Molecular Interactions of Fullerene-Based Derivatives and SARS-CoV-2

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Abstract

There are no expedient proven to stop the outbreak of SARS-CoV-2 at this phase. This leads to diversity of endeavors to find out the effective drug or vaccine. One of these possibilities is to exploit the unique characteristics of fullerene-based derivatives. A computer-aided method (molecular docking) was applied to assess the differential binding behavior of these compounds and determining hydrophobic forces, electrostatic interactions, and hydrogen bonds played vital roles in the interactions with SARS-CoV-2 spike protein. The molecular docking calculation clarifies the binding mode and the binding sites may facilitate the development of new or improved therapeutic regimes effective against COVID-19. Fulleropyrrolidine-NH2 seems to be promising candidate for interacting with SARS-CoV-2 binding site.

Introduction

RNA viruses are world-wide pathogens as a consequence of their ability to evolve rapidly and adapt to new environments. Of those, positive-stranded RNA corona viruses are a large family of pathogens that usually cause mild to moderate upper-respiratory tract illnesses, like the common cold [1]. However, three new corona viruses have originated from animal reservoirs over the past two decades to cause serious and widespread illness and death [2-4].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a member of *Betacoronavirus* genus [5, 6]. The spherical morphology of SARS-CoV-2 is composed of four main structural proteins including spike, envelope, membrane and nucleocapsid proteins that play an important role in viral synthesis and replication [7]. The viral spike (S) glycoprotein is present on the viral surface as a homo-trimer [8]. The S-protein is composed of two subunits: S1 and S2, mediating attachment and membrane fusion, respectively [9]. The receptor-binding domain (RBD) of S1 subunit is the main component of the virus that induces neutralizing antibodies against the virus and is thus considered potential targets for development of drugs and vaccines for SARS-CoV-2 [10,11]. SARS-CoV-2 and SARS-CoV strains engage the same receptor angiotensin-converting enzyme 2 (ACE2) in humans to facilitate viral entry into target cells [11-15].

Fullerene is an allotrope carbon nanostructure with a monodisperse size and morphology. Fullerene nanoparticles have received a considerable amount of attention owing to their unique physical and chemical properties. Moreover, fullerene-based nanomaterials has very wide array of applications in the field of biomedicine. Water-soluble fullerene compounds have inhibitory effects against human immunodeficiency virus (HIV) proteases, influenza A *viral infection, and HCV [16-20].* Virus-induced *redox imbalance* is a major cause of change the intracellular redox state [21-23]. However, the most prominent *fullerene* properties are its *reactive oxygen species* scavenging [24] while the antioxidant effect of fullerene derivatives depends on their chemical structure [20].

Among different routes of molecular modeling computational biophysics is one of the most important approaches that can be used to find out an effective treatment for such pandemics. Therefore, this study

has been undertaken to study the molecular interaction of fullerene-based derivatives with receptor-binding domain (RBD) of SARS-CoV-2 *spike* through docking experimentation in order to understand the underlining mechanisms to be used in designing more effective drugs for SARS-CoV-2 infection.

Methodology

Initially, the molecular models of the six Fulleropyrrolidine-1-carbodithioic acid 2; 3 and 4-substituted-benzyl esters-based derivatives at ortho, meta and para positions respectively presented in this study were previously built with the use of Gauss View [25] software. These compounds have been previously reported having antiviral activity [26-28]. Chemical structures of the derivatives were provided in figure 1. Then, the geometry of the compounds was optimized in the vacuum by performing PM6 semiempirical quantum mechanical level of theory as previously reported [29, 30].

Two different molecular docking protocols were used for predicting the binding affinities for fullerene derivatives. The co-crystallized structure of SARS-CoV-2 spike receptor binding domain in complex with Angiotensin-Converting Enzyme 2 (ACE2) (PDB 6m0j) [31] was downloaded from the protein data bank and prepared for docking using UCSF Chimera-1.14 [32]. Briefly, the receptor binding domain (RBD) was extracted from ACE2, and the N-acetyl glucosamine moieties were removed from the structure. The polar hydrogen atoms were added to the protein, and gasteiger charges were added to each atom and the non-polar hydrogen atoms were merged to the protein structure employing Autodock Tools 1.5.6 [33]. The structure was then saved in PDBQT file format for docking studies in Autodock Vina 1.1.2 software [34]. Autodock vina is employed for its ability to find bioactive conformations with a very good level of accuracy and it was also found to retain a notable efficiency as the number of rotatable bonds increased. DINC 2.0 web server [35] is applied as well. DINC is a parallelized meta-docking method for the incremental docking of large ligands. The strategy of DINC involves incrementally docking overlapping fragments with a growing number of atoms, while maintaining the number of flexible bonds constant during this incremental process. First, the spatial coordinates of ACE2 were used as a reference in determining the binding site and the docking grid box. The grid size was set to ~ 36 Å× 50 Å× 21 Å xyz points with grid spacing of 0.375 Å and grid center was designated at dimensions (x, y, and z): -30.0, 29.0 and 6.75. Such approach may give the best result for estimation of the binding between protein and ligand [36].

Results

It is interesting that these two docking protocols reveal the possibility of fulleropyrrolidine-based molecules interaction with the binding site of SARS-CoV-2 spike protein. All the generated complexes in DINC 2.0 server and Autodock vina were ranked on the bases of energy associated with the protein-ligand interactions. Top ranked binding energies (kcal/mol) in the DINC 2.0 server output files were taken as a response in each run. The obtained docking results exhibited relatively high potential for binding of fulleropyrrolidine compounds in terms of effective molecular interaction with the investigated protein,

SARS-CoV-2 spike RBD. The relative binding affinities between the ligands containing CN and NH2 groups have exhibited better binding affinity compared to the rest of compounds.

Table 1: Calculated binding affinity as kcal/mol for binding of fulleropyrrolidine derivatives, meta-Me and meta-Cl, ortho-CN and ortho-COMe, para-NH_2 and para-NHCH3 with SARS-CoV-2 via two molecular docking protocols named Autodock Vina 1.1.2 software and DINC 2.0 web server.

Structure	DINC2 web server Binding affinity (kcal/mol)	Autodock vina Binding affinity (kcal/mol)
Meta-Me-COVID-19	-7.8	-8.1
Meta-Cl-COVID-19	-8.2	-8.0
Ortho-CN-COVID-19	-8.4	-8.3
Ortho-COMe-COVID-19	-7.9	-7.8
Para-NH_2-COVID-19	-8.3	-7.9
Para-NHCH3-COVID-19	-7.80	-7.9

Ligand binding stability was then assessed by monitoring the residue contribution to protein-ligand interactions. The docked complexes are analyzed by the protein–ligand interaction profiler (PLIP) server [37] to classify the types of interactions between the fulleropyrrolidine molecules and individual amino acids within the spike RBD binding site. The fulleropyrrolidine-based molecules were surrounded in spike RBD binding site by hydrophobic residues such as Val407, Asn437, Val503, Tyr505, and Tyr508. Moreover, four ligands stabilized further through π-cation interactions with two residues Lys378 and Arg408. However, in para-NH_2 molecule, we do find significant preference for π-π stacking with Tyr449 and Tyr505 residues. It could be inferred that the hydrophobic interactions play crucial role in stabilizing of the protein-ligand complex. Also, a hydrogen bond was observed between the NH_2 group and Tyr505 amino acid residue.

Discussion

The spike protein–receptor interaction is the primary determinant for a coronavirus to infect a host species and also governs the tissue tropism of the virus [38]. On the other hand, the zinc metallopeptidase ACE2 has been identified as the main entrance (receptor) for coronavirus into the cells [39].

The cornerstone for combating the SARS-CoV-2019 pandemic is to construct inhibitors that prevent the association of both the virus and its host's receptor. No specific *treatments* for *SARS-CoV-*20*19* exist right now. However, many studies call for exploiting the possibilities of nanomaterials.

The fullerene-based nanoparticle compounds could be considered for its antiviral potential and could be a valuable source for the design and development of new anti-infective compounds. To achieve this purpose, we explore five fullerene-based formulations to bind the receptor-binding domain of spike protein. It is interesting that fulleropyrrolidine derivatives have the potentialities to bind the RBD. However, the RBD structural change associating the binding of nanoparticle is awaiting further investigations.

Declarations

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Conflicts of interest

The authors declare that they have no conflict of interest. The manuscript has been read and approved by all of the authors.

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Figures

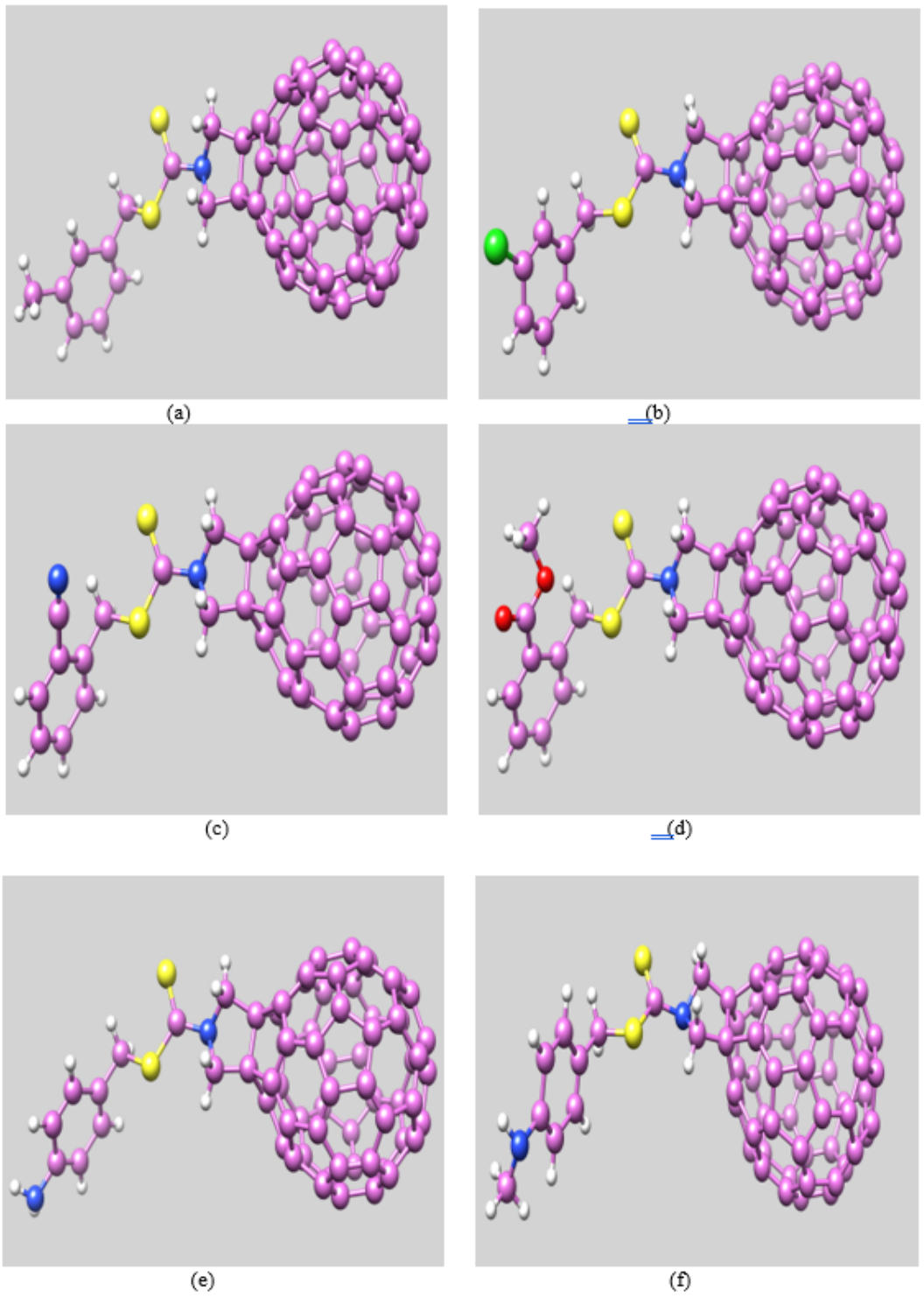

Figure 1

PM6 optimized (a) Meta-Me, (b) Meta-Cl, (c) Ortho-CN, (d) Ortho-COMe and (e) Para-NH2.

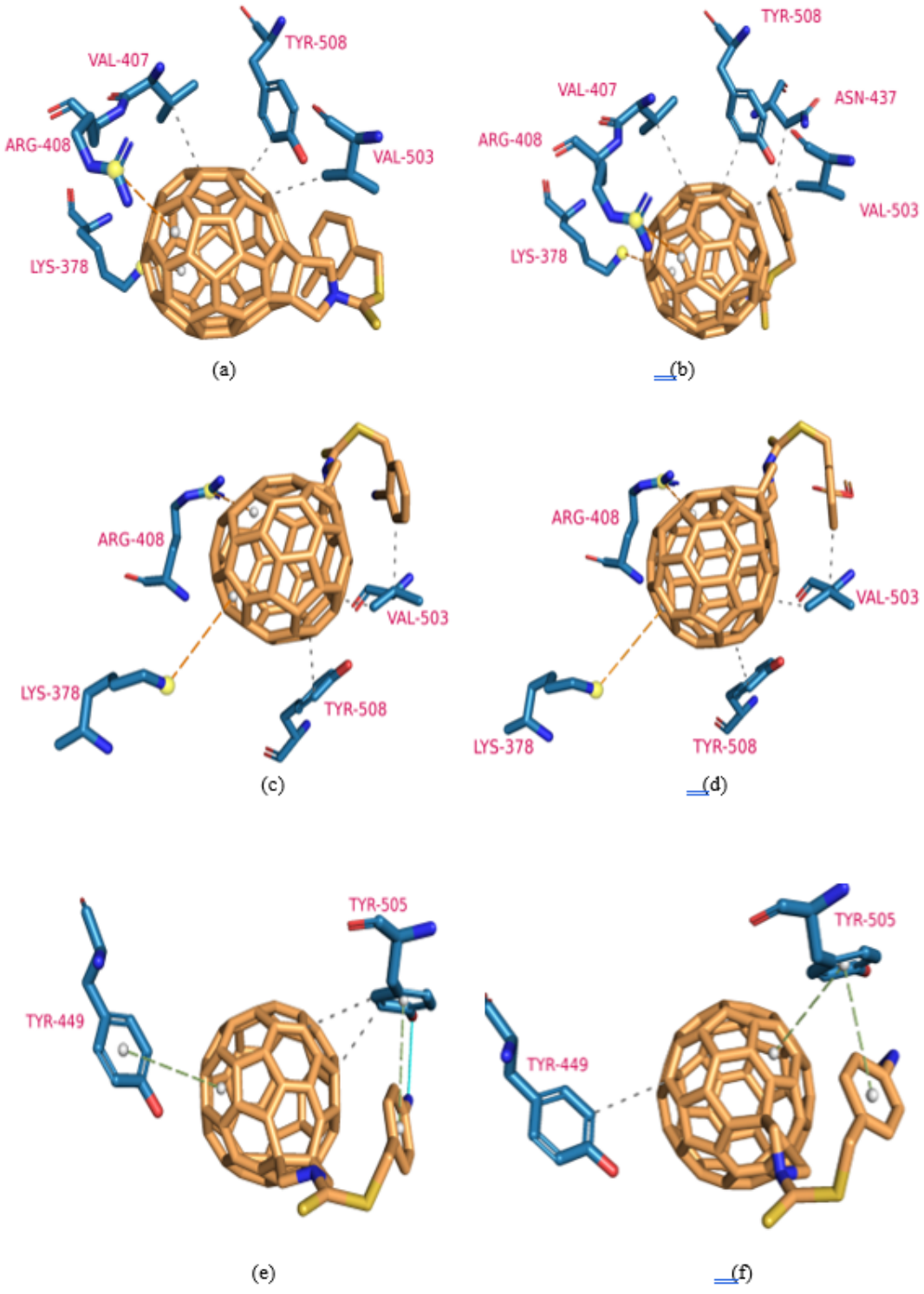

Figure 2

An interaction diagram depicts the intermolecular bonds that are formed in the complex between spike protein RBD of SARS-CoV-2 and the various fulleropyrrolidine-based molecules. The residues of protein structures are shown in blue and the ligand shown in gold. Hydrophobic contacts shown as dash gray lines, π-stacking shown as dashed green lines and hydrogen bonds shown in cyan line. Figures were prepared using PyMOL.

Supplementary Files

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- MetMe.png