Supplementary Figures:

Supplementary Fig. 1. [^{3}H]Ketanserin specific binding in wild type (WT) and 5-HT2A-KO mouse frontal cortex membrane preparations (n=6). All values represent means±SEM.

Supplementary Fig. 2. Schematic representation of agonist, antagonist, and inverse agonist binding to different functional states of the receptor. Agonists bind with higher affinity to the active conformation of the receptor (R*), whereas inverse agonists preferentially bind and stabilize the receptor in the inactive state (R). Neutral antagonists bind both coupled and uncoupled forms of the receptor with essentially identical affinity. Non-hydrolyzable GTP analogs, such as Gpp(NH)p or GTPγS, stabilize the transition state of Gα for GTP hydrolysis. This uncouples receptor-G protein complexes shifting the equilibrium to the inactive (R) state.

Supplementary Fig. 3. (**A**) [^{3}H]Ketanserin specific binding (2 nM) displacement curves by DOI in mouse frontal cortex in the presence or in the absence of GDP/GTPγS. Displacement curves are statistically different in the presence and in the absence of GDP/GTPγS ($F[5,208]=2.59$, $p<0.05$, n=4-6). In the presence of GDP/GTPγS, the triphasic displacement curve became monophasic. Vehicle buffer: $pK_{i\text{-}high}$, -8.94±0.46; fraction high, 0.11±0.04; $pK_{i\text{-}medium}$, -7.00±0.19; fraction medium, 0.66±0.09; $pK_{i\text{-}low}$, -5.65±0.55 ($F[2,155]=3.81$, $p<0.05$). GDP/GTPγS buffer: pK_i, -6.92±0.06 ($F[2,23]=2.01$, $p>0.05$). (**B**) [^{3}H]Ketanserin specific binding (2 nM) displacement curves by LSD in mouse frontal cortex in the presence or in the absence of GDP/GTPγS. Displacement curves are statistically different in the presence and in the absence of GDP/GTPγS ($F[3,50]=149.6$, $p<0.001$, n=4). In the presence of GDP/GTPγS, the monophasic displacement curve of [^{3}H]ketanserin binding by LSD is shifted to the right. Vehicle buffer: pK_i, -9.01±0.07 ($F[2,26]=6.16$, $p>0.05$). GDP/GTPγS buffer: -5.59±0.06 ($F[2,23]=0.09$, $p>0.05$). All values represent means±SEM.