Supplementary Information for

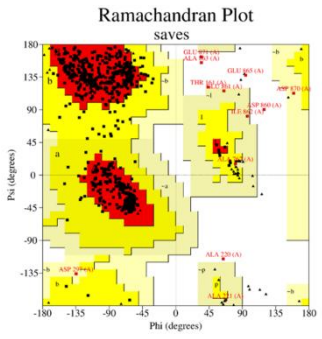
Inhibition strategies for ARGS vertical gene transfer: design of antibiotic substitutes based on drug compatibility and random forest models

Zuning Zhang [1, †], Zhixing Ren [2, †], Qikun Pu [1, †], Wenwen Wang (✉)[1], Tianyi Cheng [3, †], Yu Li [1]

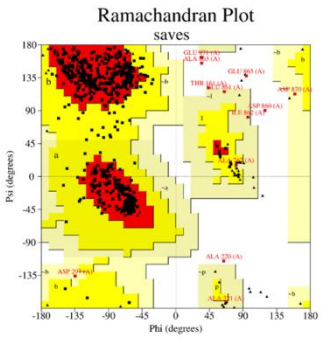
1 MOE Key Laboratory of Resources and Environmental Systems Optimization, North China Electric Power University, Beijing 102206, China

2 College of Forestry, Northeast Forestry University, Harbin 150040, China

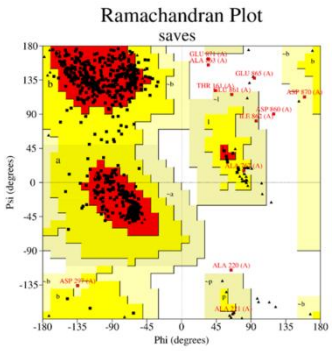
3 Business School, Lehigh University, Bethlehem 18015, USA



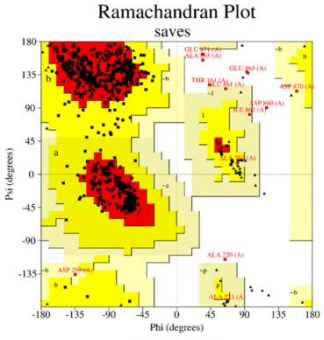
81-GLY-ASP



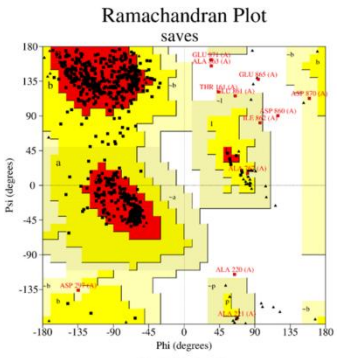
82-ASP-GLY



83-SER-ALA



83-SER-LEU



83-SER-TRP

✉ Corresponding author
E-mail: 53203032@ncepu.edu.cn
† These authors contributed equally to the study and share equal credit.

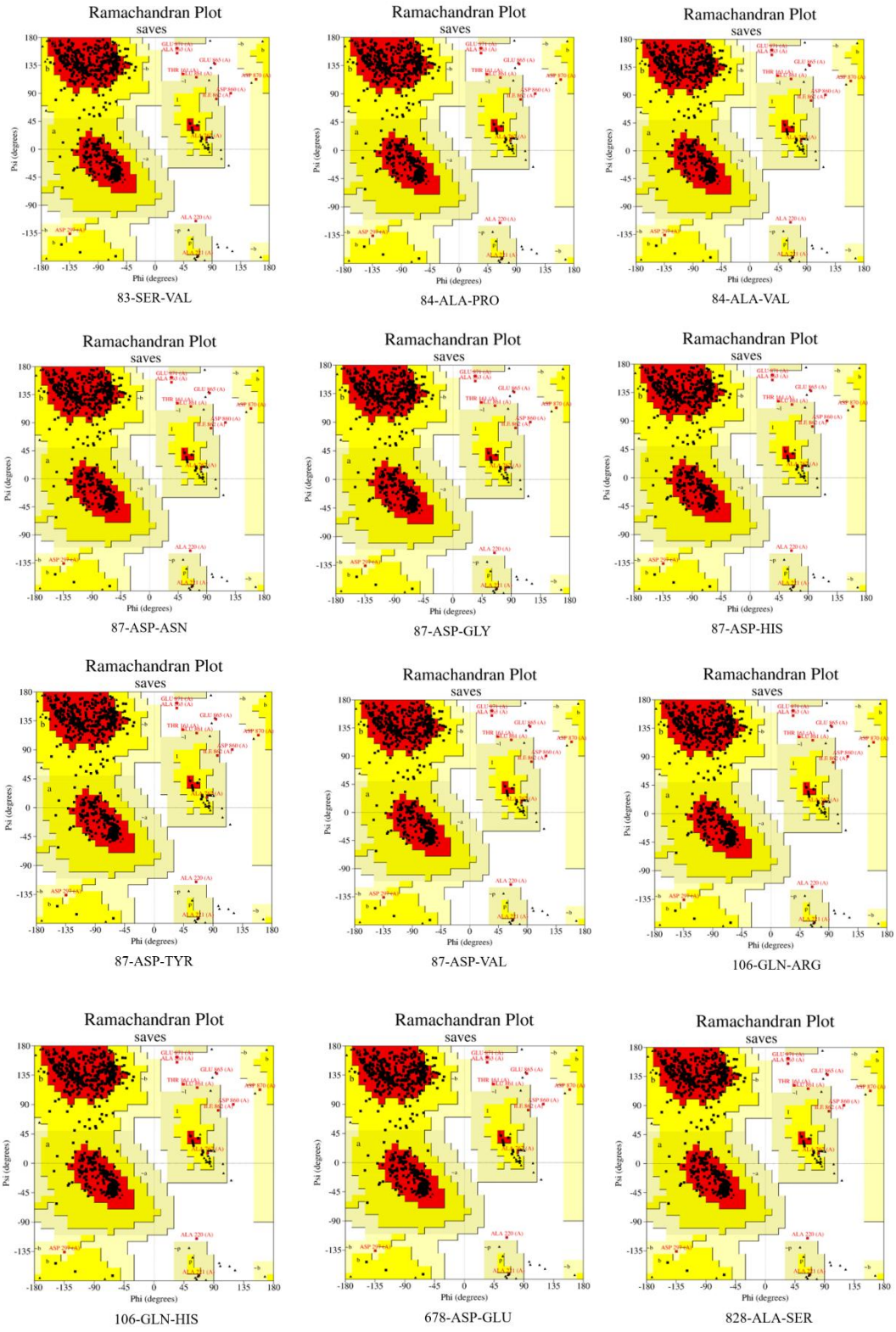


Fig. S1 Ramachandran plot of *E. coli* subunit A mutant protein

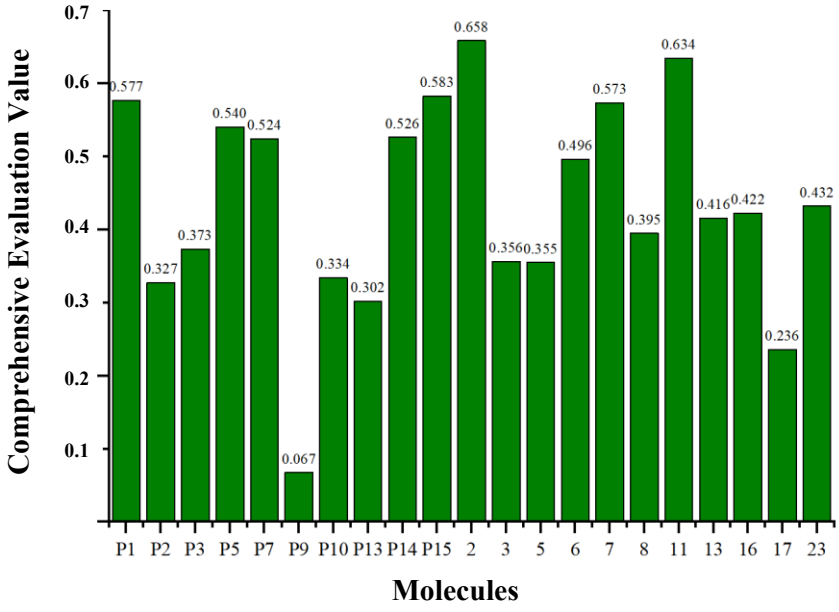
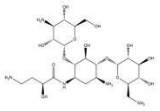
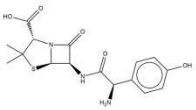
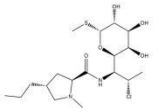
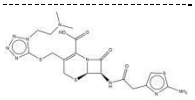
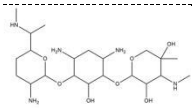
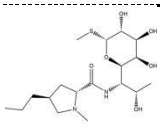
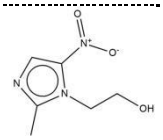
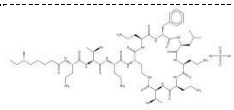
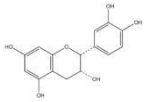
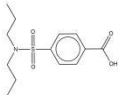
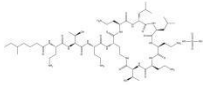
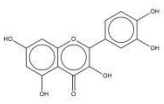


Fig. S2 Comprehensive evaluation value of QNs' ability to inhibit *E. coli* VGT

Table S1 Common sites and mutation directions of DNA gyrase subunit A resistance to QNs in *E. coli*

Mutation site	Amino acids			Mutant amino acids		
51 （Evans-Roberts et al., 2016）	A	ALA	Alanine	V	VAL	Valine
67 （Yoshida et al., 1990）	A	ALA	Alanine	S	SER	Serine
81 （Yoshida et al., 1990）	G	GLY	Glycine	D	ASP	Aspartic acid
				C	CYS	Cysteine
82 （Oram and Fisher, 1991）	D	ASP	Aspartic acid	G	GLY	Glycine
83 （Oram and Fisher, 1991）	S	SER	Serine	A	ALA	Alanine
				L	LEU	Leucine
				W	TRP	Tryptophan
				V	VAL	Valine
84 （Yoshida et al., 1990）	A	ALA	Alanine	P	PRO	Proline
				V	VAL	Valine
87 （Yoshida et al., 1990）	D	ASP	Aspartic acid	N	ASN	Asparagine
				G	GLY	Glycine
				H	HIS	Histidine
				Y	TYR	Tyrosine
				V	VAL	Valine
106 （Yoshida et al., 1990）	Q	GLN	Glutamine	R	ARG	Arginine
				H	HIS	Histidine
678 （Cullen et al., 1989）	D	ASP	Aspartic acid	E	GLU	Glutamic acid
828 （Cullen et al., 1989）	A	ALA	Alanine	S	SER	Serine

Table S2 Structures, categories, and uses of drugs used for suppressing *E. coli* VGT

Drug	Structural diagram	Category	Purpose	Reference
Amikacin		Aminoglycoside antibiotics	Anti-bacterial infection	（Ramirez and Tolmasky, 2017）
Amoxicillin		Penicillin antibiotics	Anti-bacterial infection	（Mhmoud et al., 2014）
Clindamycin		Lincomycin antibiotics	Anti-bacterial infection	（Drinkovic et al., 2001）
Cefotiam		Cephalosporin antibiotics	Anti-bacterial infection	（Hashiguchi et al., 2020）
Gentamicin		Aminoglycoside antibiotics	Anti-bacterial infection	（Moulds and Jeyasingham, 2010）
Lincomycin		Lincomycin antibiotics	Anti-bacterial infection	（Wang et al., 2012）
Metronidazole		5-nitroimidazole antibiotics	Anti bacterial and some protozoan infections	（Ceruelos et al., 2019）
Polymyxin B		Polymyxin antibiotics	Anti-bacterial infection	（Zavascki et al., 2007）
B4964		Flavanol compounds	Associated with anti-inflammatory, cardiovascular health, and some potential anti-cancer properties	（Xu et al., 2024）
Pentostam		Antiparasitic Agents	Treating helminth and parasitic infections	（Herwaldt and Berman, 1992）
Colistin sulfate-E		Polymyxin antibiotics	Anti-bacterial infection	（Guo et al., 2021）
Quercetin		Plant flavonoids	Antioxidant, anti-inflammatory, anti-allergic, anti-tumor, and	（Ulusoy and Sanlier, 2020）

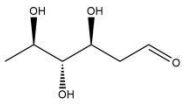
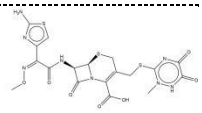
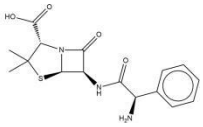
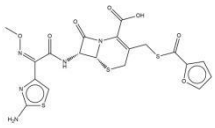
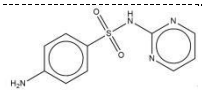
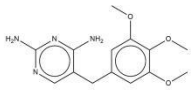
			cardiovascular protection	
2,6-Dideoxy-D-ribo-hexose		Cephalosporin antibiotics	Anti-bacterial infection	（Roush and Brown, 1982）
Ceftriaxone		Cephalosporin antibiotics	Anti-bacterial infection	（Richards et al., 1984）
Ampicillin		Penicillin antibiotics	Anti-bacterial infection	（Campoli-Richards and Brogden, 1987）
Ceftiofur		Cephalosporin antibiotics	Anti-bacterial infection	（Dutil et al., 2010）
Sulfadiazine		Sulfonamide drugs	Anti-bacterial infection	（Schauss et al., 2009）
Trimethoprim		Folate reductase inhibitor drugs	Anti-bacterial infection	（Eliopoulos and Huovinen, 2001）

Table S3 Results of protein sequence similarity comparison

Protein	Seq Similarity	QSQE
51-VAL	0.6	0.81
67-SER	0.6	0.78
81-ASP	0.6	0.8
81-CYS	0.6	0.8
82-GLY	0.6	0.78
83-ALA	0.6	0.81
83-LEU	0.6	0.81
83-TRP	0.6	0.8
83-VAL	0.6	0.81
84-PRO	0.6	0.8
84-VAL	0.6	0.81
87-ASN	0.6	0.8
87-GLY	0.6	0.8
87-HIS	0.6	0.79
87-TYR	0.6	0.8
87-VAL	0.6	0.8
106-ARG	0.6	0.81
106-HIS	0.6	0.8
678-GLU	0.6	0.8
828-SER	0.6	0.8

Table S4 Molecular docking results of QNs and subunit A protein before and after drug-resistant mutations

Ligand	GyrA	81-ASP	81-CYS	82-GLY	83-LEU	83-TRP	83-ALA	83-VAL	84-PRO	84-VAL
P1	-5.7	-4.4	-2.5	-4.8	-3.9	-3.5	-4.9	-3.1	-2.3	-2.4
P2	-4.8	-2.5	-3.8	-2.9	-2.7	-3.2	-3.6	-2.9	-2.7	-2.9
P3	-3.9	-2.9	-3.6	-3.6	-3.7	-3.7	-3.7	-3.5	-2.7	-3.6
P4	-4.1	-3.5	-2.3	-3.2	-3.6	-4.4	-4	-4.9	-3.1	-3.4
P5	-4.3	-2.6	-2.7	-2.9	-2.9	-2.7	-2.9	-4.7	-2.6	-3.1
P6	-3.1	-2.1	-2.7	-2.4	-2.8	-3.8	-2.4	-3.1	-1.9	-2
P7	-4.6	-3.4	-3.4	-3.3	-3.7	-3.6	-3.1	-4.4	-2.9	-3.6
P8	-3.7	-4.8	-3.2	-2.2	-3.2	-3.8	-4.5	-4.3	-3.2	-3.9
P9	-3.2	-4	-3.7	-3.5	-3.7	-2.7	-4.1	-4.8	-3.4	-2.2
P10	-3	-3.4	-2.8	-3.4	-3.4	-3.6	-3.4	-3.6	-2.7	-3.9
P11	-4.6	-4.6	-3.5	-2.9	-4.4	-4.3	-2.9	-4.5	-2.7	-2.2
P12	-5.9	-3.3	-3.4	-4.9	-4	-4.1	-4.8	-4.8	-3.1	-3
P13	-4.8	-2.8	-2.7	-2.3	-2.5	-2.7	-2.3	-2.7	-2.1	-2.7
P14	-3.7	-3	-3.6	-2.9	-2.8	-4.7	-2.9	-3.9	-2.8	-3.2
P15	-4.5	-2.9	-2.7	-2.4	-2.7	-3	-3	-3.5	-1.9	-2.4
P16	-4	-2.8	-2.4	-2.6	-2.9	-3.1	-2.8	-3.4	-2.2	-2.7
1	-5.9	-4.4	-3.4	-3.2	-3.7	-4.7	-3.4	-3.3	-5.5	-2.9
2	-5.2	-4.5	-4	-3.5	-3.4	-3.6	-4.2	-3.3	-4.6	-4.2
3	-4.6	-3	-2.9	-3	-3.3	-3.5	-3.3	-3.3	-2.4	-2.8
4	-5.1	-3.7	-4.1	-2.7	-4.7	-4.4	-2.8	-3.6	-2.8	-3.1
5	-4.4	-3.3	-3.2	-3	-3.9	-3.2	-3.7	-3.2	-3.7	-2.9
6	-3.5	-2.9	-2.8	-2.7	-3.6	-3.2	-2.9	-3.2	-2.9	-2.7
7	-4.3	-2.9	-2.9	-2.9	-2.9	-2.9	-2.8	-2.8	-2.3	-2.7
8	-5.4	-3	-2.9	-2.8	-2.8	-2.7	-2.7	-3.4	-2.6	-3.2
9	-3.9	-1.6	-2.5	-3.3	-2.2	-2.3	-3.7	-3	-2.9	-1.1
10	-3.7	-3.3	-3.7	-3.1	-3.4	-3.1	-3.4	-2.9	-2.9	-2.9
11	-4.2	-3.9	-3.1	-2.9	-2.7	-4.2	-2.9	-3.2	-2.5	-3.2
12	-5.1	-3.5	-3.3	-3.6	-3.7	-3.8	-3.6	-3.8	-3.9	-3.3
13	-6.7	-3.2	-2.7	-3.1	-3.4	-3.4	-3.3	-3.4	-2.6	-3.1
14	-4.8	-2.4	-2.6	-2.3	-2.4	-4.8	-2.4	-3.9	-2.3	-2.7
15	-3.4	-5.5	-6.2	-4.9	-3.6	-5.7	-3.4	-3.9	-3.7	-1.3
16	-4.3	-3.3	-3.2	-3	-3.9	-3.2	-3.7	-3.2	-3.7	-2.9
17	-3.9	-3.5	-3.4	-3.4	-3.7	-3.3	-3.6	-3.6	-3.2	-3.4
18	-4.6	-3.9	-3.3	-3.2	-3.7	-3.8	-3.4	-3.8	-2.7	-2.6
19	-4	-3.4	-4	-3.2	-4.2	-3.9	-4.2	-3.8	-2.7	-3.1
20	-5.2	-4.4	-3.3	-3.9	-2.3	-3.9	-3.4	-3.8	-3.2	-3.4
21	-4.8	-4.7	-2.9	-2.7	-3.9	-4.6	-2.7	-3.8	-2.4	-4.2
22	-4.9	-3.1	-3	-2.9	-3.7	-4.6	-3.6	-4.7	-3.6	-3
23	-5.7	-3.7	-3.2	-3.5	-4.1	-3.7	-4.4	-2.8	-3.5	-3
24	-4.1	-4.4	-4.6	-3.3	-3.7	-3.4	-3.4	-3.8	-2.8	-4.2
25	-4.7	-3.5	-3.7	-3.4	-4.8	-2.4	-3.4	-3.9	-2.8	-2.5
26	-5.9	-2.7	-1.9	-2.4	-2.8	-2.9	-2.4	-3.3	-2.4	-3.2
27	-4.2	-3.2	-3.4	-3.3	-4.4	-2.2	-3.5	-3.9	-2.6	-3.6
28	-4.9	-3.5	-3.3	-3.2	-3.7	-3.8	-3.4	-3.8	-3.3	-3.3
29	-5.4	-4.4	-3.9	-3.3	-2.3	-3.9	-4.4	-3	-4	-3.1

P1	-3.7	-2.6	-3.6	-2.2	-3.7	-3.5	-3.1	-3.2	-2.5	-3.3	-3.4
P2	-2.3	-2.1	-2.8	-4	-2.4	-3.3	-2.6	-4.2	-3.8	-3.7	-3.1
P3	-3.9	-3.7	-3.7	-3.7	-2.1	-3.6	-2.1	-3.1	-3.2	-2.1	-2.6
P4	-3.9	-3.5	-2.4	-3.5	-3.5	-3.6	-2.8	-3.4	-2.1	-3.2	-2.3
P5	-4.4	-4.4	-1.1	-4.2	-4.1	-4.4	-3.2	-3.2	-3.5	-3.9	-3.5
P6	-4.6	-4.7	-2.5	-4.3	-4.6	-3.9	-3.2	-2.1	-4.5	-4	-4.5
P7	-3.2	-3.8	-2.9	-2.2	-3.7	-3.7	-2.7	-4	-4.3	-3.8	-4.1
P8	-2.5	-3.6	-3.4	-1.9	-3.2	-3	-2.8	-2.3	-3.2	-3.4	-2
P9	-2.9	-3.7	-3.6	-3.2	-4	-1.9	-3.4	-3.1	-3.9	-3.4	-2.9
P10	-4	-3.8	-2.7	-3.6	-4	-4.4	-2.8	-3.5	-4.1	-3.5	-1.7
P11	-3.8	-3	-3.4	-3	-3.2	-2.3	-3.3	-3.5	-3.3	-3.9	-2.2
P12	-3.9	-3.5	-3.4	-3.5	-3.1	-2.3	-3.3	-3.5	-3.3	-3.9	-2.9
P13	-2.3	-2.5	-2.1	-4.4	-4.1	-4	-2.9	-3.6	-3.8	-3.4	-3.3
P14	-3.5	-3.1	-3.2	-4.3	-2.3	-4.2	-3.1	-3.7	-4.2	-3.7	-1.7
P15	-2.1	-1.4	-4.2	-3.6	-4.5	-4.3	-3.6	-3.9	-2.7	-4.3	-3.2
P16	-4.6	-4.6	-3.2	-3.5	-4.3	-3.2	-3.1	-4.5	-3.4	-4.3	-3.5
1	-3.4	-3.2	-1.7	-3.5	-3	-3.7	-2.9	-2.7	-1.9	-3.2	-3.7
2	-2.9	-3.3	-2.3	-2.1	-4.1	-3.7	-2.9	-1.7	-3.2	-4.2	-3.2
3	-4.2	-4.2	-3.8	-3.3	-3.8	-4.1	-2.9	-3.7	-4.1	-3.8	-4
4	-2.5	-3.4	-3.2	-2.6	-3.6	-3.5	-3.1	-3.8	-2.8	-3.7	-3.6
5	-3.1	-2.1	-3.7	-3.7	-4.3	-2.9	-3.1	-3.5	-4.2	-3.5	-3.6
6	-3.6	-3.2	-3.1	-3	-4.1	-3.8	-3.2	-4	-4.2	-3.9	-4.4
7	-3.6	-4.3	-2.2	-4.3	-3.9	-3.7	-3.3	-3.3	-4.3	-3.5	-2.9
8	-4.3	-4.2	-3.8	-3.5	-4	-4.1	-3.4	-3.3	-4.5	-3.5	-3.2
9	-2.1	-3.8	-2.3	-2.1	-2.8	-2	-2.6	-3.2	-1.7	-3.1	-3.5
10	-4	-4.1	-3.5	-4	-4.2	-3.9	-3.4	-4	-3.5	-4.6	-3.8
11	-4.2	-4.2	-3.5	-3.8	-4.2	-4.3	-3.6	-4.5	-4.5	-4.5	-3.7
12	-3.7	-3.8	-3.4	-3.5	-4	-3.1	-1.7	-3.6	-3.3	-3.7	-3.5
13	-4	-4.1	-3.4	-3.4	-3.8	-4.1	-2.6	-3.3	-4.2	-3.7	-4.6
14	-4.8	-4.6	-2.9	-4.8	-4.6	-2.6	-3.7	-3.9	-3.7	-4.5	-4.5
15	-3.9	-2.2	-2.2	-2.2	-2.5	-3.6	-2.5	-2.4	-2.8	-3.2	-4.3
16	-4.1	-4.1	-3.7	-3.7	-4.3	-3.9	-3.1	-3.5	-4.2	-3.5	-4.1
17	-3.7	-4	-2.6	-3.8	-3.9	-3.9	-2.8	-3.1	-4.1	-3.5	-3.7
18	-3.9	-2.8	-3.1	-3.8	-4.2	-3.8	-2.8	-4	-3.3	-4.3	-4.5
19	-3.6	-3.6	-1.6	-2.4	-4.2	-4.3	-3.3	-3.7	-3.4	-4.1	-4.4
20	-3.9	-1	-3.4	-3.5	-2.9	-1.8	-2.8	-3.6	-2.2	-3.9	-3.9
21	-3.7	-3.9	-1.4	-3.5	-3.7	-3.6	-3.1	-3.2	-3.4	-4.6	-3.6
22	-3.8	-3.8	-3.4	-3.5	-4.2	-3.6	-2.2	-2.1	-2.5	-3.3	-3.4
23	-4.3	-4	-1.8	-2.4	-4.1	-4	-3.2	-3.6	-4.2	-3.6	-4.1
24	-4	-3.8	-2.1	-3.5	-3.1	-3.6	-3.4	-2.8	-3.8	-4.1	-3.5
25	-3.9	-2.9	-3.4	-3.5	-2.9	-3.2	-3.2	-3.3	-3.1	-3.9	-4
26	-4.3	-4.6	-3.6	-2.8	-4.2	-3.5	-2.8	-4.3	-3.5	-4	-4.3
27	-3.5	-4.2	-2.9	-3.5	-3.9	-3.6	-2.6	-3.7	-3.4	-4.6	-4.2
28	-3.9	-2.3	-1.4	-3.5	-3.9	-3.6	-2.2	-3.6	-3.7	-3.6	-4.7
29	-2.6	-2.5	-2.2	-3.6	-4.1	-3.4	-2.4	-3	-3.3	-3.7	-3.7

Table S5 Subunit A amino acid resistance mutation probability (SIFT predicted value) and mutation weight coefficient

Pos	1M	…	51A	67A	81G	82D	83S	84A	87D	106Q	678D	828A	…	875E
A	0		1	1	0	0	0.02	1	0.02	0.02	0.08	0.44		0.15
C	0		0.01	0	0	0	0	0	0	0	0.02	0.04		0.01
D	0		0.01	0	0	1	0.01	0	1	0.03	1	1		0.84
E	0		0.01	0	0	0	0.01	0	0.68	0.03	1	0.49		1
F	0		0	0	0	0	0	0	0	0	0.01	0.04		0.01
G	0		0.51	0	1	0	0.01	0.02	0.07	0.03	0.63	0.67		0.08
H	0		0	0	0	0	0	0	0	0.43	0.07	0.16		0.04
I	0		0	0	0	0	0.01	0	0	0.01	0.01	0.05		0.03
K	0		0.01	0	0	0	0.01	0	0.02	0.05	0.22	0.35		0.16
L	0		0.01	0	0	0	0.06	0	0	0.01	0.02	0.09		0.05
M	1		0	0	0	0	0	0	0	0	0.01	0.03		0.02
N	0		0	0	0	0	0.02	0	0.01	0.03	0.78	0.86		0.1
P	0	…	0.02	0	0	0	0.01	0.01	0.01	0.01	0.06	0.17	…	0.07
Q	0		0	0	0	0	0.07	0	0.1	1	0.07	0.24		0.15
R	0		0	0	0	0	0.01	0	0	0.04	0.06	0.18		0.07
S	0		0.35	0	0	0	1	0.45	0.01	0.02	0.27	0.56		0.12
T	0		0.01	0	0	0	0.42	0.01	0.01	0.01	0.08	0.25		0.09
V	0		0.01	0	0	0	0.01	0.01	0	0.01	0.02	0.08		0.04
W	0		0	0	0	0	0	0	0	0	0.01	0.02		0.01
Y	0		0	0	0	0	0	0	0	0.01	0.04	0.08		0.02
	-		0	0	0	0	0	0	2.94%	18.05%	41.98%	23.51%		-
	-		-	-	0	-	2.52%	0	0	0	-	-		-
WC	-		-	-	-	-	0	-	0	-	-	-		-
	-		-	-	-	-	0	-	0	-	-	-		-
	-		-	-	-	-	-	-	0	-	-	-		-

Note: WC represents the weight coefficient.

Table S6 Molecular docking results of QNs analog molecules with protein after drug-resistant mutations in subunit A

QNs	51-VAL	67-SER	81-ASP	81-CYS	82-GLY	83-ALA	83-LEU	83-TRP	83-VAL	84-PRO	84-VAL	87-ASN	87-GLY	87-HIS	87-TYR	87-VAL	106-ARG	106-HIS	678-GLU	828-SER
PM-1	-6.5	-4.2	-6.2	-6.2	-5.8	-6.8	-7.0	-6.4	-6.8	-6.7	-7.4	-8.6	-8.0	-8.1	-8.2	-8.4	-6.8	-6.8	-4.8	-6.4
PM-2	-6.3	-5.1	-5.9	-6.1	-6.5	-7.5	-7.1	-7.9	-7.0	-8.2	-8.0	-8.5	-8.1	-8.3	-8.1	-8.1	-7.4	-7.4	-5.3	-7.0
PM-3	-5.5	-5.3	-6.2	-6.2	-5.9	-7.7	-6.8	-6.1	-7.1	-7.0	-8.0	-7.3	-7.6	-8.6	-7.9	-8.7	-9.1	-9.1	-5.2	-5.7
PM-4	-5.1	-3.6	-6.3	-6.4	-6.3	-7.3	-7.4	-6.6	-7.2	-7.3	-7.2	-8.7	-8.2	-8.7	-8.3	-8.5	-6.2	-6.2	-4.7	-6.0
PM-5	-6.2	-4.9	-5.7	-6.1	-5.8	-7.6	-8.0	-8.0	-6.8	-8.0	-7.1	-8.5	-8.1	-8.0	-8.1	-8.2	-6.9	-6.8	-5.4	-7.5
PM-6	-4.7	-4.3	-6.1	-5.9	-5.6	-6.7	-7.1	-7.1	-6.6	-6.8	-7.0	-7.8	-7.8	-8.1	-8.0	-8.0	-6.6	-6.5	-4.9	-6.3
PM-7	-4.8	-4.4	-6.0	-5.9	-5.6	-6.7	-7.1	-7.2	-6.6	-6.8	-7.0	-7.7	-7.8	-8.1	-8.1	-8.0	-6.7	-6.5	-4.8	-6.3
PM-8	-5.4	-5.6	-6.5	-6.1	-5.3	-6.8	-6.5	-7.9	-6.3	-7.9	-6.5	-8.4	-8.4	-9.2	-8.5	-8.3	-8.3	-6.1	-6.7	-6.0
PM-9	-6.0	-5.6	-6.4	-6.2	-5.9	-6.8	-7.0	-7.7	-6.9	-7.5	-6.8	-8.5	-7.7	-8.7	-8.5	-8.7	-7.4	-7.5	-5.6	-6.3
PM-10	-4.3	-6.0	-7.4	-6.7	-6.5	-7.0	-6.6	-6.9	-7.2	-6.9	-7.9	-7.8	-6.6	-6.6	-7.8	-8.5	-6.5	-6.3	-5.6	-6.6
PM-11	-6.5	-4.4	-7.3	-7.3	-7.1	-7.1	-7.0	-7.6	-7.3	-8.4	-7.6	-8.6	-8.7	-8.9	-8.8	-8.8	-2.9	-2.6	-4.9	-6.7
PM-12	-4.7	-4.4	-6.0	-5.8	-5.6	-6.7	-5.7	-7.2	-6.6	-6.8	-7.0	-7.8	-7.9	-8.1	-8.0	-8.1	-6.7	-6.5	-4.8	-6.3
PM-13	-6.2	-4.9	-6.3	-6.4	-5.7	-7.6	-7.3	-8.5	-7.6	-6.9	-8.7	-8.1	-8.7	-9.2	-9.7	-9.9	-7.8	-6.9	-5.6	-6.6
PM-14	-6.1	-5.0	-6.0	-5.9	-5.9	-7.4	-6.7	-7.2	-7.1	-5.5	-7.7	-8.2	-7.9	-7.8	-7.9	-8.2	-7.5	-7.7	-5.1	-6.5
PM-15	-6.1	-5.0	-5.8	-5.8	-6.0	-7.3	-5.6	-7.0	-6.6	-7.5	-7.6	-8.2	-8.0	-8.1	-7.9	-7.7	-6.7	-6.7	-5.2	-5.9
PM-16	-4.4	-3.2	-5.1	-5.1	-5.0	-6.6	-7.1	-6.9	-6.5	-6.9	-6.0	-7.8	-7.9	-8.1	-7.9	-7.8	-7.0	-6.6	-3.9	-4.8
PM-17	-4.3	-3.6	-4.6	-4.4	-4.6	-6.9	-7.0	-5.4	-6.6	-6.6	-5.5	-6.9	-5.7	-6.0	-6.8	-6.3	-5.1	-5.0	-3.5	-4.2
PM-18	-4.0	-3.4	-5.7	-4.3	-4.7	-6.4	-6.2	-6.6	-6.2	-6.7	-5.8	-7.0	-7.3	-7.8	-7.5	-7.5	-5.3	-5.4	-3.6	-4.7
PM-19	-3.7	-4.5	-7.6	-7.1	-7.9	-8.2	-8.0	-8.2	-8.3	-8.1	-9.2	-7.7	-9.4	-6.9	-8.9	-9.7	-8.7	-8.6	-5.5	-7.3
PM-20	-4.8	-4.3	-6.2	-5.4	-5.5	-5.4	-4.8	-6.7	-6.3	-5.1	-3.2	-4.6	-8.4	-6.9	-8.2	-6.6	-6.7	-6.5	-4.8	-5.8
PM-21	-5.0	-5.6	-7.2	-7.6	-7.8	-8.0	-8.6	-8.2	-8.1	-7.7	-8.9	-8.8	-9.8	-9.5	-8.9	-8.3	-7.4	-7.3	-5.6	-8.0
PM-22	-5.9	-4.5	-7.3	-6.7	-6.8	-7.7	-7.9	-8.5	-7.3	-6.6	-6.9	-8.8	-9.0	-7.5	-8.0	-8.5	-7.2	-7.2	-4.8	-7.3
PM-23	-5.9	-4.6	-6.3	-7.1	-6.6	-6.9	-7.5	-7.3	-7.6	-8.1	-7.0	-8.4	-8.5	-8.1	-8.9	-8.6	-8.4	-8.2	-4.9	-6.6
PM-24	-6.4	-3.5	-6.5	-7.2	-6.8	-7.3	-7.9	-7.8	-7.2	-7.9	-7.3	-8.2	-7.7	-7.9	-8.5	-7.7	-5.6	-6.6	-5.1	-7.4
PM-25	-6.1	-4.3	-6.8	-6.4	-5.3	-7.0	-8.4	-6.1	-7.2	-7.0	-7.1	-8.0	-9.9	-8.1	-7.9	-8.6	-4.9	-6.5	-5.5	-6.8
PM-26	-4.8	-4.2	-6.7	-5.9	-7.2	-6.7	-8.0	-7.3	-6.6	-6.6	-6.4	-6.8	-8.0	-7.7	-7.6	-8.1	-3.5	-3.6	-5.9	-7.2
PM-27	-6.2	-4.8	-7.1	-6.8	-6.7	-7.0	-7.4	-7.4	-7.0	-7.1	-7.5	-7.8	-7.9	-8.8	-8.7	-9.3	-4.3	-4.3	-5.4	-7.3
PM-28	-4.7	-4.9	-7.5	-7.2	-6.4	-8.3	-8.4	-9.7	-8.2	-9.1	-9.1	-7.1	-8.7	-9.5	-7.5	-7.2	-7.2	-7.3	-5.8	-8.4
PM-29	-5.2	-4.7	-6.9	-6.5	-6.0	-7.8	-7.7	-7.3	-7.3	-8.5	-8.0	-9.0	-8.9	-8.5	-8.7	-8.7	-7.4	-7.5	-5.6	-7.6
PM-30	-4.8	-4.7	-6.8	-6.9	-6.1	-7.9	-8.1	-8.0	-6.7	-8.1	-8.5	-8.7	-8.6	-8.5	-9.5	-9.1	-7.1	-7.0	-5.7	-7.7
PM-31	-5.8	-3.9	-5.7	-5.8	-6.2	-7.5	-8.0	-7.3	-8.2	-6.3	-7.3	-8.2	-8.4	-8.7	-8.3	-9.4	-5.8	-4.4	-4.2	-7.1
PM-32	-3.2	-4.1	-6.3	-6.0	-6.1	-7.1	-7.6	-6.8	-6.7	-7.8	-8.0	-8.5	-8.1	-8.3	-7.6	-8.1	-6.7	-6.7	-4.6	-6.4
PM-33	-3.9	-4.0	-5.9	-6.2	-5.3	-8.1	-8.5	-7.5	-6.6	-9.1	-8.3	-8.9	-8.7	-8.5	-8.7	-9.1	-7.0	-7.0	-5.5	-8.1
PM-34	-4.1	-2.2	-5.1	-5.6	-4.9	-6.0	-5.0	-6.2	-4.8	-6.8	-7.0	-6.5	-5.1	-7.3	-6.5	-6.7	-6.7	-4.8	-4.8	-5.8
PM-35	-4.8	-3.2	-4.3	-4.0	-5.6	-4.5	-4.8	-5.4	-5.6	-3.1	-7.0	-5.9	-7.3	-6.1	-7.3	-5.3	-6.6	-4.6	-3.7	-5.4
PM-36	-4.4	-4.4	-6.1	-4.3	-5.6	-3.9	-6.2	-5.3	-5.1	-4.8	-7.0	-7.7	-7.8	-7.3	-6.6	-7.1	-6.7	-6.6	-4.8	-6.2
PM-37	-1.3	-4.5	-7.0	-7.3	-6.2	-6.9	-7.8	-8.1	-7.1	-6.7	-7.5	-8.8	-7.9	-7.5	-8.8	-8.6	-6.7	-6.3	-4.6	-6.8
PM-38	-4.9	-4.4	-7.4	-7.2	-6.8	-7.4	-7.4	-7.7	-7.0	-7.0	-7.6	-7.6	-8.0	-8.8	-8.0	-9.2	-7.4	-8.2	-5.5	-7.1
PM-39	-6.7	-4.5	-7.2	-7.2	-5.9	-7.0	-8.8	-8.1	-7.6	-7.1	-7.9	-8.1	-8.6	-8.1	-8.5	-8.8	-8.3	-8.3	-5.1	-7.0
PM-40	-4.8	-4.4	-5.9	-4.3	-4.7	-1.9	-6.5	-6.6	-6.8	-6.9	-7.0	-6.7	-7.7	-7.4	-6.5	-8.7	-6.6	-6.5	-5.4	-7.5
PM-41	-5.6	-4.3	-5.7	-4.2	-2.3	-6.0	-6.5	-6.3	-6.2	-8.1	-5.6	-6.6	-6.2	-7.0	-7.6	-8.8	-6.7	-6.5	-4.8	-7.3
PM-42	-4.7	-2.2	-7.2	-6.5	-4.1	-3.8	-7.3	-6.6	-3.9	-5.7	-7.1	-5.5	-6.0	-6.9	-7.9	-6.1	-6.7	-6.5	-6.6	-6.2
PM-43	-4.8	-2.4	-6.2	-3.8	-5.6	-5.4	-7.6	-5.1	-7.0	-6.8	-1.7	-3.4	-7.9	-6.1	-5.9	-5.4	-6.6	-6.6	-4.8	-4.9
PM-44	-4.1	-2.3	-5.5	-4.7	-5.5	-6.8	-6.3	-6.5	-4.4	-6.8	-7.0	-3.2	-6.6	-5.5	-5.5	-4.7	-6.6	-6.5	-4.1	-4.8
PM-45	-5.8	-2.7	-4.4	-5.9	-5.5	-5.4	-4.1	-7.0	-3.3	-6.8	-7.0	-7.8	-7.8	-5.0	-6.6	-5.8	-6.6	-6.6	-4.8	-5.0

PM-46	-4.7	-3.1	-5.2	-4.1	-5.5	-3.0	-6.2	-3.9	-3.9	-1.1	-1.8	-5.8	-4.4	-6.9	-6.8	-5.3	-6.6	-6.5	-2.3	-5.4
PM-47	-4.8	-1.4	-5.5	-4.5	-3.1	-5.8	-6.3	-6.9	-3.5	-1.8	-3.6	-5.4	-5.9	-6.7	-5.4	-7.9	-6.6	-6.5	-3.3	-6.3
PM-48	-3.8	-4.4	-6.8	-5.0	-5.5	-2.8	-6.0	-6.5	-4.6	-6.1	-2.1	-6.1	-5.4	-5.8	-6.3	-7.7	-6.7	-6.5	-2.6	-5.8
PM-49	-3.4	-5.1	-7.7	-6.8	-5.7	-6.8	-7.3	-8.1	-9.2	-6.1	-8.5	-7.9	-6.7	-8.8	-8.1	-8.8	-5.6	-5.2	-5.5	-7.8
PM-50	-4.8	-4.4	-4.4	-5.0	-4.9	-4.7	-4.8	-6.0	-4.9	-4.7	-6.3	-4.4	-5.1	-5.2	-4.3	-4.9	-6.6	-4.9	-4.8	-5.7
PM-51	-4.7	-4.4	-6.3	-7.9	-4.9	-7.6	-7.0	-7.1	-6.7	-6.2	-7.1	-8.7	-8.7	-8.8	-8.7	-8.8	-8.9	-8.6	-5.5	-7.9
PM-52	-5.0	-4.7	-7.1	-6.8	-6.5	-7.2	-8.0	-8.0	-7.9	-7.1	-8.6	-8.9	-8.9	-8.7	-6.2	-4.9	-6.9	-6.1	-4.2	-6.5
PM-53	-6.8	-4.7	-6.8	-7.1	-6.7	-7.1	-7.5	-7.5	-7.3	-6.4	-8.2	-8.8	-9.1	-8.7	-5.8	-8.8	-8.8	-8.8	-4.9	-7.2
PM-54	-4.8	-4.4	-7.9	-7.3	-5.8	-8.2	-7.7	-6.5	-7.3	-8.1	-6.9	-8.7	-8.9	-9.0	-8.9	-6.6	-5.7	-3.5	-4.9	-6.5
PM-55	-5.7	-6.4	-6.3	-5.4	-5.6	-6.1	-4.8	-5.2	-6.2	-5.2	-4.6	-6.5	-4.1	-4.5	-5.8	-4.8	-3.9	-3.7	-4.9	-5.8
PM-56	-4.8	-4.8	-6.9	-6.9	-4.8	-6.7	-6.7	-7.4	-7.3	-6.0	-7.3	-7.7	-7.5	-7.4	-7.4	-7.0	-4.6	-4.6	-5.8	-6.6
PM-57	-1.2	-4.8	-7.5	-7.3	-4.5	-7.1	-7.6	-8.2	-7.3	-6.3	-7.3	-9.4	-8.1	-8.0	-7.8	-8.9	-7.1	-7.0	-5.0	-7.1
PM-58	-6.7	-5.9	-4.9	-5.6	-4.1	-5.6	-4.7	-5.6	-5.5	-4.4	-5.4	-4.7	-6.6	-4.8	-4.8	-5.1	-3.3	-4.3	-5.2	-4.1
PM-59	-6.9	-4.8	-6.5	-6.5	-5.5	-7.1	-7.2	-7.3	-6.8	-8.3	-8.3	-8.6	-8.0	-8.7	-7.9	-6.3	-6.5	-6.7	-5.1	-8.1
PM-60	-4.7	-4.5	-6.3	-6.2	-7.4	-6.8	-8.2	-7.1	-6.7	-6.5	-7.5	-7.9	-8.2	-8.1	-8.4	-8.9	-7.0	-6.8	-4.8	-8.0
PM-61	-4.8	-4.2	-6.9	-5.6	-4.9	-6.1	-6.2	-8.2	-7.4	-6.6	-5.8	-6.6	-8.1	-8.0	-8.1	-7.8	-6.2	-6.4	-3.4	-6.8
PM-62	-3.4	-4.0	-6.0	-5.9	-4.7	-7.1	-6.7	-7.7	-6.0	-8.0	-7.1	-7.4	-7.8	-7.8	-8.2	-7.9	-5.2	-5.5	-4.2	-6.9
PM-63	-4.8	-3.9	-6.1	-6.1	-6.0	-6.4	-7.7	-7.0	-6.9	-7.3	-6.6	-7.8	-8.4	-9.3	-8.8	-8.0	-6.0	-5.8	-5.7	-7.5
PM-64	-4.5	-5.2	-6.0	-6.3	-5.5	-7.8	-8.0	-8.1	-7.7	-6.5	-7.0	-7.8	-8.9	-8.9	-8.7	-9.1	-8.1	-8.0	-5.4	-7.0
PM-65	-4.3	-4.4	-7.1	-6.9	-5.4	-7.8	-7.4	-7.7	-7.4	-7.4	-7.7	-8.7	-8.0	-8.8	-9.5	-8.6	-7.7	-7.8	-4.9	-6.9
PM-66	-5.8	-4.6	-7.1	-7.1	-7.8	-8.1	-7.5	-8.1	-8.3	-7.9	-8.0	-8.6	-9.1	-9.2	-8.6	-8.0	-8.5	-8.6	-4.9	-6.6
PM-67	-4.2	-4.5	-6.4	-7.2	-6.0	-5.9	-8.5	-7.4	-7.3	-5.6	-7.7	-7.4	-8.1	-9.7	-9.4	-9.6	-7.7	-7.8	-5.8	-6.7
PM-68	-3.0	-4.4	-6.6	-7.1	-5.2	-6.3	-6.6	-7.8	-7.4	-7.2	-7.0	-7.9	-8.4	-7.9	-8.9	-8.0	-7.2	-2.2	-5.8	-6.8
PM-69	-4.6	-4.7	-6.7	-6.7	-6.7	-7.0	-7.6	-7.8	-6.9	-5.6	-7.6	-7.2	-5.2	-9.1	-7.9	-8.9	-6.8	-6.6	-5.4	-6.6
PM-70	-4.8	-4.9	-7.1	-6.9	-6.1	-8.5	-8.2	-8.5	-7.6	-8.0	-9.0	-8.6	-8.8	-5.6	-8.3	-9.1	-7.9	-8.1	-5.7	-7.5
PM-71	-3.8	-4.3	-7.0	-6.7	-5.3	-8.0	-7.5	-8.1	-6.6	-7.5	-8.1	-8.5	-7.9	-7.1	-7.6	-8.5	-7.9	-7.8	-5.1	-7.7
PM-72	-4.5	-4.4	-6.6	-6.7	-6.4	-7.3	-8.1	-7.6	-7.6	-7.7	-8.0	-8.8	-7.8	-8.5	-8.4	-8.4	-6.8	-7.1	-5.5	-7.3
PM-73	-4.8	-3.7	-4.9	-5.0	-4.5	-6.1	-6.4	-5.9	-5.9	-5.9	-6.9	-6.5	-7.0	-8.2	-7.6	-6.7	-3.3	-3.8	-4.0	-5.5
PM-74	-4.0	-4.1	-5.4	-5.9	-5.4	-8.0	-7.4	-6.7	-8.2	-8.3	-6.0	-8.2	-8.0	-8.3	-7.7	-7.8	-6.7	-6.7	-5.1	-6.8
PM-75	-3.9	-3.5	-6.5	-6.5	-5.6	-6.0	-8.2	-7.3	-6.0	-6.4	-6.6	-8.6	-7.3	-8.5	-8.3	-8.1	-6.3	-6.8	-4.5	-6.0
PM-76	-3.5	-4.2	-7.2	-6.2	-7.3	-8.3	-7.8	-7.8	-8.2	-6.3	-7.3	-7.7	-8.2	-5.5	-8.6	-8.6	-3.6	-3.8	-4.3	-7.4
PM-77	-4.0	-4.6	-7.0	-7.1	-5.8	-7.1	-8.1	-7.0	-8.1	-6.4	-7.2	-8.4	-8.2	-8.3	-8.8	-8.2	-6.4	-6.4	-4.5	-7.0
PM-78	-5.1	-4.7	-6.4	-6.5	-5.9	-6.9	-7.7	-7.1	-6.7	-6.6	-8.2	-8.7	-9.2	-9.1	-8.7	-8.8	-4.6	-5.4	-5.6	-7.3
PM-79	-4.8	-1.8	-4.8	-5.5	-2.4	-7.1	-5.6	-7.5	-6.3	-5.9	-5.6	-6.3	-7.4	-5.6	-7.3	-7.4	-6.6	-6.5	-1.8	-7.1
PM-80	-5.3	-2.8	-5.9	-5.0	-4.9	-5.8	-7.4	-7.1	-5.7	-5.1	-5.0	-8.1	-6.7	-6.7	-8.2	-6.5	-6.7	-6.5	1.0	-6.4
PM-81	-4.7	-3.0	-7.6	-5.7	-4.3	-5.7	-6.9	-6.8	-6.0	-3.0	-6.6	-8.1	-7.2	-7.6	-7.5	-6.9	-5.2	-5.2	-4.8	-5.6
PM-82	-5.8	-0.5	-2.3	-1.0	-0.7	-7.7	-6.6	-0.6	-1.3	-6.8	-7.0	-6.4	-7.8	-8.1	-4.9	-3.0	-6.6	-6.6	-1.0	-5.7
PM-83	-4.8	-2.7	-3.2	-2.7	-5.5	-6.6	-5.9	-4.9	-3.3	-3.4	-7.0	-7.8	-7.8	-6.1	-5.3	-6.5	-4.9	-5.0	-4.8	-6.0
PM-84	-6.1	-1.4	-5.0	-4.7	-5.5	-7.0	-6.0	-6.1	-5.7	-1.8	-7.3	-7.0	-6.3	-7.5	-8.1	-7.4	-6.7	-6.5	-3.1	-7.1
PM-85	-4.4	-2.4	-3.5	-3.6	-3.3	-6.0	-4.7	-6.1	-5.6	-0.9	-2.3	-4.7	-6.3	-6.1	-5.5	-4.4	-6.6	-6.6	-4.8	-5.7
PM-86	-5.7	-2.8	-5.3	-3.7	-5.8	-3.6	-6.5	-6.3	-5.7	-4.3	-5.6	-6.7	-6.4	-5.6	-6.6	-8.0	-6.7	-3.4	-3.7	-4.9
PM-87	-4.8	-4.4	-5.4	-5.1	-3.3	-3.0	-6.4	-5.2	-5.2	-6.6	-6.5	-6.0	-6.7	-7.3	-6.4	-7.4	-6.6	-6.5	-3.3	-5.2
PM-88	-5.5	-4.9	-7.0	-6.8	-7.6	-7.7	-8.0	-7.9	-7.3	-6.8	-7.9	-8.7	-8.8	-9.2	-8.7	-8.8	-7.3	-6.5	-5.0	-6.5
PM-89	-5.0	-3.9	-7.6	-7.3	-6.1	-7.8	-7.6	-8.0	-6.8	-6.5	-6.4	-9.0	-7.8	-8.9	-8.0	-4.5	-7.8	-7.8	-4.9	-7.7
PM-90	-6.9	-4.1	-7.7	-7.1	-6.7	-7.7	-8.8	-8.0	-7.3	-8.1	-7.4	-9.2	-8.4	-9.0	-8.6	-8.5	-6.7	-7.0	-5.5	-6.8
PM-91	-4.5	-2.8	-6.5	-6.5	-5.4	-6.7	-7.0	-7.3	-6.3	-5.5	-8.0	-8.4	-7.0	-8.2	-7.5	-8.0	-6.2	-5.6	-5.2	-7.2
PM-92	-3.3	-4.0	-6.7	-6.8	-7.2	-7.4	-7.7	-7.3	-6.9	-5.9	-7.2	-8.8	-7.5	-7.7	-7.6	-8.3	-5.8	-6.1	-5.9	-6.7
PM-93	-5.8	-4.5	-6.6	-6.5	-5.0	-5.7	-7.3	-7.2	-5.7	-6.3	-7.8	-8.4	-7.7	-8.2	-8.9	-8.5	-6.6	-6.5	-5.8	-6.6
PM-94	-4.8	-4.8	-6.4	-6.6	-5.3	-7.5	-8.4	-8.2	-7.4	-9.3	-8.1	-9.2	-7.8	-8.0	-8.5	-9.1	-6.3	-6.3	-4.5	-7.2

PM-95	-5.1	-3.7	-7.2	-7.1	-6.8	-6.4	-8.9	-7.6	-7.6	-7.9	-7.9	-7.9	-8.0	-7.6	-7.6	-8.4	-7.1	-7.0	-5.2	-7.2
PM-96	-4.7	-4.1	-6.6	-6.7	-5.8	-6.5	-7.3	-7.4	-7.7	-8.6	-7.8	-9.2	-8.2	-8.2	-8.9	-8.6	-8.2	-8.2	-5.3	-8.1
PM-97	-4.7	-3.9	-5.6	-5.9	-4.2	-5.5	-6.6	-6.1	-6.1	-5.9	-5.9	-6.7	-6.9	-7.5	-7.0	-7.3	-6.6	-6.5	-3.0	-5.8
PM-98	-1.0	-4.1	-6.7	-5.8	-4.9	-8.3	-7.5	-6.5	-6.3	-7.8	-7.7	-8.8	-7.6	-8.9	-7.8	-8.2	-7.4	-6.7	-4.6	-6.2
PM-99	-4.8	-3.9	-6.1	-6.4	-4.4	-8.1	-8.0	-8.6	-7.2	-6.4	-7.3	-8.4	-8.4	-9.5	-8.5	-8.3	-7.3	-7.3	-5.0	-6.0
PM-100	-5.7	-5.1	-6.3	-7.2	-6.1	-5.9	-6.1	-7.0	-6.1	-5.9	-6.7	-6.8	-7.3	-7.5	-7.5	-7.2	-5.4	-5.4	-4.6	-5.7
PM-101	-5.2	-5.7	-6.5	-6.2	-5.6	-6.4	-7.1	-7.3	-6.0	-6.6	-6.7	-8.3	-8.2	-8.6	-8.4	-7.3	-8.1	-8.1	-5.0	-5.7
PM-102	-5.7	-5.6	-6.2	-6.3	-6.0	-6.8	-6.5	-6.8	-6.9	-6.7	-6.2	-7.3	-7.3	-7.6	-7.9	-6.7	-7.7	-7.6	-5.0	-5.5
PM-103	-6.2	-4.4	-5.9	-5.5	-5.7	-7.2	-7.4	-8.2	-7.1	-8.4	-8.8	-8.2	-7.7	-8.4	-8.9	-6.8	-7.1	-7.7	-5.3	-6.8
PM-104	-4.6	-5.6	-6.3	-6.2	-5.9	-7.3	-6.7	-7.2	-6.7	-7.8	-7.7	-8.4	-8.4	-7.9	-8.7	-8.6	-8.2	-8.2	-5.2	-5.8
PM-105	-4.1	-4.7	-6.1	-6.5	-6.0	-7.2	-6.4	-7.4	-6.5	-7.9	-6.8	-7.8	-8.4	-7.8	-8.4	-8.1	-7.8	-7.6	-4.4	-6.0
PM-106	-3.6	-6.1	-5.1	-4.2	-4.3	-6.1	-5.7	-7.5	-5.8	-5.8	-6.6	-7.8	-7.5	-8.1	-8.2	-7.4	-6.9	-7.0	-3.9	-5.4
PM-107	-4.3	-3.8	-5.6	-5.2	-5.2	-6.2	-5.9	-6.8	-5.9	-6.5	-6.4	-7.4	-7.2	-7.9	-7.9	-7.8	-7.4	-7.4	-4.8	-4.7
PM-108	-5.3	-5.5	-5.8	-5.7	-5.8	-6.5	-6.6	-6.7	-6.3	-6.6	-6.3	-7.8	-7.4	-8.0	-8.1	-7.5	-7.7	-7.6	-5.0	-4.9
PM-109	-1.8	-5.0	-6.2	-6.0	-5.8	-6.1	-6.1	-7.2	-6.7	-7.4	-6.5	-7.8	-6.5	-8.8	-7.2	-8.6	-8.2	-7.6	-5.0	-6.0
PM-110	-2.3	-3.8	-6.0	-5.9	-5.8	-6.5	-5.9	-7.8	-5.8	-5.9	-6.6	-8.5	-6.1	-8.6	-8.4	-8.7	-7.2	-6.2	-4.9	-6.0
PM-111	-6.2	-4.4	-6.6	-6.0	-6.6	-6.7	-6.5	-6.3	-7.1	-5.8	-7.0	-6.6	-7.8	-7.3	-7.9	-7.9	-5.4	-5.3	-5.2	-5.4
PM-112	-3.6	-5.3	-6.4	-6.1	-6.3	-7.4	-7.2	-7.8	-7.2	-8.7	-7.0	-8.1	-7.9	-8.4	-8.2	-8.1	-8.1	-7.9	-5.4	-6.4
PM-113	-4.7	-4.5	-4.9	-5.8	-4.6	-6.1	-6.0	-7.5	-5.7	-6.5	-7.6	-7.5	-8.1	-7.1	-7.3	-8.2	-6.8	-5.3	-4.8	-4.6
PM-114	-5.1	-5.7	-6.3	-6.3	-6.2	-6.6	-7.8	-6.9	-6.8	-6.8	-8.1	-8.1	-8.3	-8.0	-8.1	-8.1	-8.3	-8.3	-4.9	-6.1
PM-115	-3.6	-5.3	-6.4	-6.1	-6.3	-7.4	-7.2	-7.8	-7.2	-8.7	-7.0	-8.1	-7.9	-8.4	-8.2	-8.1	-8.1	-7.9	-5.4	-6.4
PM-116	-4.7	-4.5	-4.9	-5.8	-4.6	-6.1	-6.0	-7.5	-5.7	-6.5	-7.6	-7.5	-8.1	-7.1	-7.3	-8.2	-6.8	-5.3	-4.8	-4.6
PM-117	-5.1	-5.7	-6.3	-6.3	-6.2	-6.6	-7.8	-6.9	-6.8	-6.8	-8.1	-8.1	-8.3	-8.0	-8.1	-8.1	-8.3	-8.3	-4.9	-6.1
PM-118	-4.8	-4.3	-6.1	-5.9	-5.9	-6.6	-6.1	-7.4	-6.3	-6.1	-6.3	-6.4	-7.1	-7.8	-7.7	-7.3	-6.2	-6.5	-6.0	-6.0
PM-119	-5.5	-5.4	-6.2	-6.4	-5.3	-6.4	-6.0	-7.0	-6.9	-7.1	-6.5	-8.1	-8.4	-8.4	-8.4	-7.6	-6.0	-3.8	-5.6	-5.8
PM-120	-5.5	-4.5	-6.1	-6.4	-5.7	-6.8	-7.1	-6.8	-7.5	-6.6	-6.7	-8.3	-7.0	-7.2	-8.8	-8.2	-6.9	-6.7	-5.0	-5.7
PM-121	-4.8	-4.7	-5.9	-6.3	-6.3	-7.0	-7.5	-8.5	-6.8	-8.2	-8.5	-8.1	-7.4	-8.5	-7.8	-5.2	-3.6	-7.8	-4.6	-5.9
PM-122	-3.7	-5.1	-6.2	-6.2	-5.1	-7.5	-6.5	-7.8	-7.5	-7.8	-7.7	-7.5	-8.0	-7.9	-8.2	-8.2	-6.8	-6.6	-4.6	-6.0
PM-123	-4.7	-4.4	-6.1	-5.8	-6.4	-6.1	-6.4	-7.6	-7.3	-6.8	-7.1	-7.5	-8.4	-8.3	-8.1	-8.3	-6.7	-6.5	-5.8	-6.0
PM-124	-4.5	-3.9	-4.4	-3.7	-5.5	-5.7	-5.4	-7.4	-5.8	-7.7	-5.1	-7.4	-8.1	-6.4	-7.6	-8.1	-6.7	-6.6	-2.5	-4.1
PM-125	-4.9	-3.5	-5.8	-5.7	-5.6	-7.3	-6.7	-6.5	-6.9	-6.7	-6.8	-7.7	-7.7	-8.3	-8.2	-7.8	-7.4	-7.3	-4.6	-5.3
PM-126	-5.0	-4.2	-5.5	-5.5	-5.5	-6.7	-6.2	-6.3	-6.1	-5.6	-6.6	-7.3	-7.6	-8.0	-7.5	-7.8	-4.2	-3.1	-4.5	-5.6
PM-127	-4.2	-5.5	-6.3	-6.3	-6.1	-7.8	-7.4	-8.6	-7.8	-8.7	-7.5	-7.3	-8.5	-8.9	-8.9	-8.4	-5.9	-4.0	-5.0	-6.1
PM-128	-6.3	-6.0	-6.3	-6.3	-5.3	-6.9	-8.2	-6.5	-7.2	-8.4	-8.6	-7.5	-8.5	-8.2	-8.1	-8.6	-6.8	-6.7	-5.2	-6.3
PM-129	-6.5	-5.4	-6.4	-6.3	-5.3	-7.1	-6.4	-6.2	-7.0	-8.2	-8.4	-7.1	-8.5	-7.9	-8.6	-8.6	-6.9	-6.9	-5.7	-6.5
PM-130	-3.4	-4.0	-4.3	-3.8	-2.8	-6.3	-5.3	-6.8	-4.9	-5.6	-4.3	-7.1	-6.9	-7.5	-7.1	-7.7	-4.8	-4.8	-3.3	-4.6
PM-131	-5.4	-6.0	-5.4	-5.4	-5.9	-7.0	-6.6	-6.0	-7.2	-6.2	-6.1	-7.6	-7.5	-8.3	-8.1	-7.7	-7.5	-7.5	-4.9	-5.4
PM-132	-6.0	-5.3	-5.4	-4.8	-6.3	-6.2	-6.5	-6.5	-6.5	-7.9	-7.1	-7.6	-7.9	-8.5	-8.0	-8.3	-7.5	-7.2	-5.1	-5.8

PM-133	-4.8	-4.3	-6.3	-6.5	-6.2	-7.1	-7.8	-8.5	-7.1	-7.1	-8.4	-8.3	-7.9	-7.8	-8.7	-8.4	-5.9	-5.8	-4.8	-6.2
PM-134	-6.1	-5.6	-6.3	-5.9	-5.3	-7.1	-8.1	-6.1	-7.3	-8.3	-8.0	-8.3	-8.3	-7.7	-7.7	-8.5	-6.6	-6.7	-6.2	-6.0
PM-135	-6.2	-5.5	-6.3	-5.8	-6.2	-7.1	-6.3	-6.4	-7.4	-8.3	-8.1	-8.1	-8.3	-7.9	-8.6	-8.6	-6.5	-6.6	-6.6	-6.2
PM-136	-0.2	-3.7	-4.9	-4.9	-4.8	-5.8	-5.7	-5.7	-5.5	-7.6	-5.0	-8.1	-7.9	-8.1	-8.2	-8.3	-4.7	-2.3	-3.9	-4.7
PM-137	-5.7	-5.2	-5.4	-5.5	-5.6	-6.8	-6.1	-5.8	-6.4	-6.8	-6.3	-7.8	-7.9	-8.5	-8.2	-7.6	-6.6	-6.5	-5.2	-5.6
PM-138	-5.9	-4.8	-5.3	-5.7	-5.8	-7.1	-6.2	-7.4	-6.2	-7.5	-6.2	-7.7	-7.4	-8.5	-7.8	-8.2	-7.3	-7.2	-5.4	-5.5
PM-139	-6.2	-6.1	-6.3	-5.9	-5.5	-8.0	-8.0	-7.5	-7.5	-8.1	-8.5	-8.2	-8.2	-8.0	-8.7	-8.3	-7.0	-7.1	-5.2	-6.4
PM-140	-4.8	-4.4	-6.0	-5.8	-5.5	-6.8	-7.0	-7.1	-6.6	-6.8	-7.0	-7.8	-7.8	-8.1	-8.0	-8.1	-6.7	-6.6	-4.8	-6.3
PM-141	-6.7	-5.6	-6.4	-6.2	-6.2	-7.9	-8.1	-8.0	-7.5	-7.6	-8.7	-7.7	-7.4	-8.1	-7.9	-9.0	-7.1	-7.1	-5.2	-6.5
PM-142	-4.4	-3.7	-4.8	-3.5	-4.6	-6.1	-5.7	-8.2	-6.2	-8.5	-5.9	-8.3	-8.2	-6.9	-8.2	-8.1	-6.6	-6.5	-3.4	-4.1
PM-143	-5.6	-6.2	-5.8	-5.5	-5.9	-6.8	-7.2	-7.6	-6.4	-7.3	-7.1	-8.0	-7.9	-8.5	-8.1	-7.9	-7.5	-7.4	-4.8	-5.5
PM-144	-5.8	-6.2	-5.5	-5.7	-5.9	-7.2	-7.1	-6.5	-6.9	-6.5	-7.5	-7.5	-8.0	-8.4	-7.9	-8.1	-7.3	-7.3	-5.5	-5.4
PM-145	-4.8	-4.2	-4.1	-4.2	-4.6	-6.2	-6.3	-6.3	-6.5	-4.1	-5.3	-7.7	-8.3	-8.6	-8.1	-8.0	-6.7	-6.5	-4.1	-5.3
PM-146	-4.9	-3.4	-4.8	-5.0	-3.9	-6.1	-6.6	-8.2	-6.1	-6.9	-8.4	-7.3	-6.0	-8.9	-8.5	-8.0	-6.7	-6.5	-2.5	-6.1
PM-147	-6.1	-4.0	-5.0	-5.1	-5.7	-6.6	-7.1	-7.3	-6.4	-7.9	-7.3	-4.5	-8.4	-5.3	-3.1	-4.1	-7.1	-7.3	-5.0	-6.4
PM-148	-1.8	-3.0	-3.6	-2.8	-1.4	-5.1	-5.8	-6.9	-5.9	-4.1	-3.6	-7.2	-7.5	-8.0	-8.2	-7.6	-3.8	-6.5	-2.9	-4.4
PM-149	-5.5	-5.1	-5.2	-5.0	-5.3	-7.5	-7.5	-6.6	-7.3	-6.3	-7.1	-7.9	-7.6	-8.3	-7.8	-7.6	-7.8	-7.8	-5.0	-5.8
PM-150	-6.0	-4.2	-5.4	-5.5	-5.2	-7.6	-6.9	-8.1	-7.4	-6.8	-6.6	-7.9	-7.7	-8.1	-8.0	-7.5	-7.1	-7.2	-5.2	-5.8
PM-151	-4.5	-3.6	-3.5	-3.5	-3.6	-5.6	-5.3	-5.6	-4.9	-5.1	-4.9	-7.3	-8.0	-7.6	-8.1	-7.8	-6.7	-6.5	-2.8	-3.8
PM-152	-5.8	-4.7	-5.2	-4.8	-5.4	-7.5	-6.8	-6.6	-7.0	-7.3	-8.1	-7.8	-8.1	-8.3	-8.3	-7.5	-8.0	-8.0	-5.5	-5.6
PM-153	-5.7	-4.8	-5.3	-5.4	-5.7	-7.4	-6.9	-8.1	-7.2	-7.9	-7.2	-7.9	-8.1	-8.2	-8.2	-7.8	-7.9	-8.0	-5.9	-6.0

Table S7 Effects of PM-55 and PM-58 alternative molecules on inhibiting *E. coli* VGT

Subunit A mutant protein	PM	PM-55	Change range (%)	PM-58	Change range (%)
51-VAL	-4.5	-5.7	26.67	-6.7	48.89
67-SER	-4	-6.4	60.00	-5.9	47.50
81-ASP	-3.5	-6.3	80.00	-4.9	40.00
81-CYS	-3.4	-5.4	58.82	-5.6	64.71
82-GLY	-3.6	-5.6	55.56	-4.1	13.89
83-ALA	-4.2	-6.1	45.24	-5.6	33.33
83-LEU	-3.3	-4.8	45.45	-4.7	42.42
83-TRP	-4.6	-5.2	13.04	-5.6	21.74
83-VAL	-4.2	-6.2	47.62	-5.5	30.95
84-PRO	-2.9	-5.2	79.31	-4.4	51.72
84-VAL	-3.3	-4.6	39.39	-5.4	63.64
87-ASN	-4.3	-6.5	51.16	-4.7	9.30
87-GLY	-2.1	-4.1	95.24	-6.6	214.29
87-HIS	-4.1	-4.5	9.76	-4.8	17.07
87-TYR	-3.7	-5.8	56.76	-4.8	29.73
87-VAL	-2.9	-4.8	65.52	-5.1	75.86
106-ARG	-1.7	-3.9	129.41	-3.3	94.12
106-HIS	-3.2	-3.7	15.63	-4.3	34.38
678-GLU	-4.2	-4.9	16.67	-5.2	23.81
828-SER	-3.2	-5.8	81.25	-4.1	28.13

Table S8 Environmental friendliness and functional assessment of QNs analog molecules

QNs	Environmental friendliness				Functionality	
	$\log t_{1/2}$	Change range (%)	$\log K_{ow}$	Change range (%)	*pLOEC*	Change range (%)
Activity value	2.730	-	1.385	-	7.271	-
PM-55	2.199	-19.45	0.567	-59.06	7.430	2.19
PM-58	2.041	-25.24	0.857	-38.12	8.039	10.56

Table S9 Comparison of non-covalent interactions between QNs before and after modification and subunit A mutant protein (87-VAL)

Binding system of PM with mutant protein				Binding system of PM-58 with mutant protein			
Type of forces	Number of forces	Average bond length (Å)	Percentage (%)	Type of forces	Number of forces	Average bond length (Å)	Percentage (%)
Hydrogen Bonds	6	2.79	42.86	Hydrogen Bonds	7	2.76	36.84
Hydrophobic Bonds	4	2.49	28.57	Hydrophobic Bonds	6	2.56	31.58
Cation-π Bonds	1	4.08	7.14	Halogen Bonds	1	3.07	5.26
Alkyl Hydrogen Bonds	1	4.24	7.14	Cation-π Bonds	1	4.30	5.26
Alkyl-π Interactions	1	4.97	7.14	Pi-Donor Hydrogen Bond	2	3.69	10.53
				Alkyl Hydrogen Bonds	1	4.29	5.26
Forces favoring binding	13	2.87	92.86	Forces favoring binding	18	3.06	94.74
Forces hindering binding	1	2.97	7.14	Forces hindering binding	1	2.33	5.26
Hydrophilic polar bond	6	2.88	42.86	Hydrophilic polar bond	7	3.51	36.84
Hydrophobic nonpolar bond	7	3.25	50.00	Hydrophobic nonpolar bond	11	2.56	52.63

Table S10 Changes in non-covalent interactions between PM-58 and mutant protein of subunit A of *E. coli* under drug combination scheme

Blank control group				Drug combination scheme system (Colistin sulfate-E)			
Type of forces	Number of forces	Average bond length (Å)	Percentage (%)	Type of forces	Number of forces	Average bond length (Å)	Percentage (%)
Hydrogen Bonds	5	2.6	62.50	Hydrogen Bonds	3	2.16	60.00
π-π Interactions	1	5.62	12.50	Pi-Donor Hydrogen Bond	1	4.16	20.00
Alkyl-π Interactions	1	4.53	12.50	Alkyl-π Interactions	1	4.99	20.00
Forces hindering binding	1	1.08	12.50				
Forces favoring binding	7	3.31	87.50	Forces favoring binding	5	3.13	100.00
Hydrophilic polar bond	7	3.71	87.50	Hydrophilic polar bond	4	2.66	80.00
Hydrophobic nonpolar bond	1	2.74	12.50	Hydrophobic nonpolar bond	1	4.99	20.00

References

Campoli-Richards D M, Brogden R N (1987). Sulbactam/ampicillin: a review of its antibacterial activity, pharmacokinetic properties, and therapeutic use. Drugs, 33(6): 577–609 doi:10.2165/00003495-198733060-00003

Ceruelos A H, Romero-Quezada L C, Ledezma J C R, Contreras L L (2019). Therapeutic uses of metronidazole and its side effects: an update. European Review for Medical and Pharmacological Sciences, 23(1): 397–401 doi:10.26355/eurrev_201901_16788

Cullen M E, Wyke A W, Kuroda R, Fisher L M (1989). Cloning and characterization of a DNA gyrase A gene from Escherichia coli that confers clinical resistance to 4-quinolones. Antimicrobial Agents and Chemotherapy, 33(6): 886–894 doi:10.1128/AAC.33.6.886

Drinkovic D, Fuller E R, Shore K P, Holland D J, Ellis-Pegler R (2001). Clindamycin treatment of Staphylococcus aureus expressing inducible clindamycin resistance. Journal of Antimicrobial Chemotherapy, 48(2): 315–316 doi:10.1093/jac/48.2.315

Dutil L, Irwin R, Finley R, Ng L K, Avery B, Boerlin P, Bourgault A M, Cole L, Daignault D, Desruisseau A, Demczuk W, Hoang L, Horsman G B, Ismail J, Jamieson F, Maki A, Pacagnella A, Pillai D R (2010). Ceftiofur resistance in Salmonella enterica serovar Heidelberg from chicken meat and humans, Canada. Emerging Infectious Diseases, 16(1): 48–54 doi:10.3201/eid1601.090729

Eliopoulos G M, Huovinen P (2001). Resistance to trimethoprim-sulfamethoxazole. Clinical Infectious Diseases, 32(11): 1608–1614 doi:10.1086/320532

Evans-Roberts K M, Mitchenall L A, Wall M K, Leroux J, Mylne J S, Maxwell A (2016). DNA gyrase is the target for the quinolone drug ciprofloxacin in Arabidopsis thaliana. Journal of Biological Chemistry, 291(7): 3136–3144 doi:10.1074/jbc.M115.689554

Guo L, Zhang D, Fu S, Zhang J, Zhang X F, He J, Peng C, Zhang Y F, Qiu Y S, Ye C, Liu Y, Wu Z Y, Hu C A A (2021). Metagenomic sequencing analysis of the effects of colistin sulfate on the pig gut microbiome. Frontiers in Veterinary Science, 8: 663820 doi:10.3389/fvets.2021.663820

Hashiguchi Y, Oda K, Katanoda T, Iwamoto T, Sugata E, Okuno Y (2020). Clinical evaluation of cefotiam in the treatment of bacteremia caused by Escherichia coli, Klebsiella species, and Proteus mirabilis: A retrospective study. Journal of Infection and Chemotherapy, 26(11): 1158–1163 doi:10.1016/j.jiac.2020.07.009

Herwaldt B L, Berman J D (1992). Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. American Journal of Tropical Medicine and Hygiene, 46(3): 296–306 doi:10.4269/ajtmh.1992.46.296

Mhmoud N A, Fahal A H, Mahgoub E S, van de Sande W W J (2014). The combination of amoxicillin-clavulanic acid and ketoconazole in the treatment of Madurella mycetomatis eumycetoma and Staphylococcus aureus co-infection. Public Library of Science Neglected Tropical Diseases, 8(6): e2959 doi:10.1371/journal.pntd.0002959

Moulds R F W, Jeyasingham M S (2010). Gentamicin: a great way to start. Australian Prescriber, 33(5): 134–135 doi:10.18773/austprescr.2010.062

Oram M, Fisher L M (1991). 4-Quinolone resistance mutations in the DNA gyrase of Escherichia coli clinical isolates identified by using the polymerase chain reaction. Antimicrobial Agents and Chemotherapy, 35(2): 387–389 doi:10.1128/AAC.35.2.387

Ramirez M S, Tolmasky M E (2017). Amikacin: uses, resistance, and prospects for inhibition. Molecules (Basel, Switzerland), 22(12): 2267 doi:10.3390/molecules22122267

Richards D M, Heel R C, Brogden R N, Speight T M, Avery G S (1984). Ceftriaxone: a review of its antibacterial activity, pharmacological properties and therapeutic use. Drugs, 27(6): 469–527 doi:10.2165/00003495-198427060-00001

Roush W R, Brown R J (1982). Total synthesis of carbohydrates: stereoselective syntheses of 2, 6-dideoxy-D-arabino-hexose and 2, 6-dideoxy-D-ribo-hexose. Journal of Organic Chemistry, 47(7): 1371–1373 doi:10.1021/jo00346a050

Schauss K, Focks A, Heuer H, Kotzerke A, Schmitt H, Thiele-Bruhn S, Smalla K, Wilke B M, Matthies M, Amelung W, Klasmeier J, Schloter M (2009). Analysis, fate and effects of the antibiotic sulfadiazine in soil ecosystems. Trends in Analytical Chemistry, 28(5): 612–618 doi:10.1016/j.trac.2009.02.009

Ulusoy H G, Sanlier N A (2020). Minireview of quercetin: From its metabolism to possible mechanisms of its biological activities. Critical Reviews in Food Science and Nutrition, 60(19): 3290–3303 doi:10.1080/10408398.2019.1683810

Wang C, Teppen B J, Boyd S A, Li H (2012). Sorption of lincomycin at low concentrations from water by soils. Soil Science Society of America Journal, 76(4): 1222–1228 doi:10.2136/sssaj2011.0408

Xu G, Li P, Xue Z, Qi Y, Li X, Zhu D, Ma H, Kong L (2024). RecA inhibitor epicatechin prolongs the development of fluoroquinolone resistance in Pasteurella multocida. International Journal of Biological Macromolecules, 255: 128026 doi:10.1016/j.ijbiomac.2023.128026

Yoshida H, Bogaki M, Nakamura M, Nakamura S (1990). Quinolone resistance determining region in the DNA syrase

gyrA gene of Escherichia coli. Antimicrobial Agents and chemotherapy, 34(6): 1271–1272 doi:10.1128/AAC.34.6.1271

Zavascki A P, Goldani L Z, Li J, Nation R L (2007). Polymyxin B for the treatment of multidrug-resistant pathogens: a critical review. Journal of Antimicrobial Chemotherapy, 60(6): 1206–1215 doi:10.1093/jac/dkm357