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γ-Carbolines: Binding at 5-HT$_{5A}$ Serotonin Receptors

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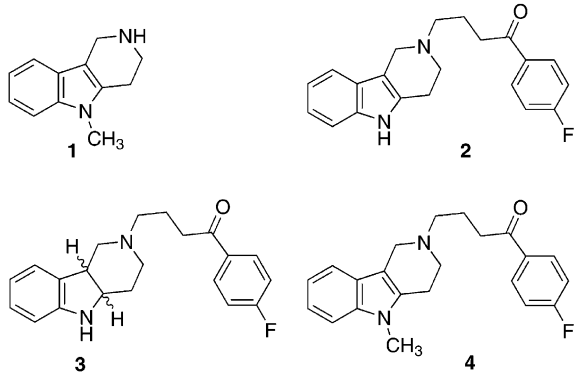
Abstract—Screening of various agents resulted in the identification of 5-methyl-1,2,3,4-tetrahydro-γ-carboline (**1**; $K_i = 5{,}300$ nM) as a compound with modest affinity for mouse 5-HT$_{5A}$ receptors. Structure–affinity studies were conducted resulting in 5-methyl-2-[3-(4-fluorophenoxy)propyl]-1,2,3,4-tetrahydro-γ-carboline (**17**; $K_i = 13$ nM). Although **17** also binds at 5-HT$_2$ receptors, it serves as a novel lead for the further development of 5-HT$_{5A}$ ligands.

Serotonin receptors have been categorized as belonging to seven different families: 5-HT$_1$-5-HT$_7$.[1–3] One population of receptors that has seen very little investigation are the 5-HT$_5$ receptors. 5-HT$_5$ receptors were first identified by Plassat et al.,[4] in 1992 and, shortly thereafter, two distinct subpopulations were cloned: 5-HT$_{5A}$ and 5-HT$_{5B}$.[5] Rat 5-HT$_{5A}$[6] and 5-HT$_{5B}$[7] receptors and human 5-HT$_{5A}$[8a] receptors have also been cloned. Human 5-HT$_{5A}$ receptors appear located throughout the brain,[8] with major distribution in the cerebral cortex, hippocampus and cerebellum.[8b] In 5-HT$_{5A}$ and 5-HT$_{5B}$ knock-out mice, evidence suggests that both receptor subtypes might be G-protein coupled.[9] Similar evidence was obtained from transfected human embryonic kidney cells.[10] With a lack of selective agents, the pharmacological significance of 5-HT$_5$ receptors is still unknown. It has been speculated, on the basis of their anatomical localization for example, that 5-HT$_{5A}$ receptors might be involved in brain development[5] and in certain CNS disorders including Alzheimers disease,[6] and that carotid 5-HT$_{5A}$ receptors might play a fundamental role in arterial chemoreception.[11] The exploratory behavior of mice and some of the psychotropic effects of lysergic acid diethylamide (LSD) might be modulated by 5-HT$_{5A}$ receptors.[12] In fact, it has been suggested that genetic variation in human 5-HT$_{5A}$ receptors might be involved in susceptibility to psychosis or depression;[13] but, a subsequent study failed to identify any relationship between 5-HT$_{5A}$ receptor gene polymorphism and the pathogenesis of affective disorders in humans.[14] Clearly, 5-HT$_5$ pharmacology could benefit from selective ligands.

To date, no 5-HT$_{5A}$-selective serotonergic ligands have been identified. We screened over 100 agents at 5-HT$_{5A}$ receptors with the intent of developing a viable lead. Some agents, such as tryptamine derivatives, displayed high affinity[15] but were also found to bind with high affinity at other populations of 5-HT receptors;[2] other agents were without appreciable affinity. One compound proved interesting. 5-Methyl-1,2,3,4-tetrahydro-γ-carboline (i.e., 5-methyl-5*H*-1,2,3,4-tetrahydropyrido[4,3-b]indole; **1**) ($K_i = 5300 \pm 300$ nM) displayed only very modest affinity for 5-HT$_{5A}$ receptors but was nonetheless attractive because, with the exception of 5-HT$_2$ receptors, γ-carbolines are not known to possess high affinity for other populations of serotonin receptors.



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Compounds **2–4**, available from an earlier study of 5-HT_2 receptor ligands,[16] were examined for their affinity for 5-HT_{5A} receptors. Their enhanced 5-HT_{5A} affinity relative to **1** served as the basis for a more systematic structure–affinity investigation.

Chemistry

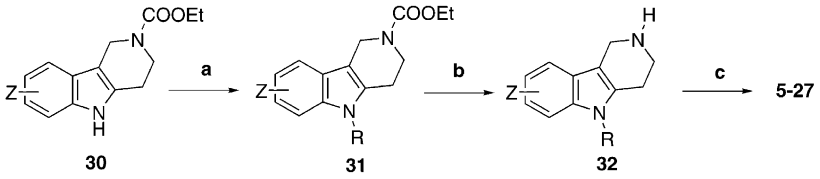
Most of the target compounds were readily prepared as shown in Scheme 1. The appropriately substituted γ-carbolines **30** were prepared by the method of Harbert and co-workers[17] and alkylated at N_5 (where required) by the method of Buchi and Mak[18] to afford derivatives **31**. Hydrolysis of **31** provided compounds **32** which were then allowed to react with Cl–$CH_2CH_2CH_2$-X-Y to give the desired targets (Table 1). A general synthetic procedure is provided in the Experimental. Compounds **28**[19] and **29** were obtained by direct alkylation of the appropriate amine.

Results and Discussion

Initial structure–affinity studies

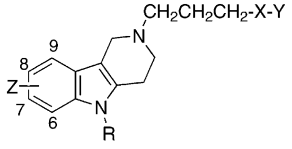
5-HT_{5A} receptor radioligand binding data are summarized in Table 1. Compound **2** ($K_i = 512$ nM) displayed 10 times the affinity of **1**. Reduction of the indolic double bond of **2** affords two isomers: *cis*-fused **3** ($K_i = 1275 \pm 220$ nM) and *trans*-fused **3** ($K_i > 10{,}000$ nM). Neither of the reduced compounds displayed higher 5-HT_{5A} affinity than **2**. Compound **4** ($K_i = 115$ nM), the *N*-methyl analogue of **2**, was found to bind with about 5-fold higher affinity than **2**, and with nearly 50-fold higher affinity than **1**. Hence, the N-methyl group was retained in most analogues subsequently examined.

des-Fluoro **4** (i.e., **5**, $K_i = 135$ nM) binds with an affinity comparable to that of **4**. The carbonyl group of **4** could be replaced with a methylene group (i.e., **6**, $K_i = 95$ nM) without loss of affinity indicating that the carbonyl group is not required for binding. Here too, replacement of the



Scheme 1. (a) RI, NaH, DMF; (b) KOH/EtOH; (c) Cl–$CH_2CH_2CH_2$-X-Y, K_2CO_3, NaI.

Table 1. Physicochemical and 5-HT_{5A} receptor binding data for compounds examined[a]

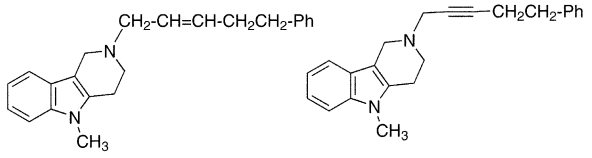


	R	Z	X	Y	Mp (°C)	Yield	Formula	Ki, nM (±SEM)	
2	–H	–H	C=O	4-F Phenyl	—	—	—	512	(80)
4	$–CH_3$	–H	C=O	4-F Phenyl	—	—	—	115	(20)
5	$–CH_3$	–H	C=O	Phenyl	254–256	51	$C_{22}H_{24}N_2O{\cdot}HCl$	135	(25)
6	$–CH_3$	–H	$–CH_2–$	4-F Phenyl	240–242	56	$C_{22}H_{25}FN_2{\cdot}HCl$	95	(15)
7	$–CH_3$	–H	$–CH_2–$	Phenyl	233–235	28	$C_{22}H_{26}N_2{\cdot}HCl$	130	(10)
8	$–CH_3$	–H	$–CH_2–$	4-OMe Ph	229–231	25	$C_{23}H_{28}N_2O{\cdot}HCl$[b]	90	(2)
9	$–CH_3$	–H	—	Phenyl	233–235	42	$C_{21}H_{24}N_2{\cdot}HCl$	250	(40)
10	$–CH_3$	–H	$–CH_2CH_2–$	Phenyl	224–227	24	$C_{23}H_{28}N_2{\cdot}HCl$[c]	120	(12)
11	$–CH_3$	–H	$–CH_2CH_2CH_2–$	Phenyl	219–221	37	$C_{24}H_{30}N_2{\cdot}HCl$	435	(10)
14	$–CH_3$	–H	–CH(OH)–	4-F Phenyl	218–219	44	$C_{22}H_{25}FN_2O{\cdot}HCl$	225	(30)
15	$–CH_3$	–H	–OH	—	227–228	27	$C_{15}H_{20}N_2O{\cdot}HCl$[b]	>1000	
16	–H	–H	–O–	4-F Phenyl	—	—	—	75	(10)
17	$–CH_3$	–H	–O–	4-F Phenyl	238–239	37	$C_{21}H_{23}FN_2O{\cdot}HCl$	13	(2)
18	–H	–H	–O–	Phenyl	181–183	47	$C_{20}H_{22}N_2O{\cdot}HCl$[d]	600	(40)
19	$–CH_3$	–H	–O–	Phenyl	239–241	36	$C_{21}H_{24}N_2O{\cdot}HCl$	25	(1)
20	$–C_2H_5$	–H	–O–	Phenyl	161–163	50	$C_{22}H_{26}N_2O{\cdot}HCl$[b]	75	(12)
21	$–CH_2Ph$	–H	–O–	Phenyl	198–200	46	$C_{27}H_{28}N_2O{\cdot}HCl$[b]	875	(590)
22	$–CH_3$	–H	–O–	1-Naphthyl	240–242	20	$C_{25}H_{26}N_2O{\cdot}HCl$	650	(30)
23	$–CH_3$	–H	–O–	2-Naphthyl	214–216	22	$C_{25}H_{26}N_2O{\cdot}HCl$	655	(275)
24	$–CH_3$	8-OMe	–O–	4-F Phenyl	216–217	56	$C_{22}H_{25}FN_2O_2{\cdot}HCl$	98	(5)
25	$–CH_3$	6-OMe	–O–	4-F Phenyl	216–217	44	$C_{22}H_{25}FN_2O_2{\cdot}HCl$	1,220	(60)
26	$–CH_3$	8-Cl	–O–	4-F Phenyl	238–240	34	$C_{21}H_{22}ClFN_2O{\cdot}HCl$	180	(55)
27	$–CH_3$	6-Cl	–O–	4-F Phenyl	228–230	39	$C_{21}H_{22}ClFN_2O{\cdot}HCl$	590	(60)

[a]Compounds recrystallized from MeOH/anhydrous Et_2O.
[b]Crystallized with 0.25 mol H_2O.
[c]Crystallized with 0.1 mol H_2O.
[d]Crystallized with 0.5 mol H_2O.

fluoro group with –H (**7**, $K_i = 130$ nM) or with an electron donating methoxy group (**8**, $K_i = 90$ nM) had little effect. It would seem that binding is not dependent upon the electronic nature of substituents on this ring.

Using an unsubstituted phenyl ring, the alkyl chain separating the aryl group of **7** from the γ-carboline system was shortened by one methylene unit (i.e., **9**, $K_i = 250$ nM) and lengthened by one or two methylene units (i.e., **10** and **11**, $K_i = 120$ and 435 nM, respectively). It was mentioned earlier that γ-carbolines bind at 5-HT_2 receptors. Because compounds **2** (5-HT_{2A} $K_i = 16$ nM)[16] and **4** (5-HT_{2A} $K_i = 6 \pm 2$ nM) bind with 32 and 20-fold selectivity, respectively, for 5-HT_{2A} versus 5-HT_{5A} receptors, and because chain-extended **10** (5-HT_{2A} $K_i = 130 \pm 20$ nM) shows reduced 5-HT_{2A} affinity relative to **2** and **4** but binds at 5-HT_{5A} receptors with an affinity similar to or greater than that of **2** and **4**, several additional analogues of **10** were prepared and examined. Unsaturation was introduced to afford ***E*12** ($K_i = 350 \pm 40$ nM) and ***Z*12** ($K_i = 330 \pm 20$ nM), and alkyne **13** ($K_i = 1710 \pm 125$ nM). None of these compounds showed enhanced 5-HT_{5A} affinity.



12 **13**

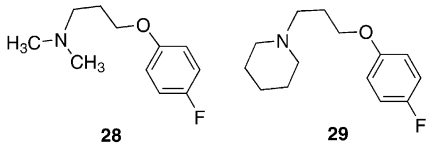
Ether analogues

The carbonyl group of **4** was reduced to racemic **14** ($K_i = 225$ nM), again showing that the carbonyl group is not essential for binding. However, removal of the 4-fluorophenyl group of **14** (i.e., **15**, $K_i > 1{,}000$ nM) resulted in decreased affinity. The carbonyl group of **2** was replaced by an ether oxygen to produce about a 7-fold increase in affinity (i.e., **16**, $K_i = 75$ nM). Likewise, the N_5-methyl analogue of **16** (i.e., **17**, $K_i = 13$ nM) displayed similarly enhanced affinity relative to **2**. The *des*-fluoro analogue of **16** (**18**, $K_i = 600$ nM) was found to bind with reduced affinity. Its N_5-methyl (**19**, $K_i = 25$ nM) and N_5-ethyl (**20**, $K_i = 75$ nM) homologues displayed enhanced affinity whereas the N_5-benzyl analogue (**21**, $K_i = 875$ nM) displayed reduced affinity. As in the carbonyl series, the N_5-methyl substituent seems optimal for 5-HT_{5A} affinity.

To this point, compound **17** ($K_i = 13$ nM) and its *des*-fluoro counterpart **19** ($K_i = 25$ nM) represent the two highest affinity compounds to emerge from this investigation. The phenyl ring of **19** was replaced both by a 1-naphthyl group (**22**, $K_i = 650$ nM) and a 2-naphthyl (**23**, $K_i = 655$ nM) group to explore bulk tolerance. In both cases, affinity was reduced. Electron donating and electron withdrawing groups were added 'para' and 'ortho' to the indolic nitrogen atom (i.e., **24**–**27**) but these had no positive impact on 5-HT_{5A} affinity. Finally, the necessity of the intact indole moiety of **17**/**19** was explored by examining abbreviated structures **28** and **29**; neither **28** nor **29** ($K_i > 10{,}000$ nM in both instances) displayed affinity for 5-HT_{5A} receptors.

Results of microanalysis

	Formula	Elemental analysis
5	$C_{22}H_{24}N_2O{\cdot}HCl$	Theory: *C* 71.63, *H* 6.83, *N* 7.59 Found: *C* 71.39, *H* 6.98, *N* 7.53
6	$C_{22}H_{25}FN_2{\cdot}HCl$	Theory: *C* 70.86, *H* 7.03, *N* 7.51 Found: *C* 70.86, *H* 7.08, *N* 7.43
7	$C_{22}H_{26}N_2{\cdot}HCl$	Theory: *C* 74.45, *H* 7.67, *N* 7.89 Found: *C* 74.38, *H* 7.75, *N* 7.94
8	$C_{23}H_{28}N_2O{\cdot}HCl{\cdot}0.25H_2O$	Theory: *C* 70.93, *H* 7.63, *N* 7.19 Found: *C* 70.81, *H* 7.60, *N* 6.96
9	$C_{21}H_{24}N_2{\cdot}HCl$	Theory: *C* 73.99, *H* 7.39, *N* 8.22 Found: *C* 73.94, *H* 7.39, *N* 8.19
10	$C_{23}H_{28}N_2{\cdot}HCl{\cdot}0.1H_2O$	Theory: *C* 74.51, *H* 7.94, *N* 7.56 Found: *C* 74.35, *H* 7.87, *N* 7.60
11	$C_{24}H_{30}N_2{\cdot}HCl$	Theory: *C* 75.27, *H* 8.16, *N* 7.31 Found: *C* 75.23, *H* 8.22, *N* 7.27
E12	$C_{23}H_{26}N_2{\cdot}HCl{\cdot}0.25H_2O$	Theory: *C* 74.37, *H* 7.46, *N* 7.54 Found: *C* 74.57, *H* 7.38, *N* 7.53
Z12	$C_{23}H_{26}N_2{\cdot}HCl{\cdot}0.25{\cdot}H_2O$	Theory: *C* 74.37, *H* 7.46, *N* 7.54 Found: *C* 74.50, *H* 7.32, *N* 7.52
13	$C_{23}H_{24}N_2{\cdot}HCl{\cdot}0.5H_2O$	Theory: *C* 73.88, *H* 7.01, *N* 7.49 Found: *C* 73.84, *H* 6.81, *N* 7.35
14	$C_{22}H_{25}FN_2O{\cdot}HCl$	Theory: *C* 67.94, *H* 6.74, *N* 7.20 Found: *C* 67.78, *H* 6.86, *N* 7.22
15	$C_{15}H_{20}N_2O{\cdot}HCl{\cdot}0.25H_2O$	Theory: *C* 63.15, *H* 7.60, *N* 9.82 Found: *C* 63.04, *H* 7.44, *N* 9.81
17	$C_{21}H_{23}FN_2O{\cdot}HCl$	Theory: *C* 67.28, *H* 6.45, *N* 7.47 Found: *C* 67.07, *H* 6.46, *N* 7.42
18	$C_{20}H_{22}N_2O{\cdot}HCl{\cdot}0.5H_2O$	Theory: *C* 68.27, *H* 6.87, *N* 7.96 Found: *C* 67.98, *H* 6.84, *N* 7.88
19	$C_{21}H_{24}N_2O{\cdot}HCl$	Theory: *C* 70.67, *H* 7.06, *N* 7.85 Found: *C* 70.47, *H* 7.02, *N* 7.75
20	$C_{22}H_{26}N_2O{\cdot}HCl{\cdot}0.25H_2O$	Theory: *C* 70.38, *H* 7.38, *N* 7.46 Found: *C* 70.54, *H* 7.32, *N* 7.56
21	$C_{27}H_{28}N_2O{\cdot}HCl{\cdot}0.25H_2O$	Theory: *C* 74.12, *H* 6.80, *N* 6.40 Found: *C* 73.88, *H* 6.74, *N* 6.42
22	$C_{25}H_{26}N_2O{\cdot}HCl$	Theory: *C* 73.78, *H* 6.69, *N* 6.88 Found: *C* 73.51, *H* 6.70, *N* 6.78
23	$C_{25}H_{26}N_2O{\cdot}HCl$	Theory: *C* 73.78, *H* 6.69, *N* 6.88 Found: *C* 73.57, *H* 6.70, *N* 6.84
24	$C_{22}H_{25}FN_2O_2{\cdot}HCl$	Theory: *C* 65.26, *H* 6.47, *N* 6.92 Found: *C* 65.26, *H* 6.49, *N* 6.89
25	$C_{22}H_{25}FN_2O_2{\cdot}HCl$	Theory: *C* 65.26, *H* 6.47, *N* 6.92 Found: *C* 65.23, *H* 6.54, *N* 6.90
26	$C_{21}H_{22}ClFN_2O{\cdot}HCl$	Theory: *C* 61.62, *H* 5.66, *N* 6.84 Found: *C* 61.79, *H* 5.53, *N* 6.84
27	$C_{21}H_{22}ClFN_2O{\cdot}HCl$	Theory: *C* 61.62, *H* 5.66, *N* 6.84 Found: *C* 61.56, *H* 5.77, *N* 6.82
29	$C_{14}H_{20}FNO{\cdot}HCl{\cdot}0.75H_2O$	Theory: *C* 58.53, *H* 7.89, *N* 4.88 Found: *C* 58.20, *H* 7.77, *N* 4.83



As previously mentioned, γ-carbolines can bind at 5-HT_2 receptors.[16] The purpose of the present investigation was to exploit an initial lead and to explore the structure–affinity relationships for the binding of γ-carbolines at 5-HT_{5A} receptors; selectivity was not a focus of the study. Nevertheless, some selectivity data were obtained. Compound **4** binds with high affinity ($K_i = 6$ nM) and 20-fold selectivity at 5-HT_{2A} receptors versus 5-HT_{5A} receptors. Compound **10** binds equally well at 5-HT_{2A} ($K_i = 130$ nM) and 5-HT_{5A} ($K_i = 120$ nM) receptors. Examination of **17** (5-HT_{2A} $K_i = 30 \pm 5$ nM) and **19** (5-HT_{2A} $K_i = 70 \pm 10$ nM) show that they bind with several-fold selectivity for 5-HT_{5A} versus 5-HT_{2A} receptors. As might be expected, the latter compounds also bind at 5-HT_{2C} receptors (Ki = 75 and 285 nM, respectively). Preliminary evidence suggests that 5-HT_{2A} and 5-HT_{5A} receptor affinity do not co-vary, and that **17** and **19** bind with about a 50-fold selectivity reversal compared to **4**. Another interesting observation is that the γ-carbolines probably bind at 5-HT_{5A} receptors in a manner that is different than that of the tryptamines. That is, although the γ-carbolines and the tryptamines both possess an indolic nucleus, methylation of the indole nitrogen atom decreases affinity in the tryptamine series[15] whereas it seems to enhance affinity in the γ-carboline series. Also, introduction of a methoxy group '*para*' to the indole nitrogen atom decreases the affinity of the **17** by about 7-fold (Table 1) whereas it enhances the affinity of tryptamines.[15]

In summary, we have identified a novel class of 5-HT_{5A} ligands (i.e., γ-carbolines); several of these γ-carbolines bind at murine 5-HT_{5A} receptors with affinities greater than that of serotonin itself ($K_i = 180 \pm 20$ nM). Although γ-carbolines **17** and **19** bind at 5-HT_{2A} receptors, they show a selectivity reversal compared to **2** and **4**. Hence, it should eventually be possible to develop derivatives with greater selectivity. Attempts are currently underway to improve the affinity and selectivity of γ-carbolines for 5-HT_{5A} versus 5-HT_{2A} receptors.

Experimental

Synthesis

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were obtained with a Varian Gemini 300 spectrometer, using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Nicolet 5ZDX FT-infrared spectrometer. Elemental analysis was performed by Atlantic Microlab, and determined values are within 0.4% of theory. Thin-layer chromatography (TLC) was performed using silica gel-coated GHIF plates (250 μ, 2.5×10 cm, Analtech, Inc., Newark, DE, USA). Dry THF was obtained by distillation over sodium metal and benzophenone. Dry CH_2Cl_2 was obtained by distillation over phosphorus pentoxide (P_2O_5). Compounds **2–4** and **16** were available from an earlier study.[15]

γ-Carbolines (2-substituted derivatives of 5-alkyl-1,2,3,4-tetrahydropyrido[4,3-b]indoles) 5–27. 2-Carbethoxy-1,2,3,4-tetrahydropyrido[4,3-*b*]indoles **30** were prepared following the general procedure of Harbert et al.,[17] by heating the appropriate phenylhydrazine hydrochloride (1 mmol) and 1-carbethoxy-4-piperidone (1 mmol) in absolute EtOH (20 mL) at reflux for 3 h. The reaction mixture was allowed to stand at room temperature overnight, and the solid product was collected by filtration, washed with 50% aqueous EtOH, and recrystallized from 95% EtOH. Where necessary, N_5-alkylation was achieved by the method of Buchi and Mak.[18] Alkyl halide (2 mmol) was added to a stirred mixture of the appropriate 2-carboethoxy-1,2,3,4-tetrahydropyrido[4,3-*b*]indole (**30**, 1 mmol) and sodium hydride (95%) (5 mmol) in dry DMF (10 mL) under N_2. The reaction mixture was allowed to stir at room temperature for 15 min, poured into an ice/H_2O mixture, and the solid product was collected by filtration and washed with cold H_2O (5 mL). Crude product was recrystallized from absolute EtOH to afford the desired 2-carbethoxy-5-alkyl-1,2,3,4-tetrahydropyrido[4,3-*b*]indoles **31.**

A suspension **31** (2 mmol) in 95% EtOH (5 mL) was added to a solution of KOH (ca. 2 g) in 95% EtOH (7 mL) and H_2O (1 mL). The resulting solution was heated at reflux under N_2 for 22 h. The dark solution was concentrated in vacuo, diluted with H_2O (20 mL) and extracted with Et_2O (2×20 mL). The organic portion was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. A mixture of the resulting 5-alkyl-1,2,3,4-tetrahydropyrido[4,3-b]indole (**32**) (1 mmol), the appropriate chloropropane derivative (1 mmol), K_2CO_3 (3.5 mmol), and a catalytic amount of NaI in MeCN (10 mL) was heated at reflux for 18 h. The reaction mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was suspended in H_2O (25 mL) and extracted twice with Et_2O (2×50 mL). The combined ethereal extract was evaporated under reduce pressure and the crude product was purified by column chromatography (silica gel; CH_2Cl_2 followed with EtOAc/MeOH; 1:1). The free base was dissolved in anhydrous MeOH and treated with methanolic HCl, and the products **5–27** were recrystallized from an anhydrous MeOH/Et_2O mixture (Table 1).

(*Z*)5-Methyl-2-(5-phenyl-2-pentenyl)-1,2,3,4-tetrahydropyrido[4,3-*b*]indole hydrochloride (*Z*12). A solution of 5-(phenyl)-2-pentyn-1-ol (0.50 g, 3.1 mmol; see **13** for preparation), absolute EtOH (30 mL), and quinoline (2–3 drops), with Lindlar's catalyst (85 mg), was stirred vigorously under an atmosphere of H_2 for 3 h. The mixture was filtered to remove the catalyst and purified by column chromatography (silica gel; CH_2Cl_2) to give 0.48 g (96%) of the desired alkenol as a yellow oil.

Thionyl chloride (0.5 mL) was added to a solution of this alkenol (0.32 g, 2 mmol) in benzene (10 mL) and the reaction mixture was heated at 70–80 °C for 24 h. The reaction mixture was poured into ice/H_2O (100 mL), and the aqueous solution was extracted with CH_2Cl_2 (2×25 mL). The combine organic fraction was washed well with H_2O (30 mL), and finally the CH_2Cl_2 was evaporated under reduced pressure to give 0.26 g (72%) of the alkenyl halide as an oil. This halide was used to alkylate **32** as described above and the product was converted to its HCl salt to give a 30% yield of ***Z*12**; mp 217–219 °C after recrystalization from MeOH/anhydrous Et_2O. Anal. $C_{23}H_{26}N_2 \cdot HCl \cdot 0.25H_2O$ C, H, N.

(*E*)5-Methyl-2-(5-phenyl-2-pentenyl)-1,2,3,4-tetrahydropyrido[4,3-*b*]indole hydrochloride (*E*12). A solution of 5-(phenyl)-2-pentyn-1-ol (0.50 g, 3.1 mmol; see **13** for preparation) in dry THF (2 mL) was added in a dropwise manner over 15 min to a stirred suspension of $LiAlH_4$ (0.16 g, 4 mmol) in THF (20 mL) at 0 °C. The suspension was warmed to 67 °C and allowed to stir for 24 h. The reaction mixture was cooled to room temperature and excess $LiAlH_4$ was destroyed by careful addition of 15% NaOH. The resulting solution was extracted with Et_2O (2×30 mL). The organic phase was washed with H_2O (30 mL), dried ($MgSO_4$) and solvent was evaporated in vacuo. The crude product was purified by column chromatography (silica gel; CH_2Cl_2) to give 0.45 g (92%) of the alkenol. The alkenol was converted to the corresponding chloro compound in 75% yield as described for ***Z*12**, and the crude product was allowed to react with **32** to afford the desired product in 32% yield after conversion to its HCl salt; mp 225–227 °C following recrystallization from MeOH/anhydrous Et_2O. Anal. $C_{23}H_{26}N_2HCl \cdot 0.25H_2O$ C, H, N.

5-Methyl-2-(5-phenyl-2-pentynyl)-1,2,3,4-tetrahydropyrido[4,3-*b*]indole hydrochloride (13). 4-Phenyl-1-butyne (98%; 1.5 g, 11.5 mmol) was added slowly to a stirred solution of Et_2O (24 mL) and 2.5 M *n*BuLi in hexane (4.6 mL, 12 mmol) at −10 °C. A suspension of paraformaldehyde (0.8 g, excess) in THF (28 mL) was added to the mixture, and the gelatinous mixture was allowed to stir at 0 °C for 45 min. The mixture was heated at reflux for a further 90 min, allowed to cool to room temperature, poured into ice/water (ca. 50 mL), and extracted with Et_2O (2×30 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel; CH_2Cl_2) to give 1.33 g (72%) of the pentynol as a yellow oil. Thionyl chloride (0.5 mL) was added to the pentynol (0.32 g, 2 mmol) in benzene (10 mL), and the reaction mixture was heated at 70–80 °C for 24 h. The reaction mixture was poured into ice/H_2O (100 mL), and the aqueous solution was extracted with CH_2Cl_2 (2×25 mL). The combined organic fraction was washed well with H_2O (30 mL), and the CH_2Cl_2 was evaporated under reduced pressure to give 0.35 g (99%) of the desired chloro compound as an oil. The chloro compound was used to alkylate **32** as described above and the product was converted to its HCl salt to give a 24% yield of **13**; mp 208–210 °C after recrystalization from an EtOAc/absolute EtOH mixture. Anal. $C_{23}H_{24}N_2HCl \cdot 0.5H_2O$ C, H, N.

1-(3-(4-Fluorophenoxy)propyl)piperidine hydrochloride (29). A mixture of 1-(3-chloropropoxy)-4-fluorobenzene (0.57 g, 3.0 mmol), piperidine (0.26 g, 3.0 mmol), K_2CO_3 (0.75 g, 5.6 mmol) and a catalytic amount of NaI in MeCN (30 mL) was heated at reflux for 18 h. After the reaction mixture was allowed to cool to room temperature, it was extracted with Et_2O (2×30 mL). The combined ethereal extract was washed with H_2O (30 mL), dried ($MgSO_4$) evaporated to dryness under vacuum, and the crude product was purified by column chromatography (silica gel; CH_2Cl_2). Ethereal HCl was added to a solution of the free base of **29** in anhydrous Et_2O to form the HCl salt. Recrystallization from absolute EtOH/anhydrous Et_2O afforded 0.33 g (40%) of the title compound as a pale yellow powder; mp 136–138 °C. Anal. ($C_{14}H_{20}FNO \cdot HCl$ $0.75H_2O$) C, H, N.

Radioligand binding assay

The radioligand binding studies were performed as previously described.[15] Tritiated (+)lysergic acid diethylamide (LSD) (0.5 nM) was used to label murine 5-HT_{5A} receptors (cell line generously donated by Dr. R. Hen) and 1 μM LSD was used to determine nonspecific binding. Typically, 11 concentrations of test agent (10^{-10}–10^{-5} M) were evaluated, except where the compound displayed <30% inhibition at 10,000 nM in which case it was not further examined. Data were analyzed using GraphPad and represent the means and SEM of three independent determinations run in triplicate.

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