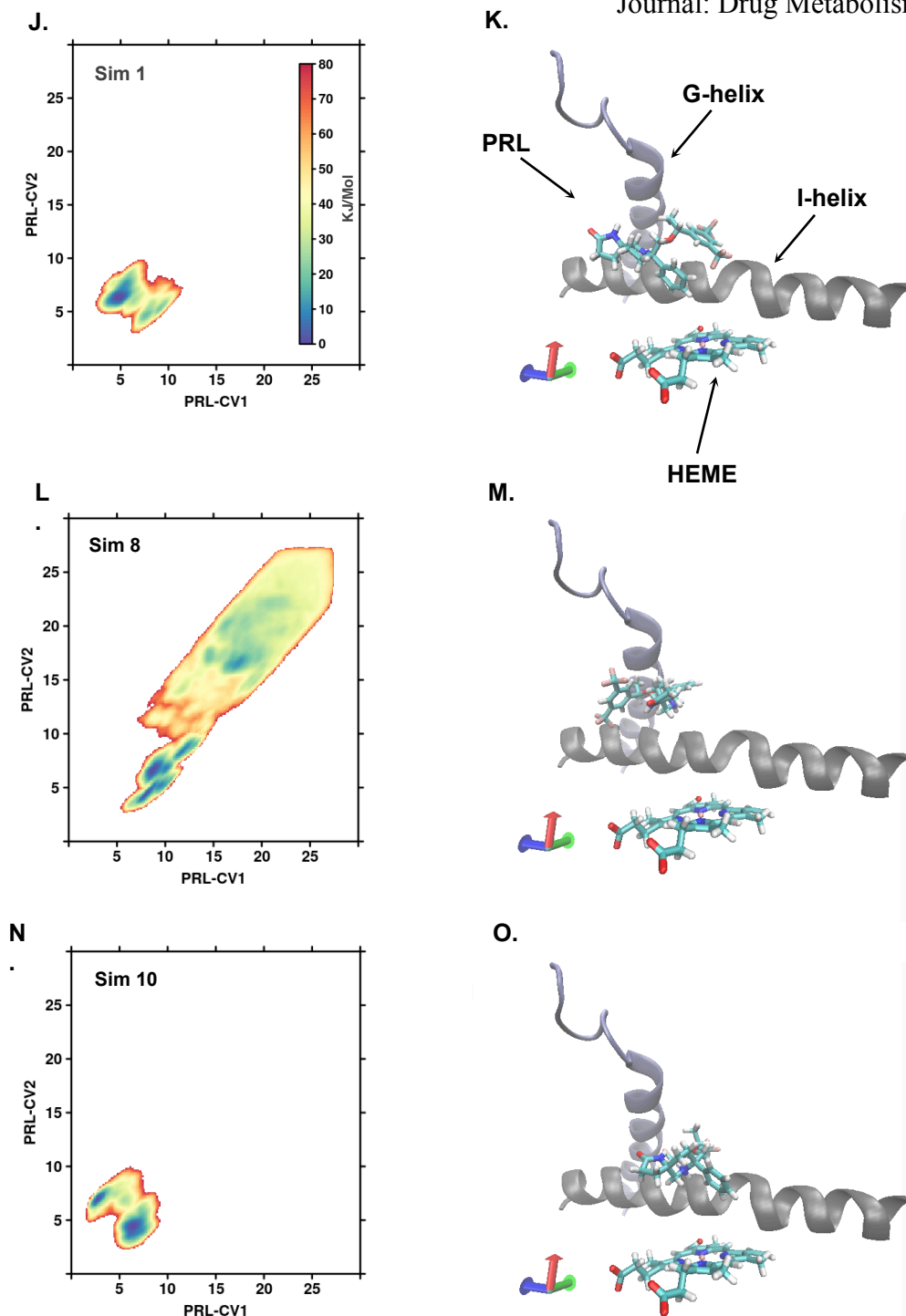


**SUPP FIGURE S4 – Part 1 of 2. Energy landscapes and lowest energy binding positions for all simulations.** Free energy landscapes are plotted as described in Supp Figure S3. (A-E) Free energy landscapes for simulations 2, 3, 4, 5, and 7 in which protonated rolapitant (PRL) adopted a similar initial low energy pose (shown in panel F). (F) Overlay of rolapitant in the lowest energy pose from simulations 2, 3, 4, 5, and 7. CYP2D6 is shown in grey. The heme and rolapitant are shown with CPK colors. (G,H) Free energy landscapes and (I) overlay of rolapitant low energy poses adopted in simulations 6 and 9. The PRL-CV1 atoms are rotated nearer to the G-helix and rolapitant is closer to the heme as compared to A-E. Free energy landscapes (J,L,N) and rolapitant low energy poses (K,M,O) for simulations 2, 8 and 10. For these simulations rolapitant adopted unique low energy poses.



**SUPP FIGURE S4 – Part 2 of 2. Energy landscapes and lowest energy binding positions for all simulations.** Free energy landscapes are plotted as described in Supp Figure S3. (A-E) Free energy landscapes for simulations 2, 3, 4, 5, and 7 in which protonated rolapitant (PRL) adopted a similar initial low energy pose (shown in panel F). (F) Overlay of rolapitant in the lowest energy pose from simulations 2, 3, 4, 5, and 7. CYP2D6 is shown in grey. The heme and rolapitant are shown with CPK colors. (G,H) Free energy landscapes and (I) overlay of rolapitant low energy poses adopted in simulations 6 and 9. The PRL-CV1 atoms are rotated nearer to the G-helix and rolapitant is closer to the heme as compared to A-E. Free energy landscapes (J,L,N) and rolapitant low energy poses (K,M,O) for simulations 2, 8 and 10. For these simulations rolapitant adopted unique low energy poses.