## Supporting Information For

# Molecular Dynamics Simulation Studies of GSK-3β ATP competitive Inhibitors: Understanding the Factors Contributing to Selectivity

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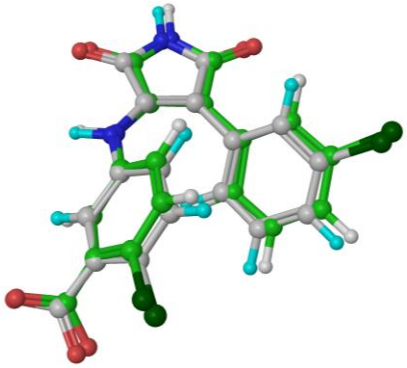

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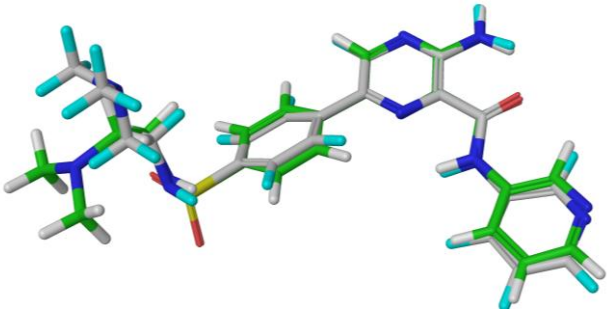

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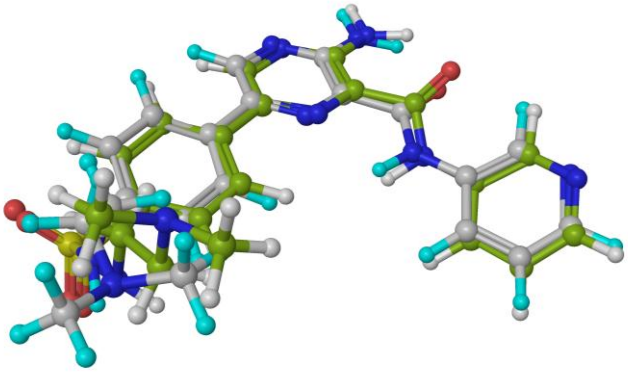

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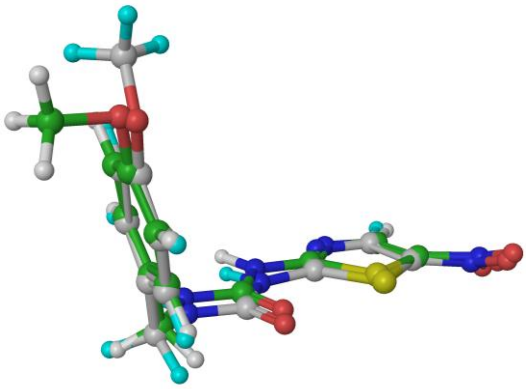

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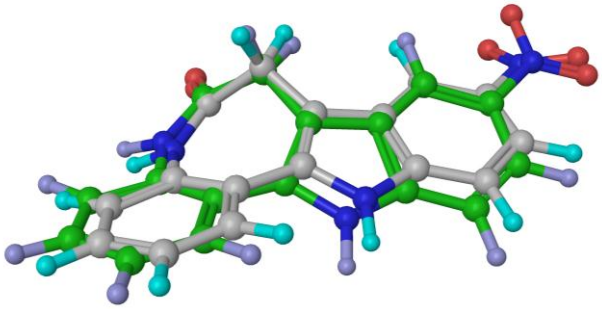

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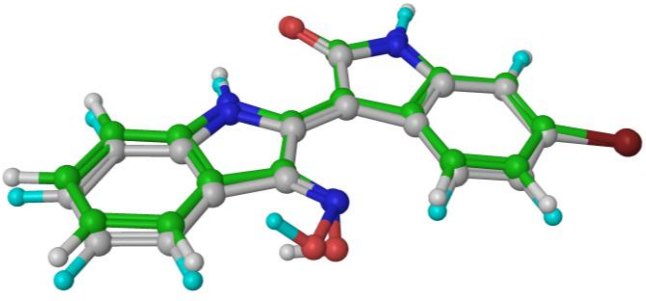

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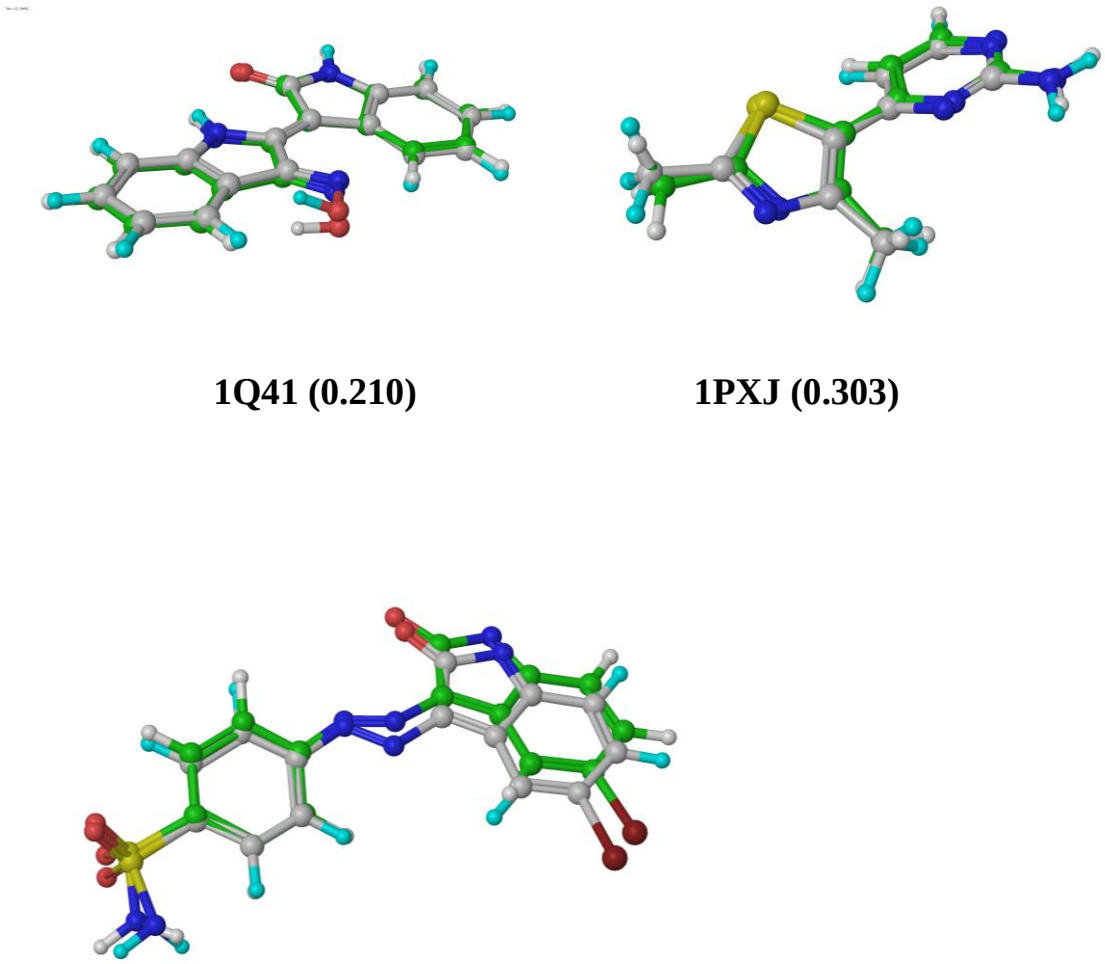
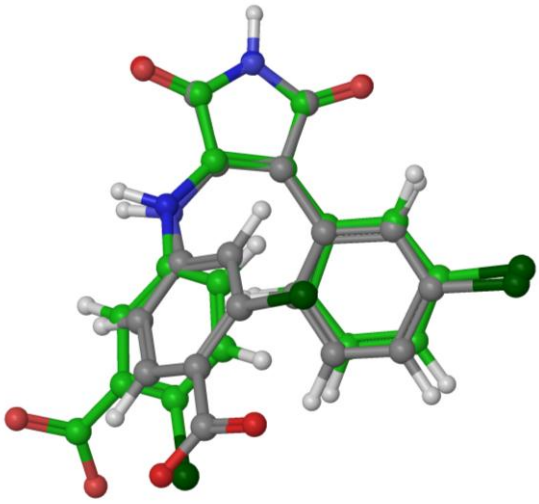



**Figure S1.** Superimposed images of docked (green) and X-ray (grey) structures of bound ligands. PDB code (RMSD values).



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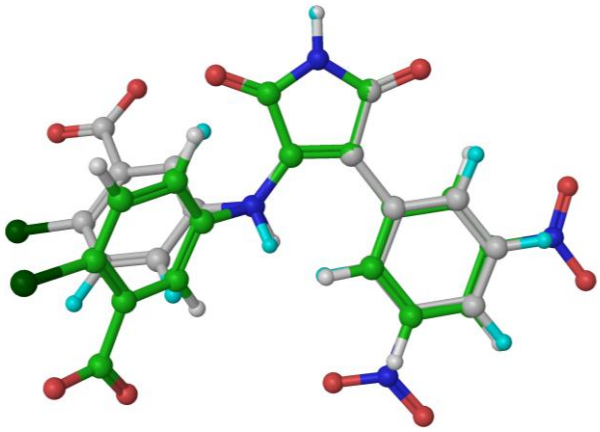

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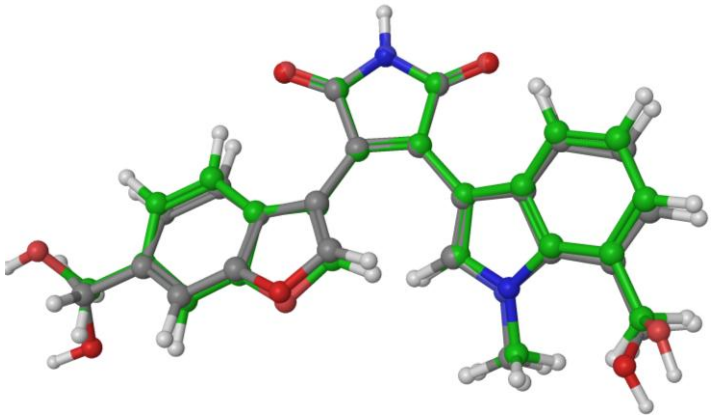

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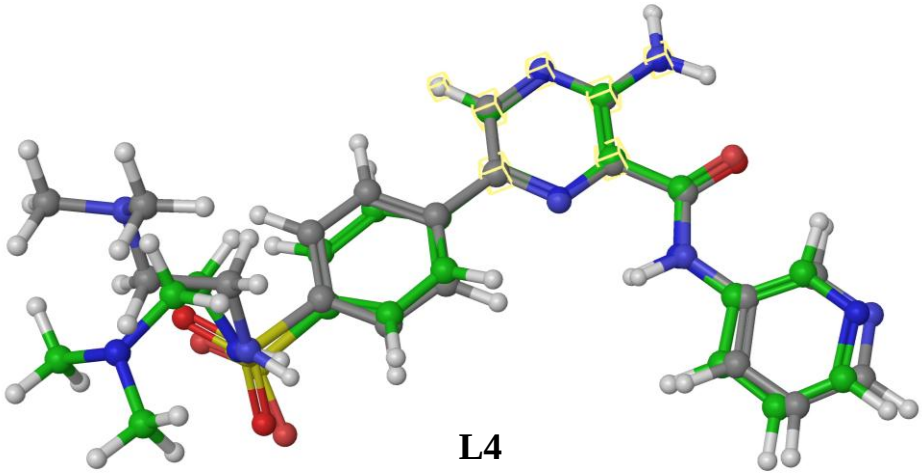

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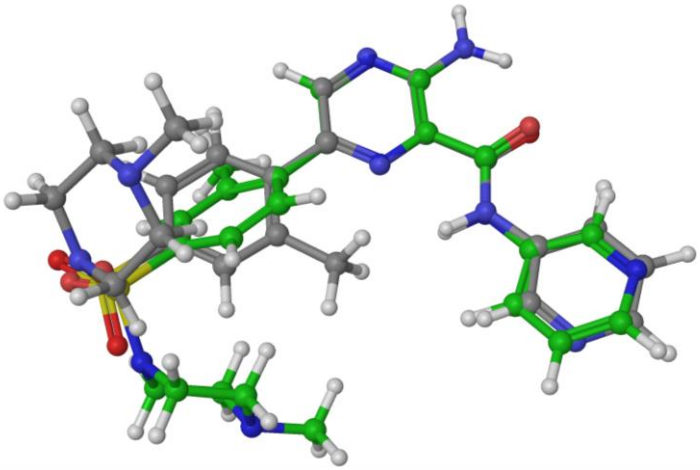

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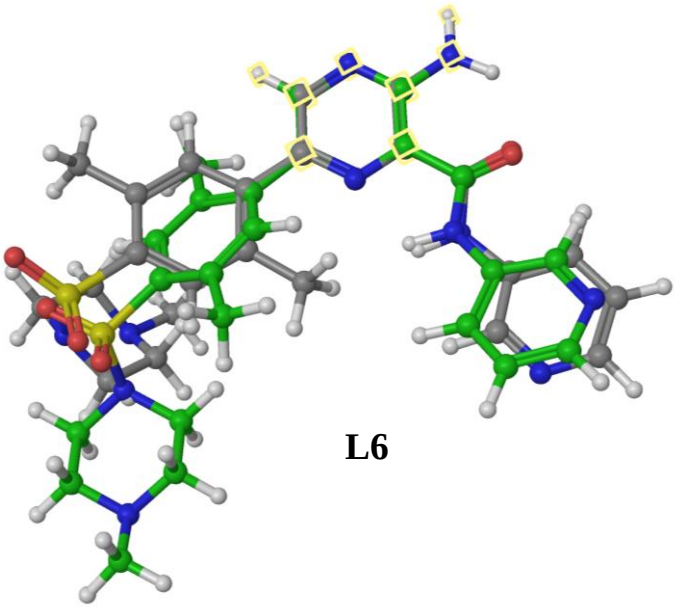

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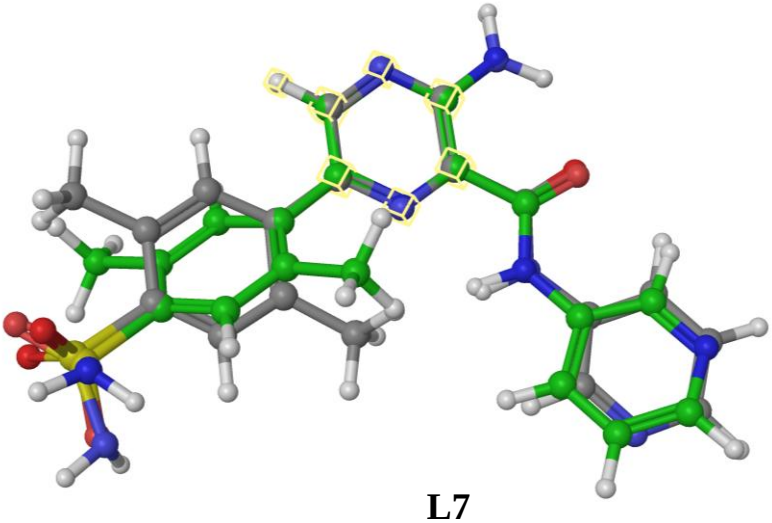

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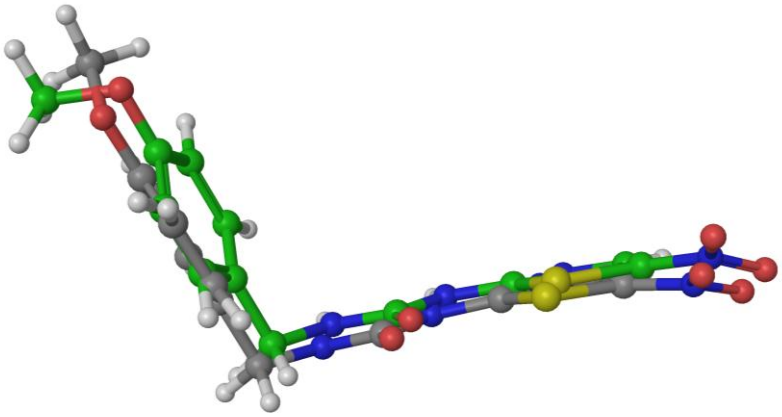

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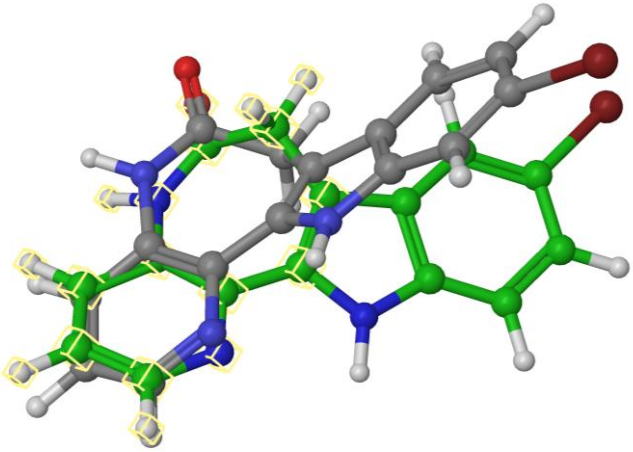

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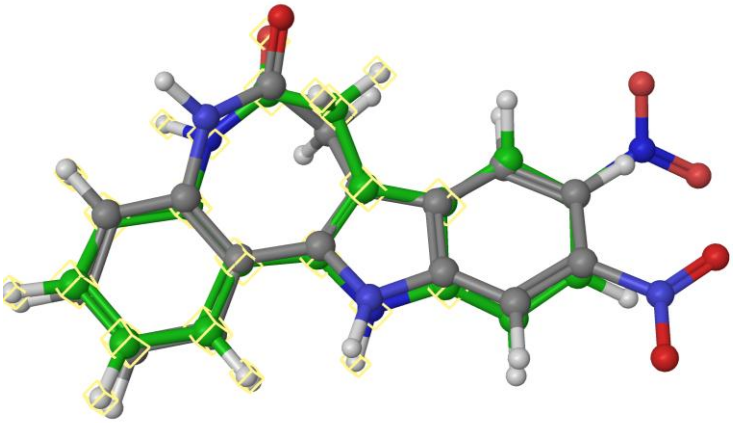

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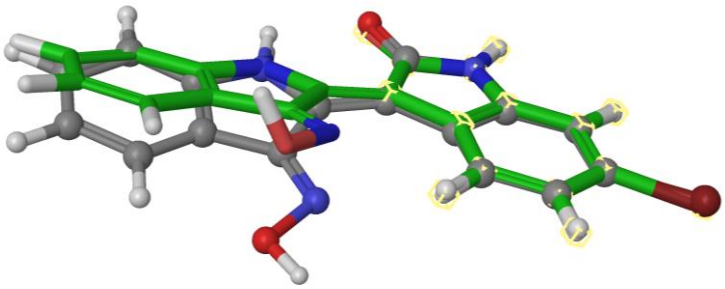

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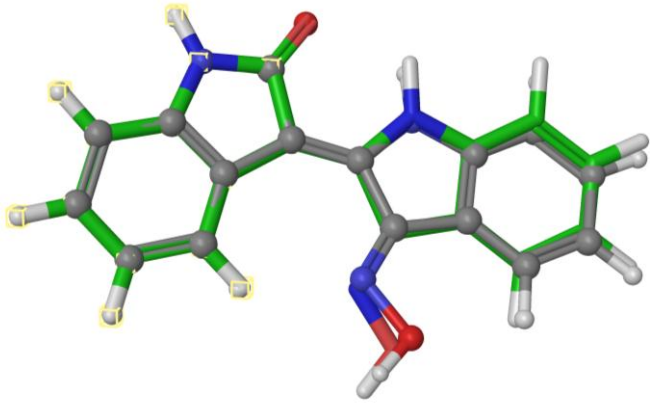
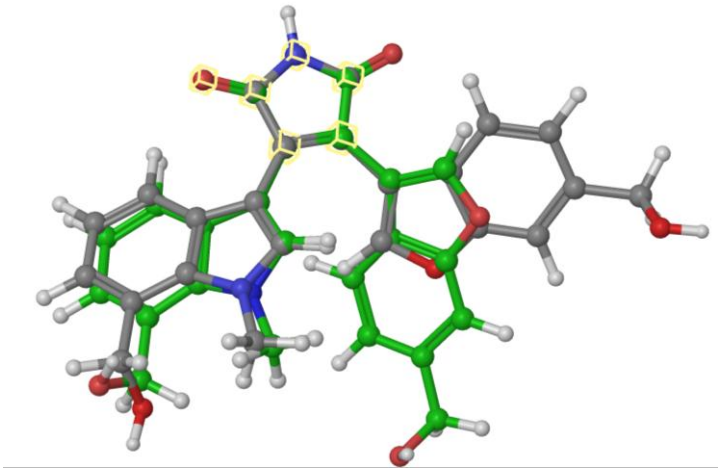


**L12**

**Figure S2**. Superimposed structures of docked (green) and low energy conformers of the ligand considered for docking in GSK-3β.



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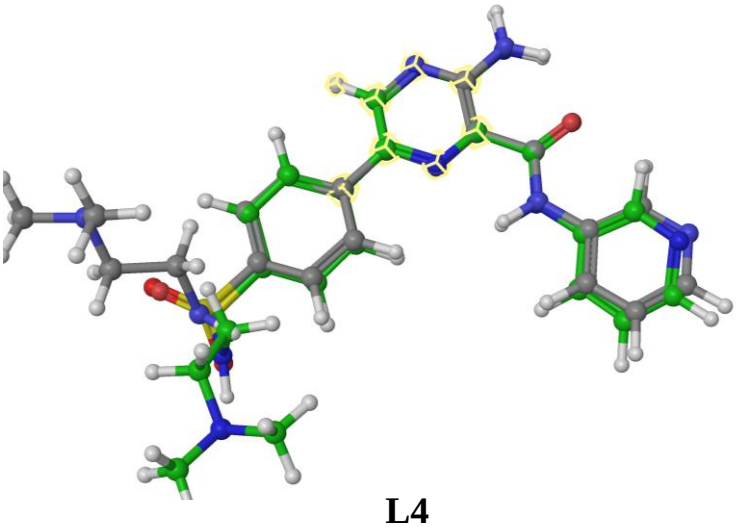

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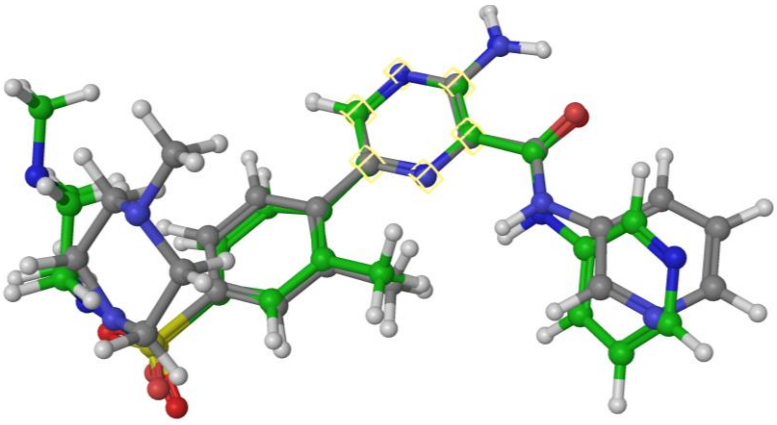

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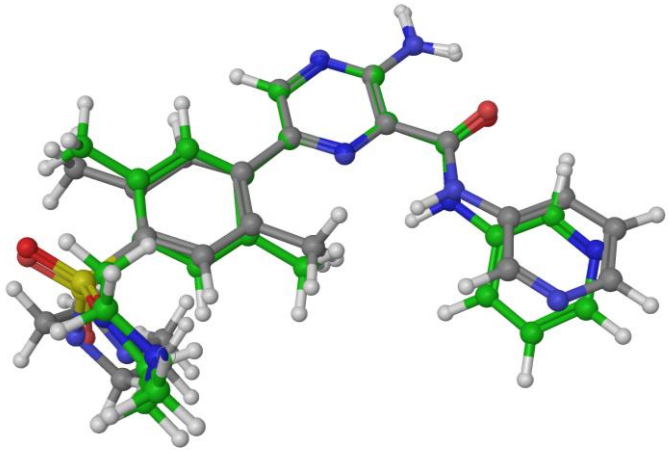

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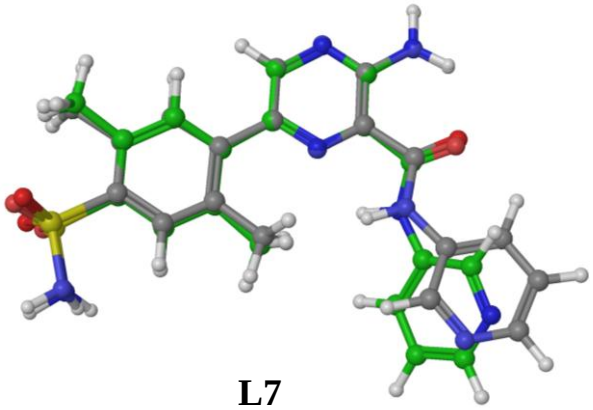

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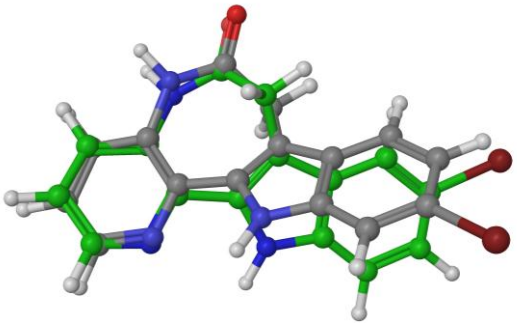

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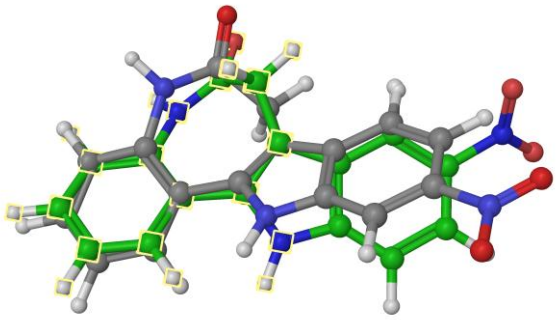

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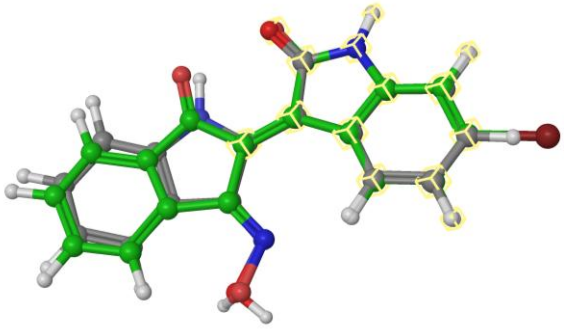

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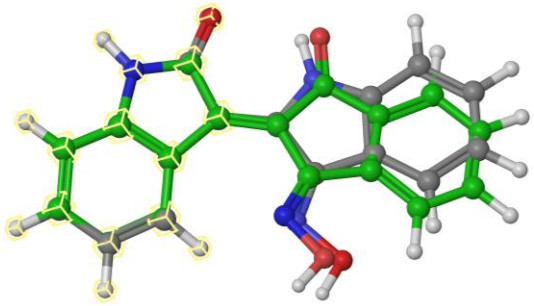

**L12**

**Figure S3.** superimposed structure docked (green) ligand and low energy conformer in CDK-2 enzyme (grey). For Ligands L1, L2 and L8 the starting structures for MD simulation was obtained by alignment of GSK-3β complex with CDK-2 and extracting followed by merging of the ligand into the ATP binding cavity of CDK-2.

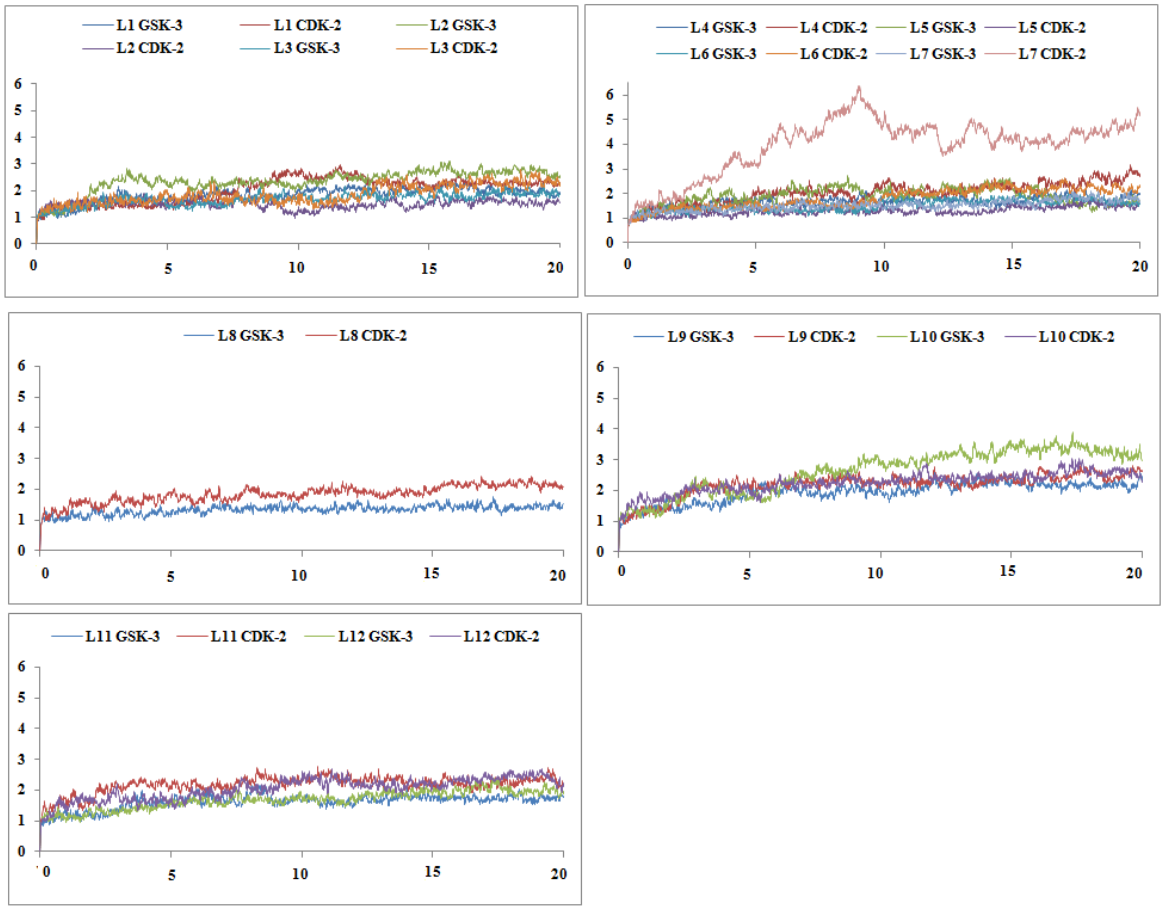


**Figure S4.** RMSD curve for whole backbone of 24 enzyme inhibitor complexes. The horizontal axis represents the time in ns, while the vertical axis represents the RMSD in Angstrom unit (Å). (A) Maleimides (L1-L3) (B) Pyrazines (L4-L7) (C) Nitrothiazoles (L8) (D) Paullones (L9-L10) (E) Indirubins (L11-L12). (with reference to the first frame after 4 ns)

**Table S1.** Root Mean Square Deviation values (RMSD) and Standard Deviation (SD) for the back bone atoms. (with reference to the first frame after 4 ns)

| | GSK-3 | SD | CDK-2 | SD |
|---|---|---|---|---|
| **L1** | 1.83 | 0.29 | 2.03 | 0.47 |
| **L2** | 2.35 | 0.42 | 1.50 | 0.16 |
| **L3** | 1.68 | 0.23 | 1.85 | 0.36 |
| **L4** | 1.68 | 0.21 | 2.04 | 0.42 |
| **L5** | 1.90 | 0.34 | 1.30 | 0.18 |
| **L6** | 1.52 | 0.23 | 1.81 | 0.39 |
| **L7** | 1.51 | 0.21 | 3.97 | 1.12 |
| **L8** | 1.34 | 0.15 | 1.84 | 0.28 |
| **L9** | 1.95 | 0.34 | 2.20 | 0.38 |
| **L10** | 2.63 | 0.70 | 2.26 | 0.33 |
| **L11** | 1.62 | 0.24 | 2.18 | 0.27 |
| **L12** | 1.69 | 0.30 | 2.05 | 0.35 |

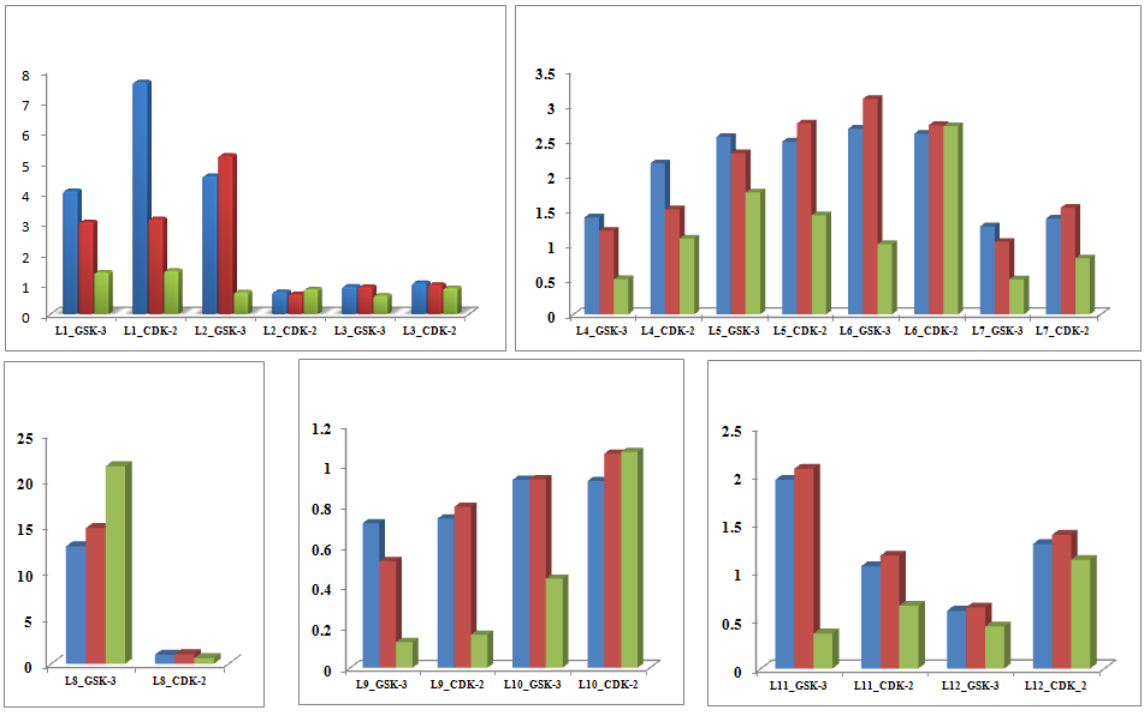


**Figure S5.** Standard deviation (SD) values calculated for the 24 enzyme-inhibitor complexes for last 20 ns (blue), last 14 ns (red), last 6 ns (green). (A) Maleimide (L1-L3), (B) Pyrazines (L4-L7), (C) Nitrothiazole ) (L8) (D) Paullones (L9 and L10) (E) Indirubbins (L11 and L12).

**Table S2.** SD values calculated for the 24 enzyme-inhibitor complexes calculated for last 20 ns, 14 ns and 6ns.

| | GSK-3 | | | CDK-2 | | |
|---|---|---|---|---|---|---|
| **Time (ns)** | **20** | **14** | **6** | **20** | **14** | **6** |
| **L1** | 4.05 | 3.03 | 1.37 | 7.62 | 3.13 | 1.43 |
| **L2** | 4.54 | 5.21 | 0.72 | 0.73 | 0.66 | 0.82 |
| **L3** | 0.91 | 0.90 | 0.61 | 1.03 | 0.97 | 0.86 |
| **L4** | 1.39 | 1.20 | 0.50 | 2.17 | 1.51 | 1.09 |
| **L5** | 2.55 | 2.31 | 1.75 | 2.48 | 2.74 | 1.42 |
| **L6** | 2.66 | 3.09 | 1.01 | 2.59 | 2.71 | 2.70 |
| **L7** | 1.26 | 1.04 | 0.50 | 1.37 | 1.53 | 0.80 |
| **L8** | 12.79 | 14.77 | 21.52 | 0.98 | 1.04 | 0.61 |
| **L9** | 0.71 | 0.53 | 0.13 | 0.74 | 0.79 | 0.16 |
| **L10** | 0.93 | 0.93 | 0.44 | 0.92 | 1.06 | 1.07 |
| **L11** | 1.95 | 2.07 | 0.36 | 1.06 | 1.17 | 0.65 |
| **L12** | 0.60 | 0.63 | 0.44 | 1.29 | 1.38 | 1.13 |

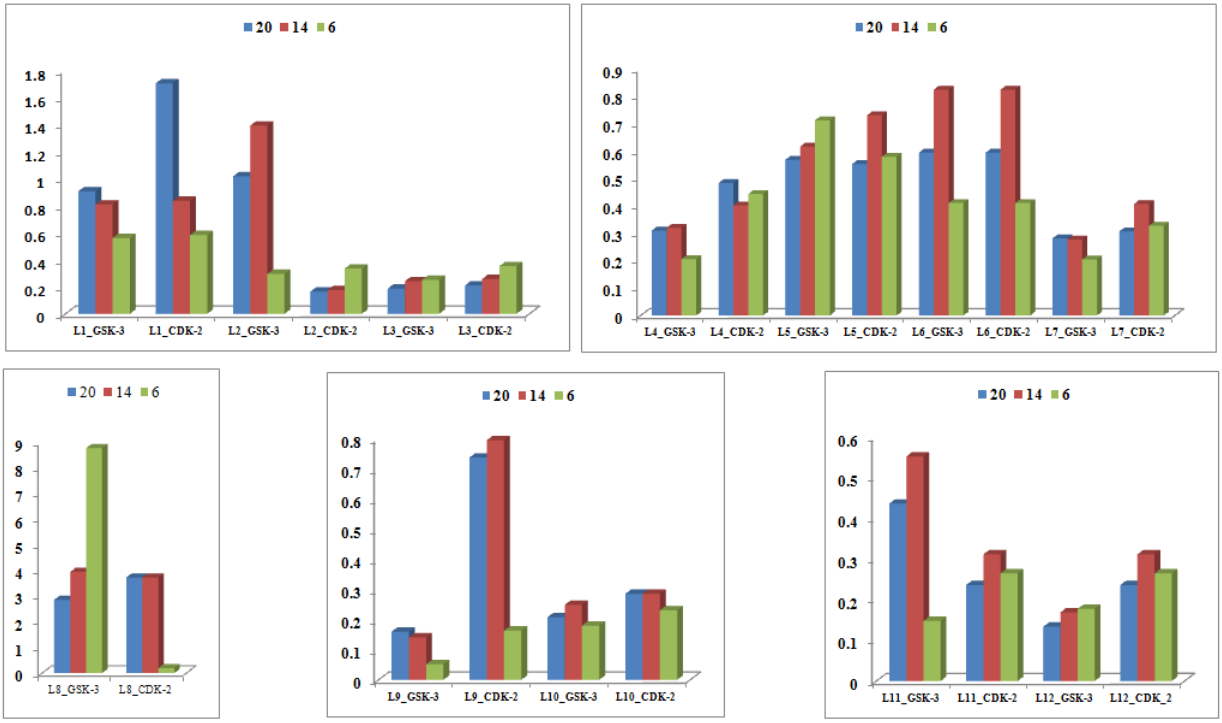


**Figure S6.** Standard Error of Mean (SEM) values calculated for the 24 enzyme-inhibitor complexes for last 20 ns (blue), last 14 ns (red), last 6 ns (green). (A) Maleimide (L1-L3), (B) Pyrazines (L4-L7), (C) Nitrothiazole ) (L8) (D) Paullones (L9 and L10) (E) Indirubbins (L11 and L12).

**Table S3.** SEM calculated for the twenty four enzyme-inhibitor complexes for last 20 ns, 14 ns, and 6 ns.

| | GSK-3 | | | CDK-2 | | |
|---|---|---|---|---|---|---|
| **Time (ns)** | **20** | **14** | **6** | **20** | **14** | **6** |
| **L1** | 0.91 | 0.81 | 0.56 | 1.70 | 0.84 | 0.58 |
| **L2** | 1.02 | 1.39 | 0.29 | 0.16 | 0.18 | 0.33 |
| **L3** | 0.19 | 0.24 | 0.25 | 0.21 | 0.26 | 0.35 |
| **L4** | 0.31 | 0.32 | 0.21 | 0.48 | 0.40 | 0.44 |
| **L5** | 0.57 | 0.62 | 0.71 | 0.55 | 0.73 | 0.58 |
| **L6** | 0.60 | 0.83 | 0.41 | 0.60 | 0.83 | 0.41 |
| **L7** | 0.28 | 0.28 | 0.20 | 0.31 | 0.41 | 0.33 |
| **L8** | 2.86 | 3.95 | 8.79 | 0.22 | 0.28 | 0.25 |
| **L9** | 0.16 | 0.14 | 0.05 | 0.74 | 0.79 | 0.16 |
| **L10** | 0.21 | 0.25 | 0.18 | 0.21 | 0.28 | 0.44 |
| **L11** | 0.44 | 0.55 | 0.15 | 0.24 | 0.31 | 0.27 |
| **L12** | 0.13 | 0.17 | 0.18 | 0.24 | 0.31 | 0.27 |

**Table S4. Binding free energy values along with the different energy components for twelve GSK-3β -inhibitor (upper) and twelve CDK-2-inhibitor complexes. All the energy values are in kcal/mol.**

| Enzyme | Ligands | ΔE(s) | Ele(g) | Van(g) | ΔE(g) | S. P_con | S. NP_con | Ele(sol) | Van(sol) |
|---|---|---|---|---|---|---|---|---|---|
| **GSK-3** | **L1** | -40.99 | -217.91 | -40.31 | -258.22 | 220.41 | -3.18 | 2.50 | -43.49 |
| | **L2** | -38.42 | -191.79 | -42.37 | -234.16 | 199.02 | -3.28 | 7.23 | -45.64 |
| | **L3** | -26.07 | -23.52 | -50.30 | -73.81 | 51.45 | -3.70 | 27.93 | -54.00 |
| | **L4** | -28.63 | -35.46 | -45.79 | -81.25 | 56.45 | -3.83 | 20.98 | -49.62 |
| | **L5** | -29.13 | -33.90 | -48.73 | -82.63 | 57.47 | -3.98 | 23.57 | -52.70 |
| | **L6** | -30.24 | -36.86 | -46.48 | -83.34 | 57.09 | -3.99 | 20.23 | -50.47 |
| | **L7** | -24.65 | -27.90 | -40.61 | -68.50 | 47.05 | -3.20 | 19.16 | -43.81 |
| | **L8** | -28.59 | -26.97 | -36.52 | -63.49 | 37.57 | -2.68 | 10.61 | -39.20 |
| | **L9** | -25.17 | -13.59 | -39.63 | -53.23 | 30.72 | -2.67 | 17.13 | -42.30 |
| | **L10** | -26.68 | -13.78 | -40.03 | -53.82 | 29.97 | -2.83 | 16.19 | -42.86 |
| | **L11** | -32.39 | -17.14 | -41.89 | -59.03 | 29.29 | -2.65 | 12.15 | -44.54 |
| | **L12** | -25.71 | -15.03 | -37.13 | -52.17 | 29.04 | -2.58 | 14.00 | -39.72 |
| **CDK-2** | **L1** | -18.88 | -108.09 | -35.33 | -143.42 | 127.73 | -3.18 | 19.64 | -38.51 |
| | **L2** | -20.59 | -75.11 | -34.71 | -109.82 | 92.20 | -2.97 | 17.08 | -37.68 |
| | **L3** | -23.82 | -23.93 | -41.70 | -65.63 | 45.23 | -3.42 | 21.29 | -45.11 |
| | **L4** | -25.66 | -35.47 | -47.14 | -82.61 | 61.05 | -4.10 | 25.58 | -51.24 |
| | **L5** | -22.70 | -24.38 | -44.85 | -69.24 | 50.44 | -3.91 | 26.06 | -48.76 |
| | **L6** | -26.00 | -23.00 | -46.84 | -69.84 | 47.87 | -4.03 | 24.87 | -50.87 |
| | **L7** | -24.24 | -32.89 | -35.04 | -67.94 | 46.78 | -3.08 | 13.89 | -38.12 |
| | **L8** | -26.54 | -28.11 | -35.59 | -63.69 | 39.81 | -2.65 | 11.70 | -38.24 |
| | **L9** | -21.92 | -15.95 | -32.90 | -48.85 | 29.44 | -2.51 | 13.49 | -35.41 |
| | **L10** | -22.80 | -23.99 | -32.85 | -56.84 | 36.52 | -2.48 | 12.53 | -35.33 |
| | **L11** | -29.74 | -21.56 | -38.66 | -60.22 | 33.08 | -2.61 | 11.52 | -41.26 |
| | **L12** | -22.71 | -16.97 | -33.19 | -50.17 | 29.87 | -2.42 | 12.89 | -35.61 |

**Table S5. Residue wise energy values for the 5Å region around inhibitor in GSK-3β. All the energy values are in kcal/mol.**

| Residues | L1 | L2 | L3 | L4 | L5 | L6 | L7 | L8 | L9 | L10 | L11 | L12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ile62** | -0.63 | -0.59 | -2.47 | -1.97 | -1.47 | -1.70 | -1.50 | -1.75 | -0.98 | -1.21 | -2.03 | -1.52 |
| **Gly63** | -0.27 | -0.27 | -0.42 | -0.24 | -0.49 | -0.21 | -0.19 | -0.08 | -0.11 | -0.10 | -0.11 | -0.09 |
| **Asn64** | 0.27 | -0.21 | -0.23 | -0.07 | -0.11 | -0.06 | -0.06 | -0.02 | 0.17 | -0.05 | -0.07 | -0.06 |
| **Gly65** | -0.58 | -0.82 | -0.09 | -0.03 | -0.04 | -0.03 | -0.03 | -0.01 | -0.16 | -0.03 | -0.04 | -0.01 |
| **Ser66** | -0.36 | -0.20 | -0.07 | -0.02 | -0.02 | -0.02 | -0.02 | -0.01 | -0.15 | -0.01 | -0.01 | -0.01 |
| **Phe67** | -0.03 | -0.01 | -1.44 | -0.67 | -0.73 | -0.65 | -0.68 | -0.01 | -0.03 | 0.00 | -0.01 | -0.19 |
| **Gly68** | 0.03 | 0.20 | -0.11 | -0.03 | -0.05 | -0.05 | -0.04 | 0.00 | -0.09 | -0.01 | -0.02 | -0.02 |
| **Val69** | -0.09 | -0.05 | -0.17 | -0.15 | -0.12 | -0.12 | -0.15 | -0.03 | -0.16 | -0.06 | -0.14 | -0.14 |
| **Val70** | -2.02 | -2.33 | -1.49 | -1.15 | -1.43 | -1.25 | -1.27 | -0.48 | -1.61 | -1.46 | -1.87 | -1.69 |
| **Tyr71** | -0.13 | -0.17 | -0.36 | -0.40 | -0.41 | -0.38 | -0.43 | -0.25 | -0.50 | -0.37 | -0.13 | -0.05 |
| **Gln72** | -0.13 | -0.16 | -0.19 | 0.02 | -0.17 | -0.40 | 0.20 | 0.19 | -0.16 | -0.12 | -0.18 | -0.24 |
| **Ala83** | -0.81 | -0.80 | -0.55 | -0.72 | -0.64 | -0.84 | -0.69 | -0.82 | -0.22 | -0.27 | -0.89 | -0.88 |
| **Ile84** | -0.15 | -0.23 | -0.22 | -0.20 | -0.19 | -0.21 | -0.21 | -0.14 | -0.18 | -0.19 | -0.05 | 0.00 |
| **Lys85** | -1.51 | -3.40 | 3.08 | 0.72 | 0.05 | -0.25 | -0.31 | -0.19 | -0.26 | -1.22 | -0.16 | 0.81 |
| **Glu97** | 0.86 | 1.63 | -0.77 | -0.44 | -0.29 | 0.23 | -0.12 | 0.00 | 0.41 | 1.00 | -0.32 | -0.89 |
| **Val110** | -0.56 | 1.63 | -0.72 | -0.41 | -0.31 | -0.60 | -0.45 | -0.61 | -0.45 | -0.44 | -0.77 | -0.48 |
| **Arg113** | -0.44 | -0.50 | -0.02 | 0.15 | 0.12 | 0.09 | 0.13 | -0.02 | -0.01 | -0.12 | 0.04 | 0.03 |
| **Leu132** | -1.26 | -1.58 | -1.17 | -0.81 | -0.71 | -0.93 | -0.80 | -1.01 | -0.72 | -0.82 | -0.49 | -0.37 |
| **Asp133** | 1.19 | 0.64 | -0.06 | -1.42 | -1.22 | -1.10 | -1.41 | 0.78 | 0.78 | 0.87 | -0.53 | -0.46 |
| **Tyr134** | -1.82 | -1.77 | -1.69 | -1.86 | -1.08 | -1.84 | -1.18 | -0.16 | -1.27 | -1.32 | -2.52 | -2.62 |
| **Val135** | -0.60 | -0.42 | 0.02 | -0.93 | -0.96 | 0.14 | -1.08 | -3.39 | -1.51 | -1.27 | -1.03 | -0.95 |
| **Pro136** | -0.08 | -0.11 | -0.23 | 0.29 | 0.31 | 0.26 | 0.11 | 0.12 | -0.41 | -0.39 | -0.04 | -0.11 |
| **Glu137** | 0.89 | 1.07 | 0.91 | 0.12 | 0.30 | 2.14 | -0.09 | 0.20 | 1.24 | 1.38 | 0.41 | 0.61 |
| **Thr138** | -2.62 | -1.77 | -0.62 | -0.24 | -0.31 | -0.41 | -0.17 | -0.89 | -0.77 | -1.23 | -0.98 | -0.78 |
| **Val139** | -0.15 | -0.16 | -0.04 | -0.04 | -0.04 | -0.05 | -0.02 | -0.04 | -0.11 | -0.15 | -0.06 | -0.07 |
| **Tyr140** | -2.37 | -1.19 | -0.04 | -0.05 | -0.07 | -0.08 | -0.03 | -0.02 | -0.10 | -0.12 | -0.07 | -0.06 |
| **Arg141** | -7.92 | -8.65 | 0.17 | -0.58 | -1.54 | -1.01 | -0.16 | -0.06 | -0.13 | -0.22 | -0.06 | 0.32 |
| **Lys183** | -0.51 | -0.54 | 0.53 | -0.06 | -0.08 | -0.05 | -0.07 | -0.05 | -0.05 | -0.06 | 0.06 | -0.01 |
| **Pro84** | 0.25 | 0.21 | -0.03 | 0.02 | 0.01 | 0.04 | -0.01 | -0.02 | 0.13 | 0.16 | 0.04 | 0.05 |
| **Gln185** | -1.56 | -3.02 | 0.31 | 0.31 | -0.02 | 0.03 | 0.16 | -0.05 | 1.06 | 1.39 | 0.14 | 0.27 |
| **Asn186** | -0.88 | -0.05 | -0.62 | 0.34 | 0.16 | 0.04 | 0.46 | -0.06 | 0.11 | 0.26 | -0.19 | -0.13 |
| **Leu187** | 0.03 | 0.00 | -0.14 | -0.03 | -0.04 | -0.02 | -0.03 | -0.08 | -0.01 | -0.05 | -0.06 | -0.06 |
| **Leu188** | -1.98 | -2.00 | -2.10 | -1.68 | -1.71 | -2.19 | -1.51 | -1.87 | -2.43 | -2.62 | -2.47 | -2.36 |
| **Leu189** | 0.06 | 0.05 | 0.04 | -0.02 | 0.02 | 0.10 | -0.04 | -0.10 | 0.09 | 0.10 | 0.03 | 0.01 |
| **Lys197** | -0.39 | -0.34 | -0.19 | 0.03 | 0.05 | -0.04 | -0.02 | -0.12 | -0.11 | -0.21 | -0.07 | -0.06 |
| **Leu198** | -0.11 | -0.13 | -0.04 | -0.17 | -0.14 | -0.14 | -0.10 | -0.05 | -0.17 | -0.15 | -0.17 | -0.15 |
| **Cys199** | -0.26 | -0.38 | -0.03 | 0.00 | -0.21 | -0.36 | -0.45 | -0.32 | 0.06 | -0.13 | -0.20 | 0.15 |
| **Asp200** | 2.03 | 2.06 | -0.43 | -0.04 | -0.20 | -0.10 | -0.10 | 0.02 | 0.22 | 0.28 | -0.05 | 0.21 |
| **Phe201** | -0.17 | -0.31 | 0.00 | -0.02 | -0.04 | -0.11 | -0.06 | -0.03 | -0.18 | -0.19 | -0.12 | 0.11 |

**Table S6. Residue wise energy values for the 5Å region around inhibitor in CDK-2. All the energy values are in kcal/mol.**

| Residues | L1 | L2 | L3 | L4 | L5 | L6 | L7 | L8 | L9 | L10 | L11 | L12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ile10** | -0.895 | -0.67 | -1.97 | -1.551 | -1.502 | -1.501 | -1.505 | -2.099 | -1.247 | -0.851 | -1.848 | -1.738 |
| **Gly11** | -0.225 | -0.384 | -0.529 | -0.32 | -0.236 | -0.306 | -0.249 | -0.126 | -0.158 | -0.088 | -0.218 | -0.254 |
| **Glu12** | 0.39 | 0.111 | -0.128 | -0.172 | -0.309 | 0.024 | -0.107 | -0.017 | -0.084 | -0.033 | -0.076 | -0.028 |
| **Gly13** | -0.41 | -0.032 | -0.02 | -0.026 | -0.357 | -0.097 | -0.05 | -0.011 | -0.008 | -0.008 | -0.008 | -0.005 |
| **Thr14** | -0.925 | -0.033 | -0.009 | -0.003 | -0.084 | -0.049 | -0.034 | -0.006 | 0.007 | -0.004 | -0.001 | -0.001 |
| **Tyr15** | 0.071 | -0.057 | -0.025 | -0.079 | -0.127 | -0.064 | -0.059 | -0.016 | -0.009 | -0.013 | -0.017 | -0.014 |
| **Gly16** | -0.227 | 0.011 | 0.026 | 0 | 0.013 | 0.027 | 0.009 | 0.006 | 0.008 | -0.004 | -0.014 | -0.007 |
| **Val17** | -0.095 | -0.126 | -0.151 | -0.108 | -0.014 | -0.005 | -0.109 | -0.073 | -0.108 | -0.072 | -0.152 | -0.143 |
| **Val18** | -0.755 | -1.236 | -1.1 | -1.132 | -0.834 | -1.054 | -1.017 | -0.64 | -1.282 | -1.376 | -1.792 | -1.666 |
| **Tyr19** | -0.126 | -0.263 | -0.405 | -0.356 | -0.26 | -0.246 | -0.342 | -0.242 | -0.367 | -0.319 | -0.126 | -0.053 |
| **Lys20** | -0.463 | -0.494 | -0.09 | 0.075 | 0.276 | 0.213 | 0.181 | 0.514 | -0.058 | -0.077 | -0.292 | -0.454 |
| **Ala31** | -0.578 | -0.637 | -0.524 | -0.486 | -0.481 | -0.495 | -0.522 | -0.726 | -0.228 | -0.506 | -0.784 | -0.856 |
| **Leu32** | -0.095 | -0.171 | -0.238 | -0.213 | -0.184 | -0.154 | -0.192 | -0.168 | -0.217 | -0.411 | -0.083 | -0.027 |
| **Lys33** | 3.979 | 1.383 | 2.387 | 1.199 | 0.19 | -0.254 | 0.896 | 1.761 | 0.204 | -0.014 | 1.532 | 2.355 |
| **Glu51** | 0.068 | 0.149 | -0.002 | -0.018 | -0.021 | 0.012 | -0.053 | 0.009 | 0.012 | 0.031 | 0.022 | 0.013 |
| **Val64** | -0.734 | 0.149 | -0.738 | -0.369 | -0.258 | -0.226 | -0.515 | -0.598 | -0.108 | -0.291 | -0.766 | -0.765 |
| **Leu67** | -0.048 | -0.067 | -0.028 | 0.015 | 0 | -0.011 | 0.024 | -0.041 | -0.021 | -0.063 | -0.028 | -0.036 |
| **Phe80** | -0.787 | -0.998 | -0.797 | -0.381 | -0.412 | -0.374 | -0.383 | -0.888 | -0.305 | -0.882 | -0.647 | -0.451 |
| **Glu81** | 0.566 | 0.412 | -0.55 | -1.398 | -0.898 | -0.564 | -1.418 | 1.415 | 0.982 | 1.318 | -0.521 | 0.073 |
| **Phe82** | -1.989 | -1.764 | -2.068 | -2.203 | -2.335 | -2.24 | -2.469 | -2.145 | -2.457 | -2.313 | -2.703 | -2.732 |
| **Leu83** | -1.885 | -1.093 | -0.134 | -0.125 | 0.089 | -0.376 | -1.019 | -4.214 | -1.633 | -1.5 | -1.475 | -1.572 |
| **Hie84** | -0.098 | 0.051 | -0.017 | -0.238 | -1.335 | -0.063 | -0.106 | -0.052 | 0.009 | -0.42 | -0.045 | 0.215 |
| **Gln85** | -0.184 | -0.122 | -0.038 | 0.003 | -0.373 | 0.237 | -0.206 | -0.392 | -0.208 | -0.041 | -0.144 | -0.336 |
| **Asp86** | 2.23 | 1.769 | 1.051 | -0.238 | 1.491 | 1.918 | 0.194 | 1.331 | 1.45 | 1.746 | 0.738 | 0.874 |
| **Leu87** | -0.128 | -0.031 | -0.01 | -0.095 | -0.048 | -0.048 | -0.006 | -0.038 | -0.102 | -0.098 | -0.039 | -0.03 |
| **Lys88** | -0.417 | -0.438 | -0.053 | -0.139 | -0.074 | -0.058 | -0.055 | -0.086 | -0.112 | -0.132 | -0.066 | -0.072 |
| **Lys89** | -0.589 | -0.438 | 0.154 | -0.553 | 0.158 | 0.157 | 0.224 | 0.254 | -0.079 | -0.067 | -0.042 | -0.018 |
| **Lys129** | -0.379 | -0.342 | 0.596 | 0.244 | 0.308 | 0.573 | 0.063 | -0.076 | 0.061 | -0.009 | 0.007 | 0.006 |
| **Pro130** | 0.18 | 0.027 | -0.034 | 0.007 | 0.033 | -0.031 | -0.019 | 0.001 | 0.104 | 0.145 | 0.038 | 0.019 |
| **Gln131** | 1.667 | 0.092 | -0.16 | 0.697 | 0.84 | -0.087 | 0.384 | -0.117 | 1.113 | 0.907 | 0.014 | -0.086 |
| **Asn132** | -0.131 | -0.155 | -0.874 | -0.559 | -0.548 | -0.387 | -0.25 | -0.083 | -0.254 | -0.125 | -0.148 | -0.075 |
| **Leu133** | -0.057 | -0.035 | -0.13 | -0.042 | -0.085 | -0.097 | -0.049 | -0.026 | -0.023 | 0.003 | -0.038 | -0.039 |
| **Leu134** | -1.537 | -1.509 | -1.905 | -2.044 | -2.081 | -1.753 | -1.544 | -1.454 | -2.139 | -2.33 | -1.873 | -1.679 |
| **Ile135** | -0.031 | 0.02 | -0.021 | -0.047 | -0.098 | -0.206 | -0.053 | -0.225 | -0.012 | 0.015 | 0.063 | 0.079 |
| **Lys142** | -0.211 | -0.392 | -0.132 | 0.016 | -0.012 | -0.057 | 0.095 | -0.044 | -0.208 | -0.246 | -0.143 | -0.198 |
| **Leu143** | -0.134 | 0.053 | 0.004 | -0.035 | -0.01 | -0.018 | -0.078 | -0.023 | 0.009 | 0.037 | -0.027 | -0.049 |
| **Ala144** | -0.834 | -0.81 | -1.075 | -0.388 | -0.327 | -0.362 | -0.46 | -0.145 | -0.465 | -0.336 | -0.557 | -0.06 |
| **Asp145** | 0.85 | 0.041 | -0.006 | 0.659 | 1.262 | 1.923 | -0.144 | -0.054 | 0.203 | 0.528 | -0.501 | -0.022 |
| **Phe146** | -0.124 | -0.032 | -0.027 | -0.02 | -0.03 | -0.007 | -0.132 | -0.008 | -0.065 | -0.03 | -0.044 | -0.182 |

**Table S7. Correlation of IC50 values and calculated binding free energies. The correlation was found to follow the same trend within the class of compounds.**

| | GSK-3 | | CDK-2 | |
|---|---|---|---|---|
| **Ligand** | **IC50** | **ΔE** | **IC50** | **ΔE** |
| **L1** | 160.00 | -40.99 | 10.00 | -18.87 |
| **L2** | 100.00 | -38.41 | 10.00 | -20.6 |
| **L3** | 5.10 | -26.07 | 27.00 | -23.82 |
| **L4** | 20.00 | -28.64 | 210.00 | -25.66 |
| **L5** | 0.46 | -29.13 | 1700.00 | -22.7 |
| **L6** | 1.50 | -30.24 | 30000.00 | -26 |
| **L7** | 12.00 | -24.65 | 100.00 | -24.23 |
| **L8** | 104.00 | -28.59 | 10.00 | -26.54 |
| **L9** | 18.00 | -25.17 | 4200.00 | -21.92 |
| **L10** | 4.00 | -26.67 | 40.00 | -22.8 |
| **L11** | 5.00 | -32.39 | 300.00 | -29.74 |
| **L12** | 22.00 | -25.72 | 440.00 | -22.72 |