The Serotonin 5-HT$_4$ Receptor. 2. Structure–Activity Studies of the Indole Carbazimidamide Class of Agonists[1]

Karl-Heinz Buchheit, Rainer Gamse, Rudolf Giger, Daniel Hoyer, Francois Klein, Edgar Klöppner, Hans-Jürgen Pfannkuche, and Henri Mattes*

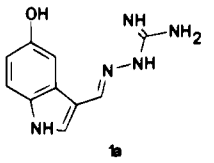
Preclinical Research, Sandoz Pharma Limited, CH-4002 Basel, Switzerland

Received November 15, 1994[⊗]

A number of substituted indole carbazimidamides were prepared and evaluated as 5-HT$_4$ receptor agonists by using the isolated field-stimulated guinea pig ileum preparation. Their selectivity for the 5-HT$_4$ receptor was established by examining their affinity for other 5-HT receptors using radioligand-binding techniques. Several selective and highly potent full as well as partial agonists emerged from this study. For example, **1b,d** were found to be the most potent, full 5-HT$_4$ receptor agonists described so far (EC_{50} = 0.5 and 0.8 nM, respectively), being 6 and 4 times more potent than serotonin itself. On the other hand, **5b** and **1h** appeared as partial 5-HT$_4$ receptor agonists in the nonstimulated guinea pig ileum preparation with potencies, evaluated against serotonin action, respectively similar (**5b**, K_i = 12 nM) to and 300-fold higher (**1h**, K_i = 0.04 nM) than serotonin.

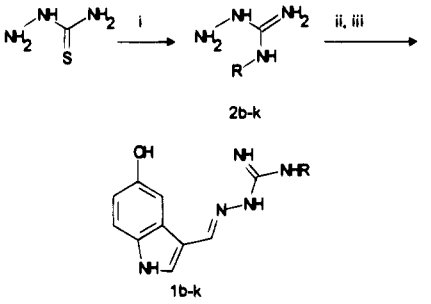
The 5-HT$_4$ class of serotonin receptors is currently of clinical interest because of its role in the regulation of gastrointestinal motility[2] and possible involvement in various affective disorders.[3] Three major classes of 5-HT$_4$ receptor agonists are known to date: indolalkylamines (like serotonin), benzamides (like cisapride), and benzimidazolones (like BIMU8). All types of ligands are in general nonselective. They bind to multiple populations of serotonin as well as other monoamine receptors[1] which limits their clinical use. We reported in the preceding paper of this series on the design and synthesis of the prototype of a new class of 5-HT$_4$ receptor agonists based on an indole nucleus,[1] like **1** (Chart 1). The key pharmacophoric elements of this new ligand can be regarded as an aromatic nucleus, bearing a substituent capable of donating a hydrogen bond, and a bifunctional basic residue (guanidine) as a potential partner in a dual interaction[4] with a carboxylic acid. In this paper, we describe structure–activity relationship data for this new ligand class which enabled us to refine our previous 5-HT$_4$ agonist recognition site model and in particular to identify regions responsible for secondary lipophilic interactions.

Chart 1



1a

Scheme 1[a]

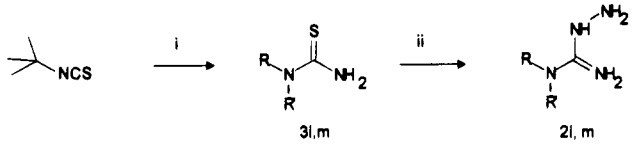


[a] Reagents: (i) MeI then RNH_2; (ii) 5-(benzyloxy)indole-3-carbaldehyde, MeOH/HCl; (iii) H_2, Pd/C.

Chemistry

The carbazimidamides **1a–n** (Table 1) were obtained by condensation of 5-(benzyloxy)indole-3-carbaldehyde with the respective aminoguanidine derivatives **2** under acidic conditions (method A) followed by hydrogenolitic removal of the benzyl group (Scheme 1). Monoalkylated aminoguanidines **2b–k** were prepared by alkylating thiosemicarbazide with MeI (Scheme 1) and subsequent reaction with the appropriate primary amine (method B). The sluggish reaction of *S*-methyl isothiosemicarbazide hydroiodide with secondary amines led us to prepare *N,N*-dialkylated-*N'*-aminoguanidines **2l,m** as indicated in Scheme 2. *t*-BuNCS was condensed with the appropriate secondary amines to yield, after cleavage of the *t*-Bu protecting group with HCl, the thioureas **3l,m** (method C). Subsequent alkylation with MeI and finally reaction with hydrazine (method D) produced **2l,m** which were used as previously described to prepare **1l,m** (Table 1). **1o,p** were obtained by reaction of **1a** with respectively $C_6H_{11}NCO$ and $(PrCO)_2O$ (method E). The cyclic aminoguanidines analogues **4a–d** (Table 2) were prepared from known hydrazine derivatives (method A), and **4e,f** were prepared according to method D from the corresponding *N,N'*-di- or trisubstituted thioureas.

Scheme 2[a]



[a] Reagents: (i) RR'NH then HCl; (ii) MeI then NH_2NH_2.

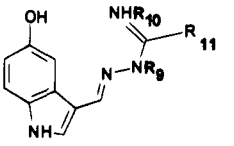
Ether and carbamate derivatives **5b–m** (Table 3) were prepared by standard procedures from 3-methyl-4-nitrophenol (Scheme 3). Alkylations or carbamoylations with the appropriate alkyl halides or ClCOX followed by reaction with *t*-BuOCH$(NMe_2)_2$ and hydro-

* Author for correspondence.

[⊗] Abstract published in *Advance ACS Abstracts*, June 1, 1995.

0022-2623/95/1838-2331$09.00/0

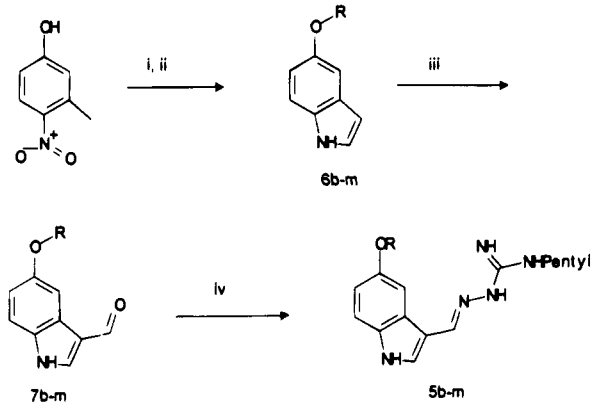
Table 1. 5-HT_4 Receptor Agonism of Alkylated Carbazimidamides



no.	R_9	R_{10}	R_{11}	mp, °C	formula[a]	pD_2 (SEM)[b]	E[c]
1a	H	H	NH_2	247	$C_{10}H_{11}N_5O$·HCl	8.8 (0.2)	1.5
1b	H	pentyl	NH_2	128	$C_{15}H_{21}N_5O$	9.3 (0.1)	0.9
1c	H	octyl	NH_2	amorph[d]	$C_{18}H_{27}N_5O$	<4	0
1d	H	CH_2CH_2Ph	NH_2	130	$C_{18}H_{19}N_5O$	9.1 (0.2)	1.0
1e	H	$(CH_2)_2$-*o*-Cl-Ph	NH_2	122	$C_{18}H_{18}N_5OCl$	8.5 (0.1)	0.5
1f	H	$(CH_2)_2$-*p*-Cl-Ph	NH_2	115	$C_{18}H_{18}N_5OCl$	8.4 (0.3)	0.2
1g	H	$(CH_2)_2$-*m*-OMe-Ph	NH_2	120	$C_{19}H_{21}N_5O_2$	8.9 (0.1)	0.5
1h	H	$(CH_2)_2$-*m*,*p*-diCl-Ph	NH_2	274	$C_{18}H_{17}N_5OCl_2$·HCl	>10	0.1
1i	H	$(CH_2)_3Ph$	NH_2	amorph[d]	$C_{19}H_{21}N_5O$	8.5 (0.1)	0.4
1j	H	$(CH_2)_3OH$	NH_2	140	$C_{13}H_{17}N_5O_2$	7.7 (0.1)	0.7
1k	H	$(CH_2)_2NHCOPh$	NH_2	110	$C_{19}H_{20}N_6O_2$	8.5 (0.2)	0.5
1l	H	H	NMeheptyl	amorph[d]	$C_{18}H_{27}N_5O$	8.0 (0.2)	1.6
1m	H	H	NMepentyl	100	$C_{16}H_{23}N_5O$	7.7 (0.1)	0.3
1n	Me	H	NH_2	175	$C_{11}H_{13}N_5O$	5.8 (0.1)	0.5
1o	H	H	$NHCONHC_6H_{11}$	135	$C_{17}H_{22}N_6O_2$	8.5 (0.1)	0.5
1p	H	H	NHCOPr	amorph[d]	$C_{14}H_{17}N_5O_2$	7.7 (0.2)	1.0

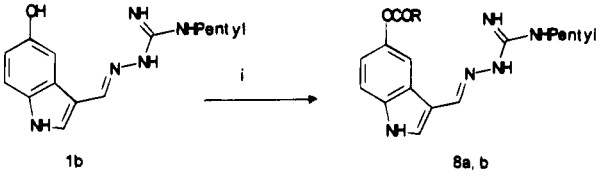
[a] All analyses were within 0.4% of the theoretical values. [b] Assay conditions: ability of compounds to enhance the "twitch" response in the electrically stimulated guinea pig ileum preparation (see the Experimental Section for details). SEM = standard error of the mean from $n > 3$. [c] Efficacy relative to serotonin = 1. [d] Amorphous solid.

Scheme 3[a]



[a] Reagents: (i) K_2CO_3, RBr or ClCOX; (ii) *t*-BuOCH(NMe_2)$_2$ then H_2, Pd/C; (iii) DMF, $POCl_3$; (iv) *N*-pentyl-*N'*-aminoguanidine, MeOH/HCl.

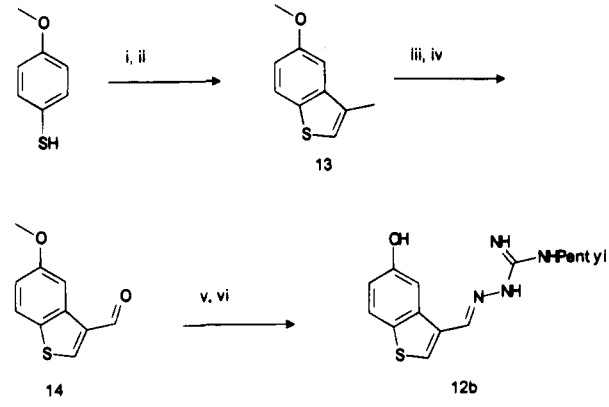
Scheme 4[a]



[a] Reagents: (i) $(RCO)_2O$, CF_3COOH.

genation[5] led to the required indole derivatives **6b**–**m** (method F). Vilsmeier–Haack[6] formylation gave aldehydes **7b**–**m** which were condensed with *N*-pentyl-*N'*-aminoguanidine under acidic conditions to afford carbazimidamides **5b**–**m**. Acylation of **1b** with the appropriate acyl chlorides (Scheme **4**) (method G) in trifluoroacetic acid led to derivatives **8a,b**. **9a** was prepared by hydrogenating the corresponding 5-nitro analogue over palladium on charcoal. The indole derivative **10**, required to prepare **9b**, was obtained by reacting 5-aminoindole with methanesulfonyl chloride and subsequent formylation with DMF/$POCl_3$. The known

Scheme 5[a]



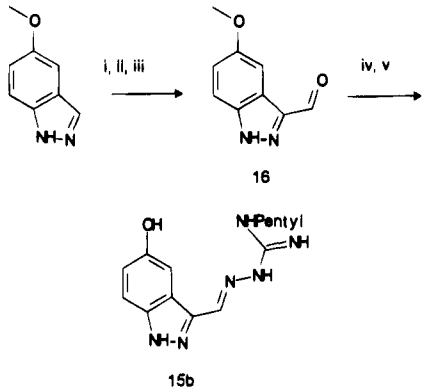
[a] Reagents: (i) K_2CO_3, chloroacetone; (ii) PPA; (iii) NBS; (iv) hexamethylenetetramine, AcOH; (v) BBr_3; (vi) *N*-pentyl-*N'*-aminoguanidine, MeOH/HCl.

5-(trimethylsilyl)indole[7] was formylated and condensed with *N*-pentyl-*N'*-aminoguanidine to yield **11**.

12a,b (Table 4) were prepared as illustrated in Scheme 5.[8] 4-Methoxythiophenol was alkylated with chloroacetone, and the thiophenyl ketone was cyclized with polyphosphoric acid to obtain **13**. **13** was then brominated with NBS, and the bromide was treated with hexamethylenetetramine under acidic conditions to yield **14** which was condensed in a conventional manner with *N*-pentyl-*N'*-aminoguanidine to afford **12a**. Alternatively, **14** was treated with BBr_3 and condensed with *N*-pentyl-*N'*-aminoguanidine to yield **12b**.

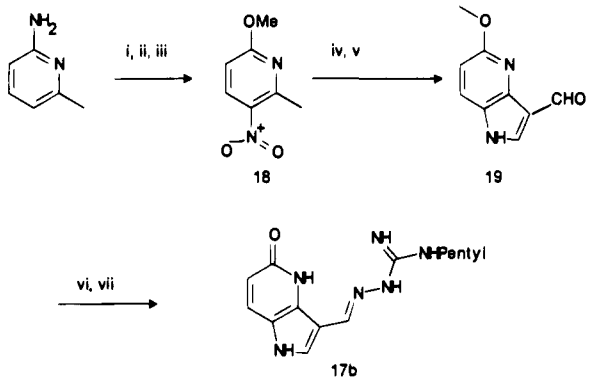
Scheme 6 outlines the preparation of **15a,b** (Table 4). The known 5-methoxyindazole[9] was carboxylated at position 3 with carbon dioxide and potassium carbonate to the 3-carboxy derivative which was reduced with lithium aluminum hydride followed by reoxidation with MnO_2 to give the required 5-methoxyindazole-3-carbaldehyde (**16**). The aldehyde **16** was utilized in one of two ways. Condensation with *N*-pentyl-*N'*-aminoguanidine afforded **15a**. Alternatively, the methoxy group was

Scheme 6[a]



[a] Reagents: (i) K_2CO_3, CO_2; (ii) LAH; (iii) MnO_2; (iv) BBr_3; (v) *N*-pentyl-*N'*-aminoguanidine, MeOH/HCl.

Scheme 7[a]



[a] Reagents: (i) HNO_2; (ii) isoamyl nitrite/$CuCl_2$; (iii) MeONa; (iv) *t*-BuOCH(NMe$_2$)$_2$ then H_2, Pd/C; (v) DMF, $POCl_3$; (vi) *N*-pentyl-*N'*-aminoguanidine, MeOH/HCl; (vii) HBr, AcOH.

cleaved with BBr_3, and the phenol was condensed with *N*-pentyl-*N'*-aminoguanidine to obtain **15b**.

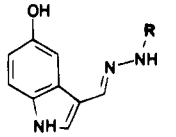
17a,b were prepared as shown in Scheme 7. 6-Amino-2-picoline was nitrosylated and reacted with isoamyl nitrite/$CuCl_2$ and subsequently with MeONa to yield **18**.[10] **18** was subjected to the procedures used previously for the synthesis of indole derivatives (method F) and formylated with DMF/$POCl_3$ to give **19**. **19** was condensed with *N*-pentyl-*N'*-aminoguanidine to afford **17a**. Alternatively, the methoxy group of **19** was cleaved with HBr in acetic acid, and the azaindole derivative was condensed with *N*-pentyl-*N'*-aminoguanidine to afford **17b**.

Results and Discussion

Interaction of Compounds with the 5-HT$_4$ Receptor. The activity of a number of known agonists (see **1**) and the new compounds (Tables 2–5) at the 5-HT$_4$ receptor was measured using the field-stimulated guinea pig ileum longitudinal muscle preparation according to previously described methods.[11] All compounds described in this paper behaved as agonists in this assay, as well as in a variety of in vivo models (stimulation of myoelectric activity in dogs, gastric emptying in rats, small intestinal transit in guinea pigs), results of which will be reported separately.

We first tried to optimize the environment of the charged guanidine (Tables 1, 2) using **1** as a starting point for the structure–activity relationship (SAR). According to our 5-HT$_4$ receptor model, a fairly large

Table 2. 5-HT$_4$ Receptor Agonism of Cyclic Carbazimidamides

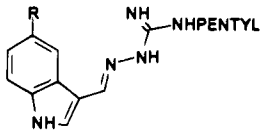


no.	R	mp, °C	formula[a]	pD_2 (SEM)[b]	E[c]
4a		amorp.[d]	$C_{14}H_{12}N_5O$ .HCl	6.1 (0.1)	0.8
4b		297	$C_{13}H_{14}N_4O$ .HCl	7.1 (0.1)	1.0
4c		165	$C_{12}H_{12}N_4OS$	6.5 (0.3)	0.5
4d		140	$C_{12}H_{11}N_5O$	8.2 (0.2)	1.0
4e		178	$C_{12}H_{13}N_5O$	7.3 (0.1)	0.7
4f		amorp.[d]	$C_{13}H_{15}N_5O$	<4	0

[a] All analyses were within 0.4% of the theoretical values. [b] Assay conditions: ability of compounds to enhance the "twitch" response in the electrically stimulated guinea pig ileum preparation (see the Experimental Section for details). SEM = standard error of the mean from $n > 3$. [c] Efficacy relative to serotonin = 1. [d] Amorphous solid.

lipophilic region, able to accommodate the side chain of cisapride or the quinuclidine ring of zacopride, was located near the basic nitrogen recognition site. In the series bearing one substituent on the guanidine function (**1b–o**), increasing the size and the lipophilic character of the side chain effectively resulted in increased activity. Among aliphatic substituents, the pentyl side chain (**1b**) was found to be optimal in terms of both potency and efficacy. The compound is a full agonist in this preparation (90% of the maximum efficacy of serotonin) with a potency (EC_{50} = 0.5 nM) 6 times higher than that of serotonin at the 5-HT$_4$ receptor. The pentyl side chain could be replaced by a phenethyl group (**1d**) without major loss of potency (EC_{50} = 0.8 nM, IA = 1.0). In line with the theory of Ariens,[12] a further increase in the size of this substituent resulted in decreased efficacy (e.g., **1e–i**). The *m*-,*p*-dichloro-substituted phenethyl derivative **1h** proved however to be the most potent partial agonist (EC_{50} < 0.1 nM, IA = 0.1) in this new class of compounds. Clearly these lipophilic substituents provide important secondary binding interactions with the putative lipophilic region present in the 5-HT$_4$ receptor. Accordingly, the introduction of more polar substituents (**1j,k**) resulted in reduced agonist activity at the 5-HT$_4$ receptor (EC_{50} respectively 10 and 18 nM). Polysubstituted derivatives were synthesized

Table 3. 5-HT_4 Receptor Agonism of Substituted Indole Carbazimidamides



no.	R	mp, °C	formula[a]	pD_2 (SEM)[b]	E[c]
5a	H	125	$C_{15}H_{21}N_5$	<6.0	0.1
5b	OMe	155	$C_{16}H_{23}N_5O$	6.9 (0.1)	0.2
5c	OEt	114	$C_{17}H_{25}N_5O$	<7	0.1
5d	O*i*-Pr	90	$C_{18}H_{27}N_5O$	6.8 (0.3)	0.5
5e	OBn	138	$C_{22}H_{27}N_5O$	<6.0	1.8
5f	$OCH_2CH{=}CMe_2$	amorph[d]	$C_{20}H_{29}N_5O$	8.15 (0.2)	2.2
5g	$O(CH_2)_2CMe_2$	amorph[d]	$C_{20}H_{31}N_5O$	5.9 (0.1)	0.8
5h	OCH_2OMe	108	$C_{17}H_{25}N_5O_2$	7.5 (0.4)	0.7
5i	$OCONMe_2$	90	$C_{18}H_{26}N_6O_2$	<7	0.7
5j	OCH_2CONMe_2	160	$C_{19}H_{28}N_6O_2$	7.3 (0.3)	1.4
5k	$O(CH_2)_2NMe_2$	amorph[d]	$C_{19}H_{30}N_6O$	7.6 (0.1)	0.3
5l	$O(CH_2)_2OMe$	amorph[d]	$C_{18}H_{27}N_5O_2$	6.6 (0.8)	0.7
5m	$O(CH_2)_2OH$	amorph[d]	$C_{17}H_{25}N_5O_2$	7.4 (0.2)	1.0
8a	OCOPh	155	$C_{22}H_235N_5O_2{\cdot}CH_2O_3$	7.0 (0.1)	0.5
8b	OCOpentyl	205	$C_{21}H_{31}N_5O_2{\cdot}C_2HO_2F_3$	<4	0
9a	NH_2	100	$C_{15}H_{22}N_6$	7.6 (0.2)	1.6
9b	$NHSO_2Me$	115	$C_{16}H_{24}N_6O_2S$	<4	0
11	$SiMe_3$	amorph[d]	$C_{18}H_{29}N_5Si$	<5.5	

[a] All analyses (except for **8a**, see the Experimental Section) were within 0.4% of the theoretical values. [b] Assay conditions: ability of compounds to enhance the "twitch" response in the electrically stimulated guinea pig ileum preparation (see the Experimental Section for details). SEM = standard error of the mean from $n > 3$. [c] Efficacy relative to serotonin = 1. [d] Amorphous solid.

in an attempt to optimize the lipophilic interactions in the vicinity of the guanidine: *N,N*-disubstitutions (**1l,m**) caused a 10-fold reduction in activity, constraining the guanidine group into a five-membered ring (**4e**) resulted in a 100-fold drop in activity, and trisubstitution (**4f**) completely abolished it.

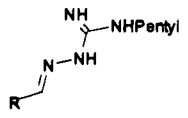
Although modifications of the aminoguanidine group resulted in decreased potency, they were consistent with the hypothesis of a dual type binding mode for this basic head group. Replacing one nitrogen in **4e** by carbon (**4b**) or sulfur (**4c**) retained activity. On the other hand the *N,N*-dimethylhydrazone of 5-hydroxyindole-3-carbaldehyde (structure not shown), lacking the second nitrogen needed to increase binding interactions, only displayed weak activity (EC_{50} = 800 nM) at the 5-HT_4 receptor. The severely reduced activity of the methylated analogue **1n** (EC_{50} = 1580 nM) might be due to a disruption of the twin nitrogen–twin oxygen interaction of the guanidine with the putative carboxylic acid counterpart.

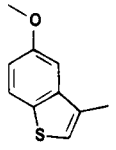
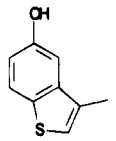
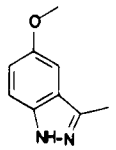
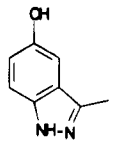
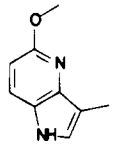
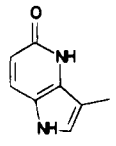
The importance of the hydroxy substituent on indole, as a hydrogen-bond donor, for high potency is emphasized by the reduced activity of **5a–m**, **8a,b**, **9a,b**, and **11** (Table 3). Removal of this substituent resulted in a dramatic drop in potency and efficacy (**5a**, EC_{50} > 1000 nM, IA = 0.1). Introducing a methoxy group at the 5-position of the indole nucleus yielded a more potent partial agonist (compare **5a** and **5b**, EC_{50} = 100 nM, IA = 0.2), possibly reflecting the hydrogen-bond-accepting capability of the ether function. Increasing the size of the ether substituent led in some cases to a further improvement in potency and efficacy (e.g., **5f**, EC_{50} = 7 nM, IA = 2.2) which might be accounted for by secondary lipophilic interactions. However, variations in the size and shape of this ether function (e.g., **5e**, EC_{50} > 1000 nM, and **5g**, EC_{50} = 1259 nM) highlighted the steric limitations around the 5-hydroxy binding site. In line with these findings, the azaindole derivative **17b** (EC_{50} = 16 nM, IA = 0.9), sharing minimal steric requirements with good hydrogen-bond-accepting and/or -donating capabilities, can be regarded as a good bioisosteric replacement for 5-hydroxyindole at the 5-HT_4 agonist recognition site. Azaindoles have previously been shown to be excellent replacements for indoles at the 5-HT_{1B} receptor.[13] Substitution at the 5-position of the indole nucleus by larger polar (e.g., **9b**, EC_{50} > 10 000 nM) or lipophilic (e.g., **11**, EC_{50} > 3000 nM) substituents abolished activity.

Finally, a variety of alternative aromatic systems (Table 4) were evaluated in an effort to identify replacements for indole:replacement by benzothiophene (**12a,b**), indazole (**15a,b**), or substituted phenyl groups (structures not shown) severely reduced or abolished activity, emphasizing the subtle electronic and steric factors governing the aromatic binding site.

Selectivity. The pharmacological selectivity of some of the new compounds was examined in a variety of radioligand-binding assays (Table 5). The low intrinsic activity of **1h** and **5b** led us to determine their potencies as antagonists of serotonin-evoked contractions in the nonstimulated guinea pig ileum assay. The pA_2 (for competitive antagonists) or pD_2' (for noncompetitive agonists) values provided a better estimation of the affinities of these compounds for the 5-HT_4 receptor and are compared with binding affinities for other receptors in Table 5. While all described compounds exhibited a high selectivity in 5-HT_4 vs 5-HT_3 affinity, structural manipulations of **1a** led to profound effects on selectivity vs other 5-HT receptors. Introduction of the dichlorophenethyl substituent (**1h**) on guanidine resulted in the most selective 5-HT_4 ligand with over 4000-fold selectivity vs all other serotonin receptors. With this substituent, we clearly identified a fairly large lipophilic pocket in the 5-HT_4 recognition site which is not present, at least at that position, in the other 5-HT receptors studied. Dialkylation of the guanidine led to an 8-fold decreased selectivity in 5-HT_4 vs 5-HT_{1A} affinity (compare **1b** and **1l**) and a 40-fold increased selectivity in 5-HT_4 vs 5-HT_{1D} affinity. Alkylation of the 5-OH function produced divergent effects. Methylation slightly decreased 5-HT_4 vs 5-HT_{2C} selectivity (compare **5b** and

Table 4. 5-HT$_4$ Receptor Agonism of Aromatic Carbazimidamides



no.	R	mp, °C	formula[a]	pD_2 (SEM)[b]	E[c]
12a		107	$C_{16}H_{22}N_4OS$	6.1 (0.2)	0.5
12b		155	$C_{15}H_{20}N_4OS$	< 7	--
15a		155	$C_{15}H_{22}N_6O$	<4	0
15b		115	$C_{14}H_{20}N_6O$	<4	0
17a		157	$C_{15}H_{22}N_6O.$ $C_4H_4O_4$	7.1 (0.1)	1.0
17b		am.[d]	$C_{14}H_{20}N_6O$	7.8 (0.2)	0.9

[a] All analyses were within 0.4% of the theoretical values. [b] Assay conditions: ability of compounds to enhance the "twitch" response in the electrically stimulated guinea pig ileum preparation (see the Experimental Section for details). SEM = standard error of the mean from $n > 3$. [c] Efficacy relative to serotonin = 1. [d] Amorphous solid.

1b) and did not alter the 25−200-fold 5-HT$_4$ selectivity over all other receptors studied. On the other hand, introduction of the dimethylallyl group almost completely abolished 5-HT$_{1A}$, 5-HT$_{1D}$, and 5-HT$_{2A}$ affinity (compare **1f** and **1b**). The secondary lipophilic interactions around the 5-OH binding site thus appear as a feature of the 5-HT$_4$ receptor which is not shared by other members (except 5-HT$_{2C}$) of the serotonin receptor family. Finally, the azaindole bioisoster **17b** displayed roughly the same 5-HT$_4$ selectivity as **1b**.

Conclusion

The substituted indole carbazimidamides described in this paper represent a completely novel class of potent and selective agonists at the 5-HT$_4$ receptor. Structural variations of **1a**, the prototype of this new class, have led to **1b,d**, the most potent, full agonists known to date at this receptor with selectivity ranging from 20- to 500-fold vs other serotonin receptors. Moreover, we have been able to prepare extremely potent, partial 5-HT$_4$ agonists exhibiting affinities similar (e.g., **5b**) to or 100-fold higher (**1h**) than serotonin which could be very useful in light of the propensity of this receptor to undergo desensitization.[14] The in vitro 5-HT$_4$ agonist properties of this new class translates well into potent gastrointestinal prokinetic activity in vivo, the results of which will be reported elsewhere. Additionally, their high polarity which limits diffusion into the central nervous system should undoubtedly make them useful and selective agents for the treatment of functional gastrointestinal disorders.

Table 5. Receptor Profiles of Some New 5-HT$_4$ Receptor Agonists: pD_2 (5-HT$_4$) or pK_i[a,b] (SEM) (All others)

no.	5-HT$_4$	5-HT$_{1A}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_3$
1a	8.8	7.23 (0.08)		6.62 (0.17)	7.36 (0.05)	<5
1b	9.3	7.39 (0.01)	8.03 (0.06)	6.65 (0.01)	7.95 (0.12)	<5
1h	10.4[c]	6.32 (0.16)	6.23 (0.03)[d]	6.72 (0.14)	6.84 (0.27)	<5
1l	8.0	5.80 (0.04)	6.06 (0.05)	5.63 (0.10)	6.82 (0.02)	
4d	8.2	6.01 (0.23)	5.75 (0.26)[d]	5.79 (0.26)	6.95 (0.22)	
5d	7.9[e]	6.49 (0.10)	6.54 (0.04)[d]	5.60 (0.11)	7.17 (0.20)	<5
5f	8.1	4.93 (0.12)	<4	5.20 (0.14)	6.74 (0.07)	<5
17b	7.8	5.38 (0.08)	6.58 (0.10)	5.87 (0.13)	6.46 (0.27)	

[a] 5-HT$_3$ receptor antagonism was determined in the guinea pig ileum assay (pA_2 values).[11] [b] Tissues and [^{3}H]radioligands used in binding assays unless otherwise stated: 5-HT$_{1A}$ (pig cortex, [^{3}H]-8-OH-DPAT), 5-HT$_{1D}$ (calf caudate, [^{3}H]-5-HT), 5-HT$_{2A}$ (rat cortex, [^{3}H]ketanserin), and 5-HT$_{2C}$ (pic choroid plexus, [^{3}H]-mesulergine). [c] Antagonism of serotonin-induced contractions in the nonstimulated guinea pig ileum preparation (see text and the Experimental Section), pA_2 value. [d] [^{125}I]GTI was used as the radioligand. [e] Antagonism of serotonin-induced contractions (see text and the Experimental Section), pD_2' value.

Experimental Section

Syntheses. Melting points were determined with a Buchi 535 apparatus (capillary method) and are uncorrected. ^{1}H NMR spectra were recorded on an AM-360 Bruker spectrometer. Flash chromatography columns were run on silica gel (60 mesh). Analyses indicated by symbols were within 0.4% of the theoretical values.

General Method A: Condensation of Aminoguanidines with Indole-3-carbaldehydes. 3-[[5-(Benzyloxy)-1*H*-indol-3-yl]methylene]-*N*-pentylcarbazimidamide Hydrochloride (5e). *N*-Pentyl-*N'*-aminoguanidine hydroiodide (5.5 g, 0.02 mol) was added portionwise to a solution of 5-(benzyloxy)indole-3-carbaldehyde (5.0 g, 0.02 mol; from Lancaster) in MeOH (100 mL). The solution was acidified (pH 3−4) with concentrated HCl (5 mL). After 5 h at room temperature, the mixture was evaporated. The residue was taken up in MeOH (50 mL) and treated with a solution of etheral HCl (15 mL). The crystals were filtered off and recrystallized from MeOH/diethyl ether to yield the title compound (4.75 g, 69%): mp 260−262 °C; ^{1}H NMR (DMSO-d_6) δ 5.2 (s, 2H, OCH_2), 6.9−7.9 (m, 13H, ArH + NH), 8.3 (s, 1H, CHN), 11.7 (br s, 2H, NH); MS *m/e* 307 (M^+). Anal. ($C_{17}H_{17}N_5O$·HCl) C, H, N, Cl.

General Method B: Preparation of Monoalkylated Aminoguanidines. *N*-Pentyl-*N'*-aminoguanidine Hydroiodide (2b). MeI (127.0 mL, 2.0 mol) was added to a suspension of thiosemicarbazide (182.3 g, 2.0 mol) in EtOH (1 L) at 60 °C. The solution was stirred at that temperature for 30 min and cooled. The resulting suspension was filtered, and the solid was washed with ether to yield *S*-methyl isothiosemicarbazide hydroiodide (390.0 g, mp 137 °C). A solution containing these crystals (233.0 g, 1.0 mol) and pentylamine (118.0 mL, 1.0 mol) in MeOH (1 L) was refluxed for 4 h. The

solution was then cooled to room temperature, and the solvent was evaporated to yield *N*-pentyl-*N'*-aminoguanidine hydroiodide, as an oil, which was used for the next step without purification.

General Method C: Preparation of Dialkylated Thioureas. *N*-Methyl-*N*-pentylthiourea (3m). A solution of *t*-BuNCS (12.5 mL, 98.8 mmol) in hexane (150 mL) was slowly added at 0 °C to a solution of *N*-methyl-*N*-pentylamine (10.0 g, 98.8 mmol) in hexane (30 mL). The solution was then stirred for 1 h, and the solvent was evaporated. The crude solid (21.0 g) was added to concentrated HCl (100 mL), and the suspension was refluxed for 45 min. The solution was cooled and neutralized with concentrated NH_3. The resulting solid was filtered off and washed with water to yield the title compound (14.7 g, 92%): mp 47 °C; MS *m/e* 307 (M^+). Anal. ($C_7H_{16}N_2S$) C, H, N, S.

General Method D: Preparation of Dialkylated Aminoguanidines. *N*-Methyl-*N'*-pentyl-*N''*-aminoguanidine Hydroiodide (2m). MeI (6 mL, 96.0 mmol) was added to a solution of thiourea **3m** (14.6 g, 91.0 mmol) in EtOH (200 mL) at 70 °C. The solution was stirred at that temperature for 30 min. The solvent was evaporated to yield **2m** as a solid (27.4 g) which was dissolved in MeOH (200 mL). Hydrazine hydrate (4.8 mL, 98.2 mmol) was added to the solution which was refluxed for 3 h. The solution was cooled, and the solvent was evaporated. The residue was dissolved in *i*-PrOH (70 mL), and ether was added to obtain a suspension. The crystals were filtered off and washed with ether to yield the title compound (22.0 g, 86%): mp 95 °C. Anal. Calcd ($C_7H_{18}N_4$·HI): C, 29.4; H, 6.7; N, 19.6. Found: C, 28.7; H, 6.2; N, 18.8.

General Method E: Acylation of Carbazimidamides. 3-[(5-Hydroxy-1*H*-indol-3-yl)methylene]-*N*-butanoylcarbazimidamide (1p). A solution of butanoylanhydride (0.7 mL, 4.0 mmol) in DMF (5 mL) was added at 0 °C to a solution of **1a** (0.8 g, 3.7 mmol). The solution was stirred for 2 h at room temperature, and the solvent was evaporated. The residue was chromatographed (eluant toluene/EtOH/NH_3, 85/15/0.3). The product crystallized upon addition of hexane to give the title compound (0.2 g, 19%): mp 90 °C; ^{1}H NMR (DMSO-d_6) δ 0.9 (t, J = 6 Hz, 3H, CH_3), 1.55 (q, J = 6 Hz, 2H, CH_2), 2.3 (t, J = 6 Hz, 2H, CH_2CO), 6.3 (br s, 2H, NH), 6.67 (dd, J = 9, 3 Hz, 1H, HC-6), 7.2 (d, J = 9 Hz, 1H, HC-7), 7.6 (br s, 4H, HC-2,4), 8.33 (s, 1H, CH=N), 8.8 (br s, 1H, CONH), 10.4 (br s, 1H, OH), 11.2 (br s, 1H, NH): MS *m/e* 287 (M^+). Anal. ($C_{14}H_{17}N_5O_2$) C, H, N.

General Method F: Preparation of 5-Alkoxy- or 5-(Carbamoyloxy)indole-3-carbaldehydes. a. 5-Ethoxy-1*H*-indole (6c). EtI (21.0 mL, 0.26 mol) was added to a solution containing 3-methyl-4-nitrophenol (30.6 g, 0.20 mol) and potassium carbonate (41.4 g, 0.30 mol) in acetone (300 mL) at room temperature. The suspension was refluxed for 5 h and cooled. The inorganic solid was filtered off, the solvent was evaporated, and the residue was crystallized from hexane to yield 2-methyl-4-ethoxynitrobenzene (31.0 g, 86%, mp 55 °C). A solution of these crystals (18.1 g, 0.1 mol) in *t*-BuOCH(NMe_2)$_2$ (30 mL) was refluxed for 3 h. The solvent was evaporated, and the residue was dissolved in a mixture of THF (100 mL) and MeOH (100 mL). Raney nickel (20.0 g) followed by hydrazine hydrate (9.7 mL, 0.2 mol) was slowly added. The suspension was stirred at room temperature for 30 min. The catalyst was filtered off, and the solvent was evaporated. The residue was chromatographed (eluant toluene) to yield 5-ethoxy-1*H*-indole which was crystallized from hexane (8.5 g, 53%, mp 35 °C).

b. 5-Ethoxy-1*H*-indole-3-carbaldehyde (7c). Phosphorus oxychloride (5.6 mL, 61.2 mmol) was slowly added to DMF (24 mL) at 0 °C. After 15 min at 0 °C, a solution of **6c** (8.3 g, 51.0 mmol) in DMF (24 mL) was added. The solution was stirred at that temperature for 1 h. Water (100 mL) was added, and the solution was again stirred for 1 h at room temperature. The solution was neutralized with 2 N NaOH, and the resulting suspension was filtered. The solid residue was dissolved in MeOH/THF, and concentrated HCl was added until the pH reached 1. The solution was left at room temperature for 45 min and then neutralized with 4 N NaOH. The aldehyde crystallized upon partial evaporation of the solvent. The crystals were filtered off and washed with water to yield the title compound (7.6 g, 79%): mp 162 °C; ^{1}H NMR (DMSO-d_6) δ 1.35 (t, J = 6 Hz, 3H, Me), 4.02 (q, J = 6 Hz, 2H, OCH_2), 6.9 (dd, J = 3, 9 Hz, 1H, HC-6), 7.5 (d, J = 9 Hz, 1H, HC-7), 8.0 (s, 1H, HC-4), 7.5 (d, J = 9 Hz, 1H, HC-7), 7.6 (d, J = 3 Hz, 1H, HC-4), 8.25 (s, 1H, HC-2), 9.5 (br s, 1H, NH), 9.9 (s, 1H, CHO); MS *m/e* 189 (MH^+). Anal. ($C_{11}H_{11}NO_2$) C, H, N.

General Method G: Acylation of 5-Hydroxyindoles. 3-[[5-(Benzoyloxy)-1*H*-indol-3-yl]methylene]-*N*-pentylcarbazimidamide (8a). Benzoyl chloride (0.5 mL, 4.2 mmol) was slowly added at 0 °C to a solution of **1** (0.8 g, 2.8 mmol) in trifluoroacetic acid (7 mL). After 3 h at 0 °C, the solution was added to a saturated $NaHCO_3$ solution. The solution was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4, and the solvent was evaporated. The residue was chromatographed (eluant toluene/EtOH/NH_3, 85:15:1.5) to yield the title compound (0.3 g, 34%): mp 155 °C; ^{1}H NMR (DMSO-d_6) δ 0.9 (t, J = 6 Hz, 3H, CH_3), 1.2–1.5 (m, 6H, CH_2), 3.1 (t, J = 6 Hz, 2H, CH_2N), 5.5 (br s, 3H, NH), 7.0 (dd, J = 9, 3 Hz, 1H, HC-6), 7.45 (d, J = 9 Hz, 1H, HC-7), 7.6–7.8 (m, 4H, HC-2,3',4',5'), 8.0 (d, J = 3 Hz, 1H, HC-4), 8.15 (s, 1H, HC-2'), 8.18 (s, 1H, HC-6'), 8.3 (s, 1H, CH=N), 11.4 (br s, 1H, NH); MS *m/e* 391 (M^+). Anal. Calcd ($C_{22}H_{25}N_5O_2$·H_2CO_3): C, 67.8; H, 6.1; N, 13.6. Found: C, 63.7; H, 6.0; N, 15.3.

3-[(5-Amino-1*H*-indol-3-yl)methylene]-*N*-pentylcarbazimidamide (9a). A solution of 3-[(5-nitro-1*H*-indol-3-yl)-methylene]-*N*-pentylcarbazimidamide (2.5 g, 7.9 mmol), obtained from 5-nitro-1*H*-indole-3-carbaldehyde by the usual procedures, in MeOH/THF (60/30) was hydrogenated over Pd on charcoal for 5 h. The catalyst was filtered off, and the solvent was evaporated. The residue was crystallized from ether to yield the title compound (1.8 g, 78%): mp 100 °C; ^{1}H NMR (DMSO-d_6) δ 0.9 (t, J = 6 Hz, 3H, CH_3), 1.3–1.5 (m, 6H, CH_2), 3.13 (t, J = 6 Hz, 2H, CH_2N), 4.5 (br s, 2H, $ArNH_2$), 5.6 (br s, 3H, NH), 6.5 (dd, J = 9, 3 Hz, 1H, HC-6), 7.05 (d, J = 9 Hz, 1H, HC-7), 7.3–7.4 (m, 2H, HC-7, HC-2), 8.2 (s, 1H, CH=N), 10.8 (br s, 1H, NH); MS *m/e* 286 (M^+). Anal. ($C_{15}H_{22}N_6$) C, H, N.

***N*-(3-Formyl-1*H*-indol-5-yl)methanesulfonamide (10).** A solution of methanesulfonyl chloride (1.3 mL, 17.0 mmol) in CH_2Cl_2 (5 mL) was added at 0 °C to a solution of 5-amino-1*H*-indole (2.0 g, 15.0 mmol) and Et_3N (4.0 mL, 30.0 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred for 1 h at that temperature. The solution was washed with a 10% aqueous solution of citric acid and then with a saturated solution of $NaHCO_3$. The organic phase was dried over Na_2SO_4 and evaporated. The residue was crystallized from ether to yield the sulfonamide (2.6 g, 84%, mp 130 °C) which was formylated with $POCl_3$/DMF as described above to afford the title compound which was crystallized from ether (1.9 g, 68%): mp 200 °C; ^{1}H NMR (DMSO-d_6) δ 2.9 (s, 3H, SO_2Me), 7.2 (d, J = 9 Hz, 1H, HC-6), 7.5 (d, J = 9 Hz, 1H, HC-7), 8.0 (s, 1H, HC-4), 8.3 (s, 1H, HC-2), 9.5 (br s, 1H, NH), 9.9 (s, 1H, CHO), 12.2 (br s, 1H, $NHSO_2$); MS *m/e* 238 (M^+). Anal. ($C_{10}H_{10}N_2O_3S$) C, H, N, S.

3-[(5-Hydroxybenzo[*b*]thiophene-3-yl)methylene]-*N*-pentylcarbazimidamide (12b). A solution of boron tribromide (7.3 mL, 72.8 mmol) in CH_2Cl_2 (15 mL) was slowly added at 0 °C to a solution of 5-methoxybenzo[*b*]thiophene-3-carbaldehyde (14)[15] (2.8 g, 14.5 mmol) in CH_2Cl_2 (70 mL). After 4 h at 0 °C, the mixture was neutralized with a 2 N solution of Na_2CO_3. Upon evaporation of the solvent, a solid separated. The solid was filtered off, washed with water, and recrystallized from MeOH/water to yield 5-hydroxybenzo[*b*]thiophene-3-carbaldehyde (2.3 g, 88%, mp 205 °C), which was condensed with *N*-pentyl-*N'*-aminoguanidine according to method A to afford the title compound which was crystallized from ether/hexane, 5/95 (2.8 g, 73%): mp 155 °C; ^{1}H NMR (DMSO-d_6) δ 0.9 (t, J = 6 Hz, 3H, CH_3), 1.3–1.5 (m, 6H, CH_2), 3.15 (t, J = 6 Hz, 2H, CH_2N), 5.75 (br s, 3H, NH), 6.9 (dd, J = 9, 3 Hz, 1H, HC-6), 7.72 (d, J = 3 Hz, 1H, HC-4), 8.09 (d, J = 9 Hz, 1H, HC-7), 8.33 (s, 1H, CH=N), 9.5 (br s, 1H, OH); MS *m/e* 304 (M^+). Anal. ($C_{15}H_{20}N_4OS$) C, H, N, S.

5-Methoxy-1*H*-indazole-3-carbaldehyde (16). A suspen-

sion of 5-methoxy-1*H*-indazole (14.8 g, 0.1 mol) and K_2CO_3 (200 g, 1.5 mol) was stirred in an autoclave at 270 °C under CO_2 (70 bar) for 4 h. The suspension was added to water (1 L), and the precipitate was filtered off. The solution was acidified (pH 2) with concentrated HCl and extracted with AcOEt/*i*-PrOH, 95/5. The organic phase was washed with brine and dried over Na_2SO_4, and the solvent was evaporated. The residue was crystallized from ether to yield 6.7 g of 5-methoxy-1*H*-indazole-3-carboxylic acid (35%) which was dissolved in THF (30 mL) and added to a suspension of LAH (3.9 g, 0.1 mol) in THF (300 mL). The solution was stirred at 50 °C for 3 h and then cooled to room temperature. A saturated solution of Na_2SO_4 was added, and the precipitate was filtered off. The solution was evaporated, and the residue was crystallized from ether to yield 5-methoxy-1*H*-indazole-3-methanol (4.2 g, 68%) which was dissolved in CH_2Cl_2 (20 mL) and THF (20 mL). MnO_2 (20.6 g, 0.23 mol) was added, and the suspension was stirred at room temperature overnight. The suspension was filtered, and the solvent was evaporated. The residue was crystallized from ether to yield the title compound (3.4 g, 83%): mp 216 °C; ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H, OMe), 7.15 (dd, J = 9, 3 Hz, 1H, HC-6), 7.5 (d, J = 3 Hz, 1H, HC-4), 7.63 (d, J = 9 Hz, 1H, HC-7), 10.18 (s, 1H, CHO), 14.2 (br s, 1H, NH); MS *m/e* 176 (M^+). Anal. ($C_9H_8N_2O_2$) C, H, N.

3-[(5-Hydroxy-1*H*-indazol-3-yl)methylene]-*N*-pentylcarbazimidamide (15b). A solution of boron tribromide (2.5 mL, 25.3 mmol) in CH_2Cl_2 (5 mL) was slowly added at 0 °C to a solution of 5-methoxy-1*H*-indazole-3-carbaldehyde (**16**) (0.9 g, 5.1 mmol) in CH_2Cl_2 (70 mL). The solution was stirred at room temperature for 3 h. The mixture was neutralized with a 2 N solution of Na_2CO_3 and extracted with AcOEt/*i*-PrOH, 8/2. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated. Upon evaporation of the solvent, a solid separated which was crystallized from ether/hexane to yield 5-hydroxy-1*H*-indazole-3-carbaldehyde (0.8 g, 95%, mp 213 °C) which was condensed with *N*-pentyl-*N'*-aminoguanidine according to method A to afford the title compound after chromatography (eluant toluene/EtOH/NH_3, 80/20/2) and crystallization from ether (0.4 g, 29%): mp 155 °C; ^{1}H NMR (DMSO-d_6) δ 0.9 (t, J = 6 Hz, 3H, CH_3), 1.3–1.5 (m, 6H, CH_2), 3.16 (t, J = 6 Hz, 2H, CH_2N), 5.9 (br s, 3H, NH), 6.9 (dd, J = 9, 3 Hz, 1H, HC-6), 7.35 (d, J = 3 Hz, 1H, HC-4), 7.55 (d, J = 9 Hz, 1H, HC-7), 8.3 (s, 1H, CH=N), 9.1 (br s, 1H, OH), 12.9 (br s, 1H, NH); MS *m/e* 289 (MH^+). Anal. ($C_{15}H_{20}N_4OS$) C, H, N, S.

5-Methoxy-1*H*-pyrrolo[3,2-*b*]pyridine-3-carbaldehyde (19). A solution of 6-methoxy-3-nitro-2-picoline (**18**)[10] (9.8 g, 58 mmol) in *t*-BuOCH(NMe_2)$_2$ (25 mL) was refluxed for 3 h. The solvent was evaporated, and the residue was dissolved in toluene and hydrogenated in a Gasstar apparatus over Pd on charcoal. The catalyst was filtered off, and the solvent was evaporated. The residue was chromatographed (eluant CH_2Cl_2/MeOH, 98/2) to yield 5-methoxy-1*H*-pyrrolo-[3,2-*b*]pyridine (6.6 g, 77%). A solution of this compound (0.4 g, 2.7 mmol) in DMF (1.2 mL) was added to a mixture prepared by adding phosphorus oxychloride (0.3 mL, 3.2 mmol) to DMF (1.2 mL) at 0 °C. The solution was stirred at that temperature for 1.5 h. Water (100 mL) was added, and the solution was again stirred for 1.5 h at room temperature. The solution was neutralized with 2 N NaOH, and the resulting mixture was extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated. The residue was chromatographed (eluant CH_2Cl_2/MeOH, 95/5) to yield the title compound which was crystallized from ether/hexane (0.2 g, 40%): mp 196 °C; ^{1}H NMR (DMSO-d_6) δ 3.9 (s, 3H, OMe), 7.3 (s, 1H, HC-4), 8.45 (s, 1H, HC-7), 8.48 (s, 1H, HC-2), 9.9 (s, 1H, CHO), 12.35 (br s, 1H, NH); MS *m/e* 176 (M^+). Anal. ($C_9H_8N_2O_2$) C, H, N.

3-[(5-Oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)methylene]-*N*-pentylcarbazimidamide (17b). A solution of **19** (0.88 g, 5.0 mmol) in a mixture of 33% HBr in AcOH (3 mL) was stirred at 100 °C for 2 h. The solution was cooled, and ether was added. A solid separated which was filtered off and washed with ether. The solid was recrystallized from CH_2Cl_2/MeOH, 95/5, to yield 5-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*b*]pyridine-3-carbaldehyde (0.75 ,g 94%, mp 198 °C) which was condensed according to method A with *N*-pentyl-*N'*-aminoguanidine to yield the title compound as an amorphous solid in 70% yield: ^{1}H NMR (DMSO-d_6) δ 0.9 (t, J = 6 Hz, 3H, CH_3), 1.2–1.6 (m, 6H, CH_2), 3.1 (t, J = 6 Hz, 2H, CH_2N), 5.5–6.3 (br s, 3H, NH), 6.1 (d, J = 9 Hz, 1H, HC-6), 7.47 (s, 1H, HC-2), 7.6 (d, J = 9 Hz, 1H, HC-7), 8.15 (s, 1H, CH=N), 10.6–11.7 (br s, 2H, NH); MS *m/e* 288 (M^+). Anal. ($C_{14}H_{20}N_6O$) C, H, N.

Biological Activities. 5-HT$_3$ Receptor Antagonism. The guinea pig longitudinal muscle with adhering plexus myentericus was prepared as described before.[1,11] Small strips (2 cm) of the preparation were mounted in an organ bath containing tyrode solution at 37 °C and bubbled with 5% CO_2 in O_2. The tyrode solution contained 0.1 μM methylsergide. 5-HT$_3$ receptor-mediated contractions were measured isotonically, and concentration–response curves were recorded in a noncumulative fashion. When putative 5-HT$_3$ antagonists were tested against serotonin, a 10 min preincubation procedure with individual antagonists was performed.

5-HT$_4$ Receptor Agonism. Field-Stimulated Guinea Pig Ileum. Longitudinal muscle strips from guinea pig ileum were prepared and maintained as described previously.[1,11] The tyrode solution contained 0.1 μM methylsergide. "Twitch" responses (rapid contractions lasting 2–3 s) were evoked using square wave pulses (0.1 Hz, 2 ms pulse duration) delivered from a Grass S48 stimulator via platinum electrodes situated on either side of a muscle strip. When a stable submaximal response was established, concentration–response curves using putative 5-HT$_4$ receptor agonists were constructed in a noncumulative fashion.

Nonstimulated Guinea Pig Ileum. Longitudinal muscle strips from guinea pig ileum were prepared and maintained as described previously.[1,11] The tyrode solution contained 0.1 μM methylsergide and 0.1 μM physostigmine. Contractions were measured isotonically, and concentration–response curves were constructed in a noncumulative fashion. When antagonistic effects of compounds (**1h**, **5b**) were examined against that of serotonin ($pD_2 = 6.97 \pm 0.11$), a 10 min preincubation procedure with the compounds was performed.

Radioligand-Binding Experiments. The radioligand-binding experiments were performed as previously described.[16] Radioligands used in the binding assays were [^{3}H]-8-OH-DPAT, [^{125}I]GTI, [^{3}H]ketanserin, and [^{3}H]mesulergin for 5-HT$_{1A}$, 5-HT$_{1D}$, 5-HT$_{2A}$, and 5-HT$_{2C}$ receptors, respectively.

References

(1) Buchheit, K. H.; Gamse, R.; Giger, R.; Hoyer, D.; Klein, F.; Klöppner, E.; Pfannkuche, H. J.; Mattes, H. *J. Med. Chem.* **1995**, *38*, 2326–2330.

(2) (a) Dumuis, A.; Sebben, M.; Bockaert, J. The Gastrointestinal Prokinetic Benzamide Derivatives are Agonists at the Non-Classical 5-HT Receptor (5-HT$_4$) Positively Coupled to Adenylate Cyclase in the Neurons. *Naunuyn-Schiedeberg's Arch. Pharmacol.* **1989**, *340*, 403–410. (b) Buchheit, K. H.; Buhl, T. Prokinetic Benzamides Stimulate Peristaltic Activity in the Isolated Guinea Pig Ileum by Activation of 5-HT$_4$ Receptors. *Eur. J. Pharmacol.* **1991**, *205*, 203–208.

(3) (a) Dumuis, A.; Bouhelal, R.; Sebben, M.; Cory, R.; Bockaert, J. A Non-Classical 5-hydroxytryptamine Receptor Positively Coupled with Adenylate Cyclase in the Central Nervous System. *Mol. Pharmacol.* **1988**, *34*, 880–887. (b) Boddeke, H. W. G.; Kalkman, H. O. Zacopride and BRL 24924 Induce an Increase in EEG-Energy in Rats. *Br. J. Pharmacol.* **1990**, *101*, 281–284.

(4) Singh, J.; Thornton, J. M.; Snarey, M.; Campbell, S. F. The geometries of interacting arginine-carboxyls in proteins. *FEBS Lett.* **1987**, *224*, 161–171.

(5) Haefliger, W.; Knecht, H. Benz[c,d]indoles -I. The Use of Tert-butoxy-bis(dimethylamino)methane as Condensation Reagent. *Tetrahedron Lett.* **1983**, *25*, 285–288.

(6) James, P. N.; Snyder, H. R. Indole-3-aldehyde. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 539.

(7) Belsky, I.; Gertner, D.; Zilkha, A. Synthesis of some 5-Trimethylsilindoles. *J. Org. Chem.* **1968**, *33*, 1348–1360.

(8) Ple, P. A.; Marnett, L. J. Synthesis of Substituted Benzo[b]-thiophenes by Acid-Catalyzed Cyclization of Thiophenylacetals and Ketones. *J. Heterocycl. Chem.* **1988**, *25*, 1271–1272.

(9) Bartsch, R. A.; Yang, I.-W. Phase Transfer Catalyzed Synthesis of Indazoles from O-Alkylbenzenediazonium Tetrafluoroborates. *J. Heterocycl. Chem.* **1984**, *21*, 1063–1064.

(10) Baumgarten, H. E.; Chien-Fan Su, H. *J. Am. Chem. Soc.* **1952**, *74*, 3829–3831.

(11) Buchheit, K. H.; Engel, G.; Mutschler, E.; Richardson, B. Study of the contractile Effect of 5-Hydroxytryptamine (5-HT) in the isolated longitudinal muscle Strip from Guinea Pig Ileum. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1985**, *329*, 36–41.
(12) Ariens, E. J. Receptor Theory and Structure-Action Relationships. In *Adv. Drug Research*; Harper, N. J., Simmonds, A. B., Eds.; Academic Press: London, 1966; Vol. 3.
(13) Macor, J. E.; Burkhart, C. A.; Heym, J. H.; Ives, J. L.; Lebel, L. A.; Newman, M. E.; Nielsen, J. A.; Ryan, K.; Schulz, D. W.; Torgensen, L. K.; Koe, B. K. 3-(1,2,5,6-Tetrahydropyrid-4-yl)pyrrolo[3,2b]pyrid-5-one: A Potent and Selective Serotonin ($5\text{-}HT_{1B}$) Agonist and Rotationally Restricted Phenolic Analogue of 5-Methoxy-3-(1,2,5,6-tetrahydropyrid-4-yl)indole. *J. Med. Chem.* **1990**, *33*, 2087–2093.
(14) Bockaert, J.; Fozard, J. R.; Dumuis, A.; Clarke, D. The $5\text{-}HT_4$ Receptor: a Place in the Sun. *Trends Pharmacol. Sci.* **1992**, *13*, 141–145.
(15) Ple, P.; Marnett, L. J. Alkylaryl Sulfides as Peroxide Reducing Substrates for Prostaglandin H Synthase: Probes for the Reactivity and Environment of the Ferryl-oxo Complex. *J. Biol. Chem.* **1989**, *264*, 13983–13993.
(16) Palacios, J. M.; Mengod, G.; Hoyer, D. Brain Serotonin Receptor Subtypes: Radioligand Binding Assays, Second Messengers, Ligand Autoradiography and in situ Hybridization Histochemistry. In *Methods in Neurosciences*; Conn, P. M., Ed.; Academic Press, Inc.: New York, 1993; Vol. 12, pp 238–261.

JM940771B