Drug	IC_{50} (μM)	Drug	IC_{50} (μM)	Drug	IC_{50} (μM)
C1	31	C9	44	C17	0.004
C2	127	C10	9	C18	17
C3	13	C11	10	C19	23
C4	2.17E+06	C12	20	C20	92
C5	25	C13	33	C21	9
C6	14	C14	45	C22	13
C7	4727	C15	13	C23	0.0858
C8	2.96E+22	C16	93	C24	12

Supplementary Table 1: The half maximal inhibitory concentrations (IC_{50}) of C1-24 calculated from respective curves in Fig. 2a.

	IC_{50} (μM)		
Drug	MTB IspH	PA IspH	PF IspH
C17	0.3567	0.0051	0.0310
C23	0.1697	0.0023	0.5043

Supplementary Table 2: IC_{50} of C17 and C23 against *Mycobacterial* (MTB), *Pseudomonas* (Pa) and *Plasmodium* (Pf) IspH calculated from respective curves in Fig. 2c.

Drug	IC_{50} (μM)
C23.07	0.0283
C23.20	0.0022
C23.21	0.0030
C23.28	0.0201
C23.47	0.0814

Supplementary Table 3: IC_{50} of C23 analogs against *E. coli* IspH calculated from respective curves in Fig. 2d.

MDR Bacteria	MIC90									
	23.07 TPP		23.20 TPP		23.21 TPP		23.28 TPP		23.47 TPP	
	µM	µg/ml	µM	µg/ml	µM	µg/ml	µM	µg/ml	µM	µg/ml
A. baumannii	>500	>250	31	16	31	16	16	8	250	125
K. pneumoniae	>500	>250	16	8	31	16	31	16	250	125
E. aerogenes	125	63	31	16	16	8	31	16	63	31
V. cholerae	125	63	16	8	16	8	16	8	63	31
S. flexneri	>500	>250	63	31	31	16	63	31	125	63
E. coli	63	31	4	2	4	2	4	2	<4	<2
H. pylori	250	125	31	16	31	16	31	16	63	31
M. tuberculosis	4	2	4	2	4	2	4	2	63	31
P. aeruginosa	>500	>250	31	16	63	31	125	63	250	125
Y. pestis	>500	>250	31	16	63	31	63	31	125	63
B. sphaericus	>500	>250	31	16	63	31	63	31	500	250

MDR Bacteria	Antibiotics					
	Ampicillin	Kanamycin	Chloramphenicol	Tetracycline	Gentamycin	Streptomycin
A. baumannii	R	R	R	R	S	R
K. pneumoniae	R	R	R	R	R	S
E. aerogenes	R	R	S	R	R	R
V. cholerae	R	S	S	R	S	R
S. flexneri	R	S	S	S	S	S
E. coli	S	S	S	S	S	S
H. pylori	R	R	S	R	R	S
M. tuberculosis	R	S	S	S	S	S
P. aeruginosa	R	R	R	R	R	R
Y. pestis	R					
B. sphaericus	R					
R = Resistant (>250µM), S = Sensitive						

Supplementary Table 4: Testing DAIA prodrugs on MDR clinical isolates of multiple bacteria and comparing against commercial antibiotics.

Bacteria permeable TPP linked prodrug forms of C23.07, C23.20, C23.21, C23.28 and C23.47 were tested for killing efficiency against multidrug resistant (MDR) clinical isolates of multiple species of pathogenic bacteria measured by resazurin blue and CFU assay. Top panel shows the respective Minimum Inhibitory Concentration required to inhibit the growth of 90% of organisms (MIC_{90}). Any organism with an MIC90 > 250µg/mL (500µM) is considered resistant to the antibiotic. Bottom panel shows resistance of the clinical isolates tested to commercial antibiotics.

Clinical isolates of P/MDR Bacteria	MIC90 (μM)									
	23.20 TPP	23.21 TPP	23.28 TPP	Ceftaroline	Meropenem	Amikacin	Ceftriaxone	Cefepime	Ciprofloxacin	Tobramycin
***A. baumannii* (AB5075-UW)**	31	31	16	500	125	125	250	250	250	125
***K. pneumoniae* (1.53)**	31	16	31	>500	125	>500	>500	125	125	>500
***E. aerogenes* (UCI15)**	31	16	63	500	125	250	>500	500	125	125
V. cholerae	16	16	16	>500	250	>500	>500	125	125	>500
***P. aeruginosa* (MRSN 5524)**	16	31	250	500	125	31	500	500	63	63

Supplementary Table 5: Comparing DAIA prodrugs against best-in class antibiotics on MDR clinical isolates of multiple bacteria. MIC90 of C23.20, C23.21 and C23.28 prodrugs against *A. baumannii, K. pneumoniae, E. aerogenes, V. cholerae* and *P. aeruginosa* compared to the respective MIC90s of Ceftaroline, Meropenem, Amikacin, Ceftriaxone, Cefepime, Ciprofloxacin and Tobramycin.