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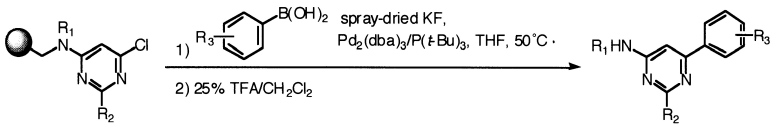

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Suzuki Cross-Coupling of Solid-Supported Chloropyrimidines with Arylboronic Acids

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The utility of the Suzuki cross-coupling to synthesize biaryl compounds is expanded herein to include reactions of resin-supported chloropyrimidines with boronic acids. In particular, an efficient method is described for the synthesis of a library of biaryl compounds from solid-supported chloropyrimidines. The Suzuki reaction was performed in an inert atmosphere using $Pd_2(dba)_3/P(t\text{-}Bu)_3$ as catalyst, spray-dried KF as base, and THF as solvent. The reaction was allowed to proceed overnight at 50 °C. Upon cleavage with acid, a library of 4-(substituted amino)-6-arylpyrimidines was obtained in moderate yield and high purity.

Introduction

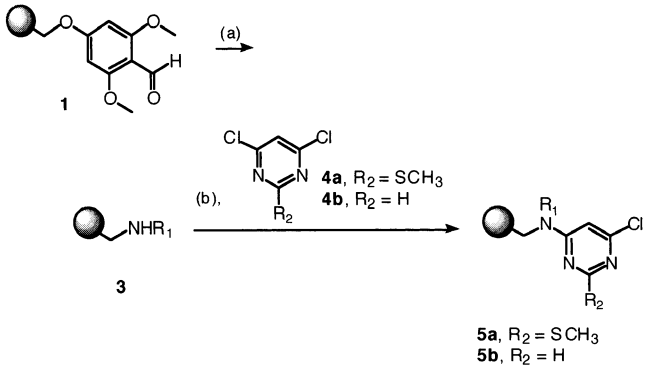
Synthesis of large combinatorial libraries of low-molecular-weight, drug-like molecules requires robust chemistry employing a wide variety of diversity elements that can be reacted with readily available, inexpensive scaffolds.[1] To this end, we developed the solid-supported synthesis of a library starting from commercially available and inexpensive dichloropyrimidines using each chloride as a site to introduce an element of diversity. This 96-compound library was synthesized as described in Schemes 1 and 2, with the critical step being a Suzuki cross-coupling reaction.

Solution-phase Suzuki couplings of aryl halides and, in particular, aryl chlorides,[2−5] chloropyridines,[2,3] and the even more activated heteroaryl chlorides, including 2,4-dichloropyrimidine,[6] have been demonstrated in the literature. Although the Suzuki reaction with chloropyrimidines and 2-chloropurine[7] has been performed in solution, performing the Suzuki coupling on solid phase was explored so that removal of any phosphine ligand, unreacted boronic acid, and palladium could be accomplished by washing the resin.

The Suzuki cross-coupling on solid support has been described in the literature.[8a,b] Immobilizing on solid support one of the key components of the reaction—the ligand,[9] the catalyst,[10] or the boronic acid[11]—has been reported and was considered in the synthesis of our library, but was ultimately rejected. All of these methods lose the advantage inherent to solid-phase synthesis of washing away unreacted reagents before cleavage of the product. Finally, resin-supported aryl bromides and aryl iodides have been used in Suzuki cross-couplings;[12,8a] however, this option was not available for the scaffolds we wished to use.

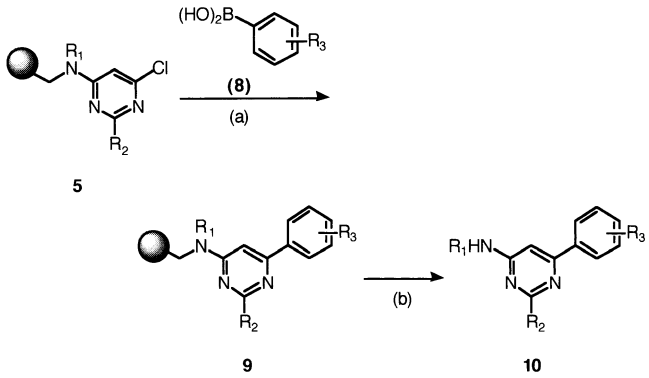
To facilitate the Suzuki reaction, we initially wanted to prepare diiodopyrimidine scaffolds, which are not commercially available, from dichloropyrimidines. Aryl iodides are more reactive than aryl chlorides to oxidative addition to the Pd(0) complex. In fact, oxidative addition to aryl chlorides in the Suzuki reaction is rate-limiting.[13] However, the halogen-exchange reaction did not go to completion with both dichloropyrimidines, and consequently, we investigated options in which the Suzuki cross-coupling could be performed with the less reactive aryl chloride. An advantage of using aryl chlorides in the synthesis of a large number of compounds is that, in general, they are less costly and more commercially available than bromides or iodides.

Scheme 1[a]



[a] Reagents and conditions: (a) 5 equiv of R_1NH_2 (**2**), 10 equiv of AcOH, 3 equiv of $NaBH(OAc)_3$, THF, r.t. (b) 4.5 equiv of **4a** or **4b**, 4.5 equiv of *N*,*N*-diisopropylethylamine, DMF.

Scheme 2[a]



[a] Reaction conditions: (a) 4 equiv of boronic acid, 10 equiv of base, 10% $Pd_2(dba)_3$, 20% ligand, 50 °C (b) 25% TFA in CH_2Cl_2.

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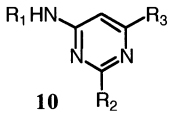
Table 1. Comparison of Suzuki Reaction Conditions[a]

	catalyst	ligand	base	solvent	% purity[b] entry A, Table 2	% purity[b] entry B, Table 2
1	$Pd(PPh_3)_4$	na	2 M Na_2CO_3 (aq)	ethylene glycol dimethyl ether/DMF	no reaction	no reaction
2[c]	$Pd(OAc)_2$	6	K_3PO_4	toluene	>99	87[e]
3	$Pd(OAc)_2$	6	K_3PO_4	THF	73[e]	95[e]
4	$Pd(OAc)_2$	6	KF	THF	76[e]	91[e]
5	$Pd(OAc)_2$	6	KF	toluene	nc[d]	40
6[c]	$Pd(OAc)_2$	7	K_3PO_4	toluene	47[f]	60
7	$Pd(OAc)_2$	7	K_3PO_4	THF	81[f]	31
8	$Pd(OAc)_2$	7	KF	THF	>99	41[e,f]
9	$Pd(OAc)_2$	P(*t*-Bu)$_3$	KF	THF	86[f]	40[e,f]
10	$Pd_2(dba)_3$	6	KF	THF	30[f]	nc[d]
11	$Pd_2(dba)_3$	7	KF	THF	51[f]	nc[d]
12	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	K_3PO_4	toluene	>99	nc[d]
13	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	K_3PO_4	THF	>99	nc[d]
14	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	KF	THF	>99	>87[f]

[a] Reactions were performed in vials or round-bottom flasks under an inert atmosphere. Pd/ligand ratio was in general 1:1. [b] Purity was determined by HPLC, AUC at 214 nm after a single coupling. [c] Using a ratio of 1:2 as described by Buchwald[2] was less successful. [d] Experiment was not conducted. [e] An unidentified impurity was observed. [f] Unreacted starting material was the only impurity.

Table 2. Representative Compounds



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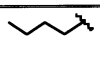
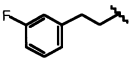
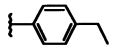
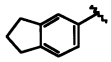
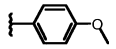
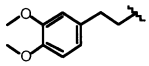
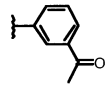
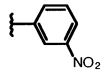
Compd	R_1	R_2	R_3	% Purity After Single Coupling[a]	% Purity After Double Coupling[a]	% Yield[b]
10a		H		95	99	35
10b		SCH_3		65	90	43
10c		SCH_3		65	82	35
10d		H		90	99	25
10e		H		65	93	31
10f		SCH_3		60	98	48

[a] Purity was determined by HPLC, AUC at 214 nm. [b] Yield was determined after SLE and silica plug purification.

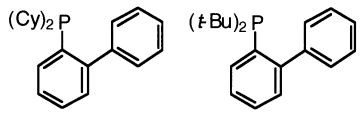
As a result, we turned our attention to the development of a general method to perform the Suzuki cross-coupling of chloropyrimidines on solid support. Suzuki reactions of solid-supported aryl chlorides with boronic acids had not been reported in the literature at the time of our study; however, Schultz and co-workers[14] recently reported their studies after our initial disclosure.[15]

Schultz and co-workers captured 15 different dichloro-heterocyclic scaffolds on solid-support via nucleophilic aromatic substitution of one chloro group with a resin-bound amine nucleophile. The remaining chloro substituent is further elaborated by aromatic substitution with amines or palladium-catalyzed cross-coupling reactions with anilines, boronic acids, and phenols. Suzuki coupling with boronic acids produced high yields and purities. When dichloropyrimidine scaffold **4b** was coupled using 3-methoxyphenyl boronic acid, they obtained an 89% yield by preparative TLC and 93% purity by HPLC. Their Experimental Section indicated the reaction was performed in a 10-mL, flame-dried Schlenk flask under argon on 0.1 mmol scale in 1,4-dioxane at 90 °C for 12 h with 5 equiv of the arylboronic acid, 7 mol % of $Pd_2(dba)_3$, 14 mol % of carbine ligand,[16] and 6 equiv of Cs_2CO_3. Two libraries of 45 and 140 small molecules were constructed using these methods.

Herein, we report a comparison of Suzuki reaction conditions using vials or round-bottomed flasks under an inert atmosphere in Table 1. The optimal conditions were then tested in a high-throughput manner in 96 deep-well plates. Single versus double coupling was investigated (Table 2), producing 96 discrete small molecules.

Results and Discussion

The first step of the synthesis was incorporation of diversity through the reductive amination of 4-formyl-3,5-



6 **7**

Figure 1.

dimethoxyphenoxymethyl resin **1** with primary amines **2** using $NaBH(OAc)_3$ as reducing agent to afford resin-supported secondary amine **3** (Scheme 1).[17] The reaction was monitored using single-bead resin FT-IR.[18] In most cases, the reactions were complete within a few hours; however, they were allowed to proceed overnight to ensure complete conversion. The resin-supported amine **3** selectively displaced the first chloride of each of the dichloropyrimidine scaffolds **4a** and **4b** through nucleophilic aromatic substitution in DMF using *N*,*N*-diiospropylethylamine at 50 °C.[19]

The last step in the synthesis before cleaving from support was the Suzuki cross-coupling. A summary of the conditions that were investigated is given in Table 1. The reactions were allowed to proceed 12−14 h at 50 °C. All reactions were assembled under nitrogen to prevent oxidation of Pd(0) and phosphine ligand and to prevent the homocoupling of aryl boronic acid, which readily occurs in the presence of Pd(0) and base.[12] Anhydrous solvents were used to avoid hydrolytic protodeboronylation, which would decrease the efficiency of the reaction. The filtrates from reactions prepared using the library conditions (Table 1, entry no. 14) were analyzed, and neither homocoupling nor hydrolytic protodeboronylation of the boronic acids was observed.

The first Suzuki coupling conditions we tried were based on work by Frenette and Friesen, who performed the Suzuki reaction using resin-supported aryl bromides and iodides.[8a] They employed a biphasic system and used tetrakis(triphenylphosphine)palladium(0) as catalyst. Where we used an iodopyrimidine, this reaction was successful.[20] However, this system was unsuccessful for any of our chloropyrimidine scaffolds (Table 1, entry no. 1).

Success was achieved by changing the palladium source and ligands (Figure 1). We found that $Pd(OAc)_2$ was less successful when used with P(*t*-Bu)$_3$ and either scaffold **5a** or **5b** (Table 1, entry 9). $Pd_2(dba)_3$ did not perform as well using ligand **6**[2] (Table 1, entry no. 10). In general, ligand **7**[2] failed to give satisfactory results with either palladium source. The success of the palladium/ligand combination also depended on which scaffold was used. Scaffold **5a** gave satisfactory results with ligand **6** and $Pd(OAc)_2$. However, reactions of scaffold **5b** with ligand **6** and either palladium source were unsatisfactory, with the exception of Table 1, entry 2. Although entries 2 and 14 (Table 1) both demonstrate successful results, reactions using $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ gave consistent, excellent results for both scaffolds and were the conditions used in the synthesis of the library.

Although either K_3PO_4 or spray-dried KF could be used successfully as the base, the latter was used in the library synthesis. Fluoride salts are mild bases that accelerate coupling reactions of base-sensitive substrates.[12] In particular, the aldol condensation of the carbonyl-containing boronic acid used in the synthesis of **10d** was of concern;[12] however, no side products were observed in the filtrate.

Incomplete reaction was observed when care was not taken to exclude water. Consequently, anhydrous THF was used as the solvent, though anhydrous toluene was an acceptable substitute. Consistent results were obtained using spray-dried KF rather than anhydrous KF because the latter is more susceptible to water absorption.

A single coupling gave satisfactory results in vials and round-bottom flasks (Table 1). When the synthesis was performed in 96-well plates, a second Suzuki cross-coupling was necessary to ensure complete conversion to the desired product (Table 2). The second coupling was performed in sequence after washing and drying the resin overnight to ensure complete removal of water. This second coupling resulted in a marked increase in purity measured by HPLC (AUC at λ 214 nm) (Table 2).

After the second Suzuki coupling, the resin was washed, and the products were cleaved from the resin with trifluoroacetic acid in CH_2Cl_2. The product was separated from the resin and precipitated catalyst by filtration. The acid and CH_2Cl_2 were removed in vacuo. The products were then neutralized with 5:1 v/v CH_2Cl_2/2 M NH_3 in MeOH, and the solvent was removed in vacuo. The product was dissolved in 9:1 v/v $CHCl_3$/MeOH and purified in a 96-well format by passing the compounds through aqueous basic diatomaceous earth in a solid-supported liquid extraction (SLE)[21] and then through a plug of silica gel. The product solutions were collected and concentrated in vacuo.

Although the purification process resulted in reduced yields, purities were high (Table 2). This process ensured that the products consistently contained less than 0.5% palladium, determined by combustion analysis.

A 96-compound library was constructed from a matrix of 8 R_1 primary amines crossed with 12 R_3 aryl boronic acids. Half of the 96 compounds were made using **4a** and half, with **4b** (R_2). Two copies of this library were prepared using single coupling and the other double coupling. Suzuki coupling was performed under nitrogen on 0.11 mmol scale in anhydrous THF at 50 °C for 18−22 h with 4 equiv of the aryl boronic acid, 10 mol % of $Pd_2(dba)_3$, 20 mol % of P(*t*-Bu)$_3$, and 8 equiv of spray-dried KF. Single coupling with the above Suzuki conditions furnished compounds with an average purity of 65% by HPLC, AUC at 214 nm, while double coupling furnished compounds with an average purity of 94% by HPLC, AUC at 214 nm. Six representative compounds are shown in Table 2 with an average purity of 93% and an average yield of 36% after SLE and silica plug purification.

Conclusion

With this method, we have examined the synthesis of biaryl compounds via Suzuki cross-coupling using resin-supported chloropyrimidines. Optimal conditions were $Pd_2(dba)_3$, P(*t*-Bu)$_3$, spray-dried KF, and THF, providing consistent results for the two chloropyrimidine scaffolds. A variety of boronic acids were tolerated using this method, including ones that contain electron-withdrawing, neutral, and electron-donating groups. We are currently employing this method in 96-well plates to expand this library as well as using other aryl chlorides in the synthesis of biaryl libraries.

Experimental Section

General. All reactions were performed in standard glassware or suitable materials for parallel library synthesis. ^{1}H NMR and ^{13}C NMR spectra were measured on a JEOL 270 and 67.5 MHz spectrometer at 296 K, respectively. Chemical shifts are reported in ppm relative to TMS ($\delta = 0$). HPLC data was obtained on a Hewlett-Packard HPLC 1100 using a Phenomenex C18 (3.0 × 100 mm) column (mobile A, water/ACN (99:1) and 0.05% TFA; mobile B, ACN/water (99:1) and 0.055% TFA); flow rate, 0.5 mL/minute; sample volume, 10.0 μL; temperature, 40 °C; gradient, 0−100% B in 6.5 min, 100% B for 3.0 min, 0% B for 2.5 min; detection, UV at 214 and 254 nm. MS and LC/MS results were obtained from either a Perkin-Elmer Sciex AP1050 spectrometer interfaced with a Hewlett-Packard HP1100 HPLC or a Finnigan TSQ7000 instrument connected to a Hewlett-Packard HP1090 HPLC. Elemental analyses were performed by Robertson Microlit Laboratories Inc., Madison, NJ. 4-Formyl-3,5-dimethoxyphenoxymethyl resin was purchased from Midwest Biotech. All reagents and solvents were reagent grade and were used without further purification.

General Procedure for the Preparation of Library Compounds. Reductive Amination with Primary Amines (3). 4-Formyl-3,5-dimethoxyphenoxymethyl resin **1** (7.3 mmol, 1.1 mmol/g loading, 6.6 g) was transferred into a 50-mL Nalgene bottle. THF (99 mL) from a freshly opened bottle was added to the Nalgene bottle to swell the resin. Primary amine **2** (37 mmol, 5.0 equiv) was added to the appropriate bottle. The bottle was placed on a shaker for 30−60 min to form the imine. The pellets of $NaBH(OAc)_3$ were crushed to a fine powder in a Ziploc bag. Glacial acetic acid (4.2 mL, 73 mmol, 10 equiv) was delivered to the bottle. The crushed $NaBH(OAc)_3$ (4.7 g, 22 mmol, 3.0 equiv) was transferred to the bottle and followed by a blanket of N_2. The bottle was capped, vented with a needle in the cap, and placed on the shaker. The process was repeated for the other amines. The reaction was allowed to proceed for 12−15 h at ambient temperature (22−27 °C). Resin **3** was collected in a coarse-fritted funnel attached to a jointed Erlenmeyer flask connected to vacuum. Resin **3** was subsequently washed with 20 mL of each of the following solvents, agitating the resin with a spatula to ensure mixing: THF, MeOH, CH_2Cl_2, 15% DIEA/CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, and MeOH. When completely dry, the resin was used to monitor completion of the reaction using single bead resin FT-IR.

Nucleophilic Aromatic Substitution Using Dichloropyrimidine Scaffolds (5a, **5b).** The scaffold **4a** or **4b** (1.6 mol, 4.0 equiv) was dissolved in DMF (1.6 L) in a 2-L glass bottle. Diisopropylethylamine (280 mL, 1.6 mol, 4.0 equiv) was then added. The bottle was capped and agitated until the dichloropyrimidine scaffold dissolved. The resin (6.6 g) from each primary amine **3** was slurried in DMF (66 mL), and 1.0 mL (0.11 mmol) was added to the appropriate well of the deep-well plate. The process was repeated with the other amines. The scaffold solution (0.5 mL) was delivered to each well of the deep-well plate. The plates were capped and rotated to mix the contents. The plates were placed in a 50 ± 3 °C oven for 15−18 h; no further agitation was required. The plates were removed from the oven and allowed to cool before unclamping. The solution was drained from the resin, and each well was washed with 1.5 mL each of the following solvents: DMF, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, and anhydrous THF. The plates were dried under vacuum.

Suzuki Coupling (9). The dry plates containing resin **5** were placed in a glovebox. The boronic acid **8** (99 mmol, 4.0 equiv) and $Pd_2(dba)_3$ (2.26−2.37 g, 2.46−2.59 mmol, 0.100−0.105 equiv) were transferred into a bottle. Anhydrous THF (224 mL) was added. The vial was shaken until all the solid dissolved. The process was repeated for the other boronic acids. Anhydrous THF (0.5 mL) was added to each well of the resin-containing deep-well plate. The resin **5** was allowed to swell for at least 5 min, and the plates were inspected to ensure that all of the resin was wetted. Potassium fluoride was added to a shallow-well plate until each well was completely full. Excess potassium fluoride was removed by scraping the top of the plate. Each well contained an equal amount of KF (51 mg, 0.88 mmol, 8.0 equiv). The wetted resin deep-well plate was flipped upside-down (the resin will not fall out if properly wetted), and the wells were aligned with the KF-containing shallow-well plate. The resin-wetted deep-well plate was then flipped right-side-up, delivering the KF. The boronic acid/catalyst solutions (1.0 mL to each well) were delivered to the appropriate well. The ligand (67.0 μL, 0.022 mmol, 0.20 equiv) of the 10 wt % solution of P(*t*-Bu)$_3$ in hexane (Strem catalog no. 15−5811) was delivered to each well. The plate was capped and flipped to mix. The process was repeated with the other plates.

The plates were removed from the glovebox and placed in a 50 ± 3 °C oven previously purged with nitrogen. A constant flow of nitrogen was maintained in the oven. The reaction was allowed to proceed for 18−22 h. The plates were agitated after 12 h and then were placed back in the oven. After 18−22 h, the plates were removed from the oven and allowed to cool to room temperature. The resin was transferred to a deep-well filter plate. Care was taken to avoid taking up the solid on the very bottom of the plates. This was precipitated catalyst and would clog the filter. The plate was allowed to drain. Transferring to another fritted plate may have been necessary if the first one became clogged. MeOH (1.0 mL) was added to each well of the original deep-well plate, swirled, and transferred to the new plate, as well. The original plate was inspected to ensure almost all of the resin **9** was transferred. The solution was allowed to drain from the reactions, and each well was washed with 1.5 mL each of the following solvents: CH_2Cl_2, 1:1 25% NH_4OAc (aq)/DMF, MeOH, 1:1 25% NH_4OAc (aq)/DMF, MeOH, 1:1 0.5 N HCl (aq)/DMF, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, anhydrous THF.

The Suzuki coupling was repeated following the procedure described above.

Cleavage and Purification (10). TFA/CH_2Cl_2 (1:3, 1 mL) was added to each well of the deep-well plate. The plates were capped and placed on a shaker for 1.25−1.75 h at ambient temperature (22−27 °C), after which they were put on dry ice for 30−45 min. Each plate was unclamped and quickly placed on top of a deep-well collection plate. The solution was allowed to drain for 20 min. CH_2Cl_2 (0.5 mL)

was delivered to each well of the plate containing the resin, and this solution was also allowed to drain into the deep-well collection plate. The plates were dried in vacuo. To each well of the deep-well collection plate was added 1.2 mL of a solution of CH_2Cl_2/2 M NH_3 in MeOH (5:1 v/v), and the collection plates were shaken for 20−30 min. The solvent was removed in vacuo. Dioxane (1.2 mL) was added to each well, and the deep-well collection plates were frozen in a −80 °C freezer for at least 3 h. The plates were then lyophilized for at least 48 h. Base-treated silica gel (230−400 mesh) was prepared. Silica (230−400 mesh, 75 mg) was added to a polypropylene bottle, followed by 2 M NH_3 in MeOH (250 μL). The bottle was capped and then shaken at room temperature for 16−18 h. The silica was then filtered through a fritted-glass funnel and vacuum-dried.

Removal of trace TFA, boronic acids, or palladium catalyst was accomplished by basic SLE using Varian ChemElut Hydromatrix material and a base-treated silica plug packed into two separate Polyfiltronics plates. The SLE material was packed by filling a 1-mL 96-well plate with Hydromatrix material and then turning it upside down into the 2-mL deep-well filter plate. The wells of each plate containing the Hydromatrix material were primed with 700 μL of 2 M aq Na_2CO_3 and allowed to stand for 10 min. The base-treated silica gel was packed by filling a shallow-well plate with ∼75 mg/well of base-treated 230−400 mesh silica gel prepared above. The silica was transferred by turning the shallow-well plate upside down into a deep-well filter plate. The silica was wetted with 500 μL $CHCl_3$/MeOH (9:1 v/v). The deep-well filter plate was placed on a Tomtec vacuum box, and the excess solvent was removed by briefly vacuum-filtering for 3−4 s. The plate was then placed on a deep-well collection plate. The SLE plate was then stacked on top of the silica gel plate. The solvent mixture, 1.1 mL $CHCl_3$/MeOH (9:1, v/v), was added and shaken for 20−30 min in order to dissolve the products. Once the contents of the wells were thoroughly mixed, the solutions were then slowly delivered to the SLE plate. After allowing the product solution to elute briefly into the silica gel plate and subsequent deep-well collection plate, the source plates containing the crude products were washed with 1.0 mL of $CHCl_3$/MeOH (9:1 v/v), which was then transferred to the top of the purification plate stack and allowed to elute for 5−10 min. After the solution **10** had completely eluted, the deep-well collection plates were concentrated in vacuo.

Representative compounds below were separated by reversed-phase gradient elution using a Waters PrepLC module fitted with three 40 × 100 mm Prep Nova-Pak HR C18, 6-μm, 60-Å column segments with a guard column. Mobile phases consisted of HPLC grade acetonitrile with 0.05% trifluoroacetic acid (TFA) and HPLC grade water with 0.05% TFA; separation gradient was from 10 to 100% organic over 28 min at a constant flow rate of 80 mL/min. The major peak was collected and dried by freezing the sample and placing it under high vacuum. The dried material was extracted with 10−20 mL of saturated $NaHCO_3$ and chloroform (3 × 3 mL) to remove residual TFA. The extracted material was then separated by normal phase gradient elution using a 21.2 × 250 mm Rx-Sil, 7-μm silica packing. The gradient was applied over 25 min from 1% methanol, 87% hexane, and 12% dichloromethane to 88% methanol and 12% dichloromethane at a constant flow rate of 25 mL/minute. The major peak observed at 254 nm was collected and the solvent was removed by evaporation. The residue was then dissolved in 2 mL of acetonitrile and lyophilized to remove residual solvent.

10a. Brown solid; ^{1}H NMR (270 MHz, CD_3OD) δ 8.43 (s, 1H), 7.89−7.85 (m, 2H), 7.49−7.44 (m, 3H), 6.83 (d, J = 1.0 Hz, 1H), 3.40 (t, J = 6.9 Hz, 2H), 1.75−1.57 (m, 2H), 1.50−1.37 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C NMR (67.5 MHz, CD_3OD) δ 163.3, 157.8, 157.5, 137.4, 129.9, 128.5, 126.6, 99.0, 40.4, 31.1, 19.8, 12.8. MS (ESI) m/z 227.6 [(M + H)$^+$]. Anal. calcd for $C_{14}H_{17}N_3$: C, 73.98; H, 7.54; N, 18.49. Found: C, 73.98; H, 7.54; N, 18.49.

10b. White powder; ^{1}H NMR (270 MHz, CD_3OD) δ 7.91 (dt, J = 8.4, 2.0 Hz, 2H), 7.32−7.26 (m, 3H), 7.06−6.90 (m, 3H), 6.41 (s, 1H), 3.68 (q, J = 6.7 Hz, 2H), 2.95 (t, J = 7.0 Hz, 2H), 2.70 (q, J = 7.7 Hz, 2H), 2.57 (s, 3H), 1.25 (t, J = 7.7 Hz, 3H). ^{13}C NMR (67.5 Hz, CD_3OD) δ 171.4, 162.8, 146.9, 134.9, 130.2, 130.1, 128.1, 126.8, 124.7, 124.6, 115.8, 115.4, 113.5, 113.2, 42.3, 35.3, 28.7, 15.3, 13.9. MS (ESI) m/z 367.8 [(M + H)$^+$]. Anal. calcd for $C_{21}H_{22}FN_3S$: C, 68.64; H, 6.03; N, 11.43. Found: C, 68.36; H, 5.95; N, 11.43.

10c. Yellow-white solid; ^{1}H NMR (270 MHz, CD_3OD) δ 7.79 (d, J = 9.2 Hz, 2H), 7.39 (s, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.07 (d, J = 7.9 Hz, 1H), 6.88 (d, J = 9.2 Hz, 2H), 6.58 (s, 1H), 3.74 (s, 3H), 2.84−2.75 (m, 4H), 2.48 (s, 3H), 2.04−1.93 (m, 2H). ^{13}C NMR (67.5 MHz, CD_3OD) δ 171.3, 162.3, 161.6, 161.4, 144.8, 139.3, 137.5, 129.7, 128.2, 124.1, 119.2, 117.3, 113.7, 96.0, 54.3, 32.7, 32.0, 25.5, 13.2. MS (ESI) m/z 365.4 [(M + H)$^+$]. Anal. calcd for $C_{21}H_{21}N_3OS$: C, 69.39; H, 5.82; N, 11.56; Found: C, 69.37; H, 5.75; N, 11.41.

10d. Off-white solid; ^{1}H NMR (270 MHz, CD_3OD) δ 8.48 (s, 1H), 8.43 (s, 1H), 8.08 (d, J = 7.4 Hz, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.46 (dd, 1H), 6.73−6.65 (m, 4H), 3.69 (s, 6H), 3.55 (d, J = 5.9 Hz, 2H), 2.81−2.76 (m, 2H), 2.53 (s, 3H). ^{13}C NMR (67.5 MHz, CD_3OD) δ 197.6, 163.1, 158.6, 149.3, 149.0, 138.1, 137.7, 131.2, 129.7, 129.0, 126.5, 120.8, 112.4, 111.8, 56.0, 42.7, 35.0, 26.7. MS (ESI) m/z 378.0 [(M + H)$^+$]. Anal. calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 69.89; H, 6.11; N, 10.99.

10e. White powder; ^{1}H NMR (270 MHz, CD_3OD) δ 8.78−8.77 (m, 1H), 8.51 (d, J = 1.2 Hz, 1H), 8.30 (dt, J = 8.1, 2.2 Hz, 2H), 7.71 (t, J = 7.9 Hz, 1H), 6.99 (d, J = 1.00 Hz, 1H), 3.62−3.59 (m, 4H), 3.38 (s, 3H). ^{13}C NMR (67.5 MHz, CD_3OD) δ 163.5, 160.1, 158.3, 158.1, 147.5, 139.3, 132.5, 129.9, 124.3, 121.5, 70.7, 58.0, 40.5. MS (ESI) m/z 274.8 [(M + H)$^+$], 272.8 [(M − H$^+$)]. Anal. calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.93; H, 5.18; N, 20.51.

10f. White powder; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 6.16 (s, 1H), 3.55−3.39 (m, 7H), 2.31 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 164.3, 163.3, 138.2, 136.4, 136.0, 129.4, 127.6, 124.1, 68.0, 66.0, 38.0, 29.3, 18.6, 18.3, 14.1. MS (ESI) m/z 324.0 [(M + H)$^+$]. Anal. calcd for

$C_{15}H_{18}FN_3O_2S$: C, 55.71; H, 5.61; N, 12.99. Found: C, 55.83; H, 5.57; N, 13.03.

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