Journal of Medicinal Chemistry

pubs.acs.org/jmc

Editorial

Advances Toward COVID-19 Therapies Special Issue

Cite This: J. Med. Chem. 2022, 65, 2713−2715

Read Online

ACCESS | Metrics & More | Article Recommendations

We are pleased to present the "Advances Toward COVID-19 Therapies Special Issue" detailing select examples of medicinal chemistry approaches to develop small-molecule drugs for the treatment of SARS-CoV-2 infection.

Two years into the COVID-19 pandemic, SARS-CoV-2 and its increasing number of variants have wreaked havoc on our lives and livelihoods at a global scale. Although the exact number of cases and the death toll may never be established, the official number of people infected with the virus globally is >371 million and >5.7 million have died as of February 1, 2022. In the United Sates alone, >75 million individuals have been infected, resulting in >906 000 deaths. As fast as the virus spreads and mutates, innovative vaccine technologies, rapid testing, and highly effective drugs are also being developed to prevent and stop the pandemic. We have witnessed remarkable progress in numerous types of technologies and disciplines to help us understand the virus and the pandemic. Unfortunately, at the same time the fake news regarding the virus origin, its infectious capabilities, and the safety and efficacy of the approved vaccines fueled by certain social media has not abated. What has clearly emerged during these two years is that

(1) Vaccines are safe and work! Currently, there are over a dozen types of vaccines around the world. A major breakthrough in this pandemic has been the discovery, production, and regulatory approval of mRNA-based vaccines in such an unprecedented timeline. Although mRNA vaccines do not produce lifelong immunity, they have proven to be remarkably safe and efficacious in preventing viral spread and hospitalization.
(2) Masks work! It is now clear that masks, especially the high quality N95 models, are quite effective in preventing viral spread.
(3) Social distancing works! Avoiding close contacts especially in a confined environment is effective in reducing viral spread.
(4) Antiviral drugs work! Several monoclonal antibodies and small-molecule drugs have been shown to be safe and efficacious in treating SARS-CoV-2 infection. The discovery of such drugs and their regulatory approval in such a short time have been unprecedented.

As a community of medicinal chemists, we are in a unique position to significantly contribute to the field. Through design of innovative assays in drug screening, modern computer-aided drug design,and machine learning technologies, high throughput synthetic chemistry, and deep knowledge in drug design and preclinical studies, we can expedite our efforts in rapidly producing highly effective antiviral drugs. It is expected that safe, effective, and "direct" acting drugs will become the front runners in eliminating the virus especially when these drugs are used in combination.

The collection of papers presented in this special issue are examples of what our colleagues have successfully produced while working safely under all the strict conditions with which we are all familiar. Two in-depth Perspectives and 14 original Articles detail some of the key discoveries achieved in the past two years. The first Perspective by Cannalire et al. focuses on drug discovery efforts to develop inhibitors of SARS-CoV-2 proteases and polymerase,[1] while the second Perspective by Osman et al. focuses on the cellular protease, furin, which has been recognized as a potential target for the treatment of SARS-CoV-2 infection.[2]

All coronaviruses use an RNA-dependent RNA polymerase (RdRp) essential for efficient replication and transcription of their RNA. Therefore, RdRp has been recognized as a high-value target for designing effective drugs against coronaviruses. Remdesivir, originally developed for the treatment of Ebola, was the first-in-class U.S. Food and Drug Administration (FDA)-approved RdRp inhibitor of SARS-CoV-2. The second nucleoside analogue, molnupiravir (a N^4-hydroxycytidine), originally designed for influenza (alphavirus or seasonal influenza infections), was approved in December 2021. Molnupiravir increases the frequency of viral RNA mutations by acting as a substrate for RdRp, leading to inhibition of SARS-CoV-2 replication.[3,4] Both remdesivir and molnupiravir escape viral RNA proofreading exonuclease. Other RdRp targeted drugs (e.g., bemnifosbuvir and galidesivir) are currently under clinical development. Li et al. demonstrate that remdesivir metabolite GS-441524 effectively inhibits SARS-CoV-2 infection in mouse models.[5] Because GS-441524 is easier to synthesize than remdesivir, it can serve as a safe and cheaper alternative.

The third FDA-approved drug, sold under the brand name paxlovid, is a two-drug combination of nirmatrelvir and ritonavir. Paxlovid is currently the most effective orally active drug against COVID-19 that reduced the risk of hospitalization or death by 89% in a Phase 2/3 EPIC-HR study.[6] Nirmatrelvir inhibits the 3-chymotrypsin-like protease (3CLpro) also known as M^{pro} or main protease. Other 3CLpro inhibitors

Special Issue: COVID-19

Published: February 9, 2022

https://doi.org/10.1021/acs.jmedchem.2c00178
J. Med. Chem. 2022, 65, 2713−2715

(e.g., lufotrelvir and rupintrivir and analogs) are under clinical development.

It is well established that SARS-CoV-2 enters cells through the interaction of the receptor binding domain (RBD) of its surface spike protein with the host receptor, angiotensin-converting enzyme 2 (ACE2). Subsequent proteolytic cleavage by the host serine proteases such as TMPRSS2 allows entry into the infected cell through endocytosis.[7] Therefore, blocking the interaction of RBD with ACE2 provides a unique opportunity to develop viral entry inhibitors. Sadremomtaz et al. used protein contact atlas data and molecular dynamics simulations to identify interaction hotspots on the secondary structure elements of ACE2.[8] The authors designed a library of discontinuous peptides based on a combination of these hotspot interactions that showed binding affinity to RBD in nanomolar range. Qian Wang et al. discuss a coarse-grained dynamic simulation method to explore conformational transitions between the closed state and the open state of the spike protein.[9] This approach was used to design allosteric regulators that inhibit the open state of the spike protein. Chao Wang et al. describe a peptide mimetic of the HIV-1 gp41 helical repeat (HR1) trimer as an effective inhibitor of SARS-CoV-2 infection.[10] Finally, Luan and Huynh performed all-atom molecular dynamics simulations for the bound (the RBD−ACE2 complex) and free (stand-alone RBD) states to better assess SARS-CoV-2's mutations that evade therapeutic human antibodies.[11]

Highly potent, safe, and efficacious protease inhibitors have changed the landscape of effective therapy for HIV and hepatitis C virus infection. Similarly, proteases implicated in efficient SARS-CoV-2 replication are promising drug targets. For example, Konno et al. describe the design and synthesis of peptidomimetics 3CLpro inhibitors having a benzothiazolyl ketone as a warhead.[12] An optimized inhibitor blocks viral replication and exhibits favorable PK properties. Dai et al. present the design and synthesis of a series of peptidomimetics having an aldehydes warhead as inhibitors of the 3CLpro of enterovirus 71 (EV71).[13] An optimized analogue also inhibits SARS-CoV-2 replication and shows desirable PK properties. Bai et al. discuss the design and synthesis of peptidomimetics having an α-acyloxymethylketone warhead as potent inhibitors of SARS-CoV-2 3CLpro.[14] Several compounds inhibit viral replication with minimal cytotoxicity. Starting from ebselen, a promiscuous protease inhibitor, Huff et al. designed and synthesized a series of 2-phenyl-1,2-benzoselenazol-3-one analogs as inhibitors of SARS-CoV-2 3CLpro.[15] A lead compound shows potent inhibition of viral replication in lung epithelial cells and 3D lung organoids. Starting from a probe compound ML300, Han et al. performed a structure-based optimization campaign to design potent inhibitors of 3CLpro.[16] The authors further solved the X-ray structures of several inhibitors in complex with SARS-CoV-1 and SARS-CoV-2 3CLpro enzymes, paving the way for further optimization to select a compound for pharmacology studies. Kitamura et al. describe the discovery of a highly potent and selective noncovalent SARS-CoV-2 inhibitor that binds to a novel binding pocket in 3CLpro.[17] These manuscripts clearly illustrate that 3CLpro can be effectively targeted as there are already numerous crystal structures and lead compounds are available for further optimization.

The second viral protease, papain-like protease (PLpro), is also a fascinating drug target, and several PLpro inhibitors are currently under development. Shen et al. designed a series of noncovalent PLpro inhibitors showing slow off-rates, improved binding affinities, and low micromolar antiviral potency in SARS-CoV-2-infected human cells.[18] The authors also solved the crystals of SARS-CoV-2 PLpro in complex with select inhibitors, providing a platform for further structure-based drug design.

Elastase is a serine protease that is mainly expressed on neutrophils and is an important cellular target to prevent acute lung injury/acute respiratory distress syndrome in COVID-19 patients. Cui et al. describe the first total synthesis of cyclotheonellazole A, a natural macrocyclic peptide elastase inhibitor, in 24 linear steps.[19] Ashhurst et al. show that the marine natural product, gallinamide A, and several synthetic analogues are potent inhibitors of cathepsin L, a key host cysteine protease important for viral entry.[20] Gallinamide A directly interacts with cathepsin L in cells and potently inhibits SARS-CoV-2 infection in the nanomolar range. Similar to furin inhibitors, these results clearly show that certain cellular targets can be effectively inhibited to block viral replication or reduce certain symptoms uniquely associated with SARS-CoV-2 infection.

In summary, abundant viral and cellular targets are currently being investigated as potential targets to develop effective therapy to stop the pandemic. We hope that the readers of this Special Issue will benefit from the wealth of new information provided on the development of new therapeutics to combat SARS-CoV-2.

Nouri Neamati orcid.org/0000-0003-3291-7131

AUTHOR INFORMATION

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.jmedchem.2c00178

Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

REFERENCES

(1) Cannalire, R.; Cerchia, C.; Beccari, A. R.; Di Leva, F. S.; Summa, V. Targeting SARS-CoV-2 Proteases and Polymerase for COVID-19 Treatment: State of the Art and Future Opportunities. *J. Med. Chem.* **2020**, DOI: 10.1021/acs.jmedchem.0c01140.

(2) Osman, E. E. A.; Rehemtulla, A.; Neamati, N. Why All the Fury over Furin? *J. Med. Chem.* **2021**, DOI: 10.1021/acs.jmedchem.1c00518.

(3) Kabinger, F.; Stiller, C.; Schmitzova, J.; Dienemann, C.; Kokic, G.; Hillen, H. S.; Hobartner, C.; Cramer, P. Mechanism of Molnupiravir-induced SARS-CoV-2 Mutagenesis. *Nat. Struct Mol. Biol.* **2021**, *28* (9), 740−746.

(4) Fischer, W. A., 2nd; Eron, J. J., Jr; Holman, W.; Cohen, M. S.; Fang, L.; Szewczyk, L. J.; Sheahan, T. P.; Baric, R.; Mollan, K. R.; Wolfe, C. R.; Duke, E. R.; Azizad, M. M.; Borroto-Esoda, K.; Wohl, D. A.; Coombs, R. W.; James Loftis, A.; Alabanza, P.; Lipansky, F.; Painter, W. P. A Phase 2a Clinical Trial of Molnupiravir in Patients with COVID-19 Shows Accelerated SARS-CoV-2 RNA Clearance and Elimination of Infectious Virus. *Sci. Transl Med.* **2022**, *14* (628), No. eabl7430.

(5) Li, Y.; Cao, L.; Li, G.; Cong, F.; Li, Y.; Sun, J.; Luo, Y.; Chen, G.; Li, G.; Wang, P.; Xing, F.; Ji, Y.; Zhao, J.; Zhang, Y.; Guo, D.; Zhang, X. Remdesivir Metabolite GS-441524 Effectively Inhibits SARS-CoV-2 Infection in Mouse Models. *J. Med. Chem.* **2021**, DOI: 10.1021/acs.jmedchem.0c01929.

(6) Owen, D. R.; Allerton, C. M. N.; Anderson, A. S.; Aschenbrenner, L.; Avery, M.; Berritt, S.; Boras, B.; Cardin, R. D.; Carlo, A.; Coffman, K. J.; Dantonio, A.; Di, L.; Eng, H.; Ferre, R.;

Gajiwala, K. S.; Gibson, S. A.; Greasley, S. E.; Hurst, B. L.; Kadar, E. P.; Kalgutkar, A. S.; Lee, J. C.; Lee, J.; Liu, W.; Mason, S. W.; Noell, S.; Novak, J. J.; Obach, R. S.; Ogilvie, K.; Patel, N. C.; Pettersson, M.; Rai, D. K.; Reese, M. R.; Sammons, M. F.; Sathish, J. G.; Singh, R. S. P.; Steppan, C. M.; Stewart, A. E.; Tuttle, J. B.; Updyke, L.; Verhoest, P. R.; Wei, L.; Yang, Q.; Zhu, Y. An Oral SARS-CoV-2 M(pro) Inhibitor Clinical Candidate for the Treatment of COVID-19. *Science* **2021**, *374* (6575), 1586−1593.

(7) Osman, E. E. A.; Toogood, P. L.; Neamati, N. COVID-19: Living through Another Pandemic. *ACS Infect Dis* **2020**, *6* (7), 1548−1552.

(8) Sadremomtaz, A.; Al-Dahmani, Z. M.; Ruiz-Moreno, A. J.; Monti, A.; Wang, C.; Azad, T.; Bell, J. C.; Doti, N.; Velasco-Velazquez, M. A.; de Jong, D.; de Jonge, J.; Smit, J.; Domling, A.; van Goor, H.; Groves, M. R. Synthetic Peptides That Antagonize the Angiotensin-Converting Enzyme-2 (ACE-2) Interaction with SARS-CoV-2 Receptor Binding Spike Protein. *J. Med. Chem.* **2021**, DOI: 10.1021/acs.jmedchem.1c00477.

(9) Wang, Q.; Wang, L.; Zhang, Y.; Zhang, X.; Zhang, L.; Shang, W.; Bai, F. Probing the Allosteric Inhibition Mechanism of a Spike Protein Using Molecular Dynamics Simulations and Active Compound Identifications. *J. Med. Chem.* **2021**, DOI: 10.1021/acs.jmedchem.1c00320.

(10) Wang, C.; Xia, S.; Wang, X.; Li, Y.; Wang, H.; Xiang, R.; Jiang, Q.; Lan, Q.; Liang, R.; Li, Q.; Huo, S.; Lu, L.; Wang, Q.; Yu, F.; Liu, K.; Jiang, S. Supercoiling Structure-Based Design of a Trimeric Coiled-Coil Peptide with High Potency against HIV-1 and Human beta-Coronavirus Infection. *J. Med. Chem.* **2021**, DOI: 10.1021/acs.jmedchem.1c00258.

(11) Luan, B.; Huynh, T. Insights into SARS-CoV-2's Mutations for Evading Human Antibodies: Sacrifice and Survival. *J. Med. Chem.* **2021**, DOI: 10.1021/acs.jmedchem.1c00311.

(12) Konno, S.; Kobayashi, K.; Senda, M.; Funai, Y.; Seki, Y.; Tamai, I.; Schakel, L.; Sakata, K.; Pillaiyar, T.; Taguchi, A.; Taniguchi, A.; Gutschow, M.; Muller, C. E.; Takeuchi, K.; Hirohama, M.; Kawaguchi, A.; Kojima, M.; Senda, T.; Shirasaka, Y.; Kamitani, W.; Hayashi, Y. 3CL Protease Inhibitors with an Electrophilic Arylketone Moiety as Anti-SARS-CoV-2 Agents. *J. Med. Chem.* **2021**, DOI: 10.1021/acs.jmedchem.1c00665.

(13) Dai, W.; Jochmans, D.; Xie, H.; Yang, H.; Li, J.; Su, H.; Chang, D.; Wang, J.; Peng, J.; Zhu, L.; Nian, Y.; Hilgenfeld, R.; Jiang, H.; Chen, K.; Zhang, L.; Xu, Y.; Neyts, J.; Liu, H. Design, Synthesis, and Biological Evaluation of Peptidomimetic Aldehydes as Broad-Spectrum Inhibitors against Enterovirus and SARS-CoV-2. *J. Med. Chem.* **2021**, DOI: 10.1021/acs.jmedchem.0c02258.

(14) Bai, B.; Belovodskiy, A.; Hena, M.; Kandadai, A. S.; Joyce, M. A.; Saffran, H. A.; Shields, J. A.; Khan, M. B.; Arutyunova, E.; Lu, J.; Bajwa, S. K.; Hockman, D.; Fischer, C.; Lamer, T.; Vuong, W.; van Belkum, M. J.; Gu, Z.; Lin, F.; Du, Y.; Xu, J.; Rahim, M.; Young, H. S.; Vederas, J. C.; Tyrrell, D. L.; Lemieux, M. J.; Nieman, J. A. Peptidomimetic alpha-Acyloxymethylketone Warheads with Six-Membered Lactam P1 Glutamine Mimic: SARS-CoV-2 3CL Protease Inhibition, Coronavirus Antiviral Activity, and in Vitro Biological Stability. *J. Med. Chem.* **2021**, DOI: 10.1021/acs.jmedchem.1c00616.

(15) Huff, S.; Kummetha, I. R.; Tiwari, S. K.; Huante, M. B.; Clark, A. E.; Wang, S.; Bray, W.; Smith, D.; Carlin, A. F.; Endsley, M.; Rana, T. M. Discovery and Mechanism of SARS-CoV-2 Main Protease Inhibitors. *J. Med. Chem.* **2021**, DOI: 10.1021/acs.jmedchem.1c00566.

(16) Han, S. H.; Goins, C. M.; Arya, T.; Shin, W. J.; Maw, J.; Hooper, A.; Sonawane, D. P.; Porter, M. R.; Bannister, B. E.; Crouch, R. D.; Lindsey, A. A.; Lakatos, G.; Martinez, S. R.; Alvarado, J.; Akers, W. S.; Wang, N. S.; Jung, J. U.; Macdonald, J. D.; Stauffer, S. R. Structure-Based Optimization of ML300-Derived, Noncovalent Inhibitors Targeting the Severe Acute Respiratory Syndrome Coronavirus 3CL Protease (SARS-CoV-2 3CL(pro)). *J. Med. Chem.* **2021**, DOI: 10.1021/acs.jmedchem.1c00598.

(17) Kitamura, N.; Sacco, M. D.; Ma, C.; Hu, Y.; Townsend, J. A.; Meng, X.; Zhang, F.; Zhang, X.; Ba, M.; Szeto, T.; Kukuljac, A.; Marty, M. T.; Schultz, D.; Cherry, S.; Xiang, Y.; Chen, Y.; Wang, J. Expedited Approach toward the Rational Design of Noncovalent SARS-CoV-2 Main Protease Inhibitors. *J. Med. Chem.* **2021**, DOI: 10.1021/acs.jmedchem.1c00509.

(18) Shen, Z.; Ratia, K.; Cooper, L.; Kong, D.; Lee, H.; Kwon, Y.; Li, Y.; Alqarni, S.; Huang, F.; Dubrovskyi, O.; Rong, L.; Thatcher, G. R. J.; Xiong, R. Design of SARS-CoV-2 PLpro Inhibitors for COVID-19 Antiviral Therapy Leveraging Binding Cooperativity. *J. Med. Chem.* **2021**, DOI: 10.1021/acs.jmedchem.1c01307.

(19) Cui, Y.; Zhang, M.; Xu, H.; Zhang, T.; Zhang, S.; Zhao, X.; Jiang, P.; Li, J.; Ye, B.; Sun, Y.; Wang, M.; Deng, Y.; Meng, Q.; Liu, Y.; Fu, Q.; Lin, J.; Wang, L.; Chen, Y. Elastase Inhibitor Cyclotheonellazole A: Total Synthesis and In Vivo Biological Evaluation for Acute Lung Injury. *J. Med. Chem.* **2022**, DOI: 10.1021/acs.jmedchem.1c01583.

(20) Ashhurst, A. S.; Tang, A. H.; Fajtova, P.; Yoon, M. C.; Aggarwal, A.; Bedding, M. J.; Stoye, A.; Beretta, L.; Pwee, D.; Drelich, A.; Skinner, D.; Li, L.; Meek, T. D.; McKerrow, J. H.; Hook, V.; Tseng, C. T.; Larance, M.; Turville, S.; Gerwick, W. H.; O'Donoghue, A. J.; Payne, R. J. Potent Anti-SARS-CoV-2 Activity by the Natural Product Gallinamide A and Analogues via Inhibition of Cathepsin L. *J. Med. Chem.* **2021**, DOI: 10.1021/acs.jmedchem.1c01494.

https://doi.org/10.1021/acs.jmedchem.2c00178
J. Med. Chem. 2022, 65, 2713−2715