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A facile reaction to access novel structural sulfonyl-hybridized imidazolyl ethanols as potential DNA-targeting antibacterial agents

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ABSTRACT

A novel type of sulfonyl-hybridized imidazolyl ethanols as potential DNA-targeting antibacterial agents was constructed *via* the unique ring-opened reaction of oxiranes by imidazoles for the first time. Some developed target hybrids showed potential antimicrobial potency against the tested microbes. Especially, imidazole derivative **5f** could strongly suppressed the growth of MRSA (MIC = 4 μg/mL), which was 2-fold and 16-fold more potent than the positive control sulfathiazole and norfloxacin. This compound exhibited quite low propensity to induce bacterial resistance. Antibacterial mechanism exploration indicated that compound **5f** could embed in MRSA DNA to form steady **5f**-DNA complex, which possibly hinder DNA replication to exert antimicrobial behavior. Molecular docking showed that molecule **5f** could bind with dihydrofolate synthetase through hydrogen bonds. These results implied that imidazole derivative **5f** could be served as a promising molecule for the exploration of novel antibacterial candidates.

The outbreak of antimicrobial resistance together with the lack of novel treatment options causes a serious threat to both human and animal health worldwide.[1] Methicillin-resistant *Staphylococcus aureus* (MRSA) appeared in recent decades due to the evolution of bacteria and the abuse of antibiotics, which can trigger various infectious diseases, such as skin and soft tissue infections.[2,3] The terrible situation prompts the efforts to construct new antibacterial alternatives to traditional antibiotics.

Sulfanilamides are the first artificial antibacterial drugs and widely applied for prevention and therapy of microbial infections in biological systems.[4] Sulfonamide drugs can inhibit the growth of microorganisms by competing dihydropteroate synthase (DHPS) with *p*-aminobenzoic acid (PABA) to prevent the biosynthesis of nucleic acid and protein. Aromatic heterocycles-derived clinical sulfanilamide drugs such as sulfathiazole, sulfamethoxazole, sulfafurazole, sulfamethizole, sulfadiazine, sulfisomidine and sulfamethoxine play a positive role in the treatment of infective diseases.[5,6] Unfortunately, the emergence of drug-resistant bacteria reduces the therapeutic efficacy of sulfanilamide drugs and limits their clinic applications.[7] Most efforts for drugs of antibacterial discovery concentrate on reinvigorating existing sulfanilamides by dexterously chemical modification. This promotes the exploitation of a series of sulfonyl imidazolyl ethanols as novel antibacterial agents.

Imidazole plays an important role in medicinal chemistry.[8] The unique structural characteristic is beneficial for imidazole derivatives to bind with a variety of therapeutic targets like DNA, enzymes and receptors through diverse non-covalent interactions, thereby exerting broad pharmacological activities.[9,10] Imidazole ring extensively exists in bioactive functional molecules in the biological metabolism including deoxyribonucleic acid, histamine and hemoglobin, which indicates that it is essential in the physiological metabolic process for important bioactivity.[11] Moreover, various imidazole-based clinical drugs have been widely used to treat numerous diseases with good therapeutic power, such as ornidazole, ketoconazole and oxiconazole, showing the enormous research value.

Alcohols as disinfectants with strong antimicrobial potentiality has aroused the attention due to their wide existence, convenience and high potency.[12] It denatures the protein and destroys the microbial

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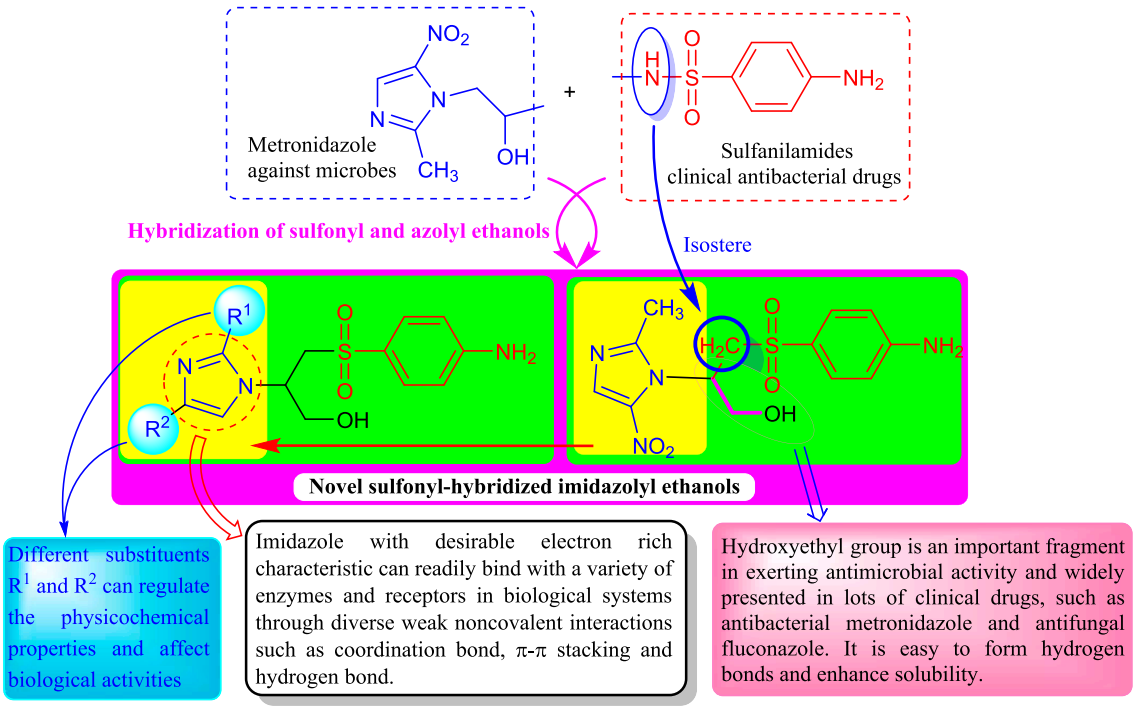
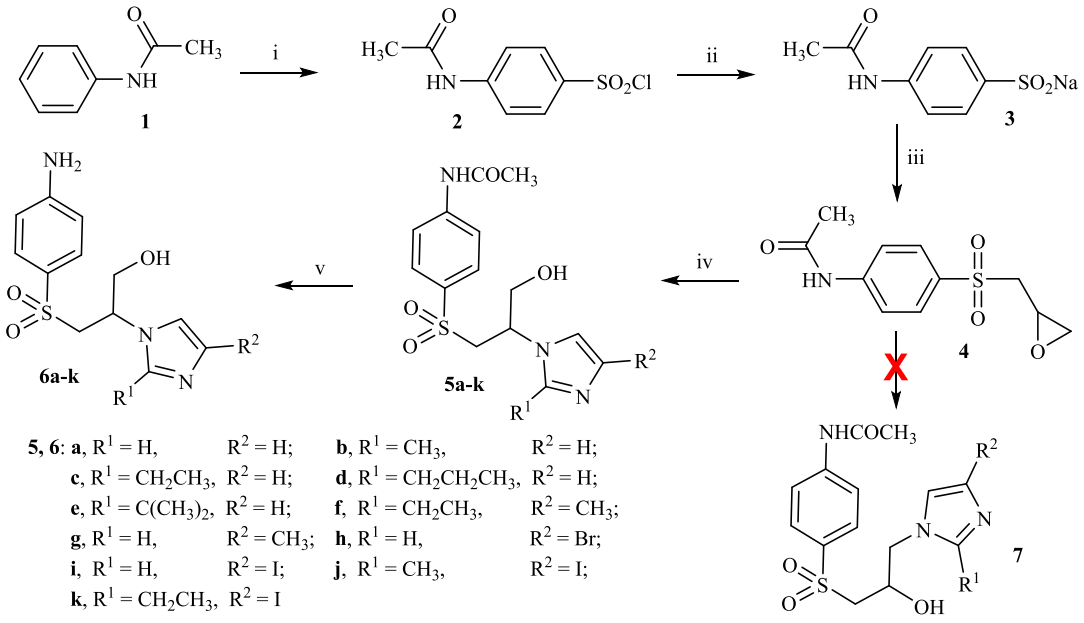


Fig. 1. Design of novel sulfonyl-hybridized imidazolyl ethanols as potential DNA-targeting antibacterial agents.



Scheme 1. Synthetic route of novel sulfonyl-hybridized imidazolyl ethanols **5a–k** and **6a–k**. Reagents and conditions: (i) Chlorosulfonic acid, 60 °C, 3 h; (ii) Sodium sulfite, sodium bicarbonate 80 °C, 2 h; (iii) Epichlorohydrin, tetrabutylammonium iodide, 80 °C, 3 h; (iv) Substituted imidazoles, potassium carbonate, acetonitrile, 70 °C, 10 h; (v) Hydrochloric acid, ethanol, 90 °C, 10 h.

physiological function. Azolyl ethanol fragment as a vital pharmacophore is widely used to develop novel bioactive molecules.[13] Particularly, imidazole type of azolyl ethanols such as ornidazole and metronidazole and thiazole alcohols including fluconazole and voriconazole were clinical drugs for the therapy of various infective diseases.[14] Therefore, it is of great interest to develop azolyl ethanol-based antibacterial agents (Fig. 1).

A unique reaction to access novel sulfonyl-hybridized imidazolyl ethanols as potential DNA-targeting antibacterial agents was discovered *via* the unique ring-opened reaction of oxiranes by imidazoles. Antibacterial evaluation *in vitro* and structure activity relationship (SAR) were discussed to guide the future design of active bioactive molecules. Molecular simulation explained the potential antimicrobial action. Interaction with DNA assays was carried out to investigate preliminary mechanism.

The desired sulfonyl hybrids of imidazole ethanols were prepared according to the synthetic routes outlined in Scheme 1 and **2**. The 4-acetamidobenzenesulfonyl chloride **2** was prepared by the sulfonylation of acetanilide **1** in chlorosulfonic acid at 60 °C for 3 h with an excellent yield of 90%. Compound **2** was treated by sodium sulfite and sodium

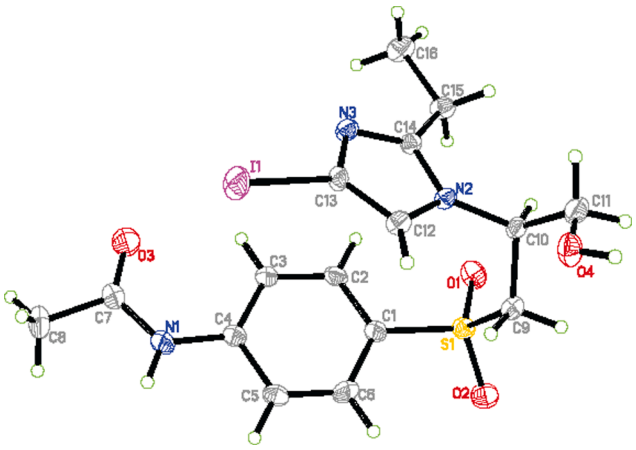


Fig. 2. Crystal structure of compound **5k** (CCDC: 2075577).

bicarbonate to afford sodium 4-acetamidobenzenesulfinate **3** with a high yield, following by the substitution reaction with 2-(chloromethyl) oxirane at 80 °C using tetrabutylammonium iodide as catalyst to give *N*-(4-((oxiran-2-ylmethyl)sulfonyl)phenyl)acetamide **4** with the yield of 53%. The intermediate **4** was then reacted with imidazole and its derivatives to provide target compounds **5a–k** with yield ranging from 57% to 72% through ring-opening reaction. Finally, compounds **5a–k** were further transformed into the deacetylate sulfonamide analogues **6a–k** in ethanol in the presence of 40% hydrochloric acid under reflux. Generally, secondary alcohol sulfanilamide derivatives were expected from the ring-opened reaction of oxiranes by azole ring according to our previous same condition, surprisingly, the sulfonyl-hybridized imidazolyl ethanols were primary alcohol structures, not second alcohol derivative **7**, which was not consistent with our previous researches.[15] This unique discovery was worthy of further exploration.

There are two equivalent tautomeric interconversions for imidazole ring in presence of base, two kinds of isomer products could be possibly produced when the reaction of intermediate **4** with imidazoles occurred. The single crystal of derivative **5k** (Fig. 2) was cultivated and X-ray diffraction analysis showed that sulfanilamide derivative was reacted with imidazole nucleus at the 3-*N* position instead of the 1-*N* position, which indicated that isomer **5k** should be the main product.

The prepared compounds **5a-k** and **6a-k** were evaluated for their antibacterial activities against the tested microorganisms as depicted in Table 1. The significant effects of substituents of imidazole ring on the biological activity were observed. Methyl-modified compound **5b** showed the same anti-MRSA activity as norfloxacin. Moreover, 2-ethyl-4-methyl imidazole derivative **5f** could effectively inhibit the growth of the MRSA and *E. faecalis* strains with low MIC values of 4 and 16 μg/mL, respectively, which were 2-fold and 16-fold more potent than the positive control drug sulfathiazole (8 and 256 μg/mL). Bromine-bearing molecule **5h** was active towards MRSA and *E. faecalis*, both MIC values were 8 μg/mL. However, the bioactivities of iodine-containing compounds **5i–k** against the same strains decreased. Notably, a few of the deprotected sulfonamide imidazole derivatives exerted better activity than the corresponding protected ones to some extent in inhibiting the growth of the tested bacteria. Data analysis revealed that derivative **5f** had great potential to become potent MRSA inhibitor.

The resistance development of stubborn strains to clinical drugs has aroused special attention to human.[16,17] Therefore, we studied the resistance of MRSA to the highly active molecule **5f**. The research findings (Fig. 3) showed that compound **5f** was sensitive to MRSA even after 13 passages. On the contrary, the MIC values of norfloxacin and sulfathiazole towards MRSA increased significantly. This result confirmed that less resistance tendency was pronounced for imidazole derivative **5f**. in comparison with clinical drug norfloxacin and sulfathiazole.

Deoxyribonucleic acid is a significant genetic material and already regarded as an important drug target to design and develop new efficient antibacterial drugs. The interaction of MRSA DNA with compound **5f** was investigated by UV–vis spectroscopy to further explore the

Table 1
In vitro antibacterial MICs (μg/mL) for compounds **5a–k** and **6a–k**[a, b].

Compds[c]	Gram-positive bacteria							Gram-negative bacteria			
	MRSA	*E. f*	*S. a*	*S. a* 25,923	*S. a* 29,213	*K. p*	*P. a.* 27,853	*P. a*	*A. b*	*E. c*	*E.c* 25,922
5a	32	32	64	64	32	128	64	128	64	64	64
5b	8	64	64	64	32	128	64	128	16	64	32
5c	32	32	64	64	16	128	64	256	16	64	32
5d	32	16	32	64	32	128	32	256	32	64	64
5e	16	32	128	64	16	64	64	256	32	64	64
5f	4	16	64	128	32	128	32	128	64	64	32
5g	16	64	128	64	32	32	32	128	64	64	64
5h	8	8	64	64	32	256	32	256	64	64	32
5i	32	64	64	64	64	64	32	32	32	128	32
5j	64	256	64	64	64	256	32	256	64	64	32
5k	128	64	64	64	64	64	32	256	64	64	32
6a	16	32	32	64	64	128	64	256	128	128	64
6b	16	8	128	64	64	128	64	128	16	128	32
6c	16	16	64	64	64	128	32	256	64	64	32
6d	8	32	128	64	128	128	32	256	32	64	64
6e	16	8	128	32	64	64	64	256	32	128	64
6f	16	16	64	64	128	128	32	128	64	64	32
6g	8	16	64	32	64	32	32	128	16	64	64
6h	16	64	64	64	64	256	32	256	64	64	32
6i	64	256	64	64	64	256	32	256	64	64	32
6j	32	64	64	64	64	64	32	128	32	128	32
6k	16	64	64	64	64	256	32	256	64	64	32
Sulfathiazole	64	512	512	512	512	128	512	128	64	256	128
Norfloxacin	8	256	8	1	1	256	16	256	8	512	512

[a] Minimal inhibitory concentrations (MIC, μg/mL) were determined by micro broth dilution method for microdilution plates.
[b] MRSA, *methicillin-resistant Staphylococcus aureus*; *S. A.*, *Staphylococcus aureus*; *S. A.* 25923, *Staphylococcus aureus* ATCC 25923; *S. A.* 29213, *Staphylococcus aureus* ATCC 29213; *E. F.*, *Enterococcus faecalis*; *K. P.*, *Klebsiella pneumonia*; *E. C.*, *Escherichia coli*; *E. C.* 25922, *Escherichia coli* ATCC 25922; *P. A.*, *Pseudomonas aeruginosa*; *P. A.* 27853, *Pseudomonas aeruginosa* ATCC 27853; *A. B.*, *Acinetobacter baumanii*.
[c] Compds = Compounds

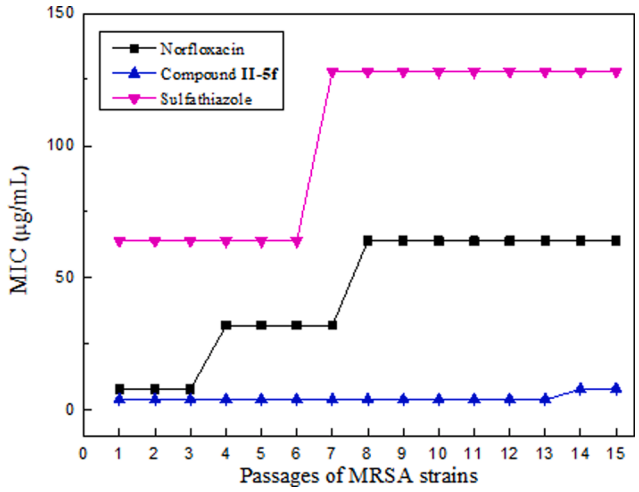


Fig. 3. Resistance development of MRSA to compound **5f.**

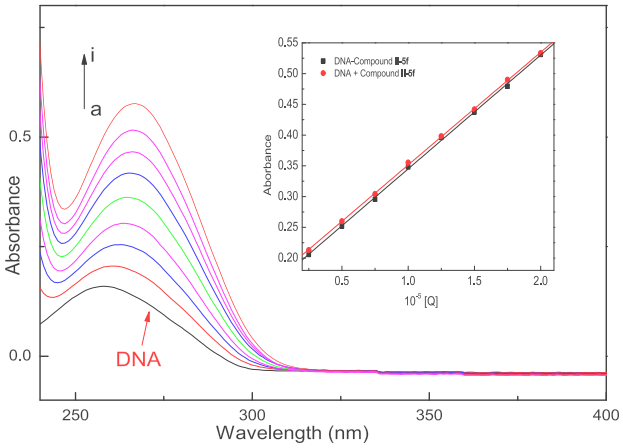


Fig. 4. UV absorption spectra of DNA with different concentrations of compound **5f** (pH = 7.4, T = 290 K). Inset: comparison of absorption at 260 nm between the value of compound **5f**-DNA complex and the sum values of free DNA and free compound **5f**. ***c***(DNA) = 2.84×10^{-5} mol/L, and *c*(compound **5f**) = 0–2.0×10^{-5} mol/L for curves **a**-**i** respectively at an increment 0.25×10^{-5}.

preliminary antimicrobial mechanism.

Hypochromism and hyperchromism are very momentous spectral features in spectroscopy to distinguish the change of DNA double-helical structure.[18] The strong interaction between the intercalating chromophore and DNA bases led to a large hypochromism, suggesting that the aromatic chromophore was close to the DNA bases.[19] As shown in Fig. 4, UV–vis spectra indicated that the maximum absorption peak of DNA at 260 nm gradually enhanced and a slightly red shift happened along with the increasing concentration of compound **5f**. Meanwhile, spectral data displayed that the sum of absorption value of free DNA and free compound **5f** was a little higher than the measured value of **5f**-DNA complex, which revealed a weak hypochromic effect between DNA and compound **5f** (inset of Fig. 4). The above phenomenon might be attributed to conformational changes in DNA duplex caused by formation of binary complexes. Moreover, the strong overlapping of π-π* states in the large-conjugated system with DNA bases was in accordance with the observed spectral changes, which further verified an intercalative binding mode between DNA and molecule **5f**.

Neutral Red (NR) is a planar phenazine dye and has been widely employed as a spectral probe due to its lower toxicity, higher stability and convenient application.[20,21] Furthermore, spectrophotometric and electrochemical techniques have already sufficiently demonstrated that

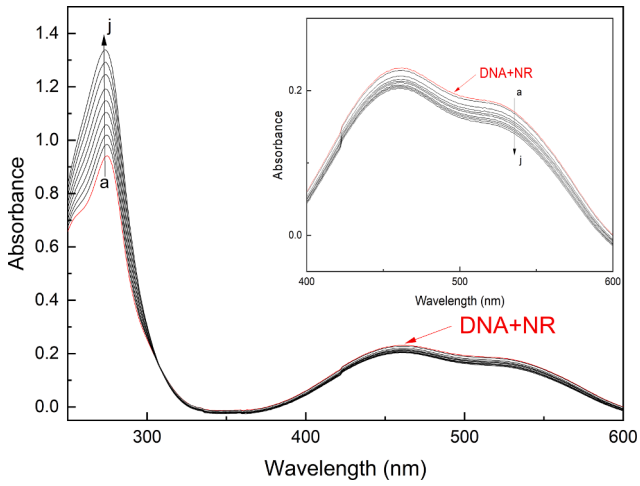


Fig. 5. UV absorption spectra of the competitive reaction between **5f** and NR with MRSA DNA. ***c***(DNA) = 2.84×10^{-5} mol/L, *c*(NR) = 2×10^{-5} mol/L, and *c* (compound **5f**) = 0–2.25×10^{-5} mol/L for curves **a**-**j** respectively at increment 0.25×10^{-5}. (Inset) Absorption spectra of the system with the increasing concentration of **5f** in the wavelength range of 350–600 nm absorption spectra of competitive reaction between compound **5f** and NR with DNA.

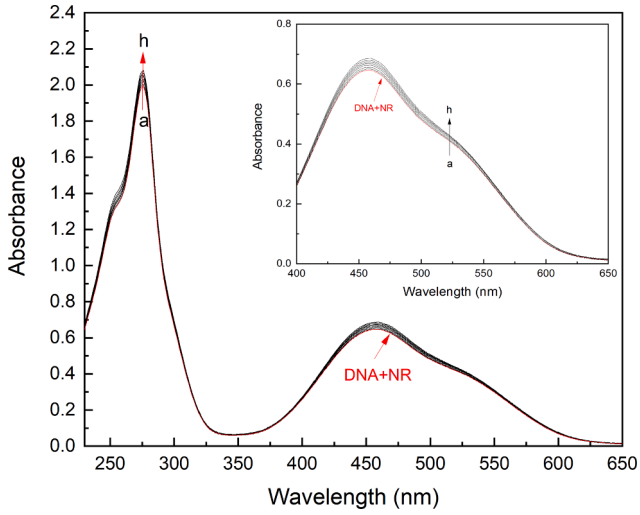


Fig. 6. UV absorption spectra of the competitive reaction between **5f** and NR with calf thymus DNA. ***c***(DNA) = 2.17×10^{-5} mol/L, ***c***(NR) = 2×10^{-5} mol/L, and c(compound **5f**) = 0–2.50×10^{-5} mol/L for curves **a**-**j** respectively at increment 0.25×10^{-5}. (Inset) Absorption spectra of the system with the increasing concentration of **5f** in the wavelength range of 400–600 nm absorption spectra of competitive reaction between compound **5f** and NR with calf thymus DNA.

NR can bind with DNA through an intercalative mode.[22,23] Experimental results displayed that the absorption peak of the NR at 460 nm gradually decreased with increasing concentration of DNA. Moreover, a new absorption band at around 530 nm was observed, which suggested the formation of new DNA–NR complex (**Fig. S2**). Meanwhile, an isoabsorptive point at 504 nm further confirmed the construction.

The absorption spectra[24,25] of the competitive binding between NR and compound **5f** with MRSA DNA was present in Fig. 5. Compared with the absorption around 530 nm of free NR in the presence of the increasing concentrations of DNA (**Fig. S2**), the absorbance at the same wavelength exhibited the reverse process (inset of Fig. 5). The result suggested that compound **5f** intercalated into the double helix of MRSA DNA by substituting NR of the DNA-NR complex. However, the absorbance around 530 nm exhibited the similar process (inset of Fig. 6) in

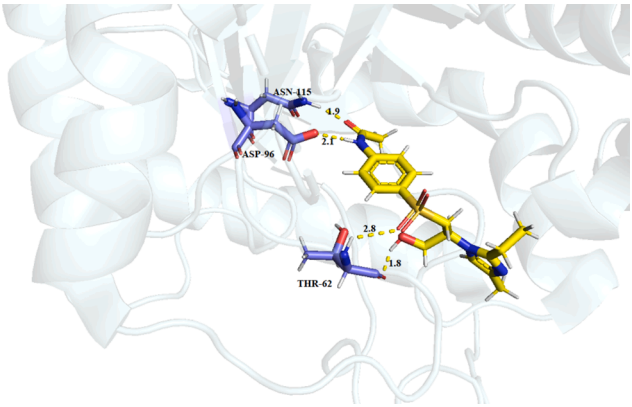


Fig. 7. Three-dimensional conformations of **5f** docked in MRSA dihydrofolate synthetase (PDB code: 5U14).

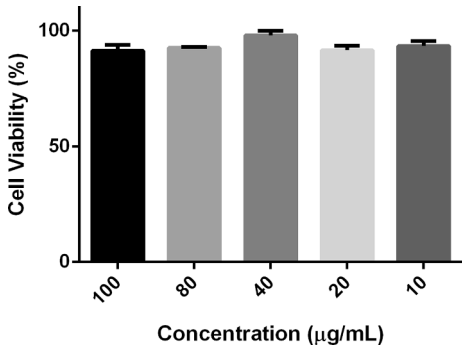


Fig. 8. Cytotoxic assay of compound **5f** on endothelial cells CCK8 evaluated by MTT method.

comparison with the absorption at the same wavelength of free NR in the presence of the increasing amount of calf thymus DNA (**Fig. S2**). This phenomenon indicated that compound **5f** could not interact with calf thymus DNA.

Dihydrofolate synthetase is essential for the synthesis of bacterial nucleic acid precursors. The absence of dihydrofolate synthetase can result in the inhibition of growth and reproduction of microbes.[26] In order to further explore possible antibacterial action, the dihydrofolate synthetase (PDB code: 5U14) was selected to dock with imidazole derivative **5f** and norfloxacin**.** The simulative result (Fig. 7) demonstrated that active molecule **5f** could bind with MRSA dihydrofolate synthetase at multiple sites *via* hydrogen bond interactions. The hydrogen of hydroxyl group and oxygen atom of SO_2 group formed two hydrogen bonds with THR-62 residues with distances of 1.8 and 2.8 Å, respectively. In addition, the hydrogen bonds also could be observed in –NH and C═O sites where bind with ASP-96 and ASN-115, respectively. The multiple non-covalent bindings might be conducive to stabilize the **5f**-enzyme complex, which might contribute to the inhibitory efficacy of compound **5f** against MRSA. Furthermore, the molecular simulation (**Fig. S3**) indicated that the hydrogen atom of carboxyl group in norfloxacin could bind with GLU-261 residue through hydrogen bond with a distance of 1.8 Å. However, there was only a hydrogen bond between norfloxacin and dihydrofolate synthetase, which might result in weaker antibacterial effect than compound **5f**.

Viability of endothelial cells CCK8 treated by different concentrations of compound **5f** was determined using MTT assay to evaluate the toxicity.[27] No obvious toxicity was observed even at the concentration of 100 μg/mL (Fig. 8). The result clearly indicated that compound **5f** could selectively inhibit MRSA cells but not CCK8 cell line, which further ascertained the therapeutic potential for bacterial infection.

Conclusions

A class of sulfonyl-hybridized imidazolyl ethanols was discovered *via* the ring-opened reaction of oxiranes by imidazoles. The *in vitro* antimicrobial evaluation revealed that some compounds were active against the tested microbes. Especially, imidazole derivative **5f** exhibited excellent antibacterial ability against drug-resistant MRSA with a low MIC value of 4 μg/mL, which was more potent than the positive control sulfathiazole and norfloxacin. Further exploration for antibacterial mechanism indicated that the compound **5f** might effectively insert into DNA of MRSA to form **5f**-DNA complex, which could block DNA replication to result in the bacterial death. The interaction between molecule **5f** and dihydrofolate synthetase revealed that **5f** could interfere the formation of nucleic acid precursor. These results suggested that compound **5f** was a promising molecule for further candidate drug study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.128198.

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