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# Activity of the new quinolones WCK 771, WCK 1152 and WCK 1153 against clinical isolates of *Streptococcus pneumoniae* and *Streptococcus pyogenes*

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***Objectives and methods*: The new fluoroquinolones WCK 771, WCK 1152 and WCK 1153 were developed to overcome quinolone resistance in Gram-positive bacteria. The activity of these new quinolones was tested against 159 clinical isolates of *Streptococcus pneumoniae* and 52 clinical isolates of *Streptococcus pyogenes* using the microbroth dilution method.**

***Results*: $MIC_{50}$/$MIC_{90}$ values (mg/L) of WCK 771, WCK 1152 and WCK 1153 for quinolone-susceptible *S. pneumoniae* (*n* = 119; 54 penicillin G-susceptible, 53 penicillin G-intermediate, and 12 penicillin G-resistant strains) were 0.25/0.5, 0.03/0.06 and 0.016/0.03, respectively. $MIC_{50}$/$MIC_{90}$ values (mg/L) for quinolone-resistant pneumococci (*n* = 40) increased to 4/16, 0.25/1 and 0.125/0.5, respectively. Against *S. pyogenes*, WCK 771, WCK 1152 and WCK 1153 were also highly active with $MIC_{50}$/$MIC_{90}$ values (mg/L) of 0.25/0.25, 0.03/0.06 and 0.03/0.03, respectively.**

***Conclusions*: Overall, WCK 771 was highly active against quinolone-susceptible, but not against quinolone-resistant *S. pneumoniae*, whereas WCK 1152 and WCK 1153 were more potent and were able to overcome quinolone resistance in both *S. pneumoniae* and *S. pyogenes*.**

Keywords: fluoroquinolones, resistance, Germany, pneumococcus

## Introduction

*Streptococcus pneumoniae* and *Streptococcus pyogenes* are major infectious agents causing pneumonia, acute exacerbations of chronic bronchitis, pharyngitis, sinusitis, otitis media, bacteraemia, meningitis and other diseases. The development of resistance to penicillin G and macrolides in pneumococci is of increasing concern, especially that of multidrug-resistance. The fluoroquinolones were introduced in Europe in the 1980s and initially fulfilled the need to overcome the multidrug resistance at that time, and today they are still important in the treatment of a wide range of infections. In general, the prevalence of fluoroquinolone resistance in Europe is still low,[1] but resistance to many members of this class of agents is emerging in *S. pneumoniae* outside Europe.

Bacterial resistance to quinolones occurs mainly by alteration of their intracellular drug targets, the DNA topoisomerase IV and DNA gyrase enzymes. Genetic and biochemical studies have shown that fluoroquinolones target primarily topoisomerase IV and secondarily DNA gyrase in *S. pneumoniae*.[2,3] Moreover, resistance mutations are localized in the quinolone resistance-determining regions (QRDRs) of *parC*, *parE* and *gyrA*. Low-level quinolone-resistant strains usually harbour mutations altering the QRDR of one of the two subunits of topoisomerase IV: (i) S79 or D83 of *parC* or (ii) D435 of *parE*. This study examined the *in vitro* activity of the three quinolones WCK 771 [a novel arginine salt of the tricyclic fluoroquinolone *S*-(–)-nadifloxacin], WCK 1152 and WCK1153 (prepared by condensing 4-amino- or 4-hydroxy piperidines with known fluoroquinolone cores and subsequent optional derivatization) against selected clinical isolates of *S. pneumoniae* and *S. pyogenes* possessing different antibiotic resistance profiles (Figure 1).

## Materials and methods

### *Bacterial isolates*

One hundred and fifty-nine isolates of *S. pneumoniae* and 52 isolates of *S. pyogenes* were chosen from the collection of the German National

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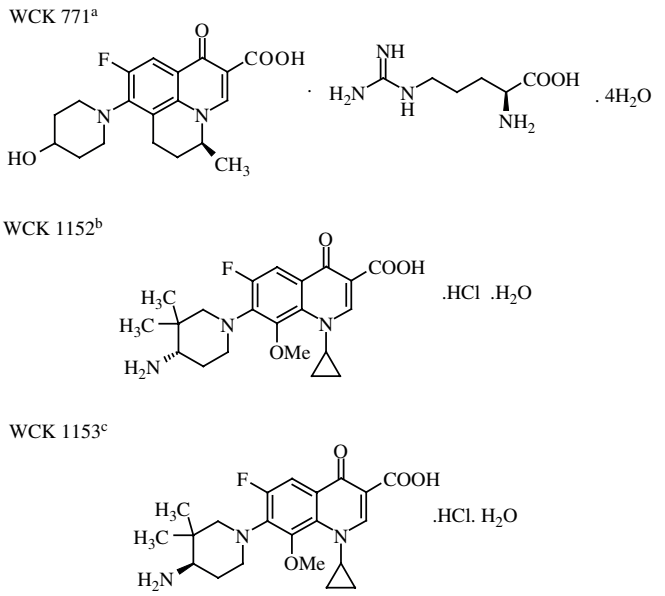


**Figure 1.** Chemical structures of WCK 771, WCK 1152 and WCK1153. [a]Chemical name: *S*-(–)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid L-arginine salt tetrahydrate. [b]Chemical name: *S*-(–)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3, 3-dimethylpiperidin-1-yl)-1,4 dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride monohydrate. [c]Chemical name: *R*-(+)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4 dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride monohydrate.

Reference Centre for Streptococci. Pneumococcal strains were isolated from blood ($n$ = 68, 42.8%), CSF ($n$ = 36; 22.6%), bronchoalveolar lavages ($n$ = 8, 5.0%), other normally sterile body sites ($n$ = 12; 7.5%), and the respiratory tract ($n$ = 35; 22.0%). Of the *S. pyogenes* isolates, 50 (96.2%) were isolated from the nasopharynx of patients with tonsillopharyngitis and 2 (3.8%) isolates were from wound infections. The strain collection included strains with different resistance profiles. Strains were isolated between 1999 and 2004.

### *Susceptibility testing*

MIC testing was performed using the broth microdilution method as recommended by the Clinical Laboratory Standards Institute (CLSI; formerly NCCLS).[4] Microtitre plates containing WCK 771, WCK 1152, WCK 1153 (all from Wockhardt Ltd, India) and comparators with cation-adjusted Mueller–Hinton broth (Oxoid, Wesel, Germany) plus 5% lysed horse blood (Oxoid) were used. *S. pneumoniae* ATCC 49619 was used as control strain.

### *Determination of resistance phenotypes and genotypes*

For determination of macrolide-resistant phenotypes, discs (Oxoid Ltd, Basingstoke, UK) of erythromycin (15 µg) and clindamycin (2 µg) were placed 15 to 20 mm apart on Mueller–Hinton agar (BBL Microbiology Systems, Cockeysville, MD, USA) with 5% sheep blood (Oxoid, Wesel, Germany). Determination of macrolide-resistance genotypes was performed by a light cycler protocol as described previously.[5,6] Nineteen pneumococcal isolates and one fluoroquinolone-resistant *S. pyogenes* isolate were randomly selected and analysed for alterations in the QRDRs. Prepared chromosomal DNA was used as a template for PCR amplification of target QRDRs. The primers and PCR conditions were those previously defined.[7]

## Results

MIC results for streptococcal isolates are presented in Table 1. WCK 1152 and WCK 1153 had the lowest MICs among the 10 quinolones tested, with $MIC_{50}$ and $MIC_{90}$ values of 0.03 and 0.06 mg/L (WCK 1152) and 0.016 and 0.03 mg/L (WCK 1153) for *S. pneumoniae*, respectively. WCK 771 was less active with $MIC_{50}$ and $MIC_{90}$ values of 0.25 and 0.5 mg/L, respectively. WCK 771, WCK 1152 and WCK 1153 were also highly active against penicillin G non-susceptible strains ($MIC_{90}$ WCK 771: 0.5 mg/L; $MIC_{90}$ WCK 1152: 0.06 mg/L; $MIC_{90}$ WCK 1153: 0.03 mg/L) and clarithromycin-resistant strains ($MIC_{90}$ WCK 771: 0.5 mg/L; $MIC_{90}$ WCK 1152: 0.06 mg/L; $MIC_{90}$ WCK 1153: 0.03 mg/L) (data not shown). WCK 1152 and WCK 1153 were more active than WCK 771 and the other quinolones against ciprofloxacin-resistant *S. pneumoniae* ($MIC_{90}$ WCK 771: 16 mg/L; $MIC_{90}$ WCK 1152: 1 mg/L; $MIC_{90}$ WCK 1153: 0.5 mg/L).

Against *S. pyogenes*, WCK 1152 and WCK 1153 also had the highest *in vitro* activity of all quinolones investigated. One strain (MSR 141) showed high-level ciprofloxacin resistance (MIC ≥ 32 mg/L). Based on the NCCLS breakpoints, this strain was also resistant to moxifloxacin (MIC, 4 mg/L) and showed a relatively high MIC for WCK 771 (MIC, 16 mg/L); however, WCK 1152 and WCK 1153 (MICs 1 mg/L and 0.5 mg/L) were both highly active (data not shown). In Table 2, mutations in the QRDRs and MICs of WCK 771, WCK 1152, WCK 1153 and comparators for 19 randomly selected ciprofloxacin-resistant *S. pneumoniae* and the one highly ciprofloxacin-resistant *S. pyogenes* are presented. Pneumococcal isolates with intermediate resistance to levofloxacin (MIC, 4 mg/L) showed the *gyrA* wild-type and relatively low MICs of WCK 771 (MICs, 1–4 mg/L), WCK 1152 (0.125 mg/L) and WCK 1153 (0.06–0.125 mg/L).

## Discussion

The spread of fluoroquinolone-resistant *S. pneumoniae* strains, despite worldwide prevalence being relatively low, is a concern to clinicians who manage respiratory tract infections. In a recent European multicentre study, a mean rate of fluoroquinolone resistance of 0.8% was reported (18 of 2279 pneumococcal strains), with the highest rates of resistance being in Italy (1.3%) and Portugal (1.2%).[1] To date, the level of fluoroquinolone resistance in *S. pyogenes* is low.[6]

New fluoroquinolones have been developed to overcome resistance. WCK 771 is an arginine salt of the *S*-(–) isomer of nadifloxacin. Because the *S*-(–) isomer is primarily responsible for antibacterial activity, the potency of WCK 771 is two to four times higher than that of racemic nadifloxacin. The comparative assessment of WCK 771 with other fluoroquinolones demonstrated that this new agent is a highly potent antistaphylococcal fluoroquinolone with improved potency against even fluoroquinolone-resistant strains of *S. aureus* and coagulase-negative staphylococci.[8] In this study, an excellent level of *in vitro* activity against both *S. pneumoniae* and *S. pyogenes* streptococci was found for WCK 771 with low $MIC_{90}$ values (0.25–0.5 mg/L).

However, WCK 771 was less potent against highly ciprofloxacin-resistant *S. pneumoniae*, confirming findings of Appelbaum and co-workers who reported WCK 771 $MIC_{50}$/$MIC_{90}$ values for 25 quinolone-resistant pneumococcal isolates

**Table 1.** MIC range, $MIC_{50}$ and $MIC_{90}$ of WCK 771, WCK 1152, WCK 1153 and comparators for *Streptococcus pneumoniae* and *Streptococcus pyogenes* isolates

| Species/antibiotic | MIC range (mg/L) | $MIC_{50}$ (mg/L) | $MIC_{90}$ (mg/L) | % Resistant |
|---|---|---|---|---|
| *S. pneumoniae* | | | | |
| WCK 771 | | | | |
| all isolates | 0.06–1 | 0.25 | 0.5 | ND |
| Cip-R[a] | 0.25–16 | 4 | 16 | ND |
| WCK 1152 | | | | |
| all isolates | 0.016–0.125 | 0.03 | 0.06 | ND |
| Cip-R[a] | 0.06–1 | 0.25 | 1 | ND |
| WCK 1153 | | | | |
| all isolates | 0.016–0.06 | 0.016 | 0.03 | ND |
| Cip-R[a] | 0.03–0.5 | 0.125 | 0.5 | ND |
| ciprofloxacin | | | | |
| all isolates | 0.25–2 | 1 | 1 | ND |
| clinafloxacin | | | | |
| all isolates | 0.03–0.06 | 0.06 | 0.06 | ND |
| Cip-R[a] | 0.06–1 | 0.25 | 0.5 | ND |
| gatifloxacin | | | | |
| all isolates | 0.06–1 | 0.25 | 0.25 | 0 |
| Cip-R[a] | 0.25–8 | 1 | 4 | 50 |
| grepafloxacin | | | | |
| all isolates | 0.125–0.5 | 0.25 | 0.25 | 0 |
| Cip-R[a] | 0.25–≥32 | 2 | ≥32 | 77.5 |
| levofloxacin | | | | |
| all isolates | 0.5–1 | 0.5 | 1 | 0 |
| Cip-R[a] | 1–≥32 | 4 | ≥32 | 60 |
| moxifloxacin | | | | |
| all isolates | 0.06–0.125 | 0.06 | 0.06 | 0 |
| Cip-R[a] | 0.125–4 | 0.5 | 4 | 40 |
| sparfloxacin | | | | |
| all isolates | 0.125–1 | 0.25 | 0.5 | 0 |
| Cip-R[a] | 0.5–≥32 | 4 | ≥32 | 92.5 |
| penicillin G[b] | 0.008–2 | 0.125 | 1 | 54.6 |
| amoxicillin | 0.008–4 | 0.06 | 2 | 8.4 |
| cefotaxime | 0.008–2 | 0.06 | 1 | 7.6 |
| clarithromycin | 0.03–≥32 | 8 | 32 | 60.5 |
| clindamycin | 0.06–≥32 | 0.06 | >32 | 26.4 |
| telithromycin | 0.016–0.5 | 0.03 | 0.25 | 0 |
| quinupristin/dalfopristin | 0.5–1 | 0.5 | 1 | 0 |
| tetracycline | 0.06–32 | 0.5 | 32 | 33.3 |
| teicoplanin | 0.03–0.125 | 0.06 | 0.125 | 0 |
| vancomycin | 0.06–1 | 0.25 | 0.5 | 0 |
| *S. pyogenes*[c] | | | | |
| WCK 771 | 0.125–16 | 0.25 | 0.25 | ND |
| WCK 1152 | 0.016–1 | 0.03 | 0.06 | ND |
| WCK 1153 | 0.016–0.5 | 0.03 | 0.03 | ND |
| ciprofloxacin[a] | 0.25–≥32 | 0.5 | 1 | 3.8 |
| clinafloxacin | 0.06–2 | 0.06 | 0.06 | ND |
| gatifloxacin | 0.125–4 | 0.25 | 0.25 | 1.9 |
| grepafloxacin | 0.25–≥32 | 0.25 | 0.5 | 3.8 |
| levofloxacin | 0.25–≥32 | 0.25 | 0.5 | 1.9 |
| moxifloxacin | 0.06–4 | 0.06 | 0.125 | 1.9 |
| sparfloxacin | 0.25–≥32 | 0.25 | 0.5 | 5.8 |
| penicillin | 0.016–0.03 | 0.016 | 0.016 | 0 |
| amoxicillin | 0.016–0.03 | 0.016 | 0.016 | 0 |
| cefotaxime | 0.016–0.03 | 0.016 | 0.016 | 0 |
| clarithromycin | 0.06–≥32 | 16 | 32 | 92.3 |
| clindamycin | 0.06–≥32 | 0.125 | 32 | 44.2 |
| telithromycin | 0.016–32 | 1 | 4 | 46.2 |
| quinupristin/dalfopristin | 0.5–1 | 0.5 | 0.5 | 0 |
| tetracycline | 0.125–≥32 | 0.25 | 16 | 26.9 |
| teicoplanin | 0.03–0.125 | 0.06 | 0.125 | 0 |
| vancomycin | 0.25–0.5 | 0.25 | 0.5 | 0 |

ND, no data.
[a]Ciprofloxacin-resistant: ciprofloxacin MIC ≥ 4 mg/L.
[b]Penicillin G-intermediate ($n$ = 53); penicillin G-resistant ($n$ = 12).
[c]The collection included one isolate with a ciprofloxacin MIC of ≥32 mg/L, one isolate with a ciprofloxacin MIC of 4 mg/L, one isolate with a ciprofloxacin MIC of 2 mg/L, 26 macrolide-resistant isolates with an *erm*(B) genotype and a $cMLS_B$ phenotype, 10 isolates with an $iMLS_B$ phenotype [*erm*(TR)], and 12 isolates with an M phenotype.

of 4/8 mg/L, compared with 0.5/1 mg/L for clinafloxacin, 2/4 mg/L for gatifloxacin and moxifloxacin, 8/16 mg/L for levofloxacin and 16/>32 mg/L for ciprofloxacin.[9]

Data on the *in vitro* activity of WCK 1152 and WCK 1153 are scarce. Both compounds were primarily developed for treatment of staphylococcal infections, including those by vancomycin- and fluoroquinolone-resistant isolates.[8,10] This study demonstrates that both compounds also showed excellent *in vitro* activity against antibiotic-resistant streptococci. Moreover, in contrast to WCK 771, WCK 1152 and WCK 1153 were also highly active against fluoroquinolone-resistant *S. pneumoniae*. Of note, based on the $MIC_{90}$ values, both WCK 1152 ($MIC_{90}$ 1 mg/L) and WCK 1153 ($MIC_{90}$ 0.5 mg/L) were up to eight times more active than moxifloxacin ($MIC_{90}$ 4 mg/L) against ciprofloxacin-resistant pneumococcal isolates. The analysis of the *in vitro* activity of WCK 1152 and WCK 1153 against fluoroquinolone-resistant streptococci showed that the primary target seems to be DNA gyrase.

In summary, WCK 771 was potent against quinolone-susceptible *S. pneumoniae in vitro*, but not quinolone-resistant *S. pneumoniae*, regardless of penicillin G and macrolide susceptibility. WCK 1152 and WCK 1153 showed potency superior even to that of newer quinolones in clinical use against streptococci. Therefore, both are promising new agents having high potency against streptococci. If clinical studies yield a favourable safety profile, and if human pharmacokinetic studies support a susceptibility breakpoint of ≤2 mg/L, both compounds will be active against both quinolone-susceptible and quinolone-resistant streptococci, features not achieved by currently available quinolones.

## Acknowledgements

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**Table 2.** Mutations in the quinolone-resistance determining regions and MICs of WCK 771, WCK 1152, WCK 1153 and comparators for 19 *S. pneumoniae* and one *S. pyogenes* isolate

| Strain | Mutations in QRDR | | | | MIC (mg/L) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *gyrA* | *gyrB* | *parC* | *parE* | WCK 771 | WCK 1152 | WCK 1153 | CIP | LEV | SPA | GRE | CLX | MOX | GAT |
| PW 802 | WT | WT | D83G | I460V | 4 | 0.125 | 0.125 | ≥32 | 4 | 8 | 4 | 0.25 | 0.5 | 1 |
| PW 1443 | WT | WT | S79F | WT | 1 | 0.125 | 0.06 | 8 | 4 | 1 | 1 | 0.125 | 0.25 | 0.5 |
| PW 1601 | WT | G486Z | S79F K137N | WT | 1 | 0.125 | 0.06 | ≥32 | 4 | 2 | 2 | 0.25 | 0.25 | 1 |
| PW 239 | S81F | WT | D83Y K137N | I460V | 8 | 0.25 | 0.125 | ≥32 | 8 | ≥32 | 16 | 0.25 | 1 | 2 |
| PW 836 | S81F | WT | D83G | I460V | 8 | 0.25 | 0.125 | >32 | 8 | 32 | 8 | 0.25 | 1 | 2 |
| PW 1872 | S81Y | WT | K137N | D435N | 4 | 0.5 | 0.25 | 16 | 8 | 2 | 1 | 0.25 | 1 | 2 |
| MSR 86 | S81F | WT | S79F | I460V | 4 | 0.5 | 0.125 | 16 | 8 | 16 | 2 | 0.25 | 0.5 | 2 |
| PW 904 | WT | WT | S79F | WT | 8 | 0.5 | 0.25 | ≥32 | 16 | ≥32 | ≥32 | 0.25 | 2 | 4 |
| PW 735 | S81F | WT | S79F K137N | I460V | 16 | 0.5 | 0.25 | ≥32 | ≥32 | ≥32 | ≥32 | 0.5 | 2 | 4 |
| PW 931 | WT | WT | S79Y | I460V | 16 | 0.5 | 0.25 | ≥32 | ≥32 | ≥32 | ≥32 | 0.5 | 2 | 4 |
| PW 1752 | E85G | WT | K137N | D435N | 4 | 0.25 | 0.06 | ≥32 | ≥32 | ≥32 | 16 | 0.25 | 2 | 2 |
| PW 603 | WT | WT | S79F | WT | 16 | 1 | 0.25 | ≥32 | ≥32 | ≥32 | ≥32 | 0.5 | 4 | 4 |
| PW 786 | S81Y S114G | WT | S79F N91D | I460V | 16 | 0.5 | 0.25 | ≥32 | ≥32 | ≥32 | ≥32 | 0.5 | 4 | 4 |
| PW 1026 | S81Y | WT | S79F K137N | WT | 8 | 0.25 | 0.125 | ≥32 | ≥32 | ≥32 | ≥32 | 0.5 | 4 | 8 |
| PW 1698 | E85K | WT | S79F | I460V | 16 | 0.5 | 0.125 | ≥32 | ≥32 | ≥32 | ≥32 | 0.5 | 4 | 4 |
| PW 1891 | S81F | WT | S79Y | WT | 16 | 1 | 0.5 | ≥32 | ≥32 | ≥32 | ≥32 | 0.5 | 4 | 4 |
| PW 2243 | S81Y | WT | S79F | WT | 16 | 1 | 0.25 | ≥32 | ≥32 | ≥32 | ≥32 | 0.5 | 2 | 4 |
| PW 2304 | WT | WT | S79F K137N | I460V | 16 | 1 | 0.25 | ≥32 | ≥32 | ≥32 | ≥32 | 0.5 | 4 | 4 |
| PW 2305 | WT | WT | S79F K137N | I460V | 16 | 1 | 0.25 | ≥32 | ≥32 | ≥32 | ≥32 | 0.5 | 4 | 4 |
| MSR 141[a] | S81F | WT | S79F D91N S140P | WT | 16 | 1 | 0.5 | ≥32 | ≥32 | ≥32 | ≥32 | 0.5 | 4 | 4 |

CIP, ciprofloxacin; LEV, levofloxacin; SPA, sparfloxacin; GRE, grepafloxacin; CLX, clinafloxacin; MOX, moxifloxacin; GAT, gatifloxacin; WT, wild-type.
[a]*S. pyogenes* isolate.

## Transparency declarations

No declarations were made by the authors of this paper.

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