Assessing hERG pore models as templates for drug docking using published experimental constraints: the inactivated state in the context of drug block

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Supporting Information

This supporting information illustrates some of the variability in low energy score docking poses produced by Flexidock and GOLD that is compatible with high binding affinities for dofetilide (Figures S1, S2), terfenadine (Figures S3, S4) and cavalli-2 (Figures S5, S6).

The supporting information also supplements Figure 7 of the main paper. As for E-4031 (Figure 7B of main paper) low energy score binding poses for terfenadine (Figure S4B) and cisapride (Figure S7) obtained with Flexidock using the MthK(1LNQ) model, show interactions with *specific* Y652 and F656 side chains that conform to the specific Y652 and F656 interactions identified for these drugs by Imai et al. using hERG tandem-dimer mutants[1]. This is indicated in Figures S4B and S7 by purple annotations that indicate the hERG channel subunit for specific Y652 and F656 side chains that make drug interactions. See figure legends for details.

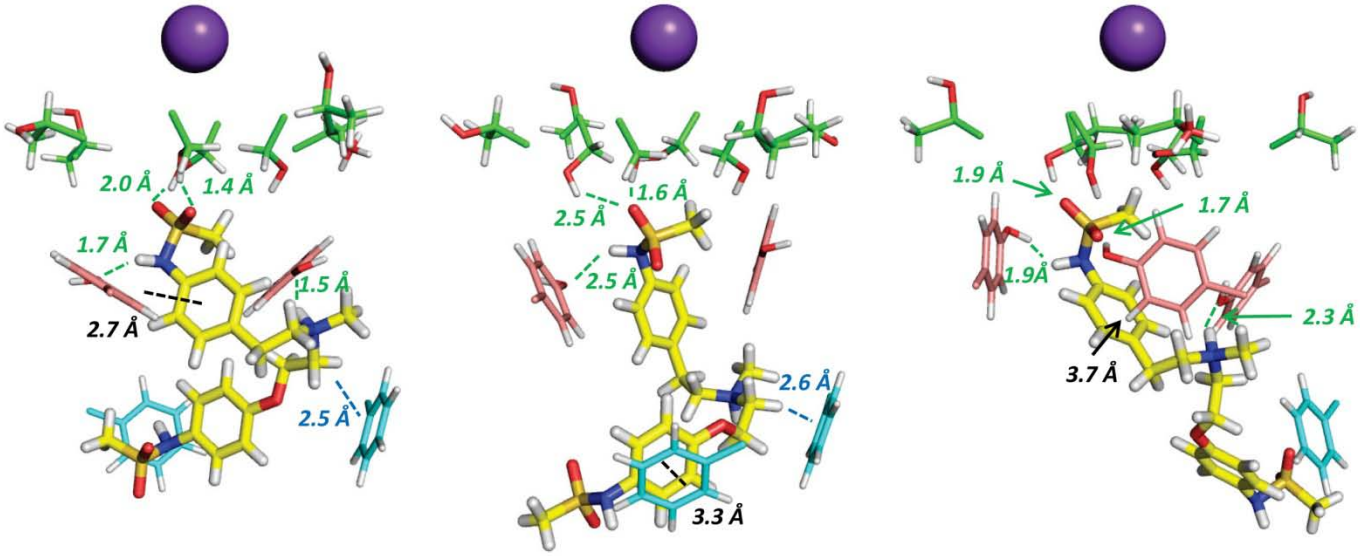

Figure S1: Low energy score poses for dofetilide docked into the MthK(1LNQ) model using GOLD with Chemscore scoring. In this and subsequent figures, the side chains of hERG pore residues are thin sticks. T623 and S624 side chains are green; Y652 (pink) andF656 (pale blue) are only shown for those side chains that make interactions with drug according to the criteria of Table 2 of the main paper. Aromatic π – π interactions are black, hydrogen bonds are green and cation – π interactions are blue. The purple sphere is the K^+ ion in the S3 site of the selectivity filter.

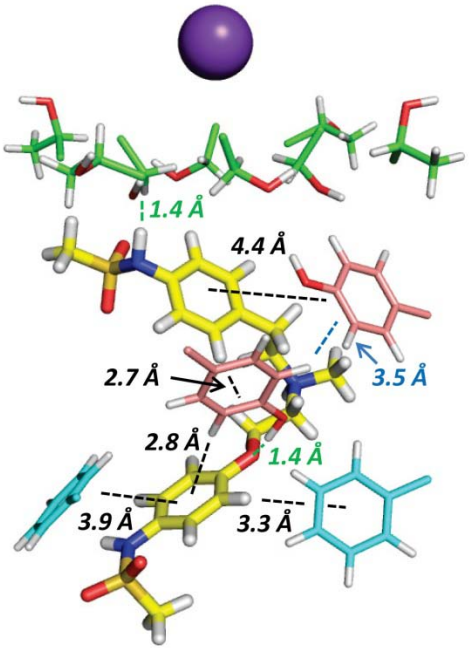

Figure S2: Low energy score pose for dofetilide docked into the MthK(1LNQ) model using Flexidock. Annotations are as described in the Figure S1 legend.

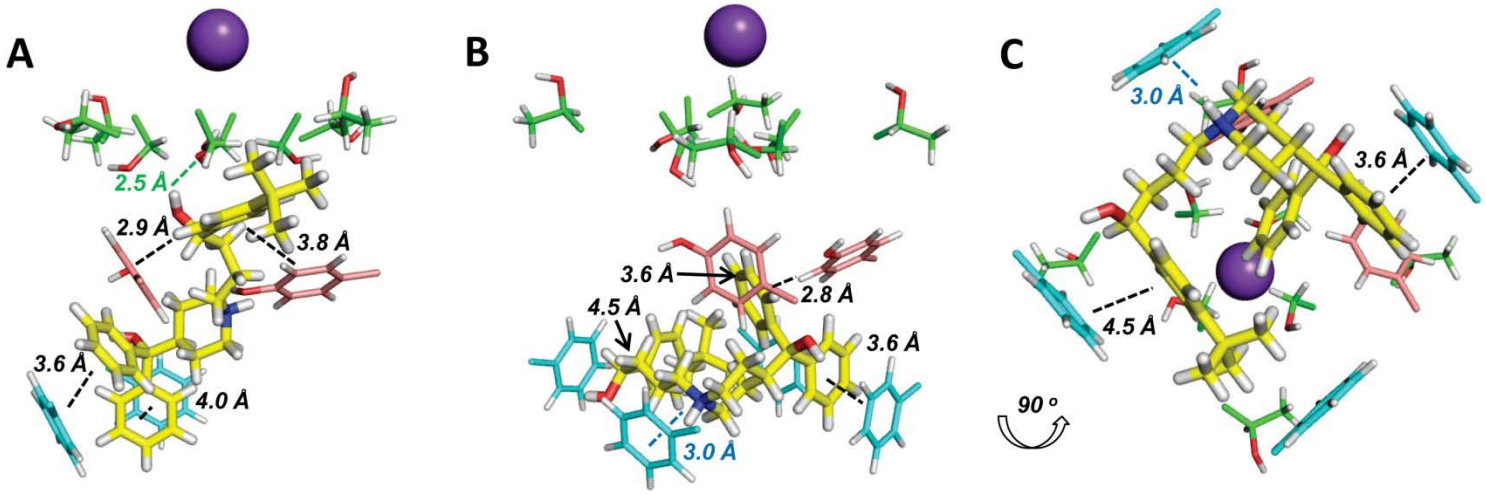

Figure S3: The two best energy score poses for terfenadine docked into the MthK(1LNQ) model using GOLD with ChemPLP scoring. Poses similar to those shown in panel B were strongly represented in GOLD docking outputs. Panel C is the same pose as panel B but viewed from below looking towards the selectivity filter. This view illustrates strong complementarity of four chemical groups on the drug with optimally-positioned F656 side chains in the MthK(1LNQ) model. Annotations are as described in the Figure S1 legend.

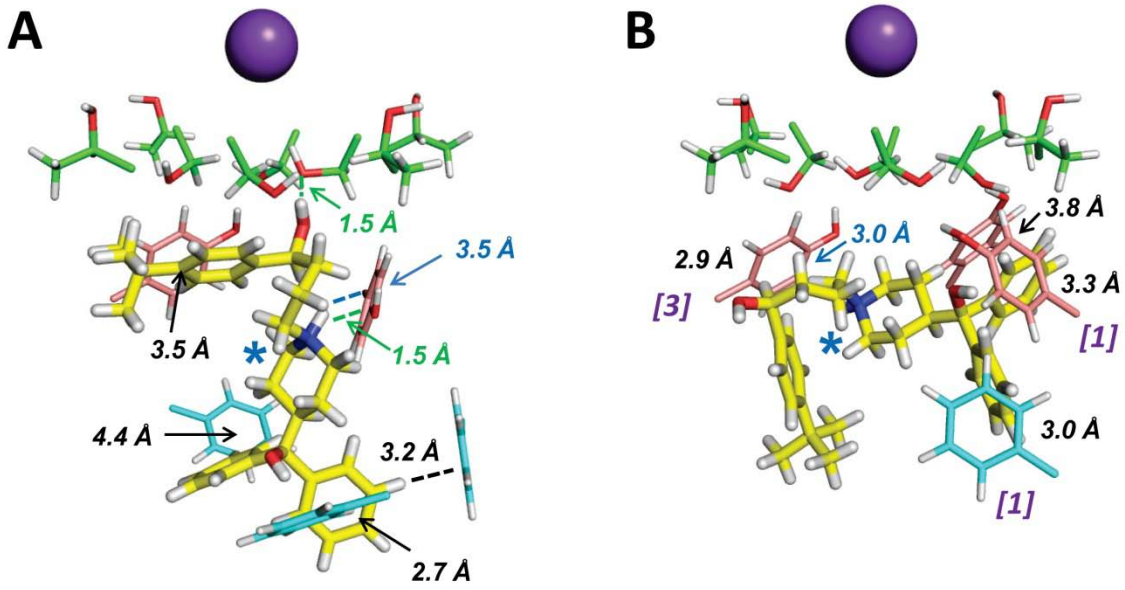

Figure S4: Low energy score poses for terfenadine docked into the MthK(1LNQ) model using Flexidock. Annotations are as described in the Figure S1 legend. The blue star indicates the location of the protonated secondary amino group near the internal binding site for a K^+ ion. The hERG pore subunits to which specific Y652 and F656 side chains correspond are indicated with purple annotations in panel B. The arrangement of terfenadine interacting with Y652 and F656 side chains on subunit 1 and a Y652 side chain on subunit 3 corresponds the predictions of Imai et al. [1] for this drug.

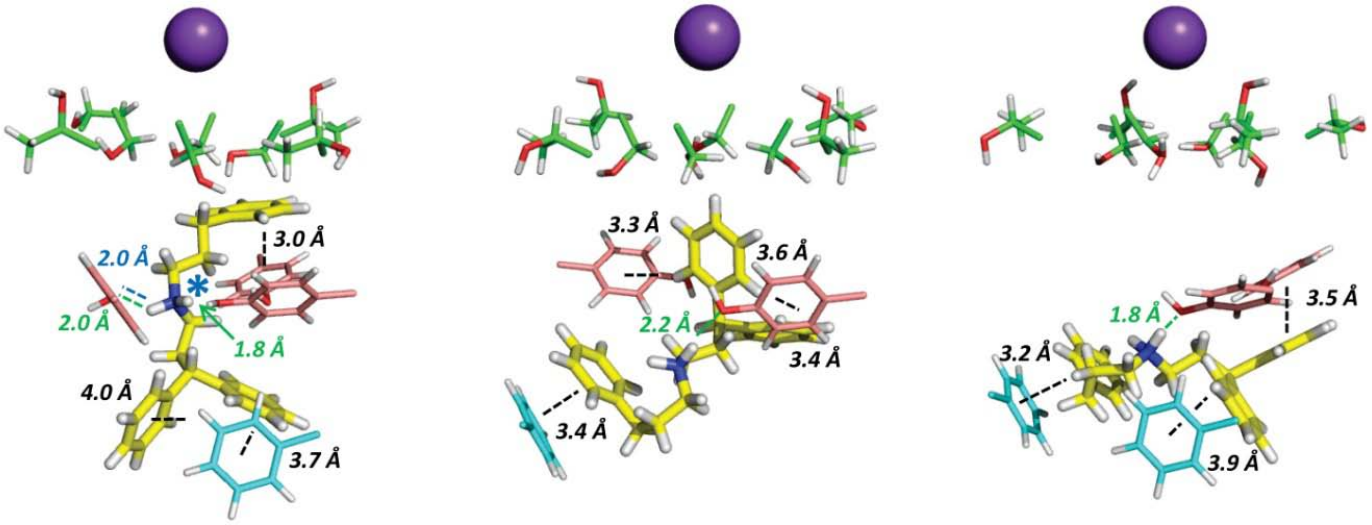

Figure S5: Low energy score poses for cavalli-2 docked into the MthK(1LNQ) model using GOLD with Chemscore. Annotations are as described in the Figure S1 legend. The blue star indicates the location of the protonated secondary amino group near the internal binding site for a K^+ ion.

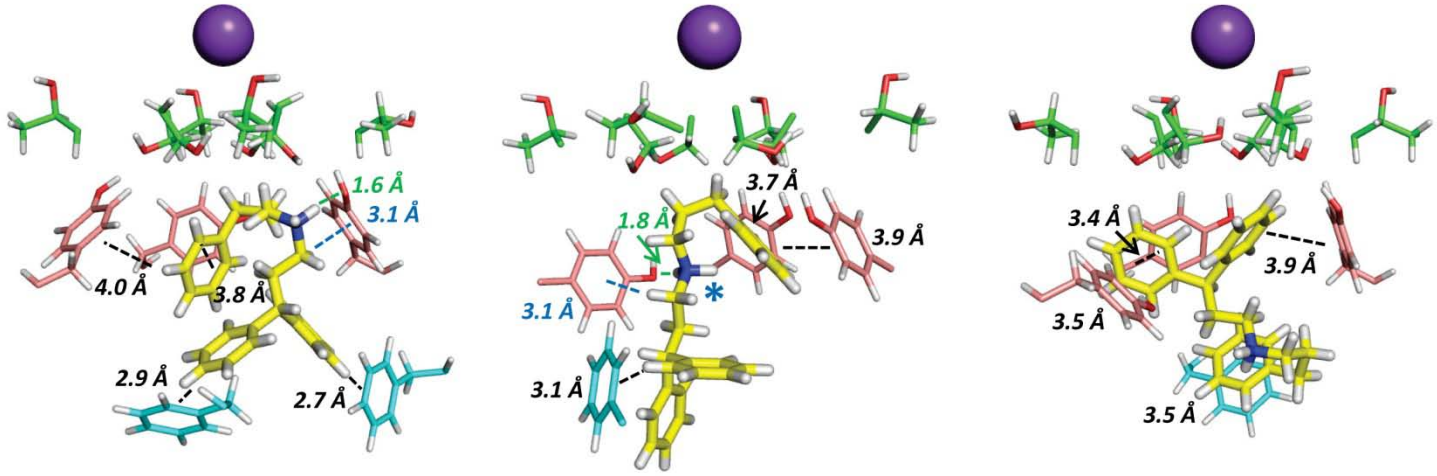

Figure S6: Low energy score poses for cavalli-2 docked into the MthK(1LNQ) model using Flexidock. Annotations are as described in the Figure S1 legend. The blue star indicates the location of the protonated secondary amino group near the internal binding site for a K^+ ion.

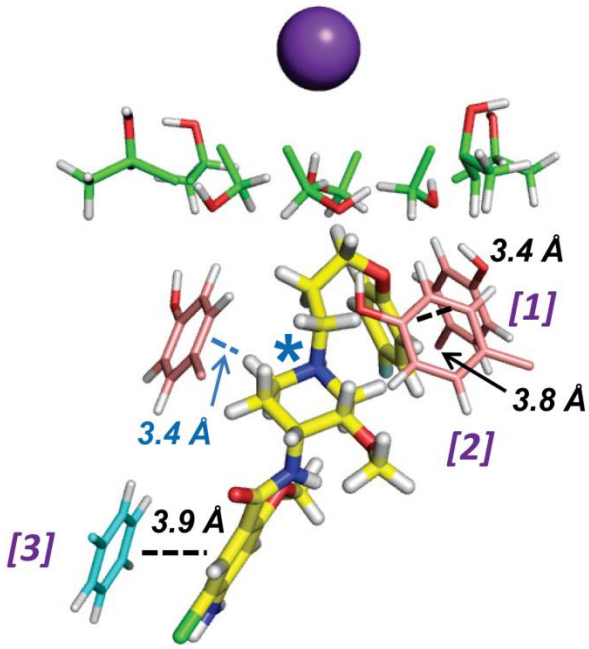

Figure S7: Low energy score pose for cisapride docked into the MthK(1LNQ) model using Flexidock. The blue star indicates the location of the protonated secondary amino group near the internal binding site for a K^+ ion. The hERG pore subunits to which specific Y652 and F656 side chains correspond are indicated with purple annotations. The arrangement of cisapride interacting with Y652 side chains on subunits 1 and 2 and an F656 side chain on subunit 3 corresponds to the predictions of Imai et al. [1] for this drug. Note that the orientation of cisapride with respect to the vertical pore axis is "upside-down" compared to its orientation in the Imai et al. model [1].

Reference:

[1] Imai, Y. N.; Ryu, S.; Oiki, S. Docking model of drug binding to the human ether-a-go-go potassium channel guided by tandem dimer mutant patch-clamp data: a synergistic approach. *J. Med. Chem.* **2009**, *52*, 1630-1638.