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Casiopeinas® as SARS-CoV-2 main protease (M^{pro}) inhibitors. A combined DFT, molecular docking and ONIOM approach

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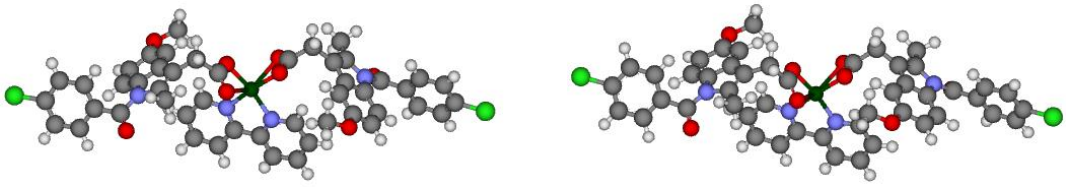
Table S1. Selected experimental and DFT (M06/LanL2DZ) estimated bond distances and angles of cooper compounds.

[Cu(indomethacin)$_2$(2,2'-bipyridine)]

X-Ray Diffraction Structure[1]	Optimized Structure

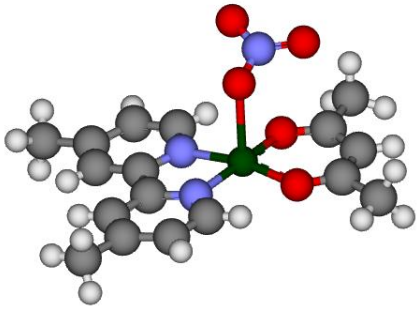
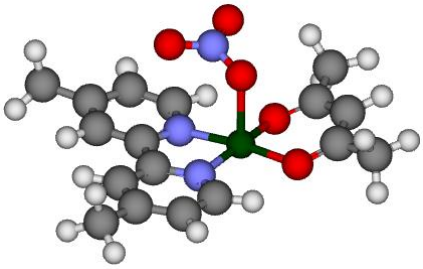


Bond/Distance	Experimental (Å/degrees)	DFT (Å/degrees)	%Error
Cu-N	1.997	2.009	0.60
Cu-N'	1.997	2.009	0.60
Cu-O	1.967	1.956	0.56

Cu-O’	2.551	2.586	1.37
Cu-O”	1.967	1.969	0.10
Cu-O”	2.551	2.666	4.51
N-Cu-N’	80.41	80.83	0.52
O-Cu-O’	94.69	93.28	1.49
N-Cu-O	92.84	93.08	0.26
N’-Cu-O’	92.84	93.68	0.90
O”’-Cu-O’	135.50	143.05	5.57
N’-Cu-O	170.20	169.94	0.15

[1] A. Tarushi, C. P. Raptopoulou, V. Psycharis, D. P. Kessissoglou, A. N. Papadopoulos and G. Psomas, *J. Inorg. Biochem*., 2014, 140, 185-198.

[Cu(acetylacetonate)(4,4’-dimethyl-2,2’bipyridine)]NO_3

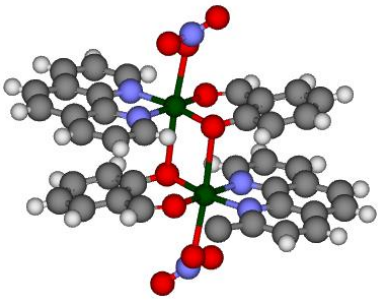
X-Ray Diffraction Structure[2]	Optimized Structure
	

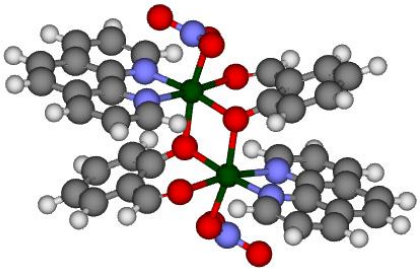
Bond/Distance	Experimental (Å/degrees)	DFT (Å/degrees)	%Error
Cu-N	1.995	1.995	0.00
Cu-N’	1.967	1.991	1.22
Cu-L	1.906	1.940	1.78
Cu-L’	1.911	1.945	1.78
N-Cu-N’	81.28	81.57	0.36
L-Cu-L’	94.98	93.01	2.07
N-Cu-L	91.02	91.80	0.86
N’-Cu-L’	91.83	93.08	1.36
N-Cu-L’	168.24	170.37	1.27
N’-Cu-L	171.49	173.34	1.08

[2] A. Tovar-Tovar, L. Ruiz-Ramirez, A. Campero, A. Romerossa, R. Moreno-Esparza, M. J. Rosales-Hoz, *J. Inorg. Biochem*., 2004, 98, 6, 1045-1053.

[Cu(salicylaldehydate)(1,10-phenanthroline)NO_3]$_2$

X-Ray Diffraction Structure[3]	Optimized Structure

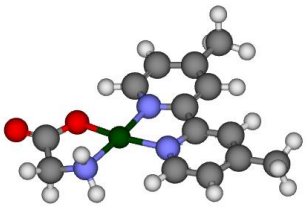




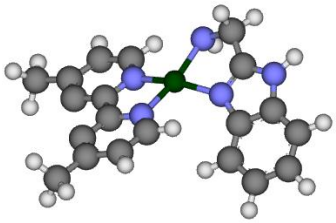
Bond/Distance	Experimental (Å/degrees)	DFT (Å/degrees)	%Error
Cu-N	1.999	1.978	1.05
Cu-N’	2.000	2.258	12.90
Cu-L	1.895	1.960	3.43
Cu-L’	1.953	2.355	20.58
N-Cu-N’	82.08	79.65	2.96
L-Cu-L’	93.38	82.81	11.32
N-Cu-L	91.96	97.21	5.71
N’-Cu-L’	92.94	100.64	8.28
N-Cu-L’	171.42	170.63	0.46
N’-Cu-L	173.70	176.20	1.44

[3] X. Solans, L. Ruiz-Ramírez, L. Gasque and J. L. Briansó, *Acta Cryst*., 1987, C43, 428-430

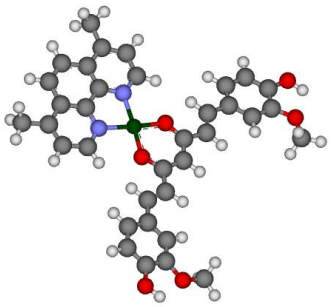
Figure S1. Compounds optimized (M06/LanL2Dz) structures.



CasIVgly

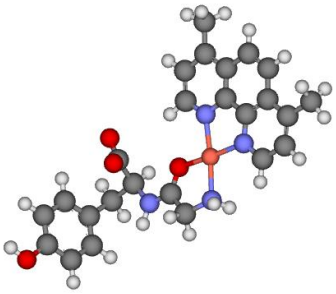


CasIV-ambz



CasII-cu

Curcumin



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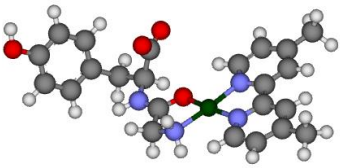

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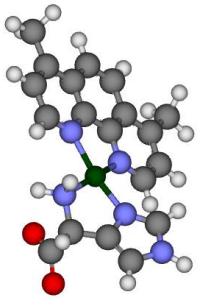
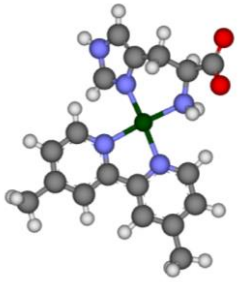


CasII-his



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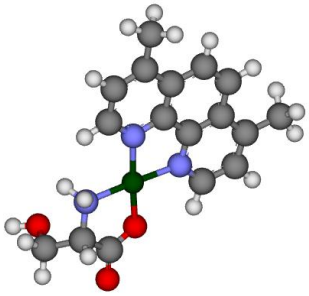	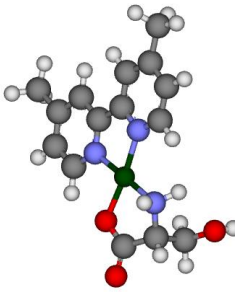	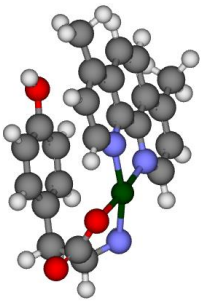	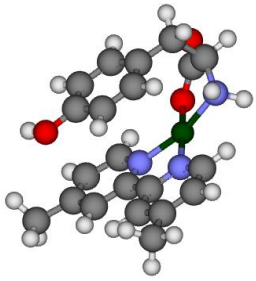
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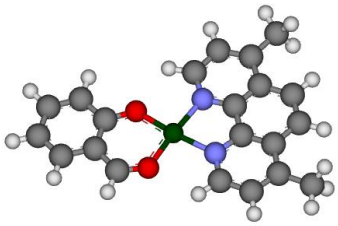	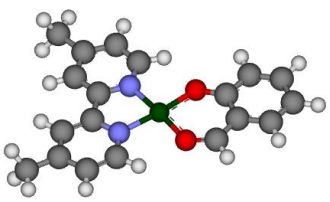	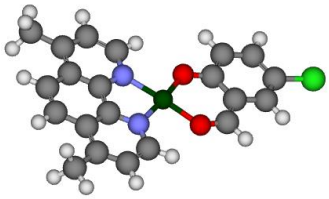	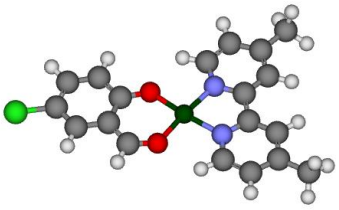
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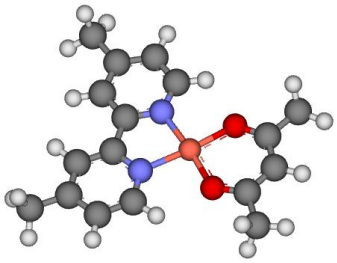	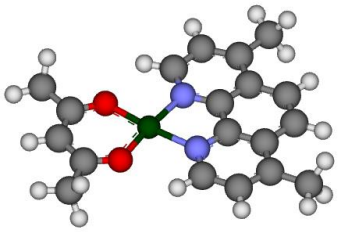	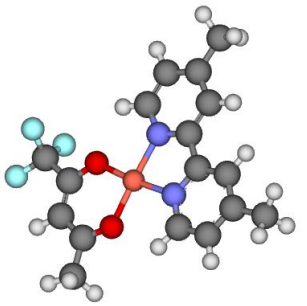	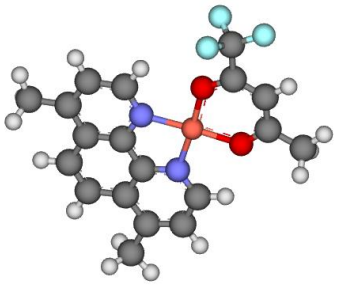
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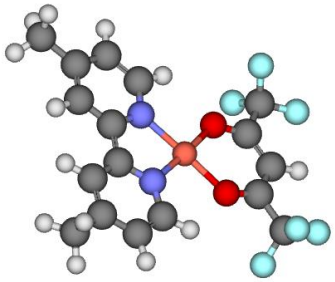	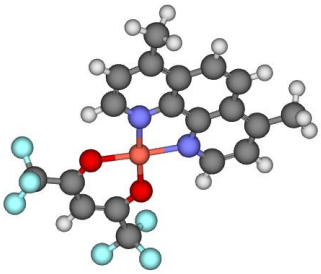	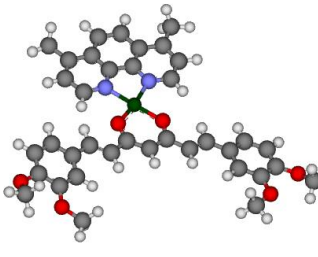	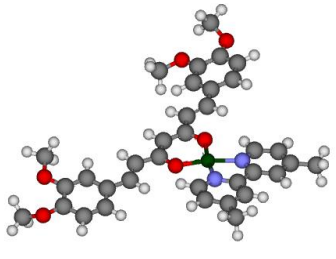
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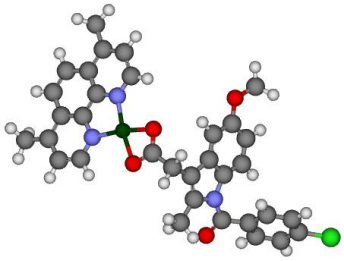	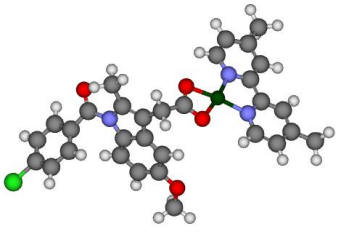	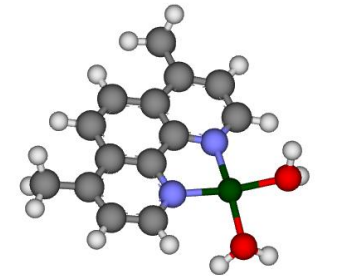	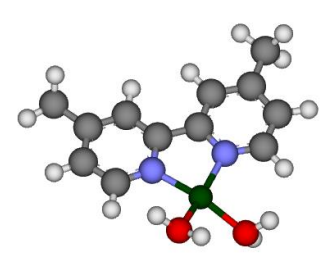
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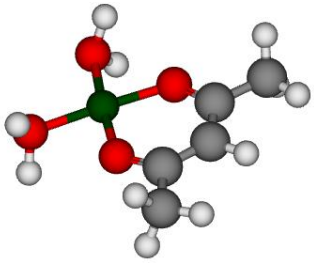	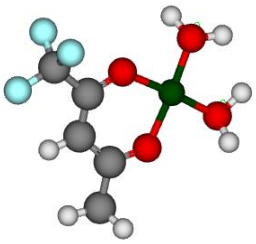	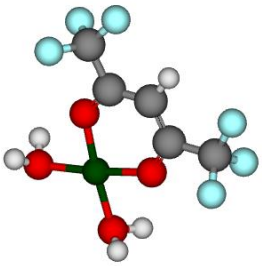	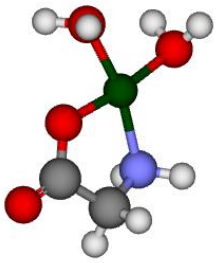
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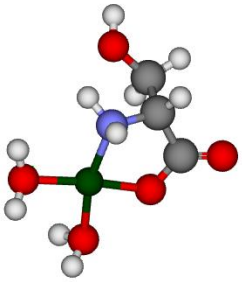
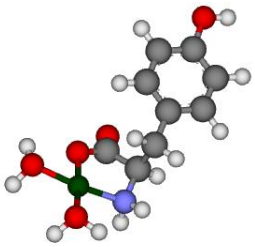
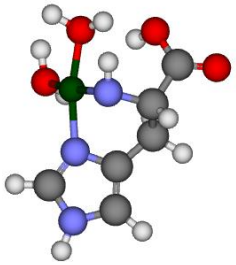
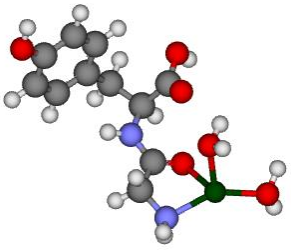
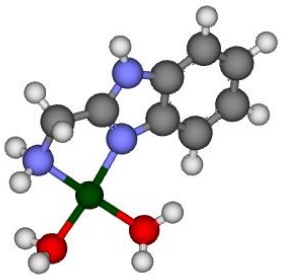
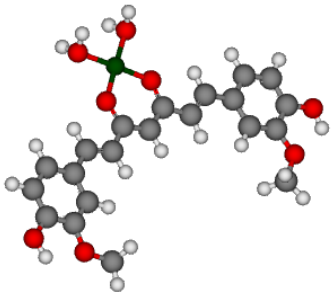
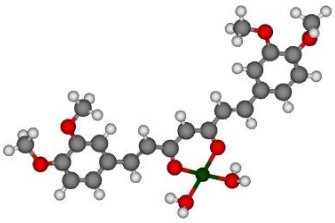
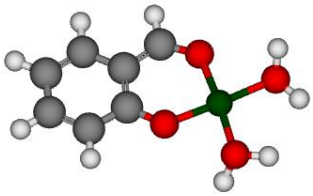
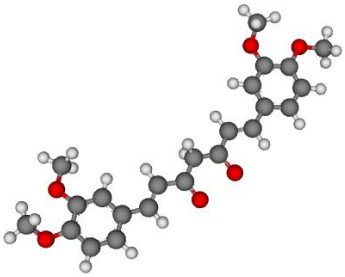
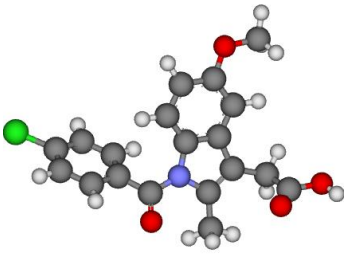
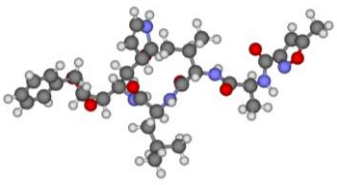
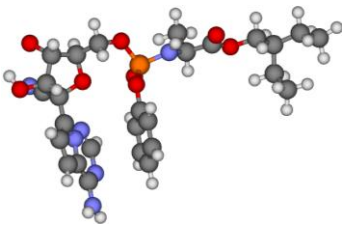
			
$[Cu(ser)(H_2O)_2]^{2+}$	$[Cu(tyr)(H_2O)_2]^{2+}$	$[Cu(his)(H_2O)_2]^{2+}$	$[Cu(GY)(H_2O)_2]^{2+}$
			
$[Cu(ambz)(H_2O)_2]^{2+}$	$[Cu(cu)(H_2O)_2]^{2+}$	$[Cu(dmcu)(H_2O)_2]^{2+}$	$[Cu(sa)(H_2O)_2]^{2+}$
			
Dimethoxycurcumin	Indomethacin	N3	Remdesivir

Table S2. Binding affinities, inhibition constants for docked M^{pro}-ligand adducts.

Casiopeinas®				**Monochelates**			
Compound	ΔG_U (kcal/mol)	Ki (mmol/L)	log Ki	Compound	ΔG_U (kcal/mol)	Ki (mmol/L)	log Ki
Cas-II-ambz	-8,84	0,33	-0,48	$[Cu(ambz)(H_2O)_2]^{2+}$	-4,99	220,20	2,34
Cas-IV-cu	-8,76	0,38	-0,42	$[Cu(cu)(H_2O)_2]^{+}$	-8,29	0,83	-0,08
Cas-II-5Clsa	-9,25	0,18	-0,74	$[Cu(sa)(H_2O)_2]^{+}$	-5,54	87,29	1,94
Cas-IV-sa	-8,64	0,46	-0,34	$[Cu(tyr)(H_2O)_2]^{+}$	-4,44	102,95	2,01
Cas-II-tyr	-8,58	0,51	-0,29	$[Cu(GY)(H_2O)_2]^{+}$	-5,99	40,76	1,61
Cas-II-cu	-8,53	0,56	-0,25	$[Cu(in)(H_2O)_2]^{+}$	-9,12	0,21	-0,68
Cas-IVGY	-8,51	0,58	-0,24	$[Cu(his)(H_2O)_2]^{+}$	-4,47	532,22	2,73
Cas-IV5Clsa	-8,37	0,73	-0,14	$[Cu(gly)(H_2O)_2]^{+}$	-3,92	1340	3,13
Cas-IV-ambz	-8,36	0,75	-0,13	$[Cu(ser)(H_2O)_2]^{+}$	-5,27	136,08	2,13
Caa-II-in	-8,17	1,03	0,01	$[Cu(dmcu)(H_2O)_2]^{+}$	-8,02	1,32	0,12
Cas-II-sa	-8,13	1,09	0,04	$[Cu(acac)(H_2O)_2]^{+}$	-5,30	129,65	2,11
Cas-IV-tyr	-8,13	1,31	0,12	$[Cu(tfa)(H_2O)_2]^{+}$	-4,77	319,23	2,50
Cas-IV-his	-7,94	1,50	0,18	$[Cu(hfa)(H_2O)_2]^{+}$	-4,27	735,56	2,87
Cas-IV-in	-7,80	1,92	0,28	$[Cu(47dmfen)(H_2O)_2]^{2+}$	-7,14	5,85	0,77
Cas-II-gly	-7,79	1,94	0,29	$[Cu(44dmbp)(H_2O)_2]^{2+}$	-7,14	5,87	0,77
Cas-IV-dmcu	-7,59	2,73	0,44	**BAHD**			
Cas-III-ia	-7,56	2,86	0,46	Compound	DG_U (kcal/mol)	Ki (mmol/L)	log Ki
Cas-III-Ea	-7,53	3,04	0,48	Indomethacin	-7,42	3,62	0,56
Cas-III-Ea-tfa	-7,51	3,14	0,50	Curcumin	-5,74	62,42	1,80
Cas-II-GY	-7,38	3,91	0,59	Dimetoxycurcumin	-5,42	107,07	2,03
Cas-III-ia-tfa	-7,37	3,94	0,60	**M^{pro} inhibitors**			
Cas-III-Ea-hfa	-7,32	4,31	0,63	Compound	DG_U (kcal/mol)	Ki (mmol/L)	log Ki
Cas-II-ser	-7,22	5,12	0,71	Bocepevir	-8,44	0,65	-0,19
Cas-II-hys	-7,20	5,23	0,72	Remdesivir	-7,17	5,53	0,74
Cas-IV-gly	-7,13	5,93	0,77	N3	-4,89	262,34	2,42
Cas-IV-ser	-7,05	6,77	0,83				
Cas-III-ia-hfa	-7,03	6,98	0,84				
Cas-II-dmcu	-7,01	7,23	0,86				

Figure S2. Estimated energy binding of Cas-M^{pro} complexes

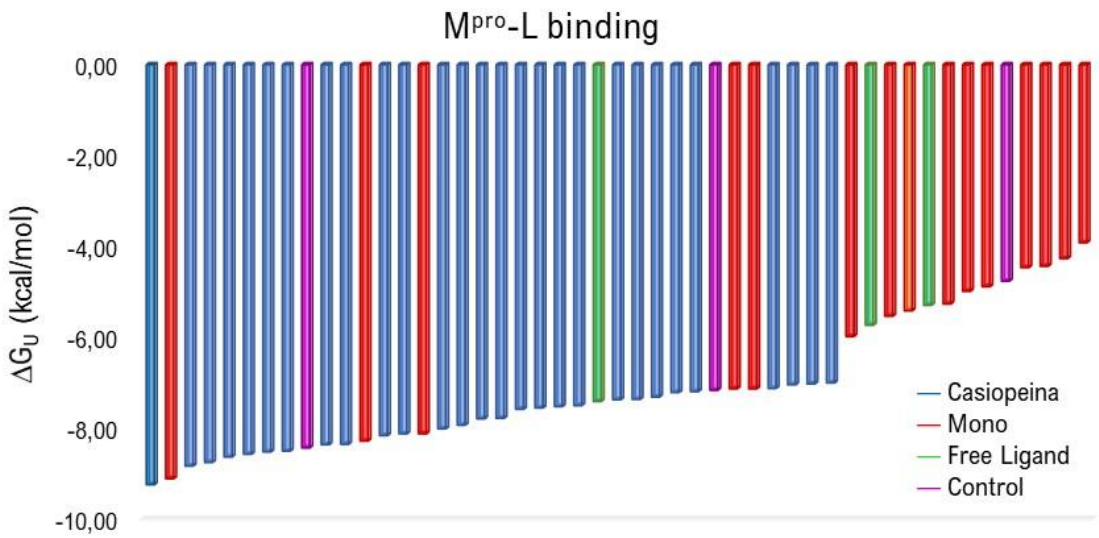
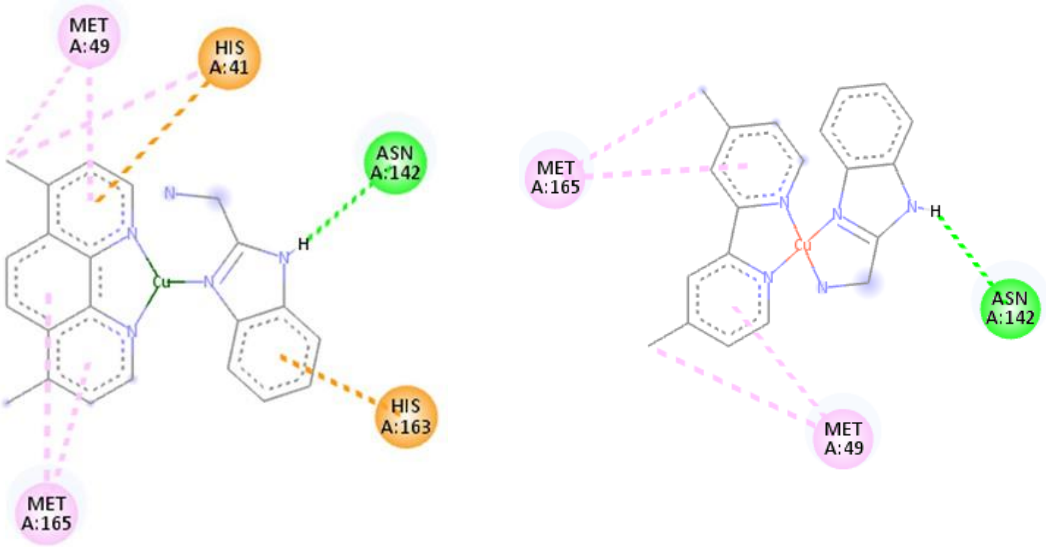
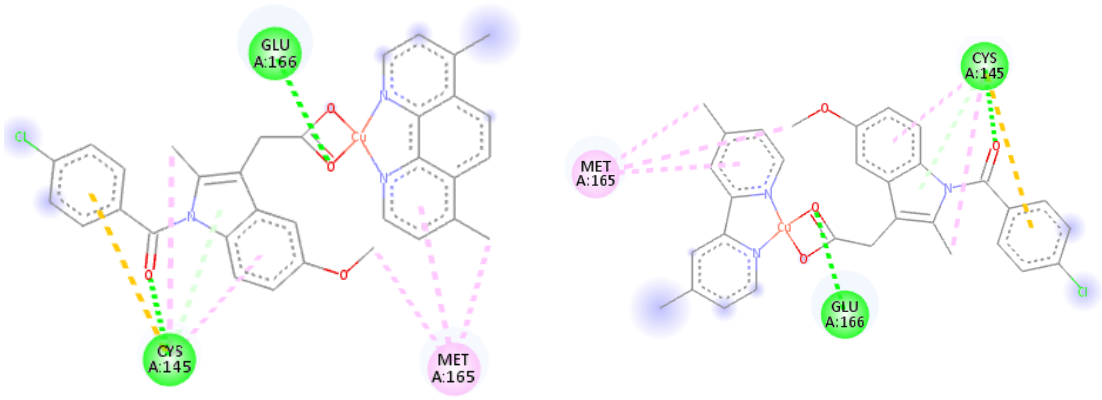


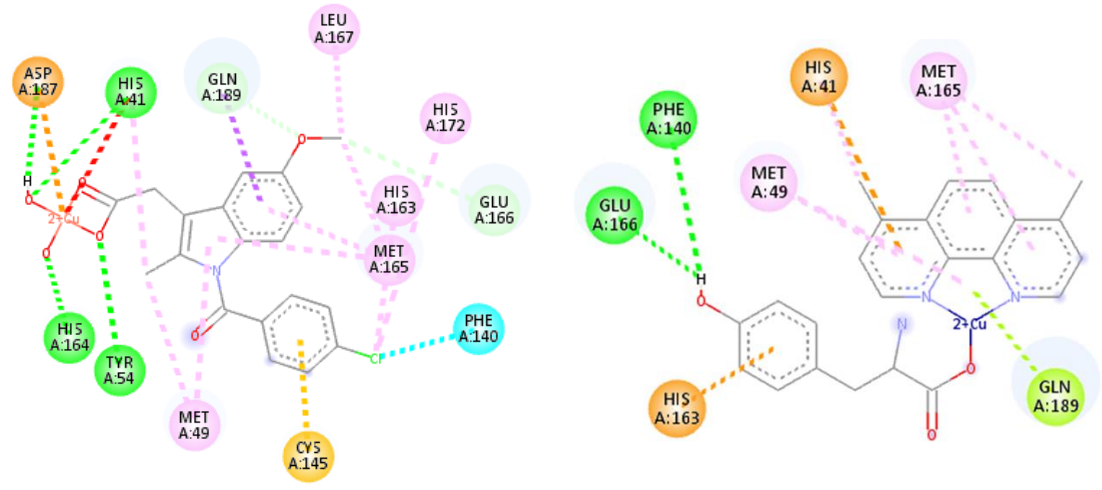
Figure S3. 2D Diagrams of stabilizing interactions of 2-aminomethylbencimidazol and indothetacin derivatives with M^{pro} active site. CasII-ambz(top-left), CasIV-ambz(top-right), CasII-in(bottom-left) and CasIV-in(bottom-right)





Compound	ΔG_U (Kcal/mol)	Ki (mmol/L)
CasII-ambz	-8.84	0.33
CasIV-ambz	-8.36	0.75
CasII-in	-8.17	1.03
CasIV-in	-7.80	1.92

Figure S4. 2D Diagrams of stabilizing interactions of some best rated copper compounds. $[Cu(indomethacin)(H_2O)_2]^+$ (top-left), CasII-tyr (top-right) and CasIV-sa (bottom).



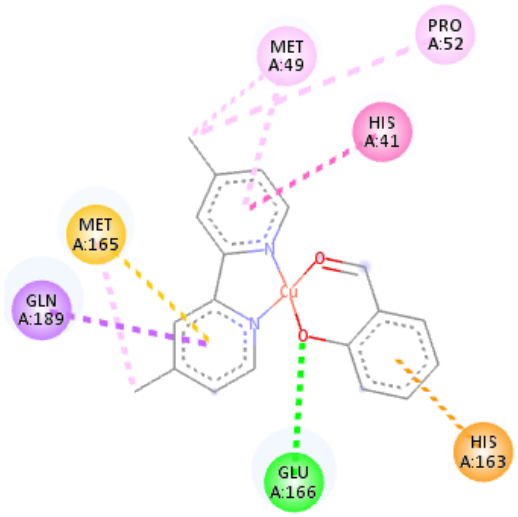


Figure S5. Stabilizing interactions in CasII-dmcu:M^{pro}. Docking simulations suggest the presence of Cu-O(Gln189) coordination bond.

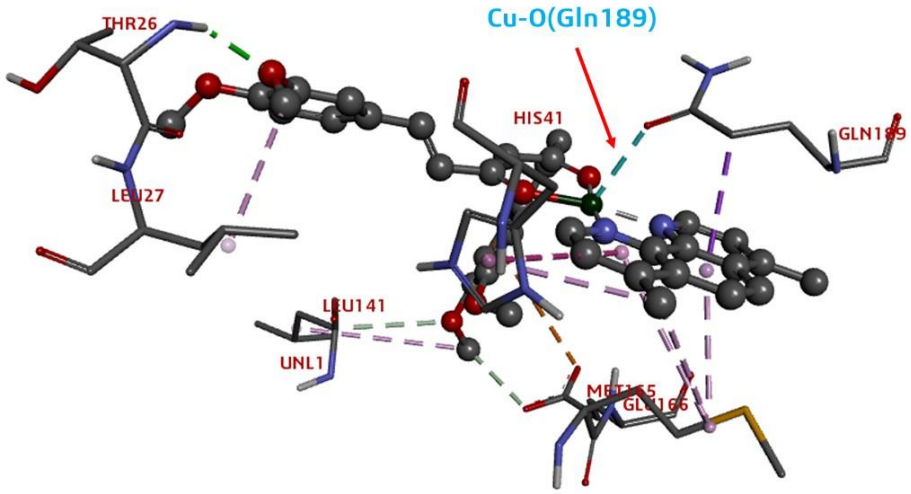
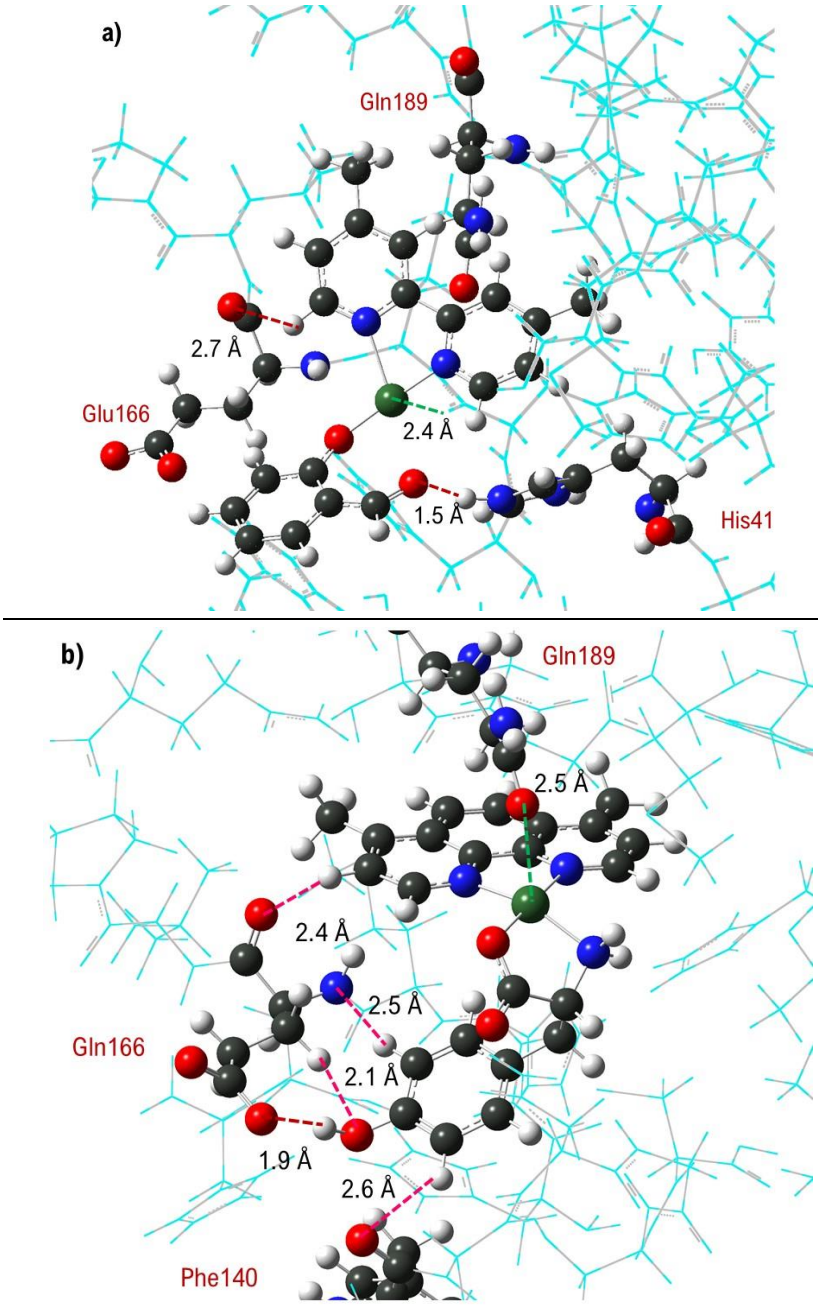
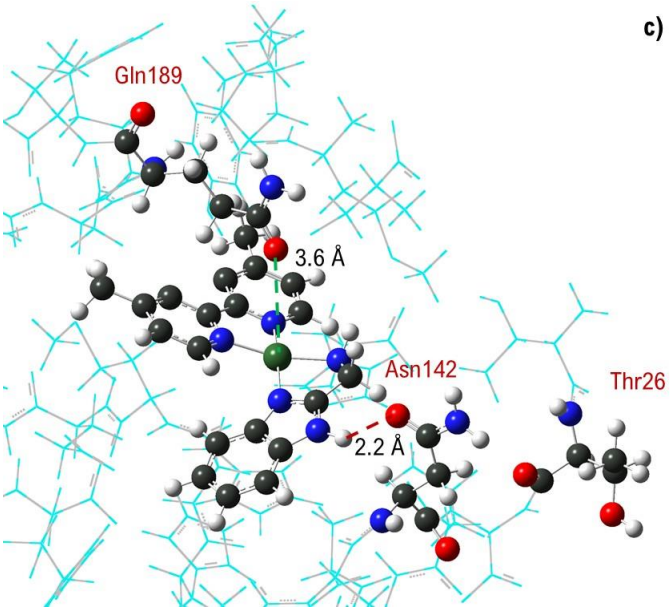


Figure S6. Close-ups of the ONIOM high layer for the complexes of M^{Pro}_{pocket} with a) CasIV-sa, b)CasII-tyr and c) CasIV-ambz




c)
Gln189
3.6 Å
Asn142
Thr26
2.2 Å