Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Bioorg. Med. Chem. Lett. 58 (2022) 128526

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

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

Weixiong Chen [a,b,1], Bo Feng [c,1], Sheng Han [b,1], Peipei Wang [b], Wuhong Chen [b], Yi Zang [b,e,*], Jia Li [b,c,d,e,*], Youhong Hu [a,b,e,*]

[a] School of Chinese Materia Medica, Nanjing University of Chinese Medicine, Nanjing 210023, China
[b] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China
[c] School of Life Science and Biopharmaceutics, Shenyang Pharmaceutical University, No.103 Wenhua Road, Shenyang 110016, China
[d] Open Studio for Druggability Research of Marine Natural Products, Pilot National Laboratory for Marine Science and Technology (Qingdao), 1 Wenhai Road, Aoshanwei Jimo, Qingdao 266237, China
[e] School of Pharmaceutical Science and Technology, Hangzhou Institute for Advanced Study, UCAS, Hangzhou 310024, China

ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Main protease inhibitors
Benzoisothiazolone

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^{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^{pro} inhibition with an IC_{50} value of 116 nM and selectivity against SARS-CoV-2 M^{pro} when compared to PL^{pro} and RdRp. This new class of compounds could be used as potential leads for further optimization in anti COVID-19 drug discovery.

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.[1] Although various vaccines have been developed including Pfizer's BioNTech and Moderna's NIAID vaccines,[2–4] transmission prevention of more infectious SARS-CoV-2 Delta variants is greatly reduced.[5,6] To date, there still lacks gold-standard treatment methods in the fight against COVID-19, [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.[8–11] The main protease (M^{pro} or 3CL^{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 nsps4-11/nsps4-16 to release non-structural proteins (nsps).[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.[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).[19–26] The first crystal structure of SARS-CoV-2 main protease is covalently combined with ligand N3.[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.[22] The development of diverse inhibitor is needed to prevent the various coronavirus for the future. Recently, researchers identified Ebsulfur, Ebselen and their derivatives

* Corresponding authors at: State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China.
E-mail addresses: yzang@simm.ac.cn (Y. Zang), jli@simm.ac.cn (J. Li), yhhu@simm.ac.cn (Y. Hu).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.bmcl.2022.128526
Received 15 November 2021; Received in revised form 27 December 2021; Accepted 1 January 2022
Available online 5 January 2022

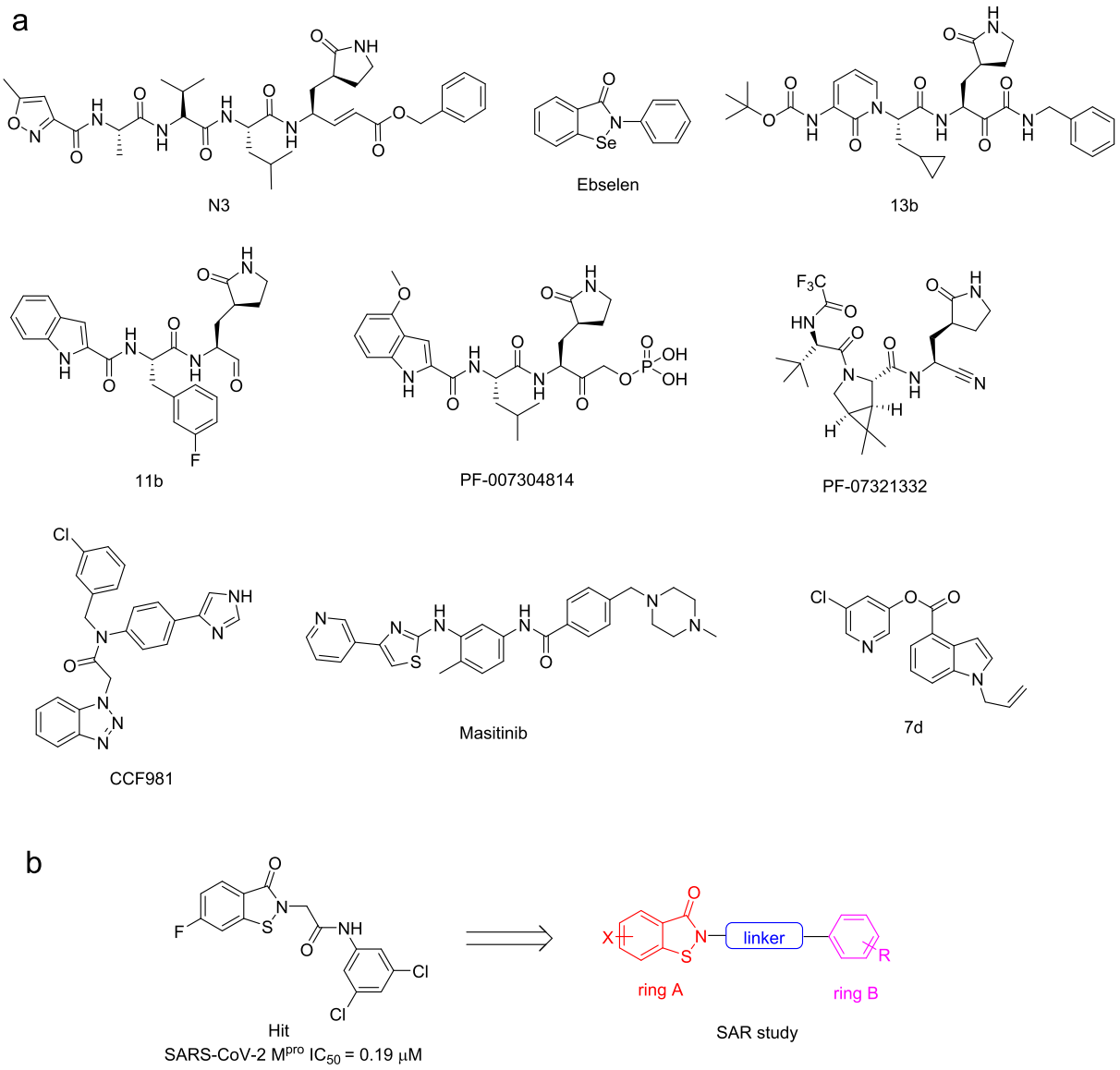
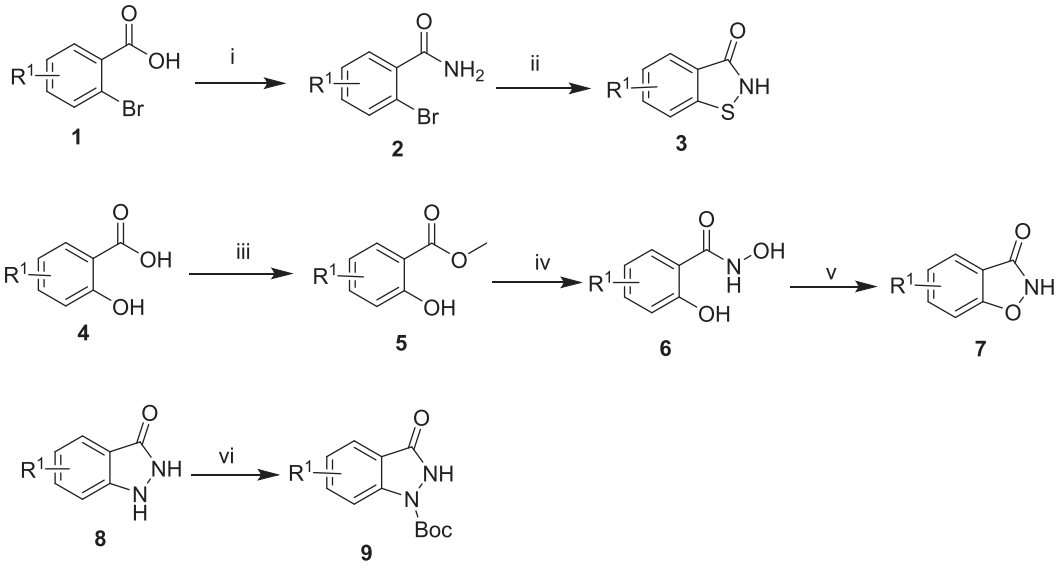


Fig. 1. (a) the presented structure of M^{pro} inhibitors; (b) the strategy of SAR study for Ebsulfur derivatives.

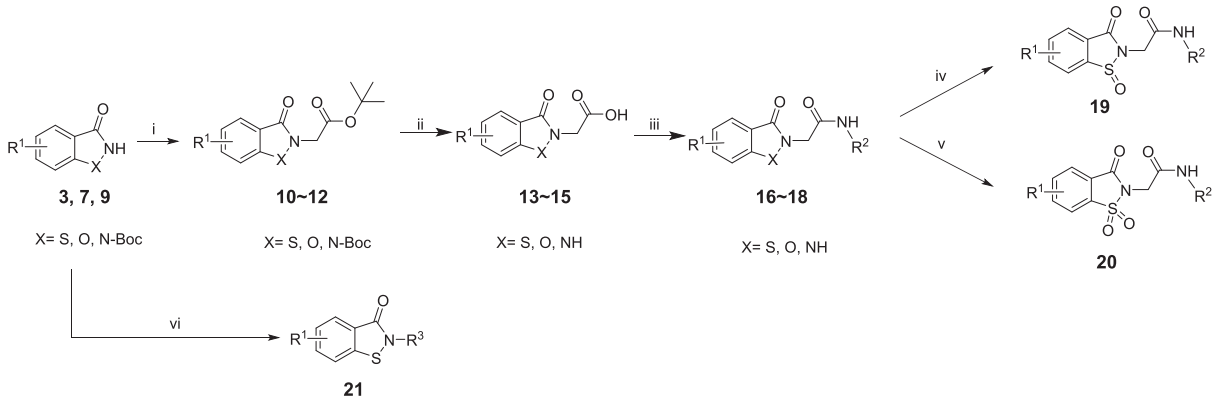
as potent main protease inhibitors that combine through covalent interactions with M^{pro}.[19,27,28] However, they did not explore the detailed structure–activity relationship of these compounds systematically. Through high-throughput screening a diverse compound library, we also identified active compound 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 *tert*-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^{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 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



Scheme 1. Synthetic routes of compounds **3, 7** and **9**. Reagents and conditions: (i) a: $SOCl_2$, 60 °C, 6 h; b: NH_4OH, 0 °C - rt, overnight; (ii) S powder, K_2CO_3, DMF, 110 °C, N_2, overnight; (iii) MeOH, H_2SO_4, reflux, 16 h; (iv) NH_2OH, dioxane, rt, 48 h; (v) PPh_3, DIAD, THF, rt, N_2, 3 h; (vi) Boc_2O, DMAP, CH_3CN, rt, overnight.



Scheme 2. Synthetic routes of compounds **16** ~ **21**. Reagents and conditions: (i) *tert*-Butyl bromoacetate, K_2CO_3, THF, rt, 5 h; (ii) CF_3COOH, DCM, rt, 6 h; (iii) amines, EDCI, HOBT, DMF, rt, 6 h; (iv) mCPBA, DCM, rt, overnight; (v) oxone, MeOH, rt, overnight; (vi) see the supplementary data.

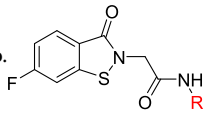
nM, respectively). There is a group with large steric hindrance in the *para* position of the benzene ring, the inhibitory activity of the compound **16m** decreased (IC_{50} = 310 nM), comparing to compound **16b** (IC_{50} = 190 nM). These results showed that the electronic effect on the ring B is 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.[28] 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.

Table 1

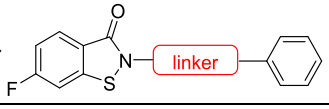
Chemical structures and in *vitro* biological activities of compounds **16b** ~ **16p**.

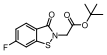
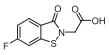


Compound	R	Inhibition rate%(40 μM)	IC_{50}(nM)	compound	R	Inhibition rate%(40 μM)	IC_{50}(nM)
Hit		107.9 ± 0.9	190.0 ± 0.0	**16i**		99.2 ± 2.8	180.0 ± 10.0
16b		101.6 ± 2.1	190.0 ± 40.0	**16j**		101.3 ± 0.4	150.0 ± 10.0
16c		97.7 ± 1.3	160.0 ± 10.0	**16k**		99.3 ± 3.9	300.0 ± 10.0
16d		95.5 ± 8.3	400.0 ± 30.0	**16l**		96.7 ± 1.5	120.0 ± 20.0
16e		101.6 ± 0.2	380.0 ± 60.0	**16m**		99.9 ± 4.9	310.0 ± 12.0
16f		94.0 ± 1.4	190.0 ± 10.0	**16n**		105.0 ± 0.9	334.8 ± 13.9
16 g		95.5 ± 2.5	140.0 ± 40.0	**16o**		98.9 ± 6.5	250.0 ± 40.0
16 h		95.7 ± 3.1	150.0 ± 10.0	**16p**		100.1 ± 3.1	210.0 ± 10.0

Table 2

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

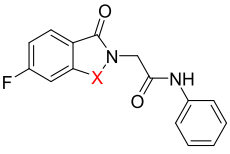


compound	linker	Inhibition rate%(40 μM)	IC_{50}(nM)
16b		101.6 ± 2.1	190.0 ± 40.0
3a		106.4 ± 2.3	2293.0 ± 30.8
10a		104.0 ± 0.2	220.2 ± 7.4
13a		98.4 ± 0.7	1571.3 ± 281.9
16q		103.6 ± 1.5	230.0 ± 30.0
16r		100.4 ± 0.7	388.3 ± 12.5
21a		101.9 ± 0.9	680.0 ± 32.0
21b		101.9 ± 1.4	253.0 ± 1.5
21c		102.3 ± 1.5	539.9 ± 22.3

Papain-like protease (PL^{pro}) 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 PL^{pro} or RdRp, we evaluated the activities of the represented compounds against PL^{pro} and RdRp. As shown in Table 5, the compounds with a benzoisothiazolone core showed high selectivity against SARS-CoV-2 M^{pro} comparing to PL^{pro} and RdRp.

Table 3

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



compound	X	Inhibition rate%(40 μM)	IC_{50}(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	SO_2	18.3 ± 9.9	NA

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,[32] is an irreversible inhibitor of SARS-CoV-2 M^{pro}.

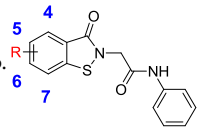
In summary, we have identified a novel series of compounds that potently inhibited the SARS-CoV-2 main protease with high selectivity against SARS-CoV-2 M^{pro} when compared to PL^{pro} and RdRp. The most efficacious compound **16b-3** displayed IC_{50} values of 116 nM against SARS-CoV-2 M^{pro}, which was more potent than Ebsulfur (IC_{50} = 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)	IC_{50}(nM)	compound	R	Inhibition rate%(40 μM)	IC_{50}(nM)
16b	6-F	101.6 ± 2.1	190.0 ± 40.0	**16b-10**	4-CF_3	99.7 ± 0.1	224.2 ± 17.3
16b-2	H	99.7 ± 0.3	165.2 ± 10.3	**16b-11**	5-CF_3	99.7 ± 0.1	392.7 ± 26.4
16b-3	4-F	99.5 ± 0.1	116.8 ± 11.4	**16b-12**	6-CF_3	100.0 ± 0.2	524.0.2 ± 16.4
16b-4	5-F	99.7 ± 0.1	286.7 ± 56.7	**16b-13**	7-CF_3	−7.6 ± 2.3	NA
16b-5	7-F	99.5 ± 0.0	328.0 ± 8.5	**16b-14**	4-NH_2	99.4 ± 0.1	1767.0 ± 358.6
16b-6	4-OCH_3	99.6 ± 0.1	333.5 ± 18.3	**16b-15**	5-NH_2	99.8 ± 0.1	416.0 ± 55.1
16b-7	5-OCH_3	99.7 ± 0.1	153.1 ± 29.3	**16b-16**	6-NH_2	99.7 ± 0.0	443.1 ± 28.2
16b-8	6-OCH_3	99.7 ± 0.0	286.6 ± 27.6	**16b-17**	7-NH_2	58.8 ± 1.1	10977.0 ± 766.5
16b-9	7-OCH_3	−6.8 ± 5.5	NA				

Table 5
The inhibitory effect of the represented compounds on M^{pro}, PL^{pro} and RdRp.

Compound	IC_{50}		
	M^{pro}(nM)	PL^{pro}	RdRp(μM)
Hit	160.0 ± 0.0	NA	NA
16b	190.0 ± 40.0	NA	6.4 ± 0.5
16c	160.0 ± 10.0	NA	7.9 ± 0.7
16 l	120.0 ± 20.0	NA	NA
16p	210.0 ± 10.0	NA	NA
16q	230.0 ± 30.0	NA	NA
21a	680.0 ± 32.0	NA	15.3 ± 2.1
21b	250.0 ± 0.0	NA	NA

Acknowledgments

This project was supported by the National Natural Science Foundation of China (No. 81872725, 31871414, 22107108 and 19430750100), Science and Technology Commission of Shanghai Municipality (No. 18431907100, 19JC1416300), and China Postdoctoral Science Foundation (No. 2021M693269).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2022.128526.

References

[1] https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
2 Kalita P, Padhi AK, Zhang KYJ, Tripathi T. Design of a peptide-based subunit vaccine against novel coronavirus SARS-CoV-2. *Microb Pathog.* 2020;145:104236–104243. https://doi.org/10.1016/j.micpath.2020.104236.
[3] Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med.* 2021;384(15):1412–1423. https://doi.org/10.1056/NEJMoa2101765.
[4] Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med.* 2021;384(5):403–416. https://doi.org/10.1056/NEJMoa2035389.
[5] Kupferschmidt K, Wadman M. Delta variant triggers new phase in the pandemic. *Science.* 2021;372(6549):1375–1376. https://doi.org/10.1126/science.372.6549.1375.
6 Bolze A, Cirulli ET, Luo S, et al. SARS-CoV-2 variant Delta rapidly displaced variant Alpha in the United States and led to higher viral loads. *medRxiv.* 2021. https://doi.org/10.1101/2021.06.20.21259195.
7 Chen X-F, Zhao X, Yang Z. Aptamer-based antibacterial and antiviral therapy against infectious diseases. *J Med Chem.* 2021;64:17601–17626. https://doi.org/10.1021/acs.jmedchem.1c01567.
[8] Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 Spike glycoprotein. *Cell.* 2020;181(2):281–292. https://doi.org/10.1016/j.cell.2020.02.058.
[9] Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* 2020;181(2):271–280. https://doi.org/10.1016/j.cell.2020.02.052.
[10] V'Kovski P, Gerber M, Kelly J, et al. Determination of host proteins composing the microenvironment of coronavirus replicase complexes by proximity-labeling. *Elife.* 2019;8, e42037. https://doi.org/10.7554/eLife.42037.
[11] Hilgenfeld R. From SARS to MERS: crystallographic studies on coronaviral proteases enable antiviral drug design. *FEBS J.* 2014;281(18):4085–4096. https://doi.org/10.1111/febs.12936.
[12] Thiel V, Ivanov KA, Putics A, et al. Mechanisms and enzymes involved in SARS coronavirus genome expression. *J Gen Virol.* 2003;84(9):2305–2315. https://doi.org/10.1099/vir.0.19424-0.
[13] Ziebuhr J, Snijder EJ, Gorbalenya AE. Virus-encoded proteinases and proteolytic processing in the Nidovirales. *J Gen Virol.* 2000;81(4):853–879. https://doi.org/10.1099/0022-1317-81-4-853.
[14] Lu XT, Sims AC, Denison MR. Mouse hepatitis virus 3C-like protease cleaves a 22-kilodalton protein from the open reading frame 1a polyprotein in virus-infected cells and in vitro. *J Virol.* 1998;72(3):2265–2271. https://doi.org/10.1128/jvi.72.3.2265-2271.1998.
[15] Roe MK, Junod NA, Young AR, Beachboard DC, Stobart CC. Targeting novel structural and functional features of coronavirus protease nsp5 (3CL(pro), M(pro)) in the age of COVID-19. *J Gen Virol.* 2021;102(3). https://doi.org/10.1099/jgv.0.001558.
[16] Subissi L, Posthuma CC, Collet A, et al. One severe acute respiratory syndrome coronavirus protein complex integrates processive RNA polymerase and exonuclease activities. *Proc Natl Acad Sci USA.* 2014;111(37):E3900–E3909. https://doi.org/10.1073/pnas.1323705111.
[17] Adedeji AO, Marchand B, Te Velthuis AJ, et al. Mechanism of nucleic acid unwinding by SARS-CoV helicase. *PLoS ONE.* 2012;7(5), e36521. https://doi.org/10.1371/journal.pone.0036521.
[18] Aartjan J.W. te Velthuis, S. H. E. v. d. W., Eric J. Snijder, The SARS-coronavirus nsp7+nsp8 complex is a unique multimeric RNA polymerase capable of both de novo initiation and primer extension. *Nucleic Acids Res* **2012,** *40* (4), 1737-1747. 10.1093/nar/gkr893.
[19] Jin Z, Du X, Xu Y, et al. Structure of M(pro) from SARS-CoV-2 and discovery of its inhibitors. *Nature.* 2020;582(7811):289–293. https://doi.org/10.1038/s41586-020-2223-y.
[20] Zhang L, Lin D, Sun X, et al. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. *Science.* 2020;368(6489):409–412. https://doi.org/10.1126/science.abb3405.
[21] Dai W, Zhang B, Jiang X-M, et al. Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease. *Science.* 2020;368(6497):1331–1335. https://doi.org/10.1126/science.abb4489.
[22] Hoffman RL, Kania RS, Brothers MA, et al. Discovery of ketone-based covalent inhibitors of coronavirus 3CL proteases for the potential therapeutic treatment of COVID-19. *J Med Chem.* 2020;63(21):12725–12747. https://doi.org/10.1021/acs.jmedchem.0c01063.
[23] Han SH, Goins CM, Arya T, et al. Structure-based optimization of ML300-derived, noncovalent inhibitors targeting the severe acute respiratory syndrome

coronavirus 3cl protease (SARS-CoV-2 3CLpro). *J Med Chem*. 2021. https://doi.org/10.1021/acs.jmedchem.1c00598.

24 Ghosh AK, Raghavaiah J, Shahabi D, et al. Indole chloropyridinyl ester-derived SARS-CoV-2 3CLpro inhibitors: enzyme inhibition, antiviral efficacy, structure-activity relationship, and X-ray structural studies. *J Med Chem*. 2021;64(19): 14702–14714. https://doi.org/10.1021/acs.jmedchem.1c01214.

[25] Drayman N, DeMarco JK, Jones KA, et al. Masitinib is a broad coronavirus 3CL inhibitor that blocks replication of SARS-CoV-2. *Science*. 2021;373(6557):931–936. https://doi.org/10.1126/science.abg5827.

[26] Ullrich S, Nitsche C. The SARS-CoV-2 main protease as drug target. *Bioorg Med Chem Lett*. 2020;30(17), 127377. https://doi.org/10.1016/j.bmcl.2020.127377.

[27] Amporndanai K, Meng X, Shang W, et al. Inhibition mechanism of SARS-CoV-2 main protease by ebselen and its derivatives. *Nat Commun*. 2021;12(1):3061. https://doi.org/10.1038/s41467-021-23313-7.

[28] Sun LY, Chen C, Su J, et al. Ebsulfur and Ebselen as highly potent scaffolds for the development of potential SARS-CoV-2 antivirals. *Bioorg Chem*. 2021;112, 104889. https://doi.org/10.1016/j.bioorg.2021.104889.

[29] Paul R, Punniyamurthy T. Copper-catalysed one-pot synthesis of N-substituted benzo[d]isothiazol-3(2H)-ones via C-S/N-S bond formation. *RSC Adv*. 2012;2(18): 7057–7060. https://doi.org/10.1039/C2RA20724A.

[30] Van Eker D, Chauhan J, Murphy WA, Conlon IL, Fletcher S. Chromatography-free, Mitsunobu-triggered heterocyclizations of salicylhydroxamic acids to 3-hydroxybenzisoxazoles. *Tetrahedron Lett*. 2016;57(48):5301–5303. https://doi.org/10.1016/j.tetlet.2016.10.045.

[31] Frost JM, DeGoey DA, Shi L, et al. Substituted Indazoles as Nav1.7 Blockers for the Treatment of Pain. *J Med Chem*. 2016;59(7):3373–3391. https://doi.org/10.1021/acs.jmedchem.6b00063.

[32] Ma C, Sacco MD, Hurst B, et al. Boceprevir, GC-376, and calpain inhibitors II, XII inhibit SARS-CoV-2 viral replication by targeting the viral main protease. *Cell Res*. 2020;30(8):678–692. https://doi.org/10.1038/s41422-020-0356-z.