5-Substituted, 6-Substituted, and Unsubstituted 3-Heteroaromatic Pyridine Analogues of Nicotine as Selective Inhibitors of Cytochrome P-450 2A6

Travis T. Denton, Xiaodong Zhang, and John R. Cashman*

Human BioMolecular Research Institute, 5310 Eastgate Mall, San Diego, California 92121

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A series of 5- and 6-substituted and unsubstituted 3-heteroaromatic analogues of nicotine were synthesized in an effort to delineate the structural requirements for selectively inhibiting human cytochrome P-450 (CYP) 2A6, the major nicotine metabolizing enzyme. Thiophene, substituted thiophene, furan, substituted furan, imidazole, substituted imidazole, pyridine, substituted pyridine, thiazole, and quinoline moieties were used to replace the *N*-methylpyrrolidine ring of nicotine. Bromo and methyl groups were introduced at the 5-position of the pyridine ring and fluoro, chloro, and methoxy groups were placed at the 6-position of the pyridine ring in order to explore the structure−activity relationship (SAR) of inhibition of CYP2A6. The inhibitory activity of the most potent CYP2A6 inhibitors on the functional activity of human cytochrome P450s 3A4, 2E1, 2B6, 2C9, 2C19, and 2D6 was also examined to determine inhibitor selectivity. We identified 36 compounds that were more potent than nicotine at inhibition of coumarin 7-hydroxylase (CYP2A6) activity. We also found a number of compounds to be highly selective for the inhibition of human CYP2A6 versus the other human CYPs examined.

Introduction

The use of tobacco products causes complex central nervous system, behavioral, cardiovascular, endocrine, neuromuscular, and metabolic effects in humans.[1−3] Currently, 1.2 billion people worldwide smoke tobacco despite clear evidence that smoking is a leading "preventable" cause of death. Active smoking is a primary cause of lung cancer,[4] and side stream smoke is also unquestionably linked to lung cancer[5] and heart disease.[6] The addiction liability and pharmacological effects of smoking are primarily mediated by the major tobacco alkaloid *S*-(−)-nicotine (nicotine).[1,7,8] In humans, nicotine is primarily C-atom-oxidized by hepatic cytochrome P-450 2A6 (CYP2A6).[9,10] Thus, almost 90% of hepatic nicotine $\Delta^{1'-5'}$-imminium ion formation (i.e., the key initial intermediate leading to cotinine formation after the action of aldehyde oxidase) is mediated by CYP2A6.[10] On the basis of extensive in vitro and in vivo studies, cDNA-expression studies, immunoblot studies, and the effect of alternative substrates at clinically relevant doses, less than 4% of nicotine oxidation is due to a single cytochrome P-450 other than CYP2A6.[9] CYP2A6 also contributes to the activation of tobacco-specific *N*-nitrosamine promutagens including 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in rodents that induces lung tumorigenesis.[11] It is possible that NNK and other related promutagens play a role in human lung cancer, and it has recently been shown that CYP2A6 is the enzyme responsible for the mutagenic activation of NNK and other tobacco-related nitrosamines.[12]

CYP2A6 is a genetically polymorphic enzyme. Male Japanese smokers with the CYP2A6*4 gene deletion have a decreased risk for lung cancer,[13,14] and betel quid chewers in Sri Lanka with the same polymorphism have a reduced risk for oral cancer.[15] Further, studies have shown that individuals with the gene deletion CYP2A6*4 and point mutation CYP2A6*2 appear to smoke fewer cigarettes.[16,17] If humans modulate their smoking to control nicotine consumption,[18] it is possible that individuals with decreased nicotine metabolism will be predisposed to smoke less tobacco and have decreased addiction liability. People smoke to achieve a specific concentration of nicotine in their blood,[1] and a deficiency in CYP2A6-mediated metabolism of nicotine may permit longer exposure to nicotine and, in turn, may decrease the number of cigarettes a person needs to smoke to obtain their desired blood nicotine concentration. A compound developed as a nonaddictive nicotine replacement agent could reduce the addiction liability to smokers and decrease the present and future harm to those around them by minimizing their contact to sidestream smoke. Current nicotine replacement therapies (i.e., nicotine gum, nicotine patch, inhaler, lozenges, etc.), while removing many of the possible injurious components of tobacco smoke, do not address the issue of decreasing or eliminating nicotine consumption.

Among the hundreds of compounds tested as inhibitors of CYP2A6,[19−21] tranylcypromine, a monoamine oxidase inhibitor antidepressant, and methoxsalen, a T-cell lymphoma chemotherapeutic, have emerged as the leading candidates possessing apparent K_i values of 0.08 and 0.8 μM, respectively.[21] Although these compounds are highly potent, the selectivity for inhibiting CYP2A6 either has not been characterized or is low. If the CYP2A6 gene defect that is associated with decreased smoking could be mimicked by a chemical inhibitor, development of a new smoking cessation agent is possible. The ideal drug candidate for use as a CYP2A6 inhibitor and a smoking cessation agent must be highly potent and selective to avoid undesirable effects.

* To whom correspondence should be addressed. Telephone: 858-458-9305. Fax: 858-458-9311. E-mail: jcashman@hbri.org.

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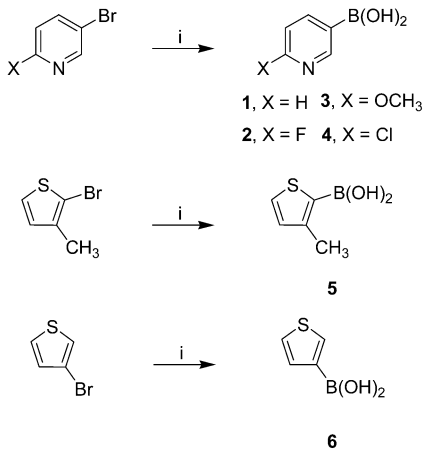
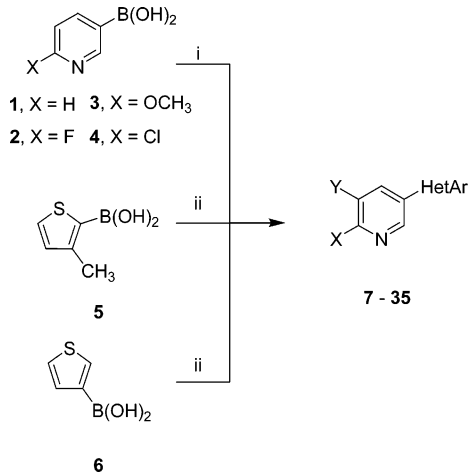
Scheme 1[a]



[a] Reagents: (i) ^{n}BuLi, B(OiPr)$_3$, HCl(aq), NaOH(aq).

Scheme 2[a]



[a] Reagents: (i) HetAr bromide, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, DME, 90 °C; (ii) 3,5-dibromopyridine, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, DME, 90 °C.

Herein, we describe the solution-phase synthesis of a library of 58 nicotine analogues and the identification of 36 compounds that are more potent inhibitors of CYP2A6 than *S*-(−)-nicotine. We also show the selectivity of CYP2A6 inhibition by comparing the interaction of the more potent compounds with the most prominent drug metabolizing human cytochrome P-450s.

Chemistry

The general synthesis of pyridin-3-ylboronic acids[22] (**1**−**6**) that were utilized in Suzuki cross-coupling reactions is shown in Scheme 1. Compounds **7**−**35** (Scheme 2) were synthesized in yields ranging from 39% to 95% by the Suzuki cross-coupling reaction using the appropriate boronic acid, heteroaryl bromide or iodide, aqueous sodium carbonate, and tetrakis(triphenylphosphine)palladium(0) in dimethoxyethane in a sealed vial at 90 °C for 1 h (Table 1).

The use of the thiophene-linked aldehyde (**13**) and furan-linked aldehyde (**23**) as common intermediates in the synthesis of the thiophene-linked *cis*/*trans* oximes (**36**) and the furan-linked *cis*/*trans* oximes **37a** and **37b** was accomplished in good yield using hydroxylamine hydrochloride and sodium acetate in refluxing ethanol (Scheme 3). Compound **36** was formed as an inseparable mixture of *cis*/*trans* isomers. The *trans* oxime **37a** and *cis* oxime **37b** were separated by flash column chromatography. The thiophene-linked aldehyde (**13**) was converted to its corresponding amine **38a** and the furan-linked aldehyde (**23**) was converted to its corresponding amine **39a** by reductive amination using ammonium acetate and sodium cyanoborohydride in methanol.[23] During the course of the reductive amination, the secondary amines **38b** and **39b** and tertiary amine **39c** were also formed as side products from amines **38a**, **39a**, and **39b**, respectively. The thiophene- and furan-linked *N*-methylamines **40** and **41** were obtained by the reductive amination of aldehydes **13** and **23**, respectively, with methylamine and sodium cyanoborohydride in methanol. The thiophene- and furan-linked *N*,*N*-dimethylamines **42** and **43** were obtained by reductive amination of aldehydes **13** and **23**, respectively, with dimethylamine and sodium cyanoborohydride in methanol. The thiophene- and furan-linked alcohols **44** and **45** were obtained by treating the aldehydes **13** and **23**, respectively, with sodium borohydride in methanol.

Sonogashira coupling of Boc-protected propargylamine with 3-bromopyridine using aqueous sodium carbonate, copper iodide, and tetrakis(triphenylphosphine)palladium(0) in dimethoxyethane in a sealed vial at 90 °C for 1 h afforded the acetylenic primary amine **48** after Boc deprotection using TFA in CH_2Cl_2 (Scheme 4). The alkylation of the *N*-Boc protected acetylenic amine (**47**) with methyl iodide after sodium hydride deprotonation in THF provided the *N*-Boc-*N*-methylacetylenic amine (**49**), which was deprotected by TFA in CH_2Cl_2 to afford the *N*-methylacetylenic amine **50**. The acetylenic tertiary amine (**51**) was obtained by the Sonogashira coupling of *N*,*N*-dimethylpropargylamine with 3-bromopyridine using the same conditions employed for the synthesis of **47**.

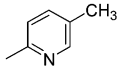
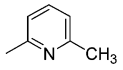
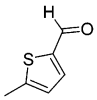
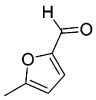
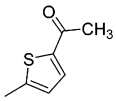
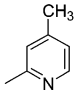
Scheme 5 shows the synthetic route for (4-(pyridin-3-yl)phenyl)methanamine (**54**). Suzuki coupling of pyridin-3-yl-3-boronic acid with 4-bromobenzaldehyde using aqueous sodium carbonate and tetrakis(triphenylphosphine)palladium(0) in dimethoxyethane in a sealed vial at 90 °C for 1 h afforded the phenyl-linked aldehyde **52**. The synthesis of the phenyl-linked *cis*/*trans* oximes (**53**) was accomplished in good yield using hydroxylamine hydrochloride and sodium acetate in refluxing ethanol. Reduction of **53** with LAH in THF provided the phenyl-linked primary amine **54**.

The 5-methyl-3-thiopheneylpyridines **55** and **56** were obtained by the Stille coupling reaction of **12** and **19**, respectively, with tetramethyltin, aqueous sodium carbonate, and tetrakis(triphenylphosphine)palladium(0) in dimethoxyethane in a sealed vial at 90 °C for 1 h (Scheme 6).

The thiophene-linked amine **57** was obtained by hydrogenation of nitrothiophene (**15**) using 10% palladium on carbon in methanol (Scheme 7).

The alkylation of 3-(1*H*-imidazol-4-yl)pyridine (**34**) with methyl iodide after sodium hydride deprotonation in THF provided the methyl-substituted imidazolylpyridines (**58a**,**b**), in a 2.5:1 ratio as determined by proton NMR analysis, in 66% combined yield (Scheme 8). Alkylation of **34** in the same manner with ethyl iodide and benzyl bromide provided the ethyl-substituted (**59**) and benzyl-substituted (**60**) imidazolylpyridines in 79% and 74% yield, respectively.

Table 1. Synthetic Compounds Obtained by Suzuki Coupling (Scheme 2) Examined for Inhibition of Coumarin 7-Hydroxylation

compd	X	Y	HetAr	compd	X	Y	HetAr	compd	X	Y	HetAr
7	H	H		**17**	F	H		**27**	H	H	
8	H	H		**18**	OCH_3	H		**28**	H	H	
9	H	H		**19**	H	Br		**29**	H	H	
10	F	H		**20**	H	H		**30**	H	H	
11	OCH_3	H		**21**	F	H		**31**	H	H	
12	H	Br		**22**	OCH_3	H		**32**	Cl	H	
13	H	H		**23**	H	H		**33**	H	H	
14	H	H		**24**	H	H		**34**	H	H	
15	H	H		**25**	H	H		**35**	H	H	
16	H	H		**26**	H	H					

SnAr reaction between 4-methylimidazole, 2-methylimidazole, 1*H*-imidazole, and 3-fluoropyridine in DMF using sodium hydride as the base afforded 3-imidazol-1-ylpyridines **61**, **62**, and **63** in 45%, 30%, and 59% yield, respectively (Scheme 9). In the case of **61**, the equilibrium between the intermediate 4- and 5-methyl-1-imidazolide ions resulted in a chromatographically inseparable mixture of 3-(4-methyl-1*H*-imidazol-1-yl)-pyridine and 3-(5-methyl-1*H*-imidazol-1-yl)pyridine.

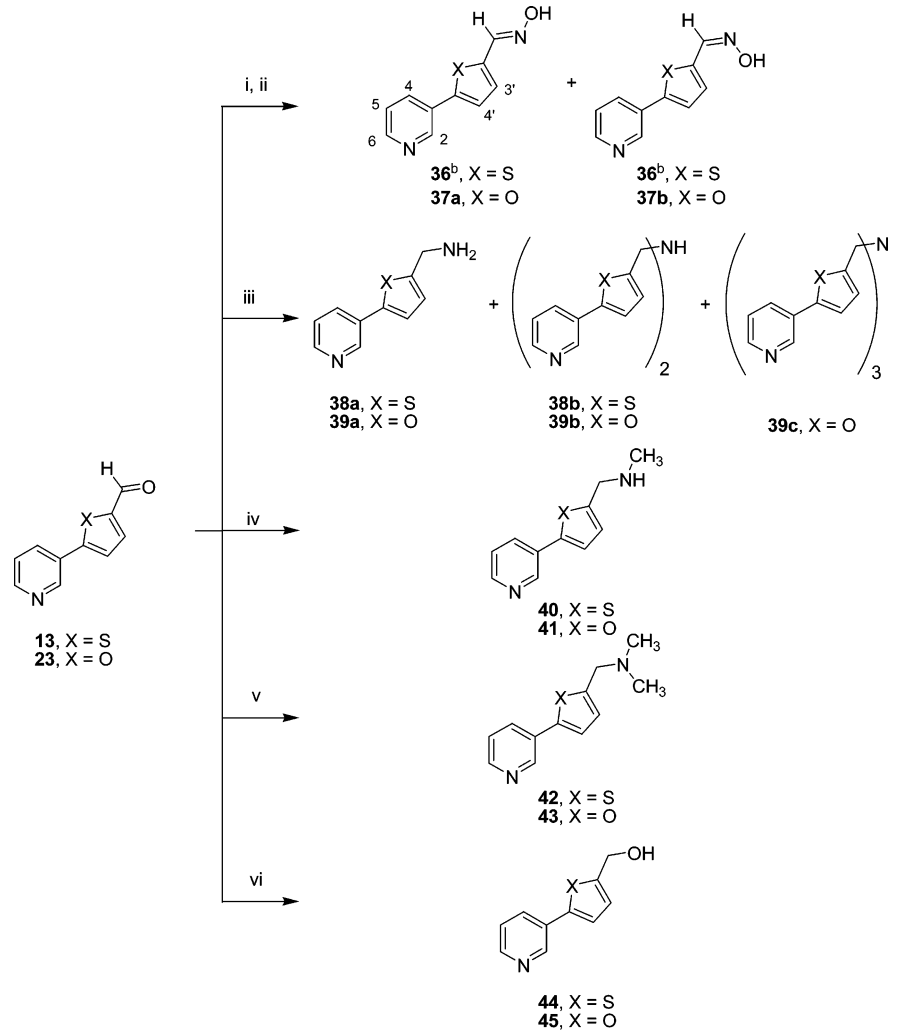
The 3-tetrazolylpyridines **64** and **65** were prepared as shown in Scheme 10. Conversion of 3-cyanopyridine to 3-(1*H*-tetrazol-5-yl)pyridine (**64**) was readily achieved by treatment with sodium nitrite and ammonium chloride in DMF.[24] Combining 3-aminopyridine with trimethyl orthoformate and sodium azide afforded 3-(1*H*-tetrazol-1-yl)pyridine (**65**).[25]

Results and Discussion

The effect of nicotine and 3-substituted heteroaryl pyridine analogues of nicotine on the functional activity of cDNA-expressed human CYP2A6 was determined by examining coumarin 7-hydroxylation. The enzyme assay was established using standard conditions, and coumarin 7-hydroxylation was shown to be linearly dependent on incubation time (0−90 min) and protein concentration (0.5−2.0 pmol of protein). Of the compounds examined, 36 nicotine analogues showed greater potency at inhibiting coumarin 7-hydroxylase functional activity compared with that of nicotine (Table 2). Two nicotine analogues (i.e., compounds **38a** and **39a**) showed K_i values of 20 ± 3 and 40 ± 4 nM, respectively. Apparently, the methylamino group of compound **38a** was essential for potent inhibition because replacement with an aldehyde (i.e., compound **13**, $K_i = 0.79 \pm 0.12$ μM), absence of the methylamino group (i.e., compound **7**, $K_i = 1.2 \pm 0.6$ μM), and replacement with a methyl ketone (i.e., compound **14**, $K_i = 1.4 \pm 0.2$ μM), a methyl alcohol (i.e., compound **44**, $K_i = 5.6 \pm 0.7$ μM), or nitro group (i.e., compound **15**, $K_i = 19.7 \pm 2.3$ μM) decreased inhibitor potency 40-, 60-, 70-, 280-, and 985-fold, respectively. The methylamino group of compound **39a** was also determined to be essential for potent inhibition because replacement with a methyl alcohol (i.e., compound **45**, $K_i = 35.2 \pm 16.7$ μM) or an aldehyde (i.e., compound **23**, $K_i \geq 67$ μM) decreased inhibitor potency 880- and 1675-fold, respectively.

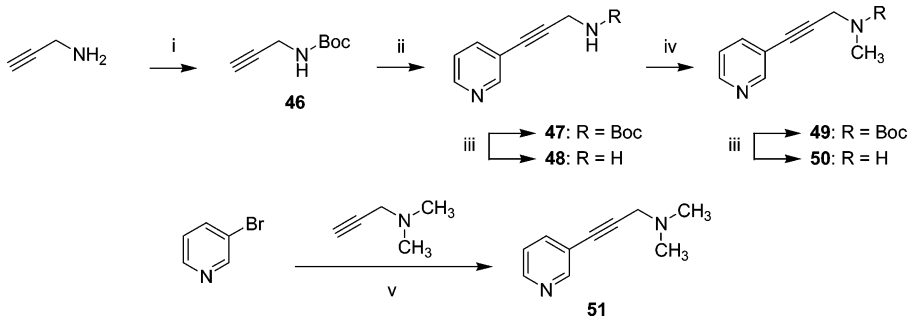
In all cases examined, modification of the methylamino group of compounds **38a** and **39a** decreased

Scheme 3[a]



[a] Reagents: (i) HO−NH_2·HCl, NaOAc, CH_3CH_2OH, heat; (ii) chromatographic separation; (iii) NH_4OAc, $NaBH_3CN$, CH_3OH; (iv) CH_3NH_2, $NaBH_3CN$, CH_3OH; (v) $(CH_3)_2NH$, $NaBH_3CN$, CH_3OH; (vi) $NaBH_4$, CH_3OH. [b] Chromatographic separation of the *cis*/*trans* isomers was not achieved.

Scheme 4[a]

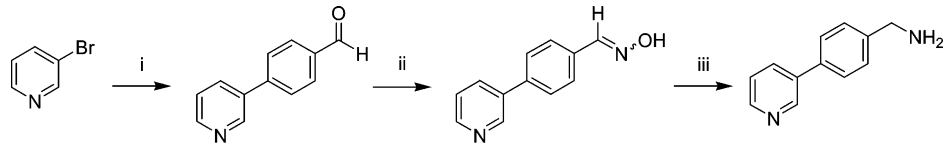


[a] Reagents: (i) Boc_2O, TEA, CH_2Cl_2; (ii) 3-bromopyridine, $Pd(PPh_3)_4$, CuI, Na_2CO_3, DME, 90 °C; (iii) TFA, CH_2Cl_2; (iv) NaH, THF, CH_3I; (v) $Pd(PPh_3)_4$, CuI, Na_2CO_3, DME, 90 °C.

inhibitor potency. For example, oxidation of compound **38a** into a mixture of *cis*/*trans* oxime isomers decreased the K_i value for inhibition of coumarin 7-hydroxylation (i.e., compound **36**, $K_i = 0.24 \pm 0.04$ μM) 12-fold. For compounds **37a** and **37b**, where *trans* and *cis* oxime regioisomers could be chromatographically separated, significant regioselectivity of coumarin 7-hydroxylase inhibition was observed (i.e., *trans* compound **37a**, $K_i = 0.71 \pm 0.08$ μM, *cis* compound **37b**, $K_i = 13.7 \pm 1.2$ μM), although, like the thiophene oxime mixture (compound **36**), the potency was significantly less (i.e., 18- and 343-fold) for the *trans* and *cis* oxime regioisomers, respectively, compared with the parent amine compound **39a** (Table 2). Modification of the primary amines **38a** and **39a** to afford secondary amines (compounds **38b** and **39b**) or a tertiary amine (compound **39c**) decreased inhibitor potency 60-, 38-, and 70-fold, respectively.

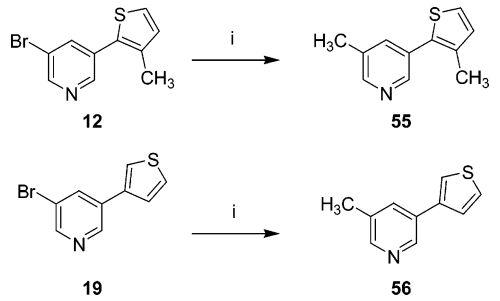
To examine the SAR of the most potent CYP2A6 inhibitors (i.e., **38a** and **39a**), variation of the amino terminus was done. In addition, the distance between

Scheme 5[a]



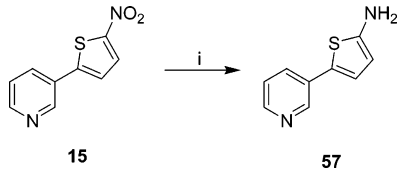
[a] Reagents: (i) 4-bromobenzaldehyde, $Pd(PPh_3)_4$, Na_2CO_3, DME, 90 °C; (ii) $HO-NH_2 \cdot HCl$, NaOAc, CH_3CH_2OH, heat; (iii) LAH, THF.

Scheme 6[a]



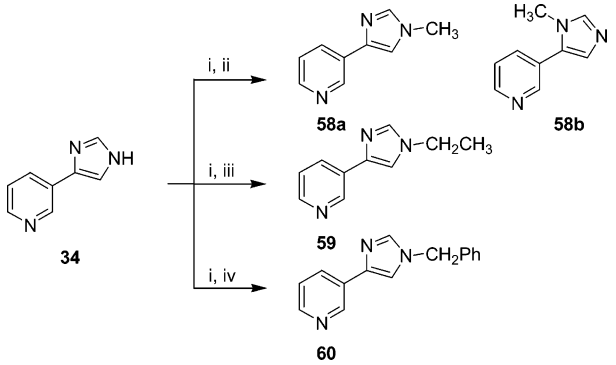
[a] Reagents: (i) $(CH_3)_4Sn$, $Pd(PPh_3)_4$, Na_2CO_3, DME, 90 °C.

Scheme 7[a]



[a] Reagents: (i) H_2, 10% Pd−C, CH_3OH.

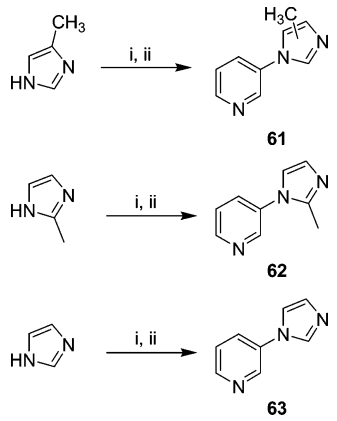
Scheme 8[a]



[a] Reagents: (i) NaH, THF; (ii) CH_3I; (iii) CH_3CH_2I; (iv) $PhCH_2Br$.

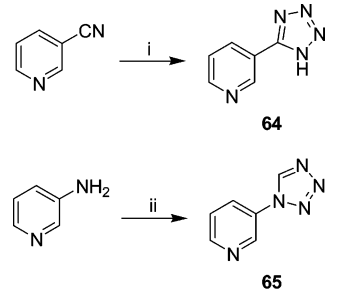
the pyridine and the terminal amino moiety was varied. Finally, the effect of substituents at the 5- and 6-position of the pyridine nucleus was examined. Elaboration of an *N*-methyl (i.e., compound **40**, $K_i = 0.18 \pm 0.02$ μM) or an *N*,*N*-dimethyl (i.e., compound **42**, $K_i = 22.2 \pm 3.3$ μM) substituent to **38a** decreased the potency of inhibition 9- and 1110-fold, respectively. Likewise, addition of an *N*-methyl (i.e., compound **41**, $K_i = 0.28 \pm 0.06$ μM) or an *N*,*N*-dimethyl (i.e., compound **43**, $K_i = 47.2 \pm 3.1$ μM) substituent to **39a** decreased the potency of inhibition 7- and 1180-fold, respectively. Thus, monomethyl substituents in the terminal amino group only moderately decreased inhibitor potency while dimethyl substituents significantly decreased inhibitor potency. Placement of an acetylenic group between the pyridine and methylamino functionality, in which the distance is approximately the same as in compounds **38a** and **39a**, resulted in a potent CYP2A6 inhibitor (i.e., compound

Scheme 9[a]



[a] Reagents: (i) NaH, DMF; (ii) 3-fluoropyridine.

Scheme 10[a]



[a] Reagents: (i) NaN_3, NH_4Cl, DMF; (ii) trimethyl orthoformate, NaN_3, HOAc.

48, $K_i = 0.09 \pm 0.01$ μM). In agreement with that observed for **38a** and **39a**, addition of an *N*-methyl (i.e., compound **50**, $K_i = 0.89 \pm 0.10$ μM) or an *N*,*N*-dimethyl (i.e., compound **51**, $K_i = 22.7 \pm 7.8$ μM) substituent to **48** decreased the potency of inhibition 10- and 252-fold, respectively. Increasing the distance between the pyridine and methylamino functionality by the insertion of a phenyl group (i.e., compound **54**, $K_i = 1.4 \pm 0.3$ μM) resulted in a 70-, 35-, and 16-fold decrease in CYP2A6 inhibitory potency when compared to the thiophene-linked, furan-linked, and acetylene-linked analogues, respectively. The effect of substituents in the 5-position of the pyridine nucleus resulted in a variable effect on CYP2A6 inhibitory potency. For example, addition of a bromine atom (i.e., compound **12**, $K_i = 1.5 \pm 0.2$ μM) or a methyl group (i.e., compound **55**, $K_i = 11 \pm 1.5$ μM) to the 5-position of **9** decreased the K_i value for inhibition of coumarin 7-hydroxylation 15- and 110-fold, respectively. Compared to compound **16** ($K_i = 0.22 \pm 0.04$ μM), addition of a bromine atom (i.e., compound **19**, $K_i = 4.5 \pm 0.8$ μM) to the 5-position decreased the potency for inhibition of coumarin 7-hydroxylation 20-fold, although the addition of a methyl group (i.e., compound **56**, $K_i = 0.17 \pm 0.05$ μM) to the 5-position of **16** increased the potency for inhibition of coumarin

Table 2. Effect of Nicotine and Synthetic Heteroaromatic Nicotine Analogues on Coumarin 7-Hydroxylation by Human Cytochrome P-450 2A6[a]

compd	$K_i \pm$ SD (μM)	compd	$K_i \pm$ SD (μM)	compd	$K_i \pm$ SD (μM)
nicotine	4.4 ± 0.6	**26**	5.1 ± 0.8	**42**	22.2 ± 3.3
7	1.2 ± 0.6	**27**	2.7 ± 0.6	**43**	47.2 ± 3.1
8	3.2 ± 0.6	**28**	9.8 ± 2	**44**	5.6 ± 0.7
9	0.10 ± 0.02	**29**	1.8 ± 0.36	**45**	35.2[b] ± 16.7
10	0.21 ± 0.02	**30**	27.4 ± 4.2	**48**	0.09 ± 0.01
11	≥67[c]	**31**	1.1 ± 0.1	**50**	0.89 ± 0.1
12	1.5 ± 0.2	**32**	6.3 ± 2.5	**51**	22.7 ± 7.8
13	0.79 ± 0.12	**33**	44.5[b] ± 41	**54**	1.4 ± 0.3
14	1.4 ± 0.2	**34**	0.25 ± 0.05	**55**	11 ± 1.5
15	19.7 ± 2.3	**35**	6.2 ± 1	**56**	0.17 ± 0.05
16	0.22 ± 0.04	**36**	0.24 ± 0.04	**57**	0.59 ± 0.05
17	0.97 ± 0.20	**37a**	0.71 ± 0.08	**58**	0.13 ± 0.02
18	9.7 ± 2.1	**37b**	13.7 ± 1.2	**59**	0.52 ± 0.05
19	4.5 ± 0.8	**38a**	0.02 ± 0.003	**60**	0.23 ± 0.03
20	0.25 ± 0.04	**38b**	1.2 ± 0.2	**61**	0.17 ± 0.04
21	2.6 ± 0.5	**39a**	0.04 ± 0.004	**62**	0.25 ± 0.06
22	6.6 ± 0.8	**39b**	1.5 ± 0.3	**63**	0.62 ± 0.13
23	≥67[c]	**39c**	2.8 ± 0.8	**64**	64.8 ± 11.3
24	7.7 ± 1.2	**40**	0.18 ± 0.02	**65**	≥67[c]
25	43.7[b] ± 11.5	**41**	0.28 ± 0.06		

[a] K_i values were determined by increasing the concentration of inhibitors added to the assay mixture containing insect cell microsomes expressing CYP2A6 in 0.1 M Tris buffer, pH 7.5, an NADPH-generating system, DETAPAC, and 3 mM $MgCl_2$. Each value is the mean of at least 3 determinations ± SD. The experimental details are described in the Experimental Section. [b] This compound has a high-fluorescence background that increases the standard deviation. [c] No inhibition was observed at 400 μM.

7-hydroxylation 1.3-fold. Although intriguing, the data suggest that the introduction of functional groups to the 5-position of the pyridine nucleus did not contribute to an appreciable increase in CYP2A6 inhibition potency and thus was not examined further.

To further evaluate the SAR of inhibition of CYP2A6 for the pyridine portion of the inhibitors, the pyridine ring was substituted at the 6-position with a methoxy, chloro, or fluoro group. Because of the ease of synthesis, compounds **9**, **16**, **20**, and **31** were chosen to be modified in the pyridine 6-postion. Compared to compounds **9** ($K_i = 0.1 \pm 0.02$ μM), **16** ($K_i = 0.22 \pm 0.04$ μM), and **20** ($K_i = 0.25 \pm 0.04$ μM), introduction of a methoxy group resulted in an increase in the K_i value to >67 μM, 9.7 ± 2.1 μM, and 6.6 ± 0.8 μM for analogues **11**, **18**, and **22**, respectively (Table 2). These data suggest either that the region that accommodates the pyridine 6-position of the active site is limited or that an electron-donating substituent at the 6-position modulates the potency of CYP2A6 inhibition in a detrimental manner. The introduction of a chlorine atom at the pyridine 6-postion of **31** ($K_i = 1.1 \pm 0.1$ μM) afforded **32** that had a K_i value of 6.3 ± 2.5 μM and afforded a 6-fold loss in potency. To determine if the electron-withdrawing properties or the size of the chlorine atom was responsible for this decreased K_i value, compounds **10**, **17**, and **21**, which contain a fluorine atom on the pyridine 6-position, were synthesized. In each case examined, the introduction of a fluorine atom increased the K_i value of the parent compound and decreased the potency of inhibition 2- to 10-fold. Thus, the K_i value of analogue **10** increased to 0.21 ± 0.02 μM from parent **9** ($K_i = 0.1 \pm 0.02$ μM), the K_i value of analogue **17** increased to 0.97 ± 0.20 μM from parent **16** ($K_i = 0.22 \pm 0.02$ μM), and the K_i value of analogue **21** increased to 2.6 ± 0.5 μM from parent **20** ($K_i = 0.25 \pm 0.04$ μM). In general, the data suggest that introduction of electron-donating or electron-withdrawing functional groups (i.e., CH_3O-, F−, Cl−) to the pyridine 6-position was detrimental to potency of coumarin 7-hydroxylase inhibition, and thus, modifications of the pyridine 6-position were not explored further.

In light of the observations above and the limited synthetic and commercial access to 4-substituted pyridin-3-yl-3-boronic acids, additional SAR studies of the pyridine 4-position were not explored.

Next, we examined if replacement of the methylamino furan or methylamino thiophene moeity (i.e., compounds **38a** and **39a**) by a different nitrogen-containing heterocycle would retain coumarin 7-hydroxylase inhibition potency. Analogue **34**, with a 1*H*-imidazole-4-yl moiety at the pyridine 3-position, possessed a K_i value of 0.25 ± 0.05 μM. To examine the allowable molecular space in the CYP2A6 active site, the 1*H* nitrogen of **34** was alkylated with methyl iodide, ethyl iodide, and benzyl bromide to afford analogues **58a**,**b** (tested as a mixture of regioisomers), **59**, and **60** that had K_i values of 0.13 ± 0.02, 0.52 ± 0.05, and 0.23 ± 0.03 μM, respectively. That negligible loss of inhibitor potency was observed upon introduction of a benzyl group into compound **60** suggested that there was a significant amount of space available in the CYP2A6 active site to accommodate large alkyl groups at this position of the heteroaryl group. The analogues **61** (tested as a mixture of 3-(4- and 5-methyl-1*H*-imidazol-1-yl)pyridine regioisomers) and compounds **62** and **63** possessed K_i values of 0.17 ± 0.04, 0.25 ± 0.06, and 0.62 ± 0.13 μM, respectively, reinforcing the suggestion that there is an adequate amount of room in the active site to allow for additional functionality to the five-membered heterocycle attached to the pyridine 3-position. To further probe the CYP2A6 active site, compounds **15** and **57** were determined to have K_i values of 19.7 ± 2.3 and 0.59 ± 0.05 μM, respectively, suggesting that the nitro group is too large or not sufficiently nucleophilic to afford potent CYP2A6 inhibition, but the amino group is appropriate to provide a potent CYP2A6 inhibitor.

Heteroaromatic analogues of nicotine that inhibited coumarin 7-hydroxylation with K_i values below 1.5 μM were selected to be examined for selectivity of P450 inhibition. The nicotine analogues were tested as inhibitors of human CYP2E1, 2B6, 2C9, 2C19, and 2D6 with high-throughput fluorescence assays using cDNA-expressed human CYPs prepared from transfected insect cell microsomes.[26] CYP3A4-mediated testosterone 6-hydroxylation inhibition was assayed using human liver microsomes and a standard HPLC-based assay.[27] Full dose-range IC_{50} values were obtained, and the CYP inhibition data were presented in Table 3. The selectivity ratios (i.e., $[IC_{50}(CYPX)]/[IC_{50}(CYP2A6)]$) are given in Table 4. Of the analogues tested, the CYP3A4/CYP2A6 selectivity ratio varied from 2 for analogue **57** to 400 for **16**, CYP2E1/CYP2A6 varied from 0.4 for **60** to 637 for **39a**, CYP2B6/CYP2A6 varied from 1.2 for **38b** to 707 for **39a**, CYP2C9/CYP2A6 varied from 0.1 for **38b** to >400 for **61**, CYP 2C19/CYP2A6 varied from 0.03 for **38b** to >294 for **61**, and CYP2D6/CYP2A6 varied from 1.7 for **38b** to 988 for **38a** (Table 3). The most potent CYP2A6 inhibitors examined, **38a** and **39a**, were found

Table 3. Selective Functional Inhibition of CYP3A4, 2E1, 2B6, 2C9, 2C19, and 2D6 by Synthetic Heteroaromatic Nicotine Analogues[a]

	$IC_{50} \pm SD$ (μM)						
compd	2A6[b]	3A4[c]	2E1[b]	2B6[b]	2C9[b]	2C19[b]	2D6[b]
7	7.8 ± 3.7	57.0 ± 21.3	4.1 ± 0.82	70.8 ± 3.6	99.2 ± 12.0	178 ± 13	>400
9	0.62 ± 0.10	6.0 ± 1.3	6.9 ± 2.1	3.9 ± 0.8	93.1 ± 8.8	20.1 ± 2.2	92.5 ± 10.8
13	4.8 ± 0.7	23.9 ± 7.3	34.3 ± 7.1	21.6 ± 2.5	55.2 ± 7.0	65.2 ± 5.8	>400
14	8.6 ± 1.3	27.0 ± 9.2	>400	217 ± 17	98.2 ± 11.3	62.7 ± 7.5	387 ± 62
16	1.4 ± 0.2	56.9 ± 19.2	>400	59.1 ± 3.9	96.3 ± 9.5	111.2 ± 6	248 ± 35
17	5.8 ± 1.2	114 ± 25	7.2 ± 1.6	72.1 ± 8.6	>400	182 ± 29	199 ± 16
20	1.5 ± 0.2	80.9 ± 13.2	6.3 ± 1.9	6.3 ± 0.7	123 ± 11	24.9 ± 1.4	193 ± 28
21	1.3 ± 0.1	39.1 ± 12.8	368 ± 79	11.8 ± 1.7	>400	40.9 ± 2.1	296 ± 66
31	6.6 ± 0.7	64.7 ± 13.7	>300	145 ± 11	>300	>300	>300
34	1.5 ± 0.3	139.9 ± 14.0	25.5 ± 3.9	103 ± 9	41.8 ± 5.2	53.5 ± 4.8	98.0 ± 7.7
36	1.4 ± 0.3	13.0 ± 3.3	4.2 ± 1.1	214 ± 25	223 ± 28	37.2 ± 3.4	191 ± 30
37b	4.2 ± 0.5	>400	>400	128 ± 22	398 ± 49	279 ± 21	>400
37a,b	9.8 ± 0.9	51.9 ± 8.2	>400	206 ± 33	141 ± 18	175 ± 22	>400
37a	82.3 ± 7.3	>400	>400	372 ± 16	86.2 ± 13.8	118 ± 7	>400
38a	0.17 ± 0.02	58.7 ± 15.3	40.2 ± 18.1	52.2 ± 7.6	8.9 ± 1.5	2.0 ± 0.22	168 ± 16
38	3.7 ± 0.78	77.5 ± 14.6	77.5 ± 14.6	256 ± 29	208 ± 21	233 ± 21	197 ± 21
38b	7.4 ± 1.3	>400	0.86 ± 0.24	9.0 ± 0.8	0.71 ± 0.75	0.21 ± 0.03	12.9 ± 1.9
39a	0.27 ± 0.02	47.1 ± 18.1	172 ± 52	191 ± 24	11.7 ± 2.2	22.0 ± 1.6	11.3 ± 2.6
57	3.5 ± 0.3	6.3 ± 1.4	31.1 ± 5.7	6.8 ± 0.8	2.1 ± 0.2	3.2 ± 0.2	14.4 ± 0.9
58	0.75 ± 0.1	262 ± 63	4.1 ± 0.7	146 ± 20	79.5 ± 8.9	122.1 ± 12.2	217 ± 20
59	3.1 ± 0.3	79.2 ± 27.7	80.0 ± 10.2	83.1 ± 4.7	75.2 ± 8.2	46.4 ± 4.2	344 ± 43
60	1.4 ± 0.2	75.1 ± 13.9	0.58 ± 0.10	5.3 ± 0.9	26.9 ± 2.9	12.1 ± 0.6	36.3 ± 4.4
61	1.0 ± 0.2	109 ± 46	57.9 ± 12.5	>300	>300	>300	297 ± 31
62	1.5 ± 0.4	152 ± 70	109 ± 11	>300	>300	>300	277 ± 40

[a] Compounds that were determined to have CYP2A6 IC_{50} values below 10 μM and the *cis*/*trans* oxime isomers were tested for inhibitory potency and regioselectivity (**33a**, **33b**, **33a,b**) in the presence of CYP isoforms. IC_{50} values were determined by increasing the concentration of potential inhibitors added to the assay mixture. Each value is the mean of at least three determinations ± SD. The experimental details are described in the Experimental Section. [b] IC_{50} values from assay mixture containing insect cell microsomes expressing the specific CYP isoform in 0.1 M Tris buffer (CYP2A6) or 0.2 M potassium phosphate buffer (CYP2E1, CYP2B6, CYP2C9, CYP2C19 and CYP2D6). [c] IC_{50} values from assay mixture containing human liver microsomes in 0.05 M potassium phosphate buffer, pH 7.5, an NADPH-generating system, DETAPAC, and 3 mM $MgCl_2$.

Table 4. Selectivity Ratio ($[IC_{50}(CYPX)]/[IC_{50}(CYP2A6)]$)[a] of Heteroaromatic Nicotine Analogues for Human CYPs 3A4, 2E1, 2B6, 2C9, 2C19, and 2D6 versus Human CYP2A6[b]

	$[IC_{50}(CYPX)]/[IC_{50}(CYP2A6)]$					
compd	3A4/2A6	2E1/2A6	2B6/2A6	2C9/2A6	2C19/2A6	2D6/2A6
7	7.3	0.53	9.1	13	23	>51
9	10	11	6.3	150	39	149
13	5.0	7.1	4.5	12	14	>100
14	3.1	>46	25	11	7	45
16	400	>286	42	69	81	177
17	20	1.2	12	>69	31	34
20	53	4.2	4.2	45	17	128
21	2	284	9.1	>308	32	227
31	10	45	22	>45	>45	>45
34	93	17	69	28	35	65
36	9.3	3	153	159	27	136
37b	>95	>95	30	94	66	>95
37a,b	5.3	>41	21	15	18	>41
37a	>5	5	5	1	1.4	>4.9
38a	345	236	307	52	12	988
38	21	21	69	56	62	53
38b	>54	0.12	1.2	0.10	0.03	1.7
39a	174	637	707	41	82	41
57	2	8.9	1.9	0.6	0.9	4.1
58	349	5	195	106	163	289
59	26	26	26	24	15	111
60	>54	0.4	4	19	9	26
61	109	58	363	>400	>294	297
62	101	73	>200	260	>200	185

[a] Each IC_{50} value was determined from a full dose range concentration of inhibitors as described in the Experimental Section. [b] Data taken from Table 3.

to be moderately to highly selective inhibitors for CYP2A6. Nicotine analogue **38a** had selectivity ratios of 345, 236, 307, 52, 12, and 988 for CYPs 3A4, 2E1, 2B6, 2C9, 2C19, and 2D6, respectively. Compound **39a** had selectivity ratios of 174, 637, 707, 41, 82, and 41 for CYPs 3A4, 2E1, 2B6, 2C9, 2C19, and 2D6, respectively. We judge that selectivity ratios greater than 10 possess significant utility, although this is somewhat dependent on the enzyme to which CYP2A6 is being compared.

Interestingly, the secondary amine, compound **38b**, showed relatively poor CYP2A6 selectivity and, conversely, was somewhat selective for inhibition of CYP2C19. It is known that CYP2C19[28] can accommodate significantly larger inhibitors than CYP2A6, but this needs to be explored further.

Conclusions

A series of substituted pyridines in which the pyridine ring was substituted with halogens or a methoxy group and/or the *N*-methylpyrrolidine ring of nicotine was replaced with substituted and unsubstituted heteroaromatic rings have been prepared and evaluated as inhibitors of human CYPs 2A6, 3A4, 2E1, 2B6, 2C9, 2C19, and 2D6 with the goal of finding a potent and selective inhibitor of human CYP2A6. Of the compounds examined, the most potent inhibitors of CYP2A6 observed were **38a** and **39a**. Compounds **38a** and **39a** were also found to be relatively selective inhibitors of CYP2A6. We have shown that inclusion of the methylamino moiety on the 5-position of the thiophene and furan rings in analogues **38a** and **39a** imparted potent inhibition, that the introduction of a bromine atom or methyl group at the 5-position either decreased or did not change the inhibitor potency, that the introduction of a methoxy, chloro, or fluoro group at the 6-position of the pyridine ring decreased inhibitory potency, and that the introduction of large alkyl groups on the heteroaromatic ring did not significantly decrease CYP2A6 inhibitory

potency. The data presented herein are interpreted to provide information about the competitive nature of CYP2A6 inhibition. Under certain conditions, however (i.e., at very high inhibitor concentrations), a few of the inhibitors of Table 4 showed time-dependent inactivation (unpublished results). Therefore, at a concentration range near the K_i value, the inhibition of CYP2A6 was competitive in nature. The compounds were also examined for type 1 versus type 2 binding to a cDNA-expressed CYP2A6 enzyme. Compounds such as **9** and **55** showed type 1 binding spectra, while compounds **38a** and **39a** showed type 2 binding spectra (unpublished results). Nicotine analogues **38a** and **39a** may serve as lead structures to develop even more potent and selective inhibitors of CYP2A6 that may prove to be valuable for the development of novel non-nicotine smoking cessation agents.

Experimental Section

General. Commercially available reagents were purchased from Aldrich Chemical Company or VWR and were used as received. All moisture sensitive reactions were carried out in flame-dried glassware under an argon atmosphere. Tetrahydrofuran (THF) and toluene were freshly distilled from calcium hydride under an argon atmosphere. Methanol (CH_3OH) was passed through a column of neutral alumina and stored over 3 Å molecular sieves prior to use.

Melting points were determined on a Mettler-Toledo FP62 melting point instrument and were uncorrected. Analytical thin-layer chromatography (TLC) was done on K6F silica gel 60 Å (Whatman) glass-backed plates. Compounds were detected using UV absorption at 254 nm and/or stained with I_2 (iodine). Flash chromatography was done on Merck (60 Å) pore silica. NMR spectra were recorded at 500 MHz by NuMega Resonance Labs, Inc. (San Diego, CA). Chemical shifts were reported in parts per million (ppm, δ) using residual solvent signals as internal standards. Low-resolution mass spectroscopy (LRMS) was done with an HP 1100 mass spectrometer at HT Laboratories (San Diego, CA) using electrospray ionization (ESI) or at the Human BioMolecular Research Institute on a Hitachi M-8000 3DQMS (ion trap) mass spectrometer using ESI. High-resolution mass spectroscopy (HRMS) was done with a Micromass LCT time-of-flight mass spectrometer at the University of Montana Mass Spectral Facility (Missoula, MT) using ESI.

The nicotine analogues were characterized by ^{1}H NMR, LRMS, and HRMS, and their purities (>95%) were determined by HPLC in two distinct solvent systems. Analytical HPLC measurements were run on a Hitachi L-6200 system equipped with a Hitachi L-7400 UV detector. Separations were done (straight-phase) with an Axxi-chrom silica column (4.6 mm × 250 mm, 5 μm) or (reverse-phase) with a Supelco HS F5 pentafluorophenyl column (4.6 mm × 250 mm, 5 μm). Standard conditions utilized an isocratic, ternary-solvent system consisting of solvents A (methanol), B (2-propanol), and C ($HClO_4$) set at a flow rate of 1.5 mL/min (straight-phase) or consisting of solvents A, D (water), and E (HCO_2H) set at a flow rate of 1.0 mL/min (reverse-phase); λ was 254 nm with retention times (t_R) evaluated in minutes. Typical analyses involved two distinct isocratic elutions per compound of interest. Solvent conditions for the isocratic elutions were varied depending on the compound and its specific chromatographic properties. ^{1}H NMR and mass spectra were consistent with the assigned structures.

Biological Assay. Microsomes from human lymphoblast cells expressing human cytochrome P-450 2A6 and human liver microsomes (CYP3A4) were purchased from BD Gentest (Woburn, MA), and microsomes from baculovirus-infected cells coexpressing cytochrome P-450s (2E1, 2B6, 2C9, 2C19, and 2D6), NADPH-cytochrome P-450 reductase, and cytochrome b_5 (BACULOSOMES) were purchased from PanVera LLC (Madison, WI).

To measure CYP2A6 activity, coumarin 7-hydroxylation was determined. Microsomes containing 5 pM CYP2A6 were added to 0.1 M Tris buffer (pH 7.5) containing 3 μM coumarin (final concentration) and individual inhibitors with final concentrations of 0.02, 0.1, 0.4, 1.6, 6.3, 25, 100, and 400 μM. The reactions were initiated by the addition of an NADPH-generating system consisting of 0.5 mM $NADP^+$, 0.5 mM glucose 6-phosphate, 5 U glucose 6-phosphate dehydrogenase, 1 mg/mL diethylenetriaminepentaacetic acid (DETAPAC), and 7 mM $MgCl_2$ for a final incubation volume of 0.2 mL. Incubations were run for 10 min at 37 °C and were terminated by the addition of 0.75 mL of ice-cold CCl_3COOH/CH_3CN (20:80, w/v). After centrifugation at 13 000 rpm for 5 min, 200 μL of the supernatant was transferred to a Packard OptiPlate 96-well plate. The formation of the coumarin metabolite, 7-hydroxycoumarin, was determined fluorometrically using a Wallac Victor^2 1420 multilabel counter (Wallac Software, version 2.00, release 9) at excitation and emissions wavelengths of 355 and 460 nm, respectively. The amount of product formed was obtained by interpolation from a standard curve of 7-hydroxycoumarin. The IC_{50} values were determined using GraphPad Prism version 3.0 and are reported as an average of three experiments ± SD. Apparent K_i values were determined from the IC_{50} values using a K_m for coumarin of 0.6 μM (average of the reported values),[19] employing the equation of Cheng and Prusoff.[29] For each assay, the reaction was a linear function of time for 60 min and of protein concentration from 0.5 to 2 pmol.

To measure CYP3A4 activity, testosterone 6-hydroxylation was determined. Individual inhibitors with final concentrations of 0.02, 0.1, 0.4, 1.6, 6.3, 25, 100, and 400 μM were added to ice-cold 0.05 M potassium phosphate buffer (pH 7.5) containing human liver microsomes (0.4 mg), an NADPH-generating system consisting of 0.5 mM $NADP^+$, 2.0 mM glucose 6-phosphate, 1 U glucose 6-phosphate dehydrogenase, 0.6 mg/mL DETAPAC, and 3 mM $MgCl_2$. The reactions were initiated by the addition of substrate (testosterone, final concentration of 0.2 mM) for a final incubation volume of 0.25 mL. Incubations were run for 30 min with shaking in air at 37 °C and were terminated by the addition of 1.5 mL of ice-cold ethyl acetate (EtOAc). After centrifugation at 13 000 rpm for 5 min, the organic phase was collected and removed with a stream of nitrogen. The residue was reconstituted in methanol (200 μL) and centrifuged at 13 000 rpm for 5 min, and the supernatant was analyzed by high-performance liquid chromatography (Altex Ultrasphere ODS column, 5 μm, 250 mm × 4.6 mm, λ = 254 nm using an isocratic mobile phase consisting of H_2O/CH_3CN/MeOH, (30:10:60, v/v/v) set at a flow rate of 1 mL/min; under these conditions the following retention times were observed, 6-hydroxytestosterone t_R = 3.94 min, testosterone t_R = 7.95 min).

To measure CYP2E1, CYP2B6, CYP2C9, CYP2C19, and CYP2D6 activity, isozyme-specific vivid blue substrate O-dealkylation was determined via a modified PanVera Vivid assay protocol. Individual inhibitors with final concentrations of 0.02, 0.1, 0.4, 1.6, 6.3, 25, 100, and 400 μM or 0.14, 1.2, 3.7, 33, 100, and 300 μM were added to a 96-well plate (BD Falcon Microtest, Black Flat Bottom) containing Vivid substrate (final concentration, CYP2B6, 5 μM; CYP2C9, 10 μM; CYP2C19, 10 μM; CYP2D6, 10 μM; CYP2E1, 10 μM) in 0.2 M potassium phosphate buffer (pH 8.0), followed by isozyme-specific BACULOSOMES (enzyme final concentration, CYP2B6, 10 nM; CYP2C9, 10 nM; CYP2C19, 5 nM; CYP2D6, 10 nM; CYP2E1, 5 nM). The reactions were initiated by the addition of an NADPH-generating system consisting of 0.5 mM $NADP^+$, 0.5 mM glucose 6-phosphate, 5 U/mL glucose 6-phosphate dehydrogenase, 1.0 mg/mL DETAPAC, and 7 mM $MgCl_2$ for a final incubation volume of 0.2 mL. After a 40 min incubation at room temperature, the formation of the fluorescent, O-dealkylated metabolite for each isozyme was determined fluorometrically at excitation and emission wavelengths of 405 and 460 nm, respectively.

The IC_{50} values were determined using GraphPad Prism version 3.00 and were reported as an average of three

experiments ± SD. For each assay, the reaction was a linear function of time for 60 min and of protein concentration from 0.5 to 2 pmol per reaction well.

General Procedure for the Preparation of Pyridin-3-ylboronic Acids (1−6). Compounds **1**-**6** were prepared by the esterification of the appropriate lithiopyridine followed by hydrolysis as previously reported.[22] The synthesis of pyridin-3-yl-3-boronic acid (**1**) is representative of compounds **2**-**6**.

Pyridin-3-yl-3-boronic Acid (1). A 500 mL three-neck flask was charged with toluene (85 mL) and cooled to below −60 °C, and a solution of *n*-BuLi (1.6 M in hexanes, 48.6 mL, 77.8 mmol) was added dropwise over 10 min. After the internal temperature reached −60 °C, a solution of 3-bromopyridine (6.8 mL, 70.7 mmol) in toluene (30 mL) was added dropwise to keep the internal temperature below −50 °C. A brownish-black solid precipitated, and the resultant slurry was stirred for 20 min. THF (30 mL) was added dropwise to keep the internal temperature below −50 °C, and the resultant slurry was stirred for 15 min. To the slurry was added triisopropyl borate (19.6 mL, 84.9 mmol) in one portion via syringe. The solution was warmed to −15 °C, the reaction was quenched with $HCl_{(aq)}$ (2.7 N, 70.0 mL), and the solution was transferred to a separatory funnel. The aqueous layer was collected, the organic layer was washed with water (10 mL), and the combined aqueous layers were neutralized to pH 7 with $NaOH_{(aq)}$ (10 N) and extracted with THF (200 mL × 1, 125 mL × 2). The combined organics were concentrated in vacuo, and the residue was dissolved in THF/CH_3OH (1:1, 140 mL), filtered, and diluted to 300 mL with CH_3CN. The solvent was switched to CH_3CN by distillation and concentrated to 100 mL. The solids were collected by filtration to afford the title compound **1** (6.4 g, 73% yield) as an off-white solid: ^{1}H NMR (CD_3OD) δ 8.64 (br s, 1H), 8.50 (m, 1H), 8.38 (br s, 1H), 7.65 (br s, 1H). This material was used directly in Suzuki cross-coupling reactions.

6-Fluoropyridin-3-yl-3-boronic Acid (2). 5-Bromo-2-fluoropyridine was treated with *n*-BuLi (1.6 M in hexanes, 19.5 mL, 31.3 mmol), triisopropyl borate (7.9 mL, 34.1 mmol), and $HCl_{(aq)}$ (2.7 N, 28.4 mL) as for **1** to give the title compound **2** (3.0 g, 74% yield) as a brown semisolid: ^{1}H NMR (CD_3OD) δ 8.45 (br s, 1H), 8.21 (br s, 1H), 7.01 (m, 1H). This material was used directly in Suzuki cross-coupling reactions.

6-Methoxypyridin-3-yl-3-boronic Acid (3). 5-Bromo-2-methoxypyridine (5.0 mL, 39.1 mmol) was treated with *n*-BuLi (1.6 M in hexanes, 26.9 mL, 43.0 mmol), triisopropyl borate (10.8 mL, 46.9 mmol), and $HCl_{(aq)}$ (2.7 N, 37.6 mL) as for **1** to give the title compound **3** (4.3 g, 89% yield) as a white solid: ^{1}H NMR (CD_3OD) δ 8.42 (m, 1H), 7.95 (br s, 1H), 6.76 (br s, 1H), 3.91 (s, 3H). This material was used directly in Suzuki cross-coupling reactions.

6-Chloropyridin-3-yl-3-boronic Acid (4). 5-Bromo-2-chloropyridine was treated with *n*-BuLi (1.6 M in hexanes, 12.0 mL, 19.1 mmol), triisopropyl borate (4.8 mL, 20.9 mmol), and $HCl_{(aq)}$ (2.7 N, 16.8 mL) as for **1** to give the title compound **4** (1.7 g, 60% yield) as a pink solid: ^{1}H NMR (CD_3OD) δ 8.58 (br s, 1H), 7.95 (br d, J = 6.7 Hz, 1H), 7.95 (d, J = 8 Hz, 1H). This material was used directly in Suzuki cross-coupling reactions.

3-Methylthiophen-2-yl-2-boronic Acid (5). 2-Bromo-3-methylthiophene was treated with *n*-BuLi (1.6 M in hexanes, 38.8 mL, 62.1 mmol), triisopropyl borate (15.1 mL, 65.4 mmol), and $HCl_{(aq)}$ (2.7 N, 52.5 mL) as for **1** to give the title compound **5** (7.2 g, 93% yield) as a brown solid: ^{1}H NMR (CD_3OD) δ 7.27 (d, J = 5.5 Hz, 1H), 6.80 (d, J = 5.5 Hz, 1H), 2.16 (s, 3H). This material was used directly in Suzuki cross-coupling reactions.

Thiophen-3-yl-3-boronic Acid (6). 3-Bromothiophene was treated with *n*-BuLi (1.6 M in hexanes, 8.4 mL, 13.5 mmol), triisopropyl borate (3.4 mL, 14.7 mmol), and $HCl_{(aq)}$ (2.7 N, 11.8 mL) as for **1** to give the title compound **6** (1.43 g, 91% yield) as a tan solid: ^{1}H NMR (CD_3OD) δ 7.85 (br d, 1H), 7.40 (m, 2H). This material was used directly in Suzuki cross-coupling reactions.

General Procedure for Suzuki Coupling Reactions. To a glass vial containing a magnetic stir bar is added the heteroaryl bromide (1.30 mmol), and the vial is purged with argon. To the vial was added a solution of tetrakis(triphenylphosphine)palladium(0) (0.03 mmol) in dimethoxyethane (2 mL) and sodium $carbonate_{(aq)}$ (2 M, 1.3 mL, 2.6 mmol), and the vial was once again purged with argon. The resultant solution was stirred at room temperature for 5 min when a slurry/solution of pyridin-3-yl-3-boronic acid (199.7 mg, 1.625 mmol) in ethanol (2 mL) was added, the vial was purged with argon and capped, and the mixture was heated to 90 °C and stirred for 1 h. The solution was cooled to room temperature and filtered through a pad of Celite (washing with dichloromethane) into a flask containing anhydrous magnesium sulfate (5 g). The solution was dried for 10 min and filtered through filter paper and the solvent was removed in vacuo to afford the crude product, which was chromatographed on silica gel.

3-(Thiophen-2-yl)pyridine (7). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 25/75, R_f = 0.22) to afford the title compound **7** (130 mg, 62% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.88 (m, 1H), 8.51 (m, 1H), 7.87 (m, 1H), 7.37 (m, 2H), 7.31 (m, 1H), 7.13 (m, 1H); LRMS (ESI) *m/z* calcd for C_9H_8NS $[M + H]^+$ 162, found 162; HRMS (ESI) *m/z* calcd for C_9H_8NS $[M + H]^+$ 162.0377, found 162.0378; HPLC >99% (t_R = 4.60 min, 60(A):40(B):0.05(C); t_R = 5.70 min, 60(A):40(B):0.02(C)).

3-(Thiazol-2-yl)pyridine (8). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 25/75, R_f = 0.14) to afford the title compound **8** (146 mg, 70% yield) as a yellow oil that crystallizes in a refrigerator at −40 °C: mp = 44−45 °C; ^{1}H NMR ($CDCl_3$) δ 9.19 (s, 1H), 8.66 (m, 1H), 8.26 (m, 1H), 7.93 (d, J = 3.1 Hz, 1H), 7.42 (d, J = 3.2 Hz, 1H), 7.40 (m, 1H); LRMS (ESI) *m/z* calcd for $C_8H_7N_2S$ $[M + H]^+$ 163, found 163; HRMS (ESI) *m/z* calcd for $C_8H_7N_2S$ $[M + H]^+$ 163.0330, found 163.0334; HPLC >99% (t_R = 5.68 min, 55(A):45(B):0.032(C); t_R = 4.52 min, 55(A):45(B):0.1(C)).

3-(3-Methylthiophen-2-yl)pyridine (9). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 25/75, R_f = 0.16) to afford the title compound **9** (197 mg, 87% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.73 (m, 1H), 8.55 (m, 1H), 7.75 (m, 1H), 7.34 (m, 1H), 7.27 (d, J = 5.2 Hz, 1H), 6.96 (d, J = 5.1 Hz, 1H), 2.34 (s, 3H); LRMS (ESI) *m/z* calcd for $C_{10}H_{10}NS$ $[M + H]^+$ 176, found 176; HRMS (ESI) *m/z* calcd for $C_{10}H_{10}NS$ $[M + H]^+$ 176.0534, found 176.0535; HPLC >99% (t_R = 11.34 min, 55(A):45(B):0.009(C); t_R = 4.42 min, 55(A):45(B):0.032(C)).

2-Fluoro-5-(3-methylthiophen-2-yl)pyridine (10). The general Suzuki coupling procedure was followed on 1.33 mmol scale. The crude material was chromatographed on silica gel (EtOAc/hexane, 5/95, R_f = 0.34) to afford the title compound **10** (175 mg, 68% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.30 (s, 1H), 7.85 (m, 1H), 7.28 (d, J = 5.1 Hz, 1H), 6.98 (m, 1H), 6.96 (d, J = 5.1 Hz, 1H), 2.30 (s, 3H); LRMS (ESI) *m/z* calcd for $C_{10}H_9FNS$ $[M + H]^+$ 194, found 194; HRMS (ESI) *m/z* calcd for $C_{10}H_9FNS$ $[M + H]^+$ 194.0440, found 194.0460; HPLC >96% (t_R = 41.15 min, 50(A):50(D):0.175(E); t_R = 8.83 min, 30(A):70(D):0.105(E)).

2-Methoxy-5-(3-methylthiophen-2-yl)pyridine (11). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 5/95, R_f = 0.30) to afford the title compound **11** (221 mg, 83% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.27 (m, 1H), 7.65 (m, 1H), 7.21 (m, 1H), 6.93 (m, 1H), 6.79 (m, 1H), 3.98 (s, 3H), 2.29 (s, 3H); LRMS (ESI) *m/z* calcd for $C_{11}H_{12}NOS$ $[M + H]^+$ 206, found 206; HRMS (ESI) *m/z* calcd for $C_{11}H_{12}NOS$ $[M + H]^+$ 206.0640, found 206.0657; HPLC >99% (t_R = 3.12 min, 60(A):40(B):0.009(C); t_R = 2.62 min, 60(A):40(B):0.02(C)).

3-Bromo-5-(thiophen-3-yl)pyridine (12). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 25/75, R_f = 0.20) to afford the title compound **12** (178 mg, 57% yield) as an orange oil: ^{1}H NMR ($CDCl_3$) δ 8.63 (m, 2H), 7.90 (m, 1H), 7.31 (d, J = 5.1 Hz, 1H), 6.96 (d, J = 5.1 Hz, 1H), 2.34 (s, 3H);

LRMS (ESI) *m/z* calcd for $C_{10}H_9BrNS$ $[M + H]^+$ 254, found 254; HRMS (ESI) *m/z* calcd for $C_{10}H_9BrNS$ $[M + H]^+$ 253.9639, found 253.9623; HPLC >99% (t_R = 6.01 min, 80(A):20(D):0.7(E)); t_R = 4.47 min, 90(A):10(D):0.035(E)).

5-(Pyridin-3-yl)thiophene-2-carbaldehyde (13). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 25/75, R_f = 0.17) to afford the title compound **13** (224 mg, 91% yield) as a yellow solid: mp = 250−254 °C dec; ^{1}H NMR ($CDCl_3$) δ 9.91 (s, 1H), 8.93 (br s, 1H), 8.62 (m, 1H), 7.92 (m, 1H), 7.77 (d, J = 4.14 Hz, 1H), 7.45 (d, J = 4.14 Hz, 1H), 7.36 (m, 1H); LRMS (ESI) *m/z* calcd for $C_{10}H_8NOS$ $[M + H]^+$ 190, found 190; HRMS (ESI) *m/z* calcd for $C_{10}H_8NOS$ $[M + H]^+$ 190.0327, found 190.0343; HPLC >99% (t_R = 11.37 min, 55(A):45(B):0.009(C); t_R = 4.46 min, 45(A):55(B):0.032(C)).

1-(5-(Pyridin-3-yl)thiophen-2-yl)ethanone (14). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 25/75, R_f = 0.17) to afford the title compound **14** (235 mg, 89% yield) as a yellow solid: mp = 104−105 °C; ^{1}H NMR ($CDCl_3$) δ 8.93 (br s, 1H), 8.60 (br s, 1H), 7.91 (m, 1H), 7.68 (m, 1H), 7.36 (m, 2H), 2.58 (s, 3H); LRMS (ESI) *m/z* calcd for $C_{11}H_{10}NOS$ $[M + H]^+$ 204, found 204; HRMS (ESI) *m/z* calcd for $C_{11}H_{10}NOS$ $[M + H]^+$ 204.0483, found 204.0495; HPLC >99% (t_R = 7.02 min, 60(A):40(B):0.02(C); t_R = 5.06 min, 60(A):40(B):0.07(C)).

3-(5-Nitrothiophen-2-yl)pyridine (15). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 25/75, R_f = 0.17) to afford the title compound **15** (224 mg, 91% yield) as a purple solid: mp = 169−171 °C; ^{1}H NMR ($CDCl_3$) δ 8.91 (m, 1H), 8.67 (m, 1H), 7.94 (d, J = 4.9 Hz, 1H), 7.90 (m, 1H), 7.41 (m, 1H), 7.30 (d, J = 4.2 Hz, 1H); LRMS (ESI) *m/z* calcd for $C_9H_7N_2O_2S$ $[M + H]^+$ 207, found 207; HRMS (ESI) *m/z* calcd for $C_9H_7N_2O_2S$ $[M + H]^+$ 207.0228, found 207.0249; HPLC >99% (t_R = 5.12 min, 55(A):45(B):0.032(C); t_R = 4.13 min, 45(A):55(B):0.1(C)).

3-(Thiophen-3-yl)pyridine (16). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 25/75, R_f = 0.18) to afford the title compound **16** (224 mg, 91% yield) as a yellow solid: mp = 75−77 °C; ^{1}H NMR ($CDCl_3$) δ 8.88 (br s, 1H), 8.53 (m, 1H), 7.87 (m, 1H), 7.52 (m, 1H), 7.44 (m, 1H), 7.40 (m, 1H), 7.32 (m, 1H); LRMS (ESI) *m/z* calcd for C_9H_8NS $[M + H]^+$ 162, found 162; HRMS (ESI) *m/z* calcd for C_9H_8NS $[M + H]^+$ 162.0377, found 162.0375; HPLC >99% (t_R = 12.45 min, 55(A):45(B):0.009(C); t_R = 4.52 min, 55(A):45(B):0.032(C)).

2-Fluoro-5-(thiophen-3-yl)pyridine (17). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 2.5/97.5, R_f = 0.21) to afford the title compound **17** (110 mg, 77% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.44 (m, 1H), 7.96 (m, 1H), 7.45 (m, 2H), 7.34 (m, 1H), 6.97 (m, 1H); LRMS (ESI) *m/z* calcd for C_9H_7FNS $[M + H]^+$ 180, found 180; HRMS (ESI) *m/z* calcd for C_9H_7FNS $[M + H]^+$ 180.0283, found 180.0278; HPLC >98% (t_R = 8.22 min, 60(A):40(D):0.140(E); t_R = 4.59 min, 30(A):70(D):0.105(E)).

2-Methoxy-5-(thiophen-3-yl)pyridine (18). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 2.5/97.5, R_f = 0.17) to afford the title compound **18** (217 mg, 87% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.41 (m, 1H), 7.78 (m, 1H), 7.42−7.26 (m, 3H), 6.79 (m, 1H), 3.97 (s, 3H); LRMS (ESI) *m/z* calcd for $C_{10}H_{10}NOS$ $[M + H]^+$ 192, found 192; HRMS (ESI) *m/z* calcd for $C_{10}H_{10}NOS$ $[M + H]^+$ 192.0483, found 192.0478; HPLC >99% (t_R = 4.65 min, 60(A):40(B):0.009(C); t_R = 3.73 min, 60(A):40(B):0.02(C)).

3-Bromo-5-(3-methylthiophen-2-yl)pyridine (19). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 2.5/97.5, R_f = 0.20) to afford the title compound **19** (175 mg, 53% yield) as a white solid: mp = 58−59 °C; ^{1}H NMR ($CDCl_3$) δ 8.77 (m, 1H), 8.59 (m, 1H), 8.02 (m, 1H), 7.55 (m, 1H), 7.46 (m, 1H), 7.37 (m, 1H); LRMS (ESI) *m/z* calcd for C_9H_7BrNS $[M + H]^+$ 240, found 240; HRMS (ESI) *m/z* calcd for C_9H_7BrNS $[M + H]^+$ 239.9483, found 239.9467; HPLC >99% (t_R = 3.56 min, 60(A):40(B):0.02(C); t_R = 2.68 min, 55(A):45(B):0.01(C)).

3-(4-Methylthiophen-3-yl)pyridine (20). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 25/75, R_f = 0.24) to afford the title compound **16** (191 mg, 84% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.66 (m, 1H), 8.57 (m, 1H), 7.70 (m, 1H), 7.33 (m, 1H), 7.26 (m, 1H), 7.01 (m, 1H), 2.27 (s, 3H); LRMS (ESI) *m/z* calcd for $C_{10}H_{10}NS$ $[M + H]^+$ 176, found 176; HRMS (ESI) *m/z* calcd for $C_{10}H_{10}NS$ $[M + H]^+$ 176.0534, found 176.0538; HPLC >99% (t_R = 4.31 min, 55(A):45(B):0.032(C); t_R = 3.57 min, 55(A):45(B):0.1(C)).

2-Fluoro-5-(4-methylthiophen-3-yl)pyridine (21). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 2.5/97.5, R_f = 0.22) to afford the title compound **21** (121 mg, 78% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.24 (m, 1H), 7.79 (m, 1H), 7.24 (m, 1H), 7.07 (m, 1H), 6.98 (m, 1H), 2.25 (s, 3H); LRMS (ESI) *m/z* calcd for $C_{10}H_9FNS$ $[M + H]^+$ 194, found 194; HRMS (ESI) *m/z* calcd for $C_{10}H_9FNS$ $[M + H]^+$ 194.0425, found 194.0460; HPLC >99% (t_R = 15.28 min, 60(A):40(D):0.14(E); t_R = 8.62 min, 30(A):70(D):0.105(E)).

2-Methoxy-5-(4-methylthiophen-3-yl)pyridine (22). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 10/90, R_f = 0.42) to afford the title compound **22** (265 mg, 99% yield) as a white semisolid: ^{1}H NMR ($CDCl_3$) δ 8.20 (m, 1H), 7.61 (m, 1H), 7.18 (m, 1H), 7.04 (m, 1H), 6.80 (m, 1H), 3.98 (s, 3H), 2.25 (s, 3H); LRMS (ESI) *m/z* calcd for $C_{11}H_{12}ONS$ $[M + H]^+$ 206, found 206; HRMS (ESI) *m/z* calcd for $C_{11}H_{12}ONS$ $[M + H]^+$ 206.0640, found 206.0633; HPLC >99% (t_R = 3.69 min, 55(A):45(B):0.009(C); t_R = 3.37 min, 55(A):45(B):0.032(C)).

5-(Pyridin-3-yl)furan-2-carbaldehyde (23). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 50/50, R_f = 0.19) to afford the title compound **23** (1.28 g, 95% yield) as an off white solid. Analytical properties are consistent with published values: mp = 112−115 °C (lit. 113−115 °C);[30] ^{1}H NMR ($CDCl_3$) δ 9.70 (s, 1H), 9.05 (m, 1H), 8.63 (m, 1H), 8.12 (m, 1H), 7.39 (m, 1H), 7.35 (d, J = 4.1 Hz, 1H), 6.94 (d, J = 4.1 Hz, 1H).

2-(Pyridin-3-yl)pyridine (24). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 50/50, R_f = 0.12) to afford the title compound **24** (141 mg, 70% yield) as a colorless oil. Analytical properties are consistent with those obtained for a commercial sample.

3-Methyl-2-(pyridin-3-yl)pyridine (25). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 50/50, R_f = 0.07) to afford the title compound **25** (94 mg, 43% yield) as a yellow semisolid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.77 (m, 1H), 8.61 (m, 1H), 8.52 (m, 1H), 7.85 (m, 1H), 7.59 (m, 1H), 7.36 (m, 1H), 7.20 (m, 1H), 2.35 (s, 3H); LRMS (ESI) *m/z* calcd for $C_{11}H_{11}N_2$ $[M + H]^+$ 171, found 171; HRMS (ESI) *m/z* calcd for $C_{11}H_{11}N_2$ $[M + H]^+$ 171.0922, found 171.0908; HPLC >99% (t_R = 10.72 min, 55(A):45(B):0.032(C); (t_R = 9.61 min, 60(A):40(B):0.002(C)).

4-Methyl-2-(pyridin-3-yl)pyridine (26). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 50/50, R_f = 0.12) to afford the title compound **26** (180 mg, 81% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.16 (br s, 1H), 8.64 (m, 1H), 8.57 (m, 1H), 8.30 (m, 1H), 7.56 (m, 1H), 7.40 (m, 1H), 7.12 (m, 1H), 2.43 (s, 3H); LRMS (ESI) *m/z* calcd for $C_{11}H_{11}N_2$ $[M + H]^+$ 171, found 171; HRMS (ESI) *m/z* calcd for $C_{11}H_{11}N_2$ $[M + H]^+$ 171.0922, found 171.0939; HPLC >99% (t_R = 8.11 min, 60(A):40(B):0.02(C); t_R = 6.74 min, 60(A):40(B):0.07(C)).

5-Methyl-2-(pyridin-3-yl)pyridine (27). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 50/50, R_f = 0.11) to afford the title compound **27** (167 mg, 76% yield) as a yellow solid: mp = 40−41 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.16 (m,

1H), 8.62 (m, 1H), 8.55 (m, 1H), 8.29 (m, 1H), 7.65 (m, 1H), 7.59 (m, 1H), 7.39 (m, 1H), 2.39 (s, 3H); LRMS (ESI) *m/z* calcd for $C_{11}H_{11}N_2$ $[M + H]^+$ 171, found 171; HRMS (ESI) *m/z* calcd for $C_{11}H_{11}N_2$ $[M + H]^+$ 171.0922, found 171.0939; HPLC >99% (t_R = 7.78 min, 60(A):40(B):0.02(C); t_R = 6.32 min, 60(A):40(B):0.07(C)).

2-Methyl-6-(pyridin-3-yl)pyridine (28). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 50/50, R_f = 0.19) to afford the title compound **28** (144 mg, 65% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.17 (m, 1 H), 8.63 (m, 1 H), 8.32 (m, 1 H), 7.68 (m, 1 H), 7.54 (m, 1 H), 7.39 (m, 1 H), 7.15 (m, 1 H), 2.64 (s, 3 H); LRMS (ESI) *m/z* calcd for $C_{11}H_{11}N_2$ $[M + H]^+$ 171, found 171; HRMS (ESI) *m/z* calcd for $C_{11}H_{11}N_2$ $[M + H]^+$ 171.0922, found 171.0939; HPLC >99% (t_R = 8.58 min, 60(A):40(B):0.02(C); t_R = 6.70 min, 60(A):40(B):0.07(C)).

2-(Pyridin-3-yl)pyrimidine (29). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 25/75, R_f = 0.07) to afford the title compound **29** (108 mg, 53% yield) as an orange solid: mp = 51−52 °C; ^{1}H NMR ($CDCl_3$) δ 9.64 (s, 1H), 8.83 (m, 2H), 8.70 (m, 2H), 7.41 (m, 1H), 7.24 (m, 1H); LRMS (ESI) *m/z* calcd for $C_9H_8N_3$ $[M + H]^+$ 158, found 158; HRMS (ESI) *m/z* calcd for $C_9H_8N_3$ $[M + H]^+$ 158.0718, found 158.0706; HPLC >99% (t_R = 5.91 min, 55(A):45(B):0.032(C); t_R = 4.82 min, 55(A):45(B):0.1(C)).

5-(Pyridin-3-yl)pyrimidine (30). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 25/75, R_f = 0.08) to afford the title compound **30** (167 mg, 82% yield) as a white solid: mp = 101−103 °C; ^{1}H NMR ($CDCl_3$) δ 9.27 (s, 1H), 8.97 (s, 2H), 8.85 (m, 1H), 8.71 (m, 1H), 7.90 (m, 1H), 7.46 (m, 1H); LRMS (ESI) *m/z* calcd for $C_9H_8N_3$ $[M + H]^+$ 158, found 158; HRMS (ESI) *m/z* calcd for $C_9H_8N_3$ $[M + H]^+$ 158.0718, found 158.0706; HPLC >99% (t_R = 5.91 min, 55(A):45(B):0.032(C); t_R = 4.82 min, 55(A):45(B):0.1(C)).

3-(Pyridin-3-yl)pyridine (31). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 75/25, R_f = 0.14) to afford the title compound **31** (182 mg, 90% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.84 (m, 2H), 8.64 (m, 2H), 7.87 (m, 2H), 7.40 (m, 2H); LRMS (ESI) *m/z* calcd for $C_{10}H_9N_2$ $[M + H]^+$ 157, found 157; HRMS (ESI) *m/z* calcd for $C_{10}H_9N_2$ $[M + H]^+$ 157.0766, found 157.0775; HPLC >99% (t_R = 3.73 min, 55(A):45(B):0.1(C); t_R = 20.4 min, 55(A):45(B):0.032(C)).

3-(6-Chloropyridin-3-yl)pyridine (32). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel(EtOAc/hexane, 50/50, R_f = 0.22) to afford the title compound **32** (123 mg, 49% yield) as an off-white solid: mp = 113−115 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.82 (m, 1H), 8.68 (m, 1H), 8.61 (m, 1H), 7.86 (m, 2H), 7.43 (m, 2H); LRMS (ESI) *m/z* calcd for $C_{10}H_8ClN_2$ $[M + H]^+$ 191, found 191; HRMS (ESI) *m/z* calcd for $C_{10}H_8ClN_2$ $[M + H]^+$ 191.0376, found 191.0372; HPLC >99% (t_R = 7.23 min, 60(A):40(B):0.02(C); t_R = 5.48 min, 60(A):40(B):0.07(C)).

3-(Pyridin-3-yl)quinoline (33). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel (EtOAc/hexane, 25/75, R_f = 0.07) to afford the title compound **33** (200 mg, 75% yield) as a white solid: mp = 117−119 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.16 (s, 1H), 8.99 (s, 1H), 8.70 (m, 1H), 8.34 (s, 1H), 8.17 (m, 1H), 8.02 (m, 1H), 7.92 (m, 1H), 7.77 (m, 1H), 7.62 (m, 1H), 7.47 (m, 1H); LRMS (ESI) *m/z* calcd for $C_{14}H_{11}N_2$ $[M + H]^+$ 207, found 207; HRMS (ESI) *m/z* calcd for $C_{14}H_{11}N_2$ $[M + H]^+$ 207.0922, found 207.0902; HPLC >99% (t_R = 18.01 min, 55(A):45(B):0.009(C); t_R = 10.17 min, 55(A):45(B):0.1(C)).

3-(1*H*-Imidazol-4-yl)pyridine (34). The general Suzuki coupling procedure was followed with the following exception: the reaction required 14 h to reach completion as determined by TLC analysis. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 10/90, R_f = 0.18) to afford the title compound **34** (74 mg, 39% yield) as an off-white oil: ^{1}H NMR ($CDCl_3$) δ 8.99 (m, 1H), 8.47 (m, 1H), 8.09 (m, 1H), 7.76 (d, J = 1.1 Hz, 1H), 7.43 (d, J = 1.1 Hz, 1H), 7.33 (m, 1H), 7.12 (d, J = 1.1 Hz, 1H); LRMS (ESI) *m/z* calcd for $C_8H_8N_3$ $[M + H]^+$ 146, found 146; HRMS (ESI) *m/z* calcd for $C_8H_8N_3$ $[M + H]^+$ 146.0718, found 146.0729; HPLC >99% (t_R = 7.68 min, 55(A):45(B):0.032(C); t_R = 4.40 min, 55(A):45(B):0.1(C)).

3-(2-Methyl-1*H*-imidazol-4-yl)pyridine (35). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 10/90, R_f = 0.25) to afford the title compound **35** (138 mg, 67% yield) as a yellow oil that partially solidifies in the freezer: ^{1}H NMR ($CDCl_3$) δ 8.94 (m, 1H), 8.43 (m, 1H), 8.04 (m, 1H), 7.28 (m, 2H), 2.46 (s, 3H); LRMS (ESI) *m/z* calcd for $C_9H_{10}N_3$ $[M + H]^+$ 160, found 160; HRMS (ESI) *m/z* calcd for $C_9H_{10}N_3$ $[M + H]^+$ 160.0875, found 160.0870; HPLC >99% (t_R = 8.76 min, 60(A):40(B):0.02(C); t_R = 5.97 min, 60(A):40(B):0.07(C)).

***cis/trans*-5-(Pyridin-3-yl)thiophene-2-carbaldehyde Oximes (36).** To a solution of **14** (214 mg, 1.13 mmol) in 95% ethanol (10 mL) was added hydroxylamine hydrochloride (86 mg, 1.24 mmol) and sodium acetate (102 mg, 1.24 mmol). The resultant slurry was heated to reflux and stirred for 25 min. The solvent was removed in vacuo, and the residue was dissolved in MeOH and absorbed onto silica gel. The solvent was removed in vacuo and the material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 5/95, R_f = 0.23) to afford the *cis*/*trans* mixture of the title compound **36** as a yellow solid: mp = 178−185 °C dec; ^{1}H NMR ($CDCl_3$) δ 9.17 (m 0.75H), 8.93 (m, 0.25H), 8.55 (m, 0.25H), 8.50 (m, 0.75H), 8.29 (s, 0.75H), 7.98−7.90 (m, 1H), 7.39−7.31 (m, 2.5H), 7.15 (m, 0.75H); LRMS (ESI) *m/z* calcd for $C_{10}H_9N_2OS$ $[M + H]^+$ 205, found 205; HRMS (ESI) *m/z* calcd for $C_{10}H_9N_2OS$ $[M + H]^+$ 205.0436, found 205.0455; HPLC >99% (t_R = 3.90 min, 55(A):45(B):0.032(C); t_R = 4.34 min, 45(A):55(B):0.1(C)).

***cis/trans*-5-(Pyridin-3-yl)furan-2-carbaldehyde Oximes (37a, 37b).** To a solution of **23** (106 mg, 0.61 mmol) in 95% ethanol (6 mL) was added hydroxylamine hydrochloride (69 mg, 0.68 mmol) and sodium acetate (55 mg, 0.68 mmol). The resultant slurry was heated to reflux, stirred for 75 min, and cooled, the solid was removed by filtration, and the solvent was removed in vacuo. The crude oil was triturated with ethyl ether and the solid was collected by filtration to afford the *cis*/*trans* mixture **37a**,**b** (17 mg, 15%): HPLC >99% (t_R = 5.16, 5.45 min, 60(A):40(B):0.02(C); t_R = 7.5, 7.92 min, 60(A):40(B):0.009(C)). The mother liquor was chromatographed on silica gel (EtOAc/hexane, 50/50) to afford the *cis* isomer **37a** (R_f = 0.21, 37 mg, 32%) as a white solid: mp = 143−150 °C dec; ^{1}H NMR (CD_3OD) δ 9.93 (m, 1H, H_2), 9.42 (m, 1H, H_6), 9.16 (m, 1H, H_4), 9.01 (s, 1H, HC=N), 8.46 (m, 1H, H_5), 8.02 (d, J = 3.7 Hz, 1H, $H_{3'}$), 7.77 (d, J = 3.7 Hz, 1H, $H_{4'}$); HPLC >99% (t_R = 5.25 min, 60(A):40(B):0.02(C); t_R = 8.67 min, 60(A):40(B)0.009(C)). The *trans* isomer **37b** (R_f = 0.36, 44 mg, 38%) was produced as a white semisolid: ^{1}H NMR (CD_3OD) δ 9.91 (m, 1H, H_2), 9.94 (m, 1H, H_6), 9.14 (m, 1H, H_4), 8.50 (s, 1H, HC=N), 8.46 (m, 1H, H_5), 8.35 (d, J = 3.7 Hz, 1H, $H_{3'}$), 8.07 (d, J = 3.7 Hz, 1H, $H_{4'}$); HPLC >99% (t_R = 4.07 min, 60(A):40(B):0.05(C); t_R = 7.51 min, 60(A):40(B):0.009(C)); LRMS (ESI) *m/z* calcd for $C_{10}H_9N_2O_2$ (**33a**,**b** mixture) $[M + H]^+$ 189, found 189; HRMS (ESI) *m/z* calcd for $C_{10}H_9N_2O_2$ (**33a**,**b** mixture) $[M + H]^+$ 189.0664, found 189.0677.

(5-(Pyridin-3-yl)thiophen-2-yl)methanamine (38a) and Bis((5-(pyridin-3-yl)thiophen-2-yl)methyl)amine (38b). To a solution of **14** (122 mg, 0.68 mmol) in absolute methanol (4 mL) was added ammonium acetate (520 mg, 6.75 mmol) followed by sodium cyanoborohydride (30 mg, 0.47 mmol), and the resultant solution was stirred at room temperature under argon for 18 h. The reaction was quenched by the addition of glacial acetic acid (1 mL), and the mixture was stirred for 5 min and subsequently poured into a stirred solution of $NaOH_{(aq)}$ (1 N, 20 mL), extracted with ethyl acetate (3 × 25 mL), dried ($MgSO_4$), and filtered. The solvent was removed in vacuo and the residue was chromatographed on silica gel ($CH_3OH/CHCl_3$, 5/95, R_f = 0.28) to afford the title compound **38b** (34 mg, 27% yield) as an orange semisolid: ^{1}H NMR ($CDCl_3$) δ 8.86 (s, 1H), 8.50 (m, 1H), 7.84 (m, 1H), 7.29 (m, 1H), 7.23 (d, J = 3.1 Hz, 1H), 6.96 (d, J = 4.1 Hz, 1H), 4.07 (s, 2H), 1.84 (br

s, 1H); LRMS (ESI) *m/z* calcd for $C_{20}H_{18}N_3S_2$ $[M + H]^+$ 364, found 364; HRMS (ESI) *m/z* calcd for $C_{20}H_{18}N_3S_2$ $[M + H]^+$ 364.0942, found 364.0978; HPLC >98% (t_R = 28.16 min, 55-(A):45(B):0.032(C); t_R = 12.09 min, 55(A):45(B):0.1(C)).

Later fractions (R_f = 0.08) afforded the title compound **38a** (14 mg, 11% yield) as an orange solid: mp = 170−172 °C; ^{1}H NMR ($CDCl_3$) δ 8.85 (s, 1H), 8.50 (m, 1H), 7.82 (m, 1H), 7.29 (m, 1H), 7.21 (d, J = 3.1 Hz, 1H), 6.92 (d, J = 4.1 Hz, 1H), 4.09 (s, 2H), 1.65 (br s, 2H); LRMS (ESI) *m/z* calcd for $C_{10}H_{11}N_2S$ $[M + H]^+$ 191, found 191; HRMS (ESI) *m/z* calcd for $C_{10}H_{11}N_2S$ $[M + H]^+$ 191.0643, found 191.0650; HPLC >98% (t_R = 12.42 min, 55(A):45(B):0.032(C); t_R = 3.26 min, 75(A):25(B):0.05(C)).

(5-(Pyridin-3-yl)furan-2-yl)methanamine, Bis((5-(pyridin-3-yl)furan-2-yl)methyl)amine, and Tris((5-(pyridin-3-yl)furan-2-yl)methyl)amine (39ac). To a solution of **23** (106 mg, 0.61 mmol) in absolute methanol (5 mL) was added ammonium acetate (473 mg, 6.13 mmol) followed by sodium cyanoborohydride (27 mg, 0.43 mmol), and the resultant solution was stirred at room temperature under argon for 48 h. The solution was adjusted to pH 2 with concentrated HCl, and the solvent was removed in vacuo. The residue was dissolved in water and washed with Et_2O (2 × 20 mL). The aqueous portion was adjusted to pH 10 with 10 N NaOH and extracted with Et_2O (3 × 50 mL), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 10/90, R_f = 0.45) to afford the title compound **39c** (44 mg, 44% yield) as an off-white solid: mp = 170−172 °C; ^{1}H NMR ($CDCl_3$) δ 8.92 (br s, 3H), 8.47 (m, 3H), 7.91 (m, 3H), 7.27 (m, 3H), 6.70 (d, J = 3.2 Hz, 3H), 6.41 (d, J = 3.3 Hz, 3H), 4.07 (s, 6H); LRMS (ESI) *m/z* calcd for $C_{30}H_{24}N_4O_3$ $[M + H]^+$ 489, found 489; HRMS (ESI) *m/z* calcd for $C_{30}H_{24}N_4O_3$ $[M + H]^+$ 489.1927, found 489.1956; HPLC >99% (t_R = 8.82 min, 60(A):40(B):0.05-(C); t_R = 4.64 min, 80(A):20(B):0.1(C)).

Later fractions (R_f = 0.41) afforded the title compound **39b** (29 mg, 28% yield) as an orange solid: mp = 170−172 °C; ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 2H), 8.47 (m, 2H), 7.90 (m, 2H), 7.28 (m, 2H), 6.68 (m, 2H), 6.34 (m, 2H), 3.92 (s, 4H), 2.09 (br s, 1H); LRMS (ESI) *m/z* calcd for $C_{20}H_{17}N_3O_2$ $[M + H]^+$ 332, found 332; HRMS (ESI) *m/z* calcd for $C_{10}H_{11}N_2S$ $[M + H]^+$ 332.1399, found 332.1418; HPLC >98% (t_R = 5.69 min, 70(A):30(B):0.05-(C); t_R = 3.51 min, 80(A):20(B):0.1(C)).

Later fractions (R_f = 0.14) afforded the title compound **39a** (23 mg, 22% yield) as a yellow oil, which solidified upon cooling in a refrigerator: ^{1}H NMR ($CDCl_3$) δ 8.90 (m, 1H), 8.47 (m, 1H), 7.90 (m, 1H), 7.29 (m, 1H), 6.67 (d, J = 3.2 Hz, 1H), 6.26 (d, J = 3.2 Hz, 1H), 3.91 (s, 2H), 1.66 (br s, 2H); LRMS (ESI) *m/z* calcd for $C_{10}H_{11}N_20$ $[M + H]^+$ 175, found 175; HRMS (ESI) *m/z* calcd for $C_{10}H_{11}N_20$ $[M + H]^+$ 175.0871, found 175.0872; HPLC >95% (t_R = 7.60 min, 55(A):45(B):0.009(C); t_R = 3.76 min, 75(A):25(B):0.05(C)).

***N*-Methyl(5-(pyridin-3-yl)thiophen-2-yl)methanamine (40).** To a solution of **13** (90 mg, 0.48 mmol) was added a solution of methylamine (2.0 M, 1.43 mL, 2.85 mmol) in anhydrous CH_3OH, a solution of HCl (4.0 M, 0.24 mL, 0.95 mmol) in anhydrous 1,4-dioxane, and sodium cyanoborohydride (30 mg, 0.48 mmol). The flask was purged with argon and stirred under an atmosphere of argon at room temperature for 24 h. The solution was adjusted to pH 2 with concentrated HCl, and the solvent was removed in vacuo. The residue was dissolved in water and washed with Et_2O (3 × 10 mL). The aqueous fraction was adjusted to pH 10 with $NaOH_{(aq)}$ (10 N), extracted with Et_2O (3 × 20 mL), dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 10/90, R_f = 0.13) to afford the title compound **40** (39 mg, 40% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.84 (m, 1H), 8.49 (m, 1H), 7.82 (m, 1H), 7.28 (m, 1H), 7.21 (d, J = 3.6 Hz, 1H), 6.93 (d, J = 3.5 Hz, 1H), 3.96 (s, 2H), 2.31 (s, 3H); LRMS (ESI) *m/z* calcd for $C_{11}H_{13}N_2S$ $[M + H]^+$ 205, found 205; *m/z* calcd for $C_{10}H_8$-NS $[M - NH(CH_3)]^+$ 174, found 174; HRMS (ESI) *m/z* calcd for $C_{11}H_{13}N_2S$ $[M + H]^+$ 205.0799, found 205.0781; HPLC >95% (t_R = 4.34 min, 80(A):20(B):0.05(C); t_R = 3.60 min, 60-(A):40(B):0.07(C)).

***N*-Methyl(5-(pyridin-3-yl)furan-2-yl)methanamine (41).** To a solution **23** (104 mg, 0.60 mmol) was added a solution of methylamine (2.0 M, 1.8 mL, 3.6 mmol) in anhydrous CH_3-OH, a solution of HCl (4.0 M, 0.3 mL, 1.2 mmol) in anhydrous 1,4-dioxane, and sodium cyanoborohydride (38 mg, 0.6 mmol). The flask was purged with argon and stirred under an atmosphere of argon at room temperature for 48 h. The solution was adjusted to pH 2 with concentrated HCl, and the solvent was removed in vacuo. The residue was dissolved in water, washed with Et_2O (3 × 10 mL), adjusted to pH 10 with $NaOH_{(aq)}$ (10 N), extracted with Et_2O (3 × 20 mL), dried (Na_2-SO_4), and filtered, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 10/90, R_f = 0.1) to afford the title compound **41** (94 mg, 84% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.89 (m, 1H), 8.46 (m, 1H), 7.91 (m, 1H), 7.28 (m, 1H), 6.67 (d, J = 3.2 Hz, 1H), 6.31 (d, J = 3.2 Hz, 1H), 3.82 (s, 2H), 2.49 (s, 3H), 2.14 (br s, 1H); LRMS (ESI) *m/z* calcd for $C_{11}H_{13}N_2O$ $[M + H]^+$ 189, found 189; *m/z* calcd for $C_{10}H_8NO$ $[M - NH(CH_3)]^+$ 158, found 158; HRMS (ESI) *m/z* calcd for $C_{11}H_{13}N_2O$ $[M + H]^+$ 189.1028, found 189.1041; HPLC >95% (t_R = 8.74 min, 60(A):40(B):0.02(C); t_R = 3.69 min, 60(A):40(B):0.07(C)).

***N*,*N*-Dimethyl(5-(pyridin-3-yl)thiophen-2-yl)methanamine (42).** To a solution of **13** (90 mg, 0.48 mmol) was added a solution of dimethylamine (2.9 M, 0.99 mL, 2.85 mmol) in anhydrous CH_3OH, a solution of HCl (4.0 M, 0.24 mL, 0.95 mmol) in anhydrous 1,4-dioxane, and sodium cyanoborohydride (30 mg, 0.48 mmol). The flask was purged with argon and stirred under an atmosphere of argon at room temperature for 24 h. The solution was adjusted to pH 2 with concentrated HCl, and the solvent was removed in vacuo. The residue was dissolved in water, washed with Et_2O (3 × 10 mL), adjusted to pH 10 with $NaOH_{(aq)}$ (10 N), extracted with Et_2O (3 × 20 mL), dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 2.5/97.5, R_f = 0.15) to afford the title compound **42** (57 mg, 55% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.85 (br s, 1H), 8.48 (m, 1H), 7.82 (m, 1H), 7.28 (m, 1H), 7.21 (d, J = 3.7 Hz, 1H), 6.91 (d, J = 3.5 Hz, 1H), 3.65 (s, 2H) 2.31 (s, 6H); LRMS (ESI) *m/z* calcd for $C_{12}H_{15}N_2S$ $[M + H]^+$ 219, found 219; *m/z* calcd for $C_{10}H_8NS$ $[M - N(CH_3)_2]^+$ 174, found 174; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}N_2S$ $[M + H]^+$ 219.0956, found 219.0955; HPLC >99% (t_R = 8.90 min, 55(A):45(B):0.009(C); t_R = 6.28 min, 55(A):45(B):0.018(C)).

***N*,*N*-Dimethyl(5-(pyridin-3-yl)furan-2-yl)methanamine (43).** To a solution of **23** (54 mg, 0.31 mmol) was added a solution of dimethylamine (2.9 M, 0.65 mL, 1.89 mmol) in anhydrous CH_3OH, a solution of HCl (4.0 M, 0.16 mL, 0.63 mmol) in anhydrous 1,4-dioxane, and sodium cyanoborohydride (20 mg, 0.31 mmol). The flask was purged with argon, and the solution was stirred under an atmosphere of argon at room temperature for 48 h. The solution was adjusted to pH 2 with concentrated HCl, and the solvent was removed in vacuo. The residue was dissolved in water, washed with Et_2O (3 × 10 mL), adjusted to pH 10 with $NaOH_{(aq)}$ (10 N), extracted with Et_2O (3 × 20 mL), dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 5/95, R_f = 0.2) to afford the title compound **43** (23 mg, 37% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.91 (m, 1H), 8.46 (m, 1H), 7.94 (m, 1H), 7.28 (m, 1H), 6.68 (d, J = 3.3 Hz, 1H), 6.32 (d, J = 3.4 Hz, 1H), 2.31 (s, 6H); LRMS (ESI) *m/z* calcd for $C_{12}H_{15}N_2O$ $[M + H]^+$ 203, found 203; *m/z* calcd for $C_{10}H_8NO$ $[M - N(CH_3)_2]^+$ 158, found 158; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}N_2O$ $[M + H]^+$ 203.1184, found 203.1205; HPLC >99% (t_R = 6.00 min, 60(A):40(B):0.07(C); t_R = 5.10 min, 60(A):40(B):0.1(C)).

(5-(Pyridin-3-yl)thiophen-2-yl)methanol (44). To a solution of **13** (116 mg, 0.61 mmol) in CH_3OH (5 mL) was added sodium borohydride (23 mg, 0.61 mmol) in one portion. The resultant solution was stirred at room temperature for 10 min and stopped by the addition of aqueous sodium bicarbonate (50:50 saturated solution/water, v/v), and the solvent was

removed in vacuo. The residue was partitioned between water (50 mL) and EtOAc (50 mL). The organic layer was collected, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed in vacuo to afford the title compound **44** (116 mg, 99% yield) as an off-white solid: mp = 89−90 °C; ^{1}H NMR ($CDCl_3$) δ 8.82 (m, 1H), 8.49 (m, 1H), 7.84 (m, 1H), 7.31 (m, 1H), 7.22 (d, J = 4.1 Hz, 1H), 7.01 (d, J = 4.1 Hz, 1H), 4.85 (s, 2H); LRMS (ESI) *m/z* calcd for $C_{10}H_{10}NOS$ $[M + H]^+$ 192, found 192; HRMS (ESI) *m/z* calcd for $C_{10}H_{10}NOS$ $[M + H]^+$ 192.0483, found 192.0476; HPLC >99% (t_R = 10.18 min, 55(A):45(B)0.009(C); t_R = 3.52 min, 55(A):45(B)0.1(C)).

(5-(Pyridin-3-yl)furan-2-yl)methanol (45). To a slurry of **23** (54 mg, 0.31 mmol) in CH_3OH (5 mL) was added sodium borohydride (12 mg, 0.31 mmol) in one portion, and the resultant solution was stirred at room temperature for 10 min. The reaction was stopped by the addition of aqueous sodium bicarbonate (50:50 saturated solution/water, v/v), and the CH_3OH was removed in vacuo. The residue was partitioned between water (20 mL) and ether (20 mL), the organic layer was collected, and the aqueous fraction was re-extracted with ether (2 × 20 mL). The combined organic portions were washed with water (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the title compound **45** (50 mg, 92% yield) as an off-white solid: mp = 119−120 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.88 (s, 1H), 8.42 (m, 1H), 7.88 (m, 1H), 7.27, (m, 1H), 6.65 (d, J = 3.1 Hz, 1H), 6.38 (d, J = 3.1 Hz, 1H), 4.66 (s, 2H); LRMS (ESI) *m/z* calcd for $C_{10}H_{10}NO_2$ $[M + H]^+$ 176, found 176; HRMS (ESI) *m/z* calcd for $C_{10}H_{10}NO_2$ $[M + H]^+$ 176.0712, found 176.0694; HPLC >98% (t_R = 4.60 min, 55(A):45(B):0.032(C); t_R = 3.64 min, 55(A):45(B):0.1(C)).

***tert*-Butyl Prop-2-ynylcarbamate (46).** To a solution of propargylamine (803 mg, 14.6 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added a solution of di-*tert*-butyl dicarbonate (2.67 g, 15.3 mmol) in CH_2Cl_2 (20 mL) via dropping funnel over 25 min, the ice bath was removed, and the resultant solution was stirred at ambient temperature for 30 min. The solvent was removed in vacuo and the crude material was chromatographed on silica gel (EtOAc/hexane, 10/90, R_f = 0.28) to afford the title compound **46** (2.23 g, 98% yield) as a white solid: mp = 39−40 °C; ^{1}H NMR ($CDCl_3$) δ 4.79 (s, 1H), 3.90 (br s, 2H), 2.20 (m, 1H), 1.43 (s, 9H); LRMS (ESI) *m/z* calcd for $C_8H_{13}NNaO_2$ $[M + Na]^+$ 178, found 178.

***tert*-Butyl 3-(Pyridin-3-yl)prop-2-ynylcarbamate (47).** To a pressure tube containing a magnetic stir bar was added **46** (202 mg, 1.3 mmol), and the vial was purged with argon. To the tube is added a solution of tetrakis(triphenylphosphine)-palladium(0) (45 mg, 0.04 mmol) in ethanol/dimethoxyethane (1:1, 2 mL), sodium carbonate$_{(aq)}$ (2 M, 4 mL, 4 mmol), and copper(I) iodide (46 mg, 0.24 mmol), and the vial was once again purged with argon. The resultant solution was stirred at room temperature for 5 min when 3-bromopyridine (483 μL, 5 mmol) was added as a neat oil. The tube was purged with argon, capped, heated to 90 °C, and stirred for 1 h. The solution was cooled to room temperature and poured into a flask containing anhydrous sodium sulfate (5 g). The solution was dried for 10 min and filtered, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 5/95, R_f = 0.43) to afford the title compound **47** (295 mg, 97% yield) as a brown solid: mp = 74−78 °C; ^{1}H NMR ($CDCl_3$) δ 8.63 (m, 1H), 8.51 (m, 1H), 7.67 (m, 1H), 7.22 (m, 1H), 5.05 (br s, 1H), 4.15 (m, 2H), 1.45 (s, 9H); LRMS (ESI) *m/z* calcd for $C_{13}H_{16}N_2O_2$ $[M + H]^+$ 233, found 233; *m/z* calcd for $C_9H_9N_2O_2$ $[M + H - CH_2C(CH_3)_2]^+$ 177, found 177; *m/z* calcd for $C_8H_9N_2$ $[M + H - t\text{-Boc}]^+$ 133, found 133.

3-(Pyridin-3-yl)prop-2-yn-1-amine (48). To a solution of **47** (104 mg, 0.45 mmol) in CH_2Cl_2 (1 mL) was added TFA (2 mL, excess), and the resultant solution was stirred at room temperature for 1 h. The solvent and excess TFA were removed under a stream of nitrogen, and the residue was partitioned between $HCl_{(aq)}$ (1.0 M, 2 mL) and EtOAc (10 mL). The aqueous fraction was collected and subsequently washed with EtOAc (2 × 10 mL). To the remaining aqueous fraction was added CH_2Cl_2 (20 mL) and water (20 mL), and the pH was adjusted to 10 with $NaOH_{(aq)}$ (10 N) while stirring. The organic fraction was collected, and the remaining aqueous fraction was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic fractions were dried (Na_2SO_4) and filtered and the solvent was removed in vacuo to afford the title compound **48** (free base, 58 mg, 97% yield) as a brown oil. Because of the high potential of autoxidation, the dihydrochloride salt was made by dissolving the amine free base in Et_2O and precipitating with etherial HCl. The solvent and excess HCl were removed in vacuo and the solid dihydrochloride was triturated with Et_2O and collected by filtration to afford the title compound **48** (dihydrochloride, 91 mg, 99% yield) as a white solid: ^{1}H NMR (D_2O) δ 8.94 (m, 1H), 8.79 (m, 1H), 8.65 (m, 1H), 8.06 (m, 1H), 4.15 (s, 2H); LRMS (ESI) *m/z* calcd for $C_8H_9N_2$ $[M + H]^+$ 133, found 133; HRMS (ESI) *m/z* calcd for $C_8H_9N_2$ $[M + H]^+$ 133.0766, found 133.0763; HPLC >98% (t_R = 5.70 min, 60(A):40(B):0.02-(C); t_R = 3.05 min, 60(A):40(B):0.07(C)).

***tert*-Butyl *N*-Methyl-3-(pyridin-3-yl)prop-2-ynylcarbamate (49).** To a solution of sodium hydride (60% dispersion in mineral oil, 30 mg, 0.95 mmol) in anhydrous THF (3 mL) at 0 °C was added a solution of **47** (109 mg, 0.47 mmol) in anhydrous THF (2 mL) dropwise over 15 min. To the resultant solution was added a solution of iodomethane (150 μL, 2.42 mmol) in THF (5 mL) over 10 min, the ice bath was removed, and the solution was stirred at ambient temperature for 16 h. The reaction was stopped by the addition of water (5 mL), the aqueous fraction was extracted with EtOAc (3 × 20 mL), washed with water, dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel (EtOAc/hexane, 25/75, R_f = 0.18) to afford the title compound **49** (69 mg, 60% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1H), 8.52 (m, 1H), 7.69 (m, 1H), 7.24 (m, 1H), 4.29 (s, 2H), 2.97 (s, 3H), 2.97 (s, 9H); LRMS (ESI) *m/z* calcd for $C_{14}H_{19}N_2O_2$ $[M + H]^+$ 247, found 247.

***N*-Methyl-3-(pyridin-3-yl)prop-2-yn-1-amine (50).** To a solution of **49** (43 mg, 0.17 mmol) in CH_2Cl_2 (0.8 mL) at 0 °C was added TFA (1.5 mL, excess), the ice bath was removed, and the resultant solution was stirred at ambient temperature for 1 h. The solvent and excess TFA were removed under a stream of argon, and the residue was dissolved in $HCl_{(aq)}$ (1.0 M, 1 mL) and washed with CH_2Cl_2 (3 × 10 mL). To the aqueous fraction was added CH_2Cl_2 (8 mL) and water (8 mL), and the pH was adjusted to 10 with $NaOH_{(aq)}$ (10 N) while stirring. The organic fraction was collected, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 10/90, R_f = 0.16) to afford the title compound **50** (13 mg, 53% yield) as an orange oil: ^{1}H NMR ($CDCl_3$) δ 8.65 (m, 1H), 8.51 (m, 1H), 7.07 (m, 1H), 7.23 (m, 1H), 3.64 (br s, 2H), 2.50 (br s, 3H); LRMS (ESI) *m/z* calcd for $C_9H_{11}N_2$ $[M + H]^+$ 147, found 147; LRMS (ESI) *m/z* calcd for C_8H_6N $[M - NH(CH_3)]^+$ 116, found 116; HRMS (ESI) *m/z* calcd for $C_9H_{11}N_2$ $[M + H]^+$ 147.0922, found 147.0921; HPLC >98% (t_R = 7.25 min, 60(A):40(B):0.02(C); t_R = 2.91 min, 60-(A):40(B):0.07(C)).

***N*,*N*-Dimethyl-3-(pyridin-3-yl)prop-2-yn-1-amine (51).** To a pressure tube containing a magnetic stir bar was added *N*,*N*-dimethylpropargylamine (333 mg, 4 mmol), and the vial was purged with argon. To the tube is added a solution of tetrakis(triphenylphosphine)palladium(0) (139 mg, 0.12 mmol) in ethanol/dimethoxyethane (1:1, 2 mL), sodium carbonate$_{(aq)}$ (2 M, 4 mL, 4 mmol), and copper(I) iodide (46 mg, 0.24 mmol), and the vial was once again purged with argon. The resultant solution was stirred at room temperature for 5 min when 3-bromopyridine (483 μL, 5 mmol) was added as a neat oil. The tube was purged with argon, capped, heated to 90 °C, and stirred for 1 h. The solution was cooled to room temperature and poured into a flask containing anhydrous sodium sulfate (5 g). The solution was dried for 10 min and filtered, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 10/90, R_f = 0.13) to afford the title compound **51** (26 mg, 4% yield) as a brown oil: ^{1}H NMR ($CDCl_3$) δ 8.67 (br s, 1H), 8.52 (m, 1H),

7.72 (m, 1H), 7.24 (m, 1H), 3.49 (s, 2H), 2.37 (s, 6H); LRMS (ESI) *m/z* calcd for $C_{10}H_{12}N_2$ $[M + H]^+$ 161, found 161; LRMS (ESI) *m/z* calcd for C_8H_6N $[M - N(CH_3)_2]^+$ 116, found 116; HRMS (ESI) *m/z* calcd for $C_{10}H_{12}N_2$ $[M + H]^+$ 161.1079, found 161.1090; HPLC >98% (t_R = 9.38 min, 60(A):40(B):0.02(C); t_R = 4.70 min, 60(A):40(B):0.07(C)).

4-(Pyridin-3-yl)benzaldehyde (52). The general Suzuki coupling procedure was followed. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 10/90, R_f = 0.4) to afford the title compound **52** (677 mg, 71% yield) as a yellow solid: mp = 53−54 °C; ^1H NMR ($CDCl_3$) δ 10.07 (s, 1H), 8.89 (s, 1H), 8.66 (m, 1H), 7.99 (d, J = 8.1 Hz, 2H), 7.91 (m, 1H), 7.75 (d, J = 8.1 Hz, 2H), 7.41 (m, 1H); LRMS (ESI) *m/z* calcd for $C_{12}H_{10}NO$ $[M + H]^+$ 184, found 184.

***cis/trans*-4-(Pyridin-3-yl)phenyl-1-carbaldehyde Oximes (53).** To a solution of **52** (547 mg, 2.99 mmol) in 95% ethanol (6 mL) was added hydroxylamine hydrochloride (228 mg, 3.28 mmol) and sodium acetate (269 mg, 3.28 mmol), and the resultant slurry was heated to reflux and stirred for 25 min. The solvent was removed in vacuo, and the residue was triturated with CH_2Cl_2. The white solid (TLC, $CH_3OH/CHCl_3$, 5/95, R_f = 0.22) was collected by filtration to afford the *cis*/*trans* mixture of the title compound **53** (580 mg, 98% yield) as a yellow solid: mp = 160−165 °C dec; ^1H NMR (DMSO-d_6) δ 11.39 (s, 1H), 8.98 (s, 1H), 8.63 (m, 1H), 8.21 (m, 2H), 7.79 (m, 2H), 7.72 (m, 2H), 7.57 (m, 1H), 7.57 (m, 1H); LRMS (ESI) *m/z* calcd for $C_{12}H_{11}N_2O$ $[M + H]^+$ 199, found 199.

(4-(Pyridin-3-yl)phenyl)methanamine (54). To a solution of **53** (146 mg, 0.74 mmol) in anhydrous THF (6 mL) under argon at room temperature was added a solution of LAH (1.0 M in THF, 923 μL, 0.923 mmol) dropwise via syringe over 10 min. The resultant solution was heated to reflux and stirred for 5 h, the heat bath was removed, and the solution was stirred at ambient temperature overnight. The reaction was stopped by the dropwise addition of 1 N HCl, diluted to 20 mL with 1 N HCl, and washed with EtOAc (20 mL), the pH was adjusted to 8 with $NaOH_{(aq)}$ (10 N), extracted with CH_2Cl_2 (3 × 40 mL), and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was chromatographed on silica gel ($CH_3OH/CHCl_3$, 10/90, R_f = 0.03−0.13) to afford the title compound **54** (47 mg, 34% yield) as a yellow oil that solidifies in a freezer: ^1H NMR ($CDCl_3$) δ 8.84 (m, 1H), 8.58 (m, 1H), 7.87 (m, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.35 (m, 1H), 3.94 (s, 2H), 1.60 (br s, 2H); LRMS (ESI) *m/z* calcd for $C_{12}H_{12}N_2$ $[M + H]^+$ 185, found 185; *m/z* calcd for $C_{12}H_{10}N$ $[M - NH_2]^+$ 168, found 168; HRMS (ESI) *m/z* calcd for $C_{12}H_{12}N_2$ $[M + H]^+$ 185.1079, found 185.1093; HPLC >99% (t_R = 7.06 min, 60(A):40(B):0.02(C); t_R = 3.19 min, 60(A):40(B):0.07(C)).

3-Methyl-5-(3-methylthiophen-2-yl)pyridine (55). To a glass vial containing a magnetic stir bar is added a solution of **12** (108 mg, 0.42 mmol) in DME (1 mL), and the vial is purged with argon. To the vial is added a solution of tetrakis-(triphenylphosphine)palladium(0) (15 mg, 0.013 mmol) in ethanol, tetramethyltin (294 μL, 2.13 mmol), and sodium carbonate$_{(aq)}$ (2 M, 0.4 mL, 0.9 mmol), and the vial is purged with argon, capped, heated to 90 °C, and stirred for 1 h. The solution is cooled to room temperature and poured into a flask containing anhydrous sodium sulfate (1 g). The solution is dried for 10 min and filtered, and the solvent is removed in vacuo. The crude material was chromatographed on silica gel (EtOAc/hexane, 10/90, R_f = 0.14) to afford the title compound **55** (29 mg, 36% yield) as a chalky oil: ^1H NMR ($CDCl_3$) δ 8.53 (m, 1H), 8.39 (m, 1H), 7.56 (m, 1H), 7.27 (d, J = 4.62 Hz, 1H), 6.96 (d, J = 5.11 Hz, 1H), 2.39 (s, 3H), 2.33 (s, 3H); LRMS (ESI) *m/z* calcd for $C_{11}H_{12}NS$ $[M + H]^+$ 190, found 190; HRMS (ESI) *m/z* calcd for $C_{11}H_{12}NS$ $[M + H]^+$ 190.0690, found 190.0706; HPLC >99% (t_R = 5.07 min, 55(A):45(B):0.01(C); t_R = 3.69 min, 60(A):40(B):0.07(C)).

3-Methyl-5-(thiophen-3-yl)pyridine (56). To a glass vial containing a magnetic stir bar is added a solution of **19** (17 mg, 0.07 mmol) in DME (1 mL), and the vial is purged with argon. To the vial is added a solution of tetrakis(triphenylphosphine)palladium(0) (3 mg, 0.002 mmol) in ethanol, tetramethyltin (12 μL, 0.08 mmol), and sodium carbonate$_{(aq)}$ (2 M, 1.3 mL, 2.6 mmol), and the vial is purged with argon, capped, heated to 90 °C, and stirred for 1 h. The solution is cooled to room temperature and poured into a flask containing anhydrous sodium sulfate (1 g). The solution is dried for 10 min and filtered, and the solvent is removed in vacuo. The crude material was chromatographed on silica gel (preparative TLC, EtOAc/hexane, 25/75, R_f = 0.22) to afford the title compound **56** (3 mg, 26% yield) as a clear oil: ^1H NMR ($CDCl_3$) δ 8.67 (br s, 1H), 8.36 (br s, 1H), 7.67 (br s, 1H), 7.49 (m, 1H), 7.43 (m, 1H), 7.38 (m, 1H), 2.38 (s, 3H); LRMS (ESI) *m/z* calcd for $C_{10}H_{10}NS$ $[M + H]^+$ 176, found 176; HRMS (ESI) *m/z* calcd for $C_{10}H_{10}NS$ $[M + H]^+$ 176.0534, found 176.0551; HPLC >99% (t_R = 5.41 min, 55(A):45(B):0.01(C); t_R = 2.89 min, 60(A):40(B):0.07(C)).

5-(Pyridin-3-yl)thiophen-2-amine (57). To a solution of **12** (233 mg, 1.13 mmol) in CH_3OH/EtOAc (1:1, 10 mL) was added a slurry of 10% Pd/C (30 mg) in CH_3OH/EtOAc (1:1, 10 mL). The resultant solution was degassed and purged with hydrogen three times and then hydrogenated under double balloon pressure for 24 h. The catalyst was removed by filtration through a pad of Celite, the solvent was removed in vacuo, and the residue was dissolved in MeOH and absorbed to silica gel. The solvent was removed in vacuo and the material was chromatographed on silica gel (EtOAc/hexane, 50/50, R_f = 0.21) to afford the title compound **57** (180 mg, 91% yield) as a yellow solid: mp = 126 °C (dec); ^1H NMR ($CDCl_3$) δ 8.72 (m, 1H), 8.39 (m, 1H), 7.69 (m, 1H), 7.23 (m, 1H), 6.98 (d, J = 4.1 Hz, 1H), 6.18 (d, J = 4.1 Hz, 1H), 3.75 (br s, 2H); LRMS (ESI) *m/z* calcd for $C_9H_9N_2S$ $[M + H]^+$ 177, found 177; HRMS (ESI) *m/z* calcd for $C_9H_9N_2S$ $[M + H]^+$ 177.0486, found 177.0472; HPLC >99% (t_R = 5.57 min, 55(A):45(B):0.018(C); t_R = 4.33 min, 60(A):40(B):0.02(C)).

3-(1-Methyl-1*H*-imidazol-4-yl)pyridine and 3-(1-Methyl-1*H*-imidazol-5-yl)pyridine (58a,b). To a solution of **34** (37 mg, 0.26 mmol) in THF (4 mL) under argon was added sodium hydride (11 mg, 0.28 mmol) in one portion, and the resultant slurry was stirred for 5 min. Iodomethane (190 μL, 0.31 mmol) was added, and the resultant solution was stirred for 10 min. The reaction was stopped by the careful addition of aqueous hydrochloric acid (0.25 N, 6 mL) and washed with ethyl ether (3 × 10 mL). The aqueous fraction was adjusted to pH 9 with $NaOH_{(aq)}$ (10 N) and extracted with ethyl ether (3 × 30 mL), dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 2.5/97.5, R_f = 0.15) to afford the title compounds **58a**,**b** as an inseparable mixture (27 mg, 66% yield) of an orange oil: **58a**, ^1H NMR ($CDCl_3$) δ 8.95 (m, 1H), 8.47 (m, 1H), 8.11 (m, 1H), 7.52 (br s, 1H), 7.31 (m, 1H), 7.26 (br s, 1H) 3.75 (s, 3H); **58b**, ^1H NMR ($CDCl_3$) δ 8.69 (m, 1H), 8.62 (m, 1H), 7.71 (m, 1H), 7.62 (br s, 1H), 7.39 (m, 1H), 7.19 (br s, 1H), 3.70 (s, 3H); LRMS (ESI) *m/z* calcd for $C_9H_{10}N_3$ $[M + H]^+$ 160, found 160; HRMS (ESI) *m/z* calcd for $C_9H_{10}N_3$ $[M + H]^+$ 160.0875, found 160.0866; HPLC >99% (t_R = 19.80 min, 55(A):45(B):0.032(C); t_R = 9.47 min, 55(A):45(B):0.1(C).

3-(1-Ethyl-1*H*-imidazol-4-yl)pyridine (59). To a solution of **34** (36 mg, 0.25 mmol) in THF (5 mL) under argon was added sodium hydride (12 mg, 0.29 mmol) in one portion, and the resultant slurry was stirred for 20 min. Iodoethane (26 μL, 0.32 mmol) was added, and the resultant solution was stirred for 10 min. The reaction was stopped by the careful addition of aqueous hydrochloric acid (1 N, 2 mL), diluted with 13 mL of water, and washed with ethyl acetate (3 × 15 mL). Dichloromethane was added (25 mL), and the aqueous fraction was adjusted to pH 9 with $NaOH_{(aq)}$ (10 N). The organic fraction was collected and the aqueous fraction was extracted with dichloromethane (20 mL), the combined organic fractions were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 2.5/97.5, R_f = 0.27) to afford the title compound **59** (34 mg, 79% yield) as a clear oil: ^1H NMR ($CDCl_3$) δ 8.93 (m, 1H), 8.44 (m, 1H), 8.07 (m, 1H), 7.54 (br s, 1H), 7.28 (m, 2H), 4.02 (q, J = 7.4 Hz, 2H), 1.49 (t, J = 7.4 Hz, 3H); LRMS (ESI) *m/z* calcd for $C_{10}H_{11}N_3$ $[M + H]^+$ 174,

found 174; HRMS (ESI) *m/z* calcd for $C_{10}H_{11}N_3$ [M + H]$^+$ 174.1031, found 174.1042; HPLC >97% (t_R = 13.28 min, 60-(A):40(B):0.02(C); t_R = 3.67 min, 80(A):20(B):0.1(C).

3-(1-Benzyl-1*H*-imidazol-4-yl)pyridine (60). To a solution of **34** (35 mg, 0.25 mmol) in THF (5 mL) under argon was added sodium hydride (12 mg, 0.29 mmol) in one portion, and the resultant slurry was stirred for 20 min. Benzyl bromide (26 μL, 0.32 mmol) was added, and the resultant solution was stirred for 10 min. The reaction was quenched by the slow addition of $HCl_{(aq)}$ (1 N, 2 mL), diluted with 13 mL of water, and washed with ethyl acetate (3 × 15 mL). Dichloromethane was added (25 mL), and the aqueous fraction was adjusted to pH 9 with $NaOH_{(aq)}$ (10 N). The organic fraction was collected, and the aqueous fraction was extracted with dichloromethane (20 mL), the combined organic fractions were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 2.5/97.5, R_f = 0.26) to afford the title compound **60** (43 mg, 74% yield) as a white semisolid: ^{1}H NMR ($CDCl_3$) δ 8.95 (br s, 1H), 8.47 (br s, 1H), 8.10 (m, 1H), 7.64 (m, 1H), 7.42−7.17 (m, 7H), 5.17 (s, 2H); LRMS (ESI) *m/z* calcd for $C_{15}H_{14}N_3$ [M + H]$^+$ 236, found 236; HRMS (ESI) *m/z* calcd for $C_{15}H_{14}N_3$ [M + H]$^+$ 236.1188, found 236.1198; HPLC >99% (t_R = 10 min, 60(A):40(B):0.02(C); t_R = 6.12 min, 60(A):40(B):0.07(C)).

3-(4-Methyl-1*H*-imidazol-1-yl)pyridine and 3-(5-Methyl-1*H*-imidazol-1-yl)pyridine (61). To a solution of 4-methylimidazole (251 mg, 3.06 mmol) in DMF (5 mL) was added NaH (60% dispersion in mineral oil, 133 mg, 3.33 mmol), and the resultant solution was stirred at room temperature for 30 min under argon. To the solution was added a solution of 3-fluoropyridine (88 μL, 1.01 mmol) in DMF (1 mL), and the resultant solution was heated to 100 °C and stirred overnight. The solution was cooled to room temperature, poured into aqueous saturated sodium bicarbonate (50 mL), extracted with ethyl acetate (3 × 50 mL), washed with brine, dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 2/98, R_f = 0.27) to afford the title compound **61** (67 mg, 41% yield), as a regioisomeric mixture in a 3:1 ratio as determined by ^{1}H NMR, as a yellow semisolid that solidified upon standing in a freezer: ^{1}H NMR ($CDCl_3$) δ 8.72 (m, 1H), 8.62 (m, 1H), 7.78 (s, 0.66H), 7.69 (M, 0.66H), 7.65 (m, 0.33H), 7.59 (s, 0.33H), 7.47 (m, 0.33H), 7.42 (m, 0.66H), 7.02 (s, 0.66H), 6.96 (s, 0.33H), 2.31 (s, 2.25H), 2.20 (s, 0.75H); LRMS (ESI) *m/z* calcd for $C_9H_{10}N_3$ [M + H]$^+$ 160, found 160; HRMS (ESI) *m/z* calcd for $C_9H_{10}N_3$ [M + H]$^+$ 160.0875, found 160.0884; HPLC >99% (t_R = 14.91 min, 10.39 min, 55(A):45(B):0.032(C); t_R = 6.74 min, 8.61 min, 60(A):40(B):0.05(C)).

3-(2-Methyl-1*H*-imidazol-1-yl)pyridine (62). To a solution of 2-methylimidazole (256 mg, 3.13 mmol) in DMF (5 mL) was added NaH (60% dispersion in mineral oil, 180 mg, 4.50 mmol), and the resultant solution was stirred at room temperature for 30 min under argon. To the solution was added a solution of 3-fluoropyridine (88 μL, 1.01 mmol) in DMF (1 mL), and the resultant solution was heated to 100 °C and stirred overnight. The solution was cooled to room temperature, poured into aqueous saturated sodium bicarbonate (50 mL), extracted with ethyl acetate (3 × 50 mL), washed with brine, dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel ($CH_3OH/CHCl_3$, 5/95, R_f = 0.12) to afford the title compound **62** (48 mg, 30% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.69 (m, 1H), 8.63 (m, 1H), 7.64 (m, 1H), 7.45 (m, 1H), 7.07 (m, 1H), 7.02 (m, 1H), 2.38 (s, 3H); LRMS (ESI) *m/z* calcd for $C_9H_{10}N_3$ [M + H]$^+$ 160, found 160; HRMS (ESI) *m/z* calcd for $C_9H_{10}N_3$ [M + H]$^+$ 160.0875, found 160.0866; HPLC >99% (t_R = 7.75 min, 55(A):45(B):0.032(C); t_R = 5.45 min, 55(A):45(B):0.01(C)).

3-(1*H*-Imidazol-1-yl)pyridine (63). To a solution of imidazole (420 mg, 6.3 mmol) in DMF (6 mL) was added NaH (60% dispersion in mineral oil, 250 mg, 6.3 mmol), and the resultant solution was stirred at room temperature for 30 min under argon. To the solution was added a solution of 3-fluoropyridine (183 μL, 2.1 mmol) in DMF (2 mL), and the resultant solution was heated to 100 °C and stirred overnight. The solution was cooled to room temperature, poured into aqueous saturated sodium bicarbonate (50 mL), extracted with ethyl acetate (3 × 50 mL), washed with brine, dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel (CH_3OH/CH_2Cl_2, 5/95, R_f = 0.12) to afford the title compound **63** (176 mg, 59% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.75 (m, 1H), 8.63 (m, 1H), 7.87 (s, 1H), 7.73 (m, 1H), 7.44 (m, 1H), 7.30 (s, 1H), 7.26 (s, 1H); LRMS (ESI) *m/z* calcd for $C_8H_8N_3$ [M + H]$^+$ 146, found 146; HRMS (ESI) *m/z* calcd for $C_8H_8N_3$ [M + H]$^+$ 146.0718, found 146.0730; HPLC >99% (t_R = 7.18 min, 55(A):45(B):0.032(C); 5.06 min, 55(A):45(B):0.1(C).

3-(1*H*-Tetrazol-5-yl)pyridine (64). To a solution of 3-cyanopyridine (1.1 g, 10.6 mmol) in DMF (15 mL) was added ammonium chloride (718 mg, 13.4 mmol) and sodium azide (824 mg, 12.7 mmol), and the resultant slurry was vigorously stirred at 90 °C for 15 h. The DMF was removed in vacuo, the residue was dissolved in aqueous potassium hydroxide (1 M, 20 mL) and washed with EtOAc (2 × 25 mL), the aqueous layer was adjusted to pH ∼ 3 with aqueous HCl (6 N), and the solid was collected by filtration to afford the title compound **64** (904 mg, 46% yield) as a white solid: mp = 239−241 °C (dec); ^{1}H NMR ($CDCl_3$) δ 9.21 (m, 1H), 8.76 (m, 1H), 8.39 (m, 1H), 7.64 (m, 1H); LRMS (ESI) *m/z* calcd for $C_6H_6N_5$ [M + H]$^+$ 148, found 148; HRMS (ESI) *m/z* calcd for $C_6H_6N_5$ [M + H]$^+$ 148.0623, found 148.0624; HPLC >99% (t_R = 4.88 min, 60(A):40(B):0.009-(C); t_R = 3.74 min, 60(A):40(B):0.02(C)).

3-Tetrazol-1-yl-pyridine (65). To a solution of 3-aminopyridine (1.3 g, 13.4 mmol) in HOAc (20 mL) was added sodium azide (1.3 g, 20.1 mmol) and trimethyl orthoformate (2.36 mL, 21.6 mmol), and the resultant slurry was stirred at room temperature overnight and subsequently refluxed for 6 h. The reaction mixture was cooled to room temperature, and the reaction was stopped by pouring the mixture into 50 mL of ice/water. EtOAc (50 mL) was added, collected, and subsequently washed with aqueous sodium hydroxide (1 N). The organic layer was collected, dried ($MgSO_4$), and concentrated in vacuo to afford the title compound **65** (1.0 g, 52%) as a white solid: mp = 74−76 °C; ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 9.36 (m, 1H), 8.98 (m, 1H), 8.56 (m, 1H), 7.88 (m, 1H); LRMS (ESI) *m/z* calcd for $C_6H_6N_3$ [M + H − N_2]$^+$ 120, found 120; HRMS (ESI) *m/z* calcd for $C_6H_6N_5$ [M + H]$^+$ 148.0623, found 148.0636; HPLC >99% (t_R = 3.44 min, 60(A):40(B):0.009(C); t_R = 2.71 min, 60(A):40(B):0.02(C)).

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