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Preliminary communication

AXL inhibitors selected by molecular docking: Option for reducing SARS-CoV-2 entry into cells

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ABSTRACT

The COVID-19 pandemic is ongoing and the benefit from vaccines is still insufficient since COVID-19 continues to be diagnosed in vaccinated individuals. It is, therefore, necessary to propose specific pharmacological treatments against COVID-19. A new therapeutic target on the human cellular membrane is AXL (*anexelekto*), proposed as an independent pathway by which interaction with the S protein of SARS-CoV-2 allows the virus to enter the cell, without the participation of ACE2. AXL serves as another gate through which SARS-CoV-2 can enter cells. Therefore, any stage of COVID-19 could be ameliorated by hindering the interaction between AXL and SARS-CoV-2. This study proposes ten compounds (**1–10**), selected by molecular docking and using a library of nearly 500,000 compounds, to develop a new drug that will decrease the interaction of AXL with the S protein of SARS-CoV-2. These compounds have a specific potential site of interaction with AXL, between Glu59, His61, Glu70 and Ser74 amino acids. This site is necessary for the interaction of AXL with the S protein. With this, we propose to develop a new adjuvant treatment against COVID-19.

Keywords: COVID-19, SARS-CoV-2, AXL ligand, molecular docking, NTD-S1, S protein

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INTRODUCTION

The development of vaccines against COVID-19 brings numerous benefits, but still, it remains necessary to continue research to develop new drugs against this disease, as SARS-CoV-2 has caused more than 220 million cases and almost 4.5 million deaths around the world (by October 2021) (1). In the process of SARS-CoV-2 infection, different proteins of the cell membrane (ACE2, TMPRSS2 and NRP1) (2, 3) interact with the S protein of the virus, and work has been done to determine selective compounds against these proteins (4–7), to identify the importance and functions of these proteins in COVID-19, and to determine their expression in the cell membrane of different tissues (3, 8, 9).

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A member of the family of receptors of tyrosine kinase (RTKs) recently showed relevance for COVID-19, specifically the AXL receptor among three TAM RTKs: TYRO3, AXL, and MERTK (10). The AXL receptor (from Greek word *anexelekto*) (11) is found on the human cell membrane (8), and while not a part of the SARS-CoV-2 virus, AXL contributes to the infectious process of SARS-CoV-2 (12–14). Because of this, new factors that interact with SARS-CoV-2 (such as AXL) and contribute to the development of COVID-19 are still being discovered.

In this study, the AXL receptor is used as a therapeutic target for the development of a drug against COVID-19. The main ligand reported to bind to AXL is growth-arrest-specific 6 (GAS6) (15); this interaction has been associated with angiogenesis, cancer, metastasis, thromboembolism, and diseases of the immune and cardiovascular system (15, 16). The expression of AXL is associated with drug resistance and diminished long-term survival in a wide range of malignancies (17). In addition, this receptor is a critical factor during vascular injury (18, 19), and AXL inhibition reduces angiogenesis and tumour growth in experimental mouse models (15, 20). As a result, developments related to AXL were mainly focused on anti-cancer drugs and/or antibodies that seek to inhibit the interaction with GAS6 to avoid the signalling of this receptor tyrosine kinase in the cytoplasm (15, 18, 20–22).

Lastly, it has been reported that SARS-CoV-2 binds to cell receptors through the S protein, in which, a fusion process with the cell membrane is proposed. For this process, the S protein is cleaved in the S1 and S2 subunits primarily by the transmembrane protease serine protease 2 (TMPRSS2). The *N*-terminal domain (NTD) region in the S1 subunit has been identified (between Lys147-Lys150, Trp152, Arg246, Ser247 and Ser256 amino acids) and must interact with the Pro57, Pro58, Glu59, His61, Ile68, Glu70, Glu85 and Phe113 amino acids in AXL (8), in order to generate the interaction between the S protein and AXL. It has been determined that the His61 and Glu85 amino acids in AXL are especially important for maintaining the interaction with the NTD-S1 of the S protein, as there are reports in which the His61 and Glu85 amino acids have been knocked out and the interaction between AXL with S protein is subsequently lost (demonstrated in mice and ferrets) (8, 9).

Through molecular docking and a compound library (502,350 compounds), this study proposes compounds with a high probability of interacting with the AXL receptor in a region that is important for interacting with the NTD-S1 region of the S protein of SARS--CoV-2. This way, the compounds would decrease the interaction between the virus and the cell and contribute to the development of a drug against COVID-19. It is possible to study the effects of these compounds when interacting with recombinant proteins experimentally, thus evaluating the effects in the aforementioned processes.

EXPERIMENTAL

Preparation of receptor protein and selection of binding site

The crystal structure of the AXL receptor (obtained from the Protein Data Bank, www.rcsb.org/structure/4RA0) was used for molecular docking using Molecular Operating Environment (MOE2014), following previously reported procedures (6, 23). The potential site in AXL is between the Glu59, His61, Ile68 and Glu70 amino acids (8); this site was used to simulate interaction with compounds.

Compounds library

The EXPRESS-pick Collection Stock screening library Chembridge Corp. (24) was used for molecular docking. This collection of compounds contains 502,350 molecules that fulfil Lipinski's rules (25) and cover a broad swath of the chemical compound space.

Molecular docking

High-throughput virtual molecular docking was carried out by MOE, the potential binding site between amino acids Glu59, His61, Ile68 and Glu70 in AXL (PDB 4RA0), and up to 100 conformers of each compound were generated for docking. A flexible ligand--rigid receptor molecular docking was performed with MOE-Dock. Later the values of up to 30 conformers of each compound were analyzed, and the average $\Delta G_{binding}$ of each compound was determined, as previously reported (6, 23). The analysis of ligand interaction per amino acid was conducted using MOE.

Selection of the ten best compounds

From the docking results, up to 30 conformers for each compound were analyzed to determine their $\Delta G_{binding}$ averages in order to select the ten best compounds as previously reported (6, 23). Standard deviation was also calculated (using Excel Microsoft-365 software); with these results, the best $\Delta G_{binding}$ averages were determined for AXL with each compound. The description of physicochemical properties using PhysChem-ACD/Labs (26) and the theoretical toxicity (mutagenicity and carcinogenicity) of each compound selected were determined (27, 28).

RESULTS AND DISCUSSION

Selection of compounds by molecular docking

In this study, the EXPRESS-pick collection library from the Chembridge Corp. (24) with 502,350 compounds (up to 100 conformers generated of each compound) was used to study interaction in the AXL receptor between the Glu59, His61, Ile68 and Glu70 amino acids (Fig. 1), by molecular docking (4, 6, 23). The selection of the ten best compounds was determined through the average $\Delta G_{binding}$ of each compound using their conformers ($\Delta G_{binding}$ of 16 to 30 conformers) (6, 23), and an average range between –6.97 to –7.96 kcal mol^{-1} for the ten best compounds was determined (Table I, details in Table S1 in the Supplementary material). Ten compounds were selected and labelled from **1** to **10**, and the analysis of the interaction of each compound with AXL was carried out with the interaction report (Table II, and details in Tables S1–S11). All calculated averages of $\Delta G_{binding}$ are related to the number of interactions generated by the conformers analyzed from the molecular docking results (mainly hydrogen bonding, Table III), which show that the **1–10** compounds interact more frequently with the amino acids Glu59, His61 and Glu70.

In addition, the tables describing theoretical toxicity (Table S12), ADME characteristics (Table S13) and chemical properties of each compound **1–10** (Table S14), are included in the supplementary material.

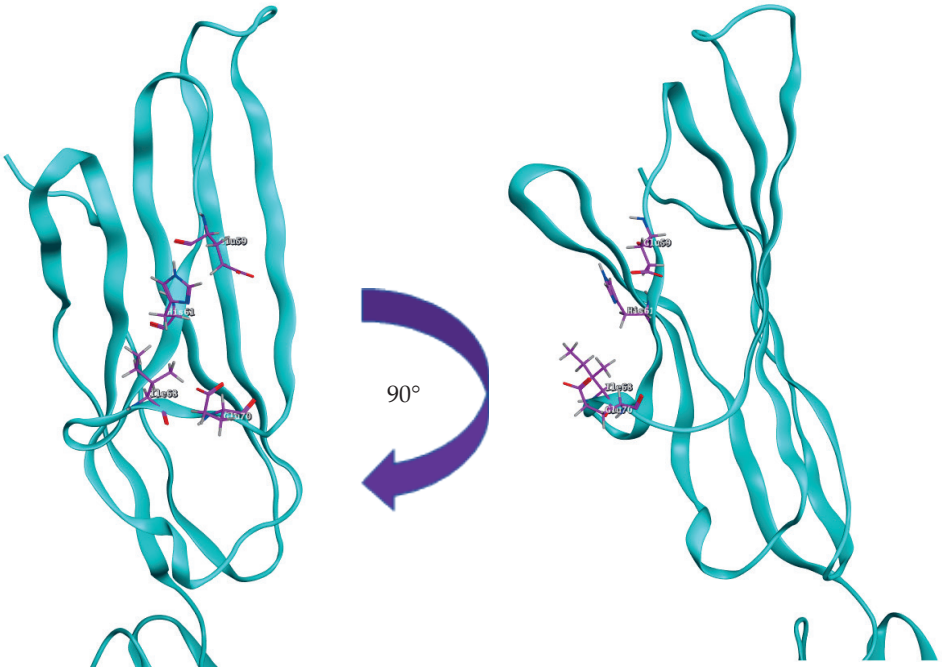

Fig. 1. AXL (cyan) shows amino acids Glu59, His61, Ile68 and Glu70 (pink) as regions chosen for molecular docking.

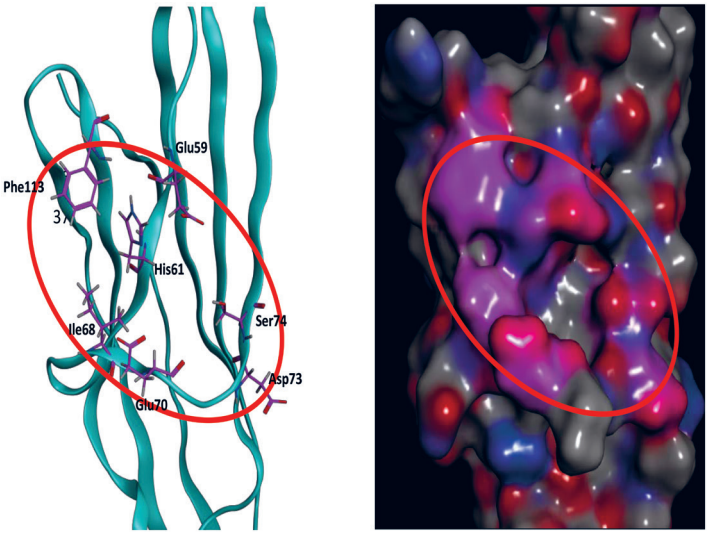

Fig. 2. Potential site with amino acids, His61 is essential for the interaction between AXL and S protein: a) Glu59, His61, Ile68, Glu70, Asp73, Ser74 and Phe113 amino acids (pink) into the red circle and b) pocket is displayed in the potential site.

*Table I. PubChem CID, ID Chembridge Corp./name and structure of the best ten compounds **1–10***

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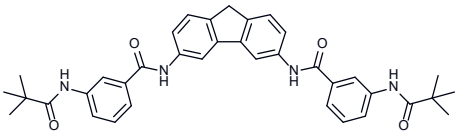	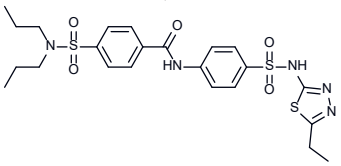
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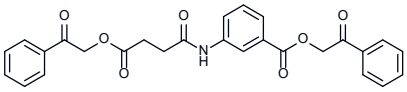	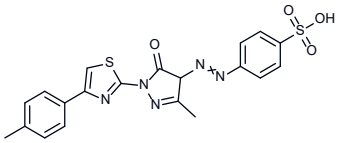
3	**4**
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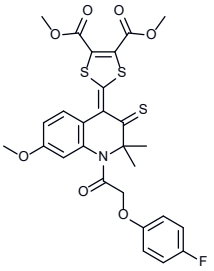
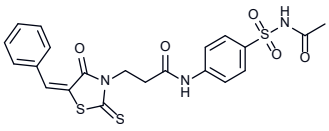
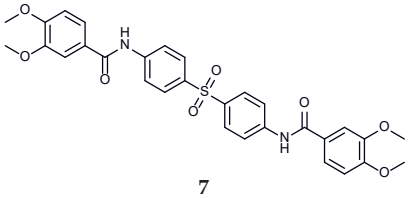
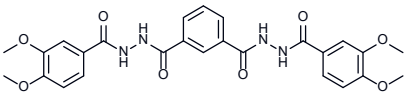
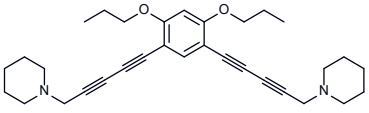
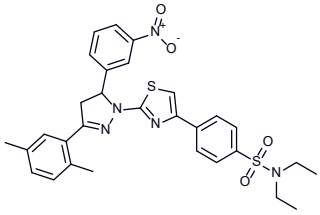
	
5	**6**
1356721, 5471527	2848441, 5479492
	
7	**8**
2848447, 5479532	2839849, 5302876
	
9	**10**

*Interaction of compounds **1–10** with AXL*

The interactions between each compound **1–10** with AXL were analyzed using up to 30 conformers of each compound interacting in the potential site (the region between the Glu59, His61, Ile68 and Glu70 amino acids) (Fig. 1). From molecular docking results (Tables S2–S11), it was determined that the main amino acids in AXL that interact with the compounds **1–10** are Glu59, His61, Trp62, Ile68, Leu69, Glu70, Ala72, Asp73, Ser74, Phe113 and Gly115. For these amino acids, the ten compounds exhibit different types of interaction with the potential site, such as H-acceptor, H-donor, ionic and pi-H (Fig. 2, Tables S2-S11), and, in particular, greater interaction with Glu59, His61 and Glu70 (mainly through hydrogen bonding interaction for the conformers analyzed). The amino acid His61, essential for AXL interaction with the S protein, could thus be blocked. The details of the interaction between AXL and the conformers of each compound are shown in the supplementary material (Figs. S1–S10).

Discussion

Global efforts continue to control and resolve the COVID-19 pandemic and to develop selective drugs that can treat COVID-19. As already mentioned, it remains necessary to understand the infectious process of SARS-CoV2, and key elements of the process continue to be reported regarding the introduction of the viral material into cells. The main known factors are TMPRSS2, ACE2, C-lectin type receptors (CLR), toll-like receptors (TLR) and NRP1 (3). Another route of entry into the cell is currently being proposed: *via* the tyrosine--protein kinase receptor (AXL), which specifically interacts with the NTD-S1 of the S protein of SARS-CoV-2 (8). This other route of entry has more support, both because AXL has effects on the reorganization of the cytoskeleton that promotes the entry of the virus (18) and because of study results that demonstrate a relationship between plasma levels of AXL and GAS6 and the severity of COVID-19 (18). Therefore, the increase of AXL expression increases the infectivity of SARS-CoV-2 and justifies the proposal of AXL as a therapeutic target.

There have been developments in anticancer drugs that use AXL as a therapeutic target, with which they seek to develop inhibitors of AXL's intracellular functions [kinase activity inhibitors: BMS-777607, bemcentinib, gilteritinib (18, 21, 22)]. In contrast, there have been few studies on the extracellular portion of AXL, but there are identified antibodies that interact in the NTD-S1 region of the S protein; this hinders interaction with the extracellular portion of the AXL (29). In addition, it has been shown that inhibiting the AXL functions does not affect viability in mice (15). A very important point to consider is limiting inhibition to AXL since there are reports where inhibiting other members of the TAM receptor family (TYRO3 and MERTK) generated harmful effects on the immune system (30).

This study is based on the region of the interaction site for GAS6 (ligand for AXL), between the Pro58 and Ile90 amino acids in AXL (15), performing a molecular docking between the amino acids reported as important for interacting with the NTD-S1 of the S protein (8). Through this, compounds **1–10** were determined with a high probability of interacting with the potential site proposed to hinder or block this region and avoid the interaction of AXL with the NTD-S1 of the S protein. It is proposed that the affinity of compounds **1–10** could be due to a better interaction with Glu59, His61, Glu70, Asp73 and Ser74 amino acids (Table III) to generate more interactions with Glu59 and His61 that are necessary for the interaction between AXL and the S protein (8). Additionally, it is reported

Table II. PubChem CID, canonical SMILES, interaction with amino acids in AXL, number of conformers analyzed, an average of $\Delta G_{binding}$*, Ames test and* LD_{50}

Comp. PubChem CID	Canonical SMILES	Interaction with amino acids in AXL[a]	Number of conformers	$\Delta G_{binding}$ ± SD (kcal mol^{-1})[b]	PreADMET Ames test and LD_{50} –TA100_10RL –TA100_NA –TA1535_10R –TA1535_NA Predicted LD_{50} (mg kg^{-1})
1 2849840	CC(C)(C)C(=O)NC1=CC=CC(=C1)C(=O)NC2=CC3=C(CC4=C3C=C(C=C4)NC(=O)C5=CC(=CC=C5)NC(=O)C(C)(C)C)C=C2	Glu56, **Glu59**, His61, Glu70, **Gln76**, **Phe113**	28	–7.96 ± 0.46	Non-mutagen -Negative -Negative -Negative -Negative 1600 mg kg^{-1}
2 2839288	CCCN(CCC)S(=O)(=O)C1=CC=C(C=C1)C(=O)NC2=CC=C(C=C2)S(=O)(=O)NC3=NN=C(S3)CC	**Glu59**, **His61**, Trp62, Leu69, **Glu70**, Ala72, Asp73, **Ser74**, Phe113	26	–7.48 ± 0.50	Non-mutagen -Negative -Negative -Negative -Negative 1650 mg kg^{-1}
3 3099147	C1=CC=C(C=C1)C(=O)COC(=O)CCC(=O)NC2=CC=CC(=C2)C(=O)OCC(=O)C3=CC=CC=C3	**Glu59**, **His61**, **Ile68**, **Glu70**, Leu71, **Phe113**	29	–7.28 ± 0.63	Non-mutagen -Negative -Negative -Negative -Negative 1000 mg kg^{-1}

4 2839425	CC1=CC=C(C=C1)C2=CSC(=N2)N3C(=O)C(C(=N3)C) N=NC4=CC=C(C=C4)S(=O)(=O)O	**Glu59**, Trp62, **Arg64**, Glu70, **Ser74**, **Phe113**	16	–7.13 ± 0.71	Mutagen -Negative -Negative -Negative -Negative 1000 mg kg^{-1}
5 2840199	CC1(C(=S)C(=C2SC(=C(S2)C(=O)OC)C(=O)OC) C3=C(N1C(=O)COC4=CC=C(C=C4)F)C=C(C=C3)OC)C	Glu59, His61, Trp62	21	–7.13 ± 0.76	Mutagen -Positive -Negative -Negative -Negative 800 mg kg^{-1}
6 2185215	CC(=O)NS(=O)(=O)C1=CC=C(C=C1)NC(=O)CCN2C(=O) C(=CC3=CC=CC=C3)SC2=S	**Glu59, His61**, Trp62, **Glu70, Ser74**, Gln78	29	–7.11 ± 0.77	Non-mutagen -Negative -Negative -Negative -Negative 1400 mg kg^{-1}
7 1356721	COC1=C(C=C(C=C1)C(=O)NC2=CC=C(C=C2)S(=O)(=O) C3=CC=C(C=C3)NC(=O)C4=CC(=C(C=C4)OC)OC)OC	Glu56, **Glu59**, **His61**, Ile68, **Glu7**0, Phe113	26	–7.01 ± 0.69	Non mutagen -Negative -Negative -Negative -Negative 1000 mg kg^{-1}

8 2848441	COC1=C(C=C(C=C1)C(=O)NNC(=O)C2=CC(=CC=C2)C(=O)NNC(=O)C3=CC(=C(C=C3)OC)OC)OC	**Glu59, His61**, Ile68, **Glu70**, Ser74, Phe113	30	−6.99 ± 0.62	Mutagen -Negative -Negative -Negative -Negative 2000 mg kg^{-1}
9 2848447	CCCOC1=CC(=C(C=C1C#CC#CCN2CCCCC2)C#CC#CCN3CCCCC3)OCCC	Glu56, Pro57, **Glu59**, **His61**, Gln67, **Glu70**, Asp73, Phe113	26	−6.98 ± 0.57	Non-mutagen -Negative -Negative -Negative -Negative 370 mg kg^{-1}
10 2839849	CCN(CC)S(=O)(=O)C1=CC=C(C=C1)C2=CSC(=N2)N3C(CC(=N3)C4=C(C=CC(=C4)C)C)C5=CC(=CC=C5)[N+](=O)[O-]	**Glu59**, **His61**, **Trp62**, **Glu70, Asp73,** Ser74	23	−6.97 ± 0.76	Non-mutagen -Negative -Negative -Negative -Negative 1000 mg kg^{-1}

[a] Tables S2–S11, in bold are greater interactions.
[b] Mean and SD obtained from the indicated number of conformers.

*Table III. Number of interactions of compounds **1**–**10** in the amino acids of AXL to hinder/block the His61 in AXL*

Compd.	Glu59	His61	Glu70	Asp73	Ser74
1	13	2	2	1	1
2	2	4	8	2	4
3	9	7	5	1	0
4	2	0	2	0	16
5	4	3	1	0	0
6	9	5	2	0	8
7	3	5	6	0	1
8	10	17	13	0	1
9	8	5	20	1	0
10	4	3	3	1	1

*Table IV. Average $\Delta G_{binding}$ (kcal mol^{-1}) of compounds **1**–**10** in AXL, TYRO3 and MERTK*

Compd.	AXL	TYRO3	MERTK
1	–7.96 ± 0.46	–4.17 ± 0.47	–4.23 ± 0.53
2	–7.48 ± 0.50	–4.24 ± 0.56	–4.52 ± 0.42
3	–7.28 ± 0.63	–4.55 ± 0.56	–4.79 ± 0.63
4	–7.13 ± 0.71	–4.40 ± 0.43	–4.16 ± 0.42
5	–7.13 ± 0.76	–4.26 ± 0.31	–4.64 ± 0.53
6	–7.11 ± 0.77	–4.52 ± 0.53	–4.40 ± 0.50
7	–7.01 ± 0.69	–4.58 ± 0.47	–4.73 ± 0.66
8	–6.99 ± 0.62	–4.85 ± 0.50	–4.92 ± 0.42
9	–6.98 ± 0.57	–4.69 ± 0.67	–4.85 ± 0.70
10	–6.97 ± 0.76	–4.71 ± 0.46	–4.48 ± 0.42

that there are interactions of Glu59-AXL with Arg246-NTD, His61-AXL with Ser247-NTD, Ile68-AXL with Lys150-NTD and Glu70-AXL, Lys147/Lys150-NTD and Phe113-AXL with Pro251-NTD (8).

To justify this study, it is necessary to emphasize the amino acid His61. The data in Table III clearly show that the conformers from the compounds **1–10** have more interactions with the Glu59, His61 and Glu70 amino acids (Tables S2-S11). These amino acids are important for the formation of interactions (mainly hydrogen bonding) and the **1–10** compounds interact in the region where His61 is located (Fig. 2). Because of this, the interactions of all the conformers from the tested compounds **1–10** with Glu59, His61, Glu70, Asp73 and Ser74 amino acids result in the $\Delta G_{binding}$ averages ranging between **–**6.97 to **–**7.96 kcal mol^{-1}.

To demonstrate the above-mentioned, the interaction of the best conformer from the **1–10** compounds is shown interacting in the site proposed (Fig. 3). The Glu59, His61, Glu70,

Asp73 and Ser74 amino acids are shown; it is suggested that these amino acids are contributing to obtaining more favourable $\Delta G_{binding}$ with AXL. The interactions of all compounds studied (with their conformers) in the potential site are shown in Figs. S1–S10, and the interactions between each conformer in the potential site are shown in Tables S2–S11.

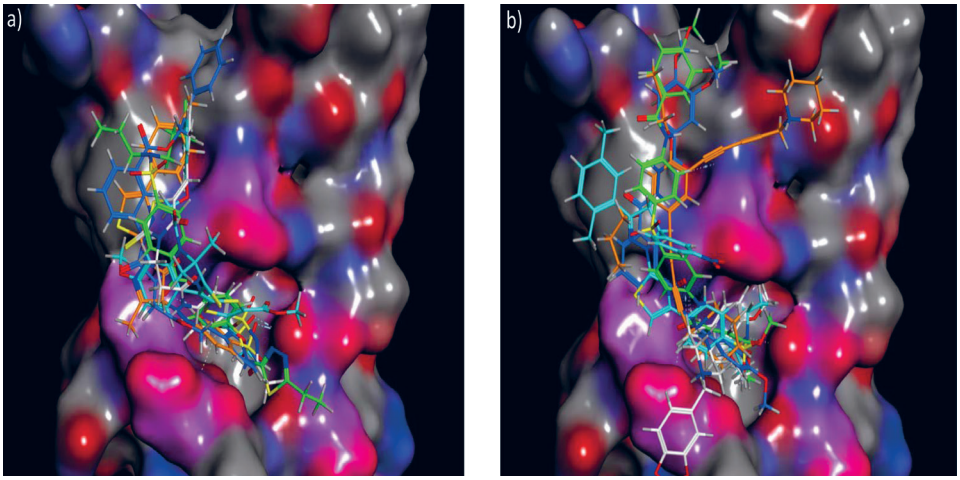


Fig. 3. The pocket of a potential site with the best conformer of each compound (**1**–**10**), Glu59, His61, Ile68, Glu70, Asp73, Ser74 amino acids (pink): a) **1** (green), **2** (blue), **3** (orange), **4** (cyan) and **5** (white), and b) **6** (green), **7** (blue), **8** (orange), **9** (cyan) and **10** (white).

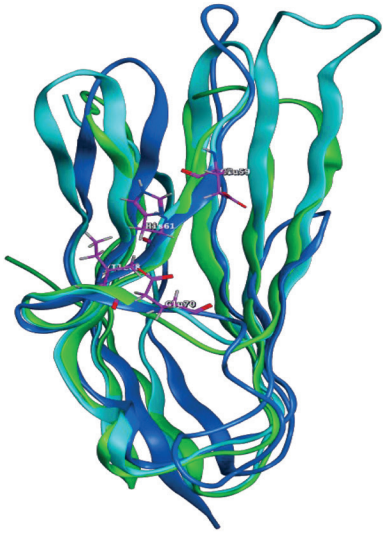


Fig. 4. Superposition of the structure of the potential site in the TAM family shows Glu59, His61, Ile68 and Glu70 amino acids (pink) as regions chosen for molecular docking: AXL (cyan), TYRO3 (green) and MERTK (blue).

The selectivity of these ten compounds for AXL is important, and it is necessary that they do not have an interaction with TYRO3 and MERTK. The selectivity for AXL can be proposed since the proposed interaction region is composed of Pro58, Glu59, Val60, His61, Trp62, Leu63, Arg64, Asp65, Gly66, Gln67, Ile68, Leu69, Glu70, Leu71, Ala72, Asp73, Ser74, Trh75, Gln76, Trh77 and Gln78 amino acids, and this sequence shows little identity with the sequence corresponding to TYRO3 and MERTK (approximately 14 %). This is confirmed by the docking values of the ten molecules in these two proteins with lower $\Delta G_{binding}$ (Table IV and Fig. S11), despite the superposition of the potential site in TAMs being similar (Fig. 4). Therefore, it can be proposed that these ten compounds are selective towards AXL and that they would probably not generate adverse effects by inhibiting the functions of TYRO3 and MERTK.

This study proposes ten compounds from a library of 502,350 compounds that are selective for a new therapeutic target in the infectious process of COVID-19. These results can contribute to the development of a drug against COVID-19 that is designed to avoid or decrease the fusion between SARS-CoV-2 and the cell membrane.

These compounds are available and exhibit satisfactory results in theoretical toxicity tests, so further tests could include *in vitro* experiments to confirmation the inhibitory effect on AXL with the S protein.

CONCLUSIONS

This study proposes ten compounds **1–10** selected by molecular docking to interact with the Glu59, His61, Glu70, Asp73 and Ser74 amino acids of AXL, which are important for inhibiting the interaction of AXL, RTK found in the human cell membrane, with the S protein of the SARS-CoV-2 coronavirus. These ten compounds are selective for AXL without affecting TYRO3 and MERTK, and are proposed for developing a new drug and to offer another method for treating COVID-19.

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Supplementary materials are available upon request. Supporting information includes figures and tables of interactions for compounds with AXL, as well as details of the interaction of each compound with AXL per amino acid, toxicity theoretical results, and ADME characteristics which support the information given in the results and discussion.

REFERENCES

1. E. Dong, H. Du and L. Gardner, An interactive web-based dashboard to track COVID-19 in real time, *Lancet Infect. Dis.* **20**(5) (2020) 533–534; https://doi.org/10.1016/S1473-3099(20)30120-1
2. M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T. S. Schiergens, G. Herrler, N.-H. Wu, A. Nitsche, M. A. Müller, C. Drosten and S. Pöhlmann, SARS-CoV-2 cell entry

depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, **181**(2) *Cell* (2020) 271–280; https://doi.org/10.1016/j.cell.2020.02.052

3. L. K. Gadanec, K. R. McSweeney, T. Qaradakhi, B. Ali, A. Zulli and V. Apostolopoulos, Can SARS-CoV-2 virus use multiple receptors to enter host cells?, *Int. J. Mol. Sci.* **22**(3) (2021) Article ID 992 (36 pages); https://doi.org/10.3390/ijms22030992
4. C. G. Benítez-Cardoza and J. L. Vique-Sánchez, Potential inhibitors of the interaction between ACE2 and SARS-CoV-2 (RBD), to develop a drug, *Life Sci.* **256** (2020) Article ID 117970; https://doi.org/10.1016/j.lfs.2020.117970
5. S. M. Kishk, R. M. Kishk, A. S. A. Yassen, M. S. Nafie, N. A. Nemr, G. ElMasry, S. Al-Rejaie and C. Simons, Molecular insights into human transmembrane protease serine-2 (TMPS2) inhibitors against SARS-CoV2: Homology modelling, molecular dynamics, and docking studies, *Molecules* **25**(21) (2020) Article ID 5007 (16 pages); https://doi.org/10.3390/molecules25215007
6. J. L. Vique-Sánchez, Potential inhibitors interacting in Neuropilin-1 to develop an adjuvant drug against COVID-19, by molecular docking, *Bioorg. Med. Chem.* **33** (2021) Article ID 116040; https://doi.org/10.1016/j.bmc.2021.116040
7. Y. Choi, B. Shin, K. Kang, S. Park and B. R. Beck, Target-centered drug repurposing predictions of human angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine subtype 2 (TMPRSS2) interacting approved drugs for coronavirus disease 2019 (COVID-19) treatment through a drug-target interaction deep learning model, *Viruses* **12**(11) (2020) Article ID 1325 (11 pages); https://doi.org/10.3390/v12111325
8. S. Wang, Z. Qiu, Y. Hou, X. Deng, W. Xu, T. Zheng, P. Wu, S. Xie, W. Bian, C. Zhang, Z. Sun, K. Liu, C. Shan, A. Lin, S. Jiang, Y. Xie, Q. Zhou, Lu Lu, J. Huang and Xu Li, AXL is a candidate receptor for SARS-CoV-2 that promotes infection of pulmonary and bronchial epithelial cells, *Cell Res.* **31** (2021) 126–140; https://doi.org/10.1038/s41422-020-00460-y
9. C. Xu, A. Wang, Ke Geng, W. Honnen, X. Wang, N. Bruiners, S. Singh, F. Ferrara, S. D'Angelo, A. R. M. Bradbury, M. L. Gennaro, D. Liu, A. Pinter and T. L. Chang, Human immunodeficiency viruses pseudotyped with SARS-CoV-2 spike proteins infect a broad spectrum of human cell lines through multiple entry mechanisms, *Viruses* **13**(6) (2021) Article ID 953 (17 pages); https://doi.org/10.3390/v13060953
10. C. Lai and G. Lemke, An extended family of protein-tyrosine kinase genes differentially expressed in the vertebrate nervous system, *Neuron* **6** (1991) 691–704; https://doi.org/10.1016/0896-6273(91)90167-X
11. Y. Tian, Z. Zhang, L. Miao, Z. Yang, J. Yang, Y. Wang, D. Qian, H. Cai and Y. Wang, Anexelekto (AXL) increases resistance to EGFR-TKI and activation of AKT and ERK1/2 in non-small cell lung cancer cells, *Oncol. Res. Featur. Preclin. Clin. Cancer Ther.* **24** (2016) 295–303; https://doi.org/10.3727/096504016146487014478l4
12. T. Pillaiyar and S. Laufer, Kinases as potential therapeutic targets for anti-coronaviral therapy, *J. Med. Chem.* (2021) in press; https://doi.org/10.1021/acs.jmedchem.1c00335
13. J. Huckriede, S. B. Anderberg, A. Morales, F. de Vries, M. Hultström, A. Bergqvist, J. T. Ortiz-Pérez, J. W. Sels, K. Wichapong, M. Lipcsey, M. van de Poll, A. Larsson, T. Luther, C. Reutelingsperger, P. G. de Frutos, R. Frithiof and G. A. F. Nicolaes, Evolution of NETosis markers and DAMPs have prognostic value in critically ill COVID-19 patients, *Sci. Rep.* **11** (2021) Article ID 15701 (12 pages); https://doi.org/10.1038/s41598-021-95209-x
14. J. Dai, X. Teng, S. Jin and Y. Wu, The antiviral roles of hydrogen sulfide by blocking the interaction between SARS-CoV-2 and its potential cell surface receptors, *Oxid. Med. Cell. Longev.* **2021** (2021) Article ID 7866992 (11 pages); https://doi.org/10.1155/2021/7866992
15. M. S. Kariolis, Y. R. Miao, A. Diep, S. E. Nash, M. M. Olcina, D. Jiang, D. S. Jones II, S. Kapur, I. I. Mathews, A. C. Koong, E. B. Rankin, J. R. Cochran and A. J. Giaccia, Inhibition of the GAS6/AXL

pathway augments the efficacy of chemotherapies, *J. Clin. Invest.* **127**(1) (2016) 183–198; https://doi.org/10.1172/JCI85610

16. S. H. Chung, J. Park, J. W. Lee, J. Song, D. Jung and K. H. Min, Structure-activity relationship of 7-aryl-2-anilino-pyrrolopyrimidines as Mer and Axl tyrosine kinase inhibitors, *J. Enzyme Inhib. Med. Chem.* **35**(1) (2020) 1822–1833; https://doi.org/10.1080/14756366.2020.1825407
17. M. L. Lotsberg, K. Wnuk-Lipinska, S. Terry, T. Z. Tan, N. Lu, L. Trachsel-Moncho, G. V. Røsland, M. I. Siraji, M. Hellesøy, A. Rayford, K. Jacobsen, H. J. Ditzel, O. K. Vintermyr, T. G. Bivona, J. Minna, R. A. Brekken, B. Baguley, D. Micklem, L. A. Akslen, G. Gausdal, A. Simonsen, J. P. Thiery, S. Chouaib, J. B. Lorens and A. S. Tenfjord Engelsen, AXL targeting abrogates autophagic flux and induces immunogenic cell death in drug-resistant cancer cells, *J. Thorac. Oncol.* **15**(6) (2020) 973–999; https://doi.org/10.1016/j.jtho.2020.01.015
18. A. Tutusaus, M. Marí, J. T. Ortiz-Pérez, G. A. F. Nicolaes, A. Morales and P. García de Frutos, Role of vitamin K-dependent factors protein S and GAS6 and TAM receptors in SARS-CoV-2 infection and COVID-19-associated immunothrombosis, *Cells* **9**(10) (2020) ID 2186 (15 pages); https://doi.org/10.3390/cells9102186
19. S. N. Batchu, J. Xia, K. A. Ko, M. M. Doyley, J.-I. Abe, C. N. Morrell and V. A. Korshunov, Axl modulates immune activation of smooth muscle cells in vein graft remodeling, *Am. J. Physiol. Circ. Physiol.* **309**(6) (2015) H1048–H1058; https://doi.org/10.1152/ajpheart.00495.2015
20. M. Tanaka and D. W. Siemann, Axl signaling is an important mediator of tumor angiogenesis, *Oncotarget* **10**(30) (2019) 2887–2898; https://doi.org/10.18632/oncotarget.26882
21. C. A. Stewart, C. M. Gay, K. Ramkumar, K. R. Cargill, R. J. Cardnell, M. B. Nilsson, S. Heeke, E. M. Park, S. T. Kundu, L. Diao, Q. Wang, L. Shen, Y. Xi, B. Zhang, C. M. Della Corte, Y. Fan, K. Kundu, B. Gao, K. Avila, C. R. Pickering, F. M. Johnson, J. Zhang, H. Kadara, J. D. Minna, D. L. Gibbons, J. Wang, J. V. Heymach and L. Averett Byers, Lung cancer models reveal SARS-CoV-2-induced EMT contributes to COVID-19 pathophysiology, *bioRxiv* preprint posted January 28, 2021; https://doi.org/10.1101/2020.05.28.122291
22. M. Bouhaddou, D. Memon, B. Meyer, K. M. White, V. V. Rezelj, M. Correa Marrero, B. J. Polacco, J. E. Melnyk, S. Ulferts, R. M. Kaake, J. Batra, A. L. Richards, E. Stevenson, D. E. Gordon, A. Rojc, K. Obernier, J. M. Fabius, M. Soucheray, L. Miorin, E. Moreno, C. Koh, Q. D. Tran, A. Hardy, R. Robinot, T. Vallet, B. E. Nilsson-Payant, C. Hernandez-Armenta, A. Dunham, S. Weigang, J. Knerr, M. Modak, D. Quintero, Y. Zhou, A. Dugourd, A. Valdeolivas, T. Patil, Q. Li, R. Hüttenhain, M. Cakir, M. Muralidharan, M. Kim, G. Jang, B. Tutuncuoglu, J. Hiatt, J. Z. Guo, J. Xu, S. Bouhaddou, C. J. P. Mathy, A. Gaulton, E. J. Manners, E. Félix, Y. Shi, M. Goff, J. K. Lim, T. McBride, M. C. O'Neal, Y. Cai, J. C. J. Chang, D. J. Broadhurst, S. Klippsten, E. De Wit, A. R. Leach, T. Kortemme, B. Shoichet, M. Ott, J. Saez-Rodriguez, B. R. tenOever, R. D. Mullins, E. R. Fischer, G. Kochs, R. Grosse, A. García-Sastre, M. Vignuzzi, J. R. Johnson, K. M. Shokat, D. L. Swaney, P. Beltrao and N. J. Krogan, The global phosphorylation landscape of SARS-CoV-2 infection, *Cell* **182**(3) (2020) 685–712; https://doi.org/10.1016/j.cell.2020.06.034
23. C. G. Benítez-Cardoza, L. G. Brieba, R. Arroyo, A. Rojo-Domínguez and J. L. Vique-Sánchez, Triosephosphate isomerase as a therapeutic target against trichomoniasis, *Mol. Biochem. Parasitol.* **246** (2021) Article ID 111413; https://doi.org/10.1016/j.molbiopara.2021.111413
24. ChemBridge Corp., *EXPRESS-Pick Stock*, https://chembridge.com/screening_libraries/#EXPRESSPick; last acces date November 10, 2020
25. C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, *Adv. Drug Deliv. Rev.* **23**(1–3) (1997) 3–25; https://doi.org/10.1016/S0169-409X(96)00423-1
26. Advanced Chemistry Development, Inc., *PhysChem, ADME & Toxicity, Version 2021.1.1*, Toronto (ON, Canada) 2021; www.acdlabs.com; last access date September 15, 2021

27. J. Dong, N.-N. Wang, Z.-J. Yao, L. Zhang, Y. Cheng, D. Ouyang, A.-P. Lu and D.-S. Cao, ADMETlab: a platform for systematic ADMET evaluation based on a comprehensively collected ADMET database, *J. Cheminform.* **10** (2018) Article ID 29 (11 pages); https://doi.org/10.1186/s13321-018-0283-x

28. P. Banerjee, A. O. Eckert, A. K. Schrey and R. Preissner, ProTox-II: a webserver for the prediction of toxicity of chemicals, *Nucleic Acids Res.* **46**(W1) (2018) W257–W263; https://doi.org/10.1093/nar/gky318

29. X. Chi, R. Yan, J. Zhang, G. Zhang, Y. Zhang, M. Hao, Z. Zhang, P. Fan, Y. Dong, Y. Yang, Z. Chen, Y. Guo, J. Zhang, Y. Li, X. Song, Y. Chen, L. Xia, L. Fu, L. Hou, J. Xu, C. Yu, J. Li, Q. Zhou and W. Chen, A neutralizing human antibody binds to the N-terminal domain of the Spike protein of SARS-CoV-2, *Science* **369**(6504) (2020) 650–655; https://doi.org/10.1126/science.abc6952

30. C. V. Rothlin, E. A. Carrera-Silva, L. Bosurgi and S. Ghosh, TAM receptor signaling in immune homeostasis, *Annu. Rev. Immunol.* **33** (2015) 355–391; https://doi.org/10.1146/annurev-immunol-032414-112103