Synthesis and Evaluation of Some New (1,2,4) Triazolo(4,3-a) Quinoxalin-4(5H)-one Derivatives as AMPA Receptor Antagonists

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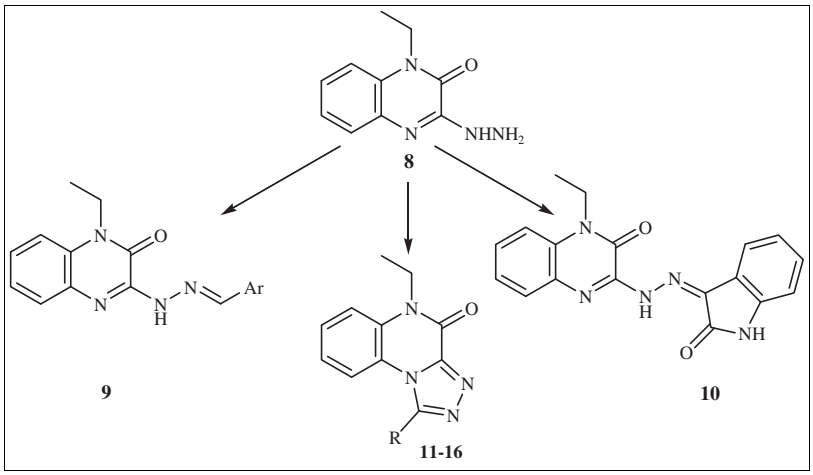


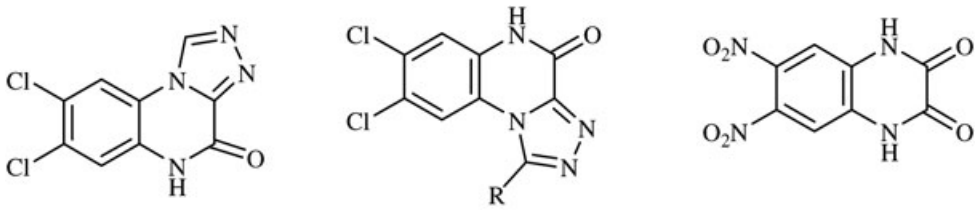
This study involves the synthesis and anticonvulsant evaluation of 1-ethyl-3-hydrazinylquinoxaline-2-(1H)-one **(8)**, its chemical confirmations **9** and **10** and certain (1,2,4) triazolo(4,3-a)quinoxalin-4(5H)-one compounds **11-16**. The structure of the synthesized compounds was confirmed chemically by elemental analyses and spectral data (IR, ^{1}H NMR, ^{13}C NMR, and Mass). Docking studies were preformed to all of the synthesized compounds to predict, in a qualitative way, the anticonvulsant activity of the proposed compounds. There is a promising correlation between the results of molecular modeling and the anticonvulsant activity of the synthesized compounds. The highest fitting value was noticed for compounds **9** and **10**, which showed the highest anticonvulsant activity.

INTRODUCTION

Synthesis of quinoxaline derivatives has attracted a great deal of attention in view of their potent pharmacological activities [1]. Approximately, 1% of the world's population is affected by epilepsy [2]. Therefore, investigation of new anticonvulsant is still a challenge.

Most of the currently used anticonvulsant drugs are associated with adverse effects, such as sedation, ataxia, and weight loss or weight gain. Rare adverse effects can be life threatening such as aplastic anemia [3]. The development of safer and more effective new anticonvulsant drugs is necessary.

It was reported that the majority of anticonvulsant agents mediates its effect though their action either by activation of the γ-amino butyric acid (GABA) receptor or by inhibition of the glutamate receptor [4]. Glutamate receptors are classified into two main subtypes, *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [5].



In fact, NMDA receptor antagonists may produce schizophrenia-like symptoms, perceptual alterations, and memory impairment; AMPA receptor antagonists have no such psychoactive properties [6].

On the other hand, from the literature survey, it was found that many quinoxaline derivatives showed anticonvulsant activity [7,8].

Furthermore, compounds **1** and $\mathbf{2_{a\text{-}d}}$ have shown high affinity towards AMPA receptor [8]. Similarly, compound **3** was reported as a potent AMPA receptor antagonist [9]. In this work, it was decided to synthesize many new (1,2,4) triazolo(4,3-a)Quinoxalin-4(5H)-one derivatives expected to have AMPA receptor antagonistic activity as well as many Schiff's bases **9** and the indolone derivative **10** were prepared as a confirmatory chemical reaction for the hydrazino derivative **8.** For preparation of the new derivatives, Scheme 1 was adopted.

RESULTS AND DISCUSSION

Docking study. All of the target compounds were subjected to docking study to explore their affinity and binding mode to AMPA receptor. As AMPA is a target for a remarkable variety of anticonvulsant agents [8], [10].

Scheme 1

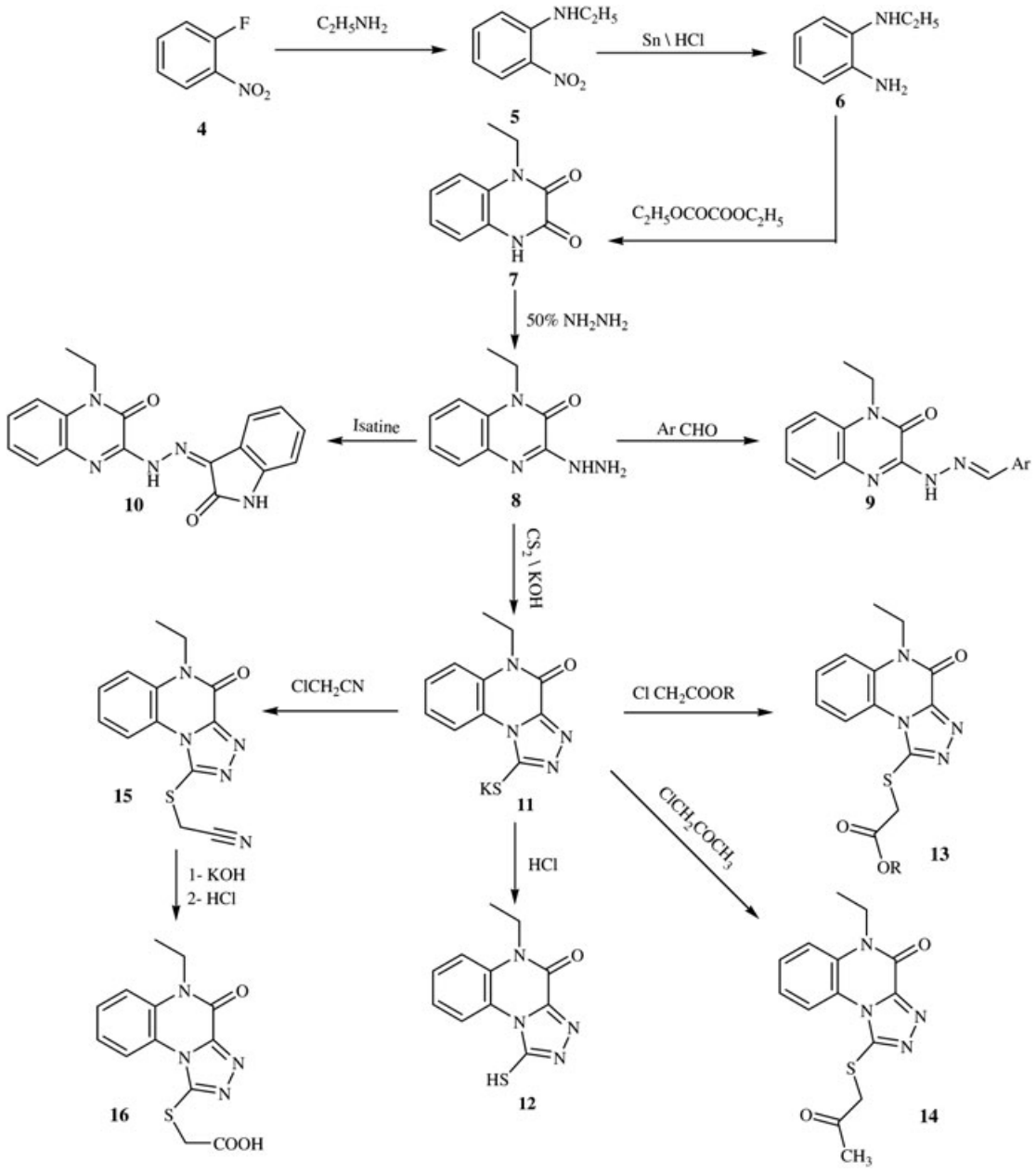
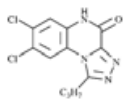
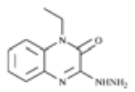
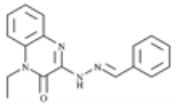
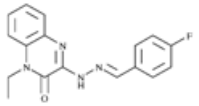
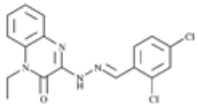
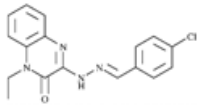
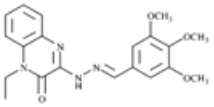
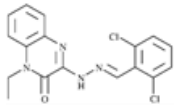
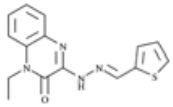
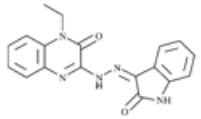
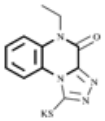
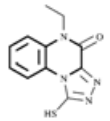
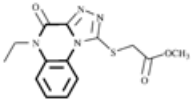
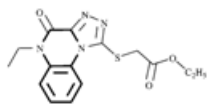
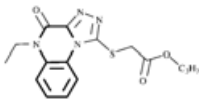
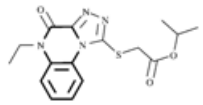
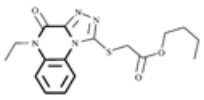
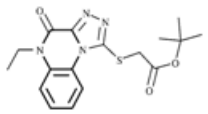
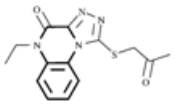
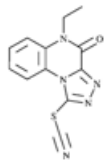
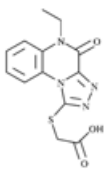


Table 1

Docking study data in Δ*E* and structures for the synthesized compounds **8–16** and the reference [1,2,4]triazolo[4,3-a]-quinoxalinone derivative $\mathbf{2_c}$.

Cpd.	Structure	*Δ*E*	Cpd.	Structure	*Δ*E*
$\mathbf{2_c}$		−185	**8**		−17
$\mathbf{9_a}$		42	$\mathbf{9_b}$		53
$\mathbf{9_c}$		33	$\mathbf{9_d}$		22
$\mathbf{9_e}$		76	$\mathbf{9_f}$		68
$\mathbf{9_g}$		61	**10**		136
11		**−131**	**12**		**−152**
$\mathbf{13_a}$		−21	$\mathbf{13_b}$		−17
$\mathbf{13_c}$		−11	$\mathbf{13_d}$		−5
$\mathbf{13_e}$		−9	$\mathbf{13_f}$		−3
14		−5	**15**		−9
16		−18	—	—	—

All modeling experiments were performed using virtual docker program and Discovery Studio program version 2.5. Each experiment used the biological target coordinates downloaded from the Brookhaven website (PDB: 1FTL). To qualify the docking results in terms of accuracy of the predicted binding conformations in comparison with the experimental procedure, the internal ligand (7,8-dichloro-1-propyl-[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-one) **2_c** was used as a reference molecule. The docking study revealed that almost all of the proposed compounds showed promising activity to be antagonists for the AMPA receptor.

From the synthesized compounds, those compounds having the highest binding energy score (Kcal/mol) were subjected to *in vivo* anticonvulsant evaluation on different groups of mice. Phenobarbitone sodium was used as a reference standard. The results of the docking study of the synthesized compounds are shown in Table 1 in comparison with compound **2_c** as a reference compound. Figure 1 shows compound **12** drawn in green and docked inside active site.

Anticonvulsant evaluation. Nine compounds of the newly synthesized derivatives were selected to be screened for their anticonvulsant activity on different groups of mice. Phenobarbitone sodium was used as a reference standard. The compounds to be tested or the standard phenobarbitone sodium were given by intraperitoneal injection to a group of adult mices each group containing six animals. After 45 min, pentylentetrazole (as convulsion inducing drug) was given intramuscularly in a dose of (60 mg/kg) body weight. Convulsions began with jerks of the head and body of the mouse consisting chiefly of clonic contractions. The seizures ended either by depression or by complete recovery [11, 12].

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 phenobarbitone sodium were recorded in Table 2.

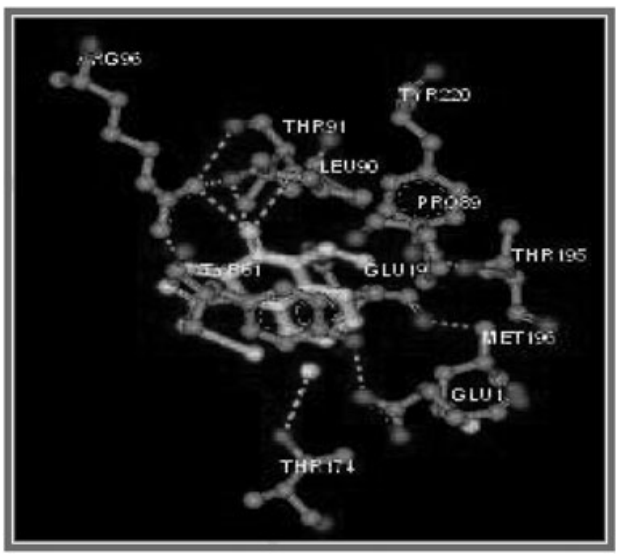


Figure 1. Compound 12 docked inside active site. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

CONCLUSIONS

From the results of docking study and biological evaluation, it was noticed that the presence of another aromatic system attached to quinoxaline nucleus like [1,2,4]triazolo nucleus increases the binding affinity with AMP receptor due to the formation of favorable kind of interaction with the active site. This effect was clearly seen in the higher relative potencies of compounds **11** and **12**. Compound **8** showed low energy score; also it found the lowest active compound, this confirms the parallel consistency between the results of modeling and biological evaluation. The higher reactivity of the potassium salt **11** over compound **12** may be attributed to the higher solubility of compound **11**. Elongation of the aliphatic side chain in the ester derivatives **13** has a moderate effect on the activity.

EXPERIMENTAL

All melting points were taken on electrothermal (LA 9000 SERIS) digital melting point apparatus and are uncorrected. IR spectra were recorded on Pye Unicam SP 1000 IR spectrophotometer at Microanalytical Center, Cairo University. The ^{1}H NMR spectra were recorded in DMSO-d_6 at 300 MHz, and ^{13}C NMR spectra were recorded in DMSO-d_6 at 75 MHz on a Varian Mercury VXR-300 NMR spectrometer at Research Services Unit, Faculty of Science, Cairo University. Chemical shifts were related to that of the solvent. Tetramethylsilane was used as a standard. Mass spectra were recorded on Hewlett Packard 5988 spectrometer at Regional Center for Mycology and Biotechnology, Al-Azhar University. Microanalyses were carried out at Microanalytical Center, Cairo University. Progresses of the reaction was monitored by tlc using tlc sheets precoated with UV fluorescent silica gel Merck 60 F254 plates and were visualized using UV lamp and n-hexane : ethyl acetate 9:1 as mobile phase. *N*-Ethyl-2-nitroaniline (5), *N*-^{1}-Ethyl-*o*-phenylendiamine (6) and 1-Ethylquinoxaline-2,3(1H,4H)-dione (7) were prepared according to the directions of Shu-Kun [13].

1-Ethyl-2-oxoquinoxalin-3-yl hydrazine (8). A mixture of 1.90 g (0.01 mole) of 1-ethylquinoxaline-2,3(1H,4H)-dione **(7)** and 10 mL hydrazine hydrate (50%), was refluxed for 2 h. After cooling, a crystalline product was obtained which collected by filtration, washed with water several times and dried. Recrystallization of the resulting product from ethanol afforded faint yellow crystalline needles, 1.93 g, (95%), mp 165-167°C; ir: NH_2 3339, CO 1645 cm^{-1}; ^{1}H NMR: δ 1.17 (t, 3H, C**H$_3$**-CH_2, J = 7.20 Hz), 4.15 (q, 2H, C**H$_2$**-CH_3, J = 7.20 Hz), 4.52 (s, 2H, N**H$_2$**) (D_2O exchangeable), 7.17-7.44(m, 4H, aromatic), and 8.68 (s, 1H, N**H**), (D_2O exchangeable); ^{13}C NMR: δ 12.30, (CH_3, aliphatic), 36.44, (CH_2, aliphatic), 113.93, 123.34, 123.43, 125.13, 127.80, 133.87, (benzene ring), 148.84 (amidic C O), 149.96 (piprazine-3-CN); ms: *m*/*z* 204 (molecular ion) (100), 189 (3.90), 175 (13.62), 145

Table 2

Results of anticonvulsant evaluation for compounds **8** and **11–13**.

Cpd. ID	Dose (mg/kg)	No. of protected animal	% protection	ED_{50} (mg/kg)	Mol wt	ED_{50} mmol/kg	R.P.[a]
Standard	12.5	6	100	6.25	254	0.02	1.00
	6.25	3	50				
	3.12	1	16.67				
8	200	5	83.33	129	204	0.63	0.04
	100	2	33.33				
	50	1	16.67				
11	25	4	66.67	12.5	246	0.05	0.48
	12.5	3	50				
	6.25	1	16.67				
12	25	6	66.67	12.5	284	0.04	0.60
	12.5	3	33.33				
	6.25	1	16.67				
13_a	200	4	66.67	150	318	0.47	0.05
	100	2	33.33				
	50	1	16.67				
13_b	200	6	100	95	332	0.29	0.09
	100	4	66.67				
	50	1	16.67				
13_c	200	4	66.67	100	346	0.29	0.09
	100	3	50				
	50	0	0				
13_d	200	5	83.33	100	346	0.29	0.09
	100	3	50				
	50	0	1				
13_e	200	4	66.67	150	360	0.42	0.06
	100	2	33.33				
	50	1	16.67				
13_f	200	4	66.67	150	360	0.42	0.06
	100	2	33.33				
	50	1	16.67				

[a]R.P. = Relative potency.

(5.90), 147 (28.47). *Anal*. Calcd. for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.63; H, 5.80; N, 27.65.

General procedure for the reaction of 1-ethyl-2-oxoquinoxalin-3-yl hydrazine (8) with different aromatic aldehydes. All of these reactions were carried out in ethanol. To a solution of 1-ethyl-2-oxoquinoxalin-3-yl hydrazine **(8)** (2.04 g, 0.01 mole) in ethanol (10 mL), a solution of the appropriate aldehydes in ethanol (5 mL), (0.01 mole) was added. The reaction mixture was refluxed for 5 h. The reaction mixture was filtered while hot and the filtrate was allowed to stand overnight to give the crystalline products of **$(9)_{a-g}$**.

3-(2-Benzylidenehydrazinyl)-1-ethylquinoxalin-2(1H)-one (9_a). This compound was obtained as dark yellow needles, 2.90 g, (90%), mp 234-236°C; ir: NH 3240, CO 1642 cm^{-1}; ^1H NMR: δ 1.24 [t, 3H, C**H$_3$**-CH_2, *J* = 7.20 Hz], 4.31 [q, 2H, C**H$_2$**-CH_3, *J* = 6.90 Hz], 7.28-7.73[m, 9H, aromatic], 8.60 [s, 1H, NCH] and11.99 [s, 1H, NH]; ms: *m/z* 292 (molecular ion) (9.62%), 263 (M+ $-CH_2CH_3$) (11.83%), 215 (M+ $-C_6H_5$) (11.98%). *Anal*. Calcd. for $C_{17}H_{16}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.63; H, 5.80; N, 27.65.

3-(2-(4-Fluorobenzylidene)hydrazinyl)-1-ethylquinoxalin-2(1H)-one (9_b). This compound was obtained as faint yellow needles, 1.86 g, (60%), mp 192-194°C; ir: NH 3252, CO 1648 cm^{-1}; ms: *m/z* 310 (molecular ion) (2.30%), 281 (M+ $-CH_2CH_3$) (14.71%), 215 (M + $-FC_6H_4$) (11.98%), 107 (M+ $-FC_6H_4C_2H_5$) (100%). *Anal*. Calcd. for $C_{17}H_{15}FN_4O$: C, 65.80; H, 4.87; N, 18.15. Found: C, 65.91; H, 4.90; N, 18.12.

2,4-Cl_2 3-(2-(2,4-Dichlorobenzylidene)hydrazinyl)-1-ethylquinoxalin-2(1H)-one. (9_c). Faint yellow crystals, 2.52 g, (70%), mp 197-199°C; ir: NH 3263, CO 1647 cm^{-1}; ms: *m/z* 361 (molecular ion) (2.01%), 363 (M+2) (0.65%), 215 (M+ $-Cl_2C_6H_3$) (17.17%), 189 (M+ $-Cl_2C_6H_3CHN$) (100%). *Anal*. Calcd. for $C_{17}H_{14}Cl_2N_4O$: C, 56.52; H, 3.91; N, 15.51. Found: C, 56.61; H, 4.03; N, 15.48.

3-(2-(4-Chlorobenzylidene)hydrazinyl)-1-ethylquinoxalin-2(1H)-one. (9_d). Faint yellow needles, 1.86 g, (60%), mp 195-197°C; ir: NH 3245, CO 1643 cm^{-1}; ms: *m/z* 326 (molecular ion) (1.31%), 328 (M+2) (0.45%), 281 (M+ $-C_2H_5$) (14.71%), 215 (M+ $-ClC_6H_4$) (28.08 %),188 (M+ $-ClC_6H_4CHN$) (100 %). *Anal*. Calcd. for $C_{17}H_{15}ClN_4O$: C, 62.48; H, 4.63; N, 17.05. Found: C, 62.63; H, 4.72; N, 17.08.

'3-(2-(3,4,5-Trimethoxybenzylidene)-1-ethylquinoxalin-2(1H)-one. (9_e). Dark yellow colored crystals, 2.48 g, (65%), mp 160-162° C; ir: NH 3258, CO 1654 cm^{-1}; ms: *m/z* 382 (molecular ion) (23.81 %), 353 (M+ $-C_2H_5$) (6.20%), 215 (M+ $-(OCH_3)_3C_6H_2$) (7.75%), 90 (C_7H_6 tropylium) (100%). *Anal*. Calcd. for $C_{17}H_{15}ClN_4O$: C, 62.82; H, 5.80; N, 14.65. Found: C, 63.09; H, 5.78; N, 14.76.

3-(2-(2,6-Dichlorobenzylidene)hydrazinyl)-1-ethylquinoxalin-2(1H)-one (9_f). Faint yellow colored crystals, 2.70 g, (75%), mp 245-247°C; ir: NH 3263, CO 1647 cm^{-1}; ms: *m/z* 361

(molecular ion) (21.30%), 363 (M+2) (7.08%), 215 (M+ $-Cl_2C_6H_3$) (15.12%), 189 (M+ $-Cl_2C_6H_3CHN$) (100%). *Anal.* Calcd. for $C_{17}H_{14}Cl_2N_4O$: C, 56.52; H, 3.91; N, 15.51. Found: C, 56.52; H, 3.98; N, 15.46.

3-(2-((Thiophen-2-yl)methylene)hydrazinyl)-1-ethylquinoxalin-2(1H)-one (9_g). This compound was obtained as a yellow crystals, 1.86 g, (60%), mp 218-220°C; ir: NH 3263, CO 1647 cm^{-1}; ^1H NMR: δ 1.23 [t, 3H, C**H**$_3$-CH_2, *J* = 7.20 Hz], 4.28 [q, 2H, C**H**$_2$-CH_3, *J* = 6.90 Hz], 7.11-7.65[m, 7H, aromatic], 8.79 [s, 1H, NC**H**] and11.21 [s, 1H, N**H**]; ms: *m/z* 298 (molecular ion) (14.95%), 269 (M+ $-CH_2CH_3$) (12.96%), 189 (M+ $-C_4H_{3SCN}$) (100%). *Anal.* Calcd. for $C_{15}H_{14}N_4OS$: C, 60.38; H, 4.73; N, 18.78. Found: C, 60.08; H, 4.56; N, 18.50.

3-(2-(2-Indolon-3-yl)hydrazonyl)-1-ethylquinoxalin-2(1H)-one (10). A mixture of 2.04 g (0.01 mol) of 1-ethyl-2-oxoquinoxalin-3-yl hydrazine **(8)** and 1.47 g (0.01 mol) isatine, was refluxed in 15 mL glacial acetic acid for 6 h. The reaction mixture was cooled to the room temperature. The orange precipitated product was filtered, washed with distilled water, dried, and crystallized from ethanol 80% to afford a faint yellow crystalline product, 3.09 g, (93%), mp 275-277°C; ir: NH 3332, CO 1653, 1708 cm^{-1} (quinoxalinone and indolone respectively); ^1H NMR: δ 1.27 [t, 3H, C**H**$_3$-CH_2, *J* = 6.60 Hz], 4.25 [q, 2H, C**H**$_2$-CH_3, *J* = 7.20 Hz], 11.20 [s, 1H, N**H**], 6.94-7.73 [m, 8H, aromatic] and 13.67 [s, 1H, N**H** exchangeable]; ms: *m/z* 333 (molecular ion) (18.97%), 304 (M+ $-C_2H_5$) (100%), 276 (M+ $-COC_2H_5$) (8.83%). *Anal.* Calcd. for $C_{18}H_{15}N_5O_2$: C, 64.86; H, 4.54; N, 21.01. Found: C, 64.92; H, 4.54; N, 20.90.

Potassium salt of 5-ethyl-1-mercapto-[1,2,4]triazolo[4,3-a] quinoxalin-4(5H)-one (11). A mixture of 2.04 g (0.01 mol) of 1-ethyl-2-oxoquinoxalin-3-yl hydrazine **(8)**, 0.76 g (0.71 mL, 0.01 mol) carbon disulphide and 0.56 g (0.01 mol) potassium hydroxide were refluxed in 20 mL ethanol for 2 h. The mixture was then allowed to reach the room temperature to afford a faint yellow precipitated product, 2.80 g, (98%), mp > 300°C; ir: CO 1656 cm^{-1}; *Anal.* Calcd. for $C_{11}H_9KN_4OS$: C, 46.46; H, 3.19; N, 19.70. Found: C, 46.58; H, 3.25; N, 19.84.

5-Ethyl-1-mercapto-[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-one (12). A mixture of 2.04 g (0.01 mol) of 1-ethyl-2-oxoquinoxalin-3-yl hydrazine **(8)**, 0.76 g (0.71 mL, 0.01 mol) carbon disulphide and 0.56 g (0.01 mol) potassium hydroxide were refluxed in 20 mL ethanol for 2 h. The mixture was then allowed to reach the room temperature and poured onto 20 mL 1N HCl. The yellow precipitated product was filtered, washed with distilled water crystallized from ethanol 80% to afford 2.23g (90%) of compound **12** as a faint yellow crystalline needles, mp 285-287°C; ir: SH 2630, CO 1683 cm^{-1}; ^1H NMR: δ 1.25 [t, 3H, C**H**$_3$-CH_2, *J* = 7.20 Hz], 4.24 [q, 2H, C**H**$_2$-CH_3, *J* = 7.20 Hz], 7.32-7.63 [m, 4H, aromatic] and 14.77 [s, 1H, S**H** exchangeable]; ms: *m/z* 246 (molecular ion) (100%), 218 (M+ −CO) (74.81%), 204 (M+ $-C_2H_5$) (5.75%). *Anal.* Calcd. for $C_{18}H_{15}N_5O_2$: C, 53.64; H, 4.09; N, 22.75. Found: C, 53.29; H, 3.96; N, 22.52.

General procedure for preparation of Alkyl 2-(5-ethyl-4, 5-dihydro-4-oxo-[1,2,4]triazolo [4,3-a]quinoxalin-1-ylthio)acetates (13). A mixture of 2.46 g (0.01 mol) of 5-ethyl-1-mercapto-[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-one **(12)**, (0.012 mol) of the appropriate alkyl chloroacetate and 1 g anhydrous potassium carbonate were stirred in (20 mL) DMF for 1 h on a water bath. The mixture was then poured onto 100 mL ice cold water with continuous stirring. The white crystalline product was filtered, washed with distilled. Recrystallization from ethanol 70% afforded the corresponding Alkyl 2-(5-ethyl-4,5-dihydro-4-oxo-[1,2,4]triazolo [4,3-a]quinoxalin-1-ylthio)acetate derivatives **(13_{a-f})**.

Methyl 2-(5-ethyl-4,5-dihydro-4-oxo-[1,2,4]triazolo [4,3-a] quinoxalin-1-ylthio)acetate (13_a). 2.38 g, (75%), mp 157-159° C; ir: CO 1679, 1743 cm^{-1} (amide and ester respectively); ^1H NMR: δ 1.29 [t, 3H, NCH_2-C**H**$_3$, *J* = 1.50 Hz], 3.70 [s, 3H, OC**H**$_3$], 4.32 [q, 2H, NC**H**$_2$-CH_3, *J* = 1.50 Hz], 4.46 [s, 2H, SC**H**$_2$] and 7.50-7.75 [m, 4H, aromatic]; ms: *m/z* 318 (molecular ion) (32.10%), 259 (M+ −CO OCH_3) (100%), 231 (M+ $-COOCH_3CO$) (60.06%); *Anal.* Calcd. for $C_{14}H_{14}N_4O_3S$: C, 52.82; H, 4.43; N, 17.60. Found: C, 52.53; H, 4.77; N, 17.44.

Ethyl 2-(5-ethyl-4,5-dihydro-4-oxo-[1,2,4]triazolo [4,3-a] quinoxalin-1-ylthio)acetate (13_b). 3.51 g, (95%), mp 165-167° C; ir: CO 1677, 1737 cm^{-1} (amide and ester respectively); ^1H NMR: δ 1.14 [t, 3H, NCH_2-C**H**$_3$, *J* = 1.50 Hz], 1.20 [t, 3H, OCH_2C**H**$_3$, *J* = 1.20 Hz], 4.08 [q, 2H, NC**H**$_2$-CH_3, *J* = 1.50 Hz], 4.26 [q, 2H, OC**H**$_2$$CH_3$, *J* = 1.20 Hz], 4.40 [s, 2H, SC**H**$_2$] and 7.43-7.73 [m, 4H, aromatic]; ms: *m/z* 332 (molecular ion) (27.83%), 259 (M+ $-COOC_2H_5$) (100%), 231 (M+ $-COOC_2H_5CO$) (22.40%); *Anal.* Calcd. for $C_{15}H_{16}N_4O_3S$: C, 54.20; H, 4.85; N, 16.86. Found: C, 52.53; H, 4.60; N, 16.94.

***n*-Propyl 2-(5-ethyl-4,5-dihydro-4-oxo-[1,2,4]triazolo [4,3-a]quinoxalin-1-ylthio)acetate (13_c).** 2.24 g, (65%), mp 190-192°C; ir: CO 1675, 1740 cm^{-1} (amide and ester respectively); ms: *m/z* 346 (molecular ion) (13.88%), 259 (M+ $-COOC_3H_7$) (100%), 231 (M+ $-COOC_2H_5CO$) (38.27%); *Anal.* Calcd. for $C_{16}H_{18}N_4O_3S$: C, 55.48; H, 5.24; N, 16.17. Found: C, 55.61; H, 5.16; N, 16.35.

Isopropyl 2-(5-ethyl-4,5-dihydro-4-oxo-[1,2,4]triazolo [4,3-a]quinoxalin-1-ylthio)acetate (13_d). 2.76 g, (80%), mp 147-149°C; ir: CO 1674, 1734 cm^{-1} (amide and ester respectively); ms: *m/z* 346 (molecular ion) (15.13%), 259 (M+ $-COOCH(CH_3)_2$) (100%), 231 (M+ $-COOCH(CH_3)_2CO$) (22.16%); *Anal.* Calcd. for $C_{16}H_{18}N_4O_3S$: C, 55.48; H, 5.24; N, 16.17. Found: C, 55.61; H, 5.43; N, 16.29.

***n*-Butyl 2-(5-ethyl-4,5-dihydro-4-oxo-[1,2,4]triazolo [4,3-a] quinoxalin-1-ylthio)acetate (13_e).** 2.95 g, (82%), mp 182-184° C; ir: CO 1670, 1741 cm^{-1} (amide and ester respectively); ms: *m/z* 360 (molecular ion) (33.77%), 287 (M+ $-OC_4H_7$) (11.94%), 259 (M+ $-COOC_4H_7$) (100%); *Anal.* Calcd. for $C_{17}H_{20}N_4O_3S$: C, 56.65; H, 5.59; N, 15.54. Found: C, 56.81; H, 5.60; N, 15.51.

***tert*-Butyl 2-(5-ethyl-4,5-dihydro-4-oxo-[1,2,4]triazolo [4,3-a]quinoxalin-1-ylthio)acetate (13_f).** 2.66 g, (74%), mp 170-172°C; ir: CO 1680, 1733 cm^{-1} (amide and ester respectively); ms: *m/z* 360 (molecular ion) (6.75%), 259 (M+ $-COOC_4H_7$) (100%), 231 (M+ $-COOC(CH_3)_3CO$) (25.68%); *Anal.* Calcd. for $C_{17}H_{20}N_4O_3S$: C, 56.65; H, 5.59; N, 15.54. Found: C, 56.71; H, 5.42; N, 15.32.

1-(2-Oxopropylthio)-5-ethyl-[1,2,4]triazolo[4,3-a]quinoxalin-4 (5H)-one (14). A mixture of 2.84 g (0.01 mol) of the potassium salt **(11)** and 1.00 mL (0.012 mol) chloroacetone in 20 mL DMF was heated on a water bath for 2h. After cooling to the room temperature, the reaction mixture was added to 200 mL cold water with continuous stirring. The white precipitated product was filtered, washed with water and crystallized from ethanol producing 1.87 g (62%), mp 206-208°C; ir: CO 1671, 1712 cm^{-1} (amide and ketone respectively); ms: *m/z* 302 (molecular ion) (10.19%), 259 (M+ −CO CH_3) (57.32%), 43 (CH_3CO) (100%); *Anal.* Calcd. for $C_{14}H_{14}N_4O_2S$: C, 55.61; H, 4.67; N, 18.53. Found: C, 55.84; H, 4.74; N, 18.87.

2-(5-Ethyl-4,5-dihydro-4-oxo-[1,2,4]triazolo[4,3-a]quinoxalin-1-ylthio)acetonitrile (15). A mixture of 2.84 g (0.01 mol) of the potassium salt **(11)** and 0.68 mL (0.01 mol) chloroacetonitrile in 20 mL DMF was heated on a water bath for 2h. After cooling to the room temperature, the reaction mixture was added to 200 mL cold water with continuous stirring. The white precipitated product was filtered, washed with water and crystallized from methyl alcohol to produce 1.85 g (85%), mp 231-233°C; ir: CO 1666 (amide), C N 2243 cm^{-1}; ^1H NMR: δ 1.27 [t, 3H, C**H**$_3$-CH_2, J = 6.90 Hz], 4.33 [q, 2H, C**H**$_2$-CH_3, J = 6.90 Hz], 4.62 [s, 2H, S**CH**$_2$] and 7.43-8.26 [m, 4H, aromatic]; ms: *m/z* 285 (molecular ion) (100%), 257 (M+ CO) (61.66%), 242 (M+ $-C_2H_5N$) (46.06%); *Anal*. Calcd. for $C_{13}H_{11}N_5OS$: C, 55.61; H, 4.67; N, 18.53. Found: C, 55.84; H, 4.74; N, 18.87.

2-(5-Ethyl-4,5-dihydro-4-oxo-[1,2,4]triazolo[4,3-a]quinoxalin-1-ylthio)acetic acid (16). A mixture of 2.85 g (0.01 mol) of A mixture of 1-cyanomethylthio-5-ethyl-[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-one **(15)** and 0.56 mL (0.01 mol) potassium hydroxide in 20 mL water was heated under reflux for 3 h. After cooling to the room temperature, the reaction mixture was added to 200 mL cold water with continuous stirring and acidified with 20 mL HCl (1N). The obtained white precipitate was filtered, washed with water, and recrystallized from ethanol to afford 2.43 g I(80%) of compound **(16)**, mp 242-244°C; ir: OH 3346 (broad), CO 1681, 1718 cm^{-1} (amide and carboxylic respectively); ms: *m/z* 304 (molecular ion) (3.32%), 259 (M+ −COOH) (21.15%), 245 (M+ $-CH_2COOH$) (100%); *Anal*. Calcd. for $C_{13}H_{12}N_4O_3S$: C, 51.31; H, 3.97; N, 18.41. Found: C, 51.48; H, 3.90; N, 18.52.

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