

SUPPLEMENTARY DATA

Structural insight into geranylgeranyl diphosphate synthase (GGDPS) for cancer therapy

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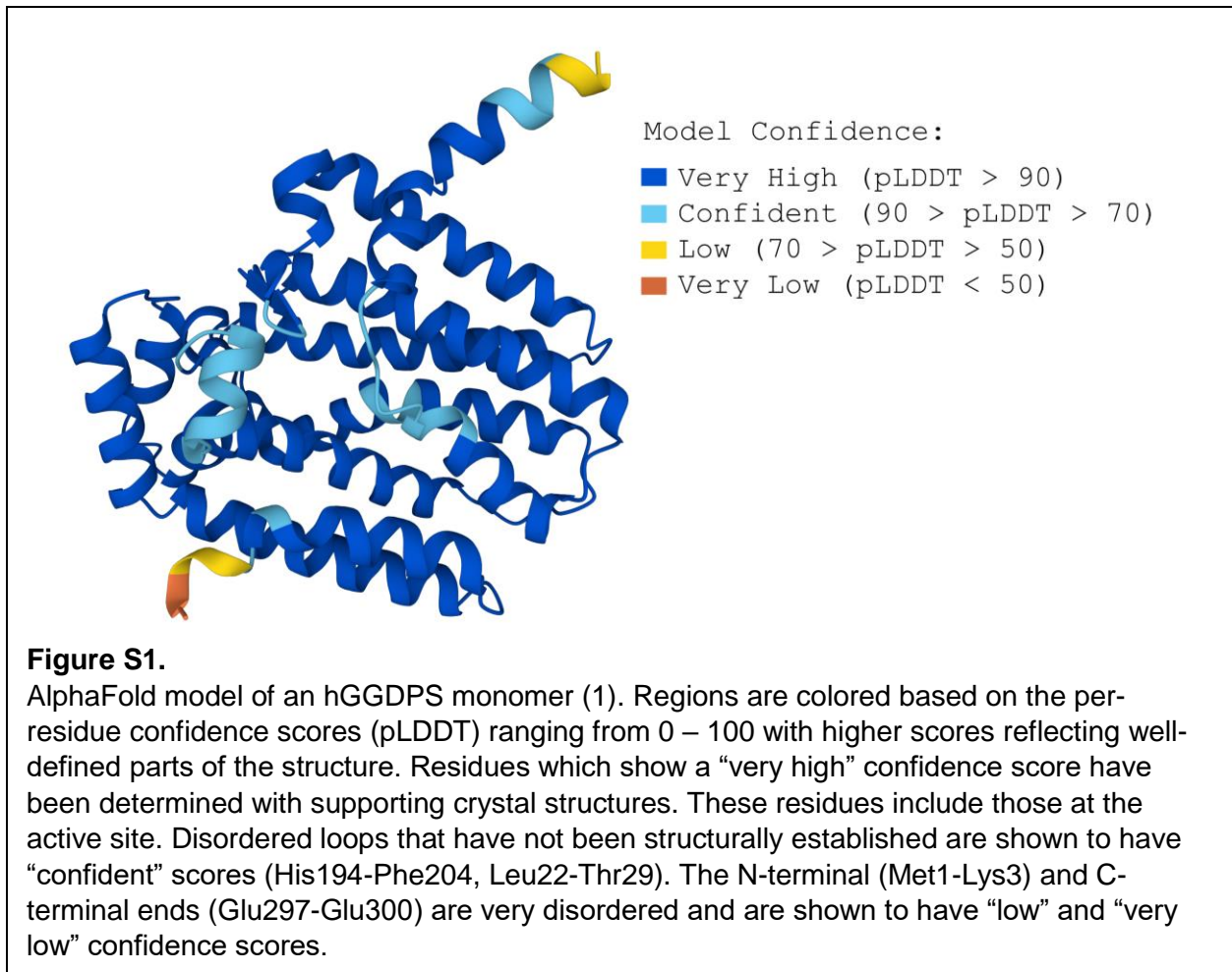
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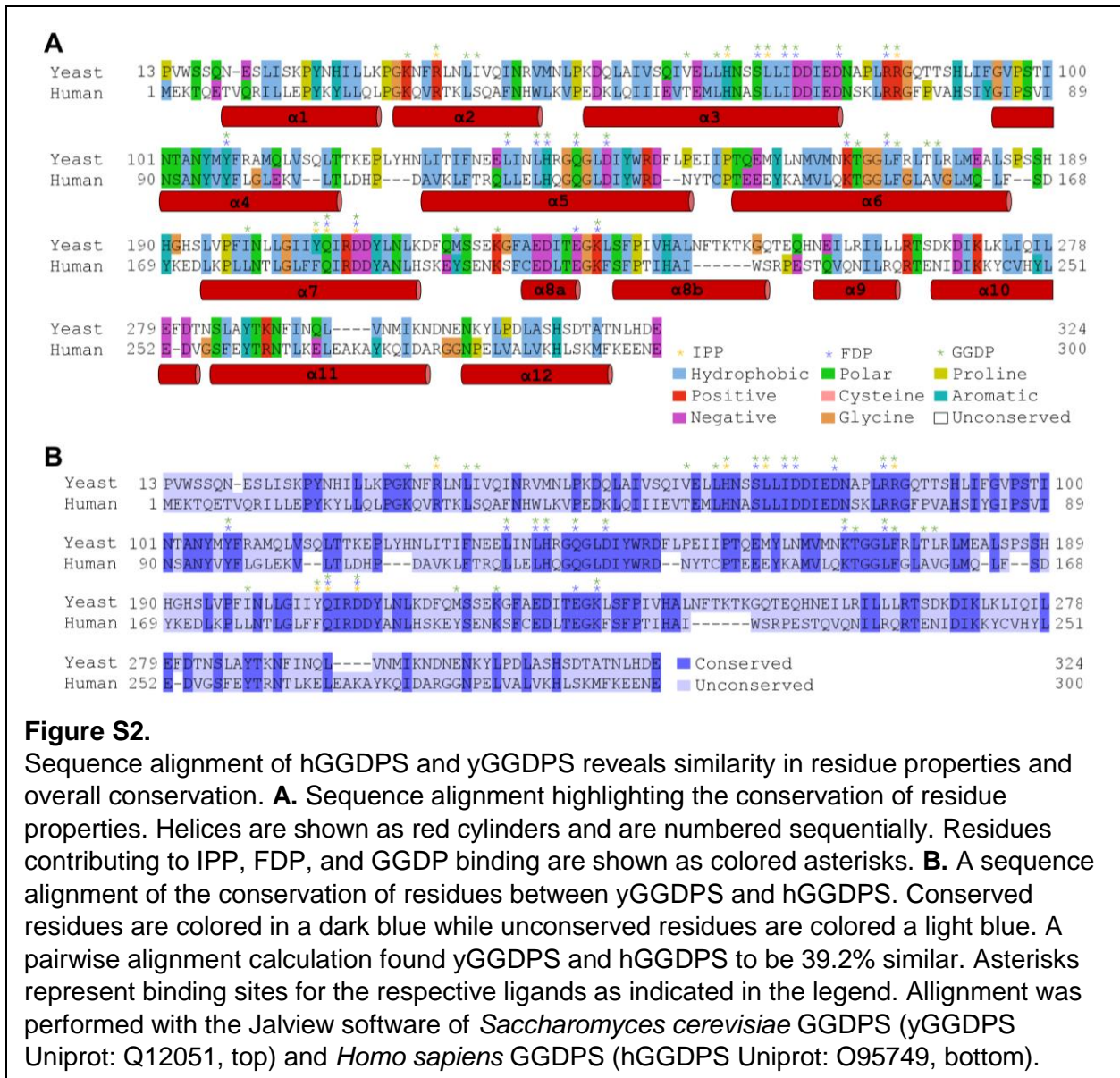


Table S1. Residues involved in the hGGDPS oligomerization

Dimer Interface ^a					Trimer Interface ^b	
α 4	α 5	α 1	α 6	α 3	Region 1	Region 2
Y83	V112	Q5	Q150	I63	R10	E226
G84	K113	V8		I66	E14	S227
I85	F115	I11		E65	Y18	T228
P86	T116	L12			Q21	Q229
S87	L119	E14			K71	N232
I89	L120				L72	I233
N90	H123				F76	R235
N93	Q124				P77	Q236
Y94	Q126				S81	N240
Y96	G127				I82	I243
F97	L126				Y83	Y246
L98	L128					Y250
L100	I130					
E101	Y131					
L104	R133					
	D134					

^a Dimer interface residues were determined utilizing the *InterfaceResidues* command in PyMOL

^b Trimer interface residues were described by Kavanaugh *et al.* (2)

Table S2. Residues involved in IPP and FDP binding

Yeast (IPP) ^a	Human (IPP) ^a	Yeast (FDP) ^b	Human (FDP) ^b
R39	R28	S71	S60
H68	H57	L72	L61
L72	L61	I74	I63
R85	R74	D75	D64
Y205	F184	D79	D68
Q206	Q185	R84	R73
D209	D188	Y107	Y96
		L135	L119
		L138	L122
		H139	H123
		Q142	Q126
		D145	D129
		K169	K151
		L173	L155
		Q206	Q185
		D209	D188
		E231	E210
		K233	K212

^a Residues found to have sidechains within 4 Å of the IPP substrate in 2E8T and AF 2Q80

^b Residues found to have sidechains within 4 Å of the FDP substrate in 2E8T and AF 2Q80

Table S3. Residues involved in GGDP binding

Yeast (GGDP) ^a	Human (GGDP) ^a	Yeast (GGDPi) ^b	Human (GGDPi) ^b
K36	K25	R39	R28
R39	R28	L42	L31
L67	L56	I43	S32
H68	H57	V64	T53
S71	S60	H68	D64
L72	L61	L72	D68
I74	I63	D75	R73
D75	D64	D79	D129
R85	R74	R84	K151
Y107	Y96	L138	T152
L135	L119	Q142	L155
L138	L122	K169	F156
H139	H123	L173	A159
Q142	Q126	F174	V160
K169	K151	T177	Q185
Y205	F184	I198	D188
Q206	Q185	Y205	Y198
		Q206	K202
		D209	K212
		K233	

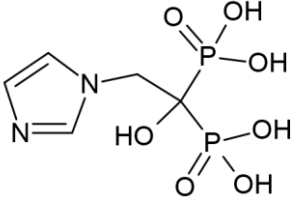
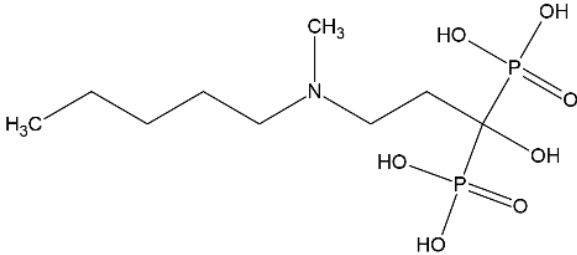
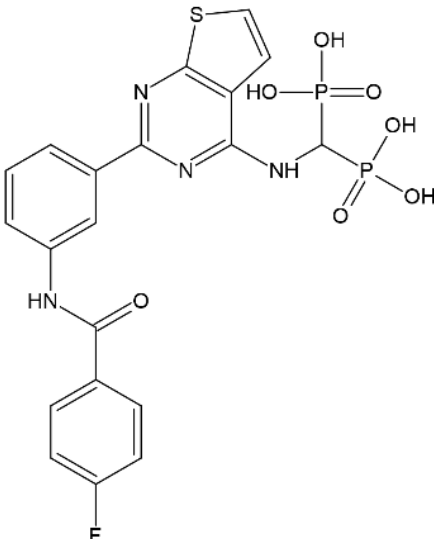
^a Residues found to have sidechains within 4 Å of the GGDP product in 2E8V and AF 2Q80

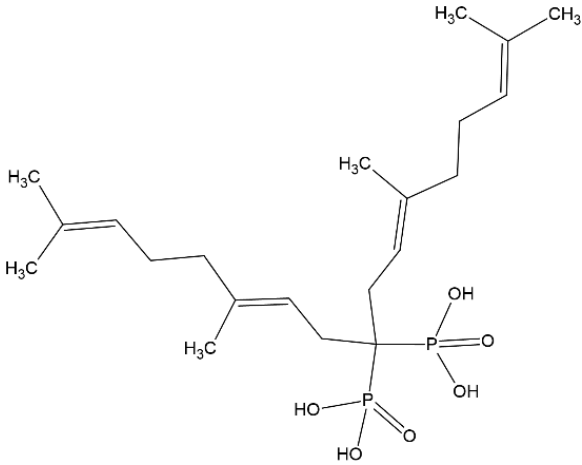
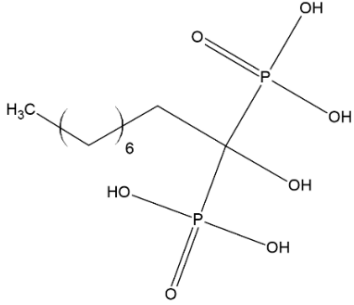
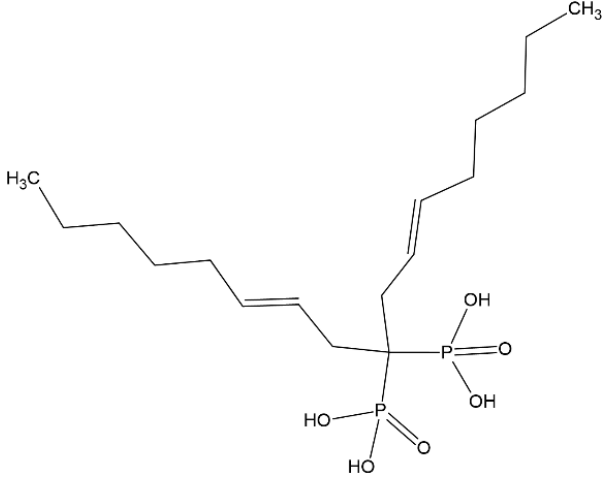
^b Residues found to have sidechains within 4 Å of the GGDP product in 2Z4V and AF 2Q80

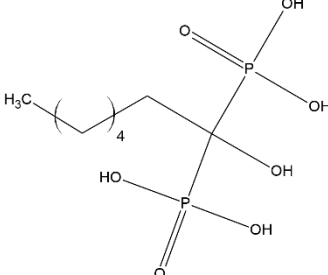
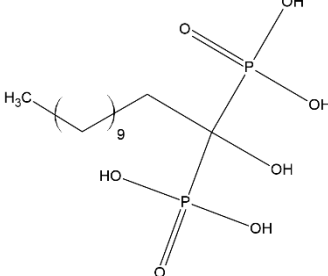
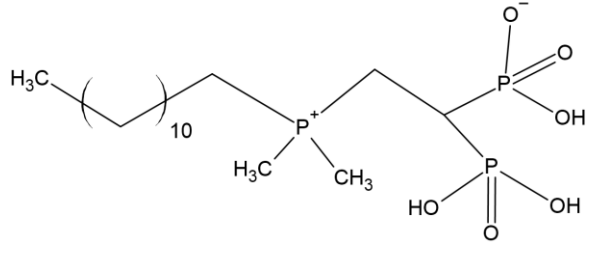
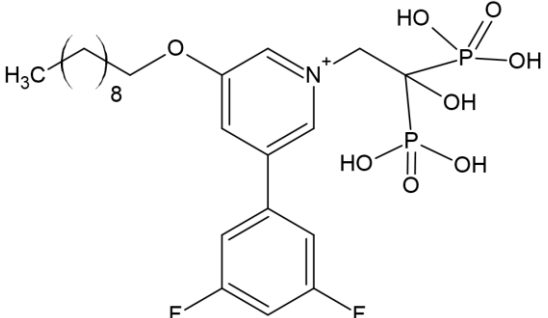
Table S4. Drug-bound PDB structures

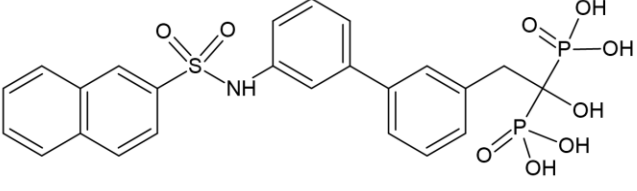
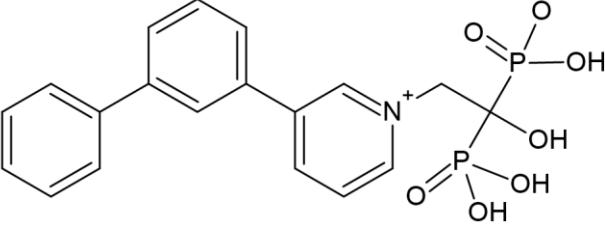
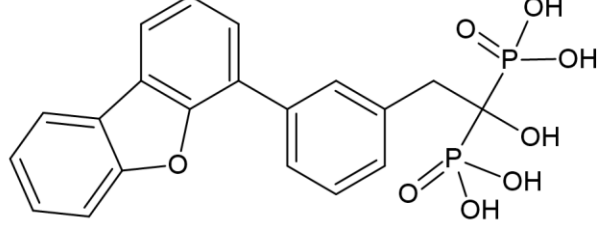
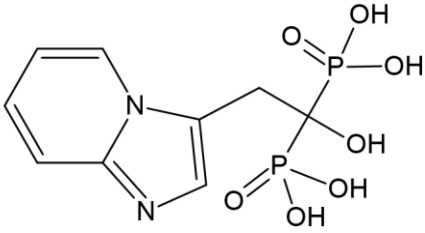
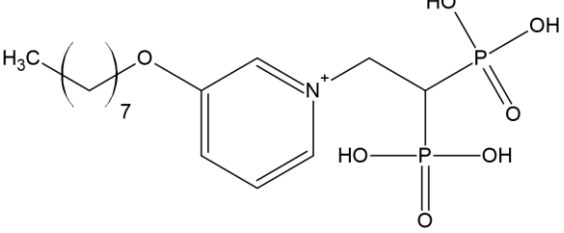
Species	PDB	Compound	Reference
Human	6G31	Zoledronic Acid	Lisnyansky et al. 2018 (3)
Human	6R4V	Ibandronate	Lisnyansky et al. 2019 (4)
Human	6C57	FV0109	Lacbay et al. 2018 (5)
Yeast	2Z4W	BPH-749 (DGBP)	Chen et al. 2008 (6)
Yeast	2Z4Y	BPH-252	Chen et al. 2008 (6)
Yeast	2Z4Z	BPH-SC01	Chen et al. 2008 (6)
Yeast	2Z50	BPH-28	Chen et al. 2008 (6)
Yeast	2Z52	BPH-23	Chen et al. 2008 (6)
Yeast	2Z7I	BPH-742	Chen et al. 2008 (6)
Yeast	2Z78	BPH-806	Chen et al. 2008 (6)
Yeast	2E95	BPH-675	Guo et al. 2007 (7)
Yeast	2E94	BPH-364	Guo et al. 2007 (7)
Yeast	2E93	BPH-629	Guo et al. 2007 (7)
Yeast	2E92	Minodronate	Guo et al. 2007 (7)
Yeast	2E91	BPH-91	Guo et al. 2007 (7)
Yeast	2ZEU	BPH-715	Zhang et al. 2009 (8)

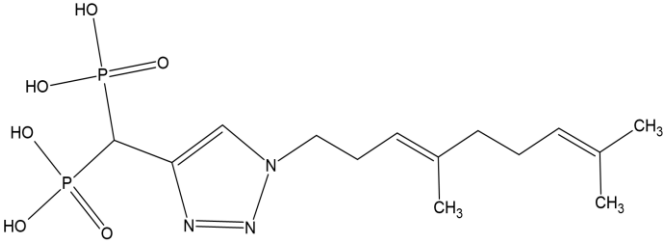
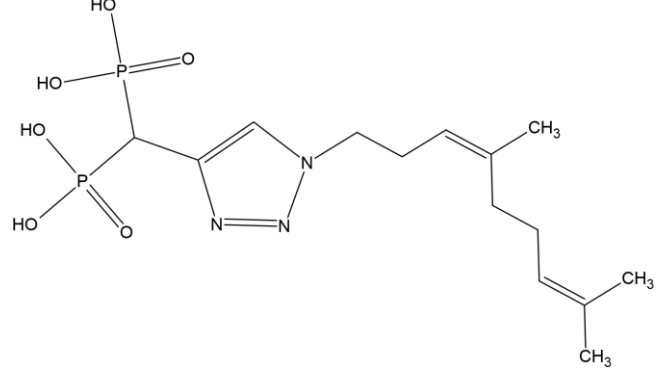
Table S5. Drug-bound PDB structures

Compound	Structure	IC ₅₀ (μM)*	PDB
Zoledronic Acid		K _i : 2.1 ^a yGGDPS IC ₅₀ : 0.66 ^b hGGDPS IC ₅₀ : 97 ^c	6G31 (3) 2E91 (7)
Ibandronate		N/A	6R4V (4)
FV0109		IC ₅₀ : 0.042 ^c EC ₅₀ : 0.70 ^d	6C57 (5)

<p>DGBP</p>		<p>IC₅₀: 0.98^c</p>	<p>2Z4W (6)</p>
<p>BPH-252</p>		<p>IC₅₀: 0.71^c</p>	<p>2Z4Y (6)</p>
<p>BPH-SC01</p>		<p>IC₅₀: 1.86^c</p>	<p>2Z4Z (6)</p>

BPH-28		IC ₅₀ : 11.22 ^c	2Z50 (6)
BPH-23		IC ₅₀ : 2.69 ^c	2Z52 (6)
BPH-742		IC ₅₀ : 0.10 ^c	2Z71 (6)
BPH-806		IC ₅₀ : 0.76 ^c	2Z78 (6)

BPH-675		yGGDPS IC ₅₀ : 0.20 ^b hGGDPS IC ₅₀ : 2.6 ^c	2E95 (7)
BPH-364		yGGDPS IC ₅₀ : 0.03 ^b hGGDPS IC ₅₀ : 8.2 ^c	2E94 (7)
BPH-629		yGGDPS IC ₅₀ : 0.28 ^b hGGDPS IC ₅₀ : 4.0 ^c	2E93 (7)
Minodronate		yGGDPS IC ₅₀ : 0.34 ^b hGGDPS IC ₅₀ : 65 ^c	2E92 (7)
BPH-715		IC ₅₀ : 2.9 ^e	2ZEU (8)

Homogeranyl		IC ₅₀ : 0.173 ^c	N/A (9)
Homoneryl		IC ₅₀ : 0.075 ^c	N/A (9)

* Unless stated, IC₅₀ refers to inhibition of hGGDPS

^a Determined from differential scanning fluorimetry of wild-type GGDPs with zoledronate

^b Determined from *in vitro* enzyme assay of γ GGDPs with the corresponding compound

^c Determined from *in vitro* enzyme assay of hGGDPS with the corresponding compound

^d Determined through MTT after 72h incubation of cells with and without compound

^e Determined through a mouse fetal metatarsal ⁴³Ca²⁺ release inhibition assay

References

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