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8-Carboxamidocyclazocine Analogues: Redefining the Structure–Activity Relationships of 2,6-Methano-3-benzazocines

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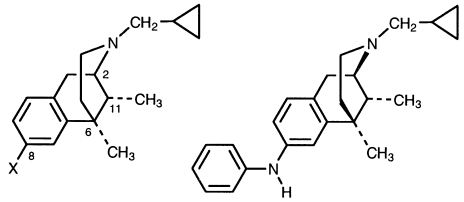
Abstract—Unexpectedly high affinity for opioid receptors has been observed for a novel series of cyclazocine analogues where the prototypic 8-OH was replaced by a carboxamido group. For μ and κ opioid receptors, the primary carboxamido derivative of cyclazocine ((±)-**15**) displayed high affinity ($K_i = 0.41$ and 0.53 nM, respectively) nearly comparable to cyclazocine. A high enantiopreference ((2*R*,6*R*,11*R*)-) for binding was also observed. Compound (±)-**15** also displayed potent antinociception activity in mice when administered icv.

We recently reported the synthesis and opioid receptor binding properties of a series of cyclazocine ((±)-**1**) analogues where the 8-OH group was replaced by various amine substituents.[1] The objective of this study was to identify bioisoteres of the 8-OH that would retain the essential H-bond donating properties of cyclazocine but have the potential for an improved ADME profile. Results from that study showed that while the 8-NH_2 analogue (±)-**2** had significant affinity for μ and κ opioid receptors, it was 30- and 23-fold less potent than cyclazocine, respectively. We also found that, relative to the 8-NH_2 derivative (±)-**2**, certain (mono)substituents on nitrogen greatly enhanced binding. For example, the (2*R*,6*R*,11*R*)-phenylamino analogue (−)-**3** had K_i values of 1.1 and 0.54 nM versus μ and κ, respectively. Our studies showed that the 8-N had to have at least one hydrogen substituent consistent with the long-standing doctrine that 2,6-methano-3-benzazocines (e.g., cyclazocine) as well as many other μ opioid-receptor interactive agents (e.g., morphine) require H-bond donation at that site provided by the prototypic phenolic OH.[2–7]



As part of our continuing studies on the SAR of the 8-position of cyclazocine, we recently prepared its, hitherto unknown, 8-carboxamido analogue ((±)-**15**), which we found to have surprisingly high (subnanomolar K_i values) affinity for μ and κ receptors nearly comparable to cyclazocine. We could not find any reports of opioid-receptor interactive agents where the prototypic phenolic OH was replaced by CONRR. In fact, there are very few papers that describe any type of carbon attachment at that position. In two studies, the 3-OH group of morphine[6] and natrindole[7] was replaced by H, alkyl, acetyl, aryl, and/or heteroaryl groups; all targets had substantially diminished affinity for opioid receptor relative to their 3-OH counterparts. A recent report described the synthesis of the 3-carboxymethoxy analogues (i.e., 3-CO_2CH_3) of the 6-dioxolane (i.e., ketal protected) derivatives of naltrexone and oxymorphone.[8] These esters were used as intermediates

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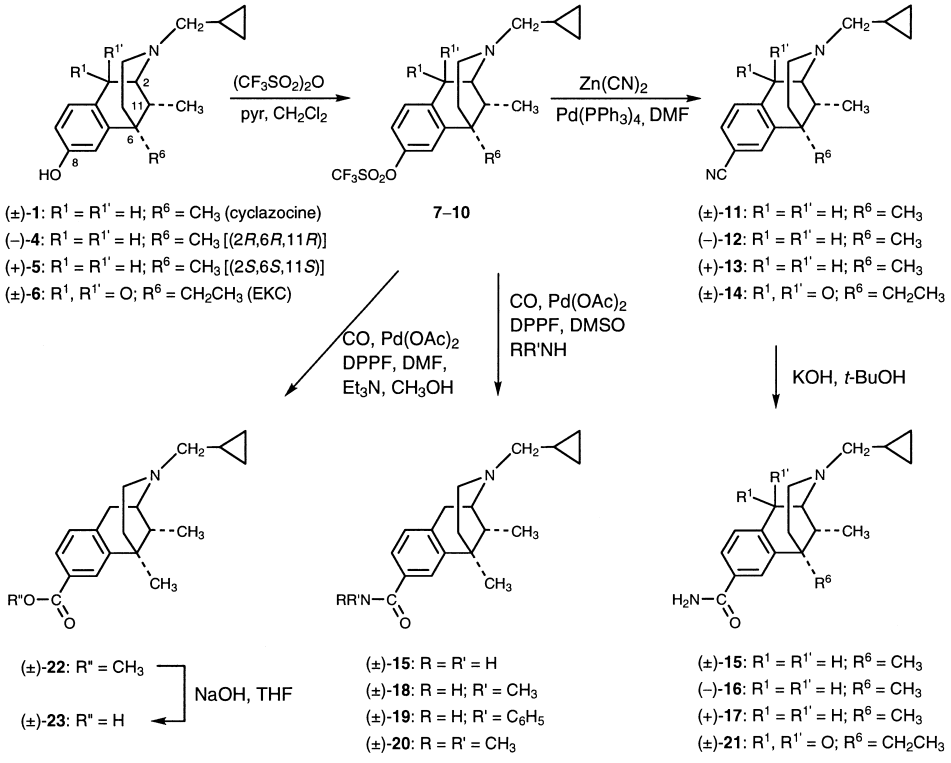
to make the 3-sulfonamido analogues (i.e., 3-$NHSO_2CH_3$) of naltrexone and oxymorphone via Curtius rearrangements; no opioid binding data were reported for these ester intermediates. We now wish to report the synthesis, opioid receptor binding properties, and in vivo antinociception data for (±)-**15**. We also made and evaluated the enantiomers of (±)-**15**, the 8-carboxamido analogue ((±)-**21**) of ethylketocyclazocine, and several related compounds having a carbonyl group attached to the 8-position of the core cyclazocine structure.

We used two general methods, both involving Pd-catalysis, to synthesize new targets (Scheme 1).[9] In one procedure (Method D),[10] the 8-triflate ester **7**[1] of cyclazocine was converted to the corresponding nitrile (±)-**11** in 80% yield using $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF using a slight modification of a procedure recently reported by Rice and co-workers.[11] Hydrolysis of (±)-**11** using KOH/*t*-BuOH provided target (±)-**15** in 95% yield after acidification. In similar fashion, both cyclazocine enantiomers, (−)-**4** and (+)-**5**,[12,13] and ethylketocyclazocine (EKC, (±)-**6**)[14,15] were converted to primary 8-carboxamido derivatives, (−)-**16**, (+)-**17**, and (±)-**21**, respectively. Compound (±)-**15** was also made directly from triflate **7** in a one-step procedure (Method E)[10] in 65% yield by treating **7** with CO/NH_3/$Pd(OAc)_2$/DPPF/DMSO. The conversion of triflate esters to secondary and teriary amides using similar (RRNH vs NH_3) conditions is well-known,[16] however, to our knowledge, this highly efficient method has never been used with ammonia to make primary carboxamides. A two-step, one-pot procedure utilizing $HN(SiMe)_3$ followed by an acidic workup has been reported.[17] We also prepared the three *N*-substituted analogues, (±)-**18**, (±)-**19**, and (±)-**20** using this one-step procedure. The novel 8-CO_2CH_3 ((±)-**22**) and 8-CO_2H ((±)-**23**) analogues were also made for comparative SAR purposes. We used a slight variation of a known method ($CO/CH_3OH/Pd(OAc)_2$/DPPF/DMF/Et_3N)[8,18] to convert triflate **7** to (±)-**22** (87%). Hydrolysis of this ester provided target acid (±)-**23** in 64% yield.

Opioid receptor binding data and a brief description of the receptor binding assays are found in Table 1. The primary carboxamido analogue (±)-**15** displayed very high affinity for μ and κ receptors (K_i values = 0.41 nM and 0.53 nM, respectively) that was nearly comparable to cyclazocine. Like cyclazocine, (±)-**15** showed much lower affinity for δ. As would be predicted from existing SAR data for enantiospecificity, the active enantiomer at opioid receptors is the (−)-((2*R*,6*R*,11*R*)) isomer (−)-**16**, which has substantially higher affinity (between 219- and 370-fold) than the (+)-((2*S*,6*S*,11*S*)) isomer, (+)-**17**. When the carboxamido nitrogen of (±)-**15** was substituted with one methyl ((±)-**18**), affinity for μ was decreased 59-fold but for κ, affinity was only 5-fold lower. The *N*-phenyl analogue (±)-**19** displayed very low affinity for all receptors as did the *N*,*N*-dimethyl derivative (±)-**20**. The 8-carbomethoxy ((±)-**22**) and 8-carboxylate ((±)-**23**) analogues were also made; relative to (±)-**15**, affinity for μ was significantly lower (110-fold and 141-fold, respectively). Against κ, (±)-**23** showed weak relative affinity, however, the 8-carbomethoxy ((±)-**22**) had a K_i value of 2.0 nM. The nitrile intermediate (±)-**11** used to make several targets showed very low affinity for opioid receptors. To determine if

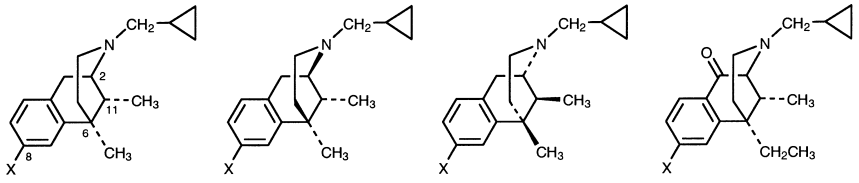


Scheme 1. Syntheses of target compounds via Pd-catalyzed procedures.

the benefits of the 8-OH→8-$CONH_2$ conversion in cyclazocine would translate to other 2,6-methano-3-benzazocine core structures, we evaluated the novel 8-carboxamido analogue (±)-**21** of ethylketocyclazocine. Similar to that observed with the cyclazocine core, (±)-**21** had very high affinity for μ and κ receptors nearly comparable to EKC. We also performed preliminary in vivo studies for (±)-**15** using the mouse acetic acid writhing test.[19] We found that the opioid receptor binding properties of the compound did, in fact, translate to potent antinociception in mice (ED_{50} = 0.21 nmol icv).

The excellent affinity for μ and κ opioid receptors that we observed for the two novel 2,6-methano-3-benzazocin-8-carboxamides ((±)-**15** and (±)-**21**) can't be rationalized by our current knowledge of SARs of opioid-interactive agents. Additional SAR function studies are underway to determine if, for example, the role of the primary carboxamide group is similar to that of the phenolic OH (or isosteric NH_2)[1,22] of typical opiates, namely, H-bond donation to the same (or different) complimentary acceptor site on the opioid receptor. Our early results do indicate that an N-H is very important for μ binding in that the *N*,*N*-dimethyl analogue (±)-**20** has very low affinity. However, the lack of binding affinity for (±)-**20** may well be a consequence of negative steric interactions of the methyl groups with the receptor since diminished binding is observed with the *N*-(mono)methyl derivative (±)-**18** and binding is abolished with the much larger *N*-phenyl carboxamide ((±)-**19**). Since our previous data for the 8-amino analogues indicated that binding affinity was enhanced by adding certain bulky substituents (e.g., phenyl in (−)-**3**), the steric requirement(s) of the 8-substituent for opioid receptor binding is unresolved and is being further explored in our laboratories.

Table 1. Opioid receptor binding data for 2,6-methano-3-benzazocin-8-carboxamide derivatives



A (–)-**4**: X = OH [2*R*,6*R*,11*R*] (+)-**5**: X = OH [2*S*,6*S*,11*S*] **B**

(–)-**16**: X = $CONH_2$ (+)-**17**: X = $CONH_2$

Compd	Method (yield,%)[b]	mp (°C)	K_i (nM ± SEM)[a] versus [^{3}H]DAMGO (μ)	[^{3}H]Naltrindole (δ)	[^{3}H]U69,593 (κ)
(±)-**1**[c] **A**: X = OH (cyclazocine)			0.32 ± 0.02	1.1 ± 0.04	0.18 ± 0.020
(−)-**4**[c]			0.10 ± 0.03	0.58 ± 0.06	0.052 ± 0.009
(+)-**5**[c]			360 ± 16	1100 ± 63	76 ± 8.2
(±)-**6**[d] **B**: X = OH; (EKC)			0.78 ± 0.10	3.4 ± 0.41	0.62 ± 0.11
(±)-**11**[b] **A**: X = CN			540 ± 50	2700 ± 1400	71 ± 13
(±)-**15**[b] **A**: X = $CONH_2$			0.41 ± 0.07	8.3 ± 0.49	0.53 ± 0.06
(−)-**16**[e]	D (95)	Foam	0.17 ± 0.04	2.6 ± 0.6	0.28 ± 0.01
(+)-**17**[f]	D (86)	Foam	63 ± 5.4	570 ± 50	67 ± 1.6
(±)-**18 A**: X = $CONHCH_3$	E (26)	155–156	24 ± 1.6	63 ± 4.1	2.6 ± 0.19
(±)-**19 A**: X = $CONHC_6H_5$	E (75)	Oil	740 ± 85	1400 ± 58	460 ± 21
(±)-**20 A**: X = $CON(CH_3)_2$	E (66)	107–109	3000 ± 160	>35,000	2500 ± 49
(±)-**21 B**: X = $CONH_2$	D (81)	194–196	1.2 ± 0.12	9.8 ± 0.50	0.70 ± 0.08
(±)-**22 A**: X = CO_2CH_3	E[g] (87)	Oil	45 ± 0.92	59 ± 2.1	2.0 ± 0.21
(±)-**23 A**: X = CO_2H	(64)[h]	240–242	58 ± 1.8	320 ± 14	31 ± 0.87

[a]Binding assays used to screen compounds are similar to those previously reported (see ref 20). 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 μM 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 21). Data are the mean ± SEM from at least three experiments performed in triplicate.

[b]See Scheme 1 and ref 10. Method and yields refer to the Pd-catalyzed carbonylation step.

[c]Known compound:see refs 12 and 13.

[d]Known compound: see ref 15.

[e]$[\alpha]_D^{25}$ −117.5° (*c* 1.0, MeOH).

[f]$[\alpha]_D^{25}$ +118.9° (*c* 1.0, MeOH).

[g]MeOH used in place of RR′NH.

[h]NaOH/THF followed by acidification with HOAc.

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9. 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.
10. Methods to make (±)-3-(cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocin-8-carboxamide ((±)-**15**): **Method D**: Using a slight modification of a known procedure,[11] the triflate ((±)-**7**, 470 mg, 1.166 mmol)[1] of cyclazocine was dissolved in 20 mL DMF and $Zn(CN)_2$ (272.6 mg, 2.322 mmol) and $Pd(PPh_3)_4$ (53.9 mg, 0.0466 mmol) were added. After stirring the mixture at 120 °C for 2 h and 25 °C for 14 h, EtOAc and aq $NaHCO_3$ were added. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated to give a crude product that was purified by flash column chromatography giving (±)-3-(cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocin-8-carbonitrile ((±)-**11**) as a colorless oil (260 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 1.5 Hz, 1H), 7.37 (dd, J_1 = 8.1, J_2 = 1.5 Hz, 1H), 7.14 (d, J = 8.1 Hz, 1H), 3.15 (m, 1H), 2.96 (d, J = 19.0 Hz, 1H), 2.66–2.74 (m, 2H), 2.45 (dd, J_1 = 12.4, J_2 = 6.3 Hz, 1H), 2.30 (dd, J_1 = 12.7, J_2 = 6.6 Hz, 1H), 1.84–1.98 (m, 3H), 1.38 (s, 3H), 1.29 (m, 1H), 0.85 (m, 1H), 0.82 (d, J = 7.1 Hz, 3H), 0.51 (m, 2H), 0.10 (m, 2H). IR (film) 2961, 2918, 2225 cm^{-1}. CI-MS, m/z (relative intensity) 281 (M + 1, 100%). Anal. calcd for $C_{19}H_{24}N_2 \cdot 0.125\ H_2O$: C, 80.78; H, 8.59; N, 9.92. Found: C, 80.75; H, 8.63; N, 9.89. Compound (±)-**11** (80 mg, 0.286 mmol) was dissolved in 1 mL *t*-butyl alcohol and KOH (58.8 mg, 1.05 mmol) was added. The reaction mixture was stirred at reflux for 20 min and the solvent was evaporated. The residue was partitioned between CH_2Cl_2/H_2O and washed with brine. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to give (±)-**15** as white foam (80 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 5.8 (br s, 2H), 3.15 (s, 1H), 2.97 (d, J = 19 Hz, 1H), 2.71 (m, 2H), 2.46 (dd, J_1 = 6.3 Hz, J_2 = 12.5 Hz, 1H), 2.32 (dd, J_1 = 6.3 Hz, J_2 = 12.5 Hz, 1H), 1.91 (m, 3H), 1.43 (s, 3H), 1.34 (d, J = 11.2 Hz, 1H), 0.85 (m, 1H), 0.83 (d, J = 7.1 Hz, 3H), 0.51 (d, J = 8.1 Hz, 2H), 0.11 (m, 2H); ^{13}C NMR (500 MHz, CD_3OD) δ 172.71, 143.32, 142.34, 133.01, 128.61, 126.61, 126.18, 60.67, 58.09, 46.92, 42.74, 42.38, 37.69, 25.92, 25.07, 14.62, 9.67, 4.64, 4.52. IR (film) 1654.2 cm^{-1}. CI-MS, m/z (relative intensity) 299 (M + 1, 100%). Anal. calcd for $C_{19}H_{26}N_2O \cdot 0.25H_2O$: C, 75.37; H, 8.76; N, 9.26. Found: C, 75.27; H, 9.02; N, 9.03. **Method E**: A flask containing triflate (±)-**7** (100 mg), $Pd(OAc)_2$ (10.2 mg), and 1,1′-bis(diphenylphosphino)ferrocene (DPPF, 25 mg) was purged with argon. The argon was replaced with gaseous CO and the reaction vessel was closed to the atmosphere. Dry DMSO (1.25 mL) was added via syringe and gaseous ammonia was added to the resulting mixture via a cannula. A balloon was used to keep the additional volume contained. The mixture was stirred for 17 h at 70 °C followed by cooling to 25 °C. The reaction mixture was diluted with water and the product was extracted into ethyl acetate. The organic extracts were washed with aq $NaHCO_3$, dried (Na_2SO_4) and concentrated to give 90 mg of a crude product. This material was purified via flash chromatography (25:1:0.1—CH_2Cl_2:MeOH:conc NH_4OH) to provide 47 mg (65.3%) of (±)-**15**.
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