Bioorganic & Medicinal Chemistry Letters 21 (2011) 1253–1256

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of new anti-depressants from structurally novel 5-HT$_3$ receptor antagonists: Design, synthesis and pharmacological evaluation of 3-ethoxyquinoxalin-2-carboxamides

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ARTICLE INFO

Article history:
Received 20 September 2010
Revised 13 December 2010
Accepted 15 December 2010
Available online 19 December 2010

Keywords:
Quinoxalines
5-HT$_3$ receptor antagonists
Anti-depressants
Forced swim test
Serotonin
Spontaneous locomotor activity

ABSTRACT

A novel series of 3-ethoxyquinoxalin-2-carboxamides were designed as per the pharmacophoric requirements of 5-HT$_3$ receptor antagonist using ligand-based approach. The desired carboxamides were synthesized from the key intermediate, 3-ethoxyquinoxalin-2-carboxylic acid by coupling with appropriate amines in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) and 1-hydroxybenzotriazole (HOBt). The 5-HT$_3$ receptor antagonism was evaluated in longitudinal muscle myenteric plexus preparation from guinea pig ileum against 5-HT$_3$ agonist, 2-methy-5-HT, which was expressed in the form of pA_2 values. Compound **6h** (3-ethoxyquinoxalin-2-yl)(4-methylpiperazin-1-yl)methanone was found to be the most active compound, which expressed a pA_2 value of 7.7. In forced swim test, the compounds with higher pA_2 value exhibited good anti-depressant-like activity and compounds with lower pA_2 value failed to show activity as compared to the vehicle-treated group.

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5-Hydroxytrptamine (5-HT, serotonin) a neurotransmitter distributed in both peripheral and central nervous system, involved in various physiological and patho-physiological conditions, acting through the receptor subtypes (5-HT$_{1-7}$).[1] Among these receptor subtypes, 5-HT$_3$ is unique and is a ligand gated ion channel receptor,[2] whereas other receptor subtypes belong to the super family of G-protein coupled receptor (GPCR). Antagonists to this receptor, displayed anti-emetic action in cancer chemo-/radio-therapy induced nausea and vomiting. In addition, they were also found to exhibit anti-depressant, anxiolytic, anti-psychotic and anti-inflammatory activities in pre-clinical studies.[3–8] Antagonizing this ligand gated ion channel receptor for the beneficial of depression would have added advantage as most of the classical anti-depressants such as MAO inhibitors and tricyclic anti-depressants are unfortunately well known for their drug–drug/–food interaction and side-effects (anti-cholinergic, cardiovascular) rather than their efficacy.[9,10] The recent introduction of SSRI's; anti-depressants with lesser side-effects, improved the clinical management of depression. However, these drugs also shared the delayed onset of action like classical anti-depressants. Further all the clinically useful agents possess withdrawal syndrome, except agomelatine.[11] This information emphasizes the demand of newer anti-depressants with a safer and faster onset of action.

Previous research works in this area by our group[12–14] and other researchers[3–6] have indicated the beneficial effects of 5-HT$_3$ antagonists in depression and other central nervous system disorders. Standard anti-depressants such as mirtazapine and mianserin have been observed to possess serotonin type 3 receptor antagonism in addition to 5-HT$_{2A}$, 5-HT$_{2C}$ and α_2 antagonism.[15] The well known 5-HT$_3$ receptor antagonists such as ondansetron, granisetron (Fig. 1), etc. exhibit their anti-emetic action with negligible or fewer side-effects. It was thought worthwhile to investigate 5-HT$_3$ receptor antagonists that would have the beneficial role in the treatment of depression. Though, the existing 5-HT$_3$ receptor antagonists have negligible side-effects, most of the compounds possess chiral centre(s), which increases the synthetic cost of these

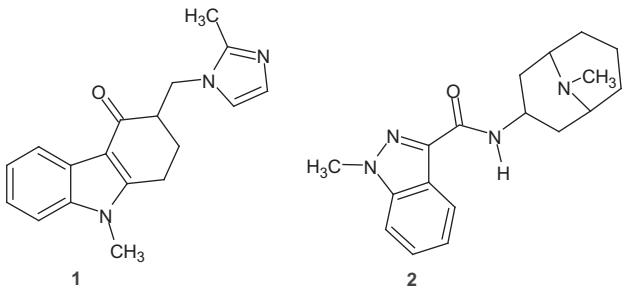

Figure 1. Chemical structures of (**1**) ondansetron (**2**) granisetron.

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doi:10.1016/j.bmcl.2010.12.064

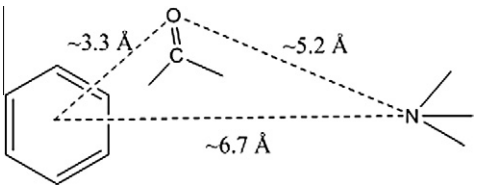


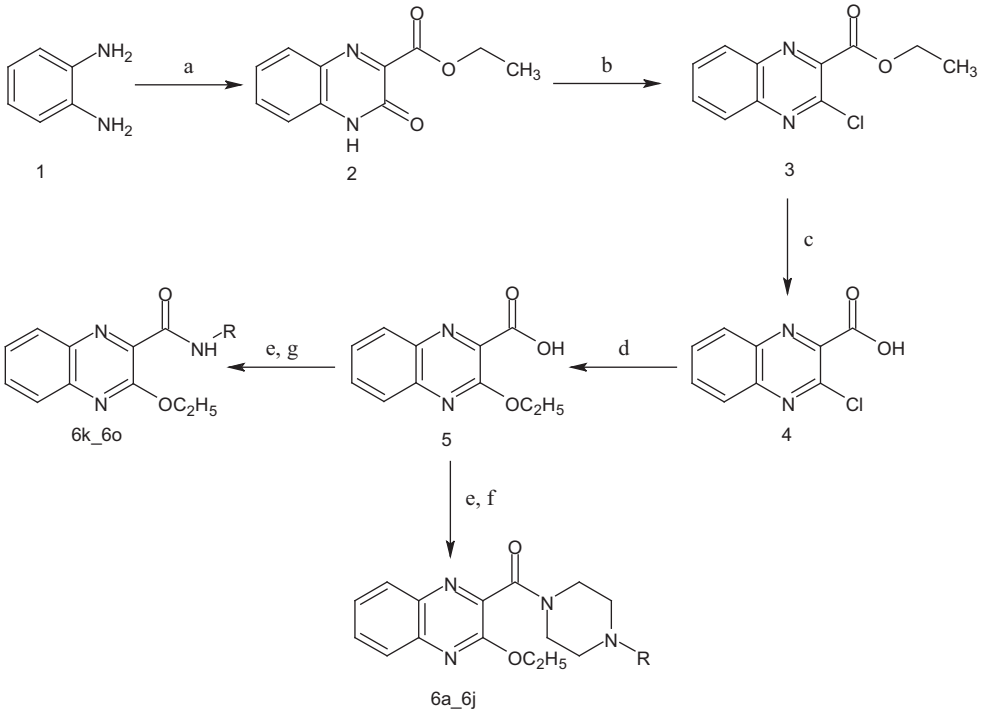
Figure 2. Basic pharmcophore of 5-HT_3 receptor antagonists.

drugs.[16] Further, very few selective 5-HT_3 antagonists are available and hence the need of newer 5-HT_3 antagonists are emphasized. Several new chemical entities for 5-HT_3 receptor antagonists have been reported so far[17,18] based on the Hibert et al. pharmacophore model[19] which consists of an aromatic ring, a linking carbonyl group and a basic nitrogen centre at specific distances (Fig. 2). In our previous study,[20] various 3-substituted quinoxalin-2-carboxamides were evaluated (consists of Mannich base as linking unit for piperazine moiety and quinoxaline nucleus) as 5-HT_3 receptor antagonists; unfortunately none of the synthesized compound exert their antagonism greater than or equal to standard 5-HT_3 receptor antagonists, ondansetron. Keeping these aspects in mind, the present study was aimed to develop newer 5-HT_3 receptor antagonists without chiral center. Attempts were focused on developing 3-ethoxyquinoxlin-2-carboxamides without Mannich base as potential 5-HT_3 receptor antagonists for the management of depression.

Objective of the present study was to develop newer antidepressants from structurally novel 5-HT_3 receptor antagonists. Molecules were designed as 5-HT_3 receptor antagonists based on the Hibert et al. pharmacophore model, as mentioned above. The minimum energy conformation (three least energy conformations for each compound) of the designed molecules were generated by ACDLABS-10.0/3D Viewer (CHARMM parameterization) and the pharmacophoric distances measured from centroid of quinoxaline ring to oxygen of the carbonyl group, carbonyl oxygen to basic nitrogen atom (N^4 of piperazines, heterocyclic nitrogen and nitrogen of tertiary amines) and centroid of quinoxaline residue to basic nitrogen. The distances between the pharmacophoric elements of the designed compounds were complied with the abovementioned pharmacophore model. Compounds **6m** and **6n** showed slight variation in the distances between centroid of quinoxaline to basic nitrogen (Supplementary data). To attain better pharmacokinetic properties that is absorption, distribution, metabolism, and elimination the "Lipinski rules of five" was also adopted for the designed molecules.[21]

The synthetic protocols of the target compounds are illustrated in the Scheme 1. The titled compounds were synthesized from the starting material, *o*-phenylenediamine (**1**) in a sequence of reactions. Initial condensation with diethyl ketomalonate followed by chlorination using phosphorous oxychloride, afforded the chloro ester compound (**3**) which on saponification followed by nucleophilic displacement with sodium ethoxide furnished the intermediate, 3-ethoxyquinoxalin-2-carboxylic acid (**5**). The carboxylic acid group of the key intermediate (**5**) was amidated with appropriate amines (aryl/alkyl substituted piperazines and primary amines) via active ester formation with the aid of EDC·HCl and HOBt to afford the desired product in good to excellent yields. IR spectral analysis of the final compounds (**6k–6o**) showed absorption bands at $3300 \pm 50\ cm^{-1}$ due to N–H stretching, C=O stretching vibrations of secondary (**6k–6o**) and tertiary carboxamides (**6a–6j**) showed absorption bands at $1680 \pm 20\ cm^{-1}$ and $1650 \pm 20\ cm^{-1}$, respectively. The molecular ion of the final compounds were observed as $(M+1)^+/(M+Na)^+$ in mass spectra. Physical constants of the title compounds are represented in the Table 1.

All the animals were obtained from Hissar Agricultural University, Hissar, Haryana, India and maintained in colony cages at 23 ± 2 °C, relative humidity of 45–55%, 12 h light/dark cycle and fed with standard animal feed and water ad libitum. The Institutional Animal Ethics Committee of the Birla Institute of Technology and Science, Pilani, India, approved the experimentation on animals (Protocol No. IAEC/RES/04/01/Rev 01, dated 13.08.08).



Scheme 1. Synthetic route of 3-ethoxyquinoxalin-2-carboxamides. Reagents and conditions: (a) Diethyl ketomalonate, ethanol, reflux, 6 h, 60%; (b) $POCl_3$, DMF, reflux, 30 min 80%; (c) 10% aq NaOH, rt, 1 h, dil HCl, 90% or Na_2CO_3, reflux, 6 h, dil HCl, 94%; (d) $NaOCH_2CH_3$, ethanol, MW, 6 min, dil HCl, 85%; (e) EDC·HCl, HOBt, THF, N_2, 0 °C–rt, 1 h; (f) piperazines, 6 h; (g) R-NH_2, 6 h.

Table 1
Physical constants of 3-ethoxyquinoxalin-2-carboxamides

Compd	R	% Yield[a]	Mp in °C	Molecular formula[c]	Log *P*[d]
6a	C_6H_5-	80	100–102	$C_{21}H_{22}N_4O_2$	3.76
6b	*o*-MeO-C_6H_4-	76	102–104	$C_{22}H_{24}N_4O_3$	3.64
6c	*p*-MeO-C_6H_4-	73	94–96	$C_{22}H_{24}N_4O_3$	3.64
6d	*p*-Cl-C_6H_4-	69	140–142	$C_{21}H_{21}ClN_4O_2$	4.32
6e	*m*-Cl-C_6H_4-	85	74–76	$C_{21}H_{21}ClN_4O_2$	4.32
6f	*m*-CF_3-C_6H_4-	88	128–130	$C_{22}H_{21}F_3N_4O_2$	4.69
6g	C_6H_5-CH_2-	75	238–240[b]	$C_{22}H_{24}N_4O_2$	3.42
6h	CH_3-	77	Semi solid	$C_{16}H_{20}N_4O_2$	1.69
6i	CH_3-CH_2-	69	Semi solid	$C_{17}H_{22}N_4O_2$	2.03
6j	CH_2=CH-CH_2-	64	Semi solid	$C_{18}H_{22}N_4O_2$	2.38
6k	$(Me)_2N$-CH_2-CH_2-	72	Semi solid	$C_{15}H_{20}N_4O_2$	1.70
6l	$(Et)_2N$-CH_2-CH_2-	68	Semi solid	$C_{17}H_{24}N_4O_2$	2.37
6m	2-(Indol-3yl)ethyl-	78	114–116	$C_{21}H_{20}N_4O_2$	3.25
6n	*p*-$N(Et)_2$-C_6H_4-	89	96–100	$C_{21}H_{24}N_4O_2$	4.32
6o	3-Pridyl-	66	116–118	$C_{16}H_{14}N_4O_2$	2.02

[a] Yields are refers to isolated pure compound.
[b] Melting point was recorded in hydrochloride salt form.
[c] Elemental (C, H, and N) analysis indicated that the calculated and observed values were within the acceptable limits (±0.4%).
[d] Log *P* values are calculated by using CHEMBIODRAW Ultra 11 (Cambridge Software).

Compounds were assessed for their serotonin type-3 receptor antagonism in male Dunkin Hartley guinea pigs (350–400 g) and for spontaneous locomotor activity (SLA) and anti-depressants potentials in Swiss Albino mice (23 ± 2 g), respectively.

The target new chemical entities were evaluated for their 5-HT_3 receptor antagonisms in longitudinal muscle myenteric plexus preparation from guinea pig ileum against 5-HT_3 agonist, 2-methy-5-HT. Antagonism was expressed as pA_2 values, which was determined according to the literature methods[20,22–24] and the results are summarized in the Table 2. Phenylpiperazine was coupled with 3-ethoxyquinoxalin-2-carboxylic acid, the formed carboxamide **6a**, showed mild antagonism (pA_2: 5.0). In order to obtain potent antagonists, various substituents were introduced in the aromatic moiety (phenyl ring) of the piperazine. First, a methoxy group, an electron releasing substituent was introduced at 2nd position of phenyl ring resulting in improved antagonism, (pA_2: 7.0), which was greater than the standard drug, ondansetron (pA_2: 6.9). Potency of the carboxamide was slightly reduced while introducing methoxy substituent at 4th position of the phenyl ring. Replacement of electron releasing group with chlorine atom on the phenyl ring, increased the lipophilicity of the carboxamide **6d**, but reduced the potency (pA_2: 6.0) of the compound **6d**. On the other hand its regioisomer, compound **6e**[25] that is chloro substituent on the 3rd position of the phenyl ring displayed antagonism (pA_2: 6.6) closer to ondansetron. Increasing the electron withdrawing nature by introducing CF_3 group in place of chlorine atom, enhanced the lipophilicity of the formed carboxamide **6f** but markedly reduced its potency (pA_2: 5.1) as compared to the compound **6e**. Incorporation of methylene group between distal nitrogen of piperazine and phenyl group further weakened the antagonism, where the pA_2 value of the obtained compound **6g** was 4.6.

Next, aromatic radical on the distal nitrogen of the piperazine was replaced with aliphatic group (phenyl group replaced with methyl group) and the resultant carboxamide **6h**[26] showed prominent antagonism (pA_2: 7.7). Higher homologation of aliphatic radical on the distal nitrogen (methylpiperazine into ethylpiperazine) resulted in increased lipophilicity but no enhancement in the antagonism (pA_2: 7.5). Further, increasing the length of alkyl chain

Table 2
Pharmacological data of 3-ethoxyquinoxalin-2-carboxamides

Compd	Antagonism to 2-Me-5-HT (pA_2)[a]	Duration of immobility in seconds (FST)[b] Dose (mg/kg)			Locomotor scores[b] (10 min) Dose (mg/kg)		
		1.0	0.5	2.0	1.0	0.5	2.0
6a	5.0	134.0 ± 26.0*	—	—	382.3 ± 29.0	—	—
6b	7.0	113.3 ± 08.8*	115.3 ± 2.6*	122.0 ± 02.5*	360.0 ± 43.4	351.0 ± 32.5	366.3 ± 46.8
6c	6.8	114.6 ± 22.4*	159.0 ± 13.8	121.6 ± 06.4*	356.4 ± 56.5	352.3 ± 56.8	361.0 ± 46.6
6d	6.0	146.6 ± 20.4	—	—	364.1 ± 24.5	—	—
6e	6.6	110.6 ± 20.0*	83.6 ± 03.7*	76.6 ± 12.9*	351.5 ± 39.3	361.3 ± 45.5	358.0 ± 31.4
6f	5.1	148.0 ± 07.6	—	—	356.5 ± 22.4	—	—
6g	4.6	160.0 ± 23.0	—	—	366.2 ± 26.4	—	—
6h	7.7	94.0 ± 18.0*	125.0 ± 10.9*	130.0 ± 09.1*	349.6 ± 41.2	353.0 ± 51.5	356.3 ± 35.0
6i	7.5	98.0 ± 20.0*	159.3 ± 07.8	128.0 ± 01.5*	360.4 ± 28.9	349.3 ± 36.3	351.6 ± 46.4
6j	6.8	127.0 ± 13.0*	152.0 ± 05.8	118.0 ± 08.7*	360.1 ± 44.3	345.3 ± 39.7	351.6 ± 39.2
6k	6.9	117.7 ± 07.6*	133.6 ± 12.1	96.0 ± 03.0*	349.3 ± 47.8	345.0 ± 31.7	342.6 ± 33.0
6l	4.7	162.0 ± 21.0	—	—	362.2 ± 33.0	—	—
6m	7.2	104.0 ± 14.0*	150.3 ± 14.3	79.3 ± 21.8*	350.4 ± 45.4	366.3 ± 34.0	355.3 ± 46.9
6n	5.0	145.0 ± 21.0	—	—	374.0±29.0	—	—
6o	4.8	144.0 ± 18.0	—	—	365.0 ± 23.0	—	—
Ondansetron	6.9	100.4 ± 10.0*	130.2 ± 18.2*	95.1 ± 06.5*	388.1 ± 10.3	368.0 ± 12.0	400.0 ± 22.0
Control	—		165.6 ± 03.2			365.5 ± 49.4	

[a] pA_2 values are the means of two separate experiments. SE was less than 10% of the mean.
[b] 10% of PEG-400 in water was used as a vehicle, the values are expressed as mean, $n = 8$ per group. Data were analyzed by GRAPH PAD PRISM (3) software through one way ANOVA followed by post hoc Dunnett's test.
* $p < 0.05$ compared with vehicle-treated group (control).

on the distal nitrogen residue; introducing allyl group in place of ethyl group, yielded the carboxamide **6j**, whose antagonism (pA_2: 6.8) was nearly equal to ondansetron but less than that of compound **6h**. In final modification, to serve the role of piperazine (as basic nitrogen centre), various primary amines viz. *N*,*N*-dimethylethylenediamine, *N*,*N*-diethylethylenediamine, tryptamine, *N*,*N*-diethyl-*p*-phenylenediamine and 3-aminopyridine were coupled with 3-ethoxyquinoxalin-2-carboxylic acid. The obtained carboxamides (**6k–6o**) exhibited antagonism towards serotonin type-3 receptor, and among them **6m**[27] displayed antagonism (pA_2: 7.2) greater than the standard drug, followed by compound **6k**, which showed antagonism (pA_2: 6.9) equal to ondansetron.

Regardless of the 5-HT_3 receptor antagonistic potency, all the carboxamides were subjected to forced swim test (FST) in mice model,[13,28] to evaluate their anti-depressants activity. In the preliminary anti-depressant screening, test compounds were administered intra-peritonealy at a dose of 1 mg/kg body weight. Among the test compounds, **6h** and **6i** significantly reduced the duration of immobility in mice as compared to vehicle-treated group, followed by compound **6m**, **6e**, **6b**, **6k** and **6j**. The anti-depressant-like effect of compound **6h** and **6i** are greater than the positive control, ondansetron. Compounds with low pA_2 values failed to show anti-depressant-like effect on FST mice model. The drug-induced stimulation/sedation sometimes leads to false-positive/-negative results respectively in mice FST. In order to eliminate the same, all the screened molecules are subjected to SLA in actophotometer.[13] Interestingly, none of the tested compounds influenced the baseline locomotion of mice when observed in actophotometer, Table 2.

Based on the preliminary anti-depressant study a dose response assay was performed for the selected (active) compounds in mice FST and the results are summarized in Table 2. Compound **6b, 6e** and **6h** significantly reduced the duration of immobility of mice in all the tested doses. Whereas, compounds **6c**, **6m**, **6j**, **6k** and **6i** were active only at 1 and 2 mg/kg body weight and failed to show activity at lower dose (0.5 mg/kg body weight). The anti-depressant-like effect of compounds **6h**, **6b** and **6m** were greater than the standard drug, ondansetron at the dose of 0.5 and 2 mg/kg body weight, respectively. Compounds **6j**, **6k** and **6m** exhibited their anti-depressant-like effects in a dose-dependent manner; on the other hand **6e** displayed its activity in a biphasic way. The dose-dependent and biphasic-effects exerted by the synthesized compounds are in agreement with earlier reports on the effects of 5-HT_3 receptor antagonists in animal models of depression.[3,14] In this study, compounds with higher pA_2 values significantly reduced the duration of immobility of mice in FST, which indicates the beneficial effects of 5-HT_3 receptor antagonists in depression. However, to map the exact mechanism of these novel compounds, molecular and interaction studies are necessary, which is expected to be carried out separately as an extension of the present study.

In summary, a series of structurally novel 3-ethoxyquinoxalin-2-carboxamides were designed as 5-HT_3 receptor antagonists, using ligand-based approach and the target molecules were synthesized from the starting material *o*-phenylenediamine involving a sequence of reactions. All the synthesized compounds exhibited 5-HT_3 receptor antagonism, whereas compounds **6h**, **6i**, **6m** and **6b** showed antagonism greater than the standard drug, ondansetron. Compounds with higher pA_2 values significantly decreased the duration of immobility of mice in FST as compared to control group, reflecting their anti-depressant-like effect. The compounds with lower pA_2 values, failed to show activity as compared to the vehicle-treated group and these results correlated the beneficial effect of 5-HT_3 antagonists in depression. Further studies on these compounds are planned to obtain clinically useful anti-depressant agents.

Acknowledgments

We are thankful to University Grants Commission (UGC), New Delhi, India, for the financial support. We are grateful to Birla Institute of Technology & Science (BITS), Pilani, India for providing infrastructural facilities and SAIF, Panjab University, Chandigarh, India for providing analytical facilities.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.12.064.

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25. *(4-(3-Chlorophenyl)piperazin-1-yl)(3-ethoxyquinoxalin-2-yl)methanone* (**6e**): ^{1}H NMR ($CDCl_3$) δ ppm: 8.03 (d, 1H, quinoxaline), 7.86 (d, 1H, quinoxaline), 7.73 (m, 1H, quinoxaline), 7.62 (m, 1H, quinoxaline), 7.21 (t, 1H, phenyl), 6.88 (d, 2H, phenyl), 6.81 (t, 1H, phenyl) 4.64 (q, 2H, OCH_2), 4.03 (t, 2H, piperazine), 3.45 (t, 2H, piperazine), 3.35 (t, 2H, piperazine), 3.19 (t, 2H, piperazine), 1.48 (t, 3H, CH_3); Mass spectra (ESI) of the compound exhibited the molecular ion peak at *m*/*z* 396 $(M)^+$, 398 $(M+2)^+$; FT-IR (KBr, cm^{-1}): 3061, 2981, 2918, 2829, 1633, 1593, 1573, 1479, 1417, 1325, 1236, 1151, 1012, 941, 912, 754, 688.
26. *(3-Ethoxyquinoxalin-2-yl)(4-methylpiperazin-1-yl)methanone* (**6h**): ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ ppm: 8.11 (dd, 1H, quinoxaline), 7.86 (dd, 1H, quinoxaline), 7.74 (m, 1H, quinoxaline), 7.63 (m, 1H, quinoxaline), 4.60 (q, 2H, OCH_2), 3.96 (t, 2H, piperazine), 3.48 (t, 2H, piperazine), 2.70 (t, 2H, piperazine), 2.58 (t, 2H, piperazine), 2.40 (s, 3H, NCH_3), 1.48 (t, 3H, CH_3); Mass spectra (ESI) of the compound exhibited the molecular ion peak at *m*/*z* 301 $(M+1)^+$; FT-IR (KBr, cm^{-1}): 3080, 2966, 2939, 2902, 1651, 1579, 1415, 1319, 1294, 1267, 1217, 1028, 1155, 763, 609.
27. *N-(2-(1H-indol-3-yl)ethyl)-3-ethoxyquinoxaline-2-carboxamide* (**6m**): ^{1}H NMR ($CDCl_3$) δ ppm: 8.22 (br s, 1H, CO*NH*), 8.00 (dd, 1H, quinoxaline) 7.82 (dd, 2H, quinoxaline), 7.73 (m, 2H, 1H, quinoxaline, 1H, indole), 7.58 (d, 1H, NH indole), 7.39 (d, 1H, indole), 7.22 (m, 1H, indole), 7.13 (m, 2H, indole), 4.60 (q, 2H, OCH_2CH_3), 3.90 (q, 2H, NCH_2), 3.16 (t, 2H, NCH_2CH_2), 1.42 (t, 3H, OCH_2CH_3); Mass spectra (ESI) of the compound exhibited the molecular ion peak at *m*/*z* 361 $(M+1)^+$; FT-IR (KBr, cm^{-1}): 3278, 3184, 3041, 2989, 2951, 2914, 1666, 1588, 1514, 1462, 1369, 1222, 1136, 752, 773, 642.
28. Porsolt, R. D.; Bertin, A.; Jalfre, M. *Arch. Int. Pharmacodyn. Ther.* **1977**, *229*, 327.