

## Chapter 9 Experimental

### 9.1 Chemistry

#### 9.1.1 1-Methyl- and 1-Cyclopropyl-4-aryl-substituted tetrahydropyridines

**General.** Reagents and starting materials were obtained from commercial suppliers and were used without further purification. The syntheses of 1-cyclopropyl-4-piperidone (**120**),<sup>238</sup> the 4- $\alpha$ - and 4- $\beta$ -naphthyl-1-methyl-4-piperidinols **124** and **125** and the corresponding tetrahydropyridines **134** and **135**,<sup>148</sup> respectively, were achieved as reported previously. THF and Et<sub>2</sub>O were distilled from sodium/benzophenone ketyl. All reactions were conducted using flame dried glassware under an atmosphere of dry nitrogen. Chromatography refers to flash column chromatography on silica gel unless otherwise noted. Proton and carbon NMR spectra were recorded on Bruker WP 270-MHz or Varian 400-MHz spectrometers. Exponential function (LB = 0.05-0.2) was applied to the FID to obtain integrals and gaussian function (LB = -1, GB = 0.25) to record coupling constants. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane ( $\delta = 0$ ). Spin multiplicities are given as s (singlet), bs (broad singlet), d (doublet), t (triplet) or m (multiplet). Coupling constants (*J*) are given in hertz (Hz). Gas chromatography-electron ionization mass spectrometry (GC-EIMS) was performed on a Hewlett Packard 5890 GC fitted with an HP-1 capillary column which was coupled to a Hewlett Packard 5870 mass-selective detector. All GC-EIMS were obtained using an initial oven

temperature of 60 °C ramping at 25 °C / min. to a final temperature of 290 °C with a solvent delay of 2 minutes and an injection port temperature of 220 °C. Data were processed using an HP 5970 Chemstation. Normalized peak heights are reported as a percentage of the base peak. UV-vis absorption spectra were recorded on a Beckman DU Series 7400 spectrophotometer. Melting points were performed on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, GA. Calculations and optimizations were performed using the semi-empirical AM1 method (Hyperchem),<sup>247</sup> with the restricted Hartree-Fock (RHF) approximation, and the Polack-Ribiere algorithm (gradient fixed at 0.0001), to obtain the lowest energy conformers. Data were saved under PDB file format and imported into MM2-MacMimic (Instar Software, version 91) software.

The 1-methyl-4-(3-indolyl)-1,2,3,6-tetrahydropyridine (**147**),<sup>250</sup> 1-methyl-4-( $\alpha$ -naphthyl)-1,2,3,6-tetrahydropyridine (**134**),<sup>148</sup> and 1-methyl-4-( $\beta$ -naphthyl)-1,2,3,6-tetrahydropyridine (**135**)<sup>148</sup> were prepared according literature methods, but isolated as their oxalate salts instead of HCl salts. Physical data were consistent with the expected structures for all three compounds.

**General Procedure for the Synthesis of 1-Methyl- and 1-Cyclopropyl-4-aryl-4-piperidinols (121 - 130).** A solution of 1-methyl-4-piperidone (**119**, 5.8 mmol) or 1-cyclopropyl-4-piperidone (**120**) in 10 mL THF was added dropwise to a solution of the Grignard (0 °C) or lithium (-78 °C, compound **116** only) reagent derived from the bromoarenes **114 - 118** (5 mmol) in 10 mL THF. After stirring the reaction mixture at -78 °C for 30 min and

at room temperature overnight, saturated aqueous  $\text{NH}_4\text{Cl}$  (25 mL) was added. The aqueous layer was washed with  $\text{Et}_2\text{O}$ , made to pH 10 with 40% aqueous  $\text{NaOH}$  and extracted 3 times with 25 mL  $\text{CH}_2\text{Cl}_2$ . The combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to yield the crude product which was purified by chromatography on silica gel.

**1-Methyl-4-(4-phenyl)phenyl-4-piperidinol (121):** Obtained as a yellow solid from  $\text{SiO}_2$  with  $\text{CH}_2\text{Cl}_2/2\%$  MeOH (38% yield), mp: 159 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.56 (6H, m), 7.40 (2H, tt,  $J = 1.4$  Hz,  $J = 7.2$  Hz), 7.33 (1H, tt,  $J = 2.1$  Hz,  $J = 7.2$  Hz), 2.75 (2H, bd,  $J = 11.2$  Hz), 2.51 (2H, dt,  $J = 2.0$  Hz,  $J = 12.4$  Hz), 2.35 (3H, s), 2.21 (2H, dt,  $J = 4.8$  Hz,  $J = 13.6$  Hz), 1.78 (2H, dd,  $J = 2.0$  Hz,  $J = 14.0$  Hz), 1.70 (1H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  140.5, 140.3, 128.8, 127.5, 127.2, 127.0, 124.9, 69.9, 51.4, 44.8, 37.0; GC ( $t_R$  10.39 min)-EIMS,  $m/z$ , (rel intensities) 267 (57%), 249 (54), 196 (22), 152 (35), 96 (30), 70 (93), 42 (100). UV (MeOH nm) 220, 253, 320. Anal. Calcd. ( $\text{C}_{18}\text{H}_{21}\text{NO}$ ): C, 80.86; H, 7.92; N, 5.24. Found: C, 80.81; H, 7.96; N, 5.17.

**1-Methyl-4-(3-phenyl)phenyl-4-piperidinol (122):** Obtained as a viscous yellow oil from  $\text{SiO}_2$  with  $\text{AcOEt}/2\%$  MeOH (42% yield).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.76 (1H, t,  $J = 1.6$  Hz), 7.57 (1H, m), 7.43 (7H, m), 2.75 (2H, bd,  $J = 11.0$  Hz), 2.47 (2H, dt,  $J = 2.5$  Hz,  $J = 12.3$  Hz), 2.33 (3H, s), 2.23 (2H, dt,  $J = 4.5$  Hz,  $J = 13.5$  Hz), 2.03 (1H, bs), 1.79 (2H, dd,  $J = 2.5$  Hz,  $J = 14.0$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  148.7, 140.8, 128.2, 127.6, 125.5, 123.8, 123.1, 71.2, 49.7, 38.4, 38.1; GC ( $t_R$  10.19 min)-EIMS,  $m/z$ , (rel intensities) 267 (48%), 249 (26), 165 (11), 152 (26), 115 (4), 96 (20), 70 (100). UV (MeOH, nm) 219, 264, 324. Anal.

Calcd. (C<sub>18</sub>H<sub>21</sub>NO): C, 80.86; H, 7.92; N, 5.24. Found: C, 81.12; H, 7.64; N, 4.93.

**1-Methyl-4-(2-phenyl)phenyl-4-piperidinol (123):** Obtained as a yellow solid recrystallized from CH<sub>2</sub>Cl<sub>2</sub>/Hexane (81% yield), mp: 112 °C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.52 (1H, dd, *J* = 1.2 Hz, *J* = 8.0 Hz), 7.32 (7H, m), 7.07 (1H, dd, *J* = 1.4 Hz, *J* = 7.4 Hz), 2.65 (2H, bd, *J* = 10.9 Hz), 2.35 (2H, bd, *J* = 12.4 Hz), 2.28 (3H, s), 2.21 (2H, bd, *J* = 12.1 Hz), 1.80 (2H, d, *J* = 10.9 Hz), 1.53 (1H, bs); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 144.2, 143.6, 140.3, 132.6, 129.3, 128.2, 127.7, 127.3, 126.5, 126.0, 72.3, 51.2, 45.3, 38.0; GC (t<sub>R</sub> 9.41 min)-EIMS, *m/z*, (rel intensities) 267 (48%), 249 (22), 165 (22), 152 (33), 115 (4), 96 (26), 70 (100), 58 (98). UV (MeOH, nm) 216, 260, 319. Anal. Calcd. (C<sub>18</sub>H<sub>21</sub>NO): C, 80.86; H, 7.92; N, 5.24. Found: C, 80.99; H, 8.17; N, 5.33.

**1-Cyclopropyl-4-(1-naphthyl)-4-piperidinol (129):** <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.82 (1H, m), 7.84 (1H, m), 7.76 (1H, d, *J* = 10.6 Hz), 7.45 (4H, m), 2.9 (2H, m), 2.7 (2H, m), 2.3 (1H, m), 1.57 (2H, bs), 1.18 (m, 2H), 0.87 (m, 2H); GC (t<sub>R</sub> 11.78 min)-EIMS, *m/z*, (rel intensities) 267 (13%), 238 (20), 169 (15), 141 (24), 127 (34), 82 (100), 68 (61). The remaining reaction mixture was evaporated and used as is.

**1-Cyclopropyl-4-(2-naphthyl)-4-piperidinol (130):** Chromatographed on silica gel (Hex/AcOEt 7:3) to give the expected product (**20**) as a yellowish solid (1.2 g, 4.5 mmol, 52% yield), mp 124-125 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (1H, d, *J* = 2.0 Hz), 7.84 (3H, m), 7.66 (1H, dd, *J* = 2.0 Hz, *J* = 8.7 Hz),

7.47 (2H, m), 3.01 (2H, m, bd like), 2.72 (2H, dt,  $J = 2.7$  Hz,  $J = 12.4$  Hz), 2.22 (2H, dt,  $J = 4.7$  Hz,  $J = 13.4$  Hz), 1.84 (2H, dq,  $J = 2.7$  Hz,  $J = 12.4$  Hz), 1.72 (1H, m), 1.68 (1H, s), 0.46 (4H, m).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  133.2, 132.4, 128.2, 128.0, 127.5, 126.1, 125.8, 123.4, 123.0, 71.6, 49.7, 38.7, 38.4, 5.2. GC ( $t_{\text{R}}$  11.78 min)-EIMS,  $m/z$ , (rel intensities) 267 (33%), 238 (24), 183 (15), 155 (28), 127 (41), 82 (100), 68 (56). UV (MeOH, nm) 212, 228, 267. Anal. Calcd. ( $\text{C}_{18}\text{H}_{21}\text{NO}$ ): C, 80.86; H, 7.92; N, 5.24. Found: C, 80.57; H, 7.99; N, 5.23.

**1-Cyclopropyl-4-(4-phenyl)phenyl-4-piperidinol (126):** Chromatographed on silica gel ( $\text{CH}_2\text{Cl}_2$  100% and then  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  92:8) to give the 1-cyclopropyl-4-(4-phenyl)phenyl-4-piperidinol (**16**) as a white solid (2.1 g, 7.16 mmol, 72% yield), mp: 145 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.58 (6H, m), 7.42 (2H, tt,  $J = 1.8$  Hz,  $J = 7.6$  Hz), 7.36 (1H, tt,  $J = 1.8$  Hz,  $J = 7.4$  Hz), 2.97 (2H, m, bd like,  $J = 11.2$  Hz), 2.70 (2H, dt,  $J = 2.6$  Hz,  $J = 12.2$  Hz), 2.14 (2H, dt,  $J = 4.7$  Hz,  $J = 13.3$  Hz), 1.78 (2H, dq,  $J = 2.6$  Hz,  $J = 11.3$  Hz), 1.70 (1H, m), 1.65 (1H, bs), 0.48 (4H, m).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  147.6, 140.7, 139.8, 128.7, 127.2, 127.0, 125.0, 71.4, 49.6, 38.7, 38.4, 5.9. GC ( $t_{\text{R}}$  12.60 min)-EIMS,  $m/z$ , (rel intensities) 293 (60%), 264 (39), 209 (16), 181 (39), 152 (48), 112 (30), 97 (47), 82 (100), 68 (58). UV (MeOH, nm) 215, 252. Anal. Calcd. ( $\text{C}_{20}\text{H}_{23}\text{NO}$ ): C, 81.87; H, 7.90; N, 4.77. Found: C, 81.68; H, 7.92; N, 4.80.

**1-Cyclopropyl-4-(3-phenyl)phenyl-4-piperidinol (127):** Syrupy (72% yield).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.74 (1H, t,  $J = 1.8$  Hz), 7.56 (1H, dt,  $J = 1.7$  Hz,  $J = 7.0$  Hz), (6H, m), 7.33 (1H, tt,  $J = 1.4$  Hz,  $J = 7.2$  Hz), 2.94 (2H, m, bd like,  $J = 12.0$  Hz), 2.69 (2H, dt,  $J = 2.7$  Hz,  $J = 12.2$  Hz), 2.15 (2H, dt,  $J = 4.7$  Hz,  $J = 13.5$

Hz), 1.78 (2H, dq,  $J = 2.4$  Hz,  $J = 13.7$  Hz), 1.70 (1H, m), 1.66 (1H, bs), 0.46 (4H, m).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  149.1, 141.3, 128.7, 127.2, 125.8, 123.6, 123.5, 71.6, 49.6, 38.7, 38.5, 5.9. GC ( $t_R$  12.35 min)-EIMS,  $m/z$ , (rel intensities) 293 (65%), 264 (42), 209 (10), 181 (19), 152 (35), 112 (17), 97 (57), 82 (100), 68 (54). UV (MeOH, nm) 215, 249. Anal. Calcd. ( $\text{C}_{20}\text{H}_{23}\text{NO}$ ): C, 81.87; H, 7.90; N, 4.77. Found: C, 81.72; H, 7.92; N, 4.75.

**1-Cyclopropyl-4-(2-phenyl)phenyl-4-piperidinol (128):** White solid (50% yield), mp: 97 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.50 (1H, dd,  $J = 1.4$  Hz,  $J = 8.0$  Hz), 7.35 (6H, m), 7.23 (1H, dt,  $J = 1.4$  Hz,  $J = 7.3$  Hz), 7.05 (1H, dd,  $J = 1.6$  Hz,  $J = 7.4$  Hz), 2.79 (2H, m, bd like,  $J = 12.0$  Hz), 2.51 (2H, dt,  $J = 2.7$  Hz,  $J = 12.2$  Hz), 2.10 (2H, dt,  $J = 4.7$  Hz,  $J = 13.2$  Hz), 1.78 (2H, dq,  $J = 2.4$  Hz,  $J = 14.0$  Hz), 1.55 (1H, m), 1.49 (1H, s), 0.39 (4H, m).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  145.2, 144.0, 140.6, 132.5, 129.4, 128.0, 127.4, 127.1, 126.1, 125.8, 73.4, 49.3, 38.9, 38.4, 5.9. GC ( $t_R$  11.41 min)-EIMS,  $m/z$ , (rel intensities) 293 (10%), 264 (19), 209 (5), 181 (22), 152 (34), 112 (11), 101 (52), 82 (100), 68 (59). UV (MeOH, nm) 213, 218, 264. Anal. Calcd. ( $\text{C}_{20}\text{H}_{23}\text{NO}$ ): C, 81.87; H, 7.90; N, 4.77. Found: C, 81.77; H, 7.87; N, 4.75.

**General procedure for the synthesis of tetrahydropyridine oxalate salts (131 - 140).** Piperidinols (2.1 mmol) were dehydrated by stirring with AcOH/HCl 3:1 (40 mL) at reflux for 24 h. After cooling, the reaction mixture was slowly basified to pH 9 using 40% NaOH and extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The crude extract was purified by silica gel chromatography to

yield the pure tetrahydropyridine which was crystallized as its oxalate salt by addition of oxalic acid in Et<sub>2</sub>O. The product was recrystallized from the appropriate solvent.

**Oxalate salt of 1-methyl-4-(4-phenyl)phenyl-1,2,3,6-tetrahydropyridine (131):** Yellow solid recrystallized from isopropanol (87% yield), mp: 233-234 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.68 (4H, m), 7.57 (2H, m), 7.46 (2H, t, *J* = 7.1 Hz), 7.37 (1H, t, *J* = 7.2 Hz), 6.26 (1H, s), 3.79 (2H, bs), 3.34 (2H, t, *J* = 5.9 Hz), 2.88 (3H, s), 2.49 (2H, d, *J* = 5.9 Hz). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 162.1, 139.9, 139.7, 137.9, 133.8, 129.4, 128.1, 127.3, 127.0, 125.8, 118.2, 52.3, 50.4, 42.6, 24.3. GC (t<sub>R</sub> 10.12 min)-EIMS, *m/z*, (rel intensities) 249 (100%), 248 (65), 220 (17), 191 (22), 167 (17), 152 (11), 115 (4), 96 (41). UV (nm, MeOH) 230, 283. Anal. Calcd. (C<sub>20</sub>H<sub>21</sub>NO<sub>4</sub>): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.52; H, 6.31; N, 4.10.

**Oxalate salt of 1-methyl-4-(3-phenyl)phenyl-1,2,3,6-tetrahydropyridine (132):** White solid recrystallized from MeOH/Et<sub>2</sub>O (58% yield), mp: 192-193 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.67 (3H, m), 7.59 (1H, m), 7.44 (5H, m), 6.30 (1H, bs), 3.77 (2H, d, *J* = 2.7 Hz), 3.33 (2H, t, *J* = 5.8 Hz), 2.80 (3H, s), 2.49 (2H, m). <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 160.6, 140.1, 139.8, 134.4, 131.8, 128.9, 128.6, 127.2, 126.7, 126.6, 123.8, 123.6, 115.8, 52.1, 50.7, 41.5, 24.4. GC (t<sub>R</sub> 9.94 min)-EIMS, *m/z*, (rel intensities) 249 (100%), 248 (59), 205 (15), 191 (24), 165 (17), 152 (13), 115 (5), 96 (57). UV (nm, MeOH) 233, 272. Anal. Calcd. (C<sub>20</sub>H<sub>21</sub>NO<sub>4</sub>): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.52; H, 6.33; N, 4.06.

**Oxalate salt of 1-methyl-4-(2-phenyl)phenyl-1,2,3,6-tetrahydropyridine (133):** White solid recrystallized from MeOH/Et<sub>2</sub>O (69% yield), mp: 187-188 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.35 (9H, m), 5.62 (1H, s), 3.62 (2H, bs), 3.02 (2H, t, *J* = 5.7 Hz), 2.69 (3H, s), 2.50 (2H, bs). <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 163.9, 140.8, 140.2, 139.1, 138.2, 130.1, 128.9, 128.5, 128.3, 128.1, 127.4, 127.1, 119.2, 51.9, 50.3, 41.3, 25.9. GC (t<sub>R</sub> 8.83 min)-EIMS, *m/z*, (rel intensities) 249 (48%), 248 (46), 205 (20), 191 (39), 178 (43), 152 (13), 115 (3), 96 (59), 58 (100). UV (nm, MeOH) 237, 270. Anal. Calcd. (C<sub>20</sub>H<sub>21</sub>NO<sub>4</sub>): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.74; H, 6.23; N, 4.10.

**Oxalate salt of 1-cyclopropyl-4-(1-naphthyl)-1,2,3,6-tetrahydropyridine (139):** The product was recrystallized from MeOH (dehydration 47% yield, recrystallization 75% yield), mp: 143-144 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.55 (2H, m), 7.46 (1H, d, *J* = 7.0 Hz), 7.09 (3H, m), 6.91 (1H, d, *J* = 7.0 Hz), 5.32 (1H, bs), 3.40 (2H, bs), 3.00 (2H, bs), 2.24 (2H, bs), 2.10 (1H, m), 0.52 (2H, m), 0.35 (2H, m). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 164.1, 140.3, 135.9, 133.8, 131.0, 128.8, 127.9, 126.7, 126.4, 126.0, 125.7, 125.3, 122.4, 51.6, 50.0, 38.5, 29.5, 4.7. GC (t<sub>R</sub> 11.46 min)-EIMS, *m/z*, (rel intensities) 249 (72%), 234 (100), 206 (9), 192 (22), 178 (35), 165 (50), 152 (20), 115 (4), 68 (7). UV (nm, MeOH) 221, 280. Anal. Calcd. (C<sub>20</sub>H<sub>23</sub>NO<sub>4</sub>): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.62; H, 6.31; N, 4.10.

**Oxalate salt of 1-cyclopropyl-4-(2-naphthyl)-1,2,3,6-tetrahydropyridine (140):** The product was recrystallized from MeOH (dehydration 52% yield, recrystallization 97% yield), mp: 192 °C. <sup>1</sup>H NMR

(DMSO- $d_6$ )  $\delta$  7.60 (4H, m), 7.40 (1H, dd,  $J = 1.7$  Hz,  $J = 8.7$  Hz), 7.19 (2H, m), 6.05 (1H, bs), 3.47 (2H, d,  $J = 1.1$  Hz), 3.03 (2H, t,  $J = 5.9$  Hz), 2.50 (2H, bs), 2.20 (1H, m), 0.52 (2H, m), 0.40 (2H, m).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  163.4, 136.2, 133.8, 133.0, 132.2, 128.1, 127.9, 127.3, 126.3, 123.2, 123.0, 119.3, 51.4, 49.3, 37.7, 25.0, 4.2. GC ( $t_R$  11.50 min)-EIMS,  $m/z$ , (rel intensities) 249 (59%), 234 (100), 206 (9), 178 (46), 165 (57), 152 (25), 115 (11), 89 (8), 68 (11), 54 (26). UV (nm, MeOH) 241, 247, 274, 282, 297. Anal. Calcd. ( $\text{C}_{20}\text{H}_{23}\text{NO}_4$ ): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.71; H, 6.19; N, 4.05.

**Oxalate salt of 1-cyclopropyl-4-(4-phenyl)phenyl-1,2,3,6-tetrahydropyridine (136):** White solid (dehydration 99% yield, recrystallization from MeOH 83% yield), mp: 213-214 °C, decomposition.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.67 (4H, m), 7.54 (2H, m), 7.46 (2H, tt,  $J = 1.4$  Hz,  $J = 7.1$  Hz), 7.36 (1H, tt,  $J = 1.3$  Hz,  $J = 7.2$  Hz), 6.24 (1H, m), 3.63 (2H, d,  $J = 2.6$  Hz), 3.21 (2H, t,  $J = 5.9$  Hz), 2.67 (2H, bs), 2.35 (1H, m), 0.66 (4H, m).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  162.7, 139.5, 139.3, 138.0, 133.7, 129.0, 127.6, 126.7, 126.5, 125.3, 118.3, 51.3, 49.4, 37.8, 24.8, 4.2. GC ( $t_R$  12.45 min)-EIMS,  $m/z$ , (rel intensities) 275 (48%), 260 (100), 203 (18), 191 (35), 178 (31), 165 (30), 152 (20), 115 (18), 68 (35), 54 (47). UV (nm, MeOH) 209, 279. Anal. Calcd. ( $\text{C}_{22}\text{H}_{23}\text{NO}_4$ ): C, 72.31; H, 6.34; N, 3.38. Found: C, 72.15; H, 6.41; N, 3.78.

**Oxalate salt of 1-cyclopropyl-4-(3-phenyl)phenyl-1,2,3,6-tetrahydropyridine (137):** White solid (dehydration 98% yield, recrystallization from MeOH 67% yield), mp: 169-170 °C.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.69 (3H, m), 7.56 (1H, m), 7.46 (4H, m), 7.36 (1H, tt,  $J = 1.3$  Hz,  $J = 7.2$  Hz),

6.27 (1H, m), 3.69 (2H, d,  $J = 2.7$  Hz), 3.23 (2H, t,  $J = 5.8$  Hz), 2.71 (2H, bs), 2.41 (1H, m), 0.72 (2H, m), 0.66 (2H, m).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  163.6, 140.5, 140.1, 139.9, 134.1, 129.1, 128.9, 127.6, 126.8, 126.0, 123.9, 123.2, 118.9, 51.3, 49.4, 37.7, 25.0, 4.2. GC ( $t_R$  12.06 min)-EIMS,  $m/z$ , (rel intensities) 275 (48%), 260 (100), 203 (20), 191 (41), 178 (34), 165 (40), 152 (25), 115 (20), 77 (23), 68 (64), 54 (76). UV (nm, MeOH) 205, 209, 245. Anal. Calcd. ( $\text{C}_{22}\text{H}_{23}\text{NO}_4 \cdot 0.153 \text{H}_2\text{O}$ ): C, 71.69; H, 6.33; N, 3.80. Found: C, 71.71; H, 6.41; N, 3.78.

**Oxalate salt of 1-cyclopropyl-4-(2-phenyl)phenyl-1,2,3,6-tetrahydropyridine (138):** White solid (dehydration 99% yield, recrystallization from MeOH 83% yield), mp: 185 °C.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.35 (8H, m), 7.24 (1H, dd,  $J = 2.2$  Hz,  $J = 6.8$  Hz), 5.62 (1H, bs), 3.52 (2H, d,  $J = 2.2$  Hz), 2.89 (2H, t,  $J = 5.7$  Hz), 2.32 (1H, m), 2.02 (2H, bs), 0.65 (2H, m), 0.59 (2H, m).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  163.7, 141.1, 140.2, 139.2, 136.9, 130.0, 129.1, 128.5, 128.4, 127.8, 127.5, 127.1, 121.8, 51.1, 49.0, 37.5, 26.8, 4.1. GC ( $t_R$  10.69 min)-EIMS,  $m/z$ , (rel intensities) 275 (68%), 260 (100), 203 (30), 191 (60), 178 (51), 165 (51), 152 (19), 115 (15), 82 (43), 68 (42), 54 (60). UV (nm, MeOH) 208. Anal. Calcd. ( $\text{C}_{22}\text{H}_{23}\text{NO}_4$ ): C, 72.31; H, 6.34; N, 3.38. Found: C, 72.33; H, 6.38; N, 3.38.

### 9.1.2 1-Methyl C4 hydroxylated tetrahydropyridines

The 1-methyl-4-(4-hydroxyphenyl)-1,2,3,6-tetrahydropyridine (**173**),<sup>197</sup> 1-methyl-4-(3-hydroxyphenyl)-1,2,3,6-tetrahydropyridine (**177**),<sup>274</sup> 1-methyl-4-(4-methoxyphenyl)-1,2,3,6-tetrahydropyridine (**183**),<sup>197</sup> 1-methyl-4-(3-

methoxyphenyl)-1,2,3,6-tetrahydropyridine (**186**)<sup>286,287</sup>, 1-methyl-4-(2-methoxyphenyl)-1,2,3,6-tetrahydropyridine (**189**),<sup>274</sup> 1-methyl-4-(2-hydroxymethylphenyl)-1,2,3,6-tetrahydropyridine (**197**),<sup>279</sup> and 1-methyl-4-(5-methoxyindol-3-yl)-1,2,3,6-tetrahydropyridine (**204**),<sup>250,288</sup> were prepared according to literature methods. Physical data were consistent with the expected structure for all compounds.

**General procedure for the synthesis of tetrahydropyridine oxalate salts (177,180, 186, 189, 193, 201).** The lithiated reagents (1 equiv.) of **175, 178, 184, 187, 191, and 198** were added to 1-methyl-4-piperidone (**119**) in anhydrous THF (15ml/mmol compound) at -78 °C. After 5-18 hrs of reaction at -78 °C warming to 25 °C, water was added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. After drying over anhydrous sodium sulfate, the organic solvent was evaporated under reduced pressure to yield the piperidinols **176, 179, 185, 188, 192, 199** which were directly dehydrated by stirring with AcOH/HCl 3:1 (40 mL) at reflux for 24 h with the exception of **199**. After cooling, the reaction mixture was slowly basified to pH 9 using 40% NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude extract was purified by silica gel chromatography to yield the pure tetrahydropyridine which was crystallized as there oxalate salts by addition of oxalic acid in Et<sub>2</sub>O. The product was recrystallized from the appropriate solvent. The piperidinol intermediate **199** was derivatized using ethyl chloroformate to yield **200** which was thermally dehydrated according to the reported procedure<sup>280</sup> to yield the tetrahydropyridine **201**.

**Oxalate salt of 1-methyl-4-(3-hydroxyphenyl)-1,2,3,6-tetrahydropyridine (177):** Light brown solid recrystallized from MeOH (80% yield).  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ )  $\delta$  7.15 (1H, t,  $J = 7.9$  Hz), 6.88 (1H, ddd,  $J = 7.7$  Hz,  $J = 1.0$  Hz,  $J = 1.6$  Hz), 6.85 (1H, t,  $J = 2.2$  Hz), 6.73 (1H, ddd,  $J = 8.0$  Hz,  $J = 2.4$  Hz,  $J = 1.0$  Hz), 6.05 (1H, ddd,  $J = 1.9$  Hz,  $J = 1.9$  Hz,  $J = 3.5$  Hz), 3.72 (2H, m), 3.29 (2H, t,  $J = 6.1$  Hz), 2.78 (3H, s), 2.70 (2H, m).  $^{13}\text{C}$  NMR ( $\text{DMSO-}d_6$ )  $\delta$  164.8, 157.6, 139.8, 133.9, 129.5, 116.5, 115.5, 114.9, 111.7, 51.3, 49.6, 41.7, 23.9. GC ( $t_R$  6.83 min)-EIMS,  $m/z$ , (rel intensities) 189 (30%), 147 (100), 117 (10), 73 (20). UV (nm, MeOH) 213, 247, 291. Anal. Calcd. ( $\text{C}_{14}\text{H}_{17}\text{NO}_5$ ): C, 60.20; H, 6.14; N, 5.02. Found: C, 60.34; H, 6.19; N, 4.97.

**Oxalate salt of 1-methyl-4-(2-hydroxyphenyl)-1,2,3,6-tetrahydropyridine (180):** White solid recrystallized from MeOH (41% yield), mp: 172-173 °C.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.17 (1H, t,  $J = 8.0$  Hz), 6.92 (1H, dq  $J = 8.0$  Hz,  $J = 2.0$  Hz,  $J = 0.92$  Hz), 6.86 (1H, t,  $J = 2.0$  Hz), 6.72 (1H, dd,  $J = 2.0$  Hz,  $J = 0.92$  Hz), 6.07 (1H, bs), 3.90 (2H, bs), 3.51 (2H, bs), 2.98 (3H, s), 2.85 (2H, bs).  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  165.1, 136.1, 129.4, 115.8, 114.9, 114.6, 111.9, 105.8, 74.0, 52.0, 50.6, 41.2, 24.2. GC ( $t_R$  6.83 min)-EIMS,  $m/z$ , (rel intensities) 189 (100%), 188 (35), 220 (17), 160 (13), 145 (39), 131 (81), 115 (23), 96 (42), 83 (92), 82 (36), 51 (21). UV (nm, MeOH) 206, 262. Anal. Calcd. ( $\text{C}_{14}\text{H}_{17}\text{NO}_5$ ): C, 60.20; H, 6.14; N, 5.02. Found: C, 60.13; H, 6.16; N, 5.03.

**Oxalate salt of 1-methyl-4-(3-methoxyphenyl)-1,2,3,6-tetrahydropyridine (186):** White solid recrystallized from MeOH/ $\text{Et}_2\text{O}$  (65% yield), mp: 147 °C.  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ )  $\delta$  7.28 (1H, t,  $J = 8.0$  Hz), 7.08 (1H, d,  $J = 7.7$  Hz), 6.99 (1H, t,  $J = 2.2$ ), 6.88 (1H, dd,  $J = 2.4$  Hz,  $J = 8.0$ ), 6.04 (1H, s),

3.79 (2H, bs), 3.77 (3H, s), 3.34 (2H, bs), 2.81 (3H, s), 2.73 (2H, bs).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  165.1, 159.5, 140.0, 133.6, 129.6, 117.2, 117.1, 113.4, 110.5, 55.1, 51.2, 49.5, 41.6, 23.8. GC ( $t_R$  7.75 min)-EIMS,  $m/z$ , (rel intensities) 203 (100%), 202 (63), 159 (20), 145 (24), 115 (20), 96 (59), 82 (15), 51 (11). UV (nm, MeOH) 213, 246, 288. Anal. Calcd. ( $\text{C}_{15}\text{H}_{19}\text{NO}_5$ ): C, 61.42; H, 6.53; N, 4.78. Found: C, 61.28; H, 6.49; N, 4.73.

**Oxalate salt of 1-methyl-4-(2-methoxyphenyl)-1,2,3,6-tetrahydropyridine (189):** White solid recrystallized from MeOH/Et<sub>2</sub>O (70% yield), mp: 196-197 °C.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  7.22 (1H, m), 7.17 (1H, dd,  $J = 1.7$  Hz,  $J = 8.0$  Hz), 6.94 (1H, dd,  $J = 1.1$  Hz,  $J = 8.0$  Hz), 6.87 (1H, td,  $J = 1.1$  Hz,  $J = 1.7$  Hz,  $J = 14.8$  Hz), 5.79 (1H, s), 3.79 (3H, s), 2.94 (2H, m), 2.49 (2H, m), 2.41 (2H, bs), 2.24 (3H, s).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  162.8, 137.3, 130.0, 116.1, 115.3, 115.0, 112.2, 107.1, 74.6, 52.0, 51.3, 50.9, 42.1, 25.2. GC ( $t_R$  7.02 min)-EIMS,  $m/z$ , (rel intensities) 203 (100%), 188 (19), 159 (15), 145 (38), 115 (44), 96 (56), 82 (35), 51 (25). UV (nm, MeOH) 212, 268. Anal. Calcd. ( $\text{C}_{15}\text{H}_{19}\text{NO}_5$ ): C, 61.42; H, 6.53; N, 4.78. Found: C, 61.14; H, 6.54; N, 4.73.

**Oxalate salt of 1-methyl-4-[(3-hydroxymethyl)phenyl]-1,2,3,6-tetrahydropyridine (193):** Pale yellow solid recrystallized from MeOH (49% yield), mp: 172-173 °C.  $^1\text{H}$  NMR (CD<sub>3</sub>OD)  $\delta$  7.16 - 7.58 (4H, m), 5.61 (1H, s), 4.71 (2H, s), 3.16 (2H, m), 2.87 (2H, t,  $J = 6.1$  Hz), 2.54 (2H, m), 2.37 (3H, s).  $^{13}\text{C}$  NMR (CD<sub>3</sub>OD)  $\delta$  160.4, 141.9, 139.0, 135.9, 128.3, 128.0, 127.4, 127.1, 123.8, 62.6, 54.7, 52.1, 43.6, 27.1. GC ( $t_R$  8.46 min)-EIMS,  $m/z$ , (rel intensities) 203 (78%), 202 (46), 172 (13), 157 (4), 129 (50), 115 (37), 96 (100), 82 (22), 53

(17). UV (nm, MeOH) 210, 264. Anal. Calcd. (C<sub>15</sub>H<sub>19</sub>NO<sub>5</sub>): C, 61.42; H, 6.53; N, 4.78. Found: C, 61.39; H, 6.48; N, 4.77.

**Oxalate salt of 1-methyl-4-(3,4-benzodioxole)-1,2,3,6-tetrahydropyridine (201):** White solid recrystallized from MeOH/Et<sub>2</sub>O (69% yield), mp: 218-219 °C. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 6.99 (1H, d, *J* = 1.8 Hz), 6.94 (1H, dd, *J* = 1.8 Hz, *J* = 8.1 Hz), 6.80 (1H, d, *J* = 8.1 Hz), 5.99 (1H, bs), 5.97 (2H, s), 4.02 (2H, bs), 3.71 (2H, bs), 2.95 (3H, s), 2.80 (2H, bs). <sup>13</sup>C NMR (CD<sub>3</sub>OD) δ 164.0, 148.0, 147.8, 134.9, 132.8, 118.7, 114.1, 107.8, 105.3, 101.4, 54.1, 51.4, 43.0, 28.8. GC (t<sub>R</sub> 8.28 min)-EIMS, *m/z*, (rel intensities) 217 (100%), 216 (70), 188 (33), 136 (43), 116 (80), 115 (89), 96 (93), 77 (43), 63 (67), 51 (63). UV (nm, MeOH) 228, 276. Anal. Calcd. (C<sub>15</sub>H<sub>17</sub>NO<sub>6</sub> · H<sub>2</sub>O): C, 55.38; H, 5.58; N, 4.31. Found: C, 55.37; H, 5.30; N, 4.23.

**Oxalate salt of 1-methyl-4-(5-hydroxyindol-3-yl)-1,2,3,6-tetrahydropyridine (205):** BBr<sub>3</sub> ( 4 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> was added to a solution of **204** in anhydrous CH<sub>2</sub>Cl<sub>2</sub> at -78 °C and kept there for 1 hr. The mixture was warmed to room temperature and stirred for 3 hrs. The mixture was cooled to 0 °C and ice - water was added, followed by NH<sub>4</sub>OH. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated in vacuo. After column chromatography on silica gel (CHCl<sub>3</sub> : 5% MEOH), oxalic acid in Et<sub>2</sub>O was added to yield **205** as a a yellow solid recrystallized from methanol (38% yield), mp: 216 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.31 (1H, s), 7.26 - 7.18 (2H, m), 6.67 (1H, dd, *J* = 2.4 Hz, *J* = 8.7 Hz), 6.04 (1H,bs), 3.49 (2H, bs), 3.06 (2H, t, *J* = 6.0 Hz), 2.78 (2H, bs), 2.62 (3H, s). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 153.9, 132.8,

130.1, 125.6, 124.0, 117.9, 116.0, 112.6, 111.2, 102.7, 56.0, 52.8, 46.4, 29.1. GC ( $t_R$  10.14 min)-EIMS,  $m/z$ , (rel intensities) 228 (100%), 227 (55), 199 (27), 141 (7), 133 (32), 120 (71), 115 (6). UV (nm, MeOH) 286. Anal. Calcd. ( $C_{16}H_{18}N_2O_5$ ): C, 60.37; H, 5.70; N, 8.80. Found: C, 60.31; H, 5.66; N, 8.74.

## 9.2 Enzymology

**Enzyme Isolation.** The isolation and purification of MAO-A from human placenta and MAO-B from beef liver were carried out using the procedures reported by Salach<sup>289</sup> with the following changes. The phospholipase A used in the preparation was obtained commercially from Sigma. We did not subject the MAO-A preparation to the Sephadex purification or the MAO-B preparation to the glucose gradient purification step. In both cases, however, we obtained highly active preparations.

In preliminary studies, solutions of the oxalate salts of the 1-methyl-4-substituted-1,2,3,6-tetrahydropyridine analogs in phosphate buffer (pH = 7.4, 0.5 mM), were treated with 20  $\mu$ L of MAO-A (final concentration 0.16  $\mu$ M) or 5  $\mu$ L of MAO-B (final concentration 0.16  $\mu$ M), and the substrate properties evaluated at 30 °C. The qualitative substrate properties were obtained from a series of UV scans (500-250 nm) vs time over a 15 min - 1 h period for each compound.

**MAO Substrate Studies analogs 131 - 135.** Solutions of the test compounds [final volume of 500  $\mu$ L, final substrate concentration (100-2000  $\mu$ M)] in 10% DMSO sodium phosphate buffer (100 mM, pH = 7.4) were incubated in the presence of 0.16  $\mu$ M MAO-A or 0.08  $\mu$ M MAO-B. The rates of oxidation were obtained by monitoring the increment in the dihydropyridinium

absorbance every 3 sec over a 2 min time period. In the case of the 4- $\alpha$ -naphthyltetrahydropyridine analog (**134**), the  $\lambda$  value monitored was 316 nm and for the 4- $\beta$ -naphthyl analog (**135**)  $\lambda = 328$  nm was monitored. The dihydropyridinium products of the C4 biphenyl analogs **131-133** appear at 322, 340, and 325 nm, respectively. The  $K_m$  and  $V_{max}$  values were calculated from Lineweaver-Burke double reciprocal plots.

**Inactivation studies for 136 - 140.** The inactivation studies on the 1-cyclopropyl-4-substituted-1,2,3,6-tetrahydropyridine analogs were conducted as follows: Standard solutions of the test compounds (ranging from 2000-500  $\mu$ M) in 10% DMSO sodium phosphate buffer (100 mM, pH = 7.4) were prepared. Each solution (50  $\mu$ L) was mixed with 50  $\mu$ L of 0.16  $\mu$ M MAO-A or 0.08  $\mu$ M MAO-B, and the resulting mixture was incubated in a 30 °C water bath. A 10  $\mu$ L aliquot of each incubation mixture was taken at time points between 0 - 20 min and added to a sample cuvette containing 490  $\mu$ L of 1 mM solution of 1-methyl-4-phenoxy-1,2,3,6-tetrahydropyridine in sodium phosphate (pH = 7.4, 100 mM) for the MAO-A studies or 490  $\mu$ L of a 5 mM solution of MPTP in sodium phosphate (pH = 7.4, 100 mM) for the MAO-B studies. The rate of oxidation of 1-methyl-4-phenoxy-1,2,3,6-tetrahydropyridine was determined at 30 °C by monitoring the formation of amino-enone at  $\lambda = 324$  nm<sup>240</sup> and the rate of oxidation of MPTP was obtained by monitoring the increment in the dihydropyridinium metabolite  $\lambda = 343$  nm every 3 sec for 2 min.

**Substrate studies of the hydroxyl MPTP analogs 173, 177, 180, 183, 186, 189, 193, 197, 201, 204, 205, and 230.** All enzyme assays were performed at 30 °C on a Beckman 7400 series spectrophotometer. In preliminary experiments, the potential MAO-A and MAO-B substrate

properties of each test compound (0.5-2 mM) were examined by recording repeated scans (500 to 250 nm) in the presence of 0.08  $\mu\text{M}$  MAO-B or 0.16  $\mu\text{M}$  of MAO-A. For kinetic analyses, initial rates of oxidation of the tetrahydropyridine derivatives were determined at four concentrations. Solutions (ranging from 2 - 0.125 mM) of the substrates were prepared in 100 mM sodium phosphate buffer (pH 7.4). A 490-495  $\mu\text{L}$  aliquot of each solution (pre-equilibrated to 30 °C) was placed in a sample cuvette. An aliquot of the MAO-A or MAO-B preparation (final concentrations of 0.08-0.16  $\mu\text{M}$ ) was added to the substrate solution. The initial rates of oxidation of each substrate were estimated by monitoring the absorbance of the corresponding dihydropyridinium metabolite every 3 s for 2 min. The  $K_m$  and  $V_{max}$  values were calculated from Lineweaver-Burke double reciprocal plots.

### 9.3 Toxicity studies and in vivo 7-nitroindazole experimental

**Materials.** Acetonitrile (EM Scientific, Gibbstown, NJ), methanol, glacial acetic acid and trichloroacetic acid (TCA, Fisher Scientific Products, Fair Lawn, NJ) and triethylamine (TEA, Aldrich Chemical Co., Milwaukee, WI) were HPLC grade. Sterile saline (Lyphomed, Deerfield, IL), peanut oil (Kroger's Food Store, Blacksburg, VA), dopamine.HCl (Sigma Chemical Co., St Louis, MO), 3,4-dihydroxybenzylamine·HBr (DHBA, Aldrich), disodium ethylenediaminetetraacetic acid dihydrate (Lancaster Synthesis Inc. Windham, NH), sodium 1-octanesulfonic acid (Eastman Kodak Co. Rochester NY), sodiumdihydrophosphate (enzyme grade, Fisher Scientific Products, Fair Lawn, NJ) 7-NI, 2,3-dihydroxyphenylacetic acid (DOPAC) and R-deprenyl HCl

(Research Biochemicals International, Natick, MA) were purchased as indicated. MPTP·HCl, MPDP<sup>+</sup>·ClO<sub>4</sub><sup>-</sup>, MPP<sup>+</sup>·I<sup>-</sup> and 1-cyclopropyl-4-(1-methylpyrrol-2-yl)pyridinium iodide (internal standard, IS) were synthesized as described.<sup>153</sup>

**HPLC (LC-EC) Instrumentation and Analysis for 133, 147, 156, 159, 162, and 7-NI.** The HPLC system used consisted of a BAS PM-80 pump, a BAS LC-4C amperometric detector, a rheodyne 7125 injector, a BAS phase II ODS column (3 mm 100 x 3.2 mm) and a Kipp & zonen BD 41 recorder. The mobile phase<sup>261</sup> contained 5.5% methanol, 1.5% acetonitrile (v:v), 200 mM sodium dihydrophosphate, 1.0 mM sodium 1-octosulfonic acid, 20 mM disodium ethyleendiaminotetraacetic acid in milli Q water. The flow rate was 0.4 mL/min. A calibration curve was made using three standards containing: A) 4.54 mM DHBA, 1.32 mM dopamine, 2.97 mM DOPAC; B) 4.54 mM DHBA, 3.96 mM dopamine, 1.49 mM DOPAC; C) 4.54 DHBA, 7.91 mM dopamine, 7.43 mM DOPAC. Quantitative estimations were calculated by comparing the peak-height ratios of the analyte/IS of the sample versus the peak-height ratios of the calibration curve.

**HPLC (LC-DA) Instrumentation and Analyses for 7-NI Experiments.** HPLC analyses were performed on a Hewlett Packard 1100 HPLC system equipped with a UV/VIS diode array detector, a Rheodyne 7725I injector, a Zorbax SB-C8 analytical column (4.6 x 250 mm, 5 μm) and an in-line pre-column filter (2 μm, Upchurch Scientific Inc., Oak Harbor, WA). The mobile phase (pH 4.70) consisted of 70% milliQ H<sub>2</sub>O containing 0.6% glacial CH<sub>3</sub>COOH (v:v) [solvent A] plus 1.0% TEA (v:v) and 30% CH<sub>3</sub>CN. For

quantitative analyses (flow rate = 1 mL/min) the compounds were monitored at the following wavelengths: 244 nm (MPTP), 285 nm (MPP<sup>+</sup>), 345 nm (MPDP<sup>+</sup>), 360 nm (7-NI) and 390 nm (IS). The following calibration standards were prepared in 90% solvent A:10% CH<sub>3</sub>CN: MPTP/MPDP<sup>+</sup>/MPP<sup>+</sup>/7-NI (a) 2.40/1.85/1.70/6.15 μM; (b) 0.96/0.74/0.68/2.46 μM; and (c) 0.48/0.37/0.34/1.23 μM. The concentration of the IS in all three standards was 0.060 μM. Each of the 3 calibration standards was injected in triplicate (100 μL) and the peak-height ratios of the analytes/IS were plotted vs pmoles of analytes. Quantitative estimations were calculated by comparing the peak-height ratios of the analyte/IS of the sample vs the peak-height ratios of the calibration curves.

**Animal Treatment in In Vivo Studies.** Male C57BL/6 mice (25–30 g; 7–8 months of age) were housed one per cage in a temperature controlled room with free access to food and water on a 12 h day/night cycle. The MPTP·HCl solutions (10–40 mM) were made in sterile saline. Suspensions of 7-NI (24 μmol/mL) in peanut oil were stirred for 24–48 h at room temperature and then were sonicated for 2 h at ambient temperature just prior to use. This yielded a clear yellow solution containing a few particles of solid which remained at the bottom of the flask.

## Chapter 10. References

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## **Vita**

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