

**Table S1.** Predicted binding free energy values ( $\Delta G_{\text{bin}}$  kcal/mol) of synthesized cytotoxic hybrids with selected proteins overexpressed in cancer.

Compounds	Target proteins															Total avge.
	DHFR	FGFR-2	VEGRF-2	NR3A1	EGFR	HER2	NR3A2	c-MET	TRKA	ERK2	MEK1	CK4	TPK	TopoII	TUB	
5e	-7.5	-8.9	-7.7	-8.7	-7.2	-8.3	-8.6	-9.8	-8.9	-9.0	-9.2	-7.6	-8.6	-6.7	-8.8	-8.34
5f	-7.6	-8.9	-6.2	-9.3	-7.4	-8.6	-6.9	-9.7	-9.1	-9.1	-8.7	-8.8	-8.2	-6.4	-9.0	-8.26
6a	-10.0	-9.6	-10.3	-9.2	-10.6	-10.8	-8.8	-10.3	-10.5	-9.4	-10.5	-9.8	-10.3	-6.6	-9.7	-9.78
6b	-9.7	-9.2	-10.0	-9.0	-10.6	-10.2	-9.5	-10.3	-10.7	-9.5	-9.8	-9.8	-10.3	-6.5	-9.4	-9.63
6c	-9.8	-9.6	-10.5	-9.2	-11.1	-10.4	-9.8	-10.6	-11.0	-9.8	-10.2	-8.8	-10.4	-7.0	-9.7	-9.86
6e	-9.0	-8.8	-10.0	-9.3	-10.0	-10.2	-8.5	-9.8	-9.6	-7.6	-9.9	-9.2	-9.9	-6.5	-8.8	-9.14
P avge.	-8.88	-9.17	-9.12	-9.12	-9.53	-9.75	-8.68	-10.08	-9.97	-9.07	-9.72	-9.00	-9.62	-6.62	-9.22	
Doxorubicin	-7.7	-9.0	-9.1	-7.7	-8.9	-6.2	-8.2	-8.7	-9.0	-9.2	-9.1	-7.2	-10.1	-7.7	-8.1	

Proteins with their respective (PDB) entries: **DHFR**: Dihydrofolate reductase (1DLS); **FGFR-2**: Fibroblast growth factor receptor 2 (1GJO); **VEGRF-2**: Vascular endothelial growth factor receptor 2 (3VHE); **NR3A1**: Estrogen receptor  $\alpha$  (3ERT); **EGFR**: Epidermal growth factor receptor (5GTU); **HER2**: Epidermal growth factor receptor 2 (7JXH); **TRKA**: Tropomyosin receptor kinase A (6PL2); **NR3A2**: Estrogen receptor beta (2QTU); **c-MET**: Mesenchymal-epithelial transition factor (3RHK); **TRKA**: Tropomyosin receptor kinase A (6PL2); **ERK2**: Extra-cellular signal-regulated kinase 2 (2OJG); **MEK1**: MAPK/ERK kinase (4AN3); **CK4**: Cyclin-dependent kinase 4 (1G3N); **TPK**: Tyrosine-protein kinase (4EHZ); **TopoII**: Topoisomerase II (5GWK); **TUB**: alpha tubulin (6WSL) P avge.: Protein average. mean of the  $\Delta G_{\text{bin}}$  values for the interactions of each protein with all the hybrids; the two proteins with the highest global chalcones-1,4-Naphthoquinone /Hydroquinones affinity are highlighted on red colour.