Supplementary Information

Supplementary 1: Selection of 300 Compounds

Table S1: List of the 300 compounds that were used in this *in silico* study. Their binding affinities from Schrödinger (Glide Energy) and AutoDock Vina (Binding Affinity) are provided.

Ligands	Glide Energy (kcal/mol)	Binding Affinity (kcal/mol)	OliveNet™
Jaspolyanoside	-82.0	-8.5	✓
Saquinavir	-77.7	-7.9	
Isojaspolyoside A	-77.5	-8.1	✓
Jaspolyoside	-77.5	-7.8	✓
Quercetin 3-O-rutinoside	-77.0	-9.4	✓
Verbascoside	-76.3	-8.5	✓
Isoacteoside	-75.1	-9.2	✓
Ligstroside derivative 5	-73.4	-7.4	✓
Luteolin-3′,7-O-diglucoside	-71.7	-8.5	✓
Ritonavir	-71.5	-7.6	
Oxidized verbascoside	-71.2	-8.1	✓
β-Hydroxy verbascoside	-71.1	-8.6	✓
Ligstroside derivative 4	-71.0	-7.8	✓
Oleuricine B	-70.6	-5.8	✓
Acteoside	-70.4	-8.6	✓
Orbanchoside	-70.3	-8.3	✓
Scolymoside	-69.7	-7.6	✓
Hellicoside	-69.4	-7.9	✓
Ligstroside derivative 3	-69.3	-7.7	✓
Rutin	-69.3	-7.8	✓
7"-S-Hydroxyoleuropein	-68.9	-7.5	✓
Neo-nüzhenide	-68.8	-7.8	✓
4'-O-β-D-Glucosyl-9-O-(6"-deoxysaccharosyl)olivil	-67.9	-8.1	✓
Suspensaside	-67.7	-8.8	✓
β-Hydroxy-acteoside	-67.7	-8.6	✓
Oleuricine A	-67.3	-7.9	✓
10-Hydroxyoleuropein	-66.7	-7.6	✓
Luteolin-7,4-O-diglucoside	-66.3	-8.3	✓
Oleuropein diglucoside	-66.3	-7.2	✓
Suramin	-66.3	-10.7	
Isoverbascoside	-66.2	-9.1	✓
Apigenin-7-O-rutinoside	-66.1	-8.6	✓
Lucidumoside C	-66.0	-7.8	✓
Nüzhenide 11-Methyl oleoside	-65.3	-8.4	✓
Isorhoifolin	-65.3	-8.6	✓
Nelfinavir	-65.2	-8.3	

Oleuropein-3'-O-β-D-glucopyranoside	-64.6	-7.3	✓
Amikacin	-64.5	-6.1	
(-)-Epicatechin gallate	-64.1	-8.2	
Hesperidin	-64.0	-8.8	✓
Oleuropein-3"-Methyl ether	-63.6	-7.8	✓
Cyanidin-3-O-glucoside	-62.7	-8.7	✓
Demethyloleuropein	-62.5	-8.2	✓
Demethyloleuropein (l-shaped)	-62.5	-7.9	✓
Oxidized isoverbascoside	-62.4	-9.1	✓
Oleuroside-10-carboxylic acid	-61.9	-7.9	✓
Nüzhenide	-61.8	-8.8	✓
D,L-Sulforaphane glutathione	-61.7	-6.3	
Luteolin-8-C-glucoside	-61.2	-8.8	✓
Quercitrin	-60.7	-8.9	✓
Quercetin-3-O-glucoside	-60.6	-8.2	✓
Dihydro-oleuropein	-60.5	-7.1	✓
Ceftazidime	-60.5	-7.7	
SRT2104	-60.5	-8.6	
SRT1720	-60.5	-9.1	
Quercetin-3-rhamnoside	-60.1	-8.8	✓
Nüzhenide oleoside	-60.1	-8.1	✓
Cyanidin-3-O-rutinoside	-60.0	-8.8	✓
Oleuropein	-59.6	-8.0	✓
Simeprevir	-59.4	-8.5	
Oleuroside	-59.1	-7.6	✓
Quercetin-7-O-glucoside	-58.4	-8.6	✓
Delphinidin-3-O-glucoside	-58.3	-8.3	✓
Darunavir	-58.2	-7.1	
Luteolin-6-C-glucoside	-58.1	-7.8	✓
Ligstroside	-58.1	-7.9	✓
Remdesivir	-58.0	-7.5	
10-Hydroxy oleuropein aglycone	-56.7	-7.2	✓
Ligstroside-3'-O-β-D-glucopyranoside	-56.6	-7.4	✓
Luteolin-4'-O-rutinoside	-56.5	-8.9	✓
Wedelosin	-56.2	-7.2	✓
Lopinavir	-56.2	-8.0	
Ligstroside derivative 2	-56.2	-6.9	✓
Hydroxytyrosol diglucoside	-56.0	-8.2	✓
Ceftriaxone	-55.9	-8.1	
Luteolin-7-O-glucoside	-55.7	-8.3	✓
Ligstroside derivative 1	-55.3	-7.5	✓
Luteolin-4’-O-glucoside	-55.0	-7.6	✓
Luteolin-7-O-rutinoside	-54.9	-8.3	✓
Elenolic acid diglucoside	-54.9	-7.4	✓
Vicenin-2	-54.8	-8.4	✓
Demethylligstroside	-54.1	-7.4	✓

Apigenin-7-O-glucoside	-53.8	-8.0	✓
Oleuropeindial - Lactone (Cannizzaro-like product of oleuropeindial)	-53.3	-7.3	✓
Caffeoyl-6'-secologanoside	-53.1	-7.8	✓
6'-β-D-Glucopyranosyl oleoside	-53.0	-8.3	✓
(+)-Fraxiresinol-1-β-D-glucopyranoside	-52.6	-7.9	✓
(+)-1-Acetoxypinoresinol-4'-β-D-glucopyranoside-4"-O-methyl ether	-52.0	-7.3	✓
(+)-1-Hydroxypinoresinol-4"-O-methyl ether	-52.0	-7.3	✓
Hydroxytyrosil elenolate	-52.0	-7.2	✓
Indinavir	-52.0	-8.2	
Hypericin	-51.7	-10.2	
Cefotaxime	-51.4	-7.2	
Comselogoside	-51.1	-8.1	✓
Tobramycin	-51.1	-5.9	
3-Acetyloxy berchemol	-50.9	-6.7	✓
Esculin	-50.6	-7.4	✓
Chrysoeriol-7-O-glucoside	-50.4	-8.1	✓
6'-Rhamnopyranosyl oleoside	-50.3	-7.7	✓
Curcumin	-50.3	-7.4	
10-Hydroxy-10-methyl oleuropein aglycone	-50.1	-6.8	✓
Demethoxycurcumin	-49.8	-7.5	
Oleuropeindial (keto form)	-49.6	-6.6	✓
Hemiacetal of dialdehydic oleuropein aglycone decarboxymethyl	-49.3	-6.8	✓
1-Acetoxypinoresinol	-49.2	-6.7	✓
Ertapenem	-48.9	-7.6	
Baricitinib	-48.8	-8.2	
(+)-1-Hydroxypinoresinol-4'-β-D-glucopyranoside	-48.8	-7.5	✓
Demethyloleuropein aglycone (enol form)	-48.8	-7.4	✓
Methoxyluteolin	-48.7	-7.6	✓
Hydroxytyrosol acyclodihydroelenolate	-48.4	-6.7	✓
Ligstroside aglycone	-48.4	-6.8	✓
Oleuropeindial (Cannizzaro-like product of oleuropeindial)	-48.3	-7.3	✓
Monoaldehydic form of Oleuropein aglycon	-48.1	-7.3	✓
Cefuroxime	-47.9	-6.6	
3,4-DHPEA-EDA (Oleuropein-aglycone di-aldehyde)	-47.8	-6.7	✓
Syringaresinol	-47.7	-7.4	✓
Baicalin	-47.6	-8.5	

Berchemol	-47.6	-7.4	✓
3,4-DHPEA-DETA	-47.6	-7.1	✓
Loganin	-47.3	-6.9	✓
Rosmarinic acid	-47.3	-7.8	✓
Delphinidin	-47.3	-7.4	✓
Hydroxytyrosil-elenolate	-47.1	-6.8	✓
Monoaldehydic form of Ligstroside aglycon	-46.9	-6.9	✓
Nafamostat	-46.7	-7.7	
3,4-DHPEA-DEDA (acetal)	-46.7	-6.3	✓
Oleacein (Dialdehydic form of decarboxymethyl Oleuropein aglycon)	-46.5	-6.8	✓
10-Hydroxy oleuropein aglycone decarboxymethyl	-46.4	-6.8	✓
Caffeoylglucose	-46.3	-8.0	✓
Oleoside dimethylester	-46.0	-6.5	✓
Ligstroside aglycone methyl acetal	-45.9	-7.4	✓
D,L-Sulforaphane N-acetyl-L-cysteine	-45.6	-5.8	
Hydroxytyrosol-1′-β-glucoside	-45.3	-7.2	✓
Sulfasalazine	-45.2	-8.0	
Hydroxytyrosol-4-β-glucoside	-45.0	-6.8	✓
Oleuropein aglycone (3,4-DHPEA-EA)	-44.9	-6.9	✓
Oleoside-11-Methylester	-44.9	-7.3	✓
Eriodictyol	-44.7	-7.5	✓
Secologanoside	-44.7	-6.5	✓
Oleohydroxypyterol	-44.6	-6.3	✓
Amoxicillin	-44.3	-7.8	
7-Deoxyloganic acid	-44.2	-7.3	✓
Azithromycin	-44.0	-5.5	
Doripenem	-44.0	-7.4	
Catechin	-43.8	-7.2	
Arbidol	-43.8	-6.3	
(+)-1-Acetoxypinoresinol-4'-β-D-glucopyranoside	-43.7	-7.4	✓
Demethyloleuropein aglycone	-43.7	-7.4	✓
Quercetin	-43.6	-7.5	✓
Luteolin	-43.6	-7.4	✓
(+)-Cycloolivil	-43.5	-6.7	✓
Cornoside	-43.4	-7.1	✓
Hemiacetal of dialdehydic ligstroside aglycone decarboxymethyl	-43.3	-6.2	✓
Fangicholine	-43.3	-7.4	
Secologanin	-43.3	-6.4	✓
Scopolin	-43.1	-7.7	✓
Hydroxytyrosol-3-β-glucoside	-43.0	-6.2	✓
1-oleyltyrosol	-42.8	-5.9	✓

Decarboxymethyl ligstroside aglycone	-42.6	-7.3	✓
Hesperitin	-42.5	-7.3	✓
(+)-1-Acetoxypinoresinol-4"-O-methyl ether	-42.4	-6.8	✓
Indomethacin	-42.3	-7.6	
Chrysoeriol	-42.2	-7.3	✓
D,L-Sulforaphane-L-cysteine	-42.2	-5.2	
Cepharanthine	-41.9	-8.0	
Elenolic acid glucoside	-41.9	-6.9	✓
Oleocanthal (Dialdehydic form of decarboxymethyl Ligstroside aglycon)	-41.8	-6.5	✓
Chlorogenic acid	-41.7	-7.6	✓
Naringenin	-41.5	-7.7	
Demethyloleuropein aglycone dialdehyde	-41.4	-7.1	✓
Kaempferol	-41.3	-7.7	
Loganic acid	-41.2	-7.1	✓
Levofloxacin	-41.1	-7.3	
Diosmetin	-41.0	-7.4	✓
Hydroxytyrosol rhamnoside	-41.0	-7.0	✓
Imipenem	-40.9	-6.2	
Secologanol	-40.9	-6.2	✓
Ivermectin	-40.7	-7.6	
Pinoresinol	-40.7	-7.8	✓
Secologanic acid	-40.7	-7.6	✓
Cyanidin (cation)	-40.4	-7.3	✓
p-HPEA-EDA	-40.0	-6.2	✓
Moxifloxacin	-39.9	-7.8	
Disulfiram	-39.7	-4.4	
Ergosterol	-39.5	-7.4	
Tetrandine	-39.3	-7.2	
Chloroquine	-39.3	-5.8	
Apigenin	-39.3	-7.7	✓
Ciprofloxacin	-39.1	-7.7	
Ampicillin	-39.1	-6.7	
Gingerol	-39.0	-5.8	
Caftaric acid	-38.3	-7.3	✓
Deoxyloganic acid lauryl ester	-38.3	-5.6	✓
Pterostilbene	-38.2	-6.5	
Salidroside	-38.2	-7.0	✓
Taxifolin	-38.2	-7.4	✓
Verucosin	-38.2	-7.3	✓
1-(3’-Methoxy-4’-hydroxy)- phenyl-6,7-dihydroxyisochroman	-37.6	-7.0	✓
Chloroquine Phosphate	-37.5	-5.7	
Meropenem	-37.4	-7.0	
Hydroxychloroquine	-37.0	-6.5	

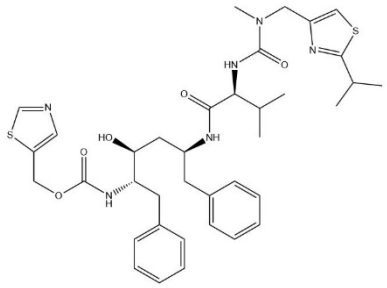
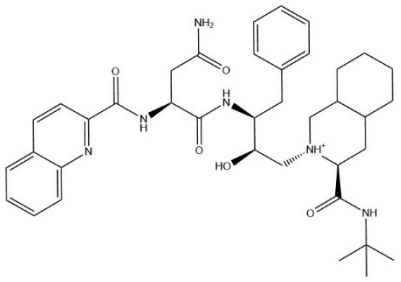
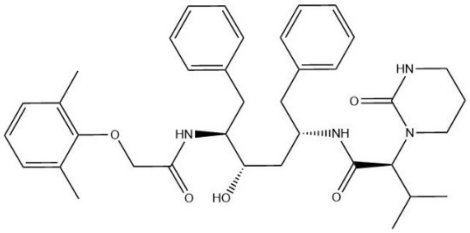
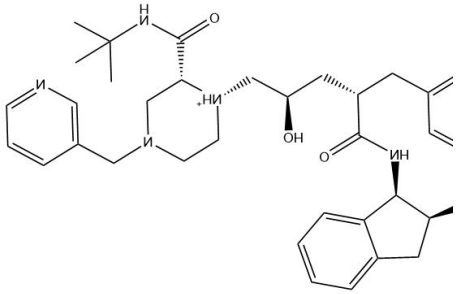
Dihydrotanshinone	-36.8	-7.8	
Oleoside	-36.5	-6.8	✓
Linoleic acid	-36.4	-5.1	✓
Oseltamivir	-36.4	-6.2	
Elaidic acid	-35.7	-4.6	✓
Penicillin	-35.5	-7.3	
Melatonin	-35.4	-6.2	
Petroselinic acid	-35.3	-4.9	✓
Emodin	-34.8	-7.3	
Quinine	-34.7	-7.0	
Elenolic acid methylester	-34.2	-5.6	✓
Oleic acid	-34.0	-4.9	✓
Linoelaidic acid	-33.9	-5.2	✓
D-(+)-Erythro-1-(4-hydroxy-3-methoxy)- 214 - phenyl-1,2,3-propantriol	-33.4	-5.9	✓
Shionone	-33.0	-7.7	
Hydroxytyrosol acetate	-32.8	-5.9	✓
Tyrosol acetate	-32.7	-5.7	✓
1-Phenyl-6,7-dihydroxyisochroman	-32.7	-6.7	✓
Cis-10-Heptadecenoic Acid	-32.3	-4.9	✓
Ebselen	-32.2	-6.5	
Resveratrol	-32.0	-6.9	
Trans-palmiteolieic acid	-31.7	-4.8	✓
Esculetin	-31.7	-6.2	✓
Sulforaphane	-31.5	-3.9	
Sulfamethoxazole	-31.2	-6.7	
Zingerol	-30.8	-5.5	
Palmitic acid	-30.7	-4.5	✓
Vaccenic acid	-30.1	-5.1	✓
Scopoletin	-29.8	-5.8	✓
Myristic acid	-29.3	-4.7	✓
Trimethoprim	-29.2	-6.4	
DEDA acetal	-28.7	-5.0	✓
2,3-dihydrocaffeic acid	-28.7	-5.4	✓
Margaric acid	-28.5	-4.8	✓
Homovanillyl alcohol	-28.2	-5.1	✓
Elenolic acid	-28.2	-5.7	✓
3,4-Dihydroxyphenylglycol	-28.1	-5.5	✓
Acetaminophen	-28.1	-5.2	
Dialdehydic elenolic ester decarboxymethyl	-27.9	-4.8	✓
3,4,5-Trimethoxybenzoic acid	-27.7	-5.5	✓
Palmitoleic acid	-27.3	-5.0	✓
2,5-Dihydroxyphenylacetic acid	-26.9	-5.3	✓
Clavulanic acid	-26.3	-6.0	
Hydroxytyrosol	-26.3	-5.2	✓

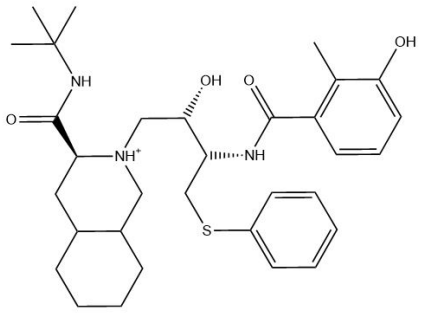
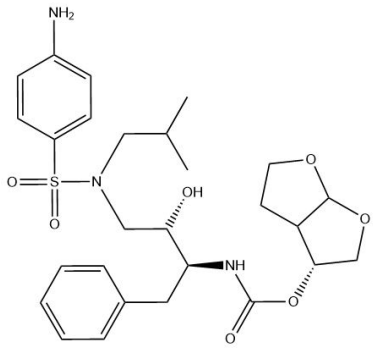
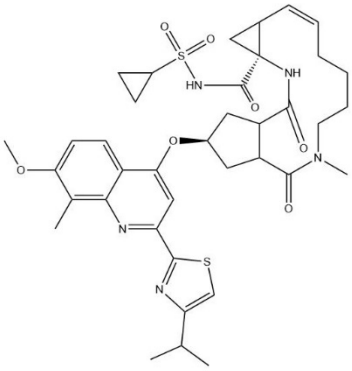
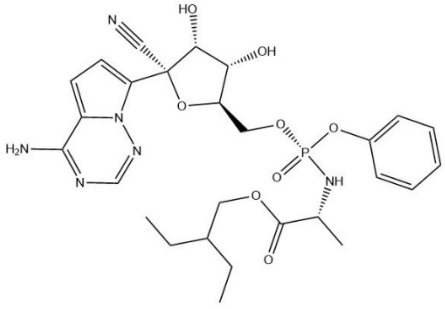
Demethyl elenolic acid	-26.2	-5.8	✓
Ferulic acid	-26.1	-5.6	✓
Homovanillin	-26.0	-5.0	✓
Lauric acid	-25.9	-4.7	✓
Syringaldehyde	-25.7	-5.2	✓
Syringic acid	-25.5	-5.5	✓
Sinapic acid	-25.4	-5.8	✓
Dialdehydic elenolic acid decarboxymethyl	-25.4	-4.7	✓
Aspirin	-25.4	-5.1	
Hydroxycaffeic acid	-25.4	-5.9	✓
m-Coumaric acid	-25.3	-5.4	✓
o-Coumaric acid	-24.5	-5.2	✓
Tyrosol	-24.2	-4.6	✓
Isoeugenol	-24.2	-5.2	✓
Caffeic acid	-24.2	-7.9	✓
4-Hydroxy-3-methoxy-phenylacetic acid	-24.0	-5.4	✓
4-O-methyl-D-glucuronic acid	-24.0	-5.4	✓
Quinic acid	-23.9	-5.4	✓
4-Ethylguaiacol	-23.8	-4.8	✓
Gallic acid	-23.6	-5.5	✓
Dihydro-p-coumaric acid	-23.5	-5.1	✓
4-Hydroxybenzaldehyde	-23.4	-4.6	✓
3,4-Dihydroxyphenylacetic acid	-23.4	-5.6	✓
Phloretic acid	-23.1	-5.2	✓
Gentisic acid	-23.0	-5.2	✓
Shikimic acid	-23.0	-5.3	✓
2,4 dihydroxybenzoic acid	-23.0	-5.3	✓
p-cresol	-23.0	-4.2	✓
DEDA (Decarboxymethyl elenolic acid dialdehyde)	-22.9	-4.8	✓
4-Vinylguaiacol	-22.8	-4.9	✓
Acetylcysteine	-22.7	-4.6	
Protocatechuic acid	-22.6	-5.3	✓
4-Vinylphenol	-21.9	-4.4	✓
Fructosamine	-21.9	-5.0	
Homovanillic acid	-21.8	-5.2	✓
Guaiacol	-21.5	-4.5	✓
Allicin	-20.9	-3.7	
3,4-Dimethoxybenzoic acid	-20.7	-5.4	✓
2-Methoxy-4-vinylphenol	-20.7	-4.9	✓
p-Coumaric acid	-20.7	-5.2	✓
Vanillic acid	-20.7	-5.3	✓
Cinnamic acid	-20.6	-5.0	✓
m-cresol	-20.3	-4.4	✓
4-Methylcatechol	-20.2	-5.0	✓

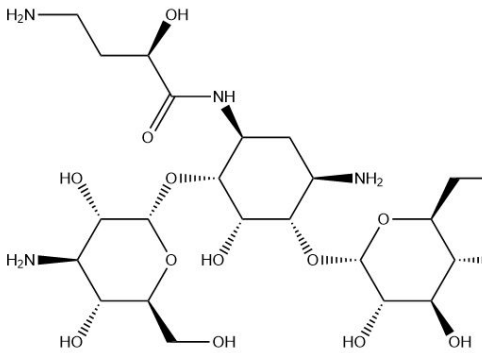
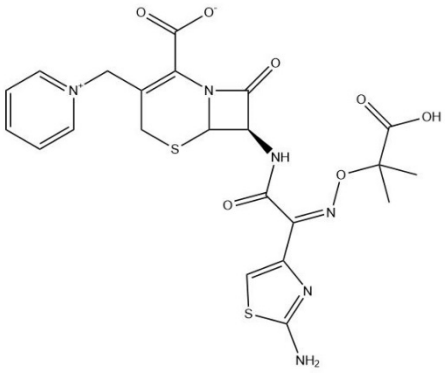
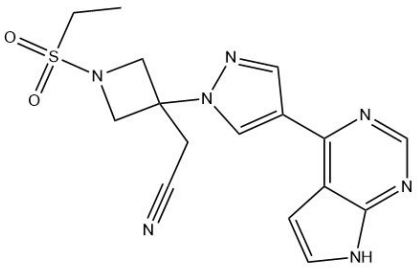
Homoveratric acid	-20.2	-5.5	✓
Menthol	-20.0	-4.7	
4-Ethylphenol	-19.8	-4.4	✓
2,6-Dihydroxybenzoic acid	-19.7	-5.1	✓
Catechol	-18.5	-4.6	✓
o-cresol	-18.3	-4.0	✓
Patchouli alcohol	-17.6	-5.1	
Phenol	-16.8	-3.9	✓
Metformin	-16.7	-4.7	
4-hydroxybenzoic acid	-16.3	-4.8	✓
α-ketoamide 13b inhibitor	-65.7	-7.7	

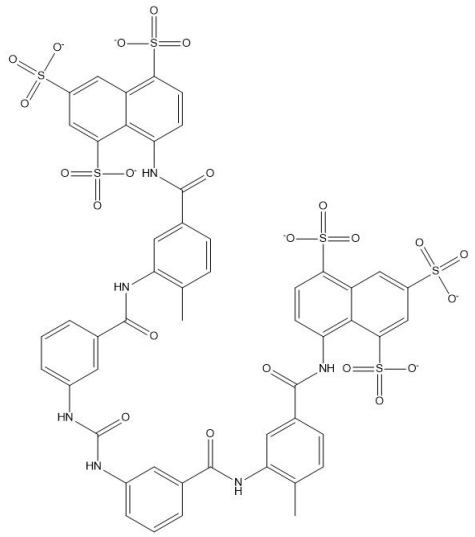
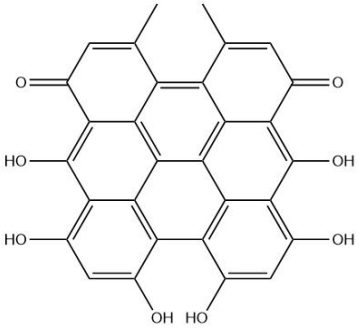
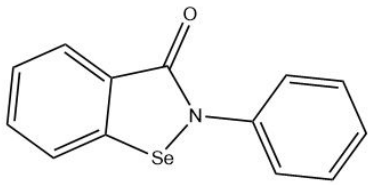
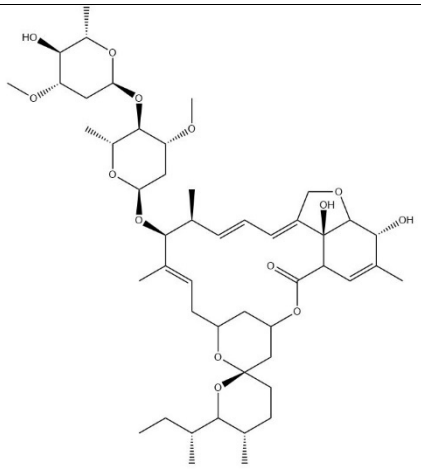
Supplementary 2: Selection of 30 compounds

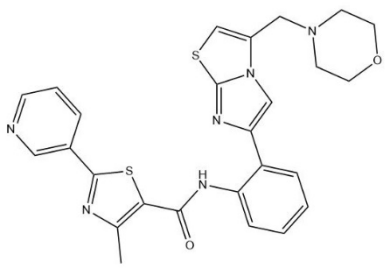
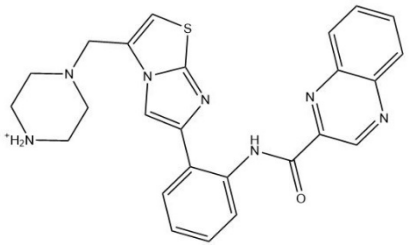
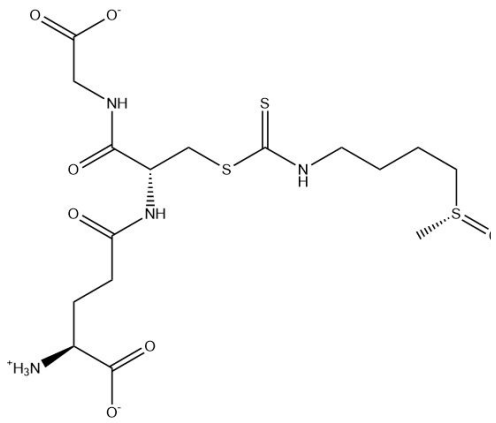
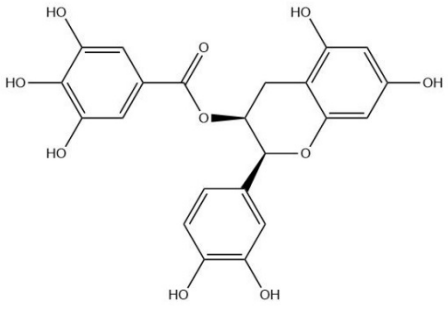
Table S2: The structures of the 30 compounds that were predicted by the Schrödinger program to bind to the active site of the M^{pro} monomer and were selected to undergo blind docking on the M^{pro} dimer are provided.

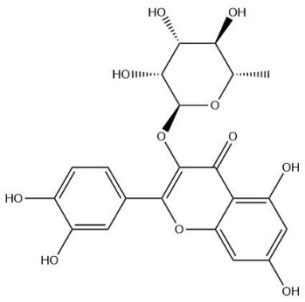
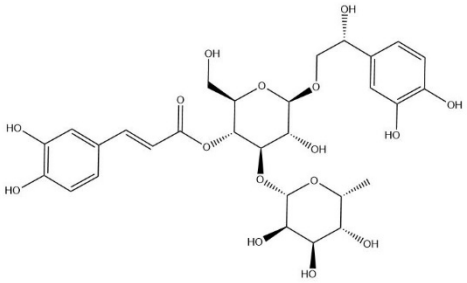
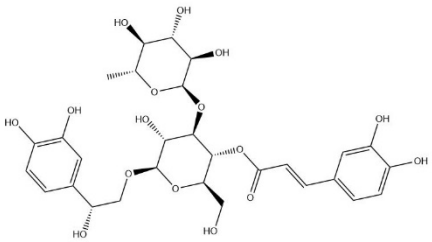
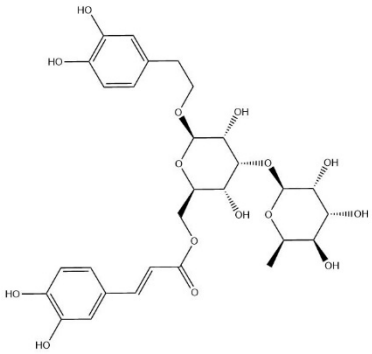
Compound	Classification	Glide Energies: kcal/mol	Structures
Ritonavir	Protease inhibitor	-71.5	
Saquinavir	Protease inhibitor	-77.7	
Lopinavir	Protease inhibitor	-56.2	
Indinavir	Protease inhibitor	-52.0	

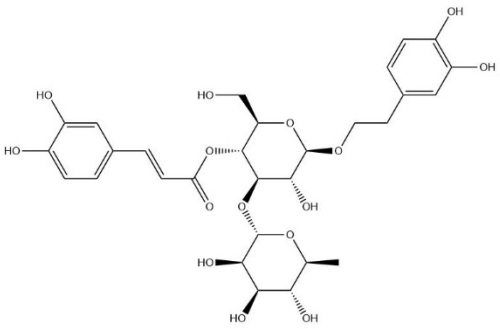
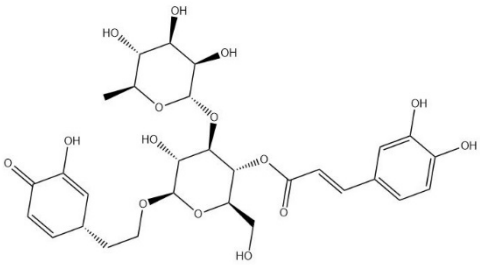
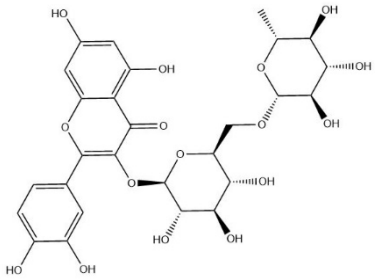
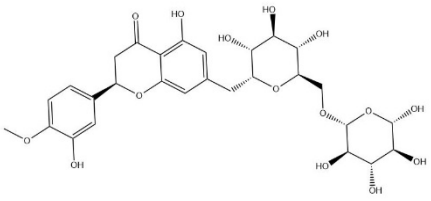
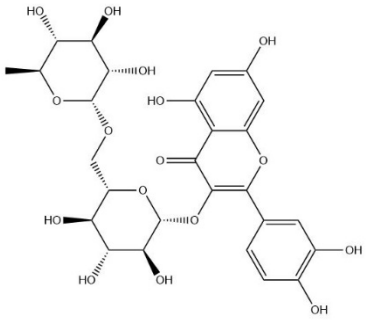
Nelfinavir	Protease inhibitor	-65.2	
Darunavir	Protease inhibitor	-58.2	
Simeprevir	Protease inhibitor	-59.4	
Remdesivir	Nucleotide analog	-58.0	

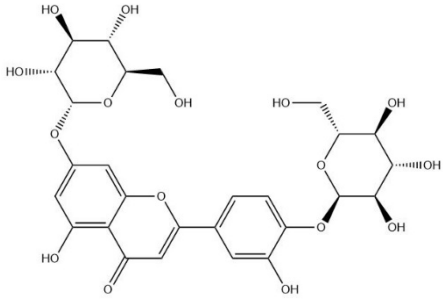
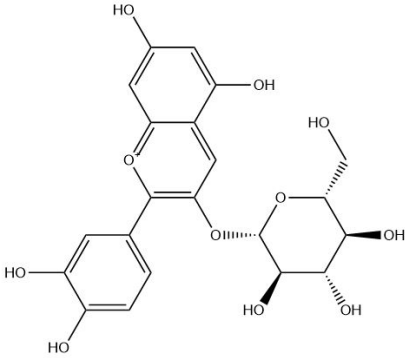
Amikacin	Antibiotic	-64.5	
Ceftazidime	Antibiotic	-60.5	
Baricitinib	Janus kinase inhibitor	-48.8	

Suramin	Antiparasitic	-66.3	
Hypericin	Anthraquinone derivative	-51.7	
Ebselen	Organoselenium drug	-32.2	
Ivermectin	Anti-parasitic drug	-40.7	

SRT2104	Sirtuin activator	-60.5	
SRT1720	Sirtuin activator	-60.5	
D,L-Sulforaphane glutathione	Isothiocyanate analog	-61.7	
(-)-Epicatechin gallate	Natural flavonoid compound	-64.1	

Quercitrin	OliveNet™	-60.7	
β-Hydroxy verbascoside	OliveNet™	-71.1	
β-Hydroxy acteoside	OliveNet™	-67.7	
Isoacteoside	OliveNet™	-75.1	

Verbascoside	OliveNet^{TM}	-76.3	
Oxidized verbascoside	OliveNet^{TM}	-71.2	
Quercetin 3-O-rutinoside	OliveNet^{TM}	-77.0	
Hesperidin	OliveNet^{TM}	-64.0	
Rutin	OliveNet^{TM}	-69.3	

Luteolin-7,4-O-diglucoside	OliveNet™	-66.3	
Cyanidin-3-O-glucoside	OliveNet™	-62.7	

Supplementary 3: Blind docking results for hypericin, cyanidin-3-O-glucoside and SRT2104

Table S3: The blind docking results from AutoDock Vina are provided for the α-ketoamide inhibitor.

Compound:	**α-ketoamide inhibitor**			
	MONOMER		**DIMER**	
Pose Ranking	**Pose affinity (kcal/mol)**	**Site of binding**	**Pose affinity (kcal/mol)**	**Site of binding**
1	-7.7	Active	-9.4	Allosteric
2	-7.7	Active	-9.4	Allosteric
3	-7.6	Active	-9.1	Allosteric
4	-7.6	Active	-9.1	Allosteric
5	-7.5	Active	-9.1	Allosteric
6	-7.4	Active	-9.1	Allosteric
7	-7.4	Active	-9.1	Allosteric
8	-7.4	Active	-9.1	Allosteric
9	-7.4	Active	-9.1	Allosteric
10	-7.3	Active	-8.9	Allosteric
11	-7.3	Active	-8.9	Allosteric
12	-7.3	Active	-8.9	Allosteric
13	-7.3	Active	-8.8	Allosteric
14	-7.3	Active	-8.8	Allosteric
15	-7.2	Allosteric	-8.8	Allosteric
16	-7.2	Active	-8.7	Active
17	-7.2	Active	-8.7	Allosteric
18	-7.2	Active	-8.7	Allosteric
19	-7.1	Allosteric	-8.7	Allosteric
20	-7.1	Active	-8.6	Allosteric
	Total poses in active site =	**18**	**Total poses in active site =**	**1**

Table S4: The blind docking results from AutoDock Vina are provided for hypericin.

Compound:	**Hypericin**			
	MONOMER		**DIMER**	
Pose Ranking	**Pose affinity (kcal/mol)**	**Site of binding**	**Pose affinity (kcal/mol)**	**Site of binding**
1	-9.4	Active	-10.2	Active
2	-9.4	Active	-10.2	Active
3	-8.6	Allosteric	-10.2	Active
4	-8.6	Allosteric	-10.2	Active
5	-8.5	Allosteric	-10.0	Allosteric
6	-8.5	Allosteric	-9.9	Allosteric
7	-8.4	Active	-9.9	Allosteric
8	-8.4	Active	-9.9	Allosteric
9	-8.4	Allosteric	-9.8	Allosteric
10	-8.4	Allosteric	-9.8	Allosteric
11	-8.4	Allosteric	-9.8	Allosteric
12	-8.3	Allosteric	-9.8	Allosteric
13	-8.3	Allosteric	-9.7	Allosteric
14	-8.3	Allosteric	-9.7	Allosteric
15	-8.3	Allosteric	-9.7	Allosteric
16	-8.3	Allosteric	-9.7	Allosteric
17	-8.2	Allosteric	-9.7	Allosteric
18	-8.1	Allosteric	-9.7	Allosteric
19	-8.0	Active	-9.7	Allosteric
20	-8.0	Active	-9.7	Allosteric
	Total poses in active site =	**6**	**Total poses in active site =**	**4**

Table S5: The blind docking results from AutoDock Vina are provided for cyanidin-3-O-glucoside.

Compound:	**Cyanidin-3-Oglucoside**			
	MONOMER		**DIMER**	
Pose Ranking	**Pose affinity (kcal/mol)**	**Site of binding**	**Pose affinity (kcal/mol)**	**Site of binding**
1	-8.7	Active	-8.8	Active
2	-8.7	Active	-8.8	Active
3	-8.6	Active	-8.6	Active
4	-8.0	Active	-8.6	Active
5	-7.9	Active	-8.5	Allosteric
6	-7.9	Active	-8.5	Allosteric
7	-7.9	Active	-8.4	Allosteric
8	-7.8	Active	-8.4	Allosteric
9	-7.8	Active	-8.4	Allosteric
10	-7.8	Active	-8.4	Allosteric
11	-7.7	Active	-8.2	Active
12	-7.7	Active	-8.2	Active
13	-7.6	Allosteric	-8.2	Allosteric
14	-7.5	Active	-8.2	Allosteric
15	-7.5	Active	-8.1	Active
16	-7.5	Active	-8.1	Allosteric
17	-7.5	Active	-8.1	Allosteric
18	-7.3	Active	-8.1	Allosteric
19	-7.6	Active	-8.0	Allosteric
20	-7.2	Active	-8.0	Allosteric
	Total poses in active site =	**19**	**Total poses in active site =**	**7**

Table S6: The blind docking results from AutoDock Vina are provided for SRT2104.

Compound:	**SRT2104**			
	MONOMER		**DIMER**	
Pose Ranking	**Pose affinity (kcal/mol)**	**Site of binding**	**Pose affinity (kcal/mol)**	**Site of binding**
1	-8.7	Active	-9.2	Active
2	-8.4	Active	-9.2	Allosteric
3	-8.4	Active	-9.2	Active
4	-8.4	Active	-9.2	Allosteric
5	-8.4	Active	-9.1	Allosteric
6	-8.4	Active	-9.1	Allosteric
7	-8.2	Active	-9.1	Allosteric
8	-8.2	Active	-9.1	Allosteric
9	-8.1	Active	-8.9	Allosteric
10	-8.1	Active	-8.8	Active
11	-8.0	Active	-8.8	Active
12	-8.0	Active	-8.8	Allosteric
13	-8.0	Active	-8.7	Allosteric
14	-7.9	Active	-8.7	Allosteric
15	-7.9	Allosteric	-8.7	Allosteric
16	-7.9	Active	-8.7	Allosteric
17	-7.9	Active	-8.6	Allosteric
18	-7.9	Allosteric	-8.6	Allosteric
19	-7.8	Active	-8.6	Allosteric
20	-7.8	Active	-8.6	Allosteric
	Total poses in active site =	**18**	**Total poses in active site =**	**4**

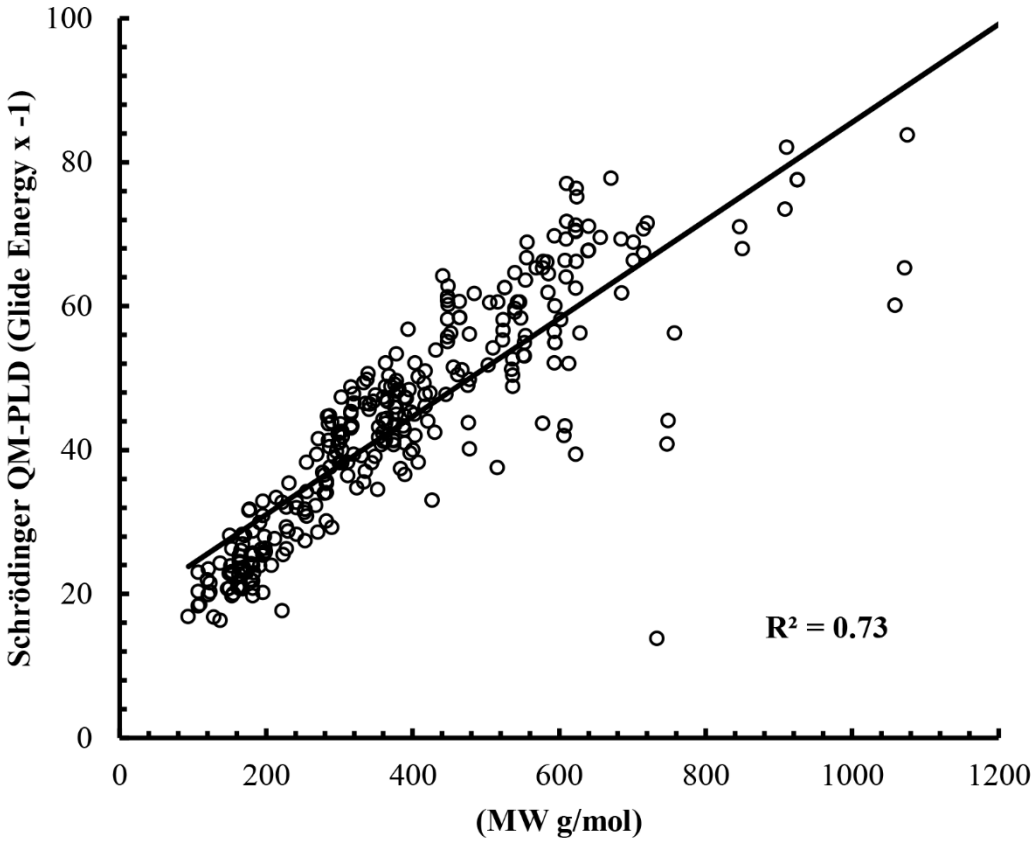


Figure S1: Correlation of Schrödinger QM-PLD Glide Energy scores with the molecular weight of the 300 compounds that were used in the initial screen.

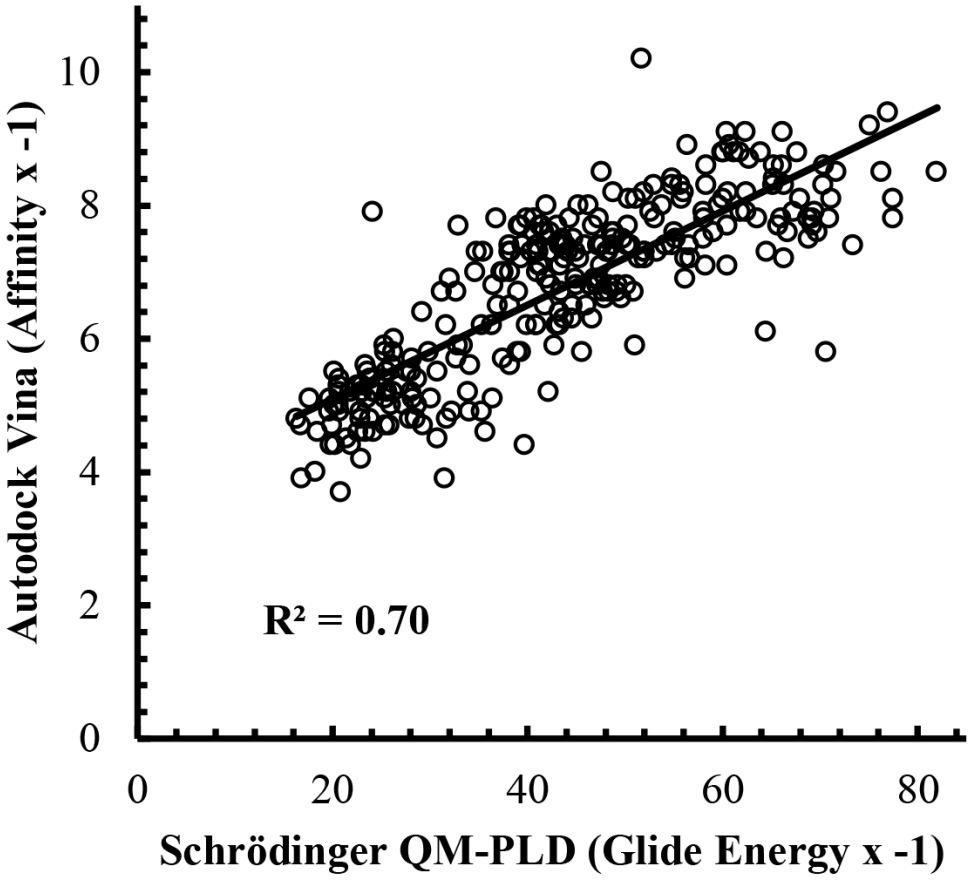


Figure S2: Correlation between Schrödinger QM-PLD Glide Energy scores and binding affinity scores from AutoDock Vina for the 300 compounds that were used in the initial screen.

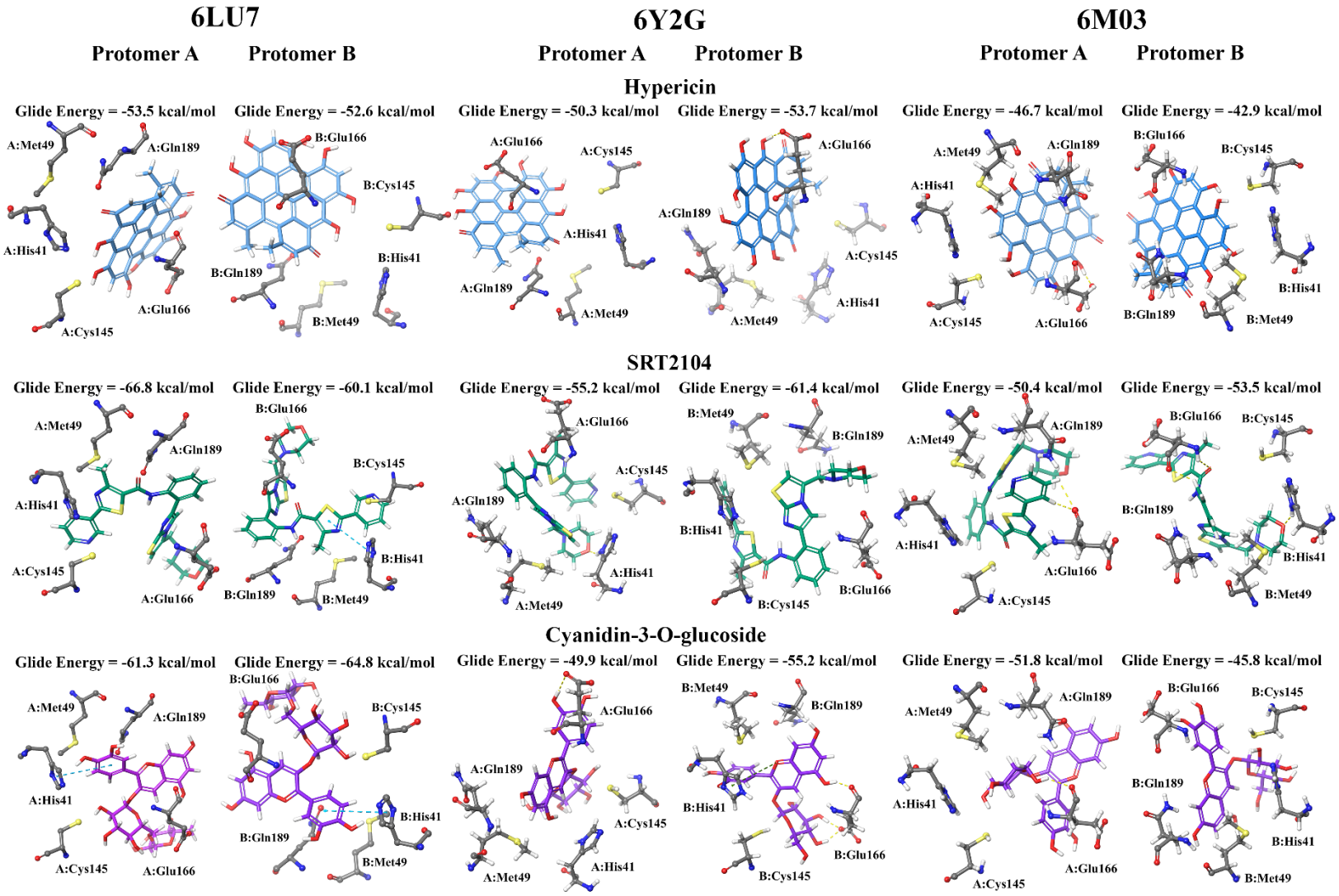


Figure S1: Comparison between docking to the active site of SARS-CoV-2 M^{pro} structures (PDB ID: 6LU7, 6Y2G, and 6M03) in protomers A and B. Hydrogen bonds are shown as yellow, pi-pi stacking in blue, and pi-cation bonds in green dashed lines.

Movie S1. 100 ns trajectory of the apo form of the SARS-CoV-2 main protease

Movie S2. 100 ns trajectory of hypericin bound to the active site of the SARS-CoV-2 main protease

Movie S3. 100 ns trajectory of SRT2104 bound to the active site of the SARS-CoV-2 main protease

Movie S4. 100 ns trajectory of cyanidin-3-O-glucoside bound to the active site of the SARS-CoV-2 main protease