Supporting Information

Discovery of a Tetracyclic Quinoxaline Derivative as a Potent and Orally Active Multifunctional Drug Candidate for the Treatment of Neuropsychiatric and Neurological Disorders

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Synthesis and analytical data of intermediates and final compounds

*4,5,7,8,9,10-Hexahydropyrido[4,3-b]pyrrolo[3,2,1-hi]indole (**27a**, X = C, m = 0, n =1).*

A mixture of 1-amino-2,3-dihydroindole hydrochloride (1.0 g, 5.9 mmol), piperidone hydrochloride monohydrate (0.91 g, 5.9 mmol) and isopropanol (29 mL) was brought to reflux for 4 h, and then cooled to room temperature. The resulting brown solid was filtered, washed with cold diethyl ether (20 mL), and dried under vacuum to give **27a** (1.01 g, 73%) as a hydrochloride salt. ^{1}HNMR (CD_3OD, 300 MHz) δ 7.15 (d, J =7.7 Hz, 1H), 6.96–6.85 (m, 2H), 4.50–4.39 (m, 4H), 3.75 (t, J =7.3 Hz, 2H), 3.57 (t, J =6.2 Hz, 2H), 3.15 (t, J = 6.2 Hz, 2H).

*5,6,8,9,10,11-Hexahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline (**27b**, X = C, m = 1, n =1).*

1,2,3,4-Tetrahydroquinoline (2.12 g, 15.9 mmol) was dissolved in AcOH (30 mL) and water (10 mL). The solution was cooled to 0°C. An aqueous solution of $NaNO_2$ (1.20 g, 17.5 mmol) in 3 mL water was added dropwise. The reaction was warmed to room temperature and stirred for 2 h. Water (20 mL) and EtOAc (20 mL) were added. The layers were separated and the aqueous phase was extracted with EtOAc (2x20 mL). The combined organic phase were washed with brine, dried over $MgSO_4$, and evaporated to dryness under vacuum to afford a crude orange oil, which was purified by column chromatography eluting with 20–40% EtOAc in hexanes to afford 1-nitroso-1,2,3,4-tetrahydroquinoline (2.48 g, 96% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J = 8.1 Hz, 1H), 7.34–7.21 (m, 3H), 3.91 (t, J = 6.2 Hz, 2H), 3.81 (t, J = 6.2 Hz, 2H), 2.05–1.97 (m, 2H).

1-Nitroso-1,2,3,4-tetrahydroquinoline (1.46 g, 9.0 mmol) was dissolved in THF. The solution was cooled to 0° C. 1.0 M lithium aluminum hydride in THF (9.0 mL, 9.0 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. The mixture was cooled to 0°C, and then quenched with a saturated aqueous Rochelle salt solution (20 mL). The suspension was stirred for 2 h and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated to afford an orange solid, which was purified by column chromatography eluting with a gradient of 20–0% hexane in CH_2Cl_2 to afford 1,2,3,4-tetrahydroquinoylamine (1.02 g, 76%) as a yellow solid. ^{1}HNMR ($CDC1_3$, 300 MHz) δ 7.18–7.09 (m, 2H), 6.97 (dd, J = 0.7, 7.3 Hz, 1H), 6.74–6.68 (m, 1H), 3.64 (m, 2H), 3.31 (t, J = 6.0 Hz, 2H), 2.77 (t, J = 6.6 Hz, 2H), 2.11–2.02 (m, 2H).

1,2,3,4-Tetrahydroquinoylamine (0.925 g, 6.25 mmol) and 4-piperidone monohydrate hydrochloride (0.960 g, 6.25 mmol) were dissolved in EtOH (15 mL). Concentrated HCl (0.52 mL, 6.25 mmol) was added. The reaction was refluxed for 3 h and then cooled to room temperature. The precipitate was collected by vacuum filtration. The residue was washed with EtOH (5 mL) to afford the title compound (1.32 g, 85% yield) as a hydrochloride salt. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.22 (d, J = 8.1 Hz,1H), 6.97–6.92 (m, 1H), 6.86 (d, J = 7.2 Hz, 1H), 4.87 (s, 2H), 4.05 (t, J = 6.0 Hz, 2H), 3.61 (t, J = 6.0 Hz, 2H), 3.14 (t, J = 6.0 Hz, 2H), 2.94 (t, J = 6.3 Hz, 2H), 2.24–2.16 (m, 2H). MS (ESI) *m/z* 213.2 $[M+H]^+$.

*1,2,7,8,9,10-Hexahydropyrido[4,3-b][1,4]thiazino[2,3,4-hi]indole hydrochloride (**27d**, X = S, m = 1, n =1).*

The title compound was prepared from 3,4-dihydro-2*H*-benzo[1,4]thiazine using a similar procedure as the synthesis of **27b**.^{1}H NMR (500 MHz, DMSO-d_6) δ 9.71–9.62 (br, 1H), 7.31–7.24 (m, 1H), 6.98–6.91 (m, 2H), 4.32–4.21 (m, 4H), 3.50–3.40 (m, 2H), 3.29 (s, 2H), 3.11–3.01 (m, 2H). MS (CI) *m/z* 231.

27e–27f were each prepared according to a similar procedure as the synthesis of **27c**. These intermediates were not purified. Instead, they were carried into the next step directly.

Cis-**28a,** *cis*-**28b**, *cis*-**28d**, *cis*-**28e** and *cis*-**28f** were each prepared according to a similar procedure as the synthesis of *cis*-**28c** using **27a, 27b**, **27d**, **27e** and **27f** as starting materials, respectively.

*cis-4,5,6a,7,8,9,10,10a-Octahydropyrido[4.3-b]pyrrolo[3,2,1-hi]indole-9-carboxylic acid tert-butyl ester (cis-**28a**, X = C, m = 0, n = 1)* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.97 (d, J = 7.3 Hz, 1H), 6.93 (d, J = 7.3 Hz, 1H), 6.75–6.60 (m, 1H), 3.90–3.75 (m, 1H), 3.72–3.50 (m, 1H), 3.48–3.05 (m, 5H), 2.90–2.70 (m, 1H), 1.90–1.70 (m, 2H). MS (CI) *m/z* 301 $[M+H]^+$.

*cis-5,6,7a,8,9,10,11,11a-Octahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline-10-carboxylic acid tert-butyl ester (cis-**28b**, X = C, m = 1, n = 1).* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.93 (d, J = 7.2 Hz, 1H), 6.86 (dd, J = 7.7, 1.2 Hz, 1H), 6.63 (t, J = 7.4 Hz, 1H), 4.31–3.53 (m, 2H,), 3.40 (br, 1H), 3.32–3.07 (m, 3H), 3.07–2.75 (m, 1H), 2.74–2.42 (m, 3H), 2.25–2.00 (m, 2H), 1.99–1.75 (m, 2H), 1.47 (s, 9H). MS (ESI) *m/z* 315.2 $[M+H]^+$.

*cis-1,2,6b,9,10,10a-Hexahydro-7H-3-thia-8,10b-diaza-fluoranthene-8-carboxylic acid tert-butyl ester (cis-**28d**, X = S, m = 1, n = 1).* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.93–6.73 (m, 2H), 6.64 (t, J = 7.5 Hz, 1H), 4.16–3.70 (m, 1H), 3.70–3.61 (m, 1H), 3.61–3.48 (m, 2H), 3.48–3.34 (m, 1H), 3.30–3.12 (m, 2H), 3.12–2.67 (m, 3H), 2.05–1.73 (m, 2H), 1.46 (s, 9H). MS (ESI) *m/z* 333.1 $[M+H]^+$.

*cis-1,2,6b,9,10,10a-Hexahydro-7H-3-oxa-8,10b-diaza-fluoranthene-8-carboxylic acid tert-butyl ester (cis-**28e**, X = O, m = 1, n = 1).* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.72 (dd, J = 6.9, 1.4 Hz, 1H), 6.69–6.59 (m, 2H), 4.54–4.33 (m, 2H), 4.25–3.65 (m, 2H), 3.38 (br, 1H), 3.31 (dt, J = 10.8,2.5 Hz, 1H), 3.23–3.05 (m, 2H), 3.05–2.65 (m, 2H), 1.99–1.70 (m, 2H), 1.48 (s, 9H). MS (ESI) *m/z* 317.1 $[M+H]^+$.

*cis-1,2,6b,8,9,10,11,11a-octahydro-7H-azepino[4,5-b][1,4]oxazino[2,3,4-hi]indole-9(2H)-carboxylic acid tert-butyl ester (cis-**28f**, X = O, m = 1, n = 2).* This intermediate was prepared using a procedure similar to the synthesis of *cis*-**28c**, and was carried directly into the next step without further purification.

29a, 29b, **29d**, **29e** and **29f** were each prepared according to a similar procedure as the synthesis of **29c** using *cis*-**28a,** *cis*-**28b**, *cis*-**28d**, *cis*-**28e** and *cis*-**28f** as starting materials respectively.

*(6aS,10aR)-4,5,6a,7,8,9,10,10a-Octahydropyrido[4.3-b]pyrrolo[3,2,1-hi]indole (**29a**, X = C, m = 0, n =1)* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.94 (d, J = 7.7 Hz, 1H), 6.88 (d, J = 6.9 Hz, 1H,), 6.63 (t, J = 7.3 Hz, 1H,), 3.64 (dt, J =8.0, 1.5 Hz, 1H), 3.29–3.5 (m, 2H), 3.29–3.05 (m, 3H), 3.03 (dd, J = 11.7, 3.6 Hz, 1H,), 3.02–2.72 (m, 2H), 1.90–1.66 (m, 2H). MS (ESI) *m/z* 201.1 $[M+H]^+$.

*(7aS,11aR)-5,6,7a,8,9,10,11,11a-Octahydro-4H-pyrido[3',4';4,5]pyrrolo[3,2,1-ij]quinoline (**29b**, X = C, m = 1, n = 1).* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.20–7.01 (m, 3H), 3.91–3.51 (m, 5H), 3.51–3.28 (m, 2H), 3.22–3.09 (m, 1H), 2.96–2.72 (m, 3H), 2.51–2.15 (m, 4H). MS (ESI) m/z 215.1 $[M+H]^+$.

*(6bR,10aS)-1,2,6b,9,10,10a-Hexahydro-7H-3-thia-8,10b-diaza-fluoranthene (**29d**, X = S, m = 1, n = 1).* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.93 (dd, J = 7.9, 1.1 Hz, 1H), 6.89–6.78 (m, 1H), 6.73 (t, J =7.6 Hz, 1H), 3.65–3.50 (m, 2H), 3.49–3.28 (m, 5H), 3.27–3.00 (m, 2H), 2.94 (td, J = 10.5, 2.2 Hz, 1H), 2.80–2.72 (m, 1H), 2.32–2.13 (m, 2H). MS (ESI) *m/z* 233.1 $[M+H]^+$.

*(6bR,10aS)-1,2,6b,7,8,9,10,10a-octahydro[1,4]oxazino[2,3,4-hi]pyrido[4,3-b]indole (**29e**, X = O, m = 1, n = 1).* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.88–6.53 (m, 3H), 4.64–4.31 (m, 2H), 3.68–3.15 (m, 7H), 3.04–2.62 (m, 2H), 2.39–2.11 (m, 2H). MS (ESI) *m/z* 217.1 $[M+H]^+$.

*(6bS, 11aS)-1,2,6b,8,9,10,11,11a-octahydro-7H-azepino[4,5-b][1,4]oxazino[2,3,4-hi]indole (**29f**, X = O, m = 1, n = 2).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.67–6.57 (m, 3H), 4.43–4.39 (m, 2H), 3.69–3.61 (m, 1H), 3.45 (dt, J = 3.3, 9.2 Hz, 1H), 3.24–3.00 (m, 3H), 2.89–2.69 (m, 3H), 2.16–2.02 (m, 2H), 1.97–1.83 (m, 2H).

Compounds **31** – **37** were prepared in an analogous fashion following the procedure described in the synthesis of compound **5**.

*4-((6bR,10aS)-2,3,6b,9,10,10a-Hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone (**31**, R_1 = H, R_2 = H).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02–7.97 (m, 2H), 7.15–7.09 (m, 2H), 6.61–6.51(m, 2H), 6.38 (dd, J = 7.3, 1.4 Hz, 1H), 3.72–3.64 (m, 2H), 3.49–3.26 (m, 2H), 3.24–3.13 (m, 2H), 3.04–2.99 (m, 2H), 2.97–2.91 (m, 1H), 2.79–2.61 (m, 2H), 2.53–2.43 (m, 2H), 2.43–2.34 (m, 1H), 2.13–1.95 (m, 4H). ^{13}C NMR (DMSO-d_6, 126 MHz,) δ 197.3, 165.0 (d, J_{CF} = 252 Hz), 136.6, 133.5, 133.2 (d, J_{CF} = 3 Hz), 130.9 (d, J_{CF} = 9 Hz), 127.8, 120.5, 115.7 (d, J = 22 Hz), 111.9, 111.3, 63.0, 55.4, 52.5, 47.5, 43.8, 41.1, 38.2, 35.3, 21.6, 17.8. MS (ESI) *m/z* 380.2 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{23}H_{27}FN_3O$ $[M+H]^+$: 380.2138; found: 380.2132. UPLC purity: 98.9%; retention time: 1.74 min (method A).

*4-((6bR,10aS)-3-Ethyl-2,3,6b,9,10,10a-Hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone (**32**; R_1 = H, R_2 = Et).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03–7.98 (m, 2H), 7.12 (t, J = 8.5 Hz, 2H), 6.64 (d, J = 7.7 Hz, 1H), 6.47 (d, J = 7.7 Hz, 1H), 6.30 (d, J = 7.7 Hz, 1H), 3.72–3.64 (m, 1H), 3.43–3.04 (m, 5H), 2.98 (t, J = 7.0 Hz, 2H), 2.87–2.77 (m, 1H), 2.77–2.63 (m, 3H), 2.42–2.30 (m, 2H), 2.30–2.20 (m, 1H), 2.03–1.75 (m, 5H), 1.15 (t, J = 7.0 Hz, 3H). MS (CI) *m/z* 408 $[M+H]^+$.

*4-((6bR,10aS)-3-Isopropyl-2,3,6b,9,10,10a-Hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone (**33**, R_1 = H, R_2 = i-Pr).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03–8.00 (m, 2H), 7.12 (t, J = 8.3 Hz, 2H), 6.64 (t, J = 7.7 Hz, 1H), 6.45 (d, J = 6.2 Hz, 2H), 4.03 (dt, J = 6.6, 2.3 Hz, 1H), 3.453.21 (m, 3H), 3.17–3.03 (m, 2H), 2.98 (t, J = 7.3 Hz, 2H), 2.87–2.79 (m, 1H), 2.68–2.64 (m, 2H), 2.41–2.29 (m, 2H), 2.29–2.21 (m, 1H), 1.94–1.82 (m, 5H), 1.18 (d, J = 6.6 Hz, 6H). MS (CI) *m/z* 422 $[M+H]^+$.

*4-((6bR,10aS)-3-Butyl-2,3,6b,9,10,10ahexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone (**34**; R_1 = H, R_2 = Bu).* Starting from the intermediate *cis*-**9** (R_1 = H), *cis*-3-butyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]-pyrrolo[1,2,3-de]quinoxaline (*cis*-**12**, R_1 = H, R_2 = Bu) was prepared in analogous fashion using butyl iodide as the alkyl halide and following the procedure of steps e–g described in the synthesis of **5**, yielding a light brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.66 (t, J = 7.7 Hz, 1H) 6.46, (d, J = 7.1 Hz, 1H), 6.38(d, J = 7.1 Hz, 1H), 3.78–3.68 (m, 1H), 3.40–3.22 (m, 6H), 3.22–3.08 (m, 3H), 3.08–2.85 (m, 1H), 2.80–2.65 (m, 2H), 2.15–1.95 (m, 2H), 1.65–1.50 (m, 2H), 1.45–1.30 (m, 2H), 0.95 (m, 3H). The obtained *cis*-3-butyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline was reacted with 4-chloro-4'-fluoro-butyrophenone following the procedure of step h described in the synthesis of **5**, followed by chiral HPLC separation to give the tile compound. MS (CI) *m/z* 436 $[M+H]^+$.

*4-((6bR,10aS)-3-benzyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone (**35**, R_1 = H, R_2 = Bn).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03–8.00 (m, 2H) 7.35–7.20 (m, 5H), 7.13 (t, J = 8.5 Hz, 2H) 6.61 (t, J = 8.1 Hz,1H), 6.50 (d, J = 7.0 Hz, 1H),) 6.40 (d, J = 8.0 Hz, 1H), 4,43 (q, J = 16.5 Hz, 2H), 3.74–3.65 (m, 1H), 3.34–3.26 (m, 2H), 3.26–3.14 (m, 1H), 3.14–3.06 (m, 1H), 2.99 (t, J = 7.3 Hz, 2H), 2.89–2.80 (m, 1H), 2.80–2.72 (m, 1H), 2.72–2.64 (m, 1H), 2.43–2.31 (m, 2H), 2.31–2.20 (m, 1H), 2.05–1.84 (m, 5H). MS (CI) *m/z* 470 $[M+H]^+$.

*4-((6bR,10aS)-5-Bromo-3-methyl-2,3,6b,9,10,10a-Hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone (**36**, R_1 = Br, R_2 = Me).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10–7.92 (m, 2H), 7.19–7.10 (m, 2H), 6.12 (s, 1H), 6.07 (s, 1H), 3.70–3.55 (m, 7H), 3.37–3.07 (m, 4H), 2.86 (s, 3H), 2.80–2.66 (m,2H), 2.40–1.82 (m, 4H), 2.00–1.30 (m, 4H). MS (CI) *m/z* 472 $[M+H]^+$.

*4-((6bR,10aS)-5-Methoxy-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone (**37**, R_1 = OMe, R_2 = Me).* ^{1}H NMR ($CDCl_3$, 300 MHz,) δ 7.92–8.10 (m, 2H), 7.21–7.06 (m, 2H), 6.12 (s, 1H), 6.07 (s, 1H), 3.75–3.55 (m, 7H), 3.32–3.07 (m, 4H), 2.86 (s, 3H), 2.79–2.66 (m, 2H), 2.50–1.92 (m, 4H), 1.79–1.42 (m, 4H). MS (CI) *m/z* 424 $[M+H]^+$.

Compounds **38**–**50**. All were prepared in a manner analogous to compound **41** by coupling the tetracyclic core *cis*-**22** with different sidechains.

*4-((6bR,10aS)-3-Methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8-yl)-1-phenyl-butan-1-one (**38**, R_3 = 4-oxo-4-phenylbutyl).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 7.2 Hz, 2H), 7.55 (d, J = 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 6.67 (t, J = 7.6 Hz, 1H), 6.52 (d, J = 7.4 Hz, 1H), 6.42 (d, J = 7.9 Hz, 1H), 3.67–3.54 (m, 1H), 3.40–3.20 (m, 4H), 3.20–3.11 (m, 1H), 3.11–2.97 (m, 3H), 2.92–2.77 (m, 4H), 2.77–2.51 (m, 3H), 2.30–1.91 (m, 5H). MS (ESI) *m/z* 376.2 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{24}H_{30}N_3O$ $[M+H]^+$: 376.2389; found: 376.2377. UPLC purity: 99.5%; retention time: 2.04 min (method A).

*4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-pyridinyl)-1-butanone (**39**, R_3 = 4-oxo-4-(pyridin-4-yl)butyl).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.79 (dd, J = 4.4, 1.8 Hz, 2H), 7.74 (dd, J = 4.4, 1.4 Hz, 2H), 6.64 (dd, J = 7.4, 7.6 Hz, 1H),6.49 (d, J = 6.9 Hz, 1H), 6.39 (d, J = 7.7Hz, 1H), 3.62–3.54 (m, 1H), 3.31–3.23 (m, 2H), 3.17–3.13 (m, 1H), 3.03–2.95 (m, 2H), 2.85 (s, 3H), 2.84–2.76 (m, 2H), 2.60–2.57 (m, 1H), 2.41–2.31 (m, 1H), 2.22 (td, J = 11.7, 2.9 Hz, 1H), 2.02–1.92 (m, 3H), 1.88–1.83 (m, 1H), 1.76–1.66 (m, 3H). ^{13}C NMR (DMSO-d_6, 126 MHz) δ 199.6, 150.7, 143.0, 137.7, 134.8, 129.6, 121.1, 119.7, 112.2, 108.5, 64.0, 57.0, 55.8, 50.0, 48.5, 43.8, 40.8, 37.1, 36.0, 24.1, 21.8. MS (ESI) *m/z* 377.1 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{23}H_{29}N_4O$ $[M+H]^+$: 377.2341; found: 377.2339. UPLC purity: 97.9%; retention time: 1.63 min (method A).

*4-((6bR,10aS)-3-Methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8-yl)-1-(4,4-difluoro-piperidin-1-yl)-butan-1-one (**40**, R_3 = 4-(4,4-difluoropiperidin-1-yl)-4-oxobutyl).* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.66 (t, J = 7.7 Hz, 1H), 6.51 (d, J = 7.5 Hz, 1H), 6.41 (dd, J = 8.0, 1.0 Hz, 1H), 3.77–3.67 (m, 2H), 3.64–3.53 (m, 3H), 3.39–3.22 (m, 3H), 3.17–3.01 (m, 1H), 2.99–2.79 (m, 6H), 2.66–2.41 (m, 4H), 2.25–2.08 (m, 1H), 2.08–1.84 (m, 7H), 1.51 (d, J = 6.7 Hz, 1H), 1.40 (t, J = 7.3 Hz, 1H). MS (ESI) *m/z* 419.2 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{23}H_{33}F_2N_4O$ $[M+H]^+$: 419.2622; found: 419.2613. UPLC purity: 95.0%; retention time: 1.90 min (method A).

*4-Fluoro-N-[2-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8-yl)-ethyl]-benzamide (**42**, R_3 = 2-(4-fluorobenzamido)ethyl).* ^{1}HNMR ($CDCl_3$, 500 MHz):δ 8.57 (br, 1H), 8.01 (dd, J = 8.5, 5.2 Hz, 2H), 7.12 (t, J = 8.6 Hz, 2H), 6.69 (t, J = 7.7 Hz, 1H), 6.50 (d, J = 7.4 Hz, 1H), 6.44 (d, J = 8.0 Hz, 1H), 3.93–3.68 (m, 2H), 3.67–3.53 (m, 2H), 3.43–3.14 (m, 5H), 3.14–2.94 (m, 2H), 2.94–2.78 (m, 5H), 2.58–2.36 (m, 2H), 2.17–2.03 (m, 1H). MS (ESI) *m/z* 395.2 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{23}H_{28}FN_4O$ $[M+H]^+$: 395.2247; found: 395.2257. UPLC purity: 99.5%; retention time: 1.85 min (method A).

*(6bR,10aS)-8-[3-(1,2-Benzisoxazol-3yl)propyl]-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido-[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline hydrochloride (**43**, R_3 = 3-(benzo[d]isoxazol-3-yl)propyl).* ^{1}HNMR ($CDCl_3$, 300 MHz) δ 7.63–7.59 (m, 1H), 7.50–7.46 (m, 2H), 7.25–7.20 (m, 1H), 6.57 (dd, J = 7.7, 7.3 Hz, 1H), 6.43 (d, J = 6.9 Hz, 1H), 6.33 (d, J = 7.3 Hz, 1H), 3.5–3.48 (m, 1H), 3.25–3.06 (m, 4H), 2.99–2.94 (m, 2H), 2.89–2.80 (m, 4H), 2.79 (s, 3H), 2.65–2.20 (m, 3H), 2.07–1.92 (m, 4H). MS (CI) *m/z* 389 $[M+H]^+$.

*(6bR,10aS)-8-[3-(6-Fluoro-1,2-benzisoxazol-3-yl)propyl]-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline (**44**, R_3 = 3-(6-fluorobenzo[d]isoxazol-3-yl)propyl)* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63 (dd, J = 8.8, 4.7 Hz, 1H), 7.24–7.20 (m, 1H), 7.10–7.03 (m, 1H), 6.65

(dd, *J* = 7.7, 7.7 Hz, 1H), 6.50 (d, *J* = 7.3 Hz, 1H), 6.41 (d, *J* = 7.3 Hz, 1H), 3.77–3.73 (m, 1H), 3.62–3.55 (m, 1H), 3.32–3.21 (m, 3H), 3.10–2.91 (m, 3H), 2.86 (s, 3H), 2.82–2.75 (m, 2H), 2.63–2.54 (m, 1H), 2.48–2.41 (m, 1H), 2.11–1.95 (m, 6H). MS (CI) *m/z* 407 $[M+H]^+$.

*(6bR,10aS)-8-[3-(6-Fluoro-1H-indazol-3-yl)-propyl]-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido-[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline formate (**45**, R_3 = 3-(6-fluoro-1H-indazol-3-yl)propyl).* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.52 (s, 1H), 8.02 (s, 1H), 7.59 (dd, *J* = 8.8, 5.0 Hz, 1H), 7.07 (dd, *J* = 9.3, 2.2 Hz, 1H), 6.90 (td, *J* = 9.0, 2.1 Hz, 1H), 6.67 (t, *J* = 7.7 Hz, 1H), 6.49 (d, *J* = 7.4 Hz, 1H), 6.42 (d, *J* = 8.0 Hz, 1H), 3.65–3.54 (m, 1H), 3.54–3.43 (m, 1H), 3.40–3.19 (m, 4H), 3.07–2.70 (m, 10H), 2.44–2.19 (m, 4H), 2.10–1.99 (m, 1H). MS (ESI) *m/z* 406.3 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{24}H_{29}FN_5$ $[M+H]^+$: 406.2407; found: 406.2392. UPLC purity: 95.0%; retention time: 2.09 min (method A).

*(6bR,10aS)-8-[3-(4-Fluoro-phenyl)-4,5-dihydro-isoxazol-5-ylmethyl]-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline (**46**, R_3 = 3-(4-fluorophenyl)-4,5-dihydro-isoxazol-5-ylmethyl).* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75–7.57 (m, 2H), 7.21–7.02 (m, 2H), 6.69 (td, *J* = 7.7, 2.9 Hz, 1H), 6.53 (dd, *J* = 13.8, 7.4 Hz, 1H), 6.48–6.37 (m, 1H), 5.39–5.17 (m, 1H), 3.68–3.40 (m, 5H), 3.38–3.23 (m, 3H), 3.22–3.03 (m, 2H), 3.02–2.72 (m, 6H), 2.51 (q, *J* = 12.0 Hz, 1H), 2.45–2.29 (m, 1H), 2.19–2.02 (m, 1H). MS (ESI) *m/z* 407.2 $[M+H]^+$.

*6-Chloro-5-[2-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8-yl)-ethyl]-1,3-dihydro-indol-2-one (**47**, R_3 = 2-(6-chloro-2-oxoindolin-5-yl)ethyl).* ^{1}HNMR (DMSO-d_6, 500 MHz) δ 10.39 (s, 1H), 7.19 (s, 1H), 6.79 (s, 1H), 6.52 (t, *J* = 7.6 Hz, 1H), 6.44 (d, *J* = 7.2 Hz, 1H), 6.34 (dd, *J* = 8.0, 1.0 Hz, 1H), 3.51–3.40 (m, 3H), 3.17 (s, 1H), 3.14–3.08 (m, 1H), 3.08–2.97 (m, 1H), 2.92–2.83 (m, 2H), 2.83–2.75 (m, 5H), 2.74 (s, 1H), 2.72–2.61 (m, 2H), 2.48–2.38 (m, 1H), 2.22 (td, *J* = 11.7, 2.9 Hz, 1H), 1.98–1.84 (m, 2H), 1.84–1.72 (m, 1H). MS (ESI) *m/z* 423.2 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{24}H_{28}ClN_4O$ $[M+H]^+$: 423.1952; found: 423.1953. UPLC purity: 95.1%; retention time: 1.83 min (method A).

*2,8-Dimethyl-3-[2-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8-yl)-ethyl]-pyrido[1,2-a]pyrimidin-4-one (**48**, R_3 = 2-(2,7-dimethyl-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)ethyl)* ^{1}HNMR ($CDCl_3$, 500 MHz) δ 8.80 (d, *J* = 7.3 Hz, 1H), 7.33 (s, 1H), 6.91 (dd, *J* = 7.4, 1.9 Hz, 1H), 6.69 (t, *J* = 7.7 Hz, 1H), 6.55 (d, *J* = 7.3 Hz, 1H), 6.43 (d, *J* = 8.0 Hz, 1H), 3.65–3.39 (m, 4H), 3.34–3.26 (m, 3H), 3.23–3.06 (m, 2H), 3.06–2.77 (m, 7H), 2.69–2.27 (m, 8H), 2.21–2.02 (m, 1H). MS (ESI) *m/z* 430.2 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{26}H_{32}N_5O$ $[M+H]^+$: 430.2607; found: 430.2624. UPLC purity: 96.3%; retention time: 1.67 min (method A).

*(3aR,7aS)-2-[4-((6bR,10aS)-3-Methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8-yl)-butyl]-hexahydro-isoindole-1,3-dione (**49**, R_3 = 4-((3aS,7aR)-1,3-dioxo-hexahydro-1H-isoindol-2(3H)-yl)butyl).*^{1}HNMR ($CDCl_3$, 500 MHz) δ 6.71 (t, *J* = 7.7 Hz, 1H), 6.52 (d, *J* = 7.4 Hz, 1H), 6.44 (d, *J* = 8.0 Hz, 1H), 3.93–3.76 (m, 1H), 3.68–3.56 (m, 1H), 3.50 (t, *J* = 6.8 Hz, 2H), 3.46–3.39 (m, 1H), 3.39–3.16 (m, 4H), 3.08–2.72 (m, 9H), 2.57–2.43 (m, 1H), 2.19–2.06 (m, 1H), 1.98–1.80 (m, 4H), 1.79–1.58 (m, 4H), 1.51–1.33 (m, 4H), 0.95–0.71 (m, 1H). MS (ESI) *m/z* 437.3 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{26}H_{37}N_4O_2$ $[M+H]^+$: 437.2917; found: 437.2905. UPLC purity: 97.4%; retention time: 2.00 min (method A).

*(3aR,7aS)-2-[3-((6bR,10aS)-3-Methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8-yl)-propyl]-hexahydro-isoindole-1,3-dione (**50**, R_3 = 3-((3aS,7aR)-1,3-dioxo-hexahydro-1H-isoindol-2(3H)-yl)propyl).* ^{1}HNMR ($CDCl_3$, 500 MHz) δ 6.65 (t, *J* = 7.7 Hz, 1H), 6.52 (d, *J* = 7.2 Hz, 1H), 6.40 (d, *J* = 7.9 Hz, 1H), 3.66–3.43 (m, 3H), 3.35–3.04 (m, 4H), 2.96–2.49 (m, 8H), 2.49–2.07 (m, 3H), 2.07–1.51 (m, 9H), 1.51–1.32 (m, 4H). MS (ESI) *m/z* 423.2 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{25}H_{35}N_4O_2$ $[M+H]^+$: 423.2760; found: 423.2746. UPLC purity: 95.2%; retention time: 1.97 min (method A).

*4-((6bS,10aR)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8-yl)-1-(4-fluorophenyl)-butan-1-one (**51**, R_4 = H, R_5 = H, m = 1, n = 1, a = S, b = R, X= N-Me)* Compound **51** is the enantiomer of **5** and was obtained as the later eluting peak relative to the peak of **5** during the chiral HPLC separation of the racemate on a Chiral AD-H column using ethanol as the mobile phase. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01–7.98 (m, 2H), 7.14–7.10 (m, 2H), 6.64 (t, J = 7.6 Hz, 1H), 6.50 (d, J = 7.2Hz, 1H), 6.40 (d, J = 7.6 Hz, 1H), 3.62–3.55 (m, 1H), 3.31–3.24 (m, 2H), 3.21–3.17 (m, 1H), 3.10–3.04 (m, 1H), 2.96–2.90 (m, 2H), 2.88–2.78 (m, 5H), 2.67–2.61 (m, 1H), 2.44–2.32 (m, 2H), 2.27–2.20 (m, 1H), 2.00–1.77 (m, 5H). ^{13}C NMR (DMSO-d_6, 126 MHz) δ 198.4, 164.8 (d, J_{CF} = 251 Hz), 137.7, 134.8, 133.8 (d, J_{CF} = 3 Hz), 130.8 (d, J_{CF} = 9.4 Hz), 129.6, 119.7, 115.6 (d, J_{CF} = 22 Hz), 112.2, 108.5, 64.1, 57.2, 56.0, 50.0, 48.7, 43.8, 41.0, 37.1, 35.7, 24.3, 21.7. MS (ESI) *m/z* 394.2 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{24}H_{29}FN_3O$ $[M+H]^+$: 394.2295; found: 394.2288. UPLC purity: 95.9%; retention time: 2.05 min (method A).

*4-(rel-(6bS,10aS)-3-Methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8-yl)-1-(4-fluorophenyl)-1-butanone (**52**, R_4 = H, R_5 =H, m = 1, n = 1, a = S, b = S, X = N-Me).*

To a solution of 3-methyl-2,3,7,8,9,10-hexahydro-1*H,*7*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline (210 mg, 0.92 mmol) in CH_2Cl_2 (6 mL) was added triethylamine (0.19 mL, 1.38 mmol) at 0 °C, followed by adding a solution of benzoyl chloride (0.13 mL, 1.12 mmol) in CH_2Cl_2 (2 mL) dropwise with vigorous stirring. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography to afford 8-benzoyl-3-methyl-2,3,7,8,9,10-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline as a white solid (240 mg, 78% yield). MS (ESI) *m/z* 332.1 $[M+H]^+$.

8-Benzoyl-3-methyl-2,3,7,8,9,10-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline (240 mg, 0.72 mmol) was dissolved in anhydrous THF (5 mL) at room temperature. Excessive LAH was carefully added in small portions with stirring to maintain the temperature of the reaction mixture below 30 °C (Caution: hydrogen gas was generated vigorously!). After the addition was completed, the mixture was heated to 70 °C for 30 min, and then cooled to room temperature. Methanol (1 mL) was carefully added dropwise to quench the reaction and then the mixture was filtrated through a Celite plug to yield 8-benzyl-3-methyl-2,3,7,8,9,10-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline as a tan solid (ca. 230 mg), which was used in the next step without further purification. MS (ESI) *m/z* 318.0 $[M+H]^+$.

To a solution of 8-benzyl-3-methyl-2,3,7,8,9,10-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline (11 mg, 0.035 mmol) in THF (0.5 mL) was added BH_3·THF (300 µL, 1.0 M, 0.3 mmol). The reaction mixture was heated at reflux for 1 h, and then cooled to room temperature. After the solvent was removed under reduced pressure, the residue was dissolved in THF (50 µL), followed by adding AcOH (60 µL) and 6 N HCl (60 µL). The mixture was heated to 94 °C for 1 h, and then cooled to room temperature. The mixture was basified with 50% NaOH aqueous solution, and then extracted with CH_2Cl_2 (2 × 5 mL).The combined organic phase was evaporated under reduced pressure and the residue was purified by HPLC on a semi-preparative C18 column to give (*trans*)-8-benzyl-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline as a white solid (6.6 mg, 59% yield). MS (ESI) *m/z* 320.2 $[M+H]^+$.

(*trans*)-8-benzyl-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline (6.6 mg, 0.021 mmol) was dissolved in methanol (10 mL), and then Pd/C (10 mg, 10%) was added. The mixture was stirred under hydrogen atmosphere at 45 °C overnight, and then cooled to room temperature. Pd/C was removed by filtration and the filtrate was evaporated under reduced pressure to give (t*rans*)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline (5.0 mg, 100% yield), which was used in the next step without further purification. MS (ESI) m/z 230.3 $[M+H]^+$.

A suspension of (t*rans*)-3-Methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline (5.0 mg, ca. 0.021 mmol), 4-chloro-4'-fluorobutyrophenone (6.0 mg, 0.030 mmol), KI (4.9 mg, 0.030 mmol), and DIPEA (5.2 μL, 0.03 mmol) in dioxane (1.0 mL) was heated at 96 °C for 18 h, and then cooled to room temperature. The solvent was removed under reduced pressure and the residue was purified by HPLC on a semi-preparative C18 column to afford 4-((*trans*)-3-methyl-2,3,6b,9,10,10a-hexahydro-1*H*,7*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxalin-8-yl)-1-(4-fluorophenyl)-1-butanone (5.8 mg, 70% yield) as a colorless oil. MS (ESI) *m/z* 394.3 $[M+H]^+$.

The racemic mixture was resolved by HPLC on a Chiral Pak AD-H column using isopropanol-hexane-diethylamine (10:90:0.05% v/v) as the eluent. The early-eluting peak was collected and evaporated to dryness to afford the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01 (dd, J = 8.6, 5.6 Hz, 2H), 7.13 (t, J = 8.6 Hz, 2H), 6.70 (t, J = 7.7 Hz, 1H), 6.46 (d, J = 7.3 Hz, 1H), 6.42 (d, J = 8.0 Hz, 1H), 3.63 (td, J = 11.0, 2.9 Hz, 1H), 3.46 (d, J = 10.3 Hz, 1H), 3.37 (dt, J = 10.0, 2.7 Hz, 1H), 3.26 (dt, J = 11.5, 2.6 Hz, 1H), 3.08 (d, J = 11.5 Hz, 1H), 3.01 (t, J = 7.1 Hz, 2H), 2.87 (s, 3H), 2.80 (td, J = 10.3, 2.8 Hz, 1H), 2.56 (t, J = 7.0 Hz, 2H), 2.38 (td, J = 12.1, 3.4 Hz, 1H), 2.23 – 2.09 (m, 2H), 2.08 – 1.94 (m, 3H), 1.90 – 1.58 (m, 2H). (ESI) *m/z* 394.3 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{24}H_{29}FN_3O$ $[M+H]^+$: 394.2295; found: 394.2296. UPLC purity: 97.6%; retention time: 2.01 min (method A).

*4-(rel-(6bR, 10aR)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8-yl)-1-(4-fluorophenyl)-1-butanone (**53**, R_4 = H, R_5 = H, m = 1, n = 1, a = R, b = R, X = N-Me).*The compound was obtained as the later-eluting peak relative to the peak of **52** during the chiral HPLC separation of the racemic mixture, 4-((*trans*)-3-methyl-2,3,6b,9,10,10a-hexahydro-1*H*,7*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxalin-8-yl)-1-(4-fluorophenyl)-1-butanone. MS (ESI) m/z 394.3 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{24}H_{29}FN_3O$ $[M+H]^+$: 394.2295; found: 394.2279. UPLC purity: 98.0%; retention time: 1.98 min (method A).

*4-((6bS,10aR)-2,3,6b,9,10,10a-Hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone (**54**, R_4 = H, R_5 = H, m = 1, n = 1, a = S, b = R, X= NH).* Compound **54** is the enantiomer of **31** and was obtained as the later-eluting peak relative to the peak of **31** during the chiral HPLC separation of the racemate on a Chiral AD-H column with ethanol containing 0.1% diethylamine as the mobile phase. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02–7.97 (m, 2H), 7.15–7.09 (m, 2H), 6.61–6.51 (m, 2H), 6.38 (dd, J = 7.3 Hz, 1.4 Hz, 1H), 3.72–3.64 (m, 2H), 3.49–3.26 (m, 2H), 3.24–3.13 (m, 2H), 3.04–2.99 (m, 2H), 2.97–2.91 (m, 1H), 2.79–2.61 (m, 2H), 2.53–2.43 (m, 2H), 2.43–2.34 (m, 1H), 2.13–1.95 (m, 4H). MS (ESI) *m/z* 380.3 $[M+H]^+$.

*(6bS,11aS)-4-(3-Methyl-2,3,6b,7,8,10,11,11a-octahydro-1H,9H-azepino[4',5':4,5]pyrrolo[1,2,3-de]quinoxalin-9-yl)-1-(4-fluorophenyl)-1-butanone (**55**, R_4 = H, R_5 = H, m = 1, n = 2, a = S, b = S, X = CH_2)*

o-Nitrophenyl hydrazine (5.22 g, 34 mmol) and azepan-4-one hydrochloride (5.09 g, 34 mmol) were dissolved in 60 mL of CF_3CH_2OH. The mixture was heated at reflux for 1 h, and then cooled to room temperature. After the solvent was removed under reduced pressure, the residue was transferred to a sealed tube, and then conc. HCI (100 mL) was added. The mixture was heated at 80 °C for 18 h, and then cooled to 0° C with ice chips. The mixture was basified with 50% NaOH until pH = 14. Dioxane (100 mL) and $(Boc)_2O$ (8.18 g, 3.7 mmol) were added. The reaction mixture was stirred at room temperature for 18 h, and then concentrated. The residue was treated with brine (50 mL) and $CHCl_3$ and the biphasic mixture was stirred at room temperature for 10 min. The layers were separated and the aqueous phase was extracted with $CHCl_3$ (2 × 30 mL). The combined organic phase was washed with brine, dried, and concentrated under vacuum. The residue was purified by column chromatography eluting with 1-2% MeOH/CH_2CI_2 to afford *tert*-butyl 7-nitro-1,4,5,6-tetrahydroazepino[4,5-b]indole-3(2H)-carboxylate (5.87 g, 52% yield) as an amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.45 (br, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.9–7.7 (m, 1H), 7.19–7.13 (m, 1H), 3.73–3.69 (m, 4H), 3.11–2.90 (m, 4H), 1.50 (s, 9H).

To a suspension of NaH in DMF (2 mL) was added dropwise a solution of *tert*-butyl 7-nitro-1,4,5,6-tetrahydroazepino[4,5-*b*]indole-3(2*H*)-carboxylate (462 mg, 1.4 mmol) in DMF (4 mL) at 0 °C. The reaction mixture was heated at 40 °C for 10 min, and then cooled to 0 °C. Ethyl 2-bromoacetate was added dropwise. The mixture was warmed to room temperature and stirred for 3 h. Brine (20 mL) and EtOAc (20 mL) were added to the reaction mixture and stirred for 10 min. The layers were separated. The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with brine, dried, and concentrated under vacuum. The residue was purified by column chromatography eluting with 30% EtOAc in hexane to afford *tert*-butyl 6-(2-ethoxy-2-oxoethyl)-7-nitro-1,4,5,6-tetrahydroazepino[4,5-*b*]indole-3(2*H*)-carboxylate as an orange amorphous solid (453 mg, 78% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, J = 7.7 Hz, 1H), 7.75–7.10 (m, 1H), 7.16–7.11 (m, 1H), 4.82 (s, 2H), 4.25 (q, J = 7.0 Hz, 2H), 3.9–3.6 (m, 4H), 3.1–2.8 (m, 4H), 1.48 (s, 9H), 1.30 (t, J =7.0 Hz, 3H,).

A reaction flask containing a mixture of *tert*-butyl 6-(2-ethoxy-2-oxoethyl)-7-nitro-1,4,5,6-tetrahydroazepino[4,5-*b*]indole-3(2*H*)-carboxylate (146mg, 0.35 mmol) and Pd/C catalyst in EtOH (15 mL) was evacuated and shaken on a Parr shaker at 55 *psi* of H_2. After 18 h, the flask was disassembled and the mixture was filtered through a cake of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography to give *tert*-butyl 2-oxo-2,3,7,8,10,11-hexahydro-1*H*,9*H*-azepino[4'5':4,5]pyrrolo[1,2,3-*de*]quinoxaline-9-carboxylate (93.6 mg, 78% yield) as a white amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96 (br, 1H), 7.17–7.11 (m, 1H), 6.98–6.92 (m, 1H), 6.50 (s, 1H), 4.86 (s, 2H), 3.73–3.68 (m, 4H), 3.05–2.91 (m, 4H), 1.59 (s, 9H).

tert-Butyl 2-oxo-2,3,7,8,10,11-hexahydro-1*H*,9*H*-azepino[4'5':4,5]pyrrolo[1,2,3-*de*]quinoxaline-9-carboxylate (501 mg, 1.5 mmol) was dissolved in DMF (5 mL). The solution was cooled to 0 °C. NaH (44.5 mg, 1.76 mmol) was added. The reaction mixture was heated at 50 °C for 45 min, cooled back to 0 °C, and then excess MeI was added. The mixture was stirred at 0 °C for 2 h, and then quenched with a saturated aqueous NH_4Cl solution. The reaction mixture was extracted with EtOAc (3 × 15 mL). The combined organic phase was washed with brine, dried, and concentrated under vacuum. The residue was purified by column chromatography eluting with 2-5% MeOH/CH_2Cl_2 to afford *tert*-butyl 3-methyl-2-oxo-2,3,7,8,10,11-hexahydro-1*H*,9*H*-azepino[4'5':4,5]pyrrolo[1,2,3-de]quinoxaline-9-carboxylate (153 mg, 29% yield) as a white amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18–7.14 (m, 1H), 7.04–6.99 (m, 1H), 6.63 (d, J = 7.3 Hz, 1H,), 4.88 (s, 2H), 3.74–3.63 (m, 4H), 3.46 (s, 3H), 2.99–2.89 (m, 4H),1.59 (m,9H).

tert-Butyl 3-methyl-2-oxo-2,3,7,8,10,11-hexahydro-1*H*,9*H*-azepino[4'5':4,5]pyrrolo[1,2,3-de]quinoxaline-9-carboxylate (153 mg, 0.43 mmol) was dissolved in THF (20 mL). 1.0 M BH_3·THF (2.1 mL, 2.1 mmol) was added dropwise. The reaction mixture was refluxed for 2 h and then cooled to room temperature. 5M HCl (12 mL) was added dropwise. After the bubbling ceased, the reaction was heated to reflux for 30 min, and then cooled to 0 °C. 50% NaOH was added dropwise until pH = 14. The mixture was extracted with $CHCl_3$ (3 × 20 mL). The combined organic phase was washed with brine, dried, and concentrated under vacuum to afford a light-brown oil (190 mg). This crude material was dissolved in dioxane (4 mL) and 1 M NaOH (2 mL), and then $(Boc)_2O$ (143 mg, 6.6 mmol) was added. The solution was stirred for 18 h, and then concentrated under reduced pressure. The residue was treated with EtOAc (20 mL) and brine (20 mL) and stirred for 10 min. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with brine, dried, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with 30% acetone in hexane to afford cis-(*tert*-butyl 3-methyl-2,3,6b,7,8,10,11,11a-octahydro-1*H*,9*H*-azepino[4',5':4,5]pyrrolo[1,2,3-de]quinoxaline-9-carboxylate) (120 mg, 81% yield) of as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.70–6.55 (m, 1H), 6.5–6.4 (m, 1H), 6.37 (d, J = 7.7 Hz, 1H), 3.9–3.8 (m, 4H), 3.7–3.1 (m, 9H), 2.1–1.7 (m, 4H), 1.46 (s, 9H).

cis-(*tert*-Butyl (6b*S*,11a*S*)-3-methyl-2,3,6b,7,8,10,11,11a-octahydro-1*H*,9*H*-azepino[4',5':4,5]pyrrolo-[1,2,3-de]quinoxaline-9-carboxylate) (115 mg, 0.33 mmol) was dissolved in 20% TFA in CH_2Cl_2 (3 mL)

at room temperature. The reaction was stirred at room temperature for 2.5 h. Ice chips were added to the reaction, and then the mixture was basified with 50% NaOH until pH = 14. Brine (5 mL) was added and then the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phase was washed with brine, dried, and concentrated under vacuum to afford *cis*-(3-methyl-2,3,6b,7,8,10,11,11a-octahydro-1*H*,9*H*-azepino[4',5':4,5]pyrrolo[1,2,3-*de*]quinoxaline) (84.1 mg, 105% yield) as a viscous oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.64–6.59 (m, 1H), 6.48 (d, J = 7.3 Hz, 1H), 6.37 (d, J = 7.7 Hz, 1H), 3.7–3.4 (m, 4H), 3.3–2.6 (m, 10H), 2.2–1.7 (m, 4H). MS (ESI) *m/z* 244.2 $[M+H]^+$.

A suspension of *cis*-(3-Methyl-2,3,7 ,8,9 ,10,11,11a-octahydro-1*H*,6b*H*-azepino[4',5':4,5]pyrrolo[1,2,3-de]quinoxaline) (72 mg, 0.30 mmol), 4-chloro-4'-fluorobutyrophenone (119 mg, 0.59 mmol), KI (49 mg, 0.30 mmol), and DIPEA(383 mg, 3.0 mmol) in dioxane (2.5 mL) was stirred at 96 °C for 18 h. The reaction was cooled to room temperature and then concentrated. The residue was purified by silica gel column chromatography eluting with a gradient of 5–10% MeOH in CH_2Cl_2 to afford the racemate of the title compound (37.5 mg, 31 % yield) as an oil. The title compound was obtained by chiral HPLC separation on a Chiralcel OD column with 8% EtOH-Hexane as the eluent. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.1–7.9 (m, 2H), 7.2–7.1 (m, 2H), 6.7–6.6 (m, 1H), 6.5–6.3 (m, 2H), 3.8–2.7 (m, 19H), 2.3–1.9 (m, 4H). MS (ESI) *m/z* 408.3 $[M+H]^+$.

*(6bR,11aR)-4-(3-Methyl-2,3,6b,7,8,10,11,11a-octahydro-1H,9H-azepino[4',5':4,5]pyrrolo[1,2,3-de]quinoxalin-9-yl)-1-(4-fluorophenyl)-1-butanone (**56**, R_4 = H, R_5 =H, m = 1, n = 2, a = R, b = R, X = CH_2).* This compound is the enantiomer of **55** and was obtained during the chiral HPLC separation of the racemate on a Chiralcel OD column with 8% EtOH-hexane as the eluent. MS (ESI) *m/z* 408.3 $[M+H]^+$.

*(6bR,10aS)-1-(4-fluorophenyl)-4-(1,3-dimethyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]-pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-butanone (**57**, R_4 = H, R_5 = Me, m = 1, n = 1, a = R, b = S, X = N-Me).*

To a solution of ethyl 2-oxo-2,3,9,10-tetrahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline-8(7*H*)-carboxylate (**8**, R_1 = H) (500 mg, 1.67 mmol) in DMF (20 mL) was added NaH (147 mg, 3.6 mmol) and MeI (0.25 mL, 4.0 mmol) at room temperature. The reaction mixture was stirred at 25 °C for 3 h, and then diluted with water (30 mL) and extracted with EtOAc (2x30 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to afford ethyl 1,3-dimethyl-2-oxo-2,3,9,10-tetrahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline-8(7*H*)carboxylate (350 mg, 64% yield) as an oil. ^{1}H NMR ($CDC1_3$, 300 MHz) δ 7.18 (d, J = 7.7 Hz, 1H), 7.01 (t, J = 7.7 Hz, 1H), 6.63 (d, J = 7.7 Hz, 1H), 4.90 (m, 1H), 4.51 (m, 1H), 3.20 (m, 5H), 3.49 (m, 1H), 3.42 (s, 3H), 2.91 (m, 1H), 2.80 (m, 1H), 1.61 (d, J = 7.0 Hz, 3H), 1.28 (t, J = 7.3 Hz, 3H). MS (ESI) *m/z* 328 $[M+H]^+$.

The subsequent synthetic procedure is the same as the procedure described in the synthesis of compound **58**. (*cis*)-1-(4-fluorophenyl)-4-(1,3-dimethyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]-pyrrolo-[1,2,3-*de*]quinoxalin-8(7*H*)-yl)-1-butanone was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89 (m, 2H), 7.15 (t, J = 8.4 Hz, 2H), 6.62 (d, J = 7.3 Hz, 1H), 6.51 (d, J = 7.4 Hz, 1H), 6.39 (d, J = 7.4 Hz, 1H), 3.86 (s, 3H), 3.65 (m, 4H), 3.63 (m, 1H), 3.52 (m, 4H), 3.15 (m, 4H), 2.17 (m, 2H), 1.81 (m, 1H), 1.21 (m, 3H), 1.13 (d, J = 6.2 Hz, 3H). MS (ESI) *m/z* 408 $[M+H]^+$. This racemate was then resolved by chiral HPLC on a Chiralcel AD column eluting with 90% acetonitrile/isopropanol as the mobile phase to afford the title compound.

*(6bR,10aS)-1-(4-Fluorophenyl)-4-(1,1,3-trimethyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]-pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-butanone (**58**, R_4 = Me, R_5 = Me, m = 1, n = 1, a = R, b = S, X = N-Me).*

NaH (60% dispersion in mineral oil, 172 mg, 4.3 mmol) and MeI (0.25 mL, 4.0 mmol) were added to a solution of ethyl 2-oxo-2,3,9,10-tetrahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline-8(7*H*)-

carboxylate (**8**, R_1 = H) (360 mg, 1.2 mmol) in DMF (20 mL) at room temperature. The reaction was stirred at 25 °C for 6 h, and then diluted with water (30 mL). The mixture was extracted with EtOAc (2 × 30 mL). The combined extracts were dried over $MgSO_4$ and purified by column chromatography to afford ethyl 1,1,3-trimethyl-2-oxo-2,3,9,10-tetrahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline-8(7*H*)carboxylate (370 mg, 90%) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, J = 7.7 Hz, 1H), 7.01 (t, J = 7.7 Hz, 1H), 6.63 (d, J =7.7 Hz, 1H), 4.69 (s, 2H), 4.23 (m,2H), 3.86 (m, 2H), 3.43 (s, 3H), 3.01 (m, 2H), 1.81 (s, 6H), 1.24 (t, J = 7.3 Hz, 3H).

To a solution of ethyl 1,1,3-trimethyl-(2-oxo)-2,3,9,10-tetrahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline-8(7*H*)-carboxylate (240 mg, 0.70 mmol) in THF (2 mL) was added 1.0M BH_3·THF complex (0.70 mL, 0.70 mmol) at 25 °C. The mixture was stirred at 80 °C for 5 h, cooled to room temperature, and then 6 N HCl (10 mL) was added. The reaction mixture was stirred for an additional hour, water (30 mL) was added, and then extracted with EtOAc (2 × 30 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to give ethyl 1,1,3-trimethyl-2,3,9,10,-tetrahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline-8(7*H*)-carboxylate (152 mg, 66% yield) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.01 (t, J = 7.7 Hz, 1H), 6.97 (d, J = 7.7 Hz, 1H), 6.41 (d, J = 7.7 Hz, 1H), 4.68 (s, 2H), 4.23 (m, 2H), 3.84 (m, 2H), 3.11 (m, 2H), 2.99 (s, 3H), 1.54(s, 6H), 1.27 (t, J = 7.3 Hz, 3H).

To a solution of ethyl 1,1,3-trimethyl-2,3,9,10-tetrahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline-8(7*H*)-carboxylate (69 mg, 0.21 mmol) in TFA (2 mL) was added $NaCNBH_3$ (53 mg, 0.84 mmol) at 0 °C. The reaction was stirred at room temperature for 4 h. TFA was removed by blowing with N_2. Water (10 mL) was added and the mixture was extracted with EtOAc (2 × 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated to afford *cis*-(ethyl 1,1,3-trimethyl-2,3,6b,9,10,10a-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7*H*)-carboxylate) (45 mg, 65% yield) as an oil, which was used directly in the next step without further purification. MS (ESI) *m/z* 330 $[M+H]^+$.

To a solution of *cis*-(ethyl 1,1,3-trimethyl-2,3,6b,9,10,10a-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7*H*)-carboxylate) (8 mg, 0.024 mmol) in *n*-butanol (5 mL) was added KOH (50 mg, 0.89 mmol) at room temperature. The mixture was stirred at 120 °C for 20 h, and then diluted with water (10 mL) and extracted with EtOAc (2 × 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated under vacuum to afford (*cis*)-1,1,3-trimethyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline (5 mg, 81% yield). MS (ESI) *m/z* 258 $[M+H]^+$.

To a solution of (*cis*)-1,1,3-trimethyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline (82 mg, 0.32 mmol) in dioxane (10 mL) was added 4-chloro-4'-fluorobutyrophenone (83 mg, 0.41 mmol), K_2CO_3 (100 mg) and KI (30 mg) at room temperature. The mixture was stirred at 25 °C for 24 h, and then diluted with water (30 mL) and extracted with EtOAc (2 × 30 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford (*cis*)-1-(4-fluorophenyl)-4-(1,1,3-trimethyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]-pyrrolo[1,2,3-*de*]quinoxalin-8(7*H*)-yl)-1-butanone (58 mg, 43% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01(m, 2H), 7.15 (t, J = 7.7 Hz, 2H), 6.65 (d, J = 7.7 Hz, 1H), 6.51 (d, J = 7.0 Hz, 1H), 6.43 (d, J = 7.0 Hz, 1H), 3.63 (m, 1H), 3.25 (d, J = 11Hz,1H), 3.09 (m, 2H), 2.89 (s, 3H), 2.63 (m, 2H), 2.25 (m, 2H), 2.17(m, 2H), 1.31 (s, 3H), 1.12 (s, 3H). MS (ESI) m/z 422 $[M+H]^+$. This racemate was then resolved by chiral HPLC on a Chiralcel AD column eluting with 50% ethanol/methanol solvent system to afford the title compound.

Compounds **59**–**61** and **63**–**65** were prepared in an analogous fashion following the procedure described in the synthesis of compound **62**.

*4-((7aS,11aR)-5,6,8,9,11,11a-Hexahydro-4H,7aH-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline-10(7aH)-yl)-1-(4-fluorophenyl)-1-butanone (**59**, R_4 = H, R_5 = H, m = 1, n = 1, a = R, b = S, X = CH_2).* ^{1}H NMR

($CDCl_3$, 300 MHz) δ 8.08–7.90 (m, 2H), 7.12 (t, J = 8.6 Hz, 2H), 6.86 (d, J = 7.3 Hz, 2H), 6.62 (t, J = 7.3 Hz, 1H), 3.32–3.18 (m, 2H), 3.15–3.05 (m, 1H), 2.99 (t, J = 7.2 Hz, 2H), 2.90–2.78 (m, 1H), 2.78–2.60 (m, 3H), 2.60–2.48 (m, 1H), 2.48–2.35 (m, 2H), 2.35–2.20 (m, 1H), 2.20–1.75 (m, 7H). MS (ESI) *m/z* 379.1 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{24}H_{28}FN_2O$ $[M+H]^+$: 379.2186; found: 379.2182. UPLC purity: 98.5%; retention time: 2.24 min (method A).

*4-((7aR,11aS)-5,6,8,9,11,11a-Hexahydro-4H,7aH-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline-10(7aH)-yl)-1-(4-fluorophenyl)-1-butanone (**60**, R_4 = H, R_5 = H, m = 1, n = 1, a = S, b = R, X = CH_2).* This compound is the enantiomer of compound **59**. Its NMR spectrum is identical to that of **59**. MS (ESI) *m/z* 379.1 $[M+H]^+$.

*4-((6aS,10aR)-4,5,7,8,10,10a-Hexahydro-6aH-pyrido[4,3-b]pyrrolo[3,2,1-hi]indol-9-yl)-1-(4-Fluoro-phenyl)-butan-1-one (**61**, R_4 = H, R_5 = H, m = 0, n = 1, a = R, b = S, X = CH_2).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03–7.90 (m, 2H), 7.01(t, J = 7.0 Hz, 2H), 6.90 (s, 1H), 6.85 (s, 2H), 3.65–3.59 (m, 1H), 3.42–3.25 (m, 2H), 3.20–3.02 (m, 2H), 2.99 (t, J = 7.0 Hz, 2H), 2.85–2.72 (m, 1H), 2.72–2.62 (m, 2H), 2.52–2.30 (m, 3H), 2.19 (t, J = 10.9 Hz, 1H), 2.02–1.80 (m, 2H), 1.70–1.80 (m, 2H). MS (ESI) m/z 365.3 $[M+H]^+$.

*4-((6bR,10aS)-1,2,6b,9,10,10a-Hexahydro-7H-3-thia-8,10b-diaza-fluoranthen-8-yl)-1-(4-Fluoro-phenyl)-butan-1-one (**63**, R_4 = H, R_5 = H, m = 1, n = 1, a = R, b = S, X =S)* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01–7.26 (m, 2 H), 7.12 (t, J = 8.4 Hz, 2H), 6.81(t, J = 7.7 Hz, 2H,), 6.19 (t, J = 7.6 Hz, 1H), 3.62–3.38 (m, 2H), 3.37–3.25 (m, 1H), 3.20–2.85 (m, 5H), 2.85–2.70 (m, 1H),2.70–2.50 (m, 1H), 2.68–2.45 (m, 2H), 2.20 (dt, J = 3.0, 11.4 Hz, 1H), 2.10–1.70 (m, 5H). MS (ESI) *m/z* 397.2 $[M+H]^+$.

*4-((6bR,10aS)-1,2,6b,9,10,10a-Hexahydro-7H-3-oxa-8,10b-diaza-fluoranthen-8-yl)-1-(4-Fluoro-phenyl)--butan-1-one (**64**, R_4 = H, R_5 =H, m = 1, n = 1, a = R, b = S, X = O).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.00–7.94 (m, 2H), 7.11–7.08 (m, 2H), 6.70–6.58 (m, 3H), 4.43–4.39 (m, 2H), 3.23–3.17 (m, 4H), 3.09–2.97 (m, 4H), 2.80–2.66 (m, 2H), 2.52–2.37 (m, 2H), 2.10–1.90 (m, 4H). ^{13}C NMR (DMSO-d_6, 126 MHz) δ 197.3, 165.0 (d, J_{CF} = 252 Hz), 143.2, 137.5, 133.2, 130.9 (d, J_{CF} = 9 Hz), 129.9, 120.4, 116.2, 115.7 (d, J_{CF} = 21.9 Hz), 113.4, 66.3, 63.3, 55.5, 51.9, 47.3, 44.0, 38.0, 35.4, 21.4, 17.8. MS (ESI) *m/z* 381.3 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{23}H_{26}FN_2O_2$ $[M+H]^+$: 381.1978; found: 381.1986. UPLC purity: 99.9%; retention time: 2.04 min (method A).

*(6bS, 11aS)-4-(1,2,6b,7,8,10,11,11a-Octahydro-9H-azepino[4,5-b][1,4]oxazino[2,3,4-hi]indol-9-yl)-1-(4-fluorophenyl)-1-butanone (**65**, R_4 = H, R_5 = H, m = 1, n = 2, a = R, b = S* Starting from 2,3-dihydro-4*H*-1,4-benzoxazin-4-amine and azepan-4-one, (6b*S*, 11a*S*)-1,2,6b,8,9,10,11,11a-octahydro-7*H*-azepino[4,5-*b*][1,4]oxazino[2,3,4-*hi*]indole was prepared in analogous fashion following the procedure of steps a–e described in the synthesis of **62**, yielding an amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.67–6.57 (m, 3H), 4.43–4.39 (m, 2H), 3.69–3.61 (m, 1H), 3.45 (dt, J =3.3,9.2 Hz, 1H), 3.24–3.00 (m, 3H), 2.89–2.69 (m, 3H), 2.16–2.02 (m, 2H), 1.97–1.83 (m, 2H). The obtained (6b*S*, 11a*S*)-1,2,6b,8,9,10,11,11a-octahydro-7*H*-azepino[4,5-*b*][1,4]oxazino[2,3,4-*hi*]indole was reacted with 4-chloro-4'-fluoro-butyrophenone following the procedure described in the last step of the synthesis of **62**, to give the title compound. MS (ESI) *m/z* 395 $[M+H]^+$.

Table S-1. Receptor binding profiles of **5** and **31**[a]

Target	Assay ID	**5** (ITI-007)	**31**
Adenosine Transporter (h)	100-0001	7.58%	11.23%
Adenosine, A1	100-0002	10.78%	6.73%
Adenosine, A2A (h)	100-0003	11.40%	10.92%
Adrenergic, Alpha 1A	100-0005	66.06%	59.11%
Adrenergic, Alpha 1B	100-0006	85.43%	73.09%
Adrenergic, Alpha 2A (h)	100-0007	27.81%	18.80%
Adrenergic, Alpha 2B	100-0008	9.09%	13.74%
Adrenergic, Alpha 2C (h)	100-0009	32.08%	37.93%
Adrenergic, Beta 1 (h)	100-0010	11.09%	-1.06%
Adrenergic, Beta 2 (h)	100-0011	12.69%	6.41%
Dopamine Transporter	100-0015	8.45%	-0.95%
Dopamine, D1 (h)	100-0016	65.97%	42.14%
Dopamine, D2s (h)	100-0017	45.95%	28.74%
Dopamine, D3	100-0018	25.30%	18.79%
Dopamine, D4.4 (h)	100-0019	64.27%	45.41%
GABA A, Agonist Site	100-0021	-0.93%	-7.00%
GABA A, BDZ, alpha 1 site	100-0022	-1.64%	1.07%
GABA-B	100-0024	1.44%	-8.00%
Glutamate, AMPA Site (Ionotropic)	100-0026	-14.72%	-3.78%
Glutamate, Kainate Site (Ionotropic)	100-0027	0.93%	-10.48%
Glutamate, MK-801 Site (Ionotropic)	100-0028	4.03%	1.90%
Glutamate, NMDA Agonist Site (Ionotropic)	100-0029	-5.16%	-1.47%
Glutamate, NMDA, Phencyclidine Site (Ionotropic)	100-0031	-16.42%	-5.71%
Glutamate,NMDA,Glycine (Stry-insens Site) (Ionotropic)	100-0032	-16.33%	4.90%
Glycine, Strychnine-sensitive	100-0033	-11.11%	1.11%
Histamine, H1	100-0034	5.33%	11.63%
Histamine, H2	100-0086	1.61%	12.28%
Histamine, H3	100-0035	10.66%	17.01%
Muscarinic, M1 (hr)	100-0038	3.40%	9.70%
Muscarinic, M2 (h)	100-0039	2.09%	11.98%
Muscarinic, M3 (h)	100-0040	19.29%	9.81%
Muscarinic, M4 (h)	100-0041	-3.08%	7.40%
Muscarinic, M5 (h)	100-0042	9.06%	6.33%
Nicotinic, Neuronal (a-BnTx insensitive)	100-0046	10.53%	4.53%
Norepinephrine Transporter	100-0048	2.37%	-6.34%
Opioid, Delta 2 (h)	100-0049	-5.20%	-9.59%
Opioid, Mu (h)	100-0051	-0.69%	-0.54%
Serotonin Transporter	100-0056	75.61%	74.46%
Serotonin, 5-HT1A (h)	100-0057	31.18%	4.09%
Serotonin, 5-HT1D	100-0058	11.45%	13.85%
Serotonin, 5-HT2A	100-0059	99.08%	106.05%
Serotonin, 5-HT2C	100-0060	-12.54%	-19.84%
Serotonin, 5-HT3	100-0061	9.08%	10.47%
Serotonin, 5-HT4	100-0062	17.56%	22.25%
Serotonin, 5-HT5A (h)	100-0063	2.89%	13.93%
Serotonin, 5-HT6 (h)	100-0064	15.84%	13.96%
Serotonin, 5-HT7 (h)	100-0065	23.60%	35.26%
Sigma 1	100-0066	-0.48%	15.23%
Sigma 2	100-0067	16.40%	25.35%
Calcium Channel, Type L (Dihydropyridine Site)	100-0013	-5.09%	-12.39%
Calcium Channel, Type N	100-0014	3.86%	5.36%
GABA, Chloride, TBOB Site	100-0023	2.30%	15.09%
Potassium Channel, ATP-Sensitive	100-0052	17.51%	12.35%
Potassium Channel, Ca2+ Act., VI	100-0054	17.17%	9.13%
Potassium Channel, I[Kr] (hERG) (h)	100-0330	23.32%	10.70%
Sodium, Site 2	100-0069	18.46%	21.29%
Nitric Oxide, NOS (Neuronal-Binding)	100-0089	-3.88%	5.25%
Leukotriene, LTB4 (BLT)	100-0036	1.10%	12.56%
Leukotriene, LTD4 (CysLT1)	100-0037	6.34%	26.92%
Thromboxane A2 (h)	100-0070	13.72%	7.17%
Angiotensin II, AT1 (h)	100-0084	-3.82%	-4.50%
Bradykinin, BK2	100-0012	-7.87%	12.35%
Endothelin, ET-A (h)	100-0085	15.56%	14.38%
Neurokinin, NK1	100-0044	-1.87%	-3.50%
Neuropeptide, NPY2 (h)	100-0045	-0.85%	9.81%
Esterase, Acetylcholine	200-0083	4.61%	3.12%

[a]Compounds were profiled at a concentration of 100 nM in duplicate against a panel of receptors, transporters, ion channels and enzymes. The data are reported as percent inhibition. Additional information about the General SEP II panel can be found on the PerkinElmer website (http://www.perkinelmer.com/Catalog/Category/ID/General%20SEP%20II).

In vitro Binding assays

Compounds were dissolved at 10 mM in DMSO fresh each day and serially diluted in binding buffer leaving no more than 1% DMSO, a concentration without influence on binding. Generally eight concentrations of inhibitor were tested in triplicate and the IC50 inhibition values were corrected to K_i affinity values using the Cheng-Prusoff relationship.[1] The reported Ki or percentage of inhibition values are the means of at least two determinations

5-HT$_{2A}$ and 5-HT$_{2C}$ receptors radioligand binding assays. Measurement of binding affinity for serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors was conducted using a method described in the literature.[2] Human full-length recombinant serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors were expressed in human embryonic kidney HEK-293E cells. Membranes were prepared from these cells and evaluated with (±)-1-(2,5-dimethoxy-4-[^{125}I]iodophenyl)-2-aminopropane (^{125}DOI) as the radioligand. We have compared values in the DOI assay, which is an agonist of 5-HT$_{2A}$ receptors, with assays performed in an identical manner, but with [3H]-Ketanserine as the radioligand. Ketanserine is an antagonist of this receptor system. Comparing the agonist and antagonist assays, we have never seen values varying greater than four-fold.

Dopamine D$_2$ receptor binding assay. The binding affinity against membranes prepared from CHO cells expressing recombinant rat D2 short receptor was performed using [^{3}H]-N-methylspiperone as the radioligand as detailed by Lee et al.[3] We have confirmed these results with measurements of [^{3}H]-sulpiride binding to rat striatal membranes according to the procedure of Imafuku with 5 mM $MgCl_2$ and 0.02% sodium ascorbate included in the binding assay.[4] We find the two measurements, recombinant versus endogenous rat striatal receptor, agree within K_i values of ~50%. For the broad off-target screen, D2 receptor binding affinities were measured using membranes prepared from human recombinant dopamine D$_2$ short receptor expressed in CHO cells, using [^{3}H]-Raclopride as the radioligand as conducted at Caliper-PerkinElmer (assay ID: 100-1006; link: http://www.perkinelmer.com/Catalog/Product/ID/100-1006). [^{3}H] Raclopride (70-90 Ci/mmol) at a concentration or 0.7 nM (the Km value) was incubated with membrane preparations in 50 mM TRIS-HCl (pH 7.4) containing 120 mM NaCl, 5 mM KCl, 5 mM $MgCl_2$, 1 mM EDTA for 90 minutes at 25 °C. The reaction was terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters was determined and compared to control values. Non-specific binding was determined by including 1 mM unlabeled haloperidol.

Serotonin transporter binding assay. The binding affinity of synthesized compounds against serotonin transporter was determined by a radioligand displacement method.[5,6] [^{3}H]-*N*-Methyl-citalopram was used as a radioligand. The assay was conducted by Caliper-PerkinElmer (assay ID: 100-0099; link: http://www.caliperls.com/products/transporter-sert-h.htm). In this assay [^{3}H] N-methyl-citalopram (70-87 Ci/mmole) was used at 0.7 nM with membranes prepared from human platelets with a receptor density of 425 fmol/mg protein. Non-specific binding was determined in the presence of 10 μM unlabeled imipramine. Standard reference compounds were tested in parallel. The reported Ki or percentage of inhibition values are the means of at least two determinations. Under these conditions citalopram has a Ki value of 3.0 nM. Binding reactions were carried out in 50 mM TRIS-HCl (pH 7.4), containing 120 mM NaCl and 5 mM KCl at 25 °C for 60 minutes. The reaction was terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters was determined using liquid scintillation spectrometry.

Homology modeling and docking studies

The amino acid sequences of human dopamine receptors (D2R and D3R) were retrieved from the Uniprot database (http://www.uniprot.org, Uniprot IDs: human D2R, P14416; human D3R, P35462). Sequence alignment (Figure S-1) was performed using ClustalW2 (http://www.ebi.ac.uk) with all settings set to the default. The sequence identity is 53% between these two dopamine receptors. It can be seen from Figure S-1 that residues in the transmembrane (TM) domains are well conserved, while those in the other regions are more diverse. Two pairs of disulfide bonds found in the D3R crystal structure are both conserved in D2R. One disulfide bond ($Cys103^{3.25}$–$Cys181^{ECL2}$, numbers in superscript correspond to the Ballesteros–Weinstein numbering system for conserved GPCR residues[7]) occurs between TM3 and extracellular loop 2 (ECL2), and the other (Cys399-Cys401) falls within ECL3.

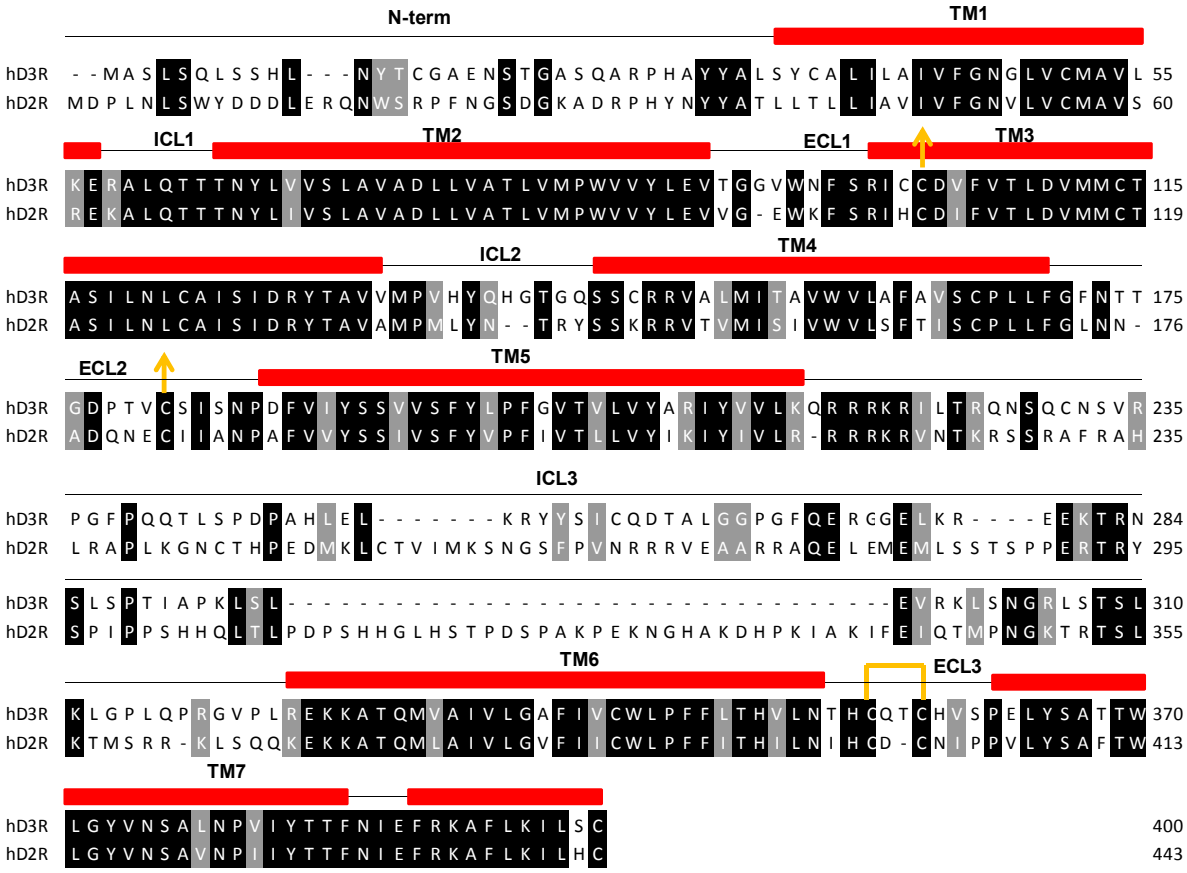

Figure S-1: Sequence alignment of human dopamine receptors D2R and D3R. The alignment is shown using Multiple Align Show (http://www.bioinformatics.org/sms/multi_align.html). Identical and similar residues are shown in black and gray, respectively. TM: transmembrane domain; ICL: intracellular loop domain; ECL: extracellular loop domain. The red cylinders at the top denote the helix regions in the D3R X-ray structure. Two disulfide bonds that exist in the D3R crystal structure are shown in orange lines.

The three-dimensional models of D2R were built using the coordinates of the D3R crystal structure (PDB ID: 3PBL[8]) as the template. Since the intracellular loop 3 (ICL3, Lys221–Gly319) is distant from the ligand-binding site of dopamine receptors, and is replaced by the T4-lysozyme in the D3R crystal structure, the ICL3 was not included in the structural models of D2R. The conserved disulfide bonds and the crystal ligand eticlopride were maintained as constraints for geometric optimization. The same boundaries of the TM domains were applied to the D2R as identified in the X-ray crystal structure for the D3R. All proce-

dures for the homology modeling were carried out with MOE2010 (Chemical Computing Group, Montreal, Quebec, Canada). Twenty-five candidate models were generated for D2R, and then optimized using the OPLS-AA force field. The one with the lowest energy was chosen for the docking studies using the GOLD docking program (version 4.0, Cambridge Crystallographic Data Centre, Cambridge, UK)[9]. All compounds were constructed with MOE2010 and protonated on basic nitrogen atoms. Energy minimization using the MMFF force filed was then applied to the protonated forms for the geometry optimization. The minimized conformations were docked to the active site of the D2R homology model. The docked conformations with the highest GOLD scores were chosen for analyses of binding poses.

The binding model of compound **5** to human D2R is shown in Figure S-2. Compound **5** occupies the binding pocket defined by sidechains of TM1, TM2, TM3, TM5, TM6 and TM7. As expected, the basic nitrogen of compound **5** forms a salt bridge with Asp114$^{3.32}$, which is conserved in most of monoaminergic G-protein coupled receptors. The butyrophenone group is buried in the pocket surrounded by sidechains of residues in TM3 (Val115, Cys118 and Thr119), TM5 (Ser193, Ser197 and Phe189) and TM6 (Trp386, Phe389 and Phe390), while the tetracyclic core interacts with residues from TM1 (Ser4), TM2 (Val91, Leu94 and Glu95) and TM7 (Tyr408 and Ser409). The butyryl linker forms hydrophobic contacts with the sidechains of Val118 (TM3), Ile184 (ECL2) and Phe389 (TM6). The carbonyl group has an electrostatic interaction with the sidechain of His393 (TM6).

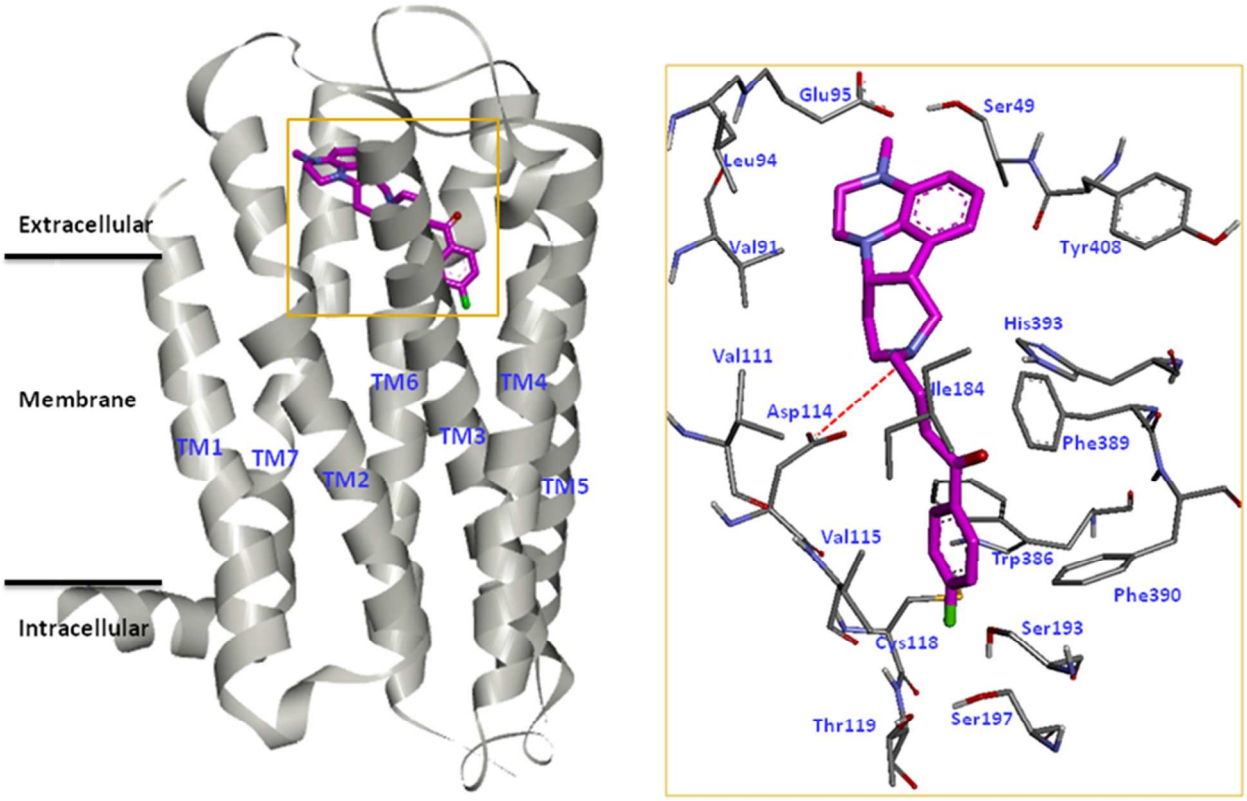

Figure S-2: Binding model of compound **5** to the human dopamine D_2 receptor. Left: the overall structure of the human D2R in complex with **5**. Compound **5** is shown as a stick model and the D2R is shown in gray ribbon. Nitrogen: blue; Oxygen: red; Carbon: magenta. The transmembrane domains 1–7 are labeled as TM1–7. Right: Close-up view of the compound **5** – D2R interactions. Amino acids of the D2R in close contact with **5** are displayed as the stick model and labeled accordingly. Carbon is colored as gray and the same color schemes as the left panel are used for oxygen and nitrogen atoms. The salt bridge between Asp114 and the basic nitrogen of **5** is shown in red dash line.

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