

Table S1. MICs for select antibiotics of *E. coli* BW25113 and *E. coli* 6146 derived mutants from NAM (gut concentration)/ciprofloxacin (1 x MIC) combination plates.

		MIC (µg/mL)									
		CIP	LEV	MIN	AMX	CAZ	FEP	MER	COL	NIT	TRS
<i>E. coli</i> BW25113 derived mutants	WT	0.015	0.03	2	8	0.5	0.06	0.03	1	16	0.5
	M1*	0.125 (8x)	0.25 (8x)	4 (2x)	16 (2x)	1 (2x)	0.125 (2x)	0.03	1	16	0.5
	IBF_M1*	0.125 (8x)	0.125 (4x)	8 (4x)	8	1 (2x)	0.125 (2x)	0.06 (2x)	1	16	0.5
	APAP_M1*	0.25 (16x)	0.125 (4x)	8 (4x)	16 (2x)	1 (2x)	0.125 (2x)	0.06 (2x)	1	16	0.5
	APAP_M2*	0.06 (4x)	0.125 (4x)	8 (4x)	16 (2x)	2 (4x)	0.125 (2x)	0.06 (2x)	1	16	0.5
	ATOR_M1*	0.125 (8x)	0.125 (4x)	4 (2x)	16 (2x)	2 (4x)	0.125 (2x)	0.06 (2x)	1	16	1 (2x)
	WT	0.015	0.03	2	8	0.5	0.03	0.03	2	16	0.5
<i>E. coli</i> 6146 derived mutants	M1*	0.125 (8x)	0.25 (8x)	4 (2x)	16 (2x)	1 (2x)	0.125 (4x)	0.03	2	16	0.5
	APAP_M1	0.125 (8x)	0.25 (8x)	2	16 (2x)	1 (2x)	0.125 (4x)	0.03	2	16	0.5
	IBF_M1*	0.125 (8x)	0.25 (8x)	2	8	1 (2x)	0.03	0.03	2	16	0.5
	DIC_M4	0.25 (16x)	0.25 (8x)	2	8	0.5	0.125 (4x)	0.06 (2x)	4 (2x)	16	0.5
	ATOR_M4	0.25 (16x)	0.25 (8x)	2	8	0.5	0.125 (4x)	0.06 (2x)	4 (2x)	16	0.5
	FRS_M1*	0.5 (32x)	0.5 (16x)	2	8	0.5	0.06 (2x)	0.03	4 (2x)	16	0.5
	WT	0.015	0.03	2	8	0.5	0.03	0.03	2	16	0.5

Wild type (WT), Ciprofloxacin (CIP), levofloxacin (LEV), minocycline (MIN), amoxicillin (AMX), ceftazidime (CAZ), cefepime (FEP), meropenem (MER), colistin (COL), nitrofurantoin (NIT), trimethoprim-sulfamethoxazole (TRS), ibuprofen (IBF), acetaminophen (APAP), atorvastatin (ATOR) diclofenac (DIC), frusemide (FRS). Asterisks indicate isolates selected for whole genome sequencing. Values in brackets indicate the fold change of MICs against antibiotics for mutants compared to the WT.

Table S2. MICs for select antibiotics of *E. coli* BW25113 and *E. coli* 6146 derived mutants from acetaminophen and ibuprofen-based NAM combinations/ ciprofloxacin exposure.

MIC (µg/mL)											
		CIP	LEV	MIN	AMX	CAZ	FEP	MER	COL	NIT	TRS
<i>E. coli</i> BW25113 derived mutants	WT	0.015	0.03	2	8	0.5	0.06	0.03	1	16	0.5
	APAP/IBF_M1*	0.5 (32x)	0.125 (4x)	4 (2x)	8	1 (2x)	0.125 (2x)	0.03	1	16	0.5
	IBF/MET_M1*	0.5 (32x)	0.25 (8x)	2	16 (2x)	0.5	0.06	0.03	2 (2x)	16	0.5
	APAP/MET_M1*	0.25 (16x)	0.25 (8x)	8 (4x)	16 (2x)	2 (4x)	0.25 (4x)	0.03	1	16	0.5
	IBF/FRS_M1*	0.125 (8x)	0.125 (4x)	8 (4x)	16 (2x)	1 (2x)	0.125 (2x)	0.03	1	16	0.5
	IBF/DIC_M1*	1 (64x)	0.25 (8x)	2	8	0.5	0.06	0.06 (2x)	1	16	0.5
	APAP/IBF_M2	0.25 (16x)	0.125 (4x)	2	8	0.5	0.06	0.03	1	16	0.5
	IBF/MET_M2	0.125 (8x)	0.125 (4x)	8 (4x)	16 (2x)	1 (2x)	0.125 (2x)	0.03	1	16	0.5
<i>E. coli</i> 6146 derived mutants	WT	0.015	0.03	2	8	0.5	0.03	0.03	2	16	0.5
	IBF/FRS_M1*	0.5 (32x)	0.5 (16x)	4 (2x)	16 (2x)	1 (2x)	0.06 (2x)	0.03	4 (2x)	16	0.5
	IBF/MET_M1	0.125 (8x)	0.125 (4x)	2	8	0.5	0.06 (2x)	0.03	2	16	0.5
	IBF/APAP_M1*	0.125 (8x)	0.25 (8x)	8 (4x)	8	1 (2x)	0.125 (4x)	0.03	2	16	0.5
	APAP/ATOR_M1	0.125 (8x)	0.25 (8x)	4 (2x)	8	0.5	0.125 (4x)	0.06 (2x)	2	16	0.5
	IBF/ATOR_M1	0.125 (8x)	0.25 (8x)	4 (2x)	8	0.5	0.06 (2x)	0.06 (2x)	2	16	0.5
	IBF/DIC_M1	0.25 (16x)	0.25 (8x)	2	8	0.5	0.06 (2x)	0.06	2	16	0.5
	APAP/FRS_M1	0.125 (8x)	0.25 (8x)	2	16 (2x)	1 (2x)	0.06 (2x)	0.06	2	16	0.5

Wild type (WT), Ciprofloxacin (CIP), levofloxacin (LEV), minocycline (MIN), amoxicillin (AMX), ceftazidime (CAZ), cefepime (FEP), meropenem (MER), colistin (COL), nitrofurantoin (NIT), trimethoprim-sulfamethoxazole (TRS), ibuprofen (IBF), acetaminophen (APAP), atorvastatin (ATOR) diclofenac (DIC), frusemide (FRS). Asterisks indicate isolates selected for whole genome sequencing. Values in brackets indicate the fold change of MICs against antibiotics for mutants compared to the WT

Table S3. Absolute number of mutants on the selective plates

	Absolute number of mutants									
Strain	Control	Acetaminophen	Atorvastatin	Diclofenac	Furosemide	Ibuprofen	Metformin	Pseudoephedrine	Temazepam	Tramadol
<i>E. coli</i> BW25113	3.6 ± 1.1	11.5 ± 0.6	3.5 ± 0.5	7.7 ± 0.4	5.7 ± 1.1	29.0 ± 1.9	5.7 ± 4.5	1.3 ± 0.5	1.8 ± 0.7	1.5 ± 0.6
	Acetaminophen +	Acetaminophen +	Acetaminophen +	Acetaminophen +	Acetaminophen +	Acetaminophen +	Acetaminophen +	Acetaminophen +		
	Atorvastatin	Diclofenac	Furosemide	Ibuprofen	Metformin	Pseudoephedrine	Temazepam	Tramadol		
	6.0 ± 0.4	10.5 ± 3.0	13.5 ± 2.5	35.5 ± 2.0	10.5 ± 2.2	4.7 ± 1.8	8.0 ± 3.2	5.0 ± 1.2		
	Ibuprofen +	Ibuprofen +	Ibuprofen +	Ibuprofen +	Ibuprofen +	Ibuprofen +	Ibuprofen +			
	Atorvastatin	Diclofenac	Furosemide	Metformin	Pseudoephedrine	Temazepam	Tramadol			
<i>E. coli</i> 6146	15.7 ± 5.3	18.5 ± 4.5	25.7 ± 6.1	13.7 ± 2.3	6.2 ± 2.1	18.5 ± 3.6	9.2 ± 1.9			
	Control	Acetaminophen	Atorvastatin	Diclofenac	Furosemide	Ibuprofen	Metformin	Pseudoephedrine	Temazepam	Tramadol
	2.7 ± 0.7	16.0 ± 3.3	2.0 ± 0.4	2.7 ± 0.2	2.2 ± 1.3	55.7 ± 22.8	3.2 ± 1.3	0.2 ± 0.2	0.4 ± 0.2	0
	Acetaminophen +	Acetaminophen +	Acetaminophen +	Acetaminophen +	Acetaminophen +	Acetaminophen +	Acetaminophen +	Acetaminophen +		
	Atorvastatin	Diclofenac	Furosemide	Ibuprofen	Metformin	Pseudoephedrine	Temazepam	Tramadol		

	2.7 ± 1.0	2.5 ± 0.9	4.7 ± 0.8	13.0 ± 7.2	3.2 ± 0.6	1.0 ± 0.7	0.7 ± 0.4	0.7 ± 0.4		
	Ibuprofen + Atorvastatin	Ibuprofen + Diclofenac	Ibuprofen + Furosemide	Ibuprofen + Metformin	Ibuprofen + Pseudoephedrine	Ibuprofen + Temazepam	Ibuprofen + Tramadol			
	12.2 ± 2.0	16.2 ± 2.4	10.0 ± 2.2	14.5 ± 2.7	7.7 ± 2.0	7.0 ± 2.4	3.0 ± 1.2			