

Novel Naphthalimide Aminothiazoles as Potential Multi-targeting Antimicrobial Agents

Ying-Ying Chen, Lavanya Gopala, Rammohan R. Yadav Bheemanaboina,
Han-Bo Liu, Yu Cheng, Rong-Xia Geng, and Cheng-He Zhou

ACS Med. Chem. Lett., **Just Accepted Manuscript** • DOI: 10.1021/acsmedchemlett.7b00452 • Publication Date (Web): 01 Dec 2017

Downloaded from <http://pubs.acs.org> on December 4, 2017

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

Novel Naphthalimide Aminothiazoles as Potential Multi-targeting Antimicrobial Agents

Ying-Ying Chen, Lavanya Gopala, Rammohan R. Yadav Bheemanaboina, Han-Bo Liu, Yu Cheng, Rong-Xia Geng, Cheng-He Zhou^{*iD}

Institute of Bioorganic & Medicinal Chemistry, Key Laboratory of Applied Chemistry of Chongqing Municipality, School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, China

KEYWORDS: Naphthalimide, aminothiazole, antibacterial, MRSA DNA, human serum albumin

ABSTRACT: A series of novel naphthalimide aminothiazoles were developed for the first time and evaluated for their antimicrobial activity. Some prepared compounds possessed good inhibitory activity against the tested bacteria and fungi. Noticeably, the piperazine derivative **4d** displayed superior antibacterial activity against MRSA and *Escherichia coli* with MIC values of 4 and 8 $\mu\text{g/mL}$ respectively to reference drugs. The most active compound **4d** showed low toxicity against mammalian cells with no obviously triggering the development of bacterial resistance, and it also possessed rapid-bactericidal efficacy and efficient membrane permeability. Preliminary investigations revealed that compound **4d** could not only bind with gyrase–DNA complex through hydrogen bonds, but also effectively intercalate into MRSA DNA to form **4d**–DNA supramolecular complex, which might be responsible for the powerful bioactivity. Further transportation behavior evaluation indicated that molecule **4d** could be effectively stored and carried by human serum albumin, and the hydrophobic interactions and hydrogen bonds played important roles in the binding process.

The emergence and spread of multidrug-resistant bacteria resulted from the overuse and misuse of antibiotics has been a major obstacle to the successful treatment of infectious diseases.^{1–3} Methicillin-resistant *Staphylococcus aureus* (MRSA) is currently a major nosocomial pathogen, which arises from the acquisition of staphylococcal cassette chromosome *mec* (SCC*mec*) through horizontal gene transfer in methicillin-susceptible *Staphylococcus aureus*. An altered penicillin-binding protein PBP2a expressed by SCC*mec* has fairly lower binding affinity for nearly all available β -lactam antibiotics, making them invalid against MRSA.³ Despite numerous efforts devoted to ensure sterility and limit spread of MRSA, the morbidity and mortality rates still remain high per year. This deeply highlights the urgent and unmet medical need for developing new type of potential antimicrobial agents against MRSA.⁴

Naphthalimides are highly versatile functional compounds, which have received an increasing attention in the development of DNA-binding agents,⁵ and established great therapeutic importance in medicinal chemistry.^{6,7} Especially as anticancer agents, some naphthalimides such as amonafide, mitonafide and aristolochic acid effectively inhibit the growth of various human and murine cancer cell lines. This type of compounds exert their anticancer function by intercalating into DNA to directly inhibit the normal replication and transcription of DNA, and/or into topoisomerase (TOP) II to stabilize supramolecular complex of TOP and DNA, and to prevent the correction of topology structure of DNA.⁸ This special interaction model of naphthalimides with DNA has

been recently applied to the rational discovery of potential antibacterial and antifungal agents, and some great achievements have been acquired.^{9–10}

Aminothiazole is a beneficial structural fragment for bioactivity and prevalently present in a broad range of therapeutic agents¹¹ due to its unique structure with both electron-donating groups (NH_2 , $-\text{S}-$) and an electron-accepting group ($\text{C}=\text{N}$), which could readily interact with DNA and many other biomacromolecules.^{12,13} A lot of drugs containing aminothiazole fragment have been launched into the market,^{14,15} such as the antibacterial cephalosporins and sulfathiazole, the antifungal drug abafungin. The successful development of various clinical aminothiazole drugs has provoked extensive studies to construct more bioactive molecules with aminothiazole fragment in antimicrobial field.^{16–18}

In view of this, we introduced aminothiazole moiety into the *N*-position of the naphthalimide backbone to generate novel naphthalimide-aminothiazole hybrids and investigated their effect on antimicrobial activity.¹⁹ It is known that the bioactivities of naphthalimides are significantly affected by functional groups on the naphthalimide ring especially at the 3- or 4-position,⁶ which are beneficial for targeting biomolecules. Alicyclic amines such as piperazine, morpholine and pyrrolidine are important structural fragments in regulating the physicochemical properties and improving pharmacokinetic profiles,²⁰ and they are prevalently present in numerous clinical antimicrobial agents. Rationally, various alicyclic amine moieties were incorporated into the 4-position

of naphthalimide skeleton to study their influence on bioactive profiles (Figure 1).⁹

The antimicrobial screening was executed among naphthalimide aminothiazoles **3–5** to investigate their biological activities. Bacterial resistance study, bactericidal kinetic assay, and cytotoxicity were explored to further assess the potentiality of the bioactive compounds as new antimicrobial agents. Additionally, the antimicrobial mechanism was also investigated through membrane permeabilization assay, molecular docking study with gyrase–DNA complex, interaction with MRSA DNA. The transportation behavior of human serum albumin (HSA) to highly active compound was also performed.

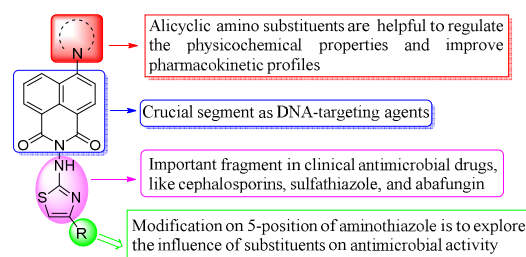
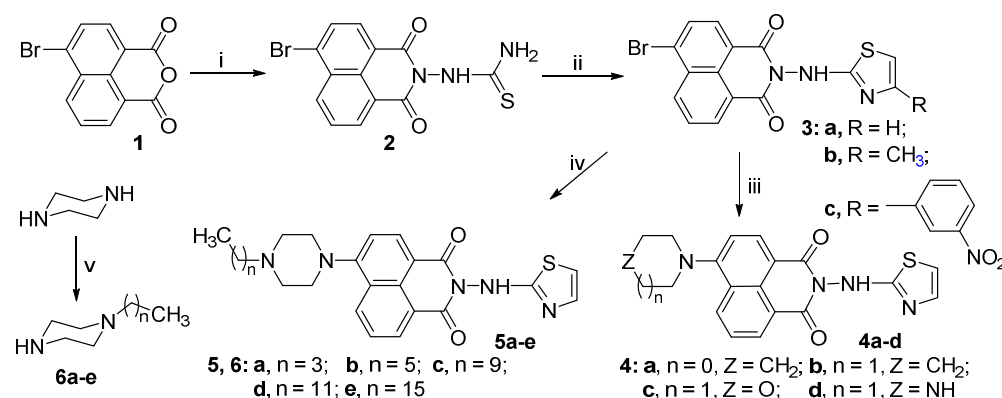


Figure 1. Design of novel naphthalimide aminothiazoles.

Scheme 1. Synthetic route of naphthalimide aminothiazoles **3–5**^a



^aReagents and conditions: (i) thiosemicarbazide, DMF, 100 °C, 8 h; (ii) α -halogenated carbonyl compounds, ethanol, 80 °C, 7 h; (iii) alicyclic amines, 2-methoxyethanol, reflux, N₂, 7 h; (iv) *N*-alkylated piperazines, 2-methoxyethanol, reflux, N₂, 7 h; (v) alkyl halides, ethanol, 80 °C, 8 h.

The target naphthalimide aminothiazoles **3–5** were synthesized *via* multi-step reactions starting from commercial 4-bromo-1,8-naphthalic anhydride according to Scheme 1. Condensation of 4-bromo-1,8-naphthalic anhydride and thiosemicarbazide afforded compound **2** in 60.1% yield, which was further cyclized with the α -halogenated carbonyl compounds in ethanol at 80 °C *via* the typical Hantzsch thiazole synthesis to give aminothiazole derivatives **3a–c** in yields of 21.1–40.2%.¹⁷ The *N*-alkylation of piperazine with alkyl halides generated mono-substituted alkyl piperazines **6a–e** with yields of 35.1–80.0%. Compound **3a** was further treated with alicyclic amines in 2-methoxyethanol at 125 °C under nitrogen atmosphere to achieve the desired compounds **4a–d** in yields of 30.0–46.2%, under the same reaction condition, the substitution of bromo atom in compound **3a** by piperazinyl derivatives **6a–e** produced the target naphthalimide aminothiazoles **5a–e** with yields ranging from 26.0% to 40.6%.⁹ All the new compounds were confirmed by ¹H NMR, ¹³C NMR, IR, and HRMS spectra. Purity was determined with the help of the quantitative nuclear magnetic resonance (QNMR) method using 1,3,5-trioxane as the internal standard. All the target compounds were found to be > 95% pure, and the spectral data were in the Supporting Information.

The antimicrobial data evaluated using two folds serial dilution technique recommended by Clinical and Laboratory

Standards Institute (CLSI)²¹ were depicted in Table S1. Some prepared compounds could effectively inhibit the growth of the tested strains *in vitro*. Preliminary active screening showed that aminothiazole derivative **3a** possessed slightly better antibacterial efficacy than 4-substituted aminothiazoles **3b–c**, it suggested that the modification on 4-position of aminothiazole ring might be unfavorable for the antibacterial activity. Among the series of compounds **4a–d**, morpholine modified naphthalimide **4c** gave the strongest anti-*A. baumannii* potency (MIC = 8 μ g/mL), 2-fold more potent than chloramphenicol (MIC = 16 μ g/mL) and equivalent to norfloxacin (MIC = 8 μ g/mL). Notably, piperazinyl derivative **4d** could effectively inhibit the growth of all the tested bacteria, except for *A. baumannii*. Especially against Gram positive bacteria, this compound demonstrated efficient bioactivity against *S. aureus* 29213 (MIC = 2 μ g/mL), *S. aureus* 25923 (MIC = 4 μ g/mL) and MRSA (MIC = 4 μ g/mL), which was more active than chloramphenicol (MICs = 4, 8 and 16 μ g/mL, respectively). Besides, it was also effective in inhibiting Gram negative bacteria including *E. coli*, *E. coli* 25922, *P. aeruginosa* and *P. aeruginosa* 27853 at low concentrations (MICs = 4–16 μ g/mL), particularly against *E. coli* 25922 strain, which was 4-fold and 2-fold more potent than chloramphenicol (MIC = 16 μ g/mL) and norfloxacin (MIC = 8 μ g/mL), respectively. These indicated that target molecule **4d** had immense potentiality to be a lead compound in the development of more effective

board-spectrum antimicrobial agents. Compounds **4a** and **4b** with pyrrolidinyl and piperidinyl substituents gave unfavorable antibacterial profile against the tested strains. Among six-membered alicyclic amine derivatives **4b–d**, it was noteworthy that the higher active compound **4d** and the lower active ones **4b–c** were attributable solely to the different substitution on the 4-position of six-membered alicyclic amines, which revealed that the NH group had quite positive influence on bioactivity than O or CH₂ moiety. So it would be interesting and rational to continue our work to modify the *N*-position on piperazine ring of derivative **4d**.

Further studies were focused on the effect of alkyl chain in piperazine ring of compound **4d** on antimicrobial activity because a large amount of work had revealed the importance of alkyl chain in affecting antimicrobial efficacy.⁹ Therefore the alkyl groups were introduced into compound **4d** to produce derivatives **5a–e** with conspicuous loss of inhibitory efficacies against the tested pathogens, which suggested the necessity of NH group for antimicrobial activity probably due to its participation in formation of hydrogen bonds so as to helpfully interact with biomolecules in biological system. Besides, the lengths of alkyl chains have different effects on biological activity, in which analogue **5b** with hexyl group gave better antibacterial activity in comparison with other alkyl derivatives. Moreover, when the alkyl substituents were extended to decyl, dodecyl and hexadecyl groups, compounds **5c–e** displayed weak or no obvious activity in inhibiting the growth of the tested bacterial strains. This fact pointed out that only suitable length of alkyl chain in piperazine ring was necessary for good antibacterial activity. The antifungal activities (Table S2) were also discussed and showed in the Supporting Information.

Many of the clinically approved drugs have suffered defeat from the resistant clinical strains due to the decreased potency or increased susceptibility to the degradation mechanisms.²² Thereby, it would be important to evaluate the ability of compound **4d** to suppress the development of resistance. The resistant pathogen MRSA was employed as the tested strains. Norfloxacin and chloromycin were used as positive control. As shown in Figure 2, this result indicated that MRSA was much more difficult to develop resistance against compound **4d** than the clinical drugs, and such structure might be a promising candidate for anti-MRSA agent with considerable therapeutic efficacy and low drug-resistance.²³

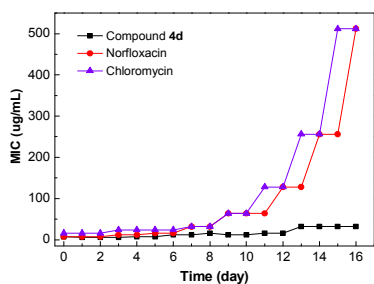


Figure 2. Propensity to induce bacterial resistance of compound **4d** against MRSA.

To understand the antibacterial nature of the piperazinyl derivative **4d**, time–kill kinetics assay was investigated against

MRSA, which would provide information about the bactericidal activity of compound **4d** against the tested bacteria.²⁴ As can be seen from Figure S1, compound **4d** could cause more than 3-Log (CFU/mL) reduction in the number of viable bacteria within an hour at a concentration of $4 \times \text{MIC}$. It was suggested that this compound showed rapid-bactericidal activity against MRSA.

The selectivity toward mammalian cells over bacterial cells has been one of the major concerns in the development of clinically available antibacterial agents for biomedical applications.^{25,26} The active molecule **4d** was further evaluated for its cytotoxicity against normal rat macrophage cells (RAW 264.7) using the MTT assay. Results in Figure S2 showed that the cell viability of compound **4d** was at least 80.1% within a concentration of 128 µg/mL. This indicated that compound **4d** exhibited relatively low toxicity toward mammalian cells within the MIC values against most of the test bacteria.

Membrane-targeting antimicrobials provide potential solutions for the problem of bacterial resistance, for the reason that the membrane-active nature gives low propensity for the development of drug resistance unless there are large-scale changes in the membrane compositions of bacteria. Therefore, bacterial membrane has been considered as a particularly valuable antibacterial target to overcome resistance.²⁷ Compound **4d** was further assessed for the ability to permeabilize the cytoplasmic membrane of bacteria using propidium iodide (PI) dye.²⁸ As can be seen from Figure S3, the rapid fluorescence intensity enhancements of the mixtures of compound **4d** and PI-treated MRSA and *Escherichia coli* appeared and became steady after 60 min, while the two control groups almost kept constant, which proved that the tested compound **4d** was efficient in permeabilizing the membranes of both Gram positive (MRSA) and Gram negative (*Escherichia coli*) bacteria.

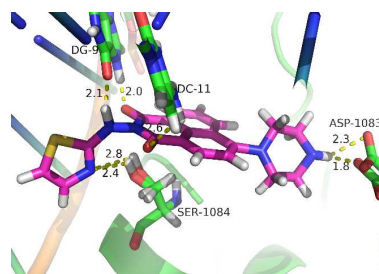


Figure 3. Three-dimensional conformation of compound **4d** docked in the gyrase–DNA complex (PDB code: 2XCS).

Molecular docking investigation was performed to rationalize the observed antibacterial activity and explore the possible action mechanism of hybrid **4d**.²⁹ Crystal structure of gyrase–DNA complex was selected as a representative target in the Protein Data Bank (PDB code: 2XCS). The docking mode with the lowest binding energy ($-11.95 \text{ kcal mol}^{-1}$) was shown in Figure 3 and Figure S4. Molecule **4d** could interact with gyrase–DNA complex through the formation of hydrogen bonds between the two carbonyl groups of naphthalimide backbone and base pairs of DNA (DG-11 and DG-9). The amino group of aminothiazole was also adjacent to DG-9 base pairs with distance of 2.1 Å. Besides, derivative **4d** could form two hydrogen bonds with residue SER-1084 of gyrase–DNA complex through the nitrogen atom of thiazole

ring. Furthermore, the NH group of piperazine ring in the 4-position of the naphthalimide fragment was in close proximity to the residue ASP-1083, which demonstrated the necessity of the NH group for the increased bioactivity and also rationalized the obtained antimicrobial result that introduction of alkyl groups at the piperazine ring of compounds **5a–e** could lead to the decreased antimicrobial potency. Compound **4d** was also disclosed to be involved in hydrophobic interactions at the active site with the hydrophobic residues. All of these cooperative bindings might be helpful to stabilize the **4d**–enzyme–DNA supramolecular complex, which might be responsible for the good inhibitory efficacy of compound **4d** against the tested strains.

The research of drug–DNA interactions is of great importance and interest in rational design and construction of novel and effective DNA–targeting drugs.³⁰ The interaction between the highly active compound **4d** and MRSA DNA was explored to further study the preliminary mechanism of antimicrobial action at molecular level by UV–vis spectroscopy. The results revealed that compound **4d** could effectively intercalate into MRSA DNA to form **4d**–DNA complex which might block DNA replication and thus exert powerful antimicrobial activity (Supporting Information).

Further binding behavior between compound **4d** and HSA was carried out to preliminarily evaluate their transportation and pharmacokinetic properties. HSA is the principal extracellular protein of the circulatory system,³¹ thorough investigations involving the interactions between drugs and HSA could not only provide the absorption, transportation, distribution, metabolism and excretion properties of drugs, but also be instructive to design, modify and screen new drug molecules.^{32,33} The transportation behavior disclosed that the association of molecule **4d** with HSA was spontaneous, and the hydrophobic interactions and hydrogen bonds played important roles in the binding process. The calculated parameters indicated that compound **4d** could be effectively stored and carried by HSA (Supporting Information).

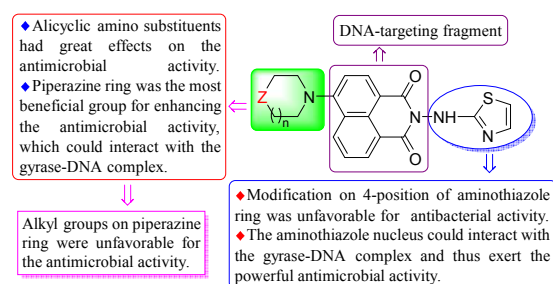


Figure 4. Preliminary summary of the structure-activity relationships for naphthalimide aminothiazoles.

In conclusion, a series of novel naphthalimide-aminothiazole hybrids were successfully developed via a convenient synthetic strategy. The structure-activity relationships were summarized in Figure 4. Piperazinyl derivative **4d** exhibited broad antibacterial spectrum. Particularly, it could effectively inhibit the growth of MRSA and *Escherichia coli* with MIC values of 4 and 8 $\mu\text{g/mL}$, respectively. Furthermore, compound **4d** was membrane active and low toxic against mammalian cells, and it could rapidly kill MRSA and did not obviously trigger bacterial

resistance. Preliminary research revealed that compound **4d** could not only bind with gyrase–DNA complex through hydrogen bonds, but also form a steady **4d**–DNA complex with MRSA DNA by intercalation, which might be responsible for the powerful bioactivity. The binding behavior revealed that the association of HSA with molecule **4d** was spontaneous, and the hydrophobic interactions and hydrogen bonds played significant roles in the transportation of **4d**. Thereby naphthalimide aminothiazole **4d** might be a potential multi-targeting anti-MRSA candidate. Further researches such as accurate antimicrobial action mechanism, metabolic stability and synergism with clinical drugs are now underway in our group.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, compounds characterization and antibacterial and antifungal activities data (Table S1, Table S2), bactericidal kinetic assay (Figure S1), cytotoxicity (Figure S2), bacterial membrane permeabilization (Figure S3), molecular docking data (Figure S4), interactions with MRSA DNA and HSA of compound **4d** (PDF).

AUTHOR INFORMATION

Corresponding Author

*Tel.: +86-23-68254967; Fax: +86-23-68254967.

E-mail: zhouch@swu.edu.cn (Cheng-He Zhou)

ORCID^{id}

Cheng-He Zhou: 0000-0003-3233-5465

Present Addresses

Author Contributions

All authors have given approval to the final version of the manuscript.

Funding Sources

This work was partially supported by National Natural Science Foundation of China [(No. 21672173, 21372186), the Research Fund for International Young Scientists from International (Regional) Cooperation and Exchange Program (No. 81650110529)] and Chongqing Special Foundation for Postdoctoral Research Proposal (No. Xm2017184, Xm2017185).

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

Grateful appreciation for the help of Dr. Gao Wei-Wei in polishing language of the revised manuscript.

ABBREVIATIONS

DMF, dimethyl formamide; MIC, minimal inhibitory concentration that completely inhibited the growth of microbes; HSA, human serum albumin.

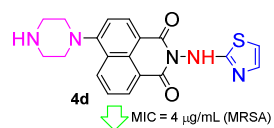
REFERENCES

- (1) Brown, E. D.; Wright, G. D. Antibacterial Drug Discovery in the Resistance Era. *Nature* **2016**, 529, 336–343.
- (2) Zhang, L.; Peng, X. M.; Damu, G. L. V.; Geng, R. X.; Zhou, C. H. Comprehensive Review in Current Developments of Imidazole-Based Medicinal Chemistry. *Med. Res. Rev.* **2014**, 34, 340–437.

- (3) Lin, S. M.; Koh, J. J.; Aung, T. T.; Sin, W. L. W.; Lim, F. H.; Wang, L.; Lakshminarayanan, R.; Zhou, L.; Tan, D. T. H.; Cao, D.; Beuerman, R. W.; Ren, L.; Liu, S. P. Semisynthetic Flavone-Derived Antimicrobials with Therapeutic Potential against Methicillin-Resistant *Staphylococcus aureus* (MRSA). *J. Med. Chem.* **2017**, *60*, 6152–6165.
- (4) Peng, X. M.; Damu, G. L. V.; Zhou, C. H. Current Developments of Coumarin Compounds in Medicinal Chemistry. *Curr. Pharm. Des.* **2013**, *19*, 3884–3930.
- (5) Gong, H. H.; Addla, D.; Lv, J. S.; Zhou, C. H. Heterocyclic Naphthalimides as New Skeleton Structure of Compounds with Increasingly Expanding Relational Medicinal Applications. *Curr. Top Med. Chem.* **2016**, *16*, 3303–3364.
- (6) Banerjee, S.; Veale, E. B.; Phelan, C. M.; Murphy, S. A.; Tocci, G. M.; Gillespie, L. J.; Frimannsson, D. O.; Kelly, J. M.; Gunnlaugsson, T. Recent Advances in the Development of 1,8-Naphthalimide Based DNA Targeting Binders, Anticancer and Fluorescent Cellular Imaging Agents. *Chem. Soc. Rev.* **2013**, *42*, 1601–1618.
- (7) Lv, J. S.; Peng, X. M.; Kishore, B.; Zhou, C. H. 1,2,3-Triazole-Derived Naphthalimides as a Novel Type of Potential Antimicrobial Agents: Synthesis, Antimicrobial Activity, Interaction with Calf Thymus DNA and Human Serum Albumin. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 308–313.
- (8) Dai, F. J.; Li, Q.; Wang, Y. X.; Ge, C. C.; Feng, C. Y.; Xie, S. Q.; He, H. Y.; Xu, X. J.; Wang, C. J. Design, Synthesis, and Biological Evaluation of Mitochondria-Targeted Flavone-Naphthalimide Polyamine Conjugates with Antimetastatic Activity. *J. Med. Chem.* **2017**, *60*, 2071–2083.
- (9) Gong, H. H.; Baathulaa, K.; Lv, J. S.; Cai, G. X.; Zhou, C. H. Synthesis and Biological Evaluation of Schiff Base-linked Imidazolyl Naphthalimides as Novel Potential Anti-MRSA Agents. *Med. Chem. Commun.* **2016**, *7*, 924–931.
- (10) Damu, G. L. V.; Wang, Q. P.; Zhang, H. Z.; Zhang, Y. Y.; Lv, J. S.; Zhou, C. H. A Series of Naphthalimide Azoles: Design, Synthesis and Bioactive Evaluation as Potential Antimicrobial Agents. *Sci. China Chem.* **2013**, *56*, 952–969.
- (11) Cui, S. F.; Wang, Y.; Lv, J. S.; Damu, G. L. V.; Zhou, C. H. Recent Advances in Application of Thiazole Compounds. *Sci. Sin. Chim.* **2012**, *42*, 1105–1131.
- (12) Gao, W. W.; Zhou, C. H. Antimicrobial 2-Aminothiazolyl Quinolones: What Is their Potential in the Clinic? *Future Med. Chem.* **2017**, *9*, 1461–1464.
- (13) Cheng, Y.; Avula, S. R.; Gao, W. W.; Addla, D.; Tangadanchu, V. K. R.; Zhang, L.; Lin, J. M.; Zhou, C. H. Multi-targeting Exploration of New 2-Aminothiazolyl Quinolones: Synthesis, Antimicrobial Evaluation, Interaction with DNA, Combination with Topoisomerase IV and Penetrability into Cells. *Eur. J. Med. Chem.* **2016**, *124*, 935–945.
- (14) Das, D.; Sikdar, P.; Bairagi, M. Recent Developments of 2-Aminothiazoles in Medicinal Chemistry. *Eur. J. Med. Chem.* **2016**, *109*, 89–98.
- (15) Peng, L. P.; Nagarajan, S.; Rasheed, S.; Zhou, C. H. Synthesis and Biological Evaluation of a New Class of Quinazolinone Azoles as Potential Antimicrobial Agents and their Interactions with Calf Thymus DNA and Human Serum Albumin. *Med. Chem. Commun.* **2015**, *6*, 222–229.
- (16) Mondal, S.; Mandal, S. M.; Mondal, T. K.; Sinha, C. Structural Characterization of New Schiff Bases of Sulfamethoxazole and Sulfathiazole, their Antibacterial Activity and Docking Computation with DHPS Protein Structure. *Spectrochim. Acta A.* **2015**, *150*, 268–279.
- (17) Cui, S. F.; Addla, D.; Zhou, C. H. Novel 3-Aminothiazolquinolones: Design, Synthesis, Bioactive Evaluation, SARs, and Preliminary Antibacterial Mechanism. *J. Med. Chem.* **2016**, *59*, 4488–4510.
- (18) Addla, D.; Wen, S. Q.; Gao, W. W.; Maddili, S. K.; Zhang, L.; Zhou, C. H. Design, Synthesis, and Biological Evaluation of Novel Carbazole Aminothiazoles as Potential DNA-targeting Antimicrobial Agents. *Med. Chem. Commun.* **2016**, *7*, 1988–1994.
- (19) Marco-Contelles, J.; Soriano, E. The Medicinal Chemistry of Hybrid-based Drugs Targeting Multiple Sites of Action. *Curr. Top Med. Chem.* **2011**, *11*, 2714–2715.
- (20) Zhang, L.; Addla, D.; Ponmani, J.; Wang, A.; Xie, D.; Wang, Y. N.; Zhang, S. L.; Geng, R. X.; Cai, G. X.; Li, S.; Zhou, C. H. Discovery of Membrane Active Benzimidazole Quinolones-Based Topoisomerase Inhibitors as Potential DNA-binding Antimicrobial Agents. *Eur. J. Med. Chem.* **2016**, *111*, 160–182.
- (21) Wang, X. L.; Wan, K.; Zhou, C. H. Synthesis of Novel Sulfanilamide-derived 1,2,3-Triazoles and their Evaluation for Antibacterial and Antifungal Activities. *Eur. J. Med. Chem.* **2010**, *45*, 4631–4639.
- (22) Li, Z. Z.; Gopala, L.; Tangadanchu, V. K. R.; Gao, W. W.; Zhou, C. H. Discovery of Novel Nitroimidazole Enols as *Pseudomonas aeruginosa* DNA Cleavage Agents. *Bioorg. Med. Chem.* **2017**, *25*, 6511–6522.
- (23) Konai, M. M.; Ghosh, C.; Yarlagadda, V.; Samaddar, S.; Haladar, J. Membrane Active Phenylalanine Conjugated Lipophilic N-spermidine Derivatives with Selective Antibacterial Activity. *J. Med. Chem.* **2014**, *57*, 9409–9423.
- (24) Fang, X. F.; Li, D.; Tangadanchu, V. K. R.; Gopala, L.; Gao, W. W.; Zhou, C. H. Novel Potentially Antifungal Hybrids of 5-Flucytosine and Fluconazole: Design, Synthesis and Bioactive Evaluation. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 4964–4969.
- (25) Cui, S. F.; Peng, L. P.; Zhang, H. Z.; Rasheed, S.; Kannekanti, V. K.; Zhou, C. H. Novel Hybrids of Metronidazole and Quinolones: Synthesis, Bioactive Evaluation, Cytotoxicity, Preliminary Antimicrobial Mechanism and Effect of Metal Ions on their Transportation by Human Serum Albumin. *Eur. J. Med. Chem.* **2014**, *86*, 318–334.
- (26) Ma, Z.; Yang, J.; Han, J. Z.; Gao, L.; Liu, H. X.; Lu, Z. X.; Zhao, H. Z.; Bie, X. M. Insights into the Antimicrobial Activity and Cytotoxicity of Engineered α -Helical Peptide Amphiphiles. *J. Med. Chem.* **2016**, *59*, 10946–10962.
- (27) Ponmani, J.; Zhang, L.; Avula, S. R.; Zhou, C. H. Design, Synthesis and Biological Evaluation of Berberine-Benzimidazole Hybrids as New Type of Potentially DNA-targeting Antimicrobial Agents. *Eur. J. Med. Chem.* **2016**, *122*, 205–215.
- (28) Gao, W. W.; Rasheed, S.; Tangadanchu, V. K. R.; Sun, Y.; Peng, X. M.; Cheng, Y.; Zhang, F. X.; Lin, J. M.; Zhou, C. H. Design, Synthesis and Biological Evaluation of Amino Organophosphorus Imidazoles as a New Type of Potential Antimicrobial Agents. *Sci. China Chem.* **2017**, *60*, 769–785.
- (29) Zhang, H. Z.; He, S. C.; Peng, Y. J.; Zhang, H. J.; Gopala, L.; Tangadanchu, V. K. R.; Gan, L. L.; Zhou, C. H. Design, Synthesis and Antimicrobial Evaluation of Novel Benzimidazole-Incorporated Sulfonamide Analogues. *Eur. J. Med. Chem.* **2017**, *136*, 165–183.
- (30) Peng, X. M.; Peng, L. P.; Li, S.; Avula, S. R.; Kumar, K. V.; Zhang, S. L.; Tam, K. Y.; Zhou, C. H. Quinazolinone Azolyl Ethanols: Potential Lead Antimicrobial Agents with Dual Action Modes Targeting MRSA DNA. *Future Med. Chem.* **2016**, *8*, 1927–1940.
- (31) Hu, Y. J.; Liu, Y.; Xiao, X. H. Investigation of the Interaction between Berberine and Human Serum Albumin. *Biomacromolecules* **2009**, *10*, 517–521.
- (32) Yin, B. T.; Yan, C. Y.; Peng, X. M.; Zhang, S. L.; Rasheed, S.; Geng, R. X.; Zhou, C. H. Synthesis and Biological Evaluation of α -Triazolyl Chalcones as a New Type of Potential Antimicrobial Agents and their Interaction with Calf Thymus DNA and Human Serum Albumin. *Eur. J. Med. Chem.* **2014**, *71*, 148–159.
- (33) Dai, L. L.; Zhang, H. Z.; Nagarajan, S.; Rasheed, S.; Zhou, C. H. Synthesis of Tetrazole Compounds as a Novel Type of Potential Antimicrobial Agents and their Synergistic Effects with Clinical Drugs and Interactions with Calf Thymus DNA. *Med. Chem. Commun.* **2015**, *6*, 147–154.

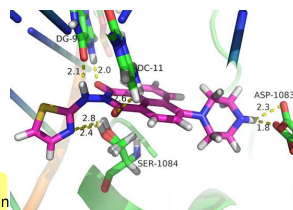
Novel Naphthalimide Aminothiazoles as Potential Multi-targeting Antimicrobial Agents

Ying-Ying Chen, Lavanya Gopala, Rammohan R. Yadav Bheemanaboina, Han-Bo Liu, Yu Cheng, Rong-Xia Geng, Cheng-He Zhou*



MIC = 4 μ g/mL (MRSA)

Low cytotoxicity to mammalian cells
Rapidly bactericidal activity against MRSA strain
No obvious triggering the development of bacterial resistance
Efficient membrane permeability



Three-dimensional conformation of compound **4d** docked in the gyrase-DNA complex (PDB code: 2XCS)

Novel Naphthalimide Aminothiazoles as Potential Multi-targeting Antimicrobial Agents

Ying-Ying Chen, Lavanya Gopala, Rammohan R. Yadav Bheemanaboina, Han-Bo Liu, Yu Cheng, Rong-Xia Geng, Cheng-He Zhou*

