

ALiBERO: Evolving a team of complementary pocket conformations rather than a single leader

Manuel Rueda¹, Max Totrov² and Ruben Abagyan¹

AUTHOR ADDRESS:

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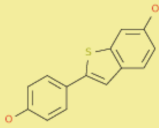
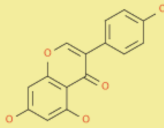
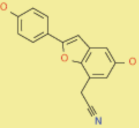
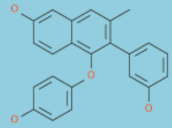
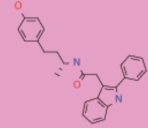
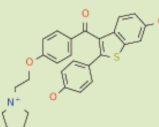
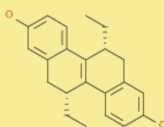
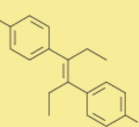
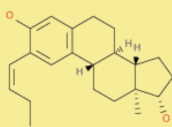
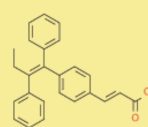
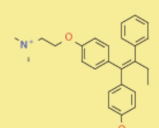
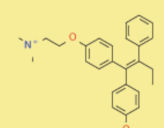
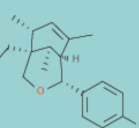
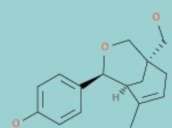
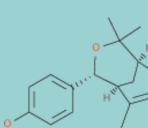
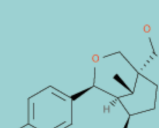
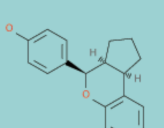
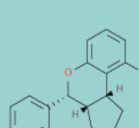
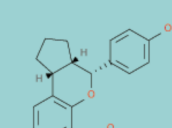
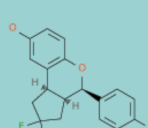
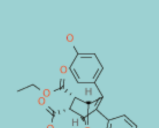
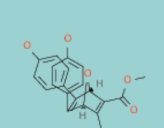
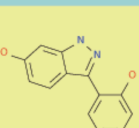
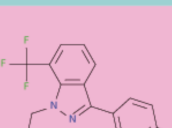
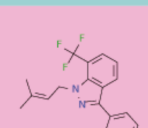
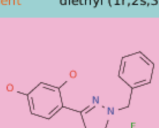
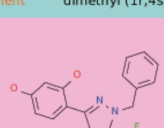
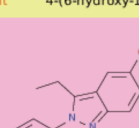
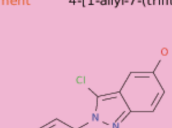
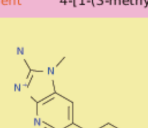
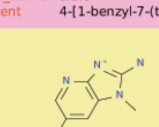
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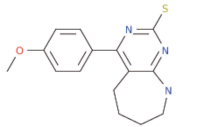
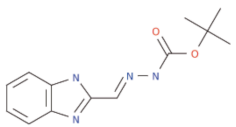
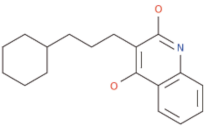
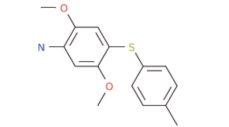
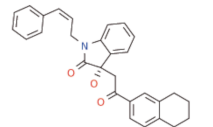
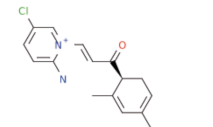
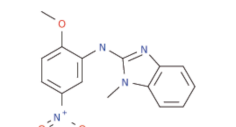
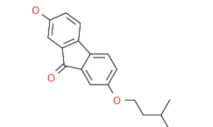
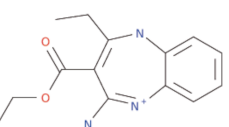
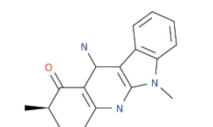
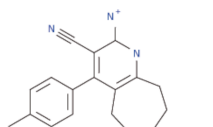
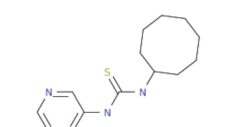
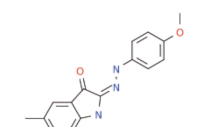
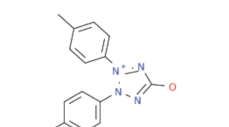
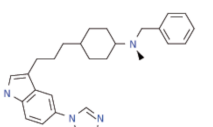
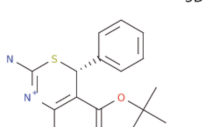
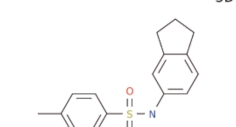
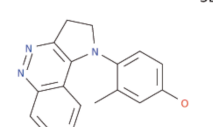
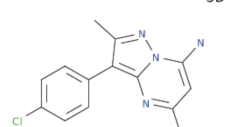
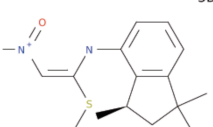
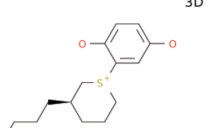
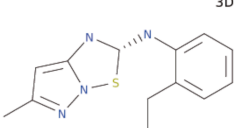
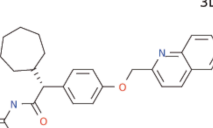
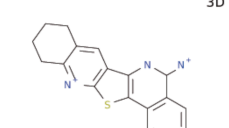
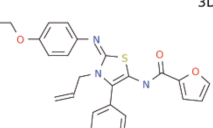
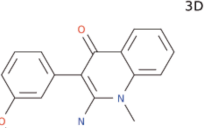
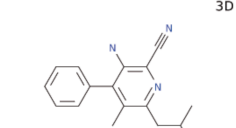
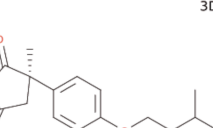
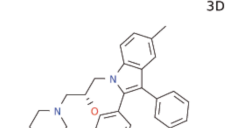
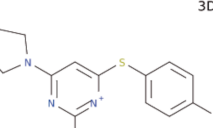
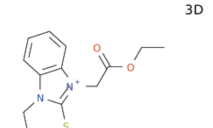
SUPPORTING INFORMATION AVAILABLE

Supporting Tables S1 and S2 including all compounds used in the training with ER α ($Tr_{1:1}$) and Supporting Figure S3. This information is available free of charge via the Internet at <http://pubs.acs.org>.

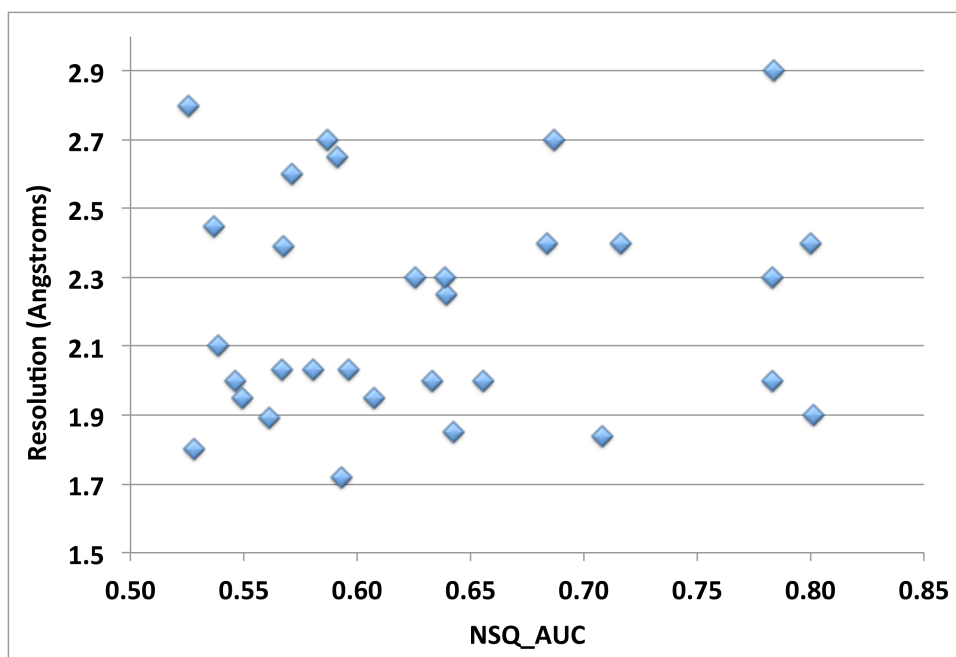
Supporting Table S1. List of the 31 active ligands (cognate ligands from the 31 PDB ID entries) used as training set ($Tr_{1,i}$) with the ER α protein.

| | | | | |
|---|---|--|---|---|
|  <p>Molecule Nam 1gwq Ligand_Name aztw comment raloxifene core</p> |  <p>Molecule Nam 1x7r Ligand_Name agen comment genistein</p> |  <p>Molecule Nam 1x7e Ligand_Name b244 comment [5-hydroxy-2-(4-hydroxyphenyl)-2H-benzofuran]</p> |  <p>Molecule Nam 3dt3 Ligand_Name a369 comment 5-(4-hydroxyphenoxy)-2,3-bis(4-chlorophenoxy)benzofuran</p> |  <p>Molecule Nam 2iok Ligand_Name aiok comment n-[(1r)-3-(4-hydroxyphenyl)propyl]-1H-benzotriazol-4-amine</p> |
|  <p>Molecule Nam 2r6y Ligand_Name allc comment [6-hydroxy-2-(4-hydroxyphenyl)-2H-benzofuran-3-yl]pyrrolidine</p> |  <p>Molecule Nam 1i2i Ligand_Name betc comment (r,r)-5,11-cis-diethyl-5,11-dihydro-2H-benzofuran</p> |  <p>Molecule Nam 3erd Ligand_Name ades comment diethylstilbestrol</p> |  <p>Molecule Nam 2g5o Ligand_Name bdrq comment (9alpha,13beta,17beta)-9,13,17-trimethyl-10,13,17-trihydro-2H-benzofuran</p> |  <p>Molecule Nam 1r5k Ligand_Name bgw5 comment (2e)-3-[4-[(1e)-1,2-dihydro-2H-benzofuran-3-yl]phenyl]acrylonitrile</p> |
|  <p>Molecule Nam 2bj4 Ligand_Name boht comment 4-hydroxytamoxifen</p> |  <p>Molecule Nam 3ert Ligand_Name aoht comment 4-hydroxytamoxifen</p> |  <p>Molecule Nam 1zky Ligand_Name a689 comment 4-[(1s,2s,5s)-5-(hydroxy(phenylamino)oxy)phenyl]-1H-indazole</p> |  <p>Molecule Nam 2b1v Ligand_Name b458 comment 4-[(1s,2s,5s)-5-(hydroxy(phenylamino)oxy)phenyl]-1H-indazole</p> |  <p>Molecule Nam 2g44 Ligand_Name bt3o comment 4-[(1s,2r,5s)-4,4,8-trimethyl-10,13,17-trihydro-2H-benzofuran-3-yl]phenyl</p> |
|  <p>Molecule Nam 2fai Ligand_Name b459 comment 4-[(1s,2s,5s,9r)-5-(hydroxy(phenylamino)oxy)phenyl]-1H-indazole</p> |  <p>Molecule Nam 2i0j Ligand_Name di0g comment (3as,4r,9br)-4-(4-hydroxyphenyl)-10,13,17-trimethyl-10,13,17-trihydro-2H-benzofuran</p> |  <p>Molecule Nam 2pog Ligand_Name awst comment (3as,4r,9br)-4-(4-hydroxyphenyl)-10,13,17-trimethyl-10,13,17-trihydro-2H-benzofuran</p> |  <p>Molecule Nam 2qe4 Ligand_Name bj3 comment (3as,4r,9br)-4-(4-hydroxyphenyl)-10,13,17-trimethyl-10,13,17-trihydro-2H-benzofuran</p> |  <p>Molecule Nam 2q70 Ligand_Name adc8 comment (3as,4r,9br)-2,2-difluoro-10,13,17-trimethyl-10,13,17-trihydro-2H-benzofuran</p> |
|  <p>Molecule Nam 2qh6 Ligand_Name bode comment diethyl (1r,2s,3r,4s)-5,6-dimethyl-10,13,17-trimethyl-10,13,17-trihydro-2H-benzofuran</p> |  <p>Molecule Nam 2qr9 Ligand_Name ahz3 comment dimethyl (1r,4s)-5,6-bis(methyl)-10,13,17-trimethyl-10,13,17-trihydro-2H-benzofuran</p> |  <p>Molecule Nam 2qa6 Ligand_Name bkn2 comment 4-(6-hydroxy-1H-indazol-3-yl)phenyl</p> |  <p>Molecule Nam 2qzo Ligand_Name bkn1 comment 4-[1-allyl-7-(trifluoromethyl)-1H-benzotriazol-4-yl]phenyl</p> |  <p>Molecule Nam 3osa Ligand_Name akn3 comment 4-[1-(3-methylbut-2-en-1-yl)-1H-benzotriazol-4-yl]phenyl</p> |
|  <p>Molecule Nam 3os8 Ligand_Name akn0 comment 4-[1-benzyl-7-(trifluoromethyl)-1H-benzotriazol-4-yl]phenyl</p> |  <p>Molecule Nam 3os8 Ligand_Name dkn0 comment 4-[1-benzyl-7-(trifluoromethyl)-1H-benzotriazol-4-yl]phenyl</p> |  <p>Molecule Nam 2qab Ligand_Name ael1 comment 3-ethyl-2-(4-hydroxyphenyl)-1H-indazole</p> |  <p>Molecule Nam 2qgw Ligand_Name aees comment 3-chloro-2-(4-hydroxyphenyl)-1H-indazole</p> |  <p>Molecule Nam 2qse Ligand_Name b1hp comment 4-(2-amino-1-methyl-1H-benzotriazol-4-yl)phenyl</p> |
|  <p>Molecule Nam 2qxm Ligand_Name bpiq comment 2-amino-1-methyl-6-phenyl-1H-benzotriazol-4-amine</p> | | | | |

Supporting Table S2. List of the 31 decoy compounds used as training set ($Tr_{1:l}$) with the ER α protein. The decoys were taken from Shoichet's directory of useful decoys (DUD) dataset.¹ The 31 ligands came from random selection among the 418 centroid clusters from all 4018 decoys in the entries "ER_agonist - Estrogen receptor agonist" and "ER_antagonist - Estrogen receptor antagonist").

| | | | | |
|--|--|---|---|--|
|  C15H17N3O5 |  C13H16N4O2 |  C18H23NO2 |  C15H17NO25 |  C29H27NO3 |
|  C16H18ClN2O |  C15H15N4O3 |  C18H18O3 |  C14H17N3O2 |  C17H19N3O |
|  C18H21N3 |  C14H21N3S |  C16H15N3O2 |  C15H15N4O |  C27H34N5 |
|  C16H20N2O25 |  C16H17NO25 |  C17H15N3O |  C14H13ClN4 |  C15H21N2O25 |
|  C15H23O25 |  C13H16N4S |  C27H30N2O3 |  C18H17N3S |  C25H23N3O3S |
|  C17H16N2O2 |  C17H19N3 |  C16H21NO3 |  C29H33N2O |  C14H15FN4S |
|  C14H17N2O3S | | | | |

Supporting Figure S3. Plot showing the poor correlation between the x-ray resolution and screening performance for the 31 PDB ID entries present in the ESR1_HUMAN_300_551 pocketome entry.



REFERENCES

1. Huang, N.; Shoichet, B. K.; Irwin, J. J., Benchmarking sets for molecular docking. *J. Med. Chem.* **2006**, 49, (23), 6789-801.