Supplementary Information

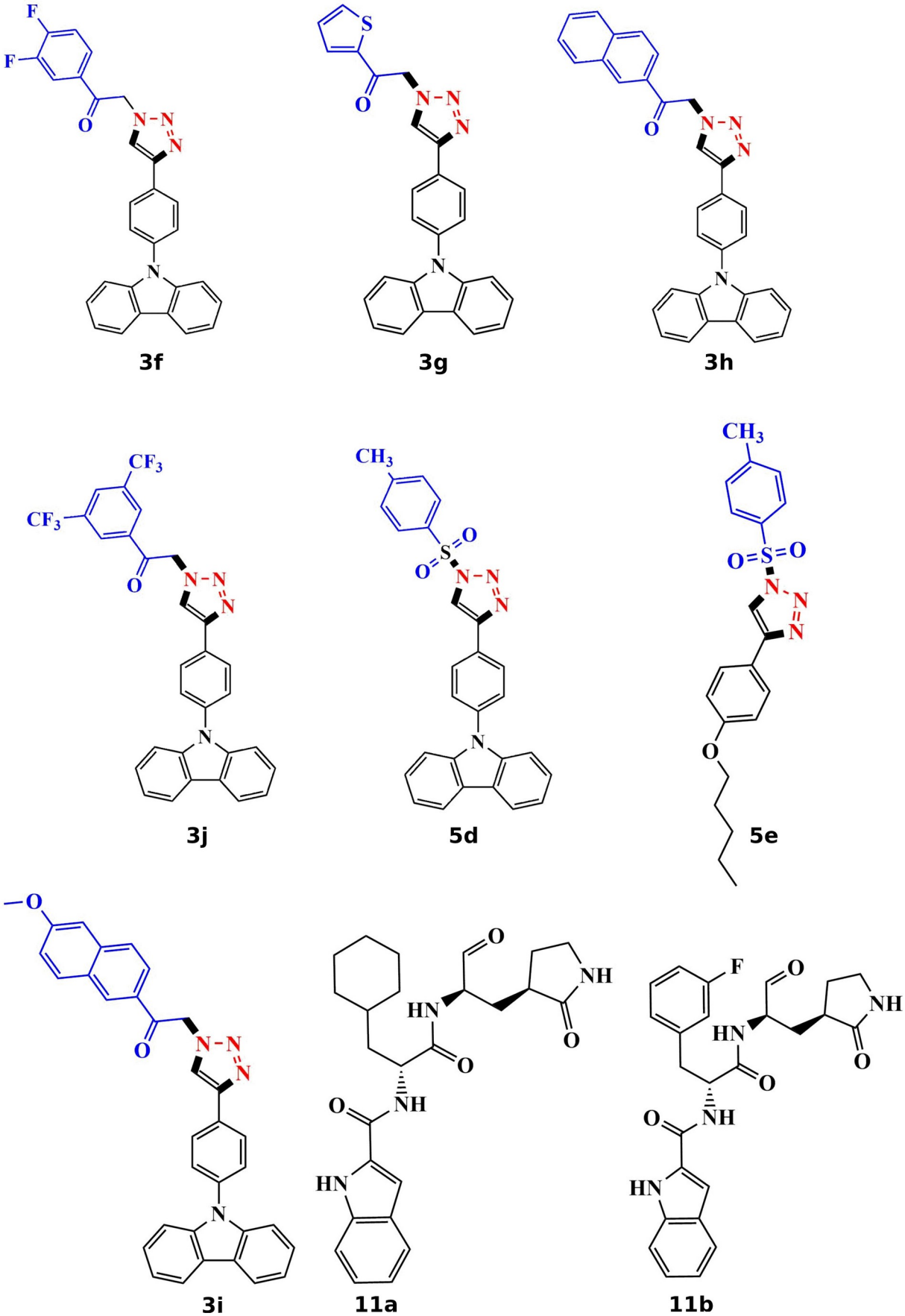

Figure S1: Structure of 1,2,3-triazole scaffolds and two co-crystallized inhibitors of M^{pro} protein.

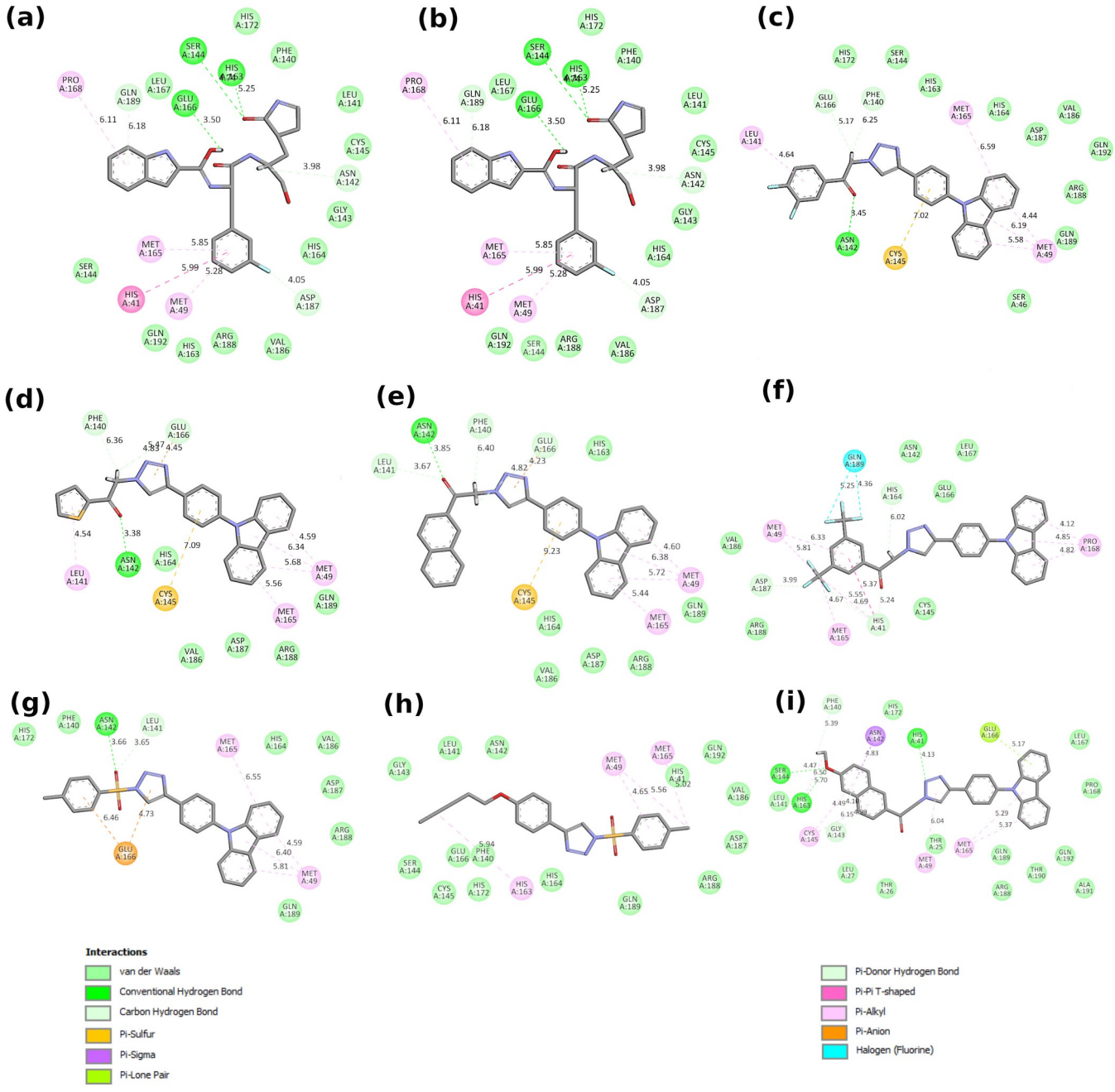

Figure S2: 2-D interactions of SARS-CoV-2 Mpro complexes with co-crystallized and 1,2,3-triazole scaffolds (a) 11a, (b) 11b, (c) 3f, (d) 3g, (e) 3h, (f) 3j, (g) 5d, (h) 5e, and (i) 3i.

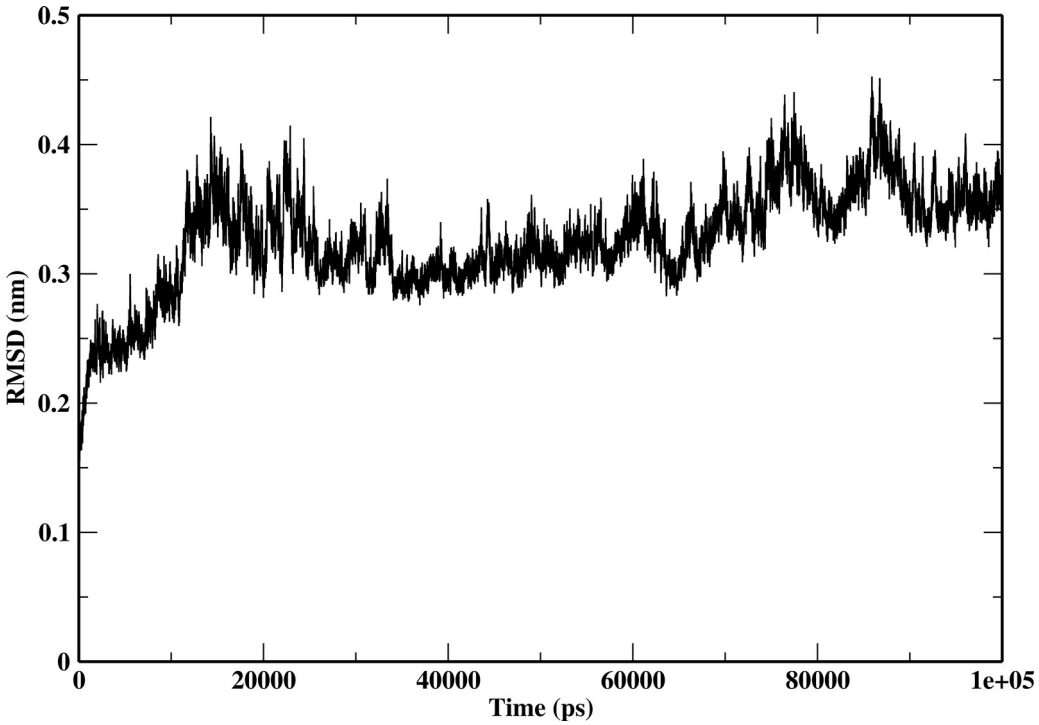

Figure S3: Backbone RMSD shown as a function of time for the apo-M^{pro} protein.

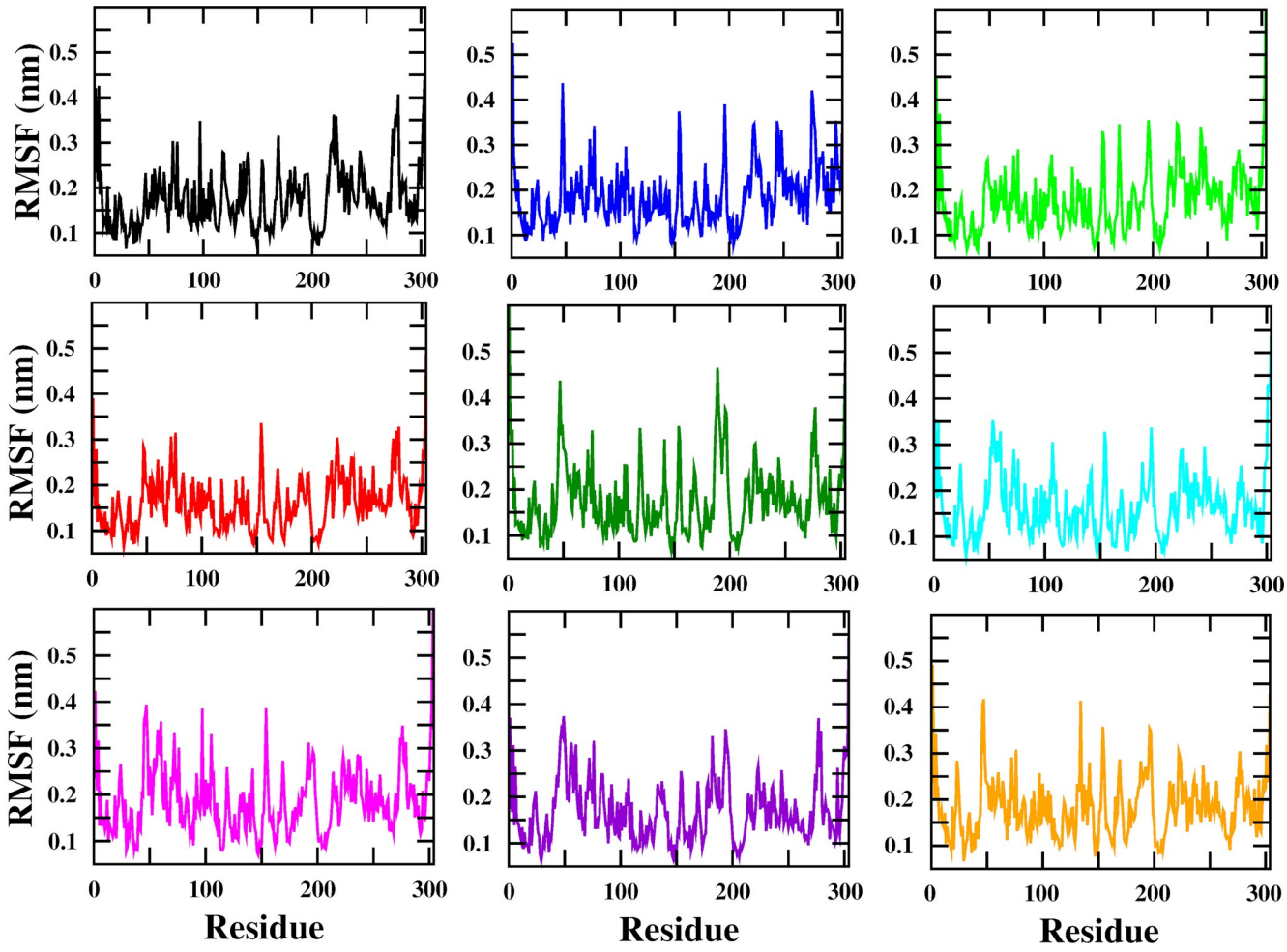

Figure S4: RMSF for the backbone C α-atoms of Mpro complexes with 11a (black), 11b (blue), 3f (green), 3g (red), 3h (dark green), 3j (cyan), 5d (magenta), 5e (violet), and 3i (yellow).

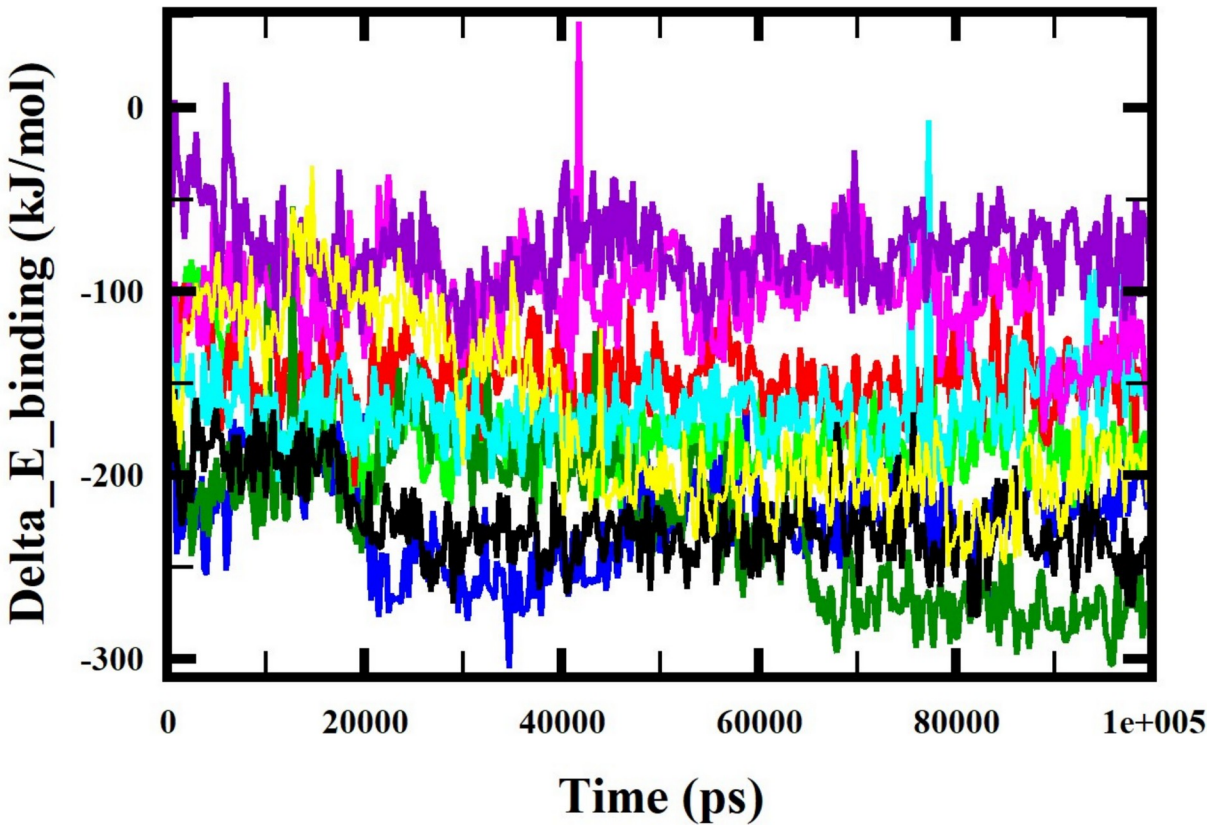

Figure S5: Graphical representation of the Delta_E_Binding free energy kJ/mol showing 11a (black), 11b (blue), 3f (green), 3g (red), 3h (dark green), 3j (cyan), 5d (magenta), 5e (violet), and 3i (yellow).

Table S1. Residues responsible for the difference in binding free energy of co-crystallized inhibitors and 3h molecule.

Residues	3h	11a	11b
LEU-27	-5.74	-3.26	-2.96
HIS-41	-4.58	-4.77	-2.75
SER-46	-2.65	-1.05	-1.11
MET-49	-3.47	-8.99	-7.92
CYS-117	-2.5	-0.41	-0.44
TYR-118	-2.95	-0.27	-0.75
ASN-119	-4.04	0.02	0.81
GLY-120	-1.46	0	0.04
LEU-141	-8.03	-1.63	-4.33
ASN-142	-4.16	-2.86	-4.24
HIS-164	-2.35	-3.85	-6.33
MET-165	-9.72	-15.45	-13.33
GLU-166	-3.22	-1.86	2.15
LEU-167	-4.97	-3.32	-5.12
PRO-168	-4.97	-2.53	-3.3
HIS-164	-2.35	-3.85	-6.33
MET-165	-9.72	-15.45	-13.33
GLU-166	3.22	-1.86	2.15
LEU-167	-4.97	-3.32	-5.12
PRO-168	-4.97	-2.53	-3.3
ASP-187	-0.74	-4.34	-2.74
ARG-188	-0.22	-1.62	-0.09
GLN-189	-0.89	-10.6	-6.63
THR-190	-1.06	-3.08	-3.43
ALA-191	-1.09	-2.07	-1.95

Table S2. Quantum-mechanical quasi-harmonic configurational entropy values for the selected complexes.

S. No.	Complexes	Entropy (J/mol K)
1.	M^{pro}-11a	34283.7
2.	M^{pro}-11b	33971.5
3.	M^{pro}-3h	34681.1