Supplemental Data

4-Aminophthalazin-1(2*H*)-one Derivatives as Melanin Concentrating Hormone Receptor 1 (MCH-R1) Antagonists

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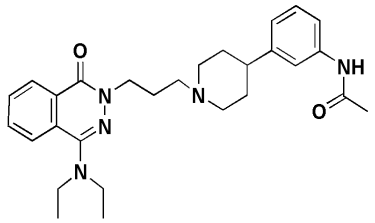
Synthesis of compounds (3)

2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-(diethylamino)phthalazin-1(2*H*)-one (3a).

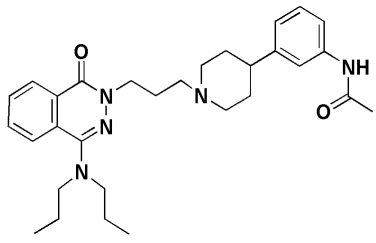


50 mg (yield 55%) of the title compound was obtained by the same procedure for the compound **3j**, using 56 mg (0.19 mmol) of 2-(3-chloropropyl)-4-(diethylamino)phthalazin-1(2*H*)-one.

R_f = 0.56 (10% MeOH in MC).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42-8.44 (m, 1H), 7.91-7.94 (m, 1H), 7.69-7.79 (m, 2H), 7.31-7.49 (m, 3H), 7.23 (d, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 4.23 (t, *J* = 7.1 Hz, 2H), 3.21-3.28 (m, 4H), 3.10 (d, *J* = 11.3 Hz, 2H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.39-2.50 (m, 1H), 2.18 (s, 3H), 2.03-2.14 (m, 4H), 1.80-1.82 (m, 4H), 1.15 (t, J = 6.8 Hz, 3H).

2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-(dipropylamino)phthalazin-1(2*H*)-one (3b).

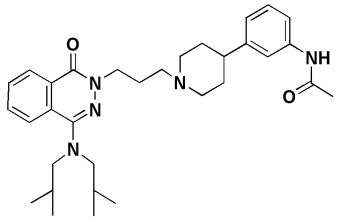


41 mg (yield 47%) of the title compound was obtained by the same procedure for the compound **3j**, using 55 mg (0.17 mmol) of 2-(3-chloropropyl)-4-(dipropylamino)phthalazin-1(2*H*)-one.

R_f = 0.48 (10% MeOH in MC)*2.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41-8.44 (m, 1H), 7.93-7.96 (m, 1H), 7.69-7.79 (m, 2H), 7.39-7.53 (m, 2H), 7.31 (s, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 4.22 (t, *J* = 7.0 Hz, 2H), 3.07-3.16 (m, 6H), 2.53 (t, *J* = 7.0 Hz, 2H), 2.39-2.46 (m, 1H), 2.17 (s, 3H), 2.05-2.14 (m, 4H), 1.79-1.82 (m, 4H), 1.53-1.63 (m, 4H), 0.89 (t, *J* = 7.4 Hz, 6H).

2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-(diisobutylamino)phthalazin-1(2*H*)-one (3c).

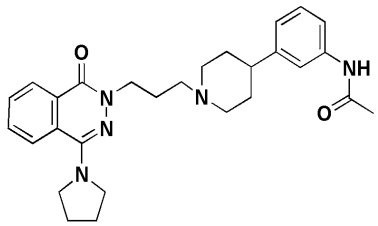


99 mg (yield 65%) of the title compound was obtained by the same procedure for the compound **3j**, using 100 mg (0.29 mmol) of 2-(3-chloropropyl)-4-(diisobutylamino)-phthalazin-1(2*H*)-one.

R_f = 0.35 (10% MeOH in MC).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42-8.44 (m, 1H), 8.02 (d, *J* = 7.2 Hz, 1H), 7.71-7.76 (m, 2H), 7.37-7.40 (m, 2H), 7.32 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 7.2 Hz, 1H), 4.21 (t, *J* = 6.8 Hz, 2H), 3.07 (d, J = 11.4 Hz, 2H), 3.01 (d, *J* = 7.2 Hz, 4H), 2.51 (t, *J* = 6.8 Hz, 2H), 2.41-2.46 (m, 1H), 2.17 (s, 3H), 1.93-2.13 (m, 6H), 1.75-1.81 (m, 4H), 0.91 (d, *J* = 6.8 Hz, 12H).

2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-(pyrrolidin-1-yl)phthalazin-1(2*H*)-one (3d).



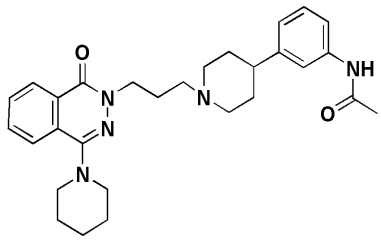
31 mg (yield 38%) of the title compound was obtained by the same procedure for the compound **3j**, using 50 mg (0.17 mmol) of 2-(3-chloropropyl)-4-(pyrrolidin-1-yl)phthalazin-

1(2*H*)-one.

R_f = 0.47 (10% MeOH in MC).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43-8.46 (m, 1H), 8.00-8.03 (m, 1H), 7.70-7.79 (m, 2H), 7.54-7.57 (m, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.31 (s, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 7.4 Hz, 1H), 4.21 (t, *J* = 6.6 Hz, 2H), 3.52-3.56 (m, 4H), 3.26 (d, *J* = 10.5 Hz, 2H), 2.73 (t, *J* = 6.6 Hz, 2H), 2.49-2.54 (m, 1H), 2.20-2.29 (m, 4H), 2.18 (s, 3H), 1.94-2.03 (m, 6H), 1.82-1.86 (m, 2H).

2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-(piperidin-1-yl)phthalazin-1(2*H*)-one (3e).

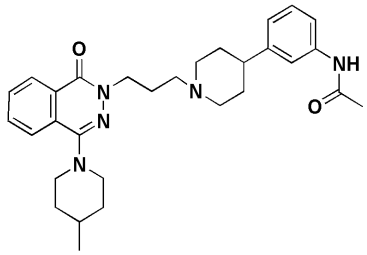


39 mg (yield 45%) of the title compound was obtained by the same procedure for the compound **3j**, using 54 mg (0.18 mmol) of 2-(3-chloropropyl)-4-(piperidin-1-yl)phthalazin-1(2*H*)-one.

R_f = 0.47 (10% MeOH in MC).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40-8.43 (m, 1H), 7.86-7.89 (m, 1H), 7.69-7.82 (m, 3H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.32 (s, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 4.23 (t, *J* = 6.8 Hz, 2H), 3.20 (t, *J* = 11.3 Hz, 2H), 3.12-3.15 (m, 4H), 2.67 (t, *J* = 6.8 Hz, 2H), 2.39-2.54 (m, 1H), 2.20-2.27 (m, 2H), 2.18 (s, 3H), 1.87-2.00 (m, 2H), 1.75-1.83 (m, 6H), 1.61-1.71 (m, 2H).

2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-(4-methylpiperidin-1-yl)phthalazin-1(2*H*)-one (3f).

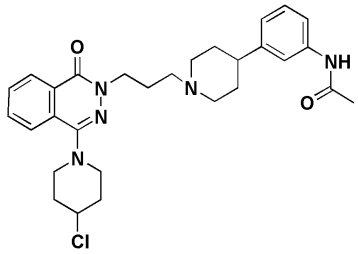


53 mg (yield 57%) of the title compound was obtained by the same procedure for the compound **3j**, using 60 mg (0.19 mmol) of 2-(3-chloropropyl)-4-(4-methylpiperidin-1-yl)-phthalazin-1(2*H*)-one.

R_f = 0.22 (10% MeOH in MC).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41-8.43 (m, 1H), 7.85-7.88 (m, 1H), 7.68-7.78 (m, 2H), 7.30-7.40 (m, 3H), 7.22 (d, *J* = 7.9 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 4.21 (t, *J* = 7.1 Hz, 2H), 3.50 (d, *J* = 12.6 Hz, 2H), 3.07 (d, *J* = 11.1 Hz, 2H), 2.79 (t, *J* = 12.0 Hz, 2H), 2.51 (t, *J* = 7.1 Hz, 2H), 2.40-2.46 (m, 1H), 2.17 (s, 3H), 1.96-2.11 (m, 4H), 1.72-1.80 (m, 4H), 1.54-1.64 (m, 1H), 1.41-1.53 (m, 2H), 1.04 (d, *J* = 6.2 Hz, 3H).

2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-(4-chloropiperidin-1-yl)phthalazin-1(2*H*)-one (3g).

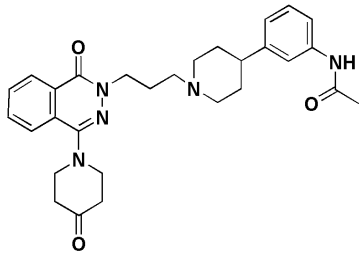


43 mg (yield 38%) of the title compound was obtained by the same procedure for the compound **3j**, using 74 mg (0.22 mmol) of 2-(3-chloropropyl)-4-(4-chloropiperidin-1-yl)-phthalazin-1(2*H*)-one.

R_f = 0.30 (10% MeOH in MC).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42-8.45 (m, 1H), 7.71-7.85 (m, 3H), 7.37-7.39 (m, 2H), 7.31 (s, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 1H), 4.27-4.29 (m, 1H), 4.22 (t, *J* = 7.0 Hz, 2H), 3.45-3.51 (m, 2H), 3.02-3.10 (m, 4H), 2.54 (t, *J* = 7.0 Hz, 2H), 2.41-2.49 (m, 1H), 2.26-2.34 (m, 2H), 2.17 (s, 3H), 2.03-2.16 (m, 6H), 1.79-1.81 (m, 4H).

2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-(4-oxopiperidin-1-yl)phthalazin-1(2*H*)-one (3h).

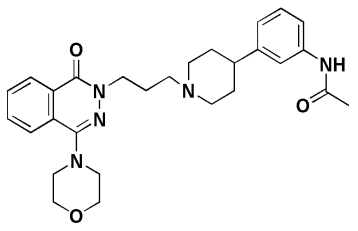


35 mg (yield 42%) of the title compound was obtained by the same procedure for the compound **3j**, using 53 mg (0.17 mmol) of 2-(3-chloropropyl)-4-(4-oxopiperidin-1-yl)-phthalazin-1(2*H*)-one.

R_f = 0.36 (10% MeOH in MC)*2.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46-8.48 (m, 1H), 7.91-7.93 (m, 1H), 7.75-7.84 (m, 2H), 7.36-7.41 (m, 2H), 7.32 (s, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 4.23 (t, *J* = 7.2 Hz, 2H), 3.56 (t, J = 6.0 Hz, 4H), 3.08 (d, J = 11.5 Hz, 2H), 2.69 (t, *J* = 6.0 Hz, 4H), 2.52 (t, *J* = 7.2 Hz, 2H), 2.43-2.48 (m, 1H), 2.17 (s, 3H), 2.00-2.13 (m, 4H), 1.71-1.82 (m, 4H).

2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-morpholinophthalazin-1(2*H*)-one (3i).

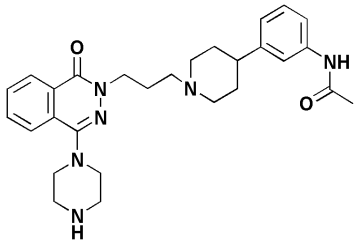


56 mg (yield 61%) of the title compound was obtained by the same procedure for the compound **3j**, using 58 mg (0.19 mmol) of 2-(3-chloropropyl)-4-morpholinophthalazin-1(2*H*)-one.

R_f = 0.28 (10% MeOH in MC).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43-8.46 (m, 1H), 7.88-7.91 (m, 1H), 7.66-7.82 (m, 3H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.32 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 4.24 (t, *J* = 6.8 Hz, 2H), 3.93 (t, *J* = 4.4 Hz, 2H), 3.21 (d, *J* = 4.4 Hz, 2H), 3.15-3.20 (m, 2H), 2.63 (t, *J* = 6.8 Hz, 2H), 2.46-2.53 (m, 1H), 2.18 (s, 3H), 2.15-2.22 (m, 4H), 1.79-1.86 (m, 4H).

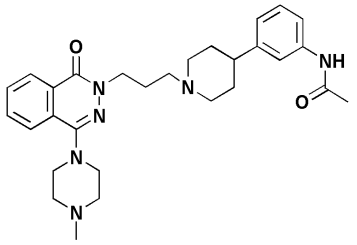
2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-(piperazin-1-yl)phthalazin-1(2*H*)-one (3k).



30 mg (yield 28%) of 2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-[4-(*t*-butoxycarbonyl)piperazin-1-yl]-phthalazin-1(2*H*)-one was obtained by the same procedure for the compound **3j**, using 75 mg (0.019 mmol) of 2-(3-chloropropyl)-4-[4-(*t*-butoxycarbonyl)piperazin-1-yl]phthalazin-1(2*H*)-one. A solution of 2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-[4-(*t*-butoxycarbonyl)piperazin-1-yl]phthalazin-1(2*H*)-one (30 mg, 0.051 mmol) in HCl solution (1.25 M in MeOH, 3 mL) was stirred at room temperature for 6 h. The mixture was evaporated under reduced pressure and dried *in vacuo* to give **3k** (26 mg, 98%).

^{1}H NMR (300 MHz, MeOH-d_4) δ 8.41-8.43 (m, 1H), 8.05-8.08 (m, 1H), 7.90-7.98 (m, 2H), 7.66 (s, 1H), 7.25-7.28 (m, 2H), 7.00-7.02 (m, 1H), 4.28-4.35 (m, 2H), 3.64-3.74 (m, 2H), 3.46-3.59 (m, 10H), 3.06-3.23 (m, 2H), 2.84-2.93 (m, 1H), 2.32-2.40 (m, 2H), 2.12 (s, 3H), 1.99-2.06 (m, 4H).

2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-(4-methylpiperazin-1-yl)phthalazin-1(2*H*)-one (3l).

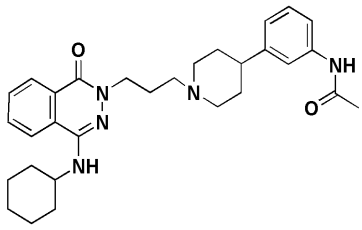


26 mg (yield 29%) of the title compound was obtained by the same procedure for the compound **3j**, using 58 mg (0.18 mmol) of 2-(3-chloropropyl)-4-(4-methylpiperazin-1-yl)-phthalazin-1(2*H*)-one.

R_f = 0.58 (10% MeOH in MC).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43-8.45 (m, 1H), 7.86-7.89 (m, 1H), 7.70-7.79 (m, 2H), 7.48-7.56 (m, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.30 (s, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 4.22 (t, *J* = 7.0 Hz, 2H), 3.29 (m, 4H), 3.03 (d, *J* = 10.8 Hz, 2H), 2.66 (m, 4H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.43-2.44 (m, 1H), 2.40 (s, 3H), 2.18 (s, 3H), 1.96-2.11 (m, 4H), 1.67-1.79 (m, 4H).

2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-(cyclohexylamino)phthalazin-1(2*H*)-one (3m).

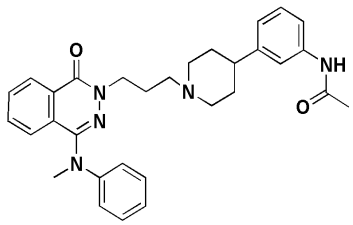


21 mg (yield 24%) of the title compound was obtained by the same procedure for the compound **3j**, using 56 mg (0.18 mmol) of 2-(3-chloropropyl)-4-(cyclohexylamino)phthalazin-1(2*H*)-one.

R_f = 0.23 (10% MeOH in MC).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45-8.47 (m, 1H), 7.72-7.77 (m, 2H), 7.60-7.62 (m, 2H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.30 (s, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 4.32 (d, *J* = 6.2 Hz, 1H), 4.21 (t, *J* = 6.5 Hz, 2H), 3.77-3.81 (m, 1H), 3.26 (d, *J* = 10.6 Hz, 2H), 2.73 (t, *J* = 6.5 Hz, 2H), 2.48-2.58 (m, 1H), 2.22-2.36 (m, 4H), 2.19 (s, 3H), 1.95-2.14 (m, 4H), 1.66-1.89 (m, 4H), 1.20-1.51 (m, 6H).

2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-[methyl(phenyl)amino]phthalazin-1(2*H*)-one (3n).

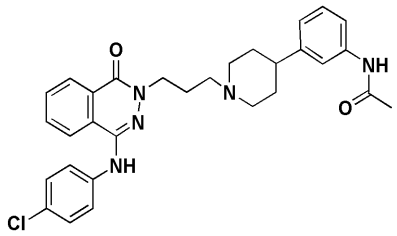


42 mg (yield 40%) of the title compound was obtained by the same procedure for the compound **3j**, using 67 mg (0.20 mmol) of 2-(3-chloropropyl)-4-[methyl(phenyl)amino]-phthalazin-1(2*H*)-one.

R_f = 0.36 (10% MeOH in MC)*2.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 7.6 Hz, 1H), 7.64-7.69 (m, 1H), 7.52-7.57 (m, 1H), 7.39-7.46 (m, 3H), 7.31 (s, 1H), 7.20-7.25 (m, 3H), 6.87-7.00 (m, 4H), 4.30 (t, *J* = 7.0 Hz, 2H), 3.42 (s, 3H), 3.12 (t, *J* = 11.0 Hz, 2H), 2.59 (t, *J* = 7.0 Hz, 2H), 2.46-2.52 (m, 1H), 2.18 (s, 3H), 2.00-2.15 (m, 4H), 1.81-1.87 (m, 4H).

2-{3-[4-(3-Acetamidophenyl)piperidin-1-yl]propyl}-4-[(chlorophenyl)amino]phthalazin-1(2*H*)-one (3o).



24 mg (yield 29%) of the title compound was obtained by the same procedure for the compound **3j**, using 55 mg (0.16 mmol) of 2-(3-chloropropyl)-4-[(4-chlorophenyl)amino]-phthalazin-1(2*H*)-one.

R_f = 0.29(10% MeOH in MC).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50-8.53 (m, 1H), 7.78-7.85 (m, 3H), 7.44-7.47 (m, 3H), 7.26-7.36 (m, 4H), 7.21 (d, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 7.3 Hz, 1H), 6.78 (s, 1H), 4.26 (t, *J* = 6.9 Hz, 2H), 3.01 (d, *J* = 11.3 Hz, 2H), 2.52 (t, *J* = 6.9 Hz, 2H), 2.38-2.41 (m, 1H), 2.20 (s, 3H), 1.96-2.14 (m, 4H), 1.61-1.74 (m, 4H).