

Article

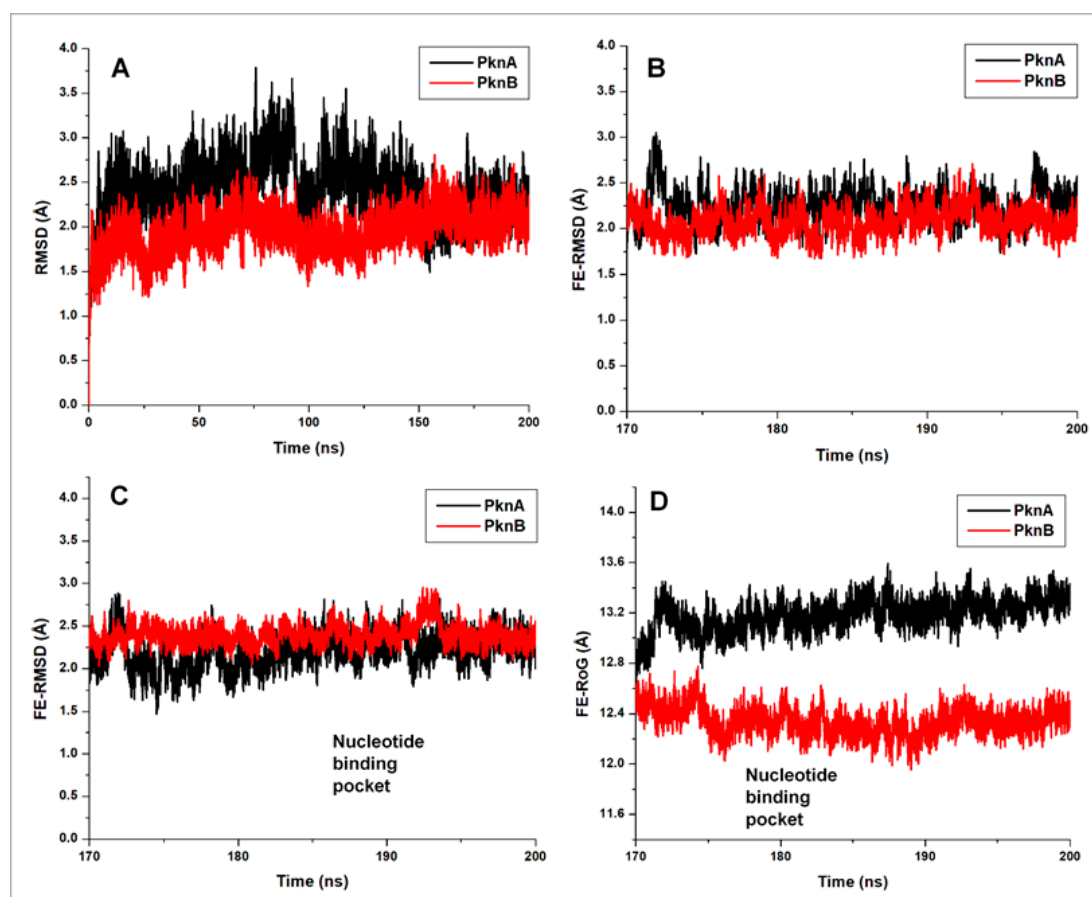
# Probing the Highly Disparate Dual Inhibitory Mechanisms of Novel Quinazoline Derivatives Against *Mycobacterium tuberculosis* Protein Kinases A and B

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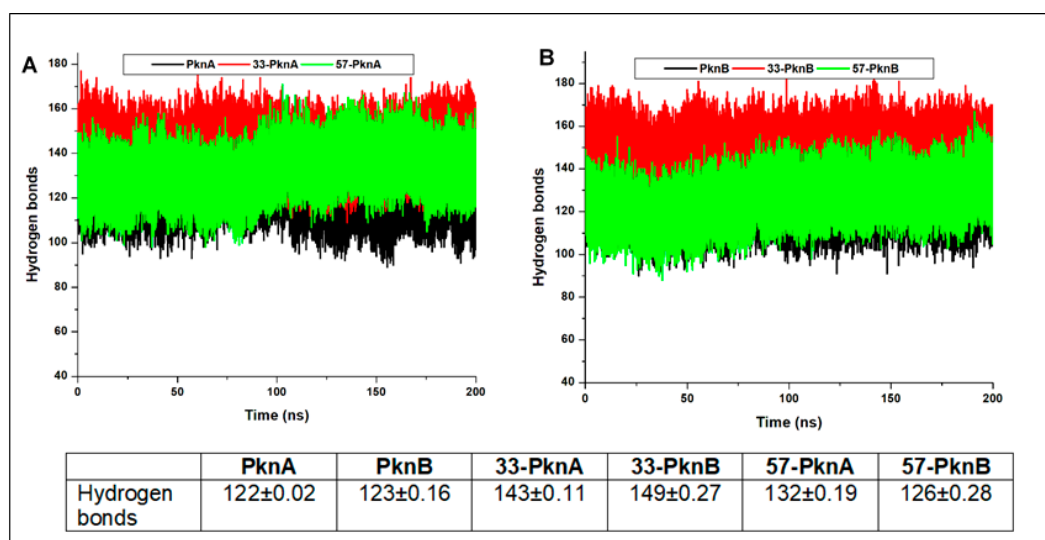
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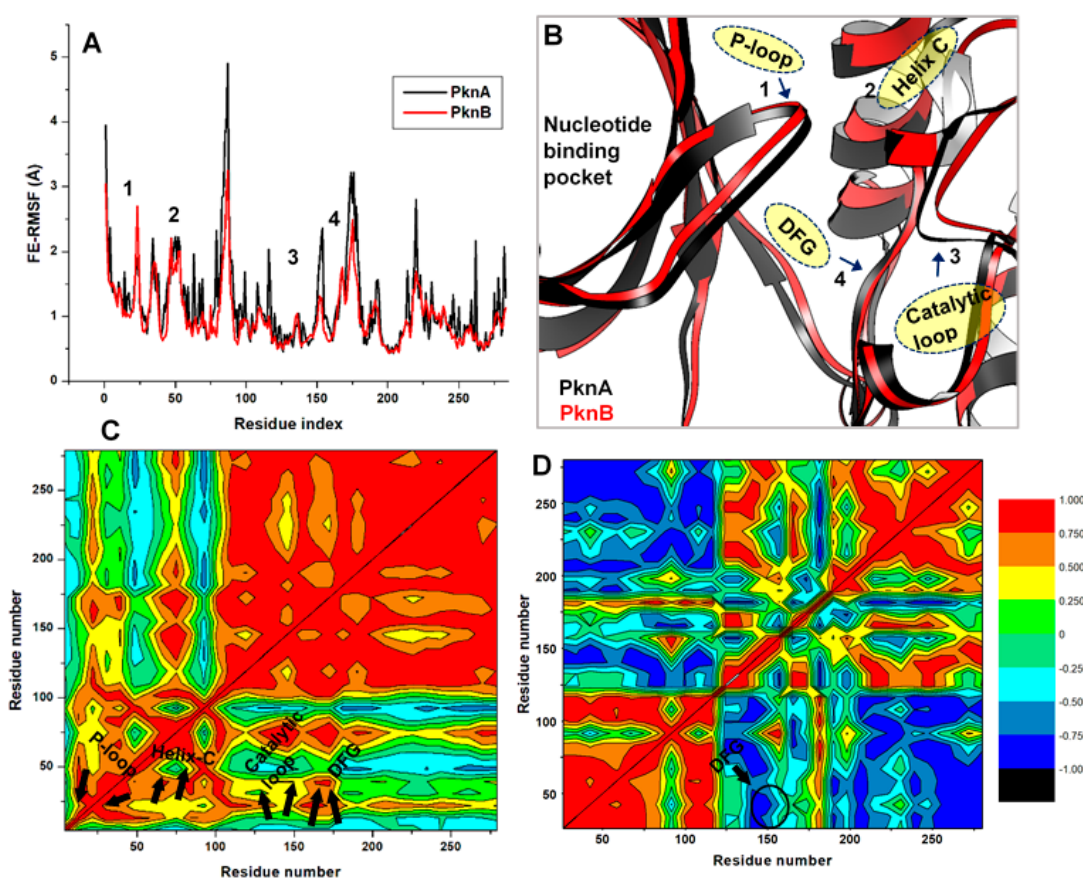
## SUPPLEMENTARY INFORMATION



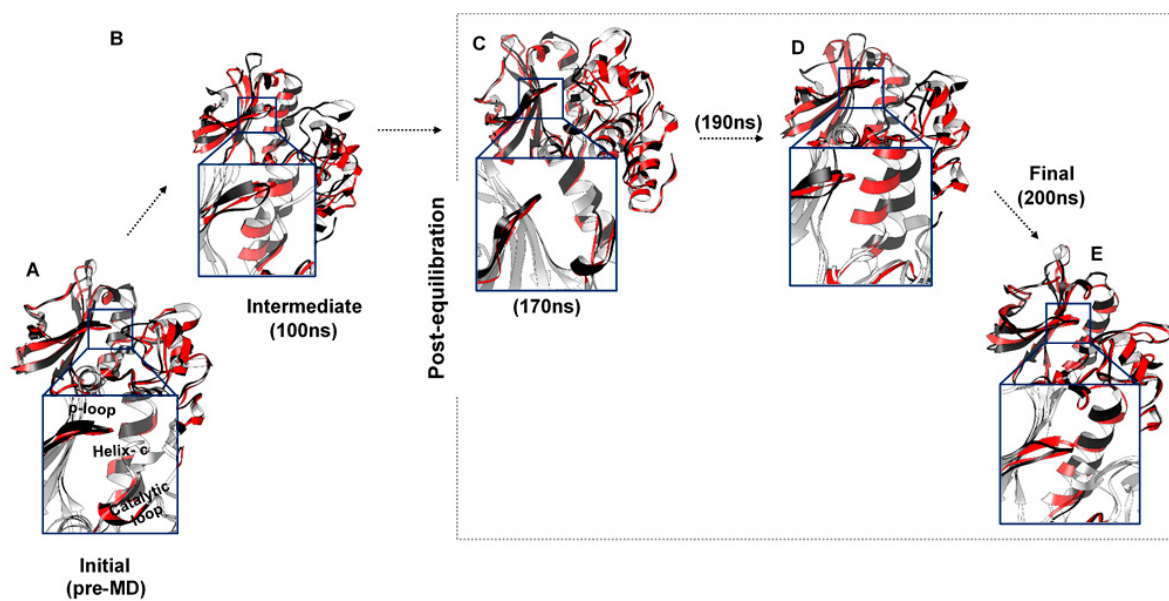
**Figure S1:** RMSD analyses of structural and NBP stability of (A) unbound PknA (black) and unbound PknB (red) (B) Comparative whole structure FE-RMSD (post-equilibrated) of unbound PknA and PknB (C) Comparative FE-RMSD analysis of unbound PknA and PknB nucleotide binding pocket (D) FE-RoG analysis of the degree of mobility (compactness) of unbound PknA and PknB.



**Figure S2:** Hydrogen bond analyses of the simulated systems across the entire trajectory (A) unbound- (black), 57- (green) and 33-bound (red) PknA (B) unbound-, 57- and 33-bound PknB. Inset is the estimation of average hydrogen bonds that occurred within each system over the entire trajectory.



**Figure S3:** Post-equilibrated (FE) RMSF analyses of unbound PknA and PknB. Highlighted in (A) and (B) are regions that correspond to the P-loop, Helix C, Catalytic loop and DFG motif. (C) DCCM analysis of residual motions across the entire unbound PknA structure and (D) DCCM analysis for unbound PknB. Highlighted are motions within the catalytic components.



**Figure S4:** Conformational variations of catalytic components in unbound PknA and PknB along the simulated trajectories.

**Table 1.** Hydrogen bond occupancies  $\geq 90\%$  in the unbound PknA, unbound PknB, 33-PknA, 33-PknB, 57-PknA and 57-PknB.

| Systems | H-Acceptor | H-Donor     | Donor      | Occupancy (%) | Distance (Å) | Angle (°) |
|---------|------------|-------------|------------|---------------|--------------|-----------|
| PknA    | GLU187-OE2 | ARG260-HH12 | ARG260-NH1 | 97.10         | 2.8          | 165       |
|         | LEU248-O   | THR252-HG1  | THR252-OG1 | 96.18         | 2.7          | 163       |
|         | MET121-O   | THR125-HG1  | THR125-OG1 | 95.20         | 2.7          | 163       |
|         | ASP199-OD2 | HIS139-H    | HIS139-N   | 93.40         | 2.8          | 161       |
|         | PRO281-O   | TYR261-HH   | TYR261-OH  | 93.34         | 2.7          | 165       |
|         | GLU187-OE1 | ARG260-HH22 | ARG260-NH2 | 93.20         | 2.8          | 164       |
|         | TYR183-O   | SER202-HG   | SER202-OG  | 92.4          | 2.7          | 165       |
| PknB    | GLU166OE2  | ARG242-HH22 | ARG242-NH2 | 97.12         | 2.8          | 165       |
|         | ILE214-O   | TYR187-HH   | TYR187-OH  | 95.71         | 2.7          | 166       |
|         | TYR162-O   | SER181-HG   | SER181-OG  | 95.54         | 2.7          | 164       |
|         | ASP30-OD2  | ARG10-HH11  | ARG10-NH1  | 93.92         | 2.8          | 160       |
|         | GLU166-OE1 | ARG242-HH12 | ARG242-NH1 | 93.90         | 2.8          | 166       |
|         |            |             |            |               |              |           |
| 33-PknA | GLU187-OE2 | ARG260-HH12 | ARG260-NH1 | 98.25         | 2.8          | 164       |
|         | TYR183-O   | SER202-HG   | SER202-OG  | 95.53         | 2.7          | 164       |
|         | GLU187-OE1 | ARG260-HH22 | ARG260-NH2 | 95.12         | 2.8          | 164       |
|         | MET121-O   | THR125-HG1  | THR125-OG1 | 94.75         | 2.7          | 164       |
|         | ARG17-O    | GLU29-H     | GLU29-N    | 92.69         | 2.8          | 164       |
|         | LEU248-O   | THR252-HG1  | THR254-OG1 | 92.38         | 2.7          | 163       |
|         | ASP199-OD2 | HIS139-H    | HIS139-N   | 91.96         | 2.8          | 164       |
|         | ASP32-OD1  | ARG12-HE    | ARG12-NE   | 91.91         | 2.8          | 164       |
|         | PRO281-O   | TYR261-HH   | TYR261-OH  | 91.50         | 2.7          | 165       |
|         | GLU29-O    | GLN16-H     | GLN16-N    | 91.27         | 2.8          | 160       |
|         | GLU61-O    | THR65-HG1   | THR65-OG1  | 90.22         | 2.7          | 163       |
|         | ASP32-OD2  | ARG12-HH21  | ARG12-NH2  | 90.11         | 2.8          | 159       |
|         | GLU187-OE1 | GLU187-H    | GLU187-N   | 90.08         | 2.8          | 151       |
|         | ASP199-OD2 | HIS133-HE2  | HIS133-NE2 | 90.03         | 2.8          | 166       |
| 33-PknB | ASP228-OD2 | SER217-HG   | SER-217-OG | 98.20         | 2.6          | 166       |
|         | GLU188-OE1 | TYR162-HH   | TYR162-OH  | 96.72         | 2.6          | 166       |
|         | GLU166-OE1 | ARG242-HH12 | ARG242-NH1 | 95.40         | 2.8          | 165       |
|         | ILE134-O   | SER129-HG   | SER129-OG  | 95.28         | 2.7          | 164       |
|         | ILE214-O   | TYR187-HH   | TYR187-OH  | 95.21         | 2.7          | 166       |
|         | ASP30-OD2  | ARG10-HH11  | ARG10-NH1  | 92.66         | 2.8          | 159       |
|         | ASP76-O    | VAL91-H     | VAL91-N    | 92.24         | 2.8          | 161       |
|         | ALA38-O    | MET92-H     | MET92-N    | 92.17         | 2.8          | 162       |
|         | GLU166-OE2 | ARG242-HH22 | ARG242-NH2 | 92.11         | 2.8          | 164       |
|         | VAL91-O    | TYR75-H     | TYR75-N    | 92.08         | 2.8          | 160       |
|         | MET145-O   | LYS153-H    | LYS153-N   | 92.06         | 2.8          | 161       |
|         | VAL25-O    | LEU17-H     | LEU17-N    | 92.01         | 2.8          | 157       |
|         | HIS26-O    | VAL39-H     | VAL39-N    | 91.19         | 2.8          | 160       |
|         | ASP178-OD2 | HIS136-H    | HIS136-N   | 91.00         | 2.8          | 156       |
|         | GLU166-OE1 | GLU166-H    | GLU166-N   | 90.06         | 2.8          | 150       |
|         |            |             |            |               |              |           |
|         |            |             |            |               |              |           |
| 57-PknA | GLU187-OE2 | SER198-HG   | SER198-OG  | 98.23         | 2.6          | 167       |
|         | TYR183-O   | SER202-HG   | SER202-OG  | 97.07         | 2.7          | 164       |
|         | GLU187-OE2 | ARG260-HH12 | ARG260-NH1 | 96.70         | 2.8          | 164       |
|         | GLU187-OE2 | ARG260-HH22 | ARG260-NH2 | 95.53         | 2.8          | 165       |
|         | LEU248-O   | THR252-HG1  | THR252-OG1 | 95.02         | 2.7          | 164       |
|         | MET121-O   | THR125-HG1  | THR125-OG1 | 92.51         | 2.7          | 162       |
|         | PRO281-O   | TYR261-HH   | TYR261-OH  | 91.89         | 2.7          | 166       |
|         | ASP32-OD2  | ARG12-HH21  | ARG12-NH2  | 91.82         | 2.8          | 157       |
|         | ASP199-OD2 | HIS139-H    | HIS139-N   | 91.42         | 2.8          | 165       |
|         | PRO235-O   | TYR208-HH   | TYR208-OH  | 91.37         | 2.7          | 163       |
| 57-PknB | ASP228-OD2 | SER217-HG   | SER217-OG  | 98.67         | 2.6          | 167       |
|         | GLU166-OE2 | ARG242-HH22 | ARG242-NH2 | 96.36         | 2.8          | 165       |
|         | ILE214-O   | TYR187-HH   | TYR187-OH  | 95.05         | 2.7          | 166       |
|         | ASP30-OD2  | ARG10-HH11  | ARG10-NH1  | 93.43         | 2.8          | 160       |
|         | GLU166-OE1 | ARG242-HH12 | ARG242-NH1 | 92.97         | 2.8          | 166       |
|         | VAL25-O    | LEU17-H     | LEU17-N    | 92.77         | 2.8          | 155       |
|         | GLU166-OE1 | GLU166-H    | GLU166-N   | 92.61         | 2.8          | 149       |
|         | VAL91-O    | TYR75-H     | TYR75-N    | 91.74         | 2.8          | 163       |
|         | ALA38-O    | MET92-H     | MET92-N    | 91.62         | 2.8          | 159       |
|         | VAL39-O    | HIS26-H     | HIS26-N    | 90.16         | 2.9          | 160       |



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