Molecular docking-assisted investigation of Cu(II) complexes carrying “SNS” pincer-type pyridine-thioether ligands as potential drug candidates against SARS-CoV-2

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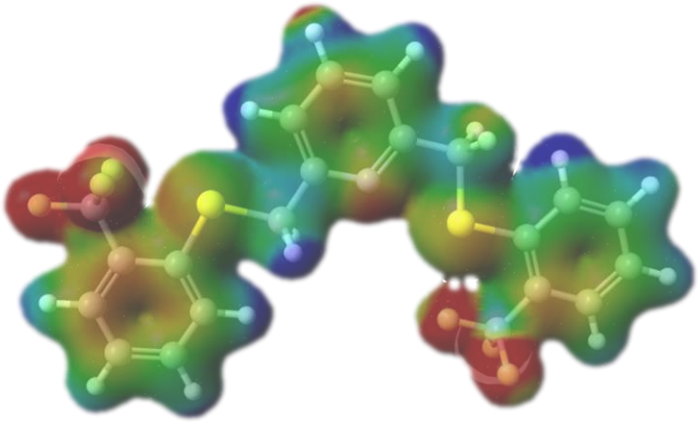
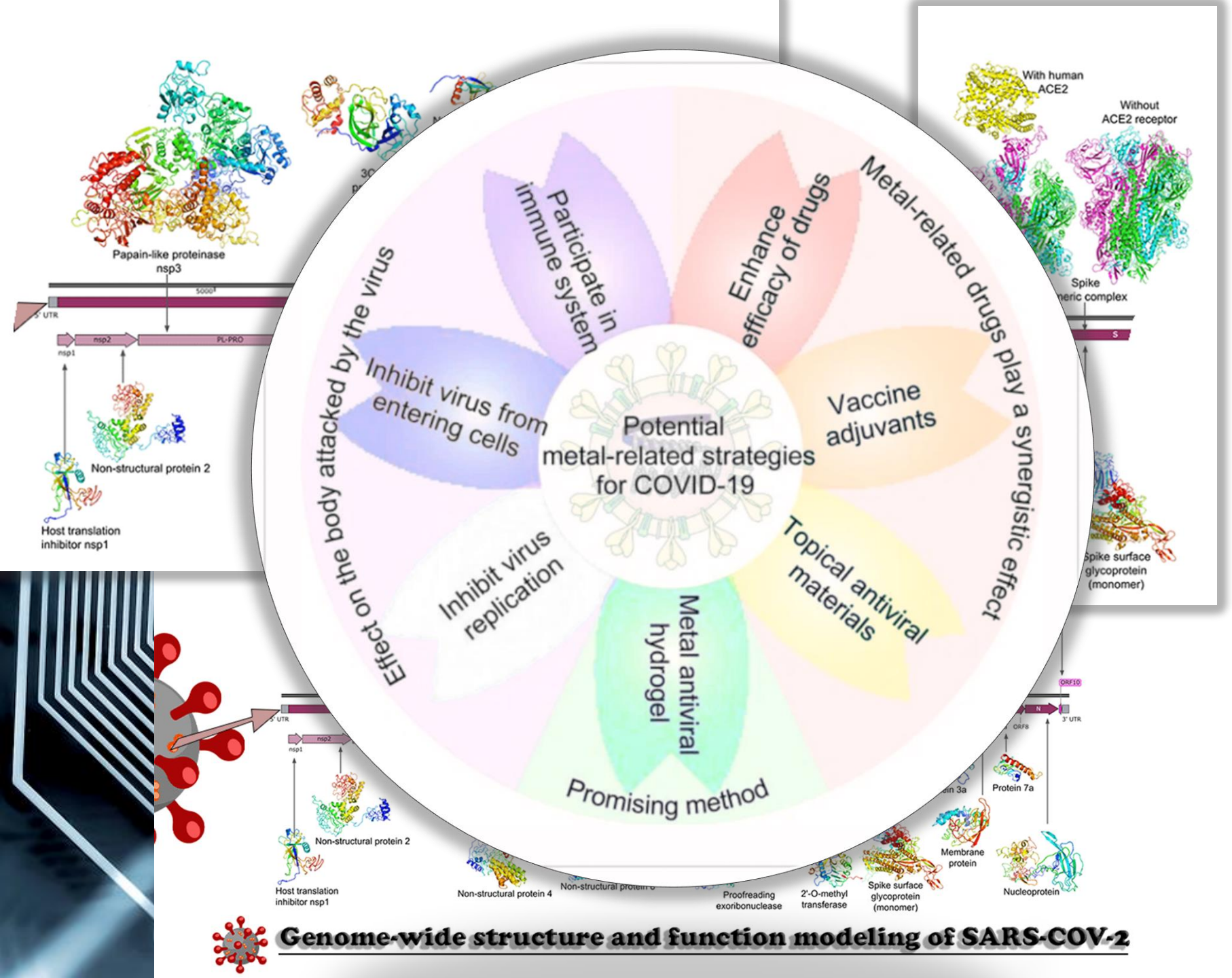


- SNS pincer type ligands (L1 and L2), and their metal complexes (L1-Cu, and L2-Cu) were synthesized and characterized by using different techniques.

- The products of reaction with the related ligands were new three tridentate pincer complexes [M(κ3-L)(Cl)2 and M(κ3-L)(OAc)2] (M = Cu).

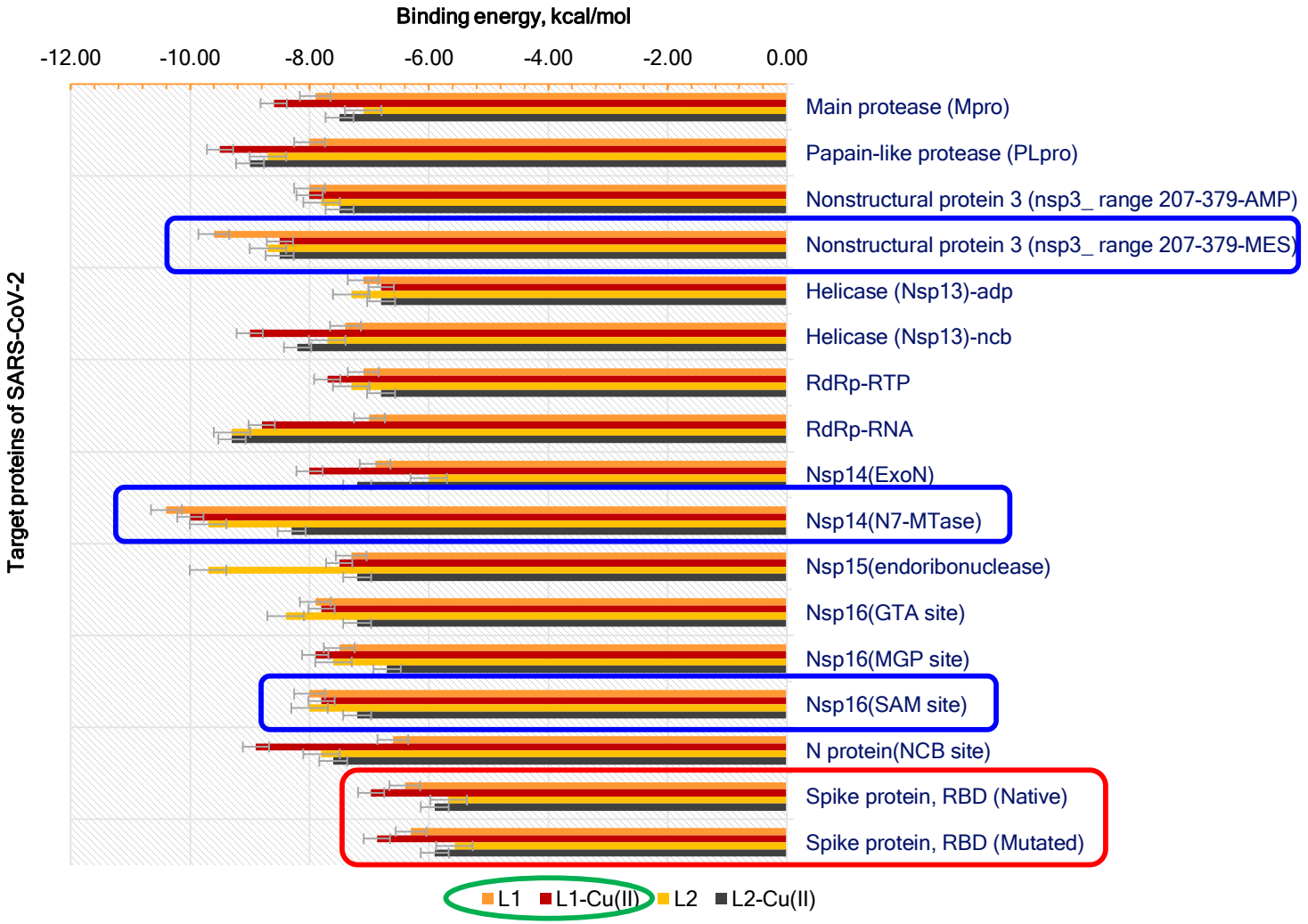
- The molecular structures of the Cu complexes were estimated by X-ray and molar conductivity measurements, in which they exhibited a trigonal bipyramidal geometry with five coordinates around their metal centers.

- Furthermore the current compounds as potential drug candidates against SARS-CoV-2 were investigated via *molecular docking simulations*.

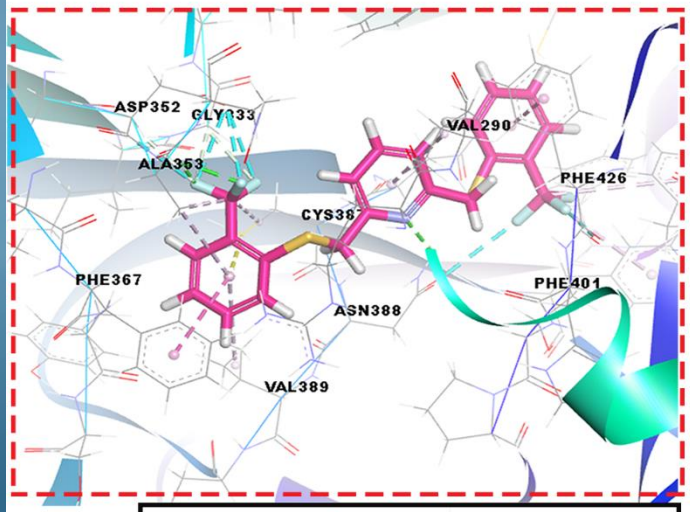


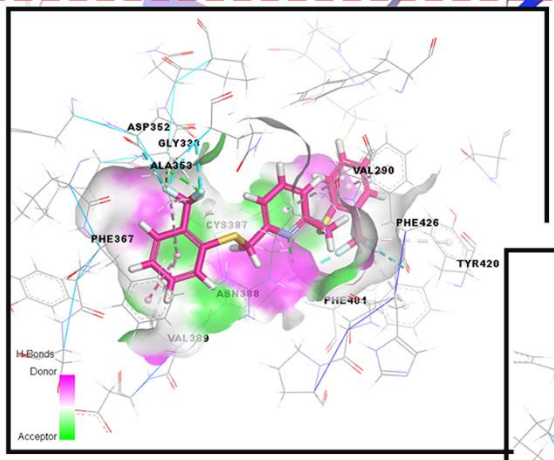
Genome-wide structure and function modeling of SARS-COV-2

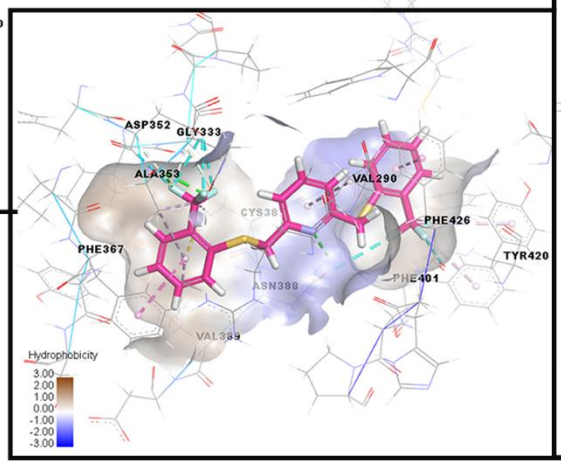
Binding Affinities of SNS pincer ligands and Cu(II) complexes against nsp and sp of SARS-CoV-2

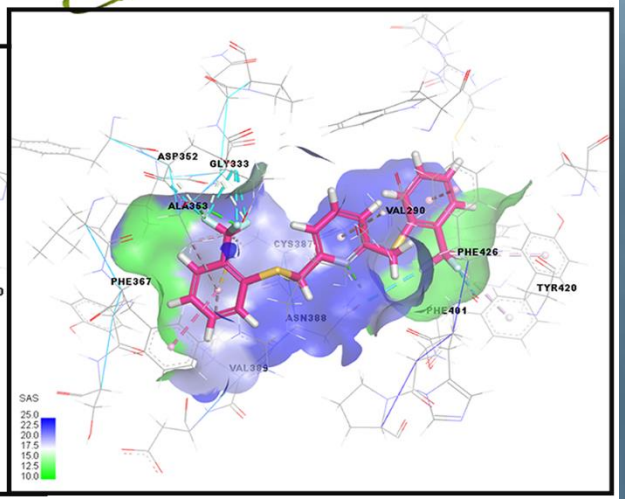


Nsp14(N7-MTase)

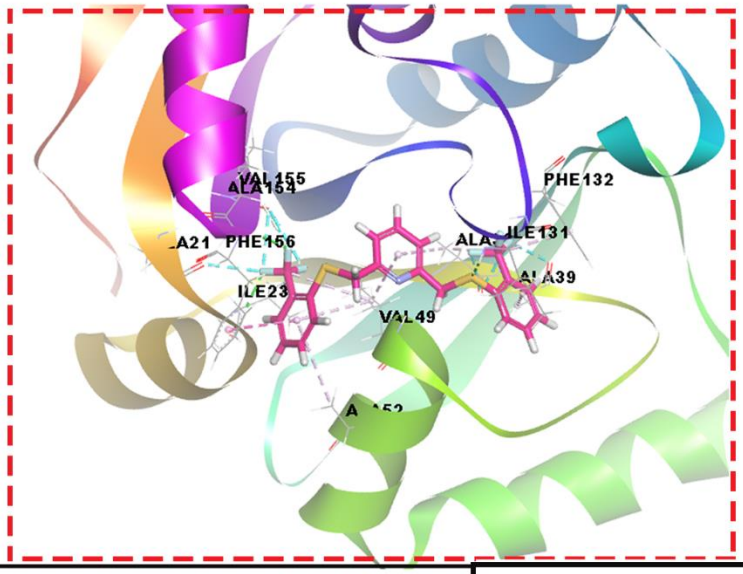


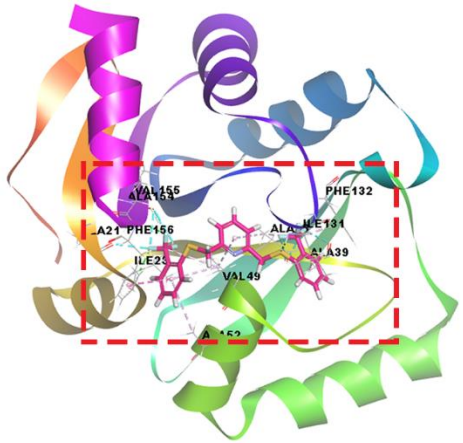


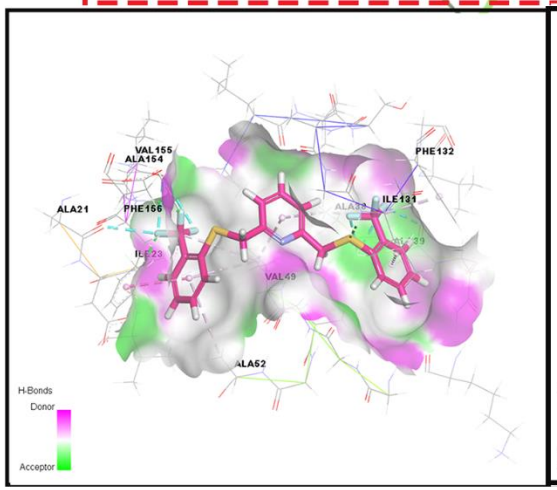


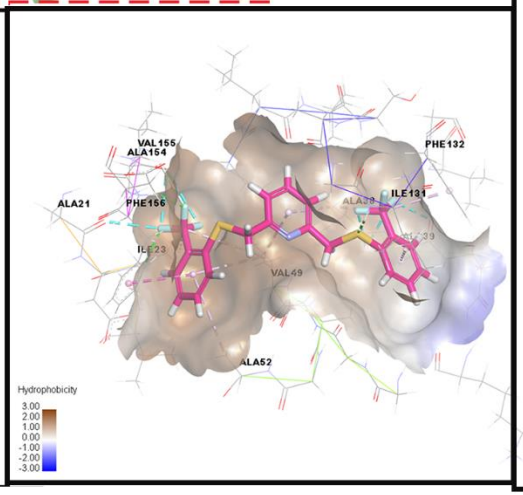


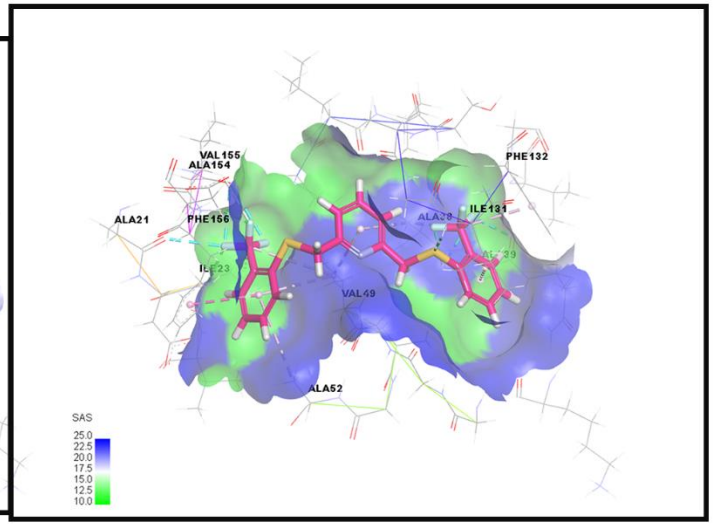
Nsp3(range 207-379-MES)



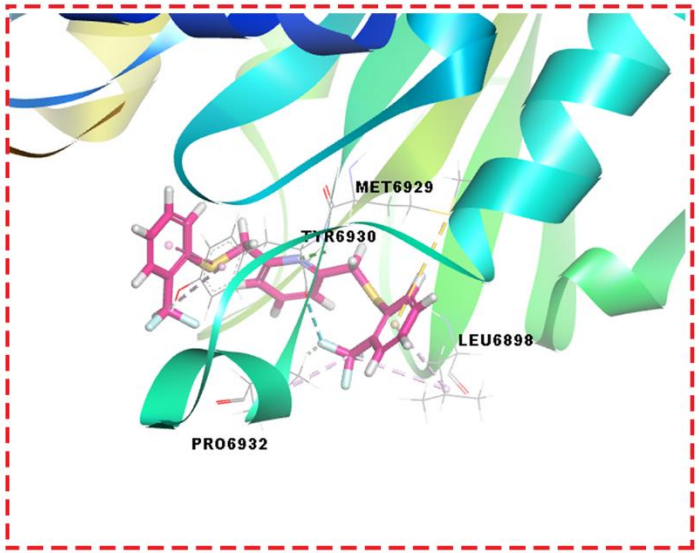


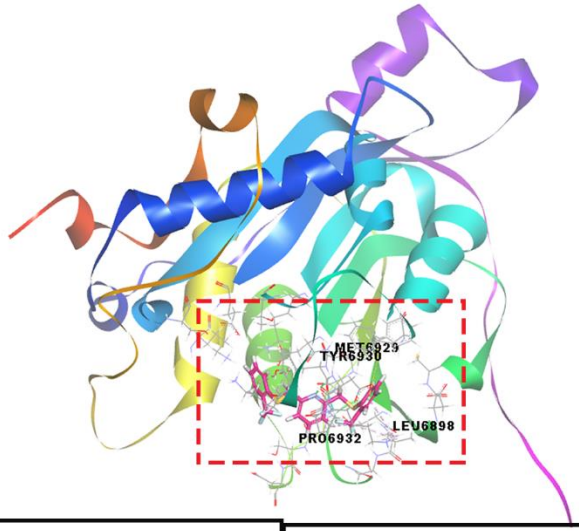


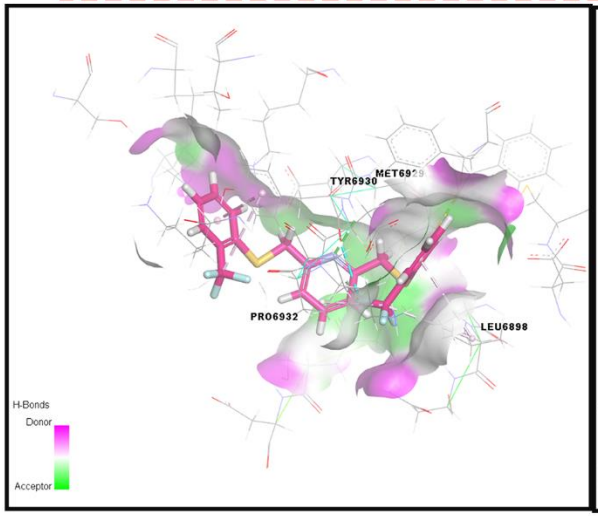


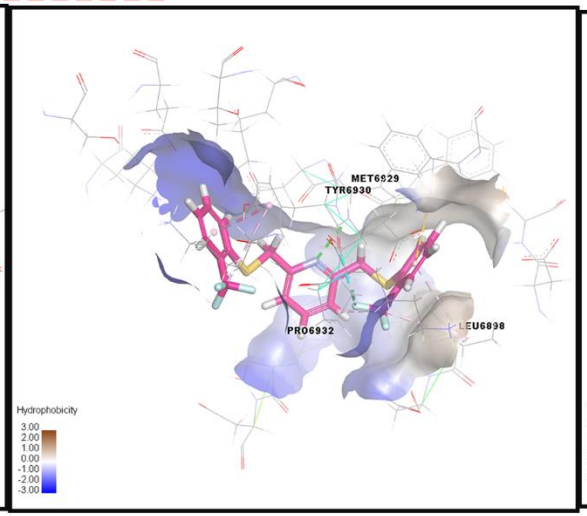


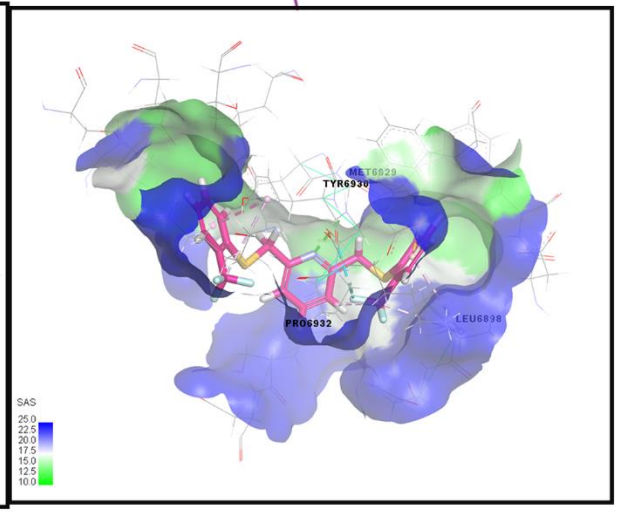
Nsp16(SAM site)



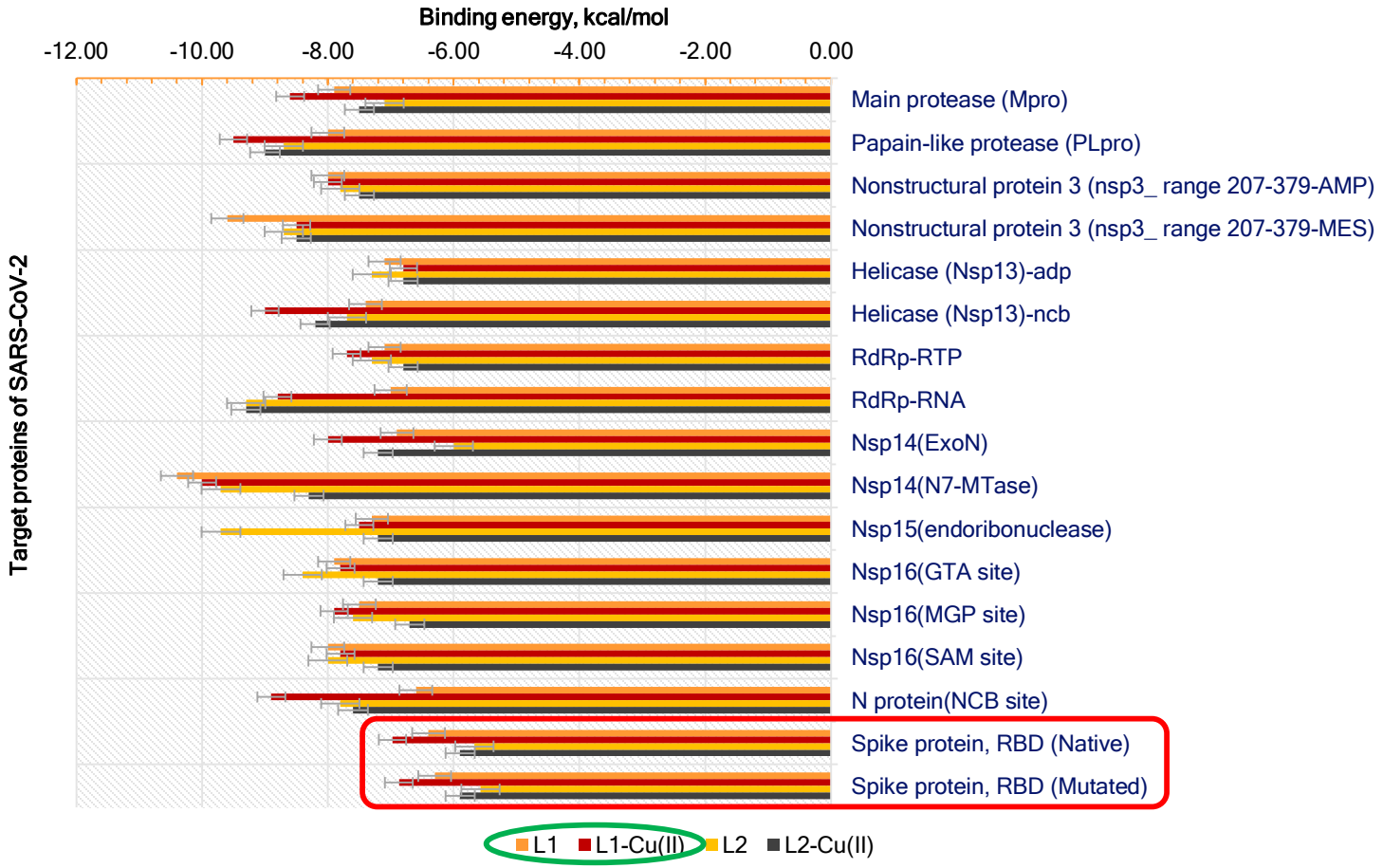






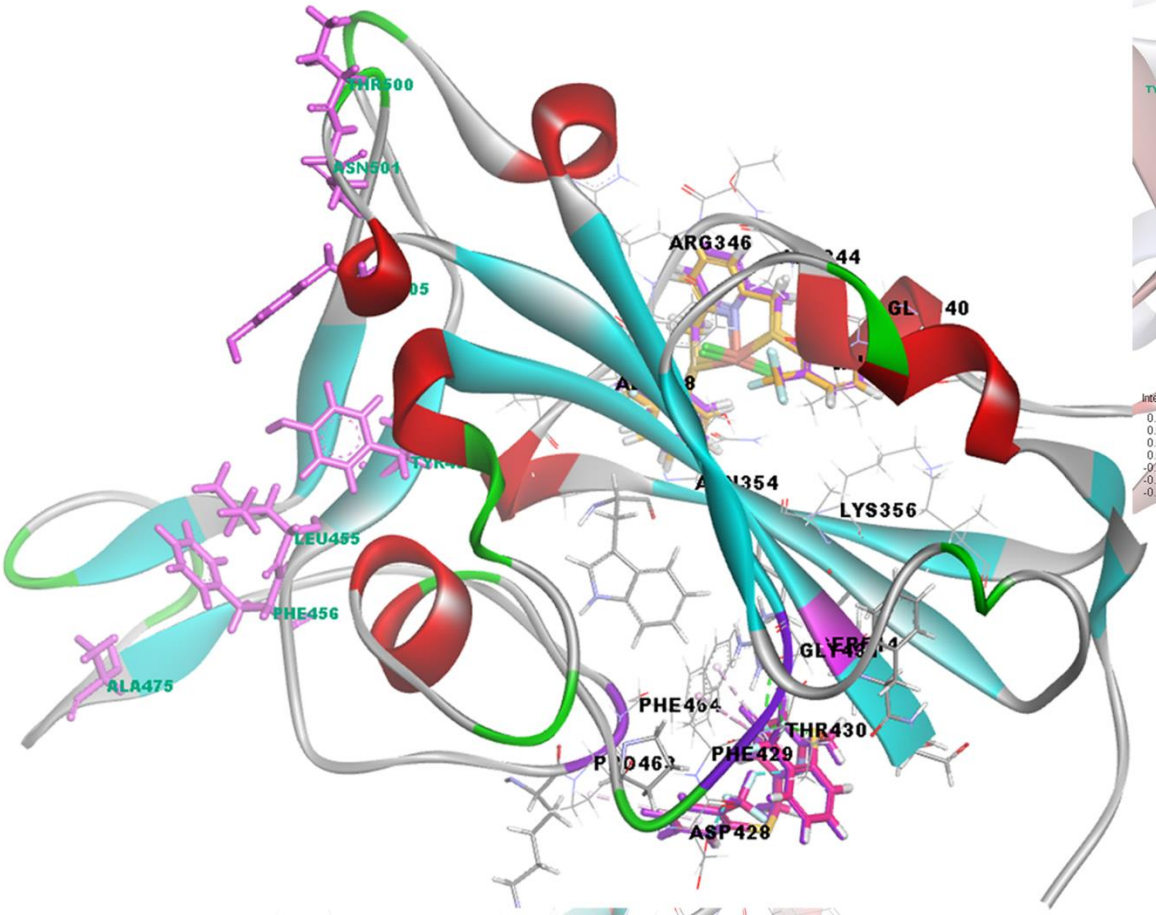


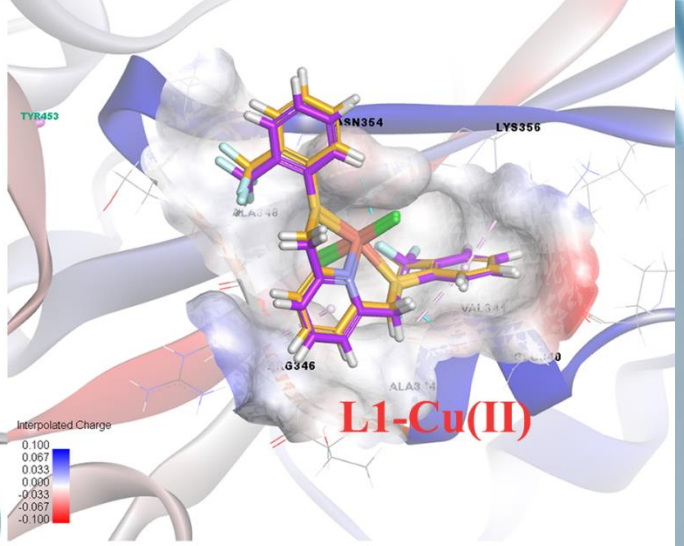
Binding Affinities of SNS pincer ligands and Cu(II) complexes against nsp and sp of SARS-CoV-2

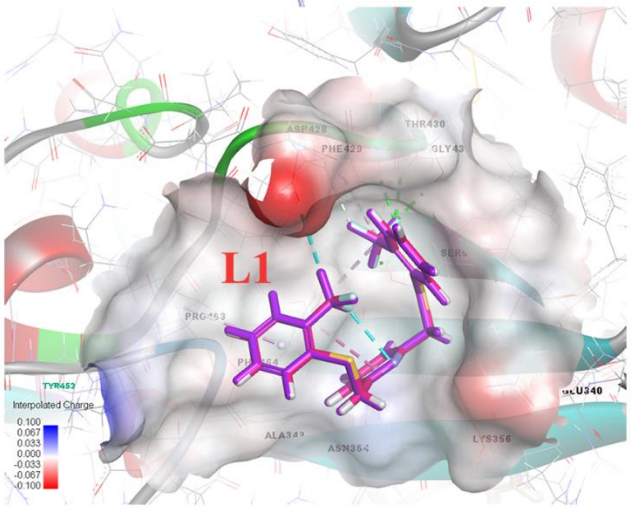


At this point, eight mutations (Y453F, L455F, F456L, A475V, A475S, T500S, N501Y, and Y505H) in the RBD and hACE2 interaction region (RBD/hACE2) were used to investigate the interaction mechanism of the reported compounds towards Spike protein, RBD as a target, [1].

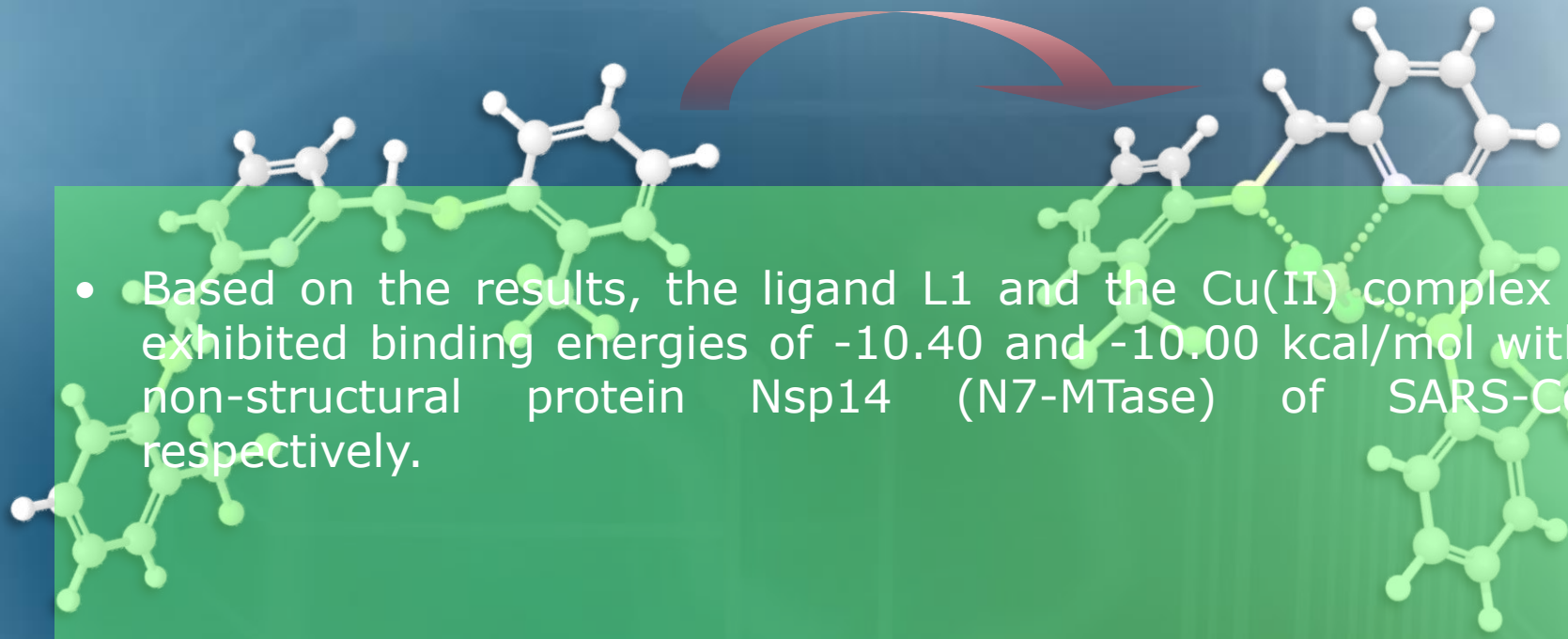
Ding, X.-C.; He, J.; Zhang, X.; Jiang, C.; Sun, Y.; Zhang, Y.; Chen, Q.; He, H.; Li, W.; Xie, J.; Liu, Z.; Gao, Y. Crucial Mutations of Spike Protein on SARS-CoV-2 Evolved to Variant Strains Escaping Neutralization of Convalescent Plasmas and RBD-Specific Monoclonal Antibodies. Front. Immunol. 2021, 12, 693775.







This shows that the activity of the related complex maintains the same in both conditions, as you can see from the 3D interaction Image, both in its poses and interactions. In the other words, this case indicates that the compound **L1-Cu(II)** and **L1** remains active against different states of the target and is unaffected,



- Based on the results, the ligand L1 and the Cu(II) complex were exhibited binding energies of -10.40 and -10.00 kcal/mol with the non-structural protein Nsp14 (N7-MTase) of SARS-CoV-2, respectively.

- On the contrary, while the L2 structure creates a binding tendency of -9.70 kcal/mol with Nsp14 (N7-MTase) protein, the Cu(II) complex of the L2 shows -9.30 kcal/mol binding energies with RdRp-RNA protein.

- These findings show that the ligand L1 and Cu(II) complex have a high potential inhibition against non-structural proteins and even also in the native and mutated form of Spike protein, which is one of the structural proteins of SARS-CoV-2.

- Based on the various findings of the related complexes, the development of these complexes may open up a new era of metallodrug. Although, there is still a lack of data and clinical trials to verify the efficacy and safety of metal-based drugs in curing COVID-19. Further researches and evaluations remain necessary.

Thank you for your interest