Norpiperidine Imidazoazepines as a New Class of Potent, Selective, and Nonsedative H_1 Antihistamines

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Received June 25, 2004

Clinical doses of available H_1 antihistamines are limited mainly by sedative side effects. However, higher doses are often required to obtain optimal therapeutic activity, especially in dermatology. We report the synthesis of three norpiperidine imidazoazepines representative of a new class of selective and nonsedating H_1 antihistamines. The compounds were at least as potent as cetirizine and loratadine as measured by H_1 receptor binding affinity, by protection against compound 48/80- and histamine-induced lethality in rats and guinea pigs, respectively, and by skin reaction tests in rats, guinea pigs, and dogs. The compounds, in particular **3a**, were less prone than the reference compounds to penetrate the brain and to occupy central H_1 receptors, suggesting absence of sedative side effects. In vitro and in vivo cardiovascular safety tests showed that **3a** had no intrinsic potential to prolong ventricular repolarization or induce cardiac arrhythmias. Compound **3a** has been selected for further clinical development, mainly for application in dermatology.

Introduction

It is widely accepted that the antihistamines have found their greatest therapeutic potential in the treatment and management of various allergic disorders, including seasonal and perennial rhinitis, as well as in urticaria and other dermatological disorders. Antihistamines are among the most commonly prescribed drugs, and numerous reviews are available.[1] Due to their ability to cross the blood−brain barrier, sedation is the most common side effect observed with the first generation of antihistamines. Sedation may severely impair daytime activities, including school performance, driving ability, and many tasks that require concentration and a high degree of alertness.[1d] Furthermore, daytime sedation also reduces patient compliance and consequently the efficacy and usefulness of sedating antihistamines.[1d] Although there is no doubt that significant improvements have been observed with the less- or nonsedating H_1 antihistamines of the second generation, such as astemizole,[2] terfenadine,[3] cetirizine,[4] and loratadine,[5] it is also clear today that many members of this class are not free of all side effects. For example, terfenadine and astemizole have been associated with prolongation of the QT interval and fatal cardiac arrhythmias at high concentrations, resulting in the withdrawal of the compounds from the major markets.[6] On the other hand, antihistamines such as cetirizine, loratadine, and desloratadine[7] penetrate the central nervous system (CNS) and display dose-related impairment of CNS function.[1d,8] The drugs are relatively free from sedative effects at the recommended clinical dose. However, when the dose is increased, there is increasing evidence of sedative activity. This sedative activity will compromise patients who, due to clinical need and their particular symptoms, require more than the recommended dose of medication, a condition commonly encountered in dermatological disorders.[9] On top of the already existing requirements to obtain cardiosafe antihistamines, truly nonsedating properties, even at higher than recommended clinical doses for the treatment of rhinitis, represent now an important criterion to differentiate the members of a new class of third-generation H_1 receptor antagonists from the current commercialized "nonsedating" antihistamines.

Herein, we report the synthesis of three nonsedating H_1-antihistamine development candidates, **1**, **2a**, and **3a** (Figure 1), of the norpiperidine imidazoazepine class. To compare the title compounds with other antihistamines, such as loratadine (Claritin, **4**) and cetirizine (Zyrtec, **5**), we have evaluated their physicochemical properties, their in vitro and in vivo pharmacology, and their potential to cross the blood−brain barrier. As antihistamines are regarded as a pharmacological class of compounds with a potential for cardiac side effects, we also evaluated the in vitro and in vivo cardiovascular safety of the title compounds. All these results taken together have led us to select compound **3a** (Hivenyl) for clinical evaluation.

Chemistry

As a general approach to the family of compounds derived from **1**, **2a**, and **3a**, we have developed an acid-catalyzed ring-closing pathway to the imidazoazepine ring system.[10] Therefore, the syntheses of the three compounds are built around the key intermediates required for this cyclization step.

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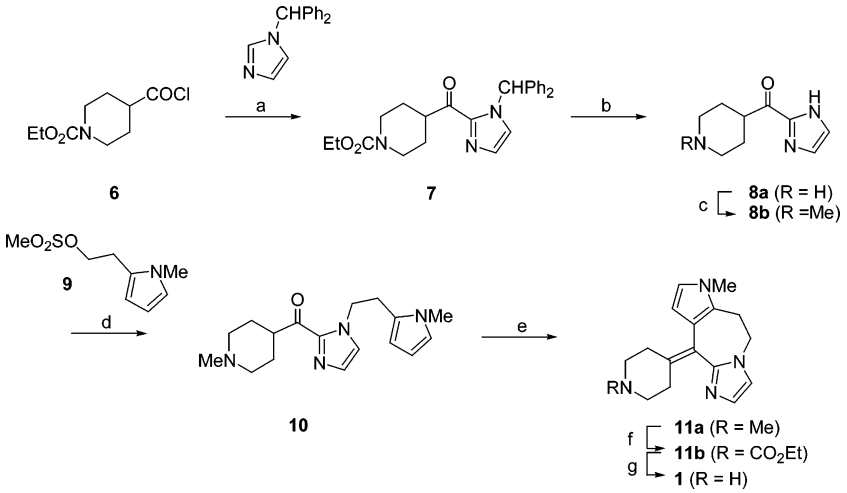
10.1021/jm049495j CCC: $30.25
Published on Web 12/22/2004

Scheme 1. Synthesis of **1**[a]



[a] Reagents and conditions: (a) Et_3N, CH_3CN, reflux; (b) 48% HBr, reflux, 7 h; (c) $(CH_2O)_n$, H_2, Pd/C, CH_3CO_2K, NaOH; (d) 60% NaH, DMF, 60 °C; (e) $MeSO_3H$, 80 °C, 18 h; (f) EtOCOCl, Et_3N, toluene, reflux, 2 h; (g) KOH, *i*-PrOH, reflux, 18 h.

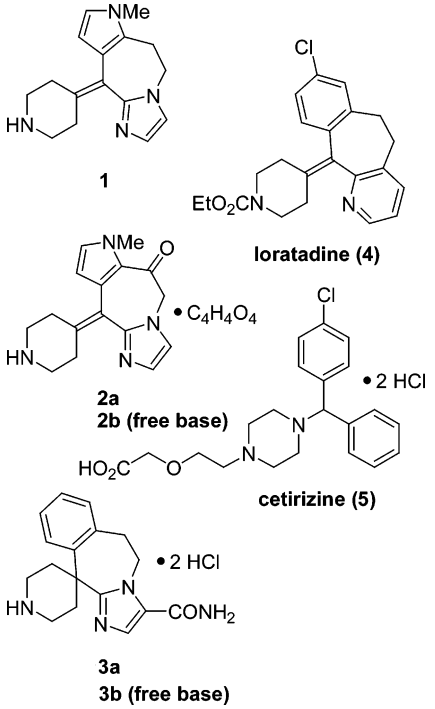


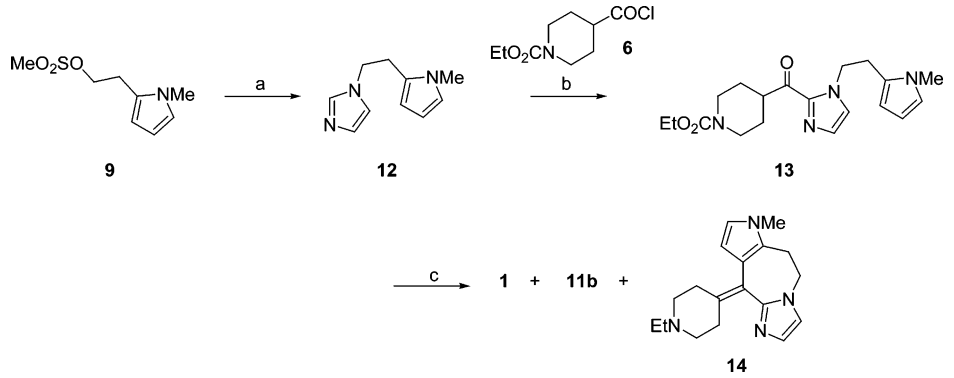
Figure 1. Structures of new norpiperidine imidazoazepines and reference H_1 antihistamines selected for evaluation.

Compound **1** was prepared from *N*-ethoxycarbonyl isonipecotyl chloride **6** in seven steps with an overall yield of 28.7% (Scheme 1). Refluxing 1-benzhydrylimidazole with acid chloride **6**[11] led to **7**. Deprotection of both the benzhydryl and the carbamate groups occurred when **7** was treated with HBr. *N*-Methylation of the piperidine **8a**, followed by alkylation on the imidazole **8b** by the mesylate **9**[12] afforded the precursor for the cyclization, **10**. Cyclization and dehydration leading to **11a** took place when **10** was warmed to 80 °C in methanesulfonic acid. Conversion of the methyl piperidine **11a** to a carbamate-protected piperidine **11b** followed by hydrolysis of **11b** finally led to **1**. An alternative preparation for **1** is shown in Scheme 2. This pathway, although shorter, was less selective. *N*-Alkylation of imidazole by the mesylate **9** afforded the *N*-(pyrroloethyl)imidazole **12**. This compound reacted with the acid chloride **6** in the presence of triethylamine to lead to the cyclization precursor **13**, an analogue of **10**, used in Scheme 1. In this case, however, the cyclization under strongly acidic conditions not only afforded the deprotected compound **1** and its carbamate-protected derivative **11b** but also the *N*-ethylpiperidine derivative **14** in a 1:4:3 ratio. The formation of this last compound could be explained by an alkylation of the piperidine by ethyl mesylate, produced in situ by acid-catalyzed hydrolysis of the carbamate **11b**.

The preparation of compound **2a** is described in Scheme 3. It was obtained in nine steps from *N*-benzylpiperidone with an overall yield of 1.8%. Knoevenagel condensation of *N*-methyl-2-(cyanomethyl)imidazole on *N*-benzylpiperidone afforded quantitatively **15**, the double bond of which was subsequently hydrogenated to **16** by sodium borohydride in refluxing 2-propanol. After quantitative conversion of the nitrile **16** to the ketone **17** by oxidative decyanation in the presence of oxygen under phase transfer catalytic conditions,[13] rearrangement to **18** occurred in the presence of trifluoroacetic acid at reflux.[14] The one-pot condensation of 1-bis(ethoxy)methyl imidazole on ketone **18** followed by deprotection quantitatively produced the carbinol **19** that was immediately dehydrated in the presence of trifluoroacetic acid to afford **20a**. Alkylation of **20a** by methyl chloroacetate produced the precursor **20b** for the key cyclization step. Heating **20b** at 120 °C in trifluoromethanesulfonic acid afforded the required imidazoazepinone **21**, along with its isomer **22** in a 1:1 ratio. Finally, **2b** was obtained by catalytic debenzylation of **21**. Over-reduction could not be avoided in this reaction, and **23** was obtained along with **2b** in a 1:1 ratio. All in vitro and in vivo experiments were performed with the fumarate salt (1:1) **2a**.

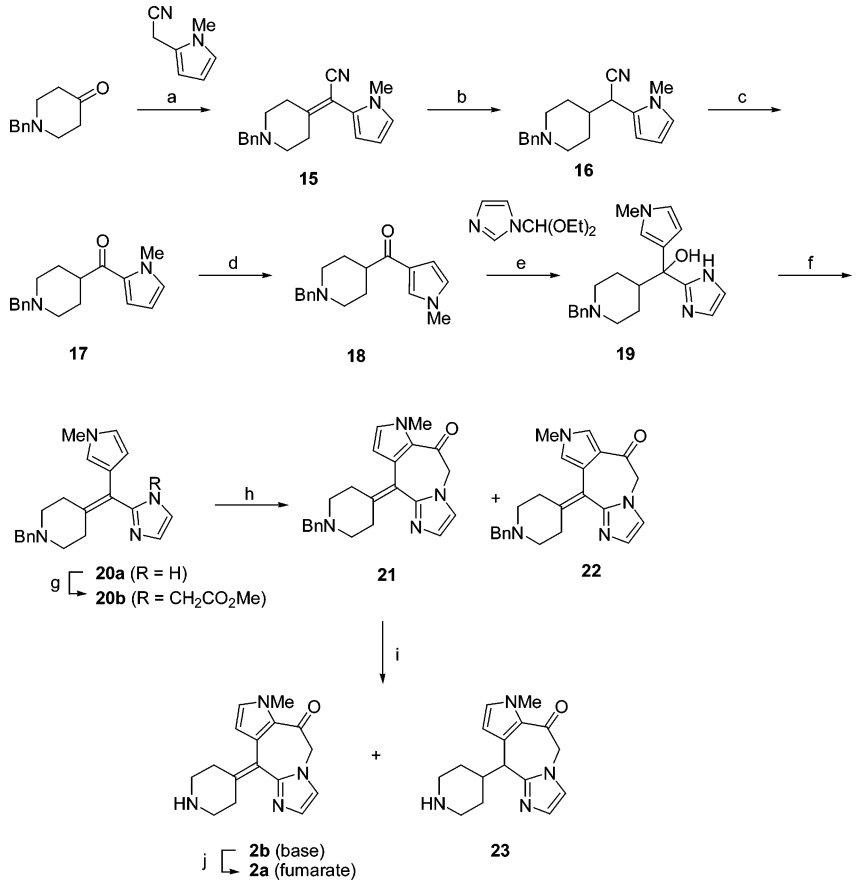
The original synthesis of **3a** is described in Scheme 4. We prepared **3a** in 10 steps from *N*-benzylpiperidone in an overall yield of 9.8%. Addition of 1-phenethylimidazole on *N*-benzylpiperidone afforded **24**. This intermediate was then cyclized in the presence of trifluoromethanesulfonic acid to the spiroimidazobenzazepine **25a**. At this stage, we performed the rest of the synthesis pathway from the benzyl-protected piperidine **25a** (not shown). However, the benzyl-protected inter-

Scheme 2. Alternative Synthesis of **1**[a]



[a] Reagents and conditions: (a) imidazole, K_2CO_3, THF, reflux, 72 h; (b) Et_3N, CH_3CN, reflux; (c) $MeSO_3H$, 80 °C, 2 h.

Scheme 3. Synthesis of **2a**[a]

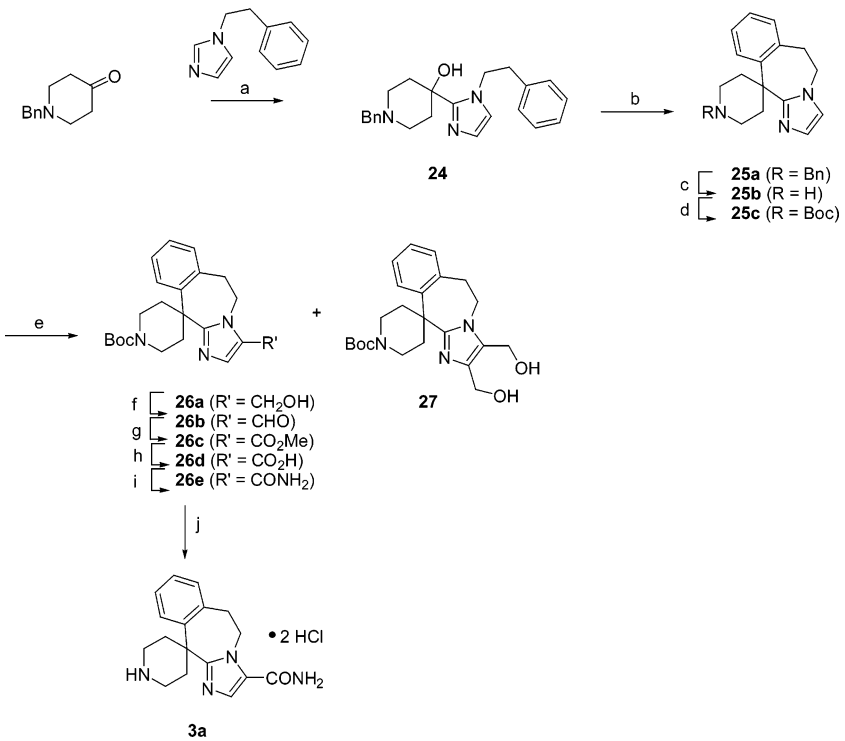


[a] Reagents and conditions: (a) MeONa, MeOH, reflux, 4 h; (b) $NaBH_4$, *i*-PrOH, reflux, 48 h; (c) 50% NaOH, BTEAC, O_2 (air), DMSO, 50 °C, 7 h; (d) CF_3CO_2H, reflux, 5 d; (e) 2.5 M BuLi, *i*-Pr_2NH, THF, −70 °C to rt, then CH_3CO_2H; (f) CF_3CO_2H, 0.5 h, reflux; (g) $ClCH_2CO_2Me$, NaH, 50%, DMF, rt, 0.5 h; (h) CF_3SO_3H, 120 °C, 4 h; (i) H_2, Pd/C 10%, MeOH, rt; (j) fumaric acid, EtOH, reflux.

mediates proved difficult to separate by column chromatography; this was less of a problem when Boc-protection was used on the piperidine. Therefore, debenzylation and subsequent Boc-protection were required before the next steps could be attempted. **25a** was thus converted to **25c** that underwent hydroxymethylation to produce **26a**, along with its bis(hydroxymethyl) analogue **27**, in a 2.5:1 ratio. Following oxidation of **26a** by manganese dioxide and conversion to the ester **26c**, standard conditions for hydrolysis and amide formation led to the protected piperidine **26e**. Finally, deprotection by hydrochloric acid afforded **3a** as a dihydrochloride salt. All in vitro and in vivo experiments were carried out with this salt **3a**.

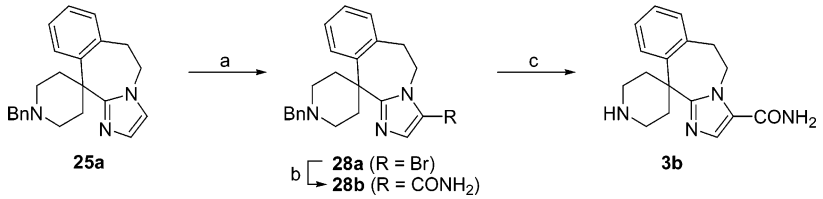
An alternative pathway, avoiding the tedious functional group interconversions from **25a** to **3a**, is shown in Scheme 5. Bromination of **25a** with *N*-bromosuccinimide at 0 °C for 1 h led to **28a**. The conversion in this reaction was voluntarily kept low by using a short reaction time to limit double bromation of the imidazole ring. A palladium-catalyzed carbon monoxide insertion on the resulting bromide **28a** in the presence of ammonia led to the amide **28b**. Finally, catalytic debenzylation provided the free base **3b** in five steps and 16.2% overall yield from *N*-benzylpiperidone. The same pathway can be followed starting from the Boc-protected **25c**, resulting in an improved selectivity toward monobromination and a better yield in the CO insertion

Scheme 4. Synthesis of **3a**[a]



[a] Reagents and conditions: (a) 2.5 M BuLi, *i*-Pr_2NH, THF, −78 to 0 °C; (b) CF_3SO_3H, 65 °C, 120 h; (c) H_2, 10% Pd/C, MeOH; (d) $(Boc)_2O$, CH_2Cl_2; (e) 37% CH_2O, AcONa, AcOH; (f) MnO_2, $CHCl_3$; (g) NaCN, MnO_2, AcOH, MeOH; (h) 1 N NaOH, THF/H_2O; (i) NH_4Cl, EDCI, Et_3N, DMAP, CH_2Cl_2; (j) HCl, MeOH, *i*-PrOH.

Scheme 5. Synthesis of **3b**[a]



[a] Reagents and conditions: (a) NBS, CH_2Cl_2, 0 °C, 1 h; (b) CO, NH_3, $Pd(OAc)_2$, 1,3-bis(diphenylphosphino)propane; (c) H_2, 10% Pd/C, MeOH.

reaction (not shown). The resulting **26e** could then also be deprotected to give directly the dihydrochloride salt **3a** as shown in Scheme 4.

Physicochemical Properties

The physicochemical properties of antihistamines have a profound influence on their side-effect profile.[1b] They not only determine the bioavailability of the compounds but also the brain penetration responsible for the sedation observed with first-generation antihistamines. Table 1 gives an overview of the properties that have been determined for the title compounds and compares them with the reference antihistamines loratadine (**4**) and cetirizine (**5**). The log $D_{7.4}$ values were calculated based on the log P_{oct} and pK_{a1} values measured for the compounds. The low log P_{oct} values of compounds **1** and **3a** led to low log $D_{7.4}$ values that are an indication for negligible brain penetration.[1b] The solubility of **3a** in water is also shown in Table 1. Although we did not directly compare the title compounds with loratadine (**4**) and cetirizine (**5**), it is clear that **3a** has a high solubility when dissolved in water. Table 2 shows that the solubility of **3a** was still higher than 20 mg/mL in water at pH 7 (resulting in a solution of pH 2) and still exceeded that value in buffer solutions up to pH 4.3. The free base **3b** also had a solubility higher than 20 mg/mL at acidic pH, while its solubility decreased to around 10 mg/mL, in buffer solutions between pH 6 and 8, and 1.1 mg/mL in water (resulting in a solution of pH 10.5).

Table 1. Experimental Physicochemical Properties of the Title Compounds and of the Reference Compounds Loratadine (**4**) and Cetirizine (**5**)

compd	MW	log P_{oct}[a]	pK_{a1}[b]	pK_{a2}[b]	log $D_{7.4}$[c]	solubility in H_2O, mg/mL
1	268.36	1.25	9.85	6.52	−1.2	ND[d]
2a	282.35	ND[d]	ND[d]	ND[d]		ND[d]
3a	296.37	1.18	9.88	3.00	−1.3	>20[e–g]
4	382.89	4.86	4.58[15]		4.58	0.01[16 h]
5	388.89	1.01−1.50[17]	8.00[17]	2.19−2.93[17]	1.5[17]	100[16 h]

[a] Octanol/pH 12 buffer. [b] Sirius PCA 101 method. [c] Calculated using the formula log $D_{7.4}$ = log P − log(1 + $10^{pK_a-7.4}$). [d] Not determined. [e] See Experimental Section for details of the method. [f] All compound put into solution during the test was dissolved. [g] Solution pH = 2.0. [h] Solution pH not available.

Pharmacology

In Vitro Pharmacology. The antihistaminic activity of the compounds was evaluated in vitro in a receptor

Table 2. Solubility[a] of **3a** and Its Free Base **3b** in Aqueous Medium at 20 °C

	3a		3b	
solvent	pH of solution	solubility, mg/mL	pH of solution	solubility, mg/mL
water	2.0	>20[b]	10.5	1.1
0.1 M HCl	1.0	>20[b]	2.7	>20[b]
SGF[c]	1.1	>20[b]	3.1	>20[b]
SIF[d]	2.3	>20[b]	10.1	1.69
buffer, pH 2	1.8	>20[b]	4.8	>20[b]
buffer, pH 4	2.9	>20[b]	5.4	>20[b]
buffer, pH 6	4.2	>20[b]	9.2	8.04
buffer, pH 8	3.8	>20[b]	9.0	12.22
buffer, pH 10	4.3	>20[b]	10.2	1.65
0.1 M NaOH	12.6	3.09	13.0	0.93

[a] See Experimental Section for details of the method. [b] All compound put into solution during the test was dissolved. [c] SGF: simulated gastric fluid. [d] SIF: simulated intestinal fluid.

Table 3. Receptor Binding Affinities for the Human Cloned Histamine H_1 Receptor

compd	K_i (nM)[a]	compd	K_i (nM)[a]
1	22	loratadine (**4**)	37
2a	12	cetirizine (**5**)	50
3a	19		

[a] Human H_1 receptor cloned and expressed in CHO cells.

Table 4. Inhibition of Compound 48/80-Induced Lethality[a] in the Rat

	ED_{50}, mg/kg (95% CL[b])	
compd	1 h after sc administration	2 h after po administration
1	0.028 (0.019−0.042)	0.76 (0.51−1.2)
2a	0.037 (0.023−0.060)	0.34 (0.21−0.55)
3a	0.056 (0.033−0.097)	1.2 (0.72−1.9)
loratadine (**4**)	0.29 (0.20−0.44)	0.22 (0.15−0.33)
cetirizine (**5**)	0.51 (0.32−0.82)	1.2 (0.78−1.8)

[a] Intravenous injection of compound 48/80 induces a lethal anaphylactic reaction. Antihistamines were given either subcutaneously (sc) or orally (po). [b] Confidence limits.

binding test with the human cloned H_1 histamine receptor, expressed in CHO cells.[18] Results are summarized in Table 3. All three title compounds displaced the radioligand from the receptor with a K_i ranging from 12 to 22 nM. In this respect, the title compounds showed an affinity for the H_1 receptor on the same order of magnitude as loratadine (**4**) (37 nM) and cetirizine (**5**) (50 nM).

In Vivo Antihistaminic Activity. The in vivo antihistaminic activity of the compounds was first evaluated in the compound 48/80-induced lethality test in rats[19] and the histamine-induced lethality test in guinea pigs[20] after subcutaneous and/or oral administration.

All compounds dose-relatedly protected against lethal anaphylactic shock after injection of compound 48/80 in the rat (Table 4). The three title compounds were more potent than the reference compounds cetirizine and loratadine when administered subcutaneously. After oral administration, however, compounds **1**, **2a**, and **3a** were several times less potent than after sc injection, whereas loratadine (**4**) and cetirizine (**5**) were about equipotent when administered by both routes in the rat. After oral administration, all tested compounds thus showed a comparable potency. In the guinea pig, all compounds exhibited a similar potency against histamine-induced lethal shock, except for **1**, which was 1 order of magnitude less potent (Table 5). All compounds showed a rapid onset of action, within 30−45 min (rat) or 60−72 min (guinea pig) (results not shown). In the rat, **3a**, loratadine (**4**) and cetirizine (**5**) showed a similar duration of action (4.5−7 h), whereas in the guinea pig, **3a** showed a prolonged duration of action (33 h) in comparison with loratadine (9 h) or cetirizine (6 h) (results not shown).

Table 5. Inhibition of Histamine-Induced Lethality[a] in the Guinea Pig

compd	ED_{50}, mg/kg (95% CL[b]), 3 h after po administration
1	0.67 (0.50−0.91)[c]
2a	0.019 (0.012−0.030)
3a	0.074 (0.050−0.11)
loratadine (**4**)	0.074 (0.055−0.10)
cetirizine (**5**)	0.032 (0.024−0.044)

[a] Intravenous injection of histamine induces a lethal shock in the guinea pig. Antihistamines were given orally (po). [b] Confidence limits. [c] Tested 1 h after po administration

In subsequent experiments, all compounds were tested for their effect on cutaneous reactions in the rat,[21] the guinea pig, and the dog.[25]

In the rat, skin reactions were induced by histamine, serotonin, *Ascaris* allergens, and a passive cutaneous reaction (PCA) to ovalbumin. ED_{50}s for inhibition and blockade of the skin reactions were obtained 2 h after the subcutaneous injection of the compounds (see the Experimental Section). All compounds dose-dependently inhibited and, at slightly higher doses, blocked the histamine-, PCA- and *Ascaris* allergens-induced reactions (Table 6). ED_{50}s for inhibition and blockade of histamine reaction, as well as blockade of PCA and *Ascaris* reaction, were comparable for all compounds tested, except for **1**, which was clearly more potent in inhibiting the cutaneous reactions to the various stimuli. Blockade of the histamine reaction occurred for all compounds at doses several times higher than the dose required to inhibit the compound 48/80-induced lethality after subcutaneous administration (factors ranging from 4.6 to 26), except for cetirizine (**5**) (factor 1.3). Of the tested compounds, only loratadine (**4**) at high doses showed some activity against the serotonin-induced reaction.

In the guinea pig, skin reactions were induced by histamine, substance P, *Ascaris* allergens, bradykinin, and platelet-activating Factor (PAF). All tested compounds, dose-dependently inhibited and, at higher doses, blocked the histamine reaction (Table 7). In contrast to the results in the rat, **1** was the least potent compound in antagonizing the cutaneous reactions to histamine and *Ascaris* allergens in the guinea pig. The ED_{50} of **3a** for complete blockade of the histamine reaction was only slightly higher than for inhibition of the histamine reaction (factor 1.4), whereas for the other compounds, a slightly larger difference was observed (factor 3−4). Inhibition of histamine-induced skin reactions occurred at doses closely related to those required for protection against histamine-induced lethality (see Table 5). Compounds **1**, **2a**, **3a** and loratadine (**4**) tended to inhibit the *Ascaris* allergens-induced reaction at high doses, exceeding their inhibitory antihistamine doses by a factor 36, 21, 12, and 5, respectively. Cetirizine (**5**) did not influence the *Ascaris* allergens-induced reaction

Table 6. Cutaneous Reaction Induced by Several Mediators in the Rat[a]

	ED_{50}, mg/kg (95% CL[b])				
	histamine		PCA	*Ascaris* allergens	serotonin
compound	inhibition	blockade	blockade	blockade	inhibition
1	0.080 (0.046−0.14)	0.13 (0.057−0.28)	0.080 (0.046−0.14)	0.13 (0.057−0.28)	>0.16
2a	0.55 (0.24−1.2)	0.95 (0.42−2.13)	0.42 (0.14−1.23)	2.9 (1.1−7.5)	>10
3a	0.51 (0.30−0.88)	1.4 (0.84−2.2)	2.3 (1.3−4.3)	2.7[c]	>10
loratadine (**4**)	0.89 (0.72−1.1)	1.8 (1.2−2.7)	1.6 (0.90−2.7)	2.7 (1.7−4.3)	6.2 (4.1−9.2)
cetirizine (**5**)	0.68 (0.45−1.1)	0.68 (0.45−1.1)	2.7[c]	3.6[c]	>10

[a] Skin reactions were induced by histamine, passive cutaneous anaphylaxis (PCA), *Ascaris* allergens, or serotonin. Antihistamines were given subcutaneously 2 h before skin challenge. Results are expressed as ED_{50} (mg/kg). [b] Confidence limits. [c] Nonlinear dose−response: confidence limits have not been calculated.

Table 7. Cutaneous Reactions Induced by Several Mediators in the Guinea Pig[a]

	ED_{50}, mg/kg (95% CL[b])			
	histamine		Substance P	*Ascaris* allergens
compd	inhibition	blockade	inhibition	inhibition
1	0.24 (0.11−0.54)	0.96 (0.52−1.8)	1.7 (0.56−4.9)	8.7 (4.8−16)
2a	0.020 (0.008−0.045)	0.080 (0.036−0.18)	>2.5	0.42 (0.18−0.93)
3a	0.10 (0.057−0.19)	0.14 (0.076−0.25)	1.6[c]	1.2[c]
loratadine (**4**)	0.080 (0.036−0.18)	0.32 (0.14−0.71)	2.2[c]	0.42 (0.14−1.3)
cetirizine (**5**)	0.046 (0.025−0.084)	0.14 (0.062−0.31)	>2.5	>2.5

[a] Skin reactions were induced by intradermal application of histamine, substance P, or *Ascaris* allergens. Antihistamines were given orally 2 h before intradermal challenge. [b] Confidence limits. [c] As, at the highest dose of 2.5 mg/kg, effect was observed in only 60% of the animals tested, confidence limits were not calculated.

up to 54 times its antihistamine dose (>2.5 mg/kg). Similarly to the *Ascaris* allergens-induced reaction, compounds **1**, **3a**, and loratadine (**4**) tended to inhibit the substance P-induced cutaneous reactions, at several times the doses required for inhibition of the histamine reaction (7, 16, and 28 times, respectively). Cetirizine (**5**) and **2a** were devoid of activity against substance P up to 2.5 mg/kg (54 and 125 times their antihistamine dose, respectively). None of the compounds were able to suppress the substance P reaction to the level of pronounced inhibition. All compounds were devoid of anti-bradykinin or anti-PAF activity in the skin, up to doses of 2.5 mg/kg (10 mg/kg for **1**) (results not shown).

After oral administration in the dog, the title compounds as well as loratadine (**4**) and cetirizine (**5**) dose-dependently inhibited the cutaneous reaction induced by *Ascaris* allergens. In terms of peak-effect dose, the title compounds were more potent than either loratadine (5−11 times) or cetirizine (4−8 times). All compounds showed a similar rapid onset of action (within 1 h), but at 4 times the ED_{50} values, the reference compounds and **1** had a longer duration of action (∼30 h) than **3a** (21 h) or **2a** (13 h). Peak effect was reached for all compounds 4 h after oral administration. At the maximal antihistamine effect, the *Ascaris* allergens-induced reaction was inhibited to a maximum of 20% of the control. Increasing the doses of the antihistamines did not further reduce the *Ascaris* allergens-induced skin reactions.

Penetration into the CNS. Occupancy of central H_1 receptors in the cerebellum of the guinea pig gives a good estimate of the sedative potential of H_1 antihistamines.[23] We evaluated the central H_1 receptor occupancy ex vivo by quantitative autoradiography 3 h after oral administration of the compounds. Preliminary experiments indicated that **3a** did not significantly bind to the central H_1 receptor of the guinea pig up to a dose of 10 mg/kg, exceeding the dose (ED_{50}) required to protect from the histamine-induced lethality in the same species by a factor >135. For **1** and **2a**, selectivity ratios of 64 and 125, respectively, were obtained. Loratadine showed a selectivity ratio of only 30. As, based on these experiments, **3a** appeared to be the least sedative compound, it was compared in more detail with loratadine. Compound **3a** did not occupy significantly the central H_1 receptors in the guinea pig up to 40 mg/kg, exceeding the dose necessary to protect from histamine lethality by a factor larger than 540, and the dose

Table 8. Protection against *Ascaris* Allergens-Induced Cutaneous Reactions[a] in Dogs

compd	peak-effect dose, ED_{50}, mg/kg	onset of action[b] (h)	duration of action[b] (h)
1	0.038	<1	35
2a	0.018	<1	13
3a	0.024	<1	21
loratadine (**4**)	0.20	<1	33
cetirizine (**5**)	0.14	<1	30

[a] Skin reactions were induced by intradermal application of *Ascaris* allergens. Antihistamines were orally administered. [b] Onset and duration of action were graphically estimated at four times the peak-effect dose.

needed to block the histamine-induced cutaneous reaction by a factor greater than 285. On the other hand, loratadine already occupied 50% of the central H_1 receptors at a dose of 2.2 mg/kg, which corresponds to 30 times the dose needed to protect from histamine lethality in the guinea pig and only 7 times the dose effective against cutaneous histamine reactions in this species. These results were corroborated by EEG power spectral analysis[24] in the awake rat, showing that **3a** had no sedative activity in this model (results not shown, will be published elsewhere). Compound **3a** thus appears to be devoid of central sedative effects.

Electrophysiological Cardiovascular Safety. Antihistamines are usually regarded as a class of compounds with a potential for inducing electrophysiological effects that may occasionally trigger life-threatening cardiac arrhythmias (Torsades de Pointes) in humans.[25] Such effects include the inhibition of the rapidly activating component of the delayed rectifier potassium current (IKr), prolongation of the action potential in isolated cardiac tissue, and prolongation of the QT-interval of the electrocardiogram in animals and/or humans.

Voltage clamp tests on human embryonic kidney (HEK-293) cells transfected with the human ether-a-go-go related gene (HERG), expressing the IKr-like outward potassium current modulating repolarization in cardiac cells, showed that **3a**, **1**, and **2** did not reduce the IKr-like current at concentrations of 3×10^{-8} and 3×10^{-7} M. At 3×10^{-7} M the observed marginal reductions for **3a**, **1**, and **2** were 1%, 2%, and 5%, respectively. Even at high concentrations of 3×10^{-6} and 10^{-5} M, **3a** did not induce a significant reduction of the IKr-like current (3% and 8%, respectively) when compared to control conditions (2.3%). In comparison, it has been reported that astemizole and terfenadine potently blocked the IKr-like current with IC_{50} values of $(0.9-1.5) \times 10^{-9}$ [26] and 50×10^{-9} M,[6f] respectively.

In isolated guinea pig papillary muscle stimulated at a normal rhythm of 60 pulses/min and under normokalemic conditions (4 mM KCl), **3a**, at concentrations up to 10^{-5} M, had no relevant effect on the duration of the action potential. The observed changes were less than 10% versus baseline. Compound **3a** did not elicit morphological changes such as early and delayed afterdepolarizations, indicating the absence of proarrhythmic effects in this preparation. In comparison, in the same model, astemizole and terfenadine significantly prolonged the action potential in isolated papillary muscles already at concentrations of 3×10^{-8} and 10^{-7} M, respectively.

In anaesthetized guinea pigs treated with **3a** at cumulative iv bolus doses of 0.08, 0.16, 0.32, 0.64, 1.25, and 5 mg/kg, administered at 15 min intervals (total dose = 7.45 mg/kg iv in 75 min), **3a** had no statistically significant effect on heart rate, mean arterial blood pressure, and the duration of the PQ-, QRS- and QT-interval. No changes in ECG morphology were noticed during the post-treatment period. Relative to solvent, **3a**, starting from 0.64 mg/kg iv, slightly decreased the duration of the QTc-interval corrected according to Bazett (QTcB; max effect +2% at 1.25 mg/kg iv versus +7% with solvent; $p < 0.05$). In comparison, in the same model, astemizole induced a significant and dose-dependent decrease in heart rate (starting at a total dose of 0.48 mg/kg) and an increase in QT and QTcB (starting at a total dose of 0.16 mg/kg). Terfenadine also significantly decreased heart rate (starting at a total dose of 4.85 mg/kg) and prolonged the QT and QTcB (starting respectively at a total dose of 2.35 and 0.47 mg/kg).

Conclusion

We described the synthesis and biological activity of three new norpiperidine imidazoazepines representative of a new class of H_1 antihistaminic compounds. The three title compounds were characterized as potent and selective H_1 antihistamines, in vitro as well as in vivo. In this respect, the compounds were at least as potent as the reference compounds cetirizine (**5**) and loratadine (**4**). However, in relation to potential sedation, the title compounds were less prone to penetrate the central nervous system than the reference compounds. Compound **3a** was even completely devoid of interaction with central H_1 receptors, suggesting absence of sedative side-effect liability. In vitro cardiovascular screening tests showed that **3a** lacked the intrinsic capacity to influence the IKr membrane ion flux or to modulate the action potential characteristics in cardiac cells at concentrations up to 10^{-5} M. Furthermore, in vivo safety pharmacology studies in anaesthetized guinea pigs indicate that systemic administration of **3a** at high doses had no intrinsic potential to prolong the QT-interval. Taking all these preclinical evaluations into consideration, we have selected **3a** for further clinical development, mainly in the field of dermatological disorders. This compound will be a suitable tool to explore the activity of a selective H_1 antihistamine in various indications, without the contamination of the sedative activity often observed with other marketed antihistamines when increasing doses.

Experimental Section

General Methods. Loratadine (**4**) and cetirizine (**5**) were obtained from commercial sources. Unless otherwise stated, all reactions were carried out in dry apparatus under an atmosphere of dry nitrogen. Commercially available absolute solvents were used. Column chromatography was carried out using Merck silica gel 60 (70−230 mesh). **Caution!** Methanesulfonic acid and trifluoromethanesulfonic acid, used in the syntheses of **1**, **11a**, **11b**, **14**, **21**, **22** and **25a** are extremely corrosive substances. All procedures using these reagents must be carefully executed wearing all appropriate personal protection.

^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer (Bruker) using $CDCl_3$ or DMSO-d_6 as internal standard. ^1H NMR and ^{13}C NMR data for the intermediates are listed in the Supporting Information. Elemental analysis were carried out on a CarloErba EA1110. Melting points were determined on a Mettler, a Büchi 545, and a Köfler apparatus and are uncorrected.

Ethyl 4-[[1-Benzyl-1H-imidazol-2-yl]carbonyl]-1-piperidinecarboxylate (7). A mixture of *N*-benzhydrylimidazole (235 g, 1 mol) and triethylamine (132 g, 1.3 mol) in acetonitrile (1250 mL) was stirred at 20 °C. *N*-Ethoxycarbonyl isonipecotyl chloride[11] **6** (264 g, 1.2 mol) was added dropwise (**exothermic**: temperature rose to 34 °C). Precipitation occurred. The reaction mixture was stirred for 4 h at reflux. The reaction mixture was cooled to room temperature and poured out into a 50% sodium hydroxide solution (160 mL). The mixture was concentrated and extracted with dichloromethane. The organic layer was washed with water, separated, dried on sodium

sulfate, and filtered, and the solvent was evaporated. Recrystallization from methylisopropyl ketone afforded 404 g of **7** (97%). Mp: 122.9 °C. Anal. ($C_{25}H_{27}N_3O_3$): C, H, N.

(1*H*-Imidazol-2-yl)(4-piperidinyl)methanone Dihydrobromide (8a). 7 (387.3 g, 0.93 mol) and 48% hydrobromic acid (1700 mL) were stirred and refluxed for 7 h. The mixture was evaporated and the residue was boiled in 2-propanol, filtered, and dried to afford 282.3 g of **8a** (92%). This compound was used in the next step without further purification.

(1*H*-Imidazol-2-yl)(1-methyl-4-piperidinyl)methanone (8b). A mixture of **8a** (141.2 g, 0.416 mol), potassium acetate (100 g, 1.02 mol), and paraformaldehyde (22 g, 0.73 mol) in methanol (700 mL) was hydrogenated at 50 °C with Pd/C 10% (5 g) as a catalyst in the presence of a 4% solution of thiophene in diisopropyl ether (10 mL). After uptake of hydrogen (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in water (100 mL). A 25% ammonia solution (150 mL) was added dropwise while cooling. The water layer was saturated with potassium carbonate and extracted with dichloromethane. The organic layer was separated, dried on magnesium sulfate, and filtered, and the solvent was evaporated. The residue was stirred in diisopropyl ether. The solid was filtered off and dried, yielding 80.5 g of **8b** (100%). Mp: 143.6 °C. Anal. ($C_{10}H_{15}N_3O$): C, H, N.

(1-Methyl-4-piperidinyl)[1-[2-(1-methyl-1*H*-pyrrol-2-yl)ethyl]-1*H*-imidazol-2-yl]methanone (10). Dimethyl formamide (800 mL) was stirred under nitrogen flow. Sodium hydride (60% in paraffin) (21.98 g, 0.55 mol) was added portionwise. **8b** (80.5 g, 0.416 mol) was added portionwise and this mixture was stirred for 2 h at room temperature. A solution of the mesylate **9**[12] (92.9 g, 0.457 mol) in dimethyl formamide was added dropwise. The reaction mixture was stirred overnight at 60 °C. The reaction mixture was cooled and quenched with water while cooling. This mixture was extracted with dichloromethane. The organic layer was separated, dried on magnesium sulfate, and filtered, and the solvent was evaporated. Column chromatography over silica gel (eluent: dichloromethane/methanol 95/5 increasing to dichloromethane/(ammonia/methanol 7 N) 90/10) afforded 94.7 g of **10** (76%) after recrystallization in diisopropyl ether. Mp: 89.8 °C. Anal. ($C_{17}H_{24}N_4O$): C, H, N.

5,6,7,10-Tetrahydro-7-methyl-10-(1-methyl-4-piperidinylidene)imidazo[1,2-*a*]pyrrolo[3,2-*d*]azepine (11a). This reaction was performed in three batches. Methanesulfonic acid (3 × 1600 mL) was added portionwise to **10** (3 × 60.68 g, 3 × 0.202 mol) cooled on an ice bath, and the mixture was stirred at room temperature. The mixture was warmed to 80 °C and stirred at this temperature overnight. The mixture was cooled, poured onto ice, alkalized with sodium hydroxide, and extracted with dichloromethane. The organic layer was separated, dried on magnesium sulfate, and filtered. The three batches were combined and evaporated. After purification by column chromatography over silica gel (eluent: dichloromethane/(ammonia/methanol 7 N) 96/4 to 90/10), the product was suspended in methylisopropyl ketone, filtered, and dried at 60 °C under vacuum overnight to afford 92.8 g of **11a** (80%). Mp: 190.0 °C. Anal. ($C_{17}H_{22}N_4$): C, H, N.

Ethyl 4-(5,6-Dihydro-7-methyl-10(7*H*)-imidazo[1,2-*a*]-pyrrolo[3,2-*d*]azepin-10-ylidene)-1-piperidinecarboxylate (11b). A mixture of **11a** (8.47 g, 0.03 mol) and triethylamine (6.07 g, 0.06 mol) in toluene (300 mL) was stirred and refluxed. Ethyl chloroformate (16.28 g, 0.15 mol) was added dropwise and the mixture was refluxed for 2 h. After cooling, water was added and the mixture was neutralized with potassium carbonate. The organic layer was separated and the aqueous layer was further extracted with chloroform. The combined organic layers were evaporated. Column chromatography over silica gel (eluent: dichloromethane/methanol 90/10) gave 11 g of solid product. This residue was boiled up in 2-propanone, filtered, and dried to afford 8.58 g of **11b** (84%). Mp: 232.0 °C. Anal. Calcd for $C_{19}H_{24}N_4O_2$: C, 67.04; H, 7.11; N, 16.46. Found: C, 66.38; H, 7.14; N, 16.33.

5,6,7,10-Tetrahydro-7-methyl-10-(4-piperidinylidene)-imidazo[1,2-*a*]pyrrolo[3,2-*d*]azepine (1). A mixture of **11b** (54.0 g, 0.165 mol) and potassium hydroxide (92.4 g, 1.65 mol) in 2-propanol (1000 mL) was stirred and refluxed overnight. After evaporation of the solvent, the residue was taken up in water and extracted with dichloromethane. The organic layer was dried, filtered, and evaporated. The residue was crystallized from ethyl acetate, yielding 28.1 g of **1** (63%). Mp: 194.8 °C. ^{1}H NMR (400 MHz): δ 2.60 (t, J = 5.7 Hz, 2 H), 2.73 (t, J = 5.7 Hz, 2 H), 2.90 (m, 6 H), 3.44 (s, 3 H), 4.32 (m, 2 H), 6.04 (d, J = 2.8 Hz, 1 H), 6.50 (d, J = 2.8 Hz, 1 H), 6.85 (d, J = 1.3 Hz, 1 H), 6.92 (d, J = 1.3 Hz, 1 H); ^{13}C NMR (101 MHz) δ 27.3, 32.5, 32.9, 33.6, 42.9, 47.9, 48.2, 109.2, 117.1, 118.1, 118.2, 120.0, 126.2, 126.4, 140.9, 150.2. Anal. ($C_{16}H_{20}N_4$): C, H, N.

1-[2-(1-Methyl-1*H*-pyrrol-2-yl)ethyl]-1*H*-imidazole (12). A mixture of **9** (17.8 g, 0.086 mol), imidazole (11.7 g, 0.172 mol), and potassium carbonate (14 g, 0.1 mol) in tetrahydrofuran (400 mL) was stirred and refluxed for 72 h. After cooling, the reaction mixture was evaporated and the residue was stirred in water. The mixture was extracted with dichloromethane and the separated organic layer was dried on magnesium sulfate, filtered, and evaporated. Purification by column chromatography over silica gel (eluent: dichloromethane/methanol 95/5) afforded 9.3 g of **12** (62%) that was used without further purification in the next step.

Ethyl 4-[[1-[2-(1-Methyl-1*H*-pyrrol-2-yl)ethyl]-1*H*-imidazol-2-yl]carbonyl]-1-piperidinecarboxylate (13). *N*-Ethoxycarbonyl isonipecotyl chloride[11] **6** (34.8 g, 0.159 mol) was added dropwise to a cooled mixture (ice bath) of **12** (9.3 g, 0.053 mol) and triethylamine (19 g, 0.19 mol) in acetonitrile (150 mL). The reaction mixture was stirred for 2 h at room temperature and for 4 h at reflux temperature. Stirring was continued overnight at room temperature. A sodium hydroxide 50% solution (16 mL) was then added dropwise. After stirring and refluxing for 30 min, the reaction mixture was concentrated. The residue was stirred in water and the mixture was extracted with dichloromethane. The separated organic layer was dried on magnesium sulfate, filtered, and evaporated to afford 25 g of **13** (100%) that was used in the next step without further purification.

5,6,7,10-Tetrahydro-7-methyl-10-(4-piperidinylidene)-imidazo[1,2-*a*]pyrrolo[3,2-*d*]azepine (1), Ethyl 4-(5,6-Dihydro-7-methyl-10(7*H*)-imidazo[1,2-*a*]pyrrolo[3,2-*d*]-azepin-10-ylidene)-1-piperidinecarboxylate (11b), and 10-(1-Ethyl-4-piperidinylidene)-5,6,7,10-tetrahydro-7-methylimidazo[1,2-*a*]pyrrolo[3,2-*d*]azepine (14). A mixture of **13** (71 g, 0.2 mol) in methanesulfonic acid (1800 mL) was stirred at 80 °C overnight. The mixture was poured into ice/sodium hydroxide, to keep the temperature below 30 °C, and was extracted with dichloromethane. The organic layer was dried on magnesium sulfate, filtered, and evaporated. Column chromatography over silica gel (eluent: dichloromethane/(ammonia/methanol 7 N) 95/5 to 90/10) afforded 33.4 g of **11b** (49%), 6 g of **1** (11%), and 20 g of **14** (34%). For analytical purposes, a sample of **14** (1.5 g) was converted into its fumarate salt (1:1) in ethanol. The analytical data reported below are those of this salt. Mp: 200.9 °C. Anal. Calcd for $C_{18}H_{24}N_4 \cdot C_4H_4O_4$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.34; H, 6.88; N, 13.31.

(1-Benzylpiperidin-4-ylidene)(1-methyl-1*H*-pyrrol-2-yl)acetonitrile (15). A mixture of *N*-benzylpiperidone (261 g, 1.38 mol), (1-methyl-1*H*-pyrrol-2-yl)acetonitrile (150 g, 1.23 mol), and sodium methanolate 30% in methanol (230 mL) was refluxed in methanol (900 mL) for 12 h. The solvent was evaporated and the residue was dissolved in water and extracted with dichloromethane. The organic layer was dried on magnesium sulfate, filtered, and evaporated to quantitatively produce 365 g of **15** that was used in the next step without further purification.

α-(1-Methyl-1*H*-pyrrol-2-yl)-1-benzyl-4-piperidineacetonitrile (16). A mixture of **15** (365 g, 1.25 mol) in 2-propanol (1600 mL) was stirred and warmed to 40 °C. Sodium borohydride (95 g, 2.5 mol) was added portionwise over 15 min and the mixture was refluxed for 48 h. After cooling, water was

added and the mixture was extracted with diisopropyl ether. The organic layer was dried on magnesium sulfate, filtered, and evaporated. The residue was recrystallized from diisopropyl ether, yielding 294 g of **16** (80%). Mp: 105.5 °C. Anal. ($C_{19}H_{23}N_3$): C, H, N.

(1-Methyl-1*H*-pyrrol-2-yl)[1-benzyl-4-piperidinyl]methanone (17). A mixture of **16** (250 g, 0.99 mol), sodium hydroxide 50% solution (96 g, 1.2 mol), and benzyltriethylammonium chloride (10 g, 0.054 mol) in dimethyl sulfoxide (800 mL) was stirred at room temperature. Air was bubbled through the mixture for 7 h (the temperature spontaneously raised to 50 °C). After cooling, the mixture was poured into water (3000 mL) and extracted with methyl isopropyl ketone. The organic layer was washed with water, dried on magnesium sulfate, filtered, and evaporated, quantitatively yielding 280 g of **17**. For analytical purposes, a sample of **17** was converted to its fumarate salt (1:1) in ethanol. The analytical data reported below are those of this salt. Mp: 183.0 °C. Anal. Calcd for $C_{18}H_{22}N_2O{\cdot}C_4H_4O_4$: C, 66.32; H, 6.58; N, 7.03. Found: C, 65.82; H, 6.53; N, 6.99.

(1-Methyl-1*H*-3-pyrrolidinyl)[1-benzyl-4-piperidinyl]-methanone (18). A mixture of **17** (275 g, 0.97 mol) in trifluoroacetic acid (2000 mL) was stirred and refluxed for 5 days. After concentration, the residue was poured out into ice/water/potassium carbonate and extracted with dichloromethane. The organic layer was dried on magnesium sulfate and filtered, and the solvent was evaporated. Column chromatography over silica gel (eluent: dichloromethane/methanol 95/5) followed by crystallization from acetonitrile afforded 121 g of **18** (44%). Mp: 145.3 °C. Anal. ($C_{18}H_{22}N_2O$): C, H, N.

(±)-α-1*H*-Imidazol-2-yl-α-(1-methyl-1*H*-pyrrol-3-yl)-1-benzyl-4-piperidinemethanol (19). A mixture of diisopropylamine (34 g, 0.337 mol) in tetrahydrofuran (1000 mL) was stirred at −78 °C. Butyllithium (2.5 M) in hexane (126 mL, 0.314 mol) was added portionwise at −70 to −50 °C. The mixture was stirred for 15 min at −50 to −78 °C. After dropwise addition of a solution of 1-bis(ethoxy)methyl imidazole (55 g, 0.323 mol) in tetrahydrofuran at −70 °C, the reaction mixture was further stirred for 1 h at −70 °C. A solution of **18** (83.1 g, 0.294 mol) in tetrahydrofuran was added dropwise at −70 °C. The reaction mixture was stirred for another hour at −78 °C. The reaction mixture was allowed to reach room temperature and was further stirred overnight at room temperature. After quenching with water, acetic acid (200 mL) was added dropwise over 15 min with the temperature rising spontaneously to 35 °C. The reaction mixture was stirred for 15 min at this temperature. The layers were separated. The organic layer was further extracted with diluted acetic acid. The combined acidic aqueous layers were alkalized with potassium carbonate and extracted with dichloromethane. This organic layer was dried on magnesium sulfate and filtered, and the solvent was evaporated to afford quantitatively 103 g of **19** that was used in the next step without further purification.

4-[1*H*-Imidazol-2-yl(1-methyl-1*H*-pyrrol-3-yl)methylene]-1-benzylpiperidine (20a). A mixture of **19** (103 g, 0.294 mol) in trifluoroacetic acid (1200 mL) was stirred and refluxed for 1 h. After evaporation of the solvent, the residue was poured out into ice/water/potassium carbonate. This mixture was extracted with dichloromethane. The organic layer was dried on magnesium sulfate and filtered, and the solvent was evaporated. Column chromatography over silica gel (eluent: dichloromethane/methanol 95/5) followed by recrystallization from acetonitrile afforded 74.0 g of **20a** (75%). Mp: 188.2 °C. Anal. ($C_{21}H_{24}N_4$): C, H, N.

Methyl 2-[(1-Methyl-1*H*-pyrrol-3-yl)[1-benzyl-4-piperidinylidene]methyl]-1*H*-imidazole-1-acetate (20b). Sodium hydride 50% (15.8 g, 0.33 mol) was added portionwise to dimethylformamide at room temperature. **20a** (74 g, 0.22 mol) dissolved in dimethyl formamide was then added dropwise and the mixture was stirred at room temperature for 1 h. Methyl chloroacetate (36.2 g, 0.33 mol) dissolved in dimethylformamide was added dropwise and the mixture was stirred at room temperature for 1 h. The mixture was poured in water, sodium bicarbonate (10 g) was added, and the mixture was extracted with dichloromethane. The organic layer was dried on magnesium sulfate, filtered, and evaporated. Column chromatography over silica gel (eluent: dichloromethane/methanol 96/4) afforded 65 g of **20b** (73%) that was used without further purification in the next step.

7,10-Dihydro-7-methyl-10-[1-(phenylmethyl)-4-piperidinylidene]imidazo[1,2-*a*]pyrrolo[3,2-*d*]azepin-6(5*H*)-one (21) and 8,10-Dihydro-8-methyl-10-[1-benzyl-4-piperidinylidene]imidazo[1,2-*a*]pyrrolo[3,4-*d*]azepin-6(5*H*)-one (22). A mixture of **20b** (65 g, 0.16 mol) in trifluoromethanesulfonic acid (650 mL) was stirred at 120 °C for 4 h. The mixture was cooled, poured into ice/potassium carbonate/water, and extracted with dichloromethane. The organic layer was dried on magnesium sulfate, filtered, and evaporated. Column chromatography over silica gel (eluent: dichloromethane/methanol 96/4) afforded fractions 1 and 2. These were recrystallized from acetonitrile, respectively yielding 11.3 g of **21** [Yield: 19%. Mp: 213.5 °C. Anal. ($C_{23}H_{24}N_4O$): C, H, N.] and 11 g of **22** [Yield: 18%. Mp: 175.1 °C. Anal. ($C_{23}H_{24}N_4O$): C, H, N.].

7,10-Dihydro-10-(4-piperidinylidene)imidazo[1,2-*a*]pyrrolo[3,2-*d*]azepin-6(5*H*)-one Fumarate Salt (2a) and 7,10-Dihydro-10-(4-piperidinyl)imidazo[1,2-*a*]pyrrolo-[3,2-*d*]azepin-6(5*H*)-one (23). A mixture of **21** (13.8 g, 0.037 mol) in methanol (150 mL) was hydrogenated at room temperature (atmospheric pressure) with Pd/C 10% (2 g) as a catalyst. After uptake of hydrogen (0.7 equiv), the catalyst was filtered off and the filtrate was evaporated. Column chromatography over silica gel (eluent: dichloromethane/methanol/(ammonia/methanol 7 N) 90/5/5 to 90/0/10) afforded **2a** (5.3 g, 51%) and **23** (5.1 g, 49%). For analytical purposes, a sample of each compound was converted to its fumarate salt (1:1). The analytical data reported below are those of these salts. Compound **2a**. Mp: 250 °C (Kofler). ^{1}H NMR (360 MHz, DMSO-d_6): δ 2.70 (m, 2 H), 2.78 (m, 2 H), 2.93 (m, 2 H), 3.12 (m, 1 H), 3.22 (m, 1 H), 3.84 (s, 3 H), 4.69 (d, J = 16.1 Hz, 1 H), 5.07 (d, J = 16.0 Hz, 1 H), 6.22 (d, J = 2.5 Hz, 1 H), 6.46 (s, 2 H), 6.82 (d, J = 1.2 Hz, 1 H), 7.25 (d, J = 2.5 Hz, 1 H), 7.28 (d, J = 1.2 Hz, 1 H). Anal. ($C_{16}H_{18}N_4O{\cdot}C_4H_4O_4$): C, H, N. Compound **23**. Mp: 243.5 °C. Anal. Calcd for $C_{16}H_{20}N_4O{\cdot}C_4H_4O_4$: C, 59.99; H, 6.04; N, 13.99. Found: C, 59.53; H, 6.12; N, 13.90.

4-[1-(2-Phenylethyl)-1*H*-imidazol-2-yl]-1-benzyl-4-piperidinol (24). A mixture of diisopropylamine (142 g, 1.4 mol) in tetrahydrofuran (3000 mL) was stirred at −70 °C. Butyllithium (2.5 M) in hexanes (520 mL, 1.3 mol) was added portionwise at a temperature below −40 °C. The mixture was stirred at −70 °C for 15 min. 1-Phenethylimidazole (172 g, 1 mol) dissolved in tetrahydrofuran was added dropwise at a temperature below −55 °C. The mixture was stirred at −70 °C for 1 h. *N*-benzylpiperidone (227 g, 1.2 mol) dissolved in tetrahydrofuran was added dropwise at a temperature below −55 °C. The mixture was stirred at −70 °C for 1 h and then brought to room temperature, stirred at room temperature overnight, and quenched with water. The organic solvent was evaporated. The aqueous concentrate was extracted with dichloromethane. The organic layer was separated, dried on magnesium sulfate, and filtered, and the solvent was evaporated. Crystallization of the residue from diisopropyl ether (1100 mL) afforded 271 g of **24** (75%). Mp: 110.5 °C. Anal. ($C_{23}H_{27}N_3O$): C, H, N.

5,6-Dihydro-1′-benzylspiro[11*H*-imidazo[2,1-*b*][3]benzazepine-11,4′-piperidine] (25a). A mixture of **24** (270 g, 0.75 mol) in trifluoromethanesulfonic acid (1500 mL) was stirred at 65 °C for 5 days and then cooled, poured out on ice, alkalized with a sodium hydroxide 50% solution, and extracted with dichloromethane. The organic layer was separated, dried on magnesium sulfate, and filtered, and the solvent was evaporated. Crystallization of the residue from diisopropyl ether/acetonitrile (99/1) (1200 mL) afforded 169.6 g of **25a** (66%). Mp: 109.9 °C. Anal. ($C_{23}H_{25}N_3$): C, H, N.

5,6-Dihydrospiro[imidazo[1,2-*b*][3]benzazepine-11-[11*H*],4′-piperidine] (25b). A mixture of **25a** (6.9 g, 0.02 mol)

in methanol (150 mL) was hydrogenated with Pd/C 10% (2 g) as a catalyst at 50 °C for 18 h. After uptake of hydrogen (1 equiv), the catalyst was filtered and the filtrate was evaporated. Recrystallization of the residue as its hydrochloride salt (1:1) in acetonitrile afforded 5 g of the hydrochloride salt of **25b** (86%). Mp: 278.5 °C (HCl salt). Anal. ($C_{16}H_{19}N_3$·HCl): C, H, N.

***tert*-Butyl 5,6-Dihydrospiro[11*H*-imidazo[2,1-*b*][3]benzazepine-11,4′-piperidine]-1′-carboxylate (25c).** Di-*tert*-butyl dicarbonate (20.7 g, 0.095 mol) dissolved in a small amount of dichloromethane was added dropwise to a stirring mixture of **25b** (free base) (20 g, 0.079 mol) in dichloromethane (250 mL). The mixture was stirred at room temperature for 48 h and then washed with water, dried, and filtered, and the solvent was evaporated. The residue was dissolved in diisopropyl ether and filtered. After evaporation of the filtrate, column chromatography over silica gel (eluent: dichloromethane/methanol 100/0 to 96/4) afforded 15.05 g of **25c** (54%). Mp: 107.4 °C. Anal. ($C_{21}H_{27}N_3O_2$): C, H, N.

***tert*-Butyl 3-Hydroxymethyl-5,6-dihydrospiro[11*H*-imidazo[2,1-*b*][3]benzazepine-11,4′-piperidine]-1′-carboxylate (26a) and *tert*-Butyl 2,3-Bis(hydroxymethyl)-5,6-dihydrospiro[11*H*-imidazo[2,1-*b*][3]benzazepine-11,4′-piperidine]-1′-carboxylate (27).** A mixture of **25c** (163 g, 0.46 mol), 37% formaldehyde in water (760 mL, 10.1 mol), and sodium acetate (113 g, 1.38 mol) in acetic acid (68 mL) was stirred and refluxed for 4 h. The mixture was cooled, poured out on ice, alkalized with a sodium hydroxide 50% solution, and extracted with dichloromethane. The organic layer was separated, dried on magnesium sulfate, and filtered, and the solvent was evaporated. Column chromatography over silica gel (eluent: dichloromethane/methanol 97/3) afforded two pure fractions that were recrystallized from acetonitrile, yielding 80.7 g of **26a** [Yield: 46%. Mp: 200.0 °C. Anal. ($C_{22}H_{29}N_3O_3$): C, H, N.] and 35 g of **27** [Yield: 18%. Anal. ($C_{23}H_{31}N_3O_4$): C, H, N.].

***tert*-Butyl 3-Formyl-5,6-dihydrospiro[imidazo[2,1-*b*][3]benzazepine-11,4′-piperidine]-1′-carboxylate (26b).** A mixture of **26a** (59.5 g, 0.155 mol) and activated manganese dioxide (300 g, 3.45 mol) in chloroform (1200 mL) was stirred and refluxed for 90 min. The warm mixture was filtered over dicalite and the filtrate was evaporated. Recrystallization of the residue from acetonitrile afforded 51.8 g of **26b** (88%). Mp: 156.5 °C. Anal. ($C_{22}H_{27}N_3O_3$): C, H, N.

Methyl *tert*-Butyl 5,6-dihydrospiro[11*H*-imidazo[2,1-*b*][3]benzazepine-11,4′-piperidine]-3,1′-dicarboxylate (26c). A mixture of **26b** (51.2 g, 0.134 mol), sodium cyanide (34.6 g, 0.705 mol), and activated manganese dioxide (233 g, 2.68 mol) in methanol (2500 mL) was stirred at room temperature. Acetic acid (45.5 mL) was added dropwise. The mixture was stirred and refluxed for 20 h and filtered over dicalite. The filtrate was evaporated and the residue was taken up in water, dichloromethane, and potassium carbonate. After separation, the aqueous layer was extracted with dichloromethane. The combined organic layers were dried on magnesium sulfate and filtered, and the solvent was evaporated. Column chromatography over silica gel (eluent: dichloromethane/ methanol 97/3) afforded 47.7 g of **26c** (87%) that was used in the next step without further purification.

1′-[*tert*-Butoxycarbonyl]-5,6-dihydrospiro[11*H*-imidazo-[2,1-*b*][3]benzazepine-11,4′-piperidine]-3-carboxylic Acid (26d). A mixture of **26c** (23 g, 0.056 mol) in 1 N sodium hydroxide (100 mL), water (250 mL), and tetrahydrofuran (250 mL) was stirred at room temperature for 18 h. The organic solvent was evaporated. The aqueous concentrate was neutralized with 1 N hydrochloric acid (100 mL) and extracted with dichloromethane. The organic layer was dried on magnesium sulfate and filtered, and the solvent was evaporated to afford 22.9 g of **26d** (100%) after recrystallization in acetonitrile. Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.85; N, 10.57. Found: C, 65.42; H, 6.74; N, 10.74.

***tert*-Butyl 3-(Aminocarbonyl)-5,6-dihydrospiro[11*H*-imidazo[2,1-*b*][3]benzazepine-11,4′-piperidine]-1′-carboxylate (26e).** A mixture of **26d** (15.9 g, 0.04 mol) and 4-dimethylaminopyridine (4.9 g, 0.04 mol) in dichloromethane (300 mL) was stirred until complete dissolution. Triethylamine (5.6 g, 0.05 mol) was added followed by EDCI (9.6 g, 0.05 mol). After stirring for 30 min at room temperature, triethylamine (5.6 g, 0.06 mol) was added followed by ammonium chloride (2.7 g, 0.05 mol). The mixture was stirred at room temperature overnight, poured out into water, and separated. The aqueous layer was extracted with dichloromethane. The combined organic layer was dried on magnesium sulfate and filtered, and the solvent was evaporated. Column chromatography over silica gel (eluent: dichloromethane/methanol 97.5/2.5) followed by crystallization from acetonitrile afforded 9.5 g of **26e** (60%). Anal. ($C_{22}H_{28}N_4O_3$): C, H, N.

5,6-Dihydrospiro[11*H*-imidazo[2,1-*b*][3]benzazepine-11,4′-piperidine]-3-carboxamide Dihydrochloride (3a). A mixture of **26e** (9 g, 0.023 mol) in 6 N hydrochloric acid in 2-propanol (25 mL) and methanol (100 mL) was stirred and refluxed for 90 min. After cooling, the precipitate was filtered and dried to afford 8 g of **3a** (94%). Mp: >250 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.57 (ddd, J = 14.7, 10.7, 4.3 Hz, 2 H), 3.02 (br.d, J = 14.6 Hz, 2 H), 3.21 (m, 4 H), 3.43 (t, J = 7.0 Hz, 2 H), 4.98 (t, J = 7.0 Hz, 2 H), 7.27 (m, 3 H), 7.46 (m, 1 H), 7.57 (br.s, 1 H), 7.93 (s, 1 H), 8.03 (br.s, 1 H), 9.29 (br.m, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 31.2, 31.5, 40.7, 41.8, 43.2, 125.3, 127.0, 127.1, 127.9, 132.5, 136.6, 138.7, 150.1, 160.5. Anal. ($C_{17}H_{20}N_4O$·2HCl): C, H, N.

3-Bromo-5,6-dihydro-1′-benzylspiro[11*H*-imidazo[2,1-*b*][3]benzazepine-11,4′-piperidine (28a). *N*-Bromosuccinimide (16 g, 0.09 mol) was added portionwise over 1 h to a solution of **25a** (31 g, 0.09 mol) in dichloromethane (1000 mL) cooled to 0 °C. Water was then added and the organic layer was separated, washed with water, dried, and filtered, and the solvent was evaporated. Column chromatography over silica gel (eluent: dichloromethane/methanol 97.5/2.5 to 95/5) afforded 10.9 g (35%) of starting material **25a** and **28a** that was converted to its fumarate salt (1:1) in ethanol, yielding 17.3 g (36%) of this salt. Mp: 218.0 °C. Anal. ($C_{23}H_{24}BrN_3$·$C_4H_4O_4$): C, H, N.

5,6-Dihydro-1′-benzylspiro[11*H*-imidazo[2,1-*b*][3]benzazepine-11,4′-piperidine]-3-carboxamide (28b). A mixture of **28a** (12.9 g, 0.03 mol), palladium(II) acetate (0.135 g, 0.0006 mol), and 1,3-bis(diphenylphosphino)propane (0.495 g, 0.0012 mol) in tetrahydrofuran (200 mL) was stirred in an autoclave at 150 °C for 16 h under pressure of carbon monoxide (30 atm) and ammonia (10 atm). The mixture was filtered and the filtrate was evaporated. Column chromatography on silica gel (eluent: dichloromethane/methanol 95/5 to 90/10) afforded 8.3 g of **28b** (72%). For analytical purposes, a sample of **28b** was converted into its fumarate salt (1:1) in ethanol. Anal. Calcd for $C_{24}H_{26}N_4O$·$C_4H_4O_4$·H_2O.0.4C_2H_6O: C, 64.16; H, 6.44; N, 10.39. Found: C, 63.74; H, 6.35; N, 10.59.

5,6-Dihydrospiro[11*H*-imidazo[2,1-*b*][3]benzazepine-11,4′-piperidine]-3-carboxamide (3b). A mixture of **28b** (36 g, 0.093 mol) in methanol (250 mL) was hydrogenated for 32 h at 50 °C in the presence of Pd/C 10% (2 g). After uptake of hydrogen (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The solid residue was triturated in diisopropyl ether, filtered, and dried at 40 °C under vacuum for 16 h, yielding 23 g (83%) of the free base **3b**. Mp: 249.0 °C.

^{1}H NMR of this compound confirmed that it was identical to a sample prepared by liberating the base from the dihydrochloride **3a** prepared according to the above procedure.

Determination of the Aqueous Solubility of 3a and 3b as a Function of the pH. Solubility was studied according to the method of Higuchi and Connors.[27] The solutes **3a** or **3b** (an excess or the amounts indicated in Table 2) were added to 25 mL glass vials containing the solvent. The closed vials were shaken for 24 h at 20 °C. If the mixture were clear solutions, the pH was recorded and no further analysis was performed. The results, reported for the clear mixtures, are based on the ratio of added solute over the volume of solvent used. For the turbid samples, the excess was removed by filtration over a 0.45 μm membrane filter (Millipore), the pH of the filtrates

were recorded, and the concentration of **3a** or **3b** in solution was determined using UV absorption analysis.

Receptor Binding Affinity for the Human Cloned Histamine H_1 Receptor Expressed in CHO Cells.[28] The radioligand used was [^{3}H]pyrilamine (1 nM, New England Nuclear NET-594). The blank was astemizole (1 μM). The tissue used was cloned human histamine-H_1 CHO-K1 cells. A Na^+, K^+ phosphate buffer (50 mM, pH 7.5) was used (a 50 mM solution of K_2HPO_4 was adjusted to pH 7.5 with 50 mM NaH_2PO_4).

CHO-cells expressing the cloned human H_1 receptor were cultured in HAM'S F12 medium (GIBCO cat. no. 21765−029) enriched with 10% HI fetal calf serum and in the presence of penicillin (105 IU/L) and streptomycin sulfate (100 mg/L). Twenty-four hours before collection, cells were induced with 5 mM sodium butyrate and prepared on the day of confluence (70−90%). On the day of experiment, cell membranes, stored at −70 °C, were thawed and homogenized in homogenization buffer using an Ultra Turrax homogenizer in an appropriate dilution, based on the results of an initial dilution experiment. Incubation was carried out for 30 min at 25 °C. Reactants were pipetted in plastic 5-mL tubes, 3 mL of ice-cold rinsing buffer was added to the tubes followed by rapid filtration over GF/B filters, and filters were rinsed twice with ice-cold rinsing buffer and placed into counting vials. LKB Ultima Gold (5 mL) was added, and counting was carried out in a Packard liquid scintillation counter. Results were expressed in dpm. The compounds were investigated for interaction with [^{3}H]pyrilamine binding at different concentrations.

Animals for the Pharmacological Tests. Wistar rats, Dunkin−Hartley−Purbright guinea pigs, and internally bred Beagle dogs were used. Unless otherwise stated, they were transferred to the air-conditioned laboratories on the day before the experiment and housed in individual cages under standard laboratory conditions (21 ± 2 °C; 65 ± 15% relative humidity; light-dark cycle set at 12 h). They were food-deprived overnight but tap water remained available ad libitum except during the test period.

Test Compounds. Compounds **1**, **2a**, **3a** and cetirizine (**5**) were prepared as solutions in distilled water, and loratadine (**4**) was dissolved in 10% hydroxypropyl-β-cyclodextrin containing 1 equiv of tartaric acid. The concentrations were selected to obtain the desired doses using a standard administration volume of 10 mL/kg. The solutions were stored at room temperature in closed containers protected from light. They were studied at a predefined interval after single subcutaneous (sc) or oral (po) administration. All doses were expressed in mg of base equivalents per kg of body weight.

General Procedure and Statistics for the in Vivo Models for Evaluation of Antihistaminic Activity in Rats, Guinea Pigs, and Dogs. All experiments were performed by unbiased trained technicians using coded solutions. Doses were selected from the geometrical series 0.04, 0.08, 0.16, 0.32, 0.63, 1.25, 2.5, 5.0, 10 mg/kg in such a way that at least three doses covered the dose−response curve. Each dose group in this most relevant part of the dose−response curve consisted of five animals that were tested in separate daily experimental sessions in order to account for day-to-day variability and to minimize systematic errors. Control injections of solvent were included in each experimental session. All-or-nothing criteria for significant ($p < 0.05$) effects were defined by analyzing a frequency distribution of a large series of historical control data. ED_{50} values and corresponding 95% confidence limits were calculated according to the method of Finney for categorical data.[29]

Compound 48/80-Induced Lethality in Rats.[19] Injection of compound 48/80 in rats results in a massive release of mast-cell mediators, which are in rats predominantly histamine and serotonin. The resulting lethal anaphylactic shock is counteracted by histamine H_1 antagonists. The compound 48/80 (0.50 mg/kg, iv)-induced lethality was recorded in female rats (225−275 g) up to 240 min after injection. Test compound or solvent was administered at specified time intervals before compound 48/80. Criterion for drug-induced protection: >240 min survival (in historical controls: 5.0%; $n > 1000$).

Histamine-Induced Lethality in Guinea Pigs.[20a] Histamine (1.25 mg/mL/kg, iv)-induced lethality was recorded in guinea pigs of both sexes (300−500 g) up to 120 min after the histamine challenge. Test compound or solvent was administered at specified time intervals before histamine. Criterion for drug-induced protection: >120 min survival (0.0% false positives controls; $n > 150$). Histamine H_1 antagonists protect against the histamine-induced lethality.

Skin Reaction Test in Rats (modification of ref 21). Fifty hours after passive sensitization of a dorsal skin site by intradermal injection (0.05 mL) of ovalbumin-specific IgE-containing serum, three additional dorsal skin sites were injected intradermally with histamine (50 μg), serotonin (0.1 μg), and *Ascaris* allergens ($^1/_2$ diluted with saline) in male rats (200−240 g). Immediately thereafter, the animals were challenged iv with a mixture (1 mL) of ovalbumin (1%) and Evans blue dye (0.2%) and sacrificed 30 min later. The intensity of the blue-colored skin reactions was scored by two independent observers in comparison with standard reactions. The scoring system was (4) maximal, (3) pronounced, (2) moderate, (1) slight, and (0) no difference with surrounding skin. The scores of the two observers were summed for further evaluation. Test compound or solvent was administered 2 h before induction of the skin reactions. Criteria for drug-induced effects are as follows: (A) serotonin reactions, score < 4 for inhibition and score < 3 for blockade (occurring in 2.1% and 1.2%, respectively, of solvent-treated control rats; $n = 521$); (B) histamine reactions, score < 4 for inhibition and score < 3 for blockade (occurring in 5.6% and 2.9%, respectively, of the control rats); (C) PCA reactions: score < 3 for inhibition (occurring in 6.3% of the control rats); and (D) *Ascaris* allergens reactions: score < 3 for inhibition (occurring in 3.6% of the control rats).

Skin Reaction Test in Guinea Pigs. Five dorsal skin sites of guinea pigs of both sexes (300−500 g) were injected intradermally (0.05 mL) with saline containing substance P (0.05 μg), histamine (0.25 μg), bradykinin (0.1 μg), PAF (0.00625 μg), and *Ascaris* allergens ($^1/_{16}$ diluted with saline). Immediately thereafter, the animals were challenged i.v. with Evans blue dye (30 mg/kg: 7.5 mg/mL, 4 mL/kg) and sacrificed 30 min later. The intensity of the blue-colored skin reactions was scored by two independent observers in comparison with standard reactions. The scoring system was: (4) maximal, (3) pronounced, (2) moderate, (1) slight, and (0) no difference with surrounding skin. The scores of the two observers were summed for further evaluation. Test compound or solvent was administered at a predefined interval before induction of the skin reactions. Criteria for drug-induced effects: (1) histamine reactions: score < 7 for inhibition and score < 3 for blockade (occurring in 3.6% and 0.0%, respectively, of solvent-treated control guinea-pigs; $n = 56$); (2) substance P reactions: score < 7 for inhibition, score < 5 for pronounced inhibition, and score < 3 for blockade (occurring in 3.6%, 0.0% and 0.0%, respectively, of controls); (3) PAF reactions: score < 7 for inhibition and score < 3 for blockade (occurring in 0.0% and 0.0%, respectively, of controls); (4) bradykinin reactions: score < 7 for inhibition and score < 3 for blockade (occurring in 0.0% and 0.0%, respectively, of controls); and, (5) *Ascaris* allergens reactions: score < 3 for blockade (occurring in 5.4% of controls).

***Ascaris* Allergens-Induced Skin Reaction Test in Dogs (modification of ref 22).** A preparation of *Ascaris* allergens (ACF; $^1/_{100}$ diluted with saline; 0.05 mL) was injected at three skin sites close to the chest in dogs of both sexes, varying in body weight, and selected for sensitivity to *Ascaris* allergens. Fifteen minutes later, the wheal diameters (ϕ, in mm) and skin thickness increases (TI; the difference in 0.1 mm between the center of the reaction and the mean of two surrounding normal skin sites) were measured. After these 0-h time values, test compound or solvent was administered orally to the dogs. The three injections of ACF and the measurements were repeated 1, 4, 20, and 72 h after the oral administration of the test compounds. The test compounds were tested at several dose

levels in separate sessions. The results are expressed as wheal volumes (in mm^3) obtained by the formula

$$\pi\left(\frac{\phi}{2}\right)^2\left(\frac{TI}{20}\right)$$

On the basis of frequency distributions of the volumes measured at the four time intervals in control animals ($n > 600$), the following all-or-nothing criteria were selected for determining ED_{50} values: <115 mm^3 for the 1-, 4-, 20-, and 72-h intervals (occurrence in 1.5%, 1.2%, 4.1%, and 1.0% in control dogs; $n = 882$).

Determination of H_1 Receptor Occupancy in Guinea Pig Brain. In vivo H_1 receptor occupancy in guinea pig brain was measured by ex vivo autoradiography according to our standard protocol.[23] Male Dunkin−Hartley guinea pigs (300 g) were treated by oral administration of vehicle or tested compounds at seven dosages ranging from 0.01 to 40 mg/kg of body weight (dosages: 0.01, 0.04, 0.16, 0.63, 2.5, 10, and 40 mg/kg, $n = 3-9$ animals per dose) and sacrificed 3 h later. The brains were immediately removed from the skull and rapidly frozen in dry-ice-cooled 2-methylbutane (−40 °C). Twenty-micrometer-thick sections were cut using a Leica CM 3050 cryostat-microtome and thaw-mounted on microscope slides. The sections were then kept at −20 °C until use. Occupancy of H_1 receptors was measured in the cerebellum of each individual guinea pig. After thawing, the sections were dried under a stream of cold air and then incubated for 10 min in 50 mM Na/K phosphate buffer (pH 7.4) containing 4 nM [^{3}H]pyrilamine. Nonspecific binding was measured on adjacent sections in the presence of 1 μM astemizole. After the incubations, the slides were washed (2 × 2 min) in ice-cold buffer, followed by a quick rinse in ice-cold water. The sections were then dried under a stream of cold air and exposed to ^{3}H-Hyperfilms (Amersham, U.K.) for 4 weeks. Autoradiograms were quantified using a MCID image analyzer (Imaging Research, St-Catharines, Ontario, Canada). Specific binding was given as the difference between total binding and nonspecific binding measured in adjacent sections. Percentages of H_1 receptor occupancy by the drug administered to the animal correspond to 100% minus the percentage of H_1 receptor labeling in the treated animal. The percentage of H_1 receptor occupancy was plotted against dosage and the sigmoidal log dose−effect curve of best fit was calculated by nonlinear regression analysis, using the GraphPad Prism program. From these dose−response curves, the ED_{50}s (the drug dose producing 50% receptor occupancy) were calculated.

Acknowledgment. The authors thank Jan D'Aubioul, Alex De Groot, An Hermans, Jef Peeters, Ard Teisman, and Jef Vermeire for their help.

Supporting Information Available: Table of detailed elemental analysis results, ^{1}H NMR data for the intermediates, and ^{13}C NMR data for selected intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a selection of representative reviews on antihistamines, see: (a) Sneader, W. Histamine and the Classic Antihistamines. *Drug News Perspect.* **2001**, *14* (10), 618−624. (b) Walsh, G. M.; Annunziato, L.; Frossard, N.; Knol, K.; Levander, S.; Nicolas, J.-M.; Taglialatela, M.; Tharp, M. D.; Tillement, J. P.; Timmerman, H. New Insights into the Second Generation Antihistamines. *Drugs* **2001**, *61* (2), 207−236. (c) Oppenheimer, J. J.; Casale, T. B. Next Generation Antihistamines: Therapeutic Rationale, Accomplishments and Advances. *Expert Opin. Investig. Drugs* **2002**, *11* (6), 807−817. (d) Hindmarch, I. CNS Effects of Antihistamines: Is There a Third Generation of Nonsedative Drugs? *Clin. Exp. All. Rev.* **2002**, *2*, 26−31. (e) Rihoux, J. P. H_1-Receptor Antagonists: A Critical Reapparaisal. *IDrugs* **1999**, *2* (12), 1295−1301.

(2) Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. J. New Antihistaminic N-Heterocyclic 4-Piperidinamines. 2. Synthesis and Antihistaminic Activity of 1-[(4-Fluorophenyl)methyl]-N−(4-piperidinyl)-1H-benzimidazol-2-amines . *J. Med. Chem.* **1985**, *28* (12), 1934−1943.

(3) McTavish, D.; Goa, K. L.; Ferrill, M. Terfenadine: An updated review of its pharmacological properties and therapeutic efficacy. *Drugs* **1990**, *39* (4), 552−574.

(4) Curran, M. P.; Scott, L. J.; Perry, C. M. Cetirizine. A Review of its Use in Allergic Disorders. *Drugs*, **2004**, *64* (5), 523−561.

(5) Haria, M.; Fitton, A.; Peters D. H. Loratadine. A Reappraisal of its Pharmacological Properties and Therapeutic Use in Allergic Disorders. *Drugs*, **1994**, *48* (4), 617−637.

(6) (a) Simons, F. E. R.; Kesselman, M. S.; Giddins, N. G.; Pelech, A. N.; Simons, K. J. Astemizole induced torsade de pointes. *Lancet* **1988**; *II* (8611), 624. (b) Davies, A. J.; Harindra, V.; McEwan, A.; Ghose, R. R. Cardiotoxic effect with convulsions in terfenadine overdose. *Br. Med. J.* **1989** *298* (6669), 325. (c) Wiley, J. F.; Gelber, M. L.; Henretig, F. M.; Wiley, C. C.; Sandhu, S.; Loiselle, J. Cardiotoxic effects of astemizole overdose in children. *J. Pediatr.* **1992** *120* (5), 799−802. (d) Woolsey, R. L.; Chen, Y.; Freiman J. P.; Gillis, R. A. Mechanisms of the cardiotoxic actions of terfenadine. *JAMA* **1993**, *269* (12), 1532−1536. (e) Woolsey, R. L. Cardiac actions of antihistamines. *Annu. Rev. Pharmacol. Toxicol.* **1996**; *36*, 233−252. (f) Salata, J. J.; Jurkiewicz, N. K.; Wallace, A. A.; Stupienski, R. F.; Guinosso, P. J.; Lynch, J. J. Cardiac electrophysiological actions of the histamine H_1-receptor antagonists astemizole and terfenadine compared with chlopheniramine and pyrilamine. *Circ. Res.* **1995**; *76* (1), 110−119. (g) Rampe, D.; Wible, B.; Brown, A. M.; Dage, R. C. Effects of terfenadine and its metabolite on a delayed rectifier K^+ channel from human heart. *Mol. Pharmacol.* **1993**, *44* (6), 1240−1245.

(7) Geha, R. S.; Meltzer, E. O. Desloratadine: A New, Nonsedating, Oral Antihistamine. *J. Allergy Clin. Immunol*. **2001**, *107* (4), 751−762.

(8) Casale, T. B.; Blaiss, M. S.; Gelfand, E.; Gilmore, T.; Harvey, P. D.; Hindmarch, I.; Simons, F. E.; Spangler, D. L.; Szefler, S. J.; Terndrup, T. E.; Waldman, S. A.; Weiler, J.; Wong, D. F. Antihistamine Impairment Roundtable. First do no harm: Managing antihistamine impairment in patients with allergic rhinitis. *J. Allergy Clin. Immunol.* **2003**, *111* (5), S835−S842.

(9) Stanaland, B. E. Treatment of Patients with Chronic Idiopathic Urticaria. *Clin. Rev. Allergy Immunol.* **2002**, *23* (2), 233−241.

(10) Janssens, F.; Leenaerts, J.; Van Roosbroeck, Y.; Sommen, C.; De Boeck, B. A Simple and General Synthesis of 4-(Spiro-[imidazobenzazepine])-piperidine and its Analogues. Manuscript in preparation.

(11) Bold, G.; Capraro, H.-G.; Faessler, A.; Lang, M.; Bhagwat, S. S.; Khanna, S. C.; Lazdins, J. K.; Mestan, J. Preparation of ethers of aspartate protease substrate isosteres as antivirals. *Eur. Pat. Appl.* 1996, EP708085.

(12) Janssens, F. E.; Diels, G. S. M.; Leenaerts, J. E.; Cooymans, L. P. Preparation of imidazo[1,2-a](pyrrolo, thieno or furano)[3,2-d]azepines as allergy inhibitors. *Eur. Pat. Appl*. 1992, EP518434.

(13) Donetti, A.; Boniardi, O.; Ezhaya, A.; Phase-Transfer Catalyzed Oxidative Decyanation of α-Secondary Nitriles; A Convenient Synthesis of Aromatic Ketones. *Synthesis* **1980**, (12), 1009−1011.

(14) Carson, J. R.; Davis, N. M.; Acid-mediated rearrangement of acylpyrroles. *J. Org. Chem.* **1981**, *46* (5), 839−843.

(15) ter Laak, A. M.; Bijloo, G. J.; Fischer, M. J. E.; Donné op den Kelder, G. M.; Wilting, J.; Timmerman, H. Serum protein binding of histamine H_1-antagonists. A comparative study on the serum protein binding of a sedating ([^{3}H]mepyramine) and a nonsedating H_1-antagonist ([^{3}H]loratadine). *Eur. J. Pharm. Sci.* **1996**, *4* (5), 307−319.

(16) Kasim, N. A.; Whitehouse, M.; Ramachandran, C.; Bermejo, M.; Lennernäs, H.; Hussain, A. S.; Junginger, H. E.; Stavchansky, S. A.; Midha, K. K.; Shah, V. P.; Amidon, G. L. Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification. *Mol. Pharm.* **2004**, *1* (1), 85−96.

(17) Pagliara, A.; Testa, B.; Carrupt, P.-A.; Jolliet, P.; Morin, C.; Morin, D.; Urien, S.; Tillement, J.-P.; Rihoux, J.-P. Molecular Properties and Pharmacokinetic Behavior of Cetirizine, a Zwitterionic H_1-Receptor Antagonist. *J. Med. Chem.* **1998**, *41* (6), 853−863.

(18) Briejer, M. R.; Bosmans, J.-P.; Van Daele, P.; Jurzak, M.; Heylen, L.; Leysen, J. E.; Prins, N. H.; Schuurkes, J. A. J. The in vitro pharmacological profile of prucalopride, a novel enterokinetic compound. *Eur. J. Pharmacol.* **2001**, *423* (1), 71−83.

(19) Niemegeers, C. J. E.; Awouters, F.; Van Nueten, J. M.; De Nollin, S.; Janssen, P. A. J. Protection of Rats from Compound 48/80-induced Lethality. A Simple Test for Inhibitors of Mast Cell-mediated Shock. *Arch. Int. Pharmocodyn. Ther*. **1978**, *234* (1), 164−176.

(20) (a) Van Wauwe, J.; Awouters, F.; Niemegeers, C. J. E.; Janssens, F.; Van Nueten, J. M.; Janssen, P. A. J. In vivo Pharmacology of Astemizole, a new type of H_1-antihistaminic Compound. *Arch. Int. Pharmocodyn. Ther*. **1981**, *251* (1), 39−51. (b) Awouters, F.; Niemegeers, C. J. E.; Janssen, P. A. J. Inhibitors of Mast Cell-

mediated shock in the Rat: Relationship to Histamine and Serotonin Antagonism. *Drug Dev. Res.* **1981**, *1* (2), 107−114.
(21) Awouters, F.; Niemegeers, C. J. E.; Janssen, P. A. J. Interaction of astemizole and other drugs with Passive Cutaeous Anaphylactic and histamine, serotonin, and compound 48/80-induced skin reactions in the rat. A procedure to determine anti-allergic effectiveness. *Drug Dev. Res.* **1985**, *5* (2), 137−145.
(22) Awouters, F.; Vermeire, J.; Smeyers, F.; Vermote, P.; Van Beek, R.; Niemegeers, C. J. E. Oral antiallergic activity in Ascaris hypersensitive dogs: A study of known antihistamines and of the new compounds ramastine (R57959) and levocabastine (R50547). *Drug Dev. Res.* **1986**, *8* (1−4), 95−102.
(23) Schotte, A.; Janssen, P. F. M.; Gommeren, W.; Luyten, W. H. M. L.; Van Gompel, P.; Lesage, A. S.; De Loore, K.; Leysen, J. E. Risperidone compared with new and reference antipsychotic drugs: In vitro and in vivo receptor binding. *Psychopharmacology* **1996**, *124* (1/2), 57−73.
(24) Ahnaou, A.; Megens, A. A. H. P.; Drinkenburg, W. H. I. M. The atypical antipsychotics risperidone, clozapine and olanzapine differ regarding their sedative potency in rats. *Neuropsychobiology* **2003**, *48* (1), 47−54.
(25) De Ponti, F.; Poluzzi, E.; Cavalli, A.; Recanatini, M.; Montanaro, N. Safety of nonantiarrhythmic drugs that prolong the QT interval or induce torsade de pointes: An overview. *Drug Saf.* **2002**, *25* (4), 263−286.
(26) Zhou, Z.; Vorperian, V. R.; Gong, Q.; Zhang, S.; January, C. T. Block of HERG potassium channels by the antihistamine astemizole and its metabolites desmethylastemizole and norastemizole. *J Cardiovasc. Electrophysiol.* **1999**, *10*, 836−843.
(27) Higuchi, T.; Connors, K. A. In *Advances in Analytical Chemistry and Instrumentation;* Reilly, C. N., Ed.; Wiley-Interscience: New York, 1995; Vol. 4, p 117.
(28) De Backer, M. D.; Gommeren, W.; Moereels, H.; Nobels, G.; Van Gompel, P.; Leysen, J. E.; Luyten, W. H. M. L. Genomic cloning, heterologous expression and pharmacological characterisation of a human histamine H_1 receptor. *Biochem. Biophys. Res. Commun.* **1993**, *197*, 1601−1608.
(29) Finney, D. J. *Probit analysis;* Cambridge University Press: Cambridge, 1962.

JM049495J