

Supporting Information

Selective NR1/2B N-Methyl-D-Aspartate Receptor Antagonists among Indole-2-carboxamides and Benzimidazole-2-carboxamides

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Experimental procedures

Compounds **6b-6p**, **7**, **8**, **9** were prepared according to the procedure described in the article for **6a**.

(6-hydroxy-1H-indole-2-yl)-[4-(4-methoxy-benzyl)-piperidine-1-yl]-methanone (6b): mp 105°C (isopropanol); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 11.07 (d, *J*=1.5 Hz, 1 H), 9.11 (s, 1 H), 7.36 (d, *J*=8.6 Hz, 1 H), 7.15-7.05 (m, 2 H), 6.90-6.80 (m, 2 H), 6.78-6.74 (m, 1 H), 6.63-6.59 (m, 1H), 6.57 (dd, *J*=8.6, 2.2 Hz, 1 H), 4.52-4.35 (m, 2 H), 3.72 (s, 3 H), 3.08-2.79 (m, 2 H), 2.48 (d, *J*=7.0 Hz, 2 H), 1.89-1.56 (m, 3 H), 1.28-1.04 (m, 2 H) ppm.

(6-Hydroxy-1H-indole-2-yl)-[3-(4-methoxybenzyl)piperidine-1-yl]-methanone (6c): mp 258°C (isopropanol); ¹H NMR (300 MHz, DMSO-*d*₆, 50 °C) δ 10.94 (s, 1 H), 9.04 (s, 1 H), 7.23 (d, *J*=8.7 Hz, 1 H), 7.15-7.08 (m, 2 H), 6.88-6.81 (m, 2 H), 6.77-6.73 (m, 1 H), 6.55 (dd, *J*=8.7, 2.2 Hz, 1 H), 6.22 (brs, 1 H), 4.40-4.20 (m, 2 H), 3.72 (s, 3 H), 3.06-2.85 (m, 1 H), 2.82-2.67 (m, 1 H), 2.60-2.36 (m, 2 H), 1.90-1.64 (m, 3 H), 1.53-1.14 (m, 2 H) ppm.

(6-Hydroxy-1H-indole-2-yl)-[2-(4-methoxybenzyl)-piperidine-1-yl]-methanone (6d): mp 84°C (hexane); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 10.99 (s, 1 H), 9.13 (s, 1 H), 7.34 (d, *J*=8.6 Hz, 1 H), 7.20-7.00 (m, 2 H), 6.87-6.78 (m, 2 H), 6.77-6.72 (m, 1 H), 6.57 (dd, *J*=8.6, 2.1 Hz, 1 H), 6.45 (brs, 1 H), 4.89-4.69 (m, 1 H), 4.43-4.25 (m, 1 H), 3.70 (s, 3 H), 3.37-3.11 (m, 1 H), 3.02-2.82 (m, 2 H), 2.00-1.33 (m, 6 H).

(6-Hydroxy-1H-indole-2-yl)-(4-phenylpiperidine-1-yl)-methanone (6e): mp 105°C (isopropanol); ¹H NMR (500 MHz, DMSO-*d*₆, 30 °C) δ 11.11 (s, 1 H), 9.12 (s, 1 H), 7.37 (d, *J*=8.7 Hz, 1 H), 7.35-7.25 (m, 4 H), 7.23-7.17 (m, 1 H), 6.80-6.76 (m, 1 H), 6.72-6.68 (m, 1H), 6.58 (dd, *J*=8.7, 2.2 Hz, 1 H), 4.66-4.57 (m, 2 H), 3.20-2.96 (m, 2 H), 2.91-2.80 (m, 1 H), 1.92-1.82 (m, 2 H), 1.70-1.57 (m, 2 H) ppm.

(6-Hydroxy-1H-indole-2-yl)-(4-phenylethylpiperidine-1-yl)-methanone (6f): mp 157-159°C (ethanol); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 11.10 (d, *J*=1.5 Hz, 1 H), 9.11 (s, 1 H), 7.37 (d, *J*=8.5 Hz, 1 H), 7.33-7.12 (m, 5 H), 6.79-6.76 (m, 1 H), 6.65-6.62 (m, 1H), 6.57 (dd, *J*=8.5, 2.4 Hz, 1 H), 4.51-4.38 (m, 2 H), 3.06-2.85 (m, 2 H), 2.67-2.56 (m, 2H), 1.86-1.74 (m, 2H), 1.63-1.48 (m, 3 H), 1.25-1.06 (m, 2 H) ppm.

(6-Hydroxy-1H-indole-2-yl)-(4-phenoxy piperidine)-methanone (6g): mp 155-156°C (isopropanol); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 11.12 (d, *J*=1.5 Hz, 1 H), 9.14 (s, 1 H), 7.37 (d, *J*=8.7 Hz, 1 H), 7.35-7.25 (m, 2 H), 7.04-6.90 (m, 3 H), 6.80-6.77 (m, 1 H), 6.71-6.67 (m, 1 H), 6.58 (dd, *J*=8.7, 2.1 Hz, 1 H), 4.75-4.62 (m, 1 H), 4.16-4.00 (m, 2 H), 3.68-3.50 (m, 2 H), 2.10-1.94 (m, 2 H), 1.75-1.58 (m, 2 H) ppm.

(4-Benzyloxy piperidine-1-yl)-(6-hydroxy-1H-indole-2-yl)-methanone (6h): mp 203-204°C (ethanol); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 11.10 (d, *J*=1.5 Hz, 1 H), 9.13 (s, 1 H), 7.40-7.24 (m, 6 H), 6.79-6.75 (m, 1 H), 6.67-6.64 (m, 1H), 6.58 (dd, *J*=8.4, 2.1 Hz, 1 H), 4.58 (s, 2H), 4.12-3.98 (m, 2 H), 3.75-3.64 (m, 1 H), 3.53-3.38 (m, 2H), 2.01-1.87 (m, 2 H), 1.64-1.48 (m, 2 H) ppm.

(6-Hydroxy-1H-indole-2-yl)-(4-phenoxyethylpiperidine-1-yl)-methanone (6i): mp 104°C (isopropanol); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 11.10 (d, *J*=1.5 Hz, 1 H), 9.13 (s, 1 H), 7.37 (d, *J*=8.5 Hz, 1 H), 7.32-7.22 (m, 2 H), 6.98-6.87 (m, 3 H), 6.80-6.76 (m, 1 H), 6.68-6.64 (m, 1H), 6.58 (dd, *J*=8.5, 2.1 Hz, 1 H), 4.59-4.41 (m, 2 H), 3.87 (d, *J*=6.4 Hz, 2 H), 3.16-2.92 (m, 2 H), 2.19-1.98 (m, 1H), 1.95-1.78 (m, 2H), 1.41-1.21 (m, 2 H) ppm.

(4-Benzoylpiperidine-1-yl)-(6-hydroxy-1H-indole-2-yl)-methanone (6j): mp 190-191°C ; ¹H NMR (500 MHz, DMSO-*d*₆, 30 °C) δ 11.10 (s, 1 H), 9.15 (brs, 1 H), 8.07-8.00 (m, 2 H), 7.70-7.62 (m, 1 H), 7.60-7.52 (m, 2 H), 7.37 (d, *J*=8.7 Hz, 1 H), 6.80-6.76 (m, 1 H), 6.70-6.65 (m, 1 H), 6.58 (dd, *J*=8.7, 2.2 Hz, 1 H), 4.55-4.45 (m, 2 H), 3.90-3.75 (m, 1 H), 3.35-3.10 (m, 2 H), 1.95-1.85 (m, 2 H), 1.70-1.50 (m, 2 H) ppm.

(6-Hydroxy-1H-indole-2-yl)-[4-(hydroxy-phenyl-methyl)-piperidine-1-yl]-methanone (6k): mp 89°C (diisopropyl ether); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 11.06 (d, *J*=1.8 Hz, 1 H), 9.11 (s, 1 H), 7.45-7.09 (m, 6 H), 6.80-6.74 (m, 1 H), 6.63-6.53 (m, 2 H), 5.22 (d, *J*=4.5 Hz, 1 H), 4.57-4.37 (m, 2 H), 4.33 (dd, *J*=6.2, 4.5 Hz, 1 H), 2.99-2.75 (m, 2 H), 1.96-1.69 (m, 2 H), 1.46-1.13 (m, 2 H) ppm.

(6-Hydroxy-1H-indole-2-yl)-(4-phenylamino-piperidine-1-yl)-methanone (6l): mp 213°C (ethanol); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 11.12 (d, *J*=1.5 Hz, 1 H), 9.14 (s, 1 H), 7.38 (d, *J*=8.4 Hz, 1 H), 7.14-7.00 (m, 2 H), 6.82-6.77 (m, 1 H), 6.70-6.47 (m, 5 H), 5.47 (d, *J*=8.1 Hz, 1 H), 4.45-4.30 (m, 2 H), 3.64-3.48 (m, 1 H), 3.34-3.14 (m, 2 H), 2.07-1.92 (m, 2 H), 1.46-1.28 (m, 2 H) ppm.

[4-(4-Fluorobenzyl)piperidine-1-yl]-(6-hydroxy-1H-indole-2-yl)-methanone (6m): mp 180-182°C (isopropanol); ¹H NMR (500 MHz, DMSO-*d*₆, 30 °C) δ 11.08 (s, 1 H), 9.12 (s, 1 H), 7.37 (d, *J*=8.7 Hz, 1 H), 7.25-7.18 (m, 2 H), 7.13-7.06 (m, 2 H), 6.80-6.76 (m, 1 H), 6.64-6.60 (m, 1 H), 6.58 (dd, *J*=8.7, 2.2 Hz, 1 H), 4.50-4.38 (m, 2 H), 3.10-2.75 (m, 2 H), 2.53 (d, *J*=7.0 Hz, 2 H), 1.88-1.73 (m, 1 H), 1.70-1.58 (m, 2 H), 1.23-1.08 (m, 2 H) ppm.

(6-Hydroxy-1H-indole-2-yl)-[4-(4-methylbenzyl)-piperidine-1-yl]-methanone (6n): mp 164°C (isopropanol); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 11.05 (d, *J*=1.5 Hz, 1 H), 9.10 (s, 1 H), 7.35 (d, *J*=8.7 Hz, 1 H), 7.14-7.01 (m, 4 H), 6.78-6.73 (m, 1 H), 6.62-6.59 (m, 1H), 6.56 (dd, *J*=8.7, 2.2 Hz, 1 H), 4.51-4.35 (m, 2 H), 3.03-2.79 (m, 2 H), 2.50 (d, *J*=7.0 Hz, 2 H), 2.26 (s, 3 H), 1.90-1.71 (m, 1 H), 1.71-1.57 (m, 2 H), 1.24-1.06 (m, 2 H) ppm.

(6-Hydroxy-1H-indole-2-yl)-[4-(2-methoxy-benzyl)-piperidine-1-yl]-methanone (6o): mp 85-86°C (hexane-diisopropyl ether); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 11.07 (d, *J*=1.5 Hz, 1 H), 9.11 (s, 1 H), 7.36 (d, *J*=8.8 Hz, 1 H), 7.20-7.15 (m, 1 H), 7.14-7.08 (m, 1 H), 6.95 (dd, *J*=8.4, 1.0 Hz, 1 H), 6.86 (td, *J*=7.5, 1.0 Hz, 1 H), 6.78-6.75 (m, 1 H), 6.63-6.60 (m, 1H), 6.57 (dd, *J*=8.8, 2.2 Hz, 1 H), 4.50-4.33 (m, 2 H), 3.78 (s, 3 H), 3.05-2.80 (m, 2 H), 2.53 (d, *J*=7.0 Hz, 2 H), 1.96-1.73 (m, 1 H), 1.73-1.58 (m, 2 H), 1.30-1.08 (m, 2 H) ppm.

[4-(3-Fluorobenzyl)-piperidine-1-yl]-(6-hydroxy-1H-indole-2-yl)-methanone (6p): mp 219°C (isopropanol); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 11.05 (s, 1 H), 9.10 (s, 1 H), 7.40-7.27 (m, 2 H), 7.10-6.96 (m, 3 H), 6.78-6.74 (m, 1 H), 6.64-6.60 (m, 1 H), 6.57 (dd, *J*=8.7, 2.3 Hz, 1 H), 4.50-4.38 (m, 2 H), 3.05-2.72 (m, 2 H), 2.57 (d, *J*=7.0 Hz, 2 H), 1.98-1.78 (m, 1 H), 1.72-1.58 (m, 2 H), 1.30-1.08 (m, 2 H) ppm.

(4-Benzylpiperidine-1-yl)-(5-hydroxy-1H-indole-2-yl)-methanone (7): mp 199°C (isopropanol); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 11.10 (s, 1 H), 8.75 (s, 1 H), 7.33-7.24 (m, 2 H), 7.24-7.14 (m, 4 H), 6.88 (dm, *J*=2.2, 1 H), 6.71 (dd, *J*=8.7, 2.2 Hz, 1 H), 6.56-6.53 (m, 1 H), 4.48-4.36 (m, 2 H), 3.10-2.80 (m, 2 H), 2.54 (d, *J*=7 Hz, 2 H), 1.92-1.72 (m, 1 H), 1.72-1.58 (m, 2 H), 1.28-1.08 (m, 2 H) ppm.

(4-Benzylpiperidine-1-yl)-(4-hydroxy-1H-indole-2-yl)-methanone (8): mp 194°C (isopropanol); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 11.18 (s, 1 H), 9.50 (s, 1 H), 7.34-7.25 (m, 2 H), 7.24-7.14 (m, 3 H), 6.95 (dd, *J*=8.1, 7.5 Hz, 1 H), 6.85 (dm, *J*=8.1 Hz, 1 H), 6.80-6.76 (m, 1 H), 6.36 (dd, *J*=7.5, 1 Hz, 1 H), 4.50-4.38 (m, 2 H), 3.10-2.80 (m, 2 H), 2.56 (d, *J*=7 Hz, 2 H), 1.95-1.76 (m, 1 H), 1.74-1.60 (m, 2 H), 1.30-1.10 (m, 2 H) ppm.

(4-Benzylpiperidine-1-yl)-(7-hydroxy-1H-indole-2-yl)-methanone (9): mp 213°C (isopropanol); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 11.02 (s, 1 H), 9.38 (s, 1 H), 7.33-7.24 (m, 2 H), 7.24-7.14 (m, 3 H), 7.04 (dd, *J*=8.0, 1.0 Hz, 1 H), 6.85 (t, *J*=8.0 Hz, 1 H), 6.69-6.65 (m, 1 H), 6.56 (dd, *J*=8.0, 1.0 Hz, 1 H), 4.48-4.30 (m, 2 H), 3.20-2.70 (m, 2 H), 2.55 (d, *J*=7.2 Hz, 2 H), 1.94-1.73 (m, 1 H), 1.72-1.58 (m, 2 H), 1.30-1.10 (m, 2 H) ppm.

(4-Benzylpiperidine-1-yl)-(5,7-dihydroxy-1H-indole-2-yl)-methanone (11). Step 1: Methyl 5,7-dibenzyloxy-1H-indole-2-carboxylate (40). **40** was prepared from 3,5-dibenzyloxybenzaldehyde (**37**) according to the procedure described above for **39**: mp 143-144°C; ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 11.90 (brs, 1 H), 7.67-7.58 (m, 2 H), 7.51-7.27 (m, 8 H), 7.05 (d, *J*=2.1 Hz, 1 H), 6.81-6.77 (m, 1 H), 6.66 (d, *J*=2.1 Hz, 1 H), 5.26 (s, 2 H), 5.07 (s, 2 H), 3.85 (s, 3 H) ppm.

Step 2: (4-Benzylpiperidine-1-yl)-(5,7-dibenzyloxy-1H-indole-2-yl)-methanone (44). **44** was prepared from **40** according to the procedure described above for **43**.

Step 3: (4-Benzylpiperidine-1-yl)-(5,7-dihydroxy-1H-indole-2-yl)-methanone (11). **11** was prepared from **44** according to the procedure described above for **10**: mp 213°C (isopropanol); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 10.68 (d, *J*=1.5 Hz, 1 H), 9.28 (s, 1 H), 8.59 (s, 1 H), 7.35-7.24 (m, 2 H), 7.23-7.13 (m, 3 H), 6.49 (d, *J*=2.2 Hz, 1 H), 6.37-6.33 (m, 1 H), 6.16 (d, *J*=2.2 Hz, 1 H), 4.47-4.30 (m, 2 H), 3.09-2.76 (m, 2 H), 2.55 (d, *J*=7.1 Hz, 2 H), 1.94-1.73 (m, 1 H), 1.73-1.55 (m, 2 H), 1.28-1.08 (m, 2 H) ppm.

Compounds **13a-14a** were prepared according to the procedure described in the article for **12a**.

(5-Amino-1H-indol-2-yl)-(4-benzyl-piperidin-1-yl)-methanone (13a). Step 1: (4-Benzyl-piperidin-1-yl)-(5-nitro-1H-indol-2-yl)-methanone (34a). **(34a)** was prepared from 5-nitroindole-2-carboxylic acid (**31**) according to the procedure described above for **33a**: mp 220-224°C, ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.10-1.30 (m, 2H), 1.60-1.75 (m, 2H), 1.75-1.96 (m, 1H), 2.57 (d, *J*=6.9 Hz, 2H), 3.00 (br m, 2H), 4.39 (br m, 2H), 7.04 (d, *J*=0.6 Hz, 1H), 7.15-7.34 (m, 5H), 6.57 (d, *J*=9.0 Hz, 1H), 8.07 (dd, *J*=9.0, 2.1 Hz, 1H), 8.64 (d, *J*=2.1 Hz, 1H), 12.30 (br s, 1H).

Step 2: (5-Amino-1H-indol-2-yl)-(4-benzyl-piperidin-1-yl)-methanone (13a). **13a** was prepared from **34a** according to the procedure described above for **12a**: mp 176-180°C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.09-1.25 (m, 2H), 1.60-1.72 (m, 2H), 1.72-1.93 (m, 1H), 2.55 (d, *J*=7.2 Hz, 2H), 2.92 (br m, 2H), 4.41 (d, *J*=13.2 Hz, 2H), 4.54 (br s, 2H), 6.43 (dd, *J*=2.1, 0.6 Hz, 1H), 6.59 (dd, *J*=8.7, 2.4 Hz, 1H), 6.80 (d, *J*=2.1 Hz, 1H), 7.11 (dt, *J*=8.7, 0.9 Hz, 1H), 7.14-7.33 (m, 5H), 11.00 (s, 1H).

(6-Amino-1H-indol-2-yl)-(4-benzyl-piperidin-1-yl)-methanone (14a). Step 1: (4-Benzyl-piperidin-1-yl)-(6-nitro-1H-indol-2-yl)-methanone (35a). 35a was prepared from 6-nitroindole-2-carboxylic acid (32) according to the procedure described above for 33a: mp 188-189 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.10-1.32 (m, 2H), 1.60-1.76 (m, 2H), 1.76-1.95 (m, 1H), 2.56 (d, *J*=7.2 Hz, 2H), 3.00 (br m, 2H), 4.38 (br m, 2H), 6.93 (d, *J*=0.9 Hz, 1H), 7.14-7.34 (m, 5H), 7.81 (dd, *J*=8.7, 0.6 Hz, 1H), 7.92 (dd, *J*=8.7, 2.1 Hz, 1H), 8.32 (d, *J*=2.1 Hz, 1H) 12.38 (br s, 1H).

Step 2: (6-Amino-1H-indol-2-yl)-(4-benzyl-piperidin-1-yl)-methanone (14a). 14a was prepared from 35a according to the procedure described above for 12a: mp 188-193°C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.08-1.25 (m, 2H), 1.59-1.73 (m, 2H), 1.73-1.93 (m, 1H), 2.55 (d, *J*=7.2 Hz, 2H), 2.91 (t, *J*=12.3 Hz, 2H), 4.44 (d, *J*=13.2 Hz, 2H), 4.92 (s, 2H), 6.43 (dd, *J*=8.4, 1.8 Hz, 1H), 6.54 (d, *J*=1.8 Hz, 2H), 6.84 (dd, *J*=8.1, 7.5 Hz, 1H), 7.14-7.33 (m, 6H), 10.82 (s, 1H).

N-[2-(4-Benzyl-piperidine-1-carbonyl)-1H-indol-5yl]-methanesulfonamide (17a). 17a was prepared from 13a according to the procedure described above for 16a: mp 111-114°C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.10-1.30 (m, 2H), 1.60-1.74 (m, 2H), 1.74-1.95 (m, 1H), 2.55 (d, *J*=6.9 Hz, 2H), 2.87 (s, 3H), 2.94 (br m, 2H), 4.40 (d, *J*=12.9 Hz, 2H), 6.73 (dd, *J*=2.1, 0.9 Hz, 1H), 7.09 (dd, *J*=8.7, 2.1 Hz, 1H), 7.14-7.33 (m, 5H), 7.37 (d, *J*=8.7 Hz, 1H), 7.47 (d, *J*=2.1 Hz, 1H), 9.31 (s, 1H), 11.57 (s, 1H).

N-[2-(4-Benzyl-piperidine-1-carbonyl)-1H-indol-6yl]-methanesulfonamide (18a). 18a was prepared from 14a according to the procedure described above for 16a: mp 207-210°C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.10-1.30 (m, 2H), 1.60-1.73 (m, 2H), 1.73-1.94 (m, 1H), 2.55 (d, *J*=7.2 Hz, 2H), 2.91 (s, 3H), 2.95 (br m, 2H), 4.41 (d, *J*=13.2 Hz, 2H), 6.70 (dd, *J*=2.1, 0.9 Hz, 1H), 6.96 (dd, *J*=8.4, 1.8 Hz, 1H), 7.14-7.33 (m, 5H), 7.35 (s, 1H), 7.54 (d, *J*=8.4 Hz, 1H), 9.51 (s, 1H), 11.43 (s, 1H).

6-(4-Benzylpiperidin-1-carbonyl)-1,5-dihydro-oxazolo[4,5-*f*]indol-2-one (19). Step 1: Methyl 6-benzyloxy-5-nitro-indole-2-carboxylate (41). To a freshly prepared solution of sodium methoxide (2.5 g, 108.7 mmol sodium) in methanol (70 ml) a mixture of 38 (6.1 g, 23.7 mmol), methyl azidoacetate (11.2 g, 97.3 mmol) and methanol (100 ml), was added dropwise at 0°C, under Ar atmosphere. The mixture was stirred at 0°C for 5 h, then diluted with water (350 ml) and the precipitated crystals were filtered off, washed with water and dried to give methyl (Z)-2-azido-3-(4-benzyloxy-3-nitrophenyl)-acrylate (4.93 g, 59 %): mp 94-95°C. This material was added in small portions to a stirred solution of boiling xylene (200 ml). After completion of the addition the reaction mixture was refluxed until the gas formation ceased (about 0.5 h), then cooled to room temperature. The precipitated product was filtered off and washed with n-hexane to give 41 (0.67 g, 15 %): mp 184-187°C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.88 (s, 3H), 5.30 (s, 2H), 7.19 (s, 1H), 7.28 (d, *J*=0.6 Hz, 1H), 7.30-7.51 (m, 5H), 8.35 (s, 1H), 12.25 (br s, 1H).

Step 2: 6-(4-Benzylpiperidin-1-carbonyl)-1,5-dihydro-oxazolo[4,5-*f*]indol-2-one (19). To a solution of 41 (0.67 g, 2.0 mmol) in THF (60 ml) 10 % Pd/C catalyst (0.1 g) was added and hydrogenated for 5 h to give methyl 5-amino-6-hydroxy-indole-2-carboxylate. The catalyst was filtered off and the filtrate was immediately used in the next step. To the above solution 20 % phosgene in toluene solution (1.2 ml, 2.28 mmol) and triethylamine (0.9 ml, 6.45 mmol) were added. The reaction mixture was stirred at room temperature for 1 h, concentrated in vacuo, water was added to the residue and extracted with EtOAc. The organic layer was washed with 5 % aqueous NaHCO₃ solution, water, 1 N HCl solution and again with water, dried over Na₂SO₄, concentrated to give 42 (0.22 g 46 %): mp 267-277 °C. A stirred mixture of 42 (1.21 g, 5.17 mmol), ethanol (60 ml), water (10 ml) and KOH (0.8 g, 14.26 mmol) was refluxed for 1 h. The mixture was concentrated, the residue was dissolved in water and acidified with 1N HCl solution.

The precipitated crystals were filtered off and washed with water to give 2-oxo-1,5-dihydro-2H-oxazolo[4,5-f]indole-6-carboxylic acid (0.83 g, 74 %): mp 288-290°C. A mixture of this material (0.41 g, 1.88 mmol), triethylamine (0.3 ml, 2.15 mmol), 4-benzylpiperidine (0.35 g, 1.96 mmol), HBTU (0.76 g, 2.0 mmol) in DMF (10 ml) was stirred at room temperature for 6 h. The reaction mixture was concentrated and purified by column chromatography (4:1 toluene/methanol) and crystallized with diethyl ether to give **19** as a white solid (0.32 g, 45 %): mp 270-271°C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.10-1.28 (m, 2H), 1.62-1.74 (m, 2H), 1.75-1.94 (m, 1H), 2.56 (d, *J*=7.2 Hz, 2H), 2.96 (br m, 2H), 4.43 (d, *J*=13.2 Hz, 2H), 6.76 (dd, *J*=2.4, 0.9 Hz, 1H), 7.14-7.34 (m, 7H), 11.38 (br s, 1H), 12.46 (s, 1H).

(4-Benzylpiperidin-1-yl)-(3,6-dihydro-pirrolo[3,2-e]indazol-7-yl)-methanone (21).

Step 1: Ethyl 3,6-dihydro-pyrrolo[3,2-e]indazole-7-carboxylate (49). **49** was prepared from 5-amino-indazole (**46**) according to the procedure described above for **48**: mp 220-221°C (methanol); ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.36 (t, *J*=7.2 Hz, 3H), 4.35 (q, *J*=7.2 Hz, 2H), 7.40 (d, *J*=2.1 Hz, 1H), 7.46 (s, 2H), 8.22 (s, 1H), 12.10 (br s, 1H).

Step 2: (4-Benzylpiperidin-1-yl)-(3,6-dihydro-pirrolo[3,2-e]indazol-7-yl)-methanone (21). **21** was prepared from **49** according to the procedure described above for **20**: mp 205-207°C (diethyl ether); ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.11-1.33 (m, 2H), 1.62-1.76 (m, 2H), 1.76-1.97 (m, 1H), 2.57 (d, *J*=6.9 Hz, 2H), 2.98 (br m, 2H), 4.50 (d, *J*=13.2 Hz, 2H), 7.04 (d, *J*=1.5 Hz, 1H), 7.15-7.34 (m, 5H), 7.35 (d, *J*=8.7 Hz, 1H), 7.44 (d, *J*=8.7 Hz, 1H), 8.17 (s, 1H), 11.79 (s, 1H), 13.02 (s, 1H).

(4-Benzylpiperidin-1-yl)-(3,6-dihydro-imidazo[4,5-e]indol-7-yl)-methanone (22).

Step 1: Ethyl 3,6-dihydro-imidazo[4,5-e]indole-7-carboxylate (50). **50** was prepared from 5-amino-benzimidazole (**47**) according to the procedure described above for **48**: solid foam; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.36 (t, *J*=7.2 Hz, 3H), 4.35 (q, *J*=7.2 Hz, 2H), 7.27-7.32 (m 2H), 7.50 (d, *J*=8.7 Hz, 1H), 8.10 (s, 1H), 12.00 (br s, 1H).

Step 2: (4-Benzylpiperidin-1-yl)-(3,6-dihydro-imidazo[4,5-e]indol-7-yl)-methanone (22). **22** was prepared from **50** according to the procedure described above for **20**: mp 256-257°C (diethyl ether); ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.12-1.33 (m, 2H), 1.62-1.76 (m, 2H), 1.76-1.96 (m, 1H), 2.58 (d, *J*=6.9 Hz, 2H), 2.99 (br m, 2H), 4.49 (d, *J*=13.2 Hz, 2H), 6.93 (d, *J*=1.5 Hz, 1H), 7.14-7.34 (m, 6H), 7.41 (br d, *J*=8.1 Hz, 1H), 8.07 (s, 1H), 11.62 (br s, 1H), 12.50 (br s, 1H).

(4-Benzylpiperidin-1-yl)-(5-hydroxybenzofuran-2-yl)-methanone (59). **59** was prepared from **72** and 4-benzylpiperidine according to the procedure described above for **56**. mp 148-153°C (diethyl ether); ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.10-1.25 (m, 2H), 1.59-1.72 (m, 2H), 1.75-1.90 (m, 1H), 2.54 (d, *J*=7.1 Hz, 2H), 2.90 (br m, 2H), 4.30 (br m, 2H), 6.86 (dd, *J*=8.5, 2.5 Hz, 1H), 6.99 (d, *J*=2.5 Hz, 1H), 7.14-7.21 (m, 4H), 7.24-7.31 (m, 2H), 7.41 (d, *J*=8.5 Hz, 1H), 9.31 (s, 1H).

Compounds **60m-60u** were prepared according to the procedure described for **56**.

[4-(4-Fluoro-benzyl)-piperidin-1-yl]-(6-hydroxy-1H-benzimidazol-2-yl)-methanone (60m): mp 176°C; ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 12.58 (s, 1H), 9.40 (s, 1H), 7.49 (d, *J*=8.8 Hz, 1H), 7.26-7.18 (m, 2H), 7.15-7.05 (m, 2H), 6.86-6.83 (m, 1H), 6.74 (dd, *J*=8.8, 2.2 Hz, 1H), 5.65-5.52 (m, 1H), 4.60-4.45 (m, 1H), 3.22-3.08 (m, 1H), 2.84-2.68 (m, 1H), 2.54 (d, *J*=7.0 Hz, 2H), 1.94-1.60 (m, 3H), 1.34-1.05 (m, 2H) ppm.

(6-Hydroxy-1H-benzimidazol-2-yl)-[4-(3-methyl-benzyl)-piperidin-1-yl]-methanone (60q): mp 176°C; ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 12.61 (s, 1 H), 9.38 (s, 1 H), 7.50 (d, *J*=8.7 Hz, 1 H), 7.17 (t, *J*=7.7 Hz, 1 H), 7.04-6.92 (m, 3 H), 6.84 (d, *J*=2.4 Hz, 1 H), 6.74 (dd, *J*=8.7, 2.4 Hz, 1 H), 5.66-5.50 (m, 1 H), 4.62-4.42 (m, 1 H), 3.25-3.02 (m, 1 H), 2.86-2.67 (m, 1 H), 2.50 (d, *J*=7.0 Hz, 2 H), 2.28 (s, 3 H), 1.94-1.76 (m, 1 H), 1.76-1.61 (m, 2 H), 1.33-1.05 (m, 2 H) ppm.

(6-Hydroxy-1H-benzimidazol-2-yl)-[4-(3-methoxy-benzyl)-piperidin-1-yl]-methanone (60r): mp 86°C; ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 12.61 (s, 1 H), 9.38 (s, 1 H), 7.50 (d, *J*=8.7 Hz, 1 H), 7.20 (t, *J*=8.0 Hz, 1 H), 6.84 (d, *J*=2.2 Hz, 1 H), 6.82-6.66 (m, 4 H), 5.68-5.48 (m, 1 H), 4.65-4.39 (m, 1 H), 3.74 (s, 3 H), 3.24-3.06 (m, 1 H), 2.86-2.70 (m, 1 H), 2.52 (d, *J*=7.0 Hz, 2 H), 1.97-1.77 (m, 1 H), 1.76-1.60 (m, 2 H), 1.34-1.06 (m, 2 H) ppm.

(6-Hydroxy-1H-benzimidazol-2-yl)-(4-p-tolyloxy-piperidin-1-yl)-methanone (60s): mp 116°C; ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 12.66 (s, 1 H), 9.41 (s, 1 H), 7.51 (d, *J*=8.9 Hz, 1 H), 7.15-7.04 (m, 2 H), 6.96-6.82 (m, 3 H), 6.75 (dm, *J*=8.9 Hz, 1 H), 5.00-4.73 (m, 1 H), 4.69-4.54 (m, 1 H), 4.28-4.12 (m, 1 H), 4.10-3.95 (m, 1 H), 3.64-3.43 (m, 1 H), 2.23 (s, 3 H), 2.13-1.91 (m, 2 H), 1.80-1.53 (m, 2 H) ppm.

[4-(4-Chloro-phenoxy)-piperidin-1-yl]-(6-hydroxy-1H-benzimidazol-2-yl)-methanone (60t): mp 194-195°C; ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 12.67 (s, 1 H), 9.41 (s, 1 H), 7.51 (d, *J*=8.7 Hz, 1 H), 7.40-7.27 (m, 2 H), 7.11-6.98 (m, 2 H), 6.85 (d, *J*=1.8 Hz, 1 H), 6.75 (dd, *J*=8.7, 1.8 Hz, 1 H), 5.04-4.80 (m, 1 H), 4.75-4.61 (m, 1 H), 4.28-3.95 (m, 2 H), 3.64-3.42 (m, 1 H), 2.19-1.90 (m, 2 H), 1.82-1.52 (m, 2 H) ppm.

[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-(6-hydroxy-1H-benzimidazol-2-yl)-methanone (60u): mp 147-148°C; ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 12.72 (s, 1 H), 9.48 (s, 1 H), 7.55 (d, *J*=8.9 Hz, 1 H), 7.19-7.08 (m, 2 H), 7.08-6.97 (m, 2 H), 6.90 (d, *J*=2.3 Hz, 1 H), 6.78 (dd, *J*=8.9, 2.3 Hz, 1 H), 5.02-4.79 (m, 1 H), 4.70-4.54 (m, 1 H), 4.33-3.94 (m, 2 H), 3.65-3.46 (m, 1 H), 2.18-1.91 (m, 2 H), 1.82-1.55 (m, 2 H) ppm.

(4-Benzyl-piperidin-1-yl)-[4(7)-hydroxy-1H-benzimidazol-2-yl]-methanone (61a). **Step 1: N-(2-Benzyloxy-6-nitro-phenyl)-oxalamic acid ethyl ester (80).** A procedure similar to that above for **79** employing **78** gave **80** as a brown oil; ¹H NMR (500 MHz, DMSO-*d*₆, 50 °C) δ 10.62 (s, 1 H), 7.60-7.44 (m, 5 H), 7.42-7.28 (m, 3 H), 5.26 (s, 2 H), 4.32 (q, *J*=7.1 Hz, 2 H), 1.30 (t, *J*=7.1 Hz, 3 H) ppm.

Step 2: N-(2-Amino-6-hydroxy-phenyl)-N'-butyl-oxalamide (82). **82** was prepared from **80** according to the procedure described above for **81**. mp 190°C (isopropanol).

Step 3: 4(7)-hydroxy-1H-benzimidazole-2-carboxylic acid butylamide (84). **84** was prepared from **82** according to the procedure described above for **83**. mp 268°C; ¹H NMR (500 MHz, DMSO-*d*₆, 50 °C) δ 13.00 (vbrs, 1 H), 9.90 (vbrs, 1 H), 8.72 (brs, 1 H), 7.17-6.85 (m, 2 H), 6.71-6.53 (m, 1 H), 3.37-3.26 (m, 2 H), 1.63-1.47 (m, 2 H), 1.41-1.24 (m, 2 H), 0.91 (t, *J*=7.2 Hz, 3 H) ppm.

Step 4: 4(7)-hydroxy-1H-benzimidazole-2-carboxylic acid (86). **86** was prepared from **84** according to the procedure described above for **85**. mp 148-153°C (diethyl ether); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 9.53 (s, 1 H), 7.35 (t, *J*=8.0 Hz, 1 H), 7.15 (d, *J*=8.0 Hz, 1 H), 6.95 (d, *J*=8.0 Hz, 1 H) ppm.

Step 5: (4-Benzyl-piperidin-1-yl)-[4(7)-hydroxy-1H-benzimidazol-2-yl]-methanone (61a). **61a** was prepared from **86** and 4-benzylpiperidine according to the procedure described above for **56**. mp 148-153°C (diethylether); ¹H NMR (300 MHz, DMSO-*d*₆, 30 °C) δ 12.84 (s, 1

H), 9.79 (s, 1 H), 7.34-7.24 (m, 2 H), 7.23-7.14 (m, 3 H), 7.06 (t, $J=7.8$ Hz, 1 H), 6.93 (dd, $J=7.8$, 1.0 Hz, 1 H), 6.59 (dd, $J=7.8$, 1.0 Hz, 1 H), 5.63-5.43 (m, 1 H), 4.62-4.43 (m, 1 H), 3.26-3.10 (m, 1 H), 2.87-2.71 (m, 1 H), 2.56 (d, $J=7.0$ Hz, 2 H), 1.98-1.78 (m, 1 H), 1.78-1.57 (m, 2 H), 1.35-1.08 (m, 2 H) ppm.

[5(6)-Amino-1H-benzimidazol-2-yl]- (4-benzyl-piperidin-1-yl)-methanone (62). Step 1: (5(6)-Nitro-1H-benzimidazol-2-yl-(4-Benzyl-piperidin-1-yl)-methanone (76). **76** was prepared from 5(6)-nitro-1H-benzimidazol-2-carboxylic acid (**73**) and 4-benzylpiperidine according to the procedure described above for **56**. mp 263°C.

Step 2: [5(6)-Amino-1H-benzimidazol-2-yl]- (4-benzyl-piperidin-1-yl)-methanone (62). A mixture of **76** (1.27 g, 3.48 mmol) and Pd/C (0.3 g, 10 %) catalyst in methanol (30 ml) was hydrogenated for 3 h. The catalyst was filtered off, and the filtrate was concentrated. The residue was purified by column gel chromatography (4:1 toluene/MeOH) and crystallized with diisopropyl ether to give **62** (0.48 g, 41.2 %): mp 74-75°C; $^1\text{H NMR}$ (500 MHz, DMSO- d_6 , 30 °C) δ 12.38 (s, 1 H), 7.35 (d, $J=8.8$ Hz, 1 H), 7.32-7.24 (m, 2 H), 7.22-7.14 (m, 3 H), 6.63-6.55 (m, 2 H), 5.70-5.60 (m, 1 H), 5.11 (s, 2 H), 4.55-4.44 (m, 1 H), 3.20-3.07 (m, 1 H), 2.80-2.68 (m, 1 H), 2.54 (d, $J=7.0$ Hz, 2 H), 1.92-1.78 (m, 1 H), 1.74-1.62 (m, 2 H), 1.30-1.08 (m, 2 H) ppm.

N-[2-(4-Benzyl-piperidin-1-carbonyl)-3H-benzimidazol-5(6)-yl]-methanesulfonamide (63). To a stirred solution of **62** (0.3 g, 0.9 mmol) and pyridine (0.1 ml, 1.2 mmol) in dichloromethane (10 ml) a solution of methanesulfonyl chloride (0.07 ml, 0.9 mmol) in dichloromethane (5 ml) was added dropwise below 10°C, and the mixture was stirred at room temperature for 5 h. The reaction mixture was poured into water (30 ml) and the precipitated crystals were filtered off to give **63** (0.2 g, 54 %): mp 222 °C; $^1\text{H NMR}$ (300 MHz, DMSO- d_6 , 30 °C) δ 13.00 (vbrs, 1 H), 9.64 (s, 1 H), 7.61 (d, $J=8.0$ Hz, 1 H), 7.53-7.44 (m, 1 H), 7.34-7.24 (m, 2 H), 7.24-7.11 (m, 4 H), 5.52-5.28 (m, 1 H), 4.62-4.41 (m, 1 H), 3.25-3.09 (m, 1 H), 2.94 (s, 3 H), 2.87-2.72 (m, 1 H), 2.55 (d, $J=7.0$ Hz, 2 H), 1.98-1.78 (m, 1 H), 1.78-1.60 (m, 2 H), 1.35-1.06 (m, 2 H) ppm.

The methods of the chromatographic purity

System A.

Instrument: Agilent 1100

Column: SymmetryShield RP18
3.9 mm * 150 mm, 5 µm (Waters)

Mobile Phase A. 0.1% (v/v) trifluoroacetic acid in 5% (v/v) acetonitrile

Mobile Phase B. 0.1% (v/v) trifluoroacetic acid in 95% (v/v) acetonitrile

Gradient:	Time (min)	Profile %B
	0	0
	35	100
	40	100
	41	0
	Post time: 10 min	0

Flow rate: 1.0 ml/min

Detection: UV at 220 nm (λ_1) and 280 nm or 300 nm (λ_2)

Temperature: 20 °C

Injection: 20 µl

Test solution: 0.20 mg per 1.0 ml

Solvent: 0.1% (v/v) trifluoroacetic acid in 80% (v/v) acetonitrile

System B.

Instrument: Spectra SYSTEM (Thermo Separation Products)

Column: NUCLEODUR C18 Gravity
4.5 mm * 250 mm, 5 µm (Macherey-Nagel)

Mobile Phase A. 10 mM ammonium acetate (pH = 6,88) : acetonitrile = 95 : 5

Mobile Phase B. 10 mM ammonium acetate (pH = 6,88) : acetonitrile = 5 : 95

Gradient:	Time (min)	Profile %B
	0	0
	30	100
	35	100
	36	0
	Post time: 10 min	0

Flow rate: 1.0 ml/min

Detection: UV at 220 nm (λ_1) and 280 nm or 300 nm (λ_2)

Temperature: 24 °C

Injection: 20 µl

Test solution: 0.20 mg per 1.0 ml

Solvent: 10 mM ammonium acetate (pH = 6,88) : acetonitrile = 20 : 80

Table 1. HPLC analysis of the final compounds

Cmpd	t_R [min]	Purity (area %) - System A		t_R [min]	Purity (area %) - System B	
		λ_1	λ_2		λ_1	λ_2
6a	20,87	99,4	99,3	21,60	98,0	97,7
6b	20,50	98,8	99,0	20,76	95,7	96,5
6c	19,40	99,1	99,3	19,88	97,2	97,5
6d	18,60	98,7	98,9	29,10	97,9	98,5
6e	19,46	96,8	96,5	20,03	97,0	96,8
6f	22,26	95,5	95,8	22,73	96,2	95,6
6g	19,04	97,1	98,6	19,42	97,0	98,6
6h	18,60	99,7	99,7	19,36	98,4	98,4
6i	20,26	97,8	97,5	20,64	96,8	96,1
6j	17,40	97,5	97,9	17,86	96,2	96,5
6k	15,33	95,2	95,9	15,87	95,1	95,0
6l	9,96	98,4	99,3	18,27	99,9	99,8
6m	21,12	96,5	97,6	21,63	95,9	97,4
6n	22,35	96,9	98,6	22,94	96,1	97,0
6o	21,20	96,1	96,1	21,61	95,9	95,8
6p	21,08	99,7	99,6	21,55	98,7	98,1
7a	20,05	98,2	97,7	20,49	98,5	98,0
8a	20,79	97,7	97,4*	20,74	98,9	97,7*
9a	22,49	96,6	96,2*	22,89	97,2	96,7*
10	17,83	97,4	97	18,48	95,1	95,0
11	18,59	97,7	97,5*	13,39	98,4	98,6*
12a	13,32	97,4	96,4	20,57	96,6	96,7
13a	13,42	97,2	97,9	19,99	98,2	98,5
14a	14,22	98,8	98,3	21,22	99,1	98,7
15a	21,37	99,2	99,3	26,61	97,7	98,4
16a	20,24	95,1	97,0	20,29	96,1	95,8
17a	20,00	96,9	96,1	20,34	96,1	95,0
18a	20,76	96,9	97,1	21,36	97,0	96,2
19	20,04	97,4	96,9	20,14	99,1	98,3
20	18,46	96,8	96,1	19,77	99,2	98,5
21	18,87	96,5	96,2	20,01	96,2	96,2
22	13,88	97,8	98,0	18,18	99,5	99,4
23	8,35	97,9	98,6	19,94	96,1	97,0
24	13,31	99,2	99,1	21,73	99,1	98,8
25	22,77	97,5	98,9	22,91	98,6	98,5
55	21,34	96,5	96,9	22,11	95,4	95,9
56	21,57	96,9	97,0	21,84	98,3	98,1
57	23,84	95,1	96,1	23,57	96,6	97,3
58	22,39	98,4	98,2*	22,61	98,9	98,4*
59	21,37	97,5	97,0*	21,91	98,3	97,9*
60a	14,86	95,1	95,8	19,15	96,1	98,9
60m	15,38	96,1	97,1	19,33	98,0	98,6
60q	16,24	98,5	98,5	20,68	98,7	98,6

60r	14,72	96,3	96,2	18,72	95,7	96,1
60s	15,12	95,0	95,8	18,95	95,2	95,6
60t	16,08	99,3	99,3	19,58	98,6	98,7
60u	14,33	95,2	95,5	17,72	96,1	95,5
61a	16,53	96,9	97,1*	19,84	98,9	98,7*
62	12,36	97,1	98,0*	18,71	98,7	97,1*
63	17,34	97,7	97,7	19,27	99,2	98,8
64	17,31	98,6	98,9	19,05	99,6	99,6
65	19,16	97,7	97,5*	19,18	97,9	97,3*

*: $\lambda_2 = 280$ nm, in the other case 300 nm

Table 2. HRMS analysis of the final compounds

Cmpd	Formula	Calculated mass	Found mass	(ppm)
6a	C ₂₁ H ₂₂ N ₂ O ₂	334,1676	334,1679	1,0
6b	C ₂₂ H ₂₄ N ₂ O ₃	364,1781	364,1780	-0,4
6c	C ₂₂ H ₂₄ N ₂ O ₃	364,1781	364,1782	0,0
6d	C ₂₂ H ₂₄ N ₂ O ₃	364,1781	364,1778	-0,9
6e	C ₂₀ H ₂₀ N ₂ O ₂	320,1519	320,1514	-1,7
6f	C ₂₂ H ₂₄ N ₂ O ₂	348,1832	348,1825	-2,2
6g	C ₂₀ H ₂₀ N ₂ O ₃	336,1468	336,1473	1,4
6h	C ₂₁ H ₂₂ N ₂ O ₃	350,1625	350,1622	-0,8
6i	C ₂₁ H ₂₂ N ₂ O ₃	350,1625	350,1622	-0,8
6j	C ₂₁ H ₂₀ N ₂ O ₃	348,1468	348,1458	-2,9
6k	C ₂₁ H ₂₂ N ₂ O ₃	350,1625	350,1627	0,6
6l	C ₂₀ H ₂₁ N ₃ O ₂	335,1628	335,1630	0,4
6m	C ₂₁ H ₂₁ N ₂ O ₂ F	352,1582	352,1575	-1,8
6n	C ₂₂ H ₂₄ N ₂ O ₂	348,1832	348,1828	-1,3
6o	C ₂₂ H ₂₄ N ₂ O ₃	364,1781	364,1777	-1,2
6p	C ₂₁ H ₂₁ N ₂ O ₂ F	352,1582	352,1581	-0,3
7	C ₂₁ H ₂₂ N ₂ O ₂	334,1676	334,1675	-0,3
8	C ₂₁ H ₂₂ N ₂ O ₂	334,1676	334,1678	0,8
9	C ₂₁ H ₂₂ N ₂ O ₂	334,1676	334,1676	-0,1
10	C ₂₁ H ₂₂ N ₂ O ₃	350,1625	350,1621	-1,0
11	C ₂₁ H ₂₂ N ₂ O ₃	350,1625	350,1623	-0,6
12a	C ₂₁ H ₂₃ N ₃ O	333,1836	333,1835	-0,2
13a	C ₂₁ H ₂₃ N ₃ O	333,1836	333,1841	1,7
14a	C ₂₁ H ₂₃ N ₃ O	333,1836	333,1834	-0,6
15a	C ₂₈ H ₂₉ N ₃ O	423,2305	423,2294	-2,6
16a	C ₂₂ H ₂₅ N ₃ O ₃ S	411,1611	411,1610	-0,3
17a	C ₂₂ H ₂₅ N ₃ O ₃ S	411,1611	411,1609	-0,5
18a	C ₂₂ H ₂₅ N ₃ O ₃ S	411,1611	411,1610	-0,2
19	C ₂₂ H ₂₁ N ₃ O ₃	375,1577	375,1572	-1,4
20	C ₂₂ H ₂₂ N ₄ O	358,1788	358,1784	-1,3
21	C ₂₂ H ₂₂ N ₄ O	358,1788	358,1787	-0,4
22	C ₂₂ H ₂₂ N ₄ O	358,1788	358,1782	-1,7
23	C ₂₁ H ₂₃ N ₃ O	333,1836	333,1833	-0,9
24	C ₂₁ H ₂₄ N ₂ O	320,1883	320,1878	-1,7
25	C ₂₀ H ₂₂ N ₂ O ₃ S	370,1346	370,1339	-1,7
55	C ₂₂ H ₂₄ N ₂ O ₂	348,1832	348,1835	0,9
56	C ₂₁ H ₂₁ NO ₃	335,1516	335,1517	0,5
57	C ₂₀ H ₂₀ N ₂ O ₂ S	352,1240	352,1243	1,0
58	C ₂₁ H ₂₁ NO ₂ S	351,1288	351,1285	-0,8
59	C ₂₁ H ₂₁ NO ₃	335,1516	335,1516	0,1
60a	C ₂₀ H ₂₁ N ₃ O ₂	335,1628	335,1622	-1,9
60m	C ₂₀ H ₂₀ N ₃ O ₂ F	353,1534	353,1536	0,4
60 q	C ₂₁ H ₂₃ N ₃ O ₂	349,1785	349,1784	-0,1
60 r	C ₂₁ H ₂₃ N ₃ O ₃	365,1734	365,1735	0,3
60 s	C ₂₀ H ₂₁ N ₃ O ₃	351,1577	351,1579	0,4
60t	C ₁₉ H ₁₈ N ₃ O ₃ Cl	371,1031	371,1031	0,1

60u	$C_{19}H_{18}N_3O_3F$	355,1327	355,1327	0,1
61a	$C_{20}H_{21}N_3O_2$	335,1628	335,1633	1,5
62	$C_{20}H_{22}N_4O$	334,1788	334,1789	0,1
63	$C_{21}H_{24}N_4O_3S$	412,1564	412,1559	-1,2
64	$C_{21}H_{20}N_4O_3$	376,1530	376,1540	2,5
65	$C_{21}H_{20}N_4O_3$	376,1530	376,1532	0,6

Table 3. Experimental and calculated biological activities (expressed as $-\log IC_{50}$) of compounds used in the CoMSIA study.

	exp pIC_{50}	calc pIC_{50}	deviation
training set			
TR1	6,41	6,37	-0,04
TR2	7,31	7,22	-0,09
TR3	7,75	7,53	-0,22
TR4	6,45	6,52	0,07
TR5	8,46	8,34	-0,12
TR6	5,97	5,91	-0,06
TR7	7,76	7,83	0,07
TR8	6,60	6,85	0,25
TR9	8,03	8,15	0,12
TR10	7,33	7,21	-0,12
TR11	7,35	7,51	0,16
TR12	7,92	7,99	0,07
TR13	8,04	8,00	-0,04
TR14	7,25	7,22	-0,03
TR15	7,51	7,43	-0,08
TR16	8,36	8,42	0,05
TR17	7,93	7,68	-0,25
TR18	8,28	8,12	-0,16
TR19	6,13	6,14	0,01
TR20	7,66	7,74	0,08
TR21	8,36	8,32	-0,04
TR22	7,05	7,16	0,11
TR23	7,62	7,71	0,09
TR24	7,76	7,86	0,10
TR25	8,05	8,06	0,01
TR26	7,26	7,19	-0,07
TR27	6,42	6,53	0,11
TR28	6,21	6,20	-0,01
TR29	6,77	6,82	0,05
TR30	8,02	8,18	0,16
TR31	7,22	7,21	-0,01
TR32	7,93	7,74	-0,19
TR33	8,16	8,32	0,16
TR34	8,05	8,07	0,01
TR35	7,57	7,53	-0,04
TR36	8,23	8,30	0,07
TR37	7,34	7,41	0,07
TR38	7,99	7,94	-0,05
TR39	8,28	8,38	0,10
TR40	7,80	7,79	-0,01
TR41	7,92	7,91	-0,01

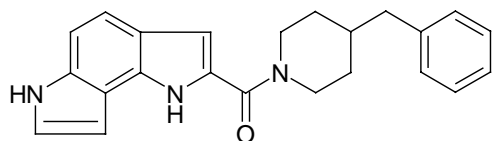
TR42	7,95	7,87	-0,08
TR43	8,24	8,24	0,00
TR44	7,73	7,61	-0,12
TR45	5,81	5,81	0,00
TR46	8,10	7,79	-0,31
TR47	7,56	7,75	0,19

test set

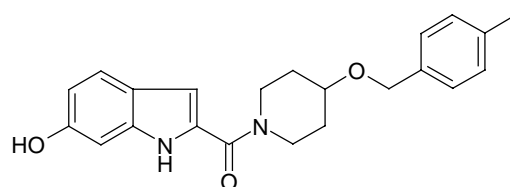
T1	7,64	6,93	-0,71
T2	6,76	6,07	-0,69
T3	7,06	6,58	-0,48
T4	6,38	5,95	-0,44
T5	7,98	7,74	-0,25
T6	6,19	6,09	-0,10
T7	7,51	7,46	-0,05
T8	8,29	8,29	0,00
T9	8,14	8,34	0,20
T10	7,81	8,03	0,22
T11	6,54	6,91	0,37
T12	7,23	7,78	0,55

Structures of molecules in the CoMSIA study

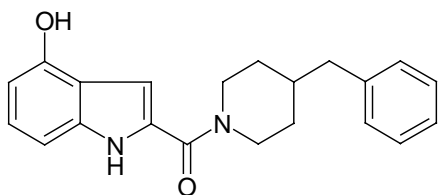
Training set



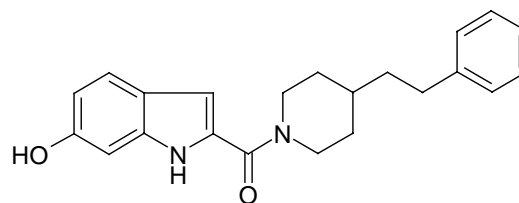
TR1



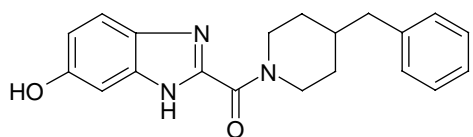
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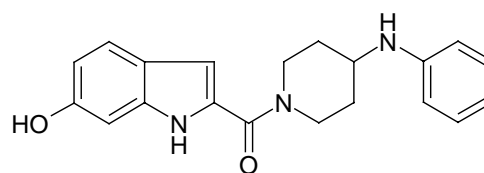
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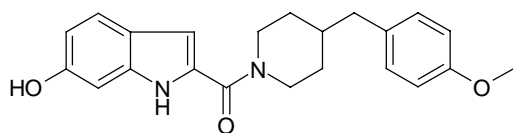
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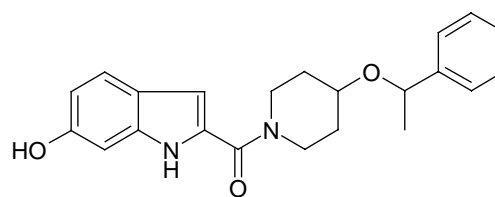
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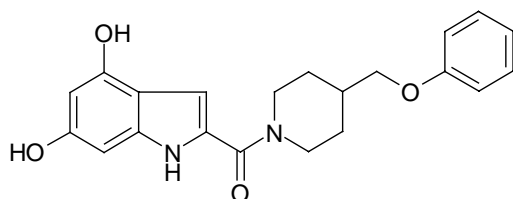
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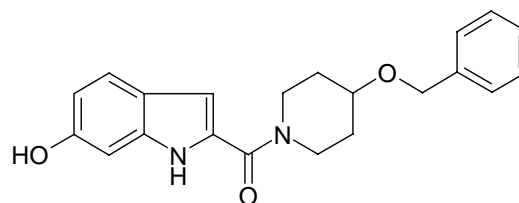
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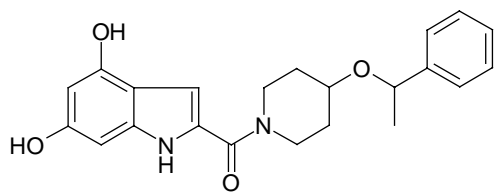
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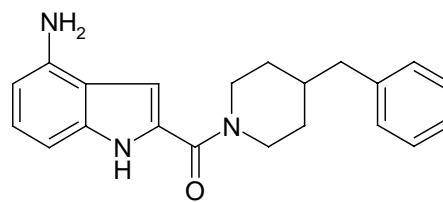
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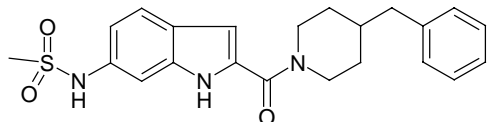
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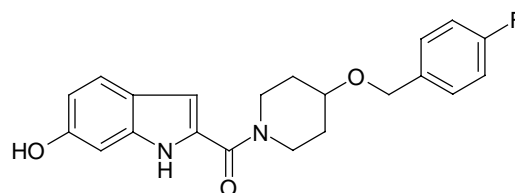
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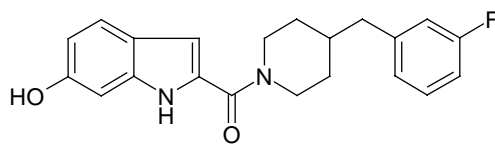
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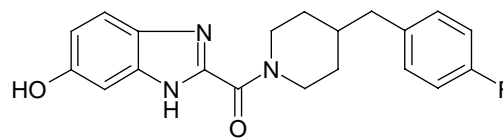
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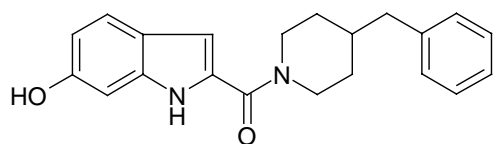
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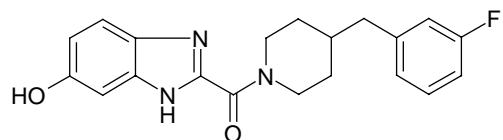
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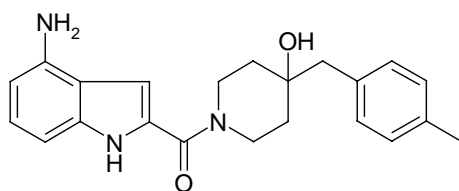
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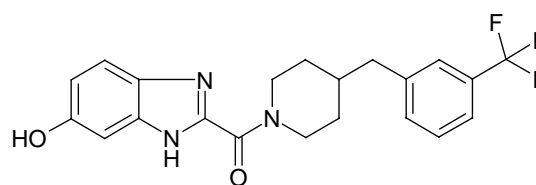
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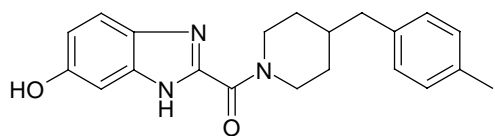
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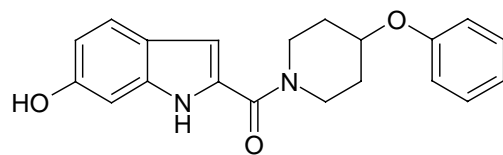
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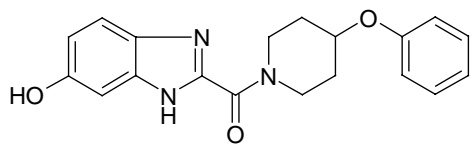
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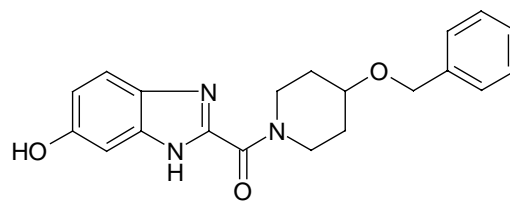
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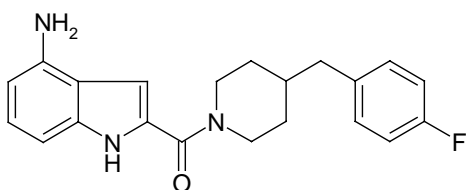
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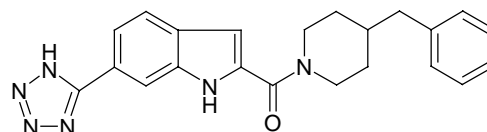
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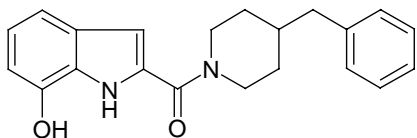
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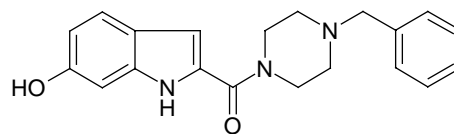
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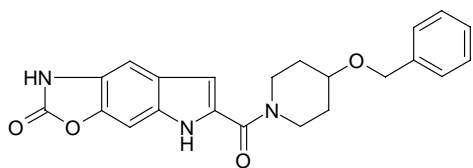
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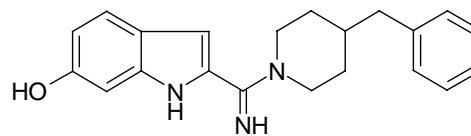
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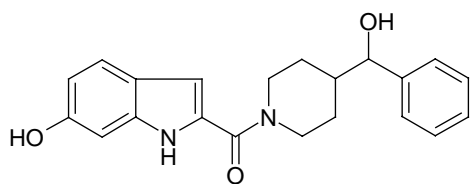
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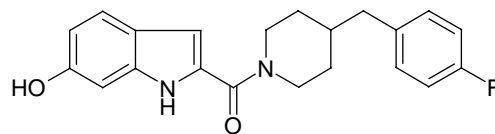
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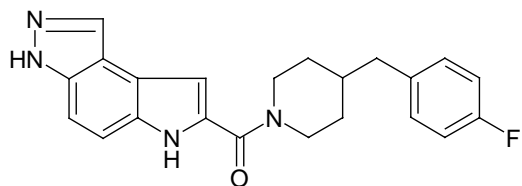
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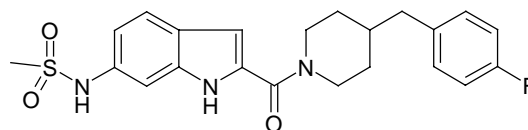
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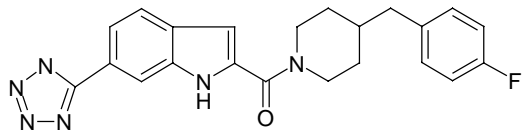
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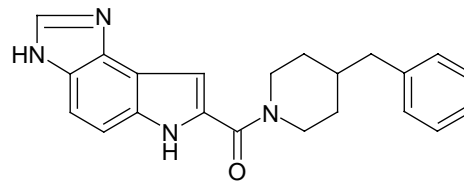
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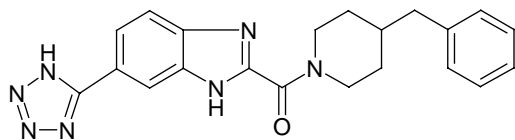
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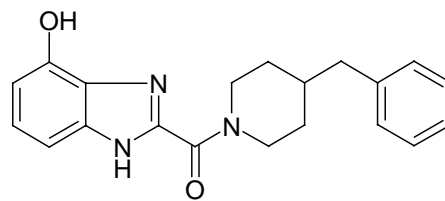
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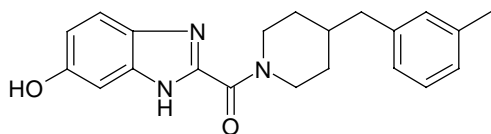
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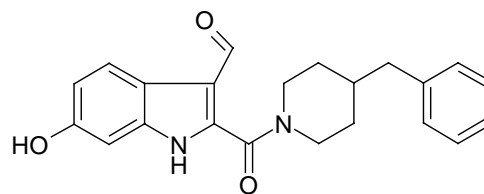
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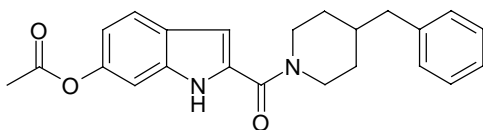
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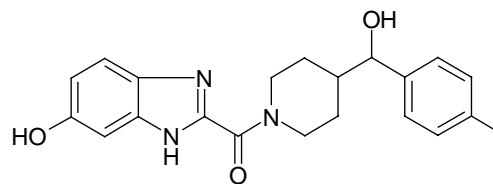
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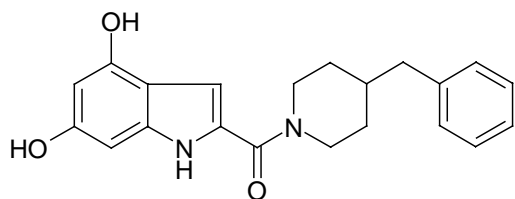
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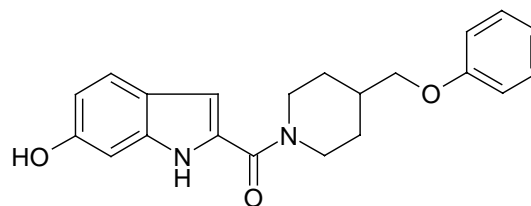
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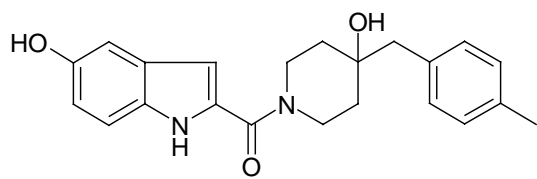
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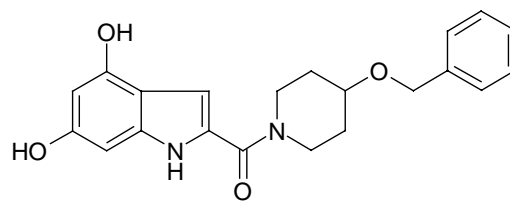
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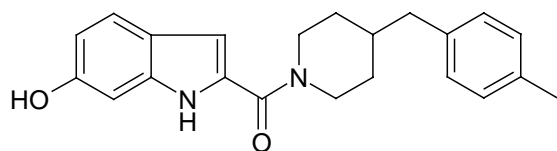
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TR45

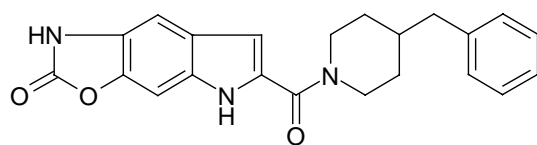


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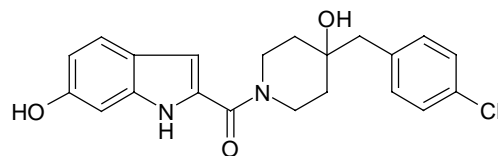


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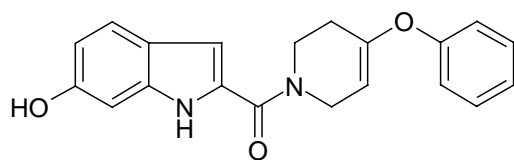
Test set



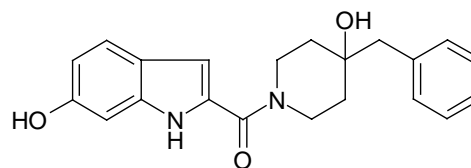
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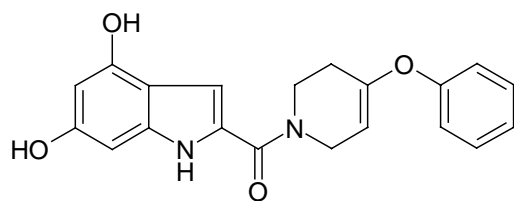
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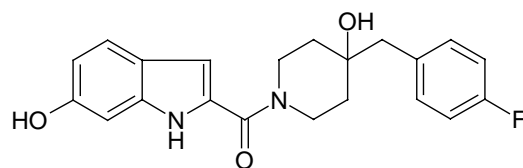
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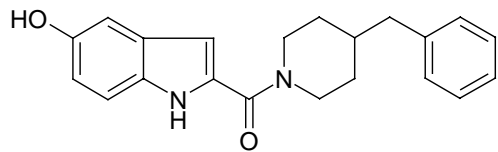
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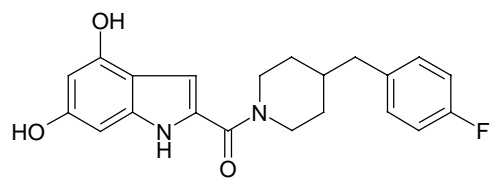
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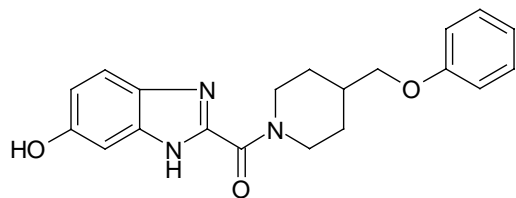
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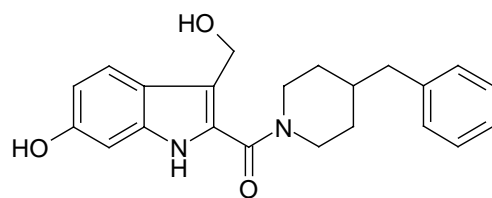
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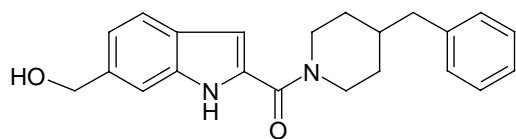
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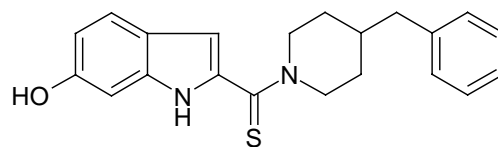
T9



T10



T11



T12