Modified Ibogaine Fragments: Synthesis and Preliminary Pharmacological Characterization of 3-Ethyl-5-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]benzothiophenes

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Five phenyl-substituted derivatives and analogues of 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole, **5**, a major fragment of ibogaine (**1**), were synthesized and tested for binding to monoamine transporters, the NMDA receptor-coupled cation channel, and dopamine and opioid receptors. All five derivatives, **9** and **17a**−**d**, displayed 8−10-fold higher affinity at the DA transporter than ibogaine and noribogaine (**4**). At the serotonin transporter, two compounds (**9** and **17a**) exhibited higher potency than ibogaine, while the rest had weaker binding affinities than the lead compound. In keeping with their structural similarity to ibogaine, all five compounds displayed weak to poor affinity for dopamine D1 and D2 receptors. However, two compounds, **17a**,**c**, demonstrated moderate binding affinities at dopamine D3 receptors. All five compounds displayed weak to poor affinities for μ and κ opioid receptors and for the NMDA receptor-coupled cation channel. Despite the qualitative differences, derivatives and analogues of **5** may serve as useful substitutes for ibogaine.

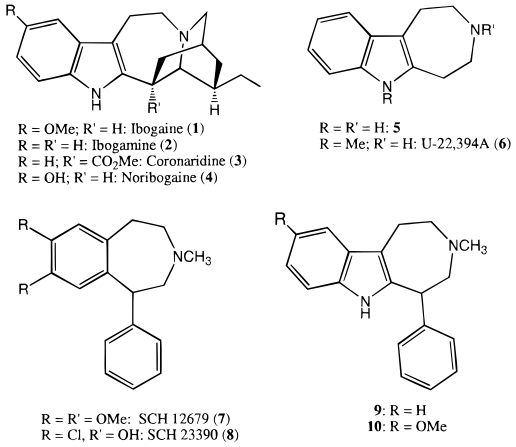
Introduction

Ibogaine (Chart 1, **1**) is the major constituent of the root of *Tabernanthe iboga*, a naturally occurring shrub commonly found in West and Central Africa.[1,2] In African folk medicine, large quantities of this root were consumed for initiation rites. In lower quantities, this compound was used to combat fatigue during periods of great physical exertion (reviewed in refs 3 and 4). Pharmacological evaluation of this agent in laboratory animals revealed unusual excitatory effects and local anesthetic activity and confirmed its psychostimulant activity.[3]

In humans, administration of ibogaine is followed by a period of visualizations (lasting several hours), followed by a longer cognitive phase of intense introspection. At the end of this period, some opiate and psychostimulant addicts report alleviation or cessation of craving, and a few have remained drug-free for several years thereafter.[5−9] Although these earlier reports were anecdotal, methods for the treatment of opiate and cocaine dependence with ibogaine were patented by Lotsoff in 1985[5] and 1986,[6] respectively. Subsequent investigation of the antiaddictive activities of **1** in animals (vide infra) has prompted the initiation of limited human trials (IND 39,680).

In rats, ibogaine reduces intravenous morphine self-administration[10,11] and decreases morphine-induced locomotor activity.[12,13] In addition, ibogaine was found to alleviate withdrawal in morphine-dependent rats.[14−16]

Chart 1



Similarly, ibogaine reduces cocaine intake in mice,[17] cocaine self-administration in rats,[11,18] and cocaine-induced locomotor activity in mice[19] and rats.[12] Ibogaine has also been reported to attenuate alcohol intake by alcohol-preferring rats.[20] The compound may also reduce the rewarding effects of nicotine.[21,22]

In view of the exciting possibilities presented by this alkaloid, we initiated a program to develop structurally simple analogues of ibogaine for evaluation as potential antiaddictive agents. This manuscript describes the synthesis and preliminary biological characterization of the first class of analogues produced by this effort.

Chemistry

The target compounds were synthesized as outlined in Scheme 1. Briefly, chloromethylation of benzothiophene provided **11** in 91% yield. Reaction of **11** with sodium cyanide followed by reduction of the product **12**

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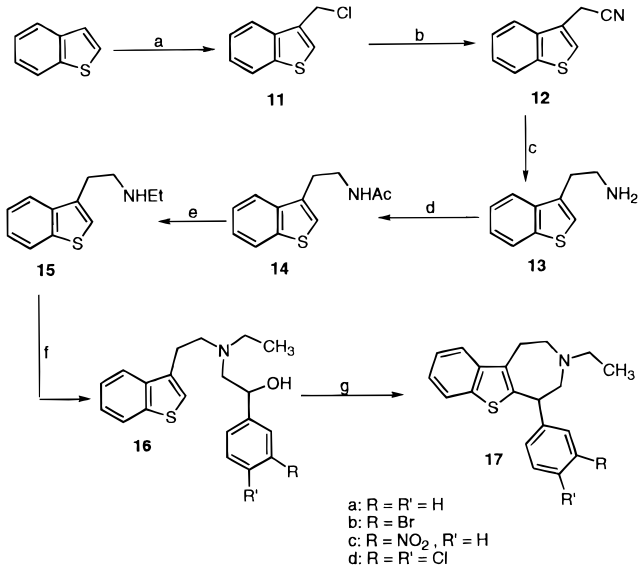
Scheme 1[a]



[a] (a) CH_2O (aq), HCl (g), concd HCl; (b) KCN, PTC, H_2O, 90−95 °C; (c) $LiAlH_4$, ether, $AlCl_3$, reflux; (d) Ac_2O, Et_3N; (e) BH_3·THF, reflux; (f) styrene oxide, EtOH, reflux; (g) CF_3CO_2H, concd H_2SO_4 (cat.).

with $LiAlH_4$ provided **13** in 20% yield from **11**. Alternatively, commercially available **12** was reduced to **13** under similar conditions. Compound **13** was reacted with acetic anhydride, and the resulting amide **14** was reduced with BH_3·THF to provide the key intermediate **15** in 61% overall yield from benzothiophene. Typically, the reaction of **15** with the styrene oxides produced **16** and a minor product resulting from the attack of the amine at the more hindered carbon. The two were easily separated by HPLC to provide **16** in yields of 30−50%. Subsequent cyclization of the amino alcohols **16a**−**d** proceeded smoothly to give the desired products **17a**−**d** in yields of 46−58%. Typically, the cyclization of the amino alcohols **16a**−**d** was associated with a δ 0.1 upfield shift in the benzylic methine proton NMR signal.

Results and Discussion

Despite its apparent complexity, the skeleton of ibogaine can be broken down into a number of easily identifiable fragments. Two of the most obvious ones are tryptaminyl and isoquinuclidinyl. Previously, tropan-3-ylindoles, synthesized as abbreviated ibogaine analogues, have been found to display comparable or slightly higher affinity for a number of molecular targets other than ibogaine.[23] However, for the current study we chose a third fragment represented by 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (**5**). This fragment was chosen because it contains the tryptaminyl fragment and a portion of the isoquinuclidinyl fragment and is thus *intermediate* in structure between ibogaine and these two principal components. A review of the literature showed that **5** and its derivatives had been developed as conformationally restricted tryptamine analogues.[24] In rats, some derivatives of **5** were found to elicit many of the symptoms associated with tryptamine. One of these compounds, 6-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (**6**, U-22,394A), was found to antagonize aggressive behavior in fighting mice, block conditioned avoidance, and induce hypothermia and anorexigenic behavior in rodents.[24] However, the compound was devoid of neuroleptic activity when tested in humans.[25] Following the initial success of SCH12679 (**7**) in the treatment of aggressive mental retardation,[26−28] Elliott et al.[29] developed the corresponding 5-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indoles in an effort to increase the selectivity of this class of fused tricyclic azepines. In mice, these compounds failed to exhibit neuroleptic activity. However, two analogues, 3-methyl-5-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (**9**) and 9-methoxy-3-methyl-5-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (**10**), displayed antidepressant activity.

Although the molecular mechanisms underlying the antiaddictive activity of **1** are not known, the compound displays moderate to high affinity for dopamine and serotonin (5-HT) transporters,[30] κ[31−33] and μ opioid[34] receptors, the MK-801 site on the NMDA receptor,[33,35−40] σ-2 receptors,[38,41−43] nicotine receptors,[44,45] and voltage-dependent Na^+, K^+, and Ca^{2+} channels.[31] In the present exploratory study, we compared the in vitro binding profiles of **1** and its principal metabolite noribogaine (**4**) with those of the previously described **9** and the isosteric benzothiophenes **17a**−**d**. Compound **9** was chosen over **5** for the same reasons cited by Elliott et al.[23]—the expectation that the phenyl group would restrict the number of potential interaction sites. The benzothiophenes were included to test the effects of isosteric replacement. A summary of the radioligand binding studies performed is presented in Table 1, and the results of the assays are shown in Table 2. Inclusion of literature values for SCH12679 (**7**) and SCH23390 (**8**) in Table 2 was prompted by the realization that the 6−5−7 fused azepines can be regarded as linearly extended 3*H*-benzazepines. Linearly extended systems such as lin-benzoguanosine have been used previously to probe the dimensions of a given binding site.[46] For the purpose of this discussion, binding affinities are defined as high (IC_{50} < 0.1 μM), moderate (IC_{50} = 0.1−1 μM), weak (IC_{50} = 1−10 μM), or poor (IC_{50} > 10 μM).

All five tricyclic compounds, **9** and **17a**−**d**, displayed comparable affinity for the dopamine transporter (DAT), suggesting (1) that benzothiophene and indole are bioisosteric at this site and (2) that a range of substituents can be tolerated on the pendant phenyl group. When compared to ibogaine and its metabolite, these tricyclic analogues displayed 8−15-fold higher affinity for the DAT. Since these tricyclic compounds are more planar than ibogaine, it would be reasonable to conclude that the cagelike isoquinuclidinyl fragment limits the extent of interaction between ibogaine and the DAT. Alternatively, the higher affinity of the tricyclic compounds (relative to ibogaine and noribogaine) may result from the interaction of the pendant phenyl group with a hydrophobic pocket. In that case, the lower affinity of ibogaine at the DAT may derive not from its cagelike structure but from its inability to benefit from this additional interaction.

In contrast to the DAT, the serotonin transporter (SERT) was more discriminating. Among the tricyclic compounds, **9** displayed the highest affinity for the SERT. Moreover, only this compound displayed comparable affinity for both DAT and SERT. Compound

Table 1. Radioligand Binding Assays for Modified Ibogaine Fragments

binding site	radioligand	nonspecific	tissue	ref
		Dopaminergic		
D1 receptor	[^{3}H]SCH23390	(+)-butaclamol	striatum	48
D2 receptor	[^{3}H]YM-09151-2	(+)-butaclamol	striatum	49
	[^{3}H]haloperidol	(+)-butaclamol	striatum	41
D3 receptor	[^{3}H]-(+)-7-OH-DPAT	(+)-butaclamol	ventral striatum	50
DA transporter	[^{125}I]RTI-121	(−)-cocaine	striatum	51
		Glutamatergic		
NMDA receptor complex	[^{3}H]-(+)-MK801	(+)-MK801	caudate	36
		Opioidergic		
κ	[^{3}H]U69593	naloxone	insular Ctx	52
μ	[3H]DAMGO	naloxone	thalamus	53
		Serotonergic		
5-HT transporter	[^{125}I]RTI-55	(−)-cocaine	occipital Ctx	54

Table 2. Relative Affinities ($IC_{50} \pm$ SD, μM) of 3-Ethyl-5-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]benzothiophenes and Reference Compounds at Selected Molecular Targets

target	DAT (WIN35,428)	SERT (RTI-55)	D1 (SCH23390)	D2 (YM-09151-2)	D3 (7-OH-DPAT)	μ (DAMGO)	κ (U69593)	NMDA (MK801)
9	0.18 ± 0.005	0.19 ± 0.001	20 ± 1.6	27.2 ± 0.35	4.2 ± 0.02	3.1 ± 0.82	21.2 ± 2.5	ND
17a	0.14 ± 0.003	0.30 ± 0.001	3 ± 0.05	5.0 ± 0.07	0.6 ± 0.01	2.2 ± 0.08	1.3 ± 0.21	42 ± 1.2
17b	0.21 ± 0.02	4.30 ± 0.01	5 ± 0.05	3.5 ± 0.28	2.0 ± 0.28	5.0 ± 0.33	12.5 ± 0.07	46.6 ± 8
17c	0.25 ± 0.01	1.10 ± 0.002	5 ± 0.06	3.1 ± 0.14	0.6 ± 0.04	3.1 ± 0.57	16.2 ± 1.53	32 ± 0.30
17d	0.25 ± 0.001	1.20 ± 0.002	70 ± 0.09	5.0 ± 0.21	2.0 ± 0.14	54.5 ± 4.5	15.9 ± 1.80	81 ± 1.6
ibogaine	4.11 ± 0.45[a]	0.59 ± 0.09[a]	>10[a]	>10[a]	>10[a]	3.76 ± 0.22[b]	25.0 ± 0.57[a]	5.2 ± 0.24[a]
noribogaine	3.35 ± 0.50[a]	0.04 ± 0.01[a]	>10[a]	>10[a]	>10[a]	0.16 ± 0.01[b]	4.24 ± 0.28[a]	31.4 ± 5.43[a]
SCH23390	ND	ND	0.0043[c]	ND	ND	ND	ND	ND
SCH12679	ND	ND	0.491[d]	5.218	ND	ND	ND	ND

[a] Reference 32. [b] Reference 55. [c] Reference 56. [d] Reference 47. Values shown for reference compounds are $K_i \pm$ SD, μM; ND, not determined.

17a was 2-fold weaker at the latter binding site, while **17b**,**c** displayed between 4- and 17-fold lower affinity for the SERT than DAT. Since the larger discrepancy between DAT and SERT is associated with substitution of the pendant phenyl group, we conclude that the DAT contains a larger hydrophobic pocket than the SERT. While the tricyclic analogues typically displayed lower affinity for SERT than for DAT, ibogaine, and particularly noribogaine, demonstrated higher affinity for SERT than for DAT, clearly underscoring the importance of the hydroxyl group in the interaction with SERT.

At the dopamine D1 receptor, both ibogaine and noribogaine displayed decidedly poor affinity. Despite the structural similarity between the 3*H*-benzazepines (such as SCH23390 and SCH12679) and the fused tricyclic azepines (**9** and **17a**−**d**), the latter displayed weak to poor affinity for the D1 receptor. In previous studies of the structurally analogous 3-benzazepines,[47] C7- and C8-hydroxy groups were found to play a critical role in the interaction with the D1 receptor. Consequently, we conclude that the poor affinity of the fused tricyclic compounds, **9** and **17a**−**d**, may be attributed to the absence of hydroxyl groups at the corresponding C9- and C10-positions. This conclusion is supported by molecular modeling studies which demonstrated that the C7- and C8-positions of SCH23390 are eclipsed by the benzo portion of **17a** (data not shown). While ibogaine and noribogaine also displayed poor affinity for dopamine D1 and D2 receptors, four (**17a**−**d**) out of five tricyclic compounds displayed weak affinity for D2 receptors and two (**17a**,**c**) of the four compounds clearly exhibited moderate affinity for dopamine D3 receptors. Although it would appear that the D3 receptor is sensitive to single-point substitution on the pendant phenyl group, a more extensive study is needed to clearly define structure−activity relationships at this binding site.

At the μ opioid receptor, noribogaine was a moderately potent ligand while ibogaine, **9**, and **17a**−**c** showed weak to poor affinity. On the other hand, noribogaine and **17a** showed weak affinity for κ opioid receptors while all other compounds showed poor affinity for this site. The 20-fold disparity in the potencies of ibogaine and its principal metabolite **1** clearly suggests that a hydroxyl group (or suitable bioisostere thereof) is required for binding to the μ opioid receptor. Finally, ibogaine, noribogaine, and the tricyclic azepines (**9** and **17a**−**d**) were all relatively poor inhibitors of [^{3}H]NMDA binding. However, ibogaine appeared to display higher affinity for this site than all the other compounds (Table 1).

Although the molecular mechanisms underlying the antiaddictive activity of ibogaine remain unclear, the present investigation clearly shows that the fused tricyclic azepines **9** and **17a**−**d** recognize many of the same molecular targets as ibogaine and/or noribogaine. Consequently, the biological actions of **9** and **17a**−**d** may be expected to demonstrate striking similarities with those of ibogaine and/or noribogaine. To explore this possibility, studies have been initiated to investigate the effects of **17a**−**d** on cocaine self-administration in rodents. These studies will be reported at a later date.

Experimental Section

General. Synthetic intermediates were purchased from Aldrich Chemical Co., Inc. (Milwaukee, WI) and Lancaster Synthesis (Windham, MA) and were used as received. Solvents were distilled immediately before use.

Standard handling techniques for air-sensitive materials were employed throughout this study. Preparative chromatography was performed on a Harrison Research chromatotron using Merck 60 PF254 silica gel. Analytical TLC was performed on Analtech GHLF silica gel plates, and the chromatograms were visualized by UV and/or methanolic iodine. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on an IBM Brucker spectrometer at 200 MHz. NMR spectra are referenced to the deuterium lock frequency of the spectrometer. Under these conditions, the chemical shifts (in ppm) of residual solvent in the ^{1}H NMR spectra are found to be as follows: $CHCl_3$, 7.26; DMSO, 2.56; HOD, 4.81. The following abbreviations are used, where appropriate, to describe the peak splitting patterns: br = broad, s, = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Both low- and high-resolution mass spectometry were performed on an AEI MS-30 instrument. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

3-(Chloromethyl)benzo[*b*]thiophene (11). HCl(g) was bubbled vigorously through a mixture of thianaphthene (17.0 g, 126.68 mmol), 37% aqueous formaldehyde (15 mL), and concentrated HCl (15 mL) until the reaction temperature rose to 65 °C. At this time, the flow of HCl gas was reduced to a slow stream which was maintained for 1.5 h. The reaction mixture was diluted with H_2O (50 mL) and subsequently extracted with ether (2 × 50 mL). The combined ethereal extracts were dried over Na_2SO_4 and concentrated under reduced pressure to yield a straw-colored liquid: 21.0 g (90.7%); ^{1}H NMR ($CDCl_3$) δ 4.90 (s, 2H, CH_2−Cl), 7.25 (s, 1H, CH−S), 7.45 (m, 2H, phenyl), 7.88 (m, 2H, phenyl).

3-(Cyanomethyl)benzo[*b*]thiophene (12). Potassium cyanide (6.65 g, 102.14 mmol) and benzyltriethylammonium chloride (23.26 g, 227.78 mmol) were dissolved in H_2O (50 mL) in a round-bottomed flask fitted with a stirrer, reflux condenser, and a dropping funnel. 3-(Chloromethyl)thianaphthene (15.0 g, 82.12 mmol) was added dropwise with cooling (water bath) to the well-stirred mixture, and the resulting emulsion was heated at 90−95 °C for 1 h. The reaction mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, and concentrated to a residue. The crude product was purified by radial flow chromatography [hexane (9)−acetone (1)] to obtain 4.0 g (28%) of a pale-colored crystalline solid: ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 2H, CH_2−Cl), 7.25−7.91 (m, 5H, aryl).

2-(Benzo[*b*]thien-3-yl)ethylamine (13). To a stirring slurry of lithium aluminum hydride (1.16 g, 30.32 mmol) in dry ether (50 mL) was added, under N_2, a slurry of aluminum chloride (4.04 g, 30.32 mmol) in dry ether (50 mL). After 5 min, a solution of 3-(cyanomethyl)thianaphthene (5.25 g, 30.32 mmol) in ether (50 mL) was slowly added over 10 min. Upon completion of the addition, the resulting mixture was refluxed for 22 h, cooled, neutralized with a 20% aqueous solution of Rochelle's salt, and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to yield the amine as a syrup. The corresponding amine hydrochloride was obtained by treating the free base with a solution of methanolic HCl: yield of hydrochloride, 4.61 g (71%); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 2H, $-NH_2$), 3.00 (m, 4H, $-CH_2-CH_2-$), 7.11 (s, 1H, CH−S), 7.36 (m, 2H, phenyl), 7.72−7.86 (m, 2H, phenyl).

2-(Benzo[*b*]thien-3-yl)ethylacetamide (14). Acetic anhydride (2.0 mL, 21.15 mmol) and Et_3N (1.77 mL, 12.69 mmol) were added to a solution of 2-(benzo[*b*]thien-3-yl)ethylamine (0.75 g, 4.23 mmol) in DMF (5 mL). The reaction mixture was stirred for 18 h at room temperature, diluted with H_2O (25 mL), and extracted with CH_2Cl_2 (2 × 25 mL). The organic extracts were dried over Na_2SO_4 and concentrated to a residue to provide 0.88 g (94%) of a viscous liquid: ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3H, $-CH_3$), 3.00 (m, 2H, $-CH_2-$), 3.54 (m, 2H, C*H*$_2$−NH), 6.29 (br s, 1H, NH), 7.10 (s, 1H, CH−S), 7.25−7.37 (m, 2H, phenyl), 7.72−7.86 (m, 2H, phenyl).

***N*-2-(Benzo[*b*]thien-3-yl)ethyl-*N*-ethylamine (15).** Compound **14** (0.85 g, 3.88 mmol) was refluxed in 1 M BH_3·THF (20 mL) for 18 h. Upon cooling, the reaction mixture was acidified with 2 N HCl (20 mL). The mixture was adjusted to pH 8 with 2 M NaOH (aq) and partitioned between water and CH_2Cl_2 (50 mL). The CH_2Cl_2 extracts were dried over Na_2SO_4 and concentrated under reduced pressure to yield a residue which was refluxed in 6 N HCl for 6 h. Finally, the resulting mixture was cooled to room temperature, made alkaline by treatment with NaOH pellets, and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to provide 0.52 g (65%) of the product as a syrup: ^{1}H NMR ($CDCl_3$) δ 1.09 (t, 3H, J = 7 Hz, $-CH_3$), 2.68 (q, 2H, J = 7 Hz, CH_3-CH_2-), 3.01 (m, 2H, C*H*$_2$−NH), 3.63 (t, J = 6 Hz, 2H, C*H*$_2$−CH_2−NH), 6.29 (br s, 1H, NH), 7.15 (s, 1H, CH−S), 7.25−7.39 (m, 2H, phenyl), 7.75−7.88 (m, 2H, phenyl).

3-Nitrostyrene Oxide. A solution of 3-nitrostyrene (1.0 g, 6.70 mmol) in CH_2Cl_2 (10 mL) was cooled in an ice bath. 3-Chloroperoxybenzoic acid (57% pure) (2.23 g, 7.38 mmol) was added in one batch, and the stirring was continued with cooling for 2 h. The ice bath was removed, and stirring was continued at room temperature for an additional 16 h. The reaction mixture was concentrated to a residue and diluted with CCl_4 (20 mL). Precipitated *m*-chlorobenzoic acid was removed by filtration, and the filtrate was washed with a 50:50 mixture of 5% aqueous $NaHCO_3$ and 5% aqueous $NaHSO_3$ (100 mL). The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure to yield 0.70 g (64%) of a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.81 (m, 1H, CH), 3.20 (m, 1H, CH−), 3.97 (m, 1H, −CH−), 7.62 (m, 2H, phenyl), 8.16 (m, 2H, phenyl).

3-Bromostyrene Oxide. A solution of 3-bromostyrene (1.0 g, 5.46 mmol) in CH_2Cl_2 (10 mL) was cooled in an ice bath. 3-Chloroperoxybenzoic acid (57% pure) (1.82 g, 6.01 mmol) was added in one batch, and the stirring was continued with cooling for 2 h. The ice bath was removed, and stirring was continued at room temperature for an additional 16 h. The reaction mixture was concentrated to a residue and diluted with CCl_4 (20 mL). Precipitated *m*-chlorobenzoic acid was removed by filtration, and the filtrate was washed with a 50:50 mixture of 5% aqueous $NaHCO_3$ and 5% aqueous $NaHSO_3$ (100 mL). The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure to yield 0.80 g (64%) of a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.74 (m, 1H, CH), 3.14 (m, 1H, CH−), 3.82 (m, 1H, −CH−), 7.21 (m, 2H, phenyl), 7.42 (m, 2H, phenyl).

3′,4′-Dichlorostyrene Oxide. To an ice-cooled solution of 3′,4′-dichlorostyrene (1.20 g, 6.93 mmol) in CH_2Cl_2 (20 mL) was added mCPBA (57% pure) (2.31 g, 7.62 mmol) in one batch, and stirring was continued with cooling for 2 h. The ice bath was removed, and stirring was continued at room temperature for an additional 16 h. The reaction mixture was diluted with hexane (50 mL) and concentrated to 1.24 g (95%) of a clear liquid. (Note: The material obtained was impure by TLC but was used without any further purification.)

Procedure A: Synthesis of Amino Alcohols 16a−d. *N*-[2-(Benzothien-3-yl)ethyl]-*N*-ethyl-*N*-(2-hydroxy-2-phenyl)ethylamine (16a). A mixture of compound **15** (0.50 g, 2.44 mmol) and styrene oxide (0.32 g, 2.93 mmol) was refluxed in EtOH (5 mL) for 3 h. The reaction mixture was concentrated under reduced pressure and the crude product was purified by radial flow chromatography [hexane (90)−acetone (10):Et_3N (1)] to yield 0.32 g (43%) of a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 3H, $-CH_3$), 2.26−3.08 (m, 8H, all methylene Hs), 4.44 (br s, 1H, −OH), 4.66 (dd, 1H, C*H*-OH), 7.17 (s, 1H, CH−S), 7.46 (m, 7H, phenyl), 7.76−7.91 (m, 2H, phenyl).

***N*-Ethyl-*N*-[2-(benzothien-3-yl)ethyl]-*N*-[2-hydroxy-2-(3-bromophenyl)ethyl]amine (16b):** procedure A, mobile phase for radial flow chromatography, hexane (83):acetone (17):Et_3N (1); yield, 30%; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, CH_3), 2.23−3.16 (m, 8H, all methylene Hs), 4.05 (br s, 1H, OH), 4.55 (dd, 1H, CH−OH), 7.15 (s, 1H, CH−S), 7.18−7.80 (m, 8H, phenyl).

***N*-Ethyl-*N*-[2-(benzothien-3-yl)ethyl]-*N*-[2-hydroxy-2-(3-nitrophenyl)ethyl]amine (16c):** procedure A, mobile

phase for radial flow chromatography, hexane (83):acetone (17):Et_3N (1); yield, 46%; ^1H NMR ($CDCl_3$) δ 1.22 (t, 3H, CH_3), 2.14−3.60 (m, 8H, all methylene Hs), 4.64 (br s, 1H, OH−), 4.66 (dd, 1H, CH−OH), 7.14 (s, 1H, CH−S), 7.30−8.25 (m, 8H, phenyl).

***N*-Ethyl-*N*-[2-(benzothien-3-yl)ethyl]-*N*-[2-hydroxy-2-(3,4-dichlorophenyl)ethyl]amine (16d):** procedure A, mobile phase for radial flow chromatography, acetone (5):hexane (95):Et_3N (1); yield, 43%; ^1H NMR ($CDCl_3$) δ 1.15 (t, 3H, CH_3−), 2.42 (dd, 2H, CH_2−CHOH), 2.60−3.15 (m, 6H, CH_2−), 4.05 (bs, 1H, OH), 4.55 (dd, 1H, −C*H*OH), 7.16 (s, 1H, phenyl), 7.18 (s, 1H, thienyl), 7.30−7.52 (m, 4H, phenyl), 7.75 (d, 1H, phenyl), 7.82 (d, 1H, phenyl).

Procedure B: Synthesis of Hexahydroazepino[4,5-*b*]-benzothiophenes. 3-Ethyl-5-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]benzothiophene (17a). Compound **16a** (0.30 g, 1 mmol) was refluxed for 3 h in a mixture of CF_3COOH (5 mL) and H_2SO_4 (100 μL). After cooling to room temperature, the reaction mixture was diluted with water (10 mL), adjusted to pH 8 with solid $NaHCO_3$, and extracted with EtOAc (2 × 50 mL). The EtOAc extracts were dried over Na_2SO_4 and concentrated under reduced pressure to provide the free amine as a yellow oil. The latter was converted to the corresponding hydrochloride with methanolic HCl and recrystallized from *i*-PrOH−ether to yield 160 mg (57%) of a yellowish brown solid: mp 92−96 °C dec; ^1H NMR ($CDCl_3$) δ 1.10 (t,3H, J = 7 Hz, CH_3−CH_2−), 2.77 (q, 2H, J = 7 Hz, CH_3−CH_2−), 2.80 (m, 2H, azepinyl), 3.20 (m, 4H, azepinyl), 4.49 (dd, 1H, benzylic methine), 7.19−7.67 (m, 9H, phenyl); CIMS calcd for $C_{20}H_{21}NS$ *m/z* 307.1395 (M^+), found 307.1419 (100%). Anal. ($C_{20}H_{21}NS\cdot HCl\cdot H_2O$) C, H, N.

3-Ethyl-5-(3-bromophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]benzothiophene hydrochloride (17b): procedure B, mobile phase for chromatography, hexane (83):acetone (17):Et_3N (1); yield, 65%; mp (HCl) 169−173 °C (*i*-PrOH−ether); ^1H NMR ($CDCl_3$) δ 1.08 (t, 3H, J = 7 Hz, CH_3−CH_2−), 2.74 (q, 2H, J = 7 Hz, CH_3−CH_2−), 2.84 (m, 2H, azepinyl), 3.14 (m, 4H, azepinyl), 4.42 (dd, 1H, benzylic methine), 7.20−7.69 (m, 8H, phenyl); CIMS calcd for $C_{20}H_{20}BrNS$ *m/z* 385.0500 (M^+), found 385.0484 (42.68%). Anal. ($C_{20}H_{20}BrNS\cdot HCl\cdot H_2O$) C, H, N.

3-Ethyl-5-(3-nitrophenyl)-1,2,3,4,5,6-hexahydroazepino-[4,5-*b*]benzothiophene hydrochloride (17c): procedure B, purified by chromatography, hexane (83)−acetone (17):Et_3N (1); yield, 46%; mp (HCl) 168−171 °C (*i*-PrOH−ether); ^1H NMR ($CDCl_3$) δ 1.08 (t, 3H, J = 7 Hz, CH_3−CH_2−), 2.74 (q, 2H, J = 7 Hz, CH_3−CH_2−), 2.94 (m, 2H, azepinyl), 3.11 (m, 4H, azepinyl), 4.55 (dd, 1H, benzylic methine), 7.25−8.27 (m, 8H, phenyl); CIMS calcd for $C_{20}H_{20}N_2O_2S$ *m/z* 352.1246 (M^+), found 352.1227 (84.20%). Anal. ($C_{20}H_{20}N_2O_2S\cdot HCl\cdot {}^3/_4H_2O$) C, H, N.

3-Ethyl-5-(3,4-dichlorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]benzothiophene (17d). Concentrated H_2SO_4 (300 μL) was added to a solution of **16d** (1.1 g, 2.79 mmol) in CF_3COOH (20 mL), and the resulting solution was refluxed for 1 h under N_2. The reaction mixture was diluted with ice-cold water, carefully adjusted to pH 8 with 2 N NaOH solution, and extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were dried over anhydrous Na_2SO_4 and passed through silica gel column (eluting with 10% acetone:hexane). Concentration of the eluent yielded a pale-yellow liquid (670 mg, 58%). The free base was converted to its hydrochloride with methanolic HCl and recrystallized from methanol−ether to yield a yellow solid (560 mg, 53%): mp 154−156 °C; ^1H NMR ($CDCl_3$) δ 1.07 (t, 3H, J = 7 Hz, CH_3−), 2.70 (q, J = 7 Hz, 2H, CH_3−CH_2−), 2.80−3.22 (m, 6H, azepinyl), 4.41 (dd, 1H, J = 1.5 Hz, J = 8 Hz, benzylic methine), 7.17−7.70 (m, 7H, phenyl); CIMS calcd for $C_{20}H_{19}Cl_2NS$ *m/z* 375.0615 (M^+), found 375.0610 (59.04%). Anal. ($C_{20}H_{19}Cl_2NS\cdot HCl\cdot H_2O$) C, H, N.

Ligand Binding Assays. Radioligands were purchased from NEN/DuPont (Boston, MA) or Amersham Corp. (Arlington Heights, IL). Ibogaine and noribogaine were obtained from s.a. Omnichem, Belgium. BIT (2-(*p*-ethoxybenzyl)-1-(diethylaminoethyl)-5-isothiocyanatobenzimidiazole-HCl) and FIT (*N*-phenyl-*N*-[1-(2-(4-isothiocyanato)phenyl)-4-piperidinyl]propanamide-HCl) were custom synthesized by Dr. Kenner Rice (Laboratory of Medicinal Chemistry, NIDDK, Bethesda, MD). All other unlabeled drugs were purchased from Research Biochemicals, Inc., Natick, MA.

All binding assays were conducted as described previously (see Table 1 for references). The ability of modified ibogaine fragments to inhibit binding to neuroreceptors or transporters was first assessed at doses of 100 nM and 10 μM. Positive controls were routinely assayed in parallel using specific reference drugs with known affinities (Table 1). Assay tubes were incubated under the specified conditions and filtered through Whatman 934AH filters on Millipore manifolds. Nonspecific binding was defined as the cpm bound in the presence of a saturating concentration of an established competing ligand. Test compounds were considered active at a given receptor site if the level of inhibition of radioligand binding was equal to or greater than 50% inhibition at the 10 μM dose. To accurately determine potency values, full competition curves were obtained at relevant binding sites using 10−15 concentrations of ibogaine (**1**) or noribogaine (**4**). Ligand competition data were analyzed using the DRUG program of EBDA/LIGAND (Biosoft, Elsevier).

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