

Supporting Information

Dihydropyridopyrazinones and Dihydropteridinones as Corticotropin-Releasing Factor-1 Receptor Antagonists: Structure Activity Relationships and Computational Modeling

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Experimental Section

Chemistry. All ^1H NMR and ^{13}C NMR spectra were obtained on a Varian Inova spectrometer (operating at 300 MHz) or a Bruker Avance (operating at 400 or 500 MHz), and the signals are reported in ppm relative to TMS. All high-resolution mass spectra (HRMS) were obtained on a VG 70-VSE instrument with NH_3 as the carrier gas for chemical ionization. Compounds were purified using silica gel chromatography (hexanes/ethyl acetate as the elutant) or by reverse phase high-pressure liquid chromatography (HPLC) (0.1% TFA in water–0.1% TFA in acetonitrile, gradient: 20–80% acetonitrile over 30 min). Purity measurements were carried out using reverse phase HPLC using two different eluting systems. Method a: 0.1% TFA in water–0.1% TFA in acetonitrile, gradient (0–100% acetonitrile over 40 min) on an Agilent HP1100 HPLC with a YMC C18 column; Method b: 0.2% phosphoric acid and 10% methanol in water–0.2% phosphoric acid and 10% water in methanol, gradient (0–100% methanol over 28 min) on a Shimadzu LC10 HPLC with a Zorbax SB–C18 column.

Compounds **1–5a–d** were prepared as previously reported.^{1,2}

8-(Butyl-ethylamino)-4-(4-methoxy-2-methylphenyl)-6-methyl-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one (1a). ^1H NMR (300 MHz, CDCl_3) δ 0.88 (t, $J = 7.3$ Hz, 3H), 1.00 (t, $J = 7.3$ Hz, 3H), 1.27 (sextet, $J = 7.3$ Hz, 2H), 1.40 (pentet, $J = 7.3$ Hz, 2H), 2.09 (s, 3H), 2.18 (s, 3H), 2.89 (t, $J = 7.3$ Hz, 2H), 2.96 (q, $J = 7.3$ Hz, 2H), 3.80 (s, 3H), 4.15–4.42 (m, 2H), 6.60 (s, 1H), 6.76 (dd, $J = 7.7$, 2.9 Hz, 1H), 6.79 (dd, $J = 2.9$, 1.1 Hz, 1H), 7.13 (dd, $J = 7.7$, 1.1 Hz, 1H), 7.91 (br s, 1H); ^{13}C NMR (300 MHz, CDCl_3) δ 12.4, 13.9, 18.6, 20.4, 24.3, 29.5, 47.7, 52.3, 54.0, 55.3, 107.6, 112.0, 113.5, 116.2, 127.3, 135.1, 137.5, 144.7, 145.9, 151.3, 157.9, 163.6; HRMS Calcd for ($\text{C}_{22}\text{H}_{30}\text{N}_4\text{O}_2$) [$\text{M} + \text{H}]^+$ 383.2447; found 383.2451; HPLC: (a) 97%; (b) >95%.

N-butyl-N-ethyl-4-(4-methoxy-2-methylphenyl)-6-methyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-8-amine (1b). ^1H NMR (300 MHz, CDCl_3) δ 7.11 (d, $J = 8.6$ Hz, 1H), 6.78 (d, $J = 3.0$ Hz, 1H), 6.74 (dd, $J = 8.6$, 3.0 Hz, 1H), 6.18 (s, 1H), 4.23 (m, 1H), 3.79 (s, 3H), 3.70 (m, 2H), 3.40 (br m, 2H), 2.94 (q, $J = 7.1$ Hz, 2H), 2.88 (t, $J = 7.1$ Hz, 2H), 2.13 (s, 3H), 2.11 (s, 3H), 1.39 (pentet, $J = 7.1$ Hz, 2H), 1.27 (sextet, $J = 7.1$ Hz, 2H), 1.00 (t, $J = 7.1$ Hz, 3H), 0.88 (t, $J = 7.1$ Hz, 3H); HRMS Calcd for ($\text{C}_{22}\text{H}_{32}\text{N}_4\text{O}$) [$\text{M} + \text{H}]^+$ 369.2654; found 369.2668; HPLC: (a) >98%; (b) 98%.

4-(butyl(ethyl)amino)-8-(4-methoxy-2-methylphenyl)-2-methyl-7,8-dihydropteridin-6(5H)-one (1c). ^1H NMR (400 MHz, CDCl_3) δ 7.39 (s, 1H), 7.10 (d, $J = 8.3$ Hz, 1H), 6.79 (m, 2H), 4.38 (m, 1H), 4.18 (m, 1H), 3.81 (s, 3H), 3.16 (m, 4H), 2.27 (s, 3H), 2.12 (s, 3H), 1.47 (pentet, $J = 7.1$ Hz, 2H), 1.30 (sextet, $J = 7.1$ Hz, 2H), 1.09 (t, $J = 7.1$ Hz, 3H), 0.90 (t, $J = 7.3$ Hz, 3H); HRMS Calcd for ($\text{C}_{21}\text{H}_{29}\text{N}_5\text{O}_2$) [$\text{M} + \text{H}]^+$ 384.2400; found 384.2404; HPLC: (a) >98%; (b) >98%.

N-butyl-N-ethyl-8-(4-methoxy-2-methylphenyl)-2-methyl-5,6,7,8-tetrahydropteridin-4-amine (1d). ^1H NMR (500 MHz, CDCl_3) δ 7.09 (d, $J = 8.5$ Hz, 1H), 6.79 (d, $J = 2.8$ Hz, 1H), 6.76 (dd, $J = 8.5$, 2.8 Hz, 1H), 3.79 (m, 4H), 3.65 (m, 2H), 3.43 (m, 2H), 3.13 (m, 4H), 2.22 (s, 3H), 2.13 (s, 3H), 1.45 (pentet, $J = 7.3$ Hz, 2H), 1.30 (sextet, $J = 7.3$ Hz, 2H), 1.06 (t, $J = 7.0$ Hz, 3H), 0.90 (t, $J =$

7.3 Hz, 3 H); HRMS Calcd for ($C_{21}H_{31}N_5O$) [$M + H]^+$ 370.2607; found 370.2599; HPLC: (a) >98%; (b) >98%.

8-(Butyl-ethylamino)-4-(2,6-dimethoxy-pyridin-3-yl)-6-methyl-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one (2a). 1H NMR (300 MHz, CD_3OD) δ 0.93 (t, $J = 7.3$ Hz, 3H), 1.17 (t, $J = 7.3$ Hz, 3H), 1.32 (sextet, $J = 7.3$ Hz, 2H), 1.55 (pentet, $J = 7.3$ Hz, 2H), 2.32 (s, 3H), 3.42 (t, $J = 7.3$ Hz, 2H), 3.48 (q, $J = 7.3$ Hz, 2H), 3.97 (s, 3H), 3.98 (s, 3H), 4.27 (m, 2H), 6.46 (d, $J = 8.4$ Hz, 1H), 6.64 (s 1H), 7.63 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (300 MHz, CD_3OD) δ 13.0, 14.1, 18.8, 21.1, 30.8, 47.0, 48.2, 51.8, 54.5, 54.7, 104.1, 108.5, 111.2, 115.9, 140.9, 144.1, 144.4, 151.3, 159.8, 164.4, 164.6; HRMS Calcd for ($C_{21}H_{29}N_5O_3$) [$M + H]^+$ 400.2349; found 400.2364; HPLC: (a) >98%; (b) >95%.

N-butyl-4-(2,6-dimethoxypyridin-3-yl)-N-ethyl-6-methyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-8-amine (2b). 1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, $J = 8.3$ Hz, 1H), 6.29 (d, $J = 8.3$ Hz, 1H), 6.20 (s, 1H), 4.20 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.68 (m, 2H), 3.38 (m, 2H), 2.94 (q, $J = 7.1$ Hz, 2H), 2.88 (t, $J = 7.1$ Hz, 2H), 2.13 (s, 3H), 1.38 (pentet, $J = 7.1$ Hz, 2H), 1.27 (sextet, $J = 7.1$ Hz, 2H), 0.99 (t, $J = 7.1$ Hz, 3H), 0.87 (t, $J = 7.1$ Hz, 3H); HRMS Calcd for ($C_{21}H_{31}N_5O_2$) [$M + H]^+$ 386.2556; found 386.2563; HPLC: (a) >98%; (b) 98%.

4-(butyl(ethyl)amino)-8-(2,6-dimethoxypyridin-3-yl)-2-methyl-7,8-dihydropteridin-6(5H)-one (2c). 1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, $J = 8.3$ Hz, 1H), 7.37 (s, 1H), 6.34 (d, $J = 8.3$ Hz, 1H), 4.29 (m, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.19 (q, $J = 7.1$ Hz, 2H), 3.13 (t, $J = 7.3$ Hz, 2H), 2.27 (s, 3H), 1.46 (pentet, $J = 7.1$ Hz, 2H), 1.29 (sextet, $J = 7.1$ Hz, 2H), 1.08 (t, $J = 7.1$ Hz, 3H), 0.89 (t, $J = 7.3$ Hz, 3H); HRMS Calcd for ($C_{20}H_{28}N_6O_3$) [$M + H]^+$ 401.2301; found 401.2307; HPLC: (a) >98%; (b) >98%.

N-butyl-8-(2,6-dimethoxypyridin-3-yl)-N-ethyl-2-methyl-5,6,7,8-tetrahydropteridin-4-amine (2d). 1H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, $J = 8.0$ Hz, 1H), 6.32 (d, $J = 8.0$ Hz, 1H), 3.92 (s, 6H), 3.70 (m, 2H), 3.63 (br s, 1H), 3.40 (m, 2H), 3.15 (m, 4H), 2.24 (s, 3H), 1.45 (pentet, $J = 7.3$ Hz, 2H), 1.29 (sextet, $J = 7.3$ Hz, 2H), 1.06 (t, $J = 7.0$ Hz, 3H), 0.89 (t, $J = 7.3$ Hz, 3H); HRMS Calcd for ($C_{20}H_{30}N_6O_2$) [$M + H]^+$ 387.2508; found 387.2520; HPLC: (a) >98%; (b) >98%.

4-(4,5-dimethoxy-2-methylphenyl)-8-((2-methoxyethyl)(propyl)amino)-6-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one (3a). 1H NMR (400, $CDCl_3$) δ 9.53 (s, 1H), 6.75 (s, 1H), 6.73 (s, 1H), 6.28 (s, 1H), 4.25 (m, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 3.54 (m, 2H), 3.51 (s, 3H), 3.05 (m, 4H), 2.20 (s, 3H), 2.05 (s, 3H), 1.47 (q, $J = 7.3$ Hz, 2H), 0.89 (t, $J = 7.3$ Hz, 3H); HRMS Calcd for ($C_{23}H_{32}N_4O_4$) [$M + H]^+$ 429.2502; found 429.2506; HPLC: (a) >98%; (b) >98%.

4-(4,5-dimethoxy-2-methylphenyl)-N-(2-methoxyethyl)-6-methyl-N-propyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazin-8-amine (3b). 1H NMR (400, $CDCl_3$) δ 6.75 (s, 1H), 6.72 (s, 1H), 6.21 (s, 1H), 4.66 (br s, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.68 (m, 2H), 3.41 (m, 4H), 3.34 (s, 3H), 3.06 (m, 2H), 2.91 (t, $J = 7.3$ Hz, 2H), 2.12 (s, 3H), 2.08 (s, 3H), 1.45 (sextet, $J = 7.3$ Hz, 2H), 0.86 (t, $J = 7.3$ Hz, 3H); HRMS Calcd for ($C_{23}H_{34}N_4O_3$) [$M + H]^+$ 415.2709; found 415.2717; HPLC: (a) 98%; (b) 98%.

8-(4,5-dimethoxy-2-methylphenyl)-4-((2-methoxyethyl)(propyl)amino)-2-methyl-7,8-dihydropteridin-6(5H)-one (3c). 1H NMR (400, $CDCl_3$) δ 9.90 (s, 1H), 6.73 (s, 1H), 6.67 (s, 1H), 4.22 (m, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.64 (m, 2H), 3.56 (s, 3H), 3.37 (m, 4H), 2.25 (s, 3H), 2.06 (s, 3H), 1.57 (m, 2H), 0.90 (t, $J = 7.3$ Hz, 3H); HRMS Calcd for ($C_{22}H_{31}N_5O_4$) [$M + H]^+$ 430.2454; found 430.2469; HPLC: (a) >98%; (b) >98%.

8-(4,5-dimethoxy-2-methylphenyl)-N-(2-methoxyethyl)-2-methyl-N-propyl-5,6,7,8-tetrahydropteridin-4-amine (3d). ^1H NMR (400, CDCl_3) δ 6.72 (s, 1 H), 6.69 (s, 1 H), 4.41 (s, 1 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 3.78 (m, 1 H), 3.64 (m, 1 H), 3.50 (t, $J = 5.23$ Hz, 2 H), 3.41 (t, $J = 5.3$ Hz, 2 H), 3.38 (s, 3 H), 3.30 (t, $J = 5.3$ Hz, 2 H), 3.17 (t, $J = 7.3$ Hz, 2 H), 2.22 (s, 3 H), 2.07 (s, 3 H), 1.51 (sextet, $J = 7.3$ Hz, 2 H), 0.87 (t, $J = 7.3$ Hz, 3 H); HRMS Calcd for ($\text{C}_{22}\text{H}_{33}\text{N}_5\text{O}_3$) [$\text{M} + \text{H}]^+$ 416.2662; found 416.2663; HPLC: (a) >98%; (b) >98%.

4-(8-(butyl(ethyl)amino)-6-methyl-2-oxo-2,3-dihydropyrido[2,3-b]pyrazin-4(1H)-yl)-3-methylbenzonitrile (4a). ^1H NMR (400, CDCl_3) δ 7.85 (s, 1 H), 7.55 (dd, $J = 8.3, 2.0$ Hz, 1 H), 7.52 (d, $J = 2.0$ Hz, 1 H), 7.24 (d, $J = 8.3$ Hz, 1 H), 6.41 (s, 1 H), 4.32 (m, 2 H), 3.00 (q, $J = 7.1$ Hz, 2 H), 2.92 (t, $J = 7.1$ Hz, 2 H), 2.20 (s, 3 H), 2.06 (s, 3 H), 1.40 (pentet, $J = 7.1$ Hz, 2 H), 1.28 (sextet, $J = 7.1$ Hz, 2 H), 1.01 (t, $J = 7.1$ Hz, 3 H), 0.88 (t, $J = 7.1$ Hz, 3 H); HRMS Calcd for ($\text{C}_{22}\text{H}_{27}\text{N}_5\text{O}$) [$\text{M} + \text{H}]^+$ 378.2294; found 378.2308; HPLC: (a) >98%; (b) >98%.

4-(8-(butyl(ethyl)amino)-6-methyl-2,3-dihydropyrido[2,3-b]pyrazin-4(1H)-yl)-3-methylbenzonitrile (4b). ^1H NMR (400, CDCl_3) δ 7.49 (d, $J = 1.5$ Hz, 1 H), 7.46 (dd, $J = 8.1, 1.5$ Hz, 1 H), 7.24 (d, $J = 8.1$ Hz, 1 H), 6.28 (s, 1 H), 4.20 (br m, 1 H), 3.73 (m, 2 H), 3.44 (m, 2 H), 2.97 (q, $J = 7.1$ Hz, 2 H), 2.90 (m, 2 H), 2.17 (s, 3 H), 2.13 (s, 3 H), 1.40 (pentet, $J = 7.1$ Hz, 2 H), 1.28 (sextet, $J = 7.1$ Hz, 2 H), 1.00 (t, $J = 7.1$ Hz, 3 H), 0.88 (t, $J = 7.3$ Hz, 3 H); HRMS Calcd for ($\text{C}_{22}\text{H}_{29}\text{N}_5$) [$\text{M} + \text{H}]^+$ 364.2501; found 364.2513; HPLC: (a) >98%; (b) 98%.

4-(4-(butyl(ethyl)amino)-2-methyl-6-oxo-6,7-dihydropteridin-8(5H)-yl)-3-methylbenzonitrile (4c). ^1H NMR (400, CDCl_3) δ 7.57 (m, 2 H), 7.33 (br s, 1 H), 7.27 (d, $J = 8.6$ Hz, 1 H), 4.29 (m, 2 H), 3.25 (m, 4 H), 2.27 (s, 3 H), 2.14 (s, 3 H), 1.51 (pentet, $J = 7.3$ Hz, 2 H), 1.31 (sextet, $J = 7.3$ Hz, 2 H), 1.12 (t, $J = 7.1$ Hz, 3 H), 0.91 (t, $J = 7.3$ Hz, 3 H); HRMS Calcd for ($\text{C}_{21}\text{H}_{26}\text{N}_6\text{O}$) [$\text{M} + \text{H}]^+$ 379.2246; found 379.2261; HPLC: (a) >98%; (b) >98%.

4-(4-(butyl(ethyl)amino)-2-methyl-6,7-dihydropteridin-8(5H)-yl)-3-methylbenzonitrile (4d). ^1H NMR (400, CDCl_3) δ 7.53 (s, 1 H), 7.50 (d, $J = 8.1$ Hz, 1 H), 7.26 (d, $J = 8.1$ Hz, 1 H), 3.74 (s, 2 H), 3.59 (s, 1 H), 3.47 (m, 2 H), 3.17 (m, 4 H), 2.22 (s, 3 H), 2.19 (s, 3 H), 1.46 (pentet, $J = 7.1$ Hz, 2 H), 1.29 (sextet, $J = 7.1$ Hz, 2 H), 1.07 (t, $J = 7.1$ Hz, 3 H), 0.89 (t, $J = 7.3$ Hz, 3 H); HRMS Calcd for ($\text{C}_{21}\text{H}_{28}\text{N}_6$) [$\text{M} + \text{H}]^+$ 365.2454; found 365.2463; HPLC: (a) >98%; (b) >98%.

4-(4-acetyl-2-methylphenyl)-8-(butyl(ethyl)amino)-6-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one (5a). ^1H NMR (400, CDCl_3) δ 7.86 (m, 3 H), 7.25 (d, $J = 8.8$ Hz, 2 H), 6.39 (s, 1 H), 4.35 (s, 1 H), 2.99 (q, $J = 7.1$ Hz, 2 H), 2.92 (t, $J = 7.1$ Hz, 2 H), 2.60 (s, 3 H), 2.20 (s, 3 H), 2.09 (s, 3 H), 1.40 (pentet, $J = 7.1$ Hz, 2 H), 1.29 (sextet, $J = 7.1$ Hz, 2 H), 1.01 (t, $J = 7.1$ Hz, 3 H), 0.89 (t, $J = 7.1$ Hz, 3 H); HRMS Calcd for ($\text{C}_{23}\text{H}_{30}\text{N}_4\text{O}_2$) [$\text{M} + \text{H}]^+$ 395.2447; found 395.2454; HPLC: (a) >98%; (b) >98%.

1-(4-(butyl(ethyl)amino)-6-methyl-2,3-dihydropyrido[2,3-b]pyrazin-4(1H)-yl)-3-methylphenylethanone (5b). ^1H NMR (400, CDCl_3) δ 7.83 (d, $J = 2.1$ Hz, 1 H), 7.78 (dd, $J = 8.3, 2.1$ Hz, 1 H), 7.24 (d, $J = 8.3$ Hz, 1 H), 6.26 (s, 1 H), 4.21 (s, 1 H), 3.75 (m, 2 H), 3.44 (m, 2 H), 2.97 (q, $J = 7.1$ Hz, 2 H), 2.90 (t, $J = 7.3$ Hz, 2 H), 2.57 (s, 3 H), 2.20 (s, 3 H), 2.13 (s, 3 H), 1.39 (pentet, $J = 7.1$ Hz, 2 H), 1.26 (sextet, $J = 7.1$ Hz, 2 H), 1.00 (t, $J = 7.1$ Hz, 3 H), 0.88 (t, $J = 7.3$ Hz, 3 H); HRMS Calcd for ($\text{C}_{23}\text{H}_{32}\text{N}_4\text{O}$) [$\text{M} + \text{H}]^+$ 381.2654; found 381.2644; HPLC: (a) >98%; (b) 98%.

8-(4-acetyl-2-methylphenyl)-4-(butyl(ethyl)amino)-2-methyl-7,8-dihydropteridin-6(5H)-one (5c). ^1H NMR (400, CDCl_3) δ 7.86 (m, 2 H), 7.34 (br s, 1 H), 7.26 (d, $J = 8.1$ Hz, 1 H), 4.33 (m, 2 H), 3.21 (m, 4 H), 2.61 (s, 3 H), 2.27 (s, 3 H), 2.17 (s, 3 H), 1.50 (pentet, $J = 7.3$ Hz, 2 H), 1.31 (sextet, $J =$

7.3 Hz, 2 H), 1.12 (t, J = 7.1 Hz, 3 H), 0.91 (t, J = 7.3 Hz, 3 H); HRMS Calcd for ($C_{22}H_{29}N_5O_2$) [M + H]⁺ 396.2400; found 396.2413; HPLC: (a) >98%; (b) >98%.

1-(4-(butyl(ethyl)amino)-2-methyl-6,7-dihydropteridin-8(5H)-yl)-3-methylphenyl)ethanone (5d). 1H NMR (400, CDCl₃) δ 7.85 (d, J = 2.0 Hz, 1 H), 7.80 (dd, J = 8.3, 2.0 Hz, 1 H), 7.26 (d, J = 8.3 Hz, 1 H), 3.76 (m, 2 H), 3.62 (s, 1 H), 3.46 (m, 2 H), 3.16 (m, 4 H), 2.59 (s, 3 H), 2.22 (s, 3 H), 2.21 (s, 3 H), 1.46 (pentet, J = 7.3 Hz, 2 H), 1.29 (sextet, J = 7.3 Hz, 2 H), 1.06 (t, J = 7.18 Hz, 3 H), 0.89 (t, J = 7.3 Hz, 3 H); HRMS Calcd for ($C_{22}H_{31}N_5O$) [M + H]⁺ 382.2607; found 382.2617; HPLC: (a) >98%; (b) >95%.

References

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