Docking validation

We performed docking on ER alpha. First, we performed docking validation on *ER alpha*. The reliability of docking accuracy was assessed in two steps. In the first step re-docking of the native ligand was performed. While, in the second step, cross-docking experiment was carried out. Three-dimensional structures of eight ER alpha enzymes were retrieved from PDB. For every available structure, each native ligand was docked.

1. Self-docking on *ERα*

Validation of the docking protocol was carried out using re-dock procedure. All the native ligands were extracted and redocked into corresponding enzyme. The root means square deviation (RMSD) was calculated for the each re-docked and experimental native ligand. Triangle Matcher place algorithm with Affinity *d*G scoring function for all the simulation was found best. Final score function was computed with GBVI/WAS *d*G score function in the rigid receptor protocol.

Table S1. Results of re-docking of native inhibitors.

PDB ID	RMSD (Å)*
1A52	0.69
3ERT	1.65
1GWQ	0.98
1UOM	1.01
5W9D	0.97

* Green box = Good pose; Yellow box = close pose.

2. Cross docking on *h*DHFR

Cross-docking experiment was performed in the next step. Three-dimensional structures of five ER*α* were retrieved from PDB. For every available structure, each native ligand was docked. The quality of docking accuracy / docking pose was assessed with the following RMSD values range.

≤ 1.10 = Good pose (Green box)
< 1.11-1.90 = close pose (yellow box)
≥ 2.00 bad pose (Red box)

Table S2. Cross-docking results for various PDB IDs from ER*α*.

	RMSD (Å)				
	1A52	**3ERT**	**1GWQ**	**1UOM**	**5W9D**
1A52	0.69	0.96	0.98	0.82	0.99
3ERT	1.18	0.91	1.48	1.28	1.01
1GWQ	1.18	1.57	1.36	0.78	1.36
1UOM	1.18	1.97	1.82	1.06	2.13
5W9D	1.09	1.15	1.04	0.84	1.04

≤ 1.10 = Good pose (Green box); < 1.11-1.90 = close pose (yellow box); ≥ 2.00 bad pose (Red box).

The results shown in **Table S2** indicates that docking simulations carried out on 3-D structures in complex with different ligand had only about 64 % of chance of reliable pose. It is revealed from the cross-docking experiment that for 1A52 and 5W9D, it is possible to dock five ligands with RMSD range of 0.81-1.37 Å. Furthermore, the native ligand of 1DLS is MTX that has structural similarity with our synthesized ligands.

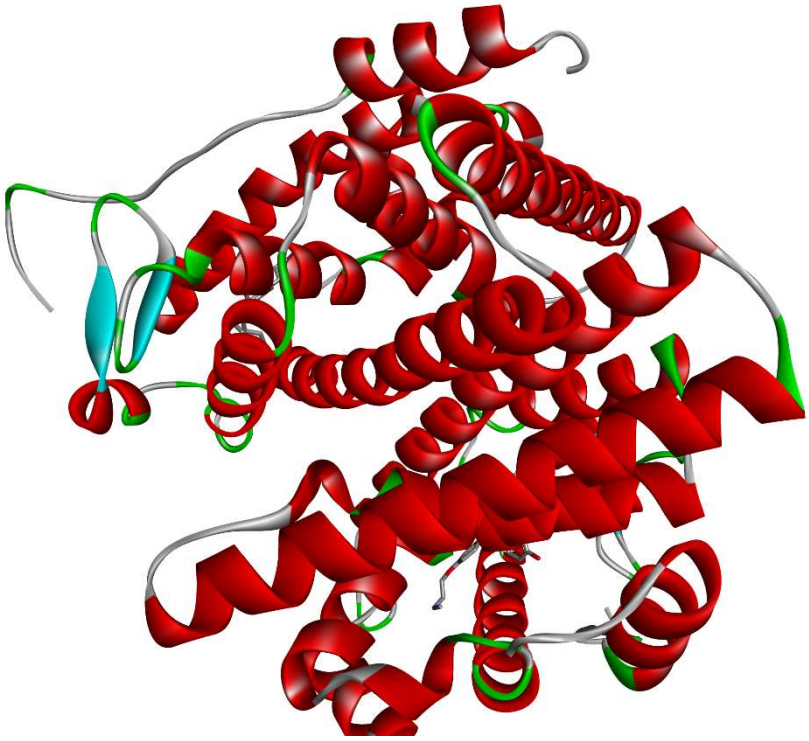

Figure S1. Structure of estrogen receptor alpha (ERα/pdb id=5W9D) protein.

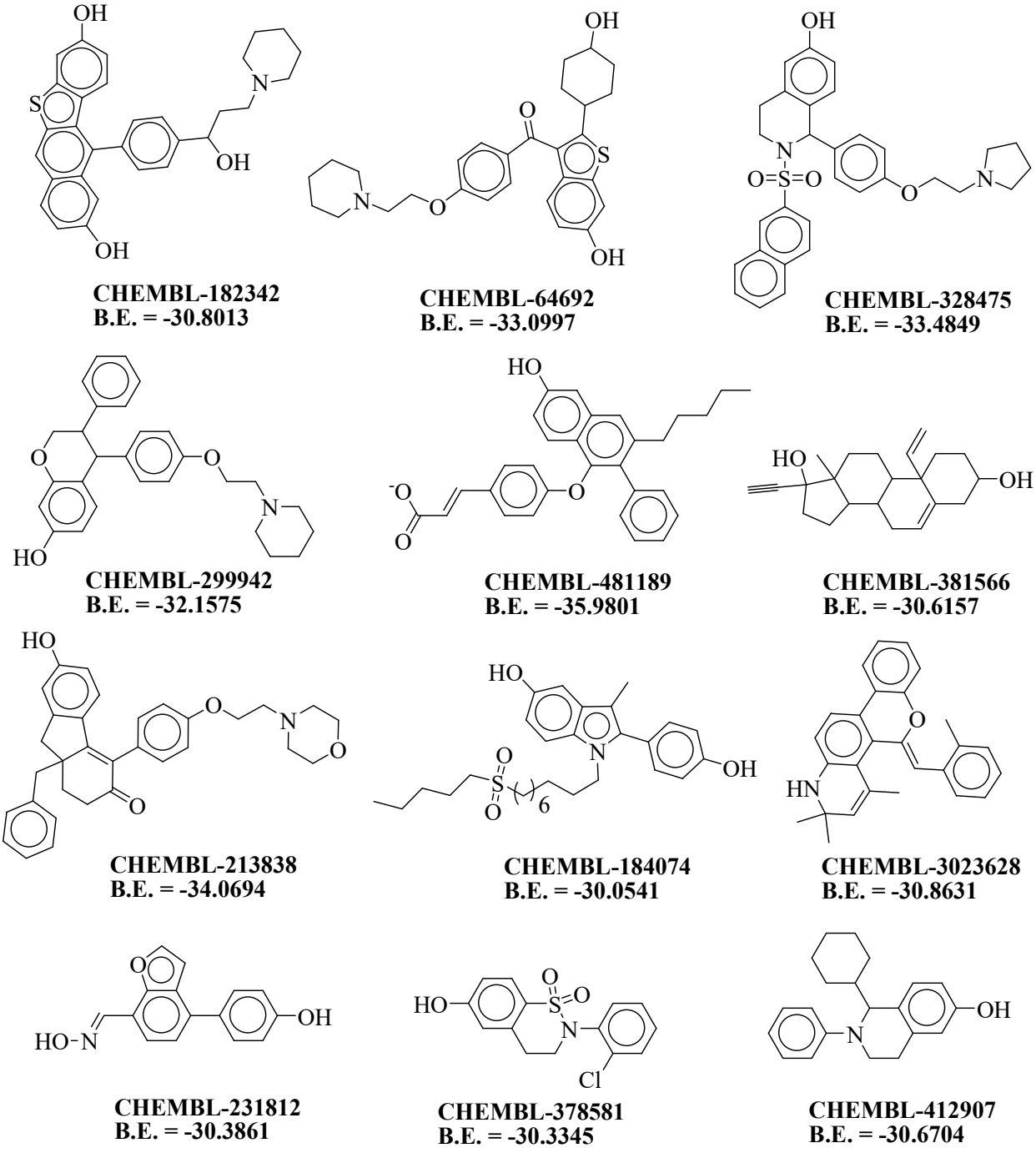

Figure S2. Chemical structures and binding energies (B.E. in kcal/mol) of the active compounds obtained from CHEMBL.

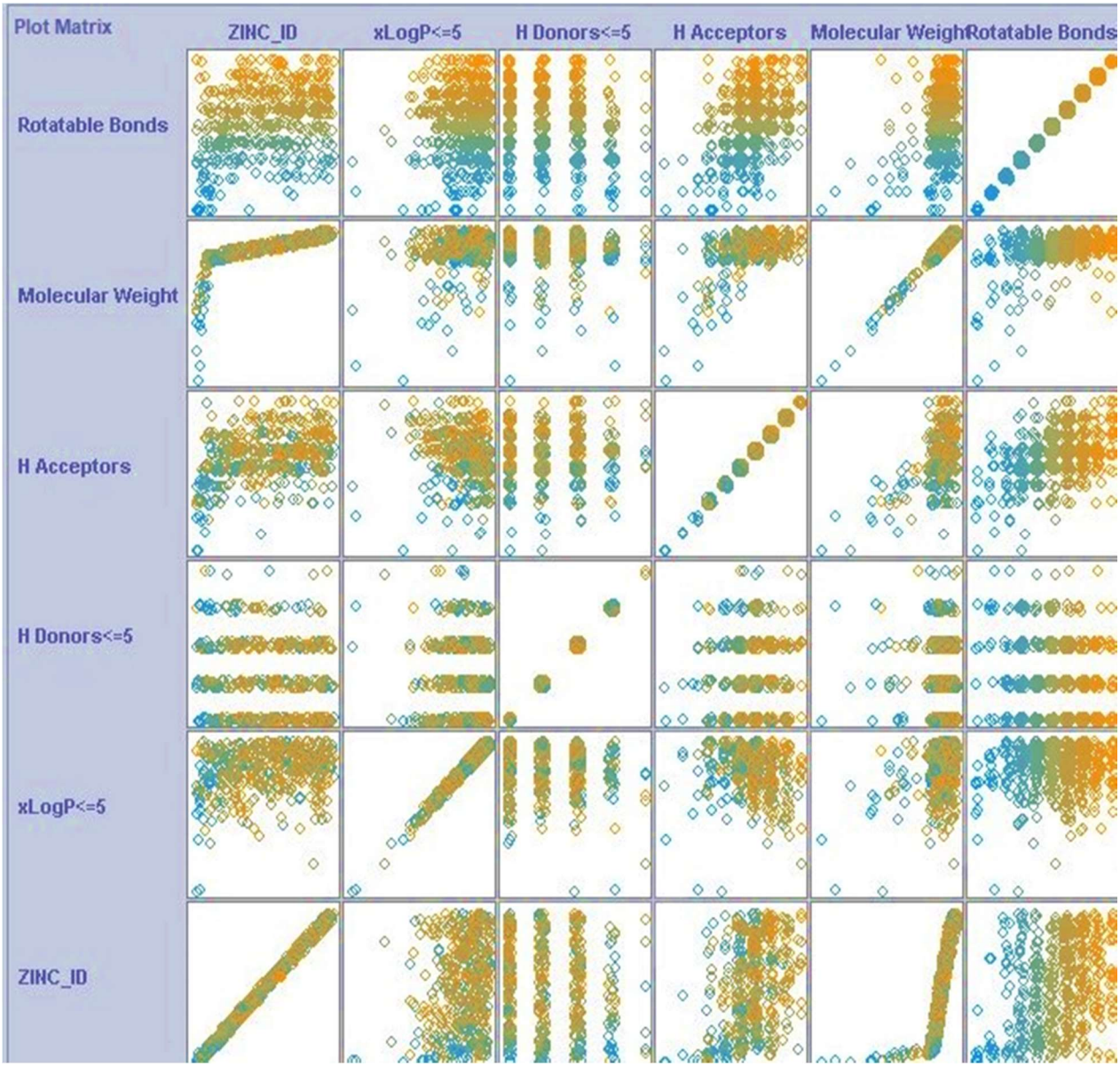

Figure S3. Plot matrix representation of drug compounds with their attributes.

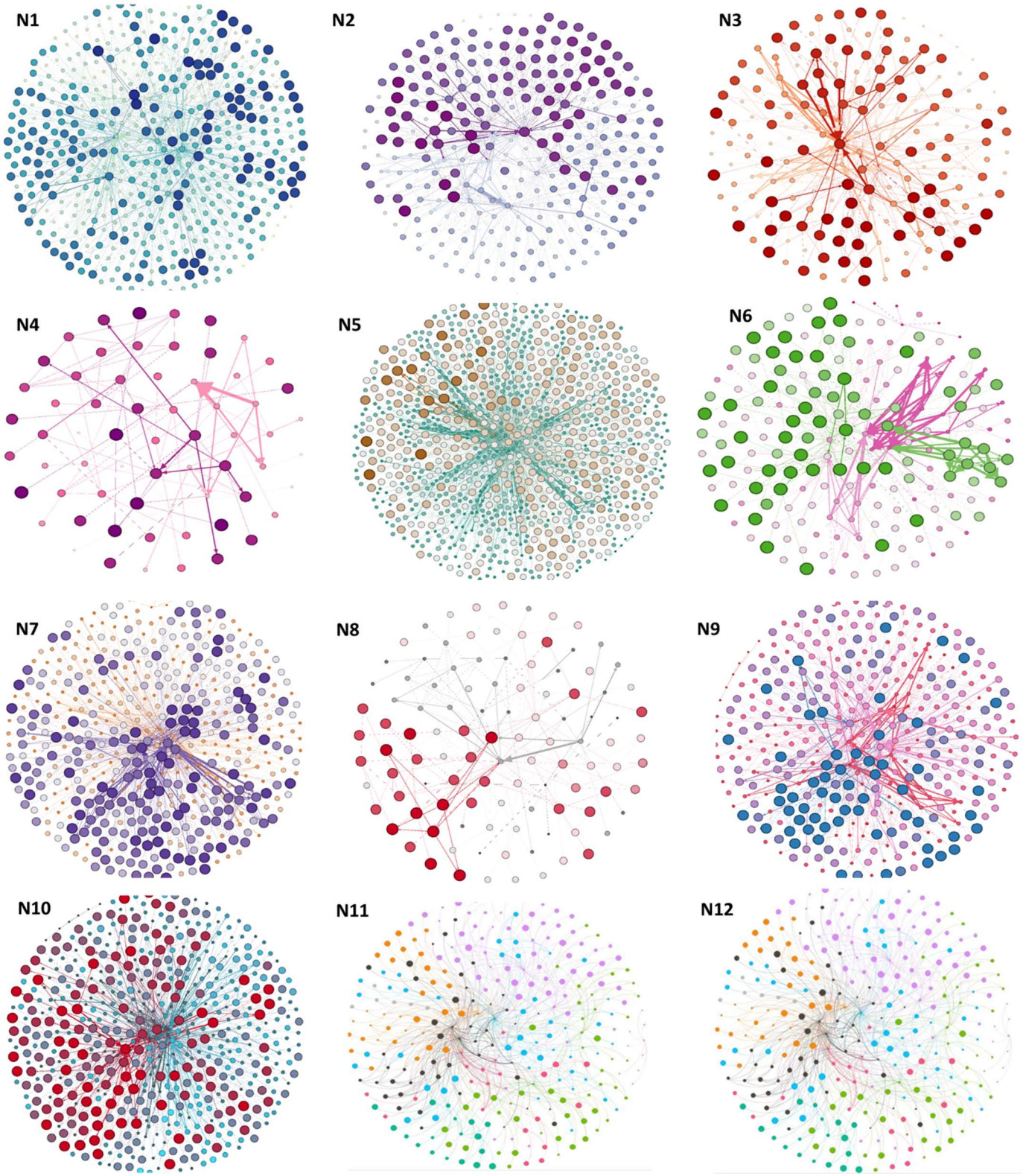

Figure S4. DDI networks generated using K means clustering algorithm and Gephi tool.