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NEMONOXACIN

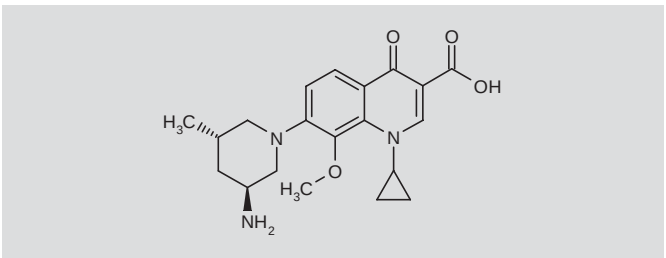
Quinolone Antibiotic

Prop INN

TG-873870

7-[3(*S*)-Amino-5(*S*)-methylpiperidin-1-yl]-1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

InChI=1/C20H25N3O4/c1-11-7-12(21)9-22(8-11)16-6-5-14-17(19(16)27-2)23(13-3-4-13)10-15(18(14)24)20(25)26/h5-6,10-13H,3-4,7-9,21H2,1-2H3,(H,25,26)/t11-,12-/m0/s1



$C_{20}H_{25}N_3O_4$
Mol wt: 371.4302
CAS: 378746-64-6
EN: 401112

ABSTRACT

Although fluoroquinolones have been used over the last few decades to successfully treat multiple bacterial infections, there is a need for new compounds that, while taking advantage of the antimicrobial properties of the quinolone nucleus, show greater potency against drug-resistant bacteria, reduced drug–drug interactions and improved patient tolerability. Nemonoxacin (TG-873870) is a nonflourinated quinolone antibiotic with remarkable in vitro activity against a wide variety of clinically relevant pathogens, including methicillin-resistant Staphylococcus aureus and multidrug-resistant Streptococcus pneumoniae. In several murine pulmonary infection models, the efficacy of nemonoxacin was greater than most of the currently available fluoroquinolones. Studies in laboratory animals have ruled out the possibility of nemonoxacin inducing significant reproductive, cardiovascular, allergic or phototoxic adverse events. In addition, this novel quinolone has a good pharmacokinetic profile and is well tolerated. Nemonoxacin is currently undergoing phase II evaluation for the oral treatment of drug-sensitive and -resistant bacterial infections.

SYNTHESIS*

Esterification of L-pyroglutamic acid (I) using $SOCl_2$ in MeOH, followed by protection of the resulting methyl ester (II) with Boc_2O and DMAP in acetonitrile affords *N*-Boc-L-pyroglutamic acid methyl ester (III). Subsequent treatment of pyroglutamate (III) with Bredereck's reagent in hot DME yields the [(dimethylamino)methylene]-pyrrolidinone (IV), which is diastereoselectively reduced to the 4(*S*)-methyl derivative (V) by catalytic hydrogenation over Pd/C. Further reduction of the amide and ester groups of compound (V) using in situ-generated $Ca(BH_4)_2$ in EtOH/MTBE furnishes diol (VI), which is converted to the bis-mesylate (VII) under the usual conditions. The bis-mesylate (VII) is then cyclized with benzylamine in refluxing dimethoxyethane followed by catalytic hydrogenolysis of the resulting *N*-benzylpiperidine (VIII) to provide 3(*S*)-Boc-amino-5(*S*)-methylpiperidine (IX). Coupling of the protected aminopiperidine (IX) with the fluoroquinolone boron chelate (X) in the presence of Et_3N in hot acetonitrile affords, after alkaline decomplexation, the piperidinyl quinolone (XI), which is finally deprotected by treatment with HCl in CH_2Cl_2 (1, 2). Scheme 1.

The intermediate quinolone boron chelate (X) is prepared as follows. Ketalization of 2',4'-difluoroacetophenone (XII) with ethylene glycol and *p*-TsOH provides compound (XIII), which is hydroxylated to phenol (XIV) by *ortho*-metalation with BuLi in THF at −65 °C, followed by treatment with trimethyl borate in AcOH and then with aqueous H_2O_2. Acidic hydrolysis of the ethylene ketal moiety of compound (XIV) provides the hydroxyketone (XV), which is alkylated with dimethyl sulfate and K_2CO_3 in toluene to give 2',4'-difluoro-3'-methoxyacetophenone (XVI). Carboxylation of acetophenone (XVI) with diethyl carbonate and NaH gives the 2-(benzoyl)acetate (XVII), which is further condensed with dimethylformamide dimethyl acetal (DMFDMA) to produce adduct (XVIII). Subsequent displacement of the dimethylamino group of (XVIII) with cyclopropylamine (XIX) in hot toluene furnishes the *N*-cyclopropyl analogue (XX) (1, 2). Then, cyclization of (XX) by means of either NaH in THF or *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in boiling toluene yields the quinolone carboxylate (XXI), which is hydrolyzed to the corresponding carboxylic acid (XXII) under acidic conditions. Finally, the boron chelate (X) is obtained by complexation of the keto

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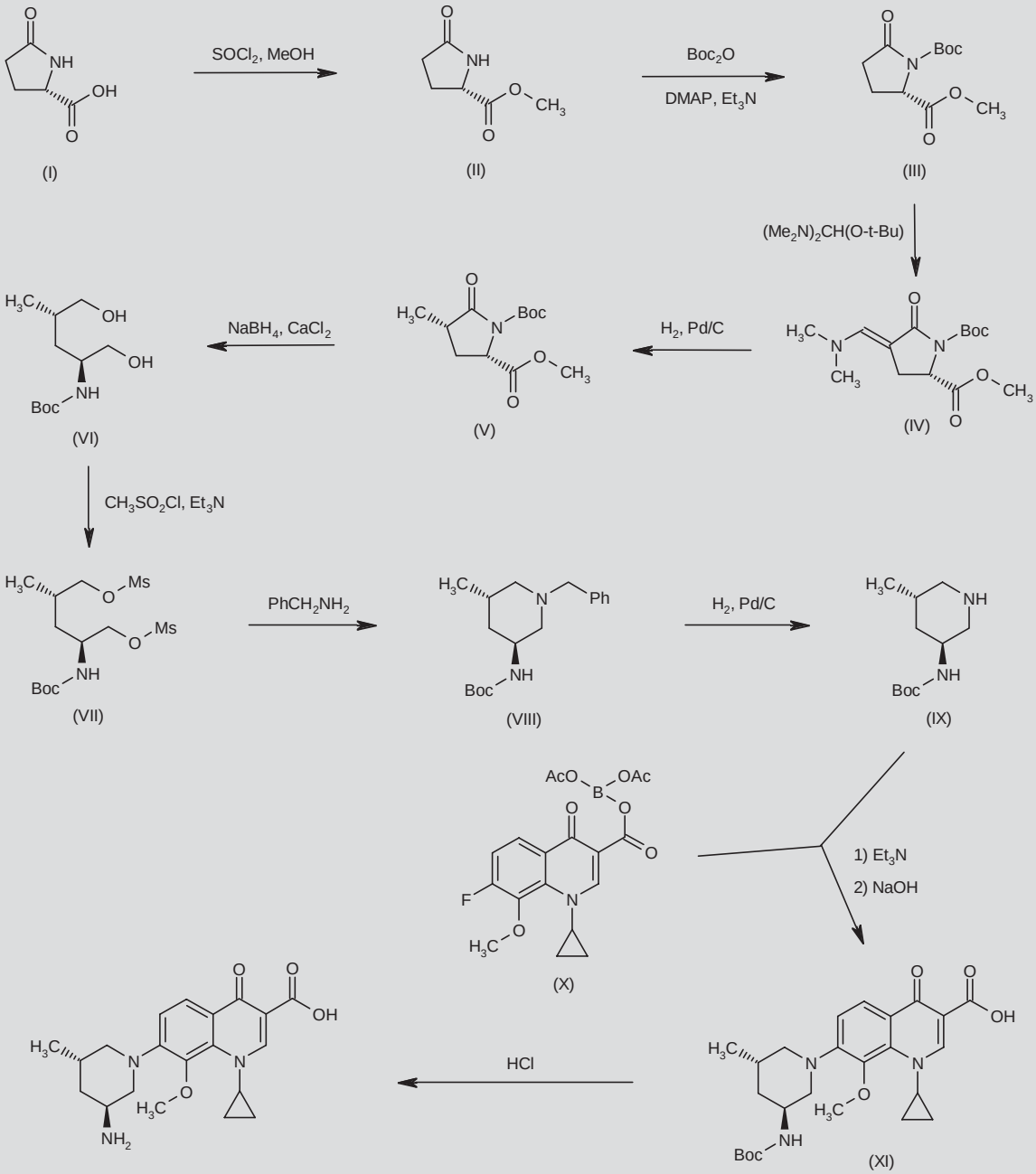
*Synthesis prepared by R. Castañer, J. Bolós. Prous Science, Provenza 388, 08025 Barcelona, Spain.

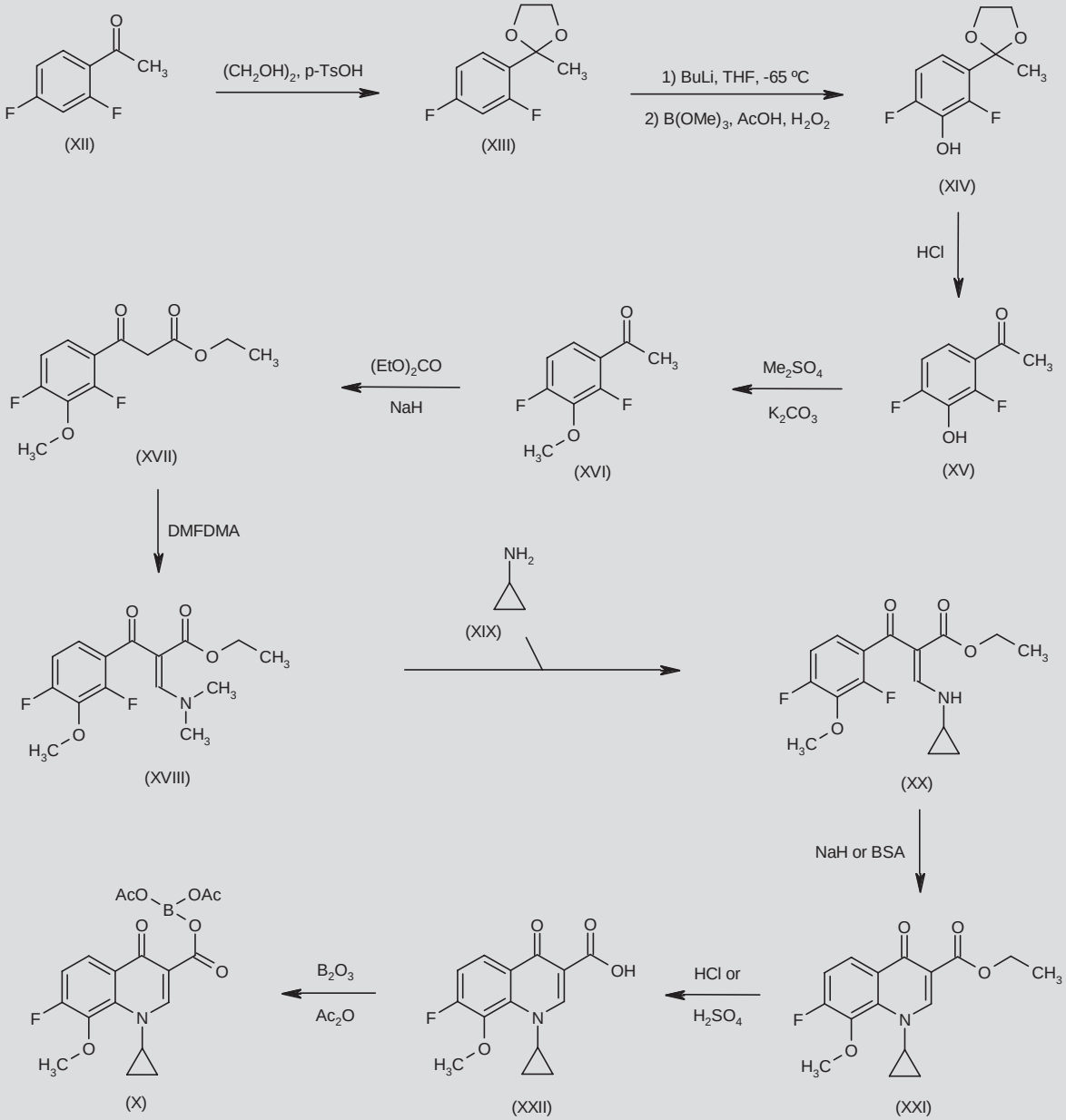
Scheme 1. Synthesis of Nemonoxacin



acid (XXII) with the reagent generated from boron oxide and acetic anhydride in AcOH (1-3). Scheme 2.

In an alternative route to the quinolone precursor (XX), deprotonation of 2,4-difluorobromobenzene (XXIII) with LDA in THF followed by addition of *tert*-butyl hydroperoxide gives 3-bromo-2,6-difluorophenol (XXIV), which is converted to the corresponding methyl ether (XXV) by treatment with iodomethane and K_2CO_3. Metalation of the aryl bromide (XXV) with butyl lithium in cold diethyl ether and subsequent addition of CO_2 gas leads to 3-methoxy-2,4-difluorobenzoic acid (XXVI). After chlorination of acid (XXVI) with oxalyl chloride and catalytic DMF, the obtained acid chloride (XXVII) is condensed with monoethyl malonate (XXVIII) in the presence of butyl lithium in THF at –50 °C to yield the 2-(benzoyl)acetate (XVII). Subsequent reaction of keto ester (XVII) with triethyl orthoformate in

Scheme 2. Synthesis of Intermediate (X)

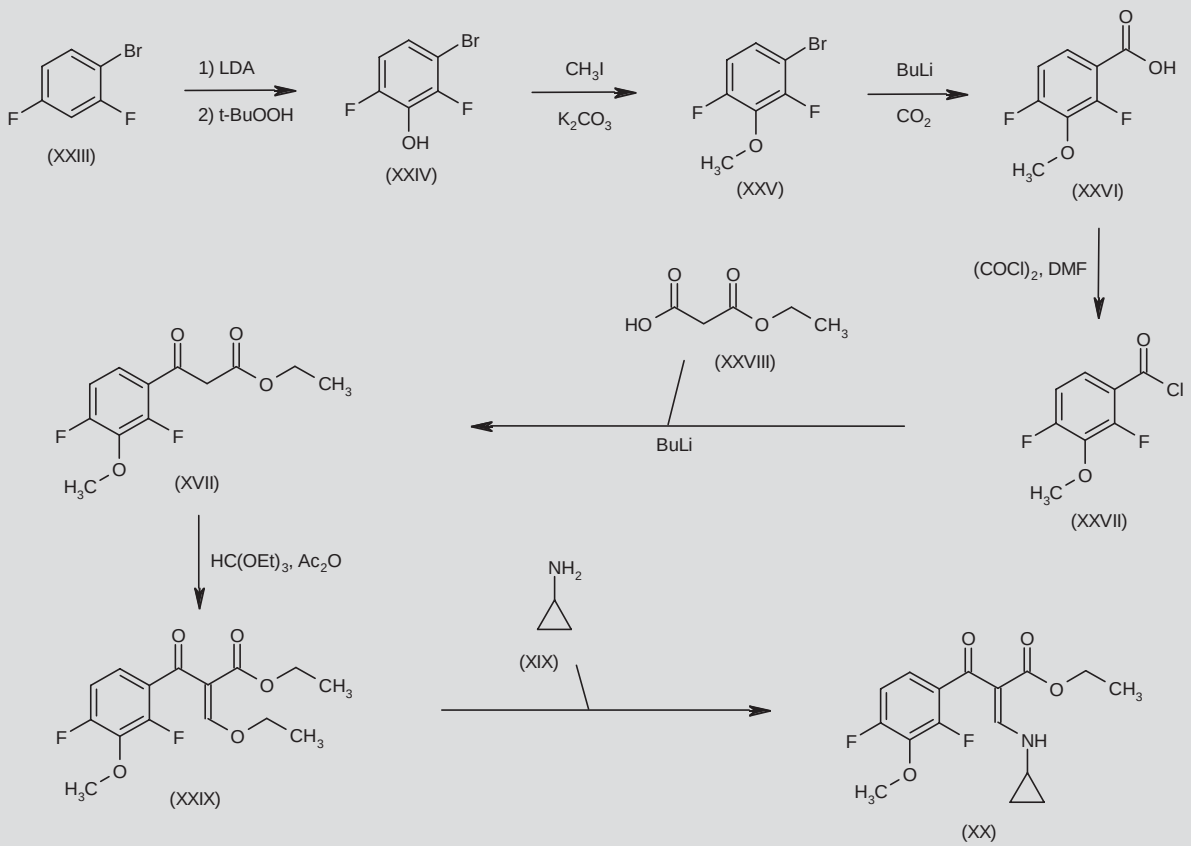


boiling Ac_2O provides the enol ether (XXIX), which is then condensed with cyclopropylamine (XIX) in EtOH to give the key enamine (XX) (3). Scheme 3.

BACKGROUND

The quinolone class of antimicrobial agents was discovered over 40 years ago. The mechanism of action of this family of drugs entails the inhibition of bacterial topoisomerase II (i.e., DNA gyrase), a key enzyme for DNA replication. Unlike other antibiotics, quinolones were not isolated from living organisms but were chemically synthesized (4). A key milestone in the development of quinolones was the addition of fluorine atoms to the quinolone nucleus. These modifications increase their topoisomerase II-inhibitory activity and improve their pharmacokinetic profile. A recent key modification was the addition of a methoxy group instead of a halide at the C-8 position, enabling the agent to target both topoisomerase II and topoisomerase IV (5).

Scheme 3. Alternative Synthesis of Intermediate (XX)



The most frequently prescribed fluoroquinolones are ciprofloxacin, levofloxacin, gatifloxacin and moxifloxacin (6). Although a considerable number of infections are successfully treated with fluoroquinolones, the incidence of resistance (particularly among *Streptococcus pneumoniae* and *Haemophilus influenzae*) is increasing steadily (7). Indeed, most methicillin-resistant *Staphylococcus aureus* (MRSA) are resistant to available quinolones. This imposes the necessity for developing newer compounds that, taking advantage of the potent antimicrobial properties of the quinolone nucleus, show greater activity, particularly against staphylococci, enterococci and anaerobic bacteria, while decreasing drug–drug interactions and enhancing patient tolerability (4).

The current data on the pharmacology, metabolism, safety and efficacy of nemonoxacin (TG-873870), a novel C8-methoxy nonfluorinated quinolone with potent antimicrobial activity against a wide range of pathogens, including MRSA and multidrug-resistant *S. pneumoniae*, are reviewed here.

PRECLINICAL PHARMACOLOGY

The in vitro antimicrobial activity of nemonoxacin was initially assessed using 7,881 clinical isolates that included 3,473 Gram-positive cocci and 3,306 Gram-negative bacilli (8). When comparing minimum inhibitory concentrations (MIC_{50} and MIC_{90}) for nemonoxacin and levofloxacin, the investigators found that the novel quinolone was more active against Gram-positive cocci, including *S. pneumoniae* (MIC_{50}/MIC_{90} = 0.015/0.015 and 0.5/1 µg/mL, respectively), methicillin-sensitive *S. aureus* (MIC_{50}/MIC_{90} = 0.03/0.12 and 0.25/0.4 µg/mL, respectively), MRSA (MIC_{50}/MIC_{90} = 0.25/0.5 and 4/8 µg/mL, respectively), vancomycin-intermediate *S. aureus* (MIC_{50}/MIC_{90} = 1/2 and 2/> 32 µg/mL, respectively), vancomycin-resistant MRSA (median MIC = 2 and 32 µg/mL, respectively), methicillin-sensitive *Staphylococcus epidermidis* (MIC_{50}/MIC_{90} = 0.03/0.5 and 4/> 32 µg/mL, respectively), methicillin-resistant *S. epidermidis* (MIC_{50}/MIC_{90} = 2/2 and > 32/> 32 µg/mL, respectively) and *Enterococcus faecalis* (MIC_{50}/MIC_{90} = 0.12/1 and 2 /> 32 µg/mL, respectively). In a parallel study, the same pool of clinical isolates was employed to assess the activity of nemonoxacin against Gram-negative bacilli (9). In this case, nemonoxacin's antimicrobial activity was similar to that of levofloxacin. MIC_{50}/MIC_{90} values against *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Klebsiella oxytoca, Stenotrophomonas maltophilia* and *Acinetobacter baumannii* were 0.12- > 4 µg/mL for nemonoxacin and < 0.06-8 µg/mL for levofloxacin.

A subsequent preclinical study aimed to evaluate the antibacterial activity of nemonoxacin along with four fluoroquinolones against

clinical isolates of *Helicobacter pylori*. The MICs of nemonoxacin, ciprofloxacin, levofloxacin, moxifloxacin and gemifloxacin for 200 isolates of *H. pylori* were determined using the agar dilution method. The MIC_{90} range of ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin and nemonoxacin was 0.12-2, 0.12-1, 0.12-4, ≤ 0.03-0.5 and 0.06-1 μg/mL, respectively. The MIC_{50}/MIC_{90} values of nemonoxacin were lower than those of ciprofloxacin, levofloxacin and moxifloxacin and comparable to those of gemifloxacin. Therefore, nemonoxacin showed excellent in vitro activity against *H. pylori*, including clarithromycin-, metronidazole- and levofloxacin-resistant isolates (10).

In order to assess the potential of *S. pneumoniae* to develop resistance to nemonoxacin and to characterize the mutations in topoisomerase II and topoisomerase IV (target genes of fluoroquinolones) associated with resistance, three unrelated clinical isolates of *S. pneumoniae* were exposed to nemonoxacin at ascending concentrations for three selection cycles. The MICs of nemonoxacin increased 2-8-fold over three cycles of selection (initial MIC = 0.03-0.06 μg/mL vs. final MIC = 0.06-0.5 μg/mL). Importantly, no highly resistant isolates were obtained. In contrast, the MIC of ciprofloxacin increased 64-128-fold over three selection cycles (initial MIC = 0.5 μg/mL vs. final MIC = 32-64 μg/mL) and yielded highly resistant isolates. The final MICs were 0.5-1 μg/mL for nemofloxacin, 4 μg/mL for moxifloxacin, 4-8 μg/mL for gatifloxacin and 16 μg/mL for levofloxacin. Mutations identified after exposure to nemofloxacin included Ser82-Tyr in *gyrA*, Ser494-Thr in *gyrB* and Pro454-Ser in *parE*. The mutations in the ciprofloxacin-resistant isolates were Ser79-Tyr in *parC* and Ser81-Tyr in *gyrA*, consistent with previous publications. Thus, nemonoxacin appears to have a unique resistance profile (no *parC* mutation) and to induce less resistance compared to other fluoroquinolones (11).

Nemonoxacin has also been proven to possess significant in vitro antibacterial activity against invasive *S. pneumoniae* and levofloxacin-nonsusceptible *S. pneumoniae* isolates. Hsueh et al. (11) showed that the MIC ranges (MIC_{90}) for all invasive isolates for levofloxacin, moxifloxacin, gemifloxacin and nemonoxacin were 0.5-32 (2), 0.06-4 (0.25), ≤ 0.03-2 (≤ 0.03) and ≤ 0.03-2 (0.06) μg/mL, respectively. The MIC range (MIC_{90}) for levofloxacin-nonsusceptible isolates for nemonoxacin was 0.12-4 (1) μg/mL, indicating that nemonoxacin has excellent in vitro activity against invasive and levofloxacin-nonsusceptible *S. pneumoniae* isolates. The nemonoxacin MIC_{50}/MIC_{90} values were lower than those of levofloxacin and moxifloxacin and comparable to those of gemifloxacin.

Pankuch et al. (12) conducted an in vitro study to examine the antimicrobial activity of nemonoxacin against MRSA compared with other quinolones (vancomycin, teicoplanin, linezolid, daptomycin, tigecycline, quinupristin/dalfopristin, ciprofloxacin, levofloxacin and moxifloxacin). Nemonoxacin had excellent activity against all MRSA strains, including vancomycin-nonsensitive and quinolone-resistant MRSA, with improved activity (MIC = 0.06-4 μg/mL) compared to ciprofloxacin (0.5-128 μg/mL), levofloxacin (0.5-32 μg/mL) and moxifloxacin (0.06-8.0 μg/mL). Among 31 quinolone-resistant MRSA strains, 5 different patterns of quinolone resistance-determining region (QRDR) mutations were reported: *gyrA* (S84L), *grlA* (S80F/Y), *grlB* (L413S, E422K/N, D432N, E471K); *gyrA* (S84L), *grlA* (S80F/Y), *gyrB* (R404L); *gyrA* (S84L), *grlA* (S80F/Y); *gyrA* (S84L), *grlA* (S80F/Y, E84V), *grlB* (E422D); and *gyrA* (S84L), *grlA* (S80F/Y, E84V/K/G or S108N). Among genotypes known to be associated with the development of resistance, nemonoxacin had the lowest MIC range compared to ciprofloxacin (average 64-fold increase in MIC), levofloxacin (average 16-fold increase in MIC) and moxifloxacin (average 3-fold increase in MIC). In conclusion, nemonoxacin showed potent activity against all MRSA tested irrespective of their phenotype and had low MICs compared to other quinolones tested in strains carrying QRDR mutations.

Another preclinical study evaluated the in vitro antibacterial activity of a nemonoxacin salt (TG-875649) against a range of Gram-positive and Gram-negative clinical isolates compared with three fluoroquinolones. The isolates were selected from a national surveillance program of clinical pathogens in Taiwan to include known fluoroquinolone-susceptible and -nonsusceptible strains. The Gram-negative bacilli comprised 80 *E. coli* and 30 isolates each of *K. pneumoniae*, *E. cloacae*, *Citrobacter freundii*, *P. mirabilis*, *A. baumannii* and *Pseudomonas aeruginosa*. The streptococci consisted of 30 each of group A and group B. Seventeen of the 50 enterococci (31 *E. faecalis* and 19 *E. faecium*) were vancomycin-resistant. Among the 150 *S. aureus* tested, 91 were MRSA. In this study, TG-875649 had a broad spectrum of activity against a wide range of pathogens. Its activity against common species of the Enterobacteriaceae family and nonfermenter Gram-negative bacilli was comparable to that of fluoroquinolones. TG-875649 exhibited potent activity against staphylococci and enterococci, including MRSA, *Neisseria gonorrhoeae* and the respiratory pathogens *H. influenzae* and *S. pneumoniae*, with MIC_{50}/MIC_{90} values lower than those of ciprofloxacin, levofloxacin and moxifloxacin (13).

When assessed in vivo, nemonoxacin's efficacy was comparable to or greater than that of currently marketed fluoroquinolones. Hsu et al. (14) assessed the in vivo activity of nemonoxacin along with six other fluoroquinolones against acute murine systemic infections caused by *S. aureus*, *S. pneumoniae*, *E. coli*, ciprofloxacin-resistant *S. pneumoniae* and ciprofloxacin-resistant MRSA. Mice were challenged i.p. with a lethal dose of the bacterial pathogen. Nemonoxacin, ciprofloxacin, moxifloxacin, levofloxacin, gatifloxacin, gemifloxacin and garenoxacin were administered s.c. or p.o. at 1 and 4 h postchallenge to determine the PD_{50} (i.e., the drug dose required to protect 50% of mice from death). The PD_{50} values for nemonoxacin (administered s.c. or p.o.) were: 1) lower than ciprofloxacin, moxifloxacin, levofloxacin and gatifloxacin and similar to gemifloxacin and garefloxacin for *S. pneumoniae*, *S. aureus* and ciprofloxacin-resistant *S. pneumoniae*; 2) similar to or greater than the other fluoroquinolones against *E. coli*; and 3) at least 2-fold lower than all fluoroquinolones against ciprofloxacin-resistant MRSA.

Another study (15) compared the efficacy of nemonoxacin and moxifloxacin in a mouse pulmonary infection model. Mice were challenged intranasally with a lethal dose of *S. pneumoniae*. Nemonoxacin and moxifloxacin were administered s.c. at 12, 18 and 24 h postchallenge at 6.25, 12.5, 25 or 50 mg/kg (total dose). Nemonoxacin dose-dependently reduced bacterial counts in blood and lung compared to vehicle-treated controls. Nemonoxacin and moxifloxacin reduced viable bacterial counts by 5.6-6.6 and 2.9-6.6 log in blood and 1.2-5.1 and 0.2-2.2 log in lung tissue, respectively. Histopathological evaluation of the lung from nemonoxacin-treated mice showed minimal to mild alveolar/interstitial inflammation, and

no distinct differences were found when compared to moxifloxacin-treated mice. Nemonoxacin protected 100% of mice from death at all doses and no adverse clinical symptoms were noted during the 7-day observation period. In contrast, the survival rates for moxifloxacin were 0%, 17%, 50% and 100%, respectively, at 6.25, 12.5, 25 and 50 mg/kg. Thus, nemonoxacin demonstrated efficacy in a mouse model of pulmonary infection caused by *S. pneumoniae* and was more effective than moxifloxacin in reducing the number of bacteria and protecting mice from mortality.

PHARMACOKINETICS AND METABOLISM

In order to recommend clinical doses for the treatment of respiratory and skin infections, a study integrated pharmacokinetic and microbiological data of the antibacterial response to nemonoxacin. Pharmacokinetic data (plasma AUC and C_{max}) were derived from a multiple-dose study of oral nemonoxacin (16), and MICs were determined according to standard methods using clinical isolates including major pathogens from respiratory tract and skin infections. The MIC_{90} of nemonoxacin was < 0.75 µg/mL against most of the pathogens tested, including major staphylococci (MRSA and ciprofloxacin-resistant MRSA), streptococci (penicillin-resistant *S. pneumoniae* and levofloxacin-resistant *S. pneumoniae*), *Moraxella catarrhalis*, *H. influenzae*, *E. coli*, *K. pneumoniae*, *P. mirabilis* and atypical pneumonia agents, except *E. faecalis* and *P. aeruginosa*. The integrated data indicated good pharmacological indices with oral doses of 500, 750 and 1000 mg once daily of nemonoxacin. The AUC_{0-24}/MIC_{90} for the 500-mg dose was > 100 for most of the pathogens, except ciprofloxacin-resistant, methicillin-sensitive *S. aureus,* ciprofloxacin-resistant MRSA, methicillin-resistant coagulase-negative staphylococci and levofloxacin-resistant *S. pneumoniae, E. faecalis. K. pneumoniae, P. mirabilis* and *P. aeruginosa*. The AUC_{0-24}/MIC_{90} for the 750- and 1000-mg doses were > 100 for most of the pathogens, except ciprofloxacin-resistant MRSA, levofloxacin-resistant *S. pneumoniae, E. faecalis, K. pneumoniae* and *P. aeruginosa*. Similar results were also observed for C_{max}/MIC_{90} profiles of nemonoxacin. The authors concluded that daily oral administration of doses of 750-1000 mg of nemonoxacin may provide clinical and microbiological success against major pathogens in both respiratory tract and skin infections, while the 500-mg dose may only be effective for the treatment of respiratory pathogens (17).

A randomized, double-blind, placebo-controlled phase Ia study investigated the pharmacokinetics of single ascending doses of nemonoxacin in healthy male and female volunteers. Fifty-six volunteers (48 males and 8 females) were randomly assigned to 1 of 7 dose cohorts. In each successive cohort, 2 subjects received placebo and 6 received a single oral dose of 25, 50, 125, 250, 500, 1000 and 1500 mg of nemonoxacin. Blood and urine samples were collected during 96 h, and pharmacokinetic parameters were calculated using noncompartmental methods. The investigators reported that plasma concentrations increased linearly over the dose range, with peak concentrations observed at 1-2 h. The elimination half-life was approximately 9-16 h. The oral clearance was about 0.22 L/h/kg and the plasma protein binding was approximately 16% (18).

Nemonoxacin has been shown to display a similar pharmacokinetic profile when administered repeatedly. In a randomized, double-blind, placebo-controlled phase Ib study, Zhang et al. (16) investigated the pharmacokinetics of repeated ascending doses of nemonoxacin in 46 healthy volunteers over a 10-day dosing period (75, 250, 500, 750 and 1000 mg). The 500-mg cohort received an additional dose with a high-fat meal on day 16 to study the effect of food. AUC and C_{max} were proportional to dose over the dose range. The elimination half-life was approximately 7-8 h at day 1 and 18-23 h at day 10. Approximately 37-58% of nemonoxacin was excreted in the urine over the first 24 h after dosing. Food affected the pharmacokinetics of nemonoxacin, decreasing C_{max} (46%) and AUC (27%) and increasing t_{max} (2-fold).

The potential effects of nemonoxacin on CYP3A4, a cytochrome P450 isoenzyme involved in many clinically relevant drug interactions, have been investigated in vitro in pooled human liver microsomes and in microsomes prepared from a human CYP3A4 cDNA expression system (19). The results of this study indicated that nemonoxacin is neither an inhibitor nor an inducer of human hepatic CYP3A4 activity in vitro. In addition, nemonoxacin demonstrated metabolic stability in vitro and was not a substrate for human hepatic CYP3A4.

SAFETY

In order to evaluate the fertility and developmental toxicity of nemonoxacin after oral administration, male and female Sprague–Dawley rats (25/sex/group) were given nemonoxacin by oral gavage (0, 30, 300 and 1000 mg/kg). Male rats were dosed once daily beginning 28 days before cohabitation and continuing through the day before sacrifice; female rats were dosed once daily beginning 14 days before cohabitation and continuing through day 7 of presumed gestation. There were no clinical signs or mortality in this study. Significant decreases in body weight gain and food consumption were observed during gestation and in the first dosing week in the mid- and high-dose female rats, respectively. There were decreases in absolute and relative weights of epididymis and prostate in the mid- and/or high-dose male rats. The authors considered these changes to be not toxicologically significant because neither semen changes nor histopathological findings were observed in these organs. These results indicate that oral administration of nemonoxacin does not produce any fertility or reproductive adverse effects (20).

The systemic hypersensitivity potential of nemonoxacin was examined in guinea pigs. Animals (three/sex) were randomly assigned to four groups receiving i.p. injections of negative control (0.9% normal saline), positive control (bovine serum albumin) and nemonoxacin at 10 and 20 mg/kg. The study consisted of induction and challenge phases. In the induction phase, animals were dosed every other day for a total of five injections. In the challenge phase, animals received 2-fold doses of the induction doses i.v. on day 10 after the last induction dose. During the induction phase, no nemonoxacin-related signs of toxicity or mortality were observed. There were no significant differences in body weight changes among all tested groups. In the challenge phase, no hypersensitivity signs were noted in the negative control or nemonoxacin-treated groups. As expected, all the positive control animals developed a hypersensitivity reaction. Based on these data, it was concluded that nemonoxacin did not demonstrate any sensitization potential and should not pose any allergenic/sensitizing risks in patients (21).

Chow et al. (22) evaluated the cardiovascular safety of nemonoxacin after daily administration to dogs and monkeys for 4 weeks. Beagle

dogs (16/sex) were randomly assigned to 4 groups receiving nemonoxacin at 0 (5/sex), 10 (3/sex), 30 (3/sex) and 100 (5/sex) mg/kg/day via a 60-min i.v. infusion. Cynomolgus monkeys (24/sex) received nemonoxacin orally at 0, 30, 100 and 300 mg/kg/day (6/sex/group). Electrocardiograms were recorded in the dogs immediately after infusion and in the monkeys at 3 h (t_{max}) after oral administration during the first and last week of treatment. The investigators found no changes in heart rate or Q-T intervals in dogs after i.v. infusion of nemonoxacin at 10 and 30 mg/kg (corresponding to peak plasma concentrations up to 18.8 µg/mL). Significant Q-T prolongations were observed with the high dose (100 mg/kg) on day 1 when plasma drug concentrations averaged 82 µg/mL. In monkeys, no ECG changes were observed in males or in females at 30 mg/kg and males at 100 mg/kg. However, prolongation of the Q-T interval was observed in females at 100 mg/kg/day on days 5 and 26 with plasma drug concentrations of 21.8 and 29.7 µg/mL, respectively. Prolongations of Q-T intervals were observed in monkeys after oral administration of nemonoxacin at 300 mg/kg with plasma drug concentrations > 50 µg/mL. When considering the projected therapeutic concentration of approximately 5 µg/mL in humans, the margin of cardiovascular safety for nemonoxacin (400%) appears adequate.

The phototoxic potential of nemonoxacin was evaluated in hairless mice. The quinolone was administered by oral gavage at doses of 0 (vehicle), 30, 300 and 1000 mg/kg to Crl:SKH1-*hr* hairless mice (6/group) either once or repeatedly (once daily for 10 consecutive days). UVR exposure from a xenon lamp simulating mid-latitude summer sunlight began approximately 30 min after completion of a single oral dose or completion of the tenth daily administration. Definitive skin reactions indicative of phototoxicity occurred in all mice administered a single dose of lomefloxacin (positive control) before simulated sunlight exposure. In contrast, skin reactions observed at the sites exposed to simulated sunlight in mice administered nemonoxacin orally at doses up to 1000 mg/kg were not indicative of cutaneous phototoxicity. In mice administered doses of 0 (vehicle), 30 and 300 mg/kg/day of nemonoxacin for 10 consecutive days, only slight edema occurred in 1 animal per group, which was not considered indicative of cutaneous phototoxicity (23).

A randomized, double-blind, placebo-controlled phase Ia study investigated the safety and tolerability of nemonoxacin in healthy male (n = 48) and female (n = 8) volunteers. In each cohort, 2 subjects received placebo and 6 received a single oral dose of 25, 50, 125, 250, 500, 1000 or 1500 mg of nemonoxacin. Tolerability was good up to the maximum tolerated dose of 1500 mg. No severe or serious adverse events were observed. The most frequent adverse events were contact dermatitis, pruritus and erythema. No significant abnormalities were noted in ECG, vital signs and laboratory tests. These data indicate that a single dose of nemonoxacin is safe and well tolerated (18).

Similarly, a randomized, double-blind, placebo-controlled phase Ib study found that orally administered nemonoxacin was generally safe and well tolerated in healthy volunteers at doses of 75-1000 mg/day for 10 consecutive days. No clinically significant changes were noted in vital signs, ECG and laboratory tests. The most common adverse events were mild and included headache, contact dermatitis and rash (16).

CLINICAL STUDIES

A randomized, double-blind, multicenter phase II study compared the efficacy of nemonoxacin and levofloxacin, both at doses of 500 or 750 mg p.o. once daily for 7 days, in adults with community-acquired pneumonia (the most common isolates included *H. influenzae*, *S. pneumoniae* and *S. aureus*). The primary endpoint was clinical cure rate at the test-of-cure (TOC) visit. The bacteriological success rate at the TOC visit was assessed in subjects with a baseline pathogen. A total of 265 subjects were randomized to 3 treatment arms in a 1:1:1 ratio. The clinical cure rates in the clinically evaluable population were 92% (66/72) for nemonoxacin 750 mg, 88% (64/73) for nemonoxacin 500 mg and 90% (65/72) for levofloxacin 500 mg. Nemonoxacin showed noninferiority to levofloxacin in clinical outcome. In the bacteriologically evaluable population, the bacteriological success rates were 92% (34/37) for nemonoxacin 750 mg, 84% (37/44) for nemonoxacin 500 mg and 94% (44/47) for levofloxacin 500 mg. It was noted that the C_{max} and the AUC_{0-24} of nemonoxacin 500 mg were lower than those of levofloxacin 500 mg. There was no significant difference among the three treatments in bacteriological outcomes by pathogen. All three treatments were well tolerated, with no drug-related serious adverse events. No clinically significant difference in drug-related adverse events was noted among the treatments. Nemonoxacin demonstrated a consistently favorable safety profile, as observed in previous evaluations. In summary, nemonoxacin 750 mg once daily is as effective and well tolerated as levofloxacin 500 mg once daily over a 7-day course for the treatment of adults with community-acquired pneumonia (24).

TaiGen Biotechnology is currently conducting an open-label phase II study assessing the safety and efficacy of nemonoxacin in patients with diabetic foot infections (25).

SOURCES

Procter & Gamble Pharmaceuticals (US); licensed to TaiGen Biotechnology for development and commercialization in China, Taiwan, Hong Kong, Singapore, Korea and other ASEAN countries.

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