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Design and biological evaluation of novel quinolone-based metronidazole derivatives as potent Cu^{2+} mediated DNA-targeting antibacterial agents

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ABSTRACT

A series of novel quinolone-based metronidazole derivatives as new type of antimicrobial agents were developed and characterized. Most of them gave good antibacterial activity towards the Gram-positive and negative bacteria. Noticeably, quinolone derivative **3i** exhibited low MIC value of 0.25 μg/mL against *Pseudomonas aeruginosa*, which was even superior to reference drugs Norfloxacin, Ciprofloxacin and Clinafloxacin. The further research revealed that compound **3i** could intercalate into *P. aeruginosa* DNA through copper ion bridge to form a steady **3i**–Cu^{2+}–DNA ternary complex which might further block DNA replication to exert the powerful bioactivities.

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Quinolones are the most important synthetic antibacterial agents,[1] and have been widely used in the treatment of many infections including urinary tract, respiratory and bone joint infections as well as sexually transmitted diseases, prostatitis, pneumonia and acute bronchitis.[2] However, the increasingly worrisome resistance caused by the prevalently clinical use and the weak potency of quinolones against some Gram-positive bacteria result in limited therapeutic efficacy in clinic.[3] Thus a large amount of effort has been devoted to the discovery of more effective derivatives with the profound potentiality to extend the antibacterial spectrum and overcome the drug-resistance.[4] In recent years, the structural modification of the *C*-7 position of quinolone ring by various types of substituents[5–7] has been attracting special interest. As it was evidenced that the *C*-7 substitution could greatly influence the inhibitory activity of DNA gyrase and cell permeability, and ultimately impact the solubility, bioactivity, spectrum and pharmacokinetics.[8]

Metronidazole and its derivatives such as ornidazole, secnidazole, tinidazole and nimorazole have been widely used in clinic to treat diseases caused by anaerobic bacteria (Fig. 1).[9] It has been found that the nitro fragment as an important moiety to enhance lipophilicity of the target compounds is favorable for tissue penetration and could induce bioactivities through the metabolic activation of nitro group.[10] Our previous work showed that the introduction of heterocyclic metronidazole-derived moiety into berberine backbone could not only enhance the antimicrobial activities, but also broaden antimicrobial spectrum.[11] Furthermore, the 1,2,4-triazole ethanol analog of metronidazole, known as the pharmacophore of antifungal fluconazole, was introduced into coumarin that has structurally similar skeleton to quinolone, and the resulting coumarin triazole hybrid showed great potentiality as new type of antibacterial agents to treat the drug-resistant bacteria infection.[12] However, to the best of our knowledge, metronidazole modified quinolone ring at *C*-7 position has not been observed. Based on above mentions and as an extension of our studies on the development of azole compounds, herein we incorporated metronidazole fragment into the *C*-7 position of quinolone ring to develop a novel class of quinolone azoles.

It is well known that the applications of 5-nitroimidazoles in medicinal aspect have been well documented. However, 5-nitroimidazole derivatives bearing 4-substitions have been rarely reported, which is probably due to their inconvenient synthesis. Actually, this kind of compounds as chemotherapeutic agents have already drawn special attention.[13] Especially, they are potentially powerful antimicrobial agents since it has disclosed that they could inhibit fungal ergosterol synthesis in a similar manner to the triazole antifungal drugs.[14] Moreover, the presence of vicinal substitution on nitro group was expected to have the potentiality to sterically protect the nitro group to reduce the adverse effect caused by the reactive intermediates of nitro group and to improve the metabolism and physicochemical property of such

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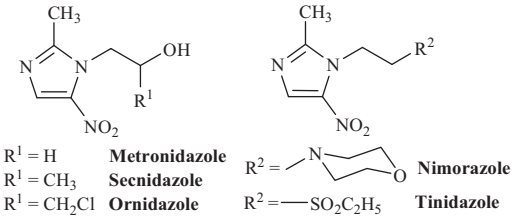

Figure 1. Structure of clinical metronidazole and its derivatives.

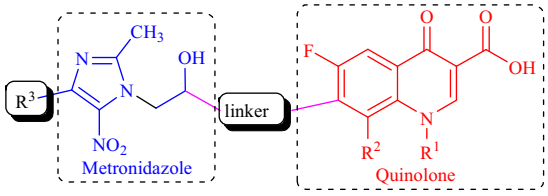

Figure 2. Structure of target quinolone-based metronidazole derivatives.

compounds.[11] Therefore, some biologically important heterocycles such as morpholine, pyrrolidine and piperidine, which might have significant effect on the antimicrobial efficacy, were also incorporated into the 4-position of nitroimidazole ring of target compounds in order to study their contribution to the antimicrobial activities.

In view of the above considerations, it is of great interest for us to combine quinolones through their C-7 position with respectively, metronidazole and its 4-cyclic amino nitroimidazole derivatives to generate a completely new structure type of antimicrobial agents (Fig. 2).

The synthetic route of quinolone-derived metronidazoles was outlined in Scheme 1. Intermediates **2a–c** were prepared in the yields of 52.4–67.4% by N-alkylation of commercially available quinolones with 2-(chloromethyl)oxirane and then treatment with formic acid to adjust the pH value to 5.5–6.5. Commercially convenient 2-methyl-5-nitroimidazole in acetonitrile was reacted with compounds **2a–c**, respectively, at 75 °C in the presence of potassium carbonate as base to produce the target quinolone azoles **3a**, **3e** and **3i** in 30.0–37.7% yields through simple treatment with formic acid to adjust the pH value to 5.5–6.5. The 4-cyclic amino nitroimidazoles including morpholine, pyrrolidine and piperidine ones were obtained through four steps including bromination, *N*-nucleophile substitution, amination, and N-deprotection starting from 2-methyl-5-nitroimidazole according to the reported synthetic procedure.[15] Unfortunately, under the same reaction condition for quinolone–metronidazole hybrid **3a**, the similar preparative procedures resulted in very low yields for the target 4-cyclic amino nitroimidazole derivatives **3b–d**, **3f–h** and **3j–l**. The experimental results manifested that the temperature significantly affected the formation of the products **3b–d**, **3f–h** and **3j–l**. Temperature higher than 60 °C led to the decomposition of these heat-sensitive 4-cyclic amino nitroimidazoles, whereas lower temperature resulted in quite poor yield. Consequently, the reaction of 4-cyclic amino nitroimidazoles with intermediates **2a–c**, respectively, was controlled at 60 °C, and the relatively high yields ranging from 19.6% to 29.5% for the corresponding target compounds **3b–d**, **3f–h** and **3j–l** were obtained. Further research to improve their yields is actively ongoing.

The newly synthesized compounds were evaluated for their antimicrobial activities in vitro against four Gram-positive bacteria (*Staphylococcus aureus* ATCC25923, *S. aureus* N315, *Bacillus subtilis* ATCC6633 and *Micrococcus luteus* ATCC4698), four Gram-negative bacteria (*Escherichia coli* JM109, *Pseudomonas aeruginosa* ATCC27853, *Salmonella enterica* ATCC14028 and *Bacillus proteus* ATCC13315) as well as five fungi (*Candida utilis* ATCC9950, *Aspergillus flavus* ATCC204304, *Beer yeast*, ATCC9763, *Candida albicans* ATCC10231, *Candida mycoderma* ATCC9888) using the standard two folds serial dilution method in 96-well microtest plates according to the National Committee for Clinical Laboratory Standards (NCCLS).[16] Minimal inhibitory concentration (MIC, μg/mL) was defined as the lowest concentration of new compounds that completely inhibited the growth of microbes. Currently available antimicrobial drugs Chloromycin, Norfloxacin, Ciprofloxacin, Clinafloxacin and Fluconazole were used as the positive control. The values of *c*log*P* were calculated using ChemDraw Ultra 10.0 software. The antibacterial and antifungal data as well as *c*log*P* values were depicted in Table 1.

The antimicrobial activity showed that the new quinolone-based metronidazoles **3a–l** exhibited effective activities against all the tested bacteria and fungi with MIC values of 0.25–256 μg/mL. Excitingly, some prepared compounds were even more active than the reference drugs. Particularly, compounds **3i–l** showed broad antimicrobial spectrum and excellent antibacterial activities in comparison with other compounds. Furthermore, the results also showed that incorporation of 4-cyclic amino metronidazole fragment had the potentiality in inhibiting the growth of all the tested bacteria.

Table 1 showed the significant effects of the types of substituents on the imidazole ring on biological activity. In comparison with other bacteria, they were relatively more sensitive to *P. aeruginosa*. Among all the metronidazole derivatives, compound **3i** gave the best anti-bacterial activity against *B. proteus*, *P. aeruginosa*, MRSA, *B. subtilis* and *M. luteus* with MIC value of 0.25 μg/mL which was more active than Clinafloxacin (MIC = 1 μg/mL). The introduction of morpholinyl group which yielded compounds **3d**, **3h** and **3l** resulted in relatively lower activity towards the tested strains. But compound **3l** still gave superior anti-*P. aeruginosa* anti-MRSA and equivalent anti-*B. proteus* activities (MIC = 0.25 μg/mL) to Clinafloxacin (MIC values were 1, 1 and 0.5 μg/mL, respectively). The replacement of 4-morpholinyl group by pyrrolidinyl fragment led to compounds **3b**, **3f** and **3j** with decreased bioactivities. Moreover, when the substituent was changed into 4-piperidyl group, compounds **3c**, **3g** and **3k** gave weaker inhibitory activity. These results suggested the noticeable effects of substituents in imidazole ring on biological activities.

Specially, the in vitro antifungal evaluation revealed that the 4-cyclic amino nitrometronidazole derivatives exhibited better antifungal activities against most of the tested fungal strains than those 4-unsubstituted ones. These results demonstrated that the existence of cyclic amines on the imidazole ring in this series of quinolone-based metronidazoles should be of special importance in microbial inhibition probably due to its easy and efficient formation of non-covalent forces with biosystem which could be helpful for the antifungal efficiency. Noticeably, all prepared compounds displayed high efficacy against Fluconazole-insensitive *A. flavus*.

The intermediates **2a–c** with oxiran-2-ylmethyl groups at C-7 position of quinolones, as shown in Table 1, also displayed moderate to good activities against all the tested bacterial strains in comparison with reference drugs. Particularly, compound **2c** gave the better antimicrobial efficiencies with MIC values of 0.25 μg/mL against *M. luteus* and *B. subtilis*, than the corresponding reference drug Clinafloxacin (MIC = 0.5 μg/mL). For Gram-negative *P. aeruginosa*, *E. coli* and *B. proteus* strains, compound **2c** (MIC = 0.5, 0.5 and 0.25 μg/mL, respectively) displayed stronger inhibitory activity than Clinafloxacin (MIC = 1, 1 and 0.5 μg/mL, respectively). The in vitro antifungal evaluation also revealed that the intermediates **2a–c** exhibited generally good antifungal activities against most of

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