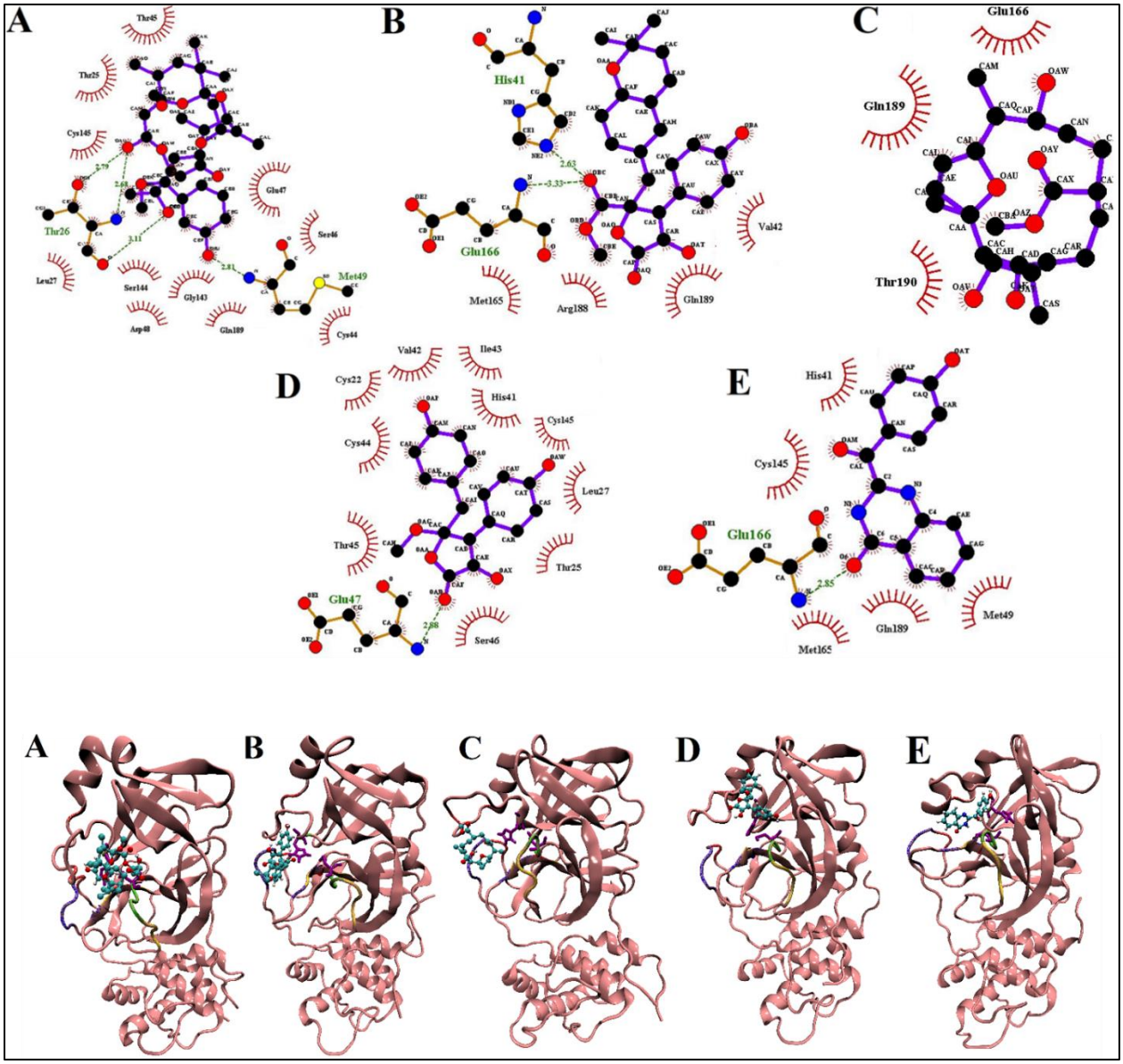
Appendix 1. Predicted pharmacokinetic properties of the five selected ligands based on SwissADME

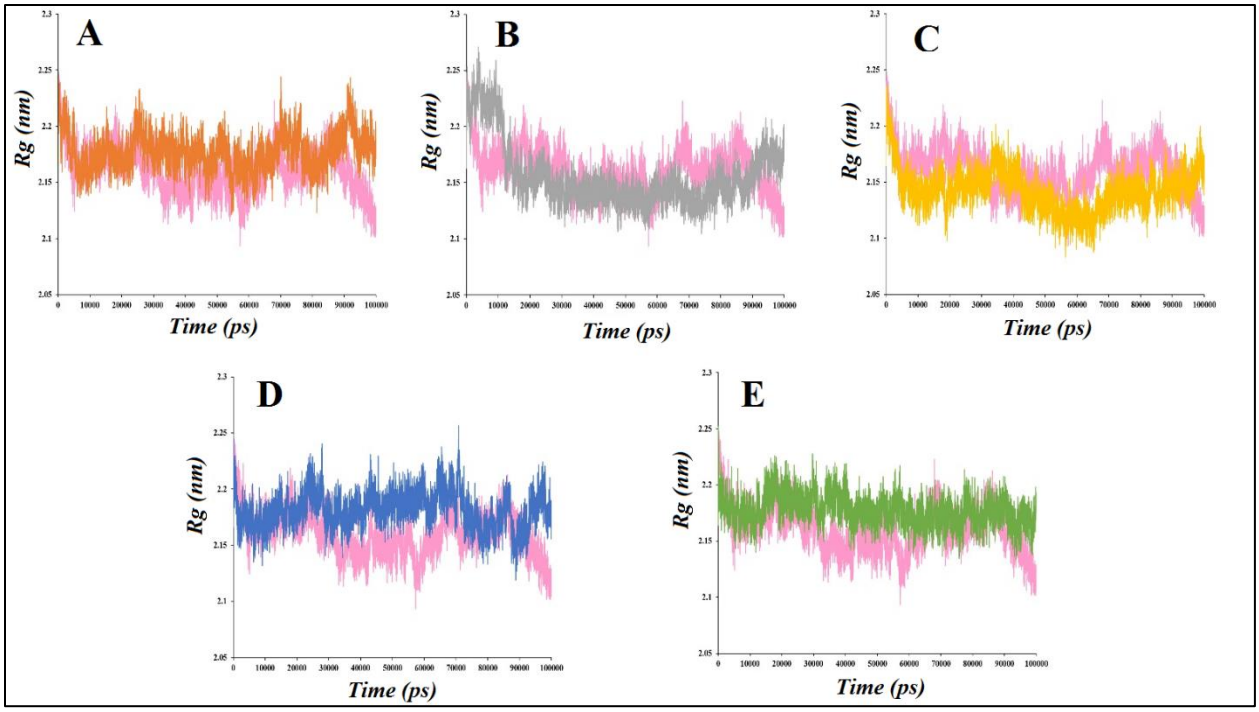
Compound	GI absorption	BBB permeation	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
3-Methoxydebromo aplysiatoxin	Low	No	Yes	No	No	No	No	Yes
Aspernolide A	High	No	Yes	No	No	Yes	No	Yes
Ehrenbergol C	High	No	Yes	No	No	No	No	No
Isobutyrolactone II	High	No	Yes	No	No	No	No	No
Penipanoid C	High	No	No	Yes	No	No	No	No

Appendix 2. Drug-likeness assessment of five selected marine-derived ligands using SwissADME.

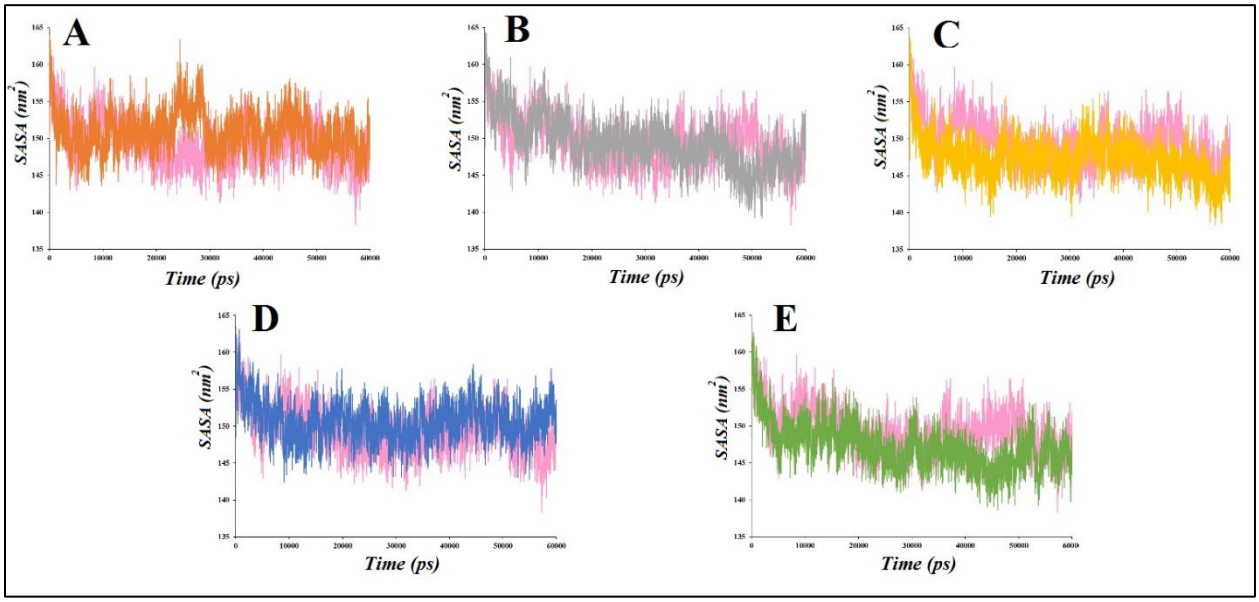
Compound	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability score
3methoxydebromo aplysiatoxin	Yes	No	Yes	Yes	No	0.55
Aspernolide A	Yes	Yes	Yes	Yes	Yes	0.55
Ehrenbergol C	Yes	Yes	Yes	Yes	Yes	0.55
Isobutyrolactone II	Yes	Yes	Yes	Yes	Yes	0.55
Penipanoid C	Yes	Yes	Yes	Yes	Yes	0.55



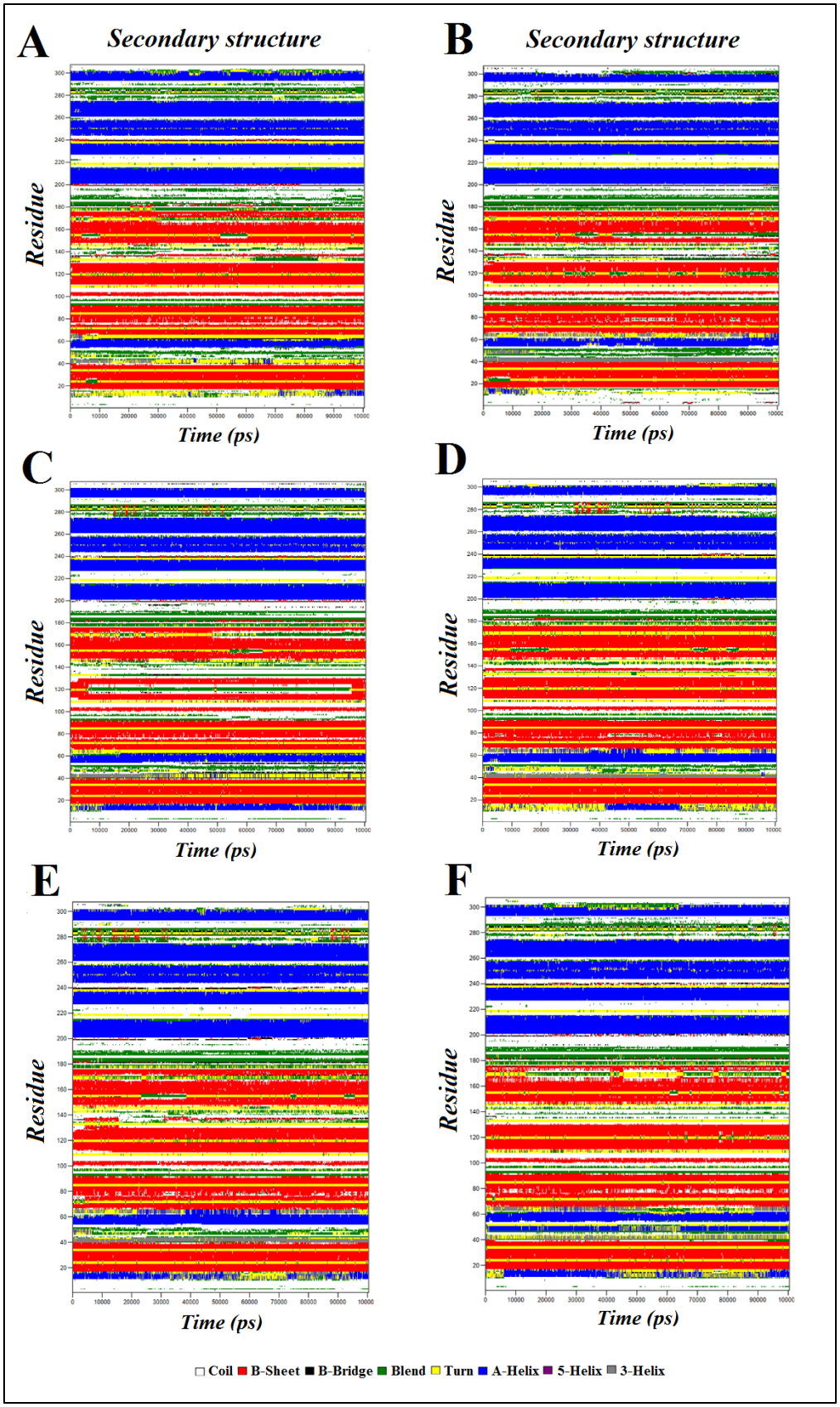
Appendix 3. 2D and 3D visualizations of selected marine compounds within the active site of SARS-CoV-2 3CLpro after MD simulation: (A) 3-Methoxydebromoaplysiatoxin, (B) Aspernolide A, (C) Ehrenbergol C, (D) Isobutyrolactone II, (E) Penipanoid C.



Appendix 4. Time-dependent radius of gyration (Rg) profiles for five protein–ligand complexes: (A) 3-Methoxy debromaplycitoxin, (B) Aspernolide A, (C) Ehrenbergol C, (D) Isobutyrolactone II, and (E) Penipanoid C; Rg profile of the free protein is shown in pink for comparison.



Appendix 5. Changes in solvent-accessible surface area (SASA) for five protein–ligand complexes: (A) 3-Methoxy debromaplycitoxin, (B) Aspernolide A, (C) Ehrenbergol C, (D) Isobutyrolactone II, and (E) Penipanoid C; SASA profile of the free protein is shown in pink for reference.


A
Secondary structure
Residue
Time (ps)
B
Secondary structure
Residue
Time (ps)
C
Residue
Time (ps)
D
Residue
Time (ps)
E
Residue
Time (ps)
F
Residue
Time (ps)
Coil B-Sheet B-Bridge Blend Turn A-Helix 5-Helix 3-Helix

Appendix 6. Changes in secondary structure, determined using Define Secondary Structure of Proteins (DSSP), for A) the free protein and its complexes with B) 3-Methoxydebromoaplysiatoxin, C) Aspernolide A, D) Ehrenbergol C, E) Isobutyrolactone II, and F) Penipanoid C.