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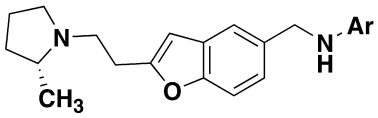
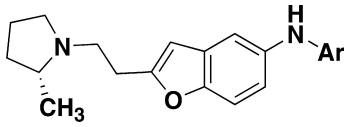


6a-6r



7a-7k

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Synthesis and SAR of 5-Amino- and 5-(Aminomethyl)benzofuran Histamine H_3 Receptor Antagonists with Improved Potency

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A new series of H_3 receptor antagonists was discovered with nanomolar and subnanomolar affinities at human and rat H_3 receptors. Starting from an earlier, more structurally limited series of benzofurans, the present series of compounds demonstrated increased structural variety and flexibility with greater in vitro potency. One compound in particular, {2-[2-(2-(*R*)-methylpyrrolidin-1-yl)ethyl]benzofuran-5-yl}(5-nitropyridin-2-yl)amine (**7h**), gave the best binding potency (human K_i of 0.05 nM, rat K_i of 0.11 nM), which represented a 9-fold (in human) and an 11-fold (in rat) improvement over ABT-239 (compound **5**), a compound previously reported to have excellent in vitro potency and in vivo efficacy. The synthesis, SAR of the H_3 binding affinities, in vitro assay for phospholipidosis, and pharmacokinetic properties of the new compounds are described.

Introduction

The effects of histamine are mediated in the central nervous system (CNS) and the periphery through four known receptors, H_1, H_2, H_3, and H_4.[1] Histamine H_1 and H_2 receptors have been successfully targeted, and therapeutic agents have been developed to treat conditions such as allergies (H_1 receptor antagonists) and gastric ulcers (H_2 receptor antagonists). The newly discovered H_4 receptor is found in immune cells, suggesting a role in regulating inflammatory responses.[2] The H_3 receptor, primarily located on nerve terminals and in the CNS, modulates the production and release of histamine.[3] Pharmacological blockade of H_3 receptors enhances the release of histamine and other neurotransmitters[1] and has been shown to enhance vigilance or alertness.[4] Consequently, H_3 receptor antagonists are thought to have potential as drug therapies for ADHD, Alzheimer's disease, Parkinson's disease, epilepsy, and sleep disorders.[5] Early generations of H_3 antagonists were based on structures containing the imidazole moiety found in histamine; some of these compounds, most prominently ciproxifan (**1**), have become reference standards for H_3 pharmacological research. However, the imidazole moiety has been associated with CYP450 inhibition,[6] leading to potential drug−drug interactions through inhibition of the metabolism of coadministered drugs. For this reason, recent efforts have been directed toward the discovery of H_3 antagonists without an imidazole moiety. Several recently disclosed classes of nonimidazoles, such as **2**,[7a] **3**,[7b] and **4**[8] (Figure 1), share common structural features of the amine−alkoxy−phenyl pharmacophore.

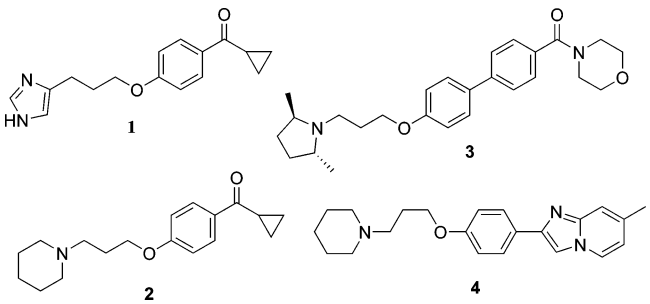
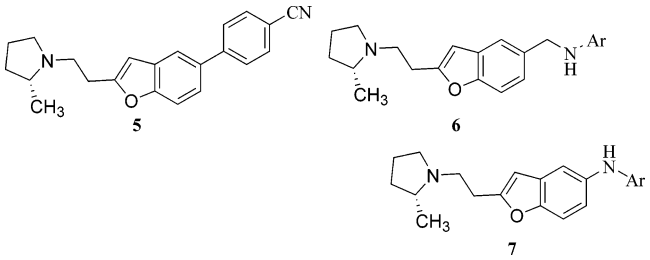


Figure 1. Structures of representative H_3 antagonists.

Recently, a series of compounds that have a more rigid ethylbenzofuran moiety to replace the previously described alkoxy−phenyl moiety was reported, as exemplified by ABT-239 (**5**).[9] The 2-aminoethylbenzofuran-based H_3 antagonist **5** had nanomolar potency at H_3 receptors and was efficacious in different rodent models of cognition and attention at doses of 0.01−0.1 mg/kg. With the goal of extending the SAR of the series, improving binding potency, and possibly increasing efficacy in behavioral models, two new subclasses of H_3 antagonists were investigated. In the new series, the 2-(2*R*)-methylpyrrolidinylethylbenzofuran moiety was retained, but 5-aminomethyl or 5-amino linkers were inserted between the benzofuran nucleus and the lipophilic aromatic ring to increase the overall flexibility, as exemplified by **6** and **7**. The precursor (compound **11**, Scheme 1) to compound **6** was a dibasic amine, a feature associated with a propensity to induce phospholipidosis.



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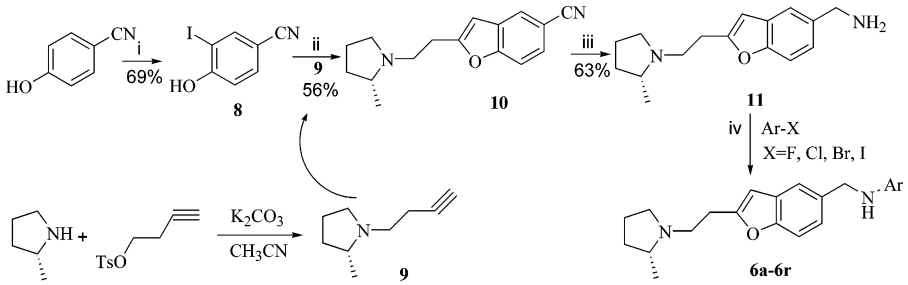
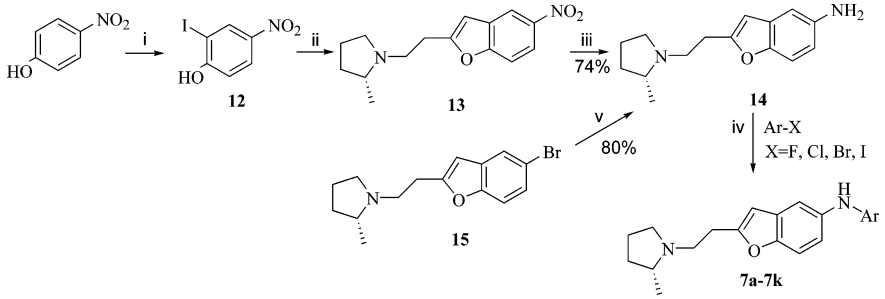
Scheme 1. Preparation of 5-Arylaminomethylbenzofuran Derivatives[a]



[a] Reagents and conditions: (i) KI, I_2, in NH_4OH; (ii) $Pd(OAc)_2$, Cy_2P(biphenylyl), CuI, Et_3N, CH_3CN; (iii) H_2, Ra/Ni, 20% NH_3/CH_3OH; (iv) method A, 1.2 equiv ArX, Et_3N, ethanol, 75 °C; method B, 1.2 equiv ArX, DIPEA, dioxane, 100 °C; method C, 1.5 equiv ArX, $Pd_2(dba)_3$, BINAP, Cs_2CO_3, toluene, 100 °C.

Scheme 2. Preparation of 5-Arylaminobenzofuran Derivatives[a]



[a] Reagents and conditions: (i) KI, I_2, in NH_4OH; (ii) **9**, $Pd(OAc)_2$, Cy_2P(biphenylyl), CuI, Et_3N, CH_3CN; (iii) 60 psi H_2, 10% Pd/C, methanol; (iv) method A, 1.2 equiv ArX, Et_3N, ethanol, 75 °C; method B, 1.2 equiv ArX, DIPEA, dioxane, 100 °C; method C, 1.5 equiv ArX, $Pd_2(dba)_3$, BINAP, Cs_2CO_3, toluene, 100 °C; (v) LiHMDS, $Pd_2(dba)_3$, Cy_2P(biphenylyl), aq HCl quench and then 2 N NaOH.

This propensity was reduced when the primary amine was arylated to give series **6** compounds, a change that served to reduce the basicity of one of the amines.

Chemistry

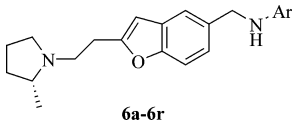
As shown in Scheme 1, commercially available 4-cyanophenol was treated with potassium iodide and iodine (1.0 equiv) in aqueous ammonium hydroxide to give 2-iodo-4-cyanophenol (**8**).[10,11] The reaction mixture contained trace amounts of unreacted starting material and the diiodo phenol, neither of which affected the next step of the sequence. Iodide **8** was coupled with alkyne **9** under Sonogashira conditions[12−14] and subsequently cyclized to form benzofuran **10**. 5-Cyanobenzofuran **10** was cleanly hydrogenated to benzylic amine **11** in the presence of Raney nickel. This intermediate was used to prepare the target compounds (**6a**−**6r**) by reacting with a variety of aryl halides. Depending on the nature of the aryl halides, this coupling could be accomplished either by simple displacement of electron-deficient heteroaryl halides or, in the case of more resistant substrates, the Pd-catalyzed coupling.[15−17]

As outlined in Scheme 2, the iodination of commercially available 4-nitrophenol with $KI/I_2/NH_4OH$ afforded iodide **12**. Compared to 4-cyanophenol, the iodination of 4-nitrophenol was much more sluggish, proceeding to only about 50% completion, even after 5 days at room temperature. It should be noted that attempts to iodinate the 4-nitrophenol by alternative conditions, such as sodium hypochlorite and sodium iodide[18] or iodine/silver (I) triflate,[19] were unsuccessful. Purification of the crude reaction mixture, which contained **12** and unreacted starting material, was unnecessary, as the subsequent reaction with **9** proceeded cleanly to form the benzofuran **13** and the 4-nitrophenol could be removed at this step. 5-Nitrobenzofuran **13** was reduced to 5-aminobenzofuran **14** under 60 psi of hydrogen in the presence of 10% palladium on carbon. Alternatively, 5-aminobenzofuran **14** could also be synthesized from 5-bromobenzofuran **15**,[9a,20] using lithium bis(trimethylsilyl)amide as the nitrogen source, under palladium catalysis.[21] The target compounds (**7a**−**7k**) were made by arylation at the amino group of **14** with aryl halides, using the same conditions as for the preparation of **6a**−**6r**.

Results and Discussion

The compounds described here were tested in in vitro binding assays[22] in membranes isolated from cells transfected with both cloned rat H_3 receptors and cloned human H_3 receptors. The binding affinities with different aromatic substitution on the 5-aminomethylbenzofuran system are summarized in Table 1. The primary amine intermediate, compound **11**, was also tested in the binding assay and was found to be very potent, with K_i values of 0.1 and 0.27 nM for human and rat receptors, respectively. But as a compound of potential interest, compound **11** suffered from a propensity to slow oxidation in air to the corresponding aldehyde. Derivatization of the primary amine **11** with aromatic and heteroaromatic halides resulted in compounds **6a**−**6r**. With the goal of improving potency over **5** in mind, it was not clear if the flexible linker with carbon and nitrogen atoms would be tolerated. 2-Nitro (**6a**) and 3-cyano (**6d**) analogues showed slightly better binding potencies than compound **5**, while 4-nitro and 4-trifluoroacetyl analogues (**6b**, **6c**) were less potent at both human and rat receptors. Substituted pyridines as the aromatic moiety resulted in substantial improvement in potencies, with the 2,6-dicyanopyridine analogue (**6o**)

Table 1. Binding Affinities (pK_i and K_i) of 5-Arylaminomethylbenzofurans at Human H_3 and Rat H_3 Receptors[a]

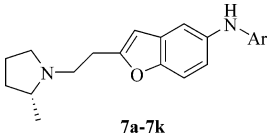


6a-6r

compd	Ar substituent	human H_3[b] pK_i ± SEM	human H_3[b] K_i (nM)	rat H_3[b] pK_i ± SEM	rat H_3[b] K_i (nM)
5		9.35 ± 0.04	0.45	8.91 ± 0.05	1.23
6a	2-nitrophenyl	9.50 ± 0.17	0.31	9.06 ± 0.22	0.87
6b	4-nitrophenyl	9.13 ± 0.13	0.74	8.67 ± 0.19	2.12
6c	4-(2,2,2-trifluoroacetyl)phenyl	9.13 ± 0.08	0.74	8.63 ± 0.19	2.36
6d	3-cyanophenyl	9.40 ± 0.14	0.40	8.93 ± 0.21	1.18
6e	6-chloropyridazin-3-yl	9.51 ± 0.08	0.31	8.80 ± 0.10	1.58
6f	3-cyanopyrazin-2-yl	8.98 ± 0.09	1.04	8.40 ± 0.18	3.96
6g	pyrazin-2-yl	9.53 ± 0.04	0.29	9.09 ± 0.07	0.80
6h	5-bromopyrimidin-2-yl	8.91 ± 0.09	1.22	8.40 ± 0.16	4.02
6i	pyrimidin-5-yl	9.16 ± 0.06	0.69	8.60 ± 0.14	2.51
6j	5-ethylpyrimidin-2-yl	9.48 ± 0.03	0.33	9.24 ± 0.18	0.58
6k	pyrimidin-2-yl	9.07 ± 0.11	0.84	8.48 ± 0.11	3.27
6l	5-nitrothiazol-2-yl	9.72 ± 0.17	0.19	9.17 ± 0.01	0.68
6m	3-nitropyridin-2-yl	9.36 ± 0.10	0.43	8.57 ± 0.13	2.71
6n	3,5-dinitropyridin-2-y l	9.15 ± 0.03	0.71	8.54 ± 0.07	2.88
6o	2,6-dicyanopyridin-4-yl	9.88 ± 0.04	0.13	9.40 ± 0.14	0.40
6p	3-cyanopyridin-2-yl	9.13 ± 0.14	0.74	8.72 ± 0.26	1.92
6q	5-cyanopyridin-2-yl	9.46 ± 0.12	0.34	8.85 ± 0.17	1.42
6r	5-nitropyridin-2-yl	9.52 ± 0.12	0.30	8.93 ± 0.14	1.19

[a] Binding potencies were assessed by displacement of [^{3}H]-*N*-α-methylhistamine, using cloned human H_3 receptors and cloned rat H_3 receptors. pK_i = −logK_i. [b] The values are reported as average of $n \geq 3$ independent measurements for all compounds.

Table 2. Binding Affinities (pK_i and K_i) of 5-Arylaminobenzofurans at Human H_3 and Rat H_3 Receptors[a]



7a-7k

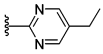
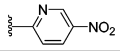
compd	Ar substituent	human H_3[b] pK_i ± SEM	human H_3[b] K_i (nM)	rat H_3[b] pK_i ± SEM	rat H_3[b] K_i (nM)
5		9.35 ± 0.04	0.45	8.91 ± 0.05	1.23
7a	2-nitrophenyl	9.66 ± 0.07	0.22	9.06 ± 0.13	0.87
7b	4-cyanophenyl	9.57 ± 0.06	0.27	8.87 ± 0.14	1.35
7c	3-cyanophenyl	9.53 ± 0.07	0.29	8.83 ± 0.15	1.47
7d	5-ethyl-pyrimidin-2-yl	9.21 ± 0.10	0.62	8.60 ± 0.09	2.51
7e	pyrimidin-2-yl	9.51 ± 0.12	0.31	8.70 ± 0.13	2.01
7f	pyrimidin-5-yl	10.12 ± 0.09	0.08	9.57 ± 0.18	0.27
7g	pyrazin-2-yl	9.98 ± 0.04	0.11	9.42 ± 0.13	0.38
7h	5-nitropyridin-2-yl	10.32 ± 0.14	0.05	9.98 ± 0.12	0.11
7i	3-nitropyridin-2-yl	9.87 ± 0.17	0.14	9.45 ± 0.13	0.35
7j	3-cyano-6-methylpyridin-2-yl	8.53 ± 0.06	2.98	7.75 ± 0.17	17.90
7k	5-trifluoromethyl-pyridin-2-yl	9.27 ± 0.11	0.54	8.56 ± 0.14	2.76

[a] Binding potencies were assessed by displacement of [^{3}H]-*N*-α-methylhistamine, using cloned human H_3 receptors and cloned rat H_3 receptors. pK_i = −logK_i. [b] The values are reported as average of $n \geq 3$ independent measurements for all compounds.

having a K_i of 0.13 nM at cloned human receptor and 0.40 nM at cloned rat receptor. Substitution at the 5-position of the pyridyl ring (**6q**, **6r**) is clearly more effective in boosting potency than 3-substitution (**6m**, **6p**) or 3,5-disubstitutions (**6n**). Other heterocycles such as substituted pyrimidines (**6h**−**6k**) were also investigated. Compound **6j** (human K_i of 0.33 nM, rat K_i of 0.58 nM), which has a 5-ethyl group, showed slightly better binding potency than **5**, whereas other pyrimidines (**6h**, **6i**, **6k**) were 2−3 times less potent than compound **5** at both receptors. Similar results were observed with the homologous pyrazines and pyridazines (**6e**−**6g**). **6e** and **6g** were about equipotent to compound **5** at both human and rat receptors, and **6f** was half as potent in human and one-third as potent in rat compared with compound **5**. One particularly advantageous heterocycle was the 5-nitrothiazol-2-yl group found in **6l**, which had twice the potency of compound **5**. Overall, the incremental increase in flexibility induced by interspersing the additional carbon and nitrogen atoms between the benzofuran and lipophilic ring was well tolerated, with the best compounds showing a 2−3-fold improvement of potency over compound **5**.

The SAR of the 5-aminobenzofurans is summarized in Table 2. This series of compounds is also more flexible than compound **5**, but compared to compounds **6a**−**6r**, which have carbon and nitrogen atoms between benzofuran and the aromatic ring, compounds **7a**−**7k** have only one nitrogen linking the benzofuran to the aromatic ring. This imparts some flexibility to the benzofuran-

Table 3. Comparison of Substituent SAR for Series 6 and Series 7 Compounds

Ar-Substituent	Compd #	Human *K*i (nM)	Rat *K*i (nM)	Compd #	Human *K*i (nM)	Rat *K*i (nM)	Human *K*i **6/7**	Rat *K*i **6/7**
	**6a**	0.31	0.87	**7a**	0.22	0.87	1.41	1.00
	**6d**	0.40	1.18	**7c**	0.29	1.47	1.38	0.80
	**6g**	0.29	0.80	**7g**	0.11	0.38	2.64	2.11
	**6i**	0.69	2.51	**7f**	0.08	0.27	8.63	9.30
	**6k**	0.84	3.27	**7e**	0.31	2.01	2.71	1.63
	**6j**	0.33	0.58	**7d**	0.62	2.51	0.53	0.23
	**6m**	0.43	2.71	**7i**	0.14	0.35	3.07	7.74
	**6r**	0.30	1.19	**7h**	0.05	0.11	6.00	10.8

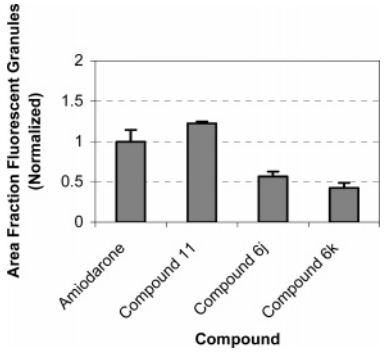
aromatic ring moiety, but less than in the series of compounds **6a**−**6r**. When the aromatic moiety was a substituted phenyl ring (**7a**−**7c**, Table 2), the human H_3 binding potencies for all three compounds were slightly better than that of compound **5** (1.5−2.0-fold), whereas the rat potencies were about the same as that of compound **5**. Again, as in the previous series (**6a**−**6r**), 2-nitro substitution (**7a**) of the phenyl ring induced the highest potency. When substituted pyridines were used as the aromatic moiety, compounds showed a wide range of potencies. The 5-nitropyridyl-2-yl analogue (**7h**) gave the best binding potency (human K_i of 0.05 nM, rat K_i of 0.11 nM), about 10-fold improvement on both human and rat receptors over compound **5**. The 3-nitropyridyl-2-yl analogue (**7i**) also showed a 3-fold improvement in potency over compound **5**. The 5-trifluoromethylpyridyl-2-yl analogue (**7k**) was slightly less potent than compound **5** (human K_i of 0.54 nM, rat K_i of 2.76 nM), whereas the 3-cyano-6-methylpyridyl-2-yl analogue (**7j**) was significantly less potent than **5** (7-fold for human and 15-fold for rat). In this series of compounds, the disubstituted analogue reduced the binding potency, even more so than in the compound **6** series. Among the pyrimidines and pyrazines investigated as aromatic substituents, unlike the compound **6** series, where 5-ethylpyrimidin-2-yl (**6j**) was slightly better than others, the unsubstituted pyrimidin-5-yl analogue (**7f**) (human K_i of 0.08 nM, rat K_i of 0.27 nM) was clearly superior, showing about a 6-fold improvement in potency at human H_3 receptor and a 5-fold potency improvement in rat, compared to compound **5**. The pyrazin-2-yl analogue (**7g**) was also a more potent compound than **5**.

In general, comparing compounds with the same substituents (Table 3), analogues in the arylamino series (**7**) were more potent than those in the arylaminomethyl series (**6**) at both human and rat H_3 receptors. The only exception to this finding was the 5-ethylpyrimidin-2-yl substituted pair (**6j**, **7d**), where **6j** was more potent than **7d**, especially in rat binding. The two best compounds in series **7** (**7f**, **7h**) were clearly more potent than their corresponding series **6** counterparts (**6i**, **6r**), leaving **7f** and **7h** the most active compounds among either series and representing an advance of 6- and 9-fold in human potency and 5- and 11-fold in rat potency over the parent compound **5**.

The dibasic compound **11** is highly potent at H_3 receptors, a finding that has also been noted with other chemical classes of H_3 antagonists that bear at least two basic amino groups.[5b,23] A potential drawback of this class of compounds is that they may have the propensity to potently induce phospholipidosis. Lipophilic compounds incorporating basic amines have reportedly been associated with the ability to increase concentrations of phospholipids due to their ability to bind to negatively charged phospholipid bilayers and to inhibit the activities of lysosomal phospholipases by neutralizing the surface negative charges required by these enzymes for optimal activity.[24] Although lipophilic monoamines can also exhibit this propensity to an extent, the presence of a second amine greatly exacerbates the potential toxicity.[25] For this reason, and because of the aforementioned chemical instability seen in **11**, this compound and similar dibasic compounds were deemed to have characteristics detrimental to their suitability as drugs. This was one of the motivations behind the strategy of making aromatic- and heteroaromatic-substituted analogues of **11**, a process that served to reduce the basicity of the second amine and produce monocationic compounds, therefore reducing the propensity to induce phospholipidosis.

To test this hypothesis, compounds **11**, **6j**, and **6k** were evaluated in an in vitro assay for phospholipidosis.[26] The results are expressed as a "phospholipidosis index" (Chart 1), which was normalized to amiodarone, a compound with a known propensity to induce phospholipidosis[27] that served as a positive control and reference standard. By this measure, a value of 1.0 indicated that the compound induces phospholipidosis to the same extend as amiodarone (at 5 μM). The

Chart 1. Normalized Phospholipidosis Index for Selected Compounds[a]



[a] Results were normalized to amiodarone (at 5 μM). Other compounds were tested at 18.75 μM, in primary cultures of rat hepatocytes.

Table 4. Rat Pharmacokinetic Properties of Selected H_3 Antagonists[a]

	1 mg/kg iv dose			1 mg/kg po dose			
compd	$t_{1/2}$	AUC	CL_b	$t_{1/2}$	C_{max}	AUC	F
5	5.7	666.8	1.54	6.7	39.6	426.2	61.8
6j	1.7	210.7	4.79	UC	7.1	18.9	9.0
6k	1.0	350.5	2.86	1.7	34.5	72.1	20.6
7f	0.3	35.9	28.50	UC	0.0	0.0	0.0
7d	3.7	355.4	2.82	4.8	16.2	103.2	29.0

[a] 1 mg/kg dose of each compound simultaneously in each rat. Units: $t_{1/2}$ (h); C_{max} (ng/mL); AUC (ng·h r/mL); F (%); CL_b (L/h·kg); $n \geq 2$. UC: uncalculated.

phospholipidosis index for compound **11** was 1.22 at a concentration of 18.75 μM, whereas the phospholipidosis index for compounds **6j** and **6k** were 0.57 and 0.42 at the same concentration. This provides experimental support for the original hypothesis: by removing one of the basic amines, the potential of inducing phospholipidosis may be greatly reduced.

The rat pharmacokinetic properties of selected compounds were also investigated, and the data are summarized in Table 4. While compound **5** displayed a favorable PK profile in rats, with an oral bioavailability of 61.8% and $t_{1/2}$ of 6.7 h, none of the newly discovered compounds tested could match this profile. The new series **6** and **7** compounds all had shorter $t_{1/2}$, lower AUC, higher clearance rates, and lower oral bioavailability. It was suspected that the presence of a heteroatom (nitrogen) between the two aromatic moieties increased the polarity of the structure and provided an extra site for metabolism. It is possible that this change affected protein binding and blood PK, resulting in poorer PK properties and faster clearance when compared with the parent compound **5**. On the other hand, in the case of **6k** and **7d**, which have an oral bioavailability of 21% and 29%, the PK profiles were considered adequate to support further studies.

In summary, highly potent (subnanomolar) H_3 antagonists with balanced affinity at human and rat H_3 receptors were discovered and several compounds showed significant improvements (5−11-fold) in binding potency compared with the benchmark compound (**5**). A wide variety of heterocycles were tolerated in both series, with compound **7h** being 9-fold and 11-fold more potent than compound **5** at human and rat receptors, respectively. Therefore, it was concluded that incorporation of flexible linker atoms between the benzofuran ring and aromatic substituent improved potency considerably, while also providing some analogues with acceptable PK properties.

Experimental Section

Chemistry Methods. Unless otherwise noted, all commercially available solvents, chemicals, and reagents were used without purification. 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 analysis was performed by Robertson Microlit Laboratories, Inc., Madison, NJ. ^{1}H NMR spectra were recorded on Bruker 300 MHz spectrometer. Chemical shifts (δ, ppm) are determined using TMS as internal standard. Abbreviations used in description of NMR spectra: s = singlet, d = doublet, t = triplet, dd = double doublet, dt = double triplet, m = multiplet, br = broad singlet. Flash column chromatography was performed with prepacked Biotage cartridges. Thin-layer chromatography was performed on 250 μM SG-60F TLC plates from Merck. All reactions were carried out under a nitrogen atmosphere. Basic methanol was prepared by mixing 10% ammonium hydroxide in methanol.

4-Hydroxy-3-iodobenzonitrile (8). In a 1-L round-bottom flask equipped with a magnetic stirring bar, 4-cyanophenol (10.0 g, 83.95 mmol) was dissolved in 450 mL of concentrated ammonium hydroxide. To this solution was added a mixture of potassium iodide (68.3 g, 411.3 mmol) and iodine (21.3 g, 83.95 mmol) in 100 mL of water quickly. The reaction mixture darkened immediately. The mixture was stirred at room temperature overnight during which it became a white suspension. The precipitate was removed by filtration, and the filtrate was concentrated. The solid was then dissolved in 500 mL of dichloromethane and washed with water (2 × 350 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to dryness under reduced pressure to give the crude product **8** (14.2 g, 69%), which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 7.97 (d, J = 2.03 Hz, 1H), 7.55 (dd, J = 8.48, 2.03 Hz, 1H), 7.05 (d, J = 8.48 Hz, 1H), 5.80 (s, 1H).

2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-carbonitrile (10). The above iodophenol **8** (10.0 g, 40.8 mmol), palladium(II) acetate (460 mg, 2.05 mmol), dicyclohexylbiphenylylphosphine (1.075 g, 3.07 mmol), and 510 mL of a 0.1 M solution of 1-but-3-ynyl-2-methylpyrrolidine **9** in acetonitrile were mixed to give a clear yellow solution. Triethylamine (57 mL, 408 mmol) was added and the mixture stirred for 15 min before copper(I) iodide (390 mg, 2.05 mmol) was added. The reaction mixture was heated to and kept at 65 °C overnight. It was then cooled to room temperature and filtered through Celite to remove the insoluble material. The filtrate was concentrated under reduced pressure, and the resulting oil was redissolved in 800 mL of dichloromethane, washed with 10% ammonium hydroxide (2 × 500 mL), followed by brine, and then dried over sodium sulfate. The organic solution was filtered and evaporated to dryness to give the crude product. Purification by flash chromatography (1−5% basic methanol in dichloromethane) gave the title compound as a yellow oil (5.84 g, 56%). ^{1}H NMR ($CDCl_3$): δ 7.82 (s, 1 H), 7.49 (d, J = 1.70 Hz, 2 H), 6.54 (s, 1 H), 3.18−3.33 (m, 2 H), 2.98−3.13 (m, 2 H), 2.39−2.63 (m, 2 H) 2.17−2.35 (m, 1 H), 1.91−2.06 (m, 1 H) 1.68−1.89 (m, 2 H) 1.40−1.58 (m, 1 H) 1.17 (d, J = 6.10 Hz, 3 H).

***C*-{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-yl}methylamine (11).** The above nitrile **10** (5.80 g, 22.8 mmol) was hydrogenated at 60 psi of H_2 in 280 mL of 20% ammonium in methanol in the presence of 58.6 g of Raney nickel at room temperature for 2 h. The catalyst was removed by filtration through Celite. The filtrate was concentrated under reduced pressure, and the resulting oil was purified by flash chromatography (5% basic methanol in dichloromethane) to give the desired product as a yellow oil (3.65 g, 63%). ^{1}H NMR ($CDCl_3$): δ 7.41 (d, J = 1.23 Hz, 1 H), 7.36 (d, J = 8.29 Hz, 1 H), 7.15 (dd, J = 8.29, 1.84 Hz, 1 H), 6.40 (s, 1 H), 3.92

(s, 2 H), 3.15−3.25 (m, 2 H), 2.94−3.02 (m, 2 H), 2.44−2.52 (m, 1 H), 2.33−2.42 (m, 1 H), 2.21 (q, J = 8.90 Hz, 1 H), 1.88−1.99 (m, 1 H), 1.66−1.86 (m, 2 H), 1.58 (Br, NH2, 2 H), 1.38−1.50 (m, 1 H), 1.13 (d, J = 6.14 Hz, 3 H). Anal. ($C_{16}H_{22}N_2O$·0.3CH_3OH) C, H, N.

General Procedures for the Coupling of Amine 11 with Aromatic Halides To Prepare Compounds 6. Method A. Compound **11** (50 mg, 0.194 mmol), aromatic halide (0.232 mmol), and triethylamine (81 μL, 0.582 mmol) were mixed in 1 mL of ethanol. The mixture was stirred at 75 °C for 1−3 days. The reaction was quenched with water and extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate and concentrated to give the crude product, which was then purified by flash chromatography.

Method B. Compound **11** (50 mg, 0.194 mmol), aromatic halide (0.232 mmol), and diisopropylethylamine (101 μL, 0.582 mmol) were mixed in 1 mL of dioxane. The mixture was stirred at 100 °C for 1−3 days. The reaction was quenched with water and extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate and concentrated to give the crude product, which was then purified by flash chromatography.

Method C. Compound **11** (50 mg, 0.194 mmol), aromatic halide (0.233 mmol), tris(dibenzylideneacetone)dipalladium-(0) ($Pd_2(dba)_3$) (9.0 mg, 0.0097 mmol), racemic-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) (9.0 mg, 0.0145 mmol), and cesium carbonate (95 mg, 0.291 mmol) were placed in a reaction vessel and dried under vacuum for 2 h. Toluene (1 mL) was added and the mixture was heated at 100 °C overnight. The reaction was cooled to room temperature, quenched with water, and then extracted with dichloromethane (3×). The combined organic layers were dried over sodium sulfate and concentrated to give the crude product, which was then purified by flash chromatography.

{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}(2-nitrophenyl)amine (6a). Compound **6a** was prepared according to method A (74%). ^{1}H NMR ($CDCl_3$): δ 8.42 (br, 1H), 8.19 (d, J = 8.59 Hz, 1H), 7.46 (s, 1H), 7.38 (m, 2H), 7.19 (d, J = 8.59 Hz, 1H), 6.85 (d, J = 8.59 Hz, 1H), 6.65 (t, J = 7.67 Hz, 1H), 6.42 (s, 1H), 4.60 (d, J = 5.52 Hz, 2 H), 3.14−3.31 (m, 2 H), 3.01 (s, 2 H), 2.33−2.59 (m, 2 H), 2.15−2.30 (m, 1 H), 1.90−2.02 (m, 1 H), 1.65−1.88 (m, 2 H), 1.36−1.54 (m, 1 H), 1.15 (d, J = 4.91 Hz, 3H). Anal. ($C_{22}H_{25}N_3O_3$) C, H, N.

{2-[2-(2-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}(4-nitrophenyl)amine (6b). Compound **6b** was prepared according to method A (22%). ^{1}H NMR ($CDCl_3$): δ 8.05 (d, J = 8.90 Hz, 2H), 7.43 (s, 1H), 7.38 (d, J = 8.29 Hz, 1H), 7.17 (dd, J = 8.29, 1.84 Hz, 1H), 6.57 (d, J = 9.21 Hz, 2H), 6.42 (s, 1H), 5.05 (br, 1H), 4.46 (d, J = 5.52 Hz, 2H), 3.17−3.31 (m, 2 H), 3.02 (t, J = 7.67 Hz, 2 H), 2.39−2.59 (m, 2 H), 2.18−2.33 (m, 1 H), 1.89−2.02 (m, 1 H), 1.67−1.88 (m, 2 H), 1.41−1.55 (m, 1 H), 1.16 (d, J = 5.83 Hz, 3H). Anal. ($C_{22}H_{25}N_3O_3$) C, H, N.

2,2,2-Trifluoro-1-[4-({2-[2-(2-methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}amino)phenyl]ethanone (6c). Compound **6c** was prepared according to method A (55%). ^{1}H NMR ($CDCl_3$): δ 7.92 (d, J = 8.14 Hz, 2H), 7.45 (s, 1H), 7.40 (d, J = 8.48 Hz, 1H), 7.18 (dd, J = 8.48, 1.70 Hz, 1H), 6.65 (d, J = 9.16 Hz, 2H), 6.43 (s, 1H), 4.87 (br, 1H), 4.49 (d, J = 5.43 Hz, 2H), 3.15−3.30 (m, 2 H), 2.93−3.10 (m, 2 H), 2.33−2.57 (m, 2 H), 2.15−2.29 (m, 1 H), 1.90−2.03 (m, 1 H), 1.67−1.88 (m, 2 H), 1.48−1.62 (m, 1 H), 1.14 (m, 3 H). Anal. ($C_{24}H_{25}N_2O_2F_3$) C, H, N.

3-({2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}amino)benzonitrile (6d). Compound **6d** was prepared according to method C (13%). ^{1}H NMR ($CDCl_3$): δ 8.03 (d, J = 1.36 Hz, 1H), 7.79 (dd, J = 8.48, 1.70 Hz, 1H), 7.52 (d, J = 8.48 Hz, 1H), 7.36−7.40 (m, 1H), 7.17−7.20 (m, 1H), 6.96 (d, J = 7.46 Hz, 1H), 6.83 (s, 1H), 6.57 (s, 1H), 4.34−4.42 (m, 2 H), 4.25−4.32 (br, 1 H), 3.14−3.30 (m, 2 H), 2.93−3.09 (m, 2 H), 2.33−2.58 (m, 2 H), 2.15−2.29 (m, 1 H), 1.89−2.02 (m, 1 H), 1.66−1.88 (m, 2 H), 1.39−1.53 (m, 1 H), 1.14 (d, J = 6.10 Hz, 3H). Anal. ($C_{23}H_{25}N_3O$) H. C: calcd, 76.85; found, 76.26. N: calcd, 11.69; found, 7.76.

(6-Chloropyridazin-3-yl){2-[2-(2-methylpyrrolidin-1-yl)-ethyl]benzofuran-5-ylmethyl}amine (6e). Compound **6e** was prepared according to method A (29%). ^{1}H NMR ($CDCl_3$): δ 7.47 (d, J = 1.36 Hz, 1H), 7.38 (d, J = 8.48 Hz, 1H), 7.20 (dd, J = 8.31, 1.86 Hz, 1H), 7.14 (d, J = 9.15 Hz, 1H), 6.60 (d, J = 9.49 Hz, 1H), 6.42 (s, 1H), 5.11 (br, 1H), 4.65 (d, J = 5.76 Hz, 2H), 3.15−3.29 (m, 2 H), 2.93−3.07 (m, 2 H), 2.33−2.58 (m, 2 H), 2.15−2.29 (m, 1 H), 1.90−2.03 (m, 1 H), 1.68−1.86 (m, 1 H), 1.39−1.63 (m, 2 H), 1.15 (d, J = 5.76 Hz, 3 H). Anal. ($C_{20}H_{23}N_4OCl$·0.2H_2O) C, H, N.

3-({2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}amino)pyrazine-2-carbonitrile (6f). Compound **6f** was prepared according to method A (63%). ^{1}H NMR ($CDCl_3$): δ 8.25 (d, J = 2.37 Hz, 1H), 7.93 (d, J = 2.37 Hz, 1H), 7.46 (s, 1H), 7.39 (d, J = 8.48 Hz, 1H), 7.20 (dd, J = 8.31, 1.86 Hz, 1H), 6.44 (s, 1H), 5.57 (br, 1H), 4.75 (d, J = 5.43 Hz, 2H), 3.15−3.33 (m, 2 H), 2.95−3.10 (m, 2 H), 2.35−2.60 (m, 2 H), 2.15−2.31 (m, 1 H), 1.90−2.03 (m, 1 H), 1.69−1.85 (m, 1 H), 1.39−1.62 (m, 2 H), 1.16 (s, 3H). Anal. ($C_{21}H_{25}N_5O$) C, H, N.

{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}pyrazin-2-ylamine (6g). Compound **6g** was prepared according to method A (14%). ^{1}H NMR ($CDCl_3$): δ 8.02 (dd, J = 2.71, 1.36 Hz, 1H), 7.90 (d, J = 1.36 Hz, 1H), 7.83 (d, J = 3.05 Hz, 1H), 7.47 (d, J = 1.36 Hz, 1H), 7.38 (d, J = 8.48 Hz, 1H), 7.20 (dd, J = 8.31, 1.87 Hz, 1H), 6.42 (s, 1H), 4.89 (br, 1H), 4.61 (d, J = 5.43 Hz, 2H), 3.15−3.29 (m, 2 H), 2.93−3.10 (m, 2 H), 2.33−2.60 (m, 2 H), 2.13−2.29 (m, 1 H), 1.89−2.05 (m, 1 H), 1.63−1.87 (m, 2 H), 1.38−1.53 (m, 1 H), 1.15 (d, J = 6.10 Hz, 3H). Anal. ($C_{20}H_{24}N_4O$) C, H, N.

(5-Bromopyrimidin-2-yl){2-[2-(2-(*R*)-methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}amine (6h). Compound **6h** was prepared according to method B (66%). ^{1}H NMR ($CDCl_3$): δ 7.41 (s, 2H), 7.13 (dd, J = 8.48, 1.70 Hz, 1H), 6.97 (s, 2H), 6.45 (s, 1H), 5.30 (br, 1H), 4.46 (d, J = 5.43 Hz, 2H), 3.17−3.30 (m, 2 H), 2.97−3.09 (m, 2 H), 2.37−2.59 (m, 2 H), 2.18−2.31 (m, 1 H), 1.90−2.04 (m, 1 H), 1.66−1.89 (m, 2 H), 1.40−1.56 (m, 1 H), 1.16 (d, J = 6.10 Hz, 3H). Anal. ($C_{20}H_{23}N_4$-OBr) C, H, N.

{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}pyrimidin-5-ylamine (6i). Compound **6i** was prepared according to method C (15%). ^{1}H NMR ($CDCl_3$): δ 8.60 (s, 1H), 8.15 (s, 2H), 7.46 (s, 1H), 7.40 (d, J = 8.48 Hz, 1H), 7.16−7.22 (m, 1H), 6.42 (s, 1H), 4.42 (d, J = 5.43 Hz, 2H), 4.13 (br, 1H), 3.15−3.31 (m, 2 H), 2.91−3.06 (m, 2 H), 2.33−2.57 (m, 2 H), 2.14−2.29 (m, 1 H), 1.88−2.04 (m, 1 H), 1.64−1.87 (m, 2 H), 1.37−1.53 (m, 1 H), 1.14 (d, J = 5.76 Hz, 3H). Anal. ($C_{20}H_{24}N_4O$·0.15H_2O) C, H, N.

(5-Ethylpyrimidin-2-yl){2-[2-(2-(*R*)-methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}amine (6j). Compound **6j** was prepared according to method B (13%). ^{1}H NMR ($CDCl_3$): δ 8.16 (s, 2H), 7.46 (d, J = 1.36 Hz, 1H), 7.35 (d, J = 8.14 Hz, 1H), 7.20 (dd, J = 8.48, 1.70 Hz, 1H), 6.40 (s, 1H), 5.29 (br, 1H), 4.67 (d, J = 6.10 Hz, 2H), 3.14−3.28 (m, 2 H), 2.93−3.05 (m, 2 H), 2.47 (q, J = 7.80 Hz, 2H), 2.32−2.42 (m, 2 H), 2.15−2.28 (m, 1 H), 1.88−2.03 (m, 1 H), 1.65−1.85 (m, 2 H), 1.37−1.53 (m, 1 H), 1.20 (t, J = 7.63 Hz, 3H), 1.14 (d, J = 6.10 Hz, 3H). Anal. ($C_{22}H_{28}N_4O$·0.15dioxane) C, H, N.

{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}pyrimidin-2-ylamine (6k). Compound **6k** was prepared according to method B (55%). ^{1}H NMR ($CDCl_3$): δ 8.30 (d, J = 4.75 Hz, 2H), 7.46 (s, 1H), 7.36 (d, J = 8.14 Hz, 1H), 7.20 (dd, J = 8.31, 1.86 Hz, 1H), 6.55 (t, J = 4.75 Hz, 1H), 6.40 (s, 1H), 5.37 (br, 1H), 4.69 (d, J = 5.76 Hz, 2H), 3.14−3.28 (m, 2 H), 2.93−3.05 (m, 2 H), 2.32−2.54 (m, 2 H), 2.13−2.27 (m, 1 H), 1.89−2.01 (m, 1 H), 1.64−1.86 (m, 2 H), 1.37−1.51 (m, 1 H), 1.14 (d, J = 5.76 Hz, 3H). Anal. ($C_{20}H_{24}N_4O$·0.16H_2O) C, H, N.

{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}(5-nitrothiazol-2-yl)amine (6l). Compound **6l** was prepared according to method C (11%). ^{1}H NMR ($CDCl_3$): δ 7.95 (s, 1H), 7.46 (d, J = 1.36 Hz, 1H), 7.42 (d, J = 8.48 Hz,

1H), 7.18 (dd, J = 8.48, 1.70 Hz, 1H), 6.90 (br, 1H), 6.44 (s, 1H), 4.54 (s, 2H), 3.16−3.30 (m, 2 H), 2.95−3.07 (m, 2 H), 2.34−2.57 (m, 2 H), 2.16−2.30 (m, 1 H), 1.89−2.02 (m, 1 H), 1.66−1.86 (m, 2 H), 1.39−1.54 (m, 1 H), 1.14 (d, J = 6.10 Hz, 3H). LC/MS (AA method): *m/z* 386.7 (M + H). LC/MS (TFA method): *m/z* 386.7 (M + H).

{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}(3-nitropyridin-2-yl)amine (6m). Compound **6m** was prepared according to method B (77%). ^{1}H NMR ($CDCl_3$): δ 8.52 (br, 1H), 8.40−8.49 (m, 2 H), 7.49 (d, J = 1.36 Hz, 1H), 7.38 (d, J = 8.48 Hz, 1H), 7.17−7.30 (m, 1 H), 6.68 (dd, J = 8.14, 4.75 Hz, 1H), 6.43 (s, 1H), 4.91 (d, J = 5.43 Hz, 2H), 3.14−3.34 (m, 2 H), 2.93−3.10 (m, 2 H), 2.35−2.60 (m, 2 H), 2.15−2.31 (m, 1 H), 1.68−2.03 (m, 3 H), 1.40−1.61 (m, 1 H), 1.17 (s, 3H). Anal. ($C_{21}H_{24}N_4O_3$) C, H, N.

(3,5-Dinitropyridin-2-yl){2-[2-(2-(*R*)-methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}amine (6n). Compound **6n** was prepared according to method B (77%). ^{1}H NMR ($CDCl_3$): δ 9.30 (d, J = 2.37 Hz, 1H), 9.24 (d, J = 2.71 Hz, 1H), 9.00 (br, 1H), 7.49 (d, J = 1.36 Hz, 1H), 7.41 (d, J = 8.14 Hz, 1H), 7.22 (dd, J = 8.48, 1.70 Hz, 1H), 6.46 (s, 1H), 5.00 (d, J = 5.76 Hz, 2H), 3.19−3.35 (m, 2 H), 2.96−3.16 (m, 2 H), 2.41−2.67 (m, 2 H), 2.16−2.36 (m, 1 H), 1.70−2.08 (m, 3 H), 1.47−1.65 (m, 1 H), 1.19 (s, 3H). Anal. ($C_{21}H_{23}N_5O_5$·0.4H_2O) C, N. H: calcd, 5.54; found, 5.03.

4-({2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}amino)pyridine-2,6-dicarbonitrile (6o). Compound **6o** was prepared according to method B (34%). ^{1}H NMR ($CDCl_3$): δ 8.29 (s, 2H), 7.44 (d, J = 1.36 Hz, 1H), 7.36 (d, J = 8.48 Hz, 1H), 7.18 (dd, J = 8.48, 2.03 Hz, 1H), 6.41 (s, 1H), 5.47 (br, 1H), 4.64 (d, J = 5.76 Hz, 2H), 3.14−3.29 (m, 2 H), 2.94−3.06 (m, 2 H), 2.34−2.56 (m, 2 H), 2.14−2.29 (m, 1 H), 1.88−2.00 (m, 1 H), 1.65−1.87 (m, 2 H), 1.39−1.51 (m, 1 H), 1.15 (d, J = 5.42 Hz, 3H). Anal. ($C_{23}H_{23}N_5O$·0.1$CDCl_3$) C, H. N: calcd, 17.47; found, 16.80.

2-({2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}amino)nicotinonitrile (6p). Compound **6p** was prepared according to method B (37%). ^{1}H NMR ($CDCl_3$): δ 8.32 (dd, J = 4.92, 1.86 Hz, 1H), 7.67 (dd, J = 7.63, 1.86 Hz, 1H), 7.47 (d, J = 1.36 Hz, 1H), 7.38 (d, J = 8.48 Hz, 1H), 7.21 (dd, J = 8.48, 1.70 Hz, 1H), 6.63 (dd, J = 7.63, 4.92 Hz, 1H), 6.43 (s, 1H), 5.43 (br, 1H), 4.76 (d, J = 5.42 Hz, 2H), 3.14−3.30 (m, 2 H), 2.94−3.08 (m, 2 H), 2.32−2.57 (m, 2 H), 2.12−2.29 (m, 1 H), 1.88−2.01 (m, 1 H), 1.65−1.86 (m, 2 H), 1.38−1.51 (m, 1 H), 1.14 (d, J = 5.42 Hz, 3H). Anal. ($C_{22}H_{24}N_4O$·0.12H_2O) C, H, N.

6-({2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}amino)nicotinonitrile (6q). Compound **6q** was prepared according to method B (39%). ^{1}H NMR ($CDCl_3$): δ 8.39 (d, J = 1.70 Hz, 1H), 7.56 (dd, J = 8.81, 2.37 Hz, 1H), 7.43 (d, J = 1.36 Hz, 1H), 7.38 (d, J = 8.48 Hz, 1H), 7.17 (dd, J = 8.48, 2.03 Hz, 1H), 6.42 (d, J = 0.68 Hz, 1H), 6.38 (dd, J = 8.81, 0.68 Hz, 1H), 5.37 (br, 1H), 4.61 (d, J = 5.76 Hz, 2H), 3.14−3.29 (m, 2 H), 2.93−3.06 (m, 2 H), 2.32−2.55 (m, 2 H), 2.13−2.27 (m, 1 H), 1.87−2.02 (m, 1 H), 1.66−1.86 (m, 2 H), 1.37−1.51 (m, 1 H), 1.14 (d, J = 6.10 Hz, 3H). Anal. ($C_{22}H_{24}N_4O$) C, H, N.

{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylmethyl}(5-nitropyridin-2-yl)amine (6r). Compound **6r** was prepared according to method B (45%). ^{1}H NMR ($CDCl_3$): δ 9.05 (d, J = 2.71 Hz, 1H), 8.18 (dd, J = 9.15, 2.71 Hz, 1H), 7.45 (s, 1H), 7.39 (d, J = 8.14 Hz, 1H), 7.18 (dd, J = 8.48, 1.70 Hz, 1H), 6.42 (s, 1H), 6.37 (d, J = 9.15 Hz, 1H), 5.64 (br, 1H), 4.68 (d, J = 5.76 Hz, 2H), 3.13−3.28 (m, 2 H), 2.92−3.07 (m, 2 H), 2.31−2.56 (m, 2 H), 2.13−2.27 (m, 1 H), 1.87−2.02 (m, 1 H), 1.65−1.86 (m, 2 H), 1.36−1.52 (m, 1 H), 1.14 (d, J = 5.76 Hz, 3H). Anal. ($C_{21}H_{24}N_4O_3$) C, H, N.

2-Iodo-4-nitrophenol (12). Compound **12** was prepared analogously to compound **8**. The reaction was run for 5 days at room temperature and was still not complete. Crude product was used in the next step without further purification. ^{1}H NMR (MeOD-d_4): δ 8.56 (d, J = 2.71 Hz, 1H), 8.08 (dd, J = 9.16, 2.71 Hz, 1H), 6.80 (d, J = 9.16 Hz, 1H).

2-(*R*)-Methyl-1-[2-(5-nitrobenzofuran-2-yl)ethyl]pyrrolidine (13). Compound **13** was synthesized the same way as compound **10**, using compound **12** as the starting material instead of compound **8**. Since compound **12** is about a 1:1 mixture of 4-nitrophenol and 2-iodo-4-nitrophenol, the yield was not calculated. From 2.97 g of crude **12**, 450 mg of pure product **13** was obtained. ^{1}H NMR ($CDCl_3$): δ 8.42 (d, J = 2.03 Hz, 1H), 8.16 (dd, J = 8.82, 2.37 Hz, 1H), 7.48 (d, J = 9.15 Hz, 1H), 6.61 (s, 1H), 3.16−3.39 (m, 2H), 2.95−3.17 (m, 2H), 2.37−2.67 (m, 2H), 2.16−2.39 (m, 1H), 1.88−2.09 (m, 1H), 1.62−1.90 (m, 2H), 1.38−1.58 (m, 1H), 1.17 (d, J = 6.10 Hz, 3H).

2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylamine (14). Compound **13** (2.15 g, 7.84 mmol) was dissolved in 55 mL of methanol, and 215 mg of 10% Pd/C was added. The compound was hydrogenated under 60 psi hydrogen atmosphere at room temperature for 16 h. After filtration, the crude product was purified by flash chromatography (3% basic methanol in dichloromethane) to give the desired product as a yellow oil (1.41 g, 74%). ^{1}H NMR ($CDCl_3$): δ 7.19 (d, J = 8.82 Hz, 1H), 6.77 (d, J = 2.37 Hz, 1H), 6.59 (dd, J = 8.65, 2.54 Hz, 1H), 6.29 (s, 1H), 3.53 (br, 2 H), 3.12−3.29 (m, 2H), 2.89−3.01 (m, 2H), 2.31−2.55 (m, 2H), 2.13−2.28 (m, 1H), 1.87−2.01 (m, 1H), 1.64−1.85 (m, 2H), 1.37−1.55 (m, 1H), 1.14 (d, J = 6.10 Hz, 3H).

2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylamine (14). Compound **14** can be made alternatively from compound **15**. Compound **15**[9a,20] (308 mg, 1.0 mmol, 1 equiv), tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) (36 mg, 0.05 mmol, 5%), and dicyclohexylbiphenylylphosphine (42 mg, 0.12 mmol, 12%) were charged into a pressure tube which was evacuated and refilled with nitrogen. To this system was added LiHMDS (1.0M in THF, 1.2 mL, 1.2 mmol, 1.2 equiv) and the mixture was heated at 65 °C for 16 h. It was quenched with 4 mL of 2 N HCl, basified with 6 mL of 2 N NaOH, and extracted with dichloromethane. The organic layer was dried over sodium sulfate and concentrated to give the crude product, which was then purified by flash chromatography using 5% basic methanol in dichloromethane to give the desired product (294 mg, 80%).

General Procedures for the Coupling of Compound 14 with Aromatic Halides To Prepare Compounds 7. Compounds **7a**−**7k** were prepared analogously to **6a**−**6r**, except using compound **14** as starting material instead of compound **11**.

{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-yl}(2-nitrophenyl)amine (7a). Compound **7a** was prepared according to method B (31%). ^{1}H NMR ($CDCl_3$): δ 9.52 (s, 1H), 8.21 (dd, J = 8.65, 1.53 Hz, 1H), 7.45 (d, J = 8.81 Hz, 1H), 7.40 (d, J = 2.37 Hz, 1H), 7.31 (t, J = 7.80 Hz, 1H), 7.12 (dd, J = 8.65, 2.20 Hz, 1H), 7.03 (d, J = 7.80 Hz, 1H), 6.68−6.76 (m, 1H), 6.49 (s, 1H), 3.20−3.39 (m, 2H), 3.00−3.19 (m, 2H), 2.20−2.71 (m, 3H), 1.75−2.05 (m, 4H), 1.27 (d, J = 5.42 Hz, 3H). Anal. ($C_{21}H_{23}N_3O_3$) C, H, N.

4-{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylamino}benzonitrile (7b). Compound **7b** was prepared according to Method C (50%). ^{1}H NMR ($CDCl_3$): δ 7.35−7.50 (m, 3H), 7.31 (d, J = 2.03 Hz, 1H), 7.03 (dd, J = 8.65, 2.20 Hz, 1H), 6.80−6.87 (m, 2H), 6.45 (s, 1H), 6.00 (s, 1H), 3.19−3.38 (m, 2H), 3.06 (s, 2H), 2.41−2.67 (m, 2H), 2.17−2.38 (m, 1H), 1.69−2.09 (m, 4H), 1.20 (s, 3H). Anal. ($C_{22}H_{23}N_3O$·0.22SiO_2) C, H, N.

3-{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylamino}benzonitrile (7c). Compound **7c** was prepared according to Method C (43%). ^{1}H NMR ($CDCl_3$): δ 7.38 (d, J = 8.82 Hz, 1H), 7.22−7.29 (m, 2H), 7.10−7.12 (m, 1H), 7.06−7.09 (m, 1H), 7.05 (d, J = 2.03 Hz, 1H), 7.00 (dd, J = 8.65, 2.20 Hz, 1H), 6.44 (s, 1H), 5.75 (s, 1H), 3.19−3.36 (m, 2H), 3.01−3.15 (m, 2H), 2.41−2.65 (m, 2H), 2.20−2.36 (m, 1H), 1.67−2.07 (m, 4H), 1.20 (s, 3H). Anal. ($C_{22}H_{23}N_3O$) C, H, N.

(5-Ethylpyrimidin-2-yl){2-[2-(2-(*R*)-methylpyrrolidin-1-yl)ethyl]benzofuran-5-yl}amine (7d). Compound **7d** was prepared according to method C (43%). ^{1}H NMR ($CDCl_3$): δ 8.26 (s, 2H), 7.79 (d, J = 2.03 Hz, 1H), 7.31−7.41 (m, 1H),

7.22−7.31 (m, 1H), 6.99 (s, 1H), 6.43 (s, 1H), 3.12−3.32 (m, 2H), 2.89−3.08 (m, 2H), 2.53 (q, J = 7.80 Hz, 2H), 2.32−2.46 (m, 2H), 2.24 (m, 1H), 1.88−2.02 (m, 1H), 1.66−1.88 (m, 2H), 1.40−1.55 (m, 1H), 1.23 (t, J = 7.63 Hz, 3H), 1.15 (d, J = 6.10 Hz, 3H). Anal. ($C_{21}H_{26}N_4O$) C, H, N.

{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-yl}pyrimidin-2-ylamine (7e). Compound **7e** was prepared according to method C (59%). ^{1}H NMR ($CDCl_3$): δ 8.39 (d, J = 4.75 Hz, 2H), 7.79 (d, J = 2.03 Hz, 1H), 7.34−7.40 (m, 1H), 7.29 (d, J = 2.37 Hz, 1H), 7.09 (s, 1H), 6.68 (t, J = 4.92 Hz, 1H), 6.44 (s, 1H), 3.16−3.31 (m, 2H), 2.94−3.08 (m, 2H), 2.35−2.59 (m, 2H), 2.17−2.32 (m, 1H), 1.89−2.04 (m, 1H), 1.60−1.87 (m, 2H), 1.43−1.55 (m, 1H), 1.17 (d, J = 5.76 Hz, 3H). Anal. ($C_{19}H_{22}N_4O$·0.12H_2O) C, H, N.

{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-yl}pyrimidin-5-ylamine (7f). Compound **7f** was prepared according to method C (59%). ^{1}H NMR ($CDCl_3$): δ 8.70 (s, 1H), 8.40 (s, 2H), 7.39 (d, J = 8.48 Hz, 1H), 7.22−7.33 (m, 1H), 7.01 (dd, J = 8.65, 2.20 Hz, 1H), 6.43 (s, 1H), 5.60 (s, 1H), 3.16−3.37 (m, 2H), 2.97−3.12 (m, 2H), 2.38−2.63 (m, 2H), 2.19−2.35 (m, 1H), 1.92−2.05 (m, 1H), 1.66−1.88 (m, 3H), 1.19 (d, J = 5.76 Hz, 3H). Anal. ($C_{19}H_{22}N_4O$) C, H, N.

{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-yl}pyrazin-2-ylamine (7g). Compound **7g** was prepared according method A (12%). ^{1}H NMR ($CDCl_3$): δ 8.15 (d, J = 1.36 Hz, 1H), 8.04−8.10 (m, 1H), 7.94 (d, J = 2.71 Hz, 1H), 7.55 (d, J = 2.03 Hz, 1H), 7.40 (d, J = 8.81 Hz, 1H), 7.16 (dd, J = 8.65, 2.20 Hz, 1H), 6.50 (s, 1H), 6.44 (s, 1H), 3.17−3.30 (m, 2H), 2.94−3.09 (m, 2H), 2.33−2.61 (m, 2H), 2.17−2.30 (m, 1H), 1.90−2.05 (m, 1H), 1.63−1.88 (m, 2H), 1.39−1.57 (m, 1H), 1.16 (d, J = 5.76 Hz, 3H). Anal. ($C_{19}H_{22}N_4O$·0.12H_2O) C, H, N.

{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-yl}(5-nitropyridin-2-yl)amine (7h). Compound **7h** was prepared according to method C (42%). ^{1}H NMR ($CDCl_3$): δ 9.08 (d, J = 2.71 Hz, 1H), 8.20 (dd, J = 9.16, 2.71 Hz, 1H), 7.40−7.50 (m, 2H), 7.20 (s, 1H), 7.13 (dd, J = 8.48, 2.37 Hz, 1H), 6.64 (d, J = 9.49 Hz, 1H), 6.48 (s, 1H), 3.16−3.32 (m, 2H), 2.95−3.10 (m, 2H), 2.35−2.62 (m, 2H), 2.15−2.31 (m, 1H), 1.89−2.05 (m, 1H), 1.68−1.88 (m, 2H), 1.35−1.58 (m, 1H), 1.16 (d, J = 5.76 Hz, 3H). Anal. ($C_{20}H_{22}N_4O_3$) C, H, N.

{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-yl}(3-nitropyridin-2-yl)amine (7i). Compound **7i** was prepared according to method C (75%). ^{1}H NMR ($CDCl_3$): δ 10.08 (s, 1H), 8.52 (dd, J = 8.48, 1.69 Hz, 1H), 8.45 (dd, J = 4.41, 1.70 Hz, 1H), 7.75 (d, J = 2.03 Hz, 1H), 7.37−7.49 (m, 1H), 7.29−7.37 (m, 1H), 6.79 (dd, J = 8.31, 4.58 Hz, 1H), 6.48 (s, 1H), 3.16−3.35 (m, 2H), 2.93−3.14 (m, 2H), 2.39−2.64 (m, 2H), 2.14−2.35 (m, 1H), 1.90−2.07 (m, 1H), 1.62−1.87 (m, 3H), 1.18 (s, 3H). Anal. ($C_{20}H_{22}N_4O_3$) C, H, N.

6-Methyl-2-{2-[2-(2-(*R*)-methylpyrrolidin-1-yl)ethyl]benzofuran-5-ylamino}nicotinonitrile (7j). Compound **7j** was prepared according to method B (76%). ^{1}H NMR ($CDCl_3$): δ 7.76 (d, J = 7.80 Hz, 2H), 7.42 (d, J = 8.82 Hz, 1H), 7.08 (dd, J = 8.82, 2.37 Hz, 1H), 6.96 (d, J = 7.80 Hz, 2H), 6.44 (s, 1H), 3.18−3.37 (m, 2H), 2.94−3.15 (m, 2H), 2.43 (s, 3H), 2.27−2.60 (m, 3H), 1.62−2.14 (m, 4H), 1.20 (s, 3H). Anal. ($C_{22}H_{24}N_4O$) C, H, N.

{2-[2-(2-(*R*)-Methylpyrrolidin-1-yl)ethyl]benzofuran-5-yl}(5-trifluoromethylpyridin-2-yl)amine (7k). Compound **7k** was prepared according to method C (38%). ^{1}H NMR ($CDCl_3$): δ 8.41 (s, 1H), 7.61 (dd, J = 8.98, 2.54 Hz, 1H), 7.47 (d, J = 2.03 Hz, 1H), 7.34−7.45 (m, 1H), 7.14 (dd, J = 8.81, 2.37 Hz, 1H), 6.79 (s, 1H), 6.70 (d, J = 8.82 Hz, 1H), 6.49 (s, 1H), 3.27−3.45 (m, 2H), 3.04−3.24 (m, 2H), 2.54−2.87 (m, 2H), 2.26−2.50 (m, 1H), 1.68−2.17 (m, 4H), 1.27 (d, J = 5.42 Hz, 3H). Anal. ($C_{21}H_{22}N_3OF_3$) C, H, N.

Primary Culture of Rat Hepatocytes. Hepatocytes were isolated from male Sprague−Dawley rats and cultured as previously described.[28] Cells were plated in Phenol-Red serum-free modified DMEM (InVitrogen, Carlsbad, CA) media supplemented with 2 mM L-glutamine, 0.3 mM of nonessential amino acids solution (InVitrogen, Carlsbad, CA), 22 μg/L gentamicin, 2 mM $NaHCO_3$, 10 mM Hepes, and 2 mM D-fructose adjusted to pH 7.37 and filtered through a 0.22 μm filter. Hepatocytes were plated at a density of 60 000 cells/mL onto collagen-coated culture slide chambers (Becton Dickinson Labware, Bedford, MA) and incubated overnight at 37 °C and 5% CO_2 until use in the phospholipidosis measurement.

Phospholipidosis Assay. Accumulation of phospholipids was assessed by quantitating the accumulation of a fluorescent probe *N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)dipalmitoylphosphatidylethanolamine (NBD-PE, Molecular Probes Inc., Eugene, OR) into lamellar bodies.[26] NBD-PE was suspended in ethanol and diluted to a concentration of 50 μM in Phenol-Red serum-free modified DMEM media containing 2 mM L-glutamine, 0.3 mM of nonessential amino acids solution, 22 μg/L gentamicin, 2 mM $NaHCO_3$, 10 mM Hepes, and 2 mM D-fructose adjusted to pH 7.4 with a final ethanol concentration of 0.46%. The mixture was placed into a sonicating water bath for 30 min and then filtered through a 0.22 μm filter. Compounds were dissolved in DMSO and then diluted into the above culture medium to a final concentration of 18.8, 37.5, 75, or 150 μM with a 0.1% final DMSO concentration. Hepatocytes were treated for 24 h with the test compounds or vehicle (0.1% DMSO) and 50 μM NBD-PE in at 37 °C and 5% CO_2. Cells were washed three times with the above media (without NBD-PE), and then fixed with 3.5% paraformaldehyde in phosphate-buffered saline (PBS), pH 7.4, and stored at 4 °C. Brightfield and fluorescence (NBD-PE, excitation 463/emission 536) images were acquired using a Leica DMIRE inverted fluorescence microscope (Wetzlar, Germany) and Optronics DEI 750 videocamera (Goleta, CA). Quantitation of the cell area percent occupied by fluorescent granules in hepatocytes exposed to various concentrations of test compound (n = 2 wells per dose) was performed using Leica QWIN image analysis software. An increase in the area percent of fluorescence is used as a surrogate for phospholipidosis.[29] Results were normalized to amiodarone,[27] a known inducer of phospholipidosis used as a positive control, and expressed as a "phospholipidosis index". A value ≥0.9 indicated that the compound induces phospholipidosis to the same extent as amiodarone and is considered to be a potent inducer of phospholopidosis. Moderate inducers have a phopholipidosis index in the range of 0.50−0.90, and a value ≤0.5 is interpreted as a compound with minimal effect.

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

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