Redefining the Structure−Activity Relationships of 2,6-Methano-3-benzazocines. 4. Opioid Receptor Binding Properties of 8-[*N*-(4′-phenyl)-phenethyl)carboxamido] Analogues of Cyclazocine and Ethylketocycalzocine

Mark P. Wentland,*,† Melissa VanAlstine,† Robert Kucejko,† Rongliang Lou,† Dana J. Cohen,‡ Amy L. Parkhill,‡ and Jean M. Bidlack‡

Department of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Troy, New York 12180, and Department of Pharmacology and Physiology, School of Medicine and Dentistry, University of Rochester, Rochester, New York 14642

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The synthesis and evaluation of a series of aryl-containing N-monosubstituted analogues of the lead compound 8-carboxamidocyclazocine were performed to probe a putative hydrophobic binding pocket of opioid receptors. High binding affinity to μ, κ, and δ opioid receptors was observed for the 8-[*N*-(4′-phenyl)-phenethyl)-carboxamido] analogue.

Introduction

8-Carboxamidocyclazocine (8-CAC;[a] **1**) has high affinity for μ and κ opioid receptors (Figure 1).[1] This result was unexpected based on the long-standing knowledge[2] that a phenolic hydroxyl group was required for the high affinity binding of many opioid-receptor interactive ligands (e.g., cyclazocine; **2**[3]). In in vivo studies, 8-CAC showed high antinociception activity and a much longer duration of action than cyclazocine (15 h vs 2 h) when both were dosed at 1 mg/kg ip in mice.[4] Preliminary structure−activity relationship studies for 8-CAC revealed that monosubstitution of the carboxamide nitrogen of **1** with methyl or phenyl reduced binding affinity for guinea pig μ receptors 75- and 2313-fold, respectively, whereas dimethylation of the carboxamide group reduced binding affinity 9375-fold.[1]

The finding that monosubstitution of the carboxamide nitrogen had such a detrimental effect was puzzling because of our results from another study indicating that opioid receptors could accommodate aryl groups on the 8-position of the cyclazocine core structure. For example, the 8-phenylamino and 8-benzylamino derivatives, **3** and **4**, respectively, of cyclazocine had approximately 7-fold higher affinity for μ than the corresponding unsubstituted (e.g., 8-NH_2) amino variant **5**.[5]

To further probe opioid receptor space for what we believe contains a putative hydrophobic pocket complementary to the aryl groups of **3** and **4**, we now report the synthesis and opioid receptor binding properties of a series of N-monosubstituted carboxamide analogues of 8-CAC (Table 1). Design of targets was based on two factors, namely, the distance between the carboxamide N and the aryl group as well as the nature of the aryl group itself. Specifically, we chose derivatives having spacers of 0−3 methylene groups and those where the aryl group was phenyl or 4-biphenyl. The 4-biphenyl group (4-$C_6H_4C_6H_5$) is known to be a privileged functional group for recognition to G protein-coupled receptors.[6] After observing the 8-[*N*-(4′-phenyl)-phenethyl)carboxamido] analogue of 8-CAC (**15**) to exhibit very high binding affinity to μ, κ, and δ opioid receptors, we also prepared its enantiomers (−)-**16** and (+)-**17** to assess enantioselectivity of drug binding as well as the corresponding 8-[*N*-(4′-phenyl)-phenethyl)carboxamido] analogue (**21**) having the ethylketocyclazocine (EKC) core.

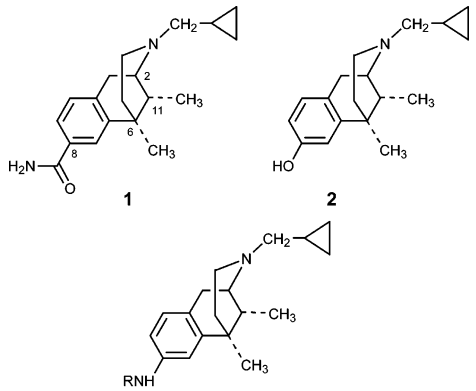

Figure 1. Structures of lead compounds for this study.

Chemistry

Using general Method A (Scheme 1), novel racemic targets **10**−**12** and **15** were conveniently made from common intermediate **7** via acylation in pyridine of the appropriate commercially available amine in yields of 42−83%. The synthesis of **7** was performed using a method we previously described[7] wherein the triflate ester **6**[5] of cyclazocine (**2**) was treated with palladium acetate, carbon monoxide, triethylamine, and *N*-hydroxysuccinamde in dimethyl sulfoxide using 1,1′-bis(diphenyl-phosphino)ferrocene or Xantphos as the palladium ligand.

Methods B and C (Scheme 2), both one-step procedures, were used to prepare target compounds **13**, **14**, **16**−**19**, and **21**. For **13**, **14**, **18**, and **19**, triflate **6** was treated with the appropriate amine and carbon monoxide/palladium acetate/1,1′-bis(diphenylphosphino)ferrocene/dimethyl sulfoxide (Method B) or carbon monoxide/dichloro[1,1′-bis(diphenylphosphino)-ferrocene]palladium (II) dichloromethane adduct/dimethylformamide (Method C). Amines were commercially available except 3-(4-biphenyl)-propylamine used to make target **18**; this amine was prepared by reducing *p*-phenyl-cinnamamide with lithium aluminum

* To whom correspondence should be addressed. Phone: 518-276-2234. Fax: 518-276-4887. E-mail: wentmp@rpi.edu.
† Rensselaer Polytechnic Institute.
‡ University of Rochester.

[a] Abbreviations: 8-CAC, 8-carboxamidocyclazocine; DAMGO, [D-Ala2,N-Me-Phe4,Gly-ol5]- enkephalin; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; nor-BNI, norbinaltorphimine; ip, intraperitoneal.

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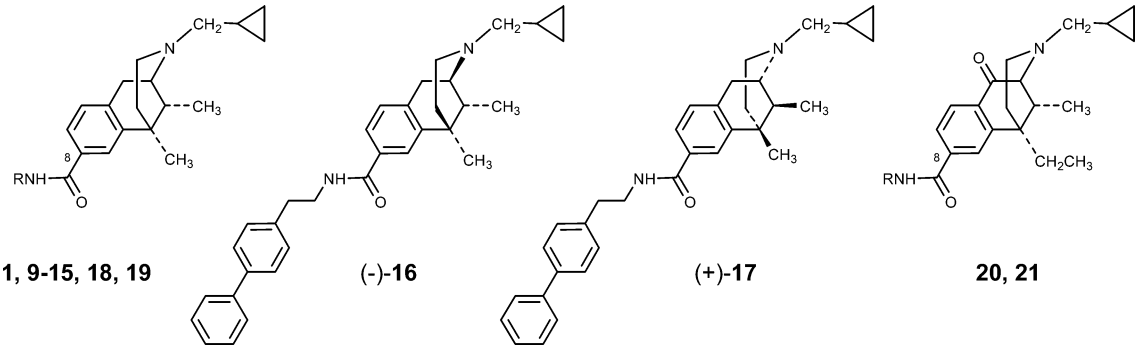
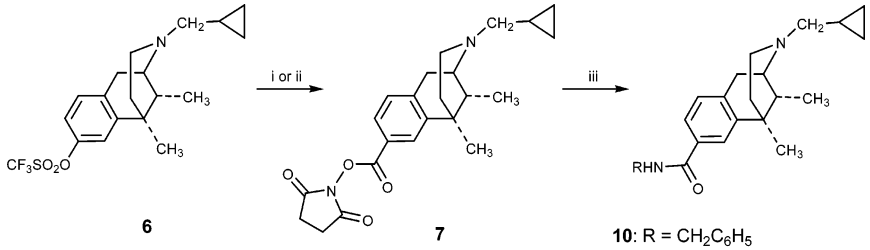
Table 1. Comparative Opioid Receptor Binding Data for 2,6-Methano-3-benzazocine Derivatives



compd	R	K_i (nM ± SEM)[a] [^{3}H]DAMGO (μ)	[^{3}H]naltrindole (δ)	[^{3}H]U69,593 (κ)
1[b]	H	0.31 ± 0.03	5.2 ± 0.36	0.06 ± 0.001
9[b]	C_6H_5	840 ± 64	2100 ± 112	270 ± 14
10[c]	$CH_2C_6H_5$	27 ± 5.5	210 ± 55	36 ± 1.1
11[c]	$(CH_2)_2C_6H_5$	3.5 ± 0.27	59 ± 6.6	1.7 ± 0.18
12[c]	$(CH_2)_3C_6H_5$	2.5 ± 0.27	47 ± 1.6	3.0 ± 0.35
13[c]	4-$C_6H_4C_6H_5$	18 ± 1.6	110 ± 7.1	27 ± 0.86
14[c]	CH_2(4-$C_6H_4C_6H_5$)	11 ± 0.40	170 ± 9.4	26 ± 2.0
15[c]	$(CH_2)_2$(4-$C_6H_4C_6H_5$)	0.30 ± 0.036	0.74 ± 0.019	1.8 ± 0.19
(−)-**16**[c]		0.25 ± 0.031	0.24 ± 0.014	0.35 ± 0.009
(+)-**17**[c]		6.4 ± 0.50	9.9 ± 0.44	8.5 ± 1.07
18[c]	$(CH_2)_3$(4-$C_6H_4C_6H_5$)	5.8 ± 0.31	72 ± 11	2.7 ± 0.21
19[c]	NHR = N(CH_3)$(CH_2)_2$(4-$C_6H_4C_6H_5$)	6.7 ± 1.7	12 ± 2.4	11 ± 0.44
20[b]	H	2.1 ± 0.30	23 ± 2.3	0.47 ± 0.024
21[c]	$(CH_2)_2$(4-$C_6H_4C_6H_5$)	3.1 ± 1.3	3.9 ± 1.4	1.3 ± 0.072

[a] See Experiemntal Section. The K_d values for [^{3}H]DAMGO, [^{3}H]U69,593, and [^{3}H]naltrindole were 0.56 nM, 0.34 nM, and 0.10 nM, respectively. These values were used to calculate the K_i values. [b] See ref 1. [c] Proton NMR, IR, and MS were consistent with the assigned structures of all new compounds. C, H, and N elemental analyses were obtained for all new targets and most intermediates and were within ±0.4% of theoretical values.

Scheme 1. Syntheses of Target Compounds via an Activated Ester Common Intermediate (Method A)[a]



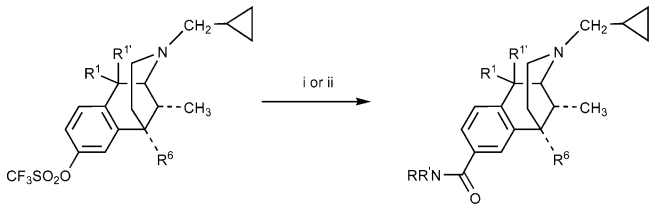
[a] (i) $Pd(OAc)_2$, dppf, CO, Et_3N, NHS, DMSO, 70 °C; (ii) $Pd(OAc)_2$, Xantphos, CO, Et_3N, NHS, DMSO, 70 °C; (ii) RNH_2, pyridine.

hydride/tetrahydrofuran (see Experimental Section). Method C was also used to convert the triflate ester of cyclazocine enantiomers[5] and the racemic triflate ester **8**[1] of EKC to novel 8-carboxamido-*N*-(2-[1,1′-biphenyl]-4-ylethyl) derivatives, (−)-**16**, (+)-**17**, and **21**, respectively.

Results and Discussion

Affinities of target compounds for human μ, δ, and κ opioid receptors stably expressed in chinese hamster ovary (CHO) cells were assessed by generating K_i values using well-documented receptor binding assays.[8] These data, compared to the binding affinities of 8-CAC (**1**), are summarized in Table 1. As stated previously, N-phenyl substitution on the carboxamide group of 8-CAC (compare **1** and **9**) significantly reduced binding affinity for μ, δ, and κ opioid receptors; for human receptors, this decrease was 2710-, 404-, and 4500-fold, respectively. For compound **10**, an analogue of **9** where the *N*-phenyl and -carboxamide groups are separated by one methylene, binding affinity is decreased 87-, 40-, and 600-fold for μ, δ, and κ, respectively, relative to **1**. However, relative to **9**, affinity is increased 31-, 10-, and 8-fold, for μ, δ, and κ, respectively. For the analogues with 2 and 3 methylene spacers, **11** and **12**, respectively, binding affinities were similar to each and have an order of magnitude higher affinity for μ and κ (ca. 4- fold for δ) compared to the single methylene spacer analogue **10**. Compared to **1**, however, compounds **11** and **12** had reduced binding affinity. From these limited data, it is apparent that contributions of the phenyl group to the receptor binding affinities of these 8-carboxamidocyclazocine derivatives is highly dependent on its spatial arrangement with regard to interaction with a putative complimentary hydrophobic pocket in the receptors. To further probe this receptor space, we prepared analogue **15** where the phenyl group of **11** was replaced with 4-biphenyl, a group known for its frequent high affinity binding for G-protein coupled receptors (i.e., a privileged structure).[6] This design strategy proved to be quite effective in

Scheme 2. Syntheses of Target Compounds via Pd-Catalyzed Carboxamidation Procedures (methods B and C)[a]



6: R^1=$R^{1'}$= H; R^6=CH_3
8: R^1,$R^{1'}$=O; R^6=CH_2CH_3

13: R=4-$C_6H_4C_6H_5$; R=R^1=$R^{1'}$= H; R^6=CH_3
14: R=CH_2(4-$C_6H_4C_6H_5$); R'=R^1=$R^{1'}$= H; R^6=CH_3
(-)-**16**: R=$(CH_2)_2$(4-$C_6H_4C_6H_5$); R'=R^1=$R^{1'}$= H; R^6=CH_3
(+)-**17**: R=$(CH_2)_2$(4-$C_6H_4C_6H_5$); R'=R^1=$R^{1'}$= H; R^6=CH_3
18: R=$(CH_2)_3$(4-$C_6H_4C_6H_5$); R'=H; R^1=$R^{1'}$= H; R^6=CH_3
19: R=$(CH_2)_2$(4-$C_6H_4C_6H_5$); R'=CH_3; R^1=$R^{1'}$= H; R^6=CH_3
21: R=$(CH_2)_2$(4-$C_6H_4C_6H_5$); R'=H; R^1,$R^{1'}$=O; R^6=CH_2CH_3

[a] (i) RR′NH, $Pd(OAc)_2$, dppf, CO, Et_3N, DMSO (Method B); (ii) R′NH, $PdCl_2$(dppf), CO, Et_3N, DMF (Method C).

that binding affinities for **15** compared to **11**, were 12-fold and 80-fold greater for μ and δ, respectively, with sub-nanomolar K_i values observed. For the κ opioid receptor, the K_i values for **11** and **15** were comparable. Compared to **1**, compound **15** had comparable binding affinity for μ, 7-fold increased affinity for δ, and 30-fold lower affinity for κ. To assess the spatial requirements of the 4-biphenyl group with respect to the carboxamide moiety, we made three analogues, **13**, **14**, and **18**, which had spacers of 0, 1, and 3 methylene groups, respectively. Not surprisingly, we found that compared to the two-methylene spacer analogue **15**, the three compounds had significant lower affinities for μ (20- to 60-fold) and δ (100- to 230-fold) receptors. For κ, however, **18** had comparable affinity as **15**, while compounds **13** and **14** had 15-fold lower affinity than **15**. What was surprising however, was the observation that with one exception, affinities of **13**, **14**, and **18** for all three receptors were about the same; that exception being that for κ compound **18** had 10-fold greater binding affinity than compounds **13** and **14**. Relative to **1**, compounds **13**, **14**, and **18** had significantly lower affinities for μ (20- to 60-fold), δ (15- to 33-fold), and κ (45- to 450-fold) receptors. To assess the enantioselectivity of binding of **15** for opioid receptors, we evaluated its enantiomers (−)-**16** and (+)-**17**. Consistent with what we observed for 8-CAC enantiomers,[1] a large enantiopreference for binding to all three receptors was observed (eudismic ratios 24−41) and the active enantiomer (−)-**16** had the expected (2*R*,6*R*,11*R*) absolute configuration.

In our early 8-CAC structure−activity relationship (SAR) study,[1] we found that dimethylation of the carboxamide essentially abolished binding affinity for opioid receptors suggesting the importance of an H-bond donating group at the 8-position. To assess if this NH is a requirement in our *N*-(4′-phenyl)-phenethyl)carboxamido series, we evaluated the *N*-methyl analogue **19** of lead **15**. While compound **19** has lower affinity for μ, δ, and κ than **15**, the difference in K_i values (22-, 16-, and 6-fold, respectively) does not come close to the much larger separation noted for the pair of 8-CAC analogues having *N*-methyl and *N*,*N*-dimethyl substitutions (125-, >550-, 962-fold, respectively). These data strongly suggest the (4′-phenyl)-phenethyl) group of **15** or **19** sustains a specific hydrophobic interaction with opioid receptors and this interaction helps anchor these ligands into the active site lessening the importance of the H-bond donor ability of the 8-$CONHCH_2CH_2C_6H_4C_6H_5$ group compared to that of the 8-$CONHCH_3$ group.

To determine the effects of *N*-(4′-phenyl)-phenethyl) substitution on other carboxamide-containing opiate core structures, we made the corresponding analogue **21** of 8-carboxamidoEKC **20**.[1] A similar trend in the SAR was noted for the EKC-derived compounds **20** and **21**, compared to the cyclazocine-derived derivatives, **1** and **15**. Relative to the unsubstituted carboxamide analogue **20**, the *N*-(4′-phenyl)-phenethyl) derivative **21** had comparable affinity for μ, enhanced affinity for δ and reduced affinity for the κ receptor.

Table 2. EC_{50} and E_{max} Values for the Stimulation of [^{35}S]GTPγS Binding and IC_{50} and I_{max} Values for the Inhibition of Agonist-Stimulated [^{35}S]GTPγS Binding to the Human μ, κ, and δ Opioid Receptors[a]

compd	EC_{50} (nM)	E_{max} (% max. stim)	IC_{50} (nM)	I_{max} (% max. inhib)
		Mu Opioid Receptor		
DAMGO	55 ± 7	116 ± 4	NI[c]	NI
1	3.7[b](1.2−7.6)	27[b](15−37)	21 ± 3.7	79 ± 3.0
15	NA[d]	5.6 ± 3.4	150 ± 25	99 ± 1.3
16	3.0 ± 0.65	55 ± 3.3		34 ± 2.7 at 1 μM[f]
		Kappa Opioid Receptor		
U50,488	36 ± 5	77 ± 11	NI	NI
1	4.4 ± 0.73	87 ± 6.5	NI	NI
15	3.0 ± 0.50	76 ± 6.7	NI	NI
16	3.2 ± 0.16	74 ± 3.9	NI	NI
		Delta Opioid Receptor		
SNC80	4.8 ± 0.60	120 ± 4.7	NI	NI
1	NT[e]	NT	NT	NT
15	3.0 ± 0.24	69 ± 8.6	NI	NI
16	6.9 ± 1.9	47 ± 5.0	NI	NI

[a] See Experimental Section. Data are the mean E_{max} and EC_{50} values ± SEM from at least three separate experiments, performed in triplicate. For calculation of the E_{max} values, the basal [^{35}S]GTPγS binding was set at 0%. [b] Data from three separate experiments, performed in triplicate, were averaged together, and are presented with 95% confidence limits. [c] NI = No inhibition. [d] NA = Not applicable. [e] NT = Not tested. [f] Compound **16** at a concentration of 1 μM inhibited 34 ± 2.7% of DAMGO-stimulated [^{35}S]GTPγS binding. An IC_{50} value was not reported because higher concentrations could not be used without having the DMSO vehicle interfere with the assay. A concentration of 200 nM DAMGO, which gave 96 ± 3.1% stimulation, was used to measure inhibition of DAMGO-stimulated [^{35}S]GTPγS binding. A concentration of 100 nM U50,488, which gave 64 ± 1.9% stimulation, was used to measure inhibition of U50,488-stimulated [^{35}S]GTPγS binding, and 10 nM SNC 80, which gave 66 ± 4.3% stimulation, was used to measure inhibition of [^{35}S]GTPγS binding, mediated by the δ opioid receptor.

Intrinsic opioid-receptor mediated activity for **15** and its active enantiomer (−)-**16** was determined using [^{35}S]GTPγS binding assays at μ, δ, and κ receptors; results compared to 8-CAC are shown in Table 2. Results from these assays indicate that at κ and δ receptors, compounds **15** and **16** exhibited agonist properties. Compound **1** was also an agonist at κ however, moderate affinity for δ receptors precluded generating functional activity data. At the μ receptor, all three compounds display partial agonist properties which may be a consequence of

overlapping concentration−response curves for agonist and antagonist effects.

Conclusions

Examination of opioid receptor binding data for this small series of N-monosubstituted carboxamide analogues of 8-CAC has yielded valuable insights into the SAR of the 8-substituent of 8-CAC and related compounds. Our observation that a (4′-phenyl)-phenethyl group situated on the carboxamide nitrogen of 8-CAC is responsible for very high affinity to opioid receptors relative to other N-substituents leads us to conclude that hydrophobics play an important role in binding in this series and affinity for the receptors is highly dependent on the nature of the hydrophobic group and the distance between it and the carboxamide. Since potency is much higher with the two-methylene spacer than with 0, 1, or 3 methylenes, conformation of the ligand also appears to play an important role. It is interesting to speculate what amino acid residues on the receptors are complementary to the hydrophobic biphenylethyl group of **1**. From the homology model of the μ receptor bound to nor-BNI,[9] there are three phenylalanine (Phe152, Phe237, and Phe241) residues in the region of the 8-position of benzomorphans which may create a hydrophobic pocket complementary to the biphenylethyl group of **1**.

Our data suggest the *N*-(4′-phenyl)-phenethyl group to be such an important part of the pharmacophore of **15** that even when it is methylated to give **19**, moderate affinity is still observed. This contrasts our earlier SAR study indicating that at least one H on the carboxamide was a prerequisite for activity. The putative hydrophobic binding pocket in the receptors that we believe is complimentary to the *N*-(4′-phenyl)-phenethyl) group of **15** has not been previously explored to any great extent because most opiate SAR studies lack the ability to probe this receptor space due to the lower (than nitrogen) valence of the oxygen of the phenolic-OH, the prototypic group of opiates. The SAR in this series appears to be additive in that the benefit of the *N*-(4′-phenyl)-phenethyl group of **15** crosses over to another core structure, namely the 8-carboxamido-EKC. In addition to high affinity for opioid receptors, other attributes of *N*-(4′-phenyl)-phenethyl)-8-CAC derivatives are high enantiospecificity of binding with the (2*R*,6*R*,11*R*)-isomer, (−)-**16**, being the active enantiomer and intrinsic activity as demonstrated in [^{35}S]GTPγS assays.

It is our belief that the knowledge gained from this study will assist in the design of new high affinity opioid receptor-interactive ligands modified at the phenolic-OH position of opiates. To further explore this novel SAR, the synthesis and evaluation of new targets related to **15** is ongoing in our laboratories. Target selection will include those analogues with a diverse array of spacer and (hetero)aryl groups on the 8-position of 2,6-methano-3-benzazocines and the 3-position of morphinans and 4,5α-eopxymorphinans.

Experimental Section

(±)-3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-*N*-(2-[1,1′-biphenyl]-4-ylethyl)-2,6-methano-3-benzazocine-8-carboxamide (15). Method A. Conditions similar to those previously reported were used.[1] A solution of (±)-**7** (140 mg, 0.35 mmol) and 2-(4-biphenylethylamine) (84 mg, 0.42 mmol) in 2.5 mL of dry pyridine was stirred at room temperature for 48 h. The solvent was removed in vacuo, and the residue was taken up in methylene chloride (40 mL) and washed once with saturated sodium bicarbonate solution, water, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated to give a brown residue, which was purified by flash chromatography (CH_2Cl_2:CH_3-OH:NH_4OH 15:1:0.1) to give **15** as an off-white foam (110 mg, 0.23 mmol, 66%).

(±)-3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-*N*-(2-phenylethyl)-2,6-methano-3-benzazocine-8-carboxamide (11). This compound was prepared using Method A and phenethylamine. Off-white foam (93 mg, 0.231 mmol, 83%).

(±)-3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-*N*-(3-phenylpropyl)-2,6-methano-3-benzazocine-8-carboxamide (12). This compound was prepared using Method A and 3-phenyl-1-propylamine. Off-white foam (72 mg, 0.174 mmol, 68%).

(±)-3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-*N*-(phenylmethyl)-2,6-methano-3-benzazocine-8-carboxamide (10). This compound was prepared using Method A and benzylamine. Off-white oil (80 mg, 0.21 mmol, 42%).

(±)-3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-*N*-[1,1′-biphenyl]-4-yl-2,6-methano-3-benzazocine-8-carboxamide (13). Method B. Conditions similar to those previously reported were used.[1] 4-Aminobiphenyl (635 mg, 3.75 mmol), palladium acetate (17 mg, 0.075 mmol), and dppf (42 mg, 0.075 mmol) were added to a two-neck flask charged with triflate **6** (300 mg, 0.75 mmol). The reaction was equipped with a condenser and sealed with a septum and a balloon. The whole system was vacuumed and backfilled with nitrogen for three cycles. DMSO (2 mL) was added via syringe. Then it was vacuumed again and backfilled with a mixture of carbon monoxide. The resulting mixture was heated at 70 °C for 18 h. The cooled reaction mixture was diluted with ethyl acetate (30 mL) and washed with saturated bicarbonate solution, water, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated to give a black oil, which was purified by flash chromatography (CH_2Cl_2:CH_3OH:NH_4-OH 25:1:0.1) to give **13** as a brown oil (191 mg, 0.42 mmol, 57%).

(±)-3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-*N*-([1,1′-biphenyl]-4-ylmethyl)-2,6-methano-3-benzazocine-8-carboxamide (14). This compound was prepared using Method B and 4-phenylbenzylamine. Off-white foam (275 mg, 0.59 mmol, 68%).

(−)-3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-*N*-(2-[1,1′-biphenyl]-4-ylethyl)-2,6-methano-3-benzazocine-8-carboxamide [(−)-16]. Method C. Conditions similar to those previously reported were used.[2] 2-(4-Biphenylethylamine) (85 mg, 0.43 mmol) $PdCl_2$(dppf) (16 mg, 0.02 mmol) were added to a two-neck flask charged with triflate ester of (−)-cyclazocine[5] (158 mg, 0.39 mmol). The reaction was equipped with a condenser and sealed with a septum and a balloon. The whole system was vacuumed and backfilled with nitrogen for three cycles. DMF (2 mL) and triethylamine (0.09 mL, 0.62 mmol) were added via syringe. Then it was vacuumed again and backfilled with a mixture of carbon monoxide. The resulting mixture was heated at 70 °C for 18 h. The cooled reaction mixture was diluted with ethyl acetate (30 mL) and washed with saturated bicarbonate solution, water, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated to give a black oil, which was purified by flash chromatography (CH_2Cl_2:CH_3OH:NH_4OH 25:1:0.1) to give (−)-**16** as an off-white foam (100 mg, 0.21 mmol, 53%).

(+)-3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-*N*-(2-[1,1′-biphenyl]-4-ylethyl)-2,6-methano-3-benzazocine-8-carboxamide [(+)-17]. This compound was prepared using Method C and triflate ester of (+)-cyclazocine.[5] Off-white foam (90 mg, 0.19 mmol, 49%).

(±)-3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-*N*-(3-[1,1′-biphenyl]-4-ylpropyl)-2,6-methano-3-benzazocine-8-carboxamide (18). This compound was prepared using Method C and 3-[1,1′-biphenyl]-4-propylamine. Off-white foam (250 mg, 0.51 mmol, 63%).

(±)-3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-*N*-(2-[1,1′-biphenyl]-4-ylethyl)-*N*-methyl-2,6-methano-3-benzazocine-8-carboxamide (19). This compound was prepared using Method C and *N*-methyl-[1,1′-biphenyl]-4-ethanamine. Off-white foam (190 mg, 0.39 mmol, 60%).

(±)-3-(Cyclopropylmethyl)-6-ethyl-1,2,3,4,5,6-hexaahydro-*cis*-11-methyl-*N*-(2-[1,1′-biphenyl]-4-ylethyl)-1-oxo-2,6-methano-3-benzazocine-8-carboxamide (21). This compound was prepared using Method C and the triflate ester **8**[1] of EKC and 2-(4-biphenylethylamine). Off-white foam (200 mg, 0.39 mmol, 61%).

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Supporting Information Available: Experimental details, NMR data, and elemental analyses for all compounds. This material is free of charge via the Internet at http://pubs/acs/org.

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