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Tandem C–N Bond Formation through Condensation and Metal-Free *N*-Arylation: Protocol for Synthesizing Diverse Functionalized Quinoxalines

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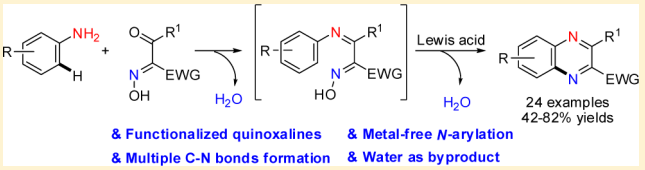
Supporting Information

ABSTRACT: Diverse functionalized quinoxalines were synthesized in good yields from arylamines and readily available β-keto oximes through condensation and metal-free *N*-arylation. The reaction was compatible with various functional groups, such as halides, cyano, and esters. A mechanism was proposed based on the experimental results. These quinoxalines were easily obtained on a gram scale and converted to various useful scaffolds. Compound LASSBio-1022 was prepared in 83% yield in two steps.



Quinoxaline derivatives are valuable synthetic targets because they are present in a range of compounds, including pharmaceuticals,[1a−g] semiconductors,[1h,i] and photoelectric materials.[1j] Since 2010, more than 8000 documents related to quinoxalines have been published.[2] About 50 pharmaceutical compounds contain the quinoxaline moiety,[3] and some representative examples of drugs, bioactive quinoxalines and their analogues are listed in Figure 1.[4] Many synthetic

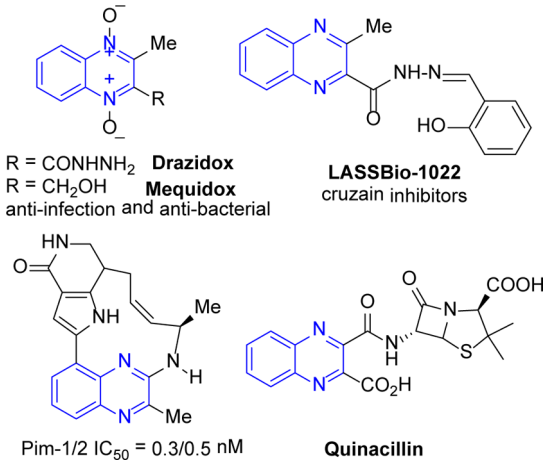


Figure 1. Examples of bioactive quinoxalines.

methods have therefore been developed for constructing quinoxaline scaffolds. Traditionally, quinoxalines have been prepared by condensation of *ortho*-phenylenediamines with diketone derivatives,[5] or *ortho*-functionalized arylamines with various ketones, alkynes, or their equivalents.[6]

Although quinoxalines have been prepared by conventional strategies using *ortho*-phenylenediamines or *ortho*-functionalized arylamines, the nitrogen sources are not always commercially available or easily obtained. Recently, Yu's group and Zeng's group developed a novel protocol for the synthesis of quinoxalines via copper-catalyzed cycloamination of *N*-aryl enamines with $TMSN_3$ or NaN_3 as the nitrogen sources, respectively (Scheme 1A).[7,8] Although much progress has been made in the copper-catalyzed synthesis of quinoxalines using $TMSN_3$ or NaN_3 as the nitrogen sources, there are safety and environmental issues associated with large-scale performance of these reactions. The development of new reagents for quinoxalines synthesis to avoid using $TMSN_3$ or NaN_3 as the nitrogen sources is important. In 2014, Zhang and co-workers reported a novel one-pot strategy for the synthesis of 3-trifluoromethylquinoxalines from *N*-aryl enamines and nitromethane under metal-free conditions (Scheme 1B).[9] Jiao and co-workers developed a novel transition-metal-free approach to the synthesis of quinoxaline *N*-oxides using readily available methyl imines and *tert*-butyl nitrite as the nitrogen source (Scheme 1C).[10] Our group studied metal-free arylation of N–O bonds with diaryliodonium salts and found that the direct *N*-arylation of oximes could be achieved because of the ambident nucleophilicity of the N–O bond.[11] We hypothesized that the condensation of β-keto oximes with arylamines would provide *N*-aryl β-keto oximes, which could be converted to various functionalized quinoxalines through Lewis-acid-mediated intramolecular *N*-arylation with production of water as a byproduct (Scheme 1D). Herein, we report an efficient tandem C–N bond formation strategy for synthesizing functionalized

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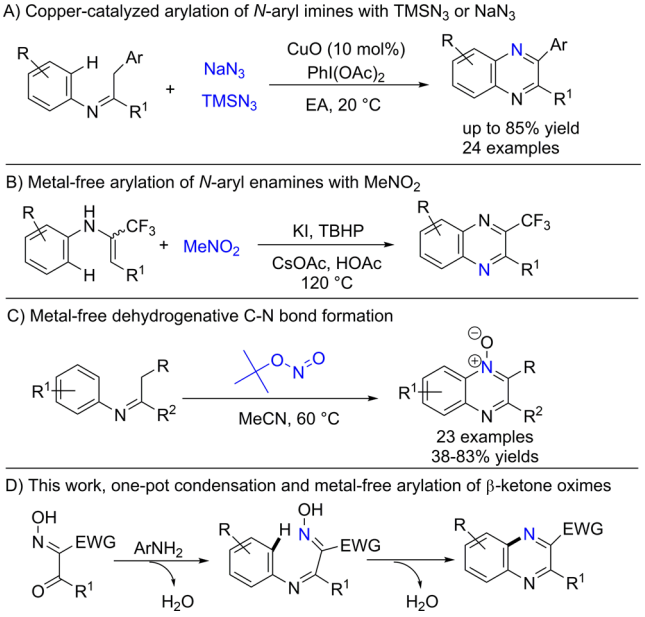
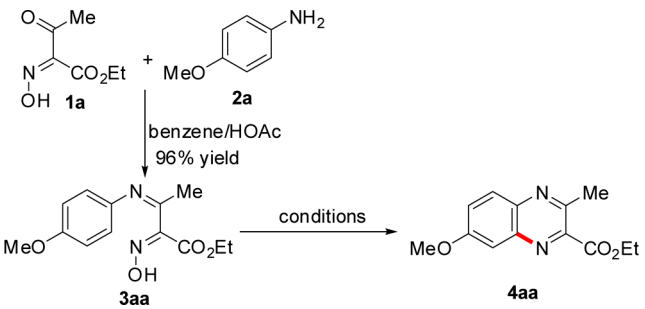
Scheme 1. Strategies for Synthesis of Quinoxalines Using Various Nitrogen Sources



quinoxalines using an oxime as the nitrogen source under mild conditions.

Initially, compound **3aa** (Table 1) was chosen as a model substrate for investigating the key step in C−N bond formation.

Table 1. Optimization of Conditions for Quinoxaline Synthesis from Oxime[a]



entry	solvent	acid	T (°C)	yield (%)[b]
1	THF	*conc*-H_2SO_4	70	52
2	THF	$BF_3{\cdot}Et_2O$	70	47
3	THF	PPA	70	42
4	THF	$POCl_3$	70	30
5	MeCN	*conc*-H_2SO_4	100	43
6	MeCN	$POCl_3$	100	87 (78)[c]
7	MeCN	$BF_3{\cdot}Et_2O$	100	45
8	DCE	$POCl_3$	85	21
9	DCM	$POCl_3$	50	27
10		$POCl_3$	110	trace

[a]Reaction conditions: **3aa** (1.0 mmol), acid (2.0 mmol), and solvent (5 mL), 0.5−24 h. [b]Isolated yield. [c]**3aa** was not purified and the yield was based on **2a**.

3aa was prepared in 96% yield by the condensation of ethyl 2-(hydroxyimino)-3-oxobutanoate (**1a**) and *p*-methoxyaniline (**2a**). When H_2SO_4 was used to promote the arylation reaction in THF, the desired product **4aa** was obtained in 52% yield (Table 1, entry 1). A series of acids in different solvents, the amount of acid, and the reaction temperature were explored to optimize the conditions for this transformation (Table 1). $POCl_3$ in MeCN gave the best result (Table 1, entry 6). The optimal conditions for producing **4aa** from **3aa** were used in the condensation and direct *N*-arylation of ethyl 2-(hydroxyimino)-3-oxobutanoate (**1a**) and *p*-methoxyaniline (**2a**). Compound **3aa**, without further purification after condensation, afforded the corresponding product **4aa** in 78% overall yield (Table 1, entry 6). This suggests that quinoxaline **4aa** can be synthesized in a one-pot reaction from ethyl 2-(hydroxyimino)-3-oxobutanoate (**1a**) and *p*-methoxyaniline (**2a**) using $POCl_3$ as a Lewis acid. Quinoxaline **4aa** was prepared as follows: ethyl 2-(hydroxyimino)-3-oxobutanoate (**1a**) and *p*-methoxyaniline (**2a**) were refluxed in benzene with HOAc as an additive for 2 h, $POCl_3$ in MeCN was added and the reaction was performed at 100 °C, providing quinoxaline in a one-pot reaction.

The scope of quinoxaline synthesis using this condensation and arylation protocol was investigated. As shown in Table 2, a series of quinoxalines were prepared from various substituted arylamines in moderate to good yields. Arylamines containing electron-donating or electron-withdrawing groups with *ortho*-, *meta*-, or *para*-substituents in the aryl ring, proceeded smoothly to provide the desired products **4**. When arylamine **2n** was used, quinoxaline **4an** was obtained in 70% yield; its structure was determined unambiguously by X-ray diffraction.[12] When unsymmetrical arylamines, such as *meta*-halo (F, Cl, Br), *meta*-isopropyl, *meta*-methoxy, or 3,4-dimethoxy aniline, were used in the reaction, the desired products were obtained regioselectively, as single isomers, in high yields (Table 2, **4af**, **4ag**, **4ah**, **4ao**, and **4ak**). However, the *meta*-methyl and 3,4-dimethyl substituted arylamines **2i** and **2l** gave two regioisomers in 1:1 ratios. These regioisomers were purified by using flash chromatography (Table 2, **4ai** and **4al**). The experimental results indicate that electronic and steric effects both play key roles in the regioselectivity of this C−N bond formation. In addition, *meta*-halo anilines gave the corresponding quinoxalines only in acceptable total yields, possibly because the condensation step was difficult (Table 2, **4af** and **4ag**). When the *para*-position of arylamines with strong electron-withdrawing groups, such as nitro, cyano, carbonyl, or trifluoromethyl, were tested, the intermediate **3** was not formed by condensation with **1a**, therefore the corresponding quinoxalines were not obtained.

Various β-keto oximes were used to determine their effect on the synthesis of functionalized quinoxalines via this condensation and metal-free arylation process. The reactions of β-keto oximes **1b−k** with **2a** provided the corresponding quinoxalines **4ba−ka** in good yields (Table 3). The R^1 group was compatible with alkyl, aryl, and heteroaryl groups. Electron-withdrawing groups (EWG), such as esters, ketone, and cyano group, can be used. Pleasingly, when unsymmetrical oxime **1j** was used, product **4ja** was obtained in 64% yield with high selectivity (Table 3, entry 10). Functionalized qunioxalines with ester, ketone, and cyano groups increase the range of potential applications of these compounds in organic synthesis.

Additional experiments (Scheme 2) were performed to clarify the reaction mechanism. When oxime **3da** was reacted with 2.0 equiv of TEMPO under the optimal conditions, the quinoxaline was obtained in 64% yield. This suggests that *N*-arylation is not a radical process (Scheme 2-1). No desired product was observed in the reaction of the methyl-protected oxime **5da** under the optimal conditions and only the oxime

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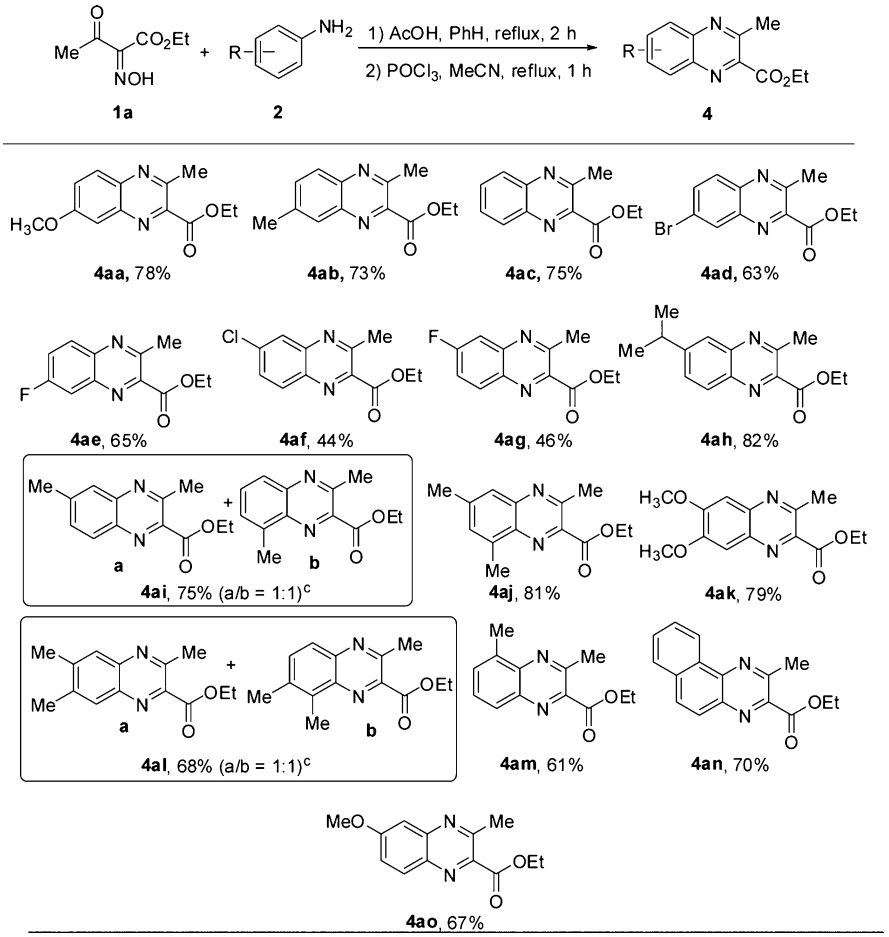
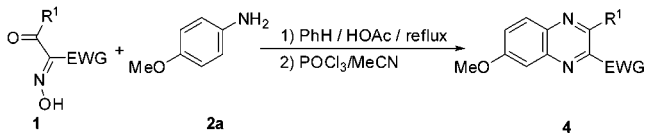
Table 2. Scope of Arylamines for Synthesis of Product 4[a,b]



[a]Reaction conditions: **1a** (1.2 mmol), **2** (1.0 mmol), $POCl_3$ (2 mmol), and MeCN (5 mL), 0.5−2 h. [b]Isolated yield. [c]Total yield of two isomers.

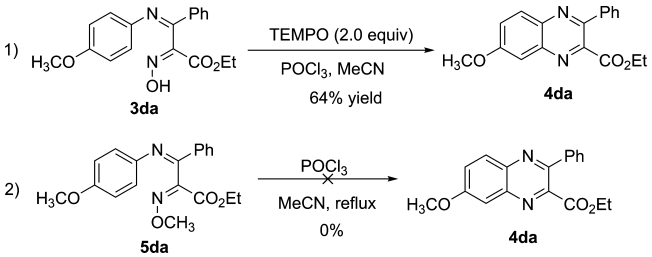
Table 3. Scope of Oximes for Synthesis of Product 4[a]



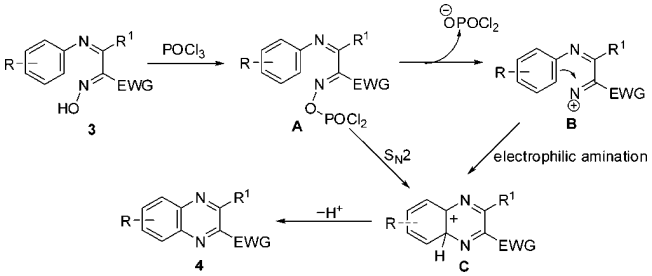
entry	1	R^1	EWG	4	yield (%)[b]
1	**1a**	Me	CO_2Et	**4aa**	78
2	**1b**	Et	CO_2Et	**4ba**	79
3	**1c**	*n*-Pr	CO_2Et	**4ca**	83
4	**1d**	Ph	CO_2Et	**4da**	59
5	**1e**	4-$MeOC_6H_4$	CO_2Et	**4ea**	49
6	**1f**	4-BrC_6H_4	CO_2Et	**4fa**	53
7	**1g**	2-MeC_6H_4	CO_2Et	**4ga**	47
8	**1h**	2-pyridinyl	CO_2Et	**4ha**	61
9	**1i**	Me	COMe	**4ia**	82
10	**1j**	Me	COPh	**4ja**	64
11	**1k**	Ph	CN	**4ka**	66

[a]Reaction conditions: **1** (1.2 mmol), **2a** (1.0 mmol), $POCl_3$ (2 mmol), and MeCN (5 mL), 0.5−2 h. [b]Isolated yield.

Scheme 2. Mechanistic Study



Scheme 3. Plausible Mechanism



was recovered (Scheme 2-2). This result shows that the hydroxyl group was the leaving group during *N*-arylation.

Although the mechanism has not been completely elucidated, a possible mechanism for quinoxaline formation is shown in Scheme 3, based on the experimental results and literature reports.[13] The oxime **3** initially reacts with $POCl_3$ to provide intermediate **A**. The phosphoryl group of intermediate **A** serves as the leaving group, forming nitrogen ion intermediate **B**, which goes through an electrophilic amination to afford intermediate **C**. Alternatively, removal of the

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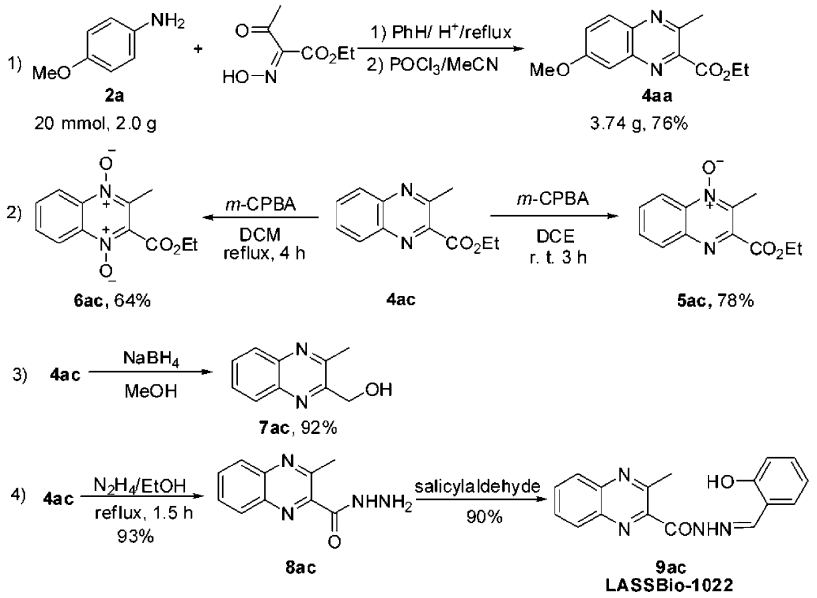
Scheme 4. Applications of Quinoxalines



phosphoryl group and cyclization might be a concerted process. Finally, aromatization of intermediate **C** furnishes the qunioxaline **4**.

To explore the practical applications of these functionalized quinoxalines, we found that the reaction could be performed using 2.0 g of arylamine **2a** to give 3.74 g of quinoxaline **4aa** in 76% yield (Scheme 4-1). Oxidation of **4ac** with *m*-CPBA at room temperature provided the N^4-oxides quinoxaline **5ac** in 78% yield while 1,4-dioxides quinoxaline **6ac** was obtained in 64% yield under reflux conditions (Scheme 4-2).[14] Treatment of **4ac** with $NaBH_4$ in MeOH afforded alcohol **7ac** in 92% yield (Scheme 4-3). The reaction of **4ac** with hydrazine gave hydrazide **8ac**, which was converted to **9ac** in 90% yield by reaction with salicylaldehyde. Compound **9ac**, named **LASSBio-1022**, is a potential lead compound for developing novel cruzain inhibitors.[4c]

In summary, we have developed an efficient one-pot protocol for the synthesis of structurally diverse functionalized quinoxalines via condensation and metal-free *N*-arylation. This method provides a metal-free and green route for preparation of functionalized quinoxalines from readily available common arylamines and β-keto oximes as the nitrogen source. The reaction can be easily performed on the gram scale and various useful scaffolds can be obtained from the obtained functionalized quinoxalines.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under an air atmosphere. Commercially available reagents were used without further purification. The NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on 400, 500, or 600 MHz instrument with TMS as the internal standard. NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz (Hz), and integration. IR spectra were recorded on FT-IR spectrometer, and only major peaks are reported in cm^{-1}. HRMS were measured in ESI mode and the mass analyzer of the HRMS was TOF. Flash column chromatography was performed on silica gel (300−400 mesh).

Synthesis of Product 3a. A round-bottle flask connected with water separator was charged with oxime **1a** (1.2 mmol), aniline **2a** (1.0 mmol), and AcOH (0.05 mL) in benzene (5 mL). The mixture was refluxed for 2 h. The solvent was removed under reduced pressure to provide the crude product. The crude product was recrystallized from the solution of ethyl acetate and petroleum ether to afford compound **3a**, a gray solid, 0.253 g, 96% yield. mp: 123−124 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.51 (s, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.74 (s, 3H), 2.04 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.6, 161.9, 156.8, 153.9, 142.4, 121.8, 114.6, 61.3, 55.6, 15.4, 14.5; IR (thin film) 3540, 3106, 2980, 2913, 1724, 1610, 1090, 758 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{17}N_2O_4$ $(M+H)^+$ 265.1183; found: 265.1180.

General Procedure for Synthesis of Product 4 (Table 2 and Table 3). A round-bottle flask connected with water separator was charged with oxime **1** (1.2 mmol), aniline **2** (1.0 mmol), and AcOH (0.05 mL) in benzene (5 mL). The mixture was refluxed for 2 h. Then the solution of $POCl_3$ in MeCN (0.4 mol/L) was added to the reaction mixture at 0 °C and heated to reflux until the oxime intermediate was completely disappeared (monitored by TLC). At this time, the reaction mixture was poured into cool saturated aqueous $NaHCO_3$ (30 mL). The organic layer was separated and the water phase was extracted with ethyl acetate (25 mL × 2). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (25 mL × 1) and brine (25 mL × 1), dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (petroleum ether/ethyl acetate, V:V = 1:4) afforded product **4**.

*Ethyl 7-Methoxy-3-methylquinoxaline-2-carboxylate (**4aa**).* Yellow solid, 0.191 g, 78% yield. mp: 59−60 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 9.4 Hz, 1H), 7.51−7.28 (m, 2H), 4.57 (q, J = 7.1 Hz, 2H), 3.97 (s, 3H), 2.94 (s, 3H), 1.51 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 160.6, 150.3, 144.0, 141.5, 138.9, 129.3, 125.5, 106.7, 62.4, 55.9, 23.4, 14.3; IR (thin film) 3106, 2989, 2921, 1725, 1621, 1449, 1379, 1089, 839 cm^{-1}; HRMS (APCI) m/z calcd for $C_{13}H_{15}N_2O_3$ $(M+H)^+$ 247.1083; found: 247.1079.

*Ethyl 3,7-Dimethylquinoxaline-2-carboxylate (**4ab**).* Yellow solid, 0.168 g, 73% yield. mp: 40−41 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.66 (dd, J = 8.6 Hz, 1.6 Hz, 1H), 4.57 (q, J = 7.1 Hz, 2H), 2.94 (s, 3H), 2.58 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 151.9, 144.2, 141.0, 140.4, 139.9, 134.2, 128.5, 127.9, 62.4, 23.6, 21.8, 14.3; IR (thin film) 3104, 2978, 2914, 1723, 1635, 1380, 1234, 1088, 835 cm^{-1}; HRMS (APCI) m/z calcd for $C_{13}H_{15}N_2O_2$ $(M+H)^+$ 231.1133; found: 231.1123.

*Ethyl 3-Methylquinoxaline-2-carboxylate (**4ac**).* Yellow solid, 0.162 g, 75% yield, mp: 65−66 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, J = 8.4 Hz, 0.9 Hz, 1H), 8.05 (dd, J = 8.4 Hz, 0.9 Hz, 1H), 7.83 (ddd, J = 8.4 Hz, 6.9 Hz, 1.4 Hz, 1H), 7.80−7.73 (m, 1H), 4.56

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(q, J = 7.1 Hz, 2H), 2.96 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 152.8, 144.4, 142.5, 139.9, 131.8, 129.8, 129.7, 128.4, 62.5, 23.8, 14.3; IR (thin film) 3207, 2971, 2916, 1718, 1632, 1371, 1081, 851, 772, 701 cm^{-1}; HRMS (APCI) m/z calcd for $C_{12}H_{13}N_2O_2$ (M+H)$^+$ 217.0972; found: 217.0973.

*Ethyl 7-Bromo-3-methylquinoxaline-2-carboxylate (**4ad**).* Yellow solid, 0.185 g, 63% yield, mp: 63−65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, J = 1.1 Hz, 1H), 8.00−7.76 (m, 2H), 4.54 (q, J = 7.1 Hz, 2H), 2.91 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 153.2, 145.1, 141.2, 140.4, 135.3, 132.0, 129.8, 123.7, 62.6, 23.7, 14.2; IR (thin film) 3132, 2982, 2925, 1725, 1641, 1475, 1274, 1092, 840 cm^{-1}; HRMS (APCI) m/z calcd for $C_{12}H_{12}N_2O_2Br$ (M+H)$^+$ 295.0082; found: 295.0069.

*Ethyl 7-Fluoro-3-methylquinoxaline-2-carboxylate (**4ae**).* Pale yellow solid, 0.152 g, 65% yield, mp: 62−63 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10−8.04 (m, 1H), 7.89−7.74 (m, 1H), 7.64−7.59 (m, 1H), 4.70−4.49 (m, 2H), 2.94 (s, 3H), 1.52−1.48 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 163.5 (d, J_{C-F} = 252.4 Hz), 152.1 (d, J_{C-F} = 3.0 Hz), 145.2, 140.5 (d, J_{C-F} = 13.2 Hz), 139.8, 130.5 (d, J_{C-F} = 9.9 Hz), 122.2 (d, J_{C-F} = 26.2 Hz), 113.1 (d, J_{C-F} = 21.7 Hz), 62.6, 23.5, 14.2; IR (thin film) 3068, 2988, 1723, 1623, 1378, 1118, 1089, 836, 753 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{12}N_2O_2F$ (M+H)$^+$ 235.0877; found: 235.0877.

*Ethyl 6-Chloro-3-methylquinoxaline-2-carboxylate (**4af**).* Yellow solid, 0.110 g, 44% yield, mp: 75−76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 9.0 Hz, 1H), 8.04 (d, J = 2.2 Hz, 1H), 7.70 (dd, J = 9.0 Hz, 2.3 Hz, 1H), 4.56 (q, J = 7.1 Hz, 2H), 2.95 (s, 3H), 1.50 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 154.0, 144.5, 142.8, 138.4, 137.8, 131.0, 130.9, 127.5, 62.6, 23.8, 14.3; IR (thin film) 3108, 2972, 1723, 1269, 1171, 1084, 866, 831, 802, 729 cm^{-1}; HRMS (APCI) m/z calcd for $C_{12}H_{12}N_2O_2Cl$ (M+H)$^+$ 251.0582; found: 251.0581.

*Ethyl 6-Fluoro-3-methylquinoxaline-2-carboxylate (**4ag**).* Yellow oil, 0.107 g, 46% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (dd, J = 9.2 Hz, 5.7 Hz, 1H), 7.69 (dd, J = 9.1 Hz, 2.8 Hz, 1H), 7.57 (ddd, J = 9.2 Hz, 8.2 Hz, 2.8 Hz, 1H), 4.58 (q, J = 7.1 Hz, 2H), 2.98 (s, 3H), 1.51 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 165.0 (d, J_{C-F} = 255.1 Hz), 154.0, 143.7 (d, J_{C-F} = 3.6 Hz), 143.5 (d, J_{C-F} = 13.6 Hz), 137.1, 132.1 (d, J_{C-F} = 10.3 Hz), 120.5 (d, J_{C-F} = 26.2 Hz), 112.1 (d, J_{C-F} = 21.7 Hz), 62.5, 23.8, 14.3; IR (thin film) 3014, 2986, 1725, 1637, 1601, 1194, 1081, 868, 784, 696 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{12}N_2O_2F$ (M+H)$^+$ 235.0877; found: 235.0871.

*Ethyl 6-Isopropyl-3-methylquinoxaline-2-carboxylate (**4ah**).* White solid, 0.212 g, 82% yield, mp: 63−64 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 1H), 7.77−7.72 (m, 1H), 7.60 (d, J = 7.2 Hz, 1H), 4.52 (q, J = 7.1 Hz, 2H), 4.24 (dt, J = 13.9 Hz, 6.9 Hz, 1H), 2.91 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H), 1.37 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 151.7, 148.6, 143.3, 142.6, 138.0, 131.6, 125.9, 125.4, 62.0, 27.4, 23.5, 23.3, 14.2; IR (thin film) 3050, 2958, 1720, 1271, 1137, 1105, 1087, 834, 781, 558 cm^{-1}; HRMS (APCI) m/z calcd for $C_{15}H_{19}N_2O_2$ (M+H)$^+$ 259.1441; found: 259.1433.

*Ethyl 3,6-Dimethylquinoxaline-2-carboxylate (**4ai-a**).* White solid, 0.087 g, 38% yield, mp: 88−89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.6 Hz, 1H), 7.83 (s, 1H), 7.60 (dd, J = 8.6 Hz, 1.7 Hz, 1H), 4.57 (q, J = 7.1 Hz, 2H), 2.96 (s, 3H), 2.62 (s, 3H), 1.51 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 152.9, 143.4, 142.8, 142.6, 138.4, 132.2, 129. 3, 127.3, 62.3, 23.8, 22.1, 14.3; IR (thin film) 3078, 2982, 2932, 1720, 1370, 1276, 1197, 1100, 804, 792, 777 cm^{-1}; HRMS (APCI) m/z calcd for $C_{13}H_{15}N_2O_2$ (M+H)$^+$ 231.1128; found: 231.1123.

*Ethyl 3,8-Dimethylquinoxaline-2-carboxylate (**4ai-b**).* White solid, 0.085 g, 37% yield, mp: 82−83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 1H), 7.74−7.68 (m, 1H), 7.59 (d, J = 7.0 Hz, 1H), 4.56 (d, J = 7.1 Hz, 2H), 2.94 (s, 3H), 2.83 (s, 3H), 1.51 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 151.9, 143.5, 142.6, 139.2, 138.4, 131.4, 129.6, 126.2, 62.1, 23.4, 17.0, 14.2; IR (thin film) 3103, 2983, 2924, 1715, 1618, 1190, 1085, 841, 824, 753 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{15}N_2O_2$ (M+H)$^+$ 231.1128; found: 231.1106.

*Ethyl 3,6,8-Trimethylquinoxaline-2-carboxylate (**4aj**).* White solid, 0.197 g, 81% yield, mp: 109−110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.42 (s, 1H), 4.54 (q, J = 7.1 Hz, 2H), 2.92 (s, 3H), 2.78 (s, 3H), 2.55 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 152.0, 142.8, 142.5, 142.3, 137.8, 132.1, 132.0, 125.1, 62.0, 23.5, 22.1, 16.9, 14.2; IR (thin film) 3011, 2982, 2929, 2856, 1715, 1621, 1274, 1235, 1104, 866, 787 cm^{-1}; HRMS (APCI) m/z calcd for $C_{14}H_{17}N_2O_2$ (M+H)$^+$ 245.1285; found: 245.1276.

*Ethyl 6,7-Dimethoxy-3-methylquinoxaline-2-carboxylate (**4ak**).* Yellow solid, 0.218 g, 79% yield, mp: 115−116 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.31 (s, 1H), 4.55 (q, J = 7.1 Hz, 2H), 4.07 (s, 3H), 4.04 (s, 3H), 2.94 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 154.6, 152.8, 151.2, 141.0, 140.4, 137.1, 107.1, 105.8, 62.2, 56.5, 56.5, 23.8, 14.4; IR (thin film) 3019, 2973, 2853, 1720, 1621, 1500, 1220, 1087, 846, 609 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{16}N_2O_4Na$ (M+Na)$^+$ 299.1002; found: 299.1004.

*Ethyl 3,6,7-Trimethylquinoxaline-2-carboxylate (**4al-a**).* Yellow solid, 0.088 g, 36% yield, mp: 74−75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.79 (s, 1H), 4.55 (q, J = 7.1 Hz, 2H), 2.94 (s, 3H), 2.51 (s, 3H), 2.45 (s, 3H), 1.50 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 152.0, 143.2, 142.9, 141.6, 140.4, 138.9, 128.7, 127.5, 62.3, 23.8, 20.6, 20.3, 14.3; IR (thin film) 3011, 2980, 2853, 1725, 1610, 1376, 1204, 1091, 877, 752 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{17}N_2O_2$ (M+H)$^+$ 245.1285; found: 245.1286.

*Ethyl 3,7,8-Trimethylquinoxaline-2-carboxylate (**4al-b**).* Yellow solid, 0.081 g, 33% yield, mp: 51−52 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 8.6 Hz, 1H), 4.55 (q, J = 7.1 Hz, 2H), 2.93 (s, 3H), 2.76 (s, 3H), 2.53 (s, 3H), 1.51 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 150.9, 143.2, 141.2, 139.1, 137.7, 135.5, 134.8, 125.1, 62.1, 23.3, 20.4, 14.3, 13.0; IR (thin film) 3058, 2981, 2928, 1721, 1261, 1101, 839, 786, 674 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{17}N_2O_2$ (M+H)$^+$ 245.1285; found: 245.1281.

*Ethyl 3,5-Dimethylquinoxaline-2-carboxylate (**4am**).* Yellow solid, 0.140 g, 61% yield, mp: 63−65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92−7.88 (m, 1H), 7.54−7.51 (m, 2H), 4.48 (q, J = 7.0 Hz, 1H), 2.86 (s, 3H), 2.69 (s, 3H), 1.40 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 151.6, 143.8, 141.7, 139.9, 136.9, 131.6, 129.4, 127.6, 62.4, 23.9, 17.1, 14.3; IR (thin film) 3013, 2979, 2929, 1721, 1274, 1196, 1124, 862, 798, 765, 664 cm^{-1}; HRMS (APCI) m/z calcd for $C_{13}H_{15}N_2O_2$ (M+H)$^+$ 231.1128; found: 231.1121.

*Ethyl 2-Methylbenzo[f]quinoxaline-3-carboxylate (**4an**).* Pale yellow solid, 0.186 g, 70% yield, mp: 105−106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30−9.27 (m, 1H), 8.06−8.02 (m, 2H), 7.99−7.94 (m, 1H), 7.83−7.78 (m, 2H), 4.61 (q, J = 7.1 Hz, 2H), 3.10 (s, 3H), 1.54 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 151.1, 142.0, 140.6, 138.4, 133.0, 130.5, 129.1, 128.6, 127.0, 126.6, 125.6, 124.1, 61.3, 22.9, 13.3; IR (thin film) 3033, 2987, 2918, 1721, 1636, 1378, 1237, 1110, 845, 761, 639 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{14}N_2O_2Na$ (M+Na)$^+$ 289.0948; found: 289.0944.

*Ethyl 6-Methoxy-3-methylquinoxaline-2-carboxylate (**4ao**).* Yellow solid, 165 mg, 67% yield. mp: 89−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 9.2 Hz, 1H), 7.34 (dd, J = 9.2, 2.7 Hz, 1H), 7.29 (d, J = 2.6 Hz, 1H), 4.48 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 2.90 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 162.7, 153.4, 144.2, 141.3, 136.2, 131.0, 123.6, 105.5, 62.3, 56.0, 23.9, 14.3; IR (thin film) 2973, 2941, 2838, 1795, 1604, 1491, 1223, 1090, 838 cm^{-1}; HRMS (APCI) m/z calcd for $C_{13}H_{15}N_2O_3$ (M+H)$^+$ 247.1083; found: 247.1080.

*Ethyl 3-Ethyl-7-methoxyquinoxaline-2-carboxylate (**4ba**).* White solid, 0.205 g, 79% yield, mp: 50−51 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, J = 9.1 Hz, 1H), 7.44 (dd, J = 9.1, 2.8 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 4.53 (q, J = 7.1 Hz, 2H), 3.93 (s, 3H), 3.20 (q, J = 7.5 Hz, 2H), 1.47 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2, 160.7, 154.6, 144.5, 141.5, 139.1, 129.6, 125.3, 106.8, 62.5, 56.0, 29.2, 14.4, 13.6; IR (thin film) 3089, 2988, 2924, 1728, 1620, 1492, 1216, 1085, 836, 771, 623 cm^{-1}; HRMS (APCI) m/z calcd for $C_{14}H_{17}N_2O_3$ (M+H)$^+$ 261.1234; found: 261.1226.

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*Ethyl 7-Methoxy-3-propylquinoxaline-2-carboxylate (**4ca**).* White solid, 0.227 g, 83% yield, mp: 113−115 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, J = 9.1 Hz, 1H), 7.43−7.37 (m, 2H), 4.50 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 3.14−3.10 (m, 2H), 1.84−1.75 (m, 2H), 1.43 (d, J = 7.1 Hz, 3H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 160.7, 153.5, 144.6, 141.4, 139.0, 129.6, 125.3, 106.7, 62.4, 55.9, 37.8, 23.0, 14.3, 14.2; IR (thin film) 3088, 2978, 2939, 1642, 1512, 1245, 1182, 1086, 835, 805, 768 cm^{-1}; HRMS (APCI) m/z calcd for $C_{15}H_{19}N_2O_3$ $(M+H)^+$ 275.1390; found: 275.1378.

*Ethyl 7-Methoxy-3-phenylquinoxaline-2-carboxylate (**4da**).* Yellow oil, 0.181 g, 59% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.9 Hz, 1H), 7.75−7.72 (m, 2H), 7.55−7.51 (m, 5H), 4.35 (q, J = 7.1 Hz, 2H), 4.02 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 161.3, 149.9, 145.5, 141.7, 138.6, 138.0, 130.3, 129.2, 128.6, 128.5, 125.4, 106.5, 62.3, 56.0, 13.8; IR (thin film) 3098, 2965, 1730, 1619, 1260, 1111, 1019, 804, 669 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{16}N_2O_3Na$ $(M+Na)^+$ 331.1053; found: 331.1047.

*Ethyl 7-Methoxy-3-(4-methoxyphenyl)quinoxaline-2-carboxylate (**4ea**).* Yellow oil, 0.165 g, 49% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 9.0 Hz, 1H), 7.67 (d, J = 8.6 Hz, 2H), 7.51−7.43 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.96 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 161.0, 160.7, 149.3, 145.4, 141.3, 138.7, 130.0, 129.9, 125.2, 114.2, 114.1, 106.5, 62.3, 55.9, 55.4, 13.9; IR (thin film) 3111, 2964, 1721, 1610, 1213, 1106, 1026, 835, 793 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{19}N_2O_4$ $(M+H)^+$ 339.1339; found: 339.1354.

*Ethyl 3-(4-Bromophenyl)-7-methoxyquinoxaline-2-carboxylate (**4fa**).* White solid, 0.204 g, 53% yield, mp: 97−98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 9.2 Hz, 1H), 7.65−7.62 (m, 2H), 7.61−7.58 (m, 2H), 7.52 (dd, J = 9.2, 2.8 Hz, 1H), 7.49 (d, J = 2.7 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 3.99 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 161.5, 148.7, 145.0, 141.8, 138.6, 136.9, 131.7, 130.2, 130.2, 125.7, 123.9, 106.5, 62.5, 56.0, 13.9; IR (thin film) 3121, 2986, 1728, 1620, 1251, 1103, 1028, 829, 751 cm^{-1}; HRMS (APCI) m/z calcd for $C_{18}H_{16}N_2O_3Br$ $(M+H)^+$ 387.0344; found: 387.0324.

*Ethyl 7-Methoxy-3-(o-tolyl)quinoxaline-2-carboxylate (**4ga**).* Yellow oil, 0.151 g, 47% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, J = 9.0 Hz, 1H), 7.55−7.50 (m, 2H), 7.37−7.33 (m, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.28−7.25 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 3.99 (s, 3H), 2.22 (s, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 161.5, 151.5, 145.5, 142.0, 138.7, 138.1, 136.3, 130.4, 130.3, 129.0, 128.9, 125.8, 125.8, 106.8, 62.2, 56.1, 19.9, 13.7; IR (thin film) 3097, 2979, 2856, 1737, 1620, 1246, 1103, 837, 741, 647 cm^{-1}; HRMS (APCI) m/z calcd for $C_{19}H_{19}N_2O_3$ $(M+H)^+$ 323.1390; found: 323.1384.

*Ethyl 7-Methoxy-3-(pyridin-2-yl)quinoxaline-2-carboxylate (**4ha**).* White solid, 0.155 mg, 61% yield, mp: 175−176 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65−8.62 (m, 1H), 8.40−8.34 (m, 1H), 8.06−8.01 (m, 1H), 7.90−7.85 (m, 1H), 7.51−7.45 (m, 2H), 7.38−7.33 (m, 1H), 4.49 (q, J = 7.1 Hz, 2H), 3.97 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 161.6, 154.6, 148.4, 146.7, 146.5, 142.3, 137.9, 136.9, 130.3, 124.9, 124.0, 122.4, 106.7, 62.1, 55.9, 14.0; IR (thin film) 3093, 2977, 1731, 1619, 1248, 1111, 1025, 828, 783, 747 cm^{-1}; HRMS (APCI) m/z calcd for $C_{17}H_{16}N_3O_3$ $(M+H)^+$ 310.1186; found: 310.1177.

*1-(7-Methoxy-3-methylquinoxalin-2-yl)ethanone (**4ia**).* Yellow solid, 0.177 g, 82% yield, mp: 92−93 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 9.2 Hz, 1H), 7.47 (dd, J = 9.2, 2.8 Hz, 1H), 7.35 (d, J = 2.8 Hz, 1H), 3.99 (s, 3H), 2.92 (s, 3H), 2.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 160.4, 150.3, 147.0, 141.3, 138.9, 129.3, 125.5, 106.6, 55.8, 28.0, 24.0; IR (thin film) 3111, 2962, 1697, 1620, 1217, 1029, 940, 837, 653, 606 cm^{-1}; HRMS (APCI) m/z calcd for $C_{12}H_{13}N_2O_2$ $(M+H)^+$ 217.0972; found: 217.0973.

*(7-Methoxy-3-methylquinoxalin-2-yl) (phenyl)methanone (**4ja**).* White solid, 0.178 g, 64% yield, mp: 171−172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (t, J = 9.4 Hz, 3H), 7.66 (t, J = 7.4 Hz, 1H), 7.53−7.48 (m, 3H), 7.38 (s, 1H), 3.95 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.3, 160.6, 150.7, 149.4, 141.0, 138.4, 135.7, 134.0, 130.6, 129.5, 128.7, 124.6, 106.7, 55.8, 22.3; IR (thin film) 3201, 2986, 1670, 1621, 1219, 1025, 903, 831 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{15}N_2O_2$ $(M+H)^+$ 279.1128; found: 279.1127.

*7-Methoxy-3-phenylquinoxaline-2-carbonitrile (**4ka**).* Yellow solid, 0.172 g, 66% yield, mp: 184−185 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 9.3 Hz, 1H), 8.07−8.02 (m, 2H), 7.63−7.58 (m, 4H), 7.43 (d, J = 2.8 Hz, 1H), 4.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 152.1, 142.5, 139.1, 135.3, 130.5, 130.4, 129.1, 128.9, 128.1, 127.6, 116.9, 105.9, 56.1; IR (thin film) 3011, 2974, 2511, 1621, 1333, 1219, 1023, 835, 758, 692 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{12}N_3O$ $(M+H)^+$ 262.0975; found: 262.0970.

*Synthesis of 3-(Ethoxycarbonyl)-2-methylquinoxaline 1-Oxide (**5ac**).* A mixture of ethyl 3-methylquinoxaline-2-carboxylate **4ac** (1.0 mmol), *m*-CPBA (4.0 mmol) in CH_2Cl_2 (3 mL) was stirred for 3 h at room temperature. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography with eluents (petroleum ether/ethyl acetate, V:V = 1:6) to provide product **5ac** (0.181 g, 78%). A white solid, mp: 85−86 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60−8.57 (m, 1H), 8.19−8.18 (m, 1H), 7.82−7.80 (m, 2H), 4.58 (q, J = 7.1 Hz, 2H), 2.80 (s, 3H), 1.50 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 147.3, 142.5, 140.1, 137.1, 131.6, 131.2, 130.7, 118.8, 62.9, 14.2; IR (thin film) 3077, 2990, 1717, 1341, 1255, 1063, 887, 773, 603 cm^{-1}; HRMS (APCI) m/z calcd for $C_{12}H_{13}N_2O_3$ $(M+H)^+$ 233.0921; found: 233.0912.

*Synthesis of 2-(Ethoxycarbonyl)-3-methylquinoxaline 1,4-Dioxide (**6ac**).* A mixture of ethyl 3-methylquinoxaline-2-carboxylate **4ac** (1.0 mmol) and *m*-CPBA (4.0 mmol) in DCE (5 mL) was refluxed for 4 h. The solvents were removed under reduced pressure and the crude product was purified by flash chromatography with eluents (petroleum ether/ethyl acetate, V:V = 1:2) to provide product **6ac** (0.159 g, 64%). A white solid, mp: 133−134 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65−8.53 (m, 2H), 7.92−7.82 (m, 2H), 4.58 (q, J = 7.1 Hz, 2H), 2.59 (s, 3H), 1.47 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 139.0, 137.9, 136.9, 135.6, 132.6, 131.5, 120.4, 120.1, 63.7, 14.4, 14.0; IR (thin film) 3098, 2947, 1741, 1636, 1335, 1247, 1064, 772, 634 cm^{-1}; HRMS (APCI) m/z calcd for $C_{12}H_{13}N_2O_4$ $(M+H)^+$ 249.0870; found: 249.0861.

*Synthesis of (3-Methylquinoxalin-2-yl)methanol (**7ac**).* A mixture of ethyl 3-methylquinoxaline-2-carboxylate **4ac** (1.0 mmol) and $NaBH_4$ (3.0 mmol) in MeOH (5 mL) was stirred for 15 min at room temperature. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography with eluents (petroleum ether/ethyl acetate, V:V = 1:1) to provide product **7ac** (0.160 g, 92%). A yellow solid, mp: 109−110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13−7.96 (m, 2H), 7.72 (dd, J = 6.5 Hz, 2.7 Hz, 2H), 4.91 (s, 2H), 4.59 (s, 1H), 2.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 151.3, 141.5, 139.5, 129.5, 129.3, 128.5, 128.2, 62.0, 20.7; IR (thin film) 3455, 2896, 1640, 1382, 1163, 1060, 775, 682 cm^{-1}; HRMS (APCI) m/z calcd for $C_{10}H_{11}N_2O$ $(M+H)^+$ 175.0866; found: 175.0860.

*Synthesis of LAssBio-1022 (**9ac**).* A mixture of ethyl 3-methylquinoxaline-2-carboxylate **4ac** (1.0 mmol) and hydrazine hydrate (85%, 20 mmol) in EtOH (5 mL) was refluxed for 0.5 h. When the **4ac** was completely consumed (monitored by TLC), the mixture was cooled to room temperature and a colorless needle crystal was precipitated. The precipitate was filtered to give **8ac** (0.200 g, 99%), mp: 171−172 °C.[4b] A round-bottle flask was charged with **8ac** (0.2 g, 1.0 mmol) and EtOH (10 mL). Salicyaldehyde (0.122 g, 1.0 mmol) was added in one portion. The mixture was stirred for 1 h. At this time, the solvent was removed under reduced pressure to afford the crude product, which was crystallized from EtOH to give product **9ac** (0.2 g, 90% yield).[4c] A white solid, mp: 228−229 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (s, 1H), 10.90 (s, 1H), 8.48 (s, 1H), 8.02 (d, J = 8.8 Hz, 2H), 7.82−7.77 (m, 1H), 7.75−7.70 (m, 1H), 6.96 (d, J = 8.1 Hz, 1H), 6.85 (t, J = 7.5 Hz, 1H), 3.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 157.7, 153.6, 150.2, 142.2, 140.6, 137.8, 131.2, 131.1, 130.0, 129.1, 128.0, 127.7, 118.4, 116.4, 23.7.

*General Procedure for Synthesis of Oxime **1**.* A solution of ethyl acetoacetate (44 mL, 4.1 g, 31.5 mmol) in glacial acetic acid (5.2 mL) was cooled to 5 °C and a solution of sodium nitrite (3.2 g, 46.2 mol) in water (7 mL) was added dropwise at 5−10 °C. The mixture was

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stirred for 1 h, then 18% solution of sodium chloride (15 mL) was added and the mixture was stirred for additional 20 min. Then it was extracted with chloroform (75 mL × 2); the extracts were sequentially washed with 18% solution of sodium chloride, 10% solution of sodium bicarbonate, 18% solution of sodium chloride; and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give **1a** as yellow oil (4.5 g, 97%). All 2-oxime-1, 3-diketone derivatives **1a**[15], **1b**[16], **1c**[17], **1d**[18], **1e**[19], **1f**[20], **1g**[21], **1h**[22], **1i**[23], **1j**[18a], **1k**[24] were obtained in a similar method and the data matched the literature.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00011.

Spectra of **3a**, **4**, **5ac**, **6ac**, **7ac**, **9ac**, and X-ray crystal structure of **4an** (CIF) (PDF)

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Notes

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