**Supplementary data**

**Table S1.** Auto-pharmacophore generated best hypotheses for epalrestat and HNE.

|  |  |  |
| --- | --- | --- |
| **Generated hypotheses** | **Features (ALR2; Epalrestat)** | **Features (ALR1; HNE)** |
| Pharmacophore 1 | 3HBA, 1H, 1NI, 1RA | 1HBA, 1HBD, 1H |
| Pharmacophore 2 | 3HBA, 2H, 1NI | 1HBA, 1HBD, 1H |
| Pharmacophore 3 | 2HBA, 1H, 1NI, 1RA | 2HBA, 1H |
| Pharmacophore 4 | 2HBA, 2H, 1NI | 2HBA, 1H |
| Pharmacophore 5 | 3HBA, 1NI, 1RA | - |
| Pharmacophore 6 | 3HBA, 1H, 1NI | - |
| Pharmacophore 7 | 2HBA, 1H, 1NI, 1RA | - |
| Pharmacophore 8 | 2HBA, 2H, 1NI | - |
| Pharmacophore 9 | 3HBA, 1H, 1NI | - |
| Pharmacophore 10 | 2HBA, 2H, 1NI | - |

HBA = Hydrogen bond acceptor, HBD = Hydrogen bond donor, H = Hydrophobic, NI = Negative ionizable, RA = Ring aromatic

**Table S2**. PAINS filter results, docking scores and binding affinities of 12 hits with the catalytic domain of ALR1 (3H4G).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Sr. No** | **Compound ID** | **Structure** | **PAINS filter** | **CDOCKER energy (kcal/mol)** | **CDOCKER interaction energy (kcal/mol)** | **Binding energy (MM-GBSA score, kcal/mol)** | **Key interactions** |
| 5 | STOCK1N-88220 |  | Passed | -16.78 | -38.83 | -35.19 | Trp22, Met302, Arg312 |
| 7 | STOCK1N-44092 |  | Passed | -24.13 | -45.09 | -48.14 | Lys23 |
| 8 | STOCK1N-46096 |  | Passed | -11.35 | -38.45 | -47.67 | Lys23 |
| 9 | STOCK1N-44771 |  | Passed | -21.54 | -40.53 | -39.89 | Trp22, Lys23 |
| 11 | STOCK1N-44713 |  | Passed | -28.90 | -42.91 | -42.07 | Lys23, Ala219 |
| 12 | STOCK1N-46041 |  | Passed | -28.55 | -44.37 | -30.99 | Lys127, Arg312 |
| 13 | STOCK1N-59369 |  | Passed | ND\* | ND\* | ND\* | ND\* |
| 14 | STOCK1N-43987 |  | Passed | -23.95 | -46.00 | -35.60 | Trp22, Arg312 |
| 19 | STOCK1N-57572 |  | Passed | -26.67 | -41.40 | -53.59 | Lys23, Ala219 |
| 20 | STOCK1N-31184 |  | Failed | -11.04 | -28.45 | -38.35 | - |
| 23 | STOCK1N-46421 |  | Passed | -35.55 | -46.55 | -59.89 | Lys127, Arg312 |
| 30 | STOCK1N-69620 |  | Passed | -11.47 | -43.73 | -53.19 | Lys23 |
|  | Epalrestat |  | Failed | -16.94 | -47.90 | -65.13 | Lys127 |

**\*Not Docked (ND)**

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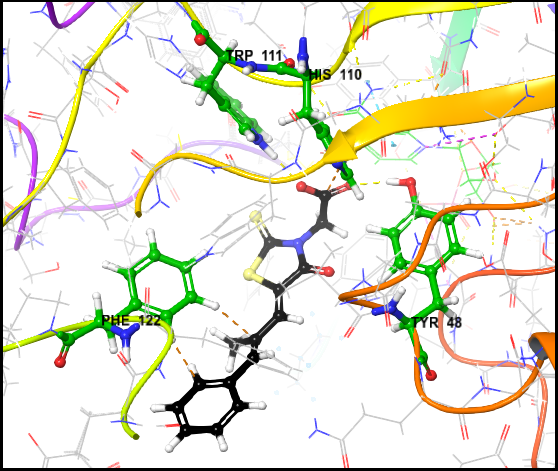
**Figure S1.** Aligned pose of ALR1 enzyme from porcine, in green; Homo sapiens, in blue (left) and similarity search data generated with SIM webserver (right).

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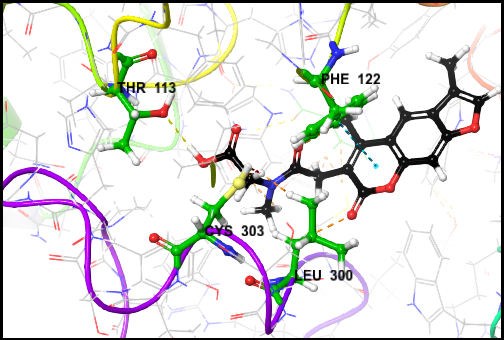
**Figure S2.** HNE mapped auto-pharmacophore showing key pharmacophoric features.

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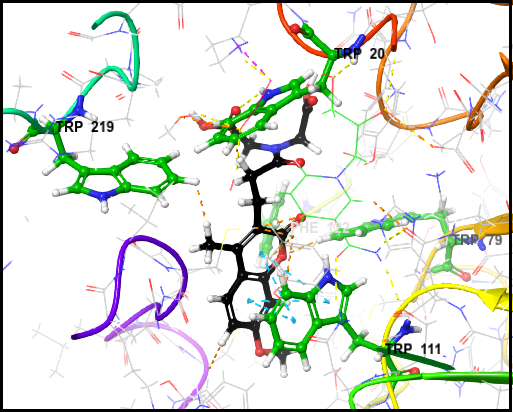
**Figure S3.** AUC score calculated on the basis of ROC analysis of the auto-pharmacophore of epalrestat (A) and HNE (B).

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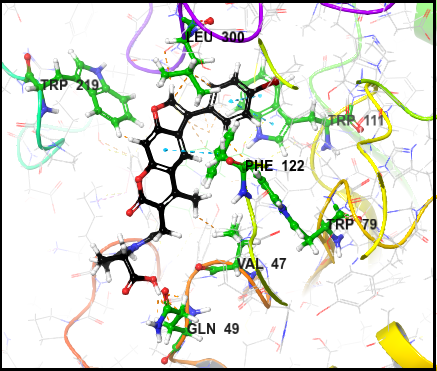
**Figure S4.** Docking pose showing key residue interaction of epalrestat with ALR2 protein.

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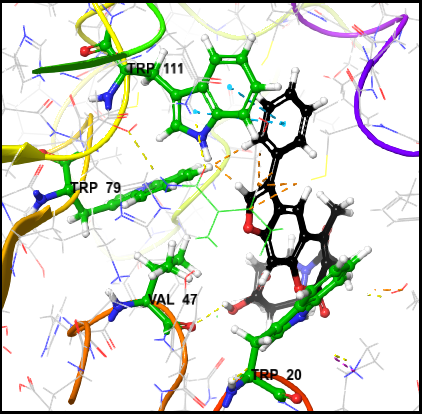
**Figure S5.** Docking pose showing key residue interaction of STOCKIN-44771 with ALR2 protein.

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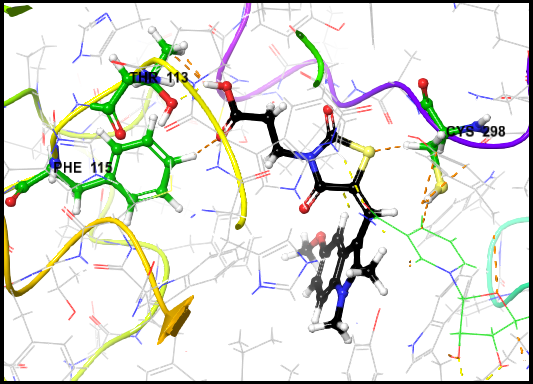
**Figure S6.** Docking pose showing key residue interaction of STOCKIN-46041 with ALR2 protein.

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**Figure S**7**.** Docking pose showing key residue interaction of STOCKIN-59369 with ALR2 protein.

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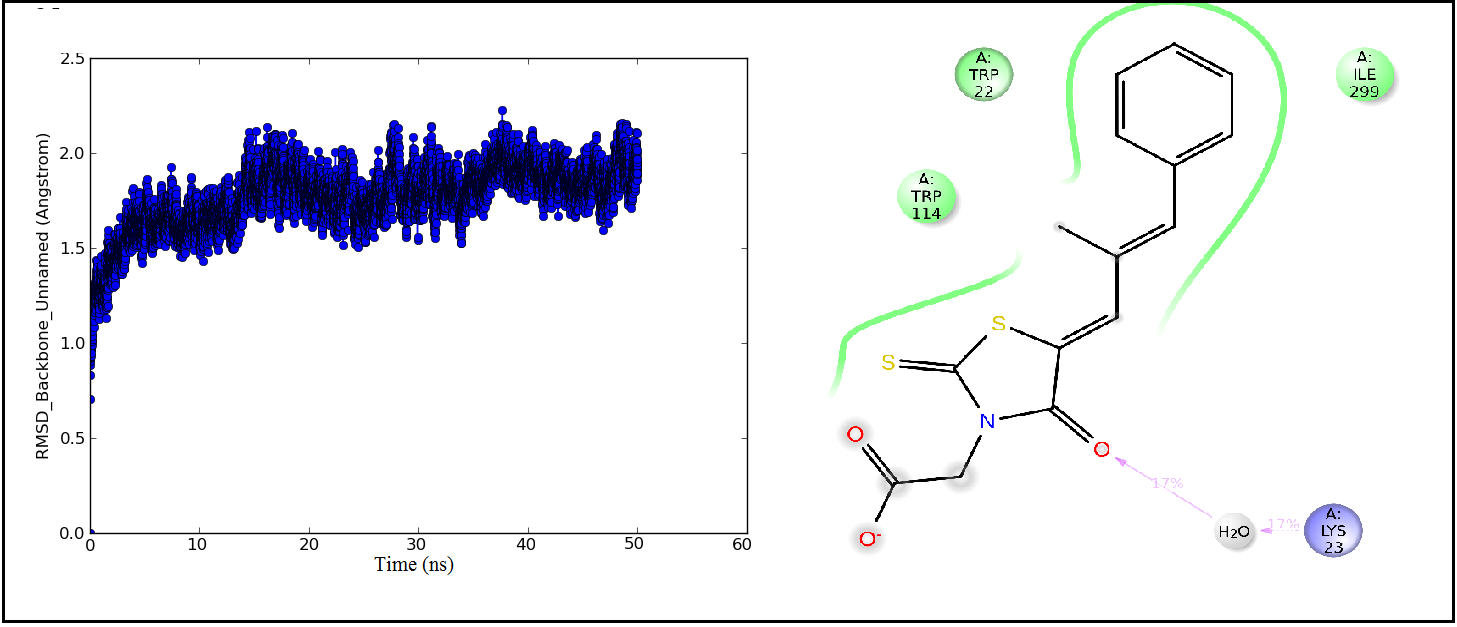
**Figure S8.** Docking pose showing key residue interaction of STOCKIN-69620 with ALR2 protein.

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**Figure S9.** Docking pose showing key residue interaction of STOCKIN-88220 with ALR2 protein.

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**Figure S10.** Histogram representing the interaction fractions of top five hits (A) STOCKIN-44771, (B) STOCKIN-46041, (C) STOCKIN-59369, (D) STOCKIN-69620, (E) STOCKIN-88220 in the catalytic domain of ALR2 throughout the simulation period of 50 ns.

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**Figure S11.** RMSD plot and contact summary of ALR1-Epalrestat complex throughout the simulation period of 50 ns.

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**Figure S12.** RMSD plot and contact summary of ALR1-44771 complex throughout the simulation period of 50 ns.

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**Figure S13.** RMSD plot and contact summary of ALR1-46041 complex throughout the simulation period of 50 ns.

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**Figure S14.** RMSD plot and contact summary of ALR1-69620 complex throughout the simulation period of 50 ns.

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**Figure S15.** RMSD plot and contact summary of ALR1-88220 complex throughout the simulation period of 50 ns.