3-(1,2,5,6-Tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one: A Potent and Selective Serotonin (5-HT_{1B}) Agonist and Rotationally Restricted Phenolic Analogue of 5-Methoxy-3-(1,2,5,6-tetrahydropyrid-4-yl)indole

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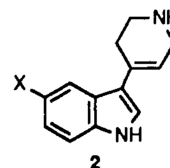
The synthesis and in vitro and in vivo characteristics of 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (1, CP-93,129) are described. This rotationally restricted phenolic analogue of RU-24,969 is a potent (15 nM) and selective (200x vs the 5-HT_{1A} receptor, 150x vs the 5HT_{1D} receptor) functional agonist for the 5-HT_{1B} receptor. Direct infusion of 1 into the paraventricular nucleus of the hypothalamus of rats significantly inhibits food intake, implicating the role of 5-HT_{1B} receptors in regulating feeding behavior in rodents. 3-(1,2,5,6-Tetrahydropyrid-4-yl)pyrrolo-[3,2-*b*]pyrid-5-one (1) has also been shown to be biochemically discriminatory in its ability to selectively inhibit forskolin-stimulated adenylate cyclase activity only at the 5-HT_{1B} receptor. The source of the selectivity of 1 appears to lie in the ability of a pyrrolo[3,2-*b*]pyrid-5-one to act as a rotationally restricted bioisosteric replacement for 5-hydroxyindole.

Introduction

With the increasing differentiation of neurotransmitter receptors into subclasses, there is the ever-growing need for the synthesis and identification of selective ligands for the individual receptor subtypes to aid in the study of receptor function, localization, and isolation. The serotonin (5-HT) receptors are no exception.[1] These receptors have been divided into three main groups: 5-HT_1, 5-HT_2, and 5-HT_3.[2] The 5-HT_1 class has been further subdivided into four accepted subtypes: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C},[3] and, more recently, 5-HT_{1D}.[4] Of the 5-HT_1 receptors, only the 5-HT_{1A} receptor has a selective and potent agonist: 8-OH-DPAT [8-hydroxy-2-(*N*,*N*-dipropylamino)tetralin]. The existence of this selective ligand for the 5-HT_{1A} receptor has led to an understanding of the functions of that receptor and its potential role in anxiety and depression. This knowledge has given rise to the development of novel serotonergic anxiolytics, i.e. the buspirone and gepirone class of drugs, which are partial 5-HT_{1A} receptor agonists.[5] The study of the other 5-HT_1 receptors has been hampered by the lack of specific pharmacological tools, i.e. potent and selective ligands.[1] This paper presents the synthesis and some characteristics of 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (1, CP-93,129), a potent and selective 5-HT_{1B} receptor agonist.

The 5-HT_{1B} receptor was first reported by Pedigo in 1981[6] and further described by Frazier in 1984[7] and Palacios and Hoyer in 1985.[3] It is negatively linked to adenylate cyclase,[8] and relatively selective 5-HT_{1B} receptor agonists have been claimed to produce anorexia in rodents.[9] Most reports to date suggest that the existence of 5-HT_{1B} receptors appears to be limited to the brains of mice and rats,[10] but the lack of a potent and selective ligand for that receptor has hampered further studies to test this hypothesis.[11] Serotonin, 5-carboxamidotryptamine, 2-cyanopindolol, and RU-24,969 [5-methoxy-3-(1,2,5,6-tetrahydropyridyl)indole, **2g**] bind to the 5-HT_{1B} receptor with high affinities (IC_{50}'s < 10 nM), but only RU-24,969 demonstrates any degree of selectivity for the 5-HT_{1B} receptor (5–10 times the selective versus the 5-HT_{1A} receptor). In 1987, a report claimed that CGS-12066B [4-(4-methylpiperazinyl)-7-(trifluoromethyl)pyrrolo[1,2-*a*]-quinoxaline, **3a**] was selective for the 5-HT_{1B} receptor;[12] however, in our hands, **3a** appears to be slightly selective for the 5-HT_{1A} receptor. This discrepancy is clearly a result of the methodological differences in the 5-HT_{1A} receptor binding assays utilized in our studies and that of Williams et al.[12] Specific 5-HT_{1A} receptor binding measured against [^{3}H]-8-OH-DPAT has generally been accepted as a more accurate measure of 5-HT_{1A} receptor binding than the older method used by Williams and coworkers[12] with [^{3}H]-5-HT. It should be noted that the desmethyl analogue of CGS-12066B [4-piperazinyl-7-

Table I. Binding Data on 5-Substituted 3-Tetrahydropyridylindoles (2)



compd	R	IC_{50}, 5HT_{1A}	IC_{50}, 5-HT_{1B}	ratio (A/B)
2a[a]	H	140 ± 20 [4]	3.7 ± 0.6 [4]	38
2b[b]	F	65 ± 11 [4]	1.9 ± 0.4 [4]	34
2c[a]	Cl	26 ± 2 [3]	3.3 ± 0.1 [3]	8
2d	Br	13 ± 2 [3]	3.2 ± 1.0 [3]	4
2e[b]	CN	32 ± 4 [4]	0.8 ± 0.1 [4]	40
2f[a]	NO_2	36 ± 5 [3]	3.5 ± 1.5 [4]	10
2g[a]	OCH_3	14 ± 7 [5]	2.0 ± 0.9 [5]	7
2h	OH	30 ± 11 [3]	1.2 ± 0.2 [3]	25

[a] Reference 14a. [b] Reference 14b. [c] The number in brackets is the number of experiments. X ± SEM.

(1) Peroutka, S. J. *Annu. Rev. Neurosci.* **1988**, *11*, 45.
(2) Peroutka, S. J.; Synder, S. H. *Mol. Pharmacol.* **1979**, *16*, 687.
(3) (a) Hoyer, D.; Engel, G.; Kalkman, H. O. *Eur. J. Pharmacol.* **1985**, *118*, 1. (b) Pazos, A.; Engel, G., Palacios, J. M. *Brain Res.* **1985**, *343*, 403.
(4) Heuring, R. E.; Peroutka, S. J. *J. Neurosci.* **1987**, *7*, 894.
(5) (a) Robinson, C. P. *Drugs Today* **1987**, *23*, 311. (b) File, S. E. *Neuropharmacol.* **1987**, *26*, 877.
(6) Pedigo, N. W.; Yamamura, H. I., Nelson, D. L. *J. Neurochem.* **1981**, *36*, 220.
(7) Sills, M. A.; Wolfe, B. B.; Frazer, A. *J. Pharmacol. Exp. Ther.* **1984**, *231*, 480.
(8) Bouhelal, R.; Smounya, L.; Bockaert J. *Eur. J. Pharmacol.* **1988**, *151*, 189.
(9) Kennett, G. A.; Dourish, C. T.; Curzon, G. *Eur. J. Pharmacol.* **1987**, *141*, 429.
(10) Heuring, R. E.; Schlegel, J. R.; Peroutka, S. J. *Eur. J. Pharmacol.* **1987**, *122*, 279.
(11) Murphy, T. J.; Bylund, D. B. *J. Pharmacol. Exp. Ther.* **1989**, *249*, 535.
(12) Neale, R. F.; Fallon, S. L.; Boyar, W. C.; Wasley, J. W. F.; Martin, L. L.; Stone, G. A.; Glaeser, B. S.; Sinton, C. M.; Williams, M. *Eur. J. Pharmacol.* **1987**, *136*, 1.

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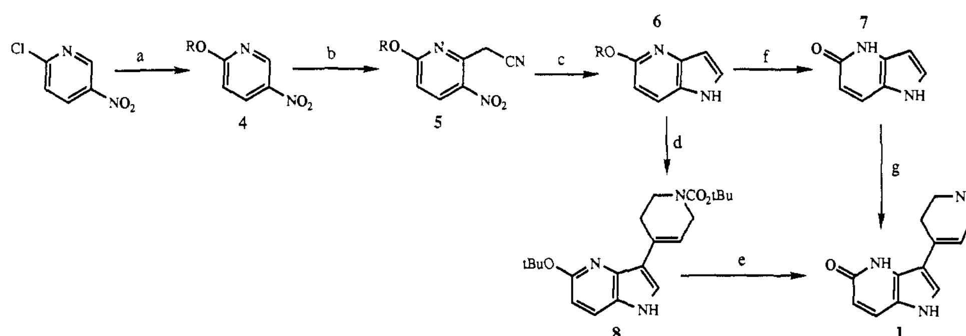
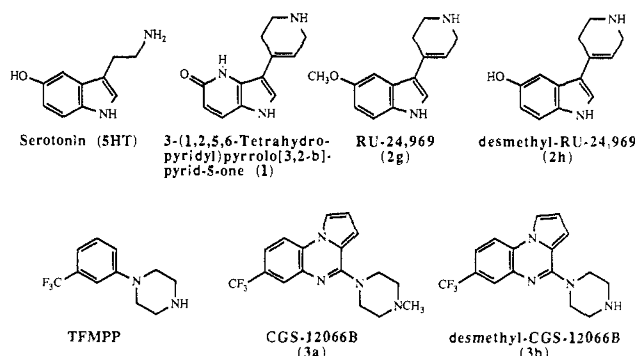
Scheme I



	R	
	CH_2Ph (a)	tBu (b)
a =	$NaOCH_2Ph/THF$	NaOtBu/THF
b =	1) KOtBu; 2) p-Cl-$PhOCH_2CN$	
c =	Raney Ni/EtOH/Δ	10% Pd on C/EtOH/Δ
d =	---	N-t-butoxycarbonyl-4-piperidone/Na in MeOH
e =	---	HCl in MeOH
f =	10% Pd/C in ethanol	---
g =	4-piperidone/Na in MeOH	---

(trifluoromethyl)pyrrolo[1,2-*a*]quinoxaline, **3b**] shows slight selectivity for the 5-HT_{1B} receptor. The need for a more selective agent was apparent, and this led us to design and synthesize potent and selective 5-HT_{1B} ligands.



While RU-24,969 (**2g**) has often been claimed to be the standard for selectivity for the 5-HT_{1B} receptor,[7] in fact, other members of the 3-(1,2,5,6-tetrahydropyridyl)indole family are considerably more selective for the 5-HT_{1B} receptor versus the 5-HT_{1A} receptor (Table I).[13] The synthesis of these compounds has been covered extensively in the patent and primary literature,[14] and 3-(1,2,5,6-tetrahydropyrid-4-yl)indoles (**2**) arise from the basic condensation of the appropriate indole derivative with 4-piperidone.[15] Taylor and Nelson[14b] have proposed that steric fit of the C5-substituent of RU-24,969 analogues determined 5-HT_{1A} receptor potency. They hypothesized that the idealized volume of 24 $Å^3$, or approximately the size occupied by the carboxamido substituent, insured potent 5-HT_{1A} receptor binding. From our study of the SAR (structure–activity relationship) of the series of 5-substituted 3-(tetrahydropyridyl)indoles (**2**) in Table I, an important trend for 5-HT_{1B} receptor selectivity was seen. We noted that the smaller the volume occupied by the 5-substituent, the greater the 5-HT_{1B} versus 5-HT_{1A} receptor selectivity. Compounds **2a** (R = H) and **2b** (R = F) were the most 5-HT_{1B} receptor selective compounds when compared to RU-24,969 (R = OCH_3, **2g**). Compounds **2c** (R = Cl) and **2d** (R = Br) lost 5-HT_{1B} receptor selectivity with their increasing steric bulk. The comparison of **2g** (R = OCH_3, RU-24,969) and **2h** [R = OH, 5-hydroxy-3-(1,2,5,6-tetrahydropyrid-4-yl)indole] further confirmed this trend. At first it appeared that **2e** (R = CN) deviated from this trend, but since this substituent was linear, the actual volume occupied by it was still very small. Using this trend for 5-HT_{1B} selective compounds (Table I), we hypothesized that either a hydrogen-bonding or a steric interaction must be occurring in the 5-HT_{1B} receptor with the C5-substituent of RU-24,969 analogues at a distance just past the first atom of the substituent. To test this hypothesis we desired to synthesize a 5-HT_{1B} receptor selective RU-24,969 analogue in which the C5-substituent: (1) occupied the least volume of space possible, while still mimicking the C5-oxygen substituent of serotonin, and (2) was rotationally restricted to possibly optimize this apparently tight hydrogen-bonding or steric interaction. Such a compound would be a rotationally restricted analogue of 5-hydroxy-3-(1,2,5,6-tetrahydropyridyl)indole (**2h**). The pyrrolo[3,2-*b*]pyrid-5-one analogue of RU-24,969 was seen as the target molecule since 2-hydroxypyridines exist almost exclusively in the amide tautomer.[16] The pyridone oxygen, since it is reported to be almost entirely amide-like, cannot rotate and represented for us the optimal structure for testing our hypothesis. This rationale led to the synthesis of 3-(1,2,5,6-tetrahydropyridyl)pyrrolo[3,2-*b*]pyrid-5-one (**1**).

Results

Chemistry. The synthetic approaches to 3-(1,2,5,6-tetrahydropyridyl)pyrrolo[3,2-*b*]pyrid-5-one (**1**) are shown in Scheme I. The initial synthesis of this molecule required the formation of pyrrolo[3,2-*b*]pyrid-5-one (**7**). The reaction of sodium benzoxide (from the reaction of sodium

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(14) (a) Guillaume, J.; Dumont, C.; Laurent, J.; Nédélec, L. *Eur. J. Med. Chem.* **1987**, *22*, 33. (b) Taylor, E. W.; Nikam, S. S.; Lambert, G.; Martin, A. R.; Nelson, D. L. *Mol. Pharmacol.* **1988**, *34*, 42. (c) U.S. Patent 4,278,677, 1981 and references cited within.

(15) Freter, K. *J. Org. Chem.* **1975**, *40*, 2525.

(16) For a review of this work, see: Tieckelmann, H.; Pyridinols and Pyridones. In *The Chemistry of Heterocyclic Compounds*; Taylor E. C., Weissberger, E., Eds.; John Wiley and Sons: New York, 1974; Vol. 14, Part 3 Supplemental, pp 733-734.

Table II. Receptor Binding Data

compd	IC_{50},[a] nM				
	5-HT_{1A}	5-HT_{1B}	5-HT_{1C}	5-HT_{1D}	5-HT_2
1	3000 ± 400 [4]	15 ± 5 [5]	6400 ± 800 [5]	2200 ± 700 [3]	>10000 [3]
RU-24969 (**2g**)	14 ± 7 [5]	2.0 ± 0.9 [5]	290 ± 60 [6]	39 ± 4 [3]	5400 ± 2000 [4]
desmethyl-RU-24969 (**2h**)	30 ± 11 [3]	1.2 ± 0.2 [3]	170 ± 40 [3]	22 ± 2 [4]	2200 ± 300 [3]
TFMPP	290 ± 60 [8]	27 ± 4 [10]	150 ± 50 [6]	610 ± 100 [4]	570 ± 60 [3]
CGS-12066B (**3a**)	19 ± 7 [6]	150 ± 70 [5]	>10000 [3]	35 ± 7 [4]	6800 ± 100 [3]
desmethyl-CGS-12066B (**3b**)	37 ± 11 [5]	21 ± 7 [5]	10000 ± 1000 [3]	190 ± 50 [3]	>10000 [3]
5-HT	5.2 ± 1.5 [15]	5.0 ± 1.7 [12]	81 ± 30 [3]	3.0 ± 0.3 [3]	4600 ± 2100 [3]

[a] The number in brackets is the number of experiments. X ± SEM.

hydride and benzyl alcohol in anhydrous tetrahydrofuran) with 5-chloro-2-nitropyridine afforded 2-(benzyloxy)-5-nitropyridine (**4a**).[17] This nitropyridine (**4a**) readily participated in a vicarious nucleophilic aromatic substitution reaction (VNASR),[18] and the product (**5a**) from this reaction was isolated as a crystalline solid as an approximately 10:1 mixture of the 2- and 4-pyridyl isomers. Reductive cyclization of **5a** could not employ the conditions (H_2, Pd/C) outlined by Makosza[18] in the synthesis of 5-methoxypyrrolo[3,2-*b*]pyridine since the benzyl group protecting the 5-hydroxy substituent would have been removed under these conditions.[19] Alternatively, hydrogenation using Raney nickel in ethanol/acetic acid led to the formation of **6a** in low yield. Removal of the benzyl group was then smoothly accomplished with 10% Pd/C to afford pyrrolo[3,2-*b*]pyrid-5-one (**7**). Subsequent condensation of **7** with 4-piperidone in sodium methoxide/refluxing methanol led directly to 3-(1,2,5,6-tetrahydropyridyl)pyrrolo[3,2-*b*]pyrid-5-one (**1**) in 10% overall yield from 2-chloro-5-nitropyridine.

As a result of the failure of the reductive cyclization to work consistently on a large scale, an alternate route to 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (**1**) was sought which was capable of producing the drug in multigram quantities. The preferred alternative sequence is outlined in Scheme I. Use of *tert*-butoxide in the chloride displacement reaction with 2-chloro-5-nitropyridine yielded **4b**. The VNASR as previously discussed yielded **5b**. The *t*-BOC protection of the pyridone allowed the use of Pd/C in the reductive cyclization, and hydrogenation of **5b** using 10% Pd/C in absolute ethanol yielded pyrrolo[3,2-*b*]pyridine **6b**. This one-pot reductive cyclization presumably occurred via the initial reduction of the aromatic nitro group to the aniline derivative at room temperature. Then intramolecular cyclization of this amine on the nitrile at 60 °C with subsequent reduction of the intermediate amidine yielded **6b**. It was found that the use of an N-protected 4-piperidone in the condensation reaction led to easier product purification and isolation. Therefore, reaction of **6b** with *N*-(*tert*-butoxycarbonyl)-4-piperidone yielded **8**. Finally, deprotection of **8** using HCl gas in methanol removed both *tert*-butyl groups to yield directly 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (**1**) in a consistently reproducible 15% overall yield from 2-chloro-5-nitropyridine even on multigram preparations.

Pharmacology. Table II summarizes the comparative receptor binding data obtained for 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (**1**) and the serotonergic literature standards RU-24,969 (**2g**), TFMPP [*N*-[*m*-(trifluoromethyl)phenyl]piperazine],[20] CGS-12066B (**3a**),[21] desmethyl-CGS-12066B (**3b**), desmethyl-RU-24,969 (**2h**),[22] and serotonin (5-HT). 3-(1,2,5,6-Tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (**1**) is virtually selective for the 5-HT_{1B} receptor vs either the 5-HT_{1A} receptor (200-fold), the 5-HT_{1C} receptor (425-fold), the 5-HT_{1D} receptor (150-fold), or the 5-HT_2 receptor (over 700-fold). Additionally, **1** has not shown any substantial affinity for any other neurotransmitter receptor studied to date (i.e. dopamine, adrenergic, opiate).

Table III. Inhibition of Forskolin-Stimulated Adenylate Cyclase Activity of 3-(1,2,5,6-Tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]-pyrid-5-one (1)

receptor	EC_{50}, nM (X ± SEM)	
	5-HT	1
5-HT_{1A}	30 ± 13	>10000
5-HT_{1B}	26 ± 4	56 ± 5
5-HT_{1D}	16 ± 7	>10000

Table IV. Effects on Food Intake (g/30 min) of 3-(1,2,5,6-Tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (1) in Rats

vehicle (saline)	5-HT (32 μg)	1 (16 μg)
2.76 ± 0.36 (10)	1.15 ± 0.44* (5)	0.12 ± 0.01** (5)

[a] X ± SEM. Numbers of rats in parentheses. *, $p < 0.05$; **, $p < 0.01$ versus vehicle.

The ability of serotonin and serotonergic agonists to inhibit forskolin-stimulated adenylate cyclase activity at 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors is well-known.[23] Schoeffter and Hoyer reported that, while a number of serotonergic agents have been claimed to be selective for the 5-HT_{1B} receptor based on receptor binding results, none of these compounds acted as functionally selective agonists at the 5-HT_{1B} receptor.[24] They concluded that there was no functionally selective agonist for the 5-HT_{1B} receptor available in the literature. Therefore, the ability of 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (**1**) to inhibit forskolin-stimulated adenylate cyclase activity in 5-HT_{1A} (guinea pig hippocampus),[25] 5-HT_{1B} (rat sub-

(17) Friedman, H. L.; Braitberg, L. D.; Tolstoouhov, A. V.; Tisza, E. T. *J. Am. Chem. Soc.* **1947**, *69*, 1204.

(18) Makosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs. Ann. Chem.* **1988**, 203.

(19) The use of Pd/C was attempted in this reaction, and none of the desired 5-hydroxypyrrolo[3,2-*b*]pyridine was isolated from that reaction.

(20) Aldrich Chemical Co.

(21) While CGS-12066B (**3a**) has been cited a number of times in the pharmacological literature, it is very unfortunate that a synthesis of this compound has not yet been disclosed in the literature. Consequently, syntheses of **3a** and **3b** are presented as supplementary material to this paper.

(22) The synthesis of desmethyl-RU-24,969 [5-hydroxy-3-(1,2,5,6-tetrahydropyridyl)indole, **2h**] is contained as supplementary material to this article.

(23) (a) 5-HT_{1A}: Schoeffter, P.; Hoyer, D. *Br. J. Pharmacol.* **1988**, *95*, 975 and references cited within. (b) 5-HT_{1B}: ref 8. (c) 5-HT_{1D}: Schoeffter, P.; Waeber, C.; Palacios, J. M.; Hoyer, D. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1988**, *337*, 602.

(24) Schoeffter, P.; Hoyer, D. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1989**, *339*, 675.

(25) De Vivo, M.; Maayani, S. *J. Pharmacol. Exp. Ther.* **1986**, *238*, 248.

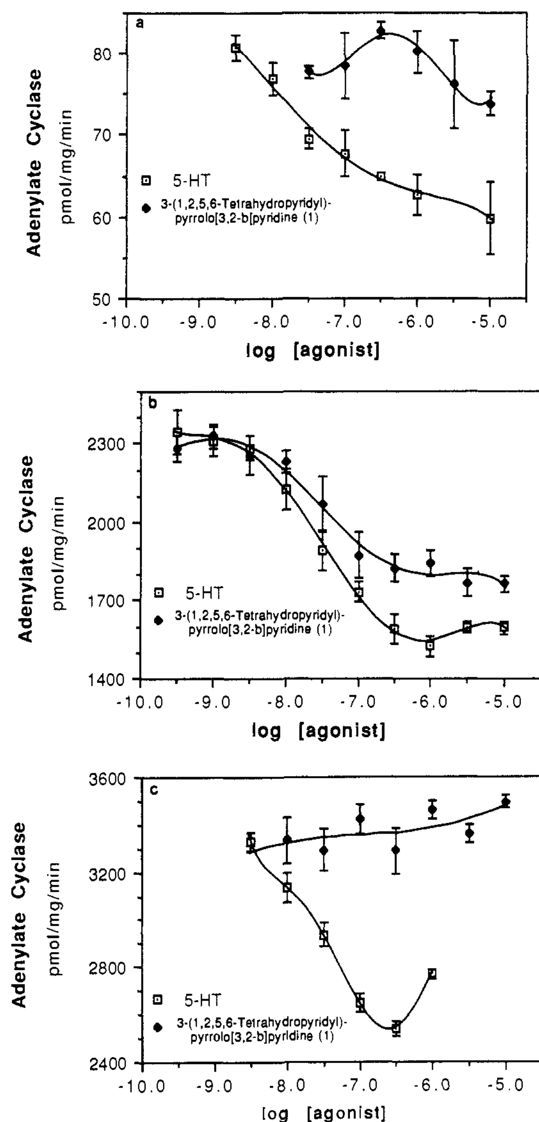

Figure 1. (a) Effects of forskolin-stimulated adenylate cyclase activity in vitro at the 5-HT_{1A} receptor (guinea pig hippocampus): 5-HT EC_{50} = 30 ± 13 nM and 3-(1,2,5,6-tetrahydropyridyl)-pyrrolo[3,2-*b*]pyridine (1) EC_{50} > 10000 nM. (b) Effects of forskolin-stimulated adenylate cyclase activity in vitro at the 5-HT_{1B} receptor (rat substantia nigra): 5-HT EC_{50} = 26 ± 4 nM and 3-(1,2,5,6-tetrahydropyridyl)pyrrolo[3,2-*b*]pyridine (1) EC_{50} = 56 ± 5 nM. (c) Effects of forskolin-stimulated adenylate cyclase activity in vitro at the 5-HT_{1D} receptor (guinea pig substantia nigra); 5-HT EC_{50} = 16 ± 7 nM and 3-(1,2,5,6-tetrahydropyridyl)pyrrolo[3,2-*b*]pyridine (1) EC_{50} > 10000 nM. Data above show mean ± SEM values for triplicate determinations within a single representative experiment. Forskolin (3 μM) elevated basal enzymatic activity 6-, 15-, and 10-fold at the 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors, respectively. Activity in the presence of forskolin alone was 80, 2197, and 3205 pmol/mg of protein per min, respectively.

stantia nigra),[8] and 5-HT_{1D} (guinea pig substantia nigra)[26] receptors was studied. As shown in Figure 1, parts a (5-HT_{1A}), b (5-HT_{1B}), and c (5-HT_{1D}), 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (1) is selective in its ability to function as a serotonin agonist. Compound 1 shows little to no ability to inhibit the forskolin-stimulated adenylate cyclase activity at the 5-HT_{1A} and 5-HT_{1D} receptors (EC_{50} > 10 μM), while showing strong agonist activity at the 5-HT_{1B} receptor (EC_{50} = 56 ± 5 nM). Table III summarizes these results. These results clearly show that 1 is functionally discriminatory within the series of 5-HT_1 receptors, acting as an agonist only at the 5-HT_{1B} receptor. 3-(1,2,5,6-Tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]-pyrid-5-one (1) represents the first truly selective agonist for the 5-HT_{1B} receptor.

It has been reported that direct infusion of serotonin into the paraventricular medial hypothalamus (PVN) of rats leads to a dose-dependent inhibition of feeding.[27] Additionally, it has been suggested that this inhibitory role of 5-HT on feeding behavior results from activation of 5-HT_{1B} receptors.[9] Therefore, the effect of direct injections of 1 and serotonin into the PVN of rats on feeding behavior was studied, and these results are summarized in Table IV. Injection of 32 μg of 5-HT directly into the PVN reduced food intake to 41% of the control (saline injected) level, while injection of only 16 μg of 1 directly into the PVN reduced food intake to *less than 5%* of the control level. This result is consistent with previous findings which ascribe satiety as a function of the rodent 5-HT_{1B} receptor.[9] Further studies to fully investigate the behavioral and physiological effects of 3-(1,2,5,6-tetrahydropyrid-4-yl)-pyrrolo[3,2-*b*]pyrid-5-one (1) are ongoing.

Discussion

3-(1,2,5,6-Tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (1) shows a selectivity for the 5-HT_{1B} receptor that is unparalleled by any other known agent. Most significant is the comparison between 1 and desmethyl-RU-24,969 (**2h**). While desmethyl-RU-24,969 (**2h**) was potent at 5-HT_1 receptors, it demonstrated little selectivity for the 5-HT_{1B} receptor. Compound 1 is spatially an atom-for-atom analogue of desmethyl-RU-24,969 (**2h**) with the only structural difference being the electronic configuration of the 5-oxygen substituent. The 5-hydroxy-4-azaindole portion (pyrrolo[3,2-*b*]pyrid-5-one) of 1 represents a rotationally restricted bioisosteric replacement of 5-hydroxyindole. The tautomerism of 2-pyridones (2-hydroxypyridines) has been well-studied,[16] and these molecules have been demonstrated to exist almost exclusively in the amide (i.e. pyridone) tautomer. Therefore, a 5-hydroxypyrrolo[3,2-*b*]pyridine would exist as the pyrrolo[3,2-*b*]pyrid-5-one. High-resolution X-ray analysis of 1 confirms that the pyrrolo[3,2-*b*]pyrid-5-one portion of the molecule exists as the amide tautomer. The amide C–O bond distance of 1.24 Å indicates that this bond is almost completely sp^2, and the amide C–N bond distance of 1.39 Å indicates that this bond is primarily sp^3. Additionally, the location of the amide proton on the ring nitrogen further confirms that 1 exists primarily in the amide tautomer, at least in the crystalline state.

In 5-hydroxy-3-(1,2,5,6-tetrahydropyridyl)indole (**2h**), the OH group has full ability to rotate, and thus, the energetically favorable area for hydrogen-bond-accepting interactions with a receptor can be seen as the light blue donut-shaped volume in Figure 2, parts a–c.[28] This promiscuity, however, is not available to 3-(1,2,5,6-tetrahydropyridyl)pyrrolo[3,2-*b*]pyrid-5-one (1) since the pyridone portion of the molecule exists almost exclusively

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(28) Contours were created with GRIN and GRID, version 5.15, supplied by Molecular Discovery Limited, Oxford OX2 9LL, England. See: Goodford, P. J. *J. Med. Chem.* **1985**, *28*, 849. The contours represent areas of favorable hydrogen-bonding interactions between the 5-HT_{1B} ligands [hydrogen-bond acceptors] and a serine-like hydroxyl probe [hydrogen-bond donor] at an energy value for bonding of −4.2 kcal/mol.

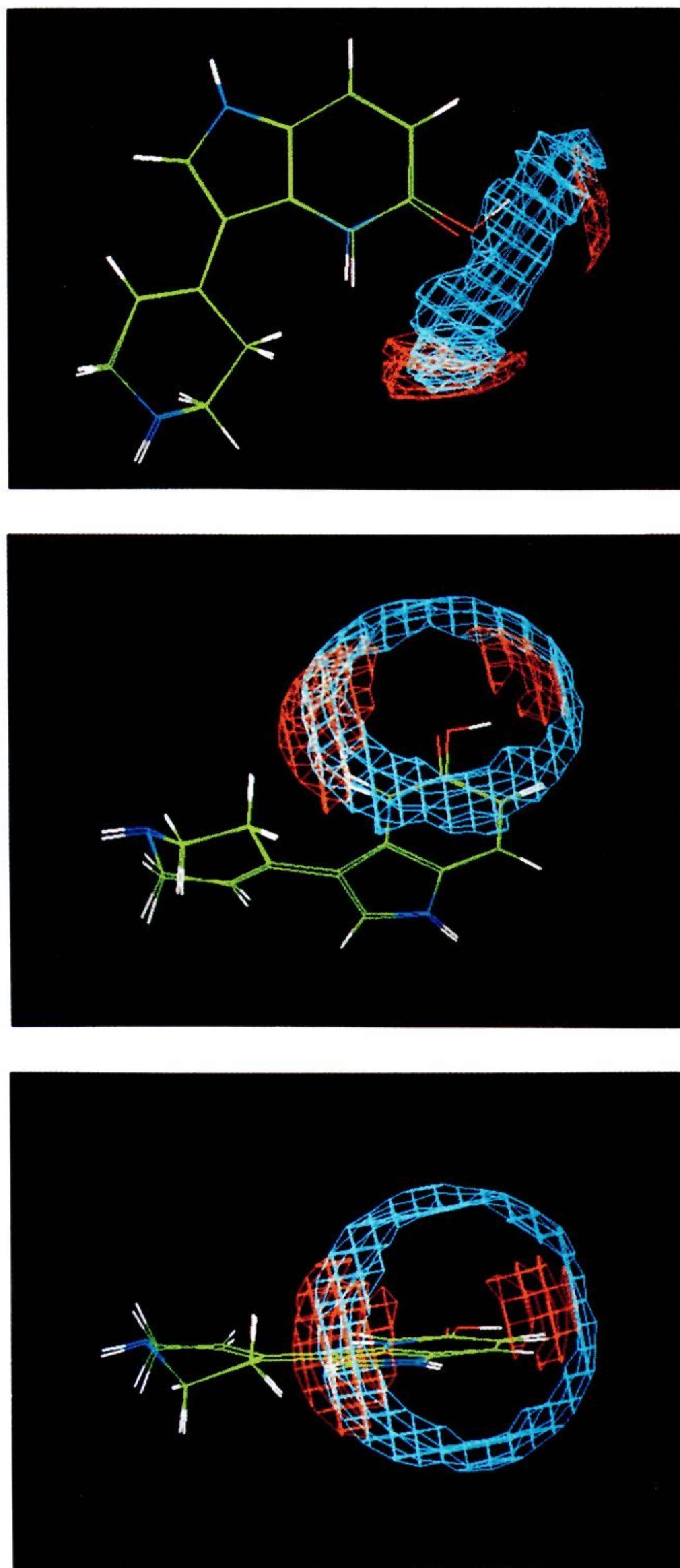

Figure 2. Contours were created with GRIN and GRID, version 5.15, supplied by Molecular Discovery Limited, Oxford OX2 9LL, England. The contours represent areas of favorable hydrogen-bonding interactions between the 5-HT_{1B} ligands (hydrogen-bond acceptors) and a serine-like hydroxyl probe (hydrogen-bond donor) at an energy value for bonding of −4.2 kcal/mol. Parts a–c (top, middle, and bottom, respectively) represent different views comparing the areas of potential hydrogen-bonding interactions between 3-(1,2,5,6-tetrahydropyridyl)pyrrolo[3,2-*b*]pyridine (**1**) (in red) and the 5-HT_{1B} receptor, and desmethyl-RU-24969 (**2h**) (in light blue) and the 5-HT_{1B} receptor.

as the amide tautomer. The electron density in the amide that would be utilized in any hydrogen-bond-accepting interaction with a receptor would therefore be directional. This is shown in the red contours in Figure 2, parts a–c. The only hydrogen-bond-accepting interactions available to compound 1 would lie in the plane of the aromatic ring. Consequently, pyrrolo[3,2-*b*]pyrid-5-one represents a rotationally restricted analogue of 5-hydroxyindole. More generally, a pyridone can represent an inplane rotationally restricted analogue of phenol in a hydrogen-bond-accepting interaction with a receptor or enzyme.

Herein lies the probable source of 5-HT_{1B} receptor selectivity of 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (1). The amide in 1 restricts hydrogen-bond-accepting interactions with a receptor to occur only in the plane of the aromatic ring. This type of restricted interaction accommodates the 5-HT_{1B} receptor only, almost to the exclusion of the other 5-HT_1 receptors. Desmethyl-RU-24,969 (**2h**) has free rotation about the 5-oxygen substituent, and this accommodates the hydrogen-bonding interactions of the all the 5-HT_1 receptors. Therefore, 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (1) represents an important breakthrough in the study of serotonin receptors as it helps to define important molecular recognition requirements for the individual 5-HT_1 receptors. In the 5-HT_{1B} receptor, the directionality of the hydrogen-bond-accepting interaction between the agonist and the receptor seems to lie in the plane of the indole molecule, while the same interaction in 5-HT_{1A} and 5-HT_{1D} receptors seems to require a different directionality, possibly above or below the plane of the indole ring. The rotationally restricted nature of the oxygen in the pyrrolo[3,2-*b*]pyridone of 1 appears to exclusively favor the directionality requirements of that area of the 5-HT_{1B} receptor.

The synthesis of radiolabeled 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (1) is presently underway and will be communicated shortly. A radiolabeled version of 1 should be superior to [^{3}H]-5-HT for the labeling 5-HT_{1B} receptors in brain tissue since its selectivity is expected to eliminate the need for masking agents. Additional pharmacological evaluations of 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (1) will also be reported at a later date.

Conclusion

3-(1,2,5,6-Tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (1, CP-93,129) represents an important tool in defining the pharmacology and molecular recognition requirements of serotonin receptors, specifically the 5-HT_{1B} receptor. Its potency at and virtual selectivity for the 5-HT_{1B} receptor should prove useful in unequivocally defining the brain distribution and function of 5-HT_{1B} receptors in rats and higher species. Since 1 inhibits forskolin-stimulated adenylate cyclase activity only at the 5-HT_{1B} receptor, 1 represents the first functionally selective agonist for that receptor. Direct injections of low doses of 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (1) into the PVN of rats greatly reduces their food intake, strongly implicating a key physiological role for hypothalamic 5-HT_{1B} receptors in the regulation of food intake in rodents. Future studies with 3-(1,2,5,6-tetrahydropyrid-4-yl)-pyrrolo[3,2-*b*]pyrid-5-one (1) should further our understanding of the distribution and function of those receptors in mammals.

The selectivity of 3-(1,2,5,6-tetrahydropyrid-4-yl)-pyrrolo[3,2-*b*]pyrid-5-one (1) results from the replacement of the 5-hydroxyindole portion of serotonin with pyrrolo-[3,2-*b*]pyrid-5-one, which forces the hydrogen-bonding-accepting interactions of the C5-substituent in 1 to occur in a directionally defined manner in the plane of the aromatic ring. This indicates that a pyridone, which is essentially locked in the amide tautomer, represents a rotationally restricted bioisosteric replacement for phenol

with its hydrogen-bond-accepting interactions occurring exclusively in the plane of the aromatic ring.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover open capillary melting point apparatus and are uncorrected. Infrared spectra were obtained from a Perkin-Elmer IR-283B infrared spectrophotometer, and NMR spectra were recorded on either a Bruker AM-300 (300-MHz) or a Varian XL300 (300-MHz) spectrometer. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent. Low-resolution mass spectra were obtained on a Finnigan 4310 instrument; high-resolution mass spectra were obtained on a AEI MS-30 instrument. Elemental analyses were performed at Central Research Division, Pfizer, Inc., Groton, CT and at Schwarzkopf Microanalytical Laboratory, Woodside, NY.

Commercial reagents (Aldrich Chemical Co.) were utilized without further purification, including Aldrich Gold-Label tetrahydrofuran (THF), diisopropylamine, and *N,N*-dimethylformamide (DMF). General procedures listed here represent typical reaction procedures for the class of compounds described. Chromatography refers to column chromatography performed with 32–63 μm silica gel and executed under nitrogen pressure (flash chromatography) conditions. Room temperature refers to 20–25 °C.

3-(1,2,5,6-Tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (1). Method A. To a stirred solution of sodium (0.80 g, 34.8 mmol, 7 equiv) in absolute methanol (30 mL) was added 7 (0.65 g, 4.84 mmol) and 4-piperidone monohydrate hydrochloride (1.89 g, 12.3 mmol, 2.5 equiv), and the resulting mixture was heated at reflux under nitrogen for 6 h. The reaction mixture was directly chromatographed with 10% triethylamine in methanol to yield a white foam. This foam was triturated in 5% methanol/ethyl acetate to yield 1 (0.68 g, 3.16 mmol, 65%) as a hygroscopic, off-white solid: mp 248.0 °C dec; IR (KBr) 3280, 1620, 1450, 1415, 1385, 1340 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.1 (br s, 1 H), 7.56 (d, J = 9.3 Hz, 1 H), 7.23 (s, 1 H), 6.39 (br m, 1 H), 6.15 (d, J = 8.9 Hz, 1 H), 3.33 (br m, 2 H), 2.88 (t, J = 5.6 Hz, 2 H), 2.26 (br m, 2 H); ^{13}C NMR (DMSO-d_6) δ 161.0, 132.3, 127.7, 126.2, 122.6, 121.8, 121.2, 112.9, 109.4, 44.7, 42.8, 27.8; LRMS m/z (relative intensity) 216 (27), 215 (M^+, 100), 214 (25), 198 (30), 197 (52), 186 (36), 185 (49), 173 (29), 172 (75), 171 (34), 147 (21); HRMS calculated for $C_{12}H_{13}N_3O$ 215.1058, found 215.1032 (2.6 × 10^{-3} amu deviation). **Method B.** To a stirred solution of 8 (3.22 g, 8.67 mmol) in absolute methanol (50 mL) at 0 °C was bubbled HCl(g) at a steady rate for approximately 15 min. The resulting reaction solution was stirred at room temperature under nitrogen for 24 h. The reaction was evaporated under reduced pressure, and the residue was dissolved in water (20 mL). The pH of this purple solution was adjusted to neutrality with solid sodium hydrogen carbonate, and the resulting aqueous solution was cooled at 0 °C. Slow crystallization afforded 1 (0.70 g) as a white solid: mp 245.0–246.0 °C dec; ^1H NMR (CD_3OD) δ 7.73 (d, J = 9.3 Hz, 1 H), 7.30 (s, 1 H), 6.30 (d, J = 9.3 Hz, 1 H), 6.00 (br m, 1 H), 4.94 (s, 5 exchangeable H), 3.69 (br m, 2 H), 3.29 (br t, 2 H), 2.61 (br m, 2 H). A second crop was collected by evaporating the filtrate under a stream of nitrogen and redissolving the residue in water (10 mL) with vigorous stirring. The undissolved solid was filtered to yield additional 8 (0.90 g, 7.43 mmol total, 86%) as an off-white powder: ^1H NMR (DMSO-d_6) δ 11.25 (br s, 1 H), 7.59 (d, J = 9.1 Hz, 1 H), 7.28 (s, 1 H), 6.5 (br s, 1 H), 6.43 (br m, 1 H), 6.19 (d, J = 9.1 Hz, 1 H), 3.39 (br m, 2 H), 2.95 (br m, 2 H), 2.32 (br m, 2 H); ^{13}C NMR (DMSO-d_6) δ 161.0, 132.5, 127.7, 126.2, 122.9, 121.3, 120.4, 112.6, 109.3, 44.1, 42.3, 27.0. The physical and spectral properties of these solids were consistent with those recorded for 8 in method A. Anal. ($C_{12}H_{13}N_3O{\cdot}2H_2O$) C, H, N. Recrystallization of 1 in refluxing methanol with cooling afforded crystals of sufficient quality for X-ray analysis.

2-*tert*-Butoxy-5-nitropyridine (4b). To a stirred solution of *tert*-butyl alcohol (70.00 g, 0.944 mol, 1.5 equiv) in anhydrous THF (2.0 L) at 0 °C under nitrogen was added sodium hydride (60% dispersion, 38.0 g, 0.950 mol, 1.5 equiv). The resultant mixture was stirred at room temperature under nitrogen for 5 h. This mixture was then cooled to −10 °C, and 2-chloro-5-nitropyridine (100.0 g, 0.631 mol) was added portionwise as a solid cautiously over the course of 1 h. The resultant reaction solution was allowed to warm to room temperature and was stirred at room temperature for 48 h. The reaction solution was then cooled in an ice bath, and a saturated solution of sodium hydrogen carbonate (500 mL) was added cautiously to the reaction solution, and this aqueous mixture was extracted with ethyl acetate (2 × 1000 mL). The extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the residual oil eluting first with hexanes then methylene chloride/hexanes gradient (1:4 to 1:1) afforded 4b as a pale yellow oil (85.61 g, 0.436 mol, 69%): IR 1600, 1580, 1510, 1470, 1390, 1365, 1345, 1320, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.01 (d, J = 2.9 Hz, 1 H), 8.25 (dd, J = 2.9 and 9.0 Hz, 1 H), 6.67 (d, J = 9.3 Hz, 1 H), 1.60 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 167.3, 144.3, 138.7, 133.4, 113.0, 82.8, 28.3; LRMS m/z (relative intensity) 197 (51), 196 (M^+, 28), 181 (32), 175 (24), 141 (34), 140 (100), 124 (42), 108 (37), 95 (49), 57 (96). Anal. ($C_9H_{12}N_2O_3$) C, H, N.

2-[6-(Benzyloxy)-3-nitro-2-pyridyl]acetonitrile (5a). A solution of 4a[17] (11.51 g, 50.0 mmol) and (4-chlorophenoxy)-acetonitrile (9.22 g, 55.0 mmol, 1.1 equiv) in anhydrous DMF (100 mL) was added dropwise to a stirred solution of potassium *tert*-butoxide (12.34 g, 110.0 mmol, 2.2 equiv) in anhydrous DMF (50 mL) under nitrogen at −10 °C. The resultant deep purple solution was stirred at −10 °C under nitrogen for 1 h, at which time an aqueous solution of 5% HCl (85 mL) was added dropwise. The resultant mixture was stirred at 0 °C, and the resulting precipitated solid was filtered to yield a brown solid (13.4 g). This solid was dissolved in methylene chloride (50 mL), and this solution was passed through a silica gel filter (approximately 500 g) followed by methylene chloride (4 L). This filtrate was evaporated under reduced pressure, and the residual oil was crystallized in ether/hexanes (1:1, 150 mL) to afford 5a (11.15 g, 41.4 mmol, 83%), as a white, crystalline solid: mp 63.0–67.0 °C; IR (KBr) 2260, 1590, 1515, 1470, 1455, 1450, 1420, 1350, 1295 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.41 (d, J = 8.8 Hz, 1 H), 7.56–7.31 (m, 5 H), 6.90 (d, J = 8.8 Hz, 1 H), 5.60 (s, 2 H), 4.43 (s, 2 H); LRMS m/z (relative intensity) 270 (12), 269 (M^+, 55), 107 (29), 92 (39), 91 (100), 65 (55). Anal. ($C_{14}H_{11}N_3O_3$) C, H, N.

2-(6-*tert*-Butoxy-3-nitro-2-pyridyl)acetonitrile (5b). To a stirred solution of potassium *tert*-butoxide (16.6 g, 148 mmol, 2.2 equiv) in anhydrous THF (150 mL) at −10 °C under nitrogen was added dropwise a solution of (4-chlorophenoxy)acetonitrile (12.40 g, 74 mmol, 1.1 equiv) and 4b (13.17 g, 67 mmol) in anhydrous THF (200 mL). The resulting deep purple solution was stirred at −10 °C under nitrogen for 3 h, at which time an aqueous solution of 5% HCl (115 mL) was added dropwise. The resultant aqueous mixture was extracted with ether (2 × 200 mL), and these extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was chromatographed with methylene chloride/hexanes (1:1) to afford 5b (9.56 g, 40.6 mmol, 61%) as a yellow solid: mp 70.0–71.0 °C; IR (KBr) 2255, 1590, 1505, 1450, 1415, 1385, 1365, 1355, 1305 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.34 (d, J = 9.1 Hz, 1 H), 6.72 (d, J = 9.1 Hz, 1 H), 4.44 (s, 2 H), 1.68 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 165.4, 146.0, 137.4, 136.1, 115.8, 113.4, 84.1, 28.3, 27.4; LRMS m/z (relative intensity) 235 (M^+, 6), 220 (5), 180 (41), 163 (6), 147 (7), 57 (100). Anal. ($C_{11}H_{13}N_3O_3$) C, H, N.

5-(Benzyloxy)pyrrolo[3,2-*b*]pyridine (6a). A mixture of Raney nickel (1 g, washed thoroughly with ethanol), 5a (6.39 g, 23.7 mmol), and absolute ethanol/acetic acid (7:3, 100 mL) was shaken under a hydrogen atmosphere (3 atm) at room temperature for 6 h. The resulting mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The residual oil was dissolved in water (25 mL), and pH was adjusted to 10 with solid sodium carbonate, and this mixture was extracted with ethyl acetate (3 × 25 mL). The extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure to yield an oil which was chromatographed with methylene chloride to yield 6a (1.45 g, 6.51 mmol, 27%) as an off-white solid: mp 146.0–148.0 °C; IR (KBr) 1605, 1580, 1500, 1470, 1450, 1410, 1300 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.47 (br m, 1 H), 7.57 (d, J = 9.0 Hz, 1 H), 7.50–7.48 (m, 2 H), 7.39–7.27 (m, 4 H), 6.67 (d, J = 8.4 Hz, 1 H), 6.60–6.58 (m, 1 H), 5.45 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 159.7, 142.6, 137.8, 128.4, 128.0, 127.7, 126.7, 124.5, 122.1, 106.0, 102.6, 67.7; LRMS m/z, (relative intensity) 225 (38), 224 (M^+, 89), 223 (40), 207 (20), 147 (61), 119 (31), 118 (75), 105 (30), 92 (22), 91 (100),

65 (36). Anal. ($C_{14}H_{12}N_2O$) C, H, N.

5-*tert*-Butoxypyrrolo[3,2-*b*]pyridine (6b). A mixture of **5b** (56.13 g, 0.239 mol), 10% Pd/C (6.5 g), and absolute ethanol (1.5 L) was shaken under a hydrogen atmosphere (3 atm) at room temperature for 3 h and then at 60 °C for 3 h. The resultant reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The residual solid was then dissolved in methylene chloride (100 mL), and this solution was passed through a silica gel filter (approximately 1 kg) followed by elution with methylene chloride (6 L). This filtrate was evaporated under reduced pressure to afford **6b** (35.04 g, 0.184 mol, 72%) as a white, crystalline solid: mp 110.0–111.0 °C; IR (KBr) 1615, 1570, 1470, 1450, 1410, 1390, 1365, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.1 (br s, NH), 7.52 (d, J = 8.6 Hz, 1 H), 7.29 (br t, 1 H), 6.56 (d, J = 8.5 Hz, 1 H), 6.54 (br t, 1 H), 1.57 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 159.1, 143.1, 126.6, 124.6, 121.1, 109.4, 103.0, 79.2, 29.0; LRMS m/z (relative intensity) 191 (22), 190 (M$^+$, 54), 175 (13), 149 (26), 135 (59), 134 (100), 106 (79), 105 (55), 79 (56). Anal. ($C_{11}H_{14}N_2O$) C, H, N.

Pyrrolo[3,2-*b*]pyrid-5-one (7). A mixture of **6a** (1.38 g, 6.15 mmol) and 5% Pd/C (0.30 g) in absolute ethanol (25 mL) was shaken under a hydrogen atmosphere (3 atm) at room temperature for 30 min. The resulting mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The residual solid was triturated in ether to yield **7** (0.80 g, 5.96 mmol, 97%) as an off-white, crystalline solid: mp 280.0–282.0 °C: IR (KBr) 1640, 1615, 1605, 1455, 1430, 1400, 1380, 1365 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.4 (br m, 2 H), 7.56 (d, J = 9.7 Hz, 1 H), 7.16 (d, J = 3.1 Hz, 1 H), 6.01–5.93 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 162.0, 131.9, 127.9, 125.0, 118.2, 112.2, 94.5; LRMS m/z (relative intensity) 135 (41), 134 (M$^+$, 100), 106 (66), 105 (42), 79 (59), 53 (31), 52 (52). Anal. ($C_7H_6N_2O$) C, H, N.

5-*tert*-Butoxy-3-[4-(*tert*-butoxycarbonyl)-1,2,5,6-tetrahydropyridyl]pyrrolo[3,2-*b*]pyridine (8). To a solution of sodium (1.75 g, 76.1 mmol, 6 equiv) in absolute methanol (50 mL) were added **6b** (2.40 g, 12.62 mmol) and *N*-(*tert*-butoxycarbonyl)-4-piperidone (5.03 g, 25.2 mmol, 2 equiv), and the resulting mixture was heated at reflux under nitrogen for 3 h. The reaction mixture was then concentrated via evaporation under reduced pressure, and the residue was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was chromatographed with ether to afford a white foam which was crystallized in ether/hexanes (1:1, 25 mL) to afford **8** (3.64 g, 9.77 mmol, 77%) as a white solid: mp 137.0–139.0 °C; IR (KBr) 3240, 1670, 1650, 1575, 1480, 1465, 1455, 1425, 1415, 1365 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.61 (br d, NH), 7.47 (d, J = 8.7 Hz, 1 H), 7.19 (d, J = 2.7 Hz, 1 H), 7.14 (br m, 1 H), 6.53 (d, J = 8.7 Hz, 1 H), 4.15 (br m, 2 H), 3.66 (t, J = 5.6 Hz, 2 H), 2.54 (br m, 2 H), 1.62 (s, 9 H), 1.49 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 159.0, 155.1, 139.7, 128.4, 125.4, 123.0, 121.6, 118.8, 116.3, 108.8, 79.6, 78.8, 43.9, 40.6, 39.8, 28.8, 28.6; LRMS m/z (relative intensity) 371 (M$^+$, 12), 315 (19), 314 (65), 259 (54), 258 (100), 214 (26), 197 (39), 185 (59), 172 (36), 57 (64). Anal. ($C_{21}H_{29}N_3O_3$) C, H, N.

Pharmacology. Binding Experiments. Receptor binding was conducted by using methods previously reported in the literature: 5-HT_{1A} assay using rat cortex and [^{3}H]-8-OH-DPAT;[29] 5-HT_{1B} assay using rat cortex and [^{3}H]serotonin;[30] 5-HT_{1C} assay using pig choroid plexus and [^{3}H]mesulergine;[31] 5-HT_{1D} assay using bovine caudate and [^{3}H]serotonin;[32] 5-HT_2 assay using rat anterior cortex and [^{3}H]ketanserin.[33] The concentration of radioligand used in competition studies was approximately equal to the K_D of the binding system.

PVN Experiments. Male CD rats (170–190 g, Charles River) were housed on a 12-h light-dark cycle. Food (PROLAB; rat, mouse, and hamster 3000 animal diet) and water were freely available unless otherwise stated. Rats were anesthetized with equithesin (3.25 mg/kg, ip), and a guide cannula (Plastic Products) was implanted approximately 1 mm above the paraventricular nucleus of the hypothalamus (PVN) by using coordinates according to Paxinos and Watson[34] as follows: A, −1.1 mm (bregma); L, 0.3 mm; H, 7.5 mm below dura; incisor bar, −3.3 mm. The guide was fitted with a dummy cannula (Plastic Products) and the animals were transferred to individual cages (24 × 46 × 22 cm). Seven days after surgery, food pellets but not water were removed from their cages. Twenty-four hours later, the dummy cannula from each animal was removed and an infusion cannula (Plastic Products), projecting 1 mm past the tip of the guide cannula, was inserted into the PVN and connected via a length of PE-50 polyethylene tubing to a 5 μL Hamilton syringe. Rats were infused at 1 μL/min with either 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo-[3,2-*b*]pyrid-5-one (**1**; 16 μg in 0.9% NaCl), serotonin[35] (32 μg in 0.9% NaCl), or vehicle (0.9% NaCl). The rats were then placed individually in plastic test chambers (16 × 46 × 18 cm) with a weighed amount of food pellets on the floor of the chamber. Thirty minutes later the rats were returned to their home cages. The difference in food weight was the amount eaten. The results were analyzed by two-tailed Student's t tests. The verification of the cannula placement was performed as follows. Rats were killed by decapitation. Brains were removed and fixed in a 10% sucrose-buffered formalin solution for at least 2 days. Frozen sections (50 μm), taken in the coronal plane, were mounted and stained with neutral red. Sections were viewed relative to the stereotaxic atlas of Paxinos and Watson.[34] The cannula track was noted to end in or alongside the PVN. Data from animals with cannula outside the PVN were not used.

Adenylate Cyclase Experiments. Washed membranes were prepared from freshly dissected guinea pig hippocampus, rat substantia nigra, or guinea pig substantia nigra. Tissue was incubated at 30 °C in a reaction medium containing [α-^{32}P]ATP, as described previously.[36] Samples also contained buffer or 3 μM forskolin, along with varying concentrations of serotonin or 3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one (**1**). Following termination of the reaction by addition of 3% sodium dodecyl sulfate, [^{32}P]cAMP was separated from [^{32}P]ATP by using a two-column chromatographic procedure.[37] The amount of [^{32}P]cAMP formed was determined by liquid-scintillation counting, with results ultimately expressed in units of picomole formed per milligram of protein per minute. EC_{50} values (mean ± SEM) were determined by performing a minimum of three experiments for each compound at each receptor subtype.

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Supplementary Material Available: X-ray data on compound **1** and details of synthesis for compounds **2d**,**h**, **3a**,**b**, and **9–11** (15 pages). Ordering information is given on any current masthead page.

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