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Potential inhibitors of the interaction between ACE2 and SARS-CoV-2 (RBD), to develop a drug

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ABSTRACT

Aims: The COVID-19 disease caused by the SARS-CoV-2 has become a pandemic and there are no effective treatments that reduce the contagion. It is urgent to propose new treatment options, which are more effective in the interaction between viruses and cells. In this study was to develop a search for new pharmacological compounds against the angiotensin-converting enzyme 2 (ACE2), to inhibit the interaction with SARS-CoV-2.

Materials and methods: Docking, virtual screening using almost 500,000 compounds directed to interact in the region between the residues (Gln24, Asp30, His34, Tyr41, Gln42, Met82, Lys353, and Arg357) in ACE2. The average of ΔGbinding, the standard deviation value and the theoretical toxicity from compounds were analyzed.

Key findings: 20 best compounds directed to interact in ACE2 with a high probability to be safe in humans, validated by web servers of prediction of ADME and toxicity (ProTox-II and PreADMET), to difficult the interaction between ACE2 and region binding domain (RBD) of SARS-CoV-2.

Significance: In this study, 20 compounds were determined by docking focused on the region of interaction between ACE2 and RBD of SARS-CoV-2 was carried out. The compounds are publicly available to validate the effect in in vitro tests.

1. Introduction

Currently, the pandemic that has developed has some antecedents related to the SARS-CoV 2002 outbreak, of which several works have been carried out to develop new drugs directed to specific regions of the coronavirus (SARS-CoV 2002). The disease caused by SARS-CoV-2 generates a wide range of signs and symptoms, causing respiratory, gastrointestinal diseases and even death [1,2]. In the first reports on the SARS-CoV-2 (COVID-19) outbreak in China reported that the average age was 47 years, with an incubation period of 4 days, 41.9% were women, with fever 88.7% and cough the 67.8% of the patients in the study, accompanied by lymphocytopenia in 83.2%. It should be noted that there was no specific treatment for SARS-CoV-2, the treatment was based on antibiotics in 58.0% and antivirals (Oseltamivir) in 36.2% [2].

There are works associated to SARS-CoV, for the development of a specific drug, which has reported the development of peptides related to the key protein for the interaction between the SARS-CoV and the host cell; the angiotensin-converting enzyme 2 (ACE2), reporting amino acids sequence that was essential for drug development (Glu22, Glu23, Lys26, Asp30, Lys31, His34, Glu35, Glu37, Asp38, Glu56 and Glu57) [8]. As well as another work that reported the important amino acids between the region binding domain (RBD) of the S-Protein SARS-CoV with the ACE2 (Gln24, Thr27, Lys31, His34, Glu35, Glu37, Asp38, Tyr41, Gln42, Leu45, Leu79, Met82, Tyr83, Asn90, Gln325, Glu329, Asn330, Lys353 and Gly354 in ACE2) [9]. Currently, has been reported the crystallographic structure of the interaction between SARS-CoV2-RBD and ACE2 (Gln24, Asp30, His34, Tyr41, Gln42, Met82, Lys353, and Arg357 in ACE2) [10], which we used in this study.

There are reports of the development of pharmacological compounds that have an effect on the interaction of SARS-CoV and ACE2 [11,12], as well as focused on important proteins in the SARS-CoV such as the Main protease (Mpro), which propose synthesized aromatic compounds [13].

Although there is a great similarity between SARS-CoV and SARS-CoV-2 sequence (sequence identity of almost 80%) [14], the same...
results of compounds or antibodies that were tested in SARS-CoV are not presented in SARS-CoV-2; the differences in the residues found in SARS-CoV-2 explain the resistance generated against compounds and antibodies (S230) [15] [16].

The affinity of SARS-CoV-2 with ACE2 has been determined to be up to 20 times higher than that reported in SARS-CoV in 2002, which may help explain why the complications that develop are more serious, and the probability of contagion is greater, having a great impact on the health of the population [17]. It was determined that in SARS-CoV, ACE2 plays a very important role so that it can cross the cell membrane and be able to replicate the SARS-CoV; taking into account that SARS-CoV-2 also interacts with ACE2. Recently, an important protein for the interaction of ACE2 with SARS-CoV-2, TMPRSS2, was identified, where it is demonstrated that if it is limited to this protein, the interaction of the virus with the cell can be affected [18].

Some works for the development of new drugs against SARS-CoV-2, propose epitopes as potential sites of interaction [19], as well as using Docking and compound libraries, as well as looking for a repositioning of drugs [5], to search for compounds that interact with some SARS-CoV-2 region and thus be able to prevent interaction with ACE2 [20]. A drug that was proposed to interact in ACE2, is Arbidol, which recently reported the crystallographic structure, demonstrating that Arbidol interacts in S-protein (domain S2) from SARS-CoV-2 [21], which demonstrates the low existence of drugs that are directly interacting with ACE2.

We use the amino acids reported in the crystallographic structure of the interaction between the S-protein-RBD of SARS-CoV-2 and ACE2 (Gln24, Asp30, His34, Tyr41, Gln42, Met82, Lys353 and Arg357 in ACE2) [10,22], therefore, by using the crystallographic structure of ACE2 (PDB 1R42), we carried out a Docking directed to these mentioned residues using a library of compounds (EXPRESS-pick Collection from Chembridge Corp.) to select the best compounds, and that these can affect the interaction between ACE2 and SARS-CoV-2, making these results an important contribution to establishing the foundations that allow the development of a drug that optimizes the resolution of this pandemic.

2. Method details

2.1. Preparation of receptor protein and definition of binding sites

Atomic coordinates of Angiotensin converting enzyme 2 (ACE2) were obtained from the Protein Data Bank (PDB: 1R42). The structure was used as protein targets for docking procedures. The protonation and energy minimization of PDB file was performed using Molecular Operating Environment (MOE) software with the default parameters and the CHARMM27 force field [23,24]. We select one region to interaction in ACE2 (Gln24, Asp30, His34, Tyr41, Gln42, Met82, Lys353 and Arg357) [10].

2.2. Screening library

The EXPRESS-pick Collection Stock of the small molecule screening library from Chembridge Corp. was used for docking [25]. This collection of small molecule screening compounds contains over 500,000 chemical compounds that fulfill the druggable properties of Lipinski's rules [26,27] and cover a broad area of chemical space.

2.3. Molecular docking

For docking, the receptors were kept rigid, while the ligand atoms were released to move to a maximal number of rotatable bonds. All crystallographic water molecules were deleted from the initial structures. High-throughput virtual molecular docking was carried out [25,28] by means of the software AutoDock and MOE, using default parameters (Placement: Triangle Matcher, Rescoring 1: London ΔG, Rescoring 2: London ΔG, for each ligand up to 20 conformations were generated and saved).

2.4. Calculation of the free binding energy (ΔGbinding)

The binding affinity of each complex (Ligand-protein) was estimated with the ratio of General Born vs Volume Integral (GB/VI), using parameters in MOE [29,30]. General Born or non-bonded interaction energies comprise Van der Waals, Coulomb electrostatic interactions and implied solvent interaction energies [30].

2.5. Selection of compounds

Each compound was simulated with up to 50 conformations, to select the best compounds, the average of the ΔGbinding interaction value of up to 20 conformers, the description of chemical properties by PhysChem - ACD/Labs [31], the theoretical toxicity [32], carcinogenicity and mutagenicity [33] were considered. The calculated interactions between ACE2 and compounds were visualized with Ligand-interaction interactions implemented in MOE.

3. Results

3.1. Selection of compounds by docking

Among the interactions in ACE2 (Gln24, Asp30, His34, Tyr41, Gln42, Met82, Lys353 and Arg357) with compounds (Fig. 1), the selection criteria of the top poses, out of almost 500,000 compounds from Chembridge library, were the frequency of the conformers of each compound and the ΔGbinding values between ~ 6.0 to ~7.3 kcal/mol⁻¹. We made the selection of compounds based on the average of the score from up to 20 conformers per compound and better probability to be safe in humans. We selected 20 compounds depicted here as C1 to C20 (Table 1) from the Express-pick Collection Stock of the small molecule screening Chembridge library (ChemBridge Corporation) and the analysis of the interaction of each compound chosen with ACE2, was carried out with the interaction report (in Supplementary material Tables S1–S20).

3.2. Best values of interaction of compounds C1–C20 with ACE2

For selection of the best compounds, the analysis from Docking's results was carried out, taking into account the average of the interaction ΔGbinding (15 to 20 conformers) was determined, as well as the standard deviation for each compound. Subsequently, the theoretical toxicity was evaluated with two website (ProTox-II - Prediction of TOXicity and PreADMET web server, prediction of carcinogenicity and mutagenicity, Table 2). Besides, we determined 30 compounds with good results, but with significant theoretical toxicity effects, we show them in Table S21.

The description of the chemical properties of each compound (C1–C20, Table S22), ADME (Table S23) and theoretical toxicity (Table S24), are shown in the supplemental material.

3.3. Interaction of compounds C1–C20 with ACE2

To propose the probable interaction sites between each compound (C1–C20) with ACE2 we analyzed up to 20 conformers of each compound that showed the better ΔGbinding Values of interaction in amino acids Gln24, Asp30, His34, Tyr41, Gln42, Met82, Lys353 and Arg357 (Fig. 1). From docking's result (Tables S1–S20), we determined the main amino acids in ACE2 to interact with the 20 compounds, these are Lys26, His34, Glu37, Asp38, Tyr41, Gln96, Gln325, Asn330, Lys353, Arg357, Ala386, Ala387, Pro389 and Arg393 (Table 2). The interaction of each compound and its conformers in ACE2 are shown in the supplementary material (Figs. S1–S20).
4. Discussion

Several works have been done to develop new drugs against SARS-CoV-2 [5-7,19,20,34], testing antibodies or compounds that affect SARS-CoV 2002 [17], also characterizing and proposing potential targets for the interaction between SARS-CoV-2 and ACE2 [18,19], to determine the effectiveness of some therapeutic options that can contribute/favor the resolution of the pandemic that is developing worldwide. In this study we carried out a Docking aimed at the reported residues that are important for the SARS-CoV-2 RBD/spike protein, to interact with ACE2 [10,22], we determined that residues Lys26, His34, Gln24, Glu37, Asp30, His34, Tyr41, Gln42, Met82, Lys353, Arg357, Ala386, Ala387, Pro389 and Arg393 are important for the majority of the compounds that we propose to interact in ACE2 (Table 1). Furthermore, we propose that the interaction site in ACE2 presents little change in the structural conformation when the S-protein-RBD is present, since we perform an alignment and superposition of the three-dimensional structures, of the apo-ACE2 (PDB: 1R42) and the ACE2 with RBD (PDB: 6M17) and there is an RMSD between them of 2.4 Å (Fig. S21), which shows that the interaction of ACE2 with RBD does not affect the three-dimensional conformation, moreover, the amino acids that we take into account to do the Docking (amino acids Gln24, Asp30, His34, Tyr41, Gln42, Met82, Lys353 and Arg357), they are in similar positions in both structures, it helps us to propose that the interaction site is maintained, and this could facilitate competition for the site of interaction in ACE2, for the compounds that we propose. Also, it has been reported that these amino acids are very important for the interaction of this type of virus with ACE2 [8,9,11], based on these results, we propose these 20 compounds (C1–C20) could be tested by some working group that has performed in vitro assays with ACE2 and SARS-CoV-2 [15-18,22].

What advantages could the approach of directing drug development to the region of interaction in ACE2 with RBD-S-Protein? Proposing a different way to attack COVID-19 could help the treatments that are currently being investigated. Despite the large number of works reported on new antivirals and compounds targeting SARS-CoV-2, there is still no 100% effective treatment. Research directed towards the RNA chain, which interacts in the RdRp region (Remdesivir, Ribavirin and Favipiravir) [35] and polyproteins (PLpro and 3CLpro, Lopinavir and Darunavir) [4,36,37], they are constantly developing a protocol to determine their effectiveness, but something characteristic of these antiviral potentials is that these drugs carry out their mechanism of action in the intracellular space, interacting with the viral RNA sequence and/or encoded protein important for the process of viral replication within the host cell. Another way to attack SARS-CoV-2 is to develop membrane fusion inhibitors (EK1 and EK1C4) [5-7], in which they seek to prevent the HR1 region of S-Protein (Fig. S22) from interacting with HR2 and its ligand in the ACE2 membrane, hindering the process of fusing the viral membrane and blocking the introduction of viral genetic material, there are currently very promising results of this type of drug, with evaluated doses with an IC50s between 1.3 and 15.8 nM against SARS-CoV-2 [7], it shows that its development is viable.

We determined that there are very few studies of new drugs against ACE2, previously Arbidol was thought to have ACE2 as a selective target, but the description of the interaction of Arbidol with S2-Domain in S-Protein of SARS-CoV-2 was made [21].

Therefore, the development of antivirals against COVID-19, still in development, shows that there are no specific drugs against SARS-CoV-2, since several of the drugs that are using, they have been developed against other diseases, such as Ebola (Remdesivir) [4], influenza (Arbidol) [21], SARS and MERS [13,14], searching a drug repurposing [38]. Besides, proposing combinations of drugs, with different mechanisms of action (such as those mentioned), will be used for the pandemic that is occurring, in addition it will be necessary to develop selective drugs against ACE2 (Fig. S23), which may be able to prevent interaction with SARS-CoV-2.

Carrying out the selection of the compounds, taking into account the results of between 15 and 20 conformers of each compound, gives us a greater probability of choosing the compounds that could be selective in the amino acids sequence Gln24, Asp30, His34, Tyr41, Gln42, Met82, Lys353 and Arg357 in ACE2 (Fig. 1), subsequently validated them by two toxicity prediction web servers (Tables 2 and S22),
obtaining important characteristics such as a lethal dose 50 (LD50) within acceptable values as well as a very low probability of toxicity; which must be fulfilled by each compound for its selection. Thus, this could reduce the time that must be waited for to be used in humans, therefore we propose compounds (C1–C20), with a high safety probability in humans. In addition, we show the next 30 compounds, which have some probability of generating side effects, such as carcinogenicity, hepatotoxicity and immunotoxicity mainly; these compounds are on the supplementary material (Table S21) which could be tested in in vitro tests with ACE2 - SARS-CoV-2 interaction.

It will be necessary to evaluate by in vivo tests, the effect of these compounds could to generate when interacting with ACE2 in humans,

| ID       | Chemical name and structure of the compound |
|----------|--------------------------------------------|
| C1       | 7781334, N,N'-[oxybis(4,1-phenylene)bis(3-methoxybenzohydrazide) | 77676800, 2,2'-[1,4-butanediylbis[(4-ethyl-4H-1,2,4-triazole-5,3-diylthio)]bis(1-phenylethanol) |
| C3       | 7956590, N,N'-bis[4-[[benzylamino]carbonyl]phenyl]malonamide | 7782787, N,N'-[methylenebis(2-hydroxy-4,1-phenylene)]bis[2-(3,4-dimethoxyphenyl)acetamide] |
| C5       | 7938481, ethyl 4-(((4-allyl-5-[[2-[[4,1-phenylene]bis(3-methoxybenzohydrazide)]bis(3-methoxybenzohydrazide) | 7517329, 2-(4-methoxyphenyl)-N-[4-methyl-5-[[2-[[5-methyl-4-phenyl-1,3-thiazol-2-yl]amino]-2-oxoethyl]thio) (4H-1,2,4-triazol-3-yl) methyl]acetamide |
| C7       | 7787375, N,N'-1,6-hexanediylbis[2-(4-isopropylphenoxy)acetamide] | 7783270, N,N'-[oxybis(4,1-phenylene)bis(3-methoxybenzohydrazide) |
| C9       | 7134636, N-5-[[2-[[4,1-phenylene]bis(3-methoxybenzohydrazide)]bis(3-methoxybenzohydrazide) | 7390655, N,N'-1,2-phenylenebis[2-(4-ethylphenoxy)acetamide] |
| C11      | 7652337, ethyl 3-(((5-[[4-methyl-4H-1,2,4-triazol-3-yl]thio]acetyl)amino)benzoate | 6898502, N,N'-[oxydi-4,1-phenylene]bis[2-(2-methoxybenzamidato)] |
| C13      | 6936307, N,N'-4,4'-biphenyldiylbis[2-(2-methoxybenzamidato)] | 7974985, 1-[[3,4-dimethoxyphenyl]acetil]-N,N'-bis[2-thienylmethyl]-1H-1,2,4-triazole-3,5-diamine |
| C15      | 7153800, N,N'-1,2-propanediylbis[2-(4-tert-butylphenoxy)acetamide] | 7588589, 4,4'-oxybis[N-(2-ethoxyphenyl)benzamide] |
| C17      | 7844832, 2-chloro-N-2-[5-[[2-[[3-cyano-4,5,6,7-tetrahydro-1-benzothien-2-yl]amino]-2-oxoethyl]thio]-4-ethyl-4H-1,2,4-triazol-3-yl]ethyl]benzamide | 7848562, N-2-[14-allyl-5-[[2-[[4-phenyl-1,3-thiazol-2-yl]amino]ethyl]thio]-4H-1,2,4-triazol-3-yl]ethyl]4-methylbenzamide |
| C19      | 7987131, N-2-[[3,4-dimethoxyphenyl]ethyl]-2-[[4-[[isobutylamino)sulfonyl]2-methylphenoxy]acetamide | 7939484, N-2-[[4-benzyloxy]phenyl]-N-1-[[4-[[2,6-dimethylphenyl]amino]sulfonyl]phenyl]-N-2-[[methylsulfonyl]glycinamide |
Table 2

| Compound ID Chembridge Corp. | Smile | Interaction with residues in ACE2 (Tables S1–S20) | Number of conformers | Average of $\Delta G_{binding}$ and SD | Toxicity model report from ProTox-B server/PreADMET Ames test | Predicted LD50 (mg/kg) |
|-----------------------------|-------|--------------------------------------------------|-----------------------|----------------------------------------|-------------------------------------------------------------|-----------------------|
| C1.- 7781334 COc1cccc(c1)X(=O)NCC(=O)C2ccccc2Oc3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | Arsp0, His34, Glu37, Asp38, Tyr41, Glu42, Lys68, Asn310, Lys353, Arg355 and Ala386 | 17 | $-5.87 \pm 0.49$ | Aryl hydrocarbon receptor (AhR) 53%/non mutagen | 575 |
| C2.- 7676800 CCn1c(nc(s1)NC(=O)CSc2nnc(n2CC=C)CC(=O)Nc3ccc4c5ccccc5oc4c3 | Lys26, His34, Glu37, His34, Glu37, Arsp0, Asp38, Tyr41, Lys42, Glu42, His42, Lys342, Lys353, Arg355 and Ala386 | 19 | $-5.84 \pm 0.60$ | Carcinogenicity 51%/mutagen | 1500 |
| C3.- 7956590 c1ccc(cc1)NCC(=O)C2ccccc2Oc3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | Lys26, His34, Glu37, Asp38, Tyr41, Glu42, His42, Lys342, Lys353, Arg355 and Ala386 | 19 | $-5.83 \pm 0.55$ | Inactive. Probably safe/non mutagen | 1000 |
| C4.- 7782787 COc1cccc(c1)CC(=O)NCC(=O)C2ccccc2Oc3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | Lys26, His34, Glu37, Tyr41, Lys343, Ala387 and Pro389 | 20 | $-5.69 \pm 0.55$ | Inactive. Probably safe/non mutagen | 2000 |
| C5.- 7938481 COCG(=O)C2ccccc2OC(=O)NCC(=O)C3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | Thr27, His34, Glu37, Asp38, Tyr41, Lys42, Glu42, His42, Lys342, Lys353, Arg355 and Ala386 | 19 | $-5.77 \pm 0.36$ | Inactive. Probably safe/non mutagen | 1000 |
| C6.- 7517329 Cc1c(nc(s1)NC(=O)CSc2nnc(n2C)CNC(=O)c3ccc(c(c3)OC)OC | Lys26, His34, Glu37, Asp38, Tyr41, Lys42, Glu42, His42, Lys342, Lys353, Arg355 and Ala386 | 19 | $-5.69 \pm 0.48$ | Inactive. Probably safe/non mutagen | 1000 |
| C7.- 7787375 OCC(Cc1cccc(c1)X(=O)NCC(=O)C2ccccc2OC(=O)NCC(=O)C3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | Lys26, Thr27, His34, Glu37, Asp38, Tyr41, Lys42, Glu42, His42, Lys342, Lys353, Arg355 and Ala386 | 19 | $-5.65 \pm 0.55$ | Inactive. Probably safe/non mutagen | 450 |
| C8.- 7788270 c1ccc(cc1)X(=O)NCC(=O)C2ccccc2OC(=O)NCC(=O)C3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | Lys26, His34, Glu37, Tyr41, Lys343, Ala387 and Pro389 | 20 | $-5.62 \pm 0.48$ | Inactive. Probably safe/non mutagen | 1000 |
| C9.- 7134636 COc1cccc(c1)OC(=O)C2ccccc2OC(=O)NCC(=O)C3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | His34, Glu37, Asp38, Tyr41, Glu42, Lys68, His96, Lys353, Arg355 and Ala386 | 20 | $-5.56 \pm 0.48$ | Inactive. Probably safe/non mutagen | 1000 |
| C10.- 7390655 CCC(c1cccc(c1)X(=O)NCC(=O)C2ccccc2OC(=O)NCC(=O)C3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | His34, Asp38, Glu37, Asp38, Tyr41, Glu42, Lys68, His353, Arg355 and Ala386 | 15 | $-5.54 \pm 0.57$ | Hepatotoxicity 57%/mutagen | 575 |
| C11.- 7656377 CCOG(=O)C2ccccc2OC(=O)NCC(=O)C3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | Arg30, His34, Glu37, Asp38, Tyr41, Glu42, Lys68, His353, Arg355 and Ala386 | 18 | $-5.54 \pm 0.83$ | Inactive. Probably safe/non mutagen | 1000 |
| C12.- 6989502 COc1cccc(c1)OC(=O)C2ccccc2OC(=O)NCC(=O)C3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | Arg30, His34, Glu37, Asp38, Tyr41, Glu42, Lys68, His353, Arg355 and Ala386 | 17 | $-5.53 \pm 0.53$ | Inactive. Probably safe/non mutagen | 1000 |
| C13.- 6936307 COc1cccc(c1)OC(=O)C2ccccc2OC(=O)NCC(=O)C3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | Arg30, His34, Glu37, Asp38, Tyr41, Glu42, Lys68, His353, Arg355 and Ala386 | 15 | $-5.53 \pm 0.56$ | Inactive. Probably safe/non mutagen | 1000 |
| C14.- 7974985 COc1cccc(c1)OC(=O)C2ccccc2OC(=O)NCC(=O)C3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | Arg30, His34, Glu37, Asp38, Tyr41, Glu42, Lys68, His353, Arg355 and Ala386 | 17 | $-5.52 \pm 0.65$ | Inactive. Probably safe/non mutagen | 1050 |
| C15.- 7153800 COc1cccc(c1)OC(=O)C2ccccc2OC(=O)NCC(=O)C3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | Arg30, His34, Glu37, Asp38, Tyr41, Glu42, Lys68, His353, Arg355 and Ala386 | 17 | $-5.51 \pm 0.55$ | Inactive. Probably safe/non mutagen | 1000 |
| C16.- 7588589 COc1cccc(c1)OC(=O)C2ccccc2OC(=O)NCC(=O)C3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | Arg30, His34, Glu37, Asp38, Tyr41, Glu42, Lys68, His353, Arg355 and Ala386 | 17 | $-5.51 \pm 0.50$ | Inactive. Probably safe/non mutagen | 1000 |
| C17.- 7944812 CCc1ccccc1OC(=O)C2ccccc2OC(=O)NCC(=O)C3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | Arg30, His34, Glu37, Asp38, Tyr41, Glu42, Lys68, His353, Arg355 and Ala386 | 17 | $-5.51 \pm 0.47$ | Inactive. Probably safe/non mutagen | 1000 |
| C18.- 7845662 CCc1ccccc1OC(=O)NCC(=O)C2ccccc2CC(=O)NCC(=O)C3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | Arg30, His34, Glu37, Asp38, Tyr41, Glu42, Lys68, His353, Arg355 and Ala386 | 17 | $-5.51 \pm 0.47$ | Inactive. Probably safe/non mutagen | 1000 |
| C19.- 7987131 CCc1ccccc1OC(=O)NCC(=O)C2ccccc2CC(=O)NCC(=O)C3cccc(c3)C(=O)NCC(=O)C4cccc(c4)OC | Arg30, His34, Glu37, Asp38, Tyr41, Glu42, Lys68, His353, Arg355 and Ala386 | 16 | $-5.51 \pm 0.50$ | Inactive. Probably safe/non mutagen | 2000 |

(continued on next page)
since the ACE2 functions on angiotensin and its effects at the cardiovascular system level [39–43], they would have to be considered to determine the therapeutic effect and the degree of impact that they could have on the health-disease process of COVID-19 and/or some alteration in the functions of ACE2.

Most of these proposed compounds do not have any specific use registered, nor a scientific article or registered patent, all the compounds are available for purchase or systematize them, to carry out in vitro assays for the interaction of SARS-CoV-2 with ACE2, this way, be able to develop a new drug that helps combat this pandemic. Furthermore, as already reported, SARS-CoV has an affinity for the same ACE2 region, which could help in the future to prevent new viruses with an affinity for this region of interaction in ACE2.

5. Conclusions

We propose 20 compounds that have a high probability of interacting in a specific region in ACE2 (Gln24, Asp30, His34, Tyr41, Gln42, Met82, Lys353 and Arg357), and thus hinder interaction with the RBD of SARS-CoV-2. Furthermore, these 20 compounds have a high probability to be safe in humans, since they were validated by the ProTox-II and PreADMET server (ADME and Toxicity Predictor). These 20 compounds are available from Chembridge Corp. (Table 1) pharmaceutical compound synthesis company, as well as other synthesis laboratories worldwide. This could facilitate in vitro assays to determine the effectiveness of new drugs with a mechanism of action in ACE2 and as a result, propose a new treatment against COVID-19.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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Authors’ contributions

J.L. V-S, and C.G. B-C. designed, performed, analyzed the data and wrote the manuscript. Authors approved the final manuscript.

Ethical approval

Not required.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lfs.2020.117970.
