Ligand-based virtual screening, molecular docking, and molecular dynamic simulations of new β-estrogen receptor activators with potential for pharmacological obesity treatment

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Supplementary material

Table S1. PDB ID of estrogen receptor beta used in this study.

PDB ID	Descripcion	PDB ID	Descripcion
1L2J	Estrogen receptor beta, 271 aa	2I0G	Estrogen receptor beta, 257 aa
1NDE	Estrogen receptor beta, 255 aa	2JJ3	Estrogen receptor beta, 257 aa
1QKM	Estrogen receptor beta, 255 aa	2NV7	Estrogen receptor beta, 238 aa
1U3Q	Estrogen receptor beta, 240 aa	2QTU	Estrogen receptor beta, 257 aa
1U3R	Estrogen receptor beta, 241 aa	2YJD	Estrogen receptor beta, 240 aa
1U3S	Estrogen receptor beta, 240 aa	2YLY	Estrogen receptor beta, 240 aa
1U9E	Estrogen receptor beta, 241 aa	2Z4B	Estrogen receptor beta, 257 aa
1X76	Estrogen receptor beta, 240 aa	3OLL	Estrogen receptor beta, 240 aa
1X78	Estrogen receptor beta, 240 aa	3OLS	Estrogen receptor beta, 240 aa
1X7B	Estrogen receptor beta, 240 aa	3OMO	Estrogen receptor beta, 240 aa
1X7J	Estrogen receptor beta, 240 aa	3OMP	Estrogen receptor beta, 240 aa
1YY4	Estrogen receptor beta, 268 aa	3OMQ	Estrogen receptor beta, 240 aa
1YYE	Estrogen receptor beta, 268 aa	4J24	Estrogen receptor beta, 240 aa
1ZAF	Estrogen receptor beta, 238 aa	4J26	Estrogen receptor beta, 240 aa
2FSZ	Estrogen receptor beta, 246 aa	4ZI1	Estrogen receptor beta, 249 aa
2GIU	Estrogen receptor beta, 241 aa	5TOA	Estrogen receptor beta, 249 aa

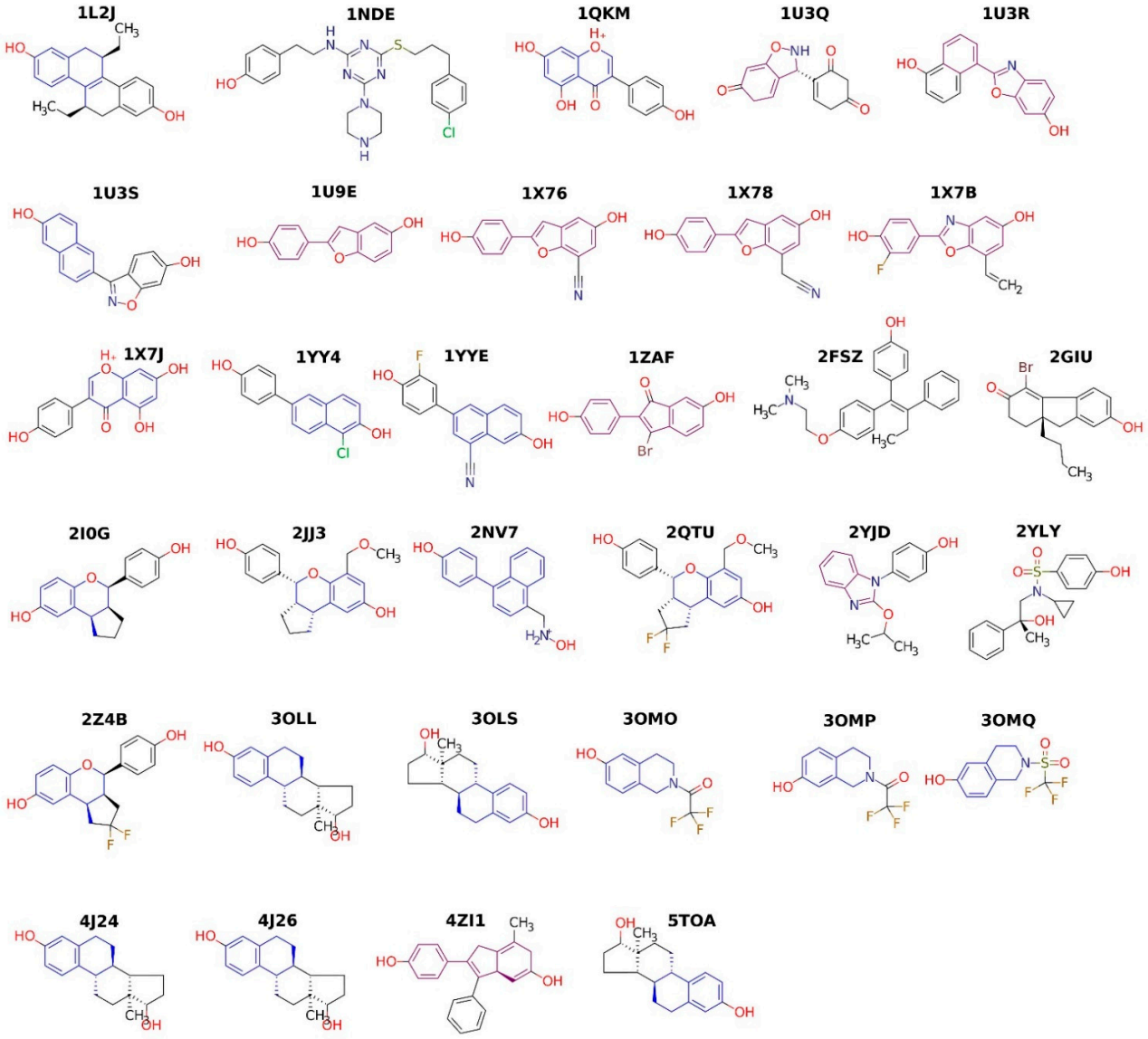

Figure S1. Co-crystallized ligands of estrogen receptor beta (ERβ). Each compound is identified by its PDB code. Compounds highlighted in blue were used to generate scaffold A and those used for scaffold B are in purple.

Table S2. Number of compounds for each stage of virtual screening.

	Sim			Sub			
Criteria	**SA**	**SB**	**SE**	**SA**	**SB**	**SE**	**Total**
Compounds retrieved from the database	2318	24571	3514	10671	46315	6796	94185
Lipinski's rule	123	1093	14	203	1097	100	2630
Elimination of duplicate compounds	109	768	13	189	595	59	1733
Compounds with a similarity > 0.8	29	104	13	189	595	59	989

Sim, similarity; Sub, substructure; SA, Scaffold A; SB, Scaffold B; SE, S-equol.

Table S3. Post-selection of potential ERβ activators by groups.

			Sim			Sub		
Criteria	**FDA**	**SA**	**SB**	**SE**	**SA**	**SB**	**SE**	**Total**
Cut-off value (-4.4 kcal/mol)	1103	15	58	11	156	625	90	2058
Interaction fingerprint	149	1	3	1	27	72	15	268

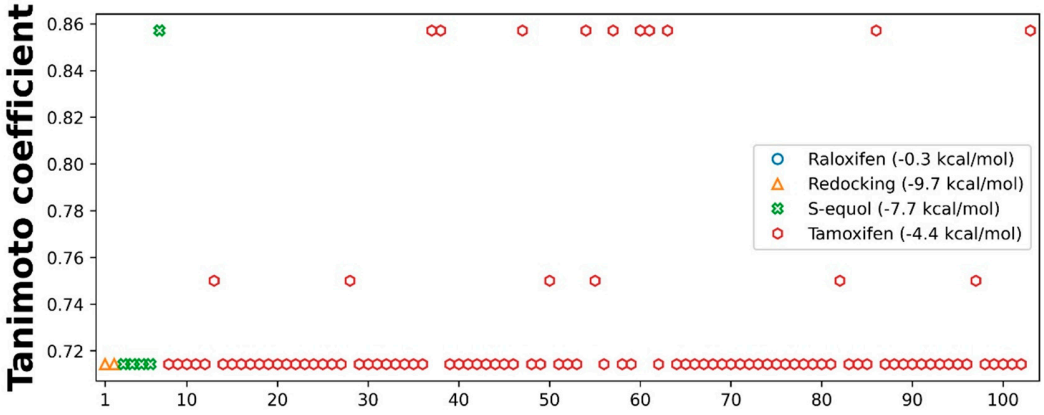

Figure S2. Interaction fingerprint of the selected compounds derived from the scaffolds A and B with a tanimoto coefficient > 0.7. Name of the compounds in the graph: 1: ZINC000000235493_sub_S2.4 (-9.1 kcal/mol); 2: ZINC000000558601_sub_S2.4 (-8.3 kcal/mol); 3: pubchem16096242_sub_S2.7 (-8.5 kcal/mol); 4: pubchem16114609_sub_S2.9 (-8.7 kcal/mol); 5: pubchem44550346_sub_S2.7 (-8.2 kcal/mol); 6: ZINC000006720868_sub_S1.3 (-7.4 kcal/mol); 7: ZINC000043152477_sub_S2.6 (-6.7 kcal/mol); 8: pubchem102029570_sub_S2.7 (-7.0 kcal/mol); 9: pubchem102159833_sub_S2.7 (-8.8 kcal/mol); 10: pubchem11290215_sub_S2.6 (-10.6 kcal/mol); 11: pubchem134968537_sub_S2.9 (-9.1 kcal/mol); 12: pubchem13901656_sub_S2.6 (-10.0 kcal/mol); 13: pubchem14387309_sub_S2.6 (-10.3 kcal/mol); 14: pubchem14387311_sub_S2.6 (-9.8 kcal/mol); 15: pubchem147054884_sub_S2.9 (-9.1 kcal/mol); 16: pubchem14920722_sub_S2.7 (-7.9 kcal/mol); 17: pubchem21032991_sub_S2.7 (-7.3 kcal/mol); 18: pubchem3027594_sim_S2.4 (-9.5 kcal/mol); 19: pubchem3784895_sub_S2.7 (-9.3 kcal/mol); 20: pubchem4253040_sub_S2.4 (-7.8 kcal/mol); 21: pubchem50850272_sub_S2.7 (-8.8 kcal/mol); 22: pubchem53423166_sub_S2.7 (-8.9 kcal/mol); 23: pubchem53497102_sim_S2.4 (-8.6 kcal/mol); 24: pubchem87145216_sub_S2.9 (-8.8 kcal/mol); 25: pubchem90477262_sub_S2.7 (-8.4 kcal/mol); 26: pubchem92045574_sub_S2.7 (-8.7 kcal/mol); 27: pubchem95910620_sub_S2.7 (-8.4 kcal/mol); 28: ZINC000000006701_sub_S2.7 (-9.0 kcal/mol); 29: ZINC000000019637_sub_S2.7 (-8.6 kcal/mol); 30: ZINC000000079780_sub_S1.3 (-8.2 kcal/mol); 31: ZINC000000099912_sub_S1.10 (-7.8 kcal/mol); 32: ZINC000000099914_sub_S1.10 (-5.5 kcal/mol); 33: ZINC000000107820_sub_S1.3 (-9.5 kcal/mol); 34: ZINC000000207155_sub_S1.10 (-6.9 kcal/mol); 35: ZINC000000207161_sub_S1.10 (-4.8 kcal/mol); 36: ZINC000000235985_sub_S2.7 (-8.5 kcal/mol); 37: ZINC000000273801_sub_S1.3 (-8.1 kcal/mol); 38: ZINC000000329772_sub_S1.3 (-8.3 kcal/mol); 39: ZINC000000349576_sub_S2.3 (-8.8 kcal/mol); 40: ZINC000000392849_sub_S1.12 (-10.0 kcal/mol); 41: ZINC000000506694_sub_S2.7 (-8.7 kcal/mol); 42: ZINC000001433321_sub_S2.7 (-8.3 kcal/mol); 43: ZINC000001650698_sub_S1.3 (-7.8 kcal/mol); 44: ZINC000001665251_sub_S1.12 (-9.2 kcal/mol); 45: ZINC000001669547_sub_S1.12 (-9.5 kcal/mol); 46: ZINC000001736836_sub_S1.3 (-5.6 kcal/mol); 47: ZINC000002584535_sub_S2.7 (-8.8 kcal/mol); 48: ZINC000002584539_sub_S2.7 (-8.5 kcal/mol); 49: ZINC000002997427_sub_S1.3 (-7.4 kcal/mol); 50: ZINC000003109197_sub_S1.3 (-7.7 kcal/mol); 51: ZINC000003844826_sub_S2.3 (-9.3 kcal/mol); 52: ZINC000003844883_sub_S2.3 (-9.0 kcal/mol); 53: ZINC000004571345_sub_S1.3 (-7.8 kcal/mol); 54: ZINC000004713938_sub_S2.3 (-9.4 kcal/mol); 55: ZINC000004736776_sub_S2.4 (-7.7 kcal/mol); 56: ZINC000005361254_sub_S2.9 (-7.4 kcal/mol); 57: ZINC000013118874_sub_S2.3 (-9.3 kcal/mol); 58: ZINC000016162088_sub_S2.7 (-7.8 kcal/mol); 59: ZINC000018051528_sub_S2.7 (-9.1 kcal/mol); 60: ZINC000019909740_sub_S1.12 (-9.5 kcal/mol); 61: ZINC000019909743_sub_S1.12 (-9.3 kcal/mol); 62: ZINC000025495200_sub_S2.5 (-7.3 kcal/mol); 63: ZINC000032264139_sub_S2.7 (-9.3 kcal/mol); 64: ZINC000032271185_sub_S1.6 (-9.6 kcal/mol); 65: ZINC000034283373_sub_S2.7 (-9.2 kcal/mol); 66: ZINC000035075930_sub_S2.7 (-8.4 kcal/mol); 67: ZINC000035963070_sim_S1.10 (-8.2 kcal/mol); 68: ZINC000036406739_sub_S1.12 (-9.1 kcal/mol); 69: ZINC000038841808_sub_S1.12 (-9.0 kcal/mol); 70: ZINC000038885998_sub_S2.5 (-7.8 kcal/mol); 71: ZINC000039120152_sim_S2.6 (-8.6 kcal/mol); 72: ZINC000039189287_sub_S2.5 (-8.5 kcal/mol); 73: ZINC000039189289_sub_S2.5 (-8.6 kcal/mol); 74: ZINC000039212519_sub_S2.7 (-9.0 kcal/mol); 75: ZINC000039304508_sub_S1.3 (-8.9 kcal/mol); 76: ZINC000045919981_sub_S2.7 (-8.9 kcal/mol); 77: ZINC000045923438_sub_S2.7 (-8.9 kcal/mol); 78: ZINC000045946712_sub_S2.7 (-9.5 kcal/mol); 79: ZINC000045946717_sub_S2.7 (-9.3 kcal/mol); 80: ZINC000045946736_sub_S2.7 (-9.4 kcal/mol); 81: ZINC000071769464_sub_S2.9 (-9.4 kcal/mol); 82: ZINC000071780618_sub_S2.6 (-7.8 kcal/mol); 83: ZINC000071784641_sub_S2.3 (-10.3 kcal/mol); 84: ZINC000096027552_sub_S1.3 (-7.8 kcal/mol); 85: ZINC000100365916_sub_S2.3 (-8.8 kcal/mol); 86: ZINC000100496590_sub_S2.6 (-9.0 kcal/mol); 87: ZINC000100531228_sub_S2.3 (-6.8 kcal/mol); 88: ZINC000103184740_sub_S2.12 (-8.7 kcal/mol); 89: ZINC000103184747_sub_S2.12 (-8.5 kcal/mol); 90: ZINC000103184834_sub_S2.12 (-9.4 kcal/mol); 91: ZINC000103185949_sub_S2.12 (-8.7 kcal/mol); 92: ZINC000103187202_sub_S2.12 (-9.4 kcal/mol); 93: ZINC000147535771_sub_S1.3 (-9.4 kcal/mol); 94: ZINC000169314377_sub_S1.3 (-9.5 kcal/mol); 95: ZINC000196467451_sub_S2.5 (-7.2 kcal/mol); 96: ZINC000199434926_sub_S2.3 (-8.6 kcal/mol); 97: ZINC000254797150_sub_S2.3 (-8.6 kcal/mol); 98: ZINC000584596711_sub_S2.9 (-8.7 kcal/mol); 99: ZINC000584596772_sub_S2.9 (-9.4 kcal/mol); 100: ZINC000584596773_sub_S2.9 (-10.1 kcal/mol); 101: ZINC000584649928_sub_S2.9 (-9.0 kcal/mol); 102: ZINC000020154399_sub_S2.4 (-9.5 kcal/mol); 103: ZINC001088689404_sub_S1.12 (-10.3 kcal/mol).

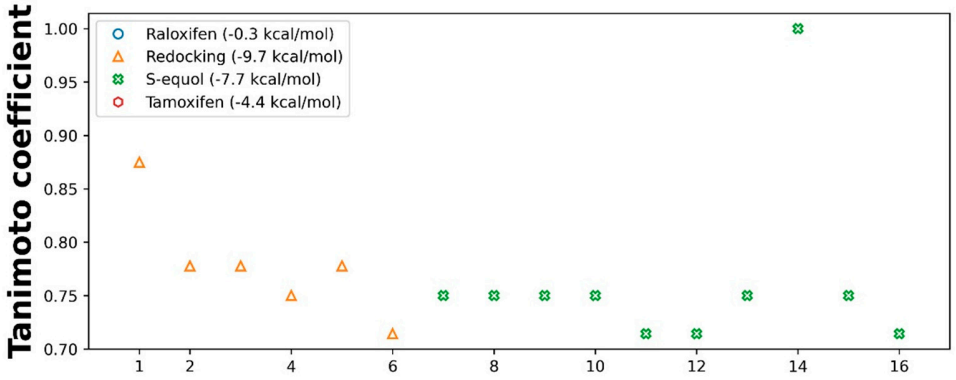

Figure S3. Interaction fingerprint of s-equol analogs with respect to control compounds. Name of the compounds in the graph. 1: ZINC000000388661_sub (-9.7 kcal/mol); 2: ZINC000000899786_sub (-10.1 kcal/mol); 3: ZINC000002558134_sub (-9.9 kcal/mol); 4: ZINC000003978471_sub (-8.7 kcal/mol); 5: ZINC000014811582_sub (-9.8 kcal/mol); 6: ZINC000014820588_sub (-8.8 kcal/mol); 7: ZINC000000899787_sub (-7.6 kcal/mol); 8: ZINC000001607536_sub (-7.5 kcal/mol); 9: ZINC000001608397_sub (-7.0 kcal/mol); 10: ZINC000003833872_sub (-7.4 kcal/mol); 11: ZINC000004655109_sub (-6.7 kcal/mol); 12: ZINC000014758732_sub (-6.5 kcal/mol); 13: ZINC000014820468_sub (-6.4 kcal/mol); 14: ZINC000028865986_sim (-7.7 kcal/mol); 15: ZINC000049601467_sub (-4.6 kcal/mol); 16: ZINC000138252870_sub (-6.3 kcal/mol).

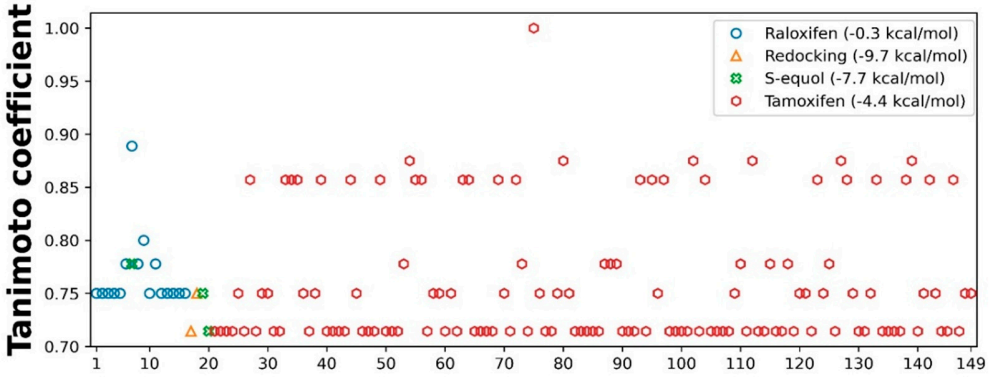

Figure S4. Selection of FDA compounds with interaction fingerprint similar to control compounds. Name of the compounds in the graph: 1: ZINC000000000346 (-8.0 kcal/mol); 2: ZINC000000000449 (-8.2 kcal/mol); 3: ZINC000000601316 (-8.6 kcal/mol); 4: ZINC000000968326 (-8.1 kcal/mol); 5: ZINC000001530706 (-7.0 kcal/mol); 6: ZINC000001548097 (-6.2 kcal/mol); 7: ZINC000001550766 (-6.7 kcal/mol); 8: ZINC000003785276 (-7.3 kcal/mol); 9: ZINC000003802417 (-5.6 kcal/mol); 10: ZINC000003927200 (-4.8 kcal/mol); 11: ZINC000012468792 (-6.2 kcal/mol); 12: ZINC000019632706 (-5.6 kcal/mol); 13: ZINC000022065398 (-7.1 kcal/mol); 14: ZINC000030691763 (-4.8 kcal/mol); 15: ZINC000085205451 (-6.6 kcal/mol); 16: ZINC000100036536 (-9.0 kcal/mol); 17: ZINC000000002272 (-9.1 kcal/mol); 18: ZINC000118912393 (-10.2 kcal/mol); 19: ZINC000000056652 (-7.0 kcal/mol); 20: ZINC000043207851 (-8.2 kcal/mol); 21: ZINC000000000347 (-5.4 kcal/mol); 22: ZINC000000000506 (-7.3 kcal/mol); 23: ZINC000000000655 (-8.0 kcal/mol); 24: ZINC000000001587 (-8.0 kcal/mol); 25: ZINC000000001982 (-7.3 kcal/mol); 26: ZINC000000002688 (-9.8 kcal/mol); 27: ZINC000000004778 (-8.2 kcal/mol); 28: ZINC000000004893 (-8.9 kcal/mol); 29: ZINC000000006251 (-7.5 kcal/mol); 30: ZINC000000011012 (-8.6 kcal/mol); 31: ZINC000000020248 (-7.5 kcal/mol); 32: ZINC000000020250 (-8.7 kcal/mol); 33: ZINC000000056556 (-7.8 kcal/mol); 34: ZINC000000057001 (-5.8 kcal/mol); 35: ZINC000000057062 (-6.3 kcal/mol); 36: ZINC000000120319 (-7.7 kcal/mol); 37: ZINC000000537752 (-6.5 kcal/mol); 38: ZINC000000538312 (-5.3 kcal/mol); 39: ZINC000000538483 (-7.3 kcal/mol); 40: ZINC000000538627 (-6.3 kcal/mol); 41: ZINC000000584092 (-5.8 kcal/mol); 42: ZINC000000591993 (-5.8 kcal/mol); 43: ZINC000000607939 (-6.0 kcal/mol); 44: ZINC000000607986 (-7.2 kcal/mol); 45: ZINC000000608382 (-5.5 kcal/mol); 46: ZINC000000896560 (-5.5 kcal/mol); 47: ZINC000000897085 (-9.4 kcal/mol); 48: ZINC000000897240 (-7.4 kcal/mol); 49: ZINC000000968273 (-8.6 kcal/mol); 50: ZINC000000968274 (-9.1 kcal/mol); 51: ZINC000000968275 (-9.0 kcal/mol); 52: ZINC000000968303 (-6.7 kcal/mol); 53: ZINC000000968336 (-8.3 kcal/mol); 54: ZINC000001530575 (-7.7 kcal/mol); 55: ZINC000001530579 (-6.5 kcal/mol); 56: ZINC000001530580 (-6.5 kcal/mol); 57: ZINC000001530613 (-7.3 kcal/mol); 58: ZINC000001530617 (-6.1 kcal/mol); 59: ZINC000001530618 (-6.5 kcal/mol); 60: ZINC000001530625 (-8.9 kcal/mol); 61: ZINC000001530689 (-5.0 kcal/mol); 62: ZINC000001530695 (-5.1 kcal/mol); 63: ZINC000001530752 (-6.9 kcal/mol); 64: ZINC000001530761 (-6.4 kcal/mol); 65: ZINC000001530814 (-9.0 kcal/mol); 66: ZINC000001530816 (-7.2 kcal/mol); 67: ZINC000001530817 (-7.2 kcal/mol); 68: ZINC000001530929 (-6.6 kcal/mol); 69: ZINC000001530939 (-7.0 kcal/mol); 70: ZINC000001530951 (-6.5 kcal/mol); 71: ZINC000001530975 (-8.4 kcal/mol); 72: ZINC000001530977 (-9.8 kcal/mol); 73: ZINC000001534965 (-5.9 kcal/mol); 74: ZINC000001542392 (-5.1 kcal/mol); 75: ZINC000001550499 (-10.0 kcal/mol); 76: ZINC000001554010 (-7.5 kcal/mol); 77: ZINC000001850374 (-7.7 kcal/mol); 78: ZINC000001850376 (-7.3 kcal/mol); 79: ZINC000001851149 (-6.3 kcal/mol); 80: ZINC000001886617 (-7.4 kcal/mol); 81: ZINC000001996117 (-4.8 kcal/mol); 82: ZINC000002016257 (-6.7 kcal/mol); 83: ZINC000002016258 (-6.8 kcal/mol); 84: ZINC000003794601 (-7.7 kcal/mol); 85: ZINC000003795819 (-9.1 kcal/mol); 86: ZINC000003798757 (-5.8 kcal/mol); 87: ZINC000003799072 (-6.6 kcal/mol); 88: ZINC000003807172 (-4.7 kcal/mol); 89: ZINC000003810860 (-9.2 kcal/mol); 90: ZINC000003812974 (-6.9 kcal/mol); 91: ZINC000003812988 (-6.5 kcal/mol); 92: ZINC000003812989 (-7.0 kcal/mol); 93: ZINC000003813088 (-6.9 kcal/mol); 94: ZINC000003830339 (-7.6 kcal/mol); 95: ZINC000003830713 (-7.1 kcal/mol); 96: ZINC000003831138 (-6.1 kcal/mol); 97: ZINC000003831165 (-7.1 kcal/mol); 98: ZINC000003831405 (-7.8 kcal/mol); 99: ZINC000003872520 (-5.6 kcal/mol); 100: ZINC000003872738 (-7.3 kcal/mol); 101: ZINC000003874950 (-6.9 kcal/mol); 102: ZINC000003875980 (-5.7 kcal/mol); 103: ZINC000003914808 (-5.2 kcal/mol); 104: ZINC000003929508 (-6.5 kcal/mol); 105: ZINC000003956788 (-8.0

kcal/mol); 106: ZINC000003972949 (-7.1 kcal/mol); 107: ZINC000003979899 (-6.3 kcal/mol); 108: ZINC000004217732 (-7.0 kcal/mol); 109: ZINC000004474414 (-4.6 kcal/mol); 110: ZINC000004474460 (-7.0 kcal/mol); 111: ZINC000004618208 (-7.4 kcal/mol); 112: ZINC000004629876 (-4.9 kcal/mol); 113: ZINC000004654889 (-7.4 kcal/mol); 114: ZINC000004676424 (-6.5 kcal/mol); 115: ZINC000004978673 (-6.9 kcal/mol); 116: ZINC000006094354 (-9.0 kcal/mol); 117: ZINC000006845963 (-7.3 kcal/mol); 118: ZINC000006920384 (-6.4 kcal/mol); 119: ZINC000007997897 (-9.7 kcal/mol); 120: ZINC000008214703 (-6.7 kcal/mol); 121: ZINC000008220878 (-6.2 kcal/mol); 122: ZINC000009212654 (-8.4 kcal/mol); 123: ZINC000011680943 (-7.2 kcal/mol); 124: ZINC000012404516 (-4.8 kcal/mol); 125: ZINC000012484958 (-8.8 kcal/mol); 126: ZINC000012503099 (-8.6 kcal/mol); 127: ZINC000012661824 (-8.3 kcal/mol); 128: ZINC000013973998 (-7.2 kcal/mol); 129: ZINC000014881137 (-6.3 kcal/mol); 130: ZINC000019156872 (-8.8 kcal/mol); 131: ZINC000019632614 (-4.7 kcal/mol); 132: ZINC000019632670 (-5.1 kcal/mol); 133: ZINC000033943508 (-8.8 kcal/mol); 134: ZINC000035801098 (-6.4 kcal/mol); 135: ZINC000035999642 (-7.6 kcal/mol); 136: ZINC000053084692 (-7.9 kcal/mol); 137: ZINC000084589076 (-9.0 kcal/mol); 138: ZINC000084758479 (-5.7 kcal/mol); 139: ZINC000096014710 (-8.2 kcal/mol); 140: ZINC000100001918 (-8.1 kcal/mol); 141: ZINC000100001965 (-5.9 kcal/mol); 142: ZINC000100006264 (-8.8 kcal/mol); 143: ZINC000100009278 (-7.8 kcal/mol); 144: ZINC000100018594 (-7.0 kcal/mol); 145: ZINC000100018854 (-5.4 kcal/mol); 146: ZINC000100296828 (-8.0 kcal/mol); 147: ZINC000101489663 (-7.7 kcal/mol); 148: ZINC000116473771 (-4.7 kcal/mol); 149: ZINC000410428674 (-4.5 kcal/mol).

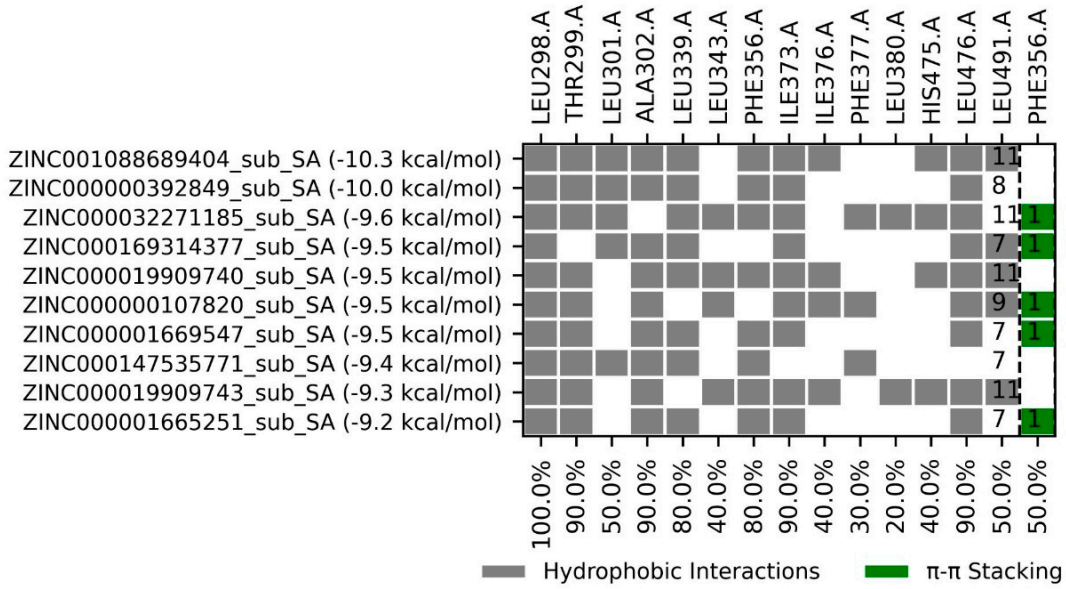

Figure S5. Interaction profile of the top ten compounds derived from scaffold A, docked to the active site of ERβ. The number at the end of each type of interaction is the total number of interactions for each compound.

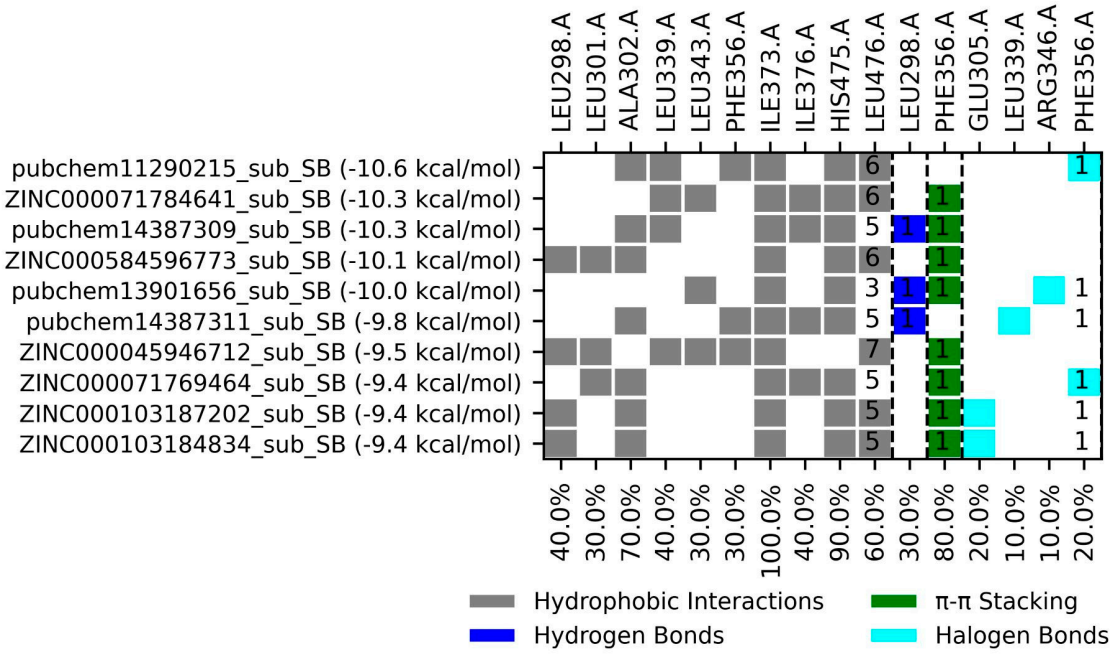

Figure S6. Interactions of the top ten scaffold B compounds docked at the active site of the ERβ.

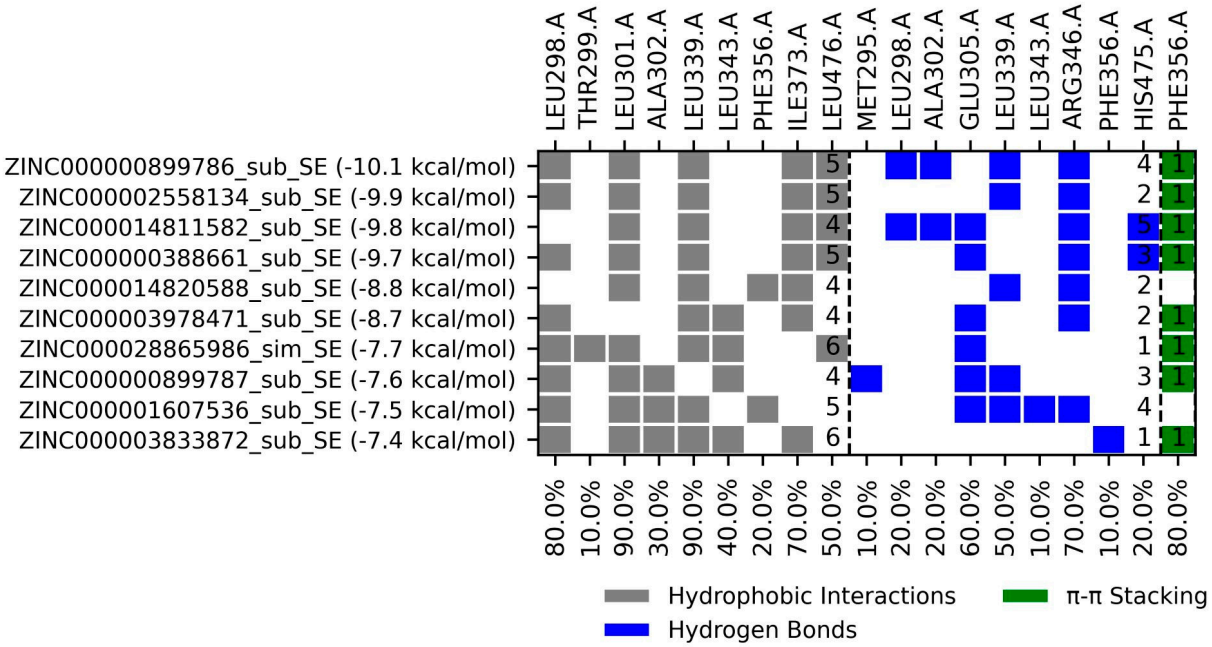

Figure S7. Interactions of the top ten compounds of s-equol analogs on the active site of ERβ.

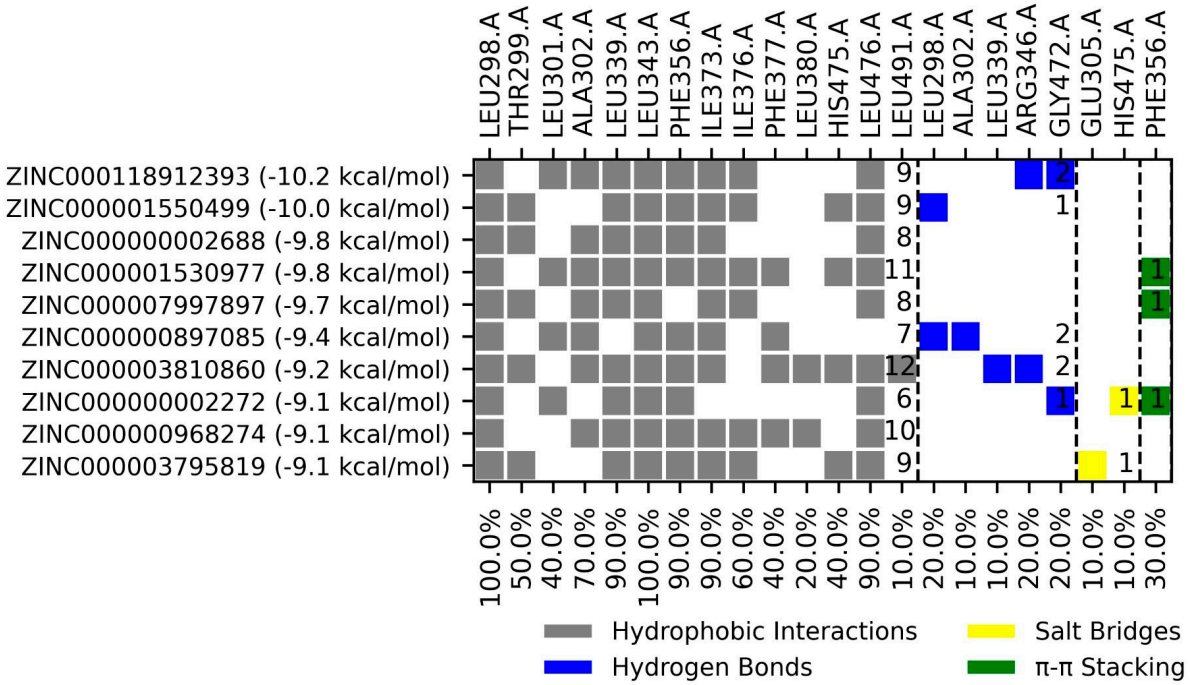

Figure S8. The top ten FDA compounds docked to the ERβ active site.

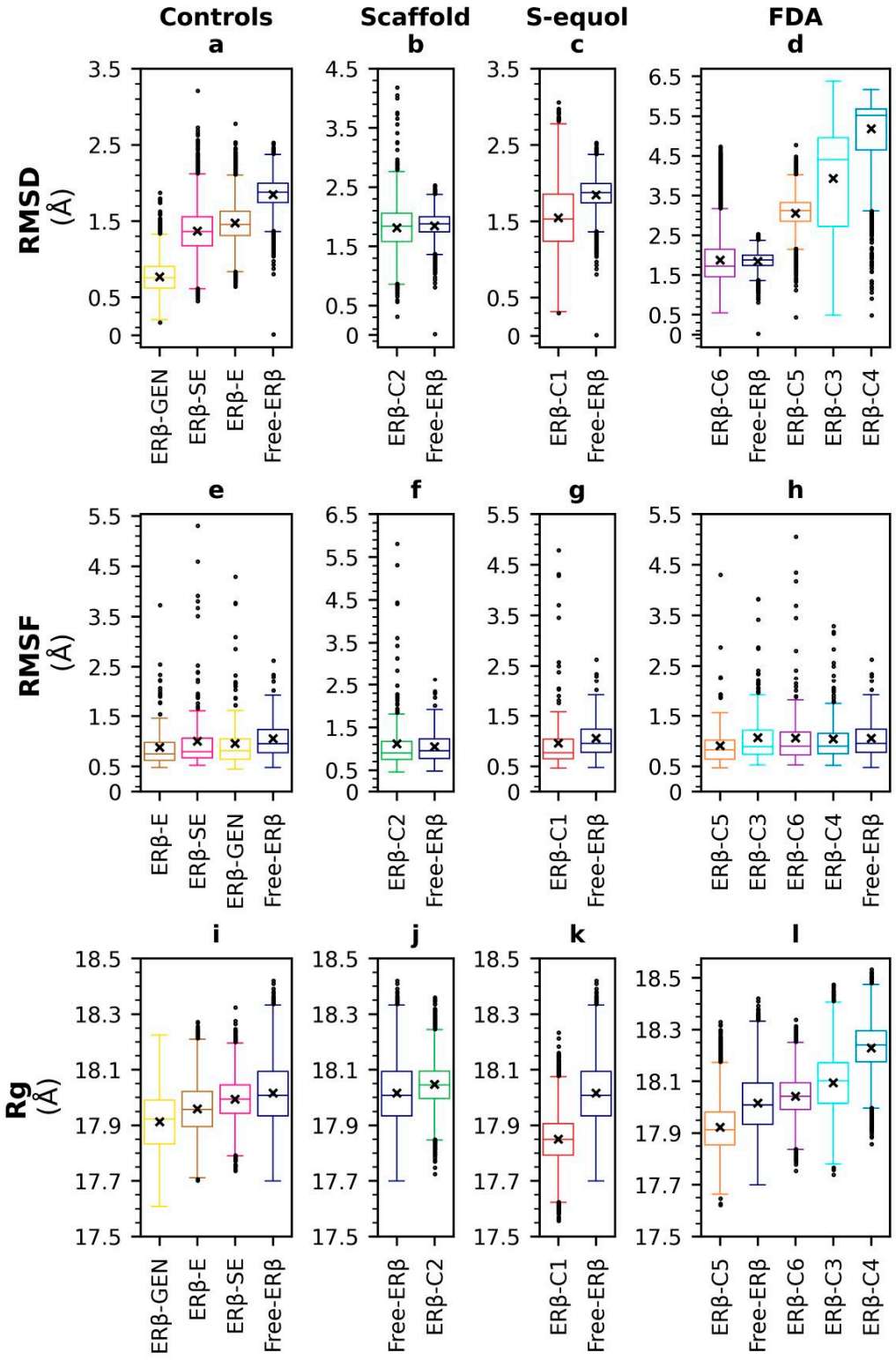

Figure S9. Box plot of RMSD (a-d), RMSF (e-h) and Rg (i-l). The graphs are ordered according to the median, the average is represented by an "x", the points denote outliers.

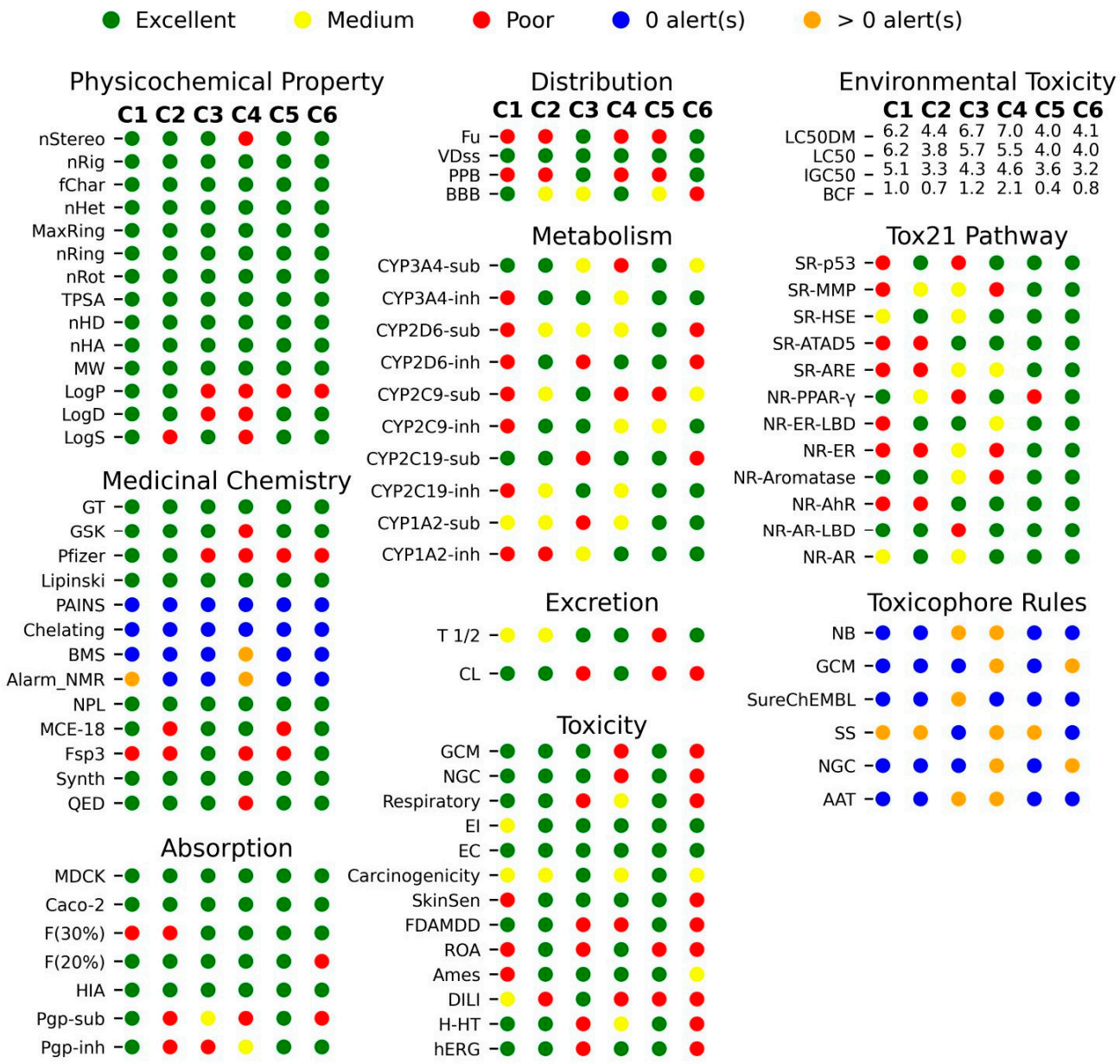

Figure S10. Evaluation ADMET of compounds C1-6.