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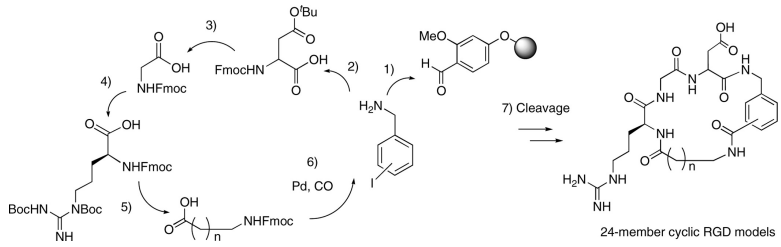

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Combinatorial Synthesis of RGD Model Cyclic Peptides Utilizing a Palladium-Catalyzed Carbonylative Macrolactamization on a Polymer Support

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A combinatorial synthesis of 24-member RGD models was accomplished on polymer-support. *Ortho*-, *meta*-, and *para*-iodobenzylamines loaded on an aldehyde linker by reductive amination were coupled with RGD sequences and various ω-amino acids by a split-and-pool method. Palladium-catalyzed carbonylative macrolactamization of the polymer-supported cyclization precursors, followed by acid cleavage, provided conformationally restricted RGD model cyclic peptides.

Introduction

Peptides capable of binding to biological receptor molecules, such as Arg-Gly-Asp (RGD),[1] angiotensin,[2] and somatostatin,[3] have been recognized as important targets for drug discovery and construction of chemical probes for use in the fields of chemical genetics, genomics, and proteomics. One potential drawback of the peptides is that they are highly flexible molecules, and hence it is difficult to define their biological active conformation and lock them into the state. One way to overcome this limitation is to prepare macrocyclic peptidomimetics that have a restricted three-dimensional structure of the significant amino acid sequences.[4] Therefore, several approaches to the construction of macrocyclic peptidomimetics have been reported, such as S_N2-alkylation with S-nucleophiles,[5,6] S_NAr-macrocyclization,[6] alkene metathesis,[7] and Mizoroki−Heck reaction.[8] However, a powerful method is required to construct a variety of macrocyclic peptidomimetics built up with assembly of the amino acid sequences of different stereochemistry and frameworks of various shapes.

Solid-phase synthesis is an effective method for the generation of a diverse library of small molecules. In addition, macrocyclization on polymer supports has the advantage of pseudodilution caused by reactive-site isolation on the polymer support at moderate to low loading.[9] Recently, we reported that palladium-catalyzed carbonylative esterification on polymer supports is a powerful reaction to synthesize a combinatorial library of macrolides. For example, we established a combinatorial synthesis of a 122-member macrosphelide library, utilizing various alkenyl bromides that are equivalents as masked activated esters.[10] Moreover, we recently reported that palladium-catalyzed carbonylative macrolactamization is an efficient reaction for the construction of a cyclic RGD model.[11] Therefore, we envisioned development of an effective method based on a diversity-oriented solid-phase synthetic approach for the rapid assembly of cyclic RGD model derivatives having variant conformations. Herein, we describe the efficient combinatorial synthesis of the RGD model cyclic peptides utilizing carbonylative macrolactamization on a polymer support.

The RGD sequence is a common recognition motif for the integrin family of receptors, which are involved in cell−cell and cell−matrix adhesion. Cyclic RGD models have been studied as a selective integrin receptor antagonist.[12] We designed RGD peptidomimetics **1** that contain a RGD sequence, an (aminomethyl)benzoic acid and an ω-amino acid. Assembly of the RGD sequences consisting of different stereochemistry, the (aminomethyl)benzoic acids substituted at the ortho, meta, and para positions and the ω-amino acids with a different number of methylene units would lead to a variety of cyclic RGD models having the different three-dimensional structures.

In the combinatorial synthesis of **1**, we chose a solid-phase synthesis utilizing the five synthetic building blocks **3**, **5**, **6**, **7**, and **8** as illustrated in Scheme 1. The diversity blocks **3**{*o-1*, *m-2*, *p-3*}, **5**{L-Asp *1*, D-Asp *2*}, and **8**{Gly *1*, β-Ala *2*, γ-aminobutyric acid *3*, ω-aminovaleric acid *4*} are illustrated in Figure 1. The iodobenzylamine **3** was selected for the attachment to a polymer support **4** through a dialkoxybenzaldehyde linker. The protecting groups in the components used in this combinatorial synthesis are acid-cleavable, such as the ^{t}Bu ester in **5** and the Boc groups in **7**. The process involves (1) attachment of the amino group in block **3** to a polymer support **4** using reductive amination, (2) sequential peptide elongation with blocks **5**, **6**, **7**, and **8**, (3) palladium-catalyzed carbonylative macrolactamization on the polymer support, and (4) deprotection of the Boc and ^{t}Bu ester groups and cleavage of the cyclic RGD models from the polymer support. Our strategy could rapidly provide

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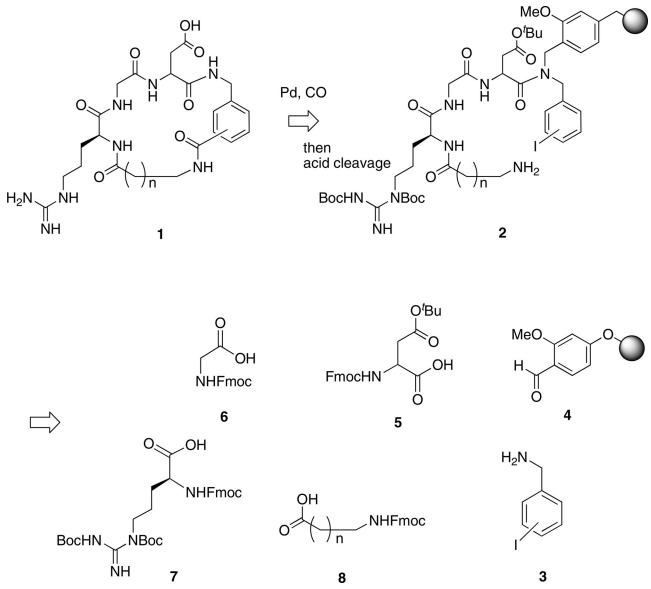
Scheme 1. Strategy for the Synthesis of Cyclic RGD Model Library **1**



a combinatorial library of a 24-member cyclic RGD models having the variant conformation.

Results and Discussion

A solid-phase synthesis of **1**{*2*, *1*, *4*} was initially investigated (Scheme 2). Attachment of *m*-iodobenzylamine **3**{*2*} to a low-loading ArgoPore resin **4**[13] via a 4-formyl-3-methoxyphenoxy linker using reductive amination provided polymer-supported secondary amine **9**{*2*}. The loading amount of **9**{*2*} was determined to be 0.23 mmol g^{-1} by isolation of *N*-Ac-3-iodobenzylamine obtained by acid cleavage from the polymer support with TFA/^{i}Pr$_3$SiH/H$_2$O (95:2.5:2.5) after acetylation (AcCl/DIEA/CH$_2$Cl$_2$/rt/6 h). To avoid epimerization of an asparagine unit, condensation of polymer-supported secondary amine **9**{*2*} with Fmoc-Asp(O^{t}Bu)-OH **5**{*1*} was performed using TFFH[14]−*N,N*-diisopropylethylamine (DIEA) in CH$_2$Cl$_2$−DMF (9:1) at ambient temperature to provide **10**{*2*, *1*} in 96% yield. The yield was determined after acid cleavage from the polymer support (TFA/^{i}Pr$_3$SiH/H$_2$O = 95:2.5:2.5). After removal of the Fmoc group using 20% piperidine in DMF, sequential peptide elongation with Fmoc-Gly-OH (**6**), Fmoc-Arg(Boc)$_2$-OH (**7**), and Fmoc-ω-aminovaleric acid **8**{*4*} was performed using PyBrop–DIEA in CH$_2$Cl$_2$−DMF (9:1) at ambient temperature to afford a polymer-supported cyclization precursor **2**{*2*, *1*, *4*} in 66% overall yield from **9**{*2*}.

Palladium-catalyzed carbonylative macrolactamization of **2**{*2*, *1*, *4*} was investigated on the polymer support (Table 1). We initially compared the effects of reaction temperature [40 °C, 50 °C, reflux]. The reaction was carried out in the presence of Pd(P^{t}Bu$_3$)$_2$[15] (1 mM) and MS4Å[16] (100 mg/mL) in THF for 36 h under CO (10 atm) using our previously reported solution-phase synthesis.[11] Acid cleavage from the polymer support and simultaneous removal of the ^{t}Bu ester and Boc groups with TFA/^{i}Pr$_3$SiH/H$_2$O (95:2.5:2.5) provided a mixture of cyclic RGD models **1**{*2*, *1*, *4*} and its trifluoroacetate derivatives. Then crude mixture was treated with silica gel 60 F$_{254}$ in MeOH−CHCl$_3$ (90:10) to remove the partially attached trifluoroacetyl groups. The cyclization precursor was completely consumed when the reaction was carried out at 50 °C (entry 2). The purity of crude **1**{*2*, *1*, *4*} was estimated by HPLC on the basis of an evaporative light-scattering detector (ELSD) to be 21%. Next, we investigated the amount of MS4Å (100, 50, and 10 mg/mL) (entries 3, 4, and 5). Actually, the yield was dramatically affected by the amount of MS4Å, and the purity increased up to 73% in the presence of MS4Å (10 mg/mL) as illustrated in Figure 2. After purification of the crude product by ODS column chromatography, cyclic RGD model **1**{*2*, *1*, *4*} was isolated in 43% overall yield in 10 steps from **9**{*2*} (entry 5). This result suggested that the amount of MS4Å had the crucial effect on purity and yield probably because efficient stirring is required to achieve the carbonylation in a three-phase system. Finally, the effect of solvent (THF, DMF) and base (MS4Å, NEt$_3$–DMAP, Ag$_2$CO$_3$) was investigated (entries 5−9). It was found to be important such that THF is more effective than DMF and MS4Å is the most effective base in our experiment.

On the basis of the above solid-phase strategy, we constructed a combinatorial library of the cyclic RGD models using radiofrequency encoded combinatorial (REC) chemistry[17] by a split-and-pool method. The twenty-four MacroKans each containing 100 mg of ArgoPore-formyl resin **4** were encoded and split into three flasks. After attachment of blocks **3**{*1*−*3*} to the resins, the MacroKans were pooled together for washing and drying. The MacroKans were decoded, split, and treated with blocks **5**{*1*−*2*} by amidation in separate flasks. The MacroKans were subsequently pooled for washing, drying, and removal of the Fmoc group. Sequential peptide elongation with blocks **6**, **7**, and **8**{*1*−*4*} provided 24-member polymer-supported cyclization precursors. The palladium-catalyzed carbonylative macrocyclization of the precursors was performed under optimized reaction conditions described above [Pd(P^{t}Bu$_3$)$_2$ (0.001 M)/CO (10 atm)/MS4Å (10 mg/mL)/THF/50 °C/36 h] in a single autoclave, and the resins were washed and dried. Finally, the MacroKans were decoded and treated with acid in parallel for removal of the Boc groups and ^{t}Bu ester and cleavage from the polymer-support. Then the crude mixtures were treated with silica gel 60 F$_{254}$ in MeOH−CHCl$_3$ (90:10) to remove the partially attached trifluoroacetyl groups. It is noted that all 24-member compounds built up with assembly of the RGD sequences consisting of different stereochemistry, the (aminomethyl)benzoyl groups substituted with the ortho, meta, and para positions and ω-amino acid with the different number of methylene unit were detected by LC-MS. Purification of the crude products by preparative HPLC (C18)

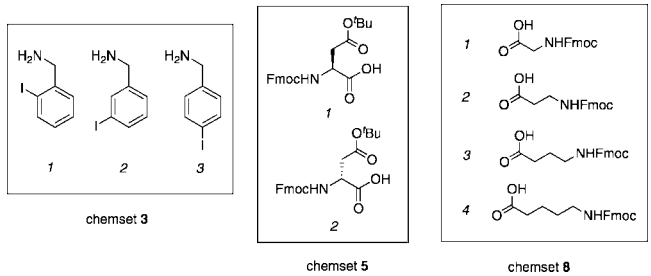


Figure 1. Structure of chemsets **3**, **5**, and **8**.

Scheme 2. Solid-Phase Synthesis of Cyclic RGD Model Library **1**

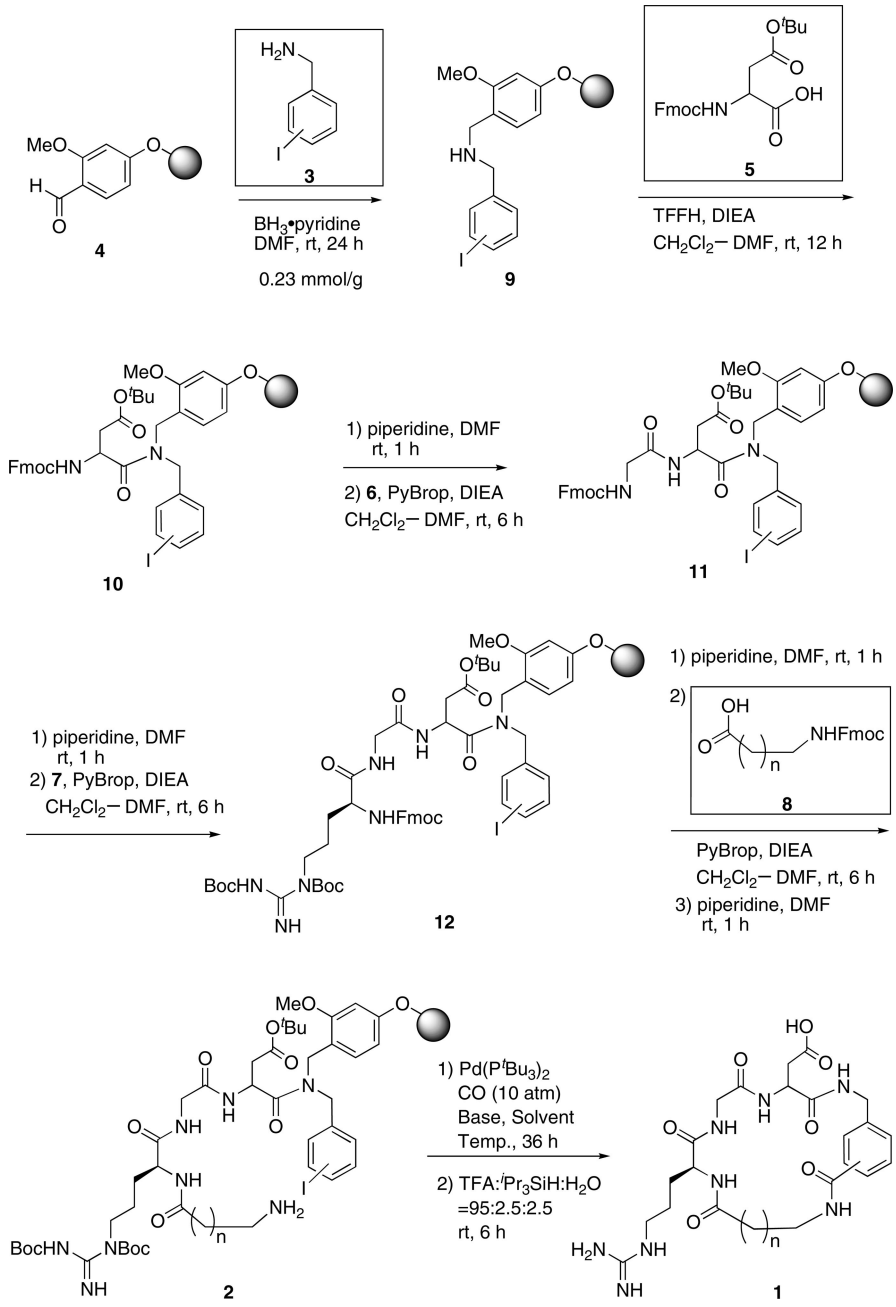


Table 1. Optimization of Palladium-Catalyzed Carbonylative Macrocyclization of **2**{*2,1,4*} on a Polymer-Support

entry	base	solvent	temp (°C)	purity of **1a**[a] (%)
1	MS4Å (100 mg/mL)	THF	40	16
2	MS4Å (100 mg/mL)	THF	50	21
3	MS4Å (100 mg/mL)	THF	reflux	18
4	MS4Å (50 mg/mL)	THF	50	16
5	MS4Å (10 mg/mL)	THF	50	73 (43)[b]
6	MS4Å (10 mg/mL)	DMF	50	49
7	NEt_3−DMAP	THF	50	48
8	NEt_3−DMAP	DMF	50	41
9	Ag_2CO_3	THF	50	38

[a] Crude product was analyzed by reversed-phase HPLC (C18). The purity was determined with peak area detected by ELSD. [b] Isolated yield in 10 steps from **9**{*2*}.

led to the isolation of pure 24-member cyclic RGD model analogues **1** (0.2−11.3 mg) in 2−92% overall yield after 11 steps from **4** (Table 2). These results suggest that the palladium-catalyzed carbonylative macrocyclization on polymer-support efficiently proceeded in all the precursors. Especially, the substrates with *m*-substituents were converted to the corresponding cyclic RGD models in moderate to good yields (entries 9−16). Surprisingly, palladium-catalyzed

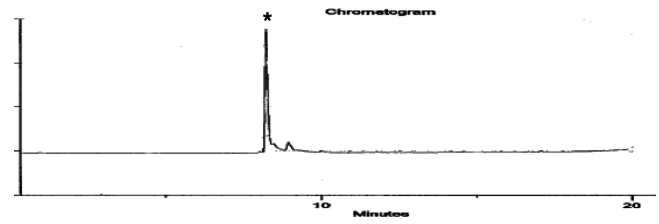


Figure 2. HPLC analysis (ELSD) of crude **1**{*2*, *1*, *4*} (entry 5) After the 10-step solid-phase synthesis from **9**{*2*}. Column: GL Sciences Inc. Inertsil-ODS-3.3 μm (4.6 × 75 mm). Linear gradient: 0−100% over 20 min. CH_3CN in H_2O (0.1% HCOOH). Flow rate: 1.0 mL/min. An asterisk indicates a peak of the desired product **1**{*2*, *1*, *4*}.

Table 2. Combinatorial Library of Cyclic RGD Model Derivatives **1** Consisting of Synthetic Building Blocks **3**, **5**, **6**, **7**, and **8**

	chemsets				
entry	**3**	**5**	**8**	yield[a] (mg)	overall yield[b] (%)
1	*1*	*1*	*1*	8.9	75
2	*1*	*1*	*2*	9.6	78
3	*1*	*1*	*3*	1.0	8
4	*1*	*1*	*4*	6.1	47
5	*1*	*2*	*1*	2.1	16
6	*1*	*2*	*2*	2.4	20
7	*1*	*2*	*3*	4.2	33
8	*1*	*2*	*4*	2.5	19
9	*2*	*1*	*1*	11.0	92
10	*2*	*1*	*2*	11.3	92
11	*2*	*1*	3	5.1	41
12	*2*	*1*	*4*	5.4	43
13	*2*	*2*	*1*	2.4	20
14	*2*	*2*	*2*	4.6	38
15	*2*	*2*	*3*	8.6	76
16	*2*	*2*	*4*	7.4	57
17	*3*	*1*	*1*	4.4	37
18	*3*	*1*	*2*	4.4	36
19	*3*	*1*	*3*	1.8	14
20	*3*	*1*	*4*	8.0	62
21	*3*	*2*	*1*	2.9	24
22	*3*	*2*	*2*	1.0	8
23	*3*	*2*	*3*	0.2	2
24	*3*	*2*	*4*	1.1	9

[a] Isolation by preparative HPLC (C18). [b] Overall yield after 11-step solid-phase synthesis from **4** (100 mg resin, 23 μmol).

carbonylative macrocyclization of the substrates with *p*-substituents also provided the corresponding cyclic RGD models in moderate to low yields, even though it seems to be difficult to construct the ring structure because of the rodlike shape of the *p*-(aminomethyl)benzoyl group (entries 17−24). The stereochemistry of the asparagine unit **5**{*1*} and arginine **7** is related to efficient cyclization. In most cases, the cyclization of **5**{*1*}-containing precursors gave better yields than **5**{*2*}-containing ones (i.e., entry 1 vs entry 5, entry 2 vs entry 6, etc.). It is conceivable that **5**{*1*}-containing precursors have turn conformation as a native RGD sequence, and it would take favorable conformation in the macrocyclization. The yields of the cyclization have no relation with the length of the methylene unit in **8**.

Conclusion

We have developed an efficient method for the construction of a combinatorial library of cyclic RGD models built up with assembly of the RGD sequences consisting of different stereochemistry and the framework of various shapes made up of the (aminomethyl)benzoyl groups substituted with the ortho, meta, and para positions and ω-amino acid with the different number of methylene unit. The attachment of the amino group in block **3** to a polymer-support was performed using reductive amination. After sequential amidation of the five synthetic building blocks **3**, **5**, **6**, **7**, and **8**, the palladium-catalyzed carbonylative macrolactamization was performed on the polymer-support. Cleavage from the polymer-support and concomitant deprotection of the Boc and ^{t}Bu ester afforded 24-membered cyclic RGD models **1** by REC chemistry using a split-and-pool method. This method will contribute to synthesize various conformationally restricted peptide sequences in the application to the drug discovery and construction of chemical probes used in the field of chemical biology.

Experimental Section

General Procedure. NMR spectra were obtained a JEOL Model ECP-400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) instrument in the indicated solvent. Chemical shifts are reported in parts per million (ppm) relative to the signal (0.00 ppm) for internal tetramethylsilane for solutions in $CDCl_3$. ^{1}H NMR spectral date are reported as follows: $CDCl_3$ (7.26 ppm), CD_3OD (3.30 ppm), DMSO-d^6 (2.50 ppm). ^{13}C NMR spectral data are reported as follows: $CDCl_3$ (77.0 ppm), CD_3OD (49.3 ppm), or DMSO-d_6 (39.5 ppm). Multiplicites are reported by using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, J = coupling constants in hertz. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. Only the strongest or structurally important absorption is reported as the IR date given in cm^{-1}. Optical rotations were measured with a JASCO P-1020 polarimeter. Synthetic compounds were detected by thin-layer chromatography on 0.2 mm E. Merck silica gel plates (60F-254) with UV light, visualized by 10% ethanolic phosphomolybdic acid, *p*-anisaldehyde solution, or 0.5% ninhydrin *n*-butanol solution. Column chromatography was performed using silica gel (Merck). ESI-TOF mass spectra were measured with Waters LCT Preimer XE. Microreactor Sorting System was performed on IRORI Accutag-100 Combinatorial Chemistry System using IRORI Macrokan reactor and radio frequency tag. Reverse-phase high performance liquid chromatography (HPLC) for analysis was performed on Hewlett-Packard HP-1100 series system with a linear gradient: 0−100% over 10 min and then 100% over 2 min CH_3CN in H_2O (0.1% HCOOH) [flow rate 1.0 mL/min, column GL Sciences Inc. Inertsil-ODS-3.3 μm, 4.6 × 75 mm]. Peak areas were integrated with UV(214 nm) and or SHIMADZU ELSD-LT evaporative light-scattering detector. Preparative HPLC was performed on Gilson 506C system with a linear gradient of 10% of B (0−5 min), 10−100% of B (5−30 min), 100% of B (30−35 min) using 0.1% HCOOH in H_2O as solvent A, 0.1% HCOOH in CH_3CN as solvent B (10.0 mL/min) [columns GL Sciences Inc. Inertsil-ODS-3.3 μm, 20.0 × 80 mm]. Peak areas were integrated with 214 nm, 254 nm, or SHIMADZU ELSD-LT evaporative light-scattering detector.

Polymer-Supported Aldehyde 4. To a suspension of Argopore-NH_2 (Loading: 0.75 mmol/g) in CH_2Cl_2−DMF (9:1) was added 10-(4-formyl-3-methoxyphenoxy)decanoic acid (0.3 M), undecanoic acid (0.7 M), DIC (1.5 M), and HOBt (1.5 M) at room temperature. After it was shaken at room temperature for 48 h, the mixture was filtered. The resin was washed consecutively with DMF (5 min × 3), methanol (5 min × 3), and CH_2Cl_2 (5 min × 3) and dried in vacuo to afford polymer-supported aldehyde **4**. IR (solid): 3321, 3058, 3026, 2923, 2855, 1677, 1602, 1510, 1493, 1452, 1370, 1262, 1206, 1115, 992, 828, 793, 700 cm^{-1}.

Loading of *m*-Iodobenzylamine 3{*2*} to Polymer-Supported Aldehyde 4 Using Reductive *N*-Alkylation. To a suspension of the polymer-supported aldehyde **4** in DMF was added *m*-iodobenzylamine hydrochloride **3**{*2*} (1.0 M)

and BH_3−pyridine (1.0 M) at room temperature. After it was shaken at room temperature for 24 h, the mixture was filtered. The resin was washed consecutively with DMF (5 min × 3), methanol (5 min × 3), and CH_2Cl_2 (5 min × 3) and dried in vacuo to afford polymer-supported iodobenzylamine **9**{*2*}. IR (solid): 3022, 2922, 1664, 1604, 1509, 1493, 1453, 771, 700 (cm^{-1}).

General Procedure for Acid Cleavage from the Polymer Support. The resins were treated with trifluoroacetic acid–triisopropylsilane−water (95:2.5:2.5) at room temperature. After it was shaken at room temperature for 6 h, the mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel column.

General Procedure for the Coupling of an Fmoc-Protected Amino Acid with the Polymer-Supported Amine. To a suspension of polymer-supported amine in CH_2Cl_2−DMF (9:1) was added Fmoc-protected amino acid (0.5 M), Condensation agent (0.5 M) and DIEA (0.5 M). After it was shaken at room temperature, the mixture was filtered. The resin was washed consecutively with DMF (5 min × 3), methanol (5 min × 3), and CH_2Cl_2 (5 min × 3) and dried in vacuo to afford the polymer-supported Fmoc-protected iodobenzylamine derivative.

General Procedure for Removal of the Fmoc Group on the Polymer Support. To a suspension of polymer-supported Fmoc-protected iodobenzylamine derivatives in DMF was added piperidine (20% piperidine in DMF) at room temperature. After it was shaken at room temperature for 1 h, the mixture was filtered. The resin was washed consecutively with DMF (5 min × 3), methanol (5 min × 3), and dichloromethane (5 min × 3) and dried in vacuo.

Acid Cleavage of Polymer-Supported 9{*2*}. To a suspension of polymer-supported *m*-iodobenzylamine **9**{*2*} in CH_2Cl_2 was added acetyl chloride (0.5 M) and DIEA (1.5 M) at room temperature. After it was shaken at room temperature for 6 h, the mixture was filtered. The resin was washed consecutively with DMF (5 min × 3), methanol (5 min × 3), and CH_2Cl_2 (5 min × 3) and dried in vacuo to afford polymer-supported *N*-acetyl-*m*-iodobenzylamine. Acid cleavage was carried out according to the general procedure. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 1H, aromatic), 7.60 (d, 1H, J = 7.8 Hz, aromatic), 7.24 (d, 1H, J = 7.8 Hz, aromatic), 7.06 (dd, 1H, J = 7.8, 7.8 Hz, aromatic), 5.90 (s, 1H, NH), 4.36 (d, 2H, J = 5.9 Hz, CH_2), 2.03 (s, 3H, Ac). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 140.7, 136.6, 136.6, 130.4, 127.0, 94.5, 42.9, 23.2; IR (solid) 3414, 2926, 2094, 1734, 1608, 1494, 1452, 1052, 824 (cm^{-1}).

Acid Cleavage of Polymer-Supported 10{*2, 1*}. $[\alpha]_D^{30}$: +1.83 (*c* 0.52, $CHCl_3$/CH_3OH = 9: 1). ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD = 9: 1): δ 7.76 (d, 1H, J = 7.3 Hz, aromatic), 7.75 (d, 1H, J = 7.3 Hz, aromatic), 7.59−7.57 (m, 4H, aromatic), 7.39 (d, 1H, J = 7.3 Hz, aromaitc), 7.37 (d, 1H, J = 7.3 Hz, aromatic), 7.31−7.28 (m, 2H, aromatic), 7.21 (d, 1H, J = 7.3 Hz, aromatic), 7.03 (dd, 1H, J = 7.3, 7.3 Hz, aromatic), 4.60−4.51 (m, 1H, CH), 4.45 (d, 2H, J = 6.4 Hz, CH_2O), 4.39 (d, 1H, J = 16.6 Hz, CH_2N), 4.32 (d, 1H, J = 16.6 Hz, CH_2N), 4.20 (t, 1H, J = 6.4 Hz, CH), 2.97−2.92 (m, 1H, CH_2CO), 2.74 (dd, 1H, J = 5.8, 16.1 Hz, CH_2CO). ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD = 9: 1): δ 173.3, 171.5, 156.4, 143.5, 141.2, 140.1, 136.3, 136.2, 130.2, 127.6, 127.0, 126.5, 124.8, 119.9, 94.2, 70.0, 51.0, 47.0, 42.6, 42.5. IR (solid): 3294, 3068, 2459, 1733, 1693, 1606, 1418, 1261, 1049, 757, 739 (cm^{-1}).

Acid Cleavage of Polymer-Supported 11{*2, 1*}. $[\alpha]_D^{25}$: −15.6 (*c* 2.53, DMSO). ^{1}H NMR (400 MHz, DMSO-d^6): δ 7.77 (d, 2H, J = 7.8 Hz, aromatic), 7.57 (d, 2H, J = 7.8 Hz, aromatic), 7.49 (d, 1H, J = 7.8 Hz, aromatic), 7.42 (s, 1H, aromatic), 7.40 (dd, 2H, J = 7.8, 7.8 Hz, aromatic), 7.31 (dd, 2H, J = 7.8, 7.8 Hz, aromatic), 7.20 (d, 1H, J = 7.8 Hz, aromatic), 6.96 (dd, 1H, J = 7.8, 7.8 Hz, aromatic), 4.84 (dd, 1H, J = 5.4, 5.9 Hz), 4.40−4.17 (m, 5H), 3.83 (d, 1H, J = 16.6 Hz), 3.77 (d, 1H, J = 16.6 Hz), 2.90 (dd, 1H, J = 5.9, 17.1 Hz), 2.79 (dd, 1H, J = 5.4, 17.1 Hz). ^{13}C NMR (100 MHz, DMSO-d^6): δ 170.8, 170.2, 170.1, 157.4, 143.4, 141.0, 140.1, 136.0, 136.0, 129.9, 127.5, 126.8, 126.2, 124.7, 119.6, 93.9, 67.0, 49.3, 46.7, 44.0, 42.4, 42.2. IR(solid): 3291, 3065, 2923, 1708, 1688, 1642, 1535, 1271, 1180, 738 (cm^{-1}).

Acid Cleavage of Polymer-Supported 12{*2, 1*}. $[\alpha]_D^{24}$: −1.70 (*c* 1.47, DMSO). ^{1}H NMR (400 MHz, DMSO-d^6): δ 9.55−9.30 (m, 1H, NH), 8.62 (m, 2H, NH), 7.88 (dd, 3H, J = 7.3 Hz), 7.72 (dd, 2H, J = 7.3, 7.8 Hz, aromatic), 7.61 (s, 1H, aromatic), 7.55 (dd, 2H, J = 7.3, 7.8 Hz), 7.41 (dd, 2H, J = 7.3, 7.8 Hz, aromatic), 7.32 (dd, 2H, J = 7.3, 7.8 Hz, aromatic), 7.26 (d, 1H, J = 7.3 Hz, aromatic), 7.05 (dd, 1H, J = 7.3, 7.8 Hz, aromatic), 4.45−4.38 (m, 1H), 4.34−4.15 (m, 5H), 4.06−4.01 (m, 1H), 3.85 (dd, 1H, J = 4.9, 16.6 Hz), 3.63 (dd, 1H, J = 4.4, 16.6 Hz), 3.18−3.14 (m, 1H), 3.03−3.00 (m, 1H), 2.63 (dd, 1H, J = 4.4, 16.6 Hz), 2.41 (dd, 1H, J = 4.4, 16.6 Hz), 1.99−1.90 (m, 1H), 1.57−1.46 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d^6): δ 173.3, 171.0, 168.5, 157.2, 156.0, 143.8, 143.7, 142.1, 140.7, 135.4, 135.2, 130.2, 127.6, 127.0, 126.1, 125.2, 120.1, 94.5, 65.6, 53.9, 49.7, 46.6, 42.7, 41.4, 37.0, 29.2, 24.8, 18.5. IR(solid): 3275, 2969, 1642, 1527, 1260, 758, 739 (cm^{-1}).

Acid Cleavage of Polymer-Supported 2{*2, 1, 4*}. $[\alpha]_D^{25}$: −2.01 (*c* 1.96, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD): δ 7.65 (s, 1H, aromatic), 7.56 (d, 1H, J = 7.8 Hz, aromatic), 7.28 (d, 1H, J = 7.8 Hz, aromatic), 7.05 (dd, 1H, J = 7.8, 7.8 Hz, aromatic), 4.73−4.69 (m, 1H), 4.32−4.23 (m, 1H), 4.31 (d, 1H, J = 15.6 Hz), 4.27 (d, 1H, J = 15.6 Hz), 3.92 (d, 1H, J = 17.1 Hz), 3.82 (d, 1H, J = 17.1 Hz), 3.20−3.10 (m, 2H), 2.95−2.88 (m, 2H), 2.81 (dd, 1H, J = 5.9, 16.6 Hz), 2.74 (dd, 1H, J = 4.4, 16.6 Hz), 2.35−2.29 (m, 2H), 1.91−1.60 (m, 8H). ^{13}C NMR (100 MHz, CD_3OD): δ 176.4, 175.9, 175.6, 173.5, 171.5, 158.7, 142.4, 137.3, 137.3, 131.3, 127.7, 94.9, 55.0, 51.9, 44.1, 43.4, 41.9, 40.4, 38.1, 35.5, 29.9, 28.0, 26.1, 23.1. IR (solid): 3251, 2918, 2849, 1633, 1537, 1177, 1128, 1052, 834, 798, 765, 719 (cm^{-1}).

Carbonylative Macrolactamization of Polymer-Supported Cyclization Precoursor 2{*2, 1, 4*}. In a glass vessel, to a suspension of polymer-supported cyclization precursor **2**{*2, 1, 4*} in THF was added $Pd(P^tBu_3)_2$ (0.001 M) and MS4Å (10 mg/mL) under Ar. The vessel was placed in an autoclave, which was purged with carbon monoxide three times before application of a pressure (10 atm). After it was stirred at 50 °C for 36 h, the mixture was filtered. The resin

was washed consecutively with DMF (5 min × 3), methanol (5 min × 3), and dichloromethane (5 min × 3) and dried in vacuo.

1{*2*, *1*, *4*} (Entry 12 in Table 2). $[\alpha]_D^{19}$: +50.0 (*c* 0.14, DMSO). ^{1}H NMR (400 MHz, DMSO-d^6): δ 10.23−10.17 (m, 1H, NH), 8.97 (dd, 1H, J = 4.9, 5.4 Hz, NH), 8.96−8.88 (m, 1H, NH), 8.69 (d, 1H, J = 8.8 Hz, NH), 8.55 (t, 1H, J = 5.4 Hz, NH), 8.38 (brs, 1H, NH), 8.05 (s, 1H, aromatic), 7.78 (d, 1H, J = 6.8 Hz, aromatic), 7.65 (d, 1H, J = 7.8 Hz, NH), 7.39 (d, 1H, J = 7.3 Hz, aromatic), 7.38 (dd, 1H, J = 6.8, 7.3 Hz, aromatic), 7.00 (dd, 1H, J = 4.4, 4.9 Hz, NH), 4.39−4.22 (m, 2H), 4.34 (dd, 1H, J = 5.8, 14.2 Hz), 4.24 (dd, 1H, J = 5.8, 14.2 Hz), 3.60 (d, 2H, J = 4.9 Hz), 3.38−3.26 (m, 2H), 3.16−3.10 (m, 1H), 2.76−2.68 (m, 1H), 2.74 (dd, 1H, J = 2.4, 16.1 Hz), 2.33−2.25 (m, 1H), 2.17−2.11 (m, 1H), 2.13 (dd, 1H, J = 4.9, 16.1 Hz), 2.02−1.93 (m, 1H), 1.60−1.23 (m, 7H). ^{13}C NMR (100 MHz, DMSO-d^6): δ 175.7, 174.8, 173.3, 170.9, 168.0, 166.5, 157.5, 138.3, 134.5, 131.6, 128.5, 126.3, 125.5, 51.8, 49.5, 43.1, 41.0, 37.5, 37.4, 34.7, 30.9, 27.5, 24.6, 23.3, 21.2. IR(solid): 3423, 2516, 2255, 2128, 1768, 1657, 1394, 1237, 1051, 1026, 1005, 826, 764 (cm^{-1}). Yield: 5.4 mg. HRMS (ESI-TOF) Calcd for $[C_{25}H_{36}N_8O_7+H]^+$: 561.2785; found 561.2777. HPLC analysis: retention time 4.90 min.

Combinatorial Synthesis of 24-Member RGD Model Cyclic Peptides

General Procedure for Preparation of Polymer-Supported Iodobenzylamine. Each MacroKans reactor contained 100 mg of polymer-supported aldehyde **4** (loading 0.23 mmol/g) and a radiofrequency tag. The 24 reactors were encoded and distributed into three SCHOTT bottles (vessel 1, vessel 2, vessel 3; 8 reactors in each). To each SCHOTT bottles containing 8 reactors was added iodobenzylamine (1.0 M), BH_3−pyridine (1.0 M), and DMF at room temperature under Ar. After it was shaken at room temperature for 24 h, the mixture was filtered. All reactors were pooled together, washed consecutively with DMF (5 min × 3), methanol (5 min × 3), and CH_2Cl_2 (5 min × 3), and dried in vacuo.

General Procedure for Amidation of Fmoc-Asp(O^{t}Bu)-OH. The above 24 reactors were sorted and distributed into two SCHOTT bottles (vessel 1, vessel 2; 12 reactors in each). To each SCHOTT bottle containing 12 microreactors was added Fmoc-Asp(O^{t}Bu)-OH (0.5 M), TFFH (0.5 M), and DIEA (0.5 M) in CH_2Cl_2–DMF (9: 1) at room temperature under Ar. After it was shaken at room temperature for 12 h under Ar, the mixture was filtered. All reactors were pooled together, washed consecutively with DMF (5 min × 3), methanol (5 min × 3), and CH_2Cl_2 (5 min × 3), and dried in vacuo.

General Procedure for Deprotection of Fmoc Group of Polymer-Supported Fmoc-Protected Iodobenzylamine Derivative. To a suspension of 24 MacroKans reactors in DMF was added piperidine (20% piperidine in DMF) at room temperature. After it was shaken at room temperature for 1 h, the mixture was filtered. All reactors were washed consecutively with DMF (5 min × 3), methanol (5 min × 3), and CH_2Cl_2 (5 min × 3) and dried in vacuo.

General Procedure for Amidation of Fmoc-Gly-OH. To a suspension of 24 MacroKans reactors in CH_2Cl_2−DMF (9: 1) were added Fmoc-Gly-OH (0.5 M), PyBrop (0.5 M), and DIEA (0.5 M) at room temperature under Ar. After it was shaken at room temperature for 6 h under Ar, the mixture was filtered. All reactors were washed consecutively with DMF (5 min × 3), methanol (5 min × 3), and CH_2Cl_2 (5 min × 3) and dried in vacuo.

General Procedure for Amidation of Fmoc-Arg(Boc)$_2$-OH. To a suspension of 24 MacroKans reactors were added Fmoc-Arg(Boc)$_2$-OH (0.5 M), PyBrop (0.5 M), and DIEA (0.5 M) in CH_2Cl_2−DMF (9: 1) at room temperature under Ar. After it was shaken at room temperature for 6 h under Ar, the mixture was filtered. All reactors were pooled together, washed consecutively with DMF (5 min × 3), methanol (5 min × 3), and CH_2Cl_2 (5 min × 3), and dried in vacuo.

General Procedure for Amidation of Fmoc-Protected *ω*-Amino Acids. The above 24 reactors were sorted and distributed into four SCHOTT bottles (vessel 1, vessel 2, vessel 3, vessel 4; 6 reactors in each). To each SCHOTT bottles containing 6 reactors were added Fmoc-protected ω-amino acids (0.5 M), PyBrop (0.5 M), and DIEA (0.5 M) in CH_2Cl_2−DMF (9: 1) at room temperature under Ar. After it was shaken at room temperature for 6 h, the mixture was filtered. All reactors were pooled together, washed consecutively with DMF (5 min × 3), methanol (5 min × 3), and CH_2Cl_2 (5 min × 3), and dried in vacuo.

General Procedure for Carbonylative Macrolactamization. In a glass vessel, to a suspension of 24 MacroKans reactors in THF were added Pd(P^{t}Bu$_3$)$_2$ (0.001 M) and MS4Å (10 mg/mL) under Ar. The vessel was placed in an autoclave, which was purged with carbon monoxide three times before application of pressure (10 atm). After it was stirred for 36 h at 50 °C, the reaction mixture was filtered. All reactors were washed consecutively with DMF (5 min × 3), methanol (5 min × 3), and CH_2Cl_2 (5 min × 3) and dried in vacuo.

General Procedure for Cleavage and Deprotection. The 24 MacroKans reactors were sorted by means of radiofrequency signals and treated with trifluoroacetic acid−triisopropylsilane−water (95:2.5:2.5, 2 mL) at room temperature for 6 h. Each of the cleavage mixtures was concentrated in vacuo. The residue was purified by reversed-phase HPLC.

Selected Spectral Data

1{*1*, *1*, *1*} (Entry 1). Yield: 8.9 mg. HRMS (ESI-TOF) Calcd for $[C_{22}H_{30}N_8O_7+H]^+$: 519.2316; found 519.2314. HPLC analysis: retention time 4.72 min.

1{*1*, *1*, *2*} (Entry 2). $[\alpha]_D^{22}$: −9.60 (*c* 0.48, DMSO). ^{1}H NMR (400 MHz, DMSO-d^6): δ 8.67−7.85 (m, 7H, NH), 7.46−7.23 (m, 4H, aromatic), 4.51−4.45 (m, 2H), 4.34−4.13 (m, 2H), 4.06−4.00 (m, 1H), 3.46−3.41 (m, 1H), 3.27−3.17 (m, 3H), 2.86−2.57 (m, 3H), 2.39−2.21 (m, 2H), 1.59−1.40 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d^6): δ 171.6, 171.1, 171.0, 169.4, 169.3, 168.8, 157.5, 137.0, 133.9, 130.3, 128.0, 127.4, 124.6, 52.0, 51.7, 49.9, 43.4, 42.1, 41.1, 36.2, 35.4, 29.1, 25.1. IR (solid): 3420, 2254, 2128, 1661, 1203, 1051, 1026, 1005, 825, 763 (cm^{-1}). Yield: 9.6 mg. HRMS (ESI-

TOF) Calcd for $[C_{23}H_{32}N_8O_7+H]^+$: 533.2472; found 533.2473. HPLC analysis: retention time 4.69 min.

1{*1*, *1*, *3*} (Entry 3). $[\alpha]_D^{22}$: −95.2 (*c* 0.05, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ 8.58−8.52 (m, 1H, NH), 8.23 (d, 2H, *J* = 7.8 Hz, NH), 8.01−7.95 (m, 2H, NH), 7.47−7.31 (m, 2H, aromatic), 7.41 (dd, 1H, *J* = 7.8, 7.8 Hz, aromatic), 7.35 (dd, 1H, *J* = 7.8, 7.8 Hz, aromatic), 4.50−4.45 (m, 1H), 4.31−4.22 (m, 1H), 4.30 (dd, 1H, *J* = 5.8, 14.2 Hz), 4.24 (dd, 1H, *J* = 5.8, 14.2 Hz), 3.96−3.87 (m, 1H), 3.63−3.56 (m, 1H), 3.38−3.30 (m, 2H), 3.15−3.06 (m, 2H), 2.77−2.65 (m, 1H), 2.55−2.45(m, 1H), 2.39−2.32 (m, 1H), 2.19−2.11 (m, 1H), 1.92−1.49 (m, 6H). ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ 172.6, 172.6, 171.8, 169.8, 169.8, 169.1, 156.9, 136.5, 130.5, 130.1, 128.0, 127.9, 127.5, 49.8, 42.5, 42.0, 40.8, 40.6, 38.8, 37.8, 35.5, 32.2, 25.6, 25.4. IR(solid): 3415, 3020, 2255, 2129, 1661, 1216, 1051, 1005, 1026, 826, 763 (cm^{-1}). Yield: 1.0 mg. HRMS (ESI-TOF) Calcd for $[C_{24}H_{34}N_8O_7+H]^+$: 547.2629; found 547.2623. HPLC analysis: retention time 4.76 min.

1{*1*, *1*, *4*} (Entry 4). $[\alpha]_D^{19}$: −15.7 (*c* 0.31, DMSO). ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ 8.53−7.82 (m, 4H, NH), 7.37−7.19 (m, 4H, aromatic), 4.62−4.50 (m, 1H), 4.43−4.24 (m, 3H), 3.89−3.83 (m, 1H), 3.72−3.57 (m, 1H), 3.15−3.06 (m, 2H), 2.96−2.91 (m, 2H), 2.65−2.50 (m, 2H), 2.32−2.25 (m, 1H), 2.13−2.08 (m, 1H), 1.77−1.44 (m, 8H). ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ 172.8, 172.7, 172.7, 170.6, 168.9, 168.9, 157.1, 139.4, 136.6, 128.3, 127.1, 127.0, 126.7, 52.3, 52.2, 49.8, 44.5, 44.0, 42.3, 34.9, 34.9, 29.9, 28.5, 25.1, 22.8. IR (solid): 3415, 2256, 2129, 1660, 1497, 1050, 1026, 1004, 826 (cm^{-1}). Yield: 6.1 mg. HRMS (ESI-TOF) Calcd for $[C_{25}H_{36}N_8O_7+H]^+$: 561.2785; found 561.2778. HPLC analysis: retention time 4.83 min.

1{*1*, *2*, *1*} (Entry 5). Yield: 2.1 mg. HRMS (ESI-TOF) Calcd for $[C_{22}H_{30}N_8O_7+H]^+$: 519.2316; found 519.2311. HPLC analysis: retention time 4.66 min.

1{*1*, *2*, *2*} (Entry 6). Yield: 2.4 mg. HRMS (ESI-TOF) Calcd for $[C_{23}H_{32}N_8O_7+H]^+$: 533.2472; found 533.2466. HPLC analysis: retention time 4.65 min.

1{*1*, *2*, *3*} (Entry 7). $[\alpha]_D^{17}$: +7.44 (*c* 0.22, DMSO). ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ 8.57−8.52 (m, 2H, NH), 8.45−8.38 (m, 2H, NH), 8.31−8.19 (m, 3H, NH), 7.79−7.75 (m, 1H, NH), 7.45−7.19 (m, 4H, aromatic), 4.45−4.37 (m, 1H), 4.40 (dd, 1H, *J* = 7.3, 14.2 Hz), 4.22−4.15 (m, 1H), 4.08 (dd, 1H, *J* = 4.4, 14.2 Hz), 3.85 (dd, 1H, *J* = 6.3, 16.6 Hz), 3.67 (dd, 1H, *J* = 4.0, 16.6 Hz), 3.42−3.18 (m, 2H), 3.09−3.03 (m, 2H), 2.50−2.39 (m, 3H), 2.21−2.15 (m, 1H), 1.88−1.44 (m, 6H). ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ 173.0, 172.9, 171.9, 170.7, 169.8, 168.7, 157.4, 137.1, 136.4, 130.5, 128.2, 127.4, 126.8, 53.0, 42.4, 41.6, 40.6, 38.9, 37.9, 36.7, 32.1, 27.9, 25.2, 23.6. IR (solid): 3413, 2256, 2130, 1659, 1261, 1050, 1025, 1001, 827, 764 (cm^{-1}). Yield: 4.2 mg. HRMS (ESI-TOF) Calcd for $[C_{24}H_{34}N_8O_7+H]^+$: 547.2629; found 547.2635. HPLC analysis: retention time 4.76 min.

1{*1*, *2*, *4*} (Entry 8). $[\alpha]_D^{22}$ +17.4 (*c* 0.39, DMSO). ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ 8.50−8.46 (m, 1H, NH), 8.33−8.27 (m, 1H, NH), 8.23−8.14 (m, 4H, NH), 7.43−7.20 (m, 4H, aromatic), 4.56−4.49 (m, 1H), 4.40 (dd, 1H, *J* = 6.4, 15.2 Hz), 4.19−4.12 (m, 1H), 4.15 (dd, 1H, *J* = 5.4, 15.2 Hz), 3.68 (d, 2H, *J* = 3.9 Hz), 3.34−3.28 (m, 1H), 3.24−3.16 (m, 1H), 3.09−3.03 (m, 2H), 2.61 (dd, 1H, *J* = 4.9, 16.6 Hz), 2.52−2.47 (m, 1H), 2.31−2.25 (m, 1H), 2.16−2.06 (m, 1H), 1.78−1.44 (m, 8H). ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ 173.2, 173.1, 172.4, 170.8, 169.0, 168.8, 157.3, 137.0, 136.4, 129.7, 129.2, 127.5, 127.1, 56.2, 52.6, 49.9, 42.8, 41.0, 38.7, 36.9, 34.7, 31.5, 26.9, 24.9, 22.6. IR (solid): 3415, 3020, 2255, 2129, 1659, 1547, 1216, 1051, 1026, 1005, 825, 763 (cm^{-1}). Yield: 2.5 mg. HRMS (ESI-TOF) Calcd for $[C_{25}H_{36}N_8O_7 + H]^+$: 561.2785, found 561.2788. HPLC analysis: retention time 4.83 min.

1{*2*, *1*, *1*} (Entry 9). $[\alpha]_D^{22}$: +39.8 (*c* 0.65, DMSO). ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ 9.25−9.19 (m, 1H, NH), 9.15−9.11 (m, 1H, NH), 9.00 (d, 1H, *J* = 8.8 Hz, NH), 8.57−8.53 (m, 1H, NH), 8.25 (d, 1H, *J* = 8.3 Hz, NH), 8.15−8.11 (m, 1H, NH), 7.88 (s, 1H, aromatic), 7.60 (d, 1H, *J* = 5.8 Hz, aromatic), 7.39−7.23 (m, 2H, aromatic), 4.64 (dd, 1H, *J* = 7.8, 16.6 Hz), 4.44−4.38 (m, 2H), 4.18 (dd, 1H, *J* = 6.8, 16.6 Hz), 4.06 (dd, 1H, *J* = 3.9, 16.6 Hz), 4.00 (dd, 1H, *J* = 7.3, 16.6 Hz), 3.73 (dd, 1H, *J* = 2.9, 16.6 Hz), 3.55−3.51 (m, 1H), 3.08−2.94 (m, 2H), 2.57 (dd, 1H, *J* = 2.4, 16.6 Hz), 2.05 (dd, 1H, *J* = 5.4, 16.6 Hz), 1.99−1.88 (m, 1H), 1.60−1.35 (m, 3H). ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ 175.6, 172.1, 171.6, 169.7, 168.7, 168.5, 157.5, 139.9, 134.8, 129.7, 128.1, 125.6, 125.1, 52.2, 49.4, 44.3, 43.3, 41.4, 40.9, 37.9, 28.3, 24.2. IR (solid): 3425, 3020, 2887, 2401, 2252, 2126, 1718, 1499, 1216, 1027, 1006, 759 (cm^{-1}). Yield: 11.0 mg. HRMS (ESI-TOF) Calcd for $[C_{22}H_{30}N_8O_7 + H]^+$: 519.2316; found 519.2315. HPLC analysis: retention time 4.66 min.

1{*2*, *1*, *2*} (Entry 10). $[\alpha]_D^{21}$: +86.8 (*c* 0.66, DMSO). ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ 10.33−10.12 (m, 2H, NH), 9.16−9.05 (m, 2H, NH), 8.54 (d, 1H, *J* = 8.8 Hz, NH), 8.44−8.41 (m, 1H, NH), 8.30−8.20 (m, 1H, NH), 8.01 (d, 1H, *J* = 6.8 Hz, aromatic), 7.71 (d, 1H, *J* = 6.8 Hz, aromatic), 7.43 (s, 1H, aromatic), 7.40 (dd, 1H, *J* = 6.8, 6.8 Hz, aromatic), 7.22−7.08 (m, 2H, NH), 4.49 (dd, 1H, *J* = 6.3, 17.1 Hz), 4.34−4.28 (m, 1H), 4.15 (dd, 1H, *J* = 9.8, 17.1 Hz), 4.06−4.00 (m, 1H), 3.70−3.59 (m, 2H), 3.35−3.29 (m, 1H), 3.13−3.04 (m, 1H), 2.89−2.73 (m, 3H), 2.50−2.42 (m, 1H), 2.24−2.14 (m, 2H), 1.68−1.47 (m, 4H). ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ 175.9, 172.5, 171.0, 168.1, 166.6, 162.5, 157.6, 137.4, 135.3, 131.5, 128.8, 127.5, 127.3, 62.2, 53.9, 49.4, 43.7, 41.2, 37.5, 36.9, 36.2, 31.0, 25.3. IR (solid): 3425, 2958, 2933, 2253, 2126, 1660, 1547, 1391, 1259, 1053, 1027, 1007, 825, 762 (cm^{-1}). Yield: 11.3 mg. HRMS (ESI-TOF) Calcd for $[C_{23}H_{32}N_8O_7 + H]^+$: 533.2472; found 533.2480. HPLC analysis: retention time 4.58 min.

1{*2*, *1*, *3*} (Entry 11). $[\alpha]_D^{19}$: +38.7 (*c* 0.28, DMSO). ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ 9.10 (d, 1H, *J* = 6.8 Hz, NH), 8.88−8.82 (m, 1H, NH), 8.69 (t, 1H, *J* = 5.4 Hz, NH), 8.22 (d, 1H, *J* = 6.8 Hz, NH), 7.95 (s, 1H, aromatic), 7.76−7.74 (m, 1H, aromatic), 7.41−7.35 (m, 1H, NH), 7.37 (d, 1H, *J* = 7.8 Hz, aromatic), 7.25 (dd, 1H, *J* = 7.8, 7.8 Hz, aromatic), 4.46 (dd, 1H, *J* = 6.9, 16.1 Hz), 4.41−4.37 (m, 1H), 4.25 (dd, 1H, *J* = 5.4, 16.1 Hz), 4.24−4.20 (m, 1H), 3.98 (dd, 1H, *J* = 7.8, 16.6 Hz), 3.56 (dd, 1H, *J* = 3.4, 16.6 Hz), 3.35−3.25 (m, 2H), 3.17−3.12 (m, 1H), 2.89−2.85 (m, 1H), 2.58 (dd, 1H, *J* = 2.9, 16.1 Hz), 2.25 (t, 2H, *J* =

5.4 Hz), 2.15 (dd, 1H, J = 5.4, 16.1 Hz), 1.99−1.93 (m, 1H), 1.85−1.74 (m, 2H), 1.55−1.44 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d^6): δ 172.5, 172.5, 171.2, 171.2, 168.6, 166.6, 157.6, 139.0, 134.4, 130.5, 126.0, 125.8, 125.5, 52.9, 49.5, 43.4, 41.9, 41.3, 37.4, 37.2, 31.4, 30.6, 25.7, 25.0. IR (solid): 3426, 3021, 2934, 2254, 2128, 1771, 1659, 1216, 1052, 1027, 1006, 825, 763 (cm^{-1}). Yield: 5.1 mg. HRMS (ESI-TOF) Calcd for $[C_{24}H_{34}N_8O_7 + H]^+$: 547.2629; found 547.2620. HPLC analysis: retention time 4.83 min.

1{*2, 2, 1*} (Entry 13). $[\alpha]_D^{20}$: −41.9 (*c* 0.12, DMSO). ^{1}H NMR (400 MHz, DMSO-d^6): δ 12.40 (brs, 1H, NH), 8.87 (brs, 1H, NH), 8.54 (d, 1H, J = 7.3 Hz, NH), 8.39 (d, 1H, J = 8.4 Hz, NH), 8.33 (dd, 1H, J = 4.4, 5.4 Hz, NH), 7.76−7.70 (m, 3H), 7.66 (s, 1H, aromatic), 7.63−7.57 (m, 1H, NH), 7.45−7.22 (m, 2H, aromatic), 4.62 (d, 1H, J = 16.1 Hz), 4.55−4.51 (m, 1H), 4.27−4.22 (m, 1H), 4.11 (d, 1H, J = 16.1 Hz), 4.02 (d, 1H, J = 16.6 Hz), 3.89 (d, 1H, J = 15.1 Hz), 3.82 (d, 1H, J = 15.1 Hz), 3.64 (d, 1H, J = 16.6 Hz), 3.12−3.04 (m, 2H), 2.76 (dd, 1H, J = 6.4, 16.6 Hz), 2.54 (dd, 1H, J = 6.8, 16.6 Hz), 1.94−1.85 (m, 1H), 1.58−1.47 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d^6): δ 171.9, 171.7, 170.8, 170.1, 168.9, 168.0, 156.8, 139.8, 133.8, 130.1, 128.1, 125.4, 125.3, 52.8, 50.4, 44.3, 41.8, 41.2, 40.5, 35.6, 27.4, 25.5. IR (solid): 3419, 2255, 2129, 1769,1661, 1494, 1501, 1379, 1026, 1005, 825, 764 (cm^{-1}). Yield: 2.4 mg. HRMS (ESI-TOF) Calcd for $[C_{22}H_{30}N_8O_7 + H]^+$: 519.2316; found 519.2316. HPLC analysis: retention time 4.69 min.

1{*2, 2, 2*} (Entry 14). $[\alpha]_D^{19}$: −37.1 (*c* 0.23, DMSO). ^{1}H NMR (400 MHz, DMSO-d^6): δ 8.69−8.63 (m, 1H, NH), 8.37−8.33 (m, 1H, NH), 8.29−8.20 (m, 2H, NH), 7.88−7.85 (m, 1H, NH), 7.73−7.71 (m, 1H, aromatic), 7.69 (s, 1H, aromatic), 7.55−7.51 (m, 1H, NH), 7.41−7.36 (m, 2H, aromatic), 7.23−7.21 (m, 1H, NH), 4.49−4.43 (m, 1H), 4.47 (dd, 1H, J = 2.9, 16.1 Hz), 4.23 (dd, 1H, J = 4.9, 16.1 Hz), 4.16−4.14 (m, 1H), 3.87−3.81 (m, 2H), 3.65−3.57 (m, 2Hi), 3.10−3.05 (m, 2H), 2.76 (dd, 1H, J = 4.4, 17.6 Hz), 2.56 (m, 1H, J = 4.4, 17.6 Hz), 2.44−2.39 (m, 2H), 1.80−1.45 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d^6): δ 172.1 × 2, 172.0, 170.7, 168.2, 168.5, 158.1, 139.5, 135.0, 129.9, 128.3, 126.2, 124.0, 52.8, 50.7, 47.4, 37.3, 36.3, 35.6, 29.1, 27.7, 26.0, 25.3. IR(solid): 3417, 2255, 2129, 1661, 1051, 1026, 1005, 825, 746 (cm^{-1}). Yield: 4.6 mg. HRMS (ESI-TOF) Calcd for $[C_{23}H_{32}N_8O_7 + H]^+$ 533.2472; found 533.2476. HPLC analysis: retention time 4.69 min.

1{*2, 2, 3*} (Entry 15). $[\alpha]_D^{20}$: +31.4 (*c* 0.43, DMSO). ^{1}H NMR (400 MHz, DMSO-d^6): δ 8.59−8.51 (m, 2H, NH), 8.25−8.08 (m, 5H, NH), 7.77−7.75 (m, 1H, aromatic), 7.64−7.60 (m, 1H, NH), 7.63 (s, 1H, aromatic), 7.41−7.35 (m, 2H, aromatic), 4.68−4.60 (m, 1H), 4.64 (dd, 1H, J = 8.8, 16.6 Hz), 4.28−4.21 (m, 1H), 4.25 (dd, 1H, J = 8.8, 16.6 Hz), 4.09 (dd, 1H, J = 4.4, 16.6 Hz), 3.77−3.65 (m, 1H), 3.60 (dd, 1H, J = 5.4, 16.6 Hz), 3.09−3.00 (m, 3H), 2.79 (dd, 1H, J = 7.3, 17.1 Hz), 2.54 (dd, 1H, J = 7.3, 17.1 Hz), 2.31−2.24 (m, 1H), 2.13−2.08 (m, 1H), 1.98−1.90 (m, 2H), 1.63−1.44 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d^6): δ 172.3, 171.9, 171.8, 170.6, 169.4, 166.6, 156.9, 139.7, 133.8, 129.8, 127.1, 125.0, 124.6, 52.4, 49.7, 42.3, 41.3, 41.1, 38.4, 37.0, 31.2, 30.6, 25.5, 24.9. IR (solid): 3411, 2256, 2129, 1661, 1203, 1050, 1026, 1004, 826, 762 (cm^{-1}). Yield: 8.6 mg. HRMS (ESI-TOF) Calcd for $[C_{24}H_{34}N_8O_7 + H]^+$: 547.2629; found 547.2624. HPLC analysis: retention time 4.73 min.

1{*2, 2, 4*} (Entry 16). $[\alpha]_D^{19}$: −33.1 (*c* 0.37, DMSO). ^{1}H NMR (400 MHz, DMSO-d^6): δ 9.24−9.16 (m, 1H, NH), 9.05−8.97 (m, 1H, NH), 8.58−8.50 (m, 1H, NH), 8.50 (d, 1H, J = 6.8 Hz, NH), 8.26−8.18 (m, 1H, NH), 8.06−8.00 (m, 1H, NH), 7.75 (s, 1H, aromatic), 7.71−7.68 (m, 1H, aromatic), 7.38−7.30 (m, 2H, aromatic), 4.52 (dd, 1H, J = 4.9, 16.1 Hz), 4.33−4.24 (m, 2H), 4.19 (dd, 1H, J = 2.9, 16.1 Hz), 3.87 (d, 1H, J = 16.1 Hz), 3.58 (d, 1H, J = 16.1 Hz), 3.54−3.46 (m, 1H), 3.11−3.08 (m, 1H), 2.99−2.90 (m, 2H), 2.53−2.49 (m, 1H), 2.48 (dd, 1H, J = 5.6, 16.1 Hz), 2.35 (dd, 1H, J = 3.9, 16.1 Hz), 2.18−2.09 (m, 1H), 1.83−1.77 (m, 1H), 1.66−1.44 (m, 7H). ^{13}C NMR (100 MHz, DMSO-d^6): δ 174.4, 173.3, 172.3, 171.8, 171.8, 166.1, 158.1, 139.8, 134.8, 129.5, 128.2, 126.2, 123.5, 52.3, 51.4, 43.4, 41.5, 40.5, 38.3, 38.2, 34.6, 28.0, 24.6, 23.1, 20.1. IR (solid): 3414, 2886, 2813, 1661, 1051, 1026, 1005, 826, 764 (cm^{-1}). Yield: 7.4 mg. HRMS (ESI-TOF) Calcd for $[C_{25}H_{36}N_8O_7 + H]^+$: 561.2785; found 561.2786. HPLC analysis: retention time 4.87 min.

1{*3, 1, 1*} (Entry 17). $[\alpha]_D^{18}$: +6.74 (*c* 0.44, DMSO). ^{1}H NMR (400 MHz, DMSO-d^6): δ 9.00−8.85 (m, 2H, NH), 8.68−8.50 (m, 3H, NH), 8.30−8.26 (m, 2H, NH), 7.95−7.23 (m, 4H, aromatic), 4.50−3.84 (m, 6H), 3.61−3.38 (m, 2H), 3.08−2.96 (m, 2H), 2.70−2.65 (m, 1H), 2.28−2.24 (m, 1H), 1.98−1.95 (m, 1H), 1.61−1.41 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d^6): δ 175.8, 173.1, 171.4, 169.3, 168.4, 165.1, 157.6, 139.4, 128.9, 128.8, 127.2, 52.0, 50.0, 43.2, 41.0, 37.5, 36.6, 29.9, 25.2, 24.4. IR (solid): 3408, 3020, 2256, 2129, 1661, 1218, 1050, 1026, 1003, 826, 769 (cm^{-1}). Yield: 4.4 mg. HRMS (ESI-TOF) Calcd for $[C_{22}H_{30}N_8O_7 + H]^+$: 519.2316; found 519.2313. HPLC analysis: retention time 4.58 min.

1{*3, 1, 2*} (Entry 18). $[\alpha]_D^{20}$: +6.53 (*c* 0.44, DMSO). ^{1}H NMR (400 MHz, DMSO-d^6, mixture of rotamers): δ 8.71−8.69 (m, 1H, NH), 8.52 (d, 1H, J = 8.3 Hz, NH), 8.39−8.35 (m, 1H, NH), 8.33 (d, 1H, J = 6.8 Hz, NH), 8.27−8.19 (m, 2H, NH), 7.88−7.84 (m, 2H, NH), 7.45 (d, 2H, J = 8.3 Hz, aromatic), 7.16 (d, 2H, J = 8.3 Hz, aromatic), 4.60−4.17 (m, 4H), 3.97−3.91 (m, 0.5H), 3.85−3.79 (m, 0.5H), 3.64−3.35 (m, 3H), 3.17−2.95 (m, 2.5H), 2.74−2.38 (m, 3H), 2.18−2.14 (m, 0.5H), 1.91−1.87 (m, 0.5H), 1.69−1.62 (m, 0.5H), 1.51−1.40 (m, 2.5H). ^{13}C NMR (100 MHz, DMSO-d^6, mixture of rotamers): δ 174.6, 173.2, 173.1, 172.0, 171.3, 171.2, 170.9, 170.7, 169.9, 168.8, 168.7, 167.2, 157.5, 157.0, 142.8, 139.4, 134.0, 128.4, 127.4, 126.7, 118.9, 115.9, 52.3, 51.5, 50.3, 50.0, 42.9, 42.2, 41.6 × 2, 41.4, 40.5, 37.3, 36.1, 35.7, 35.5, 35.4, 32.0, 31.1, 29.5, 24.8 × 2. IR (solid): 3414, 2256, 2129, 1660, 1203, 1050, 1026, 1004, 826, 763 (cm^{-1}). Yield: 4.4 mg. HRMS (ESI-TOF) Calcd for $[C_{23}H_{32}N_8O_7 + H]^+$: 533.2472; found 533.2465. HPLC analysis: retention time 4.66 min.

1{3, 1, 3} (Entry 19). $[\alpha]_D^{19}$: −2.03 (*c* 0.18, DMSO). ^{1}H NMR (400 MHz, DMSO-d^6): δ 8.71−8.62 (m, 1H, NH), 8.55−8.47 (m, 2H, NH), 8.16−8.13 (m, 1H, NH), 8.05−8.01 (m, 1H, NH), 7.83 (d, 1H, J = 8.3 Hz, aromatic), 7.60 (d,

1H, J = 7.8 Hz, aromatic), 7.34 (d, 1H, J = 8.3 Hz, aromatic), 7.24 (d, 1H, J = 7.8 Hz, aromatic), 4.61−4.58 (m, 1H), 4.48−4.42 (m, 1H), 4.44 (dd, 1H, J = 6.4, 16.1 Hz), 4.11 (dd, 1H, J = 5.4, 16.1 Hz), 3.85−3.78 (m, 1H), 3.62−3.57 (m, 1H), 3.51−3.47 (m, 2H), 3.00−2.96 (m, 2H), 2.72−2.62 (m, 1H), 2.55−2.41 (m, 2H), 2.33−2.26 (m, 1H), 2.01−1.89 (m, 2H), 1.77−1.44 (m, 4H). IR (solid): 3414, 2929, 2256, 2129, 1661, 1218, 1050, 1026, 1003, 826, 765 (cm^{-1}). Yield: 1.8 mg. HRMS (ESI-TOF) Calcd for $[C_{24}H_{34}N_8O_7 + H]^+$: 547.2629; found 547.2628. HPLC analysis: retention time 4.73 min.

1{*3*, *1*, *4*} (Entry 20). $[\alpha]_D^{22}$: +7.73 (*c* 0.80, DMSO). ^{1}H NMR (400 MHz, DMSO-d^6): δ 8.55−8.41 (m, 3H, NH), 8.25−8.19 (m, 1H, NH), 7.77−7.70 (m, 1H, NH), 7.73 (d, 2H, J = 7.8 Hz, aromatic), 7.30−7.22 (m, 1H, NH), 7.27 (d, 2H, J = 7.8 Hz, aromatic), 4.59−4.38 (m, 2H), 4.12−4.06 (m, 2H), 3.44 (dd, 1H, J = 7.3, 14.2 Hz), 3.35−3.21 (m, 2H), 3.11−3.06 (m, 2H), 2.65 (dd, 1H, J = 5.4, 16.6 Hz), 2.54 (dd, 1H, J = 7.8, 16.6 Hz), 2.32−2.26 (m, 1H), 2.11−2.04 (m, 1H), 1.71−1.39 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d^6): δ 173.0, 172.1, 171.6, 171.0, 168.7, 166.5, 157.1, 142.6, 133.3, 127.3, 126.8, 56.2, 51.9, 50.4, 41.7, 40.6, 38.5, 35.9, 34.2, 30.2, 26.8, 25.1, 23.0. IR (solid): 3412, 3020, 2255, 2129, 1660, 1548, 1216, 1050, 1026, 1004, 826, 764 (cm^{-1}). Yield: 8.0 mg. HRMS (ESI-TOF) Calcd for $[C_{25}H_{36}N_8O_7 + H]^+$: 561.2785; found 561.2792. HPLC analysis: retention time 4.83 min.

1{*3*, *2*, *1*} (Entry 21). Yield: 2.9 mg. HRMS (ESI-TOF) Calcd for $[C_{22}H_{30}N_8O_7 + H]^+$: 519.2316; found 519.2323. HPLC analysis: retention time 4.66 min.

1{*3*, *2*, *2*} (Entry 22). Yield: 1.0 mg. HRMS (ESI-TOF) Calcd for $[C_{23}H_{32}N_8O_7 + H]^+$: 533.2472; found 533.2463. HPLC analysis: retention time 4.66 min.

1{*3*, *2*, *3*} (Entry 23). Yield: 0.2 mg. HRMS (ESI-TOF) Calcd for $[C_{24}H_{34}N_8O_7 + H]^+$: 547.2629; found 547.2636. HPLC analysis: retention time 4.73 min.

1{*3*, *2*, *4*} (Entry 24). Yield: 1.1 mg. HRMS (ESI-TOF) Calcd for $[C_{25}H_{36}N_8O_7 + H]^+$: 561.2785; found 561.2782. HPLC analysis: retention time 4.83 min.

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