

## Supplementary Materials for

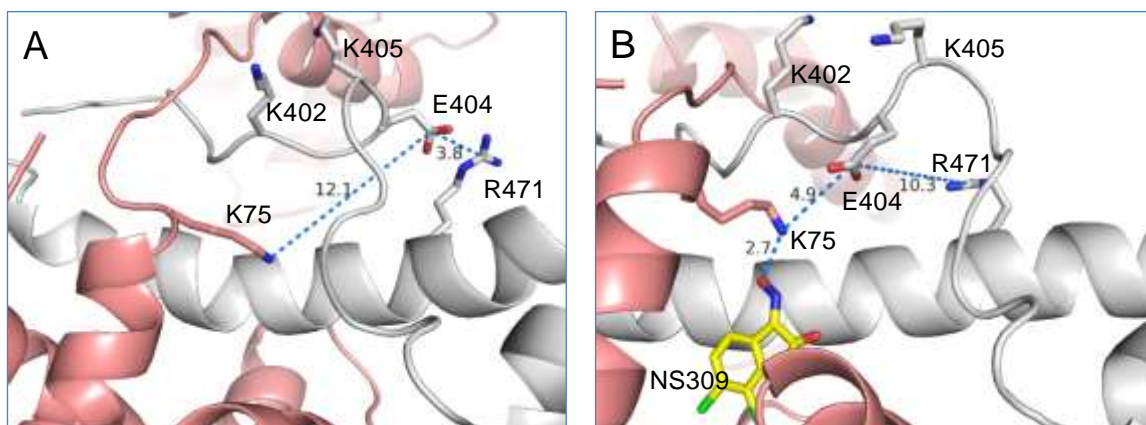
### **Molecular overlap in the regulation of SK channels by small molecules and phosphoinositides**

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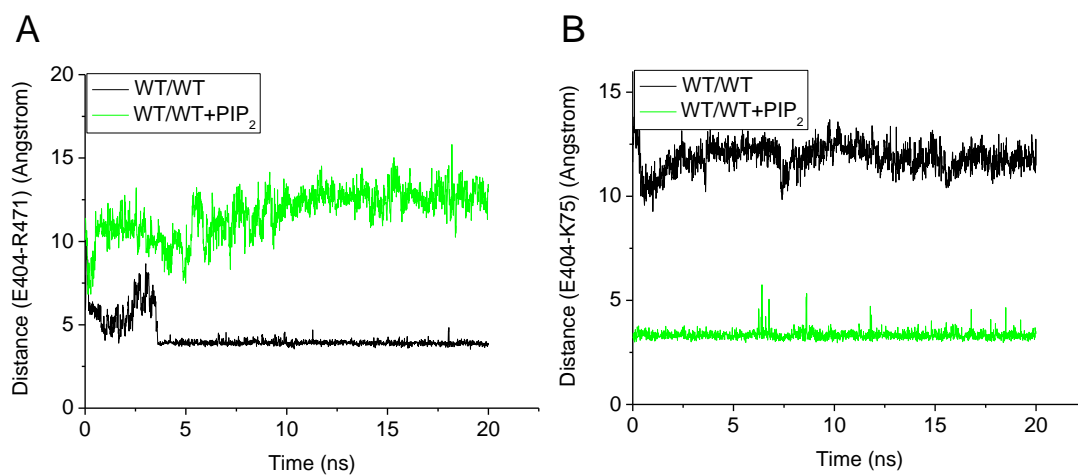
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#### **This PDF file includes:**

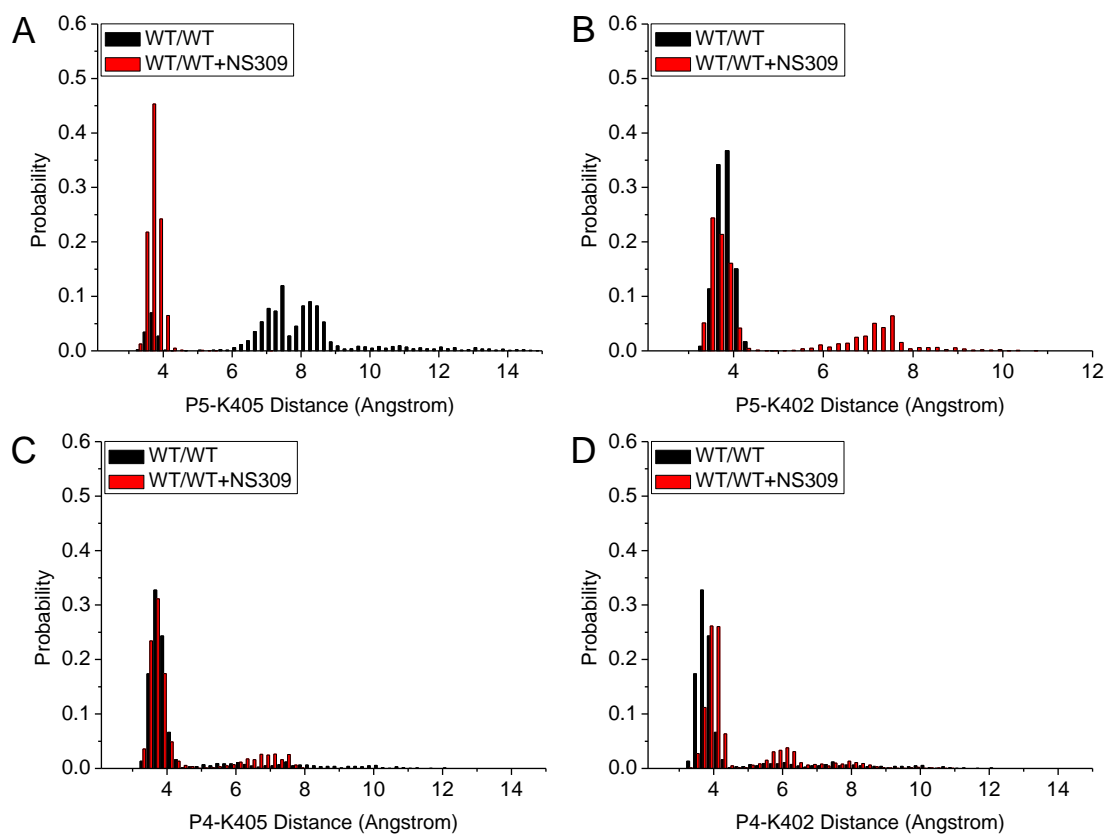
- Fig. S1. The influence of NS309 on the conformation of IDF.
- Fig. S2. The influence of PIP<sub>2</sub> on the conformation of the IDF.
- Fig. S3. The PIP<sub>2</sub>-channel interaction is affected by NS309.
- Fig. S4. The effectiveness of NS309 on the phosphomimetic T79D CaM mutant.
- Fig. S5. The proximity of NS309 and CaM T79D mutation to the PIP<sub>2</sub> binding site.
- Fig. S6. The PIP<sub>2</sub>-channel interaction is affected by NS309 in the context of T79D mutant.



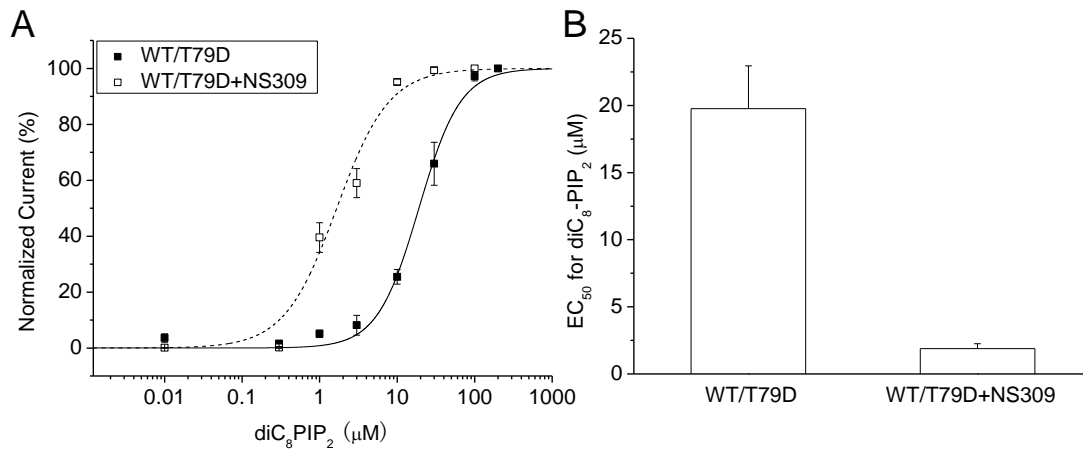
**Figure S1 The influence of NS309 on the conformation of IDF.** (A), A representative snapshot from MD simulations of CaM (salmon) and the SK2-a channel (gray) in the absence of NS309. (B), A representative snapshot from MD simulations of CaM (salmon) and SK2-a channel (gray) in the presence of NS309.



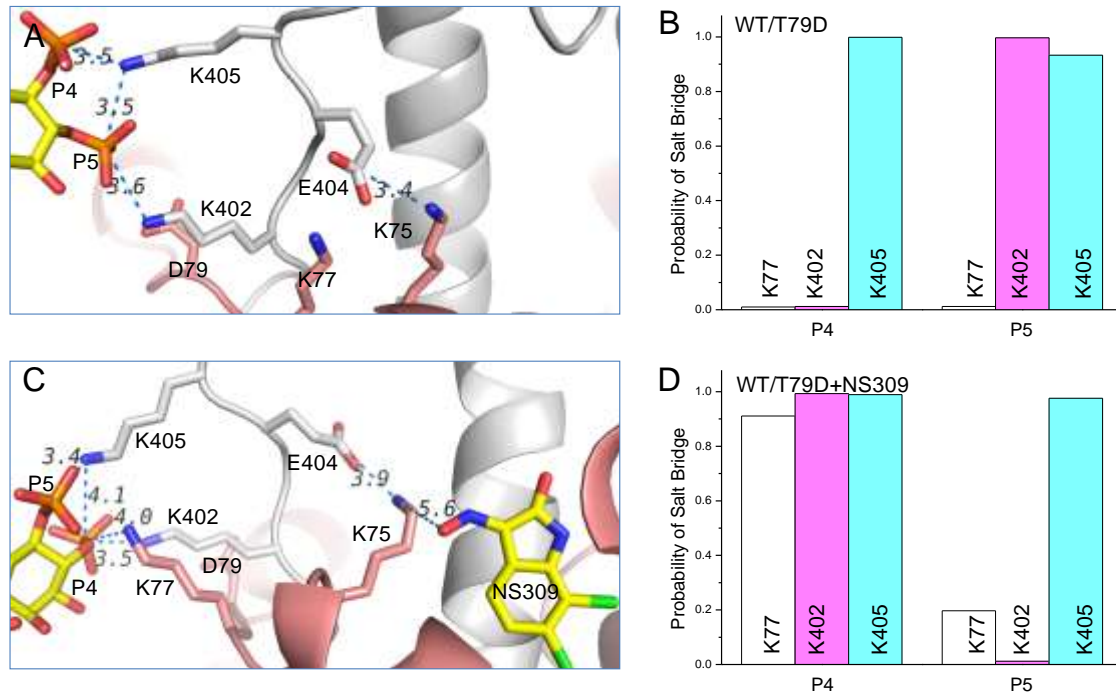
**Figure S2 The influence of PIP<sub>2</sub> on the conformation of the IDF.** (A). The E404-R471 distance from MD simulations in the absence (black) and presence (green) of PIP<sub>2</sub>. (B), The E404-K75 distance from MD simulations in the absence (black) and presence (green) of PIP<sub>2</sub>.



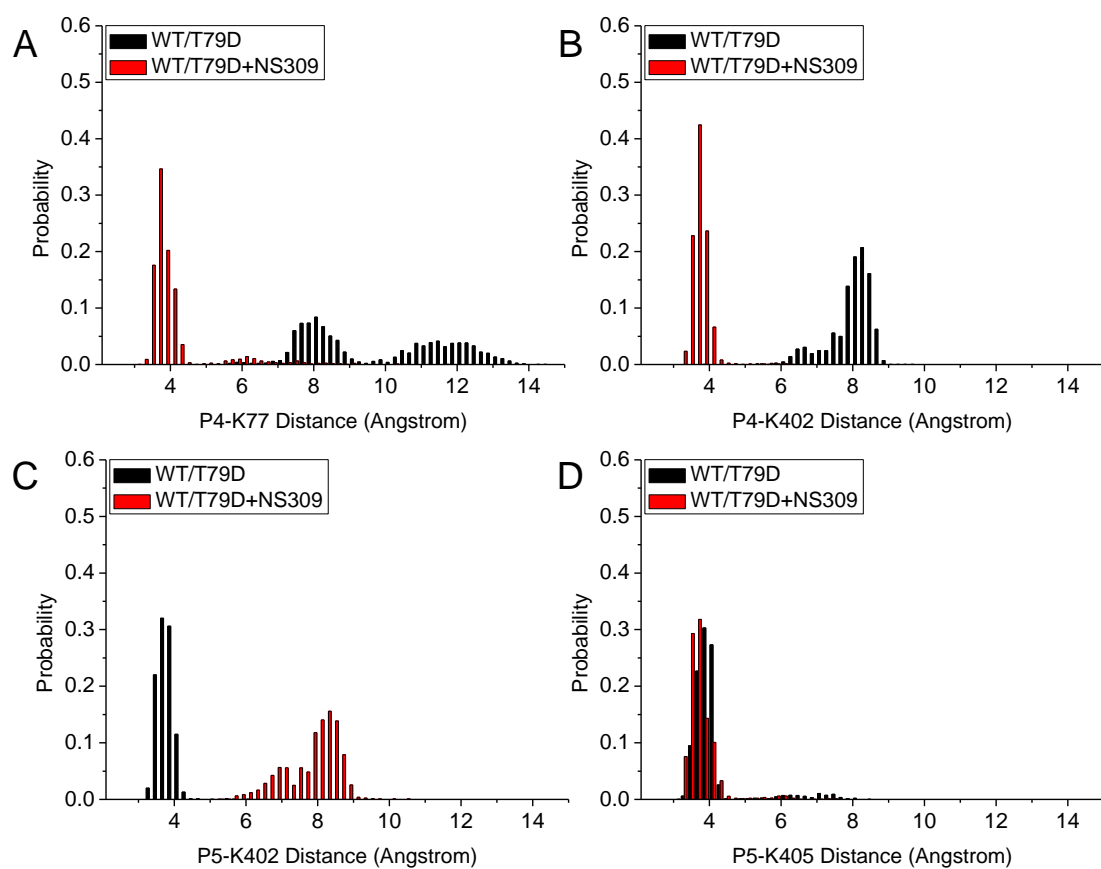
**Figure S3 The PIP<sub>2</sub>-channel interaction is affected by NS309.** The histogram of P5-K405 (A), P5-K402 (B), P4-K405 (C), P4-K402 (D) distances from MD simulations in the presence and absence of NS309.



**Figure S4 The effectiveness of NS309 on the phosphomimetic T79D CaM mutant.** (A), Dose-response curves of channel reactivation by exogenous diC<sub>8</sub>-PIP<sub>2</sub> in the absence (solid line, filled symbols) and presence (dashed line, open symbols) of 3 μM NS309, on WT/T79D (SK2-a/CaM) mutant channel. (B), The apparent diC<sub>8</sub>-PIP<sub>2</sub> affinity for the WT/T79D mutant channel is increased by 3 μM NS309.



**Figure S5 The proximity of NS309 and CaM T79D mutation to the PIP<sub>2</sub> binding site.** (A), A representative snapshot from MD simulations of PIP<sub>2</sub> binding in the absence of NS309, with the CaM T79D mutation. (B), Summarized probability of forming salt bridges between the PIP<sub>2</sub> head and positively charged residues in the absence of NS309, with the WT/T79D (SK2-a/CaM) mutant channel. (C), A representative snapshot from MD simulations of PIP<sub>2</sub> binding in the presence of NS309, with the WT/T79D mutant channel. (D), Summarized probability of forming salt bridges between the PIP<sub>2</sub> head and positively charged residues in the CaM T79D background and in the presence of NS309.



**Figure S6 PIP<sub>2</sub>-channel interaction is affected by NS309 in the context of the T79D mutant.** The histogram of P4-K77 (A), P4-K402 (B), P5-K402 (C), P5-K405 (D) distances from MD simulations in the presence and absence of NS309.