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ARTICLE *in* JOURNAL OF COMBINATORIAL CHEMISTRY · SEPTEMBER 2004

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Solid-Phase Synthesis of an Alkylaminobenzanilide Library

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Received March 30, 2004

The synthesis of a library of 2- and 3-substituted benzanilides has been achieved on solid phase. Attachment of anilines to formyldimethoxyphenyl (FDMP) resin via reductive amination was optimized to allow a wide range of anilines to be used. Acylation of this resin-bound aniline was accomplished with 2- or 3-nitrobenzoyl chloride to yield nitrobenzanilides. Following reduction of the nitro group, the resulting amine was alkylated using aromatic and heteroaromatic aldehydes in the presence of $NaBH(OAc)_3$ under controlled conditions. Finally, the products were cleaved from the resin using trifluoroacetic acid to produce a 10 800-member library.

Introduction

Benzanilides have demonstrated utility as centroid elements of ligands that bind to a wide variety of receptor types. Aminoalkyl groups adorn many of these cores. For instance, *m*-(aminomethyl)benzoic acid (Mamb) (Figure 1), originally designed as a peptidomimetic,[1] has been incorporated as a semirigid template within an Arg-Gly-Asp cyclic peptide yielding a high affinity GPIIb/IIIa ligand, **1**.[2]

Potentially the most exciting recent use of this core is in the field of kinase inhibitors. Imatinib (Gleevec), **2**, is an ATP-site binding kinase inhibitor specific for the BCR-ABL, c-Kit, and platelet-derived growth factor receptor kinases.[3] In the discovery of **2**, the benzanilide moiety resulted in specificity toward the BCR-ABL kinase. Further selectivity for this kinase was achieved with the introduction of the piperazine moiety.

Another class of benzanilide kinase inhibitors is represented by **3**, a vascular endothelial growth factor receptor (VEGF-R) tyrosine kinase inhibitor.[4] This class of kinase inhibitors was discovered through a conformational analysis of other known inhibitors.[5] In that study, it was postulated that **3** binds to the ATP-binding site pocket in a mode similar to that of the anilinophthalazine kinase inhibitors.

Additionally, benzamides have been reported to have activities as acetyl-CoA carboxylase **4**[6] and farnesyl transferase inhibitors **5**.[7] In fact, the benzanilide core is present in compounds with such a wide range of biological activities that it has been called a privileged structure.[8] Benzanilides can also serve as leads toward more conformationally constrained compounds such as benzothiadiazin-4-ones, quinazoline-2,4-diones, and benzodiazepine-2,5-diones.[9−11]

The benzanilide's potential as a source of hits against a wide variety of proteins and the ability to readily modify these hits to other compound classes make this core a good candidate for production of a discovery library. We envisioned three points of diversity: an aniline starting point, substituted benzoyl groups, and aldehydes, resulting in ortho- and meta-substituted benzanilides **6** and **7**. The design and optimization of a solid-phase approach is described along with the synthesis and characterization of a 10 800-member library.

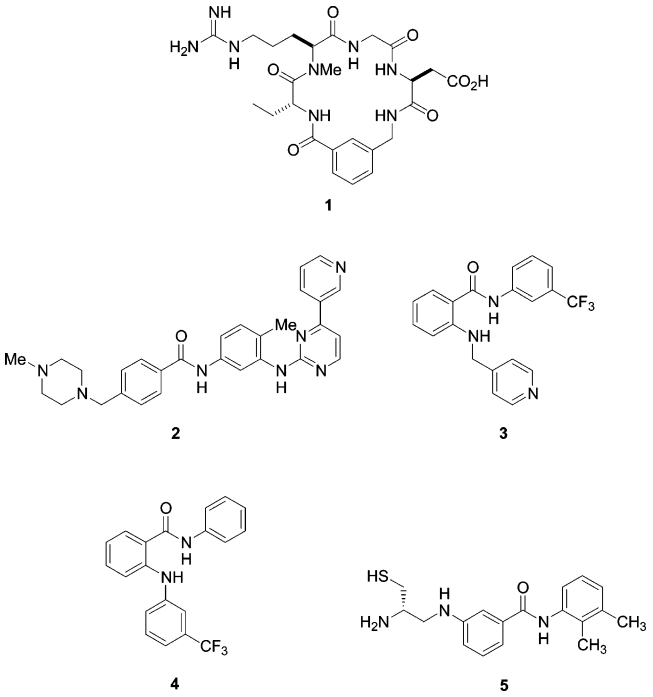
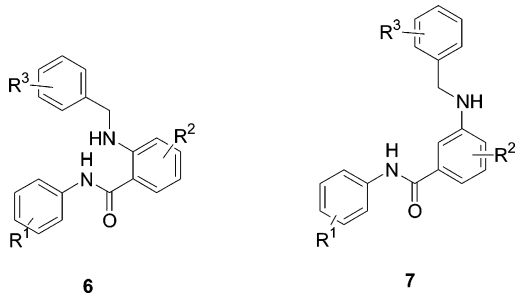


Figure 1. Biologically active benzamides.



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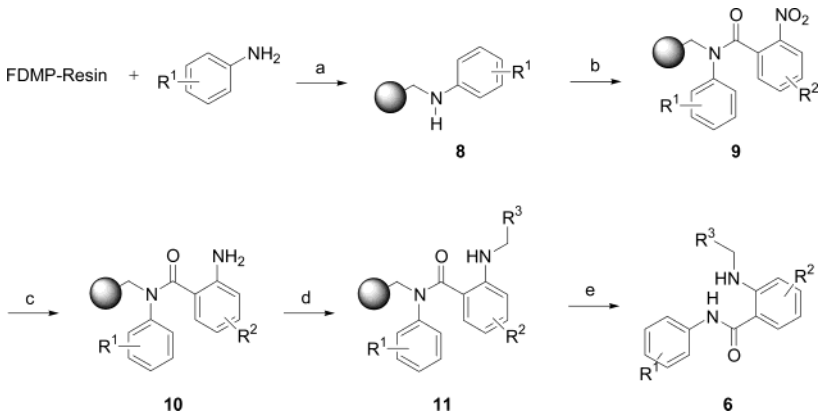
10.1021/cc0499284 CCC: $27.50
Published on Web 06/17/2004

Scheme 1. Solid-Phase Synthesis of Benzanilides[a]



[a] (a) $NaBH(OAc)_3$, DMF, AcOH; (b) 2-nitrobenzoyl chlorides, DIEA, DCM; (c) $SnCl_2 \cdot 2H_2O$, DMF; (d) R^3CHO, $NaBH(OAc)_3$, DCE, AcOH; (e) 10% TFA in DCM.

Results and Discussion

A convenient initiation of this solid-phase synthesis was the incorporation of a variety of anilines onto a resin linker. Although anilines are common building blocks in combinatorial synthesis, they have been rarely utilized as an attachment point in solid-phase chemistry. Although pyridine amines have been attached to resin through a silicon traceless linker with cleavage by fluoride reagents,[12] this strategy is unfriendly to large library productions because the cleavage reagents are either nonvolatile or excessively toxic.

Previously, *o*-hydroxyaniline has been attached to 4-formyl-3-methoxyphenoxy resin via reductive amination to make a small library of oxazepine derivatives.[13] Aniline has also been attached to 4-formylphenoxy resin via reductive amination.[14] However, neither study explored the scope of this reductive amination; therefore, we sought to investigate this reaction using FDMP resin to take advantage of the relatively mild acidic conditions necessary for product cleavage.

Reductive amination was carried out by adding 2% acetic acid in DMF followed by the addition of the aniline and $NaBH(OAc)_3$. Initial experiments revealed that a wide range of anilines could successfully be attached using this method, including electron-deficient examples such as chloro-, alkoxy-, and alkylanilines. With this broad range of resin-bound anilines, we turned our attention to the selection of an appropriate acylation strategy.

The solution-phase synthesis of ortho-substituted benzanilides has been shown to proceed through the isatoic anhydride.[4] The marginal yields this afforded, even at elevated temperatures, render it unsuitable for solid-phase synthesis. Because we wanted to use a variety of benzoyl derivatives, acylation of the resin-bound aniline was explored a variety of ways. We initially attempted acylation with Fmoc-protected 2- and 3-aminobenzoic acids. It has been reported[13] that 1-hydroxy-7-azabenzotriazole with diisopropylcarbodiimide (HOAT/DIC)[15] was used to acylate resin-bound *o*-hydroxyaniline in good yield. In our exploration of this reaction with other anilines, HOAT/DIC resulted in complete conversion only with 2-methoxyaniline, and yields for acylation of electron-deficient anilines ranged from only 2 to 15%. Steric hindrance by the Fmoc group may have contributed to these poor results; therefore, the use of 2- and 3-nitrobenzoic acids was explored. Again, complete acylation of several anilines was not achieved using HOAT/DIC with 3-nitrobenzoic acid.

Studies of additional acylating methods ultimately led to benzoyl chloride as a desirable reagent. Acylation with both 2-nitro- and 3-nitrobenzoyl chlorides followed by nitro group reduction with stannous chloride resulted in the desired amino benzanilide intermediates in very good yield and purity.

Functionalization of the emergent amine via reductive amination gave inconsistent results. We found that many products contained significant levels of the dialkylated product, especially when using the *meta*-aminobenzoyl core. Reactions using Irori MicroKans are normally carried out using high molar concentrations. In earlier work,[16] we discovered that excess molar equivalents of aldehyde resulted in dialkylation of Rink resin. Reduction of the reagent concentration to 0.2 M abolished this side reaction. Application of those results to the present case indicated that 0.15−0.2 M aldehyde was sufficient to give highly pure monoalkylated products. The optimized synthetic scheme for the solid-phase production of **6** and **7** is shown in Scheme 1, and this procedure was used to produce a larger library of anilides **6** and **7**.

The building blocks for the library synthesis (anilines, nitrobenzoic acids, and aldehydes) were selected on the basis of the diversity and physicochemical properties of the virtual library. Generally, the mean virtual product molecular weight and cLogP were kept below 500 and 5, respectively. This analysis led to the selection of 80 anilines and heteroarylamines for **R1**, 28 nitrobenzoic acids for **R2**, and 80 aldehydes for **R3**. These building blocks were then rehearsed to determine their reactivity in the synthetic pathway. The rehearsals were accomplished by two building blocks while varying the third. This study resulted in 30 anilines, 10 benzoic acids, and 36 aldehydes (Figures 2−4), which led to satisfactory purities of final products **6** and **7**.

For **R1**, the building blocks that did not give the desired product purity were sterically hindered or very electron deficient, for example, 2,6-disubstituted anilines and 4-trifluoromethylaniline. In addition, most heteroarylamines worked poorly. In these cases, no desired product was

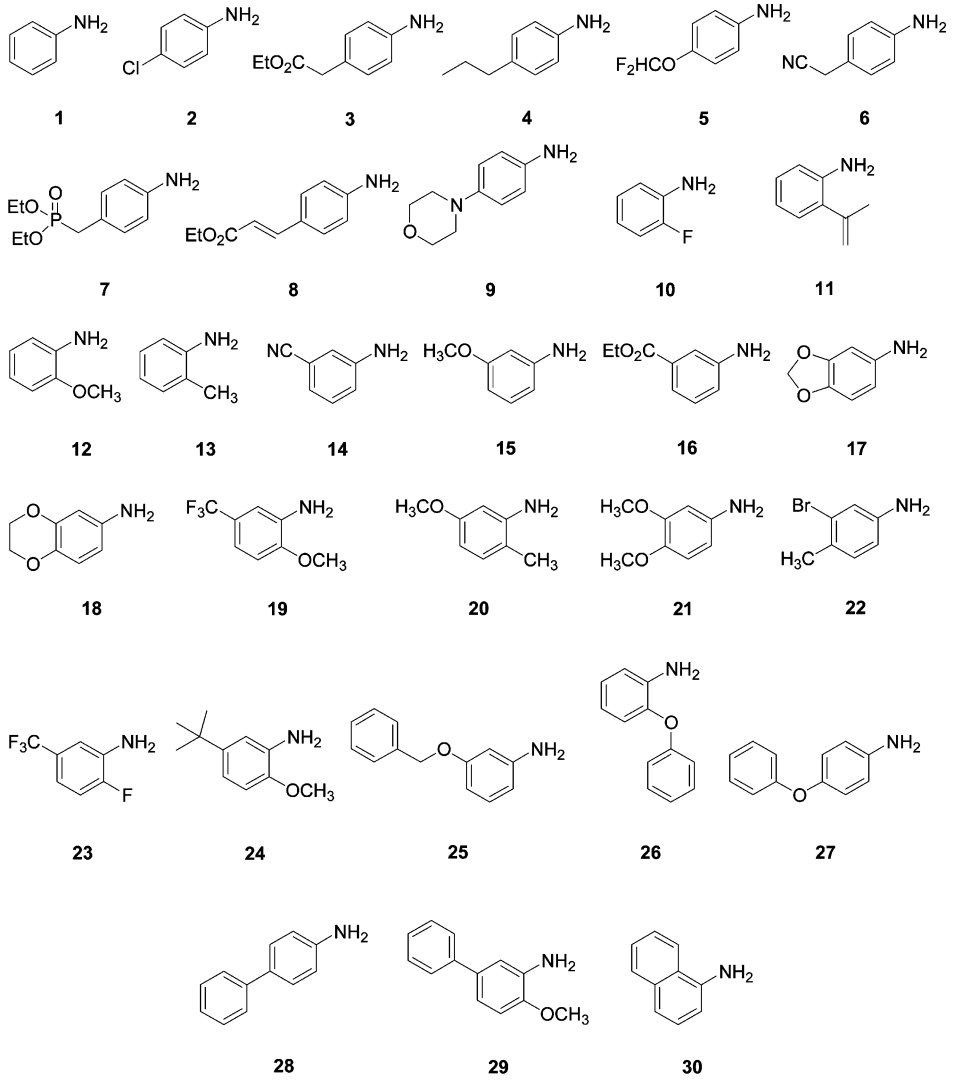


Figure 2. Set of anilines for **R1**{*1*−*30*} for the library.

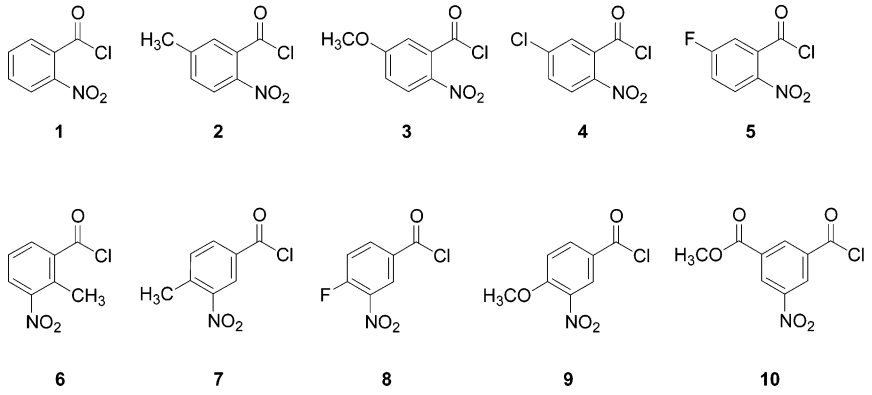


Figure 3. Set of benzoyl chlorides **R2**{*1*−*10*} for the library. Reagents **R2**{*1*−*5*} for **6** and **R2**{*6*−*10*} for **7**.

obtained, indicating that either the building block was not loaded onto the resin or that the acylation failed.

Ten different 2- or 3-nitrobenzoyl derivatives (Figure 3) were selected from commercial sources or converted to the acid chloride with oxalyl chloride.[17] The rehearsal results suggested that the primary difficulty occurred during the reductive amination rather than in the acylation step. For instance, the product derived from 2-nitrobenzoic acid was 100% pure, but the same chemistry with the meta derivative resulted in a 2:1 ratio of monoalkylated to dialkylated product. Whenever the 3-aminobenzanilides had a substituent ortho to the amine **R2**{*6,7,9*}, highly pure product **7** was obtained, suggesting that steric hindrance plays a major role in preventing the dialkylation. Electronic characteristics of the 3-aminobenzanilide also had a significant influence on the reductive amination. The presence of a *m*-carbomethoxy group, **R2**{*10*}, greatly suppressed the dialkylation. This might be attributed to the deactivating

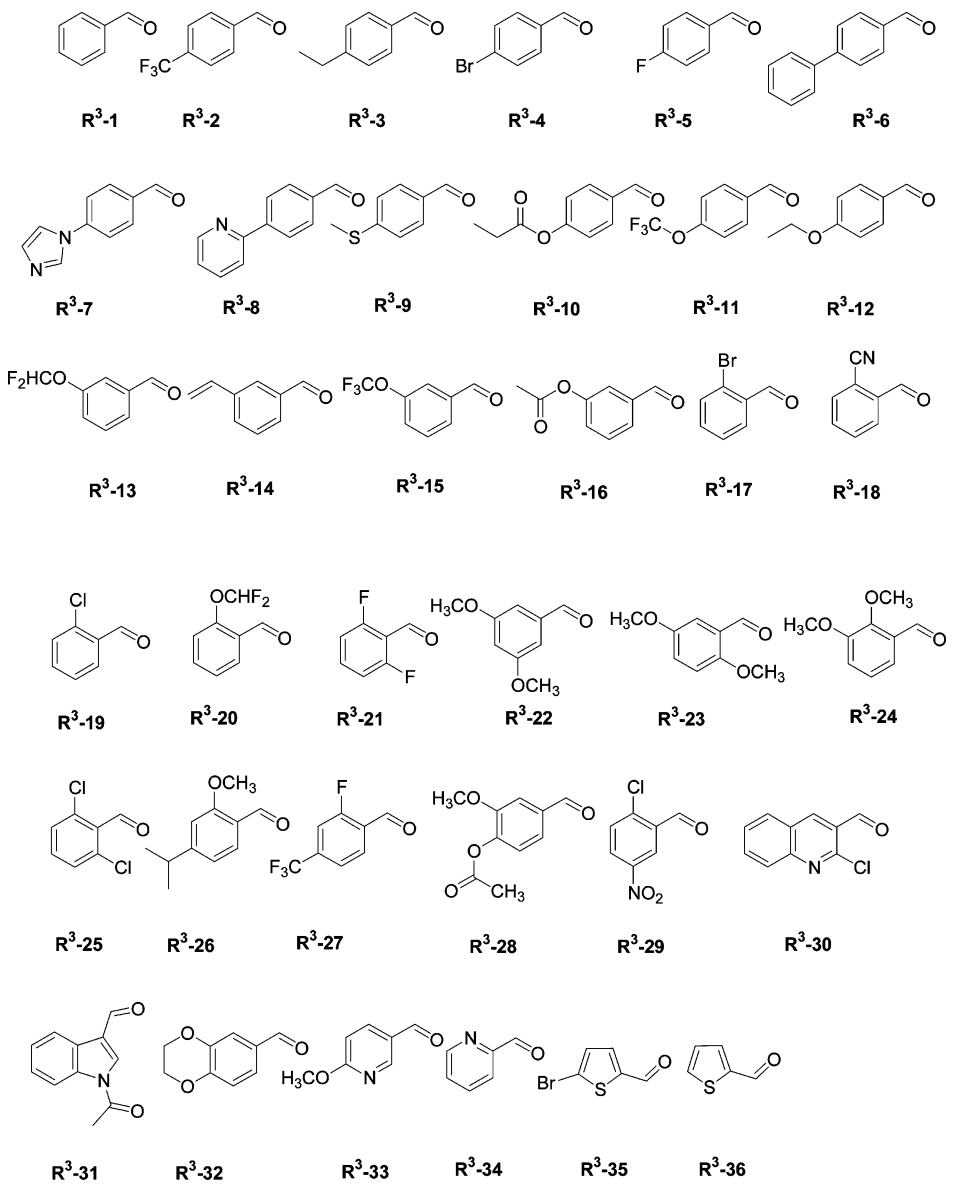


Figure 4. Set of aldehydes **R3**{*1*−*36*} for the library.

effect of the pendant ester on the amine reactivity.

The rehearsal of aryl and heteroaryl aldehydes **R3** resulted in a wide range of building blocks including sterically hindered, electron-rich, and electron-poor examples that gave the desired product in high purity. To further explore the observed dialkylation with the 3-benzoyl core described above, additional experiments were carried out using the same aldehydes with resin-bound 4-chloro-3-aminobenzanilide. In many of the aldehydes, the product purity was reduced by at least 10% with the 3-amino products as compared to the 2-amino products. These results confirmed the significance of the steric hindrance of the benzoyl group on the dialkylation.

The production of a 10 800-member library (30 × 10 × 36) was accomplished by means of Scheme 1 using the Irori system. All products were fully characterized by LC/MS using ELS detection. Additionally, 20 products were analyzed by NMR, and their full characterization is reported in the Experimental Section.

The mean molecular weight of the library was 446.0 g/mol, and its mean cLogP was 4.6. The mean purity of the library was 88% with 84% of the products having purities above 80%, and the mean yield was 4.5 mg (22%).

Conclusion

Through efficient coupling of arylamines to FDMP resin as a key step, which allowed a broad range of anilines to be utilized, 10 800 benzanilide derivatives were synthesized. Careful control of the final reductive amination step was required to prevent overalkylation of the amine. The screening of this library is in progress against a variety of biological targets.

Experimental Section

All reagents and anhydrous solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI), Fisher Scientific (Atlanta, GA), Lancaster Synthesis (Windham, NH), or TCI-America (Portland, OR). FDMP resin was purchased from Polymer Labs (Amherst, MA). All MicroKans, Rf tags, and assorted scanning and sorting equipment were purchased from Discovery Partners (San Diego, CA). Mixing of the MicroKan suspensions during reactions and all washes were

performed with Innova Shakers, New Brunswick Scientific, New Brunswick, NJ.

LC/MS data were recorded on a Waters ZQ electrospray mass spectrometer equipped with 4-channel MUX capabilities (Milford, MA) with ELS detection using a Princeton SPHER HTS 60 Å, 5-μm column (3 × 50 mm) from Princeton Chromatography (Princeton, NJ). Typical gradients were 25−100% MeCN/H_2O containing 0.1% formic acid and 0.01% TFA, 2.25 min, flow rate 1.5 mL/min. Proton NMR spectra were obtained on a Varian 300 MHz instrument using MeCN as the internal reference.

General Conditions with Microkans. Approximately 25 mg of FDMP resin (prewashed with MeOH and DCM and dried) and Rf tag bars were loaded into each MicroKan using the IRORI dry-resin loader and Rf tag dispenser. All MicroKans were sorted at each diversity step with the Autosort 10K sorter. After every reaction, two initial washes were performed in each reaction vessel, followed by pooling of the MicroKans into 5-L polypropylene carboys for thorough washing with alternating MeOH and DCM (three times each). Cleavage of the library was performed in the Accucleave 192 apparatus. The reported yields are based on the isolation of the compounds as TFA salts.

General Procedure for the Preparation of Library Compounds. Resin-Bound Arylamine (8). In a reaction vessel containing resin-charged MicroKans, anhydrous DMF containing 2% acetic acid (1 mL/MicroKans), arylamine (0.5 M), and sodium triacetoxyborohydride (1.0 M) were added. The mixture was shaken overnight, followed by filtration of the reaction mixture. The MicroKans were then washed twice with DMF followed by the DCM−MeOH general washing procedure (vide supra). The MicroKans were dried in vacuo at room temperature and sorted for the next step.

Preparation of 2- or 3-Nitrobenzoyl Chloride Monomers. In a dry flask containing nitrobenzoic acid, DCM (5 mL/mmol of acid) was added followed by oxalyl chloride (2 mol equiv). After the addition of a few drops of dry DMF, evolution of gas occurred. The mixture was stirred for 4 h at room temperature. After completion of the reaction, the excess oxalyl chloride was removed in vacuo. Complete removal of oxalyl chloride was accomplished by trituration with DCM followed by removal of the volatiles in vacuo. Freshly prepared acid chlorides were stored under argon in a cool dry location.

Resin-Bound Nitrobenzanilides (9). Anhydrous DCM was added to the MicroKans containing **11** followed by DIEA (0.5 mmol). The appropriate nitrobenzoyl chloride (0.25 mmol) was carefully added. The reaction was run overnight followed by filtering the reaction mixture. The MicroKans were washed twice with a MeOH−DCM mixture and then the additional general washes described above and dried in vacuo.

Resin-Bound Aminobenzanilide (10). DMF was added to a reaction vessel containing the MicroKans. $SnCl_2 \cdot 2H_2O$ (1 M) was added, and the mixture was shaken for 24 h. The reaction mixture was filtered, and the MicroKans were washed twice with DMF followed by the additional general washes described above and dried in vacuo.

Resin-Bound *N*′-Arylmethylbenzanilide (11). 1,2-Dichloroethane (DCE) containing 2% acetic acid was added to the MicroKans followed by the aldehyde to give a 0.15 M solution. The mixture was shaken for 2 h, and then $NaBH(OAc)_3$ was added. The resulting mixture was shaken overnight, filtered, and the reaction was quenched by washing with MeOH. The MicroKans were washed twice with DMF and then the additional general washes described above, dried in vacuo, and sorted for cleavage.

Cleavage from Resin to Title Compounds (6 and 7). First, 1.7 mL of 10% TFA in DCM was added to each well of the Accucleave 192 and then mixed at room temperature for 30 min. The solution was collected in 96-well blocks and concentrated to dryness. The residues were redissolved in MeCN and analyzed by LC/MS.

***N*-(4-Chlorophenyl)-2-(4-ethylbenzylamino)benzamide 6{*2,1,3*}.** Yield: 2.4 mg (13%). ^{1}H NMR (CD_3CN, 300 MHz): δ 8.70 (br, 1H), 7.65 (dd, 2H), 7.64 (dd, 1H), 7.35 (dd, 2H), 7.28 (m, complex, 3H), 7.18 (d, 2H), 6.70 (dd, 1H), 6.64 (m, 1H), 4.37 (s, 2H), 2.61 (q, 2H), 1.18 (t, 3H). LC/MS (ELS) m/z = 365.3 $(M + H)^+$ (100%, R_t = 1.42 min).

2-[(1-Acetyl-1*H*-indol-3-yl)methylamino]-*N*-(4-difluoromethoxyphenyl)ben zamide 6{*5,1,31*}. Yield: 8.5 mg (40%). ^{1}H NMR (CD_3CN, 300 MHz): δ 8.66 (br, 1H), 8.33 (d, 1H), 7.65 (complex, m, 2H), 7.57 (m, 1H), 7.56 (d, 2H), 7.43 (m, 1H), 7.32 (m, 1H), 7.30 (m, 1H), 7.24 (m, 1H), 7.12 (d, 2H), 7.07 (d, 1H), 6.83 (m, 1H), 6.72 (t, 1H, J = 75 Hz for CHF_2), 4.58 (s, 2H), 2.52 (s, 3H). LC/MS (ELS) m/z = 450.3 $(M + H)^+$ (100%, R_t = 1.32 min).

***N*-(4-Cyanomethylphenyl)-2-(4-fluorobenzylamino)-5-methoxybenzamide 6{*6,3,5*}.** Yield: 9.0 mg, (48%). ^{1}H NMR (CD_3CN, 300 MHz): δ 8.82 (br, 1H), 7.61 (dd, 2H), 7.36 (dd, 2H), 7.28 (complex multiplet, 3H), 7.13 (dd, 2H), 7.01 (dd, 2H), 4.44 (s, 2H), 3.83 (s, 5H). LC/MS (ELS) m/z = 390.3 $(M + H)^+$ (100%, R_t = 1.05 min).

3-{4-[2-(2-Bromobenzylamino)-5-fluorobenzoylamino]-phenyl}acrylic Acid Methyl Ester 6{*8,5,17*}. Yield: 7.8 mg (34%). ^{1}H NMR (CD_3CN, 300 MHz): δ 8.78 (br, 1H), 7.67 (m, 3H), 7.60 (m, 3H), 7.46 (dd, 1H), 7.38 (dd, 1H), 7.31 (m, 1H), 7.18 (m, 1H), 7.10 (m, 1H), 6.59 (m, 1H), 6.44 (d, 1H), 4.47 (s, 2H), 4.20 (q, 2H), 1.28 (t, 3H). LC/MS (ELS) m/z = 497.2 $(M + H)^+$ (100%, R_t = 1.46 min).

2-Benzylamino-*N*-[4-(morpholin-4-yl)phenyl]benzamide 6{*9,1,1*}. Yield: 9.9 mg (43%). ^{1}H NMR (300 MHz, CD_3CN): δ 8.68 (br, 1H), 7.69 (dd, 2H), 7.66 (m, 1H), 7.37−7.26 (complex multiplets, 8H), 6.71 (d, 1H), 6.67 (m, 1H), 4.41 (s, 2H), 3.93 (m, 4H), 3.38 (m, 4H). LC/MS (ELS) m/z = 388.3 $(M + H)^+$ (97.4%, R_t = 0.81 min).

2-[(5-Bromo-2-thienyl)methylamino]-*N*-(2-methoxyphenyl)benzamide 6{*12,1,35*}. Yield: 18.6 mg (94%). ^{1}H NMR (CD_3CN, 300 MHz): δ 8.56 (br, 1H), 8.17 (dd, 1H), 7.63 (dd, 1H), 7.33 (m, 1H), 7.12 (dd, 1H), 7.04 (dd, 1H), 6.98 (m, 1H), 6.97 (d, 1H), 6.85 (dd, 1H), 6.82 (dd, 1H), 6.74 (m, 1H), 4.57 (d, 2H), 3.89 (s, 3H). LC/MS (ELS) m/z = 417.1 and 419.1 $(M + H)^+$ (100%, R_t = 1.49 min).

***N*-(1,4-Benzodioxan-6-yl)-2-[(2-chloro-3-quinolinyl)-methylamino]-5-fluorobenzamide 6{*18,5,30*}.** Yield: 18.6 mg (86%). ^{1}H NMR (300 MHz, CD_3CN): δ 8.53 (br, 1H),

8.18 (s, 1H), 7.92 (d, 1H), 7.82 (dd, 1H), 7.73 (m, 1H), 7.56 (m, 1H), 7.45 (dd, 1H), 7.16 (d, 1H), 7.07 (m, 1H), 7.01 (dd, 1H), 6.81 (d, 1H), 6.71 (dd, 1H), 4.63 (s, 2H), 4.23 (m, 4H). LC/MS (ELS) $m/z = 464.1$ $(M + H)^+$ (100%, $R_t =$ 1.48 min).

2-(2,3-Dimethoxybenzylamino)-*N*-(2′-methoxybiphenyl-4-yl)-5-methylbenzamide 6{*29,2,24*}. Yield: 16.6 mg (74%). ^{1}H NMR (CD_3CN, 300 MHz): δ 8.64 (br, 1H), 8.39 (d, 1H), 7.62 (dd, 2H), 7.61 (m, 1H), 7.47 (dd, 2H), 7.43 (d, 1H), 7.37 (m, complex, 2H), 7.14 (dd, 2H), 6.94 (d, 1H), 6.91 (d, 1H), 6.74 (dd, 1H), 4.48 (s, 2H), 3.94 (s, 3H), 3.82 (s, 3H), 3.68 (s, 3H), 2.37 (s, 3H). LC/MS (ELS) $m/z = 483.3$ $(M + H)^+$ (98.8%, $R_t = 1.34$ min).

5-[(2-Chloroquinolin-3-ylmethyl)amino]-*N*-(4-ethoxycarbonylmethylphenyl)-isophthalamic Acid Methyl Ester 7{*3,10,30*}. Yield: 11.4 mg (47%). ^{1}H NMR (300 MHz, CD_3CN): δ 8.74 (br, 1H), 8.24 (s, 1H), 7.94 (dd, 1H), 7.85 (dd, 1H), 7.79 (dd, 1H), 7.74 (m, 1H), 7.60 (dd, 2H), 7.55 (dd, 1H), 7.42 (dd, 1H), 7.35 (dd, 1H), 7.22 (dd, 2H), 4.63 (d, 2H), 4.09 (q, 2H), 3.84 (s, 3H), 3.57 (s, 2H), 1.19 (t, 3H). LC/MS (ELS) $m/z = 532.1$ $(M + H)^+$ (100%, $R_t =$ 1.23 min).

5-(2,6-Dimethoxybenzylamino)-*N*-(4-propylphenyl)isophthalamic Acid Methyl Ester 7{*4,10,22*}. Yield: 8.5 mg (39%). ^{1}H NMR (CD_3CN, 300 MHz): δ 8.68 (br, 1H), 7.75 (d, 1H), 7.57 (d, 2H), 7.38 (dd, 1H), 7.34 (dd, 1H), 7.17 (d, 2H), 6.54 (d, 2H), 6.53 (dd, 1H), 4.43 (s, 2H), 3.84 (s, 3H), 3.73 (s, 6H), 2.56 (t, 2H), 1.61 (m, 2H), 0.91 (t, 3H). LC/MS (ELS) $m/z = 463.4$ $(M + H)^+$ (100%, $R_t = 1.47$ min).

3-[(2-Chloroquinolin-3-yl)methylamino]-4-methyl-*N*-(4-propylphenyl)benz Amide 7{*4,7,30*}. Yield: 11.2 mg (54%). ^{1}H NMR (CD_3CN, 300 MHz): δ 8.72 (br, 1H), 8.61 (md, 1H), 8.31 (m, 1H), 7.85 (d, 1H), 7.74 (m, 1H), 7.69 (dd, 1H), 7.55 (dd, 2H), 7.27 (m, 1H), 7.20 (dd, 2H), 6.76 (m, 1H), 6.56 (dd, 1H), 4.82 (s, 2H), 2.57 (t, 2H), 1.61 (m, 2H), 0.91 (t, 3H). LC/MS (ELS) $m/z = 444.3$ $(M + H)^+$ (100%, $R_t = 1.52$ min).

3-(2,6-Dichlorobenzylamino)-*N*-(4-difluoromethylphenyl)-4-methylbenzamide 7{*5,7,25*}. Yield: 10.9 (51%). ^{1}H NMR (300 MHz, CD_3CN): δ 8.71 (br, 1H), 7.73 (dd, 2H), 7.43 (dd, 2H), 7.30 (m, complex, 2H), 7.21−7.12 (m, complex, 4H), 6.72 (t, 1H, $J = 75$ Hz), 4.66 (s, 2H), 2.13 (s, 3H). LC/MS (ELS) $m/z = 451.1$ $(M + H)^+$ (100%, $R_t =$ 1.42 min).

3-{4-[3-(2-Chloro-5-nitrobenzylamino)-4-methoxybenzoylamino]phenyl}acrylic Acid Ethyl Ester 7{*8,9,29*}. Yield: 14.5 mg (62%). ^{1}H NMR (CD_3CN, 300 MHz): δ 8.66 (br, 1H), 8.13 (d, 1H), 8.06 (dd, 1H), 7.68 (dd, 2H), 7.63 (d, 1H), 7.58 (d, 1H), 7.56 (dd, 2H), 7.30 (dd, 1H), 6.93 (d, 1H, $J = 15.3$ Hz), 6.91 (d, 1H), 6.40 (d, 1H, $J =$ 15.9 Hz), 4.60 (s, 2H), 4.19 (q, 2H), 3.96 (s, 3H), 1.27 (t, 3H). LC/MS (ELS) $m/z = 510.3$ $(M + H)^+$ (99.1%, $R_t =$ 1.30 min).

***N*-(1,3-Benzodioxol-5-yl)-5-(2,6-dichlorobenzylamino)-isophthalamic Acid Methyl Ester 7{*17,10,25*}.** Yield: 8.5 mg (39%). ^{1}H NMR (300 MHz, CD_3CN): δ 8.67 (br, 1H), 7.77 (dd, 1H), 7.50 (dd, 1H), 7.43 (dd, 1H), 7.41 (d, 2H), 7.33 (d, 1H), 7.30 (dd, 1H), 7.05 (dd, 1H), 6.81 (dd, 1H), 5.95 (s, 2H), 4.61 (s, 2H), 3.68 (s, 3H). LC/MS (ELS) $m/z = 473.11$ $(M + H)^+$ (100%, $R_t = 1.39$ min).

***N*-(1,4-Benzodioxan-6-yl)-4-fluoro-3-[4-(imidazol-1-yl)-benzylamino]benzamide 7{*18,8,7*}.** Yield: 9.9 mg (39%). ^{1}H NMR (300 MHz, CD_3CN): δ 8.83 (dd, 1H), 8.41 (br, 1H), 7.71 (dd, 1H), 7.63−7.53 (m, complex, overlapped, 5H), 7.18 (d, 1H), 7.13−7.09 (m, complex, overlapped, 3H), 7.00 (dd, 1H), 6.76 (d, 1H), 4.57 (s, 2H), 4.20 (m, 4H). LC/MS (ELS) $m/z = 445.2$ $(M + H)^+$ (100%, $R_t = 0.28$ min).

***N*-(1,4-Benzodioxan-6-yl)-3-[(2,5-dimethoxybenzyl)amino]-4-fluorobenzamide 7{*18,8,23*}.** Yield: 11.1 mg (54%). ^{1}H NMR (300 MHz, CD_3CN): δ 8.44 (br, 1H), 7.20 (m, 1H), 7.11 (dd, 1H), 7.10 (d, 1H), 7.03 (dd, 1H), 7.01 (dd, 1H), 6.89 (d, 1H), 6.86 (d, 1H), 6.79 (d, 1H), 6.77 (dd, 1H), 4.39 (s, 1H), 4.21 (complex, m, 4H), 3.81 (s, 3H), 3.66 (s, 3H). LC/MS (ELS) $m/z = 439.3$ $(M + H)^+$ (100%, $R_t =$ 1.16 min).

4-Methoxy-*N*-(5-methoxy-2-methylphenyl)-3-[(2-thienyl)-methylamino]benzamide 7{*20,9,36*}. Yield: 5.1 mg (28%). ^{1}H NMR (CD_3CN, 300 MHz): δ 8.10 (br, 1H), 7.26 (m, complex, 3H), 7.17 (d, 1H), 7.13 (d, 1H), 7.05 (dd, 1H), 6.96 (dd, 1H), 6.91 (d, 1H), 6.70 (dd, 1H), 4.63 (s, 2H), 3.90 (s, 3H), 3.75 (s, 3H), 2.17 (s, 3H). LC/MS (ELS) $m/z = 502.3$ $(M + H)^+$ (100%, $R_t = 1.48$ min).

***N*-(5-*tert*-Butyl-2-methoxyphenyl)-4-fluoro-3-(3-trifluoromethoxybenzylamino)benzamide 7{*24,8,15*}.** Yield: 7.6 mg (34%). ^{1}H NMR (CD_3CN, 300 MHz): δ 8.39 (br, 1H), 8.28 (d, 1H), 7.44 (dd, 1H), 7.41 (dd, 1H), 7.31 (d, 1H), 7.18 (m, 1H), 7.14−7.10 (m, complex, 4H), 6.92 (d, 1H), 4.52 (s, 2H), 3.83 (s, 3H), 1.94 (q, 2H), 1.28 (s, 9H). LC/MS (ELS) $m/z = 491.3$ $(M + H)^+$ (100%, $R_t = 1.55$ min).

3-(2-Chloro-5-nitrobenzylamino)-*N*-(4-methoxybiphenyl-3-yl)-2-methylbenzamide 7{*29,6,29*}. Yield: 5.1 mg (22%). ^{1}H NMR (CD_3CN, 300 MHz): δ 8.65 (d, 1H), 8.28 (br, 1H), 8.15 (d, 1H), 8.10 (dd, 1H), 7.67 (d, 1H), 7.64 (d, 1H), 7.49−7.43 (m, complex, 2H), 7.39 (dd, 1H), 7.34 (m, 1H), 7.11 (d, 1H), 7.07 (m, 1H), 6.83 (dd, 1H), 6.44 (d, 1H), 4.59 (s, 2H), 3.89 (s, 3H), 2.55 (s, 3H). LC/MS (ELS) $m/z = 502.3$ $(M + H)^+$ (100%, $R_t = 1.48$ min).

5-[(6-Methoxypyridin-3-yl)methylamino]-*N*-(1-naphthyl)isophthalamic Acid Methyl Ester 7{*30,10,33*}. Yield 7.8 mg (31%). ^{1}H NMR (300 MHz, CD_3CN): δ 8.91 (br, 1H), 8.19 (d, 1H), 7.96−7.92 (complex multiplet, 2H), 7.90 (dd, 1H), 7.86 (dd, 1H), 7.83 (d, 1H), 7.64 (d, 1H), 7.55−7.52 (complex multiplet, 3H), 7.44 (dd, 2H), 6.90 (d, 1H), 4.40 (s, 2H), 3.92 (s, 3H), 3.87 (s, 3H). LC/MS (ELS) $m/z = 442.2$ $(M + H)^+$ (100%, $R_t = 0.99$ min).

Acknowledgment. We thank Denise Graziano for the analysis of all of the compounds.

Supporting Information Available. ^{1}H NMR spectra and LC/MS traces (ELSD) for each example. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC0499284