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Supporting Information

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Dipartimento di Chimica "Giacomo Ciamician", Alma Mater Studiorum - Università di Bologna, Via Francesco Selmi 2, 40126 Bologna, Italy

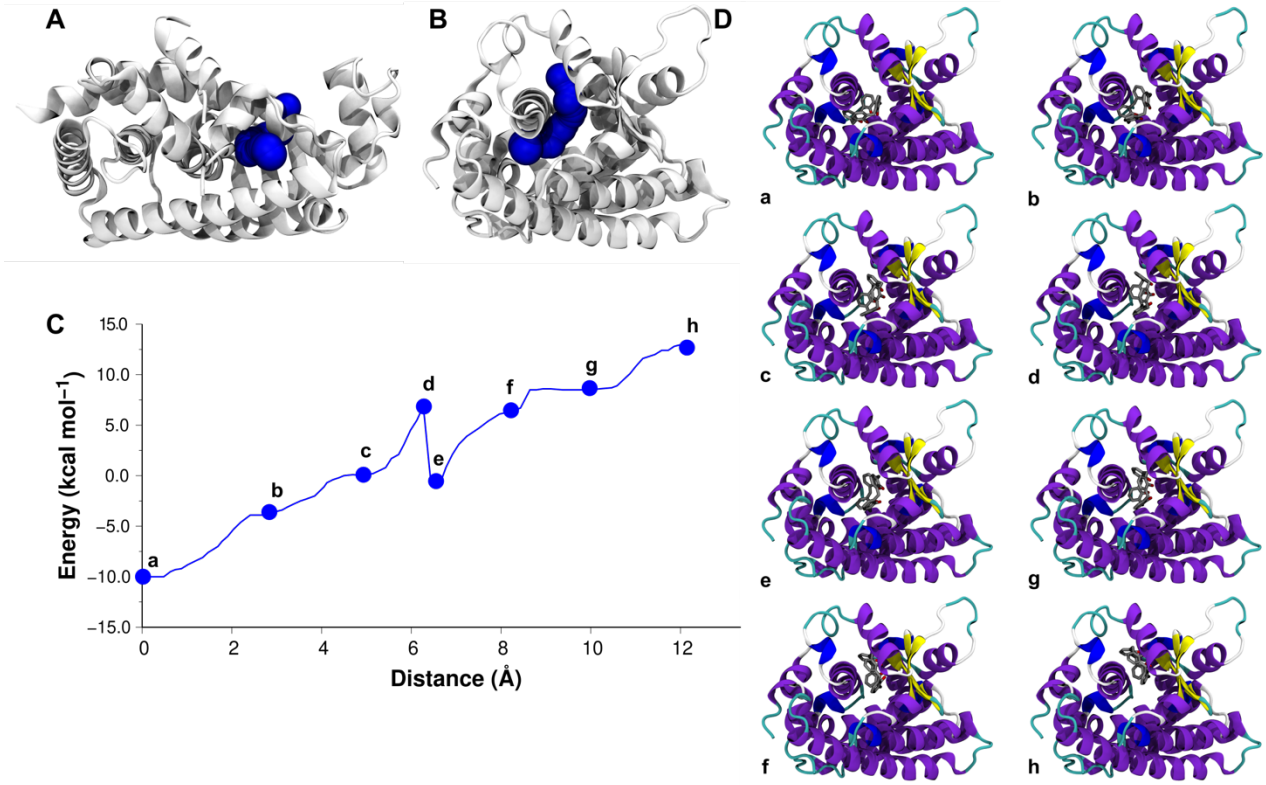

Figure S1. A,B) The most accessible tunnel (in blue) found by CAVER in PPAR-α. Two different orientations of the protein are shown. C) Energy profile obtained by the CaverDock calculation for the calix[4]arene to reach the PPAR-α binding site, passing through the most accessible tunnel identified by CAVER.

Table S1. Binding energies of the complexes between the selected proteins and their co-crystallized ligands and/or known binders.

Protein name	Crystallographic ligand	PDB ID	Crystallographic ligand@protein adduct binding affinity (kcal mol^{-1})	Calix[4]arene@protein adduct binding affinity (kcal mol^{-1})
PPAR-ALPHA	Stearic acid	6LX7	-57.4	-61.9
PPAR-ALPHA	Cipofibrate	6LX5	-38.8	-61.9
Estrogen receptor beta	Estradiol	2J7X	-42.2	-55.0
Progesterone receptor	Progesteron	1A28	-49.7	-50.5
Androgen receptor	Testosterone	2AM9	-47.8	-50.1
Androstane receptor	Androstane	1XNX	-35.7	-49.5
Retinoic acid receptor RXR beta	Retinoic acid	4DM8	-69.3	-49.3
Nuclear receptor ROR-β	Retinoic acid	1N4H	-61,3	-47.8
Pregnane X receptor	Clotrimazole	7AXA	-40.2	-40.7
Retinoic acid receptor RXR-α	Retinoic acid	3A9E	-64.3	-40.5
Estrogen receptor alpha	Estradiol	5WGQ	-38.3	-52.7
Estrogen receptor alpha	Tamoxifen	5W9C	-63.2	-52.7
Oxysterol-binding protein	Cholesterol	7V62	-40.4	-47.8
Retinol binding protein	Retinol	1RBP	-44.6	-46.3
Non-specific lipid-transfer protein	Stearic acid	1FK4	-44.4	-46.2
Epididymal retinoic acid-binding protein	Retinoic acid	1EPB	-34.9	-45.8
Intestinal fatty acid-binding protein	Palmitate	2IFB	-55.0	-41.3
Bilin-binding protein	Biliverdin IX gamma	1BBP	-68.3	-39.4
Human serum albumin	Warfarin	2BXD	-39.2	-41.3
Cyclin-dependent kinase 2 (CDK2)	Roscovitin	2A4L	-35.3	-45.1
EGFR	Gefniteb	4WKQ	-47.6	-42.1
DHFR	Methotrexate	1RG7	-62.1	-42.0
DHFR	Folate	1DHF	-70.7	-42.0
HIV-1 reverse transcriptase	Rilpivirine	6ELI	-62.4	-45.7
HIV-1 protease	Amprenavir	3NU3	-63.8	-41.4
Capsid of human rhinovirus	Pleconaril	1NCQ	-49.0	-38.1

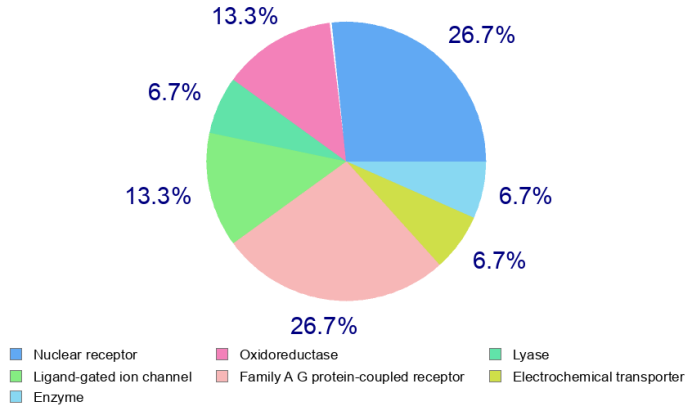

Figure S2. Pie chart of the protein target classes identified by SwissTarget in the top 15%.

Table S2. Top 100 protein target candidates for binding calix[4]arene as ranked by SwissTarget

Rank	Target	ChEMBL ID	Rank	Target	ChEMBL ID
1	Estrogen receptor alpha	CHEMBL206	51	Matrix metalloproteinase 2	CHEMBL333
2	Cyclooxygenase-1	CHEMBL221	52	Serine/threonine-protein kinase Chk1	CHEMBL4630
3	Carbonic anhydrase II	CHEMBL205	53	Mineralocorticoid receptor	CHEMBL1994
4	Estrogen receptor beta	CHEMBL242	54	Methyl-CpG-binding protein 2	CHEMBL3638346
5	GABA-A receptor; alpha-1/beta-3/gamma-2	CHEMBL2094121	55	Methyl-CpG-binding domain protein 2	CHEMBL3707462
6	Arachidonate 5-lipoxygenase	CHEMBL215	56	Hepatocyte growth factor receptor	CHEMBL3717
7	Serotonin 2b (5-HT2b) receptor	CHEMBL1833	57	Cyclin-dependent kinase 5/CDK5 activator 1	CHEMBL1907600
8	Serotonin 2c (5-HT2c) receptor	CHEMBL225	58	Tyrosine-protein kinase SYK	CHEMBL2599
9	GABA-A receptor; alpha-1/beta-2/gamma-2	CHEMBL2095172	59	Serine/threonine-protein kinase 33	CHEMBL6005
10	Norepinephrine transporter	CHEMBL222	60	Serine/threonine-protein kinase B-raf	CHEMBL5145
11	Serotonin 6 (5-HT6) receptor	CHEMBL3371	61	ATP-binding cassette sub-family G member 2	CHEMBL5393
12	Estrogen-related receptor gamma	CHEMBL4245	62	Matrix metalloproteinase 1	CHEMBL332
13	Isocitrate dehydrogenase [NADP] cytoplasmic	CHEMBL2007625	63	p53-binding protein Mdm-2	CHEMBL5023
14	Interleukin-8 receptor B	CHEMBL2434	64	Monoamine oxidase A	CHEMBL1951
15	Nuclear receptor ROR-gamma	CHEMBL1741186	65	Fibroblast growth factor receptor 1	CHEMBL3650
16	Equilibrative nucleoside transporter 1	CHEMBL1997	66	Serotonin 1a (5-HT1a) receptor	CHEMBL214
17	Androgen Receptor	CHEMBL1871	67	Carbonic anhydrase XII	CHEMBL3242
18	Adenosine A1 receptor	CHEMBL226	68	Histone deacetylase 1	CHEMBL325
19	Adenosine A2b receptor	CHEMBL255	69	Sodium channel protein type II alpha subunit	CHEMBL4187
20	Serine/threonine-protein kinase mTOR	CHEMBL2842	70	Alpha-1d adrenergic receptor	CHEMBL223
21	PI3-kinase p110-alpha subunit	CHEMBL4005	71	c-Jun N-terminal kinase 1	CHEMBL2276
22	Egl nine homolog 1	CHEMBL5697	72	Alpha-1a adrenergic receptor	CHEMBL229
23	LDL-associated phospholipase A2	CHEMBL3514	73	Alpha-1b adrenergic receptor	CHEMBL232
24	Vascular endothelial growth factor receptor 2	CHEMBL279	74	Epoxide hydratase	CHEMBL2409
25	Kinesin-1 heavy chain/ Tyrosine-protein kinase receptor RET	CHEMBL2041	75	c-Jun N-terminal kinase 3	CHEMBL2637
26	Cyclin-dependent kinase 1/cyclin B	CHEMBL2094127	76	Dual specificity mitogen-activated protein kinase 1	CHEMBL3587
27	Phosphodiesterase 4B	CHEMBL275	77	Serine-protein kinase ATM	CHEMBL3797
28	Formyl peptide receptor 1	CHEMBL3359	78	c-Jun N-terminal kinase 2	CHEMBL4179
29	Calcium-activated potassium channel subunit alpha-1	CHEMBL4304	79	Serine-protein kinase ATR	CHEMBL5024
30	Beta-secretase 1	CHEMBL4822	80	Protein kinase C (PKC)	CHEMBL3438
31	ADAMTS5	CHEMBL2285	81	Nitric oxide synthase, inducible (by homology)	CHEMBL4481
32	Serine/threonine-protein kinase RIPK2	CHEMBL5014	82	GABA receptor alpha-1 subunit (by homology)	CHEMBL1962
33	Thymidylate synthase	CHEMBL1952	83	Protein kinase C gamma (by homology)	CHEMBL2938
34	Carbonic anhydrase I	CHEMBL261	84	Nischarin	CHEMBL3923
35	Carbonic anhydrase IX	CHEMBL3594	85	NADPH oxidase 4	CHEMBL1250375
36	Phosphodiesterase 2A	CHEMBL2652	86	Carnitine O-palmitoyltransferase 1, liver isoform	CHEMBL1293194
37	Caspase-6	CHEMBL3308	87	Heat shock protein HSP 90-alpha	CHEMBL3880
38	Phosphodiesterase 10A	CHEMBL4409	88	Mitogen-activated protein kinase 5	CHEMBL5285
39	Monoamine oxidase B	CHEMBL2039	89	Prostaglandin E synthase	CHEMBL5658
40	Serine/threonine-protein kinase Aurora-B	CHEMBL2185	90	Poly [ADP-ribose] polymerase-1	CHEMBL3105
41	Focal adhesion kinase 1	CHEMBL2695	91	Tankyrase-2	CHEMBL6154
42	Serine/threonine-protein kinase PLK1	CHEMBL3024	92	Tankyrase-1	CHEMBL6164
43	Phosphodiesterase 5A	CHEMBL1827	93	Inosine-5'-monophosphate dehydrogenase 2	CHEMBL2002
44	Calcium sensing receptor	CHEMBL1878	94	Ephrin type-A receptor 2	CHEMBL2068
45	Beta secretase 2	CHEMBL2525	95	Tyrosine-protein kinase YES	CHEMBL2073
46	Vanilloid receptor	CHEMBL4794	96	Tyrosine-protein kinase BLK	CHEMBL2250
47	Myosin light chain kinase, smooth muscle	CHEMBL2428	97	Tyrosine-protein kinase CSK	CHEMBL2634
48	Signal transducer and activator of transcription 6	CHEMBL5401	98	Matrix metalloproteinase 13	CHEMBL280
49	Carboxypeptidase B	CHEMBL2552	99	Ephrin type-B receptor 2	CHEMBL3290
50	Matrix metalloproteinase 9	CHEMBL321	100	Tyrosine-protein kinase BMX	CHEMBL3834

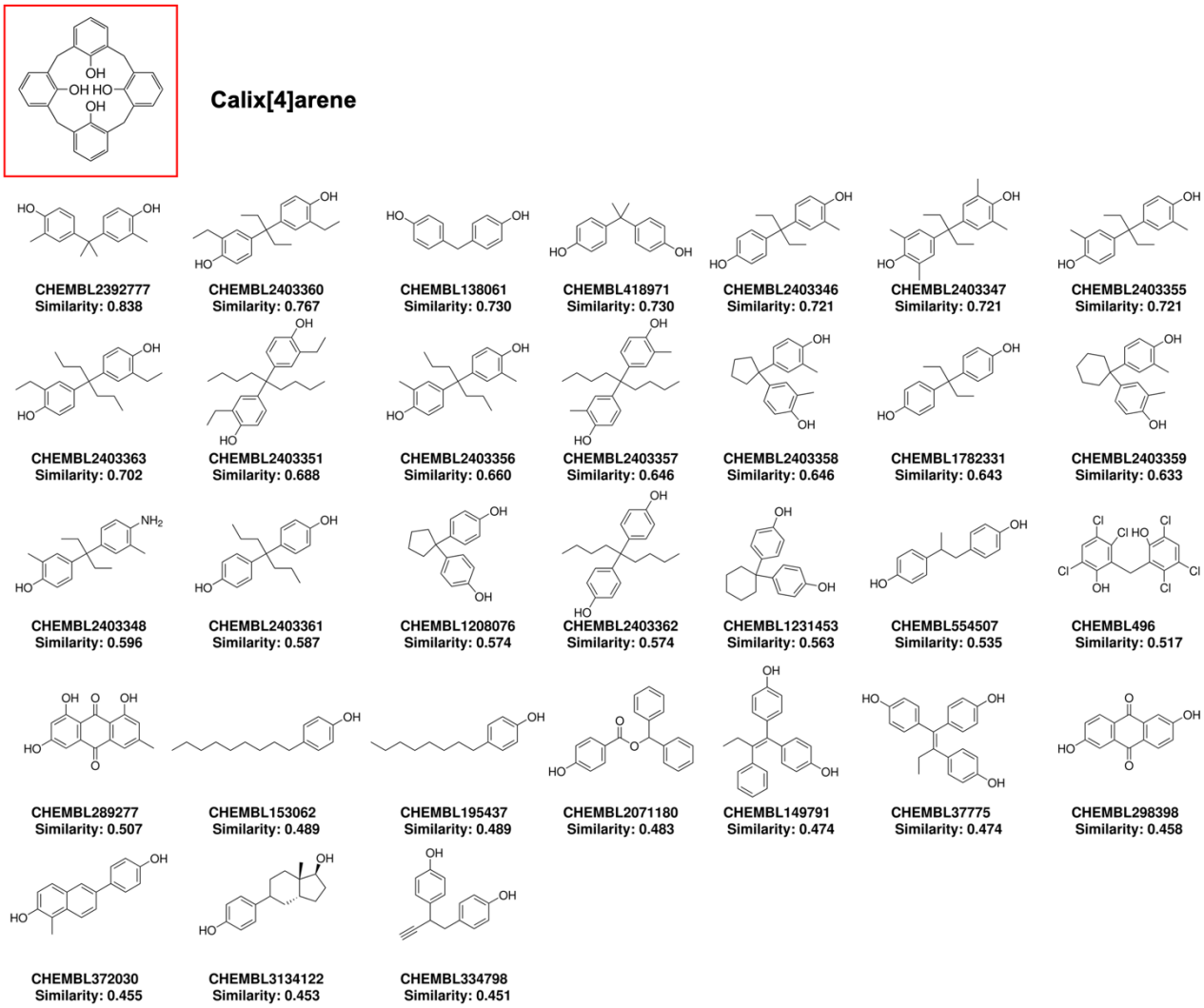

Figure S3. Lists of molecules experimentally defined as active on the Estrogen receptor α (ERα) that are highly 2D similar to the calix[4]arene.

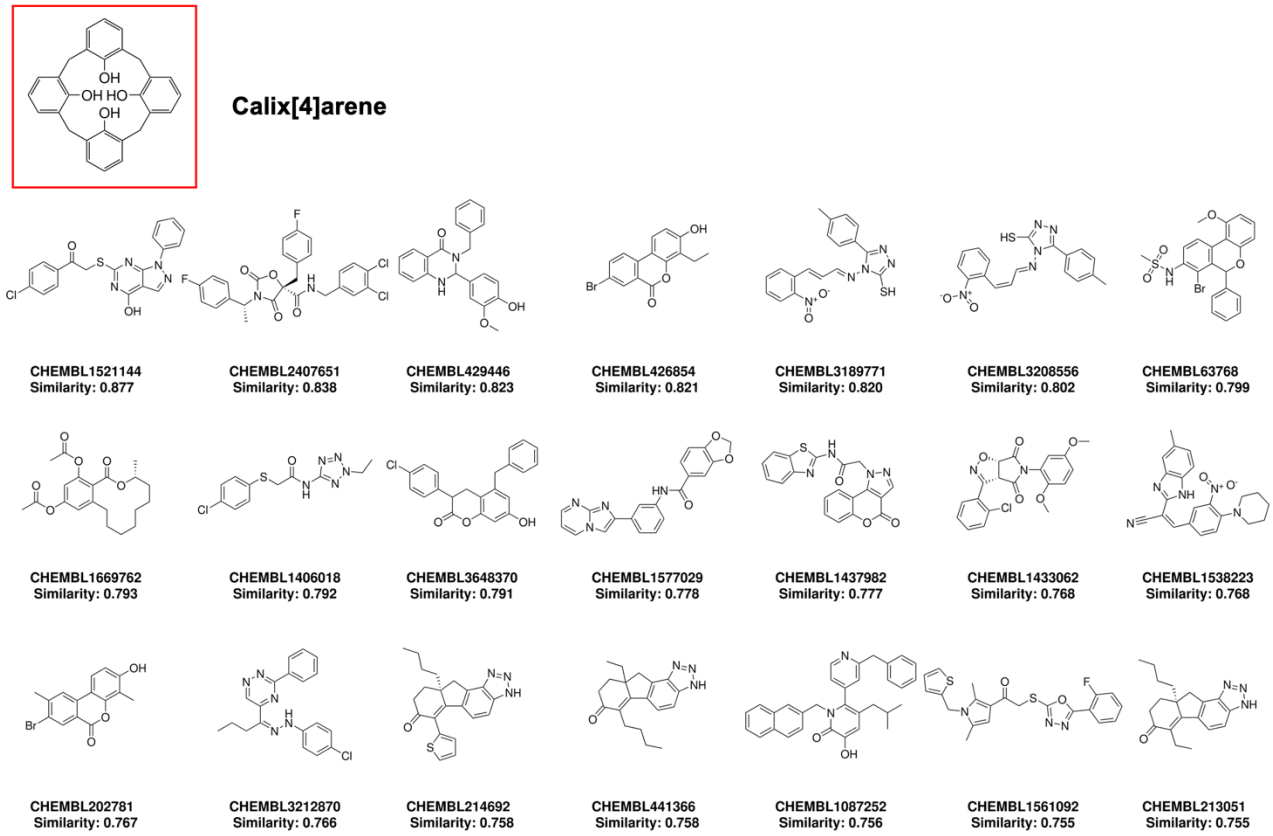

Figure S4. Lists of molecules experimentally defined as active on the Estrogen receptor α (ERα) that are highly 3D similar to the calix[4]arene.

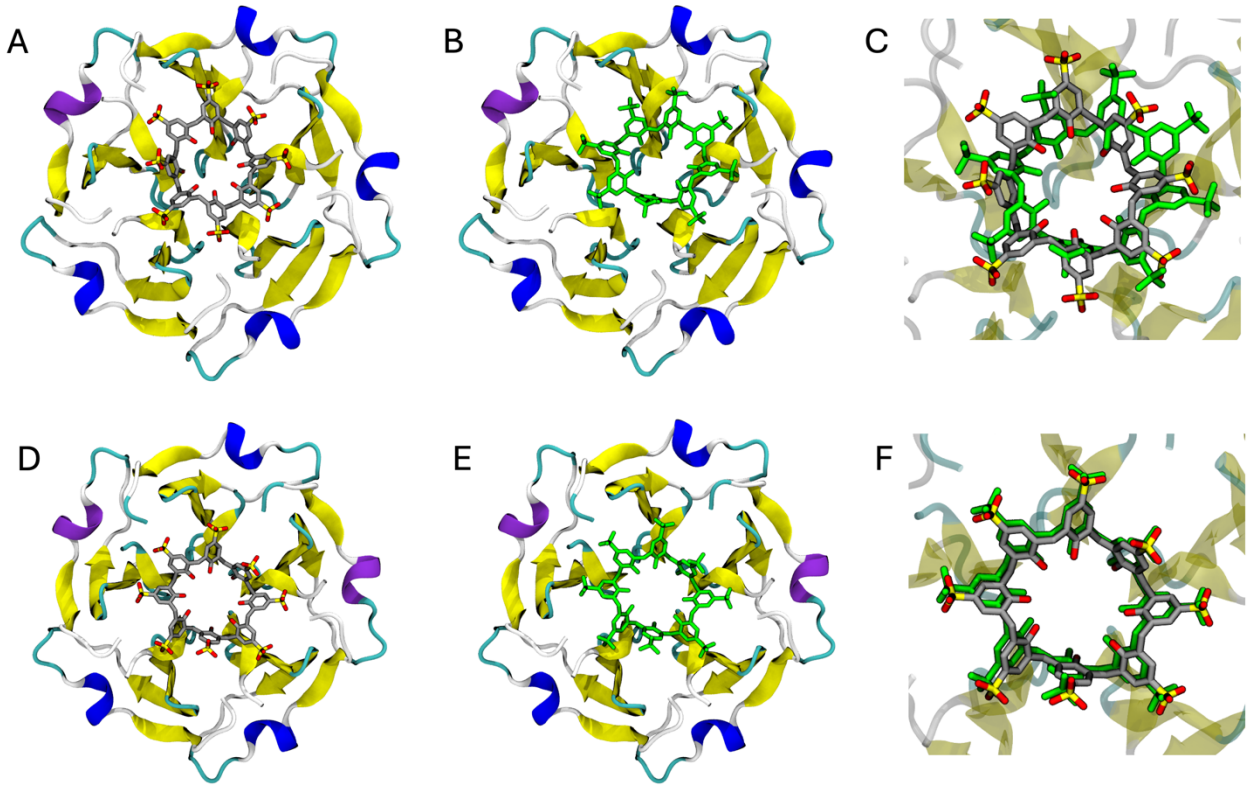

Figure S5. A,D) Crystallographic structures, B,E) Docked structures (best poses identified by the docking protocols used in the manuscript) and C,F) Superposition of the crystallographic and docked structures between a designed pentameric β-propeller and sulfonato-calix[8]arene (PDB: 8R3B in A-C, 8R3C in D-F)