## Supporting Information

Design and Synthesis of Basic Selective Estrogen Receptor Degraders (B-SERDs) for Endocrine Therapy Resistant Breast Cancer

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In-Cell Western (MCF7:ws8)


Supplementary Figure 1. Effect of 300 treatment on ER Level. ERa level in MCF7:WS8 cells treated with 300 for 24 hours. Normalized to vehicle (1) and $1 \mu \mathrm{M} 2$ (0). Data shown as mean $\pm$ SEM from analytical triplicate.


Supplementary Figure 2. Representative Full Western Blots. MCF-7:WS8 cells were treated with test compounds (100nM) for 24h.Primary Ab (Cell Signaling): anti-ERa and $\beta$-actin; Secondary Ab: anti-rabbit and mouse.

PK Data 37d


Supplementary Figure 3. PK profiles for 37d. Data show mean and S.E.M. from LC-MS/MS measurements.

Supplementary Table 1. ER isoform binding specificity

| Compound | RBA ER $\alpha$ (\%) | RBA ER $\boldsymbol{\beta}$ (\%) | $\alpha / \beta$ |
| :---: | :---: | :---: | :---: |
| 30c | $80.56 \pm 20$ | $52.19 \pm 0.4$ | 1.5 |
| 30d | $30.70 \pm 7$ | $16.73 \pm 2$ | 1.8 |
| 30e | $46.49 \pm 7$ | $22.29 \pm 0.3$ | 2.1 |
| 30f | $59.58 \pm 3$ | $13.52 \pm 3$ | 4.4 |
| 30g | $56.96 \pm 14$ | $19.21 \pm 3$ | 3.0 |
| 30h | $21.93 \pm 3$ | $11.21 \pm 3$ | 2.0 |
| 30i | $9.15 \pm 0.87$ | $8.87 \pm 3$ | 1.0 |
| 30j | $119.86 \pm 13$ | $32.19 \pm 5$ | 3.7 |
| 30m | $32.64 \pm 6$ | $16.40 \pm 4$ | 2.0 |
| 37b | $91.79 \pm 6$ | $34.32 \pm 6$ | 2.7 |
| 37d | $27.78 \pm 8$ | $17.19 \pm 2$ | 1.6 |
| 37f | $38.09 \pm 9$ | $28.67 \pm 5$ | 1.3 |

Relative binding affinity (RBA) values, determined by radioligand displacement assays expressed as IC50 estradiol/IC50 compound $\times 100$ (RBA, estradiol $=100 \%$ ).

## DFT molecular orbital calculations

To model the electronic properties of the putative B-SERD side arms, simplified structures were used as shown in Figure 2. The conformational space for each neutral, ground state structure was explored and structures representing local energy minima stabilized by intramolecular interactions were excluded to better mimic the extended conformations anticipated on the ligand binding pocket. In several cases, 2 or 3 conformations representing local minima were identified. Conformational analysis was performed at the B3LYP/6-31+G** level in Spartan 10 from Wavefunction Inc. Structures for protonated and ionized amine side arms were also optimized at the B3LYP/6-31+G** level. Full thermodynamic calculations (298.15 ${ }^{\circ}$ C) , corrected for ZPE were performed at the RI-MP2/6-311++G** level on structures optimized at the lower level. The composite RI-MP2/6-311++G**/B3LYP/6-31+G** level of calculation is suitable for energy calculations on radical and charged species.

The following reactions (shown for the piperidine side arm only) were used to calculate free energy changes:

$\Delta \mathrm{G}$ for the piperidine reactions was set as $\Delta \mathrm{G}_{0}=0$. The dG was then calculated using calculated $\Delta \mathrm{G}$ for each reaction and side arm: as shown above for dPA, dIE, dBDErH (ring H abstraction), and dBDEH. Where multiple conformers were identified, the free energy difference is given in Figure 2 for the lowest energy reaction.






















































































