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 $\Delta G_{binding}$, 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]. Recently, new antivirals have been developed, focusing on RNA-Dependent RNA Polymerase (RdRp), Polyproteins (3CLpro and PLpro), Spike Protein (S-Protein) [3,4] and membrane fusion inhibitors (HR1 and HR2 of S-Protein) [5–7] from SARS-CoV-2. Without a treatment that demonstrating an advantage therapeutic, which demonstrates the urgent need for the development of specific drugs against a selective target that alters the evolution of this disease.

There are works associated to SARS-CoV, for the development of a specific drug, which have 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, 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

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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-CoV2, 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,

Refinement: Forcefield, Rescoring 2: London ΔG, for each ligand up to 20 conformations were generated and saved).

2.4. Calculation of the free binding energy (ΔG$_{binding}$)

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 ΔG$_{binding}$ 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 ΔG$_{binding}$ 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 ΔG$_{binding}$ (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 ΔG$_{binding}$ 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).
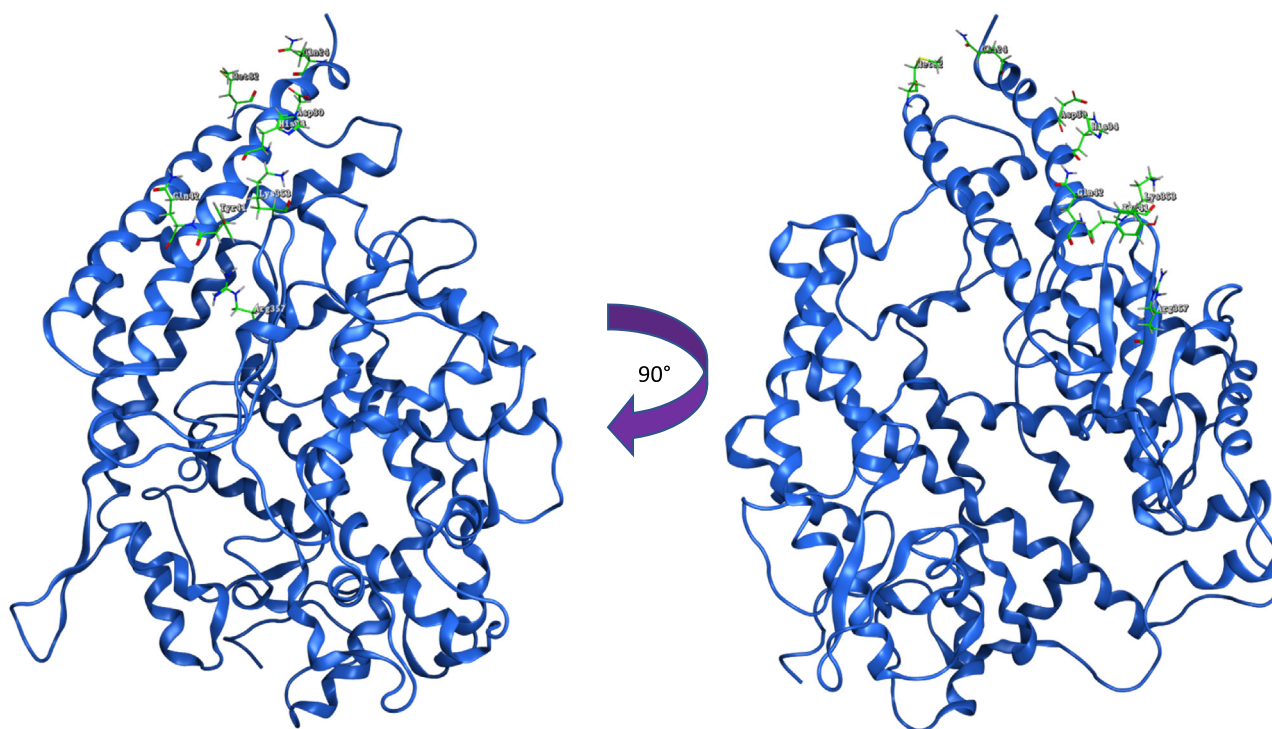
Fig. 1. ACE2 (blue) shows residues Gln24, Asp30, His34, Tyr41, Gln42, Met82, Lys353 and Arg357 (green), as region chosen for docking. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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, Glu37, Asp38, Tyr41, Gln96, Gln325, Asn330, 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].
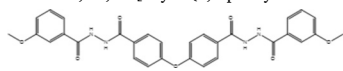
Therefore, the development of antivirals against COVID-19, still in development, shows that there are no specific drugs against SARS-CoV-2, since several of the drugs that are using, they have been developed against other diseases, such as Ebola (Remdesivir) [4], influenza (Arbidol) [21], SARS and MERS [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),
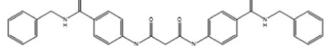
Table 1

ID Chembridge Corp., chemical name and structure of 20 best compounds, C1 to C20.
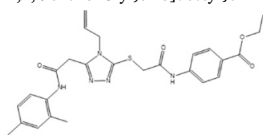
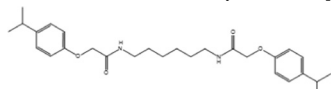**C1**.- 7781334, N′,N″-[oxybis(4,1-phenylenecarbonyl)]bis(3-methoxybenzohydrazide)

C2.- 7676800, 2,2′-{1,4-butanediylbis[(4-ethyl-4H-1,2,4-triazole-5,3-diyl)thio]}bis(1-phenylethanone)

C3.- 7956590, N,N′-bis{4-[(benzylamino)carbonyl]phenyl}malonamide
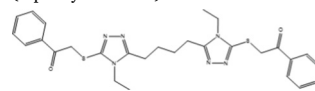
C4.- 7782787, N,N′-[methylenebis(2-hydroxy-4,1-phenylene)]bis[2-(3,4-dimethoxyphenyl)acetamide]

C5.- 7938481, ethyl 4-({[(4-allyl-5-{2-[(2,4-dimethylphenyl)amino]-2-oxoethyl}-4H-1,2,4-triazol-3-yl)thio]acetyl}amino)benzoate
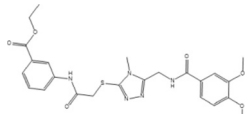

C6.- 7517329, 2-(4-methoxyphenyl)-N-{[4-methyl-5-({2-[(5-methyl-4-phenyl-1,3-thiazol-2-yl)amino]-2-oxoethyl}thio)-4H-1,2,4-triazol-3-yl]methyl}acetamide

C7.- 7787375, N,N′-1,6-hexanediylbis[2-(4-isopropylphenoxy)acetamide]

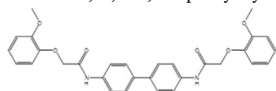**C8**.- 7783270, N′,N″-[oxybis(4,1-phenylenecarbonyl)]bis(2-chlorobenzohydrazide)

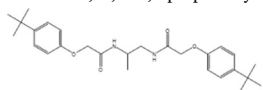**C9**.- 7134636, N-(5-{[2-(dibenzo[b,d]furan-3-ylamino)-2-oxoethyl]thio}-1,3,4-thiadiazol-2-yl)-2-methoxybenzamide
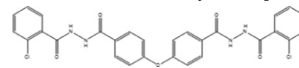
C10.- 7390655, N,N′-1,2-phenylenebis[2-(4-ethylphenoxy)acetamide]

C11.- 7652337, ethyl 3-({[(5-{[(3,4-dimethoxybenzoyl)amino]methyl}-4-methyl-4H-1,2,4-triazol-3-yl)thio]acetyl}amino)benzoate
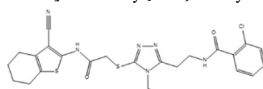

C12.- 6898502, N,N′-(oxydi-4,1-phenylene)bis[2-(2-methoxyphenoxy)acetamide]

C13.- 6936307, N,N′-4,4′-biphenyldiylbis[2-(2-methoxyphenoxy)acetamide]

C14.- 7974985, 1-[(3,4-dimethoxyphenyl)acetyl]-*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]
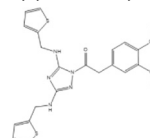
**C16**.- 7588589, 4,4′-oxybis[N-(2-ethoxyphenyl)benzamide]

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
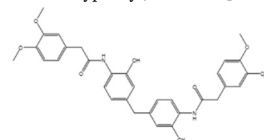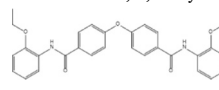

C18.- 7845662, N-{2-[4-allyl-5-({2-oxo-2-[(4-phenyl-1,3-thiazol-2-yl)amino]ethyl}thio)-4H-1,2,4-triazol-3-yl]ethyl}-4-methylbenzamide

C19.- 7987131, N-[2-(3,4-dimethoxyphenyl)ethyl]-2-{4-[(isobutylamino)sulfonyl]-2-methylphenoxy}acetamide
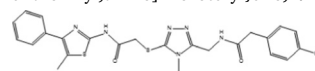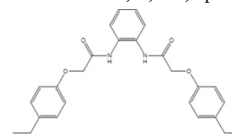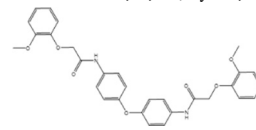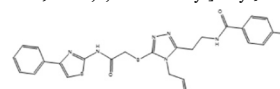

C20.- 7939484, N~2~-[4-(benzyloxy)phenyl]-N~1~-(4-{[(2,6-dimethylphenyl)amino]sulfonyl}phenyl)-N~2~-(methylsulfonyl)glycinamide
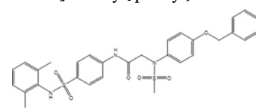
obtaining important characteristics such as a lethal dose 50 (LD50) within acceptable values as well as a very low probability of toxicity; which must be fulfilled by each compound for its selection. Thus, this could reduce the time that must be waited for to be used in humans, therefore we propose compounds (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,

Table 2
ID compound, smile, interaction with residues in ACE2, number of conformers used, $\Delta G_{binding}$ average (kcal/mol^{-1}) with standard deviation (SD), reported theoretical toxicity/Ames test and LD50.

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-II server/PreADMET Ames test	Predicted LD50 (mg/kg)
C1.- 7781334	COc1cccc(c1)C(=O)NNC(=O)c2ccc(cc2)Oc3ccc(cc3)C(=O)NNC(=O)c4cccc(c4)OC	Asp30, His34, Glu37, Asp38, Tyr41, Gln42, Lys68, Asn330, Lys353, Asp355 and Ala386	17	−5.87 ± 0.49	Aryl hydrocarbon receptor (AhR) 53%/non mutagen	575
C2.- 7676800	CCn1c(nnc1SCC(=O)c2ccccc2)CCCCc3nnc(n3CC)SCC(=O)c4cccc4	Lys26, His34, Asp38, Tyr41, Gln42, Gln96, Asn330, Lys353, Gly354, Ala386, Pro389 and Arg393	19	−5.84 ± 0.60	Carcinogenicity 51%/mutagen	1500
C3.- 7956590	c1cccc(cc1)CNC(=O)c2ccc(cc2)NC(=O)CC(=O)Nc3ccc(cc3)C(=O)NCc4cccc4	Lys26, His34, Glu35, Glu37, Asp38, Tyr41, Gln42, Gln96, Asn330, Lys353, Gly354, Ala386, Ala387 and Pro389	19	−5.83 ± 0.55	Inactive. Probably safe/non mutagen	1000
C4.- 7782787	COc1ccc(cc1OC)CC(=O)Nc2ccc(cc2O)Cc3ccc(c(c3)O)NC(=O)c4ccc(c(c4)OC)OC	Lys26, His34, Glu37, Tyr41, Lys353, Ala387 and Pro389	19	−5.77 ± 0.36	Inactive. Probably safe/non mutagen	2000
C5.- 7938481	CCOC(=O)c1ccc(cc1)NC(=O)CSc2nnc(n2CC=C)CC(=O)Nc3ccc(cc3C)C	Thr27, His34, Glu37, Asp38, Tyr41, Gln42, Gln96, Asn330, Lys353, Pro389 and Arg393	20	−5.69 ± 0.55	Inactive. Probably safe/mutagen	1000
C6.- 7517329	Cc1c(nc(s1)NC(=O)CSc2nnc(n2c)CNC(=O)Cc3ccc(cc3)OC)c4cccc4	Lys26, Asp30, His34, Glu35, Glu37, Asp38, Gln96, Lys353, Ala386, Ala387, Pro389 and Arg393	19	−5.69 ± 0.48	Inactive. Probably safe/mutagen	1000
C7.- 7787375	CC(C)c1ccc(cc1)OCC(=O)NCCCCCCNC(=O)COc2ccc2cc(cc2)C(C)C	Lys26, Thr27, His34, Glu35, Asp38, Gln42, Gln96, Lys353, Gly354, Pro389, Phe390 and Arg393	19	−5.65 ± 0.55	Inactive. Probably safe/non mutagen	450
C8.- 7783270	c1ccc(c(c1)C(=O)NNC(=O)c2ccc(cc2)Oc3ccc(cc3)C(=O)NNC(=O)c4cccc4Cl)Cl	Glu23, Asp30, Lys31, His34, Glu35, Glu37, Asp38, Tyr41, Gln42, Leu45, Lys68, Lys353, Gly354, Ala387 and Arg393	18	−5.62 ± 0.48	Hepatotoxicity 57% Aryl hydrocarbon receptor (AhR) 55% Mitochondrial 52%/mutagen	575
C9.- 7134636	COc1ccccc1C(=O)Nc2nnc(s2)SCC(=O)Nc3ccc4c5ccccc5oc4c3	His34, Glu35, Asp38, Gln42, Lys68, Gln96, Lys353, Gly354, Ala386, Ala387 and Pro389	20	−5.56 ± 0.48	Hepatotoxicity 57%/mutagen	3000
C10.- 7390655	CCc1ccc(cc1)OCC(=O)Nc2ccccc2NC(=O)COc3ccc(cc3)CC	His34, Lys353, Ala386, Pro389 and Arg393	15	−5.54 ± 0.57	Inactive. Probably safe/non mutagen	1600
C11.- 7652337	CCOC(=O)c1ccc(c1)NC(=O)CSc2nnc(n2c)CNC(=O)c3ccc(c(c3)OC)OC	His34, Asp38, Tyr41, Lys353, and Pro389	18	−5.54 ± 0.38	Inactive. Probably safe/mutagen	1000
C12.- 6898502	COc1ccccc1OCC(=O)Nc2ccc(cc2)Oc3ccc(cc3)NC(=O)COc4cccc4OC	Asp30, His34, Tyr41, Gln42, Lys68, Asn330, Lys353, Gly354, and Pro389	17	−5.53 ± 0.53	Inactive. Probably safe/non mutagen	3000
C13.- 6936307	COc1ccccc1OCC(=O)Nc2ccc(cc2)c3ccc(cc3)NC(=O)COc4cccc4OC	His34, Glu35, Leu45, Lys68, Gln96, Lys353 and Ala387	15	−5.53 ± 0.56	Inactive. Probably safe/non mutagen	1600
C14.- 7974985	COc1ccc(cc1OC)CC(=O)Nc2ccccc2NC(=O)Cc3ccc(cc3)NGc4ccs4	Asp30, His34, Glu35, Glu37, Asp38, Leu39, Lys353, Ala386 and Pro389	15	−5.53 ± 0.55	Carcinogenicity 58%/mutagen	1000
C15.- 7153800	CC(CNC(=O)Cc1ccc(cc1)C(C)(C)C)NC(=O)COc2ccc(cc2)C(C)(C)C	Asp30, His34, Glu35, Asp38, Lys353, Ala386, Ala387, Pro389 and Arg393	17	−5.52 ± 0.65	Inactive. Probably safe/non mutagen	1050
C16.- 7588589	CCOc1ccccc1NC(=O)c2ccc(cc2)Oc3ccc(cc3)C(=O)Nc4cccc4OCC	Lys26, Asp30, His34, Asp38, Gln42, Gln96, Lys353, Ala387, Pro389 and Arg393	19	−5.51 ± 0.55	Inactive. Probably safe/non mutagen	1000
C17.- 7844832	CCn1c(nnc1SCC(=O)Nc2c(c3c(s2)CCCC3)C#N)CCNC(=O)c4cccc4Cl	Asn33, His34, Glu37, Asp38, Gln96, Lys353, Gly354, Ala387, Pro389, Phe390 and Arg393	17	−5.51 ± 0.47	Inactive. Probably safe/mutagen	1000
C18.- 7845662	Cc1ccc(cc1)C(=O)NCCCc2nnc(n2CC=C)SCC(=O)Nc3nc3nc(cs3)c4cccc4	Asp30, His34, Glu37, Gln42, Lys68, Gln96, Lys353, Gly354, Asp355, Ala386 and Pro389	17	−5.51 ± 0.47	Carcinogenicity 57%/mutagen	1000
C19.- 7987131	Cc1cc(ccc1OCC(=O)NCCc2ccc(c(c2)OC)OC)S(=O)(=O)NCC(C)C	Asp30, His34, Glu37, Tyr41, Gln96, Lys353, Ala387, Pro389 and Arg393	16	−5.51 ± 0.50	Inactive. Probably safe/mutagen	2000

5

Table 2 (*continued*)

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-II server/PreADMET Ames test	Predicted LD50 (mg/kg)
C20.- 7939484	Cc1cccc(c1NS(=O)(=O)c2cccc(cc2)NC(=O)CN(c3ccc(cc3)OC4ccccc4)S(=O)(=O)C)C	Asp30, His34, Asp38, Tyr41, Gln42, Lys68, Gln96, Lys353, Ala387, Pro389 and Arg393	20	−5.50 ± 0.57	Inactive. Probably safe/non mutagen	5100

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.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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.

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