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Brief Article

Synthesis and Opioid Activity of Enantiomeric *N*-Substituted 2,3,4,4a,5,6,7,7a-Octahydro-1*H*-benzofuro[3,2-*e*]isoquinolines

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A series of enantiomeric *N*-substituted 2,3,4,4a,5,6,7,7a-octahydro-1*H*-benzofuro[3,2-*e*]isoquinolines was synthesized. The (−)-enantiomers had much greater κ-, μ-, and δ-opioid receptor binding affinity than the corresponding (+)-enantiomers. Compounds (−)-**1a**, (−)-**1b**, and (−)-**1c** displayed subnanomolar binding affinity for the μ-receptor, and (−)-**1b** had a high affinity for the κ-receptor. Compound (−)-**1a** was a μ-partial agonist and κ-antagonist. Compound (−)-**1b** was a potent neutral μ-antagonist (K_d = 0.22 nM) and a κ-partial agonist.

Introduction

A growing body of evidence suggests that ligands targeting more than one opioid receptor subtype may be beneficial. For example, buprenorphine is a mixed μ-partial agonist, κ-antagonist, and δ-antagonist that was initially marketed as an analgesic and is now used primarily for the treatment of opioid dependence.[1] Nalbuphine is a κ-agonist/μ-antagonist analgesic with a low incidence of side effects and dependence in animals and humans.[2] In behavioral studies, nonselective κ-agonists with varying activity at μ-receptors decreased the frequency of cocaine self-administration more effectively and with fewer adverse effects than highly selective κ-agonists.[3] Therefore, novel opioid receptor ligands with varying degrees of agonistic and antagonistic properties for the three subtypes of opioid receptors may be potential therapeutic agents and useful tools for determining the relative functional contribution of each opioid receptor subtype in normal physiological processes and pathological states.

Approaches based on simplification of the morphine skeleton, which consists of five rings [ABCNO (Chart 1)], for the development of novel opioid ligands have resulted in the discovery of several clinically important analgesics, such as methadone (A), pentazocine (ABN), and levorphanol (ABCN).[4] Another interesting class of morphine fragments consists of 2,3,4,4a,5,6,7,7a-octahydro-1*H*-benzofuro[3,2-*e*]-isoquinolines, the ACNO ring system of morphine. The *N*-cyclopropylmethyl-substituted ACNO derivative **1b** possessed potent oral analgesic activity and narcotic antagonism activity and is likely to have a low potential for addiction.[5] The bridged ACNO compound NIH 10412 (**2**) displayed κ-agonist and μ-partial agonist properties, which may be a potential agent for the treatment of opioid dependence.[6] However, **1b** also shows significant binding to σ-receptors (K_i = 21 nM), which indicates potential psychotomimetic effects.[7]

We observed that historically most ACNO compounds were prepared and pharmacologically evaluated in racemic form, which is the case with many other synthetic narcotic analgesics. The only chiral ACNO derivatives that have been studied are (+)-**1a** and (−)-**1a**. These compounds were prepared by optical resolution of (±)-**1a**, and (−)-**1a** was more potent than (+)-**1a** with respect to antinociceptive and narcotic antagonism activity.[5b] Further studies disclosed that the σ_1 receptor binding ability of racemic benzomorphans (e.g., SKF 10,047, cyclazocine) was primarily due to the (+)-enantiomer, whereas the (−)-enantiomer had a higher affinity for opioid receptors.[8] Therefore, we hypothesize that the opioid activity of racemic ACNO compounds may be also from (−)-enantiomers, whereas the σ-receptor binding affinity of racemic ACNO compounds was from (+)-enantiomers. Therefore, preparation of enantiomeric pure ACNO ligands for pharmacological studies is essential for the elimination of the potential side effects due to the σ-receptor affinity of the racemic ACNO ligands and precisely determine the structure−activity relationship (SAR) for ACNO compounds.

Recently, an efficient asymmetric total synthesis of the ACNO fragment of morphine has been achieved and provided (−)-**1a** in eight steps with a total yield of 27%.[9] It is well-known that the *N*-substituents play crucial roles in both the binding affinity and intrinsic activity of opioid ligands for the three subtypes of opioid receptors. Thus, a series of enantiomeric *N*-substituted ACNO derivatives (Chart 2) was synthesized, and their opioid receptor binding affinities, σ-receptor binding affinities, and intrinsic activities for κ-, μ-, and δ-opioid receptors were investigated.

Chemistry

Optically active aryl iodides (−)-**6** and (+)-**6** were synthesized from 5,6,7,8-tetrahydroisoquinoline according to established procedures in 92−93% enantiomeric excess (ee).[9] Treatment of iodides (−)-**6** and (+)-**6** with $Pd(OAc)_2$, $(o\text{-toyl})_3P$, and Et_3N in acetonitrile at 120 °C using microwave-assisted

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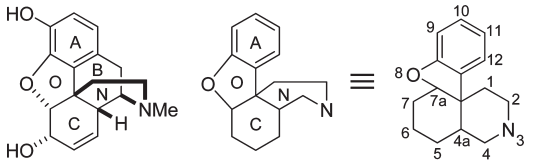
heating provided enamines (+)-**7** and (−)-**7**, respectively, with the tetracyclic ACNO ring system as shown in Scheme 1. PtO_2 catalytic hydrogenation of enamine (+)-**7** yielded the *trans*-isomer (−)-**3a** and the *cis*-isomer (−)-**5** in a ratio of 7:1. The optically active (−)-**3a** and (−)-**5** (93% ee) were then transformed to their hydrochloride salts followed by recrystallization to yield optically pure (−)-**3a** and (−)-**5** (>99% ee), respectively. The corresponding enantiomers (+)-**3a** and (+)-**5** were obtained from (−)-**7** via the same procedures. *O*-Demethylation of 9-methoxy-substituted compounds (−)-**3a**, (+)-**3a**, (−)-**5**, and (+)-**5** using BBr_3-$(CH_3)_2S$ in 1,2-dichloroethane furnished phenols (−)-**1a**, (+)-**1a**, (−)-**4**, and (+)-**4**, respectively, in moderate to high yields.

Treatment of *N*-methyl (Me)-substituted (−)-**3a** and (+)-**3a** with 2,2,2-trichloroethyl chloroformate followed by Zn reduction provided nor-analogues (−)-**8** and (+)-**8**, respectively. *N*-Alkylation of (−)-**8** using cyclopropylmethyl bromide and 2-phenylethyl bromide gave *N*-CPM-substituted (−)-**3b** and *N*-2-phenylethyl (PE)-substituted (−)-**3c**, respectively. *O*-Demethylation of (−)-**3b** and (−)-**3c** provided phenols (−)-**1b** and (−)-**1c**, respectively. Enantiomeric (+)-**3b**, (+)-**3c**, (+)-**1b**, and (+)-**1c** were obtained from (+)-**8** according to the procedure for the preparation of the corresponding (−)-enantiomers.

Chart 1



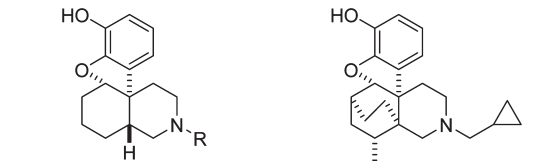
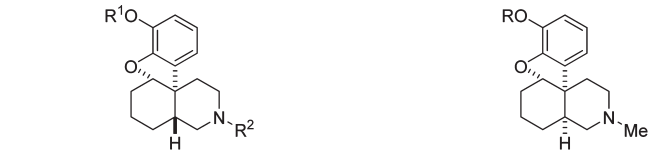


Chart 2



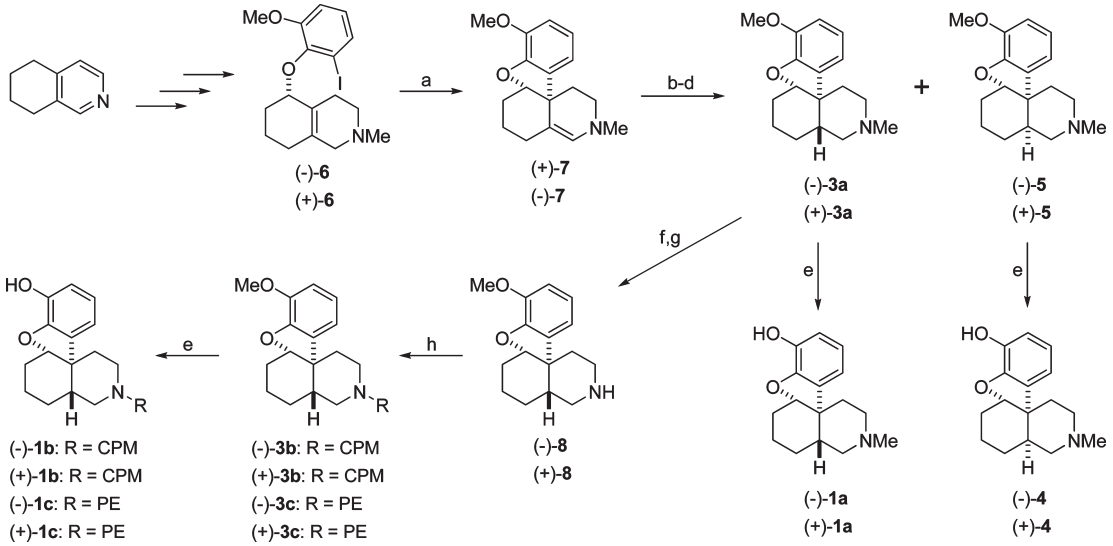
Pharmacology

The κ-, μ-, and δ-opioid receptor binding data for enantiomeric ACNO compounds are listed in Table 1. Generally, the (−)-enantiomers possessed much greater κ-, μ-, and δ-opioid receptor binding affinity than their corresponding (+)-enantiomers. The (−)-9-hydroxy-substituted analogues had higher affinity than their corresponding (−)-9-methoxy-substituted analogues for all three subtypes of opioid receptors, which is consistent with the SAR for most opioid ligands in the literature.[4]

The *trans*-(−)-isomers, (−)-**3a** and (−)-**1a**, demonstrated stronger binding affinities than the *cis*-(−)-isomers, (−)-**5** and (−)-**4**, respectively, for κ-, μ-, and δ-opioid receptors. In contrast to the (−)-enantiomers, none of the (+)-enantiomers of ACNO derivatives displayed significant binding affinity for the opioid receptors. Thus, the ability of racemic ACNO compounds to interact with opioid receptors resided with their (−)-enantiomers.

In the series, *N*-Me- and *N*-PE-substituted (−)-**1a** and (−)-**1c** were potent μ-opioid receptor ligands (K_i = 0.65 and 0.30 nM, respectively) with moderate affinities for κ- and δ-receptors. Replacement of the *N*-Me group of (−)-**1a** with

Scheme 1[a]



[a] Reagents and conditions: (a) $Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, CH_3CN, 120 °C, microwave, 30 min, 93% ee; (b) H_2, PtO_2, EtOH, rt; (c) HCl, CH_2Cl_2, rt; (d) recrystallization, 2-propanol/EtOAc, >99% ee; (e) BBr_3-Me_2S, $ClCH_2CH_2Cl$, reflux; (f) $ClCO_2CH_2CCl_3$, $ClCH_2CH_2Cl$, K_2CO_3, reflux; (g) Zn, HOAc, rt; (h) cyclopropylmethyl bromide or 2-phenylethyl bromide, DMF, K_2CO_3, 60 °C.

Table 1. Opioid Receptor Binding Data for the Enantiomeric *N*-Substituted ACNO Compounds[a]

	K_i (nM)			K_i ratio	
compd	κ	μ	δ	κ/μ	δ/μ
(−)-**3a**	3470 ± 340	236 ± 43	9750 ± 490	15	41
(−)-**3b**	41 ± 2.0	30 ± 4.0	544 ± 29	1.4	18
(−)-**3c**	1850 ± 72	24 ± 2.0	490 ± 22	77	20
(−)-**5**	> 10000	8840 ± 650	> 10000	–	–
(+)-**3a**	7230 ± 590	7610 ± 520	> 10000	0.95	–
(+)-**3b**	> 10000	> 10000	> 10000	–	–
(+)-**3c**	1140 ± 65	145 ± 16	8390 ± 320	7.9	58
(+)-**5**	> 10000	> 10000	> 10000	–	–
(−)-**1a**	14 ± 1.2	0.65 ± 0.07	44 ± 2.0	21	68
(−)-**1b**	0.10 ± 0.04	0.080 ± 0.05	2.0 ± 0.10	1.3	25
(−)-**1c**	15 ± 1.0	0.30 ± 0.02	6.0 ± 0.30	50	20
(−)-**4**	565 ± 53	27 ± 3.0	1050 ± 53	21	39
(+)-**1a**	6900 ± 620	8000 ± 1100	> 10000	0.86	–
(+)-**1b**	699 ± 51	1330 ± 190	> 10000	0.53	–
(+)-**1c**	1240 ± 92	275 ± 30	5000 ± 150	4.5	18
(+)-**4**	1850 ± 130	> 10000	> 10000	< 0.19	–
(−)-pentazocine	2.2 ± 0.20	3.9 ± 0.70	49 ± 15	0.56	13
(−)-naloxone	3.0 ± 0.02	0.98 ± 0.05	51 ± 3.0	1.8	49

[a] [^{125}I]IOXY binding used membranes prepared from CHO cells that stably express the human κ-, μ-, or δ-opioid receptor. All results include the standard deviation (n = 3). Assays were run as previously noted.[10]

Table 2. σ_1 and σ_2 Receptor Binding Affinities of N-Substituted *trans*-ACNO Compounds[a]

	K_i (nM)		K_i ratio
compd	σ_1	σ_2	σ_2/σ_1
(−)-**3a**	> 10,000	7480 ± 650	< 0.7
(−)-**3b**	285 ± 27	3270 ± 77	11
(−)-**3c**	560 ± 15	3270 ± 340	5.8
(+)-**3a**	658 ± 53	> 10,000	> 15
(+)-**3b**	62 ± 4.0	4370 ± 500	71
(+)-**3c**	278 ± 26	2550 ± 72	9.2
(−)-**1a**	> 10000	> 10000	–
(−)-**1b**	399 ± 42	> 10000	> 25
(−)-**1c**	239 ± 11	5380 ± 240	23
(+)-**1a**	2010 ± 120	> 10000	> 5.0
(+)-**1b**	201 ± 11	1030 ± 87	5.1
(+)-**1c**	131 ± 17	263 ± 20	2.0
(−)-pentazocine	16 ± 2.0	56 ± 6.0	3.5
(+)-pentazocine	6.0 ± 2.0	1360 ± 150	226
naloxone	> 10000	> 10000	–

[a] Affinities were determined in rat brain homogenates using standard assay conditions. σ_1 receptors were labeled with [^{3}H]-(+)-pentazocine. σ_2 receptors were labeled with [^{3}H]di-*o*-tolylguanidine in the presence of (+)-pentazocine to block σ_1 receptors. Nonspecific binding was assessed in the presence of haloperidol. The values in this table represent the means ± the standard error of the mean from replicate assays.[11]

an *N*-CPM group [i.e., (−)-**1b**] greatly enhanced its binding to κ-, μ-, and δ-opioid receptors. Compound (−)-**1b** was the most potent κ-, μ-, and δ-opioid receptor ligand (K_i = 0.10, 0.08, and 2.0 nM, respectively) in this study.

The σ_1 and σ_2 receptor binding affinities of the enantiomeric *trans*-ACNO compounds are listed in Table 2. None of the compounds had appreciable σ_1 or σ_2 affinity relative to (−)- and (+)-pentazocines.

The functional activities of compounds (−)-**1a**, (−)-**1b**, and (−)-**1c** were investigated using [^{35}S]GTP-γ-S assays. The *N*-Me-substituted (−)-**1a** exhibited μ-partial agonist activity (ED_{50} = 19 nM; E_{max} = 35%) and moderate κ-antagonist activity (Table 3). The *N*-CPM-substituted (−)-**1b** was a potent κ-partial agonist with an ED_{50} of 2.3 nM and an E_{max} of 23%, a potent μ-antagonist (K_d = 0.22 nM), and a moderate δ-antagonist (K_d = 20 nM). The *N*-PE-substituted (−)-**1c** was a potent μ-full agonist with an ED_{50} of 10 nM, a δ-partial agonist with an E_{max} of 64%, and a weak κ-antagonist.

In addition to treatment of opioid abuse and overdose, μ-antagonists have other clinical utilities. Alvimopan, a novel agent for the treatment of postoperative ileus, is a selective, peripherally acting μ-antagonist.[12] Naltrexone, a nonselective μ-antagonist, has been used to treat alcoholism since 1994. Further studies have identified that (−)-**1b** was an "almost neutral" μ-antagonist in CHO cells expressing the cloned human μ-opioid receptor.[13] Recently, neutral antagonists have been suggested to be a better potential treatment for opioid overdose, opioid dependence, and side effects associated with opioid analgesics.[14] Moreover, the efficacy of μ-antagonist treatments of alcohol addiction, such as naltrexone,[15] might be improved via use of a neutral μ-antagonist, since such compounds might produce less aversive effects.[14] Therefore, (−)-**1b** may be a lead for the development of novel treatments for opioid addiction and alcoholism and may be a useful pharmacological tool for studying the role that constitutive opioid receptor activity plays in various disease states.

Conclusion

In summary, a series of enantiomeric N-substituted ACNO compounds was synthesized, and the (−)-enantiomers demonstrated much greater κ-, μ-, and δ-opioid receptor binding affinities than their corresponding (+)-enantiomers. *N*-Me-substituted (−)-**1a** exhibited subnanomolar binding affinity for μ-receptor and μ-partial agonist activity in [^{35}S]GTP-γ-S assays. The *N*-CPM-substituted (−)-**1b** was a potent ligand for κ-, μ-, and δ-opioid receptors and displayed potent μ-antagonist activity and κ-partial agonist activity. In addition, (−)-**1b** was found to be a potent almost neutral μ-antagonist, which may be a better potential treatment for opioid dependence and toxicity. *N*-PE-substituted (−)-**1c** possessed subnanomolar μ-receptor binding affinity and was a full μ-agonist. These ligands are promising for the development of novel treatments for opioid receptor-related disorders and useful tools for the study of opioid pharmacology.

Table 3. [^{35}S]GTP-γ-S Functional Assay Data for ACNO Compounds (−)-**1a**, (−)-**1b**, and (−)-**1c**[a]

	κ			μ			δ		
	agonism		antagonism	agonism		antagonism	agonism		antagonism
compd	E_{max} (%)	ED_{50} (nM)	K_e (nM)	E_{max} (%)	ED_{50} (nM)	K_e (nM)	E_{max} (%)	ED_{50} (nM)	K_e (nM)
(−)-**1a**			80 ± 7	35 ± 1	19 ± 3		ND[b]		ND[b]
(−)-**1b**	23 ± 1	2.3 ± 0.7				0.22 ± 0.09			20 ± 3
(−)-**1c**			130 ± 17	101 ± 3	10 ± 2		64 ± 2	148 ± 24	
morphine	28 ± 3	1140 ± 460		86 ± 3	37 ± 6		103 ± 7[c]	316 ± 5[c]	
DAMGO	69 ± 6	8940 ± 1500		100 ± 3	42 ± 4				
naloxone			10 ± 3			2.3 ± 0.3			35 ± 5

[a] [^{35}S]GTP-γ-S binding was conducted using CHO cells that stably express the human κ-, μ-, or δ-opioid receptor. All results include the standard deviation (n = 3). E_{max} values are expressed as a percent of the maximal stimulation, where 100% is defined as the stimulation produced by 1 μM DAMGO, 500 nM SNC80, and 500 nM (−)-U50,488 (for μ-, δ-, and κ-receptors, respectively). Agonist stimulation and K_e determinations were conducted as previously described.[10a] [b] Not determined. [c] Data taken from ref 10b.

Experimental Section

Melting points were determined on a MEL-TEMP II apparatus by Laboratory Devices and are uncorrected. NMR spectra were recorded on Bruker DPX-200 and AV-400 FT-NMR spectrometers. Chemical shifts are expressed in parts per million on the δ scale relative to a tetramethylsilane (TMS) internal standard. EI mass spectra and high-resolution mass measurements (EIHRMS) were recorded using a Finnigan MAT 95S mass spectrometer. ESIHRMS data were obtained using a Bruker Daltonik micrOTOF mass spectrometer. Elemental analyses were performed with a Heraeus varioIII-NCSH instrument and were within ±0.4% for the elements indicated. The purity of all tested compounds was determined by combustion analysis or HPLC and was not less than 95%. Optical rotations were obtained using a JASCO DIP-370 polarimeter and are reported at the sodium D-line (589 nm), unless otherwise noted. Thin-layer chromatography (TLC) was performed on Merck (art. 5715) silica gel plates and visualized under UV light (254 nm), upon treatment with iodine vapor, or upon heating after treatment with 5% phosphomolybdic acid in ethanol. Medium-pressure liquid chromatography (MPLC) was performed with Merck (art. 15111) 15−40 μm silica gel 60. Anhydrous tetrahydrofuran was distilled from sodium benzophenone prior to use. No attempts were made to optimize yields.

(−)-*trans*-3-Methyl-2,3,4,4aα,5,6,7,7aα-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinolin-9-ol [(−)-1a]. A solution of (−)-**3a** (150 mg, 0.55 mmol) and BBr_3-$(CH_3)_2S$ (2.47 mmol) in 1,2-dichloroethane (25 mL) was heated to reflux for 3 h and then cooled to rt. The reaction mixture was treated with H_2O (5 mL) and basified to pH > 10 with Na_2CO_3(saturated). The solution was extracted with an IPA/CH_2Cl_2 mixture (1/4, 3 × 50 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated. The crude residue was chromatographed (MPLC, silica gel; 0.1/1/19 NH_4OH/CH_3OH/CH_2Cl_2) to afford (−)-**1a** (121 mg, 85%) as a colorless oil: mp 268 °C (HCl salt, IPA/EtOAc); $[\alpha]_D$ −34.1 (*c* 1.10, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10−1.25 (m, 1H), 1.31−1.46 (m, 2H), 1.46−1.60 (m, 2H), 1.75−1.85 (m, 2H), 1.85−1.96 (m, 1H), 1.96−2.10 (m, 1H), 2.41 (s, 3H), 2.42−2.46 (m, 1H), 2.59 (t, J = 11.8 Hz, 1H), 2.74−2.82 (m, 2H), 4.41 (t, J = 6.1 Hz, 1H), 6.69−6.74 (m, 2H), 6.98 (dd, J = 6.6, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 24.6, 28.3, 38.7, 39.0, 45.7, 48.3, 50.8, 57.1, 89.1, 115.6, 118.3, 120.0, 132.8, 142.3, 147.3; MS (EI, 70 eV) m/z 259 (M^+, base); EIHRMS calcd for $C_{16}H_{21}NO_2$ $[M]^+$ 259.1572, found 259.1572. Anal. (−)-**1a**·HCl ($C_{16}H_{21}NO_2$·HCl) C, H, N.

(−)-*trans*-3-Cyclopropylmethyl-2,3,4,4aα,5,6,7,7aα-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinolin-9-ol [(−)-1b]. Compound (−)-**1b** was synthesized from (−)-**3b** according to the procedure for the preparation of (−)-**1a**, which afforded a pale yellow solid in 76% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12−0.16 (m, 2H), 0.50−0.54 (m, 2H), 0.91−1.01 (m, 1H), 1.13−1.22 (m, 1H), 1.30−1.47 (m, 2H), 1.48−1.57 (m, 2H), 1.77−1.80 (m, 1H), 1.83−1.94 Hz (m, 2H), 2.04−2.12 (m, 1H), 2.39−2.50 (m, 3H), 2.62 (t, J = 11.8 Hz, 1H), 2.98−3.04 (m, 2H), 4.40 (t, J = 6.0 Hz, 1H), 6.66−6.74 (m, 2H), 6.97 (dd, J = 7.1, 1.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 4.0, 4.1, 7.8, 20.3, 24.8, 28.3, 38.6, 38.8, 48.7, 49.8, 55.0, 63.5, 89.1, 115.7, 118.2, 120.0, 132.9, 142.4, 147.4; MS (EI, 70 eV) m/z 299 (M^+, base); EIHRMS calcd for $C_{19}H_{25}NO_2$ $[M]^+$ 299.1885, found 299.1888.

(−)-*trans*-3-(2-Phenylethyl)-2,3,4,4aα,5,6,7,7aα-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinolin-9-ol [(−)-1c]. Compound (−)-**1c** was synthesized from (−)-**3c** according to the procedure for the preparation of (−)-**1a**, which afforded a colorless oil in 83% yield: mp 236−238 °C (HCl salt, IPA/EtOAc); $[\alpha]_D$ −48.5 (*c* 1.08, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16−1.29 (m, 1H), 1.33−1.60 (m, 4H), 1.86 (tt, J = 13.1, 3.2 Hz, 2H), 1.89−1.97 (m, 1H), 2.07 (tt, J = 12.3, 3.7 Hz, 1H), 2.50 (td, J = 11.8, 3.7 Hz, 1H), 2.66 (t, J = 11.7 Hz, 1H), 2.74−2.78 (m, 2H), 2.86−2.96 (m, 4H), 4.44 (t, J = 6.0 Hz, 1H), 6.72 (t, J = 7.6 Hz, 1H), 6.77 (dd, J = 8.0, 1.3 Hz, 1H), 7.03 (dd, J = 7.2, 1.3 Hz, 1H), 7.18−7.21 (m, 3H), 7.25−7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 24.8, 28.3, 33.4, 38.9, 39.1, 48.9, 49.0, 55.1, 60.6, 89.5, 115.5, 118.7, 120.2, 126.1, 128.4, 128.7, 132.8, 140.2, 141.9, 147.2; MS (EI, 70 eV) m/z 349 (M^+), 258 (base); ESIHRMS calcd for $C_{23}H_{28}NO_2$ $[MH]^+$ 350.2115, found 350.2113. Anal. (−)-**1c**·HCl ($C_{23}H_{27}NO_2$·HCl·1.1H_2O) C, H, N.

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Supporting Information Available: Full experimental details, including pharmacological assay methods, elemental analysis results, and HPLC purity data. This material is available free of charge via the Internet at http://pubs.acs.org.

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