ARTICLE

Supporting Information for

Synthesis and characterization of novel copper (II) complexes as potential drug candidates against SARS CoV-2 main protease
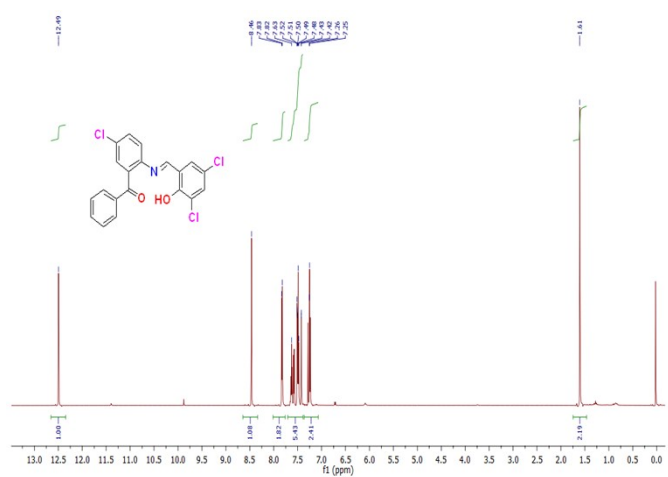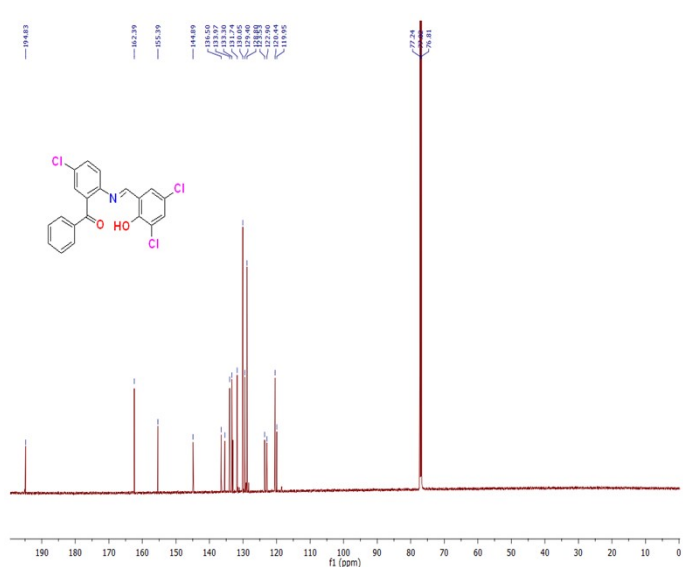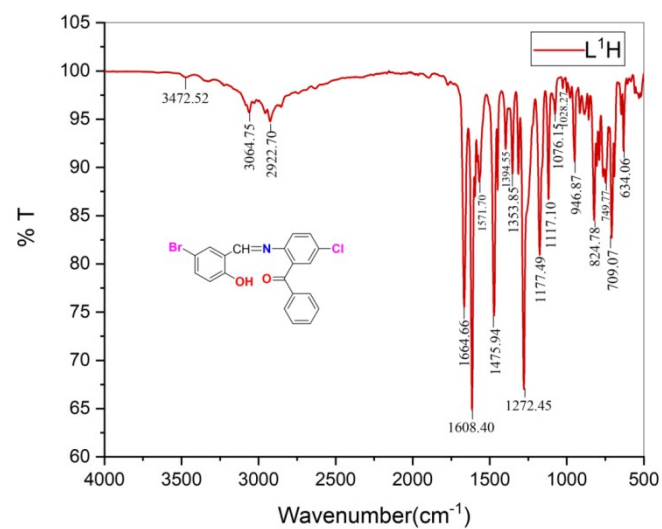
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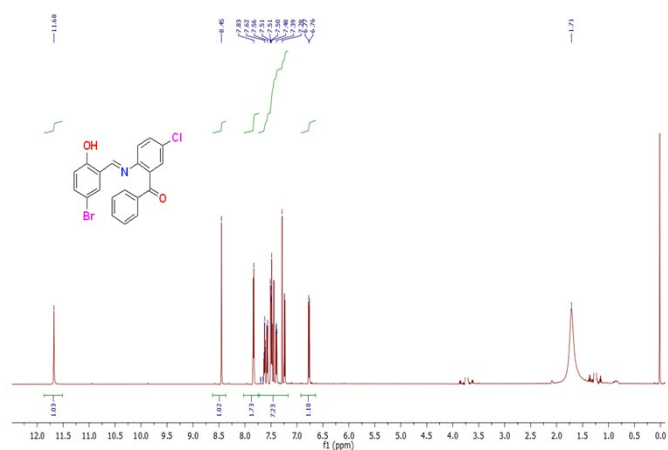
Figure S1. ^{1}H-NMR spectra of L[1]H ligand.
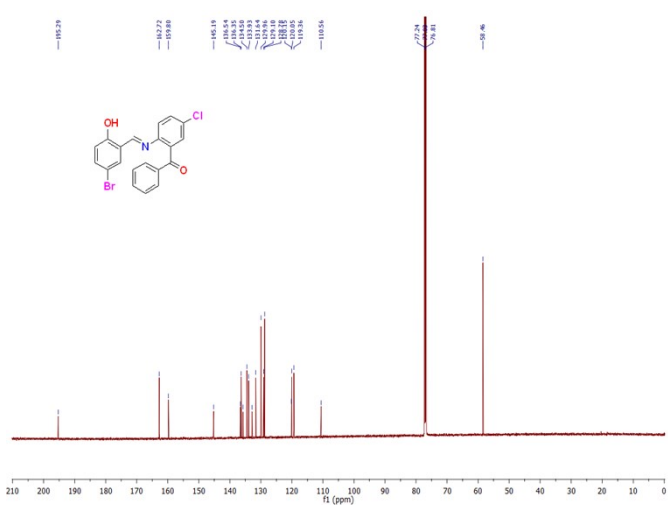
Figure S2. ^{13}C-NMR spectra of L[1]H ligand.

Figure S3. ^{1}H-NMR spectra of L[2]H ligand.

Figure S4. ^{13}C-NMRspectra of L[2]H ligand.

Figure S5. IR spectra of L[1]H ligand.
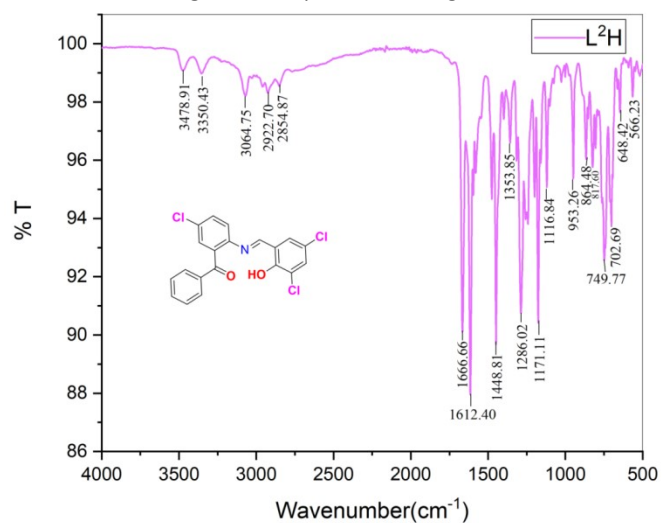
Figure S6. IR spectra of L[2]H ligand.
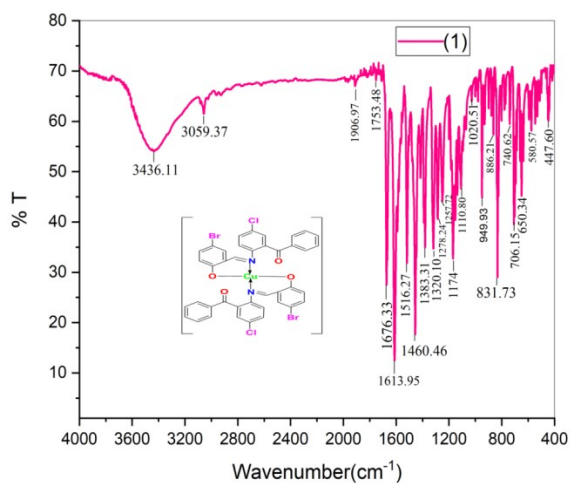
Figure S7. IR spectrum of copper(II) Schiff base complex [Cu(L^1)$_2$](**1**).
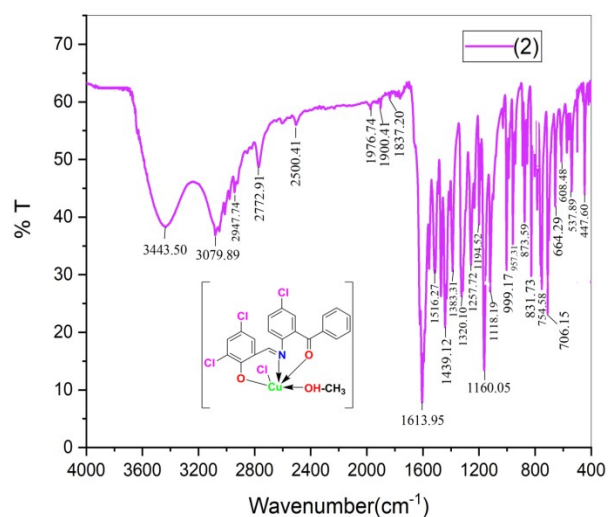
Figure S8. IR spectrum of copper(II) Schiff base complex [Cu(L^2)(CH$_3$OH)(Cl)](**2**).

Figure S10. A packing views (A & B) of copper (II) complex [Cu(L^1)$_2$](**1**)(along the a-axis).
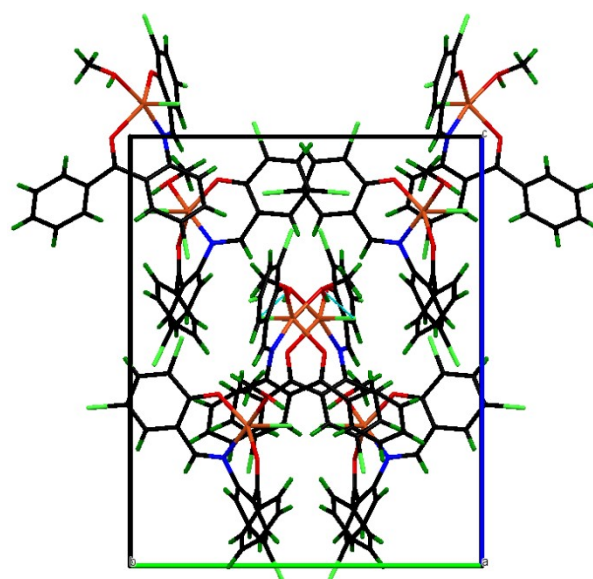
Figure S11. A packing view of copper (II) complex [Cu(L^2)(CH$_3$OH)(Cl)](**2**)(along the a-axis).

Figure S9. Electronic spectra (1×10^{-3}M) of copper (II) Schiff base complex [Cu(L^1)$_2$](**1**) and [Cu(L^2)(CH$_3$OH)(Cl)](**2**).
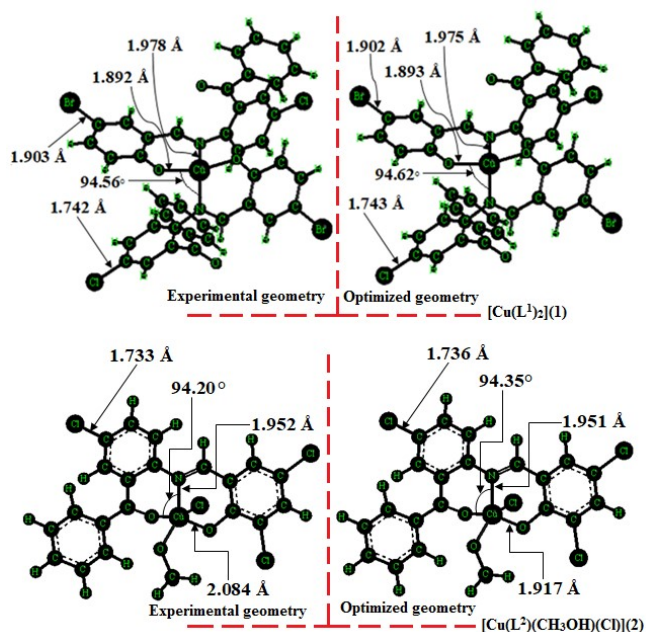
Figure S12. Experimental and optimized geometry of copper (II) complex [Cu(L^1)$_2$](**1**) and [Cu(L^2)(CH$_3$OH)(Cl)](**2**).
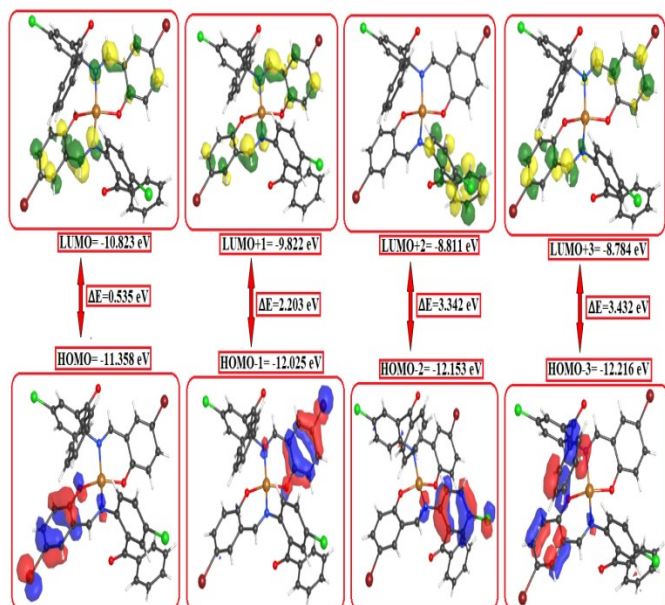
Figure S13 . Frontier molecular orbitals of copper (II) Schiff base complex [Cu(L^1)$_2$](**1**).
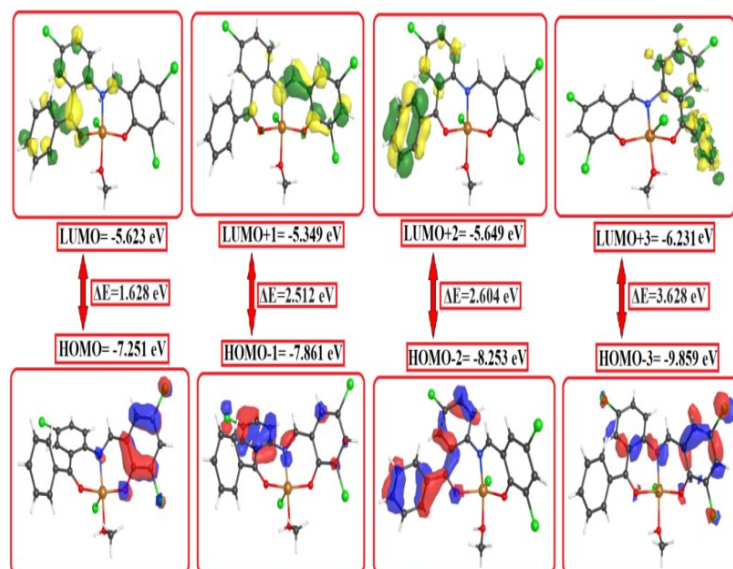
Figure S14. Frontier molecular orbital diagram of copper (II) complex [Cu(L^2)(CH$_3$OH)(Cl)](**2**).

Electrostatic Potential map

Radical Frontier density

Electrophilic(HOMO) Frontier density

Nucleophilic(LUMO) Frontier density
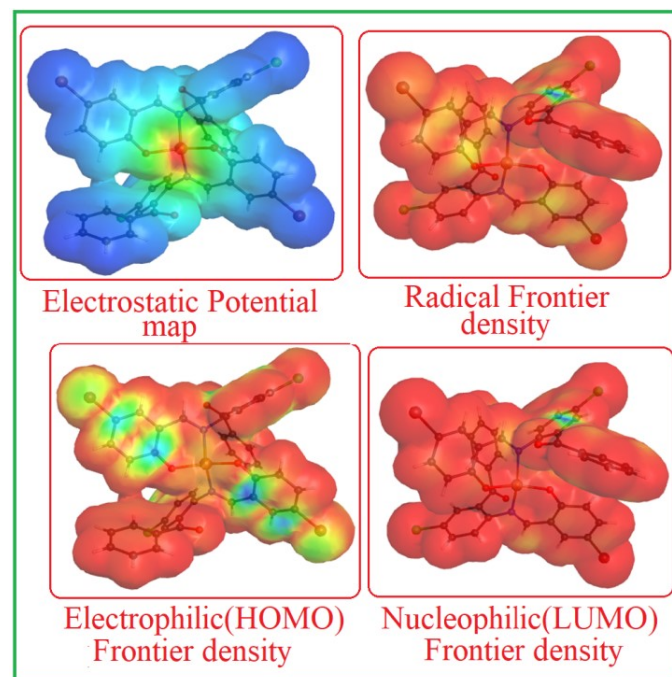
Figure S15. Electrostatic potential maps of copper (II) Schiff base complex [Cu(L^1)$_2$](**1**).
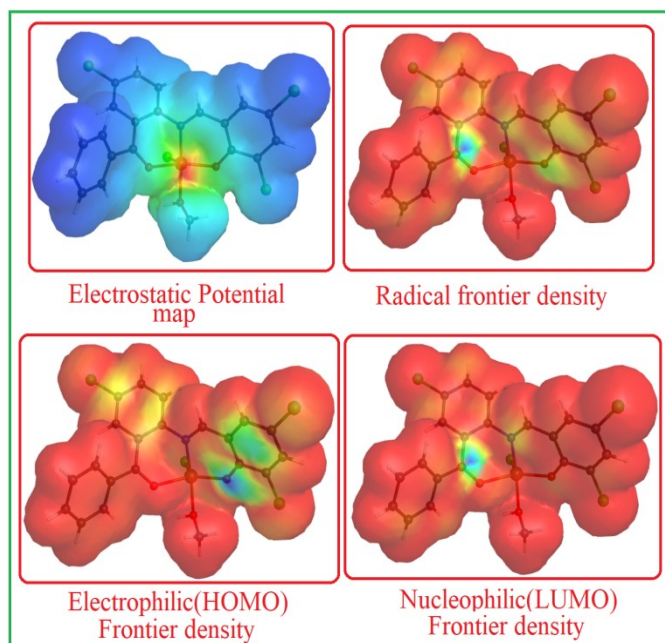
Figure S16. Electrostatic potential maps of copper (II) Schiff base complex [Cu(L^2)(CH$_3$OH)(Cl)](**2**).
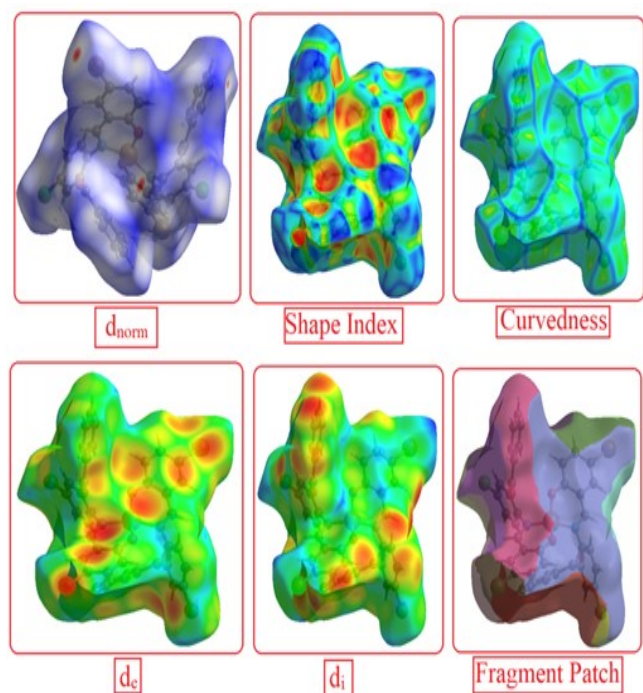
Figure S17. Graphical view of the Hirshfeld surfaces (full portion) mapped with d$_{norm}$ property; red spots represents the closest contacts and blue color the most distant contacts for copper (II) Schiff base complex [Cu(L^1)$_2$](**1**).

Figure S18. Graphical view of the Hirshfeld surfaces (full portion) mapped with d$_{norm}$ property; red spots represents the closest contacts and blue color the most distant contacts for copper (II) Schiff base complex [Cu(L^2)(CH$_3$OH)(Cl)](**2**).
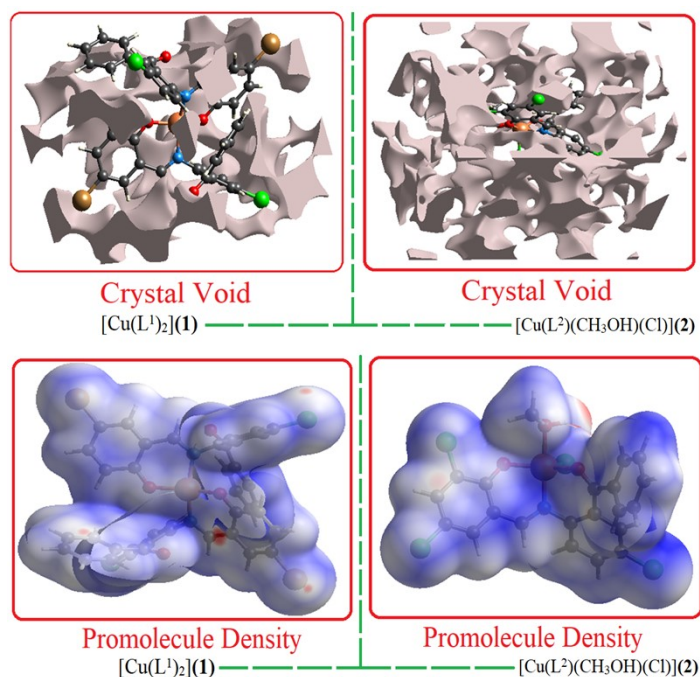
Figure S19. Crystal void and promolecule density surface of copper (II) Schiff base complex [Cu(L^1)$_2$](**1**) and [Cu(L^2)(CH$_3$OH)(Cl)](**2**).
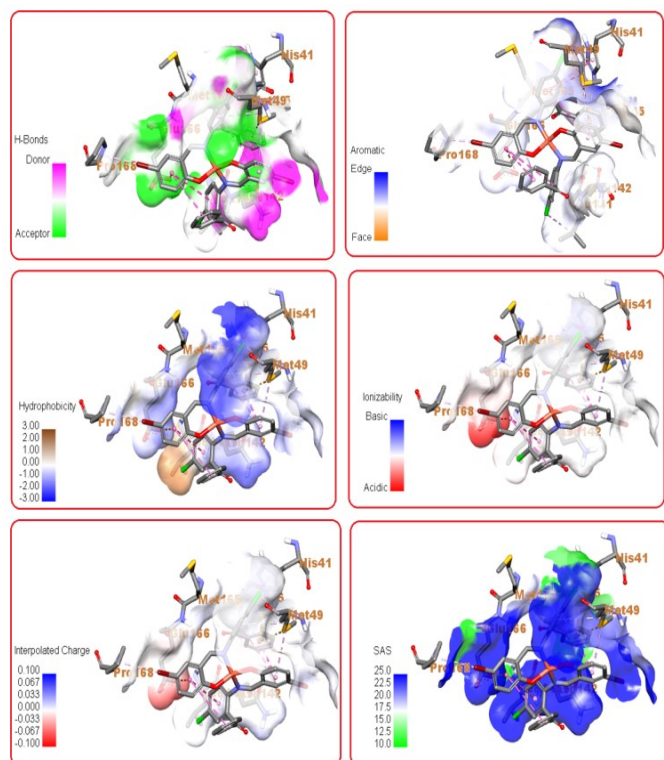
Figure S20. The representation of docked copper (II) complex [Cu(L^1)$_2$](**1**) inside the M^{pro} protein (PDB ID: 7BRP) with its focused view for interacting residues along with H bond and intermolecular interactions; (a) H-bond donor and acceptor meshes represented by pink and light green colours, respectively; (b) Aromatic receptor surface represented by blue(Edge) and orange(face) colours; (c) Hydrophobic pocket represented with blue and brown colours; (d) ionizability receptor surface represented by blue (basic) and red (acidic) colours; (e) interpolated charge receptor surface represented by blue and red colours; (f) SAS receptor surface represented by blue and green colours, respectively.
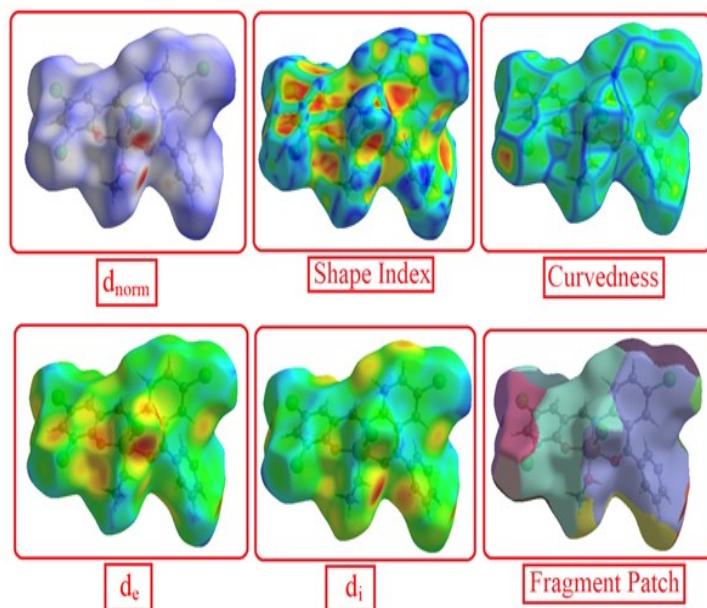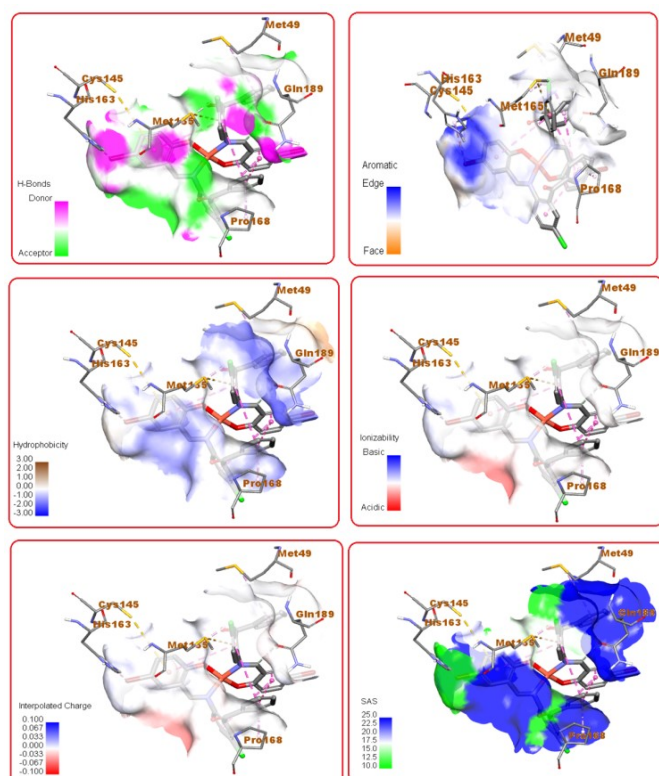
Figure S21. The representation of docked copper (II) complex [Cu(L^1)$_2$](**1**) inside the M^{pro}protein (PDB ID: 7BUY) with its focused view for interacting residues along with H-bond and intermolecular interactions; (a) H-bond donor and acceptor meshes represented by pink and light green colours, respectively; (b) Aromatic receptor surface represented by blue(Edge) and orange (face) colours; (c) Hydrophobic pocket represented with blue and brown colours; (d) ionizability receptor surface represented by blue (basic) and red (acidic) colours; (e) interpolated charge receptor surface represented by blue and red colours; (f) SAS receptor surface represented by blue and light green colours, respectively.

Figure S22. The representation of docked copper (II) complex[Cu(L^2)(CH$_3$OH)(Cl)](**2**) inside the M^{pro} protein (PDB ID: 7BUY) with its focused view for interacting residues along with H bond and intermolecular interactions; (a) H-bond donor and acceptor meshes represented by pink and light green colors, respectively; (b) Aromatic receptor surface represented by blue(Edge) and orange(face) colours; (c) Hydrophobic pocket represented with blue and brown colours; (d) ionizability receptor surface represented by blue (basic) and red (acidic) colours; (e) interpolated charge receptor surface represented by blue and red colours; (f) SAS receptor surface represented by blue and light green colours, respectively.
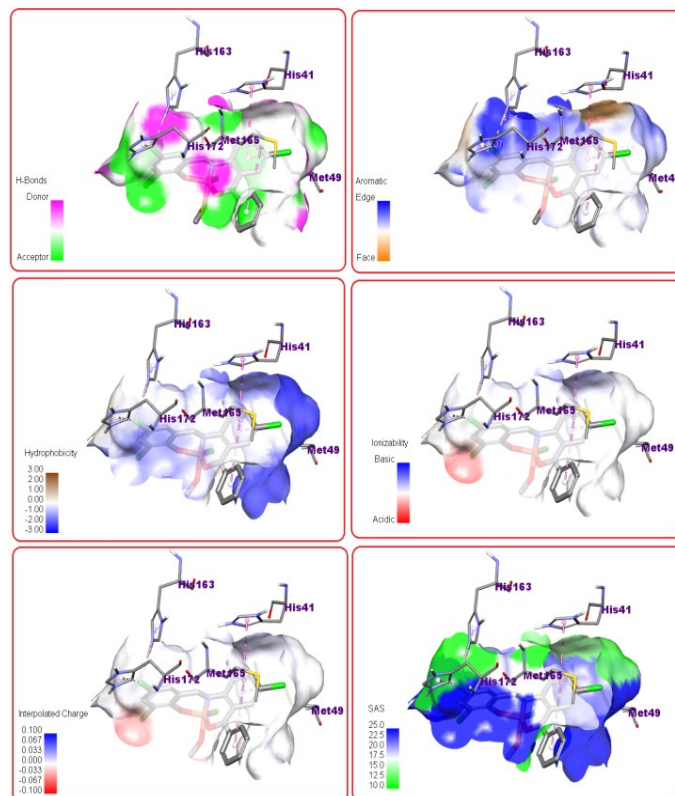
Figure S23. The representation of docked copper (II) complex[Cu(L^2)(CH$_3$OH)(Cl)](**2**) inside the M^{pro} protein (PDB ID: 7BRP) with its focused view for interacting residues along with H bond and intermolecular interactions; (a) H-bond donor and acceptor meshes represented by pink and light green colours, respectively; (b) Aromatic receptor surface represented by blue(Edge) and orange(face) colours; (c) Hydrophobic pocket represented with blue and brown colours; (d) ionizability receptor surface represented by blue (basic) and red (acidic) colours; (e) interpolated charge receptor surface represented by blue and red colours; (f) SAS receptor surface represented by blue and light green colours, respectively.
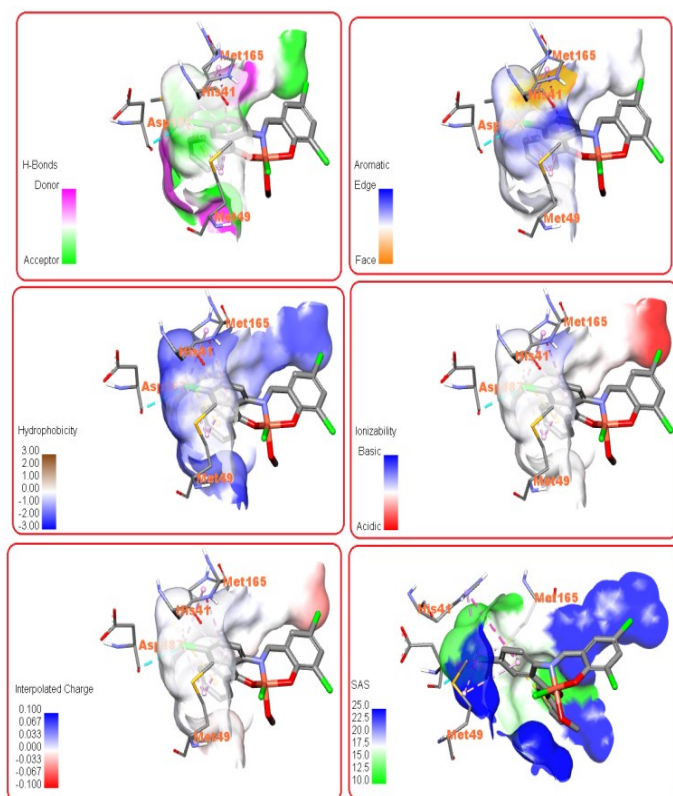
Figure S24. Two-dimensional Lig-plot image of complex $[Cu(L^1)_2]$ (**1**) with SARS-CoV-2 main protease (M^{pro}- 7BUY and 7BRP).

FigureS26. Graphical representation of antibacterial activity for the copper (II) Schiff base complex $[Cu(L^1)_2]$ (**1**) and $[Cu(L^2)(CH_3OH)(Cl)]$(**2**).

Table S1. Hydrogen bonds for copper (II) Schiff base complex $[Cu(L^1)_2]$(**1**) and$[Cu(L^2)(CH_3OH)(Cl)]$(**2**)[Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
(**1**)				
C(11)-H(11)...Br(1)#1	0.95	3.02	3.851(3)	147.0
C(29)-H(29)...Br(1)#2	0.95	3.07	3.960(3)	157.2
(**2**)				
C(14)-H(14)...O(2)#1	0.95	2.52	3.424(9)	158.1
O(3)-H(3A)...Cl(4)#2	0.84	2.20	3.018(5)	163.3

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z+2   #2 x,y+1,z for (**1**);

#1 y-1/2,-x+1,z-1/4   #2 -x+1,-y+1,z for (**2**)

Figure S25. Two-dimensional Ligplot image of the complex $[Cu(L^2)(CH_3OH)(Cl)]$(**2**) with SARS-CoV-2 main protease (M^{pro}- 7BUY and 7BRP).

Table S2. The computed values of E_{HOMO}, E_{LUMO} and energy gap $(E_{LUMO}-E_{HOMO})^a$ for complex $[Cu(L^1)_2]$(**1**) and$[Cu(L^2)(CH_3OH)(Cl)]$(**2**).
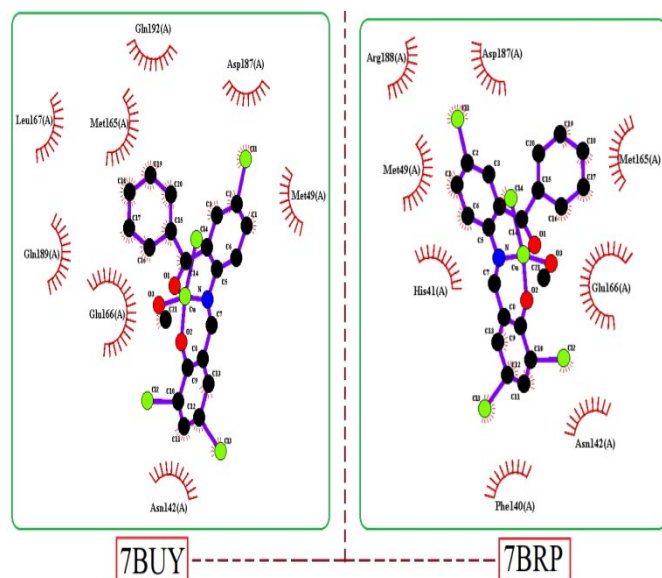
	(**1**)	(**2**)
E_{HOMO}	-11.358	-7.251
E_{LUMO}	-10.823	-5.623
ΔE	0.535	1.628
E_{HOMO-1}	-12.025	-7.861
E_{LUMO+1}	-9.822	-5.349
ΔE	2.203	2.512
E_{HOMO-2}	-12.153	-8.253
E_{LUMO+2}	-8.811	-5.649
ΔE	3.342	2.604

^{a} Energy gap (ΔE) = $E_{LUMO}-E_{HOMO}$; units in eV.

Table S3. Computed values for Global reactivity descriptors of the studied complex $[Cu(L^1)_2]$(**1**) and$[Cu(L^2)(CH_3OH)(Cl)]$(**2**).

	(**1**)	(**2**)
IP	11.358	7.251
EA	10.823	5.623
χ	11.091	6.437
η	0.634	0.407
μ	-11.091	-6.437
ω	97.011	50.903
σ	0.789	1.229

IP= ionization potential, *EA*= electron affinity, χ= electro negativity, *μ* =chemical potential, *η* = global hardness, *σ*=global softness and *ω*= global electrophilicity; units in *eV.*

Table S4. Interaction energies for complex $[Cu(L^1)_2]$ (**1**) calculated with CE-B3LYP model. It can be seen from the interaction energies that the hydrogen bonding motif between the central molecules (highlighted in yellow mesh) and the -x +1/2, y +1/2, z +1/2 symmetry-related molecule (line green) is by far the strongest interaction among near neighbours, with interaction energy of -41.2 kJ mol^{-1}.

Complex $[Cu(L^1)_2]$ (**1**)

	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	2	x, y, z	11.18	HF/3-21G	-11.9	-4.2	-52.6	23.0	-43.7
	1	-x, -y, -z	6.96	HF/3-21G	-27.7	-10.1	-111.7	52.3	-93.0
	2	x, y, z	12.55	HF/3-21G	0.0	-1.1	0.0	0.0	-0.7
	1	-x, -y, -z	10.07	HF/3-21G	-23.0	-6.6	-112.3	65.8	-75.5
	2	x, y, z	12.54	HF/3-21G	0.0	-0.9	0.0	0.0	-0.6
	1	-x, -y, -z	10.54	HF/3-21G	-16.7	-5.5	-57.0	30.6	-47.1
	1	-x, -y, -z	12.26	HF/3-21G	0.0	-3.2	0.0	0.0	-2.1
	1	-x, -y, -z	10.25	HF/3-21G	-20.5	-5.2	-95.5	58.7	-62.7
	1	-x, -y, -z	11.49	HF/3-21G	-7.3	-2.5	-44.1	21.3	-31.5
	1	-x, -y, -z	12.35	HF/3-21G	0.0	-1.9	0.0	0.0	-1.3
	1	-x, -y, -z	11.81	HF/3-21G	-1.6	-2.3	-15.2	5.1	-12.7

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-HF … HF/3-21G electron densities	1.019	0.651	0.901	0.811
CE-B3LYP … B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618

Table S5. Interaction energies for complex $[Cu(L^2)(CH_3OH)(Cl)]$(**2**) calculated with CE-B3LYP model. It can be seen from the interaction energies table that the hydrogen bonding motif between the central molecules (highlighted in yellow mesh) and the -x +1/2, y +1/2, z +1/2 symmetry-related molecule (line green) is by far the strongest interaction among near neighbors, with interaction energy of -44.6 kJmol^{-1}.

Complex $[Cu(L^2)(CH_3OH)(Cl)]$(**2**)

	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	1	-x, -y, z	8.45	HF/3-21G	-8.4	-2.6	-47.3	25.3	-32.3
	2	x+1/2, y+1/2, z+1/2	14.30	HF/3-21G	0.0	-1.8	0.0	0.0	-1.2
	2	-y, x+1/2, z+1/4	13.78	HF/3-21G	0.0	-0.5	0.0	0.0	-0.3
	2	y+1/2, -x, z+3/4	6.51	HF/3-21G	-60.7	-38.0	-67.9	46.0	-110.4
	2	-x+1/2, -y+1/2, z+1/2	12.95	HF/3-21G	0.0	-1.9	0.0	0.0	-1.2
	1	-x, -y, z	7.08	HF/3-21G	-183.6	-71.7	-76.0	150.3	-180.3
	2	-y, x+1/2, z+1/4	14.73	HF/3-21G	0.0	-0.4	0.0	0.0	-0.2
	2	-x+1/2, -y+1/2, z+1/2	11.34	HF/3-21G	-12.9	-2.1	-14.1	6.9	-21.6
	2	-y+1/2, x, z+3/4	7.87	HF/3-21G	8.6	-6.2	-33.2	13.5	-14.2

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-HF … HF/3-21G electron densities	1.019	0.651	0.901	0.811
CE-B3LYP … B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618

Table S6. The structure activity relationship established between the structures and their potential applications against SARS-CoV-2 main protease(M^{pro}) of the copper complex(II) $[Cu(L^1)_2]$(**1**) and $[Cu(L^2)(CH_3OH)(Cl)]$ (**2**)].

Complexes		Experimental bond lengths (Å)		Docked complex inside SARS-CoV-2 bond lengths (Å)	
(**1**)	7BUY	Cu(1)-O(1)	1.8926	Cu(1)-O(1)	1.8931
		Cu(1)-O(3)	1.8898	Cu(1)-O(3)	1.8902
		Cu(1)-N(1)	1.9738	Cu(1)-N(1)	1.9751
		Cu(1)-N(2)	1.9784	Cu(1)-N(2	1.9772
	7BRP	Cu(1)-O(1)	1.8926	Cu(1)-O(1)	1.8927
		Cu(1)-O(3)	1.8898	Cu(1)-O(3)	1.8899
		Cu(1)-N(1)	1.9738	Cu(1)-N(1)	1.9732
		Cu(1)-N(2	1.9784	Cu(1)-N(2	1.9779
(**2**)	7BUY	Cu(1)-O(1)	2.084	Cu(1)-O(1)	2.016
		Cu(1)-O(2)	1.917	Cu(1)-O(2)	1.918
		Cu(1)-O(3)	1.993	Cu(1)-O(3)	1.994
		Cu(1)-N(1)	1.952	Cu(1)-N(1)	1.954
	7BRP	Cu(1)-O(1)	2.084	Cu(1)-O(1)	2.082
		Cu(1)-O(2)	1.917	Cu(1)-O(2)	1.915
		Cu(1)-O(3)	1.993	Cu(1)-O(3)	1.995
		Cu(1)-N(1)	1.952	Cu(1)-N(1)	1.954

Table S7. Antibacterial screening activity of the copper(II) complex $[Cu(L^1)_2]$(**1**) and $[Cu(L^2)(CH_3OH)(Cl)]$ (**2**)].

Complexes (mM)	Diameter of inhibition zone (in mm)	
	E. coli	*S. aureus*
(**1**)		
5	8	7
10	11	9
15	19	14
(**2**)		
5	7	6
10	9	8
15	17	12
Antibiotic		
5	25	20
DMSO		
5	0	0

Note: Key to interpretation (5-15mM): less than 8 mm, inactive; 9-13 mm, moderately active; above 14 mm, highly active. DMSO (control) shows not clear inhibition zone. Each value is observed within the estimated error limits of ±1 mM.