



Mulberrofuran G, a Potent Inhibitor of SPIKE Protein of SARS Corona Virus 2

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ABSTRACT

Background: At the onset of the 2020 year, Coronavirus disease (COVID-19) has become a pandemic and infected many people worldwide. Despite all efforts, no cure was found for this infection. Bioinformatics and medicinal chemistry have a potential role in the primary consideration of drugs to treat this infection. With virtual screening and molecular docking, some potent compounds and medications can be found and modified and then applied to treat disease in the next steps.

Methods: By virtual screening method and PRYX software, some Food and Drug Administration (FDA) approved drugs and natural compounds have been docked with the SPIKE protein of SARS-CoV-2. Some more potent agents have been selected, and then new structures are designed with better affinity than them. After that, we searched for the molecules with a similar structure to designed compounds to find the most potent compound to our target.

Results: Because of the study of structures and affinities, mulberrofuran G was the most potent compound in this study. The compound has interacted strongly with residues in the probably active site of SPIKE.

Conclusion: Mulberrofuran G can be a treatment agent candidate for COVID-19 because of its good affinity to SPIKE of the virus and inhibition of virus-cell adhesion and entrance.

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Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease was firstly reported in Wuhan of China, in December of 2019. COVID-19 has infected many people all over the world, and this pandemic also caused many deaths (1). COVID-19 is a very high transmission disease with a variable prognosis in the general population, and risk factors such as age, hypertension, diabetes, cancer, and chronic respiratory and cardiovascular disease are associated with the worst prognosis (2). This infection causes infection at any age; however, older adults and people who suffer underlying diseases have more chance for infection and morbidity (3). This viral disease doesn't have any dedicated treatment or approved drug. All patients have to use undedicated drugs such as Hydroxychloroquine or HIV protease inhibitors (4).

Therefore, there is a need to discover new molecules to treat it. In this article, a new structure that can be a candidate for the treatment of COVID-19 will introduce.

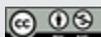
Methods

A virtual screening method with PYRX software for finding a potent molecule was chosen. In this method a target protein will choose as a macromolecule and a compound will choose as a ligand of target protein; then software surveys the interaction of protein of target and ligand and report this interaction by a number of affinity; The more negative this affinity number, the stronger the interaction between the protein and the ligand. to enhance the work precision in this method a proper grid box; a surrounded place for interaction of the target protein and ligands; and also some amino acids as flexible residues, should be determined.

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Some crystallography structure of SARS coronavirus 2(SARS-CoV-2) has published in protein data bank(PDB). The PDB file of the Structure of the SPIKE receptor-binding domain complexed with its receptor angiotensin-converting enzyme 2 (ACE2) 6LZG was chosen. The 3D structure showed how SPIKE protein of SARS-CoV-2 interacts with human receptor ACE 2. since virus-cell entrance depends on this interaction of these two proteins (ACE and SPIKE); by inhibition of this interaction, cell infection can be stopped. Therefore, this pdb file choose as our target protein. Many approved drugs, such as

antivirals, antibiotics, antifungal, antihistamines, and even medicines used for CNS disorders and natural compounds like flavonoids, used for this virtual screening; also, the molecular structures of them downloaded as a mol2 file from zinc and PubChem databases; these molecules also selected as ligands of our target protein. The grid box properties for the study were: center X=-41.0068, Y=2805839, Z=1.3444; dimensions X=31.0270, Y=45.5880, Z=16.1778 then the most involved amino acids in the active site of SPIKE was determined with spider website. The protein interface recognition result was in this way:

Table 1. The protein interface recognition result.

Highlight interface of chain	With interacting partner	Residues (Preserving PDB numeration)	ISA*, Å ²	HPI**
<input type="checkbox"/> A	B	S19 Q24 T27 F28 D30 K31 H34 E35 E37 D38 Y41 Q42 L45 L79 M82 Y83 Q325 N330 K353 G354 D355 R357 R393	906	0.73±0.66
<input type="checkbox"/> B	A	K417 G446 Y449 Y453 L455 F456 Y473 A475 G476 E484 F486 N487 Y489 F490 Q493 G496 Q498 T500 N501 G502 V503 Y505	957	0.95±0.85

The chain A was related to the ACE 2 human receptor, and the chain B was associated with SPIKE of SARS-CoV-2.

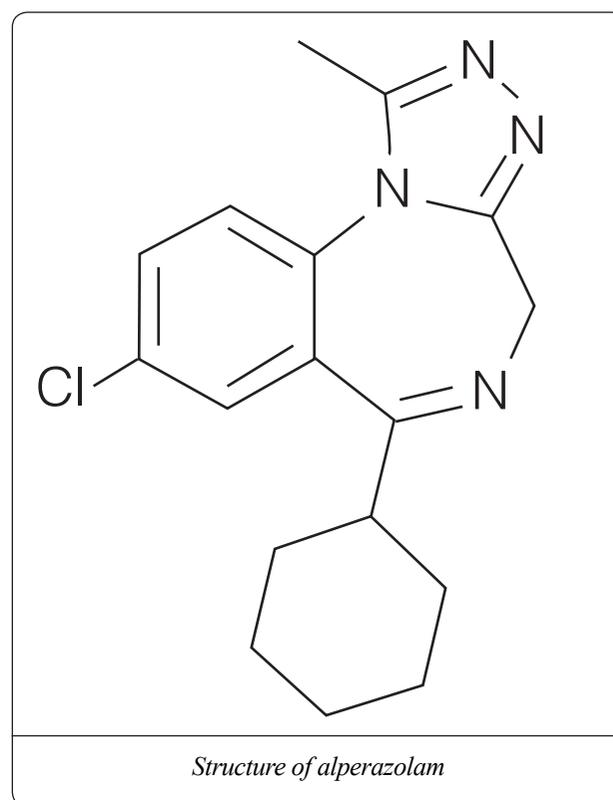
All of the amino acids that are determined in the above table can be candidates for flexible residues in molecular docking to design new compounds for COVID-19 treatment. Also, the interaction of each of these amino acids with a compound can inhibit their interaction with other proteins and, therefore, virus-cell entrance.

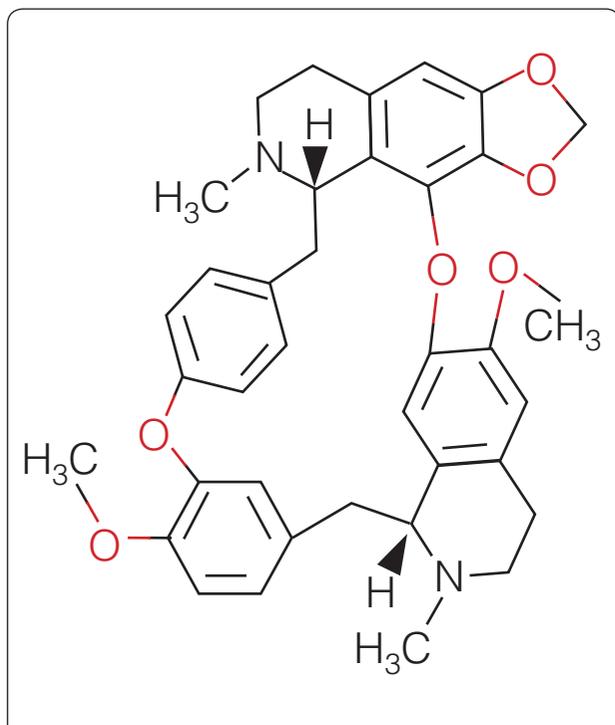
After molecular docking with PYRX software, the molecules with the lowest binding energy were chosen. Also the interaction of them with amino acids of proteins in their active site was considered; many amino acids mentioned in table 1 interact strongly with some compounds. These molecules were modified after that, and some new molecules were designed and drawn by ChemDraw software. Binding energy and interaction of them with amino acids of their target protein was considered too. In the last step, according to modified molecules, a compound was deemed that has more affinity and potency than others, even designed molecules.

Results

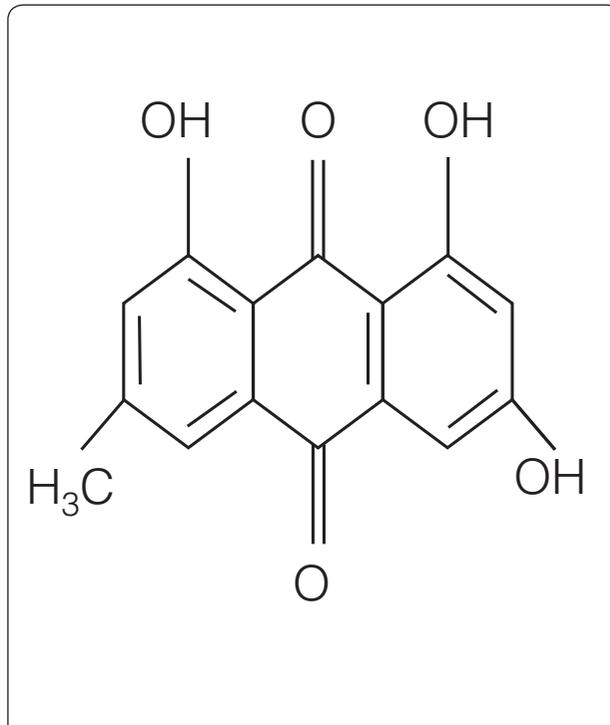
Firstly, compounds that have three rings in their structure have a better affinity than others; compounds such as cepharantin, emodin, triazolam, cyproheptadine, thiothixene, alprazolam, ivermectin, niclosamide, hesperidine. They had binding energy respectively -9.2, -7.2, -7.6, -7.3, -7.4, -7.2, -10.3, -7.9, -9.5 kcal/mol. Alprazolam interacts with aspartate 30, glutamate 35 and glutamate 37 of ace protein and tyrosine 473, glutamate 484, glutamine 493 and tyrosine 505 of SPIKE; cepharanthine only interacts with histidine 34 of ACE; emodine interacts with aspartate 30, lysine 31, histidine 34, glutamate 35 and glutamate 37 of ace protein and glutamate 484, asparagine 487, glutamine 493 and tyrosine 505 of SPIKE; thiothixene interacts with threonine 27, glutamate 37, aspartate 38 and arginine 393 of ACE; triazolam

interacts with glutamate 35 of ACE and glutamate 484 of SPIKE; ivermectin interacts with histidine 34 and aspartate 38 of ACE and tyrosine 473 of spike; niclosamide interacts with aspartate 30, histidine 34, glutamate 37, lysine 353, arginine 393 of ace and glycine 496, tyrosine 505 of spike; hesperidine interacts with aspartate 30, histidine 34, glutamate 35, aspartate 38, lysine 353, arginine 393 of ace and lysine 417, tyrosine 453 of spike.

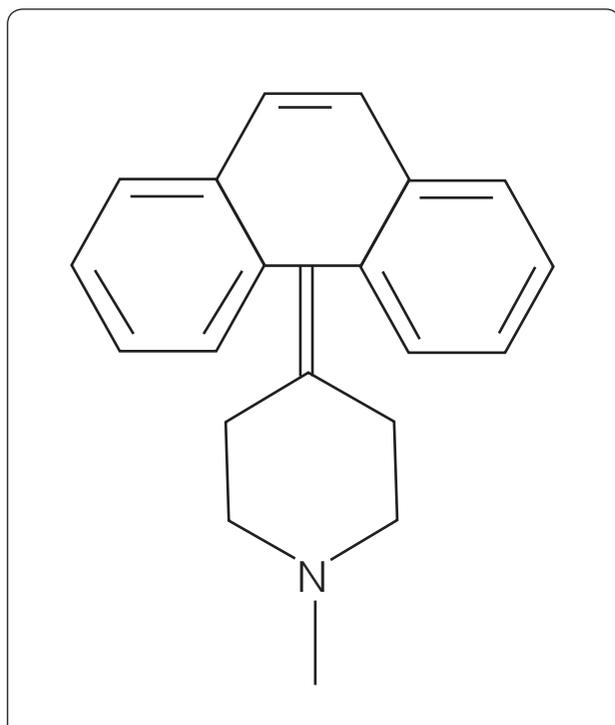




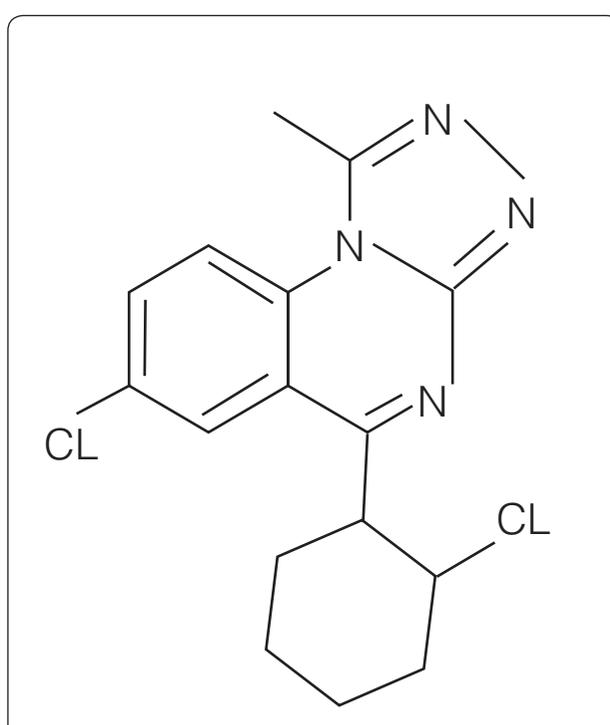
Structure of cepharantine



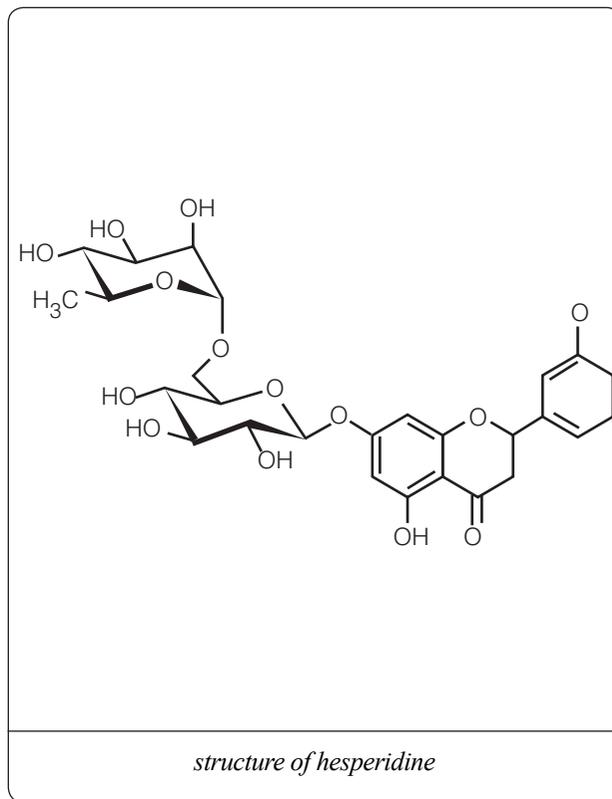
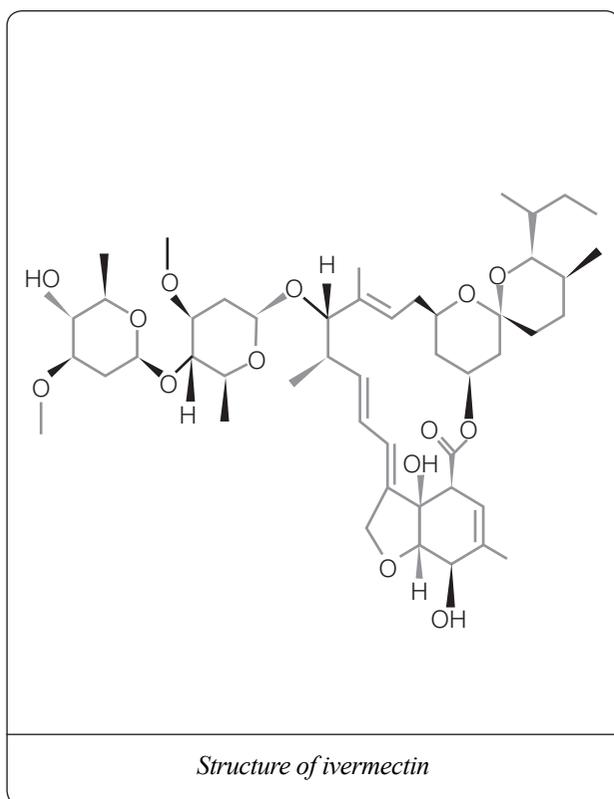
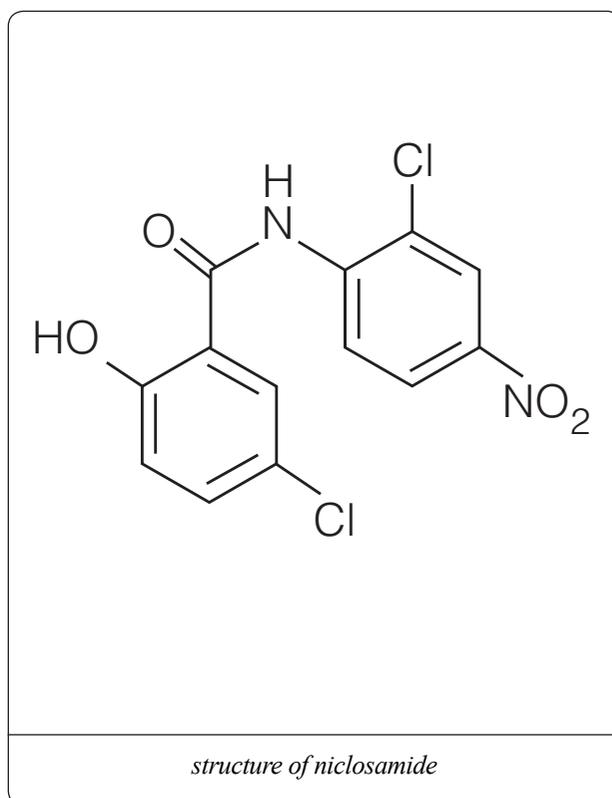
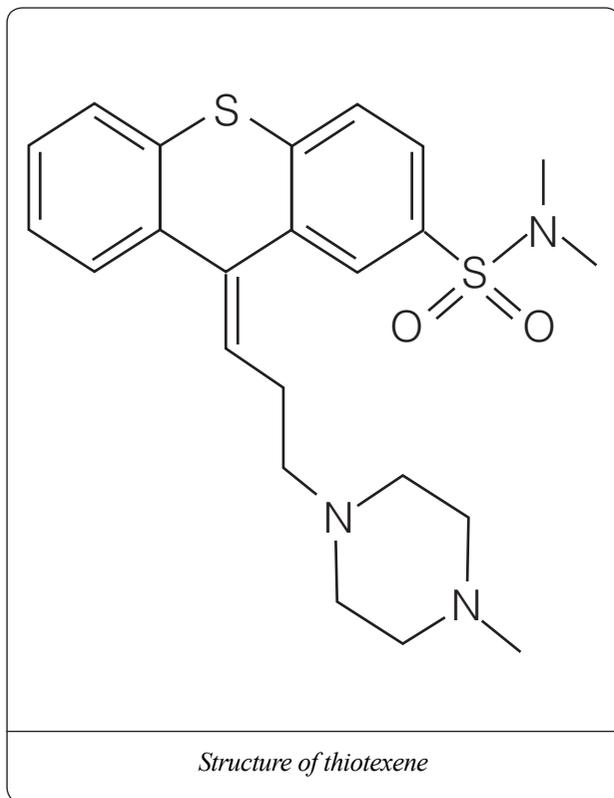
Structure of emodine



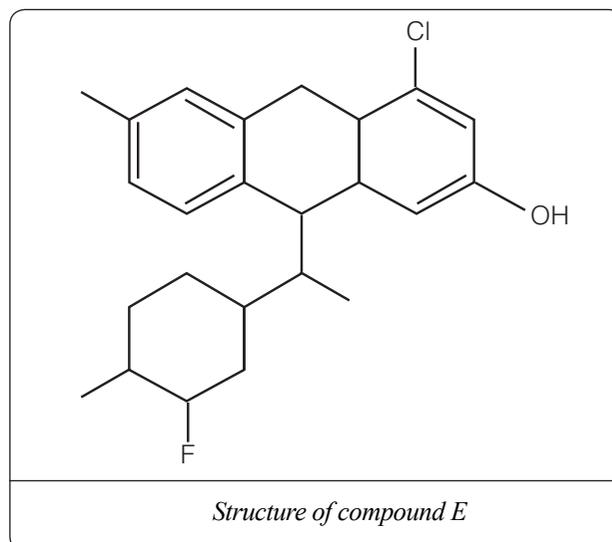
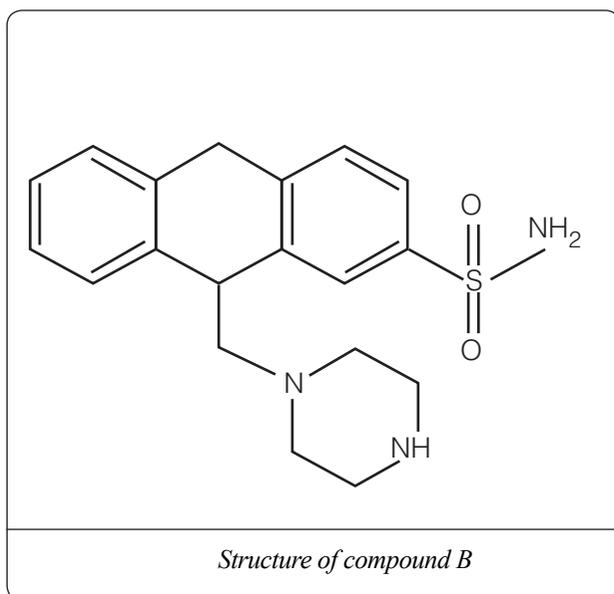
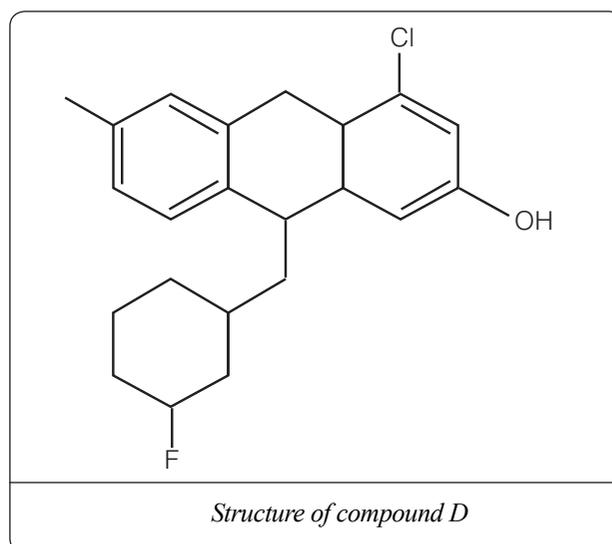
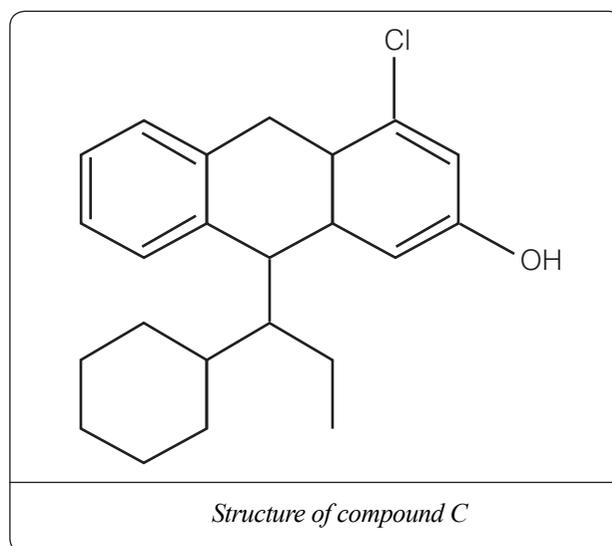
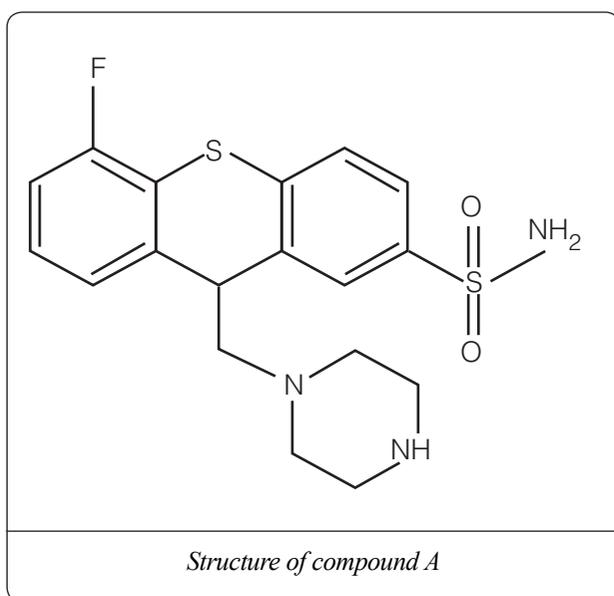
Structure of cyproheptadine

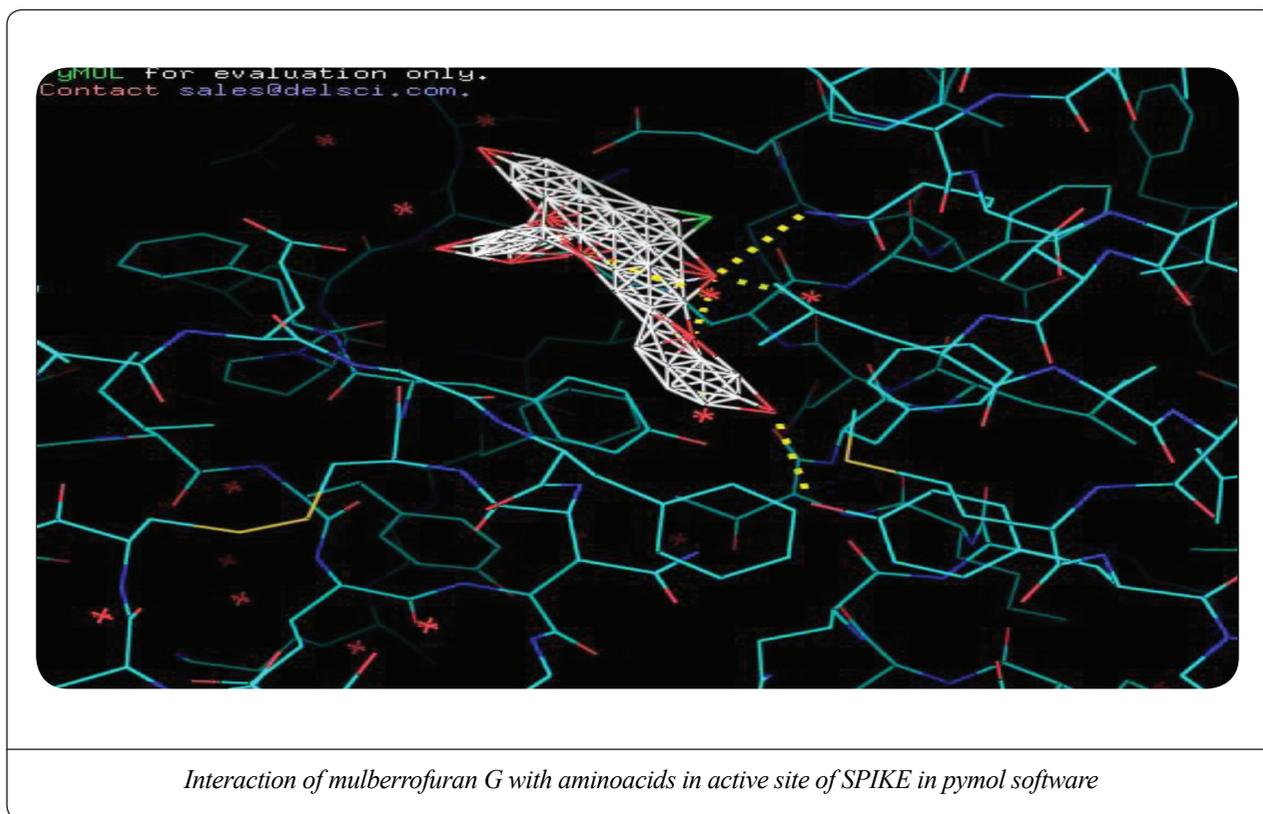
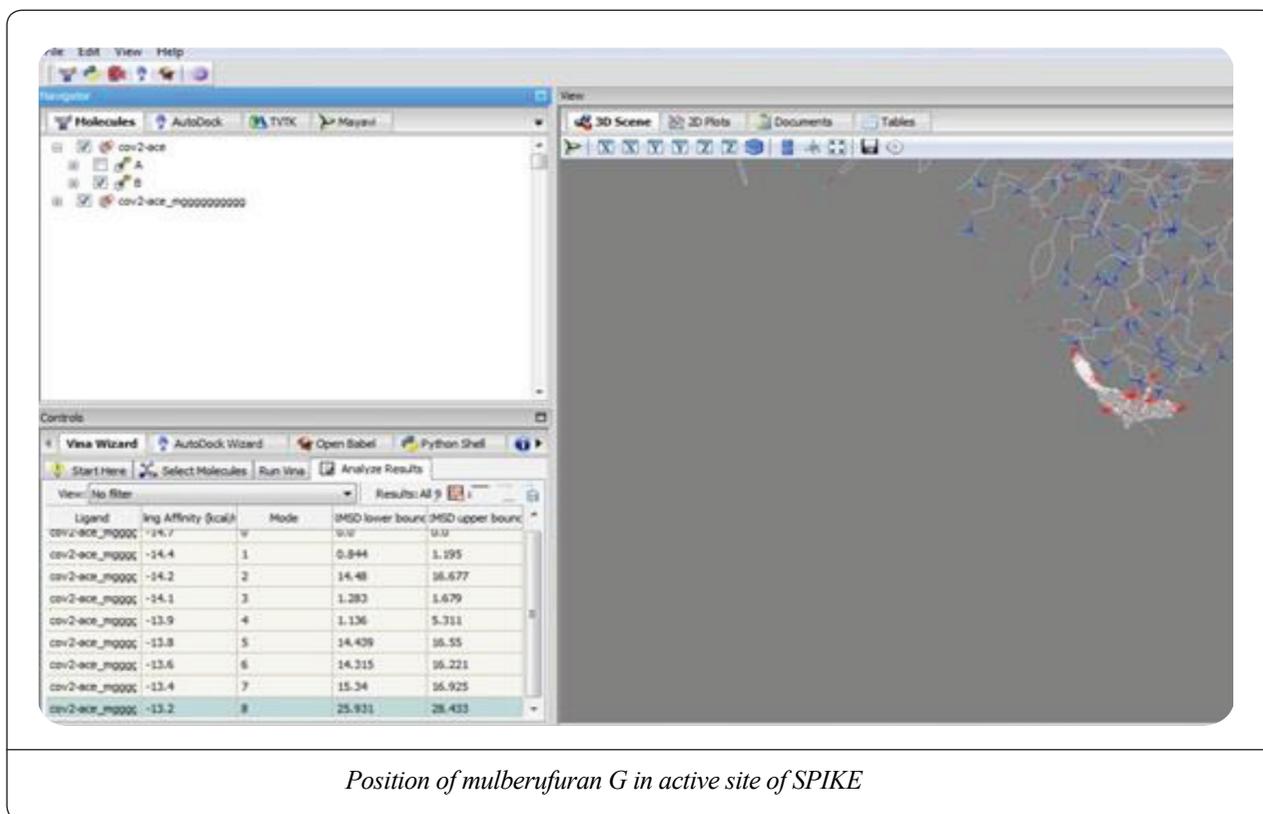


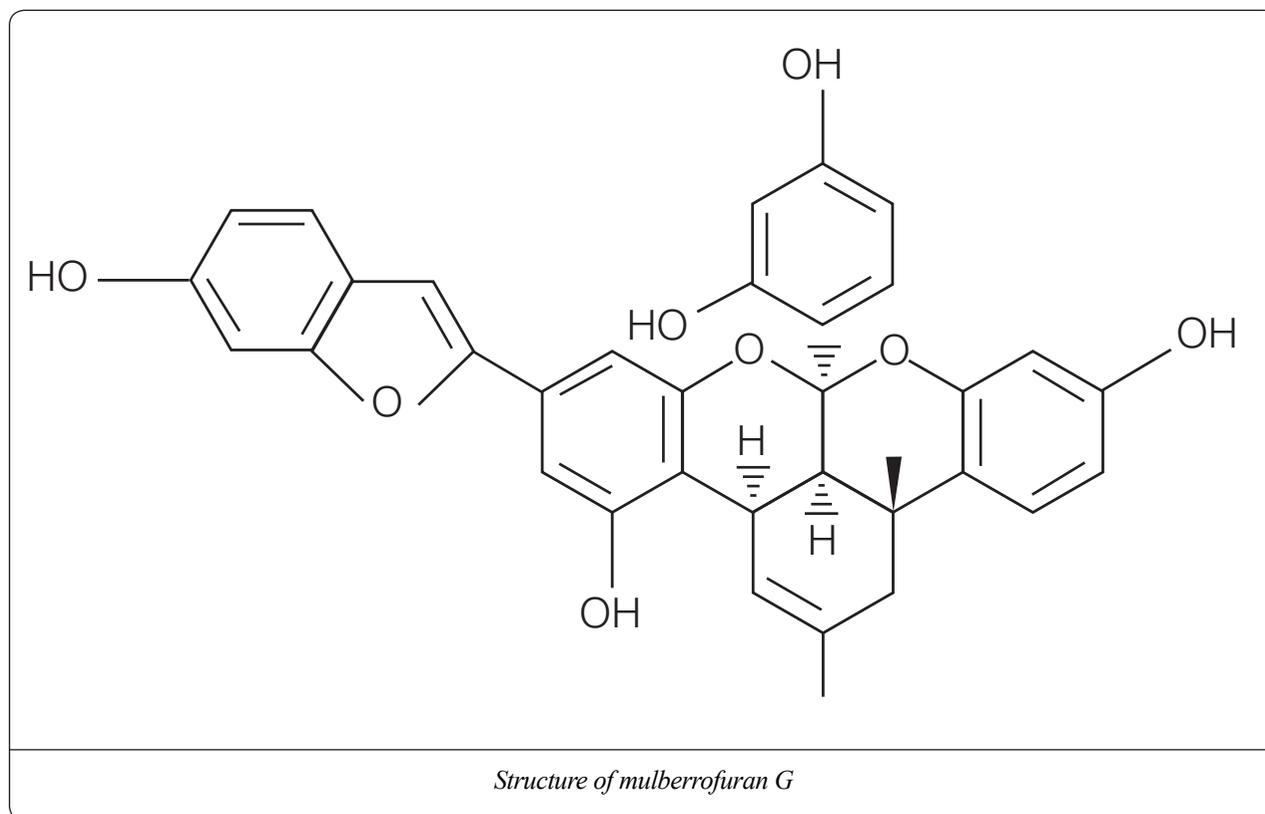
Structure of triazolam



The compounds A, B, C, D, and E were drawn in Chem-Draw, and their binding affinity was considered; their binding energy was respectively -8.5, -10.9, -11.2, -12.1, -12.8. compound A interacts with histidine 34, glutamate 37, and lysine 353 of ACE and tyrosine 453, glycine 496, and tyrosine 505 of SPIKE; compound B interacts with glutamate 37 and lysine 353 of ACE and tyrosine 453, glycine 496 and tyrosine 505 of SPIKE; compound c interacts with glycine 496 of SPIKE only; compound D interacts with leucine 45 and lysine 353 of ACE and glutamine 493 and glycine 496 of SPIKE; compound E interacts with lysine 353 of ACE and tyrosine 453, glutamine 493, glycine 496 and tyrosine 505 of SPIKE.







Also, mulberrofuran G was considered by interaction with crystallography file of lone SPIKE of SARS-CoV-2 (6wpt). the grid box properties were: center X =227.5523, Y=211.4440, Z=251.9604; dimensions: X=108.7327, Y=114.4655, Z=52.0999. the binding energy was -15.7 to -15.2, which seems proper too.

Discussion

Mulberrofuran G, is a phytochemical found in *Morus alba* bark. there are some evidence that this compound has anti hepatitis b activities (5). also anti-inflammatory, anti-bacterial and antifungal, anti-tyrosinase and anti-cancer activity has been seen by this compound (6). It seems that this compound could have potential effects in improving Covid 19 disease.

There are some research and studies confirming this in silico study method accuracy. According to a study cepharantine can inhibit SARS COV 2 virus entrance to human cell and also replication at low doses. the study performed by Vero cells (7). Emodine and hesperidine are potential inhibitors of ACE2 and spike complex (8). Ivermectin acts very effective against Covid 19 infection through some pathways. one of this pathways is inhibiting virus entrance via ace2 protein (9). Niclosamide has a key role in targeting ace2 protein (10). Mulberrofuran G appropriately interacts with some amino

acids of SPIKE of SARS-CoV-2. These amino acids interact with human ACE 2, too; it means these amino acids are proper residues for binding to any compound and inhibition of SPIKE of virus following that. This compound has properly binding energy for SPIKE of the virus compared to the same molecules, including some FDA-approved drugs or same designed and modified molecules, which was mentioned earlier; also there is a report of mulberrofuran G appropriate affinity to binding to 3cl-protease of SARS corona virus 2 (11); according to these reports, mulberrofuran G can be a potent candidate for the treatment of COVID-19. However, it needs more tests, such as in vitro and in vivo and clinical trials, to confirm its efficacy. macists' intervention can help the clinicians in this context.

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