

***In silico* drug repositioning to target the SARS-CoV-2 main protease as covalent inhibitors employing a combined structure-based virtual screening strategy of pharmacophore models and covalent docking.**

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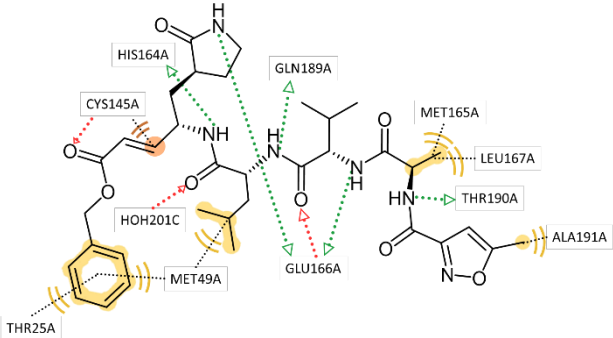
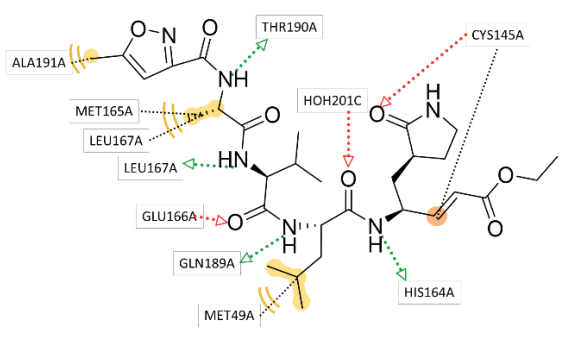
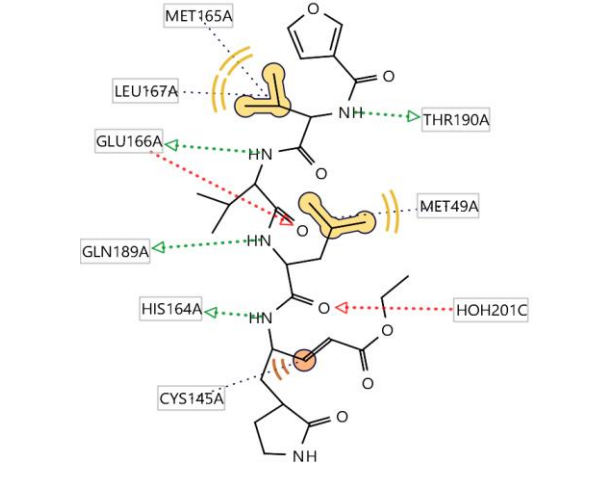
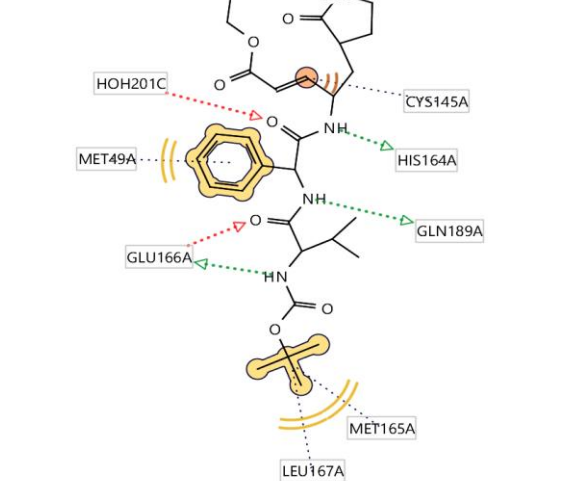
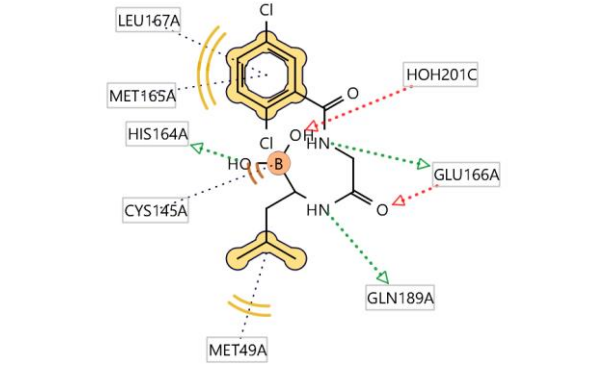
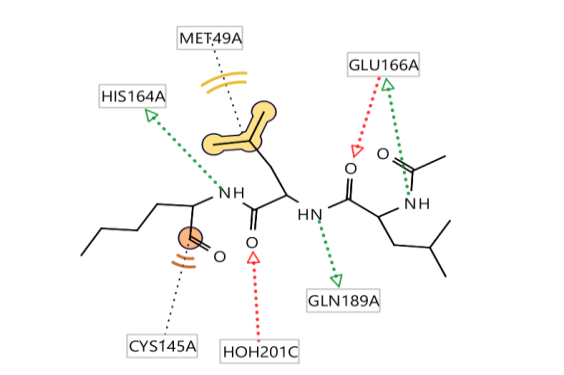
¹ Laboratorio de Diseño y Desarrollo de Nuevos Fármacos e Innovación Biotecnológica (Laboratory for the Design and Development of New Drugs and Biotechnological Innovation), Posgrado en Farmacología de la Escuela Superior de Medicina del Instituto Politécnico Nacional. Plan de San Luis y Salvador Díaz Mirón s/n, Casco de Santo Tomás, Ciudad de México 11340. Mexico.

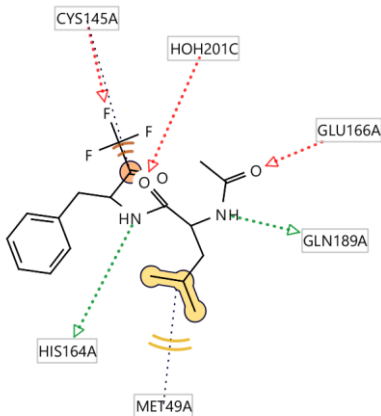
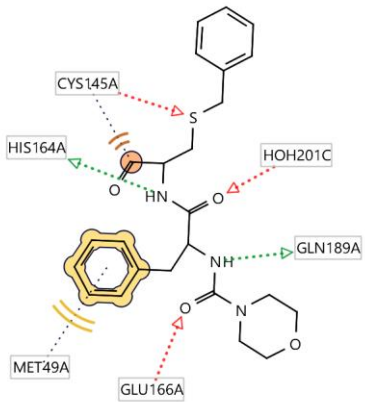
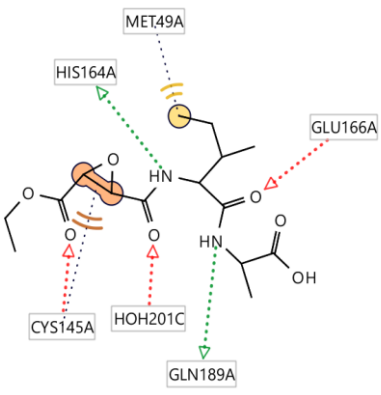
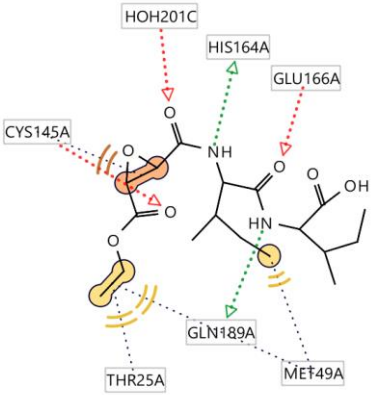
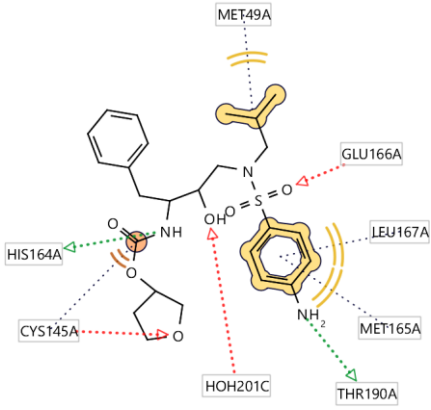
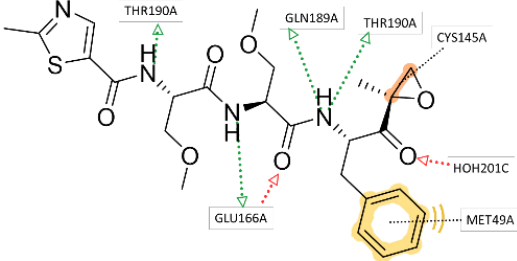
² Cátedras CONACyT

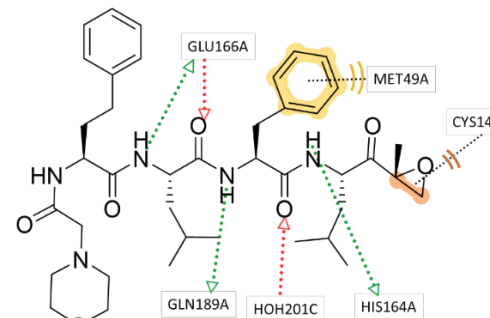
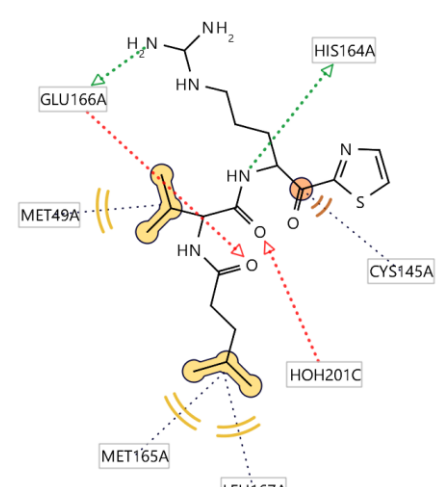
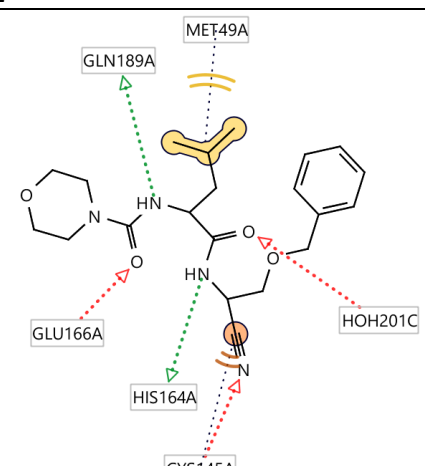
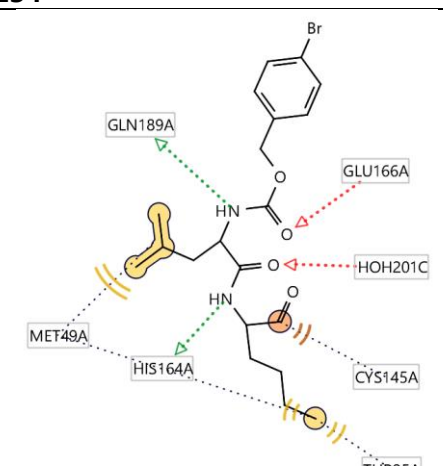
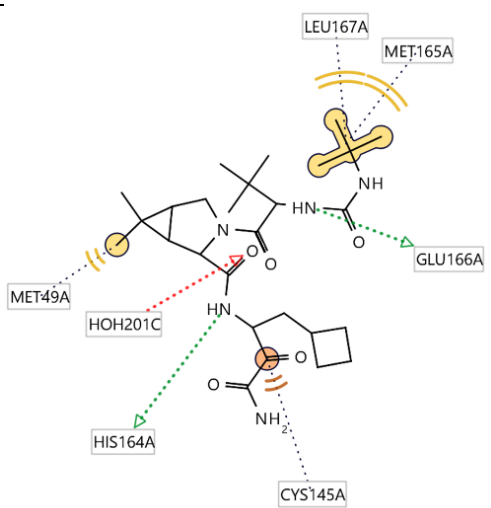
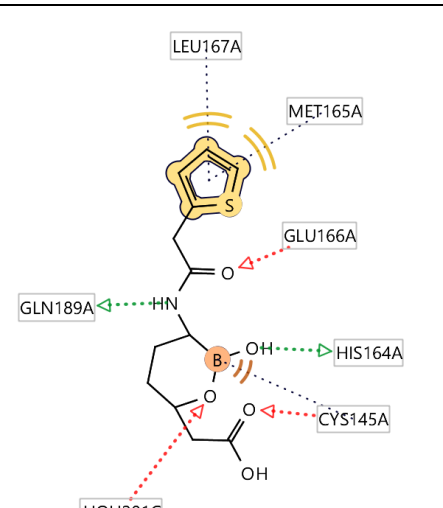
³ Laboratorio de Medicina de la Conservación, Escuela Superior de Medicina del Instituto Politécnico Nacional. Plan de San Luis y Salvador Díaz Mirón s/n, Casco de Santo Tomás, Ciudad de México 11340. Mexico.

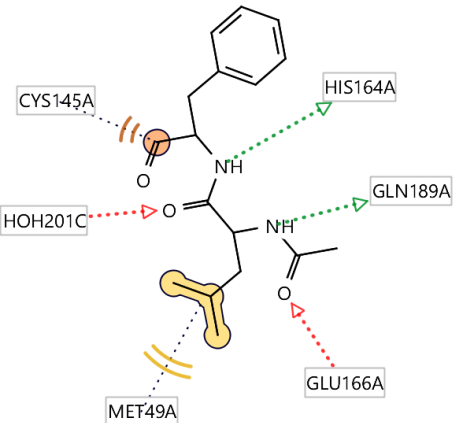
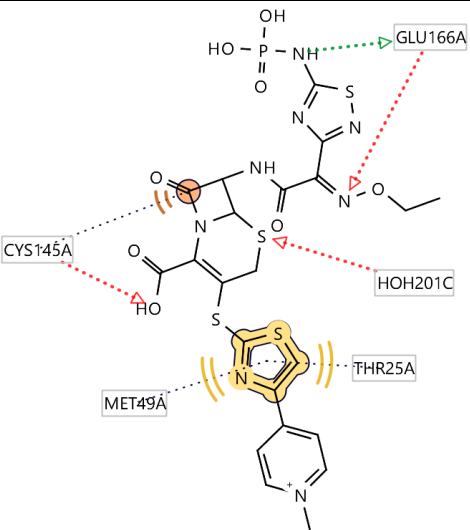
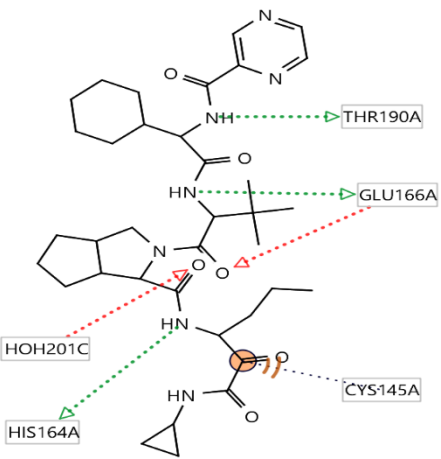
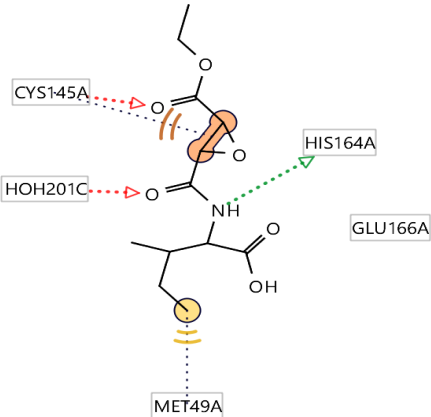
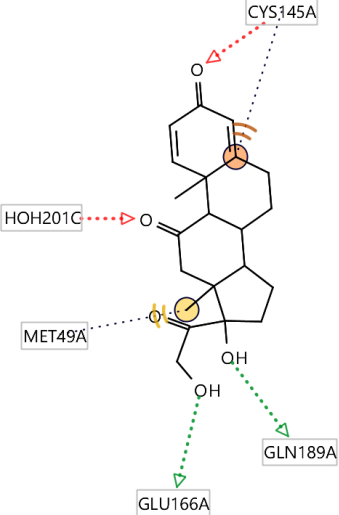
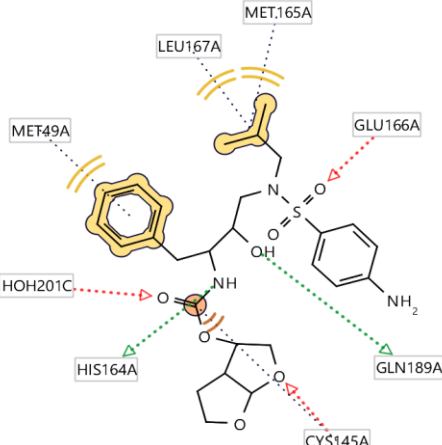
* Correspondence: H.L.M.F. hmendozaf@ipn.mx ** Co-correspondence: J.B.G.V. benjagv_5202@hotmail.com

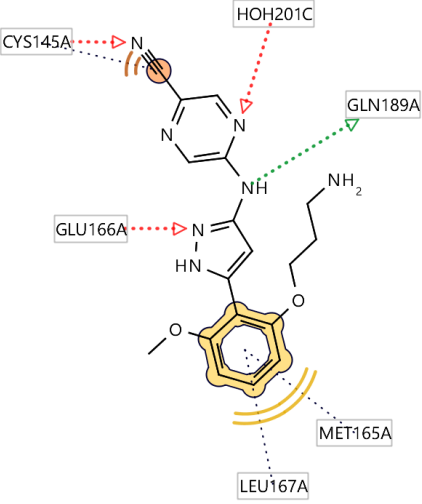
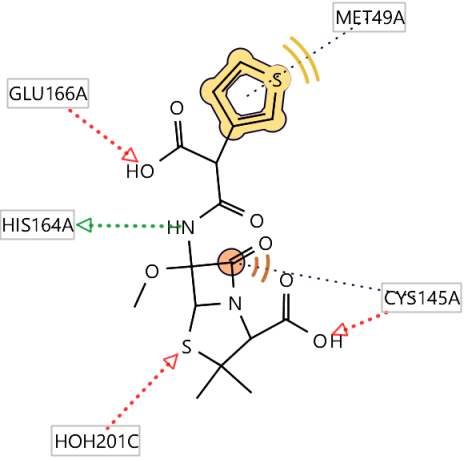
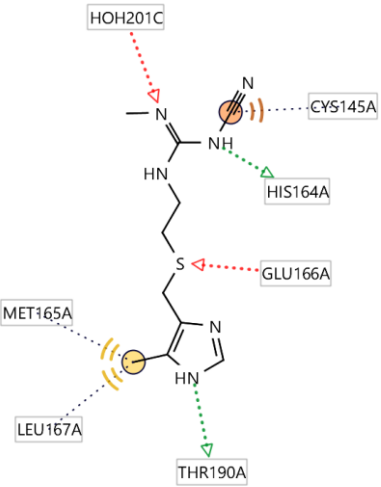
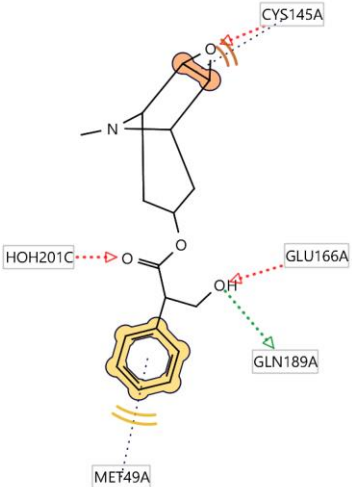
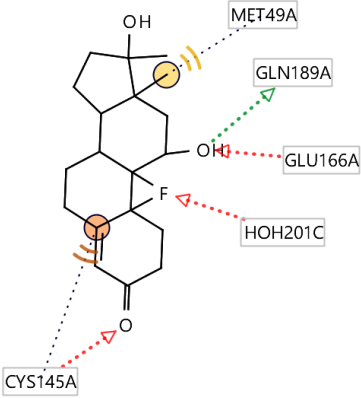
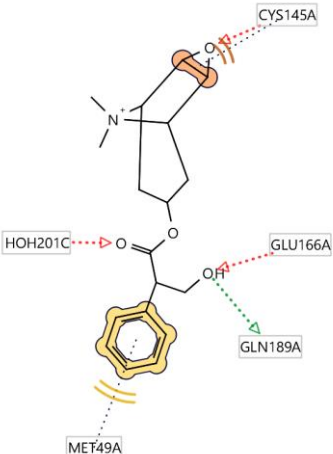
Table S1. 2D representation of the interactions of the top-ranked drugs (pharmacophore fit >60) on the virtual screening on the pharmacophoric map based on the structure of SARS-Cov-2 M^{pro}/N3.

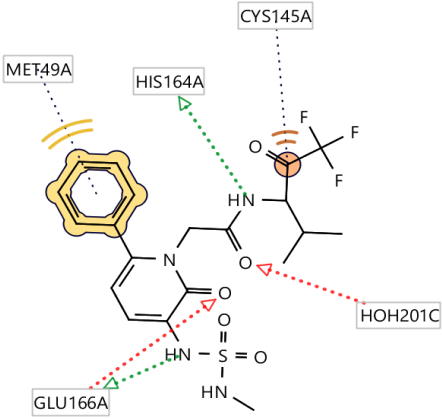
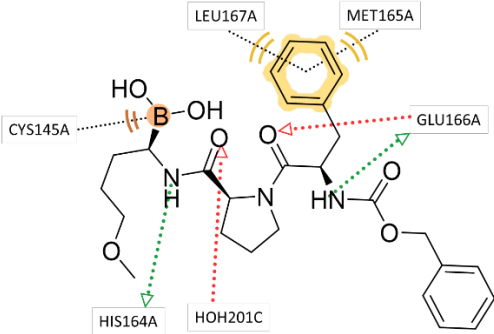
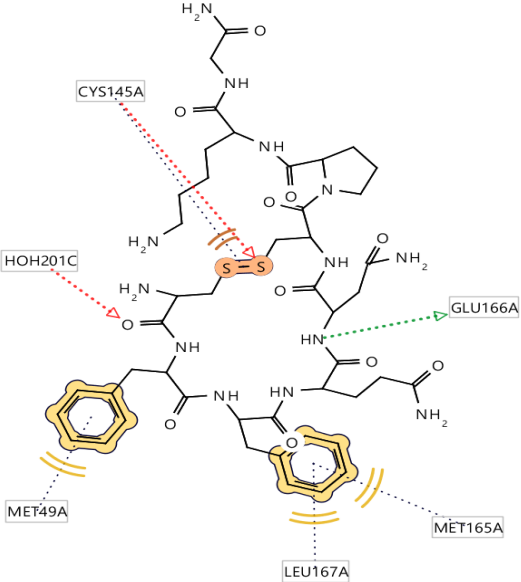
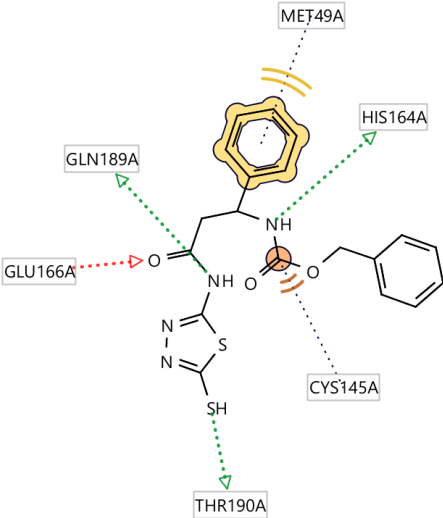
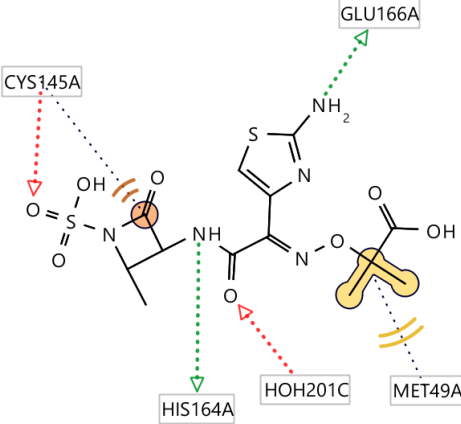
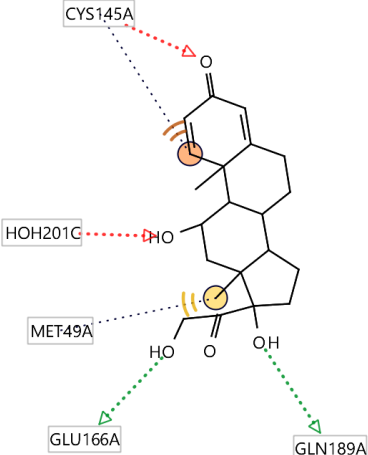
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<p>Inhibitor N9</p> 	<p>Inhibitor I2</p> 
<p>Ixazomib</p> 	<p>Calpain inhibitor I</p> 

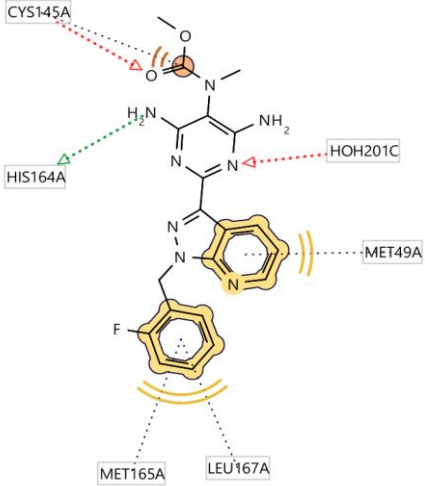
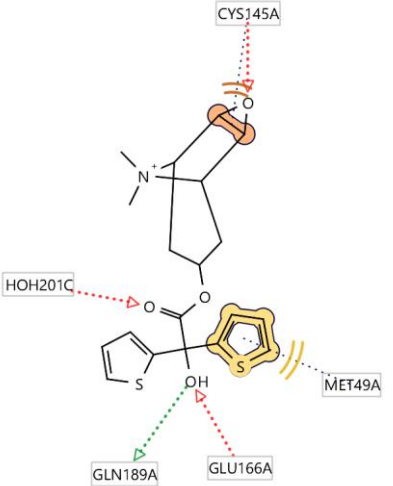
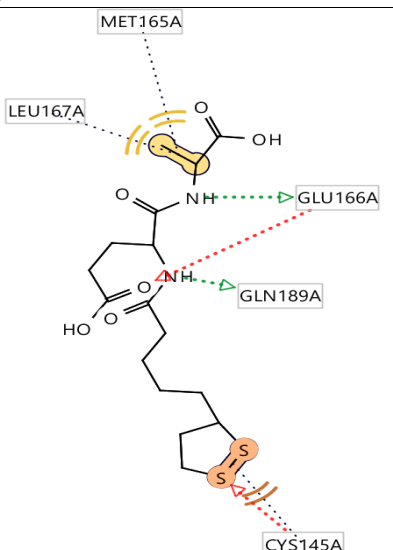
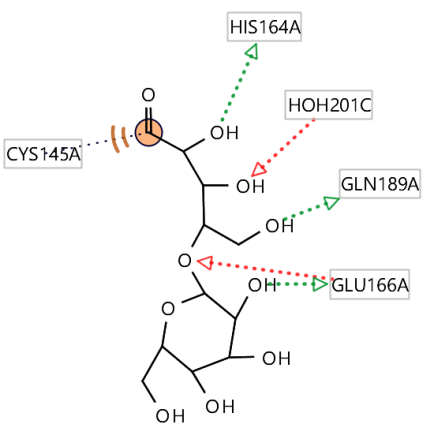
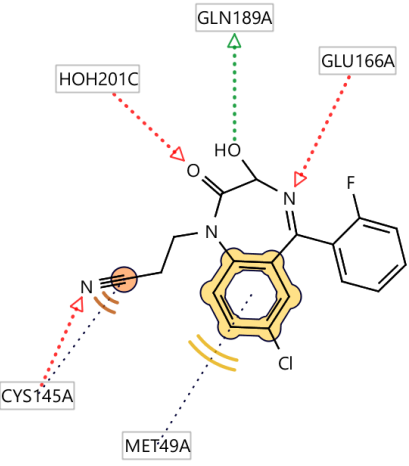
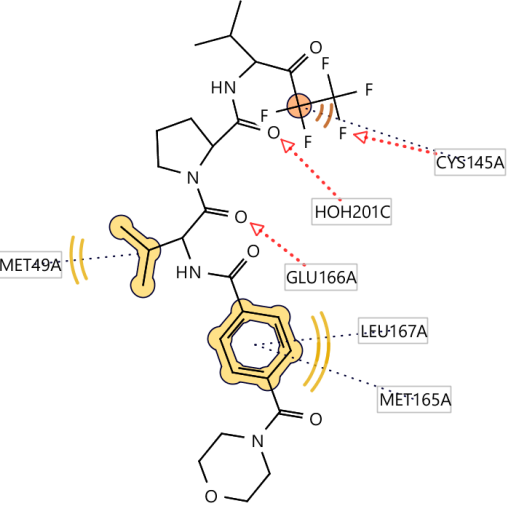
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<p>DB07224</p> 	<p>DB07225</p> 
<p>Amprenavir</p> 	<p>Oprozomib</p> 

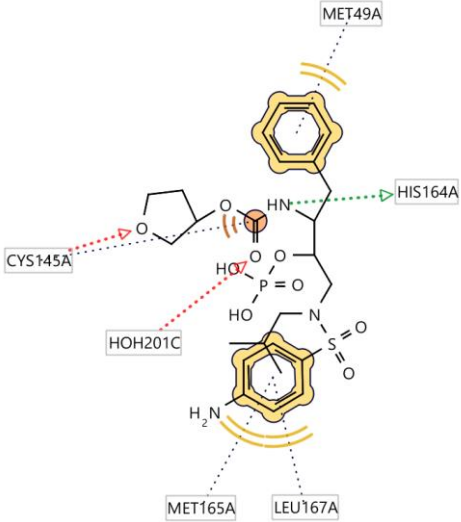
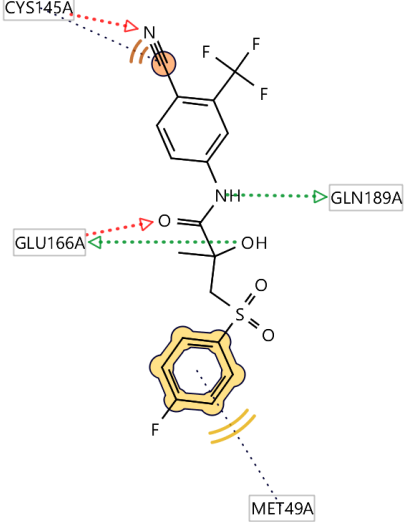
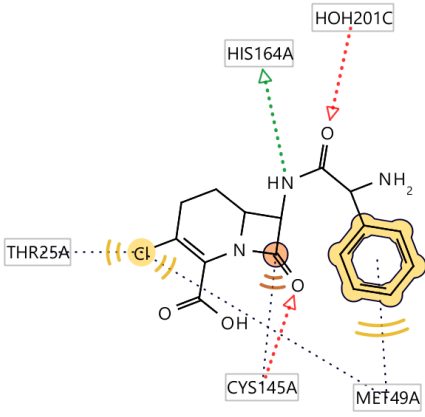
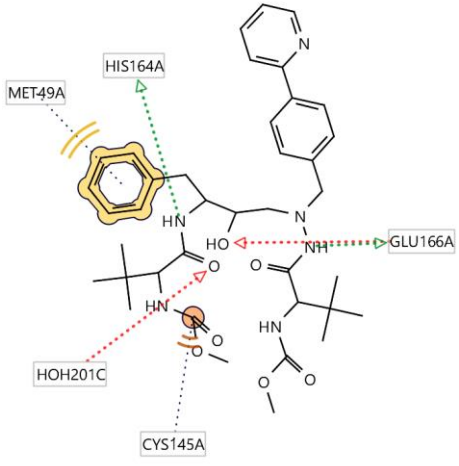
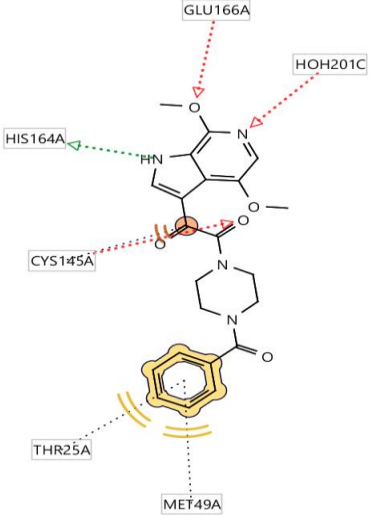
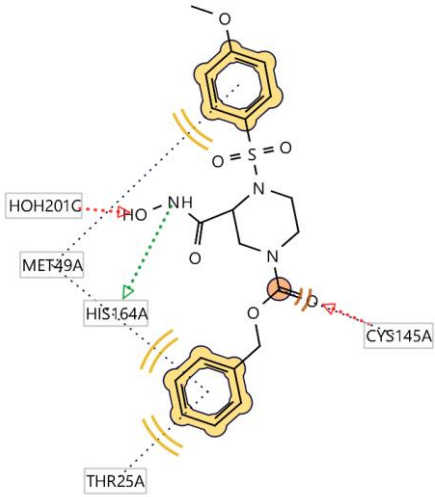
<p>Carfilzomib</p>  <p>Chemical structure of Carfilzomib (a proteasome inhibitor) is shown. It features a central benzophenone core with a morpholine-protected amide on one side and a thiazolidine ring on the other. Interactions with the proteasome active site are indicated by dashed lines: MET49A (orange), CYS164A (orange), HIS164A (green), HOH201C (red), GLN189A (green), and GLU166A (green).</p>	<p>DB07299</p>  <p>Chemical structure of DB07299 (a thiazolidine derivative) is shown. It features a thiazolidine ring with an amide and a morpholine-protected amide. Interactions with the proteasome active site are indicated by dashed lines: MET49A (orange), CYS145A (orange), HOH201C (red), MET165A (orange), LEU167A (orange), and HIS164A (green).</p>
<p>DB03767</p>  <p>Chemical structure of DB03767 (a morpholine derivative) is shown. It features a morpholine ring with an amide and a thiazolidine ring. Interactions with the proteasome active site are indicated by dashed lines: MET49A (orange), GLN189A (green), GLU166A (green), HOH201C (red), HIS164A (green), and CYS145A (orange).</p>	<p>DB04234</p>  <p>Chemical structure of DB04234 (a bromophenyl derivative) is shown. It features a bromophenyl ring with an amide and a thiazolidine ring. Interactions with the proteasome active site are indicated by dashed lines: GLN189A (green), GLU166A (green), HOH201C (red), MET49A (orange), HIS164A (green), CYS145A (orange), and THR25A (orange).</p>
<p>Boceprevir</p>  <p>Chemical structure of Boceprevir (a hepatitis C virus protease inhibitor) is shown. It features a morpholine ring with an amide and a thiazolidine ring. Interactions with the proteasome active site are indicated by dashed lines: MET49A (orange), HOH201C (red), HIS164A (green), CYS145A (orange), MET165A (orange), and LEU167A (orange).</p>	<p>Vaborbactam</p>  <p>Chemical structure of Vaborbactam (a beta-lactamase inhibitor) is shown. It features a morpholine ring with an amide and a thiazolidine ring. Interactions with the proteasome active site are indicated by dashed lines: LEU167A (orange), MET165A (orange), GLU166A (green), GLN189A (green), HIS164A (green), CYS145A (orange), and HOH201C (red).</p>
<p>DB07749</p>	<p>Ceftaroline</p>

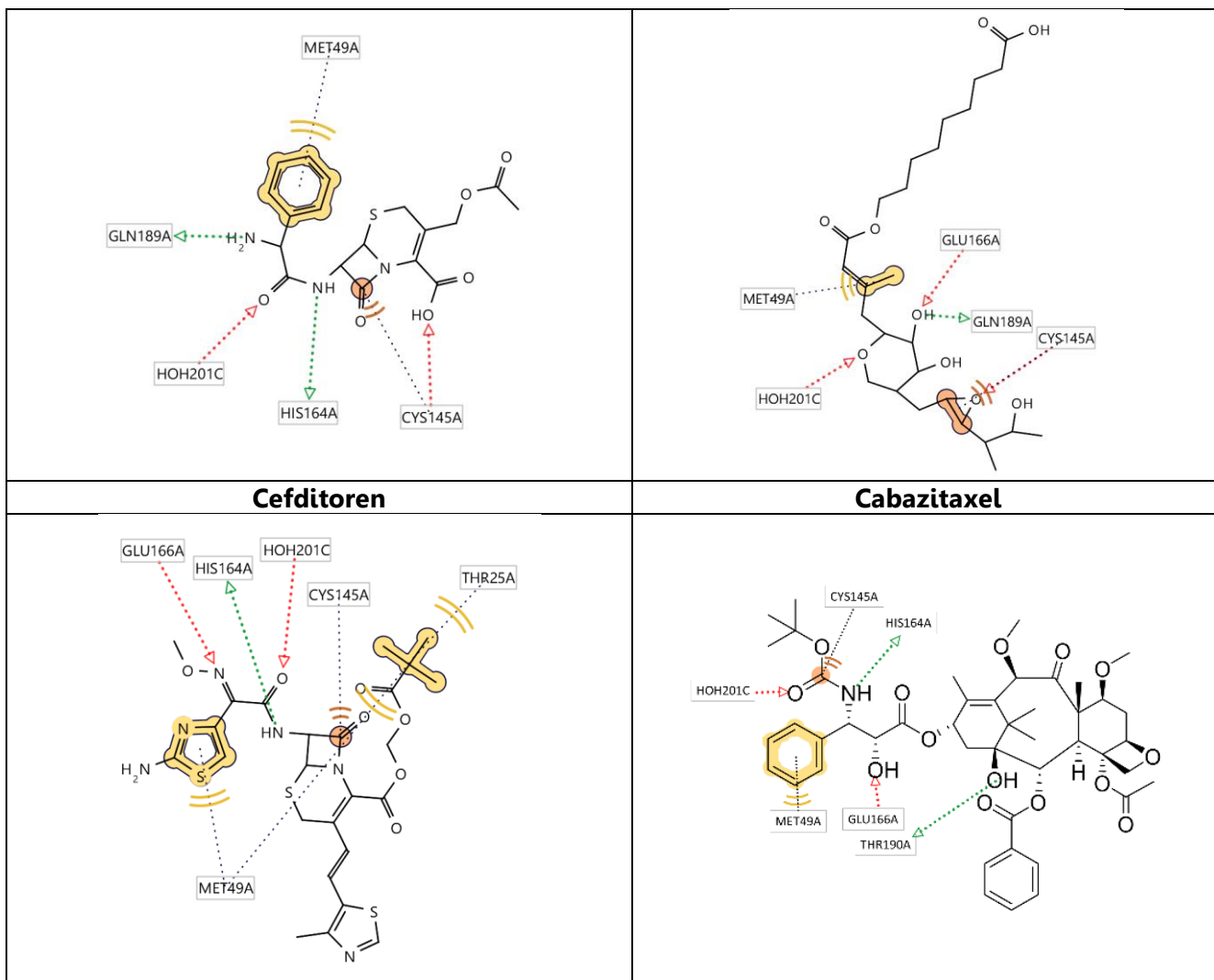
 <p>Chemical structure of Telaprevir showing interactions with CYS145A, HIS164A, GLN189A, HOH201C, MET49A, and GLU166A.</p>	 <p>Chemical structure of DB07160 showing interactions with CYS145A, HIS164A, GLU166A, HOH201C, MET49A, and THR25A.</p>
<p>Telaprevir</p>	<p>DB07160</p>
 <p>Chemical structure of Prednisone showing interactions with THR190A, GLU166A, HOH201C, HIS164A, and CYS145A.</p>	 <p>Chemical structure of Darunavir showing interactions with CYS145A, HIS164A, GLU166A, HOH201C, and MET49A.</p>
<p>Prednisone</p>	<p>Darunavir</p>
 <p>Chemical structure of Prexasertib showing interactions with CYS145A, HOH201C, MET49A, GLN189A, and GLU166A.</p>	 <p>Chemical structure of Temocillin showing interactions with MET165A, LEU167A, MET49A, HOH201C, HIS164A, GLU166A, GLN189A, and CYS145A.</p>
<p>Prexasertib</p>	<p>Temocillin</p>

 <p>Chemical structure of Cimetidine showing interactions with HOH201C, CYS145A, GLN189A, GLU166A, MET165A, and LEU167A.</p>	 <p>Chemical structure of Scopolamine showing interactions with MET49A, GLU166A, HIS164A, CYS145A, HOH201C, and MET165A.</p>
Cimetidine	Scopolamine
 <p>Chemical structure of Fluoxymesterone showing interactions with HOH201C, CYS145A, HIS164A, GLU166A, MET165A, LEU167A, and THR190A.</p>	 <p>Chemical structure of Methscopolamine showing interactions with CYS145A, HOH201C, GLU166A, GLN189A, and MET49A.</p>
Fluoxymesterone	Methscopolamine
 <p>Chemical structure of DB08614 showing interactions with MET49A, GLN189A, GLU166A, HOH201C, and CYS145A.</p>	 <p>Chemical structure of Flovagatran showing interactions with CYS145A, HOH201C, GLU166A, GLN189A, and MET49A.</p>
DB08614	Flovagatran

 <p>Chemical structure of Felypressin (a peptide) showing interactions with residues MET49A, HIS164A, CYS145A, HOH201C, and GLU166A. The structure includes a benzene ring and a sulfonamide group.</p>	 <p>Chemical structure of DB07987 (a complex organic molecule) showing interactions with residues LEU167A, MET165A, CYS145A, HIS164A, HOH201C, and GLU166A. The structure includes a benzene ring and a complex side chain.</p>
Felypressin	DB07987
 <p>Chemical structure of Aztreonam (a beta-lactam antibiotic) showing interactions with residues CYS145A, HOH201C, MET49A, MET165A, LEU167A, and GLU166A. The structure includes a beta-lactam ring and a side chain with a sulfonamide group.</p>	 <p>Chemical structure of Prednisolone (a corticosteroid) showing interactions with residues MET49A, HIS164A, GLN189A, GLU166A, CYS145A, and THR190A. The structure includes a steroid nucleus and a side chain with a ketone group.</p>
Aztreonam	Prednisolone
 <p>Chemical structure of Riociguat (a guanylate cyclase activator) showing interactions with residues CYS145A, GLU166A, HIS164A, HOH201C, and MET49A. The structure includes a guanine ring and a side chain with a sulfonamide group.</p>	 <p>Chemical structure of Tiotropium (a muscarinic antagonist) showing interactions with residues CYS145A, HOH201C, MET49A, GLU166A, and GLN189A. The structure includes a tropane ring and a side chain with a quaternary ammonium group.</p>
Riociguat	Tiotropium

 <p>Chemical structure of CMX-2043 showing interactions with CYS145A, HIS164A, HOH201C, MET49A, MET165A, and LEU167A.</p>	 <p>Chemical structure of Gaxilose showing interactions with CYS145A, HOH201C, GLN189A, and GLU166A.</p>
<p>CMX-2043</p>  <p>Chemical structure of CMX-2043 showing interactions with MET165A, LEU167A, GLU166A, GLN189A, and CYS145A.</p>	<p>Gaxilose</p>  <p>Chemical structure of Gaxilose showing interactions with HIS164A, HOH201C, CYS145A, GLN189A, and GLU166A.</p>
<p>Cinolazepam</p>  <p>Chemical structure of Cinolazepam showing interactions with GLN189A, HOH201C, GLU166A, CYS145A, and MET49A.</p>	<p>Mdl 101,146</p>  <p>Chemical structure of Mdl 101,146 showing interactions with CYS145A, HOH201C, GLU166A, LEU167A, and MET165A.</p>
<p>Fosamprenavir</p>	<p>Bicalutamide</p>

 <p>Chemical structure of DB04293 (a phosphonate derivative) showing interactions with MET49A, HIS164A, CYS145A, HOH201C, MET165A, and LEU167A.</p>	 <p>Chemical structure of Atazanavir showing interactions with CYS145A, GLN189A, GLU166A, and MET49A.</p>
DB04293	Atazanavir
 <p>Chemical structure of BMS-488043 showing interactions with HOH201C, HIS164A, THR25A, CYS145A, and MET49A.</p>	 <p>Chemical structure of DB04232 showing interactions with HIS164A, MET49A, HOH201C, CYS145A, and GLU166A.</p>
BMS-488043	DB04232
 <p>Chemical structure of Cephaloglycin showing interactions with GLU166A, HOH201C, HIS164A, CYS145A, THR25A, and MET49A.</p>	 <p>Chemical structure of Mupirocin showing interactions with HOH201C, MET49A, HIS164A, CYS145A, and THR25A.</p>
Cephaloglycin	Mupirocin



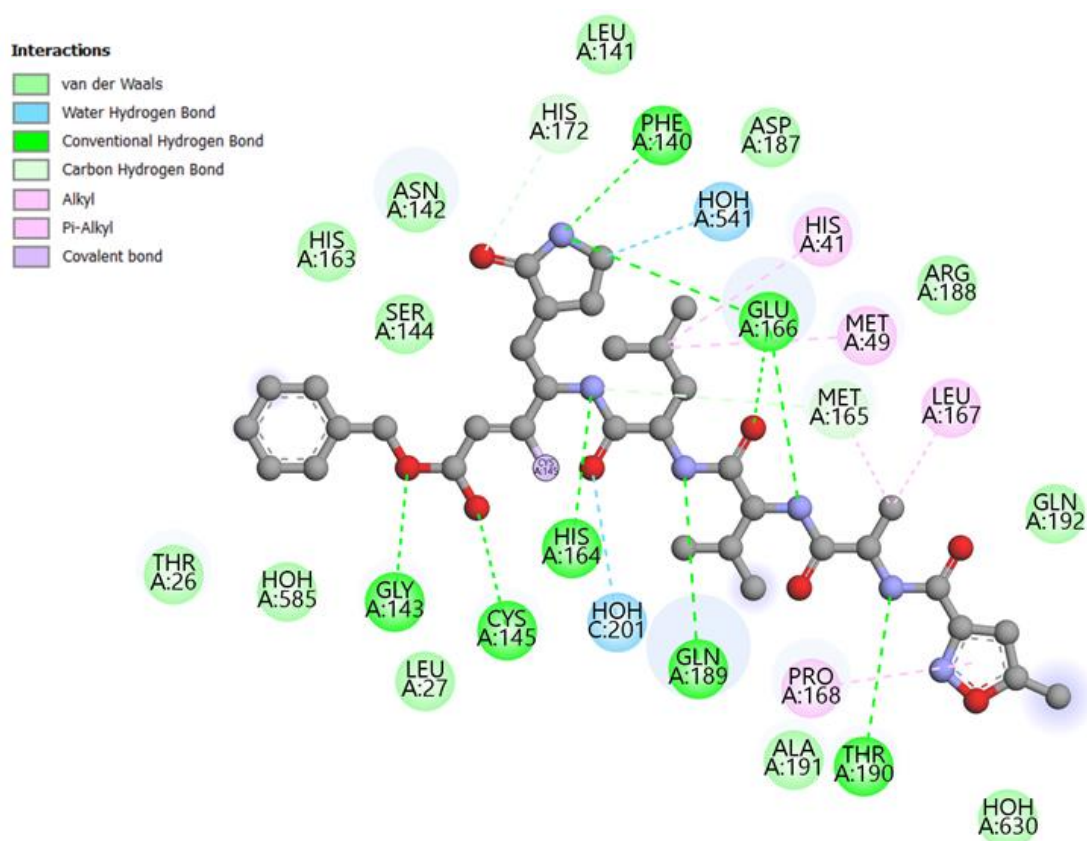
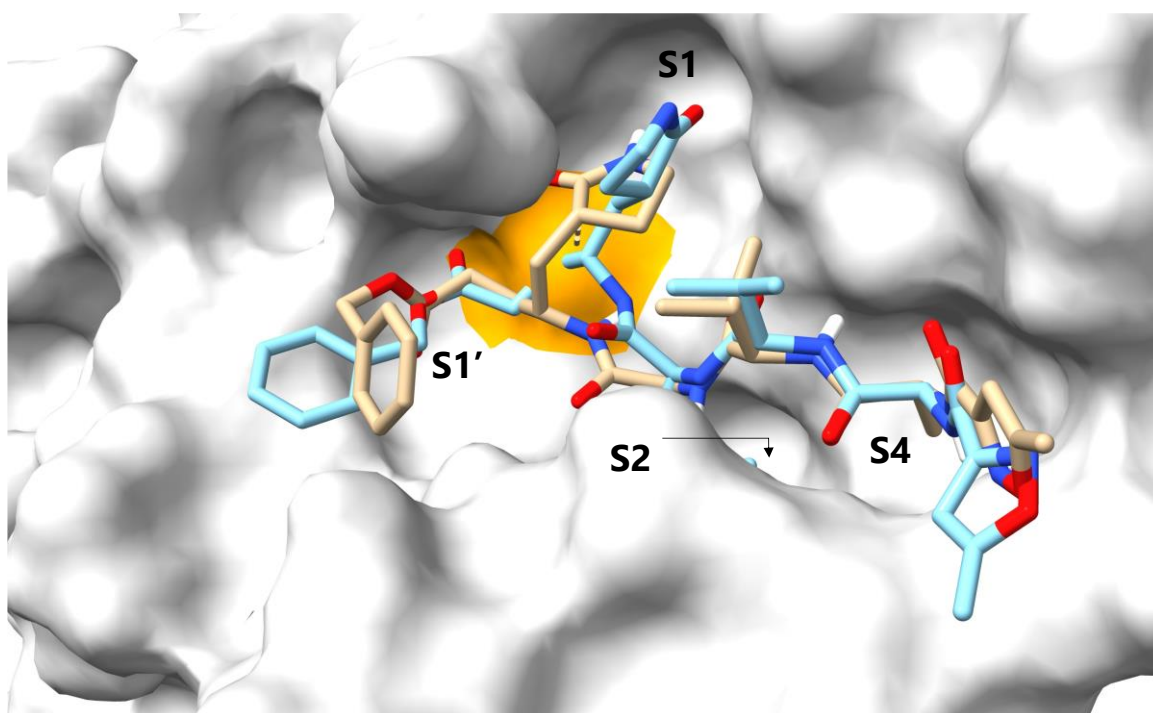


Figure S1. N3 redocking over SARS-CoV-2 M^{pro} (PDB ID: 7BQY). In blue the co-crystallized inhibitor is observed, in brown the inhibitor coupled in MOE, and in the orange color Cys145 stands out (RMSD = 0.65).

Table S2. Therapeutic applications of the best ranked drugs in virtual screening structure based.

Drug	Therapeutic indications	Target	Status	Electrophilic warhead	ΔG_{cov}
INHIBITOR N3	<i>SARS-CoV infection</i>	<i>SARS Mpro</i>	<i>Experimental</i>	<i>Michael-type acceptor</i>	-10.14
INHIBITOR N1	<i>SARS-CoV infection</i>	<i>3C-like proteinase</i>	<i>Experimental</i>	<i>Michael-type acceptor</i>	-8.51
INHIBITOR N9	<i>SARS-CoV infection</i>	<i>SARS Mpro</i>	<i>Experimental</i>	<i>Michael-type acceptor</i>	-8.22
INHIBITOR I2	<i>SARS-CoV infection</i>	<i>3C-like proteinase</i>	<i>Experimental</i>	<i>Michael-type acceptor</i>	-7.99
IXAZOMIB	<i>Multiple myeloma</i>	<i>20S proteasome</i>	<i>Approved</i>	<i>Boronic acid</i>	-5.85
CALPAIN INH I	<i>Acute and chronic inflammation</i>	<i>Calpain I; cathepsin B and L</i>	<i>Experimental</i>	<i>Aldehyde</i>	-7.40
DB08119	<i>Unknow</i>	<i>Chymotrypsinogen B</i>	<i>Experimental</i>	<i>Ketone</i>	-6.24
DB03984	<i>Hyperimmune response</i>	<i>Cathepsin S</i>	<i>Experimental</i>	<i>Aldehyde</i>	-7.37
DB07224	<i>Tumor metastatis; pulmonary emphysema; bone resorption</i>	<i>Cathepsin B</i>	<i>Experimental</i>	<i>Epoxide</i>	-6.63
DB07225	<i>Tumor metastatis; pulmonary emphysema; bone resorption</i>	<i>Cathepsin B</i>	<i>Experimental</i>	<i>Epoxide</i>	-6.59
AMPRENAVIR	<i>HIV infection</i>	<i>HIV-1 protease</i>	<i>Approved</i>	<i>Carbamate</i>	-5.82
OPROZOMIB	<i>Solid tumors; multiple Myeloma; Waldenstrom Macroglobulinemia</i>	<i>20S proteasome</i>	<i>Investigational</i>	<i>Epoxide</i>	-7.68
CARFILZOMIB	<i>Multiple myeloma</i>	<i>20S proteasome</i>	<i>Approved</i>	<i>Epoxide</i>	-8.47
DB07299	<i>Thrombosis</i>	<i>Coagulation factor XI</i>	<i>Experimental</i>	<i>Ketone</i>	-7.30
DB03767	<i>Autoimmune diseases</i>	<i>Cathepsin S</i>	<i>Experimental</i>	<i>Carbonitrile</i>	-7.21
DB04234	<i>Osteoporosis</i>	<i>Cathepsin K</i>	<i>Experimental</i>	<i>Aldehyde</i>	-7.30
BOCEPREVIR	<i>Chronic Hepatitis C</i>	<i>NS3/4A protease</i>	<i>Approved</i>	<i>Diketone</i>	-8.20
VABORBACTAM	<i>Urinary tract infections</i>	<i>Beta-lactamase</i>	<i>Approved</i>	<i>Oxaborole</i>	-5.93
DB07749	<i>Unknow</i>	<i>Chymotrypsinogen B</i>	<i>Experimental</i>	<i>Aldehyde</i>	-6.39

CEFTAROLINE	<i>Bacterial infections</i>	<i>Penicillin-binding proteins</i>	<i>Approved</i>	<i>β-lactam ring</i>	-8.56
TELAPREVIR	<i>Chronic Hepatitis C</i>	<i>NS3/4A protease</i>	<i>Approved</i>	<i>Diketone</i>	-8.34
DB07160	<i>Tumor metastasis; pulmonary emphysema; bone resorption</i>	<i>Cathepsin B</i>	<i>Experimental</i>	<i>Epoxide</i>	-6.11
PREDNISONE	<i>Inflammation; immune-mediated reactions</i>	<i>Glucocorticoid receptor</i>	<i>Approved</i>	<i>Michael-type acceptor</i>	-4.18
DARUNAVIR	<i>HIV infection</i>	<i>HIV-1 protease</i>	<i>Approved</i>	<i>Carbamate</i>	-6.75
PREXASERTIB	<i>Metastatic Castration-Resistant Prostate Cancer; leukemia</i>	<i>Protein kinase regulatory subunit</i>	<i>Investigational</i>	<i>Carbonitrile</i>	-5.25
TEMOCILLIN	<i>Liver dysfunction; urinary tract infection</i>	<i>Penicillin-binding proteins</i>	<i>Approved</i>	<i>β-lactam ring</i>	-7.13
CIMETIDINE	<i>Gastroesophageal reflux</i>	<i>Histamine H2 receptor</i>	<i>Approved</i>	<i>Carbonitrile</i>	-5.33
SCOPOLAMINE	<i>Motion sickness</i>	<i>Muscarinic acetylcholine receptors</i>	<i>Approved</i>	<i>Epoxide</i>	-5.55
FLUOXYMESTERONE	<i>Hypogonadism in males; breast neoplasms</i>	<i>Androgen receptor; Estrogen receptor alpha</i>	<i>Approved</i>	<i>Michael-type acceptor</i>	-4.18
METHSCOPOLAMINE	<i>Peptic ulcer</i>	<i>Muscarinic acetylcholine receptors</i>	<i>Approved</i>	<i>Epoxide</i>	-4.97
DB08614	<i>Ineffectively elastolytic activity</i>	<i>Chymotrypsin-like elastase family member 1</i>	<i>Experimental</i>	<i>Ketone</i>	-6.86
FLOVAGATRAN	<i>Thrombosis</i>	<i>Prothrombin</i>	<i>Investigational</i>	<i>Boronic acid</i>	-7.15
FELYPRESSIN	<i>Vasoconstrictor used in local anaesthetic injections</i>	<i>Vasopressin V1a receptor</i>	<i>Experimental</i>	<i>Disulfide bridge</i>	-8.79
DB07987	<i>Degenerative diseases; inflammatory conditions</i>	<i>Stromelysin-1</i>	<i>Experimental</i>	<i>Carbamate</i>	-5.94
AZTREONAM	<i>Sensitive gram-negative bacteria</i>	<i>Penicillin-binding protein 3</i>	<i>Approved</i>	<i>Monocyclic β-lactam</i>	-7.00
PREDNISOLONE	<i>Adrenocortical insufficiency; inflammatory conditions</i>	<i>Glucocorticoid receptor</i>	<i>Approved</i>	<i>Michael-type acceptor</i>	-5.06
RIOCIGUAT	<i>Pulmonary arterial hypertension</i>	<i>Guanylate cyclase soluble subunit alpha-2</i>	<i>Approved</i>	<i>Carbamate</i>	-5.72

TIOTROPIUM	<i>Chronic obstructive pulmonary disease</i>	<i>Muscarinic acetylcholine receptors</i>	<i>Approved</i>	<i>Epoxide</i>	-5.70
CMX-2043	<i>non-ST-segment elevation myocardial infarction (NSTEMI); unstable Angina; coronary disease</i>	<i>Insulin-Like Receptor; Creatine Kinase; Tyrosine Kinase Non Receptor 1</i>	<i>Investigational</i>	<i>disulfide bond</i>	-6.81
GAXILOSE	<i>Diagnostic of lactose intolerance</i>	<i>Lactase</i>	<i>Approved</i>	<i>Aldehyde</i>	-5.30
CINOLAZEPAM	<i>Sleep disorders</i>	<i>GABA(A) Receptor</i>	<i>Experimental</i>	<i>Carbonitrile</i>	-5.48
Mdl 101,146	<i>Ineffectively elastolytic activity</i>	<i>Chymotrypsin-like elastase family member 1</i>	<i>Experimental</i>	<i>α-halo ketone</i>	-7.49
FOSAMPRENAVIR	<i>Postexposure prophylaxis of HIV infection</i>	<i>HIV-1 protease</i>	<i>Approved</i>	<i>Carbamate</i>	-7.32
BICALUTAMIDE	<i>Stage D2 metastatic carcinoma of the prostate</i>	<i>Androgen receptor</i>	<i>Approved</i>	<i>Carbonitrile</i>	-5.46
DB04293	<i>Unknow</i>	<i>Beta-lactamase</i>	<i>Experimental</i>	<i>β-lactam ring</i>	-6.19
ATAZANAVIR	<i>HIV infection</i>	<i>HIV-1 protease</i>	<i>Approved</i>	<i>Carbamate</i>	-8.51
BMS-488043	<i>HIV infection</i>	<i>Free fatty acid receptor 4</i>	<i>Investigational</i>	<i>Diketone</i>	-6.97
DB04232	<i>Osteoarthritis; tumor metastasis; corneal ulceration</i>	<i>Stromelysin-1</i>	<i>Experimental</i>	<i>Carbamate</i>	-5.89
CEPHALOGLYCIN	<i>Bacterial infections</i>	<i>Penicillin-binding protein 1B</i>	<i>Approved</i>	<i>β-lactam ring</i>	-6.72
MUPIROCIN	<i>Impetigo; secondary skin infections</i>	<i>Isoleucine--tRNA ligase</i>	<i>Approved</i>	<i>Epoxide</i>	-7.03
CEFDITOREN	<i>Bacterial infections of the skin and respiratory tract</i>	<i>Penicillin-binding protein 2B and 1A</i>	<i>Approved</i>	<i>β-lactam ring</i>	-6.93
CABAZITAXEL	<i>Hormone-refractory metastatic prostate cancer</i>	<i>Tubulin alpha-4A and beta-1 chain</i>	<i>Approved</i>	<i>Carbamate</i>	-6.52

Bibliographic references of the drugs are reported in databases from:

<https://www.drugs.com/>

<https://go.drugbank.com/>

<https://pubchem.ncbi.nlm.nih.gov/>

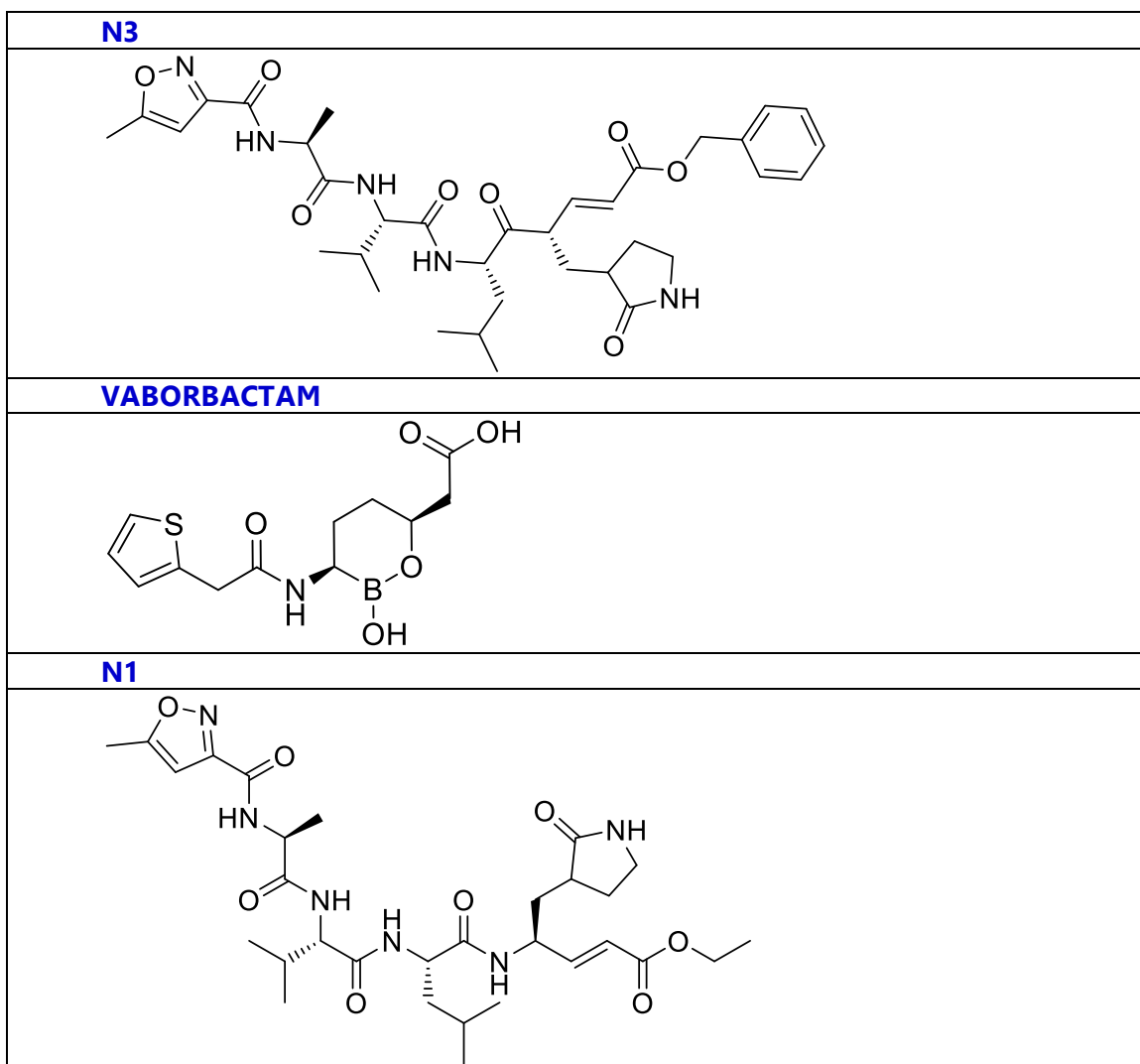
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Table S3. Drugs ordered according to the consensus score (calculation described in the methodology).

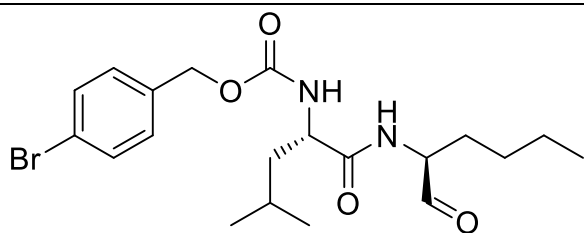
Drug	E _c	E _{BS}	S _{PF}	-ΔG _{ncov}	-ΔG _{cov}	CsScore
INHIBITOR N3	5815.39	5034.60	106.93	7.7	10.1	412.82
VABORBACTAM	453.04	10.58	73.71	6.5	5.9	436.08
INHIBITOR N1	3819.69	3132.36	106.9	6.8	8.5	454.83
DB04234	544.49	62.13	75.34	6.1	7.3	487.59
DB03456	584.84	103.11	75.87	6.8	6.1	496.79
CIMETIDINE	589.49	120.44	65.99	5.3	5.3	503.00
IXAZOMIB	674.98	170.89	83.9	6.7	5.9	521.07
CMX-2043	634.24	156.96	65.45	5.9	6.8	523.19
DB07224	659.17	156.99	76.48	6.1	6.6	529.37
DB07225	705.99	204.10	76.48	5.8	6.6	540.42
SCOPOLAMINE	646.78	122.54	65.98	6.3	5.6	558.11
DB04293	704.77	152.09	65.17	7.3	6.2	596.86
BOCEPREVIR	824.16	266.36	75.28	5.4	8.2	613.41
DB07299	934.01	398.77	75.65	6.5	7.3	621.90
DARUNAVIR	861.32	340.83	66.32	7.5	6.8	625.83
CALPAIN INHIBITOR-1	1127.00	630.46	77.81	5.1	7.4	626.71
INHIBITOR N9	2796.46	2216.40	96.23	6.3	8.2	649.65
BICALUTAMIDE	932.83	376.99	65.19	7.4	5.5	678.69
DB03767	1074.14	504.95	75.52	6.6	7.2	682.37
PREXASERTIB	921.30	339.96	66.27	7.5	5.3	687.56
RIOCIGUAT	955.36	348.80	65.57	8.3	5.7	717.46
DB08614	1151.02	623.04	65.93	7.3	6.9	730.91
INHIBITOR I2	1770.67	1112.63	86.48	7.0	8.0	795.50
AMPRENAVIR	1324.18	679.32	76.23	7.8	5.8	795.95
DB07160	1420.27	924.43	66.4	5.2	6.1	798.94
AZTREONAM	1482.14	944.90	65.62	6.8	7.0	853.04
TIOTROPIUM	1466.31	858.19	65.57	7.0	5.7	895.27
TEMOCILLIN	1660.75	1131.23	66.11	6.8	7.1	903.68
FLUOXYMESTERONE	1733.89	1110.31	65.98	7.2	4.2	993.80
DB08119	2619.91	2071.81	77.8	6.2	6.2	998.36
PREDNISONE	1738.53	1095.73	66.34	7.3	4.2	1004.01
FLOVAGATRAN	1892.44	1325.16	65.86	7.0	7.2	1010.37
METHSCOPOLAMINE	2070.99	1476.45	65.98	7.0	5.0	1088.93
DB03984	2930.08	2337.41	76.82	6.7	7.4	1123.67
PREDNISOLONE	2120.64	1507.06	65.59	7.8	5.1	1123.72
OPROZOMIB	2696.86	2033.90	76.12	6.3	7.7	1138.01
DB07987	2342.50	1777.82	65.72	6.0	5.9	1166.27
DB04232	2367.43	1768.70	65.1	6.9	5.9	1207.68
BMS-488043	2446.41	1800.92	65.15	7.9	7.0	1263.42

DB07749	3106.40	2577.53	67.84	6.1	6.4	1349.33
GAXILOSE	2999.85	2334.44	65.45	6.5	5.3	1464.24
CEFTAROLINE	3252.33	2556.58	66.62	7.1	8.6	1538.70
CINOLAZEPAM	3451.69	2514.84	65.40	7.4	5.5	1798.56
CEPHALOGLYCIN	4091.77	3432.94	64.48	7.6	6.7	1868.98
CEFDITOREN PIVOXIL	4352.81	3465.77	63.78	6.5	6.9	2133.78
Mdl 101,146	4813.17	4065.30	65.33	7.2	7.5	2147.71
TELAPREVIR	5196.13	4479.26	66.43	6.2	8.3	2210.90
CARFILZOMIB	6849.93	5948.19	76.03	8.2	8.5	2314.85
MUPIROCIN	5761.68	4899.57	63.87	6.7	7.0	2623.56
FOSAMPRENAVIR	7505.59	6894.18	65.33	7.2	7.3	2992.14
ATAZANAVIR	8900.26	7923.60	65.17	5.4	8.5	3727.38
CABAZITAXEL	9132.50	7750.80	63.67	6.7	6.5	4189.15
FELYPRESSIN	10838.66	9699.06	65.83	6.8	8.8	4443.51

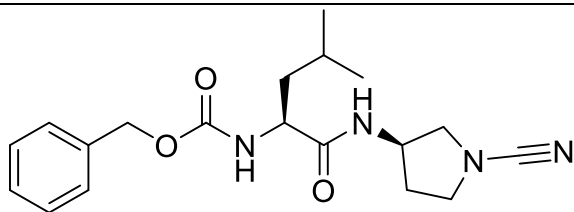
Table S4. 2D structure of the best ranked drugs according to the consensus score.



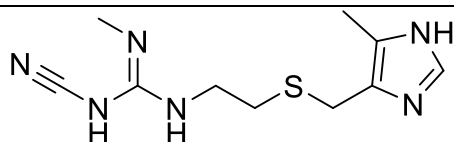
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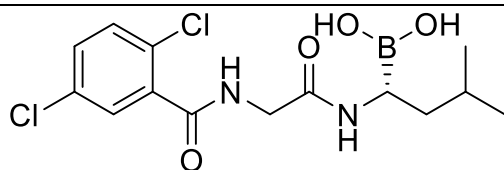
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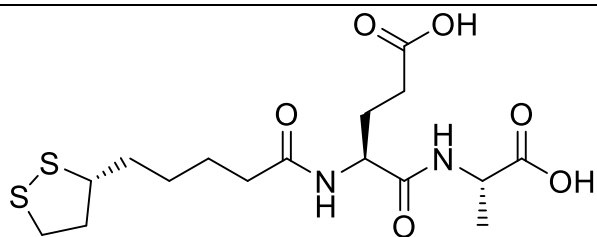
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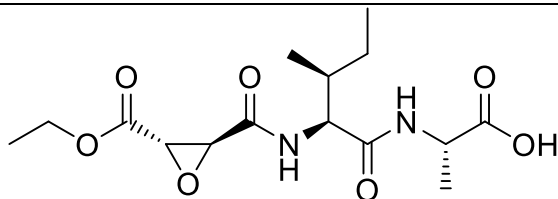
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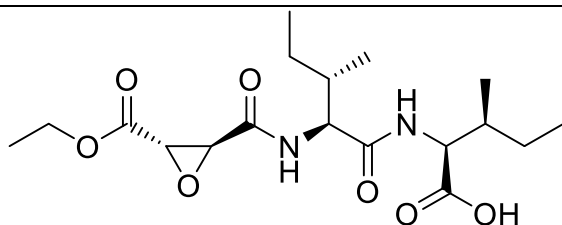
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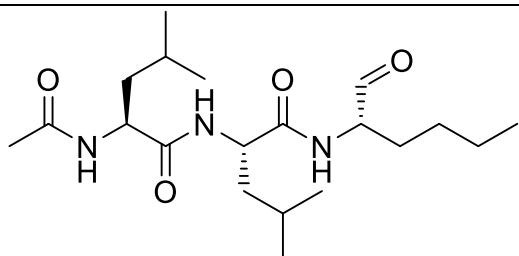


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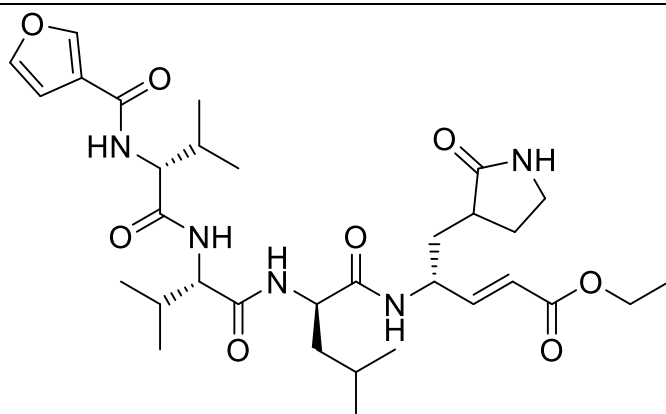


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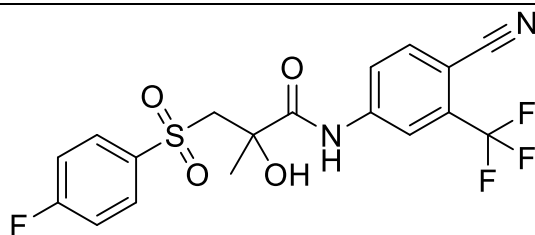




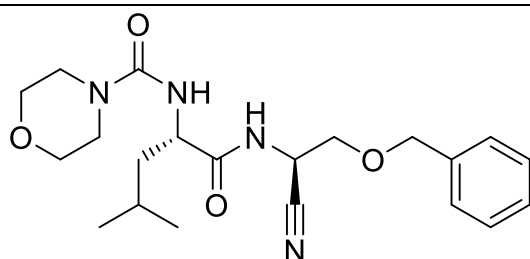
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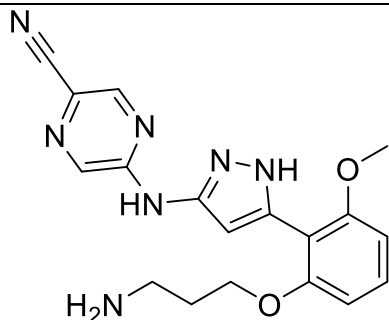
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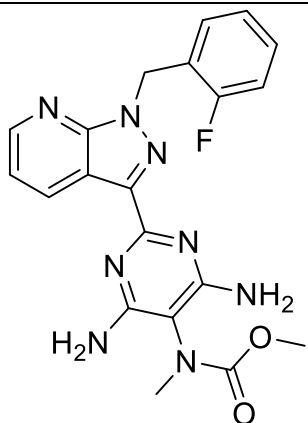
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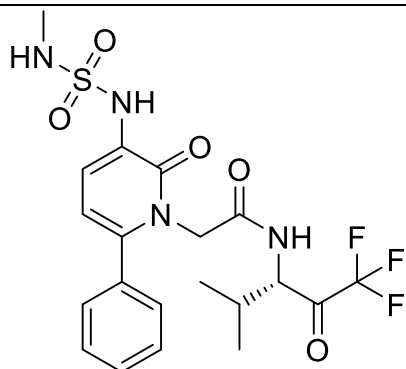
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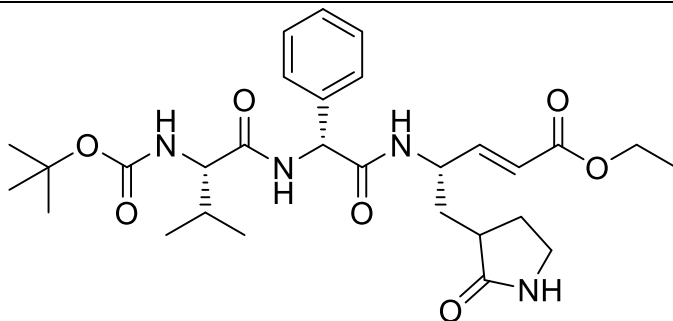
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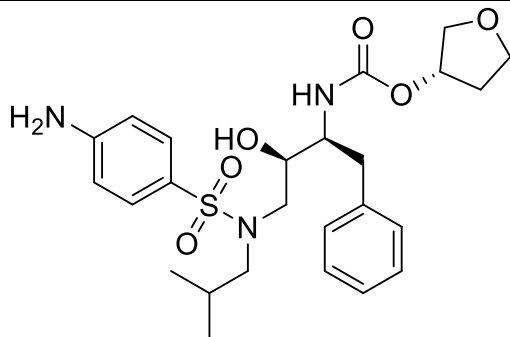
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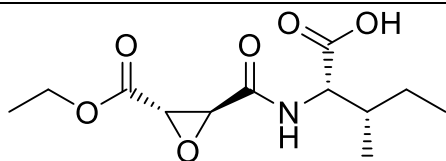
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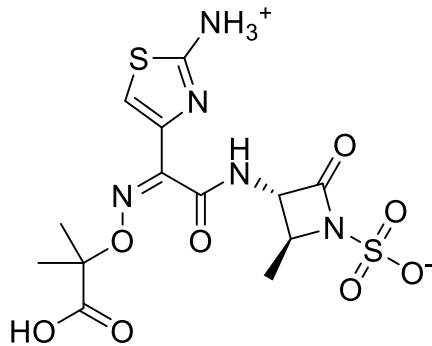
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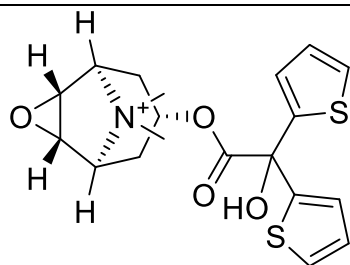
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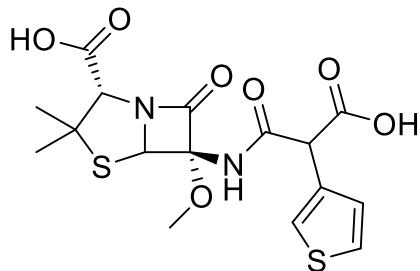
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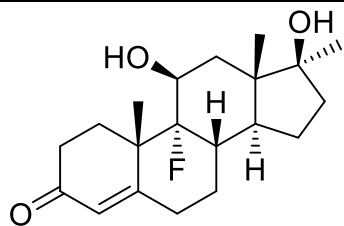
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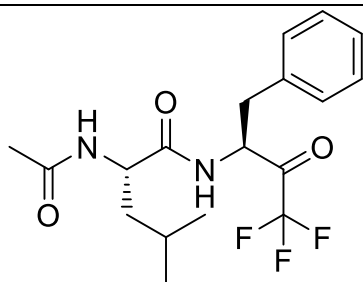
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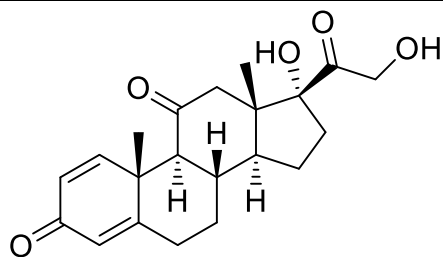
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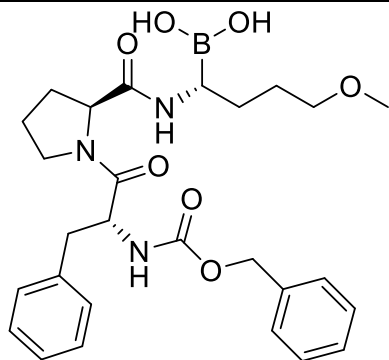
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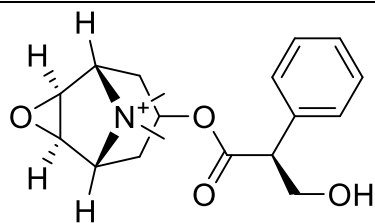
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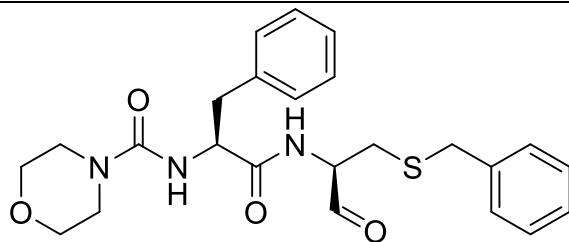
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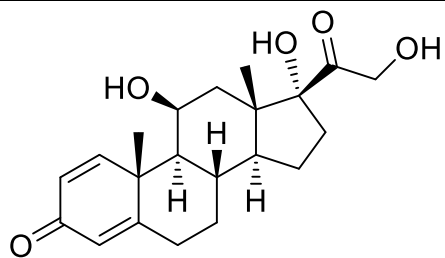
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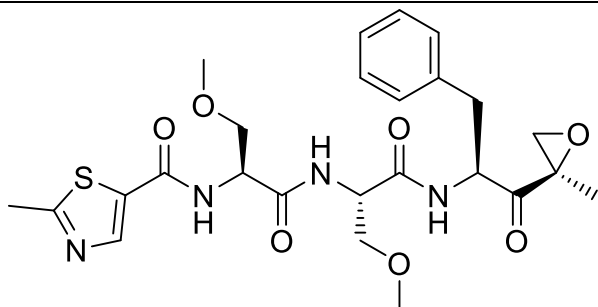
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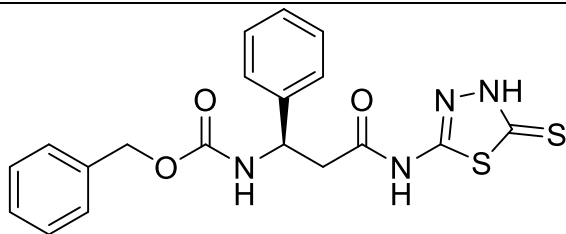
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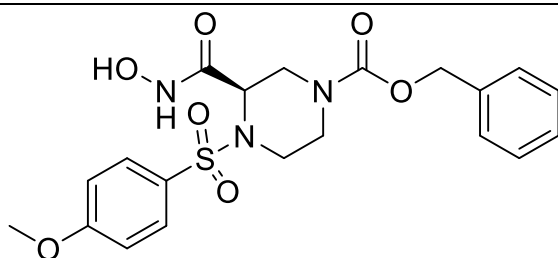
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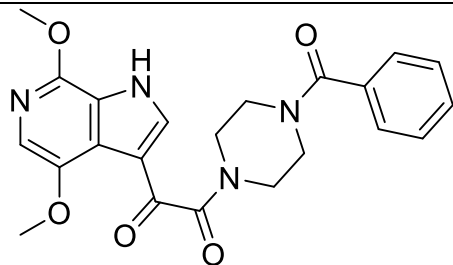
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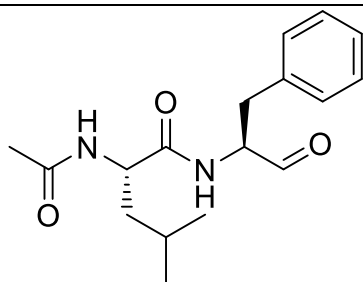
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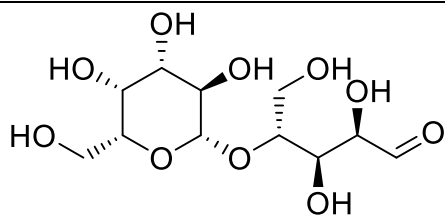
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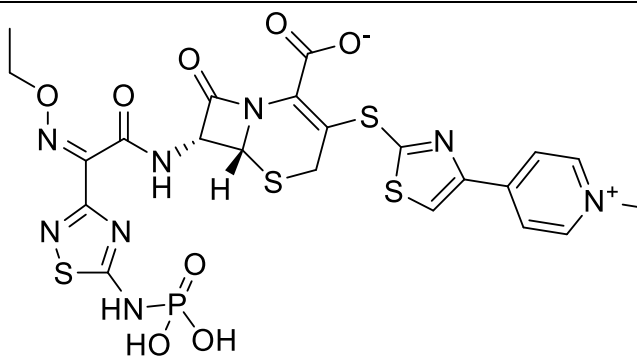
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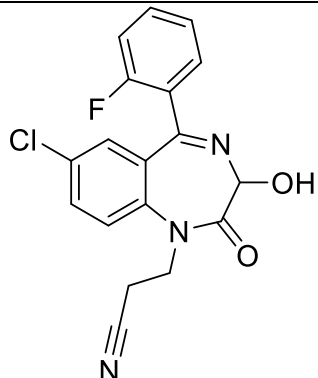
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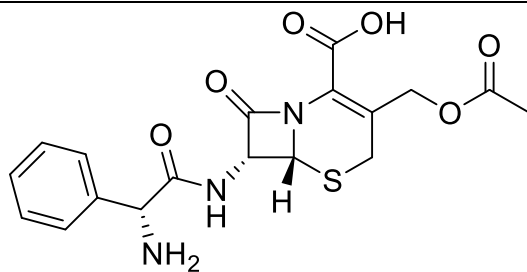
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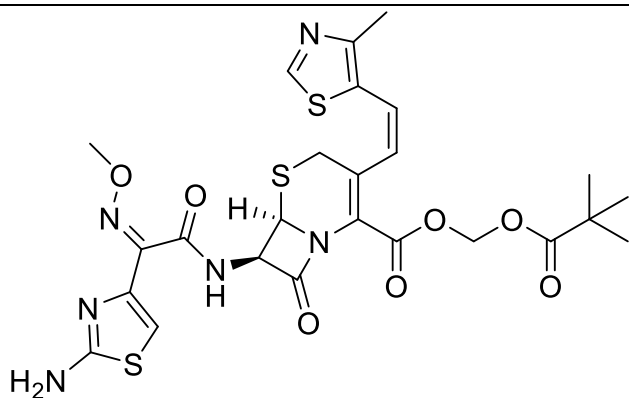
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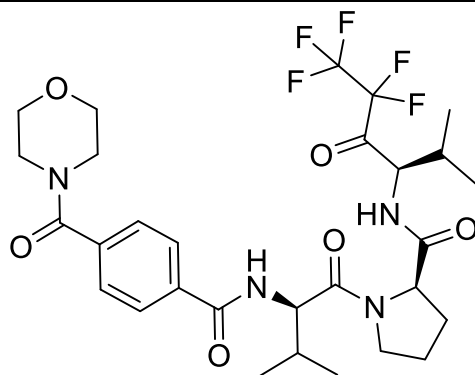
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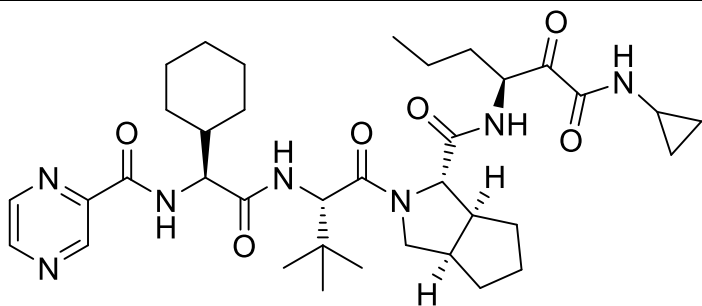
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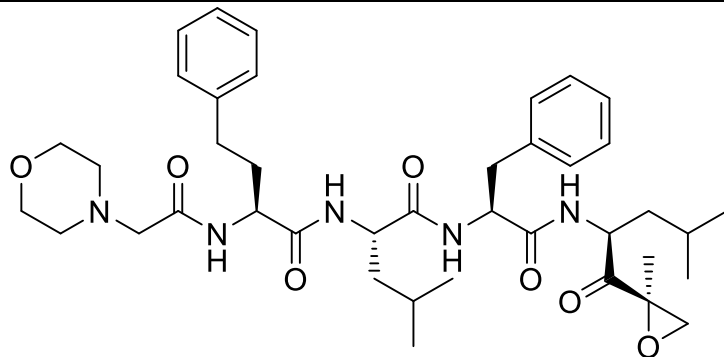
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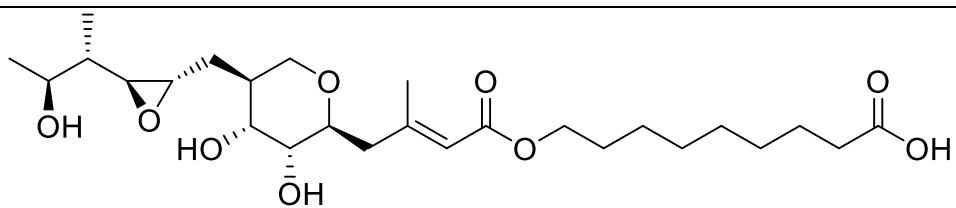
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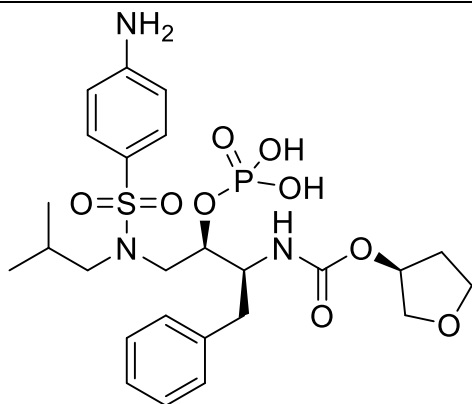
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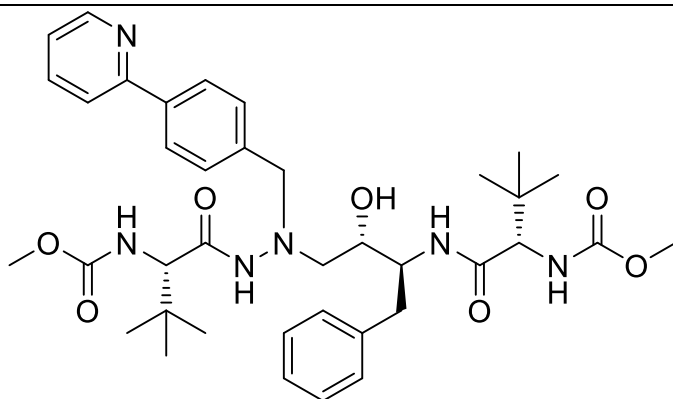
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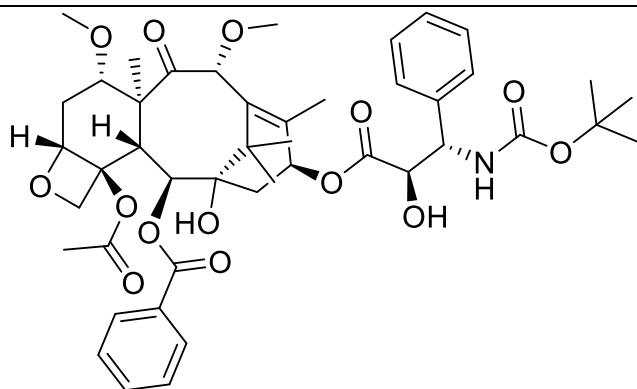
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ATAZANAVIR



CABAZITAXEL



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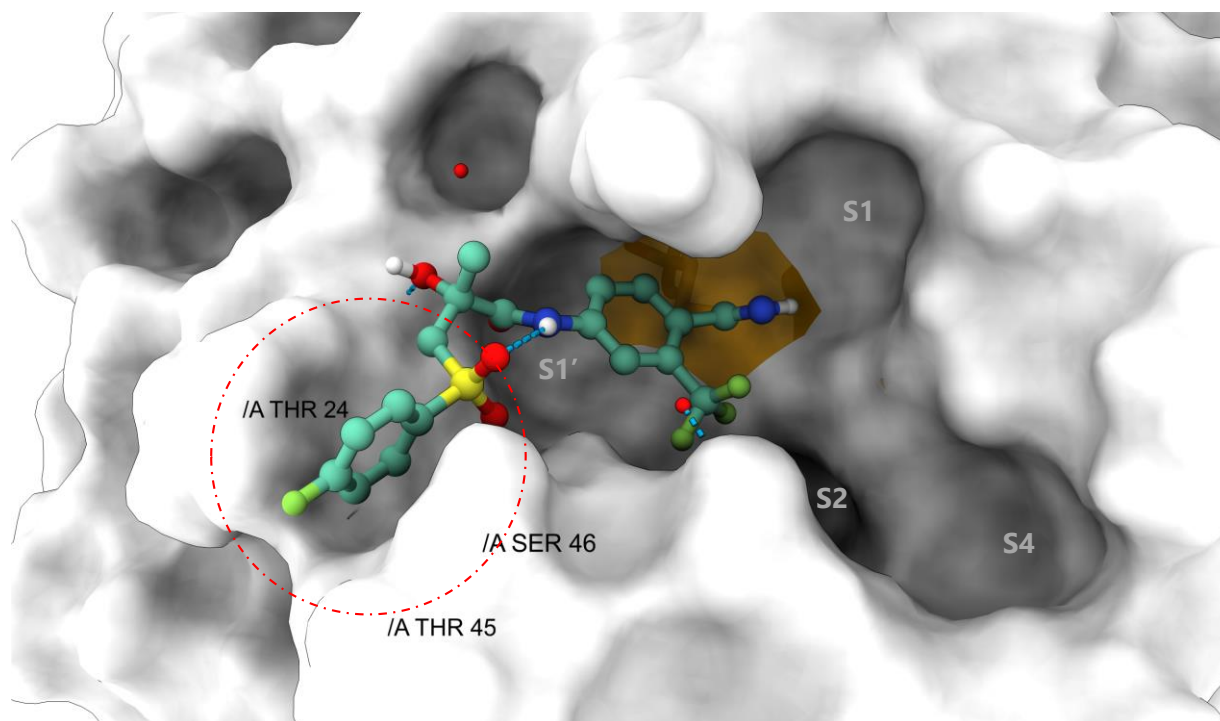
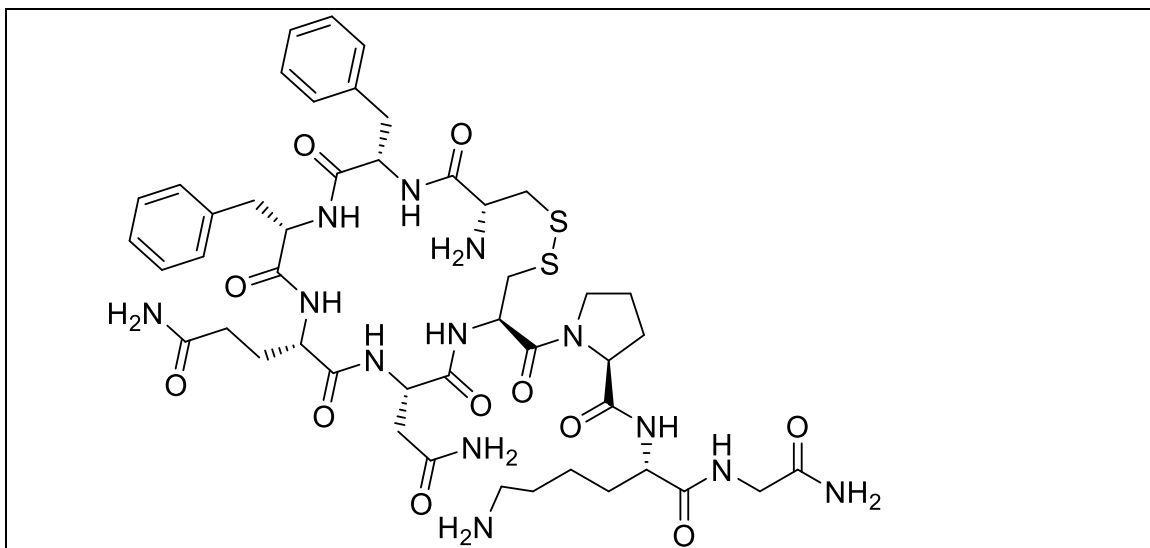


Figure S2. Binding mode of Bicatulamide in SARS-CoV-2 M^{pro}, where the subsite occupied by the 4-fluorobenzenesulfonyl substituent is highlighted.