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Comparative *In Vitro* Activities of Nemonoxacin (TG-873870), a Novel Nonfluorinated Quinolone, and Other Quinolones against Clinical Isolates▽

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The *in vitro* antibacterial activities of nemonoxacin (TG-873870), a novel nonfluorinated quinolone, against 770 clinical isolates were investigated. Nemonoxacin (tested as its malate salt, TG-875649) showed better *in vitro* activity than ciprofloxacin and levofloxacin against different species of staphylococci, streptococci, and enterococci, *Neisseria gonorrhoeae*, and *Haemophilus influenzae*. The *in vitro* activity of TG-875649 was also comparable to or better than that of moxifloxacin against these pathogens, which included ciprofloxacin-resistant, methicillin-resistant *Staphylococcus aureus* and levofloxacin-resistant *Streptococcus pneumoniae*.

Antimicrobial resistance is a global public health threat (6, 7). In Taiwan, multidrug and fluoroquinolone resistances are common in both Gram-negative and Gram-positive pathogens from inpatients as well as outpatients (3, 4, 8–10). For example, as many as 80% of nosocomial *Staphylococcus aureus* strains in Taiwan are methicillin-resistant *S. aureus* (MRSA) strains, of which 80% are fluoroquinolone resistant (9). Based on a national surveillance program of >1,200 pneumococcal isolates from recent years, the levofloxacin resistance level was 10% among non-penicillin-susceptible strains (isolates with penicillin MIC > 2 μg/ml) (3).

Development of new antibiotics is one of the means of combating multidrug-resistant bacteria (6). Nemonoxacin (TG-873870) is a novel nonfluorinated quinolone, and TG-875649 is a malate salt of nemonoxacin. The chemical structure of TG-875649 is shown in Fig. 1. The present study examined the *in vitro* antibacterial activity of TG-875649 against a spectrum of Gram-positive and Gram-negative clinical isolates in Taiwan.

(This study was presented in part at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 17 to 20 September 2007 [5].)

Nonduplicate bacterial strains were selected from a pool of clinical isolates previously studied under a national surveillance program in Taiwan (4, 9). Isolates were selected to include those with known resistance to different classes of antibiotics in addition to fluoroquinolones (levofloxacin and/or ciprofloxacin); thus, multidrug-resistant bacteria comprised a larger proportion than the wild type. A total of 770 isolates were tested, among which 688 (89.4%) were isolated in the year 2004, with the remainder isolated from 1998 to 2002. MICs were determined by the broth microdilution (BMD) method, using custom-made 96-well microtiter panels containing different antimicrobial agents at various concentrations (Trek Diagnostics, West Essex, England). The test procedure followed the instructions of the MIC panel manufacturer and guidelines of the Clinical and Laboratory Standards Institute (CLSI) (1, 2). For most species, 50 μl of the 0.5 McFarland standard organism suspension was transferred to 10 ml of cation-adjusted Mueller-Hinton broth (CAMHB) to obtain a final inoculum of 5×10^5 CFU/ml at 100 μl/well. For *Proteus mirabilis*, a 1×10^5-CFU/ml inoculum was used to avoid an inoculum effect. For fastidious organisms, 100 μl of the 0.5 McFarland standard suspension was transferred to 10 ml of MHB containing 3% lysed horse blood for *Neisseria gonorrhoeae* and streptococci and to 10 ml of Haemophilus Test Medium (HTM) broth for *Haemophilus influenzae*. All MIC plates were incubated in 35°C ambient air overnight except those for *N. gonorrhoeae*, which were incubated in 5% CO_2. Appropriate quality control strains were included during each test run. The CAMHB and HTM were purchased from Trek Diagnostics. All other media were purchased from BBL (Becton Dickinson Microbiology System, Cockeysville, MD).

Table 1 lists the antibacterial activities (MIC range, MIC_{50}, and MIC_{90}) of TG-875649 against various species of Gram-positive and Gram-negative pathogens in comparison with those of 3 fluoroquinolones (FQs) (ciprofloxacin, levofloxacin, and moxifloxacin) and nonquinolone agents. TG-875649 was more active than ciprofloxacin and levofloxacin against all staphylococcal isolates, including 150 *S. aureus*, with 4- to >32-fold lower MIC_{90}s. In addition, against ciprofloxacin-resistant (CIP^r) MRSA, the MIC_{90} of TG-875649 (1 μg/ml) was 4-fold

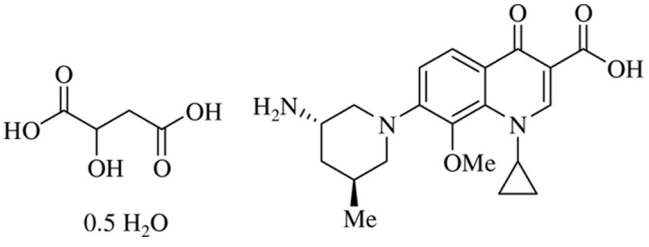

FIG. 1. Chemical structure of TG-875649, a malate salt of nemonoxacin (TG-873870). Me, methyl.

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TABLE 1. Antibacterial activities of TG-875649, a malate salt of nemonoxacin (TG-873870), and reference compounds against Gram-positive and Gram-negative bacteria

Organism (*n*) and compound	MIC (μg/ml)		
	Range	50%	90%
Staphylococcus aureus			
Methicillin susceptible (59)			
TG-875649	0.015–1	0.03	0.12
Ciprofloxacin	0.12–>16	0.5	2
Levofloxacin	≤0.06–16	0.25	1
Moxifloxacin	≤0.015–4	0.06	0.12
Ceftriaxone	2–8	4	4
Oxacillin	≤0.25–2	0.5	1
Linezolid	0.5–2	2	2
Tigecycline	0.06–0.25	0.12	0.25
Vancomycin	0.5–2	1	1
Methicillin resistant, ciprofloxacin susceptible (44)			
TG-875649	≤0.008–0.06	0.03	0.06
Ciprofloxacin	≤0.06–1	0.5	0.5
Levofloxacin	≤0.06–0.25	0.25	0.25
Moxifloxacin	≤0.015–0.12	0.06	0.06
Ceftriaxone	8–>8	>8	>8
Oxacillin	4–>8	>8	>8
Linezolid	2	2	2
Tigecycline	0.06–0.5	0.25	0.25
Vancomycin	1–2	1	1
Methicillin resistant, ciprofloxacin resistant (47)			
TG-875649	0.06–4	1	1
Ciprofloxacin	2–>16	>16	>16
Levofloxacin	0.5–>16	16	16
Moxifloxacin	0.12–8	4	4
Ceftriaxone	8–>8	>8	>8
Oxacillin	>8	>8	>8
Linezolid	1–2	2	2
Tigecycline	0.12–0.5	0.25	0.5
Vancomycin	1–2	2	2
Coagulase negative staphylococci			
Methicillin resistant (68)[a]			
TG-875649	0.03–8	0.12	0.5
Ciprofloxacin	0.12–>16	0.5	>16
Levofloxacin	0.12–>16	0.5	8
Moxifloxacin	0.03–>8	0.12	2
Ceftriaxone	4–>8	>8	>8
Oxacillin	0.5–>8	>8	>8
Linezolid	≤0.25–4	1	2
Tigecycline	0.06–0.5	0.25	0.5
Vancomycin	0.25–4	2	2
Enterococcus faecalis (31)[b]			
TG-875649	0.12–4	0.25	4
Ciprofloxacin	1–>16	2	>16
Levofloxacin	1–>16	2	>16
Moxifloxacin	0.25–>8	0.5	>8
Linezolid	1–2	1	2
Tigecycline	0.06–0.25	0.25	0.25
Vancomycin	1–>16	2	>16
Enterococcus faecium (19)[b]			
TG-875649	0.5–8	4	8
Ciprofloxacin	2–>16	>16	>16
Levofloxacin	2–>16	>16	>16
Moxifloxacin	1–>8	>8	>8
Linezolid	1–2	2	2
Tigecycline	0.03–0.25	0.06	0.12
Vancomycin	0.5–16	8	>16

Organism (*n*) and compound	MIC (μg/ml)		
	Range	50%	90%
Escherichia coli			
Ciprofloxacin resistant (43)			
TG-875649	2–>16	>16	>16
Ciprofloxacin	2–>16	>16	>16
Levofloxacin	1–>16	>16	>16
Moxifloxacin	1–>8	>8	>8
Ceftazidime	≤1–>128	16	64
Ceftriaxone	0.06–>8	>8	>8
Cefepime	≤0.06–>8	0.5	>8
Imipenem	≤0.12–2	0.5	0.5
Piperacillin	2–>128	>128	>128
Tigecycline	0.12–0.5	0.25	0.5
Ciprofloxacin susceptible (37)			
TG-875649	0.015–4	1	2
Ciprofloxacin	≤0.06–1	0.25	1
Levofloxacin	≤0.06–2	0.5	1
Moxifloxacin	≤0.015–2	0.5	1
Ceftazidime	≤1–32	1	16
Ceftriaxone	≤0.03–>8	0.06	>8
Cefepime	≤0.06–>8	≤0.06	8
Imipenem	≤0.12–1	0.25	0.5
Piperacillin	2–>128	>128	>128
Tigecycline	0.12–0.5	0.25	0.5
Klebsiella pneumoniae (30)			
TG-875649	0.25–>16	4	>16
Ciprofloxacin	≤0.06–>16	4	>16
Levofloxacin	≤0.06–>16	2	>16
Moxifloxacin	0.12–>8	4	>8
Ceftazidime	≤1–>128	16	>128
Ceftriaxone	≤0.03–>8	>8	>8
Cefepime	≤0.06–>8	2	>8
Imipenem	0.25–32	0.5	4
Piperacillin	4–>128	>128	>128
Tigecycline	0.25–2	0.5	1
Enterobacter cloacae (30)			
TG-875649	0.5–>16	4	>16
Ciprofloxacin	0.12–>16	2	>16
Levofloxacin	0.12–>16	2	16
Moxifloxacin	0.25–>8	2	>8
Ceftazidime	≤1–>128	128	>128
Ceftriaxone	0.12–>8	>8	>8
Cefepime	≤0.06–8	4	>8
Imipenem	0.25–8	1	4
Piperacillin	4–>128	>128	>128
Tigecycline	0.25–4	0.5	2
Proteus mirabilis (30)			
TG-875649	0.5–>16	8	>16
Ciprofloxacin	≤0.06–>16	2	>16
Levofloxacin	≤0.06–>16	2	>16
Moxifloxacin	0.25–>8	8	>8
Ceftazidime	≤1–8	≤1	≤1
Ceftriaxone	≤0.03–>8	≤0.03	>8
Cefepime	≤0.06–>8	≤0.06	8
Imipenem	0.25–>32	2	8
Piperacillin	1–>128	32	>128
Tigecycline	1–4	2	4
Citrobacter freundii (30)			
TG-875649	0.12–>16	0.5	4
Ciprofloxacin	≤0.06–>16	≤0.06	2

Continued on following page

TABLE 1—*Continued*

Organism (*n*) and compound	MIC (μg/ml)		
	Range	50%	90%
Levofloxacin	≤0.06–>16	0.12	2
Moxifloxacin	0.12–>8	0.5	8
Ceftazidime	≤1–>128	≤1	64
Ceftriaxone	≤0.03–>8	0.25	>8
Cefepime	≤0.06–>8	≤0.06	>8
Imipenem	0.25–4	1	2
Piperacillin	2–>128	16	>128
Tigecycline	0.25–1	0.25	0.5
Streptococcus pneumoniae			
Levofloxacin susceptible (71)			
TG-875649	0.06–0.25	0.12	0.12
Ciprofloxacin	1–16	2	4
Levofloxacin	0.5–2	1	2
Moxifloxacin	0.06–0.5	0.12	0.25
Ceftriaxone	≤0.06–>8	1	2
Linezolid	0.5–2	1	1
Tigecycline	≤0.08–0.12	0.03	0.06
Vancomycin	≤0.12–1	0.5	0.5
Levofloxacin-resistant (29)			
TG-875649	0.5–8	1	2
Ciprofloxacin	8–>16	>16	>16
Levofloxacin	8–>16	16	>16
Moxifloxacin	2–>8	2	8
Ceftriaxone	0.12–8	1	2
Linezolid	0.5–2	1	1
Tigecycline	0.015–0.12	0.06	0.06
Vancomycin	0.25–0.5	0.5	0.5
Streptococcus pyogenes (30)			
TG-875649	0.06–0.12	0.12	0.12
Ciprofloxacin	0.25–4	1	4
Levofloxacin	0.25–2	1	2
Moxifloxacin	0.06–0.5	0.25	0.5
Ceftriaxone	≤0.06	≤0.06	≤0.06
Linezolid	0.5–1	1	1
Tigecycline	0.015–0.06	0.03	0.06
Vancomycin	0.25–0.5	0.5	0.5
Streptococcus agalactiae (30)			
TG-875649	0.12–2	0.12	0.25
Ciprofloxacin	1–>16	1	2
Levofloxacin	0.5–>16	1	2
Moxifloxacin	0.12–>8	0.25	0.5
Ceftriaxone	≤0.06–>8	≤0.06	0.12
Linezolid	1–2	1	1
Tigecycline	0.03–0.06	0.03	0.06
Vancomycin	0.5–1	0.5	1
Viridans group streptococci (30)			
TG-975649	0.06–0.25	0.12	0.25
Ciprofloxacin	0.25–4	1	4
Levofloxacin	0.25–2	1	2
Moxifloxacin	0.06–9,25	0.12	0.25
Ceftriaxone	≤0.06–1	0.25	0.5
Linezolid	0.5–2	1	2
Tigecycline	0.03–1	0.06	0.12
Vancomycin	0.5–1	0.5	1
Acinetobacter baumannii (30)			
TG-875649	0.06–>16	4	>16
Ciprofloxacin	≤0.06–16	4	>16
Levofloxacin	≤0.06–>16	2	16
Moxifloxacin	0.06–>8	1	>8
Ceftazidime	8–>128	64	>128
Ceftriaxone	8–>8	>8	>8
Cefepime	4–>8	>8	>8
Imipenem	0.5–>32	2	>32
Piperacillin	16–>128	>128	>128
Tigecycline	0.12–2	1	2
Pseudomonas aeruginosa (30)			
TG-875649	1–>16	16	>16
Ciprofloxacin	0.12–>16	4	>16
Levofloxacin	0.25–>16	8	>16
Moxifloxacin	1–>8	>8	>8
Ceftazidime	2–>128	32	>128
Ceftriaxone	>8	>8	>8
Cefepime	1–>8	>8	>8
Imipenem	1–>32	8	>32
Piperacillin	4–>128	128	>128
Tigecycline	2–>8	8	>8
Haemophilus influenzae (30)			
TG-875649	≤0.008–8	0.12	4
Ciprofloxacin	≥0.06–16	0.25	16
Levofloxacin	≥0.06–8	0.25	8
Moxifloxacin	≥0.015–>8	0.25	>8
Ceftazidime	≤1	≤1	≤1
Ceftriaxone	≤0.03–0.06	≤0.03	≤0.03
Cefepime	≤0.06–0.5	0.25	0.5
Imipenem	≤0.12–8	1	4
Tigecycline	0.12–1	0.5	1

[a] Including 44 *S. epidermidis* coagulase-negative staphylococci and 24 non-*S. epidermidis* coagulase-negative staphylococci.
[b] Including 17 (7 *E. faecalis* strains and 10 *E. faecium* strains) vancomycin-resistant enterococci.

lower than that of moxifloxacin. Of the 47 CIP^r MRSA isolates, only 2 (4.3%) and 3 (6.4%) isolates had levofloxacin and moxifloxacin MICs of ≤1 μg/ml, respectively (Table 2), while the majority (45 isolates; 95.7%) had TG-875649 MICs of ≤1 μg/ml (Table 2). Among the 50 enterococci tested, 17 (7 *Enterococcus faecalis* strains and 10 *E. faecium* strains) were vancomycin resistant. The MIC_{90}s of TG-875649 were at least 2-fold lower than those of the 3 FQs for both *E. faecalis* and *E. faecium*.

Against levofloxacin-susceptible *Streptococcus pneumoniae* isolates, the MIC_{90} of TG-875649 (0.12 μg/ml) was severalfold lower than those of ciprofloxacin (4 μg/ml) and levofloxacin (2 μg/ml) and 2-fold lower than that of moxifloxacin (0.25 μg/ml). Against the 29 levofloxacin-resistant *S. pneumoniae* isolates studied, TG-875649 also had the lowest MIC_{90} (2 μg/ml), lower than those of the 3 FQs (8 to >16 μg/ml). The activity of TG-875649 was comparable to that of moxifloxacin against viridans group streptococci (MIC_{90} of 0.25 μg/ml for both drugs) and better than that of moxifloxacin against group A and group B streptococci (*S. pyogenes* and *S. agalactiae*, respectively), with MIC_{90}s of 0.12 to 0.25 μg/ml for TG-875649 and 0.5 μg/ml for moxifloxacin. Three group B streptococcal isolates were FQ resistant, with ciprofloxacin and levofloxacin MICs of >16 μg/ml and a moxifloxacin MIC of 2 to >8 μg/ml,

TABLE 2. MIC distribution of TG-875649 and comparator fluoroquinolone agents against ciprofloxacin-susceptible and -resistant, methicillin-resistant *S. aureus* (MRSA)

Antimicrobial agent		MIC (μg/ml)[a]												
		0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16
***Ciprofloxacin-Susceptible MRSA* (n=44):**														
TG-875649	No. of isolates	3	2	27	12									
	Cumulative no. of isolates	3	5	32	44									
	Cumulative % of isolates	6.8	11.4	72.7	100.0									
Ciprofloxacin	No. of isolates				3	1	8	30	2					
	Cumulative no. of isolates				3	4	12	42	44					
	Cumulative % of isolates				6.8	9.1	27.3	95.5	100.0					
Levofloxacin	No. of isolates				3	17	24							
	Cumulative no. of isolates				3	20	44							
	Cumulative % of isolates				6.8	45.5	100.0							
Moxifloxacin	No. of isolates		4	14	25	1								
	Cumulative no. of isolates		4	18	43	44								
	Cumulative % of isolates		9.1	40.9	97.7	100.0								
***Ciprofloxacin-resistant MRSA* (n=47):**														
TG-875649	No. of isolates				1	1	0	10	33	1	1			
	Cumulative no. of isolates				1	2	2	12	45	46	47			
	Cumulative % of isolates				2.1	4.3	4.3	25.5	95.7	97.9	100.0			
Ciprofloxacin	No. of isolates									2	0	0	13	32
	Cumulative no. of isolates									2	2	2	15	47
	Cumulative % of isolates									4.3	4.3	4.3	31.9	100.0
Levofloxacin	No. of isolates							2	0	0	12	5	26	2
	Cumulative no. of isolates							2	2	2	14	19	45	47
	Cumulative % of isolates							4.3	4.3	4.3	29.8	40.4	95.7	100.0
Moxifloxacin	No. of isolates					2	0	0	1	20	22	2		
	Cumulative no. of isolates					2	2	2	3	23	45	47		
	Cumulative % of isolates					4.3	4.3	4.3	6.4	48.9	95.7	100.0		

[a] MICs before vertical solid lines, between solid and dotted lines, and after dotted lines indicate susceptible, intermediate, and resistant breakpoints, respectively, based on CLSI interpretive criteria (2). The white fields denote range of dilutions tested for each agent. Values above the range denote MICs greater than the highest concentration tested. MICs equal to or lower than the lowest concentration tested are given as the lowest concentration.

while the MICs of TG-875649 were lower, at 1 to 2 μg/ml (data not shown).

TG-875649 was less active against Gram-negative pathogens *Enterobacteriaceae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. The MIC_{90}s of TG-875649 and the 3 FQs against these species (except *Citrobacter freundii* and CIP-susceptible *Escherichia coli*) were nearly all equal to or greater than the highest concentrations tested. A look at the MIC_{50}s revealed that the *in vitro* activities of TG-875649 were 2- to 4-fold less than the 3 FQs against most of these species. However, against *Haemophilus influenzae*, TG-875649 showed slightly better activity than the 3 FQs, with an MIC_{50} of 0.12 μg/ml (those of the 3 FQs were all 0.25 μg/ml), and its MIC_{90} was also ≥2-fold lower than those of the 3 FQs. It needs to be pointed out that the 30 *H. influenzae* isolates tested included 11 non-FQ-susceptible isolates. TG-875649 also showed slightly better activity against *N. gonorrhoeae*. Of the 10 *N. gonorrhoeae* isolates studied, only 2 were susceptible to ciprofloxacin. The ciprofloxacin, levofloxacin, and moxifloxacin MICs of the other 8 non-FQ-susceptible *N. gonorrhoeae* isolates ranged from 2 to 4, 1 to 4, and 0.5 to 2 μg/ml, respectively, but the MIC for TG-875649 was lower, at 0.25 to 1 μg/ml (data not shown).

In conclusion, nemonoxacin (tested as its malate salt, TG-875649) demonstrated better antibacterial activities than ciprofloxacin and levofloxacin against different species of Gram-positive bacteria, including staphylococci, streptococci, and enterococci, and against *H. influenzae* and *N. gonorrhoeae*. The *in vitro* activity of TG-875649 was also comparable to or better than that of moxifloxacin against these pathogens, including ciprofloxacin-resistant MRSA and levofloxacin-resistant *S. pneumoniae*. Based on these data, further studies of nemonoxacin pharmacology and development of bacterial resistance to nemonoxacin are warranted.

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