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# Synthesis of the compound 4-Coumarinyl 4-methoxybenzoate and molecular docking study against COVID-19

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**Abstract**

In this study, a coumarin derivative 4-coumarinyl 4-methoxybenzoate was synthesized. Mold / structure. The data of the synthesized compounds were determined to be compatible with IR, 13C and 1H NMR. The COVID-19 activity of the coumarin-derived compound that I synthesized with molecular placement studies was revealed. In addition, these results have been previously studied and compared to Nelfinavir (NFV), which is declared promising for this activity. There is an urgent need for a drug to be used against COVID-19, which negatively affects human life worldwide and causes pandemic leading to the death of many people. The activity potentials of this compound was further evaluated through molecular docking studies with AutoDock4 and AutoDock Vina softwares.

**Keywords:** Coumarinyl, docking, COVID-19

## Introduction

Coumarins are oxygen-containing heterocyclic compounds that are isolated from especially green plants. It's found naturally in the stems and leaves of plants such as Tonka beans, acacia, lavender. In addition to natural coumarins isolated from plants, synthetic coumarin derivatives are also available [1]. Coumarin and its derivatives are used in the treatment of different diseases and show many biological properties such as anticoagulant, antiallergic, antibiotic, diuretic, anti-HIV, antibacterial [2]. They can make hydrogen bonds, hydrophobic bonds, electrostatic interactions, metal coordination, and van der Waals force with proteins and enzymes [3]. Moreover, they are also used in electronic applications including optical brightening agents, fluorophores, and dyes [4]. In this study, a coumarin derivative 4-coumarinyl 4-methoxybenzoate was synthesized with the aim of preparing new functional compounds [5].

The new type of CoV was originally described at the end of 2019, called 2019-nCoV, and emerged during an epidemic in China [6]. Previous studies of CoVs, one of today's biggest health problems, have reported that CoVs can infect some animal species [7]. Today, the absence of specific therapy against COVID-19 has made research on COVID-19 therapy interesting [8]. Thanks to repositioning studies, it has been found that the compounds can be used differently from their original purpose for other biological activities [9].

There are many repositioning and molecular docking studies in the literature against well-illuminated main protease. We have revealed the COVID-19 activity of the coumarin derivative compound we synthesized by molecular docking studies. Moreover, we compared these results with Nelfinavir (NFV), which has been studied before and announced as promising for this activity [10].

## Materials and Methods

### Synthesis and physical properties of 4-coumarinyl 4-methoxybenzoate (ıı)

All of the chemicals were purchased from Merck. (0.01 mol) of 4-hydroxycoumarin (I) were dissolved in 10 mL of pyridine. (0.01 mol) of 4-methoxybenzoyl chloride(II) was then added dropwise to this solution for two hours at room at room temperature. The resulting mixture was added to ice water containing dilute hydrochloric acid. The resulting solid was collected by filtration, dried and recrystallized from ethyl alcohol. 4-Coumarinyl 4-methoxybenzoate(III): Yield 96%; m.p. 159-161 ºC; IR (ν,

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cm-1): 1785 cm-1 (C=O lactone), 1717 cm-1 (C=O ester), 1156 (C-O). 1H NMR: δ 3,90 (s,3H) CH3O; 6,60 (s, 1H) (C-3); 6,90-8,40 (m,8H) phenyl (coumarin and benzoyl).13C NMR: δ 116-134 phenyl (coumarin and benzoyl). The 1H and 13C NMR spectra were taken using Bruker ascend 600 NMR spectrometer, at 600 MHz for 1H and 150 MHz for 13C–NMR. Compound was dissolved in DMSO-d6. The infrared spectra were obtained by using Perkin-Elmer spectrum one FT-IR spectrophotometry. Besides, melting point was determined by using an electrothermal 9100 apparatus. Figure 1 shows the synthesis of 4-coumarinyl 4-methoxybenzoate.

### Molecular Docking Studies

Compound III were energy-minimized using ChemOffice. Grid box points were determined according to the size of the ligand as size of 40*40*40 Å3. The regular space of the Grid box is determined as 0.375 Å. Pdb file (PDB ID: 6LU7) was obtained (https://www.rcsb.org/) and was modified using the Maestro (Maestro, Schrödinger, LLC, New York, NY, 2020.). Lamarckian Genetic Algorithm was preferred for ligand. Docking scores were obtained using AutoDock 4.2 and AutoDock Vina software (Table 1.) [11-12].

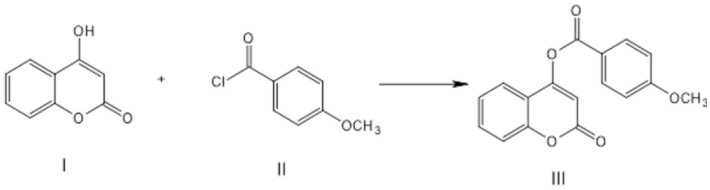


**Figure 1.** Synthesis and the structure of the title compound

## Results

### Nuclear magnetic resonance (NMR) spectra and Vibrational assignments

The Hydrogens in the 1H NMR spectrum of the methoxy were observed singlet at 3.90 ppm for OCH3. The protons (8H) coumarin and benzoyl were observed as a multiplet in the range of 6.90-8.40 ppm. Chemical shift of all carbons in coumarin and benzoyl ring were shown between 114 and 133 ppm. The C-O stretching vibration in Coumarin was observed in the 1250-850 cm-1 region [13]. In the present study, the C-O streching vibration was observed at 1156 $cm^{-1}$. The C=O stretching frequency was observed in the range of 1600-1850 $cm^{-1}$ owing to its large change in dipolemoment and its characteristic frequency used to study a wide range of the compounds [14]. The C-O stretching vibration in title compound was observed at 1785 $cm^{-1}$. All these data confirm the structure of the compound.

### Molecular Docking

Autodock Binding Energy for Nelfinavir has been previously described as -10.72. It was explained that pi-pi interaction of HIS41, the Hydrogen bond with GLU166 and more were made by Nelfinavir. These interactions have also been demonstrated by us for Compound III (Figure 2). Moreover, the interactions made by the compound were also found to show interactions with the residues similar to the N3 ligand described earlier (Figure 3) [10]

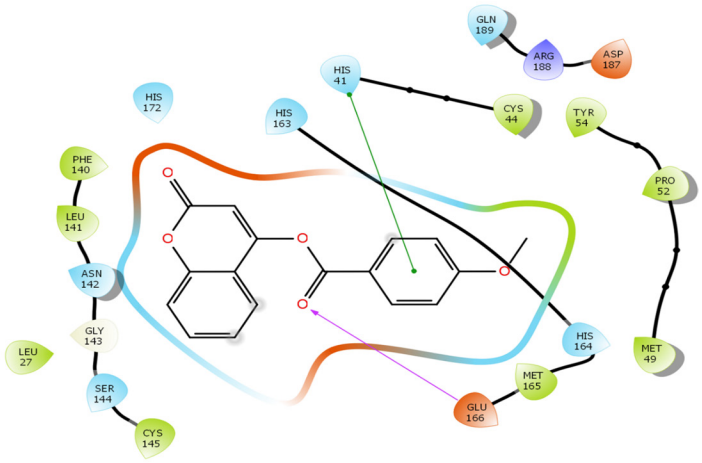


**Figure 2.** 2D interactions diagram compound III

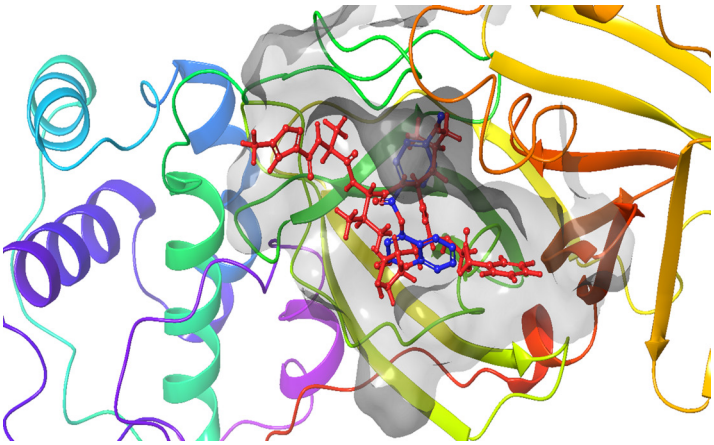

**Figure 3.** Compounds III (blue) and N3 (red) are presented in the 6LU7 binding cavity (molecular surface rendered in grey)

**Table 1.** Molecular docking binding scores of ligand, Residues participating Pi-Pi Stacking and H-bond are shown.

| Ligand | H-bonds | Pi-Pi Stacking | Autodock Result | | Vina Result |
|---|---|---|---|---|---|
| | | | Estimated Inhibition Constant, Ki | Best Docking Score | Best Docking Score |
| **Compound III** | GLU166 | HIS41 | 1.38 µM | -7.99 | -7.5 |

## Discussion

In the molecular docking studies of the compound we synthesized and the Nelfinavir, which was stated as promising in the literature, the COVID-19 main protease inhibitor activities of were evaluated. Molecular docking studies exhibited the interaction mode of Compound III with 6LU7 including pi-pi stacking, hydrophobic interactions and hydrogen bonds. It was thought that compound 3, which interacts similarly with the residues where both Nelfinavir and co-crystal ligand N3 interact, can be developed for this activity.

**Competing interests**
*The author have no financial conflicts of interest.*

**Financial Disclosure**
*The author declared that this study has received no financial support.*

**Ethical approval**
*No ethic approvell is needed to this research..*

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