**Supplementary Information**

**Contents Page no.**

1. Energy minimisation of the crystal structure of 3CLpro 02
2. Binding pose and binding affinity of library molecules for 3CLpro 03
3. In-house library of antiviral compounds from tropical mangrove plants 13

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Structure** | **Evaluation Tools** | | | | | | | | |
| R | Pro Check | | | | | | | ERRAT  quality  factor  (%) | Verify\_3D  (%) |
| Ramachandran Plot statistics G-Factors | | | | | | |
| Most  favoured  (%) | Additionally  allowed  (%) | Generously  Allowed  (%) | Disallowed  (%) | Dihedral  angles | Covalent  geometry | Overall  average |
| Initial State  (PDB ID: 6LU7) | 89.4 | 9.5 | 0.4 | 0.8 | 0.4 | 0.36 | 0.17 | 98.25 | 95.72 |
| Minimised State  (PDB ID: 6LU7) | 89 | 9.9 | 0.8 | 0.4 | -0.05 | 0.42 | 0.15 | 99.63 | 96.52 |

**Table 1:** Model evaluation of the minimised state of 3CLpro

**Table 2:** 3D interaction diagrams, estimated binding affinity and estimated inhibition constant of in-house library molecules against 3CLpro

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **S. No** | **Molecule Name** | **3D Ligand interaction diagram** | **Estimated Binding Affinity**  **(kcal/mol)** | **Estimated Inhibition constant**  **(µM)** |
| 1 | Krishnolide A |  | -6.6 | 14.52 |
| 2 | Krishnolide B |  | -6.4 | 20.35 |
| 3 | Krishnolide C |  | -6.4 | 20.35 |
| 4 | Krishnolide D |  | -6.3 | 24.1 |
| 5 | Sundarbanxylogranin A |  | -6.6 | 14.52 |
| 6 | Sundarbanxylogranin B |  | -6.6 | 14.52 |
| 7 | Sundarbanxylogranin C |  | -6.5 | 17.19 |
| 8 | Sundarbanxylogranin D |  | -6.6 | 14.52 |
| 9 | Sundarbanxylogranin E |  | -6.5 | 17.19 |
| 10 | Khayanolide I |  | -6.5 | 17.19 |
| 11 | Khayanolide K |  | -6.6 | 14.52 |
| 12 | Khayanolide M |  | -6.5 | 17.19 |
| 13 | 2,5-Didehydroxy-6-methylembelin |  | -5.4 | 110.01 |
| 14 | Embelin |  | -5.4 | 110.01 |
| 15 | 5-O-Ethylembelin |  | -5.9 | 47.33 |
| 16 | 5-O-Methylembelin |  | -5.5. | 92.97 |
| 17 | 5-O-Methyl-2-acetoxyembelin |  | -5.3 | 130.29 |
| 18 | Quinazarin |  | -6.3 | 24.1 |
| 19 | Lupeol |  | -6.6 | 14.52 |
| 20 | Butelin |  | -6.3 | 24.1 |
| 21 | β-Sitosterol |  | -6.2 | 28.53 |
| 22 | Velutin |  | -6.2 | 28.53 |
| 23 | Rutin |  | -6.7 | 12.27 |
| 24 | Chrysin |  | -6.4 | 20.35 |
| 25\* | Gallic acid |  | -5.3 | 130.29 |
| 31 | Mucic acid |  | -4.7 | 358.8 |
| 32 | Mucic acid analogue |  | -4.7 | 358.8 |
| 33. | Sulfated polysaccharide |  | -5.9 | 47.33 |

*\*2D/3D interaction diagram, binding affinity and inhibition constant for molecules 26 to 30 were already provided in the main-text*

**Table 3:** In-house library of antiviral compounds from tropical mangrove plants

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **S.No** | **Compound Name** | **Compound Structure** | **Antiviral activity** | **Description** | **Reference** |
| 1 | Krishnolide A |  | Anti-HIV activity | **Source**: *X. moluccensis*  **Chemical Formula**: C36H46O11  **Molecular Weight:** 654.75 | Zhang et al., 2017 |
| 2 | Krishnolide B |  | Anti-HIV activity | **Source**: *X. moluccensis*  **Chemical Formula**:  C36H44O10  **Molecular Weight:**  636.74 | Zhang et al., 2017 |
| 3 | Krishnolide C |  | Anti-HIV activity | **Source**: *X. moluccensis*  **Chemical Formula**:  C36H46O10  **Molecular Weight:**  638.75 | Zhang et al., 2017 |
| 4 | Krishnolide D |  | Anti-HIV activity | **Source**: *X. moluccensis*  **Chemical Formula**:  C36H46O10  **Molecular Weight:**  638.75 | Zhang et al., 2017 |
| 5 | Sundarbanxylogranin A |  | Anti-HIV activity | **Source**: *X. granatum*  **Chemical Formula**:  C32H40O8  **Molecular Weight:** 552.66 | Dai et al., 2017 |
| 6 | Sundarbanxylogranin B |  | Anti-HIV activity | **Source**: *X. granatum*  **Chemical Formula**:  C29H36O9  **Molecular Weight:**  528.60 | Dai et al., 2017 |
| 7 | Sundarbanxylogranin C |  | Anti-HIV activity | **Source**: *X. granatum*  **Chemical Formula**:  C33H42O11  **Molecular Weight:**  614.69 | Dai et al., 2017 |
| 8 | Sundarbanxylogranin D |  | Anti-HIV activity | **Source**: *X. granatum*  **Chemical Formula**:  C32H42O11  **Molecular Weight:**  602.68 | Dai et al., 2017 |
| 9 | Sundarbanxylogranin E |  | Anti-HIV activity | **Source**: *X. granatum*  **Chemical Formula**:  C32H42O10  **Molecular Weight:**  586.68 | Dai et al., 2017 |
| 10 | Khayanolide I |  | Influenza A virus (subtype H1N1) activity | **Source**: *X. moluccensis*  **Chemical Formula**: C29H34O10  **Molecular Weight:** 542.58 | Li et al. 2015 |
| 11 | Khayanolide K |  | Influenza A virus (subtype H1N1) activity | **Source**: *X. moluccensis*  **Chemical Formula**: C29H34O9  **Molecular Weight:** 526.58 | Li et al. 2015 |
| 12 | Khayanolide M |  | Influenza A virus (subtype H1N1) activity | **Source**: *X. moluccensis*  **Chemical Formula**: C29H32O9  **Molecular Weight:** 524.57 | Li et al. 2015 |
| 13 | 2,5-Didehydroxy-6-methylembelin |  | Anti- hepatitis B virus (HBV) activity. | **Source**: *A.corniculatum*  **Chemical Formula**: C18H28O2  **Molecular Weight:** 276.42 | (Thota et al., 2016; Parvez et al. 2019) |
| 14 | Embelin |  | Anti- hepatitis B virus (HBV) activity. | **Source**: *A.corniculatum* and *R. apiculata*  **Chemical Formula**: C17H26O4  **Molecular Weight:** 294.39 | (Thota et al., 2016; Parvez et al. 2019) |
| 15 | 5-O-Ethylembelin |  | Anti- hepatitis B virus (HBV) activity. | **Source**: *A.corniculatum*  **Chemical Formula**: C19H30O4  **Molecular Weight:** 322.44 | (Thota et al., 2016; Parvez et al. 2019) |
| 16 | 5-O-Methylembelin |  | Anti- hepatitis B virus (HBV) activity. | **Source**: *A.corniculatum*  **Chemical Formula**: C18H28O4  **Molecular Weight:** 308.42 | (Thota et al., 2016; Parvez et al. 2019) |
| 17 | 5-O-Methyl-2-acetoxyembelin |  | Anti- hepatitis B virus (HBV) activity. | **Source**: *A.corniculatum*  **Chemical Formula**: C20H30O5  **Molecular Weight:** 350.45 | (Thota et al., 2016; Parvez et al. 2019) |
| 18 | Quinazarin |  | Anti- hepatitis B virus (HBV) activity. | **Source**: *A.corniculatum*  **Chemical Formula**: C14H8O4  **Molecular Weight:** 240.21 | (Thota et al., 2016; Parvez et al. 2019) |
| 19 | Lupeol |  | Anti- hepatitis B virus (HBV) activity | **Source**: *A.ofﬁcinalis, R. mucronata, C. tagal,* and *Avicennia alba*  **Chemical Formula**: C30H50O  **Molecular Weight:** 426.73 | (Lakshmi etal. 2017; Ramanjaneyulu et al. 2017; Parvez et al. 2019) |
| 20 | Butelin |  | Anti- hepatitis B virus (HBV) activity | **Source**: *A.ofﬁcinalis, R. mucronata, C. tagal,* and *Avicennia alba*  **Chemical Formula**: C30H50O3  **Molecular Weight:** 458.73 | (Lakshmi etal. 2017; Ramanjaneyulu et al. 2017; Parvez et al. 2019) |
| 21 | β-Sitosterol |  | Anti- hepatitis B virus (HBV) activity | **Source**: *R. mucronata,A.ilicifolius* and *A. officinalis*  **Chemical Formula**: C29H50O  **Molecular Weight:** 414.72 | (Rao et al., 2005; Parvez et al. 2019) |
| 22 | Velutin |  | Anti- hepatitis B virus (HBV) activity | **Source**: *A. officinalis, E. agallocha* and *A. rotundifolia*  **Chemical Formula**: C17H14O6  **Molecular Weight:** 314.29 | (Kaliamurthi and Selvaraj, 2016; Ghosh et al., 2019; Parvez et al. 2019). |
| 23 | Kaempferol |  | Anti- hepatitis B virus (HBV) activity | **Source**: *A. officinalis, E. agallocha* and *A. rotundifolia*  **Chemical Formula**: C15H10O6  **Molecular Weight:** 286.24 | (Kaliamurthi and Selvaraj, 2016; Ghosh et al., 2019; Parvez et al. 2019). |
| 24 | Luteolin |  | Anti- hepatitis B virus (HBV) activity | **Source**: *A. officinalis, E. agallocha* and *A. rotundifolia*  **Chemical Formula**: C15H10O6  **Molecular Weight:** 286.24 | (Kaliamurthi and Selvaraj, 2016; Ghosh et al., 2019; Parvez et al. 2019). |
| 25 | Rutin |  | Anti- hepatitis B virus (HBV) activity | **Source**: *A. officinalis, E. agallocha* and *A. rotundifolia*  **Chemical Formula**: C27H30O16  **Molecular Weight:** 610.52 | (Kaliamurthi and Selvaraj, 2016; Ghosh et al., 2019; Parvez et al. 2019). |
| 26 | Chrysoeriol |  | Anti- hepatitis B virus (HBV) activity | **Source**: *A. officinalis, E. agallocha* and *A. rotundifolia*  **Chemical Formula**: C16H12O6  **Molecular Weight:** 300.27 | (Kaliamurthi and Selvaraj, 2016; Ghosh et al., 2019; Parvez et al. 2019). |
| 27 | Catechin |  | Anti- hepatitis B virus (HBV) activity | **Source**: *A. officinalis, E. agallocha* and *A. rotundifolia*  **Chemical Formula**: C15H14O6  **Molecular Weight:** 290.27 | (Kaliamurthi and Selvaraj, 2016; Ghosh et al., 2019; Parvez et al. 2019). |
| 28 | Chrysin |  | Anti- hepatitis B virus (HBV) activity | **Source**: *A. officinalis, E. agallocha* and *A. rotundifolia*  **Chemical Formula**: C15H10O4  **Molecular Weight:** 254.24 | (Kaliamurthi and Selvaraj, 2016; Ghosh et al., 2019; Parvez et al. 2019). |
| 29 | Diosmetin |  | Anti- hepatitis B virus (HBV) activity | **Source**: *A. officinalis, E. agallocha* and *A. rotundifolia*  **Chemical Formula**: C16H12O6  **Molecular Weight:** 300.27 | (Kaliamurthi and Selvaraj, 2016; Ghosh et al., 2019; Parvez et al. 2019). |
| 30 | Gallic acid |  | Anti- hepatitis B virus (HBV) activity | **Source**: *A. officinalis, E. agallocha* and *A. rotundifolia*  **Chemical Formula**: C7H6O5  **Molecular Weight:** 170.12 | (Kaliamurthi and Selvaraj, 2016; Ghosh et al., 2019; Parvez et al. 2019). |
| 31 | Mucic acid |  | Anti- hepatitis B virus (HBV) activity | **Source**: *R. apiculata*  **Chemical Formula**: - C6H10O8  **Molecular Weight:** 210.14 | (Kaliamurthi and Selvaraj, 2016; Parthiban et al, 2020) |
| 32 | Mucic acid analogue |  | Anti- hepatitis B virus (HBV) activity | **Source**: *R. apiculata*  **Chemical Formula**: C7H7K5O8  **Molecular Weight:** 414.62 | (Kaliamurthiand Selvaraj, 2016; Parthiban et al, 2020) |
| 33. | Sulfated polysaccharide |  | Anti- SARS-CoV-2 activity | **Source**: *R. mangle* and *A. aureum*  **Chemical Formula**: C14H23O19S33-  **Molecular Weight:** 591.50 | (Kwon et al, 2020; Aquino et al, 2011) |

**References**

1. Zhang, Q., Satyanandamurty, T., Shen, L., Jun Wu, J. (2017). Krishnolides A–D: New 2-Ketokhayanolides from the Krishna Mangrove, *Xylocarpusmoluccensis*. Mar. Drugs. 15, 333.
2. Li, W., Jiang, Z., Shen, Li., Pedpradab, P., Bruhn, T., Wu, J., Bringmann, G. (2015). Antiviral Limonoids Including Khayanolides from the Trang Mangrove Plant *Xylocarpusmoluccensis*. J. Nat. Prod. 78, 7, 1570-1578.
3. Thota, S. P. R., Sarma, N., Murthy, Y. L. M., Kantamreddi, V. S. S. N., Wright, C. W. (2016). A New embelin from the mangrove *Aegicerascorniculatum.* Indian J. Chem. 55B, 123-127.
4. Parvez MK, TabishRehman M, Alam P, Al-Dosari MS, Alqasoumi SI, Alajmi MF. Plant-derived antiviral drugs as novel hepatitis B virus inhibitors: Cell culture and molecular docking study. Saudi Pharm J. 2019;27(3):389-400.
5. Lakshmi, V., Mahdi, A. A., Agarwal, S.K., Kumar, R. (2017). Isolation and Characterization of Bioactive Terpenoids from the Leaves of *Ceriopstagal* Linn. Herbal Medicine: Open Acces ISSN :2472-0151.
6. Ramanjaneyulu, M. V. V., Venkateswara, R. B., Ramanjaneyulu, K., Suvarna, R. P. (2015). Phytochemical analysis of *Avicenniaofficinalis*of Krishna Estuary. J. Pharm. Drug. 3, 176–180.
7. Rao, B. V., Rao, C. V., Subrahmanyam. C., Jairaj, M. A. (2005). Chemical constituents of *Rhizophoramucronata* of Andaman and Nicobar Islands. J. Indian Chem. Soc. 82, 155-157.
8. Kaliamurthi, S and Selvaraj, G. (2016). Insight on *Excoecariaagallocha*: An Overview. Nat. Prod. Chem. Res. 4(2), 1-2.
9. Ghosh, D., Sumanta Mondal, S., Ramakrishna,. K. (2019). Spectroscopic characterization of phytoconstituents isolated from a rare mangrove *aegialitis rotundifolia roxb*., leaves and evaluation of antimicrobial activity of the crude extract. Asian J. Pharm. Res. 9(12), 220-224.
10. Sachithanandam, V., Parthiban, A., Lalitha, P., Muthukumaran, J., Dhanasekar, E., Kamalraja, J., R. Sridhar, Purvaja, R., Ramesh R. (2020). Biological evaluation of gallic acid and quercetin derived from *Ceriopstagal*: insights from extensive *in vitro* and *in silico* studies. J. Biomol. Struct. Dyn. DOI: 10.1080/07391102.2020.1828173.
11. Parthiban, A., Sachithanandam V., Lalitha, P., Baskaran, S., Misra, R; Sridhar., R; Purvaja., R; Ramesh, R. (2020). Isolation and characterization of novel potassium salts of 2-methoxy mucic acid from leaves of Rhizophoraapiculata: in vitro and in silico studies on its potential anticancer and antioxidant activities (unpublished work).
12. Kwon, P. S., Oh, H., Kwon, S. J., Jin, W., Zhang, F., Fraser, K., Hong, J. J., Linhardt, R. J., & Dordick, J. S. (2020). Sulfated polysaccharides effectively inhibit SARS-CoV-2 in vitro. *Cell discovery*, *6*, 50.
13. Aquino, R. S., Grativol, C., & Mourão, P. A. (2011). Rising from the sea: correlations between sulfated polysaccharides and salinity in plants. *PloS one*, *6*(4), e18862.