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Ibogaine Analogues. Synthesis and Preliminary Pharmacological Evaluation of 7-Heteroaryl-2-azabicyclo[2.2.2]oct-7-enes

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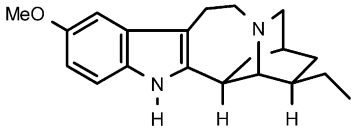
Abstract—Synthesis of 7-heteroaryl-2-azabicyclo[2.2.2]oct-7-enes by cycloaddition and subsequent cross-coupling reaction is described. Binding affinity of these novel compounds towards the characteristic receptorial targets of ibogaine is illustrated.

Introduction

Ibogaine **1** (Fig. 1) is the major constituent of the root of *Tabernanthe iboga,* a naturally occurring shrub found in West and central Africa. Ibogaine reduces cocaine intake in mice,[1] cocaine self-administration in rats,[2] and cocaine-induced locomotor activity[3] in mice and rats.[4] Ibogaine has also been reported to attenuate alcohol intake by alcohol-preferring rats.[5] The compound may also reduce the rewarding effects of nicotine.[6]



1 ibogaine

Figure 1.

Two of the most obvious identifiable fragments, that constitute the skeleton of ibogaine, are 2-ethylindolyl and isoquinuclidinyl ones. Previously, tropane-3-indoles[7a] and hexahydroazepinobenzothiophenes[7b] have been synthesized as abbreviated ibogaine analogues and they have been found to recognize many of the same molecular targets as ibogaine. The 2-azabicyclo[2.2.2]octane (or isoquinuclidine) framework is a distinctive motif in a variety of both naturally occurring[8] and pharmaceutical[9] products and its structural feature is currently encouraging the development of synthetic methods.[10] In connection with our ongoing efforts to explore the synthesis of natural nitrogen containing compounds, we searched for an useful preparation of isoquinuclidinyl derivatives. Our goal was to find a simple preparation of a functionalized isoquinuclidinyl system to be used for structure–activity relationship studies. We recently demonstrated the interesting reactivity of *N*-ethoxycarbonyl-3,4-dihydropyridin-4-one toward double Michael reaction.[11] The structural features of the resultant *N*-ethoxycarbonyl-2-azabicyclo[2.2.2]-7-methoxycarbonyloctan-5-one held considerable promise because the presence of ester and ketone functions confers to the bicyclic structures an useful potentiality to be converted to a collection of structurally related compounds. In this paper, we report a convenient approach to 7-heteroaryl-2-azabicyclo[2.2.2]oct-7-ene derivatives for evaluation of interacting specifically with an enzyme or a receptor.

Chemistry

We selected the Diels–Alder reaction of pyridin-2-ones,[12] functionalized at position 5, as promising

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strategy for the construction of 2-azabicyclo[2.2.2]-octene derivatives.

We first studied the Diels–Alder reaction of 5-indol-2-ylpyridin-2-one **2**, obtained from the corresponding 5-[1-[2-(trimethylsilyl)ethoxymethyl]indol-2-yl]pyridin-2-one,[13] with methyl acrylate in CH_2Cl_2 at 120 °C in a steel tube for 10 days (dienophile/diene, 22/1 mmol) and we observed an high regio- and stereoselectivity with the formation of the 6-*endo* carbomethoxy derivative. Unfortunately the reaction was accompanied by electrophilic substitution at position 3 of the indole nucleus with the obtainment of compound **3** (Fig. 2). Our attempts to inhibit the electrophilic substitution by reducing the concentration of dienophile, by protecting the indole nitrogen or by lowering the temperature were unsuccessful.

We then decided to introduce the indole nucleus in a second time and to construct the 2-azabicyclo[2.2.2]-octene system by [4 + 2]π cycloaddition of 5-Br-*N*-benzylpyridin-2-one[14] **4** with methyl acrylate. The presence of the bromide not only enhances the reactivity of the pyridin-2-one[12] as diene but offers the possibility to introduce an aryl or heteroaryl group by cross-coupling reaction at position 7 of the obtained bicycloadducts. When 5-Br-*N*-benzylpyridin-2-one **4** was submitted to reaction with methyl acrylate in CH_2Cl_2 at 120 °C in a steel tube for 10 days a mixture of four diastereoisomers **5**, **6**, **7** and **8** were isolated with the prevalence of the 6-*endo* adduct **6** (43%) (Fig. 3). Compounds **5–8** could be obtained as pure products only in small amount while in preparative scale they were obtained as mixtures **5**, **8** and **6**, **7**. The four isomers were easily distinguishable by NMR spectroscopy (Table 1) in analogy with literature precedent.[15] The chemical shift of H-1 permitted to determine the regiochemistry of the Diels–Alder reaction: 6-substituted derivatives (**5** and **6**) showed the signal at lower field than 5-substituted ones (**7** and **8**). Moreover, when the methoxycarbonyl group is present at position 5 an higher multiplicity of the H-1 signal is observed. The stereoisomery was ascertained considering that the signals of H-5_{endo} and H-6_{endo} appear at higher field than H-5,6_{exo} (for the magnetic anisotropic effect of the C7–C8 double bond). Moreover, the coupling constant between H-5 and H-6 is higher when the protons are in *syn* orientation. Finally, the coupling constant H-1/H-6_{exo} is higher than H-1/H-6_{endo} (on the base of the torsion angle). A further proof of the *exo* orientation of methoxycarbonyl group in compound **5**, is the difference of the chemical shift for the signals of benzylic protons. This is the consequence of the blocked rotation of the benzylic portion due to the *exo* position of the methoxycarbonyl group: the proton directed toward the methoxycarbonyl group undergoes a deshielding effect while the proton directed toward the C7–C8 double bond undergoes a shielding one. The ratios of **5–8** and consequently the yields were determined on the base of NMR integration of the H-8 signals. The compounds **5–8** appeared stable and no isomerization products were detected even if a stereogenic carbon bearing a carboxymethyl group is present. Our attempts to induce isomerization at C6 or C5 position in compounds **5–8** with LDA in THF at low temperature or with ammonium formate in CH_2Cl_2–MeOH[15d] were unsuccessful.

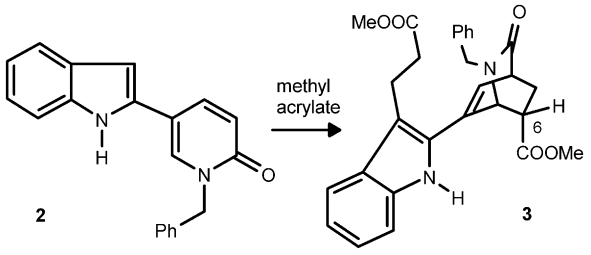

Figure 2.

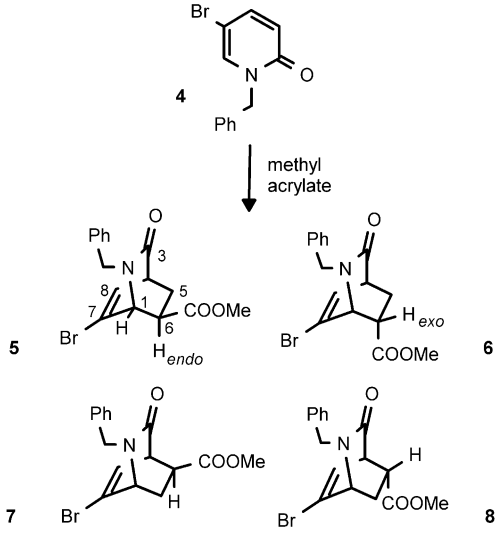

Figure 3.

We proceeded with Pd-mediated cross-coupling reaction using 2-indolylzinc chlorides **10b**[13] (Fig. 5) with the bromoderivatives as mixtures **5**, **8** and **6**, **7** (Fig. 4, Table 2) to give a mixture of **15** and **16** and a mixture of **14** and **17** (Fig. 6) respectively that were easily chromatographed to give the pure compounds. The results of these reactions moved us to use the zinc derivative of *N*-SEM-5-methoxyindole **11b** with bromoderivatives **5** and **7** (as pure compounds) in the same Negishi conditions with the obtainment of compounds **18** and **19**.

Table 1. Characteristic NMR spectroscopic data for compounds **5–8**

	5	**6**	**7**	**8**
δ H-1	4.41	4.41	4.08	4.09
δ H-8	6.42	6.51	6.48	6.37
δ H-5_{exo}	2.02–1.91	2.15–2.07	—	3.05
δ H-5_{endo}	2.02–1.91	2.15–2.07	2.60	—
δ H-6_{exo}	—	3.01	2.27	2.09
δ H-6_{endo}	2.82	—	1.70	2.29
Δδ Ph-CH_2	1.00	0.26	0.21	0.19
J H-1/H-6_{endo}	2 Hz	—	2 Hz	1.5 Hz
J H-1/H-6_{exo}	—	3 Hz	4 Hz	3 Hz
J H-6/H-5 syn	10 Hz	10 Hz	10 Hz	9 Hz
J H-6/H-5 anti	6 Hz	7 Hz	7 Hz	6 Hz
δ C-5	25.8	25.4	49.4	48.8
δ C-6	46.2	46.3	30.5	31.4

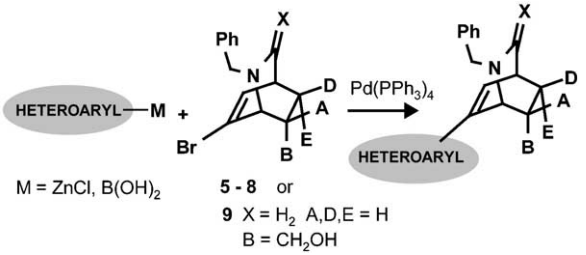

Figure 4.

Table 2. Summary of the cross-coupling reactions

Heteroaryl-M	Br-alkene	Yield %	Compd
10b	**6**	65	**14**
10b	**5**	61	**15**
10b	**8**	51	**16**
10b	**7**	58	**17**
11b	**5**	53	**18**
11b	**7**	53	**19**
12	**5**	59	**20**
12	**8**	59	**21**
13	**5**	95	**22**
13	**8**	95	**23**
13	**9**	91	**24**

Bromoalkenes **5–8** looked promising substrates for the preparation of 7-heteroaryl-2-azabicyclooctene derivatives by Suzuki reaction,[16] which has the value to require easy experimental procedure, to tolerate a number of functional groups on either coupling partners and to be applicable on commercial scale. The reaction of thiophen-2-ylboronic acid **12** (Fig. 5) with a mixture of bromides **5** and **8** proceeded to give compounds **20** and **21** (Fig. 6) in good yield (59%) using DME as solvent and $Pd(PPh_3)_4$ as catalyst in the presence of Na_2CO_3. The use of phenylboronic acid **13** with the same products mixture (**5** and **8**) gave a reaction that proceeded with excellent yield (95%) to give compounds **22** and **23**. The same reaction conditions were applied with bromide **9**, prepared by $LiAlH_4$ reduction of the corresponding bicycloadduct **6** (as pure product), with the obtainment of **24** in very good yield (91%).

Pharmacological evaluation

In the present preliminary study, we compared the in vitro binding profiles of the novel compounds with those of ibogaine **1** and a summary of the results of the radioligand binding assays are shown in Table 3. 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). The compounds possessing the *N*-SEM-indolyl or thiophenyl group (**14**, **17**, **20**, **21**) displayed poor affinity for the dopamine transporter (DAT). The presence of the phenyl group increases the affinity to verge on the one of ibogaine only in the case of compound **23** that presents the carbomethoxy group in 5-*endo* position. In the case of serotonin transporter (SERT), only compound **22** showed a weak affinity 6–20-fold higher if compared with the other congeners compounds. Differently from

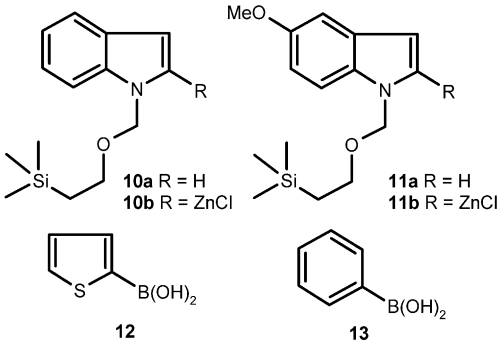

Figure 5.

ibogaine, that has a poor affinity, compounds **17** and **20-22** showed an higher affinity for *K* opioid receptors. Only the affinity of compound **23** for the *K* opioid receptors is very similar to the one of ibogaine. We have to highlight that this is the second characteristic that compound **23** and ibogaine **1** share. All the obtained compounds were poor inhibitors of [^{3}H]NMDA binding. We want to stress the possibility to gain higher receptorial affinity in the case of the enantiomeric pure form of the described compounds.

Conclusion

We have shown that a library of 7-heteroaryl-2-azabicyclo[2.2.2]oct-7-enes, structurally related to ibogaine **1**, can be obtained in two steps by cycloaddition of 5-Br-*N*-benzylpyridinone **4** with methyl acrylate and subsequent cross-coupling reaction. The absence of the azepine ring does not seem to limit a considerable affinity for the receptorial targets of ibogaine.

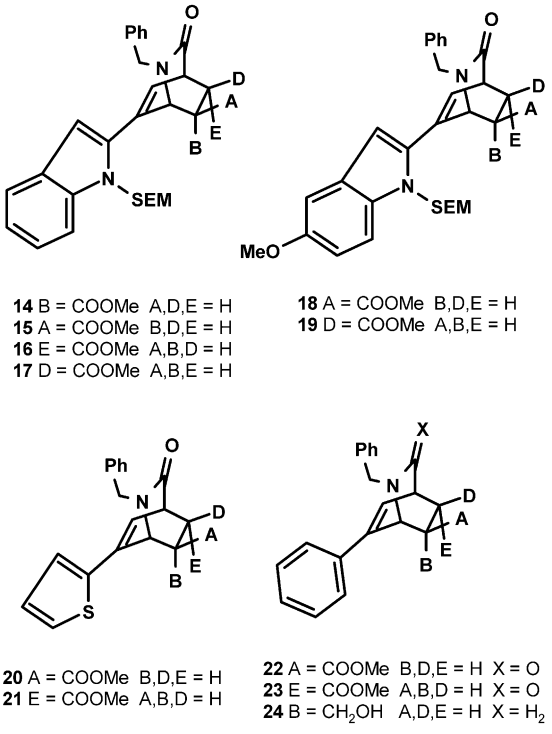

Figure 6.

Table 3. Relative affinities (IC_{50}, μM) of ibogaine and 2-azabicyclo[2.2.2]oct-7-ene derivatives and references compounds at selected molecular targets

Target	DAT (WIN35,428)	SERT (RTI-55)	K (U69593)	NMDA (MK801)
1	4.11	0.59	25	5.2
14	26.6	14.9	14.6	34.7
17	21.3	19.4	8.6	58.0
20	33.9	35.5	6.1	ND
21	14.7	28.6	3.2	33.4
22	19.7	1.7	5.1	ND
23	4.4	10.7	23.7	58.8
Reference drug	Mazindol 1.13 nM	Citalopram 0.9 nM	Naloxone 6.1 nM	MK801 4.1 nM

Experimental

General

^1H and ^{13}C NMR spectra were recorded on Bruker AC 300 (^1H, 300 MHz, ^{13}C 75.4 MHz), Bruker AC 200 (^1H, 200 MHz, ^{13}C 50.2 MHz). Elemental analysis were carried out on a Perkin–Elmer MD240 instrument. Flash column chromatography was performed on silica gel (230–400 mesh).

Preparation of 5-bromo-*N*-benzylpyridin-2-one (4). A solution of pyridine (10 mL, 0.124 mol), benzyl bromide (20 mL, 0.169 mol) in dry toluene (50 mL) was stirred at room temperature for 24 h. After filtration the solid was washed with Et_2O to give the *N*-benzylpyridinium bromide as a white solid (24.8 g, 80%). ^1H NMR ($CDCl_3$) δ 9.60 (2H, d, $J=7$ Hz), 8.45 (1H, t, $J=7$ Hz), 8.05 (2H, t, $J=7$ Hz), 7.70–7.66 (2H, m), 7.36–7.34 (3H, m), 6.30 (2H, s). To a solution of *N*-benzylpyridinium bromide (24.8 g, 0.099 mol) in water (100 mL) a solution of $K_3Fe(CN)_6$ (84.6 g, 0.257 mol) in water (170 mL) and a solution of NaOH (15.0 g, 0.376 mol) in water (130 mL) were added simultaneously maintaining the temperature below 5 °C. The resulting mixture was stirred overnight at room temperature. The extraction with EtOAc gave a brown solid that was washed with Et_2O to give the *N*-benzylpyridin-2-one as a light brown solid (12.8 g, 70%). Mp 76 °C. ^1H NMR ($CDCl_3$) δ 7.35–7.10 (7H, m), 6.55 (1H, d, $J=9$ Hz), 6.10 (1H, t, $J=9$ Hz), 5.10 (2H, s); ^{13}C NMR ($CDCl_3$) δ 162.4, 139.4, 137.5, 136.5, 128.7 (2C), 127.9 (2C), 127.8, 120.8, 106.1, 51.7. Anal. calcd for $C_{12}H_{11}NO$: C 77.81, H 5.99, N 7.56. Found: C 77.85, H 6.03, N 7.61. To a solution of *N*-benzylpyridin-2-one (7.4 g, 40 mmol) in DMF (18 mL) a solution of NBS (7.1 g, 40 mmol) in DMF (18 mL) was added dropwise at room temperature. After 20 min the solution was poured into brine and extracted with EtOAc. The organic layer was washed with brine. Evaporation of the solvent and chromatography purification (EtOAc/hexane 1:3) gave compound **4** as a light brown solid (5.0 g, 47%). Mp 93 °C. IR (nujol) 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.25 (7H, m), 6.51 (1H, d, $J=9$ Hz), 5.08 (2H, s); ^{13}C NMR ($CDCl_3$) δ 160.8, 142.2, 136.9, 135.5, 128.8 (3C), 128.0 (2C), 122.1, 97.8, 51.9. Anal. calcd for $C_{12}H_{10}NOBr$: C 54.57, H 3.82, N 5.30. Found: C 54.52, H 3.86, N 5.26.

Preparation of 7-bromo-2-benzyl-3-oxo-2-aza- carbomethoxybicyclo [2.2.2]oct-7-ene derivatives. 5-Bromo-*N*-benzylpyridin-2-one (2.5 g, 9.46 mmol) and methyl acrylate (20 mL, 220 mmol) were dissolved in CH_2Cl_2 (20 mL) in a reactor of 170 mL volume. The steel tube was heated at 120 °C for 10 days. After vacuum concentration, the mixture was directly chromatographed (EtOAc/hexane 2:3) to give a mixture of **5** and **8** (1.09 g, 33%, 1:1.2 ratio on the base of the integration of H-8 signals) and a mixture of **6** and **7** (1.69 g, 51%. 5:1 ratio on the base of the integration of H-8 signals).

7-Bromo-2-benzyl-3-oxo-2-aza-6-*exo*-carbo methoxybicyclo[2.2.2]oct-7-ene (5). Yield: 15%. Oil; R_f (EtOAc/hexane 2:3) = 0.46; IR (nujol) 1733, 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–7.12 (5H, m), 6.42 (1H, dd, $J=7$, 3 Hz), 5.00 (1H, A portion of AB system), 4.41 (1H, bs), 4.00 (1H, B portion of AB system), 3.62 (3H, s), 3.51 (1H, ddd, $J=7$, 3, 3 Hz), 2.82 (1H, ddd, $J=10$, 6, 3 Hz), 2.02–1.91 (2H, m); ^{13}C NMR ($CDCl_3$) δ 172.4, 171.9, 136.5, 131.8, 128.9, 128.8 (2C), 127.5 (2C), 121.8, 63.7, 52.2, 48.8, 46.2, 44.2, 25.8. Anal. calcd for $C_{16}H_{16}NO_3Br$: C 54.87, H 4.61, N 4.00. Found: C 54.97, H 4.74, N 3.97.

7-Bromo-2-benzyl-3-oxo-2-aza-6-*endo*-carbo methoxybicyclo[2.2.2]oct-7-ene (6). Yield: 43%. Oil; R_f (EtOAc/hexane 2:3) = 0.38; IR (nujol) 1732, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–7.20 (5H, m), 6.51 (1H, dd, $J=7$, 3 Hz), 4.62 (1H, A portion of AB system), 4.41 (1H, dd, $J=3$, 3 Hz), 4.36 (1H, B portion of AB system), 3.62 (3H, s), 3.45 (1H, ddd, $J=7$, 3, 3 Hz), 3.01 (1H, ddd, $J=10$, 7, 3 Hz), 2.15–2.07 (2H, m); ^{13}C NMR ($CDCl_3$) δ 172.1, 170.9, 136.3, 132.6, 128.8, 128.3 (2C), 127.9 (2C), 119.2, 63.5, 52.1, 48.2, 46.3, 44.9, 25.4. Anal. calcd for $C_{16}H_{16}NO_3Br$: C 54.87, H 4.61, N 4.00. Found: C 54.91, H 4.70, N 4.06.

7-Bromo-2-benzyl-3-oxo-2-aza-5-*exo*-carbo methoxybicyclo[2.2.2]oct-7-ene (7). Yield: 8%. Oil; R_f (EtOAc/hexane 2:3) = 0.38; IR (nujol) 1735, 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–7.20 (5H, m), 6.48 (1H, dd, $J=7$, 3 Hz), 4.61 (1H, A portion of AB system), 4.40 (1H, B portion of AB system), 4.08 (1H, ddd, $J=4$, 3, 2 Hz), 3.75 (3H, s), 3.58 (1H, dd, $J=7$, 3 Hz), 2.60 (1H, ddd, $J=10$, 7, 3 Hz), 2.27 (1H, ddd, $J=12.5$, 7, 4 Hz), 1.70 (1H, ddd, $J=12.5$, 10, 2 Hz); ^{13}C NMR ($CDCl_3$) δ 172.5, 169.1, 136.3, 130.5, 128.7, 128.3 (2C), 127.9 (2C), 123.9, 61.6, 52.5, 49.4, 48.2, 40.7, 30.5. Anal. calcd for $C_{16}H_{16}NO_3Br$: C 54.87, H 4.61, N 4.00. Found: C 54.92, H 4.72, N 4.06.

7-Bromo-2-benzyl-3-oxo-2-aza-5-*endo*-carbo methoxybicyclo[2.2.2]oct-7-ene (8). Yield: 18%. Oil; R_f (EtOAc/hexane 2:3) = 0.46; IR (nujol) 1733, 1677 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–7.12 (5H, m), 6.37 (1H, dd, $J=7$, 3 Hz), 4.59 (1H, A portion of AB system), 4.40 (1H, B portion of AB system), 4.09 (1H, ddd, $J=3$, 3, 1.5 Hz), 3.88 (1H, dd, $J=7$, 3 Hz), 3.69 (3H, s), 3.05 (1H, ddd, $J=9$, 6, 3 Hz), 2.29 (1H, ddd, $J=12$, 6, 1.5 Hz), 2.09 (1H, ddd, $J=12$, 9, 3 Hz); ^{13}C NMR ($CDCl_3$) δ 172.4, 170.7, 136.2, 131.8, 128.8, 128.0 (2C), 127.8 (2C), 122.6, 62.1, 52.3, 48.8, 48.2, 39.4, 31.4. Anal. calcd for $C_{16}H_{16}NO_3Br$: C 54.87, H 4.61, N 4.00. Found: C 54.99, H 4.82, N 3.89.

General procedure for the preparation of 2-benzyl-7-[1-[2-(trimethylsilyl)ethoxymethyl]indol-2-yl]-3-oxo-2-aza-carbomethoxybicyclo[2.2.2]oct-7-ene by zinc halide cross-coupling reaction. To a dry solution of 1-[2-(trimethylsilyl)ethoxymethyl]-indole **10a** (1.2 mmol) in THF (3 mL), BuLi 1.6 M in hexane (830 μL, 1.33 mmol, 1.1 equiv) was slowly added at −15 °C and the mixture was stirred for 10 min at this temperature. The resulting orange solution was then cooled to −78 °C and treated with a 0.6 M solution of anhydrous $ZnCl_2$ (fused by flame-drying under reduced pressure for 5 min) in THF (2 mL, 1.2 mmol, 1.0 equiv) and the stirring was continued for 5 min at this temperature. In a separate flask, $Pd(PPh_3)_4$ (0.036 mmol, 3%) and bromo alkene (mixture of **5** and **8** or mixture of **6** and **7**, 1.2 mmol) were dissolved in dry THF (2 mL) and stirred for 20 min at room temperature. Then the resulting solution was added to the solution of 1-[2-(trimethylsilyl)ethoxymethyl]indol-2-ylzinc chloride **10b** prepared above, at −78 °C. The mixture was allowed to stir at rt for 5 min and then refluxed. After the reaction was complete, the mixture was cooled to rt, added to 20 mL of NH_4Cl 5% and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. After vacuum concentration, the mixture was directly chromatographed (EtOAc/hexane 1:2).

2-Benzyl-7-[1-[2-(trimethylsilyl)ethoxymethyl]-indol-2-yl]-(6-*endo*)-carbomethoxy-3-oxo-2-azabicyclo [2.2.2]oct-7-ene (14). Yield: 65%. Oil; R_f (EtOAc/hexane 1:1) = 0.46; IR (nujol) 1730, 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46 (1H, d, J = 8 Hz), 7.39 (1H, d, J = 8 Hz), 7.36–7.22 (5H, m), 7.21 (1H, t, J = 8 Hz), 7.10 (1H, t, J = 8 Hz), 6.92 (1H, dd, J = 7, 2 Hz), 5.91 (1H, s), 5.28 (2H, s), 4.89 (1H, dd, J = 4, 2 Hz), 4.81 (1H, A portion of AB system), 4.43 (1H, B portion of AB system), 3.75 (1H, ddd, J = 7, 3, 3 Hz), 3.65 (2H, t, J = 8 Hz), 3.27 (3H, s), 3.07 (1H, ddd, J = 4, 6, 10 Hz), 2.18 (1H, dd, J = 6, 4 Hz), 1.75–1.58 (1H, m), 0.91 (2H, t, J = 8 Hz), 0.00 (9H, s); ^{13}C NMR ($CDCl_3$) δ 173.4, 171.5, 139.2, 136.6, 136.1, 134.1, 129.1, 128.8 (2C), 128.3 (2C), 127.8, 127.4, 123.0, 120.7, 120.4, 109.5, 103.3, 72.7, 66.0, 59.9, 51.7, 47.9, 44.6, 44.3, 29.6, 18.0, −1.4 (3C). Anal. calcd for $C_{30}H_{36}N_2O_4Si$: C 69.73, H 7.03, N 5.42. Found: C 69.72, H 7.17, N 5.49.

2-Benzyl-7-[1-[2-(trimethylsilyl)ethoxymethyl]-indol-2-yl]-(6-*exo*)-carbomethoxy-3-oxo-2-azabicyclo [2.2.2]oct-7-ene (15). Yield: 61%. Oil; R_f (EtOAc/hexane 3:1) = 0.3; IR (nujol) 1731, 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (1H, d, J = 8 Hz), 7.35 (1H, d, J = 8 Hz), 7.21 (1H, t, J = 8 Hz), 7.30–7.19 (5H, m), 7.08 (1H, t, J = 8 Hz), 6.80 (1H, dd, J = 7, 2 Hz), 5.86 (1H, s), 5.26 (2H, s), 5.09 (1H, A portion of AB system), 4.90 (1H, bs), 4.09 (1H, B portion of AB system), 3.72–3.69 (1H, m), 3.58 (2H, t, J = 8 Hz), 3.66 (3H, s), 2.78 (1H, ddd, J = 10, 6, 3 Hz), 2.41 (1H, ddd, J = 12, 5, 2 Hz), 2.03 (1H, ddd, J = 12, 10, 3 Hz), 0.93–0.89 (2H, m), 0.00 (9H, s); ^{13}C NMR ($CDCl_3$) δ 173.2, 172.7, 139.3, 137.1, 136.9, 135.5, 128.6, 128.4 (2C), 128.1 (2C), 127.8, 127.6, 125.5, 120.7, 120.6, 109.4, 103.5, 72.7, 66.0, 60.0, 52.0, 48.8, 44.7, 40.0, 26.4, 17.6, −1.49 (3C). Anal. calcd for $C_{30}H_{36}N_2O_4Si$: C 69.73, H 7.03, N 5.42. Found: C 69.80, H 7.10, N 5.39.

2-Benzyl-7-[1-[2-(trimethylsilyl)ethoxymethyl]-indol-2-yl]-(5-*endo*)-carbomethoxy-3-oxo-2-azabicyclo [2.2.2]oct-7-ene (16). Yield: 51%. Oil; R_f (EtOAc/hexane 3:1) = 0.3; IR (nujol) 1730, 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (1H, d, J = 8 Hz), 7.35 (1H, d, J = 8 Hz), 7.31–7.19 (5H, m), 7.21 (1H, t, J = 8 Hz), 7.09 (1H, t, J = 8 Hz), 6.68 (1H, dd, J = 7, 2 Hz), 5.94 (1H, s), 5.31 (2H, s), 4.73 (1H, A portion of AB system), 4.53 (1H, ddd, J = 3, 3, 2 Hz), 4.42 (1H, B portion of AB system), 4.03 (1H, dd, J = 6, 2 Hz), 3.70 (3H, s), 3.58 (2H, t, J = 8 Hz), 3.14 (1H, ddd, J = 10, 5, 2 Hz), 2.15 (1H, ddd, J = 12, 10, 3 Hz), 1.90 (1H, ddd, J = 12, 5, 1 Hz), 0.93–0.90 (2H, m), 0.00 (9H, s); ^{13}C NMR ($CDCl_3$) δ 173.2, 171.8, 139.3, 137.6, 136.7, 135.0, 129.8, 128.6 (2C), 128.4 (2C), 127.8, 127.6, 123.0, 120.7, 120.6, 109.6, 103.6, 72.8, 65.9, 57.9, 52.1, 47.9, 44.2, 39.7, 31.1, 17.9, −1.49 (3C). Anal. calcd for $C_{30}H_{36}N_2O_4Si$: C 69.73, H 7.03, N 5.42. Found: C 69.77, H 7.05, N 5.36.

2-Benzyl-7-[1-[2-(trimethylsilyl)ethoxymethyl]-indol-2-yl]-(5-*exo*)-carbomethoxy-3-oxo-2-azabicyclo [2.2.2]oct-7-ene (17). Yield: 58%. Oil; R_f (EtOAc/hexane 3:1) = 0.4; IR (nujol) 1734, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 (1H, d, J = 8 Hz), 7.38 (1H, d, J = 8 Hz), 7.30-7.15 (6H, m), 7.10 (1H, t, J = 8 Hz), 6.84 (1H, dd, J = 7, 2 Hz), 6.08 (1H, s), 5.31 (2H, s), 4.67 (1H, A portion of AB system), 4.53 (1H, B portion of AB system), 4.58–4.52 (1H, m), 3.98 (1H, dd, J = 7, 3 Hz), 3.79 (3H, s), 3.60 (2H, t, J = 8 Hz), 2.87 (1H, ddd, J = 10, 5, 3 Hz), 2.35 (1H, ddd, J = 13, 5, 4 Hz), 1.81 (1H, ddd, J = 13, 10, 3 Hz), 0.91 (2H, t, J = 8 Hz),-0.05 (9H, s); ^{13}C NMR ($CDCl_3$) δ 173.2, 170.9, 139.5, 138.4, 136.8, 135.5, 128.6, 128.3 (2C), 128.0, 127.7 (2C), 126.9, 123.2, 120.8, 120.7, 109.5, 103.5, 72.8, 66.1, 59.3, 52.4, 47.8, 44.2, 43.9, 30.7, 18.0, −1.4 (3C). Anal. calcd for $C_{30}H_{36}N_2O_4Si$: C 69.73, H 7.03, N 5.42. Found: C 69.79, H 7.07, N 5.40.

2-Benzyl-7-[1-[2-(trimethylsilyl)ethoxymethyl]-5-methoxy-indol-2-yl]-(6-*exo*)-carbomethoxy-3-oxo-2-azabicyclo[2.2.2]oct-7-ene (18). Obtained following the general procedure described for compounds **14–17** and using as starting materials 5-methoxy-1-[2-(trimethylsilyl)ethoxymethyl]-indole **11a** (0.5 mmol) and bromo alkene **5** (0.5 mmol, as pure product). Yield: 53%. Oil; R_f (EtOAc/hexane 3:1) = 0.4; IR (nujol) 1732, 1669, 1239 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35-7.15 (8H, m), 6.78 (1H, dd, J = 14, 2 Hz), 5.78 (1H, s), 5.32–5.19 (2H, AB system), 5.09 (1H, A portion of AB system), 4.90–4.85 (1H, m), 4.09 (1H, B portion of AB system), 3.85 (3H, s), 3.75–3.69 (1H, m), 3.65 (3H, s), 3.58 (2H, t, J = 8 Hz), 2.80–2.70 (1H, m), 2.10–1.80 (2H, m), 0.92–0.85 (2H, m), 0.00 (9H, s); ^{13}C NMR ($CDCl_3$) δ 173.0, 171.9, 154.6, 137.0–134.0 (4C), 128.0–120.0 (9C), 110.3, 103.2, 72.9, 65.9, 60.0, 55.7, 52.0, 47.9, 44.7, 40.0, 26.4, 17.6,-1.3 (3C). Anal. calcd for $C_{31}H_{38}N_2O_5Si$: C 68.10, H 7.01, N 5.12. Found: C 68.13, H 7.03, N 5.13.

2-Benzyl-7-[1-[2-(trimethylsilyl)ethoxymethyl]-5-methoxyindol-2-yl]-(5-*exo*)-carbomethoxy-3-oxo-2-azabicyclo[2.2.2]oct-7-ene (19). Obtained following the general procedure described for compounds **14–17** and using as starting materials 5-methoxy-1-[2-(trimethylsilyl)ethoxymethyl]-indole **11a** (0.5 mmol) and bromo

alkene **7** (0.5 mmol, as pure product). Yield: 53%. Oil; R_f (EtOAc/hexane 3:1) = 0.4; IR (nujol) 1731, 1668, 1237 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.15 (8H, m), 6.67 (1H, dd, J = 14, 2 Hz), 5.82 (1H, s), 5.22 (2H, s), 4.73 (1H, A portion of AB system), 4.55–4.48 (1H, m), 4.41 (1H, B portion of AB system), 4.03 (1H, dd, J = 6, 2 Hz), 3.85 (3H, s), 3.68 (3H, s), 3.58 (2H, t, J = 8 Hz), 3.19–3.08 (1H, m), 2.15 (1H, ddd, J = 12, 10, 3 Hz), 1.82–1.72 (1H, m), 0.92–0.85 (2H, m), 0.00 (9H, s); ^{13}C NMR ($CDCl_3$) δ 173.0, 171.9, 154.6, 137.0–134.0 (4C), 128.0-120.0 (9C), 113.2, 102.3, 72.9, 66.0, 59.4, 57.9, 52.0, 47.9, 47.6, 39.7, 31.2, 17.6, −1.3 (3C). Anal. calcd for $C_{31}H_{38}N_2O_5Si$: C 68.10, H 7.01, N 5.12. Found: C 68.15, H 7.06, N 5.11.

General procedure for the preparation of 7-heteroaryl-2-benzyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene by Suzuki reaction. To a solution of $Pd(PPh_3)_4$ (0.091 mmol) in DME (2 mL) was added a solution of bromo alkenes (mixture of **5** and **8** or **9**, 1.88 mmol) in DME (9 mL) and the mixture was stirred for 15 min under nitrogen. A solution of heteroarylboronic acid (2.83 mmol) in EtOH (2 mL) was added. The mixture was stirred for 10 min and then treated with 2 M aq Na_2CO_3 (8 mL). The resulting solution was refluxed for 5 h and maintained at room temperature for 20 h. The mixture was poured in water and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. After vacuum concentration, the mixture was directly chromatographed.

2-Benzyl-7-(thiophen-2-yl)-(6-*exo*)-carbomethoxy-3-oxo-2-aza bicyclo[2.2.2]oct-7-ene (20). Yield: 59%. Oil; R_f (EtOAc/hexane 1:1) = 0.4; IR (nujol) 1737, 1670, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.10 (6H, m), 6.80 (1H, dd, J = 5, 4 Hz), 6.60 (1H, bd, J = 4 Hz), 6.45 (1H, dd, J = 8, 4 Hz), 5.12 (1H, B portion of AB system), 4.83–4.79 (1H, m), 4.05 (1H, A portion of AB system), 3.66 (3H, s), 3.64–3.58 (1H, m), 2.71 (1H, ddd, J = 10, 6, 3 Hz), 2.37 (1H, ddd, J = 2, 5, 12 Hz), 2.08–1.90 (1H, m); ^{13}C NMR ($CDCl_3$) δ 173.4, 172.9, 139.9, 139.6, 136.6, 133.5, 129.8–127.4 (7C), 125.2, 58.2, 52.2, 48.5, 44.2, 40.1, 28.5. Anal. calcd for $C_{20}H_{19}NO_3S$: C 67.96, H 5.42, N 3.96. Found: C 67.91, H 5.51, N 4.03.

2-Benzyl-7-(thiophen-2-yl)-(5-*endo*)-carbomethoxy-3-oxo-2-aza bicyclo[2.2.2]oct-7-ene (21). Yield: 59%. Oil; R_f (EtOAc/hexane 1:1) = 0.6; IR (nujol) 1738, 1667, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.10 (6H, m), 6.85 (1H, dd, J = 5, 4 Hz), 6.57 (1H, d, J = 4 Hz), 6.38 (1H, dd, J = 7, 3 Hz), 4.70 (1H, A portion of AB system), 4.46–4.42 (1H, m), 4.38 (1H, B portion of AB system), 3.93 (1H, dd, J = 9, 3 Hz), 3.68 (3H, s), 3.10 (1H, ddd, J = 12, 4.5, 3 Hz), 2.18 (1H, ddd, J = 12, 9, 3 Hz), 1.89 (1H, ddd, J = 12, 4.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 172.9, 172.1, 140.6, 139.6, 137.9, 136.4, 133.5, 129.8–127.4 (6C), 123.5, 56.6, 52.2, 47.9, 47.0, 40.1, 31.1. Anal. calcd for $C_{20}H_{19}NO_3S$: C 67.96, H 5.42, N 3.96. Found: C 67.89, H 5.48, N 4.00.

2-Benzyl-7-phenyl-(6-*exo*)-carbomethoxy-3-oxo-2-azabicyclo[2.2.2]oct-7-ene (22). Yield: 95%. Oil; R_f (EtOAc/hexane 1:1) = 0.23; IR (nujol) 1734, 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50–7.01 (10H, m), 6.66 (1H, dd, J = 7, 3 Hz), 4.92–4.88 (1H, m), 4.75 (1H, A portion of AB system), 4.37 (1H, B portion of AB system), 3.70 (3H, s), 3.50–3.75 (1H, m), 2.7 (1H, ddd, J = 10, 6, 3 Hz), 2.42–2.30 (1H, m), 2.08–1.90 (1H, m); ^{13}C NMR ($CDCl_3$) δ 173.5, 173.0, 146.9, 138.7, 128–127 (11C), 125.7, 57.8, 52.2, 48.6, 44.4, 39.8, 26.2. Anal. calcd for $C_{22}H_{21}NO_3$: C 76.06, H 6.10, N 4.03 Found: C 76.17, H 6.21, N 4.22.

2-Benzyl-7-phenyl-(5-*endo*)-carbomethoxy-3-oxo-2-aza bicyclo[2.2.2]oct-7-ene (23). Yield: 95%. Oil; R_f (EtOAc/hexane 1:1) = 0.43; IR (nujol) 1728, 1667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50–7.01 (10H, m), 6.45 (1H, dd, J = 7, 3 Hz), 5.22 (2H, s), 4.55–4.49 (1H, m), 4.07-3.98 (1H, m), 3.70 (3H, s), 3.12 (1H, ddd, J = 9, 6, 3 Hz), 2.21 (1H, ddd, J = 12, 6, 1.5 Hz), 1.88 (1H, ddd, J = 12, 9, 3 Hz); ^{13}C NMR ($CDCl_3$) δ 173.2, 172.5, 146.0, 135.0, 128–127 (11C), 125.2, 56.1, 52.2, 47.9, 44.3, 39.8, 31.2. Anal. calcd for $C_{22}H_{21}NO_3$: C 76.06, H 6.10, N 4.03 Found: C 76.15, H 6.17, N 4.18.

2-Benzyl-7-phenyl-(6-*endo*)-hydroxymethyl-2-aza bicyclo[2.2.2]oct-7-ene (24). Yield: 91%. Oil; R_f (EtOAc/hexane 1:1) = 0.32; IR (nujol) 3367, 1672, 1249 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70–7.11 (10H, m), 6.70 (1H, dd, J = 7, 2 Hz), 4.12–4.08 (1H, m), 3.68 (1H, A portion of AB system), 3.36 (1H, B portion of AB system), 3.29 (1H, dd, J = 11, 6 Hz), 3.12 (1H, t, J = 11 Hz), 3.05 (1H, bd, J = 10 Hz), 2.70–2.50 (3H, m), 1.98 (1H, dt, J = 10, 2, 2 Hz), 1.79 (1H, ddd, J = 12, 10, 2 Hz), 0.80–0.69 (1H, m); ^{13}C NMR ($CDCl_3$) δ 140.0, 133.5, 131.0–124.0 (12C), 65.3, 61.9, 56.2, 54.1, 41.8, 31.3, 26.7. Anal. calcd for $C_{21}H_{23}NO$: C 82.58, H 7.60, N 4.58 Found: C 82.63, H 7586, N 4.53.

2-Benzyl-7-bromo-(6-*endo*)-hydroxymethyl-2-aza bicyclo[2.2.2]oct-7-ene (9). To a suspension of $LiAlH_4$ (9 mg, 0.23 mmol) in THF (5 mL) a solution of bromide **6** (as pure product, 82 mg, 0.23 mmol) in THF (3 mL) was added. After 12 h at room temperature EtOAc was added and the mixture was poured in water. The organic phase was concentrated and after chromatography (EtOAc/hexane 2:1) compound **9** (56 mg, 80%) was obtained. Oil; R_f (EtOAc/hexane 1:1) = 0.29. IR (nujol) 3349, 1681, 1097 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.18 (5H, m), 6.58 (1H, dd, J = 8, 3 Hz), 3.79 (1H, A portion of AB system), 3.70 (1H, t, J = 3 Hz), 3.48 (1H, B portion of AB system), 3.35 (1H, dd, J = 10, 6 Hz), 3.28 (1H, t, J = 10 Hz), 2.99 (1H, dd, J = 10, 2.5 Hz), 2.66–2.59 (1H, m), 2.55–2.43 (1H, m), 1.97 (1H, ddd, J = 10, 3, 3 Hz), 1.73 (1H, bs), 1.66 (1H, ddd, J = 12, 10, 3 Hz), 0.75 (1H, ddd, J = 12, 6, 2 Hz); ^{13}C NMR ($CDCl_3$) δ 139.1, 132.4, 128.8 (2C), 128.2 (2C), 126.9, 118.3, 65.5, 62.8, 61.5, 54.0, 43.1, 35.5, 26.4. Anal. calcd for $C_{15}H_{18}NOBr$:C 58.45, H 5.89, N 4.54. Found: C 58.53, H 5.82, N 4.67.

5-(Indol-2-yl)-1-benzylpyridin-2-one (2). 5-[1-[2-(trimethylsilyl)ethoxymethyl]indol-2-yl]pyridin-2-one (430 mg, 1 mmol) was dissolved in DMF (8 mL). TBAF·$3H_2O$ (950 mg, 3 mmol) and ethylendiamine (432 μL, 6.4 mmol) were added. After 6 h at 80 °C the mixture was poured into water and extracted with EtOAc. After

vacuum concentration the mixture was directly purified by chromatography (EtOAc) to give **2** (240 mg, 80%). Oil; R_f (EtOAc) = 0.41; IR (nujol) 1653 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.20 (1H, bs), 8.33 (1H, d, J = 3 Hz), 7.95 (1H, dd, J = 9, 3 Hz), 7.49 (1H, d, J = 7.5 Hz), 7.43–7.32 (6H, m), 7.09 (1H, t, J = 7.5 Hz), 6.98 (1H, t, J = 7.5 Hz), 6.71 (1H, s), 6.59 (1H, d, J = 9 Hz), 5.20 (2H, s); ^{13}C NMR (DMSO-d_6) δ 160.5, 139.1, 137.1, 136.6, 134.7, 134.2, 129.6–127.6 (6C), 121.3, 120.3, 119.6, 119.4, 111.6, 110.7, 97.7, 51.7. Anal. calcd for $C_{20}H_{16}N_2O$: C 79.97, H 5.37, N 9.33. Found: C 79.89, H 5.45, N 9.56.

2-Benzyl-7-[3-(2-carbomethoxyethyl)indol-2-yl]- 3-oxo-2-aza-6-*endo*-carbomethoxybicyclo[2.2.2]oct-7-ene (3). 5-(Indol-2-yl)-1-benzylpyridin-2-one **2** (300 mg, 1 mmol) and methyl acrylate (2 mL, 22 mmol) were dissolved in CH_2Cl_2 (20 mL) in a reactor of 170 mL volume. The steel tube was heated at 120 °C for 10 days. After vacuum concentration, the mixture was directly chromatographed (EtOAc/hexane 2:3) to give 6-endo (170 mg, 36%) as an oil. R_f (EtOAc / CH_2Cl_2 1:2) = 0.24; IR (nujol) 1727, 1671 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.84 (1H, s), 7.25 (1H, d, J = 8 Hz), 7.13 (1H, d, J = 8 Hz), 7.10–6.90 (7H, m), 6.95 (1H, dd, J = 8 Hz), 4.48 (1H, A portion of AB system), 4.42 (1H, bs), 4.36 (1H, B portion of AB system), 3.79 (3H, s), 3.70 (3H, s), 3.19–3.20 (1H, m), 2.82 (1H, ddd, J = 10, 8, 3 Hz), 2.65-2.55 (2H, m), 2.22–2.10 (3H, m), 1.70–1.53 (1H, m); ^{13}C NMR (DMSO-d_6) δ 174.4, 173.1, 172.4, 137.2, 136.3, 133.4, 128.0-127.6 (6C), 126.9, 125.2, 120.6, 118.6, 117.5, 111.3, 109.3, 57.3, 52.2, 51.7, 47.7, 44.3, 38.5, 32.1, 31.9, 25.5. Anal. calcd for $C_{28}H_{28}N_2O_5$: C 71.17, H 5.98, N 5.93. Found: C 71.26, H 6.05, N 5.86.

Ligand binding assays

Radioligands were purchased from NEN/DuPont (Boston, MA) or Amersham Corp. (Arlington Heights, IL, USA). All binding assays were conducted as described previously (see ref 7b). 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 2). 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**). Ligand competition data were analysed using the DRUG program of EBDA/LIGAND (Biosoft, Elsevier).

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