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Bioorganic & Medicinal Chemistry Letters
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Bioorganic & Medicinal Chemistry Letters 14 (2004) 689–693

A new class of potent non-imidazole H_3 antagonists: 2-aminoethylbenzofurans

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Received 3 October 2003; revised 8 November 2003; accepted 14 November 2003

Abstract—2-Aminoethylbenzofurans constitute a new class of H_3 antagonists that are more rotationally constrained than most previously reported H_3 antagonists. They retain high potency at human and rat receptors, with efficient CNS penetration observed in **35**. The SAR of the basic amine moiety was compared in three different series of analogues. The greatest potency was found in analogues bearing a 2-methylpyrrolidine, a 2,5-dimethylpyrrolidine, or a 2,6-dimethylpiperidine.

Histamine (**1**) is an important modulator of human and animal physiological processes.[1] Four distinct histamine receptor subtypes mediate the direct actions of histamine. H_1 receptors play a critical role in regulating inflammatory responses and CNS activity, and H_1 antagonists are used clinically to treat allergic asthma and rhinitis. H_2 receptors regulate gastric acid secretion, and H_2 antagonists are used clinically to treat excess acid production.[2] The newly discovered H_4 receptor is found in immune cells, suggesting a role in regulating inflammatory responses.[3]

The recent cloning of H_3 receptors from several species[4] and the molecular characterization of H_3 receptors have provided new tools, and a clearer rationale, for a role for H_3 antagonists in treating human disease. Found on presynaptic nerve terminals, the H_3 receptor is constitutively active, and acts as a 'brake' on neurotransmitter release.[5] H_3 antagonists relieve this inhibition, thereby elevating levels of histamine, acetylcholine, and other neurotransmitters. In animal models, H_3 antagonists have demonstrated efficacy in enhancing cognition and attention,[6] regulating wakefulness and weight gain,[7] and ameliorating allergic rhinitis[8] (when coadministered with H_1 antagonists). However, in spite of the likely medical utility of H_3 antagonists, no agent in the class has yet received clinical approval, perhaps due to inadequate drug-like properties.

The imidazole-based H_3 antagonists such as ciproxifan (**2**) and thioperamide (**3**) are useful tools and reference standards for pharmacological research,[1] but attention has been drawn to the potential liability of imidazole-containing compounds for clinical use, due to their potential to inhibit cytochrome-P_{450} (CYP) drug metabolizing enzymes.[8] This could then lead to drug–drug interactions by inhibiting the metabolism of co-administered drugs.[9] For this reason, non-imidazoles have been targeted as potential drug candidates, and several distinct classes of non-imidazole H_3 antagonists have been produced (Fig. 1). Several of the most potent and promising classes of non-imidazoles such as **4**[10] (UCL-1972), **5**[11] (UCL-2190), **6**,[12] and **7**[13] (A-349821) share common structural features, namely, a basic amine connected through an alkoxy chain to a lipophilic group. Of these prototypes, the amino-propyloxy-aryl combination seen in compounds **5**–**7** may represent a privileged H_3 antagonist pharmacophore.[1d,g]

A new class of H_3 antagonists, the 2-aminoethylbenzofurans (**9**) shown in Figure 2, was designed to give compounds more structurally rigidified than those comprising the established pharmacophore (**8**). By converting the proximal methylene in **8** to a sp^2 carbon, then connecting to the phenyl moiety through a newly created sp^2 carbon, the resulting benzofurans (**9**) remove two rotatable bonds. One goal was to enhance the

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doi:10.1016/j.bmcl.2003.11.032

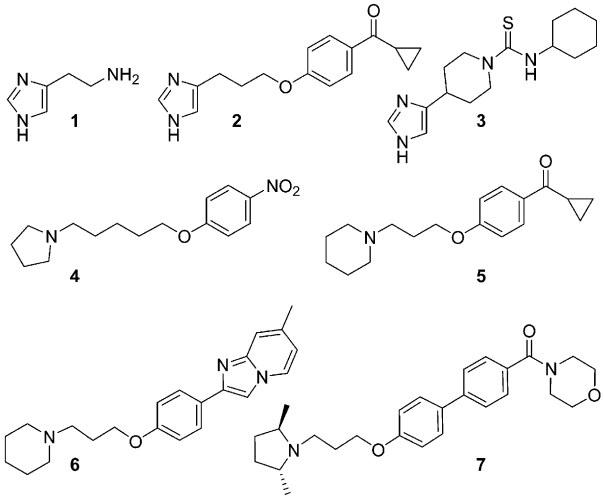


Figure 1. Structures of H_3 antagonists based on imidazoles (**2**, **3**), and non-imidazole H_3 antagonists (**4**–**7**).

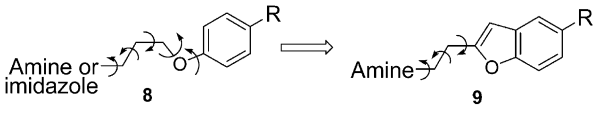


Figure 2. H_3 antagonists based on 2-aminoethylbenzofurans (**9**) have less conformational mobility than analogues (**8**) based on the 3-aminopropyloxyphenyl skeleton.

selectivity of compounds for H_3 over other receptors. It has also recently been proposed that reductions in rotatable bond count are associated with improved absorption in vivo,[14] and with increased drug-likeness.[15]

The synthesis of the target benzofurans required phenols **16**–**19** as starting materials (Fig. 3). While **19** is commercially available, and **18** was easily produced by amination of **17**, the preparation of **16** required a multistep sequence. By *trans*-lithiation of **10**, then quenching with tri-isopropyl borate, the borate ester **11** was produced, which when treated acid produced the boronic acid **12**. Suzuki coupling of **12** with **14** gave **15**, which was deprotected with fluoride to give **16**. By carefully controlled selective iodination of **16**, **18**, and **19** with sodium hypochlorite and sodium iodide at low temperature, good yields of the monoiodides **20**–**22** were produced. The palladium catalyzed Sonagashira–Stevens coupling products were readily cyclized to the 2-hydroxyethylbenzofurans **23**–**25** in high yields. For conversion to the final products (**26**–**28**), the alcohols were converted to the mesylates, which could be isolated in high yield, but typically were not purified, but reacted directly with target amines in CH_3CN at ambient temperature. For the most highly hindered amines, (2*R*,5*R*)-dimethylpyrrolidine and (*cis*-2,6)-dimethylpiperidine, heating at 80 °C for 2–48 h was required to induce displacement of the mesylates, and was accompanied by substantial amounts (50 and 90%, respectively) of the

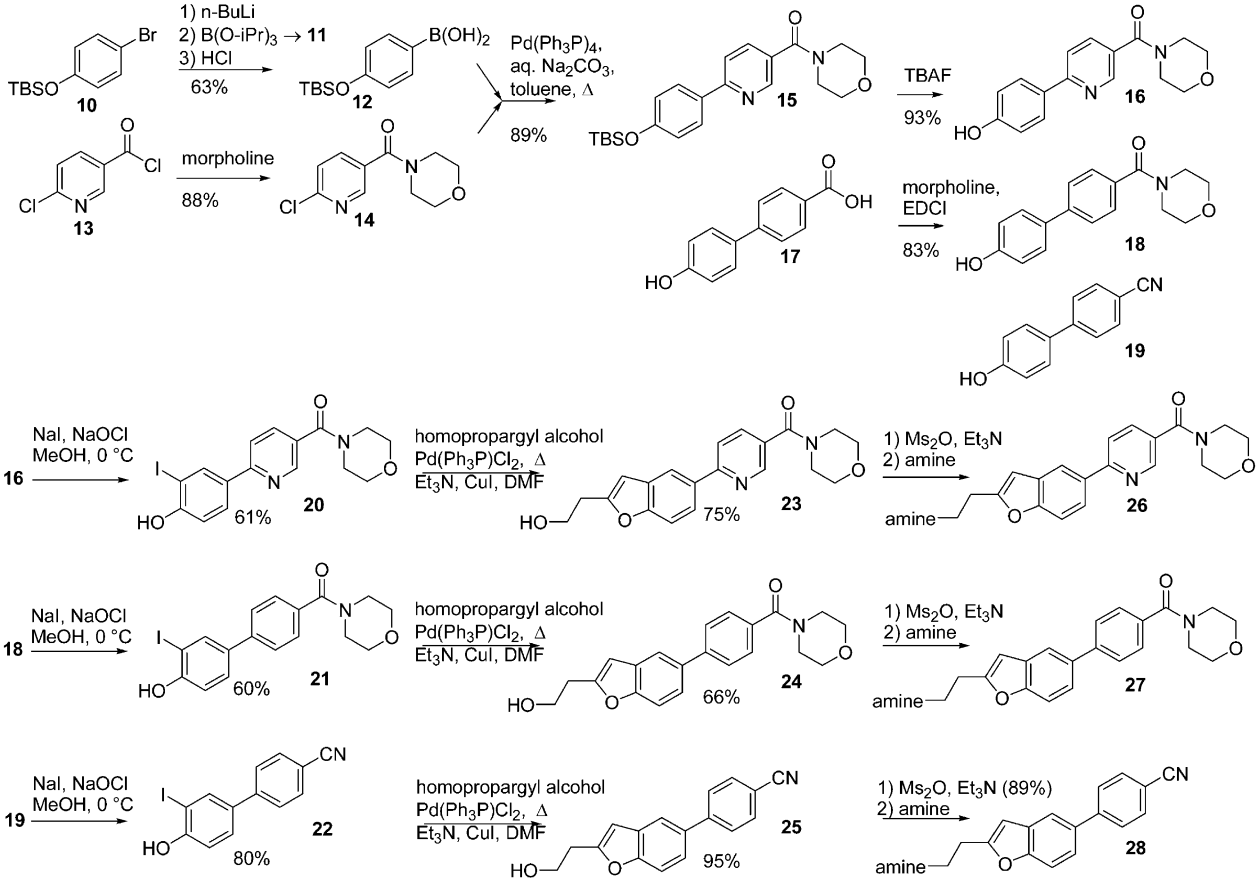


Figure 3. Synthesis of the 2-aminoethylbenzofuran H_3 antagonists.

styrene side product produced by E_2 elimination. Commercially available optically pure amines were used to prepare **30**–**34** and **37** in >96% e.e. Products were purified to >95% purity by reversed phase HPLC, eluting with acetonitrile/aqueous CF_3CO_2H.

As our ultimate goal was to find CNS drug candidates, we sought compounds with an ability to achieve selectively high brain concentrations, features associated with relatively high lipophilicity and low molecular weight. We also sought compounds combining comparable and high potency at both human and rat H_3 receptors ($K_i < 10$ nM), since this would enhance the likelihood that agents found potent and effective in the rat behavioral models would have similar effects in humans.

An assessment of the SAR of the basic amine moiety from the data in Table 1 shows that for compounds **29**–**38**, all bearing the 4-cyanophenyl aromatic group, the pyrrolidine **29**, the racemic 2-methylpyrrolidine **35** and 2-methylpiperidine **37**, and (2*S*)-hydroxymethyl pyrrolidine **33** possessed the greatest potency (<10 nM) at the human receptor, while only compound **35** possessed a similar degree of high potency at the rat receptor. Analogues bearing pyrrolidine rings with other polar substituents (**30**–**32**, **34**), and polar heterocycles (**36**, **42**, **45**) all had lower H_3 potency. When the effects of the aromatic benzofuran ring substituents are compared in the compounds bearing identical amines in Table 1 (**29** versus **43**; **33** versus **39**; **37** versus **44**), there appears to be little effect of the aromatic ring on H_3 potency. Among chiral compounds, the (3*R*)-dimethylaminopyrrolidine **31** was slightly more potent than the (3*S*)-dimethylaminopyrrolidine **30**. The (2*S*)-hydroxymethylpyrrolidines (**33**, **39**) were much more potent than the (2*R*)-hydroxymethylpyrrolidines (**32**, **44**). It might be anticipated that the potency of racemic **35** still could be increased further with the synthesis of the appropriate pure enantiomer. Since the absolute configuration of the most potent enantiomer of 2-hydroxymethylpyrrolidine (2*S*)

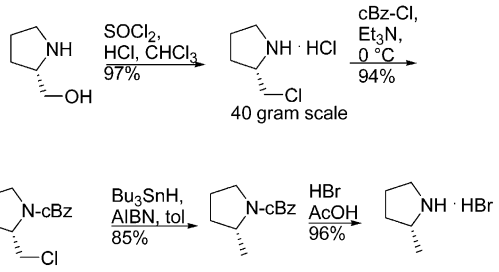
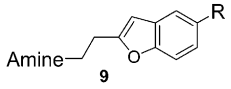


Figure 4. Synthesis of *R*-2-methylpyrrolidine.

Table 1. SAR of compounds of general structure **9**, varying the aromatic substituent R, and the amine moiety



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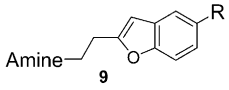
	Compd	Human H_3		Rat H_3	
		K_i nM	pK_i±SEM	K_i nM	pKi±SEM
Ar substituent **R** →	**Ph(4-CN)**				
Amine ↓					
Pyrrolidine	**29**	4.2	8.37±0.07	47	7.33±0.04
(3*S*)-Dimethylaminopyrrolidine	**30**	49	7.31±0.03	140	6.86±0.07
(3*R*)-Dimethylaminopyrrolidine	**31**	16	7.80±0.09	63	7.20±0.16
(2*R*)-Hydroxymethylpyrrolidine	**32**	18	7.75±0.19	160	6.78±0.13
(2*S*)-Hydroxymethylpyrrolidine	**33**	2.2	8.65±0.04	26	7.59±0.08
(2*R*)-Carboxymethylpyrrolidine	**34**	320	6.50±0.20	1600	5.79±0.20
(±2)-Methylpyrrolidine	**35**	0.95	9.02±0.06	6.5	8.19±0.11
N-Imidazolyl	**36**	600	6.22±0.12	2200	5.66±0.14
(±2)-Methylpiperidine	**37**	5.8	8.23±0.10	45	7.35±0.09
(Δ3,4)-Tetrahydropyridine	**38**	10	7.99±0.17	50	7.30±0.20
	Ph(4-CO morpholine)				
(2*S*)-Hydroxymethylpyrrolidine	**39**	1.9	8.72±0.04	6.9	8.16±0.06
(±2)-Methylpiperidine	**40**	3	8.52±0.19	14	7.87±0.20
(Δ3,4)-Tetrahydropyridine	**41**	5.9	8.23±0.25	17	7.77±0.16
Morpholine	**42**	45	7.35±0.20	160	6.79±0.22
	Pyridine(4-CO morpholine)				
Pyrrolidine	**43**	3.9	8.4±0.25	29	7.53±0.24
(2*R*)-Hydroxymethylpyrrolidine	**44**	36	7.44±0.32	110	6.96±0.24
Morpholine	**45**	150	6.83±0.17	260	6.59±0.08

Binding potencies were assessed by displacement of ^{3}H–N-α-methyl histamine. The human H_3 values were from cloned human H_3 expressed in C6 cells, while rat H_3 values were from rat cortical membranes. p$K_i = -\log K_i$. The number of independent pK_i determinations was ≥3 for all compounds.

Table 2. SAR of compounds of general structure **9**, varying the aromatic R substituent, and the amine moiety



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R→		Ph(4-CN)					Ph(4-COmorpholine)					Pyridine(4-COmorpholine)				
		Human H_3		Rat H_3			Human H_3		Rat H_3			Human H_3		Rat H_3		
Amine ↓	#	K_i nM	pK_i±SEM	K_i nM	pK_i±SEM	#	K_i nM	pK_i±SEM	K_i nM	pK_i±SEM	#	K_i nM	pK_i±SEM	K_i nM	pK_i±SEM
(2)-Methyl pyrrolidine	**46 (R)***	0.45	9.35±0.04	3.22	8.49±0.04	**53**	0.7	9.15±0.06	2	8.71±0.04	**60 (R)**	0.55	9.26±0.06	1.6	8.79±0.08
(2*R*,5*R*)-Dimethyl pyrrolidine	**47**	5.1	8.29±0.00	42	7.38±0.04	**54**	2.2	8.65±0.22	6.9	8.16±0.17	**61**	5.9	8.23±0.23	26	7.59±0.16
(3*R*)-Hydroxy pyrrolidine	**48**	8.8	8.05±0.03	95	7.02±0.08	**55**	6.2	8.21±0.15	35	7.46±0.20	**62**	12	7.93±0.21	67	7.17±0.14
Piperidine	**49**	8.8	8.06±0.02	59	7.23±0.13	**56**	2.3	8.64±0.20	6.2	8.21±0.18	**63**	12	7.9±0.25	49	7.31±0.21
(*cis*-2,6)-Dimethyl piperidine	**50**	2.4	8.62±0.06	22	7.67±0.08	**57**	1.2	8.92±0.23	6.6	8.18±0.21	**64**	5.6	8.25±0.2	45	7.35±0.05
4-Methyl piperidine	**51**	15	7.82±0.14	16	7.79±0.20	**58**	17	7.76±0.25	43	7.37±0.17	**65**	87	7.06±0.26	151	6.82±0.21
Hexahydro azapine	**52**	7.8	8.11±0.14	44	7.36±0.25	**59**	3.5	8.46±0.24	10	8.0±0.18	**66**	16	7.8±0.26	33	7.48±0.52

*Compound determined to be 99.9% e.e. by chiral HPLC analysis of the L-tartrate salt.

corresponds to the (2*R*) configuration of 2-methylpyrrolidine, the reported[16] synthesis of (2*R*)-methylpyrrolidine from (2*S*)-prolinol (>99% e.e.) was completed on a large scale as shown in Figure 4. High yields were obtained even when conducted on a 40 gram scale. This amine was then used to prepare **46** and **60**, bearing the 2*R*-methylpyrrolidine as the basic amine.

A comparison of the SAR of amine substituents in three different aromatic substituted series (**26**–**28**) is shown in Table 2. The amines in Table 2 were selected based on the characteristics likely to induce the highest potency among the compounds (**29**–**45**), that is, cyclic 5, 6, or 7-membered amines, especially *ortho*-methyl substituted amines. The targeted compounds were indeed potent; for example, incorporation of the (2*R*)-methylpyrrolidine in the 4-cyanophenylbenzofuran series gave the highly potent analogue **46** with K_i values of 0.45 nM at the human H_3 receptor, and 3.2 nM at the cortical rat H_3 receptor (1.35 nM at cloned rat H_3R). Thus 2-methylpyrrolidine induced high potency in all series (analogues **46**, **53**, **60**), as did (2*R*,5*R*)-dimethylpyrrolidine (analogues **47**, **54**, **61**). Similarly, (*cis*-2,6)-dimethylpiperidine (analogues **50**, **57**, **64**) induced high potency in all series, as did unsubstituted piperidine (**49**, **56**, **63**). Piperidine itself has long been known to induce high H_3 potency in disparate H_3 antagonist series.[10–13]

In comparing the SAR of the aromatic substituent, it is seen that the cyanophenyl analogues (**46**–**52**) had comparable potency to the phenylcarbonylmorpholine analogues (**53**–**59**). The pyridinecarbonylmorpholines (**60**–**66**) are heterocyclic aza analogues of **53**–**59**, and some potent analogues are potent, such as **60**, but in compounds **62**–**66** there appears to be a tendency for this series to have somewhat weaker potency.

Of the nine compounds which met the criteria for high potency (K_i <10 nM) at human and rat H_3R, and a desirable balance of affinity to both receptors (ΔpK_i <1), analogue **35** and its pure enantiomer **46** were judged most likely to penetrate the BBB efficiently and achieve high CNS concentrations, compared to blood levels. This assessment was based on the higher lipophilicity of **35** (CLogP = 5.2), compared to benzeneamide analogues like **53** (CLogP = 4.3), or pyridineamide analogues like **60** (CLogP = 2.1). Indeed, racemic compound **35** was found to efficiently penetrate CNS tissues, with brain:plasma ratios >30×, and very high brain concentrations were achieved (15,000 ng/gm) after iv dosing of **35** at 5 mg/kg.

The in vitro, metabolic, pharmacokinetic, and in vivo behavioral pharmacological profile of compounds in this series will be fully described elsewhere, but the data described here show that the new series of benzofuran-based H_3 antagonists contains compounds that achieve high CNS concentrations, as well as balanced nanomolar potency at both human and rat H_3 receptors.

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