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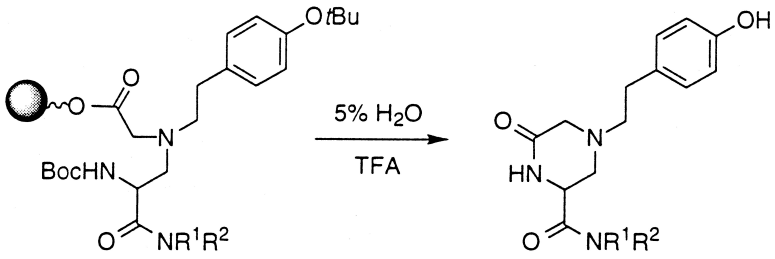

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Solid Phase Organic Synthesis of Piperazinone Containing Enkephalin Mimetics: A Readily Derivatized, Traceless Scaffold

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The solid phase synthesis of a series of piperazinone-derived Leu-enkephalin analogues is presented. The initial step in the synthesis involved the N-alkylation of Wang resin bound *N*-(4-*tert*-butyloxy-phenethyl)-glycine with D or L Boc-serine-β-lactone (the Vederas lactone). The resulting carboxylic acid was then coupled to a variety of monosubstituted benzylamine derivatives using benzotriazol-1-yloxy-tris(dimethyl-amino)phosphonium hexafluorophosphate (the BOP reagent) to yield a series of resin bound tertiary amides. Treatment with 5% H_2O in TFA resulted in the facile cleavage, deprotection, and cyclization of this linear precursor to yield a series of piperazinones (compounds **1**−**8**).

The solid phase organic synthesis of heterocycles plays an important role in modern drug discovery.[1] Heterocycles can provide a scaffold on which pharmacophores can be arranged to yield potent and/or selective drugs. When applied to combinatorial chemistry methodology, such syntheses can expedite the finding of bioactive candidates.[2]

A variety of heterocycles have been synthesized on the solid phase. Two important design elements in any such synthesis involve the construction of the heterocycles from readily available building blocks and the ability to do so without a vestigial solid phase handle (i.e., traceless). The former property allows for the synthesis of a diverse number of heterocycles derived from the large pool of commercially available building blocks (e.g., amino acids, primary amines, etc.). The latter property allows for the design of heterocycles devoid of any unwanted functionality (e.g., a carboxylic acid or amine) that might not be part of a pharmacophore profile. A variety of solid phase heterocycle syntheses that meet these criteria are known, most notably those of the benzodiazepine[3] or diketopiperazine[4] varieties.

The piperazinone heterocycle has only recently been explored synthetically by solid phase reactions.[5] To date, solid phase syntheses of this heterocycle have been based on the cyclization of an attached linear precursor. The heterocycle is then subsequently cleaved from a resin to yield, in many cases, a carboxylic acid or carboxamide bearing piperazinone.[6]

As part of our effort to design scaffold containing opioids, we previously synthesized a piperazinone containing Leu-enkephalin analogue in solution. This product possessed a modest affinity at the μ and δ opioid receptor subtypes.[7] To facilitate the search for other enkephalin mimetics based on this motif, we designed an approach to the solid phase synthesis of this heterocyclic scaffold (see Figure 1) in which the solid phase handle is incorporated into the ring structure during the final cleavage/deprotection step.

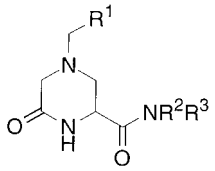

Figure 1. Generalized structure of the piperazinone scaffold synthesized here.

The syntheses of compounds **1**−**8** (see Figure 2) began with the construction of the Wang resin bound N-alkylated glycine **9** (see Figure 3), a modification of the Rink amide resin methodology developed by Zuckermann and co-workers to synthesize peptoid oligomers.[8] Acylation of the benzyl alcohol derived resin was achieved using an excess of bromoacetyl bromide (8 equiv) and DBU (3 equiv) in dichloromethane (DCM).[9] The resulting resin bound alkyl bromide was washed to remove unreacted acyl bromide and immediately treated with an excess (7 equiv) of the *tert*-butyl ether protected tyramine (**12**, for synthesis see Supporting Information) in THF. The ^{1}H NMR analysis of the TFA cleaved/deprotected product indicated the presence of the secondary amine, *N*-(4-hydroxy-phenethyl)-glycine, and the absence of contaminating byproducts.

The resin bound secondary amine **9** was treated with an excess (3 equiv) of *tert*-butyloxycarbonyl (Boc)-(D or L)-serine-β-lactone in *N*-methylpyrrolidinone (NMP) at 40° C to produce the resin bound carboxylic acid **10** (see Figure 3).[10] Two factors were important in determining the choice of solvent for this reaction. First, nucleophilic ring opening reactions of serine derived β-lactones in solution can result in two products derived from attack at either the β-methylene group or the carbonyl group. The former mode of attack is favored in more polar solvents, such as NMP.[10c,11] In addition, NMP was chosen for its excellent Wang resin swelling properties. By contrast, the use of the polar solvents CH_3CN or DMSO, which exhibit poor resin swelling

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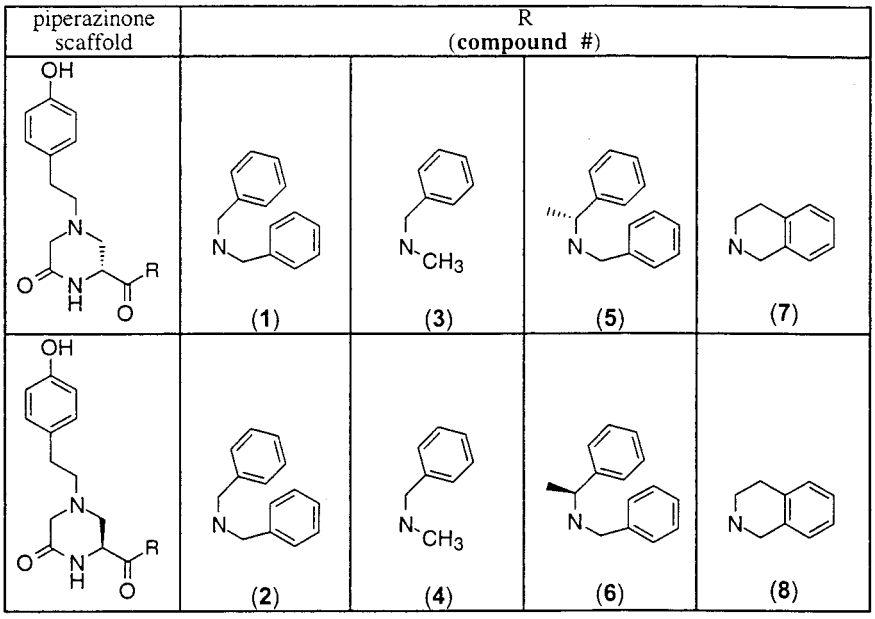

Figure 2. Enkephalin mimetics **1**−**8**.

capabilities, resulted in sluggish and largely incomplete solid phase ring opening reactions under similar conditions.

Conversion of the resin bound carboxylic acid **10** to the desired piperazinones was achieved in two steps (see Figure 3). Transformation of **10** to a resin bound tertiary amide was accomplished using an excess of benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (the BOP reagent, 4 equiv) and a monosubstituted derivative of benzylamine (4 equiv) in DCM overnight.[12] The resulting linear precursor (resin **11**) was cleaved, deprotected, and cyclized using 5% H_2O in trifluoroacetic acid for 3 h to yield the crude final product after solvent removal. Interestingly, this cyclization occurs readily at room temperature and requires no extended times or temperatures as has been reported to be necessary for the solid phase cyclization of some diketopiperazines.[4b, 4d]

Side products were relatively polar when compared to the cyclized final compounds, a result which facilitated the isolation of the target piperazinones using either normal or reverse phase chromatography. Compounds **1**−**8** were purified using preparative thin-layer chromatography and isolated in 29−72% yield (see Table 1). Using a solvent system of 10% MeOH/$CHCl_3$, each piperazinone yielded a major band that was readily visualized using UV light or ninhydrin stain reagent. In general, impurities remained at or near the baseline of the TLC plate. Compounds **1**−**8** could also be readily isolated using typical reverse phase HPLC conditions (C_{18} silica column, 0.1% TFA CH_3CN/H_2O gradient, see Experimental Section for details). For the compounds studied, reverse phase HPLC analysis indicated that the piperazinone product was the last to elute among the products in the crude cleavage reaction mixture, a result consistent with the relatively nonpolar nature of the final cyclized product (see Supporting Information). In addition, when monitored at 220 nm, the final product yielded the largest integration among all the peaks in the HPLC elution profile because of the presence of two amide bonds in the final product. Thus, the chromatographic properties make the isolation of these piperazinones well-suited for either manual or automated purifications.

Structural confirmation of the final piperazinone products was accomplished using high-resolution FAB mass spectrometry and two-dimensional TOCSY, COSY, and ROESY ^{1}H NMR spectroscopies. The ^{1}H NMR analyses of piperazinones **3**, **4**, **5**, and **6** showed two sets of peaks in the spectrum of each compound. This duality of peaks was attributed to cis−trans isomerization around the exocyclic amide bond based on three pieces of evidence. First, HPLC analysis of each compound before and after preparative TLC isolation indicated the presence of a single major piperazinone product. Second, identical ratios of the dual ^{1}H NMR signals were observed between each mirror image pair of compounds (i.e., **3**/**4** and **5**/**6**). Finally, variable temperature ^{1}H NMR experiments performed from 300 to 320 K in DMSO-d_6 demonstrated that these ratios changed as a function of temperature. When the temperature reached 315 K, the dual peaks collapsed into one set of spin systems.

The solid phase organic synthesis presented here represents a facile route amendable to the synthesis of combinatorial libraries. Key advantages of the synthesis include the incorporation of the resin handle into the ring structure, the ability to derivatize the heterocycle scaffold with a variety of amines, and the facile cyclization and isolation of the piperazinones. When compounds **1**−**8** were screened against the three opioid receptor subtypes, compound **1** was found to have an affinity for the μ receptor of 400 nM, the most potent ligand/receptor combination found (see Supporting Information). Future efforts will be focused on the lead optimization of compound **1** and the use of piperazinones as scaffolds for the pharmacophores of other physiologically important receptors.

Experimental Section

General Procedures. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a QE-300 NMR spectrom-

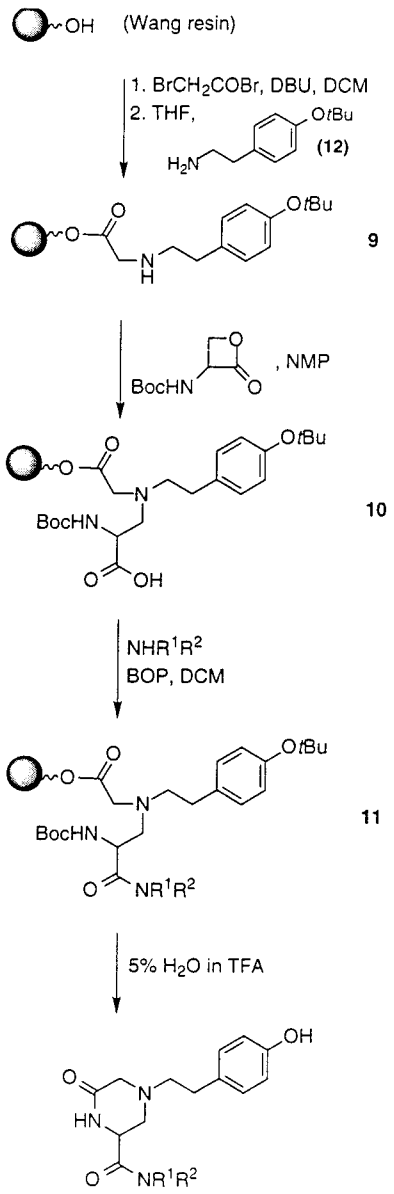

Figure 3. Solid-phase synthesis of piperazinone containing enkephalin analogues.

Table 1. Isolated Yields for Enkephalin Mimetics **1**−**8**

compound	isolated yield based on initial resin substitution (%)
1	39
2	42
3	38
4	32
5	38
6	29
7	72
8	59

eter using the residual peaks in the deuterated solvents as internal standards unless otherwise indicated. The fast atom bombardment (FAB) positive ion mass spectra were obtained on a VG ZAB-VSE double focusing high-resolution mass spectrometer equipped with a cesium ion gun. 3-Nitrobenzyl alcohol was used as the matrix for FAB mass spectrometry. Analytical reverse phase high-performance liquid chromatography (RP-HPLC) was conducted with a 300 Å C_{18} silica column (5 μm, 4.6 × 250 mm, Vydac). Analytical thin-layer chromatography was performed on precoated aluminum sheets (silica gel 60 F_{254}, 0.2 mm thickness, EM Separations Technology). Preparative thin-layer chromatography was carried out on precoated glass backed plates (silica gel GF, 20 × 20 cm, 1000 μm, Analtech).

^{1}H NMR Assignments for Compounds 1−8. The ^{1}H NMR assignment experiments were recorded at a concentration of 2 mg/mL on a Bruker AMX 500 spectrometer equipped with a variable temperature-control unit. DMSO-d_6 was used as an internal standard for the measurement of chemical shifts. One-dimensional ^{1}H NMR was acquired with 16K data points at spectral width between 4400 and 5800 Hz and processed with 16K zero filling to increase the spectrum resolution. The spectral resolution was between 0.13 and 0.17 Hz. *J* coupling constants were extracted from one-dimensional ^{1}H NMR after the spectra were fully assigned. Two-dimensional experiments, including total correlation spectroscopy (TOCSY), double-quantum-filtered correlation spectroscopy[13] (DQF-COSY), and rotating frame nuclear Overhauser enhancement spectroscopy (ROESY), were carried out to assign the proton resonances. All two-dimensional experiments were performed at 300 K, and the time proportional phase increment method was utilized.[14] In the cases involving cis−trans isomerization, experiments between 300 and 320 K were also carried out to observe the changing relative intensity of the two isomers. The TOCSY experiments employed the MLEV-17 spin-locking sequence[15] with a spin-locking field of 10 kHz and a mixing time of 75 ms. The ROESY experiments were carried out with a mixing time of 50, 150, and 300 ms, with a spin-locking field of 2.5 kHz. All the data from the two-dimensional experiments were acquired with 2K data points in the t2 domain and with 400 points in the t1 domain. Data were processed using Felix95 software (Biosym/Molecular Simulations, San Diego). Zero filling was applied in the t1 domain to result in a 1K × 1K matrix. Multiplication, with a 30° phase-shifted sine function for TOCSY and COSY and a 90° phase-shifted sine function with ROESY, was employed in the processing of the spectra.

Materials. All reagents were of the highest grade available and were purchased from the Aldrich Chemical Co. unless indicated otherwise. The Wang resin (0.95 mmol/g) was purchased from Bachem California (Torrance, CA). Dichloromethane was distilled from CaH_2 under N_2. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under N_2.

Synthesis of Resin Bound *N*-(4-*tert*-Butyloxy-phenethyl)-glycine (9). To Wang resin (1.0 g, 0.95 mmol/g, 0.95 mmol) swelled in DCM (15 mL) was added 1,8-diazabicyclo-[5.4.0]undec-7-ene (0.43 mL, 2.9 mmol), and the resin swelled for 15 min with agitation in a 20 mL solid phase reaction vessel equipped with a medium ceramic fritted filter. Bromoacetyl bromide (0.5 mL, 5.47 mmol) was then cautiously added (heat is generated), and the reaction was agitated for 5 h. The resin was then vacuum-filtered and washed with DCM (3 × 15 mL) and THF (3 × 15 mL). The resin was dried under high vacuum for 30 min and swelled in 10 mL of THF. Compound **12** (8.3 mmol) was

added, and the reaction mixture was agitated for 12 h. The resin was vacuum-filtered, washed with THF (1 × 15 mL), 5% TEA/DCM (3 × 5 mL), DCM (3 × 15 mL), and THF (3 × 15 mL), and dried briefly under high vacuum. (Note: The resin bound amine was used immediately in the next reaction to avoid decomposition that can occur with prolonged storage.) On the basis of the increase in resin weight, the yield was calculated to be 86%. For analytical purposes, approximately 30 mg of the resin was treated with 5% H_2O in TFA for 1 h followed by rotary evaporation to yield *N*-(4-hydroxy-phenethyl)-glycine as a light tan solid: ^{1}H NMR δ (D_2O) 2.94 (t, 2H, J = 7.4 Hz), 3.30 (t, 2H, J = 7.4 Hz), 3.77 (s, 2H), 6.86 (d, 2H, J = 8.4 Hz), 7.18 (d, 2H, J = 8.4 Hz); MS (FAB+) 218 (M + Na^+), 196, 121; HRMS (FAB+) $[M + H]^+$ calcd for $C_{10}H_{14}NO_3$: 196.0974, found: 196.0979.

Synthesis of the Resin Bound Carboxylic Acid 10. To a 10 mL round-bottom flask was added the resin bound N-alkylated glycine **9** (1.35 g, 1.3 mmol), and the resin swelled in 10 mL of *N*-methylpyrrolidinone (NMP). Boc-(D or L)-serine-β-lactone[10e] (0.75 g, 4.0 mmol) was added, and the reaction was heated to 40° C for 52 h with gentle stirring using a small magnetic stirbar (caution: rapid stirring can pulverize the resin and result in clogged ceramic fritted filters). The resin was then vacuum-filtered and washed with DMF (3 × 20 mL), 1:1 isopropyl alcohol/DCM (3 × 20 mL), and THF (3 × 20 mL). The resin was then dried under high vacuum overnight.

Synthesis of the Resin Bound Tertiary Amide 11. To a 20 mL solid phase reaction vessel equipped with a medium ceramic fritted filter was added the carboxylic acid bearing resin **10** (0.35 g, 0.33 mmol), and the resin swelled in 5 mL DCM. The amine (1.45 mmol; for Boc-L-serine-β-lactone derived **10**: dibenzylamine, *N*-methylbenzylamine, (*R*)-*N*-benzyl-α-methylbenzylamine, isoquinoline; for Boc-D-serine-β-lactone derived **10**: dibenzylamine, *N*-methylbenzylamine, (*S*)-*N*-benzyl-α-methylbenzylamine, isoquinoline) and benzotriazol-1-yloxy tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 1.45 mmol) were added, and the reaction was agitated for 11 h at room temperature. The resulting resin was vacuum-filtered and washed with DMF (2 × 15 mL), 5% TEA/DCM (1 × 15 mL), DCM (2 × 15 mL), and THF (2 × 15 mL). The resin was then dried briefly under high vacuum and taken directly to the next reaction.

Synthesis of Compounds 1−8. In a 20 mL solid phase reaction vessel equipped with a medium ceramic fritted filter, resin **11** was treated with 5 mL of 5% H_2O in TFA. The reaction was shaken for 3 h which resulted in resin colors ranging from red to purple depending on the resin bound compound. The resin was then vacuum-filtered and washed with THF (3 × 10 mL). The filtrates were combined and reduced to dryness. This crude material was purified using preparative TLC, using 10% MeOH/$CHCl_3$ as the eluant. In all cases, a single major UV-active band was observed and collected. This product was washed from the silica with 25% MeOH/$CHCl_3$ (2 × 15 mL), $CHCl_3$ (1 × 15 mL), and THF (2 × 15 mL). The solvent was removed under reduced pressure, and residual silica gel was eliminated via syringe filtration using a 0.45 μm filter.

(6*R*)-4-(4-Hydroxy-phenethyl)-piperazin-2-one-6-carboxylic Acid Dibenzylamide (1) and (6*S*)-4-(4-Hydroxy-phenethyl)-piperazin-2-one-6-carboxylic Acid Dibenzylamide (2): ^{1}H NMR (500 MHz, DMSO-d_6, 300 K) δ 2.44 (2H, m, NCH_2CH_2), 2.50 (2H, m, NCH_2CH_2), 2.61 (1H, dd, C_{pip}^5-*H*, J = 11.7 Hz, 6.3 Hz), 2.76 (1H, dd, C_{pip}^5-*H*, J = 11.7 Hz, 4.0 Hz), 2.94 (1H, d, C_{pip}^3-*H*, J = 15.9 Hz), 3.03 (1H, d, C_{pip}^3-*H*, J = 15.9 Hz), 4.26 (1H, d, $CH_2C_6H_5$, J = 14.7 Hz), 4.43 (1H, d, $C'H'_2C'_6H'_5$, J = 17.4 Hz), 4.50 (1H, b, C_{pip}^6-*H*), 4.64 (1H, d, $C'H'_2C'_6H'_5$, J = 16.7 Hz), 4.66 (1H, d, $CH_2C_6H_5$, J = 14.9 Hz), 6.64 (2H, d, C_6H_4OH-$H_{3,5}$, J = 8.2 Hz), 6.94 (2H, d, C_6H_4OH-$H_{2,6}$, J = 8.2 Hz), 7.20−7.37 (10H, m, C_6H_5 + $C'_6H'_5$), 7.91 (1H, s, NH), 9.18 (1H, s, O*H*); analytical RP-HPLC: 21.9 min using a gradient of 10−40% [0.1% TFA/CH_3CN in 0.1% TFA/H_2O)] over 20 min; R_f = 0.26 (10% MeOH/$CHCl_3$). Compound **1**: yield based on resin substitution, 39%; MS (FAB+) 219, 336, 444, 466 (M + Na^+); HRMS (FAB+) $[M + H]^+$ calcd for $C_{27}H_{29}N_3O_3$: 444.2287, found: 444.2299. Compound **2**: yield based on resin substitution, 42%; MS (FAB+) 336, 444, 466 (M + Na^+); HRMS (FAB+) $[M + H]^+$ calcd for $C_{27}H_{29}N_3O_3$: 444.2287, found: 444.2273.

(6*R*)-4-(4-Hydroxy-phenethyl)-piperazin-2-one-6-carboxylic Acid *N*-Methyl-benzylamide (3) and (6*S*)-4-(4-Hydroxy-phenethyl)-piperazin-2-one-6-carboxylic Acid *N*-Methyl-benzylamide (4): ^{1}H NMR (500 MHz, DMSO-d_6, 300 K), two isomers: a (*trans*-*N*-benzyl) and b (*cis*-*N*-benzyl), ratio of a to b: 2/1. Isomer a: δ 2.42 (2H, m, NCH_2CH_2), 2.59 (2H, m, NCH_2CH_2), 2.65 (1H, dd, C_{pip}^5-*H*, J = 11.5 Hz, 6.5 Hz), 2.79 (1H, d, C_{pip}^3-*H*, J = 11.5 Hz), 2.87 (1H, dd, C_{pip}^5-*H*, J = 10.9 Hz, 2.8 Hz), 2.94 (3H, s, CH_3), 2.95 (1H, b, C_{pip}^3-*H*), 4.39 (1H, d, $CH_2C_6H_5$, J = 15.2 Hz), 4.51 (1H, b, C_{pip}^6-*H*), 4.62 (1H, d, $CH_2C_6H_5$, J = 14.7 Hz), 6.64 (2H, d, C_6H_4OH-$H_{3,5}$, J = 7.4 Hz), 6.99 (2H, d, C_6H_4OH-$H_{2,6}$, J = 7.1 Hz), 7.21−7.32 (5H, m, C_6H_5), 7.72 (1H, s, N*H*), 9.12 (1H, b, O*H*). Isomer b: δ 2.47 (1H, m, C_{pip}^5-*H*), 2.48 (2H, m, NCH_2CH_2), 2.57 (2H, m, NCH_2CH_2), 2.76 (1H, dd, C_{pip}^5-*H*, J = 11.5 Hz, 4.2 Hz), 2.91 (1H, b, C_{pip}^3-*H*), 2.99 (3H, s, CH_3), 3.09 (1H, d, C_{pip}^3-*H*, J = 16.3 Hz), 4.39 (1H, b, $CH_2C_6H_5$), 4.46 (1H, b, C_{pip}^6-*H*), 4.56 (1H, b, $CH_2C_6H_5$), 6.58 (2H, b, C_6H_4OH-$H_{3,5}$), 6.93 (2H, d, C_6H_4OH-$H_{2,6}$, J = 7.0 Hz), 7.24−7.35 (5H, m, C_6H_5), 7.79 (1H, s, N*H*), 9.12 (1H, b, O*H*); analytical RP-HPLC: 16.3 min using a gradient of 10−40% [0.1% TFA/CH_3CN in 0.1% TFA/H_2O)] over 20 min; R_f = 0.21 (10% MeOH/$CHCl_3$). Compound **3**: yield based on resin substitution, 38%; MS (FAB+) 260, 368, 390 (M + Na^+); HRMS (FAB+) [M + H]$^+$ calcd for $C_{21}H_{25}N_3O_3$: 368.1974, found: 368.1985. Compound **4**: yield based on resin substitution, 32%; MS (FAB+) 260, 368, 390 (M + Na^+); HRMS (FAB+) [M + H]$^+$ calcd for $C_{21}H_{25}N_3O_3$: 368.1974, found: 368.1984.

(6*R*)-4-(4-Hydroxy-phenethyl)-piperazin-2-one-6-carboxylic Acid (*R*)-*N*-Benzyl-α-methylbenzylamide (5) and (6*S*)-4-(4-Hydroxy-phenethyl)-piperazin-2-one-6-carboxylic Acid (*S*)-*N*-Benzyl-α-methylbenzylamide (6): ^{1}H NMR (500 MHz, DMSO-d_6, 300 K), two isomers: a (*trans*-α-methylbenzylamide) and b (*cis*-α-methylbenzylamide), ratio of a to b: 1/1. Isomer a: δ 1.30 (3H, δ, CH_3, J = 7.1 Hz), 2.45 (2H, m, NCH_2CH_2), 2.48 (2H, m, NCH_2CH_2), 2.48 (1H,

m, C_{pip}^5-*H*), 2.78 (1H, dd, C_{pip}^5-*H*, J = 11.1 Hz, 3.4 Hz), 2.90 (1H, d, C_{pip}^3-*H*, J = 16.9 Hz), 3.13 (1H, d, C_{pip}^3-*H*, J = 16.6 Hz), 4.12 (1H, b, C_{pip}^6-*H*), 4.20 (1H, d, C*H*$_2$C$_6$H$_5$, J = 18.2 Hz), 4.59 (1H, d, C*H*$_2$C$_6$H$_5$, J = 18.4 Hz), 5.88 (1H, q, NC*H*(CH$_3$), J = 6.7 Hz), 6.62 (2H, d, C$_6$H$_4$OH-*H*$_{3,5}$, J = 8.2 Hz), 6.93 (2H, d, C$_6$H$_4$OH-*H*$_{2,6}$, J = 8.2 Hz), 7.16−7.24 (10H, m, C$_6$*H*$_5$), 8.00 (1H, s, N*H*). Isomer b: δ 1.41 (3H, δ, C*H*$_3$, J = 6.2 Hz), 2.55 (2H, m, NCH$_2$C*H*$_2$), 2.62 (2H, m, NC*H*$_2$CH$_2$), 2.85 (1H, dd, C_{pip}^5-*H*, J = 12.3 Hz, 4.2 Hz), 2.90 (1H, dd, C_{pip}^5-*H*), 2.92 (1H, d, C_{pip}^3-*H*, J = 16.9 Hz), 2.95 (1H, d, C_{pip}^3-*H*, J = 16.5 Hz), 3.74 (1H, d, C*H*$_2$C$_6$H$_5$, J = 15.6 Hz), 4.70 (1H, b, C_{pip}^6-*H*), 4.78 (1H, d, C*H*$_2$C$_6$H$_5$, J = 15.8 Hz), 5.37 (1H, q, C*H*(CH$_3$), J = 6.0 Hz), 6.67 (2H, d, C$_6$H$_4$OH-*H*$_{3,5}$, J = 8.2 Hz), 7.02 (2H, d, C$_6$H$_4$OH-*H*$_{2,6}$, J = 8.2 Hz), 7.23−7.40 (10H, m, C$_6$*H*$_5$), 7.86 (1H, s, N*H*); analytical RP-HPLC: 22.4 min using a gradient of 10−40% [0.1% TFA/CH$_3$CN in 0.1% TFA/H$_2$O)] over 20 min; R_f = 0.30 (10% MeOH/CHCl$_3$). Compound **5**: yield based on resin substitution, 38%; MS (FAB+) 246, 350, 458, 480 (M + Na$^+$); HRMS (FAB+) [M + H]$^+$ calcd for $C_{28}H_{31}N_3O_3$: 458.2444, found: 458.2460. Compound **6**: yield based on resin substitution, 29%; MS (FAB+) 219, 350, 458, 480 (M + Na$^+$); HRMS (FAB+) [M + H]$^+$ calcd for $C_{28}H_{31}N_3O_3$: 458.2444, found: 458.2428.

(6*R*)-4-(4-Hydroxy-phenethyl)-piperazin-2-one-6-carboxylic Acid (3,4-Dihydro-1*H*-isoquinolin-2-yl)amide (7) and (6*S*)-4-(4-Hydroxy-phenethyl)-piperazin-2-one-6-carboxylic Acid (3,4-Dihydro-1*H*-isoquinolin-2-yl)amide (8): ^{1}H NMR (500 MHz, DMSO-d_6, 300 K) δ 2.46 (1H, b, NCH$_2$C*H*$_2$), 2.50 (1H, b, NCH$_2$C*H*$_2$), 2.57 (2H, m, C_{pip}^5-*H*), 2.75 (1H, b, C_{quin*}^4-*H*), 2.78 (1H, b, NC*H*$_2$CH$_2$), 2.85 (1H, b, C_{quin}^4-*H*), 2.89 (1H, b, NC*H*$_2$CH$_2$), 2.95 (1H, b, C_{pip}^3-*H*), 3.01 (1H, b, C_{pip}^3-*H*), 3.71 (2H, b, C_{quin}^3-*H*), 4.56 (1H, b, C_{pip}^6-*H*), 4.64 (1H, d, C_{quin}^1-*H*, J = 16.7 Hz), 4.70 (1H, d, C_{quin}^1-*H*, J = 15.1 Hz), 6.62 (2H, d, $C_{quin}^{5,8}$-*H*, J = 7.8 Hz), 6.93 (2H, m, $C_{quin}^{6,7}$-*H*), 7.18 (4H, m, C$_6$*H*$_4$OH), 7.66 (1H, s, N*H*), 9.10 (1H, s, O*H*); analytical RP-HPLC: 17.3 min using a gradient of 10−40% [0.1% TFA/CH$_3$CN in 0.1% TFA/H$_2$O)] over 20 min; R_f = 0.29 (10% MeOH/CHCl$_3$). Compound **7**: yield based on resin substitution, 72%; MS (FAB+) 219, 272, 380, 402 (M + Na$^+$); HRMS (FAB+) [M + H]$^+$ calcd for $C_{22}H_{25}N_3O_3$: 380.1974, found: 380.1963. Compound **8**: yield based on resin substitution, 59%; MS (FAB+) 272, 380, 402 (M + Na$^+$); HRMS (FAB+) [M + H]$^+$ calcd for $C_{22}H_{25}N_3O_3$: 380.1974, found: 380.1980.

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Supporting Information Available. The synthesis of compound **12**, the HPLC elution profile of the crude cleavage reaction to produce compound **8**, and biological assay results for compounds **1**−**8** at the μ, δ, and κ opioid receptors. This material is available free of charge via the Internet at http://pubs.acs.org.

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