**Leveraging the Fragment Molecular Orbital Method to Explore the PLK1 Kinase Binding Site and Polo-Box Domain for Potent Small-Molecule Drug Design**

Jongwan Kim1,3,\*, Haiyan Jin2\*, and Kyoung Tai No1,2,3.

1 Department of Biotechnology, Yonsei University, Seoul, Republic of Korea

2 The Interdisciplinary Graduate Program in Integrative Biotechnology & Translational Medicine, Yonsei University, Incheon, Republic of Korea

3 Bioinformatics and Molecular Design Research Center (BMDRC), Incheon, Republic of Korea  
\* Co-first authors

\* Correspondence: Kyoung Tai No ([ktno@yonsei.ac.kr](mailto:ktno@yonsei.ac.kr))

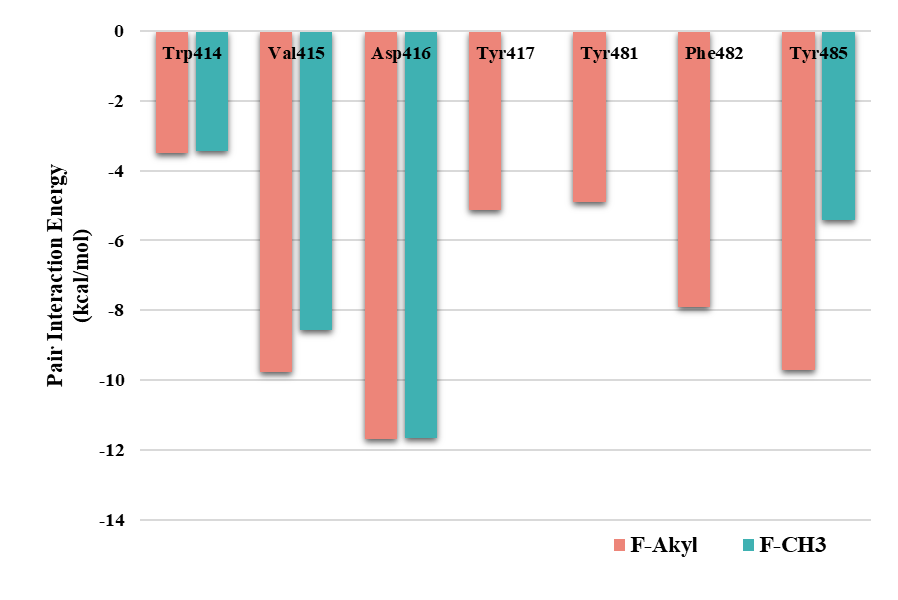


Figure S1. Comparison of F-Akyl with F-CH3 using pair interaction energy (PIE).

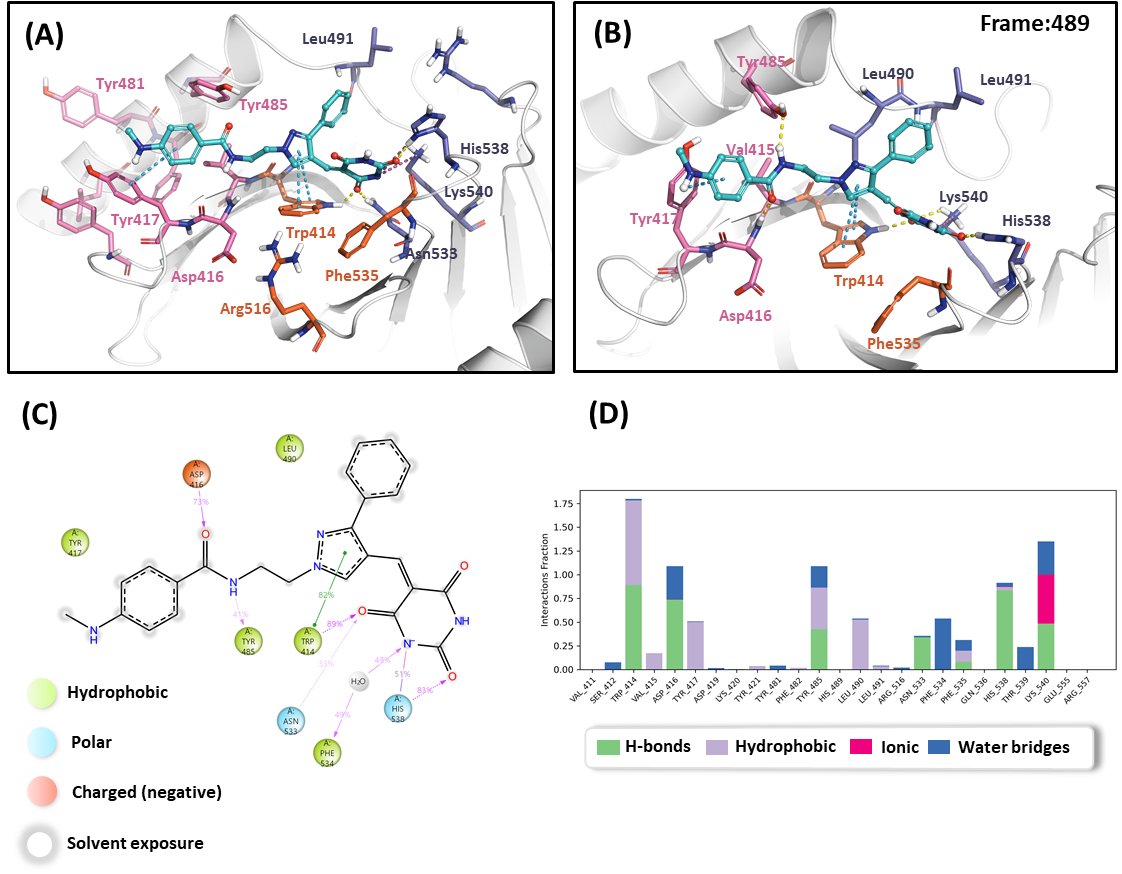


Figure S2. Molecular dynamic (MD) simulation analysis of KBJK557. (A) Docking structure of KBJK557 with the polo-box domain (PBD). (B) Structure of Frame 489 chosen from the MD simulation. (C) Protein-ligand contacts of the two-dimensional (2D) chemical structure and 2D summary reveal that interactions occur more than 30% of the simulation time. (D) Histogram of the protein-ligand interaction fraction.

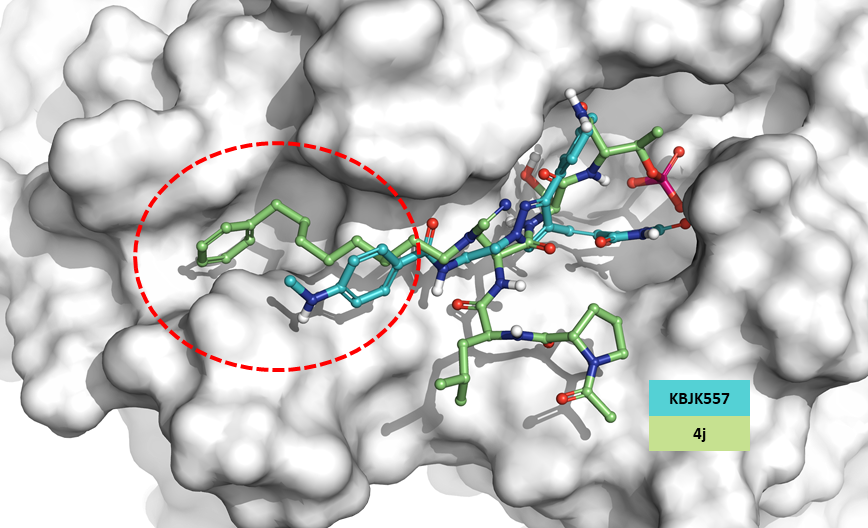


Figure S3. Superposition of 4a and KBJK557. Overlay representation of KBJK557 with 4j, where KBJK557 is light blue, 4j is light green, and the protein is presented with a white surface.

Table S1. PIEDA of ATP and PLK1 complex. All energies are in kcal/mol. The calculation was conducted at the FMO2/DFTB3/PCM level.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Residue | ΔEint | ΔEes | ΔEex | ΔEct+mix | ΔEdi | ΔGsol |
| Lys82 | -141.385 | -250.496 | 0.216 | -0.555 | -3.033 | 112.484 |
| Leu197 | -46.510 | -12.336 | 0.271 | -0.429 | -2.375 | -31.640 |
| Gly196 | -43.174 | -43.062 | 0.018 | -0.182 | -0.735 | 0.788 |
| Gly62 | -34.317 | -28.590 | 0.312 | -0.380 | -1.764 | -3.896 |
| Arg136 | -26.851 | -91.29 | 0 | 0 | -0.895 | 65.333 |
| Arg134 | -17.438 | -52.034 | 0.008 | -0.001 | -0.935 | 35.524 |
| Ala65 | -14.211 | -21.054 | -0.006 | -0.008 | -0.945 | 7.803 |
| Cys133 | -10.425 | -5.720 | -0.370 | -0.148 | -2.375 | -1.813 |
| Leu59 | -9.960 | -5.822 | -0.060 | -0.012 | -1.960 | -2.106 |
| Val114 | -7.320 | -7.105 | -0.016 | 0 | -0.977 | 0.779 |
| Phe183 | -6.702 | -1.999 | -0.084 | 0.016 | -5.790 | 1.155 |
| Cys67 | -6.390 | -7.198 | -0.182 | -0.045 | -3.571 | 4.606 |
| Ala80 | -6.080 | -7.014 | 0.038 | -0.003 | -2.004 | 2.903 |
| Leu130 | -4.936 | -4.423 | -0.002 | 0 | -1.087 | 0.576 |

Table S2. PIEDA of BI2536 and PLK1 complex. All energies are in kcal/mol. The calculation was conducted at the FMO-MP2/6-31G\*\*/PCM level.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Residue | ΔEint | ΔEes | ΔEex | ΔEct+mix | ΔEdi | ΔGsol |
| Cys133 | -14.382 | -15.497 | 12.292 | -3.133 | -7.068 | -0.976 |
| Gly60 | -14.095 | -13.257 | 5.720 | -2.618 | -5.916 | 1.976 |
| Leu132 | -12.557 | -7.003 | 4.455 | -2.848 | -6.951 | -0.21 |
| Arg136 | -11.995 | -7.929 | 4.386 | -2.637 | -9.238 | 3.423 |
| Leu59 | -8.796 | -1.082 | 7.484 | -2.854 | -12.121 | -0.223 |
| Phe183 | -8.170 | -1.082 | 3.851 | -1.380 | -8.944 | -0.615 |
| Arg57 | -4.443 | -4.717 | 1.939 | -1.406 | -3.641 | 3.382 |
| Glu69 | -4.255 | -4.070 | 0.643 | -0.980 | -1.501 | 1.653 |
| Cys67 | -3.632 | -3.406 | 7.750 | -1.659 | -6.159 | -0.158 |
| Gly62 | -3.215 | -2.520 | 1.025 | -0.841 | -2.058 | 1.179 |

Table S3. PIEDA of Onvansertib and PLK1 complex. All energies are in kcal/mol. The calculation was conducted at the FMO-MP2/6-31G\*\*/PCM level.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Residue | ΔEint | ΔEes | ΔEex | ΔEct+mix | ΔEdi | ΔGsol |
| Glu140 | -49.684 | -103.375 | 6.591 | -5.569 | -7.408 | 60.077 |
| Lys82 | -15.799 | 10.706 | 4.323 | -2.501 | -5.047 | -23.280 |
| Phe183 | -12.410 | -5.963 | 5.979 | -2.432 | -12.102 | 2.108 |
| Arg134 | -11.929 | 7.329 | 5.507 | -2.883 | -5.345 | -16.537 |
| Leu132 | -10.461 | -8.495 | 3.117 | -2.183 | -5.025 | 2.125 |
| Cys133 | -9.000 | -5.721 | 8.138 | -2.091 | -6.214 | -3.112 |
| Gly60 | -7.029 | -12.922 | 2.082 | -1.577 | -3.544 | 8.932 |
| Asn181 | -6.527 | -16.009 | 1.011 | -0.727 | -2.013 | 11.211 |
| Leu59 | -6.407 | 0.597 | 3.488 | -1.644 | -8.014 | -0.834 |
| Asp194 | -5.387 | -39.078 | 3.136 | -2.553 | -4.270 | 37.378 |
| Arg136 | -5.031 | 40.183 | 6.361 | -3.800 | -8.770 | -39.005 |
| Ser137 | -4.245 | -0.214 | 1.983 | -0.862 | -4.377 | -0.775 |
| Cys67 | -3.444 | -2.285 | 13.220 | -3.305 | -8.658 | -2.416 |
| Arg57 | -3.129 | 23.939 | 0.892 | -1.095 | -1.710 | -25.155 |

Table S4. PIEDA of GSK461364 and PLK1 complex. All energies are in kcal/mol. The calculation was conducted at the FMO-MP2/6-31G\*\*/PCM level.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Residue | ΔEint | ΔEes | ΔEex | ΔEct+mix | ΔEdi | ΔGsol |
| Glu140 | -56.329 | -120.777 | 13.802 | -6.773 | -8.460 | 65.879 |
| Lys082 | -12.529 | 0.356 | 10.821 | -2.931 | -6.761 | -14.014 |
| Phe183 | -10.389 | -8.297 | 6.331 | -1.926 | -10.167 | 3.670 |
| Cys133 | -10.248 | -3.916 | 1.592 | -0.251 | -3.187 | -4.486 |
| Asp194 | -9.998 | -38.054 | 5.523 | -3.781 | -5.619 | 31.933 |
| Asn181 | -5.220 | -12.858 | 0.545 | -0.737 | -2.068 | 9.898 |
| Leu059 | -4.066 | 0.449 | 2.725 | -1.095 | -5.254 | -0.891 |
| Gly060 | -3.419 | -12.033 | 0.704 | -0.310 | -2.527 | 10.747 |

Table S5. PIEDA of KBJK557 and PLK1 complex. All energies are in kcal/mol. The calculation was conducted at the FMO-MP2/6-31G\*\*/PCM level.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Residue | ΔEint | ΔEes | ΔEex | ΔEct+mix | ΔEdi | ΔGsol |
| His538 | -25.291 | -83.443 | 8.239 | -4.695 | -5.607 | 54.608 |
| Lys540 | -23.556 | -94.849 | 3.000 | -3.492 | -4.191 | 71.785 |
| Trp414 | -21.232 | -28.843 | 14.597 | -5.024 | -10.169 | -1.962 |
| Asp416 | -10.779 | 14.983 | 6.886 | -1.928 | -4.024 | -30.720 |
| Tyr485 | -8.698 | -5.375 | 4.851 | -1.775 | -5.641 | -6.399 |
| Tyr417 | -7.744 | -2.724 | 4.970 | -2.397 | -8.491 | -7.593 |
| Leu490 | -7.455 | -2.355 | 6.972 | -2.204 | -9.725 | -9.868 |
| Val415 | -6.996 | -1.849 | 3.192 | -2.662 | -4.504 | -5.677 |
| Leu491 | -5.033 | -7.018 | 1.092 | -0.442 | -3.068 | 1.335 |
| Phe535 | -3.763 | 2.863 | 5.310 | -2.895 | -5.023 | -9.041 |

Table S6. PIEDA of KBJK-4a and PLK1 complex. All energies are in kcal/mol. The calculation was conducted at the FMO-MP2/6-31G\*\*/PCM level.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Residue | ΔEint | ΔEes | ΔEex | ΔEct+mix | ΔEdi | ΔGsol |
| His538 | -34.010 | -110.056 | 21.855 | -7.675 | -6.445 | 68.311 |
| Trp414 | -16.658 | -21.122 | 13.368 | -4.167 | -11.114 | 6.377 |
| Lys540 | -10.549 | -59.446 | 2.091 | -2.631 | -2.826 | 52.263 |
| Leu490 | -7.450 | -3.407 | 7.553 | -2.552 | -10.104 | 1.060 |
| Phe535 | -4.603 | -0.517 | 1.522 | -2.381 | -3.560 | 0.333 |
| Asp416 | -4.029 | 19.404 | 5.679 | -2.193 | -3.998 | -22.921 |
| Thr539 | -3.637 | -4.309 | 0.006 | 0.143 | -0.185 | 0.708 |
| Val415 | -3.564 | 2.558 | 1.164 | -1.512 | -3.257 | -2.517 |
| Tyr485 | -3.540 | -0.696 | 2.877 | -0.921 | -3.650 | -1.150 |
| Leu491 | -3.347 | -6.077 | 0.665 | 0.669 | -2.375 | 3.771 |

Table S7. List of PDB IDs of protein structures used in this paper.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Entry | PDB ID | PLK1 domain | Ligands | Resolution (Å) |
| 1 | 2OU7 | KD | ATP | 2.4 |
| 2 | 3FC2 | KD | Volasertib | 2.45 |
| 3 | 2RKU | KD | BI2536 | 1.95 |
| 4 | 4J52 | KD | TAK-18 | 2.3 |
| 5 | 4J53 | KD | TAK-960 | 2.5 |
| 6 | 5TA6 | KD | Compound 15 | 2.5 |
| 7 | 5TA8 | KD | Compound 11 | 2.6 |
| 8 | 2YAC | KD | Onvansertib | 2.2 |
| 9 | 3KB7 | KD | Compound 49 | 2.5 |
| 10 | 3THB | KD | MLN0905 | 2.5 |
| 11 | 4A4O | KD | Compound 13 | 2.7 |
| 12 | 4A4L | KD | Compound 25 | 2.35 |
| 13 | 3P37 | PBD | FDPPLHSpTA | 2.38 |
| 14 | 3RQ7 | PBD | 4j | 1.55 |

KD: kinase domain

PBD: polo-box domain