Fluorquinolones (FQs) WCK 1152, WCK 771 and Derivatives thereof Inhibit Multidrug Efflux Pumps (EP) of P. aeruginosa (PA), E. coli (EC), S. pneumoniae (SPN) and S. aureus (SA)


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ABSTRACT

Background: Multidrug efflux is a major cause of intrinsic and acquired drug resistances in many microorganisms. Strategies to evade the effects of some antimicrobial agents, PA, EC, SPN and SA possess efflux pumps that transport selected classes of antibiotics, macrolides, aminoglycosides and cationic agents. One strategy to target resistant mechanisms of microbial cell wall defense is to form inhibitors of efflux pump-mediated drug resistance.

Methods: A library of about 1000 11-tetrazole FQs was screened including Solu-decadrox, the active salt (WCK 771) and WCK 1152, prepared by condensing 6-amino- or 4-diarylpyridones with ionized FQ cores and subsequent optimal dehalogenation. Screening methods for identification of potent inhibitors of 25387, EC 2051 and SPN 3514 were done by antibiotic diffusion assay in combination with W. pseudononas L1945 or EC and azithromycin (Az) for SPN. The zone diameter difference between the drug in absence and presence of the inhibitor was determined by the checkerboard inhibition method.

RESULTS & DISCUSSION: Strains expressing efflux pumps for fluorquinolones were used native P. aeruginosa 25387, clinical isolates E. coli 2951, S. pneumoniae 3514 (rif) and S. aureus 11998 (NorA). They were obtained from the Centre for Disease Control, Atlanta, S. aureus expressing NorA from obtained from Prof. G. W. K. Kozak (Wayne State University, Detroit, MI).

1) Potentiation of levofloxacin using P. aeruginosa 25387 and E. coli 2951

Mueller-Hinton agar plates with and without 15 and 5 mg/ml levofloxacin, were treated with a P. aeruginosa 25387 and E. coli 2951 respectively, and determined with in DMPO at various concentrations using ESR.

2) Potentiation of Azithromycin using S. pneumoniae 3514

Mueller-Hinton agar plates containing 5% sheep blood and 0.5 mg/ml azithromycin, were used with S. pneumoniae 3514. The test compounds dissolved in DMPO at various concentrations were added to wells. Zones of inhibition were determined with the standard medium and without it, were recorded after incubation for 24 h.

3) Inhibition of norfloxacin against S. aureus 11998

The MIC index values for fluorquinolones were obtained by a method described by Elphick, G. M., & Melling, H. C.

RESULTS & DISCUSSION

Fluorquinolone efflux pump inhibitors inhibiting efflux pumps in PA and EC are shown in Table 1, met efflux pump in SPN and Table 2 and NorA in SA is Table 3.

REFERENCES