Design and Synthesis of a Series of 6-Substituted-2-pyridinylmethylamine Derivatives as Novel, High-Affinity, Selective Agonists at 5-HT_{1A} Receptors

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A search for novel, selective agonists with high intrinsic activity at the 5-HT_{1A} subtype of serotonin (5-HT) receptors was undertaken. Mechanistic and thermodynamic considerations led to the design of 6-substituted-2-pyridinylmethylamine as a potential 5-HT_{1A} pharmacophore. Various adducts derived from the 6-substituted-2-pyridinylmethylamine moiety were tested for their affinity at 5-HT_{1A}, α_1-adrenergic, and D_2-dopaminergic receptors. Compounds with high affinity for 5-HT_{1A} receptors ($pK_i \geq 8$) were examined for agonist properties by measuring their ability to inhibit forskolin-stimulated cAMP production in HA7 cells (i.e., HeLa cells permanently transfected with the h5-HT_{1A} receptor gene and expressing the h5-HT_{1A} receptor protein). Several compounds of the type aryl{4-[(6-substituted-pyridin-2-ylmethylamino)-methyl]piperidin-1-yl}methanone had nanomolar affinity for 5-HT_{1A} binding sites and were more than 500-fold selective with respect to α_1 and D_2 sites. Importantly, their 5-HT_{1A} agonist properties were demonstrated in HA7 cells where they behaved as potent inhibitors of cAMP accumulation. In particular, (3,4-dichlorophenyl){4-[(6-oxazol-5-ylpyridin-2-ylmethylamino)-methyl]piperidin-1-yl}methanone (**70**) and (3,4-dichlorophenyl){4-[(6-azetidinopyridin-2-yl-methylamino)methyl]piperidin-1-yl}methanone (**36**) appeared to be more potent than, and at least as efficacious as, the prototypical 5-HT_{1A} agonist (±)-8-OH-DPAT. SAR studies revealed that the pyridine nitrogen atom and the nature and the position of the substituents on the pyridine ring were critically involved in the ability of the compounds to recognize and activate 5-HT_{1A} receptors. Structural modifications of the nonpharmacophoric part of the molecule showed, however, that the entire structure was required for affinity at 5-HT_{1A} binding sites.

Introduction

Serotonin (5-HT) recognizes several, distinct cell-surface receptors.[1] Among these, 5-HT_{1A} receptors, at which 5-HT has high affinity, have been implicated in many psychiatric and neurological disorders.[2] Clinical evidence of a link between 5-HT_{1A} receptor function and, for example, depression is now becoming available.[3] However, to represent a significant advance in antidepressant therapy, 5-HT_{1A} receptor ligands must achieve two objectives not yet met by currently available treatments: (1) a fast onset of action and (2) a low percentage of "non-responders".[4]

Our research program in the 5-HT_{1A} area is guided by the hypothesis that very few, if any, of the ligands reported so far possess the high level of intrinsic activity needed to exert rapid and robust antidepressant effects. Thus, we postulate that a 5-HT_{1A} agonist with an optimized level of intrinsic activity may offer a more rapid and effective antidepressant treatment than existing drugs, including 5-HT_{1A} partial agonists.[5] Numerous ligands at 5-HT_{1A} receptors have been identified.[6] They can be divided, however, into a small number of chemical classes. Our effort is aimed at discovering a structurally novel family of 5-HT_{1A} ligands, assuming this to be the best approach to obtain 5-HT_{1A} agonists with an improved profile. Here, we describe the design, synthesis, and preliminary pharmacological characterization of a series of 6-substituted-pyridin-2-ylmethylamine derivatives. Affinity of members of this class for 5-HT_{1A} binding sites was compared with their affinity for α_1-adrenergic and D_2-dopaminergic sites. Furthermore, their agonist activity at 5-HT_{1A} receptors was examined in vitro by measuring their ability to inhibit forskolin-stimulated cAMP production in HA7 cells. Several of the compounds had an affinity for, and a selectivity at, 5-HT_{1A} receptors at least as high as the prototypical 5-HT_{1A} agonist (±)-8-OH-DPAT. Finally, several compounds appeared to have greater intrinsic activity at 5-HT_{1A} receptors than (±)-8-OH-DPAT.

Chemistry

Products of general formula **4** were prepared according to the methods depicted in Scheme 1. The Schiff base **1**, obtained by condensation of the commercially available 4-(aminomethyl)piperidine with the appropriate carboxaldehydes, enabled the secondary amino group to be selectively acylated. Reduction of the crude imine **2** with KBH_4 in methanol afforded the desired derivatives **4** (method A). Pyridine-type compounds **4** (X = N), containing an N-bound 6-substituent (i.e., 6-alkylamino, 6-dialkylamino, 6-cycloalkylamino, 6-pyrrol-1-yl, or 6-imidazol-1-yl), were conveniently prepared from the 6-halogeno derivative **3** and the appropriate amine or sodium salt of the amine, via a SNAr at the last step of the synthesis (method B). The homologues

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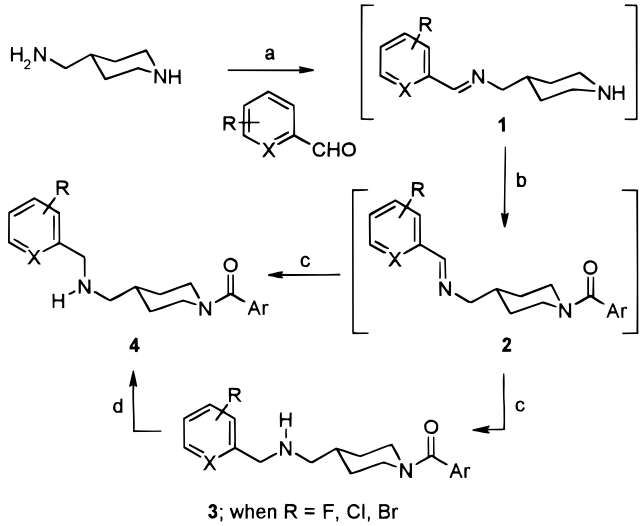
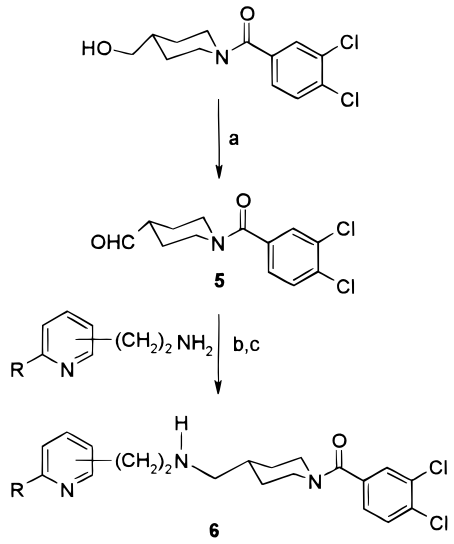
Scheme 1[a]



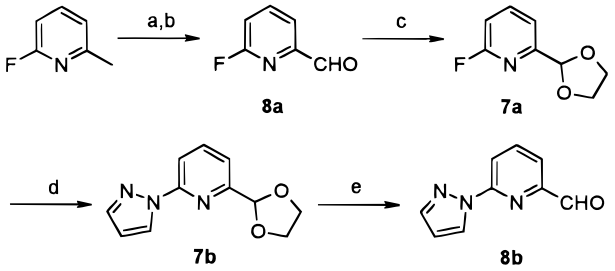
[a] Conditions: (a) toluene, 110 °C; (b) ArCOCl, THF, TEA; (c) KBH_4, CH_3OH; (d) NH_3, RNH_2, RRNH, EtOH, 100 °C or nitrogen heterocycles, HNa, DMF, 60 °C.

Scheme 2[a]



[a] Conditions: (a) Swern oxidation; (b) 2-, 3-, or 4-pyridinylethylamine, $PhCH_3$, 110 °C; (c) KBH_4, CH_3OH.

Scheme 3[a]

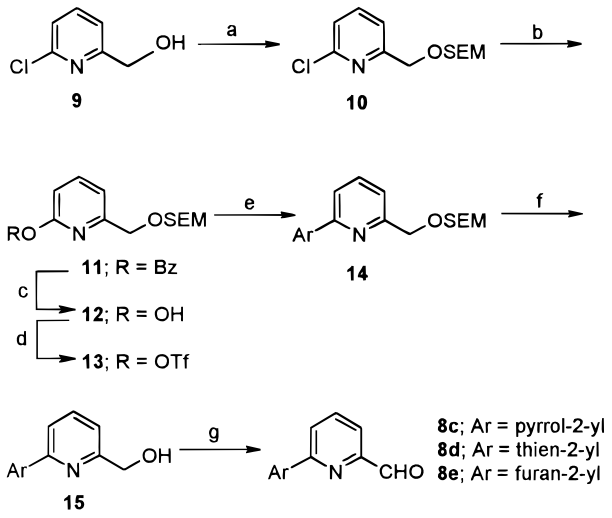


[a] Conditions: (a) $tBuOCH(NMe_2)_2$, 150 °C; (b) $NaIO_4$, H_2O, 25 °C; (c) $HOCH_2CH_2OH$, PTSA, $PhCH_3$, 110 °C; (d) HNa, pyrazole, DMF, 60 °C; (e) HCO_2H, H_2O, $CuSO_4$, 65 °C.

6 were obtained by reductive amination of aldehydes **5** with the commercially available 2-(aminoethyl)pyridine (Scheme 2).

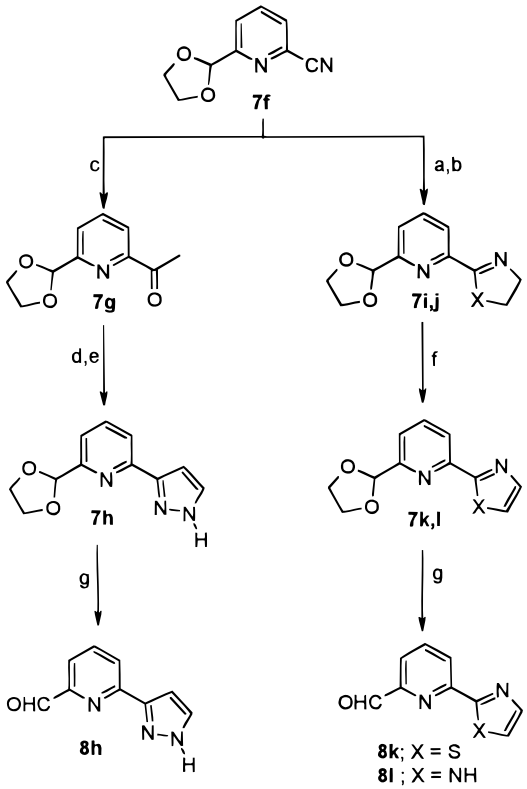
Known aldehydes of the type **8** (Schemes 3−7), such as 2-pyridinepropionaldehyde,[7] 6-methoxy-2-pyridinecarboxaldehyde,[8] 6-phenyl-2-pyridinecarboxaldehyde,[9]

Scheme 4[a]



[a] Conditions: (a) SEMCl, DIEA, CH_2Cl_2; (b) BzOH, HNa, DMF, 40 °C; (c) H_2, Raney Ni, EtOH; (d) $(CF_3SO_2)_2O$, pyridine; (e) $ArB(OH)_2$, Tl_2CO_3, $Pd(PPh_3)_4$; (f) nBu_4NF, THF, HMPA; (g) MnO_2, CH_2Cl_2, 40 °C.

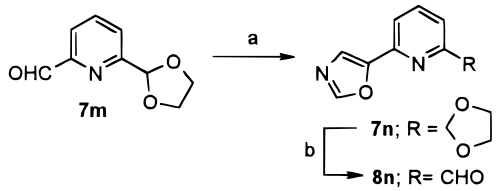
Scheme 5[a]



[a] Conditions: (a) MeONa, MeOH, 25 °C; (b) $NH_2CH_2CH_2NH_2$·HCl, EtOH, 80 °C or $NH_2CH_2CH_2SH$, 130 °C; (c) MeMgBr, THF; (d) $(Me)_2NCH(OMe)_2$, 110 °C; (e) NH_2NH_2·H_2O, EtOH, 80 °C; (f) $BaMnO_4$ or NiO_2, benzene, 80 °C; (g) HCO_2H, H_2O, 65 °C.

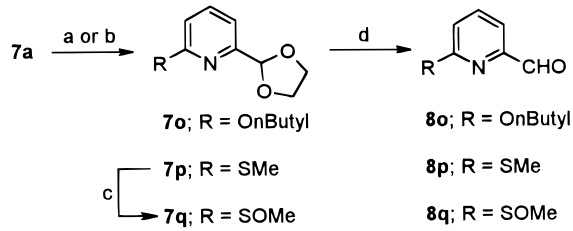
6-isopropyl-2-pyridinecarboxaldehyde,[10] 3-(dimethylamino)benzaldehyde,[11] and 3-(pyrrol-1-yl)benzaldehyde[12] used as intermediates in the synthesis of compounds **4**, have been prepared as previously reported. The synthesis of novel aldehydes **8** was carried out as follows: the enamine formed by condensation of 6-fluoro-2-picoline and *tert*-butoxy(dimethylamino)methane[13] was oxidatively cleaved[14] by $NaIO_4$ to give the 6-fluoro-2-pyridinecarboxaldehyde (**8a)** (Scheme 3). Protection of

Scheme 6[a]



[a] Conditions: (a) TOSMIC, K_2CO_3, MeOH, 65 °C; (b) HCO_2H, H_2O, 65 °C.

Scheme 7[a]



[a] Conditions: (a) Na, nBuOH, 100 °C; (b) NaSMe, DMF, 100 °C; (c) $NaIO_4$, MeOH; (d) HCO_2H, H_2O, 65 °C.

the aldehyde **8a** as a dioxolane **7a** followed by displacement of the 6-fluoro substituent by the sodium salt of pyrazole gave **7b**. Hydrolysis of the acetal group under acidic conditions furnished the aldehyde **8b**.

The preparation of the 6-heteroaryl-2-pyridinecarboxaldehydes **8c**−**e** (Scheme 4) began by protection of the 6-chloro-2-pyridinemethanol[15] (**9**) as a (trimethylsilyl)ethoxymethyl ether **10**. Replacement of the 6-chloro substituent by a hydroxyl group was performed by the method of Sieburth[16] (i.e., formation of the benzyl ether **11** and then hydrogenolysis of the benzyl group leading to the pyridol **12**). Conversion of **12** into the triflate **13** and then Suzuki cross-coupling reaction with the boronic acid of the appropriate heteroaryl derivatives yielded compounds **14**. Cleavage of the SEM group[17] and oxidation of the resulting primary alcohol **15**, under mild conditions (MnO_2/CH_2Cl_2), provided the 6-heteroaryl-2-pyridinecarboxaldehydes **8c**−**e**.

The 6-(1,3-dioxolan-2-yl)-2-pyridinecarbonitrile (**7f**) (Scheme 5), derived from the known 6-cyano-2-pyridinecarboxaldehyde,[18] was the common starting material in the synthesis of aldehydes **8h**,**k**,**l**. At first, the nitrile function of **7f** was activated as an imidoyl ether (not shown in Scheme 5) which, by reaction with ethylenediamine or cysteamine, afforded the imidazoline **7i** and thiazoline **7j**, respectively. Oxidation of **7i**,**j**[19,20] and cleavage of the acetal group produced the aldehydes **8k**,**l**. Addition of CH_3MgBr on the nitrile **7f** gave the methyl ketone **7g** which was converted to the pyrazole **7h** using known chemistry.[21] Deprotection of the carbonyl function of **7h** generated the 6-(pyrazol-3-yl)-2-pyridinecarboxaldehyde (**8h**).

Condensation of TOSMIC on the known aldehyde **7m**[22] (Scheme 6) gave the derivative **7n**.[23] Removal of the protecting group led to the expected aldehyde **8n**. Finally, acetals **7o**,**p** (Scheme 7) were prepared via a SNAr between the 6-fluoro derivative **7a** and the sodium salt of the appropriate alcohol or thiol. Acetal cleavage furnished the aldehydes **8o**,**p**. The aldehyde **8q** was obtained by a chemoselective oxidation at the sulfur atom before the deprotection of the latent aldehyde function.

Pharmacology

Binding affinities for the different receptors were determined by ligand displacement assays using the conditions summarized in the Experimental Section. All experiments were performed in triplicate. IC_{50} values were determined using nonlinear regression. K_i values were calculated using the equation $K_i = IC_{50}/1 + [C]/K_D$, where [C] is the concentration of the radioligand. The results are expressed as mean pK_i values ± SEM of 2−3 independent determinations, each performed in triplicate.

The HeLa cell line permanently transfected with the human 5-HT_{1A} receptor gene and permanently expressing the 5-HT_{1A} receptor protein (HA7), as described by Fargin,[24] was commercially obtained from Duke University (Durham, NC). Concentration−effect relationships are expressed as −log [M] of the test compound versus the cAMP content expressed as a percentage of forskolin-stimulated cAMP control values. IC_{50} values for compounds were estimated by linear interpolation between the logarithms of the concentrations that inhibited forskolin-stimulated cAMP with amounts bordering 50% of the maximal inhibition observed with the compound. The potency and maximal inhibition values represent the mean of 2 independent determinations (each performed in triplicate) for all compounds, except (±)-8-OH-DPAT whose values represent the mean of 5 determinations.

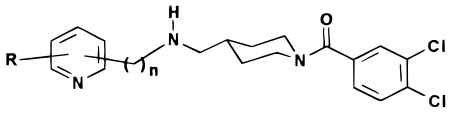
Results and Discussion

(a) Design of the Pharmacophore. At the outset of the project, we wondered about the role of the indole nitrogen lone pair of 5-HT in its ability to activate 5-HT_{1A} receptors. However, because of the inaccuracy in homology modeling methods[25] and the lack of knowledge about the conformational landscape of ligand−receptor complexes,[26] we took an approach that avoided speculations about the protein residues involved and about the nature of the interactions engaged in the complex. On the basis of the model of 5-HT_{1A} receptor activation developed by Weinstein,[27] we reasoned that the intrinsic activity of a 5-HT_{1A} ligand may be related to the ability of its pharmacophore to stabilize a positive charge generated on the receptor protein upon agonist binding. Hence, one way of increasing the intrinsic activity of a 5-HT_{1A} agonist may be to enhance the ability of its pharmacophore to stabilize a positive charge.

According to Weinstein's model, the protein cation involved is a soft nitrogen cation derived from a basic amino acid (i.e., ammonium, imidazolium, or guanidinium ion). Since soft nitrogen cations are soluble in pyridine, which means that enthalpically favorable interactions occur within N^+-pyridine pairs,[28] we suggested that a pharmacophore containing a pyridine core could efficiently stabilize the positive charge generated on the protein side. Thus, a pyridine appropriately located in the active site of the receptor could shift the equilibrium toward its G-protein-coupled state(s).

Having selected pyridine as the core component of the pharmacophore, our next concern was to find its optimal position relative to a stronger basic amino function that could serve as the prime anchoring point of the ligand inside the receptor protein.[27,29] At first, we looked at

Table 1. Effects of the Py−NH Linker Length and the Chain Orientation on 5-HT_{1A} Affinity



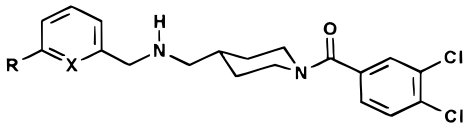
compd	chain position	n	R	5-HT_{1A} affinity pKi [a,b]
16	2	1	H	7.58 ± 0.15
17	2	2	H	8.92 ± 0.05
18	2	3	H	7.37 ± 0.03
19	3	1	H	6.38 ± 0.16[b]
20	3	2	H	6.03 ± 0.01[b]
21	4	2	H	<6.0
22	2	1	6-F	8.05 ± 0.10
23	2	2	6-F	8.50 ± 0.05
45	2	1	4-pyrazol-1-yl	6.19 ± 0.02[b]
58	2	1	6-pyrazol-1-yl	8.78 ± 0.09
61	2	2	6-pyrazol-1-yl	8.45 ± 0.06
24	2	1	4-Cl	8.04 ± 0.04
25	2	1	6-Cl	8.34 ± 0.12
33	2	1	4-$(CH_3)_2N$	5.58 ± 0.01[b]
34	2	1	6-$(CH_3)_2N$	8.85 ± 0.11

[a] See Experimental Section for details. The compound with a pK_i value indicated with a smaller than sign (<) has no binding affinity at the given concentration. Each value is the mean ± SEM of three determinations. [b] Two determinations only.

the distance between the pyridine and the secondary nitrogen atoms in (3,4-dichlorophenyl){[pyridinyl(*n*-alkylamino)methyl]piperidin-1-yl}methanones. The choice of such side chains was motivated by the availability in our laboratory of the 1-(3,4-dichlorobenzoyl)-piperidine-4-methanol precursor[30] and by its successful use with various other types of pharmacophores.[30,31] From displacement data shown in Table 1, it appears that unsubstituted 2-pyridinylmethyl, ethyl, and propylamino derivatives of (3,4-dichlorophenyl)(4-methylpiperidin-1-yl)methanone (**16**−**18**) have affinity for 5-HT_{1A} receptors. When the pyridine is monosubstituted (R = H), a two-methylene linkage is the optimum distance between the pyridine ring and the secondary amino group (**17** compared with **16**, **18**). However, in disubstituted pyridine, the nature of the R substituent influenced affinity only with ligands having a monomethylene linker between the pyridine ring and the amino group. Affinity varied over 1.2 log units for compounds of the 2-pyridinylmethylamine type (**16**, **22**, **58**) and only over 0.4 log unit for ethyl homologues (**17**, **23**, **61**). Assuming that for agonists, the elements of the pharmacophore involved in binding are also involved in the control of intrinsic activity, a positive relationship between the affinity and the intrinsic activity is expected for compounds whose pattern of interactions with the receptor is homogeneous.[32,33] Thus, a 6-substituted-pyridin-2-ylmethylamine seemed a more suited motif than a 6-substituted-pyridin-2-ylethylamine to examine structure−intrinsic activity relationships and was therefore used subsequently. Another interesting feature of a 6-substituted-pyridin-2-ylmethylamine pharmacophore is that the distance between the pyridine nucleus and the side-chain amino group is less than the distance required for recognition as predicted by steric models of 5-HT_{1A} receptors.[29] The 2-pyridinylethyl and 2-pyridinylpropylamine homologues (**17** and **18**, respectively) of compound **16** can be viewed as open-chain analogues of aminotetralins or partial ergots.

Apparently, the range of substituents accommodated in the 6-position of the pyridine ring (**25**, **34**, **58**) is much wider than that in the 4-position (**24**, **33**, **45**), even though C-4 and C-6 may be regarded as isoelectronic. The 5-HT_{1A} binding affinity of the benzene derivatives **72**−**74** was significantly lower than that of the pyridine counterparts **22, 34**, and **43** (Table 2) and decreased

Table 2. Comparison of Effects of a Pyridyl versus a Phenyl Group on 5-HT_{1A} Affinity



compd	X	R	5-HT_{1A} affinity pKi [a,b]
72	CH	F	7.83 ± 0.03
22	N	F	8.05 ± 0.10
73	CH	$(CH_3)_2N$	7.12 ± 0.14[b]
34	N	$(CH_3)_2N$	8.85 ± 0.11
74	CH	pyrrol-1-yl	6.53 ± 0.01[b]
43	N	pyrrol-1-yl	8.37 ± 0.12

[a] See footnotes of Table 1.

markedly as the R substituent became larger (**72**−**74**). These results suggest that the pyridine ring contributes to the binding of the ligand to 5-HT_{1A} receptors. Moreover, the nitrogen atom of the pyridine may be a major site of interactions of the pharmacophore with the receptor protein because the only tolerated orientation for the side chain was the 2-position of the pyridine (**16** and **17** compared to **19** and **20**, **21**, respectively, Table 1).

(b) Influences of the Chain and of the Terminal Amide Functional Group. To explore the influence on binding of the nonpharmacophoric part of the molecule (i.e., the part other than the 6-R-pyridin-2-ylmethylamino fragment), we tested diverse representative chains attached to the 6-(pyrazol-1-yl)-2-pyridinylmethylamine moiety. Usually, known classes of 5-HT_{1A} pharmacophores can accommodate various chains with only minor consequences for their in vitro biological activities. However, results summarized in Table 3 demonstrate the opposite for derivatives built around a 6-substituted-2-pyridinylmethylamine pharmacophore. Besides compound **58** (Table 1), only derivatives **78** and **82** (Table 3) achieved significant affinity for 5-HT_{1A} receptors. In addition, the drop in binding observed with the open-chain acetylenic derivative **83** and the piperidine regioisomer **85** illustrates the tight geometric constraints imposed on that part of the molecule. Compared with the conformationally restricted piperidine (**48**, **53** in Table 4 and **58** in Table 1), the open-chain molecules **81**−**83** showed only weak affinity for the 5-HT_{1A} receptors, indicating they cannot adopt suitable conformation(s) for optimal binding to the receptors. In line with these findings, changing the amide to a sulfonamide group or reducing the carbonyl oxygen atom of the amide function suppressed binding affinity (**60** and **59**, respectively, Table 4). Hence, the amide function represents a compromise between steric and conformational factors: the sulfone group being too sterically hindered, whereas the reduced amide might suffer a loss of entropic binding energy.

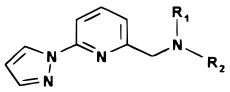
The comparison of binding data of compounds **46**−**48** (Table 4) indicates that the lipophilicity of the carbonyl amide substituent is an important property of that group. On the other hand, the 10-fold gain in affinity observed with monosubstituted benzamides **50**, **53**, and **54**, compared with the unsubstituted derivative **48**, suggested that an accessory hydrophobic effect occurred between the group in the meta position and the receptor protein. Moreover, examination of the benzamide monosubstitution pattern revealed that this interaction was subjected to strict directional and size requirements. Substitution in the meta position was the only one allowed (**50** compared to **49**, **51**), and the size of the group should be between that of a fluorine (**52**) and that of an ethoxy group (**55**). Finally, it seemed that there was no electrostatic component contributing to the meta effect (**56**). Taking into account the deleterious consequences on binding of a para substituent alone (**51**), it was puzzling that some meta−para substituent combinations on the benzamide ring could act synergistically (**58**, Table 1, compared to **50**). This synergistic effect was only observed when the substituent in the para position was not larger than a methyl group (**58**, **63**, **64** compared to **65**, **66**). With the backbone of the ligand now roughly in place, we attempted to refine our understanding of the contribution of the substituent in the 6-position of the pyridine ring.

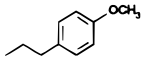
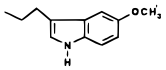
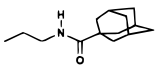
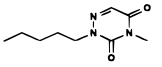
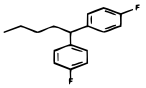
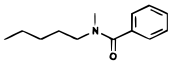
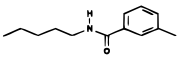
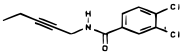
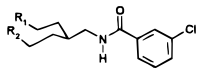
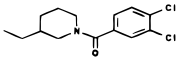
(c) Modulation of the Substituent in the 6-Position of the Pyridine. Data summarized in Table 5 showed that the R substituent modulated affinity values over more than 2 orders of magnitude. In general, electron-withdrawing groups bound poorly to the receptor (**22**, **31**, **38**, **39**), whereas electron-releasing groups (*n*-donors: **28**, **30**, **32**, **34**, **36**, **37**) and particularly π-donors, such as five-membered heteroaromatic rings C-bound to pyridine (**41**, **42**, **67**, **70**, **71**), had high affinity for 5-HT_{1A} sites.[34] Qualitatively, the effect of the R substituent is consistent with what would be expected if the pharmacophore was acting by stabilization of a positive charge on the protein. We assumed that derivative **27** may combine favorable inductive donor and steric effects. The size range of the R substituent was well-delineated, extending from an upper exclusion limit of four contiguous atoms (**29**, **35**) to a lower one of two atoms, below which some favorable hydrophobic interactions may be lost (**16, 25**, **26**).

Fortunately, the most active compounds were among the most selective toward α_1 and D_2 receptors, the degree of selectivity being, in general, similar to that of (±)-8-OH-DPAT. Selectivity is important because interactions with other receptors, in particular α_1 and D_2, are known to influence the in vivo expression of 5-HT_{1A} agonist activity.[35,36]

Derivatives shown in Table 5 displayed pEC_{50} values to inhibition of forskolin-stimulated cAMP that differed by more than 2 log units, reminiscent of the trend seen with affinity values. Moreover, derivatives having nanomolar affinity for the receptor also inhibited the accumulation of cAMP with greater efficacy (E_{max}) than (±)-8-OH-DPAT (Table 5, footnote). Hence, common elements of the pharmacophore may participate in recognition and activation of the 5-HT_{1A} receptor. Again, compounds containing a C-bound five-membered

Table 3. Effects of the Nature of the Chain on 5-HT_{1A} Affinity



compd	R_1	R_2	5-HT_{1A} affinity pKi [ab]	mp °C [c]
75	nC_3H_9	nC_3H_9	<5.0	90-95[d]
76	H		5.69 ± 0.01[b]	170-172[e]
77	H		6.18 ± 0.08[b]	123-125[e]
78	H		7.56 ± 0.15[b]	195-197[d]
79	H		6.96 ± 0.03[b]	165-167[e]
80	H		6.82 ± 0.03[b]	145-147[e]
81	H		6.77 ± 0.02[b]	179-181[d]
82	H		7.85 ± 0.05[b]	184-186[d]
83	H		6.61 ± 0.02[b]	162-164[f]
84			5.55 ± 0.03[b]	160-162[e]
85	H		6.39 ± 0.17[b]	191-193[e]

[a,b] See footnotes of Table 1. [c] Experimental Section. [d] Oxalate. [e] Fumarate. [f] Maleate.

heteroaromatic ring substituent emerged as especially potent (pEC_{50}): **41**, **42**, **67**, **70**, and **71**. Interestingly, the two exceptions in this subset were the 6-pyrrol-2-yl and the 6-imidazol-2-yl derivatives **44** and **69**, respectively. Their modest in vitro profiles compared with that of the close analogue **67** suggest that the hydrogen-bonding ability of the group in the 2′-position of the five-membered ring pyridine substituent may be one of the factors influencing the affinity and the potency of compounds belonging to this subset. This group was a hydrogen-bond donor in **44** and **69** but a hydrogen-bond acceptor in **67**.[37]

Taken together, the in vitro results pointed to a C-bound five-membered heteroaromatic ring as the 6-substituent of choice for pyridine, although some 6-amino derivatives also deserve consideration (**32**, **34**, **36**). However, it still remains unclear which properties of the 6-substituted-2-pyridinylmethylamine system (e.g., hydrogen-bonding ability, charge-transfer or chelating potentials, etc.) determine intrinsic activity.

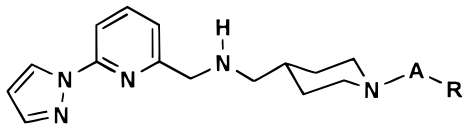
The novel 5-HT_{1A} ligands described here were found to have high intrinsic activity, and because of the hypothesized importance of intrinsic activity in the antidepressant effect of 5-HT_{1A} agonists, future studies will examine their effects in vivo.

Conclusions

In this paper, we summarized briefly the pharmacological rationale that prompted the search for novel, potent, and efficacious 5-HT_{1A} agonists. We then described the basic concept that guided the design of a structurally novel 5-HT_{1A} pharmacophore. Importantly, the approach adopted did not rely on assumptions concerning the geometry of the receptor protein. Finally, we reported the preparation of various novel compounds and discussed their preliminary in vitro pharmacological properties.

Taken together, the results show that this novel class of ligands is characterized by a high binding affinity for 5-HT_{1A} receptors and a high selectivity versus α_1 and

Table 4. Effects of the Nature of the *N*-Piperidine Substituent on 5-HT_{1A} Affinity



compd	A	R	5-HT_{1A} affinity pKi [a,b]
59	CH_2	3,4-dichlorophenyl	7.75 ± 0.03[b]
60	SO_2	3,4-dichlorophenyl	6.70 ± 0.09[b]
46	CO	cyclohexyl	7.53 ± 0.03[b]
47	CO	1-adamantyl	7.88 ± 0.06[b]
48	CO	phenyl	7.48 ± 0.02[b]
49	CO	2-chlorophenyl	6.88 ± 0.06[b]
50	CO	3-chlorophenyl	8.64 ± 0.11
51	CO	4-chlorophenyl	7.31 ± 0.02[b]
52	CO	3-fluorophenyl	7.87 ± 0.02[b]
53	CO	3-methylphenyl	8.46 ± 0.04
54	CO	3-trifluoromethylphenyl	8.45 ± 0.02
55	CO	3-ethoxyphenyl	7.97 ± 0.02
56	CO	3-cyanophenyl	7.75 ± 0.05[b]
57	CO	2,3-dichlorophenyl	7.00 ± 0.17[b]
62	CO	3,5-dichlorophenyl	7.58 ±0.07[b]
63	CO	3-chloro, 4-fluorophenyl	8.81 ± 0.04
64	CO	3-chloro, 4-methylphenyl	8.85 ± 0.04
65	CO	3-chloro, 4-methoxyphenyl	8.04 ± 0.01
66	CO	3-chloro, 4-methoxycarbonylphenyl	6.78 ± 0.08[b]

[a,b] See footnotes of Table 1.

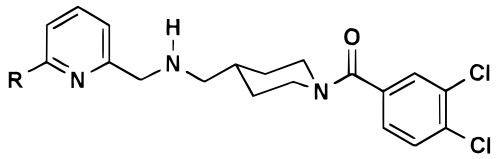
D_2 receptors. Several members of this class behave in vitro as more potent inhibitors of forskolin-induced cAMP accumulation than the prototypical agonist (±)-8-OH-DPAT. From a structural standpoint, the 6-substituted-2-pyridinylmethylamine motif was used in an effort to obtain a novel 5-HT_{1A} pharmacophore. The importance of the 6-substituent on the pyridine nucleus in the recognition and activation of 5-HT_{1A} receptors was established. In addition, examples were given of the unexpected sensitivity of 5-HT_{1A} binding to the structural integrity of the entire molecule. The very interesting in vitro profile of the most active derivatives warrants a further examination of their properties in biochemical and behavioral studies. Already, these derivatives and their analogues may provide innovative tools that could contribute to the further characterization of 5-HT_{1A} receptors and, perhaps, to a better understanding of their functional roles and therapeutic significance.

Experimental Section

Melting points were determined on a Büchi 530 melting point apparatus and were not corrected. ^{1}H NMR spectra were recorded on a Bruker AC200 (200-MHz) instrument. Chemical shifts are reported in δ value (ppm) relative to an internal standard of tetramethylsilane in $CDCl_3$ or DMSO-d_6. Infrared (IR) spectra were obtained on a Nicolet FT 510 P spectrophotometer. Microanalyses were obtained on a Fison EA 1108/CHN analyzer, and the results obtained were ±0.4% of the theoretical values. Analytical thin-layer chromatography was carried out on precoated plates (silica gel, 60 F 254 Merck). SDS silica gel (0.040−0.063 mm) was used for flash chromatography. Organic extracts were dried over $MgSO_4$ unless otherwise noted.

Method A. (3,4-Dichlorophenyl)(4-{[(6-fluoropyridin-2-ylmethyl)amino]methyl}piperidin-1-yl)methanone (22). A solution of **8a** (0.58 g, 4.62 mmol), 4-(aminomethyl)piperidine (0.53 g, 4.62 mmol), and toluene (25 mL) was heated under reflux for 2 h with water separation by a Dean−Stark trap. The solvent was removed under vacuum, and the residue was taken up in THF (10 mL) and TEA (0.68 mL, 4.9 mmol). To

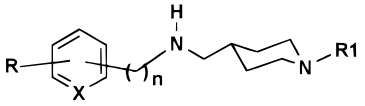
Table 5. Receptor Binding Profile and Agonist Activity of Compounds of the Type (3,4-Dichlorophenyl)(4-{[(6-substituted-pyridin-2-ylmethyl)amino]methyl}piperidin-1-yl)methanone



		receptor binding (pKi)[a,b]			agonist activity[c]
compd	R	5-HT_{1A}	D_2	α_1	pEC_{50}
16	H	7.58 ± 0.15	NT	NT	NT
22	F	8.05 ± 0.10	<5.0	5.85 ± 0.05	6.43 ± 0.08
25	Cl	8.34 ± 0.12	5.20 ± 0.09	6.24 ± 0.04	6.75 ± 0.06
26	CH_3	8.39 ± 0.05	5.32 ± 0.05	6.32 ± 0.02	7.41 ± 0.05
27	$(CH_3)_2CH$	9.20 ± 0.12	6.44 ± 0.09	6.75 ± 0.02	7.77 ± 0.12
28	CH_3O	8.46 ± 0.02	<5.0	6.43 ± 0.02	7.93 ± 0.28
29	nC_4H_9O	7.73 ± 0.02[b]	NT	NT	NT
30	CH_3S	8.59 ± 0.10	5.90 ± 0.04	6.56 ± 0.04	7.34 ± 0.09
31	CH_3SO	7.33 ±0.02[b]	NT	NT	NT
32	CH_3NH	8.76 ± 0.06	5.51 ± 0.05	6.87 ± 0.04	7.66 ± 0.12
34	$(CH_3)_2N$	8.85 ± 0.11	6.28 ± 0.04	6.92 ± 0.03	7.69 ± 0.14
35	$nC_3H_7(CH_3)N$	7.93 ± 0.04[b]	NT	NT	NT
36	azetidino	9.43 ± 0.05	6.22 ± 0.13	6.64 ± 0.04	8.15 ± 0.03
37	pyrrolidino	8.80 ± 0.17	6.43 ± 0.17	6.98 ± 0.01	7.18 ± 0.33
38	N≡—	7.30 ± 0.14[b]	NT	NT	NT
39	H_2NCO	7.33 ± 0.09[b]	NT	NT	NT
43	pyrrol-1-yl	8.37 ± 0.12	6.30 ± 0.06	6.93 ± 0.02	7.45 ± 0.12
58	pyrazol-1-yl	8.78 ± 0.09	6.00 ± 0.03	6.48 ± 0.13	7.23 ± 0.13
68	imidazol-1-yl	8.13 ± 0.12	5.24 ± 0.07	6.26 ± 0.06	7.43 ± 0.02
44	pyrrol-2-yl	8.22 ± 0.03	6.61 ± 0.03	7.14 ± 0.02	7.15 ± 0.17
69	imidazol-2-yl	8.57 ± 0.04	5.43 ± 0.04	6.45 ± 0.03	7.44 ± 0.18
67	pyrazol-3-yl	9.27 ± 0.10	6.01 ± 0.03	6.66 ± 0.07	8.52 ± 0.11
42	thien-2-yl	8.86 ± 0.04	6.54 ± 0.07	6.76 ± 0.05	8.24 ± 0.06
71	thiazol-2-yl	9.46 ± 0.08	5.47 ± 0.07	6.75 ± 0.05	8.30 ± 0.13
41	furan-2-yl	9.14 ± 0.06	6.34 ± 0.08	6.71 ± 0.07	8.28 ± 0.35
70	oxazol-5-yl	9.03 ± 0.01	6.06 ± 0.04	6.55 ± 0.02	8.70 ± 0.02
40	phenyl	8.13 ± 0.12	5.53 ± 0.08	6.68 ± 0.03	6.78 ± 0.24
8-OH-DPAT		8.85 ± 0.07	6.26 ± 0.03	5.88 ± 0.01	7.60 ± 0.17[d]

[a,b] See footnotes of Table 1. [c] See Experimental Section for details. Each value is the mean ± SEM of two independent determinations, each performed in triplicate. [d] Mean ± SEM of five determinations. NT, not tested. Forskolin-stimulated cAMP levels in HA7 cells were inhibited by (±)-8-OH-DPAT (E_{max} = 71 ± 4.3%) and to a greater extent (E_{max} > 80%) by all the other compounds (data not shown).

Table 6. Physical Data of Substituted-4-[(pyridinylalkylamino)methyl]piperidines



Compd	X	R	Chain position	n	R_1	Method	% yield	Formula[a]	mp °C
16	N	H	2	1	3,4-dichlorobenzoyl	A	57	$C_{19}H_{21}Cl_2N_3O.C_4H_4O_4$[b]	144-146
17	N	H	2	2	3,4-dichlorobenzoyl	C	54	$C_{20}H_{23}Cl_2N_3O.C_2H_2O_4$[c]	173-175
18	N	H	2	3	3,4-dichlorobenzoyl	A	39	$C_{21}H_{25}Cl_2N_3O.C_4H_4O_4$[d]	140-142
19	N	H	3	1	3,4-dichlorobenzoyl	A	42	$C_{19}H_{21}Cl_2N_3O.1.5C_2H_2O_4$[c]	159-161
20	N	H	3	2	3,4-dichlorobenzoyl	C	47	$C_{20}H_{23}Cl_2N_3O.1.5C_4H_4O_4$[d]	141-143
21	N	H	4	2	3,4-dichlorobenzoyl	C	58	$C_{20}H_{23}Cl_2N_3O.1.5C_4H_4O_4$[d]	149-151
22	N	6-F	2	1	3,4-dichlorobenzoyl	A	40	$C_{19}H_{20}Cl_2FN_3O.C_2H_2O_4$[c]	182-184
23	N	6-F	2	2	3,4-dichlorobenzoyl	C	52	$C_{20}H_{22}Cl_2FN_3O.C_4H_4O_4$[b]	155-157
24	N	4-Cl	2	1	3,4-dichlorobenzoyl	A	51	$C_{19}H_{20}Cl_3N_3O.C_4H_4O_4$[b]	150-152
25	N	6-Cl	2	1	3,4-dichlorobenzoyl	A	37	$C_{19}H_{20}Cl_3N_3O.C_4H_4O_4$[d]	174-176
26	N	6-CH_3	2	1	3,4-dichlorobenzoyl	A	56	$C_{20}H_{23}Cl_2N_3O.C_4H_4O_4$[d]	156-158
27	N	6-$CH(CH_3)_2$	2	1	3,4-dichlorobenzoyl	A	49	$C_{22}H_{27}Cl_2N_3O.C_4H_4O_4$[d]	148-150
28	N	6-OCH_3	2	1	3,4-dichlorobenzoyl	A	34	$C_{20}H_{23}Cl_2N_3O_2.C_4H_4O_4$[b]	150-152
29	N	6-OC_4H_9n	2	1	3,4-dichlorobenzoyl	A	41	$C_{23}H_{29}Cl_2N_3O_2.C_4H_4O_4$[d]	160-162
30	N	6-SCH_3	2	1	3,4-dichlorobenzoyl	A	35	$C_{20}H_{23}Cl_2N_3OS.C_2H_2O_4$[c]	142-144
31	N	6-$S(O)CH_3$	2	1	3,4-dichlorobenzoyl	A	30	$C_{20}H_{23}Cl_2N_3O_2.S.C_2H_2O_4$[c]	114-116
32	N	6-$NHCH_3$	2	1	3,4-dichlorobenzoyl	B_1	48	$C_{20}H_{24}Cl_2N_4O.C_4H_4O_4$[b]	117-119
33	N	4-$N(CH_3)_2$	2	1	3,4-dichlorobenzoyl	B_1	53	$C_{21}H_{26}Cl_2N_4O.C_2H_2O_4$[c]	169-171
34	N	6-$N(CH_3)_2$	2	1	3,4-dichlorobenzoyl	B_1	61	$C_{21}H_{26}Cl_2N_4O.C_4H_4O_4$[d]	175-177
35	N	6-$N(CH_3)C_3H_7$n	2	1	3,4-dichlorobenzoyl	B_1	36	$C_{23}H_{30}Cl_2N_4O.C_2H_2O_4$[c]	186-188
36	N	6-azetidino	2	1	3,4-dichlorobenzoyl	B_1	52	$C_{22}H_{26}Cl_2N_4O.C_2H_2O_4$[c]	219-221
37	N	6-pyrrolidino	2	1	3,4-dichlorobenzoyl	B_1	54	$C_{23}H_{28}Cl_2N_4O.C_2H_2O_4$[c]	203-205
38	N	6-cyano	2	1	3,4-dichlorobenzoyl	A	48	$C_{20}H_{20}Cl_2N_4O.C_4H_4O_4$[b]	144-146
39	N	6-carboxamido	2	1	3,4-dichlorobenzoyl	B_1	27	$C_{20}H_{22}Cl_2N_4O_2.C_4H_4O_4$[d]	211-213
40	N	6-phenyl	2	1	3,4-dichlorobenzoyl	A	52	$C_{25}H_{25}Cl_2N_3O.C_4H_4O_4$[d]	128-130
41	N	6-furan-2-yl	2	1	3,4-dichlorobenzoyl	A	47	$C_{23}H_{23}Cl_2N_3O_2.0.5C_4H_4O_4$[d]	178-180
42	N	6-thien-2-yl	2	1	3,4-dichlorobenzoyl	A	53	$C_{23}H_{23}Cl_2N_3OS.C_2H_2O_4$[c]	208-210
43	N	6-pyrrol-1-yl	2	1	3,4-dichlorobenzoyl	B_2	57	$C_{23}H_{24}Cl_2N_4O.0.5C_4H_4O_4$[d]	174-176
44	N	6-pyrrol-2-yl	2	1	3,4-dichlorobenzoyl	A	41	$C_{23}H_{24}Cl_2N_4O.C_2H_2O_4$[c]	200-210
45	N	4-pyrazol-1-yl	2	1	3,4-dichlorobenzoyl	B_2	54	$C_{22}H_{23}Cl_2N_5O.C_4H_4O_4$[b]	118-120
46	N	6-pyrazol-1-yl	2	1	cyclohexylcarbonyl	A	37	$C_{22}H_{31}N_5O.C_2H_2O_4$[c]	197-199
47	N	6-pyrazol-1-yl	2	1	1-adamantylcarbonyl	A	43	$C_{26}H_{35}N_5O.C_2H_2O_4$[c]	224-226
48	N	6-pyrazol-1-yl	2	1	benzoyl	A	51	$C_{22}H_{25}N_5O.1.5C_4H_4O_4$[d]	161-163

Table 6 (Continued)

Compd	X	R	Chain position	n	R_1	Method	% yield	Formula[a]	mp °C
49	N	6-pyrazol-1-yl	2	1	2-chlorobenzoyl	A	53	$C_{22}H_{24}ClN_5O.C_2H_2O_4$[c]	212-214
50	N	6-pyrazol-1-yl	2	1	3-chlorobenzoyl	A	55	$C_{22}H_{24}ClN_5O.C_2H_2O_4$[c]	174-176
51	N	6-pyrazol-1-yl	2	1	4-chlorobenzoyl	A	49	$C_{22}H_{24}ClN_5O.1.5C_4H_4O_4$[d]	177-179
52	N	6-pyrazol-1-yl	2	1	3-fluorobenzoyl	A	51	$C_{22}H_{24}FN_5O.1.5C_4H_4O_4$[d]	183-185
53	N	6-pyrazol-1-yl	2	1	3-methylbenzoyl	A	54	$C_{23}H_{27}N_5O.C_4H_4O_4$[d]	188-190
54	N	6-pyrazol-1-yl	2	1	3-trifluoromethylbenzoyl	A	49	$C_{23}H_{24}F_3N_5O.C_4H_4O_4$[d]	160-162
55	N	6-pyrazol-1-yl	2	1	3-ethoxybenzoyl	A	50	$C_{24}H_{29}N_5O_2.C_4H_4O_4$[d]	143-145
56	N	6-pyrazol-1-yl	2	1	3-cyanobenzoyl	A	39	$C_{23}H_{24}N_6O.C_4H_4O_4$[d]	209-211
57	N	6-pyrazol-1-yl	2	1	2,3-dichlorobenzoyl	A	47	$C_{22}H_{23}Cl_2N_5O.C_4H_4O_4$[d]	190-192
58	N	6-pyrazol-1-yl	2	1	3,4-dichlorobenzoyl	A	53	$C_{22}H_{23}Cl_2N_5O.C_4H_4O_4$[b]	152-154
59	N	6-pyrazol-1-yl	2	1	3,4-dichlorobenzyl	D	44	$C_{22}H_{25}Cl_2N_5.2C_4H_4O_4$[d]	201-203
60	N	6-pyrazol-1-yl	2	1	3,4-dichlorophenylsulfonyl	E	35	$C_{21}H_{23}Cl_2N_5O_2S.C_4H_4O_4$[d]	199-201
61	N	6-pyrazol-1-yl	2	2	3,4-dichlorobenzoyl	B_2	49	$C_{23}H_{25}Cl_2N_5O.C_4H_4O_4$[b]	148-150
62	N	6-pyrazol-1-yl	2	1	3,5-dichlorobenzoyl	A	48	$C_{22}H_{23}Cl_2N_5O.C_4H_4O_4$[d]	191-193
63	N	6-pyrazol-1-yl	2	1	3-chloro, 4-fluorobenzoyl	A	52	$C_{22}H_{23}Cl_1FN_5O.C_4H_4O_4$[d]	181-183
64	N	6-pyrazol-1-yl	2	1	3-chloro, 4-methylbenzoyl	A	44	$C_{23}H_{26}Cl_1N_5O.C_4H_4O_4$[d]	206-208
65	N	6-pyrazol-1-yl	2	1	3-chloro, 4-methoxybenzoyl	A	42	$C_{23}H_{26}ClN_5O_2.C_4H_4O_4$[d]	173-175
66	N	6-pyrazol-1-yl	2	1	3-chloro, 4-methoxycarbonylbenzoyl	A	31	$C_{24}H_{26}ClN_5O_3.C_2H_2O_4$[d]	176-178
67	N	6-pyrazol-3-yl	2	1	3,4-dichlorobenzoyl	A	54	$C_{22}H_{23}Cl_2N_5O.C_2H_2O_4$[d]	145-150
68	N	6-imidazol-1-yl	2	1	3,4-dichlorobenzoyl	B_2	53	$C_{22}H_{23}Cl_2N_5O.C_4H_4O_4$[d]	125-130
69	N	6-imidazol-2-yl	2	1	3,4-dichlorobenzoyl	A	47	$C_{22}H_{23}Cl_2N_5O.C_4H_4O_4$[d]	206-208
70	N	6-oxazol-5-yl	2	1	3,4-dichlorobenzoyl	A	38	$C_{22}H_{22}Cl_2N_4O_2.C_2H_2O_4$[c]	189-191
71	N	6-thiazol-2-yl	2	1	3,4-dichlorobenzoyl	A	52	$C_{22}H_{22}Cl_2N_4OS.C_4H_4O_4$[d]	187-189
72	CH	F	3	1	3,4-dichlorobenzoyl	A	57	$C_{20}H_{21}Cl_2FN_2O.C_2H_2O_4$[c]	199-201
73	CH	$N(CH_3)_2$	3	1	3,4-dichlorobenzoyl	A	35	$C_{22}H_{27}Cl_2N_3O.C_2H_2O_4$[c]	237-239
74	CH	pyrrol-1-yl	3	1	3,4-dichlorobenzoyl	A	48	$C_{24}H_{24}Cl_2N_3O.C_4H_4O_4$[b]	139-141

[a] The analyses for all compounds were within 0.4% of the theoretical value for C, H, and N. [b] Maleate. [c] Oxalate. [d] Fumarate.

Table 7. Experimental Details for Each of the Binding Assays

	[^{3}H]ligand		tissue (rat)		incubation		nonspecific binding		
binding site	K_D (nM)	concn (nM)	type	concn (mg/mL)	time (min)	temp (°C)	drug	concn (μM)	buffer
5-HT_{1A}[b]	8-OH-DPAT (3.1)	0.2	cortex	10	30	23	5-HT	10	A
D_2[c]	YM-09151-2 (0.036)	0.05	striatum	1	60	23	(+)-butaclamol	1	B
α_1[b]	prazosin (0.063)	0.1	cortex	5	30	23	phentolamine	50	C

[a] Buffers: (A) Tris HCl (50 mM, pH 7.4), pargyline (10 μM, $CaCl_2$ (4 mM), ascorbic acid (0.1%); (B) Tris HCl (50 mM, pH 7.4), NaCl (120 mM), KCl (5 mM); (C) Tris HCl (50 mM, pH 7.4). [b] Reference 40. [c] Reference 41.

this cooled solution (ice bath) was added 3,4-dichlorobenzoyl chloride (0.68 g, 4.62 mmol) in THF (2 mL), and stirring was continued at room temperature for 2 h. Methanol (10 mL) was added followed by KBH_4 (0.50 g, 9.27 mmol), and stirring was continued at room temperature for 4 h. The mixture was concentrated, taken up in CH_2Cl_2, washed with water and brine, dried, and concentrated. Purification by flash chromatography (5% MeOH−CH_2Cl_2) gave 0.73 g (40%) of **22** as a pale-yellow solid: mp 77−79 °C. The oxalate salt of **22** was crystallized from MeOH−EtOAc to afford a white solid (0.65 g): mp 182−184 °C; ^{1}H NMR (DMSO-d_6) δ 1.19 (m, 2H), 1.90 (m, 3H), 2.85 (m, 3H), 3.04 (m,1H), 3.47 (s, 1H), 4.24 (s, 2H), 4.39 (m, 1H), 7.20 (dd, 1H), 7.36 (dd, 1H), 7.48 (dd, 1H), 7.70 (m, 2H), 8.05 (dd, 1H), 8.15 (s, broad, 2H). Anal. ($C_{19}H_{20}C_{l2}FN_3O\cdot C_2H_2O_4$) C, H, N.

Method B1. (3,4-Dichlorophenyl)(4-{[(6-azetidin-1-ylpyridin-2-ylmethyl)amino]methyl}piperidin-1-yl)methanone (36). A solution of **22** (0.70 g, 1.77 mmol), THF (10 mL), and azetidine (0.20 g, 3.54 mmol) was heated at 100 °C for 17 h. After cooling to room temperature, the mixture was concentrated under vacuum, and water was added. The product was extracted with CH_2Cl_2, washed with water and brine, dried, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (10% MeOH−CH_2Cl_2) to give 0.40 g (52%) of **36** as a pale-yellow oil. The oxalate salt of **36** was crystallized from EtOH−EtOAc to give a white solid (0.35 g): mp 219−221 °C; ^{1}H NMR (DMSO-d_6) δ 1.19 (m, 2H), 1.80 (m, 2H) 2.00 (m, 1H), 3.35 (m, 2H), 2.75 (m, 1H), 2.88 (d, 2H), 3.04 (m, 1H), 3.49 (m, 1H), 3.95 (t, 4H), 4.09 (s, 2H), 4.39 (m, 1H), 6.31 (d, 1H), 6.68 (d, 1H), 7.35 (dd, 1H), 7.53 (t, 1H), 7.65 (d, 1H), 7.70 (d, 1H). Anal. ($C_{22}H_{26}Cl_2N_4O\cdot C_2H_2O_4$) C, H, N.

Method B2. (3,4-Dichlorophenyl)(4-{[(6-pyrrol-1-ylpyridin-2-ylmethyl)amino]methyl}piperidin-1-yl)methanone (43). To a solution of pyrrole (0.45 g, 6.70 mmol) in anhydrous DMF (5 mL), under a nitrogen atmosphere, was added NaH (60% oil dispersion, 0.27 g, 6.75 mmol). After the mixture stirred at room temperature for 1 h, a solution of **22** (1.32 g, 3.33 mmol) in DMF (2 mL) was added, and the mixture was stirred at 60 °C for 2 h. The cooled solution was poured into ice−water and extracted with EtOAc. The organic layer was washed with water and brine, dried, and filtered, and the solvent was removed under vacuum. Purification by flash chromatography (5% MeOH−CH_2Cl_2) gave an oily residue which on trituration with Et_2O gave **43** as a pale-yellow solid (0.85 g; 57%): mp 108−110 °C. The hemifumarate salt of **43** was crystallized from EtOH−EtOAc to give a white solid: mp 174−176 °C; ^{1}H NMR ($CDCl_3$) δ 1.12 (m, 2H), 1.81 (m, 3H), 2.60 (m, 2H), 2.94 (s, 1H), 3.60 (m, 2H), 3.95 (s, 2H), 4.59 (s, 1H), 6.25 (t, 2H), 6.65 (s, 1H), 7.01 (d, 1H), 7.14 (m, 2H), 7.39 (m, 4H), 7.64 (t, 1H). Anal. ($C_{23}H_{24}Cl_2N_4O\cdot 0.5C_4H_4O_4$) C, H, N.

Method C. (3,4-Dichlorophenyl){4-[(2-pyridin-4-ylethylamino)methyl]piperidin-1-yl}methanone (21). A solution of **5** (0.80 g, 2.80 mmol), 4-(2-aminoethyl)pyridine (0.34 g, 2.80 mmol), and toluene (30 mL) was heated under reflux for 2 h with water separation by a Dean−Stark trap. The solvent was removed under vacuum and then the residue taken up in MeOH (30 mL) and cooled to 0−5 °C, and KBH_4 (0.30 g, 5.6 mmol) was added portionwise. Stirring was continued at room temperature for 18 h. The mixture was concentrated, extracted with CH_2Cl_2, washed with water and brine, dried, filtered, and concentrated under vacuum to give a yellow oil. Purification by flash chromatography (10% MeOH−CH_2Cl_2) afforded 0.64 g (58%) of **21** as a pale-yellow oil. The fumarate salt of **21** was crystallized from EtOH−EtOAc to give a white solid (0.55 g): mp 149−151 °C; ^{1}H NMR (DMSO-d_6) δ 1.34 (m, 2H), 1.75 (m, 1H), 1.95 (m, 1H), 2.14 (m, 1H), 2.90−3.25 (m, 4H), 2.33−3.54 (m, 4H), 3.74 (m, 1H), 4.53 (m, 1H), 6.60 (s, 3H), 7.32 (dd, 1H), 7.60 (d, 1H), 7.64 (d, 1H), 7.95 (d, 2H), 8.71 (d, 2H). Anal. ($C_{20}H_{23}Cl_2N_3O\cdot 1.5C_4H_4O_4$) C, H, N.

Method D. [1-(3,4-Dichlorobenzyl)piperidin-4-ylmethyl](6-pyrazol-1-ylpyridin-2-ylmethyl)amine (59). A solution of the amide **58** (0.70 g, 1.57 mmol) in THF (5 mL) was added over 15 min to a suspension of $LiAlH_4$ (90 mg, 2.37 mmol) in THF (10 mL) maintained at 0 °C. Stirring was continued for 18 h at room temperature; then the reaction was quenched by addition of H_2O and 1 N NaOH. The mixture was filtered through Celite and the solid washed with THF. The filtrate was evaporated to dryness and then the residue taken up in CH_2Cl_2, dried, and concentrated. The product was purified by flash chromatography (10% MeOH−CH_2Cl_2) to give 0.30 g (44%) of **59** as a pale-yellow oil. The fumarate salt was crystallized from EtOH to afford a white solid (0.33 g): mp 201−203 °C; ^{1}H NMR (DMSO-d_6) δ 1.23 (m, 2H), 1.77 (m, 3H), 1.99 (t, 2H), 2.76 (m, 4H), 3.50 (s, 2H), 4.22 (s, 2H), 6.52 (s, 2H), 6.57 (t, 1H), 7.27 (dd, 1H), 7.38 (d, 1H), 7.53 (m, 2H), 7.83 (d, 2H), 7.99 (t, 1H), 8.82 (d, 1H). Anal. ($C_{22}H_{25}Cl_2N_5\cdot 2C_4H_4O_4$) C, H, N.

Method E. [1-(3,4-Dichlorophenylsulfonyl)piperidin-4-ylmethyl](6-pyrazol-1-ylpyridin-2-ylmethyl)amine (60). This product was prepared from aldehyde **8b**, 4-(aminomethyl)piperidine, and 3,4-dichlorobenzenesulfonyl chloride as described for compound **22**. Purification by flash chromatography (5% MeOH−CH_2Cl_2) followed by salt formation with fumaric acid gave the fumarate salt of **60** as a white solid (35%): mp 199−201 °C; ^{1}H NMR (DMSO-d_6) δ 1.18 (m, 2H), 1.57 (m, 1H), 1.80 (d, 2H), 2.32 (t, 2H), 2.55 (d, 2H), 3.63 (d, 2H), 3.96 (s, 2H), 6.55 (s, 2H), 6.57 (d, 1H), 7.35 (d, 1H), 7.69 (dd, 1H), 7.77 (m, 2H), 7.94 (m, 3H), 8.70 (d, 1H). Anal. ($C_{21}H_{23}Cl_2N_5O_2S\cdot C_4H_4O_4$) C, H, N.

1-(3,4-Dichlorobenzoyl)piperidine-4-carboxaldehyde (5). To a solution of oxalyl chloride (2.72 mL, 31 mmol) in CH_2Cl_2 (50 mL), cooled to −70 °C, was added DMSO (4.1 mL, 58 mmol) dropwise. Stirring was continued at −60 °C for 10 min followed by addition of a solution of (3,4-dichlorophenyl)[4-(hydroxymethyl)piperidin-1-yl]methanone[30] (7.50 g, 26 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 1 h at −60 °C; then DIEA (18 mL, 104 mmol) was added dropwise and the temperature allowed to reach to room temperature. Water was added, and the organic layer was washed with 1 N HCl, water, and brine, dried, filtered, and concentrated. Purification by flash chromatography (30% EtOAc−CH_2Cl_2) gave 5.65 g (76%) of **5** as a white solid: mp 101−103 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.95 (m, 2H), 2.54 (m, 1H), 3.13 (m, 2H), 3.68 (m, 1H), 4.35 (m, 1H), 7.18 (dd, 1H), 7.46 (m, 2H), 9.66 (s, 1H); IR (KBr, cm^{-1}) 1640, 1732. Anal. ($C_{13}H_{13}Cl_2NO_2$) C, H, N.

6-Fluoro-2-pyridinecarboxaldehyde (8a). A solution of 6-fluoro-2-picoline (20 g, 0.18 mol) and *tert*-butoxybis(dimethylamino)methane (47 g, 0.27 mol) was heated, under a nitrogen atmosphere, at 140 °C for 24 h. The cooled reaction mixture was diluted with THF (100 mL), and a solution of $NaIO_4$ (77 g, 0.36 mol) in water (400 mL) was added. The mixture was stirred overnight at room temperature; then the precipitate was filtered off. THF was removed under vacuum, and the product was extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and filtered. The solution was carefully concentrated (the boiling point of the product is low), and the residual brown oil was submitted to distillation to give 7.40 g (33%) of **8a** as a pale-yellow oil: bp 65−70 °C (80 mb); ^{1}H NMR ($CDCl_3$) δ 7.16 (dd, 1H), 7.82 (dd, 1H), 7.96 (m, 1H), 9.90 (s, 1H); IR (film, cm^{-1}) 1713.

6-Fluoro-2-(1,3-dioxolan-2-yl)pyridine (7a). A solution of **8a** (7.40 g, 59 mmol), ethanediol (11.2 mL, 180 mmol), and *p*-toluenesulfonic acid monohydrate (0.25 g) in benzene (80 mL) was heated under reflux for 18 h with water separation by a Dean−Stark trap. The solvent was removed under vacuum and the residue taken up in Et_2O and washed with 10% $NaHCO_3$ solution and then brine. The organic layer was dried and filtered, and the solvent was removed under reduced pressure. The oily residue was distilled to give 8 g (80%) of **7a** as a pale-yellow oil: bp 75−80 °C (0.1 mb); ^{1}H NMR ($CDCl_3$) δ 4.05 (m, 2H), 4.16 (m, 2H), 5.77 (s, 1H), 6.90 (dd, 1H), 7.39 (dd, 1H), 7.79 (dd, 1H).

6-Pyrazolo-2-(1,3-dioxolan-2-yl)pyridine (7b). To a suspension of HNa (60% dispersion in mineral oil, 7 g, 0.174 mol)

in anhydrous DMF (50 mL) under a nitrogen atmosphere was added dropwise a solution of pyrazole (11.85 g, 0.174 mol) in DMF (55 mL). After 2 h, **7a** (9.81 g, 0.058 mol) was added dropwise, and the mixture was stirred at 80 °C for 3 h. The reaction mixture was poured in ice−water and extracted with EtOAc. The combined extracts were washed with water and brine, dried, and filtered, and the solvent was removed under vacuum. The product was purified by flash chromatography (20% EtOAc−hexane) to give 9.50 g (75%) of **7b** as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ 4.10 (m, 2H), 4.22 (m, 2H), 5.87 (s, 1H), 6.45 (dd, 1H), 7.43 (dd, 1H), 7.73 (d, 1H), 7.86 (t, 1H), 7.98 (dd, 1H), 8.62 (d, 1H).

6-Pyrazol-1-ylpyridine-2-carboxaldehyde (8b). A mixture of **7b** (9.50 g, 43.7 mmol), $CuSO_4 \cdot 5H_2O$ (1.09 g, 4.37 mmol), formic acid (80 mL), and water (20 mL) was stirred at 65 °C for 5 h. The solution was concentrated under vacuum, and the residual formic acid was eliminated by azeotropic distillation with toluene. The oil was taken up in ice−water and made basic with excess K_2CO_3. The product was extracted with EtOAc, washed with diluted NH_4OH and brine, dried, and concentrated under vacuum. The product was isolated by flash chromatography (10% EtOAc−CH_2Cl_2) to give 6 g (79%) of **8b** as a pale-yellow solid: mp 75−76 °C; ^{1}H NMR ($CDCl_3$) δ 6.52 (dd, 1H), 7.78 (s, 1H), 7.84 (dd, 1H), 7.99 (t, 1H), 8.23 (dd, 1H), 8.67 (d, 1H), 10.04 (s, 1H); IR (KBr, cm^{-1}) 1701. Anal. ($C_9H_7N_3O$) C, H, N.

2-Chloro-6-[2-(trimethylsilanyl)ethoxymethoxymethyl]pyridine (10). To a solution of 6-chloro-2-pyridinemethanol[15] (2.50 g, 17.4 mmol), DIEA (3.30 mL, 19.1 mmol). and CH_2Cl_2 (20 mL), under nitrogen atmosphere and cooled to 0 °C, was added (trimethylsilyl)ethoxychloromethyl ether (3.20 mL, 18.2 mmol). Stirring was continued at room temperature for 3 h. The solvent was evaporated and the oil extracted with Et_2O, washed with water, dried, filtered, and evaporated to dryness. The product was purified by flash chromatography (CH_2Cl_2) to give 3.65 g (76.6%) of **10** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9H), 0.95 (t, 2H), 3.68 (t, 2H), 4.67 (s, 2H), 4.80 (s, 2H), 7.24 (d, 1H), 7.35 (d, 1H), 7.64 (t, 1H).

2-(Benzyloxy)-6-[2-(trimethylsilanyl)ethoxymethoxymethyl]pyridine (11). To a suspension of HNa (60% dispersion in mineral oil, 0.91 g, 22.6 mmol) in DMF (20 mL) at 0 °C and under a nitrogen atmosphere was added dropwise a solution of benzyl alcohol (2.10 mL, 19.9 mmol) in DMF (3 mL). Stirring was continued for 1.5 h at 0 °C, and a solution of **10** (3.65 g, 13.3 mmol) in DMF (3 mL) was added dropwise. The reaction mixture was heated at 40 °C for 12 h, cooled to room temperature, poured in ice−water, and extracted with Et_2O. The combined extracts were washed with water, dried, and filtered, and the solvent was evaporated to dryness. The crude product was purified by flash chromatography (40% hexane−CH_2Cl_2) to give 3 g (65%) of **11** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9H), 0.94 (t, 2H), 3.67 (t, 2H), 4.61 (s, 2H), 4.80 (s, 2H), 5.35 (s, 2H), 6.66 (d, 1H), 6.97 (d, 1H), 7.34 (m, 3H), 7,42 (m, 2H), 7.54 (t, 1H).

2-Hydroxy-6-[2-(trimethylsilanyl)ethoxymethoxymethyl]pyridine (12). To a solution of **11** (7 g, 20.26 mmol) in EtOH saturated with hydrogen chloride (75 mL) was added Raney nickel (7 g). The suspension was stirred at room temperature under hydrogen atmosphere for 1.5 h. The catalyst was filtered off through Celite and then the solvent removed under vacuum. The product was isolated by flash chromatography to give 4 g (76.8%) of **12** as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9H), 0.93 (t, 2H), 3.61 (t, 2H), 4.50 (s, 1H), 4.75 (s, 2H), 6.21 (d, 1H), 6.47 (d, 1H), 7.36 (d, 1H), 7.41 (d, 1H), 12.28 (s, 1H).

Trifluoromethanesulfonic Acid 6-[2-(Trimethylsilanyl)ethoxymethoxymethyl]pyridin-2-yl Ester (13). To a solution of **12** (3.80 g, 14.8 mmol) and DMAP (0.10 g, 0.82 mmol) in pyridine (35 mL) at 0 °C was added dropwise $(CF_3SO_2)_2O$ (2.63 mL, 14.9 mmol). After stirring for 2 h at 0 °C, the mixture was poured into ice−water and extracted with Et_2O. The combined organic layers were washed with an aqueous $KHSO_4$ solution and water, dried, filtered, and evaporated to dryness. Purification by flash chromatography (CH_2Cl_2) gave 4.30 g (75%) of **13** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9H), 0.93 (t, 2H), 3.66 (t, 2H), 4.68 (s, 2H), 4.80 (s, 2H), 7.05 (d, 1H), 7.52 (d, 1H), 7.87 (t, 1H).

2-[6-[2-(Trimethylsilanyl)ethoxymethoxymethyl]pyridin-2-yl]pyrrole-1-carboxylic Acid *tert*-Butyl Ester (14c). To a degassed solution of **13** (4 g, 10.3 mmol) in benzene (40 mL) were added Tl_2CO_3 (9.68 g, 20.6 mmol), Pd [$P(C_6H_5)_3$]$_4$ (1 g, 0.86 mmol), and [1-(*tert*-butoxycarbonyl)pyrrol-2-yl]boronic acid[38] (2.45 g, 11.6 mmol). After stirring at room temperature for 23 h, the mixture was filtered and the filtrate concentrated under reduced pressure. The oily residue was purified by flash chromatography (1% EtOAc−CH_2Cl_2) to give 3.75 g (90%) of **14c** as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9H), 0.94 (t, 2H), 1.32 (s, 9H), 3.67 (t, 2H), 4.73 (s, 2H), 4.82 (s, 2H), 6.21 (t, 1H), 6.37 (m, 1H), 7.27 (d, 1H), 7.32 (m, 1H), 7.34 (d, 1H), 7.68 (t, 1H).

6-(1*H*-Pyrrol-2-yl)pyridine-2-methanol (15c). To a solution of $(nC_4H_9)_4NF$ (1.10 M THF solution, 3 mL), anhydrous THF (45 mL), HMPA (5 mL), and 4-Å molecular sieves (10 g) was added **14c** (3 g, 7.41 mmol). The mixture was stirred at room temperature under argon for 8 h. Insoluble materials were filtered off, and the solvent was removed under vacuum. Purification by flash chromatography (1% EtOAc−CH_2Cl_2) gave 0.51 g (39%) of **15c** as a white solid: mp 73−75 °C; ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 1H), 4.74 (s, 2H), 6.30 (dd, 1H), 6.75 (m, 1H), 6.92 (m, 1H), 6.98 (d, 1H), 7.45 (d, 1H), 7.62 (t, 1H), 9.56 (s, 1H). Anal. ($C_{10}H_{10}N_2O$) C, H, N.

6-(Thien-2-yl)pyridine-2-methanol (15d). Prepared as **15c** from **13** and commercially available thien-2-ylboronic acid. Purification by flash chromatography (10% EtOAc−CH_2Cl_2) gave **15d** as a yellow oil (45%): ^{1}H NMR ($CDCl_3$) δ 3.7 (s, 1H), 4.65 (s, 2H), 7.10 (dd, 1H), 7.35 (m, 2H), 7.66 (m, 2H), 7.85 (m, 1H).

6-(Furan-2-yl)pyridine-2-methanol (15e). Prepared as **15c** from **13** and commercially available furan-2-ylboronic acid. Purification by flash chromatography (10% EtOAc−CH_2Cl_2) gave **15e** as a yellow oil (56%): ^{1}H NMR ($CDCl_3$) δ 3.99 (s, 1H), 4.74 (s, 2H), 6.50 (dd, 1H), 7.06 (m, 2H), 7.49 (d, 1H), 7.56 (d, 1H), 7.67 (t, 1H).

6-(1*H*-Pyrrol-2-yl)pyridine-2-carboxaldehyde (8c). To a solution of **15c** (0.30 g, 1.72 mmol) and anhydrous CH_2Cl_2 (3 mL) was added MnO_2 (0.75 g, 8.61 mmol), and the suspension was stirred under reflux for 1 h. Insoluble materials were filtered, and the solvent was removed under vacuum. Purification by flash chromatography (CH_2Cl_2) afforded 0.20 g (66%) of **8c** as a white solid: mp 112−113 °C; ^{1}H NMR ($CDCl_3$) δ 6.31 (dd, 1H), 6.77 (m, 1H), 6.95 (m, 1H), 7.63−7.81 (m, 3H), 9.67 (s, 1H), 10.03 (s, 1H); IR (KBr, cm^{-1}) 1701. Anal. ($C_{10}H_8N_2O$) C, H, N.

6-(Thien-2-yl)pyridine-2-carboxaldehyde (8d): mp 48−50 °C; ^{1}H NMR ($CDCl_3$) δ 7.15 (dd, 1H), 7.46 (dd, 1H), 7.69 (dd, 1H), 7.78−7.88 (m, 3H), 10.16 (s, 1H); IR (KBr, cm^{-1}) 1714. Anal. ($C_{10}H_7NOS$) C, H, N.

6-(Furan-2-yl)pyridine-2-carboxaldehyde (8e): mp 46−48 °C; ^{1}H NMR ($CDCl_3$) δ 6.55 (q, 1H), 7.16 (d, 1H), 7.55 (d, 1H), 7.82 (m, 3H), 10.07 (s, 1H); IR (KBr, cm^{-1}) 1717. Anal. ($C_{10}H_7NO_2$) C, H, N.

2-(4,5-Dihydrothiazol-2-yl)-6-(1,3-dioxolan-2-yl)pyridine (7i). A solution of 2-(1,3-dioxolan-2-yl)-6-cyanopyridine[18] (2 g, 11.35 mmol), methanol (10 mL), and sodium methoxide (0.20 g, 3.70 mmol) was stirred at room temperature for 24 h. The solvent was distilled, and the residue was taken up in EtOAc, washed with brine, dried, filtered, and concentrated under vacuum. The crude imidate (1 g, 4.80 mmol) was mixed with 2-aminoethanethiol (0.47 g, 6.10 mmol) and heated at 130 °C for 1.5 h. The cooled mixture was taken up in CH_2Cl_2, washed with water, dried, filtered, and concentrated. Purification by flash chromatography (2% MeOH−CH_2Cl_2) gave 1.10 g (97%) of **7i** as a pale-yellow solid: mp 55−57 °C; ^{1}H NMR ($CDCl_3$) δ 3.36 (t, 2H), 4.15 (m, 4H), 4.55 (t, 2H), 5.91 (s, 1H), 7.60 (dd, 1H), 7.81 (t, 1H), 8.03 (dd, 1H). Anal. ($C_{11}H_{12}N_2O_2S$) C, H, N.

2-(1*H*-Imidazolin-2-yl)-6-(1,3-dioxolan-2-yl)pyridine (7j). Prepared from **7f** and ethylenediamine (55%): ^{1}H NMR

($CDCl_3$) δ 4.10 (m, 8H), 5.82 (s, 1H), 6.03 (s, 1H), 7.56 (dd, 1H), 7.78 (t, 1H), 8.10 (dd, 1H).

2-(Thiazol-2-yl)-6-(1,3-dioxolan-2-yl)pyridine (7k). A solution of **7i** (1.33 g, 5.62 mmol) in benzene (50 mL) was treated with NiO_2 (hydrate, 10 g in 10 portions) while the reaction mixture was heated under reflux for 20 h with elimination of water with a Dean-Stark trap. The cooled reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuum. The crude product was purified by flash chromatography (15% EtOAc−CH_2Cl_2) to give 0.42 g (31%) of **7k** as a white solid: mp 70−72 °C; ^{1}H NMR ($CDCl_3$) δ 4.16 (m, 4H), 5.91 (s, 1H), 7.42 (d, 1H), 7.54 (dd, 1H), 7.81 (d, 1H), 7.89 (t, 1H), 8.17 (dd, 1H).

2-(1*H*-Imidazol-2-yl)-6-(1,3-dioxolan-2-yl)pyridine (7l). Prepared from **7j** using $BaMnO_4$ as oxidant to give after purification by flash chromatography (5% MeOH−CH_2Cl_2) **7l** as a yellow gummy solid (68%): ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 1H), 4.12 (m, 4H), 5.83 (s, 1H), 7.09 (s, 1H), 7.18 (s, 1H), 7.44 (dd, 1H), 7.78 (t, 1H), 8.11 (dd, 1H).

6-(Thiazol-2-yl)pyridine-2-carboxaldehyde (8k). Prepared from **7k** and obtained as a white solid (78%): mp 90−92 °C; ^{1}H NMR ($CDCl_3$) δ 7.48 (d, 1H), 7.96 (m, 3H), 8.38 (m, 1H), 10.09 (s, 1H); IR (KBr, cm^{-1}) 1705. Anal. ($C_9H_6N_2OS$) C, H, N.

6-(1*H*-Imidazol-2-yl)pyridine-2-carboxaldehyde (8l). Prepared from **7l** and obtained as a yellow solid (34%): mp 147−149 °C; ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 2H), 7.89 (m, 2H), 8.37 (dd, 1H), 10.05 (s, 1H), 10.77 (s, 1H). Anal. ($C_9H_7N_3O$) C, H, N.

1-[6-(1,3-Dioxolan-2-yl)pyridin-2-yl]ethanone (7g). To a solution of **7f** (0.88 g, 4.99 mmol) in anhydrous THF (10 mL), under an argon atmosphere and cooled at −10 °C, was added a solution of methylmagnesium bromide (3 M in Et_2O, 3.5 mL, 10.5 mmol). After stirring at room temperature for 3 h, the mixture was quenched with a saturated aqueous ammonium chloride solution and vigorously stirred at room temperature for 30 min. The mixture was extracted with EtOAc, washed with brine, dried, and filtered, and the solvent was evaporated under vacuum. Purification by flash chromatography (CH_2Cl_2) gave 0.80 g (83%) of **7g** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.72 (s, 3H), 4.15 (m, 4H), 5.89 (s, 1H), 7.70 (dd, 1H), 7.86 (t, 1H), 8.01 (dd, 1H); IR (film, cm^{-1}) 1700.

2-(1*H*-Pyrazol-3-yl)-6-(1,3-dioxolan-2-yl)pyridine (7h). A solution of **7g** (0.80 g, 4.14 mmol) and DMF dimethyl acetal (1 mL, 7.53 mmol) was heated under reflux for 12 h. Excess DMF acetal was removed under vacuum, and the residual oil was taken up in EtOH (5 mL). Hydrazine hydrate (0.80 mL, 25.7 mmol) was added, and the solution was heated under reflux for 10 min. The solvent was evaporated, and water was added. The mixture was extracted with EtOAc, washed with water, dried, filtered, and distilled under vacuum. Purification by flash chromatography (2% MeOH−CH_2Cl_2) gave 0.65 g (72%) of **7h** as a yellow gum: ^{1}H NMR ($CDCl_3$) δ 4.15 (m, 4H), 5.90 (s, 1H), 6.80 (d, 1H), 7.48 (dd, 1H), 7.65 (d, 1H), 7.76 (m, 2H), 11.23 (s, 1H).

6-(1*H*-Pyrazol-3-yl)pyridine-2-carboxaldehyde (8h). Prepared from **7h** and obtained as an amorphous white solid (60%): ^{1}H NMR (DMSO-d_6) δ 6.91 (d, 1H), 7.80 (m, 2H), 8.03 (t, 1H), 8.20 (d, 1H), 9.99 (s, 1H), 13.17 (s, 1H); IR (KBr, cm^{-1}) 1710.

2-(Oxazol-5-yl)-6-(1,3-dioxolan-2-yl)pyridine (7n). A mixture of **7m** (1 g, 5.58 mmol), tosylmethyl isocyanide (1.10 g, 5.63 mmol), K_2CO_3 (0.80 g, 5.79 mmol), and methanol (15 mL) was heated under reflux for 2 h. The solvent was evaporated, and water was added. The product was extracted with EtOAc, washed with brine, dried, filtered, and concentrated under vacuum. Purification by flash chromatography (50% EtOAc−hexane) gave 1.13 g (96%) of **7n** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.34 (d, 6H), 3.10 (m, 1H), 7.37 (m, 1H), 7.73 (d, 2H), 10.03 (s, 1H); IR (film, cm^{-1}) 1712.

6-(Oxazol-5-yl)pyridine-2-carboxaldehyde (8n). Prepared from **7n** and obtained as a pale-yellow solid (41%): mp 150−152 °C; ^{1}H NMR ($CDCl_3$) δ 7.81−8.01 (m, 5H), 10.08 (s, 1H); IR (KBr, cm^{-1}) 1703. Anal. ($C_9H_6N_2O_2$) C, H, N.

6-(Methylthio)-2-(1,3-dioxolan-2-yl)pyridine (7p). A mixture of **7a** (1.36 g, 5.91 mmol), $NaSCH_3$ (0.83 g, 11.82 mmol), and DMF (4 mL) was heated at 100 °C for 18 h. The cooled mixture was diluted with ice−water and extracted with EtOAc. The combined organic layers were washed with 1 N NaOH and water, dried, and filtered, and the solvent was removed under vacuum to give 0.85 g (73%) of **7p** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 4.03−4.20 (m, 4H), 5.82 (s, 1H), 7.16 (t, 2H), 7.50 (t, 1H).

6-(Methylsulfinyl)-2-(1,3-dioxolan-2-yl)pyridine (7q). To a solution of $NaIO_4$ (0.72 g, 3.36 mmol) in water (15 mL) and maintained at 0 °C was added dropwise a solution of **7p** (0.60 g, 3.04 mmol) in methanol (10 mL). The mixture was allowed to stir at room temperature for 18 h. The methanol was removed under vacuum; the residue was taken up in water and extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried, and filtered, and the solvent was removed under vacuum. The product was purified by flash chromatography (50% EtOAc−CH_2Cl_2) to give 0.48 g (67%) of **7q** as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.82 (s, 3H), 4.01−4.18 (m, 4H), 5.79 (s, 1H), 7.58 (dd, 1H), 7.97 (m, 2H).

6-(Methylthio)pyridine-2-carboxaldehyde (8p). Prepared from **7p** and obtained as a yellow oil (45%): ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 3H), 7.37 (dd, 1H), 7.60 (m, 2H), 9.99 (s, 1H); IR (film, cm^{-1}) 1709.

6-(Methylsulfinyl)pyridine-2-carboxaldehyde (8q). Prepared from **8q** and obtained as a pale-yellow oil (60%): ^{1}H NMR ($CDCl_3$) δ 2.92 (s, 3H), 8.02 (dd, 1H), 8.14 (t, 1H), 8.27 (dd, 1H), 10.03 (s, 1H); IR (film, cm^{-1}) 1710.

6-*n*-Butoxy-2-(1,3-dioxolan-2-yl)pyridine (7o). To a solution of Na (0.30 g, 0.013 atg) in *n*-butanol (3 mL) was added **7a** (0.91 g, 5.39 mmol), and the mixture was heated at 100 °C for 18 h. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water and brine, dried, and filtered, and the solvent was removed under vacuum. Residual *n*-butanol was removed by azeotropic distillation with cyclohexane to give 1.08 g (90%) of **7o** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 3H), 1.40−1.80 (m, 4H), 4.13 (m, 4H), 4.31 (t, 2H), 5.77 (s, 1H), 6.69 (d, 1H), 7.06 (d, 1H), 7.57 (dd, 1H).

6-*n*-Butoxypyridine-2-carboxaldehyde (8o). Prepared from **7o** and obtained as a yellow oil (75%): ^{1}H NMR ($CDCl_3$) δ 0.99 (t, 3H), 1.50 (m, 2H), 1.77 (m, 2H), 4.42 (m, 2H), 6.95 (dd, 1H), 7.54 (dd, 1H), 7.72 (t, 1H), 8.09 (s, 1H); IR (film, cm^{-1}) 1708.

Preparation of 6-Pyrazol-1-yl-2-pyridinylmethylamino Derivatives 75−85 (Table 3). To a mixture of **8b** and an equimolar quantity of the corresponding amine[39] in 1,2-dichloroethane was added 1.4 equiv of sodium triacetoxyborohydride. The mixture was stirred at room temperature for 24 h and then quenched by adding 1 N NaOH. The product was extracted with EtOAc, purified by flash chromatography, and converted to the appropriate salts.

Radioligand Binding. Binding affinities for the different receptors were determined by means of ligand displacement assays using the conditions summarized in Table 1. The reactions were stopped by rapid filtration through Whatman GF/B glass fiber filters, and the filters were washed with appropriate buffer. The radioactivity retained on the filters was measured by scintillation spectroscopy in 4 mL of scintillation fluid (Emulsifier Safe, Packard).

Cyclic AMP in HA7 Cells. HA7 cells were grown in Dulbecco's modified Eagle's medium (DMEM) (GIBCO) supplemented with 10% fetal calf serum, gentamicin (100 μg/mL), Geneticin (G418) (400 μg/mL) in 5% CO_2 at 37 °C in a water-saturated atmosphere. The cells were plated in 6-well culture plates and used in the experiments at a confluency of 80−90%. Culturing medium [DMEM, 10% fetal calf serum, gentamicin (100 μg/mL), G418 (400 μL/mL)] was replaced by DMEM supplemented with 10% fetal calf serum without antibiotics 24 h before experimentation.

Cells were preincubated with DMEM, 10 mM Hepes for 10 min at room temperature. Drugs, at concentrations ranging

from 0.1 nM to 100 μM, and appropriate vehicle controls [i.e., water or dimethyl sulfoxide (DMSO)] were then added in DMEM, 10 mM Hepes, 100 μM forskolin, 100 μM 3-isobutyl-1-methylxanthine (IBMX) to the cells. At the end of the treatment (10 min, room temperature), the reaction was stopped by aspiration of the medium and addition of 0.1 N HCl. Cellular extract was diluted 1:500 or 1:400 in radioimmunoassay buffer, and cyclic AMP (cAMP) content was measured by using a commercially available kit (DuPont NEN: NEK-033). Basal cAMP levels were 10 ± 0.9 pmol/well ($n = 8$).

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Supporting Information Available: Additional physical data (^{1}H NMR and elemental analyses) on final compounds and the synthetic sequences used to prepare intermediates **81**, **83**, and **85** (13 pages). Ordering information is given on any current masthead page.

References

(1) Hoyer, D.; Clarke, D. E.; Fozard, J. R.; Hartig, P. R.; Martin, G. R.; Mylecharane, E. J.; Saxena, P. R.; Humphrey, P. A. *Pharmacol. Rev.* **1994**, *46*, 157−203.
(2) Peroutka, S. J. *CNS Drugs* **1995**, *4* (Suppl. 1), 18−28.
(3) Barradell, L. B.; Fitton, A. *CNS Drugs* **1996**, *5*, 147−153. Pecknold, J. C. *CNS Drugs* **1994**, *2*, 234−251. Deakin, J. F. W. *J. Psychopharmacol.* **1993**, *7*, 283−289. Stahl, S. M. J. *Clin. Psychiatry* **1997**, *58* (Suppl. 8), 20−26.
(4) Blier, P.; Bergeron, R. *Int. Clin. Psychopharmacol.* **1997**, *12* (Suppl. 3), 21−28.
(5) Blier, P.; Bergeron, R.; De Montigny, C. *Neuropsychopharmacology* **1997**, *16*, 333−338. Matsuda, T.; Somboonthum, P.; Suzuki, M.; Asano, S.; Baba, A. *Eur. J. Pharmacol.* **1995**, *280*, 235−238. Glennon, R. A.; Malgorzata, D. *Serotonin* **1997**, *2*, 351−372.
(6) Glennon, R. A. *Drug Dev. Res.* **1992**, *26*, 251−274. Shutske, G. M. *Exp. Opin. Ther. Patents* **1994**, *4*, 1233−1241. Schechter, L. E.; Kelly, M. G. *Serotonin* **1997**, *2*, 299−309. Fletcher, A.; Cliffe, I. A.; Dourish, C. T. *Trends Pharmacol. Sci.* **1993**, *14*, 441−448.
(7) Crabb, T. A.; Fallah, A. *Magn. Reson. Chem.* **1990**, *28*, 426−430.
(8) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1990**, *55*, 69−73.
(9) Aliprantis, A. O.; Canary, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 6985−6986.
(10) Zamboni, R. Pyridine-substituted Benzyl Alcohols as Leukotriene Antagonists. WO 93/21158, 1993.
(11) Gale, D. J.; Wilshire, J. F. K. *Aust. J. Chem.* **1975**, *28*, 2447−2458.
(12) Artico, M.; Corelli, F.; Massa, S.; Stefancich, G.; Avigliano, L.; Befani, O.; Marcozzi, G.; Sabatini, S.; Mondovi, B. *J. Med. Chem.* **1988**, *31*, 802−806.
(13) Bredereck, H.; Simchem, G.; Wahl, R. *Chem. Ber.* **1968**, *101*, 4048−4056.
(14) Vetelino, M. G.; Coe, J. W. *Tetrahedron Lett.* **1994**, *35*, 219−222.
(15) Hamana, M.; Yamazaki, M. *Chem. Pharm. Bull. (Tokyo)* **1960**, *8*, 574−578.
(16) Sieburth, S.; Chen, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 8163−8164.
(17) Kan, T.; Hashimoto, M.; Yanagiya, M.; Shirahama, H. *Tetrahedron Lett.* **1988**, *29*, 5417−5418.
(18) Eichenger, K.; Berbalk, H.; Kronberger, H. *Synthesis* **1982**, *12*, 1094−1095.
(19) Hughey, J. L.; Knapp, S.; Schugar, V. *Synthesis* **1980**, *6*, 489−490.
(20) Evans, D. L.; Minster, D. K.; Jordis, V.; Hecht, S. M.; Mazzu, A. L. *J. Org. Chem.* **1979**, *44*, 497−501.
(21) Amoroso, A. J.; Cargill Thomson, A. M.; Jeffery, J. C.; Jones, P. L.; McCleverty, J. A.; Ward, M. D. *J. Chem. Soc., Chem. Commun.* **1994**, 2751−2752.
(22) Falk, H.; Suste, A. *Monatsh. Chem.* **1993**, *124*, 881−891.
(23) VanLeussen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, *23*, 2369−2372.
(24) Fargin, A.; Raymond, J. R.; Regan, J. W.; Cotecchia, S.; Lefkowitz, R. J. *J. Biol. Chem.* **1989**, *264*, 14848−14852.
(25) Bikker, J. A.; Trumpp-Kallmeyer, S.; Humblet, C. *J. Med. Chem.* **1998**, *41*, 2911−2927.
(26) Wess, J. *Faseb J.* **1997**, *11*, 346−354.
(27) Osman, R.; Topiol, S.; Rubenstein, L.; Weintein, H. *Mol. Pharmacol.* **1987**, *32*, 699−705. Pardo, L.; Weinstein, H. *Int. J. Quant. Chem.* **1997**, *63*, 767−780.
(28) Burley, S. K.; Petsko, G. A. *Adv. Protein Chem.* **1988**, *39*, 125−189. Dalpiaz, A.; Borea, P. A.; Gessi, J.; Gilli, G. *Eur. J. Pharmacol.* **1996**, *312*, 107−114.
(29) Chilmonczyk, Z. *J. Pharm. Pharmacol.* **1995**, *47*, 791−801 and references therein.
(30) Bigg, D.; Castan, F.; Koek, W.; Bonnaud, B. Novel Heterocyclic Aminomethyl-4 Piperidine Derivatives, their Preparation and Application in Therapy. WO 94/18193-A1, 1994. Bonnaud, B.; Castan, F.; Bigg, D.; Koek, W. Nouveaux dérivés de la phénoxy-2 éthylamine, leur préparation et leur application en thérapeutique. FR 2702211, 1993.
(31) Mokrosz, J. L.; Deren-Wezolek, A.; Tatarcznska, E.; Duszynska, B.; Bojarski, A. J.; Mokrosz, M. J.; Chojnacka-Wojcik, E. *J. Med. Chem.* **1996**, *39*, 1125−1129. George, P.; Sevrin, M.; Maloizel, C.; Tixidre, A.; Froissant, J. 4-Piperidinyl methyl tetrahydro isoquinolines having Selective Affinity for Serotoninergic Receptors. EP 0351255, 1989. George, P.; Sevrin, M.; Mangane, M.; Merly, J.-P.; Bigg, D. Piperidinyl Isoindoles and Benzazepines having Selecte Affinity for Serotoninergic Receptors. EP 0351283, 1989.
(32) Chidiac, P. *Trends Pharmacol. Sci.* **1995**, *16*, 83−84. Kenakin, T. *Trends Pharmacol. Sci.* **1995**, *16*, 84−85.
(33) Leff, P. *Trends Pharmacol. Sci.* **1995**, *16*, 89−87.
(34) A similar trend was observed with *trans*-2-aryl-*N*,*N*-dipropylcyclopropylamine derivatives: Vallgarda, J.; Appelberg, U.; Arvidsson, L. E.; Hjorth, S.; Svensson, B. E.; Hacksell, U. *J. Med. Chem.* **1996**, *39*, 1485−1493. Langlois, M.; Gaudy, S.; Bremont, S.; Bremont, B. *BioMed. Chem. Lett.* **1993**, *3*, 2035−2038.
(35) Van Wijngaarden, I.; Tulp, M. Th. M.; Soudijn, W. *Eur. J. Pharmacol.* **1990**, *188*, 301−312. Hamon, M.; Fattaccini, C. M.; Adrien, J.; Gallissot, M. C.; Martin, P.; Gozlan, H. *J. Pharmacol. Exp. Ther.* **1988**, *246*, 745−752.
(36) Foreman, M. M.; Fuller, R. W.; Leander, J. D.; Benvenga, M. J.; Wong, D. T.; Nelson, D. L.; Calligaro, D. O.; Swanson, S. P.; Lucot, J. B.; Flaugh, M. E. *J. Pharmacol. Exp. Ther.* **1993**, *267*, 58−71. Arylpiperazine, a metabolite of N-4-substituted arylpiperazine-containing molecules (the largest class of 5-HT$_{1A}$ ligands), affects 5-HT$_{1A}$ agonist activity: Caccia, S. *Bull. Chim. Farm.* **1990**, *129*, 183−189. Berlin, I.; Chalon, S.; Payan, C.; Schöllnhammer, G.; Cesselin, F.; Varoquaux, O.; Puech, A. J. *Br. J. Clin. Pharmacol.* **1995**, *39*, 243−249.
(37) Only N-1 methylation was observed when **67** was treated with CH$_3$I/HNa; thus we assumed that the hydrogen atom is preferentially located on N-1.
(38) Martina, S.; Enkelmann, V.; Wegner, G.; Schlüter, A. D. *Synthesis* **1991**, *8*, 613−615.
(39) Known amines used for the preparation of compounds **75**−**80**, **82**, and **84** are respectively: dipropylamine [142-84-7]; 4-methoxyphenylethylamine [55-81-2]; 5-methoxytryptamine [608-07-1]; *N*-(2-aminoethyl)tricyclo[3.3.1.13,7]decane-1-carboxamide [190657-27-3]; 2-(4-aminobutyl)-4-methyl-2*H*-[1,2,4]triazine-3,5-dione. Patoiseau, J.-F.; Faure, C.; Dupont-Passelaigue, E.; Couret, F. Novel 3,5-dioxo-(2H,4H)-1,2,4-triazine derivatives, their preparation and use as drugs. WO 96/16949, 1996. 4,4-Bis(*p*-fluorophenyl)butylamine [64630-52-0]; *N*-(4-aminobutyl)-3-methylbenzamide was prepared in an analogous manner as *N*-(4-aminobutyl)benzamide: Zaragoza-Doerwald, F.; Von Kiedrowski, G. *Synthesis* **1988**, *11*, 917−918. [4-(Aminomethyl)piperidin-1-yl](3-chlorophenyl)methanone: Roll, W. D. Piperidinylalkylbenzamide compositions for inhibiting H2 histamine receptors. US 4310532, 1980.
(40) Assié, M.-B.; Koek, W. *Eur. J. Pharmacol.* **1996**, *304*, 15−21.
(41) Assié, M.-B.; Sleight, A. J.; Koek, W. *Eur. J. Pharmacol.* **1993**, *237*, 183−189.

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