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Solid-Phase Synthesis of Benzoxazoles from 3-Nitrotyrosine

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Received January 20, 2001

A method to synthesize benzoxazoles on solid phase using 3-nitrotyrosine as a scaffold has been developed. The synthesis couples N-protected 3-nitrotyrosine to polystyrene via a Wang-type linker. The polymer-supported 3-nitrotyrosine is deprotected and the resultant primary amine converted to a tertiary amine via sequential reductive alkylation using aromatic followed by unhindered aliphatic aldehydes. The phenol is acylated, and the nitro group is reduced using $SnCl_2$. The resulting amino ester is then dehydratively cyclized to a benzoxazole. The synthesis was developed for a large mix and split ($50 \times 50 \times 50$) combinatorial library. The single compounds presented herein represent a diverse array of the types of monomers amenable to the chemistry developed.

Introduction

Solid-phase combinatorial chemistry has proven to be an efficient way of synthesizing new compounds for drug discovery.[1−3] One strategy for a successful solid-phase synthetic route is that the reactions can proceed with a near-quantitative efficiency (>95%) at each step. Another strategy is to limit the number of steps in order to maximize overall yield. If the synthesis is too lengthy, then the quantity of the desired compound necessary for testing in a biological assay may be too small in comparison to the amount of side products. This is a vital concern when designing a combinatorial mix and split library that gives one compound per bead. Thus, orchestration of the synthetic steps, which is the beauty and challenge of synthetic chemistry, is crucial in the solid-phase organic synthesis of small molecules. There are many excellent recent examples of the solid-phase synthesis of biologically important heterocycles.[4−15]

We have developed a five-step combinatorial synthesis of benzoxazoles from 3-nitrotyrosine. Benzoxazoles are recurring structural motifs found in biologically active compounds.[16] Benzoxazoles have been indicated as 5-HT$_3$ receptor partial agonists,[17] HIV protease inhibitors,[18] thrombin inhibitors,[19] α$_2$-antagonist/5-HT uptake inhibitors,[20] and inhibitors of the human cyotmegalovirus protease.[21] As part of our lead generation program, we synthesized a solid-phase combinatorial library of benzoxazoles to screen for biological activity. Unfortunately, no hits from this library were detected in our assays.

Results and Discussion

The 3-nitrotyrosine scaffold was envisioned to offer three sites of diversification, two from the primary amine and one from a benzoxazole which could be formed from the nitrophenol. To achieve this goal, we needed to develop a protocol in which the amine could be independently diversified into two positions and the aromatic nitro phenol could be transformed into a benzoxazole. In practice, the primary amine was converted into a tertiary amine using a sequential
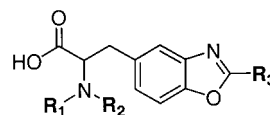

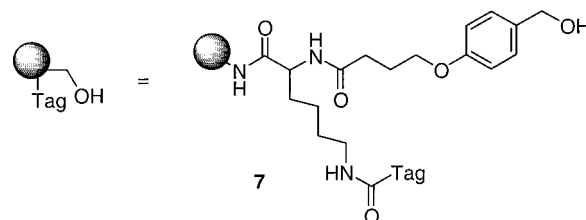**Figure 1.** Benzoxazole library from 3-nitrotyrosine.

Figure 2. Tagged Wang resin.

reductive alkylation procedure. The phenol was then esterified, the nitro group reduced, and the resulting amino ester dehydratively cyclized into the desired benzoxazole. Thus, the synthesis that we developed (Scheme 1) could be used to independently functionalize the three sites of diversity using aromatic aldehydes (Ar$_1$) for the R$_1$ position, unhindered aliphatic aldehydes for the R$_2$, and acid chlorides for the R$_3$ position (Figure 1).

Protected 3-nitrotyrosine was loaded onto the solid support as shown in Scheme 2. The starting resin **7** (Figure 2) was aminomethyllysine based polystyrene with a three-carbon Wang linker attached. The γ-position of the lysine was utilized for incorporation of nitrile-based chemical tags that encoded the first position monomer. This first position-based coding strategy coupled with MS analysis helps to rapidly deconvolute product structure in mix and split libraries.[22] Resin **7** is slightly different from commercially available Wang resin and requires longer reaction times and/or heat.

The 3-nitrotyrosine needed to be protected prior to loading onto the tagged Wang resin because of the ability of the phenol to react with tyrosine to form ester polymers under the diisopropylcarbodiimide (DIC)/*p*-dimethylaminopyridine (DMAP) coupling conditions. The amine was protected as an *N*-(fluorenylmethoxy)carbonyl (*N*-Fmoc) derivative, and

Scheme 1. Solid-Phase Synthesis of Benzoxazoles from 3-Nitrotyrosine
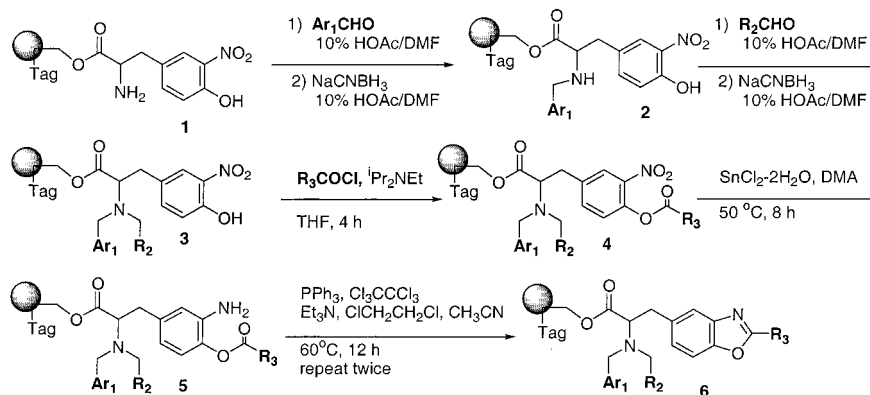
Scheme 2. Loading 3-Nitrotyrosine onto the Solid Phase
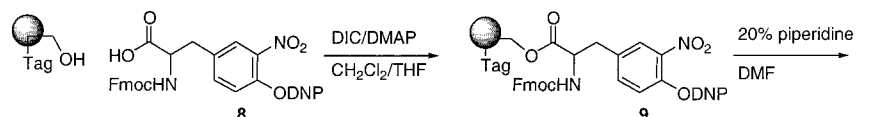
the phenol was protected with a dinitrophenyl (DNP) protecting group.[23] This protection scheme gave a doubly protected starting core **8** that was very easily purified in bulk. However, these protecting groups are not orthogonal, limiting the types of reactions that can be performed. The phenol and amine were equally reactive under acylation and sulfonylation conditions. Therefore, a reductive amination scheme was developed in which the phenol would not react. This protection scheme limits the number of reaction steps, because both protecting groups are removed at once, and benefits the overall efficiency of the synthesis.

The protected 3-nitrotyrosine **8** was loaded onto the tagged Wang resin to give resin **9** using DIC/DMAP as the coupling agents. A small amount of phenolic ester did form presumably because of partial DMAP deprotection of the phenol, which was then free to couple with more of the tyrosine. These phenolic esters were saponified when piperidine was used to remove the Fmoc and DNP groups to give the desired resin-bound 3-nitrotyrosine **1**. Complete removal of the highly colored DNP group required a longer treatment time with piperidine than would be necessary if just the Fmoc group were removed. The quantification of 3-nitrotyrosine loading on the solid support was determined to be 0.34 mmol/g by quantitative Fmoc analysis of **9** and by the quantitative ninhydrin analysis of the amine **1**. This loading was used in all yield calculations of the purified products.

A sequential reductive alkylation procedure[24] was developed to functionalize the primary amine to the tertiary amine as shown in Scheme 1. The first reductive alkylation tolerated a wide variety of aromatic aldehydes, exemplified in Tables 1 and 2. The aldehydes that did not work well all had free NH groups, such as indoles. This may be due to these products decomposing under the cleavage conditions. The imine was preformed in 10% acetic acid, and the remaining aldehyde was washed away. Sodium cyanoborohydride was used to reduce the imine to give a monosubstituted secondary amine **2**. When excess aldehyde remained, some bis-substituted tertiary amine was formed. When aliphatic

aldehydes were used in the reductive alkylation of the primary amine, the bis-substituted tertiary amine was formed even after washing excess aldehyde away. This undesired side product was probably due to bis-enamine formation and subsequent reduction.[25] The secondary amine **2** was then subjected to another reductive alkylation using unhindered aliphatic aldehydes to give the tertiary amine **3**. Aromatic aldehydes used in this reaction gave the starting material. α-Substituted aliphatic aldehydes gave incomplete reactions that could not be driven to completion. The exceptions were cyclic aldehydes such as cyclohexylaldehyde (**19, 22, 24**). Representative examples and yields after chromatographic purification of these reductive amination products are shown in Table 1.

There are a few examples of the solid-phase synthesis of benzoxazole,[15] benzothiazole,[11] and benzimidazole[12−14] heterocycles using a similar strategy of cyclization of the corresponding 2-aminophenol, 2-aminothiophenol, and 2-aminoaniline moieties. Benzoxazole formation was initially envisioned to take place between the solid-supported aminophenol with the diversity element introduced as a carboxylic acid.[26,27] The nitro group essentially served as a protecting group for the aniline that could be revealed upon reduction. However, reaction of the 2-aminophenol with a carboxylic acid under conditions[28] that would normally afford a benzoxazole only gave bis-addition from amide and ester formation. These derivatives could not be induced to cyclize. It was therefore necessary to selectively functionalize the tyrosine prior to cyclization. This was achieved by converting the nitrophenol to ester **4** using an acid chloride. The only acid chlorides that did not work contained perfluorinated alkyl groups.

Reduction of the nitro group presented a challenge because only fully soluble reducing agents could be considered. The usual reducing agents for aromatic nitro groups such as Raney nickel or Pd/C are heterogeneous. Tin chloride dihydrate[29−31] was effective in reducing the nitro group to the aniline **5**. This reaction proved to be extremely oxygen-

Table 1. Representative Secondary and Tertiary Amines off the Solid Phase

Entry	R₁ Aldehyde	R₂	purified % Yield	Entry	R₁ Aldehyde	R₂ Aldehyde	purified % Yield
10		H	54	16			31
11		H	56	17			26
12		H	52	18			52
13		H	48	19			35
14		H	47	20			27
15		H	49				

sensitive,[10] so the reactions were flushed with nitrogen or argon prior to reduction. When carried out in the presence of oxygen, the reduction would stop at the hydroxylamine. Other reducing agents such as TiCl₃[32] and copper/borohydride[14,33] combinations also failed. For convenience, the reduction and subsequent steps were carried out on an Argonaut Nautilus instrument. This reduction only required heating when performed on the lysine-tagged resin. When commercially available Wang resin was used, no heating was required. After the reduction and cleavage, LC−MS usually showed two compounds with the same mass, suggesting that an intramolecular acyl transfer was occurring with the amino ester to give both the amino ester and the amide phenol. This was of little concern because upon dehydrative cyclization one peak was observed in the HPLC to indicate that both isomers underwent cyclization.

The dehydrative cyclization to the benzoxazole **6** was then achieved using a combination of triphenylphosphine, hexachloroethane, and triethylamine.[34] The relative ratio of these three reagents was found to be crucial. The resin needed to be resubjected to the reaction conditions in order to drive the reaction to completion. Benzoxazoles are usually formed from an amino alcohol using polyphosphoric acid and high temperatures. These conditions would not be amenable to solid-phase synthesis using a Wang linker because they could cleave the tyrosine from the resin. Another method commonly used is Burgess' reagent,[35] which did not work in this case. The conditions that we used were reliable and amenable to solid phase because the excess reagents could simply be washed away after the reaction to give >90% conversion to the benzoxazole. Representative examples of

the benzoxazole products and yields after column purification are shown in Table 2.

Conclusions

We have reported an efficient five-step procedure for the solid-phase synthesis of benzoxazoles from 3-nitrotyrosine. This sequence includes a reliable method for the conversion of a primary amine to a tertiary amine via sequential reductive alkylations using a variety of aldehydes. The scope of aldehydes that participate in the reaction has been determined. Conditions for a reliable and reproducible aromatic nitro reduction[10] for solid-phase synthesis have been developed. Finally, a reliable and efficient dehydrative cyclization of amides or esters to the corresponding benzoxazole on solid support has been discovered.

Experimental Section

1. General. The ¹H and ¹³C spectra were obtained on a 500 MHz spectrometer, and chemical shifts are reported in ppm (δ) relative to TMS. Because of solubility properties, the NMR spectra were taken in DMSO-d_6. The DMSO peaks in the ¹H NMR occasionally obscured the aminomethylene protons of the tyrosine derivatives. Low- and high-resolution mass spectra were recorded using atmospheric pressure chemical ionization (APCI). HPLC analysis was performed using a 5 μm, 4.0 × 50 mm C-18 column with a gradient of 100% NH₄OAc (10 mM) to 95% CH₃CN over 11 min. All starting materials were purchased from commercial sources and used without further purification. Aminomethylpolystyrene resin was purchased from Nova Biochem. Aldrich anhydrous solvents were used for reactions. Room-temper-

Table 2. Representative Benzoxazole Products

Entry	R₁ Aldehyde	R₂ Aldehyde	R₃	purfied % Yield
21				50
22				60
23				31
24				25
25				60
26				43

ature reactions were carried out in peptide synthesis flasks (Reliance Glassware) and rotated on a Rototorque orbital mixer (Cole-Palmer). Heated and/or inert reactions were carried out using the Argonaut Nautilus instrument and glassware. Compounds were cleaved from the resin using 95% TFA/CH₂Cl₂ for 45 min. The solvent was removed in vacuo, and the resin was resuspended in CH₃CN and filtered through 4 mm syringe filters. After reaction, the resin was washed 3× each with DMF, CH₂Cl₂, CH₃OH, 1:1 DMF/CH₂Cl₂, 1:1 CH₃OH/CH₂Cl₂, and CH₂Cl₂ and dried in a vacuum desiccator overnight.

2. Procedure for Preparation of Resin 9. A total of 1.00 g of resin **7** was swollen in 2 mL of THF and 2 mL of CH₂-Cl₂. A total of 1.20 g (1.95 mmol) of protected tyrosine **8** was dissolved in 4 mL of THF and 4 mL of CH₂Cl₂, and 306 µL (1.95 mmol) of DIC was added. The mixed anhydride was allowed to form for 10 min, then added to the swollen resin and vortexed. A total of 100 µL of a 2.0 M DMAP solution (1:1 THF/CH₂Cl₂) was added to the reaction, and it was rotated at room temperature overnight. The reaction was rinsed with THF, then washed as described.

3. Procedure for Preparation of Resin 1. Resin **9** was swollen in 8 mL of DMF, and 2 mL of piperidine was added. The reaction mixture was rotated at room temperature for 30 min and then filtered, the resin was washed with DMF (3 × 10 mL), CH₂Cl₂ (3 × 10 mL), and anhydrous DMF (2 × 10 mL), and the reaction was set back up as described. The reaction mixture was rotated at room temperature overnight and then washed as described. Cleavage of 1−2

mg of resin **1** gave material that was identical to commercially available 3-nitrotyrosine. The quantitative ninhydrin test gave 0.34 mmol/g.

4. General Procedure for Preparation of Resin 2. To 1.00 g of resin **1** swollen in 10 mL of DMF was added the aldehyde (10 equiv). To the resin was added 2.5 mL of glacial acetic acid (HOAc), the reaction mixture was rotated at room temperature for 2 h. The reaction mixture was then filtered and washed with DMF (4 × 10 mL), resuspended in 7 mL of DMF and 1 mL of HOAc, and vortexed. To this suspension was added 600 mg (9.55 mmol) of NaCNBH₃. The reaction was vented and rotated at room temperature overnight, then an additional 50 mg (0.80 mmol) of NaC-NBH₃ was added, and the reaction mixture was rotated at room temperature for 1 h. The reaction mixture was then filtered and washed as described. The chloranil test performed on a small amount of resin was positive.

4.1. *N*-[(5-Chloro-2-thienyl)methyl]-4-hydroxy-3-nitrophenylalanine (10). A total of 76.8 mg of resin was cleaved to give 6.0 mg of the purified compound (54%). ¹H NMR (400 MHz, DMSO-d_6): δ 2.76 (dd, 1H, J = 8.1, 14.0 Hz), 2.87 (dd, 1H, J = 5.5, 14.0 Hz), 3.30 (dd, 1H, J = 5.5, 8.1 Hz), 3.68 (d, 1H, J = 14.8 Hz), 3.92 (d, 1H, J = 14.8 Hz), 6.74 (d, 1H, J = 3.8 Hz), 6.87 (d, 1H, J = 3.8 Hz), 7.03 (d, 1H, J = 8.5 Hz), 7.38 (dd, 1H, J = 2.1, 8.5 Hz), 7.74 (d, 1H, J = 2.1 Hz). ¹³C NMR (75 MHz, DMSO-d_6): δ 36.7, 46.0, 60.9, 118.6, 124.1, 125.4, 126.0, 126.6, 129.4, 136.0, 136.6, 144.3, 150.8, 174.5. FAB HRMS: found m/z 357.0327 (MH⁺), $C_{14}H_{14}N_2O_5SCl$ requires 357.0312.

4.2. N-(3,4-Difluorobenzyl)-4-hydroxy-3-nitrophenyl-alanine (11). A total of 78.0 mg of resin was cleaved to give 6.2 mg of purified compound (56%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.79 (dd, 1H, J = 8.1, 14.0 Hz), 2.89 (dd, 1H, J = 5.9, 14.0 Hz), 3.24 (dd, 1H, J = 5.9, 8.1 Hz), 3.59 (d, 1H, J = 14.4 Hz), 3.80 (d, 1H, J = 14.4 Hz), 7.03 (d, 1H, J = 8.5 Hz), 7.05 (m, 1H), 7.19 (ddd, 1H, J = 2.1, 8.1, 10.2 Hz), 7.28 (ddd, 1H, J = 8.1, 10.6, 16.5 Hz), 7.38 (dd, 1H, J = 2.1, 8.5 Hz), 7.74 (d, 1H, J = 2.1 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 36.4, 49.3, 61.4, 116.6, 116.8, 116.9, 117.0, 118.8, 124.6, 124.6, 124.7, 124.7, 125.4, 129.2, 136.0, 136.5, 136.9, 136.9, 146.7, 146.8, 147.4, 147.6, 149.9, 150.1, 150.7, 150.9, 173.9. FAB HRMS: found m/z 353.0957 (MH$^+$), $C_{16}H_{15}N_2O_5F_2$ requires 353.0949.

4.3. N-(1-Benzofuran-2-ylmethyl)-4-hydroxy-3-nitro-phenylalanine (12). A total of 79.1 mg of resin was cleaved to give 5.9 mg of purified compound (52%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.82 (dd, 1H, J = 7.2, 14.0 Hz), 2.89 (dd, 1H, J = 5.9, 14.0 Hz), 3.39 (dd, 1H, J = 5.9, 7.2 Hz), 3.77 (d, 1H, J = 15.0 Hz), 3.93 (d, 1H, J = 15.0 Hz), 6.58 (s, 1H), 7.00 (d, 1H, J = 8.5 Hz), 7.19 (ddd, 1H, J = 0.8, 7.6, 19.1 Hz), 7.21 (ddd, 1H, J = 1.3, 7.2, 19.1 Hz), 7.39 (dd, 1H, J = 2.1, 8.5 Hz), 7.45 (d, 1H, J = 7.6 Hz), 7.52 (d, 1H, J = 7.2 Hz), 7.76 (d, 1H, J = 2.1 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 36.6, 44.0, 61.1, 103.4, 110.7, 118.6, 120.6, 122.5, 123.6, 125.2, 128.0, 129.4, 136.0, 136.4, 150.6, 154.1, 156.9, 174.4. FAB HRMS: found m/z 357.1096 (MH$^+$), $C_{18}H_{17}N_2O_6$ requires 357.1096.

4.4. N-(2,3-Dihydro-1,4-benzodioxin-6-ylmethyl)-4-hydroxy-3-nitrophenylalanine (13). A total of 80.8 mg of resin was cleaved to give 5.8 mg of purified compound (48%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.81 (dd, 1H, J = 7.2, 14.0 Hz), 2.88 (dd, 1H, J = 5.9, 14.0 Hz), 3.24 (dd, 1H, J = 5.9, 7.2 Hz), 3.55 (d, 1H, J = 13.5 Hz), 3.72 (d, 1H, J = 13.5 Hz), 4.18 (s, 4H), 6.67−6.74 (m, 3H), 6.99 (d, 1H, J = 8.5 Hz), 7.34 (dd, 1H, J = 2.1, 8.5 Hz), 7.72 (d, 1H, J = 2.1 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 36.0, 49.7, 61.1, 63.9, 63.9, 116.5, 117.0, 118.8, 121.2, 125.3, 129.1, 130.6, 135.9, 136.5, 142.5, 143.0, 151.0, 172.7. FAB HRMS: found m/z 375.1192 (MH$^+$), $C_{18}H_{19}N_2O_7$ requires 375.1192.

4.5. 4-Hydroxy-N-(4-methoxy-2,3-dimethylbenzyl)-3-nitrophenylalanine (14). A total of 78.9 mg of resin was cleaved to give 5.6 mg of purified compound (47%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.04 (s, 3H), 2.07 (s, 3H), 2.79 (dd, 1H, J = 7.6, 14.0 Hz), 2.88 (dd, 1H, J = 5.5, 14.0 Hz), 3.56 (d, 1H, J = 13.0 Hz), 3.72 (s, 3H), 3.75 (d, 1H, J = 13.0 Hz), 6.70 (d, 1H, J = 8.1 Hz), 6.97 (d, 2H, J = 8.5 Hz), 7.34 (dd, 1H, J = 2.1, 8.5 Hz), 7.71 (d, 1H, J = 2.1 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.6, 14.8, 36.2, 49.2, 55.3, 61.5, 107.4, 118.6, 124.2, 125.2, 127.6, 127.9, 129.4, 136.0, 136.3, 136.4, 150.7, 156.4, 173.2. FAB HRMS: found m/z 375.1552 (MH$^+$), $C_{19}H_{23}N_2O_6$ requires 375.1556.

4.6. 4-Hydroxy-3-nitro-N-(2,3,4-trimethoxybenzyl)-phenylalanine (15). A total of 77.1 mg of resin was cleaved to give 6.0 mg of purified compound (49%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.86 (dd, 1H, J = 7.2, 14.0 Hz), 2.94 (dd, 1H, J = 5.5, 14.0 Hz), 3.39 (app t, 1H, J = 6.4 Hz), 3.63 (d, 1H, J = 13.1 Hz), 3.71 (s, 3H), 3.72 (s, 3H), 3.76

(s, 3H), 3.77 (d, 1H, J = 13.1 Hz), 6.71 (d, 1H, J = 8.5 Hz), 6.93 (d, 1H, J = 8.5 Hz), 7.03 (d, 1H, J = 8.5 Hz), 7.37 (d, 1H, J = 8.5 Hz), 7.75 (d, 1H, J = 8.5 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.7, 45.1, 55.8, 60.3, 60.8, 61.6, 107.5, 119.0, 122.1, 124.4, 125.4, 128.6, 136.2, 136.4, 141.5, 151.1, 151.56, 153.2, 172.2. FAB HRMS: found m/z 407.1454 (MH$^+$), $C_{19}H_{23}N_2O_8$ requires 407.1454.

5. General Procedure for Preparation of Resin 3. To 1.00 g of resin **2** swollen in 10 mL of DMF was added the aldehyde (10 equiv) and 1.2 mL of HOAc. The reaction mixture was rotated at room temperature for 3 h, then 600 mg (9.55 mmol) of NaCNBH$_3$ was added. The reaction mixture was vented and rotated at room temperature overnight, then an additional 100 mg (1.6 mmol) of NaCNBH$_3$ was added, and the reaction mixture was rotated at room temperature for 1 h. The reaction mixture was then filtered and washed as described to give a bright-orange resin **3**. The chloranil test was negative.

5.1. 4-Hydroxy-N-isopentyl-N-[(5-methyl-2-furyl)methyl]-3-nitrophenylalanine (16). A total of 78.2 mg of resin was cleaved to give 3.4 mg of purified compound (31%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.61 (d, 3H, J = 6.8 Hz), 0.65 (d, 3H, J = 6.8 Hz), 1.05 (dd, 2H, J = 7.2, 14.4 Hz), 1.25 (ddd, 1H, J = 6.8, 6.8, 7.2 Hz), 2.15 (s, 3H), 2.54 (dd, 1H, J = 4.2, 13.2 Hz), 2.55 (m, 1H), 2.58 (dd, 1H, J = 7.6, 13.2 Hz), 2.80 (dd, 1H, J = 9.3, 14.0 Hz), 2.90 (dd, 1H, J = 5.5, 14.0 Hz), 3.31 (br s, 1H), 3.45 (dd, 1H, J = 5.5, 9.3 Hz), 3.48 (d, 1H, J = 14.4 Hz), 3.78 (d, 1H, J = 14.4 Hz), 5.89 (dd, 1H, J = 1.0, 3.0 Hz), 5.99 (d, 1H, J = 3.0 Hz), 6.99 (d, 1H, J = 8.5 Hz), 7.37 (dd, 1H, J = 2.1, 8.5 Hz), 7.75 (d, 1H, J = 2.1 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.1, 21.8, 22.7, 24.7, 33.4, 36.6, 47.1, 48.2, 63.7, 105.9, 108.7, 118.4, 125.5, 130.4, 135.9, 136.4, 150.4, 150.5, 151.1, 173.1. FAB HRMS: found m/z 391.1859 (MH$^+$), $C_{20}H_{27}N_2O_6$ requires 391.1869.

5.2. N-(4-Chlorobenzyl)-4-hydroxy-N-[3-(methylsulfa-nyl)propyl]-3-nitrophenylalanine (17). A total of 81.2 mg of resin was cleaved to give 3.3 mg of purified compound (26%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.51 (m, 2H), 1.91 (s, 3H), 2.24 (dd, 2H, J = 6.8, 7.2 Hz), 2.55 (dt, 1H, J = 6.8, 12.7 Hz), 2.66 (dt, 1H, J = 7.6, 13.1 Hz), 2.83 (dd, 1H, J = 9.3, 14.4 Hz), 2.92 (dd, 1H, J = 5.9, 14.4 Hz), 3.35 (br s, 1H), 3.44 (dd, 1H, J = 5.9, 9.3 Hz), 3.56 (d, 1H, J = 14.4 Hz), 3.85 (d, 1H, J = 14.4 Hz), 7.00 (d, 1H, J = 8.5 Hz), 7.06 (d, 2H, J = 8.5 Hz), 7.20 (d, 2H, J = 8.5 Hz), 7.32 (dd, 1H, J = 2.1, 8.5 Hz), 7.65 (d, 1H, J = 2.1 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.5, 27.1, 30.8, 33.5, 49.0, 54.0, 63.5, 118.7, 125.2, 127.7, 130.0, 130.1, 131.0, 136.0, 136.2, 138.9, 150.7, 173.0. FAB HRMS: found m/z 439.1113 (MH$^+$), $C_{20}H_{24}N_2O_5SCl$ requires 439.1094.

5.3. N-Butyl-4-hydroxy-N-(mesitylmethyl)-3-nitrophenylalanine (18). A total of 76.9 mg of resin was cleaved to give 5.9 mg of purified compound (52%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.79 (t, 3H, J = 7.2 Hz), 1.21 (m, 3H), 1.39 (m, 1H), 2.06 (s, 6H), 2.14 (s, 3H), 2.51 (m, 1H), 2.61 (m, 1H), 2.70 (dd, 1H, J = 9.3, 14.0 Hz), 2.88 (dd, 1H, J = 5.9, 14.0 Hz), 3.30 (dd, 1H, J = 5.9, 8.9 Hz), 3.62 (d, 1H, J = 12.7 Hz), 3.76 (d, 1H, J = 12.7 Hz), 6.63 (s, 2H), 6.90 (d, 1H, J = 8.5 Hz), 7.08 (dd, 1H, J = 2.1, 8.5 Hz), 7.32 (d,

1H, $J = 2.1$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.8, 19.5, 20.0, 20.4, 30.0, 33.8, 48.9, 49.2, 62.4, 118.6, 124.7, 128.4, 130.4, 131.4, 135.5, 135.7, 136.2, 137.7, 150.7, 173.6. FAB HRMS: found m/z 415.2221 (MH$^+$), $C_{23}H_{31}N_2O_5$ requires 415.2233.

5.4. 4-Hydroxy-3-nitro-*N*-[3-(trifluoromethoxy)benzyl]-*N*-[2-(2,6,6-trimethyl-1-cyclohexen-1-yl)ethyl]phenylalanine (19). A total of 78.9 mg of resin was cleaved to give 4.7 mg of purified compound (35%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.70 (s, 3H), 0.80 (s, 3H), 1.26 (m, 2H), 1.32 (s, 3H), 1.42 (m, 2H), 1.71 (dt, 1H, $J = 4.2$, 12.7 Hz), 1.75 (m, 2H), 2.09 (dt, 1H, $J = 5.1$, 12.7 Hz), 2.35 (dt, 1H, $J = 4.2$, 12.7 Hz), 2.50 (m, 1H), 2.90 (dd, 1H, $J = 9.7$, 14.4 Hz), 2.99 (dd, 1H, $J = 5.9$, 14.4 Hz), 3.31 (br s, 1H), 3.59 (d, 1H, $J = 14.4$ Hz), 3.69 (dd, 1H, $J = 5.9$, 9.7 Hz), 3.98 (d, 1H, $J = 14.4$ Hz), 6.94 (s, 1H), 7.03 (d, 1H, $J = 8.5$ Hz), 7.11 (d, 1H, $J = 8.0$ Hz), 7.15 (d, 1H, $J = 7.6$ Hz), 7.30 (dd, 1H, $J = 7.6$, 8.0 Hz), 7.43 (dd, 1H, $J = 2.1$, 8.5 Hz), 7.80 (d, 1H, $J = 2.1$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.9, 19.3, 27.3, 28.0, 28.1, 32.1, 33.6, 34.1, 50.6, 53.7, 63.3, 118.8, 119.1, 120.3, 125.3, 127.2, 127.4, 129.6, 130.1, 134.3, 135.8, 136.3, 143.4, 148.4, 150.8, 173.3. FAB HRMS: found m/z 551.2365 (MH$^+$), $C_{28}H_{34}N_2O_5F_3$ requires 551.2369.

5.5. *N*-[(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)methyl]-*N*-ethyl-4-hydroxy-3-nitrophenylalanine (20). A total of 79.4 mg of resin was cleaved to give 3.3 mg of purified compound (27%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.03 (app t, 3H, $J = 7.0$ Hz), 1.89 (s, 3H), 2.01 (s, 3H), 2.44 (dt, 1H, $J = 6.4$, 13.1 Hz), 2.75 (dd, 1H, $J = 9.7$, 14.0 Hz), 2.79 (dd, 1H, $J = 7.2$, 13.1 Hz), 2.85 (dd, 1H, $J = 5.5$, 14.0 Hz), 3.38 (dd, 1H, $J = 5.5$, 9.7 Hz), 3.47 (d, 1H, $J = 13.5$ Hz), 3.56 (d, 1H, $J = 13.5$ Hz), 6.91 (d, 1H, $J = 8.5$ Hz), 7.19 (dd, 1H, $J = 2.1$, 8.5 Hz), 7.33−7.36 (m, 3H), 7.45−7.49 (m, 2H), 7.56 (d, 1H, $J = 2.1$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.3, 11.3, 13.8, 33.5, 42.8, 43.5, 61.8, 114.1, 118.6, 124.1, 125.1, 126.8, 128.9, 130.5, 135.7, 136.1, 137.6, 139.7, 148.1, 150.6, 173.3. FAB HRMS: found m/z 439.1988 (MH$^+$), $C_{23}H_{27}N_2O_5$ requires 439.1981.

6. General Procedure for Preparation of Resin 4. To 1.00 g of resin **3** swollen in 10 mL of THF was added 1.74 mL (10 mmol) of ^{i}Pr$_2$NEt followed by the acid chloride (10 equiv). The reaction mixture was rotated at room temperature for 3 h, then filtered and washed as described to give a creamy-white resin **4**.

7. General Procedure for Preparation of Resin 5. Using the Argonaut nautilus, to 1.00 g of resin **4** in an Argonaut Nautilus vial that had been thoroughly flushed with argon was added 12 mL of 1.0 M SnCl$_2$·2H$_2$O in DMA. The reaction was heated to 50 °C for 8 h, then washed as described.

8. General Procedure for Preparation of Resin 6. Using the Argonaut nautilus, to 1.00 g of resin **5** was added 6 mL of a mixture of 0.3 M PPh$_3$ and 0.33 M Et$_3$N in CH$_3$CN followed by 6 mL of 1.0 M Cl$_3$CCCl$_3$ in ClC$_2$CH$_2$Cl. The reaction was heated to 60 °C for 12 h, then the resin was washed and the reaction was repeated.

8.1. 3-(2-Cyclopropyl-1,3-benzoxazol-5-yl)-*N*-(2-furylmethyl)-*N*-(2-phenylethyl)alanine (21). A total of 63.2 mg

of resin was cleaved to give 4.6 mg of purified compound (50%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09−1.13 (m, 2H), 1.14−1.17 (m, 2H), 2.23 (ddd, 1H, $J = 4.0$, 7.3, 14 Hz), 2.44 (ddd, 1H, $J = 5.0$, 8.1, 14 Hz), 2.56 (m, 1H), 2.74 (m, 1H), 2.84 (ddd, 1H, $J = 4.7$, 6.7, 18.4 Hz), 3.04 (dd, 1H, $J = 7.7$, 13.9 Hz), 3.57 (t, 1H, $J = 7.5$ Hz), 3.73 (d, 1H, $J = 15$ Hz), 3.93 (d, 1 H, $J = 15$ Hz), 6.09 (d, 1H, $J = 2.9$ Hz), 6.33 (dd, 1H, $J = 1.8$, 3.3 Hz), 7.06 (d, 3H, $J = 7.7$ Hz), 7.13 (m, 1H), 7.20 (t, 2H, $J = 7.3$ Hz), 7.36 (d, 1H, $J = 1.1$ Hz), 7.43 (d, 1H, $J = 8.1$ Hz), 7.52 (dd, 1H, $J = 4.4$, 5.1 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 8.7, 8.8, 34.6, 35.2, 47.8, 52.8, 65.2, 107.9, 109.4, 110.2, 119.0, 125.3, 125.7, 128.1, 128.6, 135.0, 140.1, 141.0, 142.0, 148.5, 153.1, 168.4, 173.2. FAB HRMS: found m/z 431.1985 (MH$^+$), $C_{26}H_{27}N_2O_4$ requires 431.1971.

8.2. 3-(2-*tert*-Butyl-1,3-benzoxazol-5-yl)-*N*-(cyclohexylmethyl)-*N*-(3-thienylmethyl)alanine (22). A total of 65.4 mg of resin was cleaved to give 6.0 mg of purified compound (60%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.45 (m, 1H), 0.67 (m, 1H), 1.15−0.86 (m, 3H), 1.28 (m, 2H), 1.42 (s, 9H), 1.54 (m, 3H), 2.26 (dd, 1H, $J = 9.1$, 12.9 Hz), 2.38 (dd, 1H, $J = 5.1$, 12.9 Hz), 2.91 (dd, 1H, $J = 7.1$, 13.6 Hz), 3.09 (dd, 1H, $J = 7.8$, 13.6 Hz), 3.52 (t, 1H, $J = 7.5$ Hz), 3.59 (d, 1H, $J = 14.2$ Hz), 3.83 (d, 1H, $J = 14.2$ Hz), 6.90 (dd, 1H, $J = 1.1$, 4.9 Hz), 7.12 (dd, 1H, $J = 1.6$, 8.3 Hz), 7.19 (m, 1H), 7.40 (dd, 1H, $J = 3.0$, 4.9 Hz), 7.45 (d, 1H, $J = 1.5$ Hz), 7.53 (d, 1H, $J = 8.3$ Hz), 13.10−11.55 (br, 1H, $J = $ s Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.3, 25.6, 26.3, 28.1, 30.8, 31.0, 33.7, 34.8, 35.2, 50.1, 57.1, 64.3, 109.7, 119.6, 122.1, 125.6, 125.9, 128.2, 135.3, 140.8, 141.18, 148.8, 172.8, 172.9. FAB HRMS: found m/z 455.2367 (MH$^+$), $C_{26}H_{35}N_2O_3S$ requires 455.2368.

8.3. *N*-(3,3-Dimethylbutyl)-3-[2-(2-furyl)-1,3-benzoxazol-5-yl]-*N*-[4-(methylsulfanyl)benzyl]alanine (23). A total of 74.9 mg of resin was cleaved to give 3.8 mg of purified compound (31%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.79 (s, 9H), 1.17 (ddd, 1H, $J = 4.8$, 12.8, 17.6 Hz), 1.35 (dt, 1H, $J = 4.8$, 11.7, 17.6 Hz), 2.38 (s, 3H), 2.46−2.52 (m, 1H), 2.63 (ddd, 1H, $J = 5.0$, 12.0, 17.0 Hz), 2.96 (dd, 1H, $J = 8.1$, 13.9 Hz), 3.1 (dd, 1H, $J = 7.1$, 13.7 Hz), 3.5 (t, 1H, $J = 7.5$ Hz), 3.57, (d, 1H, $J = 14.3$ Hz), 3.82, (d, 1H, $J = 14.3$ Hz), 6.81, (dd, 1H, $J = 1.6$, 3.5 Hz), 6.99, (d, 2H, $J = 8.4$ Hz), 7.02, (d, 2H, $J = 8.4$ Hz), 7.18, (dd, 1H, $J = 1.5$, 8.4 Hz), 7.43, (d, 1H, $J = 3.7$ Hz) 7.49, (d, 1H, $J = 1.1$ Hz), 7.62, (d, 1H, $J = 8.1$ Hz), 8.06, (d, 1H, $J = 1.5$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.8, 29.3, 29.6, 34.7, 41.2, 46.2, 54.3, 64.2, 110.1, 112.8, 114.9, 120.1, 125.7, 126.9, 129.0, 135.9, 136.0, 141.1, 141.7, 147.0, 148.2, 154.8, 173.1. FAB HRMS: found m/z 493.2155 (MH$^+$), $C_{28}H_{33}N_2O_4S$ requires 493.2161.

8.4. *N*-([1,1′-Biphenyl]-4-methyl)-*N*-(cyclopropylmethyl)-3-[2-(3-methoxy-3-oxopropyl)-1,3-benzoxazol-5-yl]alanine (24). A total of 70.1 mg of resin was cleaved to give 4.9 mg of purified compound (41%). ^{1}H NMR (400 MHz, DMSO-d_6): δ −0.04 (dt, 1H, $J = 4.7$, 14.2 Hz), 0.09 (dt, 1H, $J = 4.6$, 14.2 Hz), 0.31 (m, 1H), 0.43 (m, 1H), 0.73 (m, 1H), 2.34 (dd, 1H, $J = 7.0$, 13.0 Hz), 2.56 (dd, 1H, $J = 5.9$, 13.0 Hz), 2.88 (t, 2H, $J = 7.0$ Hz), 2.99 (dd, 1H, $J = 8.1$, 13.9 Hz), 3.11 (dd, 1H, $J = 7.0$, 13.9 Hz), 3.16 (t, 2H, $J = $

6.8 Hz), 3.58 (s, 3H), 3.64 (d, 1H, $J = 14.5$ Hz), 3.76 (t, 1H, $J = 7.7$ Hz), 4.04 (d, 1H, $J = 14.5$ Hz), 7.14 (d, 2H, $J = 8.0$ Hz), 7.16 (dd, 1H, $J = 1.8$, 8.4 Hz), 7.33 (t, 1H, $J = 7.3$ Hz), 7.41−7.45 (m, 5H), 7.51 (d, 1H, $J = 8.0$ Hz), 7.60 (d, 2H, $J = 7.0$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 2.6, 4.9, 9.7, 23.2, 29.7, 34.9, 51.5, 53.8, 55.0, 63.7, 109.6, 119.6, 125.9, 126.1, 126.5, 127.1, 128.7, 128.8, 135.3, 138.4, 139.4, 140.1, 140.8, 148.8, 165.8, 172.0, 173.3.

8.5. 3-[2-(3,5-Dimethoxyphenyl)-1,3-benzoxazol-5-yl]-*N*-[3-(4-methoxyphenoxy)benzyl]-*N*-propylalanine (25). A total of 68.9 mg of resin was cleaved to give 8.0 mg of purified compound (60%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.67 (t, 3H, $J = 7.3$ Hz), 1.25 (m, 1H), 1.33 (m, 1H), 2.95 (dd, 1H, $J = 8.4$, 13.9 Hz), 3.10 (dd, 1H, $J = 6.7$, 13.9 Hz), 3.55−3.58(m, 2H), 3.68 (s, 3H), 3.85 (s, 6H), 3.89 (d, 1H, $J = 14.6$ Hz), 6.57 (s, 1H), 6.65 (dd, 1H, $J = 2.2$, 8.1 Hz), 6.74 (t, 1H, $J = 2.4$ Hz), 6.81 (m, 5H), 7.12 (t, 1H, $J = 7.7$ Hz), 7.18 (dd, 1H, $J = 1.8$, 8.4 Hz), 7.27 (d, 2H, $J = 2.2$ Hz), 7.54 (d, 1H, $J = 1.5$ Hz), 7.58 (d, 1H, $J = 8.4$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.4, 20.8, 35.0, 52.2, 54.3, 55.3, 55.5, 64.0, 104.0, 104.8, 110.1, 114.8, 115.5, 117.1, 120.1, 120.3, 122.3, 126.8, 128.3, 129.1, 136.0, 141.3, 142.6, 148.8, 149.5, 155.3, 157.8, 160.9, 162.0, 173.3. FAB HRMS: found m/z 597.2626 (MH$^+$), C$_{35}$H$_{37}$N$_2$O$_7$ requires 597.2601.

8.6. 3-(2-Cyclopropyl-1,3-benzoxazol-5-yl)-*N*-(2-furyl-methyl)-*N*-propylalanine (26). A total of 74.7 mg of resin was cleaved to give 4.1 mg of purified compound (43%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.65 (t, 3H, $J = 7.3$ Hz), 1.09−1.12 (m, 2H), 1.13−1.17 (m, 2H), 1.25 (m, 1H), 1.32 (m, 1H), 2.23 (ddd, 1H, $J = 4.0$, 7.3, 14.1 Hz), 2.45 (m, 1H), 2.52 (m, 1H), 2.90 (dd, 1H, $J = 7.9$, 13.9 Hz), 3.06 (dd, 1H, $J = 7.3$, 13.9 Hz), 3.46 (d, 1H, $J = 14.3$ Hz), 3.53 (t, 1H, $J = 7.5$ Hz), 3.67 (d, 1H, $J = 14.3$ Hz), 6.12 (d, 1H, $J = 1.1$ Hz), 7.10 (dd, 1H, $J = 1.8$, 8.4 Hz), 7.35−7.38 (m, 2H), 7.44−7.48 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 8.8, 8.9, 11.4, 20.8, 34.9, 45.1, 51.8, 63.9, 109.4, 110.9, 119.1, 123.7, 125.3, 135.3, 140.3, 141.0, 143.0, 148.4, 168.2, 173.2. FAB HRMS: found m/z 369.1832 (MH$^+$), C$_{21}$H$_{25}$N$_2$O$_4$ requires 369.1814.

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