Supplementary Material

Structural Basis of Inhibition of Human Insulin-Regulated Aminopeptidase (IRAP) by benzopyran-based inhibitors

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1 Supplementary Figures and Tables

Table S1 - RMSD of the ligands along the MD trajectory of the protein-ligand complex used for LIE calculations. Ligands with Kᵢ > 100 µM (i.e. non-binders) are highlighted in italics and denoted with a star. It can be appreciated the higher RMSD values, indicating instability of the binding mode proposed which resulted in lost interactions with the Zn²⁺ coordination cluster

| Compound | RMSD of ligand (in Å) +/- SEM |
|----------|-------------------------------|
| IRAP-wildtype |                               |
| 6        | 2.23 ± 0.71                   |
| 7        | 1.99 ± 0.63                   |
| 8        | 2.46 ± 0.78                   |
| 9        | 2.46 ± 0.82                   |
| I - IRAP |                               |
| 6        | 1.74 ± 0.55                   |
| 7        | 2.10 ± 0.66                   |
| 8        | 1.50 ± 0.47                   |
| 9        | 1.70 ± 0.54                   |
| V - IRAP |                               |
| 6        | 2.51 ± 0.79                   |
| 7        | 2.35 ± 0.74                   |
| 8        | 2.62 ± 0.83                   |
| 9        | 2.29 ± 0.72                   |
| HFI-Series |                           |
| 15a      | 4.68 ± 1.48                   |
| 15b      | 3.90 ± 1.23                   |
| 15c      | 4.69 ± 1.48                   |
|     |       |
|-----|-------|
| 15d | $3.75 \pm 1.19$ |
| 15e | $4.36 \pm 1.38$ |
| 15f | $3.90 \pm 1.23$ |
| 15g | $4.40 \pm 1.39$ |
| 16a | $3.98 \pm 1.26$ |
| 16b | $4.25 \pm 1.34$ |
| 16c | $2.15 \pm 0.68$ |
| 16d | $2.40 \pm 0.76$ |
| 16e | $2.61 \pm 0.83$ |
| 16f | $1.97 \pm 0.62$ |
| 16g | $1.91 \pm 0.60$ |
| 16h | $2.60 \pm 0.82$ |
| 16i*| $3.50 \pm 1.11$ |
| 16j*| $3.38 \pm 1.07$ |
| 16k*| $3.46 \pm 1.09$ |
| 16l | $2.65 \pm 0.84$ |
| 16m | $2.32 \pm 0.73$ |
| 16n | $2.59 \pm 0.82$ |
| 16o | $2.26 \pm 0.71$ |
| 16p*| $5.45 \pm 1.72$ |
| 16q | $2.33 \pm 0.74$ |
| 16r | $1.91 \pm 0.60$ |
| 17a | $2.44 \pm 0.77$ |
| 17b | $2.04 \pm 0.65$ |
| 17c | $1.84 \pm 0.58$ |
| 17d | $2.61 \pm 0.83$ |
| 17e | $1.91 \pm 0.60$ |
| 17g | $1.94 \pm 0.61$ |
| 18d | $2.32 \pm 0.73$ |
| 18f | $2.01 \pm 0.64$ |
| 18g | $2.02 \pm 0.64$ |
| 18h*| $5.29 \pm 1.67$ |