Synthesis of Novel Drug-Like Small Molecules Based on Quinoxaline Containing Amino Substitution at C-2

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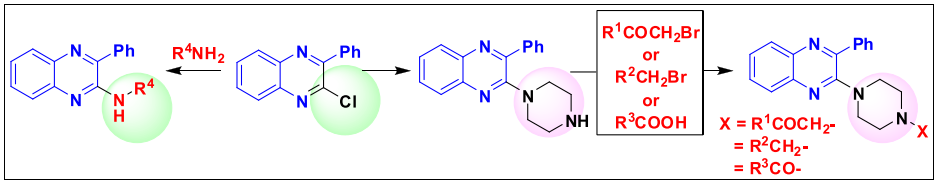

A series of novel "drug-like" small molecules based on quinoxaline containing amino substitution at C-2 were synthesized. All these molecules were prepared either via the reaction of 2-phenyl-3-(piperazin-1-yl) quinoxaline with acyl bromides or benzyl bromides or various carboxylic acids or via the reaction of 2-chloro-3-phenylquinoxaline with various amines. The structures of these novel compounds were confirmed by spectral analysis. The strategy used is simple and efficient and afforded good yields of quinoxaline derivatives.

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INTRODUCTION

Generation of a library of novel "drug-like" small molecules is of considerable importance as this can lead to the identification of preliminary hits required by pharmaceutical industries either via high throughput or traditional screen against various pharmacological targets.

Quinoxaline, an important class of fused N-heterocycle, has attracted considerable interest in the area of synthetic and medicinal chemistry [1,2] due to their broad-spectrum biological activities such as antiviral [3], antibacterial [4], anti-inflammatory [5], antiprotozoal [6], anticancer [7] (colon cancer therapies) [8], antidepressant [9], and anti-HIV [6], and as kinase inhibitors [10,11]. In particular, quinoxaline moiety has been found to be an integral part of several antibiotics such as echinomycin, levomycin, and actinoleutin that inhibit the growth of Gram-positive bacteria and showed activities against various transplantable tumors [12]. It is therefore evident that quinoxaline represents an attractive template for the design and discovery of potential new drugs. Moreover, the quinoxaline ring has been described as a bioisostere of quinoline, naphthalene, benzothiophene, and several other aromatic rings such as pyridine and pyrazine. A quinoxaline equivalent of bioactive molecules containing all these moieties therefore has high probability to show relevant pharmacological properties useful for the discovery of new chemical entities in a particular therapeutic area. Quinoxalines or analogues of quinoline derivatives possessing a piperizine ring at C-2 have shown remarkable 5-HT1A agonistic and 5-HT3 antagonistic activities as is exemplified by the discovery of TZB-30878 as an orally bioavailable agent for irritable bowel syndrome [13]. 2-Amino-substituted quinoxalines on the other hand have been reported as interleukin-8 receptor antagonists for the potential treatment of chemokine-mediated diseases [14]. These observations and our interest on quinoxalines [15–19] prompted us to devote our efforts toward the synthesis of novel quinoxaline derivatives (**C**, **D**, **E**, and **F**) containing amino substitution at C-2 (Fig. 1) of potential biological significance. In continuation of our interest in bioactive molecules [20–24], we now report our results on the library generation based on the scaffolds **C–F** by using efficient chemistry methodologies (Scheme 1).

RESULTS AND DISCUSSION

The key starting materials, that is, 2-chloro-3-phenylquinoxaline (**3**) and 2-phenyl-3-(piperazin-1-yl) quinoxaline (**4**) required for our synthesis, were prepared via a known method [13] as shown in Scheme 1.

We then prepared the 2-(4-(3-phenylquinoxalin-2-yl) piperazin-1-yl)ethanone derivatives **5** (or **C**, Fig. 2) by treating compound **4** with various acyl bromides in the presence of basic alumina in MeCN at room temperature for 10–12 h (Scheme 2). The alumina, most commonly used to perform surface chemistry [25], is basic in nature and possesses a large surface area and highly porous exteriors available to substrates. Unlike clays and zeolites, the basic alumina does not contain accessible channels or

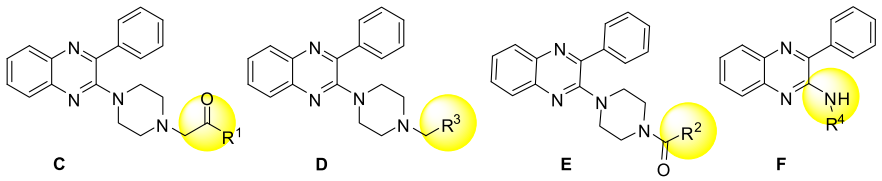
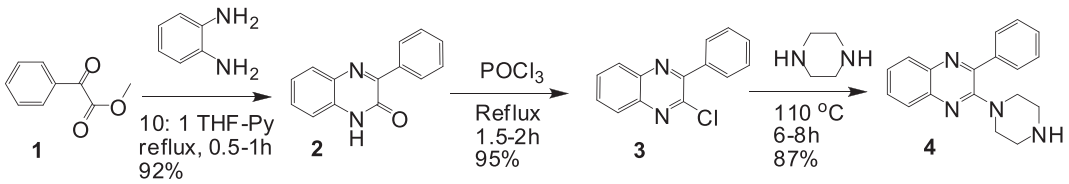


Figure 1. Novel quinoxaline derivatives (**C–F**) containing amino substitution at C-2. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Scheme 1. Preparation of starting material **3** and **4**.



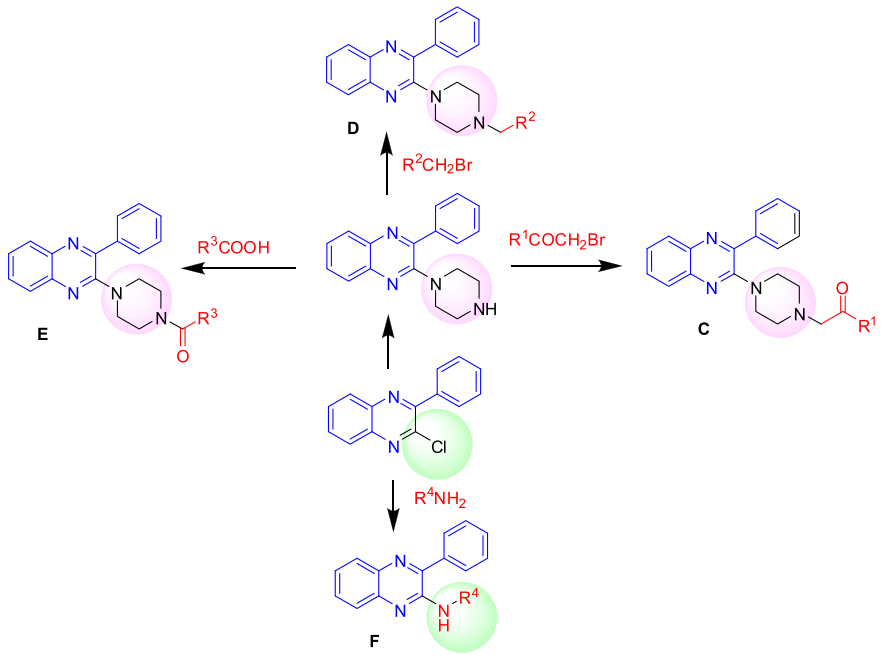
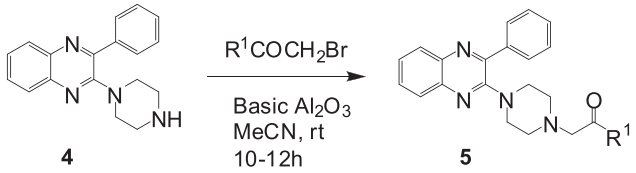


Figure 2. Library generation based on the drug-like scaffolds **C–F**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Scheme 2. Preparation of 1-(4-(3-phenylquinoxalin-2-yl)piperazin-1-yl)ethanone derivatives **5**.



5; R^1 =	% yield
5a; 1,1'-Biphenyl-4-yl	92
5b; Naphthalen-1-yl	90
5c; Phenyl	94
5d; 4-(Trifluoromethyl)phenyl	83

cavities. While as a heterogeneous catalyst it has attracted considerable attention in the organic synthesis, its use has not been explored extensively to date. The present example of alumina-mediated N-alkylation of a secondary amine **4** is not common in the literature. Nevertheless, the desired N-alkylated products **5** were obtained in 83–92% yield under mild conditions, demonstrating the potential of this methodology.

The 2-(4-benzylpiperazin-1-yl)-3-phenylquinoxaline derivatives **6** (or **D**, Fig. 2) were prepared by treating compound **4** with a number of benzyl bromides in the presence of TEA in MeCN at room temperature for 10–12 h (Scheme 3). The reaction proceeded smoothly affording the desired products **6** in 83–93% yield.

The *N*-acyl/aryl derivatives 7 (or **E**, Fig. 2) were prepared by reacting compound **4** with various carboxylic acids in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and TEA in DMF at room temperature for 8–10 h (Scheme 4). The aryl, heteroaryl, and aliphatic carboxylic acids were used in these reactions to afford the desired products **7** in 78–82% yield.

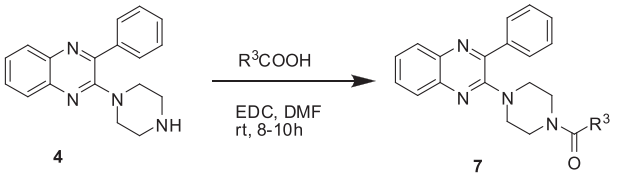
The 2-anilino-3-phenyl quinoxaline derivatives **8** (or **F**, Fig. 2) were prepared by reacting the chloro compound **3** with various amines at 100–110°C for 8–10 h in the absence of any solvent (Scheme 5). Both aryl and alkylaryl amines participated well in these reactions affording the desired products in high yields.

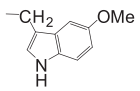
All the compounds synthesized were well characterized by spectral (^{1}H and ^{13}C NMR, MS, and HRMS) data. For example, compound **5** showed the NCH_2CO signal as a singlet in the range 3.9–4.0 δ in the ^{1}H NMR and carbonyl signal in the range 195–197 ppm in the ^{13}C NMR spectra. Compound **6** showed the CH_2 signal as a singlet near 3.5 δ. Compound **7** showed the CO signal in the range 160–172 ppm in the ^{13}C NMR spectra. Satisfactory HRMS data were also obtained for all these compounds, that is, **5–8**, indicating the formation of the desired quinoxaline derivatives.

Scheme 3. Preparation of 2-(4-benzylpiperazin-1-yl)-3-phenylquinoxaline derivatives **6**.

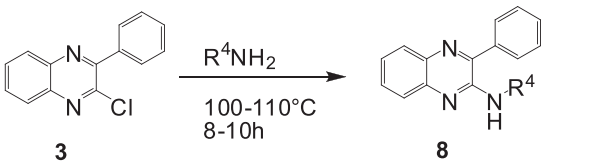
6; R^2 =	% yield
6a; C_6H_4CN-*p*	83
6b; $C_6H_4Bu^t$-*p*	93
6c; C_6H_4OMe-*p*	90
6d; $C_6H_4OCF_3$-*p*	86
6e; C_6H_3 (di-Me)-m,*p*	85

Scheme 4. Preparation of *N*-acyl/aryl derivatives **7**.



7; R^3 =	% yield
7a; 	84
7b; Furan-2-yl	89
7c; Thiophen-2-yl	92
7d; Cyclopropyl	82
7e; 4-(tert-butyl)phenyl	86
7f; 4-Fluorophenyl	78

Scheme 5. Preparation of 2-anilino-3-phenyl quinoxaline derivatives **8**.



8; R^4 =	% yield
8a; 4-(*tert*-butyl)phenyl	90
8b; $C_6H_4OCF_3$-*p*	80
8c; $C_6H_4CF_3$-*p*	82
8d; $CH_2C_6H_4OMe$-*p*	92

CONCLUSIONS

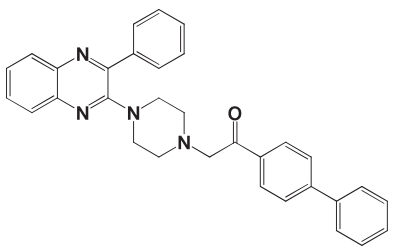
In conclusion, we have explored quinoxaline as a template for the generation of a library of novel drug-like small molecules of potential biological significance. These molecules were designed by introducing an amino substituent at C-2 of the quinoxaline ring. All these molecules were prepared either via the reaction of 2-phenyl-3-(piperazin-1-yl)quinoxaline with acyl bromides or benzyl bromides or various carboxylic acids or via the reaction of 2-chloro-3-phenylquinoxaline with various amines. The structures of these novel compounds were confirmed by spectral analysis. The strategy used for the present synthesis is simple and efficient and afforded good yields of the desired quinoxaline derivatives. It is therefore amenable for the generation of diversity-based small molecules related to the quinoxaline framework of potential pharmacological interest.

EXPERIMENTAL

All the reactants and reagents were used as received from commercial sources without further purification or prepared as described in the literature. Reactions were stirred using Teflon-coated magnetic stirring bars (IKA India Private Limited, Bangalore, India). TLC plates were visualized by UV light or by treatment with a spray of Pancaldi reagent {$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O}. Chromatographic purification of products was carried out by flash column chromatography on silica gel (230–400 mesh). Melting points were determined using an electrothermal melting point apparatus and are uncorrected. NMR spectra were measured in $CDCl_3$, acetone, DMSO-d_6 (all with TMS as internal standard) on a Varian Gemini 400-MHz FT NMR spectrometer magnetic resonance spectrometer (California, USA). Chemical shifts (δ) are reported in parts per million, and coupling constants (*J*) are in Hertz. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Mass spectra were recorded on an HP-5989A quadrapole mass spectrometer (Agilent Technologies, Texas, USA).

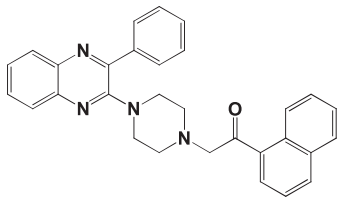
General procedure for the synthesis of compound 5. A mixture of 2-phenyl-3-(piperazin-1-yl)quinoxaline (**4**, 1.0 equiv), acyl bromide (1.0 equiv), and basic alumina (0.5 w/w) in acetonitrile (5 mL) was stirred at room temperature for 10–12 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mass was filtered and washed with acetonitrile (1 mL). Filtrates were collected, combined, and concentrated under reduced pressure. The crude product isolated was purified by column chromatography using EtOAc/*n*-hexane (20:80) on 230–400 silica gel.

1-([1, 1'-Biphenyl]-4-yl)-2-(4-(3-phenylquinoxalin-2-yl) piperazin-1-yl) ethanone (5a).



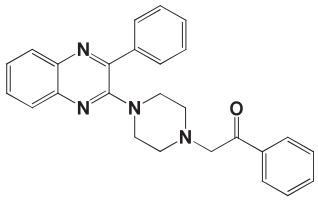
Yellow color solid; mp: 164–168°C, yield: 92%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.50 (t, J = 2.0 Hz, 4H, 2 × CH_2), 3.2 (t, J = 2.1 Hz, 4H, 2 × CH_2), 3.91 (s, 2H, N–CH_2), 7.48–7.55 (m, 7H, ArH), 7.73–7.82 (m, 6H, ArH), 7.96–7.98 (m, 3H, ArH), 8.08 (d, J = 8.4 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.5 (N–CH_2, 2 × CH_2), 52.5 (N–CH_2, 2 × CH_2), 64.6 (CH_2), 126.3, 126.9, 127.1 (2 × CH), 127.2 (2 × CH), 127.7 (2 × CH), 128.2, 128.7 (4 × CH), 128.9 (2 × CH), 129.2, 129.5, 134.6, 138.5, 139.3, 139.7, 140.3, 145.9, 148.2, 156.0, 158.6 (N═C–N), 195.0 (C═O); MS: *m/z* (%) = 485.3 (M + 1). HRMS: $[MH]^+$ 485.2357, calculated mass: 485.2341, molecular formula: $C_{32}H_{29}N_4O$.

1-(Naphthalen-1-yl)-2-(4-(3-phenylquinoxalin-2-yl)piperazin-1-yl)ethanone (5b).



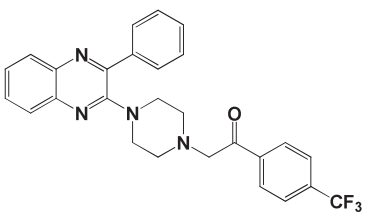
Yellow color solid; mp: 145–147°C, yield: 90%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.50 (t, J = 2.0 Hz, 4H, 2 × CH_2), 3.2 (t, J = 2.2 Hz, 4H, 2 × CH_2), 4.05 (s, 2H, N–CH_2), 7.52–7.68 (m, 8H, ArH), 7.92–8.00 (m, 6H, ArH), 8.12 (d, J = 8 Hz, 1H, ArH), 8.69 (d, J = 7.8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.4 (N–CH_2, 2 × CH_2), 52.9 (N–CH_2, 2 × CH_2), 64.5 (CH_2), 123.8, 126.3, 126.8, 126.9, 127.7 (2 x CH), 128.3, 128.5, 128.7 (3 × CH), 128.7, 129.2, 129.5 (2 × CH), 129.8, 132.4,133.2, 135.6, 138.5, 139.5, 140.3, 148.2, 154.0 (N═C–N), 196.2 (C═O); MS: *m/z* (%) = 459.2 (M + 1). HRMS: $[MH]^+$ 459.2203, calculated mass: 459.2185, molecular formula: $C_{30}H_{27}N_4O$.

1-Phenyl-2-(4-(3-phenylquinoxalin-2-yl) piperazin-1-yl) ethanone (5c).



Yellow color solid; mp: 130–133°C, yield: 94%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.50 (t, J = 2.0 Hz, 4H, 2 × CH_2), 3.2 (t, J = 2.2 Hz, 4H, 2 × CH_2), 3.89 (s, 2H, N–CH_2), 7.49–7.56 (m, 6H, ArH), 7.58–7.63 (m, 2H, ArH), 7.78 (d, J = 7.6 Hz, 1H, ArH), 7.91–7.98 (m, 5H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 48.2 (N–CH_2, 2 × CH_2), 51.8 (N–CH_2, 2 × CH_2), 63.4 (CH_2), 126.4, 126.5, 127.6 (2 × CH), 128.0 (2 × CH), 128.3 (3 × CH), 128.5 (2 × CH), 129.3, 129.8, 133.2, 135.8, 137.8, 138.9, 139.6, 147.7, 153.6 (N═C–N), 196.8 (C═O); MS: *m/z* (%) = 409.3 (M + 1). HRMS: $[MH]^+$ 409.2047, calculated mass: 409.2028, molecular formula: $C_{26}H_{25}N_4O$.

2-(4-(3-Phenylquinoxalin-2-yl)piperazin-1-yl)-1-(4-(trifluoromethyl)phenyl)ethanone (5d).

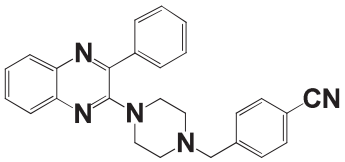


Brown color syrup; yield: 83%;^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.60 (t, J = 2.0 Hz, 4H, 2 × CH_2), 3.2 (t, J = 2.2 Hz, 4H, 2 × CH_2), 3.90 (s, 2H, N–CH_2), 7.51–7.58 (m, 5H, ArH), 7.60–7.70 (m, 2H, ArH), 7.87–7.97 (m, 4H, ArH), 8.01–8.17 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.3 (N–CH_2, 2 × CH_2), 52.7 (N–CH_2, 2 × CH_2), 64.7 (CH_2), 125.0, 125.5, 126.4, 126.9, 127.0 (2 × CH), 127.3 (2 × CH), 127.7 (2 × CH), 128.7 (2 × CH), 128.8 (2 × CH), 129.0, 129.3, 130.0, 130.3, 147.80, 152.9, 171.2 (N═C–N), 195.9 (C═O); MS: *m/z* (%) = 477.2 (M + 1). HRMS: $[MH]^+$ 477.1990, calculated mass: 477.1902, molecular formula: $C_{27}H_{24}N_4OF_3$.

General procedure for the synthesis of compound 6. A mixture of 2-phenyl-3-(piperazin-1-yl)quinoxaline (**4**, 1.0 equiv), alkyl bromide (1.0 equiv), and TEA (2.0 equiv) in acetonitrile (5 mL) was stirred at room temperature for 10–12 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was concentrated under reduced pressure. The crude product isolated was purified by

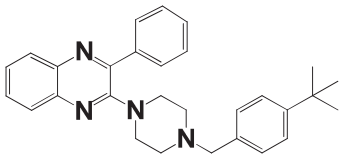
column chromatography using EtOAc/*n*-hexane (20:80) on 230–400 silica gel.

4-((4-(3-Phenylquinoxalin-2-yl)piperazin-1-yl)methyl)benzonitrile (6a).



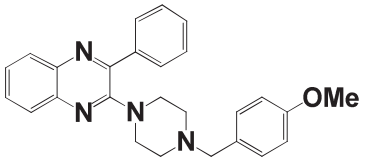
Yellow color solid; mp: 140–143°C, yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.46 (t, J = 2.0 Hz, 4H, 2 × CH_2), 3.3 (t, J = 2.2 Hz, 4H, 2 × CH_2), 3.56 (s, 2H), 7.42–7.63 (m, 9H, ArH), 7.81 (d, J = 6.8 Hz, 1H, ArH), 7.95–7.99 (m, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.6 (N–CH_2, 2 × CH_2), 52.6 (N–CH_2, 2 × CH_2), 62.3 (CH_2), 110.9, 118.9, 126.4, 126.9, 127.8 (2 × CH), 128.7 (2 × CH), 129.2 (2 × CH), 129.4 (2 × CH), 129.6 (2 × CH), 132.1 (2 × CH), 138.6, 139.5, 140.3, 148.2, 154.0; MS: *m/z* (%) = 406.20 (M + 1). HRMS: $[MH]^+$ 406.2043, calculated mass: 406.2032, molecular formula: $C_{26}H_{24}N_5$.

2-(4-(4-(tert-Butyl) benzyl) piperazin-1-yl)-3-phenylquinoxaline (6b).



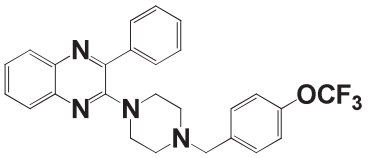
Pale yellow solid; mp: 128–130°C, yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (s, 9H, 3 × CH_3), 2.45 (t, J = 2.1 Hz, 4H, 2 × CH_2), 3.3 (t, J = 2.2 Hz, 4H, 2 × CH_2), 3.49 (s, 2H, CH_2), 7.22–7.32 (m, 2H, ArH), 7.45–7.50 (m, 7H, ArH), 7.82 (d, J = 7.8 Hz, 1H, ArH), 7.95–7.97 (m, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.3 (3 × CH_3), 34.4, 48.6 (N–CH_2, 2 × CH_2), 52.6 (N–CH_2, 2 × CH_2), 62.5 (CH_2), 125.5 (2 × CH), 126.2, 126.8, 127.8 (2 × CH), 128.7 (4 × CH), 128.8 (2 × CH), 129.2, 129.5, 138.5, 139.6, 140.4, 148.2, 150.0, 154.2; MS: *m/z* (%) = 437.3 (M + 1). HRMS: $[MH]^+$ 437.2715, calculated mass: 437.2705, molecular formula: $C_{29}H_{33}N_4$.

2-(4-(4-Methoxybenzyl) piperazin-1-yl)-3-phenylquinoxaline (6c).



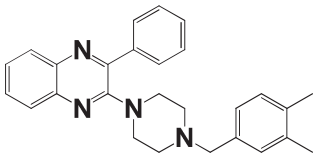
Yellow color solid; mp: 144–146°C, yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, 4H, 2 × CH_2), 3.3 (s, 4H, 2 × CH_2), 3.46 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 6.83 (d, J = 7.8 Hz, 2H, ArH), 6.85–7.23 (m, 2H, ArH), 7.40–7.50 (m, 5H, ArH), 7.82, (d, J = 8.0 Hz, 1H, ArH), 7.65–7.97 (m, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.5 (N–CH_2, 2 × CH_2), 52.4 (N–CH_2, 2 × CH_2), 55.2 (CH_3), 62.2 (CH_2), 113.7 (2 × CH), 126.1, 126.9, 127.8 (2 × CH), 128.6 (2 × CH), 128.7, 129.1, 129.4, 129.7, 130.2 (2 × CH), 138.5, 139.6, 140.4, 148.1, 156.0, 158.9; MS: *m/z* (%) = 411.20 (M + 1). HRMS: $[MH]^+$ 411.2196, calculated mass: 411.2185, molecular formula: $C_{26}H_{27}N_4O$.

2-Phenyl-3-(4-(4-(trifluoromethoxy)benzyl)piperazin-1-yl) quinoxaline (6d).



Brown color syrup; yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.45 (t, J = 4.8 Hz, 4H, 2 × CH_2), 3.30 (t, J = 5.0 Hz, 4H, 2 × CH_2), 3.51 (s, 2H, CH_2), 7.13 (d, J = 8.0 Hz, 2H, ArH), 7.44–7.51 (m, 6H, ArH), 7.60 (t, J = 7.0 Hz, 1H, ArH), 7.80 (d, J = 7.0 Hz, 1H, ArH), 7.95–7.97 (m, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.6 (N–CH_2, 2 × CH_2), 52.5 (N–CH_2, 2 × CH_2), 62.0, 119.3 (2 × CH), 120.7 (2 × CH), 121.7, 126.3, 126.9, 127.8 (2 × CH), 128.7 (2 × CH), 129.2, 129.5, 130.2 (2 × CH), 136.8, 138.5, 139.5,140.3, 148.2, 154.1; MS: *m/z* (%) = 465.20 (M + 1). HRMS: $[MH]^+$ 465.1917, calculated mass: 465.1902, molecular formula: $C_{26}H_{24}N_4OF_3$.

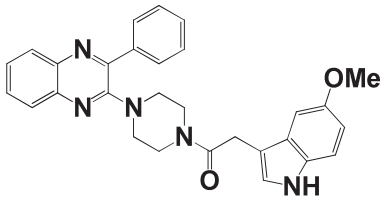
2-(4-(3,4-Dimethylbenzyl)piperazin-1-yl)-3-phenylquinoxaline (6e).



Yellow color solid; mp: 165–167°C, yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.22–2.31 (m, 6H, 2 × CH_3), 2.44 (t, J = 2.8 Hz, 4H, 2 × CH_2), 3.32 (t, J = 2.2 Hz, 4H, 2 × CH_2), 3.43 (s, 2H, CH_2), 7.95–7.97 (m, 2H, ArH), 7.10 (d, J = 6.8 Hz, 1H, ArH), 7.57–7.61 (m, 4H, ArH), 7.43–7.50 (m, 1H, ArH), 7.80 (d, J = 7.6 Hz, 1H, ArH), 7.95–7.97 (m, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.2 (CH_3), 21.0 (CH_3), 48.5 (N–CH_2, 2 × CH_2), 52.3 (N–CH_2, 2 × CH_2), 60.4 (CH_2), 126.1, 126.2, 126.8, 127.7 (2 × CH), 128.6 (4 × CH), 129.2, 129.4, 129.9, 131.1 (2 × CH), 137.3,138.5, 139.5, 140.3, 148.3, 154.1; MS: *m/z* (%) = 409.30 (M + 1). HRMS: $[MH]^+$ 409.2394, calculated mass: 409.2392, molecular formula: $C_{27}H_{29}N_4$.

General procedure for the synthesis of compound 7. A mixture of 2-phenyl-3-(piperazin-1-yl) quinoxaline (**4**, 1.0 equiv), appropriate carboxylic acid (1.0 equiv), EDC (1.5 equiv), and TEA (2.0 equiv) in DMF (5 mL) was stirred at room temperature for 8–10 h. The progress of the reaction was monitored by TLC. After completion of the reaction, water (25 mL) followed by EtOAc (25 mL) was added to the reaction mass. The separated organic layer was collected, washed with water (25 mL), and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/*n*-hexane (20:80) on 230–400 silica gel.

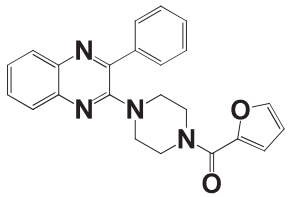
2-(5-Methoxy-1H-indol-3-yl)-1-(4-(3-phenylquinoxalin-2-yl) piperazin-1-yl)ethanone (7a).



Yellow color solid; mp: 110–112°C, yield: 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.14 (t, J = 4.8 Hz, 2H, CH_2), 3.22

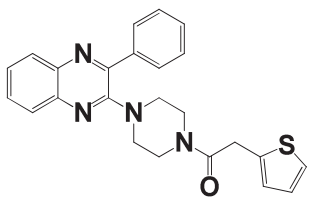
(t, J = 5.0 Hz, 2H, CH_2), 3.51 (t, J = 4.6 Hz, 2H, CH_2), 3.67 (t, J = 4.6 Hz, 2H, CH_2), 3.80 (s, 2H), 3.85 (s, 3H, OCH_3), 6.85 (dd, J = 2.4 Hz,1H, ArH), 7.05 (s, 2H, ArH), 7.25 (s, 1H, NH), 7.45–7.64 (m, 5H, ArH), 7.81 (dd, J = 1.2 Hz, 1H, ArH), 7.93–7.99 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 41.1 (CH_2), 45.5 (N–CH_2, 2 × CH_2), 48.6 (N–CH_2, 2 × CH_2), 55.8 (CH_3), 100.3, 108.6, 111.9, 112.5, 122.9, 126.8, 126.9, 127.3 (2 × CH), 127.7 (2 × CH), 128.7, 128.8, 129.4, 129.7, 131.3, 138.7, 139.0, 140.0, 148.2, 153.7, 154.1, 170.2; MS: m/z (%) = 478.30 (M + 1). HRMS: $[MH]^+$ 478.2231, calculated mass: 478.2243, molecular formula: $C_{29}H_{28}N_5O_2$.

Furan-2-yl (4-(3-phenylquinoxalin-2-yl) piperazin-1-yl) methanone (7b).



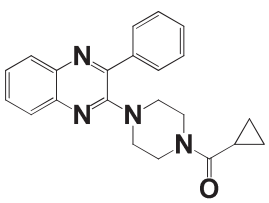
Brown color syrup; yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.36 (t, J = 4.8 Hz, 4H, 2 × CH_2), 3.89 (t, J = 5.0 Hz, 4H, 2 × CH_2), 6.47 (dd, J = 2.0 Hz, 1H, ArH), 6.55 (m, 1H, ArH), 7.0 (d, J = 7.6 Hz, 1H, ArH), 7.28–7.29 (m, 1H, ArH), 7.54–7.56 (m, 4H, ArH), 7.61–7.66 (m, 1H, ArH), 7.85 (d, J = 6.8 Hz, 1H, ArH), 8.0–8.02 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 44.8 (N–CH_2, 2 × CH_2), 48.7 (N–CH_2, 2 × CH_2), 111.3, 111.8, 116.9, 118.8, 126.7, 126.9, 127.8 (2 × CH), 128.6 (2 × CH), 129.7, 138.9, 140.0, 146.6, 147.5, 148.1, 153.7, 159.3, 161.3; MS: m/z (%) = 385.20 (M + 1). HRMS: $[MH]^+$ 385.1679, calculated mass: 385.1665, molecular formula: $C_{23}H_{21}N_4O_2$.

1-(4-(3-Phenylquinoxalin-2-yl)piperazin-1-yl)-2-(thiophen-2-yl) ethanone (7c).



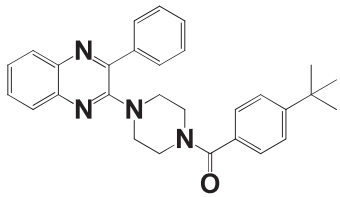
Yellow color solid; mp: 128–130°C, yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.23 (t, J = 5.0 Hz, 4H, 2 × CH_2), 3.54 (t, J = 5.2 Hz, 2H, CH_2), 3.65 (t, J = 5.2 Hz, 2H, CH_2), 3.90 (s, 2H, CH_2), 6.88–6.94 (m, 2H, ArH), 7.18–7.19 (m, 1H, ArH), 7.47–7.51 (m, 4H, ArH), 7.61–7.63 (m, 1H, ArH), 7.81 (d, J = 7.0 Hz, 1H, ArH), 7.95–8.00 (m, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ:34.9 (CH_2), 45.4 (N–CH_2, 2 × CH_2), 48.4 (N–CH_2, 2 × CH_2), 124.6, 125.9, 126.7, 126.8 (2 × CH), 127.6 (2 × CH), 128.3, 128.6, 128.7 (2 × CH), 129.6, 136.1, 138.6, 138.9, 139.9, 147.9, 153.5, 168.4; MS: m/z (%) = 415.20 (M + 1). HRMS: $[MH]^+$ 415.1612, calculated mass: 415.1593, molecular formula: $C_{24}H_{23}N_4OS$.

Cyclopropyl-(4-(3-phenylquinoxalin-2-yl)piperazin-1-yl)methanone (7d).



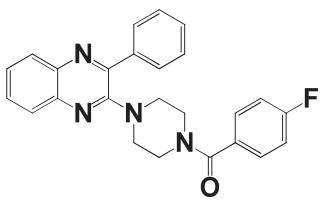
Yellow color syrup; yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.72–0.88 (m, 2H, CH_2), 1.09–1.33 (m, 2H, CH_2), 1.68–1.73 (m, 1H, CH), 3.27 (t, J = 4 Hz, 4H, 2 × CH_2), 3.63 (t, J = 5 Hz, 4H, 2 × CH_2), 7.46–7.55 (m, 4H, ArH), 7.61–7.64 (m, 2H, ArH), 7.82 (d, J = 6.8 Hz, 1H, ArH), 8.00–8.01 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 7.3 (2 × CH), 10.9, 44.8 (N–CH_2, 2 × CH_2), 48.5 (N–CH_2, 2 × CH_2), 126.6, 126.9, 127.7 (2 × CH), 128.6, 128.7 (2 × CH), 129.3, 129.6, 138.6, 139.04, 140.0, 148.0, 153.7, 172.2; MS: m/z (%) = 359.10 (M + 1). HRMS: $[MH]^+$ 359.1884, calculated mass: 359.1872, molecular formula: $C_{22}H_{23}N_4O$.

(4-(tert-Butyl)phenyl)(4-(3-phenylquinoxalin-2-yl)piperazin-1-yl)methanone (7e).



Yellow color syrup; yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (s, 9H, 3 × CH_3), 3.29–3.31 (m, 8H, 4 × CH_2), 7.27–7.31 (m, 3H, ArH), 7.33–7.55 (m, 7H, ArH), 7.8 (d, J = 7.8 Hz, 1H, ArH), 7.99–8.01 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.0 (3 × CH_3), 34.6, 43.2 (N–CH_2, 2 × CH_2), 48.8 (N–CH_2, 2 × CH_2), 113.8, 126.7, 126.8 (2 × CH), 126.9, 127.7 (2 × CH), 128.1, 128.6 (2 × CH), 128.7, 129.0 (2 × CH), 132.4, 138.9, 140.02, 152.9, 153.7, 154.6, 167.1, 170.6; MS: m/z (%) = 451.30 (M + 1). HRMS: $[MH]^+$ 451.2504, calculated mass: 451.2498, molecular formula: $C_{29}H_{31}N_4O$.

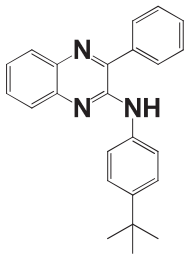
(4-Fluorophenyl)(4-(3-phenylquinoxalin-2-yl)piperazin-1-yl) methanone (7f).



Yellow color solid; mp: 185–188°C, yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.25 (s, 4H, 2 × CH_2), 3.51 (s, 4H, 2 × CH_2), 7.08–7.10 (m, 3H, ArH), 7.38–7.52 (m, 7H, ArH), 7.8 (d, J = 7.8 Hz, 1H, ArH), 8.02–8.11 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.3 (N–CH_2, 2 × CH_2), 48.7 (N–CH_2, 2 × CH_2), 115.12 (2 × CH), 126.3, 126.4, 126.8, 126.9, 127.7 (2 × CH), 128.3 (2 × CH), 128.6, 128.7, 129.3, 129.3, 129.4, 129.7, 139.9, 148.1, 153.6, 164.2, 169.6; MS: m/z (%) = 413.10 (M + 1). HRMS: $[MH]^+$ 413.1766, calculated mass: 413.1778, molecular formula: $C_{25}H_{22}N_4OF$.

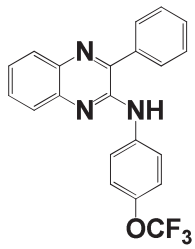
General procedure for the synthesis of compound 8. A mixture of 2-chloro-3-phenylquinoxaline (**3**, 1.0 equiv) and appropriate amine (1.0 equiv) was heated to 100–110°C for 8–10 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude isolated was purified by column chromatography using EtOAc/*n*-hexane(20:80) on 230–400 silica gel.

N-(4-(tert-Butyl)phenyl)-3-phenylquinoxalin-2-amine (8a).



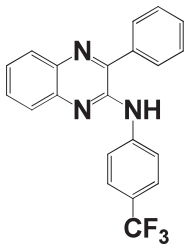
Yellow color solid; mp: 120–125°C, yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (s, 9H, 3 × CH_3), 7.00 (s, 1H, NH), 7.39 (d, J = 8.8 Hz, 2H, ArH), 7.44–7.56 (m, 1H, ArH), 7.57–7.64 (m, 4H, ArH), 7.69 (d, J = 8.2 Hz, 2H, ArH), 7.69–7.78 (m, 2H, ArH), 7.85 (d, J = 7.6 Hz, 1H, ArH), 7.94–7.96 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.4 (3 × CH_3), 34.3, 119.2 (2 × CH), 125.4, 125.7, 126.6 (2 × CH), 128.6, 128.7 (2 × CH), 129.5 (2 × CH), 129.8, 129.9, 136.4, 136.5, 137.6, 140.8, 146.0, 146.9, 147.2; MS: *m/z* (%) = 354.20(M + 1). HRMS: $[MH]^+$ 354.1961, calculated mass: 354.1961, molecular Formula: $C_{24}H_{24}N_3$.

3-Phenyl-N-(4-(trifluoro methoxy)phenyl) quinoxalin-2-amine (8b).



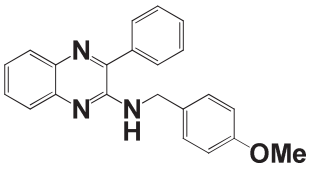
Yellow color solid; mp: 154–156°C, yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.10 (s, 1H, NH), 7.21 (d, J = 8.8 Hz, 2H, ArH), 7.49–7.58 (m, 1H, ArH), 7.60–7.78 (m, 4H, ArH), 7.80–7.87 (m, 5H, ArH), 7.97–7.99 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 119.5, 120.4 (2 × CH), 121.7 (2 × CH), 126.0, 126.7, 128.6 (2 × CH), 128.9, 129.4 (2 × CH), 129.7, 130.1 (2 × CH), 136.1, 137.8, 137.9, 140.4, 144.2, 146.8; MS : *m/z* (%) = 382.10 (M + 1). HRMS: $[MH]^+$ 382.1178, calculated mass: 382.1167, molecular formula: $C_{21}H_{15}N_3OF_3$.

***3-Phenyl-N-*(4-(trifluoro methyl)phenyl) quinoxalin-2-amine (8c).**



Yellow color solid; mp: 182–184°C, yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (s, 1H, NH), 7.54 (t, J = 7.6 Hz, 1H, ArH), 7.60–7.64 (m, 6H, ArH), 7.79 (d, J = 8.0 Hz, 2H, ArH), 7.99–8.01 (m, 3H, ArH), 8.0 (d, J = 7.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 118.7 (2 × CH), 124.6, 125.6, 126.2, 126.2, 126.4, 126.8 (2 × CH), 128.6, 128.9, 129.7 (2 × CH), 130.2 (2 × CH), 136.0, 137.9, 140.3, 142.4, 146.6, 146.9; MS: *m/z* (%) = 366.10 (M + 1). HRMS: $[MH]^+$ 366.1206, calculated mass: 366.1218, molecular formula: $C_{21}H_{15}N_3F_3$.

N-(4-Methoxybenzyl)-3-phenylquinoxalin-2-amine (8d).



Brown color syrup; yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.78 (s, 3H, OCH_3), 4.71 (d, J = 6.0 Hz, 2H, CH_2), 5.3 (s, 1H, NH), 6.86 (d, J = 5.0 Hz, 2H, ArH), 7.28 (d, J = 8.0 Hz, 2H, ArH), 7.39–7.47 (m, 1H, ArH), 7.48–7.57 (m, 4H, ArH), 7.69–7.77 (m, 3H, ArH), 7.93 (d, J = 8.0 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 44.7, 55.1, 113.9, 114.2, 124.4 (2 × CH), 125.9 (2 × CH), 128.3 (2 × CH), 128.7, 129.2, 129.6 (2 × CH), 130.8, 131.8, 136.6, 137.1, 141.5, 146.4, 149.8, 158.8. MS: *m/z* (%) = 342.20 (M + 1). HRMS: $[MH]^+$ 342.1602, calculated mass: 342.1606, molecular formula: $C_{22}H_{20}N_3O$.

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