

## Supporting Information

# Novel Pyridylmethyamines as Highly Selective 5-HT<sub>1A</sub> Superagonists

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## Experimental and Spectroscopic Data of Non-Key Compounds:

**N-[1-(Biphenyl-4-ylcarbonyl)-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8aa).** Synthesis was performed according to general procedure 1 employing 4-biphenylcarboxylic acid (12.7 mg, 0.064 mmol) yielding **8aa** (19.6 mg; 82 %) as a pale yellow oil. IR 3401, 2927, 1631, 1438, 1280, 1110, 971, 852, 752, 698  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.55-1.88 (m, 2H), 1.91-2.11 (m, 2H), 2.33 (s, 3H), 2.57 (d,  $J = 20.0$  Hz, 2H), 3.10-3.55 (m, 2H), 3.61-3.87 (m, 1H), 4.04 (s, 2H), 4.38-4.69 (m, 1H), 7.21 (d,  $J = 7.9$  Hz, 1H), 7.34-7.41 (m, 1H), 7.45-7.53 (m, 5H), 7.56-7.67 (m, 4H), 8.35-8.42 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 33.2 (2C), 38.1, 43.18, 54.6, 56.7 (d,  $J = 21.8$  Hz), 94.3 (d,  $J = 172.4$  Hz), 121.8, 127.1 (2C), 127.2 (2C), 127.5 (2C), 127.8, 128.9 (2C), 131.8, 134.6, 137.3, 140.3, 142.7, 149.6, 155.3, 170.3. APCI-MS  $m/z$  418  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  417.2220. HPLC/MS system A purity 97 % ( $t_R = 16.3$  min).

**N-[1-(Biphenyl-2-ylcarbonyl)-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ab).** Synthesis was performed according to general procedure 1 employing 2-biphenylcarboxylic acid (12.7 mg, 0.064 mmol) yielding **8ab** (18.5 mg; 78 %) as a pale yellow oil. IR 2923, 2873, 1627, 1446, 1373, 1446, 1099, 971, 779, 744, 701  $\text{cm}^{-1}$ . APCI-MS  $m/z$  418  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  417.2216. HPLC/MS system A purity 98 % ( $t_R = 13.2$  min).

**N-[1-(Biphenyl-3-ylcarbonyl)-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ac).** Synthesis was performed according to general procedure 1 employing 3-biphenylcarboxylic acid (12.7 mg, 0.064 mmol) yielding **8ac** (6.9 mg; 29 %) as a pale yellow oil.  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.48-1.72 (m, 2H), 1.86-2.21 (m, 2H), 2.32 (s, 3H), 2.80 (d,  $J = 20.2$  Hz, 2H), 3.11-3.53 (m, 2H), 3.59-3.80 (m, 1H), 3.90 (s, 2H), 4.47-4.67 (m, 1H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.33-7.41 (m, 2H), 7.42-7.53 (m, 4H), 7.55-7.68 (m, 4H), 8.36-8.41 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  (ppm) 18.1, 32.8, 33.7, 38.0, 43.6, 55.1, 57.0 (d,  $J = 22.0$  Hz), 94.5 (d,  $J = 172.3$  Hz), 121.7, 125.5, 125.6, 127.1 (2C), 127.7, 128.4, 128.9 (2C), 129.0, 131.4, 136.5, 137.1, 140.3, 141.6, 149.7, 156.5, 170.3. APCI-MS  $m/z$  418  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  417.2217. HPLC/MS system A purity 93 % ( $t_R = 17.0$  min).

**N-[4-Fluoro-1-(2-naphthoyl)piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ad).** Synthesis was performed according to general procedure 1 employing naphthalene-2-carboxylic acid (11.0 mg, 0.064 mmol) yielding **8ad** (16.1 mg; 72 %) as a pale yellow oil. IR 3401, 1923, 2360, 1631, 1477, 1434, 1280, 1060, 752, 671  $\text{cm}^{-1}$ . IR 3401, 1923, 2360, 1631, 1477, 1434, 1280, 1060, 752, 671  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.56-1.84 (m, 2H), 1.90-2.18 (m, 2H), 2.32 (s, 3H), 2.83 (d,  $J = 20.2$  Hz, 2H), 3.08-3.49 (m, 2H), 3.59-3.80 (m, 1H), 3.94 (s, 2H), 4.41-4.85 (m, 1H), 7.20 (d,  $J = 8.0$  Hz, 1H), 7.45 (dd,  $J = 7.8$  Hz, 1.7 Hz, 1H), 7.47 (dd,  $J = 8.5$  Hz, 1.7 Hz, 1H), 7.50-7.56 (m, 2H), 7.81-7.91 (m, 4H), 8.35-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 33.3 (2C), 38.1, 43.7, 54.9, 56.8 (d,  $J = 21.8$  Hz), 94.4 (d,  $J = 171.7$  Hz), 121.8, 124.2, 126.7, 126.7, 127.1, 127.8, 128.3, 128.4, 131.6, 132.7, 133.2, 133.7, 137.2, 149.6, 155.9, 170.5. APCI-MS  $m/z$  392  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  391.2060. HPLC/MS system A purity 97 % ( $t_R = 15.9$  min).

**N-[4-Fluoro-1-(1,2,3,4-tetrahydronaphth-2-ylcarbonyl)piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ae).** Synthesis was performed according to general procedure 1 employing (R,S)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (11.3 mg, 0.064 mmol) yielding **8ae** (19.2 mg; 85 %) as a pale yellow oil. IR 3567, 2927, 1635, 1450, 1295, 1234, 1060, 782, 725  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.55-1.72 (m, 2H), 1.89-1.96 (m, 1H), 1.95-2.04 (m, 2H), 2.06-2.13 (m, 1H), 2.33 (s, 3H), 2.75-3.15 (m, 8H),

3.45-3.48 (m, 1H), 3.78-3.86 (m, 1H), 4.00 (s, 2H), 4.47-4.54 (m, 1H), 7.07-7.15 (m, 4H), 7.21 (d,  $J = 7.9$  Hz, 1H), 7.47 (dd,  $J = 7.7$  Hz,  $J = 1.7$  Hz, 1H), 8.36-8.42 (m, 1H). APCI-MS  $m/z$  396  $[M+1]^+$ . HR-EIMS  $m/z$  395.2372.

**N-[4-Fluoro-1-[tricyclo[8.2.2.2<sup>4,7</sup>]]hexadeca-1(12),4,6,10,13,15-hexaen-5-ylcarbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8af).** Synthesis was performed according to general procedure 1 employing tricyclo[8.2.2.2<sup>4,7</sup>]]hexadeca-1(12),4,6,10,13,15-hexaen-5-carboxylic acid (16.2 mg, 0.064 mmol) yielding **8af** (24.8 mg; 92 %) as a pale yellow oil. IR 3729, 3625, 3328, 2927, 2854, 1631, 1430, 782, 728  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.28-1.81 (m, 4H), 2.31 (s, 3H), 2.73 (d,  $J = 20.2$  Hz, 2H), 2.86-3.02 (m, 4H), 3.04-3.31 (m, 7H), 3.88 (s, 2H), 4.48-4.64 (m, 1H), 6.34-6.45 (m, 2H), 6.45-6.60 (m, 4H), 7.02-7.13 (m, 1H), 7.18 (d,  $J = 7.9$  Hz, 1H), 7.44 (dd,  $J = 7.7$  Hz,  $J = 1.3$  Hz, 1H), 8.33-8.40 (m, 1H). APCI-MS  $m/z$  472  $[M+1]^+$ . HPLC/MS system A purity 92 % ( $t_R = 18.0$  min).

**N-[1-(Ferrocenylcarbonyl)-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ag).** Synthesis was performed according to general procedure 1 employing ferrocene carboxylic acid (36.8 mg, 0.160 mmol) yielding **8ag** (36.3 mg; 56 %) as an orange oil. IR 3629, 3093, 2923, 2337, 1612, 1415, 1106, 782, 732, 674  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.52-1.74 (m, 2H), 1.95-2.07 (m, 2H), 2.32 (s, 3H), 2.78 (d,  $J = 20.4$  Hz, 2H), 3.14-3.38 (m, 2H), 3.91 (s, 2H), 4.20-4.25 (m, 5H), 4.27-4.41 (m, 4H), 4.50-4.58 (m, 2H), 7.20 (d,  $J = 8.0$  Hz, 1H), 7.45 (dd, 1H), 8.36-8.41 (m, 1H). APCI-MS  $m/z$  450  $[M+1]^+$ . HR-EIMS  $m/z$  449.1569. HPLC/MS system A purity 95 % ( $t_R = 16.0$  min).

**N-[1-(1-Adamantylcarbonyl)-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ah).** Synthesis was performed according to general procedure 1 employing adamantane-1-carboxylic acid (28.8 mg, 0.160 mmol) yielding 16.4 mg (29 %) of **8ah** as a pale yellow oil. IR 3814, 3332, 2908, 2850, 1623, 1450, 1415, 1369, 1261, 1226, 975, 821, 725, 644  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.48-1.70 (m, 2H), 1.76-2.09 (m, 17H), 2.32 (s, 3H), 2.76 (d,  $J = 20.4$  Hz, 2H), 3.11-3.24 (m, 2H), 3.90 (s, 2H), 4.27-4.36 (m, 2H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.46 (dd, 1H), 8.36-8.40 (m, 1H). APCI-MS  $m/z$  400  $[M+1]^+$ . HR-EIMS  $m/z$  399.2687. HPLC/MS system A purity 92 % ( $t_R = 17.1$  min).

**N-[1-(Bicyclo[3.3.1]non-1-ylcarbonyl)-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ai).** Synthesis was performed according to general procedure 1 employing bicyclo[3.3.1]nonan-1-carboxylic acid (10.8 mg, 0.064 mmol) yielding **8ai** (8.1 mg; 67 %) as a pale yellow oil. IR 3328, 2923, 1627, 1415, 1238, 971  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.73-2.16 (m, 19H), 2.32 (s, 3H), 2.76 (d,  $J = 20.8$  Hz, 2H), 3.07-3.20 (m, 2H), 3.89 (s, 2H), 4.12-4.23 (m, 2H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.46 (dd,  $J = 7.8$  Hz, 1.7 Hz, 1H), 8.36-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 20.4, 27.0, 29.6, 33.2, 33.4 (d,  $J = 21.8$  Hz), 33.6, 35.0, 40.7, 41.1, 55.2, 57.1 (d,  $J = 22.5$  Hz), 94.7 (d,  $J = 171.1$  Hz), 121.7, 131.4, 137.0, 149.7, 156.7, 177.5. APCI-MS  $m/z$  388  $[M+1]^+$ . HR-EIMS  $m/z$  387.2686. HPLC/MS system A purity 95 % ( $t_R = 16.9$  min).

**N-[4-Fluoro-1-(hexahydro-2,5-methanopentalen-3a(1H)-ylcarbonyl)piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8aj).** Synthesis was performed according to general procedure 1 employing noradamantan-3-carboxylic acid (10.6 mg, 0.064 mmol) yielding **8aj** (18.8 mg; 86 %) as a pale yellow oil. IR 3509, 3328, 2927, 2869, 1623, 1423, 1276, 1241, 1120  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.49-2.14 (m, 15H), 2.25-2.32 (m, 2H), 2.32 (s, 3H), 2.77 (d,  $J = 20.4$  Hz, 2H), 3.00-3.32 (m, 2H), 3.90 (s, 2H), 3.97-4.54 (m, 2H), 7.20 (d,  $J = 7.7$  Hz, 1H), 7.46 (dd,  $J = 7.8$  Hz, 1.7 Hz, 1H), 8.34-8.40 (m, 1H).  $^{13}\text{C}$

NMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  (ppm) 18.1, 33.3, 33.6, 35.2, 37.2, 40.2, 42.7, 43.8, 48.3, 55.2 (d,  $J$  = 3.3 Hz), 56.9, 57.1 (d,  $J$  = 21.8 Hz), 94.0 (d,  $J$  = 171.1 Hz), 121.7, 131.4, 137.0, 149.7, 156.6, 175.3. APCI-MS  $m/z$  386 [M+1]<sup>+</sup>. HR-EIMS  $m/z$  385.2529. HPLC/MS system A purity 95 % ( $t_R$  = 16.2 min).

**N-[1-[(3-Chloro-1-adamantyl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ak).** Synthesis was performed according to general procedure 1 employing 3-chloroadamantan-1-carboxylic acid (13.7 mg, 0.064 mmol) yielding **8ak** (14.8 mg; 60 %) as a pale yellow oil. IR 3328, 2919, 2857, 1623, 1415, 1265, 1130, 971, 871, 840, 717 cm<sup>-1</sup>. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 1.62-1.70 (m, 2H), 1.70-1.85 (m, 2H), 1.90-2.30 (m, 12H), 2.33 (s, 3H), 2.34-2.40 (s, 2H), 2.76 (d,  $J$  = 20.4 Hz, 2H), 3.12-3.24 (m, 2H), 3.89 (s, 2H), 4.22-4.32 (m, 2H), 7.20 (d,  $J$  = 7.9 Hz, 1H), 7.46 (dd,  $J$  = 7.9 Hz,  $J$  = 1.8 Hz, 1H), 8.31-8.41 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  (ppm) 18.1, 31.4, 33.7 (d,  $J$  = 21.8 Hz), 34.6, 37.4, 41.3, 45.6, 46.8, 48.8, 55.2, 57.0 (d,  $J$  = 22.5 Hz), 67.7, 94.6 (d,  $J$  = 171.7 Hz), 121.7, 131.4, 137.0, 149.7, 156.6, 173.6. APCI-MS  $m/z$  334 [M+1]<sup>+</sup>. HR-EIMS  $m/z$  433.2296. HPLC/MS system A purity 98 % ( $t_R$  = 17.3 min).

**N-[1-[(3-Bromo-1-adamantyl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8al).** Synthesis was performed according to general procedure 1 employing 3-bromoadamantan-1-carboxylic acid (16.6 mg, 0.064 mmol) yielding **8al** (18.4 mg; 67 %) as a pale yellow oil. IR 3324, 2920, 2858, 1623, 1450, 1415 cm<sup>-1</sup>. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 1.67-1.73 (m, 2H), 1.73-1.83 (m, 2H), 1.92-2.07 (m, 6H), 2.19-2.25 (m, 2H), 2.28-2.39 (m, 7H), 2.57 (s, 2H), 2.76 (d,  $J$  = 20.4 Hz, 2H), 3.12-3.26 (m, 2H), 3.89 (s, 2H), 4.21-4.33 (m, 2H), 7.20 (d,  $J$  = 7.9 Hz, 1H), 7.45 (dd,  $J$  = 7.8 Hz,  $J$  = 1.7 Hz, 1H), 8.36-8.40 (m, 1H). APCI-MS  $m/z$  478 [M+1]<sup>+</sup>. HPLC/MS system A purity 99 % ( $t_R$  = 17.6 min).

**N-[1-[(3-Ethyl-1-adamantyl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8am).** Synthesis was performed according to general procedure 1 employing 3-ethyladamantan-1-carboxylic acid (13.3 mg, 0.064 mmol) yielding **8am** (16.8 mg; 69 %) as a pale yellow oil. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 1.37-2.13 (m, 23H), 2.32 (s, 3H), 2.76 (d,  $J$  = 20.4 Hz, 2H), 3.11-3.24 (m, 2H), 3.90 (s, 2H), 4.25-4.36 (m, 2H), 7.20 (d,  $J$  = 7.9 Hz, 1H), 7.45 (dd,  $J$  = 7.9 Hz,  $J$  = 1.6 Hz, 1H), 8.36-8.40 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  (ppm) 6.9, 18.1, 29.0, 33.1, 33.6, 33.9, 36.3, 36.5, 38.8, 41.0, 41.3, 42.6, 43.7, 55.2, 57.1 (d,  $J$  = 22.5 Hz), 94.7 (d,  $J$  = 171.1 Hz), 121.7, 131.4, 137.0, 149.7, 156.7, 175.8. APCI-MS  $m/z$  428 [M+1]<sup>+</sup>.

**3-[[4-Fluoro-4-[[[(5-methylpyridin-2-yl)methyl]amino]methyl]piperidin-1-yl]carbonyl]adamantan-1-ol (8an).** Synthesis was performed according to general procedure 1 employing 3-hydroxyadamantan-1-carboxylic acid (12.7 mg, 0.064 mmol) yielding **8an** (15.8 mg; 67 %) as a pale yellow oil. IR 3367, 2915, 2854, 1619, 1415, 1261, 1122, 1033, 971, 728 cm<sup>-1</sup>. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 1.58-1.61 (m, 3H), 1.69-1.74 (m, 5H), 1.87-1.95 (m, 6H), 1.95-2.06 (m, 2H), 2.24-2.31 (m, 2H), 2.32 (s, 3H), 2.76 (d,  $J$  = 20.4 Hz, 2H), 3.12-3.23 (m, 2H), 3.91 (s, 2H), 4.24-4.34 (m, 2H), 7.20 (d,  $J$  = 7.9 Hz, 1H), 7.46 (dd,  $J$  = 7.8 Hz,  $J$  = 1.7 Hz, 1H), 8.36-8.39 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 90 MHz)  $\delta$  (ppm) 18.1, 30.6, 33.7 (d,  $J$  = 21.8 Hz, 2C), 35.1, 37.8, 41.2, 44.4, 45.1, 46.9, 55.1, 57.0 (d,  $J$  = 22.5 Hz), 68.7, 94.5 (d,  $J$  = 171.7 Hz), 121.7, 131.5, 137.1, 149.7, 156.4, 174.3. APCI-MS  $m/z$  416 [M+1]<sup>+</sup>. HR-EIMS  $m/z$  415.2629. HPLC/MS system A purity 98 % ( $t_R$  = 14.3 min).

**N-[4-Fluoro-1-[[3-(1,1,2,3,3,3-hexafluoropropyl)-1-adamantyl]carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ao).** Synthesis was performed according

to general procedure 1 employing 3-(1,1,2,3,3,3-hexafluoropropyl)adamantan-1-carboxylic acid (21.1 mg, 0.064 mmol) yielding **8ao** (11.1 mg; 35 %) as a pale yellow oil. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ (ppm) 1.47-2.10 (m, 16H), 2.19-2.27 (m, 2H), 2.32 (s, 3H), 2.76 (d, *J* = 20.2 Hz, 2H), 3.13-3.25 (m, 2H), 3.90 (s, 2H), 4.23-4.32 (m, 2H), 4.83-5.09 (m, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.45 (dd, *J* = 7.8 Hz, *J* = 1.7 Hz, 1H), 8.35-8.40 (m, 1H). APCI-MS *m/z* 550 [M+1]<sup>+</sup>. HPLC/MS system A purity 98 % (t<sub>R</sub> = 18.3 min).

**N-[1-[(3,5-Dimethyl-1-adamantyl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ap)**. Synthesis was performed according to general procedure 1 employing 3,5-dimethyladamantan-1-carboxylic acid (13.3 mg, 0.064 mmol) yielding **8ap** (16.6 mg; 68 %) as a pale yellow oil. IR 3329, 2942, 2920, 2897, 2884, 1623, 1554, 1412 cm<sup>-1</sup>. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ (ppm) 0.84 (s, 6H), 1.09-1.70 (m, 14H), 1.93-2.06 (m, 2H), 2.09-2.16 (m, 1H), 2.32 (s, 3H), 2.76 (d, *J* = 20.4 Hz, 2H), 3.09-3.22 (m, 2H), 3.90 (s, 2H), 4.24-4.34 (m, 2H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.45 (dd, *J* = 7.9 Hz, *J* = 2.0 Hz, 1H), 8.36-8.40 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 90 MHz) δ (ppm) 18.1, 29.6, 30.8, 31.3, 33.6, 33.9, 37.7, 41.2, 42.9, 43.7, 45.4, 50.8, 55.2, 57.1 (d, *J* = 21.8 Hz), 94.7 (d, *J* = 171.7 Hz), 121.7, 131.4, 137.1, 149.7, 156.6, 175.5. APCI-MS *m/z* 428 [M+1]<sup>+</sup>.

**N-[1-[(3-Bromo-5-methyl-1-adamantyl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8aq)**. Synthesis was performed according to general procedure 1 employing 3-bromo-5-methyladamantan-1-carboxylic acid (17.5 mg, 0.064 mmol) yielding **8aq** (12.1 mg; 43 %) as a pale yellow oil. IR 3329, 2924, 2858, 1624, 1454, 1415, 1261, 752 cm<sup>-1</sup>. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ (ppm) 0.91 (s, 3H), 1.40-1.68 (m, 5H), 1.83-2.11 (m, 7H), 2.20-2.28 (m, 3H), 2.32 (s, 3H), 2.42-2.57 (m, 2H), 2.76 (d, *J* = 20.4 Hz, 2H), 3.12-3.24 (m, 2H), 3.89 (s, 2H), 4.21-4.30 (m, 2H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 7.8 Hz, *J* = 1.7 Hz, 1H), 8.36-8.40 (m, 1H). APCI-MS *m/z* 493 [M+1]<sup>+</sup>.

**N-[4-Fluoro-1-(2-thienylcarbonyl)piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ar)**. Synthesis was performed according to general procedure 1 employing thiophene-2-carboxylic acid (20.5 mg, 0.160 mmol) yielding **8ar** (23.3 mg; 42 %) as a pale yellow oil. IR 3660, 2923, 1619, 1438, 1276, 1095, 860, 736 cm<sup>-1</sup>. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ (ppm) 1.59-1.85 (m, 2H), 1.97-2.11 (m, 2H), 2.32 (s, 3H), 2.79 (d, *J* = 20.4 Hz, 2H), 3.25-3.45 (m, 2H), 3.89 (s, 2H), 4.15-4.39 (m, 2H), 7.04 (dd, *J* = 5.0 Hz, *J* = 3.6 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 3.6 Hz, *J* = 1.1 Hz, 1H), 7.43 (dd, *J* = 5.0 Hz, *J* = 1.1 Hz, 1H), 7.46 (dd, *J* = 7.4 Hz, *J* = 1.5 Hz, 1H), 8.36-8.40 (m, 1H). APCI-MS *m/z* 348 [M+1]<sup>+</sup>. HR-EIMS *m/z* 347.1467. HPLC/MS system A purity 96 % (t<sub>R</sub> = 13.3 min).

**N-[4-Fluoro-1-(3-thienylcarbonyl)piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8as)**. Synthesis was performed according to general procedure 1 employing thiophene-3-carboxylic acid (8.2 mg, 0.064 mmol) yielding **8as** (14.2 mg; 72 %) as a pale yellow oil. IR 3513, 2923, 1627, 1438, 1276, 1103, 975, 813, 740 cm<sup>-1</sup>. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ (ppm) 1.74-1.84 (m, 2H), 1.95-2.11 (m, 2H), 2.32 (s, 3H), 2.79 (d, *J* = 20.2 Hz, 2H), 3.01-3.56 (m, 2H), 3.91 (s, 2H), 4.19-4.89 (m, 2H), 7.17 (dd, *J* = 5.0 Hz, *J* = 1.1 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.33 (dd, *J* = 5.0 Hz, *J* = 3.0 Hz, 1H), 7.46 (dd, *J* = 8.0 Hz, *J* = 1.7 Hz, 1H), 7.51 (dd, *J* = 3.0 Hz, *J* = 1.1 Hz, 1H), 8.36-8.40 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 90 MHz) δ (ppm) 18.1, 33.5 (2C), 38.2, 43.3, 55.2, 57.0 (d, *J* = 22.5 Hz), 94.5 (d, *J* = 171.7 Hz), 121.7, 126.0, 126.2, 126.9, 131.4, 136.5, 137.1, 149.7, 156.6, 165.8. APCI-MS *m/z* 348 [M+1]<sup>+</sup>. HR-EIMS *m/z* 347.1468. HPLC/MS system A purity 99 % (t<sub>R</sub> = 13.4 min).

**N-[4-Fluoro-1-(2-furanyl)piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8at).** Synthesis was performed according to general procedure 1 employing furan-2-carboxylic acid (17.9 mg, 0.160 mmol) yielding **8at** (13.2 mg; 28 %) as a pale yellow oil. IR 3490, 2923, 1627, 1488, 1434, 1373, 1284, 1110, 929, 825, 755  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.60-1.88 (m, 2H), 2.00-2.13 (m, 2H), 2.32 (s, 3H), 2.79 (d,  $J = 20.6$  Hz, 2H), 3.06-3.56 (m, 2H), 3.91 (s, 2H), 4.26-4.51 (m, 2H), 6.47 (dd,  $J = 3.4$  Hz, 1.8 Hz, 1H), 6.98 (dd,  $J = 3.5$  Hz,  $J = 0.8$  Hz, 1H), 7.21 (d,  $J = 8.0$  Hz, 1H), 7.43-7.49 (m, 2H), 8.36-8.40 (m, 1H). APCI-MS  $m/z$  332  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  331.1698. HPLC/MS system A purity 96 % ( $t_{\text{R}} = 13.1$  min).

**N-[4-Fluoro-1-(3-furanyl)piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8au).** Synthesis was performed according to general procedure 1 employing furan-3-carboxylic acid (7.2 mg, 0.160 mmol) yielding **8au** (16.0 mg; 85 %) as a pale yellow oil. IR 3405, 2927, 2360, 1623, 1442, 1373, 1292, 1072, 875, 748  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.56-1.81 (m, 2H), 1.97-2.10 (m, 2H), 2.33 (s, 3H), 2.88 (d,  $J = 20.2$  Hz, 2H), 3.08-3.52 (m, 2H), 4.00 (s, 2H), 4.08-4.78 (m, 2H), 6.33 (dd,  $J = 1.9$  Hz,  $J = 0.8$  Hz, 1H), 7.22 (d,  $J = 7.9$  Hz, 1H), 7.42 (dd,  $J = 1.7$  Hz,  $J = 1.7$  Hz, 1H), 7.49 (dd,  $J = 7.8$  Hz,  $J = 1.7$  Hz, 1H), 7.70 (dd,  $J = 1.5$  Hz,  $J = 1.0$  Hz, 1H), 8.36-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 33.3 (2C), 38.4, 43.2, 54.7, 56.7 (d,  $J = 21.8$  Hz), 94.3 (d,  $J = 171.7$  Hz), 110.0, 121.0, 121.8, 131.8, 137.3, 142.9, 143.3, 149.6, 155.4, 163.8. APCI-MS  $m/z$  332  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  331.1696. HPLC/MS system A purity 95 % ( $t_{\text{R}} = 12.7$  min).

**N-[4-Fluoro-1-(1H-pyrrol-2-ylcarbonyl)piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8av).** Synthesis was performed according to general procedure 1 employing pyrrol-2-carboxylic acid (7.1 mg, 0.064 mmol) yielding **8av** (5.8 mg; 31 %) as a pale yellow oil. IR 3733, 3216, 2923, 1670, 1600, 1442, 1292, 1122, 744  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.46-1.80 (m, 2H), 1.96-2.15 (m, 2H), 2.32 (s, 3H), 2.79 (d,  $J = 20.4$  Hz, 2H), 3.19-3.54 (m, 2H), 3.91 (s, 2H), 4.19-4.48 (m, 2H), 6.24 (ddd,  $J = 3.6$  Hz,  $J = 2.7$  Hz,  $J = 3.7$  Hz, 1H), 6.52 (ddd,  $J = 3.7$  Hz,  $J = 2.4$  Hz,  $J = 1.3$  Hz, 1H), 6.91 (ddd,  $J = 2.6$  Hz,  $J = 2.6$  Hz,  $J = 1.2$  Hz, 1H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.45 (dd,  $J = 8.0$  Hz,  $J = 2.0$  Hz, 1H), 8.35-8.41 (m, 1H), 9.34 (bs, 1H). APCI-MS  $m/z$  331  $[\text{M}+1]^+$ .

**N-[4-Fluoro-1-(1H-pyrazol-3-ylcarbonyl)piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8aw).** Synthesis was performed according to general procedure 1 employing 1H-pyrazol-3-carboxylic acid (7.2 mg, 0.064 mmol) yielding **8aw** (8.1 mg; 43 %) as a pale yellow oil. IR 3736, 3124, 2927, 1616, 1492, 1454, 1292, 1218, 1130, 1045, 914, 771, 732  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.61-1.83 (m, 2H), 2.01-2.12 (m, 2H), 2.32 (s, 3H), 2.82 (d,  $J = 20.2$  Hz, 2H), 3.13-3.57 (m, 2H), 3.94 (s, 2H), 4.44-4.59 (m, 2H), 6.63 (d,  $J = 2.3$  Hz, 1H), 7.20 (d,  $J = 8.0$  Hz, 1H), 7.46 (dd,  $J = 8.0$  Hz,  $J = 1.7$  Hz, 1H), 7.57 (d,  $J = 2.2$  Hz, 1H), 8.35-8.40 (m, 1H), 11.23 (bs, 1H). APCI-MS  $m/z$  332  $[\text{M}+1]^+$ . HPLC/MS system B purity 99 % ( $t_{\text{R}} = 3.2$  min).

**N-[1-[(5-Bromo-2-thienyl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ay).** Synthesis was performed according to general procedure 1 employing 5-bromothiophene-2-carboxylic acid (13.3 mg, 0.064 mmol) yielding **8ay** (12.7 mg; 52 %) as a pale yellow oil. IR 3660, 2923, 1619, 1438, 1272, 1091, 971, 806, 732  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.79-1.90 (m, 2H), 2.00-2.12 (m, 2H), 2.32 (s, 3H), 2.79 (d,  $J = 20.2$  Hz, 2H), 3.24-3.42 (m, 2H), 3.90 (s, 2H), 4.17-4.33 (m, 2H), 7.00 (d,  $J = 3.9$  Hz, 1H), 7.05 (d,  $J = 3.9$  Hz, 1H), 7.20 (d,  $J = 8.0$  Hz, 1H), 7.46 (dd,  $J = 8.0$  Hz,  $J = 1.9$  Hz, 1H), 8.36-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 33.2, 33.4, 41.2, 41.7, 55.2, 56.9 (d,  $J = 22.5$  Hz), 94.4 (d,  $J = 171.7$  Hz), 116.4, 121.7, 129.1, 129.6, 131.4, 137.1, 138.8,

149.7, 156.6, 162.3. APCI-MS  $m/z$  428  $[M+1]^+$ . HR-EIMS  $m/z$  425.0576. HPLC/MS system A purity 96 % ( $t_R$  = 15.3 min).

**N-[1-[(3-Bromo-2-thienyl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8az).** Synthesis was performed according to general procedure 1 employing 3-bromothiophene-2-carboxylic acid (13.3 mg, 0.064 mmol) yielding **8az** (9.3 mg; 38 %) as a pale yellow oil. IR 3833, 2923, 1635, 1446, 1276, 875, 732  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.76-1.87 (m, 2H), 1.97-2.14 (m, 2H), 2.32 (s, 3H), 2.79 (d,  $J$  = 20.5 Hz, 2H), 3.07-3.75 (m, 3H), 3.90 (s, 2H), 4.36-4.79 (m, 1H), 6.97 (d,  $J$  = 5.3 Hz, 1H), 7.20 (d,  $J$  = 7.6 Hz, 1H), 7.34 (d,  $J$  = 5.3 Hz, 1H), 7.46 (dd,  $J$  = 7.9 Hz,  $J$  = 1.5 Hz, 1H), 8.36-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 33.2 (4C), 55.2, 56.9 (d,  $J$  = 21.8 Hz), 94.4 (d,  $J$  = 172.4 Hz), 109.3, 121.7, 127.0, 130.2, 131.4, 137.0, 149.7, 156.6, 162.0, 170.9. APCI-MS  $m/z$  428  $[M+1]^+$ . HR-EIMS  $m/z$  425.0573. HPLC/MS system A purity 96 % ( $t_R$  = 14.4 min).

**N-[1-[(2-Bromo-3-thienyl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ba).** Synthesis was performed according to general procedure 1 employing 2-bromothiophene-3-carboxylic acid (13.3 mg, 0.064 mmol) yielding **8ba** (12.1 mg; 49 %) as a pale yellow oil. IR 3332, 2923, 1635, 1442, 1276, 1037, 875, 752, 647  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.48-1.77 (m, 2H), 1.85-2.08 (m, 2H), 2.25 (s, 3H), 2.71 (dd,  $J$  = 20.4 Hz,  $J$  = 1.8 Hz, 2H), 3.04-3.17 (m, 1H), 3.26-3.546 (m, 2H), 3.83 (s, 2H), 4.43-4.54 (m, 1H), 6.83 (d,  $J$  = 5.7 Hz, 1H), 7.12 (d,  $J$  = 7.7 Hz, 1H), 7.22 (d,  $J$  = 5.7 Hz, 1H), 7.38 (dd,  $J$  = 8.0 Hz,  $J$  = 1.9 Hz, 1H), 8.28-8.33 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 32.8 (d,  $J$  = 22.5 Hz), 33.9 (d,  $J$  = 21.8 Hz), 37.8, 42.9, 55.2, 56.9 (d,  $J$  = 22.5 Hz), 94.4 (d,  $J$  = 172.4 Hz), 110.6, 121.7, 127.0, 127.4, 131.4, 137.1, 149.7, 156.5, 164.3, 170.2. APCI-MS  $m/z$  427  $[M+1]^+$ . HR-EIMS  $m/z$  425.0573. HPLC/MS system A purity 97 % ( $t_R$  = 14.2 min).

**N-[1-(5-Bromo-3-furanyl)-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bb).** Synthesis was performed according to general procedure 1 employing 5-bromofuran-3-carboxylic acid (12.2 mg, 0.064 mmol) yielding **8bb** (14.7 mg; 63 %) as a pale yellow oil. IR 3325, 3136, 2924, 1628, 1574, 1496, 1439, 1284, 1103, 914  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.52-1.73 (m, 2H), 1.95-2.12 (m, 2H), 2.32 (s, 3H), 2.78 (d,  $J$  = 20.0 Hz, 2H), 2.98-3.60 (m, 3H), 3.90 (s, 2H), 4.04-4.67 (m, 1H), 6.45 (d,  $J$  = 1.1 Hz, 1H), 7.19 (d,  $J$  = 7.9 Hz, 1H), 7.45 (dd,  $J$  = 7.9 Hz,  $J$  = 1.8 Hz, 1H), 7.64 (d,  $J$  = 1.1 Hz, 1H), 8.34-8.39 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  (ppm) 18.1, 32.8, 33.5, 38.0, 43.0, 55.1, 56.9 (d,  $J$  = 23.1 Hz), 94.4 (d,  $J$  = 171.2 Hz), 111.5, 121.7, 123.3, 123.7, 131.5, 137.2, 144.4, 149.7, 156.4, 162.3. APCI-MS  $m/z$  412  $[M+1]^+$ . HPLC/MS system A purity 93 % ( $t_R$  = 14.2 min).

**N-[4-Fluoro-1-[(4-methyl-2-thienyl)carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bc).** Synthesis was performed according to general procedure 1 employing 4-methylthiophene-2-carboxylic acid (9.1 mg, 0.064 mmol) yielding **8bc** (8.5 mg; 41 %) as a pale yellow oil. IR 3332, 1923, 1619, 1442, 1272, 1130, 1079, 860, 825, 763  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.75-1.86 (m, 2H), 1.99-2.08 (m, 2H), 2.26 (s, 3H), 2.32 (s, 3H), 2.78 (d,  $J$  = 20.4 Hz, 2H), 3.22-3.42 (m, 2H), 3.90 (s, 2H), 4.19-4.40 (m, 2H), 7.00 (s, 1H), 7.08 (s, 1H), 7.19 (d,  $J$  = 7.9 Hz, 1H), 7.45 (dd,  $J$  = 7.7 Hz,  $J$  = 1.3 Hz, 1H), 8.35-8.39 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  (ppm) 15.6, 18.1, 33.4 (4C), 55.2, 57.0 (d,  $J$  = 22.0 Hz), 94.6 (d,  $J$  = 171.2 Hz), 121.7, 123.9, 130.9, 131.4, 136.7, 137.0, 137.4, 149.7, 156.6, 163.7. APCI-MS  $m/z$  362  $[M+1]^+$ . HR-EIMS  $m/z$  361.1624. HPLC/MS system A purity 96 % ( $t_R$  = 14.5 min).

**N-[4-Fluoro-1-[(5-methyl-2-thienyl)carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bd).** Synthesis was performed according to general procedure 1 employing 5-methylthiophene-2-carboxylic acid (9.1 mg, 0.064 mmol) yielding **8bd** (5.9 mg; 29 %) as a pale yellow oil. IR 3567, 2923, 1616, 1461, 1427, 1276, 1091, 809, 732  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.68-1.85 (m, 2H), 2.01-2.08 (m, 2H), 2.32 (s, 3H), 2.50 (s, 3H), 2.78 (d,  $J = 20.4$  Hz, 2H), 3.26-3.41 (m, 2H), 3.91 (s, 2H), 4.24-4.37 (m, 2H), 6.67-6.72 (m, 1H), 7.10 (d,  $J = 3.8$  Hz, 1H), 7.21 (d,  $J = 7.9$  Hz, 1H), 7.46 (dd,  $J = 7.9$  Hz,  $J = 1.8$  Hz, 1H), 8.36-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 15.3, 18.1, 33.3, 33.5, 41.5, 55.2, 57.0 (d,  $J = 21.8$  Hz), 94.6 (d,  $J = 171.7$  Hz), 121.7, 125.0, 129.2, 131.4, 134.7, 137.0, 143.7, 149.7, 156.6, 163.6. APCI-MS  $m/z$  362  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  361.1624. HPLC/MS system A purity 95 % ( $t_R = 14.7$  min).

**N-[4-Fluoro-1-[(3-methyl-2-thienyl)carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8be).** Synthesis was performed according to general procedure 1 employing 3-methylthiophene-2-carboxylic acid (9.1 mg, 0.064 mmol) yielding **8be** (9.8 mg; 48 %) as a pale yellow oil. IR 3748, 2923, 1627, 1438, 1276, 1103, 968, 825, 721  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.74-1.88 (m, 2H), 1.98-2.08 (m, 2H), 2.26 (s, 3H), 2.32 (s, 3H), 2.78 (d,  $J = 20.8$  Hz, 2H), 3.22-3.36 (m, 2H), 3.89 (s, 2H), 3.94-4.49 (m, 2H), 6.83 (d,  $J = 4.9$  Hz, 1H), 7.21 (d,  $J = 7.6$  Hz, 1H), 7.24-7.26 (m, 1H), 7.46 (dd,  $J = 7.9$  Hz,  $J = 1.5$  Hz, 1H), 8.36-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 14.6, 18.1, 33.3, 33.5, 40.1, 55.2, 57.0 (d,  $J = 22.5$  Hz), 94.5 (d,  $J = 171.7$  Hz), 121.7, 125.7, 129.7, 130.4, 131.4, 137.0, 137.3, 149.7, 156.6, 164.6. APCI-MS  $m/z$  362  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  361.1624. HPLC/MS system A purity 98 % ( $t_R = 14.1$  min).

**N-[1-[(5-Chloro-2-thienyl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bf).** Synthesis was performed according to general procedure 1 employing 5-chlorothiophene-2-carboxylic acid (26.0 mg, 0.160 mmol) yielding **8bf** (32.8 mg; 60 %) as a pale yellow oil. IR 3328, 2923, 1619, 1442, 1373, 1272, 1091, 806, 732  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.78-1.91 (m, 2H), 1.99-2.12 (m, 2H), 2.32 (s, 3H), 2.80 (d,  $J = 20.2$  Hz, 2H), 3.26-3.42 (m, 2H), 3.90 (s, 2H), 4.19-4.35 (m, 2H), 6.86 (d,  $J = 4.1$  Hz, 1H), 7.07 (d,  $J = 3.9$  Hz, 1H), 7.20 (d,  $J = 7.7$  Hz, 1H), 7.45 (dd,  $J = 8.0$  Hz,  $J = 1.6$  Hz, 1H), 8.35-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 33.2, 33.4, 41.3, 55.2, 56.9 (d,  $J = 22.5$  Hz), 94.4 (d,  $J = 171.7$  Hz), 121.7, 125.9, 128.3, 131.4, 133.9, 135.9, 137.0, 149.7, 156.6, 162.3. APCI-MS  $m/z$  382  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  381.1079. HPLC/MS system A purity 96 % ( $t_R = 15.2$  min).

**N-[1-[(3-Chloro-2-thienyl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bg).** Synthesis was performed according to general procedure 1 employing 3-chlorothiophene-2-carboxylic acid (10.4 mg, 0.064 mmol) yielding **8bg** (12.8 mg; 59 %) as a pale yellow oil. IR 3745, 2919, 1635, 1446, 1276, 1095, 968, 898, 740  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.81-1.93 (m, 2H), 1.97-2.13 (m, 2H), 2.32 (s, 3H), 2.79 (d,  $J = 20.7$  Hz, 2H), 3.14-3.49 (m, 2H), 3.90 (s, 2H), 4.19-4.78 (m, 2H), 6.91 (d,  $J = 5.2$  Hz, 1H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.36 (d,  $J = 5.2$  Hz, 1H), 7.46 (dd,  $J = 7.7$  Hz,  $J = 1.8$  Hz, 1H), 8.35-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 33.3, 38.8, 43.4, 55.2, 56.9 (d,  $J = 21.8$  Hz), 94.7 (d,  $J = 172.4$  Hz), 121.6, 124.0, 126.6, 127.7, 130.3, 131.4, 137.0, 149.7, 156.6, 161.5. APCI-MS  $m/z$  382  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  381.1075.

**N-[4-Fluoro-1-[(5-fluoro-2-thienyl)carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bh).** Synthesis was performed according to general procedure 1 employing 5-fluorothiophene-2-carboxylic acid (9.4 mg, 0.064 mmol) yielding **8bh** (7.8 mg; 37 %) as a pale yellow oil. IR 3332, 2923, 1616, 1477, 1430, 1276, 1199, 1087, 964, 798, 740

cm<sup>-1</sup>. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ (ppm) 1.57-1.81 (m, 2H), 1.98-2.14 (m, 2H), 2.32 (s, 3H), 2.79 (d, *J* = 20.2 Hz, 2H), 3.28-3.43 (m, 2H), 3.91 (s, 2H), 4.20-4.34 (m, 2H), 6.44 (dd, *J* = 4.2 Hz, *J* = 3.9 Hz, 1H), 6.95 (dd, *J* = 3.9 Hz, *J* = 3.9 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 7.8 Hz, *J* = 1.7 Hz, 1H), 8.36-8.41 (m, 1H). APCI-MS *m/z* 366 [M+1]<sup>+</sup>. HPLC/MS system A purity 95 % (t<sub>R</sub> = 8.9-9.1 min).

**N-[4-Fluoro-1-[[5-(methylthio)-2-thienyl]carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bi)**. Synthesis was performed according to general procedure 1 employing 5-(methylthio)thiophene-2-carboxylic acid (11.2 mg, 0.064 mmol) yielding **8bi** (11.2 mg; 68 %) as a pale yellow oil. IR 3332, 2923, 1616, 1434, 1272, 1091, 968, 806, 748 cm<sup>-1</sup>. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ (ppm) 1.57-1.71 (m, 2H), 1.99-2.09 (m, 2H), 2.32 (s, 3H), 2.53 (s, 3H), 2.78 (d, *J* = 20.4 Hz, 2H), 3.26-3.40 (m, 2H), 3.90 (s, 2H), 4.20-4.32 (m, 2H), 6.92 (d, *J* = 3.6 Hz, 1H), 7.12 (d, *J* = 3.6 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.44 (dd, *J* = 7.8 Hz, *J* = 1.9 Hz, 1H), 8.35-8.40 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz) δ (ppm) 18.1, 21.0, 33.3, 33.4, 41.0, 41.7, 55.1, 56.9 (d, *J* = 22.0 Hz), 94.5 (d, *J* = 171.2 Hz), 121.7, 128.5, 129.2, 131.4, 137.1, 137.9, 142.3, 149.7, 156.5, 162.8. APCI-MS *m/z* 394 [M+1]<sup>+</sup>. HR-EIMS *m/z* 393.1343. HPLC/MS system A (254 nm) purity 97 % (t<sub>R</sub> = 15.3 min).

**N-[4-Fluoro-1-[(4-methoxy-3-thienyl)carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bj)**. Synthesis was performed according to general procedure 1 employing 4-methoxythiophene-3-carboxylic acid (10.1 mg, 0.064 mmol) yielding **8bj** (12.2 mg; 59 %) as a pale yellow oil. IR 3328, 2927, 1631, 1554, 1418, 1434, 1376, 1276, 1245, 1207, 1091, 802, 759 cm<sup>-1</sup>. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ (ppm) 1.49-1.73 (m, 2H), 1.89-2.12 (m, 2H), 2.32 (s, 3H), 2.79 (d, *J* = 20.4 Hz, 2H), 3.07-3.23 (m, 1H), 3.26-3.40 (m, 1H), 3.45-3.59 (m, 1H), 3.82 (s, 3H), 3.91 (s, 2H), 4.44-4.60 (m, 1H), 6.24 (d, *J* = 3.4 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 3.1 Hz, 1H), 7.46 (dd, *J* = 7.8 Hz, *J* = 1.7 Hz, 1H), 8.35-8.40 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz) δ (ppm) 18.1, 32.8, 32.9, 33.6, 33.8, 37.7, 42.9, 55.1, 56.9 (d, *J* = 22.0 Hz), 57.7, 94.6 (d, *J* = 171.2 Hz), 97.3, 121.7, 125.2, 128.7, 131.4, 137.1, 149.7, 155.1, 156.5, 164.1. APCI-MS *m/z* 378 [M+1]<sup>+</sup>. HR-EIMS *m/z* 377.1572. HPLC/MS system A purity 99 % (t<sub>R</sub> = 13.23 min).

**N-[1-[(4,5-Dibromo-2-thienyl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bk)**. Synthesis was performed according to general procedure 1 employing 4,5-dibromothiophene-2-carboxylic acid (18.3 mg, 0.064 mmol) yielding **8bk** (13.3 mg; 46 %) as a pale yellow oil. IR 2923, 1631, 1488, 1434, 1280, 1218, 979, 771 cm<sup>-1</sup>. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ (ppm) 1.56-1.78 (m, 2H), 1.99-2.13 (m, 2H), 2.32 (s, 3H), 2.78 (d, *J* = 20.2 Hz, 2H), 3.24-3.45 (m, 2H), 3.90 (s, 2H), 4.13-4.34 (m, 2H), 7.07 (s, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.45 (dd, *J* = 7.8 Hz, *J* = 1.7 Hz, 1H), 8.35-8.40 (m, 1H). APCI-MS *m/z* 506 [M+1]<sup>+</sup>. HPLC/MS system B purity 96 % (t<sub>R</sub> = 11.3 min).

**N-[1-[(4,5-Dibromo-2-furanyl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bl)**. Synthesis was performed according to general procedure 1 employing 4,5-dibromofuran-2-carboxylic acid (17.3 mg, 0.064 mmol) yielding **8bl** (12.3 mg; 44 %) as a pale yellow oil. IR 3328, 2923, 1619, 1434, 1373, 1307, 1268, 1130, 964, 914, 802, 744 cm<sup>-1</sup>. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ (ppm) 1.58-1.83 (m, 2H), 2.01-2.15 (m, 2H), 2.32 (s, 3H), 2.78 (d, *J* = 20.2 Hz, 2H), 3.09-3.57 (m, 2H), 3.90 (s, 2H), 4.12-4.54 (m, 2H), 6.99 (s, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.44 (dd, *J* = 8.0 Hz, *J* = 1.9 Hz, 1H), 8.35-8.40 (m, 1H). APCI-MS *m/z* 490 [M+1]<sup>+</sup>. HPLC/MS system B purity 96 % (t<sub>R</sub> = 10.7 min).

**N-[1-[(5-Bromo-4-methoxy-3-thienyl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bm)**. Synthesis was performed according to general

procedure 1 employing 5-bromo-4-methoxythiophene-3-carboxylic acid (15.2 mg, 0.064 mmol) yielding **8bm** (14.5 mg; 56 %) as a pale yellow oil. IR: 3324, 2927, 1635, 1546, 1481, 1434, 1353, 1272, 1091, 1025, 752  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.53-1.78 (m, 2H), 1.99-2.16 (m, 2H), 2.32 (s, 3H), 2.79 (d,  $J = 20.2$  Hz, 2H), 3.09-3.21 (m, 1H), 3.30-3.41 (m, 1H), 3.48-3.58 (m, 1H), 3.87 (s, 3H), 3.91 (s, 2H), 4.47-4.57 (m, 1H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.30 (s, 1H), 7.46 (dd,  $J = 7.8$  Hz,  $J = 1.7$  Hz, 1H), 8.36-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  (ppm) 18.1, 32.7, 32.9, 33.6, 33.8, 37.9, 43.1, 55.1, 56.9 (d,  $J = 22.0$  Hz), 61.2, 94.4 (d,  $J = 172.3$  Hz), 98.4, 121.7, 124.0, 131.2, 131.5, 137.1, 149.6, 152.4, 156.4, 163.6. APCI-MS  $m/z$  457  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  455.0675. HPLC/MS system A purity 97 % ( $t_{\text{R}} = 15.4$  min).

**N-[1-[(5-Chloro-4-methoxy-3-thienyl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bn)**. Synthesis was performed according to general procedure 1 employing 5-chloro-4-methoxythiophene-2-carboxylic acid (12.4 mg, 0.064 mmol) yielding **8bn** (15.1 mg; 64 %) as a pale yellow oil. IR 3328, 2927, 1635, 1550, 1481, 1434, 1361, 1272, 1245, 1033, 975, 790, 748  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.55-1.75 (m, 2H), 1.93-2.02 (m, 1H), 2.06-2.13 (m, 1H), 2.32 (s, 3H), 2.79 (d,  $J = 20.0$  Hz, 2H), 3.09-3.19 (m, 1H), 3.32-3.40 (m, 1H), 3.50-3.57 (m, 1H), 3.89 (s, 3H), 3.90 (s, 2H), 4.48-4.55 (m, 1H), 7.12 (s, 1H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.46 (dd,  $J = 7.8$  Hz,  $J = 1.8$  Hz, 1H), 8.37-8.39 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 32.7, 32.9, 33.6, 33.8, 37.9, 43.1, 55.2, 56.9 (d,  $J = 21.8$  Hz), 61.5, 94.5 (d,  $J = 172.4$  Hz), 114.6, 120.5, 121.7, 130.9, 131.4, 137.0, 149.7, 150.1, 156.6, 163.6. APCI-MS  $m/z$  412  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  411.1182. HPLC/MS system A purity 98 % ( $t_{\text{R}} = 15.2$  min).

**N-[4-Fluoro-1-[(5-phenyl-2-thienyl)carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bo)**. Synthesis was performed according to general procedure 1 employing 5-phenylthiophene-2-carboxylic acid (13.1 mg, 0.064 mmol) yielding **8bo** (15.4 mg; 62 %) as a pale yellow oil. IR 3340, 2923, 1616, 1454, 1423, 1276, 1095, 968, 813, 755, 690  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.61-1.74 (m, 2H), 2.01-2.12 (m, 2H), 2.32 (s, 3H), 2.80 (d,  $J = 20.2$  Hz, 2H), 3.27-3.44 (m, 2H), 3.91 (s, 2H), 4.25-4.40 (m, 2H), 7.20 (d,  $J = 7.7$  Hz, 1H), 7.21 (d,  $J = 3.6$  Hz, 1H), 7.26 (d,  $J = 3.6$  Hz, 1H), 7.29-7.35 (m, 1H), 7.36-7.42 (m, 2H), 7.45 (dd,  $J = 7.9$  Hz,  $J = 1.8$  Hz, 1H), 7.57-7.63 (m, 2H), 8.36-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  (ppm) 18.1, 33.3, 33.4, 40.8, 41.6, 55.1, 57.0 (d,  $J = 23.1$  Hz), 94.5 (d,  $J = 172.3$  Hz), 121.7, 122.6, 126.1 (2C), 128.3, 129.0 (2C), 129.8, 131.4, 133.5, 136.0, 137.1, 147.6, 149.7, 156.5, 163.4. APCI-MS  $m/z$  424  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  423.1781. HPLC/MS system A purity 99 % ( $t_{\text{R}} = 16.6$  min).

**N-[1-(2,2'-Bithien-5-ylcarbonyl)-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bp)**. Synthesis was performed according to general procedure 1 employing 2,2'-bithiophene-5-carboxylic acid (13.5 mg, 0.064 mmol) yielding **8bp** (15.7 mg; 63 %) as a pale yellow oil. IR 3340, 2923, 1616, 1457, 1427, 1272, 1091, 968, 806, 748, 701  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.60-1.73 (m, 2H), 1.99-2.10 (m, 2H), 2.32 (s, 3H), 2.79 (d,  $J = 20.4$  Hz, 2H), 3.29-3.42 (m, 2H), 3.90 (s, 2H), 4.25-4.37 (m, 2H), 7.04 (dd,  $J = 5.0$  Hz,  $J = 3.6$  Hz, 1H), 7.08 (d,  $J = 3.9$  Hz, 1H), 7.19-7.23 (m, 3H), 7.26-7.28 (m, 1H), 7.45 (dd,  $J = 7.8$  Hz,  $J = 1.7$  Hz, 1H), 8.06-8.39 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 33.3, 33.5, 41.5, 55.2, 57.0 (d,  $J = 22.8$  Hz), 94.5 (d,  $J = 171.7$  Hz), 121.7, 123.1, 124.8, 125.5, 128.0, 129.6, 131.4, 135.5, 136.3, 137.1, 140.7, 149.7, 156.6, 163.1. APCI-MS  $m/z$  430  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  429.1346. HPLC/MS system A purity 98 % ( $t_{\text{R}} = 16.4$  min).

**N-[4-Fluoro-1-[[5-(pyridin-2-yl)-2-thienyl]carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bq)**. Synthesis was performed according to general

procedure 1 employing 5-(2-pyridyl)thiophene-2-carboxylic acid (13.1 mg, 0.064 mmol) yielding **8bq** (18.1 mg; 74 %) as a pale yellow oil. IR 3324, 2923, 1616, 1454, 1430, 1276, 775, 748  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.60-1.78 (m, 2H), 2.00-2.13 (m, 2H), 2.32 (s, 3H), 2.79 (d,  $J = 20.4$  Hz, 2H), 3.27-3.42 (m, 2H), 3.91 (s, 2H), 4.26-4.41 (m, 2H), 7.16-7.23 (m, 2H), 7.32 (d,  $J = 3.9$  Hz, 1H), 7.45 (dd,  $J = 7.8$  Hz,  $J = 1.7$  Hz, 1H), 7.49 (d,  $J = 3.9$  Hz, 1H), 7.66 (ddd,  $J = 8.0$  Hz,  $J = 1.6$  Hz,  $J = 0.9$  Hz, 1H), 7.71 (ddd,  $J = 8.0$  Hz,  $J = 7.2$  Hz,  $J = 1.8$  Hz, 1H), 8.36-8.39 (m, 1H), 8.57 (ddd,  $J = 4.9$  Hz,  $J = 1.8$  Hz,  $J = 1.0$  Hz, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  (ppm) 18.1, 33.3, 33.5, 41.4, 43.4, 55.1, 56.9 (d,  $J = 22.0$  Hz), 94.5 (d,  $J = 172.3$  Hz), 119.1, 121.7, 122.6, 123.9, 130.2, 131.4, 136.8, 137.1, 137.9, 147.4, 149.7, 149.7, 151.8, 156.5, 163.4. APCI-MS  $m/z$  425  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  424.1733. HPLC/MS system A purity 98 % ( $t_{\text{R}} = 14.7$  min).

**N-[(4-Fluoro-1-[[5-(2-methyl-1,3-thiazol-4-yl)-2-thienyl]carbonyl]piperidin-4-yl)methyl-N-(5-methylpyridin-2-yl)methyl]amine (8br)**. Synthesis was performed according to general procedure 1 employing 5-(2-methyl-1,3-thiazol-4-yl)thiophene-2-carboxylic acid (14.4 mg, 0.064 mmol) yielding **8br** (16.7 mg; 65 %) as a pale yellow oil. IR 3336, 2923, 1616, 1492, 1438, 1276, 1168, 1095, 968, 813, 748, 647  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.61-1.77 (m, 2H), 2.01-2.12 (m, 2H), 2.32 (s, 3H), 2.75 (s, 3H), 2.79 (d,  $J = 20.4$  Hz, 2H), 3.29-3.42 (m, 2H), 3.91 (s, 2H), 4.27-4.39 (m, 2H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.25-7.34 (m, 2H), 7.34 (d,  $J = 3.8$  Hz, 1H), 7.46 (dd,  $J = 7.8$  Hz,  $J = 1.7$  Hz, 1H), 8.37-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 19.2, 33.3, 33.5, 41.5, 55.2, 57.0 (d,  $J = 22.5$  Hz), 94.6 (d,  $J = 171.7$  Hz), 112.6, 121.7, 123.3, 129.9, 131.4, 135.8, 137.1, 141.2, 148.6, 149.7, 156.6, 163.4, 166.5. APCI-MS  $m/z$  445  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  444.1455. HPLC/MS system A purity 98 % ( $t_{\text{R}} = 15.0$  min).

**N-[4-Fluoro-1-[[3-(1H-pyrrol-1-yl)-2-thienyl]carbonyl]piperidin-4-yl)methyl-N-(5-methylpyridin-2-yl)methylamine (8bs)**. Synthesis was performed according to general procedure 1 employing 3-(1H-pyrrol-1-yl)thiophene-2-carboxylic acid (12.4 mg, 0.064 mmol) yielding **8bs** (17.6 mg; 74 %) as a pale yellow oil. IR 3340, 2923, 1627, 1558, 1488, 1450, 1272, 1083, 748  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.38-1.66 (m, 2H), 1.84-2.15 (m, 2H), 2.32 (s, 3H), 2.60 (d,  $J = 20.2$  Hz, 2H), 2.92-3.09 (m, 2H), 3.17-3.36 (m, 1H), 3.84 (s, 2H), 4.37-4.64 (m, 1H), 6.20-6.24 (m, 2H), 6.86-6.89 (m, 2H), 7.02 (d,  $J = 5.2$  Hz, 1H), 7.17 (d,  $J = 7.9$  Hz, 1H), 7.40 (d,  $J = 5.2$  Hz, 1H), 7.45 (dd,  $J = 7.8$  Hz,  $J = 1.7$  Hz, 1H), 8.35-8.39 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 32.2, 32.4, 38.1, 42.7, 55.1, 56.8 (d,  $J = 21.8$  Hz), 94.4 (d,  $J = 172.4$  Hz), 110.3, 120.9, 121.6, 123.0, 123.7, 126.8, 131.4, 136.8, 137.0, 149.6, 156.7, 162.2. APCI-MS  $m/z$  413  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  412.1733. HPLC/MS system A purity 99 % ( $t_{\text{R}} = 15.0$  min).

**N-[1-[(1-Benzothien-3-yl)carbonyl]-4-fluoropiperidin-4-yl)methyl-N-(5-methylpyridin-2-yl)methylamine (8bt)**. IR 3332, 2923, 1631, 1515, 1434, 1272, 1238, 1126, 763, 748  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.47-1.78 (m, 2H), 1.92-2.17 (m, 2H), 2.32 (s, 3H), 2.80 (d,  $J = 20.2$  Hz, 2H), 3.23-3.42 (m, 2H), 3.53-3.80 (m, 1H), 3.90 (s, 2H), 4.18-5.03 (m, 1H), 7.20 (d,  $J = 7.7$  Hz, 1H), 7.36-7.44 (m, 2H), 7.45 (dd,  $J = 7.8$  Hz,  $J = 1.7$  Hz, 1H), 7.55 (s, 1H), 7.76-7.83 (m, 1H), 7.84-7.90 (m, 1H), 8.36-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  (ppm) 18.1, 33.1, 33.9, 38.0, 43.3, 55.1, 56.9 (d,  $J = 23.1$  Hz), 94.5 (d,  $J = 171.2$  Hz), 121.6, 122.6, 122.9, 124.9, 125.0, 126.4, 131.4, 131.8, 136.9, 137.1, 139.8, 149.6, 156.5, 164.4. APCI-MS  $m/z$  398  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  397.1624. HPLC/MS system A purity 96 % ( $t_{\text{R}} = 15.6$  min).

**N-[1-[(1-Benzothien-2-yl)carbonyl]-4-fluoropiperidin-4-yl)methyl-N-(5-methylpyridin-2-yl)methylamine (8bu)**. Synthesis was performed according to general procedure 1 employing

1-benzothiophene-2-carboxylic acid (11.4 mg, 0.064 mmol) yielding **8bu** (18.2 mg; 80 %) as a pale yellow oil. IR 2923, 2360, 2333, 1623, 1523, 1442, 1272, 752  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.74-1.80 (m, 2H), 2.00-2.12 (m, 2H), 2.32 (s, 3H), 2.80 (d,  $J = 20.2$  Hz, 2H), 3.24-3.48 (m, 2H), 3.91 (s, 2H), 4.14-4.55 (m, 2H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.35-7.42 (m, 2H), 7.42-7.49 (m, 2H), 7.77-7.88 (m, 2H), 8.35-8.41 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 33.3, 33.5, (two signals, overlapped by signals of noise), 55.2, 57.0 (d,  $J = 21.8$  Hz), 94.5 (d,  $J = 171.7$  Hz), 121.7, 122.4, 124.6, 124.8, 125.0, 125.8, 131.4, 136.7, 137.1, 138.7, 140.1, 149.7, 156.5, 163.8. APCI-MS  $m/z$  398  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  397.1626. HPLC/MS system A purity 96 % ( $t_R = 15.8$  min).

**N-[1-[(5-Bromo-1-benzothien-2-yl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bv)**. Synthesis was performed according to general procedure 1 employing 5-bromo-1-benzothiophene-2-carboxylic acid (16.5 mg, 0.064 mmol) yielding **8bv** (4.0 mg; 15 %) as a pale yellow oil.  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.70-1.79 (m, 2H), 2.03-2.08 (m, 2H), 2.32 (s, 3H), 2.80 (d,  $J = 20.6$  Hz, 2H), 3.07-3.61 (m, 2H), 3.91 (s, 2H), 3.97-4.74 (m, 2H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.38 (s, 1H), 7.45 (dd,  $J = 7.7$  Hz,  $J = 1.7$  Hz, 1H), 7.49 (dd,  $J = 8.7$  Hz,  $J = 1.9$  Hz, 1H), 7.70 (d,  $J = 8.7$  Hz, 1H), 7.95 (d,  $J = 1.9$  Hz, 1H), 8.37-8.39 (m, 1H). APCI-MS  $m/z$  477  $[\text{M}+1]^+$ . HPLC/MS system A purity 96 % ( $t_R = 17.0$  min).

**N-[1-[(1-Benzofuran-3-yl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bw)**. IR 3332, 2923, 1631, 1565, 1446, 1103, 752  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.50-1.87 (m, 2H), 1.95-2.15 (m, 2H), 2.32 (s, 3H), 2.79 (d,  $J = 20.6$  Hz, 2H), 3.21-3.55 (m, 2H), 3.90 (s, 2H), 4.06-4.91 (m, 2H), 7.19 (d,  $J = 7.9$  Hz, 1H), 7.31 (ddd,  $J = 7.4$  Hz,  $J = 7.6$  Hz,  $J = 1.0$  Hz, 1H), 7.35 (ddd,  $J = 8.1$  Hz,  $J = 7.2$  Hz,  $J = 1.0$  Hz, 1H), 7.45 (dd,  $J = 7.9$  Hz,  $J = 1.5$  Hz, 1H), 7.53 (d,  $J = 8.3$  Hz, 1H), 7.63 (d,  $J = 7.6$  Hz, 1H), 7.86 (s, 1H), 8.36-8.39 (m, 1H). APCI-MS  $m/z$  382  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  381.1853. HPLC/MS system A purity 98 % ( $t_R = 15.1$  min).

**N-[1-[(1-Benzofuran-2-yl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bx)**. Synthesis was performed according to general procedure 1 employing 1-benzofuran-2-carboxylic acid (26.1 mg, 0.160 mmol) yielding **8bx** (30.1 mg; 49 %) as a pale yellow oil. IR 2923, 2850, 1331, 1565, 1434, 1373, 1288, 1253, 1099, 971, 786, 740  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.65-1.86 (m, 2H), 2.04-2.15 (m, 2H), 2.32 (s, 3H), 2.80 (d,  $J = 20.2$  Hz, 2H), 3.00-3.68 (m, 2H), 3.91 (s, 2H), 4.11-4.73 (m, 2H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.26-7.32 (m, 2H), 7.41 (ddd,  $J = 8.3$  Hz,  $J = 7.2$  Hz,  $J = 1.2$  Hz, 1H), 7.45 (dd,  $J = 7.8$  Hz,  $J = 1.7$  Hz, 1H), 7.52 (ddd,  $J = 7.3$  Hz,  $J = 1.6$  Hz,  $J = 0.8$  Hz, 1H), 7.64 (ddd,  $J = 7.7$  Hz,  $J = 1.3$  Hz,  $J = 0.6$  Hz, 1H), 8.35-8.39 (m, 1H). APCI-MS  $m/z$  382  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  381.1852. HPLC/MS system A purity >99 % ( $t_R = 15.0$  min).

**N-[4-Fluoro-1-[pyrazolo[1,5-*a*]pyridin-3-yl]carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8by)**. Synthesis was performed according to general procedure 1 employing pyrazolo[1,5-*a*]pyridin-3-carboxylic acid (10.4 mg, 0.064 mmol) yielding **8by** (21.5 mg; 98 %) as a pale yellow oil. IR 3405, 2927, 2360, 1623, 1442, 1373, 1292, 1072, 875, 748  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.62-1.80 (m, 2H), 2.02-2.13 (m, 2H), 2.32 (s, 3H), 2.82 (d,  $J = 20.2$  Hz, 2H), 3.32-3.48 (m, 2H), 3.93 (s, 2H), 4.24-4.40 (m, 2H), 6.90 (ddd,  $J = 6.9$  Hz,  $J = 6.9$  Hz,  $J = 1.3$  Hz, 1H), 7.21 (d,  $J = 7.7$  Hz, 1H), 7.31 (ddd,  $J = 8.7$  Hz,  $J = 7.0$  Hz,  $J = 1.2$  Hz, 1H), 7.46 (dd,  $J = 7.8$  Hz,  $J = 1.7$  Hz, 1H), 7.95 (ddd,  $J = 8.8$  Hz,  $J = 1.0$  Hz,  $J = 1.0$  Hz, 1H), 8.04 (s, 1H), 8.36-8.40 (m, 1H), 8.48 (ddd,  $J = 7.0$  Hz,  $J = 1.0$  Hz,  $J = 1.0$  Hz, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  (ppm) 18.1, 33.4, 33.5, 40.2, 55.0, 57.0 (d,  $J = 22.0$  Hz), 94.6 (d,  $J = 172.3$  Hz), 106.0, 113.3, 119.1, 121.7, 125.9, 128.8,

131.5, 137.1, 140.8, 141.7, 149.7, 156.3, 164.1. APCI-MS  $m/z$  382  $[M+1]^+$ . HR-EIMS  $m/z$  381.1964. HPLC/MS system A purity >99 % ( $t_R$  = 12.7 min).

**N-[4-Fluoro-1-[(pyrazolo[1,5-*a*]pyridin-2-yl)carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8bz).** Synthesis was performed according to general procedure 1 employing pyrazolo[1,5-*a*]pyridin-2-carboxylic acid (26.0 mg, 0.160 mmol) yielding **8bz** (47.9 mg; 79 %) as a pale yellow oil. IR 3498, 2923, 1631, 1504, 1241, 1103, 883, 763  $\text{cm}^{-1}$ . IR 3498, 2923, 1631, 1504, 1241, 1103, 883, 763  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.67-1.87 (m, 2H), 1.97-2.17 (m, 2H), 2.32 (s, 3H), 2.80 (d,  $J$  = 20.6 Hz, 2H), 3.14-3.28 (m, 1H), 3.44-3.57 (m, 1H), 3.92 (s, 2H), 4.42-4.67 (m, 2H), 6.77-6.87 (m, 2H), 7.14 (ddd,  $J$  = 8.9 Hz,  $J$  = 6.8 Hz,  $J$  = 1.1 Hz, 1H), 7.21 (d,  $J$  = 7.9 Hz, 1H), 7.46 (dd,  $J$  = 7.8 Hz,  $J$  = 1.7 Hz, 1H), 7.56 (ddd,  $J$  = 8.9 Hz,  $J$  = 1.2 Hz,  $J$  = 1.2 Hz, 1H), 8.37-8.39 (m, 1H), 8.41 (ddd,  $J$  = 7.0 Hz,  $J$  = 2.0 Hz,  $J$  = 0.9 Hz, 1H). APCI-MS  $m/z$  382  $[M+1]^+$ . HR-EIMS  $m/z$  381.1965. HPLC/MS system A purity 99 % ( $t_R$  = 13.8-13.9 min).

**N-[1-[(1-Benzotellurophen-2-yl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ca).** Synthesis was performed according to general procedure 1 employing 1-benzotellurophen-2-carboxylic acid (17.5 mg, 0.064 mmol) yielding **8ca** (19.1 mg; 68 %) as a pale yellow oil. IR 3340, 2923, 1612, 1438, 1272, 752  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.57-1.82 (m, 2H), 1.99-2.10 (m, 2H), 2.32 (s, 3H), 2.80 (d,  $J$  = 20.2 Hz, 2H), 3.24- 3.41 (m, 2H), 3.90 (s, 2H), 4.24-4.41 (m, 2H), 7.14-7.23 (m, 2H), 7.35-7.42 (m, 1H), 7.45 (dd,  $J$  = 7.7 Hz,  $J$  = 1.8 Hz, 1H), 7.81 (ddd,  $J$  = 8.0 Hz,  $J$  = 1.7 Hz,  $J$  = 1.5 Hz, 1H), 7.85-7.92 (m, 2H), 8.34- 8.41 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 360 MHz)  $\delta$  (ppm) 18.1, 33.2, 33.5, 40.6, 42.0, 55.2, 57.0 (d,  $J$  = 22.5 Hz), 94.5 (d,  $J$  = 171.7 Hz), 121.7, 125.5, 125.6, 128.9, 131.4, 131.9, 134.1, 135.0, 135.9, 137.1, 147.2, 149.7, 156.6, 167.7. APCI-MS  $m/z$  494  $[M+1]^+$ . HR-EIMS  $m/z$  495.0968. HPLC/MS system A purity 98 % ( $t_R$  = 15.8 min).

**N-[4-Fluoro-1-[(1*H*-indol-2-yl)carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8cb).** Synthesis was performed according to general procedure 1 employing indol-2-carboxylic acid (25.8 mg, 0.160 mmol) yielding **8cb** (3.4 mg; 6 %) as a pale yellow oil.  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.70-1.82 (m, 2H), 2.07-2.15 (m, 2H), 2.32 (s, 3H), 2.80 (d,  $J$  = 20.2 Hz, 2H), 3.25-3.65 (m, 2H), 3.91 (s, 2H), 4.51-4.58 (m, 2H), 6.77 (dd,  $J$  = 2.3 Hz,  $J$  = 0.9 Hz, 1H), 7.14 (ddd,  $J$  = 8.1 Hz,  $J$  = 6.9 Hz,  $J$  = 1.0 Hz, 1H), 7.21 (d,  $J$  = 7.9 Hz, 1H), 7.28 (ddd,  $J$  = 8.3 Hz,  $J$  = 6.9 Hz,  $J$  = 1.0 Hz, 1H), 7.42 (dd,  $J$  = 8.3 Hz,  $J$  = 1.0 Hz, 1H), 7.45 (dd,  $J$  = 7.7 Hz,  $J$  = 1.7 Hz, 1H), 7.64 (dd,  $J$  = 8.0 Hz,  $J$  = 1.0 Hz, 1H), 8.37-8.50 (m, 1H), 9.14 (bs, 1H). APCI-MS  $m/z$  381  $[M+1]^+$ . HPLC/MS system A purity 94 % ( $t_R$  = 13.4 min).

**N-[4-Fluoro-1-[(1*H*-indol-5-yl)carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8cc).** Synthesis was performed according to general procedure 1 employing indol-5-carboxylic acid (25.8 mg, 0.160 mmol) yielding **8cc** (34.2 mg; 62 %) as a pale yellow oil. IR 3220, 2923, 1608, 1434, 1288, 1103, 732  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.69-1.87 (m, 2H), 1.93-2.09 (m, 2H), 2.32 (s, 3H), 2.79 (d,  $J$  = 20.2 Hz, 2H), 3.18-3.40 (m, 2H), 3.91 (s, 2H), 6.58 (ddd,  $J$  = 3.1 Hz,  $J$  = 2.1 Hz,  $J$  = 1.0 Hz, 1H), 3.99-4.87 (m, 2H), 7.20 (d,  $J$  = 7.9 Hz, 1H), 7.23- 7.27 (m, 2H), 7.37-7.41 (m, 1H), 7.46 (dd,  $J$  = 7.8 Hz,  $J$  = 1.7 Hz, 1H), 7.72 (s, 1H), 8.36-8.40 (m, 1H), 8.55 (bs, 1H). APCI-MS  $m/z$  381  $[M+1]^+$ . HR-EIMS  $m/z$  380.2006. HPLC/MS system A purity 99 % ( $t_R$  = 13.7-14.0 min).

**N-[1-[(1*H*-1,2,3-Benzotriazol-5-yl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8cd).** Synthesis was performed according to general procedure 1 employing 1*H*-1,2,3-benzotriazol-5-carboxylic acid (26.1 mg, 0.160 mmol)

yielding **8ce** (13.4 mg; 24 %) as a pale yellow oil. IR 3467, 2923, 1627, 1442, 825, 736  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.28-1.86 (m, 2H), 1.87-2.15 (m, 2H), 2.33 (s, 3H), 2.87 (d,  $J = 20.0$  Hz, 2H), 3.16-3.72 (m, 3H), 3.99 (s, 2H), 4.44-4.75 (m, 1H), 7.23 (d,  $J = 7.7$  Hz, 1H), 7.41 (dd,  $J = 8.6$  Hz,  $J = 1.4$  Hz, 1H), 7.49 (dd,  $J = 7.8$  Hz,  $J = 1.7$  Hz, 1H), 7.80 (dd,  $J = 8.5$  Hz,  $J = 0.9$  Hz, 1H), 7.85 (dd,  $J = 1.2$  Hz,  $J = 1.2$  Hz, 1H), 8.37- 8.43 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  (ppm) 18.2, 32.9, 33.5, 38.3, 43.7, 54.7, 56.8 (d,  $J = 23.1$  Hz), 94.2 (d,  $J = 171.2$  Hz), 114.2, 115.6, 122.0 (2C), 124.5, 132.0, 132.8, 137.6 (2C), 149.5, 155.6, 170.1. APCI-MS  $m/z$  383  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  382.1917. HPLC/MS system A purity 100 % ( $t_R = 12.4$  min).

**N-[1-[(1*H*-Benzimidazol-5-yl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ce)**. Synthesis was performed according to general procedure 1 employing 1*H*-benzimidazol-5-carboxylic acid (25.9 mg, 0.160 mmol) yielding **8ce** (21.0 mg; 38 %) as a pale yellow oil. IR 3093, 2923, 1619, 1442, 1288, 1129, 1095, 937, 879, 825, 736  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.56-1.85 (m, 2H), 1.85-2.18 (m, 2H), 2.32 (s, 3H), 2.83 (d,  $J = 20.0$  Hz, 2H), 3.14-3.41 (m, 2H), 3.94 (s, 2H), 4.18-4.92 (m, 2H), 7.21 (d,  $J = 7.8$  Hz, 1H), 7.24 (dd,  $J = 8.3$  Hz,  $J = 1.5$  Hz, 1H), 7.47 (dd,  $J = 7.9$  Hz,  $J = 1.8$  Hz, 1H), 7.53 (d,  $J = 8.3$  Hz, 1H), 7.63 (s, 1H), 7.96 (s, 1H), 8.40 (dd,  $J = 1.5$  Hz,  $J = 0.8$  Hz, 1H). APCI-MS  $m/z$  382  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  381.1963.

**N-[4-Fluoro-1-[(4,5,6,7-tetrahydro-2-benzothien-1-yl)carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8cf)**. Synthesis was performed according to general procedure 1 employing 4,5,6,7-tetrahydro-2-benzothiophene-2-carboxylic acid (11.7 mg, 0.064 mmol) yielding **8cf** (16.7 mg; 70 %) as a pale yellow oil. IR 3328, 2927, 2857, 1627, 1454, 1276, 1118, 752  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.54-1.68 (m, 2H), 1.68-1.80 (m, 4H), 1.96-2.08 (m, 2H), 2.32 (s, 3H), 2.64-2.73 (m, 4H), 2.78 (d,  $J = 20.6$  Hz, 2H), 3.22-3.34 (m, 2H), 3.90 (s, 2H), 4.05-4.22 (m, 2H), 6.91 (s, 1H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.45 (dd,  $J = 7.8$  Hz,  $J = 1.7$  Hz, 1H), 8.37-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 23.0, 23.1, 25.6, 26.1, 33.3, 33.6, 40.9 (2C), 55.2, 57.0 (d,  $J = 21.8$  Hz), 94.6 (d,  $J = 171.7$  Hz), 120.2, 121.7, 128.8, 131.4, 137.1, 138.6, 138.6, 149.7, 156.6, 164.8. APCI-MS  $m/z$  402  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  401.1937. HPLC/MS system A purity 98 % ( $t_R = 16.0$  min).

**N-[1-[(7-Bromo-2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-yl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8cg)**. Synthesis was performed according to general procedure 1 employing 7-bromo-2,3-dihydrothieno[3,4-*b*][1,4]dioxin-5-carboxylic acid (17.0 mg, 0.064 mmol) yielding **8cg** (9.7 mg; 35 %) as a pale yellow oil. IR 3324, 2923, 2873, 1612, 1496, 1442, 1361, 1276, 1087, 914, 748  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.71-1.83 (m, 2H), 1.97-2.09 (m, 2H), 2.32 (s, 3H), 2.78 (d,  $J = 20.7$  Hz, 2H), 3.21-3.35 (m, 2H), 3.90 (s, 2H), 3.99-4.17 (m, 2H), 4.23-4.32 (m, 4H), 7.19 (d,  $J = 7.9$  Hz, 1H), 7.45 (dd,  $J = 7.8$  Hz,  $J = 1.7$  Hz, 1H), 8.35-8.39 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 33.3, 33.5, 41.3 (2C), 55.2, 57.0 (d,  $J = 21.8$  Hz), 64.6, 64.9, 92.0, 94.6 (d,  $J = 171.7$  Hz), 113.0, 121.7, 131.4, 137.0, 138.7, 138.9, 149.7, 156.6, 161.2. APCI-MS  $m/z$  486  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  483.0621. HPLC/MS system A purity 94 % ( $t_R = 15.6$  min).

**N-[4-Fluoro-1-[(thieno[3,2-*b*]thien-2-yl)carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ch)**. Synthesis was performed according to general procedure 1 employing thieno[3,2-*b*]thiophene-2-carboxylic acid (11.8 mg, 0.064 mmol) yielding **8ch** (7.5 mg; 33 %) as a pale yellow oil.  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.60-1.82 (m, 2H), 2.01-2.12 (m, 2H), 2.32 (s, 3H), 2.79 (d,  $J = 20.2$  Hz, 2H), 3.30-3.44 (m, 2H), 3.90 (s, 2H), 4.28-4.40 (m, 2H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.26-7.28 (m, 1H), 7.42-7.50 (m, 3H), 8.36-8.39 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 33.3, 33.5, (two signals

overlapped by signals of noise), 55.2, 57.0 (d,  $J = 22.5$  Hz), 94.5 (d,  $J = 172.4$  Hz), 119.5, 121.1, 121.7, 129.7, 131.4, 137.1, 138.4, 138.5, 141.1, 149.7, 156.6, 163.5. APCI-MS  $m/z$  404  $[M+1]^+$ . HR-EIMS  $m/z$  403.1186. HPLC/MS system A purity 97 % ( $t_R = 15.2$  min).

**N-[4-Fluoro-1-[(thieno[2,3-*b*]thien-2-yl)carbonyl]piperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8ci).** Synthesis was performed according to general procedure 1 employing thieno[2,3-*b*]thiophene-2-carboxylic acid (11.8 mg, 0.064 mmol) yielding **8ci** (16.4 mg; 69 %) as a pale yellow oil. IR 3390, 2360, 2337, 1616, 1523, 1438, 1272, 1095, 968, 748, 647  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.61-1.75 (m, 2H), 2.02-2.13 (m, 2H), 2.32 (s, 3H), 2.80 (d,  $J = 20.2$  Hz, 2H), 3.31-3.45 (m, 2H), 3.91 (s, 2H), 4.29-4.41 (m, 2H), 7.20 (d,  $J = 8.0$  Hz, 1H), 7.23 (d,  $J = 5.4$  Hz, 1H), 7.38 (d,  $J = 5.2$  Hz, 1H), 7.42 (s, 1H), 7.45 (dd,  $J = 7.9$  Hz,  $J = 1.6$  Hz, 1H), 8.36-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 90 MHz)  $\delta$  (ppm) 18.1, 33.3, 33.5, 41.5 (2C), 55.2, 57.0 (d,  $J = 22.5$  Hz), 94.5 (d,  $J = 171.7$  Hz), 120.2, 121.3, 121.7, 128.8, 131.4, 137.1, 139.9, 140.0, 145.8, 149.7, 156.6, 163.4. APCI-MS  $m/z$  404  $[M+1]^+$ . HR-EIMS  $m/z$  403.1187. HPLC/MS system A purity 98 % ( $t_R = 15.3$  min).

**N-[1-[(3-Chlorothieno[2,3-*b*]thien-2-yl)carbonyl]-4-fluoropiperidin-4-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (8cj).** Synthesis was performed according to general procedure 1 employing 3-chlorothieno[2,3-*b*]thiophene-2-carboxylic acid (14.0 mg, 0.064 mmol) yielding **8cj** (20.6 mg; 81 %) as a pale yellow oil. IR 3340, 2923, 1631, 1488, 1438, 1380, 1276, 1110, 748, 667  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.62-1.83 (m, 2H), 2.00-2.13 (m, 2H), 2.32 (s, 3H), 2.80 (d,  $J = 20.4$  Hz, 2H), 3.22-3.53 (m, 2H), 3.91 (s, 2H), 3.97-4.58 (m, 2H), 7.20 (d,  $J = 7.9$  Hz, 1H), 7.21 (d,  $J = 5.4$  Hz, 1H), 7.42 (d,  $J = 5.2$  Hz, 1H), 7.45 (dd,  $J = 7.8$  Hz,  $J = 1.9$  Hz, 1H), 8.36-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  (ppm) 18.1, 33.3 (2C), 38.6, 43.3, 55.2, 56.9 (d,  $J = 22.0$  Hz), 94.4 (d,  $J = 172.3$  Hz), 116.6, 119.1, 121.7, 129.5, 131.4, 132.2, 136.6, 137.1, 143.9, 149.7, 156.6, 161.2. APCI-MS  $m/z$  438  $[M+1]^+$ . HR-EIMS  $m/z$  437.0799. HPLC/MS system A purity 95 % ( $t_R = 15.9$  min).

**4-[[[(5-Methylpyridin-2-yl)methyl]amino]methyl]-1-(3-thienylcarbonyl)piperidin-4-ol (11).** For the synthesis of compound **11** the benzoylpiperidinol **10** (273.0 mg, 0.80 mmol) was hydrolysed as described for **7** to get the intermediate 4-[[[(5-methylpyridin-2-yl)methyl]amino]methyl]piperidin-4-ol trihydrochloride (50.1 mg; 80 %) as a yellowish solid. APCI-MS  $m/z$  236  $[M+1]^+$  (free base). HPLC/MS system B purity 93 % ( $t_R = 12.7$  min). Subsequently, thiophene-3-carboxylic acid (10.4 mg, 0.081 mmol) and DIPEA (0.07 mL) were dissolved in dry  $\text{CH}_2\text{Cl}_2$  (2 mL) and cooled to 0 °C. TBTU (25.1 mg, 0.078 mmol) was dissolved in DMF (0.3 mL) and added dropwise to the reaction mixture which was warmed to RT. Finally, 4-[[[(5-methylpyridin-2-yl)methyl]amino]methyl]piperidin-4-ol trihydrochloride (25.0 mg, 0.072 mmol) and DIPEA (0.4 mL) were dissolved in  $\text{CH}_2\text{Cl}_2$  and added to the reaction mixture. Stirring was continued for 16 h. The mixture was washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was removed in vacuo. The product was purified by flash chromatography ( $\text{CH}_2\text{Cl}_2$ -MeOH 98:2) to give pure **11** (8.5 mg; 34 %) as a pale oil. IR 3330, 2925, 1615, 1442, 1273  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  (ppm) 1.55-1.88 (m, 5H), 2.36 (s, 3H), 2.82 (s, 2H), 2.43-3.60 (m, 1H), 3.66-3.85 (m, 1H), 4.10 (s, 2H), 4.22-4.44 (m, 1H), 7.20 (dd,  $J = 5.5$  Hz,  $J = 1.2$  Hz, 1H), 7.37 (d,  $J = 7.9$  Hz, 1H), 7.51 (dd,  $J = 4.9$  Hz,  $J = 3.0$  Hz, 1H), 7.65-7.69 (m, 2H), 7.39-8.43 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 150 MHz)  $\delta$  (ppm) 18.1, 35.6, 36.5, 39.4, 44.8, 54.1, 59.2, 69.5, 123.9, 127.6, 127.7, 127.9, 134.6, 137.3, 139.3, 150.5, 153.7, 168.0. APCI-MS  $m/z$  346  $[M+1]^+$ . HR-EIMS  $m/z$  345.1512. HPLC/MS system A purity 99 % ( $t_R = 13.0$  min).

**1-(3-Chloro-4-fluorobenzoyl)-4-[[[(5-methylpyridin-2-yl)methyl]amino]methyl]piperidin-4-ol (12).** The synthesis was performed according to the

synthesis of **11** using 3-chloro-4-fluoro benzoic acid (14.1 mg, 0.081 mmol) to give pure **12** (5.8 mg; 21 %) as a pale oil. IR 3376, 2924, 1630, 1440, 1260  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.34-1.44 (m, 1H), 1.48-1.60 (m, 2H), 1.65-1.73 (m, 1H), 2.33 (s, 3H), 2.61 (s, 2H), 3.18-3.34 (m, 1H), 3.41-3.61 (m, 2H), 3.93 (s, 2H), 4.34-4.59 (m, 1H), 7.13 (d,  $J = 7.9$  Hz, 1H), 7.16 (dd,  $J = 8.7$  Hz,  $J = 8.7$  Hz, 1H), 7.28 (ddd,  $J = 8.7$  Hz,  $J = 4.7$  Hz,  $J = 2.3$  Hz, 1H), 7.45-7.49 (m, 2H), 8.37-8.40 (m, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  (ppm) 18.2, 35.1, 36.2, 38.6, 44.1, 55.2, 59.1, 68.4, 116.7 (d,  $J = 22.0$  Hz), 121.4 (d,  $J = 17.6$  Hz), 121.9, 127.1 (d,  $J = 7.7$  Hz), 127.1, 131.8, 133.33 (d,  $J = 4.4$  Hz), 137.3, 149.7, 156.0, 158.7 (d,  $J = 252.5$  Hz), 167.9. APCI-MS  $m/z$  392  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  391.1461. HPLC/MS system A purity 98 % ( $t_R = 15.4$  min).

**8-(3-Thienylcarbonyl)-8-azabicyclo[3.2.1]octan-3-one (14)**. Thiophene-3-carboxylic acid (159 mg, 1.25 mmol) and DIPEA (1.36 mL) were dissolved in dry  $\text{CH}_2\text{Cl}_2$  (30 mL) and cooled to 0 °C. TBTU (388 mg, 1.21 mmol) was dissolved in DMF (4 mL) and added drop wise to the reaction mixture. The mixture was warmed to RT. Nortropinone was deprotonated by treating **13** (179 mg, 1.11 mmol) with 2N NaOH and subsequent extraction with  $\text{CH}_2\text{Cl}_2$ . The obtained nortropinone was dissolved in  $\text{CH}_2\text{Cl}_2$  together with DIPEA (0.4 mL) and added to the reaction mixture. Stirring was continued for 2 h. The mixture was washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was removed in vacuo. The product was purified by flash chromatography ( $\text{CH}_2\text{Cl}_2$ -MeOH 95:5) to give pure **14** (228.0 mg; 87.4 %) as a light red solid. IR 3100, 2958, 2884, 1715, 1621  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.72-1.84 (m, 2H), 2.11-2.22 (m, 2H), 2.34-2.51 (m, 2H), 2.54-3.01 (m, 2H), 4.39-5.22 (m, 2H), 7.31 (dd,  $J = 4.9$  Hz,  $J = 1.1$  Hz, 1H), 7.38 (dd,  $J = 4.9$  Hz,  $J = 3.0$  Hz, 1H), 7.69 (dd,  $J = 2.8$  Hz,  $J = 1.3$  Hz, 1H).  $^{13}\text{C}$  NMR (90 MHz, at 57 °C,  $\text{CDCl}_3$ ) 28.9 (2C), 49.3 (2C), 53.7, 126.1, 127.0, 127.3, 136.8, 163.8, 206.6. APCI-MS  $m/z$  236  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  235.0668. HPLC/MS system B purity 99 % ( $t_R = 9.7$  min).

**8-(3-Thienylcarbonyl)spiro[8-azabicyclo[3.2.1]octane-3,2'-oxirane] (endo-O) (16)**. A suspension of NaH (27.9 mg, 0.67 mmol; 60% in oil) in DMSO (2 mL) was stirred at 65 °C for 2 h. After cooling to RT trimethylsulfoxonium iodide (147.5 mg, 0.76 mmol) was added and stirring at RT was continued for 15 min. Then, **14** (150.0 mg, 0.64 mmol) dissolved in DMSO (2 mL) was added to the mixture within 30 min and the solution was stirred for 3.5 h at 60 °C. The reaction mixture was poured into water and extracted with ethyl acetate for three times. The combined organic layers were washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated in vacuo to give pure **16** (148.0 mg; 93 %) as a light brown solid.  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.21-1.40 (m, 2H), 1.97-2.11 (m, 2H), 2.14-2.24 (m, 2H), 2.28-2.67 (m, 4H), 4.27-4.55 (m, 1H), 4.80-5.03 (m, 1H), 7.27 (dd,  $J = 4.9$  Hz,  $J = 1.2$  Hz, 1H), 7.34 (dd,  $J = 5.0$  Hz,  $J = 3.0$  Hz, 1H), 7.61 (dd,  $J = 3.0$  Hz,  $J = 1.4$  Hz, 1H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 26.7, 28.4, 38.9, 40.9, 48.2, 51.9, 54.5, 56.3, 125.9, 126.7, 127.1, 137.2, 163.1. APCI-MS  $m/z$  250  $[\text{M}+1]^+$ . HPLC/MS system A purity 99 % ( $t_R = 17.6$  min).

**[3-Fluoro-8-(3-thienylcarbonyl)-8-azabicyclo[3.2.1]oct-3-yl]methanol (endo-CH<sub>2</sub>) (18)**. To a cooled solution of **16** (118.5 mg, 0.48 mmol) in 0.5 mL  $\text{CH}_2\text{Cl}_2$  poly(hydrogene fluoride)pyridine 70% (140.8 mg, 1.42 mmol) was added drop wise at -10° C. The solution was warmed to RT and was stirred for 16 h. Then, it was poured into water, which was neutralised with 50%  $\text{K}_2\text{CO}_3$  to pH = 7 and extracted with  $\text{CH}_2\text{Cl}_2$  for three times. The combined organic layers were washed with water, 1N HCl and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to get crude product. Purification was performed with preparative HPLC (MeOH/0.1% aqueous formic acid, gradient (MeOH): 30% to 43% in 13 min, 43% for 2 min, 43% to 95% in 2 min, 95% for 2 min,  $t_R = 12.3$  min) to give pure **18** (45.9 mg; 36 %) as a pale green oil.  $^1\text{H}$  NMR (360 MHz, 280K,  $\text{CDCl}_3$ ) 1.56-2.58 (m, 8H), 3.73 (d,  $J = 26.6$

Hz, 2H), 4.28-4.44 (m, 1H), 4.78-4.97 (m, 1H), 7.28 (dd,  $J = 5.0$  Hz,  $J = 1.1$  Hz, 1H), 7.36 (dd,  $J = 5.0$  Hz,  $J = 3.0$  Hz, 1H), 7.65 (dd,  $J = 3.0$  Hz,  $J = 1.4$  Hz, 1H).  $^{13}\text{C}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 27.4, 29.2, 38.1, 39.1, 50.2, 54.6, 69.3 (d,  $J = 26.4$  Hz), 95.2 (d,  $J = 169.8$  Hz), 126.0, 127.0, 127.1, 136.9, 163.2. APCI-MS  $m/z$  270  $[\text{M}+1]^+$ . HPLC/MS system B purity 99 % ( $t_{\text{R}} = 14.9$  min).

**[3-Fluoro-8-(3-thienylcarbonyl)-8-azabicyclo[3.2.1]oct-3-yl]methyl methane sulfonic acid (*endo*-CH<sub>2</sub>) (20)** The alcohol **18** (22.3 mg, 0.08 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (4 mL) and THF (1 mL) supplemented with  $\text{Et}_3\text{N}$  (14.3 mg, 0.14 mmol) and was cooled to 0 °C. Methane sulfonic acid chloride (9.48 mg, 0.08 mmol) was added drop wise and the solution was stirred for 3 h at RT until quantitative conversion of the alcohol was observed by HPLC-MS. The organic layer was washed with water and was then frozen with liquid nitrogen. The solvent was removed by sublimation in vacuo to give crude **20** (28.8 mg; 100 %) as a yellowish oil. No further purification was performed. APCI-MS  $m/z$  348  $[\text{M}+1]^+$ .

**3-(Azidomethyl)-3-fluoro-8-(3-thienylcarbonyl)-8-azabicyclo[3.2.1]octane (*endo*-CH<sub>2</sub>) (22)**. Sodium azide (183.0 mg, 2.82 mmol) and **20** (28.8 mg, 0.08 mmol) were dissolved in DMF (2 mL) and were stirred at 120 °C for 2 d. The solution was cooled to RT, treated with ethyl acetate and washed with brine. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  and all organic layers were combined and dried ( $\text{Na}_2\text{SO}_4$ ). The solvent was removed in vacuo to give crude **22** (23.7 mg; 97 %) as a brown oil. No further purification was performed. APCI-MS  $m/z$  295  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  294.0951.

**N-[3-Fluoro-8-(3-thienylcarbonyl)-8-azabicyclo[3.2.1]oct-3-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (*endo*-CH<sub>2</sub>) (24)**. A solution of **22** (15.4 mg, 0.052 mmol), 5-methylpyridine-2-carbaldehyde (5.7 mg, 0.047 mmol) and triphenylphosphine (13.6 mg, 0.052 mmol) in MeOH (3 mL) was heated to reflux for 3 h. After cooling to RT  $\text{NaCNBH}_3$  (9.0 mg, 0.143 mmol) was added and the solution was stirred at RT for 18 h. The solvent was evaporated in vacuo and the remaining residue was poured into water. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  for three times, the combined organic layers were washed with water, brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to obtain crude product. The product was purified by flash chromatography ( $\text{CH}_2\text{Cl}_2$ -MeOH 97:3) to give pure **24** (6.6 mg; 38 % relating to aldehyde) as a brown oil. IR 3333, 3098, 2925, 2854, 1615, 1434  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.53-2.04 (m, 6H), 2.21-2.29 (m, 2H), 2.32 (s, 3H), 2.90 (d,  $J = 26.8$  Hz, 2H), 3.93 (s, 2H), 4.21-4.44 (m, 1H), 4.71-5.00 (m, 1H), 7.20-7.24 (m, 1H), 7.25-7.28 (m, 1H), 7.33 (dd,  $J = 5.0$  Hz,  $J = 3.0$  Hz, 1H), 7.46 (dd,  $J = 7.8$  Hz,  $J = 2.2$  Hz, 1H), 7.62 (dd,  $J = 2.8$  Hz,  $J = 2.2$  Hz, 1H), 8.36-8.40 (m, 1H).  $^{13}\text{C}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 18.2, 27.3, 29.1, 39.7, 40.7, 50.2, 54.6, 55.1, 58.7 (d,  $J = 23.8$  Hz), 95.2 (d,  $J = 170.4$  Hz), 125.8, 126.8, 127.1, 131.5, 137.1, 137.1, 149.6, 156.7, 163.0. APCI-MS  $m/z$  374  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  373.1627. HPLC/MS system B purity 96 % ( $t_{\text{R}} = 13.9$  min).

**8-(3-Chloro-4-fluorobenzoyl)-8-azabicyclo[3.2.1]octan-3-one (26)**. Synthesis was done according to **14** when using 3-chloro-4-fluorobenzoic acid (870.0 mg, 4.984 mmol). The product was purified by flash chromatography (hexane-ethyl acetate 1:1) to give pure **26** (617.2 mg; 62 %) as a brown solid.  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.75-1.85 (m, 2H), 2.12-2.27 (m, 2H), 2.33-3.04 (m, 4H), 4.23-4.66 (m, 1H), 4.81-5.20 (m, 1H), 7.19 (dd,  $J = 8.5$  Hz,  $J = 8.5$  Hz, 1H), 7.45 (ddd,  $J = 8.4$  Hz,  $J = 4.5$  Hz,  $J = 2.3$  Hz, 1H), 7.63 (dd,  $J = 6.9$  Hz,  $J = 2.2$  Hz, 1H).  $^{13}\text{C}$  NMR (90 MHz,  $\text{CDCl}_3$ ) 28.0, 29.7, 48.8, 49.7, 51.9, 56.4, 117.0 (d,  $J = 22.0$  Hz), 121.8 (d,  $J = 18.7$  Hz), 127.4 (d,  $J = 7.7$  Hz), 130.1, 132.5 (d,  $J = 4.4$  Hz), 159.4 (d,  $J = 253.6$  Hz), 166.6. APCI-MS  $m/z$  282  $[\text{M}+1]^+$ . HR-EIMS  $m/z$  281.0619. HPLC/MS system B purity 92 % ( $t_{\text{R}} = 9.5$  min).

**8-(3-Chloro-4-fluorobenzoyl)-3-methylen-8-azabicyclo[3.2.1]octane (27).** A solution of *t*-BuOK (450.2 mg, 4.012 mmol) and methyl triphenyl phosphonium bromide (1455 mg, 4.08 mmol) in THF (15 mL) were stirred for 2 h at 80 °C. After addition of a solution of **26** (1000 mg, 3.550 mmol) in THF the reaction mixture was stirred for 16 h at RT. Addition of diethyl ether yielded in precipitation, the resulting residue was filtered and was washed twice with diethyl ether. The filtrate was evaporated under reduced pressure and purified by flash chromatography (hexane-acetone 8:2) to give pure **27** (46.5 mg; 42 %) as a yellowish solid (mp 79 °C). <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ (ppm) 1.63-1.76 (m, 2H), 1.86-2.00 (m, 2H), 2.06-2.28 (m, 2H), 2.31-2.47 (m, 1H), 2.59-2.75 (m, 1H), 4.03-4.19 (m, 1H), 4.77-4.88 (m, 1H), 4.92 (s, br, 2H), 7.18 (dd, *J* = 8.6 Hz, *J* = 8.6 Hz, 1H), 7.39 (ddd, *J* = 8.4 Hz, *J* = 4.5 Hz, *J* = 2.0 Hz, 1H), 7.58 (dd, *J* = 6.9 Hz, *J* = 2.2 Hz, 1H). <sup>13</sup>C NMR (90 MHz, CDCl<sub>3</sub>) δ (ppm) 27.3, 28.7, 40.6, 42.4, 52.8, 57.5, 114.7, 116.7 (d, *J* = 21.8 Hz), 121.4 (d, *J* = 18.5 Hz), 127.3 (d, *J* = 7.9 Hz), 130.0, 133.6 (d, *J* = 4.6 Hz), 141.0, 159.0 (d, *J* = 252.3 Hz), 165.9. APCI-MS *m/z* 280 [M+1]<sup>+</sup>. HR-EIMS *m/z* 279.0828. HPLC/MS system A purity 98 % (*t<sub>R</sub>* = 15.7 min).

**3-(Bromomethyl)-8-(3-chloro-4-fluorobenzoyl)-3-fluoro-8-azabicyclo[3.2.1]octane (endo-CH<sub>2</sub>) (28).** To a solution of **27** (61.4 mg, 0.219 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) poly(hydrogen fluoride)pyridine (22.8 mg, 0.30 mmol) was added drop wise. The mixture was cooled to 0 °C and a solution of NBS (53.4 mg, 0.300 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added drop wise. Stirring was continued for 1 h at 0 °C. The reaction mixture was then neutralised with a saturated solution of K<sub>2</sub>CO<sub>3</sub> and was subsequently extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed in vacuo. Flash chromatography (hexane-ethyl acetate 1:1) gave pure **28** (35.0 mg; 42 %) as a pale oil. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ (ppm) 1.64-1.75 (m, 2H), 1.97-2.27 (m, 5H), 2.44-2.72 (m, 1H), 3.61 (d, *J* = 21.6 Hz, 2H), 4.01-4.26 (m, 1H), 4.75-4.01 (m, 1H), 7.19 (dd, *J* = 8.6 Hz, *J* = 8.6 Hz, 1H), 7.41 (ddd, *J* = 8.5 Hz, *J* = 4.6 Hz, *J* = 2.2 Hz, 1H), 7.58 (dd, *J* = 6.8 Hz, *J* = 2.0 Hz, 1H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ (ppm) 27.7, 29.8, 40.2 (d, *J* = 29.6 Hz), 41.1, 49.6, 54.4, 91.6 (d, *J* = 176.7 Hz), 116.8 (d, *J* = 22.0 Hz), 121.6 (d, *J* = 17.6 Hz), 127.2 (d, *J* = 7.7 Hz), 129.9, 132.9 (d, *J* = 4.4 Hz), 159.2 (d, *J* = 253.6 Hz), 165.9. APCI-MS *m/z* 380 [M+1]<sup>+</sup>. HPLC/MS system B purity 98 % (*t<sub>R</sub>* = 14.9 min).

**3-(Azidomethyl)-8-(3-chloro-4-fluorobenzoyl)-3-fluoro-8-azabicyclo[3.2.1]octane (endo-CH<sub>2</sub>) (29).** A solution of **28** (18.1 mg, 0.048 mmol) and NaN<sub>3</sub> (24.9 mg, 0.0383 mmol) in DMF (2 mL) was stirred at 80 °C for 2 d. After cooling to RT, ethyl acetate (20 mL) was added to the solution. DMF was removed by washing with brine. The aqueous layer was extracted with ethyl acetate, the combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was evaporated under reduced pressure to give the crude **29** which was used directly for the further synthesis without an additional purification step.

**N-[8-(3-Chloro-4-fluorobenzoyl)-3-fluoro-8-azabicyclo[3.2.1]oct-3-yl]methyl-N-(5-methylpyridin-2-yl)methylamine (endo-CH<sub>2</sub>) (30).** A solution of **29**, 5-methylpyridine-2-carbaldehyde (5.6 mg, 0.045 mmol) and triphenyl phosphine (11.9 mg, 0.045 mmol) in MeOH (51 mL) was stirred under reflux conditions for 3 h. After cooling to RT NaCNBH<sub>3</sub> (9.0 mg, 0.14 mmol) was added and the solution was stirred for further 4 h. Then the solvent was removed in vacuo and the remainder was poured on ice water. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> several times and the combined organic layers were washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The crude product was purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>-MeOH 99:1) to give pure **30** (2.1 mg; 11 % over two steps) as a pale oil. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ (ppm) 1.52-1.75 (m, 2H), 1.92-2.12 (m, 3H), 2.15-2.26 (m, 2H), 2.32 (s, 3H), 2.35-2.45 (m, 1H), 2.82-2.94 (m, 2H), 3.91 (s, 2H),

4.00-4.14 (m, 1H), 4.73-4.87 (m, 1H), 7.18 (dd,  $J = 8.5$  Hz,  $J = 8.5$  Hz, 1H), 7.22 (d,  $J = 7.6$  Hz, 1H), 7.40 (ddd,  $J = 8.3$  Hz,  $J = 4.5$  Hz,  $J = 1.9$  Hz, 1H), 7.46 (dd,  $J = 7.9$  Hz,  $J = 1.5$  Hz, 1H), 7.58 (dd,  $J = 7.0$  Hz,  $J = 2.1$  Hz, 1H), 8.36-8.40 (m, 1H). APCI-MS  $m/z$  420  $[M+1]^+$ . HPLC/MS system B purity 96 % ( $t_R = 10.5$  min).

**3-(Aminomethyl)-8-(3-thienylcarbonyl)-8-azabicyclo[3.2.1]octane-3-ol (*exo*-CH<sub>2</sub>) (32).**

Compound **32** was synthesized starting with the oxo precursor **14** via methenylation and selective ring opening. For this, a suspension of NaH (27.9 mg, 0.67 mmol; 60% in oil) in DMSO (2 mL) was stirred at 65 °C for 2 h. After cooling to RT trimethylsulfoxonium iodide (147.5 mg, 0.76 mmol) was added and stirring was continued for 15 min at RT. Then **14** (150.0 mg, 0.64 mmol) dissolved in DMSO (2 mL) was added to the mixture within 30 min and the solution was stirred for 3 h at 60 °C. The reaction mixture was poured into water and extracted with ethyl acetate for three times. The combined organic layers were washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated in vacuo to yield the *endo*-O isomer of 8-(3-thienylcarbonyl)spiro[8-azabicyclo[3.2.1]octane-3,2'-oxiran] as a crude product (148.0 mg; 93 %) as a beige solid. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 1.21-1.40 (m, 2H), 1.97-2.11 (m, 2H), 2.14-2.24 (m, 2H), 2.28-2.67 (m, 4H), 4.27-4.55 (m, 1H), 4.80-5.03 (m, 1H), 7.27 (dd,  $J = 4.9$  Hz,  $J = 1.2$  Hz, 1H), 7.34 (dd,  $J = 5.0$  Hz,  $J = 3.0$  Hz, 1H), 7.61 (dd,  $J = 3.0$  Hz,  $J = 1.4$  Hz, 1H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 26.7, 28.4, 38.9, 40.9, 48.2, 51.9, 54.5, 56.3, 125.9, 126.7, 127.1, 137.2, 163.1. APCI-MS  $m/z$  250  $[M+1]^+$ . HR-EIMS  $m/z$  249.0822. HPLC/MS system A purity 99 % ( $t_R = 17.6$  min).

Cooled in an ice-salt bath 8-(3-thienylcarbonyl)spiro[8-azabicyclo[3.2.1]octane-3,2'-oxiran] (176.0 mg, 0.706 mmol) was dissolved in MeOH, which was saturated with NH<sub>3</sub>, for 15 min. The reaction mixture was stirred at 60 °C for 5 days. After cooling to RT, the solvent was removed in vacuo to give crude product. Purification was performed by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>-MeOH 9:1) to give pure **32** (22.2 mg; 11.0 % over two steps) as a brown oil. IR 3355, 3095, 2959, 2941, 1596, 1522, 1455 cm<sup>-1</sup>. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 1.76-2.00 (m, 6H), 2.24-2.36 (m, 2H), 2.58 (s, 2H), 4.31-4.40 (m, 1H), 4.73-4.80 (m, 1H), 7.27 (dd,  $J = 5.2$  Hz,  $J = 1.2$  Hz, 1H), 7.50 (dd,  $J = 4.9$  Hz,  $J = 3.0$  Hz, 1H), 7.77 (dd,  $J = 3.0$  Hz,  $J = 1.3$  Hz, 1H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 27.4, 28.9, 40.9, 42.6, 52.8, 54.5, 57.4, 70.7, 127.4, 128.0, 128.3, 137.6, 164.9. APCI-MS  $m/z$  267  $[M+1]^+$ . HR-EIMS  $m/z$  266.1091. HPLC/MS system B purity 98 % ( $t_R = 3.1$  min).

**3-(Aminomethyl)-8-(3-chloro-4-fluorobenzoyl)-8-azabicyclo[3.2.1]octane-3-ol (*exo*-CH<sub>2</sub>) (33).**

Compound **33** was synthesized as described for **32**. The oxo derivative **26** (350.0 mg, 1.242 mmol) was reacted with pretreated trimethylsulfoxonium iodide (574.6 mg, 2.611 mmol), worked up and purified by flash chromatography (hexane-ethyl acetate 1:1) to give the *endo*-O isomer of 8-(3-chloro-4-fluorobenzoyl)spiro[8-azabicyclo[3.2.1]octane-3,2'-oxirane] (344.5 mg; 100 %) as a pale yellow solid (mp 90 °C). IR 3054, 2973, 2944, 2922, 1634, 1419 cm<sup>-1</sup>. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 1.20-1.41 (m, 2H), 1.99-2.36 (m, 5H), 2.49 (s, br, 2H), 2.53-2.65 (m, 1H), 4.07-4.30 (m, 1H), 4.78-4.99 (m, 1H), 7.19 (dd,  $J = 8.5$  Hz,  $J = 8.5$  Hz, 1H), 7.39 (ddd,  $J = 8.4$  Hz,  $J = 4.5$  Hz,  $J = 2.0$  Hz, 1H), 7.57 (dd,  $J = 6.8$  Hz,  $J = 2.0$  Hz, 1H). <sup>13</sup>C NMR (90 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 26.7, 28.2, 38.8, 40.8, 48.2, 52.1, 54.3, 56.7, 116.8 (d,  $J = 21.1$  Hz), 121.5 (d,  $J = 17.8$  Hz), 127.3 (d,  $J = 7.3$  Hz), 130.0, 133.3 (d,  $J = 4.0$  Hz), 159.1 (d,  $J = 253.0$  Hz), 165.8). APCI-MS  $m/z$  296  $[M+1]^+$ . HR-EIMS  $m/z$  295.0775. HPLC/MS system B purity 98 % ( $t_R = 19.6$  min).

8-(3-Chloro-4-fluorobenzoyl)spiro[8-azabicyclo[3.2.1]octane-3,2'-oxirane] (51.8 mg, 0.175 mmol) was reacted and worked up as described for **32**. Purification was performed by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>-MeOH 9:1) to give pure **33** (22.6 mg; 41 %) as a yellowish resin. IR 3380, 3050, 2925, 2854, 1616, 1435 cm<sup>-1</sup>. APCI-MS  $m/z$  313  $[M+1]^+$ . HR-EIMS  $m/z$  312.1041. HPLC/MS system B purity 95 % ( $t_R = 9.3$  min).

**3-[[[(5-Methylpyridin-2-yl)methyl]amino]methyl]-8-(3-thienylcarbonyl)-8-azabicyclo[3.2.1]octan-3-ol (exo-CH<sub>2</sub>) (35).** A solution of **32** (14.3 mg, 0.054 mmol) and 5-methylpyridine-2-carbaldehyde (5.8 mg, 0.048 mmol) in MeOH (3 mL) was stirred under reflux conditions for 3 h. After cooling to RT NaCNBH<sub>3</sub> (9.0 mg, 0.143 mmol) was added and stirring at RT was continued for 18 h. The solvent was evaporated in vacuo and the remainder was poured into ice-water. The aqueous layer was then extracted with CH<sub>2</sub>Cl<sub>2</sub>, the combined organic layer was washed with water and brine and was dried (Na<sub>2</sub>SO<sub>4</sub>). Filtration and evaporation in vacuo gave crude product which was purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>-MeOH 97:3) to give pure **35** (10.1 mg; 57 % relating to aldehyde) as pale green oil. IR 3359, 3099, 2979, 2924, 2866, 1604, 1523, 1440, 1329 cm<sup>-1</sup>. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ (ppm) 1.74-2.00 (m, 6H), 2.29-2.36 (m, 2H), 2.33 (s, 3H), 2.45 (s, 2H), 3.88 (s, 2H), 4.23-4.36 (m, 1H), 4.75-4.88 (m, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.23 (dd, *J* = 5.0 Hz, *J* = 1.1 Hz, 1H), 7.30 (dd, *J* = 5.1 Hz, *J* = 3.0 Hz, 1H), 7.45 (dd, *J* = 7.8 Hz, *J* = 2.1 Hz, 1H), 7.55 (dd, *J* = 3.0 Hz, *J* = 1.4 Hz, 1H), 8.37-8.40 (m, 1H). <sup>13</sup>C NMR (90 MHz, CDCl<sub>3</sub>) δ (ppm) 18.1, 26.7, 28.3, 41.5, 43.4, 51.4, 56.0, 55.1, 61.8, 69.4, 121.8, 125.7, 126.6, 127.3, 131.7, 137.2, 137.4, 149.8, 156.1, 162.7. APCI-MS *m/z* 372 [M+1]<sup>+</sup>. HR-EIMS *m/z* 371.1668. HPLC/MS system B purity 98 % (t<sub>R</sub> = 8.5 min).

**8-(3-Chloro-4-fluorobenzoyl)-3-[[[(5-methylpyridin-2-yl)methyl]amino]methyl]-8-azabicyclo[3.2.1]octan-3-ol (exo-CH<sub>2</sub>) (36).** Compound **33** (18.6 mg, 0.059 mmol) was rected as described for **35**. Purification by flash chromatography (hexane-ethyl acetate 6:4, then CH<sub>2</sub>Cl<sub>2</sub>-MeOH 98:2) gave pure **36** (12.2 mg; 52 %) as pale yellow oil. IR 3338, 3049, 2925, 1622, 1579, 1434 cm<sup>-1</sup>. <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ (ppm) 1.56-2.00 (m, 6H), 2.29-2.38 (m, 2H), 2.33 (s, 3H), 2.45 (s, 2H), 3.88 (s, 2H), 4.01-4.09 (m, 1H), 4.73-4.85 (m, 1H), 7.11 (d, *J* = 7.9 Hz, 1H), 7.16 (dd, *J* = 8.6 Hz, *J* = 8.6 Hz, 1H), 7.34 (ddd, *J* = 8.5 Hz, *J* = 4.7 Hz, *J* = 2.2 Hz, 1H), 7.46 (dd, *J* = 7.9 Hz, *J* = 1.8 Hz, 1H), 7.52 (dd, *J* = 7.0 Hz, *J* = 2.0 Hz, 1H), 8.37-8.40 (m, 1H). <sup>13</sup>C NMR (90 MHz, CDCl<sub>3</sub>) δ (ppm) 18.5, 26.8, 28.3, 41.2, 43.3, 51.6, 55.2, 56.4, 61.9, 69.3, 116.6 (d, *J* = 22.0 Hz), 121.3 (d, *J* = 17.6 Hz), 121.8, 127.20 (d, *J* = 7.7 Hz), 129.9, 131.7, 133.5 (d, *J* = 3.3 Hz), 137.2, 149.8, 156.2, 158.9 (d, *J* = 252 Hz), 165.4. APCI-MS *m/z* 418 [M+1]<sup>+</sup>. HR-EIMS *m/z* 417.1622. HPLC/MS system B purity 95 % (t<sub>R</sub> = 10.8 min).

### Receptor binding studies.

Receptor binding studies were carried out as described.<sup>S1</sup> In brief, the dopamine D<sub>1</sub> receptor assay was done with porcine striatal membranes at a final protein concentration of 40 μg/assay tube and the radioligand [<sup>3</sup>H]SCH 23390 at 0.3 nM (K<sub>D</sub> = 0.41-0.56 nM). Competition experiments with human D<sub>2long</sub>,<sup>S2</sup> D<sub>2short</sub>,<sup>S2</sup> D<sub>3</sub><sup>S3</sup> and D<sub>4.4</sub><sup>S4</sup> receptors were run with preparations of membranes from CHO cells stably expressing the corresponding receptor and [<sup>3</sup>H]spiperone at a final concentration of 0.1-0.4 nM. The assays were carried out at a protein concentration of 5-20 μg/assay tube and K<sub>D</sub> values of 0.04-0.14 nM, 0.04-0.24 nM, 0.11-0.28 nM, and 0.17-0.35 nM for the D<sub>2long</sub>, D<sub>2short</sub>, D<sub>3</sub> and D<sub>4.4</sub> receptors, respectively. 5-HT and α<sub>1</sub> receptor binding experiments were performed with homogenates prepared from porcine cerebral cortex as described.<sup>S5</sup> Assays were run with membranes at a protein concentration per each assay tube of 100, 80, and 60 μg/mL for 5-HT<sub>1A</sub>, 5-HT<sub>2</sub> and α<sub>1</sub> receptor, respectively, and radioligand concentrations of 0.2-0.3 nM ([<sup>3</sup>H]WAY100635 and [<sup>3</sup>H]prazosin) and 0.5 nM ([<sup>3</sup>H]ketanserin) with K<sub>D</sub> values of 0.03-0.15 nM for 5-HT<sub>1A</sub>, 0.67-1.6 nM for 5-HT<sub>2</sub>, and 0.07-0.16 nM for the α<sub>1</sub> receptor. Binding affinities to α<sub>2</sub> receptors were determined similar to the protocol for α<sub>1</sub> in 24well microplates at a final volume of 800 μl employing membranes from porcine cerebral cortex at a concentration of 240 μg/ml and the subtype selective radioligand [<sup>3</sup>H]RX821002<sup>S6</sup> at 0.2-0.5 nM. K<sub>D</sub> values for the

homogenates in use were measured with 0.21-0.52 nM. Unspecific binding was determined in the presence of 10  $\mu$ M of RX821002. Protein concentration was established by the method of Lowry using bovine serum albumin as standard.<sup>S7</sup>

**Data Analysis.** The resulting competition curves of the receptor binding experiments were analyzed by nonlinear regression using the algorithms in PRISM 3.0 (GraphPad Software, San Diego, CA). The data were fit using a sigmoid model to provide an IC<sub>50</sub> value, representing the concentration corresponding to 50% of maximal inhibition. IC<sub>50</sub> values were transformed to K<sub>i</sub> values according to the equation of Cheng and Prusoff.<sup>S8</sup>

### Receptor binding data.

**Table S1.** Selectivity pattern for compounds of the library **6**, **8aa-8cj** and **9**, the hydroxylated analogs **10-12** and the bridges derivatives **24**, **25**, **30**, **34-36**, **38**, **41** and **43** employing porcine 5-HT<sub>2</sub>, D<sub>1</sub>,  $\alpha_1$ ,  $\alpha_2$  and the human human D<sub>2long</sub>, D<sub>2short</sub>, D<sub>3</sub> and D<sub>4.4</sub> receptors

| Cmpd       | K <sub>i</sub> values <sup>a</sup> $\pm$ SD [nM] |                             |                                 |                                  |                             |                               |                         |                         |
|------------|--|-----------------------------|---------------------------------|----------------------------------|-----------------------------|-------------------------------|-------------------------|-------------------------|
|            | 5-HT <sub>2</sub> <sup>c</sup>                   | D <sub>1</sub> <sup>d</sup> | D <sub>2long</sub> <sup>e</sup> | D <sub>2short</sub> <sup>e</sup> | D <sub>3</sub> <sup>e</sup> | D <sub>4.4</sub> <sup>e</sup> | $\alpha_1$ <sup>f</sup> | $\alpha_2$ <sup>g</sup> |
| <b>6</b>   | 28000 $\pm$ 2800                                 | 51000 $\pm$ 16000           | 64000 $\pm$ 25000               | 18000 $\pm$ 9900                 | 8200 $\pm$ 0                | 6800 $\pm$ 420                | 9900 $\pm$ 3000         | 1700 $\pm$ 140          |
| <b>8aa</b> | 5700 $\pm$ 1500                                  | 18500 $\pm$ 3500            | 8500 $\pm$ 3500                 | 20000 $\pm$ 2800                 | 8400 $\pm$ 2200             | 3500 $\pm$ 570                | 2700 $\pm$ 70           | 2200 $\pm$ 420          |
| <b>8ab</b> | 38000 $\pm$ 1900                                 | 28000 $\pm$ 12000           | 5400 $\pm$ 1800                 | 1200 $\pm$ 0                     | 5800 $\pm$ 990              | 27000 $\pm$ 3500              | 4500 $\pm$ 1100         | 3200 $\pm$ 0            |
| <b>8ac</b> | 5000 $\pm$ 2100                                  | 16000 $\pm$ 1400            | 5200 $\pm$ 280                  | 4100 $\pm$ 710                   | 5000 $\pm$ 1500             | 8400 $\pm$ 2300               | 3600 $\pm$ 850          | 1500 $\pm$ 71           |
| <b>8ad</b> | 14000 $\pm$ 710                                  | 22000 $\pm$ 0               | 42000 $\pm$ 43000               | 29000 $\pm$ 2800                 | 6900 $\pm$ 0                | 2500 $\pm$ 780                | 1700 $\pm$ 71           | 2700 $\pm$ 280          |
| <b>8ae</b> | 17000 $\pm$ 21000                                | 53000 $\pm$ 30000           | 9800 $\pm$ 1800                 | 23000 $\pm$ 2000                 | 6500 $\pm$ 71               | 6900 $\pm$ 280                | 1900 $\pm$ 350          | 4000 $\pm$ 140          |
| <b>8af</b> | 50000 $\pm$ 6400                                 | 26000 $\pm$ 9900            | 3800 $\pm$ 490                  | 9500 $\pm$ 710                   | 980 $\pm$ 310               | 350 $\pm$ 28                  | 5600 $\pm$ 350          | 2600 $\pm$ 280          |
| <b>8ag</b> | 6900 $\pm$ 2800                                  | 32000 $\pm$ 11000           | 1500 $\pm$ 5700                 | 7200 $\pm$ 2500                  | 4000 $\pm$ 920              | 870 $\pm$ 48                  | 3500 $\pm$ 280          | 3500 $\pm$ 420          |
| <b>8ah</b> | 12000 $\pm$ 2100                                 | 23000 $\pm$ 9200            | 11000 $\pm$ 6100                | 8200 $\pm$ 2500                  | 4200 $\pm$ 920              | 630 $\pm$ 470                 | 1500 $\pm$ 210          | 2900 $\pm$ 990          |
| <b>8ai</b> | 39000 $\pm$ 15000                                | 30000 $\pm$ 11000           | 15000 $\pm$ 710                 | 40000 $\pm$ 4200                 | 5100 $\pm$ 1600             | 420 $\pm$ 14                  | 2400 $\pm$ 210          | 5800 $\pm$ 640          |

|            |                   |                   |                   |                  |                   |                   |                 |                  |
|------------|-------------------|-------------------|-------------------|------------------|-------------------|-------------------|-----------------|------------------|
| <b>8aj</b> | $30000 \pm 0$     | $32000 \pm 3500$  | $25000 \pm 2800$  | $65000 \pm 3500$ | $81000 \pm 7800$  | $180 \pm 21$      | $2700 \pm 71$   | $5900 \pm 780$   |
| <b>8ak</b> | $46000 \pm 13000$ | $24000 \pm 1400$  | $8400 \pm 940$    | $26000 \pm 2800$ | $3400 \pm 640$    | $320 \pm 50$      | $1800 \pm 350$  | $5000 \pm 850$   |
| <b>8al</b> | $34000 \pm 5700$  | $27000 \pm 2100$  | $11000 \pm 1200$  | $13000 \pm 4200$ | $2500 \pm 140$    | $250 \pm 57$      | $2500 \pm 210$  | $5000 \pm 71$    |
| <b>8am</b> | $19000 \pm 710$   | $16000 \pm 710$   | $2500 \pm 71$     | $3000 \pm 640$   | $850 \pm 140$     | $99 \pm 2$        | $2300 \pm 0$    | $3600 \pm 0$     |
| <b>8an</b> | $48000 \pm 10000$ | $40000 \pm 6100$  | $1200 \pm 71$     | $3500 \pm 350$   | $2900 \pm 490$    | $4200 \pm 140$    | $3200 \pm 350$  | $17000 \pm 2100$ |
| <b>8ao</b> | $85000 \pm 21000$ | $18000 \pm 2100$  | $7900 \pm 280$    | $8900 \pm 850$   | $2500 \pm 71$     | $4700 \pm 1100$   | $5800 \pm 350$  | $4300 \pm 1100$  |
| <b>8ap</b> | $32000 \pm 2100$  | $1800 \pm 710$    | $3700 \pm 280$    | $5300 \pm 1200$  | $1800 \pm 71$     | $730 \pm 150$     | $6700 \pm 71$   | $3600 \pm 1900$  |
| <b>8aq</b> | $35000 \pm 6400$  | $260000 \pm 7800$ | $8100 \pm 2100$   | $10000 \pm 5100$ | $2800 \pm 710$    | $2100 \pm 710$    | $7500 \pm 210$  | $5900 \pm 1300$  |
| <b>8ar</b> | $6800 \pm 1600$   | $22000 \pm 4200$  | $100000 \pm 0$    | $87000 \pm 1900$ | $70000 \pm 16000$ | $11000 \pm 2800$  | $5500 \pm 350$  | $1300 \pm 0$     |
| <b>8as</b> | $29000 \pm 9900$  | $73000 \pm 37000$ | $63000 \pm 0$     | $100000 \pm 0$   | $27000 \pm 3500$  | $6500 \pm 0$      | $7700 \pm 490$  | $1300 \pm 210$   |
| <b>8at</b> | $18000 \pm 5600$  | $37000 \pm 9200$  | $83000 \pm 24000$ | $34000 \pm 2800$ | $31000 \pm 16000$ | $12000 \pm 2100$  | $8300 \pm 490$  | $720 \pm 110$    |
| <b>8au</b> | $38000 \pm 17000$ | $66000 \pm 8500$  | $82000 \pm 26000$ | $100000 \pm 0$   | $66000 \pm 25000$ | $21000 \pm 2100$  | $8300 \pm 850$  | $1600 \pm 280$   |
| <b>8av</b> | $15000 \pm 3200$  | $30000 \pm 1400$  | $31000 \pm 9200$  | $12000 \pm 9200$ | $16000 \pm 710$   | $3400 \pm 850$    | $2000 \pm 140$  | $4100 \pm 210$   |
| <b>8aw</b> | $12000 \pm 1400$  | $28000 \pm 6400$  | $60000 \pm 9200$  | $17000 \pm 4900$ | $29000 \pm 9200$  | $17000 \pm 11000$ | $9700 \pm 1800$ | $1600 \pm 71$    |
| <b>8ay</b> | $22000 \pm 9200$  | $23000 \pm 5700$  | $9800 \pm 71$     | $29000 \pm 710$  | $15000 \pm 0$     | $1700 \pm 71$     | $2600 \pm 0$    | $5000 \pm 850$   |
| <b>8az</b> | $44000 \pm 19000$ | $37000 \pm 5000$  | $21000 \pm 5000$  | $55000 \pm 0$    | $18000 \pm 1400$  | $4900 \pm 350$    | $3300 \pm 71$   | $2800 \pm 280$   |
| <b>8ba</b> | $38000 \pm 9200$  | $27000 \pm 8500$  | $50000 \pm 16000$ | $63000 \pm 6400$ | $11000 \pm 6200$  | $2700 \pm 350$    | $4500 \pm 280$  | $1200 \pm 500$   |
| <b>8bb</b> | $26000 \pm 11000$ | $33000 \pm 1400$  | $37000 \pm 3500$  | $46000 \pm 6400$ | $17000 \pm 7100$  | $3500 \pm 420$    | $4900 \pm 1300$ | $8300 \pm 6700$  |
| <b>8bc</b> | $37000 \pm 13000$ | $35000 \pm 12000$ | $100000 \pm 0$    | $100000 \pm 0$   | $32000 \pm 9900$  | $3800 \pm 1200$   | $5000 \pm 1100$ | $4600 \pm 1200$  |
| <b>8bd</b> | $31000 \pm 11000$ | $38000 \pm 7800$  | $84000 \pm 23000$ | $100000 \pm 0$   | $22000 \pm 1400$  | $2900 \pm 500$    | $5100 \pm 71$   | $3700 \pm 570$   |

|            |               |               |               |               |               |              |              |             |
|------------|---------------|---------------|---------------|---------------|---------------|--------------|--------------|-------------|
| <b>8be</b> | 27000 ± 9200  | 45000 ± 14000 | 75000 ± 13000 | 34000 ± 18000 | 48000 ± 2100  | 7900 ± 3000  | 10000 ± 5300 | 2300 ± 280  |
| <b>8bf</b> | 28000 ± 11000 | 49000 ± 16000 | 20000 ± 5700  | 30000 ± 17000 | 14000 ± 2100  | 2100 ± 280   | 4600 ± 570   | 4000 ± 210  |
| <b>8bg</b> | 42000 ± 710   | 58000 ± 13000 | 52000 ± 8500  | 100000 ± 0    | 19000 ± 1400  | 4600 ± 990   | 3100 ± 1100  | 1500 ± 730  |
| <b>8bh</b> | 5100 ± 350    | 24000 ± 17000 | 5700 ± 420    | 7500 ± 5000   | 12000 ± 0     | 800 ± 230    | 1300 ± 140   | 2200 ± 640  |
| <b>8bi</b> | 30000 ± 710   | 18000 ± 4200  | 9900 ± 7200   | 8400 ± 350    | 8000 ± 2500   | 3450 ± 1200  | 3100 ± 850   | 2500 ± 640  |
| <b>8bj</b> | 32000 ± 2100  | 30000 ± 16000 | 12000 ± 710   | 9900 ± 210    | 11000 ± 2400  | 3200 ± 350   | 10000 ± 990  | 2900 ± 210  |
| <b>8bk</b> | 9400 ± 850    | 33000 ± 27000 | 14000 ± 1400  | 14000 ± 7900  | 2700 ± 920    | 460 ± 21     | 1400 ± 71    | 1700 ± 420  |
| <b>8bl</b> | 12000 ± 4300  | 31000 ± 8500  | 11000 ± 12000 | 36000 ± 18000 | 4500 ± 640    | 740 ± 140    | 1900 ± 280   | 2500 ± 640  |
| <b>8bm</b> | 20000 ± 14000 | 28000 ± 1400  | 8900 ± 5800   | 11000 ± 3300  | 6300 ± 1300   | 4100 ± 1800  | 4100 ± 1500  | 1800 ± 71   |
| <b>8bn</b> | 30000 ± 13000 | 26000 ± 2800  | 9300 ± 3900   | 6100 ± 4700   | 5100 ± 1800   | 1700 ± 640   | 4100 ± 71    | 2000 ± 210  |
| <b>8bo</b> | 2300 ± 1100   | 17000 ± 5000  | 3700 ± 1100   | 5000 ± 71     | 2600 ± 210    | 6300 ± 280   | 2300 ± 350   | 2000 ± 350  |
| <b>8bp</b> | 4200 ± 1200   | 16000 ± 2100  | 5900 ± 920    | 7400 ± 1300   | 3200 ± 710    | 6800 ± 1100  | 2200 ± 350   | 1200 ± 140  |
| <b>8bq</b> | 7800 ± 2800   | 36000 ± 14000 | 24000 ± 11000 | 19000 ± 5000  | 5800 ± 500    | 26000 ± 710  | 4900 ± 570   | 4100 ± 2400 |
| <b>8br</b> | 11000 ± 3000  | 25000 ± 5700  | 11000 ± 3400  | 8300 ± 5300   | 5000 ± 1200   | 18000 ± 5000 | 4100 ± 350   | 2400 ± 0    |
| <b>8bs</b> | 49000 ± 27000 | 30000 ± 20000 | 7000 ± 420    | 11000 ± 3000  | 7300 ± 140    | 3600 ± 140   | 4100 ± 210   | 2100 ± 780  |
| <b>8bu</b> | 17000 ± 5000  | 54000 ± 14000 | 14000 ± 11000 | 23000 ± 0     | 6700 ± 920    | 1000 ± 100   | 1200 ± 71    | 1600 ± 71   |
| <b>8bv</b> | 15000 ± 5700  | 14000 ± 710   | 2200 ± 420    | 7000 ± 2100   | 1800 ± 280    | 2000 ± 71    | 320 ± 64     | 1500 ± 140  |
| <b>8bx</b> | 8700 ± 1600   | 17000 ± 4200  | 89000 ± 16000 | 44000 ± 2800  | 16000 ± 2800  | 2600 ± 1100  | 2500 ± 1800  | 3400 ± 640  |
| <b>8by</b> | 37000 ± 16000 | 36000 ± 16000 | 49000 ± 15000 | 100000 ± 0    | 28000 ± 7100  | 21000 ± 2100 | 3200 ± 280   | 7000 ± 420  |
| <b>8bz</b> | 10000 ± 71    | 55000 ± 9900  | 100000 ± 0    | 100000 ± 0    | 60000 ± 14000 | 58000 ± 5000 | 9700 ± 500   | 5600 ± 140  |

|            |               |               |               |               |               |               |              |             |
|------------|---------------|---------------|---------------|---------------|---------------|---------------|--------------|-------------|
| <b>8ca</b> | 11000 ± 1600  | 29000 ± 7800  | 1100 ± 230    | 2500 ± 0      | 1400 ± 420    | 150 ± 42      | 360 ± 85     | 1300 ± 0    |
| <b>8cb</b> | 14000 ± 5700  | 39000 ± 11000 | 11000 ± 710   | 32000 ± 710   | 3800 ± 570    | 4300 ± 210    | 2400 ± 0     | 3200 ± 990  |
| <b>8cc</b> | 12000 ± 710   | 33000 ± 9900  | 41000 ± 7800  | 23000 ± 3500  | 5400 ± 5700   | 8900 ± 500    | 7700 ± 780   | 3500 ± 920  |
| <b>8cd</b> | 32000 ± 29000 | 41000 ± 21000 | 66000 ± 23000 | 100000 ± 0    | 48000 ± 16000 | 30000 ± 11000 | 8800 ± 1800  | 4800 ± 710  |
| <b>8ce</b> | 25000 ± 9900  | 43000 ± 25000 | 84000 ± 23000 | 100000 ± 0    | 4000 ± 280    | 41000 ± 2800  | 9800 ± 1800  | 7300 ± 1100 |
| <b>8cf</b> | 21000 ± 2100  | 21000 ± 1400  | 5700 ± 710    | 7300 ± 3500   | 6000 ± 2000   | 3500 ± 990    | 3800 ± 850   | 1800 ± 350  |
| <b>8cg</b> | 19000 ± 710   | 17000 ± 1400  | 5800 ± 2000   | 20000 ± 4200  | 3800 ± 640    | 770 ± 130     | 2100 ± 570   | 5600 ± 210  |
| <b>8ch</b> | 23000 ± 5000  | 28000 ± 5700  | 9300 ± 2400   | 30000 ± 0     | 5900 ± 420    | 770 ± 110     | 1400 ± 210   | 4800 ± 850  |
| <b>8ci</b> | 8500 ± 780    | 27000 ± 5000  | 13000 ± 2800  | 12000 ± 2100  | 6800 ± 1600   | 170 ± 110     | 2800 ± 780   | 2900 ± 71   |
| <b>8cj</b> | 8400 ± 2200   | 12000 ± 1400  | 2500 ± 350    | 1800 ± 420    | 1800 ± 280    | 62 ± 3        | 810 ± 130    | 700 ± 210   |
| <b>9</b>   | 21000 ± 710   | 40000 ± 25000 | 100000 ± 0    | 100000 ± 0    | 36000 ± 13000 | 8300 ± 2200   | 14000 ± 3500 | xx ± yy     |
| <b>10</b>  | 23000 ± 7100  | 59000 ± 11000 | 83000 ± 24000 | 52000 ± 33000 | 33000 ± 4200  | 7000 ± 1900   | 8800 ± 920   | 5400 ± 1600 |
| <b>11</b>  | 19000 ± 0     | 39000 ± 1400  | 92000 ± 12000 | 87000 ± 18000 | 17000 ± 0     | 6700 ± 1500   | 8500 ± 1400  | 2500 ± 780  |
| <b>12</b>  | 30000 ± 20000 | 38000 ± 7800  | 51000 ± 8500  | 71000 ± 23000 | 23000 ± 2800  | 2400 ± 420    | 4800 ± 710   | 8500 ± 2200 |
| <b>24</b>  | 25000 ± 5000  | 56000 ± 4200  | 33000 ± 17000 | 15000 ± 5700  | 12000 ± 5000  | 17000 ± 3500  | 3600 ± 710   | 830 ± 160   |
| <b>25</b>  | 23000 ± 11000 | 64000 ± 28000 | 100000 ± 0    | 68000 ± 46000 | 39000 ± 2100  | 42000 ± 2100  | 7400 ± 1300  | 580 ± 280   |
| <b>30</b>  | 22000 ± 8500  | 49000 ± 16000 | 41000 ± 28000 | 9200 ± 5400   | 8600 ± 3500   | 7800 ± 2600   | 5600 ± 780   | 280 ± 21    |
| <b>34</b>  | 27000 ± 5000  | 39000 ± 6400  | 81000 ± 28000 | 70000 ± 3400  | 2500 ± 71     | 5100 ± 710    | 12000 ± 5200 | xx ± yy     |
| <b>35</b>  | 21000 ± 8500  | 69000 ± 2200  | 33000 ± 22000 | 31000 ± 17000 | 24000 ± 710   | 3900 ± 1800   | 6600 ± 210   | 4400 ± 350  |
| <b>36</b>  | 14000 ± 1700  | 30000 ± 4800  | 26000 ± 4600  | 42000 ± 4500  | 13000 ± 850   | 840 ± 180     | 8900 ± 140   | 4000 ± 780  |

|           |                 |                  |                 |                 |                 |                  |                 |         |
|-----------|-----------------|------------------|-----------------|-----------------|-----------------|------------------|-----------------|---------|
| <b>38</b> | 28000 ±<br>4900 | 65000 ±<br>26000 | 69000 ±<br>4400 | 47000 ±<br>1900 | 17000 ±<br>4200 | 30000 ±<br>7100  | 15000 ±<br>6400 | xx ± yy |
| <b>41</b> | 23000 ±<br>5600 | 53000 ±<br>11000 | 96000 ±<br>5700 | 100000 ± 0      | 29000 ±<br>9900 | 8400 ±<br>3700   | 16000 ±<br>2100 | xx ± yy |
| <b>43</b> | 15000 ±<br>2100 | 44000 ±<br>17000 | 5700 ± 780      | 12000 ±<br>5000 | 14000 ±<br>1400 | 24000 ±<br>16000 | 16000 ±<br>3500 | xx ± yy |

<sup>a</sup> Binding data are the means of 2-8 experiments each done in triplicate. <sup>b</sup> [<sup>3</sup>H]WAY-100635. <sup>c</sup> [<sup>3</sup>H]ketanserin. <sup>d</sup> [<sup>3</sup>H]SCH23390. <sup>e</sup> [<sup>3</sup>H]spiperone. <sup>f</sup> [<sup>3</sup>H]prazosin. <sup>g</sup> [<sup>3</sup>H]RX821002.

### X-ray Crystal Structure Determination Details:

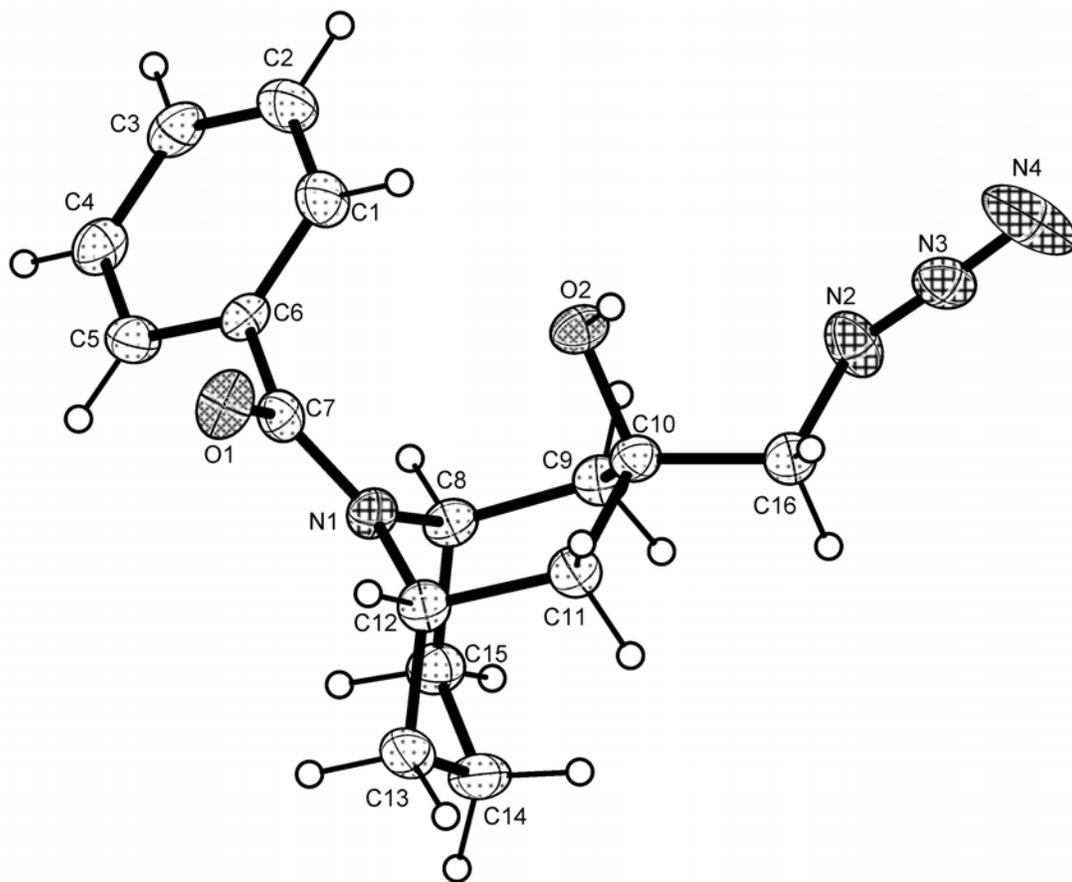
CCDC-782272 (for **42**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [http://www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif) (or from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: ++44-1223-336-033; e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk))).

Colorless prisms of C<sub>16</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub> (**42**) were recrystallized from a mixture of diisopropylether and dichloromethane. A suitable single crystal of approximate dimensions 0.23 × 0.19 × 0.16 mm<sup>3</sup> was embedded in protective perfluoro-polyalkyether oil, mounted on a glass capillary and transferred to the cold nitrogen gas stream of the diffractometer. Intensity data were collected at 150 K on a Bruker-Nonius KappaCCD diffractometer using graphite monochromatized MoK<sub>α</sub> radiation (λ = 0.71073 Å). Data were corrected for Lorentz and polarization effects, semiempirical absorption corrections were performed on the basis of multiple scans using *SADABS*<sup>S9</sup> (T<sub>min</sub> = 0.956, T<sub>max</sub> = 0.990). The structure was solved by direct methods and refined by full-matrix least-squares procedures on *F*<sup>2</sup> using *SHELXTL NT* 6.12.<sup>S10</sup>

The azide moiety is disordered. Two alternative positions were refined for the two terminal atoms N3 and N4 resulting in a site occupancy of 76(4) % for the major fraction and 24(4) % for the minor part (N3A, N4A). SIMU restraints were used in the refinement of the disorder. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in positions of optimized geometry, their isotropic displacement parameters were tied to those of the corresponding carrier atoms by a factor of either 1.2 or 1.5.

A total of 43769 reflections (−10 ≤ *h* ≤ 10, −12 ≤ *k* ≤ 12, −22 ≤ *l* ≤ 22) were collected in the *θ* range from 3.29 to 27.10°, of which 3282 were unique (*R*<sub>int</sub> = 0.0533) and 2731 were observed. The residual peak and hole electron density were 0.292 and −0.197 e.Å<sup>−3</sup>. The absorption coefficient was 0.091 mm<sup>−1</sup>. The least-squares refinement converged normally with residuals of *R*<sub>1</sub> = 0.0502, *wR*<sub>2</sub> = 0.1001, and GOF = 1.029 (all data). C<sub>16</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>, monoclinic, space group *P*2<sub>1</sub>/*n* (no. 14), *a* = 8.2815(8), *b* = 10.1298(7), *c* = 17.8918(5) Å, β = 96.742(4), *V* = 1490.6(2) Å<sup>3</sup>, *Z* = 4, ρ<sub>calcd</sub> = 1.338 Mg/m<sup>3</sup>, *F*(000) = 640, *R*<sub>1</sub>(*F*) = 0.0395, *wR*<sub>2</sub>(*F*<sup>2</sup>) = 0.0941 [*I* > 2σ(*I*)].

**X-ray Crystal Structure of Compound 42.**



## References.

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