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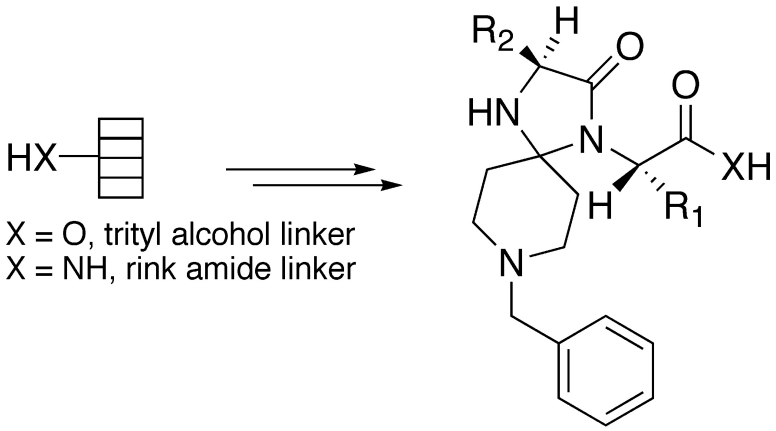

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Articles

Spiroimidazolidinone Library Derivatives on SynPhase Lanterns

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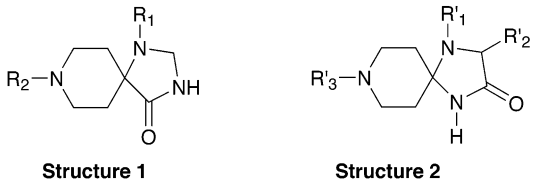
Optimization and solid-phase synthesis of new spiroimidazolidinone derivatives as highly functionalized templates is reported. The synthesis of 1,4,8-triazaspiro[4.5]decan-2-one derivatives was performed on SynPhase lanterns from dipeptides anchored on the solid support and N-protected piperidone. A library of 180 discrete compounds was prepared.

Introduction

The search for new and versatile templates that can be developed by a combinatorial chemistry approach is a current topic of great interest throughout the pharmaceutical community.[1]

Previous reports suggest that spiroimidazolidinone compounds represent a pharmacologically relevant class of molecules that are referred to as " privileged G-protein-coupled receptor structures".[2−4] This molecular framework was also used to describe potent bradykinin receptor analogues in which the central tetrapeptide was replaced by N-1-substituted 1,3,8-triazaspiro[4.5]decan-4-one moieties[5] (structure 1 reported in Figure 1). The results suggested that these molecular scaffolds might be of great interest for the design of conformationally restricted peptide surrogates. They also could offer a useful template to which can be added a variety of functional groups. In this field, a library of spirohydantoin derivatives as neurokinin-1 receptor was recently described.[6] However, the syntheses are long and tedious. We then focused our attention on the synthesis of structurally similar compounds, 1,4,8-triazaspiro[4.5]decan-2-ones (structure 2 reported in Figure 1).

One of the first syntheses of spiroimidazolidinones was described in 1961 by U. Zehavi and D. Ben-Ishai.[7] They reported the condensation of cyclohexanone with benzyloxycarbonylamino acid amides (i.e., Z-Phe-NH_2) to give the corresponding 2-spirocyclohexano-4-imidazolidinones. Other groups have applied this methodology to the preparation of other spirocyclic derivatives.[8] Specifically, 1,4,8-triazaspiro-[4.5]decan-2-ones were obtained from N-substituted 4-piperidone and amino acid amide.[8a] This molecular architecture, which can be easily obtained from commercially available piperidone and amino acid derivatives, constitutes interesting highly functionalized templates for the design of new lead compounds in the drug discovery process. However, until now, all synthetic approaches reported for their preparation were exclusively based on solution-phase chemistry. To develop a library of this scaffold, we decided to transfer the synthesis to the solid support. We have developed and optimized the synthesis of 1,4,8-triazaspiro[4.5]decan-2-ones on SynPhase lanterns to generate 180 compounds.



Structure 1 **Structure 2**

Figure 1. Spirocyclic structures **1** and **2**.

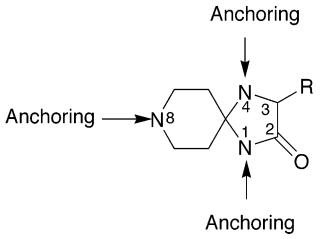


Figure 2. Different ways of anchoring the spirocyclic core to a solid support.

Results and Discussion

We pointed out different possibilities of anchoring the spirocyclic core that represents the central scaffold of our target molecules to the solid support (Figure 2). Different appended diversity elements within the template could be introduced for the molecular diversity. However, for each strategy, the piperidine moiety of the final compound was generated from a piperidone derivative, and the imidazolidinone moiety, from a dipeptide. We report herein one strategy (Scheme 1) that consisted of obtaining the spiro-

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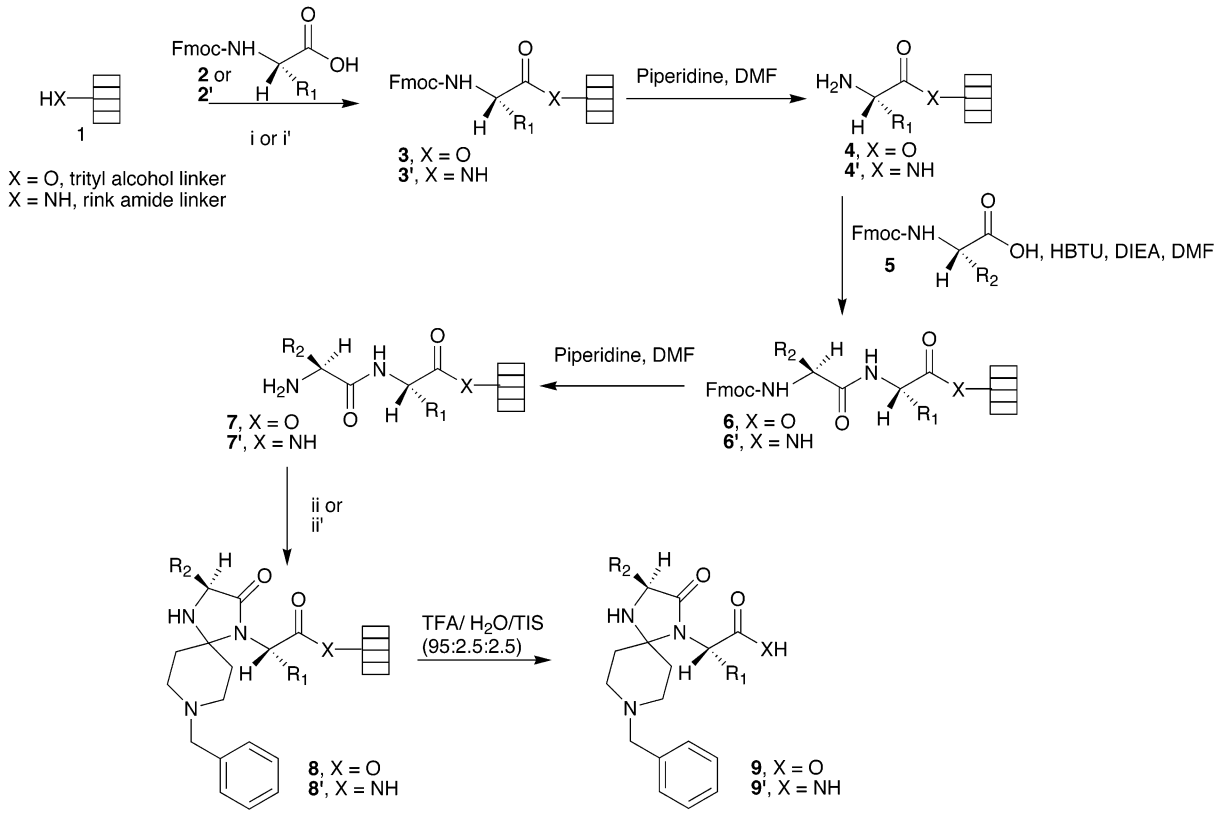
Scheme 1[a]



[a] (i) For X = OH: AcCl 10%, DCM, then **2**, DIEA, DMF/DCM (1:1). (i′) For X = NH: **2′**, HBTU, DIEA, DMF. (ii) For X = O: *N*-benzyl-4-piperidone, DMP, *p*-TsOH, 80°C. (ii′) For X = NH: *N*-benzyl-4-piperidone, toluene, *p*-TsOH, 80°C.

cycles anchored through the nitrogen in position 1. For this purpose, we synthesized on the lantern a dipeptide moiety that afforded a secondary amide and a free amine function to react with the piperidone derivative and that also constituted the diversity elements of the spirocyclic compounds via their side chain.

To manually and quickly manage the synthesis of a spiroimidazolidinone library on a pellicular solid support, we chose to use SynPhase[9] lanterns equipped with colored cogs and spindles, which may be attached to lanterns, to produce a convenient visual tagging system.[10] Spindles come in two sizes, and like cogs, they are available in eight colors.

The library was generated from commercially available Rink amide and trityl alcohol SynPhase lanterns, as depicted in Scheme 1. We prepared a library of 60 discrete members from Rink amide and a library of 120 discrete members from trityl alcohol lanterns. The use of Rink amide support led to amide spirocyclic derivatives (chemset **9′**), whereas the trityl alcohol lanterns afforded the chemset **9** as free carboxylic acids that can be used not only in small molecule ligands screening but also as a peptidomimetic sequence. We decided to use a split/pool approach to perform washings and common steps. Thus, lanterns were tagged by colored cogs and spindles (Figure 3) corresponding to the building block (Fmoc-protected amino acid) introduced at the first and second step of the synthesis. The starting solid-bound *N*-Fmoc-protected dipeptide sequences chemsets **6** and **6′** were prepared using standard solid-phase peptide synthesis on SynPhase lanterns tagged with nine different colored spindles.[11] For Rink amide linker, the first step was accomplished using chemset **2′** (Table 1) and HBTU as coupling reagent to afford lantern-bound chemset **3′**, whereas, for the trityl alcohol lantern, the first amino acid was attached to SynPhase lanterns in a two-step process. The alcohol lantern was converted into solid-bound trityl chloride with a solution of 10% AcCl in dry DCM. Then the freshly prepared trityl chloride SynPhase lanterns reacted with chemset **2** (Table 1) in the presence of DIEA to afford chemset **3**. Lanterns of chemsets **3** and **3′** were pooled together and treated with a solution of 20% piperidine in DMF to give chemsets **4** and **4′**. After common washings, lanterns were sorted and a colored cog[12] (Figure 3), which was associated with each member of chemset **5** (Table 2), was added to the spindle. Then they were treated with the 20 discrete proteogenic amino acid solutions in the presence of HBTU and DIEA to give chemsets **6** and **6′**. After Fmoc removal and washings, lanterns were split into two pools, chemsets **7** and **7′**. The cyclization step was accomplished for each pool by treatment with the commercially available *N*-benzyl-4-piperidone. For Rink amide lanterns, the reaction was carried out in toluene at 80 °C in the presence of *p*-toluenesulfonic acid as catalyst to give chemset **8′**, whereas for trityl alcohol lanterns, good conversion was obtained when the reaction was carried out in 2,2-DMP at 80 °C. Optimization of the reaction conditions were previously performed but are not described herein.

Finally, the 180 lanterns were cleaved separately into individual tubes using a TFA/H_2O/TIS solution[13] (95:2.5:2.5) to afford chemsets **9** and **9′**. After removal of the cleavage cocktail under nitrogen flow and precipitation with

Figure 3. Lanterns tagged with spindles and cogs.

Table 1. Chemsets **2** and **2′** Diversity Members

chemset 2		chemset 2′	
Fmoc-Ala-OH	**1**	Fmoc-Ala-OH	**1**
Fmoc-Asn(Trt)-OH	**2**	Fmoc-Gly-OH	**4**
Fmoc-Glu (*O*-*t*-Bu)-OH	**3**	Fmoc-Phe-OH	**5**
Fmoc-Gly-OH	**4**		
Fmoc-Phe-OH	**5**		
Fmoc-Ser(*t*-Bu)-OH	**6**		

Table 2. Chemset **5** Diversity Members

Fmoc-Ala-OH	**1**	Fmoc-Leu-OH	**11**
Fmoc-Arg (Pmc)-OH	**2**	Fmoc-Lys(Boc)-OH	**12**
Fmoc-Asn(Trt)-OH	**3**	Fmoc-Met-OH	**13**
Fmoc-Asp(OtBu)-OH	**4**	Fmoc-Phe-OH	**14**
Fmoc-Cys(Trt)-OH	**5**	Fmoc-Pro-OH	**15**
Fmoc-Gln(Trt)-OH	**6**	Fmoc-Ser(tBu)-OH	**16**
Fmoc-Glu(OtBu)-OH	**7**	Fmoc-Thr(tBu)-OH	**17**
Fmoc-Gly-OH	**8**	Fmoc-Trp(Boc)-OH	**18**
Fmoc-His(Trt)-OH	**9**	Fmoc-Tyr(tBu)-OH	**19**
Fmoc-Ile-OH	**10**	Fmoc-Val-OH	**20**

dry diethyl ether, the 180 samples were lyophilized. Each compound was solubilized in acetonitrile/water (50:50, v/v) solution containing 0.1% TFA, and an aliquot (10 μL) was taken for LC and LC/MS analyses before lyophilization.

The whole library was characterized by LC/MS analysis, showing the presence of all compounds with a purity range, determined by LC analysis, from 75 to 100%, except for 37 compounds (Table 3). Compounds bearing a proline residue in position 2, except for compounds **9**{*4,15*} and **9′**{*4,15*} and five compounds bearing a glycine residue in position 2 (**9**{*2,8*}, **9**{*3,8*}, **9**{*6,8*}, **9′**{*1,8*}, and **9′**{*5,8*}) were not detected by mass spectra analysis. Moreover, glycine gave final compounds with purities lower than those observed for the whole library (38, 58, and 67% for compounds **9**{*1,8*}, **9**{*5,8*}, and **9′**{*4,8*}, respectively). All compounds incorporating a methionine residue afforded the expected compound with an average 75% purity along with 25% of the corresponding spirocyclic compound with oxidized methionine (molecular ion + 16). When using Phe residue in position 1 as well as Trp residue in position 2, the reaction was generally not complete, and 15−30% of the starting material was observed. Longer reaction time was necessary to lead to completion. The yield calculated from the initial loading of trityl alcohol and Rink amide SynPhase lanterns for 20% of library members ranged from 50 to 60% and 75 to 88%, respectively.

In conclusion, we have developed an efficient approach for the solid-phase synthesis of a 1,4,8-triazaspiro[4.5]decan-2-one derivative library using parallel combinatorial chemistry. Among the 180 compounds prepared on SynPhase lanterns, 137 exhibited a purity exceeding 80%. These compounds designed as "privileged G-protein-coupled receptor structures" might be of particular interest as a result of their rigid three-dimensional organization.

Experimental Section

Materials. All solvents were obtained from Riedel de Häen and used without purification. L-sized polystyrene Rink amide lanterns with a 15-μmol loading, L-sized polystyrene trityl alcohol lanterns with a 15-μmol loading, cogs, and spindles were purchased from Mimotopes, Pty, Clayton, Australia. All Fmoc amino acids and HBTU reagent were obtained from Senn Chemicals (Gentilly, France). *N*-Benzyl-4-piperidone was purchased from Lancaster (Strasbourg, France). Mass spectra (electrospray ionization mode, ESI+) were recorded on a Platform II (Micromass, Manchester, U.K.) mass spectrometer and HPLC analyses on a Beckman 32 Karat HPLC 168 system. The following abbreviations were used: DMF, dimethylformamide; DCM, dichloromethane; DIEA, diisopropylethylamine; 2,2-DMP, 2,2-dimethoxypropane; AcCl, acetyl chloride; HBTU, O−(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; TFA, trifluoroacetic acid; and TIS, triisopropylsilane. Other abbreviations used were those recommended by the IUPAC−IUB Commission (*Eur. J. Biochem.* **1984**, *138*, 9−37).

HPLC and LC/MS Analysis. Samples were prepared in acetonitrile/water (50:50 v/v containing 0.1% TFA).

HPLC analyses were carried out using a Merck Chromolith C18, 4.6 × 50 mm reversed-phase column. A flow rate of 5 mL/min and a gradient of (0−100)% B over 3 min was used. Eluent A, water/0.1% TFA; eluent B, acetonitrile/0.1% TFA.

Table 3. HPLC Purities and LC/MS Analysis of Chemset **9** and Chemset **9′**

Cp	purity %[a]	LC/ MS $[M + H]^+$	Cp	purity %[a]	LC/ MS $[M + H]^+$	Cp	purity %[a]	LC/ MS $[M + H]^+$	Cp	purity %[a]	LC/ MS $[M + H]^+$	Cp	purity %[a]	LC/ MS $[M + H]^+$
9{1,1}	96	332.10	9{2,1}	95	375.17	9{3,1}	100	390.16	9{4,1}	100	318.16	9{5,1}	86	408.18
9{1,2}	100	417.21	9{2,2}	80	460.25	9{3,2}	100	475.23	9{4,2}	100	403.21	9{5,2}	100	493.21
9{1,3}	100	375.15	9{2,3}	95	418.17	9{3,3}	75	433.16	9{4,3}	73	361.16	9{5,3}	80	451.18
9{1,4}	100	376.11	9{2,4}	100	419.13	9{3,4}	100	434.16	9{4,4}	100	362.13	9{5,4}	96	452.15
9{1,5}	80	364.12	9{2,5}	100	407.13	9{3,5}	100	422.47	9{4,5}	100	350.11	9{5,5}	52	439.30
9{1,6}	95	389.16	9{2,6}	100	432.18	9{3,6}	95	447.19	9{4,6}	93	375.16	9{5,6}	97	465.17
9{1,7}	100	390.14	9{2,7}	100	433.17	9{3,7}	94	448.16	9{4,7}	100	376.15	9{5,7}	100	466.17
9{1,8}	38	318.19	9{2,8}	ND[b]		9{3,8}	ND[b]		9{4,8}	81	304.16	9{5,8}	58	394.14
9{1,9}	100	398.15	9{2,9}	100	441.19	9{3,9}	100	456.16	9{4,9}	100	384.17	9{5,9}	84	474.20
9{1,10}	70	374.19	9{2,10}	83	417.23	9{3,10}	86	432.20	9{4,10}	80	360.20	9{5,10}	80	450.20
													15[c]	279.16
9{1,11}	88	374.20	9{2,11}	93	417.23	9{3,11}	95	432.21	9{4,11}	82	360.20	9{5,11}	90	450.19
													10[c]	279.16
9{1,12}	81	389.18	9{2,12}	87	432.29	9{3,12}	100	447.24	9{4,12}	100	375.18	9{5,12}	92	465.23
9{1,13}	60	392.15	9{2,13}	75	435.18	9{3,13}	63	450.16	9{4,13}	73	378.12	9{5,13}	70	468.15
	40 Met(O)	408.14		25 Met(O)	450.99		37 Met(O)	466.18		27 Met(O)	394.14		20 Met(O)	484.15
9{1,14}	87	408.18	9{2,14}	100	451.20	9{3,14}	100	466.19	9{4,14}	100	394.17	9{5,14}	81	484.17
													19[c]	313.13
9{1,15}	ND[b]		9{2,15}	ND[b]		9{3,15}	ND[b]		9{4,15}	88	344.22	9{5,15}	ND[b]	
9{1,16}	88	348.16	9{2,16}	80	391.15	9{3,16}	90	406.17	9{4,16}	100	334.14	9{5,16}	80	424.15
9{1,17}	100	362.17	9{2,17}	100	405.15	9{3,17}	100	420.15	9{4,17}	100	348.13	9{5,17}	97	438.15
9{1,18}	71	447.20	9{2,18}	83	490.19	9{3,18}	82	505.20	9{4,18}	76	433.14	9{5,18}	68	523.20
	27[c]	276.13		17[c]	319.16		18[c]	334.14		12[c]	262.08		28[c]	352.11
9{1,19}	84	424.16	9{2,19}	100	467.20	9{3,19}	100	482.20	9{4,19}	92	410.14	9{5,19}	81	500.17
													15[c]	329.15
9{1,20}	81	360.17	9{2,20}	92	403.19	9{3,20}	80	418.16	9{4,20}	81	346.17	9{5,20}	76	436.19
													18[c]	265.10
9{6,1}	86	348.14	9′{1,1}	89	331.30	9′{4,1}	100	317.07	9′{5,1}	100	407.24			
9{6,2}	87	433.19	9′{1,2}	87	416.30	9′{4,2}	90	402.11	9′{5,2}	84	492.29			
										16[c]	321.31			
9{6,3}	83	391.12	9′{1,3}	81	374.28	9′{4,3}	93	360.04	9′{5,3}	100	450.26			
9{6,4}	94	392.10	9′{1,4}	87	375.25	9′{4,4}	100	361.04	9′{5,4}	100	451.24			
9{6,5}	91	380.09	9′{1,5}	80	363.25	9′{4,5}	86	349.03	9′{5,5}	ND[b]				
9{6,6}	92	405.11	9′{1,6}	90	388.27	9′{4,6}	100	374.04	9′{5,6}	92	464.25			
9{6,7}	100	406.12	9′{1,7}	93	389.23	9′{4,7}	100	375.05	9′{5,7}	83	465.25			
9{6,8}	ND[b]		9′{1,8}	ND[b]		9′{4,8}	67	303.06	9′{5,8}	ND[b]				
9{6,9}	89	414.15	9′{1,9}	89	397.27	9′{4,9}	87	383.0	9′{5,9}	73	473.24			
9{6,10}	81	390.15	9′{1,10}	82	373.29	9′{4,10}	86	359.13	9′{5,10}	67	449.27			
										21[c]	278.38			
9{6,11}	88	390.15	9′{1,11}	88	373.31	9′{4,11}	100	359.11	9′{5,11}	63	449.30			
										22[c]	278.38			
9{6,12}	87	405.18	9′{1,12}	86	388.30	9′{4,12}	91	374.27	9′{5,12}	70	464.26			
9{6,13}	80	408.12	9′{1,13}	80	391.25	9′{4,13}	67	377.06	9′{5,13}	49	467.25			
	15 Met(O)	424.12		20 Met(O)	407.26		33 Met(O)	393.03		36 Met(O)	483.20			
										15[c]	296.30			

9{6,14}	96	424.15	9′{1,14}	87	407.28	9′{4,14}	100	393.10	9′{5,14}	74	483.25
										14[c]	312.27
9{6,15}	ND[b]		9′{1,15}	ND[b]		9′{4,15}	100	343.30	9′{5,15}	ND[b]	
9{6,16}	72	364.10	9′{1,16}	80	347.27	9′{4,16}	100	333.07	9′{5,16}	69	423.24
9{6,17}	100	378.12	9′{1,17}	81	361.27	9′{4,17}	100	347.10	9′{5,17}	74	437.27
9{6,18}	60	463.15	9′{1,18}	74	446.25	9′{4,18}	96	432.11	9′{5,18}	75	522.27
	35[c]	292.10		21[c]	275.34					17[c]	351.27
9{6,19}	94	440.12	9′{1,19}	88	423.25	9′{4,19}	100	409.13	9′{5,19}	89	499.26
9{6,20}	87	376.15	9′{1,20}	70	359.32	9′{4,20}	93	345.12	9′{5,20}	89	435.28

[a] HPLC purities are given as area percent. [b] ND: no trace of the expected molecular ions in positive ion LC/MS was identified. [c] Percentage of the deprotected dipeptidyl amide starting material after 5 h (trityl linker) or 1 day (amide linker).

Purity estimates are based upon area percent of the peaks detected at 214 and 254 nm.

The LC/MS system consisted of a Waters Alliance 2690 HPLC coupled to a Micromass Platform II spectrometer (electrospray ionization mode, ESI+). All analyses were carried out using a RP-18, 3.5-μm, 2.1 × 30 mm reversed-phase column. A flow rate of 600 μL/min and a gradient of (0−100)% B over 5 min was used. Eluent A, water/0.1% TFA; eluent B, acetonitrile/0.1% TFA. Positive ion electrospray mass spectra were acquired at a solvent flow rate of 100 μL/min. Nitrogen was used for both the nebulizing gas and the drying gas. Data were acquired in the scan mode from *m*/*z* 400 to 1400 in 0.1-s intervals; 10 scans were summed to produce the final spectrum.

Standard Fmoc-Deprotection Protocol. Fmoc-deprotection steps were carried out by immersing lanterns in a mixture of DMF and piperidine (80:20) for 60 min. A 200-mL standard Schott flask equipped with a drilled topper was used. Solution was removed simply by reversing the flask.

Standard Washing Protocol. Washing steps after coupling or deprotection step were performed by dipping the lanterns in DMF (3 × 5 min) and DCM (2 × 5 min), successively. One single 200-mL standard Schott flask equipped with a drilled topper was used. Lanterns were allowed to air-dry for 15 min after the last DCM washing.

Standard Coupling Protocol. *Step 1*: *Rink Amide Lanterns*. Three DMF solutions (15 mL) containing each of Fmoc-protected amino acids (Table 1, chemset **2′**), HBTU, and DIEA were freshly prepared in standard 50-mL Schott flasks before the coupling step ([Fmoc-AA-OH] = 120, [HBTU] = 120, [DIEA] = 240 mM). Lanterns were immersed in the coupling solution for 3 h at room temperature. The solution was decanted, and the lanterns were washed following the standard washing protocol.

Trityl Alcohol Lanterns. One hundred twenty trityl alcohol-derivatized lanterns were suspended in a 120-mL solution of 10% AcCl/dry DCM for 3 h at room temperature in a sealed flask. The reaction mixture was then decanted from the lanterns, which were washed with dry DCM (2 × 5 min).

Six dry DMF/DCM (1:1) solutions (15 mL) containing each of the Fmoc-protected amino acids of chemset **2** (Table 1) and DIEA were prepared in standard 50-mL Schott flasks ([Fmoc-AA-OH] = 70, [DIEA] = 250 mM). Lanterns were immersed in the corresponding coupling solution. The reaction was allowed to proceed overnight at room temperature. After decanting the reaction solution, the lanterns were washed following the standard washing protocol.

Step 2. Twenty DMF solutions (8 mL) containing each of the Fmoc-protected amino acids of chemset **5** (Table 2), HBTU, and DIEA were freshly prepared before the coupling step ([Fmoc-AA-OH] = 120, [HBTU] = 120, [DIEA]= 240 mM). Solutions were prepared in standard 20-mL Schott flasks. Lanterns were immersed in the coupling solution for 3 h at room temperature. After removal of the reaction solution, lanterns were washed following the standard washing protocol.

***N*-Benzyl-4-piperidone Condensation Protocol. Trityl Alcohol Lanterns.** Chemset **7** was placed in a glass vial containing a suspension of *N*-benzyl-4-piperidone (22.2 mL,

1 M) and 1% *p*-toluenesulfonic acid monohydrate (1.2 g) in 120 mL of 2,2-DMP. The reaction mixture was allowed to stand for 5 h at 80 °C. The reaction solution was then removed via a drilled topper adapted to the Schott flask. Lanterns were consecutively washed with DMF (3 × 5 min) and DCM (2 × 5 min) and allowed to air-dry.

Rink Amide Lanterns. Chemset **7′** was placed in a glass vial containing a suspension of *N*-benzyl-4-piperidone (18.5 mL, 1 M) and 1% *p*-toluenesulfonic acid monohydrate (1 g) in 100 mL of toluene. The reaction mixture was allowed to stand for 1 day at 80 °C. The reaction solution was then removed via a drilled topper adapted to the Schott flask. The lanterns were consecutively washed with DMF (3 × 5 min) and DCM (2 × 5 min) and allowed to air-dry.

Cleavage. A 500 -μL portion of TFA/water/triisopropylsilane solution (95:2.5:2.5, v/v/v) was dispensed into 180 individual polypropylene tubes of two different 96-wells Micronic 1.5 mL plates. Cleavage was performed for 1 h. Cleavage cocktail was removed directly from the plates using a Jouan RC1010 vacuum centrifuge. Compounds were precipitated with dry diethyl ether, centrifuged, and decanted one by one. Precipitation, centrifugation, and decantation operations were repeated twice. A 100 -μL portion of acetonitrile/water (50:50, v/v) containing 0.1% TFA was dispensed into each tube to dissolve the samples. Samples were then frozen at −80°C and lyophilized. This operation was repeated twice to completely remove the TIS scavenger.

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(11) For common members of chemsets **2** and **2′**, we used two different colored spindles in order to differentiate Rink and trityl lanterns.
(12) Only eight different colored cogs were available; we then used one or two cogs to tag all the members of chemsets **6** and **6′**.
(13) The stability of the spirocyclic compounds in these acidic conditions was checked. After 15 days, 15% of hydrolyzed compound was observed. Compounds may be stocked as a powder, which was totally stable.

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