**Table S1.** Intermolecular hydrogen-bonds and hydrophobic contacts between quinacrine and Kir4.1 channels.

| Quinacrine | | Kir4.1 | | |
|---|---|---|---|---|
| | | *Hydrogen-bonds* | | |
| **Donor** | **Atom** | **Acceptor** | **Atom** | **Distance (Å)** |
| Qn | N3 | GLU158 (A) | OE2 | 3.38 |
| Qn | N4 | THR128 (D) | OG1 | 3.28 |
| Qn | N4 | THR127 (D) | O | 3.18 |
| Qn | N5 | GLU158 (B) | OE2 | 2.79 |
| | | *Hydrophobic contacts* | | |
| **Donor** | **Atom** | **Acceptor** | **Atom** | **Distance (Å)** |
| Qn | C7 | GLU158 (D) | CD | 3.60 |
| Qn | C6 | GLU158 (D) | CD | 3.29 |
| Qn | C21 | GLU158 (D) | CD | 3.57 |
| Qn | C15 | GLU158 (D) | CD | 3.72 |
| Qn | C8 | THR154 (D) | CG2 | 3.74 |
| Qn | C7 | THR154 (D) | CG2 | 3.83 |
| Qn | C8 | THR128 (D) | CG2 | 3.52 |
| Qn | C7 | THR128 (D) | CG2 | 3.77 |
| Qn | C26 | THR127 (D) | CA | 3.83 |
| Qn | C21 | THR127 (D) | CA | 3.72 |
| Qn | C25 | GLU158 (B) | CD | 3.61 |
| Qn | C22 | GLU158 (B) | CD | 3.93 |
| Qn | C16 | GLU158 (B) | CD | 3.35 |
| Qn | C22 | GLU158 (B) | CG | 3.84 |
| Qn | C23 | THR155 (B) | CB | 3.66 |
| Qn | C23 | THR154 (B) | CG2 | 3.57 |
| Qn | C22 | THR154 (B) | CG2 | 3.38 |
| Qn | C17 | THR154 (B) | CG2 | 3.47 |
| Qn | C16 | THR154 (B) | CG2 | 3.33 |
| Qn | C27 | LEU151 (B) | CD2 | 3.82 |
| Qn | C23 | LEU151 (B) | CD1 | 3.51 |
| Qn | C27 | LEU151 (B) | CG | 3.77 |
| Qn | C23 | LEU151 (B) | CG | 3.75 |
| Qn | C20 | THR128 (B) | CG2 | 3.82 |
| Qn | C14 | THR128 (B) | CG2 | 3.68 |
| Qn | C10 | THR128 (B) | CG2 | 3.79 |
| Qn | C18 | GLU158 (A) | CD | 3.62 |
| Qn | C12 | GLU158 (A) | CD | 3.77 |
| Qn | C9 | GLU158 (A) | CD | 3.83 |
| Qn | C19 | GLU158 (A) | CG | 3.72 |
| Qn | C18 | GLU158 (A) | CG | 3.86 |
| Qn | C19 | THR154 (A) | CG2 | 3.69 |
| Qn | C13 | THR154 (A) | CG2 | 3.80 |
| Qn | C18 | THR154 (A) | CG2 | 3.89 |
| Qn | C13 | THR127 (A) | C | 3.83 |
| Qn | C18 | PHE75 (A) | CE1 | 3.75 |

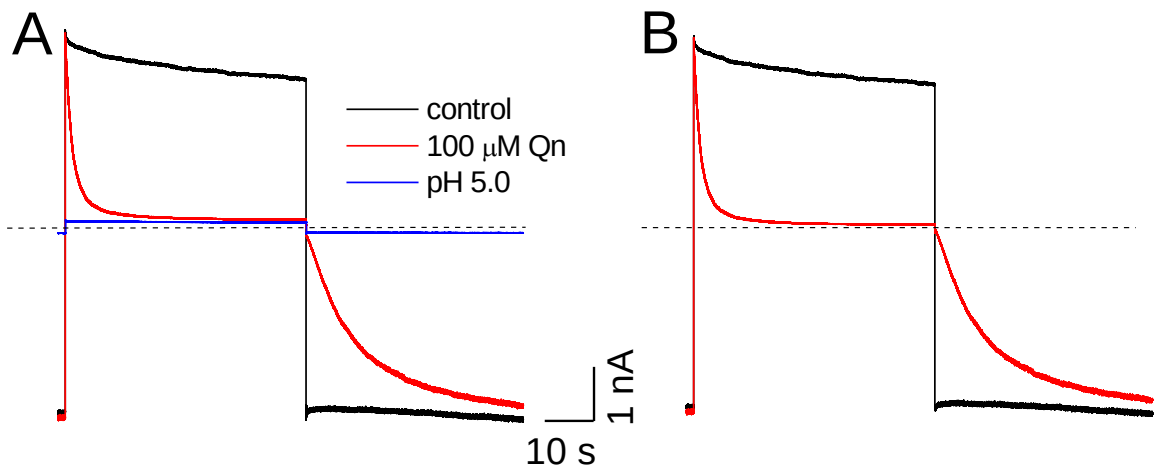


**Fig. S1.** Subtraction of endogenous/leak currents. (A) Uncorrected (raw) Kir4.1 current traces in control (black), 100 μM Qn (red) and pH 5.0 (blue) conditions. (B) Kir4.1 currents in control (black) and 100 μM Qn (red) conditions after the subtraction of endogenous/leak currents (blue trace en A).

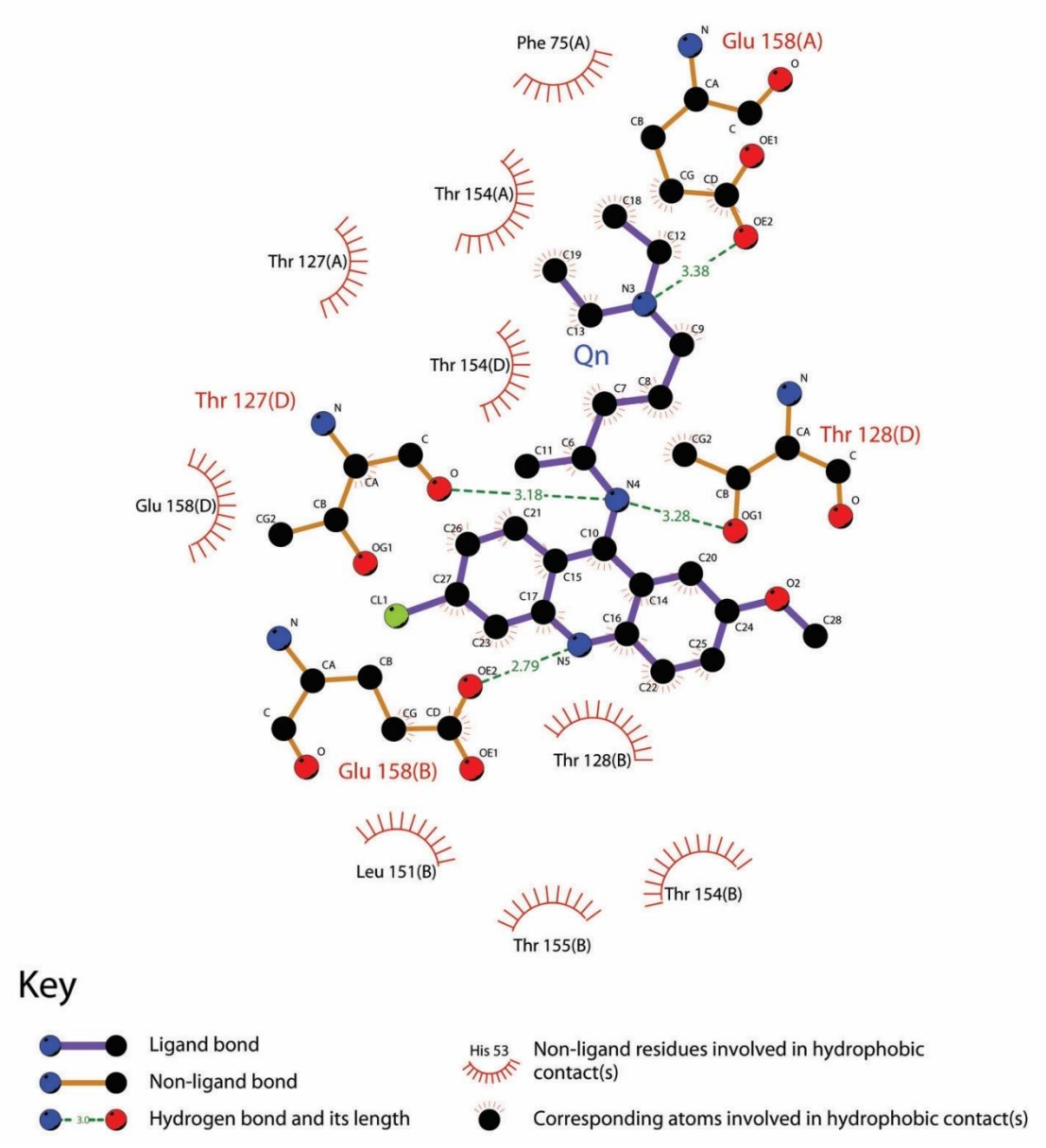


**Fig. S2.** Schematic depiction of the main interactions of Kir4.1 and quinacrine (Qn). This image was generated with LIGPLOT program. A distance between donor and acceptor of less than 3.5 Å is considered as a hydrogen-bond, and a 4.1 Å distance between two hydrophobic atoms is considered a hydrophobic interaction.

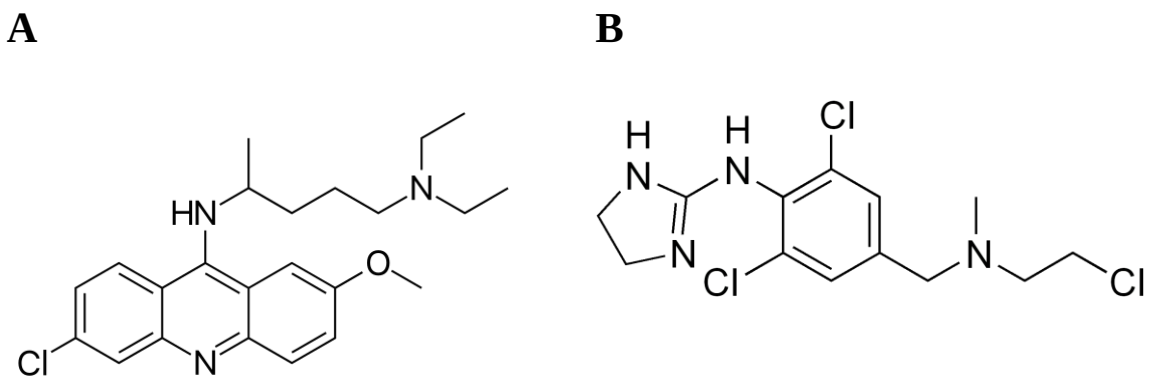


**Fig. S3.** Structures of quinacrine (A) and chloroethylclonidine (B).