In silico repositioning of cannabigerol as a novel inhibitor of the Enoyl acyl carrier protein (ACP) reductase (InhA) protein

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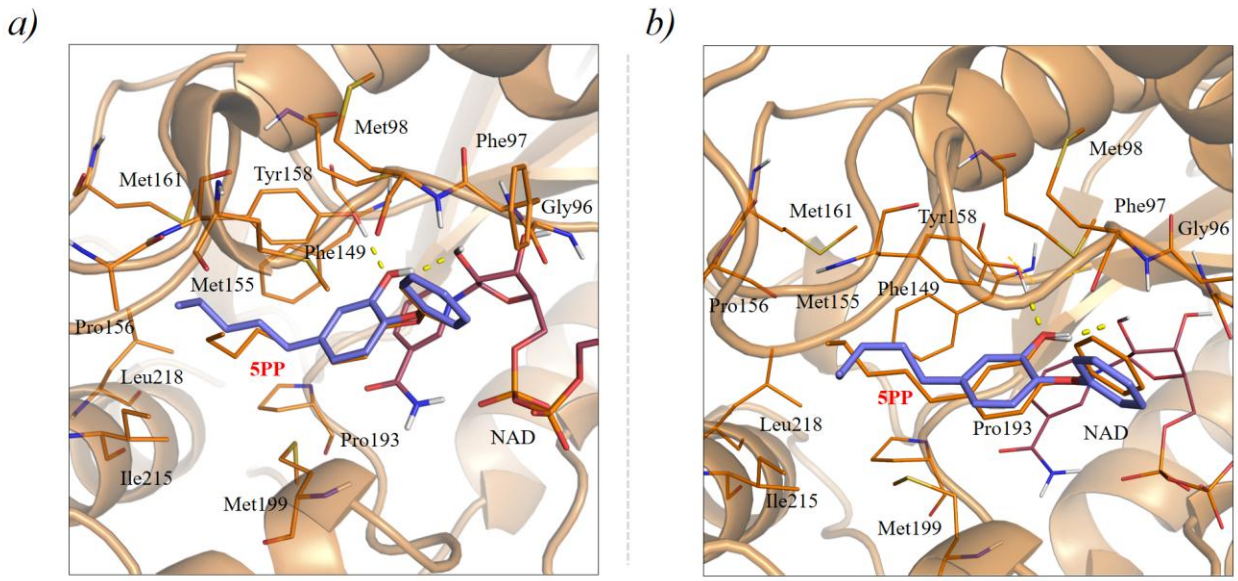
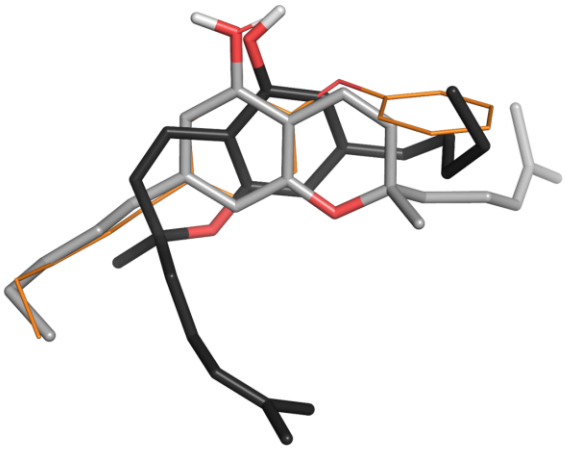
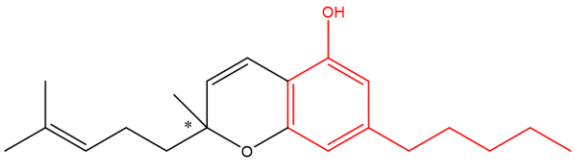


Figure S2: Superimposition of the ligand-based and structure-based poses predicted for CBC, and common sub-structure with 5PP. In particular, ***panel a)*** reports the superimposition of the ligand-based and structure-based poses of CBC predicted with ROCS and Glide, respectively. The conformation of CBC obtained by means of the shape-based screening with ROCS is represented as light grey sticks. The crystallographic conformation of 5PP is represented as orange thinner sticks. The docking pose of CBC into the 2B36 receptor predicted by Glide is represented in dark grey sticks. As shown, the two CBC poses are head to tail (RMSD of 6.3Å). ***Panel b)*** reports the chemical structures of CBC and 5PP, with highlighted their common sub-structure.

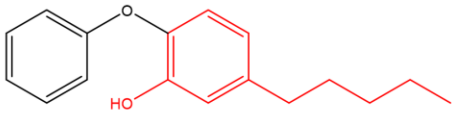
a)



b)



CBC



5PP

Figure S3: Representative *Induced Fit Docking* poses of CBG and CBC into the 2B36 crystal structure. ***Panels a)*** and ***b)*** report the predicted binding modes of CBG (dark teal sticks) and CBC (dark grey sticks) into the InhA enzyme, respectively. The NADH cofactor is represented as raspberry sticks. The image was created with PyMol (The PyMOL Molecular Graphics System, Version 1.8, Schrödinger, LLC).

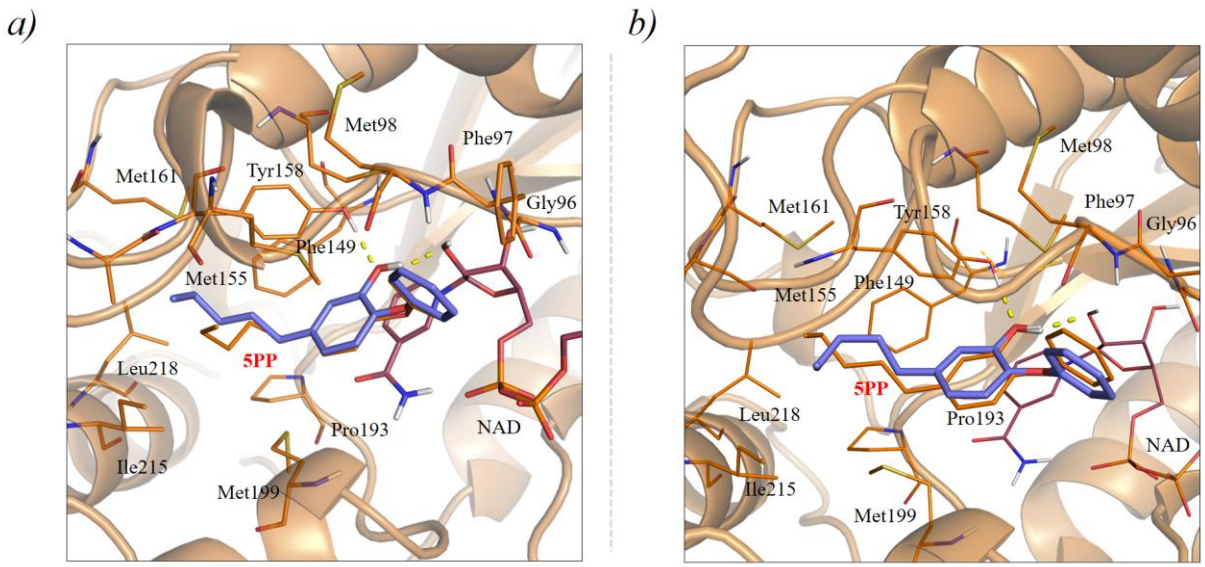


Figure S4: Dose-response curve of CBG for the inhibition of the InhA enzyme.

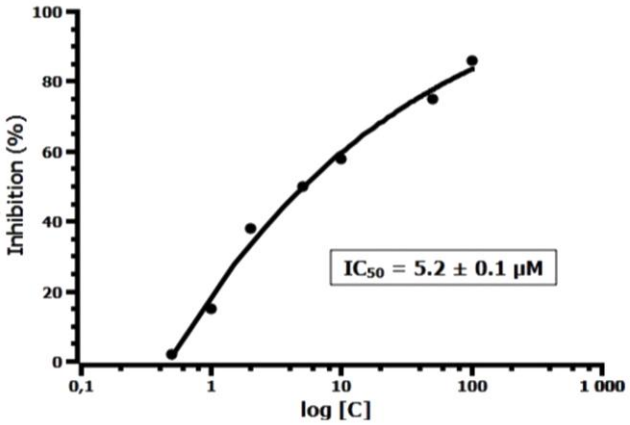


Table S1: Top five similarity values identified for CBG and CBC with respect to the ligands reported in the DrugBank database. The similarity estimations were performed through a multi-conformer *versus* multi-conformer 3D shape-based screening. Therefore, the reported similarity scores are related to the query and screening compound conformers that provided the best shape-based alignment. DrugBank compounds that resulted similar with both CBG and CBC are shown in bold. Similarity records identified for the 5PP ligand (DrugBank ID: DB07178) are highlighted in red.

Query	*Compound ID*	*Tanimoto Combo*[†]	*Shape Tanimoto*	*Color Tanimoto*	*Name*	*Groups*	*Targets*
	DB09061	**1.307**	**0.671**	**0.636**	**Cannabidiol**	**Approved, Investigational**	**Cannabinoid receptor 1; Cannabinoid receptor 2**[*]
	DB07178	**1.197**	**0.78**	**0.416**	**5-Pentyl-2-Phenoxyphenol**	**Experimental**	**Enoyl-[acyl-carrier-protein] reductase [NADH]**
CBG	DB08690	1.174	0.818	0.357	Ubiquinone-2	Experimental	Succinate dehydrogenase flavoprotein subunit; Succinate dehydrogenase iron-sulfur subunit[*]
	DB00470	**1.093**	**0.633**	**0.459**	**Dronabinol**	**Approved, Illicit**	**Cannabinoid receptor 1; Cannabinoid receptor 2**
	DB03152	1.087	0.747	0.34	B-2-Octylglucoside	Experimental	DNA polymerase I, thermostable; Aquaporin Z[*]
	DB00470	**1.386**	**0.689**	**0.697**	**Dronabinol**	**Approved, Illicit**	**Cannabinoid receptor 1; Cannabinoid receptor 2**
	DB09061	**1.228**	**0.62**	**0.608**	**Cannabidiol**	**Approved, Investigational**	**Cannabinoid receptor 1; Cannabinoid receptor 2**[*]
CBC	DB07918	1.214	0.691	0.522	2-Heptyl-4-Hydroxy Quinoline N-Oxide	Experimental	Fumarate reductase flavoprotein subunit; Fumarate reductase iron-sulfur subunit[*]
	DB07178	**1.193**	**0.694**	**0.499**	**5-Pentyl-2-Phenoxyphenol**	**Experimental**	**Enoyl-[acyl-carrier-protein] reductase [NADH]**
	DB00486	1.168	0.647	0.521	Nabilone	Approved, Investigational	Cannabinoid receptor 1; Cannabinoid receptor 2

[*] The compound showed activity annotations on more than two targets.

[†] Tanimoto Combo scores span from 0.0 to 2.0, as they result from the sum of shape fitting (Shape Tanimoto) and atom type superimposition (Color Tanimoto) similarity scores. The higher is the Tanimoto Combo score evaluated between two ligands, the higher are their shape similarity and atom type superimposition.