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Analogues of Fenarimol Are Potent Inhibitors of *Trypanosoma cruzi* and Are Efficacious in a Murine Model of Chagas Disease

Martine Keenan,*[,†] Michael J. Abbott,[†] Paul W. Alexander,[†] Tanya Armstrong,[‡] Wayne M. Best,[†] Bradley Berven,[†] Adriana Botero,[‡] Jason H. Chaplin,[†] Susan A. Charman,[§] Eric Chatelain,[∥] Thomas W. von Geldern,[∥] Maria Kerfoot,[‡] Andrea Khong,[‡] Tien Nguyen,[§] Joshua D. McManus,[†] Julia Morizzi,[§] Eileen Ryan,[§] Ivan Scandale,[∥] R. Andrew Thompson,[‡] Sen Z. Wang,[†] and Karen L. White[§]

[†]Epichem Pty Ltd, South Street, Murdoch, WA 6150, Australia

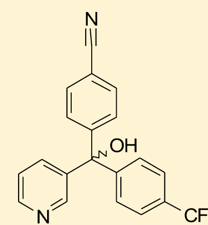
[‡]Murdoch University, South Street, Murdoch, WA 6150, Australia

[§]Centre for Drug Candidate Optimisation, Monash University, 381 Royal Parade, Parkville, Victoria 3052, Australia

[∥]Drugs for Neglected Diseases *initiative* (DND*i*), 15 Chemin Louis Dunant, 1202 Geneva, Switzerland

Supporting Information

ABSTRACT: We report the discovery of nontoxic fungicide fenarimol (**1**) as an inhibitor of *Trypanosoma cruzi* (*T. cruzi*), the causative agent of Chagas disease, and the results of structure−activity investigations leading to potent analogues with low nM IC_{50}s in a *T. cruzi* whole cell in vitro assay. Lead compounds suppressed blood parasitemia to virtually undetectable levels after once daily oral dosing in mouse models of *T. cruzi* infection. Compounds are chemically tractable, allowing rapid optimization of target biological activity and drug characteristics. Chemical and biological studies undertaken in the development of the fenarimol series toward the goal of delivering a new drug candidate for Chagas disease are reported.



INTRODUCTION

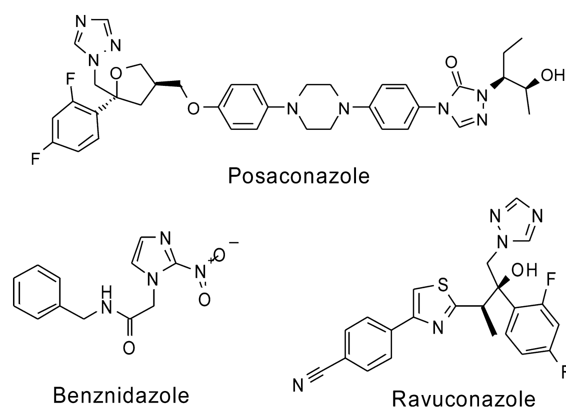
Chagas disease is currently endemic in 21 countries across Latin America, killing more people in the region each year than any other parasite-born disease including malaria. Moreover, its prevalence is growing in nonendemic developed countries, including Australia, USA, Japan, and Spain, such that the global health burden is around 10 million cases and 25 million people at risk.[1−3] Recent efforts from Product Development Partnerships (PDPs) such as the Drugs for Neglected Diseases *initiative* (DND*i*) have brought this parasitic disease to the forefront of research efforts into neglected diseases,[4] expanding on decades of work undertaken in Central and South America and in dedicated laboratories worldwide.[5,6]

The causative parasitic agent of Chagas disease, *Trypanosoma cruzi*, is transmitted to animals and humans via insect vectors known colloquially as “kissing bugs”.[7] Metacyclic trypomastigotes are released in the feces of the triatomine insect vector as it takes a blood meal and enter the bloodstream via the bite wound or a mucosal membrane. Once inside the host, metacyclic trypomastigotes invade nearby cells and differentiate into an intracellular amastigote form which multiplies by binary fission. Transformation into trypomastigotes occurs prior to release from cells back into the bloodstream, proliferating the infective cycle. Other forms of transmission include congenital, blood transfusion and, to a lesser extent, contaminated food.

The disease progresses through an acute and then indeterminate phase, presenting as a chronic illness some 10−15 years post-infection, at which point mortality is high.[8] This occurs as parasites move from the bloodstream to the muscle cells of the heart and/or the gastrointestinal tract, causing extensive damage to these (and other) organs and tissues over time. The challenge in development of new drugs to treat Chagas disease lies in demonstrating efficacy in the chronic form of the disease, a condition difficult to model in the laboratory and to monitor in clinical trials due to the lack of validated measures of clinical outcome.

The current standard of care benznidazole (Chart 1), a nitroimidazole, works well in the acute phase of the disease, but

Chart 1



clinical efficacy in patients with the chronic illness is limited and controversial. Originally thought to act via the production of

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free radicals and reactive metabolites promoting damage to parasite DNA,[9] benznidazole is now proposed to undergo enzyme-mediated activation by nitroreductases within the parasite.[10] It can cause undesirable side effects in adults ranging from gastrointestinal discomfort to neuropathy, leading to poor patient compliance over the required 60-day treatment regime.[11] Posaconazole[12] and a pro-drug of ravuconazole[13] (Chart 1) are the first new agents to enter clinical trials for the treatment of Chagas disease in over 40 years. Originally developed to target human fungal conditions and part of a large family of azole-derived antifungals, these compounds interrupt sterol biosynthesis in *T. cruzi* by inhibiting lanosterol 14α-demethylase (CYP51), an enzyme required to demethylate lanosterol an important intermediate in the biosynthetic pathway.[14,15] Concern regarding the potential for development of resistance to azole-based therapies suggests there is still a need for new treatments for Chagas disease.[16,17] These must be better tolerated than benznidazole, active against various *T. cruzi* strains, and efficacious in the chronic phase of the illness.

As part of a hit generation effort to discover new *T. cruzi* inhibitors, a diversity set of agrochemicals was prepared and screened in an in vitro whole cell parasite assay against a *T. cruzi* strain (Tulahuén) belonging to *T. cruzi* group VI (TcVI)[18] and transfected with the β-galactosidase gene.[19] The plant fungicides fenarimol (**1**) and pyrifenox (**2**), used in the control of powdery mildew and fungus on fruits and vegetables, demonstrated good activity in the assay with IC_{50}s of 350 nM (**1**) and 290 nM (**2**) (Figure 1). Compound **1** has recently

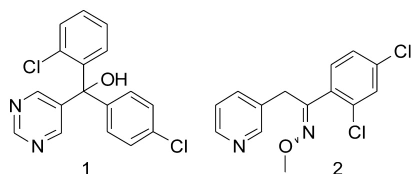


Figure 1. Fenarimol (**1**) and Pyrifenox (**2**).

been reported to be a modest inhibitor of related protozoan parasite *Leishmania donovani*,[20] and with simple aromatic components and an uncomplicated synthesis we considered it a suitable starting hit for further development. This article reports the synthesis, structure−activity and structure−property relationships, and in vivo evaluation of **1** and analogues as part of a drug discovery program to develop new treatments for Chagas disease.

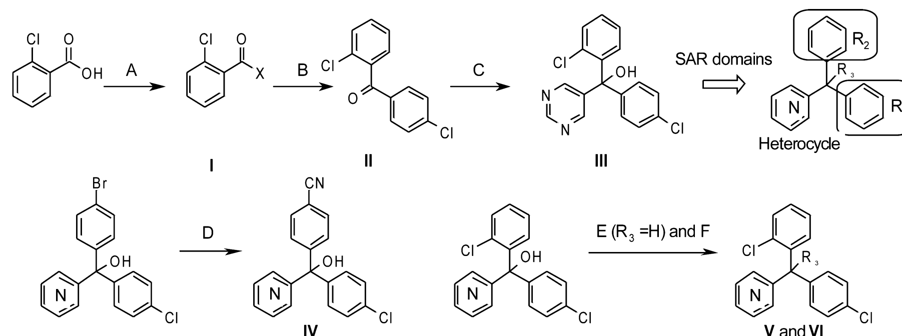
■ RESULTS AND DISCUSSION

Chemistry. Compound **1** was originally developed by agrochemical company Elanco and later investigated as an estrogen synthetase inhibitor.[21] Preparation of most triarylcarbinol compounds (**III**) reported in this study was carried out by analogy to these literature methods, introducing the three aromatic domains (designated as the heterocycle, R_1, and R_2) in a stepwise fashion (Scheme 1). Key intermediate benzophenones (**II**) were easily prepared in large quantities from activated carboxylic acids (**I**, general methods A1−3) by either Friedel−Craft acylation (general method B1), palladium-catalyzed acylation of aryl boronic acids (general method B2),[22] or by addition of aryl organometallic derivatives to the appropriate *N*-methoxy-*N*-methyl benzamides (general method B3). Some benzophenones were also purchased from commercial sources. Organometallic methods were used to introduce the remaining (hetero)aryl group to give the target triarylcarbinols (**III**) in overall good yields (general method C). In the case of the pyrimidinyl derivatives, the lithio-pyrimidine species was generated in situ at low temperature in the presence of the benzophenone to minimize side reactions (general method C (pyrimidine)). The general methods depicted in Scheme 1 were used to introduce both aryl and heteroaryl groups, providing a very flexible route to a broad range of analogues.

Potassium ferricyanide was used to convert arylbromides to the corresponding benzonitriles (**IV**, general method D).[23] Tertiary carbinols were dehydroxylated on reaction with stannous chloride according to literature procedures[21b] (**V**, general method E) or substituted by conversion to the corresponding chloro compound followed by reaction with the desired nucleophile (**VI**, general method F). The intermediate chloro derivative was easily hydrolyzed back to the hydroxy compound, which was typically observed in the final product mixture before purification. Compounds were prepared in racemic form.

Compounds prepared were assayed in the *T. cruzi* whole parasite assay described above with cytotoxicity in L6 cells

Scheme 1. General Methods for the Preparation of 1 and Analogues



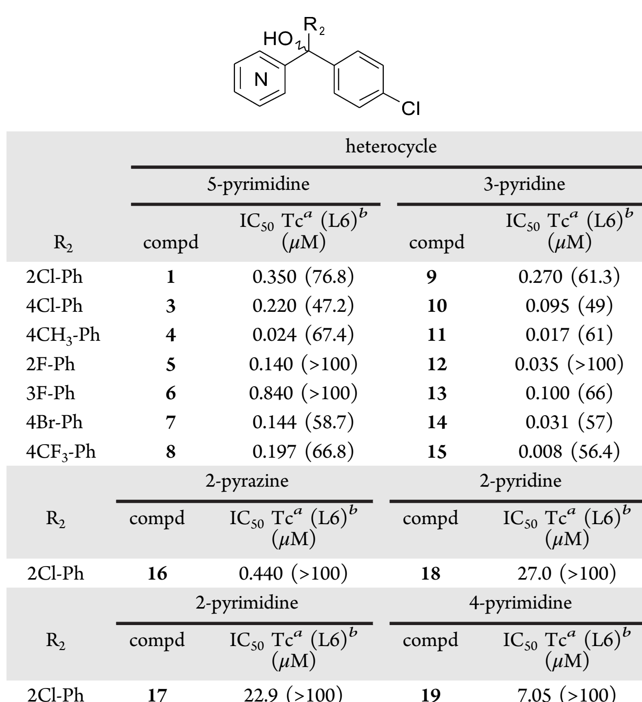
General method A: 1. $SOCl_2$, heat (X=Cl) or 2. $(COCl)_2$, DCM, DMF, 0°C (X=Cl) or 3. i. A1 or A2, ii. *N, O*-$NH(OCH_3)(CH_3)$.HCl, NEt_3, DCM, 0°C (X=NH(OCH3)(CH3).
General method B: 1. PhCl, $AlCl_3$, heat or 2. $ArB(OH)_2$, K_2CO_3, POPd, toluene, heat or 3. (Het)ArX, *n*-BuLi, Et_2O, THF, -78°C.
General method C: (Het)ArX, *n*-BuLi, Et_2O, THF, -78°C.
General method D: $K_4[Fe(CN)_6].3H_2O$, $Pd(OAc)_2$, Na_2CO_3, DMA, heat
General method E: AcOH, $SnCl_2$, c.HCl, heat
General method F: i. $SOCl_2$, toluene, heat, ii, nucleophile (R_3), base, solvent

(rat myoblasts from skeletal muscle) used as a counter screen. No significant cytotoxicity was observed for any of the compounds, with a minimum selectivity index for *T. cruzi* over cell toxicity of ca. 100-fold increasing to >500-fold for the most highly optimized analogues.

Structure−Activity Relationship (SAR). The three aromatic components of **1** (Scheme 1) naturally lent themselves to separate domains for variation in the SAR investigations: (i) 5-pyrimidyl (heterocycle), (ii) 4-chlorophenyl (R_1), and (iii) 2-chlorophenyl (R_2), and the importance of the hydroxyl substituent (R_3) was also investigated.

Variation of the Heterocycle. Keeping R_1 as 4-chlorophenyl and making simple substitutions to R_2, the impact of the heterocycle on activity was explored (Table 1).

Table 1. SAR Study of Heterocycle Moiety with Some Variation of R_2



	heterocycle			
	5-pyrimidine		3-pyridine	
R_2	compd	IC_{50} Tc[a] (L6)[b] (μM)	compd	IC_{50} Tc[a] (L6)[b] (μM)
2Cl-Ph	**1**	0.350 (76.8)	**9**	0.270 (61.3)
4Cl-Ph	**3**	0.220 (47.2)	**10**	0.095 (49)
$4CH_3$-Ph	**4**	0.024 (67.4)	**11**	0.017 (61)
2F-Ph	**5**	0.140 (>100)	**12**	0.035 (>100)
3F-Ph	**6**	0.840 (>100)	**13**	0.100 (66)
4Br-Ph	**7**	0.144 (58.7)	**14**	0.031 (57)
$4CF_3$-Ph	**8**	0.197 (66.8)	**15**	0.008 (56.4)
	2-pyrazine		2-pyridine	
R_2	compd	IC_{50} Tc[a] (L6)[b] (μM)	compd	IC_{50} Tc[a] (L6)[b] (μM)
2Cl-Ph	**16**	0.440 (>100)	**18**	27.0 (>100)
	2-pyrimidine		4-pyrimidine	
R_2	compd	IC_{50} Tc[a] (L6)[b] (μM)	compd	IC_{50} Tc[a] (L6)[b] (μM)
2Cl-Ph	**17**	22.9 (>100)	**19**	7.05 (>100)

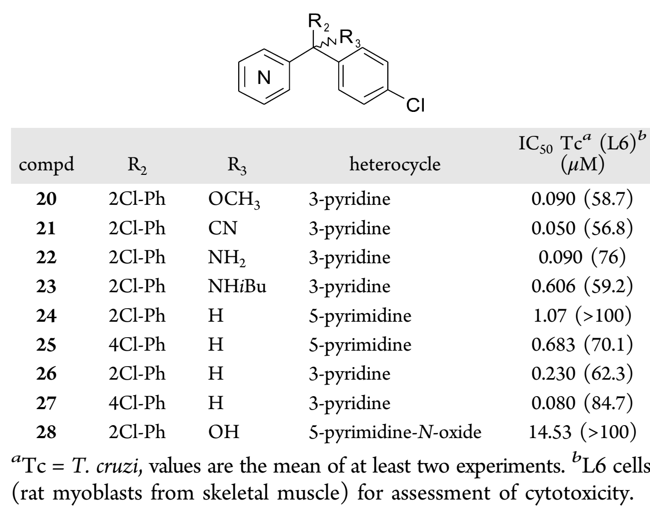
[a]Tc = *T. cruzi*, values are the mean of at least two experiments. [b]L6 cells (rat myoblasts from skeletal muscle) for assessment of cytotoxicity.

It was clear from the data that replacement of 5-pyrimidine with 3-pyridine led to significant improvements in potency (compounds **9**, **10**, and **12−15**), with activity reaching low nM values with R_2 as 4-trifluoromethylphenyl (**15**). Pyrazine analogue **16** was equipotent with **1**, while analogues **18−19** indicated a nitrogen in the 3-position was necessary for activity. Compound **9** was taken forward as the comparator compound for further optimization.

Compounds prepared containing a selection of heterocycles other than pyridine, pyrimidine, and pyrazine such as quinoline, indole, isoxazole, furan, thiophene, and triazole were notably less active (IC_{50} > 1 μM) or inactive (IC_{50} > 10 μM). This result is consistent with *T. cruzi* CYP51 inhibition as the probable mode of action for this series analogous to azole antifungals like posaconazole. Consequently, an optimally placed, sterically unencumbered heme-iron binding atom such as nitrogen is crucial for activity.

Hydroxyl SAR (R_3). Keeping R_1 as 4-chlorophenyl and once more making simple substitutions to R_2, manipulation of R_3 to incorporate methoxy (**20**), nitrile (**21**), and amine (**22**) groups yielded compounds more active than **9**, but these changes were of no particular physicochemical or pharmacokinetic benefit (Table 2). Bulky amine derivative **23** was less active, and R_3

Table 2. SAR Study of R_3 with Some Variation of the Heterocycle and R_2



compd	R_2	R_3	heterocycle	IC_{50} Tc[a] (L6)[b] (μM)
20	2Cl-Ph	OCH_3	3-pyridine	0.090 (58.7)
21	2Cl-Ph	CN	3-pyridine	0.050 (56.8)
22	2Cl-Ph	NH_2	3-pyridine	0.090 (76)
23	2Cl-Ph	NH*i*Bu	3-pyridine	0.606 (59.2)
24	2Cl-Ph	H	5-pyrimidine	1.07 (>100)
25	4Cl-Ph	H	5-pyrimidine	0.683 (70.1)
26	2Cl-Ph	H	3-pyridine	0.230 (62.3)
27	4Cl-Ph	H	3-pyridine	0.080 (84.7)
28	2Cl-Ph	OH	5-pyrimidine-*N*-oxide	14.53 (>100)

[a]Tc = *T. cruzi*, values are the mean of at least two experiments. [b]L6 cells (rat myoblasts from skeletal muscle) for assessment of cytotoxicity.

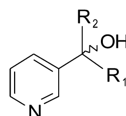
equal to fluorine was relatively unstable and readily hydrolyzed back to the starting alcohol. Removal of the hydroxyl group (R_3 = H) reduced activity by 3-fold for pyrimidinyl analogues **24** and **25**, while activity of the pyridyl analogues **26** and **27** was not affected. *N*-Oxide **28** was significantly less active than **1**, emphasizing the important binding interaction of the nitrogen atom.

Variation of R_1. Maintaining R_2 as 2-chlorophenyl and varying R_1 gave compounds as much as 10-fold less active than **9** (data not shown), and we quickly moved on from this area of the SAR.

Variation of R_2. The R_2 SAR study, keeping variations of R_1 to a minimum, was very productive and revealed clear SAR trends (Table 3). An electronic effect on activity was not evident following monosubstitution at 3- and 4-positions of R_2, with methoxy, bromo, and nitrile analogues (entries **30**, **31**, **37**, **14**, **41**, and **42**) spanning only a 2−3-fold potency range. Introduction of lipophilic substituents to the *para* position of R_2 was very beneficial, with 4-*i*-propoxy (**34**), -trifluoromethyl (**15**), -dimethylamino (**51**), and -*i*-propyl (**52**) analogues achieving activities in the low nM range. Interestingly, 4-nitrile analogue **43** was also highly active, contradicting the lipophilicity for activity enhancement trend, and the relatively good activity of 3-amido analogue **46** was also somewhat surprising given the more hydrophilic nature of this molecule. Activity was improved by introduction of a 2-fluoro substituent for some analogues such that 2,4-disubstituted analogues (e.g., compounds **44**, **45**, **54**, and **60**) were up to 10-fold more active than the *des*-fluoro comparator compounds, but this was not observed in all cases (compounds **47** and **56**). A certain amount of mixing and matching was required for optimal combinations of substituents to give the most active compounds as exemplified by **44** and **60** (1−2 nM). Symmetrical analogues **61−63** did not give additive potency effects, reinforcing the distinction in the binding interactions for R_1 and R_2.

The low nM in vitro activity of the most highly optimized analogues in Table 3 compared favorably to structurally

Table 3. SAR Study of R_2 with Some Variation of R_1



compd	R_1	R_2	IC_{50} Tc[a] (L6)[b] (μM)	compd	R_1	R_2	IC_{50} Tc[a] (L6)[b] (μM)
29	4Cl-Ph	$2CH_3$-Ph	0.370 (82)	**45**	4Cl-Ph	2F, 4Cl-Ph	0.010 (59.4)
11	4Cl-Ph	$4CH_3$-Ph	0.017 (61.2)	**46**	4Cl-Ph	$3CONH_2$-Ph	0.030 (>100)
30	4Cl-Ph	$3OCH_3$-Ph	0.060 (85.6)	**47**	2F, 4Cl-Ph	$3CONH_2$-Ph	0.025 (>100)
31	4Cl-Ph	$4OCH_3$-Ph	0.040 (68.1)	**48**	$4CF_3$-Ph	$3CONH_2$-Ph	0.070 (>100)
32	4Cl-Ph	2O*i*Pr-Ph	0.446 (48.3)	**49**	$4CF_3$-Ph	$4CONH_2$-Ph	0.120 (>100)
33	4Cl-Ph	3O*i*Pr-Ph	0.082 (67.6)	**50**	4Cl-Ph	$4NHSO_2Me$-Ph	0.030 (>100)
34	4Cl-Ph	4O*i*Pr-Ph	0.002 (56.6)	**51**	$4CF_3$-Ph	$4NMe_2$-Ph	0.006 (59.1)
35	$4CF_3$−Ph	4O*i*Pr-Ph	0.004 (47.6)	**52**	$4CF_3$-Ph	4*i*Pr-Ph	0.002 (56.3)
36	4Cl-Ph	2Br-Ph	0.070 (55.2)	**53**	4Cl-Ph	2,4F-Ph	0.016 (70.2)
37	4Cl-Ph	3Br-Ph	0.054 (54.1)	**54**	$4CF_3$-Ph	2F, 4Cl-Ph	0.002 (>100)
14	4Cl-Ph	4Br-Ph	0.031 (57)	**55**	4Cl-Ph	2F, $4CF_3$-Ph	0.021 (57.4)
38	$4CF_3$-Ph	4Br-Ph	0.020 (54.7)	**56**	4Cl-Ph	2F, 4Br-Ph	0.026 (79.2)
39	4Cl-Ph	$2CF_3$-Ph	0.120 (59.3)	**57**	4Cl-Ph	2F, 4O*i*Pr-Ph	0.026 (58.2)
40	4Cl-Ph	$3CF_3$-Ph	0.070 (60.4)	**58**	4Cl-Ph	2F, 4CN-Ph	0.026 (>100)
15	4Cl-Ph	$4CF_3$-Ph	0.008 (56.4)	**59**	4O*i*Pr-Ph	2F, $4CH_3$-Ph	0.003 (62.6)
41	4Cl-Ph	3CN-Ph	0.110 (>100)	**60**	4O*i*Pr-Ph	2F, 4Cl-Ph	0.001 (56)
42	4Cl-Ph	4CN-Ph	0.070 (>100)	**61**	4O*i*Pr-Ph	4O*i*Pr-Ph	0.016 (61.4)
43	$4CF_3$-Ph	4CN-Ph	0.012 (76.5)	**62**	$4CF_3$-Ph	$4CF_3$-Ph	0.015 (50.6)
44	$4CF_3$-Ph	2F, 4CN-Ph	0.002 (56.1)	**63**	2F, 4Cl-Ph	2F, 4Cl-Ph	0.016 (56.3)

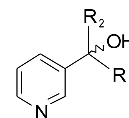
[a]Tc = *T. cruzi*, values are the mean of at least two experiments. [b]L6 cells (rat myoblasts from skeletal muscle) for assessment of cytotoxicity.

complex benchmark *T. cruzi* CYP51 inhibitor posaconazole (IC_{50} 0.7nM) and was superior to benznidazole (IC_{50} 1.15 μM).

Heterocyclic variations of R_2 (Table 4) gave active compounds, although activity decreased with increasing polarity of the heterocyclic ring. Thiophene and benzothiophene analogues (**64**−**67**) were more active than thiazole analogues **68** and **69**, although the activity of the latter compound could be increased by a 2-amido group (**71**) but decreased on addition of a 2-chloro substituent (**72**). The weak activity of pyrimidyl analogue **73** was improved by addition of key substituents identified from the R_2 phenyl SAR studies (Table 3) such that the addition of an *i*-propoxyl group to R_2 (**75**) and a 2-fluoro substituent to R_1 (**76**) made a significant impact on activity.

Pharmacokinetic Properties. Throughout the activity optimization process, we were mindful of preparing compounds with good pharmaceutic and pharmacokinetic properties to facilitate compound profiling in vivo in *T. cruzi* mouse models. As a result, we may not have fully exploited the potential for activity enhancement obtained from making R_2 increasingly lipophilic, cutting short SAR leads that resulted in high in vitro metabolism for example. Table 5 summarizes the in vitro microsomal metabolism, solubility at pH 6.5, and inhibition of cytochrome P450 3A4/5 (CYP3A4/5) in human liver microsomes of lead compounds from the SAR studies. Compounds were typically found to have low to moderate solubility and moderate to high rates of metabolism in human and rat liver microsomes. The high stability in microsomes and good solubility of compound **73** was the basis for our interest in pursuing the SAR of this molecule. An *i*-propoxyl moiety proved to be a metabolic liability across several analogues (**34**, **60**, and **76**), while compounds **43**−**45** and **54** were of specific interest given the low nM activity coupled with more moderate metabolic stability. Likewise, primary amide analogue **46** was relatively stable in hepatic microsomes with greatly improved solubility.

Table 4. SAR Study of R_2 (Heterocycles) with Some Variation of R_1



compd	R_1	R_2	IC_{50} Tc[a] (L6)[b] (μM)
64	4Cl-Ph	2-thiophene	0.013 (67.7)
65	2F, 4Cl-Ph	2-thiophene	0.005 (>100)
66	4Cl-Ph	3-thiophene	0.078 (>100)
67	$4CF_3$-Ph	2-benzothiophene	0.020 (58.7)
68	4Cl-Ph	2-thiazole	0.201 (>100)
69	4Cl-Ph	5-thiazole	0.140 (>100)
70	4Cl-Ph	$(2NH_2)$-5-thiazole	0.260 (56)
71	4Cl-Ph	(2NHCO*i*Pr)-5-thiazole	0.021 (56.6)
72	4Cl-Ph	(2Cl)-5-thiazole	0.490 (>100)
73	4Cl-Ph	5-pyrimidine	1.53 (>100)
74	4O*i*Pr-Ph	2Cl-5-pyrimidine	0.304 (>100)
75	4Cl-Ph	2O*i*Pr-5-pyrimidine	0.060 (>100)
76	2F, 4Cl-Ph	2O*i*Pr-5-pyrimidine	0.008 (89.5)

[a]Tc = *T. cruzi*, values are the mean of at least two experiments. [b]L6 cells (rat myoblasts from skeletal muscle) for assessment of cytotoxicity.

4-Trifluoromethyl was a particularly desirable substituent providing a measurable increase in metabolic stability while maintaining excellent potency (compounds **43**, **44**, and **54**), and for later compounds R_1 was fixed as a 4-trifluoromethylphenyl motif. Apart from the generally poor to moderate aqueous solubility at pH 6.5, all of the compounds had predicted physicochemical characteristics suggesting they should have no significant permeability limitations in vivo. The inhibition of CYP3A4/5

Table 5. Representative In Vitro Metabolism and Solubility Data for 1 and Analogues

compd	metabolism[a] E_H (h)	E_H (r)	solubility[b] (μg/mL)	CYP3A4/5 (IC_{50} μM)
1	0.82	0.62[c]	12.5−25	66% at 20 μM
9	0.83	0.81	3.1−6.3	0.6
34	0.89	0.88	1.6−3.1	1.9
35	0.87	0.91	1.6−3.1	1.4
43	0.5	0.5	6.3−12.5	7.6
44	0.64	0.67	6.3−12.5	4.1
45	0.39	0.58	1.6−3.1	0.9
46	0.2	0.48	50−100	2.6
47	<0.2	0.45	50−100	3.9
54	0.54	0.44	<1.6	1.4
60	0.9	0.95	1.6−3.1	1.1
73	0.27	0.37	>100	5
76	0.69	0.88	12.5−25.0	4.4
posaconazole	0.42	<0.2	3.1−6.3	98% at 20 μM

[a]Microsome predicted hepatic extraction ratio (E_H) determined in human (h) and rat (r) liver microsomes. [b]Kinetic solubility at pH 6.5 determined by nephelometry. [c]E_H value for mouse liver microsomes

has significant ramifications for adopting a combination therapy approach as a means to treat Chagas disease, a strategy widely favored to prevent drug resistance. Lead compounds in the fenarimol series demonstrated moderate activity at this enzyme, with good separation from activity against *T. cruzi* in vitro and significantly improved *T. cruzi*:CYP3A4/5 activity ratios relative to benchmark compound posaconazole, a very potent inhibitor of CYP3A4/5.

The in vivo pharmacokinetic properties of selected lead compounds were studied in noninfected, male Swiss Outbred mice following a single oral dose of up to100 mg/kg. The overall trend for oral exposure was in line with the microsomal metabolic stability data, such that compounds with predicted high hepatic extraction ratios appeared to be more rapidly cleared in vivo. **46** and **47** showed the highest maximum plasma concentrations after oral administration, which is consistent with them being among the least lipophilic and most soluble of the selected compounds at intestinal pH. **73** which appeared to have the highest solubility achieved only low plasma concentrations in vivo (Table 6). As the discovery program evolved, it was evident that extended (greater than 24 h) plasma exposure was an important determinant of in vivo efficacy and the compounds which showed good efficacy had plasma concentrations several-fold higher than their respective in vitro IC_{50} values at 24 h postdose. Indeed, 24 h plasma concentrations for the in vivo benchmark compound, posaconzole, were more than 400 times higher than the in vitro IC_{50} at 24 h postdose (20 mg/kg). In rats, the blood clearances of **43**, **46**, and **76** after intravenous (IV) administration correlated well with the in vitro data in rat liver microsomes. After oral administration, **46**, which had the highest solubility and lowest blood clearance of the three compounds, showed the highest bioavailability of 95%, whereas **76**, with moderately low aqueous solubility and high blood clearance, had a bioavailability of only 7% (Table 7).

In Vivo Efficacy. The in vivo efficacy of compounds possessing good oral exposure and high in vitro potency was evaluated in an in-house model of Chagas disease. In this model, compounds are investigated for their ability to reduce blood parasitemia levels in mice arising from an established *T. cruzi* infection derived from a sublethal dose of 25000 bloodstream forms of *T. cruzi* (TcVI; Tulahuén strain). Test compounds were administered once daily starting on day 8 post infection (pi), with posaconazole and vehicle-only treated groups included as controls.[24]

Five-Day Dosing Model. As a first indicator of in vivo efficacy, compounds **1** and **46** were dosed once daily at 100 mg/kg for 5 days (Table 8). While the activity of **1** was relatively weak, **46** demonstrated good efficacy following oral dosing and successfully decreased blood parasitemia to virtually

Table 6. Plasma Concentrations in Mice Following Oral Administration

compd	dose (mg/kg)	C_{1h}[a] (μM)	C_{8h}[a] (μM)	C_{24h}[a] (μM)
1	20	2.1	0.08	ND
34	100	9.6	0.6	ND
43	20	2.5	0.4	0.03
	50	11.8	3.6	0.25
44	20	1.4	0.3	0.05
46	10	6.8	0.4	ND
	20	10.3	1.9	ND
	50	13.7	15.9	0.06
	100	19.5	6.5	ND
47	20	10.5	0.44	0.006
54	20	1.24	0.23	0.003
73	20	0.3	<LLQ	ND
posaconazole	20	6.3	13.6	2.9
	50	6.4	11.1	3.8

[a]$C_{1h, 8h, 24h}$, = compound concentration in mouse plasma at 1 h, 8 h and 24 h, respectively; ND = not determined; <LLQ = less than the analytical limit of quantitation (0.002 μM)

Table 7. Pharmacokinetic Parameters in Rats Following Intravenous (IV) and Oral Administration

compd	IV dose (mg/kg)	half-life[a] (h)	blood CL[b] (mL/min/kg)	V_{ss}[c] (L/kg)	oral dose (mg/kg)	bioavailability[d] (%)
43	5.2	5.1	24.4	5.7	17.6	68.1
46	4.2	6.1	18.9	3.6	15.2	95.0
76	4.8	11.3	73.9	9.1	15.7	7.4

[a]Elimination half-life. [b]Blood clearance. [c]Apparent volume of distribution at steady state. [d]estimated by calculating and comparing the average dose-normalized $AUC_{0\text{-inf}}$ after oral administration to the average dose-normalized $AUC_{0\text{-inf}}$ after IV administration

Table 8. In Vivo Efficacy of Selected Compounds in *T. cruzi* Infected Mice after 5-Day Dosing

compd	dose[a] (mg/kg)	days	route[b]	survival[c]	parasitemia reduction[d] (%)
1	100	5	ip	5/5	80
46	100	5	po	4/5	>95
46	50	5	po	5/5	65
46	20	5	po	5/5	0
posaconazole	50	5	po	3/5	100
posaconazole	10	5	po	4/4	100
posaconazole	2	5	po	4/4	100

[a]Once daily. [b]ip = intra peritoneal injection; po = per os (oral administration). [c]Survival is indicated by (number of mice surviving)/(total number infected and treated). [d]Percentage efficacy calculated by: ([av parasitemia vehicle group − av parasitemia treated group)/av parasitemia vehicle group] × 100%).

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Table 9. In Vivo Efficacy of Selected Compounds in *T. cruzi* Infected Mice after 20-Day Dosing

compd	dose[a] (mg/kg)	days	route[b]	survival[c]	parasitemia reduction[d] (%)	no. of cycles of immunnosuppression before parasite rebound[e]
43	20	20	po	4/5	>99	rebound after 3 cycles
benznidazole	100	20	po	5/5	>99	rebound after 3 cycles
posaconazole[f]	20	20	po	14/15	>99	parasite free after 3 cycles (8/14) "CURE" (5/8)[g]

[a]Once daily. [b]po = per os (oral administration). [c]Survival is indicated by (number of mice surviving)/(total number infected and treated). [d]Percentage efficacy calculated by: ([av parasitemia vehicle group − av parasitemia treated group)/av parasitemia vehicle group] × 100%). [e]One cycle of immunosuppression = treatment with 50 mg/kg/day cyclophosphamide for 4 days, followed by 3 days rest. [f]Combined results from three separate experiments. [g]"CURE" confirmed by PCR of tissue samples.

undetectable levels (>95% inhibition) after five doses. Additional experiments with 50 and 20 mg/kg doses of **46** proved to be less effective and inactive, respectively, indicating a dose-dependent response.

Posaconazole was more effective than **46**, efficiently clearing parasites from the blood even at low doses (2 mg/kg).

Ten-Day Dosing Model. Compound dosing was extended to 10 days to determine if efficacy could be improved with a longer treatment time. Mice were treated once daily for 10 days with a 50 mg/kg oral dose of compound **43**, which successfully decreased parasitemia to undetectable levels in blood by the end of the treatment period. The experiment was extended into a further 10 day rest period (no compound administered) to allow for parasites in tissues to re-enter the blood from sanctuary sites. Analysis of blood samples on day 21 after this rest period indicated mice were still (apparently) parasite free.

To determine if parasites were fully cleared from organs, the experiment was taken further into a subchronic phase and animals were immunosuppressed on treatment with cyclophosphamide (one treatment cycle = 4 days cyclophosphamide at 50 mg/kg/day followed by 3 days rest)[25] to further facilitate the return of any existing parasites into blood following withdrawal of immune control.

In this very stringent form of the assay, parasites were observed in the blood of mice treated with **43** after two cycles of immunosuppression indicating a 50 mg/kg/day 10 day oral treatment of **43** had not fully cleared all parasites from sanctuary sites and thus had not "cured" the mice. Nonetheless, the efficacy of **43** was very encouraging and compared favorably to a 20 mg/kg/day 10 day oral treatment of benchmark compound posaconazole, for which parasite rebound was also observed after the second cycle of immunosuppression.

Twenty-Day Dosing Model. In a final optimization of the model, infected mice were treated with compound once daily for 20 days, left to rest for 10 days (no compound administered), and if parasites were undetectable in blood, animals were immunosuppressed for a maximum of three cycles (as described above). Table 9 illustrates the outcome of the treatment of infected mice under this regimen.

Lead compound **43** performed well under these stringent conditions, and following a 20 mg/kg/day oral dose of **43** for 20 days, parasites were not observed in blood until after the third cycle of immunosuppression had been completed. A 100 mg/kg/day treatment with benznidazole demonstrated the same level of efficacy as 20 mg/kg/day of **43**. The results reported for posaconazole are combined from three separate 20 day dosing experiments. A combined total of 8/14 mice treated with 20 mg/kg of posaconazole daily for 20 days remained parasite-free after the full course of immunosuppression (3 cycles), but only 5/8 of these animals were deemed "cured", i.e., negative for parasites in organs as confirmed by PCR of tissue samples (not shown).[26] The inconsistent ability of a clinical benchmark compound to demonstrate "cure" highlights how difficult it is to model the chronic form of infection in the laboratory.

Even though "cure" was not achieved with compound **43** in this model, the level of efficacy demonstrated in such a stringent test of in vivo efficacy is very promising. The low dose of **43** required for parasite suppression showed similar efficacy to a much higher dose of current drug therapy benznidazole, and in contrast to posaconazole, the synthetic tractability of the series meets the "low cost of goods" criteria relevant to drugs produced in a "not-for-profit" environment. Follow-up compounds are in preparation.

CONCLUSION

Fenarimol, a nontoxic fungicide, was identified as a moderately potent inhibitor of *T. cruzi* during a targeted screening exercise to find hits for a drug discovery program aimed at developing new treatments for Chagas disease. Subsequent SAR investigations led to the preparation of very active, low nM *T. cruzi* inhibitors easily prepared in multigram quantities in five steps or fewer in racemic form. The inclusion of routine physicochemical and pharmacokinetic profiling as part of the optimization cycle facilitated rapid identification of compounds suitable for profiling in mouse models of *T. cruzi* infection. Compound **43** was efficacious in a stringent model of established infection, suppressing parasitemia to negligible levels after daily oral dosing at 20 mg/kg/day for 20 days, with parasite rebound in blood only occurring after mice were subjected to three cycles of immunosuppression. This efficacy was matched by a much higher dose of Chagas disease standard of care benznidazole. Compounds in the fenarimol series represent an exciting addition to the Chagas drug discovery landscape, and further optimization is ongoing.

EXPERIMENTAL SECTION

Posaconazole was purchased as the oral suspension (Noxafil Schering Corporation, 40 mg/mL). For in vivo efficacy and pharmacokinetic studies, the oral suspension was diluted to the appropriate concentration with water. For in vitro studies, posaconazole was first isolated from the suspension by dilution with water and centrifugation, followed by extraction and recrystallization from hot *i*-propyl alcohol.

Biology: In Vitro *T. cruzi* Assay for Determination of IC_{50}. This assay uses *T. cruzi* Tulahuén trypomastigotes expressing the *β*-galactosidase gene, obtained from Dr Fred Buckner (University of Washington) and using their published protocol.[19] The parasites were maintained in vitro by serial passage in L6 cells. Briefly, L6 cells were plated into 96 well, flat-bottom tissue culture plates and incubated at 37 °C in 5% CO_2 for 24 h to allow cells to adhere. *T. cruzi* trypomastigotes were then added at a multiplicity of infection of 3, and plates were incubated for a further 48 h to allow infection to establish. All steps were carried out using RPMI media 1640 (without phenol red) supplemented with 10% Foetal Bovine Serum (FBS, Bovogen).

Extracellular trypomastigotes were then removed and compounds were added in seven-point serial dilutions performed in triplicate. Benznidazole (Epichem Pty Ltd.) was included as a control. After 96 h of incubation with the compounds, the colorimetric agent, chlorophenol red-ß-D-galactopyranoside (CPRG, Roche) was added with 0.3% v/v Nonidet P-40. After 4−6 h, a color change following catabolization of the reagent by viable *T. cruzi* was observed and absorbance was read at 530 nm using a Dynex microplate reader. The % inhibition was calculated by the following equation: %inhib = 100 − [(*T. cruzi* with compound − compound only)/(*T. cruzi* only − media only)] × 100. For each compound, % inhibition values were used to generate a standard curve from which the IC_{50} was calculated. Each assay was performed at least twice, and the average was used.

In Vitro Assay for Determination of Cytotoxicity. L6 cells were cultured in RPMI 1640 supplemented with 10% FBS in 96-well flat bottom tissue culture plates. Dose−response curve analysis was conducted by using seven-point serial dilutions performed in triplicate to determine an IC_{50} value. Cells were exposed to test compounds for 72 h in total. Podophyllotoxin was included in all assays as a control, and each assay was performed at least twice to obtain an average IC_{50} value. Alamar Blue (AbD Serotec) was added to the plates, allowing for a color change through metabolic oxidation−reduction by proliferating cells, and absorbance was read on a Dynex microplate reader at 570 and 630 nm.

In Vivo Pharmacokinetic Studies. Pharmacokinetic studies in mice and rats were performed in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes, and the study protocols were approved by the Monash Institute of Pharmaceutical Sciences Animal Ethics Committee.

The systemic exposure of compounds **1**, **34**, **43**, **44**, **46**, **47**, **54**, **73**, and posaconazole was studied following oral administration in nonfasted male Swiss Outbred mice weighing 23.8−39.9 g. Mice had access to food and water continuously throughout the pre- and postdose phases of the study. Compounds were administered orally by gavage as either a solution or suspension in an aqueous vehicle (0.2 mL dose volume per mouse). At predefined time points, blood samples were collected from mice (n = 1−3 mice per time point for each compound) via either submandibular-bleed (conscious sampling) or terminal cardiac puncture (following anaesthetization with gaseous isofluorane). Blood was transferred to heparinized tubes containing a stabilization cocktail (Complete inhibitor cocktail, potassium fluoride, and EDTA) to minimize the potential for ex vivo degradation of compound. Samples were immediately centrifuged to collect plasma for analysis as described below.

The pharmacokinetics of **43**, **46**, and **76** were also assessed in overnight fasted male Sprague−Dawley rats weighing 272−320 g after both intravenous (IV) and oral administration. Rats had access to water ad libitum throughout the pre- and postdose sampling period, and access to food was reinstated 4 h postdose. Compounds were administered intravenously in an aqueous solution vehicle as a 10 min constant rate infusion into the jugular vein (1.0 mL per rat, n = 2 rats for each compound) and orally by gavage as an aqueous suspension (1.0 mL per rat, n = 2 rats per compound). Samples of arterial blood were collected up to 24 h postdose via an in-dwelling carotid cannula. Blood was collected directly into heparinized tubes containing stabilization cocktail as described above and maintained at 4 °C. At the end of the collection period, samples were centrifuged to collect plasma for analysis.

Quantitative analysis of each compound in plasma was conducted by LC-MS (on either a Micromass Quattro Premier, Micromass Xevo TQ, or Micromass Quattro Ultima PT coupled to an Acquity UPLC; all from Waters Corporation, Milford, MA) against calibration standards prepared in blank plasma from the respective species. Both samples and standards were prepared by precipitation with acetonitrile, followed by centrifugation and analysis of the supernatant. The analytical lower limit of quantitation for each compound in plasma ranged from 0.001 to 0.015 μM.

Intravenous (IV) and oral pharmacokinetic parameter estimation for **43**, **46**, and **76** in rats were conducted using noncompartmental methods. WinNonlin software (version 5.2.1, Pharsight Corporation, Mountain View, CA) was utilized for estimation of the terminal elimination half-life ($t_{1/2}$), the area under the plasma concentration versus time profile extrapolated to infinity (AUC_{0-inf}), plasma clearance, and volume of distribution at steady state (V_{dss}). The blood clearance (CL) was estimated by dividing the plasma clearance by the blood to plasma ratio determined in vitro. The oral bioavailability was estimated by comparing the average dose-normalized AUC_{0-inf} after oral administration to the average dose-normalized AUC_{0-inf} after IV administration.

In Vivo Anti-*T. cruzi* Activity. *Mice.* Outbred, female Swiss mice approximately 8 weeks old were obtained from the Animal Resources Centre (Perth, Western Australia). All animal experimentation was carried out with approval of the Animal Ethics Committee of Murdoch University.

Generation of T. cruzi Parasites. *T. cruzi* parasites (Tulahuén strain) were kindly donated by Dr Vanessa Yardley (LSTMH, UK) and passaged through adult female Swiss mice to maintain virility. Trypomastigote-infected blood was collected and frozen in liquid nitrogen for subsequent infections in mice.

Preparation of Compounds for Dosing. Compounds were suspended in either a hydroxypropylmethylcellulose suspension vehicle (HPMC-SV; 0.5% w/v hydroxypropylmethylcellulose + 0.4% v/v Tween 80 + 0.5% v/v benzyl alcohol in deionized H_2O) and given by oral gavage (**43**, **46**, posaconazole, and benznidazole) or in a phosphate-buffered saline-based vehicle (PBS + 0.4% v/v Tween 80 + 10% v/v polyethylene glycol 400 (PEG400)) and administered by intraperitoneal (ip) injection (**1**). Posaconazole (Noxafil) was diluted to the required concentration using Water for Injection (WFI) for administration by oral gavage.

In Vivo Toxicity Testing. Compounds were first screened in an in vivo mouse toxicity assay before evaluation for efficacy in the *T. cruzi* subchronic infection model. For toxicity testing, compounds were solubilized in test vehicle at concentrations of 15 mg/mL. Two mice were used to assess each compound, with each mouse receiving a cumulative dose of up to 600 mg/kg over a period of 48 h. This represents the maximum level of compound which would be administered to an animal over the course of efficacy testing. Animals were monitored closely during the treatment period and for an additional week following the last treatment dose for signs of compound-induced toxicity. Specific criteria monitored included body weight, condition, activity, and hydration. If no adverse effects were observed, compounds were deemed nontoxic and were progressed to in vivo efficacy testing.

In Vivo Efficacy Testing. Induction of acute *T. cruzi* infection was obtained by infecting mice with 25000 trypomastigote forms of *T. cruzi* Tulahuén strain via ip injection. Five mice per group were tested for each compound and dosage. Compound administration was commenced on Day 8 post infection (pi) and continued daily for 5, 10, or 20 days. Parasitemia was determined by collection of blood by tail prick on days 8 (prior to dosing), 9, 12, 14, 16, 19, and 27 pi and counting live trypomastigotes under the microscope using a Neubauer hemocytometer. Red blood cells were lysed from the samples for ease of counting using Red Cell Lysing Buffer (Sigma). Efficacy was determined by comparison of parasitemia levels in compound treated groups to the vehicle only group, and the percentage efficacy was calculated by: ([av parasitemia vehicle group − av parasitemia treated group)/av parasitemia vehicle group] × 100%). [Note: in some cases % could not be calculated, e.g., during extended dosing where vehicle group does not survive.] If parasitemia levels were no longer detectable in the blood following compound treatment, animals were immunosuppressed to eliminate the possibility of parasitemia being harbored in tissues/organs. Cyclophosphamide-induced immunosuppression was commenced 10 days after cessation of dosing. Cyclophosphamide was administered ip at 50 mg/kg per day in three cycles; each cycle comprised 4 days treatment followed by 3 days rest.[25] Parasitemia was determined by collection of blood by tail prick as detailed above. As a final measure, the absence of parasites from organs was confirmed by conducting PCR on tissue samples; those samples that were negative for *T. cruzi* DNA were designated as a "cure".[26]

Chemistry. Reagents were purchased from commercial suppliers and used without further purification. Commercially available anhydrous solvents were used and stored under nitrogen unless indicated otherwise. Reactions involving moisture sensitive reagents were conducted under an atmosphere of dry nitrogen in glassware dried with a heat gun. Thin layer chromatography (TLC) using silica gel Merck 60 F_{254} plates and detection with UV light was used to monitor reactions. ^{1}H NMR spectra were recorded in $CDCl_3$, CD_3OD, or DMSO-d_6 solutions on a Varian 200, Bruker 300, or Varian 400 MHz machine. Chemical shifts are reported in parts per million (δ) downfield of tetramethylsilane (TMS). GC-MS were aquired on an Agilent 5973 network machine. LC-MS were acquired on an Applied Biosystems/MDS Sciex API-2000 system. Flash chromatography was carried out with silica gel (0.04−0.06 μm, 230−400 mesh), reverse phase silica gel (C_{18} 35−70 μm), or on a Flashmaster II system using cartridges prepared in-house. Microwave irradiations were conducted using a Biotage initiator. All compounds tested in the in vitro and in vivo biological screens were purified to ≥95% purity as determined by analysis of HPLC on an Agilent 1100 series machine, fitted with a C_8 reverse phase Agilent zorbax eclipse DB-LB 4.6 mm × 150 mm 5 μm column (Flow rate 1.2 mL/min. Method 1: 20% acetonitrile in water, increasing to 60% acetonitrile over 10 min. Method 2: 50% acetonitrile in water increasing to 90% acetonitrile over 10 min. Method 3: 70% acetonitrile in water increasing to 95% acetonitrile over 10 min.). ^{1}H NMR spectra (accounting for noncompound peaks and residual solvent) and LC-MS. Fenarimol [60168-88-9] (**1**) and Pyrifenox [88283-41-4] (**2**) were purchased from commercial sources.

Synthesis of Compounds. *General Method C: Triarylcarbinol Formation by Aryl Lithium Addition to Benzophenone. Pyrimidine.* A 50 mL three-necked round-bottom flask equipped with a low temperature thermometer, a gas adapter, and a suba seal and was charged with the benzenophenone (1 equiv, 2.3 mmol) and 5-bromopyrimidine (1 equiv, 2.3 mmol) dissolved in dry tetrahydrofuran (10 mL). The reaction was cooled below −80 °C with an ether/dry ice bath under an atmosphere of nitrogen. To this was added portionwise via syringe *n*-butyllithium (1.1 equiv of a 1.6 M solution in hexanes), maintaining an internal temperature of −80 °C over 2.5 h. After addition was complete, the reaction was stirred at −80 °C for 1 h and then slowly warmed to room temperature and stirred overnight. The reaction was quenched with ammonium chloride and extracted with ethyl acetate (2 × 50 mL), and the organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure.

Pyridine. A 100 mL three-necked round-bottomed flask was charged with 3-bromopyridine (3.16 mmol, 1 equiv), and dry diethyl ether (30 mL) was added. The solution was cooled to −78 °C, and *n*-butyllithium (1.6 equiv of a 1.6 M solution in hexanes) was added and the mixture stirred at −78 °C for 2 h. A solution of the benzophenone (3.16 mmol, 1 equiv) in dry tetrahydrofuran (10 mL) was added dropwise over 5 min, and the resultant mixture was stirred at low temperature for 30 min and then allowed to warm to room temperature and stirred overnight. Water (20 mL) was added and the mixture extracted with ethyl acetate (3 × 30 mL), and the organic extracts were combined and dried over magnesium sulfate, filtered, and concentrated under reduced pressure.

General Method D: Conversion of Aryl Bromide to Aryl Nitrile. A 10 mL round-bottomed flask was charged with the aryl bromide (0.33 mmol, 1 equiv), potassium ferricyanide ($K_4[Fe(CN)_6]\cdot 3H_2O$) (0.66 mmol, 2 equiv), palladium(II)acetate ($Pd(OAc)_2$) (76 μmol, 0.2 equiv), anhydrous sodium carbonate (0.66 mmol, 2 equiv), and anhydrous *N*,*N*-dimethylacetamide (3 mL). The mixture was heated at 130 °C under nitrogen overnight. On cooling, water (50 mL) was added and the mixture extracted with ethyl acetate (50 mL). The aqueous phase was back-extracted with ethyl acetate (30 mL), organic phases combined and washed with water (2 × 50 mL) and a saturated solution of sodium chloride (50 mL), and then dried over magnesium sulfate, filtered, and concentrated under reduced pressure.

General Method E: Dehydroxylation with Stannous Chloride ($SnCl_2$). In a 50 mL round-bottomed flask was added the triaryl carbinol (0.16 mmol, 1 equiv) and glacial acetic acid (0.5 mL). To this solution was added stannous chloride (0.274 mmol, 1.7 equiv), followed by c hydrochloric acid (158 μL). The mixture was heated under reflux for 1 h and then cooled to room temperature and left to stir overnight. The mixture was concentrated to dryness under vacuum to give a crude gum, which was treated with pyridine (2 mL), and the resultant precipitate was filtered and washed with tetrahydrofuran. The filtrate was concentrated under vacuum, dissolved in toluene (50 mL), washed with 10% aqueous hydrochloric acid (10 mL) and water (2 × 20 mL), dried over magnesium sulfate, filtered, and concentrated under vacuum.

General methods were used interchangeably for aryl and heteroaryl analogues and have been depicted in Scheme 1 as either one or the other for clarity. Syntheses of intermediate compounds (**5**−**9**, **13**, **16**, **29**−**31**, **35**−**40**, **47**, **51**, **53**−**54**, **56**, **63**, **67**)**A**[**i**−**iii**], (**4**−**9**, **13**, **16**−**17**, **29**−**31**, **34**−**40**, **47**, **51**−**56**, **63**, **67**)**B**[**i**−**iii**], and **77**−**87** are detailed in the Supporting Information.

*Synthesis of Compounds in Table 1. Bis(4-chlorophenyl)(pyrimidin-5-yl)methanol (**3**).* General method C (pyrimidine) with 4-chlorobenzenophenone (0.5 g, 2.3 mmol), 5-bromopyrimidine (0.369 g, 2.3 mmol), tetrahydrofuran (10 mL), and *n*-butyllithium (1.6 M in hexanes, 1.7 mL, 2.55 mmol). Purification by flash column chromatography (eluting with 20% ethyl acetate in hexanes increasing to 40% ethyl acetate) gave **3** as a white solid (360 mg, 53%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.12 (s, 1H), 8.66 (s, 2H), 7.35 (d, *J* = 8.4 Hz, 4H), 7.18 (d, *J* = 8.4 Hz, 4H), 3.26 (s, 1H). [M + 1] 331.1. HPLC (water/ACN + 0.1% TFA gradient) 98.80% at 230 nm.

*(4-Chlorophenyl)(4-methylphenyl)pyrimidin-5-yl Methanol (**4**).* General method C (pyrimidine) with **4Bi** (0.27 g, 1.15 mmol), 5-bromopyrimidine (0.406 g, 1.84 mmol), dry tetrahydrofuran (10 mL), and *n*-butyllithium (1.6 M in hexanes, 1.43 mL, 1.84 mmol). Purification by flash column chromatography (eluting with 10% ethyl acetate in hexanes increasing to 60% ethyl acetate), followed by trituration with diethyl ether gave **4** as a white solid (118 mg, 33%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.14 (s, 1H), 8.70 (s, 2H), 7.30−7.38 (m, 2H), 7.15−7.26 (m, 4H), 7.06−7.13 (m, 2H), 2.91 (s, 1H), 2.37 (s, 3H). ESI *m*/*z*: 310 (M). HPLC (water/ACN + 0.1% TFA gradient) 95.83% at 230 nm.

*(4-Chlorophenyl)(2-fluorophenyl)pyrimidin-5-yl Methanol (**5**).* General method C (pyrimidine) with **5Bi** (0.269 g, 1.15 mmol), 5-bromopyrimidine (0.406 g, 1.7 mmol), dry tetrahydrofuran (10 mL), and *n*-butyllithium (1.6 M in hexanes, 1.15 mL, 1.7 mmol). Purification by flash column chromatography (eluting with 20% ethyl acetate in hexanes increasing to 30% ethyl acetate) gave **5** as a white solid (58 mg, 16%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.18 (s, 1H), 8.66 (s, 2H), 7.30−7.52 (m, 3H), 7.04−7.24 (m, 4H), 6.85 (t, *J* = 7.4 Hz, 1H), 3.59 (d, *J* = 9.4 Hz, 1H). GCMS *m*/*z* = 314. HPLC (water/ACN + 0.1% TFA gradient) >99% at 230 nm.

*(4-Chlorophenyl)(3-fluorophenyl)pyrimidin-5-yl Methanol (**6**).* General method C (pyrimidine) with **6Bi** (0.269 g, 1.15 mmol), 5-bromopyrimidine (0.406 g, 1.7 mmol), dry tetrahydrofuran (10 mL), and *n*-butyllithium (1.6 M in hexanes, 1.15 mL, 1.7 mmol). Purification by flash column chromatography (eluting with 20% ethyl acetate in hexanes increasing to 40% ethyl acetate) gave **6** as an amorphous solid (46 mg, 13%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.16 (s, 1H), 8.69 (s, 2H), 7.31−7.42 (m, 3H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.93−7.13 (m, 3H), 3.03 (s, 1H). GCMS *m*/*z* = 314. HPLC (water/ACN + 0.1% TFA gradient) 96.1% at 230 nm.

*(4-Chlorophenyl)(4-bromophenyl)pyrimidin-5-yl Methanol (**7**).* General method C (pyrimidine) with **7Bi** (710 mg, 2.4 mmol), 5-bromopyrimidine (573 mg, 3.6 mmol), dry tetrahydrofuran (15 mL), and *n*-butyllithium (1.6 M in hexanes, 1.95 mL, 3.12 mmol). Purification by flash column chromatography (eluting with 50% ethyl acetate in hexanes) gave **7** as a white solid (380 mg, 42%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.09 (s, 1H), 8.64 (s, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.07−7.22 (m, 4H), 3.53 (s, 1H). GCMS *m*/*z* = 376. HPLC (water/ACN + 0.1% TFA gradient) >99% at 230 nm.

(4-Trifluoromethylphenyl)(4-chlorophenyl)pyrimidin-5-yl Methanol (8). General method C (pyrimidine) with **8Bii** (180 mg, 0.63 mmol), 5-bromopyrimidine (201 mg, 1.26 mmol), dry tetrahydrofuran (5 mL), and *n*-butyllithium (1.6 M in hexanes, 0.71 mL, 1.14 mmol). Purification by flash column chromatography (eluting with 35% ethyl acetate in hexanes) gave **8** as a white solid (40 mg, 17%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.18 (s, 1H), 8.70 (s, 2H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.33−7.48 (m, 4H), 7.18 (d, *J* = 8.7 Hz, 2H), 2.98 (s, 1H). GCMS *m*/*z* = 364. HPLC (water/ACN + 0.1% TFA gradient) 94.2% at 230 nm.

(2-Chlorophenyl)(4′-chlorophenyl)pyridin-3-yl Methanol (9). General method C (pyridine) with **9Bi** (0.79 g, 3.16 mmol), 3-bromopyridine (0.5 g, 3.16 mmol), dry diethyl ether (30 mL), dry tetrahydrofuran (10 mL), and *n*-butyllithium (1.6 M in hexanes, 2.6 mL, 3.48 mmol). The crude material was absorbed onto silica and purified by flash chromatography (eluting with 25% ethyl acetate in hexanes increasing to 50% ethyl acetate) to give **9** as a white solid (952 mg, 91%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.55−8.60 (m, 1H), 8.44−8.48 (m, 1H), 7.60−7.64 (m, 1H), 7.42−7.45 (m, 1H), 7.24−7.37 (m, 4H), 7.12−7.23 (m, 3H), 6.72−6.70 (m, 1H), 4.52 (s, 1H). HPLC (water/ACN + 0.1% TFA gradient) 97.6% at 230 nm.

Bis(4-chlorophenyl)(pyridin-3-yl) Methanol (10). General method C (pyridine) with 4,4′-chlorobenzenophenone (1.59 g, 6.3 mmol), 3-bromopyridine (1 g, 6.3 mmol), dry diethyl ether (20 mL), dry tetrahydrofuran (30 mL), and *n*-butyllithium (1.6 M in hexanes, 4.7 mL, 6.6 mmol). The crude material was absorbed onto silica and purified by flash chromatography (eluting with 10% ethyl acetate in hexanes increasing to 40% ethyl acetate) to give **10** as a white solid (0.97 g, 46%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 1.70, 4.80 Hz, 1H), 8.38 (dd, *J* = 0.71, 2.40 Hz, 1H), 7.57−7.62 (m, 1H), 7.26−7.33 (m, 3H), 7.15−7.25 (m, 6H), 4.03 (s, 1H), GCMS *m*/*z* = 329. HPLC (water/ACN + 0.1% TFA gradient) 99.5% at 230 nm.

(4-Chlorophenyl)(4-methylphenyl)pyridin-3-yl Methanol (11). General method C (pyridine) with **4Bi** (200 mg, 0.87 mmol), 3-bromopyridine (0.1 mL, 1 mmol), dry diethyl ether (4.3 mL), dry tetrahydrofuran (3.5 mL), and *n*-butyllithium (1.6 M in hexanes, 0.65 mL, 1 mmol). The crude material was absorbed onto silica and purified by Flashmaster II (eluting with hexanes increasing to 20% ethyl acetate in hexanes over 33 min) to give **11** as a white glassy powder (84 mg, 31%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.37−8.45 (m, 2H), 7.62 (td, *J* = 1.9, 8.1 Hz, 1H), 7.17−7.33 (m, 5H), 7.04−7.15 (m, 4H), 3.87 (s, 1H), 2.34 (s, 3H). GC/MS (*m*/*z* = 309 [M]). HPLC (method 1) 98% at 220 nm.

(4-Chlorophenyl)(2-fluorophenyl)pyridin-3-yl Methanol (12). General method C (pyridine) with **5Bi** (3.4 g, 14.5 mmol), 3-bromopyridine (3.64 g, 23.2 mmol), dry diethyl ether (40 mL), dry tetrahydrofuran (20 mL), and *n*-butyllithium (1.6 M in hexanes, 14.5 mL, 23.2 mmol). The crude material was absorbed onto silica and purified by flash chromatography (eluting with 50% ethyl acetate in hexanes) to give **12** as a white powder (2.01 g, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 1.6, 4.8 Hz, 1H), 8.48 (d, *J* = 2.1 Hz, 1H), 7.63 (td, *J* = 2.1, 8.1 Hz, 1H), 7.18−7.41 (m, 6H), 7.03−7.15 (m, 2H), 6.80 (td, *J* = 1.6, 8.1 Hz, 1H), 3.70 (d, *J* = 9.9 Hz, 1H). GC/MS (*m*/*z* = 313 [M]). HPLC (water/ACN + 0.1% TFA gradient) 98.3% at 230 nm.

(4-Chlorophenyl)(3-fluorophenyl)pyridin-3-yl Methanol (13). General method C (pyridine) with 3-fluoro bromobenzene (242 mg, 1.38 mmol), *n*-butyllithium (1.6 M in hexanes, 0.8 mL, 1.29 mmol), dry diethyl ether (3 mL), **13Biii** (200 mg, 0.92 mmol), and dry tetrahydrofuran (3 mL). Purification by flash column chromatography (eluting with 10% ethyl acetate in dichloromethane increasing to 35% ethyl acetate) gave **13** as an off-white solid (193 mg, 67%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.38−8.52 (m, 2H), 7.57−7.66 (m, 1H), 7.15−7.37 (m, 6H), 6.94−7.06 (m, 3H), 3.61 (s, 1H). GCMS *m*/*z* 313. HPLC (method 1) 96.1% at 220 nm.

(4-Bromophenyl)(4-chlorophenyl)pyridin-3-yl Methanol (14). General method C (pyridine) with **7Bi** (3.5 g, 11.8 mmol), *n*-butyllithium (1.6 molar solution in hexanes, 7.7 mL, 12.3 mmol), 3-bromopyridine (1.3 mL, 13 mmol), diethyl ether (50 mL), and tetrahydrofuran (35 mL). Purification by flash column chromatography (eluting with ethyl acetate in hexanes) gave **14** (2.17 g, 49%) as a tan solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41−8.52 (m, 2H), 7.56−7.64 (m, 1H), 7.40−7.51 (m, 2H), 7.08−7.36 (m, 7H), 3.45 (s, 1H). GC/MS (*m*/*z* = 375 [M]). HPLC (water/ACN + 0.1% TFA gradient) > 99% at 230 nm.

(4-Chlorophenyl)(4-trifluoromethylphenyl)pyridin-3-yl Methanol (15). General method C (pyridine) with **8Bii** (226 mg, 0.79 mmol), 3-bromopyridine (120 mg, 0.76 mmol), dry diethyl ether (3 mL), dry tetrahydrofuran (8 mL), and *n*-butyllithium (1.6 M in hexanes, 0.76 mL, 1.22 mmol). The crude material was absorbed onto silica and purified by flash chromatography (eluting with ethyl acetate in hexanes) to give **15** (127 mg, 44%) as an off-white gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (dd, *J* = 1.6, 4.8 Hz, 1H), 8.48 (d, *J* = 1.9 Hz, 1H), 7.57−7.65 (m, 3H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.24−7.36 (m, 3H), 7.16−7.22 (m, 2H), 3.26 (s, 1H) trace EtOAc. GC/MS (*m*/*z* = 363 [M]). HPLC (water/ACN + 0.1% TFA gradient) 96.6% at 230 nm.

(2-Chlorophenyl)(4-chlorophenyl)pyridin-2-yl Methanol (16). To a 100 mL three-necked flask was added 2-bromochlorobenzene (134 μL, 1.15 mmol) and THF (10 mL), the solution was cooled to −78 °C, and *t*-butyllithium (0.72 mL, 1.15 mmol, 1.7 M in pentane) was added slowly, dropwise over 40 min (CAUTION). Once addition was complete, the solution was stirred at low temperature for 1 h, and then a solution of **16B** in THF (5 mL) was added over 5 min. The resulting solution was stirred at low temperature for 30 min and then slowly warmed to room temperature and stirred overnight. The reaction was quenched with a saturated solution of ammonium chloride (30 mL) and extracted with ethyl acetate (2 × 50 mL), and the combined organic phases were dried over sodium sulfate, filtered, and concentrated. The crude material was absorbed onto silica gel and purified several times by flash chromatography (eluting with 10% diethyl ether in hexanes increasing to 20% diethyl ether in hexanes) to give **16** as a white solid (34 mg, 9%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.63 (s, 1H), 8.56 (s, 2H), 7.39−7.44 (m, 1H), 7.30−7.38 (m, 4H), 7.15−7.23 (m, 1H), 6.89 (dd, *J* = 1.5, 7.9 Hz, 1H), 5.26 (s, 1H). [M + 1] 331. HPLC (water/ACN + 0.1% TFA gradient) 96.7% at 220 nm.

(2-Chlorophenyl)(4-chlorophenyl)pyrimidin-2-yl Methanol (17). A 100 mL three-necked flask equipped with a gas inlet adapter, low temperature thermometer, and a suba seal was dried under nitrogen using a heat gun and then charged with 2-bromochlorobenzene (0.44 g, 2.3 mmol) and dry THF (18 mL) and cooled to −80 °C. To this solution was added slowly, dropwise, *tert*-butyllithium (1.7 mL, 2.3 mmol, 1.7 M solution in heptanes) (CAUTION) over 30 min, resulting in a pale-yellow solution. Once addition was complete, the reaction mixture was stirred at −80 °C for 1 h. After this time, **17B** (0.5 g, 2.3 mmol) as a suspension in THF (10 mL) was added dropwise, resulting a dark-colored solution. Once addition was complete, the mixture was stirred at low temperature for 1 h and slowly warmed to room temperature and stirred overnight. A saturated solution of ammonium chloride (100 mL) was added and the mixture extracted into EtOAc (2 × 50 mL), and combined organic phases were dried ($MgSO_4$), filtered, and concentrated under vacuum. Purification via flash chromatography (eluting with 80% ethyl acetate in hexanes) gave **17** as white solid (0.12 g, 16%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.77 (d, *J* = 4.7 Hz, 2H), 7.72−7.75 (m, 2H), 7.31−7.41 (m, 3H), 7.21−7.30 (m, 2H), 7.10−7.19 (m, 1H), 6.93−6.90 (m, 1H), 5.93 (s, 1H). ESI *m*/*z*: 330 (M). HPLC (water/ACN + 0.1% TFA gradient) 97.7% at 220 nm.

(2-Chlorophenyl)(4-chlorophenyl)pyridin-2-yl Methanol (18). To a 100 mL three-necked round-bottom flask equipped with gas adapter and low temperature thermometer and dried under nitrogen using a heat gun was added 2-bromopyridine (0.5 g, 3.16 mmol) and Et_2O (10 mL). The mixture was cooled to −78 °C and *tert*-butyllithium (1.7 mL, 3.38 mmol, 1.7 M solution in heptanes) (CAUTION) was added slowly, dropwise. The resulting red−brown mixture was stirred at low temperature for 1 h, and then a solution of **9Bi** (0.5 g, 3.16 mmol) in dry THF (10 mL) was added over 5 min. The reaction mixture was stirred at −78 °C for 30 min and then slowly warmed to room temperature and stirred overnight. A saturated solution of ammonium chloride (30 mL) was added, and the mixture was extracted with EtOAc (2 × 30 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum.

Purification by flash chromatography (eluting with 5% EtOAc in hexanes increasing to 20% EtOAc) gave **18** as white solid (340 mg, 32%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.64 (br s, 1H), 8.16 (br s, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.63 (br s, 1H), 7.46 (s, 5H), 7.26−7.43 (m, 2H), 6.98 (d, *J* = 7.5 Hz, 1H). ESI *m/z*: 329 (M). HPLC (water/ACN + 0.1% TFA gradient) 97.7% at 220 nm.

*(2-Chlorophenyl)(4-chlorophenyl)(pyrimidin-4-yl)methanol (**19**).* A 50 mL three-necked flask equipped with a suba seal, gas adapter, and low temperature thermometer and dried under nitrogen with a heat gun was charged with dry THF (10 mL) and tetramethylpiperidine (TMP) (0.24 g, 1.72 mmol). The mixture was cooled to −78 °C and *n*-butyllithium (1.15 mL, 1.72 mmol, 1.6 M solution in hexanes) was added dropwise over 10 min. The mixture was stirred for 30 min at −78 °C, warmed to 0 °C, and then cooled back down to −78 °C. A solution of **9Bi** (288 mg, 1.15 mmol) and pyrimidine (138 mg, 1.72 mmol) in dry THF (5 mL) was added dropwise, keeping the temperature below −60 °C. Once addition was complete (30 min), the mixture was stirred at low temperature for 1 h, warmed to room temperature, and stirred overnight. A saturated solution of ammonium chloride (30 mL) was added, and the mixture was extracted with ethyl acetate (2 × 30 mL), dried over magnesium sulfate, filtered, and concentrated under vacuum. Purification by flash chromatography (eluting with 50% ethyl acetate in hexanes), followed by trituration of the purified material with diethyl ether, gave **19** as white solid (25 mg, 6.5%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.22 (s, 1H), 8.78−8.66 (m, 1H), 7.28 −7.49 (m, 8H), 7.12−7.21 (m, 1H), 6.83−6.92 (m,1H), 5.35 (s, 1H). ESI *m/z*: 330 (M). HPLC (water/ACN + 0.1% TFA gradient) 97.7% at 220 nm.

*Synthesis of Compounds in Table 2. 3-[Methoxy(2-chlorophenyl)(4-chlorophenyl)methyl]pyridine (**20**).* A dry 25 mL round-bottomed flask was charged with methanol (8 mL) and sodium (200 mg) added portionwise under a nitrogen atmosphere. The mixture was stirred until bubbling had ceased, and then **76** (280 mg) was added and the mixture stirred for 48 h at room temperature. The mixture was concentrated under vacuum and the crude residue taken up in dichloromethane (30 mL) and washed with water (30 mL). The aqueous phase was back-extracted with water (2 × 20 mL), and the organic phases were combined, dried over sodium carbonate, filtered, and concentrated under vacuum. Purification by Flashmaster II (2 g column, eluting with 100% hexanes increasing to 25% ethyl acetate in hexanes over 22 min) gave **20** as a yellow glass (96 mg, 43%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.69 (br s, 1H), 8.50 (br d, *J* = 3.5 Hz, 1H), 7.71−7.85 (m, 2H), 7.20−7.43 (m, 8H), 3.07 (s, 3H). GC/MS (*m/z* = 343 [M]). HPLC (water/ACN + 0.1% TFA gradient) >99% at 220 nm.

*(2-Chlorophenyl)(4-chlorophenyl)(pyridin-3-yl)acetonitrile (**21**).* A 100 mL round-bottomed flask was charged with **76** (1.2 g, 3 mmol) and *N,N*-dimethylformamide (15 mL). Sodium cyanide (180 mg, 3.6 mmol) (CAUTION) was added and the reaction stirred at room temperature for 30 min and then heated at 90 °C overnight. On cooling, the mixture was poured onto water (200 mL), more water (100 mL) added, and then dichloromethane (100 mL). The layers were separated, the aqueous phase back-extracted with dichloromethane (4 × 50 mL), and the combined organic phases were washed with water (2 × 50 mL), dried over sodium carbonate, filtered, and concentrated under vacuum. Further washing with brine was required to remove traces of *N,N*-dimethylformamide. Purification by Flashmaster II (2 g column, eluting with 100% hexanes increasing to 30% ethyl acetate in hexanes over 30 min) gave **21** as sticky glass (120 mg, 12%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.65 (dd, *J* = 1.5, 4.7 Hz, 1H), 8.44 (dd, *J* = 0.6, 2.5 Hz, 1H), 7.63 (dt, *J* = 2.0, 8.1 Hz, 1H), 7.51 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.33−7.43 (m, 4H), 7.15−7.25 (m, 3H), 6.61 (dd, *J* = 1.5, 7.9 Hz, 1H), 3% EtOAc. GC/MS (*m/z* = 338 [M]). HPLC (water/ACN + 0.1% TFA gradient) 96.5% at 220 nm.

*(2-Chlorophenyl)(4-chlorophenyl)(pyridin-3-yl)methanamine (**22**).* A 50 mL round-bottomed flask was charged with **76** (500 mg, 1.43 mmol), *N,N*-dimethylformamide (5 mL), and ammonia in methanol (1 mL, 7 mmol of a 7 M solution). The reaction was stirred at room temperature overnight, poured into water (150 mL), and extracted with ethyl acetate (3 × 30 mL). The organic phases were combined, washed with water (50 mL), dried over sodium carbonate, filtered, and concentrated under vacuum. Purification by Flashmaster II (10 g column, eluting with 20% ethyl acetate in hexanes increasing to 100% ethyl acetate over 22 min) gave **22** as a yellow oil (115 mg, 24%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.49−8.58 (m, 1H), 7.60 (td, *J* = 1.98, 8.10 Hz, 1H), 7.41 (dd, *J* = 1.40, 7.82 Hz, 1H), 7.19−7.35 (m, 6H), 7.13 (dt, *J* = 1.41, 7.58 Hz, 1H), 6.79 (dd, *J* = 1.70, 7.91 Hz, 1H), 2.84 (br s, 2H). GC/MS (*m/z* = 328 [M]). HPLC (water/ACN + 0.1% TFA gradient) 95.4% at 220 nm.

*N-((2-Chlorophenyl)(4-chlorophenyl)(pyridin-3-ylmethyl)-2-methylpropan-1-amine (**23**).* A flask was charged with **76** (200 mg, 0.57 mmol), isobutyl amine (0.2 mL, 1.15 mmol), and *N,N*-dimethylformamide (12 mL) and the mixture stirred for 72 h at room temperature and then poured onto water (30 mL) and extracted with ethyl acetate (2 × 30 mL). The organic phases were combined, washed with brine (20 mL), dried over sodium carbonate, filtered, and concentrated. Purification by Flashmaster II to give **23** as a pale-yellow oil (47 mg, 22%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.72 (br s, 1H), 8.42 (dd, *J* = 1.5, 4.7 Hz, 1H), 7.72−7.81 (m, 1H), 7.41 (dd, *J* = 1.80, 6.80 Hz, 4H), 7.15−7.33 (m, 5H), 2.49−2.57 (m, 1H), 1.76−1.94 (m, 3H), 0.94 (d, *J* = 5.8 Hz, 6H). GC/MS (*m/z* = 384 [M]). HPLC (water/ACN + 0.1% TFA gradient) 96.3% at 220 nm.

*5-[(2-Chlorophenyl)(4-chlorophenyl)methyl]pyrimidine (**24**).* General method E with **1** (50 mg, 0.16 mmol), tin(II)chloride (52 mg, 0.274 mmol), c. hydrochloric acid (158 μL) and glacial acetic acid (500 μL). Purification by flash chromatography (eluting with 50% ethyl acetate in toluene) gave **24** (30 mg, 26%) as a yellow gum. ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.13 (s, 1H), 8.46 (s, 2H), 7.38−7.50 (m, 1H), 7.18−7.37 (m, 4H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.84−6.94 (m, 1H), 5.92 (s, 1H). [M + 1] 315. HPLC (water/ACN + 0.1% TFA gradient) 99.1% at 220 nm.

*5-[(2-Chlorophenyl)(4-chlorophenyl)methyl]pyrimidine (**25**).* General method E with **3** (113 mg, 0.35 mmol), tin(II)chloride (125 mg, 0.595 mmol), c hydrochloric acid (352 μL), and glacial acetic acid (1.1 mL) except compound obtained by precipitation from pyridine solution on addition of toluene to give **25** (64 mg, 55%) as a yellow gum. ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.13 (s, 1H), 8.48 (s, 2H), 7.32 (d, *J* = 8.3 Hz, 4H), 7.02 (d, *J* = 8.3 Hz, 4H), 5.47 (s, 1H). ESI *m/z*: 314 (M). HPLC (water/ACN + 0.1% TFA gradient) 99.9% at 220 nm.

*3-((2-Chlorophenyl)(4-chlorophenyl)methyl)pyridine (**26**).* General method E with **9** (200 mg, 0.6 mmol), tin(II)chloride (270 mg, 1.2 mmol), c hydrochloric acid (2 mL), and glacial acetic acid (5 mL). Purification by Flashmaster II (eluting with ethyl acetate in hexanes) gave **26** as a yellow oil (75 mg, 40%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.51 (br d, *J* = 3.9 Hz, 1H), 8.38 (br s, 1H), 7.37−7.45 (m, 1H), 7.17−7.37 (m, 6H), 7.00 (br d, *J* = 8.5 Hz, 2H), 6.85−6.92 (m, 1H), 5.94 (s, 1H). GC/MS (*m/z* = 313 [M]). HPLC (water/ACN + 0.1% TFA gradient) 99.3% at 220 nm.

*3-(Bis(4-chlorophenyl)methyl)pyridine (**27**).* General method E with **10** (57 mg, 0.17 mmol), tin(II)chloride (56 mg, 0.29 mmol), c hydrochloric acid (2 mL), and glacial acetic acid (5 mL). Reaction mixture heated under reflux for 18 h, with additional tin(II)chloride (140 mg, 0.74 mmol) added after 4 h. Purification by flash column chromatography (eluting with ethyl acetate in hexanes) gave **27** as a pale-yellow oil (9 mg, 17%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32−8.73 (m, 2H), 7.65 (br d, *J* = 7.7 Hz, 1H), 7.50 (br s, 1H), 7.28−7.37 (m, 4H), 6.95−7.08 (m, 4H), 5.57 (s, 1H). GC/MS (*m/z* = 313 [M]). HPLC (water/ACN + 0.1% TFA gradient) 99.3% at 220 nm.

*(4-Chlorophenyl)(2-chlorophenyl)pyrimidin-5-yl N-Oxide Methanol (**28**).* **1** (25 mg, 0.025 mmol) was dissolved in dichloromethane (2 mL) and the solution cooled in an ice-bath. *meta*-Chloroperbenzoic (77%, 34 mg, 0.15 mmol) was added and the reaction stirred for 48 h under an atmosphere of nitrogen. Water (10 mL) and dichloromethane (10 mL) were added, and the aqueous phase was separated and back-extracted with dichloromethane (2 × 10 mL). The organic phases were combined and washed with brine (10 mL), dried over sodium sulfate, filtered, concentrated, and solvent removed under reduced pressure. Purification by flash column chromatography (eluting

with 30% ethyl acetate in hexanes increasing to 100% ethyl acetate) gave **28** (13 mg, 50%) as a white powder. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.92 (s, 1H), 8.32 (s, 1H), 8.10 (s, 1H), 7.43−7.54 (m, 1H), 7.32−7.43 (m, 3H), 7.15−7.32 (m, 3H), 6.78 (dd, *J* = 1.2, 7.8 Hz, 1H), 4.53 (br s, 1H). HPLC (method 2) 97.9% at 220 nm.

*Synthesis of Compounds in Table 3. (4-Chlorophenyl)(2-methylphenyl)pyridin-3-yl Methanol (**29**).* General method C (pyridine) with **29Bii** (260 mg, 1.15 mmol), 3-bromopyridine (400 mg, 1.84 mmol), dry diethyl ether (6 mL), dry tetrahydrofuran (4 mL), and *n*-butyllithium (1.6 M in hexanes, 1.43 mL, 1.84 mmol). The crude material was absorbed onto silica and purified by flash column chromatography (eluting with 20% ethyl acetate in hexanes increasing to 40%). The material was further purified by reverse phase silica column chromatography (eluting with 40% methanol in water increasing to 60%). The solvent was removed under reduced pressure and the residue re-extracted into dichloromethane, washed with water, dried over magnesium sulfate, filtered, and concentrated to give **29** as a cream solid (280 mg, 79%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.42−8.62 (m, 2H), 7.57 (td, *J* = 1.84, 8.01 Hz, 1H), 7.28−7.36 (m, 2H), 7.16−7.25 (m, 4H), 7.00−7.11 (m, 1H), 6.69 (d, *J* = 7.91 Hz, 1H), 3.34 (br s, 1H), 2.12 (s, 3H). GCMS *m/z* = 309. HPLC (water/ACN + 0.1% TFA gradient) 90% at 254 nm.

*(4-Chlorophenyl)(3-methoxyphenyl)pyridin-3-yl Methanol (**30**).* General method C (pyridine) with 4-bromochlorobenzene (243 mg, 1.27 mmol), *n*-butyllithium (1.6 M in hexanes, 1.18 mL, 1.4 mmol), dry diethyl ether (3 mL), **30Biii** (180 mg, 0.84 mmol), and dry tetrahydrofuran (3 mL). Purification by flash column chromatography (eluting with 10% ethyl acetate in dichloromethane increasing to 35% ethyl acetate) gave **30** as an off-white gum (63 mg, 23%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.43−8.55 (m, 2H), 7.58−7.67 (m, 1H), 7.16−7.37 (m, 6H), 6.70−6.93 (m, 3H), 3.75 (s, 3H), 3.29 (s, 1H). GCMS *m/z* 325. HPLC (water/ACN + 0.1% TFA gradient) 99.2% at 220 nm.

*(4-Chlorophenyl)(4-methoxyphenyl)pyridin-3-yl Methanol (**31**).* General method C (pyridine) with 3-bromopyridine (0.2 mL, 2 mmol), *n*-butyllithium (1.6 M in hexanes, 1.5 mL, 2.25 mmol), dry diethyl ether (10 mL), **31Bi** (420 mg, 1.7 mmol), and dry tetrahydrofuran (10 mL). Purification by Flashmaster II (eluting with 20% ethyl acetate in hexanes increasing to 40% ethyl acetate) gave **31** as a pale-yellow glass (950 mg, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42−8.49 (m, 2H), 7.59−7.66 (m, 1H), 7.18−7.32 (m, 5H), 7.07−7.15 (m, 2H), 6.81−6.88 (m, 2H), 3.80 (s, 3H), 3.47 (br s, 1H). GC/MS (*m/z* = 325 [M]). HPLC (water/ACN + 0.1% TFA gradient) 95.5% at 220 nm.

*(4-Chlorophenyl)(2-(propan-2-yloxy)phenyl)pyridin-3-yl Methanol (**32**).* General method C (pyridine) with **77** (0.5 g, 2.3 mmol), *n*-butyllithium (1.6 M in hexanes, 1.3 mL, 2 mmol), dry diethyl ether (5 mL), **13Biii** (340 mg, 1.55 mmol), and dry tetrahydrofuran (5 mL). Purification in the first instance by flash column chromatography (eluting with 20% ethyl acetate in hexanes) and then by reverse phase silica column chromatography (eluting with 60% methanol in water) gave **32** as a pale-yellow gum (250 mg, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 1.6, 4.8 Hz, 1H), 8.44 (dd, *J* = 0.8, 2.4 Hz, 1H), 7.58−7.67 (m, 1H), 7.18−7.33 (m, 6H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.81 (dt, *J* = 1.1, 7.6 Hz, 1H), 6.50 (dd, *J* = 1.7, 7.6 Hz, 1H), 5.45 (s, 1H), 4.54 (spt, *J* = 6.0 Hz, 1H), 1.03 (d, *J* = 6.0 Hz, 3H), 1.00 (d, *J* = 6.0 Hz, 3H). GC/MS (*m/z* = 353 [M]). HPLC (water/ACN + 0.1% TFA gradient) 98.3% at 220 nm.

*(4-Chlorophenyl)(3-(propan-2-yloxy)phenyl)pyridin-3-yl Methanol (**33**).* General method C (pyridine) with **78** (0.5 g, 2.3 mmol), *n*-butyllithium (1.6 M in hexanes, 1.3 mL, 2 mmol), dry diethyl ether (5 mL), **13Biii** (340 mg, 1.55 mmol), and dry tetrahydrofuran (5 mL). Purification in the first instance by flash column chromatography (eluting with 20% ethyl acetate in hexanes) and then by reverse phase silica column chromatography (eluting with 60% methanol in water) gave **33** as a white powder (300 mg, 54%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.44−8.52 (m, 2H), 7.63 (ddd, *J* = 1.9 × 2, 8.3 Hz, 1H), 7.18−7.33 (m, 6H), 6.80−6.85 (m, 1H), 6.76 (t, *J* = 2.1 Hz, 1H), 6.70−6.75 (m, 1H), 4.47 (spt, *J* = 6.1 Hz, 1H), 3.38 (s, 1H), 1.28 (d, *J* = 6.1 Hz, 7H). GC/MS (*m/z* = 353 [M]). HPLC (water/ACN + 0.1% TFA gradient) 95.6% at 220 nm.

*(4-Chlorophenyl)(4-isopropoxyphenyl)pyridin-3-yl Methanol (**34**).* General method C (pyridine) with 3-bromopyridine (0.1 mL, 1 mmol), *n*-butyllithium (1.6 M in hexanes, 0.62 mL, 0.93 mmol), dry diethyl ether (5 mL), **34Bii** (187 mg, 0.68 mmol), and dry tetrahydrofuran (8 mL). Purification by flash column chromatography (eluting with 30% ethyl acetate in hexanes) gave **34** (40 mg, 17%) as a white solid. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.44−8.58 (m, 2H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.19−7.37 (m, 4H), 7.09−7.11 (m, 2H), 6.85−6.82 (m, 2H), 4.56 (spt, *J* = 6.1 Hz, 1H), 3.16 (s, 1H), 1.35 (d, *J* = 6.1 Hz, 6H), 3.16 (s, 1H). GCMS *m/z* = 353. HPLC (water/AcCN + 0.1% TFA gradient) 98.5% at 220 nm.

*(4-Trifluoromethylphenyl)(4-isopropoxyphenyl)pyridin-3-yl Methanol (**35**).* General method C with 4-bromobenzotrifluoride (279 mg, 1.24 mmol), *n*-butyllithium (1.6 M in hexanes, 1.16 mL, 1.25 mmol), dry diethyl ether (3 mL), **35Biii** (200 mg, 0.83 mmol), and dry tetrahydrofuran (3 mL). Purification by flash column chromatography (eluting with 5% ethyl acetate in dichloromethane increasing to 40% ethyl acetate) gave **35** as a pale-yellow semisolid (140 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48−8.59 (m, 2H), 7.54−7.62 (m, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.41−7.50 (m, 1H), 7.22−7.31 (m, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 5H), 4.55 (spt, *J* = 6.1,Hz, 1H), 2.95 (br s, 1H), 1.34 (d, *J* = 6.1 Hz, 6H). HPLC (method 1) 97.2% at 220 nm.

*(4-Chlorophenyl)(2-bromophenyl)pyridin-3-yl Methanol (**36**).* General method C (pyridine) with 3-bromopyridine (991 mg, 6.31 mmol), *n*-butyllithium (1.6 M in hexanes, 3.94 mL, 6.31 mmol), dry diethyl ether (15 mL), **36 Bi** (1.16 g, 3.95 mmol), and dry tetrahydrofuran (15 mL). Purification by Flashmaster II (10 g column, eluting with 20% ethyl acetate in hexanes over 44 min at 5 mL/min) gave **36** as an off-white solid (570 mg, 39%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.38−8.53 (m, 2H), 7.57−7.64 (m, 1H), 7.40−7.51 (m, 2H), 7.28−7.35 (m, 2H), 7.09−7.24 (m, 4H), 3.56 (br s, 1H). GCMS *m/z* = 375. HPLC (water/ACN + 0.1% TFA gradient) 99% at 220 nm.

*(4-Chlorophenyl)(3-bromophenyl)pyrid-3-yl Methanol (**37**).* General method C (pyridine) with **37 Bi** (1 g, 3.38 mmol), 3-bromopyridine (850 mg, 5.41 mmol), dry diethyl ether (10 mL), dry tetrahydrofuran (5 mL), and *n*-butyllithium (1.6 M in hexanes, 3.38 mL, 5.41 mmol). The crude material was absorbed onto silica and purified by flash chromatography (50% ethyl acetate in hexanes) to give **37** as a white powder (410 mg, 32%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.46−8.58 (m, 1H), 7.58−7.65 (m, 1H), 7.41−7.50 (m, 2H), 7.29−7.36 (m, 3H), 7.09−7.23 (m, 5H), 2.98 (s, 1H). GCMS *m/z* = 375. HPLC (method 1) 98.8% at 220 nm.

*(4-Trifluoromethylphenyl)(4-bromophenyl)pyrid-3-yl Methanol (**38**).* General method C with 4-bromobenzotrifluoride (773 mg, 3.44 mmol), dry diethyl ether (6 mL), *n*-butyllithium (1.6eq of a 1.6 M solution in hexanes, 2.0 mL, 3.21 mmol), **38Biii** (600 mg, 2.29 mmol), and dry tetrahydrofuran (6 mL). Purification by flash column chromatography (eluting with 5% ethyl acetate in dichloromethane, increasing to 33% ethyl acetate) gave **38** as an off white solid (815 mg, 87%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.40−8.54 (m, 2H), 7.57−7.68 (m, 3H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.21−7.32 (m, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 3.53 (s, 1H). GCMS *m/z* 407/409. HPLC (method 1) 99.8% at 220 nm.

*(4-Chlorophenyl)(2-trifluoromethylphenyl)pyridin-3-yl methanol (**39**).* General method C (pyridine) with 3-bromopyridine (0.23 mL, 2.3 mmol), dry diethyl ether (10 mL), *n*-butyllithium (1.4 mL, 2.3 mmol, 1.6 M solution in hexanes), and **39Bii** (160 mg, 0.56 mmol) in dry tetrahydrofuran (5 mL). The crude material was absorbed onto silica gel and purified by flash column chromatography (eluting with 25% ethyl acetate in hexanes) to give **39** as a white solid (240 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (dd, *J* = 1.6, 4.8 Hz, 1H), 8.48 (d, *J* = 1.9 Hz, 1H), 7.57−7.65 (m, 3H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.24−7.36 (m, 3H), 7.16−7.22 (m, 2H), 3.26 (s, 1H). GC/MS (*m/z* = 363 [M]). HPLC (water/ACN + 0.1% TFA gradient) 99.1% at 220 nm.

*(4-Chlorophenyl)(3-trifluoromethylphenyl)pyridin-3-yl Methanol (**40**).* General method C (pyridine) with 3-bromopyridine (0.15 mL, 1.5 mmol), dry diethyl ether (5 mL), *n*-butyllithium (0.96 mL, 1.4 mmol, 1.6 M solution in hexanes), and **40Bii** (280 mg, 0.98 mmol) in dry tetrahydrofuran (3.5 mL). The crude material was absorbed onto silica gel and purified by flash column chromatography (eluting with 20% ethyl acetate in hexanes) to give **40** as a pale-yellow gum (58 mg, 16%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40−8.52 (m, 2H), 7.65 (s, 1H), 7.55−7.63 (m, 2H), 7.37−7.49 (m, 2H), 7.23−7.35 (m, 4H), 7.15−7.21 (m, 2H), 3.68 (s, 1H). GC/MS (*m*/*z* = 363 [M]). HPLC (water/ACN + 0.1% TFA gradient) 97.7% at 220 nm.

*3-[(4-Chlorophenyl)(hydroxy)pyridin-3-yl methyl]benzonitrile (**41**).* General method D with **37** (123 mg, 0.33 mmol), potassium ferricyanide (280 mg, 0.66 mmol), palladium(II)acetate (17 mg, 76 μmol), sodium carbonate (70 mg, 0.66 mmol), and *N*,*N*-dimethylacetamide (3 mL). The crude material was absorbed onto silica and purified by flash chromatography (eluting with 30% ethyl acetate in hexanes) to give **41** as a white powder (70 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37−8.51 (m, 2H), 7.56−7.67 (m, 3H), 7.41−7.55 (m, 2H), 7.27−7.37 (m, 3H), 7.12−7.21 (m, 2H), 4.03 (br s, 1H). GC/MS (*m*/*z* = 320 [M]). HPLC (method 1) 98.8% at 220 nm.

*4-((4-Chlorophenyl)(hydroxy)pyridin-3-ylmethyl)benzonitrile (**42**).* General method D with **14** (232 mg, 0.61 mmol), potassium ferricyanide (535 mg, 1.3 mmol), palladium(II)acetate (18 mg, 80 μmol), sodium carbonate (66 mg, 0.63 mmol), and *N*,*N*-dimethylacetamide (5 mL). The crude material was absorbed onto silica and purified by flash chromatography (eluting with 30% ethyl acetate in hexanes) to give **42** as a cream powder (31 mg, 16%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 2H), 7.53−7.71 (m, 4H), 7.40−7.49 (m, 2H), 7.22−7.36 (m, 3H), 7.09−7.20 (m, 1H), 4.21 (br s, 1H). GC/MS (*m*/*z* = 320 [M]). HPLC (water/ACN + 0.1% TFA gradient) 99.5% at 220 nm.

*4-((4-Trifluoromethylphenyl)(hydroxy)pyridin-3-ylmethyl)-benzonitrile (**43**).* General method D with **38** (1.5 g, 3.66 mmol), potassium ferricyanide (3.27 g, 7.74 mmol), palladium(II)acetate (495 mg, 0.72 mmol), sodium carbonate (435 mg, 4.05 mmol), and *N*,*N*-dimethylacetamide (15 mL). The crude material was absorbed onto silica and purified by flash chromatography (eluting with dichloromethane increasing to 50% ethyl acetate in dichloromethane) to give **43** as an off-white glass (930 mg, 72%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.42−8.55 (m, 2H), 7.56−7.67 (m, 5H), 7.38−7.46 (m, 4H), 7.24−7.32 (m, 1H), 3.63 (s, 1H). GCMS *m*/*z* 354. HPLC (water/ACN + 0.1% TFA gradient) 97.2% at 220 nm.

*2-Fluoro-4-{hydroxy(pyridin-3-yl)[4-(trifluoromethyl)phenyl]-methyl}benzonitrile (**44**).* General method D with aryl bromide **81** (0.25 g, 0.604 mmol), potassium ferricyanide ($K_4[Fe(CN)_6]\cdot 3H_2O$) (0.53 g, 1.27 mmol), palladium(II)acetate (38 mg), anhydrous sodium carbonate (0.071 g, 0.66 mmol), and anhydrous *N*,*N*-dimethylacetamide (3 mL). The crude material was purified by Flashmaster II (eluting with hexanes increasing to 40% ethyl acetate over 35 min) to give a semipurified oil which was taken up in diethyl ether and washed with water, organic phases combined, dried over magnesium sulfate, filtered, and concentrated to remove residual *N*,*N*-dimethylacetamide, and then triturated with diethyl ether to give **44** (60 mg, 27%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52−8.55(m, 1H), 8.46 (s, 1H), 7.58−7.88 (m, 5H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.41 (dd, *J* = 4.7, 7.8 Hz, 1H), 7.26 (s, 1H). ESI *m*/*z*: 372 (M). HPLC (water/ACN + 0.1% TFA gradient) >99% at 220 nm.

*(4-Chlorophenyl)(4-chloro-2-fluorophenyl)pyridin-3-yl Methanol (**45**).* General method C (pyridine) with 2-fluoro-4-chlorobenzene (361 mg, 1.73 mmol), *n*-butyllithium (1.6 M in hexanes, 1.0 mL, 1.6 mmol), dry diethyl ether (3 mL), **13Biii** (250 mg, 1.15 mmol), and dry tetrahydrofuran (3 mL). Purification by flash column chromatography (eluting with 10% ethyl acetate in dichloromethane increasing to 35% ethyl acetate) gave **45** as a white solid (223 mg, 56%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.55 (dd, *J* = 1.51, 4.90 Hz, 1H), 8.47 (d, *J* = 2.26 Hz, 1H), 7.58−7.65 (m, 1H), 7.24−7.41 (m, 3H), 7.03−7.24 (m, 4H), 6.83 (t, *J* = 8.6 Hz, 1H), 3.60 (d, *J* = 8.3 Hz, 1H). GCMS *m*/*z* 347. HPLC (water/ACN + 0.1% TFA gradient) 97.2% at 220 nm.

*3-[(4-Chlorophenyl)(hydroxy)pyridin-3-ylmethyl]benzamide (**46**).* **41** (2.3 g, 7.17 mmol) was hydrolyzed by KOH (1.93 g, 34.4 mmol) in *t*-BuOH (20 mL) on heating under reflux for 45 min. The mixture was cooled, concentrated to half volume under reduced pressure, and then partitioned between ethyl acetate (100 mL) and dilute HCl (100 mL to pH7). The organic phase was washed with water (100 mL), brine (100 mL), separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography (eluent 100% DCM, 50% DCM in EtOAc, 5% 7 M NH_3 in MeOH in EtOAc), followed by trituration with 10% DCM in Et_2O, filtration, and washing with Et_2O gave **46** as a white powder (1.84 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 0.1, 1.8 Hz, 1H), 8.18 (dd, *J* = 1.2, 4.7 Hz, 1H), 7.88 (br s, 1H), 7.55−7.61 (m, 1H), 7.45−7.54 (m, 1H), 7.03−7.29 (m, 6H), 6.92 (br s, 1H), 6.45 (br s, 1H). ESI [M + H] = 339.4. HPLC (water/ACN + 0.1% TFA gradient) 99.5% at 220 nm.

*3-[(4-Chloro-2-fluorophenyl)(hydroxy)pyridin-3-ylmethyl]-benzamide (**47**).* Method as for **46** with **83** (337 mg, 1 mmol), *t*-BuOH (13.2 mL), and KOH (0.4 g, 7 mmol). Heated under reflux for 2 h. Usual work up gave **47** as a white powder (60.3 mg, %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (br s, 2H), 7.89−8.07 (m, 1H), 7.74−7.87 (m, 2H), 7.62 (d, *J* = 7.43 Hz, 1H), 7.20−7.53 (m, 6H), 6.88−7.01 (m, 1H), 3.33 (br s, 1H). ESI [M + H] = 357.3. HPLC (method 1) 95.64% at 220 nm.

*3-[(4-(Trifluoromethyl)phenyl(hydroxy)pyridin-3-ylmethyl]-benzamide (**48**).* Method as for **46** with **85** (876 mg, 2.47 mmol), *t*-BuOH (45 mL), and KOH (1.2 g, 21 mmol). Heated under reflux for 2 h. Usual work up gave **48** as a cream powder (278 mg, 51%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.14−8.46 (m, 2H), 7.89 (s, 1H), 7.28−7.72 (m, 7H), 7.01−7.25 (m, 2H), 6.47 (br s, 2H). ESI [M + H] = 373.2. HPLC (method 1) 97.28% at 220 nm.

*4-[4-(Trifluoromethyl)phenyl(hydroxy)pyridin-3-ylmethyl]-benzamide (**49**).* **43** was hydrolyzed as described for the preparation of **46** to give **49** as a white powder (15 mg, 28%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (br s, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.53−7.70 (m, 3H), 7.34−7.50 (m, 4H), 7.23−7.32 (m, 1H), 6.90 (br s, 1H), 6.17 (br s, 1H), 6.01−6.12 (m, 1H). ESI [M + H] = 373.3. HPLC (method 1) 95.1% at 220 nm.

*N-(4-((4-Chlorophenyl)(hydroxy)(pyridin-3-yl)methyl)phenyl)-methanesulfonamide (**50**).* Prepared according to Yin and Buchwald[27] from **14** to give **50** as an off-white solid (15.4 mg, 6%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.45−8.58 (m, 2H), 7.60−7.67 (m, 1H), 7.29−7.36 (m, 2H), 7.14−7.25 (m, 6H), 6.52 (s, 1H), 3.05 (s, 3H), 2.93 (s, 1H). [M + 1] 389. HPLC (water/ACN + 0.1% TFA gradient) >99% at 220 nm.

*(4-Trifluoromethylphenyl)(4-dimethylaminophenyl)pyrid-3-yl) Methanol (**51**).* General method C (pyridine) with 4-bromo benzotrifluoride (298 mg, 132 mmol), dry diethyl ether (3 L), *n*-butyllithium (1.6 equiv of a 1.6 M solution in hexanes, 0.77 mL, 1.24 mmol), **51Biii** (200 mg, 0.88 mmol), and dry tetrahydrofuran (3 mL). Purification by flash column chromatography (eluting with 10% ethyl acetate in dichloromethane, increasing to 40% ethyl acetate) gave **51** as an off-white solid (240 mg, 73%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.45−8.59 (m, 2H), 7.63−7.70 (m, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.20−7.31 (m, 1H), 7.01 (d, *J* = 6.9 Hz, 2H), 6.65 (d, *J* = 6.9 Hz, 2H), 3.01 (s, 1H), 2.96 (s, 6H). GCMS *m*/*z* 372. HPLC (method 1) 99% at 220 nm.

*4-(Trifluoromethyl)phenyl(4-(propan-2-yl)phenyl)pyridin-3-yl Methanol (**52**).* General method C (pyridine) with 3-bromopyridine (0.13 mL, 1.3 mmol), dry diethyl ether (5 mL), *n*-butyllithium (0.77 mL, 1.23 mmol, 1.6 M solution in hexanes), and **52Bii** (300 mg, 1.03 mmol) in dry tetrahydrofuran (5 mL). Purification by flash column chromatography (eluting with 20% ethyl acetate in hexanes increasing to 40%) gave **52** as an amber glass (200 mg, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 0.7, 2.3 Hz, 1H), 8.42 (dd, *J* = 1.6, 4.8 Hz, 1H), 7.61−7.66 (m, 1H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.14−7.25 (m, 3H), 7.07−7.13 (m, 2H), 3.72 (s, 1H), 2.91 (spt, *J* = 6.9 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 6H). GC/MS (*m*/*z* = 371 [M]). HPLC (method 1) 97% at 220 nm.

*(4-Chlorophenyl)-(2,4-difluorophenyl)pyridin-3-yl Methanol (**53**).* General method C (pyridine) with **53Bi** (300 mg, 1.19 mmol), 3-bromopyridine (281 mg, 1.78 mmol), dry diethyl ether (3 mL), dry

tetrahydrofuran (3 mL), and *n*-butyllithium (1.6 M solution in hexanes, 1.04 mL, 1.67 mmol). The crude material was absorbed onto silica and purified by flash chromatography (eluting with 5% ethyl acetate in dichloromethane increasing to 10% ethyl acetate) to give **53** as a white solid (262 mg, 66%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.55 (dd, *J* = 1.3, 4.7 Hz, 1H), 8.46 (d, *J* = 2.1 Hz, 1H), 7.55−7.70 (m, 1H), 7.13−7.41 (m, 5H), 6.73−6.95 (m, 3H), 3.61 (d, *J* = 8.3 Hz, 1H). GCMS *m/z* 331. HPLC (method 1) 96.2% at 220 nm.

*(4-(Trifluoromethyl)phenyl)(4-chloro-2-fluorophenyl)pyridin-3-yl Methanol (**54**).* General method C (pyridine) with 1-bromo-4-chloro-2-fluorobenzene (25 mg, 1.2 mmol), dry diethyl ether (5 mL), *n*-butyllithium (1.6 equiv of a 1.6 M solution in hexanes, 0.69 mL, 1.11 mmol), **54Biii** (200 mg, 0.8 mmol), and dry tetrahydrofuran (3 mL). Purification by flash column chromatography (eluting with 5% ethyl acetate in dichloromethane, increasing to 15% ethyl acetate) gave **54** as a white powder (100 mg, 33%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.61 (d, *J* = 3.6 Hz, 1H), 8.51 (s, 1H), 7.63−7.66 (m, 3H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.31−7.37 (m, 1H), 7.18 (dd, *J* = 2.0, 11.6 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.82 (t, *J* = 8.5 Hz, 1H), 3.49 (d, *J* = 8.7 Hz, 1H). GCMS *m/z* = 381. HPLC (method 1) 98.4% at 220 nm.

*(4-Chlorophenyl)(2-fluoro-4-(trifluoromethyl)phenyl)pyridin-3-yl Methanol (**55**).* General method C (pyridine) with 3-bromopyridine (97 mg, 0.61 mmol), dry diethyl ether (5 mL), *n*-butyllithium (0.36 mL, 0.57 mmol, 1.6 M solution in hexanes), and **55Bii** (124 mg, 0.41 mmol) in dry tetrahydrofuran (5 mL). The crude material was absorbed onto silica gel and purified by flash column chromatography (eluting with 5% ethyl acetate in dichloromethane. Further purification via reverse phase chromatography eluting with acetonitrile gave **55** as a pale-yellow powder (3 mg, 22%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.23−8.77 (m, 2H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.28−7.45 (m, 5H), 7.17−7.24 (m, 2H), 7.12 (t, *J* = 7.9 Hz, 1H), 3.66 (d, *J* = 7.8 Hz, 1H). GCMS *m/z* = 381. HPLC (water/ACN + 0.1% TFA gradient) 97.1% at 220 nm.

*(4-Chlorophenyl)(4-bromo-2-fluorophenyl)pyridin-3-yl Methanol (**56**).* General method C (pyridine) with 3-bromopyridine (524 mg, 3.3 mmol), dry diethyl ether (5 mL), *n*-butyllithium (1.93 mL, 3.08 mmol, 1.6 M solution in hexanes), and **56 Bi** (690 mg, 2.2 mmol) in dry tetrahydrofuran (5 mL). The crude material was absorbed onto silica gel and purified by flash column chromatography (eluting with 5% ethyl acetate in dichloromethane increasing to 20% ethyl acetate) to give **56** as an off-white powder (573 mg, 66%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.56 (dd, *J* = 1.8, 4.8 Hz, 1H), 8.47 (d, *J* = 2.2 Hz, 1H), 7.59−7.63(m, 1H), 7.27−7.36 (m, 3H), 7.16−7.25 (m, 3H), 6.75 (t, *J* = 8.3 Hz, 1H), 3.49 (d, *J* = 8.5 Hz, 1H). GC/MS *m/z* = 393. HPLC (water/ACN + 0.1% TFA gradient) 98% at 220 nm.

*(4-Chlorophenyl)(2-fluoro-4-(propan-2-yloxy)phenyl)pyridin-3-yl Methanol (**57**).* General procedure C (pyridine) with **87** (305 mg, 1.31 mmol), dry diethyl ether (5 mL), *n*-butyllithium (0.756 mL, 1.21 mmol, 1.6 M solution in hexanes), and **13Biii** (219 mg, 1 mmol) in dry tetrahydrofuran (5 mL). The crude material was absorbed onto silica gel and purified by flash column chromatography (eluting with 5% ethyl acetate in dichloromethane) to give **57** as an off-white powder (210 mg, 56%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.55 (d, *J* = 3.6 Hz, 1H), 8.49 (s, 1H), 7.61−7.64 (m, 1H), 7.29−7.36 (m, 2H), 7.15−7.24 (m, 2H), 6.48−6.70 (m, 3H), 4.50 (spt, *J* = 6.0 Hz,1H), 3.47−3.58 (m, 1H), 1.34 (d, *J* = 6.0 Hz, 6H). GC/MS *m/z* = 371. HPLC (water/ACN + 0.1% TFA gradient) 96% at 220 nm.

*4-((4-Chlorophenyl)(hydroxy)pyridin-3-ylmethyl)-3-fluorobenzonitrile (**58**).* General method D with aryl bromide **56** (527 mg, 1.34 mmol), potassium ferricyanide ($K_4[Fe(CN)_6]\cdot 3H_2O$) (1.13 g, 2.68 mmol), palladium(II)acetate (36 mg, 12 mol %), anhydrous sodium carbonate (213 mg, 2.01 mmol), and anhydrous *N,N*-dimethylacetamide (8 mL). The crude material was absorbed onto silica gel and purified by flash column chromatography (eluting with 10% ethyl acetate in dichloromethane) to give **58** as a pale-brown powder (68 mg, 14%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.59 (br s, 1H), 8.49 (br s, 1H), 7.62 (d, *J* = 10.8 Hz, 1H), 7.40−7.48 (m, 2H), 7.30−7.39 (m, 3H), 7.13−7.24 (m, 3H), 3.46 (br s, 1H). GC/MS *m/z* = 338. HPLC (water/ACN + 0.1% TFA gradient) 95.3% at 220 nm.

*(4-(Propan-2-yloxy)phenyl)(2-fluoro-4-methylphenyl)pyridin-3-yl Methanol (**59**).* General method C (pyridine) with 4-bromo-3-fluorotoluene (294 mg, 1.55 mmol), dry diethyl ether (4 mL), *n*-butyllithium (0.9 mL, 1.45 mmol, 1.6 M solution in hexanes), and **35Biii** (250 mg, 1.04 mmol) in dry tetrahydrofuran (4 mL). The crude material was absorbed onto silica gel and purified by flash column chromatography (eluting with 5% ethyl acetate in dichloromethane to increasing to 20% ethyl acetate) to give **59** as a yellow gummy solid (84 mg, 23%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.41−8.60 (m, 2H), 7.63−7.66 (m, 1H), 7.21−7.35 (m, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.77−6.98 (m, 4H), 6.59−6.74 (m, 1H), 4.55 (spt, *J* = 6.0 Hz, 1H), 3.52 (d, *J* = 10.0 Hz, 1H), 2.35 (s, 3H), 1.34 (d, *J* = 6.0 Hz, 6H). GC/MS *m/z* = 351. HPLC (water/ACN + 0.1% TFA gradient) 97.9% at 220 nm.

*4-((Propan-2-yloxy)phenyl)(4-chloro-2-fluorophenyl)pyridin-3-yl Methanol (**60**).* General method C (pyridine) with 1-bromo-4-chloro-2-fluorobenzene (260 mg, 1.24 mmol), dry diethyl ether (3 mL), *n*-butyllithium (0.73 mL, 1.16 mmol, 1.6 M solution in hexanes), and **35Biii** (200 mg, 0.83 mmol) in dry tetrahydrofuran (3 mL). The crude material was absorbed onto silica gel and purified by flash column chromatography (eluting with 5% ethyl acetate in dichloromethane to increasing to 10% ethyl acetate) to give **60** as a pale-yellow foam (33 mg, 11%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.53 (m, 2H), 7.64(d, *J* = 11.8 Hz, 1H), 7.27−7.37 (m, 1H), 7.03−7.17 (m, 4H), 6.79−6.92 (m, 3H), 4.55 (spt, *J* = 6.0 Hz, 1H), 3.36 (d, *J* = 7.9 Hz, 1H), 1.38−1.39 (m, 1H), 1.34 (d, *J* = 6.0 Hz, 1H). GC/MS *m/z* = 371. HPLC (method 1) 96.2% at 220 nm.

*Bis(4-(iso-propoxy)phenyl)pyridin-3-yl Methanol (**61**).* General method C (pyridine) with **34Bii** (0.759 g, 3.53 mmol), dry diethyl ether (10 mL), *n*-butyllithium (2.05 mL, 3.28 mmol, 1.6 M solution in hexanes), and **35Biii** (0.608 g, 2.52 mmol) in dry tetrahydrofuran (6 mL). The crude material was absorbed onto silica gel and purified by flash column chromatography (eluting with 5% ethyl acetate in dichloromethane increasing to 40% ethyl acetate). Further purification by reverse phase column chromatography eluting with 50% acetonitrile in water gave **61** as a pale-yellow glass (50 mg, 5%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.37−8.64 (m, 2H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.23 (m, 1H), 7.13 (d, *J* = 8.8 Hz, 4H), 6.82 (d, *J* = 8.8 Hz, 4H), 4.54 (spt, *J* = 6.0 Hz, 2H), 2.80 (s, 1H), 1.33 (d, *J* = 6.0 Hz, 12H). GC/MS *m/z* = 377. HPLC (water/ACN + 0.1% TFA gradient) >99% at 220 nm.

*Bis(4-trifluoromethylphenyl)pyridin-3-yl Methanol (**62**).* A 250 mL three-necked flask dried under an atmosphere of nitrogen was charged with magnesium turnings (630 mg, 25.9 mmol) and heated further with a heat gun under nitrogen. In the attached dropping funnel was added 4-bromobenzotrifluoride (5.95 g, 26.5 mmol) in THF (40 mL). Approximately 3 mL of the solution was added to the magnesium, along with 2 drops of 1,2-dibromoethane. The solution was warmed using a heat gun to initiate the reaction, as evidenced by the appearance of small bubbles. The remaining THF solution was added dropwise over 30 min and, upon completion of addition, the reaction mixture was heated under reflux for 30 min. On cooling to room temperature, a solution of ethyl pyridine-2-carboxylate (1 g 6.62 mmol) in THF (10 mL) was added and the mixture heated for a further 3 h under reflux and then left to stir at room temperature overnight. A saturated, aqueous solution of ammonium chloride (50 mL) was added and the mixture extracted into dichloromethane (50 mL). Brine (40 mL) was added to break down the resultant emulsion, and the mixture was filtered through a pad of Celite. The organic phase was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification via column chromatography (eluent 50% EtOAc in hexanes) gave **62** as an orange solid (176 mg, 7%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.39−8.54 (m, 2H), 7.55−7.66 (m, 5H), 7.42 (d, *J* = 8.3 Hz, 4H), 7.22−7.33 (m, 1H), 3.59 (br s, 1H). MS *m/z* = 397. HPLC (water/ACN + 0.1% TFA gradient) 98.8% at 220 nm.

*Bis(4-chloro-2-fluorophenyl)pyridin-3-yl Methanol (**63**).* General procedure C (pyridine) 1-bromo-4-chloro-2-fluorobenzene (249 mg, 1.19 mmol), dry diethyl ether (3 mL), *n*-butyllithium (0.69 mL, 1.55 mmol, 1.6 M solution in hexanes), and **63Biii** (200 mg, 0.85 mmol) in dry tetrahydrofuran (3 mL). The crude material was absorbed onto silica gel and purified by flash column chromatography (eluting with 5% ethyl acetate in dichloromethane increasing to 10% ethyl acetate)

to give **63** as a white powder (33 mg, 11%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.46−8.61 (m, 2H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.27−7.35 (m, 1H), 7.04−7.21 (m, 6H), 3.68 (t, *J* = 4.8 Hz, 1H). GC/MS *m/z* = 365. HPLC (water/ACN + 0.1% TFA gradient) 97% at 220 nm.

*Synthesis of Compounds in Table 4. (4-Chlorophenyl)(thiophen-2-yl)pyridin-3-yl methanol (**64**).* General method C (pyridine) with 2-bromothiophene (1.95 g, 12 mmol), *n*-butyllithium (1.6 M in hexanes, 7.5 mL, 12 mmol), dry diethyl ether (30 mL), **13Biii** (2 g, 9.22 mmol), and dry tetrahydrofuran (30 mL). Purification by flash column chromatography (eluting with 33% ethyl acetate in hexanes) gave **64** as a white powder (1.28 g, 46%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.60 (d, *J* = 2.0 Hz, 1H), 8.52 (dd, *J* = 1.3, 4.7 Hz, 1H), 7.67−7.75 (m, 1H), 7.19−7.37 (m, 6H), 6.97 (dd, *J* = 3.7, 5.1 Hz, 1H), 6.73 (dd, *J* = 0.9, 3.7 Hz, 1H), 3.26 (s, 1H). GCMS *m/z* = 301. HPLC (water/ACN + 0.1% TFA gradient) 99% at 220 nm.

*(4-Chloro-2-fluorophenyl)(thiophen-2-yl)pyridin-3-yl Methanol (**65**).* General method C (pyridine) with 2-bromothiophene (167 mg, 1.02 mmol), *n*-butyllithium (1.6 M in hexanes, 0.58 mL, 0.93 mmol), dry diethyl ether (4 mL), **13Biii** (200 mg, 0.85 mmol), and dry tetrahydrofuran (4 mL). Purification by flash column chromatography (eluting with 10% ethyl acetate in hexanes increasing to 20% ethyl acetate) gave **65** as a yellow glass (179 mg, 66%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.44 (br s, 2H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 4.9 Hz, 1H), 7.14−7.24 (m, 2H), 6.78−7.12 (m, 4H), 6.61 (d, *J* = 3.2 Hz, 1H), 3.54−4.27 (m, 1H). ESI *m/z*: 319 (M). HPLC (water/ACN + 0.1% TFA gradient) >99% at 220 nm.

*(4-Chlorophenyl)(thiophen-3-yl)pyridin-3-yl Methanol (**66**).* General method C (pyridine) with 3-bromothiophene (248 mg, 1.52 mmol), *n*-butyllithium (1.6 M in hexanes, 1.0 mL, 1.6 mmol), dry diethyl ether (3 mL), **13Biii** (248 mg, 1.38 mmol), and dry tetrahydrofuran (3 mL). Purification by flash column chromatography (eluting with 10% ethyl acetate in dichloromethane increasing to 25% ethyl acetate) gave **66** as an off-white foam (272 mg, 66%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.43−8.55 (m, 2H), 7.63−7.71 (m, 1H), 7.18−7.44 (m, 6H), 6.84−7.01 (m, 2H), 3.37 (s, 1H). GCMS *m/z* 301. HPLC (water/ACN + 0.1% TFA gradient) 96.90% at 220 nm.

*(2-Benzothiophenyl)(4-trifluoromethylphenyl)pyrid-3-yl) Methanol (**67**).* General method C (pyridine) with 4-bromobenzotrifluoride (282 mg, 1.25 mmol), *n*-butyllithium (1.6 M in hexanes, 0.74 mL, 1.18 mmol), dry diethyl ether (3 mL), **67Biii** (200 mg, 0.84 mmol), and dry tetrahydrofuran (3 mL). Purification by flash column chromatography (eluting with 10% ethyl acetate in dichloromethane increasing to 66% ethyl acetate) gave **67** as a white foam (202 mg, 62%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.59 (d, *J* = 1.9 Hz, 1H), 8.50 (dd, *J* = 1.1, 4.7 Hz, 1H), 7.70−7.81 (m, 2H), 7.52−7.69 (m, 5H), 7.21−7.42 (m, 3H), 6.91 (s, 1H), 4.06 (s, 1H). GCMS *m/z* 385. HPLC (method 1) 7.24 min 99.25% at 220 nm.

*(4-Chlorophenyl)(thiazol-2-yl)pyridin-3-yl Methanol (**68**).* General method C (pyridine) with 2-bromothiazole (284 mg, 1.73 mmol), *n*-butyllithium (1.6 M in hexanes, 1.0 mL, 1.6 mmol), dry diethyl ether (3 mL), **13Biii** (250 mg, 1.15 mmol), and dry tetrahydrofuran (3 mL). Purification by flash column chromatography (eluting with 33% ethyl acetate in dichloromethane) gave **68** as a yellow glass (273 mg, 78%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.53 (d, *J* = 2.1 Hz, 1H), 8.47 (dd, *J* = 1.4, 4.8 Hz, 1H), 7.83 (d, *J* = 3.2 Hz, 1H), 7.69−7.76 (m, 1H), 7.19−7.41 (m, 6H), 5.03 (s, 1H). GCMS [M + H] = 303.2. HPLC (water/ACN + 0.1% TFA gradient) 95.01% at 220 nm.

*(4-Chlorophenyl)(1,3-thiazol-5-yl)pyridin-3-yl Methanol (**69**).* General method C (pyridine) with 5-bromothiazole (153 mg, 0.93 mmol), *n*-butyllithium (1.6 M in hexanes, 0.6 mL, 0.96 mmol), dry diethyl ether (4 mL), **13Biii** (200 mg, 0.94 mmol), and dry tetrahydrofuran (2 mL). Purification by flash column chromatography (eluting with 20% ethyl acetate in hexanes) gave **69** as an off-white powder (46 mg, 16%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.80 (s, 1H), 8.47−8.60 (m, 2H), 7.68 (td, *J* = 1.9, 8.1 Hz, 1H), 7.44 (s, 1H), 7.27−7.38 (m, 5H), 3.96 (s, 1H). ESI *m/z*: 302 (M). HPLC (water/ACN + 0.1% TFA gradient) 97.63% at 220 nm.

*(4-Chlorophenyl)(2-amino-1, 3-thiazol-5-yl)pyridin-3-yl Methanol Dihydrochloride (**70**).* A dried 100 mL three-necked flask, under nitrogen, was charged with 2-aminothiazole (0.2 g, 0.002 mol) and tetrahydrofuran (5 mL). The solution was cooled to −78 °C, and *n*-butyllithium (1.6 M in hexanes, 2.5 mL, 0.008 mol) was added dropwise over 10 min. The resultant brown suspension was stirred at low temperature for 1 h. Chlorotrimethylsilane (0.5 mL, 0.004 mol) was added and the reaction slowly warmed to −20 °C, giving a solution which was recooled to −78 °C. *n*-Butyllithium (1.6 M in hexanes, 1.25 mL, 0.004 mol) was slowly added, the mixture stirred for 15 min, and then a solution of **13Biii** (0.435 g, 0.002 mol) in tetrahydrofuran (4 mL) added. After stirring at −78 °C for 30 min, the mixture was allowed to warm slowly to room temperature overnight and then quenched with a saturated solution of ammonium chloride (50 mL), extracted into ethyl acetate (2 × 30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (eluting with 20% ethyl acetate in hexanes) gave **70** (250 mg, 35%) as a tan solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.43 (br s, 2H), 8.69−8.87 (m, 2H), 8.24 (d, *J* = 8.1 Hz, 1H), 7.77−7.91 (m, 2H), 7.37−7.54 (m, 4H), 6.82 (s, 1H). [M + 1] 318. HPLC (water/ACN + 0.1% TFA gradient) 98.51% at 220 nm.

*N-{5-[(4-Chlorophenyl)(hydroxy)pyridin-3-ylmethyl]-1,3-thiazol-2-yl}-2-methyl Propanamide (**71**).* A 100 mL round-bottomed flask was charged with **70** (100 mg, 0.315 mmol) and dichloromethane (10 mL). Upon dissolution of the solid, isobutyryl chloride (50 mg, 0.47 mmol) and triethyl amine (32 mg, 0.315 mmol) were added, the mixture stirred at room temperature overnight and then quenched with water (30 mL), extracted into dichloromethane (2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by Flashmaster II (2 g column, eluting with ethyl acetate increasing to 10% methanol in ethyl acetate). Material was triturated in diethyl ether to give **71** (30 mg, 24%) as a yellow powder. ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.05 (s, 1H), 8.4−8.6 (m, 2H), 7.70−7.80 (m, 1H), 7.30−7.50 (m, 4H), 7.17 (s, 1H), 6.92 (s, 1H), 2.60−2.85 (m, 1H), 1.107−1.140 (d, *J* = 6.0 Hz, 6H). [M + 1] 388. HPLC (water/ACN + 0.1% TFA gradient) 96.67% at 220 nm.

*(4-Chlorophenyl)(2-chloro-1,3-thiazol-5-yl)pyridin-3-yl Methanol (**72**).* General method C (pyridine) with 2-chlorothiazole[28] (2 g, 0.0167 mol) in tetrahydrofuran (40 mL), *n*-butyllithium (1.6 M in hexanes, 10.4 mL, 0.0167 mol), **13Biii** (3.4 g, 0.0167 mol), and dry tetrahydrofuran (10 mL). Purification by flash column chromatography (eluting with 20% ethyl acetate in hexanes increasing to 50% ethyl acetate) gave **72** yellow glass (3.2 g, 57%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.23−8.51 (m, 2H), 7.65−7.67 (m, 1H), 7.16−7.46 (m, 5H), 6.96−7.10 (m, 1H), 5.37−6.18 (m, 1H). ESI *m/z*: 336 (M). HPLC (water/ACN + 0.1% TFA gradient) 99.52% at 220 nm.

*(4-Chlorophenyl)(pyrimidin-5-yl)pyridin-3-yl Methanol (**73**).* General method C (pyridine) except *n*-butyllithium (1.6 M in hexanes, 1.15 mL, 1.84 mmol) added to a cold (−78 °C) solution of 5-bromopyrimidine (406 mg, 1.84 mmol) and **13Biii** (249 mg, 1.15 mmol) in dry tetrahydrofuran (10 mL). Purification by flash column chromatography (eluting with 20% ethyl acetate in hexanes increasing to 80% ethyl acetate). Repurification on reverse phase silica eluting with 30% methanol in water increasing to 60% methanol gave **73** as a beige solid (102 mg, 30%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.17 (s, 1H), 8.69 (s, 2H), 8.47−8.60 (m, 2H), 7.56−7.66 (m, 1H), 7.27−7.44 (m, 3H), 7.19 (d, *J* = 8.5 Hz, 2H), 3.68 (s, 1H). GCMS *m/z* = 297. HPLC (water/ACN + 0.1% TFA gradient) 99.30% at 220 nm.

*(2-Chloropyrimidin-5-yl)[4-(propan-2-yloxy)phenyl]pyridin-3-yl Methanol (**74**).* General method C (pyridine) except *n*-butyllithium (1.6 M in hexanes, 0.8 mL, 1.28 mmol) added to a cold (−80 °C) solution of 5-bromo-2-chloropyrimidine (267 mg, 1.38 mmol) and **35Biii** (221 mg, 0.919 mmol) in dry tetrahydrofuran (8 mL). Purification by flash column chromatography (eluting with 20% ethyl acetate in hexanes increasing to 100% ethyl acetate, then 10% methanol in ethyl acetate). Repurification twice on reverse phase silica eluting with 40% methanol in water increasing to 70% methanol in water, then 50% acetonitrile in water gave **74** as an off-white glass (76 mg, 23%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.50−8.67 (m, 4H), 7.58−7.70 (m, 1H), 7.32 (dd, *J* = 4.8, 8.0 Hz, 1H), 7.06 (d, *J* = 8.9 Hz, 2H), 6.81−6.93 (m, 2H), 4.57 (spt, *J* = 6.0 Hz, 1H), 3.23 (s, 1H), 1.35 (d, *J* = 6.0 Hz, 6H). ESI *m/z*: 355 (M). HPLC (water/ACN + 0.1% TFA gradient) 98.73% at 220 nm.

*(4-Chlorophenyl)[2-(propan-2-yloxy)pyrimidin-5-yl]pyridin-3-yl Methanol (**75**).* General method C (pyridine) except *n*-butyllithium (1.6 M in hexanes, 0.8 mL, 1.28 mmol) added to a cold (−80 °C) solution of **88** (200 mg, 0.92 mmol) and **13Biii** (299 mg, 1.38 mmol) in dry tetrahydrofuran (8 mL). Purification by flash column chromatography (eluting with 20% ethyl acetate in hexanes increasing to 100% ethyl acetate, then 10% methanol in ethyl acetate). Repurification on reverse phase silica eluting with 40% methanol in water increasing to 60% methanol in water gave **75** as a white solid (124 mg, 38%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.51−8.64 (m, 2H), 8.39 (s, 2H), 7.64 (td, J = 1.9, 8.0 Hz, 1H), 7.28−7.43 (m, 3H), 7.17−7.26 (m, 2H), 5.18−5.36 (m, 1H), 3.10 (s, 1H), 1.40 (d, J = 6.2 Hz, 7H). HPLC (water/ACN + 0.1% TFA gradient) 97.02% at 220 nm.

*(4-Chloro-2-fluorophenyl)[2-(propan-2-yloxy)pyrimidin-5-yl]-pyridin-3-yl Methanol (**76**).* General method C (pyridine) except *n*-butyllithium (1.6 M in hexanes, 0.8 mL, 1.28 mmol) added to a cold (−80 °C) solution of **87** (299 mg, 1.38 mmol) and **63Biii** (21 mg, 0.92 mmol) in dry tetrahydrofuran (8 mL). Purification by flash column chromatography (eluting with 20% ethyl acetate in hexanes increasing to 100% ethyl acetate, then 10% methanol in ethyl acetate). Repurification on reverse phase silica eluting with 40% acetonitrile in water increasing to 70% methanol in water gave **76** as an off-white glass (90 mg, 26%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.58−8.62 (m, 1H), 8.51 (s, 1H), 8.38 (s, 2H), 7.56−7.72 (m, 1H), 7.34 (dd, J = 4.7, 7.9 Hz, 1H), 7.08−7.22 (m, 2H), 6.96−7.05 (m, 1H), 5.28 (quin, J = 6.2 Hz, 1H), 3.57 (d, J = 7.9 Hz, 1H), 1.41 (d, J = 6.2 Hz, 6H). ESI m/z: 373 (M). HPLC (water/ACN + 0.1% TFA gradient) >99% at 220 nm.

ASSOCIATED CONTENT

Supporting Information

Additional synthetic methods for the preparation of intermediates to final compounds and spectroscopic/analytical data. General description of solubility, microsomal stability and cytochrome P450 3A4/5 inhibition assays. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Phone: +61 (0)8 9360 6386. Fax: +61 (0)8 9360 7699. E-mail: martine.keenan@epichem.com.au.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

Tc and *T. cruzi*, (*Trypanosoma cruzi*); TcVI, (strain of *Trypanosoma cruzi* belonging to group VI)

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