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.

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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, NCCG00386945, NCCG00386477, 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, NCCG00386945, NCCG00386477, 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.

|    | PubChem CID | Name and Structure |
|----|-------------|--------------------|
| T1 | 2848720, 5483027 | ![T1](image) |
| T2 | 5650548, 5771448 | ![T2](image) |
| T3 | 2941860, 7534613 | ![T3](image) |
| T4 | 2194374, 7607092 | ![T4](image) |
| T5 | 1552161, 5526397 | ![T5](image) |
| T6 | 2851138, 5540972 | ![T6](image) |
| T7 | 2193836, 7569492 | ![T7](image) |
| T8 | 5722665, 5531741 | ![T8](image) |
**T9.** 1314888, 7507920.

25154714, Daclatasvir.

2536, Camostat.

10323598, NCGC00386477.

9846928, NCGC00386945.

9912771, Darexaban.

11641515, Letaxaban.

**T10.** 2193905, 7573429.

54767916, Ombitasvir.

10280735, Edoxaban.

5496659, Otamixaban.

3447, Gabexate.

92722, Argatroban.
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 ΔGbinding and SD | PreADMET Ames test and LD₅₀ |
|-------------|------------------|---------------------------------------------------------------------------------------------|----------------------|-----------------------------|----------------------------|
| T1. 2848720 | CCN(CC)Cl=CC=C(C=C1)C =NNC(=O)COC(=O)NN=C C2=CC=C(C=C2)N(CC)CC | His296, Asn336, Ser436, Cys437, Gly439, Gly462, Gly464, Cys465 | 29 | -8.19 ± 0.83 | Mutagen |
| T2. 5650548 | CC1=C(C=C(C=C1)OCOC2= NN=C(N2C3=CC=CC=C3)SCC(=O)NN=CC4=CC5=CC =CC=CSC4=O)C | Val280, His296, Cys297, Glu299, Ser436, Gly439 | 27 | -8.10 ± 0.90 | Mutagen |
| 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 |
| T4. 2194374 | CN1C(=NN=C1SCC(=O)NC 2=NC(=CS2)C3=CC=C3 C)CN(=O)C4=CC(=CC=C4)C | Val280, His296, Glu299, Leu302, Asn336, Ser436, Gly439, Gly462, Glu464, Cys465 | 30 | -7.99 ± 0.59 | Mutagen |
| T5. 1552161 | C1=CC(=CC(=C1)N+[=O])=O- ](CC2=CC=C(C(S2)NC(=O)CN 3C(=O)C(=CC4=CC=C(C=C 4)Br)SC3=S | Val280, His296, Cys297, Asn336, Ser436, Gly438, Gly439, Trp461, Gly462, Cys465 | 28 | -7.99 ± 0.56 | Mutagen |
| T6. 2851138 | CC1=CC=C(C=C1)S(=O) =O \NC2=CC=C(C=C2)C3=CSC (=N3)N4C(CC(=N4)C5=CC =C1=CC=C(C=C1)SC | Val280, His296, Glu299, Ser436, Gly439, Gly464 | 27 | -7.99 ± 0.81 | Non mutagen |
| PubChem CID | Canonical SMILES | Interaction with residues in TMPRSS2 (Table S2 - S26), in bold it is of greater interaction. | Number of conformers | Average of ΔG-binding and SD | PreADMET Ames test and LD₅₀ |
|-------------|------------------|------------------------------------------------------------------------------------------------|----------------------|-----------------------------|---------------------------|
| T7. 2193836 | C(C=C5)F)C6=CC=CC(=C(C6)C(C)C) | Val280, His296, Glu299, Asn336, Lys390, Gln438, Gly439, Gly462 | 28 | -7.97 ± 0.80 | Negative - Negative - Negative 1000 mg/kg |
| T8. 5722665 | COCl=CC=CC=CC=C(=O)N(C(=S)S2)CCC(=O)NC(C4=CC=CC=C4)=CC=CC=C4 | Val280, His296, Cys297, Glu299, Leu302, Lys390, Cys437, Gln438, Gly439, Trp461, Gly462, Cys465, Lys467 | 30 | -7.96 ± 0.76 | Negative - Negative - Negative - Negative - Negative 350 mg/kg |
| T9. 1314888 | CC1=C(N=C(S1)NC(=O)CSC2=NN=C(N2C)CNC3(=O)C4=CC=CC=C4)=CC=CC=C4 | Val280, His296, Cys297, Glu299, Asn336, Cys437, Gln438, Gly464, Cys465 | 28 | -7.95 ± 0.81 | Mutagen - Negative - Negative - Positive - Negative - Negative 1000 mg/kg |
| T10. 2193905 | CC1=NC(=NC(=NC(=C1)SCCC=C)CCC=C(C=C1)C)=CC=C1CCCC1C2=NN=C(N2C)CC3=C(C=C3)C(C4=CC=CC=C4)=CC=CC4 | His279, Val280, His296, Glu299, Gln438, Gly438, Cys465, Lys467 | 29 | -7.94 ± 0.83 | Mutagen - Positive - Positive - Negative - Negative - Negative 1000 mg/kg |
| Daclatasvir 25154714 | CC(C)(C(=O)N1CCCC1C2=NC=CN2)=CC=C(C=C1)C(C4=CC=CC=C4)=CC=CC=C4 | His286, Glu299, Gly391, Cys437, Gln438, Gly439, Cys465, Lys467 | 25 | -5.87 ± 0.39 | |
| Ombitasvir 54767916 | CC(C)(C(=O)N1CCCC1C2=NC=CN2)=CC=C(C=C1)C(C4=CC=CC=C4)=CC=CC=C4 | His286, Glu299, Asn336, Gly303, Gln438, Ser463, Cys465, Lys467, Arg470 | 30 | -5.61 ± 0.62 | |
| Camostat 2536 | CN(C)(C(=O)OC(=O)OC)CC1=C(C=C1)OC(=O)C2=CC=C(C=C2)N=C(N)N | His286, Glu299, Gly439, Ser447 | 24 | -5.27 ± 0.54 | |
| Edoxaban 10280735 | CN1CC=C(C=C1)NC(=NC(=N)N)C(N)=NC=NCC=CCN3C=NCC(=O)CC(=O)NC(=NC(=N)N)CCC(=O)NC3 | Val280, His296, Glu299, Gly462, Ser463, Cys465, Lys467 | 26 | -5.24 ± 0.64 | |
| NCGC0038647 7 10323598 | C1=C(C=C(=C=C1)C2=NN=N=C(O2)C)C3=CC=C(C=C3)C(=N)N=NC(=N)C | Val280, His296, Glu299, Gly462, Ser463, Cys465, Lys467 | 25 | -5.21 ± 0.52 | |
| Nafamostat 4413 | C1=CC=N=C(=CN2)C=C(N=C2)C(C=C3)C(C=C3)C(=N)N=NC(=N)C | Val280, His296, Glu299, Ser447, Cys465, Lys467 | 23 | -5.09 ± 0.45 | |
| NCGC0038694 5 9846928 | C2=C(C=C(C=C2)C(=O)OC)NC3 | His286, Glu299, Ser447, Cys437, Gly439, Cys465 | 26 | -5.03 ± 0.50 | |
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      |
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).](https://biointerfaceresearch.com/)

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).
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        | -7.8326005 |
| 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 ΔGbinding | -8.19361135 |
|          | SD         | 0.83814171 |

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).
| Compound | Conformer | ΔGbinding  |
|----------|-----------|------------|
| T2       | 12        | -8.245903  |
| T2       | 13        | -8.066647  |
| T2       | 14        | -8.0059614 |
| T2       | 15        | -7.7486528 |
| 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        | -7.011897  |
| T2       | 25        | -6.9634185 |
| T2       | 26        | -6.6150498 |
| T2       | 27        | -6.3929582 |
|          | **Average** | **-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        | -8.315903  |
| T3       | 11        | -8.3098307 |
| T3       | 12        | -8.1798973 |
| T3       | 13        | -8.0936956 |
| T3       | 14        | -8.049025  |
| T3       | 15        | -7.8540268 |
| T3       | 16        | -7.744885  |
| T3       | 17        | -7.7321877 |
| T3       | 18        | -7.6184058 |
| T3       | 19        | -7.4833121 |
| T3       | 20        | -7.4545147 |
| T3       | 21        | -7.3769569 |
| T3       | 22        | -7.335923  |
| T3       | 23        | -7.296454  |
| T3       | 24        | -7.1494551 |
| T3       | 25        | -7.1465697 |
| T3       | 26        | -7.1312723 |
| T3       | 27        | -6.8732405 |
|          | **Average** | **-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         | -8.3943264 |
| 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        | -8.0651565 |
| 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        | -7.479362  |
| T4       | 28        | -7.0788541 |
| T4       | 29        | -6.7851344 |
| T4       | 30        | -6.2144074 |
|          | **Average** | **ΔGbinding** | **SD** |
|          |           | -7.9960089  | 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** | **ΔGbinding** | **SD** |
|          |           | -7.99495452 | 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        | -6.2356368 |
| Average  | ΔGbinding | -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        | -8.423889 |
| 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        | -7.3337788 |
| 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  | ΔGbinding | -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** | **ΔGbinding** | **-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         | -8.5339894 |
| 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** | **ΔGbinding** | **-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  |
|------------|-----------|------------|
| Daclatasvir| 1         | -6.743875  |
| Daclatasvir| 2         | -6.5059676 |
| Daclatasvir| 3         | -6.412931  |
| Daclatasvir| 4         | -6.282342  |
| Daclatasvir| 5         | -6.1425152 |
| Daclatasvir| 6         | -6.1368223 |
| Daclatasvir| 7         | -6.0960999 |
| Daclatasvir| 8         | -6.061402  |
| Daclatasvir| 9         | -6.014382  |
| 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        | -5.516821  |
| Daclatasvir| 21        | -5.4841599 |
| Daclatasvir| 22        | -5.4488587 |
| Daclatasvir| 23        | -5.4191465 |
| Daclatasvir| 24        | -5.2322726 |
| Daclatasvir| 25        | -5.1832037 |
| Ombitasvir | 1         | -7.1596756 |
| Ombitasvir | 2         | -6.8764935 |
| Ombitasvir | 3         | -6.6037531 |
| Ombitasvir | 4         | -6.2976608 |
| Ombitasvir | 5         | -6.2173386 |
| Ombitasvir | 6         | -6.136923  |
| 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        | -5.6106688 |
| Ombitasvir | 16        | -5.596351  |
| 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 ΔGbinding:  -5.61341553
SD: 0.6265319
| Compound      | Conformer | ΔGbinding |
|---------------|-----------|-----------|
| Camostat      | 1         | -6.04285  |
| Camostat      | 2         | -5.9478555|
| Camostat      | 3         | -5.9108286|
| Camostat      | 4         | -5.886168 |
| Camostat      | 5         | -5.768722 |
| Camostat      | 6         | -5.729077 |
| Camostat      | 7         | -5.7062001|
| Camostat      | 8         | -5.5547781|
| Camostat      | 9         | -5.530459 |
| Camostat      | 10        | -5.4542723|
| Camostat      | 11        | -5.4302723|
| 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 ΔGbinding |          | -5.27922742|
| SD            |           | 0.54872159|
| Edoxaban      | 1         | -6.882656 |
| Edoxaban      | 2         | -6.8416786|
| Edoxaban      | 3         | -6.0505261|
| Edoxaban      | 4         | -5.7649422|
| Edoxaban      | 5         | -5.701677 |
| 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        | -5.2102714|
| 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        | -4.3654949|
| Edoxaban      | 25        | -4.3570585|
| Edoxaban      | 26        | -3.3081818|
| Average ΔGbinding |          | -5.2429742|
| 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         | -5.6306562|
| 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 ΔGbinding: -5.21140482
SD: 0.52631492

| Compound     | Conformer | ΔGbinding |
|--------------|-----------|-----------|
| 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        | -5.0621346 |
| 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        | -4.0774979 |
| Nafamostat   | 23        | -4.0382085 |

Average ΔGbinding: -5.0931603
SD: 0.45703614

| Compound     | Conformer | ΔGbinding |
|--------------|-----------|-----------|
| NCGC00386945 | 1         | -6.2677202 |
| NCGC00386945 | 2         | -5.8149794 |
| NCGC00386945 | 3         | -5.6708345 |
| NCGC00386945 | 4         | -5.6003752 |
| NCGC00386945 | 5         | -5.4396263 |
| 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 | ΔG binding |
|----------------|-----------|------------|
| NCGC00386945   | 22        | -4.6853576 |
| NCGC00386945   | 23        | -4.6217885 |
| NCGC00386945   | 24        | -4.4223056 |
| NCGC00386945   | 25        | -4.0571074 |
| NCGC00386945   | 26        | -4.0020714 |
| **Average ΔG 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 ΔG 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        | -4.8717477 |
| 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 ΔG 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        | -5.2259993|
| 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 ΔGbinding |         | -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         | -5.2313866 |
| 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        | -4.575901  |
| 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 ΔGbinding |         | -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 | ΔG<sub>binding</sub>   |
|------------------|-----------|------------------------|
| 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        | -4.7511013             |
| 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 ΔG<sub>binding</sub>** |           | -4.75745139            |
| **SD**           |           | 0.466623475            |

| Compound         | Conformer | ΔG<sub>binding</sub>   |
|------------------|-----------|------------------------|
| 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        | -4.625341              |
| 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 ΔG<sub>binding</sub>** |           | -4.59333383            |
| **SD**           |           | 0.46323607             |

| Compound         | Conformer | ΔG<sub>binding</sub>   |
|------------------|-----------|------------------------|
| 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        | -4.252153   |
| 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        | -3.8078223  |
| NCGC00385043 | 28        | -3.6315114  |
| NCGC00385043 | 29        | -3.5687988  |
| NCGC00385043 | 30        | -3.500308   |
|             |           | Average ΔGbinding | -4.21853121 |
|             |           | SD             | 0.34484591   |

| Compound     | Conformer | ΔGbinding   |
|--------------|-----------|-------------|
| 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         | -4.1072015  |
| 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 ΔGbinding | -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 | 3.21     |
| 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         | N      | GLY                 | 351         | pi-H     | 3.98     |
| 6         | N      | HIS                 | 203         | H-acceptor | 3.59     |
| 7         | N      | GLU                 | 206         | H-donor  | 2.93     |
| 8         | N      | VAL                 | 187         | H-donor  | 3.15     |
| 9         | 6-ring | GLY                 | 351         | pi-H     | 3.57     |
| 10        | 6-ring | TYR                 | 250         | pi-H     | 4.49     |
| 11        | 6-ring | GLN                 | 350         | pi-H     | 4.52     |
| 12        | S      | SER                 | 348         | H-donor  | 3.26     |
| 13        | O      | HIS                 | 203         | H-acceptor | 3.1      |
| 14        | O      | HIS                 | 203         | H-acceptor | 3.29     |
| 15        | N      | GLY                 | 351         | H-acceptor | 3.11     |
| 16        | S      | GLU                 | 206         | H-donor  | 3.35     |
| 17        | S      | SER                 | 348         | H-donor  | 3.3      |
| 18        | O      | HIS                 | 203         | H-acceptor | 3.09     |
| 19        | 6-ring | GLY                 | 351         | pi-H     | 3.45     |
| 20        | O      | HIS                 | 203         | H-acceptor | 2.91     |
| 21        | 6-ring | HIS                 | 203         | pi-H     | 3.7     |
| 22        | O      | GLY                 | 351         | H-acceptor | 3.23     |
| 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     |
| 2         | S      | SER                 | 376         | H-donor  | 3.88     |
| 3         | 5-ring | HIS                 | 203         | pi-cation | 3.33     |
| 4         | 6-ring | TRP                 | 377         | pi-H     | 4.72     |
| 5         | S      | SER                 | 348         | H-donor  | 3.83     |
| 6         | S      | CYS                 | 381         | H-donor  | 3.67     |
| 7         | N      | VAL                 | 187         | H-donor  | 4.03     |
| 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     |
| 11        | S      | GLU                 | 206         | H-donor  | 3.73     |
| 12        | 5-ring | VAL                 | 187         | pi-H     | 3.65     |
| 13        | 5-ring | VAL                 | 187         | pi-H     | 4.03     |
| 14        | N      | HIS                 | 203         | H-acceptor | 3.41     |
| 15        | N      | HIS                 | 203         | H-acceptor | 3.05     |
| 16        | O      | GLY                 | 351         | H-acceptor | 3.24     |
| 17        | O      | HIS                 | 203         | H-acceptor | 3.04     |
| 18        | S      | HIS                 | 203         | H-donor  | 3.87     |
| Conformer | Ligand | Residues in TMPRSS2 | Interaction  | Distance |
|-----------|--------|---------------------|--------------|----------|
| S         | ASN    | 249                 | H-donor      | 3.34     |
| S         | SER    | 353                 | H-donor      | 3.34     |
| S         | GLY    | 378                 | H-donor      | 3.34     |
| 14        | S      | VAL                 | H-donor      | 3.34     |
| S         | GLY    | 351                 | H-donor      | 3.34     |
| 15        | N      | GLU                 | H-donor      | 3.34     |
| S         | VAL    | 205                 | H-donor      | 3.34     |
| S         | GLU    | 206                 | H-donor      | 3.34     |
| 16        | N      | VAL                 | H-donor      | 3.34     |
| 17        | O      | HIS                 | H-acceptor   | 3.34     |
| 18        | N      | GLY                 | H-donor      | 3.34     |
| 19        | S      | GLY                 | H-donor      | 3.34     |
| 20        | S      | GLU                 | H-donor      | 3.34     |
| 21        | N      | HIS                 | H-acceptor   | 3.34     |
| 22        | O      | GLY                 | H-donor      | 3.34     |
| 23        | S      | GLY                 | H-donor      | 3.34     |
| 24        | O      | TYR                 | H-acceptor   | 3.34     |
| O         | ASN    | 249                 | H-acceptor   | 3.34     |

**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 |
|-----------|--------|---------------------|-------------|----------|
| 14        | 6-ring | ASN                 | 249         | pi-H     | 3.61     |
| 15        | N      | GLU                 | 206         | H-donor  | 2.9      |
| 16        | N      | VAL                 | 187         | H-donor  | 2.99     |
| 17        | 5-ring | VAL                 | 187         | H-donor  | 2.97     |
| 18        | N      | GLU                 | 206         | H-donor  | 3.12     |
| 19        | N      | HIS                 | 203         | H-acceptor | 3.65   |
| 20        | 5-ring | HIS                 | 203         | H-acceptor | 3.01   |
| 21        | 6-ring | HIS                 | 203         | H-acceptor | 3.86   |
| 22        | O      | HIS                 | 203         | H-acceptor | 3.01   |
| 23        | O      | GLY                 | 351         | H-acceptor | 3.42   |
| 24        | S      |val                | 187         | H-donor  | 3.4      |
| 25        | N      | GLU                 | 206         | H-donor  | 2.8      |
| 26        | N      | VAL                 | 187         | H-donor  | 2.98     |
| 27        | S      | VAL                 | 187         | H-donor  | 3.37     |
| 28        | N      | HIS                 | 203         | H-acceptor | 3.61   |
| 29        | S      | HIS                 | 186         | H-donor  | 3.9      |

| Conformer | Ligand | Residues in TMPRSS2 | Interaction | Distance |
|-----------|--------|---------------------|-------------|----------|
| 1         | S      | HIS                 | 203         | H-acceptor | 4.02   |
| 2         | O      | ASN                 | 249         | H-acceptor | 3.4     |
| 3         | O      | HIS                 | 203         | H-acceptor | 3.13    |
| 4         | N      | VAL                 | 187         | H-donor  | 3.08     |
| 5         | S      | GLY                 | 351         | H-acceptor | 3.34   |
| 6         | S      | HIS                 | 203         | H-acceptor | 3.04    |
| 7         | N      | VAL                 | 187         | H-donor  | 3.08     |
| 8         | S      | GLY                 | 351         | H-acceptor | 3.34   |
| 9         | 5-ring | CYS                 | 204         | pi-H     | 3.8      |
| 10        | N      | VAL                 | 187         | H-donor  | 3.2      |
| 11        | S      | HIS                 | 203         | H-acceptor | 3.8     |
| 12        | S      | GLY                 | 351         | H-acceptor | 3.34   |
| 13        | S      | CYS                 | 204         | H-acceptor | 3.6     |

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 |
|-----------|--------|---------------------|-------------|----------|
| 6-ring    | GLN    | 350                 | pi-H        | 4.25     |
| 14        | GLY    | 351                 | H-acceptor  | 3.76     |
| 6-ring    | HIS    | 203                 | pi-H        | 3.66     |
| 15        | HIS    | 203                 | H-acceptor  | 3.68     |
|            | TRP    | 377                 | H-acceptor  | 3.75     |
| 6-ring    | VAL    | 187                 | pi-H        | 3.86     |
| 16        | N      | 187                 | H-donor     | 3.27     |
| N         | HIS    | 203                 | H-acceptor  | 4.05     |
| S         | CYS    | 204                 | H-acceptor  | 3.94     |
| 5-ring    | VAL    | 187                 | pi-H        | 4.75     |
| 17        | GLY    | 351                 | H-acceptor  | 3.39     |
| 18        | 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     |
|            | LYS    | 302                 | H-acceptor  | 3.13     |
| 6-ring    | HIS    | 203                 | pi-H        | 4.67     |
| 19        | THR    | 254                 | H-acceptor  | 3.28     |
| 5-ring    | GLY    | 378                 | pi-H        | 4.5      |
| 20        | HIS    | 203                 | H-donor     | 3.79     |
| O         | HIS    | 203                 | H-acceptor  | 3.02     |
| 6-ring    | ASN    | 249                 | pi-H        | 3.36     |
| 21        | THR    | 305                 | H-acceptor  | 3.14     |
| 6-ring    | VAL    | 187                 | pi-H        | 4.63     |
| 22        | VAL    | 187                 | H-donor     | 3.23     |
| S         | HIS    | 203                 | H-acceptor  | 4.05     |
| 6-ring    | HIS    | 203                 | pi-cation   | 4.57     |
| 23        | HIS    | 203                 | H-acceptor  | 3.82     |
| S         | GLY    | 378                 | H-acceptor  | 3.33     |
| 24        | HIS    | 203                 | H-acceptor  | 3.73     |
| S         | TRP    | 377                 | H-acceptor  | 4.36     |
| O         | GLY    | 351                 | H-acceptor  | 3.86     |
| 25        | GLN    | 350                 | pi-H        | 4.31     |
| 5-ring    | GLY    | 351                 | pi-H        | 3.47     |
| 26        | 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        | 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.
### 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                 | H-acceptor  | 3.37     |
| 2         | C      | ASN                 | H-donor     | 3.43     |
| 3         | S      | HIS                 | H-donor     | 3.55     |
| 4         | C      | ASN                 | H-donor     | 3.43     |
| 5         | N      | VAL                 | H-donor     | 3.08     |
| 6         | N      | VAL                 | H-donor     | 3.21     |
| 7         | S      | HIS                 | H-donor     | 3.6      |
| 8         | N      | VAL                 | H-donor     | 3.07     |
| 9         | S      | HIS                 | H-donor     | 3.42     |
| 10        | S      | HIS                 | H-donor     | 3.67     |
|           | O      | GLY                 | H-acceptor  | 3.15     |
|           | O      | GLY                 | H-acceptor  | 3.33     |
|           | O      | HIS                 | H-acceptor  | 2.91     |
| 11        | N      | GLY                 | H-acceptor  | 3.22     |
|           | O      | HIS                 | H-acceptor  | 3.13     |
|           | C      | HIS                 | H-     | 4.13     |
| 12        | O      | HIS                 | H-acceptor  | 3.11     |
| 13        | N      | GLU                 | H-donor     | 2.86     |
|           | O      | GLN                 | H-acceptor  | 3.13     |
| 14        | C      | GLU                 | H-donor     | 3.32     |
|           | O      | HIS                 | H-acceptor  | 3.12     |
| 15        | S      | SER                 | H-donor     | 3.86     |
|           | O      | TYR                 | H-acceptor  | 3.04     |
| 16        | O      | HIS                 | H-acceptor  | 2.86     |
| 17        | O      | HIS                 | H-acceptor  | 2.97     |
| 18        | O      | GLY                 | H-acceptor  | 3.33     |
|           | O      | GLY                 | H-acceptor  | 3.43     |
|           | O      | GLY                 | H-acceptor  | 3.71     |
|           | 5-ring | GLY                 | pi-     | 4.14     |
|           | 12     | O      | HIS                 | H-acceptor  | 3.11     |
|           | 13     | N      | GLU                 | H-donor     | 2.86     |
|           | 14     | C      | GLU                 | H-donor     | 3.32     |
|           | 15     | S      | SER                 | H-donor     | 3.86     |
|           | 16     | O      | HIS                 | H-acceptor  | 2.86     |
|           | 17     | O      | HIS                 | H-acceptor  | 2.97     |
|           | 18     | O      | GLY                 | H-acceptor  | 3.33     |
|           | 19     | O      | GLY                 | H-acceptor  | 3.43     |
|           | 20     | S      | GLY                 | H-donor     | 3.79     |
|           | 21     | O      | LYS                 | H-acceptor  | 3.16     |
|           | 22     | S      | GLY                 | H-donor     | 3.61     |
|           | 23     | O      | LYS                 | H-acceptor  | 2.93     |
|           | 24     | N      | GLU                 | H-donor     | 3.33     |

### 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 |
|-----------|--------|---------------------|-------------|----------|
| 13        | N      | GLU                 | H-donor     | 2.93     |
| 14        | 6-ring | HIS                 | pi-cation   | 4.69     |
| 15        | N      | GLY                 | H-donor     | 3.08     |
| 16        | 6-ring | HIS                 | pi-cation   | 3.96     |
| 17        | 6-ring | HIS                 | pi-cation   | 4.11     |
| 18        | C      | GLU                 | H-donor     | 3.48     |
|           | O      | HIS                 | H-acceptor  | 3.03     |
|           | 6-ring | ASN                 | pi-     | 3.61     |
| 19        | O      | HIS                 | H-acceptor  | 2.95     |
|           | O      | HIS                 | H-acceptor  | 3.19     |
| Conformer | Ligand | Residues in TMPRSS2 | Interaction | Distance |
|-----------|--------|---------------------|-------------|----------|
| 1         | S      | GLU                 | H-donor     | 3.64     |
|           | C      | CYS                 | H-donor     | 3.8      |
|           | O      | LYS                 | H-acceptor  | 3.58     |
|           | O      | CYS                 | H-acceptor  | 3.05     |
|           | 5-ring | HIS                 | pi-cation   | 3.51     |
|           | 5-ring | GLY                 | pi-H        | 4.14     |
| 2         | S      | LYS                 | H-acceptor  | 4.01     |
|           | S      | GLY                 | H-acceptor  | 3.85     |
|           | O      | CYS                 | H-acceptor  | 3.44     |
|           | O      | LYS                 | H-acceptor  | 3.18     |
| 3         | S      | HIS                 | H-donor     | 3.09     |
|           | S      | VAL                 | H-donor     | 3.86     |
|           | S      | ASN                 | H-donor     | 3.47     |
|           | S      | CYS                 | H-acceptor  | 3.82     |
|           | S      | TRP                 | H-acceptor  | 4.26     |
|           | O      | HIS                 | H-acceptor  | 3.28     |
| 4         | S      | GLY                 | H-acceptor  | 3.45     |
|           | O      | GLN                 | H-acceptor  | 3.18     |
|           | 5-ring | CYS                 | pi-H        | 4.34     |
| 5         | S      | HIS                 | H-acceptor  | 4        |
|           | S      | GLY                 | H-acceptor  | 3.91     |
|           | O      | HIS                 | H-acceptor  | 3.08     |
|           | O      | HIS                 | H-acceptor  | 3.12     |
| 6         | O      | GLY                 | H-acceptor  | 3.11     |
|           | 6-ring | LEU                 | pi-H        | 3.77     |
| 7         | S      | GLY                 | H-donor     | 3.76     |
|           | O      | HIS                 | H-acceptor  | 3.02     |
|           | 6-ring | LEU                 | pi-H        | 3.88     |
| 8         | S      | GLU                 | H-donor     | 3.45     |
|           | O      | HIS                 | H-acceptor  | 3.24     |
|           | 3-ring | VAL                 | pi-H        | 4.57     |
|           | 3-ring | CYS                 | pi-H        | 4.43     |
| 9         | S      | HIS                 | H-donor     | 3.25     |
|           | S      | CYS                 | H-acceptor  | 3.73     |
|           | S      | TRP                 | H-acceptor  | 4.27     |
| 10        | 5-ring | GLY                 | pi-H        | 4.04     |
| 11        | N      | GLY                 | H-donor     | 3.01     |
|           | S      | CYS                 | H-acceptor  | 3.95     |
|           | O      | HIS                 | H-acceptor  | 3.29     |
| 12        | N      | SER                 | H-donor     | 3.27     |
|           | O      | HIS                 | H-acceptor  | 3.23     |
|           | 6-ring | VAL                 | pi-H        | 4.14     |
| 13        | N      | CYS                 | H-donor     | 2.99     |
|           | O      | LYS                 | H-acceptor  | 3        |
| 14        | N      | CYS                 | H-donor     | 2.98     |
|           | S      | LYS                 | H-acceptor  | 3.51     |
|           | S      | GLY                 | H-acceptor  | 4.15     |
|           | O      | HIS                 | H-acceptor  | 3.15     |
| 15        | S      | GLY                 | H-acceptor  | 4.49     |
|           | O      | HIS                 | H-acceptor  | 2.9      |
| 16        | N      | GLY                 | H-donor     | 3.19     |
|           | S      | GLY                 | H-acceptor  | 3.36     |
|           | O      | HIS                 | H-acceptor  | 2.97     |
|           | O      | HIS                 | H-acceptor  | 2.99     |
|           | 6-ring | LYS                 | pi-H        | 3.63     |
| 17        | S      | GLN                 | H-acceptor  | 3.86     |
|           | O      | HIS                 | H-acceptor  | 3.02     |
|           | 5-ring | HIS                 | pi-H        | 3.64     |
| 18        | N      | SER                 | H-donor     | 3.12     |
|           | S      | HIS                 | H-acceptor  | 3.22     |
|           | O      | GLY                 | H-acceptor  | 3        |
| 19        | S      | GLY                 | H-acceptor  | 3.43     |
|           | 6-ring | CYS                 | pi-H        | 4.62     |
| 20        | S      | LYS                 | H-acceptor  | 3.77     |
|           | O      | LYS                 | H-acceptor  | 2.91     |
|           | 6-ring | HIS                 | pi-H        | 3.84     |
| Conformer | Ligand | Residues in TMPRSS2 | Interaction | Distance |
|-----------|--------|---------------------|-------------|----------|
| 21        | S      | SER                 | H-donor     | 3.86     |
|           | S      | HIS                 | H-acceptor  | 3.86     |
| 22        | S      | HIS                 | H-acceptor  | 4.34     |
|           | O      | HIS                 | H-acceptor  | 3.1      |
| 23        | O      | HIS                 | H-acceptor  | 3.46     |
| 6-ring    | ASP    | 329                 | pi-H        | 4.82     |
| 3-ring    | SER    | 379                 | pi-H        | 4.64     |
| 24        | S      | HIS                 | H-acceptor  | 3.86     |
|           | S      | LYS                 | H-acceptor  | 3.38     |
| 6-ring    | VAL    | 187                 | pi-H        | 4.11     |
| 25        | S      | GLY                 | H-acceptor  | 3.47     |
|           | S      | THR                 | H-acceptor  | 3.47     |
|           | O      | LYS                 | H-acceptor  | 3.26     |
| 6-ring    | HIS    | 203                 | pi-cation   | 4.78     |
| 26        | S      | CYS                 | H-donor     | 4.32     |
|           | S      | CYS                 | H-acceptor  | 3.89     |
|           | S      | GLY                 | H-acceptor  | 3.43     |
| 27        | O      | GLY                 | H-acceptor  | 2.83     |
| 28        | S      | GLU                 | H-donor     | 3.42     |
|           | S      | HIS                 | H-acceptor  | 3.43     |
| 29        | O      | CYS                 | 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.
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 |
|-----------|--------|---------------------|-------------|----------|
| 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      |
| 3-ring    | GLY    | 351                 | pi-H        | 3.46     |
| 19        | S      | GLY                 | 206         | H-donor  | 3.33     |
| 5-ring    | 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     |

Conformer | Ligand | Residues in TMPRSS2 | Interaction | Distance |
1          | N      | CYS                 | 349         | H-donor  | 3.15     |
2          | O      | HIS                 | 203         | H-acceptor | 3.07     |
| 2         | C      | HIS                 | 186         | H-pi     | 3.67     |
| 3         | O      | GLY                 | 351         | H-acceptor | 3.23     |
| 4         | O      | HIS                 | 203         | H-acceptor | 3.08     |
| 5         | O      | HIS                 | 203         | H-acceptor | 2.99     |
| 6         | O      | GLY                 | 351         | H-acceptor | 3.06     |
| 7         | S      | HIS                 | 203         | H-donor  | 3.88     |
| 8         | 5-ring | VAL                 | 187         | pi-H     | 4.26     |
| 9         | N      | GLU                 | 206         | H-donor  | 2.94     |
| 10        | N      | CYS                 | 349         | H-donor  | 3.04     |
| 11        | N      | GLU                 | 206         | H-donor  | 3.17     |
| 12        | N      | VAL                 | 187         | H-donor  | 2.85     |
| 13        | S      | GLU                 | 206         | H-donor  | 3.34     |
| 14        | N      | GLU                 | 206         | H-donor  | 2.92     |
| 15        | S      | ASN                 | 249         | H-donor  | 3.48     |
| 16        | O      | GLY                 | 303         | H-acceptor | 3.17     |
| 17        | S      | GLU                 | 378         | pi-H     | 4.62     |
| 18        | N      | GLU                 | 206         | H-donor  | 2.88     |
| 19        | O      | GLY                 | 351         | H-acceptor | 3.37     |
| 20        | N      | GLU                 | 206         | H-donor  | 2.96     |
| 21        | O      | HIS                 | 203         | H-acceptor | 2.9     |
| 22        | O      | HIS                 | 203         | H-acceptor | 2.93     |
| 23        | S      | VAL                 | 187         | pi-H     | 4.6      |
| 24        | S      | HIS                 | 186         | H-donor  | 4.29     |
| 25        | N      | GLU                 | 206         | H-donor  | 3.21     |
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 |
|-----------|--------|---------------------|-------------|----------|
| C         | GLU    | 206                 | H-donor     | 3.59     |
| O         | HIS    | 203                 | H-acceptor  | 3.64     |

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         | N      | CYS                 | H-donor     | 2.99     |
| 2         | O      | GLY                 | H-acceptor  | 3.59     |
| 3         | 6-ring | VAL                 | pi-H        | 3.96     |
| 4         | 5-ring | GLY                 | H-donor     | 3.1      |
| 5         | N      | HIS                 | H-acceptor  | 2.93     |
| 6         | 5-ring | CYS                 | H-donor     | 3.68     |
| 7         | N      | GLU                 | H-donor     | 3.29     |
| 8         | 5-ring | CYS                 | pi-H        | 4.36     |
| 9         | N      | GLU                 | H-donor     | 3.28     |
| 10        | 5-ring | CYS                 | pi-H        | 4.35     |
| 11        | O      | CYS                 | H-donor     | 4.1      |
| 12        | N      | GLU                 | H-donor     | 3.38     |
| 13        | 5-ring | CYS                 | pi-cation   | 3.88     |
| 14        | N      | GLU                 | pi-H        | 3.83     |
| 15        | N      | GLY                 | H-acceptor  | 2.78     |
| 16        | O      | GLY                 | pi-cation   | 3.78     |
| 17        | N      | GLU                 | H-donor     | 3.22     |
| 18        | O      | GLY                 | H-acceptor  | 3.41     |
| 19        | N      | GLU                 | H-acceptor  | 3.04     |
| 21        | O      | GLY                 | H-acceptor  | 3.98     |
| 22        | N      | GLU                 | H-acceptor  | 3.86     |
| 23        | 6-ring | GLY                 | pi-H        | 4.05     |
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 |
|-----------|--------|---------------------|-------------|----------|
| 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     |
|           | O      | HIS 203             | H-acceptor  | 3.17     |
|           | O      | ASN 249             | H-acceptor  | 3.22     |
| 18        | N      | GLU 206             | H-donor     | 3.4      |
|           | 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     |
| 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     |
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      | GLU 206            | ionic       | 3.37     |
| 2         | O      | HIS 203            | ionic       | 3.62     |
| 3         | N      | GLU 206            | ionic       | 3.37     |
| 4         | N      | GLU 206            | H-donor     | 2.99     |
| 5         | O      | GLY 378            | H-donor     | 2.89     |
| 6         | O      | GLY 351            | H-donor     | 3.23     |
| 7         | N      | GLU 206            | pi-cation   | 3.92     |
| 8         | N      | GLU 206            | pi-cation   | 4.48     |
| 9         | O      | GLY 378            | pi-cation   | 4.32     |
| 10        | S      | VAL 187            | H-donor     | 3.74     |
| 11        | O      | GLY 351            | H-donor     | 3.16     |
| 12        | O      | GLY 351            | H-donor     | 3.08     |
| 13        | O      | GLY 351            | H-donor     | 3.07     |
| 14        | N      | GLU 206            | H-donor     | 2.84     |
| 15        | N      | GLU 206            | H-donor     | 2.75     |
| 16        | O      | HIS 203            | ionic       | 3.98     |
| 17        | N      | TRP 377            | cation-pi   | 4.23     |
| 18        | N      | GLN 350            | H-donor     | 2.96     |
| 19        | S      | SER 348            | H-donor     | 4.08     |
| 20        | O      | GLY 351            | H-donor     | 3.15     |
| 21        | C      | SER 348            | H-donor     | 3.43     |
| 22        | O      | HIS 203            | ionic       | 3.75     |
| 23        | N      | CYS 349            | H-donor     | 3.26     |
| 24        | N      | HIS 203            | H-donor     | 3.06     |
| 25        | N      | GLU 206            | H-donor     | 3.45     |
| 26        | 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 | N | Residues in TMPRSS2 | Interaction | Distance |
|-----------|---|---------------------|-------------|----------|
| 1         | N | GLU 206             | H-donor     | 2.86     |
| 2         | N | GLU 206             | H-donor     | 2.96     |
| 3         | N | GLU 206             | H-donor     | 2.95     |
| 4         | N | SER 348             | H-donor     | 2.9      |
| 5         | O | HIS 203             | H-acceptor  | 2.98     |
| 6         | N | LYS 383             | H-acceptor  | 2.99     |
| 7         | N | GLU 206             | H-donor     | 2.89     |
| 8         | N | GLU 206             | H-donor     | 2.92     |
| 9         | N | Thr 254             | H-donor     | 3.03     |
| 10        | N | LYS 302             | H-acceptor  | 3.48     |
| 11        | N | GLY 378             | H-donor     | 3.04     |
| 12        | N | HIS 203             | H-acceptor  | 3.41     |
| 13        | 5 | VAL 187             | pi-H        | 4.08     |
| 14        | N | GLU 206             | H-donor     | 2.89     |
| 15        | N | SER 348             | H-donor     | 3.24     |
| 16        | O | HIS 203             | H-acceptor  | 3.21     |
| 17        | N | GLU 206             | i-ionic     | 3.91     |
| 18        | N | GLU 206             | H-donor     | 2.88     |
| 19        | N | GLU 206             | H-donor     | 3.56     |
| 20        | N | GLU 206             | H-donor     | 2.9      |

**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 | N | Residues in TMPRSS2 | Interaction | Distance |
|-----------|---|---------------------|-------------|----------|
| 1         | N | GLU 206             | H-donor     | 2.91     |
| 2         | N | SER 348             | H-donor     | 3.01     |
| 3         | N | SER 348             | H-donor     | 3.14     |
| 4         | N | GLU 206             | H-donor     | 2.91     |
| 5         | N | SER 348             | H-donor     | 2.72     |
| 6         | N | GLU 206             | H-donor     | 3.73     |
| 7         | N | SER 348             | H-donor     | 2.94     |

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| 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     |
| 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                 | 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     |
| 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     |
| 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     |
| 18        | N      | CYS                | 349         | H-donor  | 3.02     |
| N         | GLU    | 206                 | H-donor     | 3.05     |
| N         | GLU    | 206                 | H-donor     | 3.05     |
| N         | GLU    | 206                 | ionic       | 3.05     |
| N         | GLU    | 206                 | ionic       | 3.95     |
| N         | GLU    | 206                 | ionic       | 3.79     |
| 19        | N      | GLU                | 206         | H-donor  | 3.22     |
| 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 |
|-----------|--------|---------------------|--------------|----------|
| 1         | N      | GLU 206             | H-donor      | 2.76     |
| 2         | N      | CYS 349             | H-donor      | 2.96     |
| 3         | N      | CYS 381             | H-donor      | 4.06     |
| 4         | N      | CYS 381             | H-donor      | 3.53     |
| 5         | O      | HIS 203             | H-acceptor   | 3.18     |
| 6         | N      | GLU 206             | ionic        | 2.85     |
|           | N      | GLU 206             | ionic        | 2.76     |
| 21        | N      | VAL 187             | H-donor      | 2.96     |
| 22        | N      | GLY 351             | H-donor      | 2.78     |
| 23        | N      | GLN 350             | H-donor      | 2.82     |
|           | N      | GLU 206             | ionic        | 3.03     |
|           | N      | GLU 206             | ionic        | 3.46     |
|           | N      | GLU 206             | ionic        | 3.61     |
|           | N      | GLU 206             | ionic        | 3.69     |
|           | N      | GLU 206             | ionic        | 3.64     |
|           | N      | GLU 206             | ionic        | 3.05     |
| 6-ring    | 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     |
| 22        | N      | GLY 351             | H-donor      | 2.78     |
| 23        | N      | GLN 350             | H-donor      | 2.82     |
|           | N      | GLU 206             | ionic        | 3.03     |
|           | N      | GLU 206             | ionic        | 3.46     |
|           | N      | GLU 206             | ionic        | 3.61     |
|           | N      | GLU 206             | ionic        | 3.64     |
| 6-ring    | N      | GLN 350             | H-donor      | 2.82     |
|           | N      | GLU 206             | ionic        | 3.03     |
|           | N      | GLU 206             | ionic        | 3.46     |
|           | 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        | 3.64     |
| 6-ring    | N      | GLN 350             | H-donor      | 2.82     |
|           | N      | GLU 206             | ionic        | 3.03     |
|           | N      | GLU 206             | ionic        | 3.46     |
|           | 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        | 3.64     |
| 6-ring    | N      | GLN 350             | H-donor      | 2.82     |
|           | N      | GLU 206             | ionic        | 3.03     |
|           | N      | GLU 206             | ionic        | 3.46     |
|           | N      | GLU 206             | ionic        | 3.64     |
|           | N      | GLU 206             | ionic        | 3.73     |

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.

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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      | GLU                 | 206         | ionic    | 3.09    |
| 2         | N      | GLU                 | 206         | H-donor  | 3.17    |
| 3         | N      | GLU                 | 206         | H-donor  | 2.9     |
| 4         | N      | GLU                 | 206         | H-donor  | 3.17    |
| 5         | N      | GLU                 | 206         | H-donor  | 3.04    |
| 6         | N      | GLU                 | 206         | H-donor  | 3.04    |
| 7         | N      | GLU                 | 206         | H-donor  | 3.04    |
| 8         | N      | GLU                 | 206         | H-donor  | 3.04    |
| 9         | N      | SER                 | 348         | H-donor  | 3.4     |
| 10        | N      | SER                 | 348         | H-donor  | 2.86    |
| 11        | N      | GLU                 | 206         | H-donor  | 3.54    |
| 12        | N      | GLU                 | 206         | H-donor  | 3.43    |
| 13        | N      | GLU                 | 206         | H-donor  | 2.98    |
| 14        | N      | GLU                 | 206         | H-donor  | 2.86    |
| 15        | N      | CYS                 | 381         | H-donor  | 4.47    |
| 16        | N      | GLU                 | 206         | H-donor  | 3.8     |
| 17        | N      | TRP                 | 215         | cation-pi| 4.47    |
| 18        | N      | GLU                 | 206         | H-donor  | 2.96    |
| 19        | N      | GLU                 | 206         | ionic    | 2.96    |
| 20        | N      | GLU                 | 206         | H-donor  | 3.19    |
| 21        | N      | GLU                 | 206         | H-donor  | 2.9     |
| 22        | N      | GLY                 | 378         | H-donor  | 2.76    |
| 23        | N      | GLU                 | 206         | ionic    | 3.8     |
|           | N      | GLU                 | 206         | ionic    | 3.41    |
| Conformer | Ligand | Residues in TMPRSS2 | Interaction | Distance |
|-----------|--------|---------------------|-------------|----------|
| 6         | N      | GLU 206             | ionic       | 3.87     |
| 7         | N      | CYS 349             | H-donor     | 2.88     |
| 8         | O      | HIS 203             | H-acceptor  | 2.88     |
| 9         | N      | GLY 378             | H-donor     | 2.77     |
| 10        | N      | GLU 206             | H-donor     | 2.88     |
| 11        | N      | GLU 206             | H-donor     | 2.99     |
| 12        | N      | CYS 349             | H-donor     | 2.98     |
| 13        | N      | GLY 351             | H-donor     | 2.83     |
| 14        | N      | GLY 378             | H-donor     | 2.99     |
| 15        | N      | GLU 206             | H-donor     | 2.78     |
| 16        | N      | GLU 206             | H-donor     | 2.78     |
| 17        | N      | GLU 206             | H-donor     | 2.93     |
| 18        | N      | GLU 206             | H-donor     | 2.93     |
| 19        | N      | TH 254              | H-donor     | 3.28     |
| 20        | O      | HIS 203             | H-donor     | 3.28     |
| 21        | O      | HIS 203             | H-donor     | 3.28     |
| 22        | N      | GLU 206             | H-donor     | 3.11     |
| 23        | N      | GLU 206             | H-donor     | 3.11     |
| 24        | N      | GLU 206             | H-donor     | 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    |
| 6         | 6-ring | TYR                 | 250           | pi-H     | 3.93    |
| 7         | N      | GLU                 | 206           | ionic    | 3.98    |
| 8         | O      | HIS                 | 203           | H-acceptor| 2.97    |
| 9         | N      | GLU                 | 206           | ionic    | 3.4     |
| 10        | 6-ring | VAL                 | 187           | pi-H     | 4.52    |
| 11        | O      | HIS                 | 203           | H-acceptor| 3.05    |
| 12        | N      | GLU                 | 206           | ionic    | 3.67    |
| 13        | 6-ring | GLY                 | 351           | pi-H     | 4.35    |
| 14        | 6-ring | VAL                 | 187           | pi-H     | 4.01    |
| 15        | N      | GLU                 | 206           | ionic    | 3.74    |
| 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    |
| 19        | 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    |
| 2         | N      | SER                 | 348          | H-donor  | 3.03    |
| 3         | N      | GLU                 | 206          | H-donor  | 2.89    |
| 4         | N      | GLU                 | 206          | ionic    | 3.53    |
| 5         | N      | GLU                 | 206          | ionic    | 2.89    |
| 6         | 6-ring | HIS                 | 203          | pi-H     | 3.87    |
| 7         | 6-ring | GLU                 | 206          | H-donor  | 2.87    |
| 8         | O      | GLY                 | 351          | H-acceptor| 3.27    |
| 9         | N      | GLU                 | 206          | ionic    | 2.87    |
| 10        | N      | GLU                 | 206          | ionic    | 3.43    |
| 11        | N      | GLU                 | 206          | H-donor  | 3.02    |
| 12        | N      | CYS                 | 349          | H-donor  | 3.45    |
| 13        | O      | LYS                 | 383          | H-acceptor| 3.9     |
| 14        | N      | GLU                 | 206          | H-donor  | 2.94    |
| 15        | N      | GLU                 | 206          | ionic    | 2.94    |
| 16        | 6-ring | VAL                 | 187          | pi-H     | 3.99    |
| 17        | N      | GLU                 | 206          | H-donor  | 3.12    |
| 18        | N      | GLU                 | 206          | ionic    | 3.14    |
| 19        | N      | GLU                 | 206          | H-donor  | 2.79    |
| 20        | N      | GLU                 | 206          | ionic    | 3.48    |
| 21        | 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                 | 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                 | 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                 | H-donor     | 3.14     |
| N         | SER    | 348                 | H-donor     | 2.94     |
| 6-ring    | VAL    | 187                 | pi-H        | 4.22     |
| 13        | N      | SER                 | H-donor     | 2.92     |
| 6-ring    | VAL    | 187                 | pi-H        | 4.33     |
| 14        | N      | GLY                 | H-donor     | 2.84     |
| O         | HIS    | 203                 | H-acceptor  | 3.18     |
| 6-ring    | HIS    | 203                 | pi-H        | 3.78     |
| 15        | N      | CYS                 | H-donor     | 3.13     |
| N         | CYS    | 349                 | H-donor     | 3.04     |
| 16        | N      | GLU                 | 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                 | H-acceptor  | 2.97     |
| N         | GLU    | 206                 | ionic       | 3.95     |
| 18        | N      | GLU                 | 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                 | H-donor     | 2.86     |
| N         | GLU    | 206                 | ionic       | 2.86     |
| N         | GLU    | 206                 | ionic       | 3.38     |
| 20        | N      | GLU                 | ionic       | 3.19     |
| 21        | N      | GLU                 | ionic       | 3.84     |
| N         | GLU    | 206                 | ionic       | 3.21     |
| N         | GLU    | 206                 | ionic       | 3.21     |
| 22        | O      | GLY                 | 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                 | 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                 | H-donor     | 3.1      |
| N         | SER    | 348                 | H-donor     | 2.88     |
| 25        | N      | GLU                 | H-donor     | 2.85     |
| N         | GLU    | 206                 | ionic       | 2.85     |
| 26        | N      | SER                 | H-donor     | 3.42     |
| N         | SER    | 348                 | H-donor     | 2.82     |
| 27        | N      | ASN                 | 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                 | 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     |
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                 | H-donor     | 3.01     |
| 2         | O      | HIS                 | H-acceptor  | 3.17     |
| 3         | N      | VAL                 | pi-H        | 3.89     |
| 4         | O      | VAL                 | H-donor     | 3.09     |
| 5         | O      | GLY                 | H-acceptor  | 2.87     |
| 6         | O      | GLY                 | pi-H        | 3.74     |
| 7         | O      | GLY                 | H-acceptor  | 3.25     |
| 8         | O      | VAL                 | H-donor     | 3.05     |
| 9         | O      | HIS                 | H-acceptor  | 3.3      |
| 10        | O      | HIS                 | H-acceptor  | 3.02     |
| 11        | O      | VAL                 | H-donor     | 3.91     |
| 12        | O      | HIS                 | H-acceptor  | 3.01     |
| 13        | O      | ASN                 | pi-H        | 4.12     |
| 14        | N      | SER                 | H-donor     | 3.07     |
| 15        | O      | SER                 | H-donor     | 3        |
| 16        | O      | HIS                 | pi-cation   | 4.22     |
| 17        | O      | GLN                 | H-acceptor  | 3.34     |
| 18        | O      | HIS                 | H-acceptor  | 3.32     |
| 19        | O      | HIS                 | H-acceptor  | 3.82     |
| 20        | O      | VAL                 | H-donor     | 3        |
| 21        | O      | ASN                 | pi-H        | 3.91     |
| 22        | O      | GLU                 | H-donor     | 3.46     |
| 23        | O      | HIS                 | 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                 | H-donor     | 3.09     |
| 2         | N      | GLN                 | H-donor     | 3.18     |
| 3         | O      | HIS                 | H-acceptor  | 2.87     |
| 4         | N      | GLU                 | H-donor     | 2.84     |
| 5         | N      | HIS                 | H-acceptor  | 2.91     |
| 6         | N      | GLU                 | ionic       | 3.87     |
| 7         | N      | GLU                 | pi-H        | 4.25     |
| 8         | N      | VAL                 | H-donor     | 2.91     |
| 9         | N      | HIS                 | H-donor     | 3.52     |
| 10        | N      | GLU                 | H-donor     | 3.34     |
| 11        | N      | GLU                 | H-donor     | 2.89     |
| 12        | O      | HIS                 | H-acceptor  | 3.19     |
| 13        | O      | GLY                 | H-acceptor  | 3.33     |
| 14        | O      | HIS                 | ionic       | 3.19     |
| 15        | O      | GLY                 | ionic       | 3.02     |
| 16        | N      | GLU                 | ionic       | 3.34     |
| 17        | N      | GLU                 | 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     |
|           | 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       | 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     |
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             | ionic       | 3.29     |
| 2         | N      | GLU 206             | ionic       | 2.85     |
| 3         | N      | GLU 206             | ionic       | 3.08     |
| 4         | N      | GLU 206             | ionic       | 3.6      |
| 18        | N      | GLU 206             | H-donor     | 2.84     |
| 19        | O      | HIS 203             | H-acceptor  | 2.86     |
| 20        | O      | HIS 203             | ionic       | 2.86     |
| 21        | N      | GLU 206             | ionic       | 3.2      |
| 22        | N      | GLU 206             | ionic       | 2.84     |
| 23        | O      | HIS 203             | ionic       | 3.17     |
| 24        | O      | HIS 203             | ionic       | 3.1     |
| 25        | O      | HIS 203             | ionic       | 2.9      |
| 26        | N      | GLU 206             | ionic       | 2.87     |
| 27        | O      | HIS 203             | ionic       | 2.81     |
| 28        | O      | HIS 203             | ionic       | 3.46     |
| 29        | N      | GLU 206             | ionic       | 3.26     |
| 30        | N      | GLU 206             | ionic       | 3.52     |
| 31        | O      | HIS 203             | ionic       | 2.89     |
| 32        | O      | HIS 203             | ionic       | 3.84     |
| 33        | N      | GLU 206             | ionic       | 3.43     |

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| Conformer | Ligand | Residues in TMPRSS2 | Interaction | Distance |
|-----------|--------|---------------------|-------------|----------|
| 0         | LYS    | 302                 | H-acceptor  | 3.26     |
| 0         | LYS    | 302                 | H-acceptor  | 2.94     |
| 0         | LYS    | 302                 | ionic       | 2.94     |
| 6-ring    | GLY    | 303                 | pi-H        | 3.86     |
| 5         | HIS    | 203                 | ionic       | 3.62     |
| 6-ring    | HIS    | 203                 | pi-cation   | 4.12     |
| 6         | HIS    | 203                 | H-acceptor  | 2.91     |
| 0         | HIS    | 203                 | H-acceptor  | 3.01     |
| 0         | HIS    | 203                 | ionic       | 3.01     |
| 0         | HIS    | 203                 | ionic       | 3.36     |
| 7         | CYS    | 381                 | H-donor     | 3.74     |
| 0         | GLY    | 351                 | H-acceptor  | 3.12     |
| 0         | LYS    | 383                 | H-acceptor  | 3.18     |
| 0         | CYS    | 381                 | H-acceptor  | 3.01     |
| 0         | LYS    | 383                 | ionic       | 3.06     |
| 0         | LYS    | 383                 | ionic       | 3.18     |
| 8         | CYS    | 381                 | ionic       | 3.2      |
| 0         | LYS    | 383                 | H-acceptor  | 3.16     |
| 0         | CYS    | 381                 | H-acceptor  | 3.35     |
| 0         | LYS    | 302                 | H-acceptor  | 2.86     |
| 0         | LYS    | 302                 | ionic       | 2.86     |
| 9         | CYS    | 381                 | H-donor     | 3.74     |
| 0         | LYS    | 383                 | H-acceptor  | 3.2      |
| 0         | CYS    | 381                 | H-acceptor  | 3.01     |
| 0         | LYS    | 383                 | H-acceptor  | 3.02     |
| 0         | LYS    | 383                 | ionic       | 3.2      |
| 0         | LYS    | 383                 | ionic       | 3.02     |
| 10        | HIS    | 203                 | H-acceptor  | 3.04     |
| 0         | HIS    | 203                 | ionic       | 3.97     |
| 0         | HIS    | 203                 | ionic       | 3.3      |
| 11        | HIS    | 203                 | H-acceptor  | 2.89     |
| 0         | HIS    | 203                 | H-acceptor  | 2.96     |
| 0         | HIS    | 203                 | ionic       | 3.94     |
| 0         | HIS    | 203                 | ionic       | 2.96     |
| 12        | GLY    | 351                 | H-acceptor  | 2.93     |
| 0         | HIS    | 203                 | H-acceptor  | 2.87     |
| 0         | HIS    | 203                 | ionic       | 3.43     |
| 0         | HIS    | 203                 | ionic       | 2.87     |
| 13        | GLY    | 351                 | H-acceptor  | 3.19     |
| 0         | GLN    | 350                 | H-acceptor  | 3.15     |
| 0         | LYS    | 302                 | H-acceptor  | 2.99     |
| 0         | GLY    | 303                 | H-acceptor  | 3.09     |
| 0         | LYS    | 302                 | ionic       | 2.99     |
| 0         | LYS    | 302                 | ionic       | 3.94     |
| 14        | HIS    | 203                 | H-acceptor  | 3.1      |
| 0         | HIS    | 203                 | H-acceptor  | 2.87     |
| 0         | HIS    | 203                 | ionic       | 2.87     |
| 15        | HIS    | 203                 | H-acceptor  | 3.07     |
| 0         | HIS    | 203                 | H-acceptor  | 3.08     |
| 0         | HIS    | 203                 | ionic       | 2.87     |
| 16        | HIS    | 203                 | H-acceptor  | 2.9      |
| 0         | HIS    | 203                 | ionic       | 2.9      |
| 0         | HIS    | 203                 | ionic       | 3.3      |
| 17        | GLY    | 351                 | H-acceptor  | 2.92     |
| 0         | HIS    | 203                 | H-acceptor  | 2.9      |
| 0         | HIS    | 203                 | ionic       | 2.9      |
| 0         | HIS    | 203                 | ionic       | 3.88     |
| 0         | LYS    | 383                 | H-acceptor  | 3.14     |
| 0         | LYS    | 302                 | H-acceptor  | 2.95     |
| 0         | LYS    | 302                 | ionic       | 3.41     |
| 19        | HIS    | 203                 | H-acceptor  | 2.75     |
| 0         | HIS    | 203                 | ionic       | 3.81     |
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 188             | H-donor      | 2.9      |
|           | O      | CY5 348             | H-donor      | 2.96     |
| 2         | O      | HIS 203             | H-acceptor   | 3.21     |
| 3         | O      | GLY 351             | H-acceptor   | 3.4      |
| 4         | O      | HIS 203             | H-donor      | 3.14     |
| 5         | O      | VAL 187             | H-donor      | 2.94     |
|           | O      | HIS 203             | H-donor      | 2.94     |
| 6         | O      | SER 348             | H-donor      | 2.97     |
|           | O      | GLY 378             | H-donor      | 2.82     |
| 8         | O      | SER 348             | H-donor      | 3.04     |
|           | O      | HIS 203             | H-acceptor   | 3.23     |
| 9         | O      | GLY 351             | H-acceptor   | 3.04     |
|           | O      | GLY 378             | H-donor      | 2.91     |
| 10        | O      | HIS 203             | H-donor      | 3        |
| 11        | O      | SER 348             | H-donor      | 3.05     |
| 12        | O      | SER 348             | H-donor      | 2.98     |
| 13        | O      | CY5 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     |
| 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      | CY5 349             | H-donor      | 2.96     |
| 20        | O      | SER 379             | H-donor      | 3        |
| 21        | O      | HIS 203             | H-acceptor   | 2.95     |
| 22        | O      | ASN 249             | H-acceptor   | 3.04     |
|           | 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                 | H-donor     | 2.98     |
| 2         | N      | VAL                 | H-donor     | 3.42     |
| 3         | 6-ring | GLY                 | H-donor     | 4.05     |
| 4         | N      | SER                 | H-donor     | 3.28     |
| 5         | N      | HIS                 | H-acceptor  | 3.04     |
| 6         | N      | GLY                 | H-donor     | 3.12     |
| 7         | C      | TRP                 | H-pi        | 4.41     |
| 8         | N      | VAL                 | H-donor     | 2.92     |
| 9         | N      | CYS                 | H-donor     | 2.99     |
| 10        | BR     | SER                 | H-donor     | 3.6      |
| 11        | N      | CYS                 | H-donor     | 2.87     |
| 12        | 6-ring | HIS                 | pi-cation   | 4.73     |
| 13        | BR     | VAL                 | H-donor     | 3.67     |

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

T1.-
algae_at 0.0160146
Ames_test mutagen
Carcino_Mouse negative
Carcino_Rat negative
daphnia at 0.0368447
hERG_inhibition medium_risk
medaka at 0.00317449
minnow at 0.0141893
TA100_10RLI positive
TA100 NA negative
TA1535_10RLI negative
TA1535 NA negative

T2.-
algae_at 0.00318792
Ames_test mutagen
Carcino_Mouse negative
Carcino_Rat negative
daphnia at 0.00243684
hERG_inhibition low_risk
medaka at 2.3298e-005
minnow at 0.000274219
TA100_10RLI positive
TA100 NA negative
TA1535_10RLI negative
TA1535 NA negative

T3.-
algae_at 0.00162258
Ames_test mutagen
Carcino_Mouse negative
Carcino_Rat positive
daphnia at 0.00107575
hERG_inhibition medium_risk
medaka at 6.44964e-006
minnow at 2.22289e-005
TA100_10RLI negative
TA100 NA negative
TA1535_10RLI negative
TA1535 NA negative

T4.-
algae_at 0.013343
Ames_test mutagen
Carcino_Mouse negative
Carcino_Rat positive
daphnia at 0.0123293
hERG_inhibition high_risk
medaka at 0.000530206
minnow at 0.00376132
TA100_10RLI positive
TA100 NA positive
TA1535_10RLI positive
TA1535 NA negative

T5.-
algae_at 0.00253114
Ames_test mutagen
Carcino_Mouse negative
Carcino_Rat positive
daphnia at 0.000552924
hERG_inhibition medium_risk
medaka at 1.77373e-006
minnow at 1.69902e-005
TA100_10RLI positive
TA100 NA negative
TA1535_10RLI positive
TA1535 NA negative

T6.-
algae_at 0.00292094
Ames_test mutagen
Carcino_Mouse non-mutagen
Carcino_Rat negative
daphnia at 0.000115612
hERG_inhibition medium_risk
medaka at 7.43255e-008
minnow at 6.1832e-007
TA100_10RLI negative
TA100 NA negative
TA1535_10RLI negative
TA1535 NA negative

T7.-
algae_at 0.00948831
Ames_test mutagen
Carcino_Mouse negative
Carcino_Rat negative
daphnia at 0.010758
hERG_inhibition medium_risk
medaka at 0.000413187

T8.-
algae_at 0.00163506
Ames_test mutagen
Carcino_Mouse negative
Carcino_Rat negative
daphnia at 0.00035623
hERG_inhibition low_risk
medaka at 9.18187e-007

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

| Compound | BBB | Buffer_solubility_mg_L | Caco2 | CYP_2C19_inhibition | CYP_2C9_inhibition | CYP_2D6_inhibition | CYP_2D6_substrate | CYP_3A4_inhibition | CYP_3A4_substrate | HIA | MDCK | Pgp_inhibition | Plasma_Protein_Binding | Pure_water_solubility_mg_L | Skin_Permeability | SKlogD_value | SKlogP_value | SKlogS_buffer | SKlogS_pure | Skin_Permeability | SKlogD_value | SKlogP_value | SKlogS_buffer | SKlogS_pure |
|----------|-----|------------------------|-------|---------------------|-------------------|------------------|------------------|------------------|------------------|-----------------|-------|----------------|---------------------|------------------------|----------------------|----------------|--------------|--------------|--------------|------------|----------------|--------------|--------------|--------------|------------|
| T1       | 0.0792184 | 0.014869 | 35.6274 | Non | Non | Non | Non | Non | Non | Non | 48.9391 | 98.183640 | 0.00112507 | 92.897893 | 4.417320 | 5.926930 | 8.690900 | 8.690900 | 92.897893 | 4.417320 | 5.926930 | 8.690900 | 8.690900 |
| T2       | 0.216377 | 0.014869 | 35.6274 | Non | Inhibitor | Non | Non | Non | Non | Substrate | 97.710828 | 91.538989 | 98.183640 | 0.00112507 | 92.897893 | 4.417320 | 5.926930 | 8.690900 | 8.690900 | 92.897893 | 4.417320 | 5.926930 | 8.690900 | 8.690900 |
| T3       | 0.083469 | 10.9611** | 30.3638 | Non | Inhibitor | Non | Non | Non | Non | Substrate | 86.813998 | 90.189898 | 99.658773 | 0.00631993 | 92.897893 | 4.417320 | 5.926930 | 8.690900 | 8.690900 | 92.897893 | 4.417320 | 5.926930 | 8.690900 | 8.690900 |
| T4       | 0.0532063 | 7.61522** | 30.71092 | Non | Inhibitor | Non | Non | Non | Non | Substrate | 86.813998 | 90.189898 | 99.658773 | 0.00631993 | 92.897893 | 4.417320 | 5.926930 | 8.690900 | 8.690900 | 92.897893 | 4.417320 | 5.926930 | 8.690900 | 8.690900 |
| T5       | 0.140888 | 2.46049** | 13.9488 | Non | Inhibitor | Non | Non | Non | Non | Substrate | 92.897893 | 92.897893 | 92.897893 | 92.897893 | 92.897893 | 4.417320 | 5.926930 | 8.690900 | 8.690900 | 92.897893 | 4.417320 | 5.926930 | 8.690900 | 8.690900 |
| T6       | 0.128735 | 1.64836e-006 | 23.2206 | Non | Inhibitor | Non | Non | Non | Non | Substrate | 92.897893 | 92.897893 | 92.897893 | 92.897893 | 92.897893 | 4.417320 | 5.926930 | 8.690900 | 8.690900 | 92.897893 | 4.417320 | 5.926930 | 8.690900 | 8.690900 |
HIA 99.252848
MDCK 0.0183324*
Pgp_inhibition Inhibitor
Plasma_Protein_Binding 95.313410
Pure_water_solubility_mg_L 0.00147252
Skin_Permability -2.64495
SKlogD_value 5.322230
SKlogP_value 5.322230
SKlogS_buffer -5.369000**
SKlogS_pure -8.591960

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 0.00204566
Skin_Permability -3.65081
SKlogD_value 4.626720
SKlogP_value 4.626720
SKlogS_buffer -3.638470**
SKlogS_pure -6.870820

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

T1.-
Density: 1.1±0.1 g/cm3
Boiling Point: 29.644
Vapour Pressure:
Enthalpy of Vaporization:
Flash Point: 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: 268.431
Vapour Pressure:
Enthalpy of Vaporization:
Flash Point: 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

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| Property                  | Value                  | Property                  | Value                  |
|--------------------------|------------------------|--------------------------|------------------------|
| ACD/BCF (pH 7.4)         | 1475.90                | ACD/BCF (pH 7.4)         | 2437.13                |
| ACD/KOC (pH 7.4)         | 6451.96                | ACD/KOC (pH 7.4)         | 9244.25                |
| Polarizability           | 55.4±0.5 10-24cm³      | Polarizability           | 60.1±0.5 10-24cm³      |
| Surface Tension          | 41.6±7.0 dyne/cm       | Surface Tension          | 53.3±7.0 dyne/cm       |
| Molar Volume             | 431.3±7.0 cm³          | 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 ± 2 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:    |
|                          |                        |                          | 1.779                  |
|                          |                        |                          | 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 ± 2 Å²             |
|                          |                        |                          | Polarizability         |
|                          |                        |                          | 55.0±0.5 10-24cm³      |
|                          |                        |                          | Surface Tension        |
|                          |                        |                          | 96.1±5.0 dyne/cm       |
|                          |                        |                          | Molar Volume           |
|                          |                        |                          | 331.2±5.0 cm³          |

T7

| Property                  | Value                  | Property                  | Value                  |
|--------------------------|------------------------|--------------------------|------------------------|
| ACD/BCF (pH 7.4)         | 1475.90                | ACD/BCF (pH 7.4)         | 2437.13                |
| ACD/KOC (pH 7.4)         | 6451.96                | ACD/KOC (pH 7.4)         | 9244.25                |
| Polarizability           | 55.4±0.5 10-24cm³      | Polarizability           | 60.1±0.5 10-24cm³      |
| Surface Tension          | 41.6±7.0 dyne/cm       | Surface Tension          | 53.3±7.0 dyne/cm       |
| Molar Volume             | 431.3±7.0 cm³          | Molar Volume             | 406.1±7.0 cm³          |
| T8                       | 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                  |
| Property                          | Value          | Property                          | Value          |
|----------------------------------|----------------|----------------------------------|----------------|
| ACD/KOC (pH 7.4):                | 501.71         | ACD/KOC (pH 7.4):                | 351.20         |
| Polarizability                   | 55.6±0.5 10-24cm³ | Polarizability                   | 71.1±0.5 10-24cm³ |
| Surface Tension                  | 66.0±7.0 dyne/cm | Surface Tension                  | 83.2±5.0 dyne/cm |
| Molar Volume                     | 349.8±7.0 cm³  | Molar Volume                     | 454.5±5.0 cm³  |
| Polar Surface Area               | 201 Å²         | Polar Surface Area               | 232 Å²         |
| Polarizability                   | 232 Å²         | Polarizability                   | 71.1±0.5 10-24cm³ |
| Surface Tension                  | 66.0±7.0 dyne/cm | Surface Tension                  | 83.2±5.0 dyne/cm |
| Molar Volume                     | 349.8±7.0 cm³  | 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