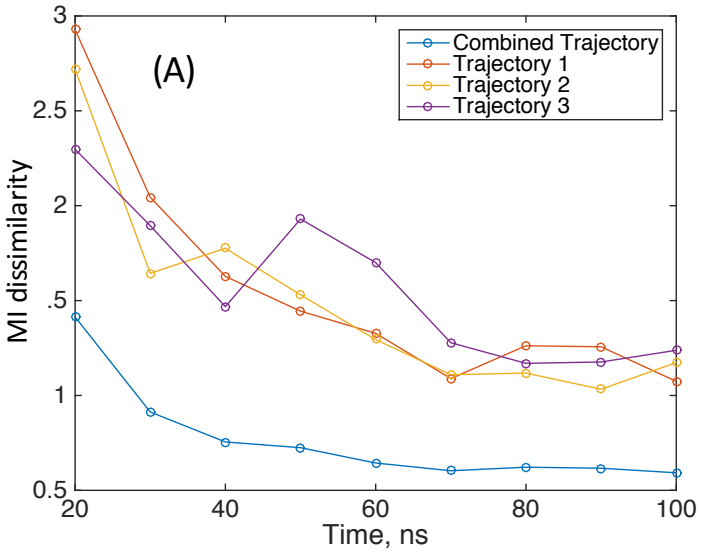


(B)

Allosteric hub score

Res no.	2Y03	4BVN
75	9	13
80	19	11
107	14	215
122	20	17
128	6	3
139	10	19
155	48	20
180	15	43
183	2	8
193	13	29
215	18	28
223	12	12
229	5	4
232	1	16
237	4	18
239	17	21
241	8	6
246	3	2
247	144	1
249	42	5
252	16	7
253	105	15
258	33	10
317	11	31
339	94	14
345	7	9

Fig. S1. (A) dissimilarity of the MI matrix with the preceding ensemble plotted with increasing trajectory length; root mean square deviation is used as the metric for dissimilarity; (B) Comparison of hub strengths of the top allosteric hubs obtained from simulations starting from two different crystal structures of β_1AR (pdb ID: 2Y03 and 4BVN); the blue shaded boxes indicate allosteric hub scores in the top 20; the residues that are identified as top allosteric hubs in both simulations are highlighted in red.

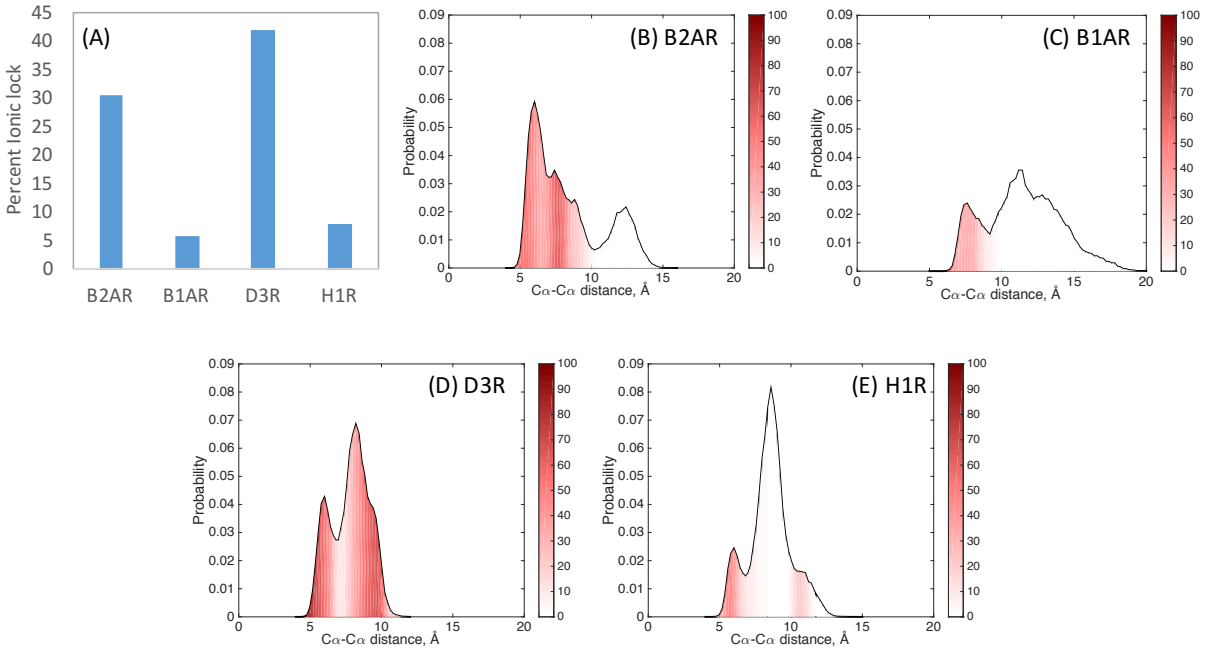


Fig. S2 (A) Percentage of conformations bearing the ionic lock during the MD simulations of biogenic amine receptors; (B-E) Probability of observing the ionic lock as function of TM3-TM6 distance; (B) β_2AR; (C) β_1AR; (D) D_3R; (E) H_1R

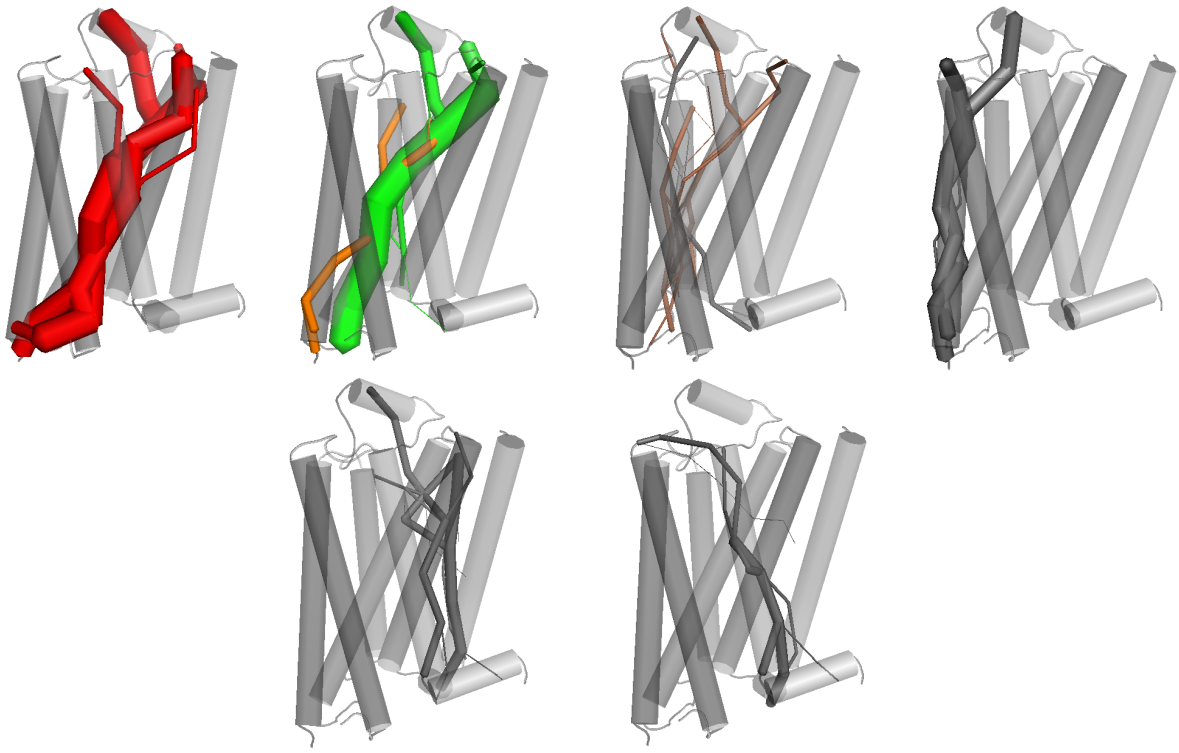


Fig. S3 Conserved allosteric pipelines in biogenic amine receptors superimposed onto the β_2AR structure

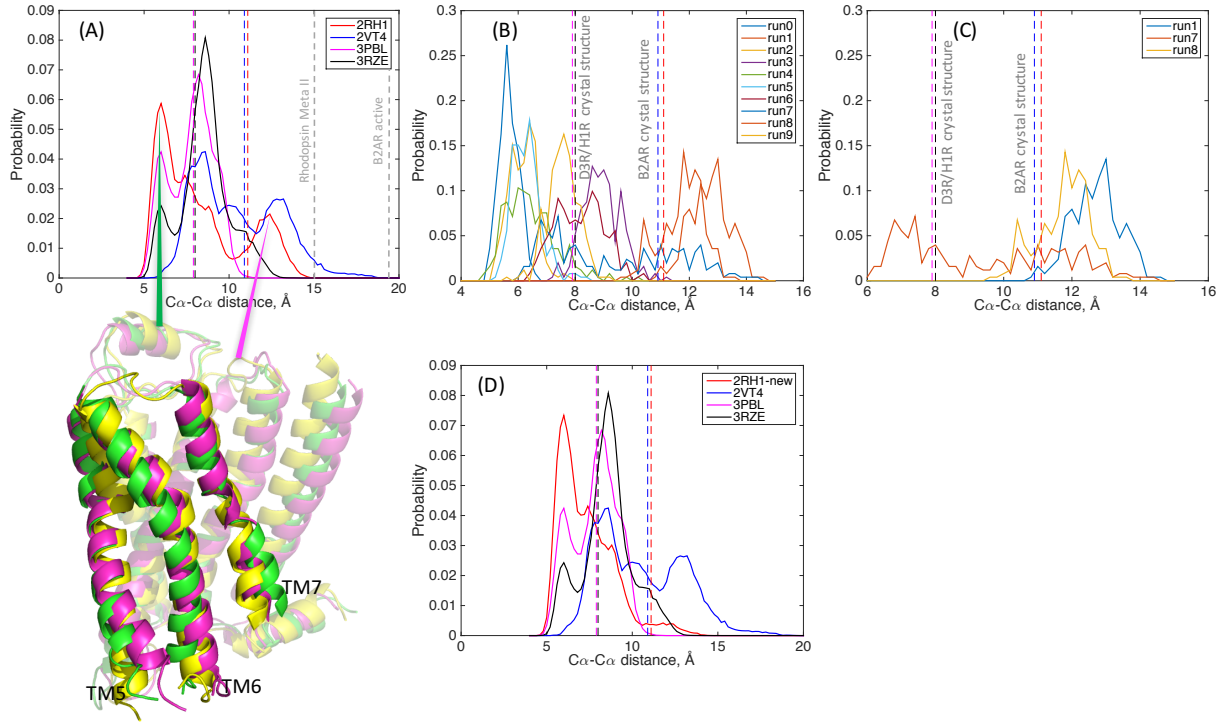


Fig. S4 (A) Representative structures from the collapsed and open states of β_2AR; green: collapsed conformation; magenta: open conformation; yellow: inactive β_2AR crystal structure; the locations of the structures in the TM3-TM6 distribution of β_2AR are shown; (B) TM3-TM6 distance distributions of individual MD trajectories of β_2AR; (C) TM3-TM6 distance distributions of the β_2AR trajectories which sample the open conformations; (D) TM3-TM6 distance distributions for β_2AR excluding the open conformations.

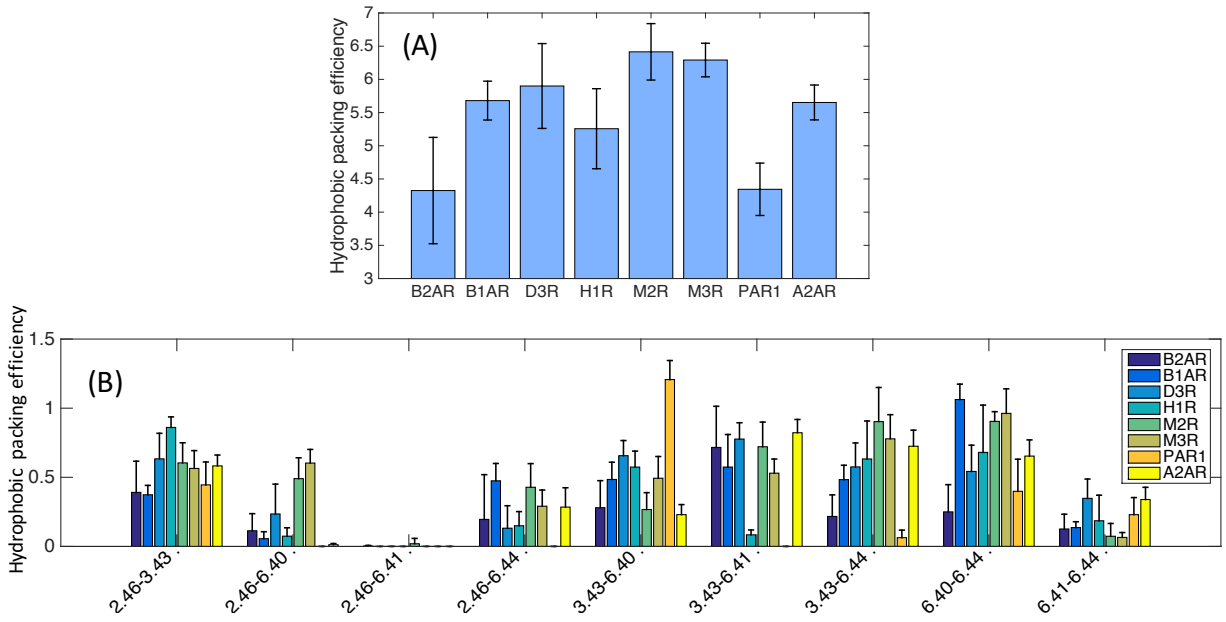


Fig. S5 (A) Interhelical residue packing efficiency among the hydrophobic residues in the middle of TM2, TM3 and TM6 as observed during the dynamics of different biogenic amine receptors as well as PAR1 and A2AR; (B) packing efficiency for each inter-residue contact; error bars represent 95% confidence limits.

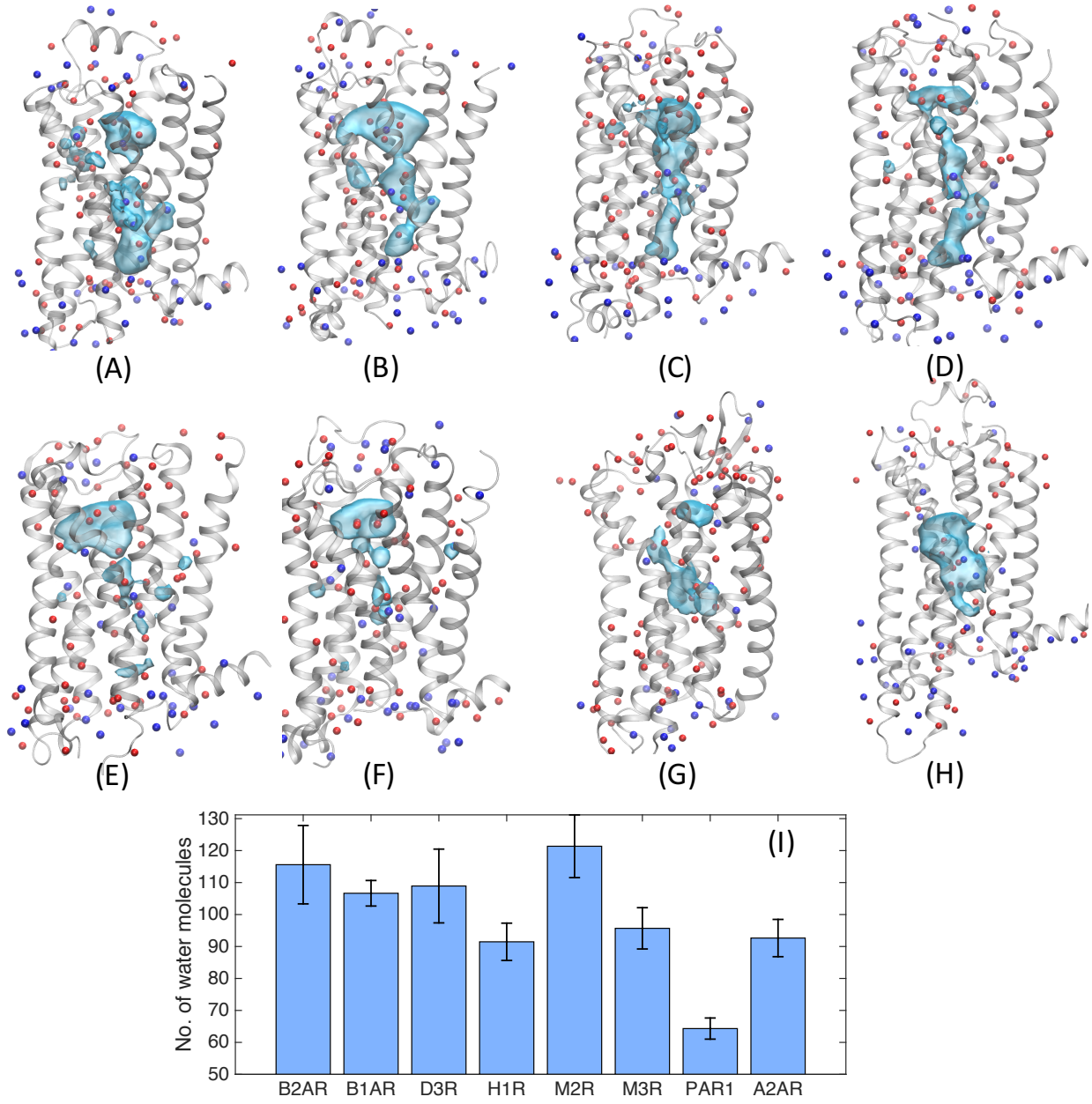
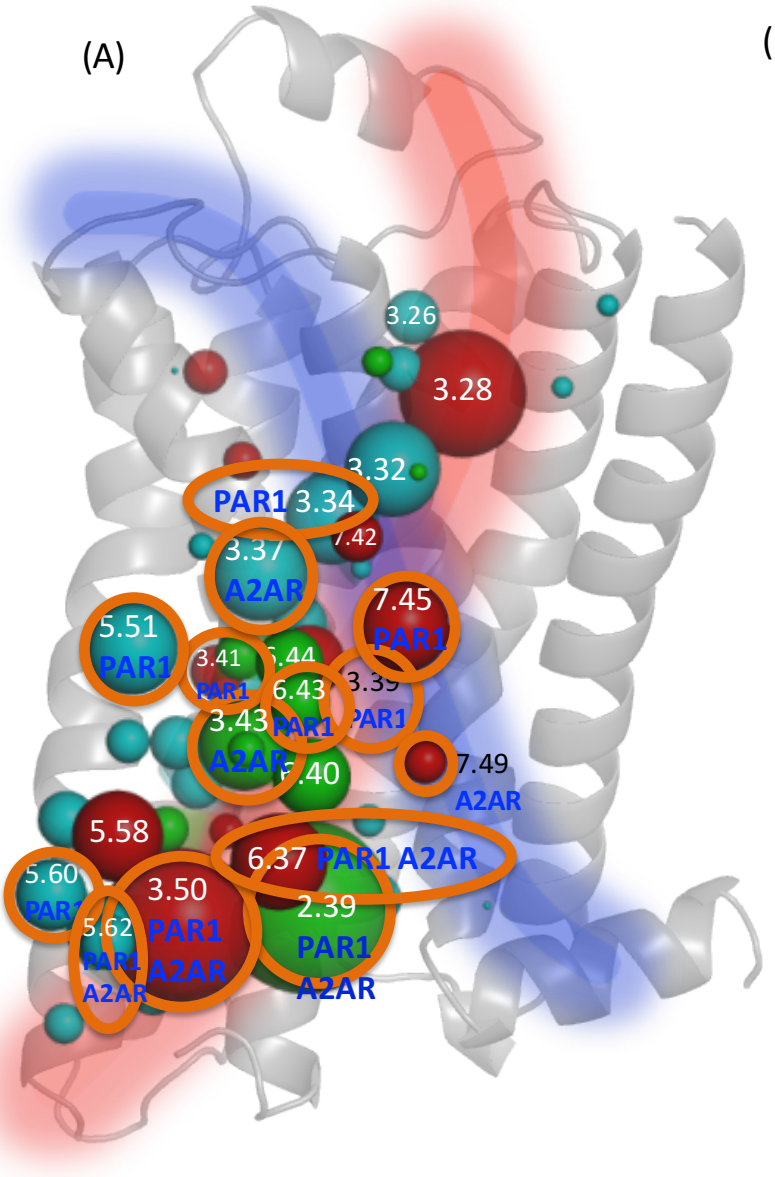


Fig. S6 (A-H) representative snapshots from the dynamics trajectories of the different GPCRs showing the water penetration within the TM domains; A: β_2AR; B: β_1AR; C: D_3R; D: H_1R; E: M_2R; F: M_3R; G: PAR1; H: A_{2A}R; the sidechain atoms with OH/H groups that are exchangeable with water are shown as red (Ser, Thr, Tyr, Asp, Glu) and blue (Asn, Gln, Lys, Arg) spheres; (I) Average

number of water molecules within the TM domain during the MD simulations; error bars represent 95% confidence limits.

(A)



(B)

BW #	PAR1 hub	A2AR hub
2.39	YES	YES
2.40		
2.43		
2.60	YES	
2.66		
3.26		
3.28		
3.29		
3.32		
3.34	YES	
3.35		
3.37		YES
3.38		
3.39	YES	
3.4		
3.41	YES	
3.43		YES
3.44	YES	
3.45		YES
3.46		YES
3.47		
3.49		YES
3.50	YES	YES
3.52	YES	
3.53		YES
3.55		YES
4.49		YES
4.56		
4.59		
5.51	YES	
5.54	YES	
5.57		
5.58		
5.60	YES	
5.61	YES	YES
5.62	YES	YES
6.37	YES	YES
6.40		
6.41		YES
6.43	YES	
6.44		
6.49		
6.55		
7.36		
7.40		
7.42		
7.45	YES	
7.46	YES	
7.49		YES
7.54		

Fig. S7. (A) Conserved allosteric hubs among the biogenic amine receptors shown as spheres; the radii of the spheres are proportional to the average strength of allosteric communication mediated by each of these residues; the allosteric hubs that are UCMs or CAMs in one or more receptors are highlighted in red and green respectively; residues that are also allosteric hubs in

two other class A GPCRs ($A_{2A}R$ and PAR1) are highlighted by orange circles along with the name of the receptor where they are conserved labeled in blue; (B) list of conserved allosteric hubs in biogenic amine receptors specified according to their Ballesteros-Weinstein (BW) numbers; residues that are also allosteric hubs in $A_{2A}R$ or PAR1 are highlighted in red.

Table S1. List of experimentally mutated residues and their effects

Residue (BW numbering)	**CAM/UCM**	**Reference**
2.39	CAM	[1]
3.28	UCM	[2]
3.39	UCM	[3]
3.40	CAM	[4]
3.41	UCM	[5]
3.43	CAM	[6]
3.46	UCM	[7]
3.47	CAM	[4]
3.50	UCM	[8]
4.56	UCM	[9]
5.58	UCM	[10]
6.37	UCM	[11]
6.40	CAM	[12]
6.43	CAM	[12]
6.44	CAM	[12]
7.36	CAM	[13]
7.42	UCM	[14]
7.45	UCM	[15]
7.46	UCM	[16]
7.49	UCM	[15]

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