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Solid Support Synthesis of 14- and 17-Membered Macrocycles *via* the SNAr Methodology.

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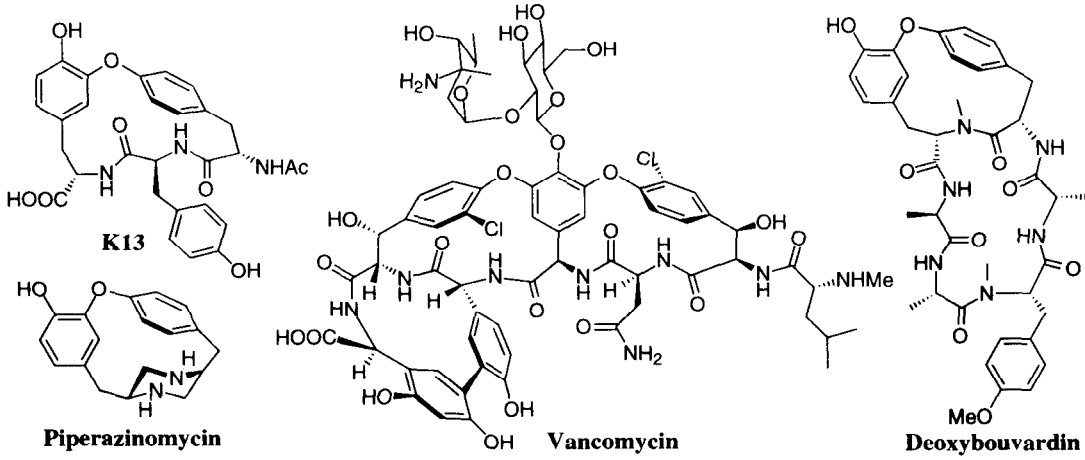
Summary: Efficient assembly of 14-membered macrocycles utilizing the SNAr of fluorine in 3-fluoro-4-nitrobenzoic acid with the OH of 3-hydroxytyrosine on solid support is reported. The flexibility of this synthesis, as well as the excellent purity (>90%) of the final products are the distinctive characteristic of the resultant library.

Key words: macrocycles; supported reagents/reactions; solid-phase synthesis

Due to their pronounced biological activity, the structurally complex vancomycin family of antibiotics has been the focal point of numerous studies.[1,2] A nonsymmetrical biaryl ether functionality found in the main core of vancomycin is a common motif for several related natural products. These include: i) K-13, a non competitive inhibitor of angiotensin I converting enzyme,[3] ii) 17-membered macrocyclic tripeptides of the OF4949 family,[3] iii) piperazinomycin, and the related 14-membered macrocycles, namely bouvardin, deoxybouvardin, and the RA class of bicyclic hexapeptide macrocycles, possessing pronounced antitumor activity.[4] Teicoplanin is yet another representative of this family of macrocycles.[5] Several strategies have been designed to address the numerous challenges in the synthesis of these compounds.[6-12]



To date, two main strategies have been developed for the assembly of the macrocyclic biaryl core: i) macrolactamization of the preformed biaryl ether,[7] and ii) traditional peptide synthesis followed by biaryl ether

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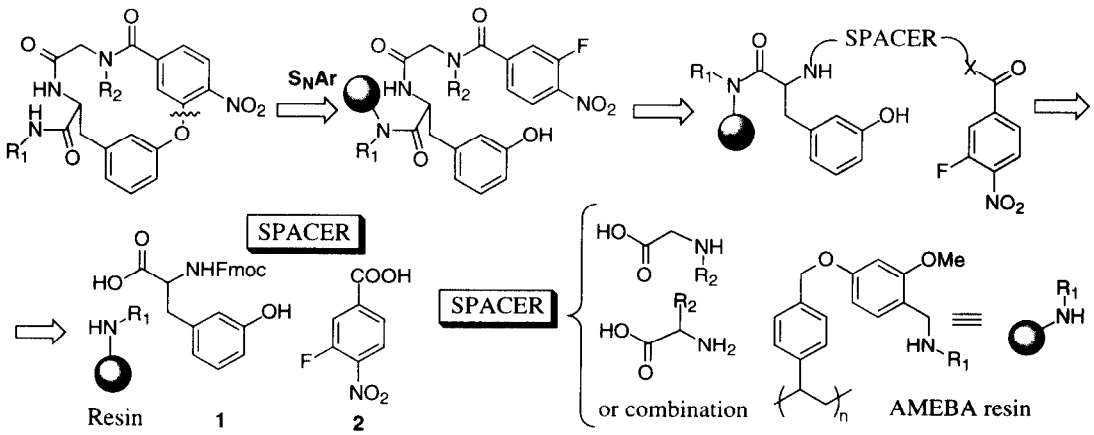
formation as a key step. The conventional macrolactamization techniques have been performed with only marginal success. The reported yields of the target macrocycles are usually quite low.[7] The second strategy involves coupling of the two aromatic units incorporated into the peptide *via* a variety of methods. Studies conducted by numerous research teams including those of Yamamura,[8] Evans,[9] Boger,[10] Zhu and Beugelmans,[11] Rao,[12] Rich,[13] and Nicolaou[14] indicate the diversity in the coupling conditions as well as the components for the biaryl ether formation step. Of these strategies, the approach developed by Zhu and others[11] deserves special attention. It is based on the nucleophilic aromatic substitution (S_NAr) of fluoride in various fluoronitroaromatic substrates with the phenolic oxygen of the tyrosine derivatives to install the biaryl ether bridge in the desired macrocycles.[15] The exceptionally mild coupling conditions, the ready availability of the starting materials, as well as the possibility to expand the diversity of substituents in the final macrocycles *via* postmodification reactions of the nitro group make this strategy amenable for solid phase assembly of 14-membered macrocycles (Scheme 1).

Scheme 1.

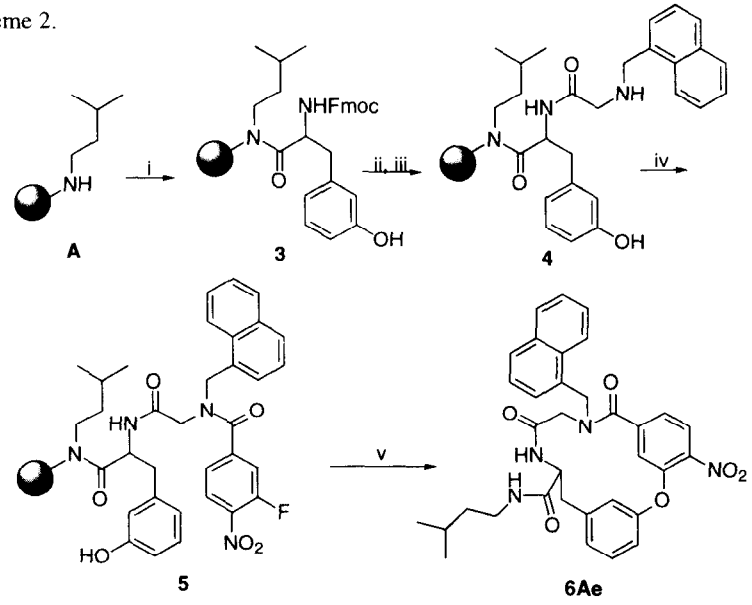


In our continuing effort toward the identification of new reaction templates to investigate by solid support methods,[16] we were interested in the versatile synthesis of 14-membered macrocycles containing the biaryl ether bridge. Solid support syntheses of related structures have been reported by Burgess.[17] In our approach, we decided to use the commercially available 3-hydroxytyrosine[18] **1**, and 3-fluoro-4-nitrobenzoic acid **2**[19] as components for the final S_NAr coupling. To further expand the size, and to introduce an additional diversity element into the library of the targeted 14-membered macrocycles, we selected the previously reported AMEBA (**A**cid sensitive **ME**thoxy **B**enz**A**ldehyde polystyrene) resin which can be easily derivatized by amines.[20] Furthermore, the coupling sequence involving bromoacetic acid followed by the nucleophilic displacement of Br with primary amines would allowed an additional dimension in the desired library.

In the initial experiment, we coupled **1** to the AMEBA resin modified with isoamylamine using the standard 1,3-dicyclohexylcarbodiimide (DCC) protocol (the loading, 0.35 mmol/g, was determined by the

standard Fmoc (9-fluorenylmethyl group) cleavage with 20% piperidine in dimethylformamide (DMF)). Notably, *protection of the OH function of the 3-hydroxytyrosine was not required in the following steps!* [17] Bromoacetic acid was coupled on to the immobilized 3-hydroxytyrosine **3** *via* the previously reported procedure, [21] and the resulting resin was treated with 1-aminomethylnaphthalene **e** in DMF to afford the resin **4**, followed by coupling of **2** using the 1-hydroxy-7-azabenzotriazole/1,3-diisopropylcarbodiimide (HOAt/DIC) strategy[22] to afford the resin **5**. Resin **5** was treated with solution of DBU in DMF, and cleaved with trifluoroacetic acid (TFA) in dichloromethane (DCM) to afford the targeted macrocycle **6Ae** (Scheme 2). Treatment of the resin **5** with a suspension of dry K_2CO_3 (20 equivalents) in DMF in the presence of a catalytic amount of 18-crown-6 for 72 h did not afford the expected macrocycle **6Ae**. The only isolated product after treatment of **6Ae** with TFA in DCM was the corresponding noncyclized material in a 75% yield, and 95% purity as determined by HPLC. Similarly, we did not observe macrocyclization when tetramethylguanidine in DMF was used as a base. Application of KOH or KO*t*-Bu in both DMF, and THF afforded the desired product **6Ae** in a very low yield (25% by LC MS), and poor purity (30%). The reaction mixture contained considerable amounts of unidentified impurities. Dry DMF was found to be the optimal solvent for the macrocyclization. Treatment of **5** with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in THF, MeCN, or DMSO afforded the expected product **6Ae** in lower yields (30-40%) along with a considerable amount of a noncyclized material.

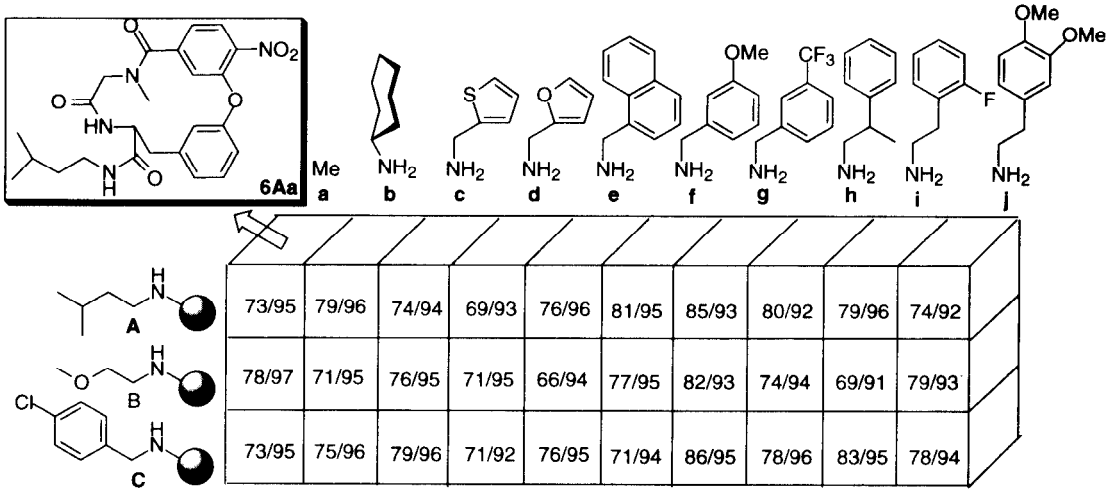
Scheme 2.



Reagents and Conditions: i) **1**, DCC, DMF/CH_2Cl_2 (1:1), RT, 24 h. (0.3 mmol/g loading); ii) 20% piperidine/DMF; $BrCH_2COOH$, DIC, DMF, RT, 3 h.; iii) $NphthCH_2NH_2$ (**e**), DMF, RT, 12 h.; iv) **2**, HOAt, DIC, DMF, RT 8 h.; v) 5% DBU/DMF, RT, 24 h.; 15% TFA in CH_2Cl_2.

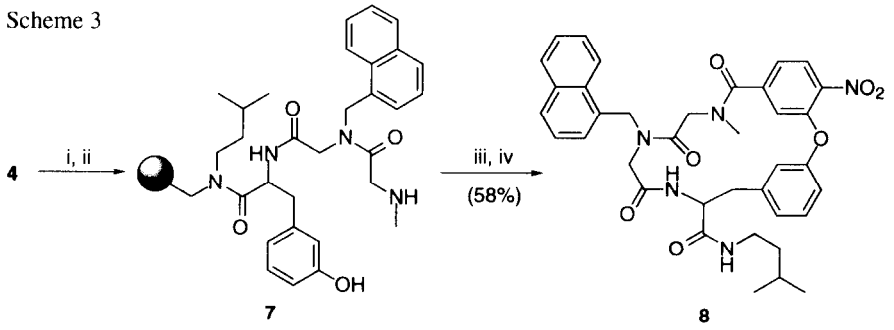
The elaboration of the reaction conditions allowed us to synthesize a library of 30 members (Table 1). Neither the nature of the AMEBA bound amines (**A**, **B**, **C**) nor the primary amines (**a-j**) used for the bromine displacement in bromoacetic acid affected the yield or purity of the final product **6**. The average yield of the targeted macrocycles ranged from 66% to 86%. The purity was determined by both ^{1}H NMR, and HPLC analyses to be in the range of 92-96%. The minor impurity (*ca.* 2-5%) in several instances was identified to be 3-hydroxytyrosine. The analytical samples were prepared by washing crude products with warm MeOH, followed by Et_2O. This procedure was also successfully scaled up to obtain 100-500 mg of the desired macrocycles.

Table 1. Yields and HPLC purities of macrocycles **6**.



This methodology was further expanded to the synthesis of 17-membered macrocycles (Scheme 3). *N*-Fmoc-Sar-OH was coupled on resin **4** using the HOAt/DIC protocol to afford the resin **7** after treatment with 20% piperidine in DMF.[22] Coupling of 3-fluoro-4-nitrobenzoic acid (**2**) to resin **7**, followed by a DBU-promoted macrocyclization, and TFA cleavage afforded the targeted 17-membered macrocycle **8** in 58% yield, and 91% purity by HPLC.

Scheme 3



Reagents and Conditions: i) Fmoc-Sar-OH, HOAt, DIC, DMF, 12 h.; ii) 20% piperidine/DMF, 20 min.; iii) **2**, HOAt, DIC, DMF, RT, 8 h.; iv) 5% DBU/DMF, RT, 24 h.; 15% TFA in CH_2Cl_2.

In summary, we have described a protocol for the efficient assembly of 14- and 17-membered macrocycles utilizing the S_NAr of fluorine in 3-fluoro-4-nitrobenzoic acid with the OH of 3-hydroxytyrosine on solid support. The flexibility of this synthesis, as well as the excellent purity of the final products are the distinctive characteristics of the resulting library.

Experimental Section

Acronyms for solvents, reagents and protective groups used:

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene;
DCC : 1,3-Dicyclohexylcarbodiimide;
DCM: Dichloromethane;
DIC: 1,3-Diisopropylcarbodiimide;
DMF: Dimethylformamide;
Fmoc: 9-fluorenylmethyl;
HOAt: 1-Hydroxy-7-azabenzotriazole;
TFA: Trifluoroacetic acid

Materials. All solid phase reactions were carried out at room temperature. Reagents were purchased from Aldrich, and Acros, and used without further purification. Wang resin (loading 0.6 mmol/g) was purchased from Novabiochem and washed with DMF, MeOH, CH_2Cl_2, and MeCN prior to use.

General Methods. All reactions were carried out in Alltech® tubes (8 mL clear filter tubes available from Alltech Associates, Inc., 250 mg of resin per reaction) or Chemglass peptide vessels. Concentration of the solutions after workup was performed by reduced pressure rotary evaporation. ^1H NMR spectra were obtained on a Bruker 500 instrument with MeOD, and DMSO-d_6 as the solvents. MS analysis (ES, and CI modes) was performed on a Perkin Elmer API 165 instrument. HPLC analysis was performed on a Beckman Gold Analytic 126 apparatus with a diode array detector model 168 at the wavelengths of 220 nm, and 254 nm. The column employed was an Ultrasphere C18 cartridge 250mm x 4.6 mm. The solvent system was MeCN/H_2O (0.1% TFA added), with a flow rate of 1 mL/min.

General Procedure for the Preparation of 3-Hydroxytyrosine on AMEBA Resin. In the standard resin preparation protocol, N-Fmoc protected 3-hydroxytyrosine (8.06 g, 20 mM) was treated with DCC (2.06 g, 10 mM) in 50 mL of dry dichloroethane. The resulting mixture was stirred for 2 h, and filtered. 50 mL of dry DMF were added, and the AMEBA resin immobilized with amine[16] (10 g, 0.45mmol/g loading as determined by coupling of 4-nitrobenzoylchloride followed by cleavage of the resultant amide with 20% TFA/DCM) was introduced. The slurry was stirred at room temperature for 24 h, filtered, washed with DMF, MeOH, CH_2Cl_2, and dried *in vacuo* to afford resin **3** (0.35 mmol/g loading as determined by Fmoc group cleavage). The resulting

resin was treated with 100 mL of a 20% solution of piperidine in DMF for 30 min, washed with DMF, MeOH, and CH_2Cl_2, and dried *in vacuo* to afford the immobilized deprotected 3-hydroxytyrosine.

General Procedure for the Preparation of the Modified 3-Hydroxytyrosine 4. This procedure was run in parallel using the following reaction conditions: a mixture of bromoacetic acid (2.78g, 20 mM), and DIC (2.77 g, 22 mM) in 100 mL of dry DMF was added to the deprotected 3-hydroxytyrosine resin (10 g). The resulting slurry was stirred for 3 h, filtered, washed with DMF, DCM, and treated with a 0.5 M solution of the amine in DMF (100 mL) at room temperature for 12 h, filtered, washed with DMF, MeOH, and DCM, and dried *in vacuo* to afford the desired modified 3-hydroxytyrosine.

General Procedure for Preparation of Macrocycles 6. This procedure was run in parallel using the following reaction conditions: 4 mL of a mixture of 3-fluoro-4-nitrobenzoic acid (1.85g, 10 mM), HOAt (1.36 g, 10 mM), and DIC (1.26 g, 10 mM) (clear solution in 100 mL of DMF) was added to the modified 3-hydroxytyrosine resin (250 mg, 0.3 mmol/g loading). The resulting slurry was stirred for 8 h, filtered, washed with DMF, MeOH, DCM, and treated with a 5% solution of DBU in DMF (5 mL) at room temperature for 24 h, filtered, washed with DMF, MeOH, and DCM, dried *in vacuo* , and cleaved with 15% TFA in DCM (5 mL) for 45 min. The resulting solution was collected, triturated with ether, and dried to afford the macrocycles **6**. All compounds were completely characterized by ^{1}H NMR, HPLC, ESI MS, HR MS, as well as elemental analysis.

Selected experimental data.

Melting points for all synthesized compounds **6** were above 280° C.

(6Aa): 25.6 mg (73%); HPLC t_R = 5.40; ^{1}H NMR (dmso-d_6): δ 0.89 (d, J = 8.0 Hz, 6H), 1.31 (m, 2H), 1.49 (m, 1H), 2.32(m, 1H), 2.34 (s, 2H), 2.83 (s, 3H), 2.93 (d, J = 9.0 Hz, 1H), 3.75-3.86 (m, 2H), 4.38 (m, 1H), 6.58 (s, 1H), 7.03 (m, 1H), 7.22 (m, 1H), 7.35 (m, 1H), 7.69 (dd, J_1 = 9.0 Hz, J_2 = 4.5 Hz, 1H), 8.12 (d, J = 9.0 Hz, 1H), 8.18 (m, 1H); ESI MS *m/z* 469 (M + H^+), 467 (M - H^+); HRMS: M+1 calcd. for $C_{24}H_{28}N_4O_6$: 469.2080, found: 469.2081. Elemental analysis, calcd. for $C_{24}H_{28}N_4O_6$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.32; H, 6.28; N, 11.81.

(6Ab): 32.6 mg (79%); HPLC t_R = 6.72; ^{1}H NMR (dmso-d_6): δ 0.75-2.02(m, 20H), 2.33 (m, 1H), 2.35 (s, 2H), 2.91 (d, J = 9.0 Hz, 1H), 3.75-3.86 (m, 2H), 4.08 (d, J = 9.0 Hz, 1H), 4.38 (m, 1H), 5.11 (d, J = 9.0 Hz, 1H), 6.56 (s, 1H), 7.06 (m, 1H), 7.18 (m, 1H), 7.38 (m, 1H), 7.68 (dd, J_1 = 9.0 Hz, J_2 = 4.5 Hz, 1H), 8.06 (d, J = 9.0 Hz, 1H), 8.12 (m, 1H); ESI MS *m/z* 551 (M + H^+), 549 (M-H^+); HRMS: M+1 calcd. for $C_{30}H_{38}N_4O_6$: 551.2870, found: 551.2872. Elemental analysis, calcd.for $C_{30}H_{38}N_4O_6$: C, 65.44; H, 6.96; N, 10.17. Found: C, 65.22; H, 7.06; N, 10.02.

(6Ac): 30.5 mg (74%); HPLC t_R = 6.21; ^{1}H NMR (dmso-d_6): δ 0.86 (d, J = 8.0 Hz, 6H), 1.28 (m, 2H), 1.46 (m, 1H), 2.30 (m, 1H), 2.33 (s, 2H), 2.94 (d, J = 9.0 Hz, 1H), 3.76-3.84 (m, 2H), 4.05 (d, J = 9.0 Hz, 1H), 4.36 (m, 1H), 5.16 (d, J = 9.0 Hz, 1H), 6.51 (s, 1H), 6.98 (m, 2H), 7.18 (d, J = 7.5 Hz, 1H), 7.24 (m, 2H),

7.41 (m, 2H), 7.83 (d, J = 7.5 Hz, 1H), 8.07 (d, J = 7.5 Hz, 1H), 8.14 (s, 1H); ESI MS m/z 551 (M + H^+), 549 (M - H^+); HRMS: M + 1 calcd. for $C_{28}H_{30}N_4O_6S$: 551.1964, found: 551.1969. Elemental analysis, calcd.for $C_{28}H_{30}N_4O_6S$: C, 61.08; H, 5.49; N, 10.18. Found: C, 60.86; H, 7.06; N, 10.02.

(6Ad): 27.6 mg (69%); HPLC t_R = 6.12; ^1H NMR (dmso-d_6): δ 0.88 (d, J = 8.0 Hz, 6H), 1.28 (m, 2H), 1.46 (m, 1H), 2.34 (m, 1H), 2.37 (s, 2H), 3.06 (d, J = 9.0 Hz, 1H), 3.74-3.85 (m, 2H), 4.03 (d, J = 9.0 Hz, 1H), 4.45 (m, 1H), 5.14 (d, J = 9.0 Hz, 1H), 6.51 (s, 1H), 6.98 (m, 2H), 7.13 (d, J = 7.5 Hz, 1H), 7.26 (m, 2H), 7.43 (m, 1H), 7.96 (d, J = 9.0 Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 8.21 (m, 1H); ESI MS m/z 535 (M + H^+), 533 (M - H^+); HRMS: M+1 calcd. for $C_{28}H_{30}N_4O_7$: 535.2193; found: 535.2183. Elemental analysis, calcd.for $C_{28}H_{30}N_4O_7$: C, 62.91; H, 5.66; N, 10.48. Found: C, 62.68; H, 5.72; N, 10.33.

(6Ae): 36.1 mg (76%); HPLC t_R = 6.98; ^1H NMR (dmso-d_6): δ 0.93 (d, J = 8.0 Hz, 6H), 1.28 (m, 2H), 1.46 (m, 1H), 2.38 (m, 1H), 2.45 (s, 2H), 3.08 (m, 1H), 3.60-3.91 (m, 2H), 4.35 (d, J = 9.0 Hz, 1H), 4.38 (m, 1H), 5.81 (d, J = 9.0 Hz, 1H), 6.56 (s, 1H), 6.89 (s, 1H), 7.02 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.27 (d, J =7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.49 (m, 1H), 7.82 (m, 2H), 7.92 (d, J = 9.0 Hz, 1H), 7.96 (d, J = 9.0 Hz, 1H), 8.09 (m, 2H); ESI MS m/z 595 (M + H^+), 593 (M - H^+); HRMS: M+1 calcd. for $C_{34}H_{34}N_4O_6$: 595.2557, found: 595.2555. Elemental analysis,calcd.for $C_{34}H_{34}N_4O_6$: C, 68.67; H, 5.76; N, 9.42. Found: C, 68.41; H, 5.85; N, 9.31.

(6Af): 34.9 mg (81%); HPLC t_R = 6.72; ^1H NMR (dmso-d_6): δ 0.89 (d, J = 8.0 Hz, 6H), 1.35 (m, 2H), 1.58 (m, 1H), 2.33 (m, 1H), 2.35 (s, 2H), 3.02 (d, J = 9.0Hz, 1H), 3.10 (m, 1H), 3.65-4.00 (m, 4H), 3.84 (s, 3H), 4.47 (m, 1H), 5.19 (d, J = 9.0 Hz, 1H), 6.61 (s, 1H), 6.73 (s, 1H), 6.76 (d, J = 7.5 Hz, 1H), 6.95 (s, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.23 (m, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.88 (d, J = 9.0Hz, 1H), 8.12 (d, J = 9.0 Hz, 1H), 8.17 (m, 1H); ESI MS m/z 575 (M + H^+), 573 (M - H^+); HRMS: M+1 calcd. for $C_{31}H_{34}N_4O_7$: 575.2713, found: 575.2716. Elemental analysis, calcd. for $C_{31}H_{34}N_4O_7$: C, 64.80; H, 5.96; N, 9.75. Found: C, 64.63; H, 6.06; N, 9.61.

(6Ag): 39.0 mg (85%); HPLC t_R = 6.92; ^1H NMR (dmso-d_6) δ 0.88 (d, J = 8.0 Hz, 6H), 1.29 (m, 2H), 1.48 (m, 1H), 2.33 (m, 1H), 2.35 (s, 2H), 2.96 (d, J = 9.0Hz, 1H), 3.08 (m, 1H), 3.75-4.00 (m, 2H), 4.42 (m, 1H), 5.14 (d, J = 9.0 Hz, 1H), 6.62 (s, 1H), 6.94 (s, 1H), 7.14 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.50-7.70 (m, 3H), 7.89 (d, J = 9.0Hz, 1H), 8.13 (m, 2H); ESI MS m/z 613 (M + H^+), 611 (M - H^+entHRMS: aM+1 calcd. for $C_{31}H_{31}F_3N_4O_6$: 613.2274, found: 613.2280. Elemental analysis, calcd.for $C_{30}H_{38}F_3N_4O_6$: C, 60.78; H, 5.10; N, 9.15. Found: C, 60.55; H, 5.18; N, 9.03.

(6Ah): 34.3 mg (80%); HPLC t_R = 6.74; ^1H NMR (dmso-d_6) δ 0.89 (d, J = 8.0 Hz, 6H), 1.25 (m, 2H), 1.51 (m, 1H), 2.35 (m, 1H), 2.37 (s, 2H), 2.98 (d, J = 9.0Hz, 1H), 3.08 (m, 1H), 3.31 (m, 4H), 3.80-4.00 (m, 2H), 4.31 (m, 1H), 5.18 (d, J = 9.0 Hz, 1H), 6.61 (s, 1H), 6.79 (m, 2H), 6.84 (m, 1H), 6.93 (s, 1H), 7.15 (d, J = 7.5 Hz, 1H), 7.20-7.30 (m, 2H), 7.48 (t, J = 7.5Hz, 1H), 7.89 (d, J = 9.0Hz, 1H), 8.13 (d, J = 9.0 Hz, 1H), 8.19 (m, 1H); ESI MS m/z 573 (M + H^+), 571 (M - H^+); HRMS: M+1 calcd. for $C_{32}H_{35}N_4O_6$: 573.2713,

found: 573.2711. Elemental analysis, calcd. for $C_{32}H_{35}N_4O_6$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.02; H, 6.41; N, 9.60.

(6Ai): 34.1 mg (79%); HPLC t_R = 6.85; ^{1}H NMR (dmso-d_6): δ 0.88 (d, J = 8.0 Hz, 6H), 1.33 (m, 2H), 1.56 (m, 1H), 2.46 (m, 1H), 2.48 (s, 2H), 2.90 (m, 2H), 3.06 (m, 2H), 3.80-4.00 (m, 3H), 4.46 (m, 1H), 6.48 (s, 1H), 6.93 (s, 1H), 7.12 (m, 3H), 7.23 (m, 2H), 7.44 (t, J = 7.5Hz, 1H), 7.88 (d, J = 9.0Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 8.21 (m, 1H); ESI MS *m/z* 577 (M + H$^+$), 575 (M - H$^+$); HRMS: M+1 calcd. for $C_{31}H_{33}FN_4O_6$: 577.2462, found: 577.2463. Elemental analysis, calcd. for $C_{31}H_{33}FN_4O_6$: C, 64.57; H, 5.77; N, 9.72. Found: C, 64.33; H, 5.84; N, 9.58.

(6Aj): 34.1 mg (79%); HPLC t_R = 7.02; ^{1}H NMR (dmso-d_6): δ 0.91 (d, J = 8.0 Hz, 6H), 1.32 (m, 2H), 1.60 (m, 1H), 2.34 (m, 1H), 2.36 (s, 2H), 2.67 (m, 1H), 2.74 (m, 1H), 2.98 (d, J = 9.0 Hz, 1H), 3.05 (m, 2H), 3.68 (s, 3H), 3.70 (s, 3H), 3.72-3.86 (m, 2H), 4.41 (m, 1H), 6.49 (s, 1H), 6.69 (d, J = 8.0Hz, 1H), 6.79 (s, 1H), 6.83 (d, J = 8.0Hz, 1H), 7.91 (s, 1H), 7.11 (d, J = 8.0Hz, 1H), 7.44 (t, J = 8.0Hz, 1H), 7.86 (d, J = 9.0Hz, 1H), 8.13 (d, J = 9.0 Hz, 1H), 8.21 (m, 1H); ESI MS *m/z* 619 (M + H$^+$), 617 (M- H$^+$); HRMS: M+1 calcd. for $C_{33}H_{38}N_4O_8$: 619.2768, found: 619.2781. Elemental analysis, calcd. for $C_{33}H_{38}N_4O_8$: C, 64.06; H, 6.19; N, 9.06. Found: C, 63.78; H, 6.32; N, 8.87.

(6Ba): 26.7 mg (78%); HPLC t_R = 5.11; ^{1}H NMR (dmso-d_6): δ 2.37 (s, 2H), 2.88 (s, 3H), 3.25 (m, 2H), 3.64 (s, 3H), 3.69 (m, 2H), 3.77-3.88 (m, 2H), 4.34 (m, 1H), 6.59 (s, 1H), 7.08 (m, 1H), 7.21 (m, 1H), 7.38 (m, 1H), 7.66 (dd, J_1 = 9.0 Hz, J_2 = 4.5 Hz, 1H), 8.07 (d, J = 9.0 Hz, 1H), 8.19 (m, 1H); ESI MS *m/z* 457 (M + H$^+$), 455 (M - H$^+$); HRMS: M+1 calcd. for $C_{22}H_{24}N_4O_7$: 457.1724, found: 457.1727. Elemental analysis, calcd. for $C_{22}H_{24}N_4O_7$: C, 57.89; H, 5.30; N, 12.27. Found: C, 57.62; H, 5.41; N, 12.08.

(6Bb): 28.6 mg (71%); HPLC t_R = 6.37; ^{1}H NMR (dmso-d_6): δ 0.98-1.98 (m, 11H), 2.35 (s, 2H), 3.29 (m, 2H), 3.71 (s, 3H), 3.73 (m, 2H), 3.76-3.88 (m, 2H), 4.04 (d, J = 9.0 Hz, 1H), 4.39 (m, 1H), 5.19 (d, J = 9.0 Hz, 1H), 6.56 (s, 1H), 7.13 (m, 1H), 7.21 (m, 1H), 7.39 (m, 1H), 7.73 (dd, J_1 = 9.0 Hz, J_2 = 4.5 Hz, 1H), 8.07 (d, J = 9.0 Hz, 1H), 8.15 (m, 1H); ESI MS *m/z* 539 (M + H$^+$), 537 (M-H$^+$); HRMS: M+1 calcd. for $C_{28}H_{34}N_4O_7$: 539.2507, found: 539.2511. Elemental analysis, calcd.for $C_{28}H_{34}N_4O_7$: C, 62.44; H, 6.36; N, 10.40. Found: C, 62.15; H, 6.48; N, 10.12.

(6Bc): 30.7 mg (76%); HPLC t_R = 5.98; ^{1}H NMR (dmso-d_6): δ 2.36 (s, 2H), 3.34 (m, 2H), 3.60 (s, 3H), 3.75-3.84 (m, 3H), 4.07 (d, J = 9.0 Hz, 1H), 4.29 (m, 1H), 5.19 (d, J = 9.0 Hz, 1H), 6.55 (s, 1H), 6.93 (m, 2H), 7.23 (d, J = 7.5 Hz, 1H), 7.28 (m, 2H), 7.39 (m, 2H), 7.86 (d, J = 7.5 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 8.13 (s, 1H); ESI MS *m/z* 539 (M + H$^+$), 537 (M - H$^+$); HRMS: M + 1 calcd. for $C_{26}H_{26}N_4O_7S$: 539.1601, found: 539.1606. Elemental analysis, calcd.for $C_{26}H_{26}N_4O_7S$: C, 57.98; H, 4.87; N, 10.40. Found: C, 57.71; H, 4.96; N, 10.22.

(6Be): 28.8 mg (66%); HPLC t_R = 6.81; ^{1}H NMR (dmso-d_6): 2.43 (s, 2H), 3.39 (m, 2H). 3.61 (s, 3H), 3.64-3.86 (m, 4H), 4.40 (d, J = 9.0 Hz, 1H), 4.43 (m, 1H), 5.86 (d, J = 9.0 Hz, 1H), 6.53 (s, 1H), 6.88 (s, 1H),

7.05 (d, J = 7.5 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.33 (d, J =7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.52 (m, 1H), 7.80 (m, 2H), 7.91 (d, J = 9.0 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 8.09 (m, 2H); ESI MS *m/z* 583 (M + H^+), 581 (M - H^+); HRMS: M+1 calcd. for $C_{32}H_{30}N_4O_7$: 583.2194, found: 583.2197. Elemental analysis,calcd.for $C_{32}H_{30}N_4O_7$: C, 65.97; H, 5.19; N, 9.62. Found: C, 65.68; H, 5.31; N, 9.41.

(6Ca): 28.6 mg (73%); HPLC t_R = 6.36; ^1H NMR (dmso-d_6): 2.33 (s, 2H), 2.44 (s, 2H), 2.89 (s, 3H), 3.70-3.77 (m, 2H), 4.31 (m, 1H), 6.59 (s, 1H), 7.11 (m, 1H), 7.24 (m, 1H), 7.32 (m, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.5 Hz, 2H), 7.72 (dd, J_1 = 9.0 Hz, J_2 = 4.5 Hz, 1H), 8.10 (d, J = 9.0 Hz, 1H), 8.19 (m, 1H); ESI MS *m/z* 523 (M + H^+), 521 (M - H^+); HRMS: M+1 calcd. for $C_{26}H_{23}ClN_4O_6$: 523.1385, found: 523.1386. Elemental analysis, calcd. for $C_{26}H_{23}ClN_4O_6$: C, 59.72; H, 4.43; N, 10.71. Found: C, 59.58; H, 4.52; N, 10.48.

(6Cg): 43.0 mg (86%); HPLC t_R = 7.03; ^1H NMR (dmso-d_6) δ 2.35 (s, 2H), 2.48 (s, 2H), 3.11 (m, 1H), 3.78-4.05 (m, 2H), 4.36 (m, 1H), 5.11 (d, J = 9.0 Hz, 1H), 6.67 (s, 1H), 6.95 (s, 1H), 7.10 (d, J = 7.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.52-7.70 (m, 5H), 7.90 (d, J = 9.0Hz, 1H), 8.12 (m, 2H); ESI MS *m/z* 613 (M + H^+), 611 (M - H^+); HRMS: M+1 calcd. for $C_{31}H_{31}F_3N_4O_6$: 667.1572, found: 667.1574. Elemental analysis, calcd.for $C_{33}H_{26}ClF_3N_4O_6$: C, 59.42; H, 3.93; N, 8.40. Found: C, 59.23; H, 4.06; N, 8.18.

(8): 28.8 mg (58%, based upon 0.3 mmol/g loading); HPLC t_R = 7.72; ^1H NMR (dmso-d_6): δ 0.96 (d, J = 8.0 Hz, 6H), 1.25 (m, 2H), 1.49 (m, 1H), 2.39 (m, 1H), 2.45-2.48 (m, 4H), 3.08 (m, 1H), 3.45 (s, 3H), 3.72-3.88 (m, 2H), 4.41 (d, J = 9.0 Hz, 1H), 4.63 (m, 1H), 5.71 (d, J = 9.0 Hz, 1H), 6.71 (s, 1H), 6.93 (s, 1H), 7.07 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.31 (d, J =7.5 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.55 (m, 1H), 7.86 (m, 2H), 7.95 (d, J = 9.0 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 8.12 (m, 2H); ESI MS *m/z* 666 (M + H^+), 664 (M - H^+); HRMS: M+1 calcd. for $C_{37}H_{39}N_5O_7$: 666.2920, found: 666.2918. Elemental analysis, calcd. for $C_{37}H_{39}N_5O_7$: C, 66.75; H, 5.90; N, 10.52. Found: C, 66.48; H, 6.01; N, 10.37.

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†This paper is dedicated to Natalie.

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