8-Methyl-3β-(1-(4-methylnaphthyl))-2β-propanoyl-8-azabicyclo [3.2.1]octane (9b). (9/1 ether/triethylamine - 8.75/0.25/1 ether/methanol/triethylamine) 73% yield: IR (neat) 2920, 1700, 1670, 1580, 740, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.01 (t, 1H, *J* = 2.2 Hz), 7.97 (t, 1 H, *J* = 2.4 Hz), 7.53 (d, 1 H, *J* = 7.6 Hz), 7.46 (d, 1 H, *J* = 5.9 Hz), 7.48 (d, 1 H, *J* = 7.8 Hz), 7.28 (d, 1 H, *J* = 7.8 Hz), 3.75 (dt, 1 H, *J* = 12.9, 4.9 Hz), 3.51 (dd, 1 H, *J* = 6.7, 2.5 Hz), 3. 44 (dd, 1 H, *J* = 6.4, 2.6 Hz), 3.17 (t, 1 H, *J* = 3.6 Hz), 2.95 (ddd, 1 H, *J* = 12.7, 12.7, 2.8 Hz), 2.62 (s, 3 H), 2.34 (q, 2 H, *J* = 7.3 Hz), 2.25 (s, 3 H), 2.01 -1.74 (m, 4 H), 1.59 (dt, 1 H, *J* = 12.4, 3.6 Hz), 0.69 (t, 3 H, *J* = 7.3 Hz); ^{13}C ($CDCl_3$) δ 209.7, 135.5, 132.8, 132.4, 131.4, 126.6, 126.5, 126.4, 125.3, 124.6, 122.9, 64.6, 62.7, 57.5, 42.1, 35.2, 34.9, 30.6, 26.7, 25.2, 19.4, 7.6; MS m/z (relative intensity) 321 (44), 264 (100), 207 (3), 179 (5), 165 (6), 97 (42), 82 (44), 57 (4). Anal. Calcd for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36: Found C, 81.96; H, 8.60; N, 4.22.

3β-(1-(4-Ethylnaphthyl))-8-methyl-2β-(propanoyl)-8-azabicyclo [3.2.1]octane (9c). (98/2 ether/triethylamine-85/10/5 ether/triethylamine/methanol), 6% yield: IR (neat) 2936, 2875, 1719, 1691, 1514, 1416, 1374, 1310, 1242, 1204, 1130, 1050, 919, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.09 - 7.97 (m, 2 H), 7.58 (d, 1 H, *J* = 7.6 Hz), 7.47 (m, 2 H), 7.31 (d, 1 H, *J* = 7.6 Hz), 3.75 (m, 1 H), 3.49 (m, 2 H), 3.17 (m, 1 H), 3.04 (q, 2 H, *J* = 7.6 Hz), 2.96 (ddd, 1 H, *J* = 13.0, 13.0, 2.4 Hz), 2.40 - 2.21 (m, 2 H), 2.26 (s, 3 H), 2.00 - 1.55 (m, 5 H), 1.33 (t, 3 H, *J* = 7.5 Hz), 0.70 (t, 3 H, *J* = 7.3 Hz); ^{13}C ($CDCl_3$) δ 209.7, 138.3, 135.4, 132.0, 131.6, 126.6, 125.2, 124.9, 124.8, 124.6, 123.1, 64.7, 62.8, 57.5, 42.2, 35.2, 35.0, 30.7, 26.7, 25.8, 25.3, 14.9, 7.7; MS *m/z* (rel intensity) 335 (42), 278 (100), 250 (1), 193 (9), 178 (12), 165 (21), 153 (16); Anal. Calcd. for $C_{23}H_{29}NO \cdot 0.5\ H_2O$: C, 80.19; H, 8.78; N, 4.07 Found C, 80.41; H, 8.61; N, 3.93.

3β-(1-(4-Isopropylnaphthyl))-8-methyl-2β-(propanoyl)-8-azabicyclo [3.2.1]octane (9d). (98/2 ether/triethylamine-85/10/5 ether/triethylamine/methanol), 38% yield: IR (neat) 2958, 2936, 2874, 1718, 1691, 1514, 1459, 1416, 1351, 1225, 920, 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (m, 1 H), 8.01 (m, 1 H), 7.62 (d, 1 H, J = 7.6 Hz), 7.47 (m, 2 H), 7.38 (d, 1 H, J = 7.6 Hz), 3.72 (m, 2 H), 3.52 (d, 1 H, J = 5.4 Hz), 3.45 (m, 1 H), 3.17 (m, 1 H), 2.97 (ddd, 1 H, J = 12.6, 12.6, 2.6 Hz), 2.38 - 2.29 (m, 2 H), 2.26 (s, 3 H), 2.18 - 1.56 (m, 5 H), 1.35 (dd, 6 H, J = 4.1, 2.6 Hz), 0.79 (t, 3 H, J = 7.3 Hz); ^{13}C ($CDCl_3$) δ 209.8, 142.5, 135.1, 131.7, 131.5, 126.7, 125.1, 124.6, 124.4, 123.2, 121.7, 64.7, 62.8, 57.4, 42.2, 35.2, 34.9, 30.6, 28.4, 26.7, 25.2, 23.7, 23.3, 7.7; MS *m/z* (rel intensity) 349 (53), 292 (100), 264 (1), 250 (4), 193 (9), 178 (11), 165 (14), 153 (13); Anal. Calcd. for $C_{24}H_{31}NO \cdot 0.9\ H_2O$: C, 78.82; H, 9.04; N, 3.83 Found C, 78.86; H, 8.77; N, 3.54.

3β-(2-(6-isopropylnaphthyl))-8-methyl-2β-(propanoyl)-8-azabicyclo [3.2.1]octane (10b). (98/2 ether/triethylamine-85/10/5 ether/triethylamine/methanol), 11% yield: IR (neat) 2957, 2936, 2875, 2797, 1691, 1514, 1449, 1374, 1226, 973, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 - 7.52 (m, 4 H), 7.31(dt, 2 H, *J* = 8.3, 2.4 Hz), 3.48 (d, 1 H, *J* = 5.6 Hz), 3.38 (m, 1 H), 3.08 (m, 2 H), 3.01 (m, 1 H), 2.68 (ddd, 1 H, *J* = 11.8, 11.8, 2.4 Hz), 2.34 - 2.09 (m, 2 H), 2.20 (s, 3 H), 1.84 - 1.69 (m, 5 H), 1.29 (d, 6 H, *J* = 7.0 Hz), 0.76 (t, 3 H, *J* = 7.3 Hz); ^{13}C ($CDCl_3$) δ 210.2, 145.6, 139.9, 132.1, 132.0, 127.6, 127.1, 125.8, 125.6, 125.2, 123.6, 64.7, 62.4, 59.4, 42.1, 35.3, 34.4, 34.1, 26.5, 25.3, 23.9, 7.7; MS *m/z* (rel intensity) 349 (50), 292 (100), 264 (4), 250 (3), 193 (9), 178 (15), 165 (17), 153 (18); Anal. Calcd. for $C_{24}H_{31}NO \cdot 0.5\ H_2O$: C, 80.39; H, 9.00; N, 3.91 Found C, 80.33; H, 8.73; N, 3.67.

3β–(2-(6-Methoxynaphthyl))-8-methyl-2β-(propanoyl)-8-azabicyclo[3.2.1]octane (10c). (99/1 ether/triethylamine), 59% yield: IR (neat) 2940, 1707, 1606, 1484, 1267, 851 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 - 7.40 (m, 4 H), 7.10 (m, 2 H), 3.86 (s, 3 H), 3.63 (dd, 1 H, *J* = 11.5, 2.1 Hz), 3.41 (d, 2 H), 3.28 (ddd, 1 H, *J* = 11.5, 11.5, 5.6 Hz), 2.51 (s, 3 H), 2.50 (dq, 1 H, *J* = 14.6, 7.3 Hz), 2.30 (dq, 1 H, *J* = 14.6, 7.3 Hz), 2.20 - 1.6 (m, 6 H), 0.71 (t, 3 H, *J* = 7.3 Hz); ^{13}C ($CDCl_3$) δ 210.8, 157.3, 137.9, 133.4, 129.1, 128.8, 127.0, 126.6, 126.3, 118.6, 105.4, 63.5, 62.2, 57.2, 55.2, 39.8, 38.3, 36.9, 36.2, 26.0, 22.1, 7.2; MS *m/z* (rel intensity) 337 (87), 280 (100), 171 (9), 108 (4), 97 (55), 82 (91), 57 (10). Anal. Calcd. for $C_{22}H_{27}NO_2 \cdot 0.5\ H_2O$: C, 78.27; H, 8.15; N, 4.04. Found C, 78.37; H, 8.11; N, 4.05.

3β-(2-(5-Ethyl-6-methoxynaphthyl))-8-methyl-2β-propanoyl-8-azabicyclo[3.2.1]octane (10d). (99/1 ether/triethylamine), 19% yield: IR ($CDCl_3$) 2962, 2936, 1717, 1689, 1598, 1506, 1463, 1450, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) 7.85 (d, 1H, *J* = 8.9 Hz), 7.63 (d, 1H, *J* = 9.0 Hz), 7.58 (sbr, 1H), 7.37 (dd, 1H, J = 8.9, 2.1 Hz), 7.21 (d, 1H, *J* = 9.0 Hz), 3.92 (s, 3H), 3.51 (dbr, 1H, *J* = 6.5 Hz), 3.43 (sbr, 1H), 3.16-2.96 (m, 4H), 2.71 (td, 1H, *J* = 12.4, 2.9 Hz), 2.42-2.04 (m, 3H), 2.24 (s, 3H), 1.87-1.56 (m, 4H), 1.20 (t, 3H, *J* = 7.5 Hz), 0.80 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$) 210.4, 153.5, 137.8, 131.1, 128.3, 127.1, 126.2, 125.5, 122.9, 114.0, 113.6, 64.7, 62.4, 59.3, 56.7, 42.1, 35.3, 34.4, 33.8, 26.5, 25.3, 18.2, 14.6, 7.7; MS m/z (rel. intensity) 365 (25), 308 (51), 239 (2), 199 (5), 165 (8), 152 (8), 97 (59), 96 (57), 83 (97), 82 (100), 57 (32), 42 (48); Anal. Calcd. for $C_{24}H_{31}NO_2 \cdot 0.5\ H_2O$: C, 76.97; H, 8.61; N, 3.74. Found C, 77.17; H, 8.76; N, 4.10.

3β-(2-(5-Isopropenyl-6-methoxynaphthyl))-8-methyl-2β-propanoyl-8-azabicyclo[3.2.1]octane (10e). (50/50 ether/petroleum ether, 2% triethylamine) 38% yield: IR (neat) 3077, 2936, 1717, 1642, 1593, 1258, 1054 cm^{-1}; ^1H NMR ($CDCl_3$) 7.82 (d, 1H, *J* = 8.9 Hz), 7.68 (d, 1H, *J* = 9.0 Hz), 7.59 (sbr, 1H), 7.32

(dd, 1H, J = 8.9, 1.7 Hz), 7.21 (d, 1H, J = 9.0 Hz), 5.48 (sbr, 1H), 4.93 (sbr, 1H), 3.90 (s, 3H), 3.50 (dbr, 1H, J = 6.3 Hz), 3.40 (dbr, 1H, J = 5.3 Hz), 3.09 (m, 2H), 2.72 (tbr, 1H, J = 12.5), 2.44-2.02 (m, 3H), 2.21 (s, 3H), 2.10 (s, 3H), 1.82-1.57 (m, 4H), 0.81 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) 210.2, 152.2, 141.4, 138.2, 130.6, 129.0, 128.0, 126.8, 126.2, 125.4, 124.4, 116.3, 113.4, 64.6, 62.4, 59.2, 56.7, 42.0, 35.1, 34.3, 33.8, 26.4, 25.2, 24.0, 7.7; MS m/z (rel. intensity) 42 (40), 57 (26), 82 (93), 83 (100), 96 (62), 97 (70), 139 (3), 153 (8), 165 (11), 211 (7), 263 (2), 320 (47), 377 (30); Anal. Calcd for $C_{25}H_{31}NO_2$ 0.2H_2O: C, 78.79; H, 8.30; N, 3.63. Found C, 78.77; H, 8.66; N, 3.33.

3β-[2-(7-Iodonaphthyl)]-8-methyl-2β-propanoyl-8-azabicyclo[3.2.1.] octane (10g). 61% yield for conjugate addition; 68% yield for iododestannylation, 92% yield for reductive methylation. (pentane/ether/Et_3N (50:50:2)): IR($CDCl_3$) 3057, 2935, 1720, 1694, 1624, 1588, 1508, 1454, 1353 cm^{-1}; ^{1}HNMR($CDCl_3$) δ 8.13(s, 1H), 7.64(d, 1H, J=8.5Hz), 7.59(dd, 1H, J=8.5, 1.5Hz), 7.50(s, 1H), 7.45(d, 1H, J=8.5Hz), 7.36(dd, 1H, J=8.5, 1.0Hz), 3.51(d, 1H, J=3.5Hz), 3.38(t, 1H), 3.07(m, 2H), 2.66(dt, 1H, J=2.5, 12.5Hz), 2.36(dq, 1H, J=17.1, 7.3Hz), 2.27-2.07(m, 3H), 2.20(s, 3H),1.80-1.60(m, 3H), 0.79(t, 3H, J=7.3Hz). ^{13}C NMR ($CDCl_3$) δ.209.8, 142.1, 136.4, 135.0, 133.5, 130.5, 129.0, 127.3, 126.5, 124.4, 91.3, 64.5, 62.3, 59.2, 42.0, 34.8, 34.1, 26.3, 25.2, 7.7. MS m/z (rel. intensity) 433 (M^+, 57), 377 (20), 376 (100), 97 (62), 96 (42), 83 (68), 83 (65). Anal. calcd for $C_{21}H_{24}INO$: C,58.21; H,5.58; Found: C,58.33; H,5.60.

3β-(2-(5-Iodo-6-methoxynaphthyl))-8-methyl-2β-propanoyl-8-azabicyclo[3.2.1]octane (10i). To a solution of **10c** (59 mg, 0.175 mmol) and ICN (0.135 g, 0.88 mmol) in 20/80 ether/nitromethane (5 mL) was added a solution of aluminum chloride (0.117 g, 0.88 mmol) in nitromethane (5 mL). The mixture was stirred at room temperature for 48 h. The mixture was poured onto 10% aqueous NaS_2O_3H/ CH_2Cl_2 and extracted with CH_2Cl_2. The organic layer was extracted with $NaHCO_3$, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography (50/50 ether/ petroleum ether, 10% triethylamine) to afforded **10i** as a white solid (49 mg, 60% yield): IR (neat) 2940, 1714, 1597, 1252, 1064 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.97 (d, 1H, J = 8.9 Hz), 7.75 (d, 1H, J = 8.9 Hz), 7.57 (sbr, 1H), 7.41 (dd, 1H, J = 8.9, 1.8 Hz), 7.17 (d, 1H, J = 9.0 Hz), 4.00 (s, 3H), 3.55 (dbr, 1H, J = 5.6 Hz), 3.45 (m, 1H), 3.12 (m, 2H), 2.71 (td, 1H, J = 12.5, 2.8 Hz), 2.45-2.09 (m, 3H), 2.24 (s, 3H), 1.88-1.60 (m, 4H), 0.81 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) 209.9, 156.2, 139.4, 134.1, 130.7, 130.2, 129.9, 128.1, 125.8, 112.9, 87.4, 64.6, 62.4, 59.1, 57.3, 42.1, 35.1, 34.3, 33.8, 26.4, 25.3, 7.8; MS m/z (rel. intensity) 463 (13), 406 (26), 280 (3), 152 (9), 97 (57), 96 (59), 83 (93), 82 (100), 55 (11), 44 (88). Anal. Calcd for $C_{22}H_{26}INO_2$: C, 57.03; H, 5.66; N, 3.02. Found C, 56.84; H, 5.71; N, 2.97.

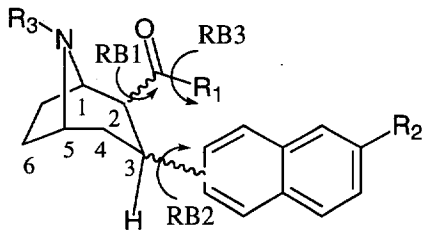
3β-(5-Acetyl-6-methoxynaphthyl)-8-methyl-2β-propanoyl-8-azabicyclo[3.2.1]octane (10j). To a stirred solution of acetyl chloride (90.6 mg, 1.15 mmol), and aluminum chloride (0.307 g, 2.3 mmol) in nitrobenzene (10 mL) was added over a period of 20 min a solution of **10c** (0.326 g, 0.97 mmol) in nitrobenzene (20 mL). After stirring overnight at room temperature, the mixture was poured onto ice (100 g) and 10 M HCl (30 mL) and then extracted with 3 M HCl (3X). The aqueous layer was made basic with concentrated NH_4OH and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography (50/50 petroleum ether/ether, 2% triethylamine) afforded **10j** as a white solid (23.3 mg, 7.2% yield): IR (neat) 3155, 2941, 1715, 1685, 1598, 1255, 1012 cm^{-1}; ^1H NMR ($CDCl_3$) 7.79 (d, 1H, J = 9.2 Hz), 7.63 (d, 1H, J = 9.2 Hz), 7.60 (sbr, 1H), 7.32 (dd, 1H, J = 8.8, 1.9 Hz), 7.21, (d, 1H, J = 9.1 Hz), 3.93 (s, 3H), 3.51 (dbr, 1H, J = 7.1 Hz), 3.42 (m, 1H), 3.08 (m, 2H), 2.72 (tbr, 1H, J = 14.6 Hz), 2.60 (s, 3H), 2.42-2.05 (m, 3H), 2.23 (s, 3H), 1.86-1.61 (m, 4H), 0.79 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) 210.1, 205.3, 153.7, 138.9, 131.5, 128.9, 128.7, 127.8, 125.8, 124.8, 123.3, 112.7, 64.5, 62.4, 58.9, 56.4, 42.0, 35.2, 34.1, 33.9, 32.7, 26.4, 25.2, 7.7; MS m/z (rel. intensity) 379 (17), 322 (44), 153 (3), 139 (3), 97 (56), 96 (55), 83 (90), 82 (100), 57 (27), 42 (52); Anal. Calcd for $C_{24}H_{29}NO_3 . 0.4H_2O$: C, 74.93; H, 8.12; N, 3.64. Found C, 74.93; H, 7.90; N, 3.38.

Molecular Modeling. Calculations were carried out using the SYBYL[1] software package. Calculations were run on Silicon Graphics Indigo, SUN Sparc 10, and Evans and Sutherland ESV workstations. For all compounds, molecular models were derived from the X-ray crystallographic coordinates for free-base cocaine[2] or on structures derived from that model. Structures were modified as needed with fragments or atoms added from the Sybyl structural library, using standard bond lengths and angles. Charges were calculated using the Gasteiger-Marsili[3] method. Structures were minimized based on both steric and electrostatic components using the MAXIMIN2 minimizer to gradient convergence with the following criteria: gradient energy change, 0.05 kcal/Å-mol (more recent work used 0.01 kcal/Å- mole, and showed no significant differences); rms displacement, 0.001 Å; non-bonded cutoff, 8.000 Å; dielectric function, distant dependent; dielectric constant, 1.000. Minimization under these conditions leads to a local energy minimum but not necessarily to the lowest or global minimum energy conformation.

Conformations used in the Comparative Molecular Field Analysis (CoMFA)[4] studies were identified using a random search procedure[5] implemented in Sybyl. Random search was carried out on non-protonated tropane

derivatives, with N-methyl (or hydrogen, compound **11f**, Table 2, see paper) in the equatorial position relative to the piperidine portion of the tropane ring, and with the piperidine portion of the tropane ring system in the chair conformation. Under this procedure, rotatable bonds were defined (Figure 2), random rotations about these bonds were carried out, and the resulting conformations were allowed to minimize. Final structures were retained when they meet certain difference criteria (rms threshold, 0.20; data convergence, 0.005) compared to previously found conformations.

Figure 2



Typically, energy cutoffs of 15 to 20 kcal/mole higher than the starting conformation's energy were used to limit the number of conformations found during this search procedure. The program terminated when either: (a) a maximum number of iterations were completed, (typically 3000 cycles); or (b) all conformations stored in the table were found a minimum of 6 times, indicating (>95% probability) that all local energy-minima conformations had been found. For selected compounds, ring bonds were also examined in the search procedure to identify boat-form conformations of the piperidine ring portion of the bicyclic system.

CoMFA - Prior to CoMFA, all conformations included in a data set were aligned through least-squares fitting of the C2, C3, C4, N and C6 atoms of the tropane ring using the 3β-(2-naphthyl)tropane-2β-ketomethyl analog, **11d** (Table 2, see paper) as the template molecule. All alignment points were given equal weight. Following alignment and placement of conformations in the CoMFA test grid (C-sp^3 probe atoms, +1 charge, 2-Å interval) steric and electrostatic interactions for each grid point were evaluated for all atoms in each molecule and added to the table as a CoMFA field. The default values of ±30 kcal/mol were used to truncate the fields. Initially, cross-validated (leave-one-out) partial least squares (PLS)[6] analyses were performed with the number of

groups equal to the number of molecules in the table. Up to ten components were allowed in these initial analyses, with the results used to identify the optimum number of components for the final non-cross-validated analysis. In general, the final number of components was selected based on that point at which addition of further components led to less that a 5% increase in cross-validated q^2 (r^2_{cv}), and provided a minimum standard error of prediction (SEOP). Final analyses were carried out with CoMFA-standard scaling. Cross-validated q^2 (r^2_{cv}), SEOP, conventional (non-cross-validated) r^2, F statistic, standard error of the estimate, probability of $r^2 = 0$, steric and electrostatic field coefficients (normalized), and fraction of contribution values were calculated and are provided.

Steric and electrostatic interactions that result in marked changes in binding affinity are typically represented as three-dimensional coefficient contour diagrams. By color-coding these regions of space, information may be conveyed on the effects of increases or decreases in steric bulk, or electrostatic charge in a given area. Steric CoMFA contributions were set at the 80% and 20% levels, with positive effects of steric bulk (increased affinity) color-coded green and negative effects of steric bulk color-coded yellow. Electrostatic CoMFA contributions were set at the 85% and 15% level, with areas where increases in negative charge lead to an increase in binding color-coded red and areas where increases in positive charge lead to an increase in binding color-coded blue.

Conformations for each compound in the data set were identified using a random search procedure. Both α- and β-C2-substituted tropane derivatives show significant rotational flexibility around RB1 (see Figure 2), with many conformations found within 1 kcal/mol of the lowest-energy conformation. Compounds showed less conformational flexibility at RB2, with high affinity β-C2-, β-C3-2-naphthyl derivatives having low-energy conformations with RB2 angles falling in either the 75° or 113° ranges. RB2 torsion angles for all compounds are defined as C2-C3-C(ar)-C(ar), with the last C(ar) selected to be that C(ar) atom in the same region of space as the tropane ring nitrogen. Boat conformations of the piperidine ring portion of the bicyclic system were of significantly higher (> 5 kcal/mole) energy than the corresponding chair conformations and were not considered further in these studies.

Conformational studies indicated that both β-C3 2- and 1-naphthyl derivatives exist as pairs of "up" or "down" conformations, i.e. one with the bridgehead of the naphthyl ring-system oriented closer to the tropane ring nitrogen or "up" and the second with the bridgehead of the naphthyl ring oriented further away from the tropane ring nitrogen, or "down" (Figure 3a and 3b, respectively). No energy difference was found between

those orientations in the 2-naphthyl derivatives, while a difference of approximately 3 kcal/mol exists between the "up" and "down" conformations for the β-C3 1-naphthyl derivatives. It seemed possible that a particular orientation of the β-C3-substituent relative to the remainder of the tropane ring system might be required for high binding affinity. Rotation about the tropane-to-C3-substituent bond (RB2) changes the relative spatial relationship of the tropane ring system nitrogen and the C3-substituent. PLS analyses, which are derived from three-dimensional interactions with a matrix of charged points surrounding a set of conformations, might provide some indication of the relative binding orientation of a set of molecules. Such a result could indicate which of several possible orientations of the naphthyl substituents play a role in binding, and whether orientation of the C3 substituent differs when binding occurs at the dopamine or serotonin transporters. Information of this kind along with separate DAT and SERT CoMFA models would be useful for the design of new compounds.

Figure 3

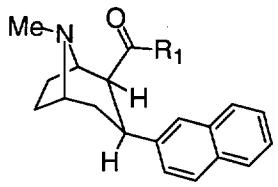


Figure 3a
naphthyl ring shown
in "up" position

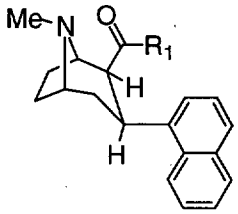


Figure 3b
naphthyl ring shown
in "down" position

Conformations were selected and placed into four subgroups with similar conformations in each group. Groups of conformations were established based on the following criteria: (1) Group 1 - all conformations showing 2- and 1-naphthyl substituents at C3 in the "up" orientation, with RB2 values of approximately 75°; (2) Group 2 - all conformations with "down" orientation of the C3 2- or 1-naphthyl substitutent, and RB2 values in the range of 60 to 100°; (3) Group 3 - all conformations with C3 naphthyl substituents in the "up" orientation, but with RB2 values of approximately 113° ; (4) Group 4 - naphthyl substituents "down", and RB2 values of approximately 113°.

Partial least squares analyses were carried out on each group, for both the DAT and SERT binding data, with analyses for each summarized in Table 3. For the DAT binding data, cross-validated q^2 values (r^2_{cv}) ranged from a low of 0.47 (Group 2) to a high of 0.74 (Group 3) with the optimum number of components equal to four for Group 1, three for Groups 3 and 4 and two for Group 2. The q^2 value for Group 3 indicates a model with good internal predictive validity, and appears to be significantly better ($\Delta q^2 > 0.2$) than those obtained for any of the other orientations of the naphthyl ring systems. The non-cross-validated r^2 value for this same set of conformations was 0.96, the standard error of estimate was 0.27, and an F value of 119.4. Contributions for the steric and electrostatic portions of the CoMFA fields were 65% and 35%, respectively. These steric and electrostatic features are shown in Figures 1a and 1b, respectively (See paper), overlaid on compound **8**, a compound with high affinity for both transporters.

For the serotonin transporter binding data, cross-validated q^2 values (r^2_{cv}) ranged from a low of 0.63 (Group 4) to a high of 0.70 (Group 2) and 0.71 (Group 3) with the optimum number of components equal to three for Groups 1 and 3 and two for Groups 2 and 4. These results indicate less sensitivity of the cross-validated q^2 value to the orientation of the C3 naphthyl derivatives for the SERT data compared to the DAT data. Based on the smaller number of components used for the Group 2 analysis compared to Group 3, this model was chosen for comparison. The steric and electrostatic features of the Group 2 SERT analysis are shown in Figure 1c and 1d, respectively (see paper). Steric components contribute 62% to the CoMFA fields, while electrostatic components contribute 38%. These are also shown overlaid on compound **8**.

For the DAT data examined, analyses of the four sub-groups gave a single analysis with a cross-validated q^2 value > 0.60. That model was based on the Group 3 sub-set of conformations with C3-naphthyl substituents oriented "up" (Figure 2a) and with RB2 bond angles in the 113° range. [An RB2 angle of 0° would correspond to one in which the tropane C2 and C3 atoms, and the naphthyl atoms used to define the torsion angle, all lie in the same plane, i.e., the C2-C3 bond and the Car-Car bond of the naphthyl ring are eclipsed.] For analyses of the serotonin transporter data, all conformational sets gave satisfactory analyses (cross-validated q^2 values ≥ 0.60). These results indicate that binding to the DAT shows a stronger requirement for a particular orientation of the bulky aromatic substituent at C3 compared to the binding to the SERT. Thus, the serotonin binding pocket may be less sensitive to the orientation of a ligand than is the DAT binding site.

This conclusion is in contrast to that of Meltzer et al., who surmise that the DAT is more flexible than the SERT with respect to binding, based on ligand displacement by 8-azabicyclo[3.2.1]oct-2-enes.[7] It is of note that

for similar conformations of 8-azabicyclo[3.2.1]octenes (chair form), α-C3-aryl-8-azabicyclo[3.2.1]octanes (boat form), or the 8-azabicyclo[3.2.1]octenes, the relative spacial position of the β-C3-aryl substituent show marked variation in their SERT binding. In contrast, the location of the C2-substituent varies considerably for these three classes of compounds (unpublished results). It is likely that the displacement of the C2-substituent, along with the slight variations in the C3 substituent positions play a significant role in the differences in SERT affinity.

Table 3. CoMFA Analyses of dopamine and serotonin transporter binding data. Groups represent subsets of conformations with similar orientations of the C3-substituents.

Dopamine Transporter								
							Relative Contribution[h]	
Group (RB2)[a]	n[b]	q^{2} [c]	SEOP[d]	r^{2} [e]	SE[f]	F[g]	Steric	Electrostatic
1 (~75°, up)	4	0.51	0.93	0.94	0.33	61.4	0.60	0.40
2 (60-110°, down)	2	0.47	0.91	0.84	0.50	47.5	0.60	0.40
3 (~113°, up)	3	0.74	0.66	0.96	0.27	119.4	0.65	0.35
4 (~113°, down)	3	0.52	0.89	0.88	0.45	40.4	0.51	0.49
Serotonin Transporter								
							Relative Contribution[h]	
Group (RB2)[a]	n[b]	q^{2} [c]	SEOP[d]	r^{2} [e]	SE[f]	F[g]	Steric	Electrostatic
1 (~75°, up)	3	0.65	0.61	0.93	0.27	74.6	0.61	0.39
2 (60-110°, down)	2	0.70	0.54	0.92	0.29	97.4	0.62	0.38
3 (~113°, up)	3	0.71	0.56	0.93	0.28	71.5	0.68	0.32
4 (~113°, down)	2	0.63	0.61	0.84	0.40	48.5	0.48	0.52

[a] Cross-validated partial least square analyses were carried out with a 2.0 kcal filter and CoMFA standard scaling. Final calculations of non-cross-validated analyses were carried out with no filter. [b]Number of components in final analysis. [c]Squared correlation coefficient of the cross-validated analysis. [d]SEOP, standard error of prediction. [e]Squared correlation coefficient of a non-cross-validated analysis. [f]SE = standard error of estimate. [g]F = F statistic (all were highly significant, with probability of $r^2 = 0$, 0.000. [h]Relative contribution of steric and electrostatic components of the CoMFA field.

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