# Upgrading nirmatrelvir to prevent SARS-CoV-2 Mpro via DeepFrag and free energy calculations

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Table S1. FPL results of the modified compounds versus PF-07321332 (nirmatrelvir).

| Source | $N^0$ | Code | $F_{Max}$ | $W$ | $\Delta G_{FPL}^{Pre\ a}$ |
|---|---|---|---|---|---|
| | | **PF-07321332** | 788.3 ± 38.1 | 103.7 ± 3.6 | -11.32 |
| **PF-07321332** | 1 | **PF_9b** | 871.1 ± 43.7 | 122.1 ± 5.0 | -12.35 |
| | 2 | **PF_9a** | 896.9 ± 55.5 | 119.8 ± 8.2 | -12.22 |
| | 3 | **PF_3** | 890.7 ± 48.4 | 116.0 ± 4.3 | -12.01 |
| | 4 | **PF_35** | 776.6 ± 61.3 | 115.4 ± 8.0 | -11.97 |
| | 5 | **PF_12** | 759.7 ± 15.5 | 107.3 ± 3.0 | -11.52 |
| | 6 | **PF_33** | 779.0 ± 56.3 | 104.5 ± 5.8 | -11.37 |
| | 7 | **PF_34** | 787.6 ± 55.8 | 103.7 ± 6.8 | -11.32 |
| | 8 | **PF_2** | 763.7 ± 69.0 | 97.5 ± 4.8 | -10.97 |
| | 9 | **PF_14** | 689.8 ± 26.6 | 94.3 ± 4.7 | -10.79 |

Table S2. FPL results of the modified compounds.

| Source | $N^0$ | Code | $F_{Max}$ | $W$ | $\Delta G_{FPL}^{Pre\ a}$ |
|---|---|---|---|---|---|
| **PF_9b** | 1 | **PF_9b_3** | 730.9 ± 26.1 | 113.6 ± 3.4 | -11.87 |
| | 2 | **PF_9b_13** | 788.2 ± 15.7 | 105.1 ± 1.9 | -11.40 |
| **PF_9a** | 1 | **PF_9a_33** | 882.6 ± 56.9 | 130.1 ± 7.3 | -12.80 |
| | 2 | **PF_9a_11** | 849.2 ± 18.2 | 117.3 ± 4.2 | -12.08 |
| | 3 | **PF_9a_32** | 781.5 ± 33.0 | 113.5 ± 5.3 | -11.87 |
| | 4 | **PF_9a_2** | 803.9 ± 58.9 | 112.4 ± 4.0 | -11.81 |
| | 5 | **PF_9a_13** | 669.9 ± 21.5 | 92.0 ± 3.2 | -10.67 |
| **PF_3** | 1 | **PF_3_4** | 827.5 ± 35.0 | 116.3 ± 2.7 | -12.03 |
| | 2 | **PF_3_34** | 852.9 ± 35.1 | 114.9 ± 3.4 | -11.95 |
| | 3 | **PF_3_2** | 764.6 ± 56.8 | 104.5 ± 5.0 | -11.36 |
| | 4 | **PF_3_13** | 713.8 ± 30.2 | 98.30 ± 4.7 | -11.02 |
| **PF_35** | 1 | **PF_35_14** | 627.1 ± 29.8 | 92.0 ± 3.8 | -10.66 |
| **PF_12** | 1 | **PF_12_33** | 869.2 ± 6.6 | 121.9 ± 1.6 | -12.34 |
| | 2 | **PF_12_9** | 877.5 ± 42.9 | 116.5 ± 5.0 | -12.04 |
| | 3 | **PF_12_3** | 836.7 ± 42.5 | 114.6 ± 6.4 | -11.93 |
| | 4 | **PF_12_32** | 833.3 ± 28.6 | 113.2 ± 4.2 | -11.85 |
| | 5 | **PF_12_34** | 842.0 ± 44.8 | 112.0 ± 3.5 | -11.79 |
| | 6 | **PF_12_13** | 654.9 ± 22.2 | 88.4 ± 2.3 | -10.46 |

Table S3. FPL results of the modified compounds.

| Source | N$^0$ | Code | $F_{Max}$ | $W$ | $\Delta G_{FPL}^{Pre\ a}$ |
|---|---|---|---|---|---|
| **PF_9a_33** | 1 | **PF_9a_33_13** | 828.4 ± 14.4 | 121.0 ± 2.6 | -12.29 |
| | 2 | **PF_9a_33_2** | 787.7 ± 47.7 | 107.3 ± 6.2 | -11.52 |
| | 3 | **PF_9a_33_3** | 806.5 ± 10.4 | 101.3 ± 5.1 | -11.18 |
| | 4 | **PF_9a_33_32** | 689.0 ± 36.5 | 95.3 ± 6.0 | -10.85 |
| **PF_3_4** | 1 | **PF_3_4_62** | 1032.2 ± 33.5 | 146.5 ± 5.2 | -13.71 |
| | 2 | **PF_3_4_32** | 978.9 ± 57.6 | 144.5 ± 4.1 | -13.60 |
| | 3 | **PF_3_4_7** | 957.6 ± 44.0 | 131.2 ± 3.0 | -12.86 |
| | 4 | **PF_3_4_33** | 922.9 ± 28.1 | 128.5 ± 3.4 | -12.70 |
| | 5 | **PF_3_4_31** | 908.5 ± 30.7 | 124.5 ± 4.6 | -12.48 |
| | 6 | **PF_3_4_12** | 811.6 ± 5.6 | 113.6 ± 2.0 | -11.87 |
| | 7 | **PF_3_4_10** | 717.1 ± 35.8 | 101.8 ± 2.1 | -11.21 |
| **PF_12_33** | 1 | **PF_12_33_3** | 882.7 ± 12.2 | 125.4 ± 5.5 | -12.53 |
| | 2 | **PF_12_33_9** | 839.7 ± 68.3 | 118.0 ± 9.6 | -12.12 |
| | 3 | **PF_12_33_32** | 802.0 ± 47.3 | 115.2 ± 3.0 | -11.96 |
| | 4 | **PF_12_33_33** | 816.6 ± 41.5 | 106.3 ± 5.0 | -11.47 |
| | 5 | **PF_12_33_5** | 706.9 ± 49.0 | 105.7 ± 1.7 | -11.43 |
| **PF_12_9** | 1 | **PF_12_9_31** | 940.2 ± 15.4 | 133.5 ± 2.2 | -12.99 |
| | 2 | **PF_12_9_3** | 906.7 ± 34.0 | 125.8 ± 4.6 | -12.55 |
| | 3 | **PF_12_9_5** | 885.3 ± 24.0 | 116.8 ± 5.2 | -12.06 |
| | 4 | **PF_12_9_32** | 726.0 ± 44.7 | 107.3 ± 4.1 | -11.52 |
| | 5 | **PF_12_9_33** | 760.3 ± 8.8 | 101.2 ± 2.5 | -11.18 |
| | 6 | **PF_12_9_12** | 683.1 ± 8.6 | 97.5 ± 1.4 | -10.97 |
| | 7 | **PF_12_9_2** | 721.8 ± 25.9 | 90.5 ± 4.0 | -10.58 |

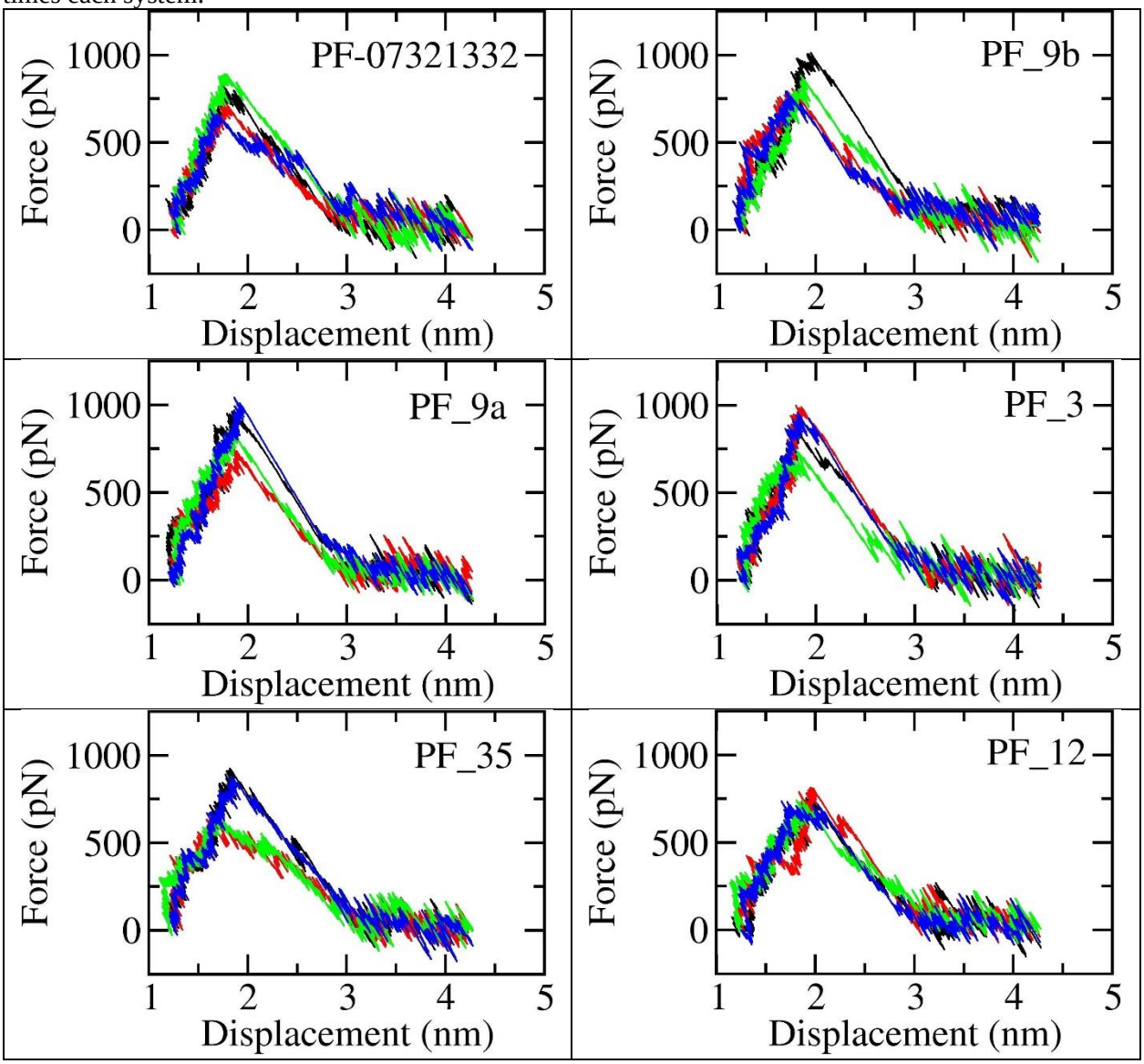
**Table S4.** FPL results of the modified compounds.

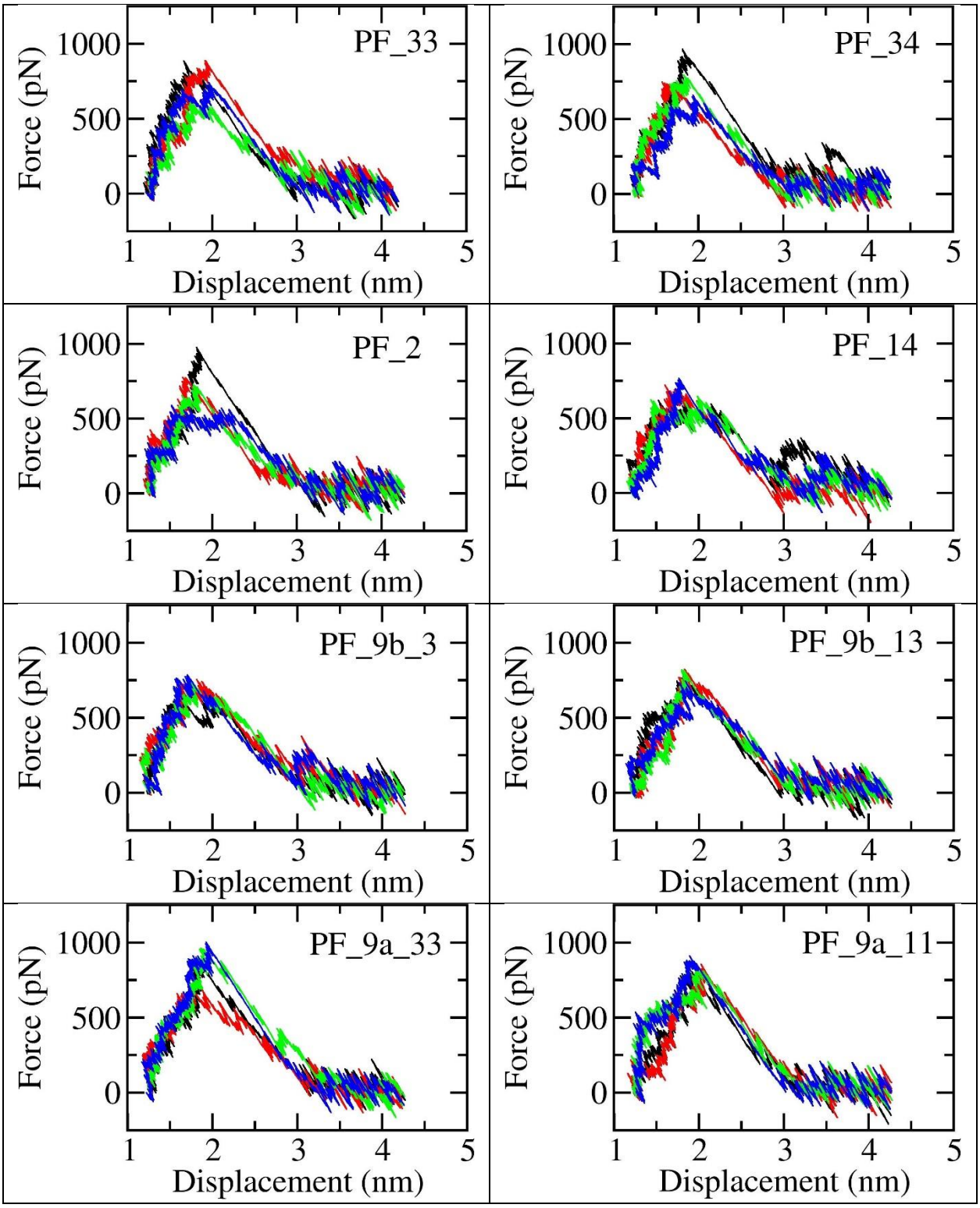
| Source | N$^0$ | Code | $F_{Max}$ | $W$ | $\Delta G_{FPL}^{Pre\ a}$ |
|---|---|---|---|---|---|
| **PF_3_4_62** | 1 | **PF_3_4_62_33** | 927.7 ± 28.0 | 122.6 ± 4.2 | -12.38 |
| | 2 | **PF_3_4_62_12** | 785.7 ± 32.5 | 101.8 ± 6.3 | -11.21 |
| | 3 | **PF_3_4_62_32** | 731.7 ± 60.3 | 100.4 ± 5.7 | -11.13 |
| | 4 | **PF_3_4_62_10** | 661.4 ± 31.4 | 86.7 ± 4.1 | -10.37 |
| **PF_3_4_32** | 1 | **PF_3_4_32_32** | 911.3 ± 24.8 | 126.3 ± 3.8 | -12.58 |
| | 2 | **PF_3_4_32_10** | 837.0 ± 60.4 | 121.1 ± 7.1 | -12.30 |
| **PF_3_4_7** | 1 | **PF_3_4_7_30** | 792.3 ± 66.8 | 119.4 ± 8.1 | -12.20 |
| | 2 | **PF_3_4_7_9** | 792.7 ± 26.7 | 103.5 ± 6.9 | -11.31 |
| | 3 | **PF_3_4_7_31** | 640.4 ± 38.9 | 89.9 ± 2.5 | -10.55 |
| | 4 | **PF_3_4_7_32** | 660.3 ± 28.9 | 89.6 ± 5.8 | -10.53 |
| | 5 | **PF_3_4_7_11** | 611.1 ± 43.3 | 76.1 ± 4.3 | -9.77 |
| **PF_3_4_33** | 1 | **PF_3_4_33_32** | 927.2 ± 39.3 | 142.2 ± 6.2 | -13.47 |
| | 2 | **PF_3_4_33_31** | 908.0 ± 63.5 | 134.7 ± 8.1 | -13.05 |
| | 3 | **PF_3_4_33_12** | 676.8 ± 22.7 | 98.3 ± 4.1 | -11.01 |
| **PF_3_4_31** | 1 | **PF_3_4_31_32** | 863.1 ± 45.1 | 123.3 ± 6.1 | -12.42 |
| | 2 | **PF_3_4_31_10** | 795.4 ± 49.9 | 109.5 ± 4.1 | -11.65 |
| | 3 | **PF_3_4_31_12** | 729.7 ± 51.4 | 105.4 ± 5.4 | -11.41 |
| **PF_12_33_3** | 1 | **PF_12_33_3_32** | 804.3 ± 28.3 | 111.8 ± 4.0 | -11.77 |
| | 2 | **PF_12_33_3_31** | 727.1 ± 53.1 | 100.2 ± 5.0 | -11.12 |
| | 3 | **PF_12_33_3_8** | 691.5 ± 32.2 | 94.9 ± 4.9 | -10.83 |
| | 4 | **PF_12_33_3_2** | 729.6 ± 21.6 | 89.9 ± 4.9 | -10.55 |
| | 5 | **PF_12_33_3_4** | 656.4 ± 36.4 | 87.6 ± 4.6 | -10.42 |
| **PF_12_9_31** | 1 | **PF_12_9_31_32** | 836.6 ± 28.1 | 126.8 ± 3.9 | -12.61 |
| | 2 | **PF_12_9_31_3** | 829.9 ± 43.2 | 112.7 ± 5.9 | -11.82 |
| | 3 | **PF_12_9_31_2** | 705.3 ± 29.1 | 89.6 ± 3.6 | -10.53 |
| **PF_12_9_3** | 1 | **PF_12_9_3_31** | 690.2 ± 44.7 | 97.7 ± 4.0 | -10.98 |
| | 2 | **PF_12_9_3_30** | 587.0 ± 43.2 | 87.6 ± 3.9 | -10.42 |
| | 3 | **PF_12_9_3_32** | 569.0 ± 35.0 | 73.7 ± 4.1 | -9.64 |
| | 4 | **PF_12_9_3_11** | 532.9 ± 40.3 | 72.9 ± 3.7 | -9.59 |

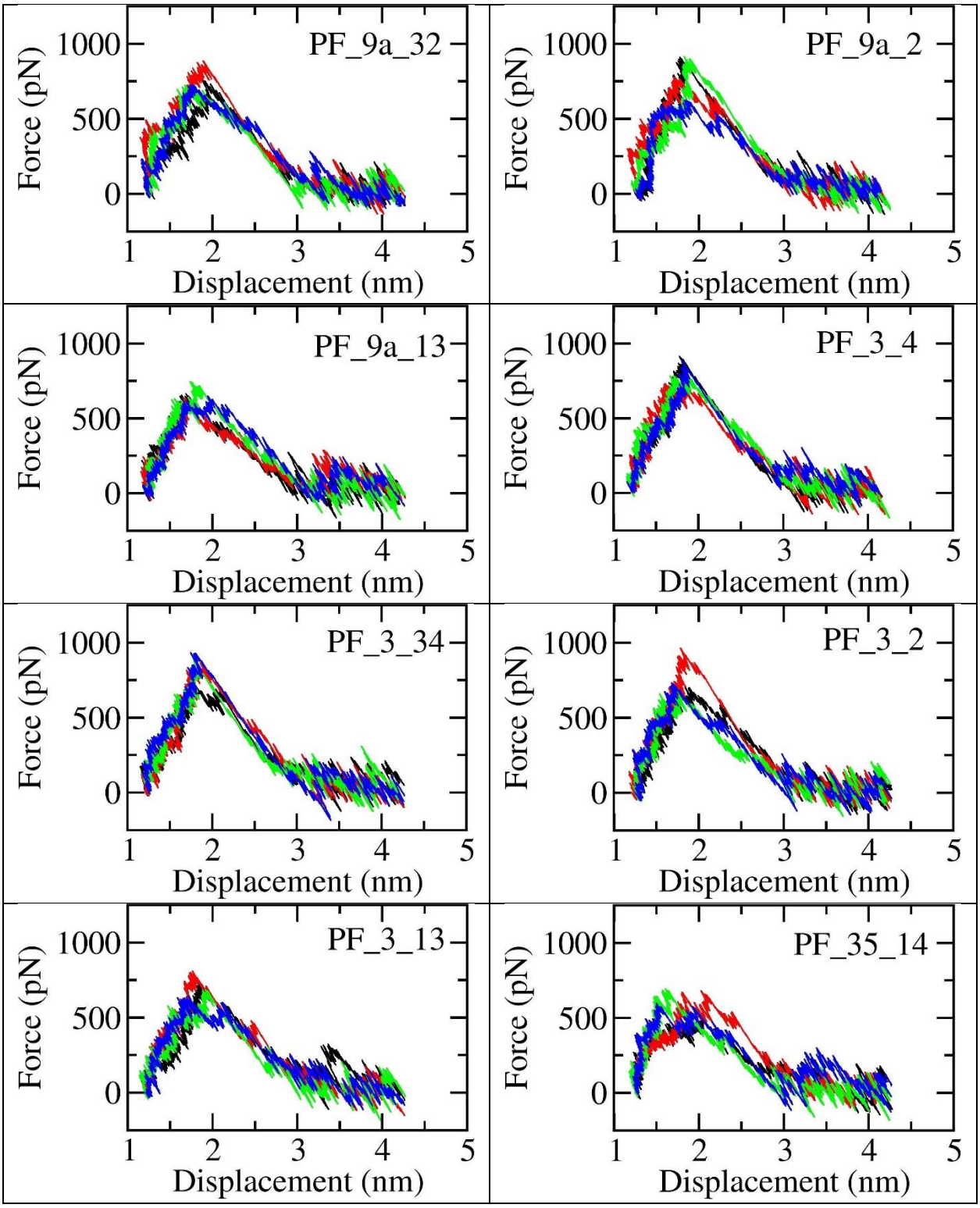
**Table S5.** FPL results of the modified compounds.

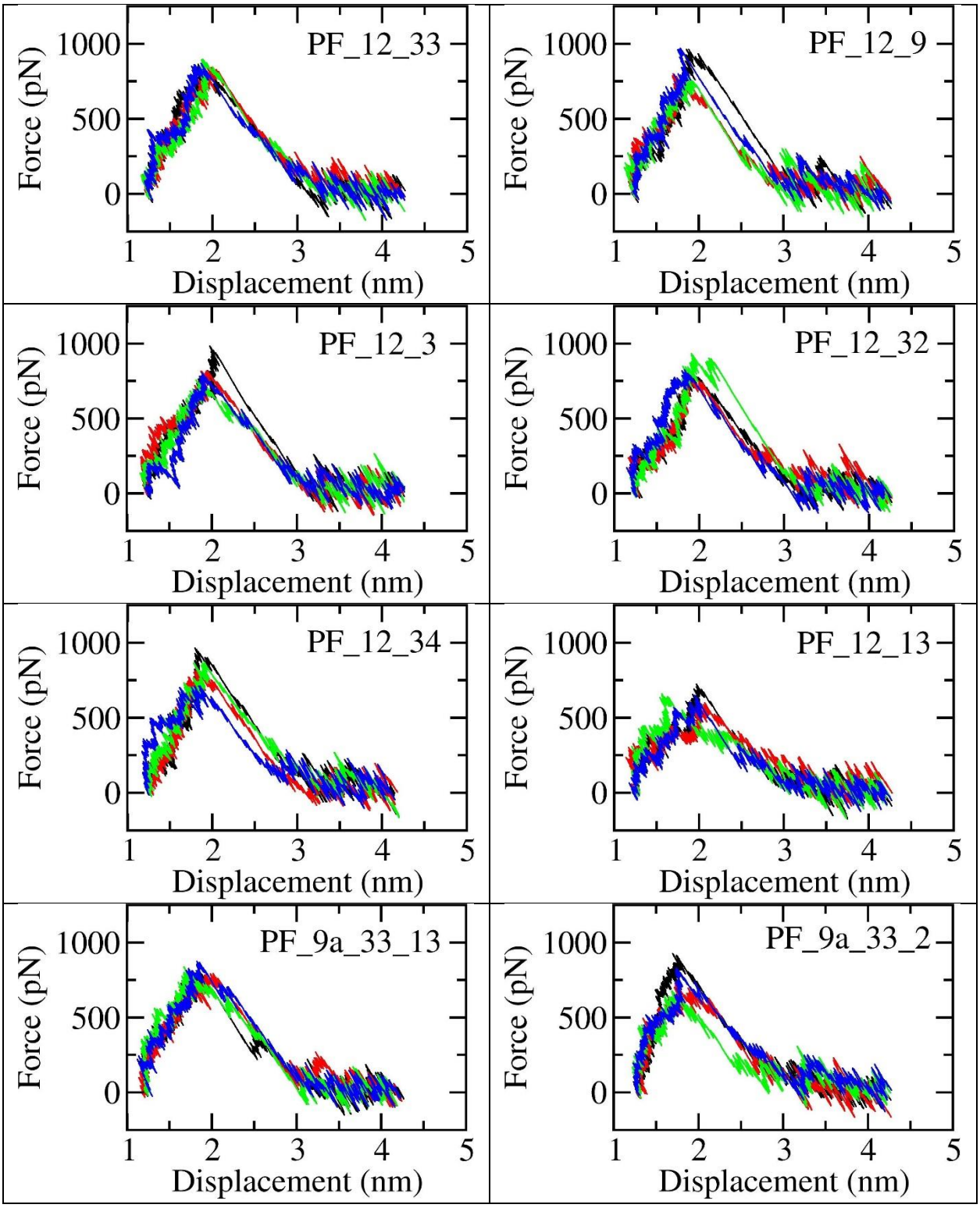
| Source | N$^0$ | Code | $F_{Max}$ | $W$ | $\Delta G_{FPL}^{Pre\ a}$ |
|---|---|---|---|---|---|
| **PF_3_4_33_32** | 1 | **PF_3_4_33_32_10** | 658.0 ± 37.5 | 95.3 ± 5.5 | -10.85 |
| | 2 | **PF_3_4_33_32_60** | 737.6 ± 19.2 | 95.2 ± 2.52 | -10.84 |
| **PF_3_4_31** | 1 | **PF_3_4_33_31_60** | 813.8 ± 12.4 | 105.0 ± 1.4 | -11.39 |
| | 2 | **PF_3_4_33_31_10** | 646.1 ± 31.5 | 95.9 ± 3.4 | -10.88 |

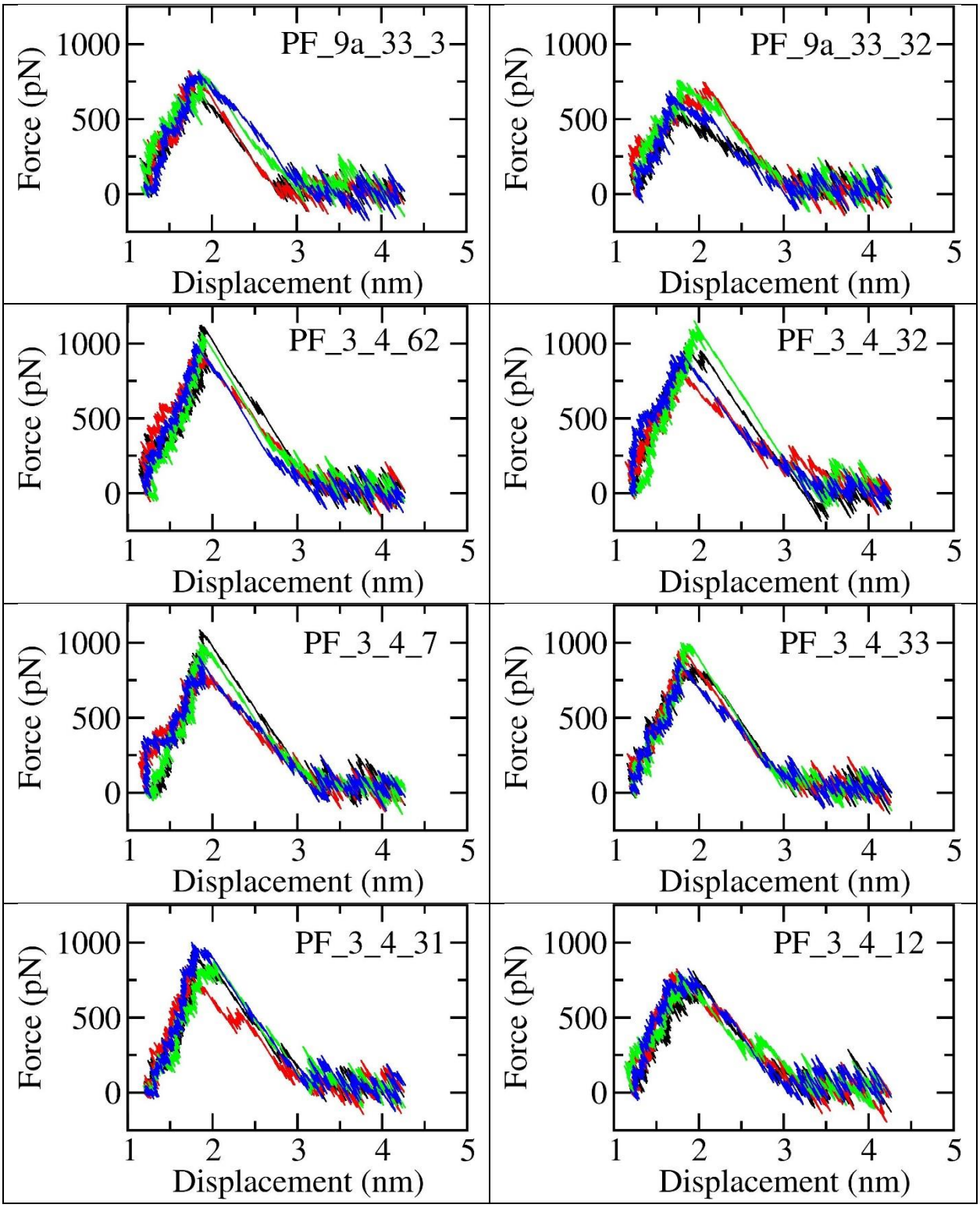
**Table S6.** The profile of pulling work over the ligand displacement. The calculations were repeated 4 times each system.

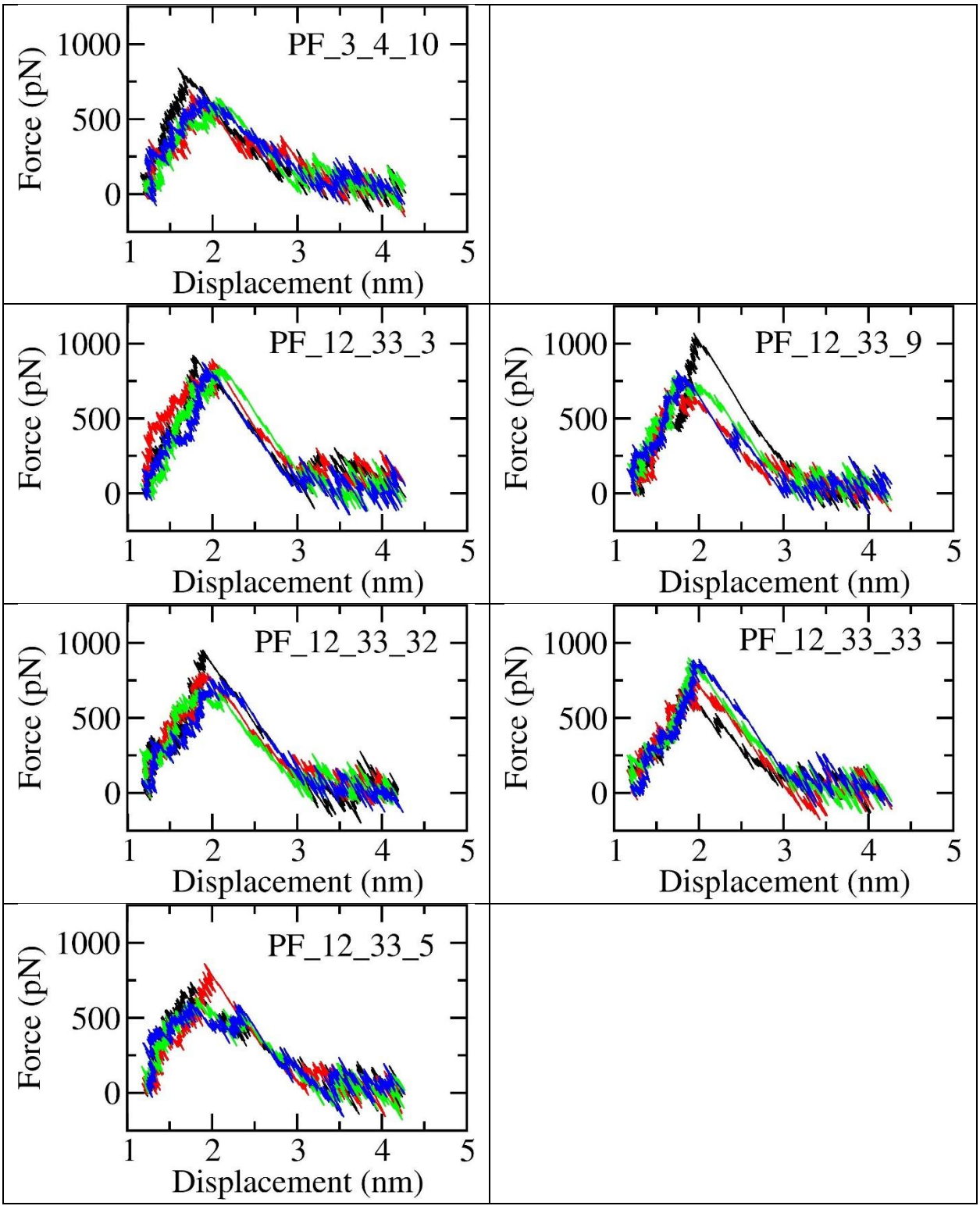


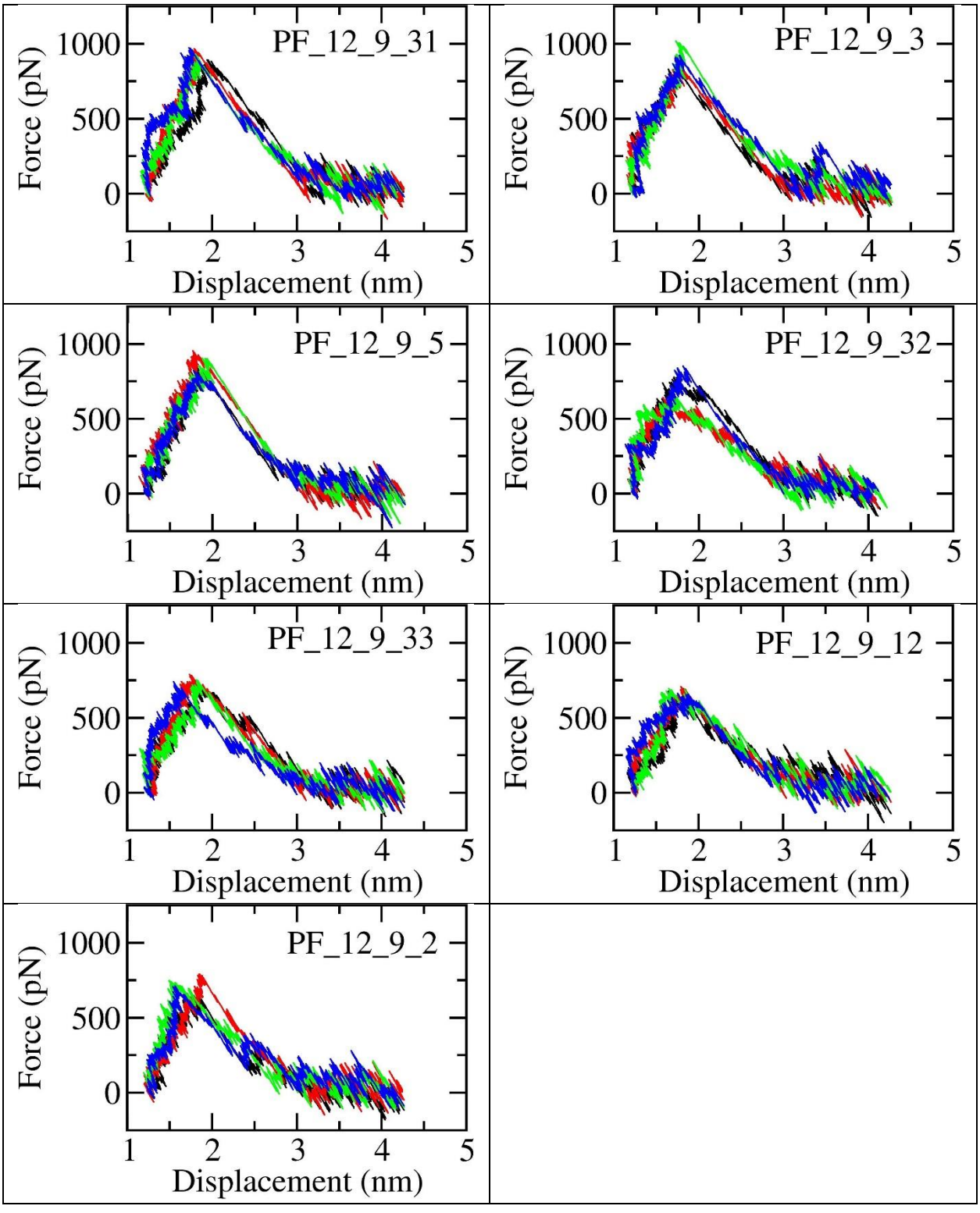

PF_33
PF_34
PF_2
PF_14
PF_9b_3
PF_9b_13
PF_9a_33
PF_9a_11
Force (pN)
Displacement (nm)
0
500
1000
1
2
3
4
5

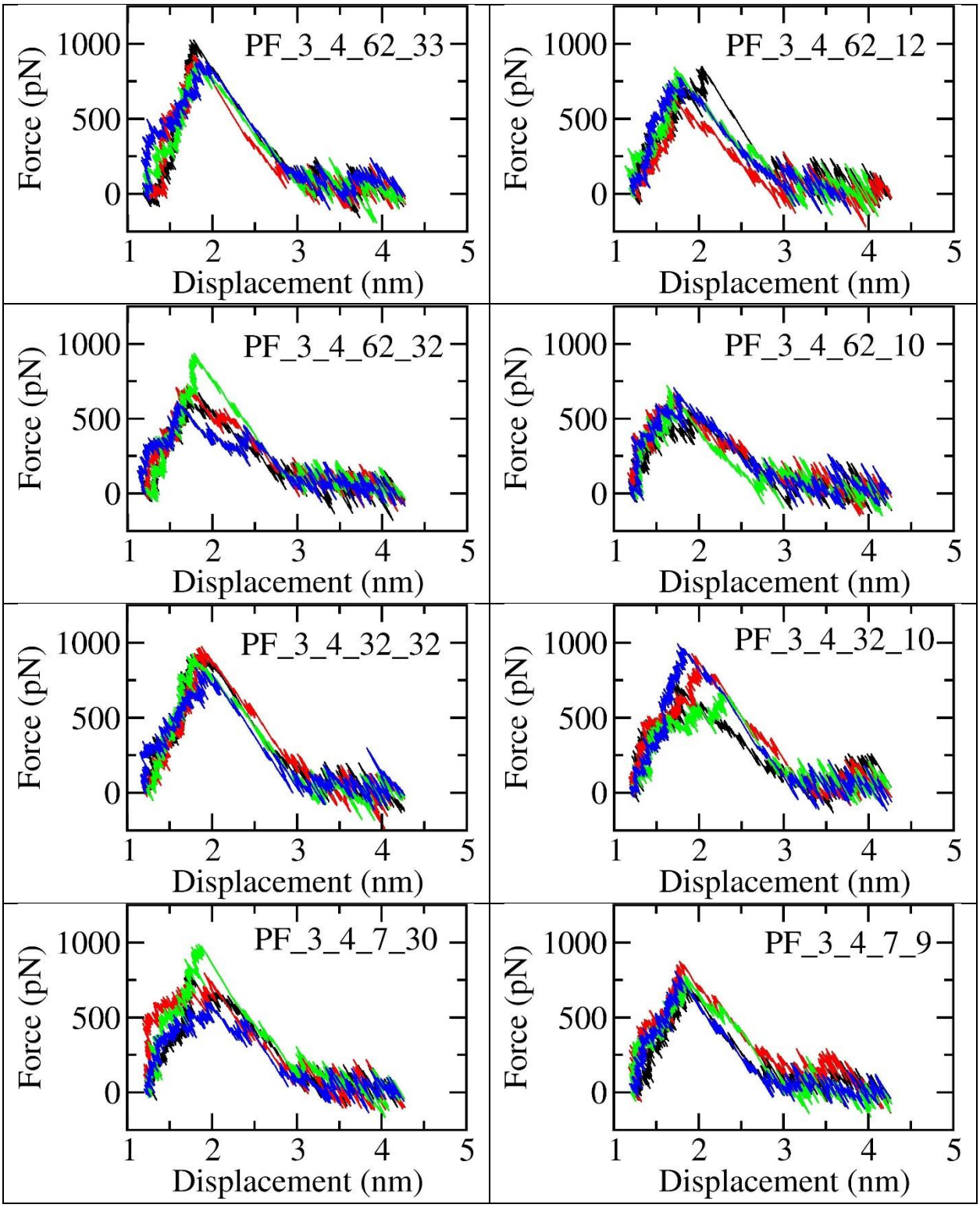

PF_9a_32
PF_9a_2
PF_9a_13
PF_3_4
PF_3_34
PF_3_2
PF_3_13
PF_35_14
Force (pN)
Displacement (nm)
1000
500
0
1
2
3
4
5

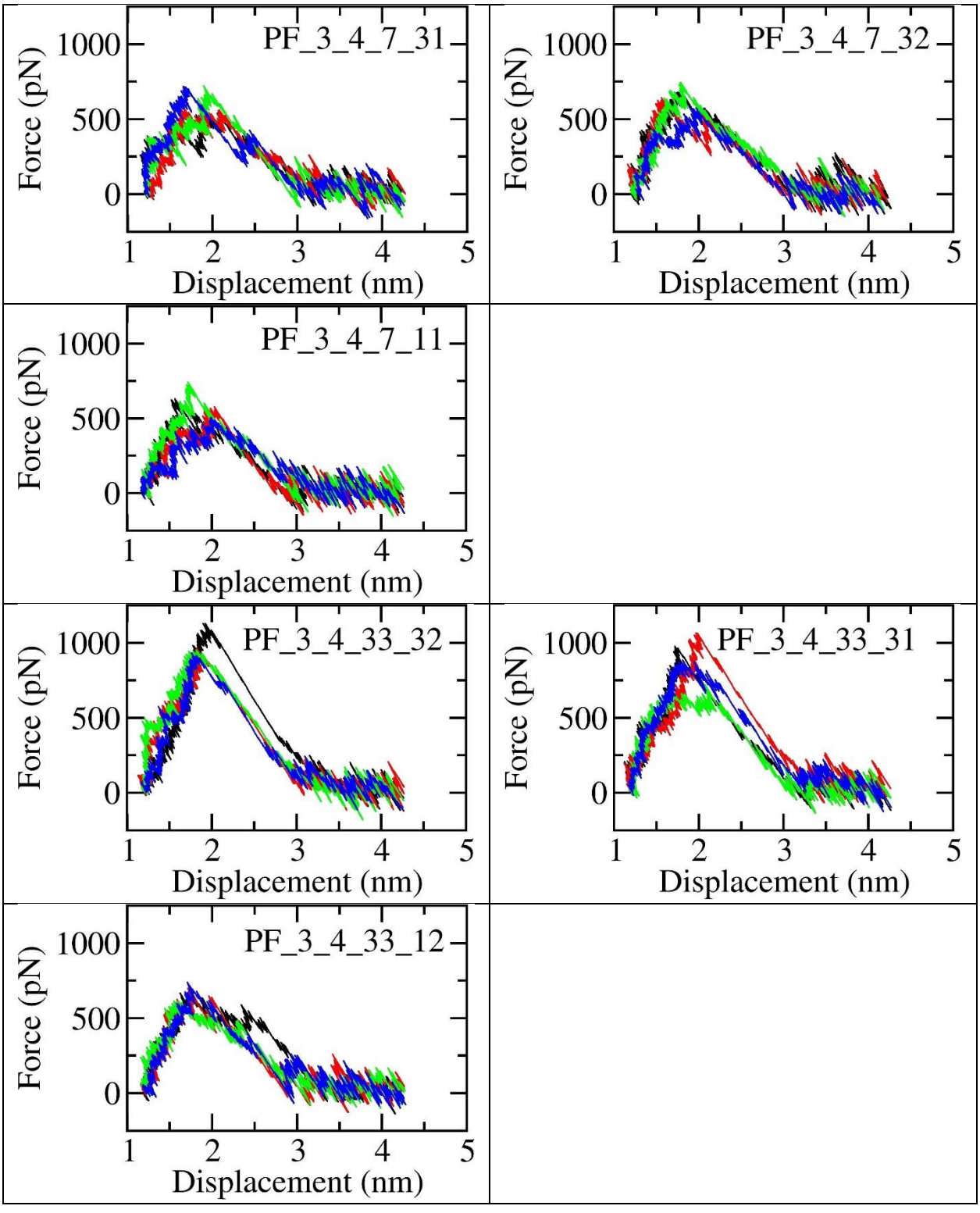

PF_12_33
PF_12_9
PF_12_3
PF_12_32
PF_12_34
PF_12_13
PF_9a_33_13
PF_9a_33_2
Force (pN)
Displacement (nm)
0
500
1000
1
2
3
4
5

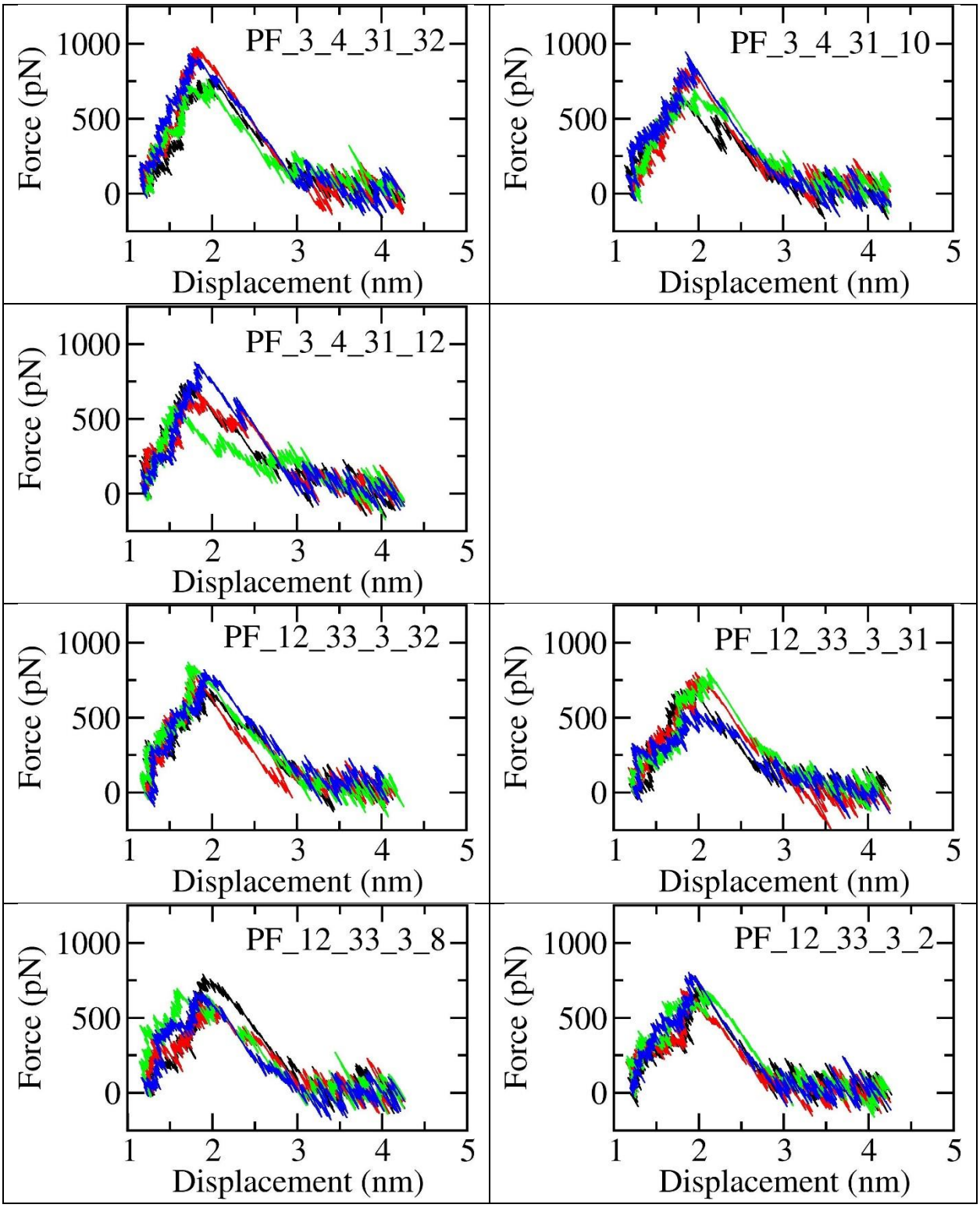

PF_9a_33_3
PF_9a_33_32
PF_3_4_62
PF_3_4_32
PF_3_4_7
PF_3_4_33
PF_3_4_31
PF_3_4_12
Force (pN)
Displacement (nm)
0
500
1000
1
2
3
4
5

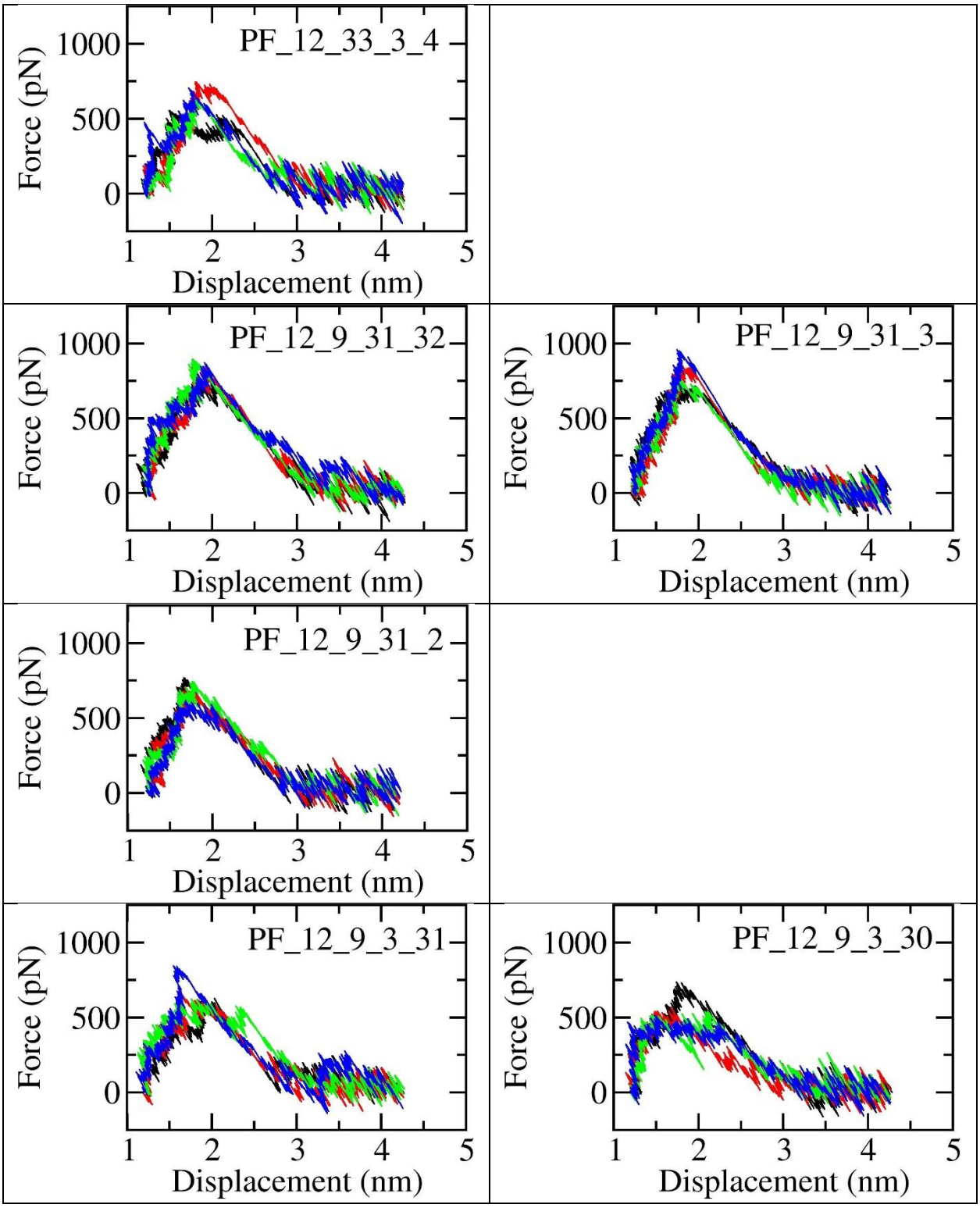

PF_3_4_10
PF_12_33_3
PF_12_33_9
PF_12_33_32
PF_12_33_33
PF_12_33_5
Force (pN)
Displacement (nm)
1000
500
0
1
2
3
4
5


PF_12_9_31
PF_12_9_3
PF_12_9_5
PF_12_9_32
PF_12_9_33
PF_12_9_12
PF_12_9_2
Force (pN)
Displacement (nm)
0
500
1000
1
2
3
4
5


PF_3_4_62_33
PF_3_4_62_12
PF_3_4_62_32
PF_3_4_62_10
PF_3_4_32_32
PF_3_4_32_10
PF_3_4_7_30
PF_3_4_7_9
Force (pN)
Displacement (nm)
0
500
1000
1
2
3
4
5


PF_3_4_7_31
PF_3_4_7_32
PF_3_4_7_11
PF_3_4_33_32
PF_3_4_33_31
PF_3_4_33_12
Force (pN)
Displacement (nm)
0
500
1000
1
2
3
4
5


PF_3_4_31_32
PF_3_4_31_10
PF_3_4_31_12
PF_12_33_3_32
PF_12_33_3_31
PF_12_33_3_8
PF_12_33_3_2
Force (pN)
Displacement (nm)
0
500
1000
1
2
3
4
5


PF_12_33_3_4
PF_12_9_31_32
PF_12_9_31_3
PF_12_9_31_2
PF_12_9_3_31
PF_12_9_3_30
Force (pN)
Displacement (nm)
0
500
1000
1
2
3
4
5

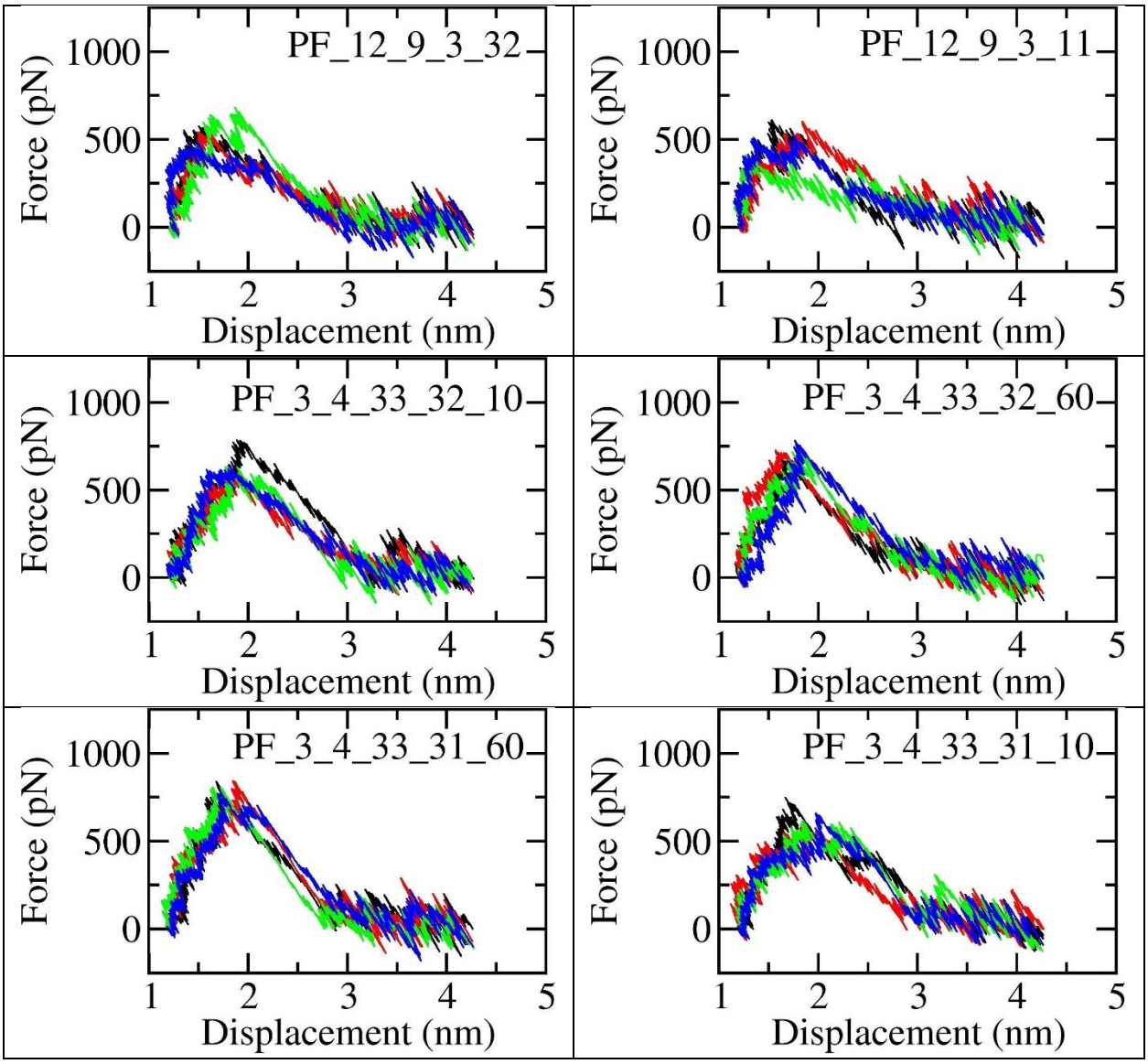
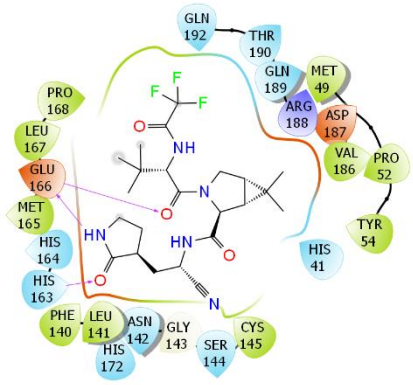
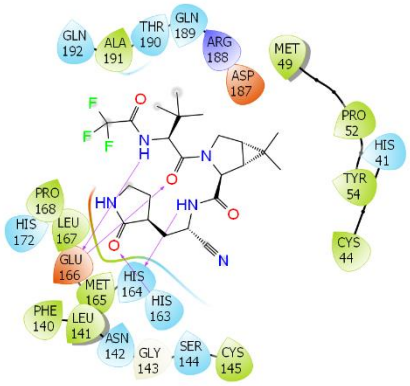
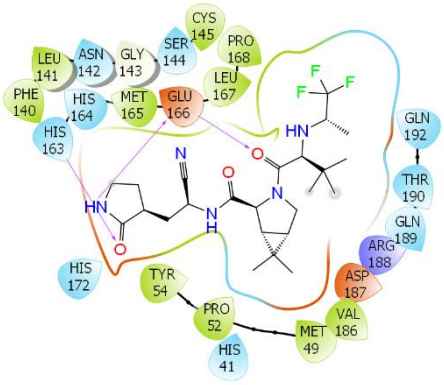
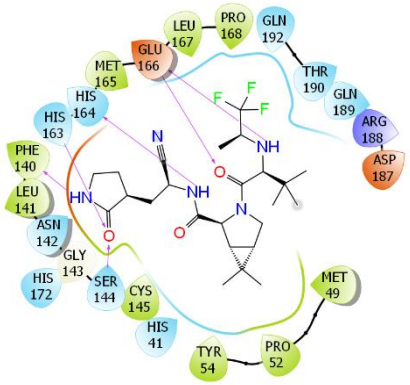
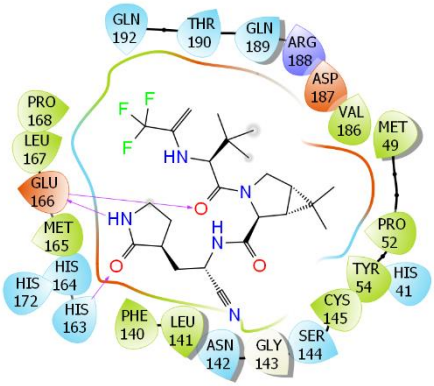
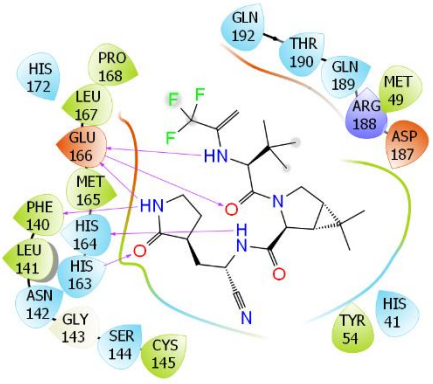
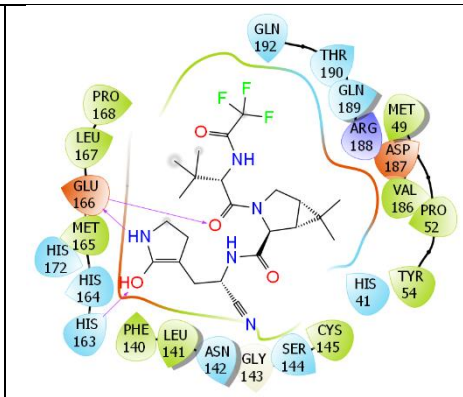
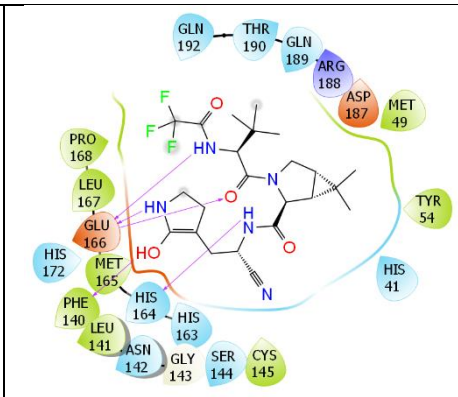
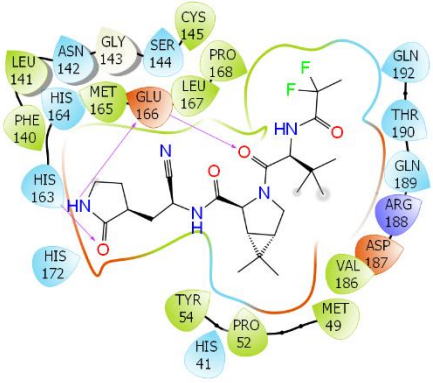
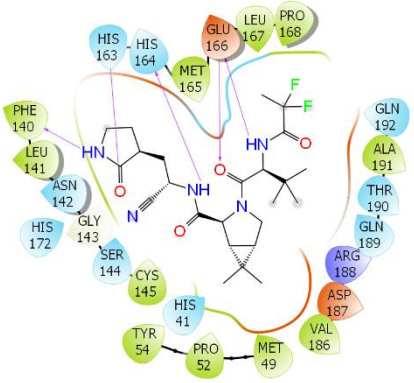
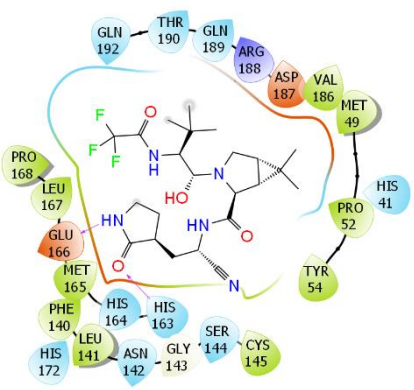
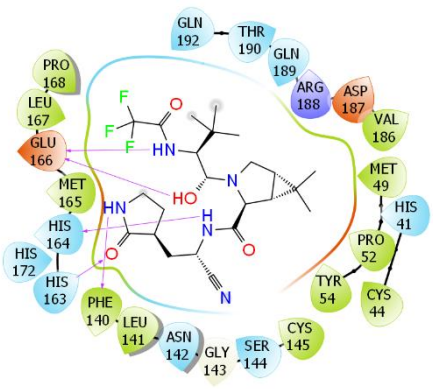
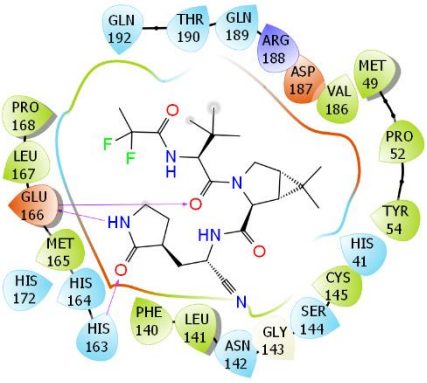
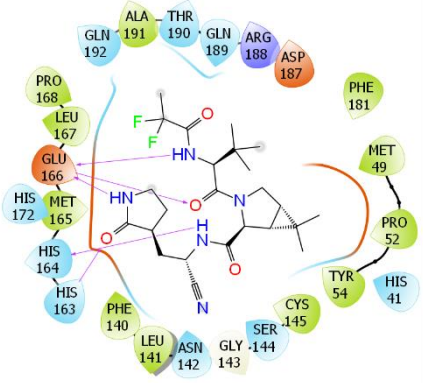

PF_12_9_3_32
PF_12_9_3_11
PF_3_4_33_32_10
PF_3_4_33_32_60
PF_3_4_33_31_60
PF_3_4_33_31_10
Force (pN)
Displacement (nm)
0
500
1000
1
2
3
4
5

**Table S7**. The 2D interaction diagram between SARS-CoV-2 Mpro + ligand.

| N[0] | Name | Initial Structure[a] | MD-refined structure[b] |
|---|---|---|---|
| 1 | PF-07321332 |  |  |
| 2 | PF_9b |  |  |
| 3 | PF_9a |  |  |

| | | | |
|---|---|---|---|
| **4** | **PF_3** |  |  |
| **5** | **PF_35** |  |  |
| **6** | **PF_12** |  |  |
| **7** | **PF_33** |  |  |

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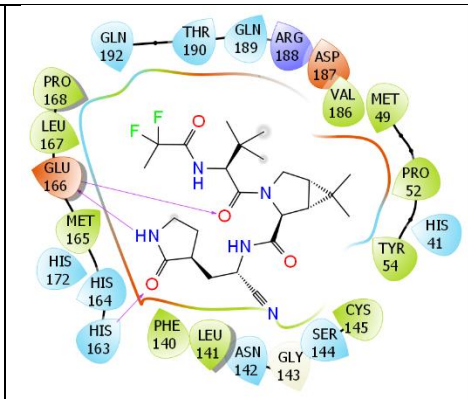
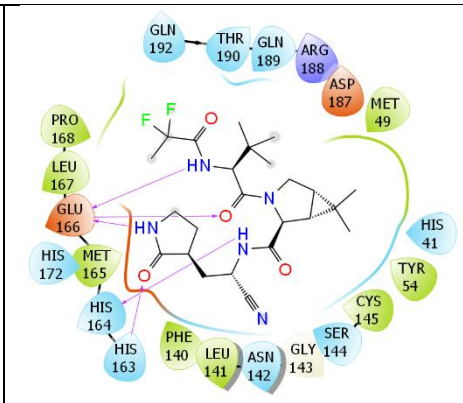
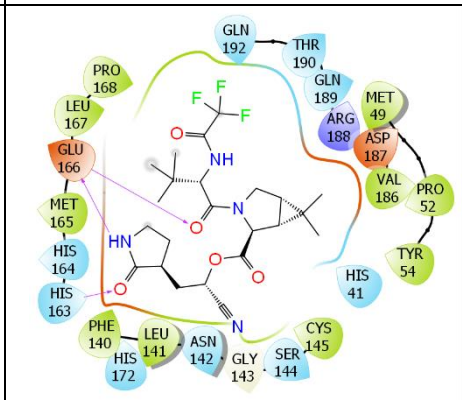
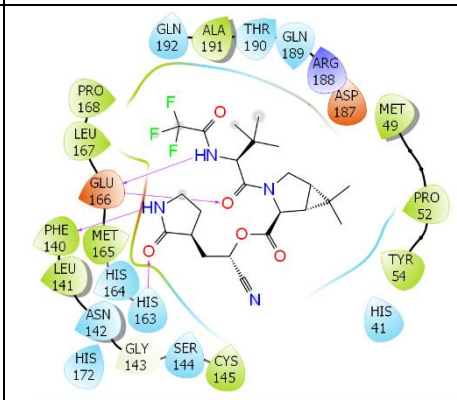
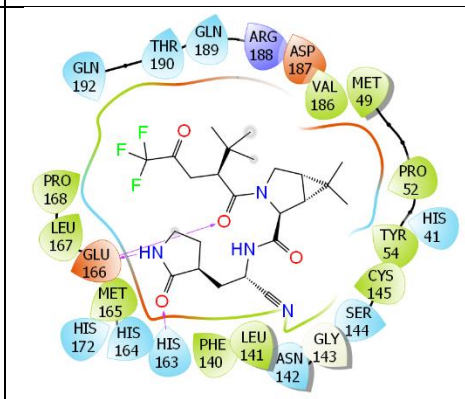
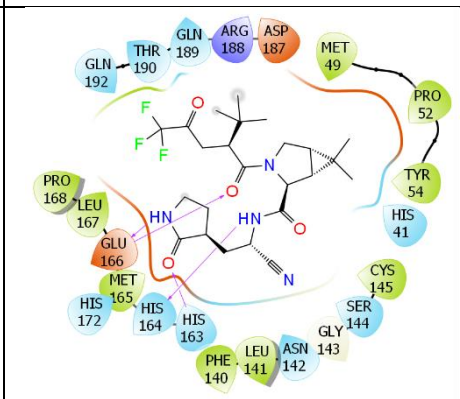
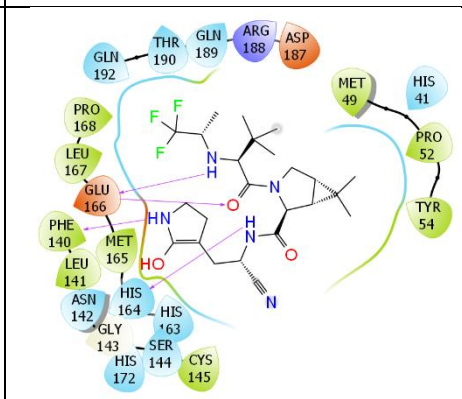
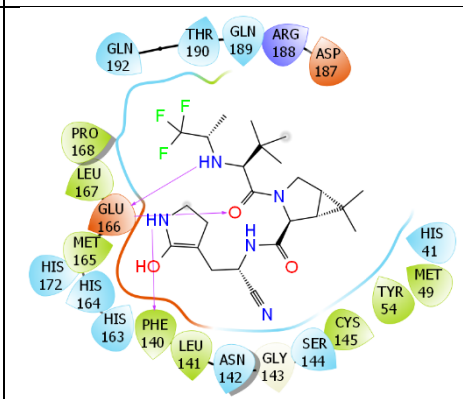
| **8** | **PF_34** |  |  |
| **9** | **PF_2** |  |  |
| **10** | **PF_14** |  |  |
| **11** | **PF_9b_3** |  |  |

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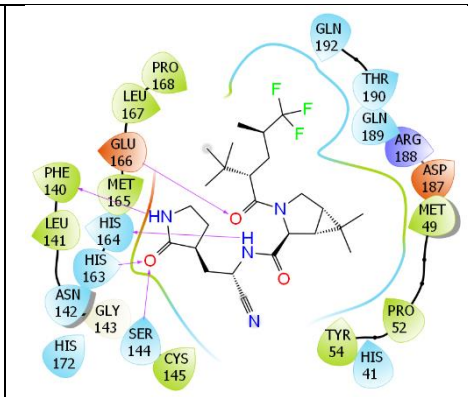
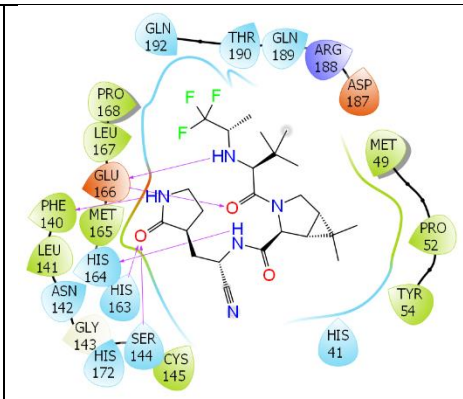
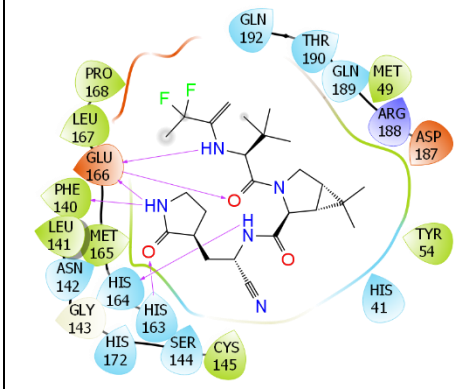
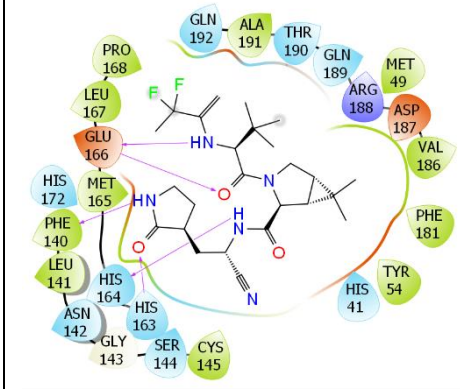
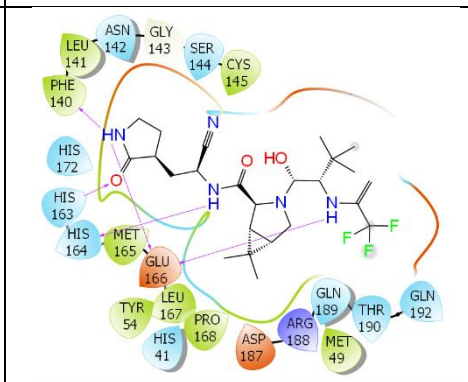
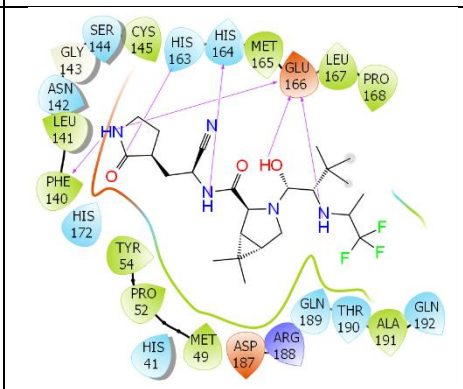
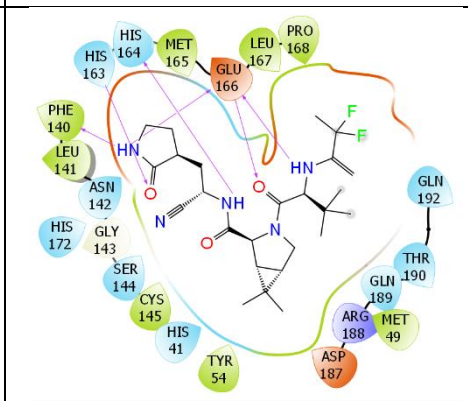
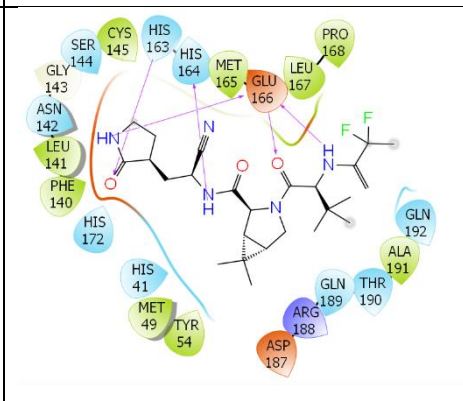
| **12** | **PF_9b_13** |  |  |
| **13** | **PF_9a_33** |  |  |
| **14** | **PF_9a_11** |  |  |
| **15** | **PF_9a_32** |  |  |

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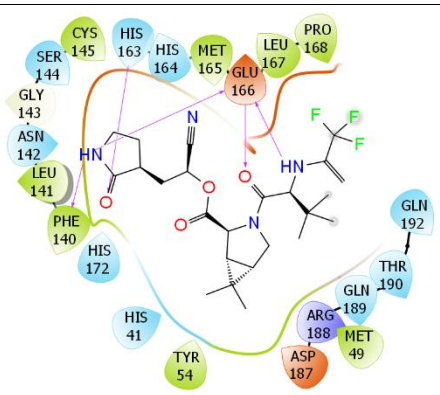
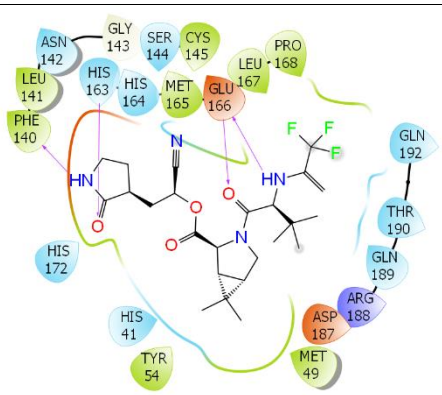
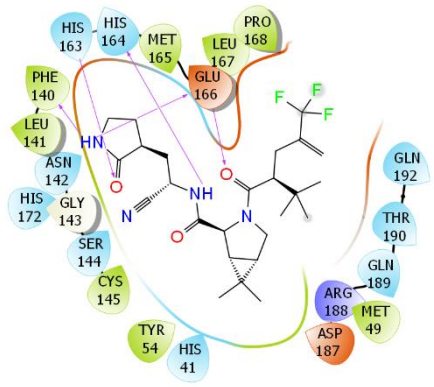
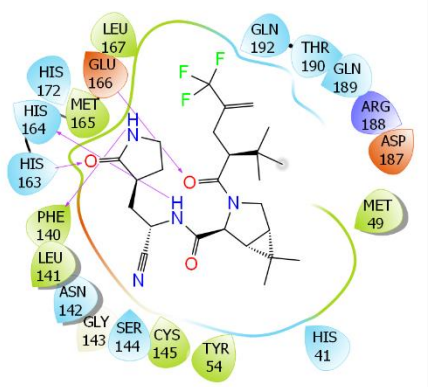
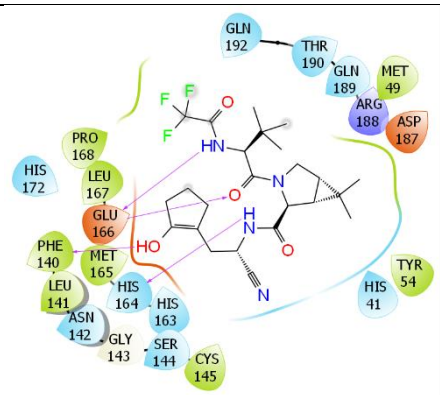
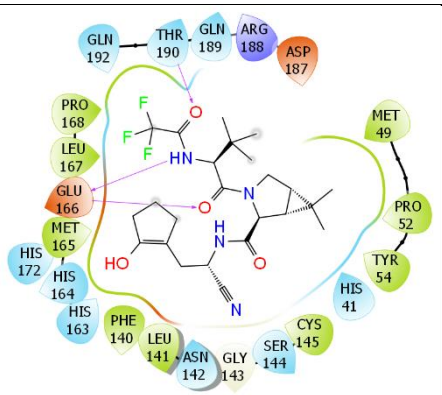
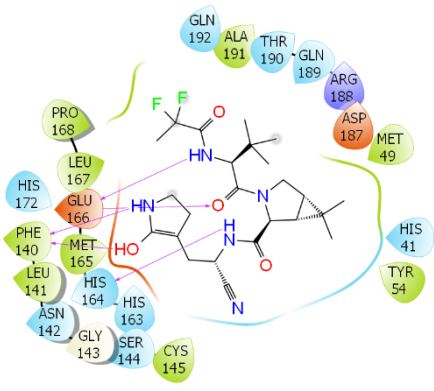
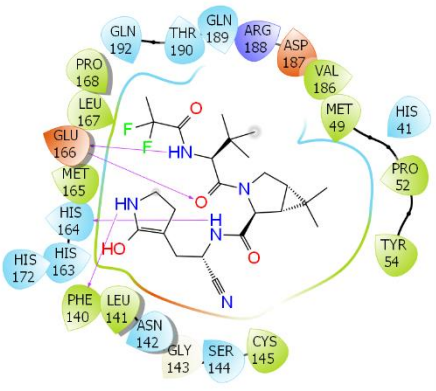
| **16** | **PF_9a_2** |  |  |
| **17** | **PF_9a_13** |  |  |
| **18** | **PF_3_4** |  |  |
| **19** | **PF_3_34** |  |  |

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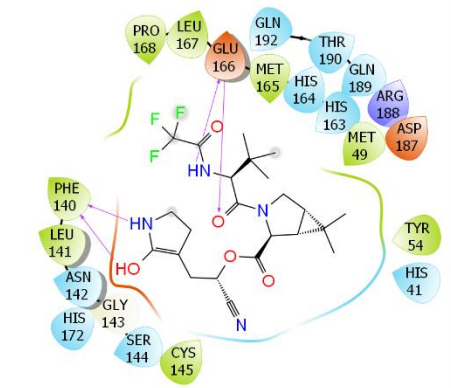
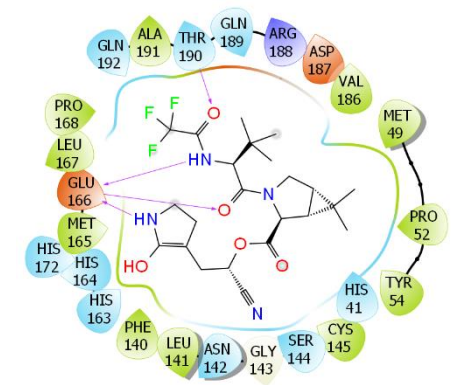
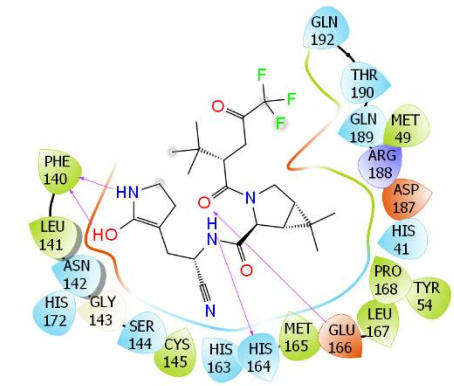
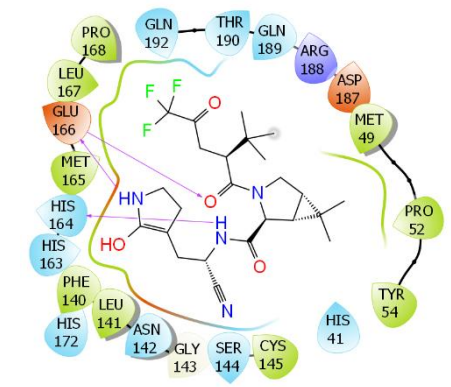
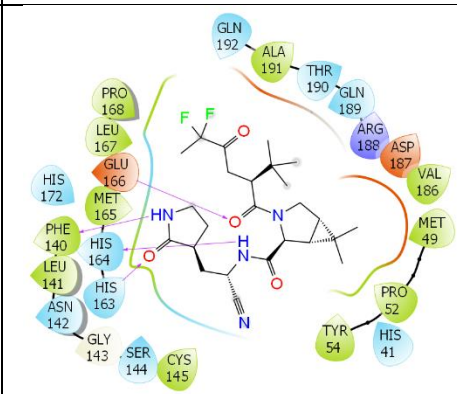
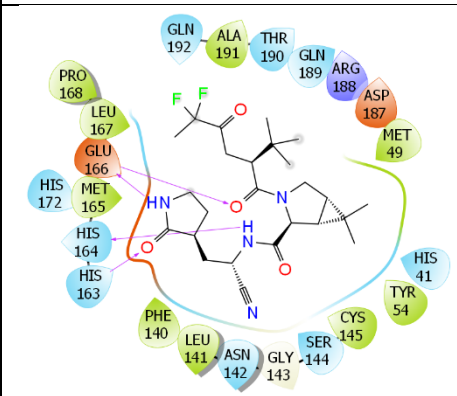
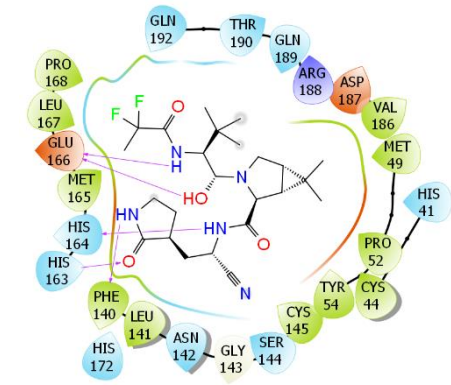
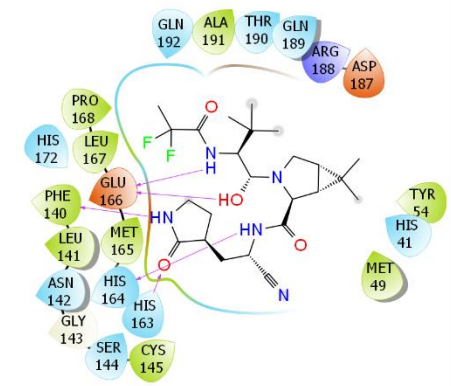
| **20** | **PF_3_2** |  |  |
| **21** | **PF_3_13** |  |  |
| **22** | **PF_35_14** |  |  |
| **23** | **PF_12_33** |  |  |

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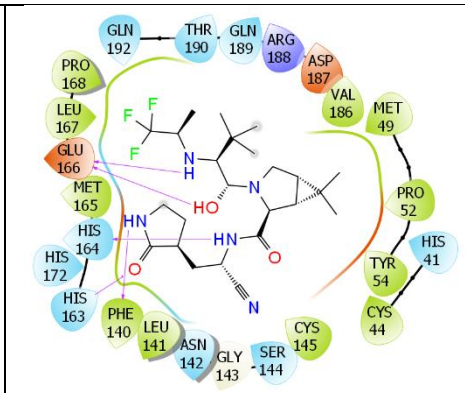
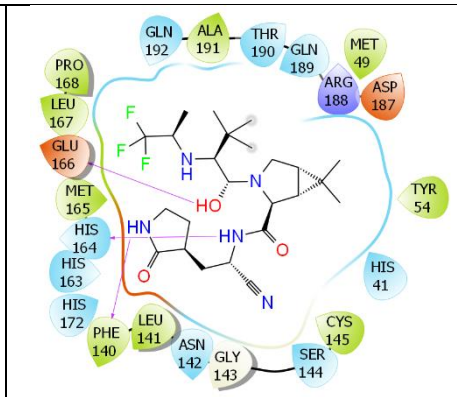
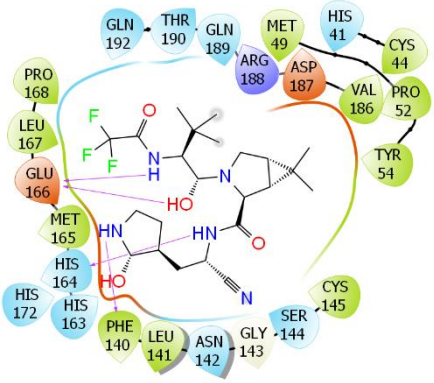
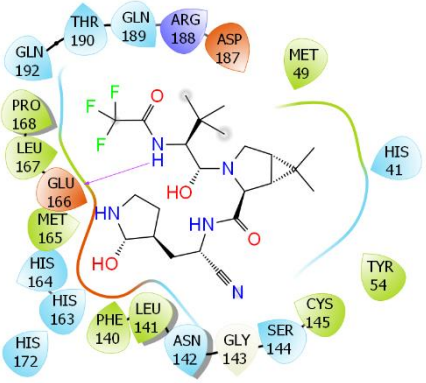
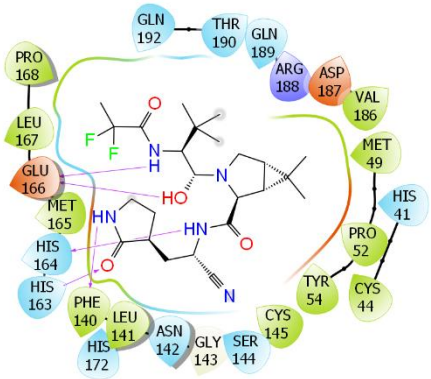
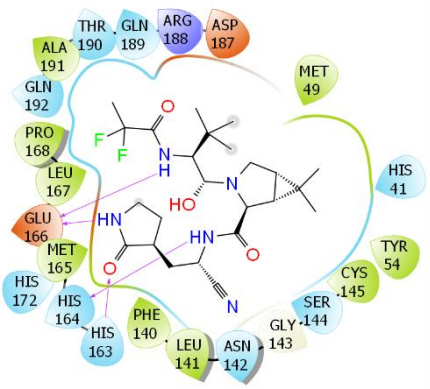
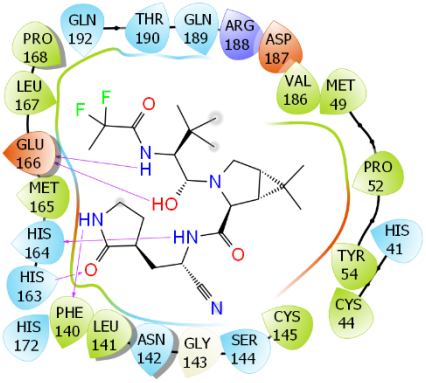
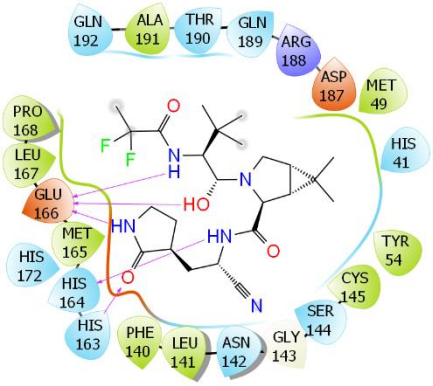
| **24** | **PF_12_9** |  |  |
| **25** | **PF_12_3** |  |  |
| **26** | **PF_12_32** |  |  |
| **27** | **PF_12_34** |  |  |

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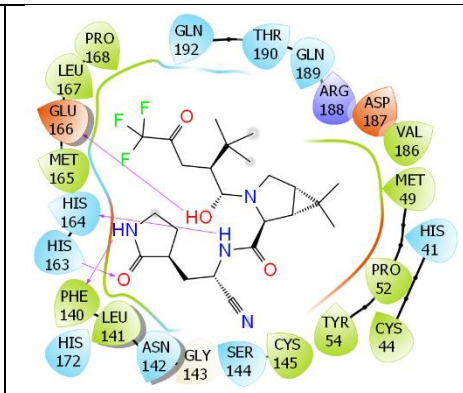
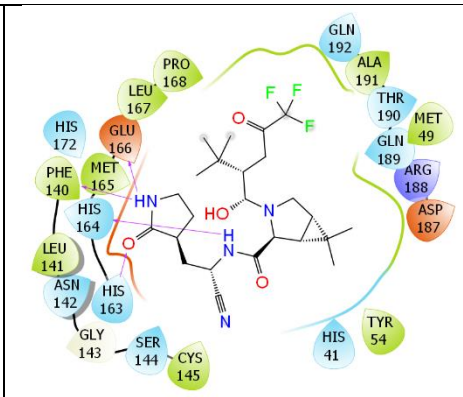
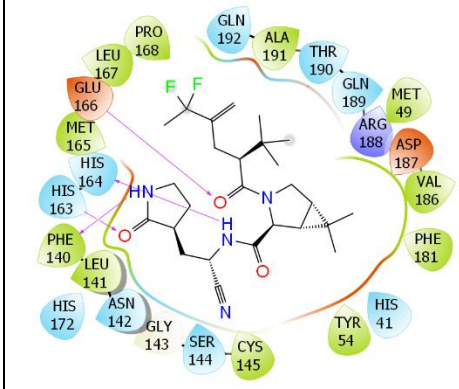
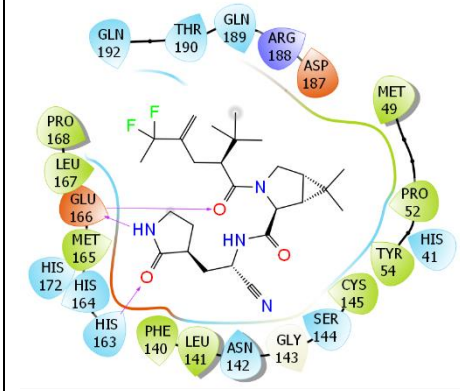
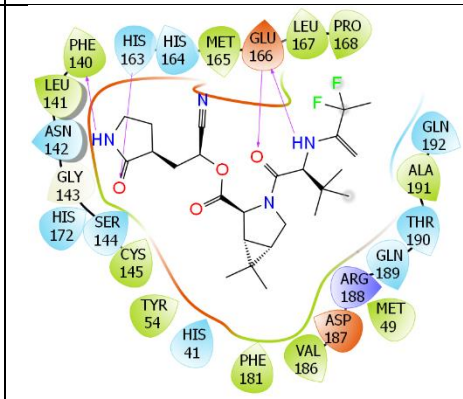
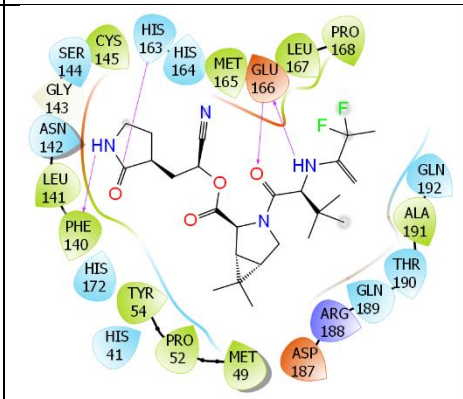
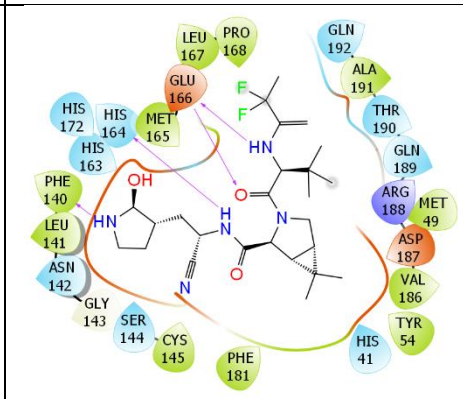
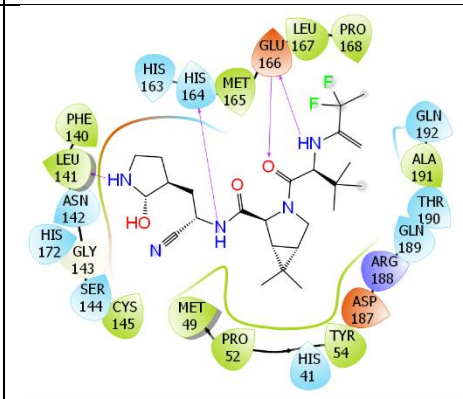
| **28** | **PF_12_13** |  |  |
| **29** | **PF_9a_33_13** |  |  |
| **30** | **PF_9a_33_2** |  |  |
| **31** | **PF_9a_33_3** |  |  |

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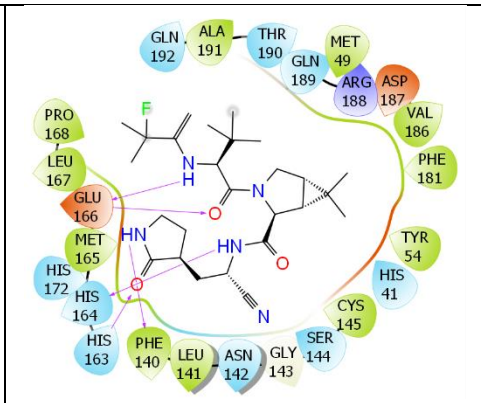
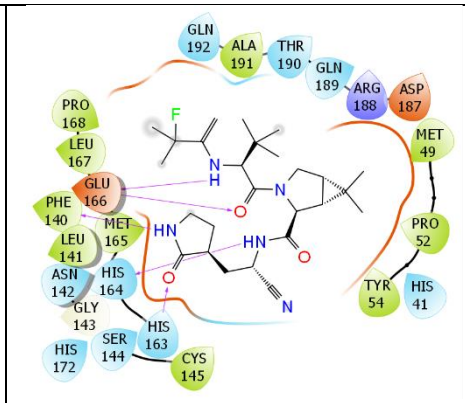
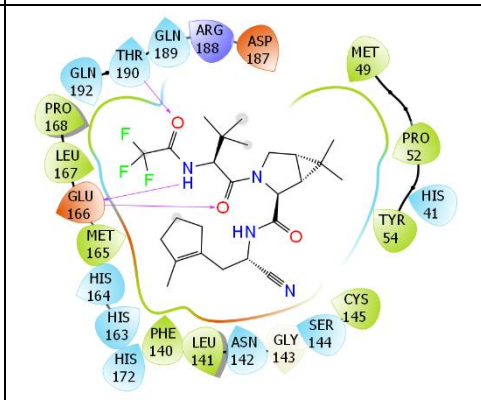
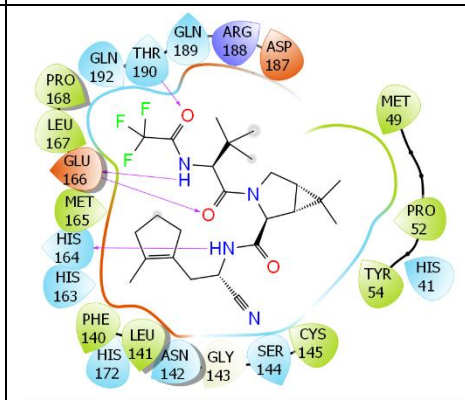
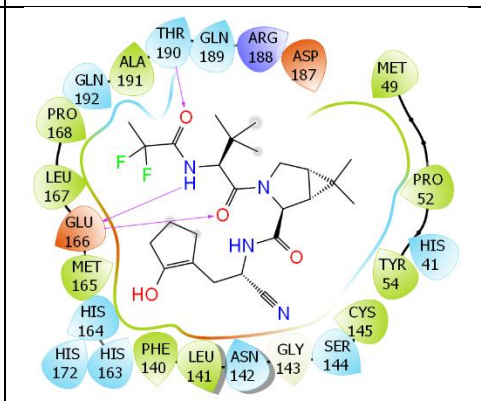
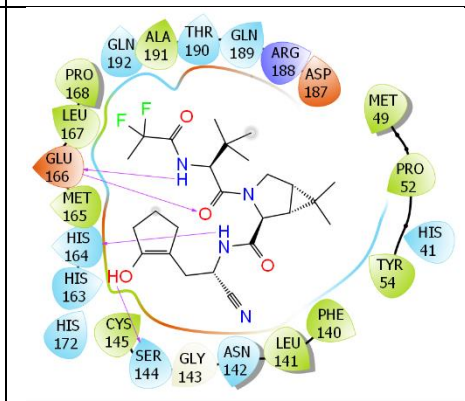
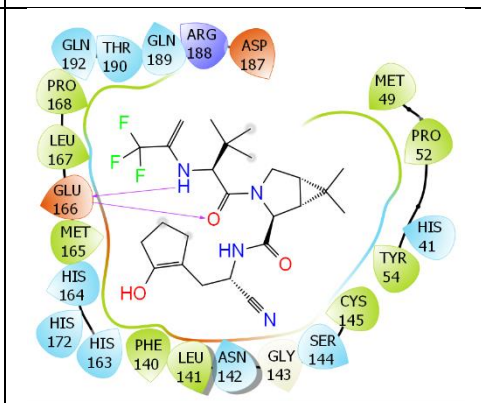
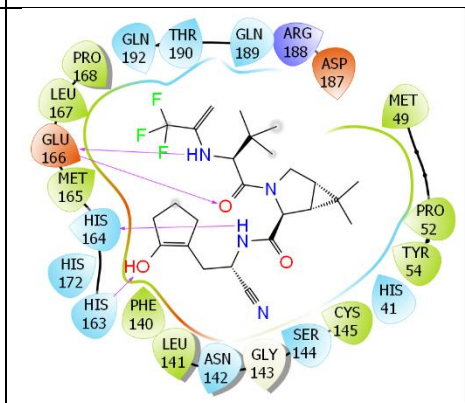
| **32** | **PF_9a_33_32** |  |  |
| **33** | **PF_3_4_62** |  |  |
| **34** | **PF_3_4_32** |  |  |
| **35** | **PF_3_4_7** |  |  |

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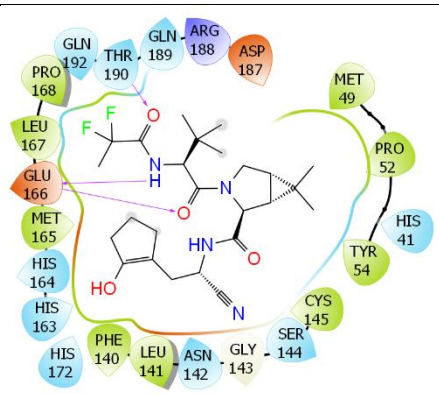
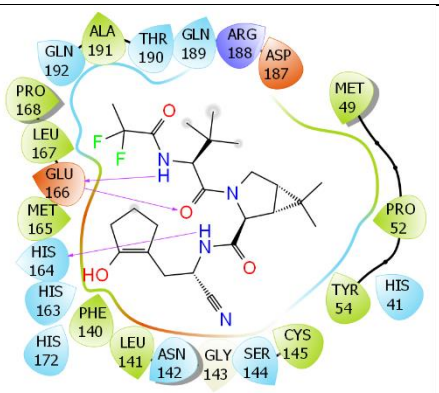
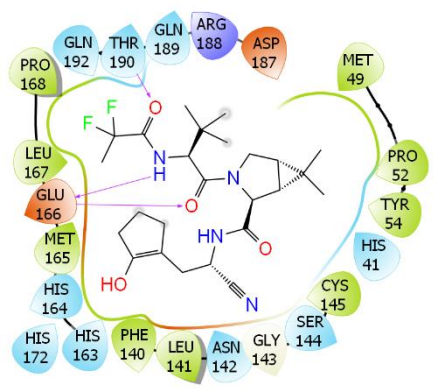
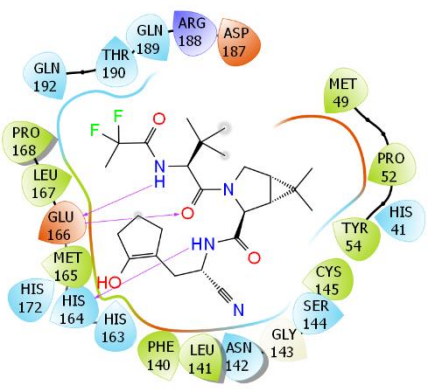
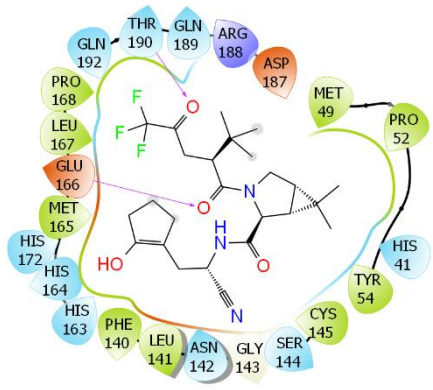
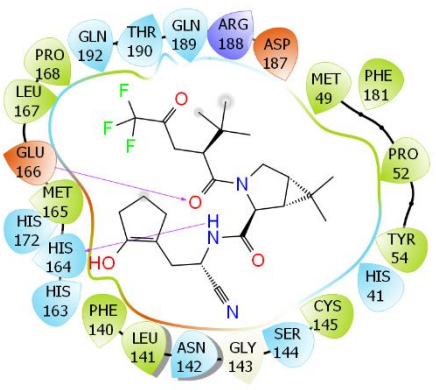
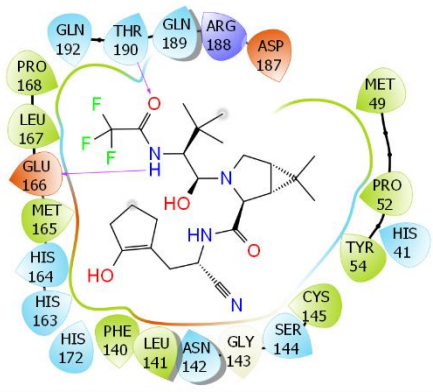
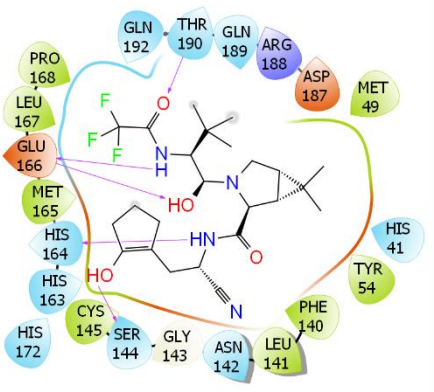
| **36** | **PF_3_4_33** |  |  |
| **37** | **PF_3_4_31** |  |  |
| **38** | **PF_3_4_12** |  |  |
| **39** | **PF_3_4_10** |  |  |

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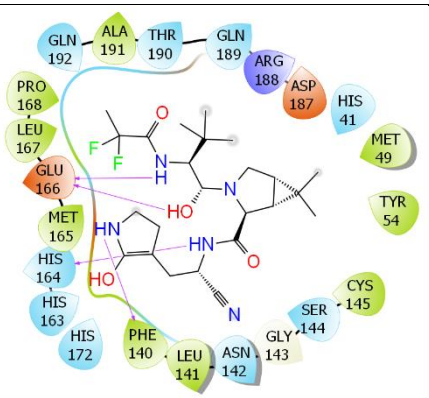
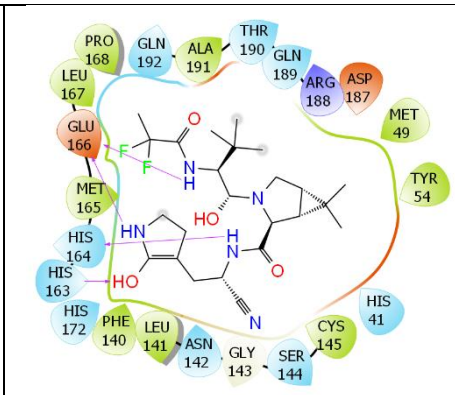
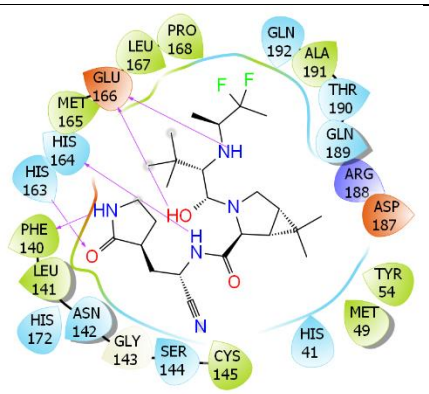
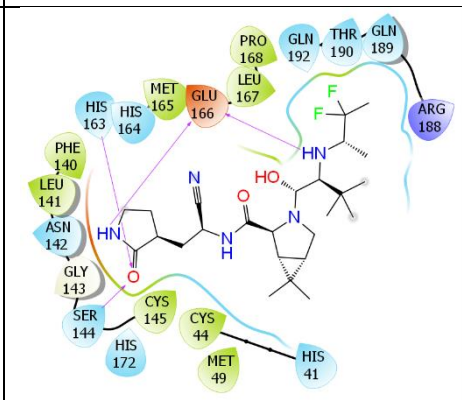
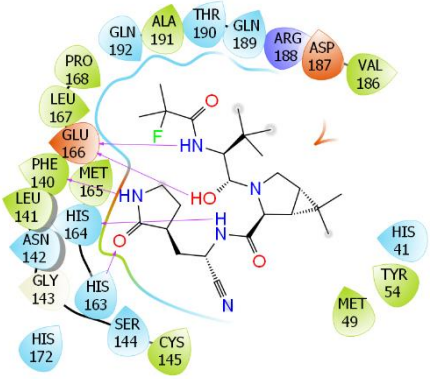
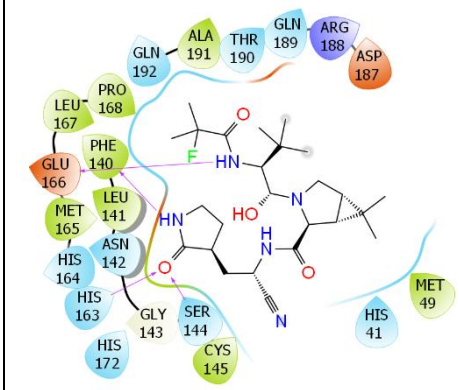
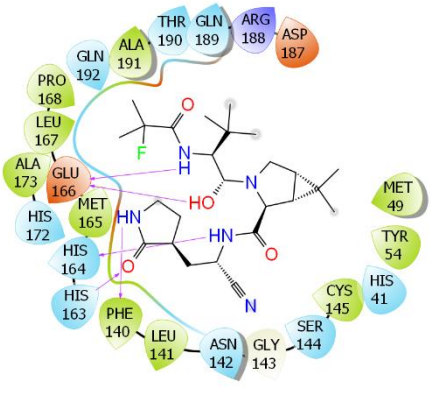
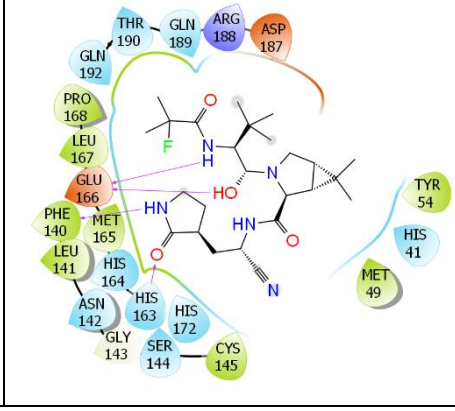
| **40** | **PF_12_33_3** |  |  |
| **41** | **PF_12_33_9** |  |  |
| **42** | **PF_12_33_32** |  |  |
| **43** | **PF_12_33_33** |  |  |

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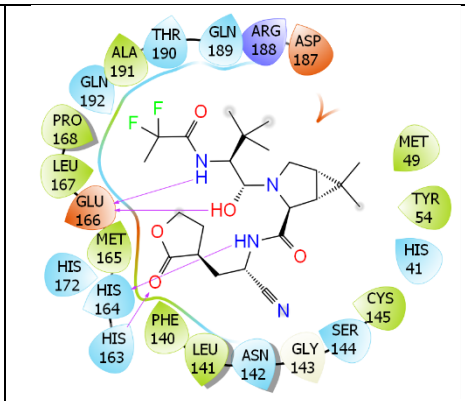
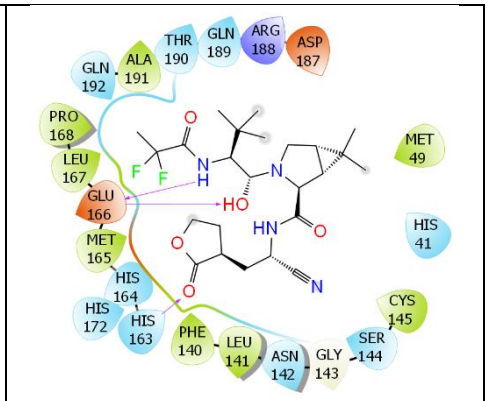
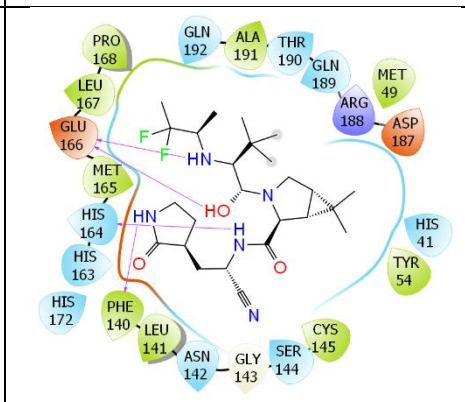
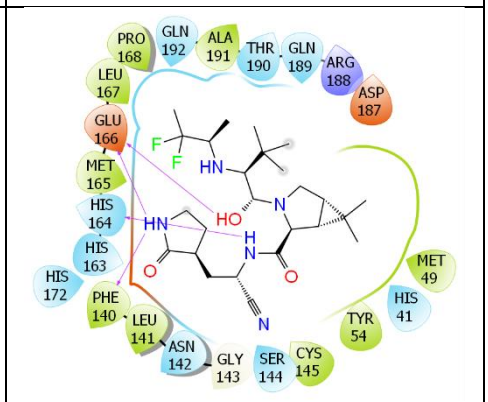
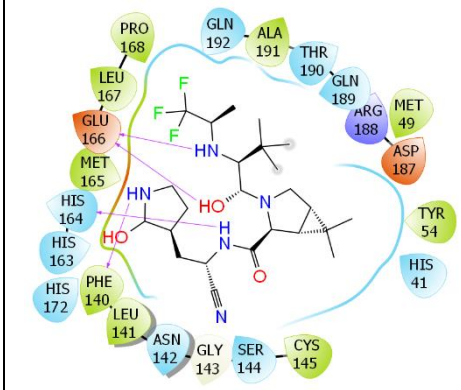
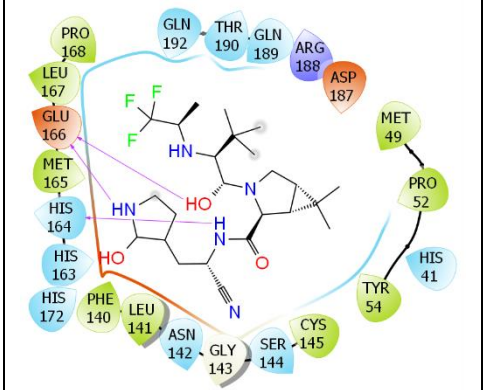
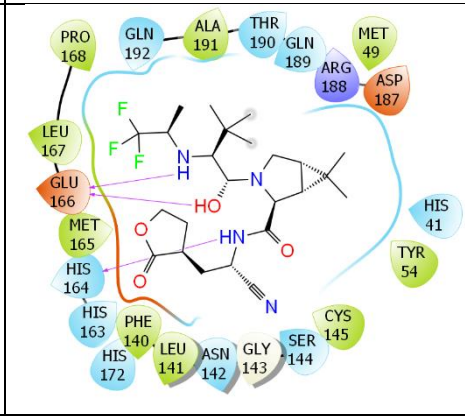
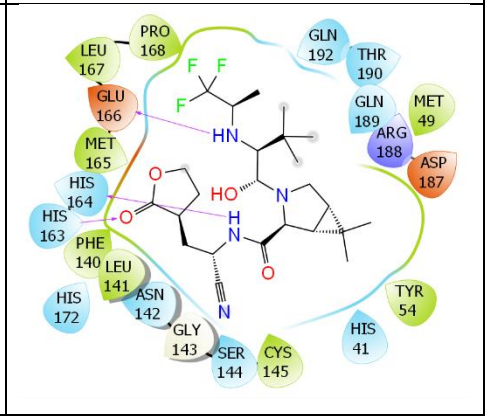
| **44** | **PF_12_33_5** |  |  |
| **45** | **PF_12_9_31** |  |  |
| **46** | **PF_12_9_3** |  |  |
| **47** | **PF_12_9_5** |  |  |

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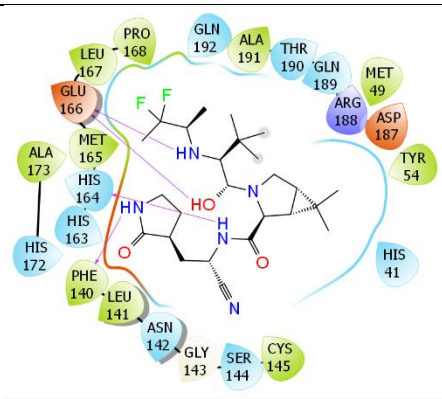
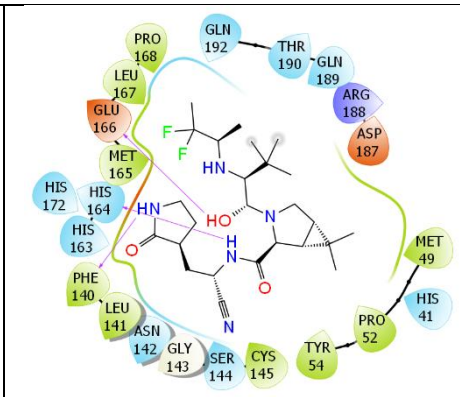
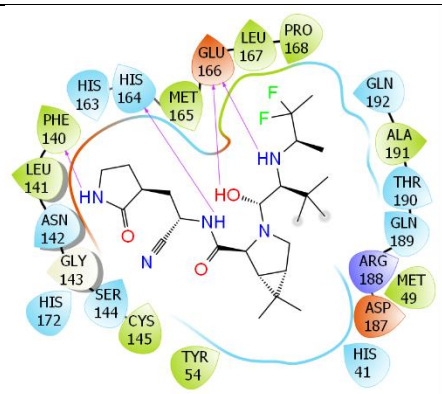
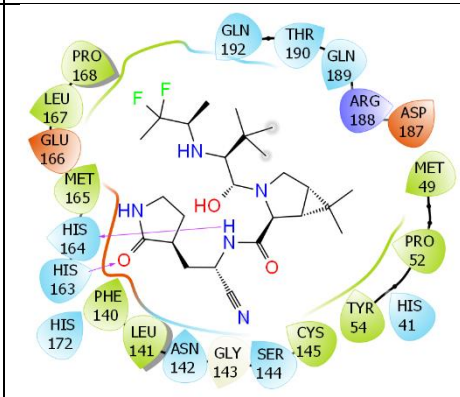
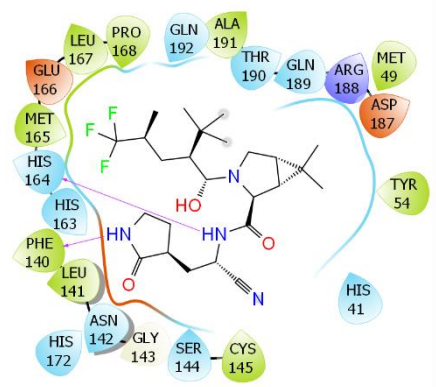
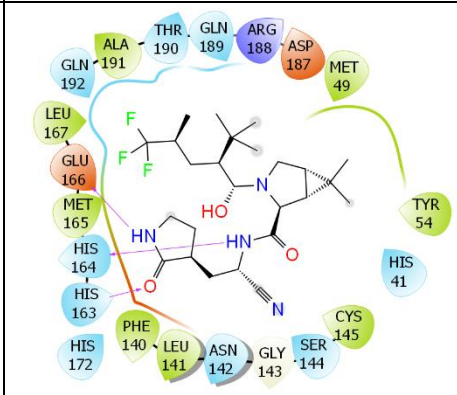
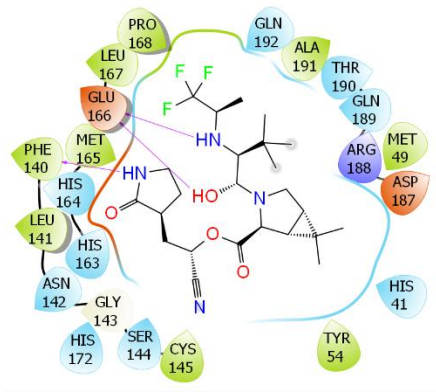
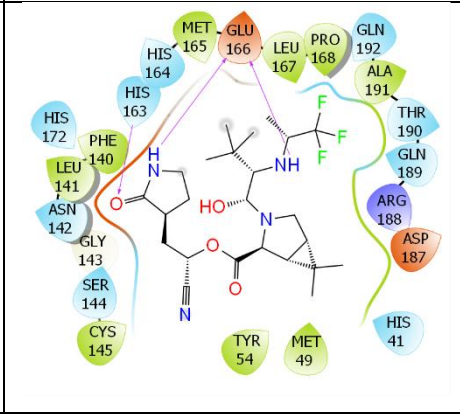
| **48** | **PF_12_9_32** |  |  |
| **49** | **PF_12_9_33** |  |  |
| **50** | **PF_12_9_12** |  |  |
| **51** | **PF_12_9_2** |  |  |

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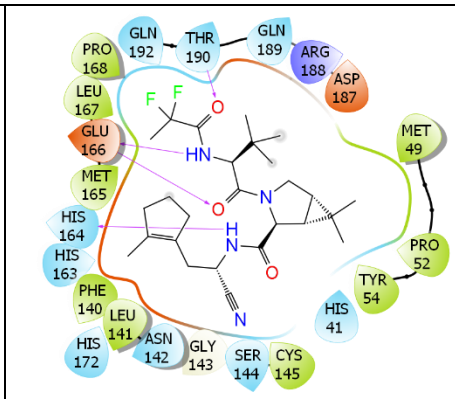
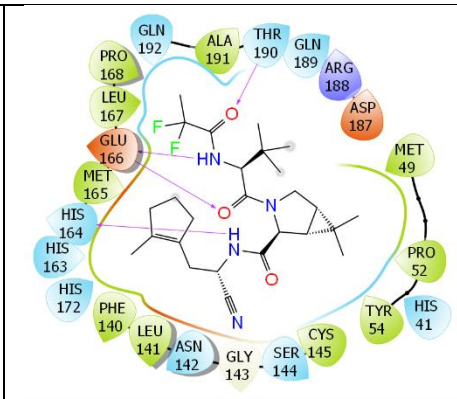
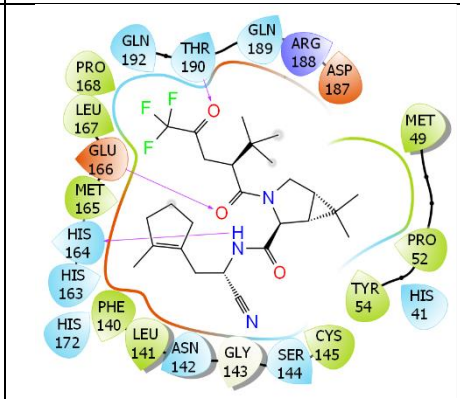
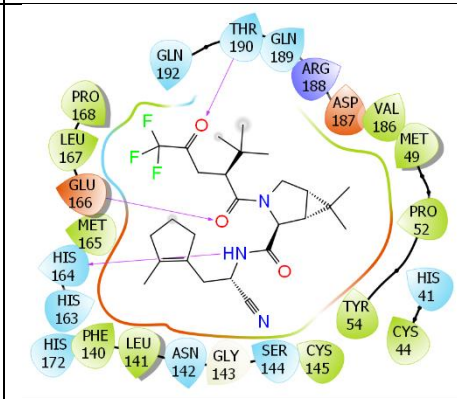
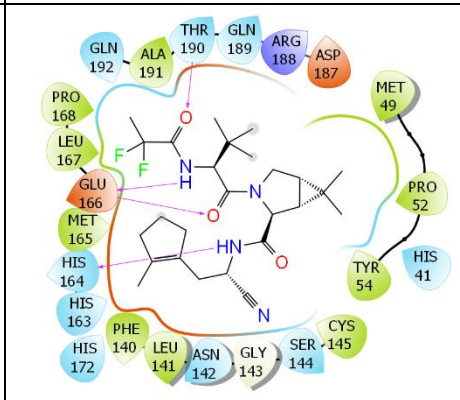
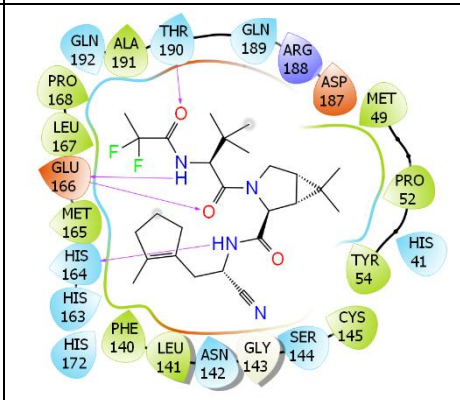
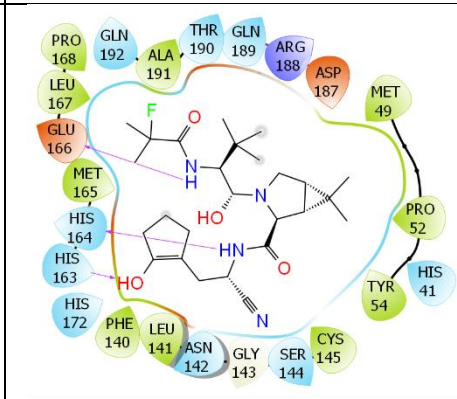
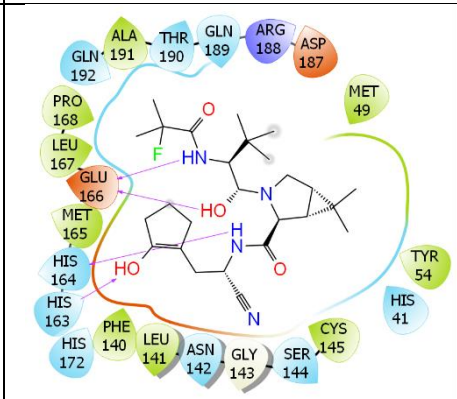
| **52** | **PF_3_4_62_33** |  |  |
| **53** | **PF_3_4_62_12** |  |  |
| **54** | **PF_3_4_62_32** |  |  |
| **55** | **PF_3_4_62_10** |  |  |

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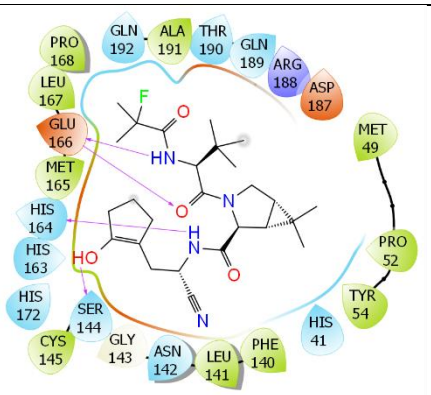
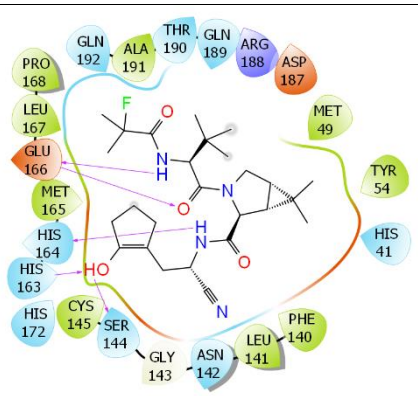
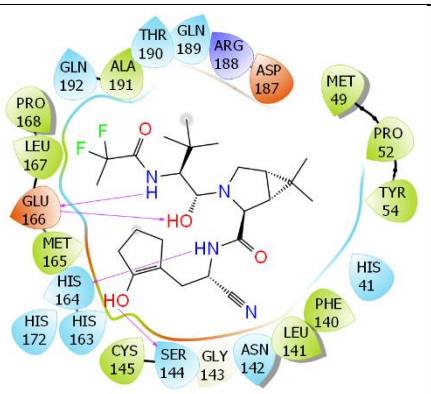
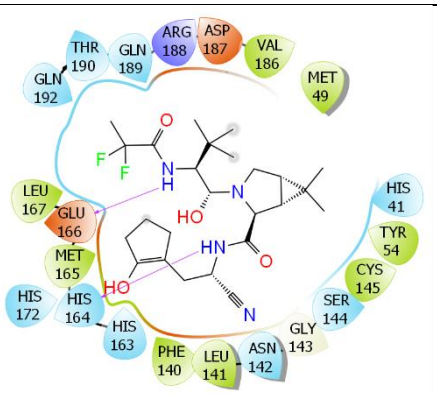
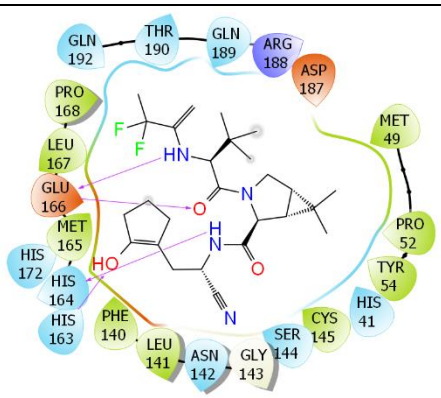
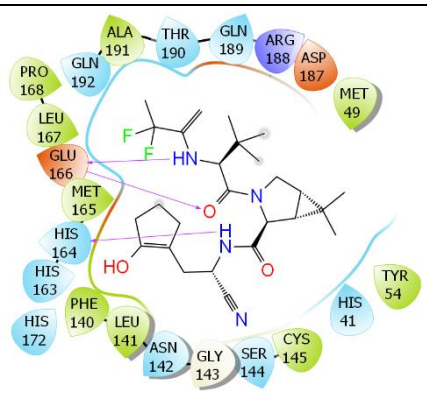
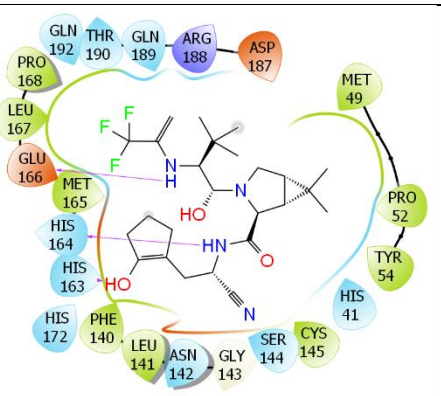
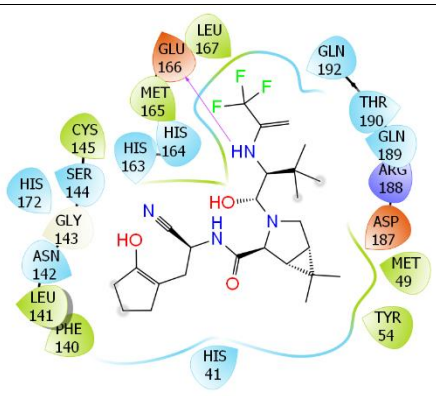
| **56** | **PF_3_4_32_32** |  |  |
| **57** | **PF_3_4_32_10** |  |  |
| **58** | **PF_3_4_7_30** |  |  |
| **59** | **PF_3_4_7_9** |  |  |

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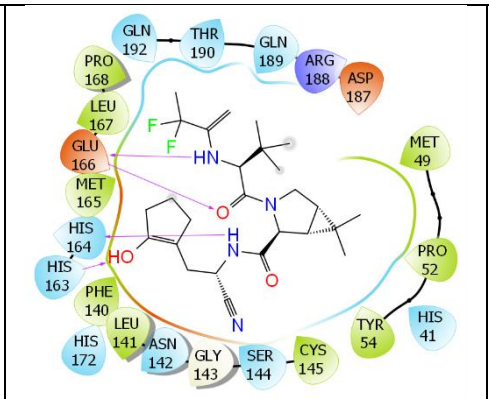
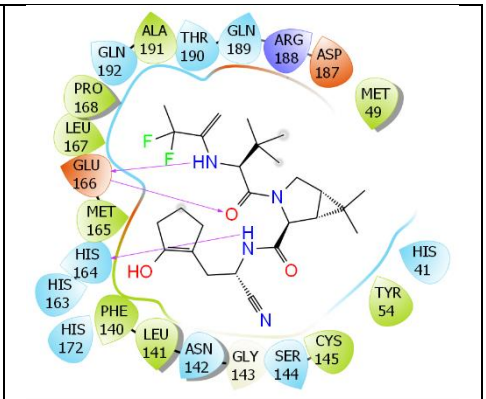
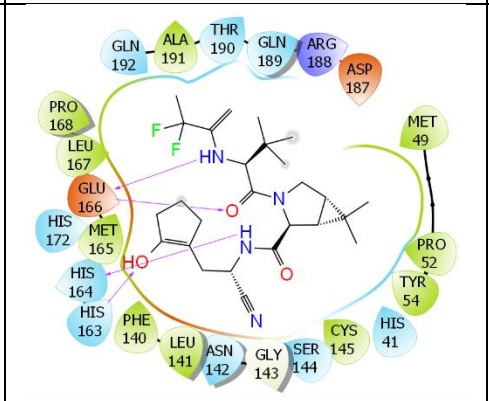
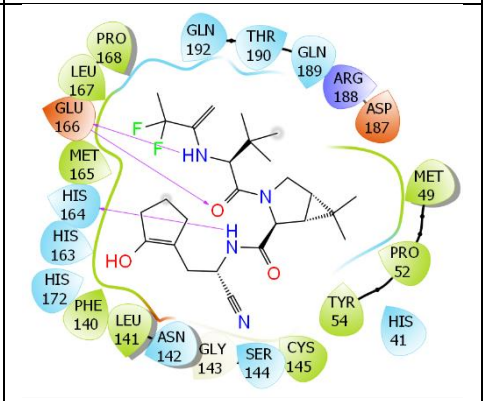
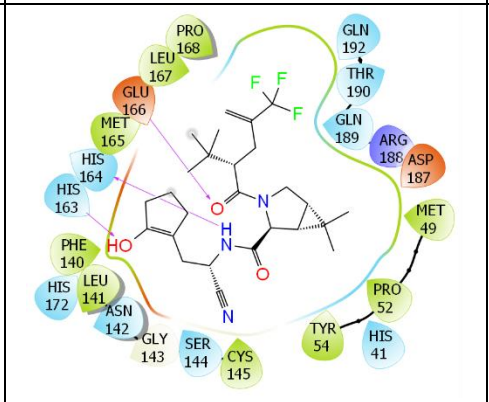
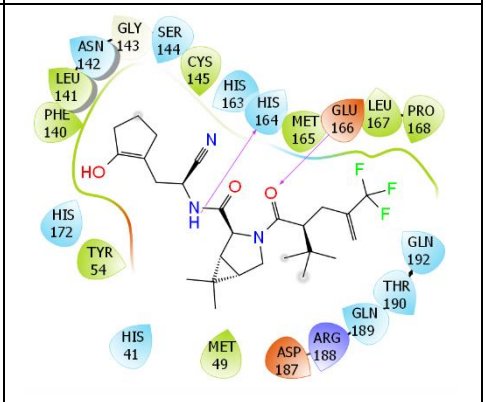
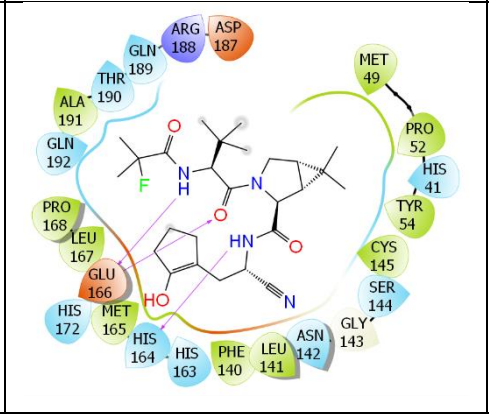
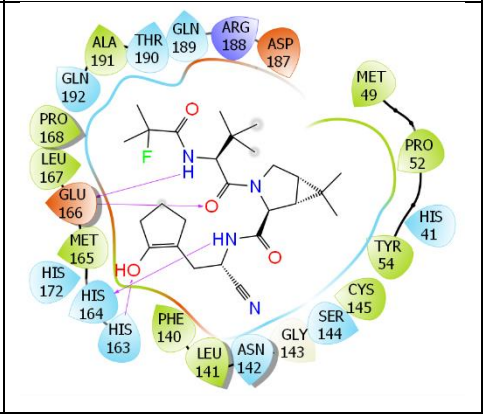
| **60** | **PF_3_4_7_31** |  |  |
| **61** | **PF_3_4_7_32** |  |  |
| **62** | **PF_3_4_7_11** |  |  |
| **63** | **PF_3_4_33_32** |  |  |

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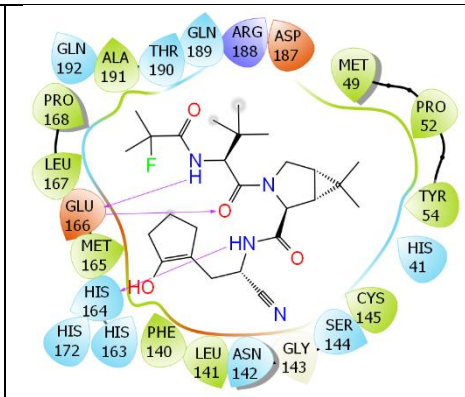
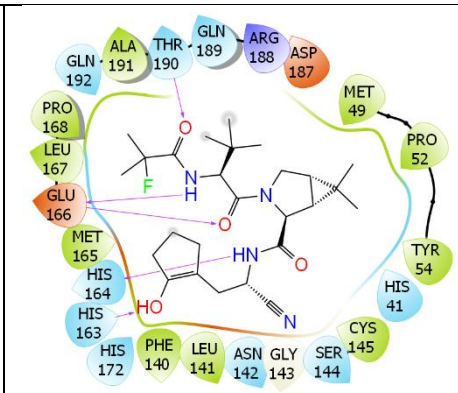
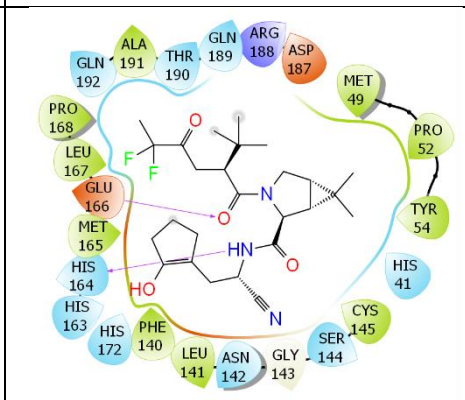
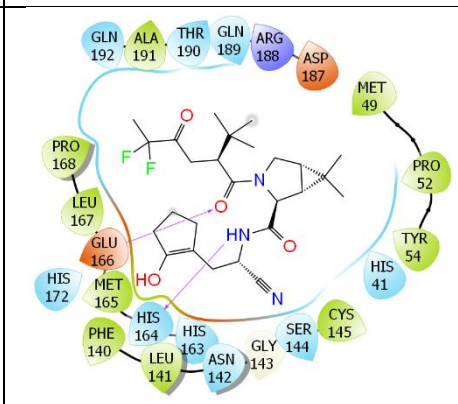
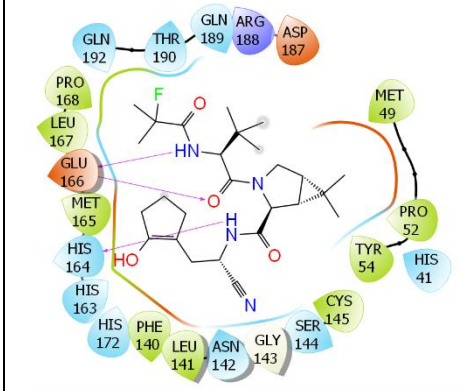
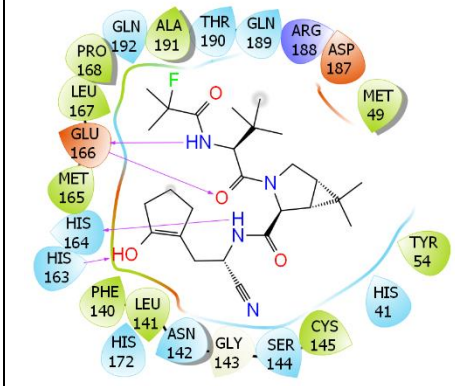
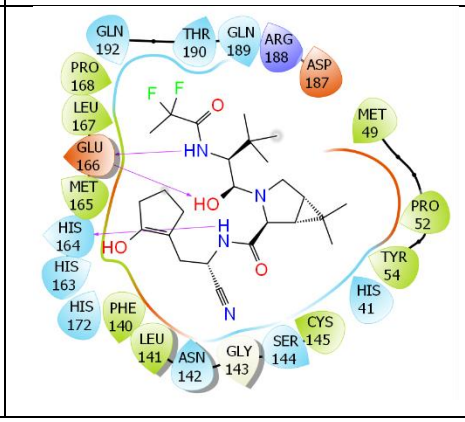
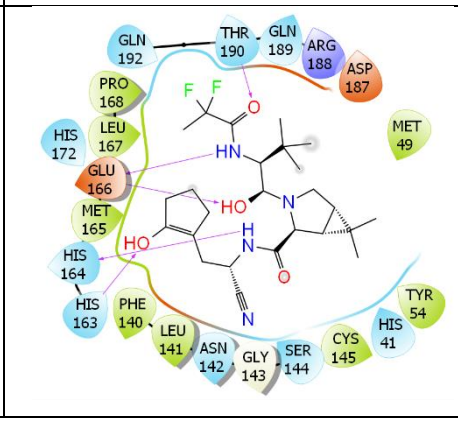
| **64** | **PF_3_4_33_31** |  |  |
| **65** | **PF_3_4_33_12** |  |  |
| **66** | **PF_3_4_31_32** |  |  |
| **67** | **PF_3_4_31_10** |  |  |

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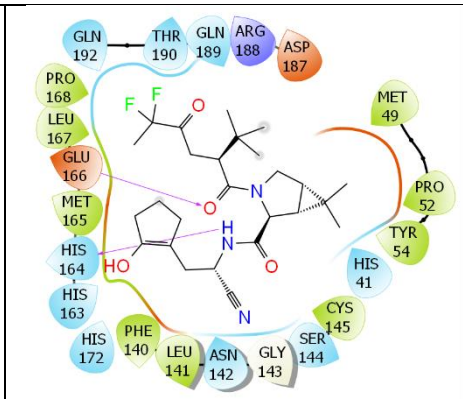
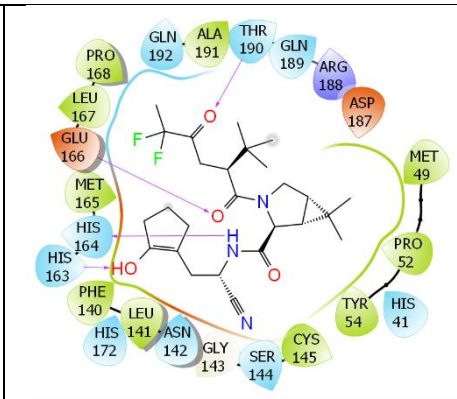
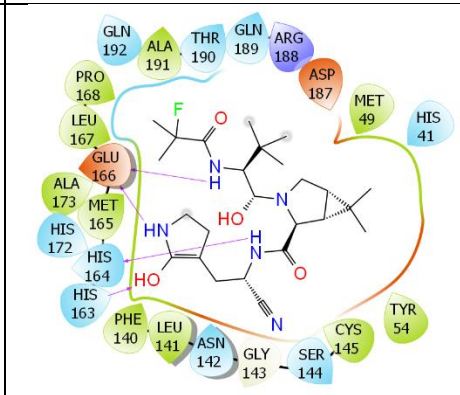
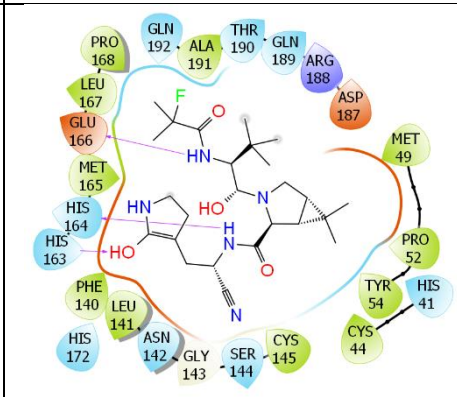
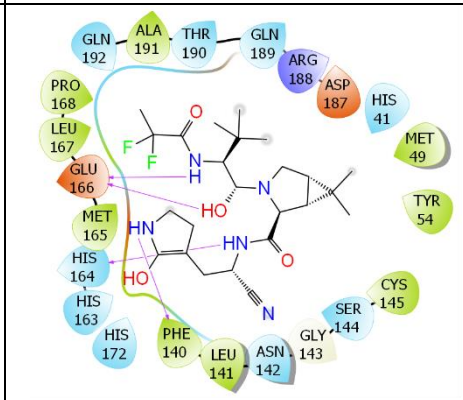
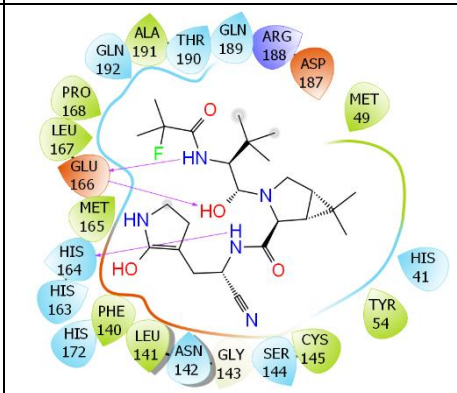
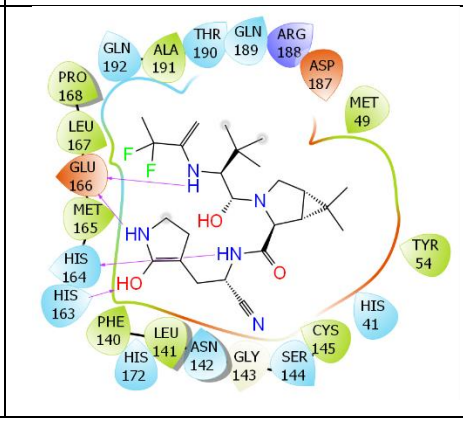
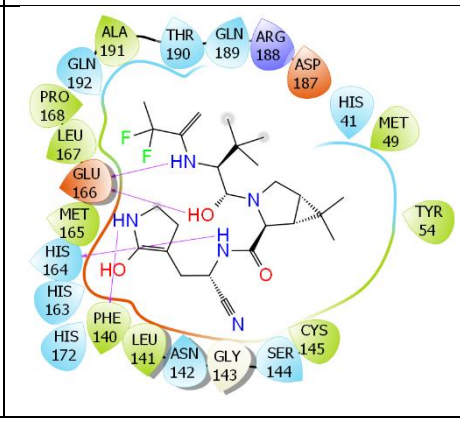
| **68** | **PF_3_4_31_12** |  |  |
| **69** | **PF_12_33_3_32** |  |  |
| **70** | **PF_12_33_3_31** |  |  |
| **71** | **PF_12_33_3_8** |  |  |

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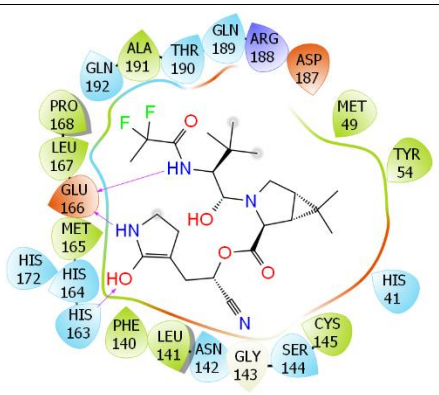
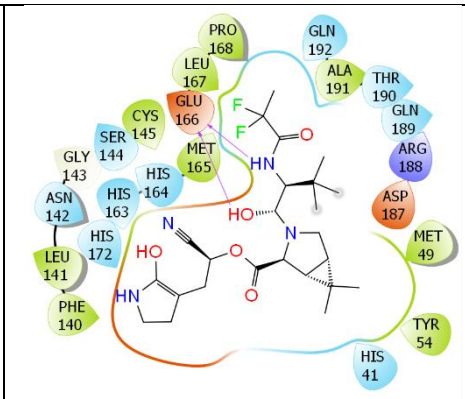
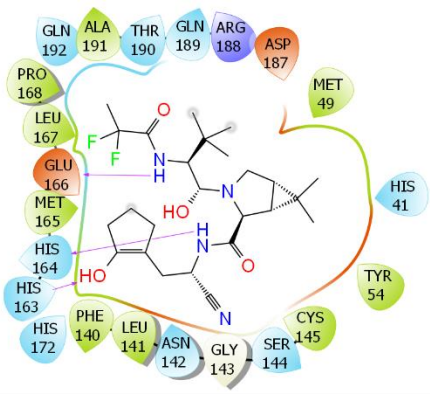
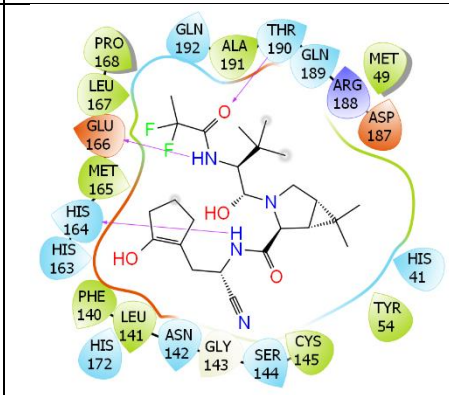
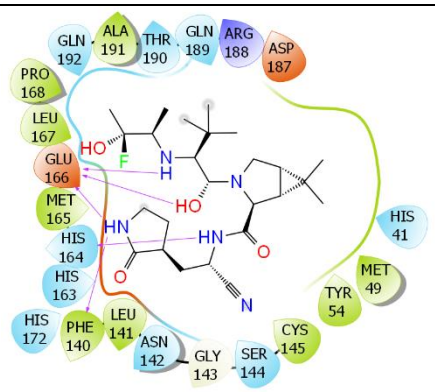
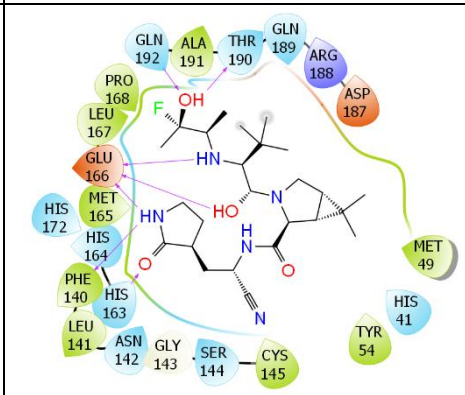
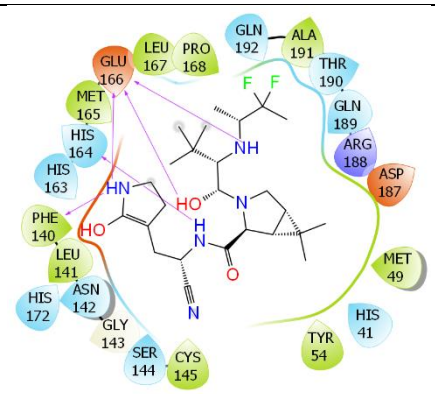
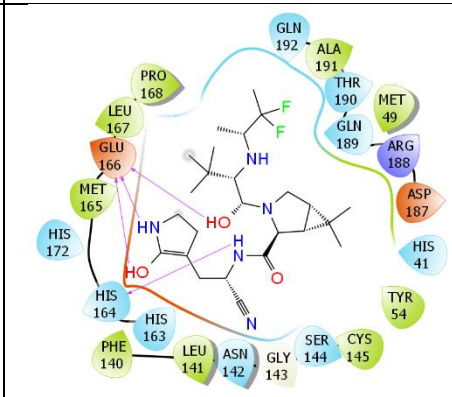
| **72** | **PF_12_33_3_2** |  |  |
| **73** | **PF_12_33_3_4** |  |  |
| **74** | **PF_12_9_31_32** |  |  |
| **75** | **PF_12_9_31_3** |  |  |

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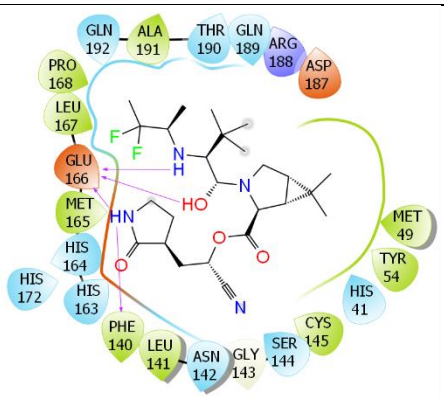
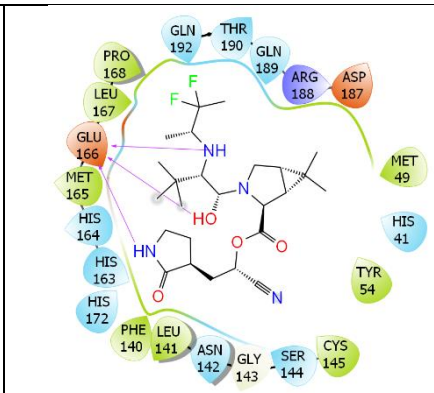
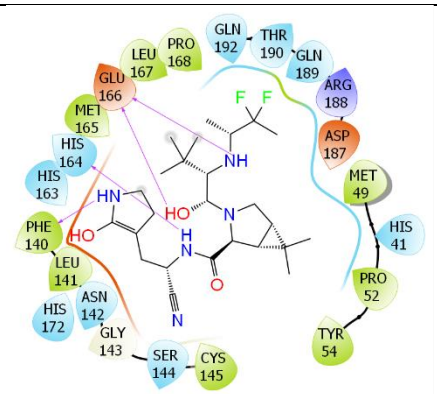
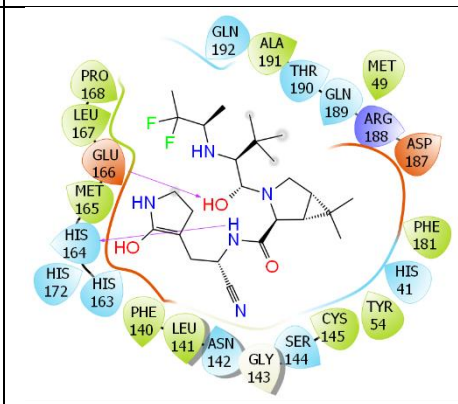
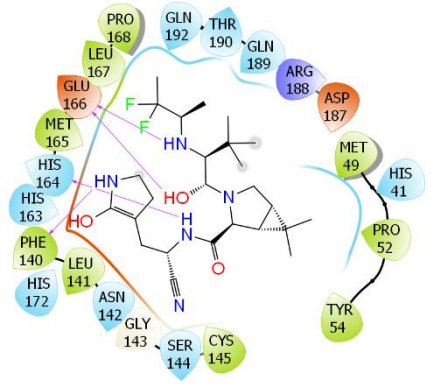
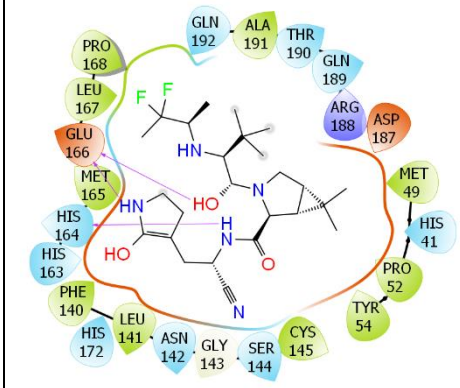
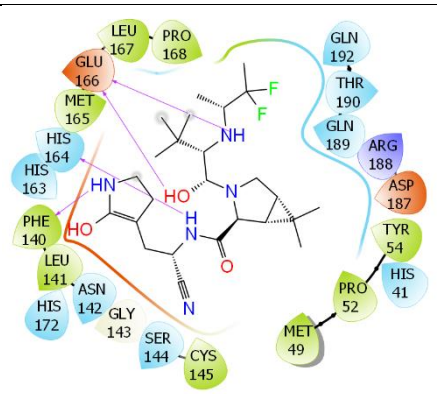
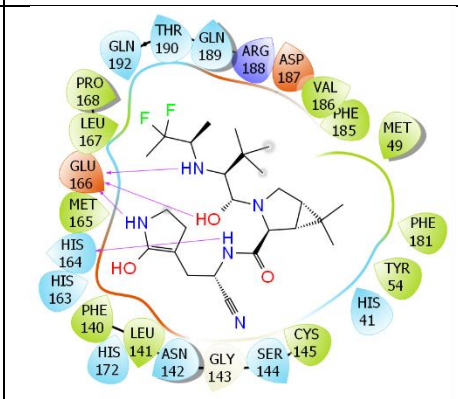
| **76** | **PF_12_9_31_2** |  |  |
| **77** | **PF_12_9_3_31** |  |  |
| **78** | **PF_12_9_3_30** |  |  |
| **79** | **PF_12_9_3_32** |  |  |

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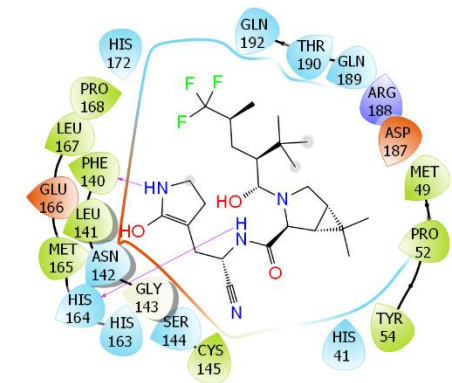
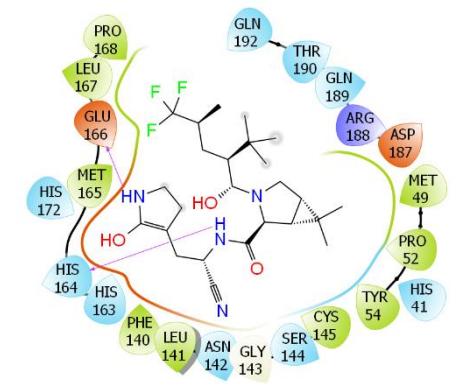
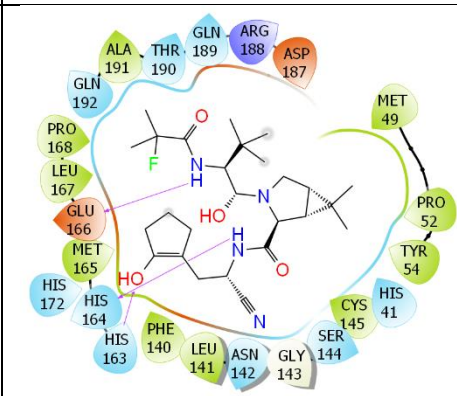
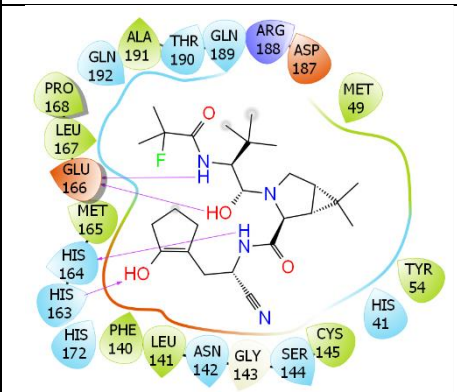
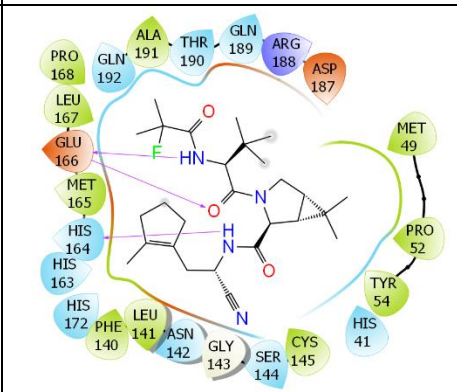
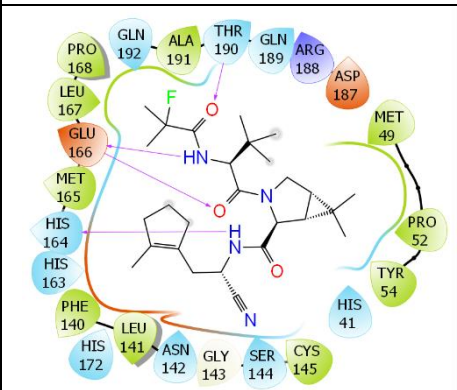
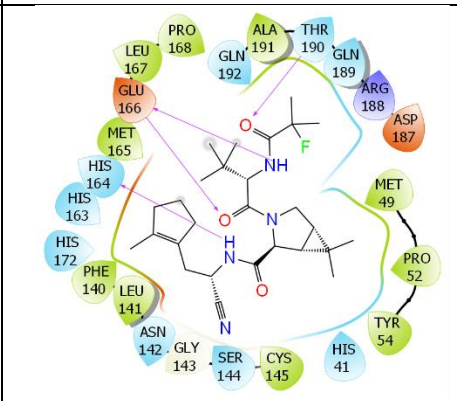
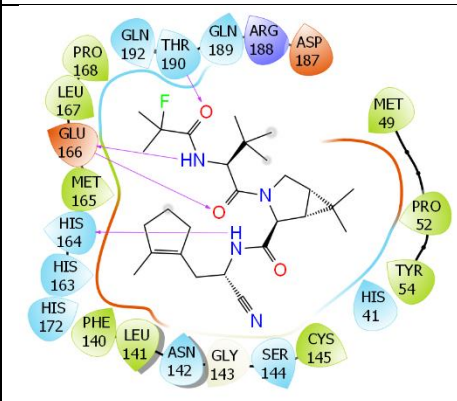
| **80** | **PF_12_9_3_11** |  |  |
| **81** | **PF_3_4_33_32_10** |  |  |
| **82** | **PF_3_4_33_32_60** |  |  |
| **83** | **PF_3_4_33_31_60** |  |  |

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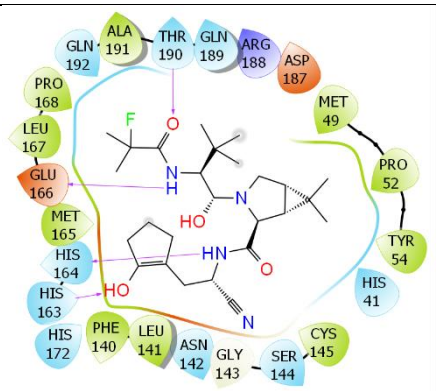
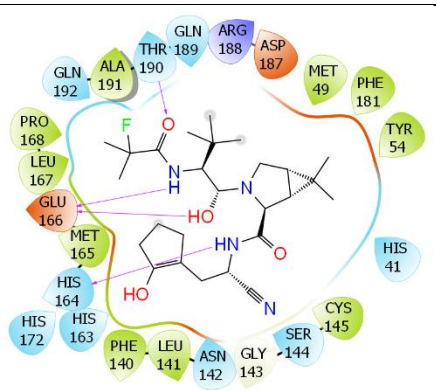
| **84** | **PF_3_4_33_31_10** |  |  |

[a]The initial conformation of the complex, which was provided by DeepFrag application. [b]The MD-refined structure of the complex.

Table S8. Toxicity prediction via PreADMET.

| $N^0$ | **Compound** | **$Carcino_{Mouse}$** | **$Ames_{test}$** | **$TA100_{10RLI}$** | **$TA100_{NA}$** | **$TA1535_{10RLI}$** | **$TA1535_{NA}$** |
|---|---|---|---|---|---|---|---|
| 1 | **PF_3_4_62** | negative | non-mutagen | negative | negative | negative | negative |
| 2 | **PF_3_4_32** | negative | non-mutagen | negative | negative | negative | negative |
| 3 | **PF_3_4_33_32** | negative | non-mutagen | negative | negative | negative | negative |
| 4 | **PF_3_4_33_31** | negative | non-mutagen | negative | negative | negative | negative |
| 5 | **PF_12_9_31** | negative | non-mutagen | negative | negative | negative | negative |
| 6 | **PF_3_4_7** | negative | non-mutagen | negative | negative | negative | negative |
| 7 | **PF_9a_33** | negative | non-mutagen | negative | negative | negative | negative |
| 8 | **PF_3_4_33** | negative | non-mutagen | negative | negative | negative | negative |
| 9 | **PF_12_9_31_32** | negative | non-mutagen | negative | negative | negative | negative |
| 10 | **PF_3_4_32_32** | negative | non-mutagen | negative | negative | negative | negative |
| 11 | **PF_12_9_3** | negative | non-mutagen | negative | negative | negative | negative |
| 12 | **PF_12_33_3** | negative | non-mutagen | negative | negative | negative | negative |
| 13 | **PF_3_4_31** | negative | non-mutagen | negative | negative | negative | negative |
| 14 | **PF_3_4_31_32** | negative | non-mutagen | negative | negative | negative | negative |
| 15 | **PF-07321332** | positive | non-mutagen | positive | positive | positive | positive |