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Synthesis of Enantiomerically Pure (+)- and (−)-18-Methoxycoronaridine Hydrochloride and Their Preliminary Assessment as Anti-Addictive Agents

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Abstract—Chemical resolution of racemic 18-methoxycoronaridine (**18-MC**) was achieved by the formation of its diastereomeric sulfonamides with either (*R*)-(−)- or (*S*)-(+)-camphorsulfonyl chloride. Preliminary assessment of (+)-, (−)-, and (±)-**18-MC**·HCl showed similar effects on morphine self-administration in a rat model, and similar affinities at the κ opioid receptors.

Racemic 18-methoxycoronaridine (**18-MC**),[1] a structural analogue of ibogaine,[2–7] has been shown in previous studies to mimic the anti-addictive effects of ibogaine in a rat model of addiction.[8–11] This mimetic effect is apparently without the side effects of ibogaine, which include damage to the rat cerebellum.[12,13] Because ibogaine exists as a single enantiomer, our early assumption was that the biological activity of (±)-**18-MC** was due primarily to the presence of the (−)-**18-MC** enantiomer, which has a similar absolute configuration to ibogaine.[14,15] To test this hypothesis, we chemically resolved the racemate to its pure (+)- and (−)-enantiomers.We then tested the racemate and each of the separated enantiomers for anti-addictive biological activity in a rat model of addiction (morphine self-administration) and in κ, μ and δ opioid receptor binding assays.[16,17]

Chemistry

Our initial attempts to efficiently resolve the enantiomers of 18–methoxycoronaridine by selective recrystallization of diastereomeric salts, formed by reaction of the racemate[18–21] with a variety of chiral acids (13 in all),[22] were uniformly unsuccessful. We then turned our attention to the preparation of diastereomers via the formation of chiral sulfonamide derivatives at the indole nitrogen using chiral sulfonyl chlorides. We found that the use of commercially available (*R*)-(+)- or (*S*)-(−)-camphorsulfonyl chloride formed a mixture of diastereomers that allowed ready separation by column chromatography, as described below.

Racemic **18-MC**[1,18–21] was converted to sulfonamides **1** and **2** as a pair of diastereomers with (*S*)-(+)-camphorsulfonyl chloride (see Scheme 1).[23] The use of potassium bis(trimethylsilyl)amide[24] as the base in this reaction gave the desired adducts **1** and **2**. Sulfonamides **1** and **2** were separated by normal phase silica gel chromatography and isolated as white foams in 27 and 25% yield, respectively.[25] The unreacted starting material (racemic **18-MC**) was recovered in 12% yield.

Treatment of the separated sulfonamides **1** and **2** each with a large excess of potassium hydroxide in methanol easily provided the desired enantiomers (+)-**18-MC** in 77% yield and (−)-**18-MC** in 74% yield, respectively. The crude products, which contained approximately 5% of the opposite enantiomers,[26] were further purified by recrystallization. In this purification method, the opposite enantiomer co-crystallized with the major enantiomer as a racemate from a solution of methylene chloride:diethyl ether:hexanes (1:5:5) at −20 °C. The solid racemate was then removed by filtration. From the filtrates, the pure enantiomers were isolated as white

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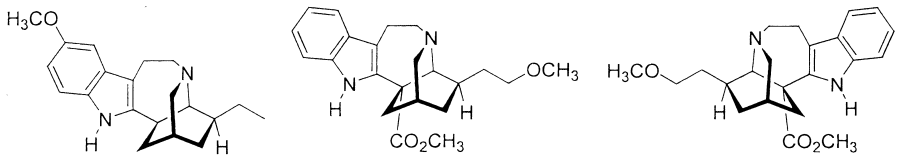


Ibogaine (−)-18-MC (+)-18-MC

solids in 61 and 58% overall yields, respectively. Finally, the enantiomerically pure free bases were converted to the corresponding hydrochloride salts in 78 and 88% yields.[27] The optical purities of both enantiomers were >99.8% ee as determined by chiral HPLC analysis.[26] In all, approximately 3 g each of (+)- and (−)-**18-MC**·HCl were prepared for the biological evaluations.

Biological Testing

Similar to previous results with intraperitoneally administered (±)-**18-MC**·HCl,[12] the present data (Fig. 1) show that orally administered (±)-**18-MC**·HCl decreases morphine self-administration without affecting response for a non-drug reinforcer (water).[28] The data further show that the (+)- and (−)-enantiomers have effects that are similar to each other as well as to (±)-**18-MC**·HCl (Fig. 1).

The previously reported affinities (binding inhibition constants, K_i) of ibogaine and noribogaine for μ and κ opioid receptors[29] led us to examine the affinities of the **18-MC** enantiomers for these sites. The results of our tests are shown in Table 1.[30] (±)-**18-MC**·HCl had low micromolar affinities at all three opioid receptors. However, while the affinities of (+)- and (−)-**18-MC**·HCl at the κ opioid receptor were equivalent, the (+)-enantiomer had more than a 10-fold higher affinity than the (−)-enantiomer at μ and δ opioid receptors. Previous work with ibogaine suggested that its affinity for κ opioid receptors is an important component of the mechanism mediating its putative anti-addictive effects.[31] The similar affinities of (±)-, (+)- and (−)-**18-MC**·HCl at κ sites and their similar effects on morphine self-administration suggest that their mechanism of action may involve κ opioid receptors. Although these κ affinities are in the micromolar range and low in

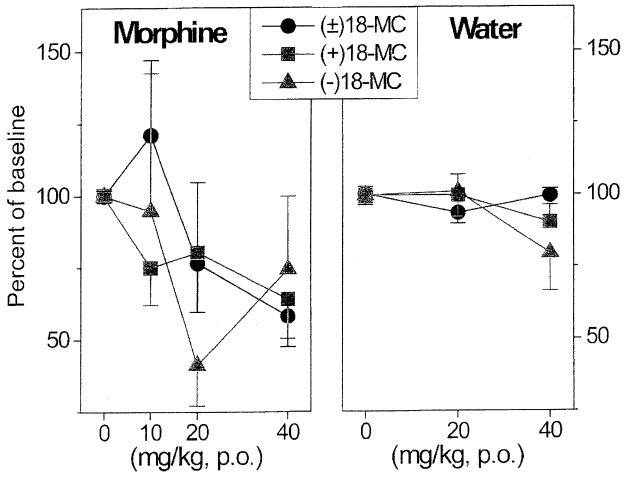
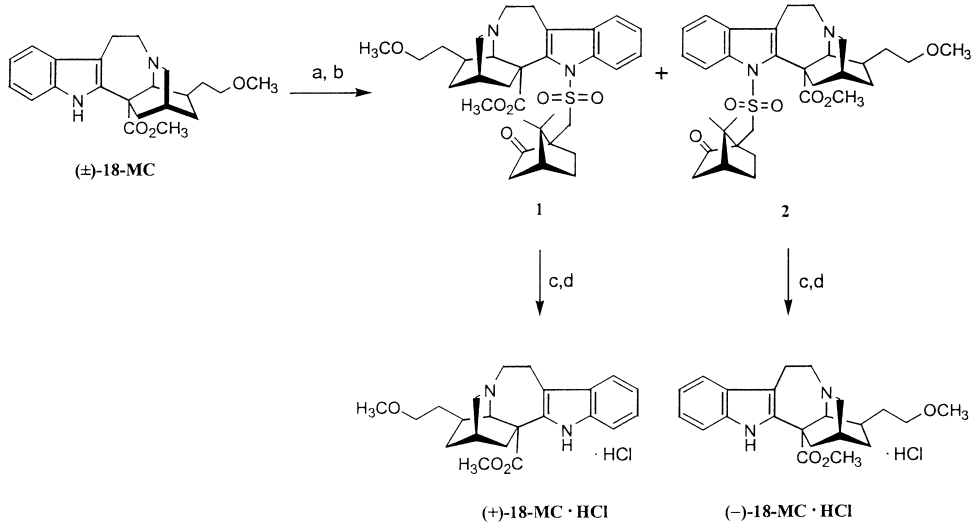


Figure 1. Effects of **18-MC**·HCl on morphine self-administration and on responding for water. Each data point represents the mean of 5–11 rats. Analyses of variance across doses showed a significant ($P < 0.05$) effect of treatments on morphine self-administration but not on response for water. There was no significant difference among the three treatments. Post-hoc tests at each dose showed significant effects of all three treatments at 40 mg/kg on morphine self-administration.



(+)-18-MC · HCl (−)-18-MC · HCl

Scheme 1. Chemical resolution of (±)-18-methoxycoronaridine. (a) KHMDS, THF, 23 °C then (*S*)-(+)-camphorsulfonyl chloride, THF, 4–23 °C; (b) flash chromatography, SiO_2, 5–10% EtOAc in CH_2Cl_2; (c) KOH, methanol, 23 °C, 1 M HCl in Et_2O, THF, 23 °C.

Table 1. Affinities (K_i) of (±)-, (+)- and (−)-**18-MC**·HCl for opioid receptors[a]

	(±)-18-**MC**·HCl	(+)-**18-MC**·HCl	(−)-**18-MC**·HCl
κ Opioid	5.1 ± 0.50 μM	4.8 ± 0.35 μM	5.5 ± 0.61 μM
μ Opioid	1.1 ± 0.30 μM	0.74 ± 0.07 μM	13 ± 0.09 μM
δ Opioid	3.5 ± 0.05 μM[b]	3.8 ± 0.10 μM	>100 μM

[a]Data are means ± SEM values of triplicate determinations from three experiments.
[b]The slight higher binding affinity than that of (+)-**18-MC**·HCl is probably due to experimental variability.

comparison to the nanomolar affinities of most other opioid compounds, the **18-MC** doses required to produce behavioral effects are relatively large and probably not inconsistent with micromolar affinities. Further studies are in progress.

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25. Analytical data for sulfonamide **1**: $[\alpha]_D^{22}$ −17.7° (*c* 0.485, $CDCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 3.73 (s, 3H, CO_2CH_3), 3.41 (t, *J* = 6.5 Hz, 2H, CH_2O), 3.34 (s, 3H, OCH_3), 1.10 (s, 3H, CH_3), 0.76 (s, 3H, CH_3), 0.8–3.6 (m, 24H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ214.3, 175.2, 140.7, 137.1, 130.4, 125.5, 123.8, 121.2, 118.8, 115.4, 71.5, 58.8, 58.2, 57.4, 56.5, 55.9, 52.4, 52.2, 48.4, 47.5, 42.9, 42.7, 38.2, 34.9, 32.2, 29.9, 28.0, 27.3, 25.1, 22.5, 19.9, 19.7; IR (KBr) 3448 (br), 2926, 2859, 1747, 1707, 1457, 1368, 1221, 1170, 1132, 762, 605, 529 cm^{-1}; MS (CI, CH_4) *m*/*z* 583 (MH^+), 582, 551, 519, 369, 367, 215. Analytical data for sulfonamide **2**: $[\alpha]_D^{22}$ +29.6° (*c* 0.29, $CDCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.53 (m, 1H), 7.32 (m, 2H), 3.74 (s, 3H, CO_2CH_3), 3.40 (t, *J* = 6.5 Hz, 2H, CH_2O), 3.32 (s, 3H, OCH_3), 1.23 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 1.0-3.6 (m, 24H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ214.3, 174.0, 140.7, 137.2, 130.4, 125.2, 123.8, 121.6, 119.1, 114.8, 71.6, 58.9, 58.8, 57.2, 56.1, 55.8, 52.6, 52.2, 47.9, 47.7, 43.3, 42.8, 38.1, 34.8, 32.3, 32.1, 28.1, 27.0, 26.4, 22.5, 20.7, 20.2; IR (KBr) 3449 (br), 2949, 1743, 1452, 1369, 1217, 1169, 1130, 761, 538 cm^{-1}; MS (CI, CH_4) *m*/*z* 583 (MH^+), 582, 369, 367, 215.
26. Optical purities were analyzed on a Spectra-Physics HPLC system with a Chiralpak AD column (4.6×250 mm, Daicel Chemical Industries, Ltd.), with a mobile phase of 60:40 hexanes:ethanol containing 0.2% ethylamine at a flow rate of 1.2 mL/min at room temperature and UV detection at 254 nm.
27. Analytical data for (+)-**18-MC**·HCl: mp 202–206 °C; $[\alpha]_D^{23.5}$ +42.4° (*c* 1.0, $CHCl_3$); HPLC (chiral analysis),[26] 99.9% pure by area percentage, R_t = 4.21 min; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.40 (s, 1H, HCl), 8.35 (s, 1H, NH), 7.50 (d, *J* = 7.0 Hz, 1H), 7.48 (m, *J* = 7.0 Hz, 1H), 7.26 (m, 1H), 7.16 (m, 1H), 4.50 (s, 1H), 4.10 (m, 1H), 3.90 (m, 1H), 3.80 (s, 3H, CO_2CH_3), 3.32 (s, 3H, OCH_3), 1.9-3.6 (m, 14H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ172.4, 136.0, 133.0, 127.2, 123.7, 120.6, 118.5, 111.3, 108.6, 70.0, 58.7, 58.5, 55.5, 53.9, 53.5, 51.1, 35.7, 33.0, 31.7, 28.2, 25.4, 19.0; IR (KBr) 3417 (br), 3262, 2929, 2589, 1730, 1458, 1248, 1120, 746, 698 cm^{-1}; MS (CI, CH_4) *m*/*z* 369 (MH^+-HCl), 337, 323. Anal. calcd for $C_{22}H_{28}N_2O_3$·HCl: C, 65.25; H, 7.22; N, 6.92. Found: C, 64.95; H, 7.28; N, 6.72. Analytical data for (−)-**18-MC**·HCl: mp 207–209 °C; $[\alpha]_D^{23.5}$ −42.4° (*c* 1.0, $CHCl_3$); HPLC (chiral analysis),[26] 99.9% pure by area percentage, R_t = 3.64 min; MS (CI, CH_4) *m*/*z* 369 (MH^+-HCl), 337, 323; ^1H NMR ($CDCl_3$), ^{13}C NMR ($CDCl_3$), and IR (KBr) are identical to the spectra of

(+)-18-MC·HCl. Anal. calcd for $C_{22}H_{28}N_2O_3$·HCl: C, 65.25; H, 7.22; N, 6.92.Found: C, 65.17; H, 7.23; N, 6.66.
28. The intravenous self-administration system consisted of polyethylene–silicone cannulae, Instech harnesses and commutators, and Harvard Apparatus infusion pumps (No. 55–2222). Cannulae were implanted in the external jugular vein. Responses on either of two levers of each operant test cage were recorded on an IBM compatible 486 computer with a Med Associates, Inc. interface. Female rats weighing approximately 250 g were trained to self-administer morphine (0.04 mg/kg/infusion) during daily 1-h test sessions; each lever-press response produced a 10 μL infusion of morphine solution (0.01 mg of morphine sulfate) in 0.1 sec. In order to provide an indication of the specificity of 18-methoxycoronaridine's effects on responding for morphine, other rats trained to bar-press for water on a comparable schedule (continuous reinforcement; 1-h session) were also treated with the drug. 18-Methoxycoronaridine hydrochloride or saline (0 dose) was administered by gavage (in 2 mL volume) 30 min prior to the beginning of test sessions.
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