3-[(2*R*)-Amino-2-phenylethyl]-1-(2,6-difluorobenzyl)-5-(2-fluoro-3-methoxyphenyl)- 6-methylpyrimidin-2,4-dione (NBI 42902) as A Potent and Orally Active Antagonist of the Human Gonadotropin-Releasing Hormone Receptor– Design, Synthesis and *in vitro* and *in vivo* Characterization

Fabio C. Tucci,[1] Yun-Fei Zhu,[1] R. Scott Struthers,[2] Zhiqiang Guo,[1] Timothy D. Gross,[1] Martin W. Rowbottom,[1] Oscar Acevedo,[1] Yinghong Gao,[1] John Saunders,[1] Qiu Xie,[2] Greg J. Reinhart,[2] Xin-Jun Liu,[2] Nicholas Ling,[1] Anne K. L. Bonneville,[3] Takung Chen,[3] Haig Bozigian,[3] and Chen Chen*,[1]

[1]Department of Medicinal Chemistry, [2]Department of Endocrinology and [3]Department of Preclinical Development

Neurocrine Biosciences, Inc. 12790 El Camino Real, San Diego, CA 92130, USA

The following compounds **13a-e** and **14a-b** were synthesized in a manner similar to the procedure described for *R*-**13b** from **10**.

3-[(2*S*)-Amino-2-phenylpropyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(2-fluoro-3-methoxyphenyl)pyrimidin-2,4-dione hydrochloride (*S*-13a). white powder; ^{1}H NMR (DMSO-d_6): 2.11 &2.12 (s, 3H), 2.46 (m, 1H), 2.59 (m, 1H), 3.20 (m, 1H), 3.79 (d, *J* = 7.2Hz, 2H), 3.84 & 3.85 (s, 3H), 5.22 (m, 2H), 6.74 (m, 1H), 7.15 (m, 7H), 7.26 (m, 2H), 7.41 (m, 1H). ^{19}F NMR: -115.9 (m, 2F), -136.1 & -136.2 (dd, *J* = 5.6, 7.5Hz); ^{13}C NMR (DMSO-d_6): 17.4, 38.6, 41.9, 47.0, 50.4 & 50.5, 56.0, 106.8, 111.9 (m, 2C), 112.3 (t, *J* = 15.0Hz), 113.4, 122.6 (d, *J* = 13.7Hz), 123.7, 124.0 (d, *J* = 3.8Hz), 125.8, 128.1 (s, 2C), 129.0 (s, 2C), 129.9 (t, *J* = 10.6Hz), 139.2 &139.3, 147.3 (d, *J* = 10.6Hz), 149.5 (d, *J* = 242Hz), 150.42 & 142.47 (s), 151.13 &151.19 (s), 160.6 (dd, *J* = 8.3, 245.7Hz), 160.69 & 160.73 (s); MS: 510 (MH^+).

3-[(2*S*)-Amino-2-phenylethyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(2-fluoro-3-methoxyphenyl)pyrimidin-2,4-dione hydrochloride (*S*-13b). white powder. ^{1}H NMR: 2.05 & 20.6 (s, 3H), 3.83 & 3.85 (s, 3H), 3.95 & 4.20 (m, 1H), 4.50 (m, 2H), 4.72- 5.48 (m, 2H), 6.80-7.60 (m, 11H), 8.82 (brs, 2H); MS: 496 (MH^+); Anal. for $C_{27}H_{24}F_3N_3O_3xHClxH_2O$: C, H, N.

3-[(2*R*)-Amino-4-methylpentyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(2-fluoro-3-methoxyphenyl)pyrimidin-2,4-dione hydrochloride (*R*-13c). white powder. ^{1}H NMR: 0.82 (d, *J* = 5.2Hz, 3H), 0.90 (t, *J* = 5.2Hz, 3H), 1.55 (m, 1H), 1.61 (m, 2H), 2.09 & 2.12 (s, 3H), 3.53 (m, 1H), 3.83 & 3.85 (s, 3H), 3.96-4.43 (m, 2.5H), 5.20-5.52 (m, 2.5H), 6.89 (m, 3H), 7.09 (m, 1H), 7.17 (m, 1H), 7.23 (m, 1H), 8.25 (brs, 3H); MS: 476 (MH^+).

3-[(2*R*)-Amino-2-cyclohexylethyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(2-fluoro-3-methoxyphenyl)pyrimidin-2,4-dione hydrochloride (*R*-13d). white powder. ^{1}H NMR (DMSO-d_6): 1.11 (m, 5H), 1.50-1.77 (m, 6H), 2.20 & 2.21 (s, 3H), 3.17 (m, 1H), 3.86 (s, 3H), 3.93 (m, 1H), 4.02 (m, 1H), 5.24 (m, 2H), 6.78 (m, 1H), 7.11 (t, *J* = 8.4Hz, 2H), 7.18 (m, 2H), 7.42 (m, 1H), 7.94 (br, 2H). ^{13}C NMR (DMSO-d_6): 17.6 & 17.7, 25.5, 25.6 (2C), 27.2 & 27.3 (2C), 27.8 & 27.9, 38.5 & 38.6, 41.2 & 41.3, 53.9 & 54.0, 55.9 & 56.0, 106.9 & 107.0, 111.8 (m, 2C), 112.1 (t, *J* = 17.4Hz), 113.4 & 113.5, 122.3 (d, *J* = 13.7Hz), 123.6 (d, *J* = 17.4Hz), 123.9 & 124.0 (d, *J* = 6.8Hz), 130.0 (t, *J* = 10.6Hz), 147.5 & 147.6, 149.5 (d, *J* = 242.7Hz), 151.0 & 151.1, 151.2 & 151.5, 160.6 (dd, *J* = 7.5, 246.4Hz, 2C), 160.8 & 160.9; MS: 502 (MH^+). Anal. for $C_{27}H_{30}F_3N_3O_3xHClx0.5H_2O$.

3-[(2*R*)-Amino-3-methylbutyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(2-fluoro-3-methoxyphenyl)pyrimidin-2,4-dione TFA salt (*R*-13e). colorless oil, ^{1}H NMR: 0.98 (d, *J* = 6.6Hz, 3H), 1.04 (d, *J* = 6.6Hz, 3H), 2.09 & 2.12 (s, 3H), 3.17-3.22 (m, 1H), 3.86 (s, 3H), 4.04-4.17 (m, 2H), 4.25-4.33 (m, 1H), 5.05 & 5.16 (d, *J* = 16.5Hz, 1H), 5.38 (d, *J* = 16.5Hz, 1H), 6.81-7.13 (m, 6H), 8.10 (brs, 3H); MS *m/z* 462.2 (MH^+).

3-[(2*S*)-Methylamino-3-phenylpropyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(2-fluoro-3-methoxyphenyl)pyrimidin-2,4-dione hydrochloride (*S*-14a). white powder. ^{1}H NMR (DMSO-d_6): 2.11 & 2.12 (s, 3H), 2.62 & 2.63 (s, 3H), 2.76 (dd, *J* = 10.0, 12.8Hz, 1H), 3.16 & 3.17 (dd, *J* = 3.6, 14.0Hz, 1H), 3.33 (s, 3H), 3.79 (m, 1H), 3.92 (dd, *J* = 5.2, 14.0Hz, 1H), 4.13 & 4.15 (dd, *J* = 8.0, 14.0Hz, 1H), 5.11 & 5.12 (d, *J* = 16.4Hz, 1H), 5.16 & 5.17 (d, *J* = 16.4Hz, 1H), 6.72 (m, 1H), 7.09 (t, *J* = 8.4Hz, 2H), 7.16 (m, 2H), 7.27 (m, 5H), 7.40 (m, 1H), 8.93 (brs, 1H), 9.14 (brs, 1H). ^{13}C NMR (DMSO-d_6): 17.5, 29.3 & 29.4, 34.1 & 34.2, 41.0 & 41.1, 56.0, 56.1 & 56.2, 106.9, 111.8 (m, 2C), 112.1, 112.2 (t, *J*= 17.7Hz), 113.4, 122.2 & 122.3 (d, *J* = 6.1Hz), 123.6 & 123.7, 123.9 & 124.0 (d, *J* = 4.5Hz), 126.7, 128. 4 (2C), 128. 9 (2C), 130.0 (t, *J* = 9.9Hz), 136.0 & 136.1, 147.4 (d, *J*= 10.6Hz), 149.5 (d, *J* = 239.7Hz), 150.8 & 150.9, 151.1 & 151.2, 160.6 (dd, *J* = 8.4, 246.5Hz, 2C), 160.7 & 160.8. Anal. Calcd for $C_{29}H_{28}F_3N_3O_3$xHClx0.5H_2O.

3-[(2*R*)-Methylamino-2-phenylethyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(2-fluoro-3-methoxyphenyl)pyrimidin-2,4-dione hydrochloride (*R*-14b). white powder. ^{1}H NMR: 2.10 (s, 3H), 2.35 (s, 3H), 3.72 (s, 3H), 4.25 (d, *J* = 13.6Hz, 1H), 4.55 (m, 1H), 4.76 (dd, *J* = 6.4, 12.8Hz, 1H), 5.16 (d, *J* = 15.2Hz, 1H), 5.27 (d, *J* = 1.2Hz, 1H), 6.77 (d, *J* = 8.0Hz, 1H), 6.85 (t, *J* = 8.0Hz, 2H), 7.16 (m, 1H), 7.22 (m, 1H), 7.34 (m, 4H), 7.53 (m, 2H), 9.26 (brs, 1H), 10.2 (brs, 1H); ^{19}F NMR: -115.2 (t, *J* = 5.6Hz); ^{13}C NMR: 17.08, 31.8, 39.3, 44.3, 55.3, 61.9, 111.8 (m, 2C), 112.1 (t, *J* = 16.7Hz), 113.4, 114.6, 116.6, 123.4, 128.5 (2C), 129.2 (2C), 129.4, 129.5, 129.6 (t, *J* = 10.7Hz), 131.9, 135.4, 149.7, 151.7, 159.4, 161.0 (dd, *J* = 6.8Hz, 248Hz, 2C), 162.6; MS: 510 (MH^+); Anal. for $C_{28}H_{26}F_3N_3O_3$xHClx0.75H_2O: C, H, N.

The following compounds **15a-f** were synthesized in a manner similar to the procedure described for *R*-**15b** from **10**.

3-[(2*S*)-Dimethylamino-2-phenylpropyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(2-fluoro-3-methoxyphenyl)pyrimidin-2,4-dione (*S*-15a). ^{1}H NMR: 2.05 (s, 3H), 2.33 (s, 6H), 2.50-2.58

(m, 2H), 2.92 (dd, *J* = 5.2, 14.1Hz, 1H), 3.88 (s, 3H), 3.97-4.16 (m, 2H), 5.12 & 5.15 (s, 2H), 6.72-6.80 (m, 1H), 6.85-6.98 (m, 3H), 7.06-7.26 (m, 7H). MS *m/z* 538.0 (MH^+).

3-[(2*S*)-Dimethylamino-2-phenylethyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(2-fluoro-3-methoxyphenyl)pyrimidin-2,4-dione hydrochloride (*S*-15b). white powder. ^{1}H NMR: 2.18 (s, 3H), 2.74 (s, 3H), 2.81 (s, 3H), 3.92 (s, 3H), 4.35 & 4.52 (d, 1H), 4.82-5.58 (m, 4H), 6.84-7.48 (m, 11H); MS m/z: 524 (MH^+); Anal. for $C_{29}H_{28}F_3N_3O_3$xHClx1.3H_2O: C, H, N.

3-[(2*S*)-Dimethylamino-4-methylpentyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(2-fluoro-3-methoxyphenyl)pyrimidin-2,4-dione (*S*-15c). colorless oil, ^{1}H NMR: 1.02 (m, 6H), 1.44 (m, 2H), 1.84 (m, 1H), 2.09 & 2.12 (s, 3H), 2.36 (brs, 2H), 2.83 (brs, 6H), 3.88 (s, 3H), 3.82-4.07 (m, 2H), 4.40 (dd, *J* = 10.5, 14.7Hz, 0.5 H), 4.51 (dd, *J* = 11.1, 15.3Hz, 0.5 H), 4.98 (d, *J* = 15.9Hz, 0.5 H), 5.12 (d, *J* = 16.2Hz, 0.5 H), 5.49 & 5.54 (d, *J* = 16.5Hz, 1H), 6.93 (m, 4H), 7.13 (m, 1H), 7.24 (m, 1H); MS m/z 504.2 (MH^+).

3-[(2*R*)-Dimethylamino-3-methylbutyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(2-fluoro-3-methoxyphenyl)pyrimidin-2,4-dione (*R*-15e) TFA Salt. colorless oil, ^{1}H NMR: 1.11 & 1.14 (d, *J* = 3.5 Hz, 3H), 1.22-1.26 (m, 3H), 2.10 & 2.13 (s, 3H), 2.88 (s, 6H), 3.76-3.81 (m, 1H), 3.87 (s, 3H), 3.95-4.08 (m, 2H), 4.51-4.70 (m, 1H), 4.98 & 5.16 (d, *J* = 16.2Hz, 1H), 5.43 & 5.55 (d, *J* = 16.2Hz, 1H), 6.87-6.99 (m, 3H), 7.09-7.15 (m, 1H), 7.24-7.29 (m, 2H); MS *m/z* 490.2 (MH^+).

The following compounds **19b-h** were synthesized in a manner similar to the procedure described for **19a** from *R*-**11b**.

3-[(2*R*)-Amino-2-phenylethyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(3,4-ethylenedioxyphenyl)-pyrimidin-2,4-dione hydrochloride (19b). white powder. ^{1}H NMR (DMSO-d_6): 2.19 (s, 3H), 4.20 (dd, J = 4.8, 10.2Hz, 1H), 4.25 (m, 1H), 4.26 (s, 4H), 4.49 (m, 1H0, 5.16 (d, *J* = 12.6Hz, 1H), 5.18 (d, *J* = 12.6Hz, 1H), 6.54 (m, 2H), 6.86 (d, *J* = 6.0Hz, 1H), 7.12 (m, 2H), 7.37 (s, 5H), 7.42 (m, 1H), 8.68 (brs, 3H); ^{19}F NMR: -115.2 (t, *J* = 7.5Hz,); ^{13}C NMR: 17.7, 38.6, 44.1, 52.4, 64.0, 64.1, 111.8 (m, 2C), 112.3 (t, J = 16.7Hz), 112.5, 116.7, 119.4, 123.7, 127.1, 127.3 (2C), 128.6 (2C), 128.9, 130.0 (t, *J* = 10.6Hz), 134.9, 142.8, 142.9, 149.7, 150.9, 160.6 (dd, *J* = 8.3, 241.1Hz, 2C), 161.3; MS: 506 (MH^+); Anal. for $C_{28}H_{25}F_2N_3O_4$xHClx0.5H_2O: C, H, N.

3-[(2*R*)-Amino-2-phenylethyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(3-methoxyphenyl)pyrimidin-2,4-dione hydrochloride (19c). white powder. ^{1}H NMR: 2.07 (s, 3H), 3.68 (brs, 3H), 3.95 (m, 1H), 4.35 (m, 1H), 4.54 (dd, J = 10.4, 14.4Hz, 1H), 5.17 (brs, 2H),

6.84 (m, 4H), 7.21 (m, 3H), 7.30 (m, 4H), 7.55 (d, *J* = 7.6Hz, 2H), 8.69 (brs, 3H); ^{19}F NMR: -114.9 (s); ^{13}C NMR: 17.7, 39.3, 46.0, 54.5, 55.2, 111.8 (m, 2C), 112.3 (m), 113.7, 114.6, 116.3, 123.5, 127.2 (2C), 128.6, 128.8, 128.9 (2C), 129.6 (t, *J* = 10.0Hz), 134.5, 135.3, 150.0, 152.0, 159.4, 161.1 (dd, *J* = 7.6, 248Hz), 161.8; MS: 478 (MH^+); Anal. for $C_{27}H_{25}F_2N_3O_3xHClx2H_2O$: C, H, N.

3-[(2*R*)-Amino-2-phenylethyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(4-methylthiophenyl)pyrimidin-2,4-dione hydrochloride (19d). white powder. ^{1}H NMR (CD_3OD): 2.23 (s, 3H), 2.50 (s, 3H), 4.38 (dd, *J* = 5.2, 14.0Hz, 1H), 4.47 (dd, *J* = 8.4, 13.6Hz, 1H), 4.67 (dd, *J* = 5.4, 8.4Hz, 1H), 5.28 (d, *J* = 16.0Hz, 1H), 5.36 (d, *J* = 16.0Hz, 1H), 7.02 (t, *J* = 8.8Hz, 2H), 7.08 (d, *J* = 8.0Hz, 2H), 7.30 (d, *J* = 8.8Hz, 2H), 7.38 (m, 1H), 7.42 (s, 5H); ^{19}F NMR: -117.3 (t, *J* = 7.5Hz); ^{13}C NMR: 15.5, 16.2, 40.3, 45.7, 55.2, 112.9 (m, 2C), 113.4 (t, *J* = 16.7Hz), 114.9, 127.3 (2C), 128.3 (2C), 130.3, 131.2 (t, *J* = 10.6Hz), 131.7, 132.4, 135.4, 140.3, 152. 3, 153.1, 162.7 (dd, *J* = 7.6, 250Hz, 2C), 164.0; MS: 494 (MH^+); Anal. for $C_{27}H_{25}F_2N_3O_2SxHClx1.2H_2O$: C, H, N.

3-[(2*R*)-Amino-2-phenylethyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(4-phenoxyphenyl)pyrimidin-2,4-dione hydrochloride (19e). white powder. ^{1}H NMR (DMSO-d_6): 2.23 (s, 3H), 4.19 (dd, *J* = 4.8, 10.2Hz, 1H), 4.26 (dd, *J* = 6.0, 10.2Hz, 1H), 4.51 (m, 1H), 5.20 (brs, 2H), 7.02-7.20 (m, 7H), 7.32-7.46 (m, 6H), 8.61 (brs, 3H); ^{13}CNMR: 17.8, 44.2, 52.5, 111.8 (m, 2C), 112.4 (t, *J* = 21Hz), 118.0, 118.9, 123.7, 127.2, 128.6, 129.1, 129.9 (t, *J* = 6.3Hz), 130.1, 132.5, 134.9, 149.8, 151.0, 156.1, 156.3, 160.6 (dd, *J* = 7.6, 245.7Hz, 2C), 161.3; MS: 540 (MH^+); Anal. for $C_{26}H_{22}ClF_2N_3O_2xHClx0.3H_2O$: C, H, N.

3-[(2*R*)-Amino-2-phenylethyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(2-chlorophenyl)pyrimidin-2,4-dione hydrochloride (19f). white powder. ^{1}H NMR (CD_3OD): 2.12 (s, 3H), 4.03 (m, 1H), 4.57 (m, 2H), 5.17 (brs, 2H), 6.80-7.38 (m, 11H), 7.56 (m, 2H), 8.61 (brs, 2H); MS: 540 (MH^+); Anal. for $C_{32}H_{27}F_2N_3O_3xHClx0.5H_2O$: C, H, N.

3-[(2*R*)-Amino-2-phenylethyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(2-fluorophenyl)pyrimidin-2,4-dione hydrochloride (19g). white powder. ^{1}H NMR: 2.14 (s, 3H), 4.16 (m, 1H), 4.62 (m, 2H), 5.20 (m, 2H), 5.60 (brs, 3H), 6.93 (m, 3H), 7.16 (m, 2H), 7.20-7.40 (m, 6H); MS: 466 (MH^+); Anal. for $C_{26}H_{22}F_3N_3O_2xHClx0.25H_2O$: C, H, N.

3-[(2*R*)-Amino-2-phenylethyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(2-fluoro-3-methylphenyl)-pyrimidin-2,4-dione hydrochloride (19h). white powder. ^{1}H NMR: 2.04 (s,

1.5H) & 2.08 (s, 1.5H), 2.12 (s, 1.5H) & 2.24 (s, 1.5H), 3.89 (d, *J* = 13.2Hz, 0.5 H) & 4.11 (d, *J* = 12.4Hz, 0.5H), 4.42 - 4.78 (m, 2H), 5.08- 5.40 (m, 2H), 6.80 - 7.56 (m, 11H), 8.80 (brs, 3H); ^{19}F NMR: - 114.9 & -114.6 (s, 2F), -118.7 & -118.6 (s, 1F); ^{13}C NMR: 14.56 & 14.57, 17.63 & 17.71, 39.4, 45.63 & 46.11, 54.33 & 54.41, 108.72 & 108.88, 111.7 & 111.8 (m, 2C), 111,98, 112.1 &112 (t, *J* = 6.7Hz), 121.0 & 121.11, 123.7, 124.4 & 124.8, 125.0 & 125.1, 127.1, 128.8 & 128.9, 129.6 & 129.7 (t, J = 10.6Hz), 130.5 & 131.0, 131.5 & 131.7 (d, *J* = 5.3Hz), 134.2 & 134.4, 151.0 & 151.1, 151.6 & 152.5, 160.7 & 160.8 (dd, *J* = 7.6, 248Hz), 161.65 & 162.97; MS: 480 (MH^+); Anal. for $C_{27}H_{24}F_3N_3O_2$xHClx1.3H_2O: C, H, N.

The following compounds **20a** and **20c** were synthesized in a manner similar to the procedure described for **20b** from *R*-**12b**.

3-[(2*R*)-Methylamino-2-phenylethyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(3-methoxyphenyl)-pyrimidin-2,4-dione hydrochloride (20a). white powder. ^{1}H NMR: 2.10 (s, 3H), 2.35 (s, 3H), 3.72 (s, 3H), 4.26 (d, *J* = 10.2Hz, 1H), 4.55 (brs, 1H), 4.76 (dd, *J* = 4.8, 9.6Hz, 1H), 5.16 (d, *J* = 11.7Hz, 1H), 5.26 (d, *J* = 11.7Hz, 1H), 6.50-7.26 (m, 4H), 7.12-7.26 (m, 3H), 7.32-7.38 (m, 4H), 7.53 (m, 2H); ^{19}F NMR: 115.2; ^{13}C NMR: 17.8, 31.8, 39.3, 44.3, 55.3, 61.9, 111.7, 111.9, 112.1 (t, *J* = 16.7Hz), 113.4, 114.6, 116.6, 128.5 (2C), 129.2 (2C), 129.4, 129.5, 129.7 (m), 131.9, 135.4, 150.0, 151.7, 159.4, 160.0 (dd, *J* = 6.8, 248.0Hz, 2C), 162.6; MS: 492 (MH^+); Anal. for $C_{28}H_{27}F_2N_3O_3$xHClxH_2O: C, H, N.

3-[(2*R*)-Methylamino-2-phenylethyl]-1-(2,6-difluorobenzyl)-6-methyl-5-(3,4-ethylenedioxyphenyl)-pyrimidin-2,4-dione hydrochloride (20c). white powder. ^{1}H NMR: 2.13 (s, 3H), 2.42 (s, 3H), 4.18 (s, 4H), 4.23 (d, *J* = 13.2Hz, 1H), 4.57 (m, 1H), 4.76 (d, *J* = 8.0Hz, 1H), 5.25 brs, 2H), 6.75 (m, 2H), 6.85 (t, *J* = 7.6Hz, 1H), 7.22 (m, 1H), 7.34 (m, 4H), 7.53 (m, 2H), 9.22 (brs, 1H), 10.2 (brs, 1H); ^{19}F NMR: -115.2; ^{13}C NMR: 18.1, 29.7, 32.0, 39.5, 44.4, 62.0, 64.2, 64.3, 111.8 (m, 2C), 114.2, 117.2, 119.9, 124.2, 127.1, 128.4 (2C), 129.3 (2C), 129.5, 129.6 (m), 131.9, 141.1, 141.2, 149.9, 151.7, 161.0 (dd, *J* = 7.6, 249.5Hz, 2C), 162.9; MS: 520 (MH^+); Anal. for $C_{29}H_{27}F_2N_3O_4$xHCx1.5H_2O: C, H, N.

The following compounds 24a-q and 24s-u were synthesized in a manner similar to the procedure described for **24o** from **22**.

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-(2-methoxyethyl)uracil trifluoro-acetic acid salt (24a). colorless oil, ^{1}H NMR: 2.11 & 2.14 (s, 3H), 3.25 & 3.31 (s, 3H), 3.50 & 3.62 (m, 2H), 3.78-4.14 (m, 3H), 4.33-4.64 (m, 2H), 6.96 & 7.10 (t, *J* = 8.7Hz, 1H), 7.13-7.48 (m, 8H); MS *m/z* 381 (MH^+-NH_3).

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-(cyclopropanemethyl)uracil trifluoroacetate (24b). colorless oil, ^{1}H NMR: 0.30-0.63 (m, 4H), 1.03 (m, 1H), 2.12 & 2.13 (s, 3H), 3.66 & 3.77 (dd, *J* = 6.3, 14.7Hz, 1H), 3.86 & 3.88 (dd, *J* = 14.7, 16.8Hz, 1H), 3.96 & 4.06 (d, *J* = 12.3Hz, 1H), 4.40 & 4.48 (d, *J* = 12.9Hz, 1H), 4.49 & 4.60 (dd, *J* = 10.5, 13.5Hz, 1H), 6.97 (t, *J* = 9.3Hz, 0.5H), 7.08-7.46 (m, 7.5H); MS *m/z* 377 (MH^+-NH_3).

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-isobutyluracil trifluoroacetate (24c). colorless oil, ^{1}H NMR: 0.90 & 0.91 (d, *J* = 7.2 Hz, 1.5Hz), 0.98 & 1.00 (d, *J* = 6.4Hz, 1.5H), 2.06 & 2.07 (s, 3H), 2.02 & 2.10 (m, 1H), 3.47 (dd, *J* = 7.8, 14.7Hz, 0.5H), 3.75 (d, *J* = 6.9Hz, 1H), 3.77 (dd, *J* = 7.8, 14.7Hz, 0.5H), 3.97 & 4.06 (d, *J* = 13.5Hz, 1H), 4.36 & 4.43 (d, *J* = 9.9Hz, 1H), 4.47 & 4.57 (dd, *J* = 10.5, 14.1Hz, 1H), 6.95 & 7.11 (t, *J* = 6.9Hz, 1H), 7.16-7.44 (m, 8H); MS *m/z* 379 (MH^+-NH_3).

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-cyclohexylmethyluracil trifluoro-acetate (24d). colorless oil, ^{1}H NMR: 0.88-1.30 (m, 4H), 1.58-1.81 (m, 6H), 2.06 & 2.07 (s, 3H), 2.75 (m, 2H), 3.96 & 4.07 (d, *J* = 13.5Hz, 1H), 4.37 & 4.45 (d, *J* = 10.2Hz, 1H), 4.46 & 4.57 (dd, *J* = 9.9, 13.1Hz, 1H), 6.95 & 7.11 (t, *J* = 9.0Hz, 1H), 7.16-7.43 (m, 8H); MS *m/z* 436 (MH^+).

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-phenethyluracil trifluoroacetate (24e). colorless oil, ^{1}H NMR: 1.87 & 1.93 (s, 3H), 2.91 (t, J = 7.5Hz, 1H) & 3.01 (t, J = 8.4Hz, 1H), 3.80-4.16 (m, 3H), 4.35-4.62 (m, 2H), 6.97 & 7.11 (t, J = 9.0Hz, 1H), 7.12-7.44 (m, 13H); MS *m/z* 427 (MH^+-NH_3).

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-(pyridine-2-yl)methyluracil trifluoroacetate (24f). colorless oil, ^{1}H NMR: 2.12 (s, 3H), 4.03 & 4.05 (d, *J* = 12.1Hz, 1H), 4.45 & 4.47 (d, *J* = 9.9Hz, 1H), 4.54 & 4.57 (dd, *J* = 9.9, 12.1Hz, 1H), 5.22 & 5.30 (d, J = 16.5Hz, 1H), 7.00 (t, *J* = 8.4Hz, 0.5H), 7.07-7.48 (m, 9.5H), 7.70 (m, 1H), 8.33 & 8.47 (d, *J* = 3.9Hz, 1H); MS *m/z* 414 (MH^+-NH_3).

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-(pyridine-3-yl)methyluracil trifluoroacetate (24g). colorless oil, ^{1}H NMR: 2.04 (s, 3H), 4.03 & 4.09 (d, *J* = 14.4Hz, 1H),

4.51 &4.54 (d, *J* = 10.2, 14.4Hz, 1H), 4.64 & 4.70 (dd, *J* = 10.2, 14.1Hz, 1H), 4.90 (d, *J* = 17.1Hz, 0.5H), 5.20 (s, 1H), 5.28 (d, *J* = 17.1Hz, 0.5H), 6.91 (t, *J* = 9.0Hz, 0.5H), 7.03-7.42 (m, 7.5H), 7.49 & 7.51 (s, 1H), 7.66 & 7.72 (d, *J* = 5.2Hz, 1H), 8.11 & 8.49 (m, 1H), 8.62 & 8.67 (s, 1H); MS *m/z* 414 (MH^+-NH_3).

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-benzyluracil trifluoroacetate (24h). colorless oil, ^{1}H NMR: 2.01 & 2.02 (s, 3H), 3.99 & 4.03 (d, J = 15.6Hz, 1H), 4.31 & 4.40 (d, J = 9.9Hz, 1H), 4.56 & 4.61 (dd, J = 10.2, 14.1Hz, 1H), 4.82 & 5.18 (d, J = 17.1Hz, 1H), 5.16 & 5.20 (d, J = 17.1Hz, 1H), 6.93 (t, J = 8.7Hz, 0.5H), 7.05-7.42 (m, 13.5H); MS *m/z* 430.0 (MH^+).

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-(4-fluorophenyl)methyluracil trifluoroacetate (24i). colorless oil, ^{1}H NMR: 2.07 (s, 3H), 4.15 & 4.20 (dd, *J* = 5.1, 9.9Hz, 1H), 4.29 (d, *J* = 9.9Hz, 0.5H), 4.35 (dd, *J* = 10.2, 12.9Hz, 0.5H), 4.47 (m, 1H), 5.11 (d, *J* = 15.9Hz, 0.5H), 5.17 (s, 1H), 5.25 (d, *J* = 15.9Hz, 0.5H), 7.01-7.45 (m, 13H); MS *m/z* 448 (MH^+).

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-(3-fluorophenyl)methyluracil trifluoroacetate (24j). colorless oil, ^{1}H NMR: 1.98 & 2.01 (s, 3H), 3.97 & 4.03 (d, *J* = 12.0Hz, 1H), 4.26 & 4.37 (d, *J* = 10.5Hz, 1H), 4.44 & 4.57 (dd, *J* = 10.5, 12.0Hz, 1H), 4.69 (d, *J* = 17.1Hz, 0.5H), 5.11 (d, *J* = 17.,1Hz, 0.5H), 5.14 (s, 1H), 6.83 (d, *J* = 9.3Hz, 0.5H), 6.92-7.42 (m, 12.5H); MS *m/z* 431 (MH^+-NH_3).

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-(2-fluorophenyl)methyluracil trifluoroacetate (24k). colorless oil, ^{1}H NMR: 2.00 & 2.03 (s, 3H), 3.97 & 4.06 (d, *J* = 14.1Hz, 1H), 4.35 & 4.38 (d, *J* = 10.5Hz, 1H), 4.52 & 4.60 (dd, *J* = 10.5, 14.1Hz, 1H), 4.90 & 5.21 (d, *J* = 17.1Hz, 1H), 5.14 & 5.25 (d, *J* = 17.1Hz, 1H), 6.95 (t, *J* = 8.7Hz, 0.5H), 7.02-7.42 (m, 12.5H); MS *m/z* 448.0 (MH^+).

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-(2-chlorophenyl)methyluracil trifluoroacetate (24l). colorless oil, ^{1}H NMR: 2.01 (s, 3H), 4.20 (m, 1H), 4.70 (m, 2H), 5.25 (m, 2H), 6.90-7.45 (m, 13H), 8.20 (brs, 3H); MS: 464 (MH^+).

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-(2-bromophenyl)methyluracil trifluoroacetate (24m). colorless oil, ^{1}H NMR: 1.95 & 1.97 (s, 3H), 3.94 & 4.09 (d, J = 13.5Hz, 1H), 4.33-4.36 (m, 1H), 4.54-4.62 (m, 1H), 5.12 & 5.23 (d, *J* = 17.7Hz, 1H), 6.92-7.35 (m, 12H), 7.57 (dd, *J* = 8.4, 9.9Hz, 1H); MS *m/z* 508.0 ($M^+ + H^+$); HRMS (CI – CH_4) calcd. for $C_{26}H_{23}BrFN_3O_2$ (MH^+): 508.10359; observed: 508.10427.

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-(2-methylphenyl)methyluracil trifluoroacetate (24n). colorless oil, ^{1}H NMR: 2.00 (s, 3H), 2.27 & 2.34 (s, 3H), 4.15 (m, 4H), 4.62 (m, 2H), 5.15 (m, 2H), 6.80-7.40 (m, 13H); MS *m/z* 444 (MH^+).

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-(2-trifluoromethylthiophenyl)-methyl-uracil trifluoroacetate (24p). colorless oil, ^{1}H NMR: 1.92 & 1.94 (s, 3H), 3.94 & 4.08 (d, J = 12.3Hz, 1H), 4.29-4.32 (m, 1H), 4.54 (dd, *J* = 10.8, 14.1Hz, 1H), 5.42 & 5.48 (d, *J* = 17.7Hz, 1H), 6.93-7.12 (m, 2H), 7.15-7.41 (m, 8H), 7.44-7.77 (m, 3H); MS *m/z* 530.0 (MH^+); HRMS (CI – CH_4) calcd. for $C_{27}H_{23}F_4N_3O_2S$ (MH^+): 530.15254; observed: 530.15313.

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-(2-trifluoromethylphenyl)methyl-uracil trifluoroacetate (24q). colorless oil, ^{1}H NMR: 1.92 & 1.94 (s, 3H), 3.94 & 4.09 (d, *J* = 12.3Hz, 1H), 4.33 (dd, *J* = 10.2, 13.5Hz, 1H), 4.50-4.60 (m, 1H), 5.15-5.54 (m, 2H), 6.93-7.12 (m, 2H), 7.18-7.44 (m, 9H), 7.51-7.61 (m, 1H), 7.70 (t, *J* = 9.0 Hz, 1 H); MS *m/z* 498.0 (MH^+). HRMS (CI – CH_4) calcd. for $C_{27}H_{23}F_4N_3O_2$: 498.1805 (MH^+); observed: 498.1789.

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluorophenyl)-1-(2-trifluoromethyl-5-fluorophenyl)-methyl-uracil trifluoroacetate (24r) oil, ^{1}H NMR: 1.94 & 1.96 (s, 3H), 3.94 & 4.10 (d, J = 12.0Hz, 1H), 4.34-4.38 (m, 1H), 4.51-4.59 (m, 1H), 5.29 & 5.27 (d, J = 17.7Hz, 1H), 6.91-7.01 (m, 1H), 7.06-7.12 (m, 3H), 7.14-7.34 (m, 7H), 7.68-7.76 (m, 1H); MS *m/z* 516.0 (MH^+); HRMS (CI – CH_4) calcd. for $C_{27}H_{22}F_5N_3O_2$ (MH^+): 516.17104; observed: 516.17209.

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluoro-6-chlorophenyl)-1-(2-chloro-6-fluorophenyl)-methyluracil trifluoroacetate (24s). colorless oil, ^{1}H NMR: 6.91-7.37 (m, 12H), 5.47 & 5.35 (d, *J* = 16.5 Hz, 1H), 5.24 & 5.14 (d, *J* = 16.5Hz, 1H), 4.44- 4.65 (m, 2H), 4.07 (m, 1H), 2.06 (s, 3H); HRMS calcd. for $C_{26}H_{22}ClF_2N_3O_2$ 482.1447 (MH^+); observed: 482.1435.

3-[2(*R*)-Amino-2-phenylethyl]-6-methyl-5-(2-fluoro-4-chlorophenyl)-1-(2-chloro-4-fluorophenyl)-methyluracil trifluoroacetate (24t). colorless oil, ^{1}H NMR: 1.95 & 1.97 (s, 3H), 3.95 & 4.06 (d, *J* = 13.2Hz, 1H), 4.32 & 4.35 (d, *J* = 10.5Hz, 1H), 4.58 (dd, *J* = 10.5, 13.2Hz, 1H), 4.95 & 5.11 (d, *J* = 16.8Hz, 1H), 5.21 & 5.31 (d, *J* = 16.8Hz, 1H), 6.90-7.40 (m, 12H); MS *m/z* 444 (MH^+).

Competitive Radioligand Binding Assay.

The affinity of compounds for the human GnRH receptor was determined by a competitive displacement of the GnRH receptor radioligand, [^{125}I-Tyr^5, DLeu^6,NMeLeu^7, Pro^9-NEt]GnRH. HEK293 cells stably transfected with the full-length human GnRH receptor (REF) were harvested, resuspended in 5% sucrose and homogenized using a polytron homogenizer (2x15 sec).[8] Nuclei were removed by centrifugation (3000 x g for 5 min.), and the supernatant centrifuged (20,000 x g for 30 min, 4° C) to collect the membrane fraction. The final membrane preparation was resuspended in binding buffer (10mM Hepes (pH 7.5), 150 mM NaCl, and 0.1% BSA) and stored at –70°C. Binding reactions were performed in a Millipore MultiScreen 96-well filtration plate assembly with polyethylenimine coated GF/C membranes. The reaction were initiated by adding membranes (25 ug protein in 130 ul binding buffer) to 50ul of [^{125}I]-labeled GnRH peptide (~100,000 cpm), and 20ul of competitor at varying concentrations. The reaction was terminated after 90 minutes by filtration and washing (2X) with phosphate buffered saline. Bound radioactivity was measured by removing the filters from the plate and direct gamma counting. K_i values were calculated from competition binding data using non-linear least squares regression by use of the Prism software package (GraphPad Software) with the Cheng Prusoff equation.[1]

Inhibition of GnRH-stimulated Ca^{++} Flux.

Functional activity of compounds for the human GnRH receptor was determined by inhibition of GnRH stimulated Ca^{++} flux. RBL cells stably expressing the full-length human GnRH receptor were seeded into 96-well, black wall clear bottom plates (Corning) at a density of 50,000 cells/well and the cells allowed to attach overnight. Cells were then loaded with the Ca^{++} sensitive dye, Fluo-4 (Molecular Probes), by incubation in loading medium [(DMEM with 20mM Hepes, 10%FBS, 2 μM Fluo-4, 0.02% pluronic acid (Molecular Probes) and 2.5mM probenecid (Sigma)] for 1 hour at 37^o C. Cells were then washed 3 times with assay buffer (Hanks balanced salt, 20mM Hepes, 2.5mM probenecid). Compounds at varying concentrations in assay buffer were pre-incubated with cells for 1 minute prior to stimulation with GnRH (5 nM). Measurement of fluorescence due to GnRH stimulated Ca^{++} flux was performed according to the manufacturer's instructions on the FLIPR system (Molecular Devices, FLIPR^{384} system). IC_{50} values for the inhibition of GnRH-stimulated Ca^{++} flux were calculated using the Prism

software package (GraphPad Software) with a “sigmoidal dose-response (variable slope)” option for curve fitting.

Microanalyses and High Resolution Mass Spectra of Key Compounds

	Found			Calculation for				
Compd	C	H	N	Formula	Addict	C	H	N
***R*-13b**	58.67	4.55	7.35	$C_{27}H_{24}F_3N_3O_3$	1 HCl + H_2O	58.97	4.74	7.90
***R*-13d**	59.67	5.86	7.46	$C_{27}H_{30}F_3N_3O_3$	1 HCl + 0.5 H2O	59.28	5.90	7.68
***S*-14a**	60.94	5.28	7.28	$C_{29}H_{28}F_3N_3O_3Cl$	1 HCl + 0.5 H2O	61.21	5.31	7.38
***R*-14b**	60.34	5.23	6.88	$C_{28}H_{26}F_3N_3O_3$	1 HCl + 0.75 H_2O	60.11	5.13	7.51
***R*-15b**	59.97	5.77	6.60	$C_{29}H_{28}F_3N_3O_3$	1 HCl + 1.3 H_2O	59.70	5.46	7.20
***S*-16a**	58.76	5.75	7.78	$C_{25}H_{28}F_3N_3O_3$	1 HCl + 0.5 H_2O	58.59	5.67	7.88
19a	59.88	5.06	7.71	$C_{27}H_{25}F_2N_3O_3$	1 HCl + 1.4 H_2O	60.15	5.38	7.79
19b	60.25	4.71	7.73	$C_{27}H_{23}F_2N_3O_4$	1 HCl + 0.5 H_2O	60.39	4.69	7.83
19c	58.16	5.28	6.89	$C_{28}H_{25}F_2N_3O_4$	1 HCl + 2 H_2O	58.18	5.23	7.27
19d	58.73	5.00	7.48	$C_{27}H_{25}F_2N_3O_2S$	1 HCl + 1.2 H_2O	58.79	5.19	7.62
19e	66.22	5.16	7.18	$C_{32}H_{27}F_2N_3O_3$	1 HCl + 0.3 H2O	66.03	4.96	7.22
19f	59.20	4.83	7.64	$C_{26}H_{22}ClF_2N_3O_2$	1 HCl + 0.5 H2O	59.21	4.59	7.97
19g	61.56	4.63	8.25	$C_{26}H_{22}F_3N_3O_2$	1 HCl + 0.25 H_2O	61.66	4.68	8.30
19h	60.62	5.51	7.74	$C_{27}H_{24}F_3N_3O_2$	1 HCl + 1.3 H_2O	60.12	5.16	7.79
20a	61.89	5.72	7.32	$C_{28}H_{27}F_2N_3O_3$	1 HCl + H_2O	61.59	5.54	7.70
20b	59.24	4.84	6.81	$C_{28}H_{25}F_2N_3O_4$	1 HCl + 1.5 H_2O	59.10	5.14	7.38
20c	59.69	4.97	6.67	$C_{29}H_{27}F_2N_3O_4$	1 HCl + 1.5 H2O	59.74	5.36	7.21
24m	508.10359			$C_{26}H_{23}BrFN_3O_2$		508.10427.		
24o	460.20210			$C_{27}H_{26}FN_3O_3$		460.20365		
24p	530.15313			$C_{27}H_{23}F_4N_3O_2S$		530.15254		
24q	498.1789			$C_{27}H_{23}F_4N_3O_2$:		498.1805		
24s	482.1435			$C_{26}H_{22}ClF_2N_3O_2$		482.1447		
25	64.99	4.95	7.67	$C_{29}H_{25}F_2N_3O_5$	none	65.29	4.72	7.88

[1] Cheng, Y. and. Prusoff, W. H Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50 per cent inhibition (IC_{50}) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099-3108.