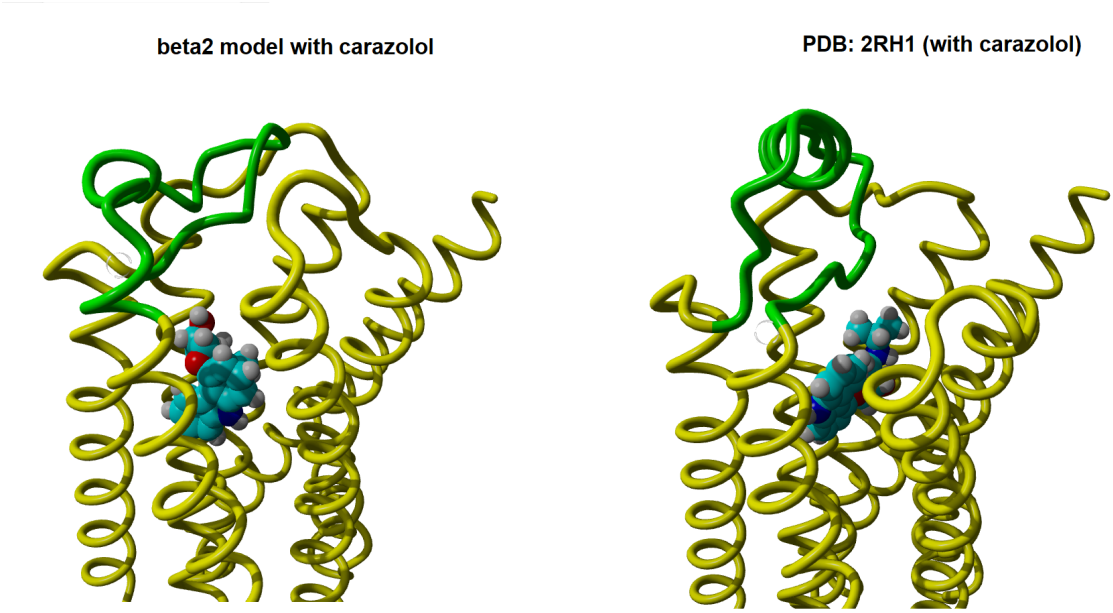
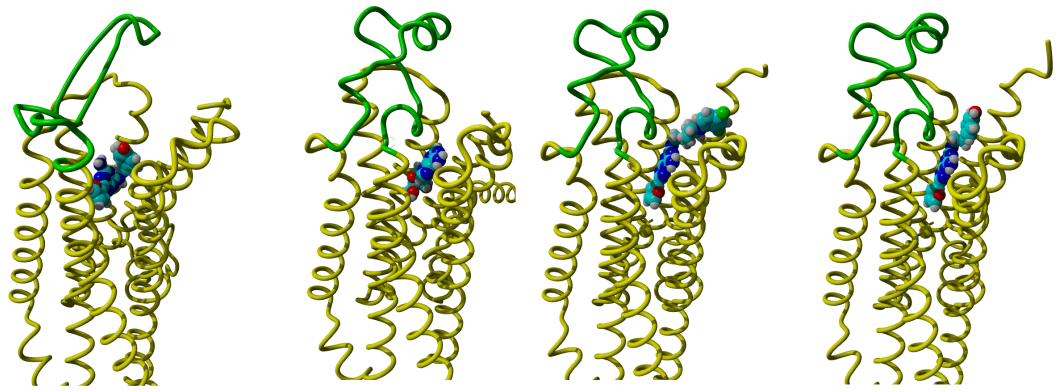
I am afraid that a few issues remain:

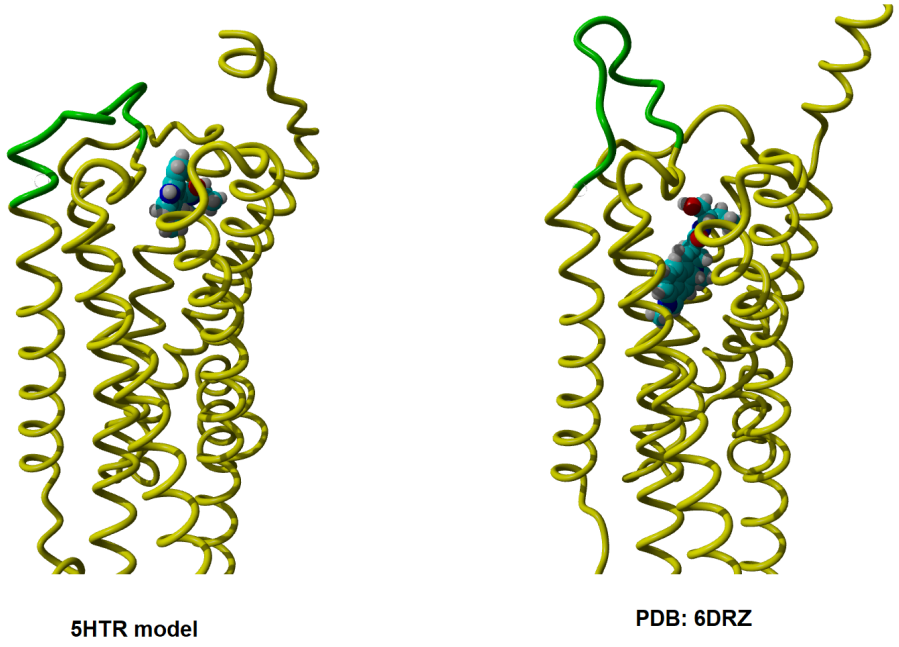
-the loops in the beta2 model (171-196) are quite different from the one in the crystal structures (3p0g, 4ldo), and (more importantly) they keep the entrance to the inner channel more open than in those crystal structure). Also, the beta2 model provided contains carazolol, but the pose is quite different (RMSD=5.9 angstrom) from the one in structure 2rh1, incorntrast to the very good fit claimed in lines 257-258. Since your method does not prevent it from finding good docking poses in beta2, the disappointing behavior you found in H1, M1 and 5HT2B models cannot simply be attributed to a bad loop model. For this reason, I would suggest rephrasing the text in lines 313-317 ("In all the failed cases (histamine H1, muscarinic M1, and serotonin 5HT2B), while the homology models were sometime accurate at the level of backbone atoms in the 7tm region, the loops were modeled poorly and disrupted the modeled ligand binding pocket. In these cases, the homology models are not accurate enough for docking or ConDockSite") .

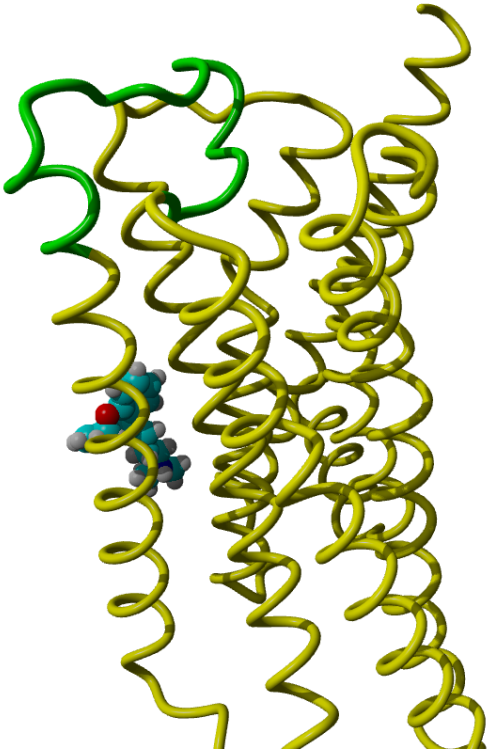



The loops in the A2A model (143-166) are also quite different from the ones in the crystal structures (2ydo, 4ug2,5iub,5k2, for A2A) : in this case, the modelled structure is more open than the crystal structures, and similar to that in structure PDB:5c1m of the mu-opioid receptor which leads me to believe that the differences in loop structure you find may suimply reflect different physiological conformations of the GPCR. Regardless of the origin of those differences, neither the A2A (or the beta2 models) deposited as SI contain adenosine (or adrenaline), but a different molecule in quite a different pose. This makes it impossible to reproduce Fig. 1A and 1C.

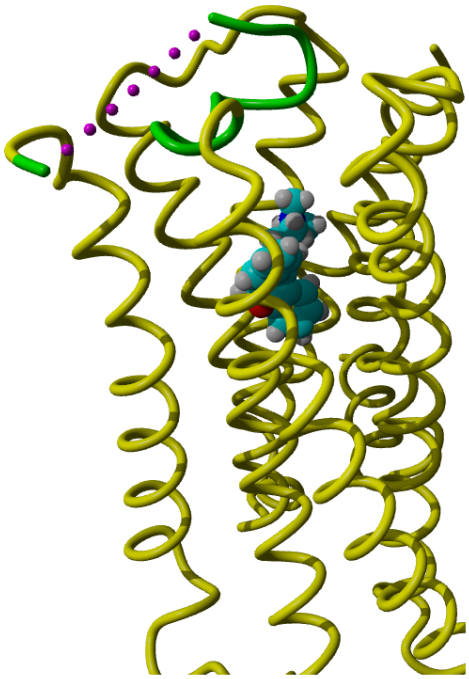



Furthermore, in the 5HT2 model, the modelled loops (corresponding to aa 194-206 in DRZ) that are different from the ones in the 6drz structure are away from the binding site entrance, and in the H1 model, the loop actually leaves the entrance to the binding site more unencumbered than in the 3rze model. It therefore does not seem at all appropriate to attribute the observed poor performance of ConDurfDock in these instances to this loop (especially in comparison to the good behavior in spite of poor loops described above).





H1 model



PDB: 6RZE