Supplementary Information of the article of

"Proposal of novel natural inhibitors of severe acute respiratory syndrome coronavirus 2 main protease: Molecular docking and *ab initio* fragment molecular orbital calculations",

Divya Shaji, Shohei Yamamoto, Ryosuke Saito, Ryo Suzuki, Shunya Nakamura, and Noriyuki Kurita

Contents

Figure S5 IFIEs (kcal/mol) between the Mpro residues and compound 4 for three clusters, and an interacting structure between the Mpro residues and compound 4 in the cluster 4. Electrostatic interactions are indicated by blue lines.

Figure S6 IFIEs (kcal/mol) between the Mpro residues and compound 5 for three clusters, and an interacting structure between the Mpro residues and compound 5 in the cluster 2. Electrostatic interactions are indicated by blue lines.

Figure S7 IFIEs (kcal/mol) between the Mpro residues and compound 6 for three clusters, and an interacting structure between the Mpro residues and compound 6 in the cluster 1. Hydrogen bonding and electrostatic interactions are indicated by red and blue lines, respectively.

Figure S8 IFIEs (kcal/mol) between the Mpro residues and compound 7 for three clusters, and an interacting structure between the Mpro residues and compound 7 in the cluster 2. Electrostatic interactions are indicated by blue lines.

Figure S9 IFIEs (kcal/mol) between the Mpro residues and compound 8 for three clusters, and an interacting structure between the Mpro residues and compound 8 in the cluster 2. Hydrogen bonding and electrostatic interactions are indicated by red and blue lines, respectively.

Figure S10 IFIEs (kcal/mol) between the Mpro residues and compound 9 for three clusters, and an interacting structure between the Mpro residues and compound 9 in the cluster 6. Hydrogen bonding and electrostatic interactions are indicated by red and blue lines, respectively.

Figure S11 IFIEs (kcal/mol) between the Mpro residues and compound 10 for three clusters, and an interacting structure between the Mpro residues and compound 10 in the cluster 2. Hydrogen bonding, electrostatic, and NH-π interactions are indicated by red, blue, and orange lines, respectively.

Figure S12 IFIEs (kcal/mol) between the Mpro residues and compound 11 for three clusters, and an interacting structure between the Mpro residues and compound 11 in the cluster 1. Hydrogen bonding and electrostatic interactions are indicated by red and blue lines, respectively.

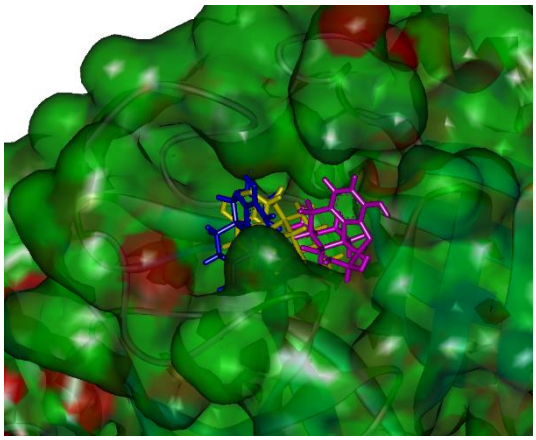
Figure S13 IFIEs (kcal/mol) between the Mpro residues and compound 12 for three clusters, and an interacting structure between the Mpro residues and compound 12 in the cluster 2. Hydrogen bonding, electrostatic, and NH-π interactions are indicated by red, blue, and orange lines, respectively.

Table S1 Chemical properties of the 12 compounds contained in *Moringa oleifera*. Their PubChem ID, molecular weight (MW), number of rotatable bonds (RB), number of H-bond acceptors (HBA), number of H-bond donors (HBD), octanol-water partition coefficient (LogP), and total polar surface area (TPSA) calculated by SwissADME web tool [23]. The number of rotatable bonds (RB) is counted by omitting the bonds connected to the hydrogen atoms.

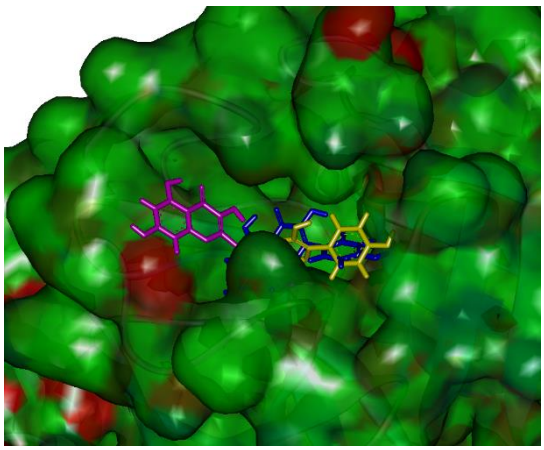
Compound	PubChem ID	MW (g/mol)	RB	HBA	HBD	LogP	TPSA (Å²)
(1) Morphine	5288826	285.3	0	4	2	1.41	52.93
(2) Kaempferol	5280863	286.2	1	6	4	1.58	111.13
(3) Quercetin	5280343	302.2	1	7	5	1.23	131.36
(4) Pterygospermin	72201063	406.5	4	2	0	3.75	89.12
(5) Benzoic acid	243	122.1	1	2	1	1.44	37.30
(6) Gallic acid	370	170.1	1	5	4	0.21	97.99
(7) Benzyl isothiocyanate	2346	149.2	2	1	0	2.91	44.45
(8) Niazirin	129556	279.3	3	6	3	0.20	102.94
(9) Niaziminin	10023860	399.5	9	7	3	1.47	138.57
(10) Niazinin	10088810	343.4	6	6	4	0.59	132.50
(11) O-Ethyl N-carbamothioate	10247749	357.4	7	6	4	0.97	132.50
(12) Niazirinin	10426197	321.3	5	7	2	0.82	109.01

Figure S1 Conformations of compound docked to the ligand-binding site of the Mpro; the compounds in the first, second, and third ranked clusters are shown in yellow, blue, and pink. Charge distribution on the Mpro is shown in red (negative) and blue (positive).

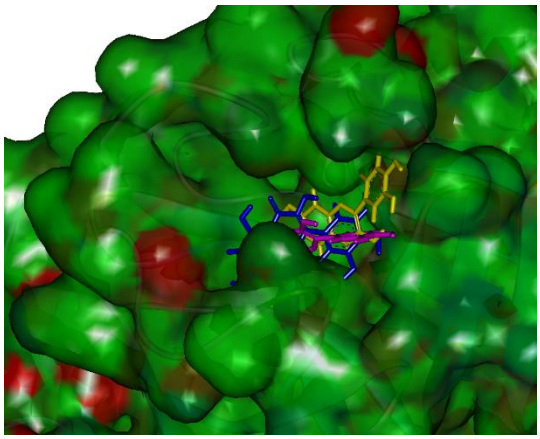
(a) Compound 1



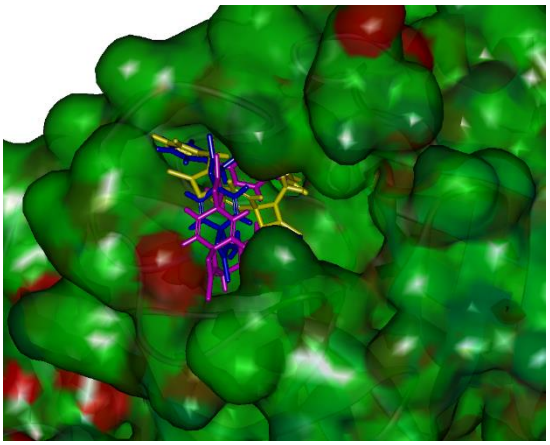
(b) Compound 2



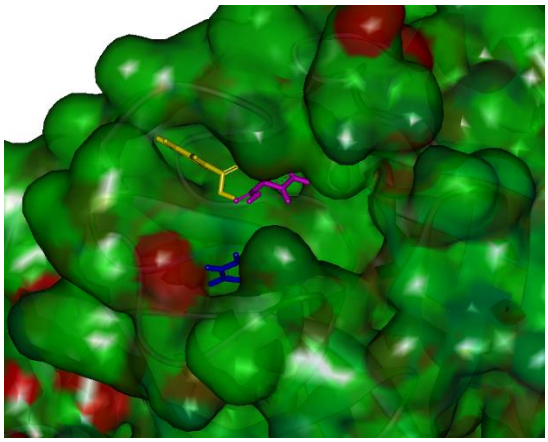
(c) Compound 3



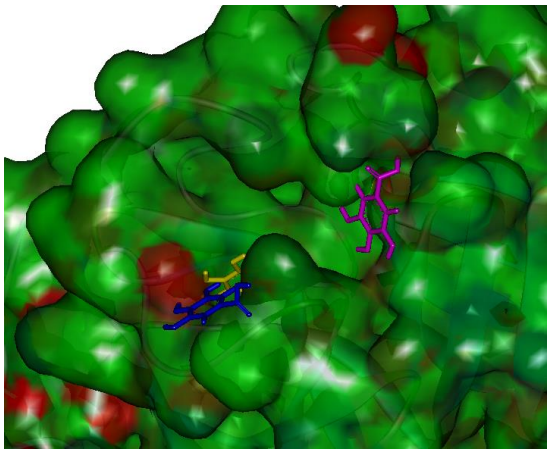
(d) Compound 4



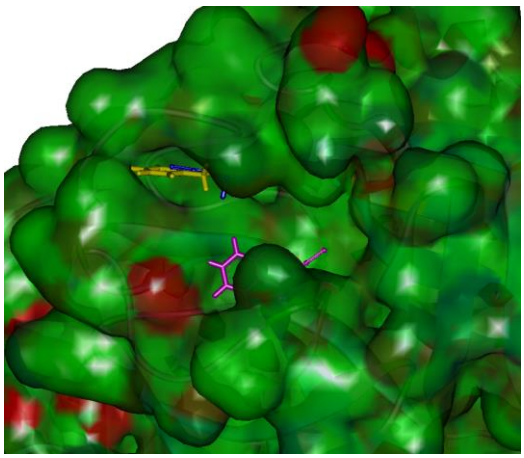
(e) Compound 5



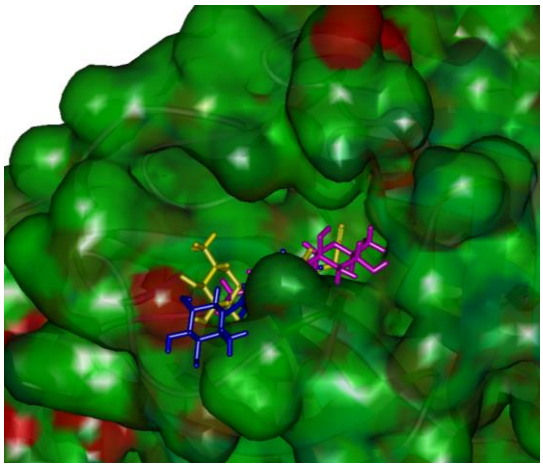
(f) Compound 6



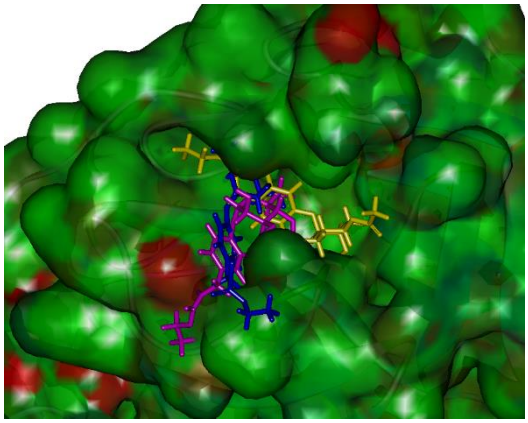
(g) Compound 7



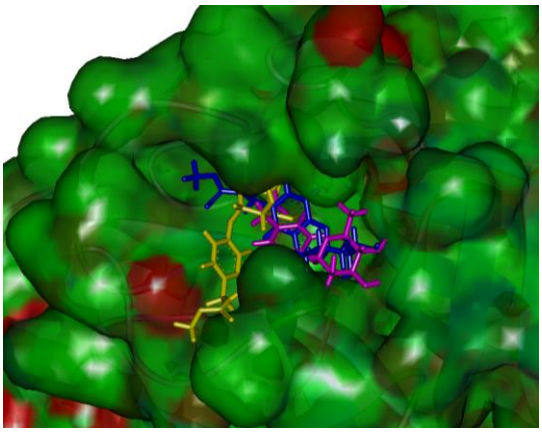
(h) Compound 8



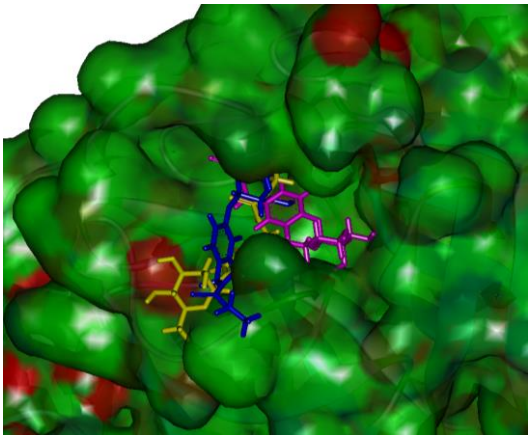
(i) Compound 9



(j) Compound 10



(k) Compound 11



(l) Compound 12

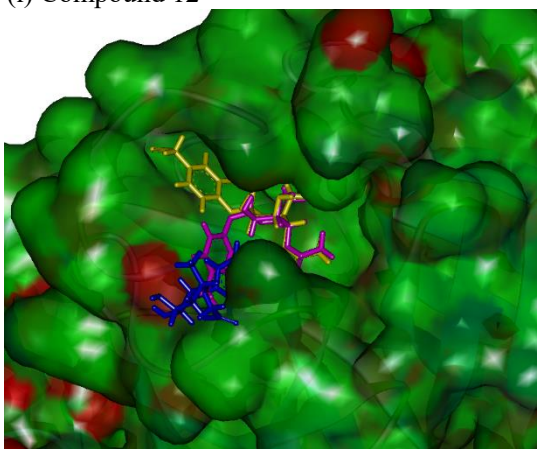
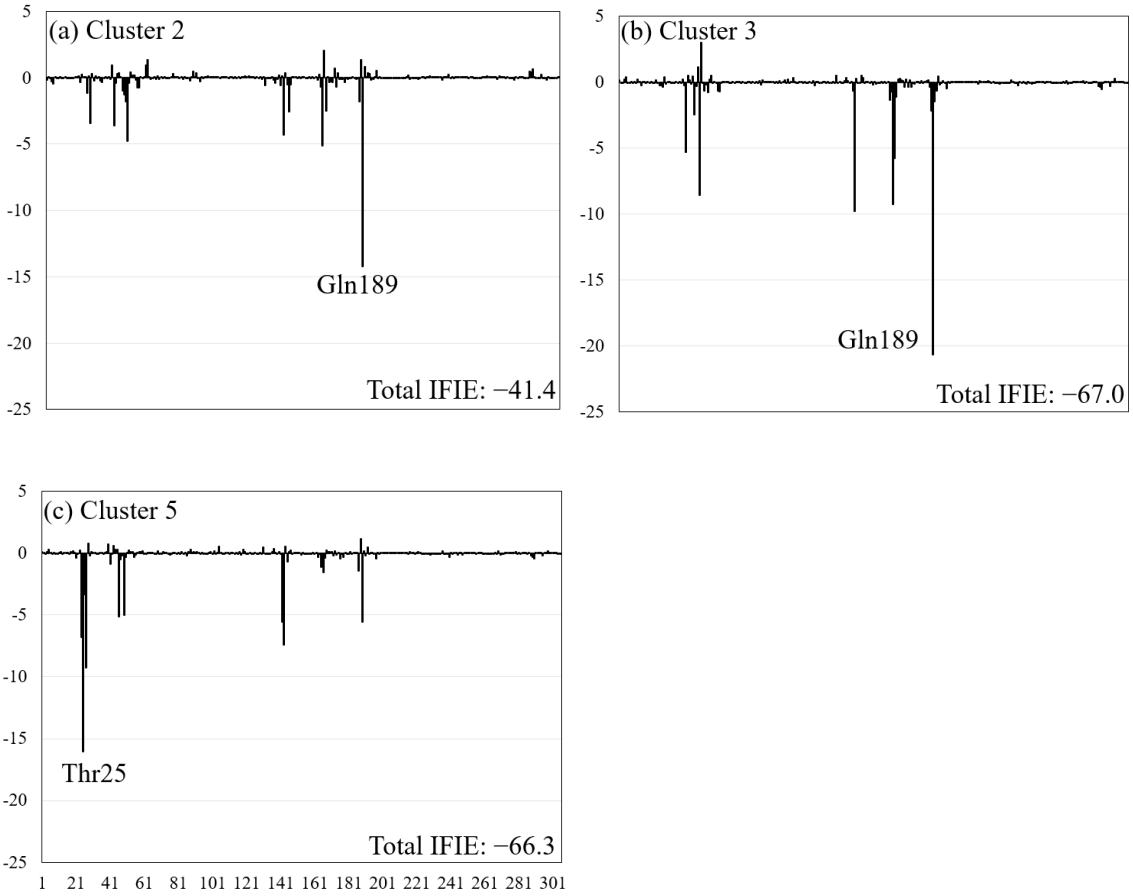


Figure S2 IFIEs (kcal/mol) between the Mpro residues and compound 1 for three clusters, and an interacting structure between Gln189 of the Mpro and compound 1 in the cluster 3. Hydrogen bonding and electrostatic interactions are indicated by red and blue lines, respectively.



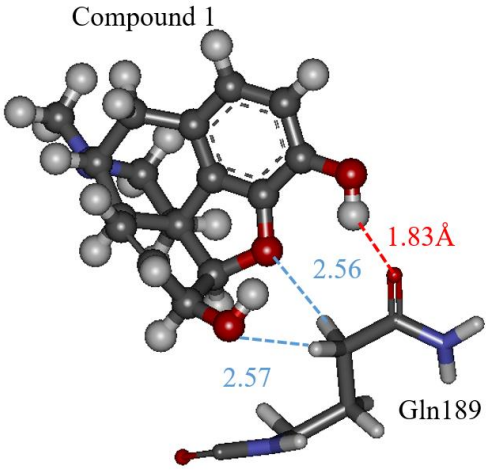
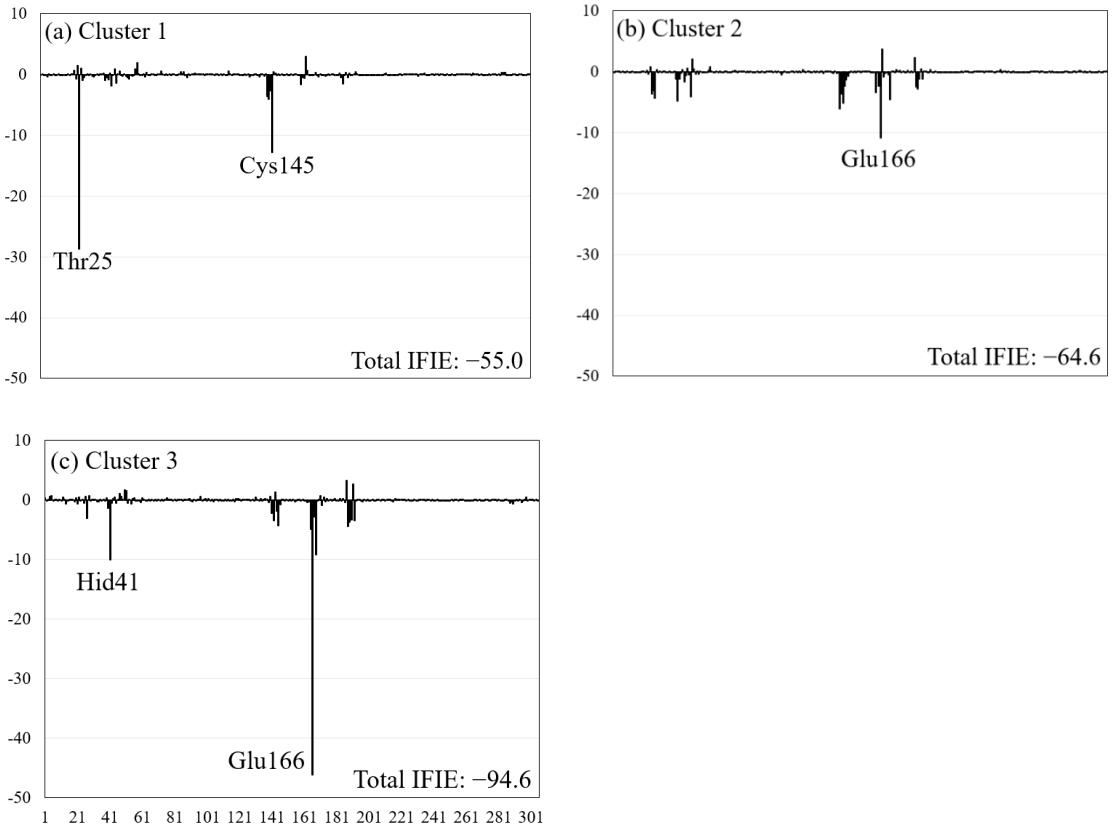


Figure S3 IFIEs (kcal/mol) between the Mpro residues and compound 2 for three clusters, and an interacting structure between the Mpro residues and compound 2 in the cluster 3. Hydrogen bonding and electrostatic interactions are indicated by red and blue lines, respectively.



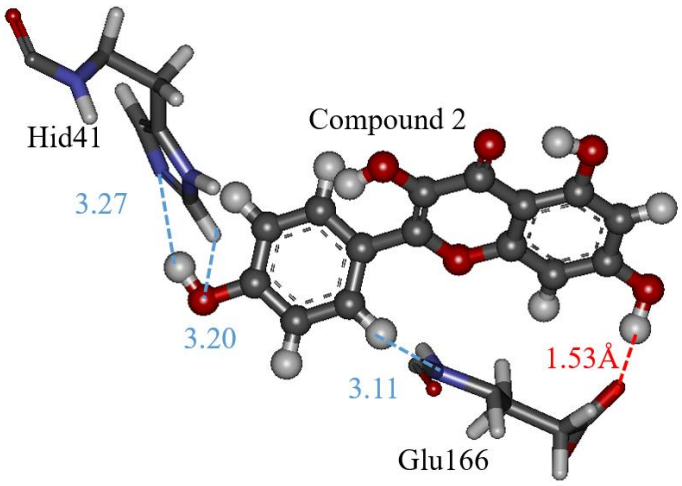
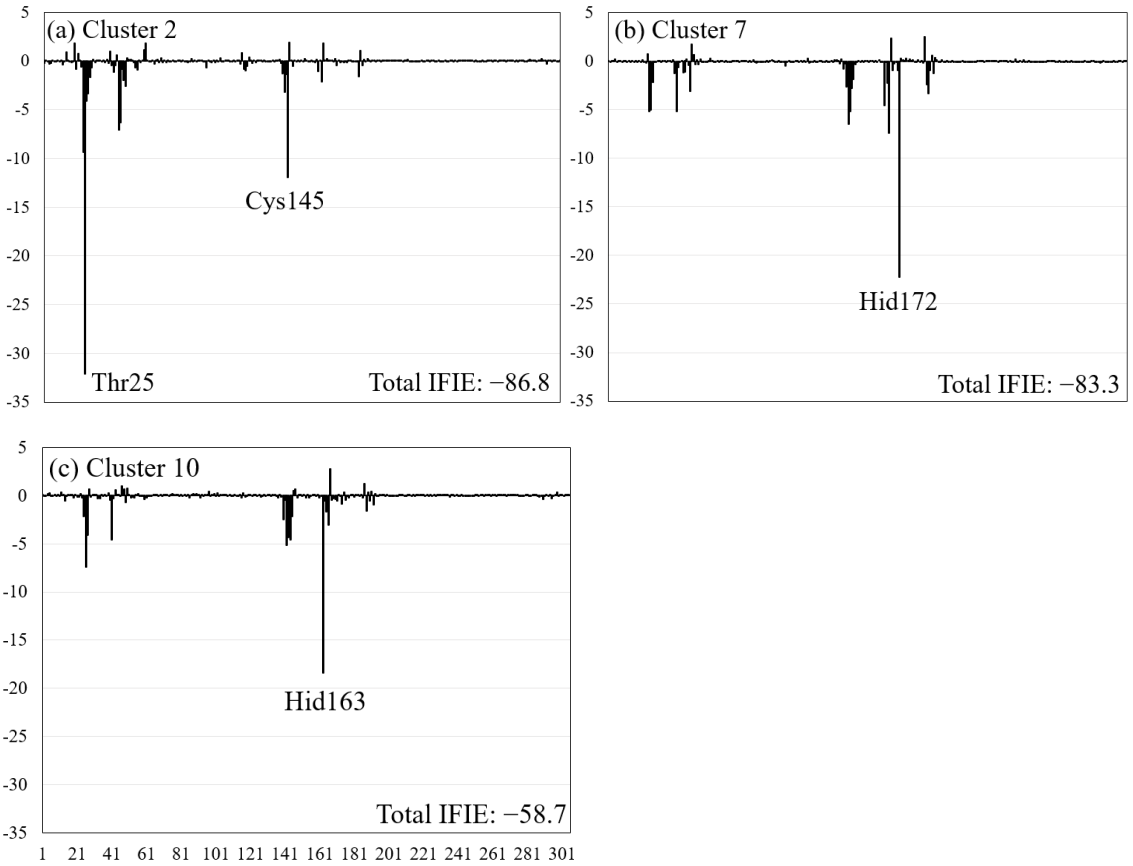


Figure S4 IFIEs (kcal/mol) between the Mpro residues and compound 3 for three clusters, and an interacting structure between the Mpro residues and compound 3 in the cluster 2. Hydrogen bonding and electrostatic interactions are indicated by red and blue lines, respectively.



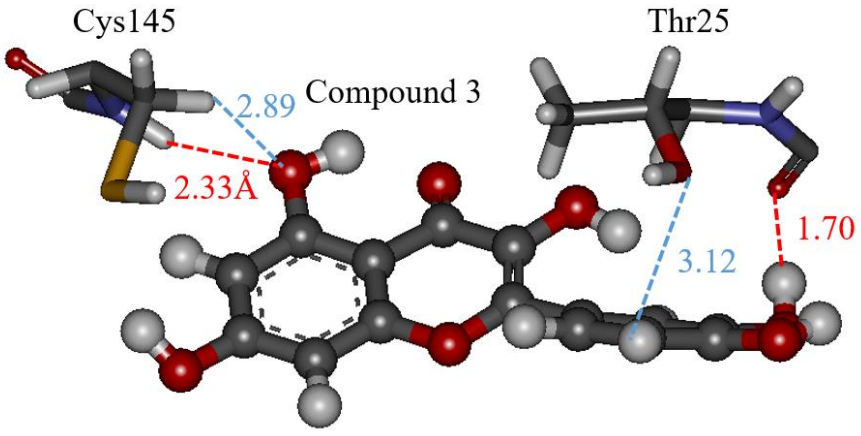
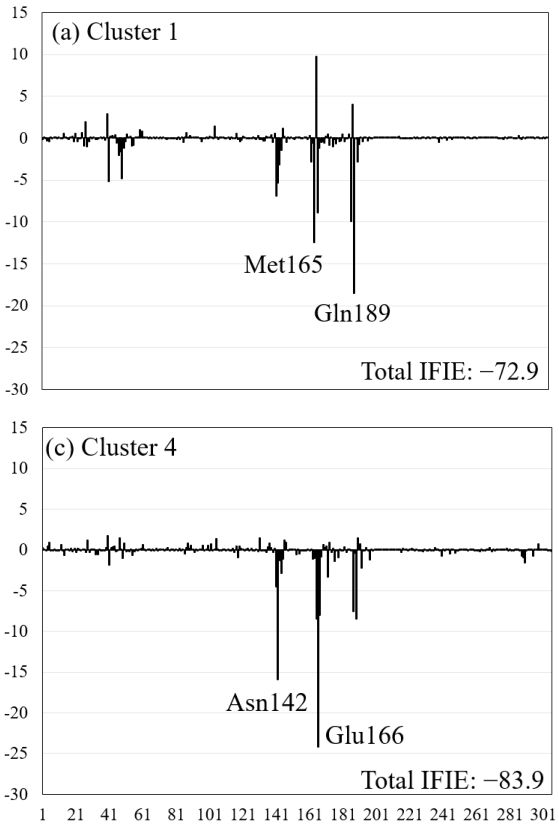


Figure S5 IFIEs (kcal/mol) between the Mpro residues and compound 4 for three clusters, and an interacting structure between the Mpro residues and compound 4 in the cluster 4. Electrostatic interactions are indicated by blue lines.



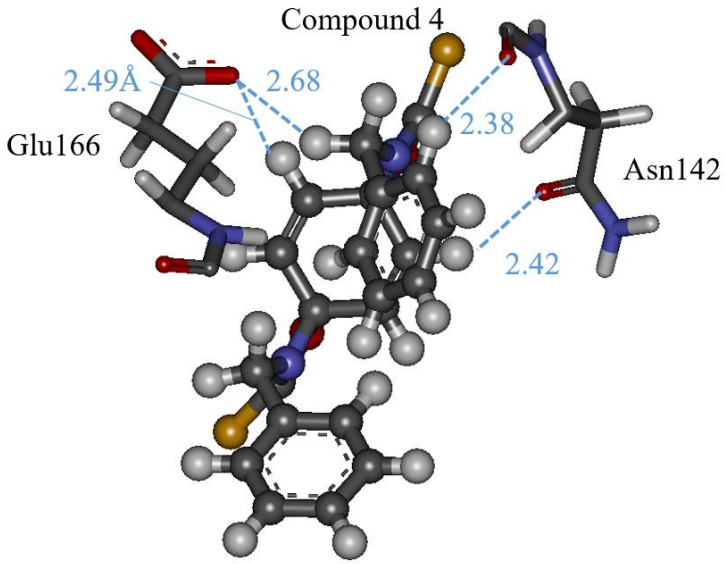
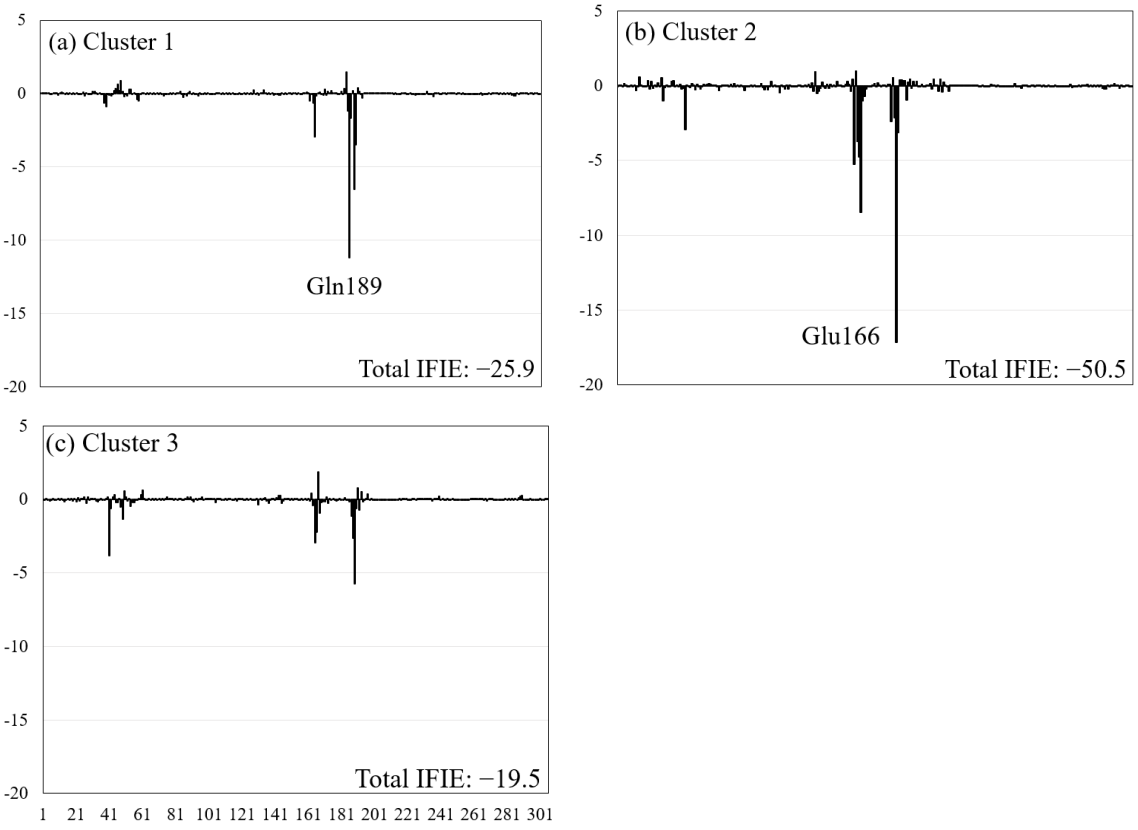


Figure S6 IFIEs (kcal/mol) between the Mpro residues and compound 5 for three clusters, and an interacting structure between the Mpro residues and compound 5 in the cluster 2. Electrostatic interactions are indicated by blue lines.



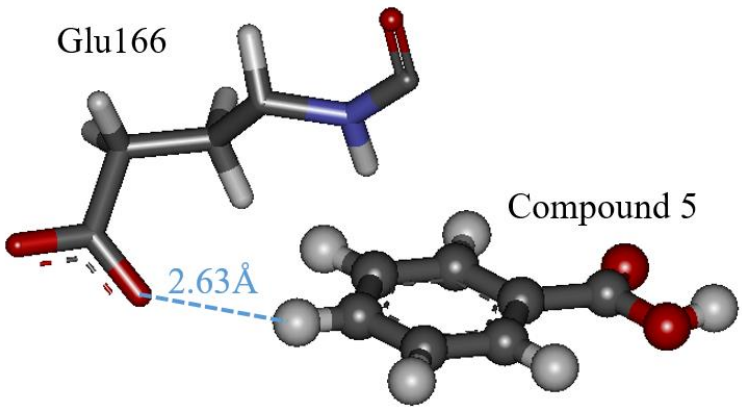
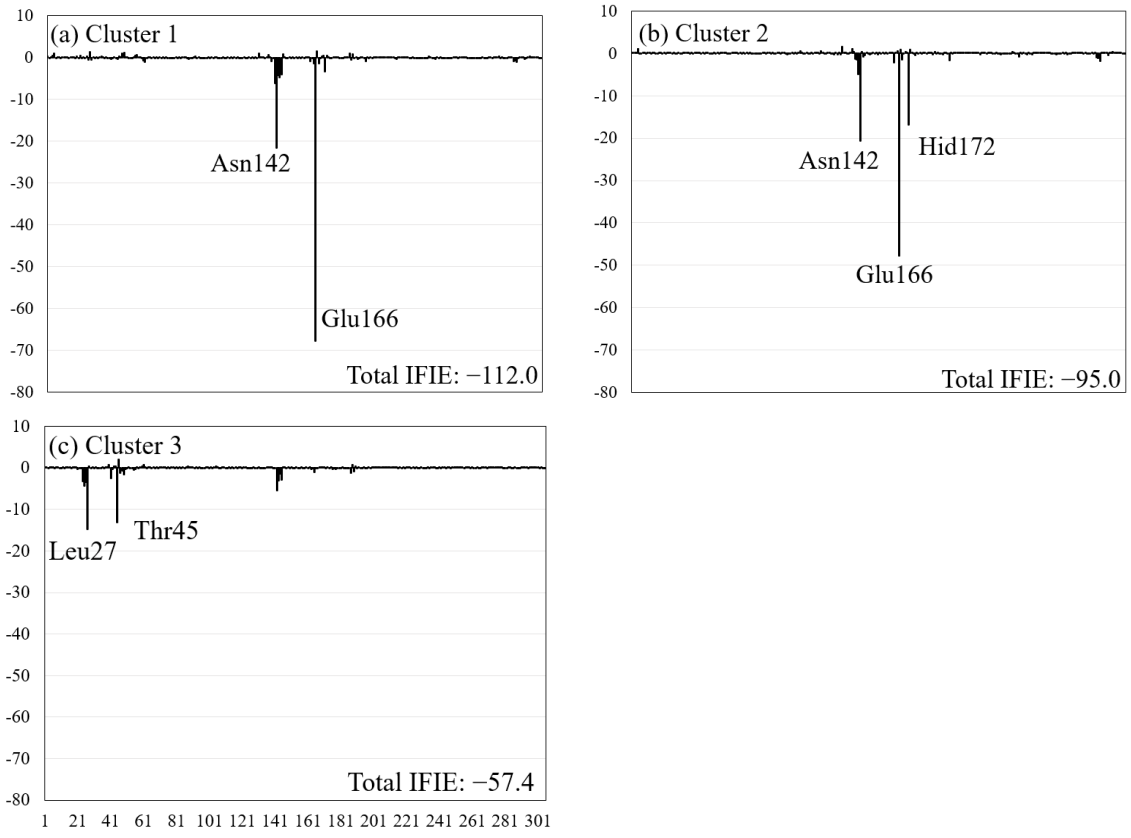


Figure S7 IFIEs (kcal/mol) between the Mpro residues and compound 6 for three clusters, and an interacting structure between the Mpro residues and compound 6 in the cluster 1. Hydrogen bonding and electrostatic interactions are indicated by red and blue lines, respectively.



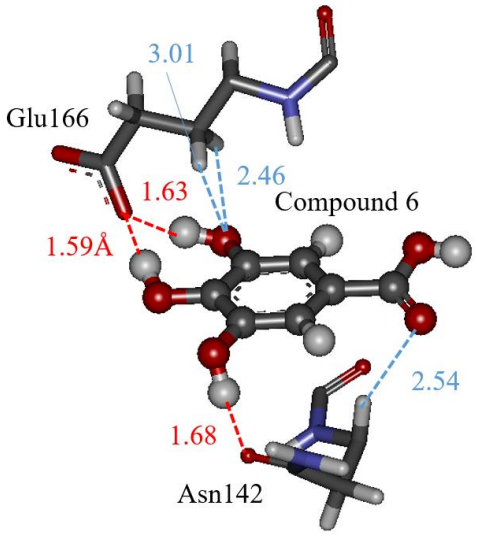
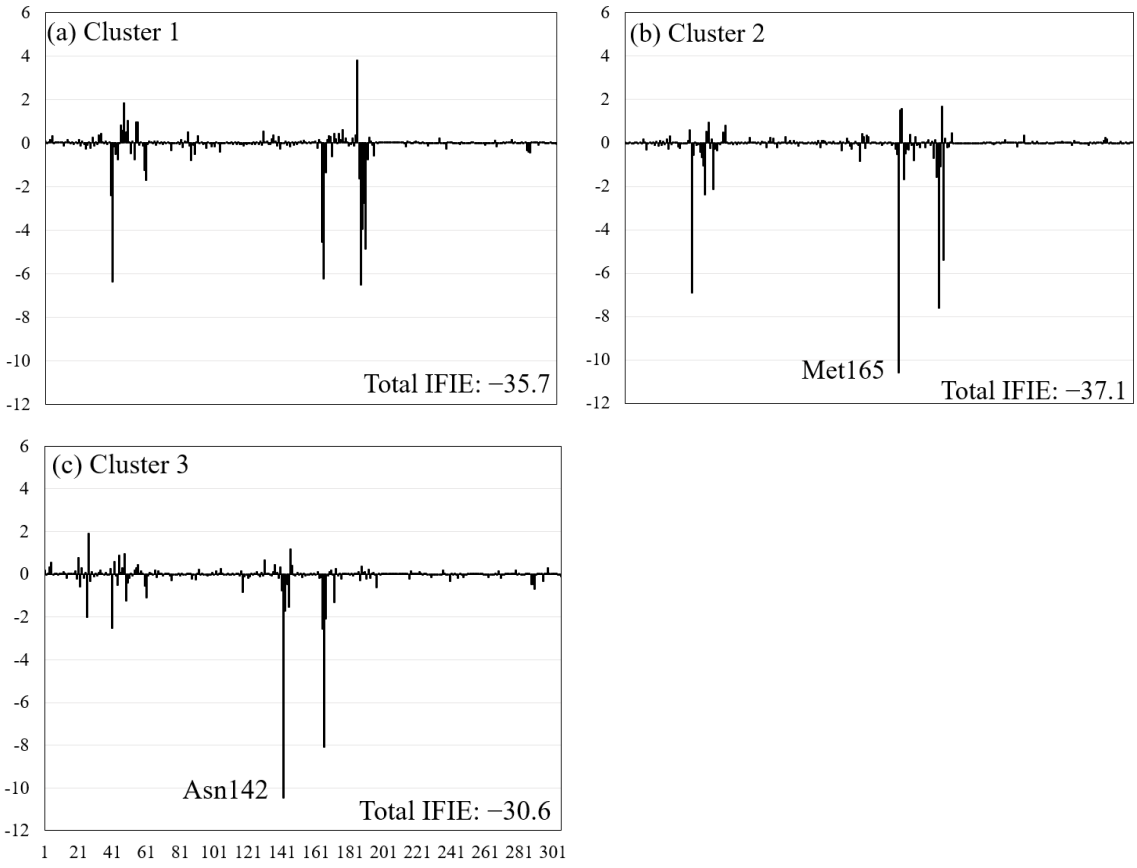


Figure S8 IFIEs (kcal/mol) between the Mpro residues and compound 7 for three clusters, and an interacting structure between the Mpro residues and compound 7 in the cluster 2. Electrostatic interactions are indicated by blue lines.



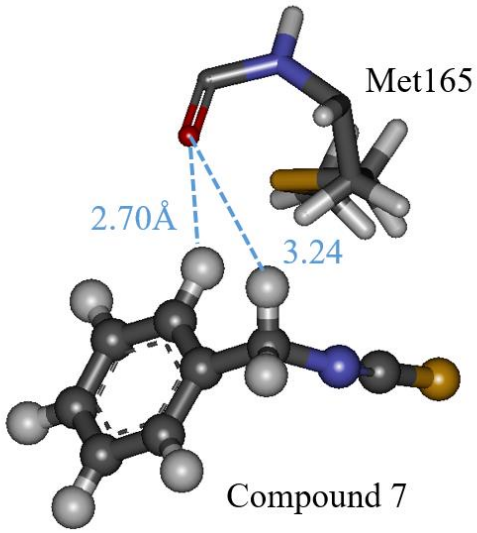


Figure S9 IFIEs (kcal/mol) between the Mpro residues and compound 8 for three clusters, and an interacting structure between the Mpro residues and compound 8 in the cluster 2. Hydrogen bonding and electrostatic interactions are indicated by red and blue lines, respectively.

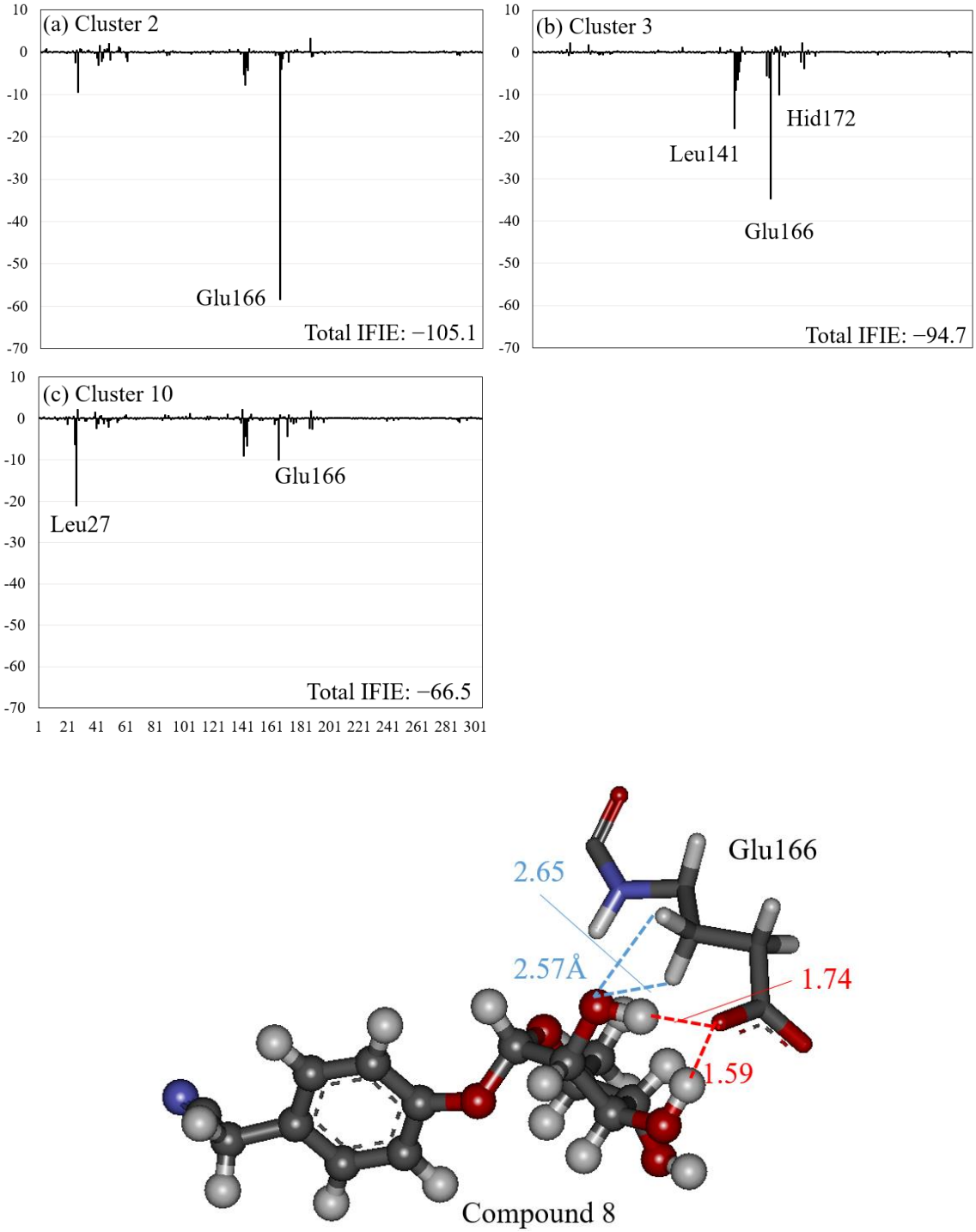
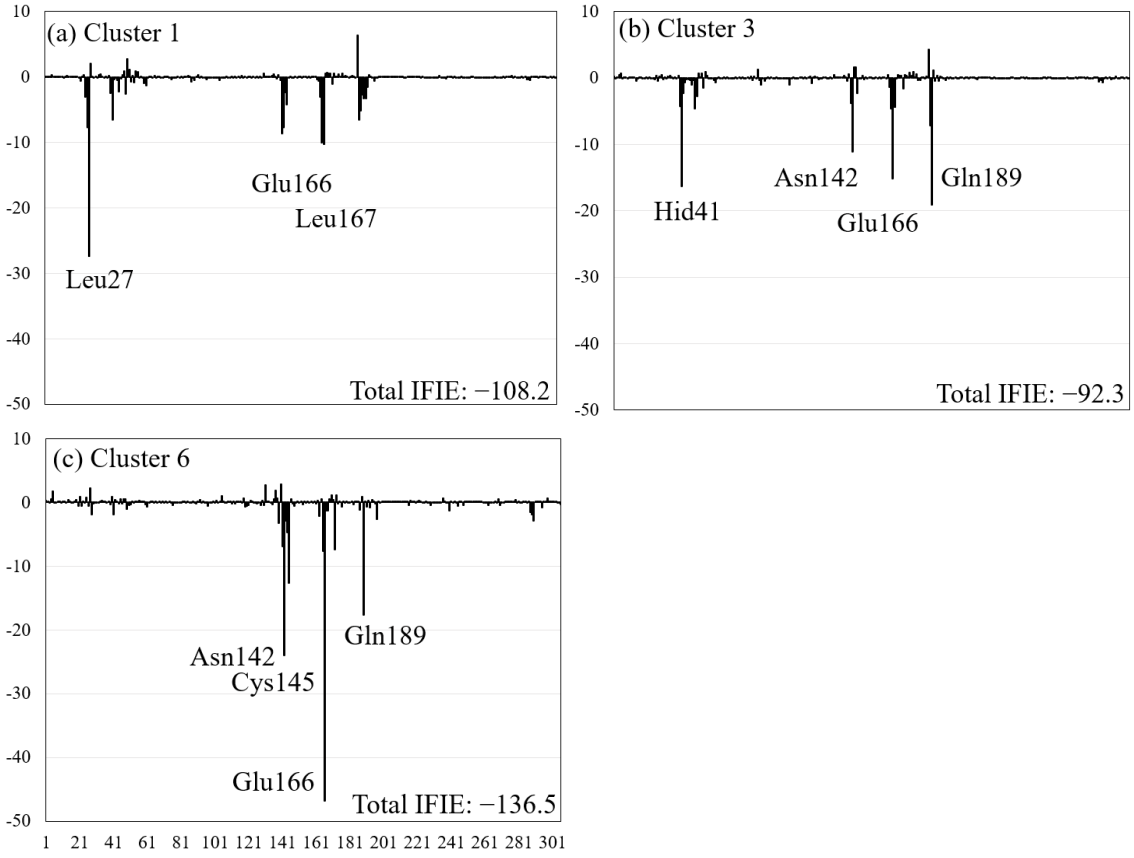
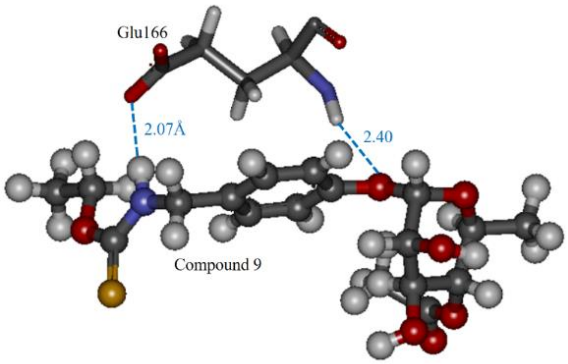


Figure S10 IFIEs (kcal/mol) between the Mpro residues and compound 9 for three clusters, and an interacting structure between the Mpro residues and compound 9 in the cluster 6. Hydrogen bonding and electrostatic interactions are indicated by red and blue lines, respectively.





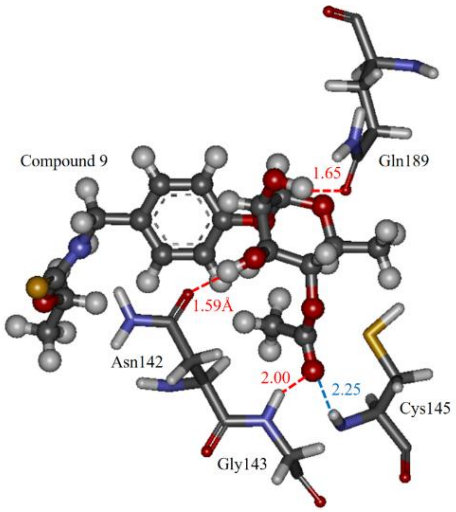
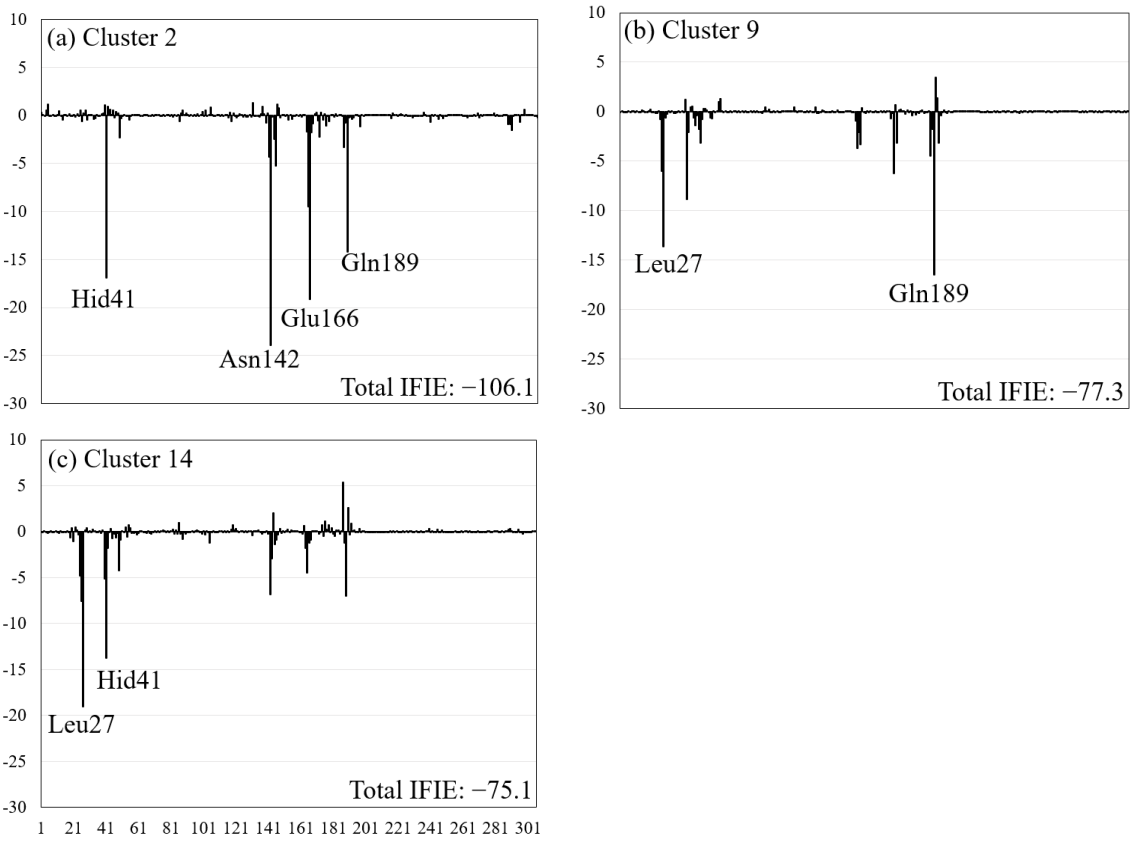


Figure S11 IFIEs (kcal/mol) between the Mpro residues and compound 10 for three clusters, and an interacting structure between the Mpro residues and compound 10 in the cluster 2. Hydrogen bonding, electrostatic, and NH-π interactions are indicated by red, blue, and orange lines, respectively.



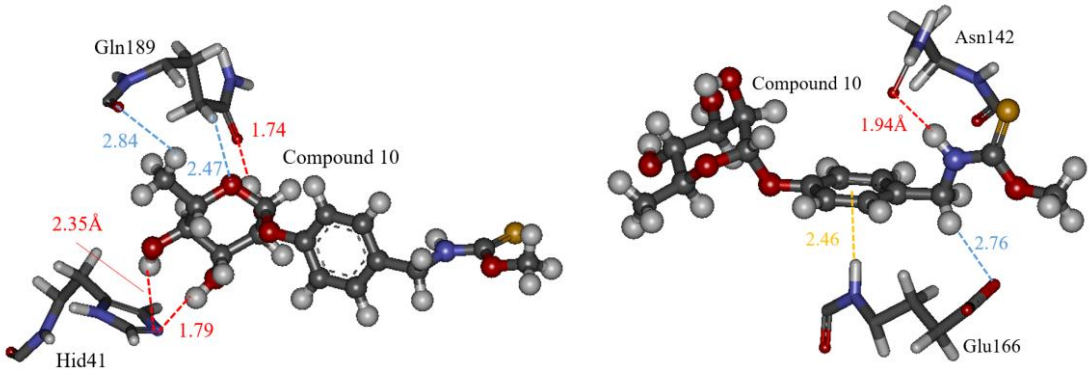
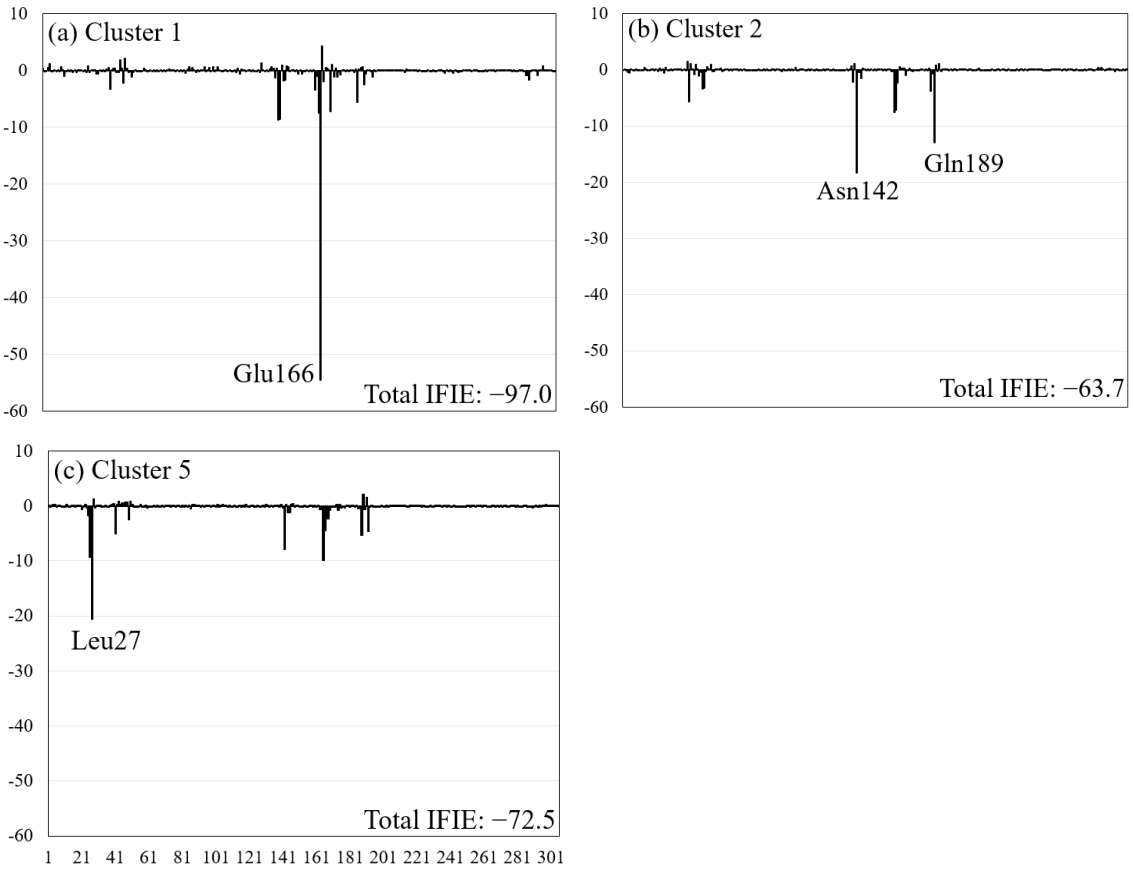
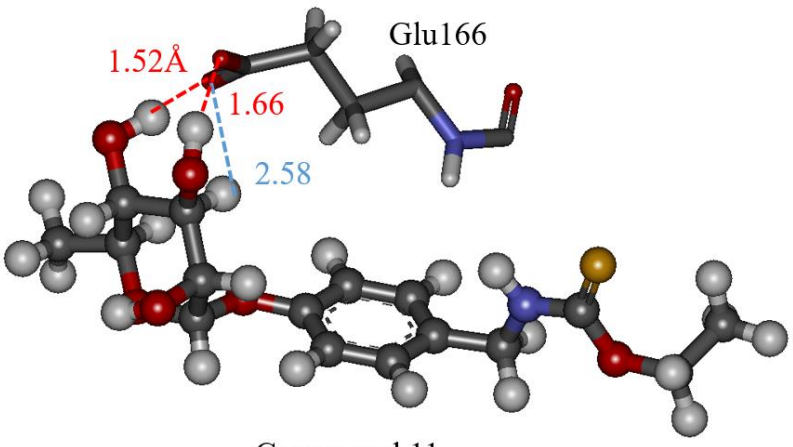


Figure S12 IFIEs (kcal/mol) between the Mpro residues and compound 11 for three clusters, and an interacting structure between the Mpro residues and compound 11 in the cluster 1. Hydrogen bonding and electrostatic interactions are indicated by red and blue lines, respectively.





Compound 11

Figure S13 IFIEs (kcal/mol) between the Mpro residues and compound 12 for three clusters, and an interacting structure between the Mpro residues and compound 12 in the cluster 2. Hydrogen bonding, electrostatic, and NH-π interactions are indicated by red, blue, and orange lines, respectively.