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Reduction of CYP450 inhibition in the 4-[(1*H*-imidazol-4-yl)methyl]piperidine series of histamine H_3 receptor antagonists

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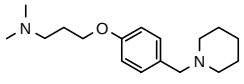
Abstract—A novel series of histamine H_3 receptor antagonists based on the 4-[(1*H*-imidazol-4-yl)methyl]piperidine template displaying low CYP2D6 and CYP3A4 inhibitory profiles has been identified. Structural features responsible for the reduction of P450 activity, a typical liability of 4-substituted imidazoles, have been established.

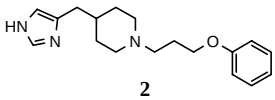
In the preceding paper, we described a series of novel histamine H_3 receptor antagonists based on the 4-[(1*H*-imidazol-4-yl)methyl]piperidine scaffold. While displaying high affinity for both guinea pig and human receptors as well as excellent functional activity, these compounds simultaneously had a high level of CYP450 enzyme inhibition, in particular CYP2D6, a notorious liability of 4-substituted imidazoles limiting their use.[1] Strong inhibition of P450 enzymes may disrupt normal metabolism of xenobiotics, potentially resulting in undesired drug–drug interactions.[2] We report here SAR investigations that have led us to establish structural features within the 1*H*-imidazol-4-yl series that allow suppression of CYP2D6 and CYP3A4 inhibitory activity, while maintaining H_3 antagonist activity.

Our earlier unpublished investigations in this area identified **1** as a non-imidazole H_3 antagonist of moderate activity.[3] While its P450 inhibitory activity was above 30 μM level with respect to both CYP2D6 and CYP3A4, H_3 activity left room for improvement. We decided to test whether we could advantageously incorporate the structural features of this analog into the previously described noticeably more potent 4-[(1*H*-imidazol-4-yl)methyl]piperidine series, exemplified by **2**.



1

K_i (H_3, gp) = 33 nM
pA_2 (gp ileum) = 7.5
IC_{50} (2D6, 3A4) > 30 μM



2

K_i (H_3, gp) = 4 nM
pA_2 (gp ileum) = 8.3
IC_{50} (2D6) = 0.03 μM
IC_{50} (3A4) > 20 μM

The compounds prepared for this study are listed in Table 1. Direct crossover analogs between the two structural types, exemplified by **1** and **2**, have the piperidine ring in the position of either of the two basic nitrogen sites in **1**. In particular, replacement of the right-side piperidine ring with the 4-[(1*H*-imidazol-4-yl)methyl]piperidine fragment gave rise to **3**—the first 4-substituted imidazole analog devoid of 2D6 and 3A4 inhibitory activity, but possessing only moderate H_3 activity.

Keywords: Histamine; H_3 antagonists; Imidazole series; 4-[(1*H*-imidazol-4-yl)methyl]piperidine; Decongestion; Allergic rhinitis; CYP450 inhibition.
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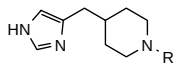
Table 1. H_3 binding affinity, functional activity, and CYP2D6 inhibition profile of H_3 antagonists



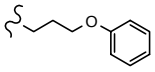
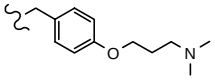
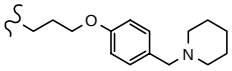
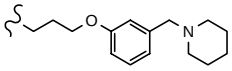
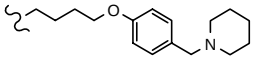
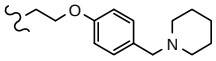
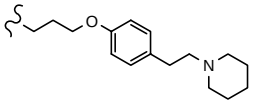
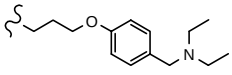
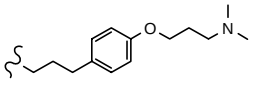
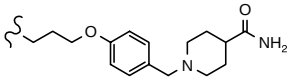
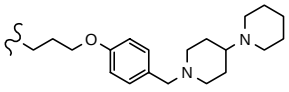
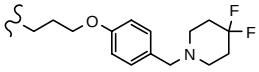
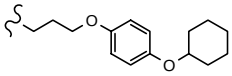
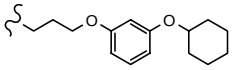
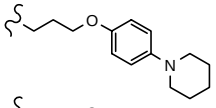
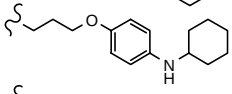
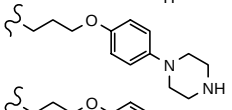
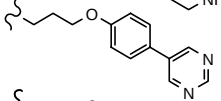
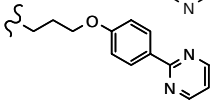
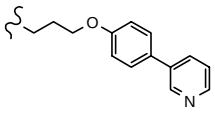
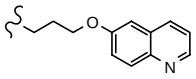
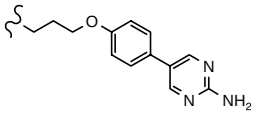
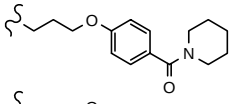
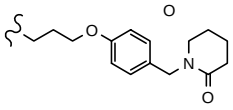
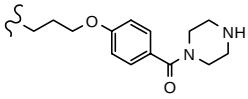
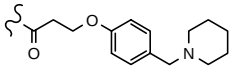
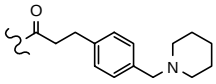
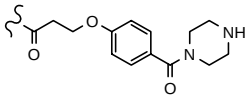
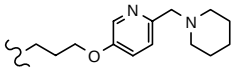
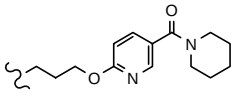
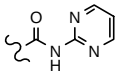
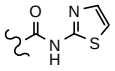
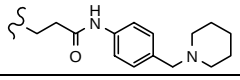
Compound	R	K_i (nM)[a]	pA_2[b]	IC_{50} (2D6) (μM)[c]
2		4	8.3	0.03
3		17	7.1	>30
4		3	8.6	14
5		1	8.4	3
6		16	7.8	>20
7		5	ND[e]	3
8		3	8.5	1[d]
9		4	8.8	6
10		13	7.3	>30
11		16	7.6	>30[d]
12		3	ND	>30
13		4	ND	6
14		6	ND	0.3
15		3	ND	2
16		15	ND	1
17		15	ND	0.9
18		12	ND	>20
19		9	ND	4
20		45	ND	6

Table 1 (*continued*)

Compound	R	K_i (nM)[a]	pA_2[b]	IC_{50} (2D6) (μM)[c]
21		12	ND	0.3
22		52	ND	2
23		12	7.7	12
24		26	7.7	2[d]
25		34	ND	5[d]
26		23	7.8	>20
27		315	ND	1
28		45	ND	3
29		51	ND	30
30		10	8.1	3
31		24	7.7	2
32		8	7.6	6
33		4	7.6	2
34		40	ND	9

[a] Inhibition of [^{3}H]-*N*-α-methylhistamine binding to guinea pig brain receptor.[4] H_3 binding K_i values are the average of at least two independent determinations. The assay-to-assay maximum variability in the series was ±3-fold. More common variability was ±2-fold.

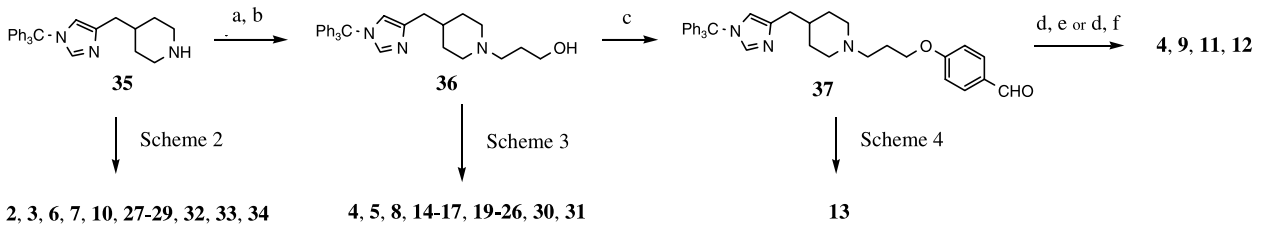
[b] Antagonist potency in an electrically stimulated guinea pig ileum.[5] pA_2 values are the average of at least four independent determinations. The assay-to-assay maximum variability in the series was ±0.2.

[c] Human liver microsome assay,[6] unless indicated otherwise. IC_{50} values are the average of at least three independent determinations. The assay-to-assay maximum variability in the series was ±15%.

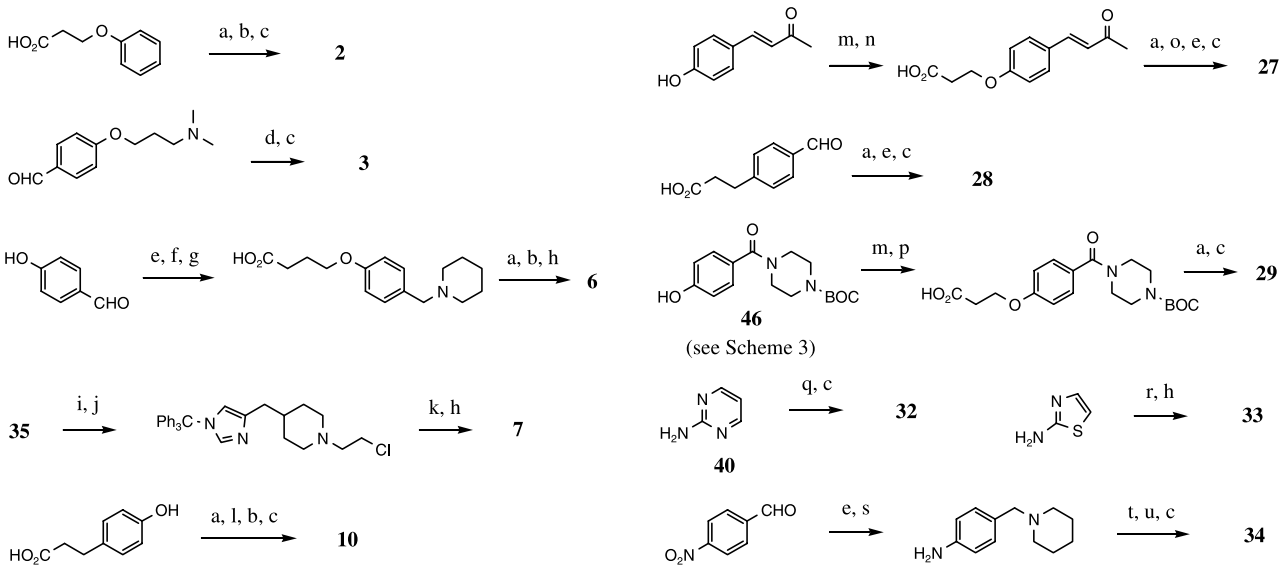
[d] Supersome™ assay.[7] IC_{50} values are the average of at least three independent determinations. The maximum variability in the series was ±15%. For very good correlation between Supersome™ and human liver microsome assays with respect to IC_{50} (CYP2D6) see ref. 7.

[e] Not determined.

At the same time substitution of the 4-[(1*H*-imidazol-4-yl)methyl]piperidine moiety for the left-side nitrogen center in **1** provided **4**, a highly potent H_3 antagonist with a favorably high threshold of 2D6 and 3A4 (IC_{50} > 30 μM) inhibition. While 2D6 activity varied significantly among the compounds listed in Table 1, 3A4 inhibitory activity was found not to be an issue in this series (IC_{50} > 20 μM). Further studies established structural features critical for the best combination of high H_3 and low CYP2D6 inhibitory activity.



Scheme 1. Reagents and conditions: (a) Methyl acrylate, toluene, 110 °C; (b) $LiAlH_4$, THF, 80% (2 steps); (c) 4-hydroxybenzaldehyde, 1,1′-(azodicarbonyl)dipiperidine, Bu_3P, THF, 90%; (d) R_1R_2NH, $NaBH(OAc)_3$, CH_2Cl_2 or dichloroethane, 45–95%; (e) HCl, MeOH, Δ, 95%; (f) maleic acid, MeOH, Δ, 95%.

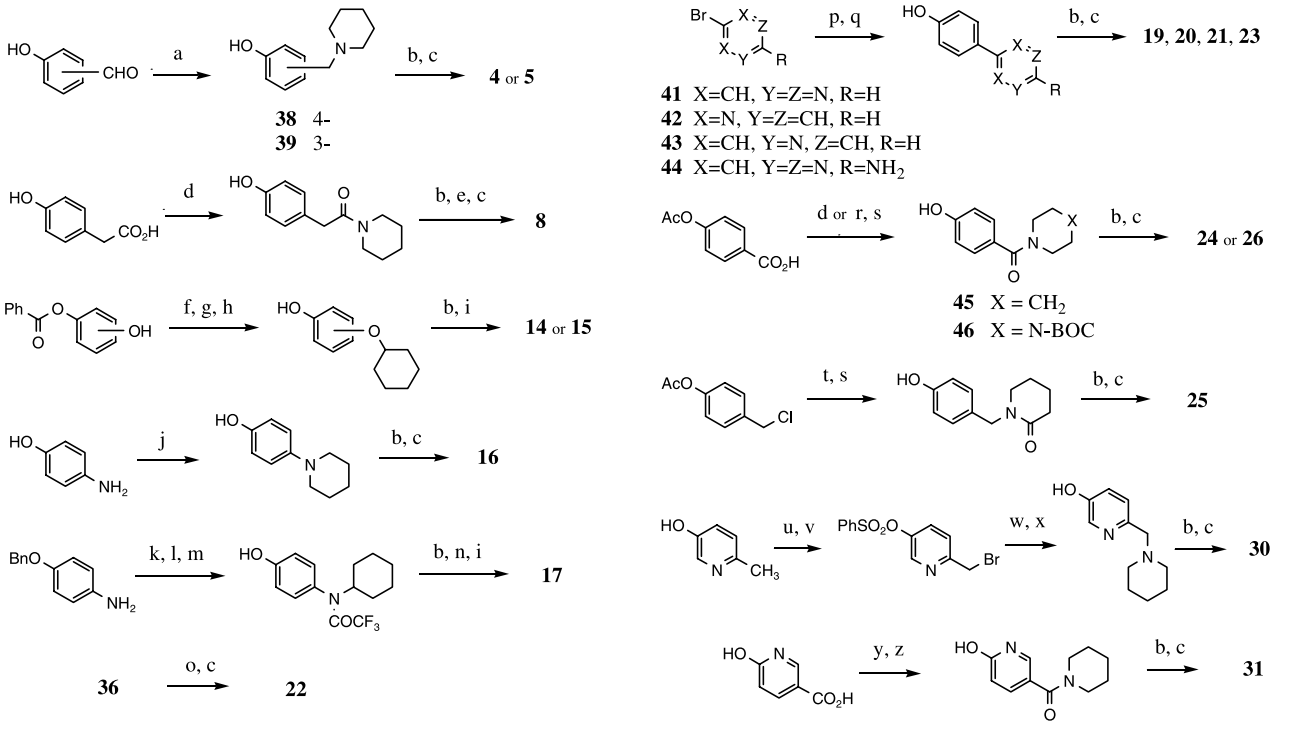


Scheme 2. Reagents and conditions: (a) **35**, EDC, HOBT, CH_2Cl_2, 60–80%; (b) $LiAlH_4$, THF, 55–80%; (c) HCl, MeOH, Δ, 95%; (d) **35**, $NaBH(OAc)_3$, CH_2Cl_2, 91%; (e) piperidine, $NaBH(OAc)_3$, CH_2Cl_2, 75–95%; (f) ethyl 4-bromobutyrate, K_2CO_3, acetone–H_2O, 63%; (g) NaOH, MeOH–H_2O-THF, 100%; (h) maleic acid, MeOH, Δ, 60–99%; (i) $BrCH_2CH_2OH$, Et_3N, DMF, 60 °C, 40%; (j) $SOCl_2$, CH_2Cl_2, 79%; (k) 1-(4-hydroxybenzyl)piperidine **38** (see Scheme 3), NaH, KI, DMF, 50 °C, 38%; (l) $HOCH_2CH_2CH_2NMe_2$, 1,1′-(azodicarbonyl)dipiperidine, Bu_3P, THF, 80%; (m) $HOCH_2CH_2CH_2OH$, 1,1′-(azodicarbonyl)dipiperidine, Bu_3P, THF, 70%; (n) CrO_3, H_2SO_4, H_2O, 90%; (o) OsO_4 (cat.), $NaIO_4$, acetone–H_2O, 95%; (p) RuO_2 (cat.), $NaIO_4$, CH_3CN-H_2O, 30%; (q) benzotriazole, $COCl_2$, toluene, 60 °C; then, **40**, Et_3N, **35**, CH_2Cl_2, 12%; (r) triphosgene, Et_3N, **35**, CH_2Cl_2, 32%; (s) H_2, 10% Pd/C, EtOAc-MeOH, 37%; (t) acryloyl chloride, Et_3N, CH_2Cl_2, 55%; (u) **35**, MeOH, 60%.

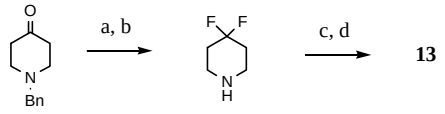
Within the 4-substituted imidazole series, typified by **4**, a low CYP2D6 inhibition profile seems to be largely dependent on the structural characteristics of the part of the molecule most distant from the imidazole ring. Most compounds appear to benefit from the basic nature of this region. In the case of aliphatic amines, the threshold of CYP2D6 inhibition is raised significantly, compared to **2**, often into the double-digit micromolar range (**6**, **10**, **11**, **12**, and **18**), although the position of the nitrogen seems to be critical (e.g., **4** vs **8** and **4** vs **5**). Aromatic amines, as well as aromatic nitrogen heterocycles, have generally been stronger CYP2D6 inhibitors (e.g., **16**, **17**, **19′**, and **21**), possibly due to the altered position of the nitrogen or reduced basicity of these compounds.

Other attempts to moderate or eliminate basicity of this part of the molecule, either through selective substitution or removal of basic nitrogen, produced compounds with a lower CYP2D6 inhibition threshold compared to **4** (e.g., **13**, **14**, and **15**).[8] In agreement with this trend, amide derivatives **24** and **25** are stronger P450 inhibitors than **4**, while reintroduction of a basic site in **26** reestablishes a much higher inhibition threshold. Modifications in other parts of the molecule, although attempted, have not generated clear SAR trends and generally did not improve the P450 profile (e.g., **27**, **29**–**34**). Compound **34** is a crossover analog to the 4-[(1*H*-imidazol-4-yl)methyl]piperidine series, described in the previous paper, in which aniline amide was shown to be the most H_3 active pharmacophore. However, with the introduction of piperidinemethyl substituent in the 4-position H_3 activity drops dramatically. Overall, 4-alkoxybenzyl amines appear to have the best combination of H_3 activity and CYP450 profile (e.g., **4**, **12**). The synthetic approaches to compounds in Table 1 utilize previously described trityl-protected imidazolylmethylpiperidine **35**[9] and are shown in Schemes 1–4.

Having achieved a significant separation between the H_3 activity and undesired CYP450 inhibitory activity, we investigated the pharmacokinetic profiles of several compounds in this series. The compound with the best biological profile, **4**, showed no plasma levels when



Scheme 3. Reagents and conditions: (a) Piperidine, $NaBH(OAc)_3$, CH_2Cl_2, 95%; (b) **36**, 1,1′-(azodicarbonyl)dipiperidine, Bu_3P, THF, 40–90%; (c) HCl, MeOH, Δ, 80–95%; (d) piperidine, EDC, HOBT, CH_2Cl_2, 88%; (e) $LiAlH_4$, THF; (f) cyclohexene, $HgSO_4$, I_2, $CHCl_3$, 34%; (g) Bu_3SnH, AIBN, toluene, Δ, 39%; (h) NaOH, MeOH, 90%; (i) maleic acid, MeOH, Δ, 90%; (j) 1,5-dibromopentane, Et_3N, CH_2Cl_2, 5%; (k) cyclohexanone, $NaBH(OAc)_3$, dichloroethane, 64%; (l) TFAA, pyridine, CH_2Cl_2, 93%; (m) H_2, $Pd(OH)_2$ (cat.), EtOAc, 100%; (n) $NaBH_4$, EtOH, 100%; (o) 6-hydroxyquinoline, 1,1′-(azodicarbonyl)dipiperidine, Bu_3P, THF, 75%; (p) 4-methoxyphenylboronic acid, $Pd[dppf]_2Cl_2$ (cat.), K_3PO_4, DME, 100 °C, 92–99%; (q) BBr_3, CH_2Cl_2, 75–90%; (r) *N*-BOC-piperazine, EDC, HOBT, CH_2Cl_2; (s) K_2CO_3, MeOH, 50–65% (2 steps); (t) 2-piperidone, KHMDS, THF, 17%; (u) $PhSO_2Cl$, Et_3N, CH_2Cl_2, 100%; (v) NBS, AIBN, CCl_4, Δ, 47%; (w) piperidine, BuLi, THF, 38%; (x) NaOH, MeOH–H_2O, Δ, 64%; (y) $ClCH_2CN$, Et_3N, acetone–H_2O, Δ, 30%; (z) piperidine, Δ, 100%.



Scheme 4. Reagents: (a) DAST, CH_2Cl_2, 79%; (b) H_2, $Pd(OH)_2$, EtOAc, 94%; (c) **37**, $NaBH(OAc)_3$, EtOH, dichloroethane, 81%; (d) maleic acid, MeOH–H_2O, 92%.

dosed orally in rats, and low levels when dosed orally in monkeys (AUC_{0-24h} = 3200 nM h (po, 3 mpk)). A study with ^3H-labeled **4** identified no major metabolites and indicated an extremely low (<2%) level of excreted radioactivity over the 24 h period, both in the case of oral and intravenous administration. This experiment was then followed up with a whole body autoradiography study in the rat. Upon oral administration poor absorption of compound from the GI tract was observed, possibly due to the highly polar nature of **4**. Intravenous administration, however, did not improve plasma levels and led to extensive tissue distribution without any particular area of concentration. No compound clearance over the 24 h period was observed. Poor plasma levels in rats appear to be a general feature of this series of compounds. For example, it was also observed with **16**, **19**, **23**, **24**, **30**, and **31**. While modifications of the right side of the molecule do not seem to have any effect on plasma levels, derivatives of the central piperidine ring seem to trend in the right direction. We observed, for example, measurable plasma levels in the rat with urea **33** (AUC_{0-6h} = 1030 nM h (po, 10 mpk)) and even higher levels with amide **27** (AUC_{0-6h} = 1830 nM h (po, 10 mpk)), however in the latter case H_3 activity was significantly diminished.

In conclusion, introduction of basic groups into the right side of 4-[(1*H*-imidazol-4-yl)methyl]piperidine series of potent H_3 antagonists generally suppressed CYP450 inhibition, usually observed with imidazole compounds, while preserving H_3 activity. The central piperidine ring of the series appears to be the main source of the poor pharmacokinetic profile in rats. Its derivatives with improved pharmacokinetic profiles have been identified. Any further developments in this area will be reported in due course.

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8. Interestingly, CYP2D6 profile of meta-substituted analogs, while inferior to that of **4**, appears to be much less sensitive to the presence of basic nitrogen or lack thereof (see **15** vs **5** compared to **14** vs **4**).
9. See preceding paper.