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Improving the Inhibition of TMPRSS2 by Molecular Docking, to Decrease the Process Infection of SARS-CoV-2

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Abstract: COVID-19 pandemic continues with several works focused on the repositioning of drugs, vaccines, and antibodies against COVID-19, as well as new therapeutic targets on the cellular membrane (ACE2, NRP1, and TMPRSS2) that interacting with SARS-CoV-2 S-protein. This study proposes ten compounds (T1 - T10) selected by molecular docking using a library of nearly 500,000 compounds, these ten compounds have better interaction than Daclatasvir, Ombitasvir, Camostat, Edoxaban, NCGC00386477, Nafamostat, NCGC00386945, Otamixaban, Darexaban, Gabexate, Letaxaban, Argatroban, Sivelestat, NCGC00385043, and Bromhexine, and all of them have an inhibitory effect reported at TMPRSS2. The T1 - T10 compounds were selected by molecular docking in the catalytic site of TMPRSS2, which could hinder/block the interaction with the S-protein and ACE2. Therefore the initial/early stage of COVID-19 could be avoided or decreased by hindering the fusion between SARS-CoV-2 and the cell membrane and this way to develop a new adjuvant treatment against COVID-19.

Keywords: TMPRSS2 inhibitors; docking; ACE2; SARS-CoV-2.

1. Introduction

COVID-19 pandemic has caused about 198 million infections and 4 million deaths (July 30, 2021) [1]; COVID-19 causes a wide range of signs and symptoms, mainly respiratory and even deaths [2 - 5]. Different therapeutic targets have been proposed to develop new antivirals, as the polyproteins 3-chymotrypsin like protease (3CLpro) and papain-like protease (PLpro), RNA-Dependent RNA Polymerase (RdRp) [6 - 8], membrane fusion inhibitors heptad repeat 1 and 2 (HR1 and HR2) of Spike protein (S-protein) of SARS-CoV-2 [9 - 15], and receptors or proteins in the cell membrane as angiotensin-converting enzyme 2 (ACE2) [16 - 21], neuropilin-1 (NRP1) [7, 22, 23], or the trans-membrane protease serine 2 (TMPRSS2) [24], due to these proteins can help to virus to introduce its genetic material and contribute in the infectious process of SARS-CoV-2 [25, 26]. Moreover, several works repurposed treatments with potential effect against COVID-19 [27, 28], and performing docking for drug repositioning and/or with compound libraries to search inhibitors between the S-protein and its receptors [10, 29 - 32].

In this study, TMPRSS2 was the chosen therapeutic target, as it is an important protein for the metabolic process of SARS-CoV-2. It is on the cell surface, expressed mainly in aerodigestive tissue, and the functions of TMPRSS2 are not yet fully described. Moreover, an

increase in its expression has been identified in prostate cancer tumor cells (metastasis and spread) [33], with changes in its expression levels at different people [34, 35].

The TMPRSS2 has functions for that the SARS-CoV-2 can introduce its genetic material through membrane fusion [26, 33], and the main amino acids have been reported for the interaction with ACE2 [34, 35], as well as it is also proposed that the TMPRSS2 has an interaction with the S-protein (in the cleavage of the S-protein) [36, 37]; the S-protein can be cleaved, and the fusion process with the cell membrane can be favored, which allows the entry of the viral genome [38 - 42], this process has been related in tissues in which there is more expression of TMPRSS2 in the cell membrane (lung tissue) [36, 39].

On the other hand, the development of vaccines/antibodies has been developing [43 - 46]. However, there are reports of mutations at different proteins in the SARS-CoV-2 that could difficult their effectivity [46, 47], for example, in the S-protein of SARS-CoV-2 (December 2020) that could increase the infectious process and decrease the effect of vaccines [48 - 53].

This study uses reference compounds/drugs that have a therapeutic effect in other diseases, mainly cancer, but that has an inhibitory effect on TMPRSS2 and could generate a therapeutic effect on COVID-19 [38 - 42, 54, 55]. Therefore, it is possible to develop a drug with a therapeutic target in the catalytic site of TMPRSS2 that would have better therapeutic effects against COVID-19. For that, this study proposes to carry out a molecular docking (using almost 500,000 compounds) to select compounds capable of interacting in the catalytic site of TMPRSS2, to decrease the interaction between TMPRSS2 and S-protein, and generating a reduction in the entry of the virus into cells, to propose compounds to develop a new drug against SARS-CoV-2.

2. Materials and Methods

2.1. The homology model of TMPRSS2.

The homology model of TMPRSS2 was built using the SWISS-MODEL server [56]. The transmembrane trypsin-like serine protease hepsin (TMPRSS1, PDB 1Z8G [57]) was used as the template structure with 24.5 % of identity in the residues of TMPRSS2 (P05981 Heps_Human vs. O15393 TMPS2_Human [58]), and the catalytic sites are highly conserved. The three-dimensional modeled structure was validated by uploading on the RAMPAGE and SAVES 6.0 web servers [59].

2.2. Preparation of receptor protein and selection of the binding site.

Atomic coordinates of the model generated of TMPRSS2 was used (the PDB 1Z8G was used as the template structure), the catalytic site in the TMPRSS2 was used as the target for molecular docking using Molecular Operating Environment (MOE), following procedures previously reported [16, 23, 60, 61]. Thus, the potential site is between His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 amino acids, the catalytic site region in TMPRSS2 [38, 40, 55].

2.3. Compound library used, and drugs/compounds against TMPRSS2 reported for molecular docking.

The EXPRESS-pick Collection Stock screening library (Chembridge Corp. [62]) was used for molecular docking. This collection of compounds druggable contains 502530 that

fulfill Lipinski's rules [63, 64] and cover a broad area of chemical compound space, as well as the structure of ombitasvir, daclatasvir [42], otamixaban, argatroban, letaxaban, darexaban, edoxaban [39], NCGC00385043, NCGC00386945, NCGC00386477, bromhexine [38, 40, 41, 54], camostat, nafamostat, gabexate and sivelestat [55] to evaluate the interaction with TMPRSS2 [32].

2.4. Molecular docking.

For molecular docking, up to 100 conformers were generated from each compound to interact with the potential binding site (compound library and drugs/compounds against TMPRSS2), following procedures previously reported [16, 23]. High-throughput virtual molecular docking was carried out by the software MOE and the analysis of ligand interaction per residue at MOE, AutoDockTools [65], and Protein-Ligand Interaction Profiler [62, 66 - 68].

2.5. Selection of the best ten compounds.

To select the best ten compounds, the results of up to 30 conformers from each compound were used to select them. It was determining the binding free energy (ΔGbinding) of each complex (Ligand-Protein), as previously reported [16, 23] using MOE [69, 70]. With these results, the best averages ΔGbinding were determined between TMPRSS2 with each compound, as well as the standard deviation for each one, using the Excel software (Microsoft-365), the description of chemical properties by PhysChem - ACD/Labs [71], and the theoretical toxicity (carcinogenicity and mutagenicity) [72 - 74].

3. Results and Discussion

3.1. Selection of compounds by Molecular Docking.

It was used the Express-pick Collection library from Chembridge Corp. [62] with 502530 compounds, and up to 100 conformers from each compound interacting in the catalytic site in TMPRSS2 (the region between amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463 and Gly464, Figure 1) for molecular docking, as is reported [16, 23], the selection criteria of the best ten compounds was based on the calculation of the average of ΔGbinding of each compound, using the values of conformers (27 to 30 conformers), determining an average range from -7.94 to -8.19 kcal mol^{-1} for the best ten compounds (Table 1, and details on the supplementary material Table S1). Ten compounds were selected, called here as T1 to T10, and the analysis of the interaction of each compound with TMPRSS2 was carried out with the interaction report (Table 2 and details in Table S1 – S11). Also, it was determined the average interaction for main drugs/compounds reported to interact with TMPRSS2 (ombitasvir, daclatasvir [42], otamixaban, argatroban, letaxaban, darexaban, edoxaban [39], NCGC00385043, NCGC00386945, NCGC00386477, bromhexine [38, 40, 41, 54], camostat, nafamostat, gabexate and sivelestat [55]), with an average of ΔGbinding between -5.87 kcal mol^{-1} and -3.99 kcal mol^{-1} (interaction details in Table S1 and S12 – S26). All averages of ΔGbinding calculated are related to the number of interactions generated by the conformers analyzed from the molecular docking results (Table 3). It is shown that the T1 - T10 compounds interact more frequently with the amino acids Val280, His296, Gly439, and Cys465.

In addition, the description of the theoretical toxicity (Table S27), ADME characteristics (Table S28), and chemical properties of each compound (T1 – T10, Table S29), are presented in the supplemental material.

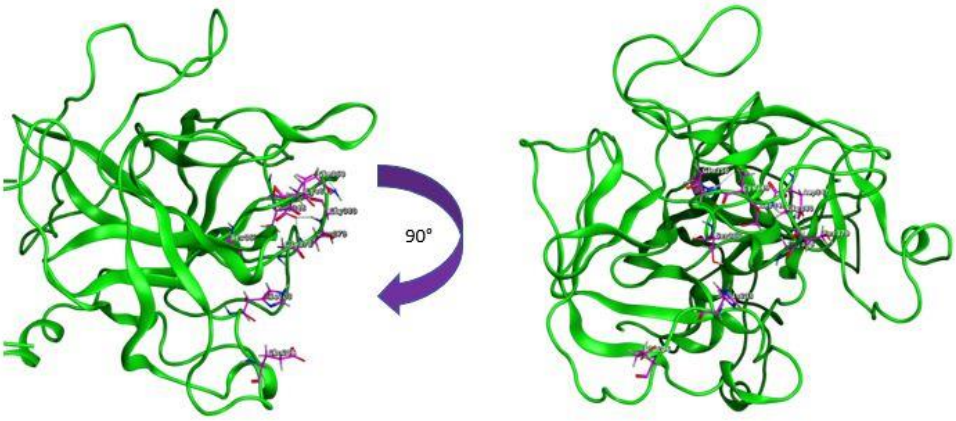
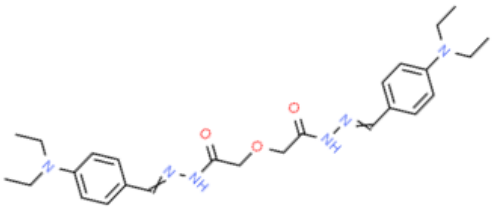
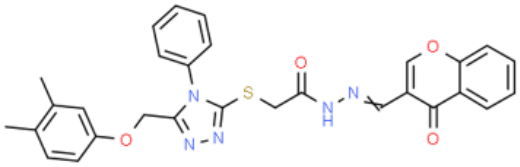
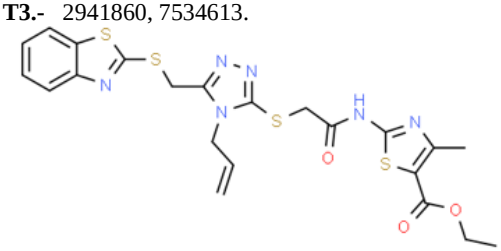
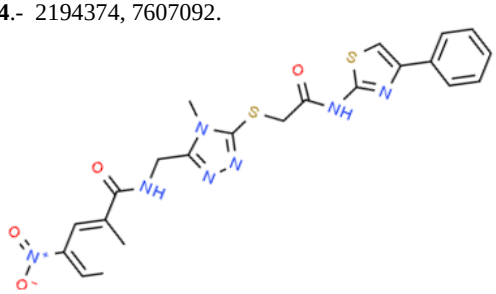
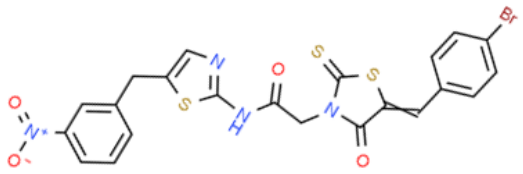
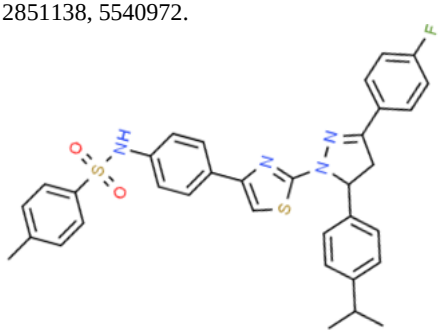
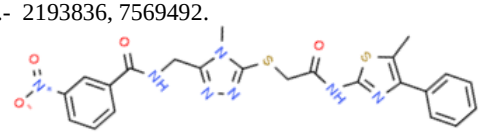
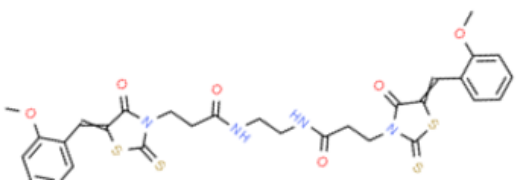
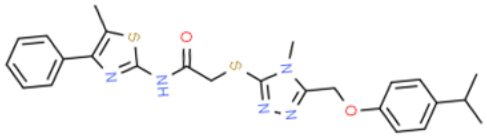


Figure 1. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as regions chosen for molecular docking.

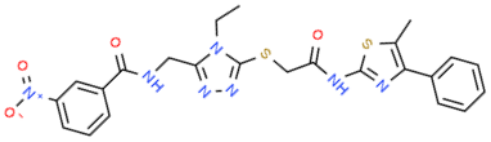
Table 1. PubChem CID, ID Chembridge Corp./Name and Structure of the best ten compounds, T1 to T10 and main compound/drugs reported against TMPRSS2.

T1.- 2848720, 5483027.	**T2.-** 5650548, 5771448.
	
T3.- 2941860, 7534613.	**T4.-** 2194374, 7607092.
	
T5.- 1552161, 5526397.	**T6.-** 2851138, 5540972.
	
T7.- 2193836, 7569492.	**T8.-** 5722665, 5531741.
	

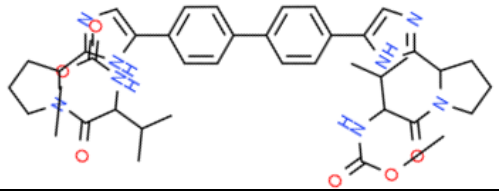
T9.- 1314888, 7507920.



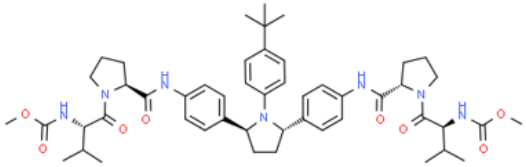
T10.- 2193905, 7573429.



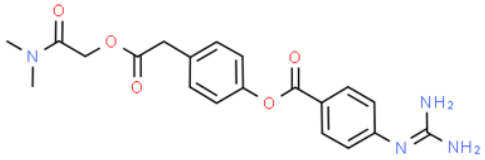
25154714, Daclatasvir.



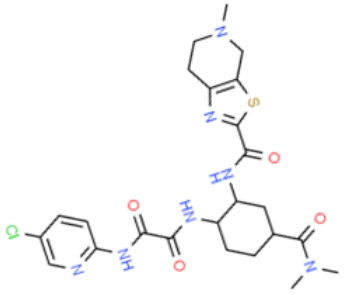
54767916, Ombitasvir.



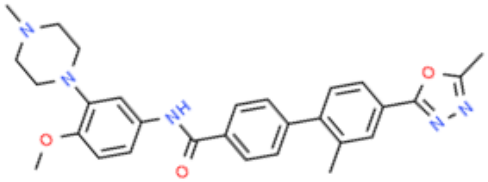
2536, Camostat.



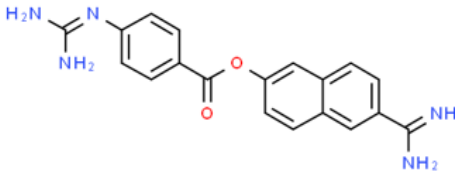
10280735, Edoxaban.



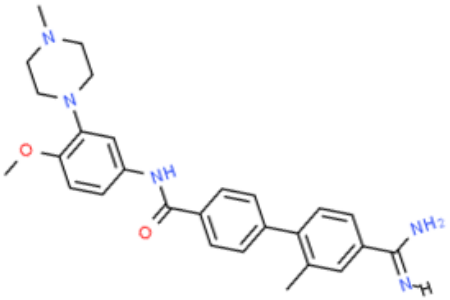
10323598, NCGC00386477.



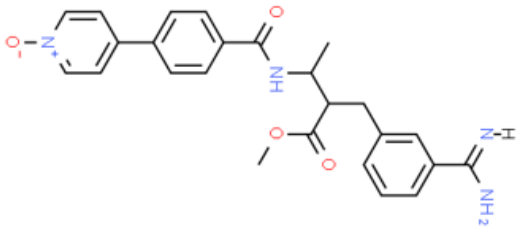
4413, Nafamostat.



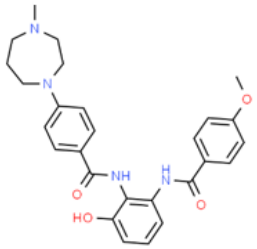
9846928, NCGC00386945.



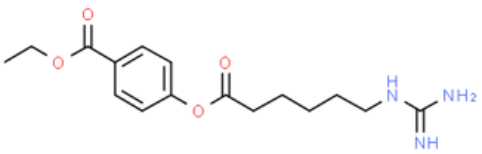
5496659, Otamixaban.



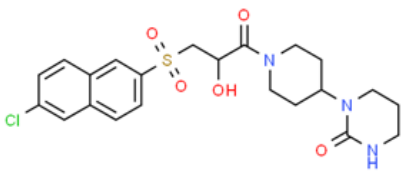
9912771, Darexaban.



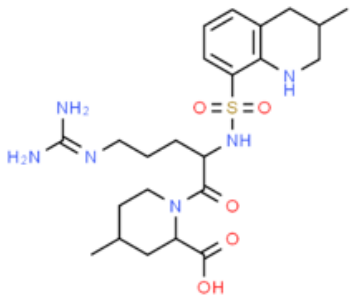
3447, Gabexate.



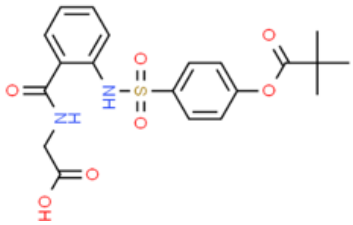
11641515, Letaxaban.



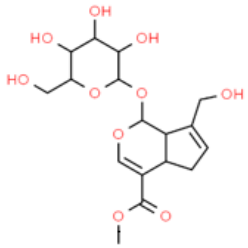
92722 , Argatroban.



107706, Sivelestat.



12004581, NCGC00385043.



2442, Bromhexine.

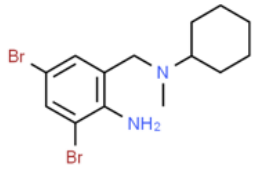


Table 2. PubChem CID, Canonical SMILES, Interaction with residues in TMPRSS2, Number of conformers used, ΔGbinding average (kcal mol^{-1}) with standard deviation (SD), Ames test and strain used (positive or negative) and LD50 [72, 74].

PubChem CID	Canonical SMILES	Interaction with residues in TMPRSS2 (Table S2 – S26), in bold it is of greater interaction.	Number of conformers	Average of $\Delta G_{binding}$ and SD	PreADMET Ames test and LD_{50} -TA100_10RL -TA100_NA -TA1535_10R -TA1535_NA Predicted LD_{50} mg/kg
T1.- 2848720	CCN(CC)C1=CC=C(C=C1)C=NNC(=O)COCC(=O)NN=CC2=CC=C(C=C2)N(CC)CC	**His296,** Asn336, Ser436, Cys437, **Gly439**, Gly462, **Gly464, Cys465**	29	-8.19 ± 0.83	Mutagen -Positive -Negative -Negative -Negative 5000 mg/kg
T2.- 5650548	CC1=C(C=C(C=C1)OCC2=NN=C(N2C3=CC=CC=C3)SCC(=O)NN=CC4=COC5=CC=CC=C5C4=O)C	**Val280, His296**, Cys297, Glu299, Ser436, Gln438, **Gly439**	27	-8.10 ± 0.90	Mutagen -Positive -Negative -Negative -Negative 1500 mg/kg
T3.- 2941860	CCOC(=O)C1=C(N=C(S1)NC(=O)CSC2=NN=C(N2CC=C)CSC3=NC4=CC=CC=C4S3)C	**Val280, His296**, Val298, Glu299, Asn336, Ser436, **Gly439**, Gly462, Cys465	27	-8.01 ± 0.68	Non mutagen -Negative -Negative -Negative -Negative 1000 mg/kg
T4.- 2194374	CN1C(=NN=C1SCC(=O)NC2=NC(=CS2)C3=CC=CC=C3)CNC(=O)C4=CC(=CC=C4)[N+](=O)[O-]	**Val280, His296, Glu299**, Leu302, **Asn336**, Ser436, Cys437, **Gly439**, Gly462, Glu464, Cys465	30	-7.99 ± 0.59	Mutagen -Positive -Positive -Positive -Negative 1000 mg/kg
T5.- 1552161	C1=CC(=CC(=C1)[N+](=O)[O-])CC2=CN=C(S2)NC(=O)CN3C(=O)C(=CC4=CC=C(C=C4)Br)SC3=S	**Val280, His296**, **Cys297**, Asn336, Ser436, Gln438, **Gly439**, Trp461, **Gly462**, Cys465	28	-7.99 ± 0.56	Mutagen -Positive -Negative -Positive -Negative 500 mg/kg
T6.- 2851138	CC1=CC=C(C=C1)S(=O)(=O)NC2=CC=C(C=C2)C3=CSC(=N3)N4C(CC(=N4)C5=CC=	Val280, **His296**, Glu299, Ser436, Gly439, Gly464	27	-7.99 ± 0.81	Non mutagen -Negative

PubChem CID	Canonical SMILES	Interaction with residues in TMPRSS2 (Table S2 – S26), in bold it is of greater interaction.	Number of conformers	Average of $\Delta G_{binding}$ and SD	PreADMET Ames test and LD_{50} -TA100_10RL -TA100_NA -TA1535_10R -TA1535_NA Predicted LD_{50} mg/kg
	C(C=C5)F)C6=CC=C(C=C6)C(C)C				-Negative -Negative -Negative 1000 mg/kg
T7.- 2193836	CC1=C(N=C(S1)NC(=O)CSC2=NN=C(N2C)CNC(=O)C3=CC(=CC=C3)[N+](=O)[O-])C4=CC=CC=C4	Val280, **His296**, Glu299, Asn336, Lys390, Gln438, **Gly439**, Gly462	28	-7.97 ± 0.80	Mutagen -Positive -Positive -Negative -Negative 1000 mg/kg
T8.- 5722665	COC1=CC=CC=C1C=C2C(=O)N(C(=S)S2)CCC(=O)NCCNC(=O)CCN3C(=O)C(=CC4=CC=CC=C4OC)SC3=S	Val280, **His296**, Cys297, Glu299, Leu302, Lys390, Gly391, Cys437, Gln438, **Gly439**, Trp461, Gly462, **Cys465, Lys467**	30	-7.96 ± 0.76	Mutagen -Negative -Negative -Negative -Negative 350 mg/kg
T9.- 1314888	CC1=C(N=C(S1)NC(=O)CSC2=NN=C(N2C)COC3=CC=C(C=C3)C(C)C)C4=CC=CC=C4	**Val280, His296**, Cys297, Glu299, Asn336, Cys437, **Gly439**, Gly464, Cys465	28	-7.95 ± 0.81	Mutagen -Negative -Negative -Positive -Negative 1000 mg/kg
T10.- 2193905	CCN1C(=NN=C1SCC(=O)NC2=NC(=C(S2)C)C3=CC=CC=C3)CNC(=O)C4=CC(=CC=C4)[N+](=O)[O-]	His279, **Val280, His296, Glu299**, Asn336, Cys437, Gln438, **Gly439**	29	-7.94 ± 0.83	Mutagen -Positive -Positive -Negative -Negative 1000 mg/kg
Daclatasvir 25154714	CC(C)C(C(=O)N1CCCC1C2=NC=C(N2)C3=CC=C(C=C3)C4=CC=C(C=C4)C5=CN=C(N5)C6CCCN6C(=O)C(C(C)C)NC(=O)OC)NC(=O)OC	His296, **Glu299**, Gly391, Cys437, Gln438, Gly439, **Cys465**, Lys467	25	-5.87 ± 0.39	
Ombitasvir 54767916	CC(C)C(C(=O)N1CCCC1C(=O)NC2=CC=C(C=C2)C3CCC(N3C4=CC=C(C=C4)C(C)(C)C)C5=CC=C(C=C5)NC(=O)C6CCCN6C(=O)C(C(C)C)NC(=O)OC)NC(=O)OC	**His296**, **Glu299**, Asn336, Gly303, Gln438, Ser463, Cys465, Lys467, **Arg470**	30	-5.61 ± 0.62	
Camostat 2536	CN(C)C(=O)COC(=O)CC1=CC=C(C=C1)OC(=O)C2=CC=C(C=C2)N=C(N)N	His296, **Glu299**, Gly439, Ser447	24	-5.27 ± 0.54	
Edoxaban 10280735	CN1CCC2=C(C1)SC(=N2)C(=O)NC3CC(CCC3NC(=O)C(=O)NC4=NC=C(C=C4)Cl)C(=O)N(C)C	Val280, **His296**, **Glu299**, Ser436, Gly439, Trp461, Gly462, Cys465	26	-5.24 ± 0.64	
NCGC00386477 10323598	CC1=C(C=CC(=C1)C2=NN=C(O2)C)C3=CC=C(C=C3)C(=O)NC4=CC(=C(C=C4)OC)N5CCN(CC5)C	Val280, His296, **Glu299**, Gly462, Ser463, Cys465, **Lys467**	25	-5.21 ± 0.52	
Nafamostat 4413	C1=CC(=CC=C1C(=O)OC2=CC3=C(C=C2)C=C(C=C3)C(=N)N)N=C(N)N	Val280, His296, **Glu299**, **Ser436**, **Cys437**, Gly439, Cys465	23	-5.09 ± 0.45	
NCGC00386945 9846928	CC1=C(C=CC(=C1)C(=N)N)C2=CC=C(C=C2)C(=O)NC3	His296, **Glu299**, Ser436, Cys437,	26	-5.03 ± 0.50	

PubChem CID	Canonical SMILES	Interaction with residues in TMPRSS2 (Table S2 – S26), in bold it is of greater interaction.	Number of conformers	Average of $\Delta G_{binding}$ and SD	PreADMET Ames test and LD_{50} -TA100_10RL -TA100_NA -TA1535_10R -TA1535_NA Predicted LD_{50} mg/kg
	=CC(=C(C=C3)OC)N4CCN(CC4)C	Gly462, Ser463, Cys465			
Otamixaban 5496659	CC(C(CC1=CC(=CC=C1)C(=N)N)C(=O)OC)NC(=O)C2=CC=C(C=C2)C3=CC=[N+](C=C3)[O-]	Val280, **His296**, Val298**, Glu299**, Ser436, Cys437, Gln438, Gly439, Trp461, Gly462, Cys465	26	-5.01 ± 0.49	
Darexaban 9912771	CN1CCCN(CC1)C2=CC=C(C=C2)C(=O)NC3=C(C=CC=C3O)NC(=O)C4=CC=C(C=C4)OC	Val280, **His296, Glu299**, Cys437, Gly439	26	-4.98 ± 0.46	
Gabexate 3447	CCOC(=O)C1=CC=C(C=C1)OC(=O)CCCCCN=C(N)N	Val280, His296**, Glu299**, Asn336, **Ser436**, Gly439	29	-4.94 ± 0.30	
Letaxaban 11641515	C1CNC(=O)N(C1)C2CCN(CC2)C(=O)C(CS(=O)(=O)C3=CC4=C(C=C3)C=C(C=C4)Cl)O	**Val280**, **His296,** Glu299, Asn336, Ser436, Gln438, Gly439	26	-4.84 ± 0.50	
Argatroban 92722	CC1CCN(C(C1)C(=O)O)C(=O)C(CCCN=C(N)N)NS(=O)(=O)C2=CC=CC3=C2NCC(C3)C	His279, Val280, **His296, Glu299**, Ser436, Gln438, Gly439	29	-4.75 ± 0.46	
Sivelestat 107706	CC(C)(C)C(=O)OC1=CC=C(C=C1)S(=O)(=O)NC2=CC=CC=C2C(=O)NCC(=O)O	**His296**, **Lys390**, Gly391, Cys437, Gln438, **Gly439**, **Cys465**, **Lys467**	26	-4.59 ± 0.46	
NCGC00385043 12004581	COC(=O)C1=COC(C2C1CC=C2CO)OC3C(C(C(C(O3)CO)O)O)O	Val280, **His296**, **Ser436**, Cys437, **Gly439**, Gly462	30	-4.21 ± 0.34	
Bromhexine 2442	CN(CC1=C(C(=CC(=C1)Br)Br)N)C2CCCCC2	Val280, Ser436, Cys437, Gly439	21	-3.99 ± 0.30	

Table 3. Number of interactions of each compound/drug in the residues of TMPRSS2 (Table S2 – S26), to hinder/block the Ser441 in TMPRSS2.

Compound/Drug	Val280	His296	Gly439	Cys465
T1	1	17	5	5
T2	5	21	7	0
T3	9	12	6	2
T4	13	17	6	2
T5	9	21	8	2
T6	3	14	2	0
T7	4	15	9	0
T8	3	27	12	6
T9	7	15	10	2
T10	6	18	7	0
Daclatasvir	0	5	2	10
Ombitasvir	0	10	1	2
Camostat	0	14	2	0
Edoxaban	1	18	6	2
NCGC00386477	2	5	0	2
Nafamostat	3	7	6	3
NCGC00386945	0	3	1	2
Otamixaban	3	13	3	2
Darexaban	3	7	4	1
Gabexate	3	6	5	1
Letaxaban	9	11	3	0
Argatroban	2	67	8	0
Sivelestat	0	49	8	7

Compound/Drug	Val280	His296	Gly439	Cys465
NCGC00385043	1	9	7	0
Bromhexine	3	2	4	0

3.2. Interaction of T1 – T10 compounds and other compounds/drugs previously reported against TMPRSS2.

To describe the interaction of each compound/drug in the potential site of TMPRSS2, it was analyzed up to 30 conformers from each compound interacting in the catalytic site (region between amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463 and Gly464) (Figure 1). From molecular docking results, the main amino acids in TMPRSS2 are Val280, His296, Cys297, Glu299, Leu302, Lys390, Gly391, Cys437, Gln438, Gly439, Trp461, Gly462, Cys465, and Lys467 that are interacting with the T1 – T10 compounds (Table S2 – S26), and these ten compounds have a better interaction in the catalytic site, in particular, greater interaction with Val280, His296, Glu299, Gly439 and Cys465 (mainly hydrogen bonding interactions). Therefore, the probably inhibitory effect in this protease is due to the blocking of the Ser441, which is essential for the catalytic activity [38, 40, 55] (Figure 2). The molecular docking results for daclatasvir, ombitasvir, camostat, edoxaban, NCGC00386477, nafamostat, NCGC00386945, otamixaban, darexaban, gabexate, letaxaban, argatroban, sivelestat, NCGC00385043, and bromhexine showed less interaction in the catalytic site (Table 3), which could be related to a lesser effect to reduce the function of this protease. The details of the interaction between TMPRSS2 with conformers from each compound/drug are shown in the supplementary material (Figure S1 – S25).

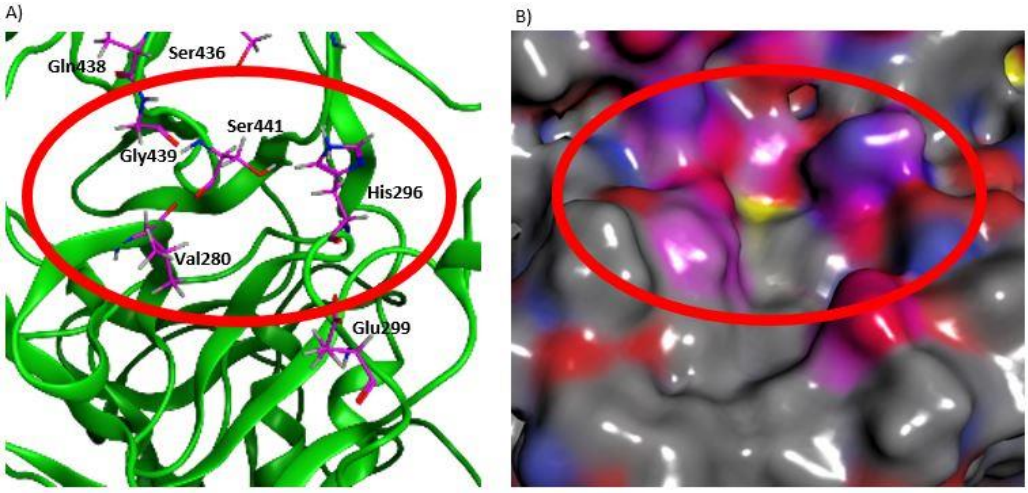


Figure 2. Potential site with some amino acids, the Ser441, is essential for the catalytic site. A) Val280, His296, Gly439, and Ser441 (Pink) into the red circle, and B) Pocket is displayed in the catalytic site.

3.3. Discussion.

The development of specific drugs against different targets in COVID-19 continues today. This study proposes compounds with a better inhibitory effect in the TMPRSS2 protease, thus hindering the infectious process of SARS-CoV-2 by decreasing the ability to fuse with the cell membrane. The expression of TMPRSS2 has been determined in different diseases such as influenza and prostate cancer (its expression increases), but it has taken an important role in COVID-19 in identifying its functions and level of expression in different tissues, with greater presence in the cell membrane of the epithelial cells of the lung and more intensely in the cells of the bronchial epithelium. TMPRSS2 has been identified to contribute to the cell membrane fusion process in the pathogenesis of COVID-19 [37, 39], as well as the

factors that increase or decrease its expression in the cell membrane can be considered; in different populations [34, 35], according to gender (women or men by androgens [33]) or treatments that decrease its mRNA [36], and compounds/drugs that could inhibit the activity of this protease from preventing fusion with the cell membrane [24, 33, 36, 37], to be used against COVID-19.

This study proposes ten compounds with a better interaction in the catalytic site of TMPRSS2, using a homology model to establish a putative 3D structure of TMPRSS2 [55] and performing molecular docking using about 500,000 compounds. Ten compounds (T1 - T10) were determined with better average interaction value than ombitasvir, daclatasvir [42], otamixaban, argatroban, letaxaban, darexaban, edoxaban [39], bromhexine [38, 40, 41, 54], otamixaban NCGC00385043, NCGC00386945, NCGC00386477 [40], camostat, nafamostat, gabexate, and sivelestat [55] (Table 2). It is proposing that the inhibitory effect of T1 - T10 compounds could be, due to a better interaction with amino acids in the catalytic site (His296 and Ser441), with better affinity with Val280, Gly439, and Cys465 (Table 3), to generate more interactions with His296 and closely of Ser441, that are necessary for TMPRSS2 protease activity [38, 40, 55].

To justify this study, it is necessary to emphasize the Ser441 in TMRPSS2. The data in Table 3 clearly show that the conformers from the T1 - T10 compounds have greater interaction with Val280, His296, and Cys465. These amino acids are important for the formation of interactions (mainly hydrogen bridges), and that the T1 – T10 compounds interact in the region of the catalytic site with Gly439 and very close to Ser441 (Figure 2); therefore, these compounds might hinder/block the accessibility or exposition of Ser441. The best interaction of all conformers from the compounds with Val280, His296, Gly439, and Cys465, generate the better averages of ΔGbinding for these ten compounds.

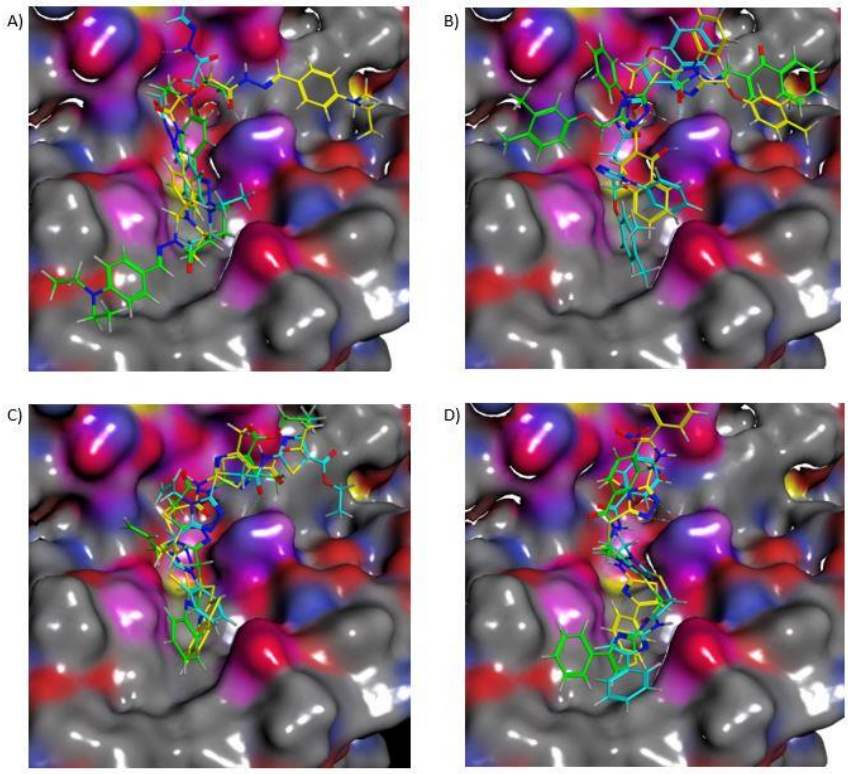


Figure 3. Three conformers (Yellow, Green, and Blue) from each compound interact in the potential site, Val280, His296, Gly439, Ser441, and Cys465 (Pink). **A**) T1, **B**) T2, **C**) T3, and **D**) T4.

To demonstrate the above, it is shown the interaction of T1 - T4 compounds with three conformations, each one interacting in the potential site proposed (Figure 3), the amino acids Val280 his296, Gly339, Ser441, and Cys465 are shown, where it is proposed that these amino acids are contributing to get a better ΔGbinding with TMPRSS2. In addition, the interaction of Daclatasvir, Ombitasvir, Camostat, and Nafamostat with three conformations each one is shown (Figure 4), these compounds/drugs show fewer interactions with Val280, His296, Gly439, and Cys465, which is related to a weaker interaction in the catalytic site (Table 2 and 3). The interactions of all compounds/drugs studied (with their conformers) in the potential site are shown in Figures S1 - S25, as well as the interactions between each conformer in the potential site are shown in Tables S2 – S26. These results can contribute to developing a drug against COVID-19, designed to avoid or decrease the fusion between SARS-CoV-2 and the cell membrane.

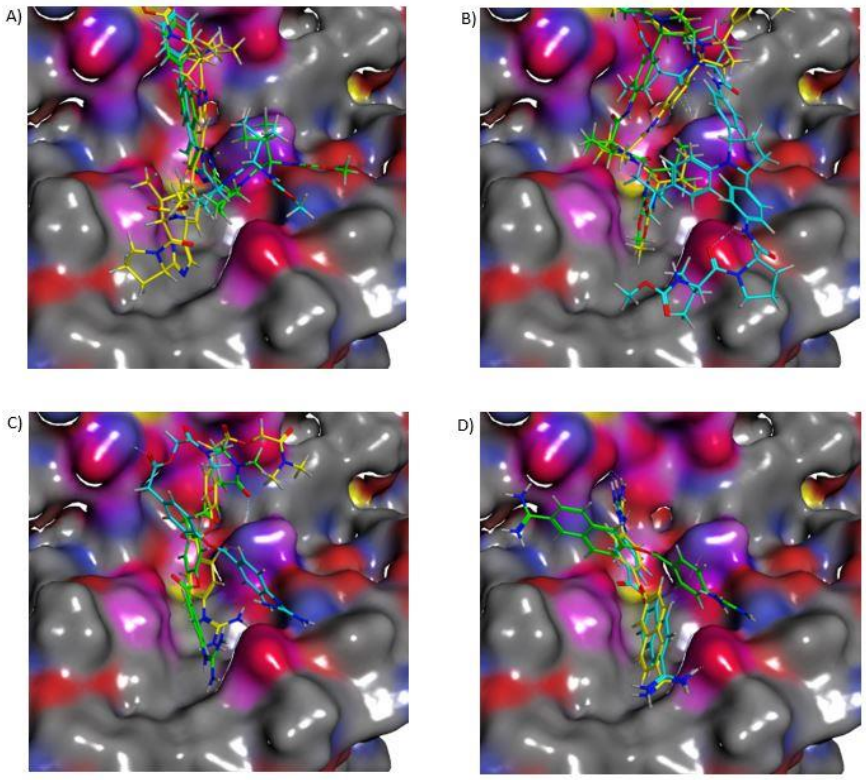


Figure 4. Three conformers (Yellow, Green, and Blue) from each compound interact in the potential site, Val280, His296, Gly439, Ser441, and Cys465 (Pink). **A**) Daclatasvir, **B**) Ombitasvir, **C**) Camostat, and **D**) Nafamostat.

On the other hand, the development of treatments with more advances is vaccines/antibodies [43 – 46]. However, there are reports of mutations at different proteins in the SARS-CoV-2 that could difficult their effectivity [46, 47], for example, in the S-protein of SARS-CoV-2 (December 2020) that could increase the infectious process and decrease the effect of vaccines [48 - 50], in which it is reported that the mutation E484K could generate resistance to several monoclonal antibodies, and the mutation N501Y could generate a greater interaction between RBD (S-protein) with ACE2, in which there are variants of the virus in the world that are related to more transmissibility and lethality of SARS-CoV-2 [52, 53]. In addition, vaccines have good opinions, but sometimes these have adverse reactions. The most common systemic adverse reaction was fatigue, fever, body pain, and a worse or lower immune response to vaccines in the elderly than in the younger population [75, 76], even some death [77]. Nevertheless, the development of vaccines continues with an acceptable safety and

efficacy profile against COVID-19, despite the adverse effects that could occur in patients and the mutations that could reduce their effectiveness.

The development of non-antiviral drugs against COVID-19 may be a way to attack this virus since it would prevent the interaction between SARS-CoV-2 with proteins at the cell membrane (as receptors for S-protein). The use of these drugs could be an adjuvant treatment that helps the immune system generate antibodies and resist this disease, which depends on factors and comorbidities in each person. These membrane receptors could be ACE2 [16, 35, 78], NRP1 [22, 23, 79, 80], and TMPRSS2 [24, 33, 37]. These three receptors could be the key to blocking the entry of SARS-CoV-2 (Figure 5). It could prevent/hinder the entry of the SARS-CoV-2 virus. With this approach, a combination of drugs could be developed as a new or complementary drug to use with conventional drugs and/or when using vaccines. But why would a combination of three drugs against COVID-19 be better? Each of these therapeutic targets (ACE2, NRP1, and TMPRSS2) are in the cell membrane that can generate advantages against antiviral drugs that have to cross the cell membrane. Some of these drugs/compounds already have toxicity results and/or have some reported use. This would facilitate experimental trials to try to make combinations between these three types of drugs, with different therapeutic targets, and that these interactions with their receptors, can generate summation or synergistic effects since there are currently reports of IC50 of some of them, with which estimates of their therapeutic effects could be made.

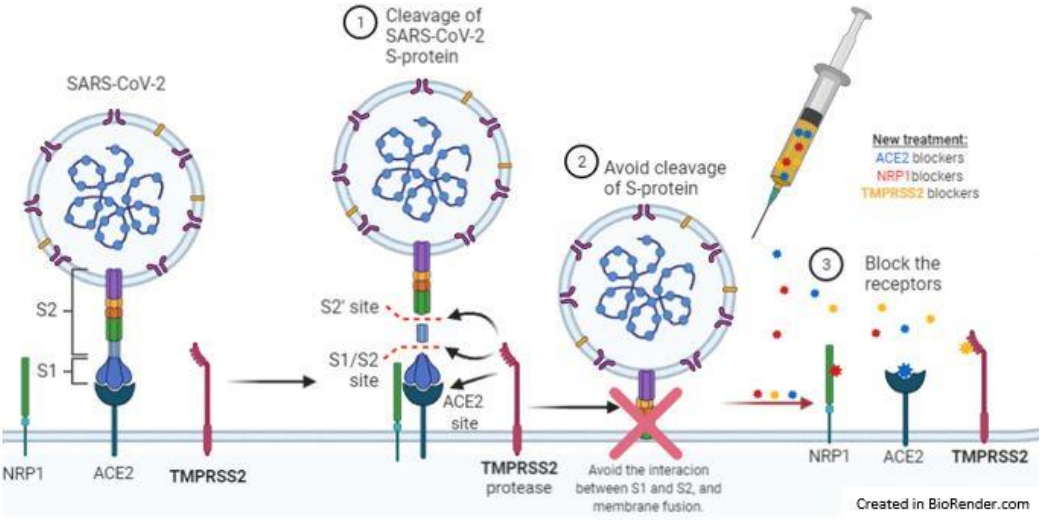


Figure 5. Blocking the interaction between S-protein of SARS-CoV-2 with its receptors (ACE2, NRP1, and TMPRSS2).

It would be necessary to evaluate the future effects of this proposal, a combination of potential compounds/drugs interacting with these three receptors on the cell membrane, could generate synergy with antiviral drugs, vaccines, or antibodies. In addition, these three receptors could have a better therapeutic effect than selective drugs, which is currently a disadvantage of the use of vaccines [48 - 50].

4. Conclusions

The development of an effective treatment against COVID-19 is still under development in the world. This study proposes ten compounds (T1 – T10) to develop a new drug to inhibit the activity protease of TMPRSS2, and it will be another way to attend COVID-19.

This therapeutic target has a significant role at COVID-19, as a cofactor for the infectious process, endosome formation, and internal management of viral material [24, 32]; therefore, the development of a selective drug for this therapeutic target would have the capacity to be an adjuvant or alternative treatment against COVID-19.

These ten compounds with a better interaction than previous compounds/drugs reported (Table 2 and 3) because T1 - T10 compounds have a better interaction with amino acids in the catalytic site (His296 and Ser441), due to the better affinity with Val280, Gly439 and Cys465 to generate more interactions with His296 and closely of Ser441, that are necessary for TMPRSS2 protease activity [38, 40, 55]. Moreover, the ten compounds have good results in theoretical toxicity servers.

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Conflicts of Interest

The author declares that he has no conflict of interest.

Supplementary Data

Supporting information includes figures and tables of interactions for compounds with TMPRSS2 and details of the interaction of each compound with TMPRSS2 per amino acid, theoretical toxicity results, ADME characteristics, and physical chemistry that support the information given in the results and discussion.

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Supplementary materials

Figure S1. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 29 conformers of compound T1 (Gray).

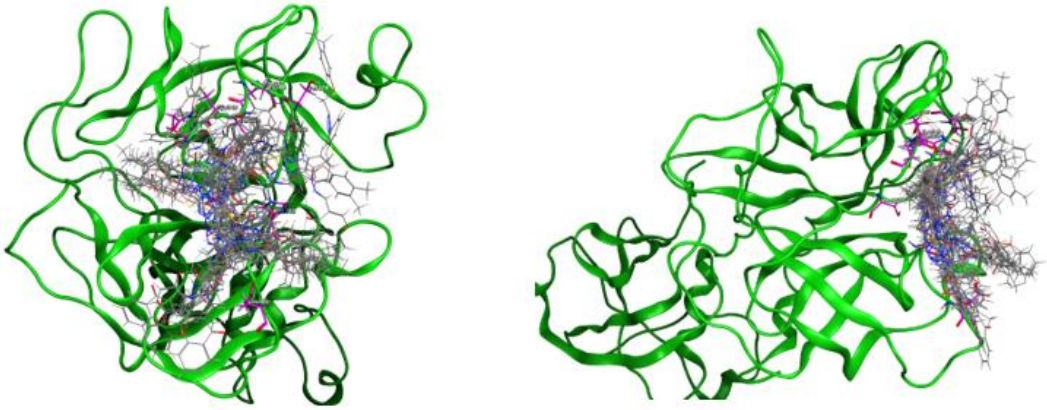

Figure S2. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 28 conformers of compound T2 (Gray).

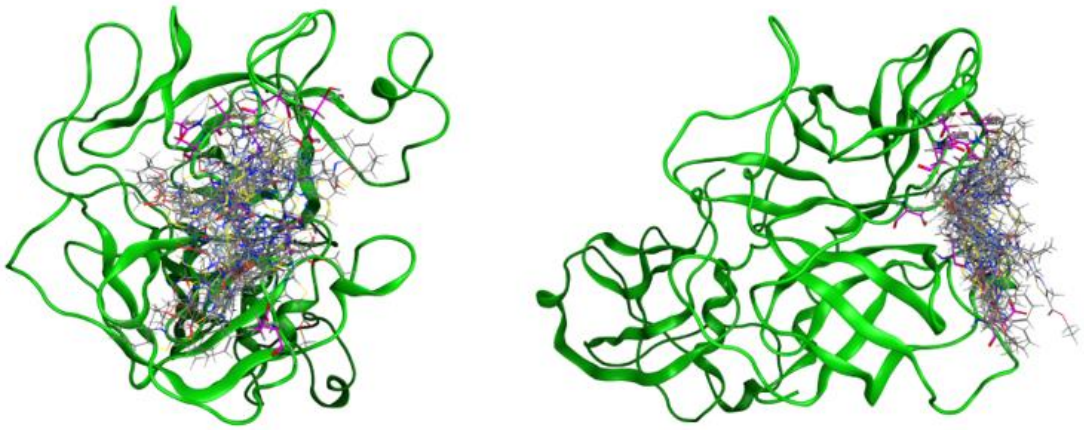

Figure S3. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 24 conformers of compound T3 (Gray).

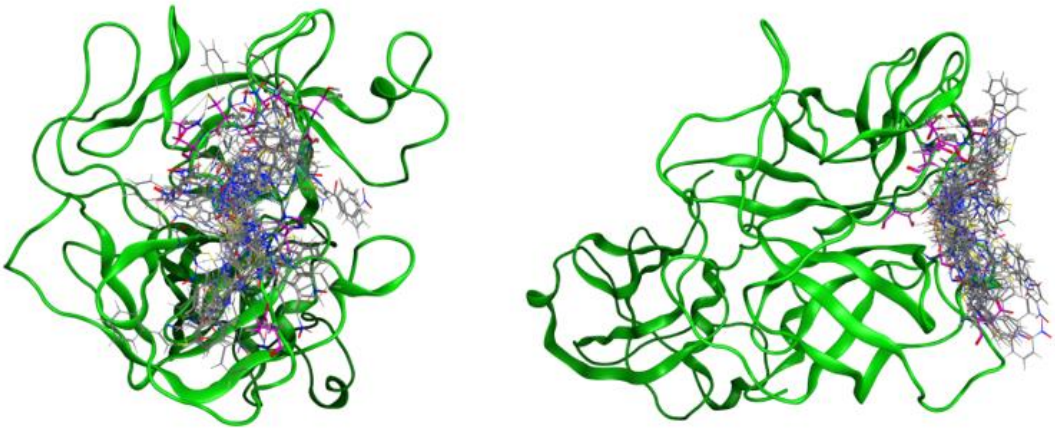

Figure S4. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 29 conformers of compound T4 (Gray).

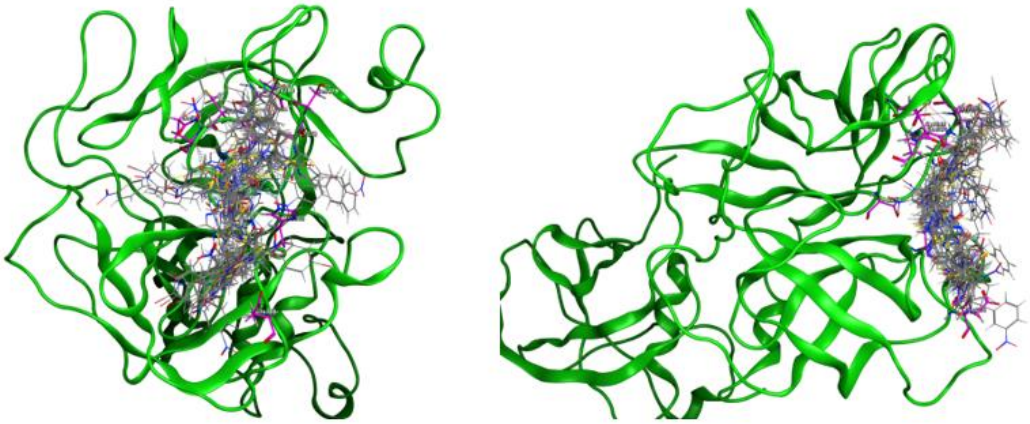

Figure S5. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 26 conformers of compound T5 (Gray).

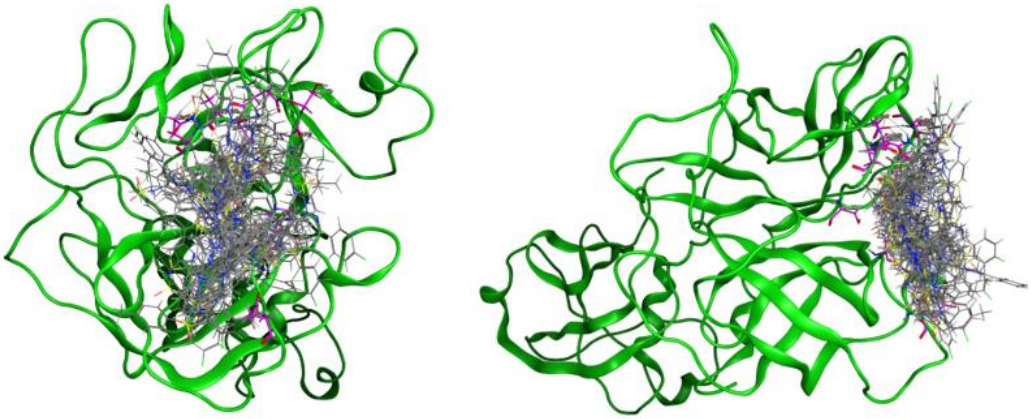

Figure S6. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 27 conformers of compound T6 (Gray).

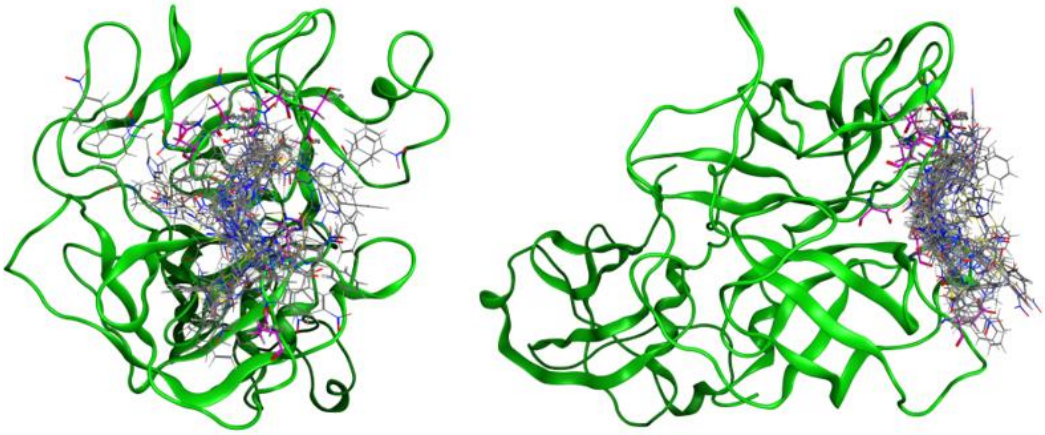

Figure S7. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 24 conformers of compound T7 (Gray).

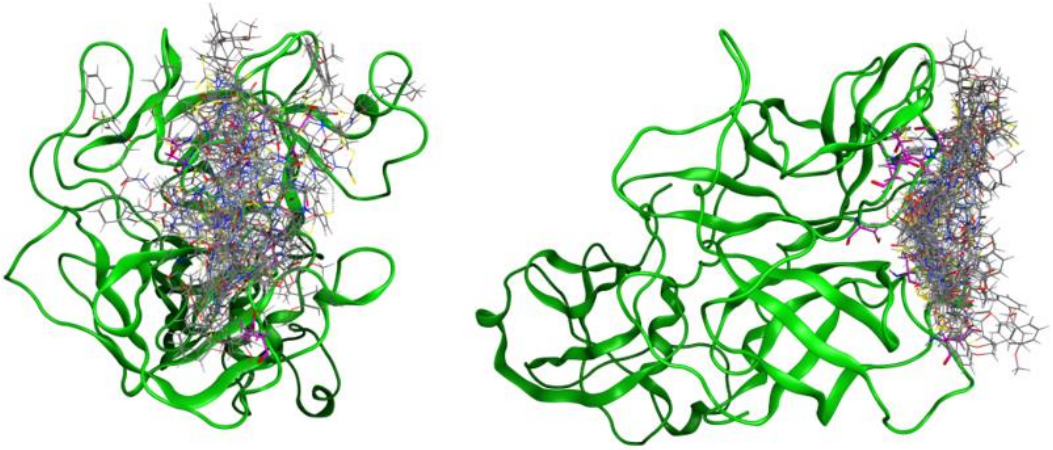

Figure S8. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 26 conformers of compound T8 (Gray).

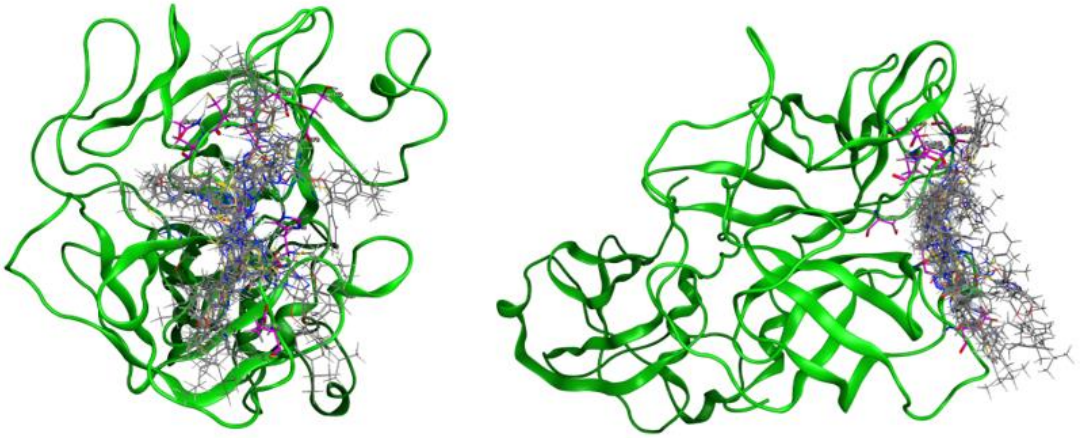

Figure S9. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 27 conformers of compound T9 (Gray).

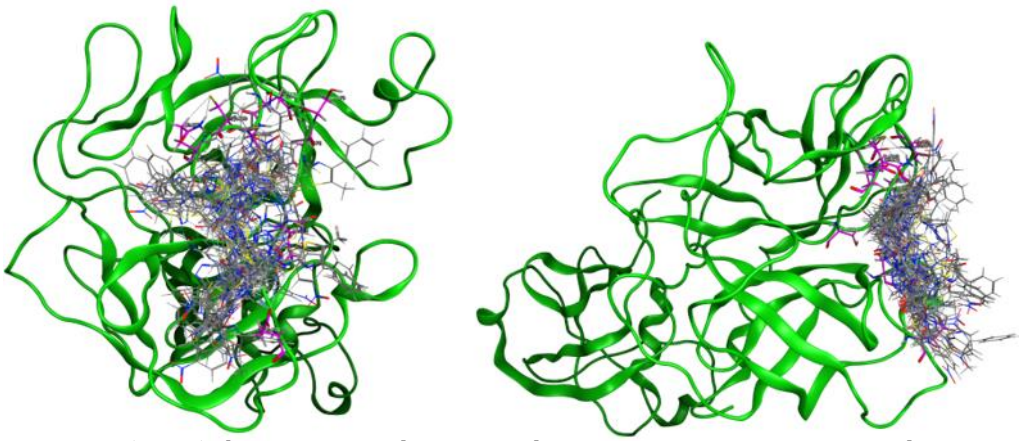

Figure S10. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 27 conformers of compound T10 (Gray).

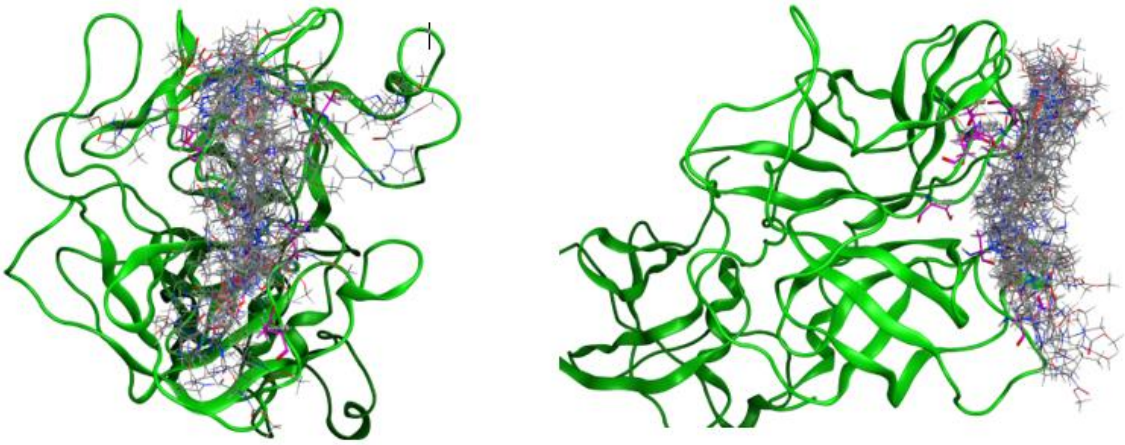

Figure S11. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 25 conformers of Daclatasvir (Gray).

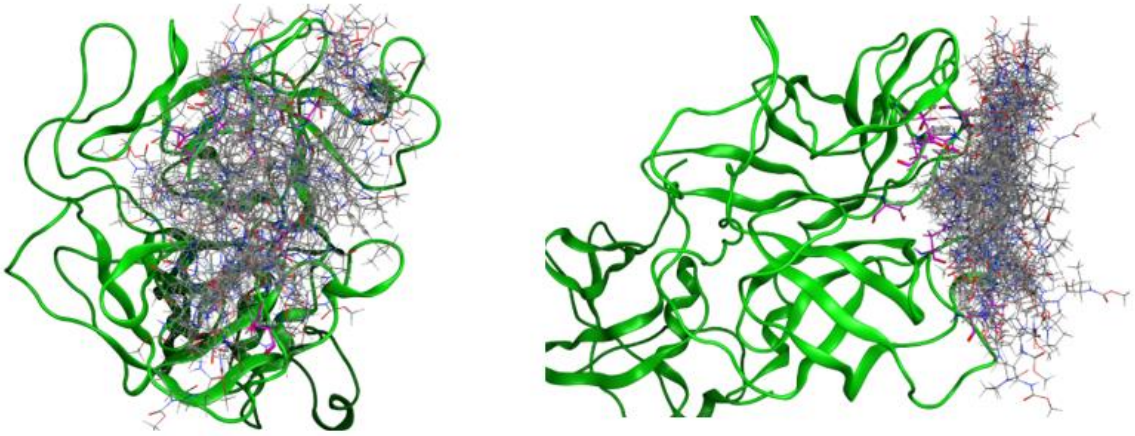

Figure S12. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 30 conformers of compound Ombitasvir (Gray).

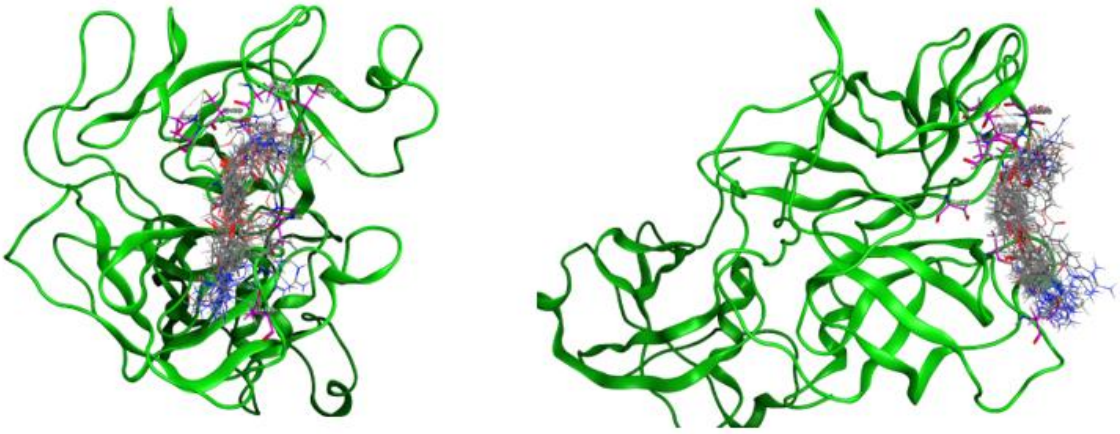

Figure S13. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 24 conformers of Camostat (Gray).

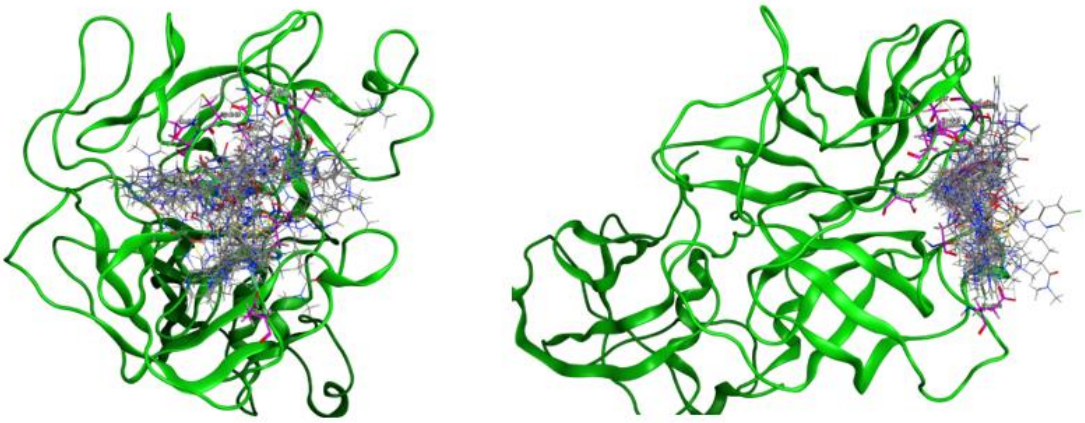

Figure S14. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 26 conformers of Edoxaban (Gray).

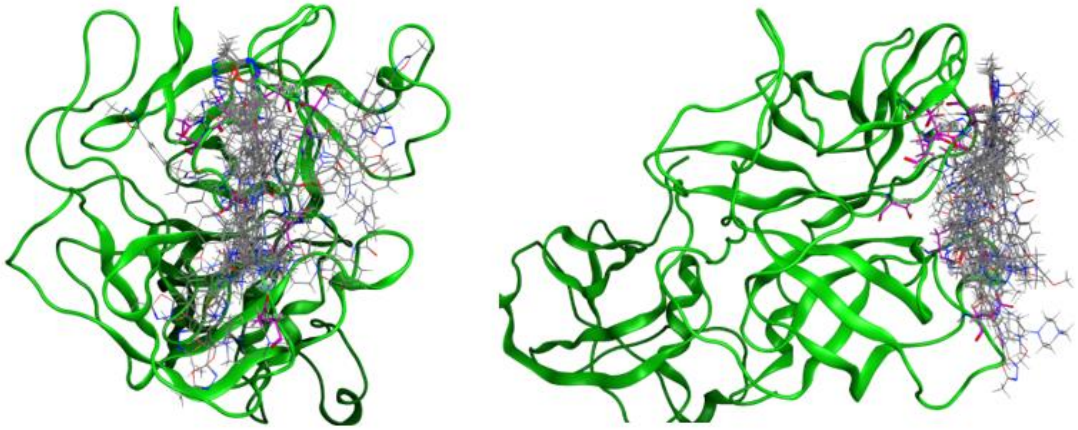

Figure S15. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 25 conformers of compound NCGC00386477 (Gray).

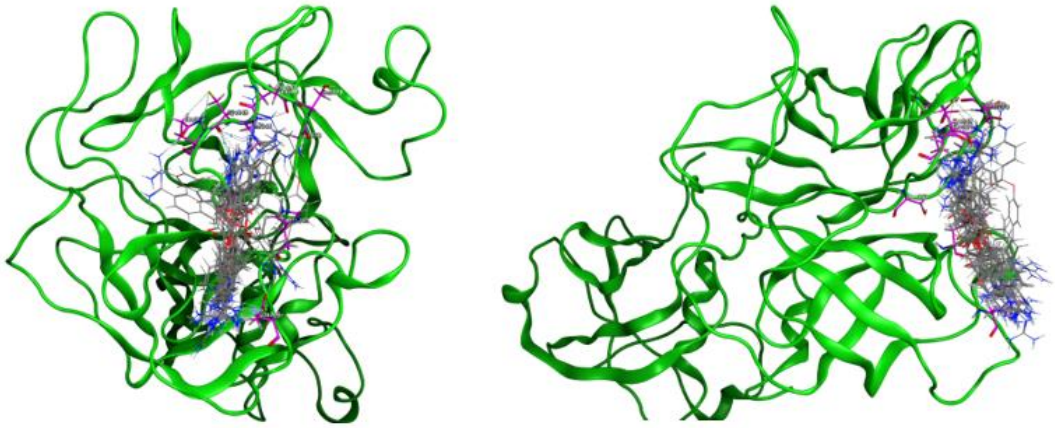

Figure S16. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 23 conformers of Nafamostat (Gray).

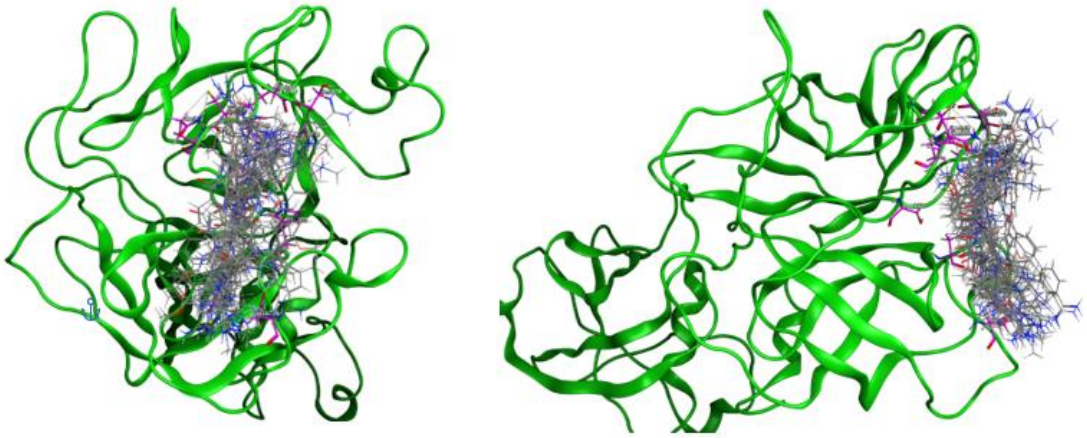

Figure S17. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 26 conformers of compound NCGC00386945 (Gray).

Figure S18. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 26 conformers of Otamixaban (Gray).

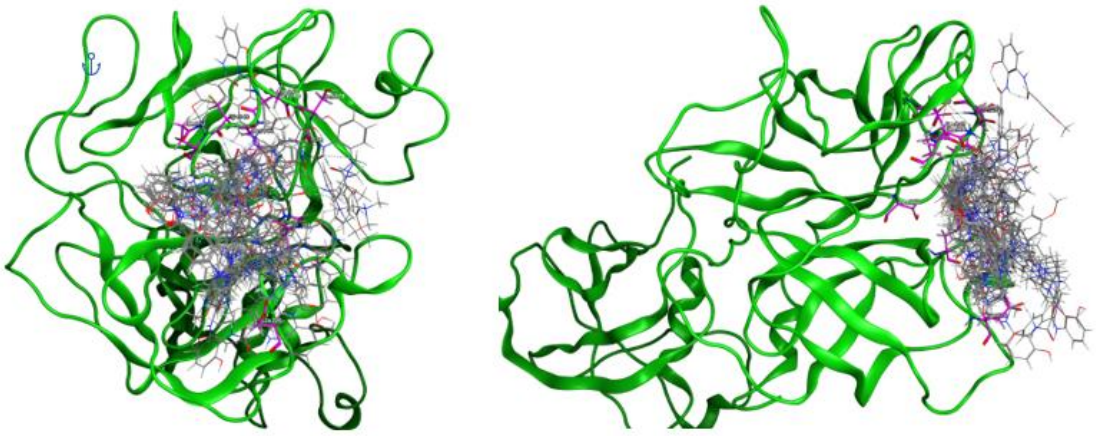

Figure S19. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 26 conformers of Darexaban (Gray).

Figure S20. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 29 conformers of Gabexate (Gray).

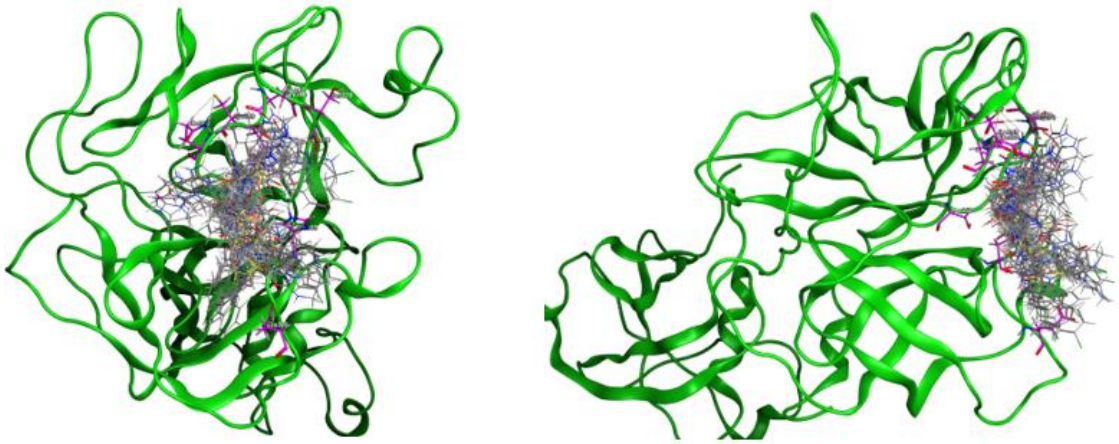

Figure S21. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 26 conformers of Letaxaban (Gray).

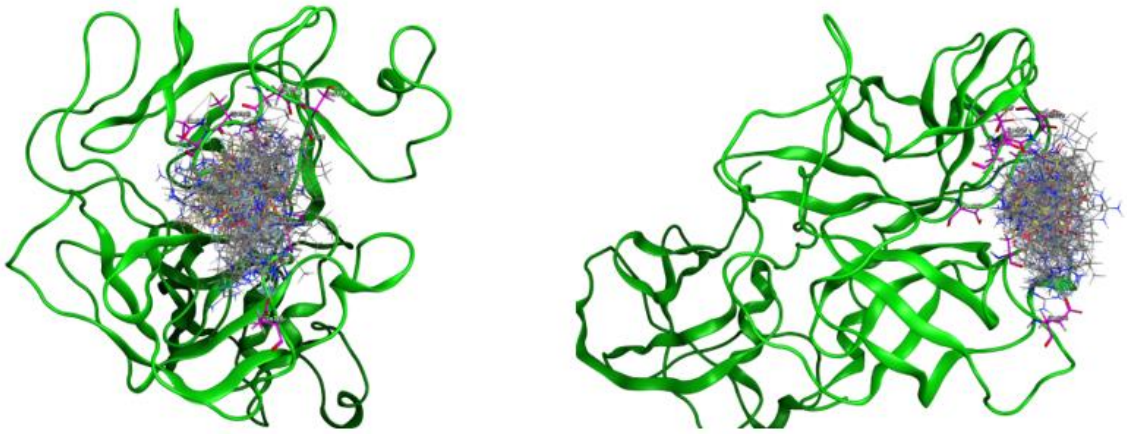

Figure S22. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 29 conformers of Argatroban (Gray).

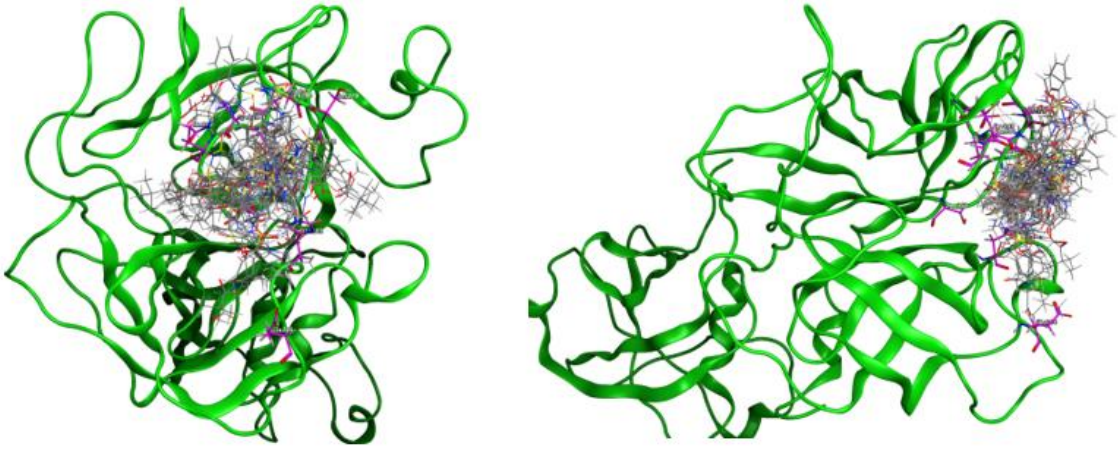

Figure S23. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 26 conformers of Sivelestat (Gray).

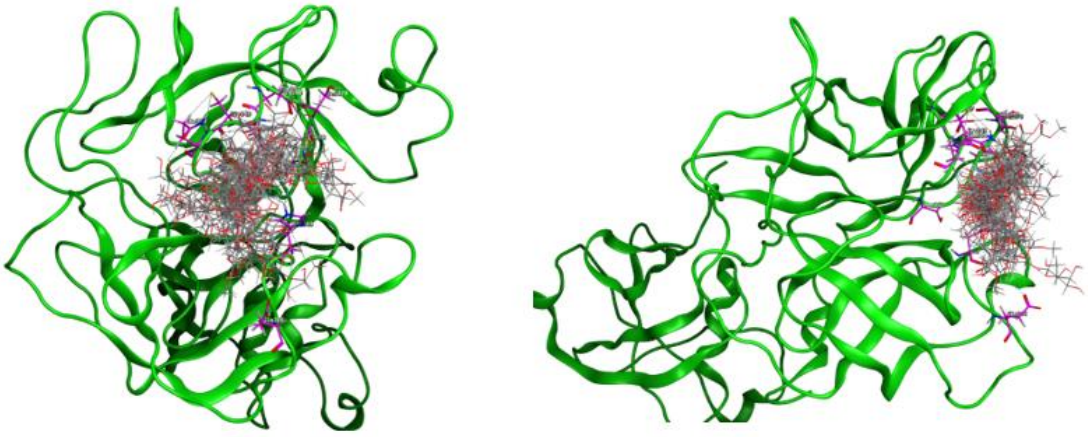

Figure S24. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 30 conformers of compound NCGC00385043 (Gray).

Figure S25. TMPRSS2 (Green) shows amino acids His296, Glu299, Asp435, Ser436, Cys437, Gln438, Ser441, Gly462, Ser463, and Gly464 (Pink) as region chosen for docking with 21 conformers of Bromhexine (Gray).

Table S1. ΔGbinding of 21 to 30 conformers from each compound, average ΔGbinding and SD.

Compound	Conformer	ΔGbinding
T1	1	-10.003396
T1	2	-9.5028162
T1	3	-9.3816652
T1	4	-9.2959499
T1	5	-9.2790861
T1	6	-9.0783291
T1	7	-9.0753641
T1	8	-8.7984352
T1	9	-8.6334057
T1	10	-8.4404917
T1	11	-8.3888254
T1	12	-8.3585405
T1	13	-8.3155022
T1	14	-8.0704679
T1	15	-7.9481745
T1	16	-7.8926687
T1	17	-7.8705177
T1	18	-7.8615508
T1	19	-7.8328905
T1	20	-7.7946715
T1	21	-7.6466455
T1	22	-7.5944762
T1	23	-7.467999
T1	24	-7.4473333
T1	25	-7.3843675
T1	26	-7.3234034
T1	27	-7.2930708
T1	28	-7.1270895
T1	29	-6.5075951
	Average $\Delta G_{binding}$	-8.19361135
	SD	0.83814171
T2	1	-10.022358
T2	2	-9.6339903
T2	3	-9.5879698
T2	4	-9.0783129
T2	5	-8.8606043
T2	6	-8.7780361
T2	7	-8.7608776
T2	8	-8.6921701
T2	9	-8.5939379
T2	10	-8.5521517
T2	11	-8.3879843

Compound	Conformer	ΔGbinding
T2	12	-8.245903
T2	13	-8.0666447
T2	14	-8.0059614
T2	15	-7.7485528
T2	16	-7.7424426
T2	17	-7.7311025
T2	18	-7.699697
T2	19	-7.5649576
T2	20	-7.5632124
T2	21	-7.5493693
T2	22	-7.4882078
T2	23	-7.4084682
T2	24	-7.0118942
T2	25	-6.9634185
T2	26	-6.6150498
T2	27	-6.3929582
	Average $\Delta G_{binding}$	-8.10171233
	SD	0.90894255
T3	1	-9.0872488
T3	2	-9.0801687
T3	3	-9.0403929
T3	4	-8.9255257
T3	5	-8.9209614
T3	6	-8.6274405
T3	7	-8.6184263
T3	8	-8.5198822
T3	9	-8.322113
T3	10	-8.315093
T3	11	-8.3098307
T3	12	-8.1798973
T3	13	-8.0936956
T3	14	-8.0496025
T3	15	-7.8540268
T3	16	-7.744885
T3	17	-7.7321877
T3	18	-7.6184058
T3	19	-7.4833121
T3	20	-7.4545417
T3	21	-7.3769569
T3	22	-7.3355923
T3	23	-7.296454
T3	24	-7.1494551
T3	25	-7.1465697
T3	26	-7.1312723
T3	27	-6.8732405
	Average $\Delta G_{binding}$	-8.01063624
	SD	0.68474912
T4	1	-9.2188988
T4	2	-8.6898699
T4	3	-8.5985565
T4	4	-8.5929041
T4	5	-8.50595
T4	6	-8.3943624
T4	7	-8.380353
T4	8	-8.3689556
T4	9	-8.3514271
T4	10	-8.3018761
T4	11	-8.2238884
T4	12	-8.2036352
T4	13	-8.1405926
T4	14	-8.0946236
T4	15	-8.089736
T4	16	-8.0655165
T4	17	-8.0641956

Compound	Conformer	ΔGbinding
T4	18	-8.0602865
T4	19	-7.9969692
T4	20	-7.9864345
T4	21	-7.8847065
T4	22	-7.8003235
T4	23	-7.7165313
T4	24	-7.6500716
T4	25	-7.5624533
T4	26	-7.510438
T4	27	-7.3479362
T4	28	-7.0788541
T4	29	-6.7855134
T4	30	-6.2144074
	Average $\Delta G_{binding}$	-7.9960089
	SD	0.59719471
T5	1	-8.8463116
T5	2	-8.7761745
T5	3	-8.7601585
T5	4	-8.7128248
T5	5	-8.6061783
T5	6	-8.4604912
T5	7	-8.4060631
T5	8	-8.2876902
T5	9	-8.2334681
T5	10	-8.2237606
T5	11	-8.1152878
T5	12	-8.1035748
T5	13	-8.0933323
T5	14	-8.0835581
T5	15	-8.0639343
T5	16	-8.0269032
T5	17	-8.0209751
T5	18	-7.9286127
T5	19	-7.9155855
T5	20	-7.9118838
T5	21	-7.816483
T5	22	-7.6477575
T5	23	-7.6306605
T5	24	-7.2972651
T5	25	-7.2300811
T5	26	-7.2121
T5	27	-6.7440133
T5	28	-6.7035975
	Average $\Delta G_{binding}$	-7.99495452
	SD	0.56635107
T6	1	-9.3085299
T6	2	-9.0219545
T6	3	-8.9738646
T6	4	-8.9567413
T6	5	-8.7691965
T6	6	-8.6345243
T6	7	-8.4675426
T6	8	-8.4069319
T6	9	-8.3941784
T6	10	-8.3859043
T6	11	-8.2488203
T6	12	-8.2265368
T6	13	-8.1576548
T6	14	-8.1375952
T6	15	-8.1242628
T6	16	-8.0387306
T6	17	-8.0217066
T6	18	-7.975193
T6	19	-7.8419881

Compound	Conformer	ΔGbinding
T6	20	-7.8149767
T6	21	-7.5745993
T6	22	-7.4310431
T6	23	-6.9749837
T6	24	-6.6369896
T6	25	-6.6182857
T6	26	-6.4696603
T6	27	-6.2355638
	Average $\Delta G_{binding}$	-7.99436884
	SD	0.81604143
T7	1	-9.2756252
T7	2	-8.9142857
T7	3	-8.9017849
T7	4	-8.7062016
T7	5	-8.6486025
T7	6	-8.647892
T7	7	-8.5693331
T7	8	-8.5575619
T7	9	-8.5386095
T7	10	-8.5009775
T7	11	-8.4386635
T7	12	-8.4243889
T7	13	-8.3803549
T7	14	-8.247942
T7	15	-8.1754227
T7	16	-8.0870533
T7	17	-8.0591297
T7	18	-7.7034016
T7	19	-7.6054735
T7	20	-7.5258908
T7	21	-7.4642801
T7	22	-7.3333788
T7	23	-7.2554908
T7	24	-7.2306013
T7	25	-7.0912528
T7	26	-6.6262579
T7	27	-6.3153048
T7	28	-6.1678081
	Average $\Delta G_{binding}$	-7.97832034
	SD	0.80859149
T8	1	-9.6677294
T8	2	-9.0873976
T8	3	-9.0046053
T8	4	-8.8117313
T8	5	-8.7953749
T8	6	-8.7727785
T8	7	-8.5950193
T8	8	-8.4820747
T8	9	-8.4754086
T8	10	-8.3118105
T8	11	-8.2353954
T8	12	-8.2215805
T8	13	-8.1239853
T8	14	-8.0981016
T8	15	-8.0912466
T8	16	-8.0639839
T8	17	-7.807765
T8	18	-7.7613025
T8	19	-7.7482762
T8	20	-7.720624
T8	21	-7.6101966
T8	22	-7.3269901
T8	23	-7.2866149
T8	24	-7.2247896

Compound	Conformer	ΔGbinding
T8	25	-7.2101569
T8	26	-7.2000165
T8	27	-7.19806
T8	28	-7.0837798
T8	29	-6.805882
T8	30	-6.2772179
	Average $\Delta G_{binding}$	-7.96999651
	SD	0.76511658
T9	1	-8.9598265
T9	2	-8.9550142
T9	3	-8.921051
T9	4	-8.7088957
T9	5	-8.6447392
T9	6	-8.5934811
T9	7	-8.5755234
T9	8	-8.5448742
T9	9	-8.5338984
T9	10	-8.4177952
T9	11	-8.2045507
T9	12	-8.1820631
T9	13	-8.1658182
T9	14	-8.1623573
T9	15	-8.1459322
T9	16	-8.135849
T9	17	-8.0513248
T9	18	-8.0358849
T9	19	-7.972672
T9	20	-7.9299703
T9	21	-7.9112868
T9	22	-7.684484
T9	23	-6.969893
T9	24	-6.8369207
T9	25	-6.5765576
T9	26	-6.5230303
T9	27	-6.3880262
T9	28	-6.1047964
	Average $\Delta G_{binding}$	-7.95844701
	SD	0.81850837
T10	1	-9.3553381
T10	2	-9.3253126
T10	3	-9.2208309
T10	4	-9.0547533
T10	5	-8.9080944
T10	6	-8.8517351
T10	7	-8.5650959
T10	8	-8.4860783
T10	9	-8.4806604
T10	10	-8.3173981
T10	11	-8.2351208
T10	12	-8.107399
T10	13	-7.9825597
T10	14	-7.9576359
T10	15	-7.9544106
T10	16	-7.8897438
T10	17	-7.7604818
T10	18	-7.7534285
T10	19	-7.5839596
T10	20	-7.583334
T10	21	-7.5752831
T10	22	-7.5171504
T10	23	-7.3344922
T10	24	-7.2096562
T10	25	-7.1749067
T10	26	-6.9748254

Compound	Conformer	ΔGbinding
T10	27	-6.5297976
T10	28	-6.4548984
T10	29	-6.2984314
	Average $\Delta G_{binding}$	-7.94630387
	SD	0.83996604
Daclatasvir	1	-6.743875
Daclatasvir	2	-6.5059676
Daclatasvir	3	-6.4129391
Daclatasvir	4	-6.2823424
Daclatasvir	5	-6.1425152
Daclatasvir	6	-6.1386223
Daclatasvir	7	-6.0960999
Daclatasvir	8	-6.0614023
Daclatasvir	9	-6.0143824
Daclatasvir	10	-6.008986
Daclatasvir	11	-5.9795341
Daclatasvir	12	-5.9727292
Daclatasvir	13	-5.9404788
Daclatasvir	14	-5.8896332
Daclatasvir	15	-5.8242784
Daclatasvir	16	-5.7552052
Daclatasvir	17	-5.6175394
Daclatasvir	18	-5.5847816
Daclatasvir	19	-5.5605044
Daclatasvir	20	-5.51682
Daclatasvir	21	-5.4841599
Daclatasvir	22	-5.4488587
Daclatasvir	23	-5.4191465
Daclatasvir	24	-5.2322726
Daclatasvir	25	-5.1832037
	Average $\Delta G_{binding}$	-5.87265112
	SD	0.3938991
Ombitasvir	1	-7.1596756
Ombitasvir	2	-6.8764935
Ombitasvir	3	-6.6037531
Ombitasvir	4	-6.2976608
Ombitasvir	5	-6.2173386
Ombitasvir	6	-6.1336923
Ombitasvir	7	-6.0335317
Ombitasvir	8	-5.9339681
Ombitasvir	9	-5.9162989
Ombitasvir	10	-5.8851943
Ombitasvir	11	-5.746839
Ombitasvir	12	-5.7327538
Ombitasvir	13	-5.6639748
Ombitasvir	14	-5.6421595
Ombitasvir	15	-5.6110668
Ombitasvir	16	-5.5996351
Ombitasvir	17	-5.4511547
Ombitasvir	18	-5.4373531
Ombitasvir	19	-5.4199243
Ombitasvir	20	-5.4113636
Ombitasvir	21	-5.3175464
Ombitasvir	22	-5.2385569
Ombitasvir	23	-5.1057653
Ombitasvir	24	-5.0913448
Ombitasvir	25	-4.9753966
Ombitasvir	26	-4.9052405
Ombitasvir	27	-4.8408008
Ombitasvir	28	-4.7974653
Ombitasvir	29	-4.776053
Ombitasvir	30	-4.5804648
	Average $\Delta G_{binding}$	-5.61341553
	SD	0.62655319

Compound	Conformer	ΔGbinding
Camostat	1	-6.04285
Camostat	2	-5.9478555
Camostat	3	-5.9108286
Camostat	4	-5.886168
Camostat	5	-5.7768722
Camostat	6	-5.7290077
Camostat	7	-5.7062001
Camostat	8	-5.5547781
Camostat	9	-5.5303459
Camostat	10	-5.4542723
Camostat	11	-5.4306221
Camostat	12	-5.3901696
Camostat	13	-5.3401365
Camostat	14	-5.2483029
Camostat	15	-5.1767559
Camostat	16	-5.1755605
Camostat	17	-5.001894
Camostat	18	-4.9898071
Camostat	19	-4.9430857
Camostat	20	-4.876555
Camostat	21	-4.7852411
Camostat	22	-4.7760358
Camostat	23	-4.2693329
Camostat	24	-3.7587805
	Average $\Delta G_{binding}$	-5.27922742
	SD	0.54872159
Edoxaban	1	-6.8826356
Edoxaban	2	-6.8416786
Edoxaban	3	-6.0505261
Edoxaban	4	-5.7649422
Edoxaban	5	-5.7016277
Edoxaban	6	-5.5783224
Edoxaban	7	-5.3962746
Edoxaban	8	-5.3227305
Edoxaban	9	-5.3205738
Edoxaban	10	-5.2506576
Edoxaban	11	-5.2484884
Edoxaban	12	-5.2288833
Edoxaban	13	-5.2250133
Edoxaban	14	-5.2120714
Edoxaban	15	-5.1705141
Edoxaban	16	-5.1128635
Edoxaban	17	-5.0910463
Edoxaban	18	-5.0524874
Edoxaban	19	-5.0045424
Edoxaban	20	-4.9296017
Edoxaban	21	-4.6752391
Edoxaban	22	-4.6085482
Edoxaban	23	-4.6075749
Edoxaban	24	-4.3654494
Edoxaban	25	-4.3570585
Edoxaban	26	-4.3081818
	Average $\Delta G_{binding}$	-5.24259742
	SD	0.64259121
NCGC00386477	1	-6.4412675
NCGC00386477	2	-5.9841232
NCGC00386477	3	-5.855576
NCGC00386477	4	-5.7207823
NCGC00386477	5	-5.6741104
NCGC00386477	6	-5.6506562
NCGC00386477	7	-5.6110411
NCGC00386477	8	-5.4478011
NCGC00386477	9	-5.4461803

Compound	Conformer	ΔGbinding
NCGC00386477	10	-5.3958054
NCGC00386477	11	-5.3548045
NCGC00386477	12	-5.2550526
NCGC00386477	13	-5.2438397
NCGC00386477	14	-5.1881876
NCGC00386477	15	-5.120954
NCGC00386477	16	-5.0300746
NCGC00386477	17	-5.0039954
NCGC00386477	18	-4.8018866
NCGC00386477	19	-4.7332406
NCGC00386477	20	-4.7234364
NCGC00386477	21	-4.636313
NCGC00386477	22	-4.5279136
NCGC00386477	23	-4.5238347
NCGC00386477	24	-4.4817915
NCGC00386477	25	-4.4324522
	Average $\Delta G_{binding}$	-5.21140482
	SD	0.52631492
Nafamostat	1	-5.783052
Nafamostat	2	-5.5672727
Nafamostat	3	-5.5662684
Nafamostat	4	-5.4643989
Nafamostat	5	-5.4622388
Nafamostat	6	-5.4363241
Nafamostat	7	-5.4281802
Nafamostat	8	-5.4156542
Nafamostat	9	-5.4117875
Nafamostat	10	-5.3318658
Nafamostat	11	-5.3077483
Nafamostat	12	-5.1793442
Nafamostat	13	-5.0623446
Nafamostat	14	-5.0086064
Nafamostat	15	-4.9340682
Nafamostat	16	-4.8842969
Nafamostat	17	-4.8719869
Nafamostat	18	-4.8711605
Nafamostat	19	-4.7926264
Nafamostat	20	-4.6345181
Nafamostat	21	-4.6133256
Nafamostat	22	-4.0774097
Nafamostat	23	-4.0382085
	Average $\Delta G_{binding}$	-5.0931603
	SD	0.45703614
NCGC00386945	1	-6.2677202
NCGC00386945	2	-5.8147974
NCGC00386945	3	-5.6708345
NCGC00386945	4	-5.6003752
NCGC00386945	5	-5.4398623
NCGC00386945	6	-5.3755302
NCGC00386945	7	-5.273097
NCGC00386945	8	-5.2591763
NCGC00386945	9	-5.2120218
NCGC00386945	10	-5.1153016
NCGC00386945	11	-5.1112304
NCGC00386945	12	-5.0974422
NCGC00386945	13	-5.0582089
NCGC00386945	14	-4.9893522
NCGC00386945	15	-4.8813934
NCGC00386945	16	-4.8760819
NCGC00386945	17	-4.8132668
NCGC00386945	18	-4.797482
NCGC00386945	19	-4.7948637
NCGC00386945	20	-4.7915201
NCGC00386945	21	-4.7686195

Compound	Conformer	ΔGbinding
NCGC00386945	22	-4.6853576
NCGC00386945	23	-4.6217885
NCGC00386945	24	-4.4223056
NCGC00386945	25	-4.0571074
NCGC00386945	26	-4.0020714
	Average $\Delta G_{binding}$	-5.03064647
	SD	0.50287184
Otamixaban	1	-6.0175567
Otamixaban	2	-5.7299685
Otamixaban	3	-5.6322932
Otamixaban	4	-5.56001
Otamixaban	5	-5.4496741
Otamixaban	6	-5.3958731
Otamixaban	7	-5.2923293
Otamixaban	8	-5.1934028
Otamixaban	9	-5.1780539
Otamixaban	10	-5.1540279
Otamixaban	11	-5.1525192
Otamixaban	12	-5.104033
Otamixaban	13	-5.0980663
Otamixaban	14	-5.0828133
Otamixaban	15	-5.0513377
Otamixaban	16	-5.0475435
Otamixaban	17	-4.9834208
Otamixaban	18	-4.7533231
Otamixaban	19	-4.73839
Otamixaban	20	-4.7017422
Otamixaban	21	-4.6069565
Otamixaban	22	-4.6006813
Otamixaban	23	-4.4703946
Otamixaban	24	-4.2730875
Otamixaban	25	-4.076292
Otamixaban	26	-3.9181862
	Average $\Delta G_{binding}$	-5.01007603
	SD	0.49946414
Darexaban	1	-5.824955
Darexaban	2	-5.7299123
Darexaban	3	-5.563283
Darexaban	4	-5.4950666
Darexaban	5	-5.4491625
Darexaban	6	-5.3575301
Darexaban	7	-5.3437848
Darexaban	8	-5.3057985
Darexaban	9	-5.2480159
Darexaban	10	-5.1242046
Darexaban	11	-5.088347
Darexaban	12	-5.0795984
Darexaban	13	-5.0567398
Darexaban	14	-4.9246492
Darexaban	15	-4.8271747
Darexaban	16	-4.8004422
Darexaban	17	-4.7597399
Darexaban	18	-4.7581606
Darexaban	19	-4.7405477
Darexaban	20	-4.7084093
Darexaban	21	-4.6985788
Darexaban	22	-4.6422806
Darexaban	23	-4.6402278
Darexaban	24	-4.3252153
Darexaban	25	-4.0919528
Darexaban	26	-3.9560533
	Average $\Delta G_{binding}$	-4.98230118
	SD	0.46754746

Compound	Conformer	ΔGbinding
Gabexate	1	-5.3681436
Gabexate	2	-5.3153243
Gabexate	3	-5.3048029
Gabexate	4	-5.2681551
Gabexate	5	-5.2648449
Gabexate	6	-5.2557278
Gabexate	7	-5.2517371
Gabexate	8	-5.251121
Gabexate	9	-5.2271938
Gabexate	10	-5.2255993
Gabexate	11	-5.0875754
Gabexate	12	-5.0553536
Gabexate	13	-4.9865375
Gabexate	14	-4.9838514
Gabexate	15	-4.9834967
Gabexate	16	-4.9718957
Gabexate	17	-4.9123788
Gabexate	18	-4.9057102
Gabexate	19	-4.8976898
Gabexate	20	-4.7917051
Gabexate	21	-4.7875376
Gabexate	22	-4.6820951
Gabexate	23	-4.6785526
Gabexate	24	-4.5578337
Gabexate	25	-4.5536962
Gabexate	26	-4.5354271
Gabexate	27	-4.5288396
Gabexate	28	-4.5122361
Gabexate	29	-4.3295536
	Average $\Delta G_{binding}$	-4.94740054
	SD	0.30095941
Letaxaban	1	-5.9555793
Letaxaban	2	-5.4709511
Letaxaban	3	-5.4403868
Letaxaban	4	-5.3879633
Letaxaban	5	-5.3490348
Letaxaban	6	-5.3032179
Letaxaban	7	-5.2313886
Letaxaban	8	-5.2235136
Letaxaban	9	-5.1020436
Letaxaban	10	-5.0208097
Letaxaban	11	-4.9803667
Letaxaban	12	-4.9308438
Letaxaban	13	-4.8757157
Letaxaban	14	-4.8737264
Letaxaban	15	-4.7332249
Letaxaban	16	-4.6809821
Letaxaban	17	-4.649158
Letaxaban	18	-4.6135006
Letaxaban	19	-4.5755901
Letaxaban	20	-4.5001082
Letaxaban	21	-4.4170842
Letaxaban	22	-4.3670373
Letaxaban	23	-4.3472133
Letaxaban	24	-4.0853858
Letaxaban	25	-3.9305549
Letaxaban	26	-3.8967683
	Average $\Delta G_{binding}$	-4.84392881
	SD	0.50794032
Argatroban	1	-5.9366364
Argatroban	2	-5.7820024
Argatroban	3	-5.5289149
Argatroban	4	-5.1951489
Argatroban	5	-5.10601

Compound	Conformer	ΔGbinding
Argatroban	6	-5.0797424
Argatroban	7	-5.0044961
Argatroban	8	-4.9989691
Argatroban	9	-4.9438901
Argatroban	10	-4.9209909
Argatroban	11	-4.8325586
Argatroban	12	-4.8318486
Argatroban	13	-4.7511015
Argatroban	14	-4.746994
Argatroban	15	-4.7196827
Argatroban	16	-4.6884422
Argatroban	17	-4.6304469
Argatroban	18	-4.5986891
Argatroban	19	-4.5740185
Argatroban	20	-4.5497618
Argatroban	21	-4.5403342
Argatroban	22	-4.479043
Argatroban	23	-4.429338
Argatroban	24	-4.3240738
Argatroban	25	-4.2996855
Argatroban	26	-4.2566605
Argatroban	27	-4.1599746
Argatroban	28	-4.1448326
Argatroban	29	-3.911803
	Average $\Delta G_{binding}$	-4.75745139
	SD	0.466623475
Sivelestat	1	-5.7663693
Sivelestat	2	-5.6685505
Sivelestat	3	-5.2513843
Sivelestat	4	-5.1074672
Sivelestat	5	-5.0676432
Sivelestat	6	-4.8846173
Sivelestat	7	-4.7638769
Sivelestat	8	-4.667614
Sivelestat	9	-4.6333213
Sivelestat	10	-4.6255341
Sivelestat	11	-4.5483212
Sivelestat	12	-4.5314074
Sivelestat	13	-4.4784012
Sivelestat	14	-4.4594836
Sivelestat	15	-4.4470592
Sivelestat	16	-4.4107747
Sivelestat	17	-4.4071817
Sivelestat	18	-4.3835483
Sivelestat	19	-4.3009076
Sivelestat	20	-4.2904139
Sivelestat	21	-4.2799411
Sivelestat	22	-4.2648997
Sivelestat	23	-4.2099204
Sivelestat	24	-4.0479288
Sivelestat	25	-3.980907
Sivelestat	26	-3.9492056
	Average $\Delta G_{binding}$	-4.59333383
	SD	0.46323607
NCGC00385043	1	-4.8091416
NCGC00385043	2	-4.8008184
NCGC00385043	3	-4.7585044
NCGC00385043	4	-4.6344757
NCGC00385043	5	-4.6077566
NCGC00385043	6	-4.5341458
NCGC00385043	7	-4.5100379
NCGC00385043	8	-4.4895115
NCGC00385043	9	-4.4750743
NCGC00385043	10	-4.4554081

Compound	Conformer	ΔGbinding
NCGC00385043	11	-4.3122907
NCGC00385043	12	-4.2755661
NCGC00385043	13	-4.26647
NCGC00385043	14	-4.2525153
NCGC00385043	15	-4.2013316
NCGC00385043	16	-4.1468425
NCGC00385043	17	-4.1188512
NCGC00385043	18	-4.1005011
NCGC00385043	19	-4.0778847
NCGC00385043	20	-4.0708661
NCGC00385043	21	-4.048614
NCGC00385043	22	-4.0453215
NCGC00385043	23	-4.0339699
NCGC00385043	24	-4.0254369
NCGC00385043	25	-3.9995716
NCGC00385043	26	-3.9956882
NCGC00385043	27	-3.8087223
NCGC00385043	28	-3.6315114
NCGC00385043	29	-3.5687988
NCGC00385043	30	-3.500308
	Average $\Delta G_{binding}$	-4.21853121
	SD	0.34484591
Bromhexine	1	-4.53442
Bromhexine	2	-4.4252768
Bromhexine	3	-4.3771749
Bromhexine	4	-4.2960958
Bromhexine	5	-4.2618198
Bromhexine	6	-4.2172284
Bromhexine	7	-4.2078066
Bromhexine	8	-4.1676679
Bromhexine	9	-4.0720615
Bromhexine	10	-4.0715098
Bromhexine	11	-4.0458279
Bromhexine	12	-4.0063806
Bromhexine	13	-3.9147584
Bromhexine	14	-3.8586266
Bromhexine	15	-3.7951355
Bromhexine	16	-3.7394795
Bromhexine	17	-3.7024744
Bromhexine	18	-3.5915985
Bromhexine	19	-3.5772321
Bromhexine	20	-3.5499673
Bromhexine	21	-3.5254657
	Average $\Delta G_{binding}$	-3.997048
	SD	0.30777818

Equivalence of the number of amino acids, between the generated model of TMPRSS2 and the Uniprot sequence O15393 TMPS2_Human, for the analysis of the interactions shown below.

O15393 TMPS2_Human	TMPRSS2 Model for molecular docking
Val280	Val187
His296	His203
Glu299	Glu206
Asp435	Asp347
Ser436	Ser348
Cys437	Cys349
Gln438	Gln350
Ser441	Ser353
Gly462	Gly378
Ser463	Ser379
Gly464	Gly380
Cys465	Cys381
Lys467	Lys383

Table S2. Interaction report of each conformer of compound T1. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	N	SER	348	H-donor	3.47
	O	HIS	203	H-acceptor	3.05
	6-ring	CYS	381	pi-H	4.17
2	N	CYS	349	H-donor	3.08
	6-ring	CYS	381	pi-H	4.16
3	N	GLY	378	H-donor	3.2
	O	HIS	203	H-acceptor	2.97
4	N	CYS	349	H-donor	3.35
	O	HIS	203	H-acceptor	2.98
5	N	CYS	349	H-donor	2.98
	6-ring	CYS	381	pi-H	4.15
6	N	CYS	349	H-donor	3.08
	6-ring	CYS	381	pi-H	4.19
7	O	HIS	203	H-acceptor	3.14
	6-ring	GLY	380	pi-H	3.87
8	N	GLY	378	H-donor	3.22
	O	HIS	203	H-acceptor	3.18
9	O	HIS	203	H-acceptor	3.04
	6-ring	GLY	380	pi-H	3.98
10	O	HIS	203	H-acceptor	3.52
	6-ring	CYS	381	pi-H	4.45
11	O	HIS	203	H-acceptor	3.05
12	N	SER	348	H-donor	3.35
	N	LYS	383	H-acceptor	3.29
	O	HIS	203	H-acceptor	3
13	N	SER	379	H-donor	3.4
	N	HIS	203	H-acceptor	3.48
14	N	VAL	187	H-donor	4.04
15	N	ASN	249	H-acceptor	3.31
	6-ring	HIS	203	pi-cation	4.45
16	N	HIS	203	H-acceptor	3.26
	6-ring	GLY	378	pi-H	4.26
17	N	ASN	249	H-acceptor	3.34
	6-ring	GLY	380	pi-H	3.81
18	O	GLY	351	H-acceptor	3.08
19	O	GLY	351	H-acceptor	3.02
20	O	HIS	203	H-acceptor	3.37
	6-ring	GLY	380	pi-H	3.76
21	O	HIS	203	H-acceptor	3.23
22	N	GLY	351	H-acceptor	3.59
	O	HIS	203	H-acceptor	3.24
23	O	HIS	203	H-acceptor	3.21
24	N	GLU	206	H-donor	3.25
25	O	HIS	203	H-acceptor	3.12
	6-ring	GLY	380	pi-H	3.93
26	N	GLY	351	H-acceptor	3.22
27	N	GLY	351	H-acceptor	3.35
	N	GLY	380	H-acceptor	3.61

Table S3. Interaction report of each conformer of compound T2. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	S	VAL	187	H-donor	3.32
	C	GLU	206	H-donor	3.55
	N	HIS	203	H-acceptor	3.4
	O	HIS	203	H-acceptor	3.43
2	S	VAL	187	H-donor	3.21
	C	GLU	206	H-donor	3.49
	N	HIS	203	H-acceptor	3.45
	O	HIS	203	H-acceptor	3.1
3	O	HIS	203	H-acceptor	3.25
	6-ring	LEU	209	pi-H	3.74
4	N	VAL	187	H-donor	3.09

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	5-ring	GLY	351	pi-H	3.98
5	N	VAL	187	H-donor	2.98
	6-ring	HIS	203	pi-cation	3.59
6	N	HIS	203	H-acceptor	3.59
	O	HIS	203	H-acceptor	3.1
	O	HIS	203	H-acceptor	3.29
7	N	GLU	206	H-donor	2.93
8	N	VAL	187	H-donor	3.15
	N	HIS	203	H-acceptor	3.82
	O	HIS	203	H-acceptor	3
9	6-ring	GLY	351	pi-H	3.57
11	6-ring	TYR	250	pi-H	4.49
	6-ring	GLN	350	pi-H	4.52
	6-ring	GLY	351	pi-H	4.34
12	S	SER	348	H-donor	3.26
	O	HIS	203	H-acceptor	3.1
	6-ring	CYS	204	pi-H	4.2
13	O	HIS	203	H-acceptor	2.96
14	O	HIS	203	H-acceptor	3.29
15	N	GLY	351	H-acceptor	3.11
16	S	GLU	206	H-donor	3.35
	6-ring	HIS	203	pi-cation	3.92
	6-ring	GLY	351	pi-H	4.07
17	S	SER	348	H-donor	3.3
	5-ring	GLN	350	pi-H	4.18
18	O	HIS	203	H-acceptor	3.09
	6-ring	GLY	351	pi-H	3.45
19	O	HIS	203	H-acceptor	2.91
	6-ring	CYS	204	pi-H	3.9
20	O	HIS	203	H-acceptor	2.99
	5-ring	GLY	351	pi-H	3.72
21	6-ring	HIS	203	pi-H	3.71
	6-ring	HIS	203	pi-cation	3.71
22	O	GLY	351	H-acceptor	3.23
	6-ring	CYS	204	pi-H	4.32
23	N	GLY	378	H-donor	3.06
24	5-ring	HIS	203	pi-cation	3.38

Table S4. Interaction report of each conformer of compound T3. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	C	GLY	378	H-donor	3.44
	O	HIS	203	H-acceptor	3.33
2	S	SER	376	H-donor	3.88
	5-ring	HIS	203	pi-cation	3.33
	6-ring	TRP	377	pi-H	4.72
3	5-ring	VAL	187	pi-H	4.1
4	S	SER	348	H-donor	3.83
	S	CYS	381	H-donor	3.67
	S	VAL	187	H-donor	4.03
	N	HIS	203	H-acceptor	3.35
5	S	SER	348	H-donor	3.53
	S	CYS	381	H-donor	4.25
6	N	VAL	187	H-donor	2.92
7	N	GLY	351	H-acceptor	3.34
8	6-ring	GLY	378	pi-H	3.99
9	N	GLY	351	H-acceptor	3.37
10	S	VAL	205	H-donor	3.55
	S	GLU	206	H-donor	3.73
	5-ring	VAL	187	pi-H	3.65
	5-ring	VAL	187	pi-H	4.03
11	N	HIS	203	H-acceptor	3.41
	N	HIS	203	H-acceptor	3.05
	O	GLY	351	H-acceptor	3.24
12	O	HIS	203	H-acceptor	3.04
13	S	HIS	203	H-donor	3.87

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	S	ASN	249	H-donor	3.28
	S	SER	353	H-donor	3.95
	S	GLY	378	H-donor	3.9
14	S	VAL	187	H-donor	3.34
	S	GLY	351	H-donor	3.24
15	N	GLU	206	H-donor	2.95
	S	VAL	205	H-donor	3.88
	S	GLU	206	H-donor	3.58
16	5-ring	VAL	187	pi-H	4.97
17	O	HIS	203	H-acceptor	2.87
	5-ring	GLY	378	pi-H	4.62
18	5-ring	GLN	350	pi-H	4.3
19	S	GLY	351	H-donor	3.67
	6-ring	HIS	203	pi-cation	3.46
20	S	GLU	206	H-donor	3.16
	N	HIS	203	H-acceptor	3.31
	N	HIS	203	H-acceptor	3.34
	N	HIS	203	H-acceptor	3
21	O	GLY	351	H-acceptor	2.86
	5-ring	VAL	187	pi-H	4.63
	5-ring	GLY	380	pi-H	4.12
22	5-ring	VAL	187	pi-H	3.76
23	S	GLY	378	H-donor	3.72
24	S	ASN	249	H-donor	3.45
	O	TYR	250	H-acceptor	3
	O	ASN	249	H-acceptor	3

Table S5. Interaction report of each conformer of compound T4. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	N	GLY	378	H-donor	3
	N	HIS	203	H-acceptor	3.41
2	N	CYS	349	H-donor	3.06
3	S	HIS	203	H-donor	4.27
	N	CYS	349	H-donor	3
	6-ring	GLY	380	pi-H	3.77
4	N	GLY	378	H-donor	3.05
	N	HIS	203	H-acceptor	3.22
	O	GLY	351	H-acceptor	2.95
	6-ring	VAL	187	pi-H	4.17
5	N	GLU	206	H-donor	2.86
	N	VAL	187	H-donor	3.03
	6-ring	LEU	209	pi-H	3.93
6	S	GLY	351	H-donor	3.49
	S	SER	348	H-donor	4.03
	O	THR	254	H-acceptor	3.15
	5-ring	HIS	203	pi-H	3.67
	6-ring	CYS	204	pi-H	3.82
7	S	SER	348	H-donor	3.63
	C	ASN	249	H-donor	3.42
	O	TYR	250	H-acceptor	3.15
	O	ASN	249	H-acceptor	3.11
8	N	HIS	203	H-acceptor	3.15
9	C	ASN	249	H-donor	3.42
	O	TYR	250	H-acceptor	3.16
	O	ASN	249	H-acceptor	3.12
10	N	VAL	187	H-donor	3.17
	6-ring	GLY	380	pi-H	4.28
11	N	HIS	203	H-acceptor	3.18
	6-ring	VAL	187	pi-H	3.98
12	S	HIS	203	H-donor	3.93
	N	CYS	349	H-donor	3.36
	C	VAL	187	H-donor	3.34
	5-ring	GLY	351	pi-H	4.11
13	S	HIS	203	H-donor	4.16
	O	CYS	381	H-donor	3.95

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	O	CYS	381	H-acceptor	3.39
14	6-ring	ASN	249	pi-H	3.61
15	N	GLU	206	H-donor	2.9
	N	VAL	187	H-donor	2.99
16	N	VAL	187	H-donor	2.97
	6-ring	LYS	302	pi-H	4.58
	6-ring	GLY	303	pi-H	3.73
17	5-ring	VAL	187	pi-H	3.84
18	N	GLU	206	H-donor	3.12
	C	GLU	206	H-donor	3.63
	C	VAL	187	H-donor	3.38
	O	HIS	203	H-acceptor	3.65
19	N	HIS	203	H-acceptor	3.45
	O	GLY	351	H-acceptor	3.23
	6-ring	GLY	378	pi-H	4.11
20	S	CYS	188	H-donor	4.15
	5-ring	HIS	203	pi-H	3.61
21	6-ring	HIS	203	pi-cation	3.86
22	O	HIS	203	H-acceptor	3.01
23	O	GLY	351	H-acceptor	3.42
	O	HIS	203	H-acceptor	3.01
	5-ring	GLU	206	pi-H	4.27
	5-ring	TRP	213	pi-H	3.78
24	S	VAL	187	H-donor	3.4
	S	GLY	351	H-donor	3.95
	O	HIS	203	H-acceptor	3.13
25	N	GLU	206	H-donor	2.8
	6-ring	LEU	209	pi-H	4.26
26	N	VAL	187	H-donor	2.98
	6-ring	GLN	350	pi-H	4.08
27	S	VAL	187	H-donor	3.37
	N	HIS	203	H-acceptor	3.53
	N	HIS	203	H-acceptor	3.37
	6-ring	ASN	249	pi-H	3.61
28	N	VAL	187	H-donor	3.09
29	S	HIS	186	H-donor	3.9

Table S6. Interaction report of each conformer of compound T5. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	S	HIS	203	H-acceptor	4.02
	S	GLY	378	H-acceptor	3.4
	O	ASN	249	H-acceptor	3.13
	O	HIS	203	H-acceptor	3.03
	5-ring	HIS	203	pi-H	3.81
2	O	HIS	203	H-acceptor	3.04
3	N	VAL	187	H-donor	3.08
	S	GLY	351	H-acceptor	3.34
	5-ring	CYS	204	pi-H	3.8
4	N	VAL	187	H-donor	3.2
	S	HIS	203	H-acceptor	3.8
	S	TRP	377	H-acceptor	3.85
5	S	HIS	203	H-acceptor	3.73
	S	GLY	378	H-acceptor	3.34
	O	HIS	203	H-acceptor	2.99
6	S	GLY	351	H-acceptor	3.4
7	N	VAL	187	H-donor	3.09
	S	GLY	351	H-acceptor	3.34
	5-ring	CYS	204	pi-H	3.83
8	S	GLY	351	H-acceptor	3.39
9	6-ring	GLN	350	pi-H	3.96
10	5-ring	HIS	203	pi-H	3.73
11	5-ring	CYS	204	pi-H	4.15
12	N	VAL	187	H-donor	3.11
	5-ring	CYS	204	pi-H	3.83
13	S	CYS	204	H-acceptor	3.6

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	6-ring	GLN	350	pi-H	4.25
14	S	GLY	351	H-acceptor	3.76
	6-ring	HIS	203	pi-H	3.66
15	S	HIS	203	H-acceptor	3.68
	S	TRP	377	H-acceptor	3.75
	6-ring	VAL	187	pi-H	3.86
16	N	VAL	187	H-donor	3.27
	S	HIS	203	H-acceptor	4.05
	S	CYS	204	H-acceptor	3.94
	5-ring	VAL	187	pi-H	4.75
17	S	GLY	351	H-acceptor	3.39
18	N	SER	348	H-donor	3.33
	C	SER	348	H-donor	3.31
	S	HIS	203	H-acceptor	3.62
	S	GLY	378	H-acceptor	3.55
	O	LYS	302	H-acceptor	3.13
	6-ring	HIS	203	pi-H	4.67
19	O	THR	254	H-acceptor	3.28
	5-ring	GLY	378	pi-H	4.5
20	S	HIS	203	H-donor	3.79
	O	HIS	203	H-acceptor	3.02
	6-ring	ASN	249	pi-H	3.36
21	O	THR	305	H-acceptor	3.14
	6-ring	VAL	187	pi-H	4.63
22	C	VAL	187	H-donor	3.23
	S	HIS	203	H-acceptor	4.05
	6-ring	HIS	203	pi-cation	4.57
23	S	HIS	203	H-acceptor	3.82
	S	GLY	378	H-acceptor	3.35
24	S	HIS	203	H-acceptor	3.73
	S	TRP	377	H-acceptor	4.36
	O	GLY	351	H-acceptor	3
25	5-ring	GLN	350	pi-H	4.31
	5-ring	GLY	351	pi-H	3.47
26	C	SER	348	H-donor	3.37
	S	HIS	203	H-acceptor	3.2
	S	GLY	378	H-acceptor	4.44
	6-ring	HIS	203	pi-H	3.86
27	O	CYS	381	H-donor	4.11
	O	LYS	383	H-acceptor	3.09
	O	CYS	381	H-acceptor	3.28

Table S7. Interaction report of each conformer of compound T6. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	N	HIS	186	H-donor	3.16
	6-ring	HIS	203	pi-H	3.56
2	N	SER	348	H-donor	3
	6-ring	VAL	187	pi-H	4.58
	6-ring	GLY	380	pi-H	3.86
3	S	GLU	206	H-donor	4.14
4	6-ring	HIS	203	pi-H	3.64
5	6-ring	HIS	203	pi-H	3.64
6	N	SER	348	H-donor	2.92
	O	HIS	203	H-acceptor	3.16
	6-ring	GLY	380	pi-H	4.44
7	N	GLY	351	H-donor	3.08
	O	HIS	203	H-acceptor	3.22
	6-ring	GLY	380	pi-H	4.46
8	6-ring	LEU	209	pi-H	3.74
9	O	HIS	203	H-acceptor	2.93
10	S	GLY	378	H-donor	3.55
	N	VAL	187	H-donor	3.26
11	S	VAL	187	H-donor	3.22
	6-ring	HIS	203	pi-cation	3.95
12	6-ring	HIS	203	pi-cation	4.19

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
13	N	GLU	206	H-donor	2.93
14	6-ring	HIS	203	pi-cation	4.69
15	N	GLY	351	H-donor	3.08
16	6-ring	HIS	203	pi-cation	3.96
17	6-ring	HIS	203	pi-cation	4.11
18	C	GLU	206	H-donor	3.48
	O	HIS	203	H-acceptor	3.03
	6-ring	ASN	249	pi-H	3.61
19	O	HIS	203	H-acceptor	2.95
	O	HIS	203	H-acceptor	3.19

Table S8. Interaction report of each conformer of compound T7. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	N	HIS	203	H-acceptor	3.37
2	C	ASN	249	H-donor	3.43
	O	ASN	249	H-acceptor	3.2
3	S	HIS	203	H-donor	3.55
	5-ring	VAL	187	pi-H	4.34
4	C	ASN	249	H-donor	3.41
5	N	VAL	187	H-donor	3.08
	N	GLY	351	H-acceptor	3.07
6	N	VAL	187	H-donor	3.21
7	S	HIS	203	H-donor	3.6
	O	HIS	203	H-acceptor	2.92
8	N	VAL	187	H-donor	3.07
	N	GLY	351	H-acceptor	3.1
9	S	HIS	203	H-donor	3.42
	O	GLY	351	H-acceptor	3.15
10	S	HIS	203	H-donor	3.67
	O	HIS	203	H-acceptor	3.01
	O	GLY	351	H-acceptor	3.33
	O	HIS	203	H-acceptor	2.91
11	N	GLY	351	H-acceptor	3.22
	O	HIS	203	H-acceptor	3.13
	C	HIS	186	H-pi	4.13
	5-ring	GLY	378	pi-H	4.06
12	O	HIS	203	H-acceptor	3.11
13	N	GLU	206	H-donor	2.86
	O	GLN	350	H-acceptor	3.13
	6-ring	GLN	350	pi-H	4.14
14	C	GLU	206	H-donor	3.32
	O	HIS	203	H-acceptor	3.12
15	S	SER	376	H-donor	3.86
	O	TYR	250	H-acceptor	3.04
16	O	HIS	203	H-acceptor	2.86
17	O	HIS	203	H-acceptor	2.97
18	O	GLY	351	H-acceptor	3.33
	O	GLY	378	H-acceptor	3.43
	5-ring	HIS	203	pi-H	3.71
19	O	GLY	351	H-acceptor	3.08
	C	TRP	377	H-pi	3.66
	5-ring	HIS	203	pi-H	3.63
20	S	GLY	351	H-donor	3.79
	O	GLN	350	H-acceptor	3.33
	6-ring	ASN	249	pi-H	4.04
21	O	LYS	302	H-acceptor	3.16
22	S	GLY	351	H-donor	3.61
	O	LYS	302	H-acceptor	2.93
23	O	LYS	302	H-acceptor	3.11
24	N	GLU	206	H-donor	3.33
	N	GLU	206	H-donor	3.15

Table S9. Interaction report of each conformer of compound T8. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	S	GLU	301	H-donor	3.64
	C	CYS	381	H-donor	3.8
	O	LYS	383	H-acceptor	3.58
	O	CYS	381	H-acceptor	3.05
	5-ring	HIS	203	pi-cation	3.51
	5-ring	GLY	303	pi-H	4.14
2	S	LYS	302	H-acceptor	4.01
	S	GLY	303	H-acceptor	3.85
	O	CYS	381	H-acceptor	3.44
	O	LYS	383	H-acceptor	3.18
3	S	HIS	203	H-donor	3.09
	S	VAL	205	H-donor	3.86
	S	ASN	249	H-donor	3.47
	S	CYS	204	H-acceptor	3.82
	S	TRP	377	H-acceptor	4.26
	O	HIS	203	H-acceptor	3.28
4	S	GLY	351	H-acceptor	3.45
	O	GLN	350	H-acceptor	3.18
	5-ring	CYS	381	pi-H	4.34
5	S	HIS	203	H-acceptor	4
	S	GLY	380	H-acceptor	3.91
	O	HIS	203	H-acceptor	3.08
	O	HIS	203	H-acceptor	3.12
6	O	GLY	351	H-acceptor	3.11
	6-ring	LEU	209	pi-H	3.77
7	S	GLY	378	H-donor	3.76
	O	HIS	203	H-acceptor	3.02
	6-ring	LEU	209	pi-H	3.88
8	S	GLU	206	H-donor	3.45
	O	HIS	203	H-acceptor	3.24
	5-ring	VAL	187	pi-H	4.57
	5-ring	CYS	204	pi-H	4.43
9	S	HIS	203	H-donor	3.25
	S	CYS	204	H-acceptor	3.73
	S	TRP	377	H-acceptor	4.27
10	5-ring	GLY	351	pi-H	4.04
11	N	GLY	378	H-donor	3.01
	S	CYS	204	H-acceptor	3.95
	O	HIS	203	H-acceptor	3.29
12	N	SER	379	H-donor	3.27
	O	HIS	203	H-acceptor	3.23
	6-ring	VAL	187	pi-H	4.14
13	N	CYS	349	H-donor	2.99
	O	LYS	383	H-acceptor	3
14	N	CYS	349	H-donor	2.98
	S	LYS	302	H-acceptor	3.51
	S	GLY	303	H-acceptor	4.15
	O	HIS	203	H-acceptor	3.15
15	S	GLY	351	H-acceptor	4.49
	O	HIS	203	H-acceptor	2.9
16	N	GLY	378	H-donor	3.19
	S	GLY	351	H-acceptor	3.36
	O	HIS	203	H-acceptor	2.97
	O	HIS	203	H-acceptor	2.99
	6-ring	LYS	383	pi-H	3.63
17	S	GLN	350	H-acceptor	3.86
	O	HIS	203	H-acceptor	3.02
	5-ring	HIS	203	pi-H	3.64
18	N	SER	379	H-donor	3.12
	S	HIS	203	H-acceptor	3.22
	O	GLY	351	H-acceptor	3
19	S	GLY	351	H-acceptor	3.43
	6-ring	CYS	204	pi-H	4.62
20	S	LYS	383	H-acceptor	3.77
	O	LYS	383	H-acceptor	2.91
	6-ring	HIS	203	pi-H	3.84

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
21	S	SER	379	H-donor	3.86
	S	HIS	203	H-acceptor	3.86
22	S	HIS	203	H-acceptor	4.34
	O	HIS	203	H-acceptor	3.1
	O	HIS	203	H-acceptor	3.46
23	O	HIS	203	H-acceptor	3.05
	6-ring	ASP	329	pi-H	4.82
	5-ring	SER	379	pi-H	4.64
24	S	HIS	203	H-acceptor	3.86
	S	LYS	302	H-acceptor	3.38
	O	GLY	351	H-acceptor	2.93
	5-ring	VAL	187	pi-H	4.11
25	S	GLY	351	H-acceptor	3.47
	S	THR	305	H-acceptor	3.47
	O	LYS	302	H-acceptor	3.26
	O	GLY	351	H-acceptor	3.07
	6-ring	HIS	203	pi-cation	4.78
26	S	CYS	381	H-donor	4.32
	S	CYS	381	H-acceptor	3.89
	S	GLY	351	H-acceptor	3.43
27	O	GLY	351	H-acceptor	2.83
28	S	GLU	206	H-donor	3.42
	S	HIS	203	H-acceptor	3.43
29	O	CYS	381	H-donor	3.18

Table S10. Interaction report of each conformer of compound T9. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	O	GLY	351	H-acceptor	3.13
2	N	GLU	206	H-donor	2.91
3	S	HIS	203	H-donor	3.64
	O	HIS	203	H-acceptor	3.32
	6-ring	VAL	187	pi-H	4.05
4	N	HIS	203	H-acceptor	3.07
	O	GLY	351	H-acceptor	2.96
	6-ring	CYS	204	pi-H	3.99
5	N	VAL	187	H-donor	2.81
	S	VAL	187	H-donor	3.25
	N	HIS	203	H-acceptor	3.39
	N	HIS	203	H-acceptor	3.47
	5-ring	CYS	204	pi-H	4.14
	5-ring	GLY	351	pi-H	3.4
6	O	GLY	378	H-acceptor	2.88
7	S	GLY	351	H-donor	3.62
	N	HIS	203	H-acceptor	3.27
	6-ring	CYS	204	pi-H	4.04
8	S	SER	376	H-donor	4.02
	N	GLY	351	H-acceptor	3.05
	6-ring	CYS	381	pi-H	4.48
9	S	SER	348	H-donor	3.33
	O	HIS	203	H-acceptor	3.22
10	5-ring	CYS	204	pi-H	4.03
11	S	HIS	203	H-donor	3.15
12	N	GLU	206	H-donor	3.09
13	N	CYS	349	H-donor	2.92
	S	CYS	349	H-donor	3.67
	5-ring	GLY	380	pi-H	3.74
14	N	GLY	351	H-acceptor	3.35
	O	HIS	203	H-acceptor	3.05
	5-ring	GLY	380	pi-H	3.99
15	S	VAL	187	H-donor	3.36
	S	GLY	351	H-donor	3.76
	5-ring	HIS	203	pi-H	3.59
	6-ring	HIS	203	pi-cation	3.85
16	S	VAL	187	H-donor	3.33
	S	GLY	351	H-donor	3.8

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	5-ring	HIS	203	pi-H	3.58
	6-ring	HIS	203	pi-cation	3.77
17	N	VAL	187	H-donor	2.88
	5-ring	GLY	351	pi-H	3.54
18	N	VAL	187	H-donor	2.9
	5-ring	GLY	351	pi-H	3.46
19	S	GLU	206	H-donor	3.33
	C	TRP	215	H-pi	4.63
20	N	ASN	249	H-acceptor	3.07
21	O	HIS	203	H-acceptor	3.31
	6-ring	CYS	381	pi-H	4.19
22	S	HIS	203	H-acceptor	3.38
	5-ring	ASN	249	pi-H	4.08

Table S11. Interaction report of each conformer of compound T10. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	N	CYS	349	H-donor	3.15
	O	HIS	203	H-acceptor	3.07
	C	HIS	186	H-pi	3.67
2	O	GLY	351	H-acceptor	3.23
	O	HIS	203	H-acceptor	3.08
	6-ring	HIS	203	pi-cation	4.83
3	6-ring	HIS	203	pi-cation	4.87
4	S	HIS	203	H-donor	3.73
	O	HIS	203	H-acceptor	3.26
5	O	HIS	203	H-acceptor	2.99
6	O	GLY	351	H-acceptor	3.06
	O	HIS	203	H-acceptor	2.98
7	S	HIS	203	H-donor	3.88
	5-ring	VAL	187	pi-H	4.26
8	5-ring	GLN	350	pi-H	4
9	N	GLU	206	H-donor	2.94
10	N	CYS	349	H-donor	3.04
	N	GLY	351	H-acceptor	3.07
	O	HIS	203	H-acceptor	3.1
11	N	GLU	206	H-donor	3.17
	5-ring	VAL	187	pi-H	4.3
12	N	VAL	187	H-donor	2.85
	N	GLU	206	H-donor	3
	O	ASN	249	H-acceptor	3.21
	5-ring	GLY	351	pi-H	3.55
13	S	GLU	206	H-donor	3.43
	N	HIS	203	H-acceptor	3.11
	6-ring	HIS	203	pi-cation	3.69
14	N	GLU	206	H-donor	2.92
	S	GLU	206	H-donor	3.53
	5-ring	HIS	203	pi-cation	3.48
15	S	ASN	249	H-donor	3.76
	5-ring	HIS	203	pi-cation	3.55
16	O	GLY	303	H-acceptor	3.17
	O	GLN	350	H-acceptor	3.17
	O	HIS	203	H-acceptor	3.38
	5-ring	VAL	187	pi-H	4.35
17	5-ring	GLY	378	pi-H	4.62
18	N	GLU	206	H-donor	2.88
19	O	GLY	351	H-acceptor	3.1
20	N	GLU	206	H-donor	2.96
21	O	HIS	203	H-acceptor	3.37
	O	GLY	351	H-acceptor	2.9
22	O	HIS	203	H-acceptor	2.93
	6-ring	VAL	187	pi-H	4.6
23	S	VAL	187	H-donor	3.8
	S	GLY	351	H-donor	3.99
24	S	HIS	186	H-donor	4.29
25	N	GLU	206	H-donor	3.21

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	C	GLU	206	H-donor	3.59
	O	HIS	203	H-acceptor	3.64

Table S12. Interaction report of each conformer of Daclatasvir. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	N	CYS	349	H-donor	2.99
	O	GLY	351	H-acceptor	3.59
2	6-ring	VAL	187	pi-H	3.96
3	5-ring	CYS	381	pi-H	4.18
4	N	ASN	249	H-donor	3.1
	O	HIS	203	H-acceptor	2.93
	5-ring	CYS	381	pi-H	4.35
5	O	HIS	203	H-acceptor	2.89
	5-ring	CYS	381	pi-H	4.38
6	N	CYS	349	H-donor	3.28
7	N	GLU	206	H-donor	3.29
	5-ring	CYS	381	pi-H	4.36
8	5-ring	CYS	381	pi-H	4.28
9	N	GLU	206	H-donor	3.28
10	5-ring	CYS	381	pi-H	4.35
11	O	CYS	381	H-donor	4.1
	N	GLU	206	H-donor	3.38
	N	GLU	206	H-donor	3.46
	N	CYS	381	H-donor	3.78
	O	CYS	381	H-acceptor	3.48
12	5-ring	HIS	203	pi-cation	3.88
13	5-ring	LYS	302	pi-cation	3.83
	6-ring	GLN	350	pi-H	3.83
14	N	GLU	206	H-donor	3.24
15	N	GLY	351	H-acceptor	3.08
	6-ring	HIS	203	pi-cation	3.78
16	O	GLY	303	H-acceptor	3.37
	O	HIS	203	H-acceptor	3.28
	N	LYS	383	H-acceptor	3.02
	5-ring	CYS	381	pi-H	4.23
16	O	GLY	378	H-acceptor	3.06
17	N	GLU	206	H-donor	3.13
	O	LYS	383	H-acceptor	3.24
18	O	LYS	383	H-acceptor	2.91
	N	GLY	303	H-acceptor	3.35
19	N	GLU	206	H-donor	3.34
	O	LYS	383	H-acceptor	2.98
20	N	GLU	206	H-donor	3.41
21	6-ring	GLN	350	pi-H	4.05

Table S13. Interaction report of each conformer of Ombitasvir. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	6-ring	HIS	203	pi-cation	3.75
2	6-ring	HIS	203	pi-cation	4.09
3	N	GLU	206	H-donor	3.11
	O	CYS	381	H-donor	3.38
4	O	SER	379	H-acceptor	3
	O	ARG	386	H-acceptor	3.16
	O	ARG	386	H-acceptor	2.91
	O	HIS	203	H-acceptor	3.05
5	O	GLY	351	H-acceptor	3.12
6	O	ARG	386	H-acceptor	3.08
7	O	HIS	203	H-acceptor	2.91
8	O	HIS	203	H-acceptor	3.52
9	N	SER	379	H-donor	3.19
	O	HIS	203	H-acceptor	3.2
10	O	CYS	381	H-donor	3.82
	O	LYS	383	H-acceptor	3.19

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
11	C	TRP	377	H-pi	4.11
12	N	SER	379	H-donor	3.4
13	N	GLU	206	H-donor	3.29
	O	HIS	203	H-acceptor	2.91
	6-ring	GLN	350	pi-H	3.66
14	N	GLU	206	H-donor	3.42
	O	LYS	383	H-acceptor	2.95
15	O	GLY	303	H-acceptor	3.39
16	O	ARG	386	H-acceptor	3.29
17	N	GLU	206	H-donor	3.54
	N	GLU	206	H-donor	3.17
	O	HIS	203	H-acceptor	3.22
	O	ASN	249	H-acceptor	3.22
18	N	GLU	206	H-donor	3.4
	N	GLU	206	H-donor	3.15
	O	HIS	203	H-acceptor	3.1
	O	ASN	249	H-acceptor	3.21
19	O	ASN	249	H-acceptor	3.22
20	O	TYR	250	H-acceptor	3.12
	O	LYS	383	H-acceptor	3.26
	O	GLY	303	H-acceptor	3.24
21	O	ASN	249	H-acceptor	3.43
	O	ARG	386	H-acceptor	2.96
22	O	LYS	383	H-acceptor	2.94
	6-ring	GLN	350	pi-H	3.64
23	O	ARG	386	H-acceptor	2.96
24	N	GLU	206	H-donor	3.15
	O	LYS	302	H-acceptor	2.94
	O	HIS	203	H-acceptor	3.11
25	O	ARG	386	H-acceptor	2.95

Table S14. Interaction report of each conformer of Camostat. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	N	SER	379	H-donor	2.8
	O	HIS	203	H-acceptor	3.19
2	O	HIS	203	H-acceptor	3.42
	N	GLU	206	ionic	3.5
	N	GLU	206	ionic	3.5
	N	GLU	206	ionic	3.83
3	O	HIS	203	H-acceptor	3.37
	O	HIS	203	H-acceptor	3.07
	N	GLU	206	ionic	3.83
	N	GLU	206	ionic	3.53
	N	GLU	206	ionic	3.87
4	O	GLY	351	H-acceptor	3.1
	N	GLU	206	ionic	3.5
	N	GLU	206	ionic	3.37
	N	GLU	206	ionic	3.98
	N	GLU	206	ionic	3.72
5	N	GLU	206	H-donor	2.99
	N	GLU	206	ionic	2.99
	N	GLU	206	ionic	3.92
	N	GLU	206	ionic	3.63
6	O	HIS	203	H-acceptor	3.39
	N	GLU	206	ionic	3.66
	N	GLU	206	ionic	3.65
	N	GLU	206	ionic	3.97
	N	GLU	206	ionic	3.16
7	N	GLU	206	H-donor	3.13
	O	GLY	351	H-acceptor	3.17
	N	GLU	206	ionic	3.13
	6-ring	HIS	203	pi-H	3.92
8	N	GLU	206	ionic	3.65
	N	GLU	206	ionic	3.86
9	O	HIS	203	H-acceptor	3.61

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	O	HIS	203	H-acceptor	3.27
	N	GLU	206	ionic	3.6
	N	GLU	206	ionic	3.7
	N	GLU	206	ionic	3.69
	N	GLU	206	ionic	3.55
10	O	HIS	203	H-acceptor	3.39
	N	GLU	206	ionic	3.77
	N	GLU	206	ionic	3.91
	N	GLU	206	ionic	3.91
	N	GLU	206	ionic	3.15
	N	GLU	206	ionic	3.64
11	N	GLU	206	ionic	3.86
	N	GLU	206	ionic	3.49
	N	GLU	206	ionic	2.93
	N	GLU	206	ionic	4
12	N	GLU	206	H-donor	2.94
	N	GLU	206	H-donor	3.3
	N	GLU	206	ionic	2.94
	N	GLU	206	ionic	3.3
13	N	GLU	206	H-donor	2.98
	N	GLU	206	ionic	2.98
	N	GLU	206	ionic	3.89
	N	GLU	206	ionic	3.67
14	N	GLU	206	ionic	3.75
	N	GLU	206	ionic	3.45
15	N	GLU	206	H-donor	3.55
	O	HIS	203	H-acceptor	2.96
	N	GLU	206	ionic	3.55
	N	GLU	206	ionic	2.87
	6-ring	ASN	249	pi-H	4.09
16	N	GLU	206	H-donor	3.24
	N	GLU	206	H-donor	2.95
	N	GLU	206	ionic	3.24
	N	GLU	206	ionic	3.51
	N	GLU	206	ionic	2.95
17	N	GLU	206	ionic	3.68
	N	GLU	206	ionic	3.91
	N	GLU	206	ionic	3.5
18	N	GLU	206	H-donor	3.23
	N	GLU	206	H-donor	2.95
	O	HIS	203	H-acceptor	3.16
	O	HIS	203	H-acceptor	2.91
	N	GLU	206	ionic	2.9
	N	GLU	206	ionic	3.23
	N	GLU	206	ionic	3.87
	N	GLU	206	ionic	2.95
19	N	SER	379	H-donor	3.03
20	N	GLU	206	H-donor	2.95
	O	HIS	203	H-acceptor	3.58
	N	GLU	206	ionic	3.15
	N	GLU	206	ionic	2.95
	N	GLU	206	ionic	3.11
21	N	SER	348	H-donor	2.9
22	N	GLU	206	H-donor	3.23
	N	GLU	206	H-donor	3.07
	N	GLU	206	ionic	3.23
	N	GLU	206	ionic	3.54
	N	GLU	206	ionic	3.07
23	N	GLU	206	H-donor	2.83
	N	GLU	206	ionic	2.83
	N	GLU	206	ionic	3.56
24	O	GLN	350	H-acceptor	3.23
	O	HIS	203	H-acceptor	2.98
	N	GLU	206	ionic	2.87
	N	GLU	206	ionic	4
	N	GLU	206	ionic	3.53

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	N	GLU	206	ionic	3.37
	N	GLU	206	ionic	3.62
	N	GLU	206	ionic	3.37

Table S15. Interaction report of each conformer of Edoxaban. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	N	HIS	186	H-donor	3.06
	O	HIS	203	H-acceptor	3.16
2	O	HIS	203	H-acceptor	3.35
3	N	GLU	206	H-donor	2.84
	O	HIS	203	H-acceptor	3.08
	N	GLU	206	ionic	2.84
4	N	GLU	206	H-donor	2.99
	O	GLY	378	H-acceptor	2.89
	O	GLY	351	H-acceptor	3.23
	N	GLU	206	ionic	2.99
5	N	GLU	206	H-donor	2.91
	O	HIS	203	H-acceptor	3.06
	N	GLU	206	ionic	2.91
	5-ring	HIS	203	pi-cation	3.92
6	N	SER	348	H-donor	3.24
	O	HIS	203	H-acceptor	3.02
7	O	CYS	381	H-donor	3.44
	O	HIS	203	H-acceptor	3.16
	6-ring	HIS	203	pi-cation	4.48
8	N	GLU	206	H-donor	2.84
	O	GLY	351	H-acceptor	3.07
	N	GLU	206	ionic	2.84
	6-ring	HIS	203	pi-cation	4.32
9	O	GLY	378	H-acceptor	2.98
10	S	VAL	187	H-donor	3.74
	N	SER	348	H-donor	3.16
11	O	GLY	351	H-acceptor	3.08
12	O	GLY	351	H-acceptor	2.86
	O	HIS	203	H-acceptor	2.98
	N	GLU	206	ionic	3.81
13	O	GLY	351	H-acceptor	3.07
	O	HIS	203	H-acceptor	3.1
	N	GLU	206	ionic	3.98
14	N	TRP	377	cation-pi	4.23
	N	TRP	377	cation-pi	4.48
15	N	GLU	206	H-donor	3.22
	O	HIS	203	H-acceptor	3.3
	O	HIS	203	H-acceptor	2.89
	N	GLU	206	ionic	3.22
	N	GLU	206	ionic	3.35
16	N	GLU	206	H-donor	2.75
	O	HIS	203	H-acceptor	3.47
	N	GLU	206	ionic	2.75
17	O	HIS	203	H-acceptor	2.92
	6-ring	GLY	380	pi-H	4.24
18	N	GLN	350	H-donor	2.96
19	S	SER	348	H-donor	4.08
	6-ring	CYS	381	pi-H	4.61
20	O	GLY	351	H-acceptor	3.15
21	CL	SER	348	H-donor	3.43
	C	TRP	215	H-pi	4.94
22	O	HIS	203	H-acceptor	2.99
23	N	CYS	349	H-donor	3.26
	N	ASN	249	H-donor	3
	O	HIS	203	H-acceptor	3.06
24	N	GLU	206	H-donor	3.45
	O	HIS	203	H-acceptor	3.32
	N	GLU	206	ionic	3.45
	N	GLU	206	ionic	3.8

Table S16. Interaction report of each conformer of NCGC00386477. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	N	GLU	206	H-donor	2.86
	N	LYS	383	H-acceptor	3.01
	N	GLU	206	ionic	2.86
	N	GLU	206	ionic	3.82
2	N	GLU	206	H-donor	2.96
	N	GLU	206	ionic	2.96
3	N	GLU	206	H-donor	2.95
	N	GLU	206	ionic	2.95
4	N	SER	348	H-donor	2.9
	N	GLY	378	H-donor	3.2
	6-ring	SER	379	pi-H	4.69
5	O	HIS	203	H-acceptor	2.98
	N	LYS	383	H-acceptor	2.99
	5-ring	CYS	381	pi-H	4.28
6	N	GLU	206	H-donor	2.89
	N	LYS	383	H-acceptor	3.03
	N	GLU	206	ionic	2.89
	5-ring	CYS	381	pi-H	4.36
7	6-ring	LEU	209	pi-H	3.9
8	N	GLU	206	H-donor	2.92
	N	GLU	206	ionic	2.92
	N	GLU	206	ionic	3.54
9	N	THR	254	H-donor	3.03
	N	LYS	302	H-acceptor	3.48
10	N	GLU	206	H-donor	2.96
	N	LYS	383	H-acceptor	3.15
	N	GLU	206	ionic	2.96
11	N	GLY	378	H-donor	3.04
	O	HIS	203	H-acceptor	3.41
	6-ring	HIS	203	pi-cation	3.82
12	N	LYS	383	H-acceptor	2.99
13	5-ring	VAL	187	pi-H	4.08
14	N	GLU	206	H-donor	2.89
	N	GLU	206	ionic	2.89
	N	GLU	206	ionic	3.79
	6-ring	VAL	187	pi-H	4.49
15	N	SER	379	H-donor	3.24
	O	HIS	203	H-acceptor	3.21
16	O	HIS	203	H-acceptor	3.29
17	N	GLU	206	ionic	3.91
18	N	GLU	206	H-donor	2.88
	N	GLU	206	ionic	2.88
19	N	GLU	206	H-donor	3.56
	N	LYS	383	H-acceptor	2.99
	N	GLU	206	ionic	3.56
	N	GLU	206	ionic	3.48
20	N	GLU	206	H-donor	2.9
	N	GLU	206	ionic	2.9
	N	GLU	206	ionic	4
	6-ring	SER	379	pi-H	4.62

Table S17. Interaction report of each conformer of Nafamostat. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	N	GLU	206	H-donor	2.91
	N	SER	348	H-donor	3.01
	N	GLY	351	H-donor	2.98
	N	SER	348	H-donor	3.14
	N	GLU	206	ionic	2.91
2	N	SER	348	H-donor	2.72
	N	GLU	206	ionic	3.73
3	N	GLU	206	H-donor	2.94
	N	SER	348	H-donor	2.98

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	N	GLY	351	H-donor	2.99
	N	SER	348	H-donor	3.04
	N	GLU	206	ionic	2.94
4	N	SER	348	H-donor	2.86
	N	GLU	206	ionic	3.46
	N	GLU	206	ionic	3.23
5	N	GLU	206	H-donor	2.88
	N	GLU	206	ionic	2.88
6	N	SER	348	H-donor	2.76
	N	GLU	206	H-donor	2.87
	N	GLU	206	ionic	2.87
7	N	GLU	206	H-donor	2.93
	N	SER	348	H-donor	3.08
	N	SER	348	H-donor	2.91
	N	GLU	206	ionic	2.93
8	N	GLY	378	H-donor	3.09
	N	SER	348	H-donor	2.78
	N	GLU	206	ionic	3.63
	N	GLU	206	ionic	3.41
	6-ring	HIS	203	pi-cation	4.35
9	N	GLU	206	H-donor	2.99
	N	CYS	349	H-donor	3.17
	N	SER	348	H-donor	2.93
	N	GLU	206	ionic	2.99
10	N	SER	348	H-donor	2.94
	N	GLY	351	H-donor	3.05
	N	SER	348	H-donor	3.08
11	N	GLU	206	H-donor	2.92
	N	CYS	349	H-donor	3.15
	N	GLU	206	ionic	2.92
12	N	GLU	206	H-donor	3.48
	N	SER	348	H-donor	3.49
	N	GLU	206	ionic	3.48
13	N	GLU	206	H-donor	2.94
	N	GLY	351	H-donor	3.17
	N	GLU	206	ionic	2.94
	N	ASP	352	ionic	3.91
14	N	GLU	206	H-donor	2.96
	N	CYS	349	H-donor	3.23
	N	SER	348	H-donor	2.81
	N	GLU	206	ionic	2.96
15	N	SER	348	H-donor	2.81
	N	GLU	206	ionic	3.48
	N	GLU	206	ionic	3.24
16	N	SER	348	H-donor	2.72
	N	CYS	349	H-donor	3.07
	N	GLU	206	ionic	3.38
	N	GLU	206	ionic	3.91
17	N	SER	348	H-donor	3.21
	N	SER	348	H-donor	2.94
	N	GLU	206	ionic	3.37
	N	GLU	206	ionic	3.26
	6-ring	VAL	187	pi-H	3.88
18	N	CYS	349	H-donor	3.02
	N	GLU	206	H-donor	3.05
	N	GLU	206	H-donor	3.22
	N	GLU	206	ionic	3.05
	N	GLU	206	ionic	3.95
	N	GLU	206	ionic	3.79
	N	GLU	206	ionic	3.22
19	N	SER	348	H-donor	2.72
	N	CYS	349	H-donor	3.07
	N	GLU	206	ionic	3.67
	N	GLU	206	ionic	3.94
	N	GLU	206	ionic	3.68
20	N	GLU	206	H-donor	2.85

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	N	GLU	206	H-donor	2.76
	N	CYS	349	H-donor	2.96
	N	CYS	381	H-donor	4.06
	N	CYS	381	H-donor	3.53
	O	HIS	203	H-acceptor	3.18
	N	GLU	206	ionic	2.85
	N	GLU	206	ionic	2.76
21	N	VAL	187	H-donor	2.96
	N	GLY	351	H-donor	2.78
22	N	HIS	186	H-donor	3.01
	N	GLU	206	ionic	2.83
	N	GLU	206	ionic	3.52
	N	GLU	206	ionic	3.61
	N	GLU	206	ionic	3.69
	N	GLU	206	ionic	3.64
23	N	GLN	350	H-donor	2.82
	N	GLU	206	ionic	3.03
	N	GLU	206	ionic	3.46
	N	GLU	206	ionic	3.05
	N	GLU	206	ionic	3.73
	6-ring	HIS	203	pi-cation	4.49
	N	CYS	381	H-donor	3.53
	O	HIS	203	H-acceptor	3.18
	N	GLU	206	ionic	2.85
	N	GLU	206	ionic	2.76
21	N	VAL	187	H-donor	2.96
	N	GLY	351	H-donor	2.78
22	N	HIS	186	H-donor	3.01
	N	GLU	206	ionic	2.83
	N	GLU	206	ionic	3.52
	N	GLU	206	ionic	3.61
	N	GLU	206	ionic	3.69
	N	GLU	206	ionic	3.64
23	N	GLN	350	H-donor	2.82
	N	GLU	206	ionic	3.03
	N	GLU	206	ionic	3.46
	N	GLU	206	ionic	3.05
	N	GLU	206	ionic	3.73
	6-ring	HIS	203	pi-cation	4.49
	N	GLU	206	ionic	3.61
	N	GLU	206	ionic	3.69
	N	GLU	206	ionic	3.64
23	N	GLN	350	H-donor	2.82
	N	GLU	206	ionic	3.03
	N	GLU	206	ionic	3.46
	N	GLU	206	ionic	3.05
	N	GLU	206	ionic	3.73
	6-ring	HIS	203	pi-cation	4.49

Table S18. Interaction report of each conformer of NCGC00386945. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	N	GLU	206	H-donor	3.46
	N	GLU	206	ionic	3.46
2	N	GLU	206	H-donor	2.88
	N	GLU	206	ionic	2.88
3	N	CYS	349	H-donor	3.07
4	N	SER	348	H-donor	2.69
	N	SER	379	H-donor	3.23
5	N	GLU	206	H-donor	2.93
	N	GLU	206	ionic	2.93
6	N	GLU	206	ionic	3.46
7	N	GLU	206	H-donor	2.94
	N	GLU	206	ionic	2.94
8	N	CYS	349	H-donor	3.08
	N	GLU	206	H-donor	2.98

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	N	GLU	206	ionic	2.98
9	N	SER	348	H-donor	3.4
10	N	SER	348	H-donor	2.86
	N	GLY	351	H-donor	3.19
	C	GLU	206	H-donor	3.54
	N	GLU	206	ionic	4
11	O	HIS	203	H-acceptor	3.33
	N	GLU	206	ionic	3.24
	N	GLU	206	ionic	3.43
12	N	GLU	206	ionic	3.41
13	N	GLU	206	H-donor	2.98
	N	GLU	206	ionic	2.98
14	N	GLU	206	H-donor	2.86
	N	CYS	381	H-donor	4.47
	N	GLU	206	ionic	2.86
15	N	GLU	206	H-donor	2.94
	N	CYS	381	H-donor	4.01
	N	GLU	206	ionic	2.94
	N	GLU	206	ionic	3.66
16	N	GLU	206	H-donor	3.38
	N	GLY	378	H-donor	2.97
	N	SER	348	H-donor	2.76
	N	GLU	206	ionic	3.38
17	N	TRP	215	cation-pi	4.47
	6-ring	HIS	203	pi-cation	4.79
18	N	GLU	206	H-donor	2.96
	N	GLU	206	ionic	2.96
19	6-ring	GLN	350	pi-H	4.78
20	N	GLU	206	H-donor	3.19
	N	GLU	206	ionic	3.19
21	N	GLU	206	H-donor	2.9
	N	SER	379	H-donor	3.32
	N	GLU	206	ionic	2.9
	N	GLU	206	ionic	3.52
22	N	GLY	378	H-donor	2.98
	C	GLU	206	H-donor	3.5
	N	GLU	206	ionic	3.71
	6-ring	HIS	203	pi-cation	3.84
23	N	GLU	206	ionic	3.87
	N	GLU	206	ionic	3.41

Table S19. Interaction report of each conformer of Otamixaban. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	N	SER	348	H-donor	3.09
	N	GLY	351	H-donor	3
	N	SER	348	H-donor	3.17
2	N	VAL	205	H-donor	2.87
	N	GLU	206	ionic	2.99
	N	GLU	206	ionic	2.84
	6-ring	HIS	203	pi-cation	3.81
3	N	VAL	205	H-donor	3.45
	N	VAL	205	H-donor	3.32
	O	HIS	203	H-acceptor	2.98
	O	LYS	383	H-acceptor	3.02
	N	GLU	206	ionic	3.05
4	N	GLU	206	H-donor	3.04
	N	GLU	206	ionic	3.04
	N	GLU	206	ionic	3.63
	6-ring	ASN	249	pi-H	4.74
	6-ring	GLN	350	pi-H	4.65
5	N	GLU	206	H-donor	3.03
	N	GLU	206	H-donor	2.93
	O	HIS	203	H-acceptor	2.89
	N	GLU	206	ionic	3.03
	N	GLU	206	ionic	2.93

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	N	GLU	206	ionic	3.87
6	N	CYS	349	H-donor	2.88
	N	CYS	381	H-donor	3.52
	O	HIS	203	H-acceptor	2.88
	6-ring	VAL	187	pi-H	4.1
7	N	GLU	206	H-donor	2.83
	N	GLU	206	ionic	2.83
8	N	GLN	350	H-donor	2.91
	O	HIS	203	H-acceptor	2.88
9	N	GLY	378	H-donor	2.77
0	N	VAL	187	H-donor	3.09
	N	GLY	351	H-donor	2.88
10	N	GLU	206	H-donor	2.88
	N	GLU	206	H-donor	2.99
	N	GLU	206	ionic	2.88
	N	GLU	206	ionic	2.99
11	N	SER	348	H-donor	3.2
	N	SER	348	H-donor	3.1
	C	CYS	381	H-donor	4.36
12	N	CYS	349	H-donor	2.98
	N	CYS	349	H-donor	3.04
	O	HIS	203	H-acceptor	2.92
13	N	GLY	351	H-donor	2.83
	O	HIS	203	H-acceptor	3.13
14	N	GLY	378	H-donor	2.99
15	N	GLU	206	H-donor	2.78
	N	GLU	206	H-donor	3.43
	N	GLU	206	H-donor	3.09
	O	HIS	203	H-acceptor	2.93
	N	GLU	206	ionic	2.78
	N	GLU	206	ionic	3.43
	N	GLU	206	ionic	3.09
	6-ring	VAL	187	pi-H	4.51
16	N	GLU	206	H-donor	3.07
	N	GLU	206	H-donor	2.93
	O	HIS	203	H-acceptor	2.95
	N	GLU	206	ionic	3.07
	N	GLU	206	ionic	2.93
	N	GLU	206	ionic	3.79
17	N	GLU	206	H-donor	3.11
	O	THR	254	H-acceptor	3.28
	N	GLU	206	ionic	3.11
	C	TRP	377	H-pi	3.99
	C	TRP	377	H-pi	3.94
18	N	GLU	206	H-donor	2.9
	N	GLU	206	H-donor	2.85
	N	GLU	206	ionic	2.9
	N	GLU	206	ionic	2.85
	6-ring	LEU	209	pi-H	4.55
19	N	GLU	206	H-donor	2.77
	N	GLU	206	ionic	2.77
	N	GLU	206	ionic	3.63
	6-ring	HIS	203	pi-cation	3.62
20	N	VAL	205	H-donor	2.97
	N	GLU	206	H-donor	2.82
	N	GLU	206	ionic	3.22
	N	GLU	206	ionic	2.82
	6-ring	HIS	203	pi-cation	3.84
21	6-ring	HIS	203	pi-cation	3.6
	6-ring	CYS	204	pi-H	4.47
22	N	CYS	349	H-donor	3.62
23	N	GLU	206	H-donor	3.36
	N	GLU	206	ionic	3.36
	N	GLU	206	ionic	2.81
24	N	GLU	206	H-donor	2.86
	N	GLU	206	H-donor	3.44

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	O	HIS	203	H-acceptor	2.9
	N	GLU	206	ionic	2.86
	N	GLU	206	ionic	3.32
	N	GLU	206	ionic	3.44

Table S20. Interaction report of each conformer of Darexaban. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	6-ring	VAL	187	pi-H	4.05
2	6-ring	HIS	203	pi-cation	4.07
3	6-ring	GLY	351	pi-H	4.59
4	N	GLU	206	ionic	3.61
5	O	HIS	203	H-acceptor	2.97
	N	GLU	206	ionic	3.94
	N	GLU	206	ionic	3.66
	6-ring	TYR	250	pi-H	3.93
6	N	GLU	206	ionic	3.98
7	C	CYS	349	H-donor	3.46
8	O	HIS	203	H-acceptor	2.97
	N	GLU	206	ionic	3.4
	6-ring	VAL	187	pi-H	4.52
9	6-ring	GLY	351	pi-H	3.62
10	6-ring	HIS	203	pi-H	4.19
	6-ring	HIS	203	pi-cation	3.52
11	O	SER	379	H-donor	2.89
	C	TRP	377	H-pi	4.54
12	N	GLU	206	ionic	3.66
	6-ring	GLN	350	pi-H	4.38
	6-ring	GLY	351	pi-H	3.69
13	O	HIS	203	H-acceptor	3.05
	N	GLU	206	ionic	3.67
	6-ring	GLY	351	pi-H	4.35
14	6-ring	VAL	187	pi-H	4.01
15	N	GLU	206	ionic	3.74
	N	CYS	349	H-donor	3.1
	O	CYS	381	H-acceptor	3.26
	O	LYS	383	H-acceptor	2.93
16	N	GLU	206	H-donor	3.29
17	6-ring	HIS	203	pi-cation	3.9
18	N	GLU	206	H-donor	2.94
	N	GLU	206	ionic	2.94

Table S21. Interaction report of each conformer of Gabexate. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	N	SER	348	H-donor	3.13
	N	SER	348	H-donor	3.03
2	N	GLU	206	H-donor	2.89
	N	GLU	206	ionic	3.53
	N	GLU	206	ionic	2.89
	6-ring	HIS	203	pi-H	3.87
3	N	GLU	206	H-donor	2.87
	O	GLY	351	H-acceptor	3.27
	N	GLU	206	ionic	2.87
	N	GLU	206	ionic	3.43
4	N	CYS	349	H-donor	3.02
5	N	CYS	349	H-donor	2.95
	6-ring	VAL	187	pi-H	3.99
6	N	GLY	351	H-donor	3.12
7	N	GLU	206	ionic	3.14
8	N	GLU	206	H-donor	2.79
	O	HIS	203	H-acceptor	3.37
	N	GLU	206	ionic	2.79
	N	GLU	206	ionic	3.48
9	N	SER	348	H-donor	2.92

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	N	CYS	349	H-donor	3.34
	N	CYS	381	H-donor	4.26
10	N	GLU	206	H-donor	3.2
	N	GLU	206	H-donor	2.94
	O	HIS	203	H-acceptor	3.02
	N	GLU	206	ionic	3.2
	N	GLU	206	ionic	2.94
11	N	GLU	206	H-donor	2.88
	N	GLU	206	H-donor	2.78
	N	GLU	206	ionic	2.88
	N	GLU	206	ionic	3.89
	N	GLU	206	ionic	2.78
12	N	SER	348	H-donor	3.14
	N	SER	348	H-donor	2.94
	6-ring	VAL	187	pi-H	4.22
13	N	SER	379	H-donor	2.92
	6-ring	VAL	187	pi-H	4.33
14	N	GLY	378	H-donor	2.84
	O	HIS	203	H-acceptor	3.18
	6-ring	HIS	203	pi-H	3.78
15	N	CYS	349	H-donor	3.13
	N	CYS	349	H-donor	3.04
16	N	GLU	206	H-donor	3.14
	N	GLU	206	H-donor	3.04
	N	GLU	206	ionic	3.98
	N	GLU	206	ionic	3.14
	N	GLU	206	ionic	3.04
17	O	HIS	203	H-acceptor	2.97
	N	GLU	206	ionic	3.95
18	N	GLU	206	H-donor	2.75
	N	ASN	249	H-donor	3.21
	N	GLU	206	ionic	3.62
	N	GLU	206	ionic	2.75
19	N	GLU	206	H-donor	2.86
	N	GLU	206	ionic	2.86
	N	GLU	206	ionic	3.38
20	N	GLU	206	ionic	3.19
21	N	GLU	206	ionic	3.84
	N	GLU	206	ionic	3.21
	N	GLU	206	ionic	2.94
22	O	GLY	351	H-acceptor	3.27
	N	GLU	206	ionic	3.3
	N	GLU	206	ionic	3.77
	N	GLU	206	ionic	2.99
23	N	GLU	206	H-donor	2.93
	N	GLU	206	H-donor	3.16
	N	GLU	206	ionic	2.93
	N	GLU	206	ionic	3.16
	N	GLU	206	ionic	3.5
24	N	SER	348	H-donor	3.1
	N	SER	348	H-donor	2.88
25	N	GLU	206	H-donor	2.85
	N	GLU	206	ionic	2.85
26	N	SER	348	H-donor	3.42
	N	SER	348	H-donor	2.82
27	N	ASN	249	H-donor	3.27
	N	GLU	206	H-donor	2.76
	O	GLY	351	H-acceptor	3.01
	N	GLU	206	ionic	2.76
28	N	GLU	206	H-donor	3.1
	N	GLU	206	H-donor	3.25
	N	GLU	206	H-donor	2.88
	O	HIS	203	H-acceptor	3.15
	O	GLY	351	H-acceptor	3.12
	N	GLU	206	ionic	3.1
	N	GLU	206	ionic	3.25

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	N	GLU	206	ionic	4
	N	GLU	206	ionic	2.88

Table S22. Interaction report of each conformer of Letaxaban. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	O	SER	348	H-donor	3.01
	O	HIS	203	H-acceptor	3.17
2	O	HIS	203	H-acceptor	2.91
	6-ring	VAL	187	pi-H	3.89
	6-ring	VAL	187	pi-H	4.65
3	N	CYS	349	H-donor	3.13
4	O	VAL	187	H-donor	3.09
	6-ring	GLY	380	pi-H	4.56
5	6-ring	HIS	203	pi-cation	3.72
6	O	GLY	351	H-acceptor	2.98
	6-ring	GLN	350	pi-H	3.74
7	O	GLY	351	H-acceptor	3.25
	6-ring	VAL	187	pi-H	4.44
	6-ring	VAL	187	pi-H	4
8	O	GLY	351	H-acceptor	3.05
9	O	VAL	187	H-donor	3.3
	O	HIS	203	H-acceptor	3.33
	6-ring	ASN	249	pi-H	4.12
10	O	HIS	203	H-acceptor	3.02
	6-ring	VAL	187	pi-H	4.46
11	O	VAL	187	H-donor	2.97
	O	HIS	203	H-acceptor	2.91
	6-ring	ASN	249	pi-H	3.82
	6-ring	ASN	249	pi-H	4.05
13	O	HIS	203	H-acceptor	2.95
14	N	SER	348	H-donor	3.07
15	O	SER	348	H-donor	3
16	6-ring	HIS	203	pi-cation	4.22
17	O	GLN	350	H-acceptor	3.34
	O	HIS	203	H-acceptor	3.32
18	O	ASN	249	H-acceptor	3.1
19	O	HIS	203	H-acceptor	2.89
20	O	VAL	187	H-donor	3
	6-ring	ASN	249	pi-H	3.91
21	C	GLU	206	H-donor	3.46
	O	HIS	203	H-acceptor	2.98

Table S23. Interaction report of each conformer of Argatroban. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	N	GLN	350	H-donor	3.09
	N	GLN	350	H-donor	3.18
	O	HIS	203	H-acceptor	2.87
	O	HIS	203	ionic	2.87
2	N	GLU	206	H-donor	2.84
	O	HIS	203	H-acceptor	2.91
	N	GLU	206	ionic	3.87
	N	GLU	206	ionic	2.84
	6-ring	GLY	351	pi-H	4.25
3	N	VAL	187	H-donor	2.91
	N	HIS	203	H-donor	3.52
	N	GLU	206	H-donor	3.34
	N	GLU	206	H-donor	2.89
	O	HIS	203	H-acceptor	3.19
	O	GLY	351	H-acceptor	3.33
	O	HIS	203	ionic	3.19
	O	HIS	203	ionic	3.02
	N	GLU	206	ionic	3.34
	N	GLU	206	ionic	2.89

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
4	N	GLU	206	H-donor	2.9
	N	HIS	203	H-donor	3.26
	N	GLU	206	H-donor	2.83
	O	HIS	203	ionic	2.9
	N	GLU	206	ionic	2.9
	N	GLU	206	ionic	2.83
5	N	GLU	206	H-donor	2.87
	N	GLU	206	H-donor	2.89
	O	HIS	203	H-acceptor	2.88
	O	HIS	203	ionic	2.88
	O	HIS	203	ionic	3.44
	N	GLU	206	ionic	2.87
	N	GLU	206	ionic	2.89
6	O	HIS	203	H-acceptor	2.78
	O	HIS	203	ionic	2.78
	N	GLU	206	ionic	3.1
	N	GLU	206	ionic	3.49
7	N	SER	348	H-donor	2.83
	N	CYS	349	H-donor	3.19
	O	GLY	351	H-acceptor	3.29
	O	HIS	203	H-acceptor	3.1
8	N	CYS	349	H-donor	3.29
	O	HIS	203	H-acceptor	3.04
	O	HIS	203	H-acceptor	2.96
	O	GLN	350	H-acceptor	3.09
	O	HIS	203	ionic	3.04
	O	HIS	203	ionic	2.96
9	N	GLU	206	H-donor	3.13
	N	VAL	205	H-donor	2.84
	N	GLU	206	H-donor	2.86
	O	HIS	203	H-acceptor	3.01
	O	HIS	203	H-acceptor	2.84
	O	HIS	203	ionic	3.01
	O	HIS	203	ionic	2.84
	N	GLU	206	ionic	3.13
	N	GLU	206	ionic	2.86
10	O	HIS	203	H-acceptor	2.98
	N	GLU	206	ionic	2.86
	N	GLU	206	ionic	3.58
	N	GLU	206	ionic	3.29
11	N	HIS	186	H-donor	2.91
12	N	GLN	350	H-donor	3.06
	O	HIS	203	H-acceptor	2.73
	O	HIS	203	ionic	2.73
13	O	HIS	203	H-acceptor	2.82
	O	GLY	351	H-acceptor	3.15
	O	HIS	203	ionic	2.82
14	N	GLN	350	H-donor	3.18
	O	GLY	351	H-acceptor	3.09
	O	HIS	203	ionic	2.96
	N	HIS	186	cation-pi	4.55
15	N	GLN	350	H-donor	2.92
	O	HIS	203	H-acceptor	2.83
	O	HIS	203	ionic	2.83
	O	HIS	203	ionic	3.41
16	N	GLU	206	H-donor	2.82
	N	GLU	206	H-donor	2.96
	O	HIS	203	H-acceptor	2.85
	O	HIS	203	ionic	2.85
	N	GLU	206	ionic	2.82
	N	GLU	206	ionic	2.96
17	N	GLU	206	H-donor	2.85
	N	GLU	206	H-donor	3.08
	O	HIS	203	H-acceptor	2.84
	O	HIS	203	H-acceptor	3.29
	O	HIS	203	ionic	2.84

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	O	HIS	203	ionic	3.29
	N	GLU	206	ionic	2.85
	N	GLU	206	ionic	3.08
	N	GLU	206	ionic	3.6
18	N	GLU	206	H-donor	2.84
	O	HIS	203	H-acceptor	2.86
	O	HIS	203	ionic	2.86
	O	HIS	203	ionic	3.5
	N	GLU	206	ionic	3.2
	N	GLU	206	ionic	2.84
19	N	GLY	351	H-donor	3.06
	O	HIS	203	H-acceptor	3
	O	HIS	203	ionic	3
	N	ASP	352	ionic	3.74
20	N	SER	348	H-donor	2.88
	O	HIS	203	H-acceptor	2.88
	O	HIS	203	ionic	2.88
	O	HIS	203	ionic	3.17
	6-ring	GLY	351	pi-H	4.58
21	N	SER	348	H-donor	3.12
	O	HIS	203	ionic	3.84
22	N	CYS	349	H-donor	2.92
	N	GLY	351	H-donor	3.08
	O	HIS	203	H-acceptor	2.84
	O	HIS	203	H-acceptor	3.31
	O	GLN	350	H-acceptor	3.08
	O	HIS	203	ionic	2.84
	O	HIS	203	ionic	3.31
23	N	GLU	206	H-donor	2.87
	N	GLU	206	H-donor	2.87
	O	HIS	203	H-acceptor	3.08
	O	HIS	203	H-acceptor	2.99
	O	HIS	203	ionic	3.08
	O	HIS	203	ionic	2.99
	N	GLU	206	ionic	2.87
	N	GLU	206	ionic	2.87
24	N	SER	348	H-donor	2.93
	O	HIS	203	H-acceptor	2.9
	O	HIS	203	ionic	3.24
	O	HIS	203	ionic	2.9
25	N	SER	348	H-donor	2.86
	O	HIS	203	H-acceptor	3.02
	O	HIS	203	H-acceptor	3.07
	O	HIS	203	ionic	3.02
	O	HIS	203	ionic	3.07
	N	GLU	206	H-donor	3.26
	O	HIS	203	H-acceptor	2.81
	O	HIS	203	ionic	2.81
	N	GLU	206	ionic	3.46
	N	GLU	206	ionic	3.26
	N	GLU	206	ionic	3.52
27	N	VAL	187	H-donor	3.19
	O	GLY	351	H-acceptor	3.58
	O	HIS	203	H-acceptor	2.89
	O	HIS	203	ionic	2.89
	O	HIS	203	ionic	3.15

Table S24. Interaction report of each conformer of Sivelestat. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	O	HIS	203	H-acceptor	2.93
2	N	CYS	349	H-donor	3
	O	HIS	203	ionic	3.26
	6-ring	GLY	351	pi-H	4.61
3	O	HIS	203	ionic	3.84
4	N	CYS	381	H-donor	3.43

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
	O	LYS	302	H-acceptor	3.26
	O	LYS	302	H-acceptor	2.94
	O	LYS	302	ionic	2.94
	6-ring	GLY	303	pi-H	3.86
5	O	HIS	203	ionic	3.62
	6-ring	HIS	203	pi-cation	4.12
6	O	HIS	203	H-acceptor	2.91
	O	HIS	203	H-acceptor	3.01
	O	HIS	203	H-acceptor	3.36
	O	HIS	203	ionic	3.01
	O	HIS	203	ionic	3.36
7	O	CYS	381	H-donor	3.74
	O	GLY	351	H-acceptor	3.12
	O	LYS	383	H-acceptor	3.18
	O	CYS	381	H-acceptor	3.01
	O	LYS	383	H-acceptor	3.06
	O	LYS	383	ionic	3.18
	O	LYS	383	ionic	3.06
8	O	CYS	381	H-donor	3.89
	O	LYS	383	H-acceptor	3.16
	O	CYS	381	H-acceptor	3.35
	O	LYS	302	H-acceptor	2.86
	O	LYS	302	ionic	2.86
9	O	CYS	381	H-donor	3.74
	O	LYS	383	H-acceptor	3.2
	O	CYS	381	H-acceptor	3.01
	O	LYS	383	H-acceptor	3.02
	O	LYS	383	ionic	3.2
	O	LYS	383	ionic	3.02
10	O	HIS	203	H-acceptor	3.04
	O	HIS	203	ionic	3.97
	O	HIS	203	ionic	3.3
11	O	HIS	203	H-acceptor	2.89
	O	HIS	203	H-acceptor	2.96
	O	HIS	203	ionic	3.94
	O	HIS	203	ionic	2.96
12	O	GLY	351	H-acceptor	2.93
	O	HIS	203	H-acceptor	2.87
	O	HIS	203	ionic	3.43
	O	HIS	203	ionic	2.87
13	O	GLY	351	H-acceptor	3.19
	O	GLN	350	H-acceptor	3.05
	O	LYS	302	H-acceptor	2.99
	O	GLY	303	H-acceptor	3.09
	O	LYS	302	ionic	2.99
	O	LYS	302	ionic	3.94
14	O	HIS	203	H-acceptor	3.1
	O	HIS	203	H-acceptor	2.87
	O	HIS	203	ionic	2.87
15	O	HIS	203	H-acceptor	3.07
	O	HIS	203	H-acceptor	3.08
	O	HIS	203	ionic	2.87
	O	HIS	203	ionic	3.08
16	O	HIS	203	H-acceptor	2.9
	O	HIS	203	ionic	2.9
	O	HIS	203	ionic	3.3
17	O	GLY	351	H-acceptor	2.92
	O	HIS	203	H-acceptor	2.9
	O	HIS	203	ionic	2.9
	O	HIS	203	ionic	3.88
18	O	LYS	383	H-acceptor	3.14
	O	LYS	302	H-acceptor	2.95
	O	LYS	302	ionic	3.41
	O	LYS	302	ionic	2.95
19	O	HIS	203	H-acceptor	2.75
	O	HIS	203	ionic	3.81

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
20	O	GLY	351	H-acceptor	2.91
	O	HIS	203	H-acceptor	2.97
	O	HIS	203	ionic	2.97
	O	HIS	203	ionic	2.99
21	O	HIS	203	H-acceptor	2.93
	O	HIS	203	ionic	2.93
22	N	CYS	349	H-donor	3.3
	O	GLY	351	H-acceptor	2.96
	O	HIS	203	H-acceptor	2.89
	O	HIS	203	H-acceptor	3.44
	O	HIS	203	ionic	2.89
	O	HIS	203	ionic	3.44
23	6-ring	HIS	203	pi-cation	4.37
24	O	HIS	203	H-acceptor	2.95
25	O	HIS	203	H-acceptor	3.21
	O	HIS	203	H-acceptor	3.01
	O	HIS	203	ionic	3.21
	O	HIS	203	ionic	3.01
26	O	GLY	351	H-acceptor	3.05
	O	GLN	350	H-acceptor	3.31
	O	LYS	302	ionic	3.26
	O	LYS	302	ionic	3.1

Table S25. Interaction report of each conformer of NCGC00385043. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	O	VAL	187	H-donor	2.9
	O	CYS	349	H-donor	2.96
	O	HIS	203	H-acceptor	3.21
2	O	GLY	351	H-acceptor	3.34
3	O	SER	348	H-donor	2.99
	O	HIS	203	H-acceptor	3.14
4	O	VAL	187	H-donor	2.94
	O	HIS	203	H-acceptor	2.94
5	O	GLU	206	H-donor	3.16
	O	HIS	203	H-acceptor	3.38
6	O	SER	348	H-donor	2.97
	O	GLY	378	H-donor	2.82
7	O	CYS	349	H-donor	3.04
	O	HIS	203	H-acceptor	3.23
8	O	SER	348	H-donor	3.01
	O	GLY	351	H-acceptor	3.04
9	O	GLY	378	H-donor	3.13
	O	GLY	378	H-donor	2.91
	O	SER	348	H-donor	2.96
10	O	HIS	203	H-acceptor	3
11	O	SER	348	H-donor	3.05
12	O	SER	348	H-donor	2.98
13	O	CYS	349	H-donor	2.96
14	O	GLY	351	H-acceptor	3.27
15	O	GLY	351	H-donor	3.13
16	O	SER	348	H-donor	2.8
	O	HIS	203	H-acceptor	3.03
	O	GLY	351	H-acceptor	3.18
17	O	HIS	186	H-donor	2.79
18	O	SER	348	H-donor	2.91
	O	GLY	378	H-donor	3.04
19	O	GLY	351	H-donor	3.06
	O	GLN	350	H-donor	3.13
	O	CYS	349	H-donor	2.96
20	O	SER	379	H-donor	3
	O	HIS	203	H-acceptor	2.95
21	O	ASN	249	H-acceptor	3.04
22	O	GLY	351	H-acceptor	3.3
	O	HIS	203	H-acceptor	3.1

Table S26. Interaction report of each conformer of Bromhexine. Number of conformer, Atom of compound, Amino acid in TMPRSS2, Type of interaction and Distance in angstroms.

Conformer	Ligand	Residues in TMPRSS2		Interaction	Distance
1	N	SER	348	H-donor	2.98
	6-ring	GLY	351	pi-H	4.15
2	N	VAL	187	H-donor	3.42
3	6-ring	GLY	351	pi-H	4.05
4	N	SER	348	H-donor	3.28
	6-ring	GLY	351	pi-H	4.06
5	N	HIS	203	H-acceptor	3.04
6	N	GLY	378	H-donor	3.12
	C	TRP	377	H-pi	4.41
7	N	CYS	349	H-donor	3.17
8	N	VAL	187	H-donor	2.92
	6-ring	GLY	351	pi-H	4.63
9	N	CYS	349	H-donor	2.99
10	BR	SER	376	H-donor	3.6
11	N	CYS	349	H-donor	2.87
12	6-ring	HIS	203	pi-cation	4.73
13	BR	VAL	187	H-donor	3.67

Table S27. Toxicity – PreADMET | Prediction of ADME/Tox of compounds T1–T10.

T1.-		**T2.-**	
algae_at	0.0160146	algae_at	0.00318792
Ames_test	mutagen	Ames_test	mutagen
Carcino_Mouse	negative	Carcino_Mouse	negative
Carcino_Rat	negative	Carcino_Rat	negative
daphnia_at	0.0368447	daphnia_at	0.00243684
hERG_inhibition	medium_risk	hERG_inhibition	low_risk
medaka_at	0.00317449	medaka_at	2.3298e-005
minnow_at	0.0141893	minnow_at	0.000274219
TA100_10RLI	positive	TA100_10RLI	positive
TA100_NA	negative	TA100_NA	negative
TA1535_10RLI	negative	TA1535_10RLI	negative
TA1535_NA	negative	TA1535_NA	negative
T3.-		**T4.-**	
algae_at	0.00162258	algae_at	0.013343
Ames_test	mutagen	Ames_test	mutagen
Carcino_Mouse	negative	Carcino_Mouse	negative
Carcino_Rat	positive	Carcino_Rat	positive
daphnia_at	0.00107575	daphnia_at	0.0123293
hERG_inhibition	medium_risk	hERG_inhibition	high_risk
medaka_at	6.44964e-006	medaka_at	0.000530206
minnow_at	2.22289e-005	minnow_at	0.00376132
TA100_10RLI	negative	TA100_10RLI	positive
TA100_NA	negative	TA100_NA	positive
TA1535_10RLI	negative	TA1535_10RLI	positive
TA1535_NA	negative	TA1535_NA	negative
T5.-		**T6.-**	
algae_at	0.00253114	algae_at	0.000292094
Ames_test	mutagen	Ames_test	non-mutagen
Carcino_Mouse	negative	Carcino_Mouse	positive
Carcino_Rat	positive	Carcino_Rat	negative
daphnia_at	0.000552924	daphnia_at	0.000115612
hERG_inhibition	medium_risk	hERG_inhibition	medium_risk
medaka_at	1.77373e-006	medaka_at	7.43255e-008
minnow_at	1.69902e-005	minnow_at	6.61832e-007
TA100_10RLI	positive	TA100_10RLI	negative
TA100_NA	negative	TA100_NA	negative
TA1535_10RLI	positive	TA1535_10RLI	negative
TA1535_NA	negative	TA1535_NA	negative
T7.-		**T8.-**	
algae_at	0.00948831	algae_at	0.00163506
Ames_test	mutagen	Ames_test	mutagen
Carcino_Mouse	negative	Carcino_Mouse	negative
Carcino_Rat	positive	Carcino_Rat	negative
daphnia_at	0.010758	daphnia_at	0.00033623
hERG_inhibition	medium_risk	hERG_inhibition	low_risk
medaka_at	0.000413187	medaka_at	9.18187e-007

minnow_at	0.00290509
TA100_10RLI	positive
TA100_NA	positive
TA1535_10RLI	negative
TA1535_NA	negative

minnow_at	9.75353e-006
TA100_10RLI	negative
TA100_NA	negative
TA1535_10RLI	negative
TA1535_NA	negative

T9.-

algae_at	0.00320645
Ames_test	mutagen
Carcino_Mouse	negative
Carcino_Rat	positive
daphnia_at	0.00278997
hERG_inhibition	medium_risk
medaka_at	2.82397e-005
minnow_at	0.000182003
TA100_10RLI	negative
TA100_NA	negative
TA1535_10RLI	positive
TA1535_NA	negative

T10.-

algae_at	0.00633173
Ames_test	mutagen
Carcino_Mouse	negative
Carcino_Rat	positive
daphnia_at	0.00731401
hERG_inhibition	medium_risk
medaka_at	0.000199172
minnow_at	0.00157733
TA100_10RLI	positive
TA100_NA	positive
TA1535_10RLI	negative
TA1535_NA	negative

Table S28. ADME - PreADMET | Prediction of ADME/Tox of compounds T1–T10.

T1.-

BBB	0.0792184
Buffer_solubility_mg_L	0.014869
Caco2	5.08791
CYP_2C19_inhibition	Non
CYP_2C9_inhibition	Non
CYP_2D6_inhibition	Non
CYP_2D6_substrate	Non
CYP_3A4_inhibition	Non
CYP_3A4_substrate	Substrate
HIA	94.733424
MDCK	48.9391
Pgp_inhibition	Non
Plasma_Protein_Binding	87.876841
Pure_water_solubility_mg_L	0.833992
Skin_Permeability	-2.29583
SKlogD_value	4.417320
SKlogP_value	4.417320
SKlogS_buffer	-7.509510
SKlogS_pure	-5.760630

T2.-

BBB	0.216377
Buffer_solubility_mg_L	0.0018581
Caco2	35.6274
CYP_2C19_inhibition	Non
CYP_2C9_inhibition	Inhibitor
CYP_2D6_inhibition	Non
CYP_2D6_substrate	Non
CYP_3A4_inhibition	Non
CYP_3A4_substrate	Substrate
HIA	97.710828
MDCK	0.0541355
Pgp_inhibition	Inhibitor
Plasma_Protein_Binding	98.183640
Pure_water_solubility_mg_L	0.00112507
Skin_Permeability	-2.28891*
SKlogD_value	5.926930
SKlogP_value	5.926930
SKlogS_buffer	-8.463010
SKlogS_pure	-8.680900

T3.-

BBB	0.0834699
Buffer_solubility_mg_L	10.9611**
Caco2	30.3638
CYP_2C19_inhibition	Non
CYP_2C9_inhibition	Inhibitor
CYP_2D6_inhibition	Non
CYP_2D6_substrate	Non
CYP_3A4_inhibition	Non
CYP_3A4_substrate	Weakly
HIA	94.801241
MDCK	0.0735266
Pgp_inhibition	Inhibitor
Plasma_Protein_Binding	91.538989
Pure_water_solubility_mg_L	0.0137368
Skin_Permeability	-3.32269
SKlogD_value	6.086980
SKlogP_value	6.086980
SKlogS_buffer	-4.697890**
SKlogS_pure	-7.599860

T4.-

BBB	0.0532063
Buffer_solubility_mg_L	7.61522**
Caco2	0.701092
CYP_2C19_inhibition	Non
CYP_2C9_inhibition	Inhibitor
CYP_2D6_inhibition	Non
CYP_2D6_substrate	Non
CYP_3A4_inhibition	Non
CYP_3A4_substrate	Weakly
HIA	86.813998
MDCK	0.35926
Pgp_inhibition	Inhibitor
Plasma_Protein_Binding	99.658773
Pure_water_solubility_mg_L	0.0631993
Skin_Permeability	-3.74129
SKlogD_value	4.494410
SKlogP_value	4.494410
SKlogS_buffer	-4.825510**
SKlogS_pure	-6.906480

T5.-

BBB	0.140888
Buffer_solubility_mg_L	2.46049**
Caco2	13.9488
CYP_2C19_inhibition	Non
CYP_2C9_inhibition	Inhibitor
CYP_2D6_inhibition	Non
CYP_2D6_substrate	Non
CYP_3A4_inhibition	Non
CYP_3A4_substrate	Substrate

T6.-

BBB	0.128735
Buffer_solubility_mg_L	1.64836e-006
Caco2	23.2206
CYP_2C19_inhibition	Non
CYP_2C9_inhibition	Inhibitor
CYP_2D6_inhibition	Non
CYP_2D6_substrate	Non
CYP_3A4_inhibition	Inhibitor
CYP_3A4_substrate	Substrate

HIA	99.252848
MDCK	0.0183324*
Pgp_inhibition	Inhibitor
Plasma_Protein_Binding	95.313410
Pure_water_solubility_mg_L	0.00147252
Skin_Permeability	-2.64495
SKlogD_value	5.322230
SKlogP_value	5.322230
SKlogS_buffer	-5.369000**
SKlogS_pure	-8.591960

HIA	97.742949
MDCK	0.0494344*
Pgp_inhibition	Inhibitor
Plasma_Protein_Binding	90.020365
Pure_water_solubility_mg_L	3.23551e-006
Skin_Permeability	-2.11357*
SKlogD_value	9.257430
SKlogP_value	9.257430
SKlogS_buffer	-11.568820
SKlogS_pure	-11.275930

T7.-	
BBB	0.0559919
Buffer_solubility_mg_L	120.369**
Caco2	0.780057
CYP_2C19_inhibition	Non
CYP_2C9_inhibition	Inhibitor
CYP_2D6_inhibition	Non
CYP_2D6_substrate	Non
CYP_3A4_inhibition	Non
CYP_3A4_substrate	Weakly
HIA	88.054458
MDCK	0.137772
Pgp_inhibition	Inhibitor
Plasma_Protein_Binding	99.860851
Pure_water_solubility_mg_L	0.0704962
Skin_Permeability	-3.65081
SKlogD_value	4.626720
SKlogP_value	4.626720
SKlogS_buffer	-3.638470**
SKlogS_pure	-6.870820

T8.-	
BBB	0.0925209
Buffer_solubility_mg_L	268.431
Caco2	27.3493
CYP_2C19_inhibition	Non
CYP_2C9_inhibition	Non
CYP_2D6_inhibition	Non
CYP_2D6_substrate	Non
CYP_3A4_inhibition	Inhibitor
CYP_3A4_substrate	Substrate
HIA	98.564667
MDCK	0.042602*
Pgp_inhibition	Inhibitor
Plasma_Protein_Binding	93.796183
Pure_water_solubility_mg_L	0.00204566
Skin_Permeability	-2.86884
SKlogD_value	3.993980
SKlogP_value	3.993980
SKlogS_buffer	-3.397780
SKlogS_pure	-8.515780

T9.-	
BBB	0.339968
Buffer_solubility_mg_L	175.429**
Caco2	29.644
CYP_2C19_inhibition	Non
CYP_2C9_inhibition	Inhibitor
CYP_2D6_inhibition	Non
CYP_2D6_substrate	Non
CYP_3A4_inhibition	Non
CYP_3A4_substrate	Substrate
HIA	98.397830
MDCK	0.0704082
Pgp_inhibition	Inhibitor
Plasma_Protein_Binding	92.817438
Pure_water_solubility_mg_L	0.00972436
Skin_Permeability	-2.74744
SKlogD_value	6.444920
SKlogP_value	6.444920
SKlogS_buffer	-3.449310**
SKlogS_pure	-7.705550

T10.-	
BBB	0.0604172
Buffer_solubility_mg_L	59.1204**
Caco2	1.07307
CYP_2C19_inhibition	Non
CYP_2C9_inhibition	Inhibitor
CYP_2D6_inhibition	Non
CYP_2D6_substrate	Non
CYP_3A4_inhibition	Non
CYP_3A4_substrate	Substrate
HIA	89.178280
MDCK	0.0500051
Pgp_inhibition	Inhibitor
Plasma_Protein_Binding	98.979883
Pure_water_solubility_mg_L	0.0432352
Skin_Permeability	-3.46339
SKlogD_value	4.998060
SKlogP_value	4.998060
SKlogS_buffer	-3.958730**
SKlogS_pure	-7.094630

Table S29. Properties predicted by PhysChem - ACD/Labs of compounds T1–T10.

T1.-	
Density:	1.1±0.1 g/cm3
Boiling Point:	
Vapour Pressure:	
Enthalpy of Vaporization:	
Flash Point:	
Index of Refraction:	1.561
Molar Refractivity:	139.8±0.5 cm3
#H bond acceptors:	9
#H bond donors:	2
#Freely Rotating Bonds:	14
#Rule of 5 Violations:	1
ACD/LogP:	6.72
ACD/LogD (pH 5.5):	4.39
ACD/BCF (pH 5.5):	1221.08
ACD/KOC (pH 5.5):	5338.00
ACD/LogD (pH 7.4):	4.47

T2.-	
Density:	1.3±0.1 g/cm3
Boiling Point:	
Vapour Pressure:	
Enthalpy of Vaporization:	
Flash Point:	
Index of Refraction:	1.669
Molar Refractivity:	151.6±0.5 cm3
#H bond acceptors:	9
#H bond donors:	1
#Freely Rotating Bonds:	9
#Rule of 5 Violations:	2
ACD/LogP:	6.41
ACD/LogD (pH 5.5):	4.76
ACD/BCF (pH 5.5):	2438.11
ACD/KOC (pH 5.5):	9247.98
ACD/LogD (pH 7.4):	4.76

ACD/BCF (pH 7.4):	1475.90
ACD/KOC (pH 7.4):	6451.96
Polar Surface Area:	99 Å2
Polarizability:	55.4±0.5 10-24cm3
Surface Tension:	41.6±7.0 dyne/cm
Molar Volume:	431.6±7.0 cm3

ACD/BCF (pH 7.4):	2437.13
ACD/KOC (pH 7.4):	9244.25
Polar Surface Area:	133 Å2
Polarizability:	60.1±0.5 10-24cm3
Surface Tension:	53.3±7.0 dyne/cm
Molar Volume:	406.1±7.0 cm3

T3.-

Density:	1.5±0.1 g/cm3
Boiling Point:	
Vapour Pressure:	
Enthalpy of Vaporization:	
Flash Point:	
Index of Refraction:	1.742
Molar Refractivity:	146.8±0.5 cm3
#H bond acceptors:	9
#H bond donors:	1
#Freely Rotating Bonds:	12
#Rule of 5 Violations:	2
ACD/LogP:	6.22
ACD/LogD (pH 5.5):	4.76
ACD/BCF (pH 5.5):	2431.27
ACD/KOC (pH 5.5):	9159.74
ACD/LogD (pH 7.4):	4.28
ACD/BCF (pH 7.4):	806.65
ACD/KOC (pH 7.4):	3039.03
Polar Surface Area:	219 Å2
Polarizability:	58.2±0.5 10-24cm3
Surface Tension:	63.2±7.0 dyne/cm
Molar Volume:	363.1±7.0 cm3

T4.-

Density:	1.5±0.1 g/cm3
Boiling Point:	
Vapour Pressure:	
Enthalpy of Vaporization:	
Flash Point:	
Index of Refraction:	1.746
Molar Refractivity:	135.8±0.5 cm3
#H bond acceptors:	11
#H bond donors:	2
#Freely Rotating Bonds:	9
#Rule of 5 Violations:	2
ACD/LogP:	3.81
ACD/LogD (pH 5.5):	2.97
ACD/BCF (pH 5.5):	106.91
ACD/KOC (pH 5.5):	981.69
ACD/LogD (pH 7.4):	2.63
ACD/BCF (pH 7.4):	47.98
ACD/KOC (pH 7.4):	440.55
Polar Surface Area:	201 Å2
Polarizability:	53.8±0.5 10-24cm3
Surface Tension:	69.4±7.0 dyne/cm
Molar Volume:	334.6±7.0 cm3

T5.-

Density:	1.7±0.1 g/cm3
Boiling Point:	
Vapour Pressure:	
Enthalpy of Vaporization:	
Flash Point:	
Index of Refraction:	1.779
Molar Refractivity:	138.8±0.4 cm3
#H bond acceptors:	8
#H bond donors:	1
#Freely Rotating Bonds:	7
#Rule of 5 Violations:	2
ACD/LogP:	5.33
ACD/LogD (pH 5.5):	4.30
ACD/BCF (pH 5.5):	1079.61
ACD/KOC (pH 5.5):	5152.38
ACD/LogD (pH 7.4):	4.13
ACD/BCF (pH 7.4):	742.89
ACD/KOC (pH 7.4):	3545.40
Polar Surface Area:	194 Å2
Polarizability:	55.0±0.5 10-24cm3
Surface Tension:	96.1±5.0 dyne/cm
Molar Volume:	331.2±5.0 cm3

T6.-

Density:	1.3±0.1 g/cm3
Boiling Point:	748.0±70.0 °C at 760 mmHg
Vapour Pressure:	0.0±2.5 mmHg at 25°C
Enthalpy of Vaporization:	109.0±3.0 kJ/mol
Flash Point:	406.2±35.7 °C
Index of Refraction:	1.666
Molar Refractivity:	173.9±0.5 cm3
#H bond acceptors:	6
#H bond donors:	1
#Freely Rotating Bonds:	8
#Rule of 5 Violations:	2
ACD/LogP:	7.24
ACD/LogD (pH 5.5):	7.00
ACD/BCF (pH 5.5):	121544.13
ACD/KOC (pH 5.5):	150499.83
ACD/LogD (pH 7.4):	6.60
ACD/BCF (pH 7.4):	48643.26
ACD/KOC (pH 7.4):	60231.64
Polar Surface Area:	111 Å2
Polarizability:	69.0±0.5 10-24cm3
Surface Tension:	49.4±7.0 dyne/cm
Molar Volume:	467.8±7.0 cm3

T7.-

Density:	1.5±0.1 g/cm3
Boiling Point:	
Vapour Pressure:	
Enthalpy of Vaporization:	
Flash Point:	
Index of Refraction:	1.734
Molar Refractivity:	140.2±0.5 cm3
#H bond acceptors:	11
#H bond donors:	2
#Freely Rotating Bonds:	9
#Rule of 5 Violations:	2
ACD/LogP:	4.27
ACD/LogD (pH 5.5):	3.08
ACD/BCF (pH 5.5):	127.88
ACD/KOC (pH 5.5):	1115.89
ACD/LogD (pH 7.4):	2.73
ACD/BCF (pH 7.4):	57.49

T8.-

Density:	1.5±0.1 g/cm3
Boiling Point:	
Vapour Pressure:	
Enthalpy of Vaporization:	
Flash Point:	
Index of Refraction:	1.719
Molar Refractivity:	179.4±0.4 cm3
#H bond acceptors:	10
#H bond donors:	2
#Freely Rotating Bonds:	13
#Rule of 5 Violations:	2
ACD/LogP:	1.92
ACD/LogD (pH 5.5):	2.15
ACD/BCF (pH 5.5):	25.27
ACD/KOC (pH 5.5):	351.20
ACD/LogD (pH 7.4):	2.15
ACD/BCF (pH 7.4):	25.27

ACD/KOC (pH 7.4):	501.71
Polar Surface Area:	201 Å2
Polarizability:	55.6±0.5 10-24cm3
Surface Tension:	66.0±7.0 dyne/cm
Molar Volume:	349.8±7.0 cm3

ACD/KOC (pH 7.4):	351.20
Polar Surface Area:	232 Å2
Polarizability:	71.1±0.5 10-24cm3
Surface Tension:	83.2±5.0 dyne/cm
Molar Volume:	454.5±5.0 cm3

T9.-

Density:	1.3±0.1 g/cm3
Boiling Point:	
Vapour Pressure:	
Enthalpy of Vaporization:	
Flash Point:	
Index of Refraction:	1.665
Molar Refractivity:	140.9±0.5 cm3
#H bond acceptors:	7
#H bond donors:	1
#Freely Rotating Bonds:	9
#Rule of 5 Violations:	1
ACD/LogP:	6.53
ACD/LogD (pH 5.5):	5.66
ACD/BCF (pH 5.5):	11774.76
ACD/KOC (pH 5.5):	28410.28
ACD/LogD (pH 7.4):	5.31
ACD/BCF (pH 7.4):	5195.31
ACD/KOC (pH 7.4):	12535.32
Polar Surface Area:	135 Å2
Polarizability:	55.8±0.5 10-24cm3
Surface Tension:	49.7±7.0 dyne/cm
Molar Volume:	379.5±7.0 cm3

T10.-

Density:	1.5±0.1 g/cm3
Boiling Point:	
Vapour Pressure:	
Enthalpy of Vaporization:	
Flash Point:	
Index of Refraction:	1.722
Molar Refractivity:	144.8±0.5 cm3
#H bond acceptors:	11
#H bond donors:	2
#Freely Rotating Bonds:	10
#Rule of 5 Violations:	2
ACD/LogP:	4.80
ACD/LogD (pH 5.5):	3.46
ACD/BCF (pH 5.5):	249.42
ACD/KOC (pH 5.5):	1800.23
ACD/LogD (pH 7.4):	3.12
ACD/BCF (pH 7.4):	113.07
ACD/KOC (pH 7.4):	816.09
Polar Surface Area:	201 Å2
Polarizability:	57.4±0.5 10-24cm3
Surface Tension:	64.2±7.0 dyne/cm
Molar Volume:	365.8±7.0 cm3