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Discovery of highly potent SARS-CoV-2 M\textsuperscript{pro} inhibitors based on benzoisothiazolone scaffold

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\textbf{ABSTRACT}

The COVID-19 pandemic has drastically impacted global economies and public health. Although vaccine development has been successful, it was not sufficient against more infectious mutant strains including the Delta variant indicating a need for alternative treatment strategies such as small molecular compound development. In this work, a series of SARS-CoV-2 main protease (M\textsuperscript{pro}) inhibitors were designed and tested based on the active compound from high-throughput diverse compound library screens. The most efficacious compound (16b-3) displayed potent SARS-CoV-2 M\textsuperscript{pro} inhibition with an IC\textsubscript{50} value of 116 nM and selectivity against SARS-CoV-2 M\textsuperscript{pro} when compared to PL\textsuperscript{pro} and RdRp. This new class of compounds could be used as potential leads for further optimization in anti COVID-19 drug discovery.

\textbf{Introduction}

COVID-19 is a viral infection caused by SARS-CoV-2 that has spread to more than 100 countries with over 211 million confirmed cases and over 4.4 million confirmed deaths worldwide as of August 22, 2021 — this global pandemic remains a threat to both worldwide economies and public health.\textsuperscript{1} Although various vaccines have been developed including Pfizer’s BioNTech and Moderna’s NIAID vaccines,\textsuperscript{2-4} transmission prevention of more infectious SARS-CoV-2 Delta variants is greatly reduced.\textsuperscript{5,6} To date, there still lacks gold-standard treatment methods in the fight against COVID-19,\textsuperscript{7} indicating an urgent need to develop antiviral drugs which may serve as an alternative therapeutic agent for SARS-CoV-2 infection.

SARS-CoV-2 is an enveloped positive-sense single-stranded RNA virus belonging to the genus β-coronavirus, which include SARS-CoV and MERS-CoV, etc. The life cycle of SARS-CoV-2 in host cells can be divided into the following processes: enter, translation, replication, transcription, assembly and release.\textsuperscript{8-11} The main protease (M\textsuperscript{pro} or 3CL\textsuperscript{pro}) plays an indispensable role in the replication and transcription process of the life cycle of coronaviruses. The main protease is initially responsible for coordinating its own autoproteolytic cleavage. Upon its own maturation cleavage, the main protease hydrolyzes the polyproteins pp1a/pp1ab on the sites of nsp4-11/nsp4-16 to release non-structural proteins (nsp5s).\textsuperscript{12-15} These non-structural proteins, including RNA-dependent RNA polymerase (nsp12) and helicase (nsp13), etc, participate in protein translation and viral genetic material synthesis, which collectively play important roles in the life cycle of coronaviruses.\textsuperscript{16-18} Inhibiting the main protease could therefore block the coronaviruses replication cycle and prevent further viral infection.

Various groups have previously reported protease inhibitors as potentially attractive targeted antiviral drug (Fig.1a).\textsuperscript{19-26} The first crystal structure of SARS-CoV-2 main protease is covalently combined with ligand N3.\textsuperscript{19} These covalent inhibitors typically contain an active warhead group that covalently binds to Cys145 of the main protease. For example, Pfizer’s compound PF-007304814 is currently undergoing clinical research from a peptide mimic.\textsuperscript{22} The development of diverse inhibitor is needed to prevent the various coronavirus for the future. Recently, researchers identified Ebsulfur, Ebselen and their derivatives

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as potent main protease inhibitors that combine through covalent interactions with \( M^{\text{pro}} \)\(^{19,27,28} \). However, they did not explore the detailed structure–activity relationship of these compounds systematically. Through high-throughput screening a diverse compound library, we also identified active compound that is similar to Ebsulfur and Ebselen derivatives in their potency as inhibitors of the SARS-CoV-2 main protease. Herein, we report the structure–activity relationship of this series of compounds and provide a deeper understand of the key structural features that are responsible for their activities. As shown in the Fig. 1b, the structural optimization and structure–activity analysis were focused on three functional groups: the tail benzene ring (ring B), linker and the core benzoisothiazolone (ring A).

The synthetic route to the designed compounds is outlined in Schemes 1 and 2. Briefly, intermediates 3, 7 and 9 were synthesized under the procedure previously reported\(^{29–31} \) as shown in Scheme 1. In Scheme 2, these intermediates were connected with the linker by nucleophilic reaction to yield \( \text{tert}-\text{butyl ester} \) 10 ~ 12, which was then hydrolyzed to give acid 13 ~ 15. The desired compounds 16 ~ 18 were obtained by the condensation reaction from acids 13 ~ 15 with the corresponding amines. Further oxidation of the thioethers resulted in a series of sulfoxides 19 and sulfone 20. The other different linker compounds 21 were synthesized from the key intermediates 3, which are described in the Supplementary Data.

First, we explored the SAR of ring B as shown in Table 1. We introduced various electronic and steric substitutions at the tail benzene ring (16b~16p) and the enzymatic activities of SARS-CoV-2 \( M^{\text{pro}} \) of these compounds were performed under the procedure previously reported\(^{19,21} \). These compounds maintained their inhibitory activities at similar levels. After replacing the tail phenyl with cyclohexyl (16c), the inhibitory activity was maintained (IC\(_{50} = 160 \, \text{nM}\)). However, when the tail phenyl was replaced with cyclopentyl (16d) or ethyl (16e), the inhibitory activities of the compounds decreased (IC\(_{50} = 400 \) and 380

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**Fig. 1.** (a) the presented structure of \( M^{\text{pro}} \) inhibitors; (b) the strategy of SAR study for Ebsulfur derivatives.
nM, respectively). There is a group with large steric hindrance in the para position of the benzene ring, the inhibitory activity of the compound 16m decreased (IC_{50} = 310 nM), comparing to compound 16b (IC_{50} = 190 nM). These results showed that the electronic effect on the ring B is not obvious without π-π interaction for the inhibition of the SARS-CoV-2 main protease. The hydrophobic spatial structure of ring B might be sensitive against the activity of SARS-CoV-2 main protease. Considering inhibitory efficacy and ease of synthesis, the phenyl was chosen as the best group for ring B.

Next, we optimized the linker. The inhibitory activities of these compounds are given in Table 2. We first tested the inhibitory activities of intermediates 3a, 10a and 13a. The results showed that the inhibitory activity of the intermediates 3a and 13a was reduced dramatically, which illustrated the importance of the hydrophobic spatial pocket. Extending (16q, 16r) or shortening (21a) the linker also decreased inhibitory activity of the compounds. After the amide group was opposed, the activity of the compound 21b (IC_{50} = 253 nM) remained at the same level as 16b. However, once the linker was replaced with an alkane chain, the inhibitory activity of compound 21c (IC_{50} = 540 nM) dropped, which indicated that the acetamide group in the linker plays an important role in the inhibitory activity.

Finally, we optimized the core ring A. When ring A of compound 16b was replaced with a similar ring to benzoisothiazolone, the resulting compounds 17~20 were inactive (Table 3). These results indicate that the core structure of 16b binds with the main protease of SARS-CoV-2 covalently, which is supported by other research. And then, we investigated the different substituents on the phenyl group (16b-2~16b-17) in Table 4. The presence of the relative bulky groups at position 7 of phenyl ring (compound 16b-9, 16b-13, 16b-17) decreased the activity drastically. The steric hindrance might block the covalent attack of Cys145 in the main protease. Introducing substituents at other position on the phenyl ring maintained the activity. Compound 16b-3 contained an F substituent of the phenyl ring at position 4 yielded the good activity with an IC_{50} value of 116 nM.
Papain-like protease (PLpro) is a cysteine protease, which hydrolyzes the polyproteins pp1a/pp1ab on the sites of nsps1-3 to release non-structural proteins. To verify whether these compounds act as covalent inhibitors of PLpro or RdRp, we evaluated the activities of the represented compounds against PLpro and RdRp. As shown in Table 5, the compounds with a benzoisothiazolone core showed high selectivity against SARS-CoV-2 Mpro comparing to PLpro and RdRp. Given the excellent potency and selectivity of this series compounds, the fast dilution experiment was performed to determine whether the inhibition of these compounds is reversible or not. The result of the fast dilution experiment (see Fig. S1 and Table S1) indicated that compound 16b, just as GC-376, is an irreversible inhibitor of SARS-CoV-2 Mpro.

In summary, we have identified a novel series of compounds that potently inhibited the SARS-CoV-2 main protease with high selectivity against SARS-CoV-2 Mpro when compared to PLpro and RdRp. The most efficacious compound 16b displayed IC50 values of 116 nM against SARS-CoV-2 Mpro, which was more potent than Ebsulfur (IC50 = 490 nM). These new compounds could be a potential lead for further optimization in anti COVID-19 drug discovery.

Table 1
Chemical structures and in vitro biological activities of compounds 16b ~ 16p.

| Compound | R   | Inhibition rate%(40 μM) | IC50(nM) |
|----------|-----|------------------------|----------|
| Hit      |     | 107.9 ± 0.9            | 190.0 ± 0.0 |
| 16b      |     | 101.6 ± 2.1            | 190.0 ± 40.0 |
| 16c      |     | 97.7 ± 1.3             | 160.0 ± 10.0 |
| 16d      |     | 95.5 ± 8.3             | 400.0 ± 30.0 |
| 16e      |     | 101.6 ± 0.2            | 380.0 ± 60.0 |
| 16f      |     | 94.0 ± 1.4             | 190.0 ± 10.0 |
| 16g      |     | 95.5 ± 2.5             | 140.0 ± 40.0 |
| 16h      |     | 95.7 ± 3.1             | 150.0 ± 10.0 |
| 16i      |     | 99.2 ± 2.8             | 180.0 ± 10.0 |
| 16j      |     | 101.3 ± 0.4            | 150.0 ± 10.0 |
| 16k      |     | 99.3 ± 3.9             | 300.0 ± 10.0 |
| 16l      |     | 96.7 ± 1.5             | 120.0 ± 20.0 |
| 16m      |     | 99.9 ± 4.9             | 310.0 ± 12.0 |

Table 2
Chemical structures and in vitro biological activities of compounds 3a, 10a, 13a, 16b, 16q, 16r and 21a-c.

| compound | linker | Inhibition rate%(40 μM) | IC50(nM) |
|----------|--------|------------------------|----------|
| 16b      |        | 101.6 ± 2.1            | 190.0 ± 40.0 |
| 16q      |        | 103.6 ± 1.5            | 230.0 ± 30.0 |
| 16r      |        | 100.4 ± 0.7            | 388.3 ± 12.5 |
| 21a      |        | 101.9 ± 0.9            | 680.0 ± 32.0 |
| 21b      |        | 101.9 ± 1.4            | 253.0 ± 1.5  |
| 21c      |        | 102.3 ± 1.5            | 539.9 ± 22.3 |

Table 3
Chemical structures and in vitro biological activities of compounds 16b and 17~20.

| compound | X  | Inhibition rate%(40 μM) | IC50(nM) |
|----------|----|------------------------|----------|
| 16b      | S  | 101.6 ± 2.1            | 190.0 ± 40.0 |
| 17       | O  | 7.0 ± 2.9              | NA       |
| 18       | NH | 26.3 ± 4.7             | NA       |
| 19       | SO | 23.5 ± 7.2             | NA       |
| 20       | SO2| 18.3 ± 9.9             | NA       |

against SARS-CoV-2 Mpro comparing to PLpro and RdRp.
Given the excellent potency and selectivity of this series compounds, the fast dilution experiment was performed to determine whether the inhibition of these compounds is reversible or not. The result of the fast dilution experiment (see Fig. S1 and Table S1) indicated that compound 16b-3, just as GC-376, is an irreversible inhibitor of SARS-CoV-2 Mpro.

In summary, we have identified a novel series of compounds that potently inhibited the SARS-CoV-2 main protease with high selectivity against SARS-CoV-2 Mpro when compared to PLpro and RdRp. The most efficacious compound 16b-3 displayed IC50 values of 116 nM against SARS-CoV-2 Mpro, which was more potent than Ebsulfur (IC50 = 490 nM). These new compounds could be a potential lead for further optimization in anti COVID-19 drug discovery.

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.
Table 4
Modification of the potent compound 16b.

| Compound | R   | Inhibition rate(%) (40 μM) | IC50(nM) |
|----------|-----|---------------------------|---------|
| 16b      | 6-F | 101.6 ± 2.1               | 190.0 ± 40.0 |
| 16b-2    | H   | 99.7 ± 0.3                | 165.2 ± 10.3 |
| 16b-3    | 4-F | 99.5 ± 0.1                | 116.8 ± 11.4 |
| 16b-4    | 5-F | 99.7 ± 0.1                | 286.7 ± 56.7 |
| 16b-5    | F   | 99.5 ± 0.0                | 328.0 ± 8.5 |
| 16b-6    | 4-CH3 | 99.6 ± 0.1               | 333.5 ± 18.3 |
| 16b-7    | 5-CH3 | 99.7 ± 0.1               | 153.1 ± 29.3 |
| 16b-8    | 6-CH3 | 99.7 ± 0.0               | 286.6 ± 27.6 |
| 16b-9    | 7-CH3 | –6.8 ± 5.5               | NA      |

Table 5
The inhibitory effect of the represented compounds on Mpro, PLpro and RdRp.

| Compound | IC50 | Mpro(nM) | PLpro | RdRp(μM) |
|----------|------|----------|-------|----------|
| Hit      | 160.0 ± 0.0 | NA       | NA    | NA       |
| 16b      | 190.0 ± 40.0 | NA       | 6.4 ± 0.5 | 7.9 ± 0.7 |
| 16c      | 160.0 ± 10.0 | NA       | NA    | 7.9 ± 0.7 |
| 16f      | 120.0 ± 20.0 | NA       | NA    | 7.9 ± 0.7 |
| 16p      | 210.0 ± 10.0 | NA       | NA    | 7.9 ± 0.7 |
| 16q      | 230.0 ± 30.0 | NA       | NA    | 15.3 ± 2.1 |
| 21a      | 680.0 ± 32.0 | NA       | NA    | NA       |
| 21b      | 250.0 ± 0.0 | NA       | NA    | NA       |

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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.2022.128526.

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