**Supplementary Material to the manuscript entitled**

**Drug Design of New anti-EBOV Inhibitors: QSAR, Homology Modeling, Molecular Docking and Molecular Dynamics Studies**

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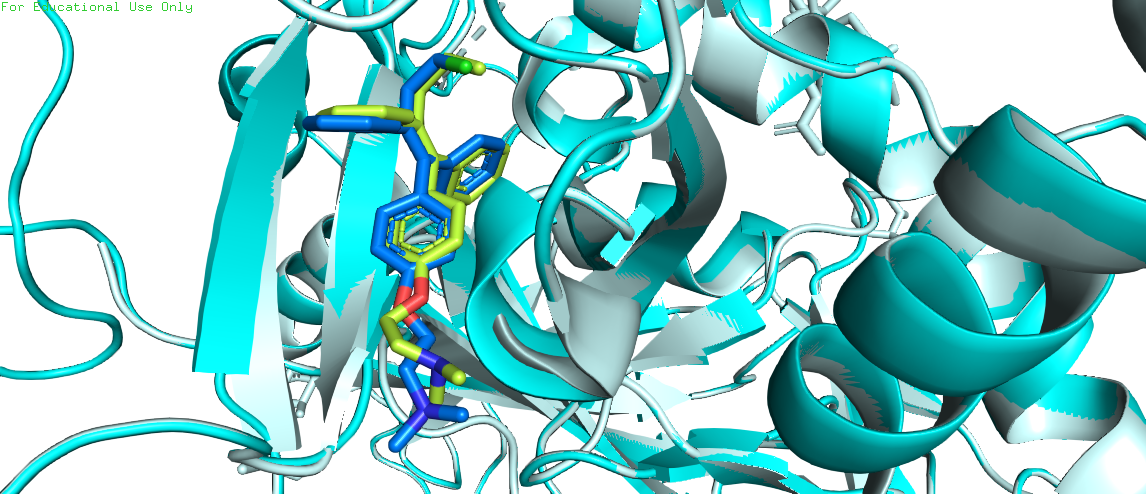
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**RMSD = 0.664**

**Figure S1:** Best predicted pose of co-crystallized ligand (blue) superimposed with X-ray (green) Inside EBOV-GP.

**Table S1:** Chemical structure of the 86 amodiaquine derivatives and their corresponding IC50

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **ID** | **Structure** | **IC50 (μM)** | **ID** | **Structure** | **IC50 (μM)** |
| **1** |  | **5.78** | **2** |  | **5.87** |
| **3** |  | **6.39** | **4** |  | **1.55** |
| **5** |  | **2.78** | **6** |  | **1.64** |
| **7** |  | **0.73** | **8** |  | **1.46** |
| **9** |  | **1.21** | **10** |  | **2.14** |
| **11** |  | **1.46** | **12** |  | **2.14** |
| **13** |  | **1.68** | **14** |  | **1.22** |
| **15** |  | **1.28** | **16** |  | **2.08** |
| 17 |  | **1.77** | **18** |  | **0.64** |
| **19** |  | **1.80** | **20** |  | **1.31** |
| **21** |  | **1.09** | **22** |  | **1.73** |
| **23** |  | **0.29** | **24** |  | **6.03** |
| **25** |  | **0.86** | **26** |  | **0.94** |
| **27** |  | **2.32** | **28** |  | **0.72** |
| **29** |  | **1.39** | **30** |  | **9.91** |
| **31** |  | **1.70** | **32** |  | **3.58** |
| **33** |  | **2.71** | **34** |  | **20.69** |
| **35** |  | **16.07** | **36** |  | **6.65** |
| **37** |  | **6.20** | **38** |  | **1.98** |
| **39** |  | **2.77** | **40** |  | **23.19** |
| **41** |  | **8.94** | **42** |  | **3.14** |
| **43** |  | **2.82** | **44** |  | **3.69** |
| **45** |  | **2.58** | **46** |  | **3.14** |
| **47** |  | **5.38** | **48** |  | **10.49** |
| **49** |  | **2.53** | **50** |  | **4.16** |
| **51** |  | **5.38** | **52** |  | **5.07** |
| **53** |  | **7.35** | **54** |  | **20** |
| **55** |  | **20** | **56** |  | **20** |
| **57** |  | **9.41** | **58** |  | **20.00** |
| **59** |  | **3.42** | **60** |  | **12.60** |
| **61** |  | **4.99** | **62** |  | **4.97** |
| **63** |  | **7.32** | **64** |  | **13.88** |
| **65** |  | **20.00** | **66** |  | **2.46** |
| **67** |  | **12.20** | **68** |  | **8.33** |
| **69** |  | **3.59** | **70** |  | **0.69** |
| **71** |  | **0.62** | **72** |  | **0.29** |
| **73** |  | **0.30** | **74** |  | **0.43** |
| **75** |  | **0.44** | **76** |  | **0.37** |
| **77** |  | **0.39** | **78** |  | **0.26** |
| **79** |  | **0.41** | **80** |  | **0.36** |
| **81** |  | **0.41** | **82** |  | **0.66** |
| **83** |  | **0.37** | **84** |  | **1.59** |
| **85** |  | **1.95** | **86** |  | **2.13** |

**Table S2:** SMILES notation of the 86 amodiaquine derivatives and their pIC50.

|  |  |  |
| --- | --- | --- |
| ID | SMILES | pIC50 |
| 1 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CC#C)CC#C)Cl | 5.24 |
| 2 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CC)CC)C(F)(F)F | 5.23 |
| 3 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(C)c1ccccc1)Cl | 5.19 |
| 4 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CC)CC)Br | 5.81 |
| 5 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CC)CC)F | 5.56 |
| 6 | c1ccc2c(c1)c(c1c(n2)cccc1)Nc1cc(c(cc1)O)CN(CC)CC | 5.79 |
| 7 | c1c(cc2c(c1)c(c1c(n2)ccc(c1)OC)Nc1cc(c(cc1)O)CN(CC)CC)Cl | 6.14 |
| 8 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(C(C)C)C)Cl | 5.84 |
| 9 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CNC(C)(C)C)Cl | 5.92 |
| 10 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(C)C)Cl | 5.67 |
| 11 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(C(C)C)CC)Cl | 5.84 |
| 12 | c1ccc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CC)CC | 5.67 |
| 13 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN1CCN(CC1)C)Cl | 5.77 |
| 14 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CCC)C)Cl | 5.91 |
| 15 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(C(C)(C)C)C)Cl | 5.89 |
| 16 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CC)C)Cl | 5.68 |
| 17 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CCO)CC)Cl | 5.75 |
| 18 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CC)CC)I | 6.19 |
| 19 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN1C[C@H](CCC1)O)Cl | 5.74 |
| 20 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)c1ccc(cc1)Cl)O)CN(CC)CC)Cl | 5.88 |
| 21 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN1CCCC1)Cl | 5.96 |
| 22 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN1CCC(C1)O)Cl | 5.76 |
| 23 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CNCCCCCC)Cl | 6.54 |
| 24 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN1CCOCC1)Cl | 5.22 |
| 25 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CNCCCC)Cl | 6.07 |
| 26 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CCC)CCC)Cl | 6.03 |
| 27 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CC=C)CC=C)Cl | 5.63 |
| 28 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CCCC)CCCC)Cl | 6.14 |
| 29 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CCC)CC)Cl | 5.86 |
| 30 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CC)CC)Cl | 5.00 |
| 31 | c1c(cc2c(c1)c(ccn2)Nc1ccc(c(c1)CN1CCC(CC1)O)O)Cl | 5.77 |
| 32 | c1(ccc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CC)CC)F | 5.45 |
| 33 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)NCc1ccc(cc1)Cl)Cl | 5.57 |
| 34 | c1c(cc2c(c1)c(ccn2)N1CC(CCC1)CO)Cl | 4.68 |
| 35 | c1c(cc2c(c1)c(ccn2)N1CC(CCC1)C(=O)OCC)Cl | 4.79 |
| 36 | c1c(cc2c(c1)c(ccn2)Nc1cc(ccc1)N(CCC)CCC)Cl | 5.18 |
| 37 | c1ccc2c(c1)c(cc(n2)C(F)(F)F)Nc1cc(c(cc1)O)CN(CC)CC | 5.21 |
| 38 | c1cc(c2c(c1)c(cc(n2)C(F)(F)F)Nc1cc(c(cc1)O)CN(CC)CC)C(F)(F)F | 5.70 |
| 39 | c1cc(c2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CC)CC)Cl | 5.56 |
| 40 | c1c(cc2c(c1)c(ccn2)N1CCN(CC1)C)Cl | 4.63 |
| 41 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1OCC)N1CCOCC1)OCC)Cl | 5.05 |
| 42 | c1c(cc2c(c1)c(ccn2)Nc1cc(ccc1)N(CC#C)CC#C)Cl | 5.50 |
| 43 | c1c(cc2c(c1)c(ccn2)N(c1cc(c(cc1)O)CN(CC)CC)C)Cl | 5.55 |
| 44 | c1c(cc2c(c1)c(ccn2)Nc1ccc(c(c1)c1ccc(cc1)Cl)O)Cl | 5.43 |
| 45 | c1c(cc2c(c1)c(ccn2)Nc1ccc(c(c1)CN1CCCCC1CCN1CCCC1)O)Cl | 5.59 |
| 46 | c1ccc2c(c1)c(cc(n2)Cl)Nc1cc(c(cc1)O)CN(CC)CC | 5.5 |
| 47 | c1(c(cc2c(c1)c(nc(n2)Cl)Nc1cc(c(cc1)O)CN(CC)CC)OC)OC | 5.27 |
| 48 | c1c(cc2c(c1)c(ccn2)Nc1cc(ccc1)N(Cc1ccc(cc1)Cl)Cc1ccc(cc1)Cl)Cl | 4.98 |
| 49 | c1c(cc2c(c1)c(ccn2)Nc1cc(ccc1)N(Cc1ccc(cc1)Cl)CC)Cl | 5.6 |
| 50 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)N1CCCC1)Cl | 5.38 |
| 51 | c1c(cc2c(c1)c(ccn2)Nc1cc(ccc1)NCCC)Cl | 5.27 |
| 52 | c1c(cc2c(c1)c(ccn2)Nc1cc(ccc1)N(C)C)Cl | 5.29 |
| 53 | c1c(cc2c(c1)c(ccn2)Nc1ccc(cc1)O)Cl | 5.13 |
| 54 | c1c(cc2c(c1)c(ccn2)Nc1cc2c(cc1)nccc2)Cl | 4.70 |
| 55 | c1c(cc2c(c1)c(ccn2)Nc1cc2c(nc1)cccc2)Cl | 4.70 |
| 56 | c1c(cc2c(c1)c(ccn2)Nc1c(=O)[nH]c(=O)[nH]c1)Cl | 4.70 |
| 57 | c1c(cc2c(c1)c(ccn2)Nc1cc2c(cc1)OCO2)Cl | 5.03 |
| 58 | c1c(cc2c(c1)c(ccn2)Nc1ccc(cc1)N(CC)CC)Cl | 4.70 |
| 59 | c1c(cc2c(c1)c(ccn2)Nc1ccc(cc1)N(CC#C)CC#C)Cl | 5.47 |
| 60 | c1c(cc2c(c1)c(ccn2)Nc1ccc(cc1)N1CCOCC1)Cl | 4.90 |
| 61 | c1c(cc2c(c1)c(ncn2)Nc1c(c(ccc1)CN(CC)CC)O)Cl | 5.30 |
| 62 | c1cc(c2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CC)CC)F | 5.30 |
| 63 | c1c(cc2c(c1)c(ccn2)Nc1ccc(c(c1)CN(CCO)CCO)O)Cl | 5.14 |
| 64 | c1c(cc2c(c1)c(nc[n+]2[O-])Nc1ccc(c(c1)CN(CCO)CC)O)Cl | 4.86 |
| 65 | c1c(cc2c(c1)c(cc[n+]2[O-])Nc1ccc(c(c1)CN1CCC(CC1)O)O)Cl | 4.7 |
| 66 | c1c(cc2c(c1)c(ccn2)Nc1ccc(c(c1)CN(CCOC(=O)C)CC)O)Cl | 5.61 |
| 67 | c1c(cc2c(c1)c(ccn2)Nc1cc(ccc1)N(CCO)CCO)Cl | 4.91 |
| 68 | c1(c(cc2c(c1)c(ncn2)Nc1cc(c(cc1)O)CN(CC)CC)OC)OC | 5.08 |
| 69 | c1c(cc2c(c1)c(ccn2)Nc1ccc(c(c1)CN1CCCCC1)O)Cl | 5.44 |
| 70 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(C)C)I | 6.16 |
| 71 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CC)C)I | 6.21 |
| 72 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(C(C)C)C)I | 6.54 |
| 73 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(C(C)(C)C)C)I | 6.52 |
| 74 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CCC)C)I | 6.37 |
| 75 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CCCC)C)I | 6.36 |
| 76 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CCCCC)C)I | 6.43 |
| 77 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CCCCCC)C)I | 6.41 |
| 78 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CCCCCCCC)C)I | 6.59 |
| 79 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CCO)CC)I | 6.39 |
| 80 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CCC)CC)I | 6.44 |
| 81 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CCCC)CC)I | 6.39 |
| 82 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN1CCCC1)I | 6.18 |
| 83 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN1CCCCC1)I | 6.43 |
| 84 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN1CCOCC1)I | 5.80 |
| 85 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN1CCSCC1)I | 5.71 |
| 86 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(cc1)O)CN(CC)CC)Cl | 5.67 |

**Table S3:** Illustration of the SMILES features.

|  |  |
| --- | --- |
| SMILES | Meaning |
| SK | One symbol or two symbols that cannot be examined separately |
| SSK | Combination of two SMILES-atoms |
| SSSK | Combination of three SMILES-atoms |
| HARD | Presence or absence of some chemical elements (halogens, Oxygen, Nitrogen, …) |
| Cmax | Total number of rings |
| Nmax | Total number of nitrogen atoms |
| Omax | Total number of oxygen atoms |

**Table S4:** Split distribution, experimental pIC50 and calculated pIC50 for the four splits using TF2 (with WIIC = 0.3).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ID | Exp. pIC50 | **Split** | | | | **Calculated pIC50** | | | | **Applicability domain** | | | |
| **1** | **2** | **3** | **4** | **Split 1** | **Spli2** | **Split 3** | **Split 4** | **Split 1** | **Spli2** | **Split 3** | **Split 4** |
| 1 | 5.24 | - | - | - | + | 5.7525 | 5.5002 | 5.7496 | 5.7793 | YES | YES | YES | YES |
| 2 | 5.23 | - | \* | \* | # | 5.7290 | 5.6749 | 5.6509 | 5.7708 | YES | YES | **NO** | YES |
| 3 | 5.19 | \* | - | + | \* | 5.4930 | 5.4686 | 5.7293 | 6.0252 | YES | YES | YES | YES |
| 4 | 5.81 | - | \* | - | - | 5.6925 | 5.6401 | 5.6553 | 5.7689 | YES | YES | YES | YES |
| 5 | 5.56 | - | # | # | - | 5.6925 | 5.6401 | 5.7297 | 5.7689 | YES | YES | YES | YES |
| 6 | 5.79 | - | + | - | - | 5.5051 | 5.5293 | 5.7597 | 5.5627 | YES | YES | YES | YES |
| 7 | 6.14 | # | # | - | - | 5.9695 | 5.8802 | 6.0204 | 5.9759 | YES | YES | YES | YES |
| 8 | 5.84 | + | - | - | + | 5.9148 | 5.8101 | 5.9251 | 5.7657 | YES | YES | YES | YES |
| 9 | 5.92 | # | - | # | - | 5.9008 | 5.7994 | 6.0378 | 5.9193 | YES | YES | YES | YES |
| 10 | 5.67 | + | - | \* | + | 5.6962 | 5.6437 | 5.9759 | 5.5819 | YES | YES | YES | YES |
| 11 | 5.84 | + | # | + | \* | 5.8830 | 5.8100 | 5.5711 | 5.7988 | YES | YES | YES | YES |
| 12 | 5.67 | # | + | \* | + | 5.4983 | 5.4637 | 5.6829 | 5.5224 | YES | YES | YES | YES |
| 13 | 5.77 | - | # | # | # | 5.6767 | 5.4268 | 5.7314 | 5.7718 | YES | YES | YES | YES |
| 14 | 5.91 | + | - | + | + | 5.7596 | 5.7580 | 6.0758 | 5.7537 | YES | YES | YES | YES |
| 15 | 5.89 | + | + | - | - | 5.9314 | 5.8223 | 5.6219 | 5.9559 | YES | YES | YES | YES |
| 16 | 5.68 | - | - | + | + | 5.6643 | 5.6436 | 5.6552 | 5.6634 | YES | YES | YES | YES |
| 17 | 5.75 | - | - | + | \* | 5.5973 | 5.6132 | 5.6109 | 5.6163 | YES | YES | YES | YES |
| 18 | 6.19 | - | + | + | \* | 6.1016 | 6.0879 | 6.2355 | 6.1892 | YES | YES | YES | YES |
| 19 | 5.74 | \* | \* | - | + | 5.8669 | 5.7537 | 6.0279 | 5.6669 | YES | YES | YES | YES |
| 20 | 5.88 | + | - | \* | # | 5.7190 | 5.8118 | 5.8345 | 6.0664 | YES | YES | YES | YES |
| 21 | 5.96 | - | - | + | - | 5.6875 | 5.6617 | 5.5191 | 5.6622 | YES | YES | YES | YES |
| 22 | 5.76 | \* | + | + | + | 5.8881 | 5.8600 | 5.8950 | 5.8181 | YES | YES | YES | YES |
| 23 | 6.54 | # | + | + | - | 6.1362 | 6.2036 | 6.1912 | 5.9063 | YES | YES | YES | YES |
| 24 | 5.22 | \* | - | - | + | 5.4410 | 5.3253 | 5.3949 | 5.5209 | YES | YES | YES | YES |
| 25 | 6.07 | # | + | - | - | 5.9455 | 5.9747 | 5.9723 | 5.7257 | YES | YES | YES | YES |
| 26 | 6.03 | + | + | # | + | 5.8231 | 5.8724 | 5.8916 | 5.9254 | YES | YES | YES | YES |
| 27 | 5.63 | + | - | - | \* | 5.7525 | 5.5002 | 5.6987 | 5.8108 | YES | YES | YES | YES |
| 28 | 6.14 | + | + | + | # | 6.0138 | 6.1013 | 5.7822 | 6.1060 | YES | YES | YES | YES |
| 29 | 5.86 | - | + | \* | \* | 5.7278 | 5.7579 | 6.1105 | 5.6668 | YES | YES | YES | YES |
| 30 | 5 | - | - | - | + | 5.6325 | 5.6435 | 4.5139 | 5.7448 | YES | YES | YES | YES |
| 31 | 5.77 | + | - | - | + | 5.6107 | 5.6608 | 5.6727 | 5.5883 | YES | YES | YES | YES |
| 32 | 5.45 | # | - | # | # | 5.4554 | 5.4520 | 5.8492 | 5.4615 | YES | YES | YES | YES |
| 33 | 5.57 | - | + | + | + | 5.5988 | 5.5002 | 5.5423 | 5.4530 | YES | YES | YES | YES |
| 34 | 4.68 | \* | \* | \* | - | 4.8663 | 5.0252 | 5.3597 | 4.4050 | YES | YES | YES | YES |
| 35 | 4.79 | - | - | # | + | 4.9030 | 5.0995 | 4.7965 | 4.7556 | YES | YES | YES | YES |
| 36 | 5.18 | \* | # | - | - | 5.3588 | 5.4751 | 5.4659 | 5.1969 | YES | YES | YES | YES |
| 37 | 5.21 | + | - | - | \* | 5.5019 | 5.4808 | 5.5001 | 5.4826 | YES | YES | YES | YES |
| 38 | 5.7 | \* | + | + | - | 5.6876 | 5.7255 | 5.4360 | 5.4971 | YES | YES | YES | YES |
| 39 | 5.56 | - | \* | # | - | 5.5875 | 5.6770 | 5.4971 | 5.6103 | YES | YES | YES | YES |
| 40 | 4.63 | - | \* | + | - | 4.8096 | 5.1032 | 5.6710 | 4.3837 | YES | YES | YES | YES |
| 41 | 5.05 | + | - | + | + | 5.2573 | 5.1459 | 4.5924 | 5.2457 | YES | YES | YES | YES |
| 42 | 5.5 | + | + | - | + | 5.2959 | 5.1029 | 5.1240 | 5.2408 | YES | YES | YES | YES |
| 43 | 5.55 | # | # | + | # | 5.7262 | 5.6939 | 5.3239 | 5.7174 | YES | YES | YES | YES |
| 44 | 5.43 | - | - | + | \* | 5.3595 | 5.4124 | 5.4843 | 5.3342 | YES | YES | YES | YES |
| 45 | 5.59 | + | + | # | - | 5.9649 | 5.7956 | 5.3669 | 6.0636 | YES | YES | YES | YES |
| 46 | 5.5 | + | + | - | - | 5.4562 | 5.5418 | 4.6742 | 5.2919 | YES | YES | YES | YES |
| 47 | 5.27 | - | + | - | - | 5.2959 | 5.3802 | 6.0957 | 5.3021 | YES | YES | YES | YES |
| 48 | 4.98 | - | + | + | # | 5.2863 | 5.2269 | 5.4705 | 5.164 | YES | YES | YES | YES |
| 49 | 5.6 | + | # | # | - | 5.1911 | 5.2171 | 5.2599 | 5.2221 | YES | YES | YES | YES |
| 50 | 5.38 | # | + | \* | \* | 5.5883 | 5.5440 | 5.1350 | 5.0893 | YES | YES | YES | YES |
| 51 | 5.27 | + | - | + | # | 5.2762 | 5.4696 | 5.1692 | 4.9098 | YES | YES | YES | YES |
| 52 | 5.29 | - | + | - | - | 5.2318 | 5.2465 | 4.4747 | 4.8534 | YES | YES | YES | YES |
| 53 | 5.13 | + | \* | - | + | 5.2729 | 5.2442 | 5.1922 | 4.8354 | YES | YES | YES | YES |
| 54 | 4.7 | + | + | - | \* | 4.8359 | 4.8652 | 5.1454 | 4.5805 | YES | YES | YES | YES |
| 55 | 4.7 | + | \* | \* | + | 4.6903 | 4.8123 | 5.0117 | 4.6656 | **NO** | **NO** | YES | YES |
| 56 | 4.7 | - | - | - | - | 5.0146 | 5.0315 | 4.7769 | 4.5539 | YES | YES | YES | YES |
| 57 | 5.03 | + | - | # | - | 5.1920 | 5.1681 | 6.1339 | 4.9139 | YES | YES | YES | YES |
| 58 | 4.7 | + | # | + | - | 5.1681 | 5.2463 | 4.7417 | 5.0163 | YES | YES | YES | YES |
| 59 | 5.47 | + | \* | - | - | 5.2959 | 5.1029 | 4.7610 | 5.2408 | YES | YES | YES | YES |
| 60 | 4.9 | - | \* | + | - | 5.0101 | 4.9872 | 5.2471 | 4.9034 | **NO** | **NO** | YES | YES |
| 61 | 5.3 | - | \* | - | # | 5.0078 | 5.1107 | 5.3239 | 5.3024 | **NO** | **NO** | YES | YES |
| 62 | 5.3 | + | + | - | - | 5.6476 | 5.6736 | 4.9059 | 5.6344 | YES | YES | YES | YES |
| 63 | 5.14 | \* | + | + | + | 5.3500 | 5.3595 | 5.4984 | 5.1522 | YES | YES | YES | YES |
| 64 | 4.86 | + | + | \* | \* | 4.6306 | 4.7137 | 5.7280 | 4.5508 | YES | YES | YES | YES |
| 65 | 4.7 | # | - | - | # | 5.2255 | 5.1892 | 5.0973 | 4.9002 | YES | YES | YES | YES |
| 66 | 5.61 | \* | - | + | + | 5.4428 | 5.5337 | 6.4879 | 5.5588 | YES | YES | YES | YES |
| 67 | 4.91 | \* | - | + | - | 5.2225 | 5.2178 | 4.7370 | 4.9198 | YES | YES | YES | YES |
| 68 | 5.08 | - | - | # | + | 5.3546 | 5.2313 | 5.4936 | 5.4330 | YES | YES | YES | YES |
| 69 | 5.44 | - | + | - | # | 5.6163 | 5.6757 | 5.0995 | 5.6019 | YES | YES | YES | YES |
| 70 | 6.16 | - | + | \* | + | 6.1653 | 6.0881 | 5.2969 | 6.0517 | YES | YES | YES | YES |
| 71 | 6.21 | + | \* | # | + | 6.1335 | 6.0880 | 5.5994 | 6.1332 | YES | YES | YES | YES |
| 72 | 6.54 | # | - | \* | - | 6.3839 | 6.2545 | 6.1847 | 6.2355 | YES | YES | YES | YES |
| 73 | 6.52 | \* | - | \* | + | 6.4006 | 6.2667 | 6.2941 | 6.4257 | YES | YES | YES | YES |
| 74 | 6.37 | \* | # | - | + | 6.2288 | 6.2024 | 6.4036 | 6.2235 | YES | YES | YES | YES |
| 75 | 6.36 | + | + | - | + | 6.3241 | 6.3169 | 6.5130 | 6.3138 | YES | YES | YES | YES |
| 76 | 6.43 | + | # | + | - | 6.4195 | 6.4313 | 6.6224 | 6.4041 | YES | YES | YES | YES |
| 77 | 6.41 | + | \* | - | \* | 6.5148 | 6.5458 | 6.6386 | 6.5066 | YES | YES | YES | YES |
| 78 | 6.59 | # | + | + | \* | 6.7054 | 6.7747 | 6.8413 | 6.6343 | YES | YES | YES | YES |
| 79 | 6.39 | # | - | + | + | 6.0664 | 6.0576 | 5.9860 | 6.1256 | YES | YES | YES | YES |
| 80 | 6.44 | - | # | # | # | 6.1969 | 6.2023 | 6.2180 | 6.3049 | YES | YES | YES | YES |
| 81 | 6.39 | - | - | - | - | 6.2923 | 6.3168 | 6.3450 | 6.3952 | YES | YES | YES | YES |
| 82 | 6.18 | - | # | \* | + | 5.9922 | 6.1050 | 6.4544 | 6.1062 | YES | YES | YES | YES |
| 83 | 6.43 | \* | # | + | - | 6.0875 | 6.2194 | 6.0955 | 6.1965 | YES | YES | YES | YES |
| 84 | 5.8 | + | + | + | + | 5.7456 | 5.7685 | 5.8619 | 5.9649 | YES | YES | YES | YES |
| 85 | 5.71 | # | + | + | # | 5.8197 | 5.8341 | 6.0362 | 6.0178 | YES | YES | YES | YES |
| 86 | 5.67 | - | + | + | + | 5.6325 | 5.6435 | 5.6727 | 5.7448 | YES | YES | YES | YES |

**+ : Training Set; - : Invisible Training Set; # : Calibration Set; \* : Validation Set**

**Table S5:** Molecular descriptors and their description.

|  |  |  |
| --- | --- | --- |
| **Abbreviation** | **Classe** | **Descriptors** |
| IC2 | Information indices | Information Content index (neighborhood symmetry of 2-order) |
| SpMin7\_Bh(s) | Burden eigenvalues | smallest eigenvalue n. 7 of Burden matrix weighted by I-state |
| P\_VSA\_charge\_7 | P\_VSA-like descriptors | P\_VSA-like on partial charges, bin 7 |
| CATS2D\_05\_DD | Pharmacophore descriptors | CATS2D Donor-Donor at lag 05 |
| T(O..O) | 2D Atom Pairs | sum of topological distances between (O..O) |

**Table S6:** Promoters of increase and decrease of pIC50 endpoint value from split 3 and their description.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Description** | **Sak** | **CWs**  **Probe 1** | **CWs Probe 2** | **CWs Probe 3** | **NTr**a | **Ninvi Tr**b | **NC**calib | **Defect [SAk]**d |
| ***Promoters of endpoint increase*** | | | | | | | | |
| Presence of aromatic nitrogen with 2 rings carbon with two rings | n...2....... | 4.90 | 3.92 | 2.86 | 30 | 29 | 13 | 0.0000 |
| Combination of two rings sp2 nitrogen and branching | n...2...(... | 4.24 | 3.41 | 3.10 | 30 | 29 | 13 | 0.0000 |
| Aromatic carbon with sp3 nitrogen | c...N....... | 2.42 | 0.76 | 1.55 | 28 | 30 | 12 | 0.0003 |
| Presence of two oxygens maximum | Omax.2...... | 2.22 | 2.42 | 1.64 | 5 | 5 | 2 | 0.0018 |
| Sp3 nitrogen surrounded by sp3 carbon and branching | c...N...(... | 1.96 | 1.12 | 1.60 | 28 | 30 | 12 | 0.0003 |
| Oxygen surrounded by two branching | (...O...(... | 1.67 | 1.50 | 1.13 | 23 | 24 | 10 | 0.0001 |
| Presence of iodine | I........... | 1.61 | 0.31 | 0.92 | 7 | 4 | 2 | 0.0088 |
| Presence of aromatic carbon with branching | c...(....... | 1.57 | 1.27 | 0.35 | 30 | 30 | 13 | 0.0000 |
| Sp3 nitrogen surrounded by two sp3 carbons | C...N...C... | 1.55 | 0.70 | 1.68 | 1 | 1 | 1 | 0.0218 |
| Combination of two rings, sp2 nitrogen, and branching | 2...n...(... | 1.41 | 0.69 | 0.64 | 1 | 5 | 0 | 1.0000 |
| Presence of Iodine with oxygen | ++++I---O=== | 1.28 | 2.00 | 2.58 | 7 | 4 | 2 | 0.0088 |
| Combination of aromatic nitrogen and two aromatic carbons | n...c...c... | 1.25 | 0.17 | 1.15 | 29 | 23 | 12 | 0.0011 |
| Presence of sp3 Nitrogen with oxygen | ++++N---O=== | 1.24 | 1.49 | 0.95 | 26 | 25 | 12 | 0.0015 |
| Sp3 carbon between two branching | (...C...(... | 1.22 | 0.74 | 0.52 | 10 | 7 | 4 | 0.0018 |
| Presence of at least two rings with branching | 2...(....... | 1.19 | 1.39 | 1.29 | 30 | 29 | 13 | 0.0000 |
| Presence of two sp2 carbons with branching | c...c...(... | 1.18 | 0.24 | 0.54 | 30 | 30 | 13 | 0.0000 |
| Sp3 carbon between sp3 carbon and sp3 nitrogen | N...C...C... | 1.17 | 1.53 | 2.46 | 3 | 1 | 2 | 0.0108 |
| Branching between Iodine and sp3 carbon | I...(...C... | 1.11 | 2.28 | 2.30 | 4 | 4 | 2 | 0.0034 |
| Presence of two rings | 2........... | 1.07 | 0.59 | 0.03 | 30 | 30 | 13 | 0.0000 |
| Presence of three sp3 carbons | C...C...C... | 1.06 | 1.09 | 0.35 | 9 | 10 | 4 | 0.0006 |
| ***Promoters of endpoint decrease*** | | | | | | | | |
| Presence of one ring with branching | 1...(....... | -0.82 | -0.76 | 0.36 | 30 | 30 | 13 | 0.0000 |
| Presence of double covalent bond | =........... | -0.73 | -0.27 | -0.47 | 1 | 2 | 1 | 0.0218 |
| Presence of oxygen with double bound | ++++O---B2== | -0.72 | -0.08 | -0.45 | 1 | 2 | 1 | 0.0218 |
| Presence of one ring with nitrogen and branching | 1...N...(... | -0.71 | -0.16 | -0.66 | 3 | 0 | 1 | 0.0058 |
| sp3 carbon between sp2 carbon and branching | c...C...(... | -0.71 | -1.41 | -0.20 | 1 | 0 | 1 | 0.0218 |
| Presence of fluorine with two branching | F...(...(... | -0.71 | -0.42 | 0.71 | 1 | 1 | 0 | 1.0000 |
| Presence of at least one ring combined with sp3 carbon and oxygen | C...O...1... | -0.71 | -0.25 | -0.51 | 1 | 0 | 0 | 1.0000 |
| Oxygen surrounded by sp3 carbon and branching | C...O...(... | -0.70 | -0.15 | -0.12 | 5 | 2 | 3 | 0.0080 |
| Presence of sp2 nitrogen with branching | n...(....... | -0.51 | -0.24 | -0.18 | 1 | 7 | 1 | 0.0218 |
| Sp3 carbon surrounded by sp2 carbon and sp3 Nitrogen | c...C...N... | -0.49 | -0.22 | 0.06 | 1 | 0 | 0 | 1.0000 |
| Presence of sp2 carbon with branching and sp3 carbon | c...(...C... | -0.49 | -0.13 | -0.45 | 1 | 0 | 0 | 1.0000 |
| Presence of sp2 nitrogen with branching and sp2 carbon | n...(...c... | -0.48 | -0.19 | -0.40 | 1 | 6 | 1 | 0.0218 |

**Table S7:** Chemical structures of the newly designed ligands.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
| **D1** | **D2** | **D3** | **D4** | **D5** |
|  |  |  |  |  |
| **D6** | **D7** | **D8** | **D9** | **D10** |
|  |  |  |  |  |
| **D11** | **D12** | **D13** | **D14** | **D15** |
|  |  |  |  |  |
| **D16** | **D17** | **D18** | **D19** | **D20** |
|  |  |  |  |  |
| **D21** | **D22** | **D23** | **D24** | **D25** |
|  |
| **D26** |

**Table S8: SMILES notation of the designed molecules, their predicted activities by CORAL and GA-MLR, and their docking scores.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ID | SMILES | CORAL pIC50 | GA-MLR pIC50 | Docking Score (Kcal/mol) |
| D1 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)CC1CCC(CC1)O)O)CN1CCCCCC(C1)I)I | 7.6336 | 7.0414 | -9.9 |
| D2 | c1c(cc2c(c1)C(=CCN2)Nc1cc(c(c(c1)CC1CCC(CC1)O)O)CN1CCCCCC(C1)I)I | 7.1239 | 7.0735 | -9.8 |
| D3 | c1c(cc2c(c1)c(cc(n2)CN(CC)CC)Nc1cc(c(c(c1)NC(CC)CC)O)CN(CCCCCCCC)CC)I | 7.8312 | 7.1001 | -9.6 |
| D4 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)CC1CCC(CC1)O)O)CN1C(CCCCC(C1)I)Cl)I | 7.6842 | 7.0420 | -9.5 |
| D5 | c1c(cc2c(c1)C(CCN2)Nc1cc(c(c(c1)CC1CCC(CC1)O)O)CN1CCCCCC(C1)I)I | 7.2649 | 7.0109 | -9.4 |
| D6 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)/C=C\1/CCC(CC1)OCCN(C)C)O)CN1CCCC(CCCC)C1)I | 7.7523 | 7.3796 | -9.1 |
| D7 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)NC1CCC(CC1)O)O)CN(CCC1CCCCC1)CI)I | 7.4050 | 7.1162 | -8.9 |
| D8 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)CC1CCC(CC1)O)O)C(=O)NCCCCCCCC)I | 7.4263 | 6.9959 | -8.5 |
| D9 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)/C=C\1/CCC(CC1)OCCN(C)C)O)CN1CCCCC1)I | 7.2136 | 7.2398 | -8.4 |
| D10 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)CC1CCC(CC1)O)O)N(Cc1cccc(c1)Cl)CCCCCCCC)I | 7.6734 | 7.3213 | -8.4 |
| TOR | CN(C)CCOC1=CC=C(C=C1)/C(=C(/CCCl)\C2=CC=CC=C2)/C3=CC=CC=C3 | Reference | Reference | -8.4 |
| D11 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)CC1CCC(CC1)O)O)CN(COCCCCCCC)CC)I | 7.3648 | 6.8603 | -8.1 |
| D12 | c1c(cc2c(c1)c(cc(n2)I)Nc1cc(c(c(c1)OC1CCC(CC1)O)O)CNCCCCCCCC)I | 7.6614 | 7.4504 | -8.0 |
| D13 | c1c(cc2c(c1)c(cc(n2)I)Nc1cc(c(c(c1)Oc1ccc(cc1)O)O)CNCCCCCCCC)I | 7.5021 | 7.6082 | -8.0 |
| D14 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)Nc1ccccc1)O)CN(CCC1CCCCC1)C)I | 7.4787 | 7.1034 | -7.9 |
| D15 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)Nc1ccccc1)O)CNCCCCCCCC)I | 7.7900 | 7.3424 | -7.9 |
| D16 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)CC1CCC(CC1)O)O)CNCCCC(CCCC)O)I | 7.6419 | 7.2300 | -7.9 |
| D17 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)Cc1ccc(cc1)OCCN(C)C)O)CN(CCCCCCCC)C)I | 7.6920 | 7.4802 | -7.9 |
| D28 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)NC1CCC(CC1)O)O)CNCCCCCCCC)I | 7.7914 | 7.6237 | -7.8 |
| D19 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)CC1CCC(CC1)O)O)CNCCC(CCCCC)O)I | 7.6419 | 7.0093 | -7.4 |
| D20 | c1c(cc2c(c1)c(cc(n2)I)Nc1cc(c(c(c1)OC(CC)CC)O)CNCCCCCCCC)I | 7.8685 | 7.6044 | -7.3 |
| D21 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)/C=C\1/CCC(CC1)OCCN(C)C)O)CN(CCCCCCCC)C)I | 7.9595 | 7.3897 | -7.3 |
| D22 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)CCCCCCN(C)C)O)CN(CCCCCCCC)C)I | 7.9586 | 7.2946 | -7.2 |
| D23 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)CC1CCC(CC1)O)O)CNC(CCCCCCC)O)I | 7.5310 | 6.9736 | -6.9 |
| D24 | c1c(cc2c(c1)c(cc(n2)CN(CCC)CCC)Oc1cc(c(c(c1)NC(CC)CC)O)CN(CCCCCCCC)CC)I | 7.7475 | 6.7185 | -6.8 |
| D25 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)CCCCCCCC)O)CN(CCCCCCCC)C)I | 7.8264 | 7.0174 | -6.5 |
| D26 | c1c(cc2c(c1)c(ccn2)Nc1cc(c(c(c1)CCCCCCCCl)O)CN(CCCCCCCCl)C)I | 7.4720 | 7.0715 | -6.2 |

**Table S9:** Details of ligand−protein interactions of the designed compounds within the EBOV-GP.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Compound** | **Binding affinity (Kcal/mol)** | **Category** | **Type** | **Residue** | **Distance (Ǻ)** |
| **D1** | -9,9 | Hydrogen Bond  Other  Hydrophobic | Conventional Hydrogen Bond  Carbon Hydrogen Bond  Pi-Donor Hydrogen Bond  Pi-Sulfur  Pi-Pi Stacked  Alkyl  Pi-Alkyl | A:VAL176  B:GLY45  B:TYR16  B:TYR16  B:MET47  B:MET47  B:TYR16  B:TYR16  A:ALA74  A:VAL39  B:LEU14  A:ALA74  B:LEU14  A:ALA74 | 2.285  3.474  3.875  4.005  5.422  5.884  3.726  3.976  4.053  3.957  4.501  4.677  5.420  5.301 |
| **D2** | -9,8 | Hydrogen Bond  Hydrophobic  Other | Conventional Hydrogen Bond  Carbon Hydrogen Bond  Pi-Pi Stacked  Alkyl  Pi-Alkyl  Pi-Sulfur | B:TYR16  A:PRO160  B:LEU46  B:TYR16  A:ALA74  A:LYS163  A:VAL39  B:LEU14  A:PRO175  A:PHE167  B:TYR16  A:ALA74  B:MET47 | 3.309  1.798  3.372  3.727  4.087  5.221  4.022  4.427  4.432  5.095  4.453  4.475  5.633 |
| **D3** | -9,6 | Hydrogen Bond  Hydrophobic  Electrostatic  Other | Conventional Hydrogen Bond  Carbon Hydrogen Bond  Pi-Donor Hydrogen Bond  Pi-Pi Stacked  Alkyl  Pi-Alkyl  Pi-Cation  Pi-Sulfur | A:ARG37  A:VAL176  B:GLY45  B:TYR16  B:TYR16  B:TYR16  B:TYR16  A:ALA74  A:LYS163  A:LYS164  A:VAL39  B:LEU14  B:TYR16  A:ALA74  A:ALA74  A:ARG371  B:MET47 | 2.909  2.016  3.495  3.776  4.117  3.686  4.136  3.915  5.265  5.385  4.062  4.523  5.312  4.750  5.485  4.345  5.383 |
| **D4** | -9,5 | Hydrogen Bond  Hydrophobic | Carbon Hydrogen Bond  Pi-Sigma  Alkyl  Pi-Alkyl | A:LYS163  A:VAL39  A:ALA74  A:VAL39  A:LEU41  B:LEU14  A:PHE167  B:MET47  A:ALA74  B:LEU14 | 3.267  3.946  4.443  3.905  5.039  4.364  5.127  5.302  4.642  5.368 |
| **D5** | -9,4 | Hydrogen Bond  Hydrophobic  Electrostatic | Conventional Hydrogen Bond  Pi-Sigma  Alkyl  Pi-Alkyl  Pi-Cation | B:THR18  B:THR18  A:ALA74  B:MET47  A:LYS163  A:VAL39  B:LEU14  B:TYR16  A:ARG37 | 2.911  3.885  3.722  5.400  4.392  4.315  4.736  4.722  3.514 |
| **D6** | -9.1 | Hydrogen Bond | Carbon Hydrogen Bond  Pi-Pi T-shaped          Pi-Alkyl | B:LEU46  A:PHE167  A:VAL39  A:ALA74  A:LYS163  B:LEU14  A:VAL39  A:LEU41  B:LEU14  A:PHE166  B:TYR16  B:TYR16  A:LYS164 | 3.244  4.995  4.384  4.080  5.447  4.503  4.008  4.511  4.359  5.389  5.247  4.679  5.391 |
| **D7** | -8.9 | Hydrogen Bond  Hydrophobic  Other | Conventional Hydrogen Bond    Carbon Hydrogen Bond  Pi-Donor Hydrogen Bond  Pi-Pi Stacked    Alkyl            Pi-Alkyl        Pi-Sulfur | B:TYR16  A:GLN161  A:LYS164  B:TYR16  B:TYR16  B:TYR16  A:ALA74  A:LYS163  A:LYS164  A:VAL39  B:LEU14  A:PRO175  A:PHE167  A:ALA74  B:LEU14  A:ALA74  B:MET47  B:MET47 | 3.399  2.782  3.679  3.872  3.750  3.988  4.065  5.223  5.254  3.991  4.470  4.900  5.403  4.655  5.484  5.270  5.446  5.964 |
| **D8** | -8.5 | Hydrogen Bond  Hydrophobic  Other | Conventional Hydrogen Bond    Carbon Hydrogen Bond  Pi-Donor Hydrogen Bond  Pi-Pi Stacked    Alkyl          Pi-Alkyl      Pi-Sulfur | B:TYR16  A:PRO160  B:LEU46  B:TYR16  B:TYR16  B:TYR16  A:ALA74  A:LEU159  A:LYS16  A:VAL39  B:LEU14  A:ALA74  B:LEU14  A:ALA74  B:MET47  B:MET47 | 2.213  2.386  3.519  3.911  3.802  4.027  4.049  5.452  5.028  4.018  4.474  4.665  5.481  5.298  5.437  5.919 |
| **D9** | -8.4 | Hydrogen Bond  Hydrophobic  Electrostatic | Carbon Hydrogen Bond    Pi-Donor Hydrogen Bond    Pi-Sigma  Alkyl  Pi-Cation | B:TYR16  A:GLU73  B:TYR16  B:THR18  B:THR18  A:ALA74  A:LYS163  A:LYS164  B:TYR16  A:ALA74  A:ARG37 | 3.484  3.496  3.953  3.745  3.786  5.373  4.585  4.680  4.962  5.102  3.488 |
| **D10** | -8.4 | Hydrogen Bond  Hydrophobic  Other | Conventional Hydrogen Bond    Pi-Donor Hydrogen Bond  Alkyl            Pi-Alkyl                  Pi-Sulfur | B:LEU46  B:MET47  B:TYR16  A:ALA74  A:ALA74  A:ALA74  A:VAL39  B:LEU14  A:LYS164  A:PHE167  B:TYR16  A:VAL39  A:ALA74  B:LEU14  A:ARG37  A:LEU159  A:LEU159  A:LYS163  B:MET47  B:MET47 | 3.221  2.952  4.057  3.941  4.678  4.461  4.060  4.530  4.039  4.967  4.986  5.255  4.979  5.494  5.257  5.076  5.430  4.990  5.482  5.214 |