**Figure 2-source data 1:** Ligand and Mutational Influences on Estrogen Receptor Alpha Cellular Turnover after 24 Hours. Data were normalized by cell count. Antiestrogens are categorized as stabilizers if their maximum signal for WT ERα at 5 µM is greater than 1.5, neutral if between 0.9 and 1.1, and degrader if less than 0.9 in this assay.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Hormone** | | | | |
| **Ligand** | **IC50(nM)** | **R2** | **Maxima (5 µM)** | |
| **Estradiol (E2)** | | | | |
| *WT* | 0.12 ± 0.02 | 0.806 | 0.68 ± 0.05 | |
| *Y537S* | 0.02 ± 0.02\* | 0.27 | 0.84 ± 0.08 | |
| *D538G* | ND\* | 0.013 | 0.87 ± 0.13 | |
| **Stabilizers (SERM-Like)** | | | | |
| **Ligand** | **IC50 (nM)** | **R2** | **Maxima (5 µM)** | |
| **4-Hydroxytamoxifen (4OHT)** | | | | |
| *WT* | 1.56 ± 0.05 | 0.92 | 2.23 ± 0.24 | |
| *Y537S* | 12.42± 0.075 | 0.9 | 2.25 ± 0.23 | |
| *D538G* | ND | 0.11 | 0.93 ± 0.37 | |
| **RU39411** | | | | |
| *WT* | ND | 0.28 | 2.11 ± 0.36 | |
| *537S* | 4.33 ± 0.10 | 0.7 | 2.01 ± 0.16 | |
| *538G* | ND | 0.287 | 1.18 ± 0.15 | |
| **Laso-Stabilizer (LA-Stab)** | | | | |
| *WT* | 1.239 ± 0.06 | 0.9143 | 2.42 ± 0.19 | |
| *537S* | 10.62 ± 0.07 | 0.934 | 2.61 ± 0.25 | |
| *538G* | ND | 0.07 | 1.17 ± 0.22 | |
| **Clomiphene (Clom)** | | | | |
| *WT* | 29.57 ± 0.11 | 0.81 | 1.92 ± 0.33 | |
| *537S* | 296.5 ± 0.12 | 0.788 | 1.66 ± 0.20 | |
| *538G* | 85.64 ± 0.08 | 0.35 | 0.79 ± 0.12 | |
| **Neutral** | | | | |
| **Ligand** | **IC50 (nM)** | **R2** | | **Maxima (5 µM)** |
| **Lasofoxifene (Laso)** | | | | |
| *WT* | ND | 0.48 | 0.9 ± 0.08 | |
| *Y537S* | 1.19 ± 0.05 | 0.55 | 1.48 ± 0.22 | |
| *D538G* | ND | 0.27 | 0.95 ± 0.27 | |
| **Degraders (SERD-Like)** | | | | |
| **Ligand** | **IC50 (nM)** | **R2** | **Maxima (5 µM)** | |
| **RU58668** | | | | |
| *WT* | 2.25 ± 0.04 | 0.92 | 0.2 ± 0.03 | |
| *537S* | 41.64 ± 0.06 | 0.90 | 0.25 ± 0.03 | |
| *538G* | 51.75 ± 7.00 | 0.8 | 0.37 ± 0.13 | |
| **Fulvestrant (ICI)** | | | | |
| *WT* | 0.40 ± 0.02 | 0.95 | 0.29 ± 0.04 | |
| *Y537S* | 3.76 ± 0.034 | 0.92 | 0.33 ± 0.08 | |
| *D538G* | ND | 0.19 | 0.67 ± 0.37 | |
| **GDC0927** | | | | |
| *WT* | 0.13 ± 0.03 | 0.72 | 0.33 ± 0.04 | |
| *537S* | 2.18 ± 0.03 | 0.90 | 0.36 ± 0.06 | |
| *538G* | 1.88 ± 0.04 | 0.75 | 0.47 ± 0.15 | |
| **OP1074** | | | | |
| *WT* | 1.09 ± 0.03 | 0.90 | 0.36 ± 0.05 | |
| *537S* | 14.07 ± 0.03 | 0.89 | 0.56 ± 0.04 | |
| *538G* | 23.35 ± 0.06 | 0.67 | 0.63 ± 0.08 | |
| **Bazedoxifene (BZA)** | | | | |
| *WT* | 0.87 ± 0.03 | 0.85 | 0.48 ± 0.06 | |
| *537S* | ND | 0.32 | 0.81 ± 0.13 | |
| *538G* | ND | 0.38 | 0.67 ± 0.11 | |
| **Pipendoxifene (PIP)** | | | | |
| *WT* | 0.77 ± 0.03 | 0.88 | 0.43 ± 0.08 | |
| *537S* | 6.28 ± 0.04 | 0.81 | 0.45 ± 0.06 | |
| *538G* | 18.29 ± 0.06 | 0.71 | 0.60 ± 0.07 | |
| **Laso-Degrader (LADeg)** | | | | |
| *WT* | 1.13 ± 0.03 | 0.78 | 0.56 ± 0.08 | |
| *Y537S* | ND | ND | 0.89 ± 0.10 | |
| *D538G* | ND | 0.09 | 1.06 ± 0.34 | |
| **OP1154** | | | | |
| *WT* | 48.92 ± 0.06 | 0.73 | 0.55 ± 0.09 | |
| *537S* | 19.85 ± 0.04 | 0.61 | 1.54 ± 0.14 | |
| *538G* | ND | 0.02 | 0.54 ± 0.09 | |
| **AZD9496** | | | | |
| *WT* | 8.78 ± 0.05 | 0.63 | 0.58 ± 0.08 | |
| *537S* | ND | 0.20 | 1.1 ± 0.18 | |
| *538G* | ND | 0.30 | 0.74 ± 0.05 | |
| **Raloxifene (RAL)** | | | | |
| *WT* | 0.85 ± 0.03 | 0.79 | 0.59 ± 0.07 | |
| *537S* | ND | 0.37 | 0.83 ± 0.06 | |
| *538G* | ND | ND | 0.85 ± 0.14 | |
| **LSZ102** | | | | |
| *WT* | 1.15 ± 0.03 | 0.73 | 0.60 ± 0.06 | |
| *537S* | ND | 0.40 | 1.30 ± 0.10 | |
| *538G* | ND | 0.58 | 0.73 ± 0.08 | |
| **GDC0810** | | | | |
| *WT* | 26.1 ± 0.05 | 0.69 | 0.60 ± 0.06 | |
| *537S* | ND | 0.59 | 1.38 ± 0.10 | |
| *538G* | ND | ND | 0.78 ± 0.10 | |