Supplemental Information

Molecular basis of metabolism-mediated conversion of PK11195 from an antagonist to an agonist of the constitutive androstane receptor

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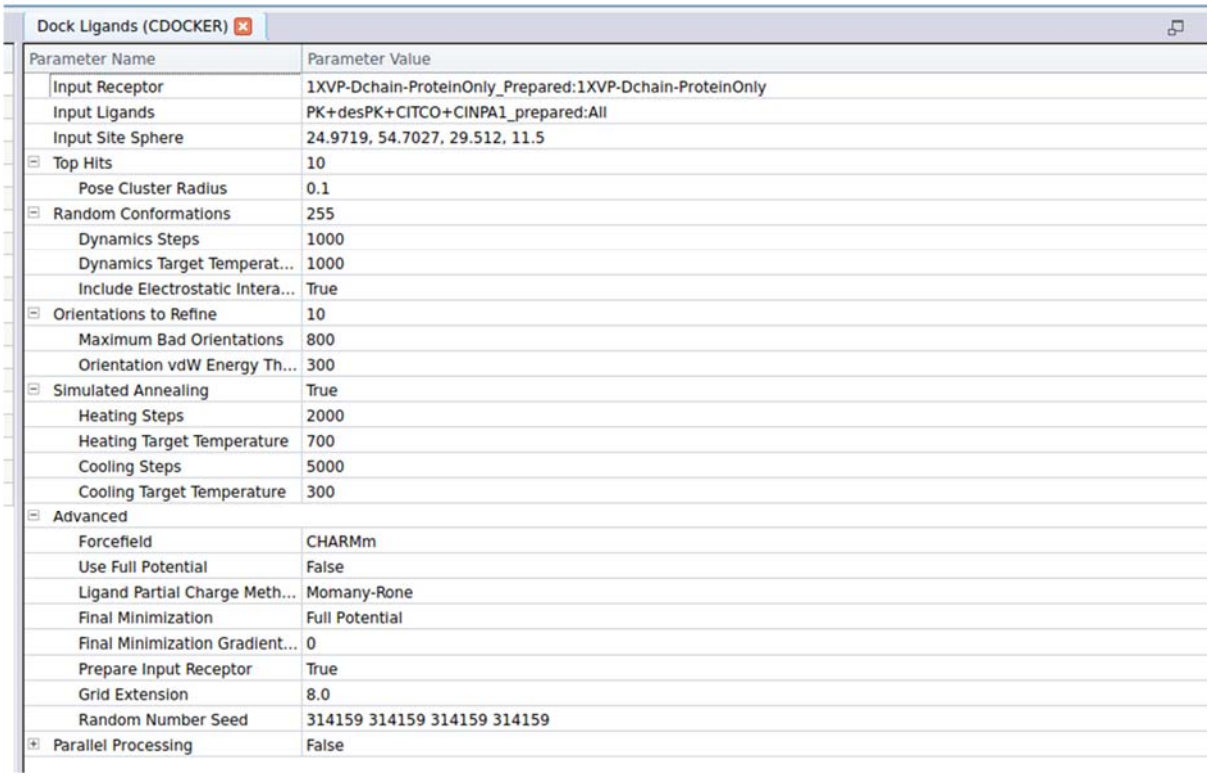
List of supplementary materials

Fig. S1. Detailed parameters used for docking studies.



Dock Ligands (CDOCKER)

Parameter Name	Parameter Value
Input Receptor	1XVP-Dchain-ProteinOnly_Prepared:1XVP-Dchain-ProteinOnly
Input Ligands	PK+desPK+CITCO+CINPA1_prepared:All
Input Site Sphere	24.9719, 54.7027, 29.512, 11.5
Top Hits	10
Pose Cluster Radius	0.1
Random Conformations	255
Dynamics Steps	1000
Dynamics Target Temperat...	1000
Include Electrostatic Intera...	True
Orientations to Refine	10
Maximum Bad Orientations	800
Orientation vdW Energy Th...	300
Simulated Annealing	True
Heating Steps	2000
Heating Target Temperature	700
Cooling Steps	5000
Cooling Target Temperature	300
Advanced	
Forcefield	CHARMm
Use Full Potential	False
Ligand Partial Charge Meth...	Momany-Rone
Final Minimization	Full Potential
Final Minimization Gradient...	0
Prepare Input Receptor	True
Grid Extension	8.0
Random Number Seed	314159 314159 314159 314159
Parallel Processing	False

Table S1. Detailed interaction data for PK11195, ND-PK, CINPA1 and CITCO

Interaction Distance Parameters													
Type	**Max. Distance (Å)**												
Hydrophobic Alkyl	5.50	From Alkyl Centroid											
Hydrophobic Stacked Pi-Pi	6.00	From Centroids											
Hydrophobic Pi-Cation	5.00												
Hydrophobic Pi-Sulfur	6.00												
Hydrogen Bond	3.80												
Halogen non-bond	3.70												
(R)-N-Desmethyl PK11195													
Name	Distance	Category	Types	From	From Chem	To	To Chemist	Theta	Theta 2	Gamma	Closest Ato	Angle DHA	Angle HAY
D:CYS219:SG - (R)-N-Desmethyl PK11195	5.09136	Other	Pi-Sulfur	D:CYS219:S	Sulfur	(R)-N-Desm	Pi-Orbitals	83.821					
D:PHE161 - (R)-N-Desmethyl PK11195	5.05838	Hydrophob	Pi-Pi T-shap	D:PHE161	Pi-Orbitals	(R)-N-Desm	Pi-Orbitals	55.583	7.624	62.004	3.894		
D:PHE217 - (R)-N-Desmethyl PK11195	5.22081	Hydrophob	Pi-Pi T-shap	D:PHE217	Pi-Orbitals	(R)-N-Desm	Pi-Orbitals	19.891	61.533	67.143	3.802		
(R)-N-Desmethyl PK11195:C16 - D:MET168	4.76552	Hydrophob	Alkyl	(R)-N-Desm	Alkyl	D:MET168	Alkyl						
(R)-N-Desmethyl PK11195:C16 - D:VAL169	4.78439	Hydrophob	Alkyl	(R)-N-Desm	Alkyl	D:VAL169	Alkyl						
(R)-N-Desmethyl PK11195:C16 - D:CYS202	3.63591	Hydrophob	Alkyl	(R)-N-Desm	Alkyl	D:CYS202	Alkyl						
(R)-N-Desmethyl PK11195:C16 - D:LEU343	4.97352	Hydrophob	Alkyl	(R)-N-Desm	Alkyl	D:LEU343	Alkyl						
(R)-N-Desmethyl PK11195:Cl24 - D:ILE164	4.8058	Hydrophob	Alkyl	(R)-N-Desm	Alkyl	D:ILE164	Alkyl						
(R)-N-Desmethyl PK11195:Cl24 - D:MET168	5.1548	Hydrophob	Alkyl	(R)-N-Desm	Alkyl	D:MET168	Alkyl						
D:PHE161 - (R)-N-Desmethyl PK11195:Cl24	4.90921	Hydrophob	Pi-Alkyl	D:PHE161	Pi-Orbitals	(R)-N-Desm	Alkyl						
(R)-N-Desmethyl PK11195 - D:LEU206	4.53538	Hydrophob	Pi-Alkyl	(R)-N-Desm	Pi-Orbitals	D:LEU206	Alkyl						
(R)-PK11195													
Name	Distance	Category	Types	From	From Chem	To	To Chemist	Theta	Theta 2	Gamma	Closest Ato	Angle DHA	Angle HAY
D:CYS219:SG - (R)-PK11195	5.10412	Other	Pi-Sulfur	D:CYS219:S	Sulfur	(R)-PK1119	Pi-Orbitals	84.2					
D:TYR224 - (R)-PK11195	3.97653	Hydrophob	Pi-Pi Stacke	D:TYR224	Pi-Orbitals	(R)-PK1119	Pi-Orbitals	17.057	47.237	30.219	3.296		
D:PHE161 - (R)-PK11195	5.25099	Hydrophob	Pi-Pi T-shap	D:PHE161	Pi-Orbitals	(R)-PK1119	Pi-Orbitals	46.896	23.229	69.026	3.853		
D:PHE217 - (R)-PK11195	5.07031	Hydrophob	Pi-Pi T-shap	D:PHE217	Pi-Orbitals	(R)-PK1119	Pi-Orbitals	23.576	78.442	62.804	3.592		
(R)-PK11195:C16 - D:VAL169	5.43645	Hydrophob	Alkyl	(R)-PK1119	Alkyl	D:VAL169	Alkyl						
(R)-PK11195:C16 - D:CYS202	4.1891	Hydrophob	Alkyl	(R)-PK1119	Alkyl	D:CYS202	Alkyl						
(R)-PK11195:C16 - D:LEU343	4.92163	Hydrophob	Alkyl	(R)-PK1119	Alkyl	D:LEU343	Alkyl						
(R)-PK11195:C17 - D:VAL199	4.26621	Hydrophob	Alkyl	(R)-PK1119	Alkyl	D:VAL199	Alkyl						
(R)-PK11195:C18 - D:LEU206	4.73733	Hydrophob	Alkyl	(R)-PK1119	Alkyl	D:LEU206	Alkyl						
(R)-PK11195:Cl25 - D:ILE164	5.4936	Hydrophob	Alkyl	(R)-PK1119	Alkyl	D:ILE164	Alkyl						
D:PHE161 - (R)-PK11195:Cl25	4.42423	Hydrophob	Pi-Alkyl	D:PHE161	Pi-Orbitals	(R)-PK1119	Alkyl						
D:HIS203 - (R)-PK11195:C17	3.92296	Hydrophob	Pi-Alkyl	D:HIS203	Pi-Orbitals	(R)-PK1119	Alkyl						
D:HIS203 - (R)-PK11195:C18	3.89159	Hydrophob	Pi-Alkyl	D:HIS203	Pi-Orbitals	(R)-PK1119	Alkyl						
D:TYR224 - (R)-PK11195:Cl25	4.65206	Hydrophob	Pi-Alkyl	D:TYR224	Pi-Orbitals	(R)-PK1119	Alkyl						
D:TYR326 - (R)-PK11195:C16	5.2036	Hydrophob	Pi-Alkyl	D:TYR326	Pi-Orbitals	(R)-PK1119	Alkyl						
D:TYR326 - (R)-PK11195:C17	3.69873	Hydrophob	Pi-Alkyl	D:TYR326	Pi-Orbitals	(R)-PK1119	Alkyl						
(R)-PK11195 - D:LEU206	5.13931	Hydrophob	Pi-Alkyl	(R)-PK1119	Pi-Orbitals	D:LEU206	Alkyl						
CITCO													
Name	Distance	Category	Types	From	From Chem	To	To Chemist	Theta	Theta 2	Gamma	Closest Ato	Angle DHA	Angle HAY
CITCO:H28 - D:ASN165:O	2.98476	Hydrogen B	Carbon Hyd	CITCO:H28	H-Donor	D:ASN165:	H-Acceptor					122.005	104.227
D:THR225:O - CITCO:Cl3	3.10208	Halogen	Halogen (C	D:THR225:(	Halogen Ac	CITCO:Cl3	Halogen						
D:TYR224 - CITCO	4.53248	Hydrophob	Pi-Pi Stacke	D:TYR224	Pi-Orbitals	CITCO	Pi-Orbitals	41.915	18.087	26.509	3.725		
CITCO - D:TYR326	4.9482	Hydrophob	Pi-Pi Stacke	CITCO	Pi-Orbitals	D:TYR326	Pi-Orbitals	61.348	33.931	27.432	3.651		
CITCO - D:TYR326	4.83915	Hydrophob	Pi-Pi Stacke	CITCO	Pi-Orbitals	D:TYR326	Pi-Orbitals	59.754	37.409	26.434	3.414		
D:PHE217 - CITCO	5.5592	Hydrophob	Pi-Pi T-shap	D:PHE217	Pi-Orbitals	CITCO	Pi-Orbitals	27.909	87.971	74.704	3.874		
D:PHE234 - CITCO	5.69556	Hydrophob	Pi-Pi T-shap	D:PHE234	Pi-Orbitals	CITCO	Pi-Orbitals	28.965	80.172	63.598	4.009		
CITCO:Cl2 - D:VAL232	4.97312	Hydrophob	Alkyl	CITCO:Cl2	Alkyl	D:VAL232	Alkyl						
D:PHE161 - CITCO:Cl2	4.62547	Hydrophob	Pi-Alkyl	D:PHE161	Pi-Orbitals	CITCO:Cl2	Alkyl						
CITCO - D:VAL199	4.90943	Hydrophob	Pi-Alkyl	CITCO	Pi-Orbitals	D:VAL199	Alkyl						
CITCO - D:CYS202	4.24481	Hydrophob	Pi-Alkyl	CITCO	Pi-Orbitals	D:CYS202	Alkyl						
CITCO - D:LEU242	5.3192	Hydrophob	Pi-Alkyl	CITCO	Pi-Orbitals	D:LEU242	Alkyl						
CINPA1													
Name	Distance	Category	Types	From	From Chem	To	To Chemist	Theta	Theta 2	Gamma	Closest Ato	Angle DHA	Angle HAY
CINPA1:H53 - D:HIS203:NE2	3.0321	Hydrogen B	Convention	CINPA1:H5	H-Donor	D:HIS203:N	H-Acceptor					105.622	103.127
CINPA1:N5 - D:PHE217	4.78064	Electrostati	Pi-Cation	CINPA1:N5	Positive	D:PHE217	Pi-Orbitals	17.465					
CINPA1:N5 - D:TYR224	4.63361	Electrostati	Pi-Cation	CINPA1:N5	Positive	D:TYR224	Pi-Orbitals	16.372					
D:PHE161 - CINPA1	4.83154	Hydrophob	Pi-Pi T-shap	D:PHE161	Pi-Orbitals	CINPA1	Pi-Orbitals	52.712	9.523	59.115	3.758		
D:PHE161 - CINPA1	4.87591	Hydrophob	Pi-Pi T-shap	D:PHE161	Pi-Orbitals	CINPA1	Pi-Orbitals	27.502	44.886	72.293	3.355		
D:TYR224 - CINPA1	5.72976	Hydrophob	Pi-Pi T-shap	D:TYR224	Pi-Orbitals	CINPA1	Pi-Orbitals	60.391	24.992	63.252	4.185		
CINPA1:C29 - D:VAL169	5.4707	Hydrophob	Alkyl	CINPA1:C2	Alkyl	D:VAL169	Alkyl						
CINPA1:C29 - D:VAL199	4.21449	Hydrophob	Alkyl	CINPA1:C2	Alkyl	D:VAL199	Alkyl						
CINPA1:C29 - D:CYS202	4.27499	Hydrophob	Alkyl	CINPA1:C2	Alkyl	D:CYS202	Alkyl						
CINPA1:C29 - D:LEU343	4.79888	Hydrophob	Alkyl	CINPA1:C2	Alkyl	D:LEU343	Alkyl						
D:PHE161 - CINPA1	5.34892	Hydrophob	Pi-Alkyl	D:PHE161	Pi-Orbitals	CINPA1	Alkyl						
D:PHE234 - CINPA1	5.41533	Hydrophob	Pi-Alkyl	D:PHE234	Pi-Orbitals	CINPA1	Alkyl						
D:TYR326 - CINPA1:C29	4.63774	Hydrophob	Pi-Alkyl	D:TYR326	Pi-Orbitals	CINPA1:C2	Alkyl						