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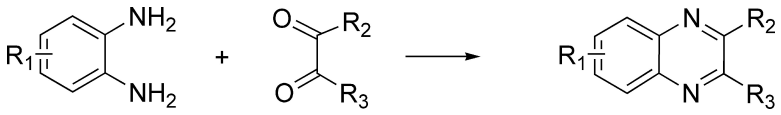

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Diverse 2-Carboxamide-3-amino-Substituted Quinoxalines: Synthesis and Reactivity Investigation for Library Generation

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Described herein is the development of a robust synthetic route applicable to parallel synthesis of diverse 2-carboxamide-3-amino-substituted quinoxalines. In addition to the scope and limitations of the methods developed, a purification strategy employing solid-phase extraction (SPE) and application of the methods to a small parallel array of compounds are discussed.

Introduction

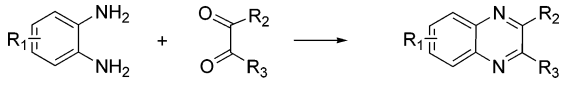
The pharmaceutical industry relies heavily on high-throughput screening. Proprietary compound collections possessing diverse organic compounds are important to success in lead identification. Like many other small molecule heterocycles, functionalized quinoxalines possess a wide range of biological activities, including anticancer,[1] antiviral,[2] antibacterial,[3] and activity as kinase inhibitors.[4] Numerous synthetic strategies exist for preparation of substituted quinoxalines,[5] including both solution-[6] and solid-phase[7] methodologies for parallel synthesis of these types of compounds. The most common preparation involves condensation of aryl 1,2-diamines with 1,2-dicarbonyl compounds under refluxing conditions (Scheme 1).[8]

Recent improvements on these conditions, employing microwave irradiation[9] or molecular iodine[10] as a catalyst, reliably generate the quinoxaline core from a variety of aryl 1,2-diamine and 1,2-dicarbonyl starting materials; however, these methods remain limited for application to library synthesis of discreet compounds when utilized as the diversification step, owing the lack of regiocontrol in the condensation. Additionally, the extent of diversity achievable using this method is limited by the diversity present in commercially available diamine and dicarbonyl starting materials.

An alternate strategy for facile preparation of diverse quinoxalines relies on functionalizing a common quinoxaline core using a two-step parallel process (Scheme 2), as opposed to generating the quinoxaline core during the diversification step.

In this manner, ethyl-3-chloroquinoxaline-2-carboxylates are reacted with amines in a S_NAr process. Subsequent saponification results in intermediate quinoxaline carboxylic acids, which can be further elaborated to afford amides from a variety of amines. Not only does this scheme obviate the regiochemistry issues encountered during the diversification step, but the intrinsic diversity afforded by using amines as inputs is also reflected in the diversity of the quinoxaline products. Although not the focus of this work, it is interesting to note that an additional diversity point on the phenyl ring (R group) or in the form of heterocyclic quinoxalines can be accommodated by this strategy. Regiochemical issues associated with generation of isomerically pure scaffolds can be resolved prior to the library diversification step either by regiospecific synthesis of the cores[7a,11] or by chromatographic separation of the isomeric cores generated by condensation of unsymmetrical diamines and dicarbonyl compounds.

Scheme 1. General Scheme for Synthesis of Quinoxalines by Condensation of Aryl 1,2-Diamines and 1,2-Dicarbonyl Compounds



The goal of this work was to develop a robust synthetic route applicable to parallel synthesis of diverse 2-carboxamide-3-amino-substituted quinoxalines. In addition to the scope and limitations of the methods developed, a purification strategy employing solid-phase extraction and application of the methods to a small parallel array of compounds are discussed.

Results and Discussion

Scheme 3 depicts the synthesis of 3-chloro-quinoxaline-2-carboxylic acid ethyl ester **1**.

This core scaffold was synthesized in multigram quantities by condensation of diethyl ketomalonate with 1,2-phenylenediamine, followed by chlorination using phosphorus oxychloride as previously reported.[12] From this scaffold, a set of intermediates was generated in parallel and with sufficient purity (>90% by UV_{219} detection) for further elaboration in a library format. A two-step process (Scheme 4), involving initial nucleophilic aromatic substitution with a variety of amines (**2**{*1*−*6*}), followed by hydrolysis of the intermediate ethyl esters (**3**{*1*−*6*}), afforded the desired acid intermediates **4**{*1*−*6*}.[13]

Reactions were conducted in parallel in capped tubes using a J-Kem reactor.[14] Intermediate ethyl esters **3**{*1*−*6*} were

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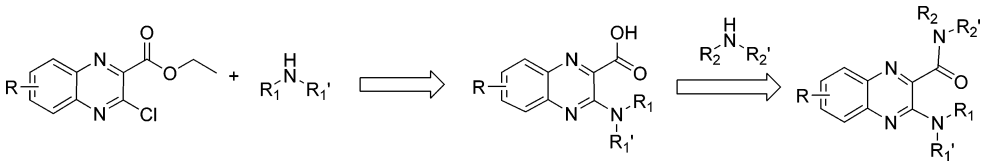
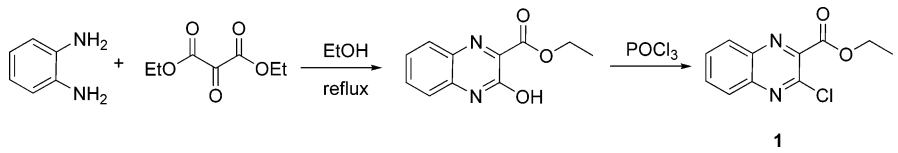
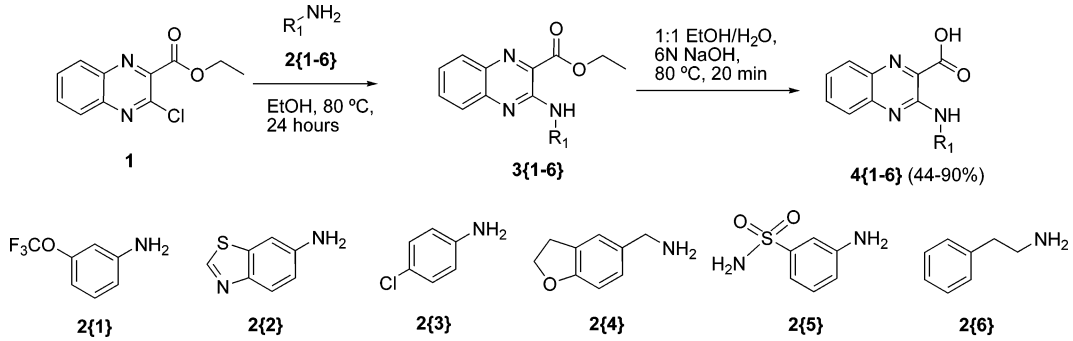
Scheme 2. General Strategy for Synthesis of 2-Carboxamide-3-amino-Substituted Quinoxalines from a Common Core



Scheme 3. Synthesis of 3-Chloroquinoxaline-2-Carboxylic Acid Ethyl Ester **1**



Scheme 4. Synthesis of 2-Carboxy-3-Aminoquinoxaline Intermediates

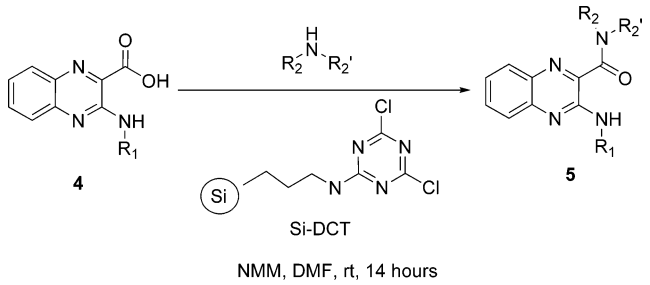


isolated by filtration, and their purities were confirmed by LC/MS prior to the hydrolysis step. The resulting acid intermediates **4**{*1*−*6*} were obtained in gram quantity, good yield, and high purity for the two-step parallel process. The yields varied depending on the nature of the amine (44−90%).

With a parallel method for generating the intermediates in hand, the next goal was to determine optimal synthetic conditions for coupling the acid intermediates with a variety of amines. The choice of reaction conditions for this step focused on the desire to obtain high-purity compounds (>80% by UV_{219} detection) without the need for chromatographic purification. A variety of reaction conditions were investigated, including homogeneous solution methods (in situ acid chloride and acid fluoride formation, which resulted in decomposition of the acid intermediates) and common polymer-assisted solution methods (PS-EDC, PS-DCC, PS-CDI, and Si-CDI). All of these approaches resulted in incomplete reactions and very low conversion to the desired products. The desire to obtain high-purity compounds without the need for chromatographic purification and the failure of carbodiimide-based solid-supported reagents led to investigation of alternate coupling methods. Ultimately, the silica-supported reagent, silica-dichlorotriazine (Si-DCT)[15] was identified as an efficient coupling agent for the library step.[16] Scheme 5 outlines the reaction conditions for the library step.

In this case, the acid intermediates are used as limiting reagents and the conditions were optimized for complete consumption of these intermediates. Utilization of the published conditions for the silica-supported reagent (1.5 equiv of Si-DCT with 2 equiv of *N*-methylmorpholine (NMM) and 1 equiv of amine) did not result in consumption of the starting acid, and doubling the equivalents of amine did not improve the outcome. Increasing the number of equivalents of Si-DCT from 2 to 4.5 resulted in complete,

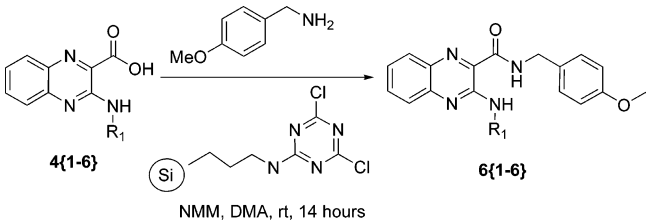
Scheme 5. Amide Coupling Using Silica-Supported Dichlorotriazine



clean, and consistent conversion of the starting acid to the desired products. In addition, the reaction worked in a variety of solvents (dichloroethane, dimethylformamide (DMF), dimethylacetamide (DMA), tetrahydrofuran, *N*-methylpyrrolidinone, and acetone). In this case, DMF or DMA was utilized to ensure solubility of a wide range of acid and amine reactants. To test the scope of these conditions with respect to the acid component, the intermediates **4**{*1*−*6*} were reacted with *p*-methoxybenzylamine under the reaction conditions (Table 1). Conversion, as determined by LC/MS, typically corresponded well to the isolated yield of desired product, following SPE purification (Table 1).

One final observation regarding the reaction conditions involves the importance of efficient agitation of the reaction suspension to the success of the coupling reaction. Although reactions were conducted in several reaction vessels throughout the course of this work, the best conversions were obtained when the reaction suspension achieved an efficient vortex within the vessel. Thus, reactions were performed in either vials or a 24-position Bohdan miniblock with 10-mL-capacity reaction tubes to ensure efficient agitation of the reaction suspensions.

Table 1. Synthesis of **6**{*1*−*6*}



entry	intermediate acid[a]	product	conversion[b] %	yield[c] %
1	**4**{*1*}	**6**{*1*}	76	64
2	**4**{*2*}	**6**{*2*}	72	72
3	**4**{*3*}	**6**{*3*}	94	74
4	**4**{*4*}	**6**{*4*}	93	91
5	**4**{*5*}	**6**{*5*}	68	67
6	**4**{*6*}	**6**{*6*}	86	86

[a] From Scheme 4. [b] Determined by LC/MS at 219 nm. [c] Isolated yield after SPE purification.

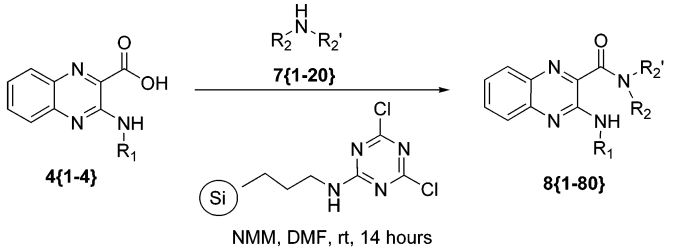
In addition to developing a robust parallel synthetic route to diverse quinoxalines, a second aim of this work was to generate high-purity compounds without the need for chromatographic purification of final compounds. The described reaction conditions cleanly afforded products in high conversions, and usually, unidentified impurities were not present in the crude reaction mixtures. Thus, these reaction conditions offer an ideal situation for applying scavenging and solid-phase extraction techniques for purification of the crude reaction mixtures. To this end, a dual layer SPE cartridge that possesses both a layer of NH_2 (aminopropyl-functionalized silica) and a layer of Cba (carboxylic acid-functionalized silica) sorbent was utilized to effect purification of the crude reaction mixtures.[17] The NH_2 sorbent was expected to remove any unreacted acid component, and the Cba sorbent was expected to remove the excess amine and NMM from the crude reaction mixtures. This technique was highly efficient in removing the undesired components, as evidenced by both LC/MS and ^{1}H NMR analysis of the products before and after SPE purification (data for **6**{*1*} is included in Supporting Information).

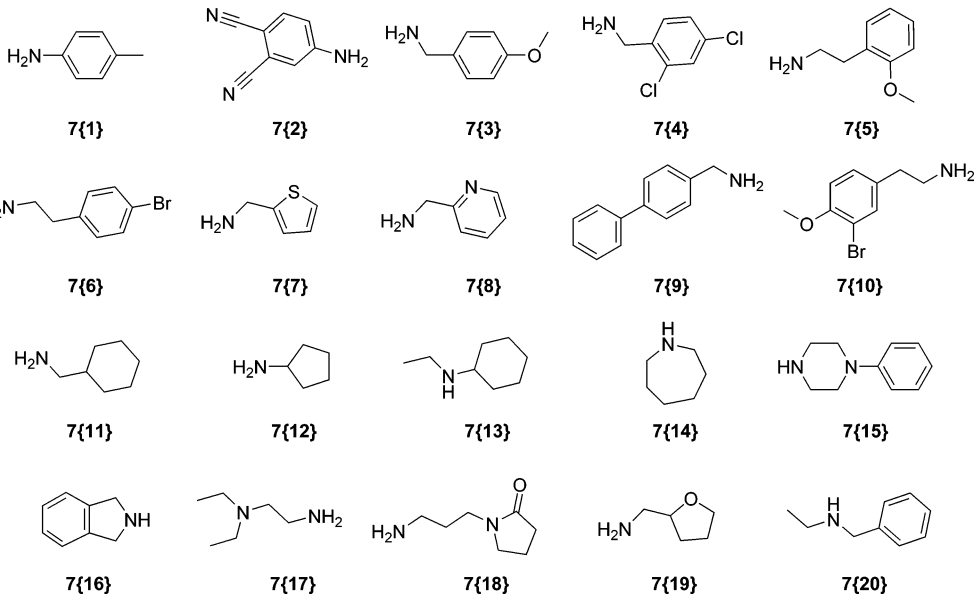
To test the scope of reactivity of the intermediate acids toward a variety of amines and the applicability of the methods for library synthesis, a small parallel array was synthesized using the reaction and SPE conditions developed. Four acid intermediates **4**{*1*−*4*} were reacted with a diverse set of 20 amines (Scheme 6).

The results of the parallel array synthesis are shown in Figure 1. The yields of isolated products were generally in the 40−60% range after the SPE purification. Only two amines failed to afford product, **7**{*2*} and **7**{*13*}. Amine **7**{*2*} possesses strongly electron-withdrawing groups, and amine **7**{*13*} is extremely hindered, which could explain their lack of reactivity in the coupling reaction.

The purity of the material isolated was typically quite good: >95% by ELSD and >80% by UV (219 nm). The purity and identity of the array compounds were confirmed using flow-injection ^{1}H NMR. In the future, the parallel methods utilized to generate this small compound array will be applied to the synthesis of a larger library of compounds.

Scheme 6. Synthesis of a 2-Carboxamide-3-Aminoquinoxaline Parallel Array





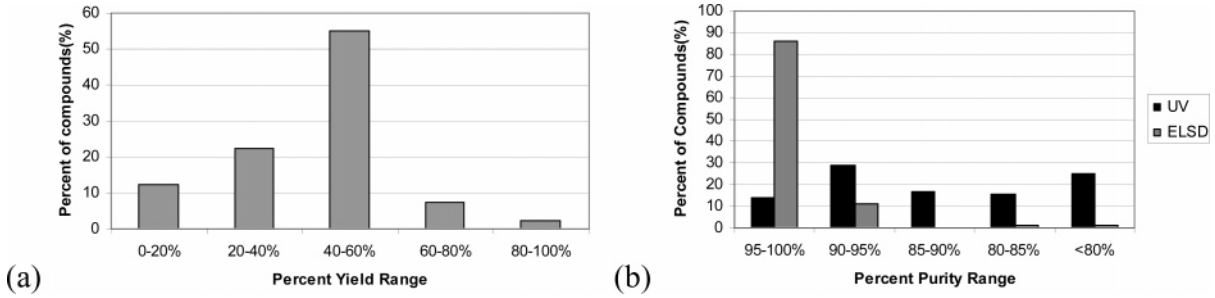


Figure 1. (a) Percent of compounds within particular yield ranges. (b) Percent of compounds within particular purity ranges, by ELSD detection and UV_{219} detection.

Conclusions

A robust synthetic route applicable to parallel synthesis of diverse 2-carboxamide-3-amino-substituted quinoxalines was developed. Key acid intermediates were generated on gram scale in parallel and with high purities. A silica-supported dichlorotriazine was utilized to cleanly and consistently form the desired amide products from the acid intermediates. The synthetic method, in conjunction with SPE purification using a dual sorbent layer SPE system, resulted in high-purity compounds without the need for chromatographic purification. With respect to the amine component, the method is of good scope with the exceptions of amines possessing strongly electron-withdrawing substituents or very hindered amines. The methods have been successfully applied to a small parallel array of compounds in library format and will be utilized to generate a larger library of diverse compounds in the future.

Experimental Section

General Information. ^{1}H NMR and ^{13}C NMR spectra of single compounds were acquired on a Bruker Avance 400-MHz spectrometer in DMSO-d_6. Flow-injection (FI) ^{1}H NMR spectra for library compounds were acquired on a Bruker DRX 500-MHz spectrometer equipped with a "BEST" (Bruker Efficient Sample Transfer) system using DMSO-d_6 as the sample and system solvent. Analytical LC/MS data were acquired on one of two systems. Mobile phases for both systems consisted of water with 0.1% formic acid (v/v) and acetonitrile with 0.1% formic acid (v/v). LC/MS data for single samples were recorded on an analytical LC/MS system consisting of a Waters ZQ mass spectrometer, an Agilent 1100 DAD, a Sedex 85 ELSD detector, and an Agilent 1100 HPLC system, equipped with a Zorbax SB-C18 rapid resolution cartridge (4.6 × 30 mm, 3.5 μm). Elution started with 95% water/acetonitrile and ended with 95% acetonitrile/water and used a linear gradient at a flow rate of 2.5 mL/min and an analysis cycle time of 4 min. LC/MS data for library samples were recorded on an analytical LC/MS system consisting of a Micromass Quattro Micro mass spectrometer, an Agilent 1100 DAD, a Sedex 55 ELSD detector, and an Agilent 1100 HPLC system equipped with an XTerra MS C18 column (4.6 × 30 mm, 3.5 μm). Elution started with 95% water and ended with acetonitrile/water (95:5, v/v) and used a linear gradient at a flow rate of 2.5 mL/min and an analysis cycle time of 8 min. Array synthesis was accomplished using Bohdan 24-position miniblocks equipped with 10-mL reaction tubes. Parallel sample concentration was performed in a HT-24 Genevac evaporator.

All solvents, reagents, and Si-DCT were purchased from Aldrich and used without further purification. SPE cartridges were purchased from Varian Inc. (part no. 7553502C).

General Procedure for Synthesis of 3-Amino-Substituted Quinoxaline-2-carboxylic Acids 4{*1*−*6*}. A suspension of 3-chloroquinoxaline-2-carboxylic acid ethyl ester **1** (9.5 mmol) and amine **2**{*1*−*6*} (10.5 mmol) in 10 mL of EtOH was heated in a capped test tube at 80 °C for 24 h. LC/MS analysis typically showed consumption of **1**. Upon cooling, the solid precipitate was filtered off and washed with cold EtOH. To the resulting solid was added 7 mL of EtOH and 7 mL water, followed by 1.9 mL of aqueous 6 N NaOH solution. The suspension was heated at 80 °C for 20 min and analyzed by LC/MS. Additional heating was required if the analysis showed that starting material remained. The reaction mixture was cooled to room temperature and then neutralized using aqueous 2 N HCl solution. The resulting precipitate was filtered off, washed with water, and dried in a vacuum oven at 50 °C overnight to afford pure products **4**{*1*−*6*} in 44−90% yields. LC/MS and ^{1}H NMR analyses were consistent with desired products.

3-(3-Trifluoromethoxyphenylamino)-quinoxaline-2-carboxylic Acid (4{*1*}). ^{1}H NMR (400 MHz): δ 11.61 (s, 1H), 8.37 (s, 1H), 8.02−8.00 (m, 1H), 7.79−7.72 (m, 2H), 7.67 (dd, J = 1.26, 8.08, 1H), 7.59−7.55 (m, 1H), 7.49 (t, J = 8.2 Hz, 1H), 7.04−7.02 (m, 1H). ^{13}C NMR (100 MHz): δ 167.18, 148.83, 148.74, 141.28, 141.23, 135.99, 135.34, 132.26, 130.41, 129.51, 126.16, 126.00, 121.50, 118.28, 114.16, 111.29. LC/MS: 349.97 $[M + H]^+$; calcd 349.12. $Purity_{UV219}$ = 100%; yield = 83%.

3-(Benzothiazol-6-ylamino)-quinoxaline-2-carboxylic Acid (4{*2*}). ^{1}H NMR (400 MHz): δ 12.00 (bs, 1H), 9.26 (s, 1H), 9.12 (d, J = 2.03 Hz, 1H), 8.06 (d, J = 8.84 Hz, 1H), 8.01 (m, 1H), 7.87 (dd, J = 1.01, 8.30, 1H), 7.79−7.73 (m, 2H), 7.56−7.52 (m, 1H). ^{13}C NMR (100 MHz): δ 167.18, 154.04, 149.06, 148.48, 141.47, 137.51, 136.12, 135.90, 134.62, 131.79, 129.39, 126.11, 125.64, 122.98, 119.41, 111.16. LC/MS: 322.98 $[M + H]^+$; calcd 322.34. $Purity_{UV219}$ = 100%; yield = 72%.

3-(4-Chlorophenylamino)-quinoxaline-2-carboxylic Acid (4{*3*}). ^{1}H NMR (400 MHz): δ 13.29 (br s, 1H), 8.00−7.97 (m, 3H), 7.72−7.64 (m, 2H), 7.49−7.45 (m, 1H), 7.41−7.39 (m, 2H). ^{13}C NMR (100 MHz): δ 166.36, 149.56, 140.98, 140.66, 139.27, 136.26, 130.61, 129.33, 128.73,

125.67, 125.00, 124.92, 120.37. LC/MS: 300.04 $[M + H]^+$; calcd 299.71. $Purity_{UV219} = 100\%$; yield = 90%.

3-[(2,3-Dihydrobenzofuran-5-ylmethyl)-amino]-quinoxaline-2-carboxylic Acid (4{*4*}). ^1H NMR (400 MHz): δ 13.80 (br s, 1 H), 8.44 (t, $J = 5.43$, 1H), 7.88 (dd, $J = 1.01$, 8.34, 1H), 7.73−7.68 (m, 1H), 7.63 (dd, $J = 1.01$, 8.34, 1H), 7.46−7.42 (m, 1H), 7.30 (br s, 1H), 7.18−7.15 (m, 1H), 6.71 (d, $J = 8.08$, 1H), 4.64 (d, $J = 5.3$, 2H), 4.49 (t, $J = 8.71$, 2H), 3.14 (t, $J = 8.59$, 2H). ^{13}C NMR (100 MHz): δ 167.23, 158.84, 151.16, 143.24, 134.96, 132.55, 131.76, 130.90, 129.54, 127.53, 127.45, 125.69, 124.74, 108.62, 70.89, 43.61, 29.06. LC/MS: 322.05 $[M + H]^+$; calcd 321.33. $Purity_{UV219} = 93\%$; yield = 44%.

3-(3-Sulfamoylphenylamino)-quinoxaline-2-carboxylic Acid (4{*5*}). ^1H NMR (400 MHz): δ 11.59 (br s, 1H), 8.52 (br s, 1H), 8.13 (m, 1H), 8.00 (d, $J = 8.34$, 1H), 7.82−7.76 (m, 2H), 7.59−7.56 (m, 2H), 7.51−7.49 (m, 1H), 7.44 (s, 2H). ^{13}C NMR (100 MHz): δ 167.22, 148.78, 144.73, 141.33, 139.93, 135.97, 135.15, 132.14, 129.52, 129.42, 126.12, 126.08, 122.28, 119.23, 116.30. LC/MS: 345.00 $[M + H]^+$; calcd 344.34. $Purity_{UV219} = 100\%$; yield = 79%.

3-Phenethylaminoquinoxaline-2-carboxylic Acid (4{*6*}). ^1H NMR (400 MHz): δ 8.43 (br s, 1H), 7.88 (d, $J = 8.09$, 1H), 7.70−7.63 (m, 2H), 7.44−7.39 (m, 1H), 7.32−7.31 (m, 4H), 7.25−7.19 (m, 1H), 3.77−3.72 (m, 2H), 2.96 (m, 2H). ^{13}C NMR (100 MHz): δ 167.18, 151.50, 143.20, 139.60, 134.93, 132.90, 132.17, 129.50, 128.76, 128.41, 126.18, 125.65, 124.45, 41.95, 34.49. LC/MS: 294.04 $[M + H]^+$; calcd 293.32. $Purity_{UV219} = 100\%$; yield = 52%.

General Procedure for Synthesis of 3-Carboxamide-2-amino-Substituted Quinoxalines. Method A (for 6{*1*−*6*}). In an 8 mL vial was placed a suspension of Si-DCT (0.225 mmol), NMM (0.1 mmol), intermediate **4** (0.05 mmol), and 4-methoxybenzylamine (0.1 mmol) in 1 mL of DMA, which was shaken (orbital motion shaker) for 14 h at room temperature. The reaction was then filtered, and the filtrate was collected. The Si-DCT was washed with 3 × 1 mL of DMA, and the filtrates were combined. The combined filtrate was concentrated in vacuo using a HT-24 Genevac evaporator. The resulting residue was taken up in 600 μL of DCM, applied directly to a Varian NH2/Cba SPE cartridge (200 mg NH2 sorbent/200 mg Cba sorbent), and the eluant was collected. The SPE cartridge was further washed with 4 × 500 μL of DCM, and the eluants were collected and combined. The combined eluants were concentrated in vacuo using a HT-24 Genevac evaporator to afford 30−90% of the desired products. LC/MS and ^1H NMR analyses were performed for the resulting products **6**{*1*−*6*}.

3-(3-Trifluoromethoxyphenylamino)-quinoxaline-2-carboxylic Acid 4-Methoxybenzylamide (6{*1*}). ^1H NMR (400 MHz): δ 11.75 (br s, 1H), 9.89 (t, $J = 6.32$, 1H), 8.38 (br s, 1H), 7.97 (dd, $J = 1.01$, 8.34, 1H), 7.83−7.74 (m, 2H), 7.67 (dd, $J = 2.02$, 8.08, 1H), 7.63−7.58 (m, 1H), 7.48 (t, $J = 8.21$, 1H), 7.35−7.31 (m, 2H), 7.04−7.02 (m, 1H), 6.91−6.87 (m, 2H), 4.51 (d, $J = 6.32$, 2H), 3.71 (s, 3H). LC/MS: 469.14 $[M + H]^+$; calcd 468.42. $Purity_{UV219} = 100\%$; yield = 64%.

3-(Benzothiazol-6-ylamino)-quinoxaline-2-carboxylic Acid 4-Methoxybenzylamide (6{*2*}). ^1H NMR (400 MHz): δ 11.84 (br s, 1H), 9.91 (t, $J = 6.44$, 1H), 9.72 (s, 1H), 9.14−9.13 (m, 1H), 8.07 (d, $J = 8.59$, 1H), 7.98 (dd, $J = 1.27$, 8.08, 1H), 7.92 (dd, $J = 1.01$, 8.34, 1H), 7.83−7.79 (m, 2H), 7.62−7.58 (m, 1H), 7.37−7.35 (m, 2H), 6.92−6.90 (m, 2H), 4.54−4.53 (m, 2H), 3.73 (s, 3H). LC/MS: 442.09 $[M + H]^+$; calcd 441.50. $Purity_{UV219} = 100\%$; yield = 72%.

3-(4-Chlorophenylamino)-quinoxaline-2-carboxylic Acid 4-Methoxy-benzylamide (6{*3*}). ^1H NMR (400 MHz): δ 11.63 (br s, 1H), 9.87 (t, $J = 6.31$, 1H), 8.00−7.95 (m, 3H), 7.80−7.79 (m, 2H), 7.61−7.57 (m, 1H), 7.45−7.42 (m, 2H), 7.36−7.33 (m, 2H), 6.92−6.89 (m, 2H), 4.52−4.50 (m, 2H), 3.73 (s, 3H). LC/MS: 419.07 $[M + H]^+$; calcd 418.87. $Purity_{UV219} = 91\%$; yield = 74%.

3-[(2,3-Dihydrobenzofuran-5-ylmethyl)-amino]-quinoxaline-2-carboxylic Acid 4-Methoxybenzylamide (6{*4*}). ^1H NMR (400 MHz): δ 9.04 (t, $J = 5.3$, 1H), 8.45 (t, $J = 5.68$, 1H), 7.68 (dd, $J = 1.01$, 8,34, 1H), 7.61 (dd, $J = 1.01$, 8.58, 1H), 7.54−7.50 (m, 1H), 7.27−7.17 (m, 4H), 7.11 (dd, $J = 1.77$, 8.08, 1H), 6.83−6.80 (m, 2H), 6.67 (d, $J = 8.08$, 1H), 4.64−4.63 (m, 2H), 4.50−4.45 (m, 4H), 3.72 (s, 3H), 3.11 (t, $J = 8.72$, 2H). LC/MS: 441.14 $[M + H]^+$; calcd 440.49. $Purity_{UV219} = 93\%$; yield = 91%.

3-(3-Sulfamoylphenylamino)-quinoxaline-2-carboxylic Acid 4-Methoxybenzylamide (6{*5*}). ^1H NMR (400 MHz): δ 11.93 (s, 1H), 9.92 (t, $J = 6.44$, 1H), 8.53−8.52 (m, 1H), 8.17−8.15 (m, 1H), 8.00−7.90 (m, 1H), 7.87−7.80 (m, 2H), 7.64−7.56 (m, 2H), 7.53−7.50 (m, 1H), 7.45 (br s, 2H), 7.37−7.34 (m, 2H), 6.93−6.90 (m, 2H), 4.53−4.52 (m, 2H), 3.73 (s, 3H). LC/MS: 464.10 $[M + H]^+$; calcd 463.51. $Purity_{UV219} = 100\%$; yield = 67%.

3-Phenethylaminoquinoxaline-2-carboxylic Acid 4-Methoxybenzylamide (6{*6*}). ^1H NMR (400 MHz): δ 9.58 (t, $J = 6.32$, 1H), 8.93 (t, $J = 5.43$, 1H), 7.85 (dd, $J = 1.01$, 8.59, 1H), 7.70−7.62 (m, 2H), 7.44−7.40 (m, 1H), 7.32−7.27 (m, 6H), 7.24−7.19 (m, 1H), 6.91−6.87 (m, 2H), 4.43 (d, $J = 6.32$, 2H), 3.76−3.70 (m, 5H), 2.95 (t, $J = 7.20$, 2H). LC/MS: 413.23 $[M + H]^+$; calcd 412.48. $Purity_{UV219} = 100\%$; yield = 86%.

Method B (for 8{*1*−*80*}). To each reaction tube in a 24-position Bohdan miniblock was added Si-DCT (0.225 mmol), followed by 0.5 mL of DMA and NMM (0.1 mmol). Intermediates **4**{*1*−*4*} were added as solutions (0.05 mmol; 250 μL/reaction tube of a 0.2 M stock solution in DMA), followed by amines **7**{*1*−*20*} (0.1 mmol; 250 μL/reaction tube of a 0.4 M stock solution in DMA). The reaction blocks were shaken for 14 h at room temperature on an orbital shaker. The reaction solutions were then filtered through the miniblocks into collection vials, and the remaining Si-DCT was washed with 3 × 1 mL of DMA. The combined filtrates were concentrated in vacuo using a HT-24 Genevac evaporator. The resulting residues were taken up in 600 μL of DCM, and SPE was performed as described in method A. LC/MS and FI ^1H NMR analyses were performed for the resulting products **8**{*1*−*80*}.

Representative Compounds. 3-(3-Trifluoromethoxyphenylamino)-quinoxaline-2-carboxylic Acid (Biphenyl-4-ylmethyl)-amide (8{*9*}). ^1H NMR (500 MHz): δ 11.73 (s,

1H), 9.99 (t, $J = 6.25$, 1H), 8.39 (br s, 1H), 8.02−8.01 (m, 1H), 7.85−7.79 (m, 2H), 7.70−7.62 (m, 6H), 7.52−7.44 (m, 5H), 7.37−7.35 (m, 1H), 7.05−7.04 (m, 1H), 4.65 (d, $J =$ 6.1, 2H). LC/MS: 515.32 $[M + H]^+$; calcd 514.25. Purity$_{UV219}$ = 100%; yield = 22%.

3-(Benzothiazol-6-ylamino)-quinoxaline-2-carboxylic Acid *p*-Tolylamide (8{*21*}). ^{1}H NMR (500 MHz): δ 11.42 (s, 1H), 10.96 (s, 1H), 9.27 (s, 1H), 9.12−910 (m, 1H), 8.10−8.06 (m, 2H), 7.96−7.90 (m, 1H), 7.86−7.79 (m, 4H), 7.65−7.62 (m, 1H), 7.26−7.25 (m, 2H), 2.33 (s, 3H). LC/MS: 412.24 $[M + H]^+$; calcd 411.15. Purity$_{UV219}$ = 92%; yield = 20%.

[3-(Benzothiazol-6-ylamino)-quinoxalin-2-yl]-(4-phenylpiperazin-1-yl)-methanone (8{*35*}). ^{1}H NMR (500 MHz): δ 9.28 (s, 1H), 9.27 (s, 1H), 8.90−8.89 (m, 1H), 8.06−8.05 (m, 1H), 7.93− 7.87 (m, 2H), 7.84−7.82 (m, 1H), 7.76−7.72 (m, 1H), 7.58−7.54 (m, 1H), 7.25−7.22 (m, 2H), 6.98−6.96 (m, 2H), 6.82−6.80 (m, 1H), 3.93−3.90 (m, 2H), 3.66−3.64 (m, 2H), 3.39−3.37 (m, 2H), 3.22−3.20 (m, 2H). LC/MS: 467.29 $[M + H]^+$; calcd 466.23. Purity$_{UV219}$ = 94%; yield = 27%.

3-(4-Chlorophenylamino)-quinoxaline-2-carboxylic Acid (2-Diethylaminoethyl)-amide (8{*57*}). ^{1}H NMR (500 MHz): δ 11.65 (s, 1H), 9.25 (t, $J = 5.88$, 1H), 8.00−7.97 (m, 2H), 7.95−7.93 (m, 1H), 7.81−7.80 (m, 2H), 7.62−7.58 (m, 1H), 7.45−7.43 (m, 2H), 3.45 (dd, $J = 6.41$, 13.43, 2H), 2.65 (t, $J = 7.02$, 2H), 2.56 (q, $J = 7.02$, 4H), 1.02 (t, $J = 7.17$, 6H). LC/MS: 398.28 $[M + H]^+$; calcd 397.21. Purity$_{UV219}$ = 89%; yield = 46%.

3-[(2,3-Dihydrobenzofuran-5-ylmethyl)-amino]-quinoxaline-2-carboxylic Acid (Tetrahydrofuran-2-ylmethyl)-amide (8{*79*}). ^{1}H NMR (500 MHz): δ 9.11 (t, $J = 5.19$, 1H), 9.00 (t, $J = 6.1$, 1H), 7.90−7.88 (m, 1H), 7.71−7.67 (m, 1H), 7.65−7.63 (m, 1H), 7.46−7.42 (m, 1H), 7.30 (m, 1H), 7.17−7.15 (m, 1H), 6.73−6.71 (m, 1H), 4.63 (d, $J = 5.19$, 2H), 4.5 (t, $J = 8.69$, 2H), 4.07−4.01 (m, 1H), 3.82−3.78 (m, 1H), 3.67−3.63 (m, 1H), 3.43−3.35 (m, 2H), 3.17−3.14 (m, 2H), 1.96−1.77 (m, 3H), 1.64−1.57 (m, 1H). LC/MS: 405.31 $[M + H]^+$; calcd 404.15. Purity$_{UV219}$ = 87%; yield = 62%.

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Supporting Information Available. LC/MS and ^{1}H NMR of crude and pure samples of **6**{*1*}; FI ^{1}H NMR spectra of 32 representative library compounds (**8**{*1*−*80*}). This material is available free of charge via the Internet at http://pubs.acs.org.

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