1. **Materials and methods**

*1.1. Preparation of the ligand*

The crystal structures of the drugs were retrieved from The Toxin and Toxin Target Database (www.t3db.ca/toxins) or drug bank (www.drugbank.com). The ligands were loaded in .sdf format and transformed automatically into a 3D structure during the docking process.

*1.2. Preparation of the viral proteins*

The crystal structures of 7 viral proteins encoded by SARS-CoV-2 were downloaded from RCSB PDB (https ://www.rcsb.org) and used as targets. The crystal structures of all viral proteins were imported into Molsoft.icm-pro v3.9-1b[1]. The PDB structures of the proteins were converted into ICM objects by deleting all water molecules contained in the X-ray structures, optimizing the hydrogens (to find the best hydrogen bonding network) as well as the amino acids histidine, proline, asparagine, glycine, cysteine (to find best orientation and protonation state). Missing side chains were treated before the receptors were set for the docking processes. To identify the binding sites and generate receptor maps, the icmPocketFinder function option was used. This method uses the protein structure to identify cavities/clefts and the “druggability” was estimated by calculating the drug-like density (DLID) score as described previously [2].

*1.3. Molecular docking*

After conversion and selection, the binding site residues of the viral proteins were docked with the ligands (Table 1). At the receptor pocket, hydrogen bonding potential, van der Waals potential with carbon-, sulphur- and hydrogen-like probes, hydrophobic potential, and electrostatic potential were taken into consideration. The conformational examination of the program depends on the Biased probability Monte Carlo (BPMC) system, which arbitrarily chooses a pose in the inside coordinate space and at that point makes a stage to another arbitrary position free of the past one, yet as indicated by a predefined constant probability distribution. In this study, the thoroughness which represents the length of the simulation was set as 10. The ligand conformations were ranked using the ICM score[1]. The higher the ICM score is, the lower the chances of protein-ligand binding.

**References**

[1] Sheridan, R.P.; Maiorov, V.N.; Holloway, M.K.; Cornell, W.D.; Gao, Y. Drug-Like Density: A Method of Quantifying the “bindability” of a Protein Target Based on a very Large Set of Pockets and Drug-Like Ligands from the Protein Data Bank. Journal of chemical information and modeling **2010***, 50*, 2029-2040.

[2] Neves, M.A.; Totrov, M.; Abagyan, R. Docking and Scoring with ICM: The Benchmarking Results and Strategies for Improvement. J. Comput. Aided Mol. Des. **2012***, 26*, 675-686.

Supplementary Table S1: List of the residues for the different pockets of SARS-CoV-2 proteins

|  |  |  |  |
| --- | --- | --- | --- |
| Protein (PDB ID) | Pocket | DLID score | Residues |
| 6LU7 | A | 0.6224 | Chain A : T25, T26, L27, H41, C44, M49, Y54, F140, L141, N142, G143, S144, C145, H163, H164, M165, E166, L167, P168, H172, D187, R188, Q189, T190, Q192 |
| B | 0.529 | Chain A: E14, G15, M17, V18, Q19, W31, Q69, A70, G71, N95, P96, K97, N119, G120, S121, P122 |
| 6VSB | A | 1.185 | Chain A: D40, K41, V42, K202, D979, S982, R983  Chain C: P330, L390, C391, L517, L518, H519, A520, P521, A522, N542, F543, N544, G545, L546, T547, Q564, F565, V576, R577, P579, L582 |
| B | 0.87 | Chain A: N907, G908, I909, G910, T912, Q913, Q1036, S1037, K1038, R1039, V1040, D1041, F1042, C1043, G1044, G1046, Y1048, H1049, P1090, R1091, E1092, G1093, V1104, T1105, Q1106, R1107, N1108, Q1113, I1114, T1116, N1119, F1121  Chain B: I712, A713, I714, P715, W886, Y904, N907, G908, I909, G910, V911, T912, Q913, G1035, Q1036, S1037, K1038, R1039, V1040, D1041, F1042, C1043, G1044, G1046, Y1047, H1048, T1066, P1079, P1090, R1091, E1092, G1093, V1094,V1104, T1106, Q1106, R1107, N1108, Q1113, N1119  Chain C: S884, G885, W886, T887, L894, I896, M900, A903, Y904, N907, Q913, Y917, Q1036, S1037, K1038, R1039, R1091, F1021 |
| Receptor binding domain spike-ACE2 |  | See Lan et al. 2020 |
| 6ZSL | A | 0.2978 | Chain A: L405, P406, P408, R409, T410, L412, G415, T416, L417, E418, P419, F422, K430, V456, Y515, D534, T552, A553, H554, N557, V558, N559, R560 |
| B | 0.00476 | Chain A : L165, W167, R173, P174, P175, L176, N177, R178, N179, E201, K202, D207, A208, V209, D483, V484, S485 S486, I488, P514, Y515, N516, S517, A520, V521, T532, D534, S535, H554 |
| 6VWW | A | 0.6227 | Chain A : E69, V70, K71, I72, Y89, K90, P158, Q160, G165, V166, T167, L168, F195, T196, Q197, S198, R199, N200, L201, Q202, E203, L252, L266, E267, D268, P271, M272, D273, S274, T275, V276, K277, Y279, V295, I296, D297, D324 |
| B | 0.531 | Chain A: K71, K90, T167, L168, T196, S198, R199, N200, L201, E203, K205, R207, L252, L266, D273, S274, T275, K277, Y279, V295, I296, D297 |
| 7BTF | A | 0.527 | Chain A: V315, S318, F326, G327, P328, Y346, H347, F348, R349, E350, C395, F396, R457, N459, L460, P461, T462, P537, P627, N628, M629, S664, E665, M666, V675, P677  Chain B: N118 |
| B | 0.4583 | Chain A: K478, Y479, C482, R583, G584, A585, T586, V588, T591, S592, F594, Y595, G596, G597, N600, M601, T604, V605, S607, D608, V609, Y746, A747, R750, K751, S754, M755, M756, V930, |
| 6W4H | A | 0.537 | Chain A: N6841, Y6845, H6867, G6869, A6870, G6871, S6872, A6877, P6878, G6879, T6880, D6897, L6898, N6899, G6911, D6912, C6913, D6928, M6929, Y6930, D6931, F6947 |
| B | 0.317 | Chain A: K6836, G6867, M6839  Chain B: P4289, I4290, T4291, N4292, C4293, K4295, E4319, F4321, T4354, A4357, N4358, D4359, P4360 |
| 5C8T | A | 0.9575 | Chain B : H260, C261, H283, F286, V287, R289, V290, W292, N306, C309, R310, Q313, D331, I332, G334, N335, P336, I338, C340, D352, A353, Q354, L366, F367, Y368, L383, W385, N386, C387, N388, V389, D390, R391, R400, F401, C414, D415, F417, Y420, N422, K423, H424, F426, H427, T428, P429, A430, D432, S434, A435, F506 |
|  | B | 0.9575 | Chain B: R81, H82, V83, R84, A85, K175, G176, L177, S178, D179, K212, Y296, P297, I298, I299, N408, L409, L411, V421, N422, |

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2. Sheridan, R.P.; Maiorov, V.N.; Holloway, M.K.; Cornell, W.D.; Gao, Y.D. Drug-like density: a method of quantifying the "bindability" of a protein target based on a very large set of pockets and drug-like ligands from the Protein Data Bank. *J Chem Inf Model* **2010**, *50*, 2029-2040, doi:10.1021/ci100312t.