Supplementary Materials for

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

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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$_2$ on the conformation of the IDF.
Fig. S3. The PIP$_2$-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$_2$ binding site.
Fig. S6. The PIP$_2$-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 PIP₂ on the conformation of the IDF. (A). The E404-R471 distance from MD simulations in the absence (black) and presence (green) of PIP₂. (B), The E404-K75 distance from MD simulations in the absence (black) and presence (green) of PIP₂.
Figure S3  The PIP2-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 diC₈-PIP₂ in the absence (solid line, filled symbols) and presence (dashed line, open symbols) of 3µM NS309, on WT/T79D (SK2-a/CaM) mutant channel. (B), The apparent diC₈-PIP₂ affinity for the WT/T79D mutant channel is increased by 3µM NS309.
Figure S5  The proximity of NS309 and CaM T79D mutation to the PIP$_2$ binding site. (A), A representative snapshot from MD simulations of PIP$_2$ binding in the absence of NS309, with the CaM T79D mutation. (B), Summarized probability of forming salt bridges between the PIP$_2$ 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$_2$ binding in the presence of NS309, with the WT/T79D mutant channel. (D), Summarized probability of forming salt bridges between the PIP$_2$ head and positively charged residues in the CaM T79D background and in the presence of NS309.
Figure S6  PIP2-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.