



**Fig. S12a-e: Sequence alignment of 47 human class A GPCR.** Highly conserved positions according to the unifying *Ballesteros and Weinstein* numbering scheme<sup>4</sup> are indicated by respective numbers below the alignment. The structural dimensions of each MC4R transmembrane helix (TM) or inter-connecting loops (IL = intracellular loop; EL = extracellular loop) are indicated above the sequences, as well as numbers for the MC4R sequence. The alignment was visualized using the software BioEdit<sup>5</sup>. Specific background colors indicating conservation (Blossum62 matrix) and reflecting chemical properties of the amino acid side chains: black, proline; blue, positively charged; cyan/green, aromatic and hydrophobic; green, hydrophobic; red, negatively charged; gray, hydrophilic; dark red, cysteines; and magenta, histidine.

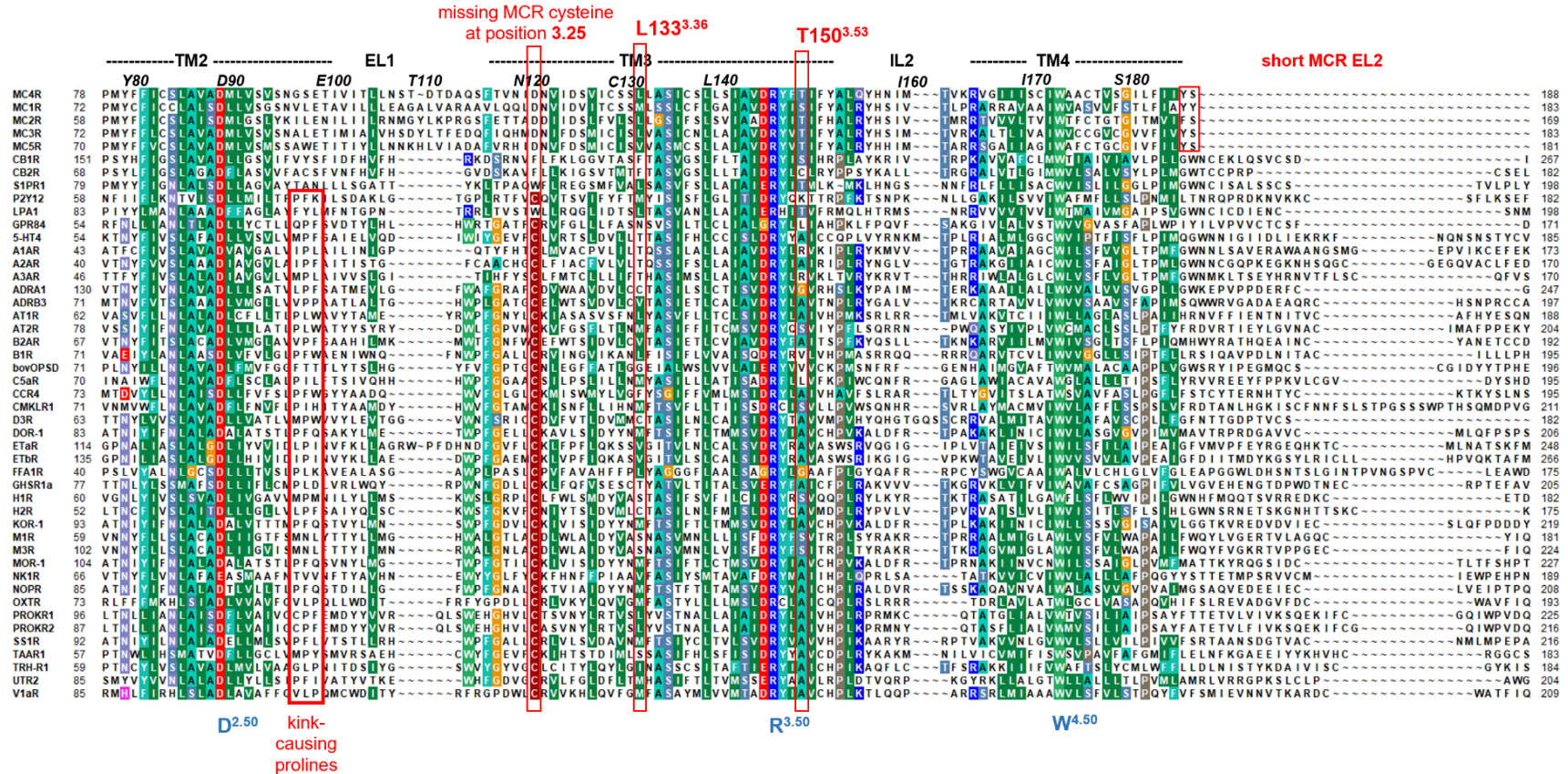


Fig. S12b

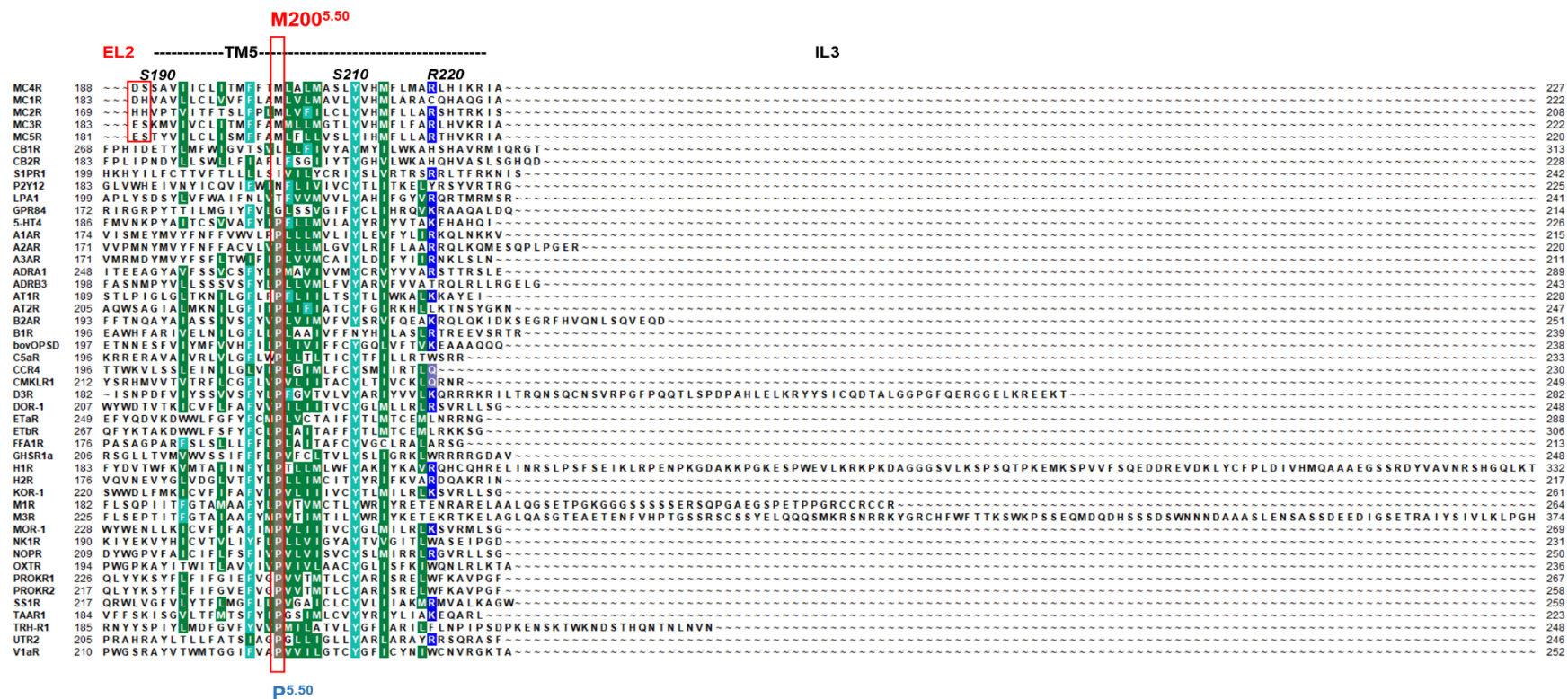


Fig. S12c

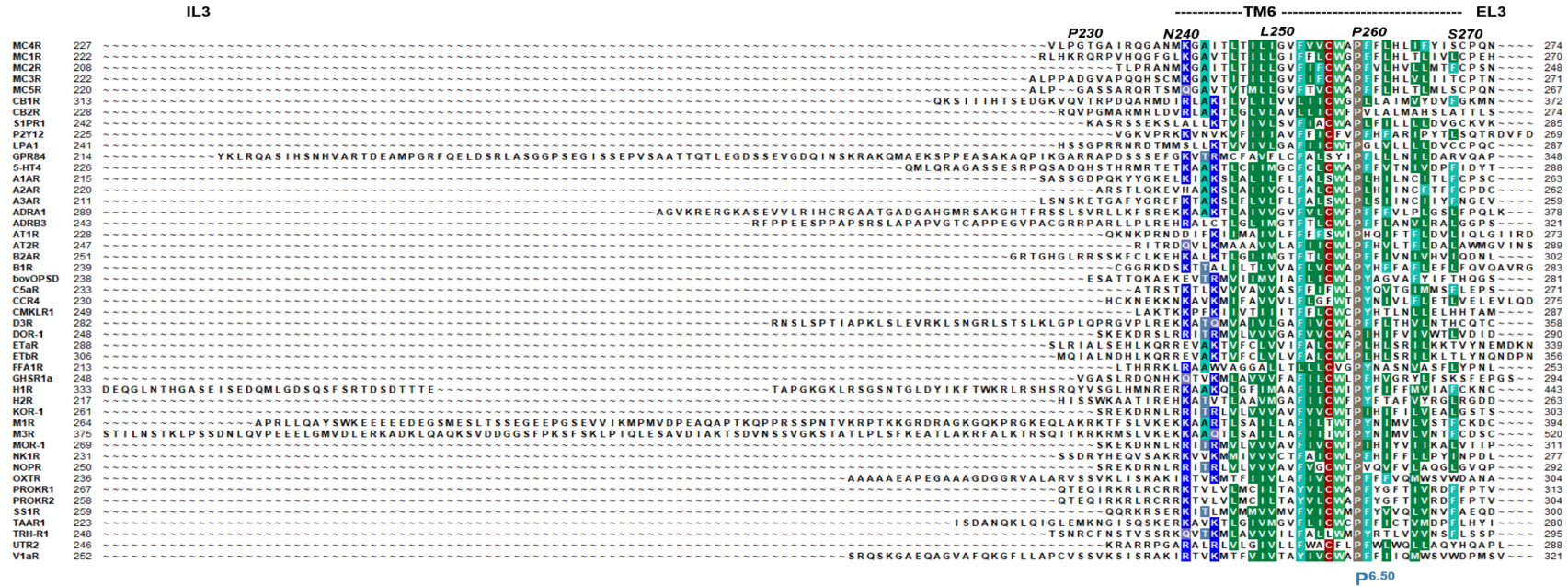


Fig. S12d

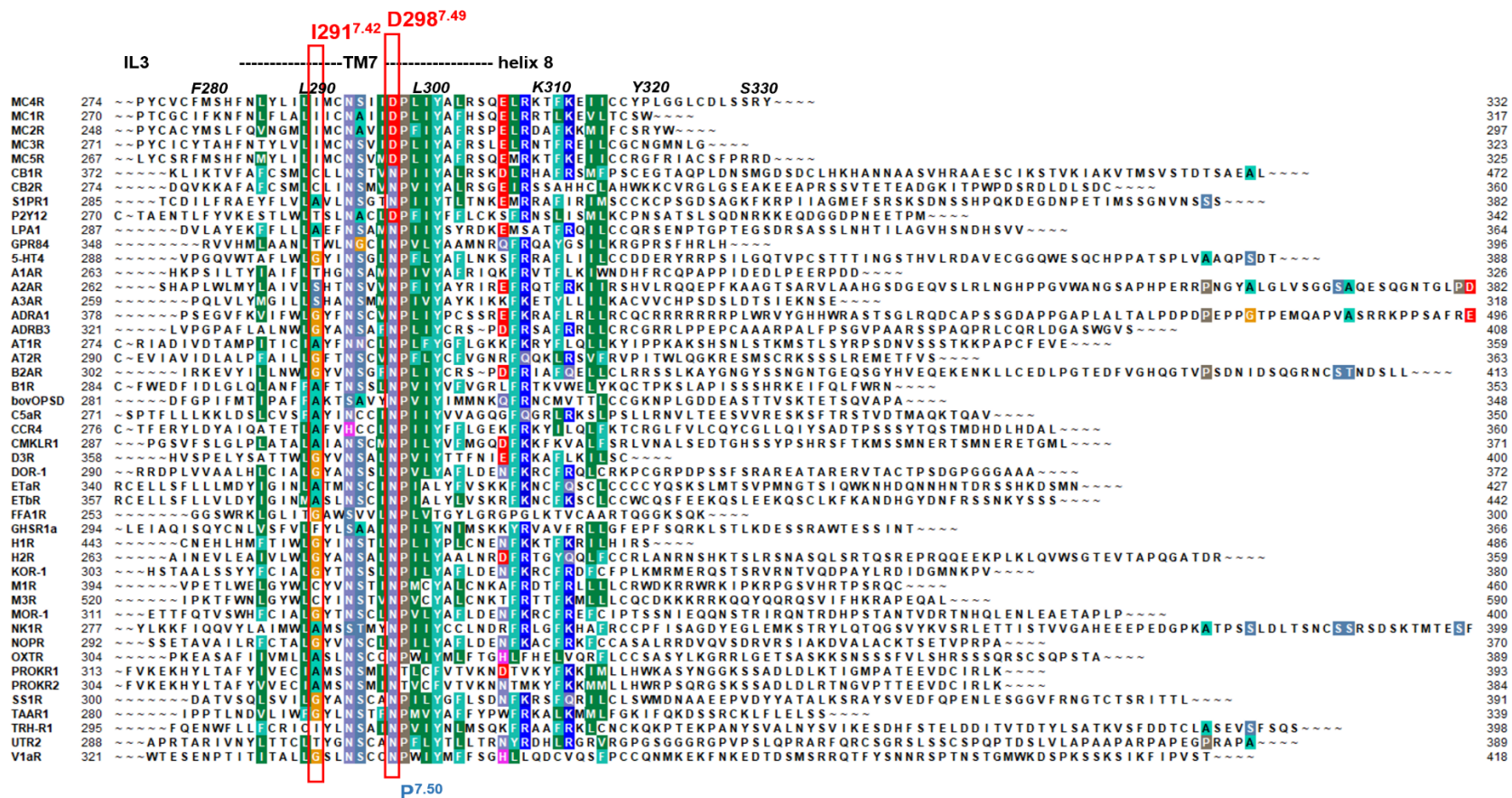


Fig. S12e