# Syntheses and Opioid Receptor Binding Affinities of 8-Amino-2,6-methano-3-benzazocines

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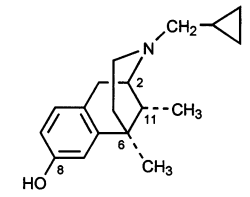
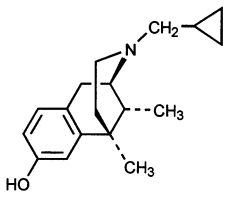
8-Amino-2,6-methano-3-benzazocine derivatives have been made using Pd-catalyzed amination procedures, and their affinities for opioid receptors were assessed. The 8-amino group was hypothesized to be a replacement for the prototypic 8-OH substituent for 2,6-methano-3-benzazocines and related opiates. This OH group is generally required for binding yet is implicated in unfavorable pharmacokinetic characteristics such as low oral bioavailability and rapid clearance via O-glucuronidation. The core structures in which the 8-OH group was replaced were cyclazocine and its enantiomers, ethylketocyclazocine and its enantiomers, ketocyclazocine, and Mr2034. Many new analogues had high affinity for opioid receptors with several in the subnanomolar range. Highest affinity was seen in analogues with secondary 8-(hetero)arylamino appendages. Binding to opioid receptors was enantioselective with the (2*R*,6*R*,11*R*)-configuration preferred and high selectivity for $\mu$ and $\kappa$ over $\delta$ opioid receptors was observed within the series. Several derivatives were shown to have intrinsic opioid-receptor-mediated activity in [$^{35}$S]GTP$\gamma$S assays.

## Introduction

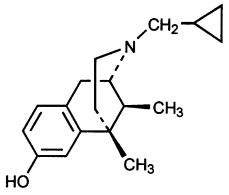
Cyclazocine [(±)-**1**] is a member of the 2,6-methano-3-benzazocine (aka benzomorphan) class of opioid receptor-interactive agents.[1−8] Numerous breakthroughs in understanding opioid receptor pharmacology (e.g., deduction of multiple opioid receptor subtypes[9]) have been made, in part through the study of cyclazocine and its enantiomers (−)-**2** and (+)-**3**.[1]In the 1960s and early




(±)-**1** (Cyclazocine)




(-)-**2** (2*R*,6*R*,11*R*)




(+)-**3** (2*S*,6*S*,11*S*)

1970s, cyclazocine was evaluated in humans for analgesia and as a possible treatment in postaddicts of heroin for preventing relapse.[1,10] Potent analgesia was observed in humans dosed with cyclazocine, and after abrupt cyclazocine withdrawal, patients did not display drug-seeking behavior.[10] Owing, in part, to dysphoric side effects and a short duration of analgesic action, further clinical development of cyclazocine ceased.[1,10,11] The short duration of action observed for cyclazocine in animals and humans may be due to O-glucuronidation; this metabolite has been observed in humans[11] and animals.[12,13]

Opioid receptor binding studies for cyclazocine performed in the late 1970s showed the compound to have high affinity for $\kappa$ and $\mu$ opioid receptors, and antinociceptive studies in rodents revealed that cyclazocine was a $\kappa$ agonist and $\mu$ antagonist.[1] The opioid receptor binding properties of cyclazocine, a racemate, reside in the (2*R*,6*R*,11*R*)-isomer (−)-**2**, whereas the (2*S*,6*S*,11*S*)-isomer (+)-**3** displays high affinity for the $\sigma$ receptor.[14,15]

The observations that cyclazocine produced opioid-induced analgesia in humans with a lower risk of dependency and to precipitate a somewhat milder withdrawal from morphine suggested that the agent might serve as a useful therapeutic for the treatment of heroin addiction.[16−18] Currently, cyclazocine is undergoing NIDA-sponsored evaluation for potential clinical utility as a treatment for cocaine abuse.[19] Results from this study did not support the use of cyclazocine for this indication; however, there was some suggestion that an analogue having a somewhat different opioid receptor profile might be useful.

In an attempt some years ago to enhance the pharmacokinetic properties of cyclazocine (i.e., retard O-glucuronidation and increase duration of action), we prepared (±)-**4** where the 8-OH group of cyclazocine was replaced with $NH_2$.[11] Relative to cyclazocine, we found that (±)-**4** had somewhat diminished antinociception potency in mice when delivered by the subcutaneous route but had comparable potency when delivered orally.[11] For example, in the mouse acetylcholine writh-

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ing test, the po/sc ratio of $ED_{50}$ values for cyclazocine was 35 and for (±)-**4** this ratio was 4, indicating the 8-OH → $NH_2$ change accounted for higher oral efficacy than would be predicted by the sc data. Whether higher gut wall permeability, lower first-pass or extrahepatic metabolism, reduced clearance, or some other factor accounts for the high oral efficacy of (±)-**4** is not known. More recently, we assessed the affinities of a small series of 8-amino-2,6-methano-3-benzazocines for opioid receptors.[20] Results from this preliminary study indicated that replacing the 8-OH of cyclazocine with an 8-$NH_2$ group conferred significantly lower affinity (>20-fold) for $\mu$ and $\kappa$ opioid receptors. However, by substituting one H of the 8-$NH_2$ group with phenyl, affinity for $\mu$ and $\kappa$ was dramatically improved where $K_i$ values were now close (4-fold higher) to cyclazocine. This led us to conclude that a new SAR for the 8-position substituent of 2,6-methano-3-benzazocines was emerging. From this small series, we chose two optically active analogues, the primary amine (−)-**4** and the *N*-phenyl analogue (−)-**11** for in vivo studies to assess their antinociception potency icv and then to determine which opioid receptors mediate antinociception and if they acted as antagonists of antinociception mediated by any of the opioid receptors.[21] Compounds (−)-**4** and (−)-**11** had similar (to each other and to (−)-cyclazocine [(−)-**2**]) antinociception potency (mouse acetic acid writhing) that was mediated by the $\kappa$ opioid receptor. Coupled with the fact that these compounds antagonize morphine-induced antinociception leads to the conclusion that, at the least, two members of this series are $\mu$ antagonists and $\kappa$ agonists.[21]

The objective of the study we are now reporting, therefore, was to prepare an expanded series of 8-amino-2,6-methano-3-benzazocines and to assess their affinities for $\mu$, $\delta$, and $\kappa$ opioid receptors in hopes of refining a new SAR around the 8-position. We also tested selected analogues for functional activity in the [$^{35}$S]-GTP$\gamma$S assay. These objectives are part of our overall goal to identify orally active and long-acting analogues of cyclazocine having potent $\kappa$ agonist and $\mu$ antagonist binding properties useful as anti-cocaine and anti-heroin medications. The efficient synthesis of new analogues in the series, including many in enantiomerically pure form, was made possible by the outbreak of new methods for the Pd-catalyzed amination of aryl triflates.[22] New target compounds made for this study were benzomorphans having secondary and tertiary amine groups at the 8-position. Secondary amines (e.g., 8-NHR) predominated the target list because of the long-standing doctrine that benzomorphans as well as other $\mu$ opioid receptor interactive agents (e.g., morphine) require H-bond donation at that site provided by the prototypic phenolic OH.[2−5] Having the 8-NHR substitution not only provided this important H-bond donor but also allowed us to probe previously unexplored receptor space by systematic variation of the R group. This is made possible by the increased valence of nitrogen compared to the valence of the oxygen of prototypic opiates. Besides using R = alkyl or aryl groups to identify potential hydrophobic sites within this space, we also used heteroaryl groups to probe potential H-bond donor/acceptor sites. Substitution of the 8-OH in other 2,6-methano-3-benzazocine core structures, besides cyclazocine, was also investigated including ethylketocyclazocine (EKC), ketocyclazocine, and the optically active 3-tetrahydrofuranylmethyl-2,6-methano-3-benzazocine, Mr2034.

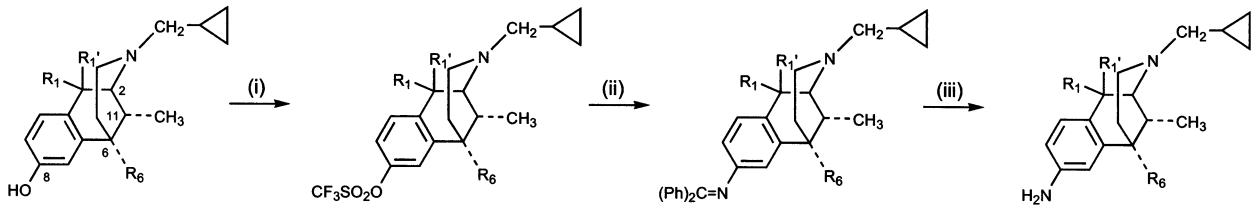
Besides our early studies[11] and the preliminary account of this work,[20] few reports of 8-amino-2,6-methano-3-benzazocines or 3-aminomorphinans have appeared. A small series of 8-amino-3-benzyl-2,6-methano-3-benzazocines were evaluated by Carroll and co-workers for binding to $\delta$ receptors.[23] For morphinan-related core structures, we recently reported the synthesis and opioid binding properties of the 3-amino derivative of morphine.[24] In addition, the 3-sulfonamido analogues (i.e., 3-$NHSO_2CH_3$) of naltrexone and oxymorphone were recently reported[25] and a 3-aminodextromorphan analogue was studied for other (than opioid receptor binding) pharmacological properties.[26] This latter compound, however, has stereochemistry that is the opposite of that of natural opiates.

## Chemistry

Our original method[11] (Birch reduction of cyclazocine methyl ether followed by Semmler−Wolf methodology) to make primary amino analogue (±)-**4** was used to prepare its enantiomers[27] (−)-**5** and (+)-**6** from the known cyclazocine enantiomers[28,29] (−)-**2** and (+)-**3**, respectively, in nearly identical yields.[11] The Birch reduction/Semmler−Wolf method, while very useful in making the primary and certain secondary amino derivatives, could not be used for the rapid introduction of a variety of amine substituents at position 8. Therefore, we applied the methodology of Buchwald,[31] Hartwig,[32] and co-workers using the Pd-catalyzed amination[22] of aryl triflates to our system with excellent results, which we recently reported in a preliminary communication.[20] By use of this methodology, our first task was to remake primary amino analogue (±)-**4** from cyclazocine (±)-**1**. This three-step process that we note as method A is shown in Scheme 1 and detailed in the Experimental Section, and except for a few minor modifications, it is identical to a literature method.[33] Cyclazocine (±)-**1** was first converted to its corresponding triflate ester (±)-**53** in 96% yield using $(CF_3CO)_2O$/pyridine. Conversion of (±)-**53** to the corresponding benzophenone imine adduct (±)-**38** was accomplished in 47% yield using $Ph_2C{=}NH$, $Pd_2(dba)_3$,[34] DPPF, NaO-t-Bu in toluene at 80 °C. Adduct (±)-**38** was converted to (±)-**4** in 84% yield by treatment with $NH_2OH{\cdot}HCl$/NaOAc in methanol. In similar fashion (Schemes 1 and 2), ethylketocyclazocine (EKC, (±)-**41**),[35−37] EKC enantiomers (−)-**42**[36,37] and (+)-**43**,[36,37] ketocyclazocine (±)-**48**,[35] and Mr2034 [(−)-**50**][38] were converted to their corresponding novel 8-$NH_2$ derivatives (±)-**44**, (−)-**45**, (+)-**46**, (±)-**49**, and (−)-**51** in combined (for the three steps) yields ranging from 35% to 73% (see Table 1).

As shown in Schemes 3 and 4, new secondary and tertiary 8-amino derivatives of numerous core benzomorphan structures were made using Pd-catalyzed aminations of aryl triflates. Two known Pd source/ligand combinations were utilized. Method B (RR′NH, $Pd_2(dba)_3$, DPPF, NaO-t-Bu, toluene, 80 °C)[32] was essentially the same as that used to convert (±)-**53** to (±)-**38**, and method C (RR′NH, $Pd(OAc)_2$, BINAP, NaO-t-Bu, toluene, 80 °C)[22] used a different catalyst source/

**Scheme 1.** Preparation of Primary Amino Targets Using Method A[a]



(±)-**1**: $R_1 = R_1' = H$; $R_6 = CH_3$
(±)-**41**: $R_1, R_1' = O$; $R_6 = CH_2CH_3$
(-)-**42**: $R_1, R_1' = O$; $R_6 = CH_2CH_3$
(+)-**43**: $R_1, R_1' = O$; $R_6 = CH_2CH_3$
(±)-**48**: $R_1, R_1' = O$; $R_6 = CH_3$

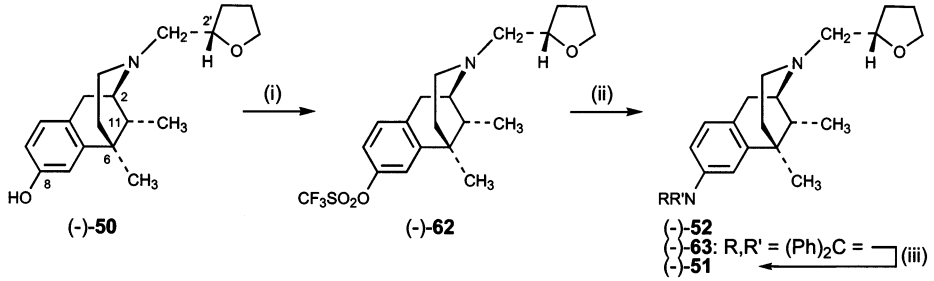
(±)-**53**: $R_1 = R_1' = H$; $R_6 = CH_3$
(±)-**54**: $R_1, R_1' = O$; $R_6 = CH_2CH_3$
(-)-**55**: $R_1, R_1' = O$; $R_6 = CH_2CH_3$
(+)-**56**: $R_1, R_1' = O$; $R_6 = CH_2CH_3$
(±)-**57**: $R_1, R_1' = O$; $R_6 = CH_3$

(±)-**38**: $R_1 = R_1' = H$; $R_6 = CH_3$
(±)-**58**: $R_1, R_1' = O$; $R_6 = CH_2CH_3$
(-)-**59**: $R_1, R_1' = O$; $R_6 = CH_2CH_3$
(+)-**60**: $R_1, R_1' = O$; $R_6 = CH_2CH_3$
(±)-**61**: $R_1, R_1' = O$; $R_6 = CH_3$

(±)-**4**: $R_1 = R_1' = H$; $R_6 = CH_3$
(±)-**44**: $R_1, R_1' = O$; $R_6 = CH_2CH_3$
(-)-**45**: $R_1, R_1' = O$; $R_6 = CH_2CH_3$
(+)-**46**: $R_1, R_1' = O$; $R_6 = CH_2CH_3$
(±)-**49**: $R_1, R_1' = O$; $R_6 = CH_3$

[a] (i) $(CF_3SO_2)_2O$, pyr, $CH_2Cl_2$; (ii) $(Ph)_2C{=}NH$, $Pd_2(dba)_3$, DPPF, NaO-t-Bu, tol, 80 °C; (iii) $NH_2OH$, NaOAc, $CH_3OH$ or 2 N HCl, THF.

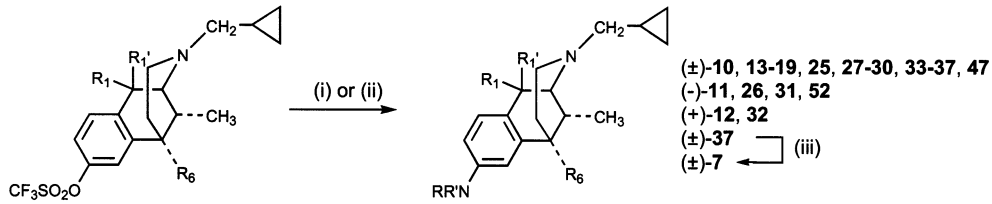
**Scheme 2.** Preparation of 8-Amino Analogues of Mr2034[a]



(-)-**50**
(-)-**62**
(-)-**52**
(-)-**63**: R,R' = $(Ph)_2C{=}$
(-)-**51**
(iii)

[a] (i) $(CF_3SO_2)_2O$, pyr, $CH_2Cl_2$; (ii) RR′NH, $Pd_2(dba)_3$, DPPF, NaO-t-Bu, tol, 80 °C; (iii) $NH_2OH$, NaOAc, $CH_3OH$.

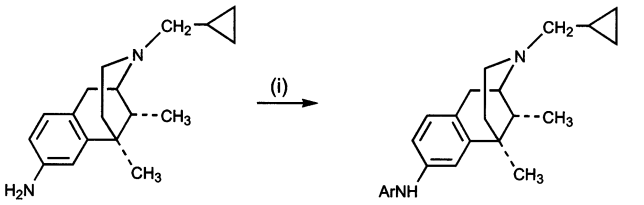
**Scheme 3.** Preparation of Aminobenzomorphan Targets Using Methods B and C[a]



(±)-**10**, **13-19**, **25**, **27-30**, **33-37**, **47**
(-)-**11**, **26**, **31**, **52**
(+)-**12**, **32**
(±)-**37**
(±)-**7**
(iii)

[a] (i) RR′NH, $Pd_2(dba)_3$, DPPF, NaO-t-Bu, tol, 80 °C (method B); (ii) RR″NH, $Pd(OAc)_2$, BINAP, NaO-t-Bu, tol 80 °C (method C); (iii) $H_2$, $Pd(OH)_2/C$, $CH_3OH$.

**Scheme 4.** Preparation of Aminobenzomorphan Targets Using Methods D[a]



(±)-**4**

(±)-**20**: Ar = 4-$CF_3C_6H_4$
(±)-**21**: Ar = 4-$N(CH_3)_2C_6H_4$
(±)-**22**: Ar = 2-pyridinyl
(±)-**23**: Ar = 3-pyridinyl
(±)-**24**: Ar = 4-pyridinyl

[a] (i) ArBr or 2-Cl-pyr, $Pd_2(dba)_3$, DPPF, NaO-t-Bu, tol, 80 °C.

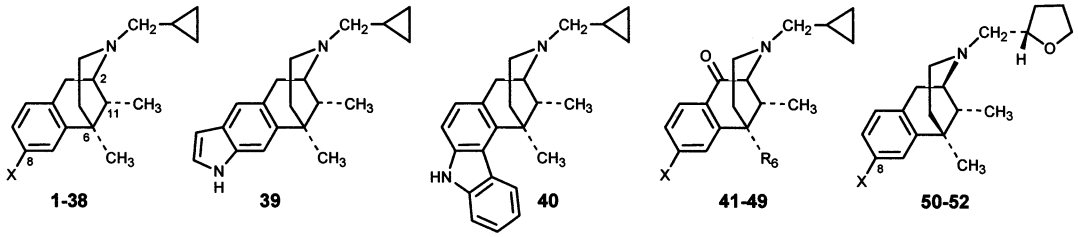
ligand. In general, the two methods could be interchanged without significant compromise in yield and we often used/tried both to make a particular analogue.

As summarized in Scheme 3 and Table 1, triflate ester (±)-**53** of cyclazocine was converted to (±)-**10** and (±)-**13**-**19** using method B in yields of 37−64%. In yields of 29−59% and using method B, the triflates of (−)-**2** and (+)-**3** were converted to (−)-**11** and (+)-**12**, respectively, and (±)-**54** and (−)-**62** were converted to (±)-**47** and (−)-**52**, respectively. By use of method C, (±)-**53** was converted to (±)-**25**, (±)-**27**−**30**, and (±)-**33**-**37** in yields of 25−84%. Also, by use of method C, the triflate of (−)-**2** was converted to (−)-**26** and (−)-**31** in 53% and 57% yield, respectively, and the triflate of (+)-**3** was converted to (+)-**32** in 52% yield. Amination conditions were generally not optimized, and in several instances where lower yields of amination products were seen, the major byproduct observed was the corresponding phenol, which we assume was formed by cleavage of the triflate by some as yet unidentified nucleophilic species.

By use of the same Pd source/ligand as method B but reversing the role of the aromatic amine and aromatic halide, an alternative strategy (method D, Scheme 4) was used to make the 8-*N*-(hetero)aryl targets (±)-**20**−**24**. Compounds (±)-**20** and (±)-**21** were made by treating (±)-**4** with 4-$CF_3C_6H_4Br$ (57%) and 4-$(CH_3)_2NC_6H_4$-Br (68%), respectively. Pd-catalyzed pyridinylations of amines using 2-chloropyridine or 2, 3-, or 4-bromopyridine have been reported.[39] For our purposes, we used 2-chloropyridine and 3- and 4-bromopyridine under conditions of method D to convert (±)-**4** to targets (±)-**22**−**24**, respectively, in yields of 25−89%.

Rather than use our original Birch reduction method to remake the known 8-methylamino analogue (±)-**7**,[11]

**Table 1.** Opioid Receptor Binding Data for Aminobenzomorphans

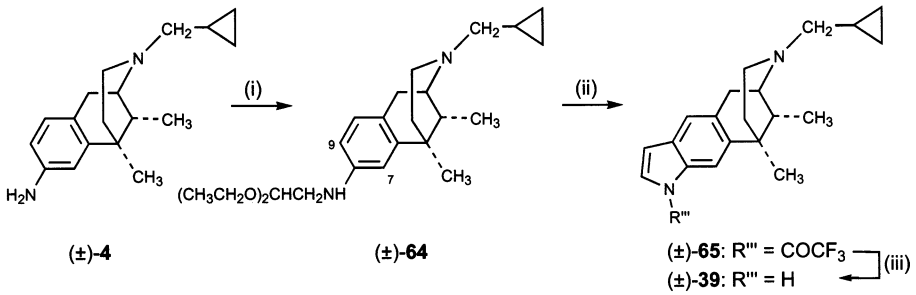



| compd | X | method[b] | yield, %[b] | mp, °C | formula | $K_i \pm$ SE,[a] nM [$^3$H]DAMGO ($\mu$) | [$^3$H]naltrindole ($\delta$) | [$^3$H]U69,593 ($\kappa$) | $\kappa$:$\mu$:$\delta$[c] |
|---|---|---|---|---|---|---|---|---|---|
| (±)-**1**[d] | OH (cyclazocine) | | | | | 0.32 ± 0.02 | 1.1 ± 0.04 | 0.18 ± 0.02 | 6:3:1 |
| (−)-**2**[d,e] | OH | | | | | 0.10 ± 0.03 | 0.58 ± 0.06 | 0.052 ± 0.009 | 11:6:1 |
| (+)-**3**[d,e] | OH | | | | | 360 ± 16 | 1100 ± 63 | 76 ± 8.2 | 14:3:1 |
| (±)-**4**[f,g] | $NH_2$ | A | 70[h] | oil | | 9.5 ± 0.14 | 110 ± 15 | 4.1 ± 0.11 | 27:12:1 |
| (−)-**5**[a,i,j] | $NH_2$ | | | | $C_{18}H_{26}N_2 \cdot 0.25H_2O$ | 1.8 ± 0.12 | 12 ± 2.3 | 1.2 ± 0.13 | 10:7:1 |
| (+)-**6**[a,i,j] | $NH_2$ | | | | $C_{18}H_{26}N_2$ | 780 ± 78 | 920 ± 27 | 506 ± 37 | 2:1:1 |
| (±)-**7**[f,g] | $NHCH_3$ | | | | | 13 ± 0.77 | 470 ± 62 | 8.5 ± 0.44 | 55:36:1 |
| (±)-**8**[f] | $NHCH_2CH_3$ | | | | | 5.1 ± 0.74 | 19 ± 3.1 | 3.3 ± 0.10 | 6:4:1 |
| (±)-**9**[a,j] | $NHCH(CH_3)_2$ | | | | $C_{21}H_{32}N_2$ | 240 ± 3.7 | 460 ± 49 | 78 ± 16 | 6:2:1 |
| (±)-**10**[j] | $NHC_6H_5$ | B | 59 | oil | $C_{24}H_{30}N_2 \cdot 0.3H_2O$ | 1.3 ± 0.072 | 9.4 ± 0.74 | 0.83 ± 0.036 | 11:7:1 |
| (−)-**11**[j−l] | $NHC_6H_5$ | B | 57 | foam | $C_{24}H_{30}N_2 \cdot 0.3H_2O$ | 1.1 ± 0.08 | 5.2 ± 0.08 | 0.54 ± 0.01 | 10:5:1 |
| (+)-**12**[j,l,m] | $NHC_6H_5$ | B | 59 | oil | $C_{24}H_{30}N_2 \cdot 1.5H_2O$[n] | 46 ± 4.4 | 270 ± 49 | 27 ± 1.5 | 10:6:1 |
| (±)-**13** | $NH(4\text{-}ClC_6H_4)$ | B | 49 | 175−178 | $C_{24}H_{29}N_2Cl$[o] | 3.0 ± 0.12 | 26 ± 2.0 | 2.5 ± 0.14 | 10:9:1 |
| (±)-**14** | $NH(3,4\text{-}Cl_2C_6H_3)$ | B | 39 | oil | $C_{24}H_{28}N_2Cl_2$ | 8.4 ± 0.86 | 29 ± 3.5 | 5.7 ± 0.46 | 5:3:1 |
| (±)-**15** | $NH(4\text{-}CH_3C_6H_4)$ | B | 54 | 170−172 | $C_{25}H_{32}N_2 \cdot 0.5H_2O$ | 0.91 ± 0.12 | 6.2 ± 0.79 | 0.57 ± 0.14 | 11:7:1 |
| (±)-**16**[a] | $NH(4\text{-}CH_3OC_6H_4)$ | B | 64 | 180−181 | $C_{25}H_{32}N_2O \cdot 0.5H_2O$ | 0.47 ± 0.077 | 8.3 ± 1.0 | 0.29 ± 0.012 | 29:18:1 |
| (±)-**17** | $NH(3\text{-}CH_3OC_6H_4)$ | B | 63 | 122−124 | $C_{25}H_{32}N_2O \cdot 0.25H_2O$ | 1.8 ± 0.21 | 13 ± 1.6 | 1.0 ± 0.07 | 13:7:1 |
| (±)-**18** | $NH(2\text{-}CH_3OC_6H_4)$ | B | 62 | oil | $C_{25}H_{32}N_2O \cdot 0.75H_2O$ | 8.5 ± 1.7 | 98 ± 17 | 2.2 ± 0.10 | 45:12:1 |
| (±)-**19** | $NH(4\text{-}t\text{-}BuC_6H_4)$ | B | 41 | oil | $C_{28}H_{38}N_2 \cdot H_2O$ | 18 ± 0.90 | 61 ± 3.2 | 14 ± 2.5 | 4:3:1 |
| (±)-**20** | $NH(4\text{-}CF_3C_6H_4)$ | D | 57 | oil | $C_{25}H_{29}N_2F_3 \cdot 0.25H_2O$ | 13 ± 0.96 | 180 ± 40 | 11 ± 2.3 | 16:14:1 |
| (±)-**21**[a] | $NH(4\text{-}NMe_2C_6H_4)$ | D | 68 | oil | $C_{26}H_{35}N_3 \cdot 0.5H_2O$ | 70 ± 3.5 | 75 ± 14 | 8.8 ± 0.36 | 9:1:1 |
| (±)-**22** | NH(2-pyridinyl) | D | 44 | foam | $C_{23}H_{29}N_3 \cdot 0.125H_2O$ | 4.2 ± 0.70 | 11 ± 4.7 | 9.2 ± 1.2 | 1:3:1 |
| (±)-**23** | NH(3-pyridinyl) | D | 89 | oil | $C_{23}H_{29}N_3 \cdot 0.125H_2O$ | 0.64 ± 0.054 | 21 ± 1.8 | 0.50 ± 0.061 | 42:33:1 |
| (±)-**24** | NH(4-pyridinyl) | D | 25 | oil | $C_{23}H_{29}N_3 \cdot 0.5H_2O$ | 18 ± 1.4 | 240 ± 20 | 2.9 ± 0.073 | 83:13:1 |
| (±)-**25**[j] | $NHCH_2C_6H_5$ | C | 66 | oil | | 1.5 ± 0.16 | 57 ± 2.5 | 4.7 ± 0.15 | 12:38:1 |
| (−)-**26**[a,j] | $NHCH_2C_6H_5$ | C | 53 | oil | $C_{25}H_{32}N_2$ | 0.67 ± 0.043 | 54 ± 3.6 | 2.1± 0.10 | 26:81:1 |
| (±)-**27** | $NHCH_2(4\text{-}CH_3OC_6H_4)$ | C | 84 | 136−138 | $C_{26}H_{34}N_2O$ | 7.8 ± 1.6 | 80 ± 11 | 71 ± 13 | 1:10:1 |
| (±)-**28** | $NHCH_2(4\text{-}ClC_6H_4)$ | C | 51 | oil | $C_{25}H_{31}N_2Cl \cdot 0.25H_2O$ | 8.8 ± 1.3 | 100 ± 16 | 7.2 ± 1.7 | 14:11:1 |
| (±)-**29**[j] | $NHCH_2CH_2C_6H_5$ | C | 55 | oil | $C_{26}H_{34}N_2 \cdot 0.25H_2O$ | 9.0 ± 2.4 | 160 ± 8.0 | 11 ± 0.084 | 15:18:1 |
| (±)-**30**[j] | $N(CH_3)_2$ | C | 45 | oil | | 82 ± 1.9 | 1500 ± 96 | 33 ± 2.5 | 46:18:1 |
| (−)-**31**[p,q] | $N(CH_3)_2$ | C | 57 | oil | $C_{20}H_{30}N_2 \cdot 0.125H_2O$ | 46 ± 9.2 | 810 ± 90 | 18 ± 1.4 | 45:18:1 |
| (+)-**32**[q,r] | $N(CH_3)_2$ | C | 52 | oil | $C_{20}H_{30}N_2$ | 5000 ± 310 | 8400 ± 380 | 3000 ± 27 | 3:2:1 |
| (±)-**33**[j] | 1-pyrrolidinyl | C | 54 | oil | $C_{22}H_{32}N_2$ | 770 ± 55 | 1800 ± 73 | 410 ± 30 | 4:2:1 |
| (±)-**34**[j] | 1-piperidinyl | C | 48 | 264 (dec) | $C_{23}H_{34}N_2 \cdot 2HCl$ | 950 ± 84 | 3600 ± 390 | 300 ± 29 | 12:4:1 |
| (±)-**35**[j] | 1-morpholinyl | C | 49 | 140−142 | $C_{22}H_{32}N_2O$ | 650 ± 38 | 2800 ± 200 | 560 ± 82 | 5:4:1 |
| (±)-**36**[j] | 1-(4-methypiperazinyl) | C | 25 | oil | $C_{23}H_{35}N_3$ | 21 ± 2.8 | 250 ± 51 | 8.8 ± 0.40 | 28:12:1 |
| (±)-**37**[j] | $N(CH_3)CH_2C_6H_5$ | C | 55 | oil | $C_{26}H_{34}N_2 \cdot 0.25H_2O$ | 56 ± 4.1 | 570 ± 33 | 44 ± 1.8 | 13:10:1 |
| (±)-**38**[a] | $N{=}C(Ph)_2$ | | | | $C_{31}H_{34}N_2$ | 360 ± 29 | 220 ± 46 | 170 ± 5.5 | 1:1:1 |
| (±)-**39**[a,s] | | | | | | 18 ± 1.9 | 250 ± 14 | 7.0 ± 0.22 | 36:14:1 |
| (±)-**40**[a] | | | | 222−224 | $C_{24}H_{28}N_2 \cdot 0.5H_2O$ | 22 ± 0.057 | 170 ± 7.7 | 9.6 ± 0.45 | 18:8:1 |
| (±)-**41**[t] | X = OH, $R_6 = CH_2CH_3$ (EKC) | | | | | 0.78 ± 0.10 | 3.4 ± 0.41 | 0.62 ± 0.11 | 5:4:1 |
| (−)-**42**[t,u] | X = OH, $R_6 = CH_2CH_3$ | | | | | 0.73 ± 0.12 | 1.1 ± 0.24 | 0.17 ± 0.016 | 6:2:1 |
| (+)-**43**[t,u] | X = OH, $R_6 = CH_2CH_3$ | | | | | 320 ± 67 | 1300 ± 150 | 73 ± 13 | 18:4:1 |
| (±)-**44** | X = $NH_2$, $R_6 = CH_2CH_3$ | A | 37[h] | oil | $C_{19}H_{26}N_2O \cdot 0.8H_2O$ | 7.3 ± 1.6 | 51 ± 4.9 | 0.34 ± 0.029 | 150:7:1 |
| (−)-**45**[v,w] | X = $NH_2$, $R_6 = CH_2CH_3$ | A | 35[h] | 200−203 | $C_{19}H_{26}N_2O \cdot H_2O$ | 2.7 ± 0.40 | 7.6 ± 1.4 | 1.1 ± 0.19 | 7:3:1 |
| (+)-**46**[w,x] | X = $NH_2$, $R_6 = CH_2CH_3$ | A | 37[h] | 198−200 | $C_{19}H_{26}N_2O \cdot 0.9H_2O$ | 17 ± 0.70 | 81 ± 7.6 | 9.1 ± 0.54 | 9:5:1 |
| (±)-**47** | X = $NHC_6H_5$, $R_6 = CH_2CH_3$ | B | 51 | oil | $C_{25}H_{30}N_2O \cdot 0.5H_2O$ | 10 ± 2.0 | 37 ± 3.0 | 2.2 ± 0.12 | 17:4:1 |
| (±)-**48**[t] | X = OH, $R_6 = CH_3$ | | | | | 3.3 ± 0.66 | 20 ± 2.7 | 1.0 ± 0.24 | 20:6:1 |
| (±)-**49** | X = $NH_2$, $R_6 = CH_3$ | A | 73[h] | 190−192 | $C_{18}H_{24}N_2O$ | 3.6 ± 0.51 | 29 ± 5.3 | 0.80 ± 0.04 | 36:8:1 |
| (−)-**50**[y] | OH (Mr2034) | | | | | 0.17 ± 0.02 | 2.5 ± 0.41 | 0.073 ± 0.004 | 34:15:1 |
| (−)-**51**[z] | $NH_2$ | A | 65[h] | oil | $C_{19}H_{28}N_2O$ | 14 ± 0.97 | 370 ± 48 | 7.8 ± 1.7 | 47:26:1 |
| (−)-**52**[aa] | $NHC_6H_5$ | B | 29 | 177−178 | $C_{25}H_{32}N_2O \cdot 0.25H_2O$ | 2.8 ± 0.35 | 35 ± 3.4 | 2.0 ± 0.12 | 18:12:1 |

[a] See Experimental Section. [b] Refers to the Pd-catalyzed amination step except as noted. [c] Ratio of the corresponding $K_i$ values. [d] Known compound. See ref 28. [e] Eudismic ratios for $\mu$, $\delta$, and $\kappa$ are 3600, 1897 and 1462, respectively. [f] Known compound. See ref 11. [g] See Experimental Section for an alternative route. [h] Combined yield for the three-step sequence. [i] Eudismic ratios for $\mu$, $\delta$, and $\kappa$ are 433, 77 and 422, respectively. [j] Reported in the preliminary account of this work (ref 20). [k] $[\alpha]^{25}_D$ −79.3° (*c* 1.0, $CHCl_3$). [l] Eudismic ratios for $\mu$, $\delta$, and $\kappa$ are 42, 52, and 50, respectively. [m] $[\alpha]^{25}_D$ +78.3° (*c* 1.0, $CHCl_3$). [n] H: calcd, 8.92; found, 8.25. N: calcd, 7.49; found, 6.66. [o] N: calcd, 7.36; found, 6.64. [p] $[\alpha]^{25}_D$ −113.6° (*c* 0.88, EtOH). [q] Eudismic ratios for $\mu$, $\delta$, and $\kappa$ are 107, 10, and 167, respectively. [r] $[\alpha]^{25}_D$ +125.4° (*c* 1.18, EtOH). [s] Known compound. See ref 40. [t] Known compound. See refs 35−37. [u] Eudismic ratios for $\mu$, $\delta$, and $\kappa$ are 438, 1182, and 429, respectively. [v] $[\alpha]^{25}_D$ −90.4° (*c* 1.0, 2% aqueous HOAc). [w] Eudismic ratios for $\mu$, $\delta$, and $\kappa$ are 6, 11, and 8, respectively. [x] $[\alpha]^{25}_D$ +88.3° (*c* 1.0, 2% aqueous HOAc). [y] Known compound. See ref 38. [z] $[\alpha]^{25}_D$ −90.4° (*c* 1.10, MeOH). [aa] $[\alpha]^{25}_D$ −97.6° (*c* 0.84, $CHCl_3$).

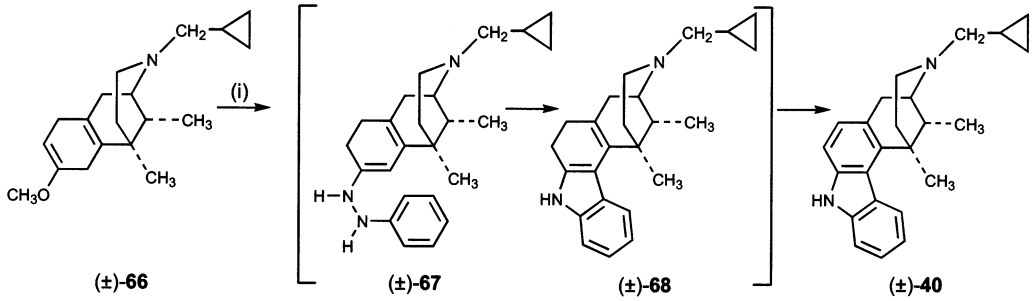
we attempted the two Pd-catalyzed procedures, methods B and C, without success. It is likely that the volatility of methylamine reduced its effective concentration to levels too low for success under these conditions; using

**Scheme 5.** Preparation of Pyrrolo-Fused Analogue (±)-**39**[a]




[a] (i) $BrCH_2CH(OCH_2CH_3)_2$, $KHCO_3$, DMF; (ii) $(CF_3CO)_2O$, $CF_3CO_2H$; (iii) KOH, MeOH.

**Scheme 6.** Preparation of Indolo-Fused Analogue (±)-**40**[a]




[a] (i) $C_6H_5NHNH_2$·HCl, HOAc.

excess gaseous methylamine did not help. Since we had a supply of the *N*-methyl-*N*-phenylmethyl analogue (±)-**37**, we removed the benzyl group with $H_2$/$Pd(OH)_2$/C (Scheme 3) to give (±)-**7** in 44% yield. The isopropylamino analogue (±)-**9** was made in 71% yield through reductive amination of (±)-**4** with $(CH_3)_2CO$, $NaBH_3CN$, and $ZnCl_2$.

In an attempt to gain insight into the nature of the bioactive conformation of these ligands, two cyclic probes, indole derivative (±)-**39** and carbazole analogue (±)-**40**, were made. The synthesis (and in vivo antinociception properties) of indole (±)-**39** has been reported from an 8-amino-3-carboethoxy-2,6-methano-3-benzazocine intermediate.[40] We felt the harshly acidic conditions of this procedure could not be used to convert (±)-**4** directly to (±)-**39** because the cyclopropyl group might not survive. We utilized an alternative procedure[41] shown in Scheme 5 and described in the Experimental Section. Compound (±)-**4** was treated with bromoacetaldehyde diethyl acetal, $KHCO_3$, and DMF to provide intermediate (±)-**64**. Cyclization of this compound with $(CF_3CO)_2O$ and $CF_3CO_2H$ occurred at the 9-position of the benzene ring to give trifluoroacetamide (±)-**65**, which was hydrolyzed in KOH/$CH_3OH$ to provide the desired target (±)-**39**. Assignment of structure, and in particular where the point of cyclization occurred (9- versus 7-position of (±)-**64**), was made using proton NMR where the two benzenoid H atoms appeared as sharp singlets at $\delta$ 7.30 and 7.33 ppm.

By use of a known procedure,[42] carbazole target (±)-**40** was made from an enol ether intermediate [(±)-**66**] we previously reported.[11] Treatment of (±)-**66** with phenylhydrazine hydrochloride and acetic acid gave only compound (±)-**40** (Scheme 6) and no expected dihydrocarbazole intermediate (±)-**68** was observed in our first attempts. It is likely that intermediate (±)-**68** was formed, but despite the fact that it was performed under a blanket of $N_2$, it was oxidized by small amounts of oxygen present in the reaction mixture. Rather than go through elaborate experiments to isolate and characterize (±)-**68**, we simply carried out the reaction as before and obtained (±)-**40** in 21% yield. Cyclization of the enamine intermediate from (±)-**66** with phenylhydrazine could have occurred at either the 7- or 9-position, giving two regioisomeric (dihydro)carbazoles. The structure of the product was assigned (±)-**40** by proton NMR where the two benzenoid H atoms that are part of the benzomorphan ring system are observed as two doublets coupled to each other at $\delta$ 7.15 ppm (d, $J$ = 8.3 Hz, 1H) and 7.21 ppm (d, $J$ = 8.3 Hz, 1H). Thus, we conclude that the regiochemistry of the Fischer indole cyclization occurred in the predicted orientation where the putative enamine intermediate (±)-**67** giving rise to the observed product would be stabilized through conjugation relative to the other possible enamine structure.

## Results and Discussion

Affinities of 8-amino-2,6-methano-3-benzazocine targets and their 8-OH counterparts for $\mu$, $\delta$, and $\kappa$ opioid receptors are reported in Table 1 and were assessed using published procedures.[43] The first part of this discussion involves the bioisosteric replacement of $NH_2$ for the 8-OH group on the following core structures: cyclazocine and both enantiomers, EKC and both enantiomers, ketocyclazocine, and Mr2034 [(−)-**50**], an optically active 3-tetrahydrofuranylmethyl-2,6-methano-3-benzazocine. Compared to cyclazocine (±)-**1**, the primary amino analogue (±)-**4** displayed 30-fold and 23-fold lower affinity for $\mu$ and $\kappa$ receptors, respectively. This significantly lower affinity is not consistent with results from our earlier in vivo studies[6] where (±)-**4** was only 5-fold less potent than (±)-**1** in rodent models of antinociception dosed sc and equipotent po. We assume, therefore, that (±)-**4** has substantially enhanced pharmacokinetic properties relative to cyclazocine especially when administered orally. Against $\delta$, (±)-**4** had very low

affinity compared to $\mu$ and $\kappa$ receptors. For both cyclazocine and the primary amino analogue, the active enantiomers at opioid receptors are the (−)-(2*R*,6*R*,11*R*)-isomers (−)-**2** and (−)-**5**, respectively; eudismic ratios versus $\mu$ were 3600 and 433, respectively, and ratios versus $\kappa$ were 1462 and 423, respectively.

Ethylketocyclazocine [EKC, (±)-**41**] is a well-documented benzomorphan that has high affinity for opioid receptors. EKC acts as a $\kappa$ agonist and, at higher doses, a $\mu$ agonist in monkeys.[44,45] Additionally, EKC has been shown to block cocaine self-administration in nonhuman primates.[46,47] Upon a comparison of the novel 8-$NH_2$ derivative (±)-**44** to (±)-**41**, higher affinity than would be predicted by the cyclazocine case was seen against all receptor types. The amino analogue (±)-**44** had 9-fold and 15-fold lower affinity than EKC (±)-**41** for $\mu$ and $\delta$, respectively; against $\kappa$, comparable affinity was observed. As expected, the active enantiomers at opioid receptors for both EKC and the amino derivative are (−)-(2*R*,6*R*,11*R*)-isomers (−)-**42** and (−)-**45**, respectively; however, a rather large divergence in eudismic ratios was observed between the two. For the EKC case, eudismic ratios for the two enantiomers, (−)-**42**, and (+)-**43** versus $\mu$, $\delta$, and $\kappa$ were 438, 1182, and 429, respectively. For the 8-aminoEKC example, the eudismic ratios for the two enantiomers, (−)-**45**, and (+)-**46** versus $\mu$, $\delta$, and $\kappa$ were only 6, 11, and 8, respectively. When an unexpectedly low eudismic ratio is observed, one suspects that the "inactive" enantiomer, in this case (+)-**46**, is contaminated with the "active" isomer [i.e., (−)-**45**]. In our case, however, the amino enantiomers were made from the very same samples of the 8-OH enantiomers [(−)-**42** and (+)-**43**] that were put into the receptor binding assays and had large ratios. At present, we have no explanation for the low eudismic ratios of (−)-**45** and (+)-**46**.

From the data just described, it appears that the presence of a 1-keto group is beneficial for the 8-OH → 8-$NH_2$ bioisosteric replacement strategy. Further support for this conclusion comes from study of another 1-keto core system, ketocyclazocine (±)-**48**, where nearly identical affinities against all receptor types were seen for the 8-OH [(±)-**48**] and 8-$NH_2$ [(±)-**49**] analogues.

We studied replacement of the 8-OH of Mr2034 [(−)-**50**].[38] This compound, and related derivatives, was pioneered by Merz and co-workers and is characterized by having very high potency in mouse antinociception models.[38] When we replaced the 8-OH of (−)-**50** with $NH_2$ to provide (−)-**51**, we found that (−)-**51** displayed considerably less affinity than (−)-**50** for all receptor types. Specifically, $K_i$ values were 82-fold, 148-fold, and 107-fold greater for (−)-**51** than (−)-**50** against $\mu$, $\delta$, and $\kappa$, respectively.

We also studied the effect on receptor binding affinity upon substitution of the 8-N of cyclazocine analogue (±)-**4**. When the primary amine of (±)-**4** was substituted with monoalkyl groups, affinity against all receptor types was not appreciably affected by methyl [(±)-**7**] or ethyl [(±)-**8**] substituents; however, it was substantially reduced (e.g., 25-fold for $\mu$) by isopropyl substitution [(±)-**9**]. For secondary amine substituents containing a phenyl ring, however, substantial affinity was observed. Against $\mu$ and $\kappa$, for example, the phenylamino analogue (±)-**10** displayed 7-fold and 5-fold greater affinity, respectively, than the primary amine comparator (±)-**4**. In fact, the affinity of (±)-**10** approached within 4-fold of the subnanomolar affinity of cyclazocine [(±)-**1**]. As we observed in several other examples, the enantiomer of (±)-**10** that displays the higher affinity is the (−)-(2*R*,6*R*,11*R*)-isomer (−)-**11**; however, large eudismic ratios were not seen (42, 52, and 50 versus $\mu$, $\delta$, and $\kappa$, respectively). We have no explanation at present to account for this.

To determine if the substantial benefit of adding a phenyl group to the 8-N of (±)-**4** was transferable to other core structures, we evaluated the corresponding *N*-phenyl analogues in the EKC and Mr2034 core structures. Compared to 8-aminoEKC [(±)-**44**], the *N*-phenyl analogue (±)-**47** had nearly the same affinity for $\mu$ and $\delta$ and displayed 6-fold less affinity for $\kappa$ receptors. For the Mr2034 core structure, addition of a phenyl group to the primary amine of (−)-**51** resulted in a compound [(−)-**52**] having 5-fold, 11-fold, and 4-fold higher affinity for $\mu$, $\delta$, and $\kappa$, respectively. It appears that the benefits of the *N*-phenyl group vary depending on the core benzomorphan structure.

We made a considerable effort to understand what role the phenyl group of (±)-**10** has in enhancing the binding affinity of (±)-**4**. We implemented a Topliss method approach[48] to probe what effect, if any, various physicochemical parameters of substituents on the phenyl ring have on binding affinity. The standard five compounds that are part of the first phase of the Topliss method were made. Review of the binding data for (±)-**10** (8-$NHC_6H_5$), (±)-**13** [$NH(4\text{-}ClC_6H_4)$], (±)-**14** [$NH(3,4\text{-}Cl_2C_6H_3)$], (±)-**15** [$NH(4\text{-}CH_3C_6H_4)$], and (±)-**16** [$NH(4\text{-}CH_3OC_6H_4)$] revealed a rank order (from highest to lowest) of affinity for $\mu$ and $\kappa$ of (±)-**16** > (±)-**15** ≥ (±)-**10** > (±)-**13** > (±)-**14**. Topliss scheme analyses of this rank order suggested that $-\sigma$ (i.e., electron donation) was an important determinant of activity. Of the several analogues suggested for additional synthesis by the Topliss algorithm, we choose the $NH(4\text{-}NMe_2C_6H_4)$ derivative (±)-**21**. This compound, however, had lower affinity (8- to 149-fold less affinity for $\mu$ and 2- to 30-fold less affinity for $\kappa$ receptors) than the five probes, leading to the likely conclusion that the larger (than methyl or methoxy) 4-dimethylamino group has a negative steric interaction with the two receptors. In an attempt to support or refute this conclusion, we made (±)-**19**, which has the bulky electron-donating group *tert*-butyl at the 4-position of the *N*-phenyl ring. Since (±)-**19** had affinity for $\mu$ and $\kappa$ that is between that of (±)-**15** (4-$CH_3$) and (±)-**21** (4-$NMe_2$), our understanding of the electronic and/or steric effects of the 4-substituent was not clarified.

We also made the following three additional analogues in this subseries: 3-$CH_3O$ [(±)-**17**], 2-$CH_3O$ [(±)-**18**], and 4-$CF_3$ [(±)-**20**]. For the two methoxy regioisomers (±)-**17** and (±)-**18**, binding affinity, while substantial, was somewhat lower (4-fold and 18-fold for $\mu$, respectively; 2-fold and 8-fold for $\kappa$, respectively) than that of (±)-**16**; the 4-$CH_3O$ derivative has the highest binding affinity within the entire series. These data suggest that not only the presence of an electron-donating group is important but also affinity is dependent on that group's position on the phenyl ring. Last,

the 4-$CF_3$ phenyl derivative (±)-**20** displayed somewhat less affinity than the 4-Cl [(±)-**13**] and 3,4-$Cl_2$ [(±)-**14**] analogues.

The 2-, 3-, and 4-pyridinyl analogues of (±)-**10** were made to probe the effects of aza substitution on the phenyl ring. Subnanomolar affinity for $\mu$ and $\kappa$ was observed for the 3-pyridinyl compound (±)-**23** that was comparable to (±)-**10**. The 2-pyridinyl analogue (±)-**22** displayed 6-fold and 18-fold lower affinity than (±)-**23** for $\mu$ and $\kappa$ receptors, respectively. The 4-pyridinyl isomer (±)-**24** had 28-fold and 6-fold lower affinity than (±)-**23** for $\mu$ and $\kappa$ receptors, respectively. In an attempt to rationalize the substantial differences in affinity within this small subseries of structurally similar analogues, one argument would be that the best affinity would be seen in those analogues where the H-bond donor ability of the anilino NH is the greatest. Since the compounds with the highest affinity, the phenyl ([(±)-**10**]) and 3-pyridinyl ([(±)-**23**]) derivatives, are the ones predicted to have the weakest H-bond donor characteristics based on electronic consideration, other factors must be considered. These limited data suggest that the enhanced affinity of the phenyl ([(±)-**10**]) and 3-pyridinyl ([(±)-**23**]) compounds relative to the affinity of others [e.g., 8-(2-pyridinylamino), 8-(4-pyridinylamino), 8-amino) is due to optimized interactions of the (hetero)aromatic group itself with the target protein rather than to the role the (hetero)aromatic group plays in modulating the physicochemical properties of other groups in the pharmacophore. One such interaction might be hydrophobic in nature; another possibility is that the 3-N of (±)-**23** acts as an H-bond acceptor for a putative complimentary donor on the receptor.

In an attempt to identify the bioactive conformation of the *N*-alkyl and/or aryl derivatives, we made two conformationally restricted analogues as probes. These are the indole derivative (±)-**39** and carbazole (±)-**40**, and we observed good to moderate binding affinity for both. In addition to (±)-**39** being a potential mimic of the *N*-ethyl derivative (±)-**8**, the indole NH fits nicely into the classic mold of a bioisosteric replacement for a phenolic OH.[49] Relative to (±)-**8**, indole (±)-**39** had 4-fold less affinity for $\mu$ and had nearly comparable affinity for $\kappa$. Carbazole derivative (±)-**40** could be considered a close analogue of the *N*-phenyl derivative (±)-**10** in that it incorporates an ortho carbon of the phenyl appendage of (±)-**10** into an additional ring with the 7-position of the benzomorphan ring system. Modest binding affinity was seen for (±)-**40** that was 17- and 12-fold less than (±)-**10** for $\mu$ and $\kappa$, respectively. Few conclusions can be drawn from these data other than the following: (a) we have yet another example of the utility of an indole NH to be a surrogate for a phenolic OH; (b) the bioactive conformation of (±)-**10** is probably not that displayed by (±)-**40**.

To further probe the receptor space that the phenyl of (±)-**10** occupies, we extended the distance between it and the benzomorphan core by one and two methylenes. Compared to (±)-**10**, the benzylamino analogue (±)-**25** had comparable affinity for $\mu$ receptors but had 6-fold lower affinity for $\kappa$. Consistent with our other observations, the activity of racemic (±)-**25** resides in the (−)-(2*R*,6*R*,11*R*)-isomer (−)-**26**. We made two substituted (on phenyl) derivatives to see if the SAR in the *N*-benzyl subseries paralleled that of the *N*-phenyl series. Compound (±)-**27**, the 4-methoxybenzyl derivative, had 5- and 15-fold less affinity for $\mu$ and $\kappa$, respectively, than (±)-**25**. This result contrasts with the *N*-phenyl case where 4-methoxy [(±)-**16**] resulted in a 3-fold increase in affinity relative to H [(±)-**10**]. When a 4-Cl was introduced into the benzyl of (±)-**27**, affinity decreased 6-fold for $\mu$ and 3-fold for $\kappa$ receptors. This was similar to the effect the 4-Cl had on the *N*-phenyl analogue (±)-**10**.

Extension of the phenyl group by one more methylene gave the phenethyl analogue (±)-**29**, which had somewhat lower affinity (approximately 7-fold) for $\mu$ than either the corresponding benzyl or phenyl derivative (±)-**25** or (±)-**10**, respectively. Against $\kappa$, (±)-**29** had only 2-fold lower affinity than (±)-**25** and had 13-fold lower affinity than (±)-**10**.

Several 8-tertiary amine derivatives of cyclazocine were also made. Relative to primary amine (±)-**4**, the 8-dimethylamino analogue (±)-**30** had 8- to 9-fold lower binding affinity for $\mu$ and $\kappa$. Consistent with SAR studies for traditional opiates where the prototypic phenolic OH is required for binding to opioid receptors,[2−5] these data indicate that at least one H on the 8-position N is required for reasonable binding affinity. While it is possible that (±)-**30** can donate an H-bond to a complimentary acceptor site on the opioid receptor when in the protonated state, the low p$K_a$ (<5) for such aromatic amines decreases the likelihood of any significant protonation at the pH (7.5) of the assay. These binding data, however, appear inconsistent with our previous in vivo antinociception studies where we observed that (±)-**4** and (±)-**30** had the same high potency in the acetylcholine writhing test (mouse) when dosed sc.[11] It is likely that the potent antinociception properties of (±)-**30** is a result of its metabolism to (±)-**4** and/or (±)-**7**, two compounds that have good affinity for opioid receptors. We have no direct evidence, however, to support or refute this assumption. We made the two enantiomers of (±)-**30** and found that the modest binding affinity resides in the (−)-(2*R*,6*R*,11*R*)-isomer (−)-**31** [versus (+)-**32**].

The *N*-(1-pyrrolidinyl), *N*-(1-piperidinyl), and *N*-(1-morpholinyl) analogues (±)-**33**, **-34**, and **-35**, respectively, all had very low affinity for the receptors; however, there were two tertiary amine derivatives that bucked this trend and displayed reasonable affinity. These were the *N*-[1-(4-methylpiperazinyl)] analogue (±)-**36** ($K_i$ = 21 nM versus $\mu$; $K_i$ = 8.8 nM versus $\kappa$) and the $N(CH_3)CH_2C_6H_5$ derivative (±)-**37** ($K_i$ = 56 nM versus $\mu$; $K_i$ = 44 nM versus $\kappa$). As discussed in an earlier section, the *N*-benzyl group is responsible for a 6-fold increase in affinity for $\mu$ relative to NH (compare (±)-**25** and (±)-**4**) and had little effect on $\kappa$ affinity. We can only speculate that the enhanced affinity of the tertiary amine derivative (±)-**37** for $\mu$ relative to other tertiary amine analogues is to due to the benefits of the *N*-benzyl appendage and may compensate somewhat for the lack of the NH H-bond donor. For (±)-**36**, the distal N of the piperazine is undoubtedly protonated at pH 7.5 and thus may sustain an electrostatic or H-bond interaction with a complementary site of the receptor. Last, we tested imine intermediate (±)-**38**, which displayed very low affinity for all receptors. Factors

**Table 2.** $E_{Max}$ and $EC_{50}$ Values for the Stimulation of [$^{35}$S]GTP$\gamma$S Binding to the Human $\kappa$ Opioid Receptor[a]

| compd | $E_{max}$ (% maximal stimulation) | $EC_{50}$ (nM) |
|---|---|---|
| (±)-**1** | 90 ± 7.5 | 1.6 ± 0.60 |
| (−)-**2** | 100 ± 2.6 | 1.2 ± 0.30 |
| (−)-**5** | 80 ± 6.5 | 20 ± 0.12 |
| (−)-**11** | 120 ± 7.7 | 3.8 ± 0.21 |
| (±)-**23** | 90 ± 8.8 | 10 ± 0.94 |
| (−)-**42** | 170 ± 11 | 1.1 ± 0.30 |
| (±)-**44** | 100 ± 6.0 | 4.4 ± 1.6 |
| (−)-**45** | 110 ± 3.2 | 2.8 ± 0.80 |
| (±)-**47** | 110 ± 8.6 | 5.9 ± 1.0 |
| (±)-**48** | 80 ± 1.2 | 3.3 ± 0.17 |
| (±)-**49** | 70 ± 6.0 | 9.7 ± 2.1 |
| (−)-**50** | 70 ± 9.2 | 4.0 ± 0.38 |
| (−)-**51** | 70 ± 5.7 | 330 ± 46 |
| U 50,488 | 140 ± 12 | 7.0 ± 4.3 |
| spiradoline | 120 ± 14 | 18 ± 4.3 |

[a] See Experimental Section. Data are the mean $E_{max}$ and $EC_{50}$ values ± SE from at least three separate experiments, performed in triplicate. For calculation of the $E_{max}$ values, the control [$^{35}$S]GTP$\gamma$S binding was set at 0%.

**Table 3.** $E_{max}$ and $EC_{50}$ Values for the Stimulation of [$^{35}$S]GTP$\gamma$S Binding to the Human $\mu$ Opioid Receptor[a]

| compd | $E_{max}$ (% maximal stimulation) | $EC_{50}$ (nM) |
|---|---|---|
| (−)-**2** | 50 ± 6.0 | 4.5 ± 0.50 |
| (−)-**11** | 50 ± 5.6 | 15 ± 4.1 |
| (−)-**42** | 70 ± 2.8 | 5.5 ± 1.1 |
| (±)-**44** | 60 ± 5.3 | 62 ± 3.6 |
| (−)-**45** | 100 ± 1.7 | 92 ± 6.3 |
| (±)-**47** | 70 ± 1.3 | 22 ± 3.1 |
| (±)-**48** | 40 ± 0.21 | 21 ± 3.2 |
| (±)-**49** | 80 ± 5.5 | 180 ± 12 |
| DAMGO | 120 ± 12 | 110 ± 9.0 |

[a] See Experimental Section. Data are the mean $E_{max}$ and $EC_{50}$ values ± SE from at least three separate experiments, performed in triplicate. For calculation of the $E_{max}$ values, the control [$^{35}$S]GTP$\gamma$S binding was set at 0%.

contributing to this observation could be the lack of an NH as H-bond donor and/or that the steric bulk of the benzophenone imine moiety might exceed the size of the complimentary pocket(s) in the receptors.

Intrinsic opioid-receptor-mediated activity for selected members of the series was determined using [$^{35}$S]GTP$\gamma$S binding assays at $\kappa$ and $\mu$ receptors. All compounds tested in these assays had high affinities ($K_i$ < 4 nM) for $\kappa$ and receptors and several pairs were chosen to compare the effect of the following structural changes on intrinsic activity: (a) 8-OH versus 8-$NH_2$ [(−)-**2** and (−)-**5**, (−)-**42** and (−)-**45**, (±)-**48** and (±)-**49**, and (−)-**50** and (−)-**51**]; (b) 8-$NH_2$ versus 8-NHphenyl [(−)-**5** and (−)-**11**, and (±)-**44** and (±)-**47**]. Results for $\kappa$ and $\mu$ opioid receptor stimulation of [$^{35}$S]GTP$\gamma$S binding are shown in Tables 2 and 3, respectively. Efficacy in these assays is quantified by the $E_{max}$ value (the percent of maximal stimulation of control), and affinity for the receptor is quantified by an $EC_{50}$ value that represents the concentration of compound that produced 50% of the maximal stimulation obtained by the compound. Intrinsic activity was observed in all compounds tested. For example, the 8-NH(3-pyridinyl) analogue (±)-**23**, that has high affinity ($K_i$ = 0.50 nM) for $\kappa$ in the binding assay, showed an $E_{max}$ of 90% (Table 2) comparable to the value displayed by cyclazocine (±)-**1**. Within this small subset of compounds, when tested for both $\kappa$ and $\mu$ receptor stimulation, these benzomorphans were generally more efficacious in stimulating $\kappa$ than $\mu$, as would be predicted from the binding data and historical data. For (−)-cyclazocine [(−)-**2**] and the 8-$NH_2$ analogue (−)-**5**, similar maximal stimulation of [$^{35}$S]GTP$\gamma$S binding to $\kappa$ receptors was seen. (−)-EKC [(−)-**42**] produced the greatest stimulation ($E_{max}$ = 170%) of [$^{35}$S]GTP$\gamma$S binding to $\kappa$ receptors among all compounds tested and was substantially more efficacious than its 8-$NH_2$ analogue (−)-**45**. In each of the other two pairs of 8-OH versus 8-$NH_2$ analogues evaluated in the $\kappa$ assay, (±)-**48** versus (±)-**49** (ketocyclazocine core) and (−)-**50** versus (−)-**51** (Merz core), similar efficacy was observed.

The two pairs of 1-keto analogues [(−)-**42** versus (−)-**45** and (±)-**48** versus (±)-**49**] were studied for stimulation of [$^{35}$S]GTP$\gamma$S binding to $\mu$ receptors (Table 3) where a different activity profile was seen. Both 8-$NH_2$ compounds showed higher efficacy (1.4- to 2-fold) than their 8-OH counterparts. We also compared the effects of phenyl substitution on the 8-N on [$^{35}$S]GTP$\gamma$S binding by using the (−)-cyclazocine-related pair (−)-**5** versus (−)-**11** for $\kappa$ and using the EKC-related pair (±)-**44** versus (±)-**47** for $\kappa$ and $\mu$ receptors. For both $\kappa$ and $\mu$, the *N*-phenyl group was responsible for a modest increase in efficacy (1.1- to 1.5-fold).

## Conclusions

Analysis of opioid receptor binding data for this expanded series of 8-amino-2,6-methano-3-benzazocines has led us to an improved understanding of the relationship between affinity for the receptors and the nature of the 8-substituent. With respect to the isosteric replacement of the 8-OH of several benzomorphans with 8-$NH_2$, the effect of the amino group on binding affinity is dependent on the nature of the ligand core and that the 8-$NH_2$ group most closely mimics the binding properties of 8-OH when the core structure contains a 1-keto group (i.e, EKC and ketocyclazocine) and the receptor type is $\kappa$. This conclusion about the interdependence of functional groups on binding affinity is further supported by data from our morphine study where we found that 3-amino-3-deshydroxymorphine had 60-fold lower affinity for $\mu$ than morphine.[24]

The significant enhancement in affinity upon monosubstitution of the 8-N with (hetero)aryl-containing groups suggests that the receptor has a specific complementary site(s) of interaction with these appendages. On the basis of the SAR that has emerged, we conclude that hydrophobics play an important role in binding and that the hydrophobic pocket may contain an H-bond donor group complementary to a heteroaryl (e.g., 3-pyridinyl) acceptor. This binding pocket has not been previously explored to any great extent because most opiates have no opportunity to probe this receptor space because of the lower (than nitrogen) valence of the oxygen of the prototypic 8-OH group. Disubstitution of the 8-amine provides ligands having relatively low affinity that we conclude is due to the absence of an NH donor as would be predicted from historical SAR data of 8-OH opiates.

Besides the high affinity for opioid receptors, other attributes of 8-OH-containing benzomorphans that were sustained by many 8-amino substitutions are (a) high enantiospecificity of binding, with the (2*R*,6*R*,11*R*)-isomers [(2*S*,6*R*,11*R*)- for the 1-keto compounds] being the active enantiomer; (b) high selectivity for $\mu$ and $\kappa$ over $\delta$ opioid receptors, and (c) intrinsic activity as demonstrated in [$^{35}$S]GTP$\gamma$S assays.

We believe the knowledge gained from this study will facilitate the design of new high-affinity opioid receptor-interactive ligands modified at the 8-position. In fact, using the knowledge we learned that the receptor can accommodate large hydrophobic 8-substituents capable of sustaining H-bond contacts with the protein, we recently made and evaluated several opiates containing a carboxamide ($CONH_2$) group at the phenolic OH position.[50,51] Many of these novel ligands display the high (subnanomolar) affinity for $\mu$, $\kappa$, and/or $\delta$ as their phenolic OH counterparts, and in one instance (cyclazocine core), this modification resulted in a substantially longer (2 versus 15 h) duration of antinociception in mice.[52] Encouraged by these results, we continue to focus our efforts in further exploration of 8- and 3-position modification of benzomorphans and morphinans, respectively.

## Experimental Section

Proton NMR and in certain cases $^{13}C$ NMR [Varian Unity-500 NMR] data, direct insertion probe (DIP) chemical ionization mass spectra (Shimadzu GC-17A GC−MS mass spectrometer), and infrared spectra (Perkin-Elmer Paragon 1000 FT-IR spectrophotometer) were consistent with the assigned structures of all test compounds and intermediates. $^1H$ NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), and br (broad). Coupling constants are in hertz. Carbon, hydrogen, and nitrogen elemental analyses for all novel targets were performed by Quantitative Technologies Inc., Whitehouse, NJ, and were within ± 0.4% of theoretical values except as noted; the presence of water was confirmed by proton NMR. Melting points were determined on a Meltemp capillary melting point apparatus and are uncorrected. Optical rotation data were obtained from a Perkin-Elmer 241 polarimeter. Reactions were generally performed under an argon or $N_2$ atmosphere. Amines used in the Pd-catalyzed amination reactions and racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) were purchased from Aldrich Chemical Co. and used as received unless otherwise indicated. Tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$], $Pd(OAc)_2$, and 1,1′-bis-(diphenylphosphino)ferrocene (DPPF) were purchased from Strem Chemicals, Incorporated. THF was distilled from sodium/benzophenone ketyl. Toluene and $Et_2O$ were distilled from sodium metal. Pyridine was distilled from KOH. Methylene chloride was distilled from $CaH_2$. DMF and DMSO were distilled from $CaH_2$ under reduced pressure. Methanol was dried over 3 Å molecular sieves prior to use. Silica gel (Bodman Industries, ICN SiliTech 2-63 D 60A, 230−400 mesh) was used for flash column chromatography.

**(−)-3-(Cyclopropylmethyl)-1,2,3,4,5,6,-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocin-8-amine [(−)-5] and (+)-3-(Cyclopropylmethyl)-1,2,3,4,5,6,-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocin-8-amine [(+)-6].** By use of procedures[11] identical to those reported for preparing (±)-**4**, cyclazocine enantiomers[28,29] (−)-**2** and (+)-**3** were converted to (−)-**5** and (+)-**6**, respectively, in yields nearly identical to those reported (48% overall) for the racemate. For (−)-**5**: mp 87−89 °C; $[\alpha]^{25}_D$ −118° (*c* 1.0, MeOH)]. Anal. ($C_{18}H_{26}N_2 \cdot 0.25H_2O$) C, H, N. For (+)-**6**: mp 88−90 °C; $[\alpha]^{25}_D$ +118° (*c* 1.0, MeOH)]. Anal. ($C_{18}H_{26}N_2$) C, H, N.

**(±)-3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,-11-dimethyl-2,6-methano-3-benzazocin-8-yltrifluoromethanesulfonic Acid Ester [(±)-53]. Method A.** To a stirred suspension of cyclazocine [(±)-**1**, 1.00 g, 3.68 mmol] and pyridine (0.76 g, 9.58 mmol) in 20 mL of dry $CH_2Cl_2$ under an $N_2$ atmosphere was added trifluoromethanesulfonic anhydride (1.25 g, 4.42 mmol) at 0 °C. The resulting bright yellow-orange suspension gradually became a solution after 15 min and was stirred at 25 °C for an additional 2 h. The reaction was then quenched with 20 mL of saturated $NaHCO_3$ solution. The organic phase was washed twice with water and once with brine. After the organic extracts ($Na_2SO_4$) were dried and concentrated in vacuo, (±)-**53** (1.42 g, 96%) was obtained as a red-orange oil: $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.15 (d, 1H, $J$ = 8.5 Hz), 7.12 (d, 1H, $J$ = 2.4 Hz), 7.00 (dd, 1H, $J$ = 8.5, 2.6 Hz), 3.19 (m, 1H), 2.98−2.94 (d, 1H, $J$ = 18.6 Hz), 2.67−2.77 (m, 2H), 2.52 (m, 1H), 2.34 (m, 1H), 1.99 (m, 3H), 1.38 (s, 3H), 1.33 (m, 1H), 0.89 (m, 1H), 0.85 (d, 3H, $J$ = 7.1 Hz), 0.51 (d, 2H, $J$ = 8 Hz), 0.12 (m, 2H); IR (film) $\nu_{max}$ 2965, 1716, 1418, 1215 $cm^{-1}$; MS (CI) *m*/*z* 404 $(M + H)^+$. Anal. ($C_{19}H_{24}F_3NO_3S \cdot 0.5H_2O$) C, H, N.

**(±)-3-(Cyclopropylmethyl)-*N*-(diphenylmethylene)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocin-8-amine [(±)-38]. Method A.** An oven-dried 25 mL two-neck flask equipped with reflux condenser was placed into a $N_2$-filled glovebox where it was charged with $Pd_2(dba)_3$ (0.052 g, 0.057 mmol), DPPF (0.094 g, 0.171 mmol), and NaO-t-Bu (0.109 g, 1.14 mmol). The system was capped with a rubber septum and removed from the glovebox. Dry toluene (4 mL) was then added to the mixture via syringe, and the resulting dark suspension was stirred at 25 °C for 10 min. A solution containing triflate (±)-**53** (0.460 g, 1.14 mmol) and benzophenone imine (0.248 g, 1.368 mmol) in 3 mL of toluene was added, and the mixture was heated to 80°C with vigorous stirring. At approximately 6 h, the reaction had gone to completion as evidenced by TLC. It was allowed to cool, diluted with 20 mL of $CH_2Cl_2$, filtered over Celite, and then directly preadsorbed onto silica gel. The crude reaction mixture was purified by flash column chromatography using hexanes/ethyl acetate as eluent (20:1 → 10:1 → 3:1 gradient) to yield (±)-**38** (0.245 g, 47%) as a yellow-orange oil: $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.75 (d, 2H, $J$ = 7.5 Hz), 7.46 (m, 1H), 7.40 (m, 2H), 7.23 (m, 3H), 7.08 (m, 2H), 6.87 (d, 1H, $J$ = 8.1 Hz), 6.63 (m, 1H), 6.44 (m, 1H), 3.08 (m, 1H), 2.81 (d, 1H, $J$ = 18.2 Hz), 2.53−2.63 (m, 2H), 2.44 (m, 1H), 2.30 (m, 1H), 1.67−1.90 (m, 3H), 1.07 (s, 3H), 0.97 (m, 1H), 0.85 (m, 1H), 0.75 (d, 3H, $J$ = 6.8 Hz), 0.50 (m, 2H), 0.10 (m, 2H); IR (film) $\nu_{max}$ 2961, 2916, 1594, 1571, 1491 $cm^{-1}$; MS (CI) *m*/*z* 435 $(M + H)^+$. Anal. ($C_{31}H_{34}N_2$ ) C, H, N.

**(±)-3-(Cyclopropylmethyl)-1,2,3,4,5,6,-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocin-8-amine [(±)-4]. Method A.** Ketimine adduct (±)-**38** (1.459 g, 3.36 mmol) was dissolved in 100 mL of methanol, and $NH_2OH \cdot HCl$ (0.467 g, 6.72 mmol) and NaOAc (0.716 g, 8.73 mmol) were added. The reaction mixture was stirred at 25 °C for 30 min, and it was concentrated in vacuo. The residue was purified by flash column chromatography ($CH_3OH/CH_2Cl_2/NH_4OH$,1:9:0.1) to give (±)-**4**[11] (0.765 g, 84%) as an oil: $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 6.83 (d, 1H, $J$ = 8.0 Hz), 6.57 (d, 1H, $J$ = 2.4 Hz), 6.47 (dd, 1H, $J$ = 8.1, 2.4 Hz), 3.50 (b, 2H), 3.10 (m, 1H), 2.82 (d, 1H, $J$ = 18.1 Hz), 2.68 (m, 1H), 2.58 (m, 1H), 2.47 (m, 1H), 2.31 (m, 1H), 2.04 (m, 1H), 1.89 (m, 1H), 1.83 (m, 1H), 1.34 (m, 1H), 1.32 (s, 3H), 0.85 (m, 1H), 0.85 (d, 3H, $J$ = 7.1 Hz), 0.49 (m, 2H), 0.10 (m, 2H); MS (CI) *m*/*z* 271 $(M + H)^+$.

**(±)-3-(Cyclopropylmethyl)-1,2,3,4,5,6,-hexahydro-*cis*-6,11-dimethyl-*N*-(4-methoxyphenyl)-2,6-methano-3-benzazocin-8-amine [(±-16)]. Method B.** $Pd_2(dba)_3$ (0.060 g, 0.066 mmol), DPPF (0.062 g, 0.197 mmol), and NaO-t-Bu (0.126 g, 1.313 mmol) were added to an oven-dried 25 mL two-neck flask equipped with reflux condenser contained in an $N_2$-filled glovebox. The flask was removed from the glovebox after being capped with a rubber septum, and 4 mL of dry toluene was added to the mixture via syringe. The resulting dark suspension was stirred at ambient temperature for 10 min when a solution of triflate (±)-**53** (0.300 g, 0.744 mmol) and *p*-anisidine (0.110 g, 0.892 mmol) in 3 mL of toluene was added. The resulting mixture was heated to 80 °C with vigorous stirring. As judged by TLC, the reaction was complete after 3 h. After cooling to ambient temperature, the mixture was diluted with 20 mL of $CH_2Cl_2$, filtered over Celite, and then preadsorbed onto silica gel. The crude reaction mixture was purified by flash chromatography using hexanes/ethyl acetate as eluent (20:1 → 10:1 → 3:1 gradient) to provide (±)-**16** as a light-yellow oil that crystallized upon treatment with

ether (0.179 g, 0.475 mmol, 64%): mp 180−181 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.00 (m, 2H), 6.90 (m, 1H), 6.84 (m, 3H), 6.74 (m, 1H), 5.43 (bs, 1H), 3.78 (s, 3H), 3.15 (m, 1H), 2.87−2.84 (d, $J$ = 18.0 Hz, 1H), 2.74 (m, 1H), 2.72 (m, 1H), 2.49−2.34 (m, 2H), 2.17 (m, 1H), 2.07 (m, 1H), 1.93 (m, 1H), 1.36 (m, 1H), 1.31 (s, 3H), 1.26 (m, 1H), 0.86 (d, $J$ = 6.9 Hz, 3H), 0.51 (m, 2H), 0.11 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 154.54, 143.01, 142.72, 136.71, 128.36, 127.80, 120.68, 114.61, 114.10, 113.78, 69.99, 59.84, 57.07, 55.54, 49.89, 45.97, 42.01, 41.67, 36.42, 25.47, 23.07, 14.22, 9.24, 4.03, 3.59; IR ($CH_2Cl_2$) $\nu_{max}$ 3356, 2094, 1652, 1506 cm$^{-1}$; MS (CI) $m/z$ 377 (M + H)$^+$. Anal. ($C_{25}H_{32}N_2O\cdot0.5H_2O$) C, H, N.

**(−)-3-(Cyclopropylmethyl)-1,2,3,4,5,6,-hexahydro-*cis*-6,11-dimethyl-*N*-(phenylmethyl)-2,6-methano-3-benzazocin-8-amine [(−)-26]. Method C.** A flask was put into a nitrogen-filled glovebox and charged with the triflate of (−)-**2** (0.430 g, 1.067 mmol), $Pd(OAc)_2$ (0.0048 g, 0.0213 mmol), BINAP (0.0146 g, 0.0235 mmol), and NaO-t-Bu (0.144 g, 1.49 mmol). The flask was then capped with a rubber septum and removed from the glovebox. A solution of benzylamine (0.137 g, 1.28 mmol) in 10 mL of dry toluene was then added to the mixture via syringe. The reaction mixture was then heated to 80 °C in an oil bath with vigorous stirring. After 8 h, the reaction mixture was cooled to 25 °C, diluted with ether, filtered, and concentrated in vacuo. The resulting crude oil was purified by flash column chromatography to give (−)-**26** (0.205 g, 53%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.27−7.41 (m, 5H), 6.87 (d, 1H, $J$ = 8.1 Hz), 6.55 (d, 1H, $J$ = 2.5 Hz), 6.47 (dd, 1H, $J$ = 8.1, 2.4 Hz), 4.28 (d, 2H, $J$ = 4.9 Hz), 3.84 (b, 1H), 3.11 (m, 1H), 2.83 (d, 1H, $J$ = 18.1 Hz), 2.70 (m, 1H), 2.60 (m, 1H), 2.48 (m, 1H), 2.32 (m, 1H), 2.06 (m, 1H), 1.89 (m, 1H), 1.84 (m, 1H), 1.34 (m, 1H), 1.32 (s, 3H), 0.86 (m, 1H), 0.86 (d, 3H, $J$ = 7.0 Hz), 0.50 (m, 2H), 0.11 (m, 2H). IR (film) $\nu_{max}$ 2913, 1613, 1505, 1321, 456, 451 cm$^{-1}$; MS (CI) $m/z$ 361 (M + H)$^+$; $[\alpha]^{25}_D$ −101.9 ° ($c$ 1.06, EtOH). Anal. ($C_{25}H_{32}N_2$) C, H, N.

**(±)-3-(Cyclopropylmethyl)-1,2,3,4,5,6,-hexahydro-*cis*-6,11-dimethyl-*N*-(4-dimethylaminophenyl)-2,6-methano-3-benzazocin-8-amine [(±)-21]. Method D.** An oven-dried 25 mL two-neck flask equipped with reflux condenser was placed into an $N_2$-filled glovebox where it was charged with $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), DPPF (0.042 g, 0.076 mmol), and NaO-t-Bu (0.005 g, 0.508 mmol). The system was capped with a rubber septum and removed from the glovebox. Dry toluene (4 mL) was then added to the mixture via syringe, and the resulting dark suspension was stirred at 25 °C for 10 min. A solution containing 4-bromo-*N*,*N*-dimethylaniline (0.101 g, 0.508 mmol) and amine (±)-**4** (0.164 g, 0.610 mmol) in 3 mL of toluene was added, and the mixture was heated to 80°C with vigorous stirring. After 6 h, the reaction had gone to completion as evidenced by TLC. The mixture was allowed to cool, diluted with 20 mL of $CH_2Cl_2$, filtered over Celite, and then directly preadsorbed onto silica gel. The crude reaction mixture was purified by flash column chromatography using hexanes/ethyl acetate as eluent (20:1 → 10:1 → 3:1 gradient) yielding (±)-**21** (0.134 g, 68%) as a brown oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.03 (d, 2H, $J$ = 1.7 Hz), 6.90 (d, 1H, $J$ = 1.9 Hz), 6.80 (s, 1H), 6.75 (d, 2H, $J$ = 1.7 Hz), 6.70 (d, 1H, $J$ = 1.8 Hz), 5.3 (m, 1H), 3.39 (m, 1H), 2.92 (s, 6H), 2.89−2.83 (m, 3H), 2.78 (m, 1H), 2.57 (m, 1H), 2.56 (m, 1H), 2.17 (m, 1H), 2.07 (m, 1H), 1.41 (m, 1H), 1.34, (s, 3H), 1.08 (m, 1H), 0.91 (d, 3H, $J$ = 7.1 Hz), 0.61 (d, 2H, $J$ = 8.1 Hz), 0.23 (m, 2H); IR ($CH_2Cl_2$) $\nu_{max}$ 3356, 2094, 1652, 1506 cm$^{-1}$; MS (CI) $m/z$ 390 (M + H)$^+$. Anal. ($C_{26}H_{35}N_3\cdot0.5H_2O$) C, H, N.

**3-(Cyclopropylmethyl)-1,2,3,4,5,6,-hexahydro-*N*,6,11-trimethyl-*cis*-2,6-methano-3-benzazocin-8-amine [(±)-7].** Compound (±)-**37** (0.080 g, 0.21 mmol) was dissolved in 5 mL of anhydrous MeOH, and 50% $Pd(OH)_2$/C (0.040 g) was added slowly. The suspension was placed in a Parr hydrogenation apparatus and was shaken for 24 h at 25 °C at a pressure of 72 psi. The reaction mixture was then filtered over Celite, and the filtrate was concentrated in vacuo. Preparative silica gel TLC ($CH_3OH/CH_2Cl_2/NH_4OH$, 1:9:0.1) gave the desired product (±)-**7**[11] (0.027 g, 44%) as white foam: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.89 (d, 1H, $J$ = 8.0 Hz), 6.50 (m, 1H), 6.43 (m, 1H), 3.53 (b, 1H), 3.10 (m, 1H), 2.83 (m, 1H), 2.82 (s, 3H), 2.69 (m, 1H), 2.60 (m, 1H), 2.48 (m, 1H), 2.32 (m, 1H), 2.05 (m, 1H), 1.90 (m, 1H), 1.84 (m, 1H), 1.36 (m, 1H), 1.35 (s, 3H), 0.86 (m, 1H), 0.86 (d, 3H, $J$ = 6.8 Hz), 0.50 (m, 2H), 0.11 (m, 2H); MS (CI) $m/z$ 285 (M + H)$^+$.

**(±)-3-(Cyclopropylmethyl)-1,2,3,4,5,6,-hexahydro-*cis*-6,11-dimethyl-*N*-(2-methylethyl)-2,6-methano-3-benzazocin-8-amine [(±)-9].** Compound (±)-**4** (0.104 g, 0.385 mmol) was dissolved in 20 mL of MeOH, and acetone (0.027 g, 0.462 mmol), $NaBH_3CN$ (0.024 g, 0.385 mmol), and $ZnCl_2$ (0.027 g, 0.193 mmol) were added. The reaction mixture was stirred at 25 °C for 12 h and quenched with 10 mL of 1 N NaOH solution. After evaporation to remove most of the MeOH, the resulting solution was extracted three times with EtOAc. The combined EtOAc extracts were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to dryness. Flash column chromatography of the resulting mixture provided the desired product (±)-**9** (0.085 g, 70%) as a yellow semisolid: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.84 (d, 1H, $J$ = 8.0 Hz), 6.46 (d, 1H, $J$ = 2.4 Hz), 6.40 (dd, 1H, $J$ = 8.1, 2.7 Hz), 3.58 (m, 1H), 3.09 (m, 1H), 2.81 (d, 1H, $J$ = 18.0 Hz), 2.68 (m, 1H), 2.57 (m, 1H), 2.47 (m, 1H), 2.32 (m, 1H), 2.05 (m, 1H), 1.88 (m, 1H), 1.83 (m, 1H), 1.35 (m, 1H), 1.32 (s, 3H), 1.20 (d, 3H, $J$ = 2.0 Hz), 1.18 (d, 3H, $J$ = 2.2 Hz), 0.85 (m, 1H), 0.85 (d, 3H, $J$ = 7.1 Hz), 0.49 (m, 2H), 0.10 (m, 2H); IR (film) $\nu_{max}$ 2962, 2915, 2834, 1613, 1506, 1462, 1429, 1379, 1320, 1256, 1177, 1099, 801 cm$^{-1}$; MS (CI) $m/z$ 313 (M + H)$^+$. Anal. ($C_{21}H_{32}N_2$) C, H, N.

**7-(Cyclopropylmethyl)-5,6,7,8,9,10-hexahydro-*cis*-10,-12-dimethyl-6,10-methano-1*H*-pyrrolo[2,3-*i*][3]benzazocine [(±)-39].** A modification of a known procedure[41] for the conversion of anilines to indoles was used as follows. A mixture of (±)-**4** (0.252 g, 0.93 mmol), bromoacetaldehyde diethyl acetal (0.203 g, 1.03 mmol), $KHCO_3$ (0.103 g, 1.03 mmol), and DMF (5 mL) was stirred at 125 °C for 20 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography ($CHCl_3$/MeOH/$H_2O$, 15 mL:1 mL:2 drops) to give (±)-**64** (0.194 g, 54%) having proton NMR and MS spectra consistent with the desired structure. Compound (±)-**64** (0.070 g, 0.18 mmol) was stirred at 90 °C in a sealed tube for 72 h with $(CF_3CO)_2O$ (0.35 mL) and $CF_3CO_2H$ (0.70 mL). After concentration of the mixture in vacuo, the crude product was purified by flash column chromatography ($CH_2Cl_2$/MeOH, 15:1) to give 0.36 g of intermediate (±)-**65** having proton NMR and MS spectra consistent with the desired structure. Without further purification or characterization, (±)-**65** was treated with 2 mL of 5% KOH in MeOH for 2 h at 25 °C. After concentration in vacuo, the residue was partitioned between $H_2O$ and $CH_2Cl_2$ and the organic layer was dried ($Na_2SO_4$) and concentrated to give a crude product that was purified by preparative silica gel TLC ($CHCl_3$/MeOH/$NH_4OH$, 33:7:1) to give 0.019 g (53% from (±)-**64**) of (±)-**39**[40] as a foam: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.04 (br s, 1H), 7.33 (s, 1H), 7.30 (s, 1H), 7.14 (d, 1H, $J$ = 2.5 Hz), 6.43 (d, 1H, $J$ = 2.2 Hz), 3.27 (s, 1H), 3.10 (d, 1H, $J$ = 8.1 Hz), 2.93 (m, 1H), 2.77 (m, 1H), 2.59 (m, 1H), 2.44 (m, 1H), 2.13 (m, 1H), 2.04 (m, 2H), 1.46 (s, 3H), 1.37 (d, 1H, $J$ = 13.5 Hz), 1.25 (s, 3H), 0.93 (m, 1H), 0.90 (d, $J$ = 7.1 Hz, 2H), 0.54 (d, $J$ = 7.8 Hz, 1H), 0.17 (m, 1H); MS (CI) $m/z$ 295 (M + H)$^+$.

**(±)-7-(Cyclopropylmethyl)-5,6,7,8,9,10-hexahydro-*cis*-10,12-dimethyl-6,10-methano-1*H*-indolo[2,3-*i*][3]benzazocine [(±)-40].** Phenylhydrazine hydrochloride (0.053 g, 0.364 mmol) was added to a solution of methyl enol ether (±)-**66**[11] (0.100 g, 0.348 mmol) in acetic acid (1 mL) under nitrogen. The mixture was stirred at room temperature for 1 h and then at reflux for 2 h. The reaction mixture was taken up in 10 mL of ethyl acetate and washed with saturated sodium bicarbonate solution and water. The organic phase was dried ($Na_2SO_4$) and concentrated in vacuo to give a crude product as a brown oil. Purification by flash column chromatography ($CH_2Cl_2$/MeOH/$NH_4OH$, 25:1:0.05) provided (±)-**40** (0.025 g, 21%) as white needles: mp 222−224 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.34 (d, 1H, $J$ = 8.3 Hz), 8.15 (s, 1H), 7.40 (d, 1H, $J$ = 8.6 Hz), 7.35

(t, 1H, $J = 7.2$ Hz), 7.21 (d, 1H, $J = 8.3$ Hz), 7.18 (t, 1H, $J = 7.7$ Hz), 7.15 (d, 1H, $J = 8.3$ Hz), 3.29 (s, 1H), 3.02 (d, 1H d, $J = 5.9$, 8.1 Hz), 2.93 (d, 1H, $J = 8.1$ Hz), 2.84 (d, 1H, $J = 11.0$ Hz), 2.59 (d, 1H, $J = 11.7$ Hz), 2.50 (dd, 1H, $J = 6.4$, 12.7 Hz), 2.30 (dd, 1H, $J = 6.8$, 12.7 Hz), 2.07 (m, 3H), 1.77 (s, 3H), 1.67 (m, 1H), 0.93 (d, 3H, $J = 7.1$ Hz), 0.91 (m, 1H), 0.50 (m, 2H), 0.13 (m, 1H), 0.08 (m, 1H); IR ($CHCl_3$) $\nu_{max}$ 3357, 2974, 1413, 1049 $cm^{-1}$; MS (CI) $m/z$ 345 $(M + H)^+$. Anal. ($C_{24}H_{28}N_2 \cdot 0.5H_2O$) C, H, N.

**Radiolabeled Ligand Binding Assays.** Binding assays used to screen compounds are similar to those previously reported.[43] Guinea pig brain membranes, 500 $\mu$g of membrane protein, were incubated with 12 different concentrations of the compound in the presence of 1 nM [$^3$H]U69,593[53] ($\kappa$), 0.25 nM [$^3$H]DAMGO[54] ($\mu$), or 0.2 nM [$^3$H]naltrindole[55] ($\delta$) in a final volume of 1 mL of 50 mM Tris-HCl, pH 7.5 at 25 °C. Incubation times of 60 min were used for [$^3$H]U69,593 and [$^3$H]DAMGO. Because of a slower association of [$^3$H]naltrindole with the receptor, a 3 h incubation was used with this radioligand. Samples incubated with [$^3$H]naltrindole also contained 10 $\mu$M $MgCl_2$ and 0.5 mM phenylmethylsulfonyl fluoride. Nonspecific binding was measured by inclusion of 10 $\mu$M naloxone. The binding was terminated by filtering the samples through Schleicher & Schuell no. 32 glass fiber filters using a Brandel 48-well cell harvester. The filters were subsequently washed three times with 3 mL of cold 50 mM Tris-HCl, pH 7.5, and were counted in 2 mL of Ecoscint A scintillation fluid. For [$^3$H]-naltrindole and [$^3$H]U69,593 binding, the filters were soaked in 0.1% polyethylenimine for at least 60 min before use. $IC_{50}$ values were calculated by a least-squares fit to a logarithm−probit analysis. $K_i$ values of unlabeled compounds were calculated from the equation

$$K_i = \frac{IC_{50}}{1 + S}$$

where $S$ = (concentration of radioligand)/($K_d$ of radioligand).[56] Data are the mean ± SE from at least three experiments performed in triplicate.

**[$^{35}$S]GTP$\gamma$S Binding Assays.** In a final volume of 0.5 mL, 12 different concentrations of each test compound were incubated with 15 $\mu$g ($\kappa$) or 7.5 $\mu$g ($\mu$) of CHO cell membranes that stably expressed either the human $\kappa$ or $\mu$ opioid receptor. The assay buffer consisted of 50 mM Tris-HCl, pH 7.4, 3 mM $MgCl_2$, 0.2 mM EGTA, 3 $\mu$M GDP, and 100 mM NaCl. The final concentration of [$^{35}$S]GTP$\gamma$S was 0.080 nM. Nonspecific binding was measured by inclusion of 10 $\mu$M GTP$\gamma$S. Binding was initiated by the addition of the membranes. After an incubation of 60 min at 30°C, the samples were filtered through Schleicher & Schuell no. 32 glass fiber filters. The filters were washed three times with cold 50 mM Tris-HCl, pH 7.5, and were counted in 2 mL of Ecoscint scintillation fluid. Data are the mean $E_{max}$ and $EC_{50}$ values ± SE from at least three separate experiments, performed in triplicate. For calculation of the $E_{max}$ values, the control [$^{35}$S]GTP$\gamma$S binding was set at 0%.

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