Biointerface Research in Applied Chemistry
Platinum Open Access Journal (ISSN: 2069-5837)

Article
Volume 11, Issue 6, 2021, 13962 - 13967
https://doi.org/10.33263/BRIAC116.1396213967

Interacting Cubane Assisted Bi-Cytidine with COVID-19 Main Protease: *In Silico* Study

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Received: 22.01.2021; Revised: 19.02.2021; Accepted: 23.02.2021; Published: 2.03.2021

Abstract: *In silico* approach, the quantum chemical computations and molecular docking simulations have been used to investigate the formation of cubane assisted cytidine (B-Cyt) derivative for examining its interactions with the COVID-19 main protease. The obtained results indicated that the new B-Cyt derivative could be stabilized without any imaginary frequency. Its orbital orbital-based electronic properties indicated that the structure could have a better interaction with the target than the singular Cyt ligand. The docking process results approved the trend, in which the value of binding energy was very much favorable regarding the singular models, and the number of interaction amino acids was increased. The idea of forming a Cyt derivative with efficient activity against COVID-19 main protease was approved here, which is very much important for protecting the patients with cancer or HIV against the COVID-19 pandemic.

Keywords: cytidine; cubane; COVID-19; quantum computing; molecular docking.

1. Introduction

Nucleobase derivatives have been seen as pharmaceutical compounds for several years with good potency and efficacy against different diseases but still could be improved [1-3]. Cytidine (Cyt) is among such derivatives with initial activity against cancer by inhibiting overexpressed enzymes [4]. In addition to the original Cyt, several other functionalized models have been developed to explore further features of Cyt for other types of pharmacotherapy [5-8]. Cyt itself is a pharmaceutical compound for cancer treatments, and earlier works have indicated that Cyt-related compounds could also work against HIV [9-12]. Since the Cyt compounds have been introduced as enzyme inhibitors, it is an important task to examine their activity against newly arisen ones such as the main protease of corona virus disease 19 (COVID-19) [13-15]. By the end of the year 2019, the COVID-19 pandemic has widely grown worldwide without and major therapeutic protocol yet, unfortunately. Therefore, it is an emergency case to innovate an efficient therapeutic protocol by drug design methodologies [16-18]. Several works have been dedicated to the topic in the last eight months, but further works are still required for the purpose [19-22]. The formation of a bi-cytidine (B-Cyt) compound with possible effects on the COVID-19 main protease was examined within this work. Cubane (Cub) trimer has been used as a molecular linker to make the possible formation

of B-Cyt compound. Cub is a cubic structure of eight carbon atoms with its characteristic properties as a small stable hydrocarbon structure [23]. Moreover, several other functionalized models of Cub have been developed [24]. Chains of Cub have been seen as stable structures, in which Cub trimers have been seen as good connecting linkers for electronic devices [25]. Therefore, the idea of B-Cyt formation has been developed using the Cub trimer liker to combine two Cyt molecules. The stabilities of molecular structures have been examined using the quantum chemical computations (Table 1 and Figure 1), and their corresponding effects on COVID-19 have been examined by molecular docking simulations (Table 2 and Figure 2) as advantages of working *in silico* [26-32].

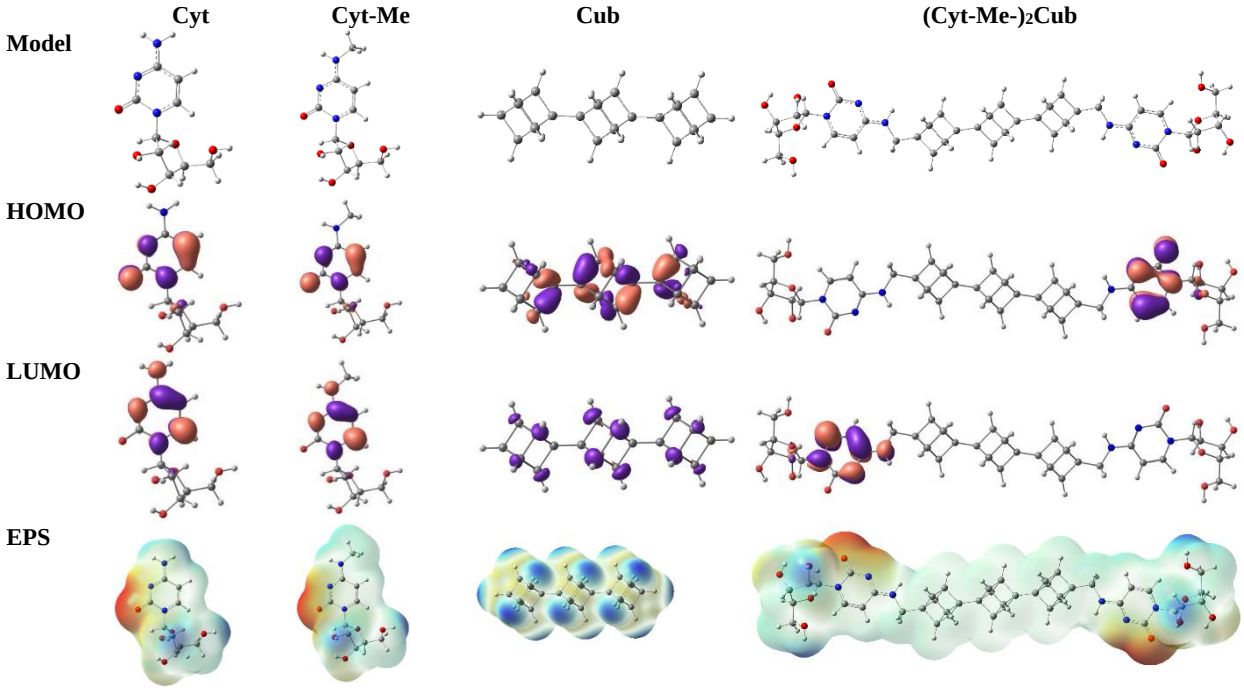


Figure 1. Molecular representations and orbitals.

Table 1. Molecular properties*.

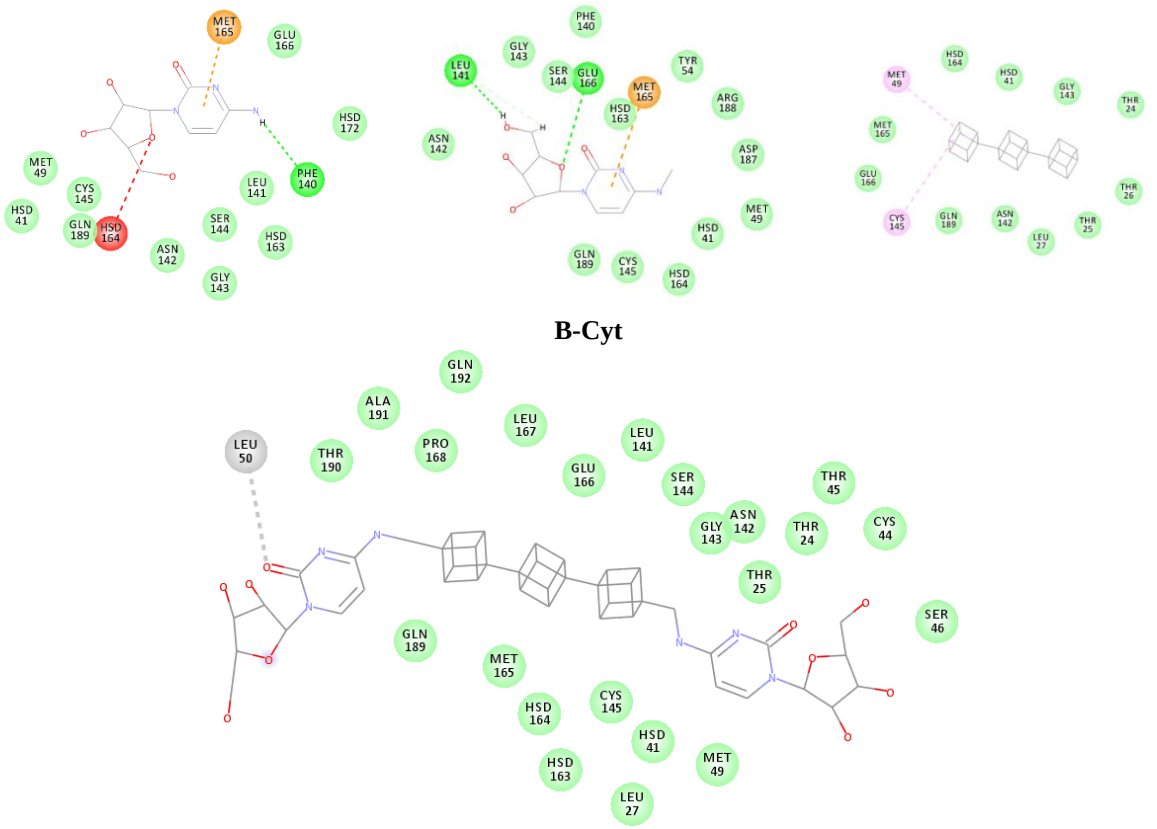
Property	Cyt	Cyt-Me	Cub	B-Cyt
Formula	$C_9H_{13}N_3O_5$	$C_{10}H_{15}N_3O_5$	$C_{24}H_{20}$	$C_{44}H_{46}N_6O_{10}$
HOMO	-6.32	-6.22	-6.49	-6.19
LUMO	-1.14	-1.11	-0.04	-1.08
MV cm^3/mol	186.87	168.532	249.569	502.981
DM Debye	9.24	9.51	0.00	7.06

*See Figure 1 for details.

Table 2. Interaction properties*.

Property	Cyt	Cyt-Me	Cub	B-Cyt
BE eV	-7.41	-7.13	-7.86	-10.26
RMS	70.07	70.54	70.62	73.38
AA	HSD41, MET49, PHE140, LEU141, ASN142, GLY143, SER144, CYS145, HSD163, HSD164, MET165, GLU166, HSD172, GLN189	HSD41, MET49, TYR54, PHE140, ASN142, LEU141, GLY143, SER144, CYS145, HSD163, HSD164, MET165, GLU166, ASP187, ARG188, GLN189	THR24, THR25, THR26, LEU27, HSD41, MET49, ASN142, GLY143, CYS145, HSD164, MET165, GLU166, GLN189	THR24, THR25, LEU27, HSD41, CYS44, THR45, SER46, MET49, LEU50, LEU141, ASN142, GLY143, SER144, , CYS145, HSD163, HSD164, MET165, GLU166, LEU167, PRO168, GLN189, THR190, ALA191, GLN192

*See Figure 2 for graphical representations.



B-Cyt

Figure 2. Representations of ligand-target interactions.

2. Materials and Methods

3D models of singular molecules of Cyt and Cub have been first obtained from ChemSpider Structural Bank [33]. To make the B-Cyt compound's possible formation, the methylated form of Cyt (Cyt-Me) and Cub trimer have been modeled and used to make the B-Cyt compound. Geometries of all molecular structures have been optimized using the B3LYP/6-31G* density functional theory (DFT) method implemented in the Gaussian program [34]. To examine the global minimization status, frequency calculations have been performed for the optimized structures avoiding the existence of imaginary frequencies for the structures. In the next step, electronic properties of molecular orbitals and electronic distribution have been calculated using the B3LYP/6-31+G* method for the optimized structures in addition to calculating their molar volumes (MV). Dipole moment (DM), the highest occupied, and the lowest unoccupied molecular orbitals (HOMO and LUMO) and electrostatic potentials (ESP) have been obtained for the investigated molecular systems to clarify their original electronic states. In the role of ligand, effects of such molecules were examined on COVID-19 main protease, in the role of a target, by performing molecular docking simulations using the SwissDock web server [35]. In such a process, the best ligand configuration against the target could be detected. The 3D file of COVID-19 main protease has been obtained from Protein Data Bank [36] (ID: 6LU7), and it has been assigned as the target to examine the possibility of ligand…target complex formation. The results of binding energy (BE) and root-mean-square (RMS) have been evaluated for the ligand…target complexes in addition to the interacting amino acids (AA). The idea of forming B-Cyt ligand with possible activity against COVID-19 main protease has been investigated here *in silico*, and the obtained results were summarized in Tables 1 and 2 and Figures 1 and 2 to be discussed to achieve the purpose of this work.

3. Results and Discussion

Within this *in silico* work, a new derivative of Cyt has been designed employing the methylated form of original Cyt and a trimer of Cub as linker (Figure 1). The B-Cyt structure has been optimized, and the stabilized model has been obtained, and its verification has been done by frequency calculations avoiding the existence of any imaginary frequencies. Comparing the obtained electronic results (Table 1) for the investigated models of this work could show that the models detect different electronic states, which is very important for determining their activity features. As indicated by HOMO and LUMO, the molecular orbital levels undergo changes, which could yield different electronic behavior for the structures. We expected to have a Cyt derivative with better activity for COVID-19 main protease; here, with the results of Figure 1, the localization of HOMO and LUMO could be seen in different parts of B-Cyt. This trend could mean that the new B-Cyt ligand could play an important role in interactions with enzymes. The HOMO part as the part of electron donor and the LUMO part as the part of electron acceptor is freely localized to have the best chance of interacting with the target. Moreover, ESP could very well approve the dual activity of B-Cyt in comparison with singular Cyt. In this case, the results indicated that the B-Cyt ligand could be expected to work better than the singular Cyt against the target.

The results of docking processes indicated the quantitative values and qualitative interacting AA counterparts. Comparing the values of BE could very well approve the idea of forming a Cyt derivative with more efficient interaction with the target. The values of BE are very much better for B-Cyt compared with each of singular molecules. Since the B-Cyt volume is larger than each of the singular molecules, it is reasonable that the RMS should be larger than each of the smaller molecules. More interestingly, RMS's value for B-Cyt is slightly larger than each of singular molecules, meaning than B-Cyt is still a good competitor in time to reach the target in competition with the small molecules. The schematic results of Figure 2 indicate that the number of interacting AA were significantly increased in the B-Cyt regarding the singular Cyt ligand. More interestingly, common AA is seen in both complexes meaning that the B-Cyt could interact as the original Cyt site but with better efficacy against the target. The role of Cub is very much important, in which it helped the Cyt to have better interactions with the target. It is important to note that Cyt is used as an anticancer or anti-HIV for the patients, and they could be protected against the COVID-19 by consuming a B-Cyt. Although the drugs should be specific for curing diseases, a dual activity could make the pharmaceutical compounds more potent agents for treating such unwanted diseases like COVID-19. For such a current situation of unknown treatments for the COVID-19 pandemic, it is unavoidable to investigate new pharmaceutical compounds for this purpose. Working on already known compounds such as Cyt with potent activity against enzymes is also very important, as they could be considered lead compounds to generate such B-Cyt derivative.

4. Conclusions

This *in silico* work has been done to investigate B-Cyt's formation as a new Cyt derivative to examine its interaction with COVID-19 main protease. The formation of such a derivative could be possible within the obtained results because of its stabilization without imaginary frequency by DFT methods. The obtained orbital-based electronic properties indicated that B-Cyt's structure could provide better sites for interactions with the target. In other parts, ligand-target interactions results indicated that the new ligand B-Cyt could interact

with the target COVID-19 main protease very much better than the original Cyt. Better value of BE and a larger AA number are all the benefits of B-Cyt versus original Cyt to be consumed against the unwanted COVID-19 pandemic.

Funding

This research received no external funding.

Acknowledgments

This research has no acknowledgment.

Conflicts of Interest

The authors declare no conflict of interest.

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