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ARTICLE

Synthesis and biological evaluation of Schiff base-linked imidazolyl naphthalimides as novel potential anti-MRSA agents‡

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Huo-Hui Gong, Kishore Baathulaa†, Jing-Song Lv, Gui-Xin Cai* and Cheng-He Zhou*

A series of novel Schiff base-linked imidazole naphthalimides were developed and their antimicrobial behavior demonstrated that compound **9i** could effectively inhibit the growth of some tested strains, especially for MRSA (MIC = 0.003 μmol/mL), which was superior to the reference drugs. Bacterial membrane permeabilization, bacterial resistance and time–kill kinetic assays of compound **9i** against MRSA manifested that it was able to permeate cell membrane, rapidly kill the tested strains and stall the development of bacterial resistance. Preliminary research revealed that compound **9i** could form a steady complex with calf thymus DNA by intercalation mode. These results suggested that compound **9i** could serve as a promising anti-MRSA candidate.

1. Introduction

Infectious diseases caused by bacteria and fungi have become one of major causes of morbidity and mortality worldwide due to the continuous use, overuse and misuse of current antimicrobial agents and the appearance of drug-resistant strains over the past decades.[1] In particular, methicillin-resistant *Staphylococcus aureus* (MRSA), one of the most common causes of bloodstream infection, is resistant not only to methicillin, but also to aminoglycosides, macrolides, tetracycline, chloramphenicol and lincosamides. In addition, it has been found gradual resistance to vancomycin, the last-resort agent against MRSA. Thus, it is of paramount importance to develop new antimicrobial agents against these resistant strains.

Naphthalimide is an important π-deficient tricyclic planar heterocycle containing cyclic double imides and naphthalene framework.[2] This special structure endows its derivatives easily to interact with series of biological active sites *via* diverse weak interactions such as hydrogen bonds, coordination, ion-dipole, cation-π, π-π stacking, hydrophobic effects, van der Waals forces and so on.[3] In particular, their interaction with DNA or topoismerase (TOP) Ⅱ could effectively induce single-strand breakage and/or double-strand breakage of DNA and have attracted increasing interest in new drug design and development like anticancer, antibacterial, antifungal, antiviral, anti-inflammatory, antidepressant agents as well as diagnostic agents.[4] So far, a lot of excellent achievements have been acquired and some naphthalimides such as amonafide and mitonafide have already entered clinic trials.[5] Moreover, recent research showed that naphthalimide compounds could effectively inhibit the growth of a broad spectrum of pathogens including MRSA, by means of intercalating DNA and inhibiting the replication of DNA.[6] This encourages our special interest in investigating naphthalimides as a novel type of potential antimicrobial agents with the expectation to overcome side effects and drug-resistance of current therapies.

Azoles are one of most important class of nitrogen-

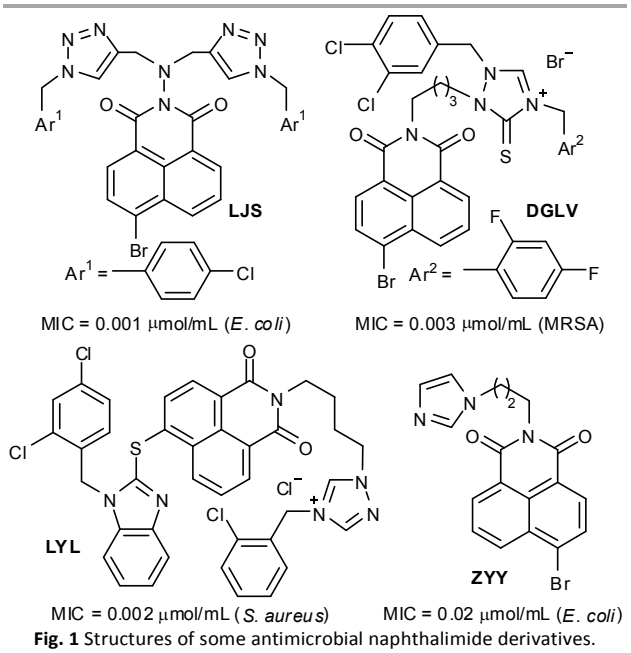

Fig. 1 Structures of some antimicrobial naphthalimide derivatives.

Institute of Bioorganic & Medicinal Chemistry, Key Laboratory of Applied Chemistry of Chongqing Municipality, School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, China
* Corresponding author; E-mail: gxcai@swu.edu.cn (G. X. Cai); zhouch@swu.edu.cn (C. H. Zhou); Tel.: +86-23-68254967; Fax: +86-23-68254967.
‡ The authors declare no competing interests.
† Postdoctoral fellow from Department of Chemistry, Kakatiya University, Warangal 506009, India.
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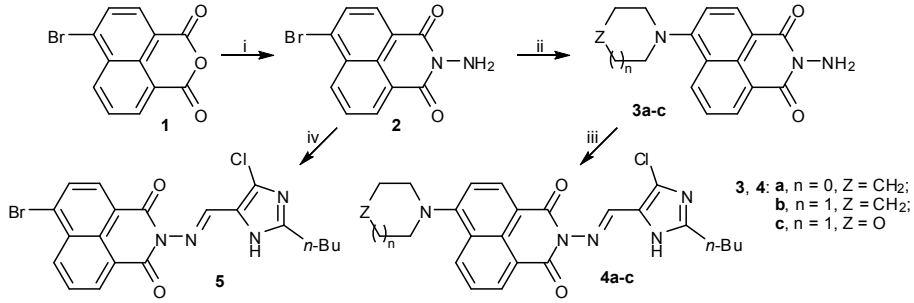
containing heterocyclic compounds that have been playing crucial roles in medicinal chemistry, in which azole rings could readily accept or donate proton and form various noncovalent interactions,[7,8] particularly the imidazole-based antimicrobial compounds.[9] Numerous efforts have been devoted to the synthesis of novel imidazole antimicrobial agents,[10,11] and some excellent drugs like metronidazole and keconazole have been successfully developed and extensively used in clinic. Our pervious work revealed that the introduction of azole into naphthalimide also led to moderate to good antimicrobial effectiveness that was even superior to the reference drugs chloromycin and fluconazole (Fig. 1).[12] However, to our best knowledge, the combination of imidazole with napthalimide skeleton has been seldom reported. Therefore, herein we introduced imidazole ring into the *N*-position of naphthalimide core *via* a Schiff base bridge, an important antimicrobial fragment, to investigate their contribution to bioactivities.[13]

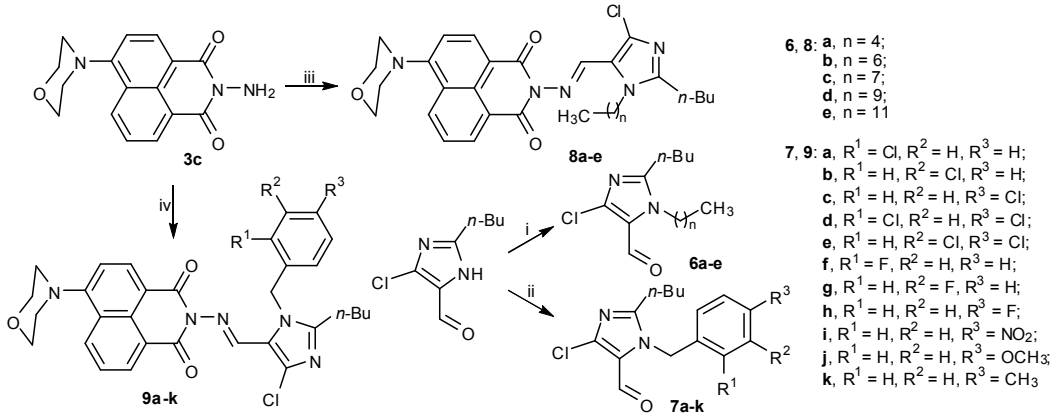
In view of the above considerations and our continuing efforts to develop naphthalimide-based antimicrobial agents, a series of new Schiff base-linked imidazolyl naphthalimides were designed and synthesized. Their antibacterial and antifungal activities were evaluated, and the preliminary antimicrobial mechanism was also investigated. Preliminary active screening was carried out among naphthalimides **4a–c** and unsubstituted compound **5** to understand the effect of alicyclic amine on antimicrobial potency and the most active one was selected for further structural optimization and biological evaluation. In addition, different alkyl and substituted benzyl moiety, and alicyclic amines were introduced into the selected structure to study their influence on structure-activity relationship and bioactive profiles.[14,15] Furthermore, in order to study the preliminary action mechanism, membrane permeabilization capability, bacterial resistance propensity, time−kill kinetic assays and the interaction with calf thymus DNA of the most active compound **9i** was further investigated.

2. Chemistry

The target imidazolyl naphthalimides **4a–c**, **8a–e** and **9a–k** were synthesized *via* multi-step reactions from 4-bromo-1,8-naphthalic anhydride **1** and the synthetic routine was outlined in Schemes 1 and 2. Compound **1** was reacted with hydrazine hydrate to afford intermediate **2** in 87% yields, and then further *N*-alkylated with alicyclic amines in ethylene glycol monomethyl ether at 125 °C under a nitrogen atmosphere to produce naphthalimides **3a–c** with high yields of 79–84%. The condensation of alicyclic amine-appended naphthalimides **3a–c** and 2-butyl-5-chloro-*1H*-imidazole-4-carbaldehyde (**BCIC**) in the presence of nitrogen using phosphorus pentoxide as dehydrating agent formed target imidazoles **4a–c** in 34–38% yields. The *N*-alkylation of **BCIC** with alkyl or substituted benzyl halides in the presence of potassium carbonate gave the



Scheme 1 Reagents and conditions: (i) $NH_2NH_2{\cdot}H_2O$, CH_3CH_2OH, r.t.; (ii) corresponding alicyclic amines, $CH_3OCH_2CH_2OH$, reflux, N_2; (iii) imidazolecarbaldehyde, P_2O_5, toluene, 100 °C, N_2; (iv) imidazolecarbaldehyde, P_2O_5, toluene, 100 °C, N_2.



Scheme 2 Reagents and conditions: (i) alkyl halides, K_2CO_3, CH_3CN, 50 °C; (ii) substituted benzyl halides, K_2CO_3, CH_3CN, 50 °C; (iii) corresponding alkyl imidazolecarbaldehydes, P_2O_5, toluene, 100 °C, N_2; (iv) corresponding substituted benzyl imidazolecarbaldehydes, P_2O_5, toluene, 100 °C, N_2.

target imidazolyl aldehydes **6a–e** and **7a–k** in good yields (75–85%), and then further condensation with naphthalimide **3c** afforded target compounds **8a–e** and **9a–k** with yields of 28% to 52%. For comparison, unsubstituted imidazolyl naphthalimide **5** was also synthesized by directly coupling compound **2** with **BCIC** under same conditions. All new compounds were confirmed by ^{1}H NMR, ^{13}C NMR, IR, MS and HRMS spectra. (Supporting Information)

3. Results and discussion

3.1. Antimicrobial activities

The *in vitro* antimicrobial activity of all the target compounds were evaluated against four Gram-positive bacteria, six Gram-negative bacteria and five fungi by two folds serial dilution technique in 96–well micro-test plates recommended by National Committee for Clinical Laboratory Standards (NCCLS) (Supporting Information). Clinically antimicrobial Chloromycin, Norfloxacin (Table 1) and Fluconazole (Table 2) were used as the positive control. As shown in Table 1, most of the prepared compounds gave weak to moderate antibacterial activity against the tested strains *in vitro*. Preliminary active screening showed that naphthalimides **4a–c** possessed better antibacterial efficacy than compound **5** without alicyclic amine, and morpholine-appended naphthalimide **4c** exhibited the strongest inhibition ability against these bacterial strains among the three alicyclic amine modified compounds.

Further studies, therefore, have been focused on the investigation of the influence of alkyl chains with different lengths and aromatic frameworks with various electro-donating or electro-withdrawing moieties on compound **4c**. It could be observed that the antibacterial efficacies of alkyl naphthalimides **8a–c** were not much different from compound **4c**, whereas those of derivatives **8d** and **8e** were better than compound **4c** against some tested strains. The experimental results indicated that long hydrophobic alkyl chain (over ten carbons) should be beneficial to regulate the flexibility of this imidazole-naphthalimide system and for their membrane penetration and antibacterial activity. It was noteworthy that compound **8e**, with prominent MIC value of 0.01 μmol/mL against *E. coli* (JM109), 10-fold more potent than clinical drug Chloromycin, had immense potentiality to be developed as anti-

Table 1 *In vitro* antibacterial activities as MIC (μmol/mL) for compounds **4–5**, **8–9** [a,b]

Compds.	Gram-positive bacteria				Gram-negative bacteria					
	MRSA	*S. aureus*	*B. subtilis*	*M. luteus*	*E. coli* (DH52)	*E. coli* (JM109)	*S. dysenteriae*	*P. aeruginosa*	*B. proteus*	*B. typhi*
4a	0.28	0.57	0.57	0.28	0.28	0.28	0.57	0.57	0.57	0.57
4b	0.28	0.28	0.28	0.28	0.56	0.56	0.28	0.56	0.56	0.56
4c	0.07	0.27	0.55	0.27	0.27	0.27	0.07	0.07	0.27	0.27
5	0.56	1.11	0.56	1.11	1.11	1.11	0.56	0.56	1.11	1.11
8a	0.48	0.24	0.24	0.24	0.48	0.48	0.48	0.96	0.48	0.24
8b	0.45	0.45	0.45	0.45	0.45	0.45	0.91	0.45	0.45	0.45
8c	0.44	0.22	0.44	0.88	0.44	0.22	0.88	0.88	0.44	0.44
8d	0.03	0.42	0.03	0.84	0.42	0.84	0.10	0.42	0.21	0.84
8e	0.20	0.40	0.80	0.40	0.80	0.01	0.80	0.80	0.80	0.80
9a	0.43	0.87	0.43	0.87	0.87	0.11	0.22	0.87	0.43	0.43
9b	0.43	0.43	0.007	0.43	0.43	0.43	0.11	0.43	0.22	0.43
9c	0.43	0.87	0.43	0.43	0.43	0.43	0.87	0.87	0.43	0.43
9d	0.37	0.18	0.37	0.18	0.74	0.37	0.37	0.18	0.37	0.37
9e	0.37	0.74	0.37	0.37	0.18	0.37	0.74	0.74	0.18	0.74
9f	0.44	0.22	0.44	0.22	0.44	0.11	0.44	0.22	0.44	0.44
9g	0.44	0.22	0.44	0.44	0.44	0.44	0.89	0.44	0.22	0.89
9h	0.44	0.89	0.44	0.44	0.89	0.44	0.89	0.89	0.44	0.44
9i	0.003	0.21	0.21	0.85	0.42	0.05	0.11	0.05	0.11	0.11
9j	0.44	0.44	0.44	0.87	0.44	0.87	0.44	0.44	0.22	0.44
9k	0.45	0.22	0.89	0.45	0.89	0.06	0.11	0.45	0.45	0.45
Chloromycin	0.05	0.05	0.10	0.02	0.10	0.10	0.05	0.10	0.10	0.10
Norfloxacin	0.02	0.006	0.01	0.006	0.003	0.003	0.05	0.05	0.02	0.01

[a] Minimal inhibitory concentrations were determined by micro broth dilution method for microdilution plates.

[b] MRSA, *Methicillin-Resistant Staphylococcus aureus* N315; *S. aureus*, *Staphylococcus aureus* ATCC25923; *B. subtilis*, *Bacillus subtilis* ATCC6633; *M. luteus*, *Micrococcus luteus* ATCC4698; *E. coli* (DH52), *Escherichia coli* DH52; *E. coli* (JM109), *Escherichia coli* JM109; *S. dysenteriae*, *Shigella dysenteriae*; *P. aeruginosa*, *Pseudomonas aeruginosa* ATCC27853; *B. proteus*, *Bacillus proteus* ATCC13315; *B. typhi*, *Bacillus typhi*.

E. coli (JM109) agent. Similarly, most of benzyl imidazole naphthalimides also gave quite high inhibitory concentrations, which might be ascribed to their poor flexibility. Specially, 3-chlorobenzyl derivative **9b** could effectively inhibit the growth of *B. subtilis* at the concentration of 0.007 μmol/mL, which was 14-fold more potent than Chloromycin and comparable to Norfloxacin. 4-Nitrobenzyl compound **9i** exhibited the highest inhibition potency against MRSA with MIC value of 0.003 μmol/mL, 17-fold and 7-fold more potent than Chloromycin and Norfloxacin, respectively, which suggested that it might be a promising anti-MRSA agent. In addition, naphthalimide **9i** also showed moderate activity toward other tested bacterial strains. Though structure **DGLV** has same MIC as the currently reported compound **9i** against MRSA, however, due to easy synthesis, good flexibility and small molecular weight in comparison to structure DGLV, so compound 9i should be a more suitable lead compound as a novel type of anti-MRSA agent.

The antifungal results in Table 2 showed that most of the target compounds had similar inhibitory tendency and intensity to their antibacterial activity. The antifungal activity of compounds **4a–c** were stronger than that of compound **5**, which confirmed that alicyclic amines were positive to antimicrobial activities. Imidazolyl naphthalimides **8a**, **8d** and **8e** displayed specific anti-*C. utilis* potency at the concentrations of 0.003–0.88 μmol/mL, particularly compound **8d** (MIC = 0.003 μmol/mL), which was 10-fold more active than the reference Fluconazole. Noticeably, 4-nitrobenzyl compound **9i** gave moderate to good antifungal activity towards most of the tested fungi, particularly *C. albicans* (MIC = 0.003 μmol/mL) and *C. utilisi* (MIC = 0.01 μmol/mL), and also encouraged us with great interest to carry out relational biological assays of highly bioactive compound **9i** to further explore their possible preliminary mechanism of action and pharmaceutical properties.

Table 2 Antifungal activities *in vitro* as MIC (μmol/mL) for compounds **4–5**, **8–9** [a]

Compds	Fungi				
	C. albicans	*C. mycoderma*	*C. utilis*	*A. flavus*	*B. yeast*
4a	0.14	0.14	0.28	0.57	0.57
4b	0.14	0.55	0.28	0.55	0.55
4c	0.27	0.14	0.55	0.55	0.27
5	1.11	1.11	1.11	1.11	0.14
8a	0.48	0.48	0.007	0.48	0.48
8b	0.23	0.45	0.45	0.45	0.45
8c	0.44	0.44	0.88	0.88	0.88
8d	0.21	0.21	0.003	0.21	0.42
8e	0.81	0.81	0.01	0.81	0.40
9a	0.43	0.87	0.43	0.22	0.43
9b	0.43	0.43	0.22	0.43	0.22
9c	0.43	0.43	0.22	0.87	0.22
9d	0.37	0.37	0.18	0.18	0.37
9e	0.37	0.37	0.37	0.74	0.18
9f	0.44	0.44	0.44	0.44	0.44
9g	0.44	0.44	0.44	0.44	0.44
9h	0.44	0.44	0.44	0.89	0.89
9i	0.003	0.05	0.01	0.11	0.42
9j	0.43	0.87	0.43	0.43	0.22
9k	0.45	0.90	0.11	0.90	0.45
Fluconazole	0.003	0.01	0.03	0.84	0.05

[a] *C. albicans*, *Candida albicans* ATCC76615; *C. mycoderma*, *Candida mycoderma* ATCC10231; *C. utilis*, *Candida utilis* ATCC9950; *A. flavus*, *Aspergillus flavus* ATCC204304; *B. yeast*, *Beer yeast* ATCC9763.

3.2. Bacterial membrane permeabilization

Bacterial membrane has been recognized as a particularly valuable and intriguing antibacterial target due to the difficult redesign process of the composition and/or organization of its lipids to resist membrane-targeted antimicrobial agents.[16] Therefore, it is reasonable to speculate that compound should have satisfactory antibacterial efficacy and low drug-resistance if it targets on or interacts with cell membrane. Herein, bacterial membrane permeabilization of compound **9i** was studied using propidium iodide (PI), a common dye that only can pass through the membrane of compromised cells and fluoresces upon binding to the DNA.[17]

As shown in Fig. 2, strong and rapid fluorescence enhancements at 617 nm of the mixtures compound **9i** and PI treated MRSA and *B. proteus* appeared and became steady after 60 min, while the two

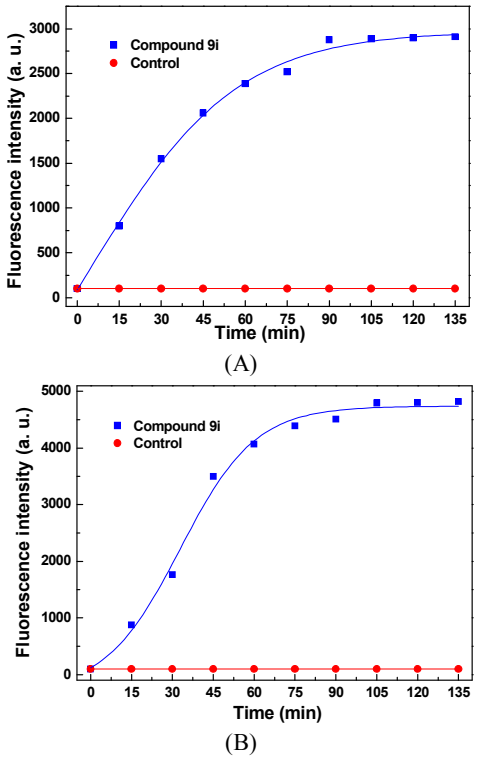


Fig. 2 Bacterial membrane permeabilization of compound **9i** (12 × MIC) against: (A) MRSA; (B) *B. proteus*.

control groups all keep constant, which demonstrated that compound **9i** could efficiently permeate the membranes of Gram-positive (MRSA) and Gram-negative (*B. proteus*) bacteria.

3.3. Propensity to induce bacterial resistance

The emergence of bacterial and fungal resistance is a crucial problem that impedes successful chemotherapeutics. Thereby, with the aim to investigate that drug-resistance ability of compound **9i**, the ability of MRSA bacteria to develop resistance against this compound was carried out, and antibacterial Norfloxacin was chosen as a positive control. The fold of MIC increased for the tested compound and control drug was plotted against the number of days and was shown in Fig. 3. The MIC for compound **9i** exhibited no obvious change after 10 passages, whereas that of Norfloxacin was started to dramatically increase after 6 passages and could reach to 100-fold after 10 passages. This result indicated that MRSA was more difficult to develop resistance against compound **9i** than clinical drug, and such structure was probably a promising candidate for anti-MRSA agent with considerable therapeutic effect and low drug-resistance.

3.4. Time–kill kinetic assay

Antibiotics can be classified into two types, bacteriostatic drugs that inhibiting cell growth, bactericidal drugs that inducing cell death. Given to the excellent bacteriostatic performance, the bactericidal activity of compound **9i** was also investigated by time–kill assay, which could provide information about the acting rate of compound against the tested bacteria. The time–kill kinetics of compound **9i** against MRSA was shown in Fig. 4. It was obvious that the compound **9i** could reduce more than 3 log (CFU/mL) number of viable MRSA within 1.5 h at a concentration of 6 × MIC. This rapid time–kill kinetic suggested that the possible anti-MRSA action mode of compound **9i** might be also related to the disruption of cell membrane integrity, which was consistent with the experimental result of bacterial membrane permeabilization assay of compound **9i** that it means to permeate through cell membrane.

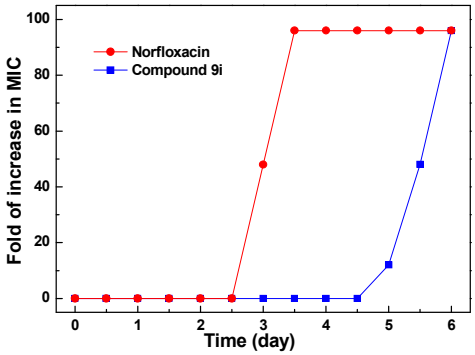


Fig. 3 Propensity to induce bacterial resistance: comparison of fold of increase in MIC of Norfloxacin and compound **9i** against MRSA.

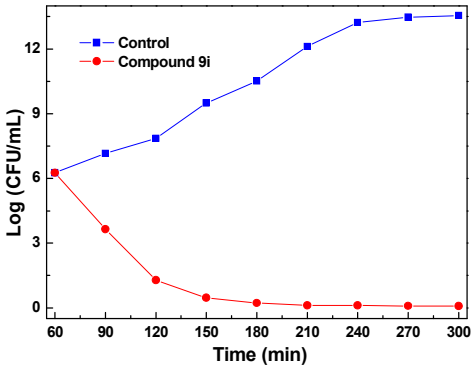


Fig. 4 Time–kill kinetic of compound **9i** (6 × MIC) against MRSA.

3.5. Interactions with calf thymus DNA

As one of the most important informational molecules and therapeutic targets, DNA has been extensively employed in studying pharmaceutical property of biologically crucial small molecules, like antimicrobial drugs.[18] Here, the binding behavior of compound **9i** with calf thymus DNA, a DNA model that is medical important, low cost and readily available, was studied on molecular level *in vitro* using neutral red (NR) dye as a spectral probe by UV–vis spectroscopic methods.

3.5.1 Absorption spectra of DNA in the presence of compound 9i

The change of DNA double-helical structure could be easily observed by different absorption spectroscopy export, where a large hypochromism would appear if a strong interaction occurs between the electronic states of intercalating chromophore and that of the DNA bases or a close proximity of the aromatic chromophore to the DNA bases. With a fixed concentration of DNA, UV–vis absorption spectra were recorded with sequentially and proportionately addition of compound **9i**. As shown in Fig. 5, the maximum absorption peak of DNA at 260 nm was gradually enhanced, accompanied by a slightly red shift during titration. Meanwhile, the absorption value of compound **9i**–DNA complex was a little lower than that of the simply sum of free DNA and free compound **9i**, which indicated that a weak hypochromic effect existed between DNA and compound **9i**. Moreover, the intercalation of the aromatic fragment of

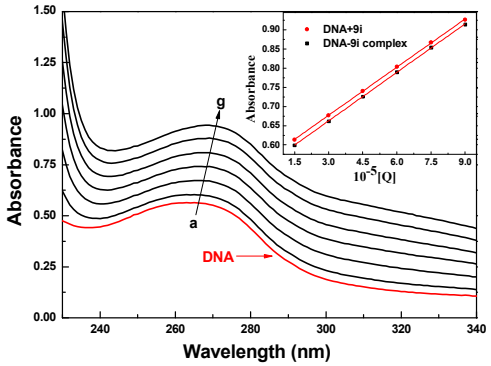


Fig. 5 UV absorption spectra of DNA with different concentrations of compound **9i** (pH = 7.4, T = 290 K). Inset: comparison of absorption at 260 nm between the compound **9i**–DNA complex and the sum values of free DNA and free compound **9i**. *c*(DNA)= 8.18 × 10^{-5} mol/L, and *c*(compound **9i**) = 0–9.00 × 10^{-5} mol/L for curves *a*–*g* respectively at increment 1.5 × 10^{-5}.

compound **9i** into the helix and the large overlap of π-π* states in the large π-conjugated system with the electronic states of DNA bases were accorded with the observed spectral changes.[19]

Based on the variations in the absorption spectra of DNA upon binding to compound **9i**, equation (1) can be utilized to calculate the binding constant (*K*).

$$\frac{A^0}{A-A^0}=\frac{\xi_C}{\xi_{D-C}-\xi_C}+\frac{\xi_C}{\xi_{D-C}-\xi_C}\times\frac{1}{K[\mathrm{Q}]} \quad (1)$$

A^0 and A represent the absorbance of DNA in the absence and presence of compound **9i** at 260 nm, ξ_C and ξ_{D-C} are the absorption coefficients of compound **9i** and compound **9i–**DNA complex respectively. The plot of $A^0/(A–A^0)$ versus 1/[compound **9i**] is constructed by using the absorption titration data and linear fitting (Supporting Information: Fig. S1), yielding the binding constant, K = 0.590 × 10^4 L/mol, R = 0.995, SD = 0.210 (R is the correlation coefficient. SD is standard deviation).

3.5.2 Absorption spectra of NR interactions with DNA

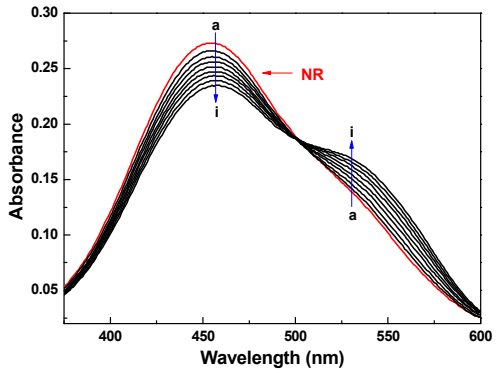


Fig. 6 UV absorption spectra of NR in the presence of DNA at pH 7.4 and room temperature. *c*(NR) = 2 × 10^{-5} mol/L, and *c*(DNA) = 0–3.81 × 10^{-5} mol/L for curves *a–i* respectively at increment 0.48 × 10^{-5}.

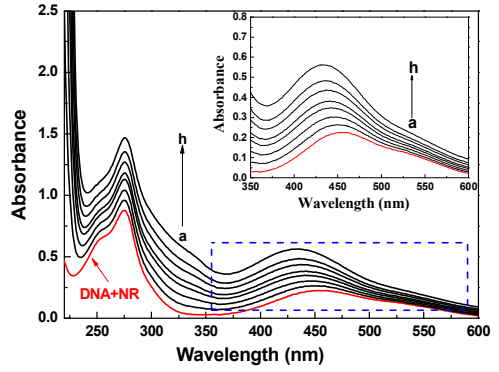


Fig. 7 UV absorption spectra of the competitive reaction between compound **9i** and NR with DNA. *c*(DNA) = 3.27 × 10^{-5} mol/L, *c*(NR) = 2 × 10^{-5} mol/L, and *c*(compound **9i**) = 0–10.5 × 10^{-5} mol/L for curves *a–h* respectively at increment 1.5 × 10^{-5}. Inset: absorption spectra of the system with the increasing concentration of compound **9i** in the wavelength range of 350–600 nm absorption spectra of competitive reaction between compound **9i** and NR with DNA.

To better understand the interaction between compound **9i** and DNA, the absorption spectra of competitive interaction of compound **9i** were also investigated. Neutral Red (NR) is a planar phenazine dye with low toxicity, high stability and convenient application properties, which has been demonstrated that the binding mode with DNA is intercalation. Therefore, NR was employed as a spectral probe to study the binding mode of compound **9i** with DNA in the present work.[20] The absorption spectra of the NR dye upon the addition of DNA were shown in Fig. 6. It could be observed that the absorption peak of the NR at around 460 nm would gradual decrease with the increasing addition of DNA, and a new band at around 530 nm appeared as a result of the formation of the new DNA**–**NR complex, and an isosbestic point at 504 nm also provided evidence of DNA**–**NR complex formation.

3.5.3 Absorption spectra of competitive interactions of compound 9i and NR with DNA

The absorption spectra of a competitive binding between NR and compound **9i** with DNA are showed in Fig. 7. The addition of compound **9i** to a solution of DNA**–**NR complex resulted in a significant absorption enhancement around 460 nm, which was a reverse process in comparison with the absorption around 460 nm of DNA**–**NR complex. Additionally, the absorbance at 258 and 275 nm extensive broadening was also observed in the spectra. These results indicated that compound **9i** was able to replace NR in the DNA–NR complex and the binding mode of compound **9i** and DNA was intercalation.

4. Conclusions

In summary, a series of Schiff base-linked imidazole naphthalimide compounds have been designed and synthesized for the first time through a simple synthetic strategy starting from commercial 4-bromo-1,8-naphthalic anhydride. The *in vitro* antimicrobial evaluation revealed that some target compounds could effectively inhibit the growth of some tested strains. Structure-activity relationship suggested that morpholine could significantly affect the antimicrobial efficacy compared to other alicyclic amines, whereas most of alkyl and substituted benzyl fragments showed negligible effects. Noticeably, 4-nitrobenzyl compound **9i** displayed strongest inhibition ability against MRSA with MIC value of 0.003 μmol/mL among the target compounds, which was much better than reference drugs. Further studies manifested that compound **9i** could efficiently permeate membrane of Gram-positive (MRSA) and Gram-negative (*B. proteus*), stall the drug-resistance of MRSA and rapidly kill MRSA. The preliminary interactive investigations of compound **9i** with calf thymus DNA demonstrated that it could effectively intercalate into DNA and form compound **9i**–DNA complex, which might block DNA replication to exert powerful antimicrobial activities. All of these indicated that compound **9i** was a promising anti-MRSA candidate with good curative effect and low drug-resistance. Further researches, including the *in vivo* bioactive evaluation, toxicity investigation, exploration of action mechanism, the incorporation of other alkyl amines

(diethylamine, diethanolamine, *etc.*) and heterocyclic azole rings (triazole, thiazole, benzimidazole, benzotriazole and their derivatives, *etc.*) into naphthalimide backbone as well as various functional groups (ester, ketone, amino ones and metal, *etc.*) linked to azolyl rings are underway and all these will be discussed in the future paper.

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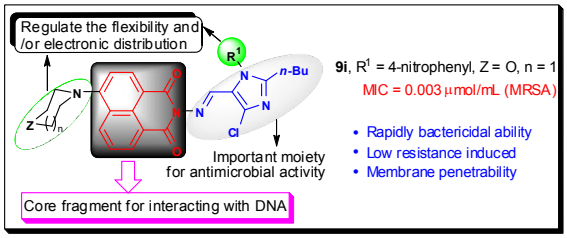
Graphical Abstract



Schiff base-linked imidazolyl naphthalimide **9i** was a potential anti-MRSA agent, which could effectively inhibit the growth of MRSA.