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Evaluation of Aryl amidines/benzimidazoles as Potential Anti-COVID-19 Agents: A computational study

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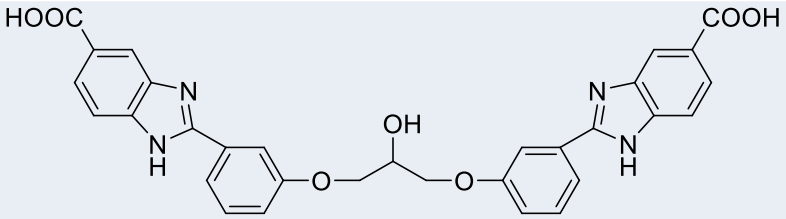
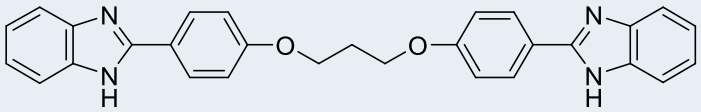
Evaluation of Aryl amidines/benzimidazoles as Potential Anti-COVID-19 Agents: A computational study

Graphical Abstract

		Binding Energy (Kcal/mol)		
		3CLpro	GRP78	TMPRSS2
1228		-9.3	-10.5	-6.3
523		-7.6	-	-7.4

Abstract

In silico drug design techniques were used to identify several small molecules as potential therapeutics against the coronavirus SARS-CoV-2 which causes COVID-19. A group of 12 approved and experimental drugs containing benzamidine or/and benzimidazoles moieties as key structural motifs were found to have good binding affinity to the viral protease 3CLpro, and the host proteins GRP78 and TMPRSS2. The targeted proteins are attractive drug targets since they are essential to the entry and replication of the virus in host cells. Two of the experimental compounds, bearing the benzimidazole moiety, were found to have stronger binding to the three targeted proteins than the approved drugs (dabigatran, nafomostat, pentamidine). The stronger binding of the compounds is attributed to greater hydrogen bonding, hydrophobic, and pi-pi interactions with the respective targeted proteins.

Keywords: 3-Chymotrpsin like protease (3CLpro); Glucose Regulated Protein 78 (GRP78); Transmembrane protease serine 2 (TMPRSS2); benzamidine; benzimidazole; molecular docking

Introduction

COVID-19 is a highly contagious viral disease for which no specific approved drugs or vaccines are currently available. Consequently, there is an urgent global effort to develop effective therapeutics. Biochemical pathways that are crucial in the life cycle of the coronavirus, SARS-CoV-2, represent attractive targets for drug development. We have identified three proteins as potential drug targets, based on the observations that several clinically used drugs, namely, dabigatran and nafamostat, may modulate the activity of these proteins.

3CLpro is the main viral protease that plays a crucial role in facilitating viral replication and transcription. GRP78 has recently been suggested to be a host receptor for the virus spike protein, which, upon binding, facilitates initial infection of host cell. TMPRSS2 is a host protease, which primes the spike protein for entry and fusion into the host cells.

Three approved drugs and nine experimental molecules, all of which contain the benzamidine and/or benzimidazole moiety, were selected for this *in silico* study.

Approved Drugs (structures shown in Table 1):

- Nafamostat is an anticoagulant used for acute pancreatitis. It inhibits SARS-CoV-2 infection of human lung cell line calu-3 with EC_{50} ~ 10nM (1). It is an inhibitor of TMPRSS2.
- Dabigatran is an anticoagulant used for strokes and systemic embolism. It has been suggested to inhibit 3CLpro (2)
- Pentamidine is used in the treatment of African trypanosomiasis, leishmaniasis, and pneumocystis pneumonia.

Experimental Compounds (structures shown in Tables 2 and 3)

Nine representative bisbenzamidines (Table 2) and bisbenzimidazoles (Table 3) were selected for this study. The synthesis, antifungal and antiparasitic properties of these compounds have been reported (3-5).

References:

(1) Yamamota, M. et al., *BioRviv preprint*:http://doi.0rg/10.1101/2020.04.22.054981
(2) Eleftheriou, P. et al., *Molecules*, **2020**, 25, 2529
(3) Mayence, A. et al., *Eur. J. Med. Chem*., **2004**, 39, 547
(4) Mayence, A. et al., *J. Med. Chem*., **2004**, 47, 2700
(5) Mayence A., et al., *Bioorg. Med. Chem*., **2011**, 19, 7493

In silico drug design techniques

- The crystallographic structures of both SARS-CoV-2 3CLpro (PDB ID: 6LU7) (6) and GRP78 (PDB ID: 5E84) (7), as well as a homology model for TMPRSS2 (8) were used as the biomacromolecular receptors in molecular docking simulations.
- The structures of the ligands were energy minimized using the Universal Force Field Molecular Mechanics method (9).
- The docking simulations were performed with AutoDock Vina 1.1.2 software (10).
- Molecular graphic representations were performed with PoseView 1.1.2 (11) softwares.

References:
(6) Jin, Z. et al., *Nature*, **2020**, 582, 289
(7) Yang, J. et al., *Structure*, **2015**, 23, 2191
(8) Rahman, N. et al., *Molecules*, **2020**, 25, 2271
(9) Rappe, A. et al., *J. Am. Chem. Soc.*, **1992**, 114, 10024
(10) Trott, O. et al., *J. Comput. Chem.*, **2010**, 31, 455
(11) Stierand, K. et al., *Med. Chem. Lett.*, **2010**, 1, 540

Results and discussion

Table 1. Structure and binding energy of approved drugs toward targeted proteins

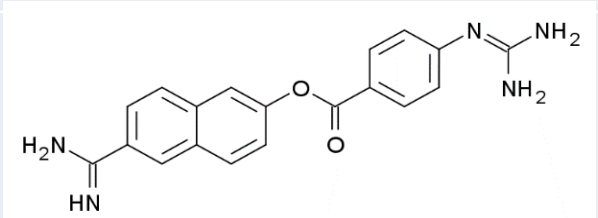
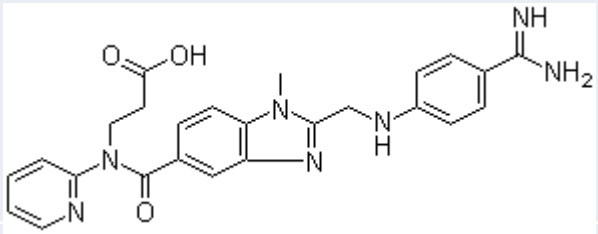
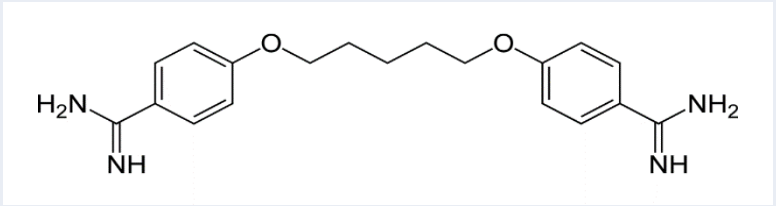
Names/Structures	Binding Energy (Kcal/mol)		
	3CLpro	GRP78	TMPRSS2
Nafamostat 	-8.6	-10.0	-7.1
Dabigatran 	-7.8	-9.8	-7.1
Pentamidine 	-6.8	-8.8	-

Table 2. Structure and binding energy of bisbenzamidines toward targeted proteins

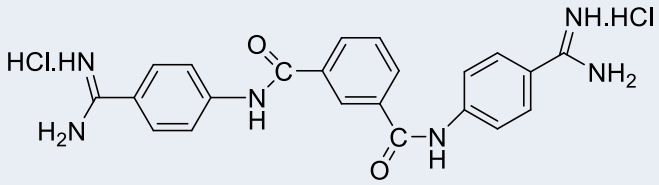
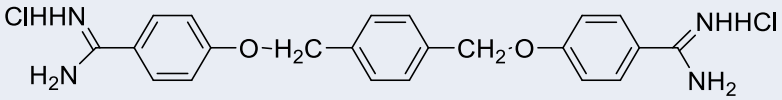
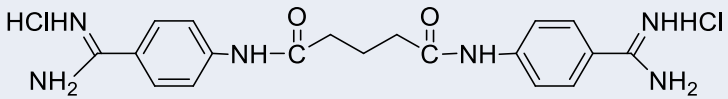
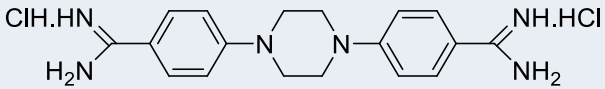
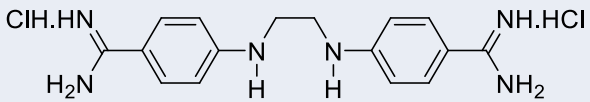
Names/Structures of bisbenzamidines	Binding Energy (Kcal/mol) 3CLpro	GRP78	TMPRSS2
322 	-7.8	-9.5	-7.3
508 	-7.4	-10.1	-7.3
701 	-7.3	-9.2	-6.8
103 	-7.1	-6.1	-
1131 	-6.8	-9.2	-6.1

Table 3. Structure and binding energy of bisbenzimidazoles toward targeted proteins

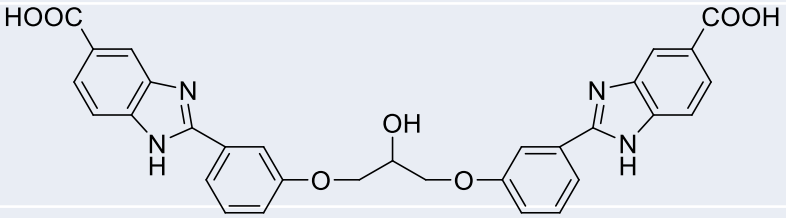
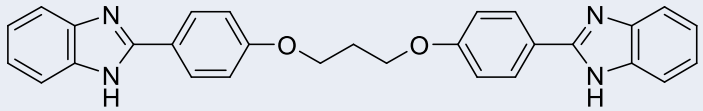
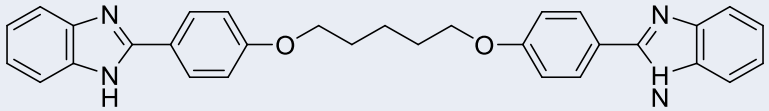
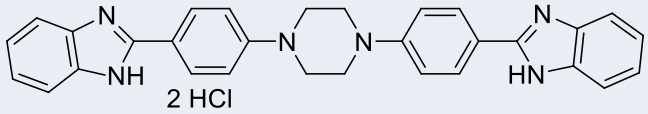
Names/Structures of bisbenzimidazoles		Binding Energy (Kcal/mol)		
		3CLpro	GRP78	TMPRSS2
1228		-9.3	-10.5	-6.3
523		-7.6	-	-7.4
1203		-6.1	-9.5	-7.2
115		-	-	-7.3

Figure 1. 2D-binding interactions of 1228 with 3CLpro

Strong binding affinity (-9.3 Kcal/mol) of 1228 to 3CLpro is due to:

- **Hydrogen bonds with Ser144, Glu166, Cys145, Thr190**
- **Hydrophobic interactions with His41, Met165, Gln189**

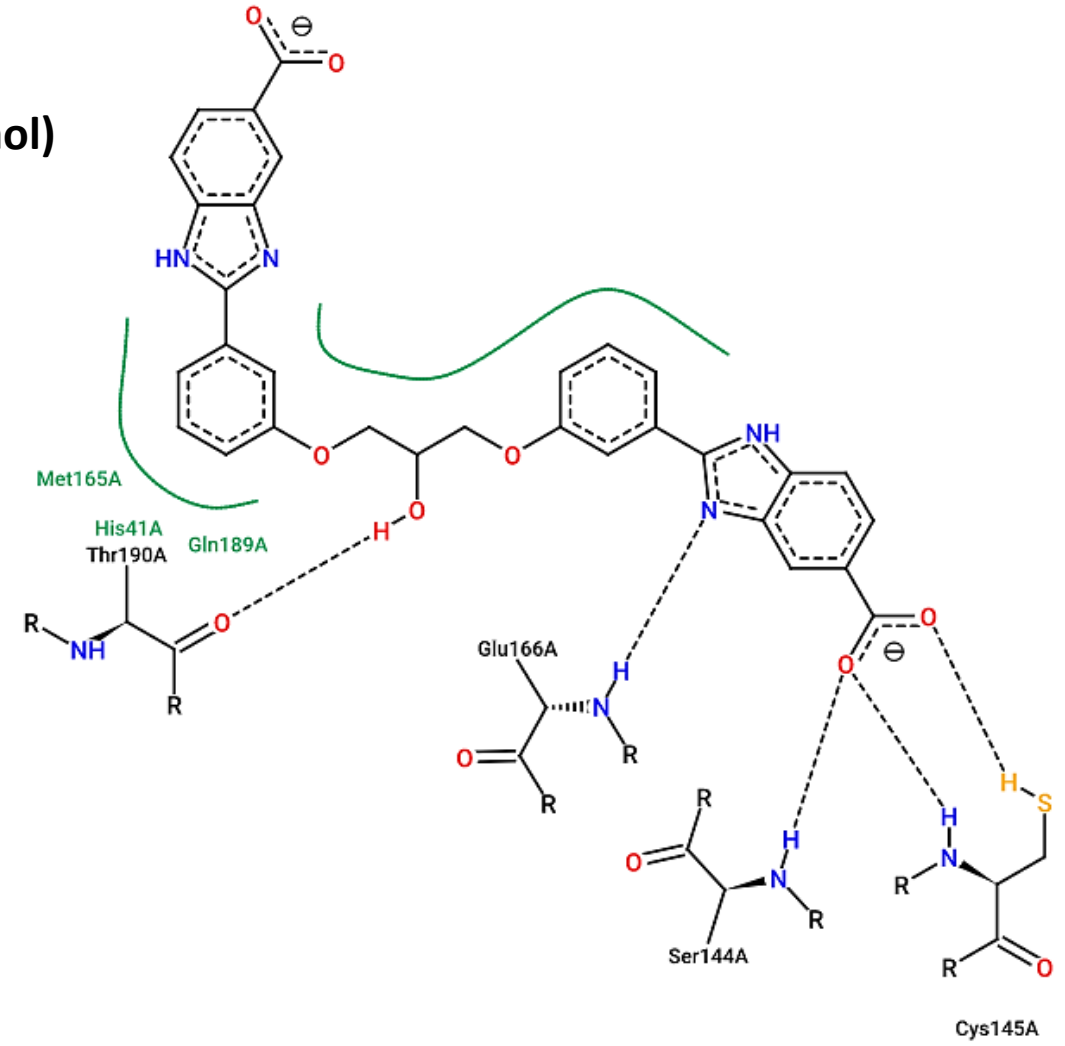


Figure 2. 2D-binding interactions of Nafamostat with 3CLpro

Strong binding affinity (-8.6 Kcal/mol) of Nafamostat to 3CLpro is due to:

- **Hydrogen bonds with Arg188, Thr190**

- **Hydrophobic interactions wit His41, Met165, Gln189**

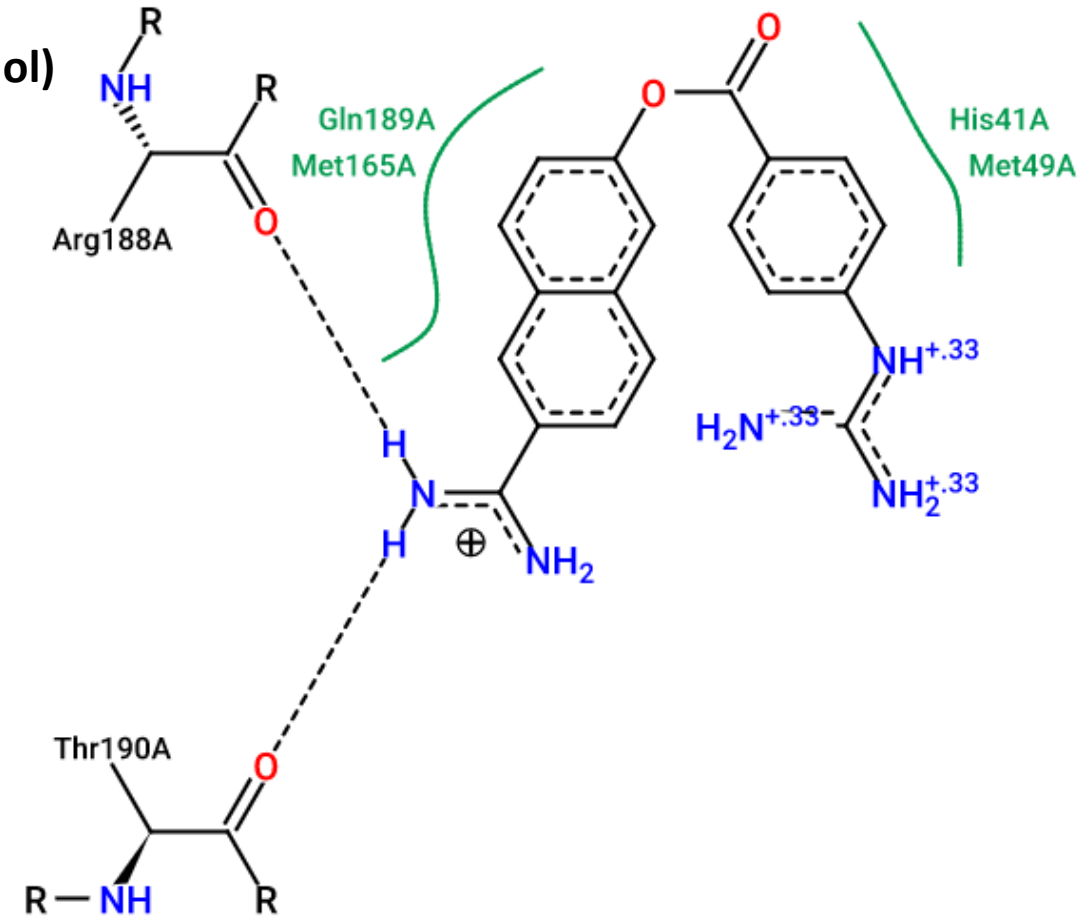


Figure 3. 2D-binding interactions of 1228 with GRP78

Strong binding affinity (-10.5 Kcal/mol) of 1228 to GRP78 is due to:

- **Hydrogen bonds with**

Thr37, Thr38, Lys96, Glu201, Lys296

- **Hydrophobic interactions with**

Tyr39, Ile61, Gly226, Arg297, Arg 367

- **Pi interactions with**

Tyr39

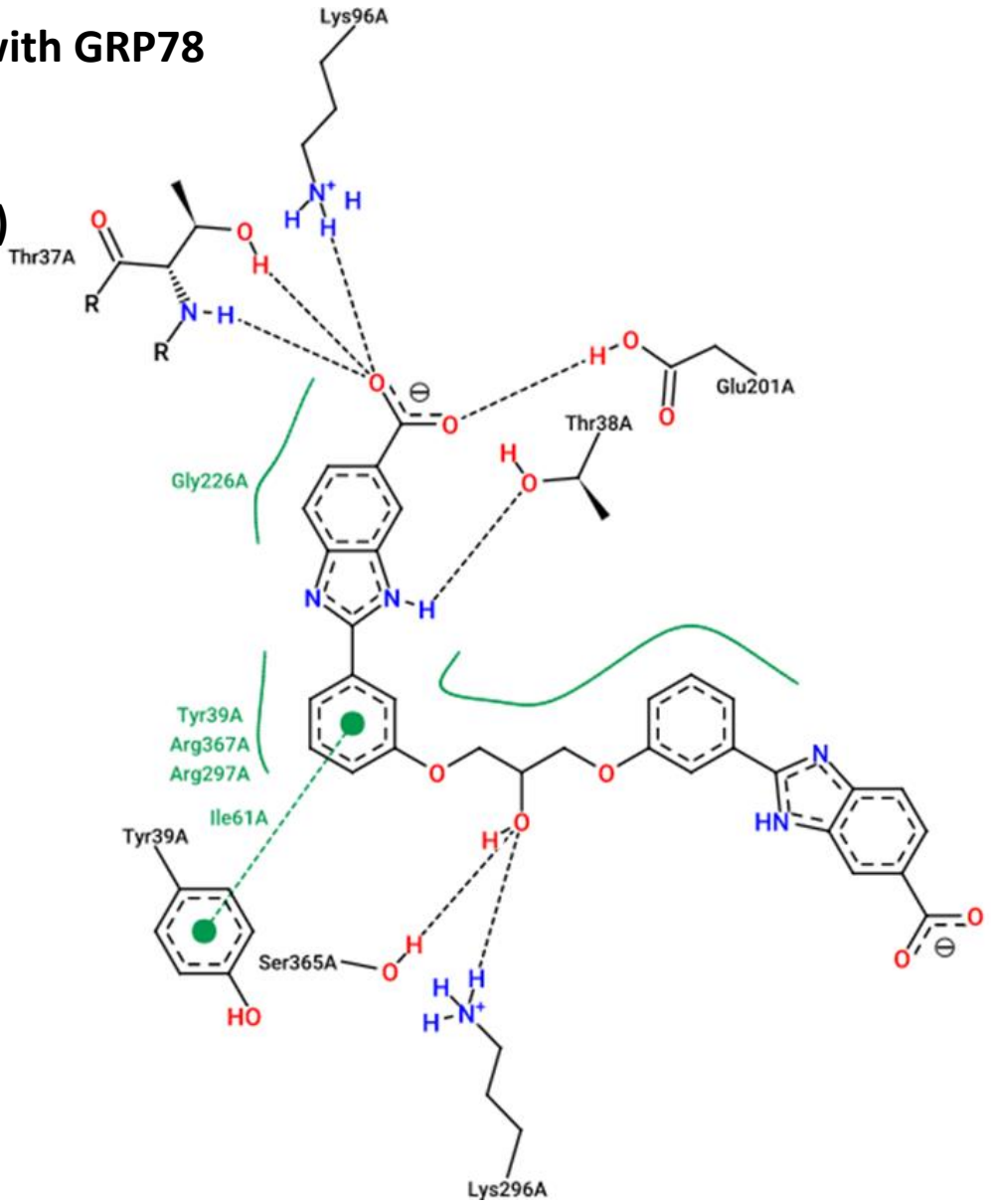


Figure 4. 2D-binding interactions of Nafamostat with GRP78

Strong binding affinity (-10.0 Kcal/mol) of Nafamostat to GRP78 is due to:

- **Hydrogen bonds with Thr38, Lys296**
- **Hydrophobic interactions with Arg297, Gly364, Arg367**

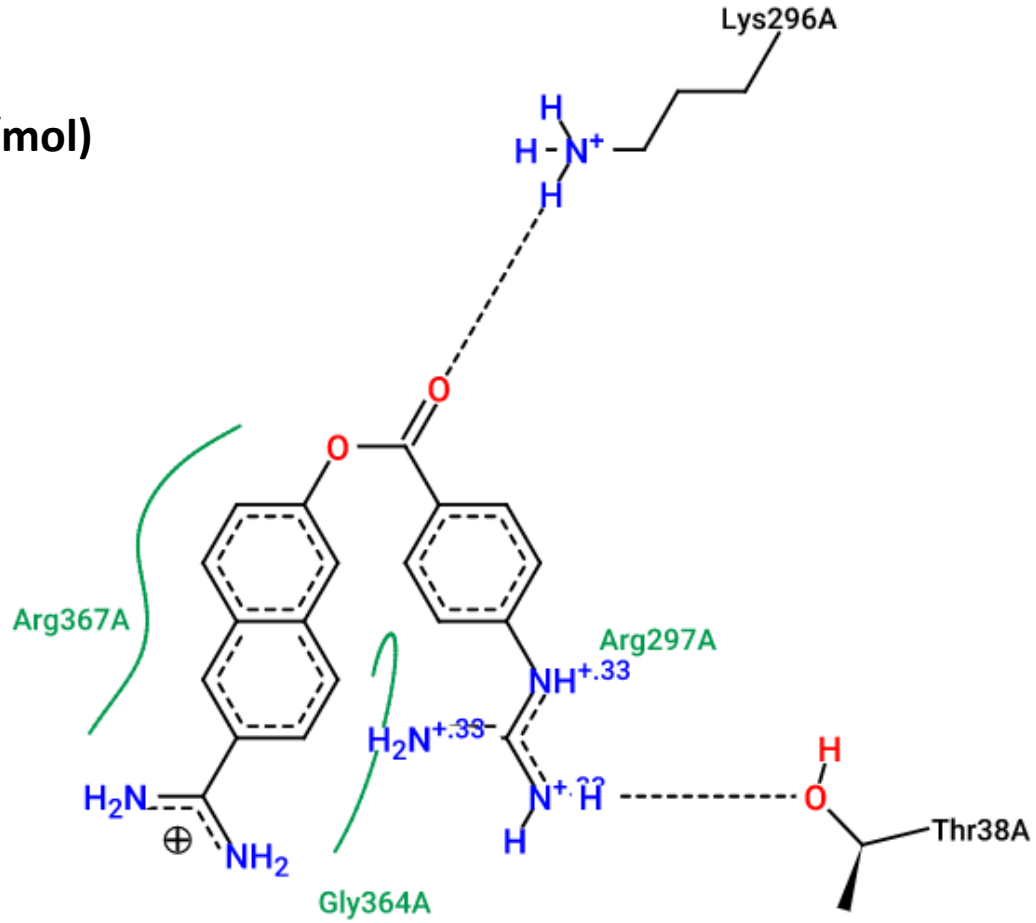


Figure 5. 2D-binding interactions of 523 with TMPRSS2

Strong binding affinity (-7.4 Kcal/mol) of 523 to TMPRSS2 is due to:

- **Hydrogen bonds with Leu151**
- **Hydrophobic interactions with Arg150, Leu151, Tyr152, Tyr190**
- **Pi interactions with Arg150, Tyr152, Tyr190**

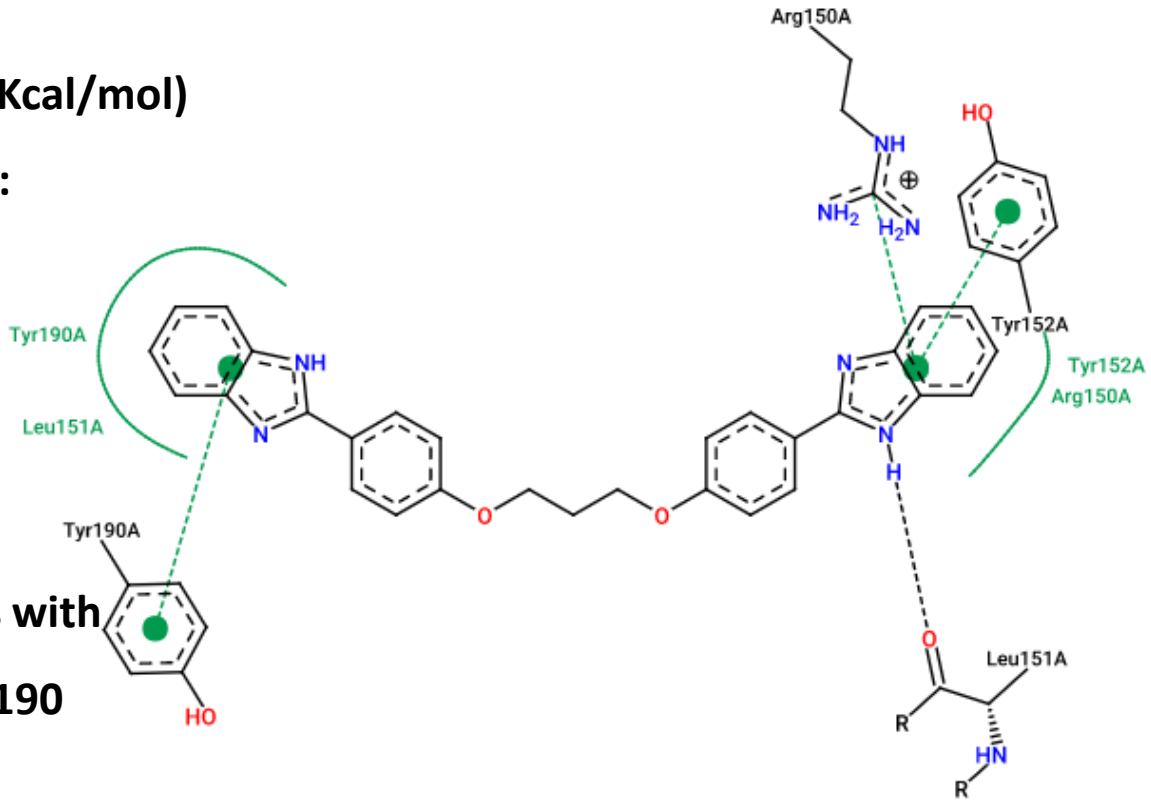
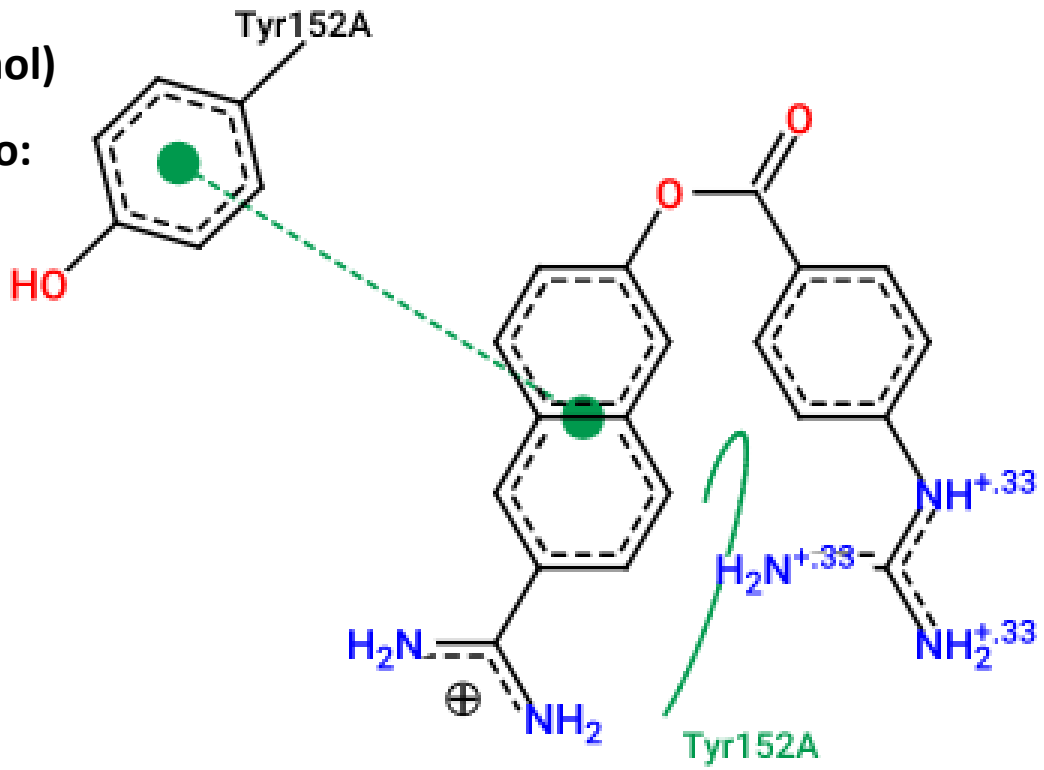


Figure 6. 2D-binding interactions of Nafamostat with TMPRSS2

Strong binding affinity (-7.1 Kcal/mol) of nafamostat to TMPRSS2 is due to:

- **Hydrophobic interactions with Tyr152**
- **Pi interactions with Tyr152**



Conclusions

- *In silico* results indicate that two experimental bisbenzimidazoles have stronger binding affinity to targeted proteins than approved drugs Nafamostat, Dabigatran, or Pentamidine
- 1228 showed the lowest binding energy of -9.3 Kcal/mol with 3CLpro and -10.5 Kcal/mol with GRP 78.
- 523 showed the lowest binding energy of -7.4 Kcal/mol with TMPRSS2.
- Strong binding affinity of above compounds is due to greater hydrogen bonding, hydrophobic interactions, and/or pi interactions with targeted proteins.

Acknowledgments

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