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# Synthesis and Biological Evaluation of Umifenovir Analogues as Anti-SARS-CoV-2 Agents

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The unprecedented novel coronavirus disease 2019 (COVID-19) pandemic is a threat to global health and the economy. Since the outbreak of COVID-19, great effort has been made to reposition existing drugs to shorten development timelines, in addition to vaccine development and drug discovery campaigns. Umifenovir is a broad-spectrum antiviral agent used to treat influenza in China and Russia and is currently undergoing clinical trials for the treatment of COVID-19. In this article, the synthesis of umifenovir analogues and their biological evaluation are reported. The inhibitory activities of analogues against the binding of the spike glycoprotein (S-protein) of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) to the ACE2 receptor, which is a possible mode of action for umifenovir to inhibit viral infection, were investigated.

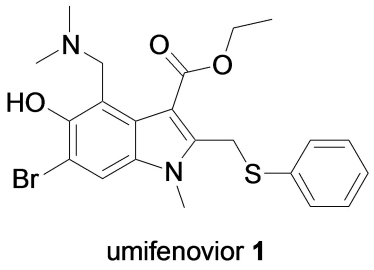
## Introduction

In December 2019, the novel coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China.[1] Since the outbreak, the COVID-19 pandemic has severely impacted the health of millions of people and the global economy. According to the World Health Organization (WHO), as of 12 December 2021, 269 million cases and 5.3 million deaths had been confirmed.[2] The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was identified as the causative virus for COVID-19, which shares a highly similar RNA genome to that of SARS-CoV-1, the coronavirus that caused the outbreak of SARS in 2003, resulting in 8,422 confirmed cases with 916 deaths.[3] The symptoms of COVID-19 include fever, cough, and difficulty breathing, which can rapidly progress into a serious condition in some cases.[1,4]

SARS-CoV-2 is an enveloped, large positive-strand RNA virus that takes advantage of its spike glycoprotein (S-protein) to enter host cells.[5] The coronavirus S-protein is comprised of two functional subunits, $S_1$ and $S_2$. The $S_1$ subunit contains a receptor-binding domain (RBD) and plays an essential role in binding to the ACE2 receptor of host cells, while the $S_2$ subunit induces cell entry via fusion of the viral envelope with cellular membranes of host cells. It has also been noted that genome sequences of the $S_2$ subunit are highly conserved among coronaviruses. Although the S-protein exists as a stable prefusion trimer at the viral surface, conformational changes take place upon receptor binding and proteolytic processing, which result in the initiation of a fusion reaction by insertion of the hydrophobic fusion peptide into the host membrane.[6]

Although vaccines and drugs including neutralizing antibodies (e.g. casirivimab/imdevimab,[7] Ronapreve™, and REGEN-COV™) as well as several antiviral agents (e.g. Molnupiravir[8]) have been approved and are used to treat COVID-19, a variety of antiviral drugs with different molecular modes of action are urgently needed to reduce not only the number of cases but also severity and rate of fatality. Since the outbreak of COVID-19, huge efforts have been made to reposition existing drugs such as remdesivir,[9] favipiravir,[10] and baricitinib,[11] as they can enable shorter development timelines.[12]

Umifenovir (**1**, arbidol, Figure 1), which has been approved in China and Russia for the treatment of influenza, is a broad-spectrum antiviral agent that works against a variety of viruses including influenza, hepatitis B (HBV), hepatitis C (HCV), Lassa, Ebola, and chikungunya.[13] The co-crystal structure of hemagglutinin (HA) of influenza virus and umifenovir (**1**) has been solved, which revealed that **1** binds in a hydrophobic cavity in the HA trimer stem, stabilizing its prefusion conformation. As a




umifenovior **1**

**Figure 1.** Structure of umifenovir (**1**).

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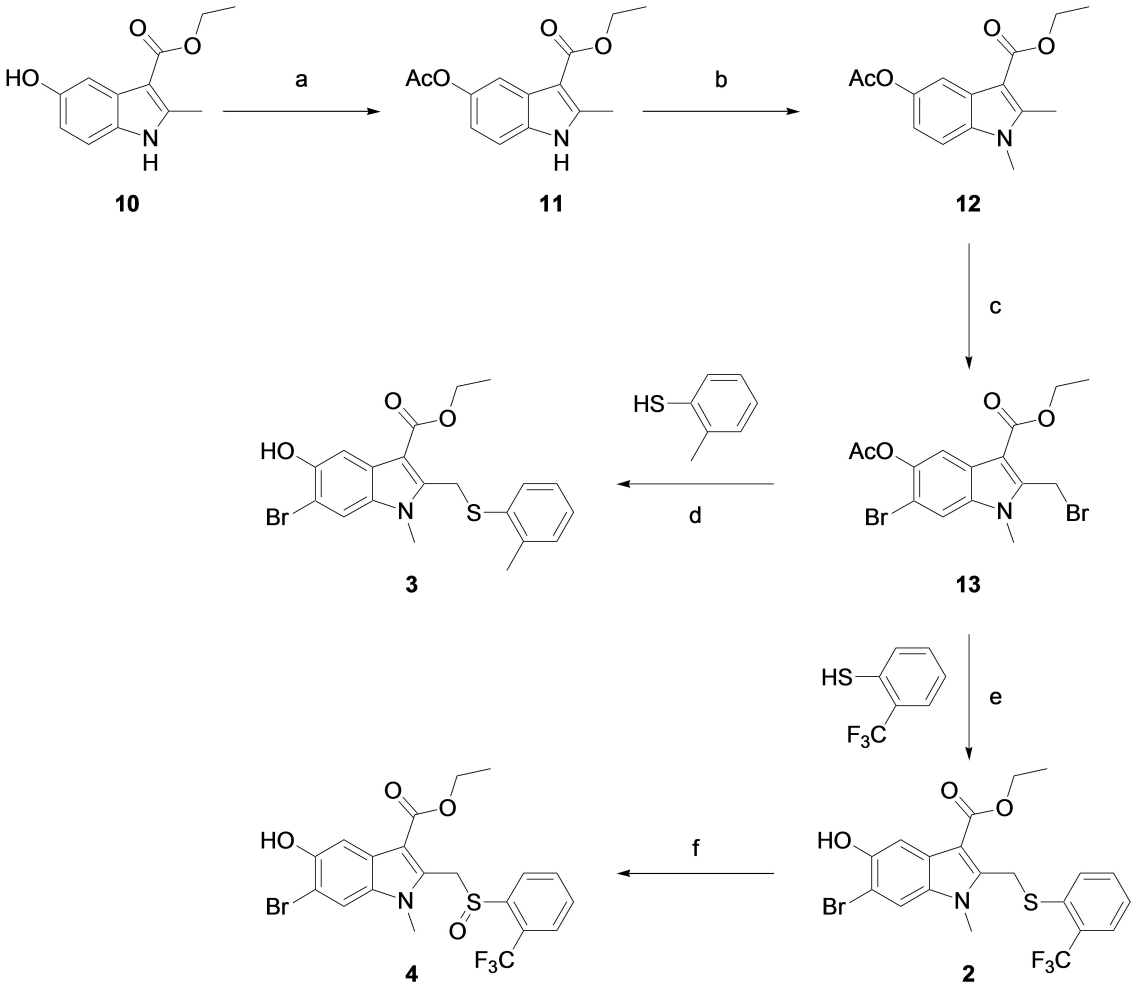
result, **1** inhibits virus-cell fusion by blocking the large conformational rearrangements associated with membrane fusion in the low pH of the endosome.[14] Although the detailed mechanism of action by which **1** can inhibit SARS-CoV-2 viral infection is not well understood, clinical pilot trials of **1** for the treatment of COVID-19 are currently underway and have been reported by several research groups. For example, Zhu and co-workers reported that monotherapy of **1** may be superior to lopinavir/ritonavir in treating COVID-19 based on a clinical study conducted with 50 patients with SARS-CoV-2 virus infection. In that study, on day 14 after administration, none of the patients treated with 0.2 g of **1** three times a day showed any viral load as determined by RT-PCR, as compared to patients who received 400 mg/100 mg of lopinavir/ritonavir twice a day (0% vs. 44%).[15] Reported clinical studies have been supported and explained by an *in vitro* study by Wang and co-workers, which showed that **1** has *in vitro* inhibitory activity against the SARS-CoV-2 virus with an $IC_{50}$ of 4.11 μM.[16]

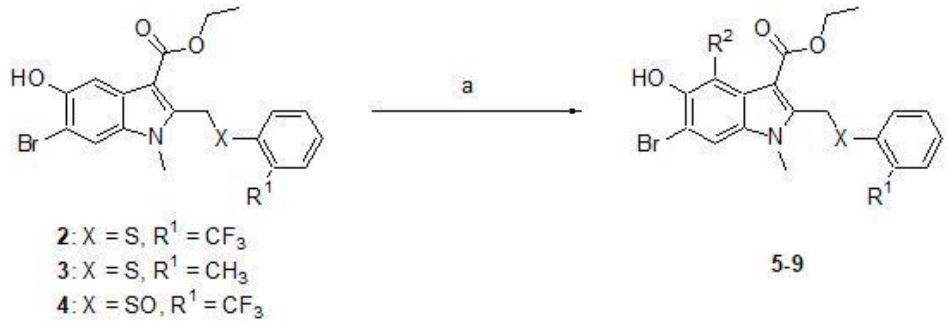
Based on these reports, structure-activity relationship (SAR) studies of umifenovir analogues may lead to the discovery of an anti-SARS-CoV-2 agent that serves as a therapeutic option for the treatment of COVID-19. Thus, in this work, the synthesis and the biological evaluation of novel analogues of umifenovir (**1**) for the treatment of COVID-19 are reported.

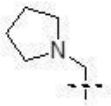
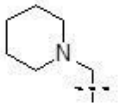
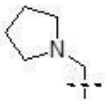
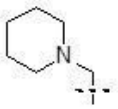
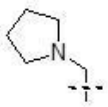
## Results and discussion

The syntheses of umifenovir analogues **2**–**9** were performed starting from commercially available ethyl-5-hydroxy-2-methylindole-3-carboxylate **10** (Scheme 1).[17] The phenolic hydroxyl group of trisubstituted indole **10** was protected with an acetyl group using acetic anhydride and pyridine in 83% yield. Next, *N*-methylation of the acetyl indole **11** gave tetrasubstituted indole **12** in 87% yield. Tetrasubstituted indole **12** was transformed to bromoindole **13** in 78% yield via double bromination on the C2 methyl and C6 using *N*-bromosuccinimide (NBS) as a bromoine source and benzoyl peroxide (BPO) as a radical initiator.[18] Thiolation of bis-bromoindole **13** was conducted to afford thioethers **2** and **3** in the presence of *o*-methyl and *o*-trifluoromethyl thiophenols in 81% and 75% yield, respectively.




**Scheme 1.** Synthesis of thioethers **2**, **3**, and sulfone **4**. Reagents and conditions: a) acetic anhydride ($Ac_2O$), pyridine, reflux, 1 h, 83%; b) iodomethane (MeI), sodium hydride (NaH), *N*,*N*-dimethylformamide (DMF), 0 °C, 2 h, 87%; c) *N*-bromosuccinimide (NBS), benzoyl peroxide (BPO), carbon tetrachloride ($CCl_4$), 90 °C, 3 h, 78%; d) potassium hydroxide (KOH), methanol (MeOH), room temperature (rt), 3 h, 75%; e) KOH, MeOH, rt, 3 h, 81%; f) *m*-chloroperoxybenzoic acid (*m*CPBA), dichloromethane ($CH_2Cl_2$), rt, 5 min., 78%.




| Starting material | $R^1$ | $R^2$ | Product | Yield (%) |
|---|---|---|---|---|
| **4** | $CF_3$ |  | **5** | 72 |
| **4** | $CF_3$ |  | **6** | 70 |
| **2** | $CF_3$ |  | **7** | 80 |
| **2** | $CF_3$ |  | **8** | 86 |
| **3** | $CH_3$ |  | **9** | 83 |

**Scheme 2.** Synthesis of umifenovir analogues. Reagents and conditions: a) amines, 37% formaldehyde solution (37% HCHO), acetic acid (AcOH), reflux, 8 h.

The resulting thioether **2** was oxidized to give sulfoxide **4** using *m*-chloroperoxybenzoic acid (*m*CPBA) in 78% yield. Finally, thioethers **2**, **3**, and sulfoxide **4** were transformed to corresponding umifenovir analogues **5**, **6**, **7**, **8**, and **9** by reaction with a range of secondary amines via the Betti reaction[19] in 70–86% yield (Scheme 2).

These compounds were designed based on the reported SAR study against chikungunya virus,[18] where the sulfinyl group at the 2-position of the indole was shown to reduce the risk of cell toxicity and the substituents on the benzene affected the activity. Although the SAR study was performed against Chikungunya virus, the similar trend would be expected because umifenovir (**1**) has a broad spectrum of antiviral activity.

Biological assays of the compounds prepared in this work were then performed, focusing on inhibition of the binding of the S-protein and ACE2 receptors. Although the detailed mechanism of action is unclear, we focused on a docking study by Hu and co-workers, which showed that umifenovir (**1**) and the RBD in the S-protein of SARS-CoV-2 have a high binding affinity of −5.38 kcal/mol, where $Asp^{428}$ forms a hydrogen bond with **1** along with two hydrophobic π-alkyl bonds associated with $Pro^{426}$ and $Phe^{464}$.[20] In this assay, the plate-coated S-protein containing RBD, $S_1$, and $S_2$ subunits of SARS-CoV-2 was subjected to biotin-labeled ACE2-His and the test substances. To identify the inhibitory effect of the test substances, the absorbance was measured as a readout following treatment

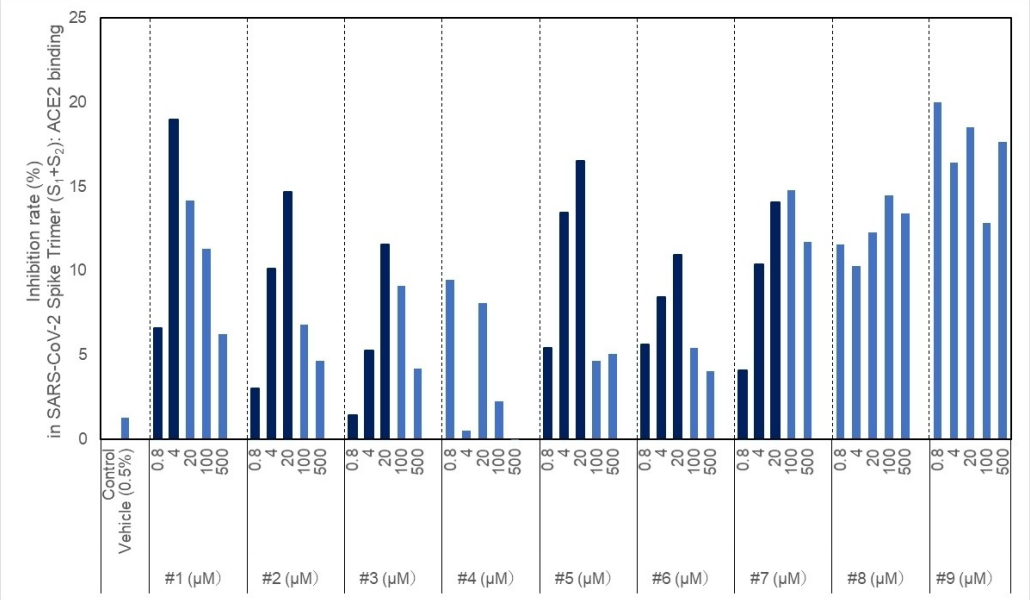



**Figure 2.** Inhibitory activity of umifenovir analogues. The result was obtained from a single experiment ($n = 1$).

with streptavidin-horseradish peroxidase (HRP). The inhibition rate was determined by comparing the absorbance of the test substances and the vehicle.

Inhibitory activity with a maximum inhibition rate of up to 20% was confirmed, so profound inhibition was not observed in this assay (Figure 2). Although concentration-dependent increases of the inhibition rate at low concentrations were observed in some cases (Figure 2, dark blue), the precipitation of the compounds in aqueous media at concentrations from 20 to 100 μM hampered evaluation at higher concentrations.

This assay was based on the hypothesis that umifenovir analogues bind to the RBD of the S-protein and affect its affinity to the ACE2 receptor; however, a decent inhibition rate was not detected. As the detailed mechanism of action for how **1** inhibits viral infection is not well understood, there still remains the chance for detecting the biological activity of umifenovir analogues based on other possible modes of action. For example, although a co-crystal of the S-protein of the SARS-CoV-2 virus and **1** has not been reported, Vankadari recently reported the therapeutic potential of **1** against SARS-CoV-2 based on a protein sequence analysis and docking study, where the sequence similarity of a short region of the trimerization domain in the $S_2$ domain (aa 947–1027) of the SARS-CoV-2 S-protein and that of influenza virus H3 N2 HA suggested that **1** might block the receptor's trimerization, resulting in inhibition of host cell adhesion and viral infection.[21] In addition, the mechanismsof action by which **1** inhibits viral infection would depend on the binding site of the S-protein, because the proposed model of coronavirus entry includes multiple steps: (A) the S-protein promotes virus attachment to host cells via binding to a transmembrane receptor using the RBD, (B) activation of the S-protein trimer via protease cleavage at the $S_2'$ site, (C) shedding of the $S_1$ subunit trimer frees the fusion machinery, and (D) subsequent conformational changes of the S-protein result in fusion of the viral and host membranes.[6] Therefore, further consideration of assay systems as well as analysis of the binding site are needed to assess the biological activity of umifenovir analogues as a therapeutic candidates for the treatment of COVID-19.

## Conclusion

In conclusion, we have synthesized a series of umifenovir analogues and evaluated their biological activities, focusing on their inhibitory activity against the binding of the S-protein of SARS-CoV-2 and the ACE2 receptor, which is a possible mode of action in which umifenovir (**1**) inhibits viral infection. A maximum inhibition rate of up to 20% was confirmed, but strong inhibition was not observed. As the detailed mode of action is still unclear, the use of alternative assay systems along with analysis of the binding site is necessary to detect the biological activity of umifenovir analogues to aid in the discovery of a novel anti-SARS-CoV-2 agent.

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## *Conflict of 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.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Keywords:** COVID-19 · SARS-CoV-2 · Umifenovir · Indole · ACE2 receptor

[1] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, *Lancet* **2020**, *395*, 497–506.

[2] World Health Organization, "Weekly Operational Update on COVID-19", 12–12-2021, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.

[3] a) P. Zhou, X. L. Yang, X. G. Wang, B. Hu, L. Zhang, W. Zhang, H. R. Si, Y. Zhu, B. Li, C. L. Huang, H. D. Chen, J. Chen, Y. Luo, H. Guo, R. D. Jiang, M. Q. Liu, Y. Chen, X. R. Shen, X. Wang, X. S. Zheng, K. Zhao, Q. J. Chen, F. Deng, L. L. Liu, B. Yan, F. X. Zhan, Y. Y. Wang, G. F. Xiao, Z. L. Shi, *Nature* **2020**, *579*, 270–273; b) F. Wu, S. Zhao, B. Yu, Y. M. Chen, W. Wang, Z. G. Song, Y. Hu, Z. W. Tao, J. H. Tian, Y. Y. Pei, M. L. Yuan, Y. L. Zhang, F. H. Dai, Y. Liu, Q. M. Wang, J. J. Zheng, L. Xu, E. C. Holmes, Y. Z. Zhang, *Nature* **2020**, *579*, 265–269; c) M. Chan-Yeung, R. H. Xu, *Respirology* **2003**, *8*, S9–14.

[4] a) Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, R. Ren, K. S. M. Leung, E. H. Y. Lau, J. Y. Wong, X. Xing, N. Xiang, Y. Wu, C. Li, Q. Chen, D. Li, T. Liu, J. Zhao, M. Liu, W. Tu, C. Chen, L. Jin, R. Yang, Q. Wang, S. Zhou, R. Wang, H. Liu, Y. Luo, Y. Liu, G. Shao, H. Li, Z. Tao, Y. Yang, Z. Deng, B. Liu, Z. Ma, Y. Zhang, G. Shi, T. T. Y. Lam, J. T. Wu, G. F. Gao, B. J. Cowling, B. Yang, G. M. Leung, Z. Feng, *N. Engl. J. Med.* **2020**, *382*, 1199–1207; b) W. J. Guan, Z. Y. Ni, Y. Hu, W. H. Liang, C. Q. Ou, J. X. He, L. Liu, H. Shan, C. L. Lei, D. S. C. Hui, B. Du, L. J. Li, G. Zeng, K. Y. Yuen, R. C. Chen, C. L. Tang, T. Wang, P. Y. Chen, J. Xiang, S. Y. Li, J. L. Wang, Z. J. Liang, Y. X. Peng, L. Wei, Y. Liu, Y. H. Hu, P. Peng, J. M. Wang, J. Y. Liu, Z. Chen, G. Li, Z. J. Zheng, S. Q. Qiu, J. Luo, C. J. Ye, S. Y. Zhu, N. S. Zhong, *N. Engl. J. Med.* **2020**, *382*, 1708–1720.

[5] a) D. Wrapp, N. Wang, K. S. Corbett, J. A. Goldsmith, C. L. Hsieh, O. Abiona, B. S. Graham, J. S. McLellan, *Science* **2020**, *367*, 1260–1263; b) A. C. Walls, Y. J. Park, M. A. Tortorici, A. Wall, A. T. McGuire, D. Veesler, *Cell* **2020**, *181*, 281–292.

[6] A. C. Walls, M. A. Tortorici, J. Snijder, X. Xiong, B. J. Bosch, F. A. Rey, D. Veesler, *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 11157–11162.

[7] a) E. D. Deeks, *Drugs* **2021**, *81*, 2047–2055; b) European Medicines Agency, "Ronapreve: EPAR - Product information", 12–11-2021, https://www.ema.europa.eu/en/documents/product-information/ronapreve-epar-product-information en.pdf.

[8] a) C. C. Lee, C. C. Hsieh, W. C. Ko, *Antibiotics* **2021**, 10. 1294; b) R. M. Cox, J. D. Wolf, R. K. Plemper, *Nat. Microbiol.* **2021**, 6, 11–18.

[9] a) J. H. Beigel, K. M. Tomashek, L. E. Dodd, A. K. Mehta, B. S. Zingman, A. C. Kalil, E. Hohmann, H. Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R. W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T. F. Patterson, R. Paredes, D. A. Sweeney, W. R. Short, G. Touloumi, D. C. Lye, N. Ohmagari, M. D. Oh, G. M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M. G. Kortepeter, R. L. Atmar, C. B. Creech, J. Lundgren, A. G. Babiker, S. Pett, J. D. Neaton, T. H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, H. C. Lane, *N. Engl. J. Med.* **2020**, *383*, 1813–1826; b) D. Siegel, H. C. Hui, E. Doerffler, M. O. Clarke, K. Chun, L. Zhang, S. Neville, E. Carra, W. Lew, B. Ross, Q. Wang, L. Wolfe, R. Jordan, V. Soloveva, J. Knox, J. Perry, M. Perron, K. M. Stray, O. Barauskas, J. Y. Feng, Y. Xu, G. Lee, A. L. Rheingold, A. S. Ray, R. Bannister, R. Strickley, S. Swaminathan, W. A. Lee, S. Bavari, T. Cihlar, M. K. Lo, T. K. Warren, R. L. Mackman, *J. Med. Chem.* **2017**, *60*, 1648–1661.

[10] a) M. Ghasemnejad-Berenji, S. Pashapour, *Drug Res.* **2021**, *71*, 166–170; b) Y. Furuta, T. Komeno, T. Nakamura, *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* **2017**, *93*, 449–463.

[11] a) S. C. J. Jorgensen, C. L. Y. Tse, L. Burry, L. D. Dresser, *Pharmacotherapy* **2020**, *40*, 843–856; b) A. C. Kalil, T. F. Patterson, A. K. Mehta, K. M. Tomashek, C. R. Wolfe, V. Ghazaryan, V. C. Marconi, G. M. Ruiz-Palacios, L. Hsieh, S. Kline, V. Tapson, N. M. Iovine, M. K. Jain, D. A. Sweeney, H. M. El Sahly, A. R. Branche, J. R. Pineda, D. C. Lye, U. Sandkovsky, A. F. Luetkemeyer, S. H. Cohen, R. W. Finberg, P. E. H. Jackson, B. Taiwo, C. I. Paules, H. Arguinchona, N. Erdmann, N. Ahuja, M. Frank, M. D. Oh, E. S. Kim, S. Y. Tan, R. A. Mularski, H. Nielsen, P. O. Ponce, B. S. Taylor, L. Larson, N. G. Rouphael, Y. Saklawi, V. D. Cantos, E. R. Ko, J. J. Engemann, A. N. Amin, M. Watanabe, J. Billings, M. C. Elie, R. T. Davey, T. H. Burgess, J. Ferreira, M. Green, M. Makowski, A. Cardoso, S. de Bono, T. Bonnett, M. Proschan, G. A. Deye, W. Dempsey, S. U. Nayak, L. E. Dodd, J. H. Beigel, *N. Engl. J. Med.* **2021**, *384*, 795–807.

[12] a) G. M. Nitulescu, H. Paunescu, S. A. Moschos, D. Petrakis, G. Nitulescu, G. N. D. Ion, D. A. Spandidos, T. K. Nikolouzakis, N. Drakoulis, A. Tsatsakis, *Int. J. Mol. Med.* **2020**, *46*, 467–488; b) C. A. Dehelean, V. Lazureanu, D. Coricovac, M. Mioc, R. Oancea, I. Marcovici, I. Pinzaru, C. Soica, A. M. Tsatsakis, O. Cretu, *J. Clin. Med.* **2020**, *9*, 2084; c) D. E. Gordon, G. M. Jang, M. Bouhaddou, J. Xu, K. Obernier, K. M. White, M. J. O'Meara, V. V. Rezelj, J. Z. Guo, D. L. Swaney, T. A. Tummino, R. Hüttenhain, R. M. Kaake, A. L. Richards, B. Tutuncuoglu, H. Foussard, J. Batra, K. Haas, M. Modak, M. Kim, P. Haas, B. J. Polacco, H. Braberg, J. M. Fabius, M. Eckhardt, M. Soucheray, M. J. Bennett, M. Cakir, M. J. McGregor, Q. Li, B. Meyer, F. Roesch, T. Vallet, A. Mac Kain, L. Miorin, E. Moreno, Z. Z. C. Naing, Y. Zhou, S. Peng, Y. Shi, Z. Zhang, W. Shen, I. T. Kirby, J. E. Melnyk, J. S. Chorba, K. Lou, S. A. Dai, I. Barrio-Hernandez, D. Memon, C. Hernandez-Armenta, J. Lyu, C. J. P. Mathy, T. Perica, K. B. Pilla, S. J. Ganesan, D. J. Saltzberg, R. Rakesh, X. Liu, S. B. Rosenthal, L. Calviello, S. Venkataramanan, J. Liboy-Lugo, Y. Lin, X. P. Huang, Y. Liu, S. A. Wankowicz, M. Bohn, M. Safari, F. S. Ugur, C. Koh, N. S. Savar, Q. D. Tran, D. Shengjuler, S. J. Fletcher, M. C. O'Neal, Y. Cai, J. C. J. Chang, D. J. Broadhurst, S. Klippsten, P. P. Sharp, N. A. Wenzell, D. Kuzuoglu-Ozturk, H. Y. Wang, R. Trenker, J. M. Young, D. A. Cavero, J. Hiatt, T. L. Roth, U. Rathore, A. Subramanian, J. Noack, M. Hubert, R. M. Stroud, A. D. Frankel, O. S. Rosenberg, K. A. Verba, D. A. Agard, M. Ott, M. Emerman, N. Jura, M. Von Zastrow, E. Verdin, A. Ashworth, O. Schwartz, C. d'Enfert, S. Mukherjee, M. Jacobson, H. S. Malik, D. G. Fujimori, T. Ideker, C. S. Craik, S. N. Floor, J. S. Fraser, J. D. Gross, A. Sali, B. L. Roth, D. Ruggero, J. Taunton, T. Kortemme, P. Beltrao, M. Vignuzzi, A. García-Sastre, K. M. Shokat, B. K. Shoichet, N. J. Krogan, *Nature* **2020**, *583*, 459–468.

[13] a) S. Y. Boriskin, A. I. Leneva, E. I. Pecheur, J. S. Polyak, *Current Med. Chem.* **2008**, *15*, 997–1005; b) C. E. Hulseberg, L. Fénéant, K. M. Szymańska-de Wijs, N. P. Kessler, E. A. Nelson, C. J. Shoemaker, C. S. Schmaljohn, S. J. Polyak, J. M. White, *J. Virol.* **2019**, *93*, e02185–18.

[14] R. U. Kadam, I. A. Wilson, *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 206–214.

[15] a) Z. Wang, B. Yang, Q. Li, L. Wen, R. Zhang, *Clin. Infect. Dis.* **2020**, *71*, 769–777; b) M. Nojomi, Z. Yassin, H. Keyvani, M. J. Makiani, M. Roham, A. Laali, N. Dehghan, M. Navaei, M. Ranjbar, *BMC Infect. Dis.* **2020**, *20*, 954; c) Z. Zhu, Z. Lu, T. Xu, C. Chen, G. Yang, T. Zha, J. Lu, Y. Xue, *J. Infect.* **2020**, *81*, e21–23.

[16] X. Wang, R. Cao, H. Zhang, J. Liu, M. Xu, H. Hu, Y. Li, L. Zhao, W. Li, X. Sun, X. Yang, Z. Shi, F. Deng, Z. Hu, W. Zhong, M. Wang, *Cell Discov.* **2020**, *6*, 28.

[17] Z. V. F. Wright, N. C. Wu, R. U. Kadam, I. A. Wilson, D. W. Wolan, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 3744–3748.

[18] M. Scuotto, R. Abdelnabi, S. Collarile, C. Schiraldi, L. Delang, A. Massa, S. Ferla, A. Brancale, P. Leyssen, J. Neyts, R. Filosa, *Bioorg. Med. Chem.* **2017**, *25*, 327–337.

[19] M. Betti, *Gazz. Chim. Ital.* **1900**, *30 II*, 301–309.

[20] X. Hu, Z. Zhou, F. Li, Y. Xiao, Z. Wang, J. Xu, F. Dong, H. Zheng, R. Yu, *Heliyon* **2021**, *7*, e06387.

[21] N. Vankadari, *Int. J. Antimicrob. Agents* **2020**, *56*, 105998.

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