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2-Aryloxymethylmorpholine histamine H_3 antagonists

Michael A. Letavic *, John M. Keith, Kiev S. Ly, Pascal Bonaventure, Mark A. Feinstein, Brian Lord, Kirsten L. Miller, S. Timothy Motley, Diane Nepomuceno, Steven W. Sutton, Nicholas I. Carruthers

Johnson & Johnson Pharmaceutical Research & Development L.L.C., 3210 Merryfield Row, San Diego, CA 92121-1126, USA

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ABSTRACT

The synthesis and biological activity of a new series of 2-aryloxymethylmorpholine histamine H_3 antagonists is described. The new compounds are high affinity histamine H_3 ligands that penetrate the CNS and occupy the histamine H_3 receptor in rat brain.

Histamine plays an important role in a variety of physiological processes, including inflammatory responses, which are regulated by the histamine H_1 receptor,[1] and gastric acid secretion, which is controlled by histamine H_2 receptors.[2] The cloning of the human histamine H_3 receptor in the late 1990s,[3] and reports that the histamine H_3 receptor is widely expressed in the CNS, led to numerous reports on the therapeutic potential for histamine H_3 agonists and antagonists. After much research, it is now clear that histamine H_3 receptors play a role in regulation of the sleep-wake cycle and that histamine H_3 antagonists may have therapeutic utility for the treatment of a variety of conditions, including excessive daytime sleepiness, ADHD, Narcolepsy and Alzheimer's disease, among other conditions.[4]

Following the cloning of the human histamine H_3 receptor numerous pharmaceutical companies initiated drug discovery efforts designed to identify histamine H_3 antagonists that were suitable for clinical trials.[5] Much progress has been made in this area and many chemotypes have been disclosed that are potent and selective histamine H_3 antagonists. Several recent reviews have described medicinal chemistry efforts in this area.[5–7] One class of histamine H_3 antagonists contains a tertiary basic amine linked to an aromatic core by a three to five atom spacer. A few of the many possible representative examples are shown below. These compounds include **1**[8] and **2**,[9] which incorporate a propyloxypiperidine moiety present in many of the reported H_3 antagonists, and compounds **3**,[10] **4**,[11] and **5**,[12] which have slightly different linkers to the terminal basic amine. As part of our efforts to discover novel histamine H_3 antagonists we now report a series of high affinity morpholine-based ligands that penetrate the CNS.

Using **6** as a conceptual starting point,[13] we devised a variety of strategies to prepare conformationally restricted linkers that might generate useful H_3 ligands. One of these strategies was to tether the tertiary basic amine to the linker as shown in compound **7**. This led generally to compounds **8** and includes the morpholine-based structures described below. We chose to prepare these morpholine compounds based on the hypothesis that they may have improved physical and pharmacokinetic properties as a result of the reduced basicity of the morpholine ring nitrogen as compared to the piperidine ring nitrogen in compounds such as JNJ-5207852 (**6**).

The desired morpholines can be prepared by several routes, including those shown in Schemes 1 and 2. Initially, we prepared compounds **12** using a Mitsunobu reaction of racemic 2-hydroxymethyl-morpholine-4-carboxylic acid *tert*-butyl ester **10** with phenols such as **9**. While we could obtain compounds **12** using this procedure, the Mitsunobu reaction was plagued by poor and variable yields. Two alternative routes are also shown in Schemes 1 and 2. In these examples, the morpholine methanol **10** was either condensed with 4-flourobenzaldehyde to give **14** or was activated as the tosylate **15** and reacted with the appropriate phenol to obtain the required intermediates. These intermediates were then converted to the final products by simple reductive amination reactions as shown in the schemes. Compounds **19** were prepared by the route shown in Scheme 1 using the appropriate phenol. Compounds **21** and **22** were prepared using the procedures shown in Scheme 2 using (*R*)- or (*S*)-2-hydroxymethyl-morpholine-4-carboxylic acid *tert*-butyl ester, which was made by literature methods.[14]

Rat and human in vitro binding and functional data for the compounds prepared are detailed in Table 1.[15,16] As can be seen in the table, compounds **19**, lacking the benzyl amine moiety, have only weak affinity for the histamine H_3 receptor. In addi-

* Corresponding author.
E-mail address: mletavic@its.jnj.com (M.A. Letavic).

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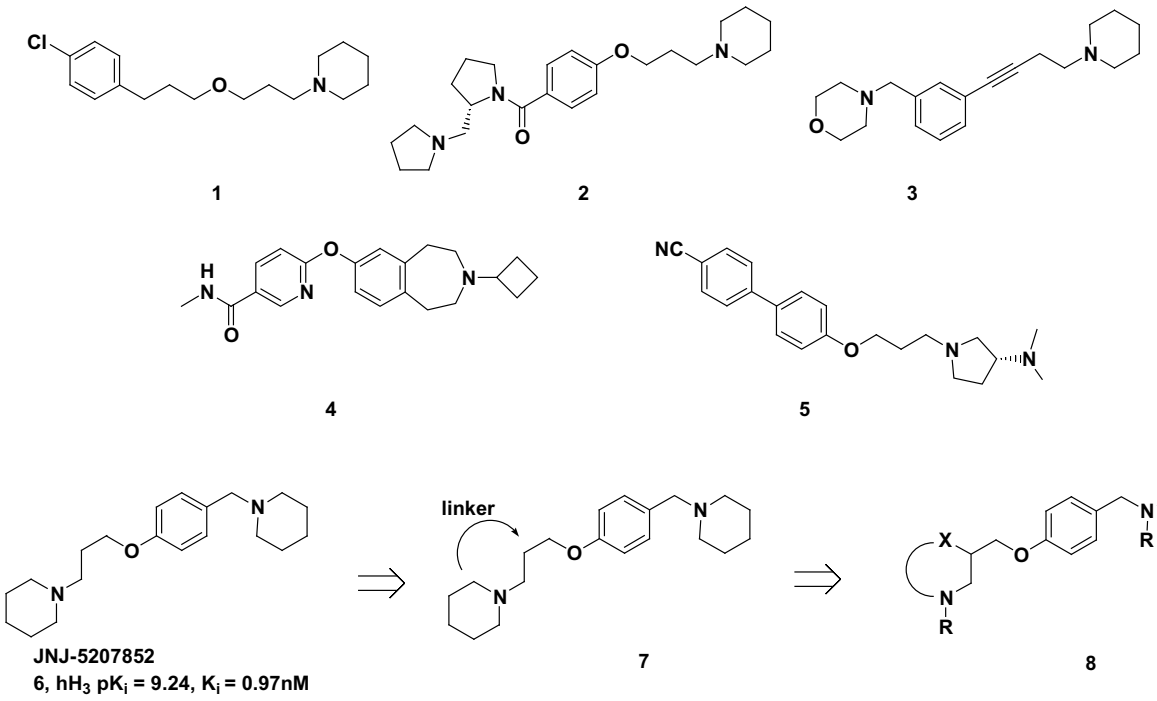
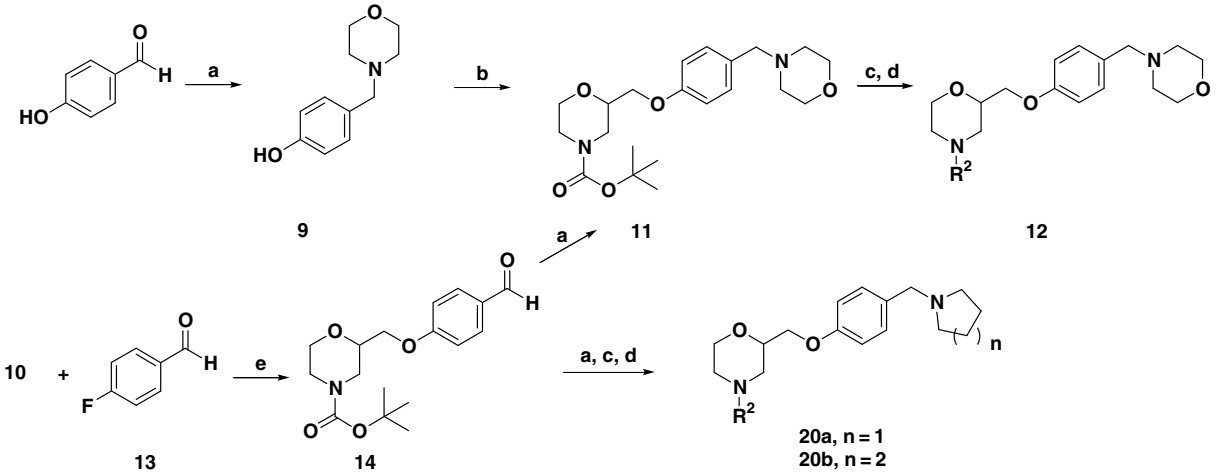
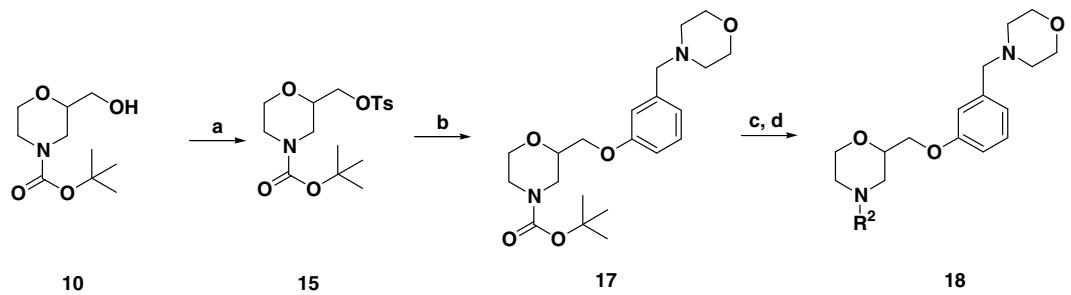


tion to this apparent requirement for the benzyl amine functionality for high affinity, branched alkyl groups at R_2 appear to have important interactions with the H_3 receptor. It is interesting to note that the meta substituted compounds **18a–c** consistently have lower affinity than the corresponding para substituted analogs **12c–e**.

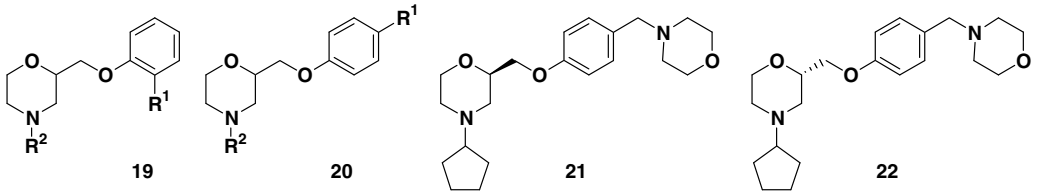


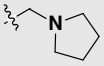
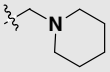
Scheme 1. Synthesis of compounds **12**. Reagents and conditions: (a) amine, $NaBH(OAc)_3$, MeOH, 23 °C, 7 h, 62–93%; (b) 2-hydroxymethyl-morpholine-4-carboxylic acid *tert*-butyl ester (**10**), PPh_3, DEAD, CH_2Cl_2, 23 °C, 24 h, 0–34%; (c) TFA, CH_2Cl_2; (d) ketone or aldehyde, $NaBH(OAc)_3$, MeOH, 23 °C, 29–97% (two steps); (e) NaH, DMF, 90 °C, 24 h, 64%.



Scheme 2. Synthesis of compounds **18**. Reagents and conditions: (a) TsCl, CH_2Cl_2, DIPEA, pyridine, 18 h, 23 °C, 96%; (b) 3-morpholin-4-ylmethyl-phenol (**16**), Cs_2CO_3, DMSO, 50 °C, 4 h, 96%; (c) TFA, CH_2Cl_2, quant.; (d) ketone or aldehyde, $NaBH(OAc)_3$, MeOH, 23 °C, 27–48%.

Table 1
Binding data for the rat and human H_3 receptors for compounds **12** and **18–22**



Compound	R^1	R^2	Rat H_3 K_i (nM)[a]	Rat H_3 pA_2[a]	Human H_3 K_i (nM)[a]	Human H_3 pA_2[a]
12a	—	Me	—	—	2100 ± 1500	—
12b	—	Et	—	—	165 ± 46	—
12c	—	*c*-Pr	—	—	106 ± 16	—
12d	—	*i*-Pr	92 ± 32	—	49 ± 9	—
12e	—	*c*-Bu	75 ± 7	7.72 ± 0.00	18 ± 6	8.51 ± 0.05
12f	—	*c*-Pent	20 ± 3	8.32 ± 0.07	3.6 ± 0.9	9.02 ± 0.08
18a	—	*c*-Pr	—	—	566 ± 193	—
18b	—	*i*-Pr	562 ± 99	6.60 (*n* = 1)	102 ± 24	7.35 ± 0.23
18c	—	*c*-Bu	277 ± 59	7.10 (*n* = 2)	37 ± 12	7.85 ± 0.05
19a	H	H	—–	—	>10,000	—
19b	H	*i*-Pr	—	—	4800 ± 2100	—
19c	OEt	*i*-Pr	—	—	9000 ± 0	—
19d	OEt	*c*-Bu	—	—	7100 ± 2300	—
19e	OEt	*c*-Pr	—	—	>10,000	—
19f	OEt	*c*-Pent	—	—	5300 ± 2900	—
20a		*c*-Pent	9.8 ± 2.9	8.80 ± 0.08	2.2 ± 0.1	9.48 (*n* = 2)
20b		*c*-Pent	10 ± 3	8.81 ± 0.14	2.5 ± 0.3	9.83 (*n* = 2)
21	—	—	121 ± 8	7.36 ± 0.07	31 ± 2	8.10 ± 0.02
22	—	—	9.7 ± 2.1	8.67 ± 0.06	1.9 ± 0.1	9.42 ± 0.04

[a] Except where indicated values are the means of at least three experiments in triplicate. K_i ± SEM is reported.

In the case of compound **12f** both enantiomers were prepared (**21** and **22**), and the (*S*)-isomer (**22**) was clearly better accommodated by the receptor. As such, **22** was chosen for in vivo evaluation in rats.

Figures 1 and 2 show dose response data for ex vivo receptor occupancy and compound levels in the brain and plasma at one hour following oral administration of compound **22** to rats. These data indicate good plasma and brain exposures (Fig. 1) and robust receptor occupancy after oral administration (Fig. 2). Compound **22** gave an 80% receptor occupancy in the ex vivo occupancy assay at 0.3 mg/kg (po). Considering that compound **22** has higher functional activity at the human histamine H_3 than at the rat receptor

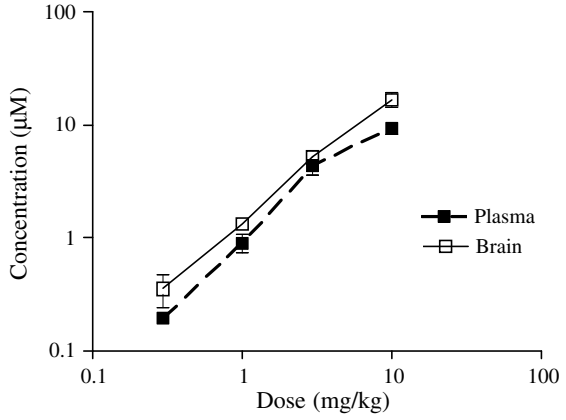


Figure 1. Plasma and brain concentrations for compound **22** in the rat after oral administration at 60 min. Results are represented as average ± SEM of *n* = 3.

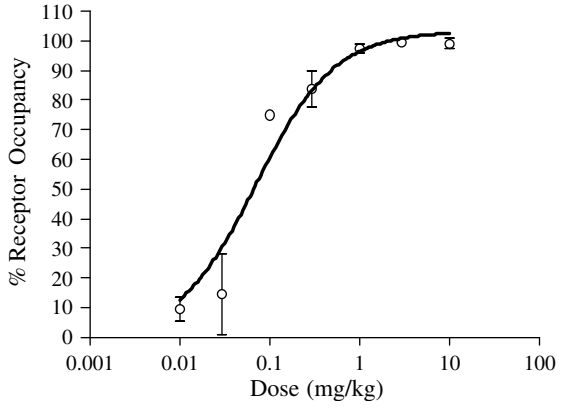


Figure 2. Ex vivo histamine H_3 receptor occupancy data in rat striatum for compound **22**: oral dose dependency at 60 min. Results are represented as average ± SEM of *n* = 3.

(human pA_2 = 9.42 vs rat pA_2 = 8.67) it is possible that the exposure required for occupancy in human may be even lower than that required in rat.

Figure 3 shows the brain and plasma concentrations of compound **22** as a function of time in rats following oral administration. The data support our hypothesis that these morpholines have improved pharmacokinetics as compared to more basic piperidines such as JNJ-5207852 (**6**), which has been reported to have sustained drug levels in the brain (out to 48 h post dose) upon oral administration to rats.[17]

In conclusion, we have demonstrated that this new series of 2-aryloxymethylmorpholines are high affinity histamine H_3 receptor

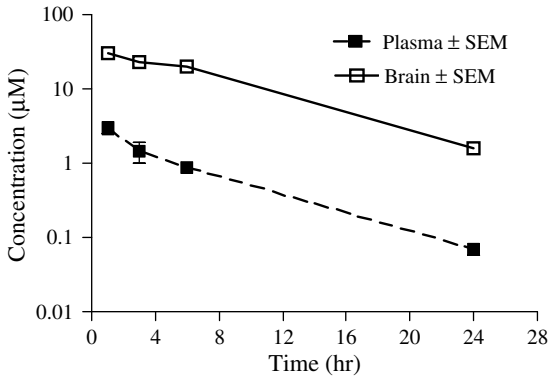


Figure 3. Plasma and brain concentrations for compound **22** as a function of time in the rat after oral administration. Results are represented as average ± SEM of $n = 3$.

antagonists and that one member of the series shows a high level of receptor occupancy after oral administration. In addition, these morpholine-based histamine H_3 antagonists have improved pharmacokinetic properties over some of the previously described propyloxypiperidines.

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