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Synthesis and Structure–Activity Relationship of 2-Amino-3-heteroaryl-quinoxalines as Non-peptide, Small-Molecule Antagonists for Interleukin-8 Receptor

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Abstract—Interleukin-8 modulation is implicated in many inflammatory and cancer diseases. Starting from a mass-screening hit, the synthesis and structure–activity relationship of 2-amino-3-heteroarylquinoxalines as non-peptide, small molecule interleukine-8 receptor antagonists have been developed. The optimized derivatives, PD 0210293 (**13y**) and PD 0220245 (**13r**), show inhibition of both IL-8 receptor binding and IL-8-mediated neutrophil chemotaxis.

Introduction

Chemokines[1] are a class of proinflammatory cytokines involved in leukocyte trafficking. The chemokines themselves are 70–80 kDa proteins that have been divided into different subclasses based on the orientation of two key cysteine residues in the N-terminus. In general, C–C chemokines are active in monocytes, macrophages, and T-cells, while the C–X–C chemokines act predominantly on lymphocytes and neutrophils. Most chemokine receptors are members of the G-protein-coupled-receptor (GPCR) superfamily. On the other hand, interleukin-8 (IL-8) is a CXC chemokine that binds to two known receptors, CXCR1 and CXCR2.[2,3] CXCR1 is a receptor for IL-8 and granulocyte chemotactic protein 2 (GCP-2) whereas CXCR2 binds IL-8 and a few other related chemokines containing the Glu-Leu-Arg (ELR) amino-acid sequence (Gro-α, β, ENA-78). CXCR1 and CXCR2 are expressed on a number of different cell types including neutrophils,[4] the $CD4^+$, $CD8^+$ population of peripheral T-cells,[5] eosinophils,[6] and basophils.[7] IL-8 binding to CXCR1- and CXCR2-bearing neutrophils causes calcium flux,[8] degranulation,[9] and chemotaxis.[10] IL-8 has also been linked to a number of inflammatory conditions such as psoriasis,[11] rheumatoid arthritis,[12] acute respiratory distress syndrome (ARDS),[13] and chronic obstructive pulmonary disease (COPD).[14] Anti-IL-8 antibody blockade studies have demonstrated significant effects in rabbit models of ischemia-reperfusion injury[15] and ARDS.[16] However, it is worth noting that fully human anti-IL-8 monoclonal antibody ABX-IL-8 has failed to show efficacy in phase II studies for the indications of both psoriasis and rheumatoid arthritis.

Due to the close relationship between IL-8 and inflammatory diseases, CXCR1 and CXCR2 antagonists are targets of small molecule drug discovery. For instance, diarylureas **1**–**4** depicted in Figure 1 are found to be specific antagonists of the CXCR2 receptor.[17,18] In particular, SB 225002 (**1**) inhibited IL-8 binding to CHO-CXCR2 transfectant membranes with an IC_{50} of 22 nM, whereas it inhibited GRO-α-stimulated calcium flux in human neutrophil with an IC_{50} of 30 nM. In binding studies, **1** has been shown to have greater than 150-fold selectivity for CXCR2 against CXCR1 and four other

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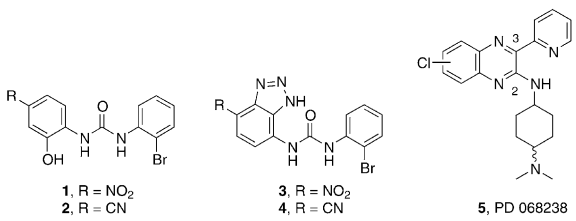


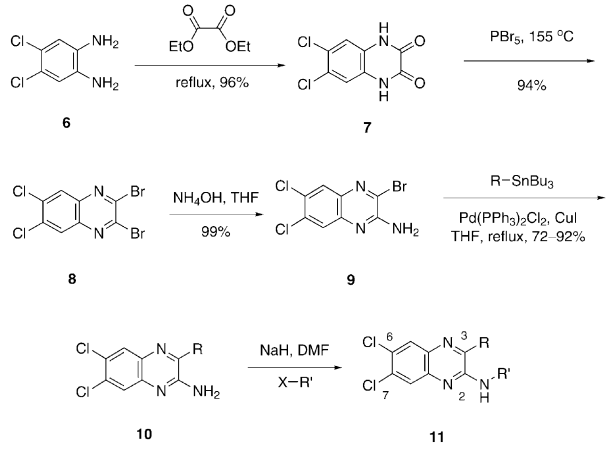
Figure 1.

GPCRs including fMLP, LTB_4, LTD_4, and C5a. In addition, data from a rabbit in vivo model indicated that co-administration of **1** with chemokines inhibited IL-8 but not fMLP effects on peripheral blood leukocyte margination in a dose-dependent manner with significant inhibition observed at 2.78 or 5.5 μg/kg/min dose, respectively

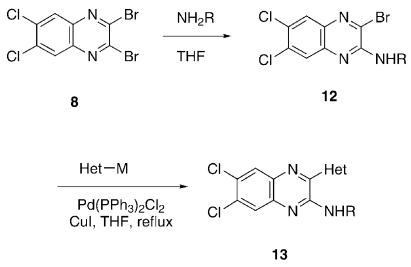
During screening of our compound collection against CXCR2, PD 068238 (**5**) was identified as an IL-8 receptor antagonist with an IC_{50} of 3.0 μM. Our investigation on the structure–activity relationship (SAR) around PD 068238 (**5**) resulted in a series of analogues possessing activities in both the binding and chemotaxis assays. Herein, we report the synthesis and SAR studies of 2-amino-3-heteroaryl-quinoxaline analogues as non-peptide, small-molecule IL-8 receptor antagonists.

Chemistry

The original synthesis for 2-amino-3-heteroaryl-quinoxalines was long and not amenable to our SAR investigations.[19] By taking advantage of the Stille coupling tactic, we devised an alternative synthetic route that was more suitable for our SAR studies.[20] Since the initial SAR investigation on the benzene ring substituents demonstrated that the 6,7-dichloro pattern was preferred in terms of both chemical and biological properties, it was chosen for our later stage SAR studies. The electrophilic coupling partners **9** of the Stille coupling reaction were prepared in three steps from phenylene diamines. Thus, as shown in Scheme 1, condensation of phenylene diamine **6** with diethyl oxalate gave quinoxalinedione **7**. Bromination of **7** was accomplished using one of two methods to furnish dibromide **8**. The first method consisted of treatment with molten PBr_5 at 150 °C. The alternate method involved refluxing **7** with $POBr_3$ in THF. The latter method was proven to be more convenient. Single S_NAr displacement on dibromide **8** afforded 2-amino-3-bromo-quinoxaline **9** as the desired substrate. The regiochemical outcome of such S_NAr displacement was dependent on the substituents on the phenyl ring. The results were disclosed in our earlier communication.[20] With the electrophile **9** in hand, the Stille coupling reactions with heterocyclic stannanes gave rise to 2-amino-3-bromo-quinoxaline **10**. Deprotonation of **10** with one equivalent of NaH was

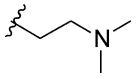
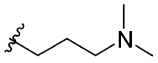
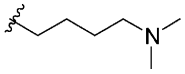
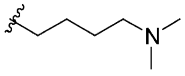
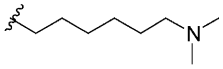
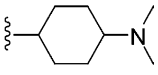
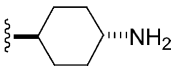
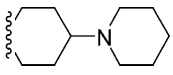
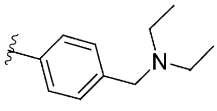


Scheme 1. Synthetic route 1.



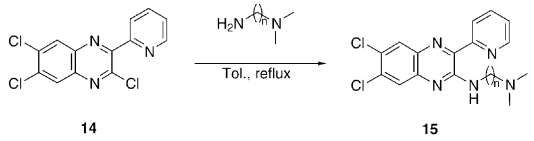
Scheme 2. Synthetic route 2.

Table 1. Initial amine SAR

Compd	Diamine linker	CXCR binding IC_{50} (μM)
15a		>40
15b		17
15c		4.0
15d		8.7
15e		7.0
15f		5.0
15g		11.5
15h		30
15i		20

followed by treatment with alkyl halides to deliver the desired analogues **11** in good yield.

Alternatively, a more efficient route was designed to prepare additional analogues. As depicted in Scheme 2, single S_NAr displacement on dibromide **8a** afforded 2-amino-3-bromo-quinoxaline **12** as the desired substrate. The second S_NAr displacement did not proceed due to deactivation by the electron-donating amine substituent. With the electrophile **12** in hand, various palladium-catalyzed coupling reactions with heterocyclic organometallics then delivered the desired analogues **13** in good yield. For the Stille coupling reactions in particular, Careful workup including hexane/acetonitrile extraction was instituted to thoroughly remove the tin contamination for stannanes at times tend to give false binding activities to some receptors.



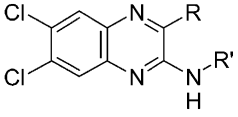
Scheme 3.

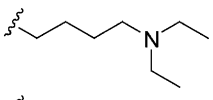
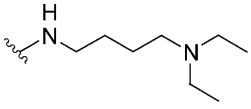
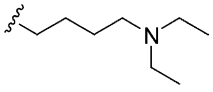
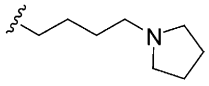
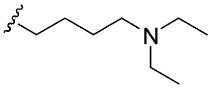
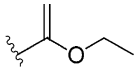
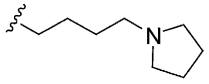
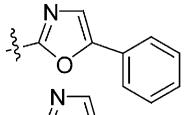
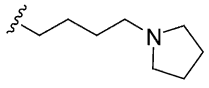
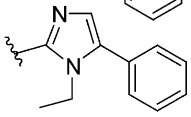
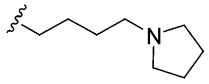
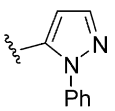
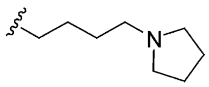
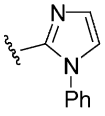
SAR Study

Initial diamine SAR

Our initial efforts were focused on the optimal chain length for the diamine side chain. Starting material **14** was prepared according to the original literature precedent using with 4,5-dichlorophenylenediamine and ethyl 2-pyridylglyoxylate oxime.[19] Treatment of **14** with diamines with different lengths of diamine linkage furnished the desired derivatives **15** in good yields (Scheme 3). From the results of compounds **15a**–**15i** (Table 1), it was concluded that the diamine side chain containing a four-carbon linker **15c** is optimal in terms of potency in the IL-8 receptor binding assay. The dimethylamino-cyclohexyl analogue **15f** also showed reasonable activity, although the other tethered analogues **15g**–**15i** were not as potent as the linear four-carbon linker, compound **15c**. The data showed that dimethylamino terminus was preferable since **15c** and **15f** possessed similar activities, whereas **15g**–**15i** were less potent.

Table 2. SAR of 3-substituted derivatives **13**



Compd	R′	R	CXCR binding IC_{50} (μM)
13a			33
13b		–Br	6.0
13c		$-OCH_3$	14
13d			30
13e			2.9
13f			2.0
13g			7.5
13h			12

(continued)

Table 2 (*continued*)

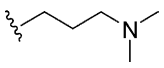
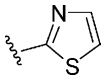
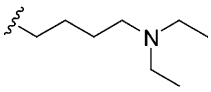
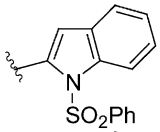
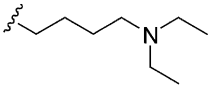
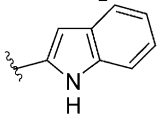
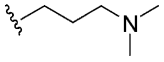
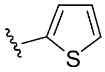
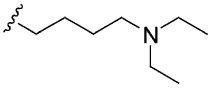
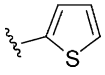
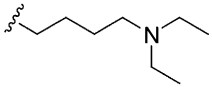
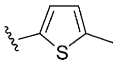
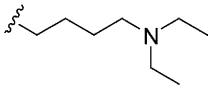
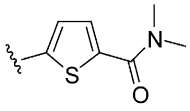
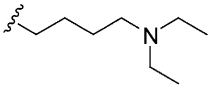
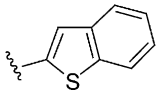
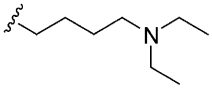
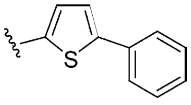
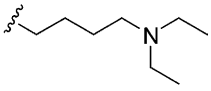
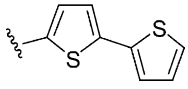
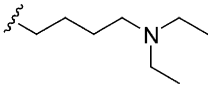
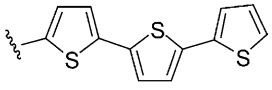
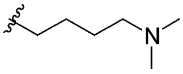
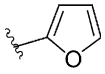
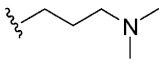
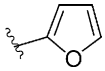
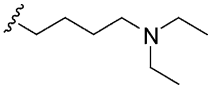
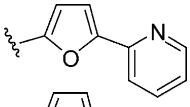
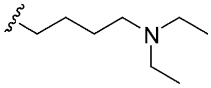
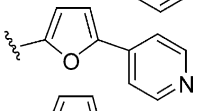
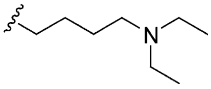
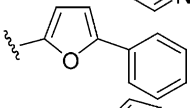
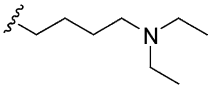
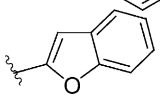
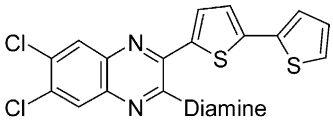
Compd	R′	R	CXCR binding IC_{50} (μM)
13i			5.0
13j			1.5
13k			1.5
13l			3.0
13m			0.90
13n			0.66
13o			0.64
13p			0.29
13q			0.24
13r			0.11
13s			0.11
13t			2.5
13u			3.25
13v			0.95
13w			0.45
13x			0.32
13y			0.09

Table 3. Bis-thiophene diamine SAR



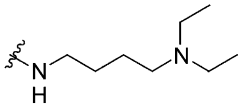
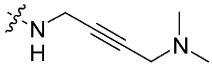
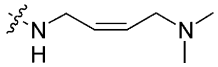
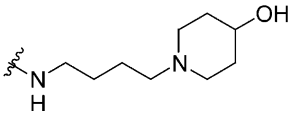
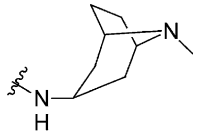
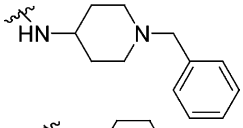
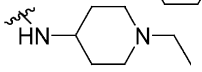
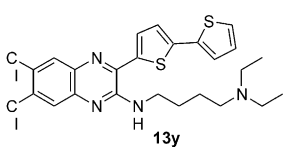
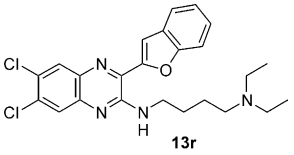
Compd	Diamine	CXCR binding IC_{50} (μM)	5-HT1a binding IC_{50} (μM)	NK2 binding IC_{50} (μM)	M2 binding IC_{50} (μM)
13r		0.11	1.0	1.1	3.6
16a		0.52	0.21	0.63	6.5
16b		0.18	0.29	1.4	0.47
16c		0.20	2.7	1.7	6.6
16d		0.21	2.2	1.0	2.7
16e		3.4	0.57	0.1	2.0
16f		0.21	0.38	0.10	0.10

Table 4. The in vitro binding profile of the two most potent analogues





Receptors	Compd **13y**, IC_{50} (μM)	Compd **13r**, IC_{50} (μM)
IL-8 (binding)	0.09	0.11
CXCR1	0.37	0.23
CXCR2	0.16	0.03
IL-8 (chemotaxis)	0.2	0.17
5HT1a	0.97 (11×)	0.57 (5×)
NK2	0.15 (2×)	0.78 (7×)
M2	0.53 (6×)	3.6 (33×)
MCP-1	>40 (>444×)	>40 (>364×)
CX3CR1		3.6 (33×)
5HT6		10 (91×)
5HT7		>10 (>91×)
a2C		>10 (>91×)

SAR of heterocycles

Initial replacement of the C-3 pyridyl substituent with a variety of heterocycles including indole, oxazole, pyrrole, imidazole, phenyl, and pyrazole derivatives (Table 2, compounds **13e**–**13i**) did not result in significant improvement in binding affinity. Only a small increment in potency was observed for indole derivatives (compounds **13j**, **13k**). On the other hand, many thienyl analogues (Table 2, compounds **13l**–**13s**) proved to be more potent antagonists of the IL-8 receptor. While the electron-density modifications did not have much impact on the IC_{50} values, the binding activity was significantly affected by steric effects of substituents on the thiophene ring, with the bisthienyl and the terthienyl analogues, **13r** and **13s**, as the most potent analogues. A similar trend was observed for the furanyl derivatives **13t**–**13y**, with the benzofuran analogue **13y** as the most active compound. Although **13r** and **13s** possessed the same binding activity, **13r** was preferable in comparison to **13s** because the former had better solubility than the latter. Therefore, the bis-thiophene and the benzofuran analogues provided the most potent IL-8 receptor

anatagonists (entries **13r**, **13y**), with IC_{50} values as 110 and 90 nM, respectively.

Subsequent diamine SAR

Upon the identification of compound **13r**, we then undertook further exploration of the diamine SAR, this time keeping the C-3 substituent constant as the bis-thiophene. We made several modifications to the diamine in order to increase potency as well as to enhance the selectivity and physical properties of our series. Since 5-HT1a, NK2, and M2 had been identified as selectivity problems in our large selectivity panel, these assays were chosen as selectivity checks for the new diamine modifications. We found that it was possible to maintain good potency against the IL-8 receptor while changing the diamine side chain within the scope delineated in Table 3. Several of the amine analogues had potencies very similar to compound **13r**. The other GPCR binding activities could be modulated somewhat by side-chain modifications. The tethered analogue **16f** showed a marked decrease in selectivity. Compounds **16c** and **16d** showed similar selectivities to compound **13r**. We concluded from this exercise that selectivity could be moderately modified through the diamine, but not improved significantly. Our most selective compounds showed approximately a 10-fold window between IL-8 receptor binding and other GPCRs. Some of the diamine modifications did result in less lipophilic compounds such as example **16c**.

For the two most potent analogues **13r** and **13y**, we have shown that the binding activities correspond well with activity in neutrophil chemotaxis assays (Table 4). These derivatives show comparable antagonism of IL-8 binding to both CXCR1 and CXCR2, therefore are CXCR1/2 dual inhibitors. Further investigation revealed these compounds also bind to some other seven-membrane G-protein-coupled receptors including M2, NK2, and 5HT1a receptors. Analogues **13r** and **13y** were not further pursued as drug candidates due to the lack of selectivities towards other GPCRs. The results are in accord to previous literature observations,[21] in which *N,N′*-dialkylaminobutylamino-styryl-quinolines have demonstrated promiscuity towards some GPCRs. It was speculated that the styrylquinolines bind to a common motif of GPCRs which is most likely distinct from the ligand-binding domains. The promiscuity of *N,N*-dialkylaminobutylaminoquinolines towards GPCRs should serve as a precaution in designing future highly selective drug candidates.

Conclusions

In our SAR studies of 2-amino-3-heteroaryl-quinoxalines as IL-8 receptor antagonists, we identified the benzofuran and bis-thiophene analogues, PD 0210293 (**13y**) and PD 0220245 (**13r**), as the most potent IL-8 antagonists (90 and 110 nM, respectively). In addition both PD 0210293 (**13y**) and PD 0220245 (**13r**), inhibited both IL-8 receptor binding and IL-8-mediated neutrophil chemotaxis with IC_{50} values of 200 and 170 nM, respectively. In contrast to SB225002 (**1**) that has been shown to have greater than 150-fold selectivity for CXCR2 against CXCR1 in binding studies, PD 0210293 (**13y**) and PD 0220245 (**13r**) bind to both CXCR1 and CXCR2 (Table 4), thus are dual inhibitors. These analogues can potentially serve as a useful tool to better define the role of IL-8 in inflammatory diseases.

Experimental

General methods

Melting points are uncorrected. The ^1H NMR spectra were recorded at 400 MHz, and the ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ or DMSO-d_6. Chemical shifts are reported in ppm (δ) and referenced to the residual proton signal for $CDCl_3$ (7.26 ppm) or DMSO-d_6 (2.49 ppm). The *J* coupling constants are reported in Hz. Elemental analyses were performed by Quantitative Technologies Inc. and are within 0.4% of theory. Reagents were purchased from commercial suppliers and used without further purification. Merck silica gel 60 was used for flash chromatography (230–400 mesh). CXCR binding assay, chemotaxis assay, as well as calcium flux assay were carried out according to literature procedures.[22,23]

6,7-Dichloro-1,4-dihydroquinoxaline-2,3-dione (7). A mixture of 4,5-dichlorophenylenediamine (**6**, 54 g, 305 mmol) and diethyl oxalate (124 mL, 146.1 g, 920 mmol) was heated at reflux overnight, cooled to room temperature and filtered. The residue was washed with ethanol and dried in vacuo to give the titled product **7** as a gray powder (67.5 g, 96% yield); mp >320 °C; IR (KBr, cm^{-1}) 3188, 3156, 3057, 2918, 1724, 1693, 1613, 1497, 1452, 1340, 1338, 1250, 1131, 877, 811, 676, 669, 565; ^1H NMR (DMSO-d_6) δ 7.18 (s, 2H), 12.00 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 154.8, 126.0, 124.4, 116.0; MS (APCI), *m/z* 231.0 (M^+). Anal. ($C_8H_4N_2O_2Cl_2$) C, H, N.

2,3-Dibromo-6,7-dichloroquinoxaline (8). 6,7-Dichloro-1,4-dihydro-quinoxaline-2,3-dione (**7**, 5.39 g, 23.3 mmol) and phosphorus pentabromide (20.1 g, 46.7 mmol) were combined in a 100 mL round-bottom flask equipped with a condenser with an outlet half submerged in 10% NaOH aqueous solution (to absorb HBr generated during the reaction). The reaction was heated at 155 °C using an oil-bath for 2 h, upon which the formation of HBr ceased. The reaction mixture was poured into ice-water (100 mL) and basified with NH_4OH. After filtration, the solid was dried and recrystallized from EtOH to give the desired product as a white solid. (7.84 g, 94% yield): mp 169–70 °C; $R_f = 0.50$, CH_2Cl_2; IR (KBr, cm^{-1}) 3088, 1539, 1451, 1240, 1128, 964, 997; ^1H NMR ($CDCl_3$) δ 8.13 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 142.4, 139.7, 136.3; MS (APCI), *m/z* 338.4 (MH^+); anal. ($C_8H_2N_2Cl_2Br_2$) C, H, N.

2-Bromo-3amino-6,7-dichloroquinoxaline (9). 2,3-Dibromo-6,7-dichloro-quinoxaline (5 g, 14.0 mmol) was dissolved in THF (100 mL). To this orange solution

concd ammonium hydroxide (50 mL) was added in one portion, causing a white precipitate to fall out of solution and the reaction to turn a dark green in color. The temperature decreased from 18.0 to 13.5 °C. The reaction was allowed to stir overnight at ambient temperature. THF was then removed in vacuo and the precipitate filtered off and washed with distilled water (3 × 30 mL). The orange solid was then dried in vacuo at 50 °C for 4 h. The solid was then triturated with *t*-butylmethyl ether to give a light orange solid (4.1 g, 99% yield): mp 222–224 °C; IR (KBr, cm^{-1}) 3488, 3347, 1617, 1588, 1443, 1406, 1338, 1114, 1037, 966, 894, 869, 577, 557; ^1H NMR (DMSO-d_6) δ 7.45 (broad s, 2H, NH_2), 7.70 (s, 1H), 7.96 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 152.1, 141.0, 135.8, 133.3, 133.2, 128.8, 126.7, 126.3; MS (APCI), *m*/*z* 291.8 [M−1]; anal. ($C_8H_4N_3BrCl_2$) C, H, N.

3-(1-Benzenesulfonyl-1*H*-indol-2-yl)-6,7-dichloro-quinoxalin-2-ylamine (10a, het = 1-benzenesulfonyl-1*H*-indole). A 50-mL round-bottom flask was charged with compound **9** (1.03 g, 3.52 mmol), 1-benzenesulfonyl-2-tributylstannyl-1*H*-indole (2.30 g, 4.21 mmol), bis(triphenylphosphine)palladium (II) chloride (259 mg, 0.352 mmol), CuI (77 mg, 0.703 mmol), and THF (40 mL). The suspension was refluxed for 30 min and cooled to room temperature. Charcoal was added and the reaction mixture was heated to boiling and filtered through a pad of Celite (1 inch thick). The filtrate was concentrated in vacuo and the residue was chromatographed using neutral alumina, eluting with 0–5% CH_3OH/EtOAc, to give the desired product as a yellow solid (1.51 g, 92% yield): mp 129–122 °C; R_f = 0.26, EtOAc–hexane (1:1); ^1H NMR (DMSO-d_6) δ 7.17 (broad s, 2H), 7.31 (dt, *J* = 7.32, 0.9 Hz, 1H), 7.43 (dt, *J* = 7.32, 1.1 Hz, 1H), 7.63 (m, 4H), 7.84 (d, 1H), 7.86 (d, *J* = 1.6 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 8.14 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 153.6, 141.8, 141.1, 136.7, 136.4, 134.7, 134.6, 134.3, 132.8, 130.0, 129.6, 129.4, 126.9, 125.9, 125.7, 125.6, 124.2, 122.0, 114.7; MS (APCI), *m*/*z* 469.0 [M + 1], 471.0 [M + 3]; anal. ($C_{22}H_{14}N_4Cl_2O_2S$) C, H, N.

2-Amino-3-(2-furanyl)- 6,7-dichloroquinoxaline (10b, het = 2-furanyl). The title compound was prepared according to the experimental procedure for example **10a** and was obtained as a yellow crystalline solid (84% yield): mp 222–223 °C; R_f = 0.16, EtOAc–hexane (1:2); IR (KBr, cm^{-1}) 3507, 3312, 1617, 1590, 1480, 1460, 1414, 1157, 1107, 876, 745, 591; ^1H NMR (DMSO-d_6) 6.80 (dd, J_1 = 1.5 Hz, J_2 = 3.3 Hz, 1H), 7.30 (broad s, 2H), 7.41 (d, *J* = 3.3 Hz, 1H), 7.73 (s, 1H), 7.80 (d, *J* = 1.1 Hz, 1H), 8.02 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 150.5, 150.3, 145.7, 140.3, 135.6, 135.2, 131.8, 128.8, 126.2, 125.7, 114.1, 112.6; MS (ACPI), *m*/*z* 280.0 [M + 1], 282.0 [M + 3]; anal. ($C_{12}H_7N_3Cl_2O$) C, H, N.

2-Amino-3-(2-thioenyl)- 6,7-dichloroquinoxaline (10c, het = 2-thienyl). The title compound was prepared according to the experimental procedure for example **10a** and was obtained as a yellow crystalline solid (77% yield): mp 235–237 °C; R_f = 0.17, EtOAc–hexane (1:2); IR (KBr, cm^{-1}) 3472, 3311, 1614, 1588, 1463, 1432, 1404, 1351, 1329, 1227, 1110, 948, 879, 849, 728, 597; ^1H NMR (DMSO-d_6) δ 7.19 (broad s, 1H), 7.24 (dd, *J* = 5.1, 3.8 Hz, 1H), 7.72 (s, 1H), 7.83 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.94 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.96 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 151.1, 140.4, 140.3, 140.2, 135.3, 131.7, 130.8, 128.8, 126.2, 125.6; MS (APCI), *m*/*z* 295.9 [M^+], 293.9 [M−2]; anal. ($C_{12}H_7N_3Cl_2S$) C, H, N.

2-Amino-3-(2-thiazole)-6,7-dichloroquinoxaline (10d, het = 2-thiazole). The title compound was prepared according to the experimental procedure for example **10a** and was obtained as a bright yellow crystalline solid (81% yield): mp 219–221 °C; R_f = 0.19, EtOAc–hexane (1:2); IR (KBr, cm^{-1}) 3426, 3363, 3320, 3200, 1624, 1459, 1341, 1235, 1208, 1109, 953, 884, 812, 462; ^1H NMR (DMSO-d_6) δ 7.29 (broad s, 1H), 7.79 (s, 1H), 8.05 (s, 1H), 8.67 (s, 1H), 9.31 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 158.0, 151.4, 143.8, 140.4, 139.2, 135.7, 132.4, 128.8, 126.5, 125.8; MS (APCI), *m*/*z* 296.9 [M + 1], 298.9 [M + 3]; anal. ($C_{11}H_6N_4Cl_2S$) C, H, N.

Compound 13a: 6,7-dichloro-*N*,*N*′-bis-(4-diethylamino-butyl)-quinoxaline-2,3-diamine. To a solution of compound **8** (850 mg, 2.38 mmol) in THF (50 mL), 4-(diethylamino)butyl amine (1.37 g, 9.52 mmol) was added. The reaction mixture was refluxed overnight. After the removal of the solvent in vacuo, the residue was chromatographed on silica gel, eluting with 80% EtOAc, 10% MeOH, and 10% Et_3N, to give the desired product as a light pink to off-white wax (1.14 g, 99% yield): ^1H NMR ($CDCl_3$) δ 0.89 (t, *J* = 7.10 Hz, 12H), 1.45 (m, 4H), 1.60 (m, 4H), 2.39 (m, 6H), 3.43 (m, 4H), 7.15 (t, *J* = 4.58 Hz, 2H), 7.58 (s, 2H); MS (APCI), *m*/*z* 497 [M + 1], 499 [M + 3]; anal. ($C_{24}H_{40}N_6Cl_2{\cdot}0.82H_2O$) C, H, N.

Compound 13b: *N*′-(3-Bromo-6,7-dichloro-quinoxalin-2-yl)-*N*,*N*-diethyl-butane-1,4-diamine. To a solution of compound 8 (10.35 g, 29.0 mmol) in THF (100 mL), 4-(diethylamino) butyl amine (8.35 g, 58.0 mmol) was added at room temperature. After 30 min, the reaction mixture was filtered to remove the precipitate. After the removal of the solvent in vacuo, the residue was chromatographed using silica gel, eluted with 2.5% Et_3N, 2.5% MeOH, 95% EtOAc, to give the desired product as a orange-yellow oil (12.18 g, 100% yield): ^1H NMR ($CDCl_3$) δ 1.03 (t, *J* = 7.14 Hz, 6H), 1.61 (m, 2H), 1.72 (m, 2H), 2.52 (m, 6H), 3.56 (m, 2H), 5.96 (t, *J* = 4.94 Hz, 1H), 7.79 (s, 1H), 7.87 (s, 1H); MS (APCI), *m*/*z* 419 [M + 1], 421 [M + 3]. Anal. ($C_{16}H_{21}N_4Br_1Cl_2$) C, H, N.

Compound 13c: (6,7-dichloro-3-methoxy-quinoxalin-2-yl)-(4-pyrrolidin-1-yl-butyl)-amine. Step 1: (3-bromo-6,7 -dichloro-quinoxalin-2-yl)-(4-pyrrolidin-1-yl-butyl)-amine. To a solution of compound **8** (31.00 g, 87.00 mmol) in THF (150 mL), K_2CO_3 (24.00 g, 174.00 mmol) and 4-pyrrolidinyl-1-butylamine (17.00 g, 119.70 mmol) were added. The reaction mixture was stirred at room temperature for 1 day. Then saturated $NaHCO_3$ solution (10 mL) was added to quench the reaction. The phases were separated and the aqueous layer was extracted

with EtOAc (3×15 mL). The combined organic phase was dried over $MgSO_4$. The crude product was chromatographed using silica gel, eluting with 1% Et_3N in EtOAc, to give the desired product as a yellow solid (21.00 g, 58% yield): ^1H NMR (MeOD) δ 1.61–1.82 (m, 8H), 2.49–2.58 (m, 6H), 3.53 (t, $J = 6.6$ Hz, 2H), 7.67 (s, 1H), 7.79 (s, 1H); MS (ESI+), m/z 419 [M + 1].

Step 2: (6,7-dichloro-3-methoxy-quinoxalin-2-yl)-(4-pyrrolidin-1-yl-butyl)-amine. A solution of (3-bromo-6,7-dichloro-quinoxalin-2-yl)-(4-pyrrolidin-1-yl-butyl)-amine (298 mg, 0.70 mmol) in anhydrous THF (10 mL) was treated with methanol (0.085 mL, 2.1 mmol), Et_3N (0.190 mL, 1.4 mmol), and $Ni(CO)_2(PPh_3)_2$ (575 mg, 0.9 mmol). The mixture was heated to reflux for 18 h, followed by removal of the solvent in vacuo. The residue was chromatographed on silica gel eluting with 10% CH_3OH and 3% Et_3N in ethyl acetate to give the free base as a viscous oil (194 mg, 74% yield). The bis·HCl salt was prepared by treating the free base with methanolic HCl. ^1H NMR (free-base, $CDCl_3$) δ, 1.80 (m, 8H), 2.55 (m, 6H), 3.56 (m, 2H), 4.10 (s, 3H), 6.13 (broad s, 1H), 7.70 (m, 2H); MS (ESI+), m/z 335 [M + 1]; anal. ($C_{17}H_{22}N_4O_1Cl_2 \cdot 2HCl \cdot 2H_2O$) C, H, N.

Compound 13d: *N′*-[6,7-dichloro-3-(1-ethoxy-vinyl)-quinoxalin-2-yl]-*N,N*-diethyl-butane-1,4-diamine. The title compound was prepared according to the experimental procedure for example **10a** using starting material **13b**, and was obtained as a yellow-orange oil: ^1H NMR ($CDCl_3$) δ 1.04 (m, 6H), 1.24 (m, 6H), 1.69 (m, 4H), 2.04 (m, 1H), 2.29 (m, 1H), 2.55 (m, 6H), 3.51 (m, 2H), 3.64 (m, 1H), 3.81 (m, 1H), 6.67 (s, 1H), 7.08 (s, 1H), 3.37 (broad t, $J = 4.59$ Hz, 1H), 7.68 (s, 1H), 7.76(s, 1H); MS (APCI), m/z 411 [M + 1], 413 [M + 3]; anal. ($C_{20}H_{28}N_4Cl_2O_1$) C, H, N.

Compound 13e: (6,7-dichloro-3-(5-phenyl-oxazol-2-yl)-quinoxalin-2-yl)-(4-pyrrolidin-1-yl-butyl)-amine. A solution of (3-bromo-6,7-dichloro-quinoxalin-2-yl)-(4-pyrrolidin-1-yl-butyl)-amine (159 mg, 0.38 mmol) in anhydrous THF (10 mL) was treated with 5-phenyloxazole (73 mg, 0.50 mmol), $PdCl_2(PPh_3)_2$ (18 mg, 0.025 mmol), CuI (10 mg, 0.05 mmol), and potassium acetate (74 mg, 0.75 mmol). The mixture was heated to reflux under argon for 24 h. Volatiles were removed in vacuo, and the residue was chromatographed on silica gel eluting with 10% CH_3OH and 3% Et_3N in ethyl acetate to give the free base as a viscous oil (80 mg, 44% yield). The bis·HCl salt was prepared by treating the free base with methanolic HCl. ^1H NMR (free-base, $CDCl_3$) δ 1.80 (m, 8H), 2.54 (m, 6H), 3.62 (m, 2H), 7.43 (m, 3H), 7.72 (s, 1H), 7.80 (m, 2H), 8.00 (s, 1H), 8.86 (broad t, 1H); MS (ESI+), m/z 482 [M + 1]; anal. ($C_{25}H_{25}N_5OCl_2 \cdot 2HCl \cdot 1.9H_2O$) C, H, N.

Example 13f: (6,7-dichloro-3-(1-ethyl-5-phenyl-imidazol-2-yl)-quinoxalin-2-yl)-(4-pyrrolidin-1-yl-butyl)-amine. A solution of 1 - ethyl - 5 - phenylimidazole (220 mg, 1.28 mmol) in anhydrous THF (10 mL) was cooled in an ice bath and treated with *n*-butyllithium (2.5 M, 0.56 mL, 1.41 mmol), and stirred for 30 min. The resulting brown solution was treated with anhydrous $ZnCl_2$ (354 mg, 2.6 mmol) in THF (10 mL) and allowed to warm to room temperature. After 30 min, the resulting organozinc reagent was treated with (3-bromo-6,7-dichloro-quinoxalin-2-yl)-(4-pyrrolidin-1-yl-butyl)-amine and the catalyst mixture (prepared by pre-treating a THF (3 mL) solution of $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol) with *n*-butyllithium (0.048 mL, 0.12 mmol) to generate the palladate complex). The mixture was heated to reflux for 18 h, followed by removal of the solvent in vacuo. The residue was chromatographed on silica gel eluting with 10% CH_3OH and 3% Et_3N in ethyl acetate to give the title compound as a viscous oil (67 mg, 20% yield). The bis·HCl salt was prepared by treating the free base with methanolic HCl. ^1H NMR (free-base, $CDCl_3$) δ 1.38 (t, 3H), 1.80 (m, 8H), 2.55 (m, 6H), 3.65 (m, 2H), 4.65 (m, 2H), 7.18 (m, 1H), 7.46 (m, 5H), 7.73 (s, 1H), 7.81 (s, 2H), 10.16 (broad s, 1H); MS (ESI+), m/z 509 [M + 1]; anal. ($C_{27}H_{30}N_6Cl_2 \cdot 2HCl$) C, H, N.

Example 13g: (6,7-dichloro-3-(1-phenyl-pyrazol-5-yl)-quinoxalin-2-yl)-(4-pyrrolidin-1-yl-butyl)-amine. The title compound was prepared using the experimental procedure for example **10a**, starting with (3-bromo-6,7-dichloro-quinoxalin-2-yl)-(4-pyrrolidin-1-yl-butyl)-amine and 1-phenyl-5-tributylstannanyl-1H-pyrazole. ^1H NMR (free-base, $CDCl_3$) δ 1.53 (m, 4H) 1.75 (m, 4H), 2.44 (m, 6H), 3.41 (m, 2H), 5.29 (m, 1H), 6.81 (d, $J = 1.8$ Hz, 1H), 7.29 (m, 5H), 7.77 (s, 1H), 7.78 (s, 1H), 7.86 (d, $J = 1.8$ Hz, 1H); MS (ESI+), m/z 481 [M + 1]; anal. ($C_{25}H_{26}N_6Cl_2 \cdot 2HCl \cdot 1H_2O$) C, H, N.

Example 13h: (6,7-dichloro-3-(1-phenyl-imidazol-2-yl)-quinoxalin-2-yl)-(4-pyrrolidin-1-yl-butyl)-amine. The title compound was prepared using the experimental for example **13f**, starting with 1-phenylimidazole. ^1H NMR (free-base, $CDCl_3$) δ 1.80 (m, 8H), 2.60 (m, 6H), 3.64 (m, 2H), 7.02 (m, 1H), 7.30 (m, 4H), 7.45 (m, 3H), 7.68 (m, 1H), 9.66 (broad s, 1H); MS (ESI+), m/z 481 [M + 1]; anal. ($C_{25}H_{26}N_6Cl_2 \cdot 2HCl \cdot 0.6H_2O \cdot 0.3CH_3OH$) C, H, N.

Example 13i: *N′*-(6,7-dichloro-3-thiazol-2-yl-quinoxalin-2-yl)-*N,N*-dimethyl-propane-1,3-diamine. To a solution of NaH (150 mg, 60% in mineral oil, 3.75 mmol) in DMF (10 mL) was added compound **10d** (420 mg, 1.50 mmol) and 3-dimethylaminopropyl chloride hydrochloride (237 mg, 1.5 mmol). The reaction was heated at 80 °C for 2 h, cooled to room temperature. After removal of DMF in vacuo, the residue was chromatographed using neutral alumina, eluted with 5–15% CH_3OH/EtOAc to give the desired product as a dark-yellow solid (94 mg, 60% yield). ^1H NMR (DMSO-d_6) 2.08 (m, 2H), 2.74 (d, $J = 4.95$ Hz, 6H), 3.14 (m, 2H), 3.57 (m, 2H), 7.59 (m, 1H), 7.87 (s, 1H), 8.05 (s, 1H), 8.70 (s, 1H), 7.37 (s, 1H), 10.59 (broad s, 1H); MS (APCI), m/z 382 [M + 1], 384 [M + 3]; anal. ($C_{16}H_{17}N_5Cl_2S \cdot 1.5HCl$) C, H, N.

Example 13j: *N′*-[3-(1-benzenesulfonyl-1*H*-indol-2-yl)-6,7-dichloro-quinoxalin-2-yl]-*N,N*-diethyl-butane-1,4-diamine. The title compound was prepared according to the experimental procedure for example **10a** using starting material **13b**, and was obtained as an orange oil:

^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 7.15 Hz, 6H), 1.59 (m, 2H), 1.68 (m, 2H), 2.55 (m, 6H), 3.57 (dd, J = 12.45, 5.49 Hz, 2H), 5.36 (broad t, J = 5.49 Hz, 1H), 6.95 (d, J = 0.73 Hz, 1H), 7.45 (m, 6H), 7.69 (s, 1H), 7.72 (s, 1H), 7.89 (s, 1H), 7.95 (s, 1H), 8.19 (dd, J = 8.33, 0.85 Hz, 1H); MS (APCI), m/z 598.1 [M + 1], 599.1 [M + 2]; anal. ($C_{16}H_{10}N_4Cl_2$·2.88HCl) C, H, N.

Example 13k: *N′*-[6,7-dichloro-3-(1*H*-indol-2-yl)-quinoxalin-2-yl]-*N*,*N*-diethyl-butane-1,4-diamine. The final product was prepared by refluxing a sodium hydroxide solution of compound **13j** in methanol to remove the sulfonamide protecting group. The title compound was obtained as a red-orange oil. The compound was then dissolved in EtOAc, and treated with HCl in EtOAc to form the HCl salt, a brown-orange solid: mp 145–147 °C; Salt ^{1}H NMR (DMSO-d_6) δ 1.15 (br t, J = 6.8 Hz, 6H), 1.72 (br s, 4H), 3.04 (br. s, 6H), 3.57 (br s, 2H), 7.03 (t, J = 7.32 Hz, 1H), 7.19 (t, J = 7.78 Hz, 1H), 7.38 (br s, 1H), 7.49 (d, J = 8.05 Hz, 1H), 7.63 (d, J = 7.81 Hz, 1H), 7.80 (s, 1H), 7.94 (s, 1H), 10.17 (br s, 1H), 11.76 (s, 1H); MS (APCI), m/z 456 [M + 1], 458 [M + 3]. Anal. ($C_{24}H_{27}N_5Cl_2$·2HCl·1.58H_2O) C, H, N.

Example 13l: *N′*-(6,7-dichloro-3-thiophen-2-yl-quinoxalin-2-yl)-*N*,*N*-dimethyl-propane-1,3-diamine. The title compound was prepared according to the experimental procedure for example **13i**, starting with compound **10c**, and was obtained as the bis·HCl salt, a yellow solid. mp = 220–223 °C; ^{1}H NMR (DMSO-d_6) δ 2.10 (m, 2H), 2.73 (δ, J = 4.8 Hz, 6H), 3.13 (m, 2H), 7.28 (dd, 5.1, 3.7 Hz, 1H), 7.58 (broad t, 1H), 7.86 (s, 1H), 7.88 (dd, J = 5.1, 1.0 Hz, 1H), 7.98 (dd, J = 4.0, 1.0 Hz, 1H), 8.00 (s, 1H), 10.80 (broad s, 1H); MS (APCI), m/z 381 [M + 1], 383 [M + 3]; anal. ($C_{17}H_{18}N_4Cl_2O$·2.0HCl) C, H, N.

Example 13m: *N′*-(6,7-dichloro-3-thiophen-2-yl-quinoxalin-2-yl)-*N*,*N*-diethyl-butane-1,4-diamine. The title compound was prepared according to the experimental procedure for example **10a** using starting material **13b**, and was obtained as a yellow-orange oil. The compound was then dissolved in EtOAc, and bubbled with HCl gas to make the corresponding HCl salt. The salt was a yellow hygroscopic powder: ^{1}H NMR (free-base, $CDCl_3$) δ 1.00 (t, J = 7.1 Hz, 6H), 1.60 (m, 2H), 1.72 (m, 2H), 2.50 (m, 6H), 3.57 (m, 2H), 5.85 (t, J = 5.2 Hz, 1H), 7.19 (dd, 5.0, 3.6 Hz, 1H), 7.57 (dd, 5.0, 1.1 Hz, 1H), 7.68 (dd, 4.8, 1.0 Hz, 1H), 7.79 (s, 1H), 7.95 (s, 1H); MS (APCI), m/z 423 [M + 1], 425 [M + 3]; anal. ($C_{20}H_{24}N_4Cl_2S$·2HCl·1.24H_2O) C, H, N.

Example 13n: *N′*-[6,7-dichloro-3-(5-methyl-thiophen-2-yl)-quinoxalin-2-yl]-*N*,*N*-diethyl-butane-1,4-diamine. The title compound was prepared according to the experimental procedure for example **10a** using starting material **13b**, and the product was obtained as a yellow oil: ^{1}H NMR (DMSO-d_6) δ 0.89 (t, J = 7.14 Hz, 6H), 1.45 (m, 2H), 1.64 (m, 2H), 2.48 (m, 2H), 2.51 (s, 3H), 3.44 (t, J = 6.23 Hz, 2H), 6.95 (d, J = 3.66 Hz, 1H), 7.27 (t, J = 5.31 Hz, 1H), 7.69 (d, J = 3.66 Hz, 1H), 7.73 (s, 1H), 7.91 (s, 1H); MS (APCI), m/z 437 [M + 1], 439 [M + 3]; anal. ($C_{21}H_{26}N_4Cl_2S$) C, H, N.

Example 13o: 5-[6,7-dichloro-3-(4-diethylamino-butylamino)-quinoxaline-2-yl]-thiophene-2-carboxylic acid dimethyl amide. The title compound was prepared according to the experimental procedure for example **10a** using starting material **13b**, and the product was obtained as a yellow wax (quantitative yield): ^{1}H NMR ($CDCl_3$) δ 1.01 (t, J = 7.0 Hz, 6H), 1.61 (m, 2H), 1.70 (m, 2H), 2.51 (m, 6H), 3.23 (broad s, 6H) 3.58 (m, 2H), 5.81 (m, 1H), 7.41(d, J = 3.9 Hz, 1H), 7.61 (d, J = 3.9 Hz, 1H), 7.80 (s, 1H), 7.95 (s, 1H); MS (APCI), m/z 494 [M + 1], 496 [M + 3].

Example 13p: *N′*-(3-benzo[b]thiophen-2-yl-6,7-dichloro-quinoxalin-2-yl)-*N*,*N*-diethyl-butane-1,4-diamine. The title compound was prepared according to the experimental procedure for example **10a** using starting material **13b**, and was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 7.14 Hz, 6H), 1.61 (m, 2H), 1.75 (m, 2H), 2.49 (m, 6H), 3.61 (dd, J = 12.35, 6.84 Hz, 2H), 6.00 (br t, J = 5.13 Hz, 1H), 7.43 (m, 2H), 7.81 (s, 1H), 7.86 (m, 2H), 7.92 (s, 1H), 7.99 (s, 1H); MS (APCI), m/z, 473 [M + 1], 475 [M + 3]; anal. ($C_{24}H_{26}N_4Cl_2S$·0.19$CHCl_3$) C, H, N.

Example 13q: *N′*-[6,7-dichloro-3-(5-phenyl-thiophen-2-yl)-quinoxalin-2-yl]-*N*,*N*-diethyl-butane-1,4-diamine. Step 1: 1-phenyl thiophene. To a solution of 2-bromothiophene (1.18 mL, 12.26 mmol) and phenyl boronic acid (1.64 g, 13.49 mmol) in toluene (50 mL), 2 M solution of Na_2CO_3 (13 mL, 27.00 mmol) and $Pd(PPh_3)_4$ (709 mg, 0.61 mmol) were added. The reaction mixture was heated to reflux for 5 h. The phases were separated and the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was chromatographed using silica gel, eluting with hexane–EtOAc (4:1), to give the desired product as a white solid (2.11 g, 98% yield): ^{1}H NMR ($CDCl_3$) δ 7.01–7.05 (m, 1H), 7.21–7.43 (m, 5H), 7.56–7.60 (m, 2H).

Step 2: 5-phenyl-1-tributylstannyl thiophene. To a solution of 1-phenyl thiophene (0.30 g, 1.87 mmol) in THF (10 mL) under Ar, *n*-BuLi (0.90 mL, 2.25 mmol, 2.5 M solution in hexane) was added. The reaction mixture was heated to reflux for 30 min and cooled to room temperature. Then tributyltin chloride was added. The mixture was stirred at room temperature for overnight. Then saturated NH_4Cl solution (10 mL) was added dropwise to quench the reaction. The phases were separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic phase was dried over $MgSO_4$ and concentrated to yield a crude desired product as a colorless oil (841 mg, 100% yield).

Step 3: *N′*-[6,7-dichloro-3-(5-phenyl-thiophen-2-yl)-quinoxalin-2-yl]-*N*,*N*-diethyl-butane-1,4-diamine. The title compound was prepared according to the general experimental procedure for example **10a** using starting material **13b** and was obtained as a light brown solid (90% yield): ^{1}H NMR (free base, $CDCl_3$) δ 0.96–1.03 (m, 6H), 1.57–1.78 (m, 4H), 2.47–2.56 (m, 6H), 3.61 (q, J = 6.9 Hz, 2H), 5.88 (t, J = 5.1 Hz, 1H), 7.34–7.47 (m, 4H), 7.65–7.71 (m, 3H), 7.81 (s, 1H), 7.97 (s, 1H); MS

(ESI+) m/z 472 [M+1]; anal ($C_{26}H_{28}N_4Cl_2S\cdot 2HCl\cdot 1.5H_2O$) C, H, N.

Example 13r: *N*-(3-[2,2′]bithiophenyl-5-yl-6,7-dichloro-quinoxalin-2-yl)-*N,N*-diethyl-butane-1,4-diamine. The title compound was prepared according to the experimental procedure for example **10a** using starting material **13b**, and the product was obtained as a brown oil. (77% yield): ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J=6.9 Hz, 6H), 1.64 (m, 2H), 1.74 (m, 2H), 2.53 (m, 6H), 3.60 (m, 2H), 5.86 (m, 1H), 7.08 (m, 1H), 7.23 (d, J=4.0 Hz, 1H), 7.31 (d, J=4.8 Hz, 1H), 7.63 (d, J=3.9 Hz, 1H), 7.79 (s, 1H), 7.96 (s, 1H); MS (APCI), m/z 503 [M−1]; anal. ($C_{24}H_{26}N_4Cl_2S_2\cdot 2.0HCl$) C, H, N.

Example 13s: *N*-(6,7-dichloro-3-[2,2′;5′,2′]terthiophen-5yl-quinoxalin-2-yl)-*N,N*-diethyl-butane-1,4-diamine. The title compound was prepared according to the experimental procedure for example **10a** using starting material **13b**, and the product was obtained as a yellow-orange oil. (97% yield): ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J=7.2 Hz, 6H), 1.65 (m, 2H), 1.75 (m, 2H), 2.55 (m, 6H), 3.60 (m, 2H), 5.86 (m, 1H), 7.05 (m, 1H), 7.13 (d, J=3.7 Hz, 1H), 7.22 (m, 2H), 7.64 (d, J=4.0 Hz, 1H), 7.79 (s, 1H), 7.95 (s, 1H); MS (APCI), m/z 585 [M$^-$−1], 587 [M$^-$+1]; anal. ($C_{28}H_{28}N_4Cl_2S_3\cdot 2HCl\cdot 0.32H_2O$) C, H, N.

Compound 13t, *N*′-(3-furan-2-yl-6,7-dichloro-quinoxalin-2-yl)-*N,N*-dimethyl-butane-1,4-diamine. Step 1: *N*′-(3-bromo-6,7-dichloro-quinoxalin-2-yl)-*N,N*-dimethyl-butane-1,4-diamine. To a solution of compound **8** (10.35 g, 29.0 mmol) in THF (100 mL), 4-(dimethylamino) butyl amine (8.35 g, 58.0 mmol) was added at room temperature. After 30 min, the reaction mixture was filtered to remove precipitate. After the removal of the solvent in vacuo, the residue was chromatographed using silica gel, eluted with 2.5% Et_3N, 2.5% MeOH, 95% EtOAc, to give the desired product as a orange-yellow oil (12.18 g, 100% yield): ^{1}H NMR ($CDCl_3$) δ, 1.63 (m, 2H), 1.75 (m, 2H), 2.25 (s, 6H), 2.35 (t, J=6.8 Hz, 2H), 3.55 (m, 2H), 6.37 (broad s, 1H), 7.78 (s, 1H), 7.86 (s, 1H). MS (APCI), m/z 391 [M+1], 393 [M+3].

Step 2: *N*′-(3-furan-2-yl-6,7-dichloro-quinoxalin-2-yl)-*N,N*-dimethyl-butane-1,4-diamine. *N*′-(3-Bromo-6,7-dichloro-quinoxalin-2-yl)-*N,N*-dimethyl-butane-1,4-diamine (890 mg, 2.27 mmol) was dissolved in THF (30 mL). To this solution was added tributylstannyl-2-furan (1.05 g, 2.95 mmol), $PdCl_2.(PPh_3)_2$ (80 mg, 0.113 mmol), and CuI (25 mg, 0.23 mmol). The resulting suspension was refluxed for 2 h, cooled to room temperature, and filtered. The volatiles were removed in vacuo, and the residue was chromatographed using silica gel eluting with 5% Et_3N and 5% CH_3OH in EtOAc to give the desired product as a viscous oil. The bis·HCl salt was prepared by bubbling HCl gas into the EtOAc solution of the free base. Mp 247–248 °C; ^{1}H NMR (DMSO-d_6) δ 1.64 (m, 2H), 2.10 (m, 2H), 2.73 (d, J=4.8 Hz, 6H), 3.13 (m, 2H), 3.60 (m, 2H), 7.44 (dd, J=3.7, 0.7 Hz, 1H), 7.66 (broad t, J=5.5 Hz, 1H, NH), 7.83 (s, 1H), 8.03 (m, 1H), 10.06 (broad s, 1H); MS (APCI), m/z 365 [M+1], 367 [M+3]; anal. ($C_{18}H_{20}N_4O_1Cl_2\cdot 2HCl\cdot 2.82H_2O$) C, H, N.

Example 13u: *N*′-(6,7-dichloro-3-furan-2-yl-quinoxalin-2-yl)-*N,N*-dimethyl-propane-1,3-diamine. The title compound was prepared according to the experimental procedure for example **13i**, starting with compound **10b**, and was obtained and then made into the HCl salt by treatment with EtOAc/HCl. The salt is a yellow solid: mp 247–248 °C ; ^{1}H NMR (DMSO-d_6) δ 2.10(m, 2H), 2.73 (d, J=4.8 Hz, 6H), 3.13 (m, 2H), 3.60 (m, 2H), 7.44 (dd, J=3.7, 0.7 Hz, 1H), 7.66 (broad t, J=5.5 Hz, 1H, NH), 7.83 (s, 1H), 8.03 (m, 1H), 10.06 (broad s, 1H); MS (APCI), m/z [M+1], 367 [M+3]; anal. ($C_{17}H_{18}N_4O_1Cl_2\cdot 2HCl\cdot 2.0H_2O$) C, H, N.

Example 13v: *N*′-[6,7-dichloro-3-(5-pyridin-2-yl-furan-2-yl)-quinoxalin-2-yl]-*N,N*-diethyl-butane-1,4-diamine. Step 1: 2-furan-2-yl-pyridine; step 1 of the procedure for compound **13q** was followed, to give the desired product as a white solid (6.68 g, 89% yield). ^{1}H NMR ($CDCl_3$) δ 6.52–6.54 (m, 1H), 7.04–7.06 (m, 1H), 7.11–7.17 (m, 1H), 7.52–7.53 (m, 1H), 7.66–7.74 (m, 2H), 8.57–8.60 (m, 1H).

Step 2: 2-(5-tributylstannanyl-furan-2-yl)-pyridine. The procedure from step 2 of example **13q** was followed, to give the desired product as a colorless oil (0.89 g, 15% yield): ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J=7.3 Hz, 9H), 1.12 (t, J=7.7 Hz, 6H), 1.25–1.43 (m, 6H), 1.54–1.65 (m, 6H), 6.68 (d, J=3.2 Hz, 1H), 7.08–7.10 (m, 2H), 7.68–7.71 (m, 2H), 8.56 (d, J=5.0 Hz, 1H).

Step 3: *N*′-[6,7-dichloro-3-(5-pyridin-2-yl-furan-2-yl)-quinoxalin-2-yl]-*N,N*-diethyl-butane-1,4-diamine. The title compound was prepared according to the general experimental procedure for example **10a**, and was obtained as a brown solid (89% yield): ^{1}H NMR (free base, $CDCl_3$) δ 0.94 (t, J=7.1 Hz, 6H), 1.59–1.77 (m, 4H), 2.43–2.52 (m, 6H), 3.52–3.59 (m, 2H), 6.92 (br, 1H), 7.11–7.19 (m, 2H), 7.37 (d, J=3.8 Hz, 1H), 7.53 (d, J=7 Hz, 1H), 7.63–7.71 (m, 2H), 7.76 (s, 1H), 8.55–8.58 (m, 1H); MS (ESI+) m/z 484 [M+1]; anal ($C_{25}H_{27}N_5Cl_2O\cdot 2HCl\cdot 2.5H_2O$) C, H, N.

Example 13w: *N*′-[6,7-dichloro-3-(5-pyridin-4-yl-furan-2-yl)-quinoxalin-2-yl]-*N,N*-diethyl-butane-1,4-diamine. Step 1: 4-furan-2-yl-pyridine. To a solution of 4-bromopyridine (5.00 g, 31.64 mmol) in THF (50 mL) under Ar, CuI (0.60 g, 3.16 mmol), bis(triphenylphosphine)palladium (II) chloride (1.11 g, 1.56 mmol) and 2-(tributylstannyl) furan (9.90 mL, 31.64 mmol) were added. The reaction mixture was heated to reflux for overnight. The reaction mixture was cooled to RT. EtOAc (30 mL) was added into the resulting residue. The organic phase was washed with saturated KF solution (3×20 mL). The resulting organic layer was dried over $MgSO_4$. The crude product was chromatographed using silica gel, eluting with EtOAc–hexane (1:3), to give the desired product as a light orange solid (3.50 g, 69% yield). ^{1}H NMR ($CDCl_3$) δ 6.51–6.53 (m, 1H), 6.87–6.88 (m, 1H), 7.50–7.55 (m, 3H), 8.58–8.60 (m, 2H).

Step 2: 4-(5-tributylstannanyl-furan-2-yl)-pyridine. The procedure from step 2 of example **13q** was followed, to give the desired product as a colorless oil (0.60 g, 10% yield): ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 9H), 1.12 (t, J = 7.7 Hz, 6H), 1.26–1.43 (m, 6H), 1.54–1.63 (m, 6H), 6.65 (d, J = 3.2 Hz, 1H), 6.89(d, J = 3.2 Hz, 1H), 7.49–7.53 (m, 2H), 8.56–8.58 (m, 2H).

Step 3: *N*′-[6,7-dichloro-3-(5-pyridin-4-yl-furan-2-yl)-quinoxalin-2-yl]-*N,N*-diethyl-butane-1,4-diamine. The title compound was prepared according to the general experimental procedure for example **10a** using starting material **13b** and was obtained as a brown solid (82% yield): ^{1}H NMR (free base, $CDCl_3$) δ 0.96 (t, J = 7.1 Hz, 6H), 1.57–1.76 (m, 4H), 2.45–2.54 (m, 6H), 3.51–3.59 (m, 2H), 6.58 (br, 1H), 6.98 (d, J = 3.7 Hz, 1H), 7.35 (d, J = 3.7 Hz, 1H), 7.40 (dd, J = 4.7, 1.5 Hz, 2H), 7.61 (s, 1H), 7.74 (s, 1H), 8.60 (dd, J = 4.7, 1.5 Hz, 2H); MS (ESI+) m/z 484 [M + 1]; anal ($C_{25}H_{27}N_5Cl_2O\cdot 3HCl\cdot 1.4H_2O$) C, H, N.

Example 13x: *N*′-[6,7-dichloro-3-(5-phenyl-furan-2-yl)-quinoxalin-2-yl]-*N,N*-diethyl-butane-1,4-diamine. Step 1: tributyl-(5-phenyl-furan-2-yl)-stannane. The procedure from step 2 of example **13v** was followed, to give the desired product as a brown oil, which was carried on to product without further purification.

Step 2 *N*′-[6,7-dichloro-3-(5-phenyl-furan-2-yl)-quinoxalin-2-yl]-*N,N*-diethyl-butane-1,4-diamine. The title compound was prepared according to the general experimental procedure for example **10a**, and was obtained as a brown solid (70% yield): ^{1}H NMR (free base, $CDCl_3$) δ 1.02 (t, J = 7.1 Hz, 6H), 1.25–1.42 (m, 4H), 2.45–2.65 (m, 6H), 4.12 (dd, J = 6.5, 2.2 Hz, 2H), 6.71–6.73 (m, 2H), 7.31–7.56 (m, 4H), 7.62–7.69 (m, 3H), 8.02 (s, 1H); MS (ESI+) m/z 484 [M + 1]; anal ($C_{26}H_{28}N_4Cl_2O\cdot 2HCl\cdot 1H_2O$) C, H, N.

Example 13y: *N*-(3-benzofuran-2-yl-6,7-dichloro-quinoxalin-2-yl)-*N,N*-diethyl-butane-1,4-diamine. The title compound was prepared according to the experimental procedure for example **10a**, and the product was obtained as a red-orange oil. The free base was dissolved in EtOAc and treated with HCl gas to produce the corresponding salt as a yellow-orange powder (88% yield). ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J = 6.9 Hz, 6H), 1.64 (m, 2H), 1.74 (m, 2H), 2.53 (m, 6H), 3.60 (m, 2H), 7.34 (m, 1H), 7.43(m, 1H), 7.64 (m, 1H), 7.71(m, 2H), 7.79 (s, 1H), 7.93 (s, 1H); MS (APCI), m/z 457 [M + 1]; anal. ($C_{24}H_{26}N_4Cl_2O\cdot 2HCl\cdot 0.22H_2O$) C, H, N.

***N*′-(6,7-Dichloro-3-pyridin-2-yl-quinoxalin-2-yl)-*N,N*-dimethyl-ethane-1,2-diamine (15a, *n* = 2).** A solution of 3-(2-pyridyl)-2,6,7-trichloroquinoxaline, (compound **14**, 0.50 g, 1.6 mmol) and dimethylaminoethylamine (0.28 g, 3.2 mmol) in toluene (20 mL) was heated to reflux for 16 h. The resulting solution was cooled, filtered, and the filtrate concentrated in vacuo. The residue was purified by flash chromatography on silica gel (5–10% methanol/chloroform) to give a yellow powder (0.253 g, 45% yield): mp 95–97 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 6H), 2.64 (t, J = 6.35 Hz, 2H), 3.71 (m, 2H), 7.36 (m, 1H), 7.73 (s, 1H), 7.85 (dt, J = 8.1, 1.9 Hz, 1H), 8.59 (m, 1H), 8.68 (d, J = 8.3 Hz, 1H), 10.37 (m, 1H); MS (APCI), m/z, 362 [M + 1], 364 [M + 3]; anal. ($C_{17}H_{17}N_5Cl_2$) C, H, N.

***N*′-(6,7-Dichloro-3-pyridin-2-yl-quinoxalin-2-yl)-*N,N*-dimethyl-propane-1,3-diamine (15b, *n* = 3).** The procedure from example **15a** was followed, to afford the title compound as a yellow powder (0.43 g, 73% yield): mp 105–106 °C; ^{1}H NMR ($CDCl_3$) δ 1.91 (m, 2H), 2.25 (s, 6H), 2.43 (t, J = 7.2 Hz, 2H), 3.66 (m, 2H), 7.38 (m, 1H), 7.73 (s, 1H), 7.88 (t, J = 7.9 Hz, 1H), 7.93(s, 1H), 8.60 (m, 1H), 8.69 (d, J = 7.9 Hz, 1H), 10.25 (broad s, 1H); MS (APCI), m/z 376 [M + 1], 378 [M + 3]; anal. ($C_{18}H_{19}N_5Cl_2$) C, H, N.

***N*′-(6,7-Dichloro-3-pyridin-2-yl-quinoxalin-2-yl)-*N,N*-dimethyl-butane-1,4-diamine (15c, *n* = 4).** The procedure from example **15a** was followed, to afford the title compound as a yellow powder (0.34 g, 55% yield): mp 81–83 °C; ^{1}NMR ($CDCl_3$) δ 1.62 (m, 2H), 1.73 (m, 2H), 2.18 (s, 6H), 2.30 (t, J = 7.3 Hz, 2H), 3.59 (m, 2H), 7.34 (m, 1H), 7.70 (s, 1H), 7.84 (dt, J = 7.8, 1.7 Hz, 1H), 7.89 (s, 1H), 8.56 (m, 1H), 8.67 (d, J = 8.3 Hz, 1H), 10.20 (broad s, 1H); MS (APCI), m/z 390 [M + 1], 392 [M + 3]. Anal. ($C_{19}H_{21}N_5Cl_2$) C, H, N.

***N*′-(6,7-Dichloro-3-pyridin-2-yl-quinoxalin-2-yl)-*N,N*-dimethyl-pentane-1,5-diamine (15d, *n* = 5).** A solution of 3-(2-pyridyl)-2,6,7-trichloroquinoxaline (2.1 g, 6.9 mmol) and (5-amino-pentyl)-carbamic acid *tert*-butyl ester (2.8 g, 14 mmol), in toluene (50 mL) was heated to reflux for 16 h. The resulting solution was cooled, filtered, and the filtrate concentrated in vacuo. The residue was purified by flash chromatography on silica gel (50% ethyl acetate/hexane) to give 2.09 g of orange powder (yield 64%). This powder was added to a solution of methanol (60 mL) and HCl. The resulting mixture was stirred 2 h, then treated with 2 N aqueous KOH (40 mL) and stirred 10 min, diluted with water and filtered. The precipitate was dried in vacuo to give 1.9 g of a orange solid. The crude aminoquinoxaline was added to a solution of water (10 mL), 90% formic acid (1.6 g, 32 mmol), and formalin (1.1 g, 14 mmol). This mixture was refluxed for 2 h, then heated below boiling for 16 h. After cooling, the reaction mixture was filtered, dissolved in methanol, treated with 2 N HCl (5 mL), stirred 20 min, treated with 2 N aqueous KOH (5 mL), and filtered. The precipitate was purified by flash chromatography over silica gel (1:5 methanol–chloroform) to give the title compound as a yellow powder (0.83 g, 34% yield): mp 100–102 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (m, 2H), 1.57 (m, 2H), 1.80 (m, 2H), 2.23 (s, 6H), 2.31 (t, J = 7.3 Hz, 2H), 3.61 (m, 2H), 7.38 (m, 1H), 7.73 (s, 1H), 7.86 (dt, J = 8.0, 1.9 Hz, 1H), 7.92 (s, 1H), 8.61 (m, 1H), 8.70 (d, J = 8.3 Hz, 1H), 10.22 (broad t, J = 4.6 Hz, 1H); MS (APCI), m/z 404 [M + 1], 406 [M + 3]; anal. ($C_{20}H_{27}N_5Cl_2$) C, H, N.

***N*′-(6,7-Dichloro-3-pyridin-2-yl-quinoxalin-2-yl)-*N,N*-dimethyl-hexane-1,6-diamine (15e, *n* = 6).** The procedure from example **15a** was followed, to afford the title compound as a yellow powder (0.41 g, 62% yield): mp 88–90 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (m, 2H), 1.43 (m,

4H), 1.69 (m, 2H), 2.15 (s, 6H), 2.20 (m, 2H), 3.56 (m, 2H), 7.34 (m, 1H), 7.70 (s, 1H), 7.85 (dt, $J=8.0$, 1.7 Hz, 1H), 7.89 (s, 1H), 8.57 (m, 1H), 8.68 (d, $J=8.1$ Hz, 1H), 10.20 (s, 1H); MS (APCI), m/z 418 [M + 1], 420 [M + 3]; anal. ($C_{21}H_{25}N_5Cl_2$) C, H, N.

Compound 15f: *N*-(6,7-dichloro-3-pyridin-2-yl-quinoxalin-2-yl)-*N′*,*N′*-dimethyl-cyclohexane-1,4-diamine. The title compound was prepared according to the experimental procedure for example **15a** and was obtained as a yellow solid (84% yield). Mp 180–182 °C; ^{1}H NMR (DMSO-d_6) δ 1.80–2.45 (m, 8H), 2.92 (s, 6H), 4.58 (broad s, 1H), 7.80 (m, 1H), 7.75 (s, 1H), 8.07 (s, 1H), 8.10 (m, 1H), 8.82 (m, 1H); MS (APCI), m/z 417 [M + 1], 419 [M + 3]; anal. ($C_{21}H_{23}N_5Cl_2$·1.04HCl) C, H, N.

Compound 15g: *N*-(6,7-dichloro-3-pyridin-2-yl-quinoxalin-2-yl)-cyclohexane-1,4-diamine. The title compound was prepared according to the experimental procedure for example **15a** and was obtained as a yellow solid (98% yield): mp 280–282 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 1.82 (m, 4H), 2.22 (m, 2H), 2.46 (m, 2H), 4.38 (broad, s, 1H), 7.74 (dd, $J=7.0$, 4.7 Hz, 1H), 8.21 (dd, $J=15.0$, 7.0 Hz, 1H), 8.82 (dd, $J=8.0$, 4.0 Hz, 1H); MS (APCI), m/z 388 [M + 1], 390 [M + 3]; anal. ($C_{19}H_{19}N_5Cl_2$·2.0HCl) C, H, N.

Compound 15h: 2-[1,4′]bipiperidinyl-1′-yl-6,7-dichloro-3-pyridin-2-yl-quinoxaline. The title compound was prepared according to the experimental procedure for example **15a** and was obtained as a bright yellow solid (92% yield): mp 275–277 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 1.33–1.82 (m, 12H), 2.48 (s, 3H), 2.75 (t, $J=12.7$ Hz, 2H), 7.35 (t, $J=6.1$ Hz, 1H), 7.87 (s, 1H), 7.37 (m, 1H), 8.06 (s, 1H), 8.76 (s, 1H); MS (APCI), m/z 441 [M + 1], 444 [M + 3]; anal. ($C_{23}H_{25}N_5Cl_2$·1.32HCl) C, H, N.

Compound 15i: (6,7-dichloro-3-pyridin-2-yl-quinoxalin-2-yl)-(4-diethylaminomethyl-phenyl)-amine. The title compound was prepared according to the experimental procedure for example **15a** and was obtained as an orange powder (83% yield). Mp 250–252 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 1.04 (t, $J=7.1$ Hz, 6H), 2.57 (q, $J=7.1$ Hz, 4H), 3.61 (s, 2H), 7.38 (d, $J=8.4$ Hz, 2H), 7.48 (dd, $J=5.0$, 1.0 Hz, 1H), 7.93 (s, 1H), 7.90(s, 2H), 7.97 (dt, $J=8.1$, 2.0 Hz, 1H), 8.03 (s, 1H), 8.73 (d, $J=4.8$ Hz, 1H), 8.84 (d, $J=8.1$ Hz, 1H), 12.87 (s, 1H); MS (APCI), m/z 347 [M + 1], 349 [M + 3]; anal. ($C_{24}H_{23}N_5Cl_2$·0.42H_2O) C, H, N.

Example 16a: *N′*-(3-[2,2′]bithiophenyl-5-yl-6,7-dichloro-quinoxalin-2-yl)-*N*,*N*-dimethyl-but-2-yne-1,4-diamine. Step 1: (3-bromo-6,7-dichloro-quinoxalin-2-yl)-prop-2-ynyl-amine. To a solution of 2,3-dibromo-6,7-dichloro-quinoxaline (1.50 g, 4.20 mmol) in THF (20 mL), K_2CO_3 (1.16 g, 8.40 mmol) and propargylamine (0.58 mL, 8.40 mmol) were added. The reaction mixture was stirred at room temperature overnight. Saturated $NaHCO_3$ solution (10 mL) was added to quench the reaction. The phases were separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic phase was dried over $MgSO_4$. The crude product was chromatographed on silica gel, eluting with EtOAc–hexane (1:8 to 1:3), to give the desired product as a white solid (1.00 g, 75% yield): ^{1}H NMR ($CDCl_3$) δ 2.31 (t, $J=2.4$ Hz, 1H), 4.35 (dd, $J=5.3$, 2.4 Hz, 2H), 5.85 (br, 1H), 7.86 (s, 1H), 7.91 (s, 1H); MS (ESI), m/z 332 [M + 1].

Step 2: *N′*-(3-bromo-6,7-dichloro-quinoxalin-2-yl)-*N*,*N*-dimethyl-but-2-yne-1,4-diamine. To a solution of paraformaldehyde (65.85 mg, 2.20 mmol), copper (II) acetate (20.00 mg, 0.11 mmol) in dioxane (10 mL) in a sealed tube, dimethylamine (1.10 mL, 2.20 mmol, 2 M solution in THF) was added. The reaction mixture was heated to 60 °C for 1 h. Then the mixture was cooled to room temperature and (3-bromo-6,7-dichloro-quinoxalin-2-yl)-prop-2-ynyl-amine (0.72 g, 2.20 mmol) was added. The final reaction mixture was heated to 80 °C overnight. After cooling to rt, 10% KOH solution (5 mL) was added to quench the reaction. The phases were separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic phases were dried over $MgSO_4$. The crude product was chromatographed on silica gel, eluting with EtOAc–MeOH–Et_3N (10:1:0.1), to give the desired product as a white solid (0.44 g, 52% yield): ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 6H), 3.25–3.26 (m, 2H), 4.34–4.38 (m, 2H), 5.87 (br, 1H), 7.81 (s, 1H), 7.87 (s, 1H); MS (ESI), m/z 389 [M + 1].

Step 3: *N′*-(3-[2,2′]bithiophenyl-5-yl-6,7-dichloro-quinoxalin-2-yl)-*N*,*N*-dimethyl-but-2-yne-1,4-diamine. The title compound was prepared according to the general experimental procedure for example **10a**, and was obtained as a light brown solid (37% yield): ^{1}H NMR (free base, $CDCl_3$) δ 2.29 (s, 6H), 3.24 (S, 2H), 4.37–4.39 (m, 2H), 5.70 (br, 1H), 7.06–7.07 (m, 1H), 7.19 (d, $J=3.9$ Hz, 1H), 7.28–7.31 (m, 2H), 7.62 (d, $J=3.9$ Hz, 1H), 7.78 (s, 1H), 7.94 (s, 1H); MS (ESI+) m/z 473 [M + 1]; anal ($C_{22}H_{18}N_4Cl_2S_2$·HCl·0.8H_2O·0.2MeOH) C, H, N.

Example 16b: *N′*-(3-[2,2′]bithiophenyl-5-yl-6,7-dichloro-quinoxalin-2-yl)-*N*,*N*-dimethyl-but-2-ene-1,4-diamine. To a solution of **16a** (150.00 mg, 0.31 mmol) in THF (30 mL), Lindlar catalyst (15.00 mg, 10 wt%) was added. The reaction mixture was hydrogenated on a Parr apparatus under H_2 at 40 PSI for 3 days. The mixture was filtered through Celite and concentrated. The resulting crude product was chromatographed using silica gel, eluting with EtOAc–MeOH–Et_3N (10:1:0.1), to give the desired product as a yellow solid (62.10 mg, 42% yield). The HCl salt was prepared by treating a solution of free base in EtOAc with 1 M HCl solution in Et_2O: ^{1}H NMR (free base, $CDCl_3$) δ 2.21 (s, 6H), 3.03 (d, $J=6.6$ Hz, 2H), 4.21 (t, $J=5.3$ Hz, 2H), 5.80–5.90 (m, 2), 6.43 (br, 1H), 7.05–7.08 (m, 1H), 7.21 (d, $J=3.9$ Hz, 1H), 7.29–7.31 (m, 2H), 7.64 (d, $J=3.9$ Hz, 1H), 7.78 (s, 1H), 7.95 (s, 1H); MS (ESI), m/z 475 [M + 1]; anal ($C_{22}H_{20}N_4Cl_2S_2$·HCl·0.5EtOAc) C, H, N.

Example 16c: 1-[4-(3-[2,2′]bithiophenyl-5-yl-6,7-dichloro-quinoxalin-2-ylamino)-butyl]-piperidin-4-ol. Step 1: 1-[4-(3-bromo-6,7-dichloro-quinoxalin-2-ylamino)-butyl]-

piperidin-4-ol. The procedure for example **13b** was followed, to yield a tan solid (61% yield): ^{1}H NMR ($CDCl_3$) δ 1.51–1.81 (m, 7H), 1.83–2.0 (m, 2H), 2.14 (t, J = 9.0 Hz, 2H), 2.38 (t, J = 7.0 Hz, 2H), 2.78 (m, 2H), 3.57 (m, 2H), 3.70 (m, 1H), 5.80 (m, 1H), 7.78 (s, 1H), 7.86 (s, 0H); MS (ESI+), m/z 447 [M + 1].

Step 2: 1-[4-(3,[2,2′]bithiophenyl-5-yl-6,7-dichloro-quinoxalin-2-ylamino)-butyl]-piperidin-4-ol. The title compound was prepared according to the procedure for example **10a**, to yield a dark red solid (30 mg, 32% yield): ^{1}H NMR (free base, $CDCl_3$) δ 1.51–2.00 (m, 8H), 2.24 (m, 2H), 2.40–2.55 (m, 3H), 2.82 (m, 2H), 3.59 (m, 2H), 3.70 (m, 1H), 5.80 (m, 1H), 7.05–7.10 (m, 1H), 7.15–7.36 (m, 3H), 7.62 (d, J = 4.0 Hz, 1H), 7.77 (s, 1H), 7.94 (s, 1H); MS (ESI+) m/z 533 [M + 1]; anal ($C_{25}H_{28}N_4O_1Cl_2S_2 \cdot 2HCl \cdot 1H_2O \cdot 1CH_3OH$) C, H, N.

Example 16d: (3-[2,2′]bithiophenyl-5-yl-6,7-dichloro-quinoxalin-2-yl)-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-amine. Step 1: (3-bromo-6,7-dichloro-quinoxalin-2-yl)-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-amine. The procedure for example **13b** was followed, to yield a light brown solid (0.59 g, 80% yield): ^{1}H NMR ($CDCl_3$) δ 1.80–1.87 (m, 4H), 2.15–2.25 (m, 2H), 2.31–2.42 (m, 5H), 3.21–3.33 (m, 2H), 4.24–4.37 (m, 1H), 6.23 (d, J = 6.2 Hz, 1H), 7.80 (s, 1H), 6.87 (s, 1H); MS (ESI), m/z, 419 [M + 1].

Step 2: (3-[2,2′]bithiophenyl-5-yl-6,7-dichloro-quinoxalin-2-yl)-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-amine. The title compound was prepared using the procedure for example **10a**, to yield a brown solid (75% yield): ^{1}H NMR (free base, $CDCl_3$) δ 1.80–1.87 (m, 4H), 2.17–2.21 (m, 2H), 2.32–2.44 (m, 5H), 3.18–3.30 (m, 2H), 4.28–4.40 (m, 1H), 6.00 (d, J = 6.2 Hz, 1H), 7.07–7.10 (m, 1H), 7.26–7.29 (m, 2H), 7.31 (d, J = 3.8 Hz, 1H), 7.61 (d, J = 3.8 Hz, 1H), 7.80 (s, 1H), 7.96 (s, 1H); MS (ESI), m/z 502 [M + 1]; anal ($C_{24}H_{22}N_4Cl_2S_2 \cdot 2HCl \cdot 1.5H_2O \cdot 0.5EtOAc$) C, H, N.

Example 16e: (1-benzyl-piperidin-4-yl)-(3-[2,2′]bithiophenyl-5-yl-6,7-dichloro-quinoxalin-2-yl)-amine. Step 1: 4-(3-bromo-6,7-dichloro-quinoxalin-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester. The procedure from example **13b** was followed, starting with 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester. The bromide intermediate was obtained as a brown solid (736 mg, 62% yield): ^{1}H NMR (free base, $CDCl_3$) δ 1.40–1.62 (m, 11H), 2.09–2.20 (m, 2H), 3.01 (t, J = 11.5 Hz, 2H), 4.03–4.29 (m, 3H), 5.60 (d, J = 7.5 Hz, 1H), 7.77 (s, 1H), 7.84 (s, 1H).

Step 2: 4-(3-[2,2′]bithiophenyl-5-yl-6,7-dichloro-quinoxalin-2-ylamino)-piperidine-1-carboxylic acid *tert*-butyl ester. The procedure from example **10a** was followed, to yield an orange solid (706 mg, 95% yield): ^{1}H NMR ($CDCl_3$) δ 1.42–1.56 (m, 9H), 2.12–2.25 (m, 2H), 3.04 (t, J = 11.2 Hz, 2H), 3.95–4.08 (m, 2H), 4.20–4.40 (m, 1H), 5.50 (d, J = 7.0 Hz, 1H), 7.06 (dd, J = 4.8, 4.0 Hz, 1H), 7.20 (d, J = 3.9 Hz, 2H), 7.29 (m, 2H), 7.54 (d, J = 3.9 Hz, 1H), 7.77 (s, 1H), 7.93 (s, 1H).

Step 3: (3-[2,2′]bithiophenyl-5-yl-6,7-dichloro-quinoxalin-2-yl)-piperidin-4-yl-amine. (4-(3-[2,2′]bithiophenyl-5-yl-6,7-dichloro-quinoxalin-2-ylamino)-piperidine-1-carboxylic acid *tert*-butyl ester, (220 mg, 0.416 mmol) was dissolved in HCl/dioxane (4 M, 5 mL, 20 mmol) and stirred for 1 h at rt. The solvent was removed in vacuo, and the residue was partitioned between aqueous NaOH and ethyl acetate. The organic layers were dried, evaporated, and chromatographed on silica gel, eluting with EtOAc–MeOH–Et_3N (10:1:0.1), to give the desired product as an orange solid (111 mg, 58% yield). The HCl salt was prepared by treating a solution of free base in methanol with 1 M HCl solution in methanol: ^{1}H NMR (free base, $CDCl_3$) δ 1.40–1.50 (m, 2H), 2.12–2.25 (m, 2H), 2.75–2.90 (m, 2H), 3.10–3.25 (m, 2H), 3.50 (s, 1H), 4.25 (m, 1H), 5.56 (d, J = 7.3 Hz, 1H), 7.05–7.10 (m, 1H), 7.20–7.35 (m, 3H), 7.58 (d, J = 4.0 Hz, 1H), 7.78 (s, 1H), 7.95 (s, 1H); MS (ESI+), m/z 461 [M + 1]; anal ($C_{21}H_{18}N_4Cl_2S_2 \cdot 2HCl \cdot 0.5H_2O \cdot 1.0MeOH$) C, H, N.

Step 4: (1-benzyl-piperidin-4-yl)-(3-[2,2′]bithiophenyl-5-yl-6,7-dichloro-quinoxalin-2-yl)-amine. A solution of (3-[2,2′]bithiophenyl-5-yl-6,7-dichloro-quinoxalin-2-yl)-piperidin-4-yl-amine·2HCl (108 mg, 0.203 mmol) in methanol (10 mL) was treated with benzaldehyde (0.05 mL, 0.5 mmol) and sodium cyanoborohydride (31 mg, 0.5 mmol). The mixture was brought to pH = 6.0 with methanolic sodium methoxide, and stirred 12 h at room temperature. The solvent was removed in vacuo, and the residue was partitioned between aqueous NaOH and ethyl acetate. The organic layers were dried, evaporated, and chromatographed on silica gel, eluting with EtOAc–MeOH–Et_3N (10:1:0.1), to give the title compound as an orange solid (20 mg, 18% yield). The HCl salt was prepared by treating a solution of free base in methanol with 1 M HCl solution in methanol: ^{1}H NMR (free base, $CDCl_3$) δ 1.50–1.72 (m, 2H), 2.08–2.25 (m, 2H), 2.28 (t, J = 10.8 Hz, 2H), 2.75–2.90 (m, 2H), 3.56 (s, 2H), 4.15 (m, 1H), 5.53 (d, J = 7.0 Hz, 1H), 7.05–7.10 (m, 1H), 7.20–7.50 (m, 8H), 7.54 (d, J = 4.0 Hz, 1H), 7.76 (s, 1H), 7.93 (s, 1H); MS (ESI+), m/z 551 [M + 1]; anal ($C_{28}H_{24}N_4Cl_2S_2 \cdot 2HCl \cdot 1.0H_2O \cdot 1.0CH_2Cl_2$) C, H, N.

Example 16f: (3-[2,2′]bithiophenyl-5-yl-6,7-dichloro-quinoxalin-2-yl)-(1-ethyl-piperidin-4-yl)-amine. The title compound was prepared using the procedure for example **16e**, step 4, to yield an orange solid (73 mg, 66% yield): ^{1}H NMR (free base, $CDCl_3$) δ 1.11 (t, J = 7.0 Hz, 3H), 1.50–1.72 (m, 2H), 2.10–2.35 (m, 4H), 2.44 (q, J = 7.25 Hz, 2H), 2.75–2.90 (m, 2H), 4.13 (m, 1H), 5.53 (d, J = 7.0 Hz, 1H), 7.05–7.10 (m, 1H), 7.18 (d, J = 3.8 Hz, 2H), 7.26–7.36 (m, 2H), 7.54 (d, J = 3.9 Hz, 1H), 7.74 (s, 1H), 7.90 (s, 1H); MS (ESI+), m/z 489 [M + 1]; anal ($C_{23}H_{22}N_4Cl_2S_2 \cdot 2HCl \cdot 1.0H_2O$) C, H, N.

Receptor binding assay.[22] The receptor-binding assay was carried out in RPMI-1640 culture media supplemented with 20 mM HEPES buffer and 0.2% BSA, pH 7.4. The binding mixture consist of 80 μL of ^{125}I-IL-8 (40 pM) with or without cold excess IL-8 (38 nM), 50 μL of the compound to be tested, and 120 μL containing

40,000 human neutrophils. The mixture was incubated at room temperature for 3 h. The reaction was terminated by centrifuging the cells through a sucrose solution and the radioactivity in the pellet was measured using a gamma counter.

Chemotaxis assay. Freshly isolated human neutrophils were resuspended in RPMI-1640 culture media-based chemotaxis buffer. The cells were pre-incubated with or without compounds for 60 min and placed into the top chamber. rhIL-8 with or without drug was placed into the lower chambers of chemotaxis plate. The plates were incubated at 37 °C for 30 min. The top chamber was then removed and the number of chemotaxed neutrophils in the bottom chamber were counted using a FACs.

Calcium flux assay.[23] Human neutrophils were incubated with the fluorescence dye FLUO3, for 1 h. The cells were washed after this loading period, resuspended in Hank's buffer, and loaded into a 96-well plate. Compound was added to each well. After a 60-min incubation period, the cells were stimulated with human IL-8 in a 96-well FLIPR instrument and the calcium flux response recorded and quantified.

Selectivity assays. Materials for NK2, M2 and 5HT1a binding were purchased from NEN Life Science Products (Boston, MA, USA), using protocols supplied by the manufacturer. Binding of 5HT6, 5HT7 and α2C was carried out at MDS Panlabs Pharmacology Services (Bothell, WA, USA).

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