Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2022, **32**, 334–335

Mendeleev Communications

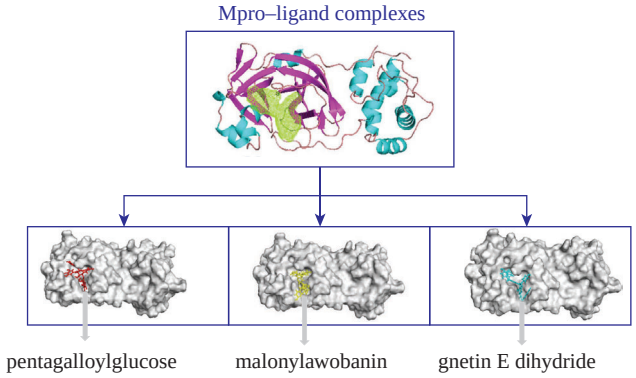
Identification of natural compounds targeting SARS-CoV-2 Mpro by virtual screening and molecular dynamics simulations

Chuanming Zhang,*[a] Chao Zhang,[b] Yanli Meng,[b] Tai Li,[b] Zhe Jin,[b] Shicheng Hou[b] and Chun Hu*[b]

[a] *School of Pharmacy, Baotou Medical College, 014040 Baotou, China. E-mail: chuanming_zhang@yeah.net*
[b] *Key Laboratory of Structure-based Drug Design & Discovery, Ministry of Education, Shenyang Pharmaceutical University, 110016 Shenyang, China. E-mail: chunhu@syphu.edu.cn*

DOI: 10.1016/j.mencom.2022.05.013

The SARS-CoV-2 main protease (Mpro) has been chosen as a conserved molecular target to develop broad-spectrum antiviral drugs. Using molecular docking and molecular dynamics (MD) simulations, a total of 5600 natural compounds available for virtual screening were tested to identify potential inhibitors of SARS-CoV-2 Mpro. As a result, three natural compounds (pentagalloylglucose, malonylawobanin and gnetin E dihydride) were found to be potential inhibitors of SARS-CoV-2, which confirms the theoretical and practical significance of this approach for the design of SARS-CoV-2 inhibitors.



Keywords: COVID-19, SARS-CoV-2 Mpro, SARS-CoV-2 inhibitors, natural compounds, molecular docking, molecular dynamics.

As the third cross-species coronavirus to infect the human population in the past two decades,[1] severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a betacoronavirus, the same as severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV).[2,3] Up to now, 418 650 474 confirmed cases of coronavirus disease 2019 (COVID-19) had been reported to WHO, including 5 856 224 deaths.[4] It is imperative to develop drugs to stop the coronavirus. Although the identification of potential vaccines or therapeutic compounds is currently under study, few specific therapies for COVID-19 are available. Therefore, identifying effective antiviral drugs to combat the disease is urgently necessary.[5]

The report on the functions and crystal structures of several target proteins is particularly important for the development of antiviral drugs. The key role of the glycerogelatin spike protein, mediating host cell invasion by binding to angiotensin-converting enzyme 2 (ACE2), makes ACE2 a potential target.[6–8] Later, the crystal structures of SARS-CoV-2 non-structural proteins, such as RNA-dependent RNA polymerase (RdRp) and coronavirus main protease (Mpro), were successfully established and deposited in the Protein Data Bank (PDB).[9,10] RdRp catalyzes the synthesis of viral RNA and thus is a central component in the replication and transcription cycle of SARS-CoV-2.[11] The Mpro, also known as 3CL protease, is believed to be required for immune regulation and cleavage of the polyproteins pp1a and pp1ab.[12]

Mpro is usually present as a homodimer. Many coronaviruses have high sequence homology regarding the three-dimensional structure and amino acid sequence of this proteolytic enzyme. Therefore, Mpro is a conserved molecular target to design broad-spectrum antiviral drugs.[13,14]

In this study, a total of 5600 natural compounds obtained from ZINC† were compiled to search for potential SARS-CoV-2 Mpro inhibitors, and we focused on investigating the binding features of natural compounds with the SARS-CoV-2 Mpro structure (PDB ID: 6LU7).

We used Glide in the Schrödinger Maestro Suite 2016 to explore protein–ligand interactions, calculate the corresponding binding free energy and elucidate the binding mechanisms between natural compounds and SARS-CoV-2 Mpro.[15,16] Remdesivir was used as a control drug that has been screened for the treatment of COVID-19 and found to bind strongly to both RdRp and SARS-CoV-2 Mpro.[17,18] Virtual screening results (Figure S1, see Online Supplementary Materials) for remdesivir, pentagalloylglucose, malonylawobanin and gnetin E dihydride are shown in Table 1.

Table 1 Virtual screening results for remdesivir, pentagalloylglucose, malonylawobanin and gnetin E dihydride.

Compound name	H-bonding and π–π interactions with Mpro	Glide score/ kcal mol^{-1}
Remdesivir	Thr26, Thr45, Asn142, Gly143	−10.437
Pentagalloylglucose	Thr26, His41, Ser46, His164, Asp187, Thr190	−13.387
Malonylawobanin	His41, Gly143, His163, His164, Glu166, Thr190	−12.020
Gnetin E dihydride	Thr26, His41, Cys145, His164, Glu166	−10.003

† ZINC, a free database of commercially available compounds for virtual screening, is accessible at https://zinc.docking.org/.

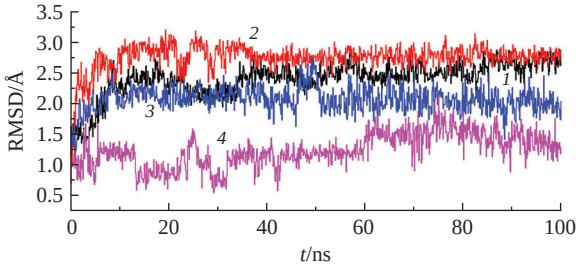


Figure 1 The RMSD curves of (*1*) Mpro, (*2*) Mpro–pentagalloylglucose, (*3*) Mpro–malonylawobanin and (*4*) Mpro–gnetin E dihydride during 100 ns simulations.

It was necessary to define a protein–ligand binding model[19,20] that would provide profound theoretical guidance for further designing novel effective ligands that form complexes with viral proteins. To do this, we performed 100-ns molecular dynamics simulations using pentagalloylglucose, malonylawobanin, and gnetin E dihydride. These compounds were taken as representative structures due to lower Glide scores and more suitable conformations. As a result, we identified three inhibitors targeting SARS-CoV-2 Mpro. Figure 1 shows the root-mean-square deviation (RMSD) plots of protein and ligand characteristics during a 100-ns simulation. Curves *1–4* of the RMSD diagrams depict the characteristics of the free protein and the complexes Mpro–pentagalloylglucose, Mpro–malonylawobanin and Mpro–gnetin E dihydride. For the Mpro–ligand complexes (Mpro–pentagalloylglucose, Mpro–malonylawobanin and Mpro–gnetin E dihydride), some fluctuations were observed in the beginning, and then the Mpro–pentagalloylglucose complex gradually tended to remain in equilibrium after 40 ns of the simulation. The RMSD values of alpha-carbons for complex Mpro–malonylawobanin changed during the first 50 ns of the simulation. However, the fluctuation curves of the Mpro–gnetin E dihydride complex tended to remain in equilibrium until the simulation time reached 70 ns. It was interesting to see that the RMSD curves for the complexes Mpro–pentagalloylglucose and Mpro–malonylawobanin were remarkably stable compared to Mpro–gnetin E dihydride, indicating that pentagalloylglucose and malonylawobanin can form a more stable complex with Mpro (Figures S2–S7 and Tables S1–S3). Three compounds (pentagalloylglucose, malonylawobanin and gnetin E dihydride) were further selected to calculate binding energy using the MM-GBSA method.[21,22] The binding free energy values of the Mpro–pentagalloylglucose, Mpro–malonylawobanin and Mpro–gnetin E dihydride complexes were −85.63, −59.59 and −53.80 kcal mol^{-1}, respectively (Table S4). It was clear that Mpro–pentagalloylglucose showed a higher binding free energy than the other complexes. Coulomb energy and van der Waals energy are the key components of the MM-GBSA value for the Mpro–pentagalloylglucose complex system.

These three natural compounds (pentagalloylglucose, malonylawobanin and gnetin E dihydride) contain multiple hydroxyl groups and adopt torsional angles that promote H-bond formation and enhance protein–ligand interaction. This study may have practical implications for the design of SARS-CoV-2 inhibitors shortly.

This work was supported by the Program for Scientific Research of Universities of Inner Mongolia Autonomous Region, China (grant no. NJZY21060) and the National Science Foundation of China (grant no. 21342006).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.05.013.

References

1 J. Chen, *Microbes Infect.*, 2020, **22**, 69.
2 J. Cui, F. Li and Z.-L. Shi, *Nat. Rev. Microbiol.*, 2019, **17**, 181.
3 E. de Wit, N. van Doremalen, D. Falzarano and V. J. Munster, *Nat. Rev. Microbiol.*, 2016, **14**, 523.
4 *WHO Coronavirus (COVID-19) Dashboard*, World Health Organization, February 18, 2022. https://covid19.who.int/.
5 M. R. Suleiman, H. Wang, D. Huang, H. Wang, J. Joseph, T. Huang, F. Zhang, J. Wang and M. Cheng, *J. Biomol. Struct. Dyn.*, 2021, **39**, 2512.
6 V. S. Stroylov and I. V. Svitanko, *Mendeleev Commun.*, 2020, **30**, 419.
7 P. Richardson, I. Griffin, C. Tucker, D. Smith, O. Oechsle, A. Phelan, M. Rawling, E. Savory and J. Stebbing, *Lancet*, 2020, **395**, e30.
8 K. Terali, B. Baddal and H. O. Gülcan, *J. Mol. Graphics Modell.*, 2020, **100**, 107697.
9 A. D. Elmezayen, A. Al-Obaidi, A. T. Şahin and K. Yelekçi, *J. Biomol. Struct. Dyn.*, 2021, **39**, 2980.
10 Y. Gao, L. Yan, Y. Huang, F. Liu, Y. Zhao, L. Cao, T. Wang, Q. Sun, Z. Ming, L. Zhang, J. Ge, L. Zheng, Y. Zhang, H. Wang, Y. Zhu, C. Zhu, T. Hu, T. Hua, B. Zhang, X. Yang, J. Li, H. Yang, Z. Liu, W. Xu, L. W. Guddat, Q. Wang, Z. Lou and Z. Rao, *Science*, 2020, **368**, 779.
11 L. Subissi, C. C. Posthuma, A. Collet, J. C. Zevenhoven-Dobbe, A. E. Gorbalenya, E. Decroly, E. J. Snijder, B. Canard and I. Imbert, *Proc. Natl. Acad. Sci. U. S. A.*, 2014, **111**, E3900.
12 J. Zhou, L. Fang, Z. Yang, S. Xu, M. Lv, Z. Sun, J. Chen, D. Wang, J. Gao and S. Xiao, *FASEB J.*, 2019, **33**, 14575.
13 F. Wang, C. Chen, W. Tan, K. Yang and H. Yang, *Sci. Rep.*, 2016, **6**, 22677.
14 H. A. Odhar, S. W. Ahjel, A. A. M. A. Albeer, A. F. Hashim, A. M. Rayshan and S. S. Humadi, *Bioinformation*, 2020, **16**, 236.
15 M. Wang, W. Li, Y. Wang, Y. Song, J. Wang and M. Cheng, *J. Mol. Graphics Modell.*, 2018, **84**, 18.
16 H. L. Nguyen, N. Q. Thai, D. T. Truong and M. S. Li, *J. Phys. Chem. B*, 2020, **124**, 11337.
17 M. Costanzo, M. A. Rachele De Giglio and G. N. Roviello, *Curr. Med. Chem.*, 2020, **27**, 4536.
18 Z. Jin, X. Du, Y. Xu, Y. Deng, M. Liu, Y. Zhao, B. Zhang, X. Li, L. Zhang, C. Peng, Y. Duan, J. Yu, L. Wang, K. Yang, F. Liu, R. Jiang, X. Yang, T. You, X. Liu, X. Yang, F. Bai, H. Liu, X. Liu, L. W. Guddat, W. Xu, G. Xiao, C. Qin, Z. Shi, H. Jiang, Z. Rao and H. Yang, *Nature*, 2020, **582**, 289.
19 W.-Q. Jia, Z. Jing, X. Liu, X.-Y. Feng, Y.-Y. Liu, S.-Q. Wang, W.-R. Xu, J.-W. Liu and X.-C. Cheng, *J. Biomol. Struct. Dyn.*, 2018, **36**, 3496.
20 Y.-Y. Liu, X.-Y. Feng, W.-Q. Jia, Z. Jing, W.-R. Xu and X.-C. Cheng, *Comput. Biol. Chem.*, 2019, **78**, 190.
21 Y. Wang, B. Hu, Y. Peng, X. Xiong, W. Jing, J. Wang and H. Gao, *J. Chem. Inf. Model.*, 2019, **59**, 2309.
22 Z.-Z. Wang, C.-Y. Ma, J. Yang, Q.-B. Gao, X.-D. Sun, L. Ding and H.-M. Liu, *J. Mol. Struct.*, 2019, **1175**, 698.

Received: 4th October 2021; Com. 21/6714