Supplementary Materials.
The supplementary material contains the following Tables and Figures.

Supplementary Table S1. Allosteric ligands affinities. Calculated binding energies for the selected hits when docked in the allosteric pocket A.

Supplementary Table S2. Affinities and structure-activity relationships for Novobiocin, and Novobiocin related derivatives. Interactions with the potential allosteric site defined by pocket A based on docking experiments using the complete Hsp90 C-terminus domain. Estimated binding energies with Novobiocin and derivatives were in good agreement with their relative inhibition potencies.

Supplementary Material Figures.

Supplementary Material Figure S1. Active Hot Spots in the coordination between the NTD and CTD, and Drug-like binding sites identified with the ICM pocketFinder module. a) Secondary structure elements active in the communication between the N-terminal and the C-terminal domains of Hsp90 in its activated form. The Hot Spot secondary structures are represented as red ribbons. **b)** 3D representations of potential ligand binding pockets identified with the ICM pocketFinder module on the HSP90 dimer X-ray crystal structure (2CG9.pdb). Side and top view representations are represented on left and right, respectively. **c)** 3D representations of potential ligand binding pockets identified with the ICM pocketFinder module on the HSP90 on the representative structure corresponding to 65200 ps of the MD simulation (cluster 2). Pocket A located at the dimer interface increases in area, volume and number of contacts with the communication hot spot residues represented with a red ribbon.

Supplementary Material Figure S2. Inhibition of Hsp90 chaperone function by selected compounds. Loss of Hsp90 client protein Akt in cancer cells treated with different compounds for 24h and analyzed by Western blotting.

Supplementary Material Figure S3. Binding of known Hsp90 C-terminal inhibitors into the Hsp90 dimer. For all ligands the lowest binding energy was obtained with a MD representative conformation (cluster 2, time = 65200 ps). The protein complex is shown in a ribbon representation colored by chain with the putative communication hot spot residues colored in red. The Hsp90 C-terminal binding pocket (pocket A) is shown as an orange line mesh and protein-ligand hydrogen bonds are represented with spheres.

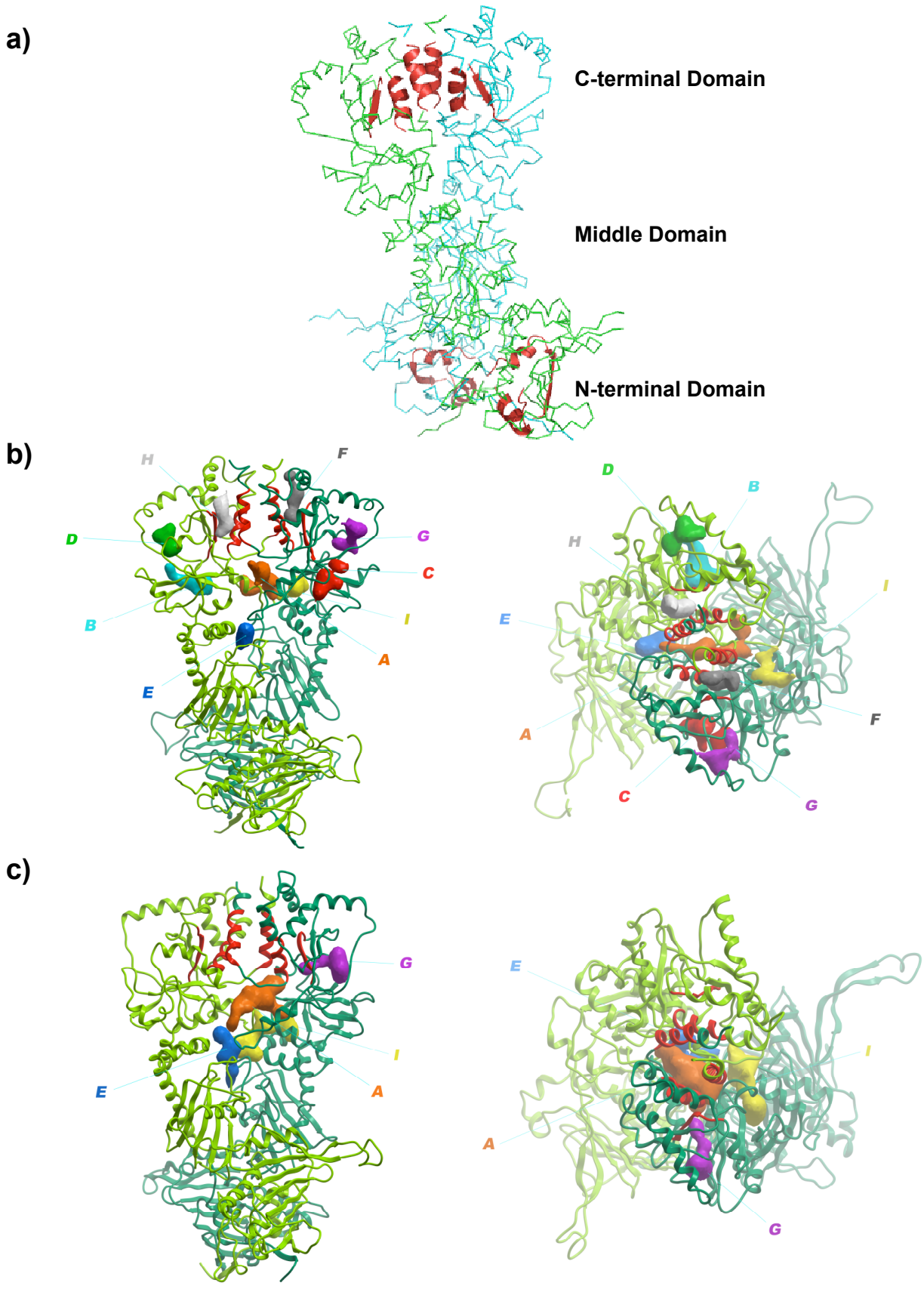
Table S1. Allosteric ligands affinities. Calculated binding energies for the selected hits when docked in the allosteric pocket A.

Compound Name	Calculated Binding Energy (kcal/mol)
4	-8.92
9	-8.59
8	-7.81
3	-7.80
2	-7.65
1	-7.22
6	-7.10
11	-6.57
7	-5.70
5	-5.42
14	-4.71
13	0.00
10	0.00
12	0.00

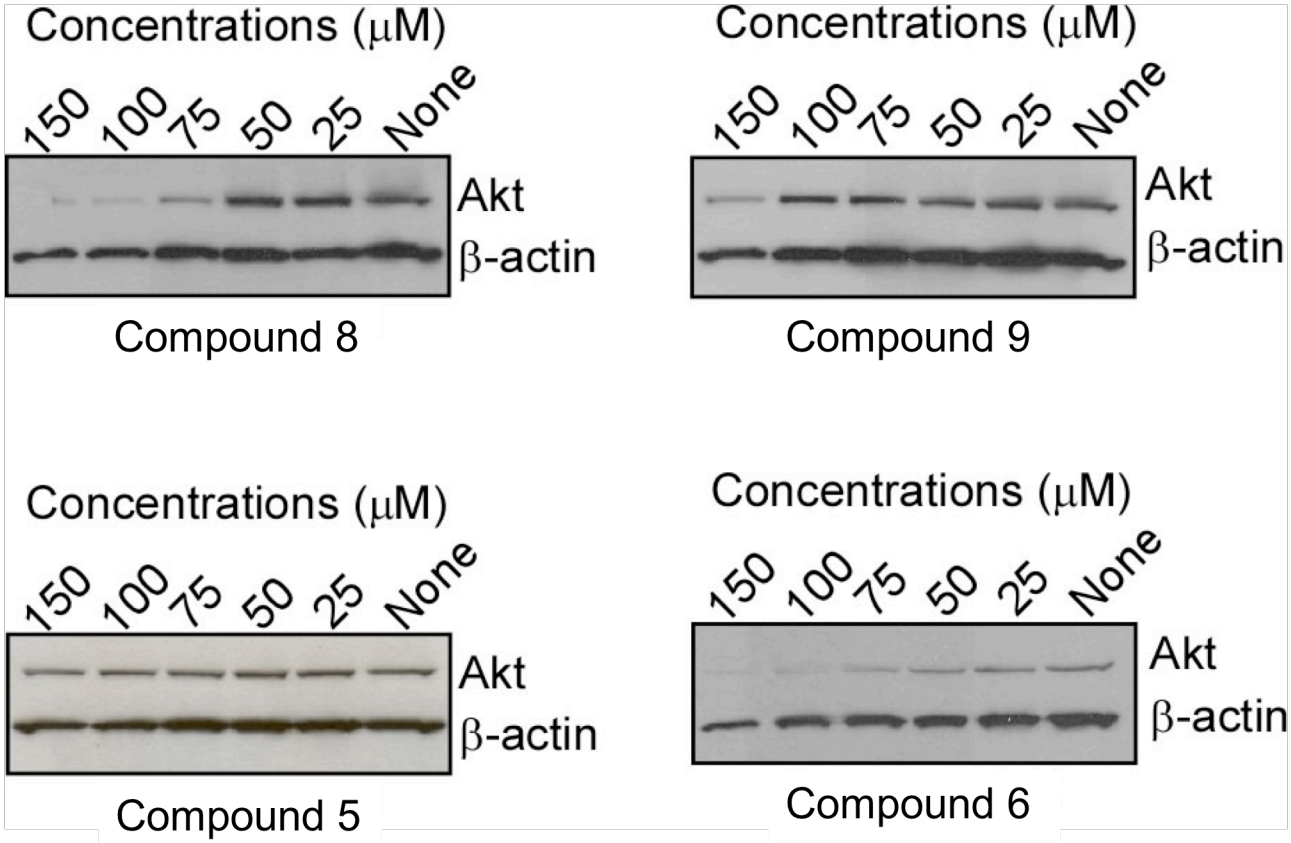
Table S2. Affinities and structure-activity relationships for Novobiocin, and Novobiocin related derivatives. Interactions with the potential allosteric site defined by pocket A based on docking experiments using the complete Hsp90 C-terminus domain. Estimated binding energies with Novobiocin and derivatives were in good agreement with their relative inhibition potencies.

Compound	Structure	Calculated Binding energy (kcal/mol)
Novobiocin	Cluster 1	-5.50
	Cluster 2	-6.02
	Cluster 3	-5.77
	Cluster 4	-6.02
	Cluster 5	-4.76
	Crystal	-5.51
1	Cluster 1	-6.13
	Cluster 2	-6.62
	Cluster 3	-5.68
	Cluster 4	-6.12
	Cluster 5	-6.18
	Crystal	-6.60
2	Cluster 1	-6.56
	Cluster 2	-8.14
	Cluster 3	-7.27
	Cluster 4	-6.66
	Cluster 5	-6.69
	Crystal	-7.58

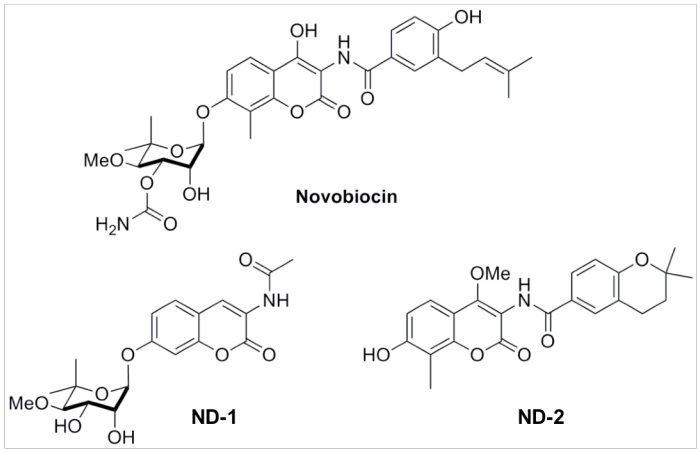
Supplementary Figure S1.

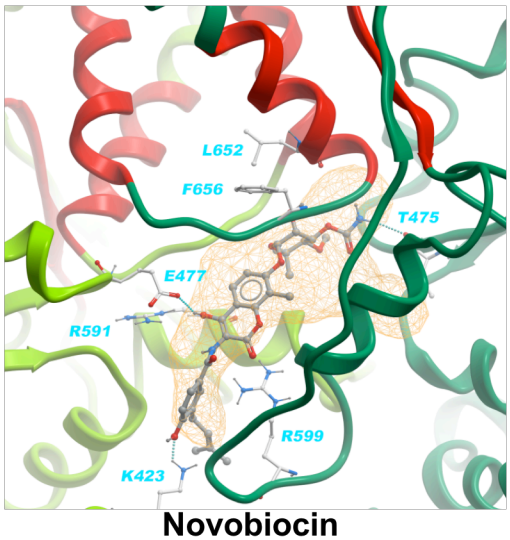


Supplementary Figure S2.

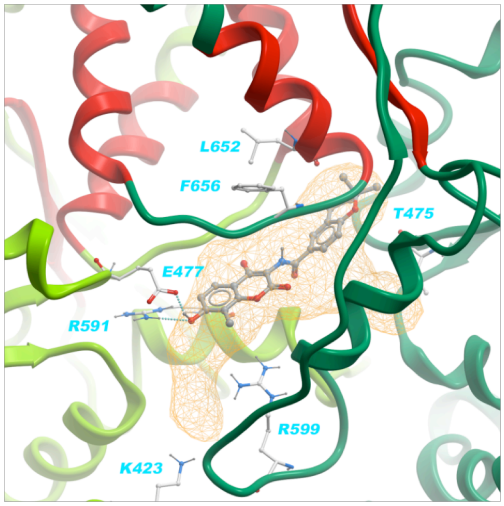


Supplementary Figure S3.





Novobiocin



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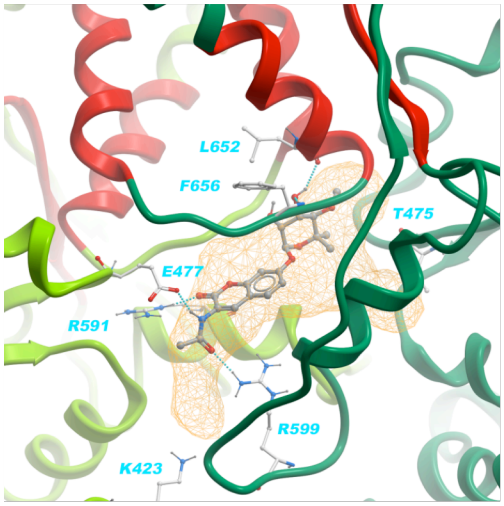

ND-2