

Supplementary material

The inhibitory potential of ferulic acid derivatives against the main protease (M^{pro}) of SARS-CoV-2: molecular docking, molecular dynamics and ADMET evaluation

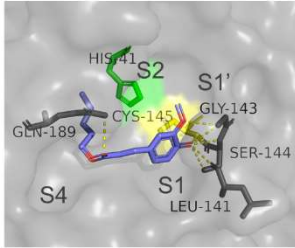
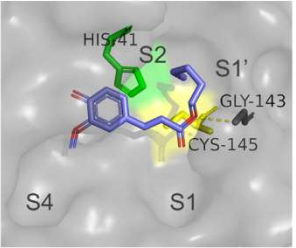
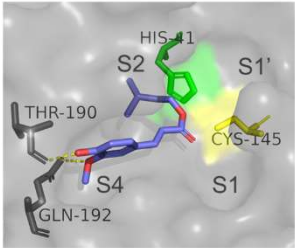
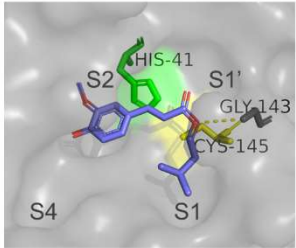
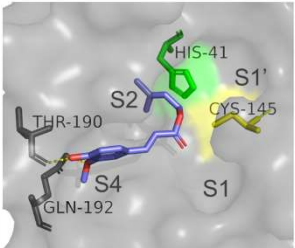
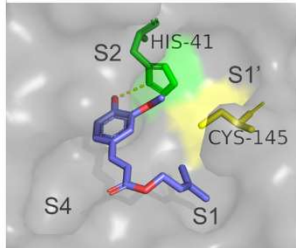
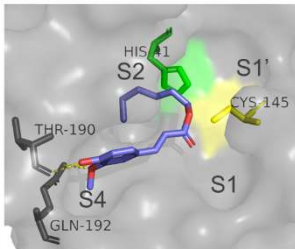
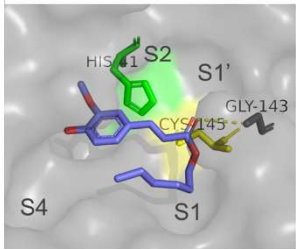
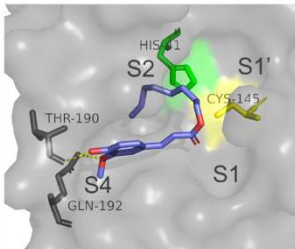
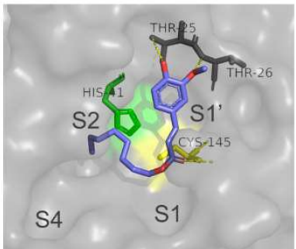
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¹: equal contribution

<p>Methyl ferulate Cluster 2 5.158 kcal/mol</p>	<p>Methyl ferulate Cluster 3 5.147 kcal/mol</p>
<p>Ethyl ferulate Cluster 2 5.525 kcal/mol</p>	<p>Ethyl ferulate Cluster 3 5.477 kcal/mol</p>
<p>Propyl ferulate Cluster 2 5.481 kcal/mol</p>	<p>Propyl ferulate Cluster 3 5.324 kcal/mol</p>
<p>Butyl ferulate Cluster 2 5.568 kcal/mol</p>	<p>Butyl ferulate Cluster 3 5.553 kcal/mol</p>
<p>Isobutyl ferulate Cluster 2 6.039 kcal/mol</p>	<p>Isobutyl ferulate Cluster 3 5.896 kcal/mol</p>

<p>Pentyl ferulate Cluster 2 5.908 kcal/mol</p> 	<p>Pentyl ferulate Cluster 3 5.489 kcal/mol</p> 
<p>Isopentyl ferulate Cluster 2 6.259 kcal/mol</p> 	<p>Isopentyl ferulate Cluster 3 5.942 kcal/mol</p> 
<p>Prenyl ferulate Cluster 2 6.147 kcal/mol</p> 	<p>Prenyl ferulate Cluster 3 5.942 kcal/mol</p> 
<p>Hexyl ferulate Cluster 2 6.309 kcal/mol</p> 	<p>Hexyl ferulate Cluster 3 5.831 kcal/mol</p> 
<p>Octyl ferulate Cluster 2 5.698 kcal/mol</p> 	<p>Octyl ferulate Cluster 3 5.525 kcal/mol</p> 

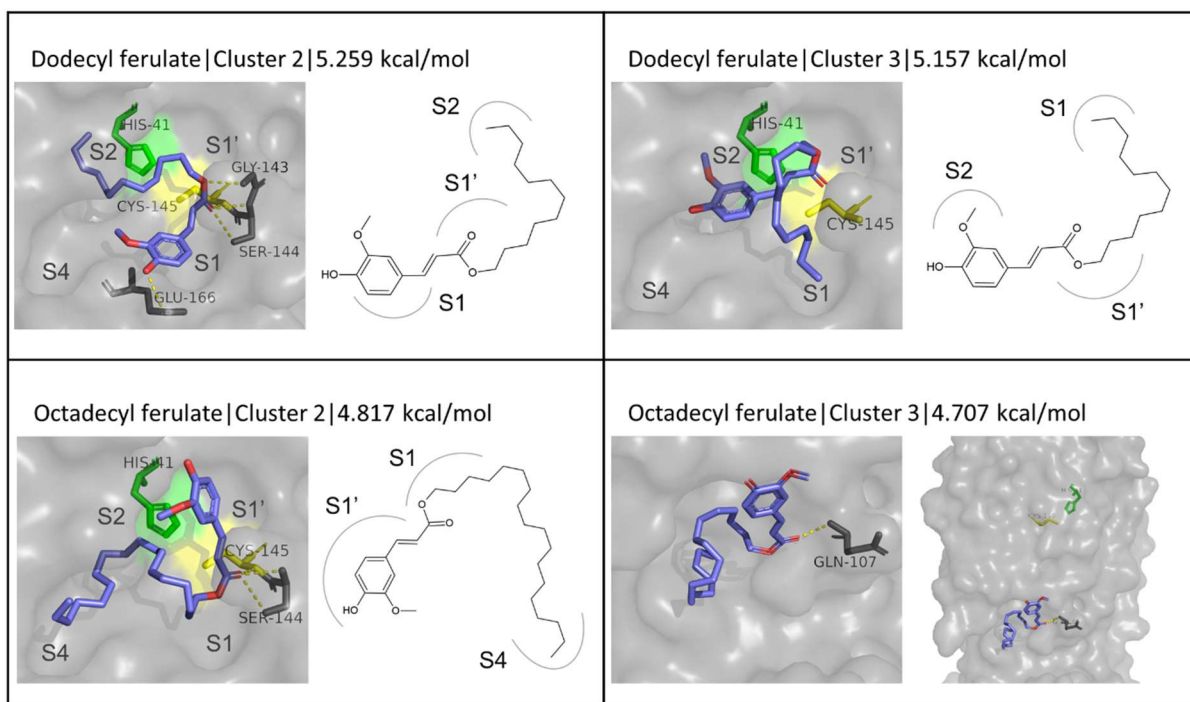


Figure S1. Binding modes of the second and third clusters for alkyl and alkenyl FA esters in the active site of M^{pro}.

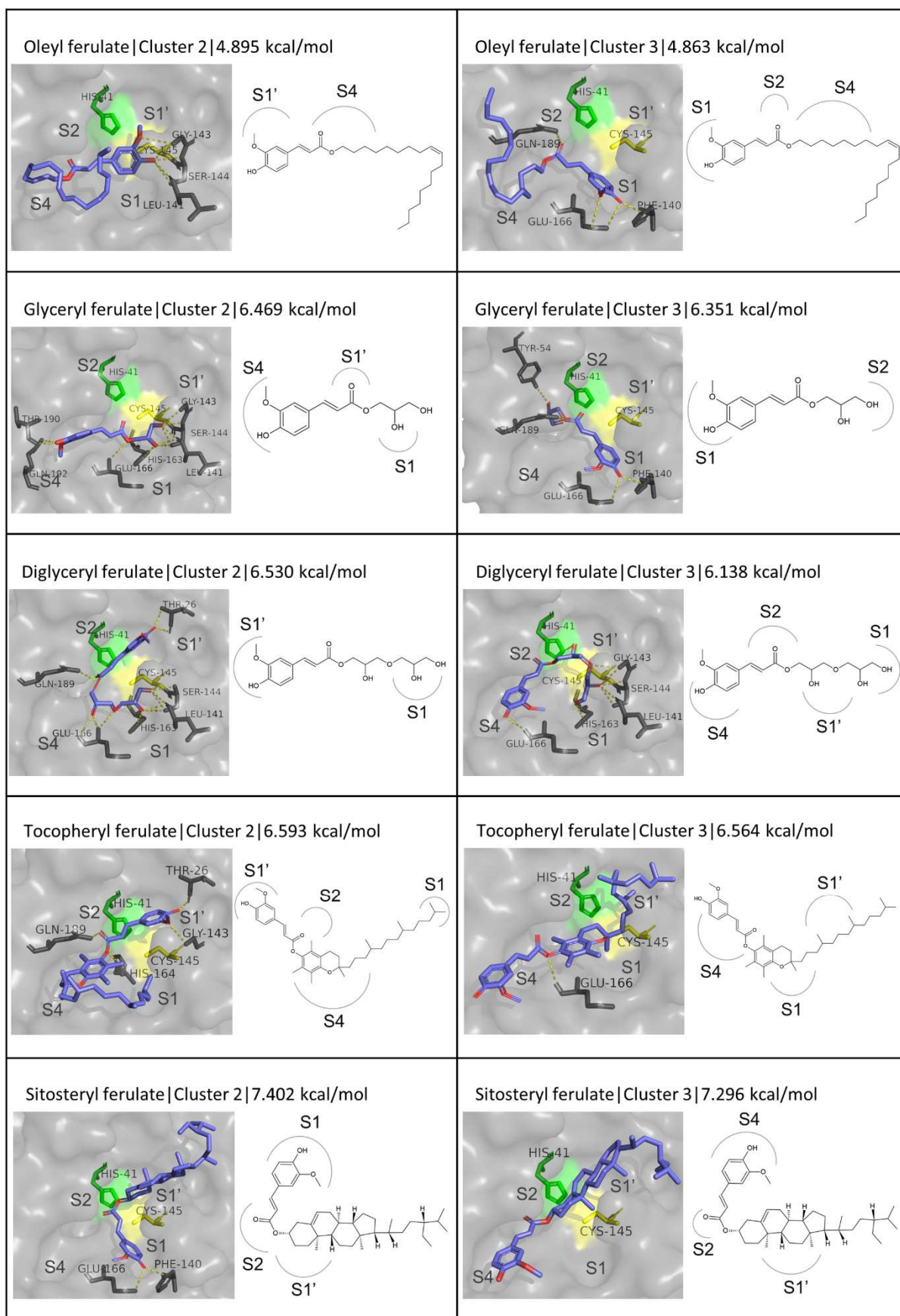
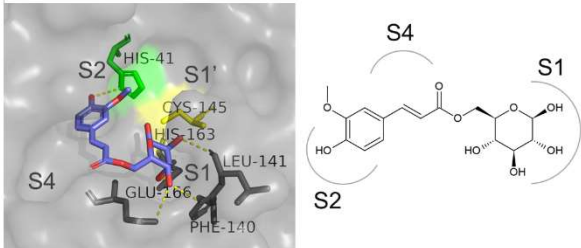
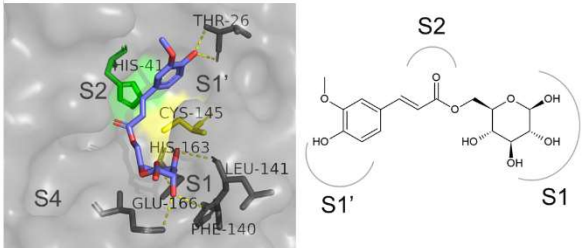
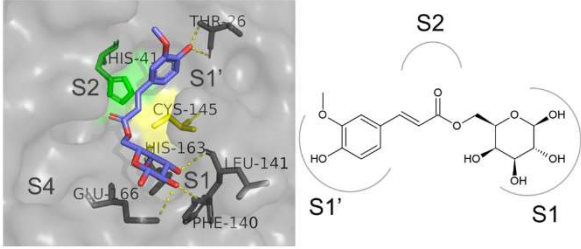
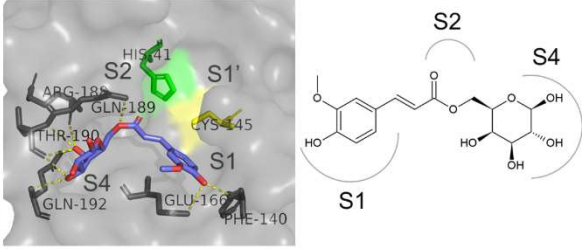
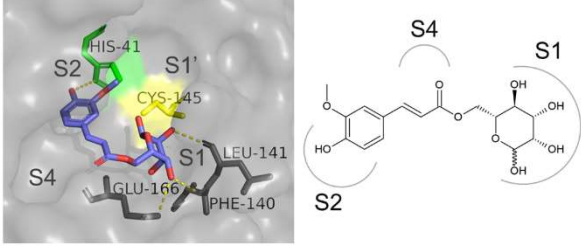
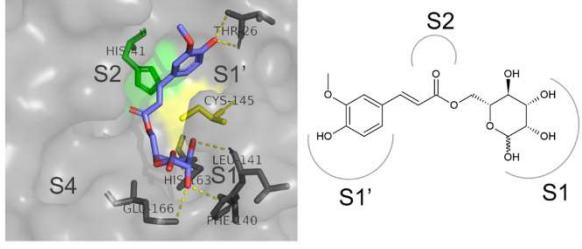
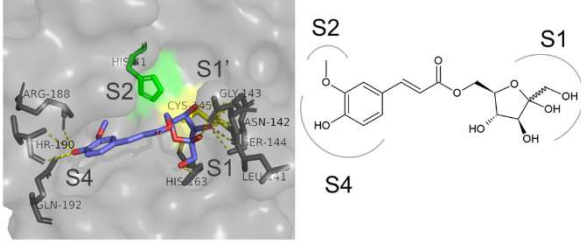
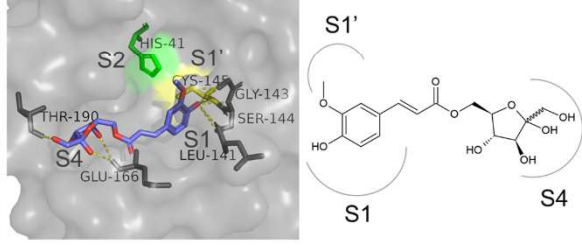
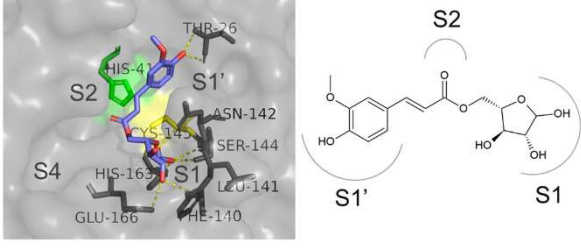
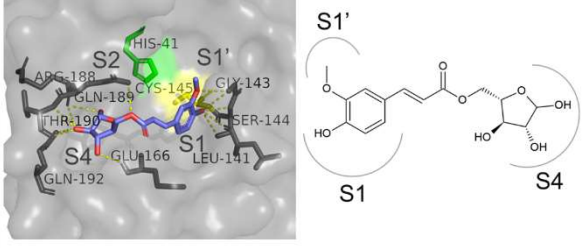


Figure S2. Binding modes of the second and third clusters for fatty acid, polyol, tocopherol and sterol FA derivatives in the active site of M^{Pro} .

<p>D-glucose ferulate Cluster 2 7.078 kcal/mol</p> 	<p>D-glucose ferulate Cluster 3 6.925 kcal/mol</p> 
<p>D-galactose ferulate Cluster 2 6.940 kcal/mol</p> 	<p>D-galactose ferulate Cluster 3 6.774 kcal/mol</p> 
<p>D-mannose ferulate Cluster 2 7.078 kcal/mol</p> 	<p>D-mannose ferulate Cluster 3 6.925 kcal/mol</p> 
<p>D-fructose ferulate Cluster 2 6.873 kcal/mol</p> 	<p>D-fructose ferulate Cluster 3 6.565 kcal/mol</p> 
<p>L-arabinose ferulate Cluster 2 6.975 kcal/mol</p> 	<p>L-arabinose ferulate Cluster 3 6.879 kcal/mol</p> 

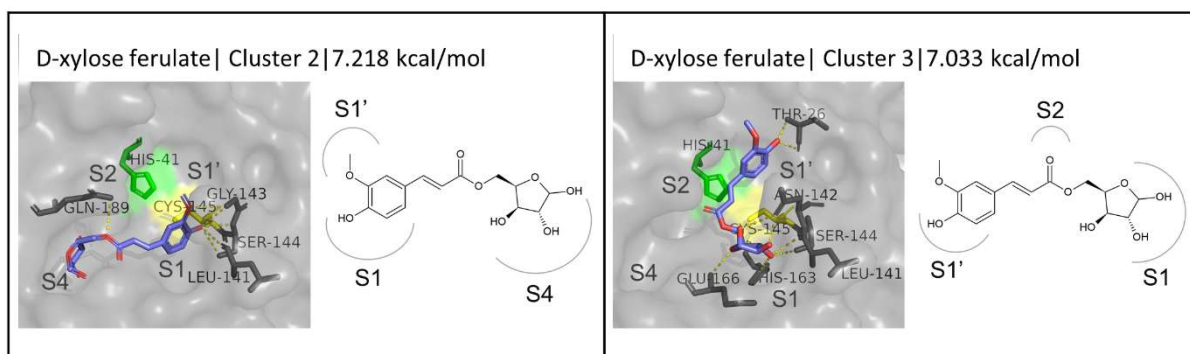
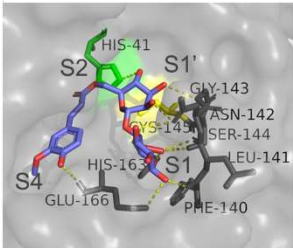
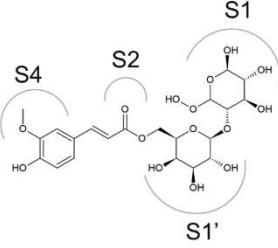
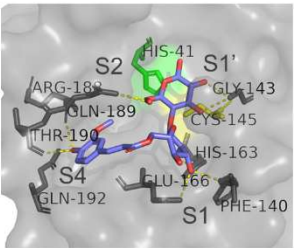
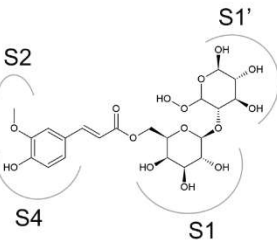
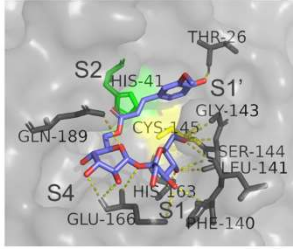
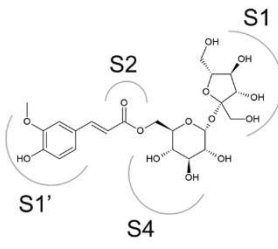
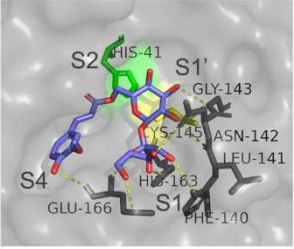
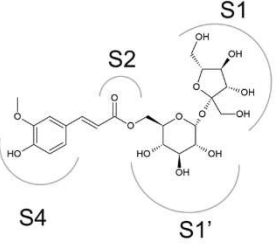
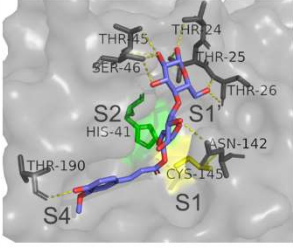
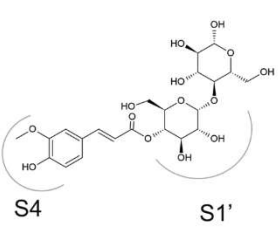
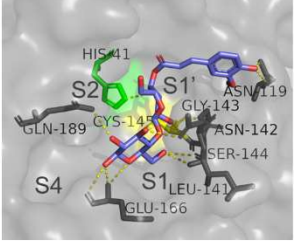
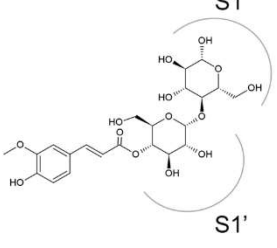
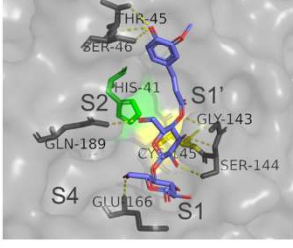
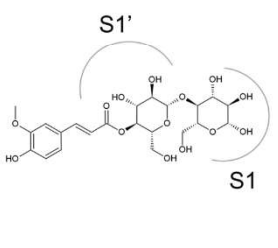
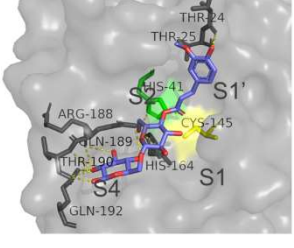
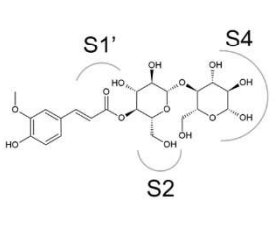
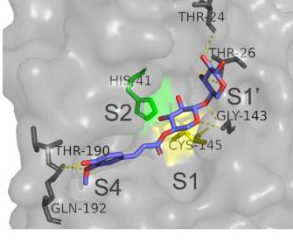
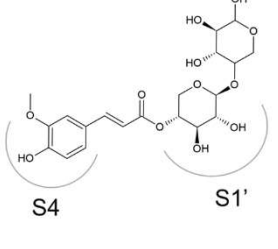
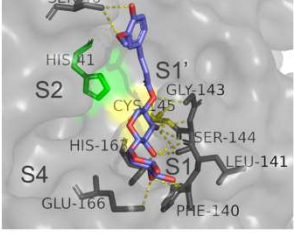
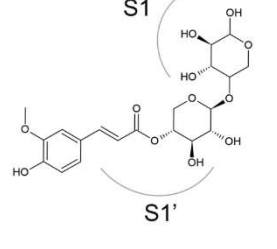


Figure S3. Binding modes of the second and third clusters for monosaccharide esters of FA in the active site of M^{pro}.

<p>D-lactose ferulate Cluster 2 7.387 kcal/mol</p>  	<p>D-lactose ferulate Cluster 3 7.368 kcal/mol</p>  
<p>D-sucrose ferulate Cluster 2 7.625 kcal/mol</p>  	<p>D-sucrose ferulate Cluster 3 7.319 kcal/mol</p>  
<p>D-maltose ferulate Cluster 2 7.028 kcal/mol</p>  	<p>D-maltose ferulate Cluster 3 6.917 kcal/mol</p>  
<p>D-cellobiose ferulate Cluster 2 7.451 kcal/mol</p>  	<p>D-cellobiose ferulate Cluster 3 7.370 kcal/mol</p>  
<p>Xylobiose ferulate Cluster 2 7.359 kcal/mol</p>  	<p>Xylobiose ferulate Cluster 3 7.328 kcal/mol</p>  

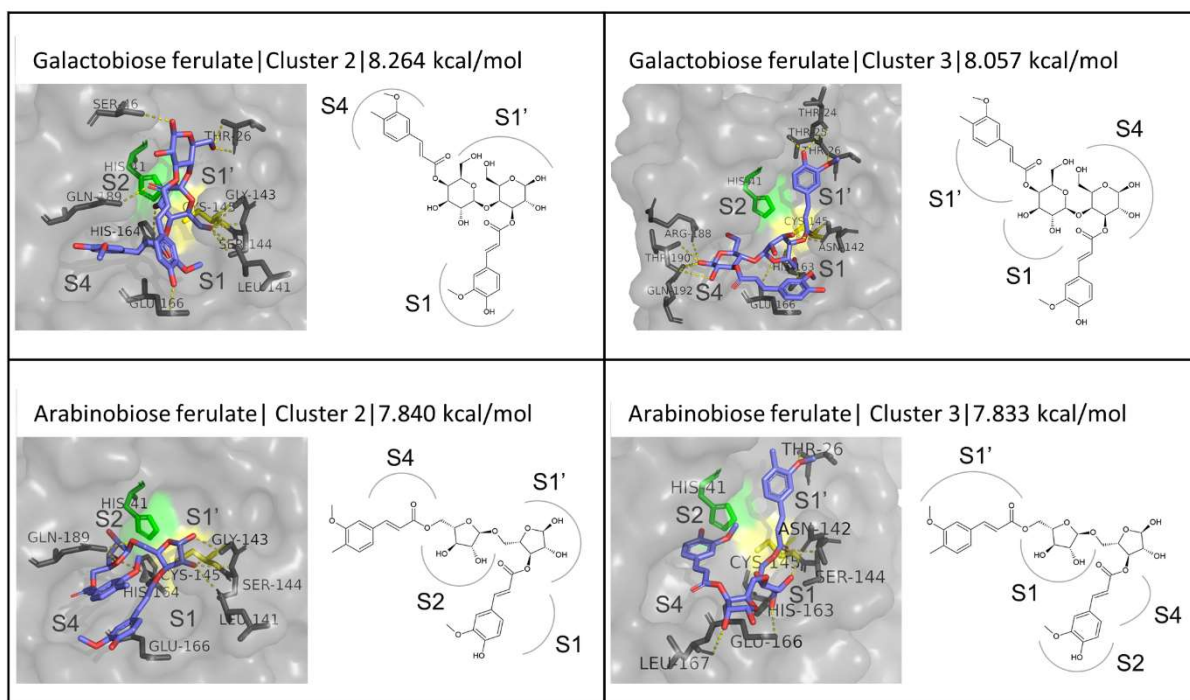


Figure S4. Binding modes of the second and third clusters for disaccharide esters of FA in the active site of M^{pro}.

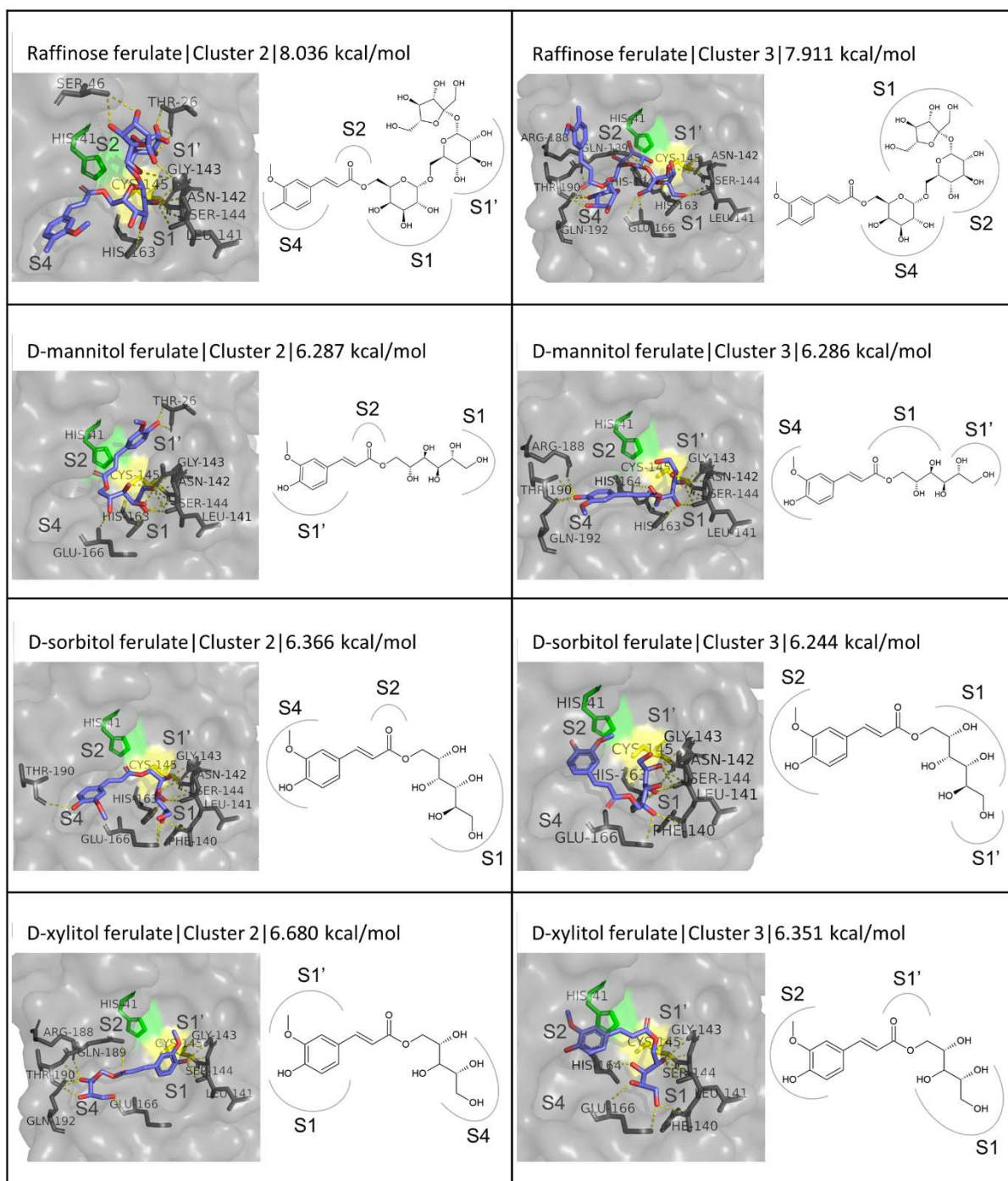


Figure S5. Binding modes of the second and third clusters for trisaccharide and sugar alcohol esters of FA in the active site of M^{pro}.

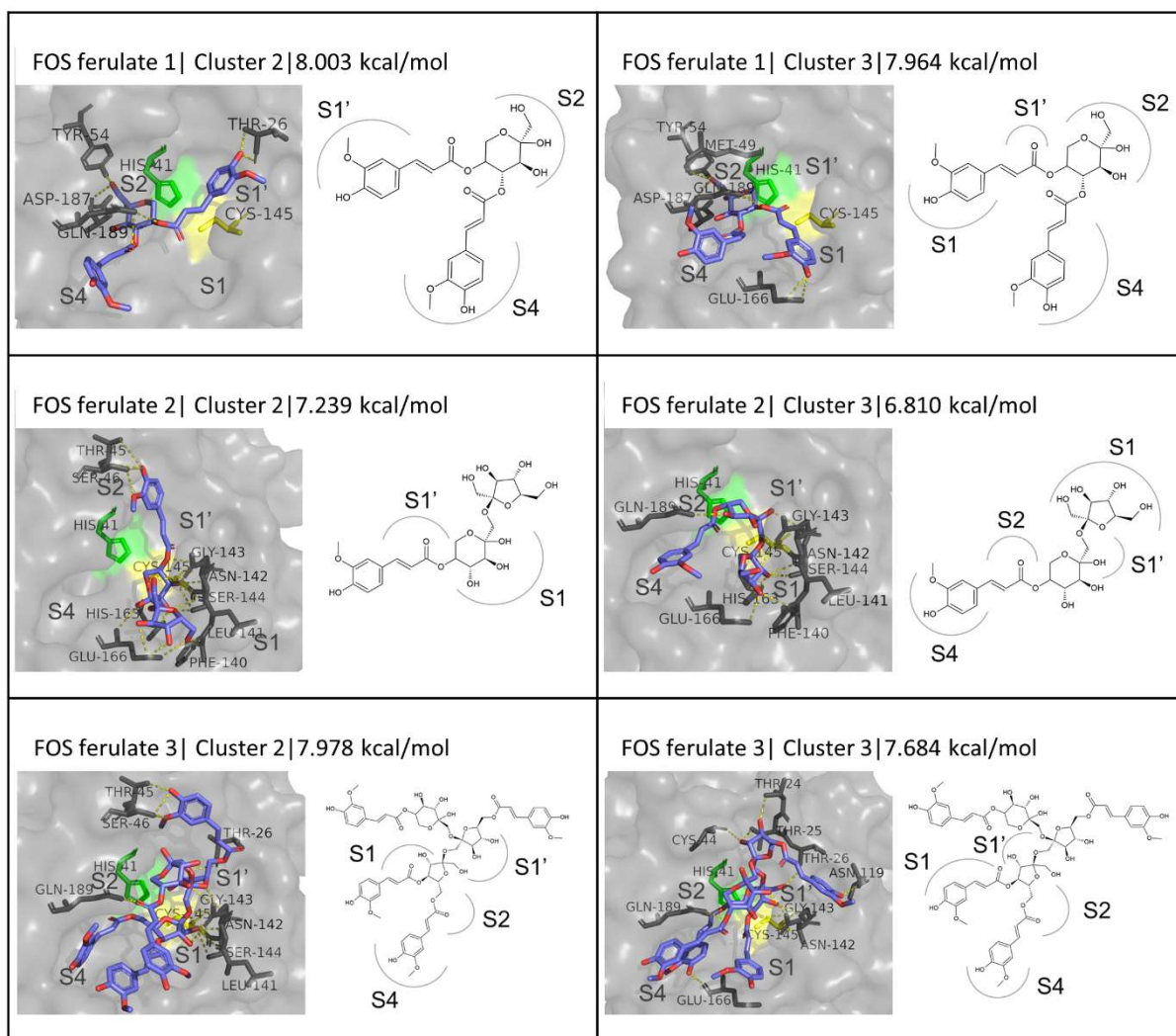


Figure S6. Binding modes of the second and third clusters for FOS esters of FA in the active site of M^{pro}.

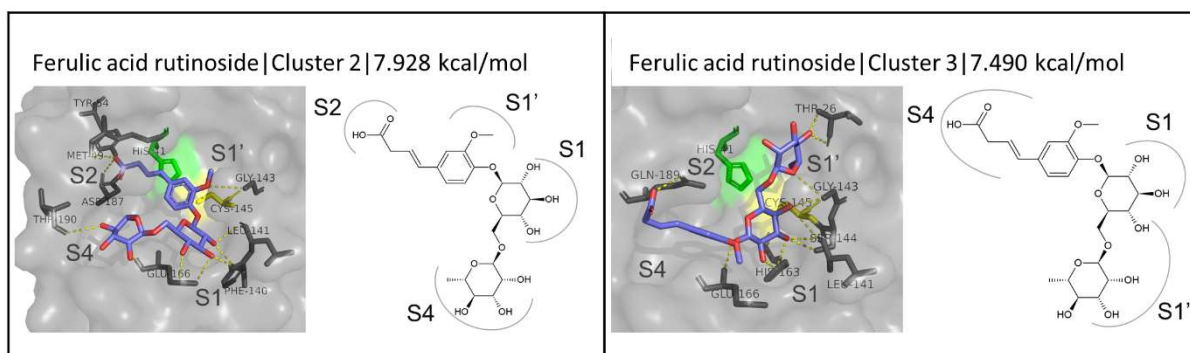
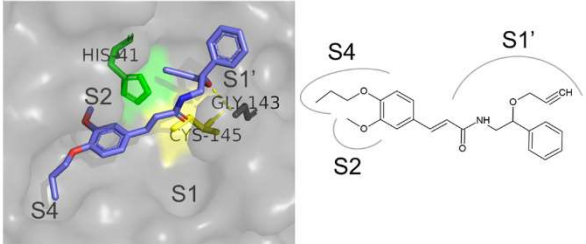
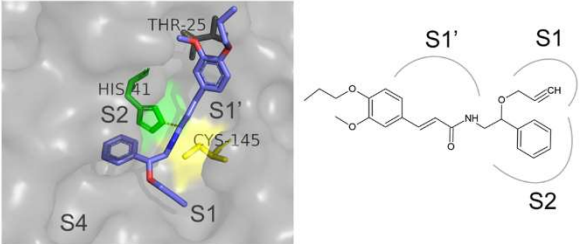
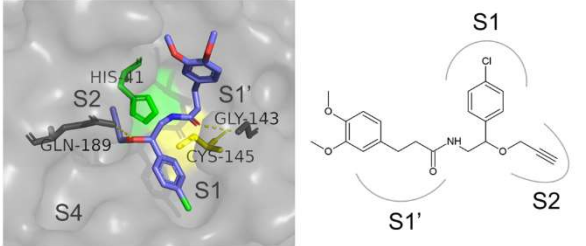
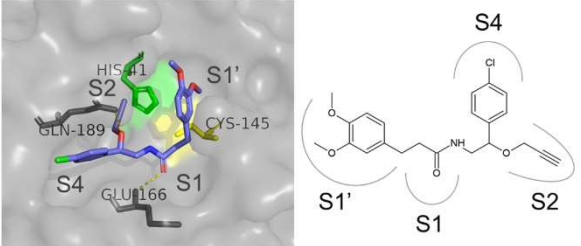
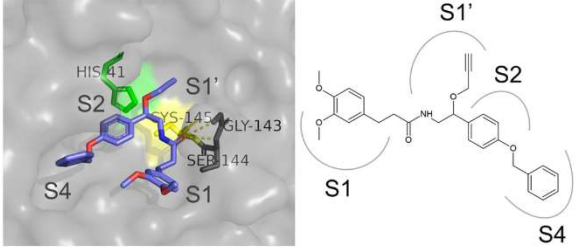
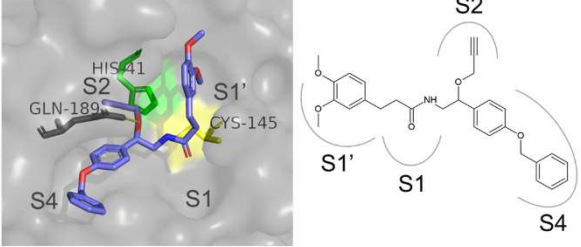
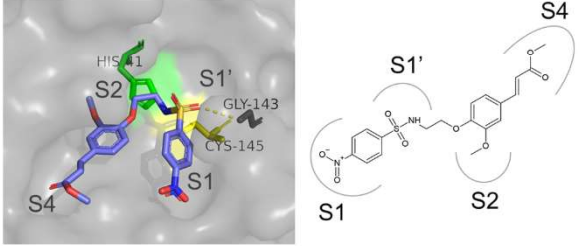
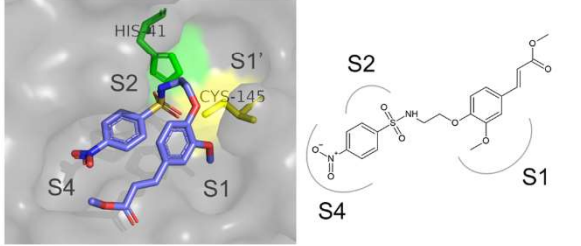
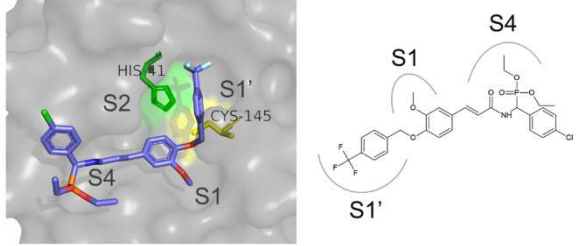
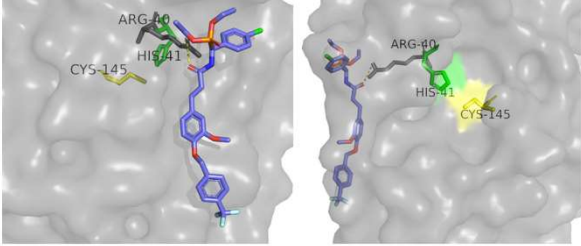
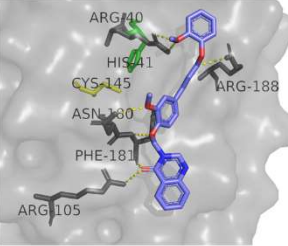
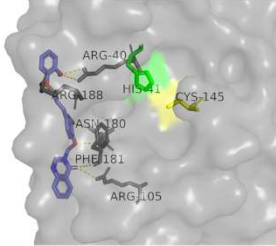
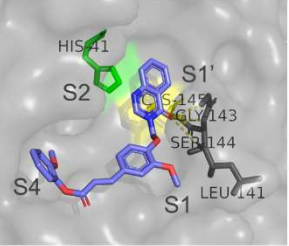
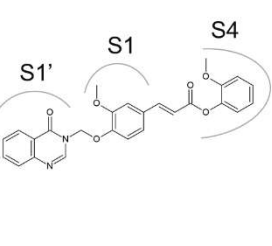
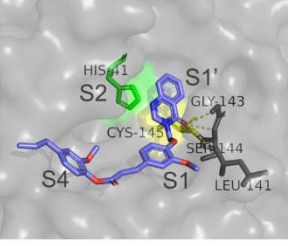
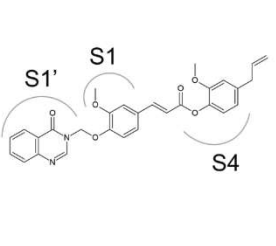
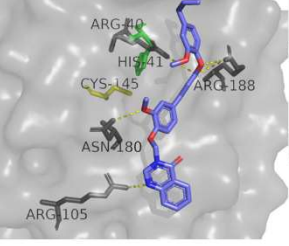
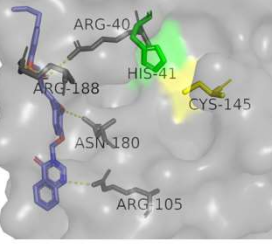
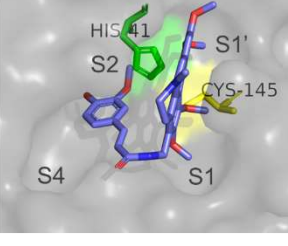
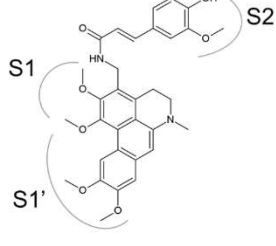
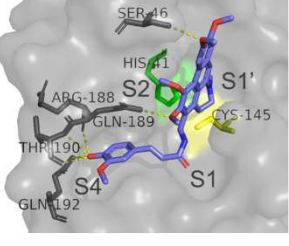
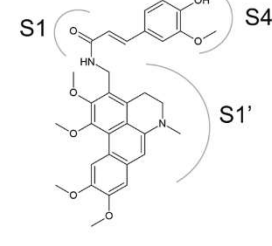
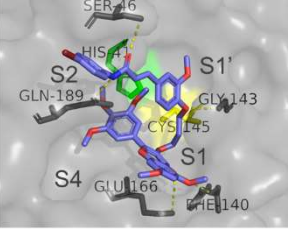
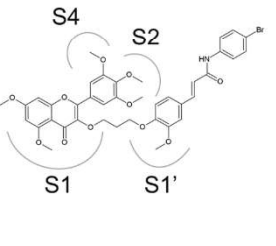
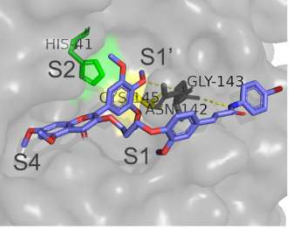
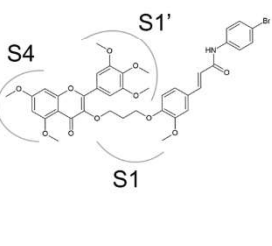
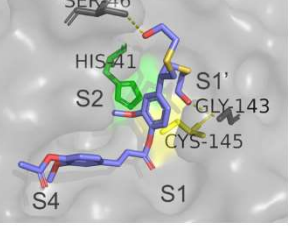
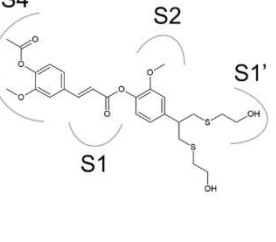
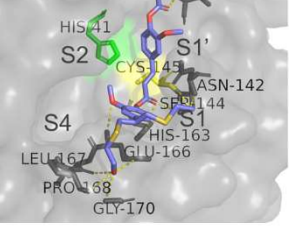
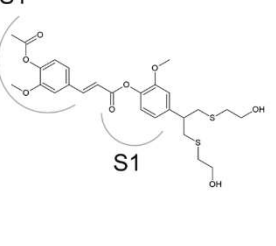
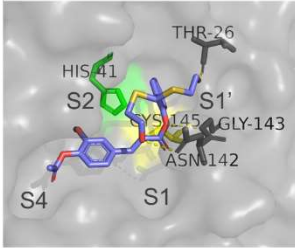
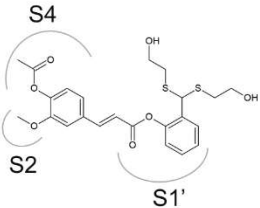
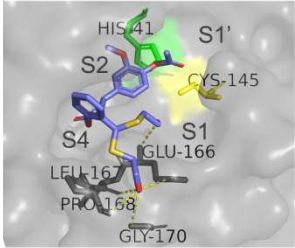
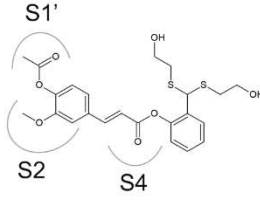
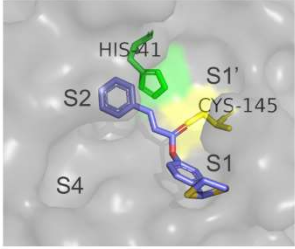
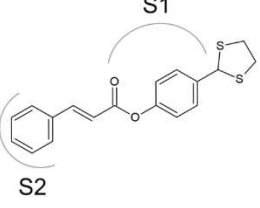
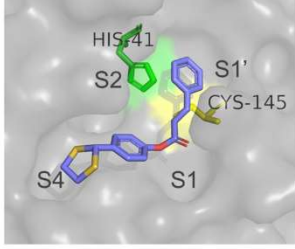
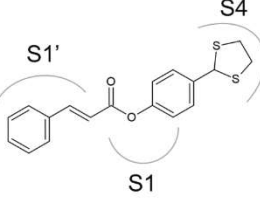
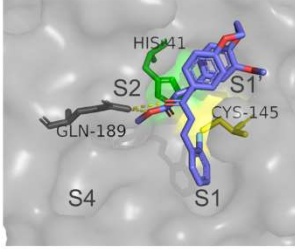
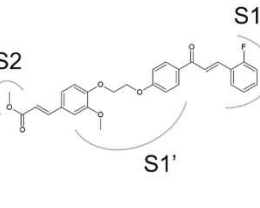
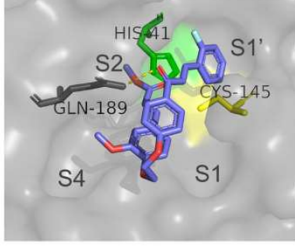
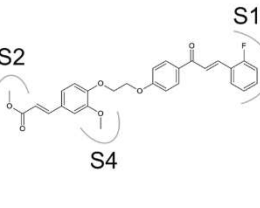
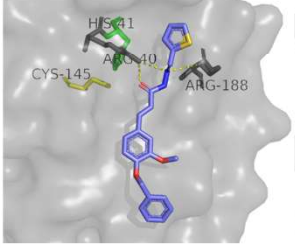
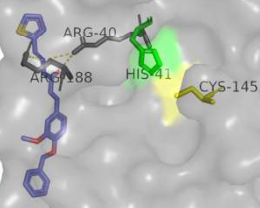
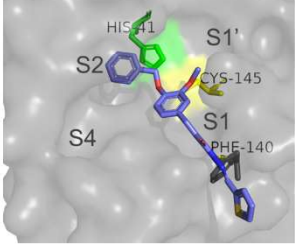
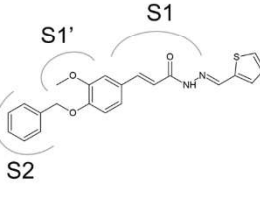
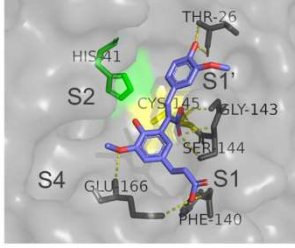
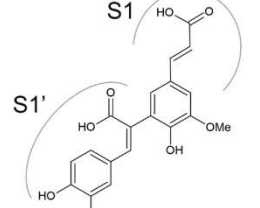
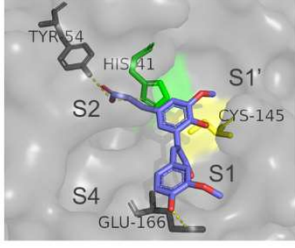
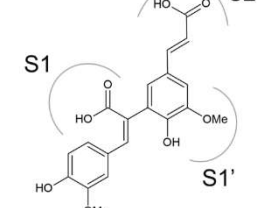


Figure S7. Binding modes of the second and third clusters for FA rutinoides in the active site of M^{pro}.

<p>Compound 7a Cluster 2 6.557 kcal/mol</p> 	<p>Compound 7a Cluster 3 6.363 kcal/mol</p> 
<p>Compound 13b Cluster 2 6.348 kcal/mol</p> 	<p>Compound 13b Cluster 3 6.212 kcal/mol</p> 
<p>Compound 4f Cluster 2 6.075 kcal/mol</p> 	<p>Compound 4f Cluster 3 5.971 kcal/mol</p> 
<p>Compound 2 Cluster 2 7.280 kcal/mol</p> 	<p>Compound 2 Cluster 3 7.266 kcal/mol</p> 
<p>Compound g18 Cluster 2 6.815 kcal/mol</p> 	<p>Compound g18 Cluster 3 6.667 kcal/mol</p> 

<p>Compound e27 Cluster 2 7.756 kcal/mol</p>  	<p>Compound e27 Cluster 3 7.705 kcal/mol</p>  
<p>Compound e28 Cluster 2 7.592 kcal/mol</p>  	<p>Compound e28 Cluster 3 7.467 kcal/mol</p>  
<p>Compound 5 Cluster 2 6.961 kcal/mol</p>  	<p>Compound 5 Cluster 3 6.868 kcal/mol</p>  
<p>Compound 4n Cluster 2 7.187 kcal/mol</p>  	<p>Compound 4n Cluster 3 6.976 kcal/mol</p>  
<p>Compound 2a Cluster 2 6.274 kcal/mol</p>  	<p>Compound 2a Cluster 3 5.886 kcal/mol</p>  

<p>Compound 2y Cluster 2 6.174 kcal/mol</p>  	<p>Compound 2y Cluster 3 6.099 kcal/mol</p>  
<p>Compound 2s Cluster 2 6.662 kcal/mol</p>  	<p>Compound 2s Cluster 3 6.313 kcal/mol</p>  
<p>Compound F3 Cluster 2 7.648 kcal/mol</p>  	<p>Compound F3 Cluster 3 7.604 kcal/mol</p>  
<p>Compound D4 Cluster 2 6.607 kcal/mol</p>  	<p>Compound D4 Cluster 3 6.509 kcal/mol</p>  
<p>Ferulic acid dimer Cluster 2 7.001 kcal/mol</p>  	<p>Ferulic acid dimer Cluster 3 6.875 kcal/mol</p>  

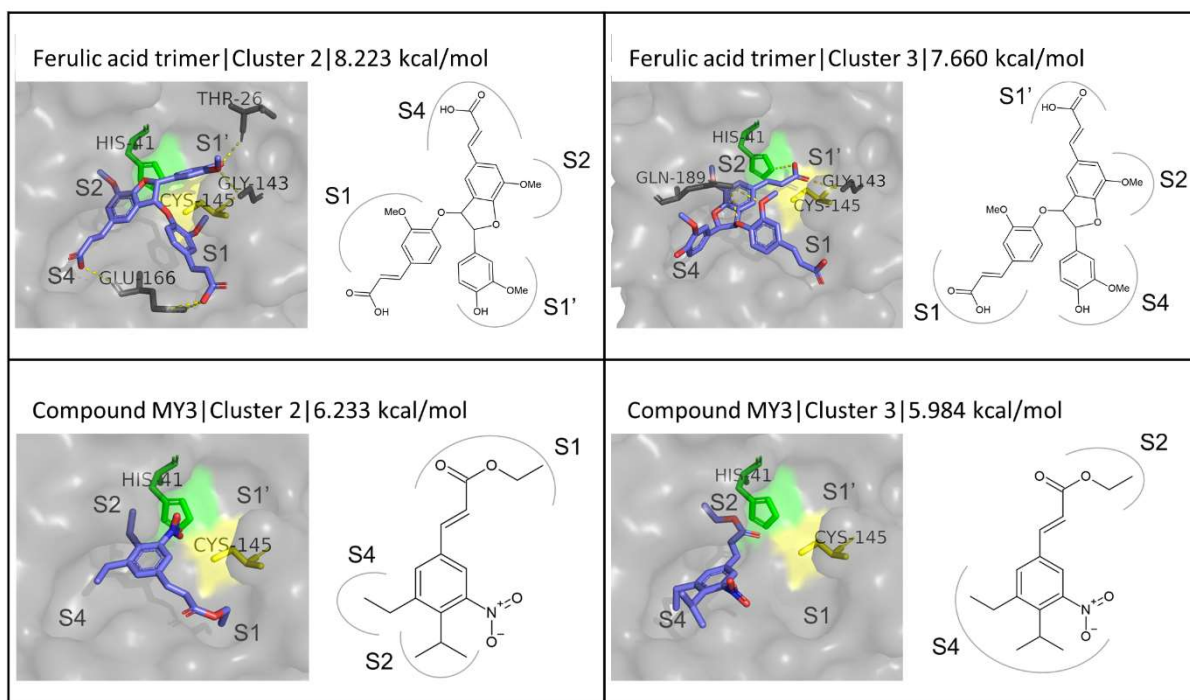


Figure S8. Binding modes of the second and third clusters for chemically synthesized FA derivatives in the active site of M^{pro} .