JOURNAL OF combinatorial CHEMISTRY

Subscriber access provided by American Chemical Society

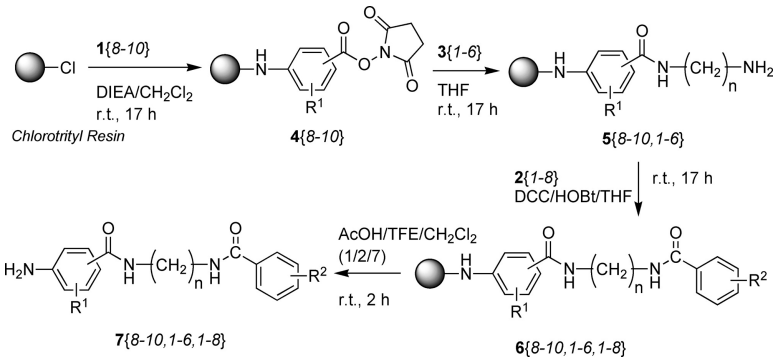
Article

Improved Loading and Cleavage Methods for Solid-Phase Synthesis Using Chlorotrityl Resins: Synthesis and Testing of a Library of 144 Discrete Chemicals as Potential Farnesyltransferase Inhibitors

Jewn Giew Park, Kevin J. Langenwalter, Carolyn A. Weinbaum, Patrick J. Casey, and Yuan-Ping Pang

J. Comb. Chem., **2004**, 6 (3), 407-413• DOI: 10.1021/cc0340729 • Publication Date (Web): 03 April 2004

Downloaded from http://pubs.acs.org on March 20, 2009



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

ACS Publications
High quality. High impact.

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Improved Loading and Cleavage Methods for Solid-Phase Synthesis Using Chlorotrityl Resins: Synthesis and Testing of a Library of 144 Discrete Chemicals as Potential Farnesyltransferase Inhibitors

Jewn Giew Park,[†] Kevin J. Langenwalter,[†] Carolyn A. Weinbaum,[‡] Patrick J. Casey,[‡] and Yuan-Ping Pang*,[†]

Computer-Aided Molecular Design Laboratory, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, Minnesota 55905, and Department of Biochemistry, Duke University Medical Center, 210A Nanaline H. Duke, Durham, North Carolina 27710

Received December 14, 2003

The use of chlorotrityl resins for the immobilization of amines is sometimes deterred by the lengthy process of loading the reactants on the resins and product decomposition caused by the reactive chlorotrityl group in the presence of 1% TFA as a cleavage agent. Here, we report improved methods developed for selective and efficient loading of aminobenzoic acid derivatives on chlorotrityl resins and for cleavage of aniline-containing products from the resins without decomposition. These methods led to the synthesis of a library of 144 discrete chemicals as potential farnesyltransferase inhibitors (FTIs) using IRORI's radio-frequency-encoded sorting technique and to the study of the applicability of the bivalence approach to the development of FTIs.

Introduction

Farnesyltransferase (FT) is a promising anticancer drug target.[1] FT inhibitors (FTIs) inhibit tumor cell proliferation without substantially interfering with normal cell growth.[1] A library of dimeric chemicals [$R^1CONH(CH_2)_nNHOCR^2$] as potential FTIs was designed according to the bivalence approach that dimerizes a drug lead with a chemical chain such as an alkylene chain to multiply the affinity and selectivity of the lead.[2,3] The library was constructed by attaching R^1CO_2X (**1**{*1*−*10*}, Figure 1) to a stationary phase, followed by two amidations that tether R^1CO_2X and R^2CO_2H (**2**{*1*−*8*}, Figure 2) with an alkylenediamine linker (**3**{*1*−*6*}, Figure 3) using IRORI's radio-frequency-encoded split-and-pool solid-phase synthesis.[4] This article reports the problems encountered in the library synthesis, the methods developed to solve these problems, and the testing results of the entire library.

Results and Discussion

Building blocks **1**{*1*−*10*} and **2**{*1*−*8*} of the designed library were identified as potential weak FTIs by a docking study of commercially available chemicals into the active site of FT according to a published protocol.[5] **2**{*9*} was used for model reactions only. Chlorotrityl resins[6−10] were used in the library synthesis. The advantages of this type of resins over other resins are that they can be regenerated by treating hydroxytrityl resins with thionyl chloride or acetyl chloride[11,12] and that they are acid-labile, thus allowing cleavage of reaction products under mild acidic conditions. The first building block (**1**{*1*−*10*}) used in the solid-phase synthesis of the library must contain two functional groups. One is used for attachment to resins as a solid support, while the other is for subsequent chemical modifications. However, both carboxyl and amino groups of the starting materials for R^1CO_2X (Figure 1) compete for reaction with the chlorotrityl group.[8,13] The initial solution to this problem was to protect the carboxyl group, reserving it for a subsequent modification, before loading the amino group onto the resins and then deprotect the carboxyl group after the loading. Later, it was found that hydroxysuccinimide esters react with neither the chlorotrityl group nor aromatic amines, although the esters react readily with aliphatic amines. Accordingly, the lengthy protection-and-deprotection loading procedure was avoided by converting aminobenzoic acids to aminobenzoic succinimide esters that were then loaded onto the resins without deprotection. These esters serve as dual-purpose reagents: they protect the acid from reacting with the trityl group, thus allowing selective attachment of the amino group to chlorotrityl resins, and they activate the acid, thus facilitating amidation in a subsequent modification.

Amines are reportedly able to react with chlorotrityl resins without the use of a base to scavenge the acid generated during the loading.[8] However, in this study, aromatic amines (Figure 1) could not be loaded onto chlorotrityl resins in the absence of a base (Table 1). Pyridine facilitated the loading of aromatic amines onto the resins, but the loading yield was low when the reaction was carried out at room temperature, and the yield worsened at 60 °C. These results indicate that pyridine[8,12] itself reacted significantly with the chlorotrityl group. Triethylamine[14] gave low loading yields as well. After experimentation with a number of bases, the more sterically

* To whom correspondence should be addressed. E-mail: pang@mayo.edu.
[†] Mayo Clinic College of Medicine.
[‡] Duke University Medical Center.

10.1021/cc0340729 CCC: $27.50 © 2004 American Chemical Society
Published on Web 04/03/2004

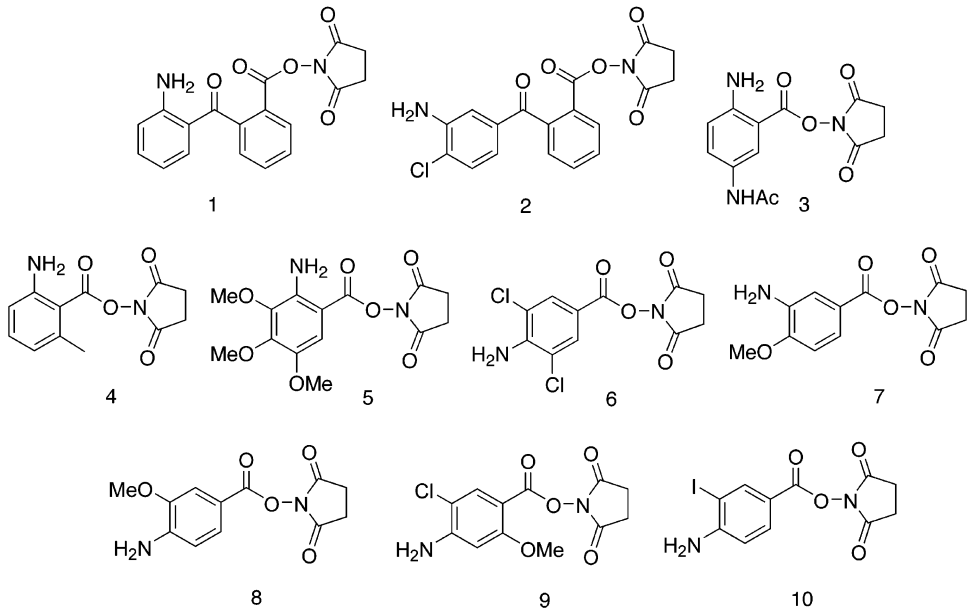


Figure 1. Chemical structures of building blocks **1**{*1*−*10*}. Note that the benzoic amide form was used in the docking study.

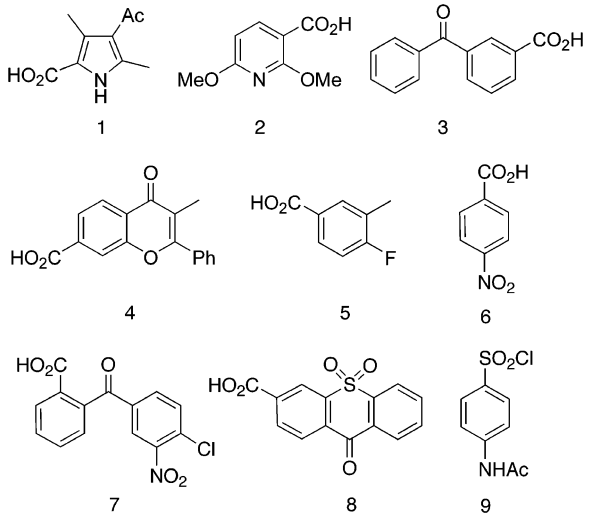


Figure 2. Chemical structures of building blocks **2**{*1*−*9*}.

$$H_2N—(CH_2)_n—NH_2$$

1: n=2, 2: n=4; 3: n=5; 4: n=7; 5: n=9; and 6: n=11

Figure 3. Chemical structures of building blocks **3**{*1*−*6*}.

Table 1. Yields for Loading of **1**{*1*} onto Trityl Chloride Resins under Different Conditions

conditions	yield[a] (%)
THF, RT,[b] 17 h	0
THF, 10 equiv NEt_3, RT, 17h	0
pyridine, RT, 17h	45
pyridine, 60 °C, 17 h	20
CH_2Cl_2, RT, 17 h	0
CH_2Cl_2, 10 equiv of CaH_2, RT, 17 h	0
CH_2Cl_2, 10 equiv of K_2CO_3, RT, 17 h	0
CH_2Cl_2, 10 equiv of DIEA, RT, 17 h	96

[a] Yields obtained without purification of reaction products after cleavage with 1% TFA−CH_2Cl_2. [b] Room temperature.

Table 2. Yields for Cleaving 7{*1,3,9*} from Trityl Chloride Resins at Different Conditions

conditions	yield[a] (%)
TFA/CH_2Cl_2 = 0.1:99.9, RT,[b] 10 min	0
TFA/TIPS/CH_2Cl_2 = 0.1:5:94.9, RT, 10 min	0
TFA/TFE: CH_2Cl_2 = 1:2:7, RT, 30 min	0
AcOH/TFE/CH_2Cl_2 = 1:2:7, RT, 2 h	>70
AcOH/TIPS/CH_2Cl_2 = 1:0.5:8.5, RT, 2 h	3

[a] Yields obtained without purification of reaction products. [b] Room temperature.

hindered base diisopropylethylamine[13] was found to give the highest loading yield in the loading of aromatic amines onto chlorotrityl resins (Table 1).

The reaction of the activated esters with alkylenediamines (**3**{*1*−*6*}, Figure 3) gave the desired intermediates (Scheme 1), which, in turn, reacted with various amidating agents (**2**{*1*−*8*}, Figure 2) to yield the desired products. Using a solution of 1% TFA in CH_2Cl_2, a common cleavage reagent for amines and alcohols,[8] the desired products were decomposed after the cleavage. Presumably, the decomposition was caused by the co-presence of the final products, the reactive trityl group, and 1% TFA. This was because no decomposition was observed when the intermediates were cleaved from the chlorotrityl resins using 1% TFA in CH_2Cl_2, nor was decomposition observed when a final product was treated with 1% TFA. Following this reasoning, a solution of acetic acid, 2,2,2-trifluoroethanol, and methylene chloride (1:1:8)[13] was used to cleave the final products in the hope that 2,2,2-trifluoroethanol could scavenge the reactive chlorotrityl group generated during the cleavage.[15] Although these cleavage conditions were reportedly effective in cleaving carboxylates from chlorotrityl resins,[13] the decomposition problem persisted until the ratio of 2,2,2-trifluoroethanol was increased to 1:2:7 (Table 2). Other attempted modifications, such as replacing 2,2,2-trifluoroethanol with triisopropylsilane, another common trityl scavenger,[16] failed to improve the cleavage yields (Table 2).

In a pilot study of the library synthesis, building blocks **1**{*8*−*10*} were converted to **7**{*8*−*10,1,9*} with reasonable yields and purities (Table 3). However, the yields and/or purities of **7**{*1*−*7,1,9*} were unacceptably low (Table 3), presumably because of the steric hindrance of **1**{*1*−*7*} or

Scheme 1

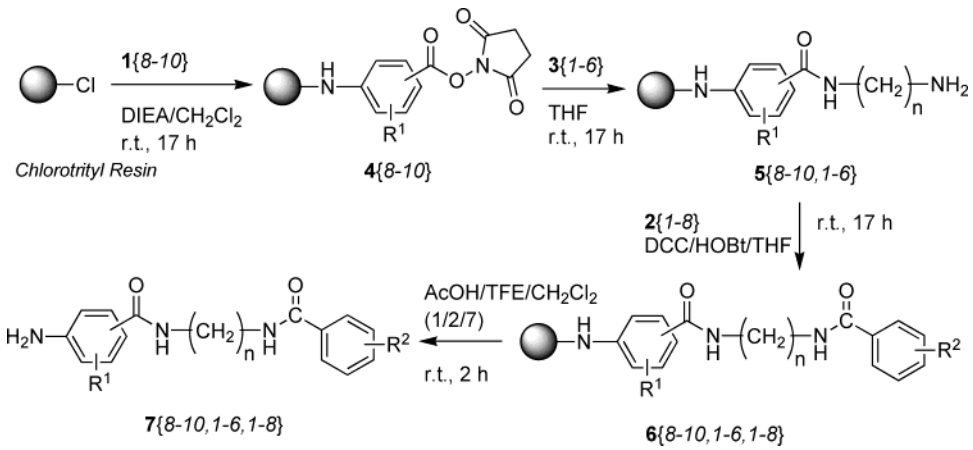


Table 3. Yields and Purity of Making 7{*1-10*,*1*,*9*} Using Scheme 1

product	yield (%) (purity, %)
7{*1*,*1*,*9*}	unidentifiable mixture
7{*2*,*1*,*9*}	22[a] (<20)
7{*3*,*1*,*9*}	68[a] (30)
7{*4*,*1*,*9*}	45 (<50)
7{*5*,*1*,*9*}	0
7{*6*,*1*,*9*}	0
7{*7*,*1*,*9*}	33 (50)
7{*8*,*1*,*9*}	40 (70)
7{*9*,*1*,*9*}	17[a] (>90)
7{*10*,*1*,*9*}	40[a] (>90)

[a] Yield obtained without purification of the reaction product.

substitution of an electron-withdrawing group in **1**{*1*−*7*}. Therefore, a library of 144 discrete chemicals was constructed with building blocks **1**{*8*−*10*}, **2**{*1*−*8*}, and **3**{*1*−*6*} according to Scheme 1. Among 24 (17%) randomly selected members of chemset **7**, 83% have purities higher than 80% according to purity analysis using NMR spectra, and 96% have molecular ion peaks of greater than 5% intensity in mass spectra. This library well satisfies the purity criterion (80/80) required for combinatorial library synthesis. In addition, all of the randomly sampled compounds have yields ranging from 19 to 78% with an average of 39%.

The in vitro FT inhibitory assay[5] of the entire library identified **7**{*10*,*4*,*7*} as demonstrating 14% inhibition of FT at a drug concentration of 500 μM, whereas other dimers showed no inhibition of FT at the same drug concentration. However, **1**{*10*} and **2**{*7*} showed 49 and 23% inhibitions of FT, respectively, at the same drug concentration. These results confirm the prediction of **1**{*10*} and **2**{*7*} as weak FTIs by the docking study and suggest that blindly tethering two members of a group of drug leads might not be effective in lead optimization.

In conclusion, effective loading of aromatic amines onto chlorotrityl resins requires diisopropylethylamine to neutralize HCl generated during the loading. Succinimidyl ester is a dual-purpose reagent that protects an acid from reacting with the trityl group, thus allowing selective attachment of the aromatic amino group of benzoic derivatives to chlorotrityl resins, and activates the acid, thus promoting amidation in a subsequent modification. TFA (1%) can decompose reaction products in the presence of the reactive trityl group. This problem can be avoided by using scavenger 2,2,2-trifluoroethanol, but not triisopropylsilane, although the latter is also a common trityl scanvenger. A solution of acetic acid, 2,2,2-trifluoroethanol, and methylene chloride (1:2:7) is most effective in cleaving aniline-containing compounds from chlorotrityl resins. These methods led to the efficient synthesis of a library of 144 discrete compounds and to the study of the applicability of the bivalence approach to the development of FTIs.

Experimental Section

NMR spectra were obtained on Bruker Avance 500 or 600 instrument. Chemical shifts are reported in δ units using TMS (δ = 0 ppm) as an internal standard for ^{1}H NMR spectra. ^{13}C NMR spectra are referenced to the solvent peak when dissolved in DMSO-d_6 or $CDCl_3$ (δ = 77.0 ppm) as an external standard when dissolved in D_2O. Coupling constants are reported in hertz. Mass spectra were obtained on an HP 5973 mass-selective detector with an SIS DIP-MS.

(a) Synthesis of 1{*1*−*10*}. 2-(2-Aminobenzoyl)benzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester, 1{*1*}. To an ice-cold and stirred solution of 5.00 g (20.7 mmol) of 2-(2-aminobenzoyl)benzoic acid in 120 mL of THF was added 2.39 g (20.7 mmol) of *N*-hydroxysuccinimide, followed by 4.28 g (20.7 mmol) of DCC. The resulting mixture was stirred for 30 min at 0 °C and for 2 h at room temperature. The white precipitate was filtered, and the filter cake was washed with EtOAc. The washings and the filtrate were combined and concentrated in vacuo. The residue was further purified by flash chromatography on silica gel to give 6.64 g (94.9%) of a yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (d, J = 7.8 Hz, 1H), 7.89 (t, J = 7.2 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.35 (brs, 2H), 7.24 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.38 (t, J = 7.6 Hz, 1H), 2.79 (s, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.9, 135.6, 135.5, 134.2, 131.9, 131.2, 130.4, 129.9, 128.9, 122.8, 117.5, 117.4, 116.75, 116.72, 114.9, 25.6.

2-(3-Amino-4-chlorobenzoyl)benzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester, 1{*2*}. The title compound was prepared from 2-(3-amino-4-chlorobenzoyl)benzoic acid following the same procedure as used for **1**{*1*}. Pale yellow solid, 88.3% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 7.8 Hz,

1H), 7.76 (m, 1H), 7.65 (m, 1H), 7.46 (d, $J = 7.4$ Hz, 1H), 7.29 (d, $J = 8.4$ Hz, 1H), 7.21 (d, $J = 1.9$ Hz, 1H), 7.02 (dd, $J = 8.4, 1.9$ Hz, 1H), 4.19 (brs, 2H), 2.79 (s, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 195.9, 170.9, 161.9, 145.9, 143.6, 136.1, 135.7, 131.2, 131.1, 130.1, 128.9, 123.4, 123.1, 118.2, 116.2, 25.6.

5-Acetylamino-2-aminobenzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester, 1{*3*}. The title compound was prepared from 5-acetylamino-2-aminobenzoic acid following the same procedure as used for **1**{*1*}. Red-brown solid, >80% yield: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.17 (d, $J =$ 2.4 Hz, 1H), 7.49 (dd, $J = 9.1, 2.4$ Hz, 1H), 6.83 (d, $J =$ 9.1 Hz, 1H), 6.61 (s, 2H), 2.86 (s, 4H), 1.97 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.7, 168.9, 163.1, 150.3, 130.2, 128.6, 120.2, 118.0, 102.6, 25.6, 23.8.

2-Amino-6-methylbenzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester, 1{*4*}. The title compound was prepared from 2-amino-6-methylbenzoic acid following the same procedure as used for **1**{*1*}. Yellow solid, 84.5% yield: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.15 (t, $J = 7.2$ Hz, 1H), 6.56 (d, $J =$ 7.6 Hz, 1H), 6.54 (d, $J = 8.4$ Hz, 1H), 2.80 (m, 4H), 2.51 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.4, 165.0, 150.5, 141.6, 134.4, 120.8, 114.9, 109.6, 25.8, 22.4.

2-Amino-3,4,5-trimethoxybenzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester, 1{*5*}. The title compound was prepared from 2-amino-3,4,5-trimethoxybenzoic acid following the same procedure as used for **1**{*1*}. White solid, >98% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (s, 1H), 5.72 (brs, 2H), 3.98 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 2.89 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 162.1, 149.1, 143.8, 143.2, 139.9, 107.0, 98.5, 60.9, 60.4, 56.3, 25.6.

4-Amino-3,5-dichlorobenzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester, 1{*6*}. The title compound was prepared from 4-amino-3,5-dichlorobenzoic acid following the same procedure as used for **1**{*1*}. Pale yellow solid, 76% yield: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.86 (s, 2H), 6.85 (brs, 2H), 2.86 (s, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.3, 159.9, 147.4, 129.8, 117.5, 110.9, 25.4.

3-Amino-4-methoxybenzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester, 1{*7*}. The title compound was prepared from 3-amino-4-methoxybenzoic acid following the same procedure as used for **1**{*1*}. White solid, 88.5% yield: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.33 (m, 2H), 6.99 (d, $J = 8.9$ Hz, 1H), 5.19 (brs, 2H), 3.87 (s, 3H), 2.85 (s, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.6, 162.8, 152.6, 139.2, 120.2, 117.1, 114.2, 110.9, 56.0, 25.6.

4-Amino-3-methoxybenzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester, 1{*8*}. To a stirred solution of 5.41 g (32.4 mmol) of 4-amino-3-methoxybenzoic acid in 150 mL of dry THF was added 3.72 g (32.4 mmol) of *N*-hydroxysuccinimide, followed by 6.68 g (32.36 mmol) of DCC at room temperature. The resulting mixture was stirred for 3 h at the same temperature. The white precipitate was filtered and then washed with EtOAc. The filtrate was concentrated in vacuo. The residue was triturated with CH_2Cl_2 to give a pale brown powder. The filter cake was washed thoroughly with acetone. Combined yield = 7.08 g (82.8%) of a pale brown powder: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.52 (d, $J = 1.5, 8.4$ Hz, 1H), 7.30 (s, 1H), 6.72 (d, $J = 8.4$ Hz, 1H), 6.15 (brs, 2H), 3.83 (s, 3H), 2.84 (s, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.9, 162.6, 146.4, 146.1, 126.5, 112.8, 111.5, 110.0, 55.8, 25.7.

4-Amino-5-chloro-2-methoxybenzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester, 1{*9*}. To a stirred solution of 5.00 g (24.8 mmol) of 4-amino-3-methoxybenzoic acid in 150 mL of dry THF was added 3.14 g (27.3 mmol) of *N*-hydroxysuccinimide, followed by 6.14 g (29.8 mmol) of DCC at room temperature. The resulting mixture was stirred for 13 h at the same temperature. The reaction solution containing the final product was collected by filtration. The final product contained in the white precipitate of DCU was extracted by repeated washing with acetone. TLC was used to determine whether the final product contained in the precipitate had been completely extracted. The combined solutions gave 6.10 g (82.8%) of a pale brown powder: ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.72 (s, 1H), 6.66 (brs, 2H), 6.49 (s, 1H), 3.77 (s, 3H), 2.82 (s, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 171.8, 162.1, 159.6, 153.0, 133.5, 109.1, 100.6, 97.8, 56.1, 25.6.

4-Amino-3-iodobenzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester, 1{*10*}. To a stirred solution of 2.31 g (36.1 mmol) of KOH in 240 mL of a 1:1 mixture of MeOH/H_2O was added 10.00 g (36.1 mmol) of methyl 4-amino-3-iodobenzoate at room temperature. The resulting mixture was heated at 75 °C for 20 h. The reaction mixture was concentrated in vacuo to one-half of its original volume. The residue was acidified to pH 4 with 1 N HCl. The white precipitate was collected by filtration and then dried under vacuum to give 9.49 g (100%) of an off-white powder. This product was essentially pure according to the NMR spectrum and was subjected to esterification without further purification: ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.32 (brs, 1H), 8.08 (d, $J = 1.9$ Hz, 1H), 7.62 (dd, $J = 1.9, 8.5$ Hz, 1H), 6.72 (d, $J = 8.5$ Hz, 1H), 4.58 (brs, 2H). The resulting acid, 9.49 g (36.1 mmol), was dissolved in 150 mL of dry THF. To this solution was added 4.57 g (39.7 mmol) of *N*-hydroxysuccinimide, followed by 8.93 g (43.3 mmol) of DCC. The mixture was stirred at room temperature for 6 h. The white precipitate was filtered and washed with EtOAc. The filtrate was concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluted initially with EtOAc/hexanes (1:1), then with EtOAc, and last with acetone to give 12.27 g (94.5%) of a white powder: ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.76 (d, $J = 8.5$ Hz, 1H), 6.81 (d, $J = 8.5$ Hz, 1H), 6.53 (brs, 2H), 2.85 (s, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 171.6, 161.2, 155.8, 153.0, 142.1, 132.3, 113.8, 112.5, 81.5, 25.6.

(b) Synthesis of 4{*8*−*10*}. Each porous polypropylene container, MicroKan (IRORI, San Diego, CA), was packed with 20 mg of chlorotrityl resins and a unique radio-frequency tag (IRORI, San Diego, CA). One hundred forty-four MicroKans were evenly distributed to three 100-mL bottles and then soaked with 2 mL of CH_2Cl_2 per MicroKan for 10 min. Diisopropylethylamine (20 equiv) and one of the building blocks **1**{*8*−*10*} (3 equiv) were then added separately to the three MicroKan-containing bottles. These bottles were then shaken at room temperature for 17 h on an orbital shaker at 100 rpm. After the solvent and the excess

reagents had been removed by suction, all MicroKans were pooled and washed by being shaken for 10 min with 2 mL of MeOH per MicroKan and then for 10 min with 2 mL of CH_2Cl_2 per MicroKan. This two-step washing process was repeated three times. The resulting resins in the MicroKans were dried in vacuo.

(c) Synthesis of 5{*8−10,1−6*}. The pooled MicroKans containing **4**{*8−10*} were split into six 100-mL bottles by using a radio-frequency reader (IRORI, San Diego, CA). Each 100-mL bottle contained eight MicroKans of **4**{*8*}, eight MicroKans of **4**{*9*}, and eight MicroKans of **4**{*10*}. After the resins had been soaked with 2 mL of anhydrous THF per MicroKan in the 100-mL bottle for 10 min, the building blocks **3**{*1−6*} (10 equiv) were added separately to the six MicroKan-containing bottles. The six 100-mL bottles were then shaken at room temperature for 17 h on an orbital shaker at 100 rpm. Afterward, all MicroKans were pooled and were washed and dried in the same manner as used for **4**{*8−10*}.

(d) Synthesis of 6{*8−10,1−6,1−8*}. The pooled MicroKans containing **5**{*8−10,1−6*} were split into eight groups by using the radio-frequency reader. Each group had 18 MicroKans, each of which carried one member of **5**{*8−10,1−6*}, and was added to a 100-mL bottle filled with a mixture of DCC (5 equiv), HOBT (5 equiv), and one member of **2**{*1−8*} (5 equiv) in 36 mL of dry THF. All bottles were shaken at room temperature for 17 h on an orbital shaker at 100 rpm. Afterward, all MicroKans were pooled and were washed and dried in the same manner as used for **4**{*8−10*}.

(e) Synthesis of 7{*8−10,1−6,1−8*}. The pooled MicroKans containing **6**{*8−10,1−6,1−8*} were split into 144 vials (each 20 mL in size) labeled accordingly by the radio-frequency reader. A cleavage solution (2 mL) of AcOH/TFE/CH_2Cl_2 (1:2:7) at room temperature was then added to each vial, and the vials were capped. After the samples in the capped vials had been soaked and shaken overnight, the cleavage solution in each labeled vial was transferred to a well of a 96-well plate, and then the structure and the position of the receiving well were recorded on a datasheet. Each MicroKan was then shaken with 2 mL of CH_2Cl_2 at room temperature for 1 h. The combined solutions stored in the 96-well plate were concentrated using a Genevac DD4 evaporation system to yield the desired discrete products.

(c) Characterization of 24 Randomly Selected Members of 7{*8−10,1−6,1−8*}. Twenty-four (17%) members of **7**{*8−10,1−6,1−8*} were randomly selected by taking the first three compounds in each row of the 96-well plate. This selection was random because the products were not sorted according to the building blocks labeled with unique radio-frequency tags when the cleavage solutions were transferred to the 96-well plates. The chemical structures of all selected members were confirmed by the spectroscopic data reported herein. EG1 and EG2 stand for building blocks **1**{*8−10*} and **2**{*1−8*}, respectively.

7{*10,1,5*}, 4-Fluoro-3-methylbenzoic Acid [2-(4-Amino-3-iodobenzoylamino)ethyl]amide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.12 (d, J = 2.1 Hz, 1H), 7.72 (dd, J = 1.9, 7.4 Hz, 1H), 7.67 (m, 1H), 7.59 (dd, J = 2.1, 8.5 Hz, 1H), 7.10 (t, J = 9.0 Hz, 1H), 6.75 (d, J = 8.5 Hz, 1H), 3.55 (s, 4H), 2.31 (d, J = 1.8 Hz, 3H); LREIMS $C_{17}H_{17}FIN_3O_2$ requires 441.03, found 441 ([M$^+$], 11%), 246 ([EG1$^+$], 100%), 137 ([EG2$^+$], 26%); purity 92%, 3.0 mg (33% yield).

7{*8,6,4*}, 3-Methyl-4-oxo-2-phenyl-4*H*-chromene-8-carboxylic Acid [11-(4-Amino-3-methoxybenzoylamino)undecyl]amide: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (dd, J = 1.8, 7.5 Hz, 1H), 8.39 (dd, J = 1.8, 7.9 Hz, 1H), 7.66 (m, 2H), 7.57 (m, 3H), 7.49 (t, J = 7.7 Hz, 1H), 7.36 (d, J = 1.7 Hz, 1H), 7.10 (dd, J = 1.9, 8.1 Hz, 1H), 6.65 (d, J = 8.1 Hz, 1H), 6.10 (brs, 2H), 3.89 (s, 3H), 3.43 (m, 4H), 2.19 (s, 3H), 1.60−1.19 (m, 18H); LREIMS $C_{36}H_{43}N_3O_5$ requires 597.32, found 263 ([EG2$^+$], 26%), 150 ([EG1$^+$], 100%); purity 56%, 5.7 mg (29% yield).

7{*8,1,4*}, 3-Methyl-4-oxo-2-phenyl-4*H*-chromene-8-carboxylic Acid [2-(4-Amino-3-methoxybenzoylamino)ethyl]amide: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (dd, J = 1.8, 8.6 Hz, 1H), 8.36 (dd, J = 1.8, 8.3 Hz, 1H), 7.71 (m, 1H), 7.67 (m, 2H), 7.54 (m, 3H), 7.46 (t, J = 7.7 Hz, 1H), 7.33 (d, J = 1.8 Hz, 1H), 7.16 (dd, J = 1.8, 8.0 Hz, 1H), 7.06 (m, 1H), 6.63 (d, J = 8.0 Hz, 1H), 3.87 (s, 3H), 3.69 (m, 2H), 3.63 (m, 2H), 2.19 (s, 3H); LREIMS $C_{27}H_{25}N_3O_5$ requires 471.18, found 471 ([M$^+$], 49%), 150 ([EG1$^+$], 100%); purity 80%, 3.3 mg (30% yield).

7{*9,6,1*}, 4-Acetyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid [11-(4-Amino-5-chloro-2-methoxybenzoylamino)undecyl]amide: ^{1}H NMR (500 MHz, CD_3OD) δ 7.79 (s, 1H), 6.49 (s, 1H), 3.90 (s, 3H), 3.34 (m, 4H), 2.49 (s, 3H), 2.48 (s, 3H), 2.48 (s, 3H), 1.58 (m, 4H), 1.33 (m, 14H); LREIMS $C_{28}H_{41}ClN_4O_4$ requires 532.28, found 532 ([M$^+$], 29%), 184 ([EG1$^+$], 100%), 164 ([EG2$^+$], 24%); purity 94%, 2.5 mg (24% yield).

7{*9,1,3*}, 3-Benzoylbenzoic Acid [2-(4-Amino-5-chloro-2-methoxybenzoylamino)ethyl]amide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.23 (t, J = 1.7 Hz, 1H), 8.09 (m, 1H), 7.93 (m, 1H), 7.79 (s, 1H), 7.78 (dd, J = 1.0, 8.3 Hz, 2H), 7.65 (m, 2H), 7.53 (m, 2H), 6.46 (s, 1H), 3.84 (s, 3H), 3.61 (s, 4H); LREIMS $C_{24}H_{22}ClN_3O_4$ requires 451.13, found 451 ([M$^+$], 51%), 184 ([EG1$^+$], 100%); purity 90%, 2.1 mg (23% yield).

7{*9,2,4*}, 3-Methyl-4-oxo-2-phenyl-4*H*-chromene-8-carboxylic Acid [4-(4-Amino-5-chloro-2-methoxybenzoylamino)butyl]amide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.29 (dd, J = 1.7, 8.0 Hz, 1H), 7.98 (dd, J = 1.7, 7.4 Hz, 1H), 7.74 (s, 1H), 7.72 (m, 2H), 7.51 (m, 4H), 6.48 (s, 1H), 3.85 (s, 3H), 3.43 (t, J = 6.7 Hz, 2H), 3.30 (overlap with CD_3OD peak, 2H), 2.15 (s, 3H), 1.65−1.54 (m, 4H); LREIMS $C_{29}H_{28}ClN_3O_5$ requires 533.17, found 533 ([M$^+$], 6%), 184 ([EG1$^+$], 100%), 263 ([EG2$^+$], 65%); purity 85%, 2.2 mg (19% yield).

7{*9,2,2*}, *N*-[4-(4-Amino-5-chloro-2-methoxybenzoylamino)butyl]-2,6-dimethoxynicotinamide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.19 (d, J = 8.3 Hz, 1H), 7.79 (s, 1H), 6.47 (s, 1H), 6.43 (d, J = 8.3 Hz, 1H), 4.08 (s, 3H), 3.97 (s, 3H), 3.89 (s, 3H), 3.43 (m, 4H), 1.68 (m, 4H); LREIMS $C_{20}H_{25}ClN_4O_5$ requires 436.15, found 436 ([M$^+$], 80%), 184 ([EG1$^+$], 100%), 166 ([EG2$^+$], 96%); purity 90%, 1.8 mg (20% yield).

7{*8,2,5*}, 4-Fluoro-3-methylbenzoic Acid [4-(4-Amino-3-methoxybenzoylamino)butyl]amide: ^{1}H NMR (500 MHz, CD_3OD) δ 7.72 (dd, J = 1.9, 7.3 Hz, 1H), 7.66 (ddd, J = 2.4, 4.9, 7.8 Hz, 1H), 7.33 (d, J = 1.7 Hz, 1H), 7.29 (dd, J

= 1.7, 8.2 Hz, 1H), 7.09 (t, J = 8.9 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 3.88 (s, 3H), 3.39 (m, 4H), 2.30 (s, 3H), 1.68 (m, 4H); LREIMS $C_{20}H_{24}FN_3O_3$ requires 373.18, found 373 ([M^+], 100%), 150 ([EG1$^+$], 77%), 137 ([EG2$^+$], 43%); purity >95%, 4.8 mg (66% yield).

7{*10,3,3*}, 3-Benzoylbenzoic Acid [5-(4-Amino-3-iodobenzoylamino)pentyl]amide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.21 (t, J = 1.6 Hz, 1H), 8.09 (d, J = 2.1 Hz, 1H), 8.05 (dt, J = 1.6, 7.7 Hz, 1H), 7.91 (dt, J = 1.6, 7.7 Hz, 1H), 7.79 (dd, J = 1.1, 8.3 Hz, 1H), 7.66 (m, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.56 (m, 2H), 6.73 (d, J = 8.3 Hz, 1H), 3.41−3.32 (m, 4H), 1.65 (m, 4H), 1.44 (m, 2H); LREIMS $C_{26}H_{26}IN_3O_3$ requires 555.10, found 555 ([M^+], 87%), 246 ([EG1$^+$], 34%), 209 ([EG2$^+$], 34%); purity 70%, 4.1 mg (28% yield).

7{*8,5,5*}, 4-Fluoro-3-methylbenzoic Acid [9-(4-Amino-3-methoxybenzoylamino)nonyl]amide: ^{1}H NMR (500 MHz, CD_3OD) δ 7.71 (dd, J = 1.9, 7.5 Hz, 1H), 7.65 (ddd, J = 2.4, 4.9, 7.9 Hz, 1H), 7.32 (d, J = 1.8, Hz, 1H), 7.28 (dd, J = 1.8, 8.2 Hz, 1H), 7.09 (t, J = 9.0 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 3.88 (s, 3H), 3.34 (m, 4H), 2.30 (d, J = 1.6 Hz, 3H), 1.59 (brs, 4H), 1.36 (brs, 10H); LREIMS $C_{25}H_{34}FN_3O_3$ requires 443.26, found 443 ([M^+], 100%), 150 ([EG1$^+$], 35%), 137 ([EG2$^+$], 42%); purity >95%, 4.5 mg (51% yield).

7{*8,2,2*}, *N*-[4-(4-Amino-3-methoxybenzoylamino)butyl]-2,6-dimethoxynicotinamide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.20 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 1.8 Hz, 1H), 7.29 (dd, J = 1.8, 8.2 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.43 (d, J = 8.4 Hz, 1H), 4.07 (s, 3H), 3.96 (s, 3H), 3.88 (s, 3H), 3.42 (m, 4H), 1.68 (m, 4H); LREIMS $C_{20}H_{26}N_4O_5$ requires 402.19, found 402 ([M^+], 87%), 150 ([EG1$^+$], 85%), 166 ([EG2$^+$], 100%); purity >95%, 5.4 mg (68% yield).

7{*10,2,1*}, 4-Acetyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid [4-(4-Amino-3-iodobenzoylamino)butyl]amide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.11 (d, J = 2.0 Hz, 1H), 7.59 (dd, J = 2.0, 8.5 Hz, 1H), 6.75 (d, J = 8.5 Hz, 1H), 3.37 (m, 4H), 2.49 (s, 3H), 2.48 (s, 3H), 2.43 (s, 3H), 1.66 (m, 4H); LREIMS $C_{20}H_{25}IN_4O_3$ requires 496.10, found 496 ([M^+], 31%), 246 ([EG1$^+$], 100%), 164 ([EG2$^+$], 29%); purity >95%, 5.1 mg (52% yield).

7{*9,6,3*}, 3-Benzoylbenzoic Acid [11-(4-Amino-5-chloro-2-methoxybenzoylamino)undecyl]amide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.22 (t, J = 1.6 Hz, 1H), 8.07 (dt, J = 1.2, 7.7 Hz, 1H), 7.91 (dt, J = 1.6, 7.7 Hz, 1H), 7.79 (dd, J = 1.4, 7.8 Hz, 2H), 7.79 (s, 1H), 7.65 (m, 2H), 7.54 (t, J = 7.7 Hz, 2H), 6.49 (s, 1H), 3.89 (s, 3H), 3.35 (m, 4H), 1.59 (m, 4H), 1.34 (m, 14H); LREIMS $C_{33}H_{40}ClN_3O_4$ requires 577.27, found 577 ([M^+], 19%), 184 ([EG1$^+$], 100%), 209 ([EG2$^+$], 30%); purity >95%, 2.6 mg (23% yield).

7{*8,1,2*}, *N*-[2-(4-Amino-3-methoxybenzoylamino)ethyl]-2,6-dimethoxynicotinamide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.23 (d, J = 8.4 Hz, 1H), 7.32 (m, 2H), 6.71 (d, J = 8.1 Hz, 1H), 6.43 (d, J = 8.4 Hz, 1H), 4.03 (s, 3H), 3.96 (s, 3H), 3.88 (s, 3H), 3.59 (m, 4H); LREIMS $C_{18}H_{22}N_4O_5$ requires 374.16, found 374 ([M^+], 100%), 150 ([EG1$^+$], 92%), 166 ([EG2$^+$], 100%); purity 60%, 4.9 mg (42% yield).

7{*10,1,2*}, *N*-[2-(4-Amino-3-iodobenzoylamino)ethyl]-2,6-dimethoxynicotinamide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.24 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 2.0 Hz, 1H), 7.61 (dd, J = 2.0, 8.5 Hz, 1H), 6.76 (d, J = 8.5 Hz, 1H), 6.43 (d, J = 8.4 Hz, 1H), 4.04 (s, 3H), 3.96 (s, 3H), 3.57 (m, 4H); LREIMS $C_{17}H_{19}IN_4O_4$ requires 470.05, found 470 ([M^+], 10%), 246 ([EG1$^+$], 100%), 166 ([EG2$^+$], 60%); purity 80%, 4.3 mg (39% yield).

7{*9,2,1*}, 4-Acetyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid [4-(4-Amino-5-chloro-2-methoxybenzoyl-amino)butyl]amide: ^{1}H NMR (500 MHz, CD_3OD) δ 7.79 (s, 1H), 6.49 (s, 1H), 3.89 (s, 3H), 3.39 (m, 4H), 2.48 (s, 6H), 2.43 (s, 3H), 1.67 (brs, 4H); LREIMS $C_{21}H_{27}ClN_4O_4$ requires 434.17, found 434 ([M^+], 31%), 184 ([EG1$^+$], 100%), 164 ([EG2$^+$], 16%); purity 90%, 2.0 mg (23% yield).

7{*8,6,2*}, *N*-[11-(4-Amino-3-methoxybenzoylamino)undecyl]-2,6-dimethoxynicotinamide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.21 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 1.8 Hz, 1H), 7.28 (dd, J = 1.8, 8.1 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 6.44 (d, J = 8.4 Hz, 1H), 4.09 (s, 3H), 3.97 (s, 3H), 3.88 (s, 3H), 3.36 (m, 4H), 1.59 (m, 4H), 1.33 (m, 14H); LREIMS $C_{27}H_{40}N_4O_5$ requires 500.30, found 500 ([M^+], 100%), 166 ([EG2$^+$], 23%); purity >95%, 5.0 mg (51% yield).

7{*10,3,2*}, *N*-[5-(4-Amino-3-iodobenzoylamino)pentyl]-2,6-dimethoxynicotinamide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.19 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 2.3 Hz, 1H), 7.57 (dd, J = 2.3, 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 8.4 Hz, 1H), 4.04 (s, 3H), 3.96 (s, 3H), 3.40 (t, J = 6.9 Hz, 2H), 3.34 (t, J = 6.9 Hz, 2H), 1.64 (m, 4H), 1.44 (m, 2H); LREIMS $C_{20}H_{25}IN_4O_4$ requires 512.09, found 512 ([M^+], 33%), 246 ([EG1$^+$], 100%), 166 ([EG2$^+$], 88%); purity 78%, 5.1 mg (42% yield).

7{*8,2,1*}, 4-Acetyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid [4-(4-Amino-3-methoxybenzoylamino)butyl]amide: ^{1}H NMR (500 MHz, CD_3OD) δ 7.33 (d, J = 1.7 Hz, 1H), 7.29 (dd, J = 1.7, 8.1 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 3.88 (s, 3H), 3.39 (m, 4H), 2.49 (s, 3H), 2.48 (s, 3H), 2.42 (s, 3H), 1.67 (m, 4H); LREIMS $C_{21}H_{28}N_4O_4$ requires 400.21, found 400 ([M^+], 100%), 150 ([EG1$^+$], 37%), 166 ([EG2$^+$], 28%); purity >95%, 6.1 mg (78% yield).

7{*10,1,3*}, 3-Benzoylbenzoic Acid [2-(4-Amino-3-iodobenzoylamino)ethyl]amide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.22 (s, 1H), 8.09 (d, J = 2.0 Hz, 1H), 8.08 (d, J = 7.9 Hz, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.78 (d, J = 7.2 Hz, 2H), 7.64 (m, 2H), 7.57 (dd, J = 2.0, 8.5 Hz), 7.53 (t, J = 7.8 Hz, 2H), 6.74 (d, J = 8.5 Hz, 1H), 3.57 (m, 4H); LREIMS $C_{23}H_{20}IN_3O_3$ requires 513.05, found 513 ([M^+], 35%), 246 ([EG1$^+$], 87%), 209 ([EG2$^+$], 38%); purity 80%, 6.2 mg (52% yield).

7{*10,6,5*}, 4-Fluoro-3-methylbenzoic Acid [11-(4-Amino-3-iodobenzoylamino)undecyl]amide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.11 (d, J = 2.0 Hz, 1H), 7.71 (dd, J = 1.6, 7.3 Hz, 1H), 7.65 (ddd, J = 2.4, 4.9, 7.9 Hz, 1H), 7.59 (dd, J = 2.0, 8.5 Hz, 1H), 7.09 (t, J = 9.0 Hz, 1H), 6.76 (d, J = 8.5 Hz), 3.32 (m, 4H), 2.30 (d, J = 1.6 Hz, 3H), 1.58 (m, 4H), 1.31 (m, 14H); LREIMS $C_{26}H_{35}FIN_3O_2$ requires 567.18, found 567 ([M^+], 25%), 246 ([EG1$^+$], 97%), 137 ([EG2$^+$], 70%); purity >95%, 5.0 mg (45% yield).

7{*10,6,2*}, *N*-[11-(4-Amino-3-iodobenzoylamino)undecyl]-2,6-dimethoxynicotinamide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.21 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 2.0 Hz,

1H), 7.59 (dd, $J = 2.0, 8.5$ Hz, 1H), 6.75 (d, $J = 8.5$ Hz, 1H), 6.44 (d, $J = 8.4$ Hz, 1H), 4.09 (s, 3H), 3.97 (s, 3H), 3.37 (t, $J = 7.1$ Hz, 2H), 3.30 (t, $J = 7.1$ Hz), 1.58 (m, 4H), 1.33 (m, 14H); LREIMS $C_{26}H_{37}IN_4O_4$ requires 596.19, found 596 ([M^+], 10%), 246 ([EG1$^+$], 100%), 166 ([EG2$^+$], 93%); purity >95%, 5.5 mg (48% yield).

7{*9,1,2*}, *N*-[2-(4-Amino-5-chloro-2-methoxybenzoylamino)ethyl]-2,6-dimethoxynicotinamide: ^{1}H NMR (500 MHz, CD_3OD) δ 8.24 (d, $J = 8.4$ Hz, 1H), 7.82 (s, 1H), 6.48 (s, 1H), 6.44 (d, $J = 8.4$ Hz, 1H), 4.05 (s, 3H), 3.97 (s, 3H), 3.87 (s, 3H), 3.61 (s, 4H); LREIMS $C_{18}H_{21}ClN_4O_5$ requires 408.12, found 408 ([M^+], 8%), 184 ([EG1$^+$], 100%), 166 ([EG2$^+$], 74%); purity >95%, 2.0 mg (25% yield).

7{*9,2,5*}, 4-Fluoro-3-methylbenzoic Acid [4-(4-Amino-5-chloro-2-methoxybenzoylamino)butyl]amide: ^{1}H NMR (500 MHz, CD_3OD) δ 7.79 (s, 1H), 7.71 (dd, $J = 1.6, 7.3$ Hz, 1H), 7.66 (ddd, $J = 2.4, 4.9, 7.9$ 1H), 7.09 (t, $J = 9.0$ Hz, 1H), 6.49 (s, 1H), 3.89 (s, 3H), 3.41 (m, 4H), 2.30 (d, $J = 1.6$ Hz, 3H), 1.67 (m, 4H); LREIMS $C_{20}H_{23}ClFN_3O_3$ requires 407.14, found 407 ([M^+], 32%), 184 ([EG1$^+$], 100%), 137 ([EG2$^+$], 91%); purity >95%, 1.8 mg (23% yield).

(d) In Vitro Inhibition Assay. The in vitro inhibition of FT by the selected compounds was measured by using the FT [^{3}H]-SPA kit. In this assay, recombinant rat FT at a final concentration of 0.625 ng/μL was incubated for 1 h in the presence of [^{3}H] FPP, a human lamin-B carboxy-terminal sequence peptide (biotin-YRASNRSCAIM), and a testing compound or control. The sequence peptide was [^{3}H] farnesylated at the cysteine near the C terminus when processed by FT. The resultant [^{3}H] farnesyl-(CYS)-biotin lamin B was captured by a streptavidin-linked SPA bead. Radioactivity of the sequence peptide in a 150-μL Eppendorf tube was measured on a Beckman LS 6000IC scintillation counter. The test compounds were dissolved in DMSO and diluted 1:10 in the final assay solution. The solvent effect on FT activity was corrected by using a 10% DMSO-containing control. Each assay was carried out in duplicate with deviations of less than 10%.

Acknowledgment. This work was supported by DARPA (DAAD19-01-1-0322); ARO (DAAD19-03-1-0318); USAMRAA (W81XWH-04-2-0001); NIH/NIAID (1R01AI054574-01); NIH/NCI (CA15083); Attenuon, L.P.; and the University of Minnesota Supercomputing Institute. We thank F. G. Prendergast for his vision and support for the combinatorial chemistry program and T. M. Kollmeyer for introducing the IRORI technology and discussion.

References and Notes

(1) Gibbs, J. B.; Oliff, A. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 143−166.
(2) Pang, Y. P.; Quiram, P.; Jelacic, T.; Hong, F.; Brimijoin, S. *J. Biol. Chem.* **1996**, *271*, 23646−23649.
(3) Carlier, P. R.; Du, D.-M.; Han, Y.-F.; Liu, J.; Perola, E.; Williams, I. D.; Pang, Y. P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1775−1777.
(4) Nicolaou, K. C.; Xiao, X.-Y.; Parandoosh, Z.; Senyei, A.; Nova, M. P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2289.
(5) Perola, E.; Xu, K.; Kollmeyer, T. M.; Kaufmann, S. H.; Prendergast, F. G.; Pang, Y. P. *J. Med. Chem.* **2000**, *43*, 401−408.
(6) Leznoff, C. C. *Acc. Chem. Res.* **1978**, *11*, 327−333.
(7) Chen, C.; Randall, L. A. A.; Miller, R. B.; Jones, A. D.; Kurth, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 2661−2662.
(8) Bunin, B. A. *The Combinatorial Index*; Academic Press: San Diego, 1998.
(9) Barlos, K.; Gatos, D.; Kallitsis, I.; Papaioannou, D.; Sotiriou, P. *Liebigs Ann. Chem.* **1988**, *11*, 1079−1081.
(10) Barlos, K.; Gatos, D.; Kallitsis, J.; Papaphotiu, G.; Sotiriu, P.; Wenqing, Y.; Schaefer, W. *Tetrahedron Lett.* **1989**, *30*, 3943−3946.
(11) Bennett, W. D.; Christensen, J. W.; Hamaker, L. K.; Teterson, M. L.; Rhodes, M. R.; Saneii, H. H. *Advanced ChemTech Handbook of Combinatorial and Solid-Phase Organic Chemistry*; Advanced ChemTech: Louisville, KY, 1998.
(12) Frechet, J. M. J.; Nuyens, L. J. *Can. J. Chem.* **1976**, *54*, 926−934.
(13) Barlos, K.; Gatos, D.; Schafer, W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 590−592.
(14) *Advanced ChemTech Handbook of Combinatorial, Organic & Peptide Chemistry 2003−2004*; Advanced ChemTech: Louisville, KY, 2003; p 173.
(15) Schadt, F. L.; Schleyer, P. V. R. *Tetrahedron Lett.* **1974**, *27*, 2335−2338.
(16) Pearson, D. A.; Blanchette, M.; Baker, M. L.; Guindon, C. A. *Tetrahedron Lett.* **1989**, *30*, 2739−2742.

CC0340729