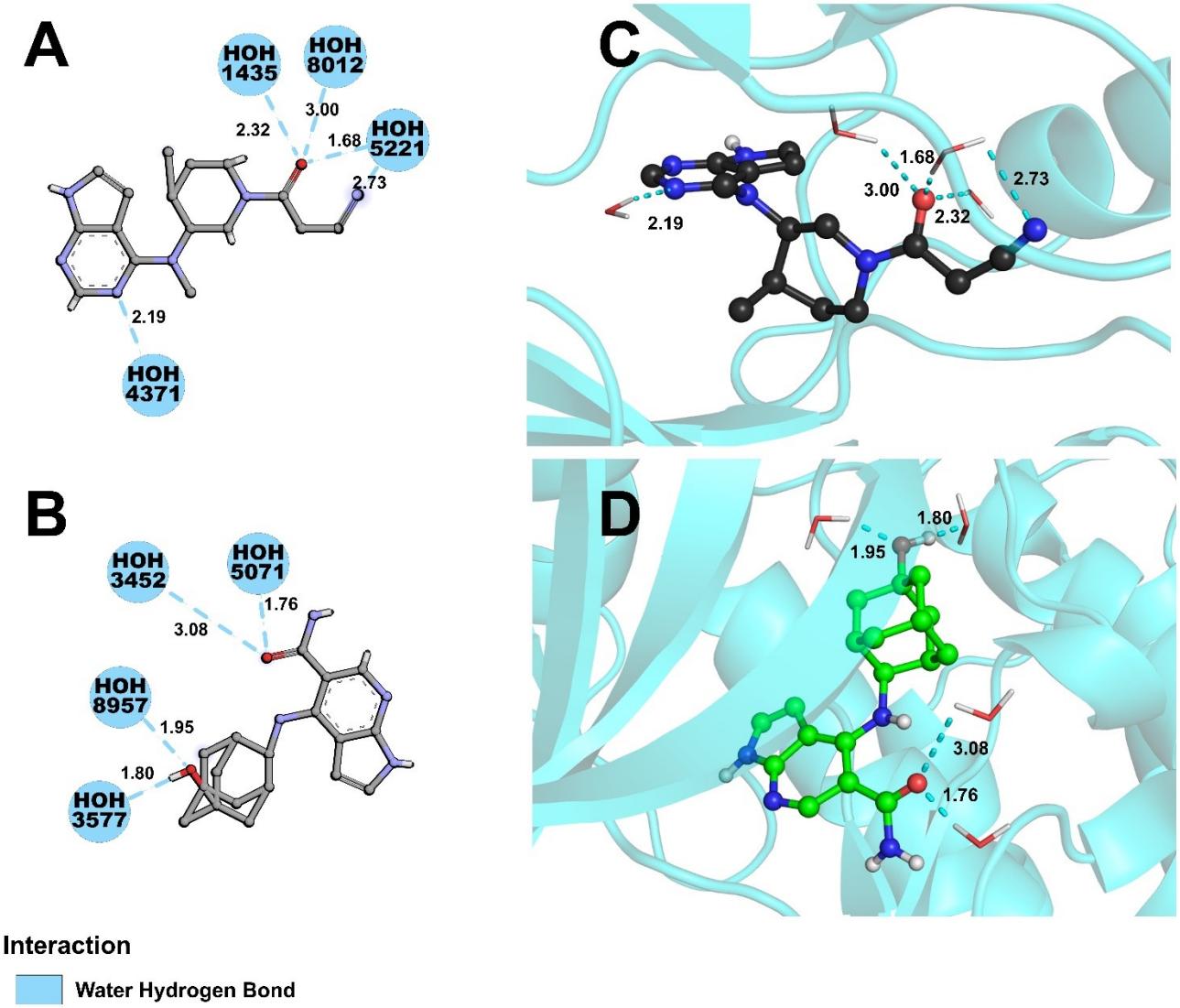
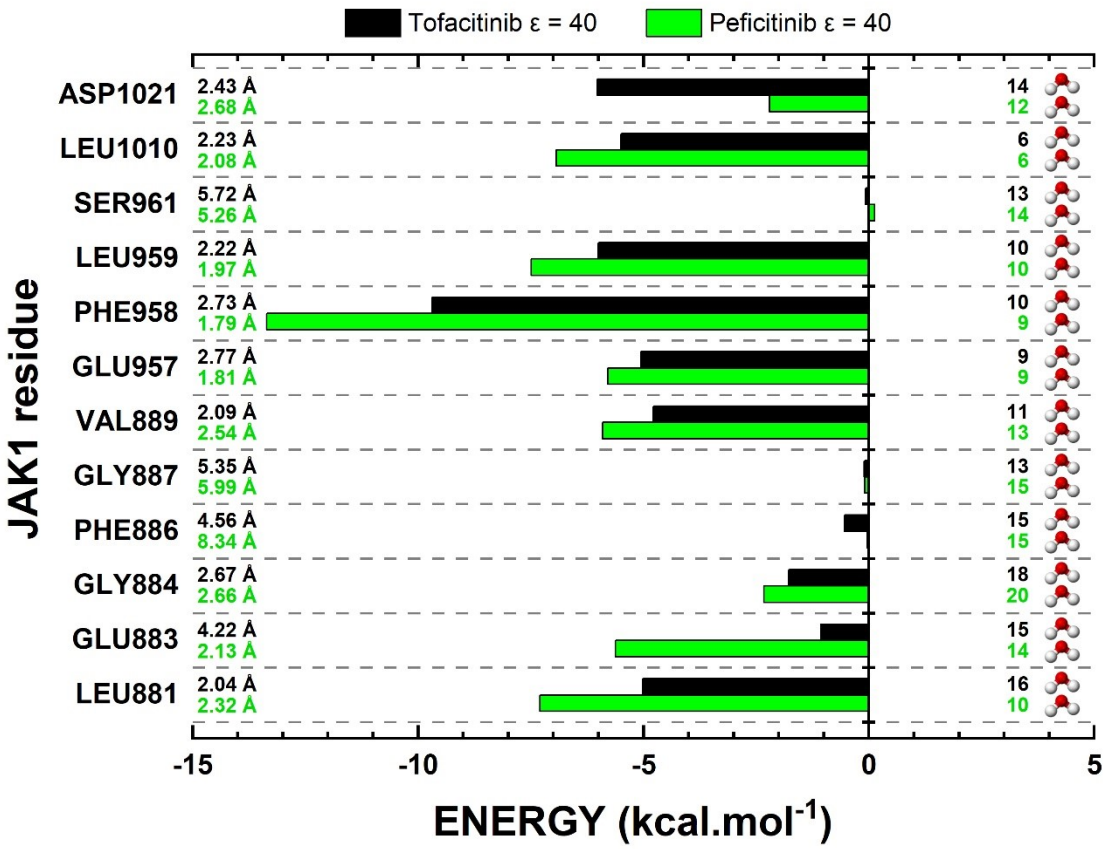
Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

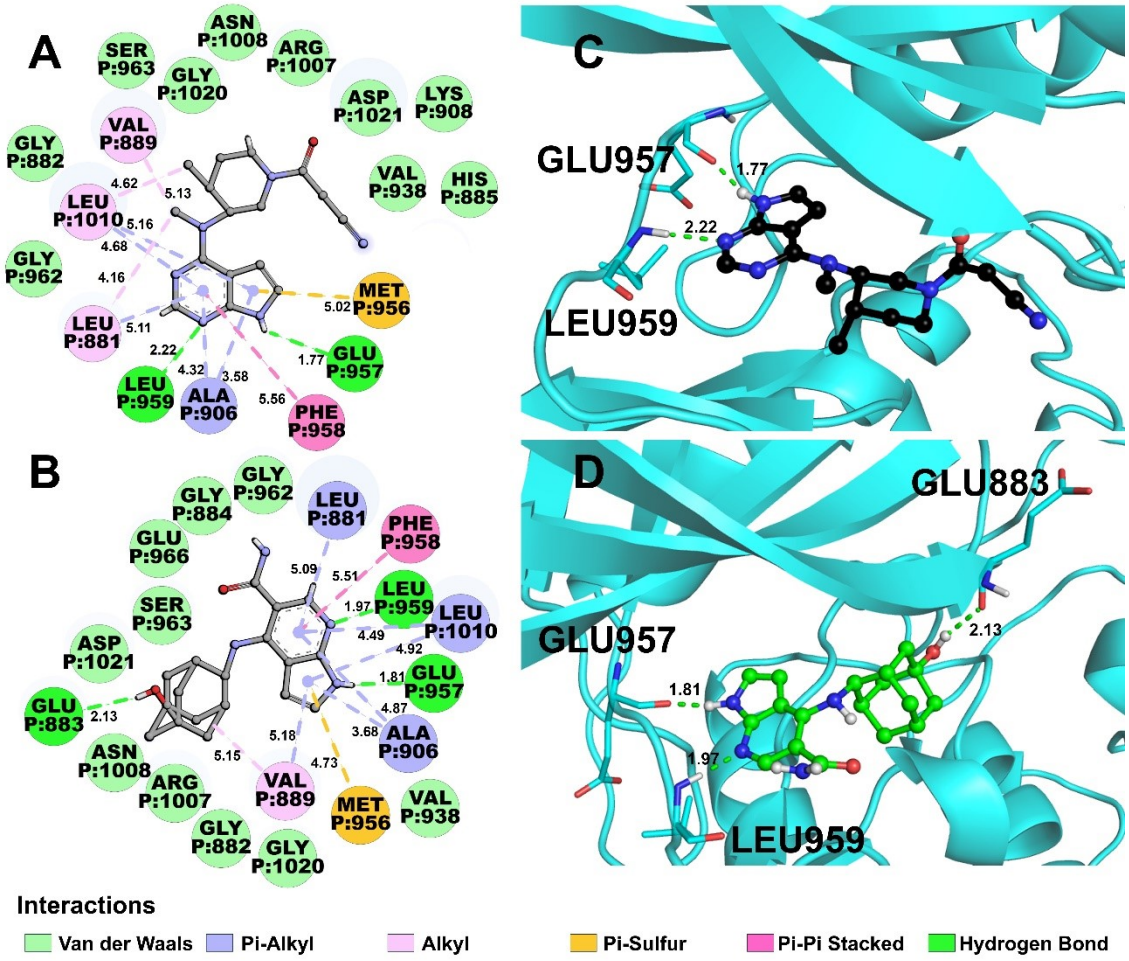

**Supplementary Figure 1.** Interactions between tofacitinib and peficitib. (A) and (B) 2D Representation of hydrogen bonds between water molecules and tofacitinib or peficitinib, respectively. (C) and (D) 3D Representation of these interaction.



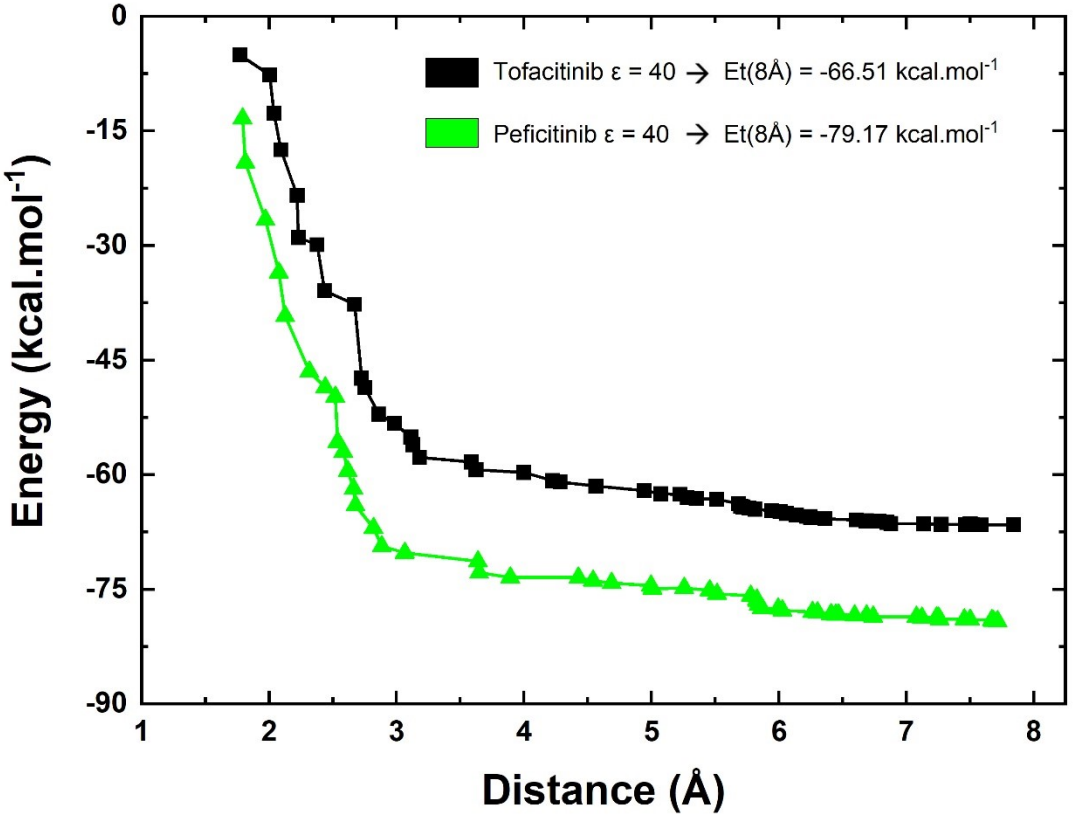
**Supplementary Figure 2.** JAK1 main residues involved in the interaction with tofacitinib and peficitinib at dielectric constant homogeneous based on MD's conformation resultant of CHARMM36 forcefield and TIP3P water. The graph provides the interaction energy between both ligands and JAK1. Tofacitinib and peficitinib are represented in black and lime green, respectively.



**Supplementary Figure 3.** Interactions between tofacitinib and peficitib with JAK1 residues resulting from molecular dynamics simulation using the TIP3P water model. (A) and (B) show 2D interactions with tofacitinib and peficitinib, respectively. (C) and (D) show 3D interactions with tofacitinib and peficitinib, respectively. In 2D representations, the light green discs represent Van Der Waals interactions, the pink discs represent alkyl interactions (Hydrophobic), the purple disks represent Pi-Alkyl interactions (Hydrophobic), the dark pink represent Pi-Pi Stacked contacts (hydrophobic), the orange disc represents a Pi-Sulfur interaction, and finally, the lime green discs represent hydrogen bonds.



**Supplementary Figure 4.** Sum and convergence of energy based on final conformation provided by using CHARMM36 and TIP3P water model. The graph represents the interaction energy variation as a function of radius between ligand and JAK1 residues. Tofacitinib and Peficitinib with homogeneous constant are represented black and in lime green, respectively. Et represents the interaction energy sum.



**Supplementary Table 1**. Quantum description of the interactions between JAK1 and Tofacitinib using homogeneous dielectric function.

| JAK1 Residue | Distance (Å) | Interaction Energy (kcal/mol) | JAK1 Residue Atom | Tofacitinib Atom | Tofacitinib Region |
|---|---|---|---|---|---|
| GLU957 | 1.78 | -4.27 | O | H20(N12) | i |
| LEU959 | 2.10 | -7.59 | HN | N17(C18) | i |
| MET956 | 2.11 | -2.48 | HB1 | H18(C11) | I |
| LEU1010 | 2.12 | -5.91 | HD22 | H8(C6) | iii |
| VAL889 | 2.18 | -5.63 | HG22 | H2(C2) | iii |
| SER963 | 2.23 | -1.52 | HB2 | H11(C7) | iii |
| LEU881 | 2.25 | -3.81 | HB2 | H15(C9) | ii |
| ASP1021 | 2.42 | -5.97 | OD2 | H10(C22) | iv |
| PHE886 | 2.65 | -3.34 | HN | N24(C23) | iv |
| GLY884 | 2.84 | -2.39 | HA2 | N24(C23) | iv |
| PHE958 | 2.90 | -8.51 | HA | N17(C18) | i |
| VAL938 | 2.93 | -1.66 | HG22 | H18(C11) | i |
| GLY1020 | 2.98 | -1.47 | O | H6(C5) | iii |
| ALA906 | 3.02 | -2.85 | HB1 | H20(N12) | i |
| LYS908 | 3.06 | -2.69 | HE1 | N24(C23) | iv |
| ARG1007 | 3.16 | -1.02 | O | H7(C5) | iii |
| ASN1008 | 3.20 | -1.25 | HA | H7(C5) | iii |
| GLY962 | 3.31 | -1.21 | HA1 | H19(C18) | i |
| GLY887 | 3.61 | 1.14 | O | N24(C23) | iv |
| HIS885 | 3.74 | -2.70 | HN | N24(C23) | iv |
| PRO960 | 4.33 | -0.48 | HA | H19(C18) | i |
| GLY1023 | 5.01 | -0.10 | HN | H10(C22) | iv |
| PHE1022 | 5.11 | -0.51 | HN | H10(C22) | iv |
| GLY882 | 5.12 | -0.25 | O | H16(C9) | ii |
| VAL1009 | 5.19 | -0.48 | N | H7(C5) | iii |
| SER961 | 5.20 | -0.07 | N | H19(C18) | i |
| LYS888 | 5.33 | -0.30 | C | O21(C20) | iv |
| LEU929 | 5.54 | -0.11 | HD13 | H18(C11) | i |
| GLU883 | 5.61 | -1.76 | C | N24(C23) | iv |
| LEU954 | 5.65 | -0.19 | HG | H18(C11) | i |
| LEU964 | 5.76 | -0.12 | HN | H11(C7) | iii |
| LYS939 | 5.77 | -0.24 | O | H18(C11) | i |
| LEU891 | 5.87 | -0.21 | HD11 | H19(C18) | i |
| ALA1006 | 5.89 | -0.10 | O | H11(C7) | iii |
| LYS965 | 6.01 | -0.11 | HB2 | H11(C7) | iii |
| GLU925 | 6.04 | -0.12 | OE2 | N24(C23) | iv |
| VAL1011 | 6.04 | -0.24 | HN | H19(C18) | i |
| ILE955 | 6.14 | 0.00 | C | H18(C11) | i |
| VAL907 | 6.14 | -0.25 | N | H18(C11) | i |

| | | | | | |
|---|---|---|---|---|---|
| LYS1018 | 6.39 | -0.15 | HD2 | H20(N12) | i |
| GLU966 | 6.42 | -0.09 | HG2 | H12(C7) | iii |
| VAL905 | 6.45 | -0.10 | HA | H20(N12) | i |
| ILE1019 | 6.57 | -0.13 | HG22 | H7(C5) | iii |
| GLU890 | 6.64 | -0.14 | N | H16(C9) | ii |
| TYR940 | 6.64 | -0.06 | HA | H18(C11) | i |
| SER909 | 6.75 | -0.16 | HN | O21(C20) | iv |
| ASP880 | 6.76 | 0.08 | C | H15(C9) | ii |
| LYS941 | 6.84 | -0.07 | HG1 | H18(C11) | i |
| GLU1012 | 7.06 | 0.00 | HA | H19(C18) | i |
| ASP1003 | 7.12 | -0.15 | OD2 | H10(C22) | iv |
| LEU1024 | 7.16 | -0.03 | HN | H10(C22) | iv |
| ARG879 | 7.44 | -0.23 | HH21 | H15(C9) | ii |
| LYS911 | 7.48 | -0.32 | HB1 | N24(C23) | iv |
| ALA1005 | 7.57 | -0.04 | O | H7(C5) | iii |
| LEU910 | 7.69 | -0.01 | HA | N24(C23) | iv |
| HIS1001 | 7.80 | -0.05 | HE1 | H7(C5) | iii |

**Supplementary Table 2**. Quantum description of the interactions between JAK1 and Tofacitinib using inhomogeneous dielectric function.

| JAK1 Residue | Distance (Å) | Dielectric Constant | Interaction Energy (kcal/mol) | JAK1 Residue Atom | Tofacitinib Atom | Tofacitinib Region |
|---|---|---|---|---|---|---|
| GLU957 | 1.78 | 23.60 | -4.46 | O | H20(N12) | i |
| LEU959 | 2.10 | 27.14 | -7.64 | HN | N17(C18) | i |
| MET956 | 2.11 | 24.44 | -2.44 | HB1 | H18(C11) | I |
| LEU1010 | 2.12 | 24.85 | -5.95 | HD22 | H8(C6) | iii |
| VAL889 | 2.18 | 26.41 | -5.62 | HG22 | H2(C2) | iii |
| SER963 | 2.23 | 30.72 | -1.51 | HB2 | H11(C7) | iii |
| LEU881 | 2.25 | 29.90 | -3.83 | HB2 | H15(C9) | ii |
| ASP1021 | 2.42 | 30.48 | -6.15 | OD2 | H10(C22) | iv |
| PHE886 | 2.65 | 33.29 | -3.35 | HN | N24(C23) | iv |
| GLY884 | 2.84 | 40.33 | -2.39 | HA2 | N24(C23) | iv |
| PHE958 | 2.90 | 28.34 | -8.56 | HA | N17(C18) | i |
| VAL938 | 2.93 | 30.03 | -1.65 | HG22 | H18(C11) | i |
| GLY1020 | 2.98 | 29.07 | -1.48 | O | H6(C5) | iii |
| ALA906 | 3.02 | 26.31 | -2.88 | HB1 | H20(N12) | i |
| LYS908 | 3.06 | 33.97 | -2.77 | HE1 | N24(C23) | iv |
| ARG1007 | 3.16 | 39.66 | -1.02 | O | H7(C5) | iii |
| ASN1008 | 3.20 | 30.28 | -1.28 | HA | H7(C5) | iii |
| GLY962 | 3.31 | 34.03 | -1.22 | HA1 | H19(C18) | i |
| GLY887 | 3.61 | 34.78 | 1.16 | O | N24(C23) | iv |

| | | | | | | |
|---|---|---|---|---|---|---|
| HIS885 | 3.74 | 38.76 | -2.70 | HN | N24(C23) | iv |
| PRO960 | 4.33 | 33.55 | -0.49 | HA | H19(C18) | i |
| GLY1023 | 5.01 | 36.80 | -0.10 | HN | H10(C22) | iv |
| PHE1022 | 5.11 | 28.84 | -0.51 | HN | H10(C22) | iv |
| GLY882 | 5.12 | 42.72 | -0.25 | O | H16(C9) | ii |
| VAL1009 | 5.19 | 24.01 | -0.49 | N | H7(C5) | iii |
| SER961 | 5.20 | 34.97 | -0.08 | N | H19(C18) | i |
| LYS888 | 5.33 | 29.47 | -0.31 | C | O21(C20) | iv |
| LEU929 | 5.54 | 35.08 | -0.11 | HD13 | H18(C11) | i |
| GLU883 | 5.61 | 44.91 | -1.75 | C | N24(C23) | iv |
| LEU954 | 5.65 | 27.96 | -0.19 | HG | H18(C11) | i |
| LEU964 | 5.76 | 27.28 | -0.11 | HN | H11(C7) | iii |
| LYS939 | 5.77 | 26.61 | -0.25 | O | H18(C11) | i |
| LEU891 | 5.87 | 28.36 | -0.21 | HD11 | H19(C18) | i |
| ALA1006 | 5.89 | 29.72 | -0.10 | O | H11(C7) | iii |
| LYS965 | 6.01 | 40.53 | -0.11 | HB2 | H11(C7) | iii |
| GLU925 | 6.04 | 38.41 | -0.11 | OE2 | N24(C23) | iv |
| VAL1011 | 6.04 | 30.70 | -0.24 | HN | H19(C18) | i |
| ILE955 | 6.14 | 25.98 | 0.01 | C | H18(C11) | i |
| VAL907 | 6.14 | 26.09 | -0.24 | N | H18(C11) | i |
| LYS1018 | 6.39 | 25.56 | -0.11 | HD2 | H20(N12) | i |
| GLU966 | 6.42 | 44.60 | -0.09 | HG2 | H12(C7) | iii |
| VAL905 | 6.45 | 23.81 | -0.07 | HA | H20(N12) | i |
| ILE1019 | 6.57 | 25.94 | -0.12 | HG22 | H7(C5) | iii |
| GLU890 | 6.64 | 21.68 | -0.05 | N | H16(C9) | ii |
| TYR940 | 6.64 | 23.44 | -0.06 | HA | H18(C11) | i |
| SER909 | 6.75 | 26.37 | -0.13 | HN | O21(C20) | iv |
| ASP880 | 6.76 | 32.12 | 0.09 | C | H15(C9) | ii |
| LYS941 | 6.84 | 25.33 | -0.03 | HG1 | H18(C11) | i |
| GLU1012 | 7.06 | 28.85 | -0.01 | HA | H19(C18) | i |
| ASP1003 | 7.12 | 33.44 | -0.18 | OD2 | H10(C22) | iv |
| LEU1024 | 7.16 | 35.03 | -0.03 | HN | H10(C22) | iv |
| ARG879 | 7.44 | 31.64 | -0.24 | HH21 | H15(C9) | ii |
| LYS911 | 7.48 | 36.01 | -0.34 | HB1 | N24(C23) | iv |
| ALA1005 | 7.57 | 29.87 | -0.05 | O | H7(C5) | iii |
| LEU910 | 7.69 | 27.74 | 0.01 | HA | N24(C23) | iv |
| HIS1001 | 7.80 | 25.74 | -0.06 | HE1 | H7(C5) | iii |

**Supplementary Table 3**. Quantum description of the interactions between JAK1 and Peficitinib using homogeneous dielectric function.

| JAK1 Residue | Distance (Å) | Interaction Energy (kcal/mol) | JAK1 Residue Atom | Peficitinib Atom | Peficitinib Region |
|---|---|---|---|---|---|
| LEU959 | 1.83 | -11.58 | O | H20(N12) | Iv |
| GLU957 | 1.94 | -4.57 | O | H18(N7) | I |
| VAL889 | 2.17 | -4.47 | HG23 | H13(C16) | Iii |
| LEU1010 | 2.22 | -6.61 | HD13 | H17(C18) | Iii |
| PHE958 | 2.38 | -13.44 | HD1 | H2(C3) | I |
| GLY962 | 2.48 | -0.80 | HN | H19(N12) | Iv |
| LEU881 | 2.52 | -8.08 | HB2 | H6(C23) | Iii |
| VAL938 | 2.57 | -1.24 | HG21 | H3(C8) | I |
| GLY884 | 2.62 | -3.19 | HA2 | O24(H22) | Iii |
| ASP1021 | 2.73 | -4.25 | HB1 | H11(C15) | Iii |
| MET956 | 2.75 | -1.87 | SD | H3(C8) | I |
| GLY882 | 3.12 | -1.27 | HA2 | H14(C21) | Iii |
| GLU883 | 3.16 | -2.48 | C | H8(C22) | Iii |
| PRO960 | 3.32 | -2.46 | HA | H20(N12) | Iv |
| ALA906 | 3.42 | -1.62 | HB3 | H18(N7) | I |
| GLY1020 | 3.44 | -1.21 | O | H1(C9) | I |
| SER961 | 3.85 | 1.90 | N | H20(N12) | Iv |
| LYS908 | 3.89 | -2.11 | HZ2 | H13(C16) | Iii |
| HIS885 | 4.25 | -0.35 | HN | H22(O24) | Iii |
| SER963 | 4.61 | -0.56 | HB1 | H15(C14) | Iii |
| ARG879 | 4.62 | -0.57 | HH12 | H19(N12) | Iv |
| LEU891 | 4.74 | -0.40 | HD11 | H2(C3) | I |
| ARG1007 | 5.02 | -0.92 | O | H15(C14) | Iii |
| ASN1008 | 5.06 | -0.52 | HA | H11(C15) | Iii |
| PHE1022 | 5.08 | -0.50 | HE1 | H3(C8) | I |
| GLY887 | 5.12 | -0.18 | O | H8(C22) | Iii |
| VAL1011 | 5.23 | -0.36 | O | H20(N12) | Iv |
| LYS888 | 5.40 | -0.48 | HA | H8(C22) | Iii |
| LEU929 | 5.65 | -0.08 | HD11 | H3(C8) | I |
| LYS939 | 6.15 | -0.13 | HN | H18(N7) | I |
| GLU890 | 6.19 | -0.23 | N | H7(C23) | Iii |
| ILE1019 | 6.22 | -0.18 | O | H3(C8) | I |
| ASP880 | 6.43 | -0.07 | C | H6(C23) | Iii |
| GLU925 | 6.45 | 0.05 | OE1 | H12(C16) | Iii |
| VAL905 | 6.54 | -0.13 | HA | H18(N7) | I |
| VAL1009 | 6.55 | -0.32 | O | H15(C14) | Iii |
| GLY1023 | 6.55 | -0.06 | HA2 | H22(O24) | Iii |
| GLU1012 | 6.60 | -0.08 | HA | H20(N12) | Iv |
| LYS1018 | 6.96 | -0.10 | HD2 | H18(N7) | I |

| | | | | | |
|---|---|---|---|---|---|
| ASP1003 | 7.08 | -0.23 | OD2 | H22(O24) | Iii |
| GLU966 | 7.13 | -0.11 | OE1 | H5(C19) | Iii |
| LEU954 | 7.15 | -0.06 | HD23 | H3(C8) | I |
| VAL907 | 7.25 | -0.16 | N | N7(H18) | I |
| LYS941 | 7.41 | -0.04 | HG1 | H18(N7) | I |
| LEU964 | 7.45 | -0.05 | HN | H15(C14) | Iii |
| ILE955 | 7.73 | -0.06 | C | H18(N7) | I |
| TYR940 | 7.77 | -0.03 | HA | H3(C8) | I |
| ILE937 | 7.81 | 0.00 | HG23 | H3(C8) | I |
| GLN904 | 7.83 | -0.05 | HB2 | H2(C3) | I |
| PHE886 | 7.94 | -0.08 | N | O24(H22) | Iii |
| CYS892 | 7.98 | -0.03 | HN | H2(C3) | I |

**Supplementary Table 4**. Quantum description of the interactions between JAK1 and Peficitinib using inhomogeneous dielectric function.

| JAK1 Residue | Distance (Å) | Dielectric Function | Interaction Energy (kcal/mol) | JAK1 Residue Atom | Peficitinib Atom | Peficitinib Region |
|---|---|---|---|---|---|---|
| LEU959 | 1.83 | 24.49 | -11.71 | O | H20(N12) | iv |
| GLU957 | 1.94 | 22.10 | -4.80 | O | H18(N7) | i |
| VAL889 | 2.17 | 26.29 | -4.48 | HG23 | H13(C16) | iii |
| LEU1010 | 2.22 | 26.13 | -6.62 | HD13 | H17(C18) | iii |
| PHE958 | 2.38 | 24.01 | -13.49 | HD1 | H2(C3) | i |
| GLY962 | 2.48 | 35.69 | -0.81 | HN | H19(N12) | iv |
| LEU881 | 2.52 | 29.75 | -8.06 | HB2 | H6(C23) | iii |
| VAL938 | 2.57 | 25.23 | -1.25 | HG21 | H3(C8) | i |
| GLY884 | 2.62 | 31.52 | -3.18 | HA2 | O24(H22) | iii |
| ASP1021 | 2.73 | 34.19 | -4.30 | HB1 | H11(C15) | iii |
| MET956 | 2.75 | 27.77 | -1.87 | SD | H3(C8) | i |
| GLY882 | 3.12 | 31.44 | -1.26 | HA2 | H14(C21) | iii |
| GLU883 | 3.16 | 35.65 | -2.48 | C | H8(C22) | iii |
| PRO960 | 3.32 | 28.61 | -2.46 | HA | H20(N12) | iv |
| ALA906 | 3.42 | 29.25 | -1.63 | HB3 | H18(N7) | i |
| GLY1020 | 3.44 | 30.47 | -1.22 | O | H1(C9) | i |
| SER961 | 3.85 | 34.27 | 1.89 | N | H20(N12) | iv |
| LYS908 | 3.89 | 30.94 | -2.18 | HZ2 | H13(C16) | iii |
| HIS885 | 4.25 | 38.92 | -0.35 | HN | H22(O24) | iii |
| SER963 | 4.61 | 37.18 | -0.56 | HB1 | H15(C14) | iii |
| ARG879 | 4.62 | 31.13 | -0.60 | HH12 | H19(N12) | iv |
| LEU891 | 4.74 | 24.54 | -0.40 | HD11 | H2(C3) | i |

| | | | | | | |
|---|---|---|---|---|---|---|
| ARG1007 | 5.02 | 47.90 | -0.92 | O | H15(C14) | iii |
| ASN1008 | 5.06 | 38.01 | -0.52 | HA | H11(C15) | iii |
| PHE1022 | 5.08 | 32.26 | -0.50 | HE1 | H3(C8) | i |
| GLY887 | 5.12 | 33.28 | -0.18 | O | H8(C22) | iii |
| VAL1011 | 5.23 | 31.61 | -0.36 | O | H20(N12) | iv |
| LYS888 | 5.40 | 29.81 | -0.49 | HA | H8(C22) | iii |
| LEU929 | 5.65 | 33.18 | -0.09 | HD11 | H3(C8) | i |
| LYS939 | 6.15 | 24.72 | -0.12 | HN | H18(N7) | i |
| GLU890 | 6.19 | 23.51 | -0.20 | N | H7(C23) | iii |
| ILE1019 | 6.22 | 29.58 | -0.18 | O | H3(C8) | i |
| ASP880 | 6.43 | 27.96 | -0.05 | C | H6(C23) | iii |
| GLU925 | 6.45 | 37.62 | 0.05 | OE1 | H12(C16) | iii |
| VAL905 | 6.54 | 24.17 | -0.12 | HA | H18(N7) | i |
| VAL1009 | 6.55 | 24.93 | -0.32 | O | H15(C14) | iii |
| GLY1023 | 6.55 | 39.57 | -0.06 | HA2 | H22(O24) | iii |
| GLU1012 | 6.60 | 27.01 | -0.10 | HA | H20(N12) | iv |
| LYS1018 | 6.96 | 25.13 | -0.07 | HD2 | H18(N7) | i |
| ASP1003 | 7.08 | 34.26 | -0.24 | OD2 | H22(O24) | iii |
| GLU966 | 7.13 | 46.78 | -0.11 | OE1 | H5(C19) | iii |
| LEU954 | 7.15 | 25.75 | -0.05 | HD23 | H3(C8) | i |
| VAL907 | 7.25 | 24.31 | -0.15 | N | N7(H18) | i |
| LYS941 | 7.41 | 25.56 | -0.03 | HG1 | H18(N7) | i |
| LEU964 | 7.45 | 25.21 | -0.05 | HN | H15(C14) | iii |
| ILE955 | 7.73 | 25.49 | -0.05 | C | H18(N7) | i |
| TYR940 | 7.77 | 26.17 | -0.03 | HA | H3(C8) | i |
| ILE937 | 7.81 | 24.36 | 0.00 | HG23 | H3(C8) | i |
| GLN904 | 7.83 | 28.18 | -0.06 | HB2 | H2(C3) | i |
| PHE886 | 7.94 | 38.65 | -0.08 | N | O24(H22) | iii |
| CYS892 | 7.98 | 26.23 | -0.03 | HN | H2(C3) | i |

**Supplementary Table 5.** The relation between the types of interactions of amino acid residues of JAK1 using homogeneous dielectric function with tofacitinib and their associated energies.

| Interaction type | JAK1 residue | Interaction energy (kcal.mol$^{-1}$) | Interaction energy sum (kcal.mol-1) |
|---|---|---|---|
| Van der Waals | LEU$^{881}$ | -3.81 | -28.67 |
| | HIS$^{885}$ | -2.70 | |
| | GLY$^{887}$ | 1.14 | |
| | VAL$^{889}$ | -5.63 | |
| | LYS$^{908}$ | -2.69 | |
| | PHE$^{958}$ | -8.51 | |
| | GLY$^{962}$ | -1.21 | |
| | SER$^{963}$ | -1.52 | |
| | ARG$^{1007}$ | -1.02 | |
| | ASN$^{1008}$ | -1.25 | |
| | GLY$^{1020}$ | -1.47 | |
| Hydrogen bonds | GLU$^{957}$ | -4.27 | -11.86 |
| | LEU$^{959}$ | -7.59 | |
| Hydrophobic (Alkyl and Pi-Alkyl) | ALA$^{906}$ | -2.85 | -4.51 |
| | VAL$^{938}$ | -1.66 | |
| π-Sulfur | MET$^{956}$ | -2.48 | -2.48 |

**Supplementary Table 6**. The relation between the types of interactions of the amino acid residue of JAK1 using inhomogeneous dielectric function with tofacitinib and their associated energies.

| Interaction type | JAK1 residue | Interaction energy (kcal.mol$^{-1}$) | Interaction energy sum (kcal.mol-1) |
|---|---|---|---|
| Van der Waals | LEU$^{881}$ | -3.83 | -28.83 |
| | HIS$^{885}$ | -2.70 | |
| | GLY$^{887}$ | 1.16 | |
| | VAL$^{889}$ | -5.62 | |
| | LYS$^{908}$ | -2.77 | |
| | PHE$^{958}$ | -8.56 | |
| | GLY$^{962}$ | -1.22 | |
| | SER$^{963}$ | -1.51 | |
| | ARG$^{1007}$ | -1.02 | |
| | ASN$^{1008}$ | -1.28 | |
| | GLY$^{1020}$ | -1.48 | |
| Hydrogen bonds | GLU$^{957}$ | -4.46 | -12.10 |
| | LEU$^{959}$ | -7.64 | |
| Hydrophobic (Alkyl and Pi-Alkyl) | ALA$^{906}$ | -2.88 | -4.53 |
| | VAL$^{938}$ | -1.65 | |
| π-Sulfur | MET$^{956}$ | -2.44 | -2.44 |

**Supplementary Table 7.** The relation between the types of interactions of amino acid residues of JAK1 with peficitinib and their associated energies considering homogeneous dielectric function.

| Interaction type | JAK1 residue | Interaction energy (kcal.mol$^{-1}$) | Interaction energy sum (kcal.mol-1) |
|---|---|---|---|
| Van der Waals | GLY$^{882}$ | -1.27 | -30.55 |
| | GLU$^{883}$ | -2.48 | |
| | GLY$^{884}$ | -3.19 | |
| | LYS$^{908}$ | -2.11 | |
| | VAL$^{938}$ | -1.24 | |
| | PHE$^{958}$ | -13.44 | |
| | PRO$^{960}$ | -2.46 | |
| | SER$^{961}$ | 1.90 | |
| | GLY$^{962}$ | -0.80 | |
| | GLY$^{1020}$ | -1.21 | |
| | ASP$^{1021}$ | -4.25 | |
| Hydrogen bonds | GLU$^{957}$ | -4.57 | -16.15 |
| | LEU$^{959}$ | -11.58 | |
| Hydrophobic (Alkyl and Pi-Alkyl) | ALA$^{906}$ | -1.62 | -10.10 |
| | MET$^{956}$ | -1.87 | |
| | LEU$^{1010}$ | -6.61 | |

**Supplementary Table 8.** The relation between the types of interactions of amino acid residues of JAK1 with peficitinib and their associated energies considering inhomogeneous dielectric function.

| Interaction type | JAK1 residue | Interaction energy (kcal.mol$^{-1}$) | Interaction energy sum (kcal.mol-1) |
|---|---|---|---|
| Van der Waals | GLY$^{882}$ | -1.26 | -30.74 |
| | GLU$^{883}$ | -2.48 | |
| | GLY$^{884}$ | -3.18 | |
| | LYS$^{908}$ | -2.18 | |
| | VAL$^{938}$ | -1.25 | |
| | PHE$^{958}$ | -13.49 | |
| | PRO$^{960}$ | -2.46 | |
| | SER$^{961}$ | 1.89 | |
| | GLY$^{962}$ | -0.81 | |
| | GLY$^{1020}$ | -1.22 | |
| | ASP$^{1021}$ | -4.30 | |
| Hydrogen bonds | GLU$^{957}$ | -4.80 | -16.51 |
| | LEU$^{959}$ | -11.71 | |
| Hydrophobic (Alkyl and Pi-Alkyl) | ALA$^{906}$ | -1.63 | -10.12 |
| | MET$^{956}$ | -1.87 | |
| | LEU$^{1010}$ | -6.62 | |

**Supplementary Table 9.** Quantum description of the surface interactions (conformation obtained by using CHARMM36 and TIP3P) between JAK1 and Tofacitinib using homogeneous dielectric function (40).

| JAK1 Residue | Distance (Å) | Interaction Energy (kcal/mol) | JAK1 Residue Atom | Tofacitinib Atom | Tofacitinib Region |
|---|---|---|---|---|---|
| GLU957 | 1.77 | -5.05 | O | H20(N12) | I |
| MET956 | 2.00 | -2.60 | HB2 | H18(C11) | I |
| LEU881 | 2.04 | -5.01 | HD13 | H16(C9) | Ii |
| VAL889 | 2.09 | -4.78 | HG12 | H2(C2) | Iii |
| LEU959 | 2.22 | -6.00 | HN | N17(C18) | I |
| LEU1010 | 2.23 | -5.50 | HD22 | H13(C7) | Iii |
| SER963 | 2.38 | -0.94 | HB1 | H13(C7) | iii |
| ASP1021 | 2.43 | -6.02 | HB1 | H9(C22) | iv |
| GLY884 | 2.67 | -1.78 | HA1 | N24(C23) | iv |
| PHE958 | 2.73 | -9.69 | HE1 | H19(C18) | i |
| VAL938 | 2.75 | -1.23 | HG12 | H18(C11) | i |
| ALA906 | 2.86 | -3.46 | HB3 | H20(N12) | i |
| ASN1008 | 2.98 | -1.23 | HÁ | H7(C5) | iii |
| GLY1020 | 3.11 | -1.75 | O | H6(C5) | iii |
| GLY882 | 3.13 | -1.03 | HA1 | H14(C9) | ii |
| ARG1007 | 3.18 | -1.67 | O | H7(C5) | iii |
| LYS908 | 3.59 | -0.59 | HZ3 | H10(C22) | iv |
| HIS885 | 3.62 | -1.03 | HN | N24(C23) | iv |
| GLY962 | 4.00 | -0.35 | HA2 | H19(C18) | i |
| GLU883 | 4.22 | -1.07 | O | N24(C23) | iv |
| PRO960 | 4.28 | -0.16 | HÁ | H19(C18) | i |
| PHE886 | 4.56 | -0.54 | HD2 | H10(C22) | iv |
| VAL1009 | 4.94 | -0.60 | N | H7(C5) | iii |
| GLU925 | 5.07 | -0.40 | OE1 | H10(C22) | iv |
| GLY1023 | 5.22 | -0.08 | HN | H9(C22) | iv |
| PHE1022 | 5.28 | -0.44 | HN | H9(C22) | iv |
| GLY887 | 5.35 | -0.11 | O | O21(C20) | iv |
| LEU929 | 5.51 | -0.08 | HD12 | H18(C11) | i |
| LYS888 | 5.68 | -0.57 | C | O21(C20) | iv |
| GLU966 | 5.70 | -0.37 | OE1 | H12(C7) | iii |
| SER961 | 5.72 | -0.07 | N | H19(C18) | i |
| LEU964 | 5.77 | -0.12 | HN | H13(C7) | iii |
| VAL905 | 5.81 | -0.18 | HA | H20(N12) | i |
| LYS939 | 5.94 | -0.20 | O | H18(C11) | i |
| ALA1006 | 6.01 | -0.12 | O | H13(C7) | iii |
| VAL907 | 6.06 | -0.26 | N | C11(H18) | i |

| | | | | | |
|---|---|---|---|---|---|
| LEU891 | 6.14 | -0.19 | HD12 | H19(C18) | i |
| LYS965 | 6.22 | -0.18 | HB2 | H13(C7) | iii |
| ILE955 | 6.24 | 0.01 | C | H18(C11) | i |
| ARG879 | 6.25 | -0.21 | HH11 | H16(C9) | ii |
| LEU954 | 6.36 | -0.10 | HG | H18(C11) | i |
| LYS1018 | 6.61 | -0.14 | HD1 | H20(N12) | i |
| VAL1011 | 6.69 | -0.14 | HN | H19(C18) | i |
| LYS941 | 6.79 | -0.05 | HG1 | H20(N12) | i |
| ILE1019 | 6.85 | -0.15 | HA | H7(C5) | iii |
| GLU890 | 6.88 | -0.15 | HA | H14(C9) | ii |
| LEU1024 | 7.13 | -0.05 | HN | H9(C22) | iv |
| SER909 | 7.27 | -0.06 | HN | O21(C20) | iv |
| TYR940 | 7.46 | -0.03 | HA | H18(C11) | i |
| ASP880 | 7.50 | 0.08 | C | H14(C9) | ii |
| GLN904 | 7.52 | -0.07 | O | H20(N12) | i |
| ALA1005 | 7.59 | -0.05 | O | H7(C5) | iii |
| ASP1003 | 7.84 | 0.04 | OD2 | N24(C23) | iv |

**Supplementary Table 10.** Quantum description of the surface interactions (conformation obtained by using CHARMM36 and TIP3P) between JAK1 and Peficitinitb using homogeneous dielectric function (40).

| JAK1 Residue | Distance (Å) | Interaction Energy (kcal/mol) | JAK1 Residue Atom | Peficitinib Atom | Peficitinib Region |
|---|---|---|---|---|---|
| PHE958 | 1.79 | -13.36 | HE1 | H20(N12) | iv |
| GLU957 | 1.81 | -5.79 | O | H18(N7) | i |
| LEU959 | 1.97 | -7.49 | HN | N4(C6) | i |
| LEU1010 | 2.08 | -6.93 | HD22 | H4(C19) | iii |
| GLU883 | 2.13 | -5.62 | O | H22(O24) | iii |
| LEU881 | 2.32 | -7.30 | HD23 | H19(N12) | iv |
| GLY882 | 2.44 | -2.07 | HA1 | H7(C23) | iii |
| MET956 | 2.52 | -1.22 | HG1 | H3(C8) | i |
| VAL889 | 2.54 | -5.91 | HG11 | H1(C9) | i |
| GLY962 | 2.58 | -1.32 | HA2 | H2(C3) | i |
| ALA906 | 2.62 | -2.46 | HB2 | H3(C8) | i |
| GLY884 | 2.66 | -2.33 | HA2 | H22(O24) | iii |
| ASP1021 | 2.68 | -2.21 | HB1 | H10(C15) | iii |
| SER963 | 2.82 | -2.95 | HB2 | H15(C19) | iii |
| ARG1007 | 2.88 | -2.39 | O | H4(C19) | iii |
| VAL938 | 3.07 | -0.85 | HG22 | H18(N7) | i |
| GLY1020 | 3.64 | -1.12 | O | H15(C14) | iii |
| ASN1008 | 3.65 | -1.47 | HA | H10(C15) | iii |
| GLU966 | 3.89 | -0.68 | OE1 | H14(C21) | iii |
| ARG879 | 4.43 | 0.03 | HH22 | H19(N12) | iv |
| PRO960 | 4.54 | -0.43 | N | H2(C3) | i |
| LYS888 | 4.69 | -0.28 | HA | H12(C16) | iii |
| HIS885 | 4.99 | -0.37 | HN | H22(O24) | iii |
| LYS908 | 5.01 | -0.42 | HB1 | H3(C8) | i |
| SER961 | 5.26 | 0.13 | C | H2(C3) | i |
| LEU891 | 5.46 | -0.33 | HB1 | H20(N12) | iv |
| VAL1009 | 5.51 | -0.44 | O | H4(C19) | iii |
| VAL907 | 5.78 | -0.26 | N | H3(C8) | i |
| ASP880 | 5.83 | -0.46 | C | H16(C17) | iii |
| LEU964 | 5.83 | -0.18 | HN | H4(C19) | iii |
| GLU890 | 5.84 | -0.50 | HA | H16(C17) | iii |
| LYS965 | 5.87 | -0.44 | HB2 | H14(C21) | iii |
| GLY887 | 5.99 | -0.08 | O | H22(O24) | iii |
| VAL1011 | 6.03 | -0.22 | HN | H2(C3) | i |
| VAL905 | 6.26 | -0.20 | HA | H18(N7) | i |
| ALA1006 | 6.30 | -0.07 | O | H4(C19) | iii |

| | | | | | |
|---|---|---|---|---|---|
| PHE1022 | 6.41 | -0.25 | HN | H11(C15) | iii |
| LEU929 | 6.44 | -0.03 | HD23 | H3(C8) | i |
| ASP1003 | 6.47 | 0.05 | OD1 | O24(H22) | iii |
| LYS939 | 6.59 | -0.14 | HN | H18(N7) | i |
| ILE955 | 6.69 | -0.03 | HA | H3(C8) | i |
| LYS1018 | 6.74 | -0.16 | HD1 | H18(N7) | i |
| LEU954 | 7.08 | -0.05 | HG | H3(C8) | i |
| GLY1023 | 7.12 | -0.07 | HN | H11(C15) | iii |
| GLU1012 | 7.24 | 0.02 | HA | H2(C3) | i |
| ALA1005 | 7.25 | -0.05 | HB2 | H9(C22) | iii |
| ILE1019 | 7.26 | -0.17 | C | H15(C14) | iii |
| LYS941 | 7.46 | -0.01 | HG1 | H18(N7) | i |
| SER909 | 7.50 | -0.06 | HN | H12(C16) | iii |
| HIS1001 | 7.67 | -0.03 | HE1 | H10(C15) | iii |
| TYR967 | 7.68 | -0.10 | HN | H14(C21) | iii |
| GLN904 | 7.71 | -0.07 | OE1 | H20(N12) | iv |