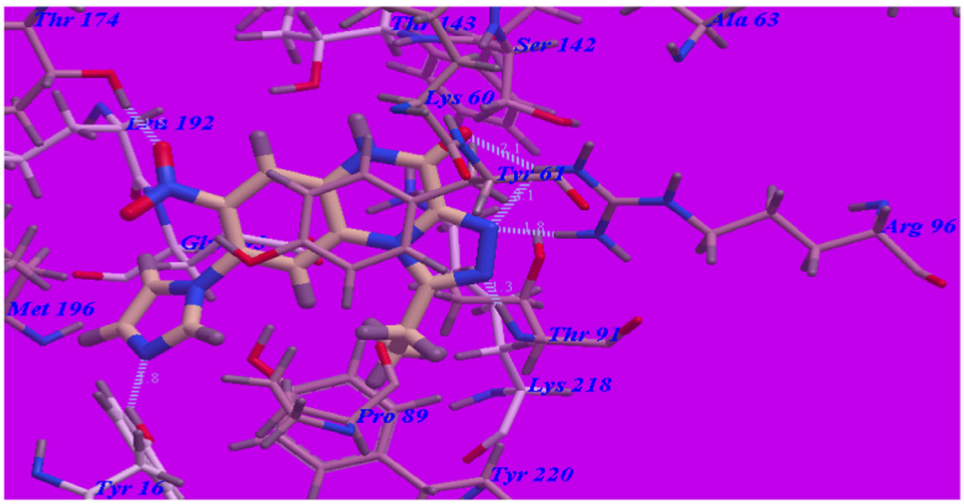


Fig. 5 Predicted binding mode for compound III with 1FTL

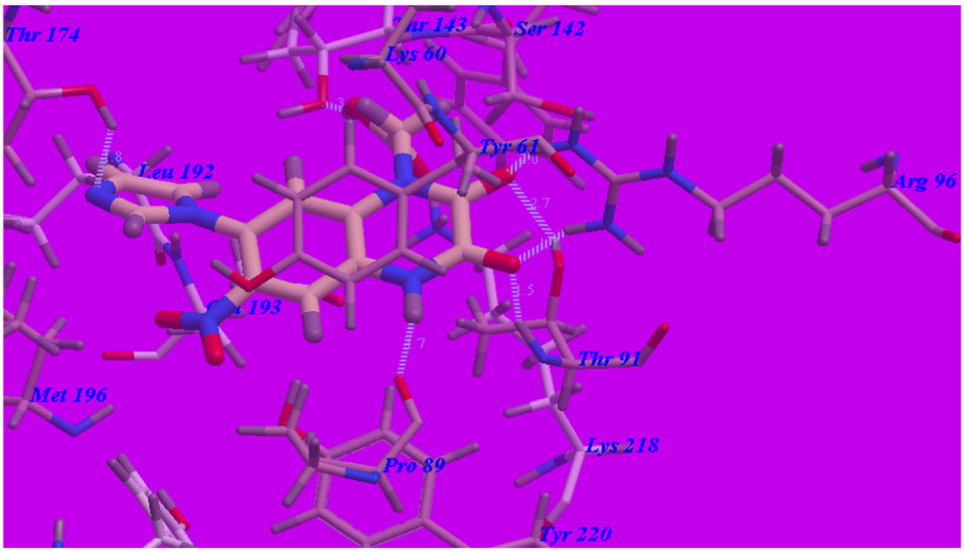


Fig. 6 Predicted binding mode for **YM872** with 1FTL

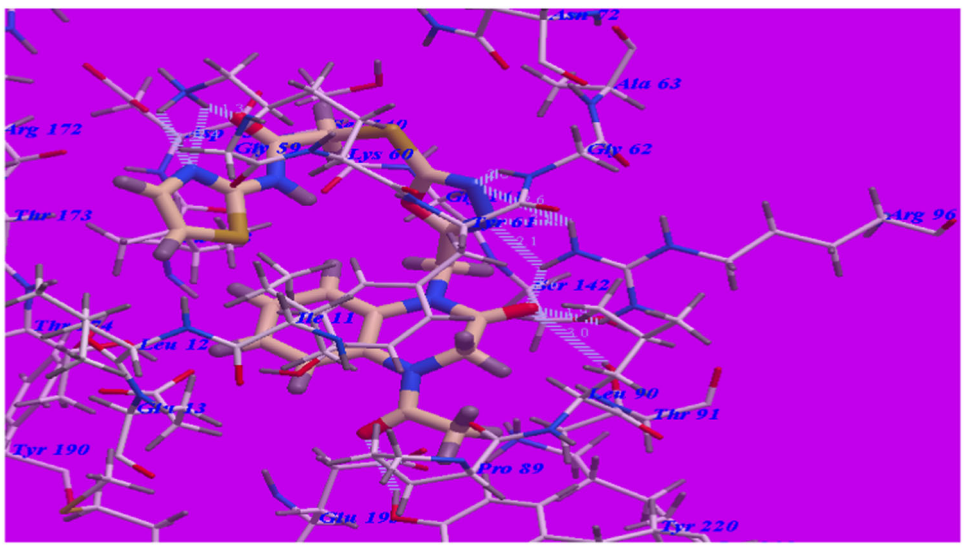


Fig. 7 Predicted binding mode for $\mathbf{14_b}$ with 1FTL

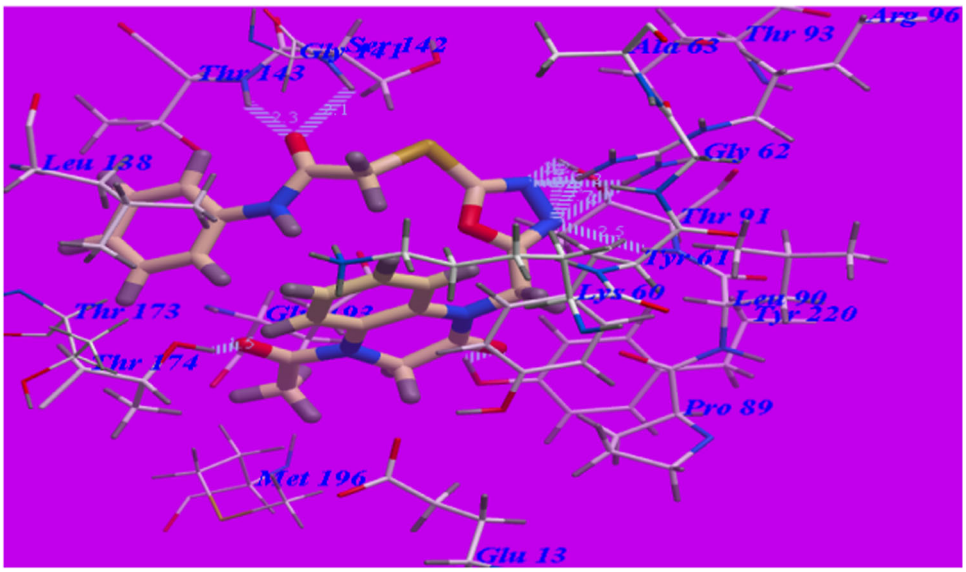


Fig. 8 Predicted binding mode for $\mathbf{14_a}$ with 1FTL

affinity value of −82.30 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 1.34 and 2.51 Å. The carbonyl group at position-2 formed 2 H-bonds with *Arginine96* (–NH groups) with distances of 1.65 and 2.22 Å. The carbonyl group of acetyl moiety at position-4 formed 1 H-bond with *Tyrosine220* (–OH group) with a distance of 1.68 Å. The oxadiazole moiety occupied the hydrophobic pocket formed by *Threonine143*, *Serine142*, *Lysine218*, and *Lysine60*. The S-butyl of the distal moiety occupied the hydrophobic pocket formed by *Threonine174*, *Leucine192*, *Glutamate193*, and *Threonine143*. 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. 9). These interactions of compound $\mathbf{13_b}$ may explain the high anticonvulsant activity.

Biological screening

In the present study, twelve 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). Twelve 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 0.31 to 1.89 of diazepam (Fig. 10). Compounds $\mathbf{14_b}$, $\mathbf{14_a}$, and $\mathbf{13_b}$ showed the highest anticonvulsant activities in experimental mice with relative potencies of 1.89, 1.83, and 1.51 respectively. Compounds $\mathbf{3_a}$ and $\mathbf{5_b}$ exhibited the lowest relative potencies of 0.31 and 0.43 respectively. Other compounds exhibited relative potencies higher than 50% of diazepam. Compounds $\mathbf{13_b}$, $\mathbf{14_a}$, and $\mathbf{14_b}$ caused 100% protection in a dose of 500 mcg/kg body weight. Compounds $\mathbf{3_a}$, $\mathbf{3_c}$, $\mathbf{5_b}$, **9**, $\mathbf{11_c}$, and $\mathbf{13_a}$ caused 100% protection in a dose of 1000 mcg/kg body weight. Compounds $\mathbf{5_c}$, **10**, and $\mathbf{11_a}$ caused 83.33% protection at the same dose (Table 2). Compounds $\mathbf{13_b}$, $\mathbf{14_a}$, and $\mathbf{14_b}$ 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. 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 1-position and the data shown in Table 2 we can divide these tested compounds into six groups. The first group is 1-alkyl substitutions $\mathbf{3_a}$ and $\mathbf{3_c}$. In this group, the presence of electron releasing long chain (butyl group at $\mathbf{3_c}$) enhanced the activity when compared to the short chain ethyl group at $\mathbf{3_a}$. The second group is *N*-substituted-acetamide derivatives $\mathbf{5_b}$ and $\mathbf{5_c}$. The benzyl (electron deficient) and butyl groups

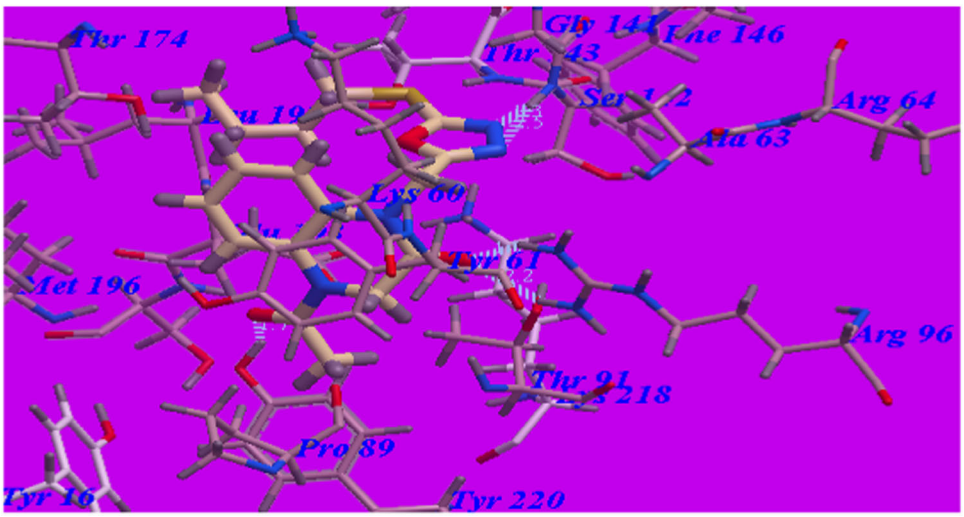


Fig. 9 Predicted binding mode for $\mathbf{13_b}$ with 1FTL

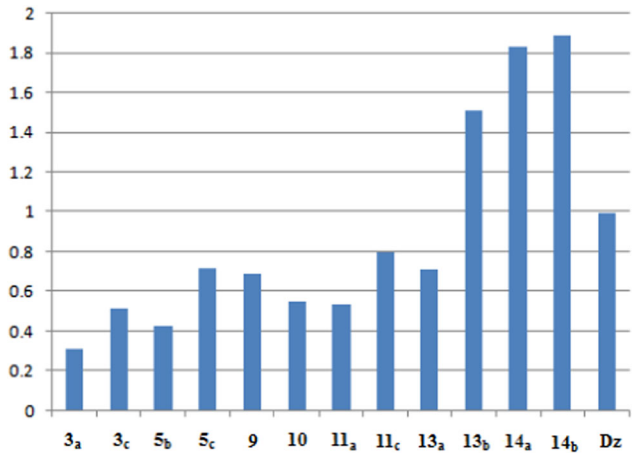


Fig. 10 Relative potencies of the tested compounds to Diazepam

(electron releasing) at $\mathbf{5_c}$ and $\mathbf{5_b}$ respectively, produced high difference in activity in spite of slight difference in lipophilicity. The third group is 3,5-dimethyl-1*H*-pyrazole **9**, and 2-oxoindoline **10** derivatives. In this group, compound **9** had higher lipophilicity and exhibited higher activity which may due to the presence of two electron releasing methyl groups also.

The fourth group is Schiff's bases $\mathbf{11_a}$ and $\mathbf{11_c}$. Among these compounds, $\mathbf{11_c}$ with electron releasing group (4-OCH_3) exhibited higher activity than $\mathbf{11_a}$ with electron deficient group (4-Cl). The fifth group is oxadiazole-5-sulfanyl alkyl derivatives $\mathbf{13_a}$ and $\mathbf{13_b}$. The presence of lipophilic electron releasing long chain (butyl group at $\mathbf{13_b}$) exhibited higher activity when compared to the short chain ethyl group at $\mathbf{13_a}$. The sixth group is oxadiazole-5-sulfanyl amide derivatives $\mathbf{14_a}$ and $\mathbf{14_b}$. The thiazole moiety at $\mathbf{14_b}$ showed practically the same highest 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 $\mathbf{3_a}$, $\mathbf{3_c}$, $\mathbf{5_b}$, $\mathbf{5_c}$, **9**, **10**, $\mathbf{11_a}$, $\mathbf{11_c}$, $\mathbf{13_a}$, $\mathbf{13_b}$, $\mathbf{14_a}$, and $\mathbf{14_b}$ 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, expensive, time-consuming, not always available and not suitable to screen a large collection of new chemicals. Therefore, an alternative method was used based on computerized models and/or at http://www.molinspiration.com/cgi-bin/properties. 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 0.12 to 2.39. C log P for diazepam, **III** and **YM872**(**IV**) were calculated and were found to be 2.74, 0.65, and 0.89 respectively. It is worthwhile to note that the C log *P* values for compounds $\mathbf{14_b}$, $\mathbf{14_a}$, and $\mathbf{13_b}$ which had higher potency were found to be 0.12, 1.06 and 1.70 respectively. It is noted that, C log *P* values for compounds $\mathbf{13_a}$ **and** $\mathbf{14_b}$ was found to be less than that for compounds **III** and **YM872**(**IV**). This indicated that, the water solubility of our designed compounds, $\mathbf{13_a}$ **and** $\mathbf{14_b}$ were higher than that of the reference ligands **III** and **YM872**(**IV**).

Compound $\mathbf{3_c}$ had higher anticonvulsant potency than compounds $\mathbf{3_a}$ and had higher C log *P* value with good correlation with the lipophilicity factor while compound $\mathbf{5_b}$ had slightly higher C log *P* values than $\mathbf{5_c}$ (1.68 and 1.64 respectively) and had lower relative potency (0.43 and 0.72 respectively) with no correlation with the lipophilicity factor. Interestingly, the values of C log P for compounds **10** and $\mathbf{11_a}$ were 0.95 and 2.39 respectively and had no significant effect on biological activity. Moreover compound

Table 2 Anticonvulsant activity of the selected compounds

Test comp.	Dose (mcg/kg)	Protection (%)	ED_{50} (mcg/kg)	ED_{50} (mmol/kg)	Relative potency	C log P
$\mathbf{3_a}$	250	33.33	375	1.72	0.31	1.01
	500	83.33				
	1000	100.00				
$\mathbf{3_c}$	250	50.00	250	1.02	0.52	2.08
	500	83.33				
	1000	100.00				
$\mathbf{5_b}$	250	33.33	375	1.24	0.43	1.68
	500	66.67				
	1000	100.00				
$\mathbf{5_c}$	250	50.00	250	0.74	0.72	1.64
	500	66.67				
	1000	83.33				
9	250	50.00	250	0.77	0.69	1.03
	500	83.33				
	1000	100.00				
10	250	33.33	375	0.96	0.55	0.95
	500	66.67				
	1000	83.33				
$\mathbf{11_a}$	250	33.33	375	0.98	0.54	2.39
	500	66.67				
	1000	83.33				
$\mathbf{11_c}$	250	50.00	250	0.66	0.80	1.77
	500	66.67				
	1000	100.00				
$\mathbf{13_a}$	250	50.00	250	0.75	0.71	0.64
	500	66.67				
	1000	100.00				
$\mathbf{13_b}$	250	83.33	125	0.35	1.51	1.70
	500	100.00				
	1000	100.00				
$\mathbf{14_a}$	250	83.33	125	0.29	1.83	1.06
	500	100.00				
	1000	100.00				
$\mathbf{14_b}$	250	83.33	125	0.28	1.89	0.12
	500	100.00				
	1000	100.00				
Diazepam	75	16.67	150	0.53	1.00	2.74
	150	50				
	300	100				

$\mathbf{11_c}$ showed C log *P* values of 1.77 it showed higher relative potency (0.80) than $\mathbf{11_a}$ (0.54) and also had no correlation of the lipophilicity factor with their potency levels. Compounds $\mathbf{13_a}$ and $\mathbf{13_b}$ exhibited C log *P* values of 1.70 and 0.64 and relative potencies of 1.51 and 0.71, respectively with good correlation with their lipophilicity factor. In spite of high difference in C log *P* values for compounds $\mathbf{14_a}$ and $\mathbf{14_b}$, they showed virtually the same anticonvulsant potency.

Conclusion

The molecular design was performed to assess the proposed binding mode of the new 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 **III** and **YM872**(**IV**) as reference ligands which may considered as

possible mode of their anticonvulsant activity. 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 0.31 to 1.89 of that of diazepam. Compounds **14_b**, **14_a**, and **13_b** showed the highest anticonvulsant activities in experimental mice with relative potencies of 1.89, 1.83, and 1.51 respectively in comparing to diazepam as a reference drug. C log *P* value for compound **14_b** was found to be less than that for compounds **III** and **YM872**(**IV**). This indicated that, the water solubility of our designed compound, **14_b** was higher than that of the reference ligands.

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.

Materials and methods

Chemistry

All melting points were carried out by open capillary method on a Gallen kamp Melting point apparatus at faculty 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 disc technique. Proton magnetic resonance ^{1}HNMR spectra were recorded on a Bruker 400 MHZ-nuclear magnetic resonance (NMR) spectrometer at Microanalytical Center, Zagazig University—Zagazig. ^{13}C NMR spectra were recorded on an Agilent 400 MHZ-NMR spectrometer at and Chemical Laboratory—Ministry of Defense—Cairo. Tetramethylsilane 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 analyzes (C, H, N) were performed on a CHN analyzer at Regional Center for Mycology and Biotechnology, Al-Azhar University. All compounds were within $\pm$ 0.4 of the theoretical values. The reactions were monitored by thin-layer chromatography (TLC) using TLC sheets precoated with ultraviolet (UV) fluorescent silica gel Merck 60 F254 plates and were visualized using UV lamp and different solvents as mobile phases.

Compounds **1**, **2**, **4**, and **6** were obtained according to the reported procedures (El-Helby et al. 2016).

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

Yellowish white powder (C_2H_5OH) (This compound was prepared by drop wise addition of acetyl chloride (7.85 g, 0.1 mol) 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. It was obtained as yellowish white solid); yield, 80%; mp 165–168 °C; IR (KBr) ν_{max} 3192, 3072, 2992, 1672 cm^{-1}; ^{1}HNMR (dimethyl sulfoxide (DMSO), 400 MHz): $\delta = 10.68$ (1H, s, NH) (D_2O exchangeable), 7.48 (1H, d, H-5 quinox.), 7.19 (1H, m, H-7 quinox.), 7.03 (2H, m, H-6 and H-8 quinox.), 4.32 (2H, s, CH_2 quinoxaline), 2.17 (3H, s, CH_3 acetyl); ^{13}CNMR (DMSO, 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 (CH, C-6, C-7), 123.15 (CH, C-8), 45.92 (CH_2, C-3), 22.12 (CH_3, CH_3CO); EIMS *m/z* 191 [$M^+ + 1$] (4.76), 190 [M^+] (35), 148 (82), 119 (100). Anal. calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.31; H, 5.36; N, 14.89.

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

White powder (C_2H_5OH) (This compound was prepared by heating a mixture of 4-acetyl-3,4-dihydroquinoxalin-2(1*H*)-one (**2**) (0.19 g, 0.001 mol) and ethyl bromide (0.11 g, 0.001 mol) in dry acetone (15 ml) in the presence of anhydrous K_2CO_3 (0.42 g, 0.003 mol) under reflux for 10 h while stirring. The acetone was allowed to evaporate at room temperature. The obtained solid product was filtered, dried and re-crystallized from ethanol. It was obtained as white solid); yield, 60%; mp 170–172 °C; IR (KBr) ν_{max} 3068, 2971, 1664 cm^{-1}; ^{1}H NMR (DMSO, 400 MHz): $\delta =$ 7.53 (1H, d, H-5 quinox.), 7.31–7.32 (2H, m, H-6 and H-7 quinox.), 7.11–7.15 (1H, m, H-8 quinox.), 4.39 (2H, s, CH_2 quinox.), 3.92 (2H, q, $J = 7.2$ Hz, CH_2CH_3), 2.15 (3H, s, CH_3 acetyl), 1.16 (3H, t, $J = 7.2$ Hz, CH_2CH_3); anal. calcd. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.31; H, 6.53; N, 12.93.

*4-Acetyl-1-propyl-3,4-dihydroquinoxalin-2(1*H*)-one (**3_b**)*

White powder (C_2H_5OH) (This compound was prepared by heating a mixture of 4-acetyl-3,4-dihydroquinoxalin-2(1*H*)-one **(2)** (0.19 g, 0.001 mol) and propyl bromide (0.12 g,

0.001 mol) in dry acetone (15 ml) in the presence of anhydrous K_2CO_3 (0.42 g, 0.003 mol) under reflux for 10 h while stirring. The acetone was allowed to evaporate at room temperature. The obtained solid product was filtered, dried and re-crystallized from ethanol. It was obtained as white solid); yield, 70%; mp 175–177 °C; IR (KBr) ν_{max} 3068, 2937, 1664 cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta =$ 7.53 (1H, d, H-5 quinox.), 7.32 (2H, m, H-6 and H-7 quinox.), 7.13–7.15 (1H, d, H-8 quinox.), 4.39 (2H, s, CH_2 quinox.), 3.86 (2H, t, $J = 7.2$ Hz, $\underline{CH_2}CH_2CH_2CH_3$), 2.15 (3H, s, CH_3 acetyl), 1.58 (2H, m, $CH_2\underline{CH_2}CH_2CH_3$), 0.87 (3H, t, $J =$ 7.2 Hz, $CH_2CH_2CH_2CH_3$); ^{13}CNMR (DMSO, 400 MHz): $\delta =$ 169.12 (C, CH_3CO), 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 (CH, C-5, C-8), 45.95 (CH_2, C-3), 42.93 (CH_2, NCH_2), 22.12 (CH_3, CH_3CO), 20.30 (CH_2, CH_2CH_3), 11.27 (CH_3, CH_2CH_3). Anal. calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.28; H, 6.98; N, 12.31.

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

Yellowish white powder (C_2H_5OH) (This compound was prepared by heating a mixture of 4-acetyl-3,4-dihydroquinoxalin-2(1*H*)-one (**2**) (0.19 g, 0.001 mol) and butyl bromide (0.14 g, 0.001 mol) in dry acetone (15 ml) in the presence of anhydrous K_2CO_3 (0.42 g, 0.003 mol) under reflux for 10 h while stirring. The acetone was allowed to evaporate at room temperature. The obtained solid product was filtered, dried and re-crystallized from ethanol. It was obtained as yellowish white solid); yield, 75%; mp 190–192 °C; IR (KBr) ν_{max} 3068, 2937, 1663 cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta = 7.53$ (1H, d, H-5 quinox.), 7.31 (2H, m, H-6 and H-7 quinox.), 7.13 (1H, d, H-8 quinox.), 4.39 (2H, s, CH_2 quinox.), 3.90 (2H, t, $J = 7.2$ Hz, $\underline{CH_2}CH_2CH_2CH_3$), 2.15 (3H, s, CH_3 acetyl), 1.53 (2H, m, $CH_2\underline{CH_2}CH_2CH_3$), 1.28 (2H, m, $CH_2CH_2\underline{CH_2}CH_3$), 0.87 (3H, t, $J = 7.2$ *Hz*, $CH_2CH_2CH_2CH_3$), anal. calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.39; H, 7.44; N, 11.49.

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

Yellowish crystals (C_2H_5OH) (This compound was prepared by heating a mixture of 4-acetyl-3,4-dihydroquinoxalin-2(1*H*)-one **(2)** (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) under reflux 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. It was obtained as yellowish solid); yield, 80%; mp 73–75°C; IR (KBr) ν_{max} 3072, 2990, 1741, 1676 cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta = 7.56$ (1H, d, $J = 7.6$ Hz, H-5 quinox.), 7.29 (1H, d, $J = 7.6$ Hz, H-8 quinox.), 7.16 (2H, m, H-6 and H-7 quinox.), 4.69 (2H, s, NCH_2), 4.46 (2H, s, CH_2 quinox.), 4.15 (2H, q, $J = 7.2$ Hz, CH_2CH_3), 2.16 (3H, s, CH_3 acetyl), 1.19 (3H, t, $J = 7.2$ Hz, CH_2CH_3); ^{13}CNMR (DMSO, 400 MHz): $\delta = 169.12$ (C, 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 (CH, 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); anal. calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 61.02; H, 5.89; N, 10.31.

*2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)-N-methylacetamide (**5$_a$**)*

Yellowish white powder (C_2H_5OH) (This compound was prepared by heating a mixture of ethyl ester (**4**) (0.28 g, 0.001 mol) and methyl amine (0.06 g, 0.002 mol) in ethanol (30 ml) under reflux for 8 h. The reaction mixture was cooled to room temperature and the precipitated solid was filtered and re-crystallized from ethanol. It was obtained as yellowish white solid); yield, 80%; mp 265–267°C; IR (KBr) ν_{max} 3109, 3066, 2948, 1662 cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta = 7.98$ (1H, s, NH) (D_2O exchangeable), 6.82–6.84 (1H, m, H-5 quinox.), 6.72–6.74 (1 H, d, $J = 8$ Hz, H-8 quinox.), 6.66–6.67 (2H, m, H-6 and H-7 quinox.), 4.40 (2H, s, CH_2 quinox.), 3.83 (2H, s, NCH_2), 2.60 (3H, s, NCH_3), 2.16 (3H, s, CH_3 acetyl); anal. calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.84; H, 5.86; N, 16.22.

*2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)-N-butylacetamide (**5$_b$**)*

Light yellow powder (C_2H_5OH) (This compound was prepared by heating a mixture of ethyl ester (**4**) (0.28 g, 0.001 mol) and butyl amine (0.15 g, 0.002 mol) in ethanol (30 ml) under reflux for 8 h. The reaction mixture was cooled to room temperature and the precipitated solid was filtered and re-crystallized from ethanol. It was obtained as light yellow solid); yield, 80%; mp 254–255 °C; IR (KBr) ν_{max} 3308, 3065, 2947, 1669 cm^{-1}; ^{13}CNMR (DMSO, 400 MHz): $\delta =$ 166.87 (C, CH_3CO, CONH), 165.97 (C, C-2), 133.34 (C, C-8′), 131.42 (C, C-4′), 124.87 (CH, C-6), 123.94 (CH, C-7), 116.41 (CH, C-5), 115.14 (CH, C-8), 45.34 (CH_2, C-3), 44.67 (CH_2, NCH_2), 38.67 (CH_2, $NHCH_2$), 31.51 (CH_2, $NHCH_2CH_2$), 22.29 (CH_3, CH_3CO), 19.86 (CH_2, CH_2CH_3), 14.08 (CH_3, CH_2CH_3); EIMS *m/z* 305 [$M^+ + 2$] (3.10), 303 [M^+] (13.3), 265 (34), 182 (29), 149 (28), 76 (100); anal. calcd. for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.49; H, 7.05; N, 14.01.

*2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)-N-benzylacetamide (**5c**)*

Light brown powder (C_2H_5OH) (This compound was prepared by heating a mixture of ethyl ester (**4**) (0.28 g, 0.001 mol) and phenylmethyl amine (0.22 g, 0.002 mol) in ethanol (30 ml) under reflux for 8 h. The reaction mixture was cooled to room temperature and the precipitated solid was filtered and re-crystallized from ethanol. It was obtained as light brown solid); yield, 85%; mp 287–289 °C; IR (KBr) ν_{max} 3284, 3060, 2928, 1665 cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta = 8.78$ (1H, s, NH) (D_2O exchangeable), 7.85–7.87 (1H, m, H-5 quinox.), 7.61–7.65 (1H, d, H-8 quinox.), 7.38–7.43 (2H, m, H-6 and H-7 quinox.), 7.30–7.34 (2H, m, H-2 and H-6 Ph.), 7.22–7.26 (3H, m. H-3, H-4 and H-5 Ph.), 4.95 (2H, s, CH_2 quinox.), 4.31 (2H, s, NCH_2), 4.29 (2H, s, CH_2-phenyl), 2.16 (3H, s, CH_3 acetyl); anal. calcd. for $C_{19}H_{19}N_3O_3$ (m.w. 337): C, 67.64; H, 5.68; N, 12.46. Found: C, 67.80; H, 5.72; N, 12.63.

*2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl) acetohydrazide (**6**)*

White powder (C_2H_5OH) (This compound was prepared by heating 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 4 h. The reaction mixture was cooled and the solid produced was collected by filtration, washed with water, dried and re-crystallized from ethanol. It was obtained as white solid); yield, 80%; mp 230–231 °C; IR (KBr) ν_{max} 3299, 3229, 3044, 2930, 1672 cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta = 9.30$ (1H, s, NH) (D_2O exchangeable), 7.53 (1H, d, H-5 quinox.), 7.25–7.28 (1H, d, $J = 7.6$ Hz, H-8 quinox.), 7.11–7.15 (1H, m, H-7 quinox.), 7.00–7.04 (1H, m, H-6 quinox.), 4.46 (2H, s, CH_2 quinox.), 4.45 (2H, s, NCH_2), 4.26 (2H, s, NH_2) (D_2O exchangeable), 2.16 (3H, s, CH_3 acetyl); ^{13}CNMR (DMSO, 400 MHz): $\delta =$ 169.34 (C, CH_3CO), 166.71 (C, CONH, C-2), 137.02 (C, C-8′), 126.94 (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 (CH_2, C-3, NCH_2), 22.31 (CH_3, CH_3CO); EIMS *m/z* 263 [$M^+ + 1$] (1.03), 262 [M^+] (4.72), 231 (43), 190 (1.8), 147 (6), 133 (100); anal. calcd. for $C_{12}H_{14}N_4O_3$ (m.w. 262): C, 54.96; H, 5.38; N, 21.36. Found: C, 55.12; H, 5.43; N, 21.49.

*2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)-N'(2-chloroacetyl)acetohydrazide (**7**)*

White powder (C_2H_5OH) (This compound was prepared by drop wise addition of chloroacetyl chloride (0.45 g, 0.004 mol) to the stirred solution of the acid hydrazide (**6**) (1.05 g, 0.004 mol) in dry DMF (20 ml) in the presence of potassium carbonate (0.55 g, 0.004 mol) using ice-bath. After addition, the solution was stirred at room temperature for one hour. The contents of the reaction flask were then poured slowly into crushed ice with continuous stirring and the resulting precipitate was filtered, washed with water, dried and crystallized from ethanol. It was obtained as white solid); yield, 70%; mp 238–239 °C; IR (KBr) ν_{max} 3191, 3058, 2930, 1676, 1622 cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta = 10.38$ (2H, s, 2NH) (D_2O exchangeable), 7.56 (1 H, d, H-5 quinox.), 7.27–7.28 (1H, d, $J = 7.2$ Hz, H-8 quinox.), 7.13–7.17 (1 H, m, H-7 quinox.), 7.08–7.10 (1 H, m, H-6 quinox.), 4.60 (2H, s, N–CH_2), 4.46 (2H, s, CH_2 quinox.), 4.12 (2H, s, CH_2–Cl), 2.16 (3H, s, CH_3 acetyl); anal. calcd. for $C_{14}H_{15}ClN_4O_4$ (m.w. 338.5): C, 49.64; H, 4.46; N, 16.54. Found: C, 49.72; H, 4.50; N, 16.78.

*4-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl) tetrahydropyridazine-3,6-dione (**8**)*

Yellowish white powder (C_2H_5OH) (This compound was prepared by drop wise addition of chloroacetyl chloride (0.45 g, 0.004 mol) to the stirred solution of the acid hydrazide (**6**) (1.05 g, 0.004 mol) in dry DMF (20 ml) in the presence of potassium carbonate (0.55 g, 0.004 mol) using ice-bath. After addition, the solution was stirred at room temperature for one hour and then refluxed at 100 °C for 4 h. The contents of the reaction flask were then poured slowly into crushed ice with continuous stirring and the resulting precipitate was filtered, washed with water, dried and crystallized from ethanol. It was obtained as yellowish white solid); yield, 70%; mp 175–177°C; IR (KBr) ν_{max} 3191, 3058, 2930, 1676, 1622 cm^{-1}; ^{13}CNMR (DMSO, 400 MHz): $\delta = 171.07$ (C, CH_2CONH), 169.32 (C, CH_3CO), 167.32 (C, CHCONH, C-2), 137.02 (C, C-8′), 133.21 (C, C-4′), 124.88 (CH, C-6), 123.39 (CH, C-7), 118.43 (CH, C-5), 116.73 (CH, C-8), 59.69 (CH, CHCO), 48.48 (CH_2, C-3), 44.16 (CH_2, $NCHCH_2$), 22.25 (CH_3, CH_3CO); EIMS *m/z* 302 [M^+] (2.92), 265 (2.50), 239 (5.20), 224 (5.34), 194 (9.31), 185 (100); anal. calcd. for $C_{14}H_{14}N_4O_4$ (m.w. 302): C, 55.63; H, 4.67; N, 18.53. Found: C, 55.78; H, 4.72; N, 18.74.

*4-Acetyl-1-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxoethyl)-3,4-dihydroquinoxalin-2(1 H)-one (**9**)*

White powder (C_2H_5OH) (This compound was prepared by addition of acetylacetone (0.40 g, 0.004 mol) to a solution of the acid hydrazide (**6**) (1.05 g, 0.004 mol) in dioxan (20 ml) and few drops of TEA. The reaction mixture was refluxed for 4 h, concentrated, cooled to room temperature and the formed precipitate was filtered and crystallized from ethanol. It was obtained as white solid); yield, 75%; mp 184–186°C; IR (KBr) ν_{max} 3058, 2966, 1665

cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta = 7.54$ (1 H, d, H-5 quinox.), 7.25–7.26 (1 H, d, H-8 quinox.), 7.11–7.16 (2H, m, H-6 and H-7 quinox.), 6.05 (1 H, s, CH_3–C=CH), 4.54 (2H, s, N–CH_2), 4.45 (2H, s, CH_2 quinox.), 2.39 (3H, s, CH_3–C=CH), 2.29 (3H, s, CH_3–C=N), 2.16 (3H, s, CH_3 acetyl); ^{13}CNMR (DMSO, 400 MHz): $\delta = 169.31$ (C, CH_3CO), 167.26 (C, NNCO), 166.45 (C, C-2), 150.30 (C, $NNCCH_3$), 140.40 (C, $NCCH_3$), 133.18 (C, C-8′), 131.49 (C, C-4′), 124.91 (CH, C-6), 124.14 (CH, C-7), 116.84 (CH, C-5), 115.62 (CH, C-8), 112.83 (CH, $CHCCH_3$), 44.11 (CH_2, C-3, NCH_2), 22.24 (CH_3, CH_3CO), 14.89 (CH_3, $NCCH_3$), 14.75 (CH_3, $NNCCH_3$); EIMS *m/z* 326 [M^+] (0.96), 186 (34.53), 131 (66.49), 96 (95.94), 43 (100); anal. calcd. for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.81; H, 5.64; N, 17.29.

*2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)-N'-(2-oxoindolin-3-ylidene)acetohydrazide (**10**)*

Orange powder (C_2H_5OH) (This compound was prepared by heating a mixture of the acid hydrazide (**6**) (0.52 g, 0.002 mol) and isatine (0.29 g, 0.002 mol) under reflux in glacial acetic acid (15 ml) for 6 h. The reaction mixture was allowed to attain room temperature, and then poured carefully onto crushed ice. The resulted precipitate was filtered, washed with water and crystallized from ethanol. It was obtained as orange solid); yield, 75%; mp 297–298°C; IR (KBr) ν_{max} 3252, 3060, 2940, 1672 cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta = 13.18$ (1 H, s, NH) (D_2O exchangeable), 11.29 (1 H, s, NH isatine) (D_2O exchangeable), 7.88–7.90 (1 H, d, $J = 7.6\,Hz$, H-5 quinox.), 7.63–7.65 (1 H, d, H-8 quinox.), 7.57–7.61 (1 H, m, H-6 quinox.), 7.40–7.44 (1 H, m, H-7 quinox.), 7.37–7.39 (1 H, d, $J = 6.8\,Hz$, H-4 phenyl), 7.16–7.18 (1 H, d, H-7 phenyl), 7.10–7.13 (1 H, m, H-6 phenyl), 6.96–6.98 (1 H, m, H-5 phenyl), 5.59 (2H, s, N–CH_2), 4.49 (2H, s, CH_2 quinox.), 2.18 (3H, s, CH_3 acetyl); anal. calcd. for $C_{20}H_{17}N_5O_4$: C, 61.38; H, 4.38; N, 17.89. Found: C, 61.49; H, 4.36; N, 18.04.

*2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)-N'-(4-chlorobenzylidene)acetohydrazide (**11$_a$**)*

Yellowish white powder (C_2H_5OH) (This compound was prepared by heating equimolar amounts of (**6**) (0.52 g, 0.002 mol) and 4-chlorobenzaldehyde (0.28 g, 0.002 mol) under reflux in ethanol (25 ml) for 4 h. The mixture was cooled and the formed solid was filtered and re-crystallized from ethanol. It was obtained as yellowish white solid); yield, 83%; mp 255–257°C; IR (KBr) ν_{max} 3191, 3082, 2994, 1672 cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta = 11.87$ (1 H, s, NH) (D_2O exchangeable), 8.43 (1 H, s, N=CH), 8.03–8.05 (1 H, d, H-5 quinox.), 7.52–7.54 (1 H, d, H-8 quinox.), 7.39–7.47 (2H, m, H-6 and H-7 quinox.), 7.25–7.29 (2H, m, H-2 and H-6 phenyl), 7.11–7.18 (2H, m, H-3 and H-5 phenyl), 5.07 (2H, s, N–CH_2), 4.47 (2H, s, CH_2 quinox.), 2.17 (3H, s, CH_3 acetyl); ^{13}CNMR (DMSO, 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), 131.70 (CH, N=CH), 130.35 (C, C_6H_4 (C-1)), 128.02 (CH, C_6H_4 (C-2, C-6)), 127.45 (CH, C_6H_4 (C-3, C-5)), 124.91 (CH, C-6), 123.32 (CH, C-7), 116.79 (CH, C-5, C-8), 44.75 (CH_2, NCH_2), 44.29 (CH_2, C-3), 22.21 (CH_3, CH_3CO); EIMS *m/z* 386 [$M^+ + 1$] (6.95), 384 [M^+] (21.90), 231 (48.00), 188 (44.00), 133 (100); anal. calcd. for $C_{19}H_{17}ClN_4O_3$: C, 59.30; H, 4.45; N, 14.56. Found: C, 59.51; H, 4.47; N, 14.70.

*2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)-N'-(4-hydroxybenzylidene)acetohydrazide (**11$_b$**)*

Yellowish white powder (C_2H_5OH) (This compound was prepared by heating equimolar amounts of (**6**) (0.52 g, 0.002 mol) and 4-hydroxybenzaldehyde (0.24 g, 0.002 mol) under reflux in ethanol (25 ml) for 4 h. The mixture was cooled and the formed solid was filtered and re-crystallized from ethanol. It was obtained as yellowish white solid); Yield, 86%; mp 260–262°C; ^{1}HNMR (DMSO, 400 MHz): $\delta = 11.48$ (1 H, s, NH) (D_2O exchangeable), 9.91 (1 H, s, OH) (D_2O exchangeable), 7.94 (1 H, s, N=CH), 7.56–7.58 (2H, d, H-5 and H-8 quinox.), 7.51–7.53 (1 H, m, H-6 quinox.), 7.24–7.28 (1 H, m, H-7 quinox.), 7.07–7.15 (2H, m, H-2 and H-6 phenyl), 6.81–6.82 (2H, m, H-3 and H-5 phenyl), 5.01 (2H, s, N–CH_2), 4.46 (2H, s, CH_2 quinox.), 2.17 (3H, s, CH_3 acetyl); anal. calcd. for $C_{19}H_{18}N_4O_4$: C, 62.29; H, 4.95; N, 15.29. Found: C, 62.38; H, 5.01; N, 15.43.

*2-(4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl)-N'-(4-methoxybenzylidene)acetohydrazide (**11$_c$**)*

Yellowish white powder (C_2H_5OH) (This compound was prepared by heating of equimolar amounts of (**6**) (0.52 g, 0.002 mol) and 4-methoxybenzaldehyde (0.27 g, 0.002 mol) under reflux in ethanol (25 ml) for 4 h. The mixture was cooled and the formed solid was filtered and re-crystallized from ethanol. It was obtained as yellowish white solid); yield, 79%; mp 260–262°C; IR (KBr) ν_{max} 3202, 3062, 2955, 1673 cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta = 11.56$ (1 H, s, NH) (D_2O exchangeable), 7.99 (1 H, s, N=CH), 7.63–7.68 (2H, m, H-5 and H-8 quinox.), 7.55 (1 H, m, H-6 quinox.), 7.24–7.28 (1 H, m, H-7 quinox.), 7.08–7.16 (2H, m, H-2 and H-6 phenyl), 6.99–7.01 (2H, m, H-3 and H-5 phenyl), 5.03 (2H, s, N–CH_2), 4.47 (2H, s, CH_2 quinox.), 3.80 (3H, s, OCH_3), 2.17 (3H, s, CH_3 acetyl); ^{13}CNMR (DMSO, 400 MHz): $\delta = 169.34$ (C, CH_3CO), 168.21 (C,

CONH), 163.67 (C, C-2), 147.37 (C, C_6H_4 (C-4)), 144.27 (C, C-8′, C-4′), 129.07 (C, C_6H_4 (C-1)), 128.97 (CH, C_6H_4 (C-2, C-6)), 127.06 (CH, N = CH), 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, C-5)), 55.74 (CH_3, OCH_3), 44.60 (CH_2, C-3), 44.23 (CH_2, NCH_2), 22.21 (CH_3, CH_3CO); EIMS *m/z* 381 [$M^+ + 1$] (9.64), 380 [M^+] (37.32), 231 (21.00), 177 (75.50), 133 (100); anal. calcd. for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.28; H, 5.34; N, 14.87.

4-Acetyl-1-((5-sulfanyl-1,3,4-oxadiazol-2-yl)methyl)-3,4-dihydroquinoxalin-2(1 H*)-one (**12**)*

Dark yellow powder (C_2H_5OH) (This compound was prepared by dissolving the acid hydrazide (**6**) (2.62 g, 0.01 mol) 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. It was obtained as dark yellow solid); yield, 90%; mp 246–248°C; IR (KBr) ν_{max} 3068, 2913, 2590, 1684, 1621 cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta = 14.56$ (1 H, s, SH) (D_2O exchangeable), 7.57–7.59 (1 H, d, H-8 quinox.), 7.38–7.44 (1 H, d, $J = 7.6$ Hz, H-5 quinox.), 7.30–7.33 (1 H, m, H-7 quinox.), 7.17–7.21 (1 H, m, H-6 quinox.), 5.23 (2H, s, N–CH_2), 4.50 (2H, s, CH_2 quinox.), 2.16 (3H, s, CH_3 acetyl); ^{13}CNMR (DMSO, 400 MHz): $\delta = 169.37$ (C, CH_3CO, C-2), 159.99 (C, CN_2, CSH), 154.27 (C, C-8′), 150.36 (C, C-4′), 125.17 (CH, C-6), 123.97 (CH, C-7), 116.82 (CH, C-5), 115.33 (CH, C-8), 37.85 (CH_2, C-3, NCH_2), 22.23 (CH_3, CH_3CO); anal. calcd. for $C_{13}H_{12}N_4O_3S$: C, 51.31; H, 3.97; N, 18.41. Found: C, 51.43; H, 3.95; N, 18.63.

4-Acetyl-1-((5-(ethylsulfanyl)-1,3,4-oxadiazol-2-yl)methyl)-3,4-dihydroquinoxalin-2(1 H*)-one (**13_a**)*

White powder (C_2H_5OH) (This compound was prepared by heating a mixture of **13** (0.61 g, 0.002 mol) and ethyl bromide (0.22 g, 0.002 mol) under reflux in dry acetone (50 ml) in the presence of anhydrous K_2CO_3 (0.83 g, 0.006 mol) for 6 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. It was obtained as white solid); yield, 85%; mp 163–165°C; IR (KBr) ν_{max} 3020, 2945, 1664 cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta = 270$ (13.68), 91 (100), 7.54 (1 H, d, H-8 quinox.), 7.25–7.27 (1 H, d, H-5 quinox.), 7.15–7.17 (2H, m, H-6 and H-7 quinox.), 4.62 (2H, s, N–CH_2), 4.46 (2H, s, CH_2 quinox.), 3.57 (2H, m, CH_2CH_3), 2.16 (3H, s, CH_3 acetyl), 1.06–1.09 (3H, t, CH_2CH_3); EIMS *m/z* 333 [$M^+ + 1$] (1.17), 332 [M^+] (1.28), 315 (3.97); anal. calcd. for $C_{15}H_{16}N_4O_3S$: C, 54.20; H, 4.85; N, 16.86. Found: C, 54.35; H, 4.95; N, 16.95.

4-Acetyl-1-((5-(butylsulfanyl)-1,3,4-oxadiazol-2-yl)methyl)-3,4-dihydroquinoxalin-2(1 H*)-one (**13_b**)*

Yellowish white powder (C_2H_5OH) (This compound was prepared by heating a mixture of **13** (0.61 g, 0.002 mol) and butyl bromide (0.27 g, 0.002 mol) under reflux in dry acetone (50 ml) in the presence of anhydrous K_2CO_3 (0.83 g, 0.006 mol) for 6 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. It was obtained as yellowish white solid); yield, 80%; mp 167–169°C; IR (KBr) ν_{max} 3034, 2945, 1664 cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta = 7.87$–7.89 (1 H, d, $J = 7.6$ Hz, H-8 quinox.), 7.70–7.72 (1 H, d, $J = 7.6$ *Hz*, H-5 quinox), 7.65–7.67 (1 H, m, H-7 quinox.), 7.41–7.44 (1 H, m, H-6 quinox.), 5.72 (2H, s, N-CH_2), 4.78 (2H, s, CH_2 quinox.), 3.16–3.19 (2H, t, S$\underline{CH_2}CH_2$), 2.14 (3H, s, CH_3 acetyl), 1.62–1.65 (2H, m, $CH_2\underline{CH_2}CH_2$), 1.30–1.36 (2H, m, $J = 7.2$ *Hz*, $\underline{CH_2}CH_3$), 0.86 (3H, t, CH_2CH_3); EIMS m/z 360 [M^+] (1.00), 316 (53.93), 227 (100); anal. calcd. for $C_{17}H_{20}N_4O_3S$: C, 56.65; H, 5.59; N, 15.54. Found: C, 56.79; H, 5.67; N, 15.80.

*2-((5-((4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)methyl)-1,3,4-oxadiazol-2-yl)sulfanyl)-*N*-phenyl-acetamide (**14_a**)*

Light yellow powder (C_2H_5OH) (This compound was prepared by heating a mixture of **13** (0.61 g, 0.002 mol) and 2-chloro-*N*-phenylacetamide (0.34 g, 0.002 mol) in dry acetone (50 ml) in the presence of anhydrous K_2CO_3 (0.83 g, 0.006 mol) under refluxed for 6 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. It was obtained as light yellow solid); yield, 85%; mp 162–164°C; IR (KBr) ν_{max} 3196, 3057, 2916, 1654 cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta =$ 11.69 (1 H, s, NH) (D_2O exchangeable), 7.69–7.74 (2H, m, H-5 and H-8 quinox.), 7.43–7.47 (4 H, m, H-2, H-6 phenyl and H-6, H-7 quinox.), 7.25–7.29 (1 H, m, H-4 phenyl), 7.10–7.17 (2H, m, H-3 and H-5 phenyl), 5.06 (2H, s, N–CH_2), 4.65 (2H, s, CH_2 quinox.), 4.47 (2H, s, SCH_2), 2.17 (3H, s, CH_3 acetyl); anal. calcd. for $C_{21}H_{19}N_5O_4S$: C, 57.66; H, 4.38; N, 16.01. Found: C, 57.75; H, 4.50; N, 15.90.

*2-((5-((4-Acetyl-2-oxo-3,4-dihydroquinoxalin-1(2H)-yl) methyl)-1,3,4-oxadiazol-2-yl)sulfanyl)-N-(thiazol-2-yl)-acetamide (**14$_b$**)*

Light yellow powder (C_2H_5OH) (This compound was prepared by heating a mixture of **13** (0.61 g, 0.002 mol) and 2-chloro-*N*-(thiophen-2-yl)acetamide (0.35 g, 0.002 mol) in dry acetone (50 ml) in the presence of anhydrous K_2CO_3 (0.83 g, 0.006 mol) under refluxed for 6 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. It was obtained as light yellow solid); yield, 80%; mp 158–159°C; IR (KBr) ν_{max} 3191, 3058, 2930, 1676 cm^{-1}; ^{1}HNMR (DMSO, 400 MHz): $\delta = 10.82$ (H, s, NH) (D_2O exchangeable), 7.84–7.86 (1 H, d, $J = 7.6$ *Hz*, H-8 quinox.), 7.63–7.65 (1 H, d, $J = 8$ Hz, H-5 quinox.), 7.58–7.61 (1 H, m, H-7, quinox.), 7.31–7.42 (3H, m, H-4, H-5 thiazole and H-6 quinox.), 4.99 (2H, s, N–CH_2), 4.87 (2H, s, CH_2 quinox.), 4.18 (2H, s, SCH_2), 2.19 (3H, s, CH_3 acetyl); EIMS *m/z* 444 [M^+] (1.12), 396 (18.08), 248 (50.44), 246 (100), 218 (49.65); anal. calcd. for $C_{18}H_{16}N_6O_4S_2$: C, 48.64; H, 3.63; N, 18.91. Found: C, 48.45; H, 3.52; N, 18.95.

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 (compound **III** and **YM872(IV)**) 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 Tween 80 (2%) and were given intraperitoneally (*i.p.*) in doses ranging from 250 to 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 dissolved in normal saline in 2% concentration and it 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 min 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 competing interests.

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