# Supplemental Material

# Identification of the A293 (AVE1231) Binding Site in the Cardiac Two-Pore-Domain Potassium Channel TASK-1: a Common Low Affinity Antiarrhythmic Drug Binding Site

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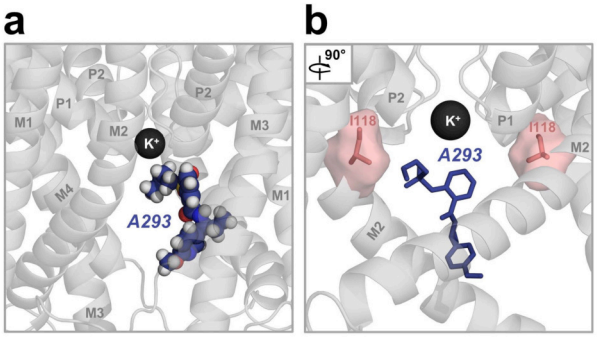
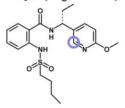
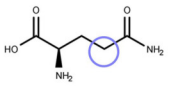
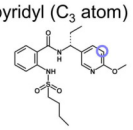
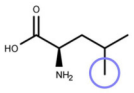
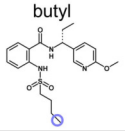
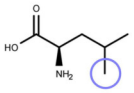
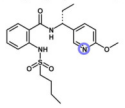
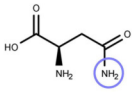
# Supplementary Figure 1




**Supplementary Figure 1: Illustration of the best A293 docking solution.**
(a) A293 is in the final docking solution predicted to block the potassium flow, as the butyl side chain is located underneath the selectivity filter. (b) I118 might be also relevant for the interaction with A293, as it is within less than 4 Å to the butyl group of A293.

# Supplementary Figure 2

| TASK-1 residue | interaction | group (A293) | group (residue) |
|---|---|---|---|
| Q126 (*subunit A*) | hydrophobic | pyridyl ($C_5$ atom)  | gamma carbon  |
| L239 (*subunit A*) | hydrophobic | pyridyl ($C_3$ atom)  | delta carbon  |
| L239 (*subunit B*) | hydrophobic | butyl  | delta carbon  |
| N240 (*subunit A*) | hydrogen bond | pyridyl ($N_1$ atom)  | amide (H atom)  |

**Supplementary Figure 2: Interactions of A293 with TASK-1.**
Summary of the most important interactions of A293 with residues identified by site directed mutagenesis. We identified several hydrophobic interactions of the pyridil-group and the butyl side chain of A293 with Q126 and/or L239 in TASK-1, as well as a H-bond of the pyridil nitrogen atom of A293 to the amide group of N240.

# Supplementary Table 1

| | WT | Q126A | L239A | N240A |
|---|---|---|---|---|
| **$IC_{50}$ (µM)** | 0.2 ± 0.1 | 8.3 ± 2.5 | 21.6 ± 12.2 | 15.6 ± 4.4 |
| **$IC_{50}$ (fold change)** | n.a. | 42-fold | 108-fold | 78-fold |
| **Hill coefficent** | 1.1 ± 0.1 | 0.9 ± 0.2 | 0.9 ± 0.3 | 1.5 ± 0.5 |

**Supplementary Table 1: Changes in $IC_{50}$ for Q126A, L239A and N240A.**
The $IC_{50}$ value and the hill coefficient of A293 for WT, Q126A, L239A and N240A mutants were obtained by voltage-clamp measurements of *Xenopus* oocytes at +40 mV with five different concentrations of A293 (n = 3 - 6 cells per concentration). Data are given as mean ± S.E.M..