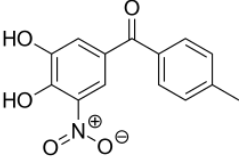


## SUPPLEMENTARY INFORMATION

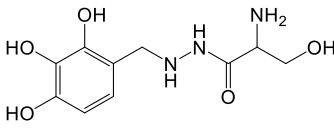
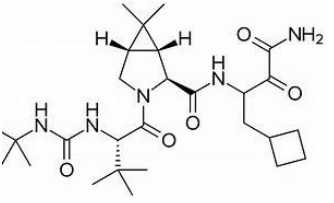
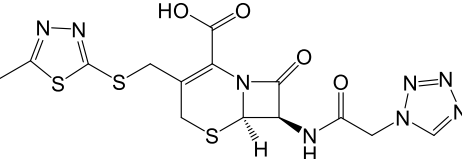
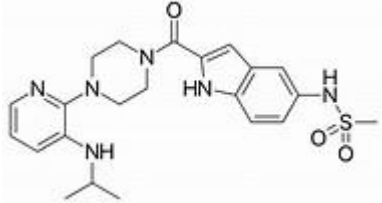
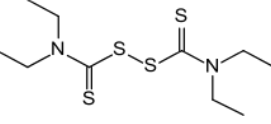
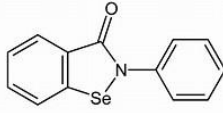
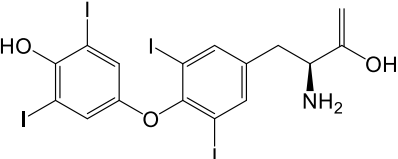
**Table S1: Chemical structures of the effective drug against SARS-CoV-2 3CL<sup>pro</sup>**

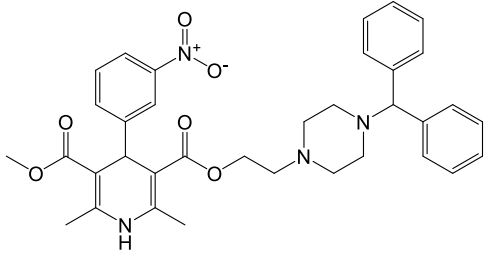
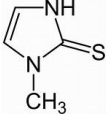
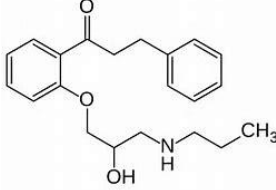
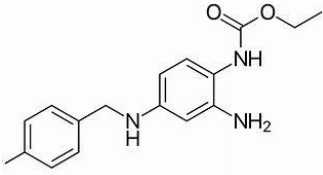
**screened out of 1068 drugs.**

Drug	Structure
Tolcapone	 <p>The chemical structure of Tolcapone is shown. It consists of a central benzene ring with two hydroxyl groups (HO) at the 3 and 4 positions and a nitro group (NO<sub>2</sub>) at the 1 position. This ring is connected via a carbonyl group (C=O) to another benzene ring, which has a methyl group (CH<sub>3</sub>) at the 4 position.</p>

**Table S2: Chemical structures of the additional 11 effective drugs against SARS-**

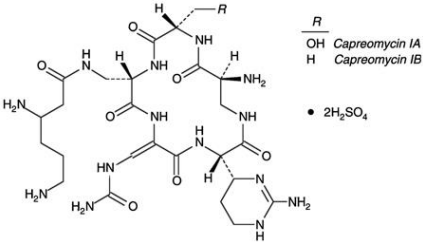
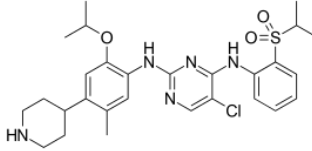
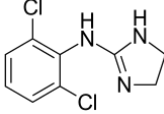
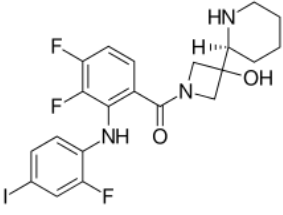
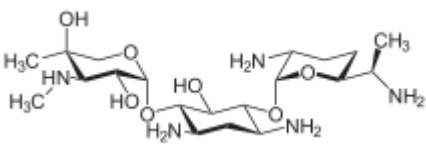
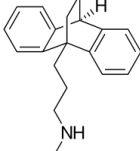
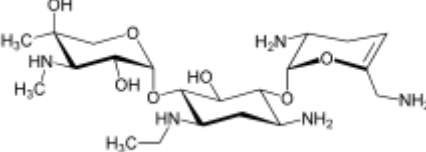
**CoV-2 3CL<sup>pro</sup> screened from 2701 drugs.**

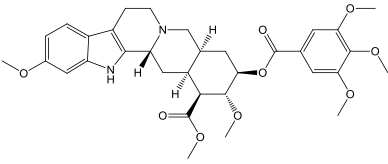
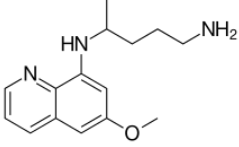
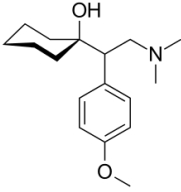
Drug	Structure
Benserazide HCl (aromatic L-amino acid decarboxylase or DOPA decarboxylase inhibitor)	
Boceprevir (HCV protease inhibitor, published 3CL <sup>pro</sup> inhibitor)	
Cefazolin (antibiotic)	
Delavirdine (non-nucleoside reverse transcriptase inhibitor)	
Disulfiram (acetaldehyde dehydrogenase inhibitor for anti-alcoholism, published 3CL <sup>pro</sup> inhibitor)	
Ebselen (scavenger of hydroperoxides, published 3CL <sup>pro</sup> inhibitor)	
Levothyroxine (thyroid hormone)	

<p>Manidipine 2HCl (calcium channel blocker used clinically as an anti-hypertensive)</p>	 <p>The structure shows a central 1,4-dihydropyridine ring with methyl groups at the 2 and 6 positions. At the 4-position, there is a nitro group (-NO<sub>2</sub>) and a methoxycarbonyl group (-COOCH<sub>3</sub>). At the 3-position, there is a propyl chain ending in a piperazine ring, which is further substituted with two phenyl groups.</p>
<p>Methimazole (treats overactive thyroid)</p>	 <p>The structure is a five-membered imidazole ring with a sulfur atom at the 2-position and a methyl group (-CH<sub>3</sub>) attached to the nitrogen at the 1-position.</p>
<p>Propafenone HCl (class 1C anti-arrhythmic medication)</p>	 <p>The structure features a benzofuran core. At the 3-position of the benzene ring, there is a propyl chain ending in a phenyl group. At the 4-position of the furan ring, there is a propyl chain ending in a secondary amine group (-NH-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), which also has a hydroxyl group (-OH) on the adjacent carbon.</p>
<p>Retigabine 2HCl (anticonvulsant)</p>	 <p>The structure consists of a central benzene ring with an amino group (-NH<sub>2</sub>) at the 1-position and an ethyl carbamate group (-NH-CO-O-CH<sub>2</sub>-CH<sub>3</sub>) at the 2-position. A benzyl group (-CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>) is attached to the nitrogen at the 4-position.</p>

**Table S3: Chemical structures of the 10 effective drugs against SARS-CoV-2**

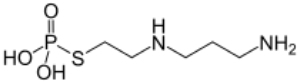
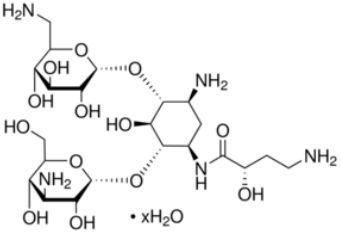
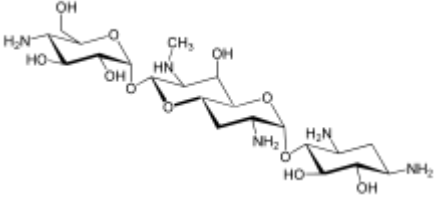
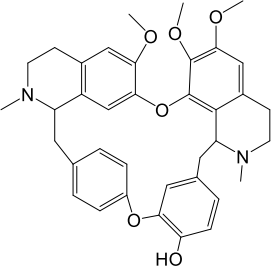
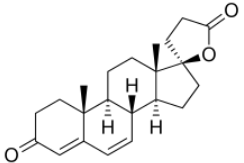
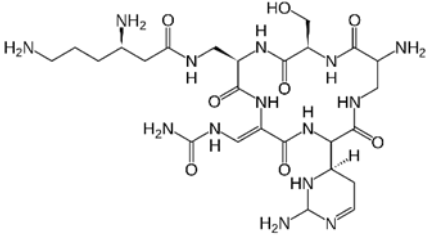
PL<sup>pro</sup> screened out of 1068 drugs

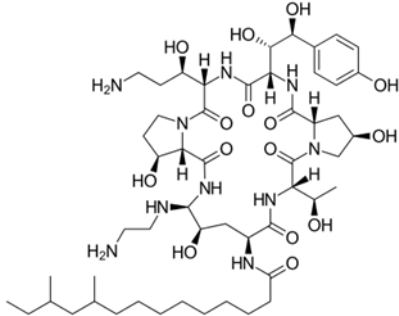
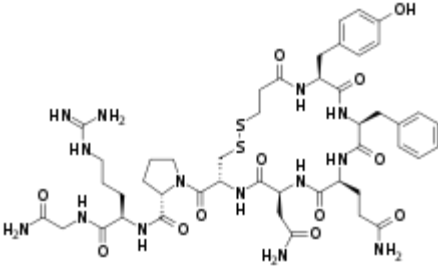
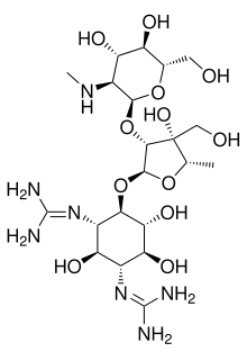
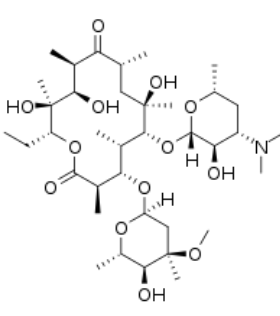
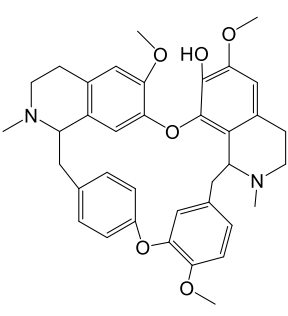
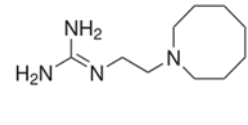
Drug	Structure
Capastat sulfate (polypeptide antibiotic)	
Ceritinib [anaplastic lymphoma kinase (ALK)-positive inhibitor for the treatment of metastatic lung cancer]	
Clonidine HCl (treats high blood pressure)	
Cobimetinib (MEK inhibitor to treat skin cancer)	
Gentamycin sulfate (aminoglycoside antibiotic)	
<b>Maprotiline HCl (anti-depressant)</b>	
Netilmicin sulfate (aminoglycoside antibiotic)	

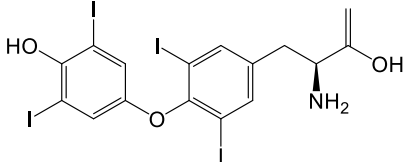
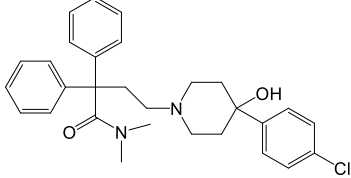
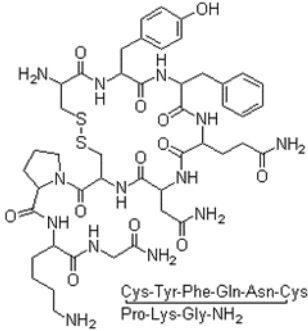
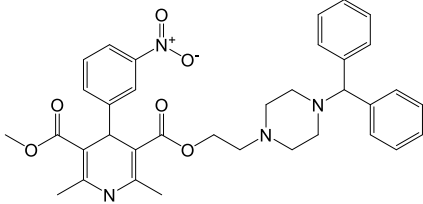
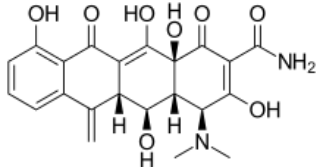
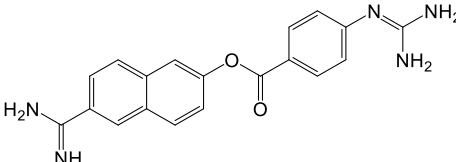
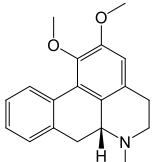
<p>Reserpine (blocks the H<sup>+</sup>-coupled vesicular monoamine transporters, VMAT1 and VMAT2, for the treatment of high blood pressure)</p>	 <p>The chemical structure of Reserpine is a complex pentacyclic alkaloid. It features a central indole ring system fused to a piperidine ring, which is further fused to a hexahydroindole ring. A decalin-like ring system is attached to the piperidine ring. The structure is highly substituted with several methoxy groups and a complex side chain containing a tertiary amine and a carboxylate group.</p>
<p>Primaquine diphosphate (anti-malarial)</p>	 <p>The chemical structure of Primaquine shows a quinoline ring system. The quinoline ring is substituted with a methoxy group at the 8-position and a 4-amino-2-methylbutylamino group at the 6-position.</p>
<p>Venlafaxine HCl (serotonin and norepinephrine reuptake inhibitor used as antidepressant)</p>	 <p>The chemical structure of Venlafaxine is a cyclohexane ring in a chair conformation. It has a hydroxyl group at the 1-position and a 2-(4-methoxyphenyl)ethyl-N,N-dimethylamino group at the 2-position.</p>

**Table S4: Chemical structures of the additional 26 effective drugs against SARS-**

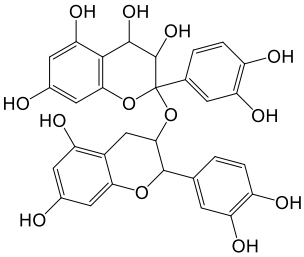
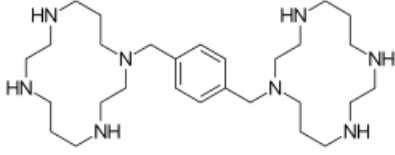
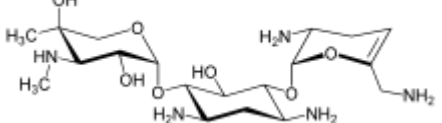
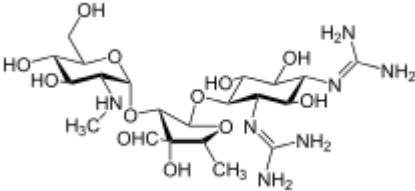
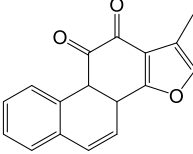
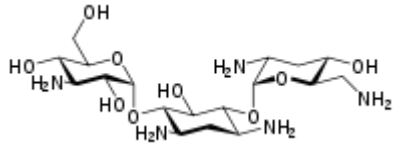
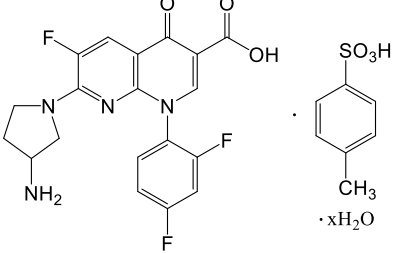
**CoV-2 PL<sup>pro</sup> screened from 2701 drugs**

Drug	Structure
Amifostine (cytoprotective adjuvant used in cancer chemotherapy)	
Amikacin hydrate (aminoglycoside antibiotic)	
Apramycin sulfate (aminoglycoside antibiotic)	
Berberine 2HCl (calcium channel blocker)	
Canrenone (steroidal anti-mineralocorticoid)	
Capreomycin sulfate (polypeptide antibiotic)	

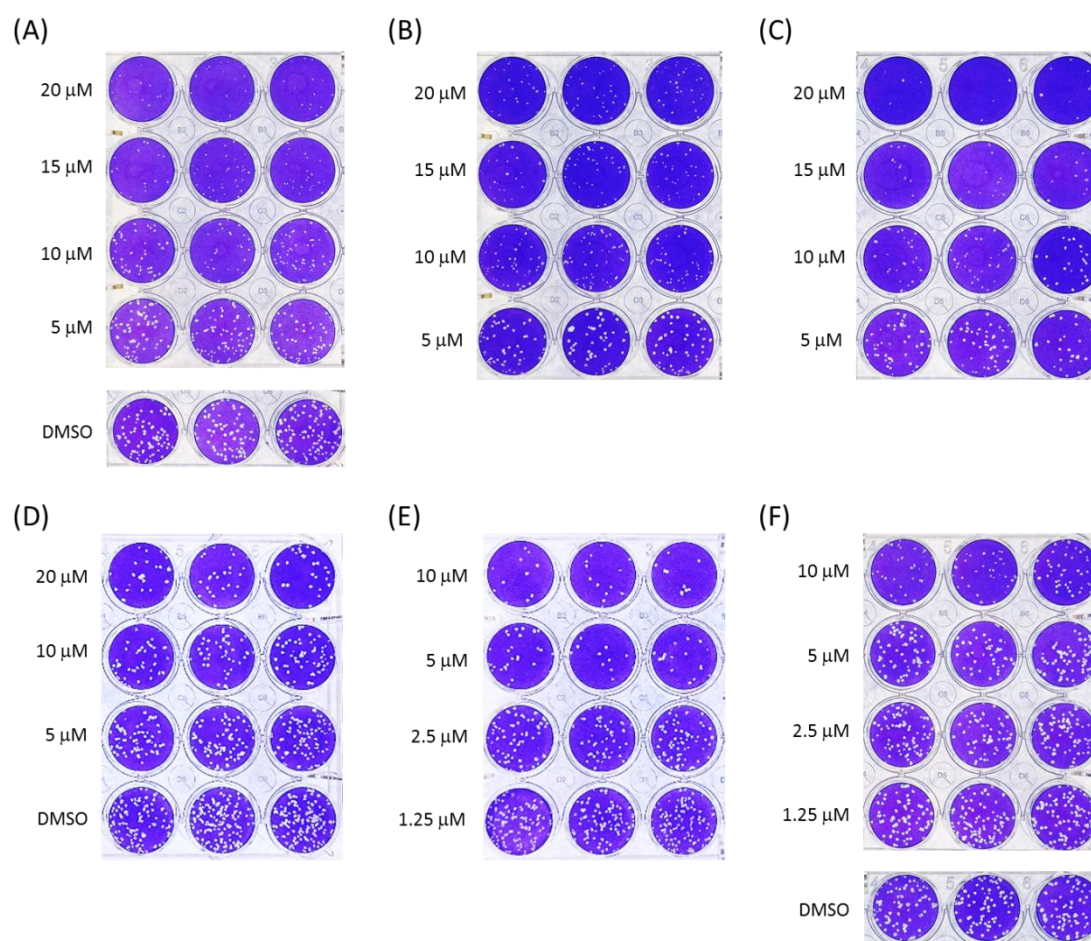
<p>Caspofungin acetate (lipopeptide anti-fungal drug)</p>	
<p>Desmopressin acetate (controls the amount of urine made by kidney)</p>	
<p>Dihydrostreptomycin sulfate (aminoglycoside antibiotic)</p>	
<p>Erythromycin thiocyanate (aminoglycoside antibiotic)</p>	
<p>Fangchinoline (anti-cancer)</p>	
<p>Guanethidine sulfate (anti-hypertensive drug)</p>	

<p>Levothyroxine (thyroid hormone)</p>	 <p>The structure shows a central benzene ring with two iodine atoms at the 3 and 5 positions. This ring is linked via an ether oxygen to another benzene ring with iodine atoms at the 3 and 5 positions. A propyl chain is attached to the 4 position of the second ring, with an amino group (NH<sub>2</sub>) on the second carbon and a carboxylic acid group (COOH) on the third carbon.</p>
<p>Loperamide (Imodium, used to decrease the frequency of diarrhea)</p>	 <p>The structure features a central piperidine ring. One carbon of the piperidine ring is substituted with a hydroxyl group (OH) and a 4-chlorophenyl ring. Another carbon is substituted with a propyl chain that has a dimethylamino group (N(CH<sub>3</sub>)<sub>2</sub>) at the end. A third carbon is substituted with a diphenylmethyl group (CH<sub>2</sub>Ph<sub>2</sub>).</p>
<p>Lypressin acetate (neuron hormone)</p>	 <p>The structure is a complex cyclic peptide consisting of two rings. The amino acid sequence is Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH<sub>2</sub>. The structure shows various side chains including a hydroxyl group, a phenyl ring, and a long-chain amide group.</p>
<p>Manidipine 2HCl (calcium channel blocker used clinically as an anti-hypertensive)</p>	 <p>The structure shows a central dihydropyridine ring system. It has a nitro group (NO<sub>2</sub>) at the 4-position, a methyl group at the 2-position, and a side chain at the 3-position that includes a methoxy group, a carbonyl group, and a piperazine ring substituted with a diphenylmethyl group.</p>
<p>Methacycline (tetracycline antibiotic)</p>	 <p>The structure is a tetracycline derivative. It features a central tetracycline core with a methylamino group (NHCH<sub>3</sub>) at the 7-position and a dimethylamino group (N(CH<sub>3</sub>)<sub>2</sub>) at the 8-position. Various hydroxyl and carbonyl groups are also present.</p>
<p>Nafamostat mesylate (serine protease inhibitor used for anti-coagulant)</p>	 <p>The structure shows a naphthalene ring system. One ring has a primary amide group (NH<sub>2</sub>CH=NH) at the 1-position. The other ring is linked via an ester group to a side chain that includes a benzene ring and a guanidino group (N=C(NH<sub>2</sub>)<sub>2</sub>).</p>
<p>Nuciferine (morphine analgesia)</p>	 <p>The structure is a morphine derivative. It features a pentacyclic ring system with a nitrogen atom in a bridgehead position. There are two methoxy groups (OCH<sub>3</sub>) on the aromatic ring and a methyl group on the nitrogen atom.</p>



<p>Proanthocyanidin (a flavan-3-ol in plants)</p>	
<p>Plerixafor 8HCl (immunostimulant)</p>	
<p>Sisomicin sulfate (aminoglycoside antibiotic)</p>	
<p>Streptomycin sulfate (aminoglycoside antibiotic)</p>	
<p>Tanshinone I (anti-inflammatory)</p>	
<p>Tobramycin sulfate (aminoglycoside antibiotic)</p>	
<p>Tosufloxacin p-toluenesulfonate hydrate (fluoroquinolone antibiotic)</p>	

**Figure S1. Plaque Reducing Activities of 6 FDA-approved drugs.** Reduction of virus plaques was observed in the presence of 1.25–20  $\mu\text{M}$  of (A) Loperamide, (B) Manidipine, (C) Maprotiline, (D) Levothyroxine, (E) Proanthocyanidin, and (F) Reserpine. Loperamide, Maprotiline, and Manidipine were post-treatment; Levothyroxine and Proanthocyanidin were entry-treatment; Reserpine was full-time treatment. Being tested at the same time, Loperamide, Maprotiline, and Manidipine shared the same DMSO control. Levothyroxine and Proanthocyanidin shared the same DMSO control.



**Figure S1**