**Supporting information**

Investigating the Antiviral Therapeutic Potentialities of Marine Polycyclic Lamellarin Pyrrole Alkaloids as Promising Inhibitors for SARS-CoV-2 and Zika Main Proteases (Mpro)

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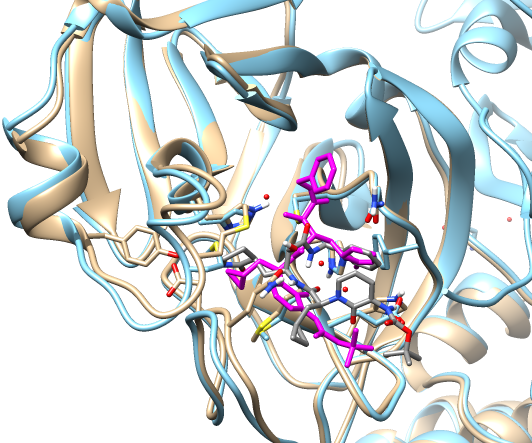
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**Figure S1**. Reported lamellarin pyrrole alkaloids (**1-22**)



**Figure S2**. Reported lamellarin pyrrole alkaloids (**23-39**)

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**Figure S3.** The re-docking experiment of the positive control compound O6K against Mpro of SARS-CoV-2. The solved structure (PDB ID:6Y2G, Chain A) (blue cartoon with pink sticks for **O6K**) was superimposed on the docked complex (beige cartoon with sticks for O6K by element).

**Table S2**. Calculated binding free energies (∆GB, in kcal/mol) by molecular docking for the top 10 selected lamellarin derivatives and the positive control (**O6K)**, for each target, as well as their reported biological activities.

|  |  |  |  |
| --- | --- | --- | --- |
| **Lamellarins** | **Molecular Docking**  **∆GB, in kcal/mola** | | **Reported Biological Activities** |
| **SARS-CoV-2 Mpro** | **Zika Mpro** |
| D (**7**) | --- | -8.13 | Potent inhibitor of Topoisomerase I (Ishibashi et al., 2002); cytotoxic activity against cancer cell lines e.g. HeLa, XC, Vero, MDCK (nM) (Ishibashi et al., 2002). |
| E (**9**) | -8.40 | --- | --- |
| G (**12**) | -8.57 | -8.47 | --- |
| H (**14**) | **-9.37** | -8.40 | Topoisomerase I (IC50 = 0.23 mM) (C. P. Ridley et al., 2002). |
| J (**16**) | -8.47 | -8.13 | --- |
| K (**17**) | **-9.40** | --- | Toxic against Topoisomerase I (Christian Bailly, 2004a). |
| L (**20**) | -8.67 | -8.17 | --- |
| S (**26**) | -9.00 | **-8.53** | --- |
| U (**30**) | -8.47 | -8.10 | --- |
| Z (**39**) | -9.30 | **-8.63** | --- |
| B 20-sulfate (**3**) | -8.40 | --- | --- |
| G 8-sulfate (**13**) | --- | -8.30 | --- |
| L 20-sulfate (**22**) | --- | -8.30 | --- |
| (**O6K**)b | -7.90 | -7.83 | --- |

a The lamellarin derivatives selected have a calculated ∆GB ≤ -8.4 kcal/mol and -8.1 kcal/mol for SARS-CoV-2 Mpro and Zika Mpro, respectively. b Positive Control.

**Table S3.** The detailed hydrogen bonds and hydrophobic interactions established upon docking the (**O6K**), and lamellarin derivatives (**1-39**) against the SARS-CoV-2 Mpro (PDB ID: 6LU7) chain A.

|  |  |  |  |
| --- | --- | --- | --- |
| **Lamellarins** | **Common amino acids (aa)** | | **Common aa number** |
| **H-bond residues** | **Hydrophobic interaction residues** |
| F (**11**), J (**16**), N (**24**), T 20-sulfate (**29**) | none | Gln189, Glu166, His163, His164, Leu141, Met165, Phe140 | 7 |
| B (**2**), B 20-sulfate (**3**), D triacetate (**8**) | Gly143 | Arg188, Asn142, Cys145, Gln189, Glu166, His41, His164, Met165, Pro168, Thr190 | 11 |
| I (**15**) | His41 | Arg188, Asn142, Cys145, Gln189, Glu166, Gly143, His164, Leu141, Met165, Phe140, Pro168, Thr190 | NAa |
| E (**9**), E 20-sulfate (**10**), L (**20**), U (**30**), U 20-sulfate (**31**), W (**34**), V 20-sulfate (**33**) | HIS163 | Arg188, Asn142, Asp187, Cys145, Gln189, Glu166, Gly143, His41, Met165 | 10 |
| G (**12**) | Asn142, His163 | Arg188, Asp187, Cys145, Gln189, Glu166, Gly143, His41, Met49, Met165 | NAa |
| D (**7**) | Asn142, Leu141 | Arg188, Asp187, Gln189, Glu166, His41, His163, His164, Met165, Phe140 | NAa |
| K triacetate (**19**), L triacetate (**21**), L 20-sulfate (**22**), N triacetate (**25**), T diacetate (**28**), X triacetate (**36**) | Cys145, His41 | Arg188, Asn142, Gln189, Glu166, Gly143, His164, Leu141, Met49, Met165, Phe140, Pro168 | 13 |
| K diacetate (**18**) | Cys145, Ser144 | Arg188, Asn142, Asp187, Gln189, Glu166, Gly143, His41, His164, Leu141, Met49, MetT165, Phe140, Tyr54 | NAa |
| Y 20-sulfate (**38**) | Cys145, Thr190 | Ala191, Gln189, Glu166, His163, His164, Leu141, Met165, Phe140, Pro168 | NAa |
| V (**32**) | Glu166, His163 | Arg188, Asn142, Asp187, Cys145, Gln189, Gly143, His41, His164, Leu141, Leu167, Met165 | NAa |
| A (**1**) | Gly143, Glu166 | Arg188, Asn142, Asp187, Gln189, His41, His164, Leu141, Leu167, Met165 | NAa |
| C (**4**) | Gly143, Leu141 | Arg188, Asn142, Asp187, Gln189, Glu166, His41, His163, His164, Met165, Phe140 | NAa |
| K (**17**)c | Gly143, Ser144 | Arg188, Asn142, Asp187, Cys145, Gln189, Glu166, His41, His163, His164, Leu141, Met49, Met165 | NAa |
| M (**23**) | Gly143, Thr190 | Arg188, Asn142, Cys145, Gln189, Glu166, His41, His164, Met165, Phe140, Pro168 | NAa |
| X (**35**) | Arg188, Gly143, Thr190 | Asn142, Cys145, Gln189, Glu166, His41, His164, Met165, Pro168 | NAa |
| G 8-sulfate (**13**) | Asn133, Leu287, Lys137 | Arg131, Asn238, Asp197, Asp289, Leu272, Leu286, Thr199, Tyr239, Val171 | NAa |
| S (**26**)c, Z (**39**)c | Cys145, Gly143, Ser144 | Asn142, Gln189, Glu166, His41, His163, His164, Leu141, Met49, Met165 | 12 |
| C diacetate (**5**), C 20-sulfate (**6**) | Cys145, Ser144, Tyr54 | Arg188, Asn142, Asp187, Gln189, Glu166, Gly143, His164, Leu141, Met49, Met165 | 13 |
| T (**27**), Y (**37**) | Gly143, His41, Thr190 | Arg188, Asn142, Asp187, Cys145, Gln189, Glu166, His164, Leu141, Met49, Met165, Ser144, Thr25 | 15 |
| H (**14**)3 | Asn142, Gly143, His163, Ser144 | Asp187, Cys145, Gln189, Glu166, His41, His164, Leu141, Met165 | NAa |
| **O6K**b | Gln189, Glu166, Tyr54 | Asn142, Asp187, Cys145, His41, His163, His164, Met49, Met165, Phe140, Thr190 | NAa |

a Not applicable. b Positive Control. c Best docking scored molecules.

**Table S4**. The detailed hydrogen bonds and hydrophobic interactions established upon docking the (**O6K**), and lamellarin derivatives (**1-39**) against the Zika Mpro (PDB ID: 5H4I) chains A and B.

|  |  |  |  |
| --- | --- | --- | --- |
| **Lamellarins** | **Common amino acids (aa)** | | **Common aa number** |
| **H-bond residues** | **Hydrophobic interaction residues** |
| B 20-sulfate (**3**),  N triacetate (**25**),  U 20-sulfate (**31**) | none | Ala132, Asp129, Gly151, Gly153, Ser135, Tyr130, Tyr161, Val155 | 8 |
| T 20-sulfate (**29**) | Ala132, Gly153, Tyr161 | Asn152, Asp83a, HisS51, Phe84a, Pro131, Tyr130, Val155 | NAb |
| H (**14**)d | Asn152, Gly151, Gly153, Pro131, Tyr130 | Ala132, Ser135, Tyr161, Val155 | NAb |
| K diacetate (**18**) | Asp129 | Ala132, Asn152, Asp75, Asp83a, Gly151, Gly153, His51, Phe84a, Tyr130, Tyr161, Val154, Val155 | NAb |
| E 20-sulfate (**10**) | Asp129, His51, Lys54, Ser135 | Ala132, Asp83a, Tyr161, Val155 | NAb |
| A (**1**), C (**4**), I (**15**), V (**32**) | Asp129, His51, Ser135, Tyr130 | Ala132, Asp83a, Gly151, Tyr161, Val155 | 9 |
| E (**9**), F (**11**) | Asp129, Val155 | Ala132, Asn152, Asp83a, Gly151, His51, Ser135, Tyr130, Tyr161, Val154 | 11 |
| V 20-sulfate (**33**) | Asp83a | Ala132, Asp129, Gly151, His51, Pro131, Ser135, Tyr130, Tyr161, Val154, Val155 | NAb |
| D (**7**), N (**24**) | Asp83a, Asp129, His51, Ser135 | Ala132, Gly151, Gly153, Tyr130, Tyr161, Val154, Val155 | 11 |
| K (**17**) | Asp83a, Asp129, His51, Ser135, Tyr130 | Ala132, Gly151, Gly153, Tyr161, Val154, Val155 | NAb |
| J (**16**), L (**20**), G (**12**)d, S (**26**)d, Z (**39**)d | Asp83a, Asp129, Ser135 | Ala132, Gly151, His51, Tyr130, Tyr161, Val154, Val155 | 10 |
| G 8-sulfate (**13**),  U (**30**) | Asp83a, Ser135 | Ala132, Asn152, Asp129, GLY151, His51, Tyr130, Tyr161, Val154, Val155 | 11 |
| M (**23**), X (**35**) | Asp83a, Ser135, Tyr130 | Ala132, Asn152, Asp129, Gly151, Tyr161, Val154, Val155 | 10 |
| B (**2**), W (**34**) | Asp83a, Ser135, Val155 | Ala132, Asn152, Asp129, Gly153, Tyr130, Tyr161, Val154 | 10 |
| Y 20-sulfate (**38**) | Gly151 | Ala132, Asn152, Asp129, Gly151, Tyr130, Tyr161, Val154 | NAb |
| **O6K**c | Asp83a, Asn152, Gly153, His51, Ser135, Tyr161 | Ala132, Gly151, Lys54, Ser81a, Trp50, Val36, Val72 | NAb |

a From chain A. b Not applicable. c Positive Control. d Best docking scored molecules.



**Figure S4**: SARs studies for most promising lamellarins compounds against SARS-Cov-2 Mpro based on their binding affinities values and compered to positive control (**OK6**)



**Figure S5**: SARs studies for most promising lamellarins compounds against Zika Mpro based on their binding affinities values and compered to positive control (**OK6**)