



**S1** - Cytoplasmic view of a homology model of the  $\mu$ OR active state (*red*) superimposed on a homology model of the inactive  $\mu$ OR (*grey*). The loop regions have been omitted for clarity. The stick representation shows the polar interaction between R165<sup>3.50</sup> and T279<sup>6.34</sup>, which has been proposed to be equivalent in the opioid receptors to the 'ionic lock' found in rhodopsin (40). For simplicity, only the generic number (see (41)) is reported. All images were made using Pymol (42).

From this figure, we note that the most tangible difference between these structures consists of the different relative positions of residues R165<sup>3.50</sup> and T279<sup>6.34</sup>, which are supposed to be involved in ionic-lock breaking upon receptor activation (40). Residues here and throughout the text are numbered both according to their position in the mouse  $\mu$ OR sequence, and to the Ballesteros-Weinstein generic two-number (N1.N2) scheme (41) reported as a superscript. In this scheme, N1 indicates the TM the residue belongs to, while N2 refers to the residue position in the TM relative to its most conserved residue (position number 50).