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Binding of β-Carbolines at 5-HT_2 Serotonin Receptors

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Abstract—A series of ring-substituted (i.e., methoxy and bromo) 3,4-dihydro- and 1,2,3,4-tetrahydro-β-carbolines was examined at 5-HT_{2A} and 5-HT_{2C} serotonin receptors. Whereas most of the methoxy-substituted derivatives typically displayed affinities similar to their unsubstituted parents, certain (particularly 8-substituted) bromo derivatives displayed enhanced affinity. A binding profile was obtained for selected β-carbolines.
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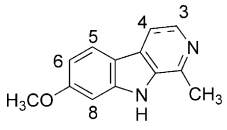
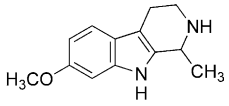
β-Carbolines, conformationally-constrained tryptamine analogues, are a fascinating and under-investigated class of compounds. Certain β-carbolines, such as harmaline (**1**), are reported to be hallucinogenic. Harmaline (**1**) and several related β-carbolines are naturally-occurring in plant species such as *Banisteropsis caapi* and *Peganum harmala*.[1] The first reported use of β-carboline-containing plants in the Western hemisphere was by Columbus, who wrote of New World Indians using a snuff termed *cohoba*.[1] Such snuffs and related preparations are still in use today[2] but the action of β-carbolines as hallucinogens is controversial. Some believe that β-carbolines enhance the actions of other hallucinogenic tryptamines typically found in plant-derived concoctions primarily by impeding their metabolism via inhibition of monoamine oxidase (e.g., refs 2 and 3). Others have reported that harmaline (**1**), harmine (**2**), and tetrahydroharmine (**3**) are hallucinogenic when administered alone (reviewed in refs 1,4 and 5).



1 (3,4-saturated)
2 (3,4-unsaturated)



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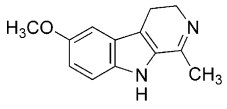

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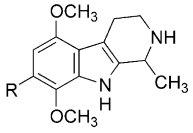

5a R = H
5b R = CH_3

Classical hallucinogens (i.e., phenylalkylamine- and tryptamine-containing hallucinogenic agents) are thought to exert their common behavioral effects primarily via agonist action at 5-HT_{2A} serotonin receptors (reviewed in ref 6). It was shown some time ago that β-carbolines bind at 5-HT receptors of isolated rat fundus tissue,[7] and these receptors are now known to represent a member of the 5-HT_2 family (i.e., 5-HT_{2B} receptors).[8] More recently, it was demonstrated that β-carbolines bind at 5-HT_{2A} and 5-HT_{2C} receptors depending upon the degree of ring saturation, and the presence and position of a methoxy group.[5,9] Consistent with these findings, several β-carbolines, including harmaline (**1**) and its positional isomer 6-methoxyharmalan (**4**) substituted for the

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hallucinogenic (5-HT_{2A} agonist) phenylalkylamine 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) in a drug discrimination task with rats trained to discriminate DOM from saline vehicle.[10] However, neither harmaline (**1**; $K_i = 7790$ nM) nor 6-methoxyharmalan (**4**; $K_i = 5600$ nM) binds with high affinity at 5-HT_{2A} receptors, and both were found to lack action as 5-HT_{2A} agonists in a phosphoinositol (PI) hydrolysis assay.[5,9] In contrast, **5a** ($K_i = 210$ nM) and **5b** ($K_i = 98$ nM) behaved as a 5-HT_{2A} antagonists in the PI hydrolysis assay (although the possibility was raised that they might be low-efficacy partial agonists).[11] At this time, it is not known if the actions of **1** and **4** in the PI hydrolysis assay reflect their low affinity, low efficacy, or whether the actions of the β-carbolines (in drug discrimination and/or other assays) is attributable to, or compromised by, their actions at other populations of receptors—particularly 5-HT receptors—or by possible interactions with the serotonin transporter.

In as much as β-carbolines represent a relatively novel and poorly explored class of 5-HT_2 ligands, it was of interest to further examine their structure–affinity relationships for 5-HT_2 binding. First, we wished to obtain a binding profile for harmaline (**1**), 6-methoxyharmalan (**4**), harmalan (**6**), the *des*methoxy analogue of **1**, and compound **7**, the 1-*des*methyl tetrahydro counterpart of harmaline, at a broad spectrum of neurotransmitter receptors and the serotonin (SERT), dopamine (DAT), and norepinephrine (NET) transporters to obtain clues for other possible common mechanisms of action for these agents. Next, because harmaline (**1**) and most of the previously investigated β-carbolines differed only by the presence and location of an electron donating methoxy substituent,[5] the influence of an electron withdrawing bromo group on 5-HT_{2A} receptor affinity was examined. Earlier investigations of harmalan derivatives showed that methoxy substitution at the 6-, 7-, or 8-positions typically resulted in decreased affinity relative to the parent unsubstituted compound, whereas 5-methoxy β-carbolines displayed enhanced affinity.[5,9] Evidently, binding is sensitive to the electronic nature of substituents on the β-carboline ring, and the possibility exists that β-carbolines with electron withdrawing groups might bind with enhanced affinity relative to their methoxy-substituted counterparts. Fully aromatic β-carbolines are optimal as inhibitors of monoamine oxidase (i.e., MAO_A);[12] hence, this study did not include such derivatives. Also, because the presence of a 1-methyl group seems to have relatively little effect on 5-HT_2 affinity,[9] and because its presence in the tetrahydro-β-carboline series results in optical isomers that might complicate data interpretation, most of the targeted compounds lacked this substituent. The corresponding 1-*des*methyl methoxy counterparts were also prepared for direct comparison with the binding of the bromo compounds. Because preliminary results indicated that bulky substituents at the β-carboline 5-position might influence 5-HT_{2A} versus 5-HT_{2C} selectivity, several new 5-substituted β-carbolines were also prepared and examined.

Synthesis

Most of the 3,4-dihydro-β-carbolines (Table 1) were prepared by $POCl_3$ cyclization of the requisite *N*-formyltryptamines,[9] which were obtained by formylation of readily available tryptamines. In some instances, the tryptamine precursors were prepared according to literature procedures.[13–16] Reduction of 3,4-dihydro-β-carbolines with $NaBH_4$ afforded the desired tetrahydro derivatives (Table 1). The 8-bromo β-carboline **21** was obtained by Fischer cyclization of 3-(2-bromophenylhydrazono)piperidin-2-one (mp 133–136 °C) to 8-bromo-1,2,3,4-tetrahydro-β-carbolin-1-one (mp 205–208 °C) which was subsequently reduced by alane (AlH_3) to **21**. Oxidation of **21** with I_2 under the general conditions reported by Sotomayor et al.,[17] afforded **12** (Table 1).

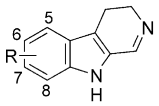
Binding Profile

Four β-carbolines were examined at >30 populations of receptors and neurotransmitter transporters (Table 2).[18] Harmaline was found to bind with low affinity ($K_i > 1000$ nM) at most receptors and displayed little to no affinity for SERT ($K_i > 10{,}000$ nM), DAT ($K_i > 10{,}000$ nM) or NET ($K_i = 3260$ nM). We previously reported that harmaline binds with high affinity ($K_i = 22$ nM) at I_2 imidazoline receptors.[19] 6-Methoxyharmalan (**4**), a positional isomer of **1**, displayed a similar profile, but showed somewhat enhanced affinity for 5-HT_{2C} receptors ($K_i = 924$ nM). Removal of the methoxy group to afford harmalan (**6**) resulted in enhanced affinity for 5-HT_{1A}, 5-HT_{5A}, and I_1 imidazoline receptors and decreased affinity for I_2 imidazoline receptors. Compound **7**, the 1-*des*methyl tetrahydro analogue of **1** behaved in a manner similar to **1** except that affinity for 5-HT_6 receptors was decreased and affinity for α_{2B}-adrenergic receptors was enhanced by about 10-fold. With the exception of their modest affinity for α-adrenergic receptors, and the high affinity of **1** and **7** for I_2 imidazoline receptors, the β-carbolines bind with low affinity at most populations of receptors and no single population (with perhaps the exception of I_2 imidazoline receptors) stands out as being an obvious, common, high-affinity target of their action.

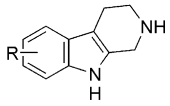
5-HT_{2A} Binding[20]

Both in the 3,4-dihydro- and 1,2,3,4-tetrahydro-β-carboline series, the 5-methoxy derivatives **13** ($K_i = 470$ nM) and **22** ($K_i = 130$ nM) displayed the highest affinity and about 5- and 30-fold enhanced affinity relative to their parent unsubstituted compounds **8** and **17** ($K_i = 2560$ and 3800 nM, respectively) (Table 1). 8-Methoxy-1,2,3,4-tetrahydro-β-carboline (**24**; $K_i = 640$ nM) also showed slightly enhanced affinity. All of the bromo derivatives displayed an affinity at least comparable to their unsubstituted parents. In both series, the highest affinity derivatives were the 8-bromo compounds **12** and **21** ($K_i = 110$ and 22 nM, respec-

Table 1. Physicochemical characteristics and 5-HT_2 binding properties of 3,4-dihydro- and 1,2,3,4-tetrahydro-β-carbolines



8-16



7, 17-23, 24

		Mp (°C)	Recryst. solvent	Yield (%)	Empirical formula[a]	K_i, nM (±SEM)		
						5-HT_{2A}[b]	5-HT_{2C}[b]	5-$HT_{2A(DOB)}$[p]
				3,4-Dihydro derivatives				
8	H[b]	203–204	MeOH	45	$C_{11}H_{10}N_2{\cdot}C_2H_2O_4$	2560 (90)	1100 (120)	2150 (10)
9	5-Br	318–320	MeOH	53	$C_{11}H_9BrN_2{\cdot}HCl$	390 (20)	140 (15)	—
10	6-Br	238 (d)	MeOH/Et_2O	46	$C_{11}H_9BrN_2{\cdot}HCl$	1720 (140)	1200 (100)	—
11	7-Br[d]	266–268	MeOH/Et_2O	28	$C_{11}H_9BrN_2{\cdot}HCl$[m]	1330 (50)	2100 (260)	—
12	8-Br[e]	265–266	MeOH	27	$C_{11}H_9BrN_2{\cdot}C_2H_2O_4$[n]	110 (10)	140 (15)	115 (15)
13	5-OMe[f]	208–209	MeOH	7	$C_{12}H_{12}N_2O_2{\cdot}C_2H_2O_4$	470 (20)	75 (10)	500 (40)
14	6-OMe	204–205	MeOH/Et_2O	21	$C_{12}H_{12}N_2O_2{\cdot}HCl$[o]	2370 (210)	1170 (20)	—
15	7-OMe[c]				—	>10,000	>10,000	>10,000
16	8-OMe[g]	203–205	MeOH	10	$C_{12}H_{12}N_2O_2{\cdot}C_2H_2O_4$[m]	3240 (170)	1350 (70)	2550 (270)
				1,2,3,4-Tetrahydro derivatives				
17	H[c]				—	3800 (200)	>10,000	3000 (100)
18	5-Br	274–275	MeOH	11	$C_{11}H_{11}BrN_2O{\cdot}C_2H_2O_4$	180 (20)	130 (15)	80 (10)
19	6-Br[h]	285–286	MeOH/Et_2O	20	$C_{11}H_{11}BrN_2O{\cdot}C_2H_2O_4$[m]	500 (50)	210 (15)	—
20	7-Br[i]	269–271	MeOH	18	$C_{11}H_{11}BrN_2O{\cdot}C_2H_2O_4$[n]	240 (50)	250 (25)	—
21	8-Br	265–266	MeOH	24	$C_{11}H_{11}BrN_2O{\cdot}C_2H_2O_4$[n]	22 (4)	48 (3)	21 (6)
22	5-OMe[j]	275–277	MeOH	52	$C_{12}H_{14}N_2O{\cdot}C_2H_2O_4$[m]	130 (5)	140 (10)	75 (10)
23	6-OMe	271–273[k]	EtOH	43	$C_{12}H_{14}N_2O{\cdot}HCl$	4780 (560)	2190 (220)	1400 (400)
7	7-OMe[c]				—	4620 (500)	>10,000	2200 (100)
24	8-OMe[l]	252–255	MeOH	30	$C_{12}H_{14}N_2O{\cdot}C_2H_2O_4$	640 (40)	1270 (30)	400 (35)

[a]Compounds, as their HCl or oxalate salts, analyzed within 0.4% of theory for C,H,N where empirical formula is provided.
[b]Radioligand binding studies were conducted as previously reported using [^{3}H]ketanserin (cloned rat 5-HT_{2A} receptors) or [^{3}H]mesulergine (cloned rat 5-HT_{2C} receptors).[9] K_i values represent a minimum of three determinations.
[c]Synthesis previously reported.[10]
[d]Melting point of free base; 110–112 °C.
[e]Melting point of free base: 205–208 °C.
[f]Free base described, but no mp reported.[22]
[g]Free base: mp 64–65 °C. Free base described, but no mp reported.[23]
[h]Free base reported.[24]
[i]Free base reported.[15]
[j]Free base: mp 199–202. Free base reported; mp 213–214 °C.[25]
[k]Lit.[26] mp 262–263 °C.
[l]Free base: mp 204–206. Free base reported; mp 217–218 °C.[27]
[m]Crystallized with 0.5 moles H_2O.
[n]Crystallized with 0.25 moles H_2O.
[o]Crystallized with 1.25 moles H_2O.
[p]High-affinity agonist ([^{3}H]DOB-labeled) 5-HT_{2A} sites.

tively). It is likely that the two series, the 3,4-dihydro series and the 1,2,3,4-tetrahydro series, are binding in a similar manner because parallel substituent modifications resulted in parallel shifts in affinity ($r = 0.873$).

5-HT_{2C} Binding[20]

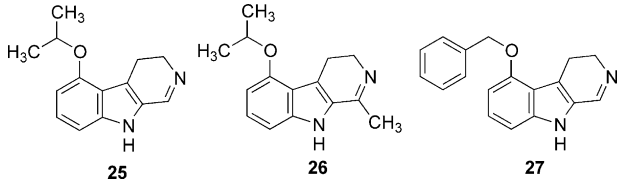
In general, the β-carbolines possessed similar to several-fold lower affinity for 5-HT_{2C} receptors than 5-HT_{2A} receptors. In both series, the 5-methoxy analogues **13** ($K_i = 75$ nM) and **22** ($K_i = 140$ nM) were again the highest-affinity methoxy-substituted derivatives and displayed enhanced affinity relative to their unsubstituted parent compounds **8** ($K_i = 1100$ nM) and **17** ($K_i > 10{,}000$ nM), respectively. In the 3,4-dihydro series, both the 5-bromo and 8-bromo analogues **9** and **12** displayed high affinity ($K_i = 140$ nM in each case), and in the tetrahydro series, these same two bromo analogues displayed high affinity (**18** and **21**; $K_i = 130$ and 48 nM). Curiously, the 5-methoxy and 5-bromo analogues of 3,4-dihydro-β-carboline displayed 3- to 6-fold selectivity for 5-HT_{2C} receptors.

This latter finding was further explored by examining the 5-*i*PrO analogues **25** and **26**, and the 5-benzyloxy analogue **27**.[21] Compound **25** ($K_i = 1410 \pm 135$ nM) was found to bind with reduced affinity at 5-HT_{2A} receptors and unchanged affinity at 5-HT_{2C} receptors ($K_i = 72 \pm 5$ nM) relative to **13**, resulting in 20-fold 5-HT_{2C} selectivity. Introduction of a 1-methyl group (**26**; 5-HT_{2A} $K_i = 470 \pm 60$ nM, 5-HT_{2C} $K_i = 26 \pm 3$ nM) resulted in similar 5-HT_{2C} selectivity. However, the 5-benzyloxy compound **27** (5-HT_{2A} $K_i = 124 \pm 20$ nM, 5-HT_{2C} $K_i = 200 \pm 20$ nM) showed reversal of this trend and was a nonselective agent.

Table 2. Receptor binding profiles for harmaline (**1**), 6-methoxyharmalan (**4**), harmalan (**6**), and 7-methoxy-1,2,3,4-tetrahydro-β-carboline (**7**)[a]

	K_i, nM (±SEM)			
	Harmaline (**1**)	6-Methoxy- harmalan (**4**)	Harmalan (**6**)	7-Methoxy-1,2,3,4-tetrahydro-β-carboline (**7**)
5-HT_{1A}	>10,000	>10,000	1670 (270)	>10,000
5-HT_{1B}	>10,000	>10,000	>10,000	>10,000
5-HT_{1D}	>10,000	>10,000	>10,000	>10,000
r5-HT_{2A}[b]	7790	5600	1150	4620[c]
5-HT_{2C}[b]	9340	924	1860	>10,000[c]
5-HT_3	>10,000	>10,000	>10,000	>10,000
5-HT_{5A}	>10,000	>10,000	845 (320)	>10,000
5-HT_6	1480 (250)	1930 (230)	1450 (220)	>10,000
5-HT_7	5500 (1400)	2960 (550)	280 (60)	1400 (670)
Dopamine (D_1–D_5)	>10,000	>10,000	>10,000	—
GABA (rBZ)	>10,000	>10,000	>10,000	—
Glutamate (rPCP)	>10,000	>10,000	>10,000	—
Muscarinic (m_1–m_5)	>10,000	>10,000	>10,000	>10,000
α_{1A}-Adrenergic	>10,000	—	—	>10,000
α_{1B}-Adrenergic	>10,000	—	—	>10,000
α_{2A}-Adrenergic	2540 (740)	—	—	1370 (370)
α_{2B}-Adrenergic	1130 (200)	—	—	140 (30)
α_{2C}-Adrenergic	810 (240)	—	—	1740 (230)
β_1-Adrenergic	>10,000	—	—	>10,000
β_2-Adrenergic	>10,000	—	—	>10,000
SERT	>10,000	>10,000	>10,000	—
NET	3260 (1360)	4100	>10,000	—
DAT (bovine)	>10,000	>10,000	>10,000	—
Imidazoline I_1[d]	13,800	—	46	>10,000
Imidazoline I_2[d]	22	—	148	12

[a]Radioligand binding studies were conducted in quadruplicate by the NIMH Psychoactive Drug Screening Program[18] and utilized human receptor types except where indicated. Five populations of dopamine receptors were examined: D_1, rD_2, rD_3, rD_4, and D_5; five populations of muscarinic cholinergic receptors were examined.
[b]5-HT_2 receptor binding data were previously reported where SEM is not provided.[5,10]
[c]Data from Table 1.
[d]Imidazoline binding data were recently reported.[19]



5-HT_{2A} agonists typically display higher affinity for 5-HT_{2A} receptors labeled by agonist rather than antagonist radioligands.[9] Thus, a comparison of affinities using the two radioligands provides an indication of whether a compound might be an agonist or antagonist. Selected β-carbolines were examined (Table 1) and none of the bromo derivatives displayed even 2-fold enhanced affinity for the agonist-labeled sites as compared to the antagonist-labeled sites. The results suggest they are unlikely to behave as 5-HT_{2A} agonists in functional assays.

The present investigation has demonstrated that harmaline (**1**) lacks significant affinity at most populations of receptors and transporters, and binds with submicromolar affinity only at α_{2C}-adrenergic and I_2 imidazoline receptors. Other β-carbolines show a similar binding profile, except that **6** binds at 5-HT_7 receptors and **7** binds at α_{2B}-adrenergic receptors. Nevertheless, the only receptor population for which the compounds consistently displayed high affinity is the I_2 imidazoline receptors. We have initiated a structure–affinity investigation to determine the binding requirements of β-carbolines at imidazoline receptors,[19] and further studies with this receptor population are currently underway.

With respect to the methoxy-substituted derivatives (Table 1), only the 5-methoxy analogues showed higher affinity at 5-HT_{2A} receptors than their unsubstituted parents; a similar finding was previously reported for their 1-methyl counterparts in the 3,4-dihydro series.[9] Interestingly, the bromo compounds displayed higher affinity than their unsubstituted parents, and the 8-bromo analogues **12** and **21**, in particular, displayed 23- and 170-fold enhanced 5-HT_{2A} affinity, respectively. In general, few of the compounds displayed higher affinity for 5-HT_{2C} receptors versus 5-HT_{2A} receptors. However, limited bulk at the 5-position resulted in compounds (i.e., **25**, **26**) with up to 20-fold 5-HT_{2C} selectivity.

The present study did not identify any new receptor population that might account for the collective behavioral or hallucinogenic actions of the β-carbolines (with perhaps the exception of imidazoline I_2 receptors, which remain to be investigated). Nevertheless, it was demonstrated that incorporation of an electron withdrawing bromo substituent has a significant impact on 5-HT_2 affinity. Because β-carbolines might represent a 'new' class of 5-HT_2 ligands with potential for agonist, antagonist and partial agonist actions, and because there is some indication that it might be possible to reverse 5-HT_{2A} versus 5-HT_{2C} selectivity, given the proper ring substituents, further investigation of β-carbolines as 5-HT_2 ligands seems warranted.

Acknowledgements

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20. 5-HT_{2A} and 5-HT_{2C} radioligand binding studies were performed as described previously.[9]
21. Compounds **25** oxalate (mp 203–205 °C from *i*PrOH), **26** hydrochloride (mp 127–129 °C from *i*PrOH) and **27** oxalate (mp 179–182 °C from MeOH) analyzed within 0.4% of theory for C, H, and N.
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