4-(2-[2-(2(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-yl)benzonitrile and Related 2-Aminoethylbenzofuran H_3 Receptor Antagonists Potently Enhance Cognition and Attention

Marlon Cowart,*,† Ramin Faghih,† Michael P. Curtis,† Gregory A. Gfesser,† Youssef L. Bennani,# Lawrence A. Black,† Liping Pan,§ Kennan C. Marsh,§ James P. Sullivan,† Timothy A. Esbenshade,† Gerard B. Fox,† and Arthur A. Hancock†

Department of Neuroscience Research and Department of Drug Metabolism and Pharmacokinetics, Abbott Laboratories, Abbott Park, Illinois 60064-6123

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H_3 receptor antagonists based on a 2-aminoethylbenzofuran skeleton have been discovered, which are potent in vitro at human and rat H_3 receptors, with K_i values of 0.1−5.8 nM. Analogues were discovered with potent (0.01−1 mg/kg) cognition and attention enhancing properties in animal models. One compound in particular, 4-(2-[2-(2(*R*)-methylpyrrolidin-1-yl)ethyl]benzofuran-5-yl)benzonitrile (ABT-239), combined potent and selective H_3 receptor antagonism and excellent pharmacokinetic and metabolic properties across species, with full efficacy in two behavioral models: a five-trial inhibitory avoidance acquisition model in rat pups at 0.1 mg/kg and a social recognition memory model in adult rats at 0.01 mg/kg. Furthermore, this compound did not stimulate locomotor activity and showed high selectivity for the induction of behavioral efficacy versus central nervous system based side effects. The potency and selectivity of this compound and of analogues from this class support the potential of H_3 receptor antagonists for the treatment of cognitive dysfunction.

Introduction

Histamine receptors play well recognized and important roles in human disease, and drugs acting at these receptors are clinically important.[1−3] Peripheral-selective H_1 antagonists are used in the treatment of allergic asthma and allergies, and H_2 antagonists offer treatment for gastric distress due to hyperacidity. The safety and efficacy of H_1 and H_2 antagonists have enabled the use of some of these drugs as "over the counter nonprescription medications. A third type of histamine receptor, the H_3 receptor, is a pharmacologically distinct histamine receptor located predominantly on presynaptic nerve terminals, where it modulates the release of histamine and other neurotransmitters.[4] The H_3 receptor has recently gained attention for its potential role in modulating cognitive, psychiatric, appetitive, allergic, and other physiological processes,[5] and there is much recent interest in finding potent and efficacious H_3 receptor antagonists to treat these diseases.[6]

On presynaptic histaminergic nerve terminals, the H_3 receptor acts as an autoreceptor through an inhibitory feedback loop, suppressing the neuronal release of histamine.[4,7,8] H_3 receptor antagonists block this autoinhibitory feedback and thereby induce elevations of the neurotransmitter histamine, which then stimulates postsynaptic H_1 and H_2 receptors. H_3 receptors are also located on heterotopic nerve terminals, exerting negative control over the release of other neurotransmitters and hormones, including acetylcholine, glutamate, and dopamine,[1,2] and by blockade of these receptors, H_3 receptor antagonists can enhance the release of these neurotransmitters. H_3 receptors have been found in, and cloned from, several animal species,[9] and the pharmacology of these diverse receptors has been characterized.[10] In native cells and in cells expressing cloned H_3 receptors, a high degree of intrinsic activity is present.[11,12] In some systems, as much as 25% of the human H_3 receptor pool may be activated in the absence of endogenous agonist.[11] This has led to the suggestion that "inverse agonists" that block this intrinsic receptor activity may be able to play a special role in disease treatment, possibly even distinct from "antagonists".[11a] As generally used, the term "inverse agonist" constitutes a special category of receptor antagonists, able not only to counteract the actions of exogenous agonists but to reduce the intrinsic activity of the receptor. While the more general term "antagonist" is used in this report, it is with the understanding that many H_3 receptor antagonists have varying degrees of inverse agonism.[11,12]

In animal models, H_3 receptor antagonists have been shown to enhance attentive and cognitive behaviors,[5] to enhance wakefulness, and when coadministered with H_1 antagonists to act as nasal decongestants.[13] The molecular mechanisms whereby H_3 antagonists induce these effects are indirect and probably mediated by the enhanced release of neurotransmitters such as histamine, acetylcholine, dopamine, and others. The demonstrations of in vivo activity have heightened interest in finding H_3 receptor antagonists with optimal druglike properties for potential clinical use. Some of the first potent H_3 receptor antagonists were analogues of the

* To whom correspondence should be addressed. Phone: (847) 938-8170. Fax: (847) 937-9195. E-mail: marlon.d.cowart@abbott.com.
† Department of Neuroscience Research, Abbott Laboratories.
# Present address: Vertex Pharmaceuticals, 130 Waverly St., Cambridge, MA 01239.
§ Department of Drug Metabolism and Pharmacokinetics, Abbott Laboratories.

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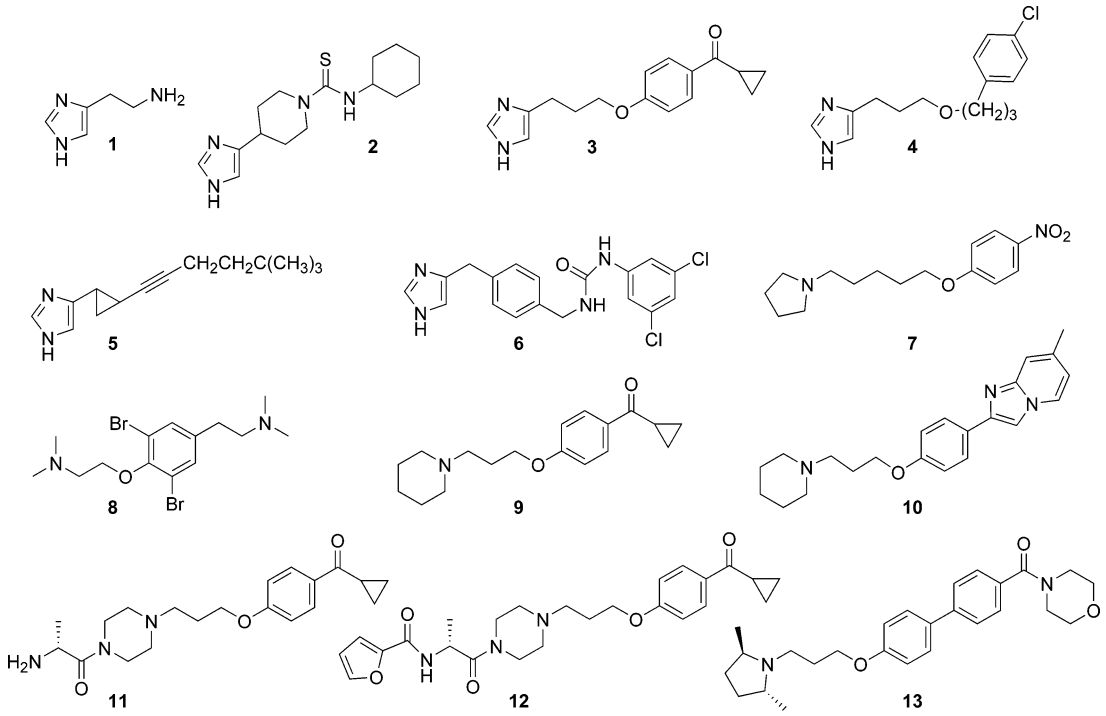


Figure 1. Structures of histamine (**1**), imidazole-based H_3 antagonists **2**−**6**, and non-imidazole H_3 antagonists **7**−**13**.

endogenous ligand histamine (**1**) and therefore contain an imidazole moiety. Examples of compounds in this class include thioperamide (**2**), ciproxifan[14] (**3**), and FUB-181[15] (**4**), seen in Figure 1. These compounds have robust effects in vitro and in vivo and constitute reference standards against which newer antagonists are often compared. Two newer imidazole-based compounds, GT-2331[16] (**5**) and SCH-79876[13b] (**6**), have also been described in the literature as potent H_3 receptor antagonists. Compound **6**, in combination with an H_1 antagonist, was active as a nasal decongestant in a feline model at 3−10 mg/kg.[13a]

As potential candidates for a drug targeted for the treatment of central nervous system (CNS) symptoms, two potential liabilities have been reported for imidazole-based H_3 receptor antagonists.[17] One is the association of imidazole-based analogues with poor CNS penetration. For example, **6**, which is targeted for a peripheral indication (allergic rhinitis), had a brain/plasma ratio of 0.02 in rats at 10 mg/kg.[13a] While low CNS penetration may be a desirable property in a drug targeted to the treatment of peripheral diseases, it is likely a liability in drugs targeted to the treatment of CNS diseases.

The other property associated with imidazole-based structures is their propensity to potently inhibit cytochromes P_{450} (CYP).[18] In this way, such drugs can perpetrate drug−drug interactions against coadministered drugs by inhibiting hepatic clearance.[19] A well-known historical example of this phenomenon is the potentially fatal interaction of orally administered ketoconazole (an imidazole-containing antifungal) with terfenadine. Additionally, drugs that inhibit CYP enzymes have the potential to alter the endogenous metabolism of important circulating hormones, as reported for the H_3 receptor antagonist thioperamide[18a] (**2**). Because of these liabilities, much of the recent interest in the field has been directed toward the design of potent non-imidazole H_3 receptor antagonists.

There are many examples of non-imidazole H_3 receptor antagonists, many of which share certain structural features.[6] Potent compounds all possess a basic tertiary amine as an imidazole replacement, connected through a flexible linker chain to a lipophilic moiety. The requirement for the basic amine as the imidazole replacement probably reflects a requirement to maintain a key ionic interaction between the positively charged ammonium group of the drug and an aspartate (D114) residue present in H_3 receptor isoforms from all species.[20] Many other G-protein-coupled receptors (GPCRs) also have a negatively charged aspartate at positions analogous to the aspartate (D114) in the H_3 receptor, and the aspartate likely plays a critical role in the binding of endogenous ligands in those GPCRs as well. A prominent subset of potent H_3 receptor antagonists is built on a common pharmacophore: a tertiary basic amine or imidazole connected through an alkyloxy (often propyloxy) chain connected to a lipophilic moiety[6] (usually an aromatic ring). This structural motif is present in several reported H_3 receptor antagonists, for example, UCL-1972[21] (**7**), the natural product aplysamine **8**, **9**, **10**,[22] **11**,[23] **12**,[23] and **13**.[24] Pharmacophore **14** may therefore constitute a "privileged structure", a structural class likely to be a rich source of H_3 receptor antagonists.

2-Aminoethylbenzofurans (**15**) constitute a new structural class of H_3 receptor antagonists, of which the discovery and potent human and rat H_3 receptor binding of the first members of the series, including ABT-239 (**20**), have been described.[25] As illustrated in Figure 2, the benzofurans can be considered rigidified versions of the aforementioned aminepropyloxyphenyl pharmacophore (**14**), but with structure **15** having two fewer rotatable bonds. Rigidification has been empirically associated with improved absorption and druglikeness[26]

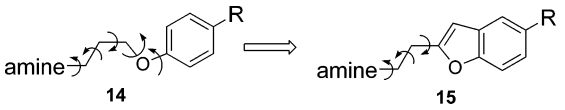


Figure 2. Protypical H_3 antagonist **14** has five freely rotatable bonds linking the basic amine and the lipophilic moiety. The benzofuran antagonists **15** are similar, but more rigid, with three freely rotatable bonds.

and may in part underlie the high in vivo potency of the benzofurans.[25c] Aspects of the SAR between the basic amine moiety of **15** and in vitro H_3 receptor binding have been described, but this report describes the in vitro pharmacological profiles of new analogues with variant R substituents at the 5-position of the benzofuran ring of **15**, as well as the potent behavioral activity of the series in animal models of cognition and attention.

Materials

Synthesis. The preparation of the target benzofuran H_3 receptor antagonists **15** required several distinct synthetic routes, which are depicted in Schemes 1 and 2. The new target analogues (Table 1) incorporate aromatic and benzoyl substituents at the 5-position of the benzofuran ring, and except for **21**, all the compounds bear (*R*)-2-methylpyrrolidine as the amine. The synthesis of **20** (Scheme 1) required as a first step the selective iodination of 4′-hydroxybiphenyl-4-carbonitrile (**16**). By judicious choice of conditions, using NaOCl, NaOH, and NaI in aqueous methanol,[27] monoiodide **17** could be selectively formed in good yield (53%) with minimal formation of the diiodide side product. The cyclization of **17** to **18** in 95% yield was effected by the $Pd(Ph_3P)_2Cl_2$/CuI catalyzed reaction of **17** with homopropargyl alcohol in the presence of base. Though this reaction may proceed by a two-step process, with a Pd-catalyzed coupling of the 2-iodophenol **36** with homopropargyl alcohol to give an acetylene intermediate followed by cyclization to give **18**, we never observed any intermediate acetylenes, only the benzofuran products. The alcohol **18** was activated for displacement by conversion to a mesylate (**19**, 89%), followed by treatment with (*R*)-2-methylpyrrolidine[28] in CH_3CN, which proceeds at room temperature over several hours or days to give **20** (34%). The displacement reaction can be accelerated by elevated temperatures, but this increases the formation of the styrene side product, formed through base-catalyzed elimination. In a similar fashion, **21**, the *S*-enantiomer of **20**, was formed in 63% yield by the reaction of **19** with (*S*)-2-methylpyrrolidine.[29]

The goal of making additional analogues of **20**, for instance, the target benzophenone analogues **26a**−**c**, motivated development of a synthesis that is more efficient than that described for **20** and **21**. (*R*)-2-Methylpyrrolidine was alkylated with the tosylate ester of homopropargyl alcohol to give the acetylene **23**, use of which was envisioned to eliminate the need to form and displace mesylate intermediates. As an alternative to the method used to monoiodinate **16**, the monoiodination of **24a**−**c** was effected with I_2 and NH_4OH as base. The Pd-catalyzed reaction of **23** with iodophenols **25a**−**c** did give the target benzophenones **26a**−**c** but in much lower yield (18%) than the yield in the formation of **18** (95%). We have observed that the presence of a basic nitrogen on the homopropargylamine **23** often leads to lower yields of benzofurans compared to the yields of benzofurans produced using homopropargyl alcohol as the acetylenic coupling partner.

A different synthetic route was used to make the target benzophenone analogues **33a**−**i**, with **32** envisioned to allow efficient synthesis of a large number of analogues through reaction of this penultimate intermediate with Grignard reagents. To make **32**, the carboxylic acid **27** was treated with oxalyl chloride to give **28** (99%), which was converted to the Weinreb[30] amide **29** (95%). The benzyl group of **29** was removed by Pd-catalyzed hydrogenolysis, and the product **30** was monoiodinated with I_2 and NH_4OH as base to give **31** in 67% yield. The iodophenol **31** was converted to the *N*-methoxy-*N*-methylbenzamide **32** in 21% yield as described above, which was then reacted with aryl Grignard reagents to produce the target benzophenones **33a**−**i** in 12−68% yields.

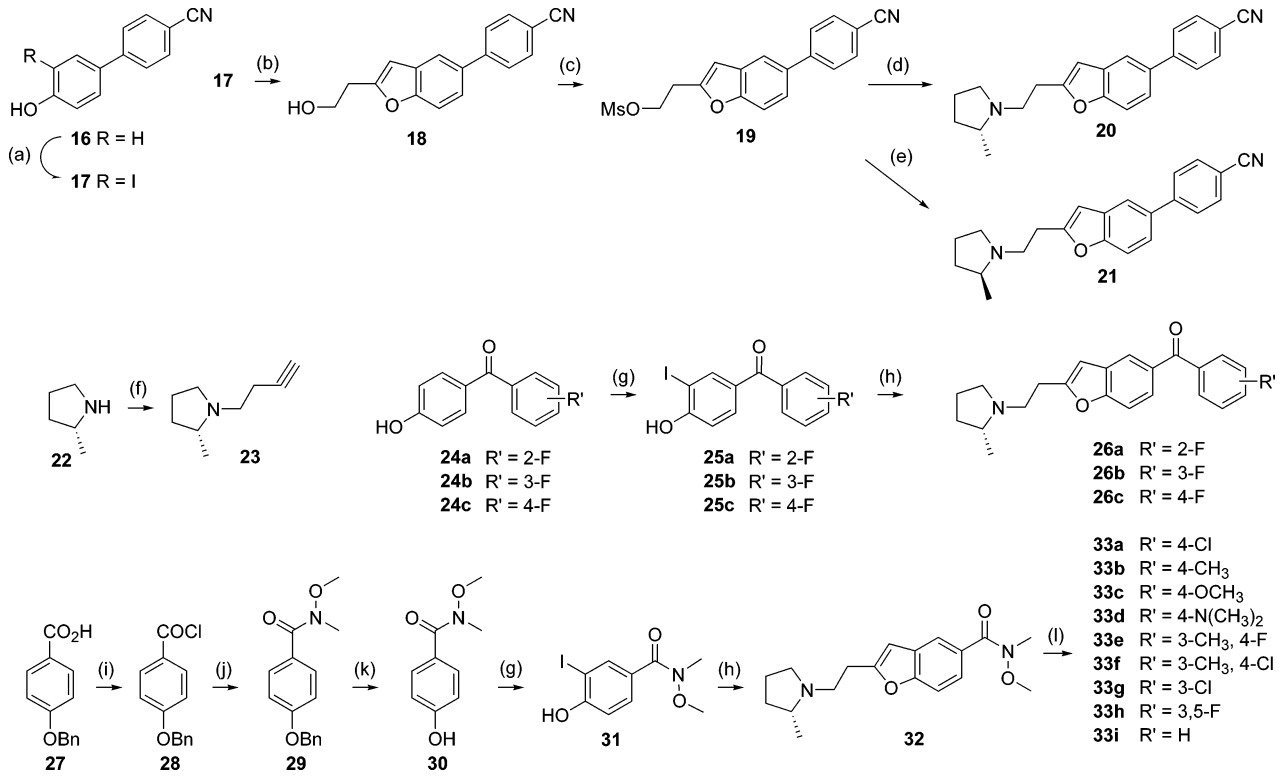
For the preparation of targets **37**−**39** (Scheme 2), 4-iodophenol (**34**) was converted to **35** in 97% yield through a Suzuki reaction, after which monoiodination of **35** gave **36** (21%). Reaction of **36** with **23** under Pd catalysis gave ketone **37** in 30% yield. The ketone **37** could be reacted with MeMgBr to give **38** (27%) or with $NaBH_4$ to give **39** in 37% yield. To prepare **44**−**46**, 4-iodophenol (**34**) was converted to **40** in 71% yield through a Suzuki reaction and **40** was transformed into the iodophenol **41** (37%) with I_2 and NH_4OH as base. Compound **41** reacted with **23** under Pd catalysis to give a benzofuran ethyl ester intermediate which was hydrolyzed with NaOH to give the aminocarboxylic acid **42**. This acid was treated with oxalyl chloride to give the acid chloride, which was treated with *O*,*N*-dimethylhydroxylamine hydrochloride to give the Weinreb amide **43**. The carboxylic acid **42** reacted with BH_3 to give **44** (70%), **43** with EtMgBr to give **45** (65%), and with cyclopropylmagnesium bromide gave **46** (69%).

When 4-bromophenol (**47**) was treated with NaOCl, NaI, and NaOH in aqueous CH_3OH, the monoiodophenol **48** was produced in 89% yield. This material was treated with **23** to give the 5-bromobenzofuran **49** in 26% yield, which was subjected to the Suzuki reaction to give **50** in 66% yield. The 2-iodophenol **48** was converted to the benzofuran **51** (8%) by a copper-catalyzed reaction with homo-propargyl alcohol, after which **51** was subjected to the Suzuki reaction with 3-cyanophenylboronic acid to give **52** in 82% yield. In a two-step process, **52** was mesylated and then treated with (*R*)-2-methylpyrrolidine as described for **20** to give **53** in 28% yield. In one case, target compound **20** could itself be directly transformed into a new target compound; in this case, reaction of **20** with cyclopropylmagnesium bromide under CuI catalysis gave the cyclopropyl ketone **54** in 44% yield.

Results and Discussion

Pharmacological Properties. The compounds described here were selected from a larger group of related analogues as being particularly potent at H_3 receptors, as assessed in in vitro binding assays[23b] in membranes isolated from cells transfected with either cloned rat H_3 receptors or human H_3 receptors.

Scheme 1[a]



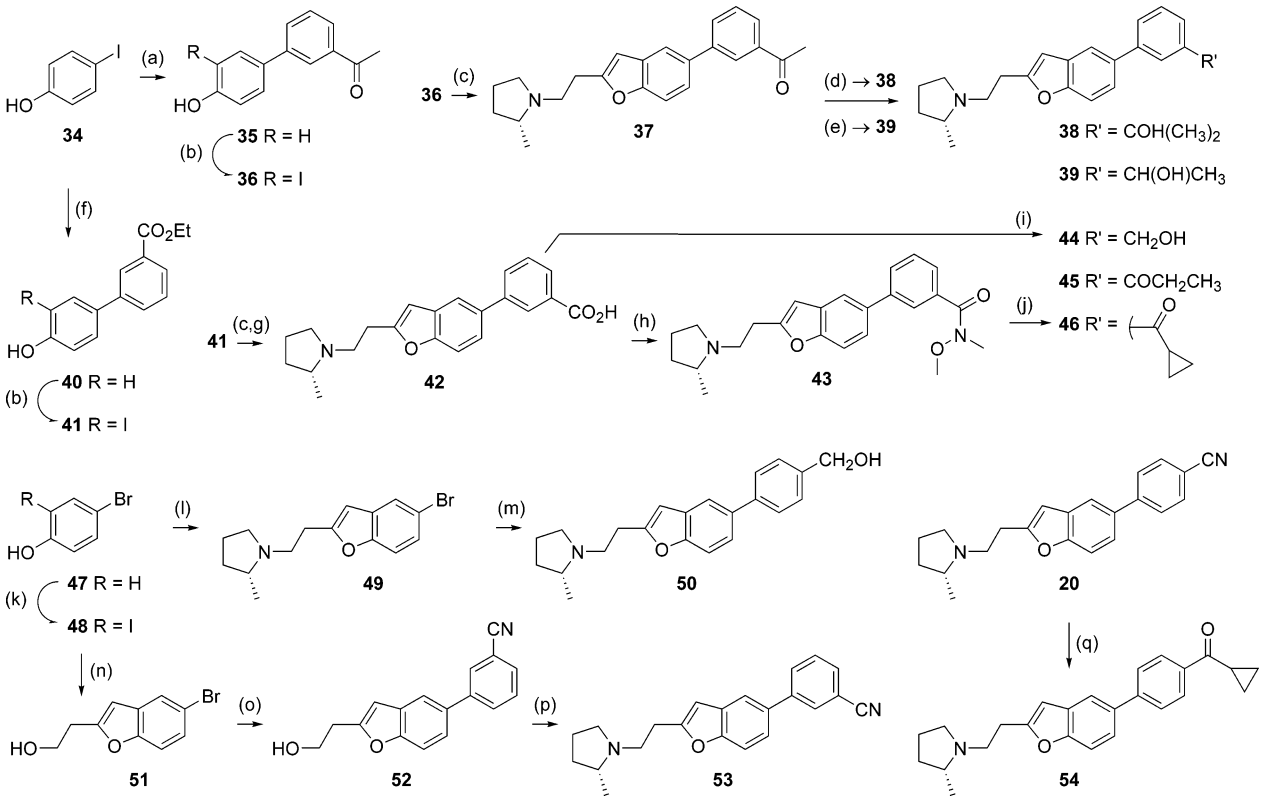
[a] (a) NaI, NaOCl, NaOH; (b) 3-butyn-1-ol, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, DMF; (c) CH_3SO_2Cl, Et_3N; (d) 22, Na_2CO_3, CH_3CN; (e) (*S*)-2-methylpyrrolidine, Na_2CO_3, CH_3CN; (f) 3-butynyl 4-toluenesulfonate, K_2CO_3, CH_3CN, 50 °C; (g) I_2, NaI, NH_4OH; (h) 23, Pd(OAc) $_2$, (p-tol)$_3$P, IPr_2NH, CuI, CH_3CN; (i) oxalyl chloride, DMF, CH_2Cl_2; (j) $HN(OCH_3)CH_3$, Et_3N; (k) H_2, Pd(C), CH_3OH; (l) RMgX, 0 °C → **33a**−**33i**.

A wide variety of amines have been found in potent H_3 receptor antagonists from different chemical series.[6,15b,17,21,24] It was previously determined[25] that benzofurans bearing cyclic amines such as pyrrolidine and piperidine have high binding potency. In that SAR study, the dependence of potency on the structure of the amine moiety in the benzofuran series of analogues **15** (Figure 2) was more sharply defined than with homologous alkoxyphenyl analogues **14**.[25b] In particular, it was found that for the benzofurans **15**, 2-alkyl cyclic amines such as (*R*)-2-methylpyrrolidine imparted high in vitro potency at human and rat H_3 receptors. For this reason and to allow a clear comparison of the potency of compounds with a variety of substituents at the 5-position of the benzofuran ring, the compounds in this report bear (*R*)-2-methylpyrrolidine as the amine. Some of the 5-substituents chosen for incorporation into the analogues **15** were similar to substituents found in disparate H_3 receptor antagonist series reported previously. For example, the cyclopropyl ketone in **46** and **54** is found in the imidazole-based H_3 receptor antagonist ciproxifan[14] **3** and in the non-imidazoles **11** and **12**.[23] Also, imidazole-based benzophenones have been described[31] with some structural similarity to **26c**, and the 4-cyanophenyl moiety found in **20** has been described in two series of non-imidazole H_3 receptor antagonists.[21,32]

All of the target benzofuran analogues (Table 1) were highly potent in in vitro binding assays, with K_i values at the human receptor ranging from 0.1 to 0.69 nM, as assessed by competitive displacement of the H_3 receptor specific ligand [^{3}H]-*N*-α-methylhistamine. Potent binding to the rat H_3 receptor was most important for determining which compounds to advance to behavioral testing because compounds were ultimately to be tested in rat behavioral models; on this point, the target compounds all showed potent binding to the rat H_3 receptor, with K_i values ranging from 0.52 to 5.75 nM. It is noted that other 2-substituted cyclic amines such as (*S*)-2-methylpyrrolidine were able to support potent binding in benzofuran analogues,[25a] as illustrated by the *S*-enantiomer **21** (human H_3 K_i = 0.69 nm; rat H_3 K_i = 2.57 nM). Thus, the compounds of the series have potencies at rat H_3 receptors comparable to the potencies of reference H_3 receptor antagonists such as thioperamide (**2**), ciproxifan (**3**), **11**, and **12**. However, in comparison to the reference H_3 receptor antagonists, the new benzofuran analogues have 100−1000 times greater potency at the human H_3 receptor in binding assays.

The benzofuran analogues in Table 1 were competitive antagonists of the H_3 receptor in a variety of assays; they completely blocked H_3 receptor activation by the agonist *R*-α-methyl histamine in a Ca^{2+} flux assay in whole cells, as assessed using assays based on FLIPR (fluorometric imaging plate reader) technology.[23b] The benzofuran analogues were also found to be potent inverse agonists at H_3 receptors; at low nanomolar drug concentrations, these new compounds reduced basal GTP-γ-S binding in H_3 receptor transfected cells.[11b,23b] Compounds were also assessed for the ability to bind to native H_3 receptor preparations from rat or human cortex. The potencies found in these native preparations closely paralleled those shown in Table 1. For example, **20** had a K_i of 3.22 nM at membranes isolated from native rat cortex and had a K_i of 4.60 nM in native human cortical membranes.

Scheme 2[a]



[a] (a) 3-Acetyl-PhB(OH)$_2$, Pd(OAc)$_2$, Na_2CO_3; (b) I_2, NaI, NH_4OH; (c) **23**, Pd(OAc) $_2$, Biphenyl-2-yl-dicyclohexyl-phosphane, CuI, IPr_2NH, CH_3CN; (d) CH_3MgBr; (e) $NaBH_4$; (f) 3-EthoxycarbonylPhB(OH)$_2$, Pd(OAc)$_2$, Na_2CO_3; (g) Aq. NaOH; (h) Oxalyl Chloride, DMF, CH_2Cl_2; $HN(OCH_3)CH_3$, Et_3N; (i) BH_3; (j) RMgX; (k) NaI, NaOCl, NaOH; (l) **23**, Pd(OAc)$_2$, CuI, IPr_2NH, CH_3CN; (m) 4-HydroxymethylPhB(OH)$_2$, $PdCl_2(Ph_3P)_2$, Na_2CO_3; (n) 3-butyn-1-ol, Cu_2O, pyridine, NMP; (o) 3-CN-PhB(OH)$_2$, $Pd(Ph_3P)_4$, Na_2CO_3; (p) CH_3SO_2Cl, Et_3N; **22**, Cs_2CO_3, CH_3CN; (q) cyclopropyl-MgBr, CuI.

The analogues were tested for their selectivity for H_3 receptors by screening for binding at a variety of other receptors. When tested at histamine H_1, H_2, and H_4 receptors, all compounds had K_i > 1000 nM and were therefore more than 4000× selective for H_3. When tested for binding at dopamine ($D_{4.2}$, D_{2S}, D_1) and serotonin (5-HT_1, 5-HT_2, 5-HT_3) receptors or at neurotransmitter transporters for norepinephrine, dopamine, or serotonin, compounds were >100× selective for the human H_3 receptor. When tested against a battery of adrenergic and muscarinic receptors, selectivity was similarly high for **20**. However, one exception to such high selectivity was found with compound **21**, which was only 30× selective for the α_{2C} adrenergic receptors and 75× selective for α_{1B} adrenergic receptors. After H_3, the receptor next most likely to demonstrate measurable affinity for most analogues was the adrenergic (α_{2C}) receptor. After that, for three compounds, weak binding to muscarinic (M_2) receptors (**26c**, K_i = 41 nM; **33a**, K_i = 119 nM; **33e**, K_i = 68 nM) was demonstrated. It has been reported that the α_{2C} adrenergic agonists clonidine and guanfacine enhance cognitive performance in some animal behavioral models, whereas the antagonist yohimbine impairs memory.[33] It was not determined whether these compounds were agonists or antagonists at adrenergic (α_{2C}) or M_2 receptors, but the selectivity of the new compounds for H_3 receptors was in all cases very high, greater than 50-fold versus other receptors. Furthermore, the analogue with the greatest potency at the M_2 receptor (**26c**) is still 150-fold more potent at human H_3 receptors than M_2. Therefore, although M_2 receptor antagonists have previously demonstrated activity in animal models of attention,[34] the high selectivity of **26c** for H_3 receptors argues for an H_3-specific mechanism for the behavioral activity. Similarly, other benzofurans show potent behavioral activity but minimal binding at the M_2 receptor (**20**, K_i = 582 nM; **53**, K_i = 573 nM), supporting an H_3-specific mode of action for these compounds, a finding which also applies to GT-2227, a selective H_3 receptor antagonist from a different chemical series with potent activity in a behavioral model.[35] Because the H_3 receptor is the only receptor bound by all of the analogues with potent behavioral activity (Table 2) and because these analogues were highly potent and selective for H_3 receptors, the cognitive and attention-enhancing activity of these analogues is likely solely due to H_3 receptor antagonism.

Because the compounds were selected as candidates for testing in rodent cognitive models, the pharmacokinetic profiles were assessed to determine the suitability of compounds for administration to rats (Table 1). Clearance rates and volumes of distribution for the compounds varied, as did compound half-lives after iv administration. While all of the compounds (except for **50**; $t_{1/2}$ = 20 min) possessed pharmacokinetic properties that would allow assessment of behavioral activity following iv administration, the ultimate goal was to find agents suitable for treatment of human disease. For the purposes of comparison, agents with low oral bioavailability in rats were less favored, since this route would be precluded for in vivo testing. Also, such compounds may be more likely to have poor oral

Table 1. Pharmacological Profiles of Target Compounds in in Vitro Binding Assays and Important Pharmacokinetic (PK(Properties

R substituent on benzofuran **15**	compd	human H_3 binding[a] K_i (nM)	human H_3 binding[a] $pK_i \pm$ SEM	rat H_3 binding[a] K_i (nM)	rat H_3 binding[a] $pK_i \pm$ SEM	human H_3 antagonism Ca^{2+} flux[b] $pK_b \pm$ SEM	PK parameters[c] $t_{1/2}$ (h) iv	Vβ iv	CLb iv	oral bioavl F (%)	CNS penetration[d] brain concn	brain/plasma ratio
Ph (4-CN)	**20**	0.45	9.35 ± 0.04	1.35	8.87 ± 0.04	7.87 ± 0.15	5.3 rat	11.6	1.5	53	3082	36−52×
							8.3 dog	9.3	0.78	74		
							29.2 mky	12.7	0.3	89		
Ph (4-CN)	**21**	0.69	9.16 ± 0.09	2.57	8.59 ± 0.09	7.87 ± 0.11	17.7 rat	12.4	0.48	73		
COPh (2-F)	**26a**	0.51	9.29 ± 0.08	1.96	8.71 ± 0.08	8.02 ± 0.13	2.6 rat	11.5	3.08	32		
COPh (3-F)	**26b**	0.10	10.0 ± 0.13	0.57	9.24 ± 0.09	8.42 ± 0.09	4.9 rat	12.1	1.73	26	1322	12×
							8.1 dog	18.9	1.61	1.4		
							3.7 mky	8.9	1.62	10		
COPh (4-F)	**26c**	0.27	9.57 ± 0.16	1.00	9.00 ± 0.08	8.09 ± 0.06	4.8 rat	12.2	1.77	57	1997	21×
							6.4 dog	11.3	1.21	5		
							9.8 mky	13.3	0.9	14		
COPh (4-Cl)	**33a**	0.19	8.75 ± 0.12	0.77	9.11 ± 0.12	7.84 ± 0.11	12.4 rat	12.3	0.68	62	1776	22×
COPh (4-CH_3)	**33b**	0.21	9.67 ± 0.07	1.73	8.76 ± 0.10	7.93 ± 0.06	3.3 rat	13.1	2.68	46		
COPh (4-OCH_3)	**33c**	0.52	9.28 ± 0.14	2.69	8.57 ± 0.10	8.09 ± 0.03	2.5 rat	11.6	3.05	20	848	11×
COPh (4-$N(CH_3)_2$)	**33d**	0.52	9.28 ± 0.14	4.57	8.34 ± 0.08							
COPh (3-CH_3, 4-F)	**33e**	0.21	9.69 ± 0.08	5.75	8.24 ± 0.24	7.49 ± 0.06	3.3 rat	26.8	5.78	9		
COPh (3-CH_3, 4-Cl)	**33f**	0.35	9.45 ± 0.07	1.05	8.98 ± 0.14	7.42 ± 0.03	7.6 rat	24.1	2.18	46		
COPh (3-Cl)	**33g**	0.19	9.71 ± 0.08	0.65	9.19 ± 0.10	7.92 ± 0.16	5.2 rat	10.5	2.82	49		
COPh (3,5-di-F)	**33h**	0.09	10.07 ± 0.14	0.54	9.27 ± 0.06	8.30 ± 0.07	7.8 rat	14.3	1.25	68		
COPh	**33i**	0.22	9.66 ± 0.23	0.52	9.28 ± 0.34	7.98 ± 0.14	3.6 rat	14.6	2.84	24		
Ph (3-$COCH_3$)	**37**	0.08	10.08 ± 0.11	0.41	9.39 ± 0.07	8.09 ± 0.15	3.0 rat	27.1	8.48	6	649	44×
							6.5 dog	37.2	3.89	27		
							5.4 mky	13.2	1.70	72		
Ph (3-$(CH_3)_2OH$)	**38**	0.25	9.61 ± 0.09	2.04	8.69 ± 0.08	8.12 ± 0.09	2.8 rat	5.0	1.23	69		
Ph (3-$CH(CH_3)OH$)	**39**	0.44	9.36 ± 0.13	1.40	8.85 ± 0.06	8.25 ± 0.15	7.6 rat	23.0	2.09	55		
Ph (3-CH_2OH)	**44**	0.49	9.31 ± 0.11	2.31	9.64 ± 0.02	8.42 ± 0.13	3.0 rat	13.6	3.1	3		
Ph (3-$COCH_2CH_3$)	**45**	0.23	9.64 ± 0.19	1.00	9.00 ± 0.10	7.91 ± 0.07						
Ph (3-CO cyclopropyl)	**46**	0.21	9.69 ± 0.11	0.72	9.14 ± 0.06	7.83 ± 0.13	5.0 rat	6.2	0.86	70		
Ph (4-CH_2OH)	**50**	0.88	9.06 ± 0.09	3.34	8.48 ± 0.03	8.49 ± 0.06	0.3 rat	8.0	18.1	0		
Ph (3-CN)	**53**	0.27	9.57 ± 0.12	0.91	9.04 ± 0.07	7.72 ± 0.13	4.3 rat	7.5	1.2	38	2477	27×
Ph (4-CO cyclopropyl)	**54**	0.26	9.58 ± 0.07	1.36	8.87 ± 0.06	7.28 ± 0.15	9.3 rat	8.2	0.61	48	3548	61×
reference H_3 antagonists												
thioperamide	**2**	72	7.14 ± 0.06	3.63	8.44 ± 0.07	6.82 ± 0.06					48	0.24×
ciproxifan	**3**	63	7.20 ± 0.05	0.51	9.29 ± 0.09	6.84 ± 0.08	1.7 rat	2.5	0.89	51	500[e]	3.6×
GT-2331	**5**	2.15	8.67 ± 0.05	0.08	10.1 ± 0.14							
A-304121	**11**	760	6.12 ± 0.08	2.50	8.60 ± 0.07	5.95 ± 0.10	4.4 rat	17.8	2.7	83	13[e]	0.9×
A-317920	**12**	93	7.03 ± 0.04	0.71	9.15 ± 0.08	7.26 ± 0.14	0.7 rat	2.3	2.3	32	5[e]	0.08×
A-349821	**13**	0.41	9.39 ± 0.08	1.66	8.78 ± 0.12	8.27 ± 0.12	1.3 rat	6.3	3.2	121	75[e]	0.6×
							2.6 dog	2.3	0.6	33		
							5.3 mky	7.5	1.0	78		

[a] Assessed by displacement of ^{3}H-*N*-α-methyl histamine from cell membranes isolated from C6 cells expressing cloned rat and human H_3 receptors. K_i values are listed for reader convenience, where $pK_i = -\log(K_i)$. Three or more independent K_i determinations for all compounds. [b] Determined by FLIPR. [c] PK properties were determined after administration of 1−5 mg/kg of drug; $n = 3$ animals; Vβ (volume of distribution, L/h); CLb (clearance, L $h^{-1}kg^{-1}$); F (oral bioavailability, %). [d] Brain concentrations were normalized for the amount of compound administered and expressed as tissue concentration of compound in ng (g of tissue)$^{-1}$ (mg of compound)$^{-1}$, administered iv to rats, measured 1 h after dosing. [e] Administered po.

bioavailability in humans. Not surprisingly, the compounds with the lowest oral bioavailability in rats, for example, **33c** ($F = 20\%$), **33e** ($F = 9\%$), **50** ($F = 0\%$), **37** ($F = 6\%$), and **44** ($F = 3\%$), tended to also have the highest clearance rates (CL). Although the routes of metabolism were not determined, the rapid clearance for compound **50** might have been due to the presence of a primary alcohol, which might be a target for metabolic conjugation or oxidation. The benzofuran analogues also had high volumes of distribution relative to the reference H_3 receptor antagonists. This is very likely a reflection of the high lipophilicity of the benzofurans; the CLogP values of the new compounds range from 4.7 (for **44**) to 5.73 (for **54**). It has been found that higher lipophilicity is strongly correlated with higher volumes of distribution in rats and humans.[36] The two benzophenones (**26b** and **26c**) had poorer oral bioavailability in dog and monkey than in rat, while the acetophenone **37** had improved pharmacokinetic properties in these other species. Overall, **20** had the most promising pharmacokinetic profile, with high oral bioavailability and low clearance across different species (Figure 3).

For agents targeted for treatment of CNS diseases, high brain levels are likely a positive attribute, as is efficient CNS penetration, expressed as the brain/blood concentration ratio. The rationale is that high brain levels should maximize exposure of drug to the H_3 receptors in the CNS that mediate the pharmacological effects compared to receptors in the periphery, which should thereby allow lower doses for efficacy. Also, where behavioral efficacy can be achieved with low-circulating drug levels, the risk of side effects due to interaction with peripheral H_3 receptors or other sites can be minimized. The previously disclosed compounds **2**, **11**, **12**, and **13** have low brain/blood ratios (0.24×, 0.9×, 0.08×, and 0.6×, respectively) and do not achieve high brain concentrations (Table 1). In contrast, compounds **20**, **26b**, **26c**, **33a**, **37**, **53**, **54** all have high brain/blood ratios (11×−61×) and achieve high brain concentrations (649−3548 ng g^{-1} mg^{-1} dosed), probably as a consequence of their high lipophilicity (CLogP ≥ 5.1). This high lipophilicity contrasts with that of many known reference H_3 receptor antagonists (CLogP: **2**, 2.3; **3**, 3.0, **5**, 3.3; **11**, 2.4; **12**, 3.1; **13**, 4.6). We believe this achievement of higher CNS drug concentrations best

Table 2. Activity of H_3 Receptor Antagonists in Two Behavioral Models: Inhibitory Avoidance Acquisition in Rat Pups and Social Memory in Adult Rats[a]

compd	inhibitory avoidance acquisition[b] (mg/kg)	social memory[c,d] (mg/kg)	lowest dose to CNS side effects[d] (mg/kg)	therapeutic index vs inhibitory avoidance acquisition	therapeutic index vs social memory
20	0.1	0.01	28	280×	2800×
21	0.1[e]		28	280×	
26a	0.3	0.3	98	325×	325×
26b	0.3[e]		98	330×	
26c	0.3	0.003−0.03	29	97×	9700×
33b	1	1	>97	97×	97×
33h	0.3[e]	0.3	100	330×	330×
37	1				
46	0.1[f]		31	310×	
53	0.03−0.3	0.1	9	30×	90×
reference H_3 antagonists					
2	10	15	82	8×	6×
3	3	0.3	30	10×	90×
5	1		18	18×	
11	10	3[f]−10	280	28×	28×
12	3[f]−10	1[f]−3[f]	280	42×	93×
13	1[f]−10		118	12−118×	

[a] The lowest dose to induce CNS side effects is shown, along with the therapeutic index. [b] Unless otherwise noted, $p < 0.05$ versus saline and fully efficacious, effects were equal to the reference standard ciproxifan at 3 mg/kg. All drugs dosed sc. [c] Unless otherwise noted, $p < 0.05$ versus saline and fully efficacious, effects were equal to reference at 1 mg/kg. [d] Drugs dosed ip. [e] Partially effective, $p > 0.05$, 60−80% effect compared to ciproxifan. [f] Partially effective, $p < 0.05$, 60−80% effect compared to ciproxifan.

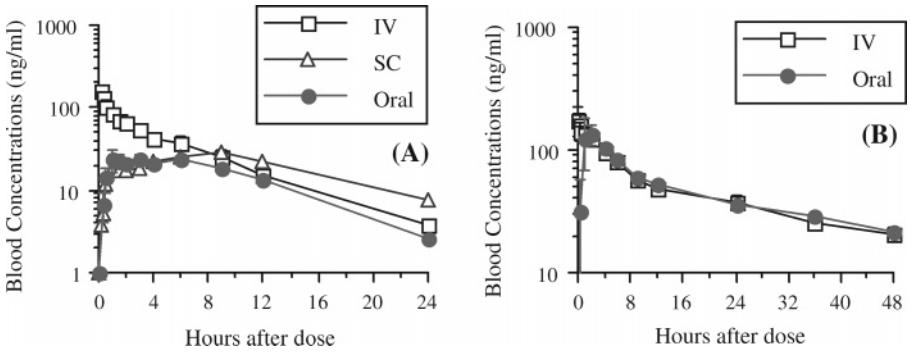


Figure 3. (A) Mean (±SEM, $n = 3$) blood concentrations of **20** after a 1 mg/kg intravenous, subcutaneous, or oral dose in rat. (B) Mean (±SEM) blood concentrations of **20** after a 1 mg/kg intravenous or oral dose in monkey.

explains the increased potency of the new analogues in behavioral models (Table 2). At the same time, it is important to consider that drug lipophilicity introduces additional factors that can temper a portion of the beneficial effect of high CNS drug concentrations. Although lipophilicity may increase CNS penetration and drug levels, it also likely increases binding of the drug to tissue lipids and proteins. This may result in lower concentrations of "free unbound" drug available to bind the target receptor. Possibly as a reflection of its lipophilic character, **20** was found to have relatively high binding to plasma proteins across species, with 94.1% bound to plasma proteins in rats, 91.2% in dogs, 93.6% in monkeys, and 97.3% in humans.

Activity in Animal Models of Cognition and Attention. H_3 receptor antagonists from a variety of structural classes have shown positive effects in animal models of wakefulness, cognition, attention, and memory.[5] Meguro found that thioperamide (**2**) at 15 mg/kg increased acquisition of avoidance behavior in a strain of senescence-accelerated mice in a 5-day, 5-trial passive avoidance (PAR) paradigm.[37] Similarly, Orsetti found that intracranial administration of **2** improved place-recognition memory in rats.[38] Miyazaki also found that **2** improved memory in scopolamine-treated mice in an elevated plus maze model, but the effect was small and seen at the high dose of 20 mg/kg, ip.[39] In the same model, Onodera found that the more lipophilic FUB-181 (**4**) at 2.5−5 mg/kg ip reversed the scopolamine-induced deficit.[15c]

In addition to memory, the inhibitory avoidance acquisition paradigm is thought to model aspects of impulsive behavior. Consistent with this, drugs that suppress impulsiveness in humans are active in this model. Methylphenidate is used in the clinic to treat attention deficit hyperactivity disorder and is fully effective in a 5-trial version of this model at 1−3 mg/kg, as described by Fox,[40] and by Yates[35] in a related 10-trial version. In this model, an imidazole-based H_3 receptor antagonist, GT-2227, was active in rat pups at 1−3 mg/kg.[35] Ciproxifan (**3**) significantly improved performance in a five-choice task in rats at 3 mg/kg, ip.[14] Fox has reported the activity of thioperamide (**2**), ciproxifan (**3**), and **5** in the 5-trial inhibitory avoidance model used in this report and used ciproxifan as a positive control to gauge activity of new H_3 receptor antagonists in animal models, seen in Table 2.[40,41] In previous reports by our group, non-imidazole H_3 receptor antagonists **11**[42] (A-304121), **12**[42] (A-317920), and **13**[24,43] (A-349821) were also shown to significantly improve performance in this assay (Table 2).

Activity in the 5-Trial Inhibitory Avoidance Acquisition Model. H_3 receptor antagonists were tested for their ability to enhance learning in the 5-trial

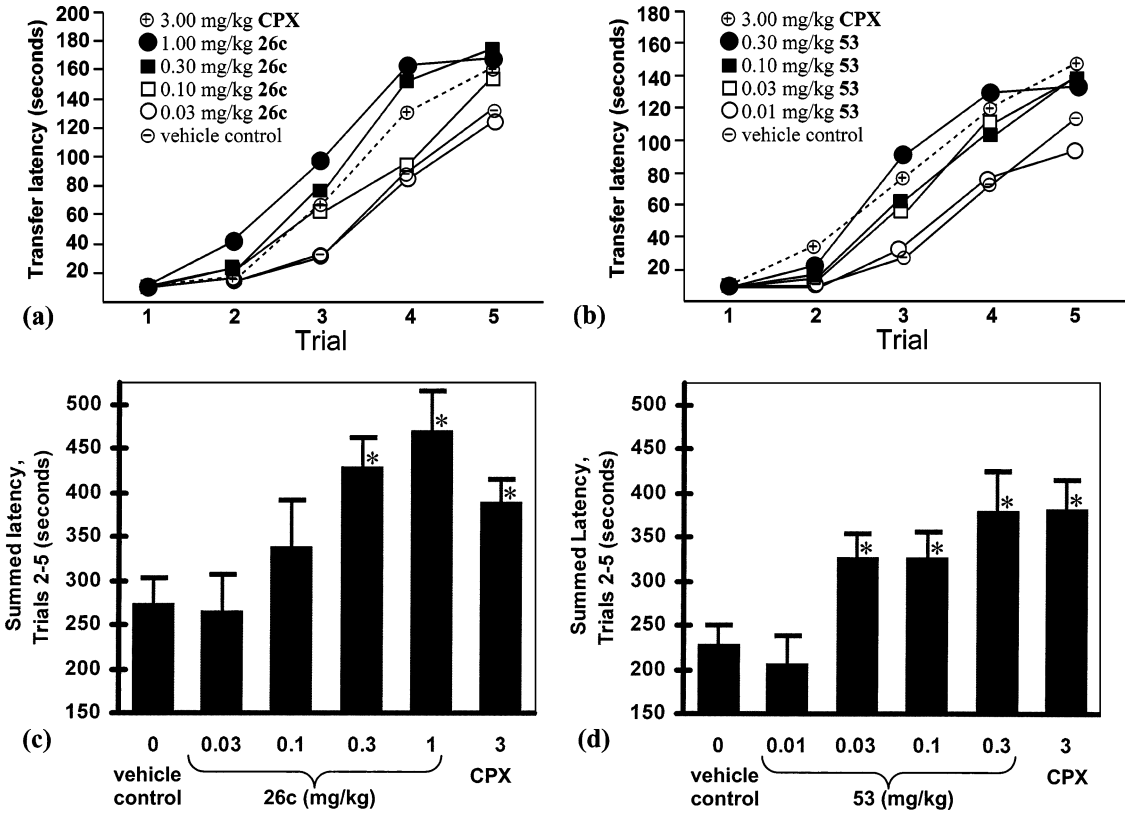


Figure 4. Effect of H_3 antagonists in the 5-trial inhibitory avoidance acquisition model. As depicted in parts a and b, the transfer latency tracks learning, with latency increasing over successive trials to a maximum of 180 s per trial as animals acquire the avoidance behavior. The H_3 antagonists **26c** (a), **53** (b), and ciproxifan (CPX, 3 mg/kg) increase the rate of acquisition compared to vehicle-treated controls. Drugs were administered sc 30 min prior to testing in animals, with separate positive and negative controls for each compound; SEM was omitted for clarity. In parts c (compound **26c**) and d (compound **53**), after the training trial (T1), the summed latency shows the improvement in acquisition for the next four trials (T2−T5) compared to vehicle-treated controls. Error bars depict SEM; (∗) $P < 0.05$, Mann−Whitney test; $n = 27$ animals for **26c**; $n = 12$ for **53**.

inhibitory avoidance acquisition model.[40] In the model, rat pups (spontaneously hypertensive strain) are placed in a brightly lit half of a bipartite chamber, whereupon their inherent preference for the dark leads them to escape (transfer) into the darkened half. Pairing this transference with a mild aversive stimulus motivates the animals to learn to remain in the brightly lit chamber, which is assessed over the course of four more trials conducted under the same conditions. Agents that are thought to enhance attention or learning, such as methylphenidate or nicotinic agonists, enhance the rate at which this avoidance behavior is acquired.[40] The new benzofuran-based compounds are also active in this model, with full efficacy being attained at doses of less than 1 mg/kg. For example, as seen in Figure 4a and 4b, learning of the avoidance behavior increased with successive trials, as assessed by transfer latency, and was dose-dependently increased after administration of **26c** and **53**, compared to vehicle-treated control animals. To better analyze the dose dependence of the learning, the transfer latencies from the training trials 2−5 were added together and analyzed for statistical significance versus vehicle-treated controls, as seen in Figure 4c and 4d. It is clear that both **26c** (at 0.3 mg/kg) and **53** (at 0.03 mg/kg) induce a significant increase in learning compared to control animals, as efficacious as the reference standard ciproxifan at 3 mg/kg. Besides **26c** and **53**, other compounds such as **20**, **26a**, **33b**, and **37** were found to be similarly efficacious (Table 2).

Activity in the Social Recognition Memory Model. Another behavioral model used to assess the memory-enhancing ability of compounds is a social recognition memory test, which measures the ability of agents to improve the retention of encounters between animals. Prast has demonstrated the importance of histamine in general, and H_3 receptors in particular, in a model of social memory in adult rats, where intracerebroventricular administration of histamine, the histamine precursor L-histidine, and thioperamide (**2**) all potently enhanced retention of encounters with juvenile rats.[44] As used in this report, adult rats are observed for the amount of time they spend investigating a novel juvenile rat, with the adult typically sniffing and closely following the juvenile.[42a] After the adult rats gain familiarity with the juvenile, this duration of investigation is reduced, and on retesting, the duration drops to about 60% of that of the initial encounter. The investigation duration remains reduced as long as the memory of the social encounter is retained through at least 30 min in adult rats. However, as more time passes, 2 h or more, the memory of the social encounter is lost and the adult reverts to reinvestigating the juvenile for the same duration as in the initial encounter. Several previously reported H_3 receptor antagonists are able to delay[42] this time-dependent memory loss at doses of 0.3−15 mg/kg (Table 2). Figure 5 depicts the ability of **33b** to improve retention of the social encounter, where, at a dose of 1 mg/kg, **33b** significantly

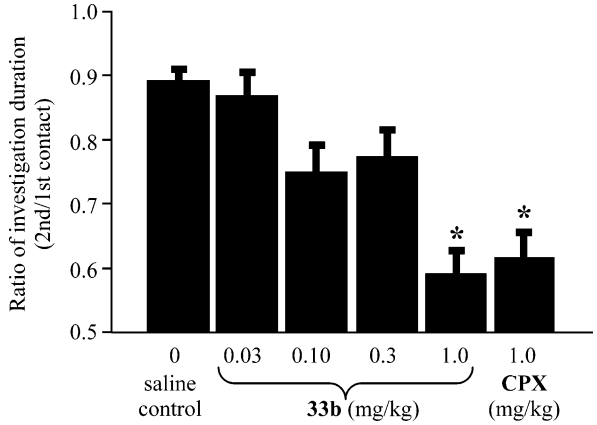


Figure 5. Effect of **33b** on the social memory test in adult rats. After 120 min, adults forget an initial encounter with a juvenile rat and reinvestigate the juvenile for the same amount of time as the initial encounter (ratio of second/first contact = 0.9−1). With increasing doses of **33b** or the reference H_3 antagonist ciproxifan (CPX), recall of the encounter is improved, with a reduction in the time spent reinvestigating the juvenile (ratio of second/first contact = 0.6): (∗) $P < 0.0001$, Fisher's post hoc test; $n = 12$ animals, dosed ip.

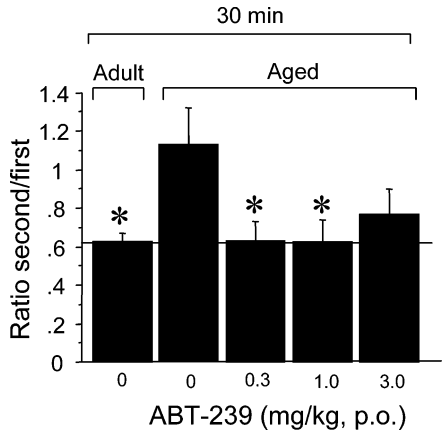


Figure 6. Effect of ABT-239 (**20**) on the social memory test in aged rats. Adults recall their encounter with a juvenile after 30 min and through this period will reduce the amount of time they spend reinvestigating the juvenile (ratio of second/first contact = 0.6). In contrast, even after 30 min, aged rats do not recall their encounter with the juvenile and reinvestigate juveniles for the same time as on first exposure (ratio of second/first contact = 1). However, after oral dosing with ABT-239 (0.3−3 mg/kg), the aged animals recall the juvenile as well as the adults: (∗) $P < 0.05$, Fisher's post hoc test.

reduced the reinvestigation duration and did so with an efficacy equivalent to that of ciproxifan dosed at 1 mg/kg. In this model, **20**, at 0.01 mg/kg, also produced a fully efficacious response equivalent to ciproxifan.[42b] Other benzofuran analogues such as **26a**, **26c**, **33b**, **33h**, and **53** were also fully effective in this model at low doses.

Next, a group of aged rats were tested in the social memory model instead of adult rats but with only a 30 min interval before reintroduction of the juvenile because aged rats do not retain the memory of the juvenile for 30 min. As seen in Figure 6, after administration of **20** at doses as low as 0.3 mg/kg, the aged rats retain the memory of the first encounter and, in retesting after 30 min, perform as well as nonaged adults.

CNS Therapeutic Index. The propensity of compounds to induce CNS side effects was assessed in a general behavioral screen by dosing animals with successively higher doses of compounds and then noting any unusual behavioral or physiological effects (Table 2).[42a] At doses higher than those effective in enhancing cognition, it has previously been reported that some H_3 receptor antagonists can induce hypothermia, piloerection, loss of righting reflexes, hypoactivity, ptosis, tremors, or even seizures.[42a] The lowest dose found to induce a significant incidence of any of these side effects is noted in Table 2. The therapeutic index (TI) was defined as this dose divided by the dose found effective in the avoidance acquisition or social memory model. A goal was to find compounds with a high TI (∼300×) in both models. Only partial efficacy in cognitive tests was noted for compounds **21**, **26b**, **33h**, and **46** at an initial screening dose, and testing at higher doses was not attempted because the TI would have been inadequate, even if greater efficacy could have been attained. The high potency of **20** in the cognition models contributed to its high TI in the acquisition avoidance model (280×) and social recognition memory model (2800×). The favorable profile of **20** in behavioral models and in vitro assays, coupled with favorable pharmacokinetic properties in several species, motivated an examination of this compound in more detail.

The propensity of an agent to stimulate locomotor behavior and stereotypy in rodents may be a predictor of stimulant properties in humans. Both amphetamine[45] and methylphenidate[41,42a] stimulate locomotion and stereotypy in rodents, which can under some conditions become sensitized to the locomotor effects, and cross-sensitized.[46] As seen in Figure 7a, methylphenidate (MPH) was efficacious in the 5-trial inhibitory acquisition avoidance model at 1−3 mg/kg, as measured by an increase in latency, but at comparable doses (3−10 mg/kg), it also stimulated spontaneous locomotor behavior, as measured by the distance travelled. In contrast, the H_3 receptor antagonist **20** was active in the inhibitory avoidance model at 0.1 mg/kg (Figure 7b) and in the social recognition memory model at 0.01 mg/kg but did not stimulate spontaneous locomotor behavior at (10−100)× higher doses (tested to 1 mg/kg). These results are consistent with previous reports that the H_3 receptor antagonists thioperamide,[41] GT-2227,[35] ciproxifan,[43] and A-349821[43] do not stimulate locomotor activity at behaviorally active doses. Together, the animal data suggest that H_3 receptor antagonists in general are able to enhance cognition and suppress impulsiveness without inducing CNS stimulation.

Lack of CYP Inhibition. As has been discussed in the literature, it is highly desirable that the potential for drug−drug interactions of candidate compounds be minimized; compounds should not alter the metabolism of, or have their metabolism altered by, coadministered compounds.[19] An important tenet motivating efforts to find non-imidazole H_3 receptor antagonist drug candidates is the hypothesis that such agents will not inhibit hepatic cytochromes P_{450}[17] and therefore will have minimal liability to inhibit the metabolism of coadministered drugs. This allows greater safety in the clinic and negates concerns when interpreting pharmacological results with coadministered agents. This goal was realized with **20**. When incubated with human liver microsomes at 2 μM, **20** showed no inhibition of the

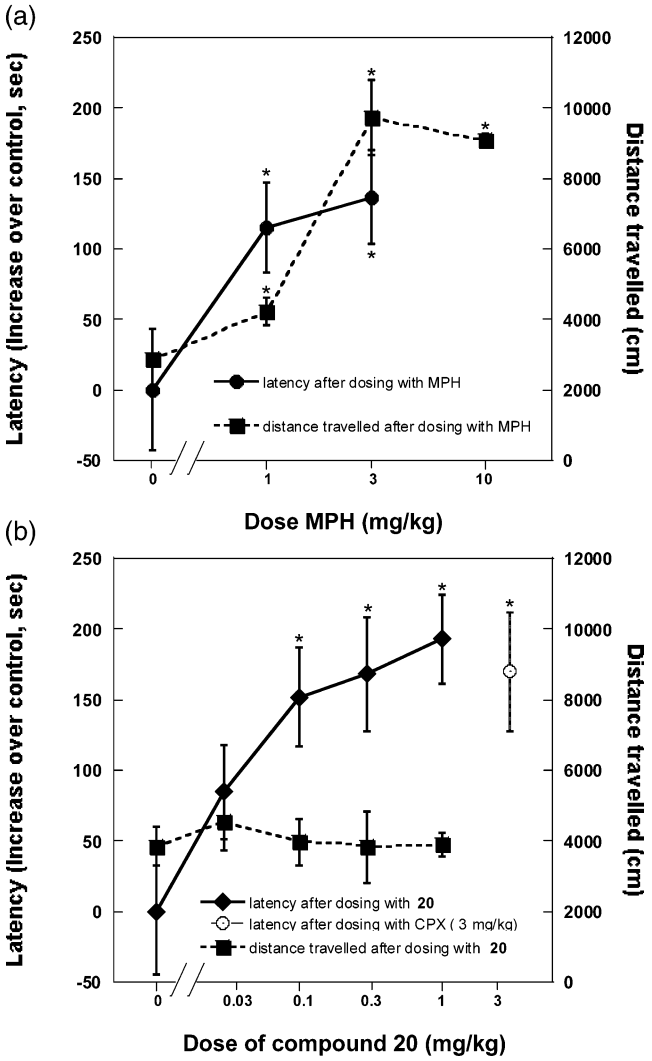


Figure 7. Methylphenidate (MPH) enhanced acquisition of inhibitory avoidance response at 1−3 mg/kg (a), as measured by an increase in latency but also increased locomotion at 3−10 mg/kg.[41,42a] The H_3 antagonist **20** enhanced acquisition[25c] at 0.1 mg/kg (b) without effects on locomotion (0.03−1 mg/kg). Latency = summed improvement in inhibitory avoidance acquisiton over four trials (sum: T2−T5) compared to vehicle-treated controls: (∗) $P < 0.05$, Mann−Whitney test. Doses were administered sc 30 min prior to testing. Spontaneous locomotor activity was measured as distance travelled: (∗) $P < 0.05$, post hoc Tukey's test.

metabolism of the CYP-specific substrates listed in Table 3. At 20 μM, only weak inhibition of CYPs 2D6 and 2C9 was noted. Because these concentrations are much higher than the blood levels necessary for efficacy in the cognition models, which ranged from 0.22 to 4.7 ng/mL (0.7−14 nM), it is likely that **20** and perhaps similar non-imidazole H_3 receptor antagonists will have low liability to perpetrate drug−drug interactions. The small amount of inhibition seen at 20 μM may be due to competition as substrate; **20** was found to be a substrate for human CYPs 3A4, 1A2, and 2D6, as well as flavin monooxygenases FMO-1 and FMO-3, where turnover was seen in c-DNA expressed enzyme preparations (L. Pan, unpublished results).

Concluding Summary

New benzofuran-based H_3 receptor antagonists have been synthesized. The new compounds have balanced nanomolar potency at rat and human H_3 receptors and very high selectivity over other receptors. Many of the compounds had excellent pharmacokinetic profiles in rats; as a consequence of their highly lipophilic nature, the new compounds achieve high CNS concentrations and have large brain/plasma ratios. When tested in two rodent models of cognition and attention, six benzofuran analogues showed robust efficacy and were highly potent, with full efficacy achieved at doses ranging from 0.003 to 1 mg/kg.

One compound, **20**, combined high potency (0.1 mg/kg) in an inhibitory avoidance acquisition model of learning/impulsiveness, high potency (0.01 mg/kg) in a social memory model, and excellent pharmacokinetic properties across different species.[47] Furthermore, **20** did not inhibit hepatic cytochromes P_{450}, consistent with a hypothesis that non-imidazole H_3 receptor antagonists would be free of this liability. Additionally, **20** displayed a high CNS therapeutic index for cognitive enhancement (it did not stimulate locomotor behavior or induce stereotypy), a profile that suggests that H_3 receptor antagonists will be free of CNS stimulant liability. The overall profile of these compounds, and of **20** in particular, supports the potential utility of H_3 receptor antagonists in the treatment of cognitive dysfunction in such human diseases as attention deficit hyperactivity disorder, schizophrenia, mild cognitive impairment, and Alzheimer's dementia.

Experimental Section

Chemistry Methods. Unless otherwise noted, all solvents, chemicals, and reagents were obtained commercially and used without purification and reactions were conducted under N_2 atmosphere at 23 °C. The ^{1}H NMR spectra were obtained at 300 MHz on a Nicolet/GE QE300 spectrometer, with chemical shifts (δ, ppm) reported relative to TMS or TSP as in internal standard. Mass spectra were obtained on a Kratos MS-50 instrument, and unless otherwise indicated, all MS instruments were operated in the +APCI or +DCI mode to detect positively charged ions. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Flash chromatography was carried out using silica gel 60 (E. Merck, 230−400 mesh) or with prepacked 40 mm silica gel columns from BioTage. Thin-layer chromatography was performed on 250 μM silica-coated glass plates from EM Science. Samples were analyzed by HPLC−MS-ELSD on a Finnigan Navigator/Agilent 1100/Sedere Sedex 75 system using a Phenomenex

Table 3. At 2 and 20 μM, the Non-Imidazole H_3 Receptor Antagonist **20** Shows Little or No Inhibition of CYPs, As Assessed by Effect of **20** on the Rate of Oxidation of CYP-Specific Substrates

enzyme isoform: substrate: metabolic process:	CYP 1A2 phenacetin O-deethylation	CYP 2C9 tolbutamide hydroxylation	CYP 3A4 terfenadine hydroxylation	CYP 2C19 *S*-mephenytoin 4′-hydroxylation	CYP 2D6 dextromethorphan O-demethylation	CYP 2E1 chlorzoxazone 6-hydroxylation	CYP 2A6 coumarin 7-hydroxylation
% enzyme inhib by **20** (2 μM)	0	0	0	3.1	2.2	0	4.0
% enzyme inhib by **20** at (20 μM)	2.4	21.9	3.2	4.8	23.6	1.6	3.0

Luna C8 column (5 μm, 2.1 mm × 50 mm). The elution system used was a gradient of either 10−100% CH_3CN/0.1% aqueous CF_3CO_2H, or CH_3CN/10 mM aqueous NH_4OAc over 4.5 min at 1.5 mL/min. Purification by preparative HPLC was carried out on a Waters Symmetry C8 column (40 mm × 100 mm, 7 μm particle size), eluting with a gradient (12 min) of either CH_3CN:/0.1% aqueous CF_3CO_2H, or CH_3CN/10 mM aqueous NH_4OAc. Melting points were determined on a Buchi 510 melting point apparatus and are uncorrected. NH_4OH refers to a saturated aqueous solution of NH_3, and brine refers to a saturated aqueous solution of NaCl. Calculations of CLogP were made using ChemDraw Ultra, from CambridgeSoft Corp.

4′-Hydroxy-3′-iodo[1,1′-biphenyl]-4-carbonitrile (17). To a solution of 6.00 g (30.8 mmol) of 4-hydroxy-4′-cyanobiphenyl (**16**), 4.61 g (30.8 mmol) of NaI, and 1.23 g (30.8 mmol) of NaOH in CH_3OH (90 mL) at 0 °C was added an aqueous solution of 5.25% NaOCl (47 mL of Clorox, 2.29 g, 30.8 mmol) over 45 min. The mixture was stirred at 0 °C for 1 h, warmed to 23 °C, and diluted with saturated aqueous sodium thiosulfate (10 mL), H_2O (80 mL), then adjusted to pH 7 by addition of saturated aqueous NaH_2PO_4. The mixture was extracted with CH_2Cl_2 (2 × 90 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum to give a white powder. The solid was purified by flash chromatography, eluting with CH_2Cl_2 to give **40** (5.19 g, 53%). ^{1}H NMR (DMSO-d_6) δ 10.70 (s, 1H), 8.08 (d, 1H, J = 1.2 Hz), 7.85 (d, 2H, J = 8.3 Hz), 7.78 (d, 2H, J = 8.3 Hz), 7.76 (dd, 1H, J = 7.5, 1.2 Hz), 7.02 (d, 2H, J = 7.5 Hz); MS (DCI) *m/z* 339 $(M + NH_4)^+$.

4-[2-(2-Hydroxyethyl)-1-benzofuran-5-yl]benzonitrile (18). To a solution of **17** (5.19 g, 16.2 mmol), Et_3N (5.60 mL, 40.4 mmol), and 3-butyn-1-ol (1.90 g, 27.2 mmol) in 13 mL of DMF at 20 °C was added CuI (0.46 g, 2.4 mmol) and $(Ph_3P)_2PdCl_2$ (0.56 g, 0.80 mmol). The mixture was stirred at 65 °C for 12 h, cooled, and diluted with CH_2Cl_2 (20 mL) and hexane (100 mL). Celite (5 g) was added with stirring, and the solids were removed by filtration. The filtrate was washed with H_2O (600 mL), the organic layer separated and saved, and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum to give a tan solid. The solid was purified by flash chromatography, eluting with 3% CH_3OH/CH_2Cl_2 to give **18** (4.02 g, 95%). ^{1}H NMR (CD_3OD) δ 7.80 (m, 5H), 7.52 (m, 2H), 6.62 (s, 1H), 3.93 (t, 2H, J = 6.9 Hz), 3.03 (t, 2H, J = 6.9 Hz); MS (DCI) *m/z* 281 $(M + NH_4)^+$.

2-[5-(4-Cyanophenyl)-1-benzofuran-2-yl]ethyl Methanesulfonate (19). To a solution of **18** (0.57 g, 2.2 mmol) and Et_3N (0.9 mL, 6.5 mmol) in CH_2Cl_2 (10 mL) at 20 °C was added CH_3SO_2Cl (0.79 g, 4.5 mmol). The mixture was stirred for 30 min, diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash chromatography, eluting with CH_2Cl_2 to give **19** (0.66 g, 89%). ^{1}H NMR ($CDCl_3$) δ 7.73 (m, 5H), 7.51 (d, 1H, J = 8.1 Hz), 7.46 (dd, 1H, J = 8.1, 1.8 Hz), 4.60 (t, 2H, J = 6.3 Hz), 3.29 (t, 2H, J = 6.3 Hz), 2.97 (s, 3H); MS (DCI) *m/z* 359 $(MH)^+$.

4-(2-(2-[2(*R*)-Methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)benzonitrile (20). A suspension of 0.19 g (0.55 mmol) of **19**, 0.17 g (1.0 mmol) of (*R*)-2-methylpyrrolidine hydrobromide[28a] (**22**), and Na_2CO_3 (0.23 g, 2.2 mmol) in CH_3CN (0.4 mL) was heated with stirring at 50 °C for 48 h. The reaction mixture was cooled to 23 °C and diluted with CH_3CN, and the solids were removed by centrifugation. The supernatant was concentrated under vacuum and the residue was purified by preparative HPLC, eluting with aqueous CH_3CN/0.1% aqueous CF_3CO_2H to give **20** (0.065 g, 34%). ^{1}H NMR (CD_3OD) δ 7.88 (m, 1H), 7.71 (m, 4H), 7.50 (m, 2H), 6.82 (s, 1H), 3.72−3.9 (m, 2H), 3.58 (m, 1H), 3.25−3.5 (m, 4H), 2.48 (m, 1H), 2.05−2.2 (m, 2H), 1.75 (m, 1H), 1.50 (d, J = 6 Hz, 3H); MS (DCI) *m/z* 331 $(MH)^+$.

As an alternative route, powdered methane sulfonic anhydride (1.57 g, 9.0 mmol) was added to a (−10 °C) solution of 2.25 g (8.57 mmol) of **18** and 1.73 g (17 mmol) of Et_3N in 20 mL of CH_2Cl_2. The reaction mixture was allowed to warm to 23 °C over the course of 2 h and then poured into CH_2Cl_2, whereupon the organic phase was washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated under vacuum. Residual CH_2Cl_2 was removed by addition of toluene, then concentrated under vacuum. The mesylate ester thus obtained was dissolved in 8 mL of CH_3CN, and 4 g of 4 Å molecular sieves was added, together with 0.95 g (9.0 mmol) of Na_2CO_3 and 0.50 g of (*R*)-2-methylpyrrolidine hydrobromide. The mixture was heated at 70 °C for 4 days, diluted with CH_3OH, and filtered through Celite. The filtrate was added to 200 mL of Et_2O, washed with 700 mL of 0.5 M Na_2CO_3, concentrated under vacuum, and purified by flash chromatography, eluting with 5% CH_3OH/0.1% NH_4OH in CH_2Cl_2 to give 0.52 g (53%) of **20** as a glass. The L-tartrate salt of **20** crystallized from water as white crystals. Anal. ($C_{22}H_{22}N_2O\cdot C_4H_4O_6\cdot H_2O$) C, H, N. The phosphate salt was obtained as a white powder after recrystallization from methanol, mp 203−204 °C. Anal. ($C_{22}H_{22}N_2O\cdot H_3PO_4$) C, H, N. The phosphate salt is more soluble in water (10 mg/mL) than the L-tartrate salt (3 mg/mL).

4-(2-(2-[2(*S*)-Methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)benzonitrile (21). To a suspension of 0.682 g (2.00 mmol) of **19** in 3 mL of CH_3CN was added a solution of 6.0 mmol of (*S*)-2-methylpyrrolidine in 3 mL of toluene (prepared by treating 1.41 g of (*S*)-2-methylpyrrolidine tartrate with 6 mL of 25% aqueous NaOH, then extracting the mixture with 3 mL of toluene). The reaction mixture was stirred at 23 °C for 4 days, poured into 80 mL of H_2O containing 1 mL of saturated aqueous NH_4OH, and extracted with 40 mL of CH_2Cl_2. After concentration of the CH_2Cl_2 extract under vacuum, the residue was purified by flash chromatography, eluting with 2% CH_3OH and 0.1% NH_4OH in CH_2Cl_2 to give 0.418 g (63%) of **21**. This was dissolved in 3 mL of *i*-PrOH, and 0.183 g of D-tartaric acid was added. Upon slow evaporation of the solvent, white crystals were deposited, which were recrystallized from anhydrous EtOH to give 0.49 g of **21** as the D-tartrate salt, mp 151−152 °C. ^{1}H NMR (DMSO-d_6) δ 7.96 (m, 1H), 7.90 (m, 4H), 7.62 (m, 2H), 6.78 (s, 1H), 3.35 (m, 1H), 3.10 (m, 3 H), 2.80 (m, 3H), 2.00 (m, 1H), 1.78 (m, 2H), 1.40 (m, 1H), 1.18 (d, J = 7 Hz, 3H); MS (DCI) *m/z* 331 $(MH)^+$. Anal. ($C_{22}H_{22}N_2O\cdot C_4H_4O_6$) C, H, N.

1-(3-Butynyl)-2(*R*)-methylpyrrolidine (23). (*R*)-2-Methylpyrrolidine tartrate (**22**) (1.65 g, 7.00 mmol) and powdered K_2CO_3 (2.03 g, 14.7 mmol) in CH_3CN (60 mL) were heated at 50 °C in a sealed bottle for 24 h. The mixture was allowed to cool to 23 °C and treated with 3-butynyl 4-toluenesulfonate (1.24 mL, 7.0 mmol). The mixture was stirred for 1 h at 23 °C and then heated at 50 °C for 24 h. The mixture was allowed to cool to 23 °C and filtered, and the filter cake was washed with CH_3CN. The filtrate was diluted to a total volume of 70 mL with CH_3CN and used as a 0.1 M solution of **23** in subsequent steps without purification.

(3-Fluorophenyl)(4-hydroxyphenyl)methanone (24b). To a well-stirred solution of 1.0 g (4.34 mmol) of 3-fluorophenyl(4-methoxyphenyl)methanone in 50 mL of CH_2Cl_2 at −78 °C was added 13.03 mL of (13.03 mmol) of 1 M BBr_3 dropwise over 20 min. The mixture was allowed to warm to 25 °C and stirred for 18 h. The mixture was cautiously treated with H_2O (1 mL) and stirred for 5 min, followed by additional H_2O (2 mL). After the mixture was stirred for 10 min, 50 mL of H_2O was added, and after 20 min, the mixture was then extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography, eluting with 5% CH_3OH/CH_2Cl_2 to provide **24b** (0.69 g, 74% yield). ^{1}HNMR (300 MHz, CD_3OD) δ 7.79 (d, 2H, J = 8.9 Hz), 7.50 (m, 3H), 7.26 (m, 1H), 6.92 (d, 2H, J = 8.9 Hz); MS (DCI) *m/z* 217 $(MH)^+$, 234 $(M + NH_4)^+$.

(2-Fluorophenyl)(4-hydroxy-3-iodophenyl)methanone (25a). A solution of 2.0 g (9.25 mmol) of **24a** in 120 mL of NH_4OH was stirred at 25 °C for 15 min, then treated with a solution of KI (7.48 g, 45.1 mmol) and I_2 (2.35 g, 9.25 mmol) in 240 mL of H_2O. The reaction mixture was adjusted to pH 7, extracted with EtOAc, washed with H_2O and brine, dried,

and filtered, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography, eluting with 95% CH_2Cl_2/5% MeOH to give **25a** (2.41 g, 76%). MS (DCI) *m/z* 343 $(MH)^+$, 360 $(M + NH_4)^+$.

(3-Fluorophenyl)(4-hydroxy-3-iodophenyl)methanone (25b). Compound **24b** (2.0 g, 9.25 mmol) was iodinated by the method used to prepare **25a**, using an aqueous solution (20 mL) of KI (7.48 g, 45.05 mmol) and I_2 (2.35 g, 9.25 mmol) in NH_4OH (100 mL) to give **25b** (2.30 g, 73%) after purification by flash chromatography (95% CH_2Cl_2, 5% MeOH). ^{1}HNMR (300 MHz, CD_3OD) δ 8.18 (s, 1H), 7.67 (d, 1H, J = 8.9 Hz), 7.45 (m, 4H), 6.92 (d, 1H, J = 8.9 Hz); MS (DCI) *m/z* 343 $(MH)^+$, 360 $(M + NH_4)^+$. Anal. ($C_{22}H_{22}FNO_2 \cdot 1.3\ C_4H_6O_6 \cdot 0.5\ H_2O$) C, H, N.

(4-Fluorophenyl)(4-hydroxy-3-iodophenyl)methanone (25c). A solution of 20.0 g (92.5 mmol) of **24c** in 770 mL of NH_4OH was stirred at 25 °C for 15 min, then treated with a solution of KI (74.79 g, 450.5 mmol) and I_2 (23.48 g, 92.5 mmol) in 185 mL of H_2O. The reaction mixture was stirred at 25 °C for 18 h and then filtered. The precipitate was dissolved in ethyl acetate, washed with H_2O and brine, dried, and filtered and the filtrate was concentrated under vacuum to provide **25c** as a pale-green solid (23.4 g, 74% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.17 (s, 1H), 7.78 (m, 2H), 7.64 (dd, 1H, J = 8.9, 2.1 Hz), 7.26 (t, 2H, J = 8.9 Hz), 6.91 (d, 1H, J = 8.9 Hz); MS (DCI) *m/z* 342.9 $(MH)^+$, 360 $(M + NH_4)^+$.

(2-Fluorophenyl)(2-(2-[2(*R*)-methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)methanone (26a). To 2.0 g (5.85 mmol) of **25a** was added 70.2 mL (7.02 mmol) of a 0.1 M solution of **23** in CH_3CN, followed by $Pd(OAc)_2$ (0.039 g, 0.175 mmol), tris(4-methylphenyl)phosphine (0.107 g, 0.351 mmol), and CuI (0.167 g, 0.877 mmol). After the mixture was stirred at 25 °C for 10 min, the reaction mixture was treated with *i*-Pr_2NH (8.4 mL, 59 mmol) and then heated at 60 °C under N_2 for 16 h. The reaction mixture was allowed to cool and filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 95% CH_2Cl_2/4.5% MeOH/0.5% NH_4OH to give **26a** (0.38 g, 19%). ^{1}HNMR (300 MHz, CD_3OD) δ 7.99 (s, 1H), 7.79 (d, 1H, J = 8.9 Hz), 7−50−7.67 (m, 3H), 7.30 (m, 2H), 6.76 (s, 1H), 3.45 (m, 2H), 3.18 (m, 2H), 2.93 (m, 2H), 2.10−2.78 (m, 2H), 1.93 (m, 2H), 1.59 (m, 1H), 1.28 (d, 3H, J = 6.1 Hz); MS (ESI) *m/z* 352.1 $(MH)^+$. The tartrate salt was formed by addition of l-tartaric acid in aqueous methanol, followed by evaporation to give a glass. Anal. ($C_{22}H_{22}FNO_2 \cdot C_4H_6O_6 \cdot H_2O$) C, H, N.

(3-Fluorophenyl)(2-(2-[2(*R*)-methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)methanone (26b). A mixture of 2.0 g (5.85 mmol) of **25b**, 70.2 mL (7.02 mmol) of a 0.1 M solution of **23** in CH_3CN, $Pd(OAc)_2$ (0.039 g, 0.175 mmol), tris(4-methylphenyl)phosphine (0.107 g, 0.351 mmol), and CuI (0.167 g, 0.877 mmol) was heated at 60 °C for 16 h. The reaction mixture was allowed to cool and filtered through Celite, and the filtrate was concentrated under vacuum and purified by flash chromatography, eluting with 95% CH_2Cl_2/4.5% MeOH/0.5% NH_4OH to provide **26b** (0.37 g, 18%). ^{1}HNMR (300 MHz, CD_3OD) δ 7.98 (s, 1H), 7.76 (d, 1H, J = 8.9 Hz), 7.48 (m, 5H), 6.76 (s, 1H), 3.42 (m, 2H), 3.18 (m, 2H), 2.87 (m, 2H), 2.36 (m, 2H), 1.91 (m, 2H), 1.57 (m, 1H), 1.26 (d, 3H, J = 6.1 Hz); MS (ESI) *m/z* 352.1 $(MH)^+$. The tartrate salt was formed by addition of L-tartaric acid in aqueous methanol, followed by evaporation to give a glass. Anal. ($C_{22}H_{22}FNO_2 \cdot 1.3C_4H_6O_6 \cdot 0.5\ H_2O$) C, H, N.

(4-Fluorophenyl)(2-(2-[2(*R*)-methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)methanone (26c). To 6.5 g (18.5 mmol) of **25c** was added 230 mL (23.0 mmol) of a 0.1 M solution of 1-(3-butynyl)-2(*R*)-methylpyrrolidine (**23**) in CH_3CN, followed by $Pd(OAc)_2$ (0.127 g, 0.566 mmol), tris(4-methylphenyl)phosphine (0.344 g, 1.130 mmol), and CuI (1.08 g, 95.72 mmol). After being stirred at 25 °C for 10 min, the reaction mixture was treated with *i*-Pr_2NH (26.6 mL, 189 mmol) and then heated at 60 °C under N_2 for 16 h. The reaction mixture was allowed to cool and filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified on silica gel, eluting with 90% CH_2Cl_2/9.9% MeOH/0.1% NH_4OH to provide **26c** (1.21 g, 18.0% yield). ^{1}HNMR (300 MHz, CD_3OD) δ 7.97 (s, 1H), 7.86 (m, 2H), 7.71 (dd, 1H, J = 8.9, 2.1 Hz), 7.58 (d, 1H, J = 8.9 Hz), 7.27 (t, 2H, J = 8.9 Hz), 6.68 (s, 1H), 3.28 (m, 2H), 3.06 (m, 2H), 2.49 (m, 2H), 2.02−2.28 (m, 2H), 1.81 (m, 2H), 1.46 (m, 1H), 1.09 (d, 3H, J = 6.1 Hz); MS (ESI) *m/z* 352 $(MH)^+$. Anal. ($C_{22}H_{22}FNO_2$) C, H, N. The tartrate salt was formed by addition of L-tartaric acid in aqueous CH_3OH, followed by concentration under vacuum to give a glass. Anal. ($C_{22}H_{22}FNO_2 \cdot C_4H_6O_6 \cdot H_2O$) C, H, N.

4-(Benzyloxy)benzoyl Chloride (28). To a solution of 15.0 g (65.72 mmol) of **27** (4-benzyloxybenzoic acid) and 0.75 mL of DMF in 150 mL of CH_2Cl_2 at 0 °C was added oxalyl chloride (11.5 mL, 131.44 mmol) dropwise over 25 min. The resulting mixture was stirred at 23 °C for 2 h, followed by concentration under vacuum to give **28** as a light-yellow solid (16.1 g, 99% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, 2H, J = 8.9 Hz), 7.33 (m, 5H), 7.03 (d, 2H, J = 8.9 Hz).

4-(Benzyloxy)-*N*-methoxy-*N*-methylbenzamide (29). To a solution of 19.7 g (80.26 mmol) of 4-(benzyloxy)benzoyl chloride (**28**) in CH_2Cl_2 was added powdered *N*,*O*-dimethylhydroxylamine hydrochloride (7.83 g, 80.26 mmol). The reaction mixture was cooled to 0 °C and after 30 min was treated with Et_3N (25.47 mL, 182.41 mmol). The reaction mixture was allowed to warm to 25 °C, stirred for 16 h, diluted with CH_2Cl_2 (150 mL), and washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, and H_2O. The organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under vacuum to provide **29** as a pale-yellow solid (18.65 g, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, 2H, J = 8.9 Hz), 7.40 (m, 5H), 6.98 (d, 2H, J = 8.9 Hz), 3.56 (s, 3H), 3.36 (s, 3H); MS (ESI) *m/z* 272 $(MH)^+$.

4-Hydroxy-*N*-methoxy-*N*-methylbenzamide (30). To a suspension of 10% Pd(C) (4.5 g) in 10 mL of CH_3OH was added a solution of 18.60 g (68.55 mmol) of **29** (4-(benzyloxy)-*N*-methoxy-*N*-methylbenzamide) in 150 mL of CH_3OH. The mixture was shaken under an atmosphere of H_2 at 67 psi until TLC indicated complete consumption of **29**, then filtered. The filtrate was concentrated under vacuum and purified by flash chromatography, eluting with 90% CH_2Cl_2/10% CH_3OH to provide **30** (10.3 g, 83% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 7.59 (d, 2H, J = 8.9 Hz), 6.81 (d, 2H, J = 8.9 Hz), 3.58 (s, 3H), 3.32 (s, 3H); MS (DCI) *m/z* 182 $(MH)^+$, 199 $(M + NH_4)^+$.

4-Hydroxy-3-iodo-*N*-methoxy-*N*-methylbenzamide (31). A suspension of 10.3 g (56.84 mmol) of 4-hydroxy-*N*-methoxy-*N*-methylbenzamide (**30**) in NH_4OH (400 mL) was stirred at 25 °C for 15 min, then treated with KI (45.96 g, 276.83 mmol) and I_2 (14.43 g, 56.84 mmol) in 65 mL of H_2O. After the mixture was stirred for 16 h, the solvent was removed under vacuum, and the residue was redissolved in CH_2Cl_2 (500 mL) and washed with H_2O (2 × 350 mL). The organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography, eluting with 90% CH_2Cl_2/10% CH_3OH, to provide **31** as a white solid (11.6 g, 67% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.06 (s, 1H), 7.58 (d, 1H, J = 8.9 Hz), 6.83 (d, 1H, J = 8.9 Hz), 3.59 (s, 3H), 3.32 (s, 3H); MS (DCI) *m/z* 308 $(MH)^+$, 325 $(M + NH_4)^+$.

***N*-Methoxy-*N*-methyl-2-(2-[2(*R*)-methyl-1-pyrrolidinyl]-ethyl)-1-benzofuran-5-carboxamide (32).** To a solution of 11.6 g (37.77 mmol) of 4-hydroxy-3-iodo-*N*-methoxy-*N*-methylbenzamide (**31**) in CH_3CN (50 mL) was added in sequential fashion 378 mL (45.33 mmol) of a 0.12 M solution of 1-(3-butynyl)-2(*R*)-methylpyrrolidine (**23**) in CH_3CN, $Pd(OAc)_2$ (0.254 g, 1.13 mmol), tris(4-methylphenyl)phosphine (0.518 g, 1.699 mmol), and *i*-Pr_2NH (39.7 mL, 283.3 mmol). After being stirred at 25 °C for 10 min, the mixture was treated with CuI (2.16 g, 11.33 mmol) and heated at 50 °C under N_2 for 18 h. The reaction mixture was cooled to 23 °C and filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 95% DCM/9.9% MeOH/0.1% NH_4OH to provide **32** (1.22 g) with a recovery of 6 g of iodophenol, which was resubjected to the reaction conditions (adjusting for scale) to

give an additional 1.10 g of **32** for a total yield of 2.32 g (21%) of **32**. Note that the Pd-catalyzed cyclization appeared somewhat dependent on the scale, with reactions starting with 1, 5, and 6 g of iodophenol giving yields of **32** of 42%, 47%, and 44%, respectively. ^{1}H NMR (300 MHz, CD_3OD) δ 7.84 (s, 1H), 7.51 (q, 2H, J = 10.5 Hz), 6.63 (s, 1H), 3.59 (s, 3H), 3.38 (s, 3H), 3.26 (m, 2H), 3.06 (m, 2H), 2.50 (m, 2H), 2.12 (m, 2H), 1.78 (m, 2H), 1.47 (m, 1H), 1.18 (d, 3H, J = 6.1 Hz); MS (ESI) m/z 317.2 $(MH)^+$. Anal. ($C_{18}H_{24}N_2O_3 \cdot 0.85CH_3OH$) C, H, N.

(4-Chlorophenyl)(2-(2-[2(*R*)-methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)methanone (33a). A solution of 0.250 g (0.79 mmol) of **32** in 20 mL of THF at 0 °C was treated with 4-chlorophenylmagnesium bromide (1.58 mL of a 1.0 M THF solution, 1.58 mmol). The mixture was allowed to warm slowly to 25 °C and stirred for 18 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (2 × 50 mL). The organic phases were combined, dried over Na_2SO_4, and filtered, and the filtrate was evaporated under vacuum. The residue was purified by flash chromatography, eluting with 95% CH_2Cl_2/4.5% MeOH/0.5% NH_4OH to provide **33a** (0.061 g, 21% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 7.97 (s, 1H), 7.78 (m, 3H), 7.57 (m, 3H), 6.67 (s, 1H), 3.23 (m, 2H), 3.03 (m, 2H), 2.50 (m, 2H), 2.01−2.36 (m, 2H), 1.78 (m, 2H), 1.46 (m, 1H), 1.18 (d, 3H, J = 6.1 Hz); MS (ESI) m/z 368.1 $(MH)^+$. The tartrate salt was formed by addition of L-tartaric acid in aqueous methanol, followed by evaporation to give a glass. Anal. ($C_{22}H_{22}ClNO_2 \cdot 1.2C_4H_6O_6$) C, H, N.

(4-Methylphenyl)(2-(2-[2(*R*)-methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)methanone (33b). By the method used to prepare **33a**, a solution of **32** (0.20 g, 0.63 mmol) and 4-methylphenylmagnesium bromide (3.16 mL of a 1 M solution in THF, 3.16 mmol) was reacted to provide **33b** (0.118 g, 54% yield) after purification by flash chromatography, eluting with 95% CH_2Cl_2/4.5% MeOH/0.5% NH_4OH). ^{1}H NMR (300 MHz, CD_3OD) δ 8.0 (d, 1H, J = 2.1 Hz), 7.75 (dd, 1H, J = 8.9, 2.1 Hz), 7.70 (d, 2H, J = 8.9 Hz), 7.60 (d, 1H, J = 8.9 Hz), 7.38 (d, 2H, J = 8.9 Hz), 6.85 (s, 1H), 3.80 (m, 2H), 3.57 (m, 1H), 3.30 (m, 4H), 2.45 (s, 3H), 2.38 (m, 1H), 2.1 (m, 2H), 1.75 (m, 1H), 1.48 (d, 3H, J = 6.1 Hz); MS (ESI) m/z 348 $(MH)^+$. The tartrate salt was formed by addition of L-tartaric acid in aqueous methanol, followed by evaporation to give a glass. Anal. ($C_{23}H_{25}NO_2 \cdot 2.0C_4H_6O_6$) C, H, N.

(4-Methoxyphenyl)(2-(2-[2(*R*)-methyl-1-pyrrolidinyl]-ethyl)-1-benzofuran-5-yl)methanone (33c). By the method used to prepare **33a**, a solution of **32** (0.080 g, 0.253 mmol) in THF and 4-methoxyphenylmagnesium bromide (0.61 mL of a 0.5 M solution in THF, 0.30 mmol) was reacted to provide **33c** (0.014 g, 12% yield) after purification by flash chromatography (95% CH_2Cl_2/ 4.5% MeOH/0.5% NH_4OH). ^{1}H NMR (CD_3OD) δ 7.92 (s, 1H), 7.80 (d, 2H, J = 8.9 Hz), 7.68 (d, 1H, J = 8.9 Hz), 7.54 (d, 1H, J = 8.9 Hz), 7.05 (d, 2H, J = 8.9 Hz), 6.67 (s, 1H), 3.88 (s, 3H), 3.24 (m 2H), 3.06 (m, 2H), 2.50 (m, 2H), 2.26 (m, 1H), 2.07 (m, 1H), 1.78 (m, 2H), 1.46 (m, 1H), 1.18 (d, 3H, J = 6.1 Hz); MS (ESI) m/z 364 $(MH)^+$. The tartrate salt was formed by addition of L-tartaric acid in aqueous methanol, followed by evaporation to give a glass. Anal. ($C_{23}H_{25}NO_3 \cdot C_4H_6O_6 \cdot H_2O$) C, H, N.

[4-(Dimethylamino)phenyl](2-(2-[2(*R*)-methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)methanone (33d). By the method used to prepare **33a**, a solution of **32** (0.05 g, 1.26 mmol) and 4-(dimethylamino)phenylmagnesium bromide (1.58 mL of a 0.5 M solution in THF, 0.79 mmol) was reacted to provide **33d** (0.016 g, 27% yield) after purification by preparative HPLC. ^{1}H NMR (300 MHz, CD_3OD) δ 7.95 (d, 1H, J = 2.1 Hz), 7.75 (d, 2H, J = 8.9 Hz), 7.65 (dd, 1H, J = 8.9, 2.1 Hz), 7.56 (d, 1H, J = 8.9 Hz), 6.85 (s, 1H), 6.80 (d, 2H, J = 8.9 Hz), 3.80 (m, 2H), 3.55 (m, 1H), 3.50 (m, 2H), 3.18 (s, 6H), 2.35 (m, 1H), 2.15 (m, 2H), 1.80 (m, 2H), 1.73 (m, 1H), 1.44 (d, 3H, J = 6.1 Hz); MS (ESI) m/z 377 $(MH)^+$. Anal. ($C_{24}H_{28}N_2O_2 \cdot 1.5CF_3CO_2H$) C, H, N.

(4-Fluoro-3-methylphenyl)(2-(2-[2(*R*)-methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)methanone (33e). By the method used to prepare **33a**, a solution of **32** (0.080 g, 0.253 mmol) in THF and (4-fluoro-3-methyl)phenylmagnesium bromide (0.30 mL of a 1 M solution in THF, 0.30 mmol) was reacted to provide **33e** (0.016 g, 13% yield) after purification by flash chromatography (95% CH_2Cl_2/4.5% MeOH/ 0.5% NH_4OH). ^{1}H NMR (300 MHz, CD_3OD) δ 7.95 (d, 1H, J = 2.1 Hz), 7.70 (dd, 2H, J = 8.9, 2.1 Hz), 7.63 (m, 1H), 7.57 (d, 1H, J = 8.9 Hz), 7.19 (t, 1H, J = 8.9 Hz), 6.65 (s, 1H), 3.25 (m, 2H), 3.05 (m, 2H), 2.50 (m, 2H), 2.30 (m, 4H), 2.0 (m, 1H), 1.80 (m, 2H), 1.45 (m, 1H), 1.17 (d, 3H, J = 6.1 Hz); MS (ESI) m/z 366 $(MH)^+$. The tartrate salt was formed by addition of L-tartaric acid in aqueous methanol, followed by evaporation to give a glass. Anal. ($C_{23}H_{24}FNO_2 \cdot C_4H_6O_6 \cdot 0.5H_2O$) C, H, N.

(4-Chloro-3-methylphenyl)(2-(2-[2(*R*)-methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)methanone (33f). By the method used to prepare **33a**, a solution of **32** (0.35 g, 1.11 mmol) in THF and 4-chloro-3-methylphenylmagnesium bromide (11.1 mL of a 0.5 M solution in THF, 5.53 mmol) was reacted to provide **33f** (0.290 g, 68% yield) after purification by flash chromatography (95% CH_2Cl_2, 4.5% MeOH, 0.5% NH_4OH). ^{1}H NMR (300 MHz, CD_3OD) δ 8.01 (d, 1H, J = 2.1 Hz), 7.79 (dd, 1H, J = 8.9, 2.1 Hz), 7.7 (bs, 1H), 7.50 (m, 3H), 6.85 (s, 1H), 3.80 (m, 2H), 3.55 (m, 1H), 3.50 (m, 2H), 2.44 (s, 3H), 2.38 (m, 1H), 2.10 (m, 2H), 1.80 (m, 2H), 1.75 (m, 1H), 1.47 (d, 3H, J = 6.1 Hz); MS (ESI) m/z 382 $(MH)^+$. The tartrate salt was formed by addition of L-tartaric acid in aqueous methanol, followed by evaporation to give a glass. Anal. ($C_{23}H_{24}ClNO_2 \cdot 1.0C_4H_6O_6 \cdot 0.5H_2O$) C, H, N.

(3-Chlorophenyl)(2-(2-[2(*R*)-methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)methanone (33g). A solution of 0.400 g (1.26 mmol) *N*-methoxy-*N*-methyl-2-(2-[(2*R*)-2-methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-carboxamide (**32**) in 20 mL of THF at 0 °C was treated with 3-chlorophenylmagnesium bromide (12.6 mL of a 0.5 M THF solution, 6.32 mmol). The mixture was allowed to warm slowly to 25 °C and stirred for 18 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (2 × 50 mL). The organic phases were combined, dried over Na_2SO_4, and filtered, and the filtrate was evaporated under vacuum. The residue was purified by flash chromatography, eluting with 95% DCM/ 4.5% MeOH/0.5% NH_4OH to provide **33g** (0.18 g, 39% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.02 (d, 1H, J = 1.2 Hz), 7.65 (m, 6H), 6.90 (s, 1H), 3.80 (m, 2H), 3.55 (m, 1H), 3.30 (m, 4H), 2.35 (m, 1H), 2.10 (m, 2H), 1.72 (m, 1H), 1.50 (d, 3H, J = 6.1 Hz); MS (ESI) m/z 368 $(MH)^+$. The tartrate salt was formed by addition of L-tartaric acid in aqueous methanol, followed by evaporation to give a glass. Anal. ($C_{22}H_{22}ClNO_2 \cdot C_4H_6O_6$) C, H, N.

(3,5-Difluorophenyl)(2-(2-[2(*R*)-methyl-1-pyrrolidinyl]-ethyl)-1-benzofuran-5-yl)methanone (33h). By the method used to prepare **33a**, a solution of **32** (0.40 g, 1.26 mmol) and 3,5-difluorophenylmagnesium bromide (12.6 mL of a 0.5 M THF solution, 6.32 mmol) was reacted to provide **33h** (0.115 g, 25% yield) after purification by flash chromatography, eluting with 95% CH_2Cl_2/4.5% MeOH/0.5% NH_4OH. ^{1}H NMR (300 MHz, CD_3OD) δ 8.05 (d, 1H, J = 2.1 Hz), 7.80 (dd, 1H, J = 8.9, 2.1 Hz), 7.63 (d, 1H, J = 8.9 Hz), 7.30 (m, 3H), 6.88 (s, 1H), 3.82 (m, 2H), 3.56 (m, 1H), 3.30 (m, 4H), 2.35 (m, 1H), 2.13 (m, 2H), 1.75 (m, 1H), 1.45 (d, 3H, J = 6.1 Hz); MS (ESI) m/z 370 $(MH)^+$. The tartrate salt was formed by addition of L-tartaric acid in aqueous methanol, followed by evaporation to give a glass. Anal. ($C_{22}H_{21}F_2NO_2 \cdot 1.25C_4H_6O_6$) C, H, N.

(2-(2-[2(*R*)-Methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)(phenyl)methanone (33i). By the method used to prepare **33a**, a solution of **32** (0.40 g, 1.26 mmol) and PhMgBr (12.6 mL of a 0.5 M THF solution, 6.32 mmol) was reacted to provide **33i** (0.161 g, 38% yield) after purification by flash chromatography, eluting with 95% CH_2Cl_2/4.5% MeOH/0.5% NH_4OH. ^{1}H NMR (300 MHz, CD_3OD) δ 7.98 (d, 1H, J = 2.1 Hz), 7.80 (m, 3H), 7.65 (m, 1H), 7.55 (m, 3H), 6.63 (s, 1H), 3.30 (m, 4H), 2.50 (m, 2H), 2.30 (m, 1H), 2.00 (m, 1H), 1.80 (m, 2H), 1.45 (m, 1H), 1.15 (d, 3H, J = 6.1 Hz); MS (ESI) m/z 334 $(MH)^+$. The tartrate salt was formed by addition of L-tartaric acid in aqueous methanol, followed by evaporation to give a glass. Anal. ($C_{22}H_{23}NO_2 \cdot C_4H_6O_6$) C, H, N.

1-(4′-Hydroxy-1,1′-biphenyl-3-yl)ethanone (35). A mixture of 4-iodophenol (**34**, 5.39 g, 24.5 mmol) and 3-acetylphenylboronic acid (4.42 g, 26.95 mmol) in 15 mL of DMF and 75 mL of 1 M aqueous Na_2CO_3 was treated with 110 mg (0.49 mmol) of $Pd(OAc)_2$, heated at 55 °C for 1 h, and then cooled, diluted with 100 mL of CH_2Cl_2, and filtered. The aqueous filtrate was extracted with CH_2Cl_2, and the combined organic phases were washed consecutively with potassium phosphate buffer (pH 7) and brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography, eluting with a 33−100% gradient of CH_2Cl_2/hexane, then 0−3% EtOAc/CH_2Cl_2, to provide an oil that crystallized to a white solid on standing (**35**, 6.3 g, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, 1 H, J = 1.7, 1.7 Hz), 7.88 (m, 1 H), 7.74 (m, 1 H), 7.47−7.53 (m, 3 H), 6.97 (d, 2 H, J = 9.1 Hz), 2.65 (s, 3 H); MS (ESI APCI negative ion mode) *m/z* 211 $(M - H)^-$.

1-(4′-Hydroxy-3′-iodo-1,1′-biphenyl-3-yl)ethanone (36). A mixture of **35** (5.76 g, 27 mmol) in 400 mL of NH_4OH was treated with a solution of KI (23.3 g, 140 mmol) and I_2 (7.24 g, 28.5 mmol) in 100 mL of H_2O. After 1 h, additional KI (15.8 g, 95 mmol) and I_2 (4.83 g, 19 mmol) in 50 mL of H_2O were added, and after an hour, the reaction mixture was concentrated under vacuum to remove NH_4OH. The resulting residue was extracted with EtOAc, washed consecutively with potassium phosphate buffer (pH 7) and brine, dried over Na_2SO_4, concentrated under vacuum, and purified by flash chromatography, eluting with 0−5% EtOAc/CH_2Cl_2/1% CH_3CO_2H to give **36** as a beige powder (1.97 g, 21% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, 1 H, J = 1.4 Hz), 7.88−7.93 (m, 2 H), 7.71 (m, 1 H), 7.48−7.55 (m, 2 H), 7.08 (d, 1 H, J = 5.9 Hz), 5.37 (bs, 1 H), 2.65 (s, 3 H). MS (ESI APCI negative ion mode) *m/z* 337 $(M - H)^-$.

1-[3-(2-(2-[2(*R*)-Methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)phenyl]ethanone (37). To a suspension of **36** (1.15 g, 3.40 mmol), $Pd(OAc)_2$ (38 mg, 0.17 mmol), biphen-2-yldicyclohexylphosphine (119 mg, 0.34 mmol), and CuI (76 mg, 0.40 mmol) in *i*-Pr_2NH (4.8 mL, 34 mmol) and 10 mL of DMF was added 4.0 mmol of **23** in 45 mL of CH_3CN. The mixture was heated at 45 °C for 12 h, cooled, and poured into a mixture of 100 mL of CH_2Cl_2 and 100 mL of 5% aqueous NH_4OH (100 mL). After filtration to remove solids, the organic phase was washed consecutively with water and brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography, eluting with 0−4% CH_3OH/CH_2Cl_2, then again by flash chromatography, eluting with 0−5% CH_3OH/CH_2Cl_2 to give **37** (0.35 g, 30% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.22 (m, 1 H), 7.96 (ddd, 1 H, J = 7.9, 1.7, 1.7 Hz), 7.88 (ddd, 1 H, J = 7.9, 2.0, 2.0 Hz), 7.78 (m, 1 H), 7.57 (dd, 1 H, J = 7.8, 7.8 Hz), 7.49−7.52 (m, 2 H), 6.62 (s, 1 H), 3.19−3.32 (m, 2 H), 2.95−3.14 (m, 2 H), 2.67 (s, 3 H), 2.40−2.58 (m, 2 H), 2.23−2.34 (m, 1 H), 1.94−2.07 (m, 1 H), 1.73−1.86 (m, 2 H), 1.38−1.52 (m, 1 H), 1.17 (d, 3 H, J = 6.0 Hz); MS (APCI) *m/z* 348 $(MH)^+$. The tartrate salt was formed by addition of L-tartaric acid in methanol, followed by evaporation to give a glass. Anal. ($C_{23}H_{25}NO_2 \cdot 1.2C_4H_6O_6$) C, H, N.

2-[3-(2-(2-[2(*R*)-Methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)phenyl]-2-propanol (38). A solution of 87 mg (0.25 mmol) of **37** in 5 mL of THF was treated with 0.3 mL (0.9 mmol) of a 3 M solution of CH_3MgBr in Et_2O. The reaction mixture was stirred for 12 h, treated with 0.5 M aqueous K_2HPO_4, and then diluted with EtOAc and CH_2Cl_2. The aqueous phase was separated and reextracted with EtOAc. The combined organic phases were washed consecutively with 0.5 M aqueous K_2HPO_4 and brine, dried over Na_2SO_4, concentrated under vacuum, and purified by flash chromatography, eluting with 2−20% CH_3CN/CH_2Cl_2 followed by 10% CH_3OH/CH_2Cl_2 to provide **38** (0.025 g, 27% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 1.20 (d, 3 H), 1.42−1.58 (m, 1 H), 1.58 (s, 6 H), 1.76−1.90 (m, 2 H), 1.96−2.12 (m, 1 H), 2.3−2.7 (m, 3 H), 2.97−3.13 (m, 2 H), 3.22−3.4 (m, 2 H), 6.62 (s, 1 H), 7.38 (dd, 1 H), 7.40−7.46 (m, 2 H), 7.46−7.48 (m, 2 H), 7.72 (dd, 1 H), 7.76 (dd, 1 H); MS (ESI) *m/z* 364 $(M + H)^+$. Anal. ($C_{24}H_{29}NO_2 \cdot C_4H_6O_6 \cdot 1.5CH_3OH$) C, H, N.

[3-(2-(2-[2(*R*)-Methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)phenyl]ethanol (39). A solution of 256 mg (0.73 mmol) of **37** in 2 mL of EtOH and 0.5 mL of THF was treated with 38 mg (1.0 mmol) of $NaBH_4$. After 2.5 h the mixture was treated with 3 M aqueous HCl (8 mL), stirred for 10 min, and adjusted to pH 7 by addition of aqueous K_3PO_4. The mixture was extracted with EtOAc, and the organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography, eluting with 2−8% CH_3OH in 1:1 EtOAc/CH_2Cl_2 followed by 8−20% CH_3OH/CH_2Cl_2 to provide **39** (0.197 g, 77%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.71 (m, 1 H), 7.62 (m, 1 H), 7.50 (m, 1 H), 7.46−7.49 (m, 2 H), 7.39 (dd, 1 H, J = 7.8, 7.8 Hz), 7.32 (m, 1 H), 6.62 (s, 1 H), 4.90 (q, 1 H, J = 6.4 Hz), 3.23−3.42 (m, 2 H), 2.97−3.18 (m, 2 H), 2.55−2.65 (m, 2 H), 2.35−2.50 (m, 1 H), 1.99−2.13 (m, 1 H), 1.78−1.90 (m, 2 H), 1.49 (d, 3 H, J = 6.4 Hz), 1.42−1.57 (m, 1 H), 1.17 (d, 3 H, J = 6.1 Hz); MS (ESI) *m/z* 350 $(MH)^+$. The tartrate salt was formed by addition of L-tartaric acid in methanol, followed by evaporation to give a glass. Anal. $C_{23}H_{27}NO_2 \cdot 1.2C_4H_6O_6 \cdot 0.3\ CH_3OH$ C, H, N.

Ethyl 4′-Hydroxy-1,1′-biphenyl-3-carboxylate (40). A mixture of **34** (9.90 g, 45 mmol) and 3-ethoxycarbonylphenylboronic acid (9.70 g, 50.0 mmol) in 15 mL of DMF and 135 mL of 1 M aqueous Na_2CO_3 was treated with 224 mg (1.0 mmol) of $Pd(OAc)_2$ and stirred at 23 °C for 16 h, then cooled, diluted with 50 mL of CH_2Cl_2, acidified with 140 mL of 1 M HCl, and filtered. The aqueous filtrate was extracted with CH_2Cl_2, and the combined organic phases were washed consecutively with potassium phosphate buffer (pH 6) and brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography, eluting first with 50% CH_2Cl_2/hexanes and then with a gradient of 0−1% MeOH/CH_2Cl_2 to give **40** as a white powder (7.73 g, 71% yield). MS (ESI APCI negative ion mode) *m/z* 241 $(M - H)^-$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1 H), 8.11 (m, 1 H), 7.83−7.89 (m, 2 H), 7.50−7.59 (m, 3 H), 6.89 (d, 2 H, J = 8.9 Hz), 4.34 (q, 2 H, J = 7.1 Hz), 1.34 (t, 3 H, J = 7.1 Hz).

Ethyl 4′-Hydroxy-3′-iodo-1,1′-biphenyl-3-carboxylate (41). A solution of 7.71 g (31.8 mmol) of **40** in 30 mL of DMF and 320 mL of NH_4OH was treated with a solution of KI (27.72 g, 167 mmol) and I_2 (8.48 g, 33.4 mmol) in 100 mL of H_2O. The mixture was stirred for 1 h, then concentrated under vacuum. The residual solution was adjusted to pH 7 with aqueous HCl and extracted with EtOAc (200 mL). The aqueous phase was reextracted with EtOAc, and the organic phases were combined and washed consecutively with water and brine, dried over Na_2SO_4, concentrated under vacuum, and purified by flash chromatography, eluting with a 33−100% gradient of CH_2Cl_2/hexane to give **41** as a white solid (4.36 g, 37% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (bs, 1 H), 8.08 (m, 1 H), 7.97 (d, 1 H, J = 2.1 Hz), 7.90 (m, 1 H), 7.86 (m, 1 H), 7.53−7.60 (m, 2 H), 7.00 (d, 1 H, J = 8.3 Hz), 4.35 (q, 2 H, J = 7.1 Hz), 1.35 (t, 3 H, J = 7.1 Hz).

3-(2-(2-[2(*R*)-Methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)benzoic Acid (42). To 1.47 g (4.0 mmol) of **41**, 45 mg (0.20 mmol) of $Pd(OAc)_2$, 105 mg (0.30 mmol) of biphen-2-yldicyclohexylphosphine, and 38 mg (0.20 mmol) of CuI under nitrogen was added a mixture of 5.6 mL (40 mmol) of Et_3N and 50 mL (5.0 mmol) of **23** in CH_3CN. The reaction mixture was heated at 65 °C for 15 h, then cooled, and poured into a mixture of 70 mL of CH_2Cl_2 and 40 mL of 5% aqueous NH_4OH (40 mL). The layers were separated, and the aqueous phase was reextracted with 70 mL of CH_2Cl_2. The organic phase was washed consecutively with water and brine, dried over Na_2SO_4, and concentrated under vacuum to give 0.79 g (52%) of crude ethyl 3-(2-(2-[(2*R*)-2-methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)benzoate, which was used without further purification. MS (ESI APCI) *m/z* 378 $(MH)^+$. The ethyl ester was dissolved in EtOH (20 mL) and treated with 2 M aqueous NaOH (2 mL). The mixture was heated at 55 °C for 40 min, cooled, concentrated under vacuum, and poured into 20 mL of *i*-PrOH and a mixture of 2 mL of 1 M aqueous KH_2PO_4 and 2 mL of saturated aqueous NaCl. A biphasic mixture was formed from which the organic phase was separated. The

aqueous phase was reextracted three times with 2 mL of *i*-PrOH, and the organic phases were combined and washed with a mixture of 0.5 mL of pH 7 potassium phosphate and 2 mL of brine. The aqueous phase was separated and extracted with 2-propanol (3 × 2 mL), and the combined organic phases were washed with saturated aqueous NaCl. Again, the aqueous phase was separated and extracted with 2-propanol (3 × 2 mL), and the combined organic phases were diluted with EtOAc and filtered. The filtrate was dried (Na_2SO_4) and concentrated. The resulting amino acid was purified by flash chromatography, eluting with 50% EtOAc/CH_2Cl_2, then 10% MeOH/45% EtOAc/CH_2Cl_2, then with 30% MeOH/CH_2Cl_2. Product-containing fractions were concentrated under vacuum to give a solid, which was triturated with EtOAc/CH_2Cl_2 to provide **42** as a white powder. ^{1}H NMR (300 MHz, CD_3OD) δ 8.23 (s, 1 H), 7.92 (d, 1 H, J = 7.8 Hz), 7.79 (s, 1 H), 7.69 (d, 1 H, J = 7.1 Hz), 7.39−7.59 (m, 3 H), 6.70 (s, 1 H), 3.50−3.71 (m, 2 H), 3.08−3.3 (m, 4 H), 2.89−3.04 (m, 1 H), 2.16−2.31 (m, 1 H), 1.91−2.10 (m, 2 H), 1.58−1.76 (m, 1 H), 1.39 (d, 3 H, J = 6.4 Hz). MS (ESI APCI) m/z 350 $(M + H)^+$.

***N*-Methoxy-*N*-methyl-3-(2-(2-[2(*R*)-methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)benzamide (43).** The amino acid **42** was suspended in CH_2Cl_2 (25 mL) and treated with 3.0 mL (6.0 mmol) of 2 M oxalyl chloride in CH_2Cl_2. After the gas evolution subsided, 0.3 mL of DMF was added over 15 min, and after 60 min, more DMF (0.1 mL) was added. The mixture was concentrated under vacuum after 30 min, and the residue was poured into 5 mL of CH_2Cl_2 and treated with *N*,*O*-dimethylhydroxylamine hydrochloride (0.488 g, 5.0 mmol) and pyridine (1 mL). After being stirred for 12 h, the reaction mixture was concentrated under vacuum, diluted with 1,2-dichloroethane (5 mL), and heated at 85 °C for 4 h, then cooled and poured into a mixture of CH_2Cl_2, H_2O, and saturated aqueous $NaHCO_3$. The organic phase was separated, the aqueous phase was reextracted with CH_2Cl_2, and the combined organic extracts were washed consecutively with H_2O and brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography, eluting with 0−4% CH_3OH/CH_2Cl_2 to give **43** as a syrup (0.495 g, 60% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 7.86 (m, 1 H), 7.73−7.81 (m, 2 H), 7.46−7.83 (m, 4 H), 6.62 (s, 1 H), 3.63 (s, 3 H), 3.39 (s, 3 H), 3.20−3.3 (m, 2 H), 2.95−3.17 (m, 2 H), 2.45−2.64 (m, 2 H), 2.27−2.39 (m, 1 H), 1.95−2.09 (m, 1 H), 1.73−1.88 (m, 2 H), 1.37−1.54 (m, 1 H), 1.19 (d, 3 H, J = 6.1 Hz); MS (ESI APCI) m/z 393 $(MH)^+$.

[3-(2-(2-[2(*R*)-Methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)phenyl]methanol (44). A solution of 167 mg (0.48 mmol) of **42** in 2 mL (2 mmol) of 1 M BH_3 in THF was stirred at 23 °C for 12 h, then poured into 0.5 M aqueous K_2HPO_4, and diluted with EtOAc. The organic phase was separated and washed consecutively with 0.5 M aqueous K_2HPO_4 and brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography, eluting with 0−5% CH_3OH/CH_2Cl_2, and again by flash chromatography, eluting with 0−5% CH_3CN/CH_2Cl_2. Product-containing residues were combined and freed of residual borate adducts by dissolving in 1.5 mL of CH_3OH and 0.3 mL of 0.1 M aqueous HCl and heating the mixture at 60 °C for 4 h. After concentration under vacuum, the residue was purified by flash chromatography, eluting with 2−10% 2 M NH_3 in MeOH/CH_2Cl_2 to provide **44** as a white powder (21 mg, 13% yield). Compound **44** was also prepared by an alternative procedure in which a suspension of 247 mg (0.80 mmol) of **49**, 182 mg (1.20 mmol) of 3-(hydroxymethyl)phenylboronic acid, and 28 mg (0.040 mmol) of $PdCl_2(PPh_3)_2$ in 4 mL of *i*-PrOH and 1.2 mL of 2.0 M aqueous Na_2CO_3 was heated at 80 °C for 12 h. The reaction mixture was cooled to 23 °C and partitioned between 15 mL of CH_2Cl_2 and 2 mL of 2 M aqueous NaOH. The aqueous phase was separated and extracted with CH_2Cl_2, and the combined organic phases were filtered through Celite, concentrated under vacuum, and purified by flash chromatography, eluting with 2−8% MeOH/CH_2Cl_2 to give **44** (190 mg, 70%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.73 (dd, 1 H, J = 1.4, 1.4 Hz), 7.62 (s, 1 H), 7.52 (m, 1 H), 7.46−7.49 (m, 2 H), 7.40 (dd, 1 H, J = 7.6, 7.6 Hz), 7.28−7.34 (m, 1 H), 6.60 (s, 1 H), 4.68 (s, 2 H), 3.19−3.34 (m, 2 H), 2.94−3.14 (m, 2 H), 2.41−2.60 (m, 2 H), 2.24−2.36 (m, 1 H), 1.94−2.08 (m, 1 H), 1.73−1.87 (m, 2 H), 1.38−1.53 (m, 1 H), 1.18 (d, 3 H, J = 6.1 Hz). MS (ESI APCI) m/z 336 $(MH)^+$. The tartrate salt was formed by addition of L-tartaric acid in methanol, followed by evaporation to give a glass. Anal. $(C_{22}H_{25}NO_2 \cdot 1.1C_4H_6O_6)$ C, H, N.

1-[3-(2-(2-[2(*R*)-Methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)phenyl]-1-propanone (45). A solution of 245 mg (0.62 mmol) of **43** in 10 mL of THF was cooled to 0 °C and treated with 1.5 mL (1.5 mmol) of a 1.0 M solution of EtMgBr in THF. The reaction mixture was stirred at 23 °C for 12 h, then treated with more EtMgBr (0.75 mL, 0.75 mmol). After 4.5 h, 2 mL of saturated aqueous NH_4Cl was added to the reaction mixture and then the mixture was made basic and extracted with 10 mL of EtOAc. The combined organic extract was washed consecutively with 0.5 M aqueous K_2HPO_4 and brine, concentrated under vacuum, and purified by preparative HPLC to give **45** (147 mg, 65% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.22 (dd, 1 H, J = 1.7, 1.7 Hz), 7.96 (m, 1 H), 7.87 (m, 1 H), 7.78 (m, 1 H), 7.58 (dd, 1 H, J = 7.7, 7.7 Hz), 7.50−7.52 (m, 2 H), 6.63 (s, 1 H), 3.20−3.35 (m, 2 H), 2.94−3.18 (m, 4 H), 2.42−2.61 (m, 2 H), 2.24−2.37 (m, 1 H), 1.95−2.09 (m, 1 H), 1.74−1.87 (m, 2 H), 1.39−1.53 (m, 1 H), 1.21 (t, 3 H, J = 7.1 Hz), 1.18 (d, 3 H, J = 6.1 Hz). MS (ESI APCI) m/z 362 $(MH)^+$. The tartrate salt was formed by addition of L-tartaric acid in methanol, followed by evaporation to give a glass. Anal. $(C_{24}H_{27}NO_2 \cdot 1.1C_4H_6O_6)$ C, H, N.

Cyclopropyl[3-(2-(2-[2(*R*)-methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)phenyl]methanone (46). By the method used to prepare **45**, a solution of 245 mg (0.62 mmol) of **43** in 10 mL of THF was reacted with 2.2 mL (1.5 mmol) of 0.6 M cyclopropylmagnesium bromide in THF. The reaction mixture was worked up as described for **45** and purified by flash chromatograhy, eluting with 1−6% CH_3OH/CH_2Cl_2, then repurified by flash chromatography, eluting with 0−4% CH_3OH in 1:1 EtOAc/CH_2Cl_2 to give **46** (161 mg, 69% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.25 (dd, 1 H, J = 1.7, 1.7 Hz), 8.02 (m, 1 H), 7.89 (m, 1 H), 7.80 (m, 1 H), 7.60 (dd, 1 H, J = 7.8, 7.8 Hz), 7.48−7.55 (m, 2 H), 6.63 (s, 1 H), 3.19−3.35 (m, 2 H), 2.87−3.15 (m, 3 H), 2.41−2.60 (m, 2 H), 2.23−2.35 (m, 1 H), 1.95−2.08 (m, 1 H), 1.73−1.86 (m, 2 H), 1.39−1.53 (m, 1 H), 1.08−1.22 (m, 7 H). MS (ESI APCI) m/z 374 $(M + H)^+$. The tartrate salt was formed by addition of L-tartaric acid in methanol, followed by evaporation to give a glass. Anal. $(C_{25}H_{27}NO_2 \cdot 0.4CH_3OH)$ C, H, N.

4-Bromo-2-iodophenol (48). To a solution of 4-bromophenol (**47**, 34.60 g, 200 mmol), 29.98 g (200 mmol) of NaI, and 8.00 g (200 mmol) of NaOH in CH_3OH (400 mL) at 0 °C was added an aqueous solution of 5.25% NaOCl (283 g, 200 mmol) over 45 min. The mixture was stirred at 0 °C for 1 h, warmed to 23 °C, and diluted with saturated aqueous sodium thiosulfate (50 mL) and H_2O (500 mL), then adjusted to a pH of 7 by addition of saturated aqueous NaH_2PO_4. Saturated aqueous NaCl (50 mL) was added, and the mixture was extracted with 250 mL of 80% EtOAc/hexanes (250 mL). The aqueous phase was reextracted, and the combined organic phases were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under vacuum to provide **48** (89% yield). A portion was purified by chromatography on silica, eluting with 25−80% CH_2Cl_2/hexanes. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.59 (s, 1H), 7.79 (d, 1H, J = 2.4 Hz), 7.36 (dd, 1H, J = 8.4, 2.4 Hz), 6.83 (d, 1H, J = 8.4 Hz).

1-[2-(5-Bromo-1-benzofuran-2-yl)ethyl]-2(*R*)-methylpyrrolidine (49). 4-Bromo-2-iodophenol (**48**, 32.99 g, 90% pure, 9 mmol), $Pd(OAc)_2$ (112 mg, 0.50 mmol), Ph_3P (262 mg, 1.0 mmol), CuI (571 mg, 3.0 mmol), and *i*-Pr_2NH (14 mL, 100 mmol) were added to 120 mL of CH_3CN containing (10.8 mmol) of 1-but-3-ynyl-2(*R*)-methylpyrrolidine (**23**) and stirred at 23 °C for 3 days, then heated at 80 °C for 12 h. The reaction mixture was cooled, concentrated under vacuum, and purified by flash chromatography, eluting with 2:1 hexanes/CH_2Cl_2 followed by a 0−1% gradient of CH_3OH/CH_2Cl_2. Product-containing fractions were concentrated, partitioned between

CH_2Cl_2 and 1 M aqueous Na_2CO_3, dried (Na_2SO_4), and concentrated under vacuum to give **49** as dark-red syrup (717 mg, 26% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.75 (d, 1 H, J = 2.4 Hz), 7.48 (d, 1 H, J = 8.9 Hz), 7.35 (dd, 1 H, J = 8.9, 2.4 Hz), 6.65 (s, 1 H), 3.18−2.84 (m, 4 H), 2.25−2.45 (m, 2 H), 2.06−2.15 (m, 1 H), 1.80−1.93 (m, 1 H), 1.57−1.68 (m, 2 H), 1.20−1.34 (m, 1 H), 1.02 (d, 3 H, J = 6.0 Hz); MS (ESI APCI) m/z 308, 310 $(MH)^+$.

[4-(2-(2-[2(*R*)-Methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)phenyl]methanol (50). A suspension of 247 mg (0.80 mmol) of **49**, 182 mg (1.2 mmol) of 4-(hydroxymethyl)-phenylboronic acid, 28 mg (0.04 mmol) of $PdCl_2(PPh_3)_2$ in 4 mL of *i*-PrOH, and 1.2 mL of 2 M aqueous Na_2CO_3 was heated at 80 °C for 12 h. The reaction mixture was cooled to 23 °C and partitioned between 15 mL of CH_2Cl_2 and 2 mL of 2 M aqueous NaOH. The aqueous phase was separated and extracted with CH_2Cl_2, and the combined organic phases were filtered through Celite, concentrated under vacuum, and purified by flash chromatography, eluting with a gradient of 2−8% MeOH/CH_2Cl_2 to provide **50** as a thick orange syrup (177 mg, 66%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.72 (dd, 1 H, J = 1.4, 1.4 Hz), 7.60 (d, 2 H, J = 8.2 Hz), 7.45−7.48 (m, 2 H), 7.42 (d, 2 H, J = 8.2 Hz), 6.61 (s, 1 H), 4.64 (s, 2 H), 3.2−3.4 (m, 2 H), 2.97−3.18 (m, 2 H), 2.35−2.77 (m, 3 H), 1.99−2.13 (m, 1 H), 1.77−1.91 (m, 2 H), 1.42−1.58 (m, 1 H), 1.21 (d, 3 H, J = 6.1 Hz). MS (ESI APCI) m/z 336 $(MH)^+$. The tartrate salt was formed by addition of L-tartaric acid in methanol, followed by concentration under vacuum to give a glass. Anal. $C_{22}H_{25}NO_2 \cdot 1.1C_4H_6O_6$) C, H, N.

2-(5-Bromo-1-benzofuran-2-yl)ethanol (51). A mixture of 4-bromo-2-iodophenol (**48**) (26.9 g, 80 mmol), 3-butyn-1-ol (6.05 mL, 79.9 mmol), and Cu_2O (7.15 g, 50.0 mmol) in a mixture of 40 mL of pyridine and 160 mL of NMP was heated at 70 °C overnight, then heated further at 100 °C for 3.5 h. The mixture was cooled to 23 °C, diluted with Et_2O, and filtered to remove solids. The filtrate was diluted with Et_2O and washed consecutively with 5% aqueous NH_4OH, 0.5 M aqueous NaOH, and saturated aqueous NaCl, then dried over Na_2SO_4, and concentrated under vacuum. The syrupy residue was diluted with 2:1 hexanes/CH_2Cl_2 and cooled to −78 °C. When the mixture was warmed to 23 °C, the product (**51**) crystallized and was collected by filtration and washed with 4:1 hexane/CH_2Cl_2 to give a solid (1.55 g, 8% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.75 (d, 1H, J = 2.3 Hz), 7.48 (d, 1H, J = 8.7 Hz), 7.35 (dd, 1H, J = 8.7, 2.3 Hz), 6.63 (t, 1H, J = 0.7 Hz), 4.82 (t, 1H, J = 5.4 Hz), 3.75 (dt, 2H, J = 6.4, 5.4 Hz), 2.92 (td, 2H, J = 6.4, 0.7 Hz).

3-[2-(2-Hydroxyethyl)-1-benzofuran-5-yl]benzonitrile (52). A suspension of 193 mg (0.80 mmol) of **51**, 3-cyanophenylboronic acid (147 mg, 1.00 mmol), and $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) in a mixture of 3 mL of dioxane and 2.1 mL (2.1 mmol) of 1.0 M aqueous Na_2CO_3 was heated at 90 °C for 3.5 h, then cooled to 23 °C, then partitioned between EtOAc and H_2O, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography, eluting with 0−2% EtOAc/CH_2Cl_2 to provide **52** as a syrup (0.174 g, 82% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.15 (dd, 1H, J = 1.6, 1.6 Hz), 8.04 (ddd, 1H, J = 7.8, 1.6, 1.6 Hz), 7.91 (dd, 1H, J = 1.6, 1.6 Hz), 7.80 (ddd, 1H, J = 7.8, 1.6, 1.6 Hz), 7.66 (dd, 1H, J = 7.8, 7.8 Hz), 7.57−7.63 (m, 2H), 6.70 (s, 1H), 4.83 (t, 1H, J = 5.5 Hz), 3.78 (dt, 2H, J = 6.6, 5.5 Hz), 2.95 (t, 2H, J = 6.6 Hz); MS (DCI) m/z 263 $(M)^+$.

3-(2-(2-[2(*R*)-Methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)benzonitrile (53). A solution of **52** (170 mg, 0.65 mmol) and Et_3N (0.1 mL, 0.72 mmol) in 3 mL of CH_2Cl_2 at 0 °C was treated with CH_3SO_2Cl (55 μL, 0.71 mmol), and after 10 min the mixture was allowed to warm to 23 °C. More CH_3SO_2Cl (10 μL, 0.13 mmol) and Et_3N (10 μL, 0.072 mmol) were added, and the mixture was stirred until all starting alcohol **52** was consumed, as assessed by TLC. The reaction mixture was diluted with CH_2Cl_2, washed consecutively with water and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under vacuum to give a glass, 2-[5-(3-cyanophenyl)-1-benzofuran-2-yl]ethyl methanesulfonate, which was used without purification in the next step.

The 2-[5-(3-cyanophenyl)-1-benzofuran-2-yl]ethyl methanesulfonate, 306 mg (1.3 mmol) of (*R*)-2-methylpyrrolidine L-tartrate, and Cs_2CO_3 (652 mg, 2.0 mmol) were suspended in 3 mL of CH_3CN and heated at 40 °C for 12 h. More Cs_2CO_3 (326 mg, 1.0 mmol) and CH_3CN (0.5 mL) were added, and the reaction mixture was stirred at 40 °C for 4 days before being cooled to 23 °C, diluted with CH_2Cl_2, filtered, and concentrated under vacuum. The residue was purified twice by flash chromatography, eluting with a 0−5% MeOH/CH_2Cl_2 to give **53** as an orange-tan gum (0.12 g, 28% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 7.98 (m, 1 H), 7.95 (m, 1 H), 7.78 (m, 1 H), 7.67 (m, 1 H), 7.62 (dd, 1 H, J = 7.8, 7.8), 7.49−7.52 (m, 2 H), 6.63 (s, 1 H), 3.20−3.35 (m, 2 H), 2.95−3.15 (m, 2 H), 2.46−2.63 (m, 2 H), 2.27−2.39 (m, 1 H), 1.96−2.09 (m, 1 H), 1.75−1.87 (m, 2 H), 1.39−1.54 (m, 1 H), 1.18 (d, 3 H, J = 6.0 Hz); MS (DCI) m/z 331 $(MH)^+$. Anal. ($C_{22}H_{22}N_2O \cdot HCl$) C, H, N.

Cyclopropyl[4-(2-(2-[2(*R*)-methyl-1-pyrrolidinyl]ethyl)-1-benzofuran-5-yl)phenyl]methanone (54). To a solution of 10 mg of CuI and 330 mg (1.0 mmol) of **20** in 1 mL of THF was added 2 mL (1.4 mmol) of a 0.7 M solution of cyclopropylmagnesium bromide in THF. The reaction mixture was heated at 45 °C for 24 h, at 60 °C for 48 h, then cooled and poured into a stirred mixture of EtOAc and 0.4 M aqueous HCl. After the solids dissolved, the mixture was made basic with 0.5 M aqueous K_2HPO_4 and brine, and the organic phase was separated and washed consecutively with 0.5 M aqueous K_2HPO_4 and brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by preparative HPLC to give **54** (166 mg, 44% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.12 (d, 2 H, J = 8.6 Hz), 7.82 (d, 1 H, J = 2.0 Hz), 7.79 (d, 2 H, J = 8.6 Hz), 7.56 (dd, 1 H, J = 8.7, 2.0 Hz), 7.51 (d, 1 H, J = 8.7 Hz), 6.62 (s, 1 H), 3.19−3.34 (m, 2 H), 2.83−3.15 (m, 3 H), 2.40−2.59 (m, 2 H), 2.23−2.34 (m, 1 H), 1.94−2.08 (m, 1 H), 1.73−1.86 (m, 2 H), 1.38−1.53 (m, 1 H), 1.06−1.21 (m, 7 H); MS (ESI APCI) m/z 374 $(MH)^+$. The tartrate salt was formed by addition of L-tartaric acid in methanol, followed by evaporation to give a glass. Anal. $C_{25}H_{27}NO_2 \cdot 0.5\ CH_3OH$) C, H, N.

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Supporting Information Available: Results from combusion analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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