**Breadfruit (*Artocarpus altilis)* contains some promising inhibitors of the Mpro enzyme of SARS-CoV-2: an *in silico* molecular docking and pharmacological analysis**

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**Abstract**

The world experienced a sudden outbreak of an abruptly emerging virus, SARS-CoV-2, in late December 2019 in the city of Wuhan, China. Within a few months, the resulting disease, COVID-19, had taken over a major portion of the world. Researchers have since been working with the viral targets, aiming to unwrap an absolute cure. Because of the severity and concerns about the virus, we conducted a computational assessment of compounds derived from breadfruit (*Artocarpus altilis*) to study. The assessment aims to unveil some promising compounds as inhibitors of SARS-CoV-2. We selected the main protease (Mpro) enzyme of SARS-CoV-2, since this enzyme is responsible for the replication process of the virus. Initially we had gone for a drug-likeness analysis to screen the most suitable compounds. Afterwards, molecular dockings were performed with the selected compounds from *A. altilis*. Nirmatrelvir was taken as a standard inhibitor in this study, as it is an FDA approved drug in combination with ritonavir. In molecular docking, the test compounds, cycloartomunin, dihydrocycloartomunin, cycloartobiloxanthone, artomunoxanthentrione, and cycloartomunoxanthone exhibited binding affinities of −7.6, −7.7, −7.7, −8.3, and −8.1 kcal/mol, respectively. Nirmatrelvir showed an affinity of −8.1 kcal/mol while docking on the same server. Consequently, a pharmacological analysis was conducted with the top five test compounds compared with the standard inhibitor. A computational toxicity analysis was also involved in this assessment. Finally, the test compounds were found to have promising docking outputs, and moderate pharmacological profiles. After all, this study scrutinized the test compounds and suggests further validations to confirm the potentiality of the compounds inhibiting the SARS-CoV-2 Mpro enzyme.

**Keywords**: COVID-19, SARS-CoV-2, mpro, breadfruit, *Artocarpus altilis*, molecular docking.

**Table 1:** The binding affinities and noncovalent (hydrogen bonds and hydrophobic) interactions of the test compounds and the standard inhibitor (nirmatrelvir).

| **Chemical ID (Source)** | **Compound Name** | **Binding affinity (kcal/mol)** | **Interactions** |
| --- | --- | --- | --- |
| IMPHY000132  (IMPPAT) | Cycloartomunin | −7.6 | GLN107 PRO108 GLY109 GLN110 PRO132 ILE200 VAL202 GLU240 PRO241 HIS246 ILE249 THR292 PRO293 PHE294 |
| IMPHY000674  (IMPPAT) | Dihydrocycloartomunin | −7.7 | THR24 THR25 THR26 LEU27 HIS41 CYS44 THR45 SER46 MET49 PHE140 LEU141 ASN142 GLY143 ALA144 CYS145 HIS163 HIS164 GLU166 HIS172 GLN189 |
| IMPHY001232  (IMPPAT) | Cycloartobiloxanthone | −7.7 | HIS41 MET49 LEU141 ASN142 GLY143 CYS145 HIS163 HIS164 MET165 GLU166 LEU167 PRO168 GLN189 |
| IMPHY001629  (IMPPAT) | Artomunoxanthentrione | −8.3 | THR24 THR25 THR26 LEU27 HIS41 CYS44 THR45 SER46 MET49 PHE140 LEU141 ASN142 GLY143 ALA144 CYS145 HIS163 GLU166 LEU167 PRO168 GLN189 |
| IMPHY001678  (IMPPAT) | Cycloartomunoxanthone | −8.1 | THR24 THR25 THR26 HIS41 CYS44 THR45 SER46 MET49 PHE140 LEU141 ASN142 GLY143 ALA144 CYS145 HIS163 HIS164 MET165 GLU166 HIS172 GLN189 |
| 155903259 (PubChem) | Nirmatrelvir | −8.1 | THR25 THR26 LEU27 HIS41 CYS44 THR45 SER46 MET49 PHE140 LEU141 ASN142 GLY143 ALA144 CYS145 HIS163 HIS164 MET165 GLU166 ARG188 GLN189 |

**Table 2:** The physicochemical, pharmacokinetic, and pharmacodynamic properties of the molecules with the top 6 docking scores retrieved from SwissADME and Protox-II.

| **Property** | **Cycloartomunin** | **Dihydrocycloartomunin** | **Cycloartobiloxanthone** | **Artomunoxanthentrione** | **Cycloartomunoxanthone** | **Nirmatrelvir (standard)** |
| --- | --- | --- | --- | --- | --- | --- |
| **MW (g/mol)** | 448.46 | 450.48 | 434.44 | 444.43 | 448.46 | 499.53 |
| **TPSA (Å2)** | 98.36 | 109.36 | 109.36 | 103.04 | 96.36 | 131.40 |
| **MLogP** | 1.77 | 1.77 | 1.63 | 1.06 | 1.84 | 0.41 |
| **LogS (ESOL)** | −6.10 | −6.39 | −5.46 | −6.05 | −5.67 | −3.58 |
| **ESOL Class** | Poorly soluble | Poorly soluble | Moderately soluble | Poorly soluble | Moderately soluble | Soluble |
| **GI absorption** | High | High | High | High | High | High |
| **Bioavailability score** | 0.55 | 0.55 | 0.55 | 0.56 | 0.55 | 0.55 |
| **BBB permeant** | No | No | No | No | No | No |
| **P-gp substrate** | No | No | Yes | No | Yes | Yes |
| **Lipinski’s RO5 vio.** | 0 | 0 | 0 | 0 | 0 | 0 |
| **Ghose filter vio.** | 0 | 0 | 0 | 0 | 0 | 0 |
| **LD50 (mg/kg)** | 5000 | 5000 | 2500 | 120 | 5000 | 3000 |
| **Toxicity class** | 5 | 5 | 5 | 3 | 5 | 5 |

MW: molecular weight; TPSA: topological polar surface area; MLogP: lipophilicity; LogS (ESOL): water solubility; ESOL class: water solubility class; GI absorption: gastrointestinal absorption; bioavailability score: Abbott bioavailability score; BBB permeant: blood-brain barrier permeability; P-gp substrate: interaction with P-glycoprotein; Lipinski Vio: number of violations of Lipinski’s rule of Gve; Ghose Vio: number of violations of Ghose’s rule; LD50 (mg/kg):lethal dose 50; toxicity class: class based on LD50 value.