Structure−Activity Relationships of Potent, Selective Inhibitors of Neuronal Nitric Oxide Synthase Based on the 6-Phenyl-2-aminopyridine Structure

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The synthesis and structure−activity relationships of a series of 6-phenyl-2-aminopyridines that potently and selectively inhibit the neuronal isoform of nitric oxide synthase (nNOS) are described. Compound **14bi** from this series exhibits potent in vivo activity in harmaline-induced cGMP formation in rat cerebellum, a functional model of nNOS inhibition, and in the PCP-induced hypermotility model in the rat. These results suggest that **14bi** may be a useful reagent for evaluating potential therapeutic applications of nNOS inhibitors in the central nervous system.

Introduction

Nitric oxide synthase (NOS), the enzyme that produces the neurotransmitter and cytotoxic agent nitric oxide (NO), has long been recognized as a potentially important target for new therapeutic agents.[1,2] NOS consists of three isoforms, including the inducible (iNOS) enzyme which produces large quantities of NO during bacterial infection or tumor cell cytolysis and the endothelial isoform (eNOS), a constitutive, calcium-dependent enzyme which produces vasorelaxant NO to balance the vasoconstrictor adrenaline. The third isoform, neuronal NOS (nNOS), is also constitutive and calcium-dependent, and is thought to play a role in neurotransmission in the brain and spinal cord, and in skeletal muscle by virtue of its localization to these tissues. There is evidence from studies in transgenic mice[3] and with selective nNOS inhibitors[4] for a role of nNOS in producing cytotoxic levels of NO following cerebral ischemia and reperfusion, such as might occur during a stroke.

In addition, several reports have presented evidence for the role of nNOS in spinal transmission of pain sensation. For example, upregulation of nNOS in the spinal cord has been demonstrated following formalin injection in the rat hindpaw.[5] In addition, formalin injection also upregulates spinal levels of cGMP-dependent protein kinase I alpha, which propagates the pain signal initiated by spinally produced NO.[6] The selective nNOS inhibitor 7-nitroindazole, **1** (Figure 1), blocks this upregulation. Compound **1** has been used extensively in studies addressing the role of nNOS in pain.[7] Specifically, **1** was shown to inhibit carrageenin-induced mechanical and thermal hyperalgesia in the rat paw without affecting pain perception in the nontreated paw.[8] Another study with compound **1** indicated nNOS plays a role throughout the hyperalgesic response, in contrast to iNOS, which was suggested to play a role in the later stages only.[9] Two limitations of **1**, however, complicate the interpretation of these studies: (1) **1** is actually a nonselective inhibitor of both nNOS and eNOS (see below), and (2) **1** is an inhibitor of monoamine oxidase B (MAO-B).[10] The latter property was shown to contribute to the neuroprotective activity of **1** in a model of Parkinson's disease,[11] which had originally been ascribed to nNOS inhibition.[12]

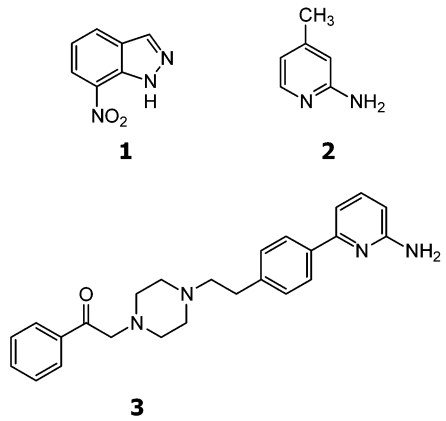

Figure 1. NOS inhibitor literature standards.

Nevertheless, there seems to be sufficient evidence to suggest that centrally acting nNOS inhibitors might prove therapeutically useful in the treatment of pain, stroke, and/or Parkinson's disease, provided they are adequately selective to avoid interfering with the important functions of iNOS and eNOS. Finding the required reagent for proof-of-concept studies, however, has been challenging. There are several classes of compounds currently under investigation for this potential,[13] among them the 2-aminopyridine class, exemplified by 2-amino-4-methylpyridine, **2** (Figure 1). Compound **2** is reported to be a potent, nonselective inhibitor of all three NOS isoforms, with potent inhibition of NO production in vivo.[14] We recently reported a new series of NOS inhibitors with modest selectivity for nNOS from the 6-phenyl-2-aminopyridine structural class, exemplified by compound **3** (Figure 1).[15] Compound **3** exhibits good selectivity for nNOS over other

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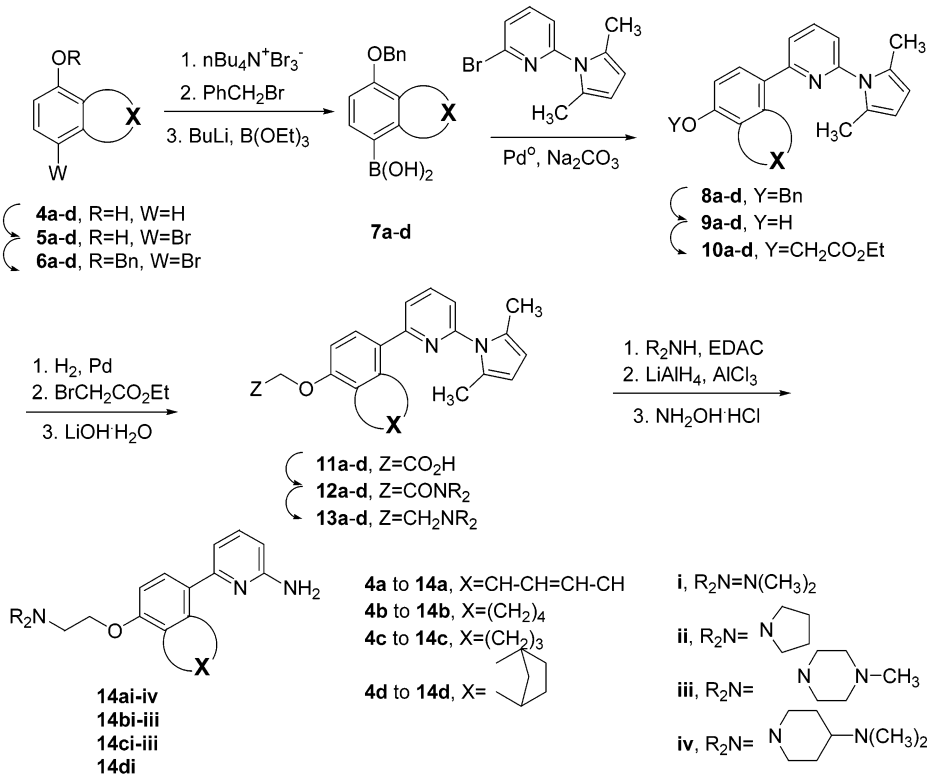
Scheme 1



enzyme and receptor targets, as well as promising pharmacokinetic properties suggesting its utility in examining the role of nNOS in vivo. In searching for analogues with improved nNOS selectivity, we examined: (1) substitution on the 6-phenyl ring, and (2) adding an oxygen atom to the linking group to the terminal amine function. We report herein the synthesis and SAR of a series of 6-phenyl-2-aminopyridines that led to the selection of compound **14bi**, a potent, selective nNOS inhibitor that may be useful for elucidating the therapeutic potential of nNOS inhibition.

Chemistry

The compounds in series **14**, **18**, **23**, and **25** were prepared as shown in Schemes 1 through 4. In Scheme 1, the key carbon−carbon bond is formed by a palladium-mediated Suzuki coupling reaction between a suitably substituted boronic acid, **7a**−**d**, and the 2,5-dimethylpyrrolyl protected derivative of 2-amino-6-bromopyridine. Attachment of the dialkylamino group is achieved by water soluble carbodiimide-mediated coupling to a suitable carboxylic acid precursor followed by reduction. Deblocking using hydroxylamine hydrochloride affords the final products **14a**−**d**. Scheme 2 illustrates an abbreviated synthesis in which the dimethylaminoethoxy side chain is installed near the beginning of the route, followed by boronic acid formation, Suzuki coupling, and deprotection. This route was used to produce larger quantities of compound **14bi** for in vivo study, as well as analogue **18ei**. Appending side groups more highly substituted around the dialkylamino group proved challenging and was dealt with as shown in Schemes 3 and 4. In Scheme 3, an aromatic fluoro precursor **21** was reacted with a dialkylamine-containing alcohol as the sodium alkoxide in a nucleophilic aromatic substitution reaction, followed by deblocking to afford the final products **23i**,**ii**. In Scheme 4, the more conventional approach using displacement of a mesylate leaving group by the sodium salt of a suitable phenol precursor, followed by deblocking, affords the desired products **25i**,**ii**.

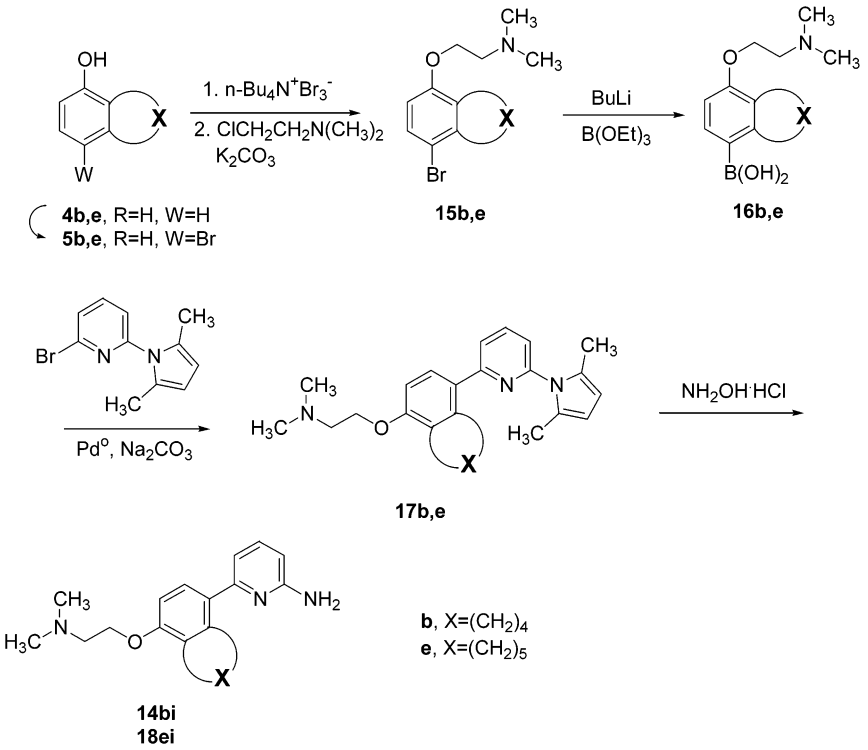
Biology

The NOS inhibitory activity of the compounds reported herein was measured in vitro using human NOS isoforms derived from the cloned genes expressed in baculovirus in Sf9 cells. The assay was based on one reported earlier.[16] The in vitro activity of **14bi** was confirmed by measuring the functional inhibition of cGMP formation, which is dependent on NO stimulation of guanylate cyclase, induced by the proconvulsant alkaloid harmaline in the rat.[17] The activity of a standard NOS inhibitor, L-nitroarginine, in this test reflects its in vitro activity against nNOS. Inhibition of PCP-induced hypermotility[18] was then used to measure the in vivo behavioral efficacy of **14bi**.

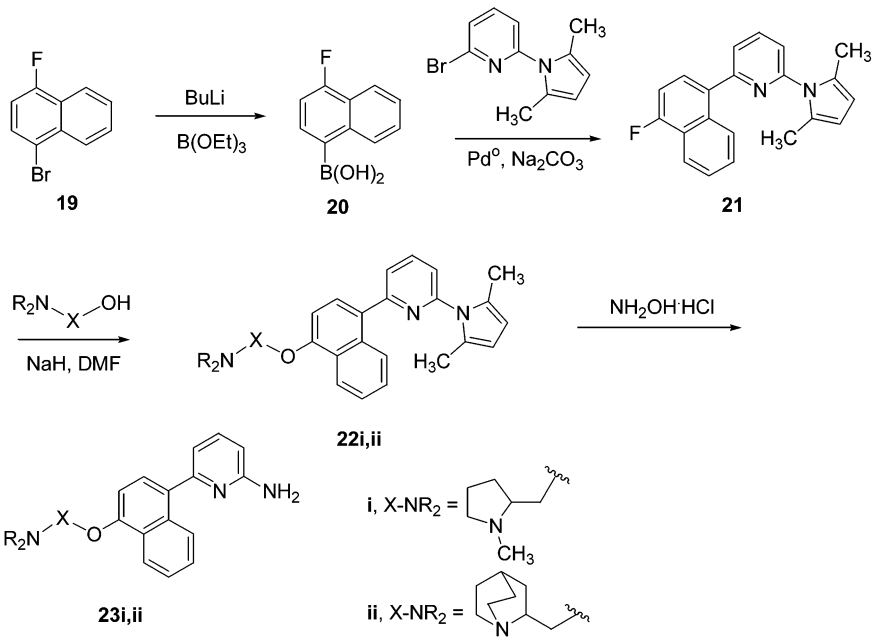
Results and Discussion

Table 1 displays the in vitro activity of the compounds in the 2-amino-6-phenylpyridine series, determined as IC_{50} values against the three NOS isoforms. While all new compounds reported here show improved selectivity over literature standards **1** and **2**, as well as our previously reported compound **3**, some important trends within the new series are evident. For example, the inhibitory potency and selectivity for human nNOS inhibitory activity increases in going from the naphthyl series (**14a**) to the tetralin (**14b**) and indane (**14c**) series. This may indicate that nNOS prefers a more electron

Scheme 2



Scheme 3



rich ring at the 6-phenyl position of the pyridine group. There are more subtle differences among the various terminal amine side chains, but the simple dimethylamino group generally affords good nNOS inhibitory activity. On the basis of compound **14bi**'s combination of inhibitory human nNOS potency and selectivity over human eNOS, it was selected for further profiling.

The NOS inhibitory activity of **14bi** was confirmed in vivo using the harmaline-induced formation of cGMP in rat cerebellum. Harmaline is a neurotoxin known to stimulate cGMP formation via opening of NMDA channels, followed by calcium influx, activation of nNOS and subsequent NO-activation of guanylate cyclase. Thus measuring cGMP levels following a harmaline challenge, in the presence and absence of an nNOS inhibitor, is a measure of in vivo functional efficacy. As shown in Figure 2, **14bi** gave an ED_{50} value of 7 mg/kg when administered subcutaneously in the rat harmaline test. As a control compound, **1** gave an ED_{50} value of 30 mg/kg sc. This increase in in vivo potency of **14bi** relative to **1** may result from both increased in vitro potency and improved aqueous solubility, although distribution and elimination of these compounds may also play a role.

Inhibition of PCP-induced hypermotility[18] was then used as another assessment of the in vivo activity of **14bi**. As shown in Figure 3, **14bi** gave an ED_{50} value of

Scheme 4

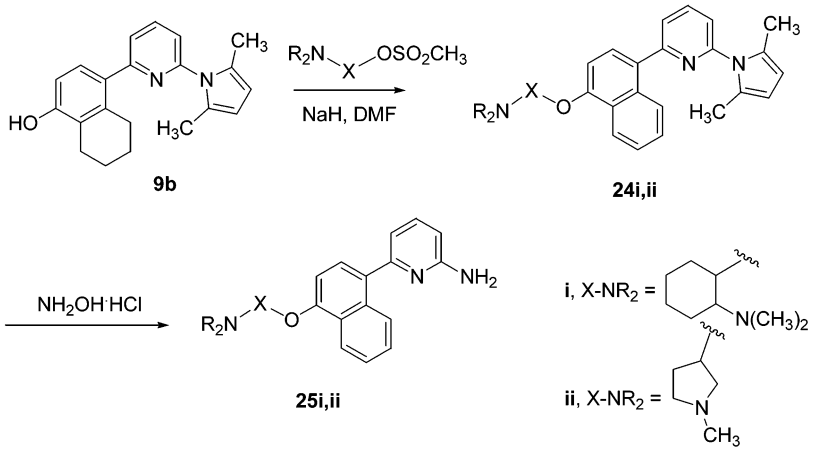
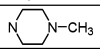
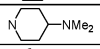
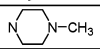
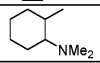
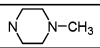


Table 1. In Vitro NOS Inhibitory Data for Compounds **14**, **18**, **23**, and **25**

Cpd	R_2N/R_2N-X	n	nNOS IC_{50}[a]	N	eNOS IC_{50}[b]	N	iNOS IC_{50}[c]	N	r-nNOS IC_{50}[d]	N
14ai	Me_2N	2	220 ± 113	6	5785 ± 3330	7	4600 ± 511	6	167 ± 29	3
14aii		2	250 ± 103	6	3713 ± 2066	6	1767 ± 51.6	6	175	2
14aiii		2	390 ± 166	3	12,000	2	9380	2	306 ± 121	3
14aiv		1	203 ± 20.8	3	7025 ± 2414	4	5750	2	195 ± 31.1	4
23i		1	112 ± 57.0	3	2930 ± 2250	3	2850	2	80.5	2
23ii		1	96.3 ± 21.8	3	3767 ± 3406	3	5800 ± 2107	3	88 ± 19.9	3
14bi	Me_2N	2	70.9 ± 35.9	9	3533 ± 2472	9	517 ± 352	6	34 ± 10.2	5
14bii		2	141 ± 68.9	3	2215 ± 979	4	357.7 ± 158	4	80	2
14biii		2	121 ± 46.1	4	10550 ± 7552	5	1280 ± 381	3	99.2 ± 59.1	5
25i		0	161 ± 127	3	12953±10894	3	2367 ± 208	3	140 ± 115	3
25ii		0	70.3 ± 14.1	3	13,000	2	2067 ± 451	3	48 ± 2.64	3
14ci	Me_2N	2	50.6 ± 14.6	10	1572 ± 1103	9	592 ± 144	6	21.75 ± 12.6	4
14cii		2	117 ± 35.1	3	785 ± 59.2	4	450 ± 134	4	59 ± 18	3
14ciii		2	123 ± 11.5	3	3033 ± 961	3	2200	1	82 ± 17.1	3
18ei	Me_2N	2	109 ± 12.1	3	5750	2	2100 ± 436	3	93 ± 14.7	3
14di	Me_2N	2	120 ± 36.5	3	19,000± 8185	3	1080	2	185	2
1 7-NI			2500		2500					
2			40		100		10		40	
3[e]			140 ± 20	3	887 ± 392	3			127 ± 8.8	3

[a] Inhibition of human neuronal nitric oxide synthase activity given as an IC_{50} value in nM units followed by the SEM value. N in the following column indicates the number of determinations. [b] Inhibition of human endothelial nitric oxide synthase activity given as an IC_{50} value in nM units followed by the SEM value. N in the following column indicates the number of determinations. [c] Inhibition of human inducible nitric oxide synthase activity given as an IC_{50} value in nM units followed by the SEM value. N in the following column indicates the number of determinations. [d] Inhibition of rat neuronal nitric oxide synthase activity given as an IC_{50} value in nM units followed by the SEM value. N in the following column indicates the number of determinations. [e] Values for compound **2** are taken from ref 14, and values for compound **3** are taken from ref 15.

2.8 mg/kg administered subcutaneously. This result is in contrast to that reported for compound **3**, which does not appreciably inhibit the hypermotility response to PCP in the rat. The greater in vitro potency and selectivity of **14bi** may contribute to this difference. Although the PCP-induced hypermotility model is used to test antipsychotic agents such as dopamine D2 receptor antagonists, the activity of **14bi** in the model is not a guarantee of clinically effective antipsychotic activity. The significance of the result is rather that the potent in vivo activity of **14bi** makes it a useful reagent for investigating the role of nNOS in the central nervous system and the eventual unraveling of the therapeutic potential of nNOS inhibitors.

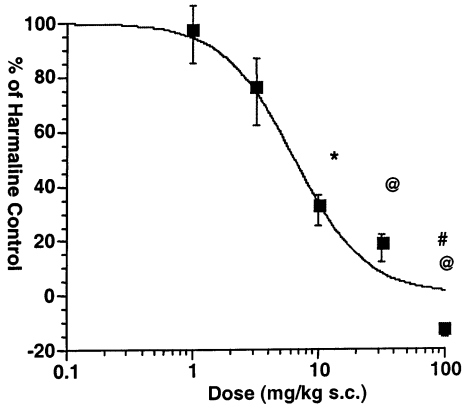


Figure 2. A representative dose−response curve depicting reversal by **14bi** of harmaline-induced cerebellar cGMP formation measured ex vivo by ELISA. **14bi** was given 2 h before harmaline, using 10 rats per dose group. The calculated ED_{50} from this experiment is 6.36 mg/kg sc, with an *r* value of 0.98. The mean ED_{50} from this and two other experiments was 7 ± 2 mg/kg. * $p < 0.0005$; @ $p < 0.00005$ difference from harmaline; # $p < 0.0005$ difference from vehicle.

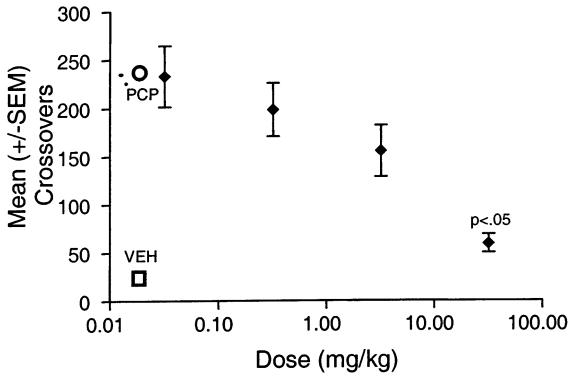


Figure 3. Dose−response curve depicting reversal by **14bi** of phencyclidine-induced hyperactivity. Data are combined from three experiments, indicating an ID_{50} value of 2.8 mg/kg sc and 95% confidence limits of 1.96−4.0.

Experimental Section

Melting points were obtained on a Hoover melting point apparatus and are uncorrected. NMR spectra were obtained on a Varian Unity 400 MHz NMR spectrometer. Low resolution mass spectra were obtained on a Fisons VG Platform APCI mass spectrometer or a Micromass Platform LCZ LC mass spectrometer under EI or CI conditions. GC mass spectra were obtained on a Hewlett-Packard Model 5973 Mass Spectrometer coupled to a Hewlett-Packard Model 6890 GC System. High-resolution mass spectra were obtained on a VG Analytical ZAB 2SE high field mass spectrometer by M-Scan, Inc. in the FAB mode. Rotation data were obtained on a Perkin-Elmer 241 MC Polarimeter. Tlc analyses were carried out on EM Kieselgel 60 F_{254} 5 × 20 cm plates. Elemental analyses were carried out by Schwarzkopf Laboratories, Inc. and are within ±0.4% of theory unless otherwise noted.

6-[4-(2-Dimethylaminoethoxy)naphthalen-1-yl]pyridin-2-ylamine, 14ai: **Method A**. **4-Bromo-1-benzyloxynaphthalene**, **6a**. The known[19] 4-bromo-1-naphthol, prepared from 2.88 g (20 mmol) of 1-naphthol with 1 equiv of tributylammonium tribromide, was dissolved in 100 mL of acetonitrile, treated with 3.57 mL (30 mmol) of benzyl bromide and 5.53 g (40 mmol) potassium carbonate, and refluxed 14 h. TLC showed a major spot at $R_f = 0.2$ in 5% methylene chloride/hexane. The reaction was cooled and poured into dilute aqueous hydrochloric acid/ethyl acetate, and the organic layer was separated, washed with water and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using methylene chloride/hexane as eluant to afford 5.8 g (93%) of an oil. ^{1}H NMR (δ, $CDCl_3$): 5.22 (s, 2H), 6.74 (d, $J = 8$, 1H), 7.4−7.7 (m, 8H), 8.21 (d, $J = 8$, 1H), 8.39 (d, $J = 8$, 1H). ^{13}C NMR (δ, $CDCl_3$): 70.3, 105.9, 113.6, 122.7, 126.1, 126.9, 127.0, 127.4, 127.9, 128.1, 128.7, 129.5, 132.6, 136.7, 154.3. MS (%): 314 (parent + 1, 100).

4-Bromo-5,6,7,8-tetrahydro-1-benzyloxynaphthalene, **6b.** Prepared in 63% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.77 (m, 4H), 2.75 (m, 4H), 5.045 (s, 2H), 6.62 (d, $J =$ 9, 1H), 7.3−7.5 (m, 6H). ^{13}C NMR (δ, $CDCl_3$): 22.2, 22.9, 24.0, 30.7, 69.9, 109.8, 116.7, 127.1, 127.9, 128.6, 129.1, 129.3, 137.2, 137.5, 155.6.

4-Bromo-1-benzyloxyindane, **6c.** Prepared in 96% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 2.14 (m, 2H), 3.00 (t, $J = 7.5$, 2H), 3.07 (t, $J = 7.5$, 2H), 5.09 (s, 2H), 6.63 (d, $J = 8.5$, 1H), 7.3−7.6 (m, 6H). ^{13}C NMR (δ, $CDCl_3$): 23.8, 30.9, 34.9, 70.0, 110.8, 111.5, 127.1, 157.8, 128.5, 130.0, 134.0, 137.1, 146.0, 154.4.

Bicyclo[2.2.1]cyclohexylphenol, 4d. A solution of 5.38 g (48.0 mmol) of 2-hydroxypyrone (ref: *Synth. Commun.* **1975**, *5*, 461) and 18.1 g (190 mmol) norbornylene was heated at 125 °C for 28 h in a sealed tube and then cooled and chromatographed on silica gel using hexane/ethyl acetate as eluant to give a mixture of olefin isomers in 49% yield. This mixture was treated with 500 mg of palladium oxide and 1.0 g of magnesium sulfate in 80 mL of dry toluene at reflux for 18 h. The reaction was cooled and filtered through Celite, and the filtrate was concentrated and chromatographed on silica gel using hexane/ethyl acetate as eluant to afford 2.65 g (71%) of a yellow oil. ^{1}H NMR (δ, $CDCl_3$): 1.25 (m, 2H), 1.52 (m, 1H), 1.78 (m, 1H), 1.93 (m, 2H), 3.40 (m, 1H), 3.62 (m, 1H), 5.82 (bs, 1H), 6.65 (d, $J = 8$, 1H), 6.86 (d, $J = 8$, 1H), 7.00 (t, $J =$ 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 26.45,,27.0, 39.3, 44.0, 49.1, 113.2, 113.6, 126.8, 132.7, 148.5, 150.8. GC MS (%): 160 (parent, 100).

4-Bromo-5,6,7,8-tetrahydro[2.2.1]bicyclo-1-benzyloxynaphthalene, **6d.** Prepared from **4d** in 94% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.24 (m, 2H), 1.49 (m, 1H), 1.76 (m, 1H), 1.94 (m, 2H), 3.57 (m, 1H), 3.77 (m, 1H), 6.61 (d, $J = 8.5$, 1H), 7.14 (d, $J = 8.5$, 1H), 7.3−7.5 (m, 5H). ^{13}C NMR (δ, $CDCl_3$): 25.96, 26.23, 41.04, 44.72, 48.51, 70.57, 107.57, 112.64, 127.30, 127.94, 128.56, 128.59, 128.85, 137.24, 149.46, 151.50. MS (%): 327/329 (100, parent + 1, Br^{79}/Br^{81}).

1-Benzyloxynaphthalene-4-boronic Acid, **7a**. To a 125 mL round-bottomed flask equipped with N_2 inlet were added 5.95 g (19 mmol) of 4-bromo-1-benzyloxynaphthalene and 20 mL of dry tetrahydrofuran. The solution was cooled to −70 °C, 9.12 mL (22.89 mmol) of a 2.5 M solution of *n*-butyllithium in hexane was added over 5 min, and the reaction was stirred at −70 °C for 10 min. The solution was then treated with 3.88 mL (22.8 mmol) of triethyl borate, stirred 5 min at −70 °C, and then warmed to room temperature and stirred 40 h. The reaction was quenched with aqueous ammonium chloride solution, poured into 0.5 N hydrochloric acid, and extracted into ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated to a white solid after trituration with hexane, mp 149−152 °C, 2.89 g (55%). ^{1}H NMR (δ, $CDCl_3$): 5.18 (s, 2H), 6.82 (m, 1H), 7.2−7.8 (m, 8H), 8.28 (m, 2H). ^{13}C NMR (δ, $CDCl_3$): 69.9, 104.5, 104.7, 122.2, 122.4, 124.8, 125.0, 126.5, 126.6, 127.6, 127.7, 127.9, 128.0, 128.5, 130.9, 132.9, 136.9.

5,6,7,8-Tetrahydro-1-benzyloxynaphthalene-4-boronic Acid, **7b.** Prepared as a solid, mp 199−205 °C, in 72% yield. ^{1}H NMR (δ, $CDCl_3$): 1.72 (m, 4H), 2.70 (m, 4H), 5.005 (s, 2H), 6.66 (m, 1H), 7.01 (d, $J = 8$, 1H), 7.2−7.4 (m, 5H). ^{13}C NMR (δ, $CDCl_3$): 22.6, 22.9, 23.4, 30.0, 107.8, 125.9, 127.0, 127.6, 128.4, 131.1, 137.5, 140.8, 156.9.

1-Benzyloxyindane-4-boronic Acid, **7c**. mp 222−223.5 °C, in 58.5% yield. ^{1}H NMR (δ, $CDCl_3$): 1.97 (m, 2H), 2.83 (t, $J = 8.5$, 2H), 3.03 (t, $J = 7.5$, 2H), 5.04 (s, 2H), 6.65 (d, $J = 8$, 1H), 7.2−7.5 (m, 6H). ^{13}C NMR (δ, $CDCl_3$): 24.7, 29.1, 34.25, 69.4, 108.7, 127.1, 127.7, 128.4, 131.7, 131.9, 133.9, 137.3, 156.9.

Bicyclo[2.2.1]-1-benzyloxynaphthalene-4-boronic Acid, **7d**. An oil in 100% yield. ^{1}H NMR (δ, $CDCl_3$): 1.2−1.9 (m, 6H), 3.7−3.8 (m, 2H), 6.83 (d, J = 8.3, 1H), 7.2−7.5 (m, 5H), 7.92 (d, J = 8.3, 1H).

2-(2,5-Dimethylpyrrolyl)-6-(4-benzyloxy-1-naphthyl)-pyridine, 8a. To a 100 mL round-bottomed flask equipped with condenser and N_2 inlet were added 953 mg (3.795 mmol) of *N*-(2,5-dimethylpyrrolyl)-6-bromopyridyl-2-amine, 1055 mg (3.795 mmol) of 1-benzyloxynaphthalene-4-boronic acid, 1.61 g (15.2 mmol) of sodium carbonate, 44 mg (0.04 mmol) of tetrakistriphenylphosphine palladium, 18 mL of ethanol, and 2 mL of water, and the reaction was heated at 80 °C for 13 h. TLC showed a major spot at R_f = 0.2 in 15% ethyl acetate in hexane, and LCMS showed a major peak at P + 1 = 319. The reaction was cooled, poured into water, and extracted into ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate as eluant to afford 1.53 g (∼100%) of an oil. ^{1}H NMR (δ, $CDCl_3$): 2.25 (s, 6H), 5.29 (s, 2H), 5.92 (s, 2H), 6.95 (d, J = 8, 1H), 7.21 (d, J = 7.5, 1H), 7.3−7.6 (m, 9H), 7.89 (t, J = 8, 1H), 8.14 (m, 1H), 8.45 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.5, 70.1, 104.8, 106.8, 119.7, 122.5, 123.4, 125.2, 125.3, 125.9, 126.4, 126.9, 127.3, 127.9, 128.2, 128.6, 130.5, 132.0, 136.9, 138.0, 151.8, 155.0, 159.1. MS (%): 405 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-benzyloxy-5,6,7,8-tetrahydronaphthalen-1-yl]pyridine, **8b.** Prepared in 100% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.81 (m, 2H), 1.91 (m, 2H), 2.29 (s, 6H), 2.93 (m, 4H), 5.19 (s, 2h), 6.02 (s, 2H), 6.91 (d, J = 8, 1H), 7.21 (d, J = 8, 1H), 7.32 (d, J = 8, 1H), 7.4−7.6 (m, 6H), 7.89 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.5, 22.5, 23.0, 24.0, 28.9, 69.8, 106.8, 108.2, 119.6, 123.1, 126.8, 127.2, 127.8, 12.9, 128.6, 128.7, 132.8, 136.8, 137.6, 138.0, 151.4, 156.8, 160.4. MS (%): 409 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-benzyloxyindan-1-yl]-pyridine, **8c.** Prepared in 100% yield as an amorphous solid. ^{1}H NMR (δ, $CDCl_3$): 2.09 (m, 2H), 2.18 (s, 6H), 2.97 (t, J = 7.5, 2H), 3.20 (t, J = 7.5, 2H), 5.15 (s, 2H), 5.90 (s, 2H), 6.83 (d, J = 8, 1H), 7.08 (d, J = 7.5, 1H), 7.2−7.6 (m, 7H), 7.82 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.4, 25.3, 29.5, 34.3, 69.7, 106.5, 109.9, 119.1, 120.9, 127.1, 127.8, 128.5, 128.6, 133.2, 137.3, 138.0, 144.7, 151.4, 155.7, 158.6. MS (%): 395 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-benzyloxybicyclo[2.2.1]-naphthalen-1-yl]pyridine, **8d.** Prepared in 94% yield as an amorphous solid. ^{1}H NMR (δ, $CDCl_3$): 1.2−2.0 (m, 6H), 2.22 (s, 6H), 3.73 (m, 1H), 3.85 (m, 1H), 5.15 (s, 2H), 5.92 (s, 2H), 6.81 (d, J = 8.5, 1H), 7.10 (d, J = 7.5, 1H), 7.2−7.6 (m, 7H), 7.845 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.51, 26.40, 26.67, 39.72, 43.12, 48.95, 70.15, 106.70, 110.65, 119.01, 121.01, 126.34, 126.43, 127.82, 128.54, 128.71, 137.42, 138.05, 148.38, 151.59, 152.73, 158.05. MS (%): 421 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-(4-hydroxy-1-naphthyl-) pyridine, 9a. To a 125 mL round-bottomed flask equipped with condenser and N_2 inlet were added 1.53 g (3.795 mmol) of 2-(2,5-dimethylpyrrolyl)-6-(4-benzyloxy-1-naphthyl)pyridine, 1.20 g (18.975 mmol) of ammonium formate, 100 mg of 10% palladium-on-carbon, and 30 mL of ethanol. The reaction was refluxed 4 h, with additional catalyst and formate added at 2 and 3 h, and then cooled and filtered through Celite with ethanol and methylene chloride. The filtrate was evaporated and the residue taken up in ethyl acetate/aqueous sodium bicarbonate solution. The organic layer was washed with brine, dried over sodium sulfate, and evaporated to a light brown solid, 1.21 g (∼100%). ^{1}H NMR (δ, $CDCl_3$): 2.105 (s, 6H), 5.775 (s, 2H), 6.66 (d, J = 8, 1H), 7.04 (d, J = 8, 1H), 7.29 (m, 2H), 7.38 (d, J = 8, 1H), 7.72 (t, J = 8, 1H), 7.95 (m, 1H), 8.18 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.8, 106.7, 106.8, 107.6, 119.6, 122.55, 124.5, 124.7, 125.0, 126.5, 128.4, 128.5, 128.7, 132.0, 138.2, 151.5, 153.9, 159.3. MS (%): 315 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]pyridine, **9b.** Prepared in 100% yield as an low melting solid. ^{1}H NMR (δ, $CDCl_3$): 1.67 (m, 2H), 1.77 (m, 2H), 2.16 (s, 6H), 2.63 (m, 2H), 2.73 (m, 2H), 5.89 (s, 2H), 6.3 (bs, 1H, OH), 6.51 (d, J = 8, 1H), 7.02 (d, J = 8, 1H), 7.13 (d, J = 8, 1H), 7.35 (d, J = 8, 1H), 7.83 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.3, 22.3, 22.8 23.3, 28.6, 106.6, 112.1, 119.7, 123.3, 124.2, 127.8, 128.7, 131.9, 136.6, 138.1, 151.2, 154.4, 160.5. MS (%): 319 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-hydroxyindan-1-yl]pyridine, **9c.** Prepared in 100% yield as an low melting solid. ^{1}H NMR (δ, $CDCl_3$): 1.95 (m, 2H), 2.05 (s, 6H), 2.785 (t, J = 7.5, 2H), 3.02 (t, J = 7.5, 2H), 5.78 (s, 2H), 6.61 (d, J = 8, 1H), 6.96 (d, J = 7.5, 1H), 7.32 (d, J = 8, 1H), 7.39 (d, J = 8, 1H), 7.73 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 12.95, 25.30, 28.94, 33.85, 106.40, 113.31, 119.26, 121.43, 127.47, 128.43, 128.56, 130.71, 138.36, 144.68, 151.23, 153.85, 158.97. MS (%): 305 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-hydroxybicyclo[2.2.1]-naphthalen-1-yl]pyridine, **9d.** Prepared in 100% yield as an low melting solid. ^{1}H NMR (δ, $CDCl_3$): 1.2−2.0 (m, 6H), 2.215 (s, 6H), 3.59 (m, 1H), 3.81 (m, 1H), 5.93 (s, 2H), 6.59 (d, J = 8.5, 1H), 7.11 (d, J = 7.5, 1H), 7.38 (d, J = 8.5, 1H), 7.50 (d, J = 8, 1H), 7.85 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.4, 26.4, 26.6, 39.3, 43.0, 48.9, 106.8, 113.9, 119.2, 121.4, 127.6, 128.8, 133.5, 138.3, 148.6, 151.6, 150.0, 158.4, 163.8. MS (%): 329 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-(4-(2-carboethoxymethyloxy)-1-naphthyl)pyridine, 10a. To a 125 mL round-bottomed flask equipped with condenser and N_2 inlet were added 1.19 g (3.795 mmol) of 2-(2,5-dimethylpyrrolyl)-6-(4-hydroxy-1-naphthyl)-pyridine, 0.505 mL (4.554 mmol) of ethyl bromoacetate, 1.05 g (7.59 mmol) of potassium carbonate, and 25 mL of acetonitrile. The mixture was refluxed 12 h, cooled (TLC R_f = 0.6 in 1/1-ethyl acetate/hexane), poured into water, and extracted into ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate as eluant to afford 2.05 g (∼100%) of an oil. ^{1}H NMR (δ, $CDCl_3$): 1.31 (t, J = 7, 3H), 2.26 (s, 6H), 4.29 (q, J = 7, 2H), 4.82 (s, 2H), 5.94 (s, 2H), 6.78 (d, J = 8, 1H), 7.20 (d, J = 8, 1H), 7.5−7.6 (m, 5H), 7.87 (t, J = 8, 1H), 8.15 (m, 1H), 8.50 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.6, 14.2, 61.4, 65.7, 104.6, 107.0, 119.9, 122.6, 123.6, 125.3, 125.6, 125.8, 127.2, 128.0, 128.6, 131.4, 132.1, 138.3, 151.8, 154.3, 158.9, 168.6. MS (%): 401 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-carboethoxymethoxy-5,6,7,8-tetrahydronaphthalen-1-yl]pyridine, 10b. Prepared in 83.5% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.31 (t, J = 7, 3H), 1.71 (m, 2H), 1.83 (m, 2H), 2.19 (s, 6H), 4.26 (q, J = 7, 2H), 4.66 (s, 2H), 5.90 (s, 2H), 6.64 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.20 (d, J = 8, 1H), 7.35 (d, J = 8, 1H), 7.82 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.4, 14.2, 22.3, 22.9, 23.7, 28.7, 61.2, 65.5, 106.7, 107.8, 119.6, 123.0, 126.9, 127.7, 128.5, 133.4, 137.0, 138.1, 151.3, 156.0, 160.1, 169.0. MS (%): 405 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-carboethoxymethoxyindan-1-yl]pyridine, 10c. Prepared in 100% yield as an amorphous solid. ^{1}H NMR (δ, $CDCl_3$): 1.285 (t, J = 7, 3H), 2.07 (m, 2H), 2.165 (s, 6H), 2.97 (t, J = 7.5, 2H), 3.18 (t, J = 7.5, 2H), 4.25 (q, J = 7, 2H), 4.67 (s, 2H), 5.88 (s, 2H), 6.64 (d, J = 8.5, 1H), 7.07 (d, J = 7.5, 1H), 7.50 (d, J = 8, 1H), 7.58 (d, J = 8.5, 1H), 7.81 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.38, 14.18, 21.04, 25.36, 29.43, 34.21, 61.32, 65.44, 106.57, 109.48, 112.49, 119.23, 120.90, 128.53, 128.63, 129.68, 133.35, 138.01, 145.09, 151.43, 154.86, 158.37, 169.00. MS (%): 391 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-carboethoxymethoxybicyclo[2.2.1]naphthalen-1-yl]pyridine, 10d. Prepared in 80% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.29 (t, J = 7, 3H), 1.3−1.4 (m, 2H), 1.51 (m, 1H), 1.74 (m, 1H), 1.97 (m, 2H), 2.20 (s, 6H), 3.73 (m, 1H), 3.83 (m, 1H), 4.25 (q, J = 7, 2H), 4.67 (s, 2H), 5.89 (s, 2H), 6.63 (d, J = 8.7, 1H), 7.09 (d, J = 8, 1H), 7.5 (m, 2H), 7.835 (t, J = 8, 1H).

^{13}C NMR (δ, $CDCl_3$): 13.4, 14.1, 26.25, 26.5, 39.7, 43.0, 48.8, 61.2, 65.8, 106.6, 110.1, 119.0, 120.9, 122.0, 127.4, 128.6, 136.3, 137.9, 148.5, 149.1, 151.8, 157.8, 169.0.

2-(2,5-Dimethylpyrrolyl)-6-(4-(2-carboxymethyloxy)-1-naphthyl)pyridine, 11a. To a 125 mL round-bottomed flask equipped with condenser and N_2 inlet were added 1.52 g (3.795 mmol) of 2-(2,5-dimethylpyrrolyl)-6-(4-(2-carboethoxymethyloxy)-1-naphthyl)-pyridine, 15 mL of tetrahydrofuran, and 478 mg (11.385 mmol) of lithium hydroxide hydrate in 15 mL water, with additional methanol to maintain a solution. The reaction was stirred at room temperature for 12 h, (LCMS P + 1 = 373), poured into dilute aqueous hydrochloric acid, and extracted into ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated to a solid, 1.27 g (90%). ^{1}H NMR (δ, $CDCl_3$): 2.20 (s, 6H), 4.74 (s, 2H), 5.89 (s, 2H), 6.765 (d, J = 8, 1H), 7.20 (d, J = 8, 1H), 7.4−7.6 (m, 4H), 7.885 (t, J = 8, 1H), 8.04 (m, 1H), 8.44 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.3, 65.3, 104.5, 106.9, 120.3, 122.6, 124.0, 125.0, 125.6, 125.7, 127.2, 128.0, 128.7, 130.8, 132.0, 138.6, 151.7, 154.3, 158.9, 170.9. MS (%): 373 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-carboxymethoxy-5,6,7,8-tetrahydronaphthalen-1-yl]pyridine, 11b. Prepared in 100% yield as a solid, mp 199−206 °C. ^{1}H NMR (δ, $CDCl_3$): 1.62 (m, 2H), 1.72 (m, 2H), 2.08 (s, 6H), 2.66 (m, 2H), 2.75 (m, 2H), 4.56 (s, 2H), 5.81 (s, 2H), 6.58 (d, J = 8, 1H), 7.09 (m, 2H), 7.31 (d, J = 8, 1H), 7.80 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 12.95, 22.1, 22.6, 23.4, 28.4, 65.0, 106.5, 107.7, 119.9, 0.123.3, 126.7, 127.4, 128.5, 132.8 136.6, 138.3, 151.1, 155.9, 160.1, 171.2. MS (%): 377 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-carboxymethoxyindan-1-yl]pyridine, 11c. Prepared in 75% yield as an amorphous solid. ^{1}H NMR (δ, $CDCl_3$): 2.09 (m, 2H), 2.16 (s, 6H), 2.97 (t, J = 7.5, 2H), 3.17 (t, J = 7.5, 2H), 4.64 (s, 2H), 5.90 (s, 2H), 6.62 (d, J = 8.5, 1H), 7.12 (d, J = 8, 1H), 7.52 (d, J = 8, 1H), 7.62 (d, J = 8.5, 1H), 7.85 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 12.94, 25.05, 25.30, 29.10, 33.77, 64.46, 106.24, 109.13, 119.34, 121.07, 128.49, 129.96, 132.84, 138.05, 144.75, 147.40, 151.14, 154.39, 158.03, 172.84. MS (%): APCI positive 363 (parent + 1, 100). APCI negative 361 (100, parent − 1).

2-(2,5-Dimethylpyrrolyl)-6-[4-carboxymethoxybicyclo-[2.2.1]naphthalen-1-yl]pyridine, 11d. Prepared in 65% yield as an amorphous solid. ^{1}H NMR (δ, $CDCl_3$): 1.28 (m, 2H), 1.51 (m, 1H), 1.70 (m, 1H), 1.95 (m, 2H), 2.13 (s, 6H), 3.715 (m, 1H), 3.76 (m, 1H), 4.67 (s, 2H), 5.82 (s, 2H), 6.70 (d, J = 8.5, 1H), 7.15 (d, J = 8, 1H), 7.38 (d, J = 8.5, 1H), 7.55 (d, J = 8, 1H), 7.95 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 12.3, 25.9, 26.3, 39.6, 42.85, 65.0, 110.0, 119.7, 121.8, 126.5, 127.2, 128.15, 136.0, 138.8, 148.4, 151.6, 152.1, 158.1, 171.4. MS (%): 389 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-(4-(*N*,*N*-dimethylcarboxamido)methyloxy)-1-naphthyl)pyridine, 12ai. To a 100 mL round-bottomed flask equipped with condenser and N_2 inlet were added 150 mg (0.403 mmol) of 2-(2,5-dimethylpyrrolyl)-6-(4-(2-carboxymethyloxy)-1-naphthyl)-pyridine, 33 mg (0.403 mmol) of dimethylamine hydrochloride, 77 mg (0.403 mmol) of *N*-ethyl,*N*-3-dimethylaminopropylcarbodiimide, 0.185 mL (1.33 mmol) of triethylamine, 10 mg of *N*-hydroxybenzotriazole, and 7 mL of dry acetonitrile. The reaction was stirred at room temperature 80 h (LCMS showed P + 1 = 451 and TLC showed R_f = 0.3 in 10% methanol/methylene chloride) and evaporated and the residue chromatographed on silica gel using methanol/methylene chloride as eluant to afford 161 mg of the product (100% yield) as an oil. ^{1}H NMR (δ, $CDCl_3$): 2.225 (s, 6H), 2.97 (s, 3H), 3.10 (s, 3H), 4.90 (s, 2H), 5.89 (s, 2H), 6.93 (d, J = 8, 1H), 7.21 (d, J = 8, 1H), 7.4−7.6 (m, 4H), 7.90 (t, J = 8, 1H), 8.09 (m, 1H), 8.38 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.5, 35.8, 36.8, 67.9, 104.7, 106.8, 119.9, 122.2, 123.5, 125.4, 125.56, 125.63, 127.1, 128.1, 128.6, 131.2, 132.1, 138.2, 151.8, 154.1, 159.0, 167.7. MS (%): 400 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-(4-(pyrrolidinylcarboxamido)methyloxy)-1-naphthyl)pyridine, 12aii. Prepared in 93% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.80 (m, 2H), 1.90 (m, 2H), 2.22 (s, 6H), 3.54 (m, 4H), 4.84 (s, 2H), 5.88 (s, 2H), 6.93 (d, J = 8, 1H), 7.21 (d, J = 8, 1H), 7.4−7.6 (m, 4H), 7.90 (t, J = 8, 1H), 8.10 (m, 1H), 8.38 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.5, 23.7, 26.3, 46.2, 46.3, 68.5, 104.7, 106.8, 119.9, 122.2, 123.5, 125.4, 125.5, 125.6, 127.0, 128.2, 128.6, 131.2, 132.0, 138.2, 151.8, 154.2, 159.0, 166.4. MS (%): 426 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-(4-((4-methylpiperazinyl)-carboxamido)methyloxy)-1-naphthyl)pyridine, 12aiii. Prepared in 63.5% yield as a foam. ^{1}H NMR (δ, $CDCl_3$): 2.21 (s, 6H), 2.24 (s, 3H), 2.35 (m, 4H), 3.64 (m, 4H), 4.885 (s, 2H), 5.88 (s, 2H), 6.93 (d, J = 8, 1H), 7.21 (d, J = 7.5, 1H), 7.4−7.6 (m, 4H), 7.90 (t, J = 8, 1H), 8.11 (m, 1H), 8.33 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.54, 42.07, 45.37, 45.99, 54.56, 55.12, 68.01, 104.70, 106.87, 119.89, 122.05, 123.50, 125.40, 125.56, 125.62, 127.08, 128.11, 128.63, 131.31, 132.05, 138.24, 151.76, 154.04, 158.90, 166.16. MS (%): 455 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-(4-((4-dimethylaminopiperidine)carboxamido)methyloxy)-1-naphthyl)pyridine, 12aiv. Prepared in 45% yield as a foam. ^{1}H NMR (δ, $CDCl_3$): 1.37 (m, 2H), 1.82 (m, 1H), 2.20 (s, 6H), 2.21 (s, 6H), 2.32 (m, 1H), 2.7 (m, 1H), 3.06 (m, 1H), 4.1 (m, 1H), 4.6 (m, 1H), 4.89 (AB, 2H), 5.88 (s, 2H), 6.935 (d, J = 8, 1H), 7.20 (d, J = 8, 1H), 7.4−7.6 (m, 4H), 7.90 (t, J = 8, 1H), 8.10 (m, 1H), 8.35 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.39, 27.84, 29.02, 41.43, 44.47, 61.72, 68.03, 104.65, 106.78, 119.77, 122.00, 123.36, 125.31, 125.48, 126.95, 127.99, 128.54, 131.20, 131.99, 138.08, 151.70, 154.02, 158.85, 165.90. MS (%): 483 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-(*N*,*N*-dimethylcarboxamido)methoxy-5,6,7,8-tetrahydronaphthalen-1-yl]pyridine, 12bi. Prepared in 100% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.67 (m, 2H), 1.77 (m, 2H), 2.14 (s, 6H), 2.76 (m, 4H), 2.96 (s, 3H), 3.08 (s, 3H), 4.71 (s, 2H), 5.86 (s, 2H), 6.75 (d, J = 8, 1H), 7.11 (d, J = 8, 1H), 7.16 (d, J = 8, 1H), 7.34 (d, J = 8, 1H), 7.82 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.3, 22.2, 22.8, 23.6, 28.6, 35.7, 36.7, 67.7, 106.5, 107.7, 119.6, 122.9, 126.5, 127.8, 128.6, 133.2, 136.8, 138.0, 151.2, 155.9, 160.2, 168.1. MS (%): 404 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-(pyrrolinylcarboxamido)-methoxy-5,6,7,8-tetrahydronaphthalen-1-yl]pyridine, 12bii. Prepared in 64.75% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.66 (m, 2H), 1.77 (m, 2H), 1.82 (m, 2H), 1.92 (m, 2H), 2.13 (s, 6H), 2.75 (m, 4H), 3.51 (m, 4H), 4.64 (s, 2H), 5.85 (s, 2H), 6.73 (d, J = 8, 1H), 7.11 (d, J = 8, 1h), 7.15 (d, J = 7.5, 1H), 7.33 (d, J = 8, 1H), 7.81 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.21, 22.14, 22.68, 23.56, 26.22, 28.50, 46.01, 46.14, 68.23, 106.44, 107.68, 119.54, 122.85, 126.34, 127.68, 128.51, 133.11, 136.73, 137.87, 151.14, 155.88, 160.09, 166.70. MS (%): 430 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-((4-methylpiperazinyl)-carboxamido)methoxy-5,6,7,8-tetrahydronaphthalen-1-yl]pyridine, 12biii. Prepared in 90% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.68 (m, 2H), 1.76 (m, 2H), 2.14 (s, 6H), 2.275 (s, 3H), 2.37 (m, 4H), 2.74 (m, 4H), 3.63 (m, 4H), 4.69 (s, 2H), 5.85 (s, 2H), 6.75 (d, J = 8.5, 1H), 7.11 (d, J = 8, 1H), 7.17 (d, J = 8, 1H), 7.33 (d, J = 8, 1H), 7.81 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.27, 22.14, 22.68, 23.60, 28.51, 41.91, 45.23, 45.96, 54.50, 55.07, 67.67, 106.49, 107.60, 119.55, 122.86, 126.23, 127.72, 128.48, 133.22, 136.79, 137.91, 151.12, 155.70, 160.02, 166.44. MS (%): 459 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-(*N*,*N*-dimethylcarboxamido)methoxyindan-1-yl]pyridine, 12ci. Prepared in 93% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 2.065 (m, 2H), 2.165 (s, 6H), 2.94 (m, 2H), 2.96 (s, 3H), 3.08 (s, 3H), 3.18 (t, J = 7.5, 2H), 4.73 (s, 2H), 5.88 (s, 2H), 6.77 (d, J = 8.5, 1H), 7.07 (d, J = 8, 1H), 7.49 (d, J = 8, 1H), 7.57 (d, J = 8.5, 1H), 7.81 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.40, 25.28, 29.42, 34.16, 35.71, 36.65, 67.57, 106.56, 109.56, 119.21, 120.91, 128.64, 128.68, 129.50, 132.97, 138.08, 144.95, 151.38, 154.88, 158.46, 167.92. MS (%): 390 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-(pyrrolidinylcarboxamido)methoxyindan-1-yl]pyridine, 12cii. Prepared in 64% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.79 (m, 2H), 1.90 (m, 2H), 2.01 (m, 2H), 2.10 (s, 6H), 2.88 (t, J = 7, 2H), 3.10 (t, J = 7, 2H), 3.4−3.6 (m, 4H), 4.62 (s, 2H), 5.82 (s, 2H), 6.70 (d, J = 8.5, 1H), 7.03 (d, J = 8, 1H), 7.4−7.5 (m, 2H), 7.78 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.21, 23.66, 25.24, 26.16, 29.37, 33.98, 46.14, 46.29, 67.78, 106.45, 109.42, 119.39, 121.16,

128.62, 129.45, 132.92, 138.20, 144.90, 151.34, 154.84, 158.46, 167.02. MS (%): 416 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-((4-methylpiperazinyl)-carboxamido)methoxyindan-1-yl]pyridine, 12ciii. Prepared in 78% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 2.07 (m, 2H), 2.16 (s, 6H), 2.72 (s, 3H), 2.38 (m, 4H), 2.91 (t, J = 7, 2H), 3.18 (t, J = 7, 2H), 3.61 (m, 4H), 4.72 (s, 2H), 5.88 (s, 2H), 6.78 (d, J = 8.5, 1H), 7.07 (d, J = 8, 1H), 7.49 (d, J = 8, 1H), 7.57 (d, J = 7.5, 1H), 7.805 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.31, 25.19, 29.37, 34.06, 41.94, 45.21, 45.94, 54.53, 55.09, 67.60, 106.51, 109.37, 119.16, 120.81, 128.54, 128.65, 129.53, 132.75, 137.98, 144.90, 151.32, 154.66, 158.33, 166.29. MS (%): 445 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-(*N*,*N*-dimethylcarboxamido)methoxybicyclo[2.2.1]naphthalen-1-yl]pyridine, 12di. Prepared in 93.5% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.2−1.4 (m, 2H), 1.48 (m, 1H), 1.72 (m, 1H), 1.97 (m, 2H), 2.21 (s, 6H), 2.98 (s, 3H), 3.10 (s, 3H), 3.71 (m, 1H), 3.85 (m, 1H), 4.74 (s, 2H), 5.90 (s, 2H), 6.75 (d, J = 8.7, 1H), 7.09 (d, J = 8, 1H), 7.5 (m, 2H), 7.84 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.42, 26.36, 26.54, 35.65, 36.57, 39.61, 42.99, 48.85, 67.75, 106.62, 110.01, 118.99, 120.90, 126.90, 127.52, 128.58, 135.97, 138.00, 148.43, 151.52, 151.78, 157.87, 167.93. MS (%): 416 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-(4-(2-(2-dimethylaminoethyl)methyloxy)-1-naphthyl)pyridine, 13ai. To a 100 mL round-bottomed flask equipped with condenser and N_2 inlet were added 160 mg (1.20 mmol) of aluminum chloride and 5 mL of dry tetrahydrofuran. The solution was cooled to 0 °C, and 2.81 mL (2.81 mmol) of a 1.0 M solution of lithium aluminum hydride in tetrahydrofuran was added. Stirring was continued at room temperature for 20 min, the solution was cooled to −70 °C, and a solution of 161 mg (0.403 mmol) of 2-(2,5-dimethylpyrrolyl)-6-(4-(2-(dimethylaminocarbonyl)-methyloxy)-1-naphthyl)pyridine in 7 mL of dry tetrahydrofuran was added. Stirring was continued 1 h at −70 °C and then 2 h at room temperature (LCMS showed P + 1 = 386), followed by careful quenching with 5 mL of 1 N hydrochloric acid. After stirring for 20 min, the reaction was treated with 6 mL of 6 N aqueous sodium hydroxide solution and extracted with several portions of methylene chloride. The organic phase was dried over sodium sulfate and evaporated to afford an oil, which was converted to the hydrochloride salt using HCl in ether, affording 164 mg of the product (∼100% yield) as an oil. ^{1}H NMR (δ, $CDCl_3$): 2.24 (s, 6H), 2.42 (s, 6H), 2.915 (t, J = 6, 2H), 4.30 (t, J = 6, 2H), 5.91 (s, 2H), 6.90 (d, J = 8, 1H), 7.20 (d, J = 8, 1H), 7.5−7.7 (m, 4H), 7.89 (t, J = 8, 1H), 8.13 (m, 1H), 8.37 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.5, 46.2, 58.2, 67.0, 104.3, 106.8, 119.7, 122.5, 123.5, 125.2, 125.3, 123.8, 126.9, 128.3, 138.6, 130.4, 132.0, 138.1, 151.8, 155.3, 159.1. MS (%): 386 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-(4-(2-(2-pyrrolidinylethyl)-methyloxy)-1-naphthyl)pyridine, 13aii. Prepared in 100% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.83 (m, 4H), 2.25 (s, 6H), 2.72 (m, 4H), 3.08 (t, J = 6, 2H), 4.35 (t, J = 6, 2H), 5.91 (s, 2H), 6.90 (d, J = 8, 1H), 7.20 (d, J = 8, 1H), 7.4−7.6 (m, 4H), 7.91 (t, J = 8, 1H), 8.13 (m, 1H), 8.38 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.6, 23.6, 54.9, 55.0, 68.0, 104.2, 106.8, 119.7, 122.5, 123.5, 125.2, 125.9, 126.9, 128.4, 128.7, 130.3, 132.0, 138.1, 151.8, 155.3, 159.2. MS (%): 412 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-(4-(2-(2-(4-methylpiperazinyl)ethyl)methyloxy)-1-naphthyl)pyridine, 13aiii. Prepared in 35% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 2.225 (s, 6H), 2.30 (s, 3H), 2.5 (m, 4H), 2.7 (m, 4H), 2.99 (t, J = 6, 2H), 4.33 (t, J = 6, 2H), 5.89 (s, 2H), 6.88 (d, J = 8, 1H), 7.20 (d, J = 8, 1H), 7.4−7.6 (m, 4H), 7.90 (t, J = 8, 1H), 8.11 (m, 1H), 8.33 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.44, 45.94, 53.57, 55.07, 57.03, 66.71, 104.23, 106.72, 119.64, 122.32, 123.39, 125.11, 125.20, 125.73, 126.85, 128.24, 128.58, 130.31, 131.86, 137.98, 151.70, 155.06, 159.01. MS (%): 441 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-(4-(2-(2-(4-dimethylaminopiperidinyl)ethyl)methyloxy)-1-naphthyl)pyridine, 13aiv. Prepared in 76% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.57 (m, 2H), 1.82 (m, 2H), 2.2 (m, 3H), 2.23 (s, 6H), 2.28 (s, 6H), 2.97 (t, J = 6, 2H), 3.11 (m, 2H), 4.32 (t, J = 6, 1H), 5.89 (s, 2H), 6.88 (d, J = 8, 1H), 7.20 (d, J = 8, 1H), 7.4−7.6 (m, 4H), 7.89 (t, J = 8, 1H), 8.10 (m, 1H), 8.33 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.41, 28.37, 41.61, 53.61, 57.03, 62.02, 66.82, 104.29, 106.75, 119.61, 122.34, 123.36, 125.14, 125.78, 126.80, 128.24, 128.55, 130.28, 131.90, 137.95, 151.73, 155.12, 159.05. MS (%): 469 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-(*N*,*N*-dimethylamino-ethoxy)-5,6,7,8-tetrahydronaphthalen-1-yl]pyridine, 13bi. Prepared in 93% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.69 (m, 2H), 1.78 (m, 2H), 2.16 (s, 6H), 2.36 (s, 6H), 2.73 (t, J = 7, 2H), 2.78 (m, 4H), 4.11 (t, J = 7, 2H), 5.88 (s, 2H), 6.74 (d, J = 8, 1H), 7.11 (d, J = 8, 1H), 7.20 (d, J = 8, 1H), 7.36 (d, J = 8, 1H), 7.81 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.3, 22.3, 22.9, 23.7, 28.7, 46.2, 58.4, 66.6, 106.6, 107.6, 119.5, 122.95, 126.5, 127.7, 128.6, 132.4, 136.6, 137.9, 151.2, 156.9, 160.35. MS (%): 390 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-(pyrrolidinylethoxy)-5,6,7,8-tetrahydronaphthalen-1-yl]pyridine, 13bii. Prepared in 90% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.80 (m, 4H), 2.15 (s, 6H), 2.65 (m, 2H), 2.72 (m, 2H), 2.72 (m, 2H), 2.93 (t, J = 6, 2H), 4.14 (t, J = 6, 2H), 6.73 (d, J = 8.5, 1H), 7.11 (d, J = 8, 1H), 7.19 (d, J = 7.5, 1H), 7.35 (d, J = 8, 1H), 7.81 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.24, 22.25, 22.78, 23.50, 28.57, 30.23, 34.13, 54.87, 67.40, 106.44, 107.50, 119.36, 122.85, 125.43, 126.31, 127.63, 128.52, 132.29, 136.45, 137.74, 151.12, 156.80, 160.28. MS (%): 416 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-((4-methylpiperaizinyl)-ethoxy)-5,6,7,8-tetrahydronaphthalen-1-yl]pyridine, 13biii. Prepared in 65% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.67 (m, 2H), 1.75 (m, 2H), 2.15 (s, 6H), 2.29 (s, 3H), 2.5 (m, 4H), 2.7 (m, 4H), 2.70 (t, J = 6, 2H), 2.76 (t, J = 6, 2H), 2.85 (t, J = 6, 2H), 4.13 (t, J = 6, 2H), 5.86 (s, 2H), 6.72 (d, J = 8.5, 1H), 7.10 (d, J = 8, 1H), 7.18 (d, J = 8.5, 1H), 7.35 (d, J = 8, 1H), 7.81 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.25, 22.24, 22.77, 23.61, 28.56, 45.96, 53.55, 55.09, 57.13, 66.29, 106.45, 107.53, 119.38, 122.83, 126.34, 127.62, 128.51, 132.41, 136.50, 137.74, 151.14, 156.70, 160.22. MS (%): 445 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-(*N*,*N*-dimethylamino-ethoxy)indan-1-yl]pyridine, 13ci. Prepared in 100% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 2.06 (m, 2H), 2.19 (s, 6H), 2.36 (s, 6H), 2.77 (t, J = 6, 2H), 2.92 (t, J = 7, 2H), 3.19 (t, J = 7, 2H), 4.15 (t, J = 6, 2H), 5.90 (s, 2H), 6.79 (d, J = 8, 1H), 7.07 (d, J = 8, 1H), 7.51 (d, J = 8, 1H), 7.61 (d, J = 8, 1H), 7.81 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.41, 25.33, 29.49, 34.26, 46.16, 58.29, 66.60, 106.57, 109.42, 119.06, 120.84, 128.60, 128.75, 133.04, 137.97, 144.63, 151.40, 155.85, 158.61. MS (%): 376 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-(pyrrolidinylethoxy)indan-1-yl]pyridine, 13cii. Prepared in 100% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.80 (m, 2H), 2.06 (m, 2H), 2.18 (s, 6H), 2.66 (m, 2H), 2.93 (m, 4H), 3.19 (t, J = 7, 2H), 4.19 (t, J = 6, 2H), 5.90 (s, 2H), 6.78 (d, J = 8, 1H), 7.07 (d, J = 8, 1H), 7.51 (d, J = 8, 1H), 7.61 (d, J = 8, 1H), 7.81 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.41, 23.56, 25.31, 29.52, 30.33, 34.26, 54.94, 67.42, 106.54, 109.41, 119.05, 120.83, 125.53, 128.60, 128.66, 132.98, 137.96, 144.61, 151.40, 155.83, 158.63. MS (%): 402 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-((4-methylpiperazinyl)-ethoxy)indan-1-yl]pyridine, 13ciii. Prepared in 91% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 2.055 (m, 2H), 2.175 (s, 6H), 2.29 (s, 3H), 2.5 (m, 4H), 2.7 (m, 4H), 2.84 (m, 2H), 2.89 (t, J = 7.5, 2H), 3.18 (t, J = 7, 1H), 4.17 (t, J = 6, 2H), 5.89 (s, 2H), 6.76 (d, J = 8.5, 1H), 7.06 (d, J = 8, 1H), 7.50 (d, J = 8, 1H), 7.60 (d, J = 8.5, 1H), 7.80 (d, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.31, 25.19, 29.39, 34.16, 45.97, 53.57, 55.09, 57.08, 66.31, 106.48, 109.37, 118.96, 120.71, 128.52, 128.71, 132.94, 137.85, 144.54, 151.32, 155.67, 158.49. MS (%): 431 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-(*N*,*N*-dimethylamino-ethoxy)bicyclo[2.2.1]naphthalen-1-yl]pyridine, 13di. Prepared in 77% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.27 (m, 2H), 1.49 (m, 1H), 1.73 (m, 1H), 1.96 (m, 2H), 2.22 (s, 6H), 2.37 (s, 6H), 2.78 (t, J = 6, 2H), 3.67 (m, 1H), 3.85 (m, 1H), 4.15 (t, J = 6, 2H), 5.91 (s, 2H), 6.76 (d, J = 8.5, 1H), 7.09 (d,

J = 8, 1H), 7.5 (m, 2H), 7.83 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.52, 26.42, 26.66, 39.69, 43.10, 46.13, 48.91, 58.32, 66.89, 106.68, 110.21, 118.93, 120.94, 125.55, 126.28, 127.48, 128.66, 136.12, 137.98, 148.29, 151.63, 152.78, 158.10. MS (%): 402 (parent + 1, 100).

6-[4-(2-Dimethylaminoethoxy)naphthalen-1-yl]pyridin-2-ylamine, 14ai. To a 100 mL round-bottomed flask equipped with condenser and N_2 inlet were added 155 mg (0.403 mmol) of 2-(2,5-dimethylpyrrolyl)-6-(4-(2-(2-dimethylaminoethyl)-methyloxy)-1-naphthyl)pyridine, 500 mg of hydroxylamine hydrochloride, 9 mL of ethanol, and 1 mL of water. The solution was refluxed 40 h (LCMS P + 1 = 308), cooled, poured into dilute aqueous hydrochloric acid, and washed with ethyl acetate. The aqueous layer was adjusted to pH 12 with 6 N aqueous sodium hydroxide solution and extracted with several portions of methylene chloride. The organic layer was dried over sodium sulfate and evaporated to a solid, 81 mg (65%), mp 98−106 °C. ^{1}H NMR (δ, $CDCl_3$): 2.395 (s, 6H), 2.89 (t, J = 6, 2H), 4.27 (t, J = 6, 2H), 4.65 (bs, 2H, NH_2), 6.43 (d, J = 8, 1H), 6.84 (m, 2H), 7.4−7.6 (m, 4H), 8.10 (m, 1H), 8.32 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 46.2, 58.2, 66.9, 104.2, 106.6, 115.2, 122.2, 125.1, 125.7, 125.8, 126.7, 127.2, 131.4, 132.2, 138.0, 154.7, 157.8, 158.2. MS (%): 308 (parent + 1, 100). Anal. ($C_{19}H_{21}N_3O\cdot{}^1/_4H_2O$) C, H, N.

6-[4-(2-Pyrrolidin-1-ylethoxy)naphthalen-1-yl]pyridin-2-ylamine, **14aii.** Prepared by Method A in 69% yield, mp 245−255 °C, as the hydrochloride salt. ^{1}H NMR (δ, $CDCl_3$): 1.79 (bs, 4H), 2.685 (bs, 2H), 3.035 (t, J = 6, 2H), 4.30 (t, J = 6, 2H), 4.68 (bs, 2H, NH_2), 6.41 (d, J = 8, 1H), 6.82 (m, 2H), 7.4−7.6 (m, 4H), 8.10 (m, 1H), 8.31 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 23.6, 54.9, 55.0, 67.8, 104.2, 106.6, 115.1, 122.2, 125.0, 125.7, 125.8, 126.6, 127.3, 131.4, 132.2, 138.0, 154.7, 157.7, 158.2. MS (%): 334 (parent + 1, 100). Anal. ($C_{21}H_{23}N_3O\cdot$ 2HCl): C, H; N: calcd, 10.34; found, 9.56.

6-{4-[2-(4-Methyl-piperazin-1-yl)ethoxy]naphthalen-1-yl}pyridin-2-ylamine, 14aiii. Prepared by Method A in 74% yield, as an amorphous solid as the hydrochloride salt. ^{1}H NMR (δ, $CDCl_3$): 2.26 (s, 3H), 2.5 (m, 4H), 2.7 (m, 4H), 2.955 (t, J = 6, 2H), 4.29 (t, J = 6, 2H), 4.55 (bs, 2H), 6.44 (d, J = 8, 1H), 6.82 (m, 2H), 7.4−7.6 (m, 4H), 8.08 (m, 1H), 8.27 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 45.97, 53.61, 55.11, 57.10, 66.69, 104.31, 106.41, 115.20, 122.09, 125.00, 125.62, 125.82, 126.55, 127.11, 131.50, 132.11, 137.86, 154.63, 157.79, 157.99. MS (%): 363 (parent + 1, 100). Anal. ($C_{22}H_{26}N_4O\cdot 3HCl\cdot{}^7/_4H_2O$) C, H, N.

6-{4-[2-(4-Dimethylaminopiperidin-1-yl)ethoxy]naphthalen-1-yl}pyridin-2-ylamine, 14aiv. Prepared by Method A in 73% yield, as an amorphous solid as the hydrochloride salt. ^{1}H NMR (δ, $CDCl_3$): 1.56 (m, 2H), 1.80 (m, 2H), 2.18 (m, 3H), 2.26 (s, 6H), 4.28 (t, J = 6, 2H), 3.10 (m, 2H), 4.28 (t, J = 6, 2H), 4.58 (bs, 2H), 6.43 (d, J = 8, 1H), 6.83 (m, 2H), 7.44 (m, 4H), 8.09 (m, 1H), 8.29 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 28.33, 41.61, 53.65, 57.12, 62.11, 66.77, 76.76, 104.33, 106.51, 115.22, 122.15, 125.09, 125.70, 125.85, 126.64, 127.23, 131.49, 132.15, 137.97, 154.65, 157.80, 158.08. MS (%): 391 (parent + 1, 100). Anal. ($C_{24}H_{30}N_4O\cdot 3HCl\cdot 3H_2O\cdot{}^1/_2(C_4H_{10}O)$) C, H, N. HRMS Calcd for $C_{24}H_{31}N_4O$: 391.2498. Found: 391.2485.

6-[4-(*N*,*N*-Dimethylaminoethoxy)-5,6,7,8-tetrahydronaphthalen-1-yl]pyridin-2-ylamine, 14bi. Prepared by Method A in 57% yield as the hydrochloride salt, mp 239−242 °C from methanol/isopropyl ether. ^{1}H NMR (δ, $CDCl_3$): 1.64 (m, 2H), 1.71 (m, 2H), 2.33 (s, 6H), 2.67 (m, 4H), 2.74 (t, J = 6, 2H), 4.07 (t, J = 6, 2H), 4.55 (bs, 2H), 6.36 (d, J = 8, 1H), 6.62 (d, J = 8, 1H), 6.67 (d, J = 8, 1H), 7.07 (d, J = 8, 1H), 7.40 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 22.3, 22.8 23.6, 28.1, 46.0, 58.2, 66.4, 106.0, 107.4, 114.3, 126.2, 126.8, 133.5, 136.2, 137.6, 156.3, 157.6, 158.8. MS (%): 312 (parent + 1, 100). Anal. ($C_{19}H_{25}N_3O\cdot 2HCl\cdot{}^1/_4H_2O$) C, H, N.

6-[4-(2-Pyrrolidin-1-ylethoxy)-5,6,7,8-tetrahydronaphthalen-1-yl]pyridin-2-ylamine, 14bii. Prepared by Method A in 58% yield, as a hygroscopic solid as the hydrochloride salt. ^{1}H NMR (d, $CDCl_3$): 1.64 (m, 2H), 1.74 (m, 2H), 1.77 (m, 4H), 2.62 (m, 4H), 2.68 (m, 4H), 2.89 (t, J = 6, 2H), 4.10 (t, J = 6, 2H), 4.52 (bs, 2H), 6.37 (d, J = 8, 1H), 6.63 (d, J = 8, 1H), 6.65 (d, J = 8, 1H), 7.07 (d, J = 8, 1H), 7.40 (t. J = 8, 1H). ^{13}C NMR (d, $CDCl_3$): 22.4, 22.9, 23.5, 23.7, 28.2, 54.9, 55.0, 67.4, 106.1, 107.5, 114.4, 126.3, 126.9, 133.5, 136.3, 137.7, 156.4, 157.7, 158.9. MS (%): 338 (parent + 1, 100). Anal. ($C_{21}H_{27}N_3O\cdot$ 2HCl·3H_2O) C, H, N.

6-{4-[2-(4-Methyl-piperazin-1-yl)ethoxy]5,6,7,8-tetrahydronaphthalen-1-yl}pyridin-2-ylamine, 14biii. Prepared by Method A in 100% yield, as an amorphous solid, as the hydrochloride salt. ^{1}H NMR (δ, $CDCl_3$): 1.62 (m, 2H), 1.72 (m, 2H), 2.26 (s, 3H), 2.4−2.8 (m, 12H), 2.81 (t, J = 6, 2H), 4.09 (t, J = 6, 2H), 4.50 (bs, 2H), 6.35 (d, J = 8, 1H), 6.63 (m, 2H), 7.07 (d, J = 8, 1H), 7.39 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 22.4, 22.9, 23.37, 28.2, 46,1, 53.37, 55.2, 57.3, 66.3, 106.1, 107.6, 114.4, 126.3, 126.9, 133.6, 136.3, 137.7, 156.3, 157.7, 158.9. MS (%): 367 (parent + 1, 100). Anal. ($C_{22}H_{30}N_4O\cdot 3HCl\cdot H_2O\cdot{}^1/_2(C_4H_{10}O)$) C, H, N.

6-[7-(2-Dimethylaminoethoxy)indan-4-yl]pyridin-2-ylamine, 14ci. Prepared by Method A starting with 1-indanol, in 57% yield, mp 215−218 °C, as the hydrochloride salt. ^{1}H NMR (δ, $CDCl_3$): 2.00 (quin, J = 6, 2H), 2.32 (s, 6H), 2.72 (t, J = 6, 2H), 2.86 (t, J = 7, 2H), 3.06 (t, J = 7, 2H), 4.10 (t, J = 6, 2H), 4.63 (bs, 2H), 6.32 (d, J = 8, 1H), 6.71 (d, J = 8, 1H), 6.76 (d, J = 8, 1H), 7.39 (m, 2H). ^{13}C NMR (δ, $CDCl_3$): 25.31, 29.56, 33.78, 46.07, 58.24, 66.46, 106.02, 109.34, 112.88, 127.97, 129.99, 132.66, 137.80, 144.30, 155.24, 157.34, 158.08. MS (%): 298 (parent + 1, 100). Anal. ($C_{18}H_{23}N_3O\cdot 2HCl\cdot{}^1/_2H_2O$) C, H, N.

6-[7-(2-Pyrrolidin-1-ylethoxy)indan-4-yl]pyridin-2-ylamine, 14cii. Prepared by Method A in 72% yield, mp 113−117 °C, as the hydrochloride salt. ^{1}H NMR (δ, $CDCl_3$): 1.77 (m, 4H), 2.01 (uqin, J = 7, 2H), 2.62 (m, 4H), 2.89 (m, 4H), 3.08 (t, J = 7, 2H), 4.15 (t, J = 6, 2H), 4.52 (bs, 2H), 6.34 (d, J = 8, 1H), 6.73 (d, J = 8, 1H), 6.79 (d, J = 8, 1H), 7.40 (m, 4H). ^{13}C NMR (δ, $CDCl_3$): 23.53, 25.30, 29.57, 33.78, 54.88, 54.98, 67.37, 105.94, 109.36, 112.99, 127.97, 129.94, 132.65, 137.80, 144.28, 155.27, 157.45, 157.95. MS (%): 324 (parent + 1, 100). Anal. ($C_{20}H_{25}N_3O\cdot 2HCl\cdot{}^3/_2H_2O$) C, H, N.

6-{7-[2-(4-Methylpiperazin-1-yl)ethoxy]indan-4-yl}-pyridin-2-ylamine, 14ciii. Prepared by Method A in 81% yield, as a tan solid, mp > 205 °C, as the hydrochloride salt. ^{1}H NMR (δ, $CDCl_3$): 2.00 (quin, J = 7, 2H), 2.26 (s, 3H), 2.4−2.7 (m, 8H), 2.8−2.9 (m, 4H), 3.08 (t, J = 7, 2H), 4.13 (t, J = 6, 2H), 4.49 (bs, 2H), 6.34 (d, J = 8, 1H), 6.71 (d, J = 8, 1H), 6.79 (d, J = 8, 1H), 7.40 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 25.20, 29.46, 33.72, 45.96, 53.55, 55.04, 57.08, 66.24, 105.85, 109.32, 112.86, 127.86, 129.97, 132.61, 137.69, 144.23, 155.08, 157.31, 157.87. MS (%): 353 (parent + 1, 100). HRMS Calcd for $C_{21}H_{29}N_4O$: 353.2345. Found: 353.2341.

6-[7-(2-Dimethylaminoethoxy)bicyclo[2.2.1]naphthalen-1-yl]pyridin-2-ylamine, 14di. Prepared by Method A in 78% yield, mp 130 °C (dec), as the hydrochloride salt. ^{1}H NMR (δ, $CDCl_3$): 1.1−1.3 (m, 2H), 1.43 (m, 1H), 1.68 (m, 1H), 1.89 (m, 2H), 2.34 (s, 6H), 2.74 (t, J = 6, 2H), 3.61 (m, 1H), 3.74 (m, 1H), 4.11 (t, J = 6, 2H), 4.52 (bs, 2H), 6.35 (d, J = 8, 1H), 6.70 (d, J = 8.5, 1H), 6.80 (d, J = 7.5, 1H), 7.36 (d, J = 8.5, 1H), 7.42 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 26.49, 26.73, 39.79, 42.90, 46.06, 48.84, 58.29, 66.89, 105.92, 110.24, 113.24, 126.94, 127.51, 135.82, 137.78, 148.00, 152.22, 156.88, 158.20. MS (%): 324 (parent + 1, 100). Anal. ($C_{20}H_{25}N_3O\cdot 2HCl\cdot 3/2H_2O\cdot({}^1/_2C_4H_{10}O)$) C, H, N.

Method B. 4-Bromo-1-(*N*,*N*-dimethylaminoethoxy)-5,6,7,8-tetrahydronaphthalene, 15b. To a 1 L round-bottomed flask equipped with condenser and N_2 inlet were added 10.0 g (44 mmol) of 4-bromo-5,6,7,8-tetrahydro-naphthalen-1-ol, 19 g (130 mmol) of 2-dimethylaminoethyl chloride hydrochloride, 30.3 g (220 mmol) of powdered potassium carbonate, and 600 mL of acetonitrile. The reaction was refluxed 60 h, followed by an additional portion of the chloride, and then refluxed for an additional 24 h. The reaction was cooled, filtered, and concentrated. The residue was chromatographed on silica gel using methanol/methylene chloride as eluant to afford 8.55 g (65%) of a light brown oil. ^{1}H NMR (δ, $CDCl_3$): 1.72 (m, 4H), 2.33 (s, 6H), 2.63 (m, 2H), 2.68 (m, 2H), 2.73 (t, J = 6, 2H), 4.01 (t, J = 6, 2H), 6.53 (d, J = 8, 1H), 7.28 (d, J = 8, 1H). ^{13}C NMR (δ,

$CDCl_3$): 22.1, 22.8, 23.7, 30.5, 46.0, 538.2, 66.6, 109.2, 116.4, 128.8, 129.2, 137.2, 155.6. MS: 298/300 (parent + 1).

1-(*N*,*N*-Dimethylaminoethoxy)-5,6,7,8-tetrahydronaphthalene-4-boronic Acid, 16b. To a 1 L three-neck round-bottomed flask equipped with septum and N_2 inlet were added 8.55 g (28.7 mmol) of 4-bromo-1-(2-dimethylaminoethoxy)-5,6,7,8-tetrahydro-naphthalene and 300 mL of dry tetrahydrofuran. The solution was cooled to −70 °C, and 13.8 mL (34.4 mmol) of a 2.5 M solution of butyllithium in hexanes was added. The reaction was stirred at −70 °C for 1 h, 5.9 mL (34.4 mmol) triethyl borate was added, and the reaction was stirred at −70 °C for 2 h and warmed to room-temperature overnight. The reaction was quenched with aqueous saturated ammonium chloride solution and extracted three times with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was triturated with hexane to a white solid, 6.3 g (83.5%). ^{1}H NMR (δ, $CDCl_3$): 1.79 (m, 4H), 2.44 (s, 6H), 2.68 (m, 2H), 2.89 (m, 2H), 3.32 (m, 2H), 4.19 (m, 2H), 6.74 (d, J = 8, 1H), 8.03 (d, J = 8, 1H).

2-(2,5-Dimethylpyrrolyl)-6-[4-(*N*,*N*-dimethylaminoethoxy)-5,6,7,8-tetrahydronaphthalen-1-yl]pyridine, 13b. To a 500 mL round-bottomed flask equipped with condenser and N_2 inlet were added 6.3 g (23.4 mmol) of 1-(*N*,*N*-dimethylaminoethoxy)-5,6,7,8-tetrahydro-naphthalene-4-boronic acid, 6.0 g (23.4 mmol) of 6-bromo-2-(2,5-dimethylpyrrolyl)pyridine, 10.1 g (95.6 mmol) of sodium carbonate, 552 mg of tetrakistriphenylphosphine palladium, 200 mL of ethanol, and 20 mL of water. The reaction was refluxed 20 h, cooled, and filtered. The filtrate was concentrated, taken up in 1 N sodium hydroxide solution, and extracted into ethyl acetate 3×. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using methanol/methylene chloride as eluant to afford 7.67 g (82%) of the product as an oil, which matched **13b** prepared previously. This material was converted to **14b** as described above.

4-Hydroxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene, 4e. Prepared in analogy with **4d** by reaction of 8 g (71.4 mmol) of 2-hydroxypyrone (ref: *Synth. Commun.* **1975**, *5*, 461) and 20 mL cycloheptene in a sealed tube at 150 °C for 24 h, followed by chromatography on silica gel using hexane/ethyl acetate as eluant, to give 1-oxo-3,4,6,7,8,9-hexahydro-5*H*-benzocycloheptene in 49.5% yield, followed by reaction with isopropenyl acetate to afford the enol acetate and treatment with 2,3-dichloro-5,6-dicyanobenzoquinone at 90 °C for 1.5 h (ref: *J. Med. Chem.* **1994**, *37*, 3803) to afford 4-acetoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene in 69% yield as an oil. Hydrolysis with 3.7 equiv of powdered potassium hydroxide in ethanol at room temperature for 2 h gave a 44% yield of the desired 4-hydroxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene after purification by column chromatography as a white solid. ^{1}H NMR (δ, $CDCl_3$): 1.64 (m, 4H), 1.85 (m, 2H), 2.79 (m, 2H), 2.86 (m, 2H), 6.64 (d, J = 8, 1H), 6.72 (d, J = 7, 1H), 6.94 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 25.8, 27.6, 28.2, 32.8, 36.6, 113.4, 121.6, 126.2, 129.6, 146.0, 152.4. GC MS: 162 (parent + 1, 100).

4-Bromo-1-(*N*,*N*-dimethylaminoethoxy)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene, 15e. Prepared in 25% yield as a light brown oil. ^{1}H NMR (δ, $CDCl_3$): 1.54 (m, 4H), 1.79 (m, 2H), 2.32 (s, 6H), 2.72 (t, J = 6, 2H), 2.91 (m, 2H), 3.01 (m, 2H), 3.99 (t, J = 6, 2H), 6.57 (d, J = 9, 1H), 7.27 (d, J = 9, 1H). ^{13}C NMR (δ, $CDCl_3$): 25.9, 26.5, 27.1, 32.1, 34.2, 46.0, 58.2, 67.5, 111.7, 115.5, 130.0, 134.4, 143.7, 154.9. MS: 312/314 (parent + 1, 100, Br^{79}/Br^{81}).

1-(*N*,*N*-Dimethylaminoethoxy)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-4-boronic Acid, 16e. Prepared in 49.5% yield as a tan amorphous solid. ^{1}H NMR (δ, $CDCl_3$): 1.57 (m, 4H), 1.71 (m, 2H), 1.83 (m, 2H), 2.38 (s, 6H), 2.83 (t, J = 6, 2H), 2.94 (m, 2H), 3.39 (m, 2H), 4.13 (t, J = 6, 2H), 6.75 (d, J = 8, 1H), 7.90 (d, J = 8, 1H).

2-(2,5-Dimethylpyrrolyl)-6-[4-(*N*,*N*-dimethylaminoethoxy)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-1-yl]-pyridine, 17e. Prepared in 40% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.63 (m, 4H), 1.82 (m, 2H), 2.17 (s, 6H), 2.35 (s, 6H), 2.77 (t, J = 6, 2H), 2.80 (m, 2H), 2.96 (m, 2H), 4.09 (t, J = 6, 2H), 5.87 (s, 2H), 6.79 (d, J = 8, 1H), 7.13 (d, J = 7.5, 1H), 7.18 (d, J = 8.5, 1H), 7.30 (d, J = 8, 1H), 7.81 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.33, 25.51, 27.29, 27.74, 31.28, 32.41, 46.10, 58.38, 67.45, 106.61, 109.87, 119.38, 123.09, 128.30, 128.57, 132.68, 132.89, 137.68, 142.93, 151.40, 155.87, 160.77. MS (%): 404 (parent + 1, 100).

6-[4-(2-Dimethylaminoethoxy)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-1-yl]pyridin-2-ylamine, 18ei. Prepared in 89% yield to give the product as an amorphous solid as the hydrochloride salt from ether, mp 90 °C (dec). ^{1}H NMR (δ, $CDCl_3$): 1.58 (m, 4H), 1.79 (m, 2H), 2.34 (s, 6H), 2.75 (m, 4H), 2.93 (m, 2H), 4.06 (t, J = 6, 2H), 4.48 (bs, 2H), 6.39 (d, J = 8, 1H), 6.62 (d, J = 8, 1H), 6.74 (d, J = 8, 1H), 7.10 (d, J = 8, 1H), 7.41 (d, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 25.51, 27.36, 27.75, 31.21, 32.46, 46.03, 58.35, 67.43, 105.94, 109.95, 114.72, 127.58, 132.85, 133.74, 137.54, 142.88, 155.43, 157.74, 159.32. MS (%): 326 (parent + 1, 100). FAB HRMS: Calcd for $C_{20}H_{28}N_3O$: 326.2232. Found: 326.2229.

Method C. 6-[4-(1-Methylpyrrolidin-2-ylmethoxy)-naphthalen-1-yl]pyridin-2-ylamine, 23i: **4-Bromo-1-fluoronaphthalene, 19**. To a 50 mL round-bottomed flask equipped with condenser and N_2 inlet were added 3.75 mL (5.0 g, 34.25 mmol) of 1-fluoronaphthalene and 10 mL of carbon tetrachloride, followed by dropwise addition of 1.7 mL (5.5 g., 34.375 mmol) of bromine over 3 min. The reaction was heated to 50−60 °C as HBr was evolved for 2 h and then cooled and concentrated. The residue was dissolved in methanol and kept overnight at 0 °C. After filtration with cold methanol, the product, with mp close to room temperature, was 4.62 g (60%) of a yellow oil. ^{1}H NMR (δ, $CDCl_3$): 7.02 (t, J = 8, 1H), 7.6−7.7 (m, 3H), 8.10 (d, J = 8.5, 1H), 8.20 (d, J = 8.5, 1H). GCMS (%): 224/226 (parent, Br^{79}/Br^{81} 100).

4-Fluoronaphthalene-1-boronic Acid, 20. To a 250 mL three-necked round-bottomed flask equipped with septum and N_2 inlet were added 4.62 g (20.53 mmol) of 4-bromo-1-fluoronaphthalene and 100 mL of dry tetrahydrofuran. The solution was cooled to −70 °C, and 15.4 mL (24.64 mmol) of a 1.6 M solution of butyllithium in hexane was added dropwise over 5 min. The reaction was stirred at −70 °C for 10 min, 4.2 mL (3.59 g, 24.64 mmol) triethyl borate was added, and the reaction was stirred at −70 °C for 20 min and warmed to room temperature. After stirring overnight at room temperature, the reaction was quenched with saturated aqueous ammonium chloride solution, acidified with 1 N hydrochloric acid, and extracted into ethyl acetate (twice). The combined organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was triturated with hexane to give an off-white powder, 1.97 g (51%), as a mixture of monoaryl and diaryl boronic acids. ^{1}H NMR (δ, $CDCl_3$): 7.2−7.4 (m, 1H), 7.5−7.7 (m, 3H), 8.0−8.5 (m, 1H), 8.5 and 9.2 (m, 1H). APCI (−) (%): 189 (parent-1, 60).

2-(2,5-Dimethylpyrrolyl)-6-(4-fluoronaphth-1-yl)pyridine, 21. To a 50 mL round-bottomed flask equipped with condenser and N_2 inlet were added 404 mg (2.13 mmol) of 4-fluoronaphthalene-1-boronic acid, 534 mg (2.13 mmol) of 2-(2,5-dimethylpyrrolyl)-6-bromopyridine, 902 mg (8.51 mmol) of sodium carbonate, 150 mg of tetrakistriphenylphosphine, 10 mL of ethanol, and 2 mL of water. The reaction was refluxed overnight, cooled, poured into water, and extracted into ethyl acetate. After being combined with another run on a larger scale, the organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate as eluant to afford 4.72 g (85%) of an oil. ^{1}H NMR (δ, $CDCl_3$): 2.25 (s, 6H), 5.92 (s, 2H), 7.1−7.2 (m, 2H), 7.4−7.6 (m, 4H), 7.95 (t, J = 8, 1H), 8.12 (d, J = 8, 1H), 8.19 (d, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.41, 106.97, 108.82, 109.02, 120.18, 120.78, 120.84, 123.42, 123.81, 123.96, 125.48, 126.20, 127.32, 127.68, 127.76, 128.56, 132.35, 133.90, 138.22, 151.87, 157.82, 158.30, 160.34. MS (%): 317 (parent + 1, 100). HRMS Calcd for $C_{21}H_{18}N_2F$ (parent + 1): 317.1454. Found: 317.1462.

2-(2,5-Dimethylpyrrolyl)-6-(4-((1-methylpyrrolidin-2-ylmethoxy)naphth-1-yl)pyridine, 22i. To a 20 mL round-bottomed flask equipped with condenser and N_2 inlet were added 145 mg (1.266 mml) (*S*)-(−)-1-methyl-pyrrolidin-2-ylmethanol and 8 mL of dry dimethylformamide, followed by 76 mg (1.989 mmol) of sodium hydride (60% in oil). The reaction was heated to 70 °C to ensure complete formation of the alkoxide, 200 mg (0.633 mmol) of 2-(2,5-dimethylpyrrolyl)-6-(4-fluoro-naphth-1-yl)pyridine in 2 mL of dry dimethylformamide was added, and the reaction was heated at 80 °C for 2 h. The reaction was cooled, poured into water, and extracted into ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using methanol/methylene chloride as eluant to afford 235 mg (90%) of an oil. ^{1}H NMR (δ, $CDCl_3$): 1.83 (m, 2H), 1.90 (m, 1H), 2.15 (m, 1H), 2.23 (s, 6H), 2.38 (m, 1H), 2.585 (s, 3H), 2.89 (m, 1H), 3.17 (m, 1H), 4.17 (AB multiplet, J = 60, 2H), 5.89 (s, 2H), 6.89 (d, J = 8, 1H), 7.22 (m, 1H), 7.49 (m, 2H), 7.56 (m, 2H), 7.90 (t, J = 8, 1H), 8.12 (m, 1H), 8.33 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.44, 22.97, 28.89, 41.80, 57.77, 64.36, 71.45, 104.11, 106.72, 119.64, 122.30, 123.42, 125.15, 125.68, 126.80, 128.29, 128.58, 130.21, 131.86, 138.00, 151.68, 155.24, 159.06. MS (%): 412 (parent + 1, 100). HRMS Calcd for $C_{27}H_{29}N_3O$ (parent + 1): 412.2389. Found: 412.2377.

2-(2,5-Dimethylpyrrolyl)-6-(4-(1-azabicyclo[2.2.2]oct-2-ylmethoxy)naphth-1-yl)pyridine, 22ii. Prepared as for **22i**, using 1-azabicyclo[2.2.2]oct-2-ylmethanol, in 67% yield as a tan oil. ^{1}H NMR (δ, $CDCl_3$): 1.4−1.6 (m, 5H), 1.90 (m, 2H), 2.24 (s, 6H), 2.84 (m, 1H), 3.0−3.2 (m, 3H), 3.43 (m, 1H), 4.23 (AB, $\Delta\nu$ = 87, 2H), 5.90 (s, 2H), 6.93 (d, J = 8, 1H), 7.23 (d, J = 8, 1H), 7.5−7.6 (m, 4H), 7.90 (t, J = 8, 1H), 8.12 (m, 1H), 8.37 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.54, 21.60, 25.71, 26.76, 30.48, 42.87, 50.06, 55.15, 70.89, 104.56, 106.81, 119.72, 122.58, 123.52, 125.19, 125.23, 125.92, 126.92, 128.36, 128.67, 130.38, 131.96, 138.10, 151.77, 155.49, 159.14. HRMS Calcd for $C_{29}H_{31}N_3O$ (parent + 1): 438.2545. Found: 438.2521.

6-[4-(1-Methylpyrrolidin-2-ylmethoxy)naphthalen-1-yl]pyridin-2-ylamine, **23i**: Deblocking was carried out as described for compound **14ai** in 88% yield to give the product as a tan solid, mp 80−95 °C, α_D = −36.47° (c = 1, CH_2Cl_2). ^{1}H NMR (δ, $CDCl_3$): 1.8 (m, 2H), 1.9 (m, 1H), 2.12 (m, 1H), 2.34 (m, 1H), 2.56 (s, 3H), 2.83 (m, 1H), 3.13 (m, 1H), 4.13 (AB, 2H), 4.63 (bs, 2H), 6.41 (d, J = 8, 1H), 6.83 (m, 2H), 7.46 (m, 4H), 8.10 (m, 1H), 8.31 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 23.00, 28.92, 41.87, 57.79, 64.27, 71.57, 104.06, 106.45, 115.09, 122.07, 124.97, 125.64, 125.73, 126.01, 126.53, 127.20, 131.29, 132.06, 137.89, 154.78, 157.69, 158.07. MS (%): 334 (parent + 1, 100). Anal. ($C_{21}H_{23}N_3O\cdot{}^1/_3H_2O$) C, H, N.

6-[4-(1-Azabicyclo[2.2.2]oct-2-ylmethoxy)naphthalen-1-yl]pyridin-2-ylamine, 23ii. Prepared by Method C using 1-aza-bicyclo[2.2.2]oct-2-yl-methanol in 79% yield, mp 180−190 °C as the free base and mp 145−155 °C, as the hydrochloride salt. ^{1}H NMR (δ, $CDCl_3$): 1.56 (m, 5H), 1.86 (m, 2H), 2.75 (m, 1H), 2.93 (m, 2H), 3.10 (m, 1H), 3.36 (m, 1H), 4.07 (AB multiplet, J = 65, 2H), 6.43 (d, J = 8, 1H), 6.74 (d, J = 7, 1H), 6.83 (d, J = 8, 1H), 7.39 (m, 4H), 7.93 (m, 1H), 8.28 (m, 1H). ^{13}C NMR (δ, $CDCl_3$): 21.21, 25.11, 26.10, 29.80, 42.44, 48.91, 49.13, 49.50, 55.08, 69.91, 104.23, 107.04, 115.02, 122.13, 125.15, 125.46, 125.63, 126.67, 127.07, 131.37, 132.10, 138.27, 154.70, 157.08, 158.30. MS (%): 360 (parent + 1, 100). Anal. Calculated for a sample of the free base, which formed the N-carboxy derivative from CO_2 in the air, ($C_{23}H_{25}N_3O\cdot CO_2$) C, H, N.

Method D. 2-(2,5-Dimethylpyrrolyl)-6-[4-(2-(dimethylamino)cyclohexyloxy)-5,6,7,8-tetrahydronaphthalen-1-yl]-pyridine, 24i. To a 100 mL round-bottomed flask equipped with condenser and N_2 inlet were added 185 mg (0.58 mmol) of **9b**, 173 mg (0.58 mmol) of *N*,*N*-dimethyl (2-tosyloxycyclohexyl)amine, 320 mg (2.3 mmol) of potassium carbonate, and 10 mL of dry dimethylformamide. The reaction was heated at 140 °C for 18 h, cooled, and poured into 1 N aqueous sodium hydroxide solution. The aqueous phase was extracted three times with ethyl acetate, and the combined organic layers were washed three times with water and once with brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using methanol/methylene chloride as eluant to afford 112 mg (43.5%) of the product as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.29 (m, 3H), 1.5 (m, 1H), 1.6−1.8 (m, 6H), 1.9 (m, 1H), 2.1 (m, 1H), 2.16 (s, 6H), 2.43 (s, 6H), 2.7 (m, 1H), 2.755 (dd, J = 7, 10, 4H), 4.39 (m, 1H), 5.87 (s, 2H), 6.78 (d, J = 8, 1H), 7.11 (d, J = 8, 1H), 7.18 (d, J = 8, 1H), 7.37 (d, J = 8, 1H), 7.82 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.32, 22.42, 22.86, 23.69, 24.11, 24.54, 27.84, 28.71, 30.26, 42.11, 66.03, 76.04, 106.50, 108.92, 119.46, 122.94, 127.57, 128.60, 132.17, 136.79, 137.81, 151.25, 155.37, 160.41. MS (%): 444 (parent + 1, 100).

2-(2,5-Dimethylpyrrolyl)-6-[4-(1-methylpyrrolidin-3-yloxy)-5,6,7,8-tetrahydronaphthalen-1-yl]pyridine, 24ii. Prepared as for **24i**, using *N*-methyl-3-pyrrolidinol, in 9% yield as an oil. ^{1}H NMR (δ, $CDCl_3$): 1.65 (m, 2H), 1.74 (m, 2H), 2.0 (m, 1H), 2.14 (s, 6H), 2.31 (m, 1H), 2.41 (s, 3H), 2.6 (m, 1H), 2.7−2.8 (m, 6H), 3.0 (m, 1H), 4.85 (m, 1H), 5.86 (s, 2H), 6.61 (d, J = 8, 1H), 7.11 (d, J = 7.5, 1H), 7.16 (d, J = 8, 1H), 7.35 (d, J = 8, 1H), 7.81 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 13.33, 22.72, 22.84, 23.79, 28.67, 32.66, 33.16, 42.33, 62.54, 106.50, 108.47, 119.50, 122.94, 126.89, 127.53, 128.62, 132.32, 136.74, 137.83, 151.23, 155.73, 160.28. MS (%): 402 (parent + 1, 100).

6-[4-(2-Dimethylamino-cyclohexyloxy)-5,6,7,8-tetrahydronaphthalen-1-yl]pyridin-2-ylamine, 25i: Deblocked as described for compound **7a**, affording the product in 76% yield, as an amorphous solid. ^{1}H NMR (δ, $CDCl_3$): 1.06 (m, 1H), 1.27 (m, 3H), 1.43 (m, 1H), 1.6−1.8 (m, 4H), 1.86 (m, 1H), 2.12 (m, 1H), 2.41 (s, 6H), 2.6−2.8 (m, 6H), 4.36 (m, 1H), 4.47 (bs, 2H), 6.38 (d, J = 8, 1H), 6.66 (d, J = 8, 1H), 6.72 (d, J = 8, 1H), 7.07 (d, J = 8, 1H), 7.42 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 22.41, 22.78, 23.63, 24.03, 24.53, 28.01, 28.20, 30.18, 42.01, 46.07, 65.91,75.88, 105.95, 108.66, 114.39, 126.63, 127.36, 133.18, 136.42, 137.64, 154.75, 157.54, 158.93. MS (%): 366 (parent + 1, 100). HRMS Calcd for $C_{23}H_{32}N_3O$ (parent + 1): 366.2545. Found: 366.2556.

6-[4-(1-Methylpyrrolidin-3-yloxy)-5,6,7,8-tetrahydronaphthalen-1-yl]pyridin-2-ylamine, 25ii: Prepared by deblocking **24ii** as for **25i** in 93.5% yield as an amorphous solid. ^{1}H NMR (δ, $CDCl_3$): 1.64 (m, 2H), 1.72 (m, 2H), 2.31 (m, 2H), 2.40 (s, 3H), 2.56 (m, 1H), 2.67 (m, 4H), 2.99 (m, 1H), 4.53 (bs, 2H), 4.83 (m, 1H), 6.39 (d, J = 8, 1H), 6.57 (d, J = 8, 1H), 6.64 (d, J = 8, 1H), 7.06 (d, J = 8, 1H), 7.42 (t, J = 8, 1H). ^{13}C NMR (δ, $CDCl_3$): 22.4, 22.9, 23.8, 25.8, 25.2, 33.1, 42.3, 55.2, 62.6, 106.2, 108.4, 112.5, 114.5, 126.7, 133.3, 136.5, 137.8, 155.3, 157.7, 158.8. MS (%): 366 (parent + 1, 100). HRMS Calcd for $C_{20}H_{26}N_3O$ (parent + 1): 324.2076. Found: 324.2083.

Biological Assays. NOS Enzyme Assays. NO synthase activity was measured by a modification of the procedure described in Bredt, D. S.; Snyder, S. H. *Proc. Natl. Acad. Sci., U. S. A.* **1990**, *87*, 714. Using this procedure, 10 μL of enzyme solution and 10 μL of ^{3}[H]-arginine were added to 80 μL of buffer (contents of which varied depending on the NOS isoform being tested). After incubation for 50 min at 30 °C, the reaction was terminated by application to a 0.15 mL column containing Biorex-60 cation-exchange resin, sodium form, and washed with 90 μL water. ^{3}[H]-Citrulline was quantified by liquid scintillation spectroscopy of the eluant.

Harmaline-Induced cGMP Protocol. Male Sprague Dawley rats 75−85 g are administered the test compound subcutaneously in 5/5/90 DMSO/Emulphor/saline and then, 20 min later, injected (ip) with 20 mg/kg harmaline·HCl in saline using an injection volume of 0.5 mL/100 g. Ten minutes after injection, animals are sacrificed with focused microwave irradiation to quench brain enzymatic activity. The cerebellum is removed and frozen at −70 °C until assay. On the day of assay, cerebellum is extracted with 0.5 mL of 0.5 N HCl. Briefly, the tissue is probe-sonicated with 0.5 mL of the 0.5 N HCl for 15 s using a Branson Sonifier 250 at a constant output of 20. The resulting homogeneous mixture is centrifuged at 15 000*g* for 20 min at 4 °C. The supernatant is removed and assayed immediately for cGMP by ELIZA (R and D systems). A cGMP standard curve of 0.8−500 pg/mL was utilized. A 10

μL aliquot of the supernatant was sufficient to cover the range of expected cGMP levels. The pellet was solubilized with 1 mL of 0.2% sodium sulfate in 0.5 N NaOH and protein content determined by the BCA protein assay method. Results are reported as pmol/mg protein. The induction of cGMP in harmaline-treated rats was 5−10-fold over vehicle-injected rats.

Inhibition of PCP-Induced Hypermotility. Three groups of rats are used, vehicle−vehicle, 3.2 mg/kg PCP−vehicle, and 3.2 mg/kg PCP−drug. The drug was administered subcutaneously in 5/5/90 DMSO/Emulphor/saline followed by PCP. Rats were placed in hypermotility boxes in which they had been previously acclimated, and crossovers and rears were measured over a 2 h period. Results are expressed as inhibition of mean crossovers, with SEM.

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