

Supporting Information

In silico evaluation of new fluoroquinolones as possible inhibitors of bacterial gyrases in resistant Gram-negative pathogens[†]

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Table S1. Biologically relevant criteria used in the scoring system to classify molecules with greater affinity for GyrA

No	Criterion	Basis
1	Binding Free Energy	Lower values are related to the spontaneity of the reaction and affinity between the drug-protein involving physico-chemical phenomena [51].
2	Inhibition Constant	Represents the concentration at which 50% of the protein is inhibited (IC_{50}) [52].
3	Total Intermolecular Energy	Represents the sum of all energies that are involved in the process of molecular docking, minor values imply processes that occur spontaneously [53].
4	Electrostatic Energy	Associated with the attraction or repulsion between the drug and the protein, lower values imply a better bond [53].

Table S2. Identity percentage between structures of GyrA WT

	<i>E. coli</i>	<i>C. jejuni</i>	<i>N. gonorrhoeae</i>	<i>P. aeruginosa</i>	<i>S. enteritidis</i>	<i>S. typhi</i>
<i>E. coli</i>	-	54.07%	53.02%	67.40%	83.46%	95.16%
<i>C. jejuni</i>	54.07%	-	51.57%	54.91%	54.49%	54.07%
<i>N. gonorrhoeae</i>	53.02%	51.57%	-	62.20%	60.43%	53.41%
<i>P. aeruginosa</i>	67.40%	54.91%	62.20%	-	74.80%	66.60%
<i>S. enteritidis</i>	83.46%	54.49%	60.43%	74.80%	-	86.22%
<i>S. typhi</i>	95.16%	54.07%	53.41%	66.60%	86.22%	-

Table S3. Identity percentage between structures of GyrA MT

	<i>E. coli</i>	<i>C. jejuni</i>	<i>N. gonorrhoeae</i>	<i>P. aeruginosa</i>	<i>S. enteritidis</i>	<i>S. typhi</i>
<i>E. coli</i>	-	53.65%	52.64%	67.20%	82.87%	95.89%
<i>C. jejuni</i>	53.65%	-	51.15%	54.70%	54.07%	53.86%
<i>N. gonorrhoeae</i>	52.64%	51.15%	-	62.00%	60.24%	53.22%
<i>P. aeruginosa</i>	67.20%	54.70%	62.00%	-	74.60%	66.60%
<i>S. enteritidis</i>	82.87%	54.07%	60.24%	74.60%	-	85.83%
<i>S. typhi</i>	95.89%	53.86%	53.22%	66.60%	85.83%	-

Table S4. Molecules with higher affinity for GyrA MT of *C. jejuni*

Molecule	Conformation	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
3	2	-6.94	8.21	-8.43	-1.29
4	2	-6.93	8.39	-8.42	-1.33
4	7	-7.05	6.85	-8.54	-1.36
4	10	-7.09	6.39	-8.58	-1.37
5	5	-6.75	11.22	-7.95	-1.93
7	3	-7.14	5.82	-8.93	-1.22
7	8	-7.12	6.07	-8.91	-1.25
7	9	-6.92	8.41	-8.71	-1.35
9	2	-6.79	10.52	-7.98	-2.03
CPX	4	-6.32	23.29	-7.22	-0.84

Table S5. Statistical treatment for docking in gyrA WT of *C. jejuni*

	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
Min.	-7.64	2.51	-9.43	-2.58
Max.	-5.1	183.57	-0.9	0.07
R	2.54	181.06	8.53	2.65
R/5	0.508	36.212	1.706	0.53
Threshold Value	-7.132	38.722	-7.724	-2.05

Min.: the minimum value obtained among all the data. Max.: the maximum value obtained among all the data.

R: difference between the maximum value and the minimum value. R/5: lowest quintile. Threshold Value: min. - (R/5).

Table S6. Molecules with higher affinity for GyrA WT of *C. jejuni*

Molecule	Conformation	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
2	3	-7.46	3.42	-8.65	-0.68
7	5	-7.64	2.51	-9.43	-0.83
7	7	-6.15	30.82	-7.94	-2.58
CPX	2	-6.2	28.52	-7.1	-1.64

Table S7. Statistical treatment for docking in gyrA MT of *E. coli*

	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
Min.	-7.45	3.44	-9.24	-2.9
Max.	-4.2	831.09	-5.69	0.46
R	3.25	827.65	3.55	3.36
R/5	0.65	165.53	0.71	0.672
Threshold Value	-6.8	168.97	-8.53	-2.228

Min.: the minimum value obtained among all the data. Max.: the maximum value obtained among all the data.

R: difference between the maximum value and the minimum value. R/5: lowest quintile. Threshold Value: min. - (R/5).

Table S8. Molecules with higher affinity for GyrA MT of *E. coli*

Molecule	Conformation	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
7	6	-7.45	3.44	-9.24	-1.3
7	7	-7.33	4.25	-9.12	-1.21
7	10	-7.4	3.74	-9.19	-1.27
CPX	6	-6.46	18.53	-7.35	-1.09

Table S9. Statistical treatment for docking in gyrA WT of *E. coli*

	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
Min.	-7.44	3.54	-9.23	-2.87
Max.	-4.4	593.91	-0.66	0.26
R	3.04	590.37	8.57	3.13
R/5	0.608	118.074	1.714	0.626
Threshold Value	-6.832	121.614	-7.516	-2.244

Min.: the minimum value obtained among all the data. Max.: the maximum value obtained among all the data.

R: difference between the maximum value and the minimum value. R/5: lowest quintile. Threshold Value: min. - (R/5).)

Table S10. Molecules with higher affinity for GyrA WT of *E. coli*

Molecule	Conformation	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
4	10	-6.51	16.97	-8	-2.42
7	2	-6.23	26.9	-8.02	-2.65
7	8	-7.44	3.54	-9.23	-1.24
CPX	8	-6.29	24.65	-7.18	-0.94

Table S11. Statistical treatment for docking in gyrA MT of *N. gonorrhoeae*

	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
Min.	-6.83	9.91	-8.32	-2.76
Max.	-4	1110	-0.16	0.07
R	2.83	1100.09	8.16	2.83
R/5	0.566	220.018	1.632	0.566
Threshold Value	-6.264	229.928	-6.688	-2.194

Min.: the minimum value obtained among all the data. Max.: the maximum value obtained among all the data.

R: difference between the maximum value and the minimum value. R/5: lowest quintile. Threshold Value: min. - (R/5).)

Table S12. Molecules with higher affinity for GyrA MT of *N. gonorrhoeae*

Molecule	Conformation	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
2	4	-6.48	17.84	-7.67	-1.35
2	5	-6.42	19.82	-7.61	-0.84
3	4	-6.81	10.21	-8.3	-2.53
3	9	-6.83	9.91	-8.32	-1.87
6	2	-6.79	10.59	-8.28	-0.43
6	8	-6.28	24.89	-7.77	-0.91
7	6	-6.34	22.42	-8.13	-0.65
9	7	-6.58	15.03	-7.77	-1.37
CPX	8	-6.52	16.51	-7.42	-1.53

Table S13. Statistical treatment for docking in gyrA WT of *N. gonorrhoeae*

	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
Min.	-7.11	6.14	-8.9	-3.23
Max.	-3.49	2760	-4.9	0.04
R	3.62	2753.86	4	3.27
R/5	0.724	550.772	0.8	0.654
Threshold Value	-6.386	556.912	-8.1	-2.576

Min.: the minimum value obtained among all the data. Max.: the maximum value obtained among all the data.

R: difference between the maximum value and the minimum value. R/5: lowest quintile. Threshold Value: min. - (R/5).

Table S14. Molecules with higher affinity for GyrA WT of *N. gonorrhoeae*

Molecule	Conformation	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
7	9	-7.11	6.14	-8.9	-1.74
CPX	5	-6.15	31.21	-7.04	-1.86

Table S15. Statistical treatment for docking in gyrA MT of *P. aeruginosa*

	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
Min.	-8.13	1.1	-9.92	-2.14
Max.	-4.17	877.59	-5.41	-0.12
R	3.96	876.49	4.51	2.02
R/5	0.792	175.298	0.902	0.404
Threshold Value	-7.338	176.398	-9.018	-1.736

Min.: the minimum value obtained among all the data. Max.: the maximum value obtained among all the data.

R: difference between the maximum value and the minimum value. R/5: lowest quintile. Threshold Value: min. - (R/5).

Table S16. Molecules with higher affinity for GyrA MT of *P. aeruginosa*

Molecule	Conformation	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
7	2	-8	1.37	-9.79	-1.5
7	3	-7.97	1.44	-9.76	-1.51
7	5	-7.41	3.73	-9.2	-1.28
7	7	-8.13	1.1	-9.92	-1.51
CPX	4	-6.38	21.22	-7.27	-1.54

Table S17. Statistical treatment for docking in gyrA WT of *P. aeruginosa*

	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
Min.	-7.95	1.48	-9.74	-3.25
Max.	-4.03	1110	-0.15	-0.39
R	3.92	1108.52	9.59	2.86
R/5	0.784	221.704	1.918	0.572
Threshold Value	-7.166	223.184	-7.822	-2.678

Min.: the minimum value obtained among all the data. Max.: the maximum value obtained among all the data.

R: difference between the maximum value and the minimum value. R/5: lowest quintile. Threshold Value: min. - (R/5).

Table S18. Molecules with higher affinity for GyrA WT of *P. aeruginosa*

Molecule	Conformation	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
7	2	-7.95	1.48	-9.74	-1.43
CPX	2	-6.5	17.13	-7.4	-1.46

Table S19. Statistical treatment for docking in gyrA MT of *S. enteritidis*

	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
Min.	-7.91	1.58	-9.33	-2.68
Max.	-4.67	374.97	-0.88	0.11
R	3.24	373.39	8.45	2.79
R/5	0.648	74.678	1.69	0.558
Threshold Value	-7.262	76.258	-7.64	-2.122

Min.: the minimum value obtained among all the data. Max.: the maximum value obtained among all the data.

R: difference between the maximum value and the minimum value. R/5: lowest quintile. Threshold Value: min. - (R/5).

Table S20. Molecules with higher affinity for GyrA MT of *S. enteritidis*

Molecule	Conformation	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
3	3	-6.3	23.91	-7.8	-2.15
3	5	-6.89	8.89	-8.38	-2.16
5	1	-7.73	2.17	-8.92	-0.94
5	2	-7.81	1.9	-9	-0.89
5	3	-7.78	1.99	-8.97	-0.86
5	4	-7.78	1.99	-8.97	-0.89
5	5	-7.77	2.01	-8.9	-0.86
5	6	-7.91	1.58	-9.11	-0.99
5	7	-7.83	1.81	-9.03	-0.95
5	10	-7.88	1.68	-9.07	-0.97
6	8	-7.83	1.82	-9.32	-1.05
7	2	-7.54	2.96	-9.33	-1.61
7	10	-7.49	3.23	-9.28	-1.67
9	1	-6.99	7.57	-8.18	-2.59
9	2	-6.99	7.57	-8.18	-2.58
9	6	-6.71	12.07	-7.9	-2.18
9	8	-6.9	8.73	-8.09	-2.68
9	9	-6.59	14.8	-7.78	-2.13
CPX	9	-6.49	17.56	-7.38	-0.93

Table S21. Statistical treatment for docking in gyrA WT of *S. enteritidis*

	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
Min.	-7.75	2.07	-9.25	-2.87
Max.	-4.47	533.44	-5.66	0.31
R	3.28	531.37	3.59	3.18
R/5	0.656	106.274	0.718	0.636
Threshold Value	-7.094	108.344	-8.532	-2.234

Min.: the minimum value obtained among all the data. Max.: the maximum value obtained among all the data.

R: difference between the maximum value and the minimum value. R/5: lowest quintile. Threshold Value: min. - (R/5).

Table S22. Molecules with higher affinity for GyrA WT of *S. enteritidis*

Molecule	Conformation	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
5	5	-7.72	2.18	-8.92	-0.83
5	6	-7.75	2.1	-8.94	-0.87
5	9	-7.74	2.13	-8.93	-0.82
5	10	-7.73	2.14	-8.93	-0.83
6	3	-7.7	2.26	-9.19	-0.97
6	4	-7.75	2.07	-9.25	-0.92
6	6	-7.27	4.66	-8.77	0.01
CPX	2	-6.43	19.44	-7.32	-1.3

Table S23. Statistical treatment for docking in gyrA MT of *S. typhi*

	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
Min.	-7.38	3.92	-9.17	-2.2
Max.	-4.19	854.06	-3.87	0.2
R	3.19	850.14	5.3	2.4
R/5	0.638	170.028	1.06	0.48
Threshold Value	-6.742	173.948	-8.11	-1.72

Min.: the minimum value obtained among all the data. Max.: the maximum value obtained among all the data.

R: difference between the maximum value and the minimum value. R/5: lowest quintile. Threshold Value: min.-(R/5).

Table S24. Molecules with higher affinity for GyrA MT of *S. typhi*

Molecule	Conformation	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
4	2	-6.75	11.32	-8.24	-1.37
4	4	-6.89	8.87	-8.38	-1.32
4	7	-6.9	8.71	-8.39	-1.27
7	2	-7.23	4.99	-9.02	-1.23
7	4	-7.32	4.34	-9.11	-1.27
7	5	-7.38	3.92	-9.17	-1.2
7	6	-7.31	4.36	-9.1	-1.24
7	7	-7.23	5.03	-9.02	-1.24
7	10	-6.91	8.66	-8.7	-1.23
CPX	4	-6.28	24.96	-7.17	-0.93

Table S25. Statistical treatment for docking in gyrA WT of *S. typhi*

	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
Min.	-7.38	3.89	-9.17	-2.43
Max.	-4.31	692.39	-5.59	0.56
R	3.07	688.5	3.58	2.99
R/5	0.614	137.7	0.716	0.598
Threshold Value	-6.766	141.59	-8.454	-1.832

Min.: the minimum value obtained among all the data. Max.: the maximum value obtained among all the data.

R: difference between the maximum value and the minimum value. R/5: lowest quintile. Threshold Value: min.-(R/5).

Table S26. Molecules with higher affinity for GyrA WT of *S. typhi*

Molecule	Conformation	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
7	1	-7.34	4.18	-9.13	-1.25
7	2	-7.22	5.12	-9.01	-1.23
7	3	-7.35	4.06	-9.14	-1.31
7	4	-7.38	3.89	-9.17	-1.27
7	6	-6.91	8.65	-8.7	-1.21
7	7	-6.87	9.19	-8.66	-1.24
7	8	-7.13	5.91	-8.92	-1.17
7	10	-6.99	7.48	-8.78	-1.21
CPX	4	-6.31	23.84	-7.2	-0.99

Table S27. Docking results in ciprofloxacin with higher affinity for GyrA

Microorganism	Conformation	Binding Free Energy (kcal/mol)	Inhibition Constant (μM)	Total Intermolecular Energy (kcal/mol)	Electrostatic Energy (kcal/mol)
<i>C. jejuni</i> MT	4	-6.32	23.29	-7.22	-0.84
<i>C. jejuni</i> WT	2	-6.2	28.52	-7.1	-1.64
<i>E. coli</i> MT	6	-6.46	18.53	-7.35	-1.09
<i>E. coli</i> WT	8	-6.29	24.65	-7.18	-0.94
<i>N. gonorrhoeae</i> MT	8	-6.52	16.51	-7.42	-1.53
<i>N. gonorrhoeae</i> WT	5	-6.15	31.21	-7.04	-1.86
<i>P. aeruginosa</i> MT	4	-6.38	21.22	-7.27	-1.54
<i>P. aeruginosa</i> WT	2	-6.5	17.13	-7.4	-1.46
<i>S. enteritidis</i> MT	9	-6.49	17.56	-7.38	-0.93
<i>S. enteritidis</i> WT	2	-6.43	19.44	-7.32	-1.3
<i>S. typhi</i> MT	4	-6.28	24.96	-7.17	-0.93
<i>S. typhi</i> WT	4	-6.31	23.84	-7.2	-0.99

Table S28. Average scores for new molecules in molecular docking with GyrA

Molecule	<i>C. jejuni</i>		<i>E. coli</i>		<i>N. gonorrhoeae</i>		<i>P. aeruginosa</i>		<i>S. enteritidis</i>		<i>S. typhi</i>	
	MT	WT	MT	WT	MT	WT	MT	WT	MT	WT	MT	WT
1	4.6	1	5	7.8	4.6	4.6	3.8	3.8	1.4	1.8	3	3
2	4.2	14.6	7	5	31	5	4.	5	6.6	4.2	5	5
3	22.2	15.4	11	19	87.8	7	5.8	10.6	40.6	6.6	5	5
4	39.8	5	7.8	16.2	14.2	7	7.8	19	2.2	8.6	40.2	15
5	25	2.2	4.2	5	13.8	5	7	9	100.2	52.2	5	5
6	3	8.6	2.6	2.2	28.2	1.8	3.8	6.6	17.4	40.2	3.4	3.8
7	51	38.2	41.8	36.2	25.4	19	53	31	38.2	4.6	81	101
8	12.2	2.2	4.6	6.2	5.4	4.6	15	4.2	4.2	4.2	4.2	4.2
9	21	4.6	7	5	22.2	10.6	5	7	66.2	9	7	13

Table S29. Molecular docking interactions with GyrA residues

Microorganism	GyrA	Molecule	Interactions
<i>Campylobacter jejuni</i>	MT		Arg94 , Ser175, Ser114, Ser110
	WT	7	Asn270, Arg273, Phe99, Asp118, Phe112, Gln268, Ser100, Gly117, Arg94 , Val193
	MT	CPX	Arg94 , Gln268, Ile115, Phe99
	WT		Lys45, His48, Arg94 , Gln268, Ser100, Asn172
	MT		Phe109, Gly110, Asn108, Asp104 , Gly105, Pro95 , Met101 , Phe109
	WT	7	Phe109, Gly110, Asp108, Asp104 , Gly105, Pro95 , Gly107, Ala93, Met101
	MT	CPX	Arg518, Arg99 , Met101 , Phe513, Tyr100
<i>Escherichia coli</i>	WT		Asp104 , Phe109, Gly110, Gly105, Ala93, Pro95 , Phe96
	MT	3	Lys137, Asp112, Asn523, Tyr108 , Val109, Ala136, Tyr524, Ile138
	WT	7	Met128, Gly89, Asp95 , His88 , Asp90 , Tyr94, Ala125, Val98, Ala127
	MT	CPX	Arg129, Asp90 , Met128, His88
<i>Neisseria gonorrhoeae</i>	WT		Lys72, Arg76 , Glu132, Lys73, Ala70
	MT		Lys42, His45, Asn169, Tyr267, Arg91 , Ser171, Gly170, Ser172, Phe331
	WT	7	Lys42, His45, Asn169, Tyr267, Arg91 , Ser171, Gly170, Ser172, Tyr267, Phe331
	MT	CPX	His45, Lys42, Arg91 , Tyr267, Asn169
	WT		Arg91 , Lys42, His45, Tyr266, Gln267, Asn165, Ser172, Gly40, Asn169, Gly170, Leu41, Leu98
	MT	5	Arg91 , Lys42, His45, Ser172, Tyr266, Gln267, Gly170, Asn169, Leu41
	WT		Arg91 , Ser172, Tyr266, Gln267, Asn165, Gly40, Asn169, Gly170, His45
<i>Pseudomonas aeruginosa</i>	MT	CPX	Asp515, Lys129, Gly514, Gln512, Phe513, Met101 , Ile130, Tyr100
	WT		Phe109, Gly110, Asn108, Asp104 , Pro95 , Ser111, Gly105 , Ala93, Met101
	MT	7	Phe109, Asn108, Asp104 , Pro95 , Ser111, Gly105 , Gly107, Ala93, Met101
	WT		Asp104 , Phe109, Gly105 , Ser111, Ala93 , Pro95 , Phe96
	MT	CPX	
	WT		

Note. Interactions with amino acids from the molecular docking result are indicated for each enzyme and microorganism. Those residues included in the QRDR region are highlighted in yellow, and those amino acids matching two or more enzymes are indicated in bold for the same microorganism

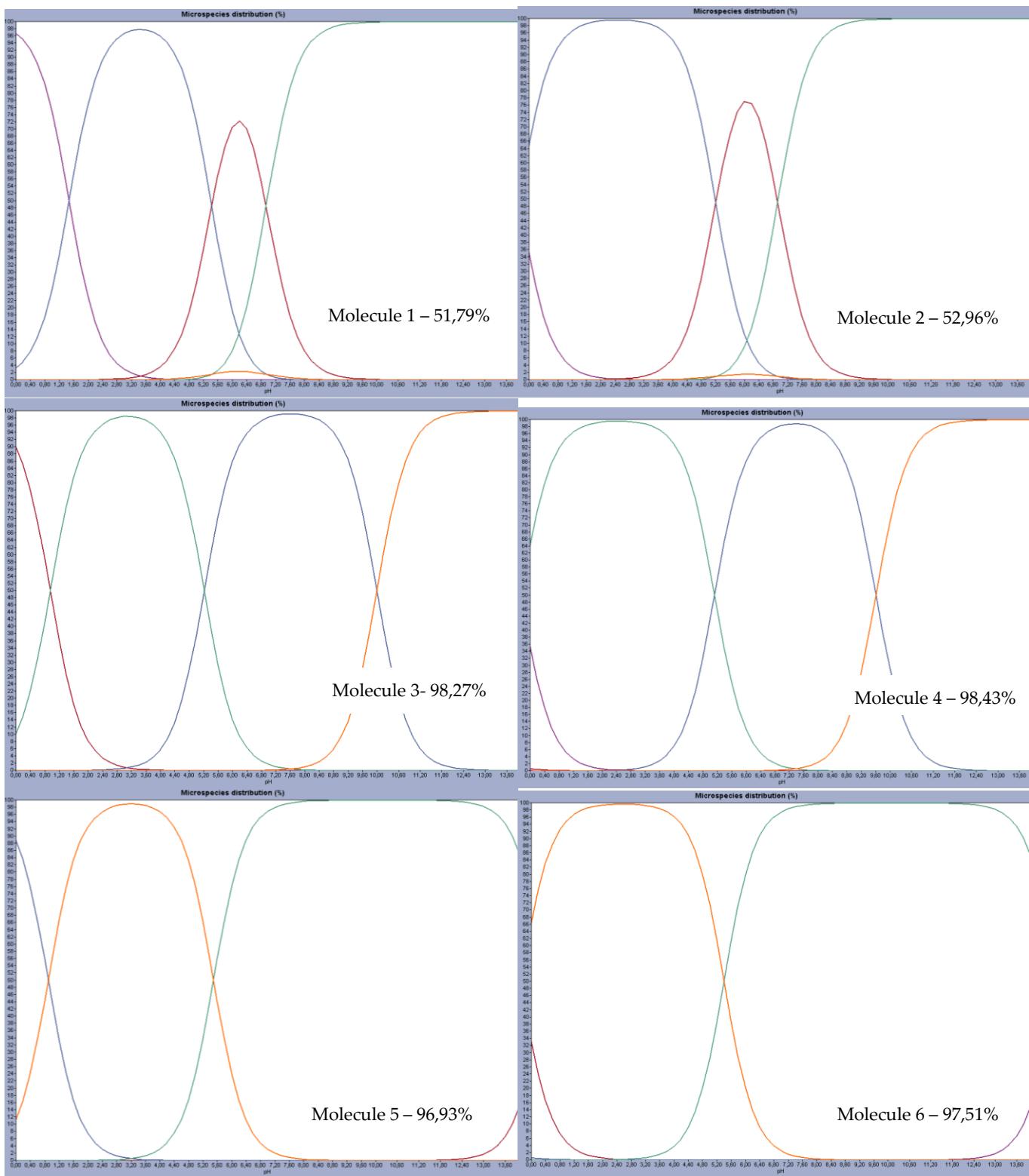


Figure S1. Species distribution curve as a function of pH for the designed fluoroquinolones. The percentage of the majority microspecies at pH 7.0 is shown

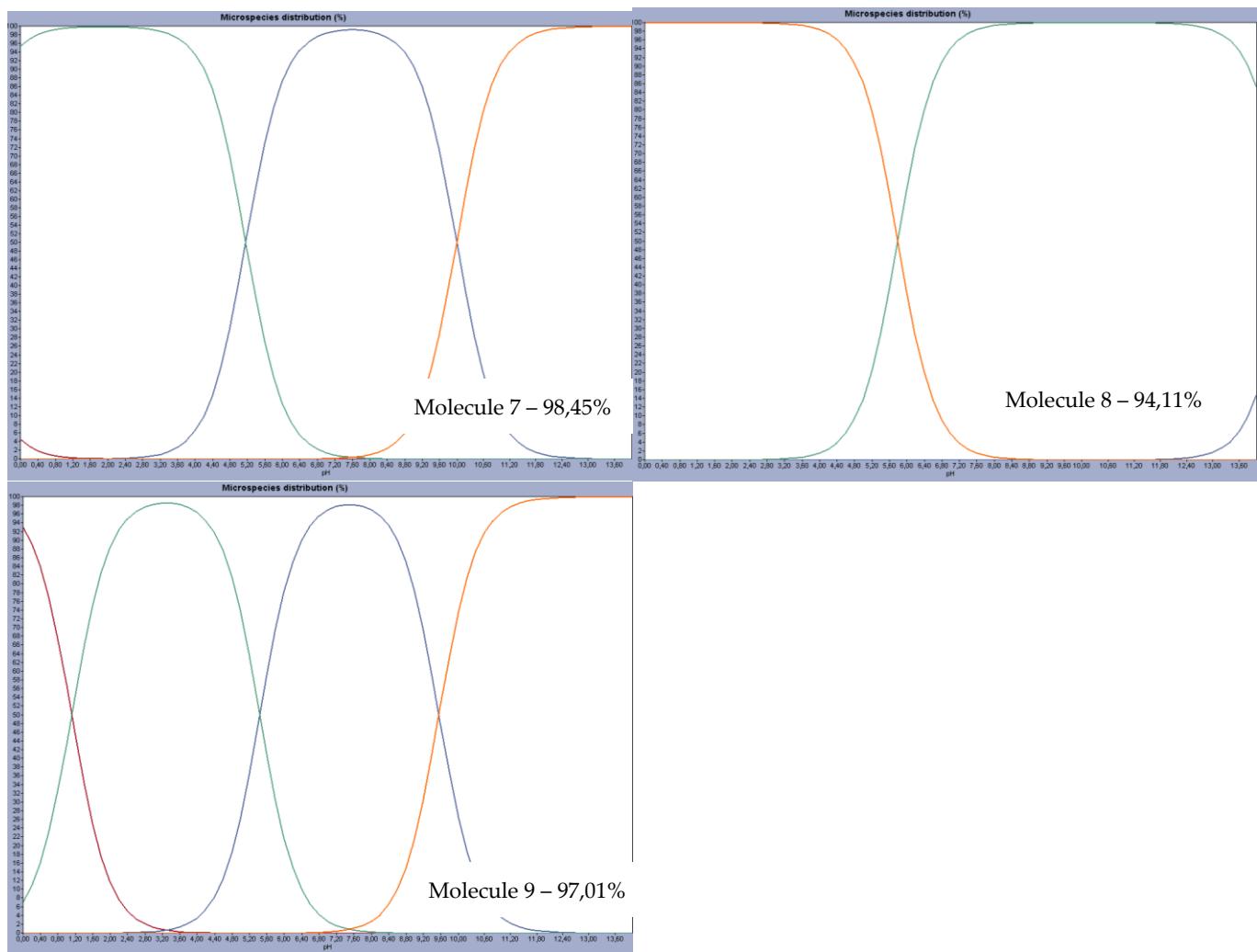
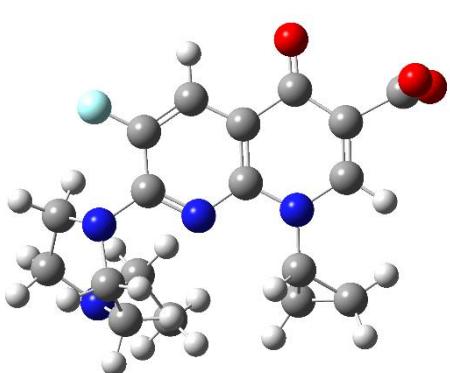
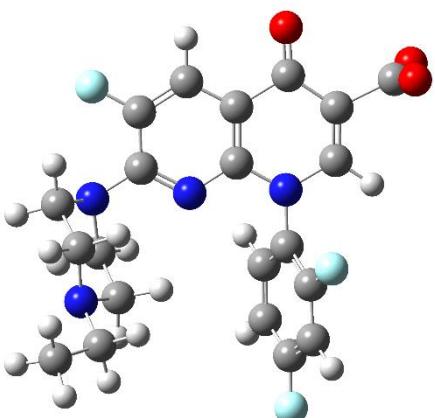


Figure S1. Species distribution curve as a function of pH for the designed fluoroquinolones. The percentage of the majority microspecies at pH 7.0 is shown

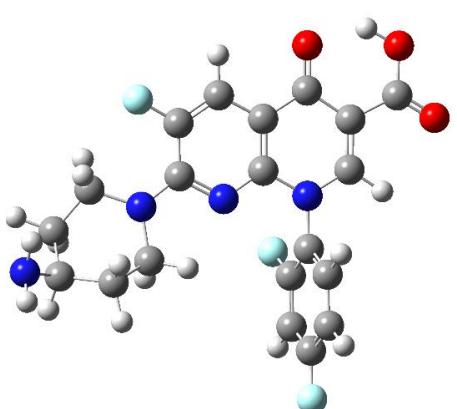
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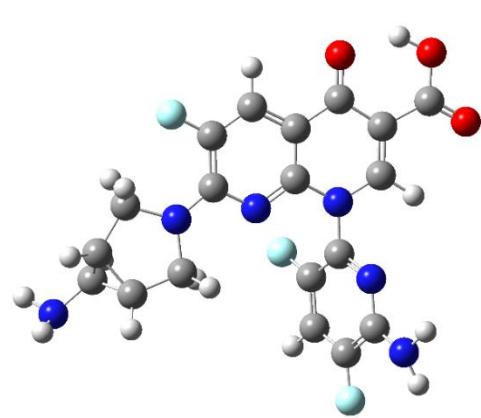
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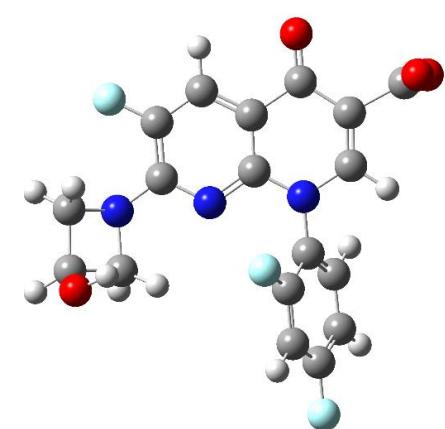
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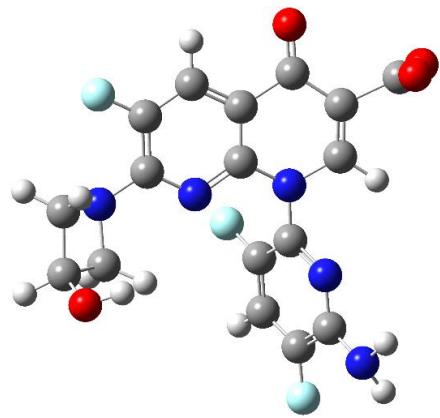
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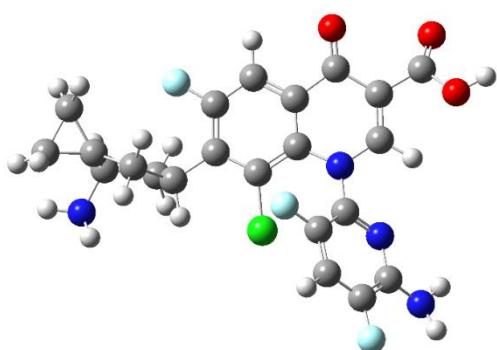
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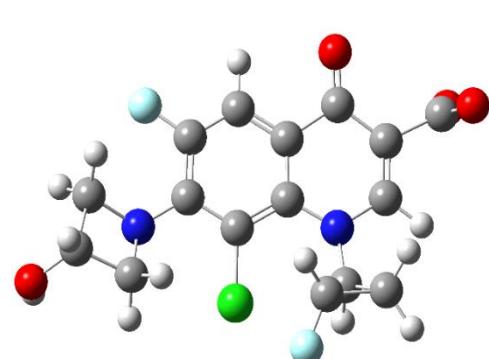
Molecule 6



Molecule 7



Molecule 8



Molecule 9

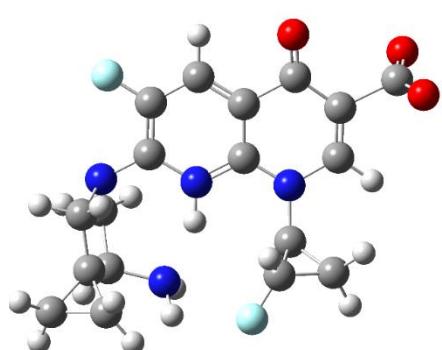


Figure S2. Low-energy 3D structures of designed fluoroquinolones

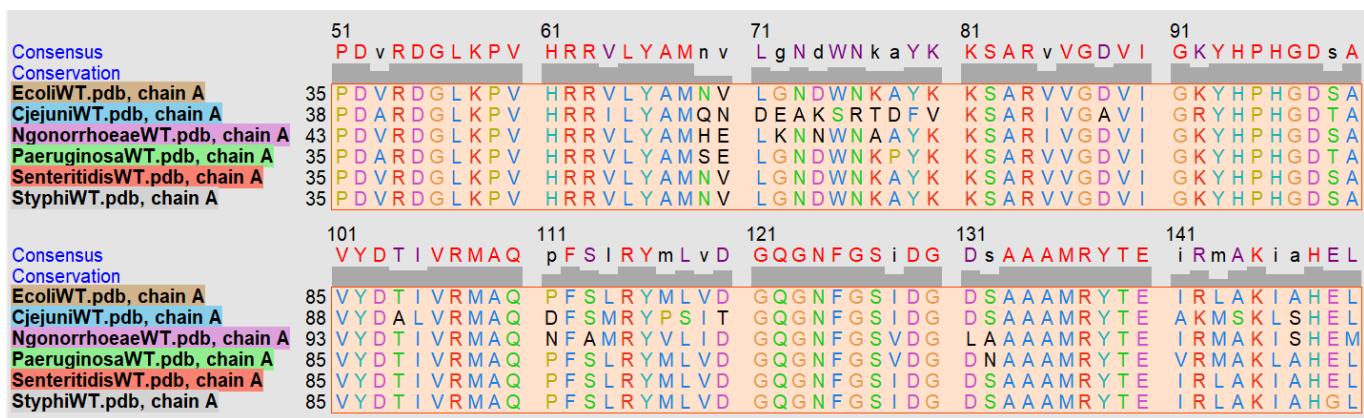


Figure S3. Multiple sequences alignment on the QRDR for GyrA WT obtained through the UCSF Chimera program

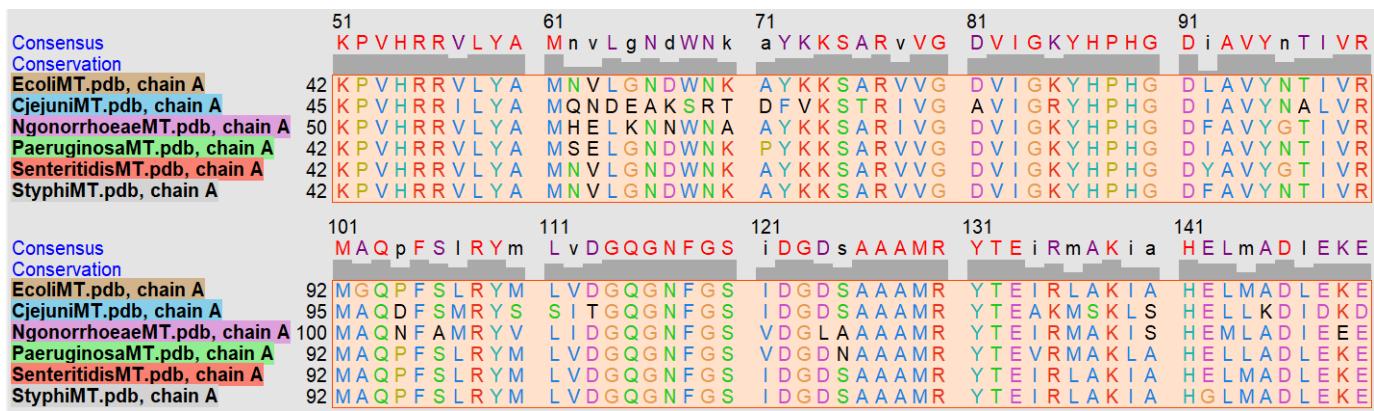


Figure S4. Multiple sequences alignment on the QRDR for GyrA MT obtained through the UCSF Chimera program

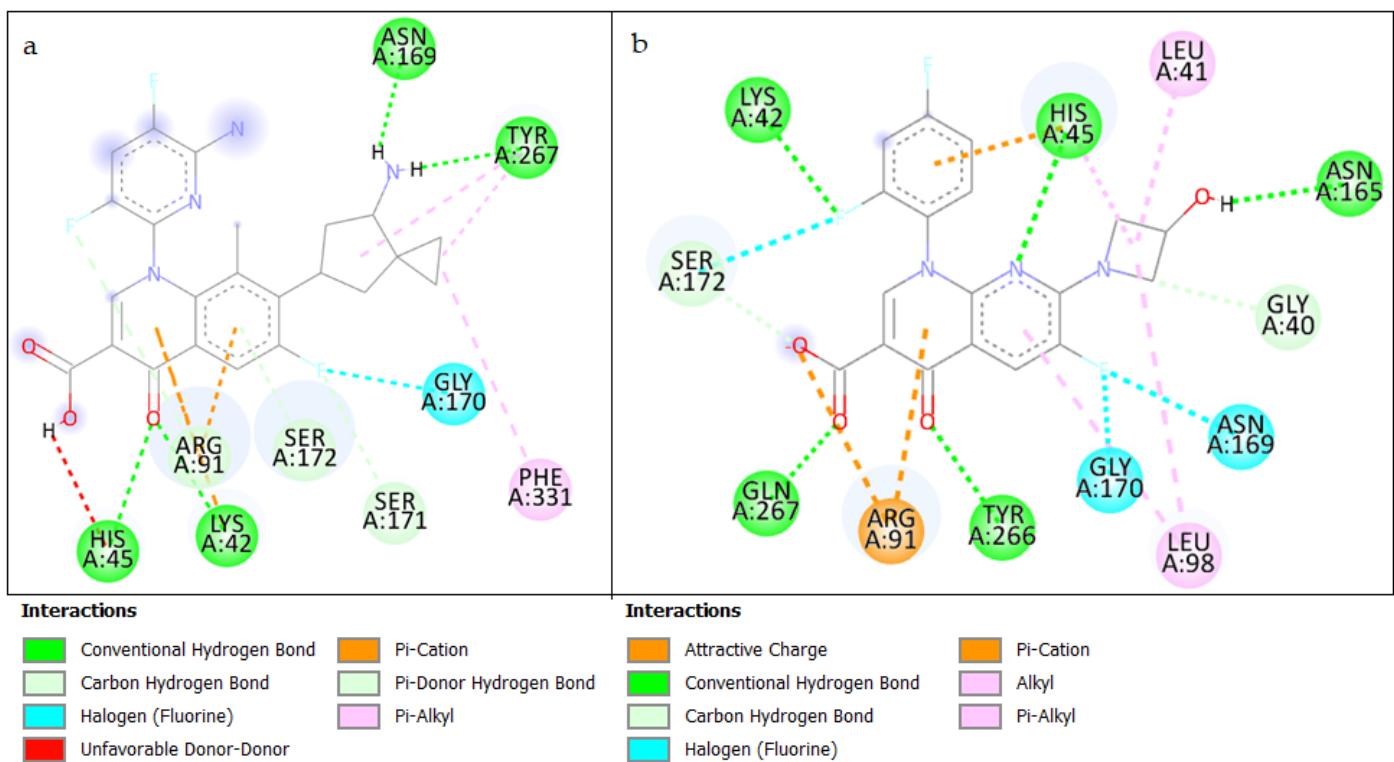


Figure S5. Interactions with GyrA residues MT from a) molecule 7 in *P. aeruginosa*, and b) molecule 5 in *S. typhi*; obtained after molecular coupling through the Discovery Studio program

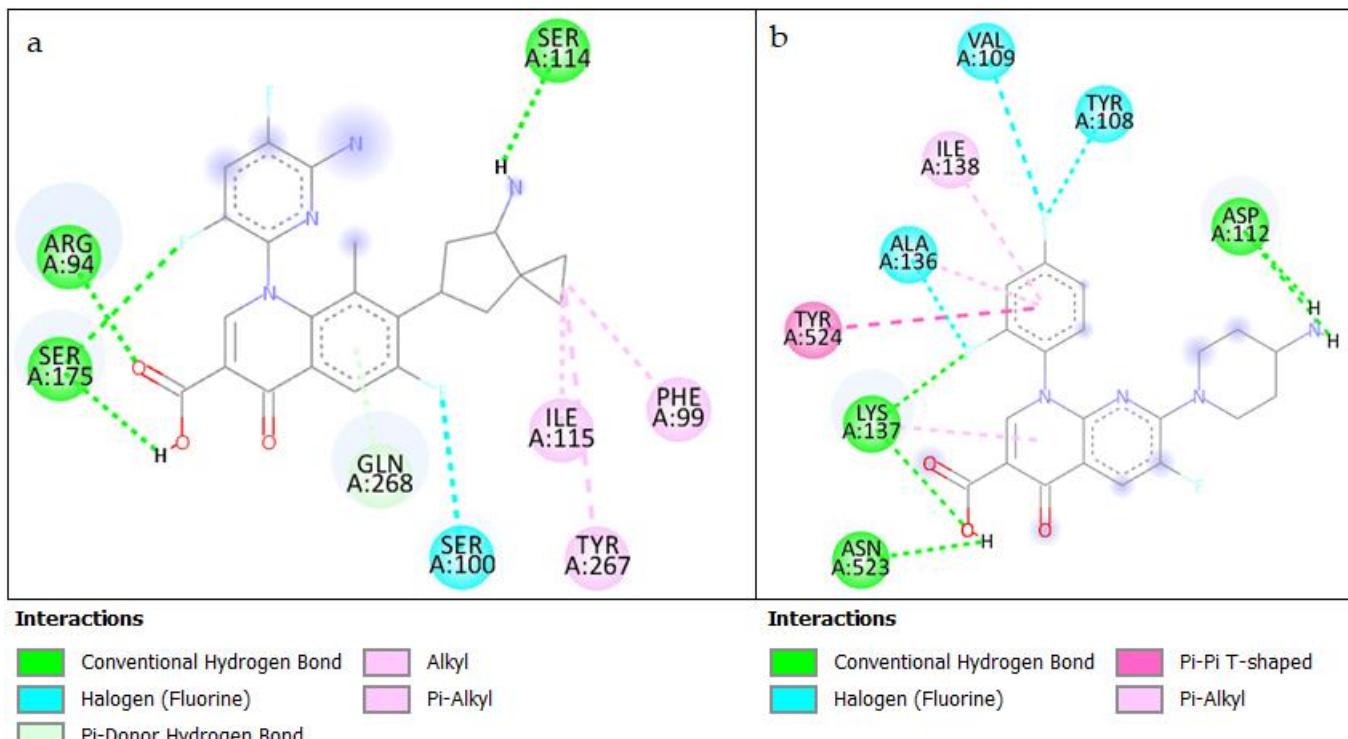


Figure S6. Interactions with GyrA residues MT from a) molecule 7 in *C. jejuni*, and b) molecule 3 in *N. gonorrhoeae*; obtained after molecular coupling through the Discovery Studio

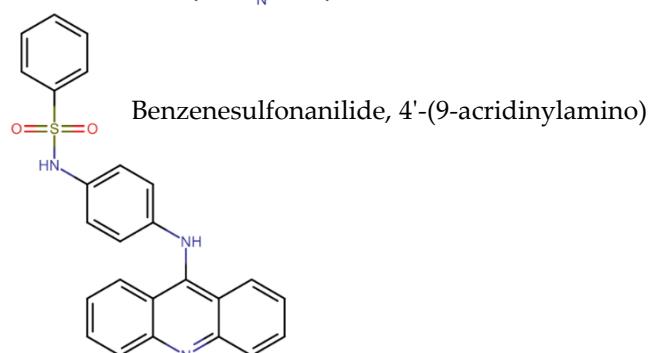
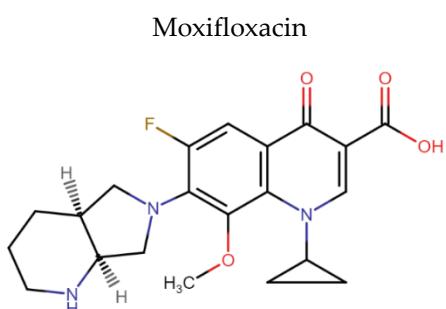
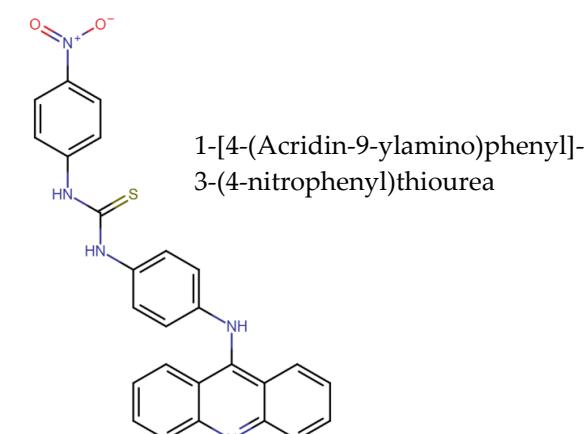
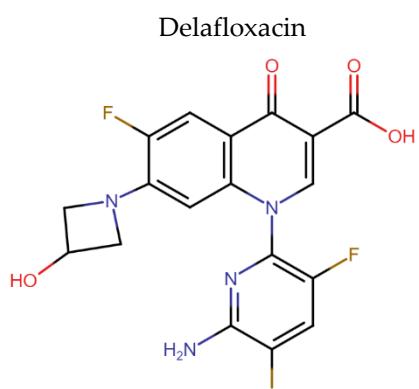
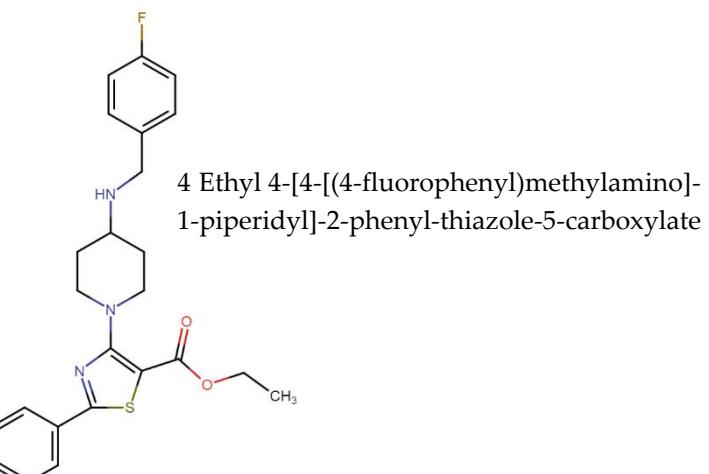
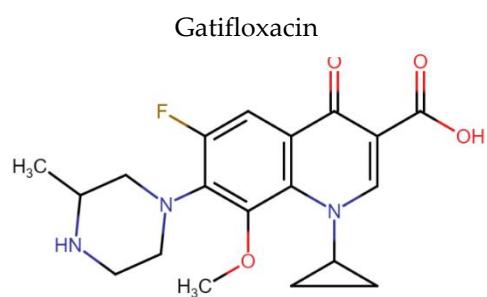
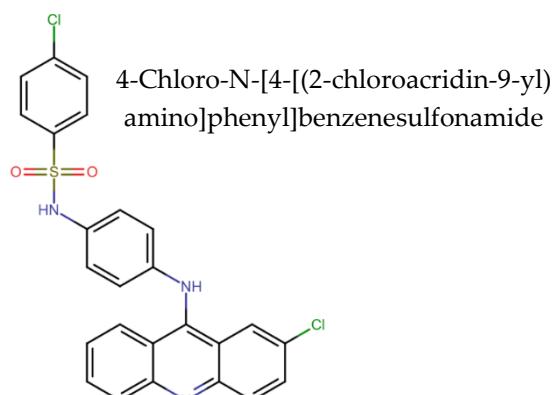
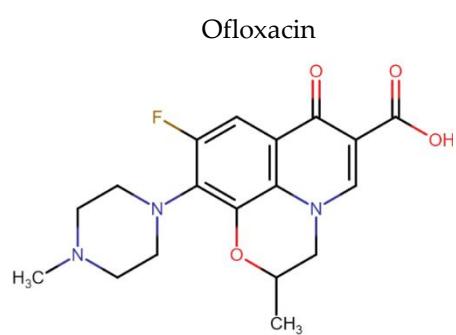


Figure S7. Structures of active and inactive compounds used for retrospective docking

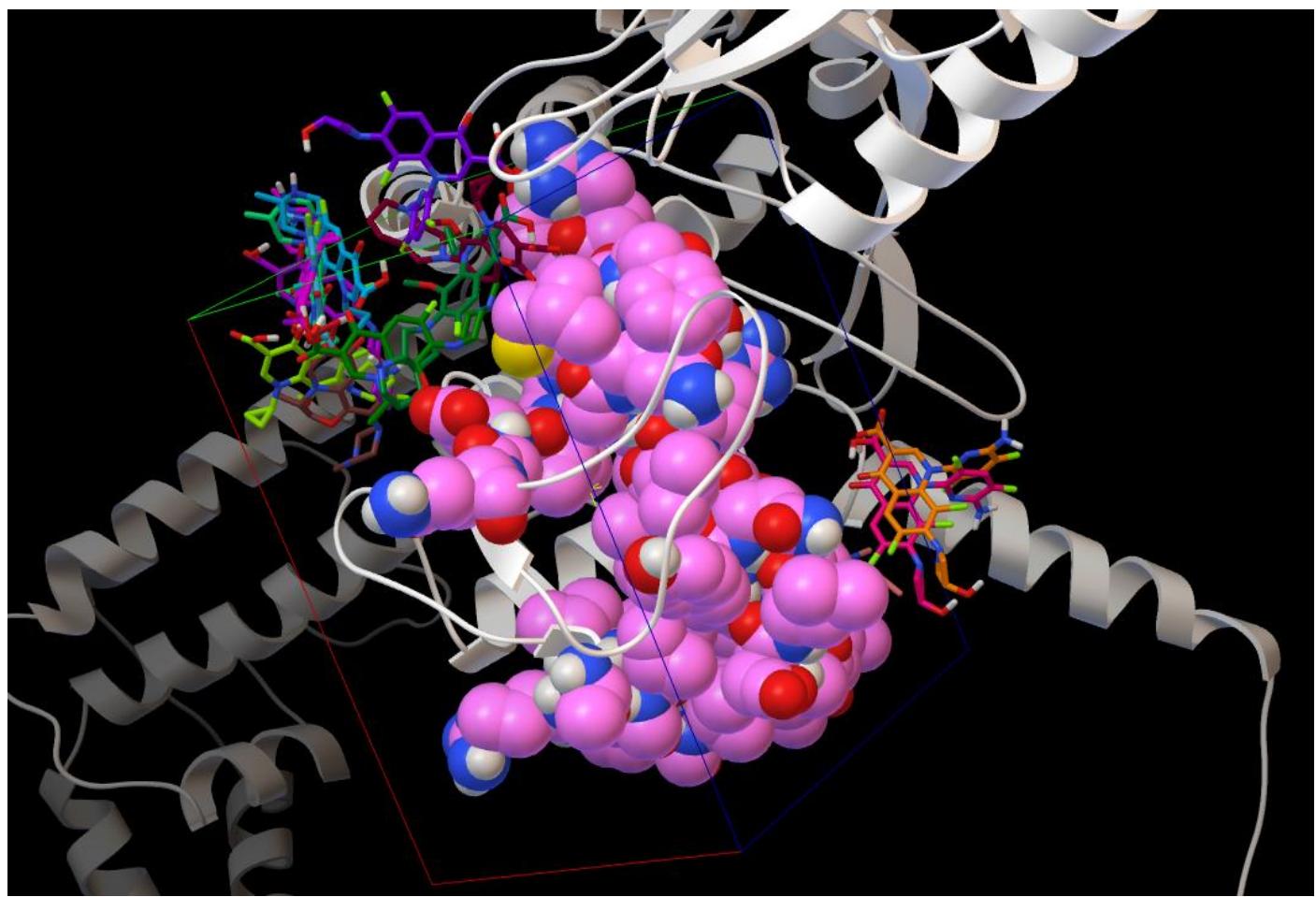


Figure S8. Blind docking result with active ligands in GyrA of *E. coli*

Note. Image obtained using the AutoDockTools program that shows the grid box that was used in the docking with the new molecules encompassing the QRDR in space-filling model; together with the result of the blind docking performed with active ligands of various colors under a stick model against the GyrA MT of *E. coli* in a ribbon diagram.

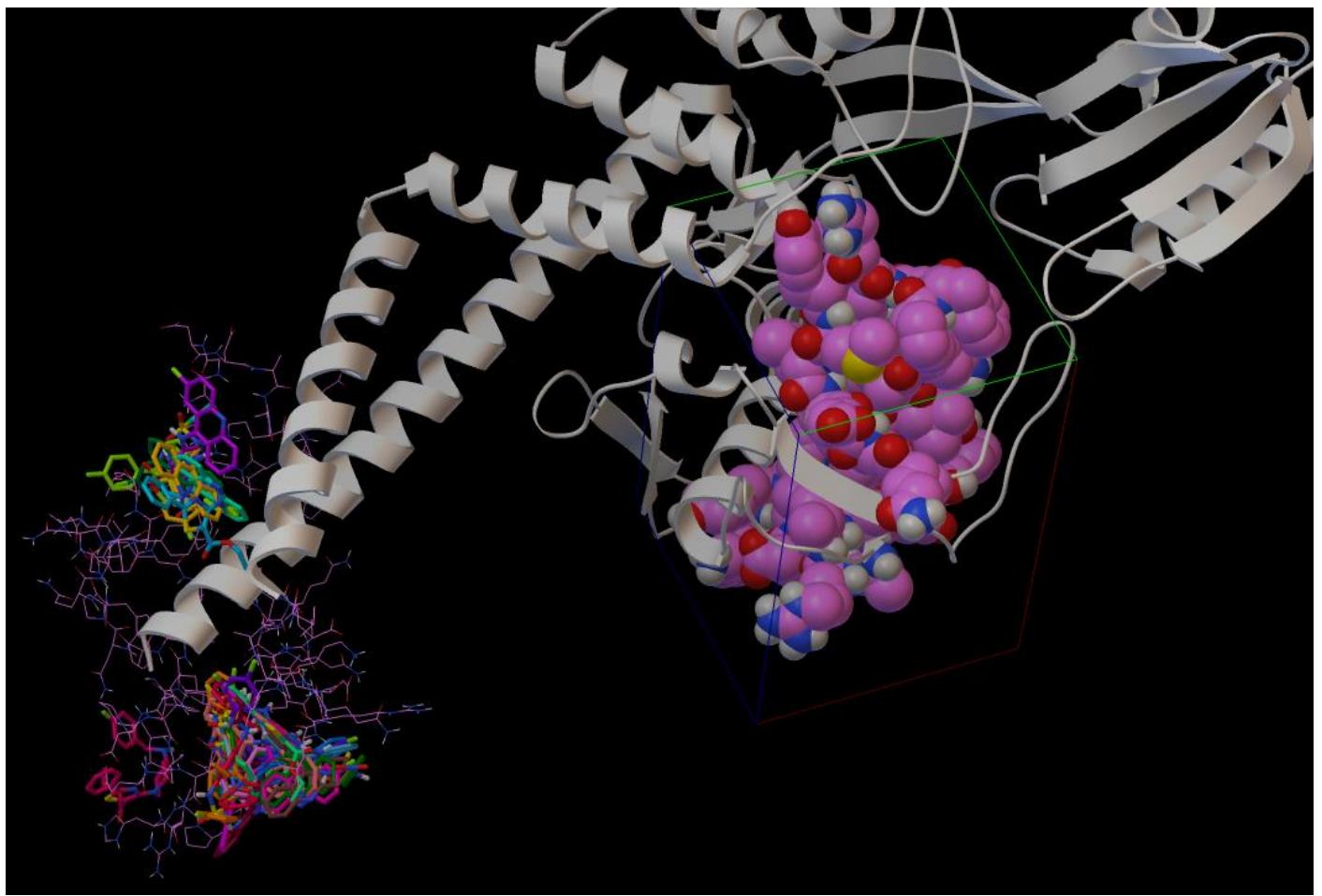


Figure S9. Blind docking result with inactive ligands in GyrA of *E. coli*

Note. Image obtained using the AutoDockTools program that shows the grid box that was used in the docking with the new molecules encompassing the QRDR in space-filling model; together with the result of the blind docking performed with inactive ligands of various colors under a stick model against the GyrA MT of *E. coli* in a ribbon diagram and some areas as a stick model.

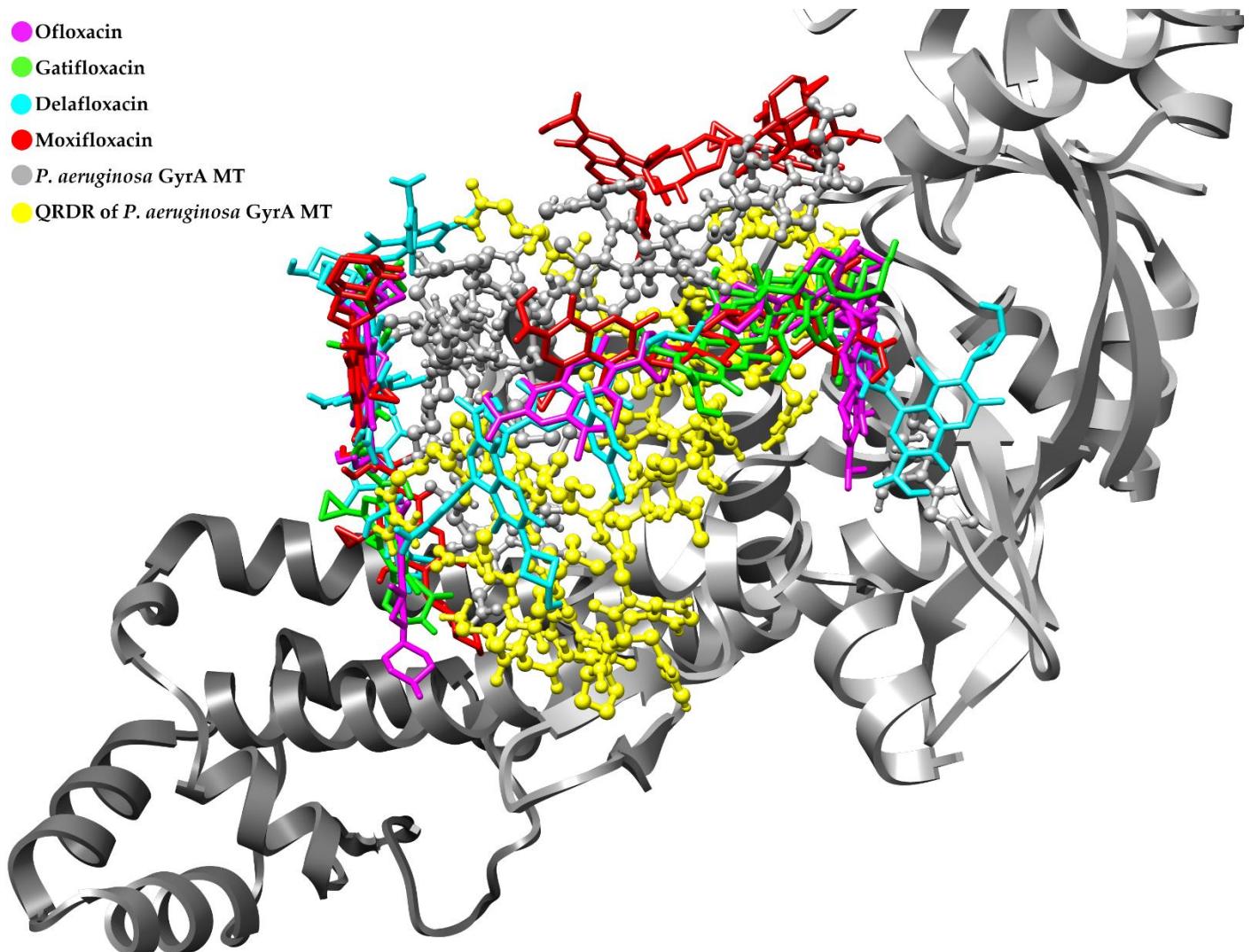


Figure S10. Molecular docking of the active ligands against the GyrA of *P. aeruginosa*

Note. Image obtained using the UCSF Chimera program showing the blind docking results with some conformations for the active molecules, each one represented in stick model by a characteristic color; docked in GyrA MT of *P. aeruginosa* in the ribbon diagram and ball & stick model in gray as target, QRDR is highlighting in yellow.

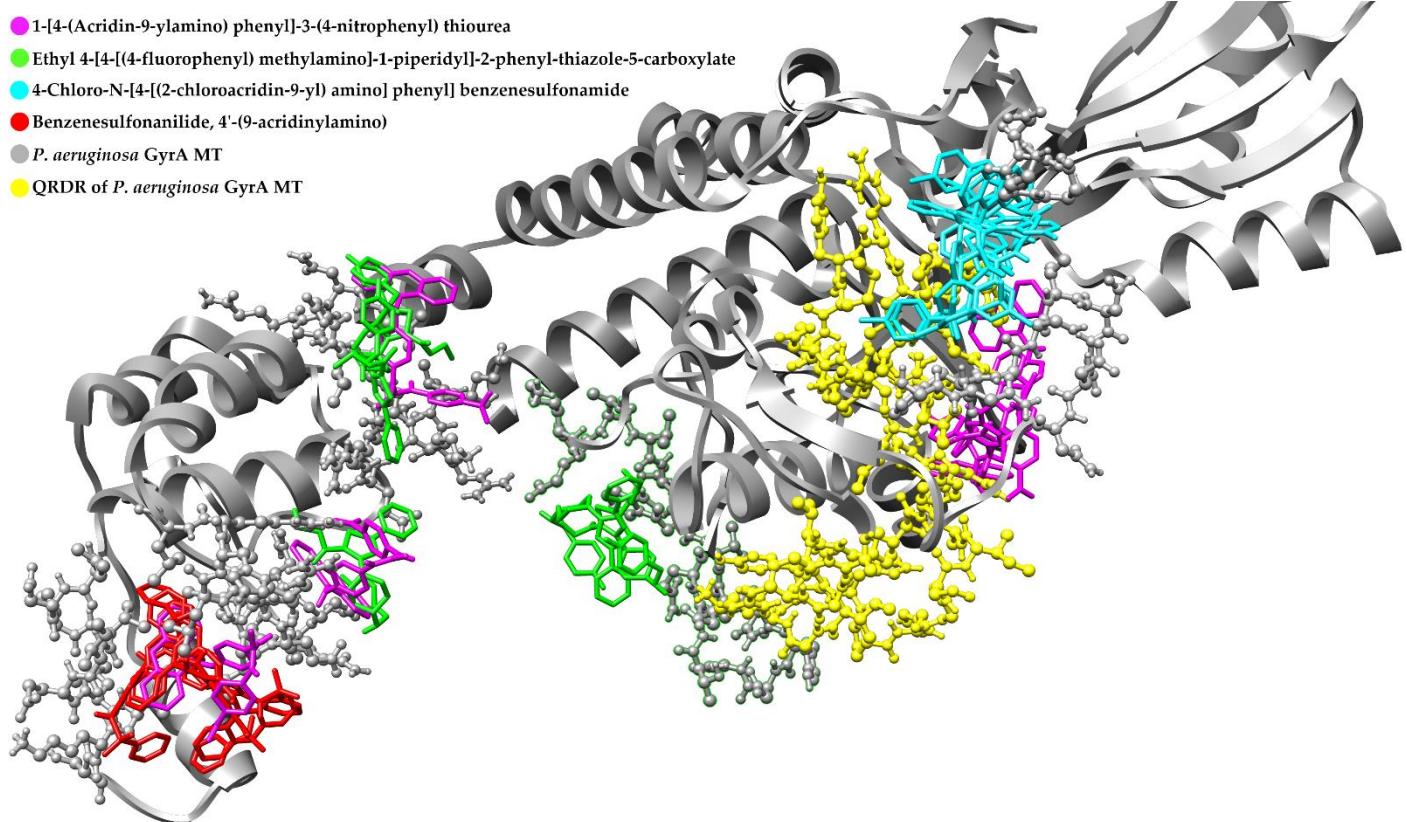


Figure S11. Molecular docking of the inactive ligands against the GyrA of *P. aeruginosa*

Note. Image obtained using the UCSF Chimera program showing the blind docking results with some conformations for the inactive molecules, each one represented in stick model by a characteristic color; docked in GyrA MT of *P. aeruginosa* in the ribbon diagram and ball & stick model in gray as target, QRDR is highlighting in yellow.

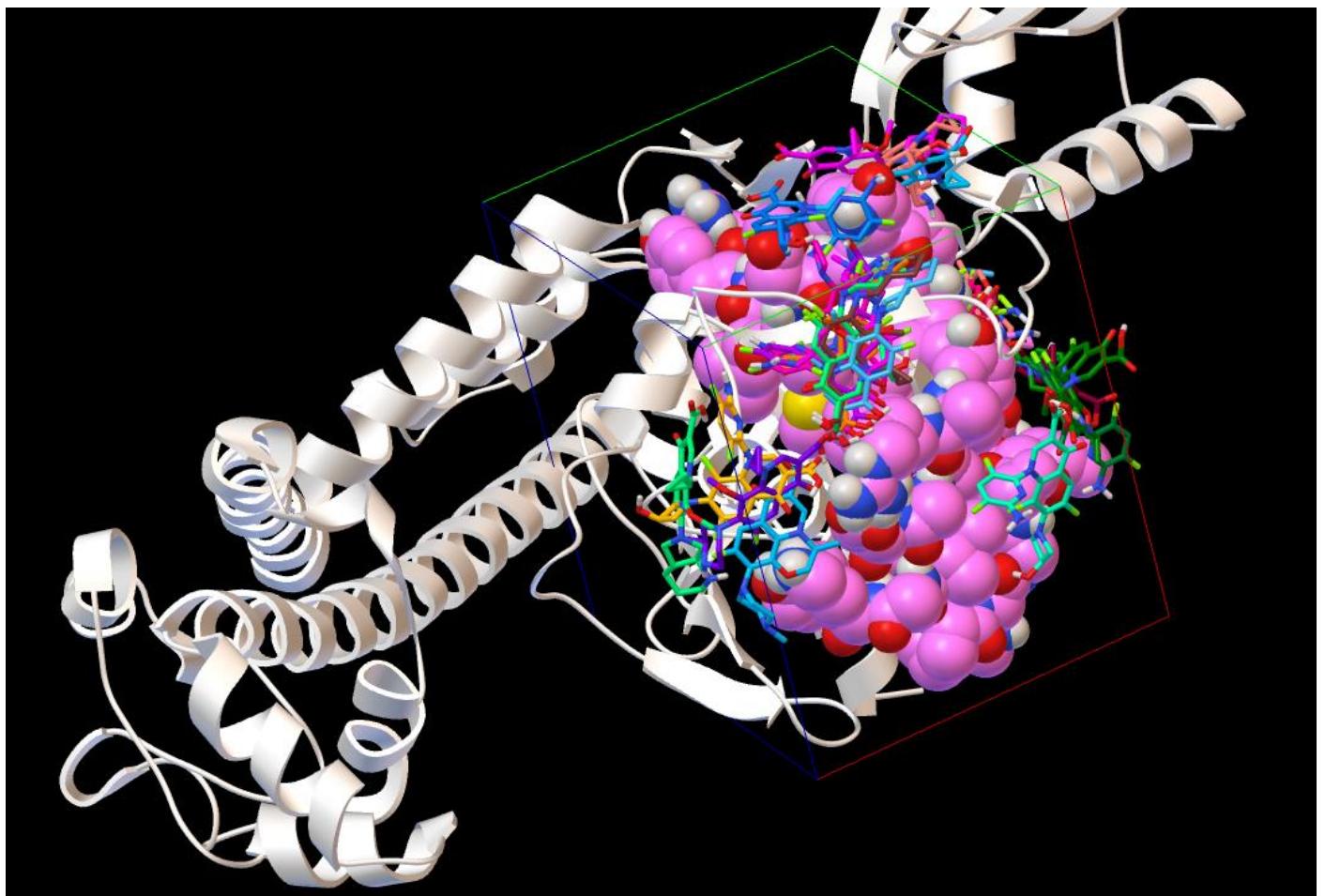


Figure S12. Blind docking result with active ligands in GyrA of *P. aeruginosa*

Note. Image obtained using the AutoDockTools program that shows the grid box that was used in the docking with the new molecules encompassing the QRDR in space-filling model; together with the result of the blind docking performed with active ligands of various colors under a stick model against the GyrA MT of *P. aeruginosa* in a ribbon diagram.

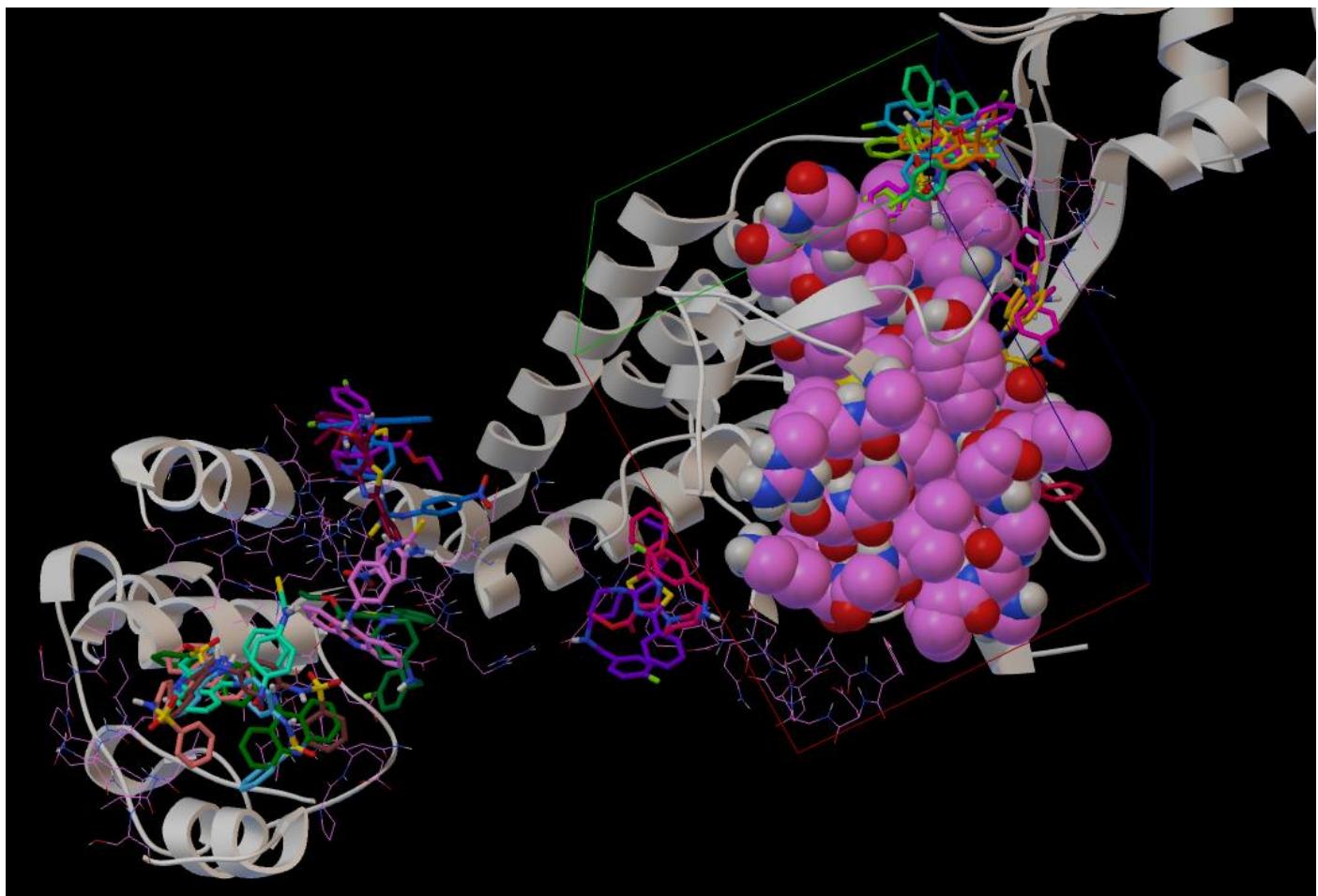


Figure S13. Blind docking result with inactive ligands in GyrA of *P. aeruginosa*

Note. Image obtained using the AutoDockTools program that shows the grid box that was used in the docking with the new molecules encompassing the QRDR in space-filling model; together with the result of the blind docking performed with inactive ligands of various colors under a stick model against the GyrA MT of *P. aeruginosa* in a ribbon diagram and some areas as a stick model.

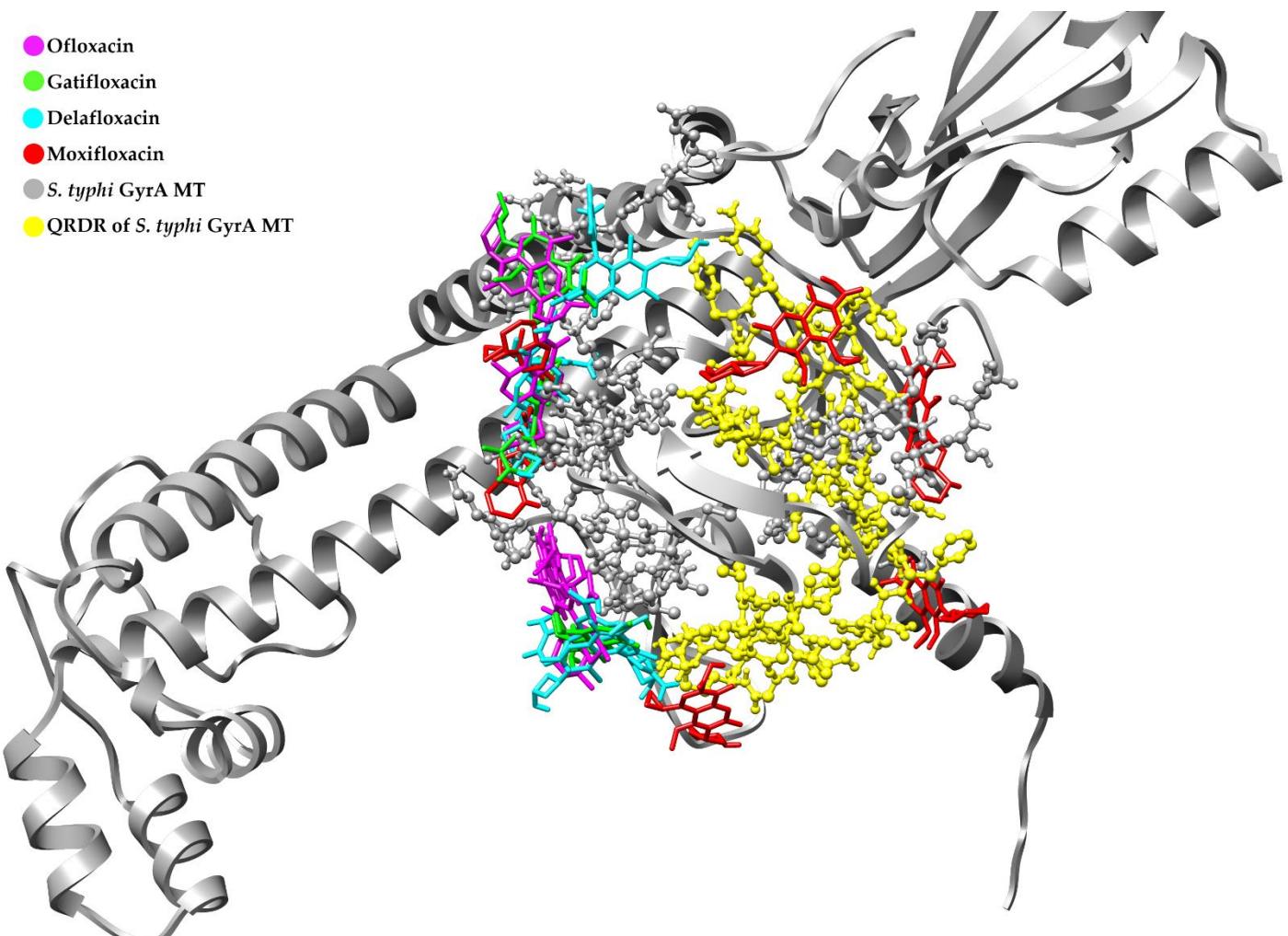


Figure S14. Molecular docking of the active ligands against the GyrA of *S. typhi*

Note. Image obtained using the UCSF Chimera program showing the blind docking results with some conformations for the active molecules, each one represented in stick model by a characteristic color; docked in GyrA MT of *S. typhi* in the ribbon diagram and ball & stick model in gray as target, QRDR is highlighting in yellow.

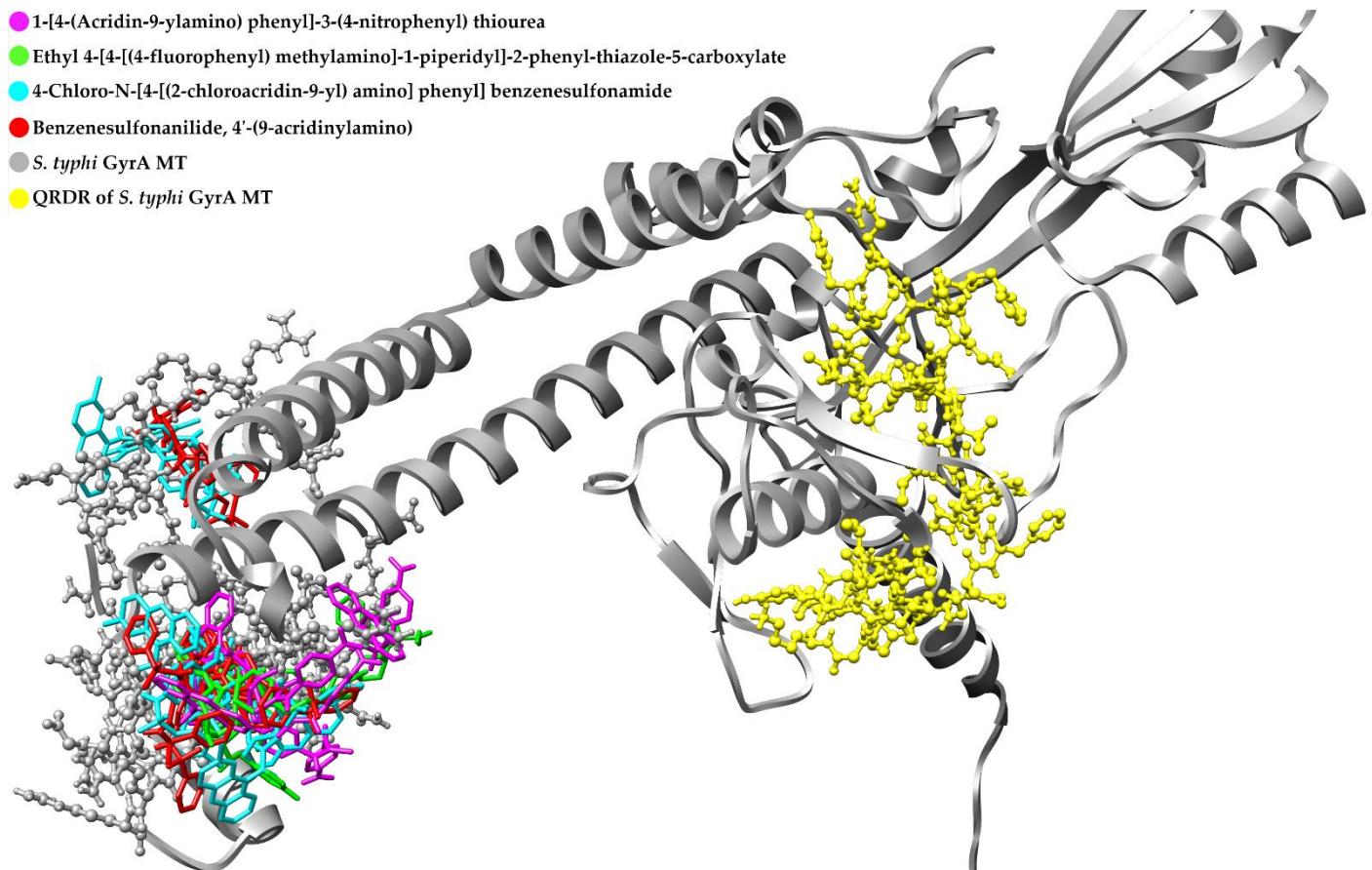


Figure S15. Molecular docking of the inactive ligands against the GyrA of *S. typhi*

Note. Image obtained using the UCSF Chimera program showing the blind docking results with some conformations for the inactive molecules, each one represented in stick model by a characteristic color; docked in GyrA MT of *S. typhi* in the ribbon diagram and ball & stick model in gray as target, QRDR is highlighting in yellow.

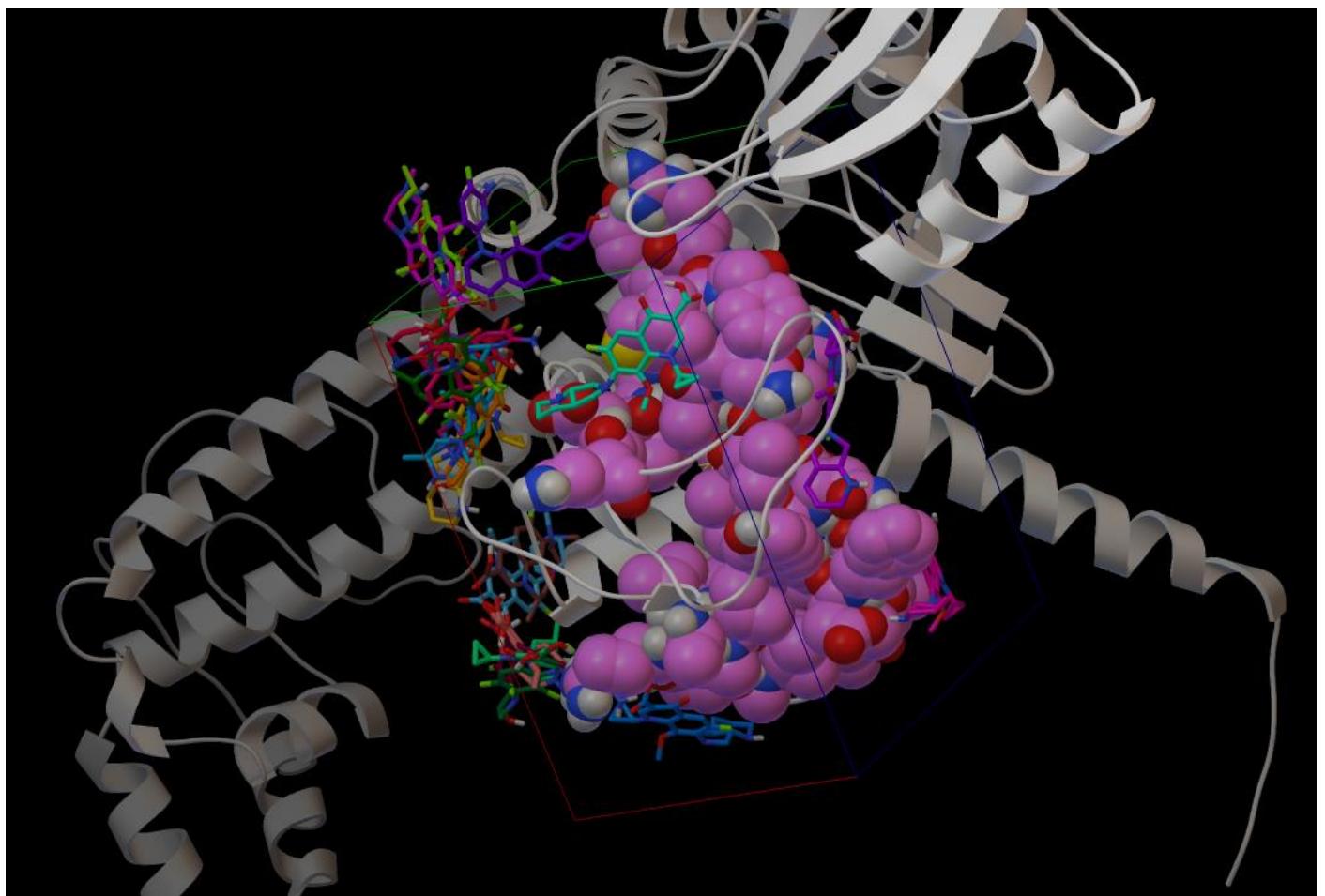


Figure S16. Blind docking result with active ligands in GyrA of *S. typhi*

Note. Image obtained using the AutoDockTools program that shows the grid box that was used in the docking with the new molecules encompassing the QRDR in space-filling model; together with the result of the blind docking performed with active ligands of various colors under a stick model against the GyrA MT of *S. typhi* in a ribbon diagram.

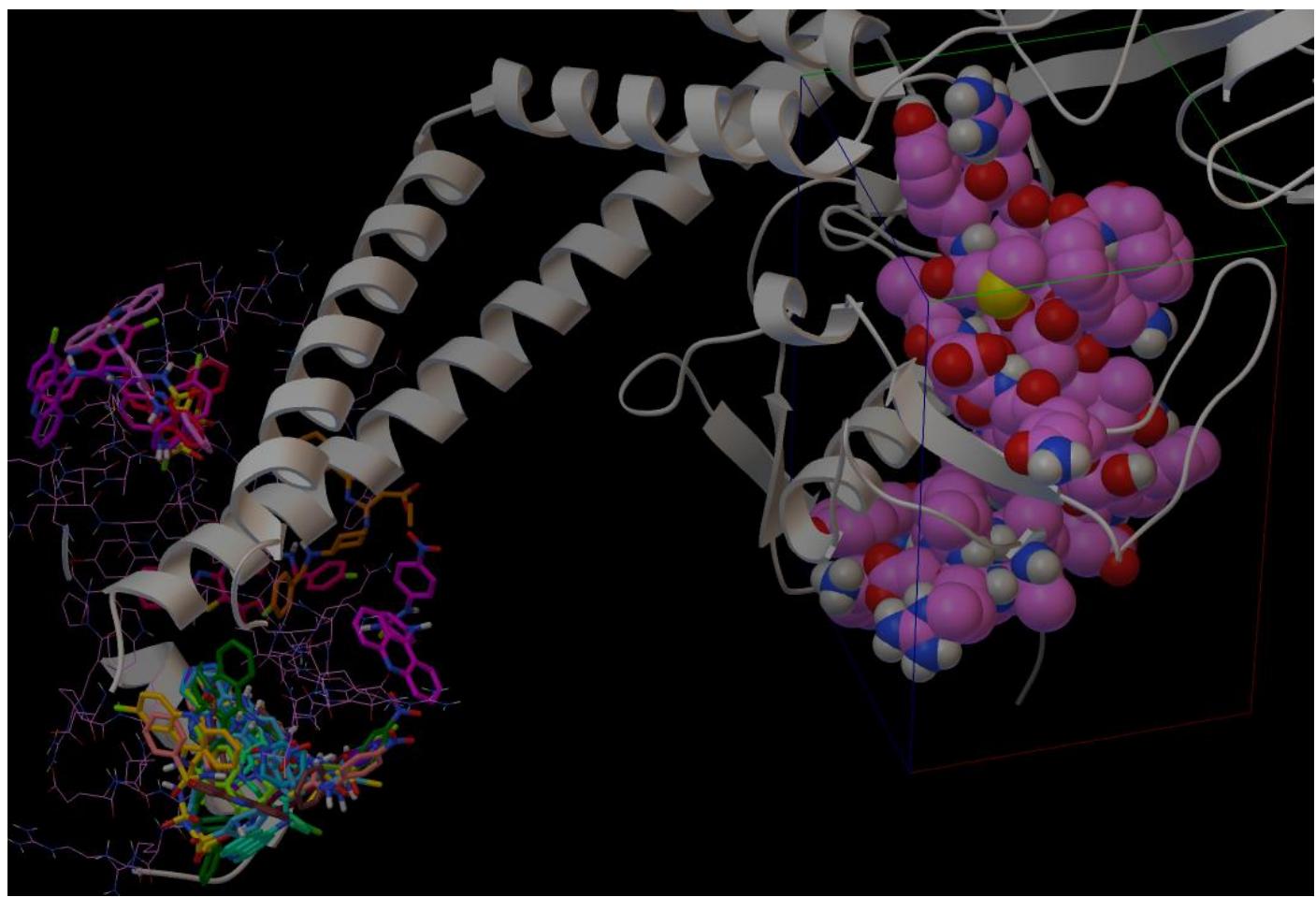


Figure S17. Blind docking result with inactive ligands in GyrA of *S. typhi*

Note. Image obtained using the AutoDockTools program that shows the grid box that was used in the docking with the new molecules encompassing the QRDR in space-filling model; together with the result of the blind docking performed with inactive ligands of various colors under a stick model against the GyrA MT of *S. typhi* in a ribbon diagram and some areas as a stick model.