**Supplementary material**


**Estrogen receptor modulators in viral infections such as SARS-CoV-2: Therapeutic consequences**

Nikita Abramenko, Fréderic Vellieux, Petra Tesařová, Zdeněk Kejík, Robert Kaplánek, Lukáš Lacina, Barbora Dvořánková, Daniel Rösel, Jan Brábek, Milan Jakubek and Karel Smetana Jr.

**Content**

Table S1. Molecular docking of SARS-CoV-2 main protease (M^pro) with ERMs

| | SARS-CoV-2 main protease (M^pro; PDB id 6YB7) | | | | | | |
|---|---|---|---|---|---|---|---|
| ERM | estradiol | estrane | estriol | estrone | bazedoxifene | genistin | raloxifene |
| Binding energy [kcal/mol] | -7.14 | -7.59 | -7.90 | -8.96 | -10.13 | -7.70 | -8.61 |
| Residue | PRO (108,132), VAL 202, GLN (110,107), ILE 200, GLU 240, GLY 109, HIS 246 | LEU 141, GLU 166, MET (165,49), CYS 145, ASN 142, SER 144, GLN 189, HIS (163,164), PHE (140) | MET 6, PRO 9, PHE (305,8), THR 304, VAL 303, ASP 235, ARG 238, GLN 233, ALA 7 | MET 6, PRO 9, PHE (305,8), THR 304, VAL 303, ASP 295, ARG 298, GLN (127, 299), ALA 7, GLY 302 | GLU (288, 290), LYS 137, THR (199, 198, 196), ASN 238, ARG 131, ASP (197, 289), TYR (237, 239), LEU (287, 286) | ARG 298, MET 6, ASP 295, GLN (127, 299), PRO 9, VAL 303, PHE (8, 305), ALA 7, THR 304 | PHE 305, ARG 298, SER 10, MET 6, PHE 8, ARG 4, PRO 9, VAL 125, ALA 7, GLN 127 |
| H-bond | - | - | 1 × | - | 2 × BZD:O1 - ASP 289:N BZD:O3 - ASN 238:2HD2 | 1 × GNST:H9 - ASP 295:OD1 | 1 × RLX:O4 - SER 10:HN |

Abbreviations: BZD = bazedoxifene; GNST = genistin; RLX = raloxifene

Table S2. Molecular docking of SARS-CoV-2 papain-like protease (mono PL^pro) with ERMs

| ERM | SARS-CoV-2 papain-like protease (mono PL^pro; PDB id 6W9C) | | | | | | |
|---|---|---|---|---|---|---|---|
| | estradiol | estrane | estriol | estrone | bazedoxifene | genistin | raloxifene |
| Binding energy [kcal/mol] | -6.86 | -6.28 | -6.43 | -6.94 | -5.54 | -6.07 | -6.14 |
| Residue | ASN (308,177), SER (239,180), GLU (238,124), PRO 240, CYS 181, LEU (125,178), LYS 126 | ASP (164,302), SER 245, TYR (273,264), PRO (247,248), THR 301, MET 208, ARG 166, ALA 246 | LYS (217,306), TYR (305,213), THR (257,259), GLU 214, GLY 256, PHE 258 | ASN (308,177), SER (239,180), GLU (238,124), PRO 240, CYS 181, LEU (125,178), LYS 126 | ASP 134, ASN 177, ILE 14, LYS 126, PHE 127, GLU 70, PRO 130, TYR 71, ASN 128, HIS 73 | TYR 95, LYS (91, 94), GLY 142, PRO 96, GLU 143, TRP 93, ALA (145, 144) | LEU (125, 178), SER (180, 239), ASN (177, 308), LYS 126, CYS 181, GLU (238, 124), PRO 240, ASP 179 |
| H-bond | 2 × | - | 1 × | 2 × | 2 × BZD:H34 - GLU 70:OE1 BZD:H33 - ASP 134:OD2 | 1 × GNST:H9 - LYS 91:O | - |

Abbreviations: BZD = bazedoxifene; GNST = genistin; RLX = raloxifene

Table S3. Molecular docking of SARS-CoV-2 papain-like protease (trimer PL$^{pro}$) with ERMs

| | SARS-CoV-2 papain-like protease (trimer PL$^{pro}$; PDB id 6W9C) | | | | | | |
|---|---|---|---|---|---|---|---|
| ERM | estradiol | estrane | estriol | estrone | bazedoxifene | genistin | raloxifene |
| Binding energy [kcal/mol] | -7.32 | -7.51 | -7.82 | -7.61 | -7.69 | -6.25 | -7.49 |
| Residue | ASN 267-A, LEU 289-B, GLY 266-A, GLY 287-B, TRP 106-B, ALA 288-B, TYR (264,268-A), PRO 248-A, ASP 286-B | ASN 109-A,B,C, GLU 161-A, LEU 162-A,B, GLN 269-C,B,A, GLY 160-A,B | ASN 267-C, PRO 248-C, LEU 289-A, LYS 105-A, TRP 106-A, ASP 286-A, TYR (268,264-C), GLY 266-C, GLY 287-A, ALA 288-A | ASN 267-C, PRO 248-C, LEU 289-A, ALA 288-A, TRP 106-A, ASP 286-A, TYR (268,264-C), GLY 287-A, ALA 288-B, GLY 266-C | VAL 159-A, HIS 89-A, GLU 161-C, LEU 162-B, THR 158-A, GLY 160-A, ASP 108-A, ASN 109-A | ALA 288-B, LEU 289-B, GLY 287-B, GLY 266-A, TYR (268, 264-A), TRP 106-B, ASP 286-B, ASN 267-A, PRO 248-A, LYS 105-B | ASP 164-C, ALA 288-A, LYS 105-A, PRO (247, 248-C), ASP 286-A, TRP 106-A, LEU 162-C, GLY 287-A, GLU 167-C, GLY 163-C |
| H-bond | 2 × | - | 4 × | 2 × | 3 × BZD:H34 - VAL 159-A:O LEU 162-B:HN - BZD:O2 LEU 162-C:HN - BZD:O1 | 4 × TRP 106-B:HN - GNST:O4 TYR 268-A:HH - GNST:O2 GNST:H10 - GLY 266-A:O ALA 288-B:HN - GNST:O4 | 3 × RLX:H27 - ASP 286-A:O LYS 105-A:HZ2 - RLX:O2 ALA 288-A:HN - RLX:O4 |

Abbreviations: BZD = bazedoxifene; GNST = genistin; RLX = raloxifene

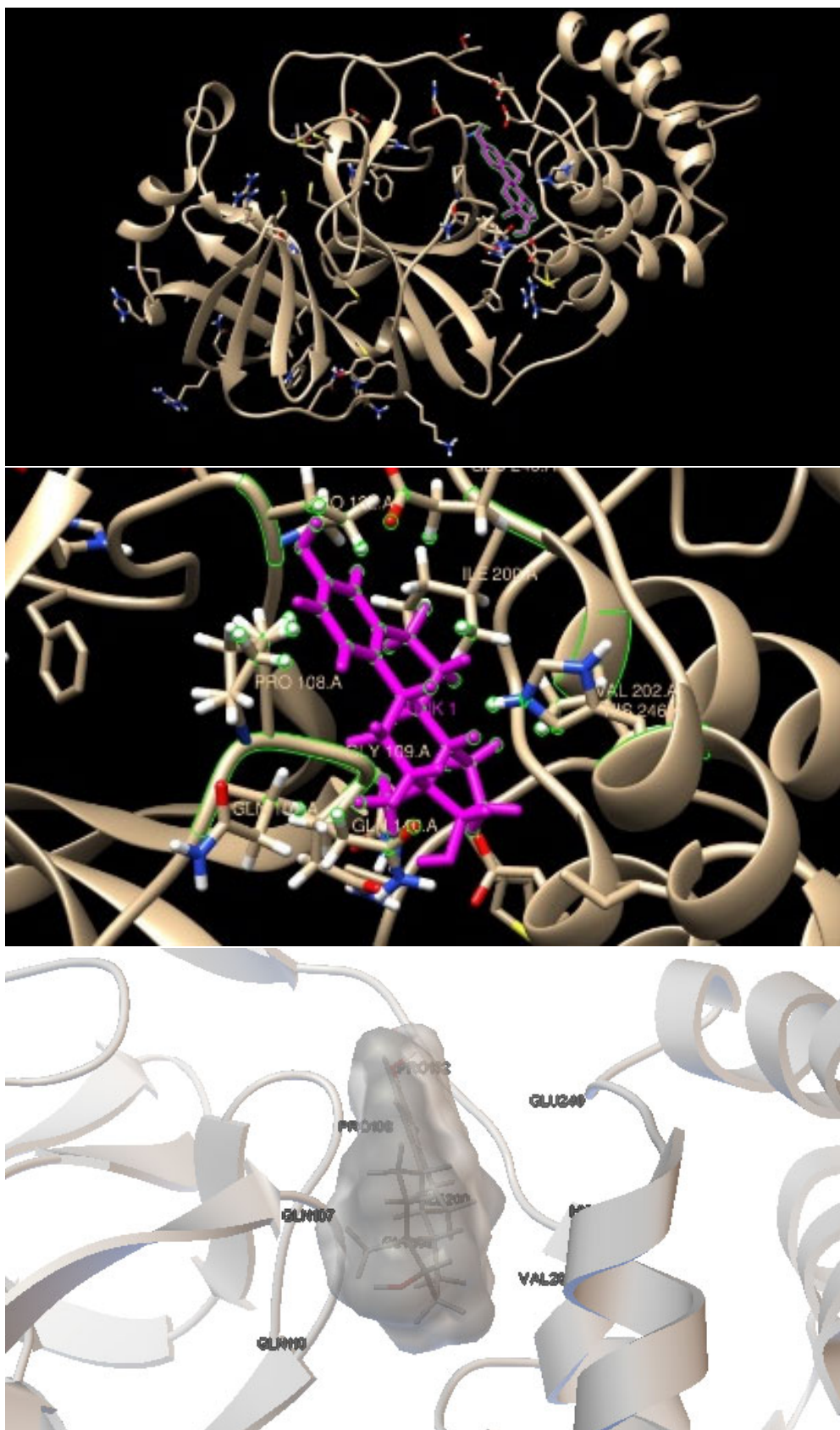Figure S1. Structures of ERMs used for docking studies

Figure S2. The best docking pose of estradiol to the SARS-CoV-2 main protease (M$^{pro}$)
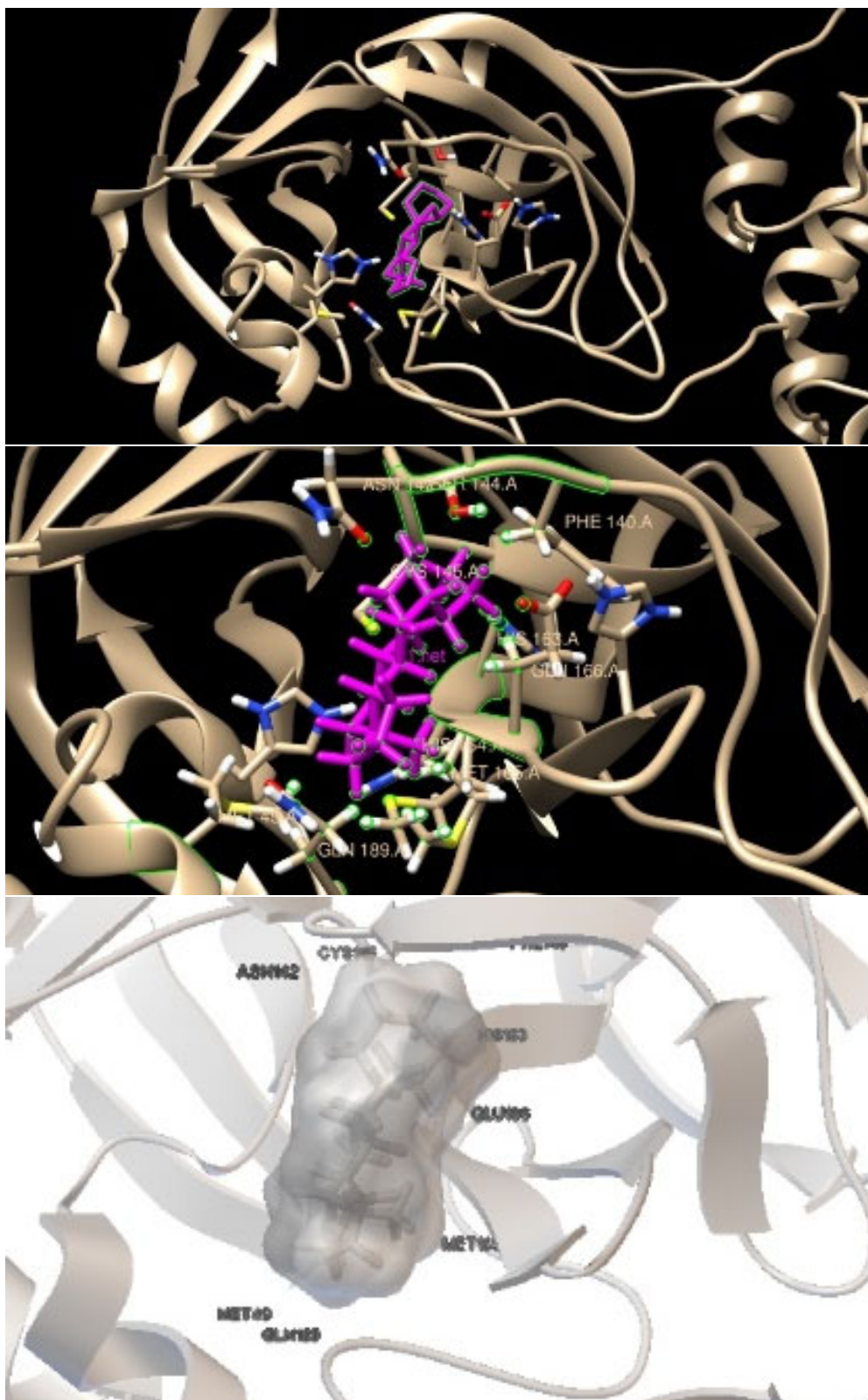
Figure S3. The best docking pose of estrane to the SARS-CoV-2 main protease (M$^{pro}$)

Figure S4. The best docking pose of estriol to the SARS-CoV-2 main protease ($M^{pro}$)
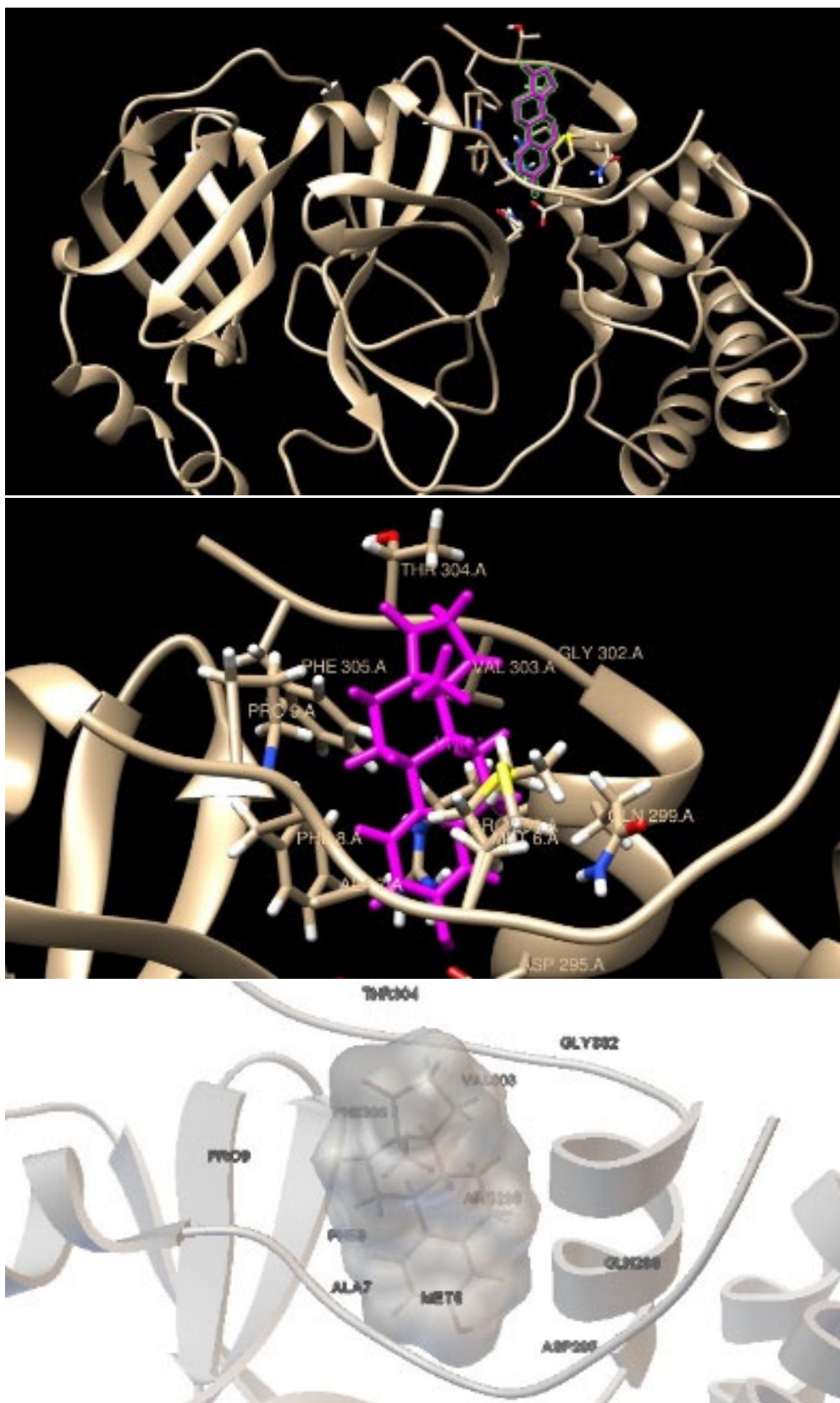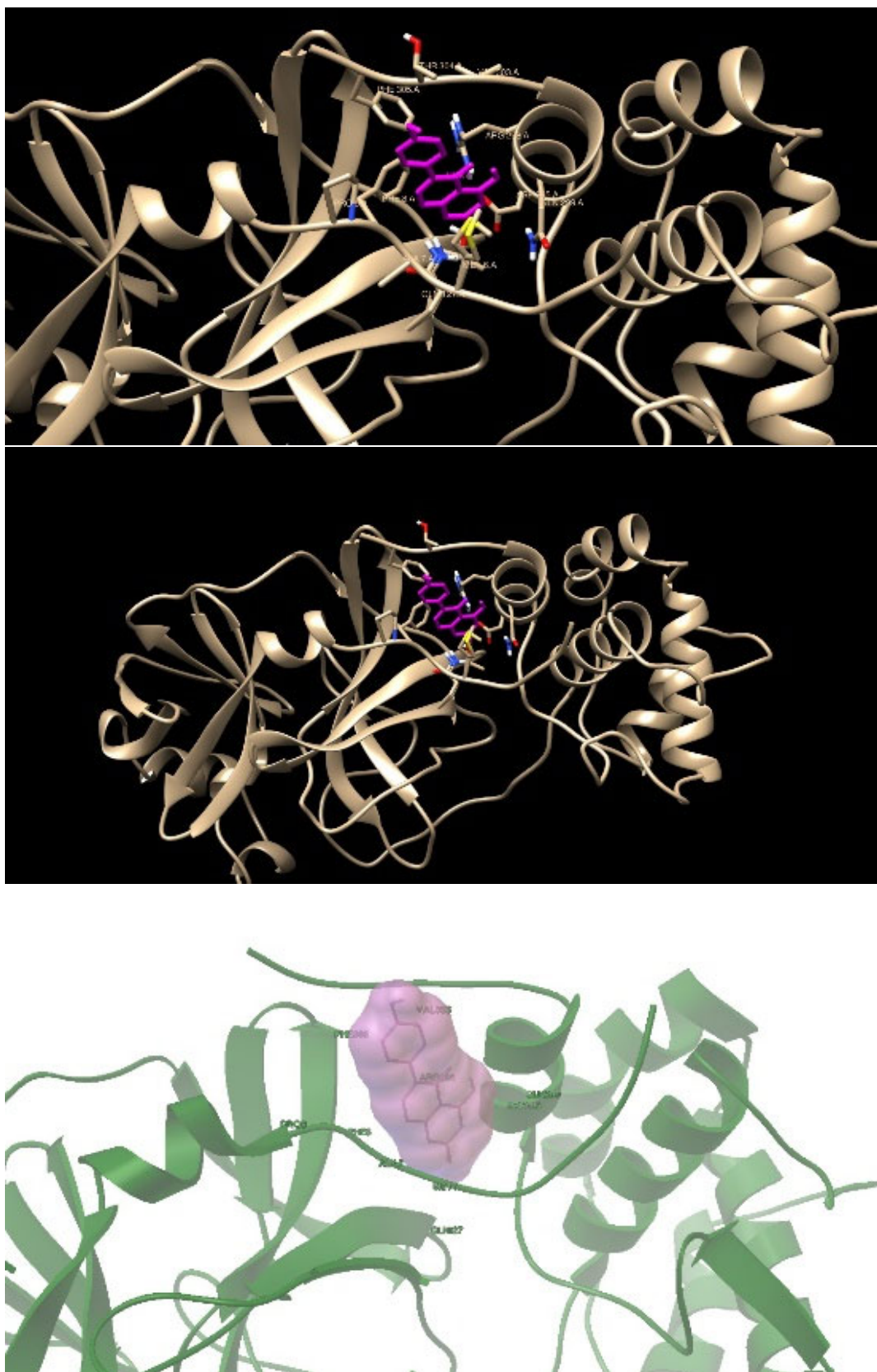
Figure S5. The best docking pose of estrone to the SARS-CoV-2 main protease (M$^{pro}$)

Figure S6. The best docking pose of bazedoxifen to the SARS-CoV-2 main protease (M$^{pro}$)

Figure S7. The best docking pose of genistin to the SARS-CoV-2 main protease (M$^{pro}$)
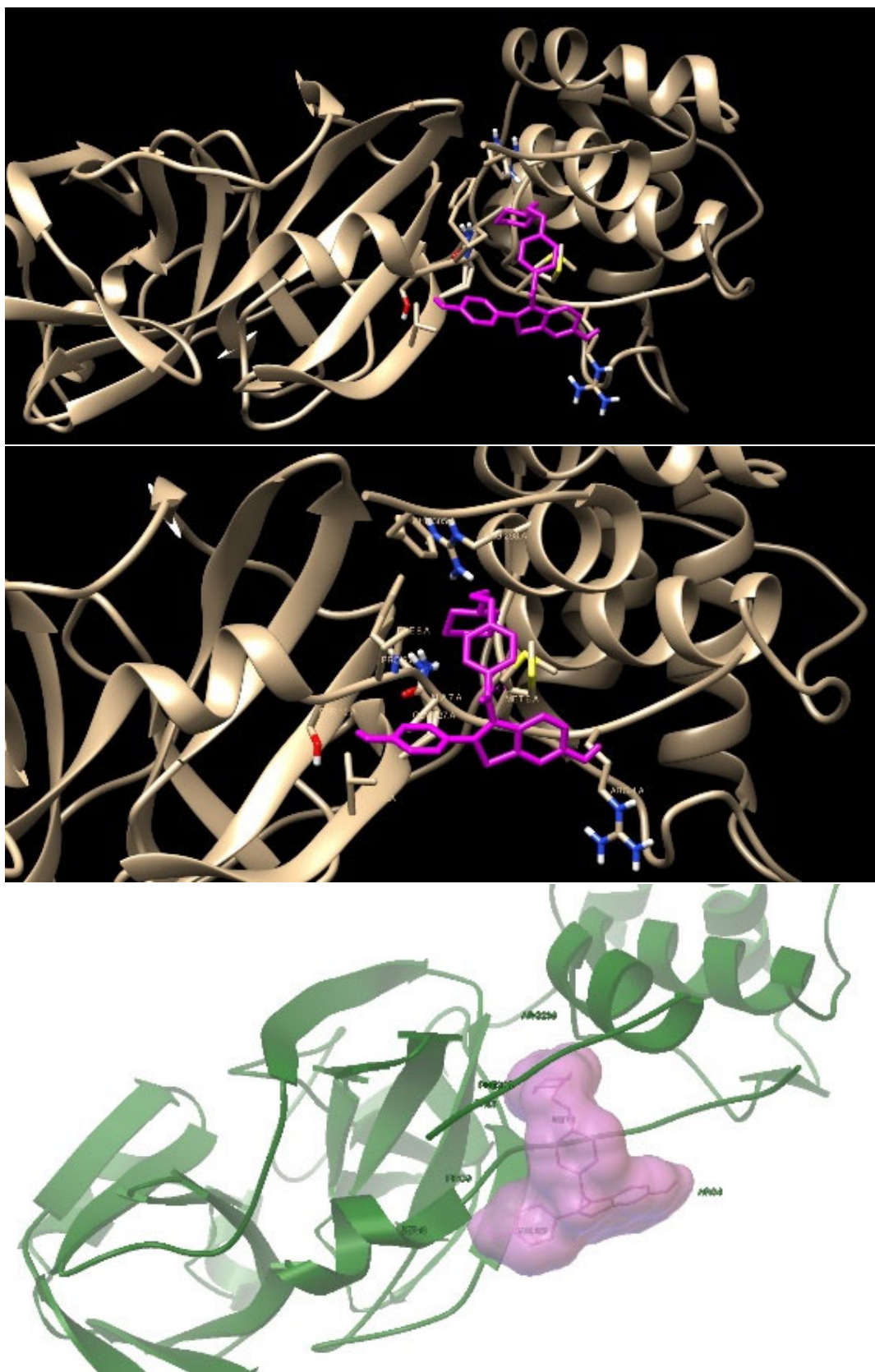
Figure S8. The best docking pose of raloxifene to the SARS-CoV-2 main protease (M$^{pro}$)

Figure S9. The best docking pose of estradiol to the SARS-CoV-2 papain-like protease (mono PL$^{pro}$)
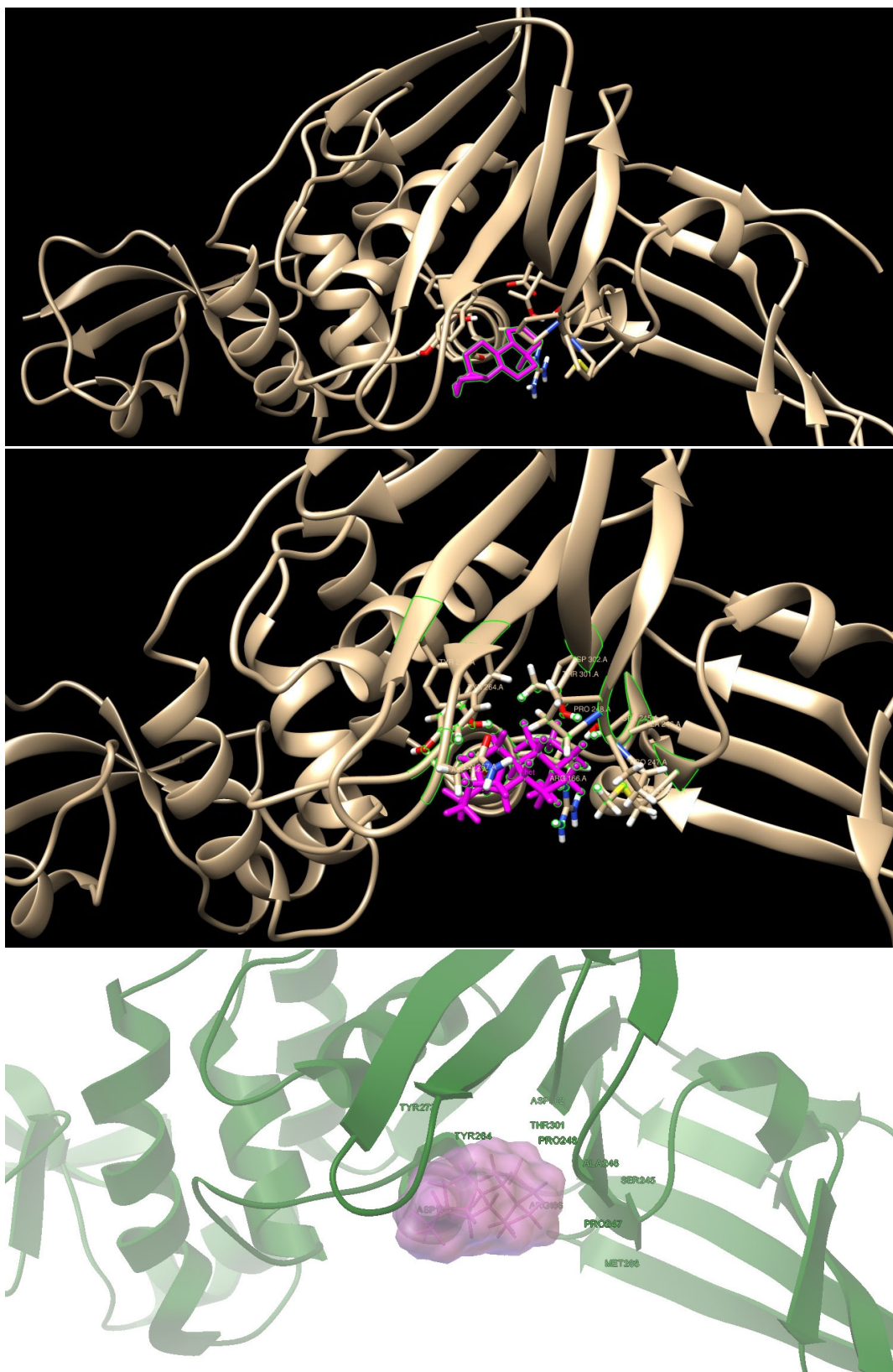
Figure S10. The best docking pose of estrane to the SARS-CoV-2 papain-like protease (mono PL<sup>pro</sup>)

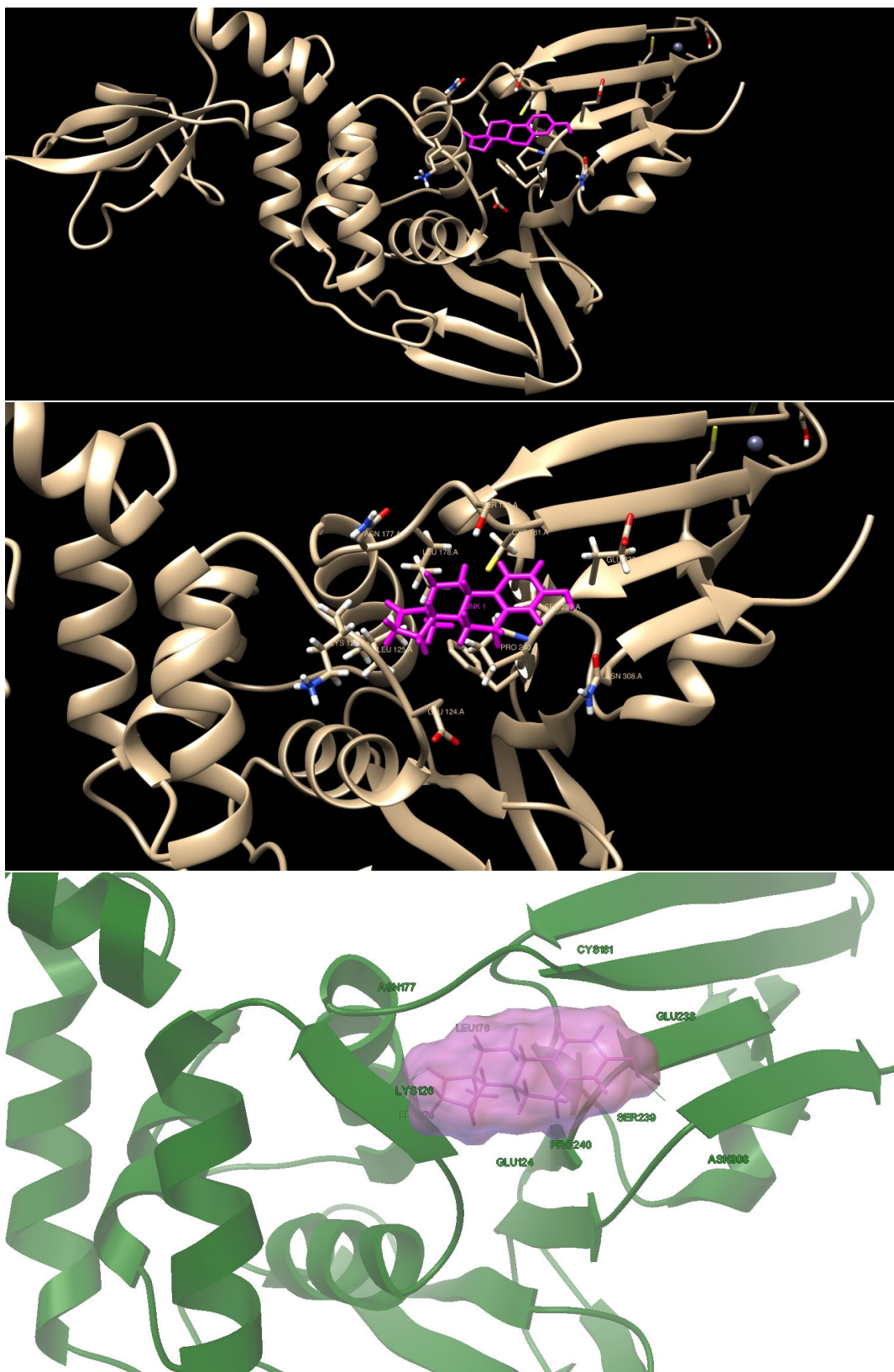Figure S11. The best docking pose of estriol to the SARS-CoV-2 papain-like protease (mono PL$^{pro}$)
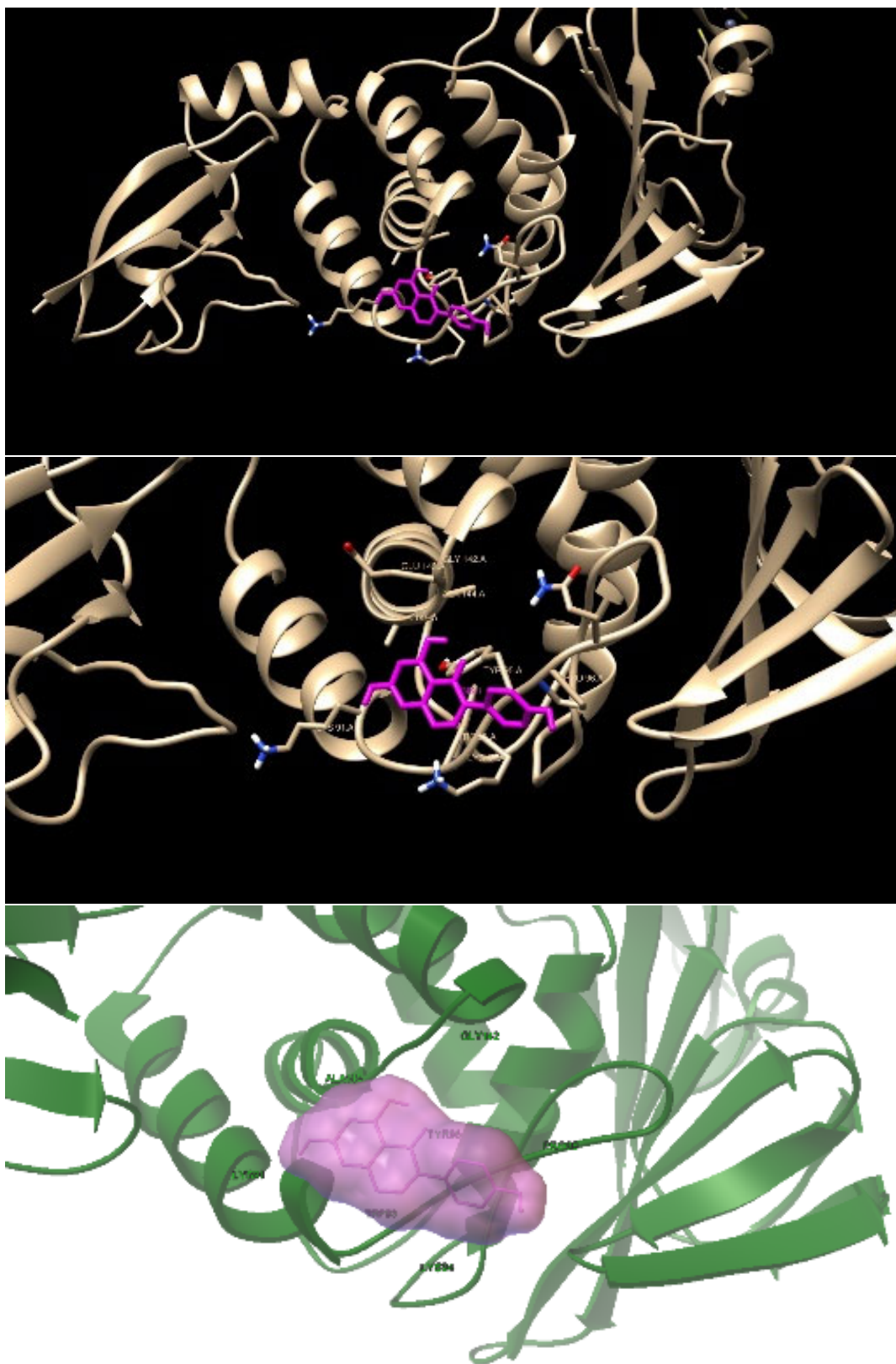
Figure S12. The best docking pose of estrone to the SARS-CoV-2 papain-like protease (mono PL$^{pro}$)

Figure S13. The best docking pose of bazedoxifene to the SARS-CoV-2 papain-like protease (mono PL$^{pro}$)

Figure S14. The best docking pose of genistin to the SARS-CoV-2 papain-like protease (mono PL$^{pro}$)
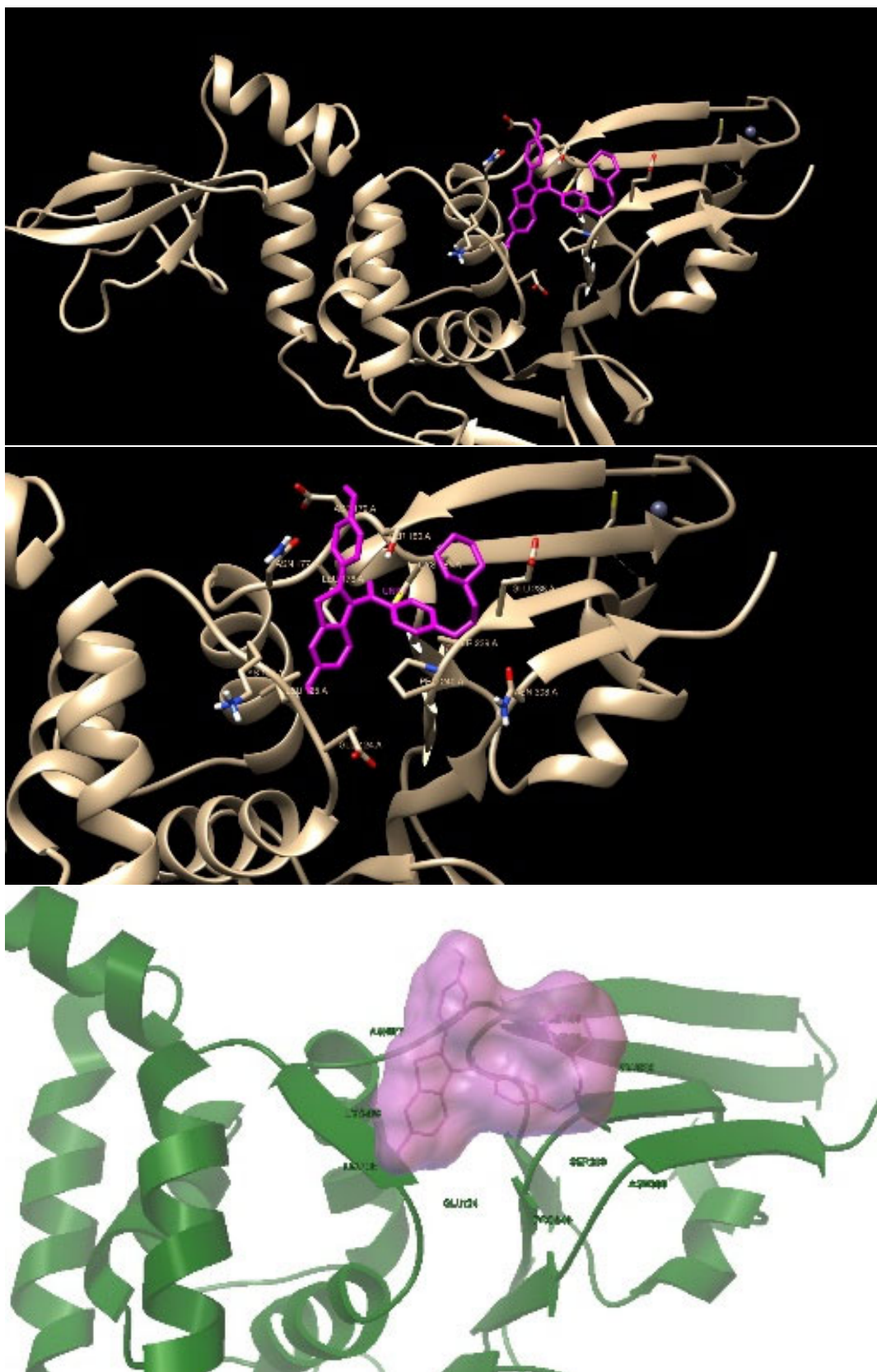
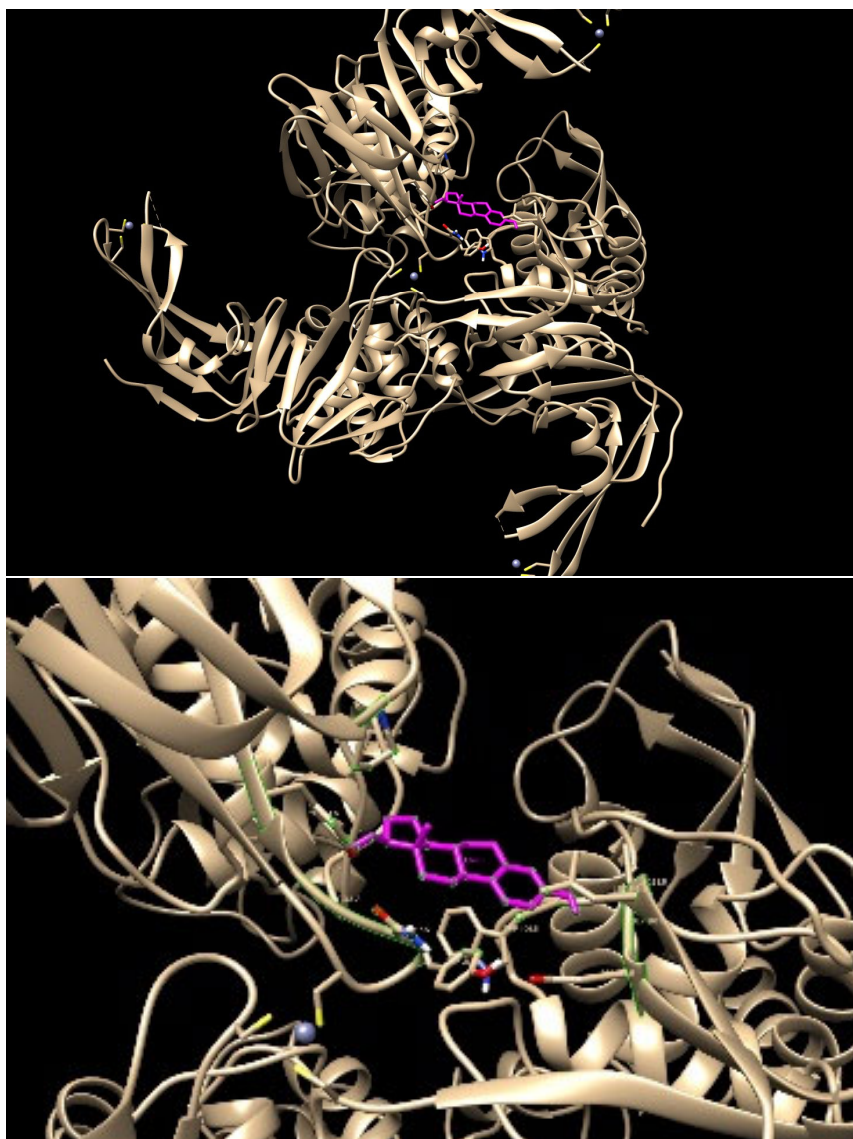Figure S15. The best docking pose of raloxifene to the SARS-CoV-2 papain-like protease (mono PL<sup>pro</sup>)

Figure S16. The best docking pose of estradiol to the SARS-CoV-2 papain-like protease (trimer PL$^{pro}$)
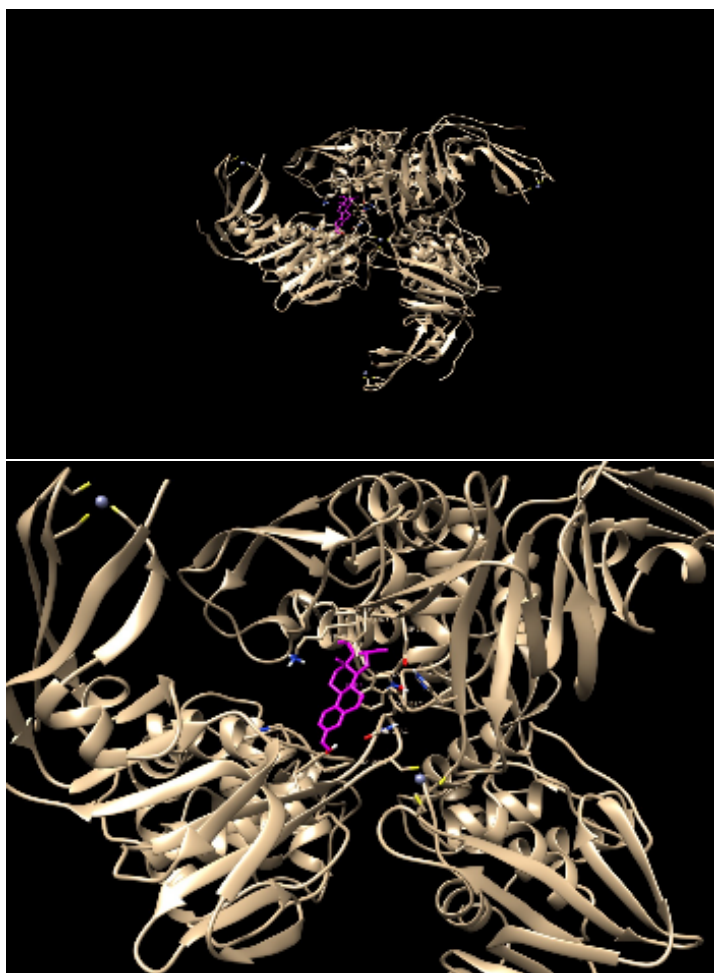
Figure S17. The best docking pose of estrane to the SARS-CoV-2 papain-like protease (trimer PL^pro)

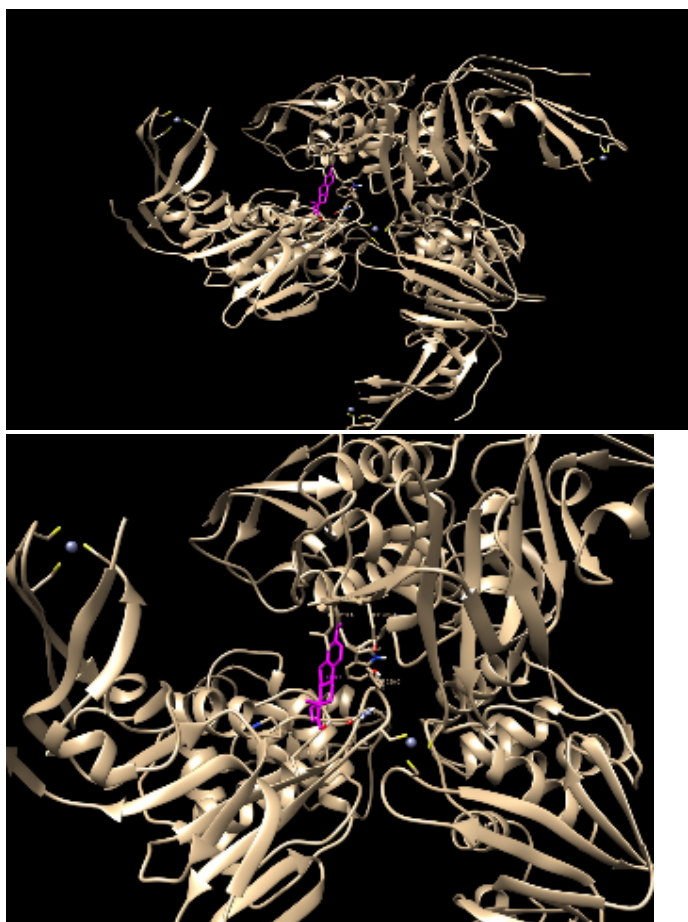Figure S18. The best docking pose of estriol to the SARS-CoV-2 papain-like protease (trimer PL$^{pro}$)

Figure S19. The best docking pose of estrone to the SARS-CoV-2 papain-like protease (trimer PL$^{pro}$)
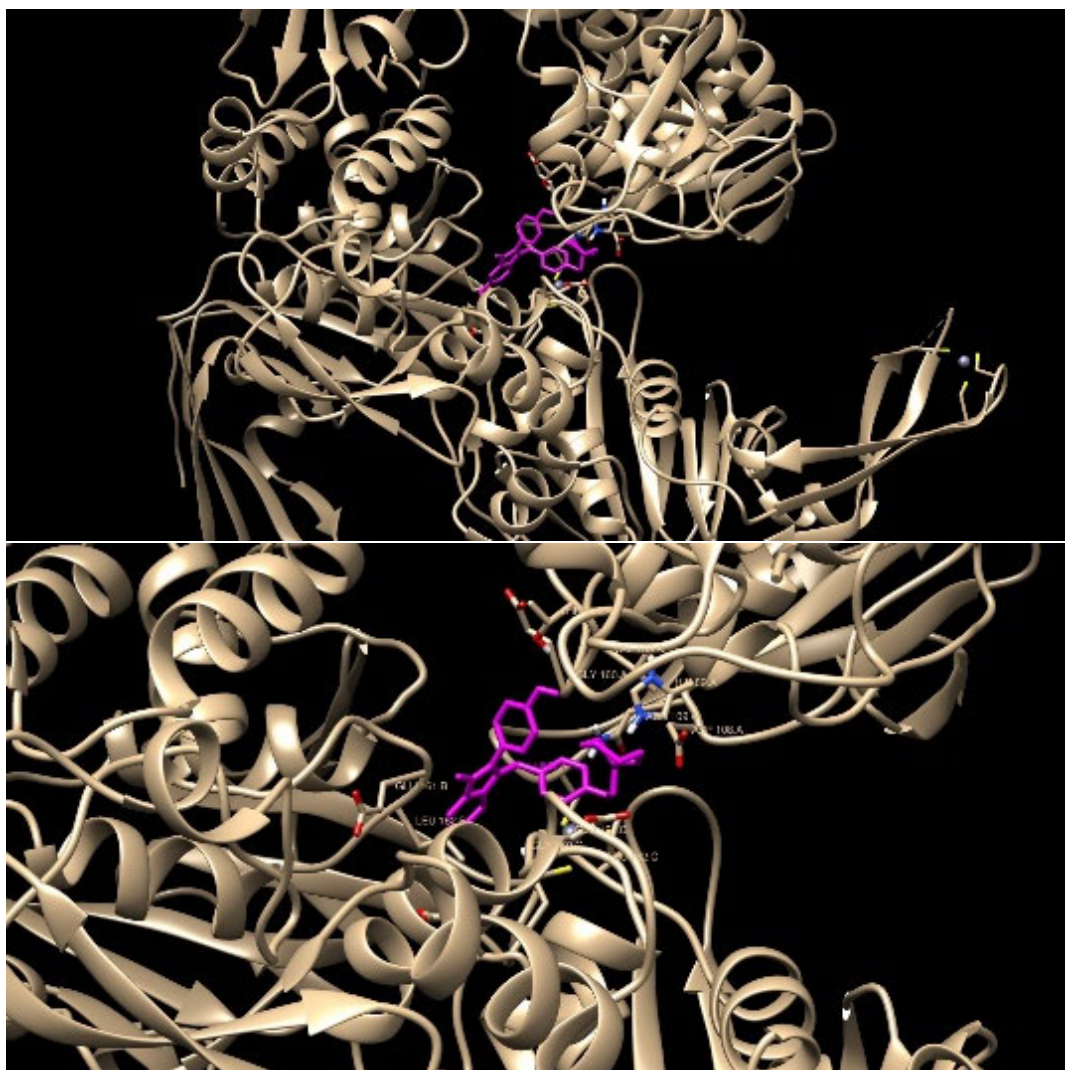
Figure S20. The best docking pose of bazedoxifene to the SARS-CoV-2 papain-like protease (trimer PL$^{pro}$)
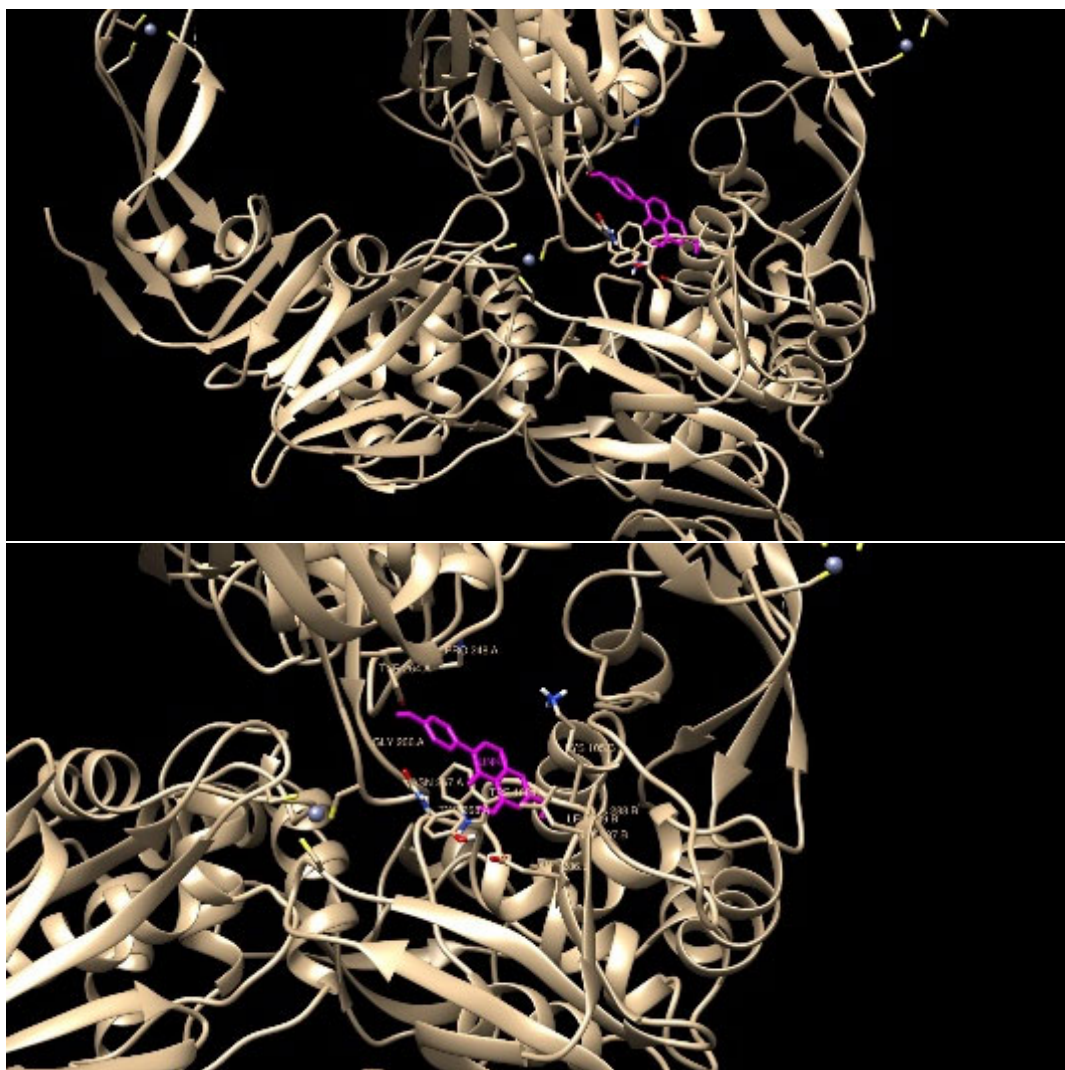
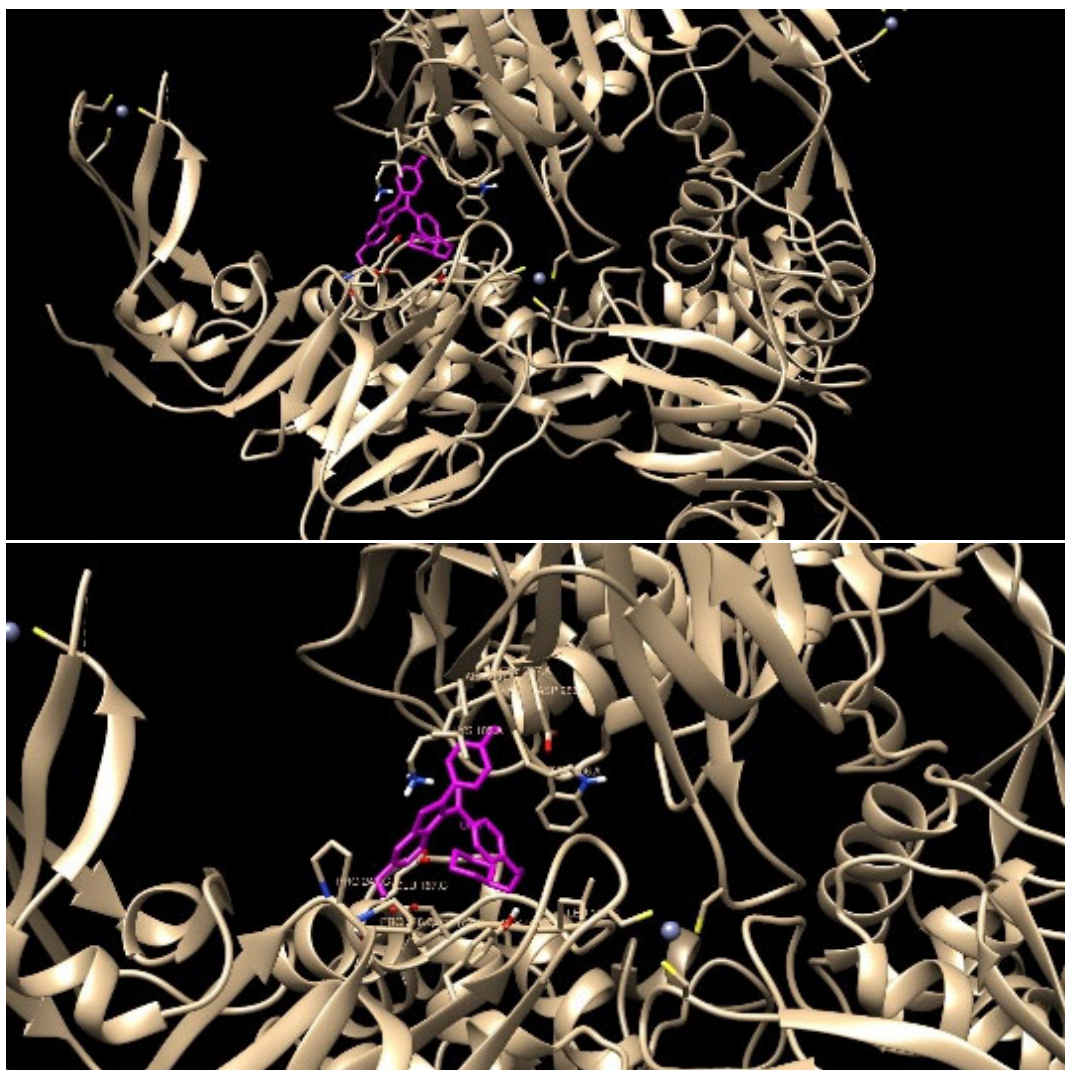Figure S21. The best docking pose of genistin to the SARS-CoV-2 papain-like protease (trimer PL$^{pro}$)

Figure S22. The best docking pose of raloxifene to the SARS-CoV-2 papain-like protease (trimer PL$^{pro}$)