SI-Video 1. (file: video\_1.mp4). Animations of the energetically most favorable pose of the agonists collected in Figure 1 (yellow atoms) obtained by molecular docking simulation using three differ models of human A3 adenosine receptor: top left, model based on the adenosine bound hA2A AR crystal structure (PDB code: 2YDO); top right, model based on the adenosine bound hA1 AR crystal structure (PDB code: 6D9H without induce fit); center bottom, model based on the adenosine bound hA1 AR crystal structure (PDB code: 6D9H with induce fit). The most relevant residues are highlighted. Hydrogen atoms are omitted. Each frame of the video corresponding to the ligand depicted in the left panel side in which are also reported the name. In the background of the 3D molecular representation, the heatmap generated by the per-residue analysis for each ligand is shown (see Methods section). The contributes to electrostatic (ele) and hydrophobic (hydro) energy interactions are color-coded into a blue to green palette corresponding to the interaction strength. The blue spots indicated negative values (favorable for the electrostatic term) while green spots designate for positive values (favorable for the hydrophobic term).

SI-Video 2. (file: video\_2.mp4). Animations of the energetically most favorable pose of the antagonists collected in Figure 2 (magenta atoms) obtained by molecular docking simulation using three differ models of human A3 adenosine receptor: top left, model based on the ZM241385 bound hA2A AR crystal structure (PDB code: 3PWH); top right, model based on the ZM241385 bound hA2A AR crystal structure (PDB code: 5NM2); center bottom, model based on the DU172 bound hA1 AR crystal structure (PDB code: 5UEN). all “antagonist-driven” hA3 AR models have been built up considering the sodium cation and its first hydration sphere as an integral part of the orthostatic site.

The most relevant residues are highlighted. Hydrogen atoms are omitted. Each frame of the video corresponding to the ligand depicted in the left panel side in which are also reported the name. In the background of the 3D molecular representation, the heatmap generated by the per-residue analysis for each ligand is shown (see Methods section). The contributes to electrostatic (ele) and hydrophobic (hydro) energy interactions are color-coded into a blue to green palette corresponding to the interaction strength. The blue spots indicated negative values (favorable for the electrostatic term) while green spots designate for positive values (favorable for the hydrophobic term).