2-(4-Alkylpiperazin-1-yl)quinolines as a New Class of Imidazole-Free Histamine H_3 Receptor Antagonists

Florencio Zaragoza,* Henrik Stephensen, Bernd Peschke, and Karin Rimvall

Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Måløv, Denmark

Received August 19, 2004

With the aim of identifying structurally novel, centrally acting histamine H_3 antagonists, a series of 2-(4-alkylpiperazin-1-yl)quinolines was prepared. Systematic variation of the substituents led to highly potent histamine H_3 antagonists with low polar surface area and appropriate log *P* for blood−brain barrier penetration.

Introduction

The histamine H_3 receptor, discovered in 1983,[1] is a presynaptic autoreceptor mainly localized in the central nervous system that modulates the biosynthesis and release of histamine from histaminergic neurons.[2,3] The human,[4] rat,[5] mouse,[6] guinea pig,[7] and monkey[8] histamine H_3 receptors have recently been cloned, leading to renewed interest in histamine research. Because the histamine H_3 receptor is widely distributed in the central nervous system (CNS), either as autoreceptor on histaminergic neurons or as heteroreceptor on serotonergic,[9] cholinergic,[10] noradrenergic,[11] and dopaminergic[12] neurons, an important influence on physiological processes of centrally acting histamine H_3 receptor antagonists is to be anticipated. Centrally administered histamine H_3 antagonists lead to increased central histamine levels and may therefore be useful for the treatment of a variety of CNS disorders, such as attention deficit and hyperactivity disorder, cognitive disorders, schizophrenia, or obesity.[2,11b,13] The precise therapeutic potential of histamine H_3 antagonists remains, however, to be established.

Most of the early histamine H_3 receptor antagonists, identified by their functional activity or binding affinity in rodent tissue, were imidazole derivatives, such as thioperamide, ciproxifan, or clobenpropit (Chart 1).[2] After the successful cloning of the human histamine H_3 receptor, several examples of imidazole-free H_3 ligands have, however, been discovered,[14−19] such as the potent piperidine derivatives sketched in Chart 1.[15,19c]

We recently reported the discovery of a new class of histamine H_3 antagonists, namely 1-alkyl-4-acylpiperazines such as **1** (Chart 2).[20] Despite their high polar surface area (PSA), which is currently the most generally accepted descriptor for predicting the ability of compounds to cross the blood−brain barrier,[21] some of these acyl piperazines are able to reach the brain and lead to significant food-intake inhibition in rats at high doses.[22] Nevertheless, compounds with lower PSA, low molecular weight, and fewer rotatable bonds should show higher oral availability[23] and penetrate the blood−brain barrier more efficiently than piperazine amides as **1**.[21] Therefore, with the aim of identifying more potent histamine H_3 antagonists, suitable as orally available, centrally acting anorectics, we decided to explore other, less polar piperazine derivatives. Because aryl- or heteroarylpiperazine derivatives, such as clozapine (Chart 2),[24] efficiently cross the blood−brain barrier and also bind to rodent histamine H_3 receptors, we

Chart 1. Representative Histamine H_3 Receptor Antagonists and Antagonist Potencies at the Human Histamine H_3 Receptor

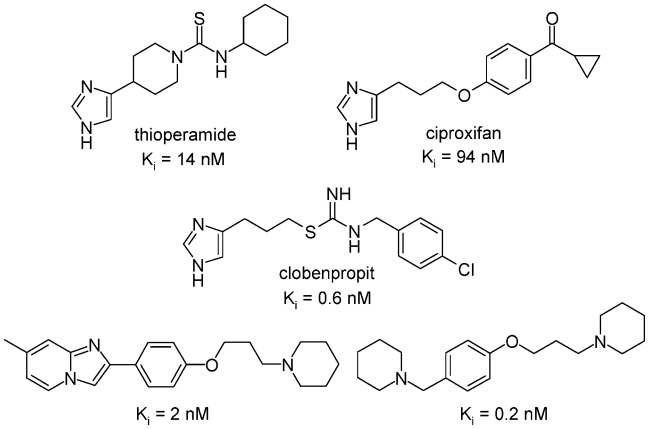
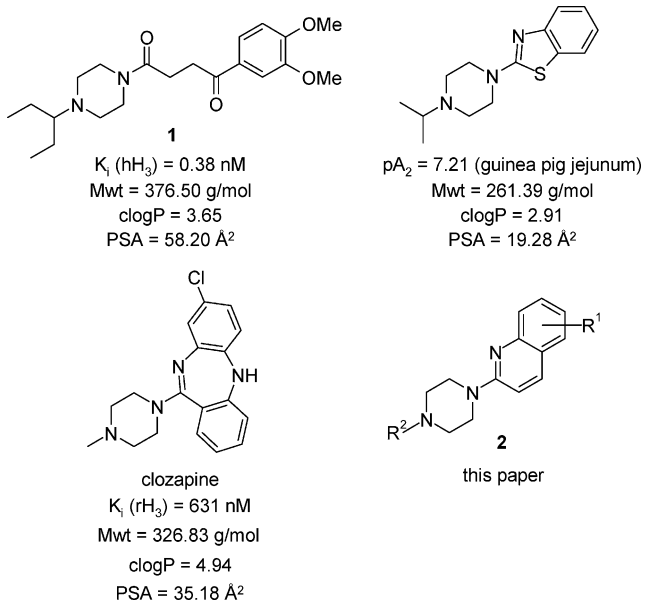


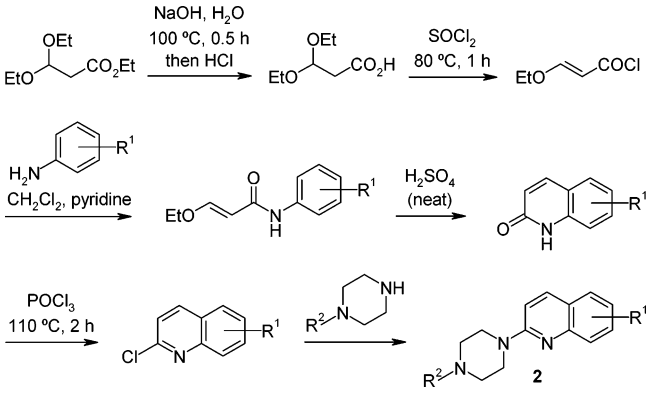
Chart 2. Piperazine Derivatives with Affinity and/or Antagonist Activity at Histamine H_3 Receptors[2,19b,20,27]



* To whom correspondence should be addressed. Phone: (+45) 4443 4828. Fax: (+45) 4466 3450 E-mail: flo@novonordisk.com.

10.1021/jm040873u CCC: $30.25
Published on Web 12/13/2004

Scheme 1. Synthesis of 2-(piperazin-1-yl)quinolines



decided to investigate 2-(1-piperazinyl)quinolines **2** as potential centrally acting histamine H_3 antagonists. Such quinoline derivatives would also be similarly small, as a closely related benzothiazolyl derivative described earlier (Chart 2), which showed weak H_3 antagonistic acitivity at rodent tissue.[19b] We considered quinoline derivatives **2** to be synthetically better accessible and to enable easier variation of the substituent pattern at the arene than benzothiazoles or dibenzodiazepines. Compounds **2** appeared, furthermore, particularly promising because some few 2-(1-piperazinyl)-quinolines had previously been investigated by others and shown to be orally available, centrally acting, nonselective serotonin receptor ligands[25] and serotonin reuptake inhibitors.[26] The affinity of these compounds for serotonin receptors usually drops off upon *N*-alkylation of the piperazine ring,[26b] and because in our series of piperazine amides (e.g. amide **1**) a bulky *N*-alkyl group was required for high binding affinity to the human H_3 receptor,[20] we did not anticipate our new histamine H_3 antagonists to interact significantly with serotonin receptors.

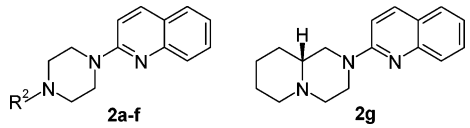
Chemistry

2-(1-Piperazinyl)quinolines **2** were prepared as sketched in Scheme 1. Commercially available ethyl 3,3-diethoxypropionate was saponified[28] and converted to 3-ethoxyacryloyl chloride by treatment with thionyl chloride.[29] Treatment of various anilines with this reagent yielded quantitatively the corresponding anilides, which were cyclized to quinolones by treatment with concentrated sulfuric acid.[30] These quinolones were heated with phosphorus oxychloride to yield 2-chloroquinolines, which were converted into the target compounds by treatment with various 1-alkylpiperazines.[26a,29] 1-Cyclopropylpiperazine was prepared as described earlier.[20] The bicyclic diamine required for the preparation of compound **2g** (see Table 1) was prepared from Boc-D-pipecolic acid as described by de Costa.[31]

When this reaction sequence was performed with 3-chloroaniline, the acid-mediated cyclization yielded a mixture of two isomeric quinolones (quantified by ^{1}H NMR, Scheme 2). The main 7-chloro isomer was obtained by recrystallization of the product mixture from acetic acid (see Experimental Section). No pure 5-substituted quinolones could be readily prepared by this methodology.

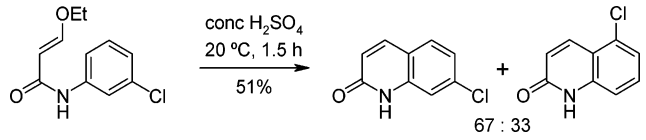
The quinolone required for the synthesis of compound **2m** (R^1 = 6-cyano) could not be prepared from 4-cyanoaniline; upon treatment of the corresponding 3-ethoxyacrylanilide with sulfuric acid (110 °C, 20 h), only water-soluble material was obtained, probably due to hydrolysis of the cyano group. The desired cyanoquinolone could, however, be obtained in good yield by aromatic nucleophilic substitution of bromide by cyanide at the corresponding bromoquinolone (Scheme 3). Similarly, this bromoquinolone, upon copper-catalyzed aromatic nucleophilic substitution with pyrazole, yielded 6-(pyrazol-1-yl)-2-quinolone (Scheme 3), which was used as intermediate for the preparation of compound **2o**. The cyanoquinoline **2m** was converted in low yields into ketones **2p** and **2q** by treatment with a large excess of the corresponding Grignard reagents at room temperature (Scheme 3).

Table 1. Antagonist Potency of Piperazinylquinolines **2a-g** at the Human H_3 Receptor, Determined by a Functional GTPγ[S]-Assay, and clogP[27] and PSA

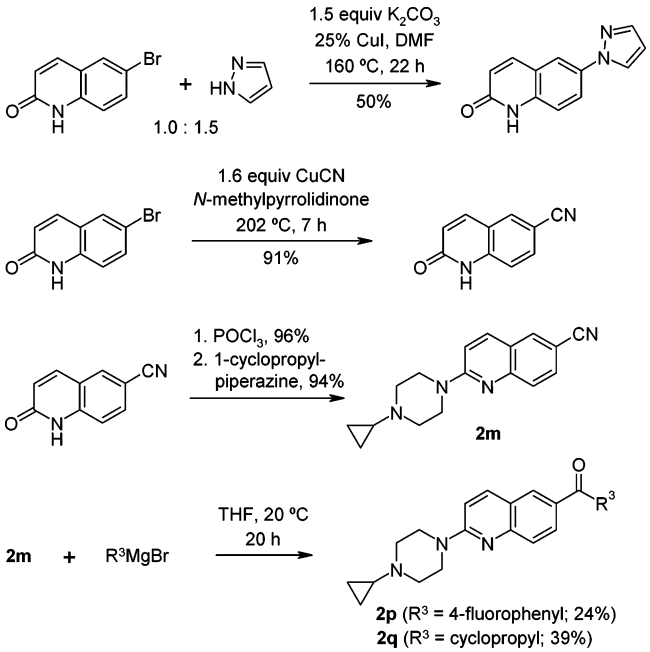


compd	R^2	clogP	PSA (Å^2)	K_i (nM) ±SEM (n)
2a	methyl	1.98	19.8	410 ± 37 (3)
2b	ethyl	2.51	18.9	6.0 ± 0.79 (3)
2c	isopropyl	2.82	18.5	6.8 ± 2.1 (3)
2d	3-pentyl	3.88	16.0	2.9 ± 0.88 (3)
2e	cyclopropyl	2.25	18.8	13 ± 0.33 (3)
2f	cyclopentyl	3.37	18.6	28 ± 5.5 (3)
2g	structure above	3.75	18.0	18 ± 1.3 (4)

Scheme 2



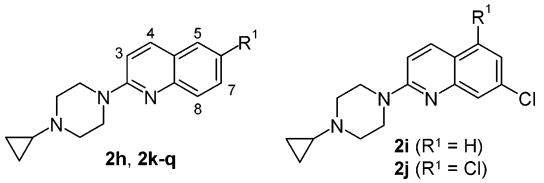
Scheme 3



Results and Discussion

Initially we sought to identify the optimal substituent R^2 for piperazinylquinolines **2** devoid of substituents at

Table 2. Antagonist Potency of Piperazinylquinolines **2h**−**q** at the Human H_3 Receptor, Determined by a Functional GTPγ[S]-Assay, and clogP[27] and PSA



compd	R^1	clogP	PSA (Å^2)	K_i (nM) +SEM (n)
2h	Cl	2.83	19.1	24 ± 7.2 (4)
2i	H	2.83	18.8	323 ± 74 (3)
2j	Cl	3.56	18.8	300 ± 58 (3)
2k	OMe	2.35	30.4	3.0 ± 0.6 (3)
2l	CF_3	3.04	19.1	52 ± 6 (3)
2m	cyano	1.62	41.0	4.8 ± 0.77 (4)
2n	cyclohexyl	4.68	19.1	33 ± 4.6 (3)
2o	1-pyrazolyl	2.86	35.6	1.1 ± 0.14 (3)
2p	4-FC_6H_4CO	3.55	39.2	110 ± 19 (4)
2q	cyclopropanoyl	2.14	36.9	1.8 ± 0.38 (3)

the heteroarene (R^1 = H; Table 1). Interestingly, the small increase of bulkiness of substituent R^2 when exchanging R^2 = methyl by R^2 = ethyl was sufficient to provide potent H_3 ligands. As in the series of acylpiperazines,[20] the 3-pentyl-substituted piperazine **2d** showed the highest potency at the human histamine H_3 receptor. Substituents R^2 containing heteroatoms (e.g. 2-methoxyethyl) led to inactive compounds.

Although the *N*-ethyl, *N*-isopropyl, or *N*-(3-pentyl) derivatives (**2b**−**d**) were rather potent, we decided to focus on *N*-cyclopropyl derivatives (**2e**), because cyclopropylamines are approximately 10 times less basic than normal aliphatic amines[20] and a higher fraction of nonprotonated amine at physiological pH should facilitate penetration of the blood−brain barrier. Thus, a series of 2-(4-cyclopropylpiperazin-1-yl)quinolines with different substituents at the heteroarene were prepared and tested (Table 2). Substituents at position 6 were generally well-tolerated, whereas substituents at position 7 (**2i**, **2j**) or at position 3, 4, 5, or 8 of the heteroarene (data not shown) consistently lowered the potency of these quinoline derivatives. Lipophilic substituents at position 6 (e.g. Cl or CF_3) led to weaker compounds than substitution with hydrogen, as did sterically very demanding substituents at this position (cyclohexyl, 4-fluorobenzoyl). Small, polar groups (OMe, CN, pyrazolyl, cyclopropanoyl), on the other hand, improved the potency of these compounds at the human H_3 receptor.

Selected compounds were also tested at serotonin, acetylcholine, and the other histamine receptors but showed no significant affinity to these. For instance, derivatives **2e** and **2q** did not bind to either the human 5-HT_2 receptor ([^{3}H]ketanserine binding; IC_{50} > 10 000 nM) or to the rat cortex muscarinic receptor ([^{3}H]-oxotremorine binding; IC_{50} > 10 000 nM), and **2q** did not bind to the human H_1 ([^{3}H]pyrilamine binding; IC_{50} > 1000 nM), H_2 ([^{125}I]aminopotentidine binding; IC_{50} > 10 000 nM), or H_4 ([^{3}H]histamine binding; IC_{50} > 10 000 nM) histamine receptors.

Conclusion

We have identified 2-(4-alkylpiperazin-1-yl)quinolines as a new class of potent antagonists at the human histamine H_3 receptor. The calculated PSA and clogP values suggest these compounds to be orally available and able to cross the blood−brain barrier efficiently. Because of their high potency, low molecular weight, few rotatable bonds, and appropriate PSA and clogP values, we expect that these quinoline derivatives will be better suited as CNS drugs than the acylpiperazines reported earlier, despite the higher in vitro potency of the acylpiperazines. Being cyclopropylamine derivatives, these new compounds are the least basic, imidazole-free H_3 antagonists reported until now. Further evaluation of these quinoline derivatives is currently in progress.

Experimental Section

Cloning and expression of the human histamine H_3 receptor and the [^{35}S]GTPγ[S] binding assay and data analysis were performed as described earlier.[20]

Compound affinities for the human 5-HT_2, H_1, H_2, and H_4 receptors were determined using conventional binding assays. Membranes from cells recombinantly expressing the respective receptor were used together with the selective radioligands [^{3}H]ketanserin, [^{3}H]pyrilamine, [^{125}I]aminopotentidine, and [^{3}H]histamine. The binding affinities of compounds for the rat muscarinic receptor were determined using rat cortical membranes and [^{3}H]oxotremorine as radioligand.

Chemistry. General Procedures. Melting points were determined with a B-545 melting point apparatus (Büchi) and are uncorrected. ^{1}H NMR spectra were recorded on a 300 MHz instrument. NMR signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broad. 2-(4-Methylpiperazin-1-yl)quinoline (*N*-methylquipazine), 1-methylpiperazine, 1-ethylpiperazine, 1-isopropylpiperazine, 1-(3-pentyl)piperazine, 1-cyclopentylpiperazine, 2-chloroquinoline, 2,6-dichloroquinoline, and 2-chloro-6-methoxyquinoline were commercially available, and were used without further purification. (*R*)-1,4-Diazabicyclo[4.4.0]octane was prepared as reported.[31]

3,3-Diethoxypropionic Acid.[28] A mixture of ethyl 3,3-diethoxypropionate (42.0 g, 0.22 mol), water (80 mL), and NaOH (11.0 g, 0.28 mol) was stirred at 110 °C for 0.5 h. The resulting clear solution was cooled to room temperature and acidified by careful addition of 12 M HCl (20 mL, approx 240 mmol). The product was extracted with AcOEt and CH_2Cl_2 (after each extraction the aqueous phase was acidified with HCl), and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield 30.3 g (85%) of the title acid: ^{1}H NMR (DMSO-d_6) δ 0.89 (t, J = 7 Hz, 6H), 2.29 (d, J = 7 Hz, 2H), 3.27 (m, 2H), 3.38 (m, 2H), 4.61 (t, J = 7 Hz, 1H), 12.05 (br s, 1H).

3-Ethoxyacryloyl Chloride.[29] To the crude 3,3-diethoxypropionic acid (32.0 g, 197 mmol) was slowly added thionyl chloride (70 mL), whereby strong gas evolution took place. The mixture was heated to 80 °C for 1 h and then concentrated carefully (T < 50 °C, 20 mbar). The remaining oil (31.0 g) was a mixture of the title compound and 3,3-diethoxypropanoyl chloride (84:16, ^{1}H NMR): ^{1}H NMR ($CDCl_3$, signals of title compound only) δ 1.40 (t, J = 7 Hz, 3H), 4.04 (q, J = 7 Hz, 2H), 5.51 (d, J = 12 Hz, 1H), 7.78 (d, J = 12 Hz, 1H).

General Procedure for the Preparation of Substituted 1*H*-2-Quinolones. 7-Chloro-2-quinolone.[30] A solution of the crude 3-ethoxyacryloyl chloride (approximately 84 mmol) in CH_2Cl_2 (40 mL) was added in portions to a stirred solution of 3-chloroaniline (7.72 g, 60.5 mmol) and pyridine (10 mL, 124 mmol) in CH_2Cl_2 (75 mL). After stirring at 20 °C overnight, water (300 mL) and 12 M HCl (10 mL, 120 mmol) were added, phases were separated, and the aqueous layer was extracted twice with AcOEt. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield crude *N*-(3-chlorophenyl)-3-ethoxyacrylamide (15.3 g) as a dark oil: ^{1}H NMR (DMSO-d_6) δ 1.28 (t, J = 7 Hz, 3H), 3.97 (q, J = 7 Hz, 2H), 5.51 (d, J = 12 Hz, 1H), 7.06 (m, 1H), 7.31 (t, J = 8 Hz, 1H), 7.42 (m, 1H), 7.50 (d, J = 12 Hz, 1H), 7.84 (m, 1H), 9.90 (s, 1H). To this product was added

concentrated sulfuric acid (95−97%, 80 mL, 0 °C), and the mixture was stirred at 20 °C for 1.5 h. The resulting mixture was poured into a mixture of water and ice (500 mL), and after stirring for 1 h, the product was isolated by filtration. The solid was dried by coevaporation with EtOH/MeCN/PhMe and then recrystallized from boiling MeCN (800 mL) to give 5.50 g (51%) of a mixture of 7-chloro-2-quinolone and 5-chloro-2-quinolone (67:33; ^{1}H NMR). Recrystallization of this mixture from boiling AcOH (200 mL) yielded 2.94 g (27%) of the title compound as needles: ^{1}H NMR (DMSO-d_6) δ 6.52 (d, J = 10 Hz, 1H), 7.21 (m, 1H), 7.32 (m, 1H), 7.69 (d, J = 9 Hz, 1H), 7.91 (d, J = 10 Hz, 1H), 11.84 (br s, 1H).

5,7-Dichloro-2-quinolone: yield 71%; ^{1}H NMR (DMSO-d_6) δ 6.66 (d, J = 10 Hz, 1H), 7.32 (d, J = 2 Hz, 1H), 7.47 (d, J = 2 Hz, 1H), 8.04 (d, J = 10 Hz, 1H), 12.05 (br s, 1H).

6-Trifluoromethyl-2-quinolone: yield 44%; ^{1}H NMR (DMSO-d_6) δ 6.63 (d, J = 10 Hz, 1H), 7.46 (d, J = 8 Hz, 1H), 7.81 (d, J = 8 Hz, 1H), 8.03 (d, J = 10 Hz, 1H), 8.13 (br s, 1H), 12.10 (br s, 1H).

6-Cyclohexyl-2-quinolone: yield 90%; ^{1}H NMR (DMSO-d_6) δ 1.15−1.50 (m, 5H), 1.65−1.89 (m, 6H), 6.46 (d, J = 10 Hz, 1H), 7.23 (d, J = 8 Hz, 1H), 7.38 (dd, J = 2 Hz, 8 Hz, 1H), 7.48 (d, J = 2 Hz, 1H), 7.86 (d, J = 10 Hz, 1H), 11.70 (br s, 1H).

6-Bromo-2-quinolone:[32] yield 64%; ^{1}H NMR (DMSO-d_6) δ 6.54 (d, J = 10 Hz, 1H), 7.24 (d, J = 8 Hz, 1H), 7.63 (dd, J = 2 Hz, 8 Hz, 1H), 7.88 (d, J = 10 Hz, 1H), 7.92 (d, J = 2 Hz, 1H), 11.85 (br s, 1H).

6-Cyano-2-quinolone. A mixture of 6-bromo-2-quinolone (9.18 g, 41.0 mmol), *N*-methyl-2-pyrrolidinone (32 mL), and CuCN (5.90 g, 65.9 mmol) was stirred at 20 °C overnight and then at reflux temperature (202 °C) for 7 h. The mixture was poured into water (250 mL) and filtered, and the solid was washed twice with water. The solid was then mixed with 1 N HCl (300 mL) and $FeCl_3$·6 H_2O (32.5 g, 120 mmol) and stirred at 20 °C for 3 d. The mixture was filtered, and the solid was washed twice with water, coevaporated with EtOH, and dried under reduced pressure to give 6.37 g (91%) of the title compound: ^{1}H NMR (DMSO-d_6) δ 6.63 (dd, J = 2 Hz, 10 Hz, 1H), 7.40 (d, J = 8 Hz, 1H), 7.88 (dd, J = 2 Hz, 10 Hz, 1H), 7.94 (d, J = 8 Hz, 1H), 8.24 (d, J = 2 Hz, 1H), 12.13 (br s, 1H).

6-(1-Pyrazolyl)-2-quinolone. A mixture of 6-bromo-2-quinolone (3.58 g, 16.0 mmol), DMF (15 mL), pyrazole (1.66 g, 24.4 mmol), K_2CO_3 (3.33 g, 24.1 mmol), and CuI (0.76 g, 3.99 mmol) was stirred at 160 °C for 22 h. The mixture was poured into water (300 mL) and the product was isolated by filtration. After washing with water the solid was coevaporated with EtOH and then heated to reflux in a mixture of EtOH (50 mL) and MeCN (50 mL). After standing at 20 °C overnight the product was filtered off, washed with MeCN, and dried under reduced pressure to yield 1.7 g (50%) of the title compound as a green solid: ^{1}H NMR (DMSO-d_6) δ 6.50−6.68 (m, 2H), 7.39 (br s, 1H), 7.74 (br s, 1H), 7.97 (br s, 2H), 8.12 (br s, 1H), 8.47 (br s, 1H), 11.85 (br s, 1H).

General Procedure for the Preparation of Substituted 2-Chloroquinolines. 2-Chloro-6-trifluoromethylquinoline.[33] A mixture of 6-trifluoromethyl-2-quinolone (3.59 g, 16.8 mmol) and $POCl_3$ (30 mL) was stirred at 110 °C for 2 h and then at 20 °C overnight. The mixture was carefully poured into a mixture of water and ice (400 mL) while being stirred energetically. The product was isolated by filtration and dried by coevaporation with MeCN/PhMe to yield 3.52 g (91%) of the title compound as yellow solid: ^{1}H NMR (DMSO-d_6) δ 7.78 (d, J = 8 Hz, 1H), 8.08 (m, 1H), 8.17 (m, 1H), 8.61 (br s, 1H), 8.67 (d, J = 8 Hz, 1H).

2,7-Dichloroquinoline:[34] yield 76%; ^{1}H NMR (DMSO-d_6) δ 7.65 (d, J = 9 Hz, 1H), 7.72 (d, J = 9 Hz, 1H), 8.05 (br s, 1H), 8.12 (d, J = 9 Hz, 1H), 8.51 (d, J = 9 Hz, 1H).

2,5,7-Trichloroquinoline: yield 67%; ^{1}H NMR (DMSO-d_6) δ 7.78 (d, J = 9 Hz, 1H), 8.03 (br s, 1H), 8.09 (d, J = 2 Hz, 1H), 8.59 (d, J = 9 Hz, 1H).

2-Chloro-6-cyanoquinoline: yield 80%; ^{1}H NMR (DMSO-d_6) δ 7.78 (d, J = 9 Hz, 1H), 8.12 (m, 2H), 8.58 (d, J = 9 Hz, 1H), 8.73 (s, 1H).

2-Chloro-6-cyclohexylquinoline: yield 56%; ^{1}H NMR (DMSO-d_6) δ 1.27 (m, 1H), 1.35−1.55 (m, 4H), 1.73 (m, 1H), 1.85 (m, 4H), 2.71 (m, 1H), 7.55 (d, J = 9 Hz, 1H), 7.73 (dd, J = 2 Hz, 9 Hz, 1H), 7.84 (br s, 1H), 7.88 (d, J = 9 Hz, 1H), 8.38 (d, J = 9 Hz, 1H).

2-Chloro-6-pyrazol-1-ylquinoline: yield 81%; ^{1}H NMR (DMSO-d_6) δ 6.64 (t, J = 2 Hz, 1H), 7.66 (d, J = 9 Hz, 1H), 7.85 (d, J = 2 Hz, 1H), 8.08 (d, J = 9 Hz, 1H), 8.38 (dd, J = 2 Hz, 9 Hz, 1H), 8.51 (m, 2H), 8.69 (d, J = 2 Hz, 1H).

General Procedure for the Preparation of 2-(4-Alkylpiperazin-1-yl)quinolines. 2-(4-Cyclopropylpiperazin-1-yl)-6-pyrazol-1-ylquinoline Dihydrochloride (2o). A mixture of 1-cyclopropylpiperazine (0.25 g, 1.98 mmol), 2-chloro-6-pyrazol-1-ylquinoline (0.23 g, 1.00 mmol), and propionitrile (1.0 mL) was stirred at 95 °C for 20 h. More 1-cyclopropylpiperazine (0.25 g) was added and heating was continued for 24 h. Saturated aqueous $NaHCO_3$ (50 mL) was added and the product was extracted with AcOEt. The combined extracts were washed twice with water and then extracted with 0.1 M HCl (25 mL). The acidic aqueous extract was concentrated under reduced pressure, and the residue was coevaporated once with EtOH and then recrystallized from EtOH to give 225 mg (57%) of the title compound as a yellow solid: mp 315−329 °C; ^{1}H NMR (DMSO-d_6) δ 0.83 (m, 2H), 1.22 (m, 2H), 2.88 (m, 1H), 3.30−3.80 (m, 6H), 4.79 (m, 2H), 6.61 (m, 1H), 7.59 (d, J = 6 Hz, 1H), 7.81 (s, 1H), 8.10−8.30 (m, 2H), 8.34 (s, 1H), 8.41 (d, J = 6 Hz, 1H), 8.59 (s, 1H), 11.47 (br s, 1H); HPLC-MS m/z 320 (MH^+). Anal. ($C_{19}H_{21}N_5$·2HCl·0.25H_2O) C, H, N.

2-(4-Ethylpiperazin-1-yl)quinoline dihydrochloride (2b): yield 100%; mp 290 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 1.31 (t, J = 7 Hz, 3H), 3.16 (m, 4H), 3.60−3.80 (m, 4H), 4.82 (m, 2H), 7.47 (m, 1H), 7.54 (m, 1H), 7.74 (m, 1H), 7.90 (m, 1H), 8.15 (m, 1H), 8.41 (m, 1H), 11.35 (br s, 1H); HPLC-MS m/z 242 (MH^+). Anal. ($C_{15}H_{19}N_3$·2HCl) C, H, N.

2-(4-Isopropylpiperazin-1-yl)quinoline dihydrochloride (2c): yield 50%; mp 271−274 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 1.31 (d, J = 7 Hz, 6H), 3.19 (m, 2H), 3.52 (m, 3H), 3.72 (m, 2H), 4.79 (m, 2H), 7.45 (m, 2H), 7.68 (m, 1H), 7.86 (m, 1H), 8.03 (m, 1H), 8.31 (m, 1H), 11.45 (br s, 1H); HPLC-MS m/z 256 (MH^+). Anal. ($C_{16}H_{21}N_3$·2HCl) C, H, N.

2-[4-(1-Ethylpropyl)piperazin-1-yl]quinoline dihydrochloride (2d): yield 48%; mp 260−263 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 0.99 (t, J = 7 Hz, 6H), 1.65 (m, 2H), 1.94 (m, 2H), 3.12 (br s, 1H), 3.33 (m, 2H), 3.57 (m, 2H), 3.93 (m, 2H), 4.83 (m, 2H), 7.44−7.58 (m, 2H), 7.76 (m, 1H), 7.92 (m, 1H), 8.25 (br s, 1H), 8.42 (m, 1H), 11.20 (br s, H); HPLC-MS m/z 284 (MH^+). Anal. ($C_{18}H_{25}N_3$·2HCl·H_2O) C, H, N.

2-(4-Cyclopropylpiperazin-1-yl)quinoline dihydrochloride (2e): yield 16%; mp 240−242 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 0.83 (m, 2H), 1.19 (m, 2H), 2.87 (br s, 1H), 3.30−3.80 (m, 6H), 4.74 (m, 2H), 7.45 (m, 1H), 7.52 (d, J = 8 Hz, 1H), 7.73 (m, 1H), 7.89 (d, J = 8 Hz, 1H), 8.02 (br s, 1H), 8.38 (m, 1H), 11.22 (br s, 1H); HPLC-MS m/z 254 (MH^+). Anal. ($C_{16}H_{19}N_3$·2HCl·H_2O) C, H, N.

2-(4-Cyclopentylpiperazin-1-yl)quinoline dihydrochloride (2f): yield 13%; mp 272−275 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 1.62 (m, 2H), 1.82 (m, 2H), 1.96 (m, 2H), 2.09 (m, 2H), 3.25 (m, 2H), 3.55−3.70 (m, 5H), 4.83 (m, 2H), 7.46−7.60 (m, 2H), 7.80 (m, 1H), 7.94 (m, 1H), 8.13 (m, 1H), 8.42 (m, 1H), 11.52 (br s, 1H); HPLC-MS m/z 282 (MH^+). Anal. ($C_{18}H_{23}N_3$·2HCl·H_2O) C, H, N.

(9a*R*)-2-Quinolin-2-yloctahydropyrido[1,2-*a*]pyrazine dihydrochloride (2g): yield 59%; mp 302−304 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 1.40−1.55 (m, 1H), 1.65−2.10 (m, 5H), 2.92 (m, 1H), 3.25 (m, 1H), 3.35−3.90 (m, 5H), 4.90 (m, 2H), 7.49 (m, 1H), 7.59 (d, J = 8 Hz, 1H), 7.77 (m, 1H), 7.92 (d, J = 8 Hz, 1H), 8.32 (br s, 1H), 8.46 (m, 1H), 11.69 (br s, 1H); HPLC-MS m/z 268 (MH^+). Anal. ($C_{17}H_{21}N_3$·2HCl·1.5 H_2O) C, H, N.

6-Chloro-2-(4-cyclopropylpiperazin-1-yl)quinoline dihydrochloride (2h): yield 16%; mp 234−235 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 0.81 (m, 2H), 1.14 (br s, 2H), 2.88 (br s, 1H), 3.25−3.70 (m, 6H), 4.67 (m, 2H), 7.44 (d, J = 8 Hz, 1H),

7.61 (d, J = 8 Hz, 1H), 7.72 (m, 1H), 7.91 (br s, 1H), 8.18 (br d, J = 8 Hz, 1H), 10.75 (br s, 1H); HPLC-MS *m/z* 288 (MH^+). Anal. ($C_{16}H_{18}ClN_3 \cdot 2HCl \cdot 1.75H_2O$) C, H, N.

7-Chloro-2-(4-cyclopropylpiperazin-1-yl)quinoline dihydrochloride (2i): yield 46%; mp 257−259 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 0.82 (m, 2H), 1.20 (m, 2H), 2.87 (br s, 1H), 3.25−3.75 (m, 6H), 4.72 (m, 2H), 7.40 (d, J = 8 Hz, 1H), 7.46 (d, J = 8 Hz, 1H), 7.87 (d, J = 8 Hz, 1H), 7.94 (br s, 1H), 8.29 (d, J = 8 Hz, 1H), 11.29 (br s, 1H); HPLC-MS *m/z* 288 (MH^+). Anal. ($C_{16}H_{18}ClN_3 \cdot 2HCl \cdot H_2O$) C, H, N.

5,7-Dichloro-2-(4-cyclopropylpiperazin-1-yl)quinoline dihydrochloride (2j): yield 46%; mp 283−291 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 0.82 (m, 2H), 1.19 (m, 2H), 2.86 (m, 1H), 3.20−3.65 (m, 6H), 4.69 (m, 2H), 7.51 (d, J = 8 Hz, 1H), 7.56 (s, 1H), 7.68 (s, 1H), 8.30 (d, J = 8 Hz, 1H), 11.24 (br s, 1H); HPLC-MS *m/z* 322 (MH^+). Anal. ($C_{16}H_{17}Cl_2N_3 \cdot 2HCl$) C, H, N.

2-(4-Cyclopropylpiperazin-1-yl)-6-methoxyquinoline dihydrochloride (2k): yield 20%; mp 249−251 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 0.81 (m, 2H), 1.20 (br s, 2H), 2.86 (br s, 1H), 3.25−3.75 (m, 4H), 3.85 (s, 3H), 4.09 (m, 2H), 4.73 (m, 2H), 7.41 (m, 2H), 7.55 (m, 1H), 8.14 (m, 1H), 8.37 (m, 1H), 11.51 (br s, 1H); HPLC-MS *m/z* 284 (MH^+). Anal. ($C_{17}H_{21}N_3O \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

2-(4-Cyclopropylpiperazin-1-yl)-6-(trifluoromethyl)-quinoline dihydrochloride (2l): yield 16%; mp 230−232 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 0.81 (m, 2H), 1.19 (br s, 2H), 2.88 (br s, 1H), 3.25−3.65 (m, 6H), 4.77 (m, 2H), 7.53 (d, J = 8 Hz, 1H), 7.88 (m, 2H), 8.26 (br s, 1H), 8.37 (br d, J = 8 Hz, 1H), 11.12 (br s, 1H); HPLC-MS *m/z* 322 (MH^+). Anal. ($C_{17}H_{18}F_3N_3 \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

2-(4-Cyclopropylpiperazin-1-yl)quinoline-6-carbonitrile dihydrochloride (2m): yield 51%; mp 280−283 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 0.83 (m, 2H), 1.15 (m, 2H), 2.87 (br s, 1H), 3.20−3.65 (m, 6H), 4.74 (m, 2H), 7.49 (d, J = 8 Hz, 1H), 7.72 (d, J = 8 Hz, 1H), 7.86 (d, J = 8 Hz, 1H), 8.24 (d, J = 8 Hz, 1H), 8.35 (s, 1H), 10.88 (br s, 1H); HPLC-MS *m/z* 279 (MH^+). Anal. ($C_{17}H_{18}N_4 \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

6-Cyclohexyl-2-(4-cyclopropylpiperazin-1-yl)quinoline dihydrochloride (2n): yield 28%; mp 286−293 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 0.83 (m, 2H), 1.10−1.55 (m, 8H), 1.70−1.93 (m, 4H), 2.65 (m, 1H), 2.86 (m, 1H), 3.30−3.70 (m, 6H), 4.72 (m, 2H), 7.50 (m, 1H), 7.66 (m, 1H), 7.72 (m, 1H), 7.99 (br s, 1H), 8.35 (br s, 1H), 11.29 (br s, 1H); HPLC-MS *m/z* 336 (MH^+). Anal. ($C_{22}H_{29}N_3 \cdot 2HCl \cdot 0.25H_2O$) C, H, N.

[2-(4-Cyclopropylpiperazin-1-yl)quinolin-6-yl](4-fluorophenyl)methanone Dihydrochloride (2p). To a solution of 2-(4-cyclopropylpiperazin-1-yl)quinoline-6-carbonitrile (0.21 g, 0.75 mmol) in THF (5.0 mL) was added a solution of 4-fluorophenylmagnesium bromide in Et_2O (3.75 mL, 2 M, 7.5 mmol), and the mixture was stirred at 20 °C overnight. Water and 1 N HCl were added until the mixture was acidic, followed by the addition of saturated aqueous $NaHCO_3$. The product was extracted with AcOEt and purified by preparative HPLC. Conversion to the dihydrochloride by coevaporation with dilute HCl and EtOH yielded 80 mg (24%) of the title compound as colorless solid: mp 255−257 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 0.84 (m, 2H), 1.14 (m, 2H), 2.89 (m, 1H), 3.25−3.90 (m, 6H), 4.77 (m, 2H), 7.44 (m, 3H), 7.76 (m, 1H), 7.86 (m, 2H), 7.98 (m, 1H), 8.21 (s, 1H), 8.34 (d, J = 8 Hz, 1H), 10.65 (br s, 1H); HPLC-MS *m/z* 376 (MH^+). Anal. ($C_{23}H_{22}FN_3O \cdot 2HCl$) C, H, N.

Cyclopropyl[2-(4-cyclopropylpiperazin-1-yl)quinolin-6-yl]methanone Hydrochloride (2q). Cyclopropylmagnesium bromide was prepared from magnesium (6.68 g, 275 mmol) and cyclopropyl bromide (18.4 mL, 230 mmol) in THF (145 mL). To the freshly prepared Grignard reagent at 12 °C was added a solution of 2-(4-cyclopropylpiperazin-1-yl)quinoline-6-carbonitrile (4.25 g, 15.3 mmol) in THF (70 mL) and the resulting mixture was stirred at 20 °C for 5 h. Water and ice (200 mL) were carefully added, followed by acidification with 6 M HCl. After stirring for 20 min, CH_2Cl_2 (200 mL) was added, and the pH was adjusted to 8.5 with aqueous 4 M NaOH. The mixture was filtered, phases were separated, and the aqueous phase was extraced twice with CH_2Cl_2. The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel; elution with PhMe/AcOEt), followed by conversion to the dihydrochloride by coevaporation with dilute HCl and recrystallization from EtOH to yield 2.49 g (39%) of the title compound: mp 241−243 °C; ^{1}H NMR (DMSO-d_6) δ 0.83 (m, 2H), 1.07 (m, 4H), 1.18 (m, 2H), 2.88 (m, 1H), 3.00 (quint, J = 7 Hz, 1H), 3.30−3.70 (m, 6H), 4.76 (m, 2H), 7.50 (d, J = 8 Hz, 1H), 7.82 (br s, 1H), 8.18 (d, J = 8 Hz, 1H), 8.37 (d, J = 8 Hz, 1H), 8.66 (s, 1H), 11.05 (br s, 1H); HPLC-MS *m/z* 322 (MH^+). Anal. ($C_{20}H_{23}N_3O \cdot 2HCl \cdot H_2O$) C, H, N.

Acknowledgment. The excellent technical assistance by Rita Nielsen, Vivian Lind Tychsen, Marianne Lambert Jacobsen, and Bent Kolling is gratefully acknowledged. We also thank Birgitte S. Wulff, Dorthe Viuff, Ingrid Viveka Pettersson, Sanne Møller Knudsen, Knud Erik Andersen, and Rolf Hohlweg for stimulating discussions.

Supporting Information Available: Elemental analyses for **2b**−**q**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Arrang, J. M.; Garbarg, M.; Schwartz, J.-C. Auto-inhibition of brain histamine release mediated by a novel class (H_3) of histamine receptors. *Nature* **1983**, *302*, 832−837.
(2) Stark, H.; Schlicker, E.; Schunack, W. Developments of histamine H_3 receptor antagonists. *Drugs Future* **1996**, *21*, 507−520.
(3) Wulff, B. S.; Hastrup, S.; Rimvall, K. Characteristics of recombinantly expressed rat and human histamine H_3 receptors. *Eur. J. Pharm.* **2002**, *453*, 33−41.
(4) Lovenberg, T. W.; Roland, B. L.; Wilson, S. J.; Jiang, X. X.; Pyati, J.; Huvar, A.; Jackson, M. R.; Erlander, M. G. Cloning and functional expression of the human histamine H_3 receptor. *Mol. Pharmacol.* **1999**, *55*, 1101−1107.
(5) Lovenberg, T. W.; Pyati, J.; Chang, H.; Wilson, S. J.; Erlander, M. G. Cloning of rat histamine H_3 receptor reveals distinct species pharmacological profiles. *J. Pharm. Exp. Ther.* **2000**, *293*, 771−778.
(6) Chen, J.; Liu, C.; Lovenberg, T. W. Molecular and pharmacological characterization of the mouse histamine H_3 receptor. *Eur. J. Pharmacol.* **2003**, *467*, 57−65.
(7) Tardivel-Lacombe, J.; Rouleau, A.; Héron, A.; Morisset, S.; Pillot, C.; Cochois, V.; Schwartz, J.-C.; Arrang, J.-M. Cloning and cerebral expression of the guinea pig histamine H_3 receptor: Evidence for two isoforms. *Neuroreport* **2000**, *11*, 755−759.
(8) Yao, B. B.; Sharma, R.; Cassar, S.; Esbenshade, T. A.; Hancock, A. A. Cloning and pharmacological characterization of the monkey histamine H_3 receptor. *Eur. J. Pharmacol.* **2003**, *482*, 49−60.
(9) Fink, K.; Schlicker, E.; Neise, A.; Gothert, M. Involvment of presynaptic H_3 receptors in the inhibitory effect of histamine on serotonin release in the rat brain cortex. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1990**, *342*, 513−519.
(10) Clapham, J.; Kilpatrick, G. J. Histamine H_3 receptors modulate the release of [^{3}H]-acetylcholine from slices of rat entorhinal cortex: Evidence for the possible existence of H_3 receptor subtypes. *Br. J. Pharmacol.* **1992**, *107*, 919−923.
(11) (a) Molderings, G. J.; Weibenborn, G.; Schlicker, E.; Likungu, J.; Gothert, M. Inhibition of noradrenaline release from the sympathetic nerves of the human saphenous vein by presynaptic histamine H_3 receptors. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1992**, *346*, 46−50. (b) Kurose, Y.; Terashima, Y. Histamine regulates food intake through modulating noradrenaline release in the para-ventricular nucleus. *Brain Res.* **1999**, *828*, 115−118.
(12) Schlicker, E.; Fink, K.; Detzner, M.; Gothert, M. Histamine inhibits dopamine release in the mouse striatum via presynaptic H_3 receptors. *J. Neural. Transm. Gen. Sect.* **1993**, *93*, 1−10.
(13) Masaki, T.; Chiba, S.; Yoshimichi, G.; Yasuda, T.; Noguchi, H.; Kakuma, T.; Sakata, T.; Yoshimatsu, H. Neuronal histamine regulates food intake, adiposity, and uncoupling protein expression in Agouti yellow (*A^y/a*) obese mice. *Endocrinology* **2003**, *144*, 2741−2748.
(14) (a) Faghih, R.; Dwight, W.; Pan, J. B.; Fox, G. B.; Krueger, K. M.; Esbenshade, T. A.; McVey, J. M.; Marsh, K.; Bennani, Y. L.; Hancock, A. A. Synthesis and SAR of aminoalkoxybiaryl-4-carboxamides: Novel and selective histamine H_3 receptor antagonists. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1325−1328. (b) Hancock, A. A.; Bennani, Y. L.; Bush, E. N.; Esbenshade, T. A.;

Faghih, R.; Fox, G. B.; Jacobson, P.; Knourek-Segel, V.; Krueger, K. M.; Nuss, M. E.; Pan, J. B.; Shapiro, R.; Witte, D. G.; Yao, B. B. Antiobesity effects of A-331440, a novel nonimidazole histamine H_3 receptor antagonist. *Eur. J. Pharmacol.* **2004**, *487*, 183−197.

(15) Chai, W.; Breitenbucher, J. G.; Kwok, A.; Li, X.; Wong, V.; Carruthers, N. I.; Lovenberg, T. W.; Mazur, C.; Wilson, S. J.; Axe, F. U.; Jones, T. K. Non-imidazole heterocyclic histamine H_3 receptor antagonists. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1767−1770.

(16) Mikó, T.; Ligneau, X.; Pertz, H. H.; Gannelin, C. R.; Arrang, J.-M.; Schwartz, J.-C.; Schunack, W.; Stark, H. Novel nonimidazole histamine H_3 receptor antagonists: 1-(4-(Phenoxymethyl)benzyl)piperidines and related compounds. *J. Med. Chem.* **2003**, *46*, 1523−1530.

(17) Linney, I. D.; Buck, I. M.; Harper, E. A.; Kalindjian, S. B.; Pether, M. J.; Shankley, N. P.; Watt, G. F.; Wright, P. T. Design, synthesis, and structure−activity relationships of novel nonimidazole histamine H_3 receptor antagonists. *J. Med. Chem.* **2000**, *43*, 2362−2370.

(18) Gannelin, C. R.; Leurquin, F.; Piripitsi, A.; Arrang, J.-M.; Garbarg, M.; Ligneau, X.; Schunack, W.; Schwartz, J.-C. Synthesis of potent nonimidazole histamine H_3 receptor antagonists. *Arch. Pharm. (Weinheim, Ger.)* **1998**, *331*, 395−404.

(19) (a) Walczynski, K.; Guryn, R.; Zuiderveld, O. P.; Timmerman, H. Nonimidazole histamine H_3 ligands. Part 1. Synthesis of 2-(1-piperazinyl)- and 2-(hexahydro-1*H*-1,4-diazepin-1-yl)benzothiazole derivatives as H_3-antagonists with H_1 blocking activities. *Farmaco* **1999**, *54*, 684−694. (b) Walczynski, K.; Guryn, R.; Zuiderveld, O. P.; Timmerman, H. Nonimidazole histamine H_3 ligands. Part 2: New 2-substituted benzothiazoles as histamine H_3 antagonists. *Arch. Pharm. (Weinheim, Ger.)* **1999**, *332*, 389−398. (c) Apodaca, R.; Dvorak, C. A.; Xiao, W.; Barbier, A. J.; Boggs, J. D.; Wilson, S. J.; Lovenberg, T. W.; Carruthers, N. I. A new class of diamine-based human histamine H_3 receptor antagonists: 4-(Aminoalkoxy)benzylamines. *J. Med. Chem.* **2003**, *46*, 3938−3944. (d) Peschke, B.; Bak, S.; Hohlweg, R.; Pettersson, I.; Refsgaard, H. H. F.; Viuff, D.; Rimvall, K. Cinnamic amides of (*S*)-2-(aminomethyl)pyrrolidines are potent H_3 antagonists. *Bioorg. Med. Chem.* **2004**, *12*, 2603−2616.

(20) Zaragoza, F.; Stephensen, H.; Knudsen, S. M.; Pridal, L.; Wulff, B. S.; Rimvall, K. 1-Alkyl-4-acylpiperazines as a new class of imidazole-free histamine H_3 receptor antagonists. *J. Med. Chem.* **2004**, *47*, 2833−2838.

(21) (a) Kelder, J.; Grootenhuis, P. D. J.; Bayada, D. M.; Delbressine, L. P. C.; Ploemen, J.-P. Polar molecular surface as a dominating determinant for oral absorption and brain penetration of drugs. *Pharm. Res.* **1999**, *16*, 1514−1519. (b) Van de Waterbeemd, H.; Camenisch, G.; Folkers, G.; Chretien, J. R.; Raevsky, O. A. Estimation of blood-brain barrier crossing of drugs using molecular size and shape, and H-bonding descriptors. *J. Drug Target.* **1998**, *6*, 151−165.

(22) Malmlöf, K.; Zaragoza, F.; Golozoubova, V.; Refsgaard, H. H. F.; Cremers, T.; Rømer, J.; Raun, K.; Wulff, B. S.; Johansen, P. B.; Westerink, B.; Rimvall, K. Influence of a selective histamine H_3 receptor antagonist on hypothalamic neural activity, food intake and body weight. Submitted for publication.

(23) (a) Wenlock, M. C.; Austin, R. P.; Barton, P.; Davis, A. M.; Leeson, P. D. A comparison of physiochemical property profiles of development and marketed oral drugs. *J. Med. Chem.* **2003**, *46*, 1250−1256. (b) Veber, D. F.; Johnson, S. R.; Cheng, H.-Y., Smith, B. R.; Ward, K. W.; Kopple, K. D. Molecular properties that influence the oral bioavailability of drug candidates. *J. Med. Chem.* **2002**, *45*, 2615−2623.

(24) Baldessarini, R. J.; Frankenburg, F. R. Clozapine, a novel antipsychotic agent. *New Engl. J. Med.* **1991**, *324*, 746−754.

(25) (a) Dukat, M.; Abdel-Rahman, A. A.; Ismaiel, A. M.; Ingher, S.; Teitler, M.; Gyermek, L.; Glennon, R. A. Structure−activity relationships for the binding of arylpiperazines and arylbiguanides at 5-HT_3 serotonin receptors. *J. Med. Chem.* **1996**, *39*, 4017−4026. (b) Glennon, R. A.; Slusher, R. M.; Lyon, R. A.; Teitler, M.; McKenney, J. D. 5-HT_1 and 5-HT_2 binding characteristics of some quipazine analogues. *J. Med. Chem.* **1986**, *29*, 2375−2380.

(26) (a) Lee, B. S.; Chu, S.; Lee, B. C.; Chi, D. Y.; Choe, Y. S.; Jeong, K. J.; Jin, C. Syntheses and binding affinities of 6-nitroquipazine analogues for the serotonin transporter. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1559−1562. (b) Mathis, C. A.; Taylor, S. E.; Enas, J. D.; Akgün, E. Binding potency of 6-nitroquipazine analogues for the 5-hydroxytryptamine reuptake complex. *J. Pharm. Pharmacol.* **1994**, *46*, 751−754. (c) Mebius, E. J. Farmacologisch werkzame 2-(1-piperazinyl)-chinolinederivaten. NL Patent 7904723, 1979. For instance, 2-(1-piperazinyl)quinoline (quipazine) shows an in vitro inhibition binding constant (displacement of [^{3}H]paroxetin, K_i) at rat cortex of 68 ± 18 nM.[26b]

(27) clogP: Pomona college log *P* (water/octanol partition coefficient), calculated with version 4.0 of the clogP algorithm (included in Sybyl 6.6, Tripos Inc.) and version 18 of its associated fragment database, provided by BioByte Corp. PSA: polar surface area, calculated with SAVol 3.7, developed by R. S. Pearlman, J. M. Skell, and F. Deanda, Laboratory for Molecular Graphics and Theoretical Modeling, College of Pharmacy, University of Texas, Austin, TX 78712. Polar atoms are oxygen, nitrogen, and hydrogen attached to oxygen or nitrogen.

(28) Valade, A.-G.; Dugat, D.; Jeminet, G.; Royer, J.; Husson, H.-P. Structural features in the seven-membered vs fourteen-membered ring cyclization of hydroxyamido ketals derived from β-amino alcohols. *Eur. J. Org. Chem.* **2001**, 2041−2053.

(29) Janiak, C.; Deblon, S.; Uehlin, L. Synthesis of 6,6′-diamino-2, 2′-biquinoline and 2, 2′-bi-1,6-naphthyridine. *Synthesis* **1999**, 959−964.

(30) Effenberger, F.; Hartmann, W.; Synthesen mit β-Äthoxyacrylsäurechloriden. *Chem. Ber.* **1969**, *102*, 3260−3267.

(31) de Costa, B. R.; He, X.-S.; Linders, J. T. M.; Dominguez, C.; Gu, Z. Q.; Williams, W.; Bowen, W. D. Synthesis and evaluation of conformationally restricted *N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(1-pyrrolidinyl)ethylamines at σ receptors. 2. Piperazines, bicyclic amines, bridged bicyclic amines, and miscellaneous compounds. *J. Med. Chem.* **1993**, *36*, 2311−2320. The optical purity of (*R*)-1,4-diazabicyclo[4.4.0]decane was determined to be >90% by acylation with (*S*)-*N*-Boc-valine followed by HPLC-analysis.

(32) Osborne, A. G.; Miller, L. A. D. Regioselective alkoxydehalogenation of 2,4-dihalogenoquinolines and a reinvestigation of the bromination of 2-methoxyquinoline. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 181−184.

(33) Lee, B. S.; Lee, J. H.; Chi, D. Y. Novel synthesis of 2-chloroquinolines from 2-vinylanilines in nitrile solvent. *J. Org. Chem.* **2002**, *67*, 7884−7886.

(34) Hazeldine, S. T.; Polin, L.; Kushner, J.; White, K.; Bouregeois, N. M.; Crantz, B.; Palomino, E.; Corbett, T. H.; Horwitz, J. P. Synthesis and biological evaluation of some bioisosteres and congeners of the antitumor agent, 2-{4-[(7-chloro-2-quinoxalinyl)-oxy]phenoxy}propionic acid (XK469). *J. Med. Chem.* **2002**, *45*, 3130−3137.

JM040873U