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Identification of Potential COVID-19 Mpro Inhibitors through Covalent Drug Docking, Molecular Dynamics Simulation, and MMGBSA Calculation

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Abstract

The viral main protease (Mpro) is a key drug target due to its integral role in the life cycle of SARS-CoV-2. Given the urgent need for effective therapeutics against COVID-19, extensive research has focused on the development of inhibitors targeting this enzyme. This study focuses on the exploration of covalent docking for Mpro inhibition. Using computational methods, the interactions between potential inhibitors and SARS-CoV-2 Mpro are investigated. Using protein structures (7JKV and 7TDU), fragment-based ligand selection and covalent docking via SeeSAR were performed. Pharmacokinetic properties, toxicity assessments using SwissADME and molecular dynamics simulations were performed using GROMACS. Molecular dynamics simulations were performed and parameters such as RMSD, RMSF, and MM/GBSA were analyzed for two specific ligands. These inhibitors exhibit pharmacological properties that may affect drug interactions and metabolism in vivo. In addition, the toxicity profiles of covalent ligands highlight complex interactions across physiological systems and underscore the need for comprehensive safety evaluations prior to therapeutic considerations.

Key words: COVID-19, Main Protease (Mpro), Computational Drug Design, Covalent Drug Design.

References

[1] S. ichiro Hattori, N. Higashi-Kuwata, H. Hayashi, S. R. Allu, J. Raghavaiah, H. Bulut, D. Das, B. J. Anson, E. K. Lendy, Y. Takamatsu, N. Takamune, N. Kishimoto, K. Murayama, K. Hasegawa, M. Li, D. A. Davis, E. N. Kodama, R. Yarchoan, A. Wlodawer, S. Misumi, A. D. Mesecar, A. K. Ghosh, H. Mitsuya, Nature Communications, 2021, DOI:10.1038/s41467-021-20900-6.

[2] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi, R. Lu, P. Niu, F. Zhan, X. Ma, D. Wang, W. Xu, G. Wu, G. F. Gao, W. Tan, New England Journal of Medicine, 2020, DOI:10.1056/nejmoa2001017.

[3] J. Cui, F. Li, Z. L. Shi, Origin and evolution of pathogenic coronaviruses, Nature Reviews Microbiology, 17. 181–192, 2019.

[4] F. Bayani, N. S. Hashkavaei, S. Arjmand, S. Rezaei, V. Uskoković, M. Alijanianzadeh, V. N. Uversky, S. O. Ranaei Siadat, S. Mozaffari-Jovin, Y. Sefidbakht, An overview of the vaccine platforms to combat COVID-19 with a focus on the subunit vaccines, Progress in Biophysics and Molecular Biology. 2023.

[5] T. Pillaiyar, M. Manickam, V. Namasivayam, Y. Hayashi, S. H. Jung, An overview of severe acute respiratory syndrome-coronavirus (SARS-CoV) 3CL protease inhibitors: Peptidomimetics and small molecule chemotherapy, Journal of Medicinal Chemistry, 59. 6595–6628, 2016.

[6] P. C. Y. Woo, S. K. P. Lau, C. S. F. Lam, C. C. Y. Lau, A. K. L. Tsang, J. H. N. Lau, R. Bai, J. L. L. Teng, C. C. C. Tsang, M. Wang, B.-J. Zheng, K.-H. Chan, K.-Y. Yuen, Journal of Virology, 2012, DOI:10.1128/jvi.06540-11.

[7] C. Huang, H. Shuai, J. Qiao, Y. Hou, R. Zeng, A. Xia, L. Xie, Z. Fang, Y. Li, C. Yoon, Q. Huang, B. Hu, J. You, B. Quan, X. Zhao, N. Guo, S. Zhang, R. Ma, J. Zhang, Y. Wang, R. Yang, S. Zhang, J. Nan, H. Xu, F. Wang, J. Lei, H. Chu, S. Yang, Signal transduction and targeted therapy, 2023, DOI:10.1038/s41392-023-01392-w.

[8] F. Bayani, N. Safaei Hashkavaei, M. R. Karamian, V. Uskoković, Y. Sefidbakht, Journal of Biomolecular Structure and Dynamics, 2023, DOI:10.1080/07391102.2023.2170470.

[9] S. Rezaei, Y. Sefidbakht, V. Uskoković, Briefings in Bioinformatics, 2021, DOI:10.1093/bib/bbab241.

[10] Y. Unoh, S. Uehara, K. Nakahara, H. Nobori, Y. Yamatsu, S. Yamamoto, Y. Maruyama, Y. Taoda, K. Kasamatsu, T. Suto, K. Kouki, A. Nakahashi, S. Kawashima, T. Sanaki, S. Toba, K. Uemura, T. Mizutare, S. Ando, M. Sasaki, Y. Orba, H. Sawa, A. Sato, T. Sato, T. Kato, Y. Tachibana, Journal of Medicinal Chemistry, 2022, DOI:10.1021/acs.jmedchem.2c00117.

[11] S. Konno, K. Kobayashi, M. Senda, Y. Funai, Y. Seki, I. Tamai, L. Schäkel, K. Sakata, T. Pillaiyar, A. Taguchi, A. Taniguchi, M. Gütschow, C. E. Müller, K. Takeuchi, M. Hirohama, A. Kawaguchi, M. Kojima, T. Senda, Y. Shirasaka, W. Kamitani, Y. Hayashi, Journal of Medicinal Chemistry, 2022, DOI:10.1021/acs.jmedchem.1c00665.

[12] D. K. Verma, S. Kapoor, S. Das, K. G. Thakur, Biomedicines, 2023, DOI:10.3390/biomedicines11010085.

[13] S. H. Han, C. M. Goins, T. Arya, W. J. Shin, J. Maw, A. Hooper, D. P. Sonawane, M. R. Porter, B. E. Bannister, R. D. Crouch, A. A. Lindsey, G. Lakatos, S. R. Martinez, J. Alvarado, W. S. Akers, N. S. Wang, J. U. Jung, J. D. MacDonald, S. R. Stauffer, Journal of Medicinal Chemistry, 2022, DOI:10.1021/acs.jmedchem.1c00598.

[14] E. Cho, M. Rosa, R. Anjum, S. Mehmood, M. Soban, M. Mujtaba, K. Bux, S. T. Moin, M. Tanweer, S. Dantu, A. Pandini, J. Yin, H. Ma, A. Ramanathan, B. Islam, A. S. J. S. Mey, D. Bhowmik, S. Haider, Journal of Chemical Information and Modeling, 2021, DOI:10.1021/acs.jcim.1c00449.

[15] W. C. Hsu, H. C. Chang, C. Y. Chou, P. J. Tsai, P. I. Lin, G. G. Chang, Journal of Biological Chemistry, 2005, DOI:10.1074/jbc.M502556200.

[16] G. Macip, P. Garcia-Segura, J. Mestres-Truyol, B. Saldivar-Espinoza, M. J. Ojeda-Montes, A. Gimeno, A. Cereto-Massagué, S. Garcia-Vallvé, G. Pujadas, Haste makes waste: A critical review of docking-based virtual screening in drug repurposing for SARS-CoV-2 main protease (M-pro) inhibition, Medicinal Research Reviews, 42. 744–769, 2022.

[17] A. Hegyi, J. Ziebuhr, Journal of General Virology, 2002, DOI:10.1099/0022-1317-83-3-595.

[18] D. W. Kneller, H. Li, G. Phillips, K. L. Weiss, Q. Zhang, M. A. Arnould, C. B. Jonsson, S. Surendranathan, J. Parvathareddy, M. P. Blakeley, L. Coates, J. M. Louis, P. V. Bonnesen, A. Kovalevsky, Nature Communications, 2022, DOI:10.1038/s41467-022-29915-z.

[19] Q. Wu, S. Y. Huang, Briefings in bioinformatics, 2023, DOI:10.1093/bib/bbac559.

[20] Q. Song, L. Zeng, Q. Zheng, S. Liu, ACS Omega, 2022, DOI:10.1021/acsomega.2c08147.

[21] A. K. Ghosh, I. Samanta, A. Mondal, W. R. Liu, Covalent Inhibition in Drug Discovery, ChemMedChem. 2019.

[22] F. Sutanto, M. Konstantinidou, A. Dömling, Covalent inhibitors: A rational approach to drug discovery, RSC Medicinal Chemistry, 11. 876–884, 2020.

[23] D. Kahne, W. C. Still, Journal of the American Chemical Society, 1988, DOI:10.1021/ja00230a041.

[24] F. Huang, X. Han, X. Xiao, J. Zhou, Covalent Warheads Targeting Cysteine Residue: The Promising Approach in Drug Development, Molecules. 2022.

[25] D. Oksenberg, K. Dufu, M. P. Patel, C. Chuang, Z. Li, Q. Xu, A. Silva-Garcia, C. Zhou, A. Hutchaleelaha, L. Patskovska, Y. Patskovsky, S. C. Almo, U. Sinha, B. W. Metcalf, D. R. Archer, British Journal of Haematology, 2016, DOI:10.1111/bjh.14214.
[26] D. Schaefer, X. Cheng, Recent Advances in Covalent Drug Discovery, Pharmaceuticals. 2023.
[27] H. Kim, Y. S. Hwang, M. Kim, S. B. Park, Recent advances in the development of covalent inhibitors, RSC Medicinal Chemistry. 2021.
[28] S. Zhou, E. Chan, W. Duan, M. Huang, Y. Z. Chen, Drug bioactivation, covalent binding to target proteins and toxicity relevance, Drug Metabolism Reviews. 2005.
[29] J. Uetrecht, D. J. Naisbitt, Idiosyncratic adverse drug reactions: Current concepts, Pharmacological Reviews. 2013.
[30] J. Lei, Y. Zhou, D. Xie, Y. Zhang, Journal of the American Chemical Society, 2015, DOI:10.1021/ja5112964.
[31] J. R. Vane, R. M. Botting, in Thrombosis Research; 20032003.
[32] A. K. Ghosh, I. Samanta, A. Mondal, W. R. Liu, Covalent Inhibition in Drug Discovery, ChemMedChem, 14. 889–906, 2019.
[33] R. A. Bauer, Covalent inhibitors in drug discovery: From accidental discoveries to avoided liabilities and designed therapies, Drug Discovery Today. 2015.
[34] [Internet], Covalent Docking Software Update: SeeSAR 11.2 and CovXplorer Workflow [Internet]. 2021. 2021.
[35] A. Daina, O. Michielin, V. Zoete, Scientific Reports, 2017, DOI:10.1038/srep42717.
[36] D. E. V. Pires, T. L. Blundell, D. B. Ascher, Journal of Medicinal Chemistry, 2015, DOI:10.1021/acs.jmedchem.5b00104.
[37] H. C. Andersen, The Journal of Chemical Physics, 1980, DOI:10.1063/1.439486.
[38] M. S. Valdés-Tresanco, M. E. Valdés-Tresanco, P. A. Valiente, E. Moreno, Journal of Chemical Theory and Computation, 2021, DOI:10.1021/acs.jctc.1c00645.
[39] C. Ma, Z. Xia, M. D. Sacco, Y. Hu, J. A. Townsend, X. Meng, J. Choza, H. Tan, J. Jang, M. V. Gongora, X. Zhang, F. Zhang, Y. Xiang, M. T. Marty, Y. Chen, J. Wang, Journal of the American Chemical Society, 2021, DOI:10.1021/jacs.1c08060.
[40] H. S. Fernandes, S. F. Sousa, N. M. F. S. A. Cerqueira, Molecular Diversity, 2022, DOI:10.1007/s11030-021-10259-7.
[41] H. E. A. MH, AI-Driven Covalent Drug Design Strategies Targeting Main Protease (Mpro) Against SARS-CoV-2: Structural Insights and Molecular Mechanisms. Journal of Biomolecular Structure and Dynamics., 2024.
[42] A. Ghasemlou, V. Uskoković, Y. Sefidbakht, Biotechnology and Applied Biochemistry, 2023, 70, 439–457.
[43] A. Ghassemlou, Y. Sefidbakht, M. Rahmandoust, The Main Protease of SARS COV-2 and Its Specific Inhibitors, COVID-19. Springer Singapore, Singapore, 121–147, 2021.