

Table 1: p97–VCIPI1 Complex hit rate:21/30 (PDB 8YKA)rank 30 reactive?—
R = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	C:ILE206	NC	Buried core; no evidence	
2	A:ILE206	NC	Buried core; no evidence	
3	C:ILE423	Ind	Pore-loop “staircase” wall in D2 ring; substrate threading	[1]
4	3:LYS657	R	VCIP135 ubiquitination regulates DUB activity	[2]
5	2:LYS657	R	VCIP135 ubiquitination regulates DUB activity	[2]
6	1:LYS657	R	VCIP135 ubiquitination regulates DUB activity	[2]
7	D:GLN337	Ind	Pore-loop “staircase” wall in D1 ring; substrate threading	[1]
8	E:PRO648	R	CB-5083 inhibitor pocket residue	[3]
9	E:ASP592	R	D592N allosteric mutant disrupts inter-domain coupling	[3]
10	B:GLN337	Ind	Pore-loop “staircase” wall in D1 ring; substrate threading	[1]
11	F:ALA15	NC	N-domain core; no residue-level evidence	
12	F:GLN337	Ind	Pore-loop “staircase” wall in D1 ring; substrate threading	[1]
13	A:ARG239	Ind	Predicted ataxin-3 interface patch	[4]
14	E:GLU466	R	D1–D2 linker hinge (L464 region)	[5]
15	A:ARG709	NC	C-tail; residue-specific data lacking	
16	C:ASP592	R	D592N allosteric mutant disrupts inter-domain coupling	[3]
17	2:GLY311	NC	Structural; no evidence	
18	1:GLY311	NC	Structural; no evidence	
19	3:GLY311	NC	Structural; no evidence	
20	C:ARG239	Ind	Predicted ataxin-3 interface patch	[4]
21	E:GLY591	Ind	ΦXG pore-pivot motif in D2 loop	[6]
22	C:CYS174	Ind	Core structure; predicted covalent Cys hotspot	[7]
23	A:GLN43	Ind	Val38-Gln43 strip contacts p47/UBXD1 UBX domains	[8]
24	C:GLU466	R	D1–D2 linker hinge (L464 region)	[5]
25	B:HIS317	R	Pore-1 loop sensor essential for ERAD	[6]
26	C:LEU445	Ind	Predicted hinge-region residue	[5]
27	A:ASN36	Ind	Part of VIM-groove contact surface (p47 UBX)	[8]
28	D:GLN473	NC	Structural; no evidence	
29	E:ASN36	Ind	Part of VIM-groove contact surface (p47 UBX)	[8]
30	E:ASP640	NC	Structural; no evidence	

Table 2: Human p97/VCP AAA⁺ ATPase hit rate:30/30 (PDB 8OOI)rank 30 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	C:ASP577	R	D2 Walker B catalytic Asp; Mg ²⁺ -ATP	[9, 10]
2	F:ASP577	R	D2 Walker B catalytic Asp; Mg ²⁺ -ATP	[9, 10]
3	D:ASP577	R	D2 Walker B catalytic Asp; Mg ²⁺ -ATP	[9, 10]
4	A:ASP577	R	D2 Walker B catalytic Asp; Mg ²⁺ -ATP	[9, 10]
5	E:ASP577	R	D2 Walker B catalytic Asp; Mg ²⁺ -ATP	[9, 10]
6	B:ASP577	R	D2 Walker B catalytic Asp; Mg ²⁺ -ATP	[9, 10]
7	A:ASP304	R	D1 Walker B catalytic Asp; Mg ²⁺ -ATP	[9, 10]
8	D:ASP304	R	D1 Walker B catalytic Asp; Mg ²⁺ -ATP	[9, 10]
9	C:ASP304	R	D1 Walker B catalytic Asp; Mg ²⁺ -ATP	[9, 10]
10	F:ASP304	R	D1 Walker B catalytic Asp; Mg ²⁺ -ATP	[9, 10]
11	B:ASP304	R	D1 Walker B catalytic Asp; Mg ²⁺ -ATP	[9, 10]
12	E:ASP304	R	D1 Walker B catalytic Asp; Mg ²⁺ -ATP	[9, 10]
13	E:GLY250	R	D1 Walker A P-loop Gly (phosphate clamp)	[9, 10]
14	B:GLY250	R	D1 Walker A P-loop Gly (phosphate clamp)	[9, 10]
15	A:GLY250	R	D1 Walker A P-loop Gly (phosphate clamp)	[9, 10]
16	D:GLY250	R	D1 Walker A P-loop Gly (phosphate clamp)	[9, 10]
17	C:GLY250	R	D1 Walker A P-loop Gly (phosphate clamp)	[9, 10]
18	F:GLY250	R	D1 Walker A P-loop Gly (phosphate clamp)	[9, 10]
19	F:GLY544	R	D2 Walker A P-loop Gly (phosphate clamp)	[9, 10]
20	D:GLY544	R	D2 Walker A P-loop Gly (phosphate clamp)	[9, 10]
21	A:GLY544	R	D2 Walker A P-loop Gly (phosphate clamp)	[9, 10]
22	E:GLY544	R	D2 Walker A P-loop Gly (phosphate clamp)	[9, 10]
23	C:GLY544	R	D2 Walker A P-loop Gly (phosphate clamp)	[9, 10]
24	B:GLY544	R	D2 Walker A P-loop Gly (phosphate clamp)	[9, 10]
25	F:GLY518	R	D2 P-loop linker Gly; nucleotide latch	[9, 10]
26	B:GLY518	R	D2 P-loop linker Gly; nucleotide latch	[9, 10]
27	C:GLY518	R	D2 P-loop linker Gly; nucleotide latch	[9, 10]
28	A:GLY518	R	D2 P-loop linker Gly; nucleotide latch	[9, 10]
29	E:GLY518	R	D2 P-loop linker Gly; nucleotide latch	[9, 10]
30	D:GLY518	R	D2 P-loop linker Gly; nucleotide latch	[9, 10]

Table 3: *E. coli* 70S ribosome hit rate:60/60 (PDB 6Q97)rank 60 reactive?—
R = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	C:HIS140	Ind	tmRNA-contact side-chain (BioLiP contact map)	[11]
2	D:ARG79	R	L4 tunnel hairpin; macrolide-resistance hotspot	[12]
3	N:HIS32	Ind	Early-assembly N-tail docks on 23S rRNA (cryo-EM)	[13]
4	f:HIS33	R	Zn-finger ligand of L36; Zn ²⁺ essential for 50S	[14]
5	f:CYS27	R	Second Zn-finger cysteine in L36	[14]
6	X:LYS62	Ind	Basic patch of L28 on h25/26 (ConSurf 9)	[15]
7	U:SER68	Ind	L24 hinge loop closing CP; mobile in early assembly cryo-EM	[13]
8	G:VAL108	R	Central hinge of L9; smFRET shows domain motion	[16]
9	B:GLY235	R	C-arm cross-links to 23S D-IV in XL-MS	[17]
10	F:LYS176	R	L6 C-tail binds GTPase centre; assembly defect when truncated	[18]
11	h:LEU157	Ind	30S head-body hinge residue (swivel cryo-EM)	[19]
12	W:GLY42	R	L27 tail reaching P-site; antibiotic footprint	[20]
13	W:GLY48	R	Same L27 P-site tail	[20]
14	g:GLY99	Ind	uS2 hinge; highly conserved	[15, 19]
15	g:GLY224	Ind	uS2 C-tail flexes during swivel	[19]
16	W:GLY34	R	Cross-links to P-site tRNA (XL-MS)	[20]
17	R:GLY57	R	XL-MS to 23S rRNA; late 50S assembly delay	[17]
18	G:HIS135	Ind	RNA-binding face; FoldX $\Delta\Delta G = 1.2$ kcal mol ⁻¹	[21, 17]
19	k:GLY34	R	S6-S18 KD \uparrow (ITC) when G34A	[22]
20	F:GLN143	Ind	L6 GAR helix; FoldX $\Delta\Delta G = 1.4$	[18]
21	Q:VAL4	R	L20 N-tail essential for early LSU nucleation	[23]
22	D:GLN136	R	L4 tunnel loop; azithromycin MIC \uparrow mutants	[12]
23	E:PHE138	Ind	L5 β -sandwich stacks on 5S rRNA	[24]
24	F:GLN139	Ind	Second L6 GAR contact	[18]
25	H:THR131	Ind	L10 stalk hinge (factor-binding cryo-EM)	[25]
26	X:ARG11	Ind	Basic N-end clamps h25 (ConSurf 8)	[15]
27	D:GLY151	R	Tunnel tip; macrolide resistance hotspot	[12]
28	g:LEU157	Ind	uS2 hinge network	[19]
29	v:VAL83	Ind	L25 β -sheet supports 5S E-loop (NMR + MD ΔG)	[26, 27]
30	i:ASN85	Ind	uL11 hinge contacting factors (cryo-EM)	[25]
31	B:GLY209	R	L2 C-arm cross-links to 23S D-IV	[17]
32	W:ASP15	R	L27 N-tail positions P-site tRNA	[20]

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Rank	Chain:Residue	Class	Evidence summary	Key refs
33	P:THR104	R	Bridge B8 mutation lowers fidelity	[28]
34	o:ASN58	R	S10 loop alanine-scan shifts tigecycline MIC	[29]
35	v:LEU8	Ind	Primary S17 rRNA binder; conserved	[15]
36	D:ASN163	R	Tunnel loop macrolide-resistance variant	[12]
37	f:GLU30	R	Acidic ligand in L36 Zn-finger; assembly defect	[14]
38	O:TYR64	Ind	L18 bridges 5S/23S; packs loop-E	[26]
39	G:GLY85	R	L9 hinge RMSF 0.9Å (smFRET dynamics)	[16]
40	h:GLY74	Ind	S3 head latch; hinge MD	[19]
41	a:LYS47	R	Δ L31 translation \downarrow 40 %; Lys47 solvent-exposed (MS)	[14, 30]
42	R:GLU70	R	L21 helix clamps CP; deletion lethal	[23]
43	J:GLN136	Ind	L13 clamp; FoldX $\Delta\Delta G = 1.2$ kcal mol ⁻¹ ; early 50S assembly defect	[21, 23]
44	I:ILE100	Ind	L11 GAR contact; cryo-EM factor density shift	[25]
45	F:LEU117	Ind	L6-SRL contact $\Delta\Delta G = 1.1$	[18]
46	E:GLY151	R	Deep-mutational scanning fitness 0.22	[31]
47	i:LEU82	R	S4 miscoding mutant increases error rate	[32]
48	r:GLN100	R	Bridge B1b cross-link to L5	[17]
49	R:GLN18	R	N-tail deletion blocks 50S assembly	[23]
50	C:GLY135	R	“Rocker-switch” loop; tRNA accommodation defect	[33]
51	J:GLY26	Ind	Early nucleator N-tail (ConSurf 10)	[23]
52	l:GLU139	Ind	S7 head MD hinge contact	[19]
53	i:LEU9	R	S4 miscoding mutant set	[32]
54	V:MET1	R	N-Met inserts into 5S; removal prevents 50S assembly	[26, 34]
55	C:GLY76	R	L3 N-arm deletion impairs accommodation	[33]
56	n:GLU92	Ind	S9 C-tail contacts P-site tRNA (cryo-EM)	[19]
57	T:ASN92	Ind	L23 SRP/Trigger-factor docking site	[20]
58	q:VAL63	R	Classic streptomycin-resistance hotspot	[12]
59	D:PHE158	R	L4 tunnel loop lines macrolide pocket	[12]
60	J:THR3	R	L13 N-tail essential for 50S nucleation	[23]

Table 4: GroEL-GroES chaperonin Complex hit rate:45/50 (PDB 2C7C)rank 50 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	J:Ser43	R	Pyrene-label mutant traps R ₂ state — encapsulation gate	[35]
2	D:Gly431	Ind	Markov hub transmitting ATP signal	[36]
3	D:Gly337	R	G337D thermo-sensitive hinge-1 mutant	[37]
4	P:Asn68	Ind	SCA allosteric path node	[38]
5	N:Gly318	Ind	High-betweenness 310–320 axis hub	[39]
6	J:Gly375	R	Triple-gly hinge-2 buffer (G375W vs G192W)	[40]
7	E:Gly198	R	G192W traps GroEL–GroES dead-end	[40]
8	J:Gly198	R	= Rank 7, chain J	[40]
9	F:Gly119	Ind	Apical “door” pivot (AWD cluster)	[39]
10	J:Gly414	Ind	ATP pocket pivot G414+D494	[36]
11	M:Val174	R	V174F suppresses ts mutant EL44; wiring node	[41, 42]
12	L:Asp316	R	HDX peptide 302–319 protected in ATP γ S	[43]
13	H:Gly375	R	= Rank 6, chain H	[40]
14	L:Gly318	Ind	= Rank 5, chain L	[39]
15	N:Gly198	R	= Rank 7, chain N	[40]
16	K:Gly298	R	R277–G298 H-bond critical to CnoX redox complex	[44]
17	D:Gly119	Ind	= Rank 9, chain D	[39]
18	I:Gly375	R	= Rank 6, chain I	[40]
19	B:Gly119	Ind	= Rank 9, chain B	[39]
20	M:Gln366	NC	No published evidence (May 2025)	
21	J:Gly19	R	G19I strap mutant breaks (–) cooperativity	[45]
22	I:Gly318	Ind	= Rank 5, chain I	[39]
23	C:Gly119	Ind	= Rank 9, chain C	[39]
24	N:Gly19	R	= Rank 21, chain N	[45]
25	E:Gly439	Ind	Δ 432–451 tail slows folding; tail–substrate contact	[46, 47]
26	J:Asp473	Ind	K80–D473 salt-bridge breaks in R→T reset	[48]
27	N:Gly119	Ind	= Rank 9, chain N	[39]
28	M:Ser139	Ind	Ser139–Asp140 bridge in Markov cluster 11	[49]
29	E:Gly119	Ind	= Rank 9, chain E	[39]
30	H:Gln366	NC	No published evidence	
31	C:Gly19	R	= Rank 21, chain C	[45]
32	C:Gly439	Ind	= Rank 25, chain C	[46, 47]
33	L:Asp179	NC	No functional data available	
34	G:Gly337	R	= Rank 3, chain G	[37]
35	A:Gly382	NC	No functional data available	

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Rank	Chain:Residue	Class	Evidence summary	Key refs
36	J:Ile493	Ind	ATP adenine “sandwich”; I493A $\Delta\Delta G$ +3 kcal	[50]
37	A:Gly439	Ind	= Rank 25, chain A	[46, 47]
38	C:Gly198	R	= Rank 7, chain C	[40]
39	M:Gly318	Ind	= Rank 5, chain M	[39]
40	H:Gly318	Ind	= Rank 5, chain H	[39]
41	G:Gly198	R	= Rank 7, chain G	[40]
42	A:Gly337	R	= Rank 3, chain A	[37]
43	A:Gly119	Ind	= Rank 9, chain A	[39]
44	J:Gly318	Ind	= Rank 5, chain J	[39]
45	G:Gly119	Ind	= Rank 9, chain G	[39]
46	E:Gly159	Ind	155–160 coil minimal-frustration hub	[51, 52]
47	D:Gly159	Ind	= Rank 46, chain D	[51, 52]
48	G:Gly318	Ind	= Rank 5, chain G	[39]
49	I:Leu365	Ind	L365A $\Delta\Delta G$ +3 k; SCA co-evolving node	[50, 53]
50	H:Gly198	R	= Rank 7, chain H	[40]

Table 5: Ribulose-1,5-bisphosphate carboxylase/oxygenase holoenzyme hit rate:30/30 (PDB 4RUB)rank 30 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	D:GLU204	R	Essential Mg^{2+} general base; Glu→Gln mutant inactive	[54]
2	A:GLU204	R	As above (symmetry mate)	[54]
3	C:GLU204	R	As above	[54]
4	B:GLU204	R	As above	[54]
5	A:ASP203	R	Partners Glu204 in Mg^{2+} chelation; Asp→Asn inactive	[54]
6	B:ASP203	R	As above	[54]
7	C:ASP203	R	As above	[54]
8	D:ASP203	R	As above	[54]
9	D:GLY344	R	Central hinge of loop 6; G344S lowers CO_2/O_2 specificity	[55, 56]
10	C:GLY344	R	As above	[55]
11	B:GLY344	R	As above	[55]
12	U:GLY49	Ind	SSU βA – βB loop; alanine scan reduces k_{cat}/K_{O_2}	[57]
13	C:GLY380	Ind	Start of loop 7 Gly stretch; stretch mutants abolish P_1 binding	[58]

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Rank	Chain:Residue	Class	Evidence summary	Key refs
14	D:ALA9	Ind	LSU N-tail truncation destabilises loop 1 and lowers activity	[59]
15	A:GLY344	R	Fourth chain copy of loop-6 hinge	[55]
16	A:GLY416	Ind	Tail helix 16 latch over closed loop 6 (helix-17 study)	[60]
17	B:GLY416	Ind	As above	[60]
18	A:GLY322	Ind	Secondary hinge modulating loop 6 kinetics	[56]
19	T:GLY49	Ind	SSU copy of rank 12	[57]
20	T:TYR94	Ind	SSU β A- β B loop hotspot for LSU-SSU crosstalk	[57]
21	A:GLY373	Ind	Loop 7 hinge; X-ray and MD studies show Gly373-Thr378 flexibility window	[61, 62]
22	U:TRP38	R	Trp38Ala abolishes pyrenoid formation (helix A/B)	[63]
23	D:GLY308	Ind	Dimer-interface loop L ₂ alters specificity in Form II enzyme	[64]
24	B:ASN432	Ind	C-tail residue contacting loop 6 (1.5 Å structure)	[62]
25	C:SER452	Ind	Tail insert locking loops 6/7 closed	[60]
26	D:GLY196	Ind	First residue of GXKXDE catalytic motif; universally conserved	[65]
27	A:GLU460	Ind	Helix 17 salt bridge reinforcing closed active site	[60]
28	C:GLY441	Ind	Central glycine within tail insert packing onto loops 6/7	[60]
29	C:GLY195	Ind	Pre-motif diglycine kink; loop-2 flexibility (X-ray)	[66]
30	D:GLY333	Ind	Loop-6 swivel; Form III N333F lowers V_c (cross-family hint)	[67]

Table 6: *E. coli* F₁F_o-ATP synthase hit rate:9/10 (PDB 6VWK)rank 10 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	a:Glu196	R	Loss-of-function Ala/Lys mutants abolish H ⁺ translocation and ATP synthesis	[68, 69]
2	a:Gly208	Ind	TMH4-TMH5 hinge Gly; MD and topology studies show indispensable flexibility	[70]

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Rank	Chain:Residue	Class	Evidence summary	Key refs
3	R:Gly27	Ind	c-ring N-terminus “breathing” couples to rotary dwell (phylo-MD analysis)	[71]
4	Q:Gly23	Ind	Same c-ring breathing cluster as rank 3	[71]
5	a:Asp119	Ind	Cys119 chemical reactivity + D119H rescue experiments identify periplasmic half-channel gate	[72, 73]
6	N:Gly23	Ind	c-ring protomer equivalent of rank 3	[71]
7	P:Gly27	Ind	c-ring protomer equivalent of rank 3	[71]
8	a:Leu155	NC	No experimental or structural evidence to date	
9	S:β-Gly58	Ind	β-subunit DELSEED loop; mutations shorten torque-coupling loop and slow rotation	[74]
10	N:Gly27	Ind	Another c-ring protomer equivalent of rank 3	[71]

Table 7: SecA pre-protein translocase motor hit rate:10/10 (PDB 1TF5)rank 10 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	A:Gly265	R	PPXD–NBD2 hinge; Gly→A/P mutations stiffen the swing and slow signal-peptide-triggered ATPase activity.	[75, 76, 77]
2	A:Glu497	R	Acidic partner of Gate-1 (E497-R322-D217); E497Q stalls secretion <i>in vivo</i> .	[78, 77]
3	A:Arg322	R	Basic partner of Gate-1; R322E/K uncouple pre-protein binding from ATPase stimulation.	[78, 77]
4	A:Ile454	R	Core of HSD α6 “power-lever”; I454F/K and Δα6 mutants abolish mechanical force generation.	[79, 80, 81]
5	A:Gly225	R	Dominant-negative hot-spot in PPXD stem; FRET & SCAM place Gly225 inside the signal-peptide clamp hinge.	[82, 83, 84]
6	A:Glu552	R	C-terminal acidic patch contacting SecB/uL23; E552Q reduces ribosome docking and causes cold-sensitive export.	[85, 86, 87]
7	A:His289	R	Contacts signal-peptide carbonyl in NMR/X-ray complexes; H289A lowers affinity and initiation rate.	[88]
8	A:Asp732	R	Within FLD–ZnBD linker; D732A and Δ726-768 abolish SecB binding and ribosome docking.	[89, 90]

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Rank	Chain:Residue	Class	Evidence summary	Key refs
9	A:Glu420	R	Acidic lid of NBD2; E420Q decreases k_{cat} five-fold and perturbs clamp allostery.	[91, 92, 77]
10	A:Leu654	R	Hydrophobic core of the HWD wing helix; L654F and $\Delta 650$ -660 mutants act dominantly negative.	[90, 93, 81]

Table 8: SARS-CoV-2 Spike (prefusion trimer) hit rate:24/30 (PDB 6VSB)rank 30 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	C:Asn360	Ind	DMS fitness -2σ ; quaternary nAb 12-19 contacts	[94, 95]
2	C:Gly1059	Ind	HR2 pivot; DMS -1.4σ loss of entry	[94]
3	C:Gly648	Ind	630-loop hinge; HDX-MS ΔG_{max} , DMS -0.8σ	[96, 94]
4	B:Asn360	Ind	Same evidence as rank 1 (chain B)	[94, 95]
5	A:Gly1059	Ind	Same evidence as rank 2 (chain A)	[94]
6	C:Leu828	Ind	FPPR hydrophobic core; pH-switch ΔG_{max}	[96]
7	B:Trp104	Ind	NTD tetrapyrrole (heme/biliverdin) π -clamp	[97, 98]
8	B:Gly857	Ind	Fusion-peptide C-term wedge; FPPR MD hinge	[99, 96]
9	A:Gly566	Ind	SD1–SD2 hinge; DMS -1σ ; cryo-EM bend pivot	[94, 100]
10	B:Gly1059	Ind	Same evidence as rank 2 (chain B)	[94]
11	B:Leu582	Ind	SD2 core; mAb S3H3 lock-patch	[101]
12	A:Leu518	Ind	BA.4/5 escape hot-spot (E1/E3 class)	[101]
13	C:Gly103	NC	—	—
14	B:Phe347	Ind	Heparan-sulfate π -cluster; R346 supersite escape	[102, 103]
15	A:Ile233	Ind	NTD “supersite”; BA.1 escape residue	[104]
16	B:Gly601	Ind	RBD-opening network hub; DMS -1σ	[105, 94]
17	A:Cys1043	R	Disulfide C1028–C1043 break \rightarrow fusion \downarrow	[106]
18	C:Gly601	Ind	Same evidence as rank 16 (chain C)	[105, 94]
19	C:Gln506	Ind	ACE2 anchor; engineered decoy escape-proof	[107]
20	A:Asn360	Ind	Same evidence as rank 1 (chain A)	[94, 95]
21	C:Phe58	NC	—	—
22	C:Asp808	Ind	FPPR \longleftrightarrow RBD allosteric gate (MD network)	[108]
23	A:Asp985	R	Stem N-glycan removal destabilises spike	[109]
24	B:Gly648	Ind	Same evidence as rank 3 (chain B)	[96, 94]
25	B:Gly404	NC	—	—
26	B:Leu959	R	HR1 fusion core; L959F lowers syncytium	[94, 110]

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Rank	Chain:Residue	Class	Evidence summary	Key refs
27	C:Pro579	NC	—	—
28	A:Gly107	NC	—	—
29	B:Gly566	Ind	Same evidence as rank 9 (chain B)	[94, 100]
30	B:Gly283	NC	—	—

Table 9: RNA polymerase II elongation complex hit rate:35/40 (PDB 5C3E)rank 40 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	J:Cys10	R	Rpb2 Zn-ribbon Cys; C10S causes Zn loss and mis-folding	[111]
2	A:Cys67	R	Rpb1 Zn-ribbon Cys; C67S abolishes activity	[111]
3	B:Cys1163	R	Rpb2 C-terminal Zn-finger ligand, essential for activity	[112]
4	A:Asp481	R	Catalytic Asp–Mg ²⁺ triad; D481N inactivates Pol II	[113]
5	A:His80	R	Zn-ribbon His; H80A slows elongation rate	[114]
6	J:Cys72	R	Second Rpb2 Zn-ribbon ligand	[111]
7	L:Cys34	R	Rpb11 Zn-cluster Cys; C34S is lethal	[115]
8	C:Cys86	R	Rpb3 Zn-finger 1 ligand	[115]
9	L:Cys51	R	Second Rpb11 Zn-cluster ligand	[115]
10	C:Cys95	R	Rpb3 Zn-finger 1 ligand	[115]
11	C:Cys92	R	Rpb3 Zn-finger 1 ligand	[115]
12	C:Cys88	R	Rpb3 Zn-finger 1 ligand	[115]
13	B:Cys1185	R	Rpb2 Zn-finger Cys; C1185S reduces activity	[112]
14	A:Cys110	R	Rpb1 Zn-ribbon Cys; folding essential	[111]
15	I:Cys75	R	Rpb9 Zn-ribbon Cys; controls start-site choice	[116]
16	I:Cys106	R	Rpb9 Zn-ribbon Cys	[116]
17	I:Cys10	R	Rpb9 Zn-ribbon Cys	[116]
18	I:Cys29	R	Rpb9 Zn-ribbon Cys	[116]
19	I:Cys32	R	Rpb9 Zn-ribbon Cys	[116]
20	B:Ile343	NC	No functional or structural evidence to date	—
21	B:Asp106	NC	No mutational or structural evidence	—
22	E:Gly189	Ind	Rpb5–Mediator contact; deletion 186–203 impairs binding	[117]
23	B:Gly897	Ind	G897D slows growth; β -flap shoulder	[118]
24	G:His158	Ind	Rpb7 H158A causes heat-sensitive transcription	[119]
25	A:Gly807	Ind	Switch-1 hinge; limits clamp motion	[113]

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Rank	Chain:Residue	Class	Evidence summary	Key refs
26	A:Leu391	Ind	Switch-2 torsion hotspot (MD study)	[120]
27	B:Gly207	NC	No experimental data available	—
28	G:Gly59	Ind	Rpb7 Δ 59 heat-sensitive phenotype	[119]
29	A:Gly1065	Ind	CTD truncation beyond repeat 13 reduces Ser2-P	[121]
30	A:Leu470	Ind	Switch-2 adjacent; stabilises clamp	[113]
31	A:Glu1121	Ind	α -Amanitin pocket rim; Q \rightarrow L increases drug resistance	[122]
32	A:Gly342	Ind	Jaw hinge; open \longleftrightarrow closed HDX shift 25 %	[123]
33	C:Gly68	NC	No functional evidence	—
34	A:Gly916	Ind	CTD scaffold; Ser2-P reduced when deleted	[121]
35	A:Gly1340	Ind	CTD repeat 1; controls phosphorylation	[121]
36	A:Gly1413	Ind	CTD repeat 2; Ser2-P reduced	[121]
37	C:Gln224	Ind	Activator hot-spot cluster proximity	[124]
38	A:Asp188	Ind	D188A destabilises DNA jaw	[125]
39	B:Asn121	NC	No experimental evidence	—
40	A:Asp177	Ind	D177A impairs jaw clamping	[125]

Table 10: RNA Polymerase II hit rate:35/40 (PDB 5C4X)rank 40 reactive?—
R = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	A:Cys67	R	Zn-ribbon Cys ₄ ligand; Cys \rightarrow Ser mis-folds Rpb1	[126]
2	J:Cys10	R	Rpb2 Zn-ribbon Cys ₄ ; mutation disrupts RNA exit	[112]
3	A:His80	R	Zn-ribbon His ligand; His \rightarrow Ala lowers elongation velocity	[127]
4	J:Cys72	R	Zn-ribbon Cys; part of Cys ₄ tetrahedron	[112]
5	B:Cys1166	R	Rpb2 C-terminal Zn-binding finger	[112]
6	L:Ser36	R	Rpb11 Zn-loop Ser interacts with Zn ²⁺	[124]
7	B:Cys1182	R	Same Zn finger cluster as rank 5	[112]
8	C:Cys86	R	Rpb3 Zn-finger 1 ligand	[115]
9	C:Cys92	R	Rpb3 Zn-finger 1 ligand	[115]
10	C:Cys95	R	Rpb3 Zn-finger 1 ligand	[115]
11	C:Cys88	R	Rpb3 Zn-finger 1 ligand	[115]
12	A:Cys110	R	Rpb1 Zn-ribbon Cys; folding essential	[126]
13	B:Cys1185	R	Same Zn finger cluster as rank 5	[112]
14	I:Cys75	R	Rpb9 Zn-ribbon Cys; start-site control	[116]

Continued on next page

Rank	Chain:Residue	Class	Evidence summary	Key refs
15	I:Cys106	R	Rpb9 Zn-ribbon Cys; start-site control	[116]
16	I:Cys10	R	Rpb9 Zn-ribbon Cys; start-site control	[116]
17	I:Cys29	R	Rpb9 Zn-ribbon Cys; start-site control	[116]
18	I:Cys32	R	Rpb9 Zn-ribbon Cys; start-site control	[116]
19	I:Cys78	R	Rpb9 Zn-ribbon Cys; start-site control	[116]
20	L:Thr43	NC	Rpb11 N-loop; no phenotype reported	—
21	B:Glu923	Ind	E923A 6-AU sensitive; affects elongation	[112]
22	B:Gly867	R	Gly867S lowers elongation velocity (back-tracking)	[112]
23	E:Gly189	NC	β -turn; no data	—
24	C:Ala159	R	A159G + C92R double mutant: 100 \times activator defect	[124]
25	A:Gly1437	Ind	CTD truncation beyond repeat 14 abolishes Ser2-P	[121]
26	B:Glu922	Ind	E922K 6-AU sensitive; read-through \uparrow	[112]
27	K:Gly43	R	Rpb9 G43D alters start-site selection	[116]
28	B:Gly897	Ind	G897D growth delay; β -flap shoulder	[112, 118]
29	A:Gln1188	Ind	Q1188L increases α -amanitin resistance	[122]
30	B:Ile502	NC	Protrusion helix; no functional data	—
31	G:Gly59	Ind	Rpb7 Δ 59 heat-sensitive transcription	[119]
32	A:Ile61	NC	Rpb1 jaw loop; no data	—
33	B:Gly1039	Ind	G1039R pauses \uparrow ; λ -N contact	[128]
34	B:His1025	Ind	H1025A increases back-tracking	[128]
35	A:Gly604	Ind	G604D limits clamp closing	[113]
36	C:Gly162	Ind	Activation hot-spot cluster 159–162	[124]
37	A:Gly1413	Ind	CTD repeat-2; Ser2-P reduced when deleted	[121]
38	B:Gly1167	Ind	G1167E increases pausing (MD)	[129]
39	A:Asp157	Ind	D157A destabilises DNA jaw	[125]
40	E:Gly206	NC	Rpb5 N-loop-2; no phenotype	—

Table 11: iC3b–CR3 α I-domain complex hit rate:25/30 (PDB 7AKK)rank 30 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	A:Asp1144	R	2.8 Å acid–base pair with CR3 MIDAS; visible in 2.2 Å complex crystal	[130]
2	D:Ser144	R	MIDAS-adjacent Ser; Ser \rightarrow Ala abolishes iC3b binding	[131]

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Rank	Chain:Residue	Class	Evidence summary	Key refs
3	H:Ser142	R	Symmetric copy of Rank 2 Ser motif	[131]
4	D:Thr209	Ind	β D- α 5 loop anchor that stabilises MG6 face (structural)	[132]
5	H:Ser144	R	Same as Rank 2 on mirror chain	[131]
6	D:Ser142	R	Part of Asp-Ser-Ser-Ser oxygen cluster essential for binding	[131]
7	A:Gly1355	Ind	Major hinge (ϕ/ψ flip) enabling 40 Å MG8 swing (cryo-EM)	[133]
8	A:Asp708	Ind	Acidic anchor 5 aa upstream of factor I first-cut site	[134]
9	D:His295	Ind	Metal-tuning His; antagonist structure shows coordination shift	[135]
10	E:Glu1494	Ind	C345C apex acidic patch docking CR3/CRIg β -propeller	[136]
11	B:Gly245	Ind	Peptide 235–248 gains ~40% protection in C3→C3b HDX-MS	[137]
12	C:Gly621	Ind	MG3 side hinge (ϕ/ψ flip cluster) in open C3*	[133]
13	A:Cys907	R	C345C disulfide; mutation disrupts folding and secretion	[138]
14	A:Asn911	R	Conserved N-glycan anchoring C345C to MG8; mutation mis-folds	[138]
15	B:Gly106	Ind	MG2–MG3 minor hinge observed in cryo-EM open state	[133]
16	B:Gly383	Ind	MG5 loop pivot in open C3*	[133]
17	H:Gln282	NC	No structural contact, mutagenesis or variant data (May 2025)	—
18	C:Asp373	R	D373–R1177 salt bridge; pathogenic M373T abolishes activity	[133, 139]
19	C:Gly138	Ind	MG1 hinge (ϕ/ψ flip) in cryo-EM	[133]
20	A:Arg1031	NC	No peer-reviewed evidence; AI saliency ~0.1; variant data absent	—
21	A:Glu874	NC	Surface acidic residue without reported binding/variant data	—
22	E:Ser1403	Ind	Fast-exchange segment in MG8–C345C linker (sub-sec HDX)	[137]
23	A:Gly914	Ind	MG8 rotation hinge in open C3*	[133]
24	A:Asp863	Ind	HDX peptide 830–839 becomes exposed during activation	[137]
25	A:Gly949	Ind	Auxiliary hinge supporting MG8 swing	[133]
26	D:Asn310	NC	Only MD-network prediction; no experimental support	—

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Rank	Chain:Residue	Class	Evidence summary	Key refs
27	B:Arg293	R	R261A/R293A mutant lowers iC3b affinity five-fold	[130]
28	H:Gly207	Ind	α I-domain minor hinge (cryo-EM)	[133]
29	B:Leu409	NC	Elastic-network calculation only; no biochemical data	—
30	B:Gly546	Ind	MG4–MG5 pivot Gly in open C3*	[133]

Table 12: Human arginase $\mathbf{I} \bullet \text{Mn}^{2+}$ -inhibitor complex hit rate:36/40 (PDB 7K4J)rank 40 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	D:Asp234	R	Bridges $\text{Mn}_A\text{--Mn}_B$; D234A abolishes activity	[140, 141]
2	B:Asp234	R	As above (other chain)	[140, 141]
3	E:Asp234	R	As above	[140, 141]
4	A:Asp234	R	As above	[140, 141]
5	A:Asp124	R	D124 \rightarrow A eliminates Mn binding and activity	[140]
6	B:Asp124	R	As above	[140]
7	B:Asp232	R	Second Mn ligand; D232A inactive	[140]
8	D:Asp124	R	As in rank 5	[140]
9	C:Asp124	R	As in rank 5	[140]
10	D:Asp232	R	As in rank 7	[140]
11	F:Asp124	R	As in rank 5	[140]
12	C:Asp234	R	As in rank 1	[140, 141]
13	F:Asp234	R	As in rank 1	[140, 141]
14	E:Asp232	R	As in rank 7	[140]
15	E:Asp124	R	As in rank 5	[140]
16	F:Asp232	R	As in rank 7	[140]
17	D:Asp128	R	Proton-shuttle; D128G pathogenic, zero activity	[142]
18	A:Asp128	R	As above	[142]
19	E:Asp128	R	As above	[142]
20	F:Asp128	R	As above	[142]
21	C:Asp128	R	As above	[142]
22	B:Asp128	R	As above	[142]
23	F:His126	R	Mn ligand; H126A inactive	[140]
24	A:His126	R	As above	[140]
25	C:His126	R	As above	[140]
26	D:His126	R	As above	[140]
27	E:His126	R	As above	[140]

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Rank	Chain:Residue	Class	Evidence summary	Key refs
28	B:His101	R	Mn ligand; H101A eliminates activity	[140]
29	B:His126	R	See rank 23	[140]
30	A:Asp232	R	Mn ligand; see rank 7	[140]
31	C:His101	R	As in rank 28	[140]
32	A:His101	R	As in rank 28	[140]
33	C:Asp232	R	As in rank 7	[140]
34	D:His101	R	As in rank 28	[140]
35	E:His101	R	As in rank 28	[140]
36	F:His101	R	As in rank 28	[140]
37	A:Asn69	NC	No published functional data	—
38	B:Gly106	NC	No published functional data	—
39	C:Ile58	NC	No published functional data	—
40	A:Gly106	NC	No published functional data	—

Table 13: T4 lysozyme (WT*) hit rate:10/10 (PDB 2LZM)rank 10 reactive?—
R = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	A:Gly156	R	G156D temperature-sensitive mutant shows backbone strain and 6 °C loss in T_m .	[143]
2	A:Trp158	R	Helix-capping W158L/Y mutants widen the mouth and lower stability, confirming cap-rules tests.	[144]
3	A:Gly77	R	G77A restricts backbone entropy and raises T_m by ≈ 3 °C; classic stability design.	[145]
4	A:Gly56	Ind	Large-scale amber scan found most substitutions here deleterious, implying buried packing role.	[146]
5	A:Arg125	Ind	gREST MD pinpoints Arg125 side-chain re-orientation during ligand accommodation in L99A cavity.	[147]
6	A:Gly107	Ind	Spin-label EPR + MD show helix F/G breathing at Gly107 gates transient cavity opening.	[148]
7	A:Lys124	R	L124G demonstrates left handed α_L conformer is dispensable for fold and activity.	[149]
8	A:Phe4	Ind	μ s-MD reveals Phe4 “hydrophobic-lock” that initiates global hinge-bending allostery.	[150]
9	A:Ala134	Ind	Helix G scan: A134R1 immobilisation reports tight tertiary contact (spin-label EPR/crystal).	[151]

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Rank	Chain:Residue	Class	Evidence summary	Key refs
10	A:Gln122	Ind	GaMD ligand-binding pathway captures benzene intermediate contacting Gln122 side chain.	[152]

Table 14: Tumour-suppressor p53 core domain hit rate:10/10 (PDB 2OCJ)rank 10 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	C:HIS179	R	Zn ²⁺ ligand; H179Y abolishes folding & DNA binding	[153, 154]
2	A:HIS179	R	as above (symmetry copy)	[153, 154]
3	B:HIS179	R	as above (symmetry copy)	[153, 154]
4	D:HIS179	R	as above (symmetry copy)	[153, 154]
5	A:CYS238	R	Zn ²⁺ ligand; C238S eliminates DNA affinity	[155, 153]
6	B:CYS176	R	Zn ²⁺ ligand; C176F destabilises core fold	[156, 157]
7	B:CYS242	R	Zn ²⁺ ligand; C242S lowers thermal stability	[155, 153]
8	A:CYS176	R	as row 6 (symmetry copy)	[156, 157]
9	B:CYS238	R	as row 5 (symmetry copy)	[155, 153]
10	D:CYS238	R	as row 5 (symmetry copy)	[155, 153]

Table 15: T4 Lysozyme hit rate:10/10 (PDB 3FA0)rank 10 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	A:Gly156	R	<i>G156D</i> lowers T_m by ~ 6 °C; core packing disrupted	[143]
2	A:Trp158	Ind	Buried Trp; high-pressure fluorescence probe of micro-environment	[158]
3	A:Gly12	Ind	Residues 11–14 form the principal N/C-domain hinge axis	[159]
4	A:Gly56	Ind	Helix B–C pivot in MD/ENM collective-motion analyses	[159]
5	A:Trp138	Ind	Spectral shifts upon Q105 mutants reveal local dynamics sensor	[160]
6	A:Lys124	R	Engineered surface salt bridge (Q123E–K124); $\Delta\Delta G \sim 0.2$ kcal mol ^{−1}	[161]

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Rank	Chain:Residue	Class	Evidence summary	Key refs
7	A:Tyr18	R	Y18H/D second-site mutants remodel substrate cleft; activity rescue	[162]
8	A:Leu39	R	Backbone ester (Lac) substitution destabilises α -helix by ~ 0.9 kcal mol ⁻¹	[163]
9	A:His31	R	Buried His31–Asp70 salt bridge stabilises fold by 3–5 kcal mol ⁻¹	[164]
10	A:Gln122	R	S90H/Q122D double mutant tests semi-buried His–Asp pair	[161]

Table 16: 14-3-3 σ hit rate:10/10 (PDB 6Y58)rank 10 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	A:Glu35	Ind	Contacts acetate/sulfate (≤ 3.5 Å) in 6Y58; no functional effect reported	[165]
2	A:Ile168	R	+4 hydrophobic pocket wall; direct contacts in multiple peptide/glue complexes	[166]
3	A:His106	R	Mg ²⁺ -bridged hydrogen bond to phosphopeptides (e.g., 3SMK)	[166]
4	A:Ile65	R	Dimer core hinge; I65→A mutation disrupts dimerization	[167, 168]
5	A:Lys87	R	Asp21–Lys87 salt bridge; K87→A lowers signalling efficiency	[169]
6	A:Leu131	Ind	Phosphate-clamp rim; direct contact in Cotylenin A complex (4IHL)	[170]
7	A:Ala147	Ind	Loop 143–149 pivot; ≤ 4 Å peptide approach in 7OBS	[171, 165]
8	A:Leu12	R	N-terminal clasp hinge; L12→Q monomerises the protein	[167, 168]
9	A:Gln221	R	NV1/NV2 secondary pocket; CLR01/fragment direct binding	[172, 173]
10	A:Lys27	Ind	N-terminal loop ≤ 4 Å from phosphopeptide in 6Y40, 6Y3V	[165, 173]

Table 17: CFTR (human) – cryo-EM active dimer hit rate:10/10 (PDB 6MSM)rank 10 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	A:Ser1251	R	Class-III gating mutant S1251N; ivacaftor restores P_o	[174, 175]
2	A:Gln493	R	Q-loop coupler; nonsense variant Q493Ter pathogenic	[176, 177]
3	A:Thr465	R	Walker-A Thr; VX-809-bound open-state structure confirms H-bond network	[178]
4	A:Gly144	Ind	TM2 pivot: MD shows residues 140–148 swivel during gate opening	[179, 180]
5	A:Gly970	R	G970R gating and cryptic-splicing defect; TM8 hinge in MD	[177, 181]
6	A:His954	R	Fe^{3+} bridge C832/D836–H954 locks pore (electrophysiology)	[182]
7	A:Gly1249	Ind	Rare pathogenic G1249R; ETI (Trikafta) rescue in nasal organoids	[183]
8	A:Gln30	Ind	Part of N-terminal RXR trafficking motif; removal improves surface expression	[184]
9	A:Gly1130	Ind	Pore-lining TM12 hinge; G1130A CBAVD variant	[177]
10	A:Gly91	R	G91R folding/ER-exit defect; thiol accessibility mapping	[185]

Table 18: Green fluorescent protein hit rate:10/10 (PDB 1EMA)rank 10 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	A:Gly104	Dyn	Deletion or mis-alignment abolishes fluorescence; nucleates β -barrel folding	[186]
2	A:Gly40	Dyn	Superfolder GFP: G40 substitutions slow high-temperature folding	[187]
3	A:Gly160	Dyn	G160V/L mutants delay chromophore maturation rate	[187]
4	A:Gly4	Dyn	N-cap variants retard chromophore formation and folding	[188]

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Rank	Chain:Residue	Class	Evidence summary	Key refs
5	A:Phe130	Opt	F130A/G mutants non-fluorescent; π -stack locks longest loop	[189]
6	A:Gly134	Dyn	Internal-deletion study: G134 indispensable for correct folding	[190]
7	A:Phe71	Opt	F71L causes blue-shift; π -network stabilises chromophore pocket	[191]
8	A:His139	Bind	His139 deletion kills fluorescence; Zn^{2+} ligand in engineered 4KW8	[192, 193]
9	A:Phe83	Opt	Δ 83-88 deletion eliminates fluorescence; hydration-barrier π -stack	[191]
10	A:Asp129	Bind	roGFP variants: D129 modulates redox-sensor oxidation kinetics	[194, 195]

Table 19: SpCas9–sgRNA–DNA ternary complex hit rate:9/10 (PDB 5F9R)rank 10 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	B:ASN609	NC	Predicted REC2–REC3 hinge loop (603–612); listed in high-fidelity Cas9 patent variants; no peer-reviewed data yet	–
2	B:HIS1297	R	π -stack with tDNA backbone; H1297A lowers cleavage efficiency	[196]
3	B:GLY907	Ind	Flexible L2 hinge; NMR + μ s-MD allosteric pathway	[197]
4	B:SER1351	R	H-bond to sgRNA stem-loop 2 stabilises RNP	[198]
5	B:ILE1057	Ind	RuvC-III loop gating non-target DNA egress	[196]
6	B:ASP603	Ind	REC3 dynamic hub modulating specificity (network analysis)	[199]
7	B:GLU1056	Ind	ABE8e cryo-EM shows TadA8e contact enhancing editing	[200]
8	B:PHE1174	Ind	PI β -hairpin π -stacking stabilises PAM duplex (structural)	[201]
9	B:TRP1074	Ind	RuvC-III loop “backbone pin” observed in mismatch structures	[196]
10	B:ASN854	R	N854A nickase boosts prime-editing purity	[202]

Table 20: TEM-1 β -lactamase hit rate:7/10 (PDB 1BTL)rank 10 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	A:GLY251	R	Ω -loop allosteric hotspot; G251W/R lowers k_{cat} and reshapes μs dynamics	[203]
2	A:HIS112	R	BLIP inhibitor-binding loop; H112A shifts $k_{\text{on}}/k_{\text{off}}$	[204]
3	A:GLN90	NC	All single substitutions neutral in 10k DMS map	[205]
4	A:GLY238	R	Catalytic Ω -loop residue; G238S expands ESBL spectrum	[206]
5	A:GLY144	Ind	Highly conserved contact; hydrogen-bonds to β -lactam carbonyl	[207]
6	A:LEU225	R	Global hinge-shift; L225M tilts open/closed equilibrium	[208]
7	A:GLY54	NC	Loop-insertion tolerant; activity unchanged	[209]
8	A:HIS153	R	Global suppressor; H153R rescues destabilising active-site mutants	[210]
9	A:HIS96	Ind	Binds cryptic allosteric inhibitor in 1PZP structure	[211]
10	A:GLU28	NC	Surface residue; substitutions fully neutral	[205]

Table 21: Hsp90-p23 complex hit rate:10/10 (PDB 2CG9)rank 10 reactive?— **R** = direct experiment, **Ind** = indirect/structural, **NC** = no current evidence.

Rank	Chain:Residue	Class	Evidence summary	Key refs
1	B:GLY428	Ind	CTD hinge; closed-state clamp interface	[212]
2	A:GLY428	Ind	Same as B-chain; hinge in CTD dimer	[212]
3	A:ASN271	Ind	Charged-linker tip bridging N/MD; NMR shows transient contacts	[213]
4	B:GLY81	Ind	NTD lid hinge enabling ATP-driven closure	[214]
5	B:LEU571	Ind	CTD helix-2 core of coumarin allosteric pocket & co-chaperone interface	[215]
6	A:GLY81	Ind	Lid hinge (chain A) identical to B	[214]
7	B:ASN271	Ind	Charged-linker hinge (chain B)	[213]
8	B:TYR24	R	Y24 phosphorylation by Swe1/Wee1 modulates ATPase and clientele	[216]
9	B:PHE329	Ind	Client-binding loop; F329 mutations disrupt activation	[217]

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Rank	Chain:Residue	Class	Evidence summary	Key refs
10	Y:ASP36	Ind	p23 acidic anchor forming salt-bridge with Hsp90 NTD	[212]

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