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Structure–activity relationships of arylbenzofuran H_3 receptor antagonists

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Abstract—An SAR study of histamine H_3 receptor antagonists based on substituted (*R*)-2-methyl-1-[2-(5-phenyl-benzofuran-2-yl)-ethyl]-pyrrolidines is presented.

In the CNS, the histamine H_3 receptor (H_3R) modulates the release of neurotransmitters such as histamine, serotonin, dopamine, and acetylcholine.[1] H_3R antagonists induce the release of these neurotransmitters, and in animal models they have been demonstrated to enhance attention and cognition, and influence feeding, and so may prove useful in the treatment of attention-deficit disorder, Alzheimer's disease, schizophrenia, and obesity.[2] The efforts of a number of laboratories have been directed toward discovering potent H_3 antagonists for the treatment of these and other indications.[2b,3]

We previously reported the benzofuran series **1**, where R = CN or C(O)-morpholine, X = CH or N, and a variety of amines were present (Fig. 1).[3d] One of these analogs, **ABT-239** (**2**), was potent in vitro and in animal models showed a desirable pharmacokinetic profile and cognition-enhancing effects at low doses.[4] To explore the structure–activity relationships of the series and to produce more potent analogs, we prepared a variety of arylbenzofurans bearing a much wider variety of substituents.

Two of the first compounds were prepared in five steps from 4-bromophenol (Scheme 1). After *ortho*-iodination at 0 °C with NaI/NaOCl,[5] the phenol was cyclized with

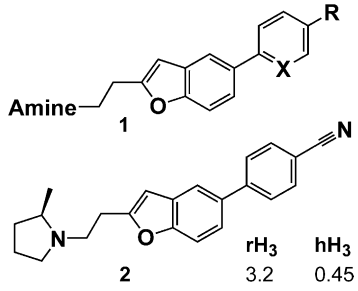

Figure 1. Previously reported arylbenzofurans. Values in nanomolar units.

3-butyn-1-ol in the presence of copper (I) oxide at 100 °C to afford benzofuran **3**.[6] This intermediate was then coupled with either 3-cyanophenylboronic acid or 4-fluorophenylboronic acid under Suzuki conditions, the products were mesylated, and then converted to the final products **4a**–**b** by displacement of the mesylates with (*R*)-2-methylpyrrolidine[3d] under gentle heating (40 °C). Later, the copper-catalyzed cyclization was replaced by a shorter route, wherein a Sonogashira reaction was run with 1-but-3-ynyl-2-methyl-pyrrolidine to give **5**. In this sequence, the terminal Suzuki reaction allowed a wider variety of aromatic moieties to be readily appended (compounds **4c**–**x**).

A second route began with a Suzuki reaction[7] between 4-methoxyphenylboronic acid and 4-bromobenzonitriles to afford **6** (Scheme 1). Demethylation of **6** with BBr_3 at −78 °C gave phenols (4′-bromo-biphenyl-4-ol is commercially available), which were either *ortho*-iodinated

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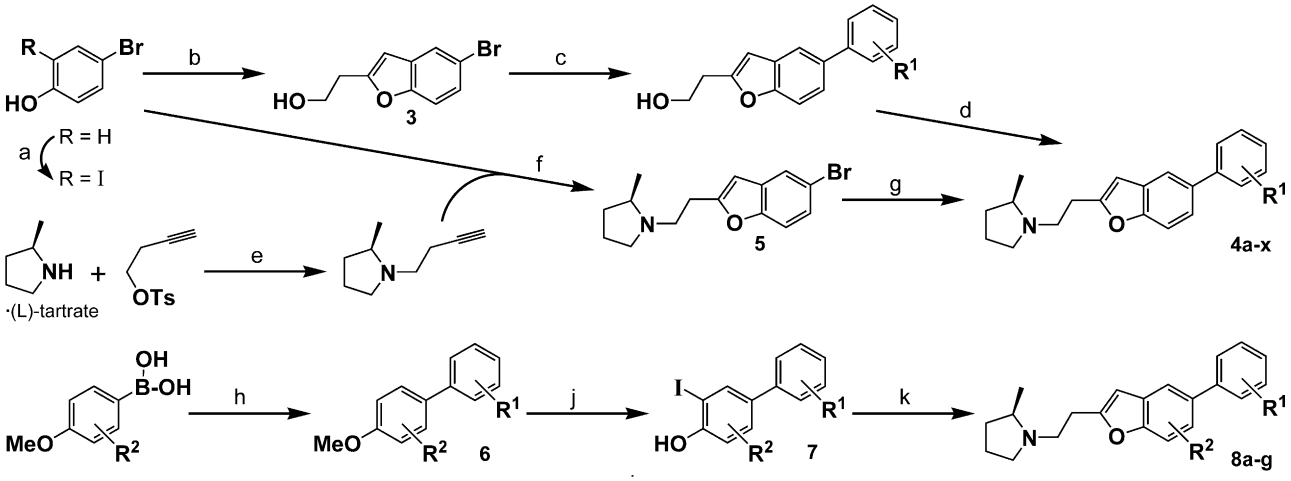
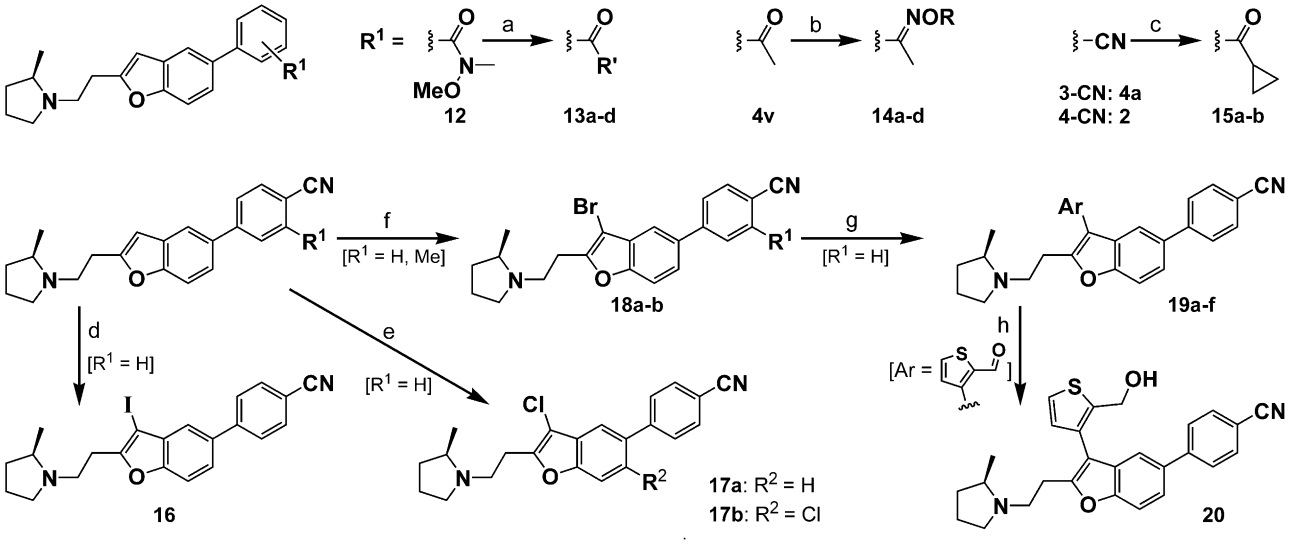


Scheme 1. Reagents: (a) NaOCl, NaI, NaOH, aq MeOH; (b) 3-butyn-1-ol, Cu_2O, Py/NMP; (c) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, aq dioxane; (d) (i) MsCl, Et_3N, CH_2Cl_2, (ii) (*R*)-2-methylpyrrolidine tartrate, Cs_2CO_3, MeCN; (e) 325 mesh K_2CO_3, MeCN, 55 °C, sealed bottle 2 days; (f) $Pd(OAc)_2$, PPh_3, CuI, *i*-Pr_2NH, MeCN; (g) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, H_2O/EtOH/PhH, or, $ArB(OH)_2$, $PdCl_2(PPh_3)_2$, Na_2CO_3, aq *i*-PrOH; (h) $R^1C_6H_4Br$, $Pd(PPh_3)_4$, Na_2CO_3, H_2O/EtOH/PhH; (j) (i) BBr_3, CH_2Cl_2, (ii) NaOCl, NaI, NaOH, aq MeOH, or NIS, DMF; (k) (2*R*)-1-but-3-ynyl-2-methylpyrrolidine, CuI, $Pd(OAc)_2$, PR_3, *i*-Pr_2NH, MeCN.

at 0 °C with NaI/NaOCl or at room temperature with NIS (R^2 = 2-F, 2-Me) to provide intermediates **7**, which were then reacted under Sonogashira reaction conditions to give final target products **8a**–**g**.

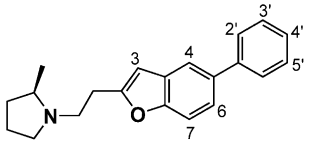
Additional analogs of **4v** were then prepared (Scheme 2). The preparation of alcohols **9**–**10**, acid **11**, and Weinreb amide **12** have been described.[4a] This flexible intermediate (**12**) was treated with Grignard reagents (EtMgBr, *i*-BuMgCl, or 3-F–C_6H_4–MgBr) to give the expected ketones **13a**–**c**. Treatment of **12** with cyclopentyl magnesium bromide afforded a low yield of the unexpected aldehyde **13d**, likely arising from hydride transfer from the Grignard reagent to the nitrile. Target oxime analogs (**14a**–**d**) were produced by condensation of methylketone **4v** with hydroxylamine at 70 °C or with alkoxyamines at 20 °C.

Other target molecules were prepared from **2** or structurally related nitriles **4a** and **8c** (Scheme 2). Cyclopropyl ketones **15a**–**b** were prepared from the nitriles with cyclopropyl magnesium bromide in the presence of CuI;[8] in other H_3 antagonists, such as ciproxifan, cyclopropyl ketones have been found to increase potency. Compound **2** was iodinated at the 3-position of the benzofuran ring with NIS in TFA to give **16**. Compound **2** could also be chlorinated with NCS in TFA, to give a four-to-one ratio of chloroarenes **17a** and **17b**. The use of trifluoroacetic acid to protonate the pyrrolidine nitrogen and protect it from oxidation was also important in the synthesis of bromides **18a**–**b**. Compound **18a** (R^1 = H) was further reacted with several boronic acids under Suzuki conditions to give **19a**–**f**. Product **19f** was reduced by $NaBH_4$ to afford **20**.



Scheme 2. Reagents: (a) RMgX, THF; (b) H_2NOR·HCl, Na_2CO_3, MeOH; (c) *c*-PrMgBr, CuI, THF; (d) NIS, TFA; (e) NCS, TFA; (f) Br_2, TFA; (g) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, aq DME; (h) (i) $NaBH_4$, MeOH, (ii) aq HCl.

Table 1. Binding affinities[a] (K_i) of substituted arylbenzofurans at rat cortical H_3 receptors and cloned human H_3 receptors



Compd	Benzofuran substituent	Phenyl substituent	rH_3[c]	hH_3
2[b]	H	4′-CN	3.2	0.45
4a[b]	H	3′-CN	2.5	0.27
4b	H	4′-F	65	3.2
4c	H	3′-F	17	2.2
4d	H	4′-Cl	82	6.3
4e	H	3′-Cl	48	5.0
4f	H	2′-Cl	24	5.3
4g	H	4′-CF_3	150	5.7
4h	H	3′-CF_3	95	3.9
4i	H	4′-Me	160	7.9
4j	H	3′-Me	30	2.7
4k	H	2′-Me	33	4.1
4l	H	4′-OCF_3	200	7.6
4m	H	3′-OCF_3	130	11
4n	H	4′-OMe	56	9.1
4o	H	3′-OMe	23	1.2
4p	H	2′-OMe	76	15
4q	H	3′-Cl, 4′-Cl	110	3.6
4r	H	3′-Cl, 5′-Cl	24	5.0
4s	H	3′-Me, 4′-Me	65	5.9
4t	H	3′-Me, 5′-Me	19	3.6
4u	H	4′-COOMe	42	1.9
4v[b]	H	3′-C(O)Me	0.44	0.084
4w[b]	H	4′-CH_2OH	4.1	0.88
4x[b]	H	3′-CH_2OH	2.8	0.49
8a	H	4′-Br	300	7.7
8b	H	4′-CN, 2′-Me	31	2.0
8c	H	4′-CN, 3′-Me	2.6	0.28
8d	H	4′-CN, 3′-F	9.3	0.64
8e	7-F	4′-CN	5.7	0.43
8f	7-Me	4′-CN	16	1.1
8g	6-Me	4′-CN	4.2	0.77
9[b]	H	3′-CH(OH)Me	2.8	0.44
10[b]	H	3′-C(OH)Me_2	1.3	0.25
11	H	3′-COOH	66	15
12	H	3′-C(O)N(Me)OMe	4.9	0.62
13a[b]	H	3′-C(O)Et	2.3	0.23
13b	H	3′-C(O)CH_2CHMe_2	19	0.68
13c	H	3′-C(O)–(3″-F)C_6H_4	53	2.6
13d	H	3′-CHO	3.3	0.40
14a	H	3′-C(=NOH)Me	3.1	0.49
14b	H	3′-C(=NOMe)Me	4.5	0.42
14c	H	3′-C(=NOEt)Me	51	3.2
14d	H	3′-C(=NO–*t*-Bu)Me	41	4.3
15a[b]	H	4′-C(O)–*c*-Pr	6.4	0.26
15b[b]	H	3′-C(O)–*c*-Pr	2.5	0.21
16	3-I	4′-CN	8.4	0.51
17a	3-Cl	4′-CN	3.7	0.39
17b	3-Cl, 6-Cl	4′-CN	9.7	0.83
18a	3-Br	4′-CN	3.4	0.29
18b	3-Br	4′-CN, 3′-Me	16	1.3
19a	3-Ph	4′-CN	390	21
19b	3-(3″,5″-$DiMeC_6H_3$)	4′-CN	840	60
19c	3-(3″-Pyridyl)	4′-CN	18	13
19d	3-(2″-Furyl)	4′-CN	42	2.8
19e	3-(3″-Thienyl)	4′-CN	41	2.1
19f	3-(3″(2″CHO)thienyl)	4′-CN	5.8	0.73
20	3-(3″(2″CH_2OH)thienyl)	4′-CN	20	1.9

[a] Values reported are in nanomolar units, converted from the average of at least three pK_i determinations (pK_i SEM < 0.25).
[b] The data for these compounds at *cloned* rat and human H_3Rs has been reported.[4a]
[c] The source of rH_3 was membranes from rat cortex.

The synthesized compounds were tested for binding at both the rat cortical (rH_3) and human clonal (hH_3) receptors, with the data shown in Table 1. In every instance H_3 receptor binding was more potent at hH_3 than at rH_3, although SAR trends were similar at hH_3 and rH_3. Because potency was weaker at the rat receptor and because pharmacokinetic assays and behavioral models were to be run in rats, potency at the rat receptor was the primary constraint in choosing compounds for further advancement.

Examination of the in vitro data (Table 1) for SAR revealed that addition of a methyl or halogen to either aromatic ring of **2** did not increase binding. In most cases (**8c–e**, **8g**, **16**, **17a–b**, **18a**) the binding potencies were comparable to the parent or slightly weaker (rH_3 = 2.6–9.7 nM, hH_3 = 0.28–0.83 nM); however, appending a methyl group to either the 2′ (**8b**) or 7 (**8f**) positions, or appending both a 3′-methyl and 3-bromo (**18b**) resulted in compounds with greater reductions in potency (rH_3 = 16–31 nM, hH_3 = 1.1–2.0 nM). It was also seen that appending an aromatic ring to position 3 of the benzofuran did not increase binding. Except for one case (**19f**) where binding was similar to the parent **2**, these molecules showed lower affinity for the H_3Rs (**19a–e, 20**; rH_3 = 18–840 nM, hH_3 = 1.9–60 nM).

Replacement of the nitrile in the parent species with a bromide (**8a**), a fluoride (**4b–c**), one or two chlorides (**4d–f**, **4q–r**) or methyls (**4i–k**, **4s–t**), a trifluoromethyl (**4g–h**) or trifluoromethoxy moiety (**4l–m**), a methoxy group (**4n–p**), a methyl ester (**4u**), or a carboxylic acid (**11**) resulted in compounds with modest to weak binding (rH_3 = 17–300 nM, hH_3 = 1.2–15 nM). The larger, more hydrophobic bromide, trifluoromethyl, and trifluoromethoxy substituents possessed the lowest potencies, and compounds with any of the above groups in position 4′ bound less easily to rH_3 than those with groups at position 3′ or 2′, with the exception of methyl ether **4p**. This trend toward reduced potency extended even to the disubstituted **4q–t**, where 3′,4′ substitution was weaker than 3′,5′. Potency at hH_3 also diminished, but was less affected by these substituents.

Certain molecules with more hydrophilic substitution on the phenyl group—such as ketones and alcohols—bound more tightly to the H_3Rs, and usually showed a decrease in potency as larger hydrophobic groups were attached. Again, the trend was more pronounced at rH_3 than at hH_3. Oxime **14a** and *O*-methyl oxime **14b** showed higher affinity than the *O*-ethyl and *O*-*t*-butyl analogs **14c–d** for both rH_3 (3.1–4.5 nM vs 41–51 nM) and hH_3 (0.42–0.49 nM vs 3.2–4.3 nM). Larger ketones **13b–c** (rH_3 = 19–53 nM, hH_3 = 0.68–2.6 nM) were less potent than cyclopropyl ketones **15a–b** and ethyl ketone **13a** (rH_3 = 2.3–6.4 nM, hH_3 = 0.21–0.26 nM), which were in turn less potent than the methyl ketone **4v** (rH_3 = 0.44 nM, hH_3 = 0.084 nM). However, the 3′-alcohol series **10** [$C(OH)Me_2$], **9** [CH(OH)Me], and **4x** [CH_2OH] showed no such trend upon the removal of methyl groups; each possessed a potency similar to **2**, as did nitrile **4a**, amide **12**, and aldehyde **13d** (rH_3 = 1.3–4.9 nM, hH_3 = 0.25–0.62 nM).

It seems likely that some open space exists in the binding pocket around both the benzofuran and phenyl rings, based on the finding that the addition of substituents on either ring (e.g., **4v–x**, **8c–e**, **16–17**, **19f**) can be tolerated. Although the addition of hydrophobic substituents results in compounds which retain (e.g., **8c**, **8g**) or, more frequently, lose (e.g., **8a**, **19a**) potency, the addition of small hydrophilic substituents on the phenyl ring may be advantageous (**4v**, **10**). These data also leave open the possibility that at a short distance from this ring hydrogen-bond acceptors are the species preferred.

The pharmacokinetic (PK) properties of select compounds were also examined (Table 2). Whereas reference compound **2** and its regioisomer **4a** both had good PK in rat,[4a] another close analog which differed from **2** only by the addition of a methyl group (**8c**) had poor PK, with a low C_{max} and AUC p.o., and a bioavailability of only 9%. The most potent compound in the series, **4v**, also gave very poor data in rat. Oral bioavailability was better in dog (F = 27%) and very good in monkey (F = 72%), and we hypothesized that the high clearance rate of this methyl ketone in rats resulted from rapid hepatic metabolism [as in primary alcohols **4w–x** and oximes **14a–b** (F_{rat} = 0−9%)] directed toward the ketone moiety. In order to test this hypothesis, we examined the PK profile of secondary alcohol **9**, tertiary alcohol **10**, and cyclopropyl ketones **15a–b**, and found that each possessed very good bioavailability coupled with both high C_{max}s (p.o.) and good AUCs (i.v. and p.o.). Furthermore, both **4a** and **15b** were active in a five-trial inhibitory avoidance model for learning.[4a]

Table 2. Pharmacokinetic properties of selected arylbenzofurans

Compd	1 mg/kg i.v.				1 mg/kg p.o.			
	$t_{1/2}$, h	V_β, L/kg	$AUC_{0-\infty}$, ng h/mL	CL_b, L/h kg	C_{max}, ng/mL	$t_{1/2}$, h	$AUC_{0-\infty}$, ng h/mL	F %
2	5.3	12	673	1.5	29	5.2	349	53
4a	4.3	7.5	835	1.2	27	5.5	320	38
4v	3.0	27	160	8.5	~2	UC	10	6
8c	3.2	11	510	2.0	~8	UC	50	9
9	7.6	23	482	2.1	24	9.4	265	55
10	5.6	21	391	2.6	38	9.0	315	81
15a	9.3	8.2	1649	0.61	31	13	788	48
15b	5.0	6.2	1177	0.86	76	5.1	828	70

Selected data for some of these compounds were previously reported[4a] but are included to present a more complete profile. UC = uncalculated.

The results here show that among the wide variety of new arylbenzofurans synthesized and described, many of the compounds had nanomolar potency at rat and human H_3 receptors. Good pharmacokinetic properties were found for a subset of the most potent analogs tested, offering the possibility that analogs of **ABT-239** having favorable behavioral efficacy and PK properties could be used to further explore the potential clinical efficacy of H_3R antagonists.

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