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# 8-Aminocyclazocine Analogues: Synthesis and Structure–Activity Relationships†

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**Abstract**—Opioid binding affinities were assessed for a series of cyclazocine analogues where the prototypic 8-OH substituent of cyclazocine was replaced by amino and substituted-amino groups. For μ and κ opioid receptors, secondary amine derivatives having the (2*R*,6*R*,11*R*)-configuration had the highest affinity. Most targets were efficiently synthesized from the triflate of cyclazocine or its enantiomers using Pd-catalyzed amination procedures. 

## Introduction

Cyclazocine [(±)-**1**] was evaluated in humans in the 1960's and early 1970's as an analgesic and as a possible treatment for preventing relapse in post-addicts of heroin.[1,2] In humans dosed with the drug, potent analgesia was observed and following abrupt cyclazocine withdrawal, patients did not display drug-seeking behavior. Further clinical development of cyclazocine was ceased due, in part, to a short duration of analgesic action.[1,2] Cyclazocine is *O*-glucuronidated in humans which may account for its short duration of action.[3] In an attempt to retard this metabolic inactivation and increase its duration of action, we discovered some years ago that replacement of the 8-OH group of (±)-**1** with $NH_2$ provided the novel compound (±)-**4** which had somewhat diminished antinociception potency in mice when delivered by the subcutaneous route but comparable [to (±)-**1**] efficacy when delivered orally.[3] For example, in the mouse acetylcholine writhing 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. Whether high oral bioavailability due to lower first-pass metabolism, higher gut wall permeability, reduced clearance or some other factor accounts for the higher (than would be predicted by sc data) oral efficacy of (±)-**4** is not known.

Since these in vivo studies for (±)-**1** and (±)-**4** were performed prior to the full characterization of opioid receptors, receptor binding data were not obtained. In the late 1970's opioid receptor binding studies for cyclazocine revealed the compound to have high affinity for κ and μ opioid receptors.[1] Antinociceptive studies demonstrated that cyclazocine was a κ agonist and μ antagonist.[1] In further studies it was found that the opioid receptor binding properties of cyclazocine (which is racemic) resided in the (2*R*,6*R*,11*R*)-isomer (−)-**2** and that potent σ-receptor binding potency was resident in the (2*S*,6*S*,11*S*)-isomer (+)-**3**.[4–6] As part of our recent goal to identify orally-active analogues of cyclazocine having potent κ agonist and μ antagonist binding properties, we recently resynthesized (±)-**4**, made its hitherto unknown enantiomerically pure counterparts (−)-**5** and (+)-**6**, and made several related 8-amino analogues as probes to identify a preliminary structure–activity relationship. We now report the synthetic methods and μ, δ and κ opioid binding data for these new racemic, and in

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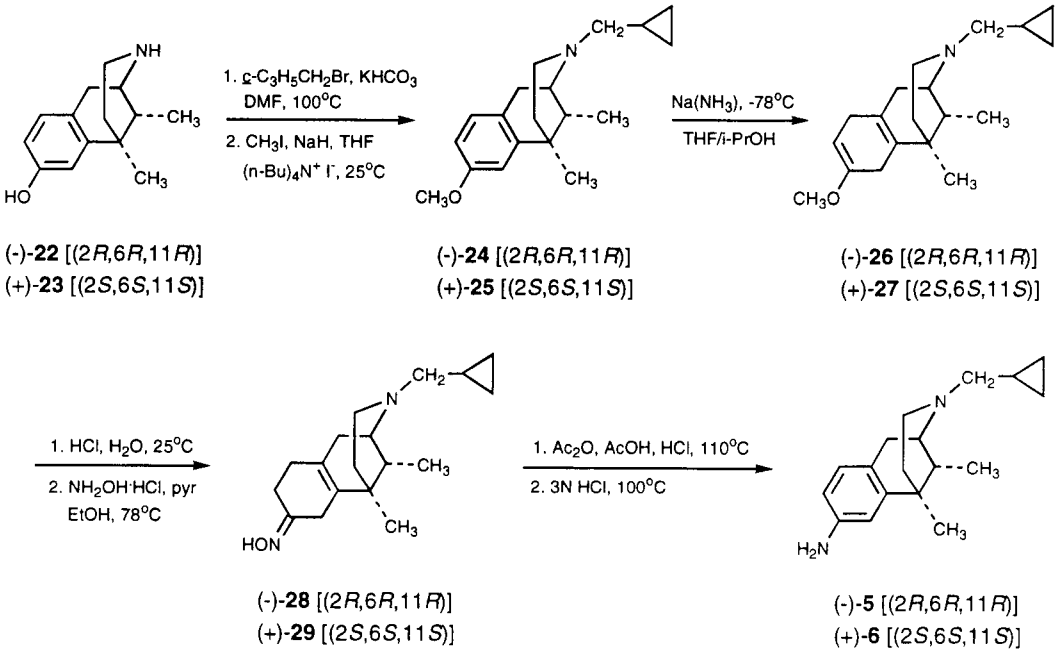
certain cases, enantiomerically pure 8-(substituted)-amino cyclazocine analogues compared to cyclazocine and its enantiomers.

## Chemistry

We used two approaches to synthesize new targets. Our original method[3] to make (±)-**4** was applied to make the enantiomeric counterparts, (−)-**5** and (+)-**6**. After derivatization with (*S*)-(−)-α-methylbenzylisocyanate to ensure optical purity,[7] the enantiomers of normetazocine (−)-**22**[8] and (+)-**23**[8] (Scheme 1) were alkylated with cyclopropylmethyl bromide to give the corresponding known enantiomers[8,9] of cyclazocine; conversion to the corresponding methyl ethers (−)-**24** and (+)-**25** was accomplished using known methodology.[10] Using our Birch reduction/Semmler-Wolf methodology (Scheme 1) for the conversion of cyclazocine methyl ether to (±)-**4**,[3] we converted (−)-**24** and (+)-**25** to (−)-**5** [(2*R*,6*R*,11*R*)] and (+)-**6** [(2*S*,6*S*,11*S*)], respectively.[11] For these transformations, very similar yields were observed to known racemic example.

While the Birch reduction/Semmler-Wolf method was very useful, we needed another procedure for the rapid introduction of a variety of amine substituents at position-8. The Pd-catalyzed amination[12] of aryl halides and




(-)-**22** [(2*R*,6*R*,11*R*)]
(+)-**23** [(2*S*,6*S*,11*S*)]

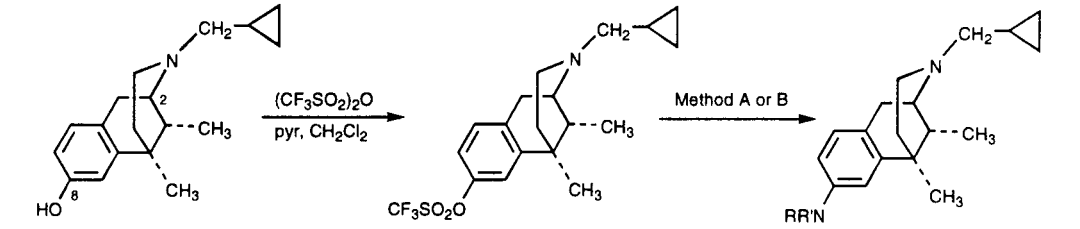
(-)-**24** [(2*R*,6*R*,11*R*)]
(+)-**25** [(2*S*,6*S*,11*S*)]

(-)-**26** [(2*R*,6*R*,11*R*)]
(+)-**27** [(2*S*,6*S*,11*S*)]

(-)-**28** [(2*R*,6*R*,11*R*)]
(+)-**29** [(2*S*,6*S*,11*S*)]

(-)-**5** [(2*R*,6*R*,11*R*)]
(+)-**6** [(2*S*,6*S*,11*S*)]

**Scheme 1.** Synthesis of chiral 8-amino-2,6-methano-3-benzacines.




(±)-**1** [cyclazocine - (2*RS*,6*RS*,11*RS*)]
(-)-**2** [(2*R*,6*R*,11*R*)]
(+)-**3** [(2*S*,6*S*,11*S*)]

(±)-**30** [(2*RS*,6*RS*,11*RS*)]
(-)-**31** [(2*R*,6*R*,11*R*)]
(+)-**32** [(2*S*,6*S*,11*S*)]

(±)-**8,10,13,15-21,33**
(-)-**11,14**
(+)-**12**

(±)-**21** ⟶ (±)-**7** ($H_2$, $Pd(OH)_2$/C, $CH_3OH$, 44%)

(±)-**33** [R,R' = C(Ph)2] ⟶ (±)-**9**

1. $NH_2OH$, NaOAc, $CH_3OH$, 87%
2. $(CH_3)_2CO$, $NaBH_3CN$, $ZnCl_2$, 71%

Method A: R'R"NH, $Pd_2(dba)_3$, DPPF, NaO-t-Bu, tol, 80 °C
Method B: R'R"NH, $Pd(OAc)_2$, BINAP, NaO-t-Bu, tol 80 °C

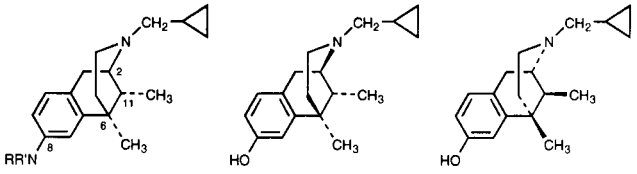
**Scheme 2.** Synthesis of target compounds via palladium-catalyzed aminations.

triflates pioneered by Buchwald,[13] Hartwig,[14] and co-workers served our needs very well. As shown in Scheme 2, cyclazocine [(±)-**1**] and its enantiomers, (−)-**2** and (+)-**3**, were converted to the corresponding triflates (±)-**30**, (−)-**31**, and (+)-**32**, respectively, in 94–96% yield using standard conditions. Triflate derivative (±)-**30** was converted to racemic targets (±)-**8**, (±)-**10**, (±)-**13**, and (±)-**15**–**21** using two known Pd-catalyzed amination methods, Method A (RR′NH, $Pd_2(dba)_3$, DPPF, NaO-t-Bu, tol, 80 °C)[14,15] or Method B (RR′NH, $Pd(OAc)_2$, BINAP, NaO-t-Bu, tol, 80 °C).[13,16] Method A was used to convert the optically active triflates (−)-**31**, and (+)-**32** to the phenylamino derivatives (−)-**11**, and (+)-**12**, respectively (yields shown in Table 1). The known 8-methylamino analogue, (±)-**7**,[3] was made by reducing (±)-**21** with $H_2/Pd(OH)_2/C$. The isopropylamino analogue (±)-**9** was made by first coupling (±)-**30** with $Ph_2C{=}NH$ following a modification of a known procedure[17] (Method A, 86.9%) to provide (±)-**33** (Scheme 2) which was subjected to imine exchange conditions to provide (±)-**4**. Subsequent reductive amination provided target (±)-**9**.

## Results and Discussion

Opioid receptor binding data and a brief description of the receptor binding assays are found in Table 1. While

**Table 1.** Opioid binding data for 8-(substituted)aminocyclazocine analogues




**A** **(-)-2** [2*R*,6*R*,11*R*] **(+)-3** [2*S*,6*S*,11*S*]

| Compound | R | R′ | Method[b] | Yield, %[b] | mp, °C | $K_i$ (nM ± S.E.)[a] vs [$^3$H]DAMGO (μ) | [$^3$H]Naltrindole (δ) | [$^3$H]U69,593 (κ) |
|---|---|---|---|---|---|---|---|---|
| (±)-**1**[c] | (cyclazocine) | | | | | 0.32 ± 0.02 | 1.1 ± 0.04 | 0.18 ± 0.020 |
| (−)-**2**[c] | | | | | | 0.10 ± 0.03 | 0.58 ± 0.06 | 0.052 ± 0.009 |
| (+)-**3**[c] | | | | | | 360 ± 16 | 1100 ± 63 | 76 ± 8.2 |
| (±)-**4**[d] | H | H | | | | 9.5 ± 0.14 | 110 ± 15 | 4.1 ± 0.11 |
| (−)-**5**[e] | H | H | | | 87–89 | 1.8 ± 0.12 | 12 ± 2.3 | 1.2 ± 0.13 |
| (+)-**6**[f] | H | H | | | 88–90 | 780 ± 78 | 920 ± 27 | 506 ± 37 |
| (±)-**7**[d] | H | $CH_3$ | | | | 13 ± 0.77 | 470 ± 62 | 8.5 ± 0.44 |
| (±)-**8**[d] | H | $CH_2CH_3$ | | | | 5.1 ± 0.74 | 19 ± 3.1 | 3.3 ± 0.10 |
| (±)-**9** | H | i-Pr | | | Oil | 240 ± 3.7 | 460 ± 49 | 78 ± 16 |
| (±)-**10** | H | $C_6H_5$ | A | 59 | Oil | 1.3 ± 0.072 | 9.4 ± 0.74 | 0.83 ± 0.036 |
| (−)-**11**[g] | H | $C_6H_5$ | A | 57 | Foam | 1.1 ± 0.08 | 5.2 ± 0.08 | 0.54 ± 0.01 |
| (+)-**12**[h] | H | $C_6H_5$ | A | 59 | Oil | 46 ± 4.4 | 270 ± 49 | 27 ± 1.5 |
| (±)-**13** | H | $CH_2C_6H_5$ | B | 53 | Oil | 1.5 ± 0.16 | 57 ± 2.5 | 4.7 ± 0.15 |
| (−)-**14**[i] | H | $CH_2C_6H_5$ | B | 66 | Oil | 0.67 ± 0.043 | 54 ± 3.6 | 2.1 ± 0.10 |
| (±)-**15** | H | $(CH_2)_2C_6H_5$ | B | 55 | Oil | 9.0 ± 2.4 | 160 ± 8.0 | 11 ± 0.084 |
| (±)-**16** | $CH_3$ | $CH_3$ | B | 57 | Oil | 82 ± 1.9 | 1500 ± 96 | 33 ± 2.5 |
| (±)-**17** | -$(CH_2)_4$- | | B | 54 | Oil | 770 ± 55 | 1800 ± 73 | 410 ± 30 |
| (±)-**18**[j] | -$(CH_2)_5$- | | B | 48 | 264 (dec) | 950 ± 84 | 3600 ± 390 | 300 ± 29 |
| (±)-**19** | -$(CH_2)_2OCH_2)_2$- | | B | 49 | 140–142 | 650 ± 38 | 2800 ± 200 | 560 ± 82 |
| (±)-**20** | -$(CH_2)_2NCH_3(CH_2)_2$- | | B | 25 | Oil | 21 ± 2.8 | 250 ± 51 | 8.8 ± 0.40 |
| (±)-**21** | $CH_3$ | $CH_2C_6H_5$ | B | 55 | Oil | 56 ± 4.1 | 570 ± 33 | 44 ± 1.8 |

[a]Binding assays used to screen compounds are similar to those previously reported (see ref 21). Guinea pig brain membranes, 500 μg of membrane protein, were incubated with 12 different concentrations of the compound in the presence of either 1 nM [$^3$H]U69,593 (κ), 0.25 nM [$^3$H]DAMGO (μ) or 0.2 nM [$^3$H]naltrindole (δ) 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 mM $MgCl_2$ and 0.5 mM phenylmethylsulfonyl fluoride. Nonspecific binding was measured by inclusion of 10 mM 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 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 will be calculated by least squares fit to a logarithm-probit analysis. $K_i$ values of unlabeled compounds were calculated from the equation $K_i = (IC_{50})/1 + S$ where $S$ = (concentration of radioligand)/($K_d$ of radioligand) — see ref 22. Data are the mean ± S.E. from at least three experiments performed in triplicate.

[b]Method and yields refer to the Pd-catalyzed amination step — see Scheme 2 and ref 15.

[c]Known compound — see refs 8 and 9.

[d]Known compound — see ref 3.

[e]$[\alpha]_D^{25} = -118°$ ($c = 1.0$, MeOH).

[f]$[\alpha]_D^{25} = +118°$ ($c = 1.0$, MeOH).

[g]$[\alpha]_D^{25} = -79.3°$ ($c = 1.0$, $CHCl_3$).

[h]$[\alpha]_D^{25} = +78.3°$ ($c = 1.0$, $CHCl_3$).

[i]$[\alpha]_D^{25} = -101.9°$ ($c = 1.06$, EtOH).

[j]Dihydrochloride salt.

the primary amino analogues, (±)-**4** and (−)-**5**, have high affinity for μ and κ receptors, potency was substantially reduced (>20-fold) compared to the corresponding phenols, cyclazocine [(±)-**1**] and (−)-**2**. Since (±)-**4** was only 5-fold less potent than (±)-**1** in rodent models of antinociception dosed sc and equipotent po, we assume that (±)-**4** has substantially enhanced pharmacodynamic properties especially when administered orally. For both the phenols and primary amino analogues, the active enantiomers at opioid receptors are the (−)-[(2*R*,6*R*,11*R*)] isomers. In addition, greater affinity is evident for μ/κ receptors than δ; between μ and κ, there is a modest preference for κ. When the primary amine of (±)-**4** was substituted with monoalkyl groups, binding affinity was not effected by methyl [(±)-**7**] and ethyl groups [(±)-**8**], however, it was substantially reduced by isopropyl substitution [(±)-**9**]. For secondary amine substituents containing a phenyl ring, however, substantial affinity was observed—the phenylamino analogue (±)-**10** and the benzylamino analogue (±)-**13** had only 4-fold less affinity for μ receptors. The phenethyl analogue (±)-**15** was somewhat less potent. For these phenyl derivatives, binding to κ receptors follows the same rank order of potency although the PhNH compound (±)-**10** is the most potent and selective for κ. Consistent with our other observations, the activity of these racemic 8-phenylamino [(±)-**10**] and 8-benzylamino [(±)-**13**] compounds resides in the (−)-[(2*R*,6*R*,11*R*)] isomers. All tertiary amine derivatives [(±)-**16**–**21**] had reduced binding affinity relative to the primary or secondary amino analogues suggesting that at least one H on the 8-position N is required for reasonable binding affinity. This is consistent with known SAR studies for opioids where the prototypic phenolic OH is required for binding to opioid receptors.[18–20] H-bond donation by the tertiary amine derivatives is possible when in the protonated state, however, the low p$K_a$ (<5) for such aromatic amines decreases their likelihood of any significant protonation at the pH (7.5) of the assay.

## Conclusions

Our earlier rodent data indicating that an 8-$NH_2$ group was an effective bioisosteric replacement for 8-OH in cyclazocine did not translate to the same degree of effectiveness in opioid receptor binding assays. However, by modifying the nitrogen substitution, a new receptor binding SAR was revealed. These new data showing that high affinity binding to κ and μ opioid receptors are seen in a novel series of 8-(substituted)-amino cyclazocine derivatives opens new opportunities to understand and enhance binding of benzomorphans to their receptors. The expanded valence going from the 8-position oxygen to nitrogen provides us with the opportunity to explore new molecular contacts between receptor and an N-substituent while still maintaining the important H-bond interaction between drug (as donor) and opioid receptor (acceptor). Following generation and analysis of in vivo and additional SAR binding data, including adding (substituted)amino groups to other opioid core structures (e.g. 3-aminomorphine), a full account of this work will appear. A 3-aminodextromorphan analogue has been reported.[23] This analogue, however, has the opposite stereochemistry to natural opiates and was studied for other (than opioid receptor binding) pharmacological properties.[23,24]

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Discussions with Dr. Arthur Schultz and the late Dr. Sydney Archer and the contributions of Dr. Qun Zhou (all at Rensselaer) are gratefully acknowledged. Funding of this research was from NIDA (DA01674, DA03742, DA12180 and KO5-DA00360).

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11. Proton NMR, IR, 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.
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15. **Cis-(±)-3-(cyclopropylmethyl)-1,2,3,4,5,6,-hexahydro-6,11-dimethyl-*N*-(phenyl)-2,6-methano-3-benzazocin-8-amine [(±)-10]. Method A**. An oven-dried 25-mL two-neck flask equipped with reflux condenser was placed into a $N_2$ filled glove box where it was charged with $Pd_2(dba)_3$ (0.057 g, 0.062 mmol), DPPF (0.103 g, 0.186 mmol), and NaOt-Bu (0.119 g, 1.239 mmol). The system was capped with rubber septa and removed from the glove box. Approximately 4 mL of dry, distilled toluene (Na, benzophenone ketyl) were then added to the mixture via syringe and the resulting dark suspension was allowed to stir at ambient temperature for 10 min. A solution

containing triflate (±)-**30** (0.500 g, 1.239 mmol) and aniline (0.138 g, 1.487 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 flashed with hexanes:ethyl acetate (20:1 to 10:1 to 3:1 gradient) yielding (±)-**10** as a light-brown oil (0.255 g, 0.736 mmol, 59.3%): $^1$H NMR (500 MHz, $CDCl_3$) δ 7.23 (m, 2H), 6.99–6.90 (m, 4H), 6.87–6.85 (m, 2H) 5.65 (bs, 1H), 3.19 (m, 1H), 2.90–2.86 (d, $J$ = 18.3 Hz, 1H), 2.78 (m, 1H), 2.75 (m, 1H), 2.54–2.38 (m, 2H), 2.17 (m, 1H), 1.97 (m, 1H), 1.95 (m, 1H), 1.36 (m, 1H), 1.34 (s, 3H), 0.91 (m, 1H), 0.89 (d, $J$ = 7.1 Hz, 3H), 0.54 (m, 2H), 0.14 (m, 2H); $^{13}$C NMR (500 MHz, $CDCl_3$) δ 143.94, 142.96, 140.74, 129.23, 127.82, 120.01, 116.61, 116.34, 116.02, 59.77, 57.08, 45.92, 41.92, 41.55, 36.37, 25.41, 23.18, 14.14, 9.17, 4.01, 3.60; IR ($CH_2Cl_2$) 2923, 2095, 1597 cm$^{-1}$; MS (CI/isobutane) $m/z$ 347 (M + 1, 100%). Anal. calcd. For $C_{24}H_{30}N_2$.0.33 $H_2O$: C, 81.77; H, 8.58; N, 7.95. Found: C, 81.60; H, 8.64; N, 7.78. This reaction was performed on a larger scale (3-fold) giving a similar yield of (±)-**10** (mp, 144–146 °C).

16. Method B was essentially identical to Method A except $Pd(OAc)_2$ and BINAP were used catalyst source and Pd-ligand, respectively, rather than $Pd_2(dba)_3$ and DPPF. BINAP-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; $Pd_2(dba)_3$-Tris(dibenzylideneacetone)dipalladium(0); DPPF-1,1′-bis(diphenylphosphino)-ferrocene.
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