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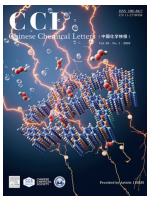

Editorial

Targeting novel sites represents an effective strategy for combating drug resistance

Drug resistance poses an escalating global challenge in the battle against infections. The effectiveness of conventional antibiotics and other anti-infective drugs is waning as microbes develop heightened resistance to existing treatments. Antimicrobial resistance poses a formidable challenge to global health and development, ranking among the top 10 public health threats to humanity as declared by the World Health Organization. Projections indicate that if left unaddressed, antimicrobial resistance could inflict an annual economic burden on the global GDP ranging from $1 trillion to $3.4 trillion by 2030. Consequently, the management of common infections becomes increasingly arduous, while the likelihood of disease transmission, severe illness, and mortality escalates.

The mechanisms underlying drug resistance are multifaceted and diverse, encompassing accelerated drug metabolism, mutations in drug targets, and activation of bypass signaling pathways. Reactive resistance resulting from target mutations poses a significant challenge in the treatment of anti-infective conditions. Current strategies for combating drug resistance primarily involve enhancing efficacy and selectivity, modifying mechanisms of action (such as covalent drugs and proteolysis targeting chimeras), improving blood-brain barrier permeability, and targeting allosteric sites. The development of drugs targeting novel sites holds promise for providing innovative therapeutic options that can effectively overcome existing resistance problems.

Bacteria have developed resistance to nearly all known antimicrobials, underscoring the imperative to identify antibiotics with novel mechanisms of action. To address this challenge and inhibit clinical isolates of fluoroquinolone-resistant *Escherichia coli*, a small compound library was screened, leading to the discovery of an isoquinoline-sulfonamide hit compound. Subsequent medicinal chemistry optimization efforts yielded the more promising antibacterial agent LEI-800 (Fig. 1A). Target identification studies revealed that this class of compounds targets the DNA gyrase complex, specifically occupying an allosteric hydrophobic pocket in the GyrA subunit. Importantly, its mode of action differs from clinically utilized fluoroquinolones or any other reported spinase inhibitors, thus explaining its efficacy against resistant strains [1].

In addition to the field of antibacterial drugs, targeting novel sites in the design of antiviral drugs is also a prevalent strategy employed against drug resistance. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is capable of inducing respiratory infections and, in severe cases, fatality. The emergence of multiple mutated variants such as Omicron and Delta during the coronavirus disease 2019 pandemic has prompted scientists to explore novel treatments to combat drug resistance in these mutants. Presently, the Food and Drug Administration has approved three antiviral drugs encompassing an RNA-dependent RNA polymerase inhibitor and a main protease (M^{pro}) inhibitor; however, resistant strains against both classes of drugs have been identified. In order to discover new mechanisms for antiviral therapy, papain-like protease (PL^{pro}) has been investigated as a potential target. Building upon the reported non-covalent PL^{pro} inhibitor XR8–24 and covalent PL^{pro} inhibitor Cp7, the design of a covalent PL^{pro} inhibitor, named Jun11313, has been accomplished. The co-crystal structure revealed that the thiophene moiety of Jun11313 occupied the same hydrophobic pocket as ubiquitin Val70 ($Val70^{Ub}$). Based on this observation, the structure of Jun11313 has been optimized, resulting in Jun12682 that targets both $Val70^{Ub}$ and the BL2 groove (Fig. 1B), exhibited inhibitory activity against Omicron, Delta variants as well as three nirmatrelvir-resistant virus strains [2].

Based on the complex structure of SARS-CoV-2 PL^{pro}−GRL0617, systematic structure-activity relationship studies revealed that the incorporation of oxadiazole and aryl carboxylic acid groups into GRL0617 significantly enhanced its enzymatic inhibitory activity, affinity, and deubiquitination ability towards PL^{pro}. Through a ring formation strategy, a series of 1,2,4-oxadiazole derivatives were designed and synthesized. Among them, compound **26r** (Fig. 1C) exhibited potent PL^{pro} inhibitory activity (half maximal inhibitory concentration (IC_{50}) = 1.0 μmol/L) and antiviral efficacy (median effective dose (EC_{50}) = 4.3 μmol/L). Notably, compound **26r** demonstrated moderate oral bioavailability at 39.1%. These findings provide novel insights for the discovery of antiviral agents targeting PL^{pro} [3].

The M^{pro} of SARS-CoV-2 represents a promising target for the discovery of antiviral drugs. To date, most efforts in drug discovery have focused on the S4-S1 pocket of M^{pro}; however, it remains unclear whether the S1′-S3′ pocket itself can serve as a novel site for drug development. It has been observed that Phe or Trp residues are favored at position S3′ in M^{pro}, while Ala is preferred at position S1′. Therefore, leveraging an α-bromoacetamide warhead, the design of a peptidyl inhibitor, named D-4–77, was accomplished (Fig. 1D). This compound exhibits an IC_{50} value of 0.95 μmol/L and an antiviral EC_{50} value of 0.49 μmol/L. The co-crystal structure analysis between M^{pro} and the inhibitor confirms its binding mode to the S1′-S3′ pocket and reveals a covalent mechanism of

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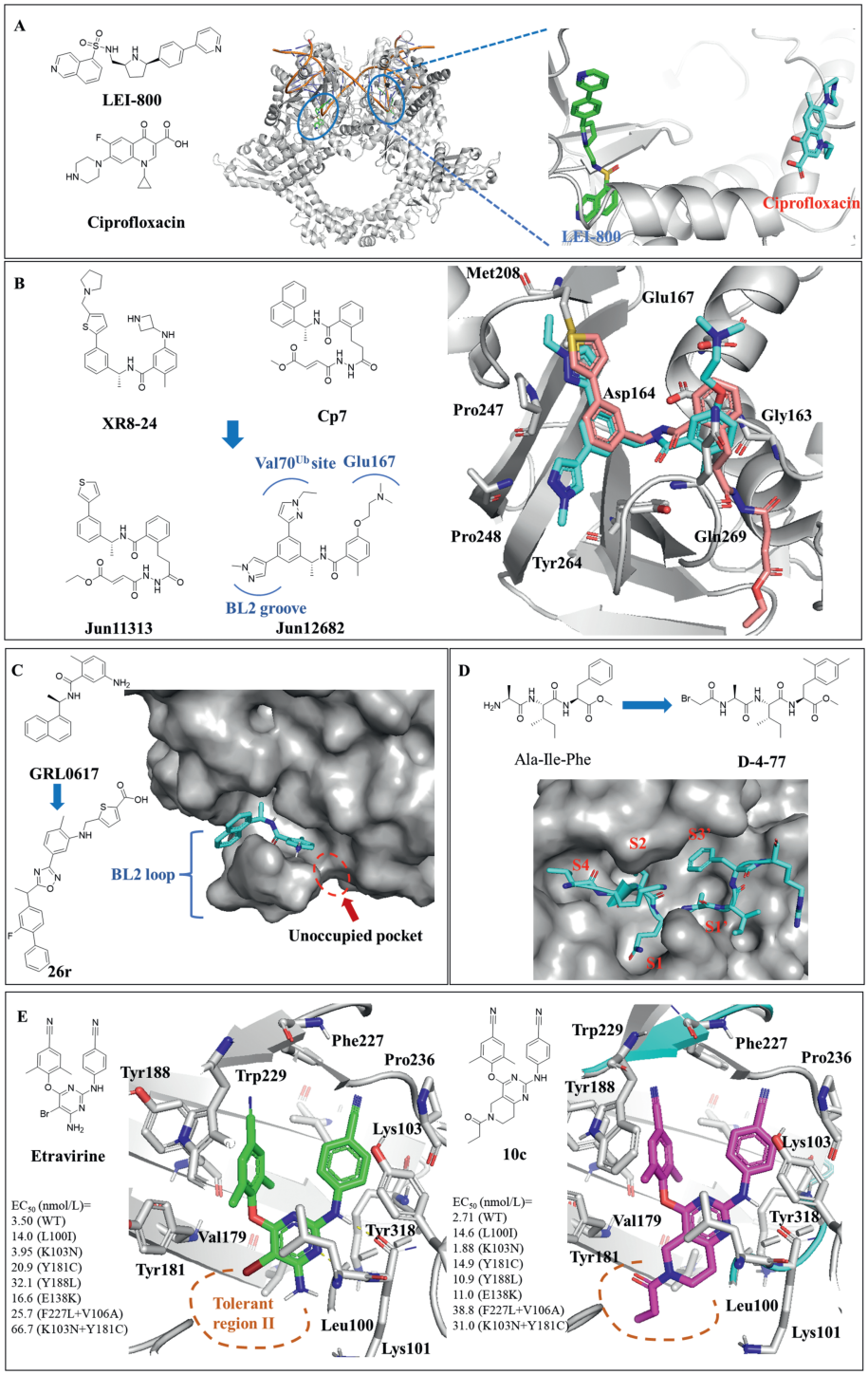

Fig. 1. The application of targeting novel sites in drug design. (A) A comparison of LEI-800 (PDB code: 8QQI) and ciprofloxacin (PDB code: 2XCT) binding sites on the GyrA DNA-binding surface. LEI-800 is shown as green and ciprofloxacin as cyan stick representations. (B) Atomic model of the Jun12682 (cyan balls and sticks) and Jun11313 (pink balls and sticks) binding site in SARS-CoV-2 PL^{pro} (residues within 5 Å of the inhibitor are shown as light gray sticks, PDB code: 8UOB, 8UVM). (C) Design strategy for target compounds **26r** (PDB code: 7CMD), GRL0617 is presented as a stick model (cyan). (D) The co-crystal structure of peptide **4** and the SARS-CoV-2 M^{pro} (PDB code: 8GWS). Peptide **4** is presented as a stick model (cyan). (E) The co-crystal structure of etravirine (green) and HIV-1 reverse transcriptase (RT) complex PDB code: 3MEC, the binding mode of **10c** (magentas) and wild type (WT) RT complex.

action. Furthermore, D-4–77 acts as an immune protectant by inhibiting the antagonism of host nuclear factor κB innate immune response induced by SARS-CoV-2 M^{pro} [4].

There remains an urgent demand for novel non-nucleoside reverse transcriptase inhibitors (NNRTIs) that exhibit enhanced drug resistance and safety profiles within the current antiretroviral treatment options. By targeting tolerant region II (Fig. 1E), a series of innovative tetrahydropyrido[4,3-*d*]pyrimidine derivatives were discovered. In comparison to etravirine, the most potent inhibitor, compound **10c** demonstrates broad-spectrum antiviral activity and improved resilience against NNRTI-resistant variants. Notably, compound **10c** exhibits lower cytochrome P450 inhibition

and reduced liability for human ether-à-go-go-related gene blockade when compared to etravirine.

While targeting new sites shows promise as a strategy, numerous challenges persist. These include the high cost of drug development, low success rates in clinical trials, and potential for drug resistance to emerge even with novel drugs. Further research is necessary to precisely identify mechanisms of resistance, develop more effective combination therapies, and explore innovative therapeutic modalities such as combining immunotherapy with targeted therapy.

The targeting of novel sites in strategies offers new perspectives and possibilities for overcoming drug resistance in anti-infective therapy [5], thereby indicating their potential to play an increasingly pivotal role in the future treatment of infection, owing to the continuous advancements in science and technology as well as our deepening understanding of biology.

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.

CRediT authorship contribution statement

Shaoqing Du: Writing – original draft, Conceptualization. **Xinyong Liu:** Writing – review & editing. **Xueping Hu:** Writing – review & editing. **Peng Zhan:** Writing – review & editing, Conceptualization.

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