Novel Derivatives of 2-Pyridinemethylamine as Selective, Potent, and Orally Active Agonists at 5-HT$_{1A}$ Receptors

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The aim of this work was to improve the oral bioavailability of a recently discovered, novel structural class of 5-HT$_{1A}$ receptor agonists: aryl-{[4-(6-*R*-pyridin-2-ylmethyl)-amino]-methyl}-piperidin-1-yl-methanone. Incorporation of a fluorine atom in the β-position to the amino function in the side chain led to analogues that exhibited, in general, enhanced and long-lasting 5-HT$_{1A}$ agonist activity in rats after oral administration. Location of the fluorine atom at the C-4 position of the piperidine ring was the most favorable, and among the various substituents tested, the ability of the fluorine was unique in improving the oral activity of this family of ligands. Thus, the derivatives **39**, **46**, and **61** bound with higher affinity and selectivity to 5-HT$_{1A}$ receptors (versus dopaminergic D$_2$ and adrenergic α_1 receptors) and displayed more potent 5-HT$_{1A}$ agonist activity in vitro and in vivo than their C-4 desfluoro analogues. To examine the relationship between the conformation of the pharmacophore and the level of agonistic activity of this type of ligand, we synthesized a series of 3-chloro-4-fluorophenyl-(4-fluoro-4{[(5-(H or CH$_3$)-6-R-pyridin-2-ylmethyl)-amino]-methyl}-piperidin-1-yl-methanone derivatives and found that the combination of a 5-methyl and a 6-methylamino substituent on the pyridine ring synergistically affected their 5-HT$_{1A}$ agonist properties. Thus, the 3-chloro-4-fluorophenyl-(4-fluoro-4{[(5-methyl-6-methylamino-pyridin-2-ylmethyl)-amino]-methyl}-piperidin-1-yl-methanone **40** behaved as a more potent 5-HT$_{1A}$ receptor agonist in vitro and in vivo than its 5-unsubstituted analogue **38**. The antidepressant potential of the lead compounds **40**, **45**, and **54** was examined by means of the forced swimming test (FST) in rats. The results indicated that, after a single oral administration, these compounds inhibited immobility in the FST more potently and more extensively than the clinically used antidepressant imipramine. Thus, **40**, **45**, and **54** are potent, orally active 5-HT$_{1A}$ receptor agonists with marked antidepressant potential.

Introduction

Many studies have focused on specific alterations of monoaminergic neurotransmission in depression.[1] The role of central serotoninergic (5-HT) systems, and in particular of 5-HT$_{1A}$ receptor subtype-mediated neurotransmission, has attracted special interest over the last two decades.[2] However, the antidepressant effects of 5-HT$_{1A}$ partial agonists, such as buspirone and ipsapirone, do not exceed those of currently available treatments, neither in terms of clinical efficacy[3] nor in terms of rapidity of onset.[4] It is conceivable that their limited clinical efficacy is related to their low level of intrinsic activity at 5-HT$_{1A}$ receptors.[5] Thus, our research efforts are guided by the hypothesis that the antidepressant efficacy of 5-HT$_{1A}$ agonists is a direct, positive function of their intrinsic activity, and therefore, aimed at discovering 5-HT$_{1A}$ agonists with a high level of intrinsic activity.[6]

In a recent paper,[7] we described a novel 5-HT$_{1A}$ pharmacophore and reported a series of aryl-{[4-(6-R-pyridin-2-ylmethyl)-amino]-methyl}-piperidin-1-yl-methanones that bind with high affinity and selectivity to 5-HT$_{1A}$ receptors. Of primary interest, several members of this series inhibited intracellular cAMP accumulation in forskolin-stimulated HA7 cells more potently and more extensively than the prototypical 5-HT$_{1A}$ agonist (±)-8-OH-DPAT. Unfortunately, despite their promising in vitro profiles, these compounds exerted only weak 5-HT$_{1A}$ agonist activity in vivo,[8] possibly because of low bioavailability. Attempts to enhance the brain concentration of these novel 5-HT$_{1A}$ agonists led to the design of a series of aryl-(4-fluoro-4{[(6-R-pyridin-2-ylmethyl)-amino]-methyl}-piperidin-1-yl-methanones that exhibited very potent 5-HT$_{1A}$ agonist properties, not only in vitro but also in vivo. Several of these compounds demonstrated marked antidepressant-like effects in the FST.[9] Finally, this novel series provided further insight into some of the structural determinants involved in the activation of 5-HT$_{1A}$ receptors.

Chemistry

Compounds of the general formula **4** (Scheme 1, Table 7) were prepared from the appropriate pyridine-2-carboxaldehydes **3** either by reductive amination with primary amines of the type **1** (method A) or by an aza-Wittig reaction with azides of the type **2** (method B).

The synthesis of amines **1a**, as shown in Scheme 2, began with acylation of the commercially available 4-piperidone-ethylene ketal by the appropriate aroyl

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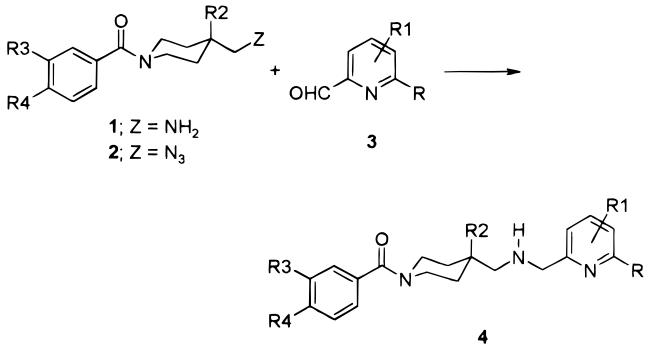
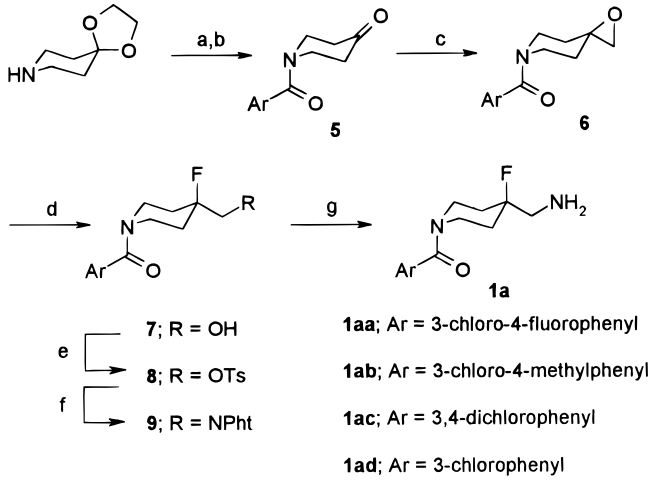
Scheme 1[a]



[a] Conditions: **1**, toluene, 110 °C, then KBH_4, MeOH, 20 °C (method A), or **2**, PPh_3, MeOH, reflux, then KBH_4, 20 °C (method B).

Scheme 2[a]

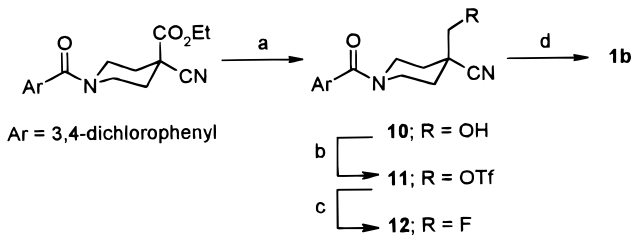


[a] Conditions: (a) ArCOCl, TEA, $CHCl_3$; (b) HCO_2H, $CuSO_4$, 80 °C; (c) trimethylsulfoxonium iodide, HNa, DMSO; (d) HF−pyridine, CH_2Cl_2; (e) pTSCl, pyridine; (f) K-phthalimide, DMF, 150 °C; (g) $NH_2(CH_2)_2OH$, 50 °C.

chloride (NEt_3, CH_2Cl_2, 0 °C). After removal of the C-4 carbonyl protecting group, the oxirane function was installed by treatment of the piperidones **5** with dimethyloxosulfonium methylide, as described by Fishman[10] for the epoxidation of the *N*-benzyl-piperidone analogue. The spiro derivatives **6** underwent a regioselective ring-opening reaction with hydrogen fluoride−pyridine complex[11] to afford the fluoro alcohol **7**. The end of the synthesis was straightforward: the primary alcohol **7** was activated as the tosylate **8**, which was then converted to the desired primary amine **1a** via the phthalimide **9** (Gabriel synthesis). The 4-cyano-1-(3,4-dichloro-benzoyl)-piperidine-4-carboxylic acid ethyl ester[12] was used as the precursor to the amine **1b** (Scheme 3). Thus, the ester function was first reduced to the alcohol **10** and then transformed into the triflate **11**. Displacement of the triflate **11** by fluoride anion, under Grieco conditions,[13] provided the intermediate **12**. Subsequent hydrogenation of the cyano group over Raney Ni gave the fluoromethylated amine **1b**. The amine **1c** (Scheme 4) was prepared by C-methylation of the lithium salt generated from 1-(3,4-dichloro-benzoyl)-piperidine-4-carbonitrile[14] (LDA, CH_3I) followed by hydrogenation of the cyano group.

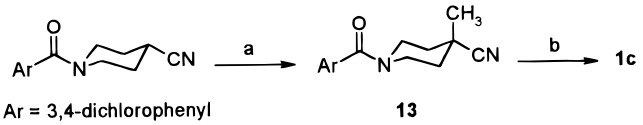
The azide **2a** was obtained by ring-opening of epoxide **6** by NaN_3 (Scheme 5). Under standard conditions (NH_4-

Scheme 3[a]



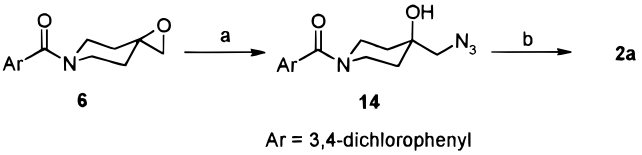
[a] Conditions: (a) $LiBH_4$, THF, 20 °C; (b) $(CF_3SO_2)_2O$, 2,4-lutidine, CH_2Cl_2; (c) diethylene glycol, KF, 100 °C; (d) Raney Ni, EtOH, NH_4OH.

Scheme 4[a]



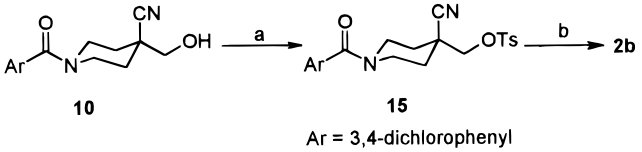
[a] Conditions: (a) LDA, MeI, THF; (b) Raney Ni, EtOH, NH_4OH.

Scheme 5[a]



[a] Conditions: (a) NaN_3, NH_4Cl, MeOH, H_2O, reflux; (b) HNa, MeI, THF.

Scheme 6[a]

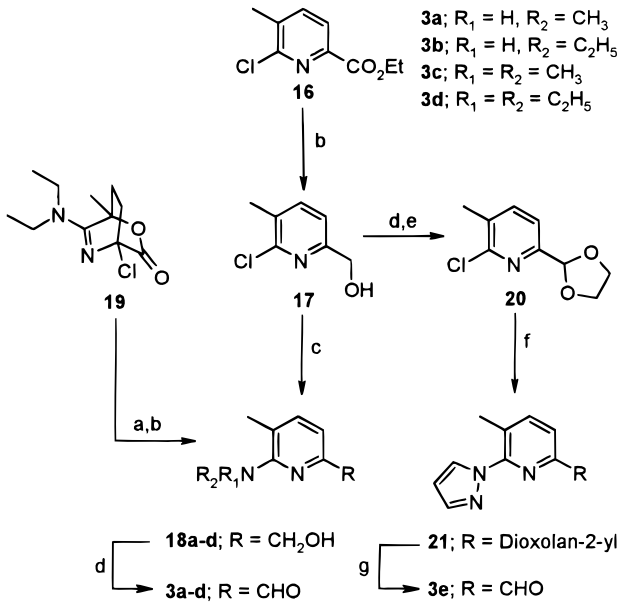


[a] Conditions: (a) pTSCl, pyridine; (b) NaN_3, Bu_4NN_3, DMSO, 100 °C.

Cl, CH_3OH/H_2O), attack of the nucleophile occurred at the less substituted carbon exclusively. O-Methylation of the resulting β-hydroxyazide **14** then yielded the azide **2a**. The azide **2b** could be derived from the intermediate **10** by the two-step sequence shown in Scheme 6.

The preparation of the 5-unsubstituted-6-substituted-pyridine-2-carboxaldehydes used in this work has been reported previously.[7] The synthesis of the novel 5-methyl-6-substituted-2-pyridinecarboxaldehydes was carried out as depicted in Scheme 7. The ester **16**, obtained by the method of Hoornaert,[15] was reduced to the alcohol **17**. Treatment of the latter with a large excess of methyl, ethyl, or dimethylamine under harsh reaction conditions led to the 6-alkylamino-5-methyl-2-pyridinemethanol derivatives **18a**−**c** in moderate yields. Displacement of the 6-chlorine atom by amines was much more difficult than in the 5-unsubstituted series, demonstrating that the 5-methyl group has a pronounced effect on the reactivity of the pyridine ring. As a consequence, the derivative **18d**, bearing a more hindered 6-diethylamino group, was best prepared from the intermediate **19**, according to a variant also developed by Hoornaert.[16] Thus, treatment of the amidine **19** with DBU and ethanol (lactone cleavage and aromatization) gave the 6-diethylamino-5-methyl-pyridine-2-carboxylic acid ethyl ester (not shown in Scheme 7) which was reduced as

Scheme 7[a]



[a] Conditions: (a) DBU, EtOH, THF; (b) $NaBH_4$, EtOH; (c) R_1R_2NH, EtOH, 100 °C, 72 h; (d) MnO_2, $CHCl_3$, reflux; (e) $(CH_2OH)_2$, pTSA, $PhCH_3$, 110 °C; (f) HNa, pyrazole, DMF, 60 °C; (g) HCO_2H, H_2O, $CuSO_4$, 65 °C.

described above (**16** → **17**) to afford the expected 6-diethylamino-5-methyl-2-pyridinemethanol **18d** in modest overall yield. The primary alcohols **18a**−**d** were subsequently oxidized to the target pyridine-2-carboxaldehydes **3a**−**d** (MnO_2/$CHCl_3$).[17]

The synthetic sequence had to be modified slightly for the synthesis of the 6-pyrazol-1-yl-5-methyl-2-pyridinecarboxaldehyde **3e**. Thus, the alcohol **17** was first oxidized and then the aldehyde function protected as the dioxolane **20**.[18] Reaction of **20** with the sodium salt of pyrazole yielded the intermediate **21**, which upon removal of the protecting group, afforded the desired 6-pyrazolo-5-methyl-pyridine-2-carboxaldehyde derivative **3e**.

Pharmacology

Binding affinities for the different receptors were determined by means of ligand competition assays using the conditions summarized in the Experimental Section (Table 8). All experiments were performed in triplicate. IC_{50} values were determined using nonlinear regression. K_i values were calculated using the equation $K_i = IC_{50}/1 + [C]/K_D$, and the results are expressed as mean pK_i values ± SEM of three independent determinations.

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[19] was obtained commercially (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 2−4 independent determinations (each performed in triplicate) for all compounds, except (±)-8-OH-DPAT whose values represent the mean of five determinations.

The methods used to examine the ability of compounds to produce lower lip retraction (LLR) in rats were the same as those described previously.[20] Rats were observed at two time points, centered at 15 and 60 min after the injection and each lasting 10 min. During a 10 min period, an animal was observed once every minute for 10 s and the presence (1) or absence (0) of LLR was recorded. Because an animal was observed 10 times during a 10 min period, the incidence of LLR could vary from 0 to 10. Dose−response functions were determined from the percentage of rats (*n* at least 2 per dose) showing LLR scores of 1 or more. This criterion was based on the incidence of LLR observed in control animals treated with saline, fewer than 5% of which had an LLR score of 1 or more; drugs were therefore considered to produce an effect in an individual animal when scores higher than zero were obtained. ED_{50} estimates are obtained by linear interpolation. Because the pharmacological studies were conducted using doses differing by factor 4, the range of doses which encompassed the interpolated ED_{50} values could not exceed this factor. Further, the coefficient of dispersion (i.e, $ED_{50} \times 100$/range) varied from 43 to 138%.

The forced swimming test was conducted in a manner similar to that described by Porsolt:[21] the procedure involved placing a rat in a cylinder (height: 45 cm, diameter: 20 cm) containing 17 cm water (25 °C) for 15 min on the first day of the experiment and again in the cylinder 24 h later for 5 min. The duration of immobility during the 5 min period was measured by an observer who was unaware of the treatment conditions. Each animal was treated (volume: 10 mL/kg) with vehicle after the session on day 1 and, on day 2, with a particular dose of a test compound ($n = 10$ per dose) or its vehicle control, given p.o. 60 min before placement in the cylinder. For each dose, the percentage inhibition of immobility was calculated by expressing the difference between the median immobility times of vehicle controls (i.e., 204 s) and of drug-treated animals as a percentage of the median immobility time of vehicle controls. In addition, dose−response functions were determined from the percentage of rats with an immobility time less than 138 s. Immobility times shorter than this criterion value occurred in less than 5% of the vehicle controls and were therefore considered significant. ED_{50} estimates are obtained by linear interpolation.

Results and Discussion

Oxidative N-debenzylation is known to be a major biotransformation pathway for biogenic amines and nitrogen-containing xenobiotics.[22] Thus, we assumed that the pyridin-2-yl-methylamine fragment in structures such as **4** (Scheme 1; R_2 = H) may be a likely target for redox active enzymes (cytochrome P 450's, MAO's ...). This assumption was supported by the finding that electron rich pyridine derivatives, even though being more potent to inhibit adenyl-cyclase in vitro than their electron deficient pyridine counterparts, displayed, in general, much weaker 5-HT_{1A} agonist

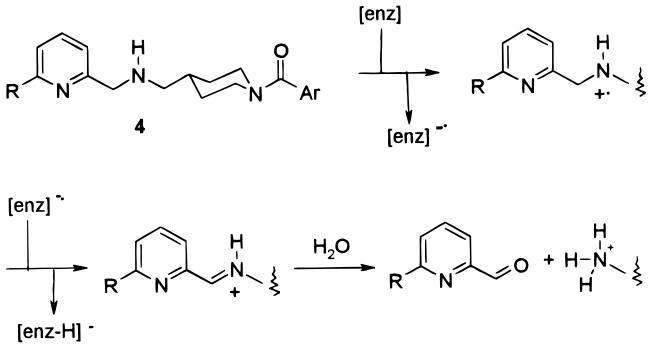
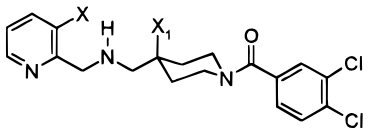


Figure 1.

Table 1. Effects of a Fluorine Atom and Its Position on 5-HT_{1A} Affinity and on 5-HT_{1A} Agonist Activity in Vivo



compd	X	X_1	5-HT_{1A} affinity pK_i[b,c]	5-HT_{1A} agonist activity LLR,[d] ED_{50}[e] i.p. 15 min	p.o. 60 min
22[a]	H	H	7.58 (0.15)	0.89	5.0
32	H	F	8.29 (0.10)	0.11	1.3
33	F	H	7.82 (0.08)	0.62	5.0

[a] Derivative described in ref 7 whose appropriate pharmacological data have been completed. [b] See Experimental Section for details. [c] Each value is the mean ± SEM of three determinations. [d] LLR = lower lip retraction. [e] ED_{50} (mg/kg) values were obtained by linear interpolation.

activity in vivo.[23] The mechanism postulated for the benzylic C−N bond cleavage in compounds of type **4**, catalyzed by oxido-reductases, involved a nitrogen radical cation in the first step (Figure 1). Thus, we reasoned that an electronegative fluorine atom[24] in the β-position to the benzylic amino function should (1) retard the oxidation-dependent processes by raising the redox potential of the secondary amino function ($E_{N^{\bullet}/N^{+\bullet}}$) and (2) facilitate absorption by reducing the pK_a of the secondary amine[25] and increasing the lipophilicity of the ligand.[26]

There were two options available for introducing a fluorine atom in a suitable position relative to the secondary amino function: either at the C-4 of the piperidine ring or, in a vinylogous fashion, at C-3 of the pyridine nucleus. We examined the influence of fluorine incorporation in either of these positions.[27]

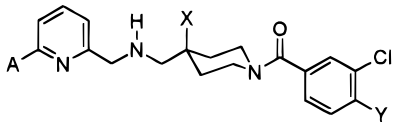
The binding affinities of compounds **32** and **33** were only marginally improved by incorporation of a fluorine atom in either position (compared with **22** in Table 1). In contrast, 5-HT_{1A} agonist potency in vivo (ED_{50} to induce LLR) increased markedly after i.p. and p.o. administration of the fluorinated derivative **32** as compared with the desfluoro compound **22**. In particular, fluorine substitution for hydrogen at the Csp^3-4 of the piperidine ring (**32**) provided a clear advantage in terms of in vivo activity (LLR, i.p. and p.o.) over its Csp^2-3 location (**33**). These findings prompted us to extend the Csp^3-4 replacement of hydrogen by fluorine to other ligands of this family.[7]

The compounds shown in Table 2 could be separated into two groups: (1) derivatives bearing an aliphatic amino substituent in the 6-position of the pyridine ring and (2) those having a five-membered heteroaromatic ring in this position. Within the first group (**23**−**25**, **39**, **46**, **52**), fluorine incorporation enhanced 5-HT_{1A} receptors binding whereas the affinity for D_2 and α_1 receptors remained in the micromolar range. The selectivity of the fluorinated ligands for 5-HT_{1A} binding sites (versus D_2 and α_1), therefore, improved over that of the desfluoro analogues.[28a] In addition, the fluoro derivatives were, in general, more potent (**39** and **46**), and at least as efficacious at inhibiting forskolin-stimulated cAMP accumulation in HA7 cells than their desfluoro counterparts (**23** and **24**, respectively). Of particular interest, they showed clear superiority over their desfluoro analogues in terms of their ability to induce LLR in rats after i.p or p.o administration (**39**, **46**, **52** compared with **23**, **24**, **25**). In the second group (**53**−**57**, **26**−**30**, **61**), the selectivity of the fluorinated ligands also improved, but mainly because of further decreases of their D_2 and α_1 affinity.[28b] Although the influence of the C-4 fluorine on the oral performance of the compounds shared the positive trend seen in the first group, there were marked differences among members of this group in terms of their in vitro potency (pEC_{50}). Thus, depending on the type of the heterocycle in the 6-position, the presence of the C-4 fluorine was either deleterious (**56** and **57** versus **29** and **30**), neutral (**53** and **55** versus **26** and **27**), or advantageous (**61** versus **28**). Such broad variations in potency data (over more than 1 log unit) suggested that the pattern of interactions used by these molecules to activate 5-HT_{1A} receptors may not overlap, notwithstanding they are structurally closely related.

The LLR activity of the desfluoro derivatives listed in Table 2, except for **24**, was sustained at 60 min after i.p. injection. Moreover, the ED_{50}'s to produce LLR were not, in general, dependent on the route of administration (**26**, **27**, **29**, and **30**). Given these results, we assumed that low brain exposure was the major factor limiting the central activity of the C-4 desfluoro agonists. In this regard, ligands displaying comparable in vitro profiles but different in vivo activities, irrespectively of the nature of the C-4 substituent (H or F), told us about the pharmacokinetic input of the C-4 fluorine atom (e.g., **25** compared with **52**, **28** versus **61**, **26** versus **53**, and **27** versus **55**). Thus, it became clear that a C-4 fluorine has the ability to enhance concentration of the compound into the brain. Improved pharmacokinetics would be also one of the features that would, qualitatively, account for the greater in vivo effects produced in the more hydrophilic 6-amino ligands (e.g., **23**, **24**, **25** compared with **39**, **46**, **52**, respectively). As discussed below, the contribution of the C-4 fluorine to the pharmacological profile of the ligand is, however, probably multifactorial. At present, even the possibility of specific metabolic activation of the fluorinated compounds cannot be ruled out.[29]

Having identified several orally active 5-HT_{1A} agonists, we investigated various substituents at C-4 position to refine our understanding of the role of the fluorine atom. Depending on the nature of the R group at C-4, the affinity and the potency of compounds varied over 1 order of magnitude (Table 3). Various C-4 substitutents led to ligands with substantial affinity for, and agonist potency at, 5-HT_{1A} receptors (e.g., **31**, **58**, **65**, **67**, **68**, and **69**). Among them, however, only a

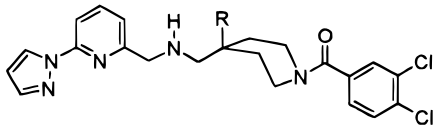
Table 2. Fluorinated and Nonfluorinated Derivatives: Comparisons of Their Receptor Binding Profiles and Their Potencies at 5-HT_{1A} Receptors in Vitro (cAMP) and in Vivo (LLR)



							5-HT_{1A} agonist activity			
								ED_{50} (mg/kg) to produce LLR[e]		
				receptor affinity (p*K*i)[b,c]				i.p		p.o
compd	A	X	Y	5-HT_{1A}	D_2	α_1	cAMP[d] pEC_{50}	15 min	60 min	60 min
23[a]	CH_3NH	H	Cl	8.76 (0.06)	5.51 (0.05)	6.87 (0.04)	7.66 (0.12)	5.0	5.0	>10
39	CH_3NH	F	Cl	9.67 (0.15)	6.40 (0.18)	6.92 (0.03)	8.18 (0.06)	0.11	0.23	0.32
24[a]	$(CH_3)_2N$	H	Cl	8.85 (0.11)	6.28 (0.04)	6.92 (0.03)	7.69 (0.14)	0.08	7.0	5.0
46	$(CH_3)_2N$	F	Cl	9.61 (0.07)	6.48 (0.22)	6.76 (0.04)	8.53 (0.09)	0.62	0.45	0.32
25[a]	azetidino	H	Cl	9.43 (0.05)	6.22 (0.13)	6.64 (0.04)	8.15 (0.02)	1.30	3.60	>10
52	azetidino	F	Cl	9.70 (0.12)	6.51 (0.09)	6.35 (0.05)	7.97 (0.14)	0.32	0.45	0.45
26[a]	furan-2-yl	H	Cl	9.14 (0.06)	6.34 (0.08)	6.71 (0.07)	8.28 (0.35)	1.30	1.30	1.30
53	furan-2-yl	F	Cl	8.98 (0.04)	5.92 (0.07)	6.39 (0.04)	8.58 (0.07)	0.16	0.23	0.32
54	furan-2-yl	F	F	9.55 (0.04)	5.65 (0.13)	6.12 (0.05)	8.46 (0.05)	0.08	0.11	0.32
27[a]	thien-2-yl	H	Cl	8.86 (0.04)	6.54 (0.07)	6.76 (0.05)	8.24 (0.06)	1.30	1.30	5.0
55	thien-2-yl	F	Cl	8.91 (0.04)	6.34 (0.08)	6.72 (0.07)	7.92 (0.25)	0.32	0.32	1.30
28[a]	pyrazol-3-yl	H	Cl	9.27 (0.10)	6.01 (0.03)	6.66 (0.07)	8.52 (0.11)	5.0	5.0	>10
61	pyrazol-3-yl	F	Cl	9.52 (0.07)	5.39 (0.17)	6.10 (0.04)	8.95 (0.08)	0.32	0.32	1.30
29[a]	oxazol-5-yl	H	Cl	9.03 (0.01)	6.06 (0.04)	6.55 (0.02)	8.70 (0.01)	0.45	0.89	1.30
56	oxazol-5-yl	F	Cl	9.33 (0.14)	5.65 (0.14)	5.90 (0.03)	8.05 (0.01)	0.32	0.32	1.30
30[a]	thiazol-2-yl	H	Cl	9.46 (0.08)	5.47 (0.07)	6.75 (0.02)	8.30 (0.13)	0.32	1.30	5.0
57	thiazol-2-yl	F	Cl	9.10 (0.08)	5.47 (0.23)	6.26 (0.07)	7.64 (0.14)	0.45	0.89	1.30

[a–c] See footnotes of Table 1. [d] Forskolin-stimulated cAMP levels in HA7 cells were inhibited by (±)-8-OH-DPAT (pEC_{50} = 7.60 (0.17), E_{max} = 71% ± 4.3%) and to a greater extent (E_{max} > 80%) by all compounds reported in the table (data not shown). [e] LLR = lower lip retraction.

Table 3. Effect of the Nature of the C-4 Piperidine Substituent on Affinity, and Agonist Potency at 5-HT_{1A} Receptors in Vitro (cAMP) and in Vivo (LLR)



			5-HT_{1A} agonist activity	
compd	R	5-HT_{1A} affinity pK_i[b,c]	cAMP pEC_{50}[d]	LLR[e] ED_{50} (mg/kg)[f]
31[a]	H	8.78 (0.09)	7.51 (0.09)	5.0
58	F	8.77 (0.09)	7.55 (0.12)	1.30
64	CH_3	7.43 (0.06)	NT	NT
65	CN	8.16 (0.10)	6.79 (0.40)	>10
66	OCH_3	7.52 (0.07)	NT	NT
67	OH	8.79 (0.03)	7.40 (0.02)	>10
68	CH_2F	8.04 (0.05)	6.51 (0.18)	>10
69		8.22 (0.16)	6.57 (0.15)	>10

[a–d] See footnotes of Table 2. [e] LLR = lower lip retraction. NT = not tested.

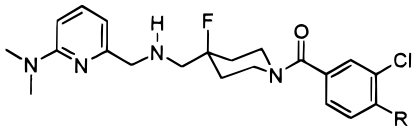
fluorine atom was able to confer an in vivo activity to the compound exceeding that of the corresponding C-4 unsubstituted derivative (LLR of **58** versus **31**). Moreover, changing the piperidine moiety by a tetrahydropyridine (**69**) was detrimental for recognition and activation of 5-HT_{1A} receptors, despite the fact that a Csp^2-4 produced minimal steric hindrance, and generated a negative electrostatic potential around the C-4 region of the molecule which could mimic that of a fluorine atom. The contribution of the R group to 5-HT_{1A} binding is, therefore, best understood in terms of conformational distribution effects rather than in terms of specific interactions of the C-4 substituent with the receptor protein. Thus, if we assume that the variation of the affinity constants (K_i), throughout the homogeneous set of compounds shown in Table 3, reflects the differences in the relative populations of molecules achieving active conformation(s), then it appears that the C-4 fluorine atom is able to select conformer(s) energetically close to the bioactive conformation(s) of the ligand. When R is small (R = H; **31**), or not sterically too demanding and inducing a strong permanent dipole moment (R = F; **58**), it tends to be axially oriented on the piperidine.[30] As a result, the piperidine ring is locked in (a) conformation(s) where the C-4 methylamino chain occupies an equatorial position.[31]

Apparently, an intramolecular hydrogen bond between the fluorine atom and one of the vicinal ammonium protons did not participate in binding when the fluorine is directly attached to C-4 of the piperidine[32] (**58** compared with **31**). On the other hand, there may be some entropic contributions to binding of such a hydrogen bond in the higher homologue **68** (compared with **64**).

The synergy seen in the desfluoro series,[7] between a few combinations of meta−para benzamide substituents, no longer occurred in the fluorinated series (Table 4). Nonetheless, a 3-chloro, 4-fluoro-benzamide group (**45**) still had the best overall profile, in vitro and in vivo.

To examine the relationship between the conformation of the pharmacophore and the level of agonist activity, we prepared 5-methylated congeners of several 6-alkylamino and 6-heteroaromatic derivatives (Table 5). It was expected that, because of the presence of the 5-methyl group, the size of the 6-substituent would control the degree of planarity of the 6-substituent-pyridine system: a n-π or p-π overlap should be allowed if the 6-substituents are small, but should become less favored as the size of the 6-substituents increases. Incorporation of a 5-methyl substituent in the 6-pyrazol-

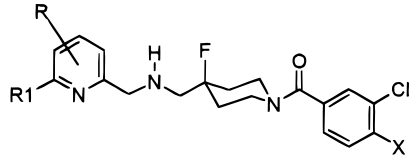
Table 4. Effect of the Nature of the Para Substituent on Receptor Affinity Profile and on 5-HT_{1A} Agonist Activity in Vitro (cAMP) and in Vivo (LLR)



					5-HT_{1A} agonist activity			
						ED_{50} (mg/kg)[e] to produce LLR[f]		
		receptor affinity (pK_i)[b,c]				i.p.		p.o.
compd	R	5-HT_{1A}	D_2	α_1	cAMP[d] pEC_{50}	15 min	60 min	60 min
43	H	10.01 (0.04)	6.21 (0.04)	6.81 (0.03)	8.00 (0.45)	0.08	0.11	0.32
44	CH_3	9.57 (0.05)	6.89 (0.15)	6.86 (0.06)	8.24 (0.22)	0.08	0.08	0.32
45	F	9.92 (0.09)	6.56 (0.06)	6.68 (0.09)	8.44 (0.09)	0.29	0.11	0.16
46	Cl	9.61 (0.07)	6.48 (0.22)	6.76 (0.04)	8.53 (0.09)	0.62	0.45	0.32

[b−d] See footnotes of Table 2. [e] ED_{50} values were obtained by linear interpolation. [f] LLR = lower lip retraction.

Table 5. 5-Unsubstituted and -Substituted Derivatives: Comparisons of Their Affinity and Agonist Activity at 5-HT_{1A} Receptors in Vitro (cAMP) and in Vivo (LLR)



					5-HT_{1A} agonist activity		
						LLR, ED_{50} (mg/kg)[e]	
compd	R	R_1	X	receptor affinity 5-HT_{1A} pK_i[b,c]	cAMP[d] pEC_{50}	i.p. (15 min)	p.o. (60 min)
34	5-CH_3	H	Cl	9.24 (0.07)	7.68 (0.13)	NT	0.62
35	5-CH_3	H	F	9.07 (0.05)	7.59 (0.04)	0.08	0.11
36	5-CH_2CH_3	H	F	8.05 (0.10)	6.39 (0.25)	1.30	1.80
37	5-$CH(CH_3)_2$	H	F	7.45 (0.05)	NT	NT	NT
38	H	CH_3NH	F	9.69 (0.05)	7.90 (0.38)	0.11	0.32
40	5-CH_3	CH_3NH	F	10.12 (0.11)	8.67 (0.02)	0.02	0.08
41	H	CH_3CH_2NH	F	9.73 (0.06)	7.88 (0.02)	0.11	0.32
42	5-CH_3	CH_3CH_2NH	F	9.83 (0.01)	8.08 (0.24)	0.08	0.45
45	H	$(CH_3)_2N$	F	9.92 (0.09)	8.44 (0.09)	0.29	0.16
47	3-CH_3	$(CH_3)_2N$	F	9.33 (0.03)	7.32 (0.12)	0.63	1.30
48	4-CH_3	$(CH_3)_2N$	F	9.25 (0.05)	7.48 (0.03)	0.32	0.89
49	5-CH_3	$(CH_3)_2N$	F	9.50 (0.09)	8.43 (0.15)	0.04	0.08
50	H	$(CH_3CH_2)_2N$	F	8.94 (0.01)	7.83 (0.10)	0.11	1.0
51	5-CH_3	$(CH_3CH_2)_2N$	F	8.86 (0.07)	7.54 (0.08)	0.32	0.11
59	H	pyrazol-1-yl	F	9.31 (0.06)	7.91 (0.04)	0.32	1.30
60	5-CH_3	pyrazol-1-yl	F	9.35 (0.06)	7.83 (0.09)	0.32	1.30
62	H	pyrazol-3-yl	F	9.34 (0.12)	9.14 (0.18)	0.32	0.32
63	5-CH_3	pyrazol-3-yl	F	8.66 (0.04)	8.56 (0.01)	0.32	0.89

[b−d] See footnotes of Table 2. [e] LLR = lower lip retraction; ED_{50} values were obtained by linear interpolation.

3-yl-pyridine derivative **63** significantly decreased its 5-HT_{1A} affinity and potency (compared with **62**). In contrast, the N-bound isomer **60** showed a pharmacological profile very similar to that of the 5-unsubstituted control **59**. Thus, intriguingly, either the conformation of the pharmacophore plays a different role in C-bound (**63**) than in N-bound (**60**) aromatic 6-substituted ligands or the 5-methyl group reduces the steric tolerance in the region occupied by the 6-substituent only in C-bound 6-substituted derivatives. In all cases, the binding mode of the C-versus N-bound aromatic 6-substituted ligands at 5-HT_{1A} receptors is likely to be different.

The impact of an additional 5-methyl group in the nonaromatic 6-substituted series was more encouraging. For instance, the 5-methylated derivative **34** (Table 5) had 10 times higher affinity than its 5-unsubstituted congener **32** (Table 1). Thus, clearly, the methyl group in the 5-position on the pyridine nucleus interacts with the receptor protein through hydrophobic effects.

When the methyl group was moved around the pyridine ring, affinity for 5-HT_{1A} receptors was retained but potency and in vivo activity were reduced markedly (**47** and **48** compared with **49**). In addition, in the 6-dialkylamino series, incorporation of a 5-methyl group did not seem to affect the in vitro responses of the corresponding ligands (**49** and **51** compared with **45** and **50**, respectively). This suggests that, in the 5,6-disubstituted series, the gain in free energy of stabilization of the receptor−ligand complex, provided by the 5-methyl effects, is partially offset by a less favorable contribution of the 6-substituents as compared to the 6-monosubstituted series, possibly for steric reasons.

Evidence in favor of such a scheme came from the 5-methyl-6-methylamino pyridine derivative **40**. In this compound the 5- and the 6-substituents act synergistically, as shown by the substantial improvement of all the 5-HT_{1A} parameters over those of the 5-unsubstituted and the 6-dimethyl congeners (**38** and **49**, respectively).

Table 6. Effects of **40**, **45**, **54**, and the Reference Compound Imipramine in the Rat Forced Swimming Test

compd[a]	immobility[b] inhibition ED_{50} (mg/kg)	inhibition[c] max (%)
40	0.05	>80
45	0.16	>80
54	0.09	>80
imipramine	80	31

[a] Compounds given orally 60 min before test. [b] Potency to produce a significant inhibition of immobility in 50% of the animals tested. [c] Estimated maximum inhibition of immobility, expressed as a percentage of immobility observed in vehicle controls.

Hence, not only do the 5- and the 6-substituents in **40** (fully) cooperate in the stabilization of the receptor−ligand complex (i.e., gain in affinity) but, of prime interest, they seem to cooperate in the stabilization of a G-protein coupled state(s) of the receptor (i.e., gain in efficacy). Also consistent with the scheme proposed above, the steric constraints imposed on each component of the 5,6-pair are very tight. Thus, the synergistic effect between the 5- and the 6-groups vanished when the size of one of them was larger than a 5-methyl or a 6-methylamino group: the derivatives **36**, **37**, and **42** suffered marked losses in affinity and potency at 5-HT_{1A} receptors.

Compounds **40**, **45** (Table 5), and **54** (Table 2), which emerged as the most active derivatives in each group, were then assessed in the FST. As summarized in Table 6, all three compounds potently decreased immobility after a single administration, and maximal effects were greater than that of the tricyclic antidepressant imipramine. These novel 5-HT_{1A} receptor agonists have, therefore, the potential to exert antidepressant effects in humans.[33]

Currently, these compounds, and others within this series, are being evaluated further in various preclinical models.

Conclusion

The present study is part of an effort to improve the in vivo properties of a recently described, novel class of 5-HT_{1A} receptor agonists. Here, we reported the preparation of, and discussed pharmacological results obtained with, a series of aryl-[4-fluoro-4-({[5-H or CH_3, 6-substituted-pyridin-2-ylmethyl]-amino}-methyl)-piperidin-1-yl]-methanones. These compounds have, in general, high affinity for and selectivity at 5-HT_{1A} receptors (versus D_2 and α_1). Among them, several inhibited forskolin-stimulated cAMP accumulation in HA7 cells more potently than the prototypical agonist (±)8-OH-DPAT. Importantly, their 5-HT_{1A} agonist activity, when administered i.p. and p.o. to rats, was superior to that of the aryl-[4-({[5-H or CH_3, 6-substituted-pyridin-2-ylmethyl]-amino}-methyl)-piperidin-1-yl]-methanone analogues. Furthermore, their ability to reduce immobility in the FST after a single oral administration, compared with that of imipramine (tricyclic antidepressant), suggests that they have marked antidepressant potential.

From a structural standpoint, a Csp^3-4 fluorine atom proved unique in its ability to enhance the central 5-HT_{1A} activity of the ligands when administered orally. This effect may result from improved pharmacokinetics, possibly combined with some stereoelectronic contributing factors, rather than increased agonist properties of the fluorinated ligand at 5-HT_{1A} receptors. From a conformational standpoint, we proposed that the chain linked at C-4 on the piperidine ring assumed an equatorial or a pseudoequatorial orientation in the bioactive conformation(s) of the ligand.

The outstanding in vitro and in vivo profile of several compounds in this series, together with the novelty of their structures, warrants a further examination of their properties in other preclinical models. Already, these derivatives and analogues will provide innovative tools that could contribute to a better understanding of the therapeutic significance of 5-HT_{1A} receptors.

Experimental Section

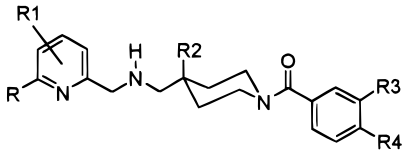
Melting points were determined on a Büchi 530 melting point apparatus and were not corrected. ^{1}H NMR spectra were recorded on a Bruker AC200 (200 MHz) instrument. Chemical shifts are reported in δ value (ppm) relative to an internal standard of tetramethylsilane in $CDCl_3$ or DMSO-d_6. Infrared (IR) spectra were obtained on a Nicolet FT 510 P spectra photometer. 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. *N*-(3-Chloro-4-fluorobenzoyl)-4-fluoro-4-[(5-methyl-6-dimethylaminopyridyl-2)-methylamino-methyl]-piperidine (49). A solution of amine **1aa** (1.43 g, 4.95 mmol), aldehyde **3c** (0.68 g, 4.14 mmol), and toluene (50 mL) was heated under reflux for 2 h with water separation by a Dean−Stark trap. The solvent was removed under reduced pressure, the residue was taken up in MeOH (25 mL) and cooled to 0−5 °C, and KBH_4 (0.45 g, 8.28 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, and then dried and filtered. Evaporation of the solvent gave a pale yellow oil which was purified by flash chromatography, MeOH−CH_2Cl_2 (1:9), to afford 1.56 g of **49** (86%) as a pale yellow oil. The oxalate salt of **49** was crystallized from MeOH−Et_2O to give 1.46 g of a white solid: mp 204−206 °C; ^{1}H NMR (DMSO-d_6) δ 1.75 (m, 1H), 1.84 (m, 2H), 1.99 (m, 1H), 2.25 (s, 2H), 2.82 (s, 6H), 3.07 (m, 1H), 3.18 (d, 2H), 3.25 (m, 1H), 3.44 (m, 1H), 4.08 (s, 2H), 4.30 (m, 1H), 6.89 (d, 1H), 7.46 (m, 3H), 7.66 (dd, 1H); Anal. ($C_{22}H_{27}ClF_2N_4O\cdot C_2H_2O_4$) C, H, N, and Cl.

***N*-(3-Chloro-4-fluorobenzoyl)-piperidine-4-one (5a).** To a cooled solution of piperidin-4-one ethyleneketal (82.05 g, 0.573 mol), TEA (160 mL, 1.15 mol), and chloroform (300 mL) was added dropwise a solution of 3-chloro-4-fluorobenzoyl chloride (110.6 g, 0.573 mol) in anhydrous chloroform (100 mL). After stirring for 17 h at room temperature, the solution was washed successively with 1 N HCl, H_2O, aqueous $NaHCO_3$, and brine then dried and filtered. The solvent was evaporated under vacuum to give 172 g of the protected amide (quantitative) as an oil which was treated with 80% formic acid (500 mL) containing $CuSO_4$ (2 g) at 80 °C for 16 h. Formic acid was eliminated by azeotropic distillation with toluene, and the oily residue obtained was neutralized with aqueous K_2CO_3. The mixture was extracted twice with CH_2Cl_2, dried, and filtered, and the solvent was evaporated to give an oil which crystallized on standing. Recrystallization from CH_2Cl_2−diisopropyl ether afforded 105 g of **5a** (71.6%): mp 118−120 °C; ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 4H), 3.86 (s, 4H), 7.20 (t, 1H), 7.37 (m, 1H), 7.55 (dd, 1H); IR (KBr, cm^{-1}) 1635 and 1710. Anal. ($C_{12}H_{11}ClFNO_2$) C, H, N, and Cl.

***N*-(3-Chloro-4-methylbenzoyl)-piperidin-4-one (5b).** This compound was prepared in 64% yield as described for **5a** using 3-chloro-4-methylbenzoyl chloride as starting material. **5b** was obtained as a white solid: mp 74−75 °C; ^{1}H NMR ($CDCl_3$) δ

Table 7. Physical Data of Pyridin-2-ylmethylamino Derivatives



compd	R	R_1	R_2	R_3	R_4	method	% yield	formula[a]	mp (°C)
32	H	H	F	Cl	Cl	A	60	$C_{19}H_{20}Cl_2FN_3O \cdot C_4H_4O_4$[b]	161−163
33	H	3-F	H	Cl	Cl	A	78	$C_{19}H_{20}Cl_2FN_3O \cdot C_4H_4O_4$[b]	155−157
34	H	5-CH_3	F	Cl	Cl	A	51	$C_{20}H_{22}Cl_2FN_3O \cdot C_4H_4O_4$[b]	162−164
35	H	5-CH_3	F	Cl	F	A	49	$C_{20}H_{22}ClF_2N_3O \cdot C_4H_4O_4$[b]	156−158
36	H	5-C_2H_5	F	Cl	F	A	47	$C_{21}H_{24}ClF_2N_3O \cdot C_4H_4O_4$[b]	153−155
37	H	5-iC_3H_7	F	Cl	F	A	37	$C_{22}H_{26}ClF_2N_3O \cdot C_4H_4O_4$[b]	155−157
38	CH_3NH	H	F	Cl	F	A	78	$C_{20}H_{23}ClF_2N_4O \cdot C_4H_4O_4$[b]	164−166
39	CH_3NH	H	F	Cl	Cl	A	71	$C_{20}H_{23}Cl_2FN_4O \cdot C_4H_4O_4$[b]	167−169
40	CH_3NH	5-CH_3	F	Cl	F	A	91	$C_{21}H_{25}ClF_2N_4O \cdot C_4H_4O_4$[d]	162−164
41	C_2H_5NH	H	F	Cl	F	A	57	$C_{21}H_{25}ClF_2N_4O \cdot C_2H_2O_4$[c]	173−175
42	C_2H_5NH	5-CH_3	F	Cl	F	A	79	$C_{22}H_{27}ClF_2N_4O \cdot C_4H_4O_4$[b]	130−132
43	$(CH_3)_2N$	H	F	Cl	H	A	45	$C_{21}H_{26}ClFN_4O \cdot C_4H_4O_4$[b]	152−154
44	$(CH_3)_2N$	H	F	Cl	CH_3	A	61	$C_{22}H_{28}ClFN_4O \cdot C_4H_4O_4$[b]	166−168
45	$(CH_3)_2N$	H	F	Cl	F	A	67	$C_{21}H_{25}ClF_2N_4O \cdot C_4H_4O_4$[b]	158−160
46	$(CH_3)_2N$	H	F	Cl	Cl	A	58	$C_{21}H_{25}Cl_2FN_4O \cdot C_4H_4O_4$[b]	173−175
47	$(CH_3)_2N$	3-CH_3	F	Cl	Cl	A	65	$C_{22}H_{27}Cl_2FN_4O \cdot C_2H_2O_4$[c]	169−171
48	$(CH_3)_2N$	4-CH_3	F	Cl	F	A	51	$C_{22}H_{27}ClF_2N_4O \cdot C_4H_4O_4$[b]	140−142
49	$(CH_3)_2N$	5-CH_3	F	Cl	F	A	86	$C_{22}H_{27}ClF_2N_4O \cdot C_2H_2O_4$[c]	204−206
50	$(C_2H_5)_2N$	H	F	Cl	F	A	77	$C_{23}H_{29}ClF_2N_4O \cdot C_2H_2O_4$[c]	198−200
51	$(C_2H_5)_2N$	5-CH_3	F	Cl	F	A	69	$C_{24}H_{31}ClF_2N_4O \cdot C_4H_4O_4$[b]	140−142
52	6-azetidin-1-yl	H	F	Cl	Cl	A	52	$C_{22}H_{25}Cl_2FN_4O \cdot C_2H_2O_4$[c]	215−216
53	6-furan-2-yl	H	F	Cl	Cl	A	49	$C_{23}H_{22}Cl_2FN_3O_2 \cdot {}_{0.5}C_4H_4O_4$[b]	142−144
54	6-furan-2-yl	H	F	Cl	F	A	75	$C_{23}H_{22}ClF_2N_3O_2 \cdot {}_{0.5}C_4H_4O_4$[b]	158−160
55	6-thien-2-yl	H	F	Cl	Cl	A	43	$C_{23}H_{22}Cl_2FN_3OS \cdot {}_{0.5}C_4H_4O_4$[b]	171−173
56	6-oxazol-5-yl	H	F	Cl	Cl	A	75	$C_{22}H_{21}Cl_2FN_4O_2 \cdot C_2H_2O_4$[c]	182−184
57	6-thiazol-2-yl	H	F	Cl	Cl	A	62	$C_{22}H_{21}Cl_2FN_4OS \cdot C_4H_4O_4$[b]	146−148
58	6-pyrazol-1-yl	H	F	Cl	Cl	A	39	$C_{22}H_{22}Cl_2FN_5O \cdot {}_{0.5}C_4H_4O_4$[b]	138−140
59	6-pyrazol-1-yl	H	F	Cl	F	A	75	$C_{22}H_{22}ClF_2N_5O \cdot C_4H_4O_4$[b]	173−175
60	6-pyrazol-1-yl	5-CH_3	F	Cl	F	A	81	$C_{23}H_{24}ClF_2N_5O \cdot C_4H_4O_4$[b]	171−173
61	6-pyrazol-3-yl	H	F	Cl	Cl	A	51	$C_{22}H_{22}Cl_2FN_5O \cdot C_2H_2O_4$[c]	150−152
62	6-pyrazol-3-yl	H	F	Cl	F	A	48	$C_{22}H_{22}ClF_2N_5O \cdot C_2H_2O_4$[c]	165−167
63	6-pyrazol-3-yl	5-CH_3	F	Cl	F	A	58	$C_{23}H_{24}ClF_2N_5O \cdot C_4H_4O_4$[b]	172−174
64	6-pyrazol-1-yl	H	CH_3	Cl	Cl	A	70	$C_{23}H_{25}Cl_2N_5O \cdot {}_{1.5}C_4H_4O_4$[b]	131−133
65	6-pyrazol-1-yl	H	CN	Cl	Cl	B	42	$C_{23}H_{22}Cl_2N_6O \cdot C_2H_2O_4$[c]	178−180
66	6-pyrazol-1-yl	H	OCH_3	Cl	Cl	B	62	$C_{23}H_{25}Cl_2N_5O_2 \cdot C_2H_2O_4$[c]	187−189
67	6-pyrazol-1-yl	H	OH	Cl	Cl	C[d]	56	$C_{22}H_{23}Cl_2N_5O_2 \cdot {}_{1.5}C_4H_4O_4$[b]	191−193
68	6-pyrazol-1-yl	H	CH_2F	Cl	Cl	A	53	$C_{23}H_{24}Cl_2N_5O \cdot C_2H_2O_4$[c]	208−210
69[e]	6-pyrazol-1-yl	H		Cl	Cl	A	54	$C_{22}H_{21}Cl_2N_5O \cdot C_4H_4O_4$[b]	120−125

[a] Analyses for all compounds were within 0.4% of the theoretical value for C, H, and N. [b] Fumarate. [c] Oxalate. [d] Method C involved a reductive amination between the 6-(pyrazol-1-yl)-2-pyridinecarboxaldehyde[7] and the *N*-(3,4-dichlorobenzoyl)-4-hydroxy-4-aminomethylpiperidine in the same experimental conditions used for method A. [e] The piperidine ring is replaced by a 1,2,5,6-tetrahydropyridine.

2.42 (s, 3H), 2.51 (s, 4H), 3.87 (s, 4H), 7.25 (d, 1H), 7.28 (d, 1H), 7.47 (s, 1H); IR (KBr, cm^{-1}) 1626 and 1714. Anal. ($C_{13}H_{14}ClNO_2$) C, H, N, and Cl.

***N*-(3,4-Dichlorobenzoyl)-piperidin-4-one (5c).** This compound was prepared in 76% yield as described for **5a** using 3,4-dichlorobenzoyl chloride as starting material. Compound **5c** was obtained as a white solid: mp 115−117 °C; ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 4H), 3.86 (s, 4H), 7.30 (dd, 1H), 7.52 (d, 1H), 7.57 (d, 1H); IR (KBr, cm^{-1}) 1645 and 1721. Anal. ($C_{12}H_{11}Cl_2NO_2$) C, H, N, and Cl.

***N*-(3-Chlorobenzoyl)-piperidin-4-one (5d).** This compound was prepared in 67% yield as described for **5a** using 3-chlorobenzoyl chloride as starting material. Compound **5d** was obtained as a white solid: mp 62−64 °C; ^{1}H NMR ($CDCl_3$) δ 2.51 (m, 4H), 3.87 (m, 4H), 7.34−7.47 (m, 4H); IR (KBr, cm^{-1}) 1638 and 1721. Anal. ($C_{12}H_{12}ClNO_2$) C, H, N, and Cl.

***N*-(3-Chloro-4-fluorobenzoyl)-1-oxa-6-azaspiro[2,5]-octane (6a).** A solution of dimethylsulfoxonium methylide was prepared, under nitrogen, from sodium hydride (1.52 g of a 60% dispersion in mineral oil, 37.8 mmol) and trimethylsulfoxonium iodide (8.32 g, 37.8 mmol) in anhydrous DMSO (20 mL). A solution of **5a** (9.21 g, 36 mmol) in DMSO (20 mL) was added in 30 min and stirring was continued at 60 °C for 3.5 h. The cooled reaction mixture was poured into ice−water and extracted twice with ethyl acetate. The combined organic layer was washed with water and brine and then dried and concentrated. The residue was purified by a short flash chromatography on silica gel, eluting with $CHCl_3$−EtOAc (9:1), to give 7.68 g of **6a** (79%) as an oil which crystallized on standing: mp 75−77 °C; ^{1}H NMR ($CDCl_3$) δ 1.50 (m, 2H), 1.92 (m, 2H), 2.74 (s, 2H), 3.52 (m, 2H), 3.87 (m, 1H), 4.19 (m, 1H), 7.18 (t, 1H), 7.32 (m, 1H), 7.51 (dd, 1H); IR (KBr, cm^{-1}) 1620. Anal. ($C_{13}H_{13}ClFNO_2$) C, H, N, and Cl.

***N*-(3-Chloro-4-methylbenzoyl)-1-oxa-6-azaspiro[2,5]-octane (6b).** This compound was prepared in 60% yield as described for **6a** starting from **5b**. Compound **6b** was obtained as a white solid: mp 104−105 °C; ^{1}H NMR ($CDCl_3$) δ 1.48 (m, 2H), 1.92 (m, 2H), 2.40 (s, 3H), 2.74 (s, 2H), 3.54 (m, 2H), 3.63 (m, 1H), 4.24 (m, 1H), 7.21 (dd, 1H), 7.27 (d, 1H), 7.42 (d, 1H); IR (KBr, cm^{-1}) 1628. Anal. ($C_{14}H_{16}ClNO_2$) C, H, N, and Cl.

***N*-(3,4-Dichlorobenzoyl)-1-oxa-6-azaspiro[2,5]octane (6c).** This compound was prepared in 72% yield as described for **6a** starting from **5c**. Compound **6c** was obtained as a white solid: mp 95−97 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 2H), 1.88 (m, 2H), 2.71 (s, 2H), 3.50 (m, 3H), 4.19 (m, 1H), 7.22 (dd, 1H), 7.49 (m, 2H); IR (KBr, cm^{-1}) 1625. Anal. ($C_{13}H_{13}Cl_2NO_2$) C, H, N, and Cl.

***N*-(3-Chlorobenzoyl)-1-oxa-6-azaspiro[2,5]octane (6d).** This compound was prepared in 56% yield as described for **6a** starting from **5d**. Compound **6d** was obtained as a pale yellow

oil: ^{1}H NMR ($CDCl_3$) δ 1.48 (m, 2H), 1.89 (m, 2H), 2.62 (s, 2H), 3.54 (m, 2H), 3.72 (m, 1H), 4.26 (m, 1H), 7.26−7.46 (m, 4H).

***N*-(3-Chloro-4-fluorobenzoyl)-4-fluoro-4-hydroxymethylpiperidine (7a).** To a solution of the epoxide **6a** (11.90 g, 44.1 mmol) and anhydrous CH_2Cl_2 (20 mL), stirred at −10 °C, was added dropwise 70% poly(hydrogenfluoride)-pyridine (12.60 g, 441 mmol). The solution was stirred at −10 °C for 15 min and then at room temperature for 16 h. The dark-red solution was poured into ice−water and carefully neutralized with K_2CO_3, and the product was extracted three times with CH_2Cl_2. The combined organic layer was washed with water, 1 N HCl, and brine and dried, and the solvent was evaporated off. The solid obtained was recrystallized from ethanol−ethyl acetate to give 6.40 g of **7a** (50%) as a white solid: mp 188−190 °C; ^{1}H NMR ($CDCl_3$) δ 1.50 (m, 1H), 1.63 (s, 1H exchangeable), 1.70 (m, 1H), 1.99 (m, 2H), 3.30 (m, 3H), 3.61 (dd, 2H), 4.53 (m, 1H), 7.16 (t, 1H), 7.29 (m, 1H), 7.46 (dd, 1H); IR (KBr, cm^{-1}) 3328 and 1612. Anal. ($C_{13}H_{14}ClF_2NO_2$) C, H, N, and Cl.

***N*-(3-Chloro-4-methylbenzoyl)-4-fluoro-4-hydroxymethylpiperidine (7b).** This compound was prepared in 48% yield as described for **7a** starting from **6b**. Compound **7b** was obtained as a white solid: mp 148−150 °C; ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 1H), 1.83 (s, 1H, exchangeable), 1.96 (m, 1H), 2.40 (s, 3H), 3.27 (m, 2H), 3.62 (d, 1H), 3.68 (m, 1H), 4.55 (m, 1H), 7.19 (d, 1H), 7.27 (d, 1H), 7.40 (s, 1H); IR (KBr, cm^{-1}) 3370 and 1617. Anal. ($C_{14}H_{17}ClFNO_2$) C, H, N, and Cl.

***N*-(3,4-Dichlorobenzoyl)-4-fluoro-4-hydroxymethylpiperidine (7c).** This compound was prepared in 46% yield as described for **7a** starting from **6c**. Compound **7c** was obtained as a white solid: mp 178−180 °C; ^{1}H NMR (DMSO d_6) δ 1.46−1.61 (m, 4H), 3.04 (m, 2H), 3.31 (s, 1H, exchangeable), 3.38 (dd, 2H), 4.18 (m, 1H), 4.99 (t, 1H), 7.36 (dd, 1H), 7.67 (m, 2H). Anal. ($C_{13}H_{14}Cl_2FNO_2$) C, H, N, and Cl.

***N*-(3-Chlorobenzoyl)-4-fluoro-4-hydroxymethylpiperidine (7d).** This compound was prepared in 35% yield as described for **7a** starting from **6d**. Compound **7d** was obtained as a white solid: mp 130−132 °C; ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 2H), 1.93 (s, 1H exchangeable), 2.05 (m, 2H), 3.28 (m, 2H), 3.63 (m, 3H), 4.57 (m, 1H), 7.27 (m, 1H), 7.37 (m, 2H); IR (KBr, cm^{-1}) 3365 and 1613. Anal. ($C_{13}H_{15}ClFNO_2$) C, H, N, and Cl.

***N*-(3-Chloro-4-fluorobenzoyl)-4-fluoro-4-(4-methylphenylsulfonyloxymethyl)-piperidine (8a).** To a solution of **7a** (47.65 g, 0.164 mol) in anhydrous pyridine (235 mL), cooled to 0−5 °C, was added dropwise *p*-toluenesulfonyl chloride (34.32 g, 0.18 mol), and the solution was stirred at room temperature overnight. The suspension was poured into ice−water and extracted twice with CH_2Cl_2. The combined organic layer was washed successively with 1 N HCl, water, and brine, dried, filtered, and concentrated under vacuum. Crystallization from diisopropyl ether afforded 64.40 g of **8a** (83%) as a white solid: mp 90−92 °C; ^{1}H NMR ($CDCl_3$) δ 1.58 (m, 1H), 1.71 (m, 1H), 1.86 (m, 2H), 2.43 (s, 3H), 3.23 (m, 2H), 3.64 (m, 1H), 3.97 (d, 2H), 4.46 (m, 1H), 7.15 (t, 1H), 7.25 (m, 1H), 7.34 (d, 2H), 7.44 (dd, 1H), 7.76 (d, 2H); IR (KBr, cm^{-1}) 1622. Anal. ($C_{20}H_{20}ClF_2NO_4S$) C, H, N, and Cl.

***N*-(3-Chloro-4-methylbenzoyl)-4-fluoro-4(4-methylphenylsulfonyloxymethyl)-piperidine (8b).** This compound was prepared in 78% yield as described for **8a** starting from alcohol **7b**. Compound **8b** was obtained as a white solid: mp 122−123 °C; ^{1}H RMN ($CDCl_3$) δ 1.62 (m, 1H), 1.88 (m, 1H), 2.40 (s, 3H), 2.46 (s, 3H), 3.13 (m, 1H), 3.31 (m, 1H), 3.64 (m, 1H), 4.01 (d, 2H), 4.54 (m, 1H), 7.16 (d, 1H), 7.26 (d, 1H), 7.38 (m, 3H), 7.79 (d, 2H); IR (KBr, cm^{-1}) 1618. Anal. ($C_{21}H_{23}ClFNO_4S$) C, H, N, and Cl.

***N*-(3,4-Dichlorobenzoyl)-4-fluoro-4-(4-methylphenylsulfonyloxymethyl)-piperidine (8c).** This compound was prepared in 81% yield as described for **8a** starting from alcohol **7c**. Compound **8c** was obtained as a white solid: mp 142−144 °C; ^{1}H NMR ($CDCl_3$) δ 1.61 (m, 2H), 1.85 (m, 2H), 2.45 (s, 3H), 3.26 (m, 2H), 3.60 (m, 1H), 4.01 (d, 2H), 4.51 (m, 1H), 7.20 (dd, 1H), 7.35 (d, 2H), 7.48 (m, 2H), 7.78 (d, 2H).

***N*-(3-Chlorobenzoyl)-4-fluoro-4-(4-methylphenylsulfonyloxymethyl)-piperidine (8d).** This compound was prepared in 85% yield as described for **8a** starting from alcohol **7d**. Compound **8d** was obtained as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 2H), 1.89 (m, 2H), 2.46 (s, 3H), 3.12 (m, 1H), 3.34 (m, 1H), 3.63 (m, 1H), 4.02 (d, 2H), 4.56 (m, 1H), 7.25 (d, 1H), 7.37 (m, 5H), 7.79 (d, 2H).

***N*-(3-Chloro-4-fluorobenzoyl)-4-fluoro-4-phthalimidomethylpiperidine (9a).** The mixture of **8a** (60 g, 0.0135 mol), K-phthalimide (32.4 g, 0.175 mol), and anhydrous DMF (500 mL) was stirred at 150 °C for 7 h. The cooled suspension was poured into ice−water and extracted twice with CH_2Cl_2. The combined organic layer was washed with brine, dried, and filtered through a pad of silica. Evaporation of the solvent gave an oil which crystallized upon addition of a mixture of diisopropyl ether−cyclohexane. Filtration of the solid gave 49.32 g of **9a** (87%): mp 123−125 °C; ^{1}H NMR ($CDCl_3$) 1.85 (m, 4H), 3.16 (m, 1H), 3.34 (m, 1H), 3.65 (m, 1H), 3.91 (d, 2H), 4.56 (m, 1H), 7.18 (t, 1H), 7.29 (m, 1H), 7.49 (dd, 1H), 7.76 (m, 2H), 7.88 (m, 2H); IR (KBr, cm^{-1}) 1776, 1720 and 1623. Anal. ($C_{21}H_{17}ClF_2N_2O_3$) C, H, N, and Cl.

***N*-(3-Chloro-4-methylbenzoyl)-4-fluoro-4-phthalimidomethylpiperidine (9b).** This compound was prepared in 85% yield as described for **9a** starting from **8b**. Compound **9b** was obtained as a white solid: mp 149−151 °C; ^{1}H NMR ($CDCl_3$) δ 1.62−1.95 (m, 4H), 2.39 (s, 3H), 3.13 (m, 1H), 3.32 (m, 1H), 3.63 (m, 1H), 3.90 (d, 2H), 4.56 (m, 1H), 7.18 (m, 1H), 7.25 (d, 1H), 7.39 (s, 1H), 7.76 (m, 2H), 7.88 (m, 2H); IR (KBr, cm^{-1}) 1777, 1720, and 1625; Anal. ($C_{22}H_{20}ClFN_2O_3$) C, H, N, and Cl.

***N*-(3,4-Dichlorobenzoyl)-4-fluoro-4-phthalimidomethylpiperidine (9c).** This compound was prepared in 83% yield as described for **9a** starting from **8c**. Compound **9c** was obtained as a white solid: mp 152−154 °C; ^{1}H NMR ($CDCl_3$) δ 1.60−1.90 (m, 4H), 3.22 (m, 2H), 3.62 (m, 1H), 3.90 (d, 2H), 4.58 (m, 1H), 7.25 (dd, 1H), 7.50 (m, 2H), 7.75 (m, 2H), 7.88 (m, 2H); IR (KBr, cm^{-1}) 1776, 1723, and 1635. Anal. ($C_{21}H_{17}Cl_2FN_2O_3$) C, H, N, and Cl.

***N*-(3-Chlorobenzoyl)-4-fluoro-4-phthalimidomethylpiperidine (9d).** This compound was prepared in 80% yield as described for **9a** starting from **8d**. Compound **9d** was obtained as a white solid: mp 126−127 °C; ^{1}H NMR ($CDCl_3$) δ 1.62−1.99 (m, 4H), 3.13 (m, 1H), 3.34 (m, 1H), 3.63 (m, 1H), 3.90 (d, 2H), 4.59 (m, 1H), 7.26 (d, 1H), 7.36 (m, 2H), 7.76 (dd, 2H), 7.89 (dd, 2H). Anal. ($C_{21}H_{18}ClFN_2O_3$) C, H, N, and Cl.

***N*-(3-Chloro-4-fluorobenzoyl)-4-fluoro-4-aminomethylpiperidine (1aa).** A mixture of **9a** (2.60 g, 6.20 mmol) and ethanolamine (8 mL) was stirred at 60 °C for 2 h. The cooled solution was poured into ice−water and extracted twice with CH_2Cl_2. The organic layers were washed with brine, dried, and concentrated to give 1.50 g of **1aa** (87%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.37 (s broad, exchangeable), 1.63 (m, 2H), 1.91 (m, 2H), 2.79 (d, 2H), 3.22 (m, 2H), 3.62 (m, 1H), 4.49 (m, 1H), 7.15 (t, 1H), 7.26 (m, 1H), 7.45 (dd, 1H).

***N*-(3-Chloro-4-methylbenzoyl)-4-fluoro-4-aminomethylpiperidine (1ab).** This compound was prepared from **9b** (90%) using the same procedure as described for the preparation of **1aa**. Compound **1ab** was obtained as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.23 (s broad, exchangeable), 1.59 (m, 2H), 1.95 (m, 2H), 2.40 (s, 3H), 2.83 (d, 2H), 3.14 (m, 1H), 3.37 (m, 1H), 3.64 (m, 1H), 4.56 (m, 1H), 7.19 (d, 1H), 7.26 (m, 1H), 7.39 (d, 1H).

***N*-(3,4-Dichlorobenzoyl)-4-fluoro-4-aminomethylpiperidine (1ac).** This compound was prepared from **9c** (82%) using the same procedure as described for the preparation of **1aa**. Compound **1ac** was obtained as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.32 (s broad, exchangeable), 1.64 (m, 2H), 1.94 (m, 2H), 2.81 (d, 2H), 3.27 (m, 2H), 3.59 (m, 1H), 4.52 (m, 1H), 7.26 (m, 1H), 7.48 (m, 2H).

***N*-(3-Chlorobenzoyl)-4-fluoro-4-aminomethylpiperidine (1ad).** This compound was prepared from **9d** (87%) using the same procedure as described for the preparation of **1aa**. Compound **1ad** was obtained as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.35 (s broad, exchangeable), 1.61 (m, 2H), 1.93 (m, 2H), 2.80 (d, 2H), 3.25 (m, 2H), 3.65 (m, 1H), 4.54 (m, 1H), 7.28 (d, 1H), 7.39 (m, 3H).

***N*-(3,4-Dichlorobenzoyl)-4-cyano, 4-hydroxymethylpiperidine (10).** To a mixture of KBH_4 (0.92 g, 17 mmol), LiCl (0.73 g, 17.2 mmol), and anhydrous THF (30 mL) under a nitrogen atmosphere was added dropwise at room temperature a solution of *N*-(3,4-dichlorobenzoyl)-4-cyano, 4-ethoxycarbonylpiperidine[12] (5.48 g, 15.4 mmol) and THF (20 mL). Stirring was continued at room temperature for 18 h. The mixture was concentrated under vacuum, and water was added. The product was extracted with EtOAc, washed with water and brine, dried, and filtered, and the solvent was evaporated under vacuum. The crude product was crystallized from diisopropyl ether to give 3.19 g (66%) of **10** as a white solid: mp 188−190 °C; ^{1}H NMR (DMSO-d_6) δ 1.51 (dt, 2H), 1.87 (m, 2H), 2.96 (m, 1H), 3.17 (m, 1H), 3.46 (d, 2H), 3.65 (m, 1H), 4.44 (m, 1H), 5.49 (t, 1H), 7.36 (d, 1H), 7.41 (d, 1H), 7.70 (dd, 1H). Anal. ($C_{14}H_{14}Cl_2N_2O_2$) C, H, N.

***N*-(3,4-Dichlorobenzoyl)-4-cyano, 4-Trifluoromethylsulfonyloxymethylpiperidine (11).** Trifluoromethanesulfonic anhydride (1.08 mL, 6.4 mmol) was added dropwise to an ice-cold mixture of **10** (1.60 g, 5.1 mmol), 2,6-dimethylpyridine (1 mL, 8.6 mmol), DMAP (62 mg, 0.51 mmol), and anhydrous CH_2Cl_2 (15 mL). Stirring was continued for 1 h at 0 °C and for 3 h at room temperature. The suspension was successively washed with water, aqueous citric acid solution, and water. The organic layer was dried and filtered, and the solvent was removed under vacuum to give 2.16 g (95%) of **11** as an oil which crystallized on standing: mp 120−122 °C; ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 2H), 2.08 (m, 2H), 3.32 (m, 2H), 3.97 (m, 1H), 4.46 (s, 2H), 4.80 (m, 1H), 7.21 (d, 1H), 7.25 (d, 1H), 7.51 (m, 2H).

***N*-(3,4-Dichlorobenzoyl)-4-cyano, 4-Fluoromethylpiperidine (12).** The solution of **11** (2.05 g, 4.6 mmol), KF (2.9 g, 50 mmol), and diethyleneglycol (12 mL) was stirred at 100−105 °C for 1 h. The cooled mixture was poured into 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, EtOAc−CH_2Cl_2 (1:9) gave an oil which was crystallized from diisopropyl ether to afford 0.99 g (68%) of **12** as a white solid: mp 135−137 °C; ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 2H), 1.98 (m, 2H), 3.25 (m, 2H), 3.83 (m, 1H), 4.40 (d, 1H), 4.74 (m, 1H), 7.19 (dd, 1H), 7.49 (m, 1H). Anal. ($C_{14}H_{13}Cl_2FN_2O$) C, H, N.

***N*-(3,4-Dichlorobenzoyl)-4-aminomethyl, 4-Fluoromethylpiperidine (1b).** To a solution of **12** (0.82 g, 2.6 mmol), methanol (20 mL), and concentrated NH_4OH (0.25 mL) was added Raney nickel (1.50 g). The suspension was stirred under hydrogen atmosphere for 4 h. The catalyst was filtered off through Celite, and the solution was concentrated under vacuum. The oily residue was taken up in chloroform and washed with water and brine, dried, and filtered. The solvent was removed in a vacuum to give 0.80 g (96%) of **1b** as an yellow oil: ^{1}HNMR ($CDCl_3$) δ 1.13 (m, 2H), 1.52 (m, 4H), 2.76 (s, 2H), 3.39 (m, 1H), 3.68 (m, 1H), 4.38 (d, 2H), 7.21 (dd, 1H), 7.48 (m, 2H).

***N*-(3,4-Dichlorobenzoyl)-4-cyano, 4-Methylpiperidine (13).** LDA (2 mL, 3.9 mmol as a 2 M solution in heptane/THF/ethylbenzene) was added to the solution of *N*-(3,4-dichlorobenzoyl)-4-cyanopiperidine[14] (1.0 g, 3.5 mmol), 1,3-dimethyl-2-imidazolidinone (0.1 g), and anhydrous THF (30 mL) under stirring and cooling at −15 °C. Stirring was continued for 30 min in the same conditions. ICH_3 (0.25 mL, 3.9 mmol) was added dropwise, and the mixture was stirred at room temperature for 2 h. The solvents were removed under vacuum, and the residue was taken up in $CHCl_3$ and washed with water and brine. The organic layer was dried and filtered, and the solvent was removed under vacuum. Purification of the residue by flash chromatography, EtOAc−$CHCl_3$ (1:9), gave 0.70 g (66%) of **13** which crystallized on standing: mp 116−118 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 3H), 1.50 (m, 2H), 1.93 (m, 2H), 3.25 (m, 2H), 3.70 (m, 1H), 4.64 (m, 1H), 7.21 (dd, 1H), 7.47 (m, 2H). Anal. ($C_{14}H_{14}Cl_2N_2O$) C, H, N.

***N*-(3,4-Dichlorobenzoyl)-4-aminomethyl, 4-Methylpiperidine (1c).** Compound **1c** was prepared in a quantitative yield from **13** as described for the preparation of **1b** from **12** and obtained as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 3H), 1.41 (m, 6H), 2.56 (m, 2H), 3.27 (m, 3H), 4.07 (m, 1H), 7.22 (m, 1H), 7.43 (m, 2H).

***N*-(3,4-Dichlorobenzoyl)-4-azidomethyl, 4-Hydroxypiperidine (14).** A suspension of **6** (0.50 g, 1.75 mmol), NaN_3 (0.57 g, 8.7 mmol), NH_4Cl (0.20 g, 3.7 mmol), MeOH (8 mL), and H_2O (1 mL) was refluxed under stirring for 5 h. The solvent was removed under vacuum, water was added, and the product was extracted with EtOAc. The organic layer was washed with water and brine, dried, and filtered. The solvent was distilled off to give an oil which crystallized on standing: mp 115−117 °C; ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 4H), 2.01 (m, 1H), 3.30 (s, 3H), 3.46 (m, 2H), 4.43 (m, 1H), 7.20 (dd, 1H), 7.46 (m, 2H). Anal. ($C_{13}H_{14}Cl_2N_4O_2$) C, H, N.

***N*-(3,4-Dichlorobenzoyl)-4-azidomethyl, 4-Methoxypiperidine (2a).** A solution of **14** (2.0 g, 6.08 mmol) and anhydrous THF (5 mL) was added dropwise to a suspension of HNa (60% dispersion in mineral oil, 0.365 g, 9.1 mmol) and THF (10 mL) under stirring and cooling in an ice-bath. Stirring was continued for 15 min at 0 °C and for 1 h at room temperature. ICH_3 (0.57 mL, 9.1 mmol) was added dropwise, and stirring was continued for 18 h at room temperature. 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 vaccuum. The product was crystallized from hexane to give 1.50 g (72%) of **2a** as a white solid: mp 83−85 °C; ^{1}H NMR (DMSO-d_6) δ 1.44 (m, 2H), 1.71 (m, 2H), 3.0 (m, 1H), 3.17 (s, 3H), 3.26 (m, 2H), 3.37 (s, 2H), 4.13 (m, 1H), 7.35 (dd, 1H), 7.67 (m, 2H). Anal. ($C_{14}H_{16}Cl_2N_4O_2$) C, H, N.

***N*-(3,4-Dichlorobenzoyl)-4-cyano, 4-*p*-Toluenesulfonyloxymethylpiperidine (15).** Compound **15** was obtained from **10** and purified by flash chromatography, MeOH−$CHCl_3$ (1:99), and then by crystallization from diisopropyl ether as a white solid (75%): mp 169−171 °C; 1 NMR ($CDCl_3$) δ 1.58 (m, 2H), 1.97 (m, 2H), 2.48 (s 3H), 3.27 (m, 2H), 3.84 (m, 1H), 4.02 (s 2H), 4.70 (m, 1H), 7.22 (dd, 1H), 7.39 (d, 2H), 7.50 (m, 2H), 7.82 (d, 2H).

***N*-(3,4-Dichlorobenzoyl)-4-azidomethyl, 4-Cyanopiperidine (2b).** The suspension of **15** (2.03 g, 4.34 mmol), NaN_3 (0.56 g, 8.6 mmol), *n*-tetrabutylammoniun azide (0.07 g, 0.25 mmol), and DMSO (6 mL) was stirred at 100−105 °C for 15 h. The cooled reaction mixture was poured in ice−water and extracted with EtOAc. The combined extracts were washed with water and brine, dried, and filtered. The solvent was removed under vacuum to give 1.4 g (95%) of **2b** as a thick pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.52 (m, 2H), 2.01 (m, 2H), 3.25 (m, 2H), 3.50 (s 2H), 3.86 (m, 1H), 4.74 (m, 1H), 7.22 (dd, 1H), 7.49 (m, 2H).

Method B. *N*-(3,4-Dichlorobenzoyl)-4-methoxy-4-{[(6-pyrazol-1-yl-pyridin-2-ylmethyl)amino]methyl}-piperidine (66). The mixture of **2a** (0.87 g, 2.53 mmol), 6-pyrazol-1-ylpyridine-2-carboxaldehyde (0.44 g, 2.54 mmol), triphenylphosphine (0.67 g, 2.55 mmol), and methanol (40 mL) was refluxed under stirring for 3 h. After the mixture cooled to room temperature, KBH_4 (0.41 g, 7.59 mmol) was added, and stirring was continued for 18 h. The solvent was distilled off, and the residue was poured in ice−water and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried, and filtered. Purification by flash chromatography, MeOH−EtOAc (1:9), gave 0.75 g (62%) of **58** as a pale yellow oil. The oxalate salt was crystallized from EtOH−EtOAc to afford a white solid (0.60 g): mp 187−189 °C; ^{1}H NMR (DMSO-d_6) δ 1.55 (m, 2H), 1.90 (m, 2H), 2.90−3.30 (m, 8H), 4.08 (m, 1H), 4.31 (s, 2H), 6.59 (t, 1H), 7.35 (dd, 1H), 7.44 (d, 1H), 7.67 (m, 2H), 7.86 (m, 2H), 8.04 (t, 1H), 8.83 (d, 1H). Anal. ($C_{23}H_{25}Cl_2N_5O_2 \cdot C_2H_2O_4$) C, H, N.

5-Methyl-6-chloro-2-pyridinemethanol (17). To a solution of 5-methyl-6-chloro-2-pyridinecarboxylic acid ethyl ester **16**[15] (8.80 g, 44 mmol) in ethanol (100 mL), maintained at room temperature, was added portionwise $NaBH_4$ (2.80 g, 74 mmol), and the mixture was stirred overnight at room temperature. The suspension was concentrated under vacuum, poured into brine, and extracted twice with EtOAc. The organic layer was

Table 8. Experimental Details for Each of the Binding Assays[a]

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

[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 34. [c] Reference 35.

dried, filtered, and evaporated under vacuum to give 6.10 g of **17** (88%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 3.10 (s, 1H, exchangeable), 4.71 (s, 2H), 7.16 (d, 1H), 7.55 (d, 1H).

5-Methyl-6-methylamino-2-pyridinemethanol (18a). A solution of **17** (3.49 g, 22 mmol) and methylamine (33% in ethanol, 27 mL), was heated at 100 °C in a closed vessel for 48 h. After the mixture cooled to room temperature, the solvent was removed under vacuum and the residue extracted twice with EtOAc. The organic layer was washed with water and brine, dried, and filtered. The residue was purified by flash chromatography on silica gel, eluent EtOAc−cyclohexane (6:4), to give 1.68 g of **18a** (50%) as an oil which crystallized on standing: mp 86−88 °C; ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H), 3.05 (d, 3H), 4.13 (s, 1H, exchangeable), 4.24 (s, 1H, exchangeable), 4.59 (s, 2H), 6.39 (d, 1H), 7.18 (d, 1H).

5-Methyl-6-(ethylamino)-2-pyridinemethanol (18b). This compound was prepared in 63% yield as described for **18a** using ethylamine in place of methylamine. Compound **18b** was obtained as an oil: ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H), 2.07 (s, 3H), 3.53 (dt, 2H), 4.14 (s, 2H, exchangeable), 4.58 (s, 2H), 6.37 (d, 1H), 7.18 (d, 1H).

5-Methyl-6-(dimethylamino)-2-pyridinemethanol (18c). This compound was prepared in 55% yield as described for **18a** using dimethylamine in place of methylamine. Compound **18c** was obtained as an oil: ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.88 (s, 6H), 4.17 (s, 1H, D_2O exchange), 4.62 (s, 2H), 6.65 (d, 1H), 7.34 (d, 1H).

5-Methyl-6-diethylamino-2-pyridinemethanol (18d). To a solution of 4-chloro-6-diethylamino-1-methyl-2-oxa-5-aza-bicyclo[2.2.2]oct-5-en-3-one **19**[16] (9.37 g, 39.6 mmol), DBU (22.4 mL, 159 mmol), and anhydrous THF (130 mL) at room temperature was added ethanol (2.77 mL, 47.5 mmol), and the mixture was heated under reflux for 24 h. The solvent was distilled under vacuum and the residue was poured into water and extracted twice with ethyl acetate. The combined organic layer was washed with brine and water, dried, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel, eluent cyclobexane−EtOAc (95:5), to afford 1.89 g of 5-methyl-6-diethylamino-2-pyridinecarboxylic acid ethyl ester as an oil. This oil was taken up in EtOH (25 mL), treated at room temperature with $NaBH_4$ (875 mg, 23 mmol), and then heated at reflux for 2 h. The solvent was distilled off, and the residue was taken up in ice−water and then extracted twice with CH_2Cl_2. The organic layers were dried, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel, eluent CH_2Cl_2−EtOAc (95:5), to give 0.92 of **18d** (12%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 6H), 2.25 (s, 3H), 3.25 (q, 4H), 4.21 (s, 1H, exchangeable), 4.62 (s, 2H), 6.63 (d, 1H), 7.35 (d, 1H).

5-Methyl-6-methylamino-2-pyridinecarboxaldehyde (3a). To a solution of **18a** (0.93 g, 6.11 mmol) and anhydrous $CHCl_3$ (20 mL) was added MnO_2 (5 g, 57.5 mmol), and the suspension was stirred vigorously under reflux for 2 h. Insoluble material was filtered off, and then the compound was purified on a short silica gel column eluting with $CHCl_3$. Removal of the solvent under vacuum gave 0.75 g of **3a** (80%) as an oil which crystallized on standing: mp 78−80 °C; ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H), 3.12 (d, 3H), 4.36 (m, 1H), 7.22 (d, 1H), 7.35 (d, 1H), 9.91 (s, 1H); IR (KBr, cm^{-1}) 1701.

5-Methyl-6-(ethylamino)-2-pyridinecarboxaldehyde (3b). This compound was prepared in 50% yield as described for **3a** using **18b** as starting material. The aldehyde **3b** was obtained as a white solid: mp 68−70 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H), 2.15 (s, 3H), 3.60 (q, 2H), 4.25 (s, 1H), 7.21 (d, 1H), 7.35 (d, 1H), 9.90 (s, 1H); IR (KBr, cm^{-1}) 1698.

5-Methyl-6-(dimethylamino)-2-pyridinecarboxaldehyde (3c). This compound was prepared in 60% yield as described for **3a** starting from **18c**. Compound **3c** was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 2.93 (s, 6H), 7.44 (d, 1H), 7.49 (d, 1H), 9.93 (s, 1H); IR (KBr, cm^{-1}) 1705.

5-Methyl-6-diethylamino-2-pyridinecarboxaldehyde (2d). This compound was prepared in 53% yield as described for **3a** starting from **18d**. Compound **3d** was obtained as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.13 (ts, 6H), 2.33 (s, 3H), 3.28 (q, 4H), 7.44 (d, 1H), 7.50 (d, 1H), 9.95 (s, 1H); IR (KBr, cm^{-1}) 1708.

5-Methyl-6-chloro-2-(1.3-dioxolan-2-yl)-pyridine (20). To a solution of **17** (5.49 g, 34.8 mmol) and anhydrous $CHCl_3$ (200 mL) was added MnO_2 (26 g, 300 mmol), and the suspension was stirred under reflux for 3 h. Insoluble materials were filtered off, and then the compound was purified on a short silica gel column. The solvent was removed under vacuum to give 4.03 g of 5-methyl-6-chloro-2-pyridinecarboxaldehyde (74%) as an oil which crystallized on standing: mp 70−72 °C; ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 7.75 (d, 1H), 7.83 (d, 1H), 9.98 (s, 1H). A solution of this aldehyde (3.98 g, 25.6 mmol), ethylene glycol (4.4 mL, 78.9 mmol), and *p*-toluenesulfonic acid monohydrate (0.30 g) in toluene (150 mL) was heated under reflux for 8 h with water separation by a Dean−Stark trap. The solvent was evaporated off, and the residue was taken up in EtOAc and washed with 10% $NaHCO_3$ and then brine. The combined organic layer was dried and filtered through a pad of silica. The solvent was removed under reduced pressure to give 3.90 g of **20** (76%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 4.06 (m, 2H), 4.15 (m, 2H), 5.79 (s, 1H), 7.39 (d, 1H), 7.59 (d, 1H).

5-Methyl-6-(pyrazol-1-yl)-2(1.3-dioxolan-2-yl)-pyridine (21). To a suspension of HNa (0.60 g, 60% dispersion in mineral oil, 15 mmol) in anhydrous *N*-methypyrrolidone (4 mL) under a nitrogen atmosphere, was added dropwise a solution of pyrazole (1 g, 15 mmol) in *N*-methylpyrrolidone (2 mL). After 30 min at room temperature, **20** (0.95 g, 5.10 mmol) was added and the mixture was stirred at 100 °C for 5.5 h. The cooled reaction mixture was poured into ice−water and extracted twice with EtOAc. The combined organic layers were washed with water and brine, dried, and filtered, and the solvent was removed under vacuum. The product was purified by flash chromatography, eluent cyclohexanes−EtOAc (70:30), to give 0.61 g of **21** (76%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.58 (s, 3H), 4.10 (m, 2H), 4.18 (m, 2H), 5.84 (s, 1H), 6.43 (t, 1H), 7.42 (d, 1H), 7.72 (m, 2H), 8.29 (d, 1H).

5-Methyl-6-(pyrazol-2-yl)-2-pyridinecarboxaldehyde (3e). A suspension of **21** (0.60 g, 2.73 mmol), formic acid (4 mL), H_2O (1 mL), and $CuSO_4$ (0.03 g) was stirred at 65 °C for 2.5 h. The solution was concentrated under vacuum, and then the residual formic acid was eliminated by azeotropical distillation with toluene. The residue was taken up in ice−water, and an excess of K_2CO_3 was added. The product was extracted twice with EtOAc, washed with diluted NH_4OH and brine, dried, and concentrated under vacuum. The product was purified by flash chromatography, eluent hexanes−EtOAc (80:20), to give 0.29 g of **3e** (55%) as a pale yellow oil which crystallized on standing: mp 46−48 °C; ^{1}H NMR ($CDCl_3$) δ 2.70 (s, 3H), 6.50 (t, 1H), 7.26 (s, 1H), 7.78 (d, 1H), 7.85 (s, 2H), 8.39 (d, 1H), 10.02 (s, 1H); IR (KBr, cm^{-1}) 1713.

Radioligand Binding. Binding affinities for the different receptors were determined by means of ligand competition assays using the conditions summarized in Table 8. 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), and Geneticin (G418) (400 μg/mL) in 5% CO_2 at 37 °C in a water-saturated atmosphere. The cells were plated in six-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 μg/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, and 100 μM 3-isobutyl-1-methylxanthine (IBMX) to the cells. Antagonists were added at the same time as the agonists, as described by Fargin.[19] 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 radio immunoassay buffer, and 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).

In Vivo Studies. Male Sprague Dawley rats (Ico: OFA SD [IOPS Caw], Iffa Credo, l'Arbresle, France), weighing 160−200 g upon arrival, were group housed (five animals per cage) with food and water freely available in a quarantine room for 4−8 days before being used in the experiments. Twenty-four hours before use in the experiments, the animals were transferred to individual, hanging cages ($l \times w \times h$: 28 × 21 × 18 cm; Iffa Credo, France) with metal grid floors, in the room where the experiments were conducted, with unlimited access to filtered (0.22 μ) water and (except for the LLR experiments) standard laboratory food (UAR A03; UAR, Epinay/s/Orge, France).

All animals were housed in environmentally controlled rooms (21 ± 1 °C, relative humidity: 55 ± 5%) under a 12 h light−dark cycle (lights on at 7:00 a.m.), both during quarantine and during the experiments. The experimental procedures were in accordance with the European Communities Counsel Directive of November 24, 1986 (86/609/EEC) and the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH publication No. 85-23, revised 1985) and were approved by the institutional Protocol Review Committee.

Compounds were dissolved in distilled water. Compounds not soluble in distilled water were suspended in distilled water by adding Tween 80 (2 drops/10 mL). Doses are expressed as the weight of the free base.

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Supporting Information Available: Additional physical data (^{1}H NMR and elemental analyses) on final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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