

Supplementary Table S I Model evaluation criteria's used and their corresponding values. (Following proteins had their crystal structures solved and deposited in PDB : InhA, KatG, AhpC, PncA, EmbR, ManB, EthA, FabD)

Sequence ID /Gene Name	Model Template (PDB-ID)	Sequence Identity with Template (%)	Model coverage	Model Sequence Length	Model Sequence Segment	CE ZScore	LG Score	Max Subscore	Errat Overall Quality factor	Function Annotation
Rv0667/rpoB	1YNJ (C)	51	94.31	1110	4 - 1114	8.6	3.380	0.299	56.222%	beta and beta-prime subunits of DNA dependent RNA-polymerase
Rv0682/rpsL	1FJG (L)	74	97.58	120	5 - 126	6.6	1.185	0.160	55.660%	Nucleic acid-binding proteins
Rv1694/tlyA	1UFK (A)	22	34.7	92	125 - 217	1.6	1.391	0.133	90.698%	S-adenosyl-L-methionine-dependent methyltransferases
Rv2764c/ thyA	2G8M (A)	66	99.24	261	2 - 264	7.7	5.932	0.603	83.399%	-
Rv3264c/manB	1HV9 (A)	26	96.1	344	6 - 341	7.4	3.394	0.272	48.521%	TrimericLpxA-like enzymes
Rv3266c/rmlD	1VL0 (A)	37	93.75	285	0 - 279	6.9	5.322	0.443	88.849%	NAD(P)-binding Rossmann-fold domains
Rv3854c/ethA	1W4X(A)	23	96.93	473	15 - 531	7.5	3.940	0.364	39.400%	FAD/NAD(P)-binding domain
Rv3919c/gidB	1JSX (A)	38	55.36	124	52 - 173	1.2	2.873	0.341	57.265%	S-adenosyl-L-methionine-dependent methyltransferases

Supplementary Table S II Drug resistant mutants of different targets in *M. tuberculosis* H37Rv. For each drug, its known target(s), number of mutations observed in drug resistant strains, number of mutations in the binding site and number of mutations in outer zones are shown.

Drug	Target	Name of the target	No. Mutants	Zone 1	Zone 2	Zone 3+
Amikacin	Rv1694	tlyA (cytotoxin/haemolysin homologue)	8		1	3
Aminosalicylic Acid	Rv2764c	thyA (Probable thymidylate synthase)	2		1	
Ciprofloxacin	Rv0005	gyrB (DNA gyrase subunit B)	5			
Ciprofloxacin	Rv0006	gyrA (DNA gyrase subunit A)	15			
Ethambutol	Rv0341	iniB (isoniazid-inducible gene B)	1			
Ethambutol	Rv0342	iniA (isoniazid-inducible gene A)	2			
Ethambutol	Rv0343	iniC (isoniazid-inducible gene C)	1			
Ethambutol	Rv1267c	embR (Probable embR, regulatory protein)	1			
Ethambutol	Rv3124	Rv3124 (Probable transcriptional regulatory protein)	-			
Ethambutol	Rv3264c	manB (D-alpha-D-mannose-1-phosphate guanylyltransferase)	1			
Ethambutol	Rv3266c	rmlD (dTDP-6-deoxy-L-lyxo-4-hexulose reductase)	2	2		1
Ethambutol	Rv3793	embC (indolylacetylinositol arabinosyltransferase)				
Ethambutol	Rv3794	embA (indolylacetylinositol arabinosyltransferase)	3			
Ethambutol	Rv3795	embB (indolylacetylinositol arabinosyltransferase)	54			
Ethionamide	Rv1484	inhA (NADH-dependent enoyl-[acyl-carrier-protein] reductase)	2	2		
Ethionamide	Rv3854c	ethA (monooxygenase required for activation of the pro-drug ethionamide)	14	3	5	6
Isoniazid	Rv0129c	fbpC (secreted antigen 85c (fibronectin-binding protein C))	1			
Isoniazid	Rv0340	Rv0340 (Conserved hypothetical protein)	1			
Isoniazid	Rv0341	iniB (isoniazid-inducible gene B)	1			
Isoniazid	Rv0342	iniA (isoniazid-inducible gene A)	2			
Isoniazid	Rv0343	iniC (isoniazid-inducible gene C)	1			
Isoniazid	Rv1483	fabG1/mabA (3-oxoacyl-[acyl-carrier protein] reductase)	1	1		
Isoniazid	Rv1484	inhA (NADH-dependent enoyl-[acyl-carrier-protein] reductase)	10	8	2	
Isoniazid	Rv1592c	Rv1592c (Conserved hypothetical protein)	2			
Isoniazid	Rv1772	Rv1772 (Conserved hypothetical protein)	1			
Isoniazid	Rv1854c	ndh (Probable ndh, NADH dehydrogenase)	5			
Isoniazid	Rv1908c	katG (catalase-peroxidase-peroxynitritase T)	191	7	21	52

Isoniazid	Rv1909c	furA (Ferric uptake regulation protein)	1			
Isoniazid	Rv2243	fabD (malonyl CoA-acyl carrier protein transacylase)	1			
Isoniazid	Rv2245	kasA (beta-ketoacyl-ACP synthase)	7			3
Isoniazid	Rv2247	accD6 (Acetyl/Propionyl CoA Carboxylase)	1			
Isoniazid	Rv2428	ahpC (alkyl hydroperoxide reductase C)	8		2	2
Isoniazid	Rv2846c	efpA (integral membrane efflux protein)	1			
Isoniazid	Rv3139	fadE24 (fatty-acid-CoA synthetase)	1			
Isoniazid	Rv3566c	nat (arylamine N-acetyltransferase)	2			
Isoniazid	Rv3795	embB (indolylacetylinositol arabinosyltransferase)	1			
Kanamycin	Rv1694	tlyA (cytotoxin/haemolysin homologue)	8		1	3
Norfloxacin	Rv0005	gyrB (DNA gyrase subunit B)	5			
Norfloxacin	Rv0006	gyrA	15			
Ofloxacin	Rv0005	gyrB (DNA gyrase subunit B)	5			
Ofloxacin	Rv0006	gyrA (DNA gyrase subunit A)	15			
Pyrazinamide	Rv2043c	pncA (pyrazinamidase/nicotinamidase)	180	16	88	76
Rifampin	Rv0667	rpoB (DNA-directed RNA polymerase, beta chain)	88	1		
Rifampin	Rv2629	Rv2629 (Conserved hypothetical protein)	-			
Rifampin	Rv3795	embB (indolylacetylinositol arabinosyltransferase)	2			
Streptomycin	Rv0682	rpsL (30S ribosomal protein S12)	16	2	12	2
Streptomycin	Rv3919c	gidB (Probable glucose-inhibited division protein B)	15	1	1	2

Supplementary Table S III
Table describing the inferences drawn from individual parameters, explaining the resistant mutation.

✓ - Explained

✗ - Not Explained

<i>Gene Name</i>	<i>Mutant</i>	<i>ACM</i>	<i>DBA</i>	<i>CI</i>	<i>RMSD</i>	<i>SASA</i>	<i>DDG</i>	<i>Zone1</i>	<i>IMI</i>
rpoB	V138F	✗	✗	✓	✓	✓	✓	✗	2.46
rpoB	A254V	✗	✗	✓	✓	✓	✓	✓	0
rpoB	Q377H	✗	✗	✓	✗	✗	✓	✗	0
rpoB	E391A	✗	✗	✓	✓	✓	✓	✗	0
rpoB	F392L	✗	✗	✓	✓	✓	✓	✗	2.19
rpoB	G394D	✗	✗	✓	✓	✓	✓	✗	.87
rpoB	T395S	✗	✗	✓	✓	✓	✓	✗	0
rpoB	S396T	✗	✗	✓	✓	✓	✓	✗	2.40
rpoB	S396R	✗	✗	✓	✓	✓	✓	✗	2.40
rpoB	Q397H	✗	✗	✓	✓	✓	✓	✗	0
rpoB	L398V	✗	✗	✓	✓	✓	✓	✗	2.22
rpoB	L398P	✗	✗	✓	✓	✓	✓	✗	2.22
rpoB	L398R	✗	✗	✓	✓	✓	✓	✗	2.22
rpoB	S399T	✗	✗	✓	✓	✓	✓	✗	2.55
rpoB	S399I	✗	✗	✓	✓	✓	✓	✗	2.55
rpoB	S399R	✗	✗	✓	✓	✓	✓	✗	2.55
rpoB	S399G	✗	✗	✓	✓	✓	✓	✗	2.55
rpoB	Q400K	✗	✗	✓	✓	✓	✓	✗	0
rpoB	Q400L	✗	✗	✓	✓	✓	✓	✗	0
rpoB	Q400P	✗	✗	✓	✓	✓	✓	✗	0
rpoB	Q400H	✗	✗	✓	✓	✓	✓	✗	0
rpoB	Q400R	✗	✗	✓	✓	✓	✓	✗	0
rpoB	F401V	✗	✗	✓	✓	✓	✓	✗	0
rpoB	F401L	✗	✗	✓	✓	✓	✓	✗	0
rpoB	M402V	✗	✗	✓	✓	✓	✓	✗	2.16
rpoB	M402I	✗	✗	✓	✓	✓	✓	✗	2.16
rpoB	D403F	✗	✗	✓	✓	✓	✓	✗	.75
rpoB	D403N	✗	✗	✓	✓	✓	✓	✗	.75
rpoB	D403Y	✗	✗	✓	✓	✓	✓	✗	.75
rpoB	D403E	✗	✓	✓	✓	✓	✓	✗	1.00

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rpoB	D403V	✗	✗	✓	✓	✓	✓	✗	.75
rpoB	D403A	✗	✗	✓	✓	✓	✓	✗	.75
rpoB	D403G	✗	✗	✓	✓	✓	✓	✗	.75
rpoB	Q404L	✗	✗	✓	✓	✓	✓	✗	1.62
rpoB	N405T	✗	✗	✓	✓	✓	✓	✗	2.79
rpoB	N405H	✗	✗	✓	✓	✓	✓	✗	2.79
rpoB	N405D	✗	✗	✓	✓	✓	✓	✗	2.79
rpoB	N405I	✗	✗	✓	✓	✓	✓	✗	2.79
rpoB	L408M	✗	✗	✓	✓	✓	✓	✗	2.79
rpoB	L408P	✗	✗	✓	✓	✓	✓	✗	1.86
rpoB	S409Q	✗	✗	✓	✓	✓	✓	✗	3.00
rpoB	S409L	✗	✗	✓	✓	✓	✓	✗	3.00
rpoB	S409W	✗	✗	✓	✓	✓	✓	✗	3.00
rpoB	G410W	✗	✗	✓	✓	✓	✓	✗	2.67
rpoB	L411W	✗	✗	✓	✓	✓	✓	✗	2.85
rpoB	T412P	✗	✗	✓	✓	✓	✓	✗	1.92
rpoB	T412I	✗	✗	✓	✓	✓	✓	✗	2.88
rpoB	H413T	✗	✗	✓	✓	✓	✓	✗	1.83
rpoB	H413N	✗	✗	✓	✓	✓	✓	✗	1.83
rpoB	H413Y	✗	✗	✓	✓	✓	✓	✗	1.83
rpoB	H413E	✗	✗	✓	✓	✓	✓	✗	1.83
rpoB	H413Q	✗	✗	✓	✓	✓	✓	✗	1.83
rpoB	H413C	✗	✗	✓	✓	✓	✓	✗	1.83
rpoB	H413L	✗	✗	✓	✓	✓	✓	✗	1.83
rpoB	H413P	✗	✗	✓	✓	✓	✓	✗	1.83
rpoB	H413D	✗	✗	✓	✓	✓	✓	✗	1.83
rpoB	H413R	✗	✗	✓	✓	✓	✓	✗	1.83
rpoB	H413G	✗	✗	✓	✓	✓	✓	✗	1.22
rpoB	K414N	✗	✗	✓	✓	✓	✓	✗	2.61
rpoB	K414Q	✗	✗	✓	✓	✓	✓	✗	2.61

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rpoB	R415P	×	>	>	>	>	>	×	1.74
rpoB	R415H	×	>	>	>	>	>	×	2.61
rpoB	S418F	×	>	>	>	>	>	×	1.98
rpoB	S418Y	×	>	>	>	>	>	×	1.98
rpoB	S418Q	×	>	>	>	>	>	×	1.98
rpoB	S418C	×	>	>	>	>	>	×	1.98
rpoB	S418L	×	>	>	>	>	>	×	1.98
rpoB	S418W	×	>	>	>	>	>	×	1.98
rpoB	L420P	×	>	>	>	>	>	×	.99
rpoB	P422S	×	>	>	>	>	>	×	.51
rpoB	E428G	×	>	>	>	>	>	×	0
rpoB	S440A	×	>	>	>	>	>	×	2.19
rpoB	I448T	×	>	>	>	>	>	×	2.28
rpoB	I448V	×	>	>	>	>	>	×	2.28
rpoB	L458V	×	>	>	>	>	>	×	2.70
rpoB	I459F	×	>	>	>	>	>	×	.66
rpoB	S461L	×	>	>	>	>	>	×	2.88
rpoB	R520C	×	>	>	>	>	>	×	0
pncA	M1T	×	>	>	>	>	>	×	0
pncA	M1I	×	>	>	>	>	>	×	0
pncA	A3E	×	>	>	>	>	>	×	1.54
pncA	A3P	×	>	>	>	>	>	×	1.54
pncA	L4S	×	>	>	>	>	>	×	1.48
pncA	L4W	×	>	>	>	>	>	×	2.22
pncA	I5S	×	>	>	>	>	>	×	.42
pncA	V7F	×	>	>	>	>	>	×	1.26
pncA	V7D	×	>	>	>	>	>	×	.78
pncA	V7I	×	>	>	>	>	>	×	1.95
pncA	V7G	×	>	>	>	>	>	×	.78
pncA	D8Y	×	>	>	>	>	>	✓	2.73

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pncA	D8E	✗	✓	✓	✓	✓	✓	✓	2.73
pncA	D8G	✗	✓	✓	✓	✓	✓	✓	2.73
pncA	V9S	✗	✓	✓	✓	✓	✗	✗	1.24
pncA	V9L	✗	✓	✓	✓	✓	✓	✗	2.28
pncA	V9A	✗	✓	✓	✓	✓	✗	✗	1.24
pncA	V9G	✗	✓	✓	✓	✓	✗	✗	1.24
pncA	Q10K	✗	✓	✓	✓	✓	✓	✗	2.61
pncA	Q10P	✗	✓	✓	✓	✓	✓	✗	2.61
pncA	Q10R	✗	✓	✓	✓	✓	✓	✗	2.61
pncA	D12N	✗	✓	✓	✓	✓	✓	✗	1.92
pncA	D12A	✗	✗	✗	✗	✗	✗	✗	1.92
pncA	F13S	✗	✗	✗	✗	✗	✓	✓	1.26
pncA	C14Y	✗	✓	✗	✗	✓	✓	✗	3.92
pncA	C14H	✗	✓	✗	✗	✓	✓	✗	2.94
pncA	C14R	✗	✓	✗	✗	✓	✓	✗	3.92
pncA	G17V	✗	✓	✓	✓	✓	✓	✗	1.41
pncA	G17D	✗	✓	✓	✓	✓	✓	✗	1.41
pncA	L19P	✗	✓	✓	✓	✓	✓	✓	1.17
pncA	L19R	✗	✓	✓	✓	✓	✓	✓	2.32
pncA	V21G	✗	✓	✓	✓	✓	✓	✓	1.62
pncA	G23V	✗	✓	✓	✓	✓	✓	✗	.46
pncA	A25E	✗	✓	✓	✓	✓	✓	✗	1.20
pncA	A26G	✗	✓	✓	✓	✓	✓	✗	0
pncA	A28D	✗	✓	✓	✓	✓	✓	✓	3.00
pncA	Y34S	✗	✓	✓	✓	✓	✓	✗	.52
pncA	L35R	✗	✓	✓	✓	✓	✓	✗	1.36
pncA	Y41H	✗	✓	✓	✓	✓	✓	✗	1.53
pncA	H43P	✗	✓	✓	✓	✓	✓	✗	.54
pncA	V45G	✗	✓	✓	✓	✓	✓	✗	2.00
pncA	A46E	✗	✓	✓	✓	✓	✓	✗	2.00

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pncA	A46V		x	v	v	v	v	v	x	3.00
pncA	A46P		x	v	v	v	v	x	x	2.00
pncA	T47S		x	v	v	v	v	x	x	2.61
pncA	T47A		x	v	v	v	v	x	x	1.74
pncA	T47P		x	v	v	v	v	x	x	1.74
pncA	D49V		x	v	v	v	v	v	v	3.52
pncA	D49A		x	v	v	v	v	v	v	2.07
pncA	D49H		x	v	v	v	v	v	v	2.64
pncA	D49G		x	v	v	v	v	v	v	1.50
pncA	H51N		x	v	v	v	v	v	v	3.48
pncA	H51Y		x	v	v	v	v	v	v	2.61
pncA	H51Q		x	v	v	v	v	v	v	2.61
pncA	H51P		x	v	v	v	v	x	x	2.61
pncA	H51R		x	v	v	v	v	x	x	2.61
pncA	D53N		x	v	v	v	v	x	x	0
pncA	D53A		x	v	v	v	v	x	x	0
pncA	P54T		x	v	v	v	v	x	x	2.55
pncA	P54L		x	v	v	v	v	x	x	2.55
pncA	H57Y		x	v	v	v	v	v	v	2.25
pncA	H57L		x	v	v	v	v	v	v	2.25
pncA	H57P		x	v	v	v	v	v	v	2.25
pncA	H57D		x	v	v	v	v	v	v	2.25
pncA	F58L		x	v	v	v	v	x	x	1.02
pncA	S59P		x	v	v	v	v	x	x	.45
pncA	T61P		x	v	v	v	v	x	x	0
pncA	P62L		x	v	v	v	v	x	x	.96
pncA	P62H		x	v	v	v	v	x	x	.96
pncA	P62R		x	v	v	v	v	x	x	.96
pncA	D63H		x	v	v	v	v	x	x	0
pncA	D63G		x	v	v	v	v	x	x	0

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pncA	Y64D	✓	✗	✓	✗	✗	✓	✗	0
pncA	S66P	✓	✗	✓	✗	✓	✓	✗	0
pncA	S67P	✗	✗	✓	✓	✗	✓	✗	1.36
pncA	W68S	✗	✗	✓	✓	✗	✓	✓	1.14
pncA	W68L	✗	✗	✓	✓	✓	✓	✓	1.52
pncA	W68R	✗	✗	✓	✓	✓	✓	✓	1.52
pncA	W68G	✗	✗	✓	✓	✓	✓	✓	1.14
pncA	P69L	✗	✗	✓	✓	✓	✓	✗	1.50
pncA	P69R	✗	✗	✓	✓	✓	✓	✗	1.50
pncA	H71Y	✗	✗	✓	✓	✓	✓	✓	2.70
pncA	H71E	✗	✗	✓	✓	✓	✓	✓	3.60
pncA	H71D	✗	✗	✓	✓	✓	✓	✓	1.80
pncA	H71R	✗	✗	✓	✓	✓	✓	✓	3.60
pncA	C72Y	✗	✗	✓	✓	✓	✓	✓	3.00
pncA	C72W	✗	✗	✓	✓	✓	✓	✓	3.00
pncA	C72R	✗	✗	✓	✓	✓	✓	✓	3.00
pncA	G75T	✗	✗	✓	✓	✓	✓	✗	0
pncA	T76P	✗	✗	✓	✓	✗	✗	✗	0
pncA	T76I	✗	✗	✓	✓	✓	✓	✓	0
pncA	G78D	✗	✗	✓	✓	✓	✓	✓	2.37
pncA	A79G	✗	✗	✓	✓	✓	✓	✓	2.64
pncA	D80V	✗	✗	✓	✓	✗	✗	✗	0
pncA	H82Y	✗	✗	✓	✓	✓	✓	✓	1.88
pncA	H82L	✗	✗	✓	✓	✓	✓	✓	1.41
pncA	H82R	✗	✗	✓	✓	✓	✓	✓	1.88
pncA	L85P	✗	✗	✓	✓	✓	✓	✗	1.00
pncA	L85R	✗	✗	✓	✓	✓	✓	✓	2.00
pncA	T87M	✗	✗	✓	✓	✓	✓	✗	0
pncA	I90S	✗	✗	✓	✓	✓	✓	✗	0
pncA	F94P	✗	✗	✓	✓	✓	✓	✗	1.50

<i>Gene Name</i>	<i>Mutant</i>	<i>ACM</i>	<i>DBA</i>	<i>CI</i>	<i>RMSD</i>	<i>SASA</i>	<i>DDG</i>	<i>Zone1</i>	<i>IMI</i>
pncA	K96T	✗	✓	✗	✓	✓	✓	✓	2.52
pncA	K96N	✗	✓	✗	✓	✓	✓	✓	2.52
pncA	K96E	✗	✓	✗	✓	✓	✓	✓	2.52
pncA	K96Q	✗	✓	✗	✓	✓	✗	✓	2.25
pncA	G97S	✗	✓	✗	✓	✓	✗	✓	2.25
pncA	G97D	✗	✓	✗	✓	✓	✗	✓	2.10
pncA	A102T	✗	✓	✗	✓	✓	✓	✓	2.10
pncA	A102V	✗	✓	✗	✓	✓	✓	✓	2.10
pncA	Y103S	✗	✓	✗	✓	✓	✓	0	
pncA	Y103C	✗	✓	✗	✓	✓	✓	0	
pncA	Y103H	✗	✓	✗	✓	✓	✓	0	
pncA	S104R	✗	✓	✓	✓	✓	✓	2.88	
pncA	E107K	✗	✓	✗	✓	✓	✗	0	
pncA	T114P	✗	✓	✗	✓	✓	✗	0	
pncA	L116V	✗	✓	✓	✓	✓	✗	0	
pncA	L116R	✗	✓	✓	✓	✓	✗	0	
pncA	N118T	✗	✓	✗	✓	✓	✗	0	
pncA	W119R	✗	✓	✓	✓	✓	✗	0	
pncA	L120P	✗	✓	✓	✓	✓	✗	0	
pncA	R121P	✗	✓	✗	✓	✓	✗	0	
pncA	V125D	✗	✓	✓	✓	✓	✗	0	
pncA	V128G	✗	✓	✓	✓	✓	✗	0	
pncA	V130G	✗	✓	✓	✓	✓	✗	0	
pncA	G132S	✗	✓	✓	✓	✓	✗	0	
pncA	G132D	✗	✓	✓	✓	✓	✗	0	
pncA	I133T	✗	✓	✓	✓	✓	✓	0	
pncA	I133N	✗	✓	✓	✓	✓	✓	0	
pncA	A134V	✗	✓	✓	✓	✓	✓	0	
pncA	T135P	✗	✓	✓	✓	✓	✓	0	
pncA	D136N	✗	✓	✓	✓	✓	✓	0	

	<i>Gene Name</i>	<i>Mutant</i>	<i>ACM</i>	<i>DBA</i>	<i>CI</i>	<i>RMSD</i>	<i>SASA</i>	<i>DDG</i>	<i>Zone1</i>	<i>IMI</i>
pncA	D136Y	x	>	x	>	>	>	x	x	2.55
pncA	D136H	x	>	x	>	>	>	x	x	2.55
pncA	D136G	x	>	x	>	x	x	x	x	1.46
pncA	H137P	x	>	x	>	x	>	x	x	0
pncA	H137R	x	>	x	>	x	>	x	x	0
pncA	C138S	x	>	x	>	x	>	x	x	2.13
pncA	C138Y	x	>	x	>	x	>	x	x	2.84
pncA	V139M	x	>	x	>	x	>	x	x	3.00
pncA	V139L	x	>	x	>	x	>	x	x	3.00
pncA	V139A	x	>	x	>	x	>	x	x	2.00
pncA	V139G	x	>	x	>	x	>	x	x	2.00
pncA	R140S	>	x	>	>	x	>	x	x	.42
pncA	Q141P	x	>	>	>	>	>	x	x	.12
pncA	T142K	x	>	>	>	>	>	x	x	3.00
pncA	T142M	x	>	>	>	>	>	x	x	3.00
pncA	T142A	x	>	>	>	>	>	x	x	3.00
pncA	T142P	x	>	>	>	>	>	x	x	2.00
pncA	A146T	x	>	>	>	>	>	x	x	2.31
pncA	A146V	x	>	>	>	>	>	x	x	2.58
pncA	R148S	x	>	>	>	>	>	x	x	0
pncA	T153N	x	>	x	>	>	>	x	x	2.19
pncA	R154G	x	>	x	>	>	>	x	x	.33
pncA	V155A	x	>	x	>	x	>	x	x	1.74
pncA	V155G	x	>	x	>	x	>	x	x	1.74
pncA	L159P	x	>	x	>	x	>	x	x	1.20
pncA	L159R	x	>	x	>	x	>	x	x	2.40
pncA	T160P	x	>	x	>	x	>	x	x	1.12
pncA	A161P	x	>	x	>	x	>	x	x	1.28
pncA	G162D	x	>	x	>	x	>	x	x	.78
pncA	T168N	x	>	x	>	x	>	x	x	1.23

<i>Gene Name</i>	<i>Mutant</i>	<i>ACM</i>	<i>DBA</i>	<i>CI</i>	<i>RMSD</i>	<i>SASA</i>	<i>DDG</i>	<i>Zone1</i>	<i>IMI</i>
pncA	A171T	×	✓	✗	✓	✓	✓	✗	2.16
pncA	A171E	✗	✓	✗	✓	✓	✓	✗	2.16
pncA	A171V	✗	✓	✓	✓	✓	✓	✗	2.16
pncA	A171P	✗	✓	✓	✓	✓	✓	✗	2.16
pncA	L172A	✗	✓	✓	✓	✓	✓	✗	.30
pncA	L172P	✗	✓	✓	✓	✓	✓	✗	.20
pncA	M175V	✗	✓	✓	✓	✓	✓	✗	.42
pncA	S179R	✗	✓	✓	✓	✓	✓	✗	0
pncA	V180F	✗	✓	✓	✓	✓	✓	✗	1.54
pncA	E181D	✗	✓	✓	✓	✓	✓	✗	0
pncA	L182S	✗	✓	✓	✓	✓	✓	✗	0
pncA	S185T	✗	✓	✓	✓	✓	✓	✗	0
pncA	S185I	✗	✓	✓	✓	✓	✓	✗	0
rpsL	R8H	✓	✓	✓	✓	✓	✓	✗	0
rpsL	T39I	✗	✓	✓	✓	✓	✓	✗	1.02
rpsL	T40S	✓	✓	✓	✓	✓	✓	✗	0
rpsL	K42T	✗	✓	✓	✓	✓	✓	✗	0
rpsL	K42R	✗	✓	✓	✓	✓	✓	✗	0
rpsL	K50N	✗	✓	✓	✓	✓	✓	✓	0
rpsL	V51G	✗	✓	✓	✓	✓	✓	✓	3.00
rpsL	G83V	✗	✓	✓	✓	✓	✓	✗	1.32
rpsL	R85W	✗	✓	✓	✓	✓	✓	✓	0
rpsL	R85P	✗	✓	✓	✓	✓	✓	✓	0
rpsL	V86L	✗	✓	✓	✓	✓	✓	✓	1.72
rpsL	K87T	✗	✓	✓	✓	✓	✓	✓	0
rpsL	K87Q	✗	✓	✓	✓	✓	✓	✓	0
rpsL	K87M	✗	✓	✓	✓	✓	✓	✓	0
rpsL	K87R	✗	✓	✓	✓	✓	✓	✓	0
rpsL	V92M	✗	✓	✓	✓	✓	✓	✗	3.44
ahpC	L3S	✗	✗					✗	0

<i>Gene Name</i>	<i>Mutant</i>	<i>ACM</i>	<i>DBA</i>	<i>CI</i>	<i>RMSD</i>	<i>SASA</i>	<i>DDG</i>	<i>Zone1</i>	<i>IMI</i>
ahpC	L4K	✗	✗	✗	✓	✓	✓	✗	.02
ahpC	P11I	✗	✗	✗	✓	✓	✓	✗	.62
ahpC	Y34N	✗	✗	✗	✓	✓	✓	✗	.06
ahpC	K70L	✗	✗	✗	✓	✓	✓	✗	0
ethA	G41S	✗	✓	✓	✓	✓	✓	✗	1.74
ethA	G41C	✗	✓	✗	✓	✓	✓	✗	1.74
ethA	P49L	✗	✓	✓	✓	✓	✓	✗	.72
ethA	S53A	✗	✗	✗	✓	✓	✓	✗	1.34
ethA	D56A	✗	✗	✓	✓	✓	✓	✗	.62
ethA	Y82D	✗	✓	✓	✓	✓	✓	✗	1.38
ethA	T184K	✗	✓	✗	✓	✓	✓	✓	.93
ethA	E221K	✗	✗	✓	✓	✓	✓	✗	0
ethA	I336S	✗	✗	✓	✓	✓	✓	✗	0
ethA	T340K	✓	✓	✓	✓	✓	✓	✗	0
ethA	A379P	✗	✗	✓	✓	✓	✓	✗	0
ethA	G383D	✗	✓	✗	✓	✓	✓	✗	1.14
ethA	T390A	✗	✗	✓	✓	✓	✓	✗	1.08
ethA	G411D	✗	✗	✗	✓	✓	✓	✗	0
ethA	R461S	✗	✗	✓	✓	✓	✓	✗	1.24
Rv3264c	D147N	✗	✗	✓	✓	✓	✓	✗	0
katG	N35D	✗	✓	✓	✓	✓	✓	✗	0
katG	L48Q	✗	✓	✓	✓	✓	✓	✗	2.37
katG	A61T	✗	✗	✗	✓	✓	✓	✗	0
katG	D63E	✗	✓	✓	✓	✓	✓	✗	0
katG	A65T	✗	✗	✓	✓	✓	✓	✗	.30
katG	A66P	✗	✗	✓	✓	✓	✓	✗	0
katG	I71N	✗	✗	✗	✓	✓	✓	✗	.18
katG	D72K	✗	✗	✓	✓	✓	✓	✗	0
katG	D72G	✗	✗	✓	✓	✓	✓	✗	0
katG	V73N	✗	✗	✗	✓	✓	✓	✗	2.19

<i>Gene Name</i>	<i>Mutant</i>	<i>ACM</i>	<i>DBA</i>	<i>CI</i>	<i>RMSD</i>	<i>SASA</i>	<i>DDG</i>	<i>Zone1</i>	<i>IMI</i>
katG	D74Y	✗	✓	✓	✗	✗	✓	✗	0
katG	D74G	✗	✓	✓	✗	✓	✓	✗	0
katG	M84I	✗	✓	✓	✓	✓	✓	✓	1.80
katG	T85P	✗	✓	✓	✗	✓	✓	✓	0
katG	Q88R	✗	✓	✓	✗	✗	✗	✗	0
katG	W91R	✓	✓	✓	✓	✓	✓	✓	1.42
katG	D94A	✓	✓	✓	✓	✓	✓	✗	1.47
katG	D94G	✓	✓	✓	✓	✓	✓	✗	1.47
katG	G96C	✗	✓	✓	✓	✓	✓	✗	0
katG	G99E	✗	✓	✓	✓	✓	✓	✗	1.86
katG	R104Q	✓	✗	✓	✓	✓	✓	✗	.36
katG	R104L	✓	✗	✓	✓	✓	✓	✗	.36
katG	A106V	✗	✓	✓	✓	✓	✓	✗	1.32
katG	W107R	✓	✗	✓	✓	✓	✓	✗	.92
katG	H108E	✗	✓	✓	✓	✓	✓	✗	2.31
katG	H108Q	✓	✓	✓	✓	✓	✓	✗	2.31
katG	H108D	✓	✓	✓	✓	✓	✓	✗	2.31
katG	A109V	✗	✓	✓	✓	✓	✓	✗	2.04
katG	A110V	✓	✗	✓	✓	✓	✓	✗	2.79
katG	D117A	✗	✓	✓	✓	✓	✓	✗	2.10
katG	G121V	✗	✓	✓	✓	✓	✓	✗	1.74
katG	G121C	✗	✓	✓	✓	✓	✓	✗	2.61
katG	G125C	✗	✓	✓	✓	✓	✓	✗	2.61
katG	M126I	✗	✓	✓	✓	✓	✓	✓	1.83
katG	Q127P	✗	✓	✓	✓	✓	✓	✗	2.10
katG	R128P	✗	✓	✓	✓	✓	✓	✗	.87
katG	N138S	✗	✓	✓	✓	✓	✓	✗	3.00
katG	N138T	✗	✓	✓	✓	✓	✓	✗	3.00
katG	N138H	✓	✗	✓	✓	✓	✓	✗	4.00
katG	N138D	✗	✗	✓	✓	✓	✓	✗	3.00

<i>Gene Name</i>	<i>Mutant</i>	<i>ACM</i>	<i>DBA</i>	<i>CI</i>	<i>RMSD</i>	<i>SASA</i>	<i>DDG</i>	<i>Zone1</i>	<i>IMI</i>
katG	A139P	✗	✓	✗	✓	✓	✗	✗	.20
katG	S140N	✗	✓	✓	✓	✓	✓	✗	2.07
katG	S140A	✗	✓	✓	✓	✓	✓	✗	1.23
katG	S140G	✗	✓	✓	✓	✓	✓	✗	2.64
katG	L141F	✗	✓	✓	✓	✓	✓	✗	4.00
katG	D142A	✗	✓	✓	✓	✓	✓	✗	2.82
katG	K143T	✓	✗	✓	✓	✓	✓	✗	2.28
katG	L148A	✗	✓	✓	✓	✓	✗	✗	1.96
katG	L148R	✗	✓	✓	✓	✓	✗	✗	1.96
katG	P150A	✗	✓	✓	✓	✓	✓	✗	0
katG	Y155S	✗	✗	✗	✗	✗	✗	✗	1.20
katG	Y155C	✗	✗	✗	✗	✗	✗	✗	1.20
katG	S160L	✗	✗	✗	✗	✓	✓	✗	2.82
katG	A162T	✗	✗	✗	✓	✓	✓	✗	2.13
katG	G169A	✗	✓	✓	✓	✓	✓	✗	3.00
katG	A172T	✗	✓	✓	✓	✓	✓	✗	2.67
katG	A172V	✗	✓	✓	✓	✓	✓	✗	2.67
katG	M176I	✗	✓	✓	✓	✓	✓	✗	1.35
katG	T180K	✗	✓	✓	✓	✓	✓	✗	2.52
katG	T180C	✗	✓	✓	✓	✓	✓	✗	2.52
katG	G186V	✗	✓	✓	✓	✓	✓	✗	2.46
katG	G186H	✗	✓	✓	✓	✓	✓	✗	2.46
katG	W191R	✗	✗	✓	✓	✓	✓	✓	0
katG	E195K	✗	✗	✓	✓	✓	✓	✓	0
katG	N218K	✗	✗	✓	✓	✓	✓	✗	0
katG	Q224E	✗	✗	✗	✓	✓	✓	✗	.82
katG	Y229F	✗	✓	✓	✓	✓	✓	✓	2.52
katG	V230A	✓	✗	✓	✓	✓	✓	✗	1.83
katG	G234E	✗	✗	✓	✓	✓	✓	✗	1.28
katG	G234R	✗	✗	✓	✓	✓	✓	✗	1.28

<i>Gene Name</i>	<i>Mutant</i>	<i>ACM</i>	<i>DBA</i>	<i>CI</i>	<i>RMSD</i>	<i>SASA</i>	<i>DDG</i>	<i>Zone1</i>	<i>IMI</i>
katG	N236T	✗	✗	✗	✗	✓	✗	✗	0
katG	A243S	✗	✗	✓	✗	✓	✓	✓	.54
katG	R249C	✗	✗	✗	✓	✓	✗	✗	.57
katG	T251M	✗	✗	✓	✓	✓	✗	✗	3.00
katG	F252L	✓	✗	✓	✓	✓	✗	✗	2.64
katG	M257T	✗	✗	✓	✓	✓	✗	✗	2.70
katG	M257I	✗	✗	✓	✓	✓	✗	✗	2.70
katG	N258S	✗	✗	✓	✓	✓	✗	0	
katG	T262R	✗	✗	✓	✓	✓	✗	✗	
katG	A264T	✗	✗	✓	✓	✓	✗	✗	1.83
katG	T275S	✓	✓	✓	✓	✓	✗	✗	2.22
katG	T275A	✗	✗	✓	✓	✓	✗	✗	2.22
katG	T275P	✓	✓	✓	✓	✓	✗	✗	1.48
katG	G279D	✗	✗	✓	✓	✓	✗	✗	1.50
katG	P280H	✗	✗	✓	✓	✓	✗	✗	0
katG	A281V	✓	✗	✗	✓	✓	✗	✗	0
katG	E289D	✗	✗	✗	✓	✓	✗	✗	0
katG	A291P	✗	✗	✓	✓	✓	✗	✗	1.50
katG	Q295P	✗	✗	✓	✓	✓	✗	✗	0
katG	G297V	✗	✗	✓	✓	✓	✗	✗	0
katG	G299C	✗	✗	✓	✓	✓	✗	✗	2.91
katG	W300G	✓	✗	✗	✓	✓	✗	✗	1.00
katG	S302R	✗	✗	✓	✓	✓	✗	✗	.94
katG	G307E	✓	✗	✓	✓	✓	✗	✗	2.43
katG	T308P	✓	✗	✓	✓	✓	✗	✗	0
katG	G309D	✓	✗	✓	✓	✓	✓	✓	2.46
katG	D311G	✗	✗	✓	✓	✓	✓	✓	1.53
katG	S315T	✗	✗	✓	✓	✓	✗	✗	0
katG	S315N	✗	✗	✓	✓	✓	✓	✓	0
katG	S315L	✗	✗	✓	✓	✓	✓	✓	0

<i>Gene Name</i>	<i>Mutant</i>	<i>ACM</i>	<i>DBA</i>	<i>CI</i>	<i>RMSD</i>	<i>SASA</i>	<i>DDG</i>	<i>Zone1</i>	<i>IMI</i>
katG	S315I	✓	✗	✗	✗	✗	✓	✗	0
katG	S315R	✓	✗	✗	✗	✓	✓	✗	0
katG	S315G	✓	✗	✗	✗	✓	✓	✗	0
katG	G316S	✗	✓	✓	✓	✗	✗	✗	1.78
katG	G316D	✗	✓	✗	✓	✗	✗	✗	1.78
katG	I317L	✗	✓	✓	✓	✓	✓	✗	1.68
katG	W321R	✗	✓	✓	✓	✓	✗	✗	1.56
katG	T324P	✗	✓	✓	✓	✓	✓	✗	2.10
katG	W328C	✗	✓	✓	✓	✓	✗	✗	.54
katG	W328L	✗	✓	✓	✓	✓	✓	✗	.81
katG	W328G	✗	✓	✓	✓	✓	✗	✗	.54
katG	E334T	✗	✓	✓	✓	✓	✓	✗	0
katG	I335T	✗	✓	✓	✓	✓	✓	✗	.96
katG	I335V	✗	✓	✓	✓	✓	✓	✗	.90
katG	Y337F	✗	✓	✓	✓	✓	✓	✗	1.65
katG	Y337C	✗	✓	✓	✓	✓	✓	✗	.80
katG	W341S	✗	✓	✓	✓	✓	✓	✗	1.32
katG	K345T	✗	✓	✓	✓	✓	✓	✗	0
katG	A350S	✗	✓	✓	✓	✓	✓	✗	2.28
katG	A350T	✗	✓	✓	✓	✓	✓	✗	2.28
katG	T380I	✗	✓	✓	✓	✓	✓	✗	2.96
katG	D381G	✗	✓	✓	✓	✓	✓	✗	3.00
katG	L384R	✗	✓	✓	✓	✓	✓	✗	.66
katG	Y390I	✗	✓	✓	✓	✓	✓	✗	3.00
katG	I393N	✗	✓	✓	✓	✓	✓	✗	.76
katG	T394A	✗	✓	✓	✓	✓	✓	✗	2.43
katG	A409D	✗	✓	✓	✓	✓	✓	✗	2.10
katG	A409R	✗	✓	✓	✓	✓	✓	✗	2.10
katG	R418Q	✗	✓	✓	✓	✓	✓	✗	2.34
katG	R418L	✗	✓	✓	✓	✓	✓	✗	2.34

<i>Gene Name</i>	<i>Mutant</i>	<i>ACM</i>	<i>DBA</i>	<i>CI</i>	<i>RMSD</i>	<i>SASA</i>	<i>DDG</i>	<i>Zone1</i>	<i>IMI</i>
katG	A424E	✗	✗	✗	✗	✓	✗	✗	0
katG	A424V	✗	✗	✗	✗	✓	✗	✗	0
katG	P429S	✗	✗	✗	✗	✓	✗	✗	0
katG	R463L	✗	✗	✗	✗	✓	✗	✗	0
katG	R484S	✗	✓	✗	✗	✓	✗	✗	2.49
katG	G485V	✗	✗	✗	✗	✓	✗	✗	.86
katG	K488N	✓	✗	✗	✗	✓	✗	✗	.60
katG	G490C	✗	✗	✗	✗	✓	✗	✗	1.56
katG	G491C	✗	✗	✗	✗	✓	✗	✗	2.52
katG	W505R	✗	✗	✗	✗	✗	✗	✗	1.72
katG	E506K	✗	✗	✗	✗	✓	✗	✗	0
katG	R515C	✗	✗	✓	✗	✓	✗	✗	0
katG	Q525P	✗	✗	✓	✗	✓	✗	✗	.14
katG	N529D	✗	✗	✓	✗	✓	✗	✗	1.38
katG	A550D	✗	✗	✓	✗	✓	✗	✗	1.32
kasA	P67N	✗	✗	✗	✗	✓	✗	✗	0
kasA	R78I	✗	✓	✗	✗	✓	✗	✗	0
kasA	I122K	✗	✓	✗	✗	✓	✗	✗	0
kasA	I270S	✗	✓	✗	✗	✓	✗	✗	.21
kasA	T313S	✗	✓	✗	✓	✓	✗	✗	2.58
kasA	E388D	✗	✓	✗	✓	✓	✗	✗	0
kasA	G414L	✗	✓	✗	✓	✓	✗	✗	3.00
gidB	R1Q	✗	✗	✗	✗	✓	✗	✗	0
gidB	I9S	✗	✗	✗	✗	✓	✗	✗	0
gidB	D21H	✗	✗	✓	✓	✓	✓	✗	2.94
gidB	S24R	✗	✗	✓	✓	✓	✓	✗	2.94
gidB	G25V	✗	✗	✓	✓	✓	✓	✗	1.78
gidB	P29A	✗	✗	✓	✓	✓	✓	✗	1.22
gidB	E46D	✗	✗	✓	✓	✓	✓	✗	2.19
gidB	Q81P	✗	✗	✓	✓	✓	✓	✓	0

<i>Gene Name</i>	<i>Mutant</i>	<i>ACM</i>	<i>DBA</i>	<i>CI</i>	<i>RMSD</i>	<i>SASA</i>	<i>DDG</i>	<i>Zone1</i>	<i>IMI</i>
gidB	A88E	✗	✗	✓	✓	✓	✗	✗	.20
gidB	A92E	✗	✗	✓	✓	✓	✓	✗	0
thyA	G202A	✗	✗	✓	✓	✓	✓	✗	1.98
thyA	E222G	✗	✗	✗	✓	✓	✓	✗	0
tlyA	A5E	✗	✗	✓	✓	✓	✓	✗	2.73
tlyA	L32P	✗	✗	✓	✓	✓	✗	✗	1.92
tlyA	V42E	✗	✗	✓	✓	✓	✓	✗	.44
tlyA	L64P	✗	✗	✓	✓	✓	✓	✗	1.56
inhA	I16T	✗	✗	✓	✓	✓	✓	✓	0
inhA	I21T	✗	✗	✓	✓	✓	✓	✓	.90
inhA	I21V	✗	✗	✓	✓	✓	✓	✓	1.35
inhA	I47T	✗	✗	✓	✓	✓	✓	✗	0
inhA	V78A	✗	✗	✓	✓	✓	✓	✗	.16
inhA	S94L	✗	✗	✓	✓	✓	✓	✓	1.18
inhA	S94A	✗	✗	✓	✓	✓	✓	✓	1.53
inhA	I95T	✗	✗	✓	✓	✓	✓	✓	.54
inhA	I95P	✗	✗	✓	✓	✓	✓	✓	0
inhA	I194T	✓	✓	✓	✓	✓	✓	✗	0

ACM - Access channel mutation

DBA - Delta binding affinity

CI - Conservation index

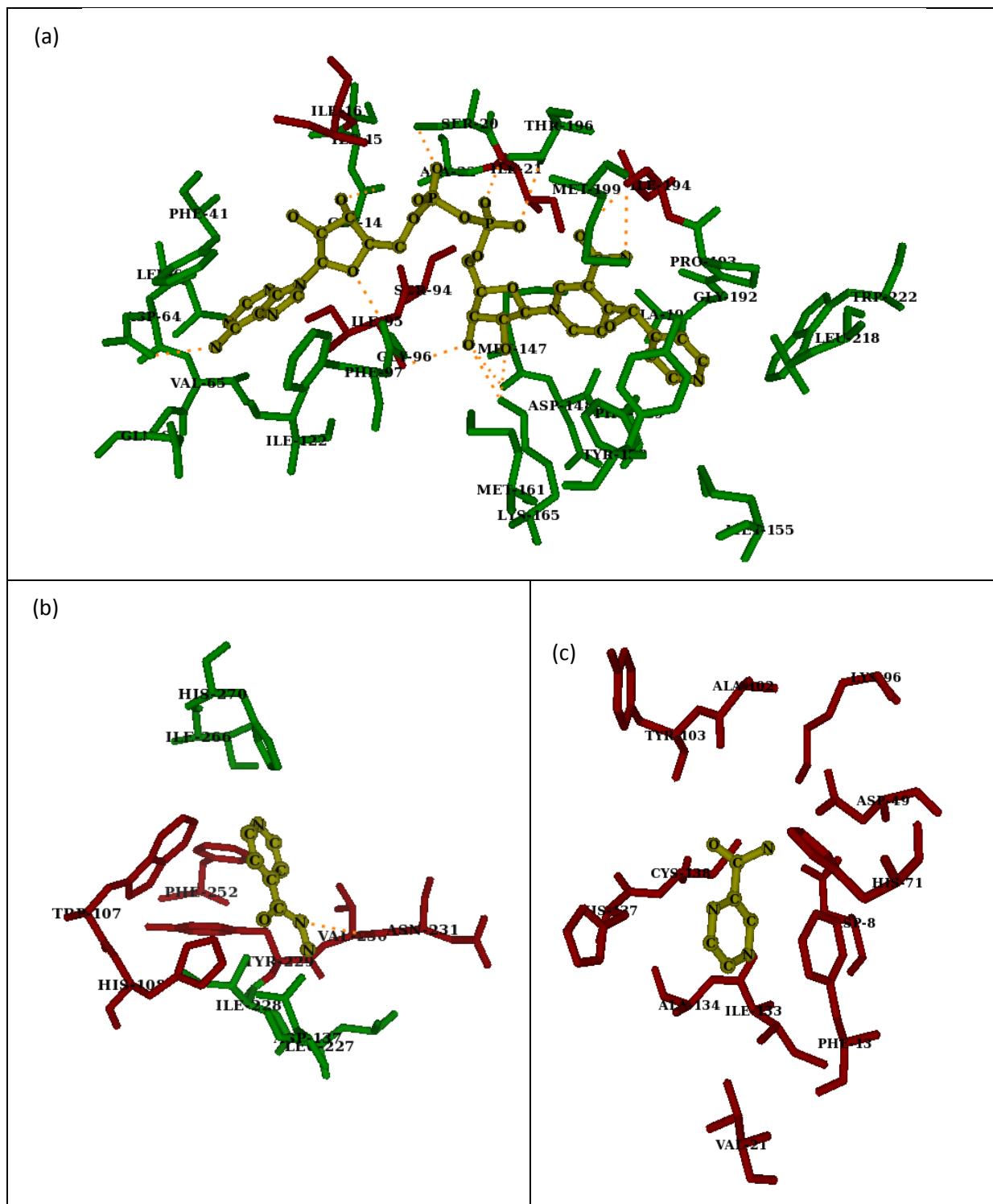
RMSD - Binding site RMSD

SASA - Solvent accessible area

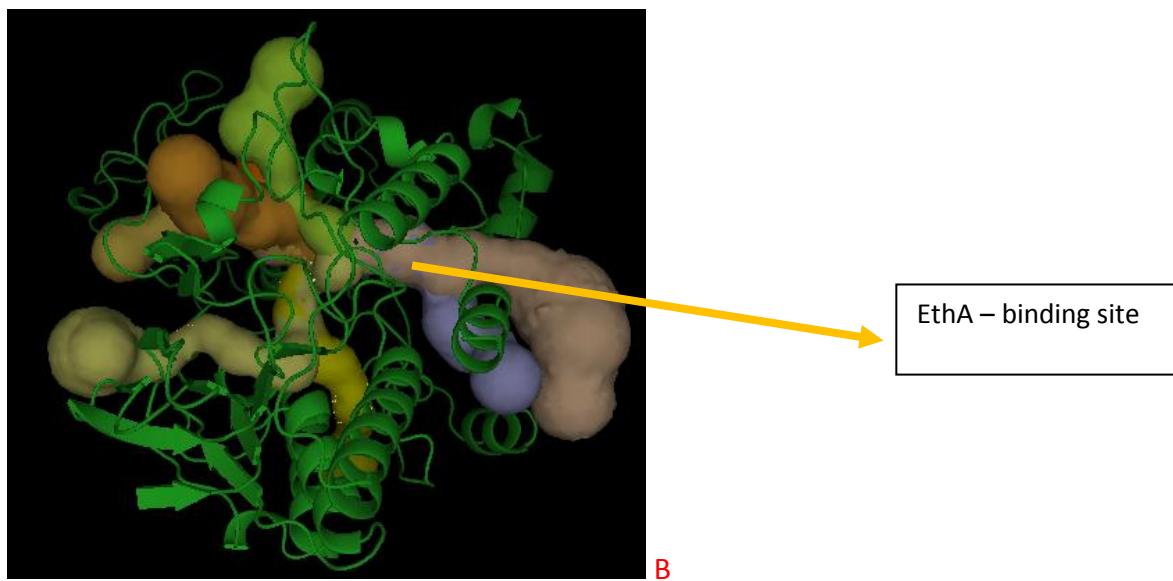
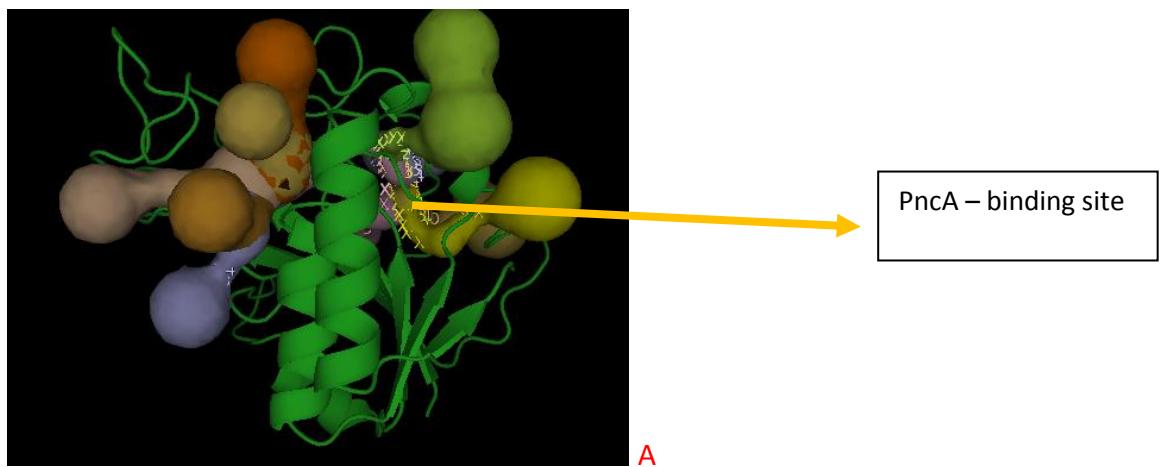
DDG - Stability in terms of $\Delta\Delta G$

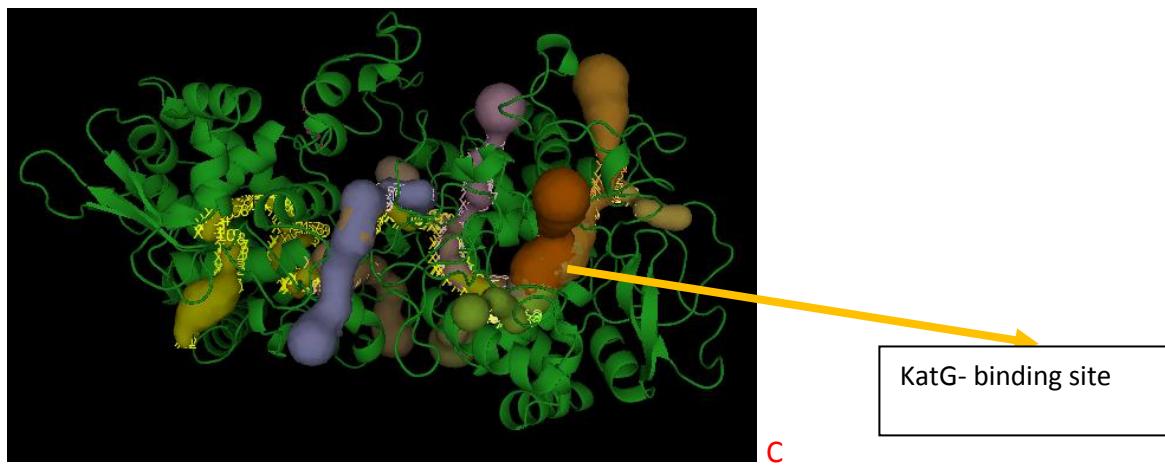
Zone1 - Zone1 residue mutation

IMI - Integrated mutability index



Supplementary_Figure:S1 Examples showing drug binding sites (a) Isoniazid adduct bound to InhA (b) Isoniazid prodrug in KatG, (c) Pyrazinamide in PncA .Drug molecules are shown in orange , while the binding site residues are in green. Those residues that have been mutated in one or the other clinically observed drug resistant mutations are coloured red to indicate positions that can acquire resistant mutations.

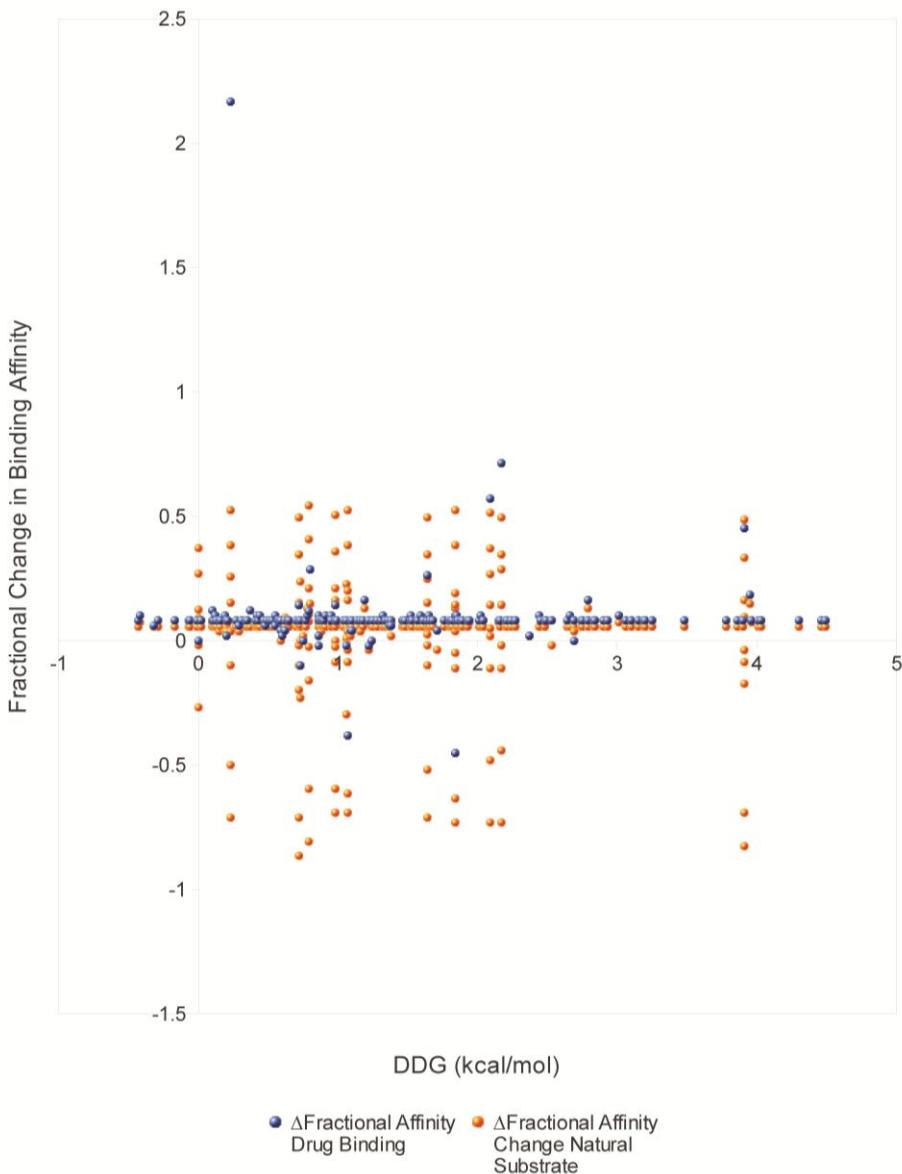




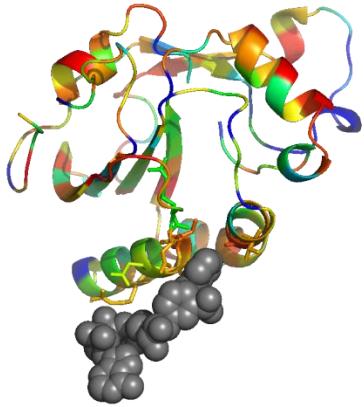
Supplementary_Figure:S2 Access Channel predicted using Caver for (A)PncA, (B) EthA, and (C) KatG . The top four ranks of the predicted access channels were used in this analysis and the drug binding sites are depicted.

Structural Stability Vs Binding Affinity Changes

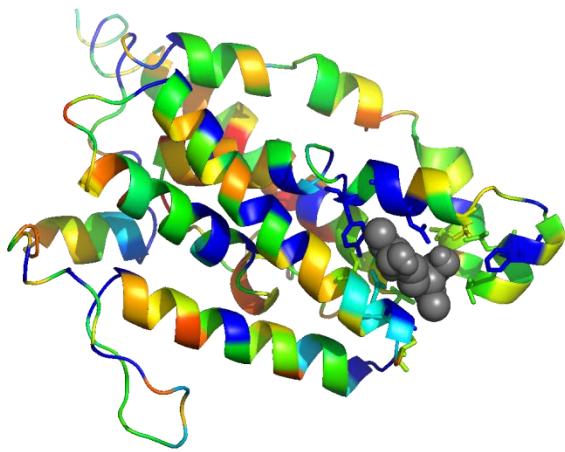
(Structural Stability measured using PoPMusic & Binding Affinity Using Autodock Vina)



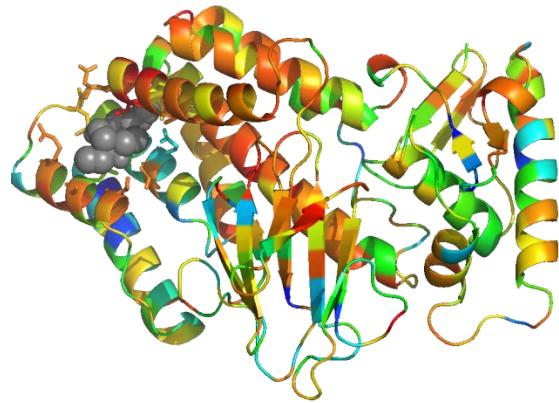
Supplementary_Figure: S3 The fractional change in binding affinities for the drug and natural substrates in different drug targets. On the whole, in observed drug resistant mutants, the affinities for the drugs are poorer as compared to that of the corresponding substrates of the target proteins. Most proteins show little change in stability as compared to their wild type varieties. There are some cases where stability has been decreased as well.



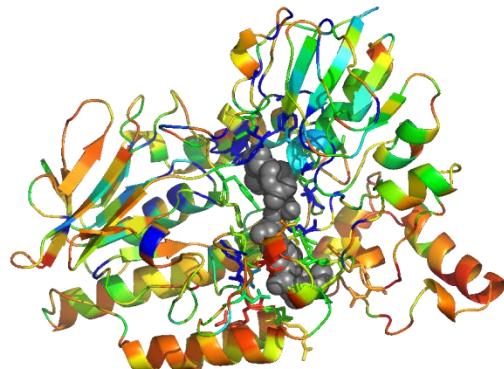
A



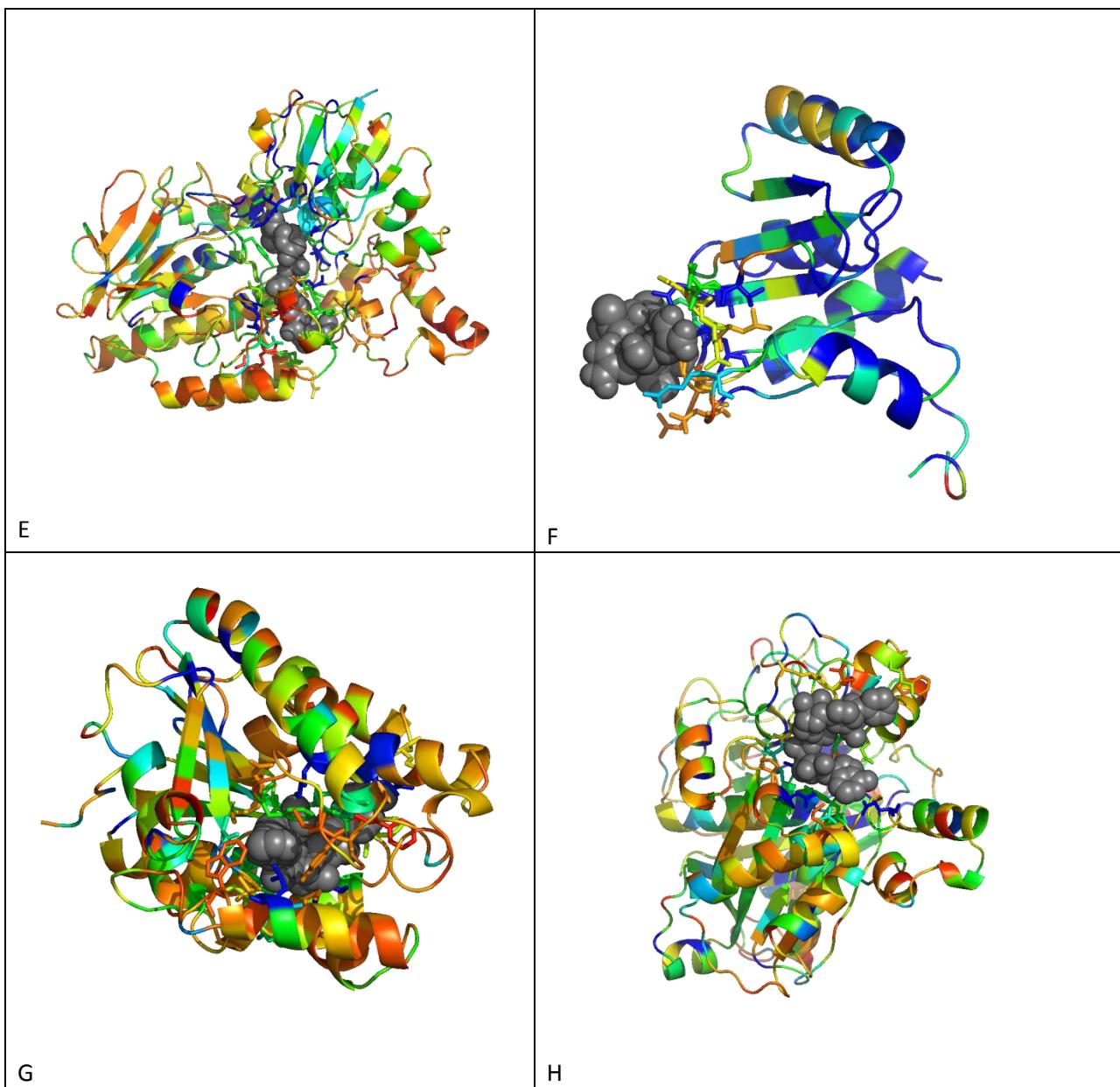
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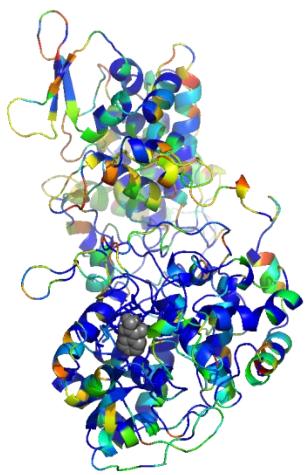


C

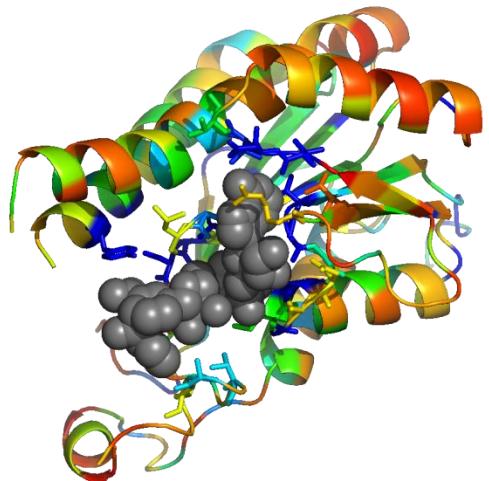


D

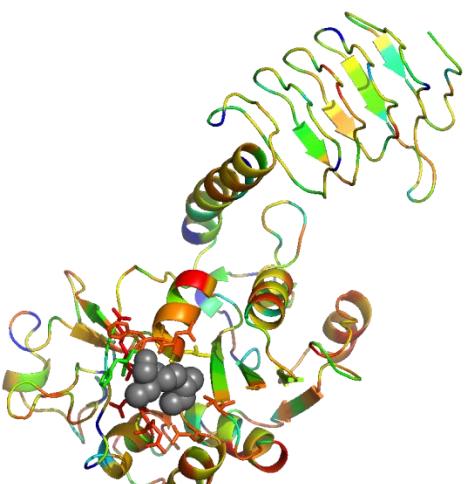




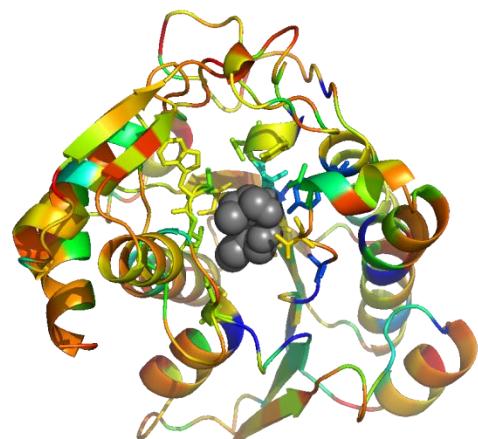
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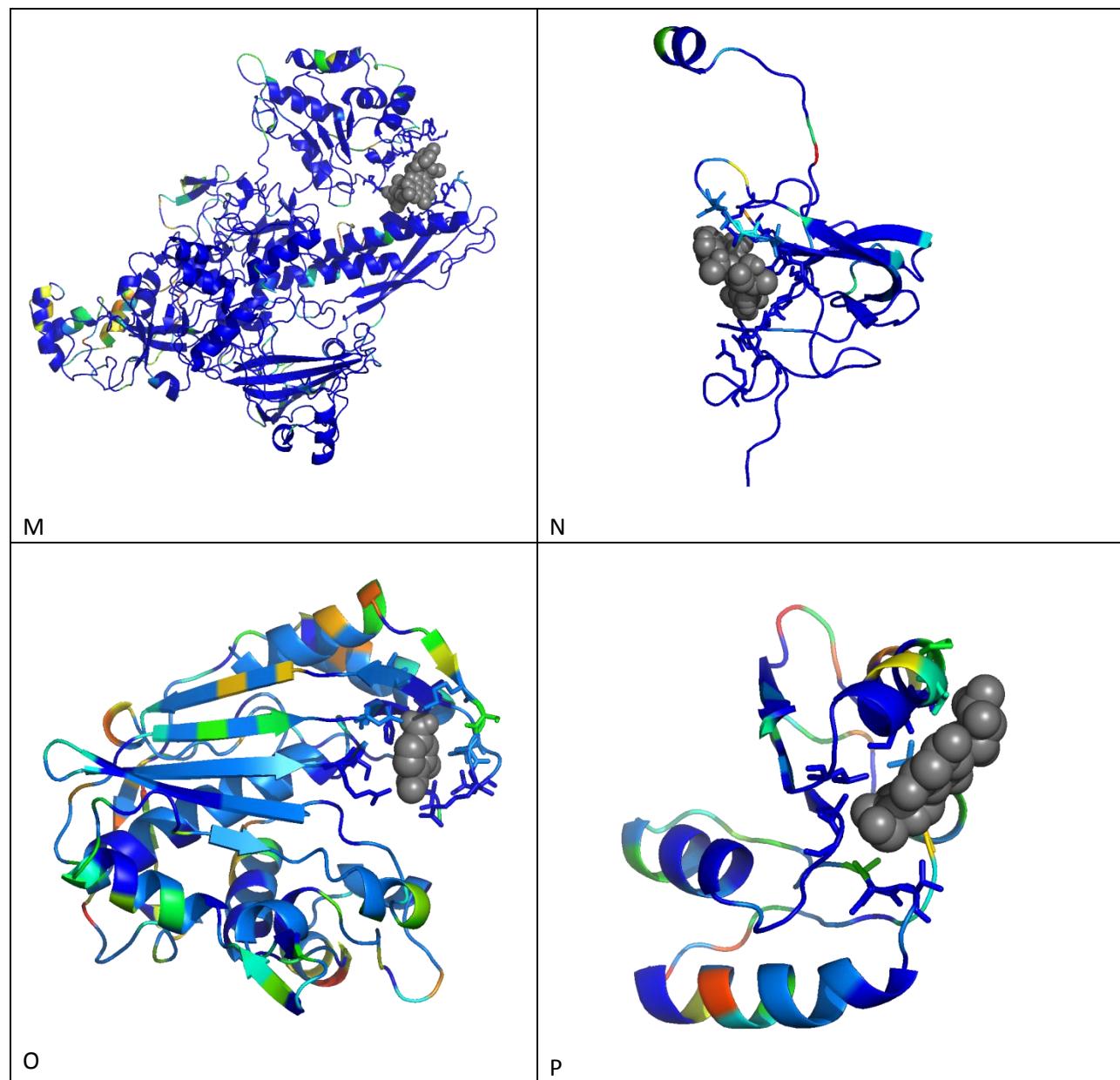
J



K



L



Supplimentary_figure: S4 Illustration of the distribution of residue-wise conservation indices of the target proteins ((A) AhpC, (B) EmbA, (C) EmbR, (D) EthA, (E) GidB, (F) InhA, (G) KasA, (H) KatG, (I) MabA, (J) ManB, (K) PncA, (L) RmID, (M) RpoB, (N) RpsL, (O) ThyA and (P) TlyA). The proteins are represented in cartoon and the corresponding docked drug molecules are represented in grey spheres. Blue indicates least mutable or highly conserved residues, whereas red indicates most mutable or highly variable residues.