1-Alkyl-4-acylpiperazines as a New Class of Imidazole-Free Histamine H_3 Receptor Antagonists

Florencio Zaragoza,* Henrik Stephensen, Sanne M. Knudsen, Lone Pridal, Birgitte S. Wulff, and Karin Rimvall

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

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With the aim of identifying structurally novel, centrally acting histamine H_3 antagonists, arrays of monoacyldiamines were screened. This led to the discovery of a series of 1-alkyl-4-acylpiperazines which were potent antagonists at the human histamine H_3 receptor. The most potent amides had antagonist potencies in the subnanomolar range.

Introduction

The histamine H_3 receptor, discovered in 1983,[1] is a presynaptic autoreceptor mainly localized in the central nervous system and which, among other things, modulates the biosynthesis and release from histaminergic neurons of histamine.[2,3] The human,[4] rat,[5] mouse,[6] and guinea pig[7] histamine H_3 receptors have recently been cloned, and this has led to renewed interest in histamine research. Because the histamine H_3 receptor is widely distributed in the CNS either as autoreceptor on histaminergic neurons or as heteroreceptor on serotonergic,[8] cholinergic,[9] noradrenergic,[10] and dopaminergic[11] 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.[2,10b,12] The precise therapeutic potential of histamine H_3 antagonists remains, however, to be clarified.

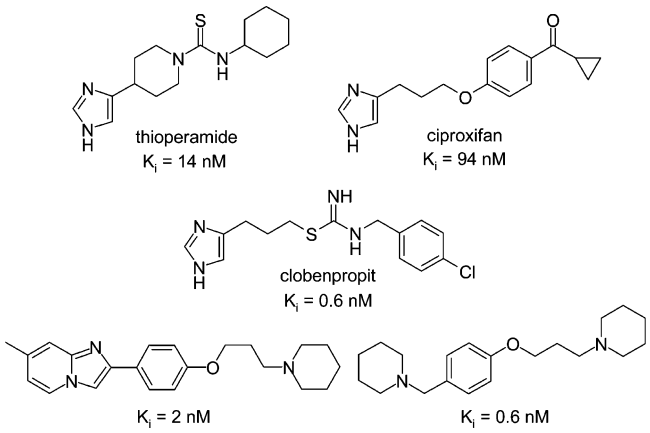
Most of the previously described histamine H_3 receptor antagonists, identified by their functional activity or binding affinity in rodent tissue, were imidazole derivatives, such as thioperamide, ciproxifan, or clobenpropit (Chart 1).[2] However, several examples of imidazole-free H_3 ligands have recently been described,[13−18] such as the potent piperidine derivatives sketched in Chart 1.[14,18c]

In this publication we wish to present the discovery and optimization of a new class of imidazole-free histamine H_3 antagonists. Because the affinity of compounds to the histamine H_3 receptor is strongly species dependent,[3,5,19] we used membranes from cells expressing the human histamine H_3 receptor in all our assays. Our initial hits, which were identified by screening arrays of various monoacyl diamines prepared by parallel synthesis, were 1-alkyl-4-acylpiperazines, which could quickly be optimized with the aid of further, more focused arrays of acylpiperazines.

Chemistry

Most agonists and antagonists of histamine or other, related monoamine neurotransmitters are compounds with a positive charge at physiological pH. Accordingly, we considered the screening of structurally diverse monoamines to be the most straightforward approach for the identification of new histamine H_3 antagonists. We thus decided to prepare and screen arrays of monoacyldiamines, which can be readily prepared by acylation of a polymeric phenol (sparsely cross-linked aminomethyl polystyrene acylated with 4-hydroxy-3-nitrobenzoic acid) with a carboxylic acid, followed by nucleophilic cleavage with a diamine.[20] Larger amounts of amides were prepared in solution using standard protocols (see Experimental Section). The crude amides were converted into the corresponding hydrochlorides by coevaporation with hydrochloric acid and purified by recrystallization from ethanol.

Chart 1. Representative Histamine H_3 Receptor Antagonists and Affinities to the Human Histamine H_3 Receptor



Most 1-alkylpiperazines and carboxylic acids used in this work were commercially available. The alkylpiperazines required for the synthesis of amides **1**, **2**, **7**, **8**, and **11**−**14** were prepared by *N*-alkylation of 1-Boc-piperazine, followed by Boc-group removal with TFA (Scheme 1). These reactions generally proceeded in high yields, with the exception of the reductive amination of 4-heptanone (for the preparation of amide **11**), which only yielded 7% of the desired 1-(4-heptyl)-4-Boc-piperazine. 1-(1,1-Dimethyl-2-propynyl)-4-Boc-piperazine, required for the synthesis of amide **13**, was prepared by copper(I) iodide-catalyzed alkylation of 1-Boc-piperazine with 3-chloro-3-methyl-1-butyne.[21] Careful cata-

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

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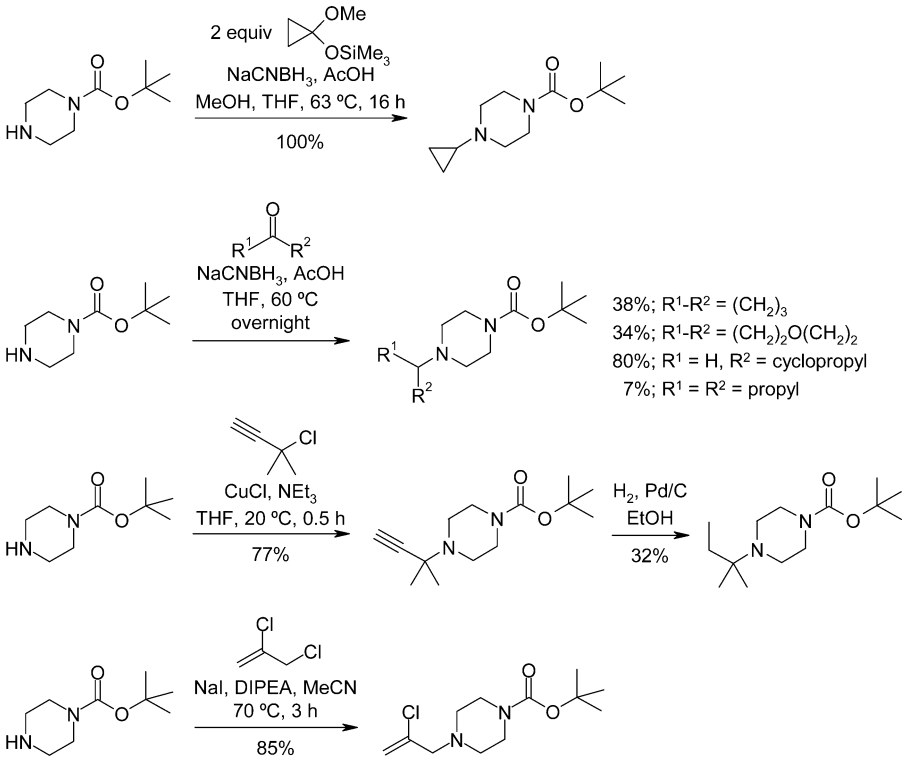
Scheme 1. Syntheses of 1-Alkyl-4-Boc-piperazines



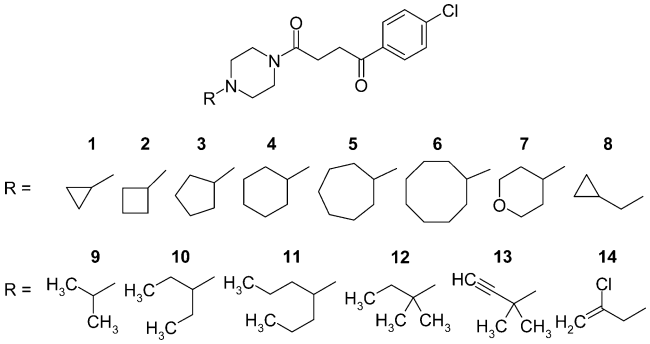
lytic hydrogenation of this product (Pd/C, EtOH) yielded 1-(1,1-dimethylpropyl)-4-Boc-piperazine, required for the preparation of amide **12**. Extensive hydrogenolytic dealkylation of the heterocycle was, though, observed during this hydrogenation.[22] Alkylation of 1-Boc-piperazine with 1,2-dichloro-2-propene (MeCN, NaI, 70 °C) yielded the amine required for the preparation of amide **14**.

Results and Discussion

Approximately 700 monoacyldiamines were initially screened using the previously described binding assay with radioactively labeled iodoproxyfan (^{125}IPF).[3] Various piperazine-derived amides inhibited radioligand binding to the human H_3 receptor efficiently. Subsequently, the screening of further, more focused arrays of acylpiperazines resulted in the identification of a series of amides with high affinity to the human H_3 receptor. Resynthesis and testing in a novel, functional GTPγ[S]-assay[23] confirmed these compounds to be potent antagonists at the human H_3 receptor.

Initially, the most potent acylpiperazines found were those derived from 4-aryl-4-oxobutyric acid and 1-alkylpiperazines. Nonalkylated piperazine or 1-alkylpiperazines with aryl-, hydroxy-, or alkoxy-substituted alkyl groups gave inactive or significantly less potent amides. A series of amides was then prepared, in which the alkyl group of the piperazine was systematically modified, with the aim of exploring the structure−activity relationship of this novel class of histamine H_3 antagonists, and for identifying compounds with high in vivo activity. As illustrated by the results shown in Table 1, branched C_4 and C_5 alkyl groups generally led to highly potent compounds, with the 3-pentyl and the 1,1-dimethylpropyl derivatives **10** and **12** showing the highest affinities to the human H_3 receptor. The optimal cyclic alkyl groups were four- to six-membered cycloalkyl groups. The results shown in Table 1 suggest that the potency of these amides is both dependent on the sterical

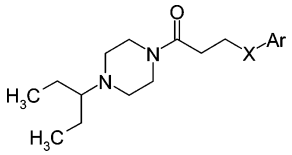
Table 1. Antagonist[a] Potency of Acylpiperazines **1**−**14** and Representative Reference Compounds at the Human H_3 Receptor, Determined by a Functional GTPγ[S]-assay



no.	K_i (nM) ± SEM (n)
1	13.3 ± 0.3 (3)
2	1.2 ± 0.1 (3)
3	1.2 ± 0.1 (10)
4	3.6 ± 0.6 (3)
5	34 ± 3 (3)
6	450 ± 150 (3)
7	9.2 ± 1.4 (4)
8	8.3 ± 0.7 (3)
9	4.4 ± 1.4 (3)
10	0.86 ± 0.17 (3)
11	480 ± 160 (4)
12	0.54 ± 0.17 (4)
13	89 ± 25 (3)
14	1100 ± 250 (4)
thioperamide	14.0 ± 3.5 (6)
ciproxifan	94 ± 32 (6)
clobenpropit	0.58 ± 0.13 (6)
RAMHA[b]	2.70 ± 0.15 (60)

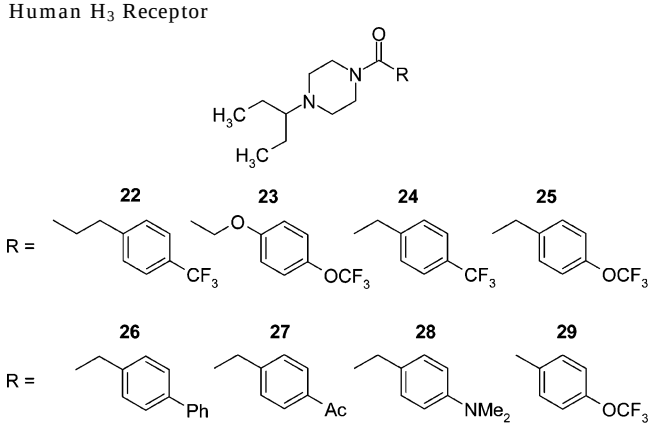
[a] All the compounds described in this work were inverse agonists.[3] [b] (*R*)-α-Methylhistamine, a selective H_3 agonist.

Table 2. Antagonist Potency of Acylpiperazines **15**−**21** at the Human H_3 Receptor



no.	X	Ar	K_i (nM) ± SEM (*n*)
15	CO	C_6H_4-4-F	1.5 ± 0.2 (3)
16	CO	C_6H_4-4-CF_3	1.4 ± 0.3 (3)
17	CO	C_6H_4-4-OCF_3	2.7 ± 0.3 (3)
18	CO	C_6H_3-3-F-4-OCH_3	0.43 ± 0.07 (3)
19	CO	C_6H_3-3,4-$(OCH_3)_2$	0.38 ± 0.08 (4)
20	O	C_6H_4-4-Cl	1.2 ± 0.5 (3)
21	O	C_6H_4-4-CN	0.74 ± 0.07 (5)

Table 3. Antagonist Potency of Acylpiperazines **22**−**29** at the Human H_3 Receptor



no.	K_i (nM) ± SEM (*n*)
22	8.5 ± 1.8 (4)
23	110 ± 10 (5)
24	2.3 ± 0.6 (4)
25	2.6 ± 0.6 (5)
26	2.9 ± 0.4 (3)
27	24 ± 1 (3)
28	0.96 ± 0.07 (3)
29	93 ± 28 (4)

demand of the *N*-alkyl group, as well as on its electron-withdrawing ability. Groups larger than 3-pentyl or cyclohexyl (e.g., **5**, **6**, and **11**) led to compounds with decreased potency. Similarly, electron-withdrawing alkyl groups, such as the cyclopropyl, 1,1-dimethyl-2-propyn-1-yl, or 2-chloro-2-propen-1-yl groups (**1**, **13**, and **14**), which lower the basicity of amines,[24] also led to less potent compounds.

After having identified a set of potentially suitable 1-alkylpiperazines, the effect of structural variations of the acyl group on the biological activity of acylated 1-(3-pentyl)piperazines was investigated. Amides with three atoms between the carbonyl group and the arene (Table 2) were generally highly potent, with little dependence on the precise substitution pattern of the aryl group. The precise structure of the spacer between the acyl group and the arene had no strong influence on the potency either, and 3-aryloxy derivatives such as **20**, for instance, was similarly potent as the corresponding ketone **10** (Table 1).

Finally, a series of structurally more diverse acylated 1-(3-pentyl)piperazines was prepared (Table 3). Amides with two atoms between the carbonyl and aryl group (**22** and **23**) showed lower potency at the human H_3 receptor than those amides with a three-atom spacer (**10**, **15**−**21**). Arylacetamides **24**, **25**, **26**, and **28**, however, again were potent, the only exception being the 4-acetylphenylacetamide **27**. In the arylacetamide series a high electron density at the arene appeared to have a positive effect on the biological activity. Thus, while the 4-(dimethylamino)phenylacetamide **28** was a strong antagonist (Table 3), the corresponding 4-acetylphenylacetamide **27** was more than 20 times weaker. Complete removal of the spacer led to benzamides such as **29**, which displayed significantly reduced potency if compared to amides with a longer spacer, such as **17**, **23**, and **25**.

As illustrated by the results shown in Tables 1−3, we succeeded in identifying a group of structurally diverse acylpiperazines with high antagonist potency at the human H_3 receptor. A selection of the amides listed in Tables 1−3 was also tested at the human H_1, H_2, and H_4 receptors,[25] but did not bind significantly to these. Compound **3** was selected for further in vivo profiling, and the results will be presented in another communication (K. Malmlöf et al., manuscript in preparation).

Conclusion

We have identified a new class of highly potent and selective antagonists of the human histamine H_3 receptor by iterative screening of arrays of monoacyldiamines. Because unsophisticated chemistry was chosen at the outset of the project, the initial hits could be optimized quickly, and the preparation of larger amounts of selected compounds could be accomplished easily. In-depth evaluation of the biological properties of these amides is currently in progress.

Experimental Section

Cloning and Expression of the Human Histamine H_3 Receptor. The human histamine H_3 receptor was cloned as described previously.[3] The DNAs were inserted into the mammalian cell expression vector pIRESneo2 (Clontech), and cells, stably expressing the histamine H_3 receptors, were generated by transfecting the histamine H_3 receptor expression vector into CHO cells and using G418 to select for stable histamine H_3 receptor expressing clones. The cells were cultured in Dulbecco's Minimal Essential Medium with glutamax, 10% fetal calf serum, 1% penicillin and streptomycin mixture, and 1 mg/mL G418 at 37 °C and 5% CO_2.

[^{35}S]GTPγ[S] Binding Assay. CHO cells, stably expressing the human histamine H_3 receptor, were harvested, and membranes were prepared by 3-fold homogenization in a HEPES buffer (20 mM HEPES, 0.1−10 mM EDTA; pH 7.4). The functional, antagonist potency of H_3 antagonists was measured as their ability to inhibit the binding of [^{35}S]GTPγ-[S] in the presence of 10 nM (*R*)-α-methylhistamine (RAMHA). The test compound was diluted in assay buffer (20 mM HEPES, 120 mM NaCl, 10 mM $MgCl_2$, pH 7.4) at various concentrations followed by addition of 10 nM RAMHA, 3 μM GDP, 2.5 μg membranes, 0.5 mg SPA beads, and 0.1 nM [^{35}S]-GTPγ[S]. After 2 h incubation at room temperature with gentle shaking of the plate, the plate was centrifuged at 370 RCF for 10 min and subsequently the radioactivity was counted in a Cobra II auto gamma topcounter.

Data Analysis. The IC_{50} values of H_3 antagonists were calculated by nonlinear regression analysis using GraphPad Prism (GraphPad Software, Inc.). The functional K_i values for the H_3 antagonists were calculated from the IC_{50} values using the Cheng−Prusoff relationship: $K_i = IC_{50}/(1 + (S/EC_{50}))$ where *S* represents the concentration of RAMHA used (10 nM) and EC_{50} represents the mean EC_{50} value (± SEM) of RAMHA

in more than 60 separate agonist [^{35}S]GTPγ[S]-binding experiments (i.e., 2.70 ± 0.15 nM).

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; sept, septet; m, multiplet; br, broad. Commercially available reagents were used without further purification. 3-(4-Chlorophenoxy)propionic acid and 3-(4-cyanophenoxy)propionic acid were prepared in low yields by etherification of the corresponding phenols with 3-chloropropionic acid as described in the literature.[26] 1-Cyclopropylpiperazine was prepared by Boc-group removal as described below from 4-cyclopropylpiperazine-1-carboxylic acid *tert*-butyl ester, which was synthesized by reductive cyclopropylation of 1-Boc-piperazine with 1-ethoxy-1-(trimethylsilyloxy)cyclopropane.[27] The 1-alkylpiperazines required for the synthesis of amides **2**, **7**, **8**, and **11** were prepared similarly, namely by reductive alkylation ($NaCNBH_3$, AcOH, THF, H_2O, 60 °C) of 1-Boc-piperazine with the corresponding ketones or aldehydes.

General procedure for the Reductive Alkylation of 1-*tert*-Butyloxycarbonylpiperazine: 4-Cyclobutylpiperazine-1-carboxylic Acid *tert*-Butyl Ester. To a solution of 1-*tert*-butyloxycarbonylpiperazine (2.24 g, 12.0 mmol) in THF (20 mL) were added water (0.2 mL), cyclobutanone (1.35 mL, 18.1 mmol), AcOH (2.20 mL), and $NaCNBH_3$ (18 mL, 1 M in THF, 18 mmol). The mixture was stirred at 60 °C overnight and concentrated, and the residue was mixed with water (50 mL) and aqueous HCl (1 M, 15 mL). The solution was washed with AcOEt (2 × 30 mL), made basic by addition of K_2CO_3, and extracted (2 × 20 mL AcOEt), and the combined extracts were washed with brine, dried with $MgSO_4$, and concentrated. The title compound (1.1 g, 38%) was obtained as a colorless oil, which was used without further purification. ^{1}H NMR (DMSO-d_6) δ 1.38 (s, 6H), 1.60 (m, 2H), 1.73 (m, 2H), 1.94 (m, 2H), 2.13 (m, 4H), 2.67 (m, 1H), 3.27 (m, 4H).

4-(Tetrahydropyran-4-yl)piperazine-1-carboxylic acid *tert*-butyl ester: mp 79−80 °C (heptane). ^{1}H NMR (DMSO-d_6) δ 1.35 (m, 2H), 1.39 (s, 9H), 1.69 (m, 2H), 2.41 (m, 4H), 3.28 (m, 7H), 3.84 (m, 2H).

4-Cyclopropylmethylpiperazine-1-carboxylic acid *tert*-butyl ester: oil. ^{1}H NMR (DMSO-d_6) δ 0.05 (m, 2H), 0.43 (m, 2H), 0.79 (m, 1H), 1.38 (s, 9H), 2.16 (d, J = 7 Hz, 2H), 2.33 (m, 4H), 3.30 (m, 4H).

4-(1-Propylbutyl)piperazine-1-carboxylic acid *tert*-butyl ester: oil. ^{1}H NMR (DMSO-d_6) δ 0.86 (t, J = 7 Hz, 6H), 1.12 (m, 2H), 1.28 (m, 4H), 1.39 (m, 11H), 2.38 (m, 4H), 2.59 (m, 1H), 3.25 (m, 4H).

4-(1,1-Dimethylpropyl)piperazine-1-carboxylic Acid *tert*-Butyl Ester. To palladium on charcoal (10% Pd, 48 mg) was added a solution of 4-(1,1-dimethylprop-2-ynyl)piperazine-1-carboxylic acid *tert*-butyl ester (0.50 g, 1.98 mmol) in EtOH (50 mL), and the mixture was stirred under hydrogen until 116 mL (5.2 mmol) had been absorbed. Filtration and concentration yielded a mixture (1:2) of the title compound and 1-Boc-piperazine. This mixture was acetylated by treatment with Ac_2O (3.0 mL), AcOEt (20 mL), and a saturated aqueous solution of $NaHCO_3$ (20 mL) for 1.5 h. After acidification with aqueous HCl (1 M), the mixture was washed with AcOEt, made basic with K_2CO_3, and extracted with AcOEt (3 × 30 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated, to yield 0.16 g (32%) of the title compound as an oil, which was used without further purification. ^{1}H NMR (DMSO-d_6) δ 0.78 (t, J = 7 Hz, 3H), 0.92 (s, 6H), 1.38 (m, 11H), 2.37 (m, 4H), 3.26 (m, 4H).

4-(1,1-Dimethylprop-2-ynyl)piperazine-1-carboxylic Acid *tert*-Butyl Ester. To a stirred mixture of 1-*tert*-butyloxycarbonylpiperazine (1.10 g, 5.91 mmol), 3-chloro-3-methyl-1-butyne (0.88 mL, 7.81 mmol), THF (10 mL), and NEt_3 (1.10 mL, 7.91 mmol) under nitrogen was added CuCl (45 mg, 0.46 mmol). An exothermic reaction ensued and a precipitate formed. After stirring for 0.5 h at room-temperature, water (20 mL) and aqueous HCl (1 M, 8 mL) were added and the mixture was concentrated under reduced pressure to 2/3 of its original volume. The mixture was washed with AcOEt (2 × 20 mL) and made basic by addition of K_2CO_3. Extraction with AcOEt (3 × 20 mL), washing of the combined extracts with brine (30 mL), drying with $MgSO_4$, and concentration under reduced pressure yielded 1.15 g (77%) of the title compound as a colorless solid, which was used without further purification: mp 109−110 °C (MeOH). ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 6H), 1.47 (s, 9H), 2.29 (s, 1H), 2.58 (m, 4H), 3.47 (m, 4H).

4-(2-Chloroallyl)piperazine-1-carboxylic Acid *tert*-Butyl Ester. To a solution of 1-*tert*-butyloxycarbonylpiperazine (1.01 g, 5.42 mmol) in MeCN (10 mL) were added diisopropylethylamine (2.0 mL), 2,3-dichloro-1-propene (0.56 mL, 6.06 mmol), and NaI (0.89 g, 5.94 mmol), and the mixture was stirred at 70 °C for 3 h. The mixture was concentrated under reduced pressure, and the residue was redissolved in aqueous HCl (1 M, 40 mL). The solution was washed once with AcOEt, made basic by addition of K_2CO_3, and extracted with AcOEt (3 × 30 mL). The combined extracts were washed with brine, dried with $MgSO_4$ and concentrated, to yield 1.20 g (85%) of the title compound as a solid, which was used without further purification: mp 78−79 °C (MeOH). ^{1}H NMR (DMSO-d_6) δ 1.40 (s, 9H), 2.36 (m, 4H), 3.14 (s, 2H), 3.32 (m, 4H), 5.38 (s, 1H), 5.51 (s, 1H).

General Procedure for Boc-Group Removal from 4-Alkyl-1-Boc-piperazines. To a solution of the Boc-piperazine (35 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added a mixture of CH_2Cl_2 (50 mL) and trifluoroacetic acid (75 mL). The mixture was kept at room temperature for 1 h and concentrated, and the residue was mixed with a solution of K_2CO_3 (60 g) in water (150 mL). The product was extracted with AcOEt (3 × 200 mL). Careful concentration of the combined extracts yielded the free 1-alkylpiperazines, which were used without further purification.

General Procedure for the Preparation of Amides 1−29. 1-(4-Chlorophenyl)-4-(4-cyclopentylpiperazin-1-yl)butane-1,4-dione Hydrochloride (3). To a mixture of 3-(4-chlorobenzoyl)propionic acid (31.9 g, 150 mmol), DMF (200 mL), and *N*-hydroxybenzotriazole (40.6 g, 301 mmol) was added a solution of *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (28.8 g, 150 mmol) in DMF (100 mL). The mixture was stirred at room temperature for 1.5 h, and a solution of 1-cyclopentylpiperazine (23.2 g, 150 mmol) in CH_2Cl_2 (100 mL) was added. The mixture was stirred at room temperature for 4 h and concentrated under reduced pressure, and the residue was distributed between AcOEt (1.0 l) and a saturated, aqueous $NaHCO_3$ solution (1.0 l). Phases were separated, the organic layer was dried ($MgSO_4$) and concentrated, and the residue was redissolved in aqueous HCl (1 M, 150 mL). The solution was concentrated, and the residue was dried by coevaporation with EtOH. Recrystallization of the residue from EtOH yielded 31.1 g (54%) of the title compound. Concentration of the mother liquor gave additional 19.4 g (34%) of product: mp 230−234 °C. ^{1}H NMR (DMSO-d_6) δ 1.53 (m, 2H), 1.64−1.90 (m, 4H), 1.98 (m, 2H), 2.71−3.18 (m, 5H), 3.23 (t, J = 7 Hz, 2H), 3.42−3.67 (m, 4H), 4.15 (m, 1H), 4.39 (m, 1H), 7.60 (d, J = 8 Hz, 2H), 7.99 (d, J = 8 Hz, 2H), 11.20 (br s, 1H). Anal. ($C_{19}H_{25}ClN_2O_2$ × HCl) C, H, N.

1-(4-Chlorophenyl)-4-(4-cyclopropylpiperazin-1-yl)butane-1,4-dione hydrochloride (1): mp 206−208 °C. ^{1}H NMR (DMSO-d_6) δ 0.80 (br d, J = 7 Hz, 2H), 1.12 (m, 2H), 2.71−2.89 (m, 3H), 3.08 (m, 2H), 3.23 (t, J = 7 Hz, 2H), 3.44−3.62 (m, 4H), 4.15 (m, 1H), 4.40 (m, 1H), 7.60 (d, J = 8 Hz, 2H), 7.98 (d, J = 8 Hz, 2H), 11.00 (br s, 1H). Anal. ($C_{17}H_{21}ClN_2O_2$·HCl·0.25H_2O) C, H, N.

1-(4-Chlorophenyl)-4-(4-cyclobutylpiperazin-1-yl)butane-1,4-dione hydrochloride (2): mp 243−248 °C. ^{1}H NMR (DMSO-d_6) δ 1.65−1.83 (m, 2H), 2.18 (m, 2H), 2.38 (m, 2H), 2.61−2.93 (m, 4H), 3.07 (m, 1H), 3.23 (t, J = 7 Hz, 2H), 3.32 (m, 2H), 3.50−3.71 (m, 2H), 4.15 (m, 1H), 4.40 (m, 1H), 7.60 (d, J = 8 Hz, 2H), 7.99 (d, J = 8 Hz, 2H), 11.43 (br s, 1H). Anal. ($C_{18}H_{23}ClN_2O_2$·HCl·H_2O) C, H, N.

1-(4-Chlorophenyl)-4-(4-cyclohexylpiperazin-1-yl)butane-1,4-dione hydrochloride (4): mp 227−230 °C. ^{1}H NMR (DMSO-d_6) δ 1.05−1.65 (m, 6H), 1.82 (m, 2H), 2.11 (m, 2H),

2.72−2.98 (m, 3H), 3.04−3.28 (m, 5H), 3.42 (m, 2H), 3.63 (m, 1H), 4.14 (m, 1H), 4.41 (m, 1H), 7.61 (d, J = 8 Hz, 2H), 7.99 (d, J = 8 Hz, 2H), 10.80 (br s, 1H). Anal. ($C_{20}H_{27}ClN_2O_2$·HCl) C, H, N.

1-(4-Chlorophenyl)-4-(4-cycloheptylpiperazin-1-yl)butane-1,4-dione hydrochloride (5): mp 240−242 °C. ^{1}H NMR (DMSO-d_6) δ 1.35−1.78 (m, 10H), 2.12 (m, 2H), 2.73 (m, 2H), 2.90 (m, 1H), 3.08−3.36 (m, 7H), 3.68 (m, 1H), 4.13 (m, 1H), 4.42 (m, 1H), 7.59 (d, J = 8 Hz, 2H), 7.98 (d, J = 8 Hz, 2H), 10.85 (br s, 1H). Anal. ($C_{21}H_{29}ClN_2O_2$·HCl) C, H, N.

1-(4-Chlorophenyl)-4-(4-cyclooctylpiperazin-1-yl)butane-1,4-dione hydrochloride (6): mp 248−251 °C. ^{1}H NMR (DMSO-d_6) δ 1.41−1.76 (m, 12H), 2.02 (m, 2H), 2.75 (m, 2H), 2.92 (m, 1H), 3.06−3.45 (m, 7H), 3.64 (m, 1H), 4.13 (m, 1H), 4.41 (m, 1H), 7.61 (d, J = 8 Hz, 2H), 7.99 (d, J = 8 Hz, 2H), 10.85 (br s, 1H). Anal. ($C_{22}H_{31}ClN_2O_2$·HCl) C, H, N.

1-(4-Chlorophenyl)-4-[4-(tetrahydropyran-4-yl)piperazin-1-yl]butane-1,4-dione hydrochloride (7): mp 214−217 °C. ^{1}H NMR (DMSO-d_6) δ 1.72 (m, 2H), 1.99 (m, 2H), 2.76 (m, 2H), 2.85 (m, 1H), 3.10 (m, 2H), 3.21−3.68 (m, 8H), 3.97 (m, 2H), 4.16 (m, 1H), 4.41 (m, 1H), 7.60 (d, J = 8 Hz, 2H), 7.99 (d, J = 8 Hz, 2H), 11.15 (br s, 1H). Anal. ($C_{19}H_{25}ClN_2O_3$·HCl·0.25H_2O) C, H, N.

1-(4-Chlorophenyl)-4-(4-cyclopropylmethylpiperazin-1-yl)butane-1,4-dione hydrochloride (8): mp 220−224 °C. ^{1}H NMR (DMSO-d_6) δ 0.39 (m, 2H), 0.64 (m, 2H), 1.11 (m, 1H), 2.77 (q, J = 7 Hz, 2H), 2.80−3.18 (m, 5H), 3.22 (t, J = 7 Hz, 2H), 3.46−3.62 (m, 3H), 4.18 (m, 1H), 4.40 (m, 1H), 7.58 (d, J = 8 Hz, 2H), 7.98 (d, J = 8 Hz, 2H), 10.82 (br s, 1H). Anal. ($C_{18}H_{23}ClN_2O_2$·HCl) C, H, N.

1-(4-Chlorophenyl)-4-(4-isopropylpiperazin-1-yl)butane-1,4-dione hydrochloride (9): mp 225−227 °C. ^{1}H NMR (DMSO-d_6) δ 1.28 (d, J = 7 Hz, 6H), 2.73 (m, 2H), 2.85 (m, 1H), 3.09 (m, 2H), 3.22 (m, 2H), 3.33−3.67 (m, 4H), 4.16 (m, 1H), 4.42 (m, 1H), 7.60 (d, J = 8 Hz, 2H), 7.99 (d, J = 8 Hz, 2H), 10.75 (br s, 1H). Anal. ($C_{17}H_{23}ClN_2O_2$·HCl) C, H, N.

1-(4-Chlorophenyl)-4-[4-(1-ethylpropyl)piperazin-1-yl]-butane-1,4-dione hydrochloride (10): mp 207−209 °C. ^{1}H NMR (DMSO-d_6) δ 0.98 (t, J = 7 Hz, 6H), 1.62 (m, 2H), 1.85 (m, 2H), 2.74 (m, 2H), 2.88−3.26 (m, 6H), 3.39 (m, 2H), 3.68 (m, 1H), 4.12 (m, 1H), 4.39 (m, 1H), 7.59 (d, J = 8 Hz, 2H), 7.98 (d, J = 8 Hz, 2H), 10.45 (br s, 1H). Anal. ($C_{19}H_{27}ClN_2O_2$·HCl) C, H, N.

1-(4-Chlorophenyl)-4-[4-(1-propylbutyl)piperazin-1-yl]-butane-1,4-dione hydrochloride (11): mp 223−226 °C. ^{1}H NMR (DMSO-d_6) δ 0.92 (t, J = 7 Hz, 6H), 1.28−1.60 (m, 6H), 1.80 (m, 2H), 2.76 (m, 2H), 2.93 (m, 1H), 3.05−3.55 (m, 7H), 3.64 (m, 1H), 4.15 (m, 1H), 4.42 (m, 1H), 7.61 (d, J = 8 Hz, 2H), 8.00 (d, J = 8 Hz, 2H), 10.24 (m, 1H). Anal. ($C_{21}H_{31}$-ClN_2O_2·HCl·0.5H_2O) C, H, N.

1-(4-Chlorophenyl)-4-[4-(1,1-dimethylpropyl)piperazin-1-yl]butane-1,4-dione hydrochloride (12): mp 222−224 °C. ^{1}H NMR (DMSO-d_6) δ 0.92 (t, J = 7 Hz, 3H), 1.31 (s, 6H), 1.72 (q, J = 7 Hz, 2H), 2.76 (t, J = 7 Hz, 2H), 2.88 (m, 1H), 3.15 (m, 2H), 3.24 (q, J = 7 Hz, 2H), 3.47 (m, 2H), 3.68 (m, 1H), 4.14 (m, 1H), 4.43 (m, 1H), 7.61 (d, J = 8 Hz, 2H), 7.99 (d, J = 8 Hz, 2H), 10.22 (br s, 1H). Anal. ($C_{19}H_{27}ClN_2O_2$·HCl·0.75H_2O) C, H, N.

1-(4-Chlorophenyl)-4-[4-(1,1-dimethylprop-2-ynyl)piperazin-1-yl]butane-1,4-dione hydrochloride (13): mp 217−220 °C. ^{1}H NMR (DMSO-d_6) δ 1.69 (br s, 6H), 2.70−2.93 (m, 3H), 3.02−3.29 (m, 3H), 3.64 (m, 4H), 4.03 (br s, 1H), 4.19 (m, 1H), 4.48 (m, 1H), 7.60 (d, J = 8 Hz, 2H), 7.99 (d, J = 8 Hz, 2H), 12.05 (br s, 1H). Anal. ($C_{19}H_{23}ClN_2O_2$·HCl) C, H, N.

1-[4-(2-Chloroallyl)piperazin-1-yl]-4-(4-chlorophenyl)-butane-1,4-dione hydrochloride (14): mp 205−207 °C. ^{1}H NMR (DMSO-d_6) δ 2.75 (m, 2H), 2.80−3.15 (m, 2H), 3.24 (t, J = 7 Hz, 2H), 3.30−3.80 (m, 6H), 4.11 (m, 2H), 5.81 (br s, 1H), 5.94 (br s, 1H), 7.61 (d, J = 8 Hz, 2H), 8.00 (d, J = 8 Hz, 2H), 11.14 (br s, 1H). Anal. ($C_{17}H_{20}Cl_2N_2O_2$·HCl) C, H, N.

1-[4-(1-Ethylpropyl)piperazin-1-yl]-4-(4-fluorophenyl)-butane-1,4-dione hydrochloride (15): mp 207−209 °C. ^{1}H NMR (DMSO-d_6) δ 0.97 (t, J = 7 Hz, 6H), 1.62 (m, 2H), 1.88 (m, 2H), 2.75 (m, 2H), 2.85−3.30 (m, 5H), 3.38 (m, 2H), 3.73 (m, 1H), 4.14 (m, 1H), 4.40 (m, 1H), 7.36 (t, J = 8 Hz, 2H), 8.07 (t, J = 8 Hz, 2H), 10.76 (br s, 1H). Anal. ($C_{19}H_{27}FN_2O_2$·HCl) C, H, N.

1-[4-(1-Ethylpropyl)piperazin-1-yl]-4-(4-trifluoromethylphenyl)butane-1,4-dione hydrochloride (16): mp 213-215 °C. ^{1}H NMR (DMSO-d_6) δ 0.97 (t, J = 7 Hz, 6H), 1.62 (m, 2H), 1.85 (m, 2H), 2.79 (m, 2H), 2.95 (m, 1H), 3.00−3.50 (m, 7H), 3.68 (m, 1H), 4.14 (m, 1H), 4.41 (m, 1H), 7.91 (d, J = 8 Hz, 2H), 8.18 (d, J = 8 Hz, 2H), 10.42 (br s, 1H). Anal. ($C_{20}H_{27}F_3N_2O_2$·HCl) C, H, N.

1-[4-(1-Ethylpropyl)piperazin-1-yl]-4-(4-trifluoromethoxyphenyl)butane-1,4-dione hydrochloride (17): mp 206−208 °C. ^{1}H NMR (DMSO-d_6) δ 0.97 (t, J = 7 Hz, 6H), 1.63 (m, 2H), 1.85 (m, 2H), 2.77 (m, 2H), 2.95 (m, 1H), 3.00−3.31 (m, 5H), 3.35−3.55 (m, 2H), 3.68 (m, 1H), 4.14 (m, 1H), 4.41 (m, 1H), 7.52 (d, J = 8 Hz, 2H), 8.12 (d, J = 8 Hz, 2H), 10.47 (br s, 1H). Anal. ($C_{20}H_{27}F_3N_2O_3$·HCl) C, H, N.

1-[4-(1-Ethylpropyl)piperazin-1-yl]-4-(3-fluoro-4-methoxyphenyl)butane-1,4-dione hydrochloride (18): mp 214−217 °C. ^{1}H NMR (DMSO-d_6) δ 0.98 (t, J = 7 Hz, 6H), 1.61 (sept, J = 7 Hz, 2H), 1.87 (m, 2H), 2.72 (m, 2H), 2.85−3.28 (m, 6H), 3.40 (m, 2H), 3.72 (m, 1H), 3.93 (s, 3H), 4.11 (m, 1H), 4.39 (m, 1H), 7.29 (t, J = 7 Hz, 1H), 7.76 (br d, J = 14 Hz, 1H), 7.84 (br d, J = 7 Hz, 1H), 10.75 (br s, 1H). Anal. ($C_{20}H_{29}FN_2O_3$·HCl·0.25H_2O) C, H, N.

1-(3,4-Dimethoxyphenyl)-4-[4-(1-ethylpropyl)piperazin-1-yl]butane-1,4-dione hydrochloride (19): mp 195−196 °C. ^{1}H NMR (DMSO-d_6) δ 0.97 (t, J = 7 Hz, 6H), 1.63 (m, 2H), 1.84 (m, 2H), 2.72 (m, 2H), 2.95 (m, 1H), 3.00−3.25 (m, 5H), 3.39 (m, 2H), 3.63 (m, 1H), 3.81 (s, 3H), 3.85 (s, 3H), 4.14 (m, 1H), 4.42 (m, 1H), 7.08 (d, J = 8 Hz, 1H), 7.45 (s, 1H), 7.66 (d, J = 8 Hz, 1H), 10.12 (br s, 1H). Anal. ($C_{21}H_{32}N_2O_4$·HCl) C, H, N.

3-(4-Chlorophenoxy)-1-[4-(1-ethylpropyl)piperazin-1-yl]propan-1-one hydrochloride (20): mp 206−208 °C. ^{1}H NMR (DMSO-d_6) δ 0.96 (t, J = 7 Hz, 6H), 1.62 (m, 2H), 1.85 (m, 2H), 2.87 (t, J = 7 Hz, 2H), 2.90−3.28 (m, 4H), 3.41 (m, 2H), 3.65 (m, 1H), 4.08 (m, 1H), 4.20 (t, J = 7 Hz, 2H), 4.47 (m, 1H), 6.96 (d, J = 8 Hz, 2H), 7.33 (d, J = 8 Hz, 2H), 10.45 (br s, 1H). Anal. ($C_{18}H_{27}ClN_2O_2$·HCl) C, H, N.

4-{3-[4-(1-Ethylpropyl)piperazin-1-yl]-3-oxo-propoxy}-benzonitrile hydrochloride (21): mp 198−201 °C. ^{1}H NMR (DMSO-d_6) δ 0.96 (t, J = 7 Hz, 6H), 1.61 (m, 2H), 1.83 (m, 2H), 2.91 (t, J = 7 Hz, 2H), 2.92−3.45 (m, 6H), 3.71 (m, 1H), 4.07 (m, 1H), 4.30 (t, J = 7 Hz, 2H), 4.46 (m, 1H), 7.10 (d, J = 8 Hz, 2H), 7.77 (d, J = 8 Hz, 2H), 10.76 (br s, 1H). Anal. ($C_{19}H_{27}N_3O_2$·HCl·0.25H_2O) C, H, N.

1-[4-(1-Ethylpropyl)piperazin-1-yl]-3-(4-trifluoromethylphenyl)propan-1-one hydrochloride (22): mp 218−220 °C. ^{1}H NMR (DMSO-d_6) δ 0.95 (t, J = 7 Hz, 6H), 1.62 (m, 2H), 1.84 (m, 2H), 3.04 (m, 1H), 2.75 (m, 2H), 2.80−3.50 (m, 7H), 3.64 (m, 1H), 4.05 (m, 1H), 4.43 (m, 1H), 7.48 (d, J = 8 Hz, 2H), 7.64 (d, J = 8 Hz, 2H), 10.71 (br s, 1H). Anal. ($C_{19}H_{27}F_3N_2O_2$·HCl) C, H, N.

1-[4-(1-Ethylpropyl)piperazin-1-yl]-2-(4-trifluoromethoxyphenoxy)ethanone hydrochloride (23): mp 219−222 °C. ^{1}H NMR (DMSO-d_6) δ 0.97 (t, J = 7 Hz, 6H), 1.61 (m, 2H), 1.86 (m, 2H), 2.90−3.10 (m, 2H), 3.22 (m, 2H), 3.39 (m, 2H), 3.69 (m, 1H), 3.98 (m, 1H), 4.40 (m, 1H), 4.94 (s, 2H), 7.04 (m, 2H), 7.29 (m, 2H), 10.61 (br s, 1H). Anal. ($C_{18}H_{25}F_3N_2O_3$·HCl·H_2O) C, H, N.

1-[4-(1-Ethylpropyl)piperazin-1-yl]-2-(4-trifluoromethylphenyl)ethanone hydrochloride (24): mp 264−266 °C. ^{1}H NMR (DMSO-d_6) δ 0.96 (t, J = 7 Hz, 6H), 1.61 (m, 2H), 1.85 (m, 2H), 2.90−3.50 (m, 6H), 3.69 (m, 1H), 3.90 (m, 2H), 4.15 (m, 1H), 4.45 (m, 1H), 7.45 (d, J = 8 Hz, 2H), 7.68 (d, J = 8 Hz, 2H), 10.71 (br s, 1H). Anal. ($C_{18}H_{25}F_3N_2O$·HCl) C, H, N.

1-[4-(1-Ethylpropyl)piperazin-1-yl]-2-(4-trifluoromethoxyphenyl)ethanone hydrochloride (25): mp 263−265 °C. ^{1}H NMR (DMSO-d_6) δ 0.96 (t, J = 7 Hz, 6H), 1.62 (m, 2H), 1.84 (m, 2H), 2.85−3.46 (m, 6H), 3.65 (m, 1H), 3.82 (m, 2H), 4.14 (m, 1H), 4.43 (m, 1H), 7.32 (m, 4H), 10.53 (br s, 1H). Anal. ($C_{18}H_{25}F_3N_2O_2$·HCl) C, H, N.

2-Biphenyl-4-yl-1-[4-(1-ethylpropyl)piperazin-1-yl]ethanone hydrochloride (26): mp 261−263 °C. ^{1}H NMR (DMSO-d_6) δ 0.95 (t, J = 7 Hz, 6H), 1.62 (m, 2H), 1.82 (m, 2H), 2.80−3.50 (m, 6H), 3.60 (m, 1H), 3.82 (m, 2H), 4.17 (m, 1H), 4.45 (m, 1H), 7.25−7.55 (m, 5H), 7.64 (m, 4H), 10.29 (br s, 1H). Anal. ($C_{23}H_{30}N_2O\cdot HCl\cdot 0.25H_2O$) C, H, N.

2-(4-Acetylphenyl)-1-[4-(1-ethylpropyl)piperazin-1-yl]-ethanone hydrochloride (27): mp 189−191 °C. ^{1}H NMR (DMSO-d_6) δ 0.97 (t, J = 7 Hz, 6H), 1.62 (m, 2H), 1.86 (m, 2H), 2.52 (s, 3H), 2.90−3.10 (m, 3H), 3.15−3.50 (m, 3H), 3.71 (m, 1H), 3.99 (m, 1H), 4.41 (m, 1H), 5.02 (s, 2H), 7.05 (d, J = 8 Hz, 2H), 7.92 (d, J = 8 Hz, 2H), 10.64 (br s, 1H). Anal. ($C_{19}H_{28}N_2O_2\cdot HCl\cdot 2H_2O$) C, H, N.

2-(4-Dimethylaminophenyl)-1-[4-(1-ethylpropyl)piperazin-1-yl]ethanone dihydrochloride (28): mp 194−195 °C. ^{1}H NMR (DMSO-d_6) δ 0.96 (t, J = 7 Hz, 6H), 1.61 (m, 2H), 1.85 (m, 2H), 2.90−3.15 (m, 7H), 3.24 (m, 1H), 3.38 (m, 2H), 3.62−4.30 (m, 6H), 4.43 (m, 1H), 7.25−7.55 (m, 4H), 10.87 (br s, 1H). Anal. ($C_{19}H_{31}N_3O\cdot 2HCl\cdot 1.5H_2O$) C, H, N.

[4-(1-Ethylpropyl)piperazin-1-yl]-(4-trifluoromethoxyphenyl)methanone hydrochloride (29): mp 228−230 °C. ^{1}H NMR (DMSO-d_6) δ 0.97 (t, J = 7 Hz, 6H), 1.61 (m, 2H), 1.88 (m, 2H), 3.06 (m, 1H), 3.17 (m, 2H), 3.40−3.90 (m, 5H), 4.53 (br s, 1H), 7.47 (d, J = 8 Hz, 2H), 7.65 (d, J = 8 Hz, 2H), 10.63 (br s, 1H). Anal. ($C_{17}H_{23}F_3N_2O_2\cdot HCl$) C, H, N.

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) 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-Schmiedburg's Arch. Pharmacol.* **1990**, *342*, 513−519.

(9) 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.

(10) (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-Schmiedburg'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.

(11) 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.

(12) 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.

(13) 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.

(14) 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. Nonimidazole heterocyclic histamine H_3 receptor antagonists. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1767−1770.

(15) 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.

(16) 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.

(17) 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.

(18) (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-1H-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.

(19) Ireland-Denny, L.; Parihar, A. S.; Miller, T. R.; Kang, C. H.; Krueger, K. M.; Esbenshade, T. A.; Hancock, A. A. Species-related pharmacological heterogeneity of histamine H_3 receptors. *Eur. J. Pharm.* **2001**, *433*, 141−150.

(20) (a) Cohen, B. J.; Karoly-Hafeli, H.; Patchornik, A. Active esters of polymer-bound 4-hydroxy-3-nitrobenzophenone as useful acylating reagents. Application to peptide synthesis. *J. Org. Chem.* **1984**, *49*, 922−924. (b) Zaragoza Dörwald, F. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, New York, 2002; pp 70−71.

(21) Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S. Copper(I)-catalyzed amination of propargyl esters. Selective synthesis of propargylamines, 1-alken-3-ylamines, and (*Z*)-allylamines. *J. Org. Chem.* **1994**, *59*, 2282−2284.

(22) Hennion, G. F.; Teach, E. G. Reactions of acetylenic primary amines. *J. Am. Chem. Soc.* **1953**, *75*, 4297−4399.

(23) Rouleau, A.; Ligneau, X.; Tardivel-Lacombe, J.; Morisset, S.; Gbahou, F.; Schwartz, J.-C.; Arrang, J.-M. Histamine H_3-receptor-mediated [^{35}S]GTPγ[S] binding: evidence for constitutive activity of the recombinant and native rat and human H3 receptors. *Br. J. Pharmacol.* **2002**, *135*, 383−392.

(24) pK_A (cyclopropyl-/propargyl-/isopropylamine): 9.1/7.9/10.2. (a) Love, P.; Cohen, R. B.; Taft, R. W. Polar substituent effects in gas-phase Lewis acid−base equilibria. 1. Intrinsic basicity of amines. *J. Am. Chem. Soc.* **1968**, *90*, 2455−2462. (b) Hine, J.; Yeh, C. Y.; Schmalstieg, F. C. Polar effects on the formation of imines from isobutyraldehyde and primary aliphatic amines. *J. Org. Chem.* **1970**, *35*, 340−344.

(25) H_1, H_2, and H_4 receptor binding affinities for selected compounds were measured using conventional filtration assays. For H_1 receptor binding, we used membranes from CHO-cells, stably expressing the human histamine H_1 receptor, and ^{3}H-pyrilamine as radioligand. Smit, M. J.; Timmerman, H.; Hijselendoorn, J. C.; Fukui, H.; Leurs, R. Regulation of human histamine H_1 receptor stably expressed in Chinese hamster ovary cells. *Br. J. Pharm.* **1996**, *117*, 1071−1080. For H_2 receptor binding, we used membranes from CHO-cells, stably expressing the human histamine H_2 receptor, and ^{125}I-aminopotentidine as radioligand. Leurs, R.; Smit, M. J.; Menge, W. M. B. P.; Timmerman, H. Pharmacological characterization of the human histamine H_2 receptor stably expressed in Chinese hamster ovary cells. *Br. J. Pharm.* **1994**, *112*, 847−854. For H_4 receptor binding, we used membranes from HEK293 cells, stably expressing the human histamine H_4 receptor and ^{3}H-histamine as radioligand. Compounds **1**−**4**, **10**, **12**, **15**, **18**, **21**, and **25** had an affinity lower than 10 μM at the human histamine H_1 receptor. Compounds **1**−**4**, **10**, **12**, **15**−**18**, **21**, **25**, and **28** had an affinity lower than 10 μM at the human histamine H_2 receptor. Compounds **3**, **18**, **21**, and **25** had an affinity lower than 10 μM at the human histamine H_4 receptor.

(26) Sarges, R.; Schnur, R. C.; Belletiere, J. L.; Peterson, M. J. Spiro hydantoin aldose reductase inhibitors. *J. Med. Chem.* **1988**, *31*, 230−243.

(27) Gillaspy, M. L.; Lefker, B. A.; Hada, W. A.; Hoover, D. J. A simple method for the formation of cyclopropylamines: the first synthesis of tricyclopropylamine. *Tetrahedron Lett.* **1995**, *36*, 7399−7402.

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