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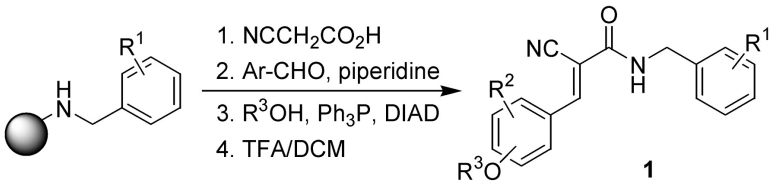

4500 compound library

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Solid-Phase Synthesis of a Tyrphostin Ether Library

Guihua Guo, Elena A. Arvanitis, Richard S. Pottorf, and Mark R. Player*

3-Dimensional Pharmaceuticals, Inc., 8 Clarke Drive, Cranbury, New Jersey 08512

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The solid-phase synthesis of a 4500-member (30 × 15 × 10) tyrphostin library is demonstrated utilizing the Irori-directed sorting system. Fmoc-protected PL-Rink resin was used as the solid support. After Fmoc-deprotection, aryl aldehydes were attached to the resin through reductive amination. Acylation of the resulting secondary amines with cyanoacetic acid was followed by a Knoevenagel condensation with phenolic aldehydes. Mitsunobu coupling of primary alcohols to the resin-bound phenols yielded the final library of compounds **1**.

Introduction

Protein tyrosine kinases (PTKs) are a class of enzymes that catalyze the transfer of the γ-phosphate of ATP to the phenolic group of specific tyrosines in endogenous peptides and proteins. There is a wealth of evidence that the phosphorylation of tyrosine plays a critical role in many cell regulatory processes.[1] Because it has been suggested that the phosphorylation of tyrosine may be the primary indicator of signal transduction in multicellular organisms,[2] it is not surprising that the disruption of PTKs results in numerous disease states. PTKs account for over 60% of the oncogenes and proto-oncogenes involved in human cancers. Additionally, enhanced activity of PTKs has been implicated in several nonmalignant diseases, including psoriasis, pulmonary fibrosis, and human papilloma virus 16, and premature coronary occlusion (restenosis) in patients undergoing heart transplantation, coronary artery bypass grafting, and angioplasty.[3]

Once it became apparent that enhancement of PTK activity contributed to oncogenesis, efforts began in the search for PTK inhibitors. Levitzki and co-workers designed a series of small molecules that interact with the PTK active site and that were designed on the basis of the structure of the smallest PTK inhibitor known, erbstatin (**2**, Figure 1). Erbstatin is a natural product inhibitor of protein tyrosine kinase, isolated from fungal extracts, which exhibits nonspecific PTK inhibitory activity in the micromolar range.[4] Through the incorporation of elements of erbstatin and tyrosine, Levitzki designed a series of benzylidenemalononitrile (BMN) compounds (**3**, Figure 1) that proved to be effective PTK inhibitors. These compounds were termed tyrphostins[5] (*ty*-*r*osine *phos*phorylation *in*hibitors) and are composed of an alkene, which is cis-substituted with a nitrile and an oxygenated benzene group. A similar class of molecules was synthesized and found to inhibit the 12- and 15-lipoxygenase pathways, which have been implicated in cancer formation and metastasis.[6,7]

In a series of papers, Levitzki and co-workers reported structure−activity relationship studies indicating tolerance for substitutions at R^4 and demonstrated that substitution on the oxygenated phenyl ring can lead to selectivity between even closely related kinases.[8,9] A series of aryl-substituted thiomethyl groups in the R^5 position provided selectivity for the HER2 kinase over the highly homologous HER1 kinase. Conversely, substitution at the R^4 position led to compounds that were selective for the HER1 kinase over the HER2 kinase.[10,11] More recently, Levitzki and co-workers reported a series of dimeric analogues of tyrphostins in attempts to target the dimerized epidermal growth factor receptor.[12]

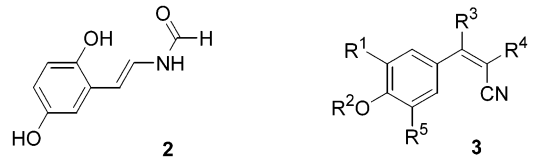

Figure 1. PTK inhibitors: erbstatin (**2**) and tyrphostin class (**3**).

As part of our drug-discovery program to discover new tyrphostin analogues, we designed a library of tyrphostin ethers in which the final step of the synthesis incorporates a novel substituent in the R^2 position of **3**. The synthetic route used is shown in Scheme 1. This novel substituent (designated R^3 in our final product **1**) may occupy a similar binding mode as the thiomethyl substituent in Levitzki's series, potentially conveying specificity between kinases. Additionally, the unique R^4 substituents employed in this library may provide more potent inhibitors. Utilizing IRORI's "directed sorting" techniques, we were able to accomplish the solid-phase synthesis of a 4500-member (30 × 15 × 10) tyrphostin library utilizing split-and-pool[13−15] technology. A smaller tyrphostin library has been previously reported[16] utilizing this technology with microtubes, but here we have extrapolated these techniques to MicroKans and modified them to a larger, unique ether library.

Results and Discussion

The previously reported synthesis of a tyrphostin library[16] involved an acylation of the resin-bound phenol to potentially enhance the enzyme specificity of these compounds through the ester bond. Since ester bonds are known to be labile in vivo, we explored the Mitsunobu reaction to form an ether bond with the phenol, thus providing the enhanced stability of our postulated specificity functionality. The key interme-

* To whom correspondence should be addressed. Phone: 609-655-6950. E-mail: mark.player@3dp.com.

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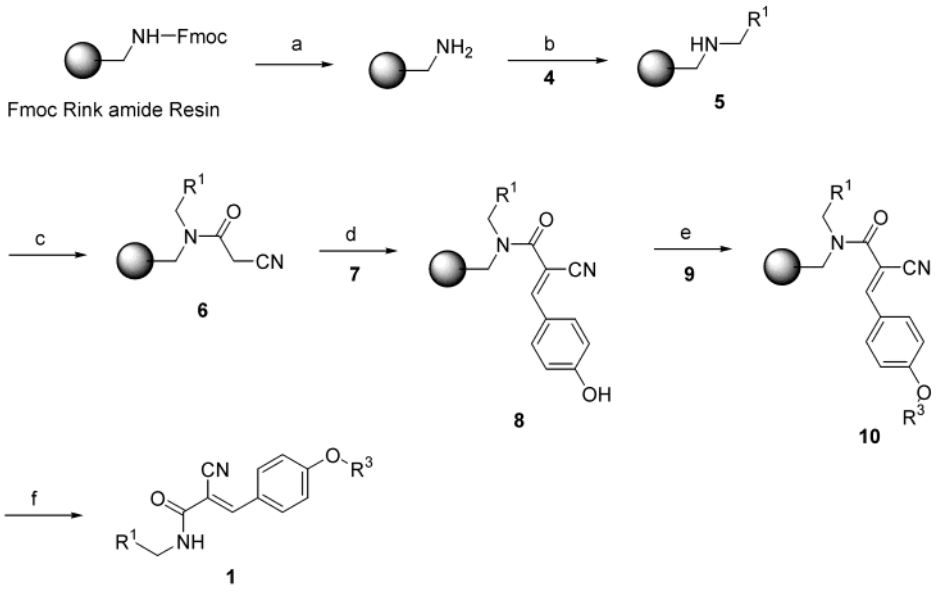
Scheme 1. Synthesis of Tyrphostin Ether Library[a]



[a] Reagents and conditions: (a) 20% piperidine/DMF, rt, 1 h; (b) 0.25 M aldehyde **4**, 2% HOAc/1,2-dichloroethane, rt, 2 h, filter; 0.25 M NaBH(OAc)3/1,2-dichloroethane, rt, 12 h, MeOH quench; (c) 1 M DIEA/DMF, 0.5 M cyanoacetic acid, 0.5 M DIC, rt, 5 h; filter recouple with fresh reagent, rt, 12 h; (d) DMF/MeOH (10:1), 0.5 M aldehyde **7**, 0.25 M piperidine, rt, 12 h; (e) 0.25 M Ph_3P/THF, 0.5 M alcohol **9**, 0.25 M DIAD, rt, 12 h; (f) 30%TFA/DCM, rt, 1 h.

diate of our tyrphostin ethers is the resin-bound phenolic product from the Knoevenagel condensation.

The reported conditions for the synthesis of this resin-bound phenol worked well, except for the reductive amination step. Significant yields of the secondary amine were isolated after cleavage. This side reaction with Rink amide resin has previously been observed,[17] although in the previous tyrphostin library synthesis, this overalkylation was not reported. Since the diffusion of reagents into the MicroKans tends to be slow, optimum reaction conditions require high reagent concentrations (0.25−0.5 M). We postulated that the high reagent concentrations resulted in this overalkylation. To optimize this reaction we explored (1) lowering of the reagent concentration, (2) imine preformation, and (3) imine preformation along with filtration and addition of fresh solvent. All of these methods reduced the amount of secondary amine, and we found that the last method was optimal. We did not explore alternative reducing agents or solvents, as was demonstrated previously.[17]

The acylation with cyanoacetic acid and subsequent Knoevenagel condensation proceeded smoothly. In contrast to the previous report,[16] the triple coupling of the cyanoacetic acid was reduced to a double coupling (Scheme 1c) with no drop in purity of the final products.

A variety of conditions have been reported for the solid-phase Mitsunobu reaction.[18,19] Some of these conditions require the use of Bu_3P/TMAD.[19] We felt that the high reactivity of Bu_3P and the high cost of TMAD made them less appealing choices for large-scale library production. We found that the more useful Ph_3P/DIAD combination gave the most consistent results with several alcohols, including alkanols.

Rehearsal libraries were synthesized to explore the scope and limitation of each diversity step in this synthetic route. This exploration involved varying one step while holding the other diversity steps constant. Specifically, the reagents held constant in this rehearsal were those that worked well in development of the route and are noted below. For the reductive amination: R2 = **7**{*4*}, R3 = **9**{*8*}; for the Knoevenagel condensation: R1 = **4**{*9*}, R3 = **9**{*7*}; and for the Mitsunobu reaction: R1 = **4**{*9*}, R2 = **7**{*4*}.

For a given reagent to be considered for the library production, the final product purities should be >85%. Ninety aldehydes **4** were explored for the reductive amination step. Even with imine preformation, we found significant yields of the overalkylated byproduct. The aldehydes that resulted in this byproduct were generally electron-deficient. We postulated that although excess aldehyde was removed, enough remained trapped in the MicroKan to allow this undesired reaction to occur with very reactive aldehydes. In the case of electron-rich aldehydes, overalkylation was not observed. Thirty aldehyde monomers resulted in products of sufficient purity that they could be used in the library production. Several functional groups are tolerated in this reaction, including tertiary amines, ethers, and amides.

Thirty phenol aldehydes **7** were explored for the Knoevenagel condensation. Fifteen of these passed our purity criteria and were used in the library synthesis. Functional groups that were not tolerated in this set were primarily those with steric hindrance for either the condensation or the subsequent Mitsunobu reaction. Nineteen primary alcohols **9** were explored for the Mitsunobu reaction. Nine of these alcohols were reactive enough to result in products of >85% purity.

The library was produced as a full 30 × 15 × 10 array, using the reagents listed in Figures 2−4. For the Mitsunobu step, nine reagents plus one "no substitution" were used. The 4500 compounds were cleaved with TFA/DCM. Each compound was analyzed by LC/MS with evaporative light scattering (ELS) detection to determine the purity of the compounds, and electrospray MS was used to confirm the

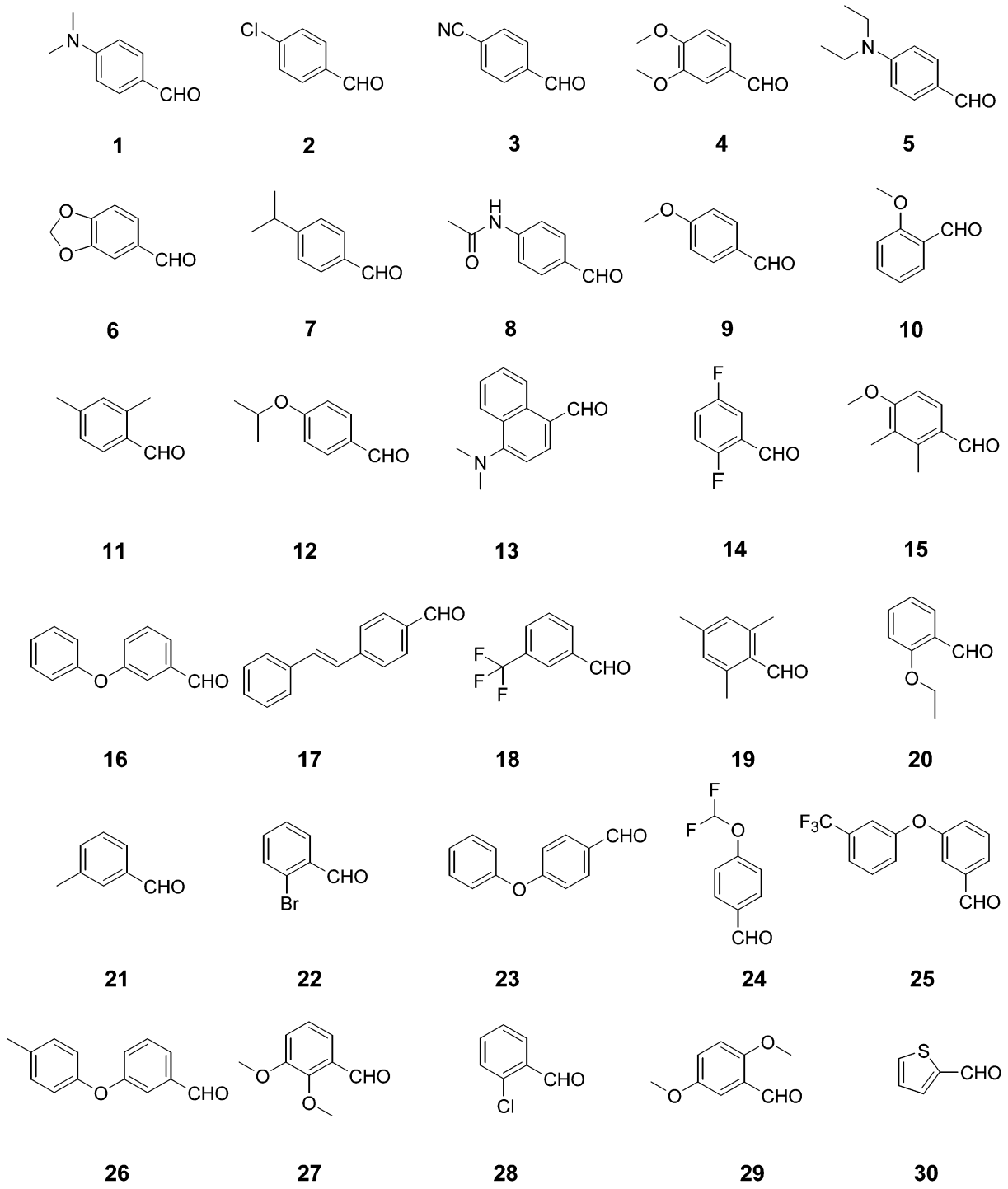


Figure 2. Diversity reagents **4**{*1*−*30*}.

identity of the compounds. The mean purity of the 4500 compounds was determined to be 86%, and the mean yield was 46%. For each diversity step, the mean purity of all of the compounds arising from a reagent in that step permits an assessment of how well that reagent performed in the library synthesis. These data are summarized in Tables 1−3.

This analysis shows that certain reagents used at R1, **4**{*6*, *11*,*12*,*17*,*19*,*23*}, worked very well, exhibiting a mean purity >90%. Although this set displays a variety of electronic and steric effects, there is no clear reactivity trend. Conversely, **4**{*1*,*5*,*13*} resulted in mean purities in the 65−75% range. These aldehydes contain tertiary amines, confirming that tertiary amine-containing aldehydes or amines display poor reactivity. Because these reagents are in very high concentration, as compared to the acetic acid, the imine formation equilibrium may be altered unfavorably.

The reagents used at R2, **7**, resulted in mean purities ranging from 77 to 91%. One of the poorest reagents in this group was **7**{*6*}, which contains a tertiary amine at the para position. Reagent **7**{*10*} is a sterically hindered phenol; however, this reagent has a mean purity of 85%, indicating that this steric hindrance did not interfere with the Mitsunobu

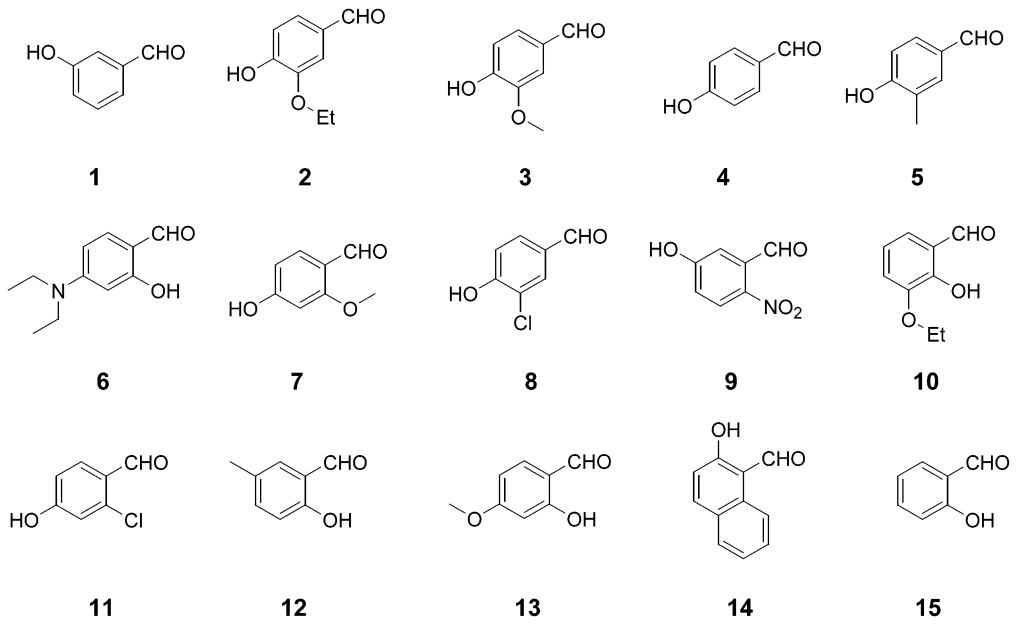


Figure 3. Diversity reagents **7**{*1*−*15*}.

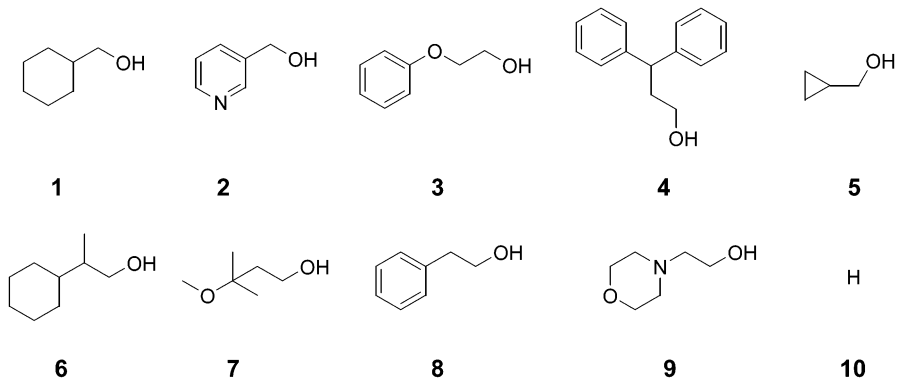


Figure 4. Diversity reagents **9**{*1*−*10*}.

Table 1. Mean Purity of Compounds Analyzed per R1

R1	ELS (%)	R1	ELS (%)	R1	ELS (%)
4{*1*}	75	**4**{*11*}	91	**4**{*21*}	88
4{*2*}	87	**4**{*12*}	92	**4**{*22*}	86
4{*3*}	77	**4**{*13*}	73	**4**{*23*}	92
4{*4*}	89	**4**{*14*}	89	**4**{*24*}	84
4{*5*}	67	**4**{*15*}	84	**4**{*25*}	84
4{*6*}	90	**4**{*16*}	88	**4**{*26*}	88
4{*7*}	88	**4**{*17*}	90	**4**{*27*}	88
4{*8*}	82	**4**{*18*}	81	**4**{*28*}	86
4{*9*}	87	**4**{*19*}	90	**4**{*29*}	88
4{*10*}	89	**4**{*20*}	88	**4**{*30*}	89

reaction. The reagents used at R3, **9**, gave good results, with the exception of **9**{*1, 6*}. These two reagents are β-substituted primary alcohols that display some steric limitations.

Conclusion

The solid-phase synthesis of a 4500-member tyrphostin ether library was achieved using Irori MicroKans and directed sorting. The reaction conditions used in this synthesis are mild, and compounds were obtained in good yields and excellent purities. The screening of this library is in progress against a variety of kinase and nonkinase targets.

Table 2. Mean Purity of Compounds Analyzed per R2

R2	ELS (%)	R2	ELS (%)
7{*1*}	85	**7**{*9*}	89
7{*2*}	82	**7**{*10*}	85
7{*3*}	84	**7**{*11*}	87
7{*4*}	91	**7**{*12*}	85
7{*5*}	88	**7**{*13*}	87
7{*6*}	78	**7**{*14*}	77
7{*7*}	89	**7**{*15*}	88
7{*8*}	86		

Table 3. Mean Purity of Compounds Analyzed per R3

R3	ELS (%)	R3	ELS (%)
9{*1*}	72	**9**{*6*}	73
9{*2*}	96	**9**{*7*}	92
9{*3*}	89	**9**{*8*}	92
9{*4*}	82	**9**{*9*}	92
9{*5*}	81	**9**{*10*}	87

Experimental Section

All reagents and anhydrous solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI), Fisher Scientific (Atlanta, GA), Lancaster Synthesis (Windham, NH), or Ryan Scientific (Isle of Palms, SC) in the highest available purity and were used as such. PL-Rink resin (0.7 mmol/g, 75−150

μM) 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 for the reactions and all washes was performed with New Brunswick Innova shakers.

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 (Cranbury, NJ). Typical gradients were 25−100% CH_3CN/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 $CHCl_3$ as the internal reference

General Reaction Conditions with MicroKans. Approximately 25 mg of resin and an Rf tag were loaded into each MicroKan using the Irori dry-resin loader and Rf tag dispenser. All MicroKans were sorted at each step with the Autosort 10K sorter (Discovery Partners). After every reaction, initial washes were performed in each reaction vessel, followed by pooling of the MicroKans into 5-L polypropylene carboys for thorough washing with DMF 1−2 times and alternating EtOH and DCM, 3 times each. Cleavage of the library compound was performed in the Accucleave 192 apparatus.

General Procedure for Fmoc-Deprotection. The resin was treated with 20% piperidine in DMF for 1 h and washed thoroughly as described above.

General Procedure for Reductive Amination. The MicroKans (150/reagent) were suspended in 2% HOAc in DCE (225 mL), and the appropriate aryl aldehyde was added to make a 0.25 M solution. After mixing for 2 h, the reaction mixture was removed, and fresh DCE containing 0.25 M $NaBH(OAc)_3$ was added and mixed overnight. The reactions were quenched with MeOH for 10 min and then washed with 2 N NH_3/MeOH (1 × 10 min), followed by the normal washing procedures.

General Procedure for Acylation. All Kans (4500) were suspended in anhydrous DMF (4L), and DIEA (1 M) was added and mixed for 10 min. Cyanoacetic acid (0.5 M) and DIC (0.5 M) were added, and the reaction was mixed for 5 h at room temperature. The reaction mixture was drained, and additional DMF and reagents were added for a double coupling and mixed overnight. The reaction mixture was drained, and the Kans were washed by the normal procedures.

General Procedure for Knoevenagel Condensation. The Kans (300/reagent) were suspended in a mixture of anhydrous DMF/MeOH 10:1 (400 mL), the phenol aldehyde (0.5 M) and piperidine (0.25 M) were added, and the reactions were mixed overnight. The reaction mixture was drained, and the Kans were washed by the normal procedures, except that 5 cycles of DCM and EtOH were required to remove all soluble byproducts.

General Procedure for Mitsunobu Coupling. The Kans (450/reagent) were suspended in THF (500 mL), and Ph_3P (0.25 M) and the primary alcohol (0.5 M) were added and mixed for 10 min. DIAD (0.25 M) was added slowly with mixing, and then all reactions were mixed overnight at room temperature. The reactions were drained, and the MicroKans were washed by the normal procedures.

General Procedure for Final Cleavage. All products were cleaved from the resin with 30% TFA/DCM for 30 min and collected into 96-well deep-well blocks. The solvent was removed in vacuo, and the residues were dissolved in CH_3CN and analyzed by LC/MS.

2-Cyano-3-(2-cyclopropylmethoxy-4-methoxyphenyl)-*N*-(3-phenoxybenzyl)acrylamide 1{*16,13,5*}**.** ^{1}H NMR ($CDCl_3$): δ 8.9 (s, 1H), 8.3 (d, 1H), 6.2−7.40 (m, 11H), 4.60 (d, 2H), 3.98 (d, 2H), 3.80 (s, 3H), 1.30 (m, 1H), 0.70 (dt, 2H), 0.38 (dt, 2H). LC/MS m/z = 454.9 $[M + H]^+$; (100%, R_t = 1.93 min).

2-Cyano-3-(5-cyclohexylmethoxy-2-nitrophenyl)-*N*-(2,4-dimethylbenzyl)acrylamide 1{*11,9,1*}**.** ^{1}H NMR ($CDCl_3$): δ 8.82 (s, 1H), 8.29 (d, 1H), 6.95−7.19 (m, 6H), 4.59 (d, 2H), 3.86 (d, 2H), 2.35 (s, 3H), 2.33 (s, 3H), 1.25−1.52 (m, 11H). LC/MS m/z = 447.9 $[M + H]^+$ (100%, R_t = 2.02 min).

2-Cyano-3-(5-cyclohexylmethoxy-2-nitrophenyl)-*N*-thiophen-2-ylmethylacrylamide 1{*30,9,1*}**.** ^{1}H NMR ($CDCl_3$): δ 8.83 (s, 1H), 8.26 (d, 1H), 6.98−7.40 (m, 5H), 4.81 (d, 2H), 3.86 (d, 2H), 1.25−1.52 (m, 11H). LC/MS m/z = 426.5 $[M + H]^+$ (87.5%, R_t = 2.32 min).

3-[2-Chloro-4-(pyridin-3-ylmethoxy)phenyl]-2-cyano-*N*-(3-phenoxybenzyl)acrylamide 1{*16,11,2*}**.** ^{1}H NMR ($CDCl_3$): δ 9.03 (s, 1H), 8.83 (d, 1H), 8.74 (s, 1H), 8.26 (d, 1H), 8.23 (d, 1H), 7.90 (d, 1H), 6.90−7.40 (m, 11H), 4.60 (d, 2H), 4.02 (d, 2H). LC/MS m/z = 495.8 $[M + H]^+$ (100%, R_t = 1.92 min).

***N*-Benzo[1,3]dioxol-5-ylmethyl-2-cyano-3-[2-(3,3-diphenylpropoxy)-4-methoxyphenyl]acrylamide 1**{*6,13,4*}**.** ^{1}H NMR ($CDCl_3$): δ 8.84 (s, 1H), 8.25 (d, 1H), 7.05−7.40 (m, 10H), 6.84 (m, 4H), 6.58 (m, 2H), 5.96 (s, 2H), 4.52 (d, 2H), 4.20 (t, 1H), 3.98 (t, 2H), 3.81 (s, 3H), 2.62 (dt, 2H). LC/MS m/z = 546.9 $[M + H]^+$ (96%, R_t = 2.01 min).

2-Cyano-3-(3-phenethyloxyphenyl)-*N*-thiophen-2-ylmethylacrylamide 1{*30,1,8*}**.** ^{1}H NMR ($CDCl_3$): δ 8.33 (s, 1H), 7.20−7.50 (m, 8H), 6.95−7.10 (m, 4H), 4.79 (d, 2H), 4.23 (t, 2H), 3.12 (t, 2H). LC/MS m/z = 389.0 $[M + H]^+$ (100%, R_t = 1.88 min).

***N*-(2-Bromobenzyl)-2-cyano-3-(2-cyclopropylmethoxynaphthalen-1-yl)acrylamide 1**{*22,14,5*}**.** ^{1}H NMR ($CDCl_3$): δ 8.87 (s, 1H), 7.10−7.79 (m, 10H), 4.75 (d, 2H), 4.08 (d, 2H), 1.20 (m, 1H), 0.62 (dt, 2H), 0.40 (dt, 2H). LC/MS m/z = 460.8 $[M + H]^+$ (100%, R_t = 1.87 min).

2-Cyano-*N*-(2,5-dimethoxybenzyl)-3-[4-(3-methoxy-3-methylbutoxy)-3-methylphenyl]acrylamide 1{*29,5,7*}**.** ^{1}H NMR ($CDCl_3$): δ 8.22 (s, 1H), 7.80 (d, 2H), 6.82 (m, 4H), 4.58 (d, 2H), 4.15 (t, 2H), 3.87 (s, 3H), 3.77 (s, 3H), 2.23 (s, 3H), 2.05 (t, 2H), 1.27 (s, 6H). LC/MS m/z = 453.0 $[M + H]^+$ (100%, R_t = 1.85 min).

2-Cyano-*N*-(2,5-difluorobenzyl)-3-[4-methoxy-2-(pyridin-3-ylmethoxy)-phenyl]acrylamide 1{*14,13,2*}**.** ^{1}H NMR ($CDCl_3$): δ 9.09 (s, 1H), 8.91 (d, 1H), 8.75 (s, 1H), 8.50 (d, 1H), 8.26 (d, 1H), 7.98 (m, 1H), 6.80−7.10 (m, 3H), 6.80 (dd, 1H), 6.70 (d, 1H), 6.56 (d, 1H), 4.60 (d, 2H), 4.20 (d,

2H), 3.92 (s, 3H). LC/MS m/z = 435.9 $[M + H]^+$ (100%, R_t = 1.57 min).

2-Cyano-3-[3-ethoxy-4-(2-phenoxyethoxy)phenyl]-*N*-(4-phenoxybenzyl)acrylamide 1{*23,2,3*}**.** ^{1}H NMR ($CDCl_3$): δ 8.28 (s, 1H), 7.66 (s, 1H), 7.46 (d, 1H), 7.00−7.36 (m, 15H), 6.62 (m, 1H), 4.59 (d, 2H), 4.41 (m, 4H), 4.15 (q, 2H), 1.49 (t, 3H). LC/MS m/z = 534.8 $[M + H]^+$ (100%, R_t = 2.39 min).

2-Cyano-3-[4-diethylamino-2-(3,3-diphenylpropoxy)-phenyl]-*N*-(4-isopropoxybenzyl)acrylamide 1{*12,6,4*}**.** ^{1}H NMR ($CDCl_3$): δ 8.80 (s, 1H), 8.22 (d, 1H), 7.20−7.34 (m, 12 H), 6.88 (d, 2H), 6.60 (m, 1H), 6.45 (d, 1H), 6.20 (s, 1H), 4.56 (d, 2H), 4.24 (m, 4H), 3.99 (t, 2H), 3.42 (m, 4H), 2.60 (m, 2H), 1.32 (d, 6H), 1.25 (t, 3H), 1.18 (t, 3H). LC/MS m/z = 602.0 $[M + H]^+$ (93.5%, R_t = 2.43 min).

2-Cyano-3-(3-methyl-4-phenethyloxyphenyl)-*N*-(4-phenoxybenzyl)acrylamide 1{*23,5,8*}**.** ^{1}H NMR ($CDCl_3$): δ 8.24 (s, 1H), 7.77 (d, 2H), 6.80−7.40 (m, 15H), 6.60 (m, 1H), 4.58 (d, 2H), 4.25 (t, 2H), 3.14 (t, 2H), 2.23 (s, 3H). LC/MS m/z 488.9 $[M + H]^+$ (100%, R_t = 2.07 min).

2-Cyano-3-(3-ethoxy-2-phenethyloxyphenyl)-*N*-(4-isopropylbenzyl)acrylamide 1{*7,10,8*}**.** ^{1}H NMR ($CDCl_3$): δ 8.80 (s, 1H), 7.75 (d, 1H), 7.00−7.30 (m, 11H), 6.60 (s, 1H), 4.59 (d, 2H), 4.34 (t, 2H), 4.06 (q, 2H), 3.13 (t, 2H), 2.90 (m, 1H), 1.43 (t, 3H), 1.26 (d, 6H,). LC/MS m/z = 468.9 $[M + H]^+$ (100%, R_t = 2.06 min).

2-Cyano-3-[2-(3,3-diphenylpropoxy)-phenyl]-*N*-(4-methoxybenzyl)acrylamide 1{*9,15,4*}**.** ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 1H), 8.15 (d, 1H), 6.70−7.80 (m, 17H), 4.55 (d, 2H), 4.20 (t, 1H), 4.00 (t, 2H), 3.79 (s, 3H), 2.60 (dt, 2H). LC/MS m/z = 502.9 $[M + H]^+$ (93.5%, R_t = 2.10 min).

3-[2-Chloro-4-(3-methoxy-3-methylbutoxy)phenyl]-2-cyano-*N*-(4-difluoromethoxybenzyl)acrylamide 1{*24,11,7*}**.** ^{1}H NMR ($CDCl_3$): δ 8.76 (s, 1H), 8.22 (d, 1H), 7.36 (t, 2H), 7.13 (t, 2H), 6.90 (d, 1H), 6.60 (m, 1H), 6.50 (d, 1H), 6.22 (d, 1H), 4.60 (d, 2H), 4.13 (t, 2H), 3.22 (s, 3H), 2.01 (t, 2H), 1.24 (s, 6H). LC/MS m/z = 478.9 $[M + H]^+$ (100%, R_t = 2.29 min).

2-Cyano-3-[4-(2-cyclohexylpropoxy)-2-methoxyphenyl]-*N*-(2,3-dimethoxy-benzyl)acrylamide 1{*27,7,6*}**.** ^{1}H NMR ($CDCl_3$): δ 8.76 (s, 1H), 8.22 (d, 1H), 7.05 (t, 1H), 6.95 (m, 2H), 6.60 (d, 1H), 6.47 (s, 1H), 4.60 (d, 2H), 4.00 (t, 2H), 3.80 (s, 9H), 3.05 (m, 1H), 1.06 (s, 3H), 1.10−1.80 (m, 11H). LC/MS m/z = 493.0 $[M + H]^+$ (92.5%, R_t = 2.20 min).

***N*-(4-Acetylaminobenzyl)-2-cyano-3-(3-methyl-4-phenethyloxyphenyl)acrylamide 1**{*8,5,8*}**.** ^{1}H NMR ($CDCl_3$): δ 8.25 (s, 1H), 7.80 (d, 2H), 7.50 (d, 2H), 7.20−7.30 (m, 5H), 7.18 (d, 1H), 6.85 (d, 1H), 6.60 (d, 1H), 4.60 (d, 2H), 4.25 (t, 2H), 3.20 (t, 2H), 2.30 (s, 3H), 2.25 (s, 3H). LC/MS m/z = 454.0 $[M + H]^+$ (100%, R_t = 1.70 min).

2-Cyano-*N*-(4-methoxybenzyl)-3-[3-(2-morpholin-4-ylethoxy)phenyl]acrylamide 1{*9,1,9*}. ^{1}H NMR ($CDCl_3$): δ 8.36 (s, 1H), 7.48 (m, 3H), 7.30 (d, 2H), 7.10 (d, 1H), 6.90 (d, 2H), 6.60 (t, 1H), 4.60 (d, 2H), 4.50 (t, 2H), 4.00 (m, 4H), 3.80 (s, 3H), 3.70(t, 4H), 3.05 (t, 2H). LC/MS m/z = 422.0 $[M + H]^+$ (100%, R_t = 1.39 min).

2-Cyano-3-[4-diethylamino-2-(2-phenoxyethoxy)phenyl]-*N*-(4-isopropyl-benzyl)acrylamide 1{*7,6,3*}**.** ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1H), 8.28 (d, 1H), 7.20−7.30 (m, 5H), 6.98 (d, 2H), 6.20−6.60 (m, 4H), 4.60 (d, 2H), 4.40 (s, 4H), 3.45 (t, 4H), 2.90 (m, 1H), 1.15 (m, 12H). LC/MS m/z = 512.0 $[M + H]^+$ (100%, R_t = 2.24 min).

***N*-(2-Bromobenzyl)-3-[3-chloro-4-(2-morpholin-4-ylethoxy)phenyl]-2-cyanoacrylamide 1**{*22,8,9*}**.** ^{1}H NMR ($CDCl_3$): δ 8.20 (s, 1H), 8.00 (s, 1H), 7.85 (d, 1H), 7.60 (d, 1H), 7.40 (d, 1H), 7.30 (t, 1H), 7.20 (t, 1H), 7.00 (d, 1H), 6.85 (t, 1H), 4.60 (d, 2H), 4.50 (t, 2H), 4.00 (m, 4H), 3.70 (t, 2H), 3.60 (t, 2H), 3.10 (t, 2H). LC/MS m/z = 503.8$[M + H]^+$ (100%, R_t = 1.63 min).

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Supporting Information Available. ^{1}H NMR spectra with internal standards and ELS LC/MS traces are included for each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) al-Obeidi, F. A.; Wu, J. J.; Lam, K. S. *Biopolymers* **1998**, *47*, 197−223.
(2) Ullrich A.; Schlessinger, J. *Cell* **1990**, *61*, 203−212.
(3) Levitzki, A. *Top. Curr. Chem.* **2001**, *211*, 1−15.
(4) Levitzki, A.; Gazit, A. *Science* **1995**, *267*, 1782−1788.
(5) Levitzki, A. *FASEB J.* **1992**, *6*, 3275−3282.
(6) Cho, H.; Ueda, M.; Tamaoka, M.; Hamaguchi, M.; Aisaka, K.; Kiso, Y.; Inoue, T.; Ogino, R.; Tatsuoka, T.; Ishihad, T.; Noguchi, T.; Morita, I.; Murota, S. *J. Med. Chem.* **1991**, *34*, 1503−1505.
(7) Simpson, J.; Rathbone, D. L.; Billington, D. C. *Tetrahedron Lett.* **1999**, *40*, 7031−7033.
(8) Gazit, A.; Yaish, P.; Gilon, C.; Levitzki, A. *J. Med. Chem.* **1989**, *32*, 2344−2352.
(9) Gazit, A.; Osherov, N.; Posner, I.; Yaish, P.; Poradosu, E.; Gilon, C.; Levitzki, A. *J. Med. Chem.* **1991**, *34*, 1896−1907.
(10) Gazit, A.; Osherov, N.; Posner, I.; Bar-Sinai, A.; Gilon, C.; Levitzki, A. *J. Med. Chem.* **1993**, *36*, 3556−3564.
(11) Osherov, N.; Gazit, A.; Gilon, C.; Levitzki, A. *J. Biol. Chem.* **1993**, *268*, 11134−11142.
(12) Gazit, A.; Osherov, N.; Gilon, C.; Levitzki, A. *J. Med. Chem.* **1996**, *39*, 4905−4911.
(13) Furka, A.; Sebestyen, F.; Asgedon, M.; Dibo, G. *Int. J. Pept. Protein Res.* **1991**, *37*, 487−493.
(14) Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J. *Nature* **1991**, *354*, 82−84.
(15) Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H. *Nature* **1991**, *354*, 84−86.
(16) Shi, S.; Xiao, X.; Czarnik, A. W. *Biotech. Bioeng. (Comb. Chem.)* **1998**, *61*, 7−12.
(17) Chan, W. C.; Mellor, S. L. *J. Chem. Soc. Chem. Commun.* **1995**, 1475−1477.
(18) Richter, L. S.; Gadek, T. R. *Tetrahedron Lett.* **1994**, *35*, 4705−4706.
(19) Rano, T. R.; Chapman, K. T. *Tetrahedron Lett.* **1995**, *36*, 3789−3792.

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