

Proceedings

Interactions of Alkyl-Gallates with SARS-CoV-2 Main Protease: A Molecular Docking Approach †

Amalia Stefaniu *, Lucia Pintilie, Bujor Albu and Lucia Pirvu

National Institute for Chemical-Pharmaceutical Research and Development, 112 Vitan Av., 031299 Bucharest, Romania; lucia.pintilie@gmail.com (L.P.); abujor@gmail.com (B.A.); lucia.pirvu@yahoo.com (L.P.)

* Correspondence: astefaniu@gmail.com

† Presented at the 24th International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2020; Available online: <https://ecsoc-24.sciforum.net/>.

Received: date; Accepted: date; Published: date

Abstract: Ten natural and semi-synthetic compounds (gallic acid and alkyl gallates) are investigated by in silico methods in order to evaluate their potential inhibitory activity against SAR-CoV-2 using X-ray structure of SARS-CoV-2 main protease bound to Boceprevir at 1.45 Å (PDB ID: 6WNP). Evaluation of drug-likeness in terms of Lipinski's rule of Five and docking results in terms of docking score and interactions with the amino acids residues form the active binding site of the target protein, are reported.

Keywords: gallic acid; alkyl gallates; SAR-CoV-2; molecular docking

1. Introduction

Severe acute respiratory syndrome coronavirus 2 has become a global health issue. Tremendous research efforts to elucidate the virus action mechanisms and to find specific treatments are in progress all over the world. Gallic acid possesses a promising structure for new drug designing and development [1]. Antimicrobial activity was reported for alkyl gallates [2,3]. In our study, we intended to screen by molecular docking approach, a homologue series of alkyl gallates, starting from the lead compound—gallic acid, against SARS-CoV-2 main protease.

2. Methods for Molecular Docking Simulations

The molecular docking study was realized using CLC Drug, Discovery Work Bench. Protein fragment, SARS-CoV-2 main protease bound to Boceprevir at 1.45 Å (PDB ID: 6WNP) [4] was imported from Protein Data Bank. Ligands' structures were constructed using Spartan'16 program [5,6]; the lowest energy conformers were obtained and used forward for docking simulations. The viral protein contains three binding pockets: 48.13 Å³, 40.45 Å³, 36.62 Å³. Water molecules were removed and amino acids residues from the binding site were protonated. The docking protocol was validated by redocking the co-crystallized ligand (Boceprevir). Intermolecular interactions occurring in Boceprevir and alkyl gallates - protein complexes were identified. The length of Hydrogen-bonding interactions was measured. The results are given in terms of docking score function and RMSD (Root mean square deviation).

3. Results and Discussions

Figure 1 reveals the obtained docking scores for the co-crystallized ligand, gallic acid and alkyl gallates against SARS-CoV-2 main protease (PDB ID: 6WNP). Boceprevir exhibit the greatest score 63.95, due to their numerous interactions with the amino acid residues from the protein's active binding site: eight Hydrogen bonding interactions with nitrogen or oxygen atoms of amino acids residues thus: N sp² CYS145 (2.900 Å), N sp² SER144 (3.053 Å), N sp² GLY143 (2.783 Å), N sp² HIS41

(2.604 Å), O sp² HIS164 (3.103 Å), N sp² GLU166 (3.118 Å), O sp² GLU166 (2.908 Å and O sp² GLU166 (3.229 Å). Remarkable is the resulted docking score of octyl-gallate (60.22, RMSD 1.12), close to Boceprevir.

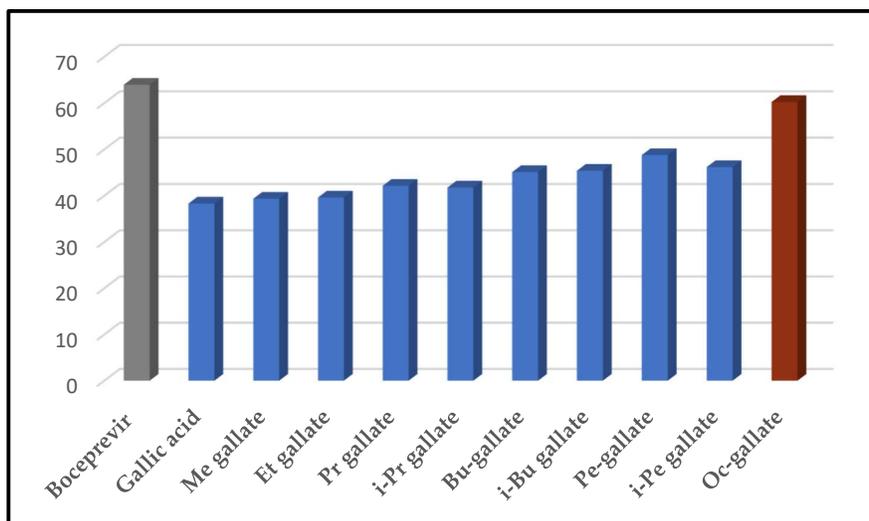


Figure 1. Docking scores for Boceprevir and investigated alkyl gallates against SARS-CoV-2 main protease (PDB ID: 6WNP).

Figure 2 illustrates the hydrogen bond formed by octyl-gallate (a) red-brown colored, and Boceprevir (b), in grey, respectively, with the amino-acids from the active binding site, along with their surrounding interaction group-Figure 2c,d, respectively.

In Table 1 we listed the amino acids group interactions, type and length of Hydrogen-bonding interactions formed by the co-crystallized Boceprevir and the alkyl-gallate derivative with the greatest docking result, octyl-gallate, respectively. The atomic numbering scheme of octyl gallate structure, as given arbitrary by Spartan software is given as Supplementary Material S1, available online. Its structure presents two flexible bonds, three hydrogen bond donors and five hydrogen bond acceptors. The molecular weight and the calculated water-octanol partition coefficient do not exceed the restrictions imposed by Lipinski's statement [7] regarding the oral bioavailability assessment. Thus, this molecule has no violations of this rule, good permeation and absorption through biological membranes. Clinical studies have revealed that gallic acid, catechins, flavones and quercetin glucosides have the best bio-availability in humans [8]. The 3,4,5-trihydroxybenzoic acid (gallic acid) is one of the most abundant phenolic acids in plants with various health benefits including anti-inflammatory and antioxidant activities [9]. The presence of phenyl ring, carboxyl moieties, and ester, hydroxyl and methoxy groups seems to be the basis of plant phenolics antiviral efficacy [10,11]. On the other hand, semi synthetic compounds, such as methylated or alkyl chain gallates are good alternative for designing and developing anti-viral agents. Their pharmacological activity is associated with the length with their alkyl side chain, that influences the membrane binding abilities [2]. Generally, membrane binding of the alkyl gallates increased with increasing alkyl chain length and are correlated with their anti-viral activity. Increasing docking results were observed, with the increasing length of n-alkyl side chain.

O sp³(O3)—N
sp²CYS145
O sp³(O1)—O
sp³SER144
O sp³(O1)—N
sp²HIS163

5. Conclusions

This in silico screening reveals the potential inhibitory action of alkyl-gallates, mainly of octyl-gallate against SARS-CoV-2 main protease. The molecular docking simulations has led to a similar docking results for octyl-gallate, compared to the natural ligand, Boceprevir. Further investigations are required in order to demonstrate and develop these preliminary conclusions. Similar docking results are consequence of similar interactions. Amino acid residues CYS145 and SER144 interact by Hydrogen-bonding both, with Boceprevir and with Octyl-gallate. Propyl gallate and Pentyl gallate have reveal the same intra-molecular interactions with: N sp² GLU166, N sp² HIS163, O sp³SER144, O sp³SER144, O sp² LEU141, N sp² SER144, N sp² GLY143, N sp² CYS145, N sp² GLY143, O sp² ASN142. Their obtained docking score were 42.13 and 48.77, respectively, lower than for octyl-gallate, but greater than the results for gallic acid (38.31). These findings prove that alkyl-gallates are good alternative for develop new therapeutical antiviral agents.

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