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Novel antibacterial series identified through integrated drug discovery technology platform

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The mechanism of efflux is a tour de force in bacterial armoury that has thwarted discovery of novel antibiotics. We reported the discovery of a novel series of compounds with potent antibacterial properties that is devoid of efflux liability. Starting from a phenotypic screen with a library diverse molecule on a panel of efflux deficient *E. coli* strains, we progressed a nitro-thiophene carboxamide derivative that effluxed selectively via the efflux pump AcrAB-TolC. Binding of these molecules to AcrB was evaluated by fluorescent thermal shift and Nile red dye-based assays. Prospective *in silico* modeling using computational methodologies viz. molecular docking and MD simulations were done. Iterative design and synthesis based on binding potency by *in vitro* assays and *in silico* prediction led to the generation of a series of molecules that were potent on wild type and multi-drug resistant clinical isolates of *E. coli, Shigella* spp. and *Salmonella* spp. Using a novel system biology reverse MOA (mechanism of action) protocol that measures the synergistic sensitivity on library of specially curated single gene knockout sub-library from the KIEO strains we identified these molecules to be pro-drugs that are activated inside *E. coli* by specific bacterial nitro reductases NfsA and NfsB. The conversion of these pro-drugs was characterized by *in vitro* enzymatic assay of purified NfsA and NfsB. Furthermore, these molecules were shown to be bactericidal and efficacious in a mouse thigh infection model.

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