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Original Research

In Silico Analyses of Fluorinated Coumarins for Interacting with the MPro of Coronavirus

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Abstract: The appearance of coronavirus disease (COVID-19) has emerged the researchers to focus on investigations of new compounds for medication of this unknown disease. Accordingly, the fluorinated coumarin (FC) compounds were investigated here to work as inhibitors against the activity of main protease (MPro) enzyme of coronavirus. By addition of one fluorine atom to the structure of parental coumarin, six FC compounds were evaluated in which their stabilities were different by the obtained energies. Furthermore, examining their interactions with the MPro target through the molecular docking simulations yielded FC-MPro complexes with different strength levels. FC1 with the lowest stability of optimization yielded the highest strength of interacting FC-MPro complex model. In conclusion, the models of FC ligands were stabilized and their interaction with the MPro target yielded considerable complexes for dealing with the coronavirus.

Keywords: Coronavirus; Covid-19; Coumarin; Molecular docking; Inhibitor.

Introduction

The end of year 2019 had a bad news for the people of all around the world by introducing the mysterious coronavirus disease so called COVID-19 [1]. Very soon after such disappointing introduction, several people were infected by this disease and the human life system has experiences a new era [2]. To this time, so many research activities were done for investigating various sides of COVID-19, but the story has not been solved yet [3]. The results of the investigations indicated an emergency case for preventing the spreading of such disease at the earliest time by working on available pharmaceutical compounds or innovating new ones [4]. To this aim, the available structures were monitored to find potent compounds for fighting against such uknown disease [5]. After identification of the main protease (MPro) target of coronavirus, the research works have been oriented to looking for new inhibitors for preventing the activity of the enzyme [6]. To this aim, the works have been performed in all media of *in vitro*, *in vivo*, and *in silico* to provide insightful information about the unknown and serious problem [7-9]. In this regard, working with the *in silico* medium has been useful for investigating details of the biologically complicated systems, especially for knowing about details of ligand-target interactions [10]. Accordingly, molecular docking approaches have helped researchers for approaching their goals [11].

Within this work, fluorinated coumarins were investigated for interacting with the MPro target of coronavirus using the *in silico* molecular docking approaches. Coumarin (Figure 1) is a naturally extracted product with significant roles in pharmaceutical sciences for developing further compounds [12-14]. Earlier works indicated the inhibiting roles of coumarins for preventing the activity of enzymes for medication of diseases [15]. Accordingly, the fluorinated derivatives of coumarins were investigated in this work for preventing the activity of MPro of coronavirus. By perming theoretical calculations and molecular docking simulations, the required results were obtained for approaching the goal of this work to lean about the role of fluorinated coumarins for medication of COVID-19. All the materials and information of this work were exhibited in Table 1 and Figures 1-3.

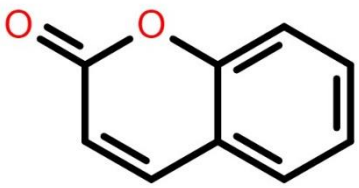

Figure 1: The parental model of coumarin.

Materials and Methods

The materials of this work are six models of fluorinated coumarin (FC) as shown in Figure 2 by adding one fluorine atom to the structure of parental coumarin. All models were optimized to find the minimized energy structures using the PM3 level of Gaussian program [16]. Additionally, the single-point calculations were performed by the B3LYP/6-31G* level on the optimized structures to evaluate the minimized energies for a better comparison the stability of FC compounds. Next, the optimized models were located individually at the ligand position for participating in interactions with the MPro target of coronavirus obtained by the protein data bank with the code of 6lu7 [17]. To this aim, molecular docking simulations were performed using the HDOCK webserver [18] and the results were exhibited in Table 1 and Figure 3. Based on the evaluated values of interaction energies and types of interactions and surrounding amino acids, the main goal of this work to learn about the inhibitory activity of fluorinated coumarin against the MPro of COVID-19 was achieved.

Table 1: Minimized and interaction energies (kcal/mol) of fluorinated coumarins.

Result	Coumarin	FC1	FC2	FC3	FC4	FC5	FC6
Min. Energy	-311628.17	-373842.31	-373847.92	-373846.78	-373845.71	-373846.91	-373842.73
ΔMin.	n/a	5.61	0	1.15	2.21	1.01	5.19
Int. Energy	-96.79	-103.62	-100.69	-100.19	-102.53	-102.67	-99.82
ΔInt.	n/a	0	2.93	3.43	1.09	0.95	3.8

Results and Discussion

Within this work, the models of fluorinated coumarin (FC) compounds (Figure 2) were selected as possible ligands for interacting with the MPro of coronavirus to maybe prevent the enzyme activity. To this aim, the models were stabilized and their single-point energies were calculated as listed in Table 1 besides exhibition of compounds in Figure 2. The models were located in the role of ligand for interacting with the MPro target enzyme using the molecular docking simulations.

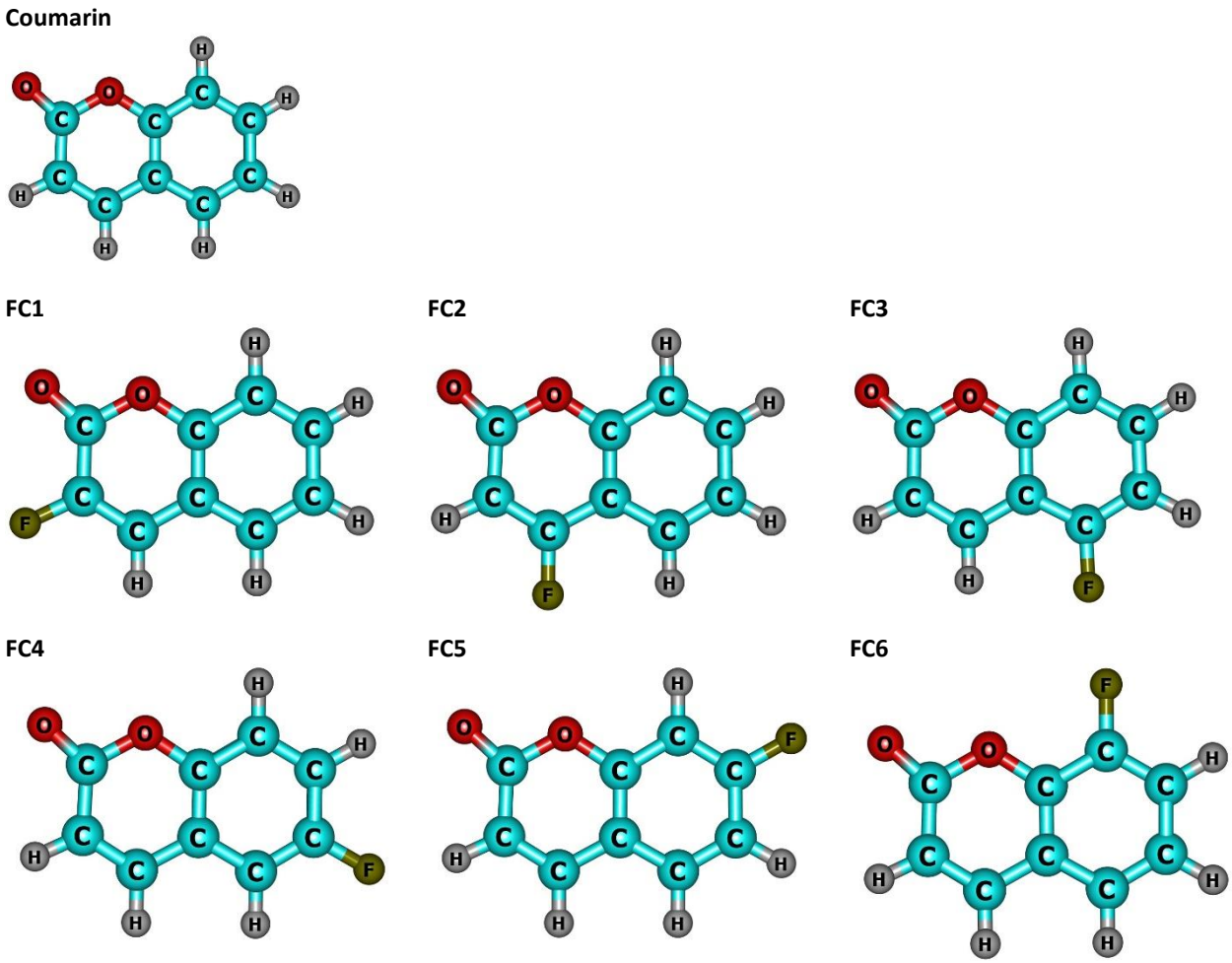

Figure 2: The fluorinated coumarin (FC) compounds.

From the obtained FC compounds, it could be found that the fluorination of the parental coumarin yielded the compounds with different stabilities. The fluorine atom was moved from the available hydrogen atom sites for building the fluorinated models, in which the obtained energies (Table 1) showed different levels of stability for FC1-FC6 compounds. Based on the results, FC2 was found to be the compound at the highest stability and FC1 was found to be at the lowest stability among the FC compounds. The values of ΔMin. Indicated the energy differences of each FC compound from the highest stable one; FC2. Accordingly, the models were recognized by their energy levels and stabilities. It is worth to mention that the advantage of computational works could be seen here by making variations among the models with the same closed formulas. In this regard, the calculated values of Min. Energy and ΔMin. Helped to distinguish the models compounds by their obtained energies in corresponding to the assigned structure. The shapes of models were almost planar structures and their energy features were different based on the movement of fluorine atom instead of the original hydrogen atoms. The criteria of such modification was to attach only one fluorine atom instead of one hydrogen atom but in different positons. This is indeed a type of lead optimization starting from a known structure to reach new modified structures by both of atomic and molecular functionalization processes. Accordingly, the models showed importance of such modifications about the coumarin compounds, in which six models were obtained from a parental compound by modifying the atomic site positions. As a result of such molecular calculations, the ligands were prepared for participating in interactions with the MPro target to make ligand-target complexes (Figure 3).

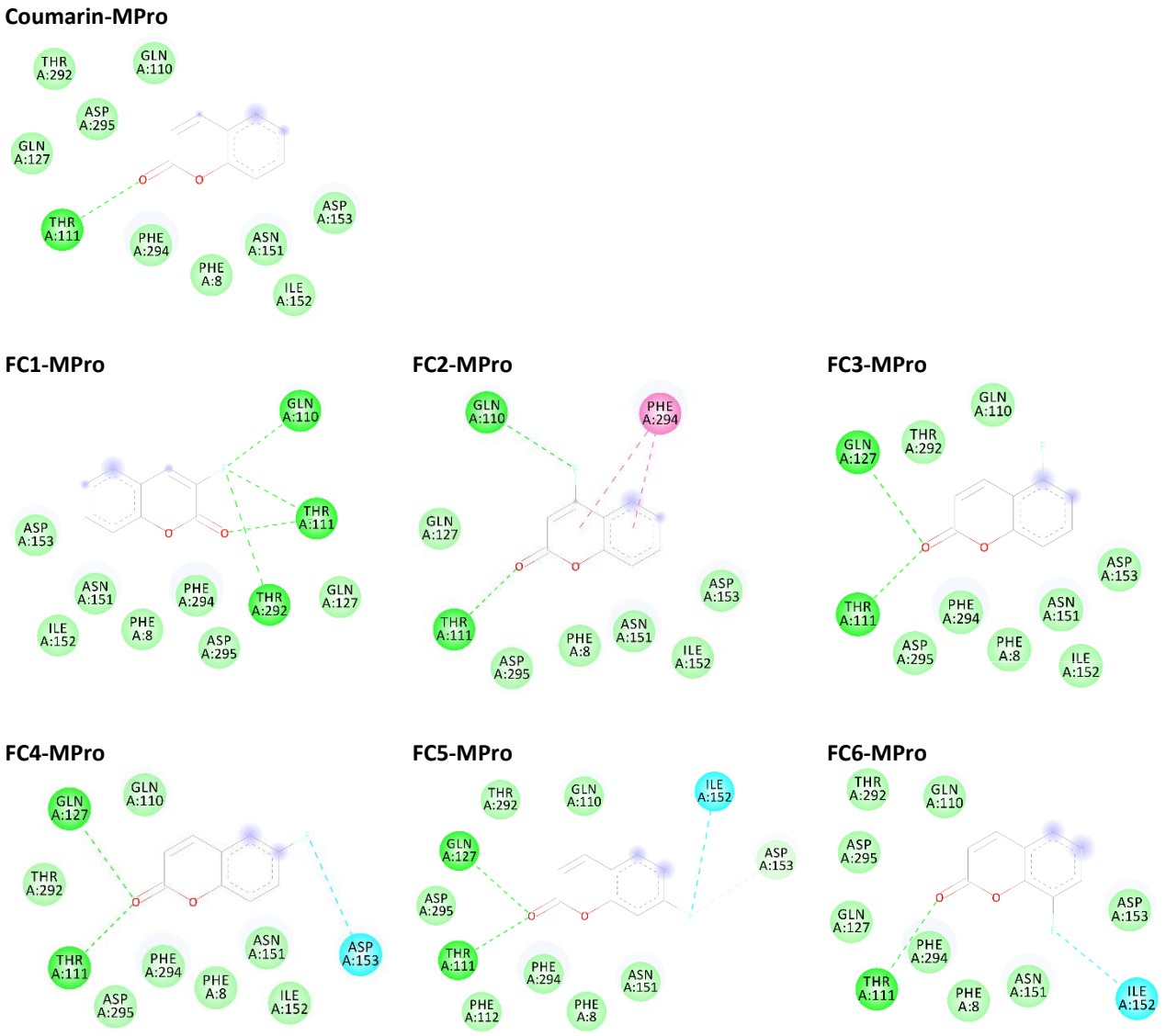

Figure 3: The interacting FC-MPro complexes.

Interestingly, the fluorinated models participated in different types of interactions with the MPro target, in which their representations could show such variations besides the evaluated values of interaction energies of Table 1. As could be found by Figure 3, the fluorine atom has a significant role for increasing numbers of interactions with the MPro target in comparison with the parental coumarin. In the parental complex model, only one hydrogen bond interaction (green dashed lines) was observed whereas at least two hydrogen bond interactions were observed for the FC related complex models. Moreover, other types of interactions such pi-interactions (violet dashed lines), halogen-interactions (blue dashed lines), and van der Waal interactions (individualized green circles) were all available for the FC complex models in more significant level in comparison with the parental complex model. Based on the achievements of Table 1, FC1 was at the highest level of interaction energy strength with the MPro target among other FC models. In this regard, the models were recognized by the values of Int. Energy obtained from the molecular docking simulations. Moreover, the values of differences between each complex and FC1-MPro complex were assigned by ΔInt. to recognize the orders of interacting strengths of ligand-target complexes. In this regard, the FC1-MPro complex was the most favorable one based on the evaluated values of energies showing that the ligand structure with the lowest stability had the significance of contribution to

interactions with the target to make the complex model with the highest strength. It is worth to mention that the position of fluorine atom at the molecular structure of parental coumarin was also important for achieving such results.

Conclusion

In this work, the hypothesis of interactions of fluorinated coumarins (FC) and the MPro target of coronavirus was examined by employing the *in silico* approach. The models of FC ligands were optimized and they were prepared as ligands for individually participating in interactions with the MPro target using the molecular docking simulations. The results of optimizations yielded different structures based on the evaluated energies and the models were ordered in such modes for recognition the strength levels. Accordingly, different complexes of FC-MPro were simulated and the results indicated that the FC compound with the lowest stability has the most significant role for interacting with the MPro target to make complexes at the highest strength. The complex models were recognized by their values of energies and types of interactions and amino acids. As a consequence, the models of fluorinated coumarins could be considered further for working against the MPro of coronavirus.

Disclosure Statement

The author(s) did not report any potential conflict of interest.

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