Antibiotics

Inhibition of Erythromycin and Erythromycin-Induced Resistance Among *Staphylococcus aureus* Clinical Isolates

Aya A. Mahfouz [a,c], Heba S. Said [a], Sherin M. Elfeky [b], Mona I. Shaaban [a*]

[a] Department of Microbiology and Immunology, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt.

[b] Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt.

[c] Department of Microbiology and Immunology, Faculty of Pharmacy, Horus University-Egypt, New Damietta 34518, Egypt.

* Corresponding author: Mona I. Shaaban

E-mail addresses: mona_ibrahem@mans.edu.eg; sarafawzy2002@yahoo.com

Telephone: 01066944268

Table S1. Antimicrobial susceptibility of tested *S. aureus* clinical isolates to different classes of antimicrobial agents.

Isolate no.	Clinical Source	β-lactams							Aminoglycosides		Fluoroquinolones		Macrolides			Lincosamides	Streptogramins	Oxazolidinones	MRSA or MSSA
		AMC	OX	Fox	CAZ	CTX	FEP	IPM	CN	AK	CIP	LEV	CLR	AZM	E	DA	RP	LZD	
1	Wound	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
2	Wound	R	R	R	R	R	R	S	R	R	R	R	R	R	R	R	R	S	MRSA
3	Wound	R	R	R	R	R	R	S	R	S	S	S	R	R	R	R	R	S	MRSA
4	Wound	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
5	Wound	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
6	Wound	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
7	Wound	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
8	Wound	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
9	Wound	R	R	R	R	R	R	S	R	I	R	R	R	R	R	R	R	S	MRSA
10	Wound	R	R	R	R	R	R	S	S	S	S	S	R	R	R	S	R	S	MRSA
11	Wound	R	S	R	R	I	I	S	R	S	R	S	R	R	R	S	R	S	MRSA
12	Wound	R	I	R	R	R	R	S	R	R	R	S	R	R	R	S	R	S	MRSA
13	Wound	R	R	R	R	R	R	S	R	S	S	S	R	R	R	S	R	S	MRSA
14	Wound	R	R	R	R	I	I	S	S	S	R	R	R	R	R	S	R	S	MRSA
15	Wound	R	R	R	R	I	R	S	S	S	S	S	R	R	R	S	R	S	MRSA
16	Wound	R	R	R	R	R	R	R	S	S	R	R	R	R	R	S	R	S	MRSA
17	Wound	R	R	R	R	R	R	S	R	S	S	S	R	R	R	S	R	S	MRSA
18	Wound	R	I	R	R	R	R	S	S	S	S	S	R	R	R	S	R	S	MRSA
19	Wound	R	I	R	R	R	R	S	S	S	S	S	R	R	R	S	R	S	MRSA
20	Blood	R	R	R	R	R	R	S	S	S	S	S	I	R	R	R	R	S	MRSA
21	Blood	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
22	Blood	R	R	R	R	R	R	R	R	S	S	R	R	R	R	R	R	S	MRSA
23	Blood	R	R	R	R	R	R	S	R	S	R	S	R	R	R	R	R	S	MRSA
24	Blood	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
25	Blood	R	R	R	R	R	R	R	R	S	R	R	R	R	R	R	R	S	MRSA
26	Blood	R	R	R	R	R	R	I	R	R	R	R	R	R	R	R	R	S	MRSA
27	Blood	R	R	R	R	R	R	S	S	S	I	S	R	R	R	S	R	S	MRSA
28	Skin tissue	R	R	R	R	R	R	S	R	R	S	S	R	R	R	S	R	S	MRSA
29	Nasal swab	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	MRSA

30	**Nasal swab**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**S**	**MRSA**
31	Nasal swab	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
32	Nasal swab	R	R	R	R	S	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
33	Nasal swab	R	R	R	R	S	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
34	Nasal swab	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
35	Nasal swab	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
36	Nasal swab	R	R	R	R	R	R	R	R	R	R	S	R	R	R	S	R	S	MRSA
37	Nasal swab	S	R	R	R	R	R	R	R	S	R	S	R	R	R	R	R	S	MRSA
38	Nasal swab	S	S	S	R	R	S	S	S	S	S	S	R	R	R	S	R	S	MSSA
39	Nasal swab	S	R	R	R	I	S	S	R	S	S	S	R	R	R	R	R	S	MRSA
40	Nasal swab	R	R	R	R	I	R	S	S	S	S	S	R	R	R	R	R	S	MRSA
41	Nasal swab	S	R	R	R	R	S	S	R	R	R	R	R	R	R	R	R	S	MRSA
42	Nasal swab	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
43	Nasal swab	S	R	R	R	R	S	S	S	S	S	S	R	R	R	R	R	S	MRSA
44	Nasal swab	R	R	R	R	I	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
45	Nasal swab	S	R	R	R	R	R	S	R	S	I	S	R	R	R	R	R	S	MRSA
46	Nasal swab	R	R	R	R	R	R	I	R	R	R	R	R	R	R	R	R	S	MRSA
47	Nasal swab	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	S	MRSA
48	Nasal swab	R	R	R	R	R	R	S	R	R	R	R	R	R	R	R	R	S	MRSA
49	Nasal swab	S	R	R	R	R	I	S	S	S	R	R	R	R	R	S	R	S	MRSA
50	Nasal swab	R	R	R	R	R	I	S	R	S	S	S	R	R	R	R	R	S	MRSA
51	Nasal swab	S	S	R	R	R	I	S	I	S	R	I	R	R	R	S	R	S	MRSA
52	Nasal swab	R	R	R	R	R	R	S	S	S	I	S	R	R	R	S	R	S	MRSA
53	Wound	R	R	R	R	R	R	S	R	R	S	S	S	S	S	S	S	S	MRSA
54	Wound	R	R	R	R	R	R	S	R	I	S	S	S	S	S	S	S	S	MRSA
55	Wound	R	R	R	R	I	I	S	R	S	S	S	S	S	S	S	S	S	MRSA
56	Wound	R	R	R	R	I	R	S	R	S	S	S	S	S	S	S	S	S	MRSA

57	Wound	R	R	R	R	I	I	S	S	S	S	S	S	S	S	S	S	S	MRSA
58	Wound	S	R	R	R	I	I	S	R	S	S	S	S	S	S	S	S	S	MRSA
59	Wound	R	R	R	R	R	R	S	S	S	I	S	S	S	S	S	S	S	MRSA
60	Wound	R	R	R	R	I	I	S	S	S	S	S	S	S	S	S	S	S	MRSA
61	Wound	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	MSSA
62	Wound	R	S	R	R	I	S	S	R	S	S	S	S	S	S	S	S	S	MRSA
63	Wound	R	S	R	R	I	S	S	R	R	I	S	S	S	S	S	S	S	MRSA
64	Wound	R	I	R	R	I	I	S	R	R	R	S	S	S	S	S	S	S	MRSA
65	Wound	R	S	R	R	I	I	S	R	S	S	S	S	S	S	S	S	S	MRSA
66	Wound	R	R	R	R	R	R	S	R	S	R	R	S	S	S	S	S	S	MRSA
67	Wound	R	R	R	R	I	R	S	R	R	R	S	S	S	S	S	S	S	MRSA
68	Wound	R	R	R	R	I	R	S	R	S	R	R	S	S	S	S	S	S	MRSA
69	Blood	R	S	R	R	I	S	S	R	R	S	S	S	S	S	S	S	S	MRSA
70	Blood	R	S	R	R	I	I	S	R	S	S	S	S	S	S	S	S	S	MRSA
71	Blood	R	S	R	I	I	I	S	R	R	S	S	S	S	S	S	S	S	MRSA
72	Blood	R	S	R	R	I	S	S	S	S	S	S	S	S	S	S	S	S	MRSA
73	Blood	R	R	R	R	I	I	S	S	S	S	S	S	S	S	S	S	S	MRSA
74	Blood	S	S	R	R	I	S	S	S	S	S	S	S	S	S	S	S	S	MRSA
75	Blood	R	S	R	R	I	I	S	S	S	S	S	S	S	S	S	S	S	MRSA
76	Blood	R	S	R	R	I	S	S	S	S	S	S	S	S	S	S	S	S	MRSA
77	Blood	R	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	MSSA
78	Blood	S	S	S	S	S	S	S	R	S	S	S	S	S	S	S	S	S	MSSA
79	Blood	R	S	R	R	R	R	S	R	S	S	S	S	S	S	S	S	S	MRSA
80	Blood	R	S	R	R	I	S	S	S	S	S	S	S	S	S	S	S	S	MRSA
81	Blood	R	R	R	R	R	R	R	R	R	R	R	S	S	S	S	S	S	MRSA
82	Blood	S	I	R	R	R	S	S	I	S	S	S	S	S	S	S	S	S	MRSA
83	Blood	S	S	R	R	R	S	S	R	S	S	S	S	S	S	S	S	S	MRSA
84	Blood	S	I	R	R	R	S	S	S	S	S	S	S	S	S	S	S	S	MRSA
85	Blood	S	R	R	R	R	S	S	S	S	S	S	S	S	S	S	S	S	MRSA
86	Blood	S	S	R	R	R	S	S	S	S	S	S	S	S	S	S	S	S	MRSA
87	Blood	R	R	R	R	R	R	R	R	R	R	R	S	S	S	S	S	S	MRSA
88	Blood	R	R	R	R	R	R	S	S	S	R	S	S	S	S	S	S	S	MRSA
89	Blood	S	S	S	R	R	S	S	S	S	S	S	S	S	S	S	S	S	MSSA
90	Blood	R	R	R	R	R	R	R	R	R	R	R	S	S	S	S	S	S	MRSA
91	B A L	R	S	R	R	S	S	S	S	S	S	S	S	S	S	S	S	S	MRSA

Isolate no.: the number of isolate, AMC: amoxicillin-clavulanic acid, OX: oxacillin, FOX: cefoxitin, CAZ: ceftazidime, CTX: cefotaxime, FEP: cefepime, IPM: imipenem, CN: gentamicin, AK: amikacin, CIP: ciprofloxacin, LEV: levofloxacin, CLR: clarithromycin, AZM: azithromycin, E: erythromycin, DA: clindamycin, RP: quinapristin/dalfopristin, LZD: linezolid, MRSA: methicillin resistant *S. aureus*, MSSA: methicillin sensitive *S. aureus*, MDR: multidrug-resistant, XDR: extensively drug-resistant, PDR: pandrug-resistant, S: susceptible, I: intermediate, R: resistant, BAL: broncho-alveolar lavage.

Table S2. Effect of different tested compounds on erythromycin resistance against *S. aureus* isolate no. 10 (D phenotype).

Isolate no.	MIC of E (µg/mL)	The effect of tested compounds on erythromycin resistance				
		Tested compound	**MICs (µg/mL)**	**Conc. of inhibitor (µg/mL)**	**MICs of E in combination with inhibitor (µg/mL)**	**Fold change**
Isolate no. 10	1750	CCCP	0.5	0.25	1750	—
		Caffeine	22,000	2,750	875	2-fold ⬇
		Quinine	1250	625	437.5	**4-fold** ⬇
		Quinidine	625	312.5	875	2-fold ⬇
		Emetine	6250	3125	875	2-fold ⬇
		Cancidase	97.656	48.828	875	2-fold ⬇
		Piperine	20,000	5000	875	2-fold ⬇
		Fosfomycin	2	1	437.5	**4-fold** ⬇
		Neomycin	1	0.5	109.375	**16-fold** ⬇
		Ciprofloxacin	0.25	0.125	875	2-fold ⬇
		Doxorubicin	8	4	218.75	**8-fold** ⬇
		5-Fluorouracil	0.5	0.25	875	2-fold ⬇
		Cisplatin	128	64	875	2-fold ⬇
		Meloxicam	2048	1024	437.5	**4-fold** ⬇
		Ketoprofen	3125	1562.5	218.75	**8-fold** ⬇
		Omeprazole	625	312.5	875	2-fold ⬇
		Vitamin D3	1024	512	875	2-fold ⬇
		Vitamin K	2500	1250	875	2-fold ⬇
		Verapamil	1024	512	875	2-fold ⬇
		Digoxin	62.5	31.25	875	2-fold ⬇
		Diazepam	256	128	875	2-fold ⬇

Table S3. Effect of different tested compounds on erythromycin resistance against *S. aureus* isolate no. 36 (MS phenotype).

Isolate no.	MIC of E (µg/mL)	The effect of tested compounds on erythromycin resistance				
		Tested compound	MICs (µg/mL)	Conc. of inhibitor (µg/mL)	MICs of E in combination with inhibitor (µg/mL)	Fold change
Isolate no. 36	100	CCCP	2	1	25	**4-fold ⬇**
		Caffeine	22,000	2,750	25	**4-fold ⬇**
		Quinine	625	312.5	100	__
		Quinidine	625	312.5	50	2-fold ⬇
		Emetine	6250	3125	50	2-fold ⬇
		Cancidase	58.594	29.297	100	__
		Piperine	20,000	5000	100	__
		Fosfomycin	4	2	50	2-fold ⬇
		Neomycin	64	32	0.781	**128-fold ⬇**
		Ciprofloxacin	32	16	50	2-fold ⬇
		Doxorubicin	4	2	50	2-fold ⬇
		5-Fluorouracil	0.125	0.0625	100	__
		Cisplatin	1000	500	100	__
		Meloxicam	1024	512	12.5	**8-fold ⬇**
		Ketoprofen	3125	1562.5	12.5	**8-fold ⬇**
		Omeprazole	5000	2500	12.5	**8-fold ⬇**
		Vitamin D3	1024	512	100	__
		Vitamin K	2500	1250	100	__
		Verapamil	625	312.5	50	2-fold ⬇
		Digoxin	62.5	31.25	100	__
		Diazepam	128	64	100	__

Isolate no.: number of isolate, E: erythromycin, conc.: concentration, ⬇: decrease.

Table S4. Effect of different tested compounds on inducible clindamycin resistance against *S. aureus* isolate no. 10 (D phenotype).

Isolate no.	ICR			Inhibition of ICR				
	DA (µg/mL)	DA/E (µg/mL)	Fold change	Tested compound	MICs (µg/mL)	Conc. of inhibitor (µg/mL)	MICs of DA/E in combination with inhibitor (µg/mL)	Fold change
Isolate no. 10	0.0625	1	16-fold⬆	CCCP	0.5	0.25	1	__
				Caffeine	22,000	2,750	0.5	2-fold⬇
				Quinine	1250	625	0.25	**4-fold⬇**
				Quinidine	625	312.5	0.5	2-fold⬇
				Emetine	6250	3125	1	__
				Cancidase	97.656	48.828	0.5	2-fold⬇
				Piperine	20,000	5000	0.5	2-fold⬇
				Fosfomycin	2	1	0.25	**4-fold⬇**
				Neomycin	1	0.5	0.5	2-fold⬇
				Ciprofloxacin	0.25	0.125	0.5	2-fold⬇
				Doxorubicin	8	4	0.5	2-fold⬇
				5-Fluorouracil	0.5	0.25	1	__
				Cisplatin	128	64	0.5	2-fold⬇
				Meloxicam	2048	1024	0.5	2-fold⬇
				Ketoprofen	3125	1562.5	0.25	**4-fold⬇**
				Omeprazole	625	312.5	0.5	2-fold⬇
				vitamin D3	1024	512	1	__
				Vitamin K	2500	1250	1	__
				Verapamil	1024	512	0.5	2-fold⬇
				Digoxin	62.5	31.25	0.5	2-fold⬇
				Diazepam	256	128	0.5	2-fold⬇

Isolate no.: number of isolate, ICR: inducible clindamycin resistance, E: erythromycin, DA: clindamycin, ⬆: increase, conc.: concentration, ⬇:decrease.

Table S5. Docking results for sinefungin and doxorubicin binding at ErmC` protein (PDB ID: 1QAQ).

Compound	Docking score (ΔG) (kcal/mol)	*H*-bond (length Å)	Hydrophobic interactions
Sinefingin	-9.75	Glu38 (2.96) Glu59 (2.4, 2.65) Asn101 (2.89, 2.55) Ile85 (2.98) Ile13 (3.02) Asp84 (3.39)	Pro103 Asn101 Asn11 Gly38 Gln10 Ile60 Ile106
Doxorubicin	-7.59	Glu38 (2.62) Glu59 (2.96) Asn11 (2.84) Ile58 (2.95) Ile60 (3.29) Gly40 (3.56)	Pro103 Asn101 Asn11 Gly38 Gln10 Ile60 Ile106 Ile85 Asp61 Ser9

Table S6. Docking results for erythromycin, neomycin and omeprazole binding at MsrA protein (UniProtKB ID: Q9ZNK9).

Compound	Docking score (ΔG) (kcal/mol)	*H*-bond (length Å)	Hydrophobic interactions
Erythromycin	-5.91	Glu449 (3.54) Met450 (3.4)	Glu446 Met450 Tyr280 Gln189 Tyr192 Ile442 Glu193 Gln196 Leu197 His471 Glu282
Neomycin	-7.21	Glu449 (3.21) Met450 (3.14) Glu446 (3.23) Lys443 (3.15) Asp171 (3.44, 3.55)	Glu446 Met450 Tyr280 Gln189 Tyr192 Ile442 Glu193 Lys443
Omeprazole	-6.93	Glu446 (2.9)	Glu446 Tyr280 Tyr192 Ile442 Glu193 Gln196 Lys443 Gly38 Tyr188

Table S7. Docking results for S-adenosyl-L-methionine (SAM), quinine, ketoprofen, and fosfomycin binding at ErmC` protein (PDB ID: 1QAO).

Ligand	Docking score (ΔG) (kcal/mol)	*H*-bond (length Å)	Hydrophobic interactions
SAM	-8.58	Gly38 (2.66) Glu59 (2.62, 2.44, 3.31) lle85 (2.91) lle13 (3.52) Asn101 (2.95) Asp84 (3.01)	Pro103 Gly38 Ile60 Gln10 Ile106 Asn11 Asn101
Quinine	-6.87	Gly38 (3.25) Glu59 (3.1)	Pro103 Gly38 Ile60 Gln10 Ile106 Asn11 Asn101
Ketoprofen	-6.52	Ile85 (3.03) Ile60 (3.43)	Pro103 Gly38 Ile60 Gln10 Ile106
Fosfomycin	-4.19	Ile13 (2.99) Asn101 (2.95) Lys41 (2.85) Gly40 (3.84) Phe44 (2.84)	–

Table S8. Primers used for detection of macrolide-lincosamide-streptogramin B (MLS_B)-resistance determinants.

Gene name		Type	Nucleotide Sequence (5' to 3')	AT	Amplicon size (bp)	Ref
Erythromycin resistance methylase (*erm*) genes	***ermC***	Fw	AATCGTCAATTCCTGCATGT	57°C	299	(1)
		Rv	TAATCGTGGAATACGGGTTTG			
	ermA	Fw	GTTCAAGAACAATCAATACAGAG	56°C	421	(2)
		Rv	GGATCAGGAAAAGGACATTTTAC			
	ermB	Fw	CGAAATTGGAACAGGTAAAGG	53°C	359	This study
		Rv	GAATCGAGACTTGAGTGTGC			
Macrolide-streptogramin B resistance (*msr*) genes	***msrA***	Fw	GGCACAATAAGAGTGTTTAAAGG	57°C	940	(3)
		Rv	AAGTTATATCATGAATAGATTGTCCTGTT			
	msrB	Fw	TATGATATCCATAATAATTATCCAATC	50°C	595	(3)
		Rv	AAGTTATATCATGAATAGATTGTCCTGTT			
Lincosamide nucleotidyl-transferase (*lnu*) genes	***lnuA***	Fw	GGTGGCTGGGGGGTAGATGTATTAACTGG	57°C	310	This study
		Rv	GCTTCTTTTGAAATACATGGTATTTTTCGATC			
	lnuB	Fw	CCTACCTATTGTTTGTGGAA	54°C	943	(4)
		Rv	ATAACGTTACTCTCCTATTC			
Macrolide phospho-transferase (*mphC*) genes	***mphC***	Fw	GAGACTACCAAGAAGACCTGACG	56°C	722	(5)
		Rv	CATACGCCGATTCTCCTGAT			

Fw: forward, Rv: reverse, AT: annealing temperature, bp: base pair, Ref: reference.

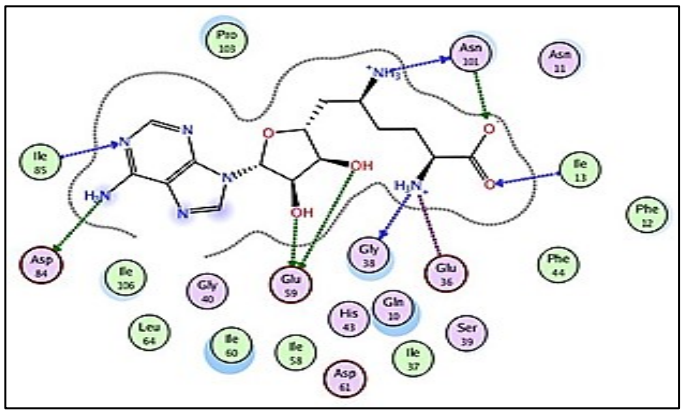
Table S9. Different compounds screened for their activity on erythromycin resistance and inducible clindamycin resistance.

Type of inhibitor	Name of inhibitor
Efflux pump inhibitors	CCCP
Natural compounds	Caffeine Quinine Quinidine Emetine Piperine
Antimicrobial agents	Fosfomycin Neomycin Ciprofloxacin Cancidas
Chemotherapeutic agents	Doxorubicin 5-Fluorouracil Cisplatin
NSAIDs	Meloxicam Ketoprofen

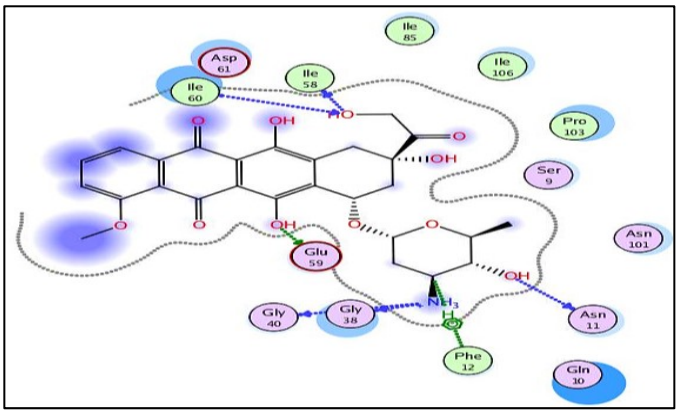
Proton pump inhibitors	Omeprazole
Vitamins	Vitamin D3 Vitamin K
Antihypertensive drugs	Verapamil Digoxin
Sedatives	Diazepam

CCCP: carbonyl cyanide m-chlorophenylhydrazine, NSAIDs: non-steroidal anti-inflammatory drugs.

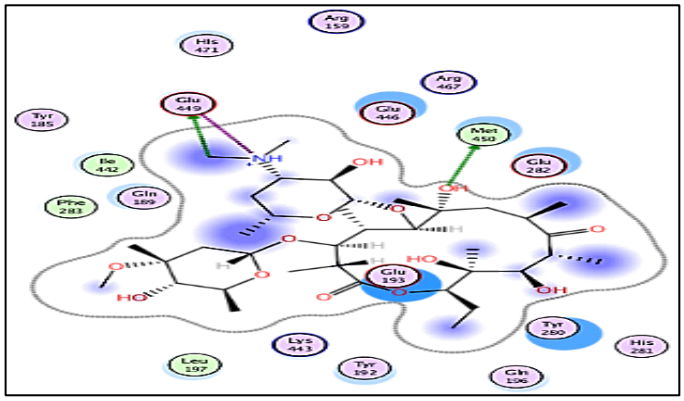
(a)



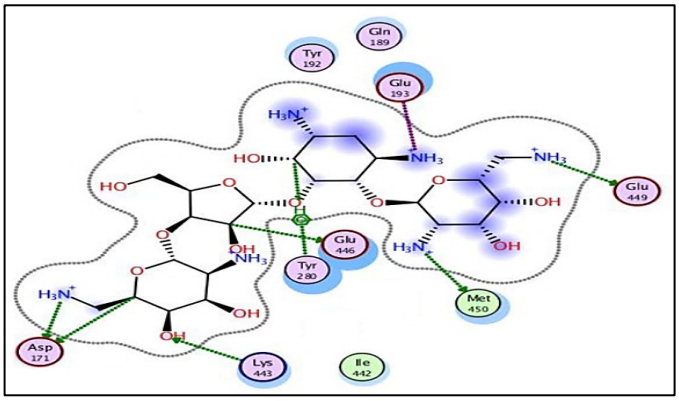
(b)



(c)



(d)



(e)

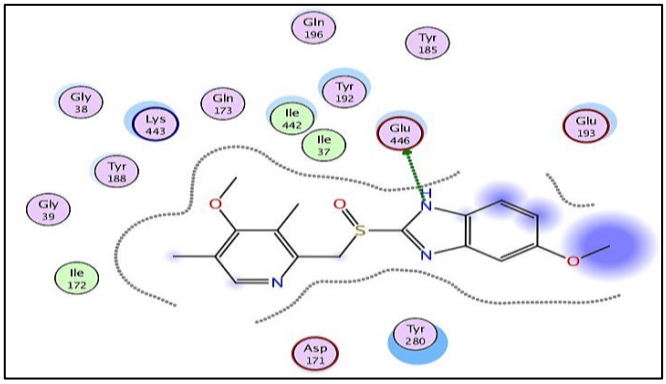
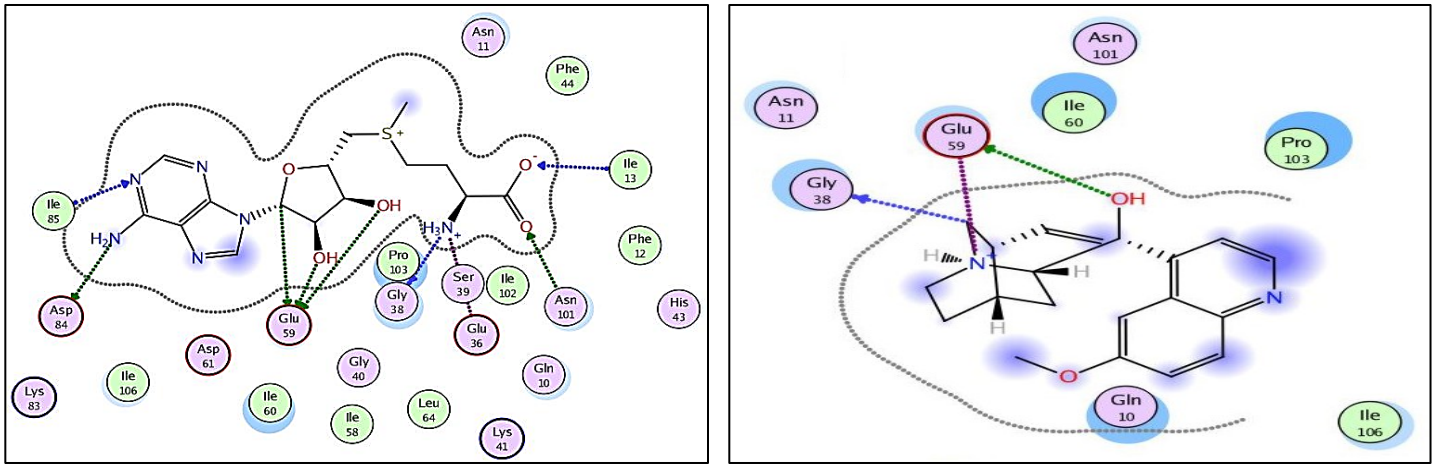


Figure S1. The 2D interactions of sinefungin and doxorubicin at S-adenosyl-L-methionine (SAM)-binding site of ErmC` protein, and erythromycin, neomycin, and omeprazole at MsrA protein. (a)** 2D diagram of sinefungin at SAM-binding site of ErmC` protein. **(b) 2D diagram of doxorubicin at SAM-binding site of ErmC`. **(c)** 2D representation of erythromycin at active site of MsrA protein. **(d)** 2D representation of neomycin at active site of MsrA. **(e)** 2D representation of omeprazole at active site of MsrA.

(a) **(b)**



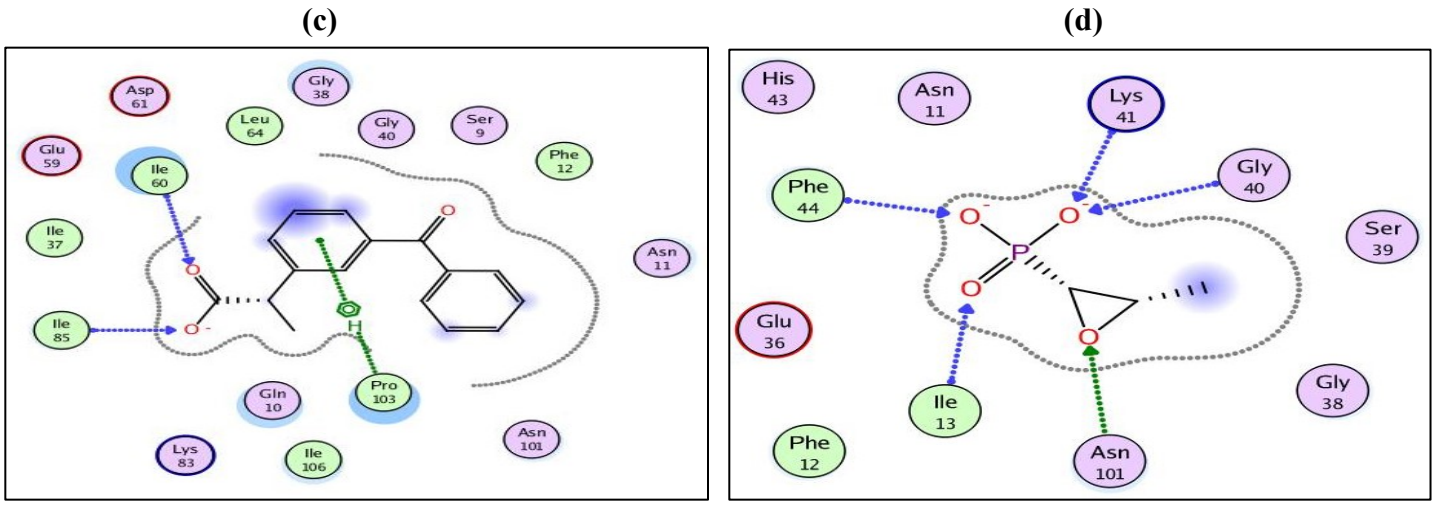


Figure S2. The 2D interactions of SAM, quinine, ketoprofen, and fosfomycin at SAM-binding site of ErmC` protein. (a)** 2D diagram of SAM at SAM-binding site of ErmC` protein. **(b) 2D diagram of quinine at SAM-binding site of ErmC`. **(c)** 2D diagram of ketoprofen at SAM-binding site of ErmC`. **(d)** 2D diagram of fosfomycin at SAM-binding site of ErmC`.

References

1. Strommenger, B.; Kettlitz, C.; Werner, G.; Witte, W. Multiplex PCR assay for simultaneous detection of nine clinically relevant antibiotic resistance genes in *Staphylococcus aureus*. *J. Clin. Microbiol.* **2003**, 41, 4089-94.
2. Leclercq, R.; Bauduret, F.; Soussy, C. Selection of constitutive mutants of gram-positive cocci inducible resistant to macrolides, lincosamides and streptogramins (MLS): comparison of the selective effects of the MLS. *Pathol. Biol.* **1989**, 37, 568-72.
3. Ross, J.; Eady, E.; Cove, J.; Cunliffe, W.; Baumberg, S.; Wootton, J. Inducible erythromycin resistance in staphlyococci is encoded by a member of the ATP-binding transport super-gene family. *Mol. Microbiol.* **1990**, 4, 1207-14.
4. Bozdogan, B.l.; Berrezouga, L.; Kuo, M.-S.; Yurek, D.A.; Farley, K.A.; Stockman, B.J., et al. A new resistance gene, *linB*, conferring resistance to lincosamides by nucleotidylation in *Enterococcus faecium* HM1025. *Antimicrob. Agents Chemother.* **1999**, 43, 925-9.

5. Lüthje, P.; Schwarz, S. Antimicrobial resistance of coagulase-negative staphylococci from bovine subclinical mastitis with particular reference to macrolide–lincosamide resistance phenotypes and genotypes. *J. Antimicrob. Chemother.* **2006**, 57, 966-9.
6. Sutcliffe, J.; Grebe, T.; Tait-Kamradt, A.; Wondrack, L. Detection of erythromycin-resistant determinants by PCR. *Antimicrob. Agents Chemother.* **1996**, 40, 2562-6.
7. Allignet, J.; Loncle, V.; El Solh, N. Sequence of a staphylococcal plasmid gene, *vga*, encoding a putative ATP-binding protein involved in resistance to virginiamycin A-like antibiotics. *Gene* **1992**, 117, 45-51.
8. Loncle, V.; Casetta, A.; Buu-Hoi, A.; El Solh, N. Analysis of pristinamycin-resistant *Staphylococcus epidermidis* isolates responsible for an outbreak in a Parisian hospital. *Antimicrob. Agents Chemother.* **1993**, 37, 2159-65.
9. Hammerum, A.M.; Jensen, L.B.; Aarestrup, F.M.l. Detection of the *satA* gene and transferability of virginiamycin resistance in *Enterococcus faecium* from food-animals. *FEMS Microbiol. Lett.* **1998**, 168, 145-51.
10. Allignet, J.; Liassine, N.; El Solh, N. Characterization of a staphylococcal plasmid related to pUB110 and carrying two novel genes, *vatC* and *vgbB*, encoding resistance to streptogramins A and B and similar antibiotics. *Antimicrob. Agents Chemother.* **1998**, 42, 1794-8.