SUPPLEMENTARY INFORMATION

Nitric Oxide Synthase as a Target for Methicillin Resistant *Staphylococcus aureus*

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Table S1 Related to Figure 2. Cytochrome-c reductase activity measured using 100 nM bBidomain and 1 μM YumC in the presence of inhibitors **19** and **32** at varying concentrations. Inhibitors do not have significant effects on cytochrome-c reductase activity indicating inhibitors do not interfere with redox activity of bBiDomain and YumC.

$[Inhibitor]_{assay}$, μM	Cytochrome C Turnover (min^{-1})
No Inhibitor	538 ± 32
19, 1 μM	521 ± 70
19, 10 μM	552 ± 12
19, 50 μM	561 ± 19
32, 1 μM	503 ± 15
32, 10 μM	529 ± 11
32, 50 μM	506 ± 18

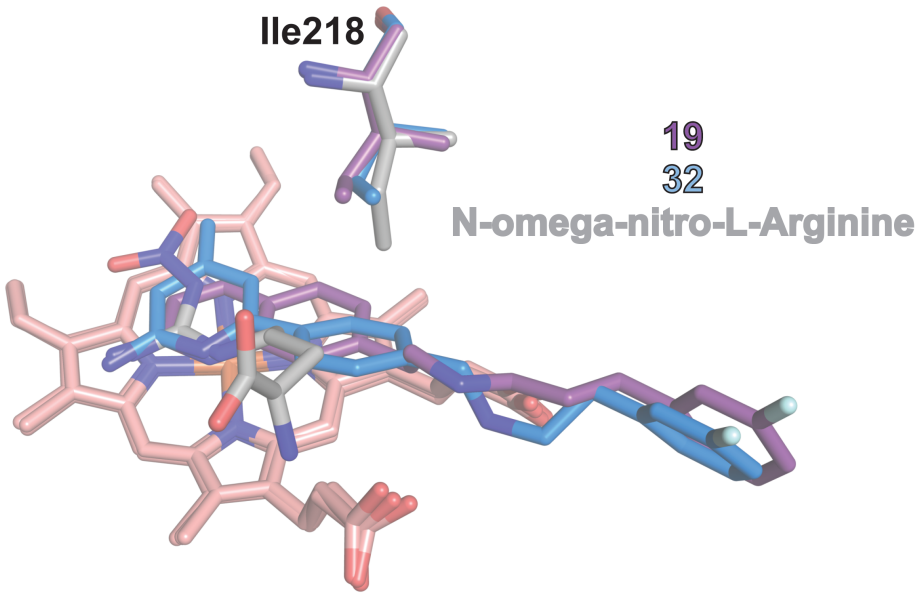


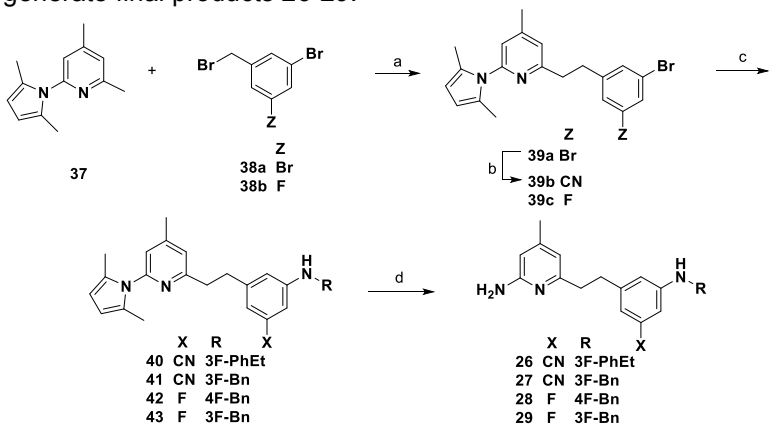
Figure S1 Related to Figure 3. Ile218 of bsNOS contributes a hydrophobic patch to facilitate binding of **19** and **32**. Binding of either **19** or **32** induces a subtle change in the rotomeric position of Ile218. The alternate rotomeric position of Ile218 is best observed by direct comparison to the binding mode of N-omega-nitro-L-Arg (redrawn from PDB 4UQR), an inhibitor that does not utilize the hydrophobic patch contributed by Ile218 for binding. The heme is colored salmon, 19 is shown in, 32 in blue, and N-omega-nitro-L-Arg in grey. Ile218 is colored to correspond with the inhibitor-color scheme.

Table S2 Related to Figure 2. Cytotoxicity of NOS inhibitors evaluated against mouse embryonic fibroblast cells in tissue culture after 72 h incubation. An IC50 for L-NAME could not be determined over the 40 μM to 0.3125 μM inhibitor range evaluated.

	NOS Inhibitor		
	19	**32**	L-NAME
IC_{50} (μM)	5.84	11.86	n.d.

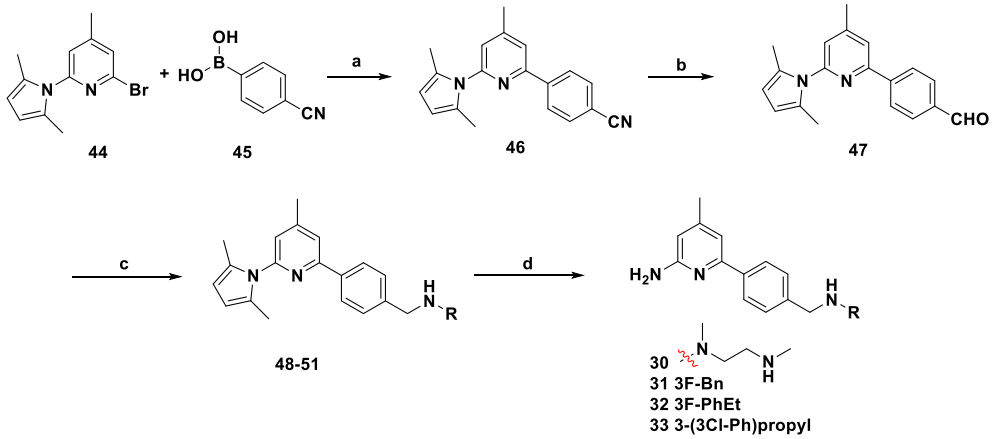
All Schemes Related to Figure 1.

Compounds **26**-**29** were synthesized using previously established methods (Holden et al., 2015) (**Scheme 1**); dibromophenethyl derivative **39a-c** were prepared by coupling of benzyl bromide (**38a-b**) with lithiated pyrrolyl-4,6-lutidine. Intermediate **39a** underwent microwave-assisted Rosenmund-von Braun reaction with CuCN to introduce a nitrile moiety (**39b**). Buchwald–Hartwig reaction of **39b** and **39c** with several aryl amines using $Pd_2(dba)_3$ and DavePhos gave **40-43**. The 2,5-dimethylpyrrole protecting group was removed with $NH_2OH{\cdot}HCl$ using a microwave to generate final products **26**-**29**.



Scheme 1. Reagents and conditions: a) (i) BuLi, 0 °C, 30 min, THF; (ii): I or II, 81-86%; b) CuCN, DMF, microwave, 220 °C, 20 min, 57%; c) amine, $Pd_2(dba)_3$, DavePhos, NaO*t*Bu, THF, 1,4-dioxane, 5~10 h, 100 °C, 69-90%; d) $NH_2OH(HCl)$ (5 equiv), EtOH, H_2O, microwave, 120 °C, 25 min, 60-80%

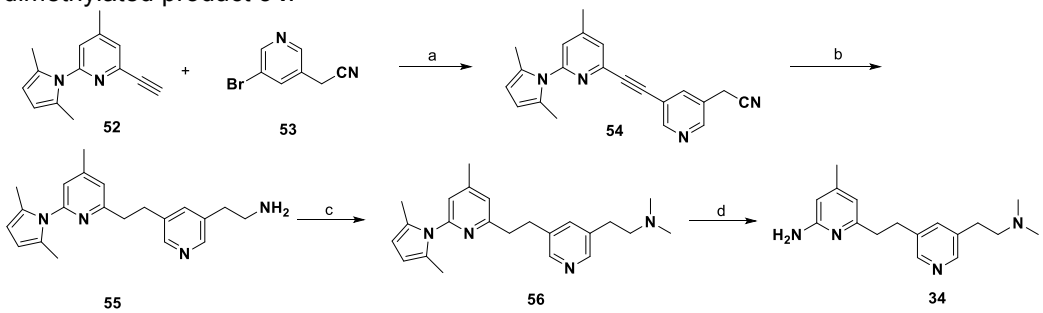
Compounds **30-33** were prepared using the synthetic pathway shown in Scheme 2. Palladium-catalyzed Suzuki cross coupling between pyridinyl bromide and phenylboronic acid yielded **46**. For addition of an amine tail in **30-33**, the aromatic nitrile moiety of **46** was converted to the prerequisite benzaldehyde; this was accomplished with DIBALH. The aldehyde of **47** was then condensed by reductive amination with several amines to give the corresponding benzylamines (**48-51**). The 2,5-dimethylpyrrole protecting group on **48-51** was removed with $NH_2OH{\bullet}HCl$ using a microwave to generate final products **30**-**33**.



Scheme 2. a) $Pd(PPh_3)_4$, Na_2CO_3, toluene, 12 h, 100 °C, 71%; b) DIBAL, CH_2Cl_2, 51% c) $NaBH(OAc)_3$, AcOH, CH_2Cl_2, room temperature, 12 h, 62%, d) $NH_2OH(HCl)$ (5 equiv), EtOH, H_2O, microwave, 120 °C, 25 min, 60-80%

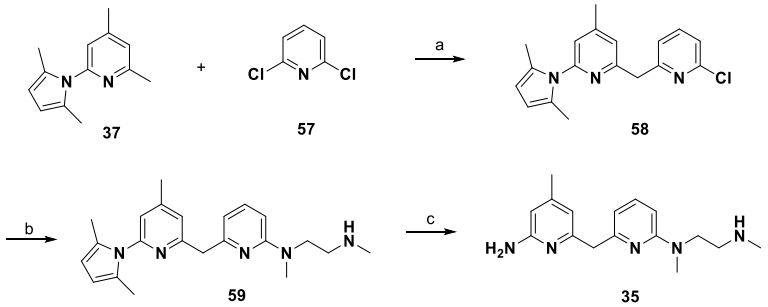
Chemical synthesis of **34** required Sonogashira coupling between **52** and **53** as shown in Scheme 3. Hydrogen reduction of acetylene and nitrile moieties of **54** with Raney-Nickel yielded desired aryl ethylamine **55**. Treatment of formaldehyde with $NaBH(OAc)_3$ and the following deprotection of 2,5-dimethylpyrrole gave N-

dimethylated product **34**.



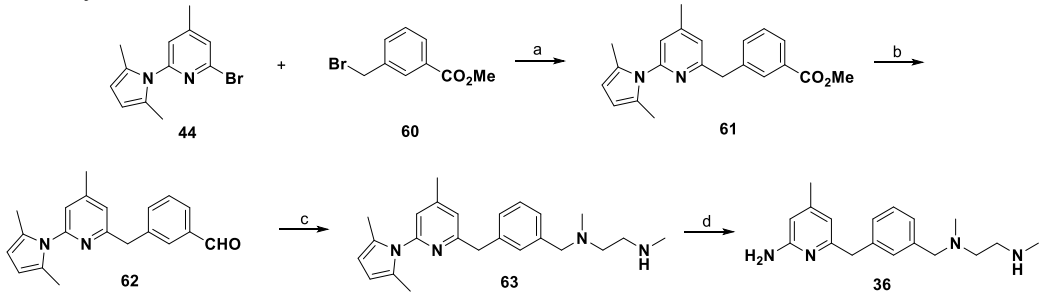
Scheme 3. Reagents and conditions: a) $Pd(PPh_3)_2Cl_2$, CuI, PPh_3, DEA, DMF; b) Raney-Ni, H_2, MeOH/EtOH; c) formaldehyde (35%), $NaBH(OAc)_3$, $MeOH/CH_2Cl_2$; d) $NH_2OH(HCl)$ (5 equiv), EtOH, H_2O, microwave, 120 °C, 25 min

The methylene-linked bis(pyridine) derivative (**35**) was synthesized from addition of lithiated 2-(2,5-dimethyl-1H-pyrrol-1-yl)-4,6-dimethylpyridine (**37**) to 0.5 equiv of 2,6-dichloropyridine (**57**) as a nucleophilic component (Scheme 4) (Yamamoto et al., 2001). Although branched byproducts were produced, using 2 equiv of the lithiated pyridine was crucial because **58** contains an acidic methylene unit. Buchwald–Hartwig reaction with N^1,N^2-dimethylethane-1,2-diamine and deprotection of dimethylpyrrole gave final product **35**.



Scheme 4. Reagents and conditions: a) BuLi, THF, ice bath to reflux; b) amine, $Pd_2(dba)_3$, DavePhos, NaO*t*Bu, THF, 1,4-dioxane, 12 h, 100 °C; c) $NH_2OH(HCl)$ (5 equiv), EtOH, H_2O, microwave, 120 °C, 25 min

The synthetic procedure for **36** is shown in Scheme 5. $Pd(PPh_3)_4$-catalyzed cross coupling between 2-bromopyridine and benzylzinc bromide, which was prepared from benzyl bromide and Zn, afforded 2-benzylpyridine (**61**). Similar to the synthesis of **30-33**, N^1,N^2-dimethylethane-1,2-diamine tail was installed after conversion of the carboxylate in **61** to **62** with DIBAL.



Scheme 5. Reagents and conditions: a) Zn dust, $Pd(PPh_3)_4$, THF, room temp, 12 h; b) DIBAL, toluene; c) $NaBH(AcO)_3$,AcOH, CH_2Cl_2, room temp, 12 h; d) $NH_2OH(HCl)$ (5 equiv), EtOH, H_2O, microwave, 120 °C, 25 min.

Synthesis and Spectral Data
General Experimental Procedures

General procedure for coupling reaction of benzyl bromide with lithiated pyrrolyl-lutidine; Method A. n-BuLi (1.6 M solution in hexanes, 3.75 mL, 6.0 mmol) was added dropwise to a solution of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-4,6-dimethylpyridine (1.2 g, 6.0 mmol) in THF (25 mL) at 0 °C. After being stirred for 30 min at the same temperature, the mixture was transferred to a solution of benzyl bromide (5.0 mmol) in THF (25 mL) at -78 °C via cannula. The reaction mixture was allowed to stir for an additional 20 min, and then quenched by addition of H_2O (50 mL) and ethyl acetate (50 mL). The organic layer was partitioned, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/hexanes) to yield the corresponding products.

2-(3,5-Dibromophenethyl)-6-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4-methylpyridine (39a). The title compound was prepared using General Method A from 3,5-dibromobenzyl bromide (**38a**). 86%; pale yellow oil; ^{1}H NMR (500 MHz, CDCl3) δ 7.51 (s, 1H), 7.26 (ss, 2H), 6.91 (s, 2H), 5.92 (s, 2H), 3.06 (q, *J* = 2.8 Hz, 4H), 2.40 (d, *J* = 1.6 Hz, 3H), 2.15 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.76, 151.73, 149.72, 145.43, 131.65, 130.43, 128.48, 122.77, 122.74, 120.42, 106.76, 39.02, 34.89, 21.01, 13.27; MS ESI $[M + H]^+$ = 449.3.

3-Bromo-5-(2-(6-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4-methylpyridin-2-yl)ethyl)benzonitrile (39b).
To a 5 mL microwave vial equipped with a magnetic stir bar was added **39a** (448 mg, 1.0 mmol), CuCN (108 mg, 1.20 mmol), and DMF (2 mL). After capping the vial, the sample was heated in the microwave irradiator for 20 min at 220 °C. After being cooled to room temperature, the reaction mixture was treated with dichloromethane (20 mL), filtered, and concentrated in *vacuo*. The residue was purified by flash chromatography to give the title compound (225 mg, 57%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.57 (s, 1H), 7.41 (s, 1H), 6.93 (ss, 2H), 5.92 (s, 2H), 3.19 – 3.03 (m, 4H), 2.41 (s, 3H), 2.13 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.27, 151.82, 149.88, 145.04, 136.39, 132.31, 130.76, 128.44, 122.77, 122.75, 120.59, 117.45, 113.92, 106.81, 38.69, 34.58, 21.01, 13.26; MS ESI $[M + H]^+$ = 394.5.

2-(3-Bromo-5-fluorophenethyl)-6-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4-methylpyridine (39c). The title compound was prepared using General Method A from 3-bromo-5-fluoro-benzyl bromide (**38b**). 81%; pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (s, 1H), 7.10 (dt, *J* = 8.2, 2.1 Hz, 1H), 6.95 (s, 1H), 6.92 (s, 1H), 6.87 (m, 1H), 5.94 (s, 2H), 3.16 – 3.03 (m, 4H), 2.42 (s, 3H), 2.17 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.60 (d, *J* = 250.1 Hz), 159.89, 151.75, 149.71, 145.63 (d, *J* = 7.8 Hz), 128.46, 127.56 (d, *J* = 3.0 Hz), 122.74, 122.29 (d, *J* = 10.2 Hz), 120.40, 116.69 (d, *J* = 24.4 Hz), 114.42 (d, *J* = 20.9 Hz), 106.79, 38.98, 35.04 (d, *J* = 1.8 Hz), 21.01, 13.28; MS ESI $[M + H]^+$ = 387.2.

General procedure for Buchwald Hartwig amination using $Pd_2(dba)_3$ and DavePhos: Method B; A mixture of 3-bromobenzene (0.25 mmol), amine (0.30 mmol), $Pd_2(dba)_3$ (12 mg, 0.0125 mmol), DavePhos (10 mg, 0.025 mmol), and NaO*t*Bu (29 mg, 0.30 mmol) in THF (1.0 mL) and 1,4-dioxane (1.0 mL) was stirred at 80 °C for 12 h. The reaction mixture was then treated with diethyl ether (10 mL), filtered, and concentrated in *vacuo*. The residue was purified by flash chromatography (EtOAc/hexanes) to give the corresponding products.

General procedure for deprotection of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)pyridine derivatives using microwave irradiation(Mukherjee et al., 2014): Method C; To a 5 mL microwave vial equipped with a magnetic stir bar the protected aminoyridine (0.1~ 0.5 mmol), hydroxylamine HCl (5 equiv), ethanol (2 mL), and water (1 mL) were added. After capping the vial, the contents were shaken vigorously and then heated in the microwave irradiator for 30 min at 120 °C. The reaction mixture was concentrated in *vacuo* and purified by flash column chromatography using a C18 flash cartridge (12 -25g, 40-63 µm / 230-400 mesh, Pore Size 60 Å) with 5 to 90% MeOH in water as the mobile phase. This method was applied to give pure (> 95% by HPLC) final compounds (65% - 80% yield).

3-(2-(6-(2,5-Dimethyl-1H-pyrrol-1-yl)-4-methylpyridin-2-yl)ethyl)-5-((3-fluorophenethyl)amino)benzonitrile (40). The title compound was prepared using General Method B from 2-(3-fluorophenyl)ethylamine. 86%, colorless gel; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 1H), 7.01 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.00 – 6.92 (m, 3H), 6.90 (s, 1H), 6.81 (s, 1H), 6.66 (s, 1H), 6.63 (s, 1H), 5.92 (s, 2H), 3.96 (t, *J* = 5.9 Hz, 1H), 3.38 (q, *J* = 6.6 Hz, 2H), 3.11 – 3.05 (m, 2H), 3.05 – 2.99 (m, 2H), 2.92 (t, *J* = 6.9 Hz, 2H), 2.41 (s, 3H), 2.15 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.98, 162.02, 160.21, 151.68, 149.70, 148.20, 143.91, 141.38, 141.32, 130.25, 130.19, 128.44, 124.45, 124.43, 122.69, 120.96, 120.29, 119.58, 117.45, 115.69, 115.53, 113.68, 113.51, 113.05, 112.81, 106.76, 44.34, 39.14, 35.40, 34.93, 21.01, 13.28; MS ESI $[M + H]^+$ = 453.7.

3-(2-(6-Amino-4-methylpyridin-2-yl)ethyl)-5-((3-fluorophenethyl)amino)benzonitrile (26). The title compound was prepared using General Method C from **40**. 70%; pale yellow gel; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 1H), 7.01 – 6.90 (m, 3H), 6.86 (s, 1H), 6.64 (s, 2H), 6.28 (s, 1H), 6.16 (s, 1H), 3.37 (q, *J* = 6.7 Hz, 2H), 2.90 (dd, *J* = 8.3, 5.4 Hz, 4H), 2.85 – 2.76 (m, 2H), 2.18 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.98 (d, *J* = 246.1 Hz), 158.31 (d, *J* = 22.4 Hz), 156.44, 149.67, 148.05, 144.22, 141.36 (d, *J* = 7.2 Hz), 130.18 (d, *J* = 8.4 Hz), 124.43 (d, *J* = 2.7 Hz), 121.28, 119.68, 117.67, 115.61 (d, *J* = 21.0 Hz), 114.12, 113.57 (d, *J* = 21.2 Hz), 112.86, 112.70, 106.95, 44.37, 39.18, 35.81, 34.92 (d, *J* = 1.7 Hz), 21.00; HRMS (ESI): calcd for $C_{23}H_{24}FN_4$ $[M + H]^+$, 375.1980; found, 375.1976.

3-(2-(6-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-4-methylpyridin-2-yl)ethyl)-5-((3-fluorobenzyl)amino)-benzonitrile (41). The title compound was prepared using General Method B from 3-fluorobenzylamine. 69%; brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.03 – 6.98 (m, 1H), 6.98 – 6.93 (m, 1H), 6.88 (s, 1H), 6.85 (s, 1H), 6.77 (ss, 1H), 6.62 (s, 1H), 6.60 (s, 1H), 5.87 (s, 2H), 4.35 – 4.30 (m, 1H), 4.29 (s, 2H), 3.10 – 2.89 (m, 4H), 2.36 (s, 3H), 2.09 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.16 (d, *J* = 246.6 Hz), 160.14, 151.66, 149.67, 148.06, 143.90, 141.05 (d, *J* = 6.8 Hz), 130.38 (d, *J* = 8.2 Hz), 128.45, 122.69 (d, *J* = 2.8 Hz), 122.64, 121.37, 120.28, 119.50, 117.57,

114.45 (d, *J* = 21.1 Hz), 113.99 (d, *J* = 21.8 Hz), 113.01, 112.83, 106.76, 47.28, 39.03, 35.32, 21.02, 13.26; MS ESI [M + H]$^+$ = 439.1.

3-(2-(6-Amino-4-methylpyridin-2-yl)ethyl)-5-((3-fluorobenzyl)amino)benzonitrile (27). The title compound was prepared using General Method C from **41**. 78%; pale yellow gel; ^{1}H NMR (500 MHz, MeOD) δ 7.35 (td, *J* = 7.9, 5.8 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.08 (dt, *J* = 10.0, 2.0 Hz, 1H), 6.98 (td, *J* = 8.5, 2.6 Hz, 1H), 6.75 (s, 1H), 6.68 (s, 2H), 6.31 (s, 1H), 6.26 (s, 1H), 4.33 (s, 2H), 2.84 (dd, *J* = 8.8, 5.8 Hz, 2H), 2.76 (dd, *J* = 8.8, 5.8 Hz, 2H), 2.18 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 164.54 (d, *J* = 244.4 Hz), 160.10, 158.00, 156.10, 151.99, 150.43, 145.04, 143.86 (d, *J* = 6.8 Hz), 131.30 (d, *J* = 8.2 Hz), 123.90 (d, *J* = 2.9 Hz), 121.07, 120.52, 118.34, 114.77, 114.60, 113.99, 113.39, 108.35, 47.38, 39.39, 36.71, 21.51; HRMS (ESI): calcd for $C_{22}H_{22}FN_4$ [M + H]$^+$, 361.1823; found, 361.1832.

3-(2-(6-(2,5-Dimethyl-1H-pyrrol-1-yl)-4-methylpyridin-2-yl)ethyl)-5-fluoro-N-(4-fluorobenzyl)aniline (42). The title compound was prepared using General Method B from **39c** and 4-fluorobenzylamine. 75%; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.10 – 7.01 (m, 2H), 6.95 (s, 1H), 6.89 (s, 1H), 6.31 – 6.24 (m, 2H), 6.16 (dt, *J* = 11.2, 2.2 Hz, 1H), 5.92 (s, 2H), 4.27 (s, 2H), 3.10 – 3.01 (m, 2H), 3.01 – 2.92 (m, 2H), 2.40 (s, 3H), 2.15 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.04 (d, *J* = 241.8 Hz), 161.13, 160.70, 151.61, 149.51, 149.41 (d, *J* = 11.5 Hz), 144.56 (d, *J* = 9.4 Hz), 134.51 (d, *J* = 3.3 Hz), 129.02 (d, *J* = 8.0 Hz), 128.47, 122.58, 120.11, 115.55 (d, *J* = 21.6 Hz), 108.85, 106.71, 104.41 (d, *J* = 21.4 Hz), 97.38 (d, *J* = 25.7 Hz), 47.51, 39.30, 35.84 (d, *J* = 1.9 Hz), 21.02, 13.26; MS ESI [M + H]$^+$ = 432.1.

6-(3-Fluoro-5-((4-fluorobenzyl)amino)phenethyl)-4-methylpyridin-2-amine (28). The title compound was prepared using General Method C from **42**. 63%; pale yellow gel; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.04 (t, *J* = 8.7 Hz, 2H), 6.37 – 6.28 (m, 3H), 6.17 (s, 1H), 6.16 – 6.11 (m, 1H), 4.27 (d, *J* = 5.3 Hz, 2H), 4.18 (t, *J* = 5.7 Hz, 1H), 2.92 – 2.78 (m, 4H), 2.20 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.99 (d, *J* = 242.4 Hz), 162.06 (d, *J* = 245.1 Hz), 158.62, 158.22, 156.73 (d, *J* = 55.5 Hz), 156.40, 149.72, 149.45 (d, *J* = 11.3 Hz), 144.86 (d, *J* = 9.5 Hz), 134.65 (d, *J* = 3.1 Hz), 129.01 (d, *J* = 8.1 Hz), 115.51 (d, *J* = 21.4 Hz), 114.06, 108.96 (d, *J* = 1.9 Hz), 106.86, 104.37 (d, *J* = 21.5 Hz), 97.17 (d, *J* = 25.6 Hz), 47.47, 39.15, 36.11, 21.04; HRMS (ESI): calcd for $C_{21}H_{22}F_2N_3$ [M + H]$^+$, 354.1776; found, 354.1782.

3-(2-(6-(2,5-Dimethyl-1H-pyrrol-1-yl)-4-methylpyridin-2-yl)ethyl)-5-fluoro-N-(3-fluorobenzyl)aniline (43). The title compound was prepared using General Method B from 3-fluorobenzylamine. 71%; pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 1H), 7.17 – 7.11 (m, 1H), 7.10 – 7.06 (m, 1H), 7.02 – 6.96 (m, 1H), 6.94 (s, 1H), 6.89 (s, 1H), 6.31 – 6.25 (m, 2H), 6.15 (dt, *J* = 11.1, 2.3 Hz, 1H), 5.92 (s, 2H), 4.32 (s, 2H), 3.05 (dd, *J* = 9.3, 5.8 Hz, 2H), 2.97 (dd, *J* = 9.2, 5.7 Hz, 2H), 2.40 (s, 3H), 2.15 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.55 (d, *J* = 112.3 Hz), 162.61 (d, *J* = 116.1 Hz), 160.69, 151.60 , 149.52, 149.31 (d, *J* = 11.4 Hz), 144.57 (d, *J* = 9.3 Hz), 141.70 (d, *J* = 6.8 Hz), 130.22 (d, *J* = 8.4 Hz), 128.48, 122.76 (d, *J* = 2.7 Hz), 122.60, 120.12, 114.25 (d, *J* = 16.9 Hz), 114.08 (d, *J* = 17.4 Hz), 108.87, 106.72 (d, *J* = 4.7 Hz), 104.49 (d, *J* = 21.4 Hz), 97.38 (d, *J* = 25.8 Hz), 47.63, 39.28, 35.82 (d, *J* = 1.9 Hz), 21.01, 13.25; MS ESI [M + H]$^+$ = 432.1.

6-(3-Fluoro-5-((3-fluorobenzyl)amino)phenethyl)-4-methylpyridin-2-amine (29). The title compound was prepared using General Method C from 43. 65%; pale yellow gel. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (td, *J* = 7.9, 5.9 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 9.8 Hz, 1H), 6.98 (td, *J* = 8.5, 2.7 Hz, 1H), 6.33 (dt, *J* = 9.5, 1.7 Hz, 1H), 6.31 – 6.27 (m, 2H), 6.17 (s, 1H), 6.13 (dt, *J* = 11.3, 2.2 Hz, 1H), 4.31 (d, *J* = 4.6 Hz, 2H), 4.28 (d, *J* = 5.5 Hz, 1H), 2.90 – 2.78 (m, 4H), 2.20 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.03 (d, *J* = 242.1 Hz), 162.12 (d, *J* = 247.0 Hz), 158.55, 158.23, 156.78 (d, *J* = 52.3 Hz), 156.45, 149.77, 149.34 (d, *J* = 11.3 Hz), 144.86 (d, *J* = 9.5 Hz), 141.85 (d, *J* = 6.8 Hz), 130.18 (d, *J* = 8.2 Hz), 122.76 (d, *J* = 2.8 Hz), 114.21 (d, *J* = 8.1 Hz), 114.04 (t, *J* = 4.3 Hz), 109.02 (d, *J* = 1.9 Hz), 106.89, 104.45 (d, *J* = 21.4 Hz), 97.15 (d, *J* = 25.6 Hz), 47.59 (d, *J* = 1.8 Hz), 39.11, 36.11 (d, *J* = 1.9 Hz), 21.04; HRMS (ESI): calcd for $C_{21}H_{22}F_2N_3$ [M + H]$^+$, 354.1776; found, 354.1781.

4-(6-(2,5-Dimethyl-1H-pyrrol-1-yl)-4-methylpyridin-2-yl)benzonitrile (46). (4-Cyanophenyl)boronic acid (5.5 mmol) in 2 M Na_2CO_3 (aqueous solution, 5 mL) and methanol (5 mL) was added to a stirred solution of 2-bromo-6-(2,5-dimethyl-1H-pyrrol-1-yl)-4-methylpyridine (5 mmol) and $Pd(Ph_3)_4$ (0.25 mmol) in toluene (20 mL) under a nitrogen atmosphere. The mixture was stirred at 100 °C for 24 h. After the solvent was removed under vacuum, the residue was partitioned between ethyl acetate (200 mL) and water (50 mL). The organic layer was dried (sodium sulfate), evaporated, and purified by column chromatography on a silica gel cartridge, using hexanes/ethyl acetate (70/30, v/v) to give the title product in a 71% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 – 8.08 (m, 2H), 7.86 – 7.72 (m, 2H), 7.64 (t, *J* = 1.0 Hz, 1H), 7.08 (t, *J* = 1.0 Hz, 1H), 5.96 (s, 2H), 2.55 (s, 3H), 2.23 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.43, 152.14, 150.49, 142.64, 132.54, 128.59, 127.49, 121.97, 120.10, 118.82, 112.62, 107.15, 21.36, 13.51; MS ESI [M + H]$^+$ = 288.1

4-(6-(2,5-Dimethyl-1H-pyrrol-1-yl)-4-methylpyridin-2-yl)benzaldehyde (47). A solution of DIBAL in hexane (1.0 M, 5.5 mL, 5.5 mmol) was added slowly to a solution of **46** (5 mmol) in CH_2Cl_2 (20 mL). The solution was stirred at room temp for 1 h and was then diluted with ethyl ether (20 mL). After careful addition of 1 N HCl (20 mL), the mixture was stirred for 15 min. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. Chromatography on silica gel gave the title product **47** (51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.33 – 8.16 (m, 2H), 8.04 – 7.91 (m, 2H), 7.68 (s, 1H), 7.07 (s, 1H), 5.96 (s, 2H), 2.54 (s, 3H), 2.24 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.02, 155.09, 152.08, 150.33, 144.08, 136.53, 130.12, 128.60, 127.53, 121.78, 120.33, 107.07, 21.34, 13.51; MS ESI $[M + H]^+$ = 291.8

General procedure for reductive amination: Method D; To a stirred solution of benzldehyde (1 mmol) in dichloromethane (10 mL), amine (1 mmol), acetic acid (1 mmol), and $NaBH(OAc)_3$ (1.1 mmol) were added, and the resulting mixture was stirred at room temperature for 12 h. The organic materials were extracted with ethyl acetate and dried over anhydrous $MgSO_4$. After removal of the solvent under vacuum, the crude product was purified by flash column chromatography on a silica gel cartridge to give the target compound.

***N*^{1}-(4-(6-(2,5-Dimethyl-1H-pyrrol-1-yl)-4-methylpyridin-2-yl)benzyl)-*N*^{1},*N*^{2}-dimethylethane-1,2-diamine (48).** The title compound was prepared using General Method D from **47** and *N*^{1},*N*^{2}-dimethylethane-1,2-diamine. 62%; colorless gel; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.7 Hz, 2H), 7.59 (s, 1H), 7.43 (d, *J* = 7.9 Hz, 2H), 6.98 (s, 1H), 5.94 (s, 2H), 3.61 (d, *J* = 6.5 Hz, 2H), 3.40 (dt, *J* = 39.9, 7.0 Hz, 2H), 2.87 (s, 3H), 2.67 – 2.53 (m, 2H), 2.51 (s, 3H), 2.30 (s, 3H), 2.24 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.51, 155.75, 151.76, 149.82, 140.25, 137.37, 129.21, 128.62, 126.88, 120.61, 119.41, 106.75, 62.34, 54.92, 46.93, 42.56, 34.59, 28.47, 21.33, 13.50; MS ESI $[M + H]^+$ = 363.0

***N*^{1}-(4-(6-Amino-4-methylpyridin-2-yl)benzyl)-*N*^{1},*N*^{2}-dimethylethane-1,2-diamine (30).** The title compound was prepared using General Method B from **48**. 60%; colorless gel; ^{1}H NMR (500 MHz, MeOD) δ 7.98 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 1.5 Hz, 1H), 6.88 (t, *J* = 1.2 Hz, 1H), 4.77 (d, *J* = 13.9 Hz, 1H), 4.52 (s, 1H), 3.75 (s, 0H), 3.65 (d, *J* = 6.2 Hz, 3H), 2.93 (s, 3H), 2.83 (s, 3H), 2.50 (d, *J* = 1.0 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 159.13, 156.41, 146.29, 134.90, 133.66, 133.42, 129.24, 114.58, 112.36, 60.83, 52.71, 44.41, 40.24, 33.95, 22.12; HRMS (ESI): calcd for $C_{17}H_{25}N_4$ $[M + H]^+$, 285.2074; found, 285.2078.

6-(4-(((3-Fluorobenzyl)amino)methyl)phenyl)-4-methylpyridin-2-amine (31). The title compound was prepared using General Methods D and B from **47** and 3-fluorobenzylamine. 39%; pale yellow gel;^{1}H NMR (500 MHz, MeOD) δ 7.95 (d, *J* = 5.7 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.52 (td, *J* = 8.0, 5.8 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.27 – 7.16 (m, 1H), 7.07 (s, 1H), 6.71 (s, 1H), 4.38 (s, 2H), 4.35 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 162.88 (d, *J* = 246.4 Hz), 156.78, 154.79, 135.85, 133.66 (d, *J* = 7.5 Hz), 133.11, 130.81 (d, *J* = 8.3 Hz), 130.56, 130.48, 127.51, 125.75 (d, *J* = 3.1 Hz), 116.62 (d, *J* = 22.3 Hz), 116.10 (d, *J* = 21.3 Hz), 112.48, 109.76, 50.35, 50.19, 20.36; HRMS (ESI): calcd for $C_{20}H_{21}FN_3$ $[M + H]^+$, 322.1714; found, 322.1723.

***N*-(4-(6-(2,5-Dimethyl-1H-pyrrol-1-yl)-4-methylpyridin-2-yl)benzyl)-2-(3-fluorophenyl)ethan-1-amine (49)** The title compound was prepared using General Method D from (3-fluorophenyl)ethylamine. 81%; white gel; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 – 7.99 (m, 2H), 7.60 – 7.54 (m, 1H), 7.43 – 7.38 (m, 2H), 7.28 – 7.24 (m, 1H), 7.03 – 6.97 (m, 2H), 6.96 – 6.88 (m, 2H), 5.95 (s, 2H), 3.90 (s, 2H), 2.95 (dd, *J* = 7.5, 6.0 Hz, 2H), 2.87 (t, *J* = 6.7 Hz, 2H), 2.51 (s, 3H), 2.24 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.92 (d, *J* = 245.7 Hz), 156.34, 151.78, 149.86, 142.26 (d, *J* = 7.3 Hz), 140.43, 137.52, 129.93 (d, *J* = 8.3 Hz), 128.63, 128.59, 127.10, 124.42 (d, *J* = 2.7 Hz), 120.71, 119.42, 115.56 (d, *J* = 20.9 Hz), 113.18 (d, *J* = 20.9 Hz), 106.78, 53.18, 49.83, 35.74, 21.33, 13.50; MS ESI $[M + H]^+$ = 414.1

6-(4-(((3-Fluorophenethyl)amino)methyl)phenyl)-4-methylpyridin-2-amine (32). The title compound was prepared using General Method B from **50**. 60%; colorless gel; ^{1}H NMR (500 MHz, MeOD) δ 7.98 – 7.91 (m, 2H), 7.82 – 7.73 (m, 2H), 7.40 (td, *J* = 7.9, 6.0 Hz, 1H), 7.14 (d, *J* = 1.5 Hz, 1H), 7.11 (m, 2H), 7.08 – 7.01 (m, 1H), 6.86 (s, 1H), 4.39 (s, 2H), 3.37 (m, 2H), 3.18 – 3.05 (m, 2H), 2.49 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 164.49 (d, *J* = 245.3 Hz), 159.05, 156.46, 146.57, 140.46 (d, *J* = 7.4 Hz), 135.64, 134.42, 132.21, 131.83 (d, *J* = 8.4 Hz), 129.10, 125.74 (d, *J* = 2.9 Hz), 116.61 (d, *J* = 21.8 Hz), 115.11 (d, *J* = 21.1 Hz), 114.43, 112.18, 51.74, 49.63, 32.91, 22.09; HRMS (ESI): calcd for $C_{21}H_{23}FN_3$ $[M + H]^+$, 336.1871; found, 336.1876.

3-(3-Chlorophenyl)-N-(4-(6-(2,5-dimethyl-1H-pyrrol-1-yl)-4-methylpyridin-2-yl)benzyl)propan-1-amine (51). The title compound was prepared using General Method D from 3-(3-fluorophenyl)propylamine. 81%; white gel; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 – 7.98 (m, 2H), 7.62 – 7.56 (m, 1H), 7.46 – 7.39 (m, 2H), 7.26 – 7.15 (m, 3H), 7.08 (dt, *J* = 7.3, 1.6 Hz, 1H), 6.99 – 6.95 (m, 1H), 5.94 (s, 2H), 3.86 (s, 2H), 2.69 (dt, *J* = 12.8, 7.4 Hz, 4H), 2.51 (s, 3H), 2.24 (s, 6H), 1.95 – 1.78 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.45, 151.78, 149.83, 144.16, 141.41, 137.32, 134.05, 132.15, 132.07, 129.60, 128.63, 128.53, 128.48, 127.04, 126.62, 125.99, 120.65, 119.40, 106.76, 53.61, 48.61, 33.28, 31.44, 21.33, 13.50; MS ESI $[M + H]^+$ = 444.1.

6-**(4-(((3-(3-Chlorophenyl)propyl)amino)methyl)phenyl)-4-methylpyridin-2-amine (33).** The title compound was prepared using General Method B from **51**. 70%; colorless gel; ^{1}H NMR (500 MHz, MeOD) δ 7.95 – 7.91 (m, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.28 (m, 2H), 7.25 (dt, *J* = 8.4, 1.3 Hz, 1H), 7.21 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.12 (d, *J* = 1.4 Hz, 1H), 6.82 (s, 1H), 4.33 (s, 2H), 3.18 – 3.05 (m, 2H), 2.76 (q, *J* = 7.6 Hz, 2H), 2.48 (s, 3H), 2.13 – 2.03 (m, 2H); ^{13}C NMR (126 MHz, MeOD) δ 159.16, 156.38, 146.45, 144.00, 135.78, 132.20, 132.12, 131.24, 129.50, 129.12, 129.06, 127.95, 127.62, 114.45, 112.22, 51.63, 48.30, 33.16, 28.68, 22.10; HRMS (ESI): calcd for $C_{21}H_{25}ClN_3$ $[M + H]^+$, 366.1732; found, 366.1737.

2-(5-((6-(2,5-Dimethyl-1H-pyrrol-1-yl)-4-methylpyridin-2-yl)ethynyl)pyridin-3-yl)acetonitrile (54). A reaction mixture of **52** (300 mg, 1.4 mmol), **53**, (320 mg, 1.6 mmol), $Pd(PPh_3)_2Cl_2$ (45 mg, 0.070 mmol), CuI (11 mg, 0.070 mmol), PPh_3 (74 mg, 0.28 mmol), diethylamine (3 mL), and DMF (3 mL) was heated at 120 °C for 20 min in the microwave cavity. Then diethyl ether (50 mL) was added to the reaction mixture, which was filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (EtOAc/hexanes) to give the title compound (342 mg, 75%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.56 (s, 1H), 7.92 (s, 1H), 7.44 (s, 1H), 7.07 (s, 1H), 5.90 (s, 2H), 3.81 (s, 2H), 2.48 (s, 3H), 2.16 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.42, 152.15, 150.14, 148.46, 141.63, 138.28, 128.54, 127.09, 125.88, 123.02, 119.88, 116.44, 107.06, 92.31, 84.58, 21.03, 20.97, 13.22; MS ESI $[M + H]^+$ = 327.1.

2-(5-(2-(6-(2,5-Dimethyl-1H-pyrrol-1-yl)-4-methylpyridin-2-yl)ethyl)pyridin-3-yl)ethan-1-amine (55). A solution of **54** (300 mg, 0.92 mmol) in EtOH (10 mL) and MeOH (10 mL) was stirred with Raney-Ni (50% in water, 0.5 mL) for 1 h at room temperature under a hydrogen atmosphere. The reaction mixture was filtered through a PTFE membrane filter (diam. 25 mm, pore size 0.2 µm) and concentrated in *vacuo* to give the crude title compound (300 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 2.3 Hz, 1H), 8.31 – 8.26 (m, 2H), 5.90 (s, 2H), 3.09 (s, 3H), 2.95 (t, *J* = 7.0 Hz, 2H), 2.71 (t, *J* = 7.0 Hz, 2H), 2.38 (s, 3H), 2.12 (s, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.09, 151.72, 149.69, 147.89, 147.82, 136.46, 136.43, 134.75, 128.43, 122.72, 120.33, 106.73, 43.22, 39.14, 37.01, 32.63, 20.99, 13.24; MS ESI $[M + H]^+$ = 335.2.

2-(5-(2-(6-(2,5-Dimethyl-1H-pyrrol-1-yl)-4-methylpyridin-2-yl)ethyl)pyridin-3-yl)-N,N-dimethylethan-1-amine (56). Primary amine **55** (300 mg, ~ 0.9 mmol) and aqueous formaldehyde (10 mL) were dissolved in MeOH (10 mL) and CH_2Cl_2 (40 mL) and stirred for 30 min. After addition of $NaBH(OAc)_3$ (1.27g, 6.0 mmol), the reaction mixture was stirred for 20 h at room temperature. Then the reaction mixture was treated with CH_2Cl_2 (60 mL) and saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was partitioned, dried with $MgSO_4$, and concentrated in *vacuo*. The residue was purified by flash chromatography (CH_2Cl_2/MeOH) to give the title compound (231 mg, 71%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.14 (s, 1H), 7.19 (s, 1H), 6.78 (s, 1H), 6.75 (s, 1H), 5.77 (s, 2H), 3.01 – 2.88 (m, 4H), 2.68 – 2.55 (m, 2H), 2.40 – 2.34 (m, 2H), 2.25 (s, 3H), 2.17 (s, 6H), 1.99 (d, *J* = 13.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.14, 151.75, 149.62, 147.78, 147.68, 136.32, 136.21, 135.23, 128.43, 122.75, 120.30, 106.74, 60.99, 45.42, 39.23, 32.67, 31.29, 21.00, 13.27; MS ESI $[M + H]^+$ = 363.2.

6-(2-(5-(2-(Dimethylamino)ethyl)pyridin-3-yl)ethyl)-4-methylpyridin-2-amine (34). The title compound was prepared using General Method B from **56**. 61%, pale yellow gel; ^{1}H NMR (500 MHz, MeOD) δ 8.88 (s, 1H), 8.83 (s, 1H), 8.80 (s, 1H), 6.76 (s, 1H), 6.72 (s, 1H), 3.62 (dd, *J* = 9.9, 6.4 Hz, 2H), 3.42 (dd, *J* = 10.0, 6.3 Hz, 2H), 3.36 – 3.33 (dd, *J* = 10.0, 6.3 Hz, 2H), 3.20 (dd, *J* = 9.6, 6.4 Hz, 2H), 3.04 (s, 6H), 2.40 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 159.09, 155.86, 149.20, 147.51, 147.26, 140.94, 138.48, 135.16, 115.04, 111.10, 62.82, 34.75, 33.80, 32.67, 30.18, 21.97; HRMS (ESI): calcd for $C_{17}H_{25}FN_4$ $[M + H]^+$, 285.2074; found, 285.2077.

2-((6-Chloropyridin-2-yl)methyl)-6-(2,5-dimethyl-1H-pyrrol-1-yl)-4-methylpyridine (58). A solution of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-4,6-dimethylpyridine (400 mg, 2.0 mmol) in THF (20 mL) was treated with BuLi (1.0 M in hexanes, 2.1 mmol) in an ice bath. After 30 min of stirring, a solution of 2,6-dichloropyridine (148 mg, 1.0 mmol) in THF (10 mL) was added dropwise, and the mixture was heated to reflux for 1 h. After being cooled to room temperature the mixture was quenched with brine (50 mL) and CH_2Cl_2 (50 mL), the organic layer was separated, dried with $MgSO_4$, and concentrated in a vacuum. The residue was subjected to flash chromatography to give the title compound as a brown oil (48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.14 (s, 1H), 6.91 (s, 1H), 5.89 (s, 2H), 4.31 (s, 2H), 2.41 (s, 3H), 2.10 (s, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.22, 158.15, 151.62, 150.69, 150.08, 139.10, 128.48, 123.16, 122.39, 122.09, 120.54, 106.79, 46.31, 21.07, 13.26; MS ESI $[M + H]^+$ = 312.1.

***N*^{1}-(6-((6-(2,5-Dimethyl-1H-pyrrol-1-yl)-4-methylpyridin-2-yl)methyl)pyridin-2-yl)-*N*^{1},*N*^{2}-dimethylethane-1,2-diamine (59).** The title compound was prepared using General Method B from XII and *N*^{1},*N*^{2}-dimethylethane-1,2-diamine. 55%, brown gel; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, *J* = 8.5, 7.2 Hz, 1H), 7.14 (s, 1H), 6.87 (s, 1H), 6.52 (d, *J* = 7.2 Hz, 1H), 6.38 (d, *J* = 8.5 Hz, 1H), 5.89 (s, 2H), 4.16 (s, 2H), 3.72 (t, *J* = 6.3 Hz, 2H), 3.06 (s, 3H), 2.82 (t, *J* = 6.3 Hz, 2H), 2.44 (s, 3H), 2.38 (s, 3H), 2.12 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.99, 158.51, 157.33, 151.28,

149.31, 137.72, 128.49, 123.08, 120.04, 111.16, 106.60, 103.11, 49.94, 49.66, 47.05, 36.70, 36.54, 21.08, 13.23; MS ESI $[M + H]^+$ = 364.1.

***N*^{1}-(6-((6-Amino-4-methylpyridin-2-yl)methyl)pyridin-2-yl)-*N*^{1},*N*^{2}-dimethylethane-1,2-diamine (35).** The title compound was prepared using General Method C from **59**. 63%, pale yellow gel; ^{1}H NMR (500 MHz, MeOD) δ 7.68 (t, 1H), 6.82 (d, 1H), 6.76 (d, *J* = 7.3 Hz, 1H), 6.71 (s, 1H), 6.69 (d, *J* = 1.4 Hz, 1H), 4.20 (s, 2H), 4.00 (t, *J* = 5.9 Hz, 2H), 3.31 (t, *J* = 5.8 Hz, 2H), 3.15 (s, 3H), 2.74 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 159.14, 155.82, 115.55, 113.57, 111.19, 34.24, 21.97. HRMS (ESI): calcd for $C_{16}H_{24}N_5$ $[M + H]^+$, 286.2026; found, 286.2029

Methyl 3-((6-(2,5-dimethyl-1H-pyrrol-1-yl)-4-methylpyridin-2-yl)methyl)benzoate (61). Benzyl bromide (458 mg, 2.0 mmol) was added dropwise to a suspension of zinc dust (500 mg, 8.0 mmol) in dry THF. After being stirred for 15 min, the mixture was added to a solution of 2-bromo-6-(2,5-dimethyl-1H-pyrrol-1-yl)-4-methylpyridine (795 mg, 3.0 mmol) and $Pd(PPh_3)_4$ (50 mg, 0.4 mmol) in THF (20 mL). After being stirred overnight the mixture was filtered using a short alumina column, and then concentrated under vacuum. Column chromatography gave the title product as a colorless oil (68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.93 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.53 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 6.96 (s, 1H), 6.90 (s, 1H), 5.90 (s, 2H), 4.20 (s, 2H), 3.93 (s, 3H), 2.38 (s, 3H), 2.11 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.10, 159.94, 151.63, 150.00, 139.80, 133.84, 130.36, 130.18, 128.61, 128.51, 127.74, 122.60, 120.33, 106.79, 52.14, 43.98, 21.08, 13.24; ESI MS m/z $(M+H)^+$ = 335.2.

3-((6-(2,5-Dimethyl-1H-pyrrol-1-yl)-4-methylpyridin-2-yl)methyl)benzaldehyde (62). A solution of DIBALH in hexane (1.0 M, 1.4 mL, 1.4 mmol) was added slowly to a solution of **61** (400 mg, 1.2 mmol) in toluene (10 mL) at -78 °C. The solution was stirred at the same temperature for 1 h and then diluted with ethyl ether (20 mL). After careful addition of 1 N HCl (5 mL) at room temperature, the mixture was stirred for 10 min. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. Column chromatography with a silica gel cartridge gave title product **62** as a colorless oil (38%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.82 (d, *J* = 1.8 Hz, 1H), 7.77 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.62 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.23 (td, *J* = 7.7, 1.7 Hz, 1H), 7.00 (s, 1H), 6.91 (s, 1H), 5.90 (s, 2H), 4.24 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.46, 159.59, 151.72, 150.22, 140.58, 136.64, 133.45, 130.11, 128.50, 128.18, 128.04, 122.69, 120.52, 106.85, 43.78, 21.10, 13.23; ESI MS m/z $(M+H)^+$ = 305.1.

***N*^{1}-(3-((6-(2,5-Dimethyl-1H-pyrrol-1-yl)-4-methylpyridin-2-yl)methyl)benzyl)-*N*^{1},*N*^{2}-dimethylethane-1,2-diamine (63).** The title compound was prepared using General Method D from **62**. 55%; brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 2H), 7.23 – 7.14 (m, 2H), 6.96 (d, *J* = 6.3 Hz, 1H), 6.87 (s, 1H), 5.90 (s, 2H), 4.14 (s, 2H), 3.60 – 3.47 (m, 2H), 3.45 – 3.27 (m, 3H), 2.84 (s, 3H), 2.61 – 2.46 (m, 2H), 2.37 (s, 3H), 2.25 (s, 4H), 2.12 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.73, 155.72, 151.48, 149.74, 139.43, 139.31, 129.64, 128.48, 127.83, 126.95, 122.59, 120.10, 106.69, 62.58, 54.94, 46.95, 44.23, 42.54, 34.56, 21.06, 13.25; ESI MS m/z $(M+H)^+$ = 377.1.

***N*^{1}-(3-((6-Amino-4-methylpyridin-2-yl)methyl)benzyl)-*N*^{1},*N*^{2}-dimethylethane-1,2-diamine (36).** The title compound was prepared using General Method C from **63**. 75%; pale yellow gel; ^{1}H NMR (500 MHz, MeOD) δ 7.74 (s, 1H), 7.57 (s, 1H), 7.52 (s, 1H), 7.47 (s, 1H), 6.71 (s, 1H), 6.69 (s, 1H), 4.63 (d, *J* = 12.9 Hz, 1H), 4.40 (d, *J* = 12.7 Hz, 1H), 4.16 (s, 2H), 3.80 – 3.66 (m, 3H), 3.62 – 3.55 (m, 1H), 2.89 (s, 3H), 2.81 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 159.30, 156.15, 148.59, 138.79, 133.28, 132.09, 131.71, 131.14, 131.11, 115.70, 111.31, 61.48, 52.41, 44.42, 40.21, 39.17, 33.91, 22.04; HRMS (ESI): calcd for $C_{18}H_{27}N_4$ $[M + H]^+$, 299.2230; found, 299.2234.

References

Holden, J.K., Kang, S., Hollingsworth, S.A., Li, H., Lim, N., Chen, S., Huang, H., Xue, F., Tang, W., Silverman, R.B.*, et al.* (2015). Structure-based design of bacterial nitric oxide synthase inhibitors. J. Med. Chem. *58*, 994-1004.

Mukherjee, P., Cinelli, M.A., Kang, S., and Silverman, R.B. (2014). Development of nitric oxide synthase inhibitors for neurodegeneration and neuropathic pain. Chem. Soc. Rev. *43*, 6814-6838.

Yamamoto, K., Shimamura, K., Sekiguchi, F., and Sunano, S. (2001). Effects of NG-nitro-L-arginine on the blood pressure of spontaneously hypertensive rats with different degrees of hypertension. Clin. Exp. Hypertens. *23*, 533-544.