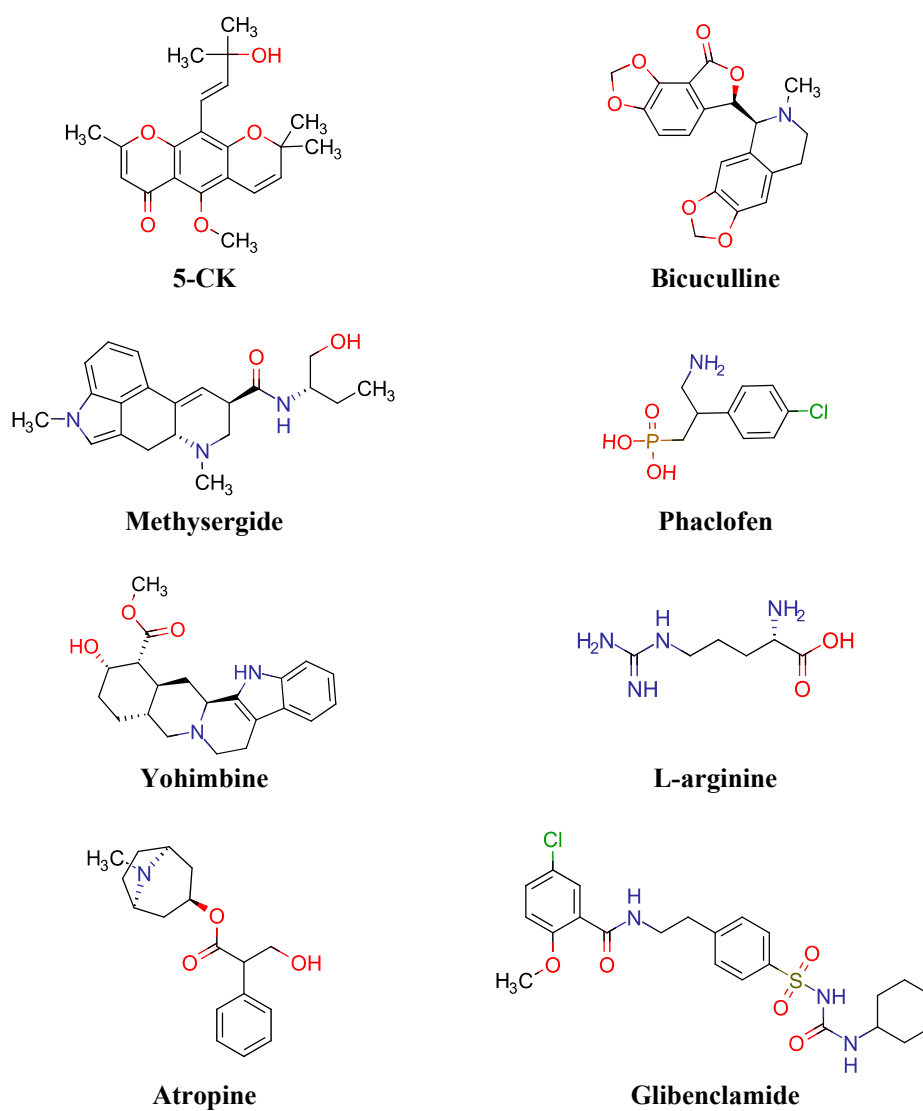
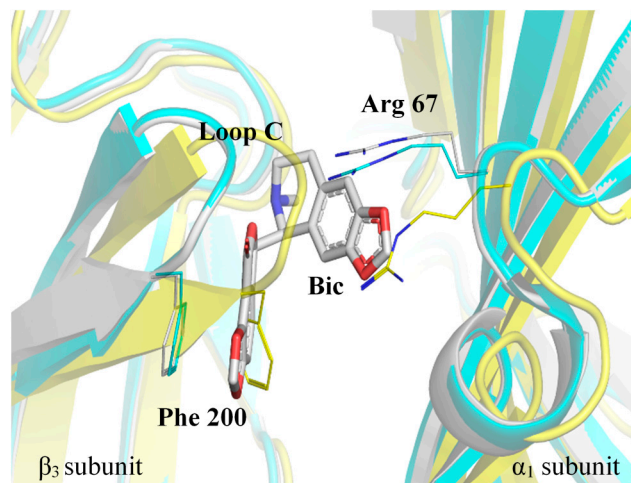


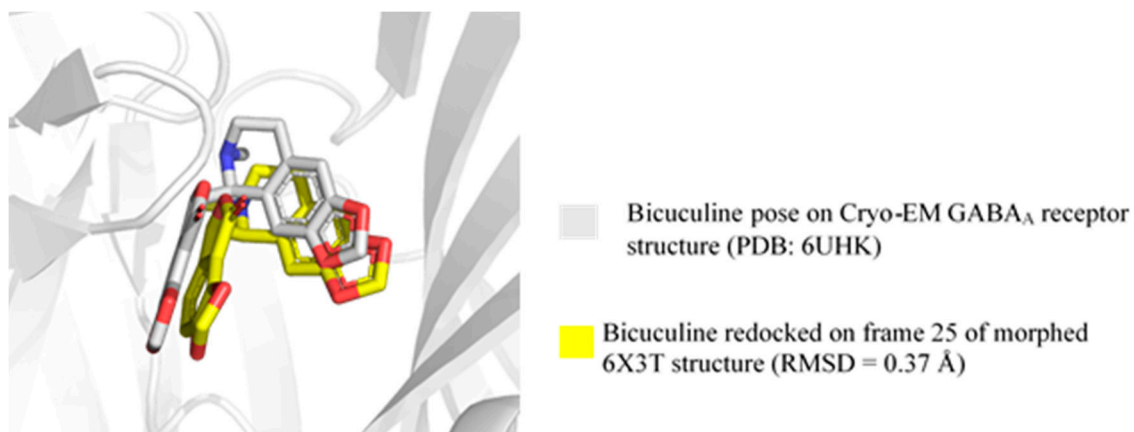
## Supplementary Material



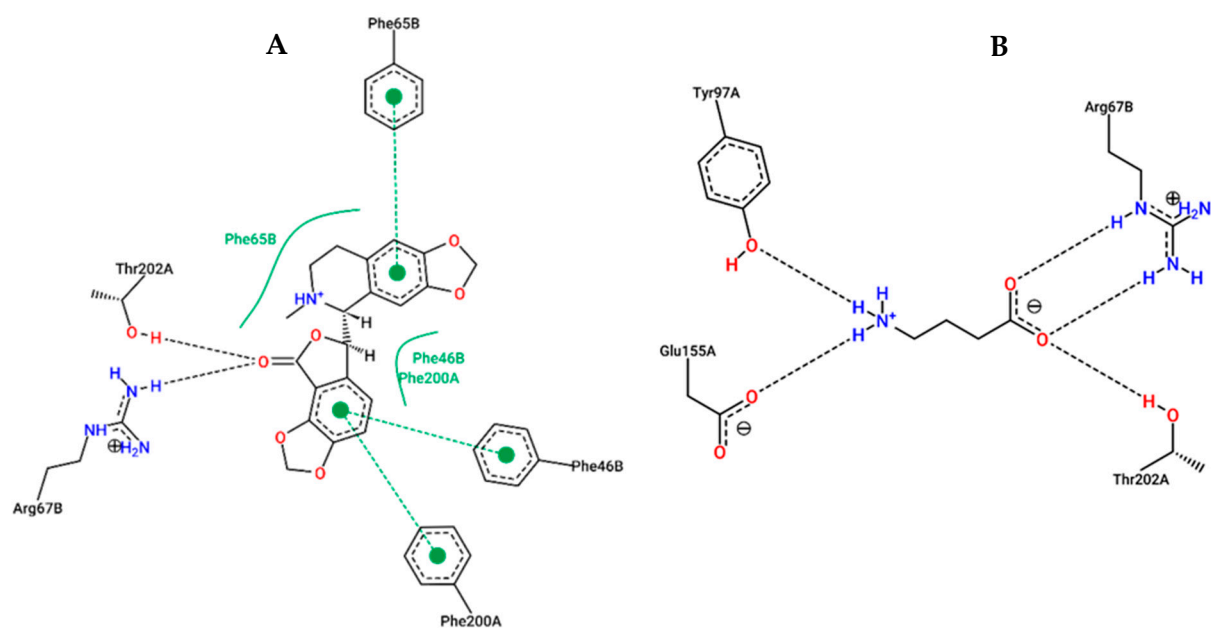
**Figure S1** - Two-dimensional (2D) structures of 5-CK and several antagonists of receptors and ion channels related to endogenous analgesia pathway: methysergide; yohimbine; atropine; bicuculline; phaclofen; L-arginine; and glibenclamide.



**Figure S2** - Bicuculline binding site highlighting the conformational change of residues Phe 200 ( $\beta_3$ ) and Arg 67 ( $\alpha_1$ ) in bonded (PDB: 6HUK, white) and unbonded (PDB: 6T3X, yellow) GABA<sub>A</sub> receptor with bicuculline. The selected morph (frame 25) was colored in cyan.



**Figure S3** – Bicuculline re-docking pose (yellow) in relation to Cryo-EM bicuculline position (white) on GABA<sub>A</sub> receptor structure.



**Figure S4** - Interaction profile of Bicuculline; (A) and GABA; (B) on GABA binding site generated by Poseview server.