Supplementary Results

Supplementary Figure 1 Structure of Compounds

TOP05300

TOP5668
Supplementary Figure 2. TOP5300 stimulates similar follicular growth whether administered twice per day (BID) or once per day (QD) by oral gavage. rh-FSH was administered by subcutaneous injection twice daily. Stimulation of follicular growth was measured by the ability of hCG to induce ovulation of mature follicles and the recovery of cumulus-enclosed oocytes from the oviduct 16-18 hours after injection of hCG. Data is mean±SEM, n=2-3 expts. with 5 animals/group/expt. *p<0.05 vs 0.29IU FSH, ANOVA
Supplementary Figure 3: Toxicokinetic (TK) profile of TOP5300 in rat treated for 14-days.
Data is mean+SD, n=3 animals/timepoint

Day 1 Female

Day 14 Female

Day 1 Male

Day 14 Male
**Supplementary Table 1: Broad safety and selectivity profile of TOP5300.**

| Assay name                        | Assay content                          | Result                                           |
|-----------------------------------|----------------------------------------|--------------------------------------------------|
| hERG channel inhibition @ 10 uM [Cyprotex] | hERG                                   | 16 % inhibition – No significant effect          |
| Gentotoxicity test                | Ames test                              | Negative                                         |
| Chromosomal Aberrations           | Micronucleus Test (MNT)                | Negative                                         |
| [Cyprotex]                        |                                        |                                                  |
| Phosphodiesterase (PDE) profile @ 10 uM [Eurofins] | Tested against 9 isoforms PDE | No significant inhibition on any isoform          |
| Kinase profile@ 10 uM [Eurofins]  | Tested against 211 kinases             | No significant inhibition on any target          |
| Single concentration              |                                        |                                                  |
| Cerep profile @ 10 uM [Eurofins]  | Tested against 55 targets,            | 52 targets < 60% 3 targets > 60% inhibition       |
| Concentration response curve      | Dose response tests against 3 targets (A3(h), NK2(h), Cl-channel (GABA-gated)) | Good safety margin compared to FSHR; safety margin > 400 X for all three targets compared to FSHR |
Supplementary Table 2. Serum level of thyroid hormone (Free T3, Free T4 & TSH) in beagle dogs treated with TOP5300 for 14 days, A-female dog and B-male dog. Hormone levels were measured predosing (0hr), 24h after 1\textsuperscript{st} dosing (24h) and 24hr following the 13\textsuperscript{th} dose (Day14). The values are normalized to vehicle treated animals (0 mg/Kg). Data is mean of n=2/sex/dose group.

### A

| Dose mg/Kg | Free T3 | Free T4 | TSH |
|------------|---------|---------|-----|
|            | 0h 24h Day 14 | 0h 24h Day 14 | 0h 24h Day 14 |
| 0          | 1 1 1 | 1 1 1 | 1 1 1 |
| 30         | 0.9 0.8 1.0 | 1.1 1.1 0.8 | 1.2 0.9 1.1 |
| 100        | 1.0 0.9 1.1 | 1.2 1.1 1.1 | 1.3 1.0 1.1 |
| 1000       | 1.1 0.9 1.2 | 1.0 0.9 0.9 | 1.2 0.8 0.8 |

### B

| Dose mg/Kg | Free T3 | Free T4 | TSH |
|------------|---------|---------|-----|
|            | 0h 24h Day 14 | 0h 24h Day 14 | 0h 24h Day 14 |
| 0          | 1 1 1 | 1 1 1 | 1 1 1 |
| 30         | 1.3 1.3 1.3 | 1.0 1.0 1.0 | 0.8 0.9 1.0 |
| 100        | 1.1 1.1 1.1 | 0.9 0.8 0.9 | 0.8 0.9 1.0 |
| 1000       | 1.0 0.9 1.0 | 0.9 0.9 1.0 | 0.7 0.9 0.8 |