

**Table S1. Results for statistical tests of all time series HDX/HRF-MS data, Related to Figures 2 and 3**

	Methodology	Statistical test employed	Residue Numbers	$\alpha$ Test value	F statistic	P value significance	N	Note	
Figure 2B	HDX 10 sec pulse	rANOVA	133-144	p=.01	10.61	p<0.0001	3		
	HDX 10 sec pulse	rANOVA	223-240	p=.01	54.85	p<0.0001	3		
Figure 2C	HDX 10 sec pulse (A2A) at RT	rANOVA	46-59	p=.01	38.26	p<0.0001	4		
	HDX 10 sec pulse (b2AR) at RT	rANOVA	46-59	p=.01	54.02	p<0.0001	4		
	HDX 10 sec pulse (A2A) at RT	rANOVA	367-371	p=.01	4.843	p=0.0012	4		
	HDX 10 sec pulse (b2AR) at RT	rANOVA	367-371	p=.01	10.84	p=0.0001	3		
	HDX 100 sec pulse (A2A) at RT	rANOVA	372-381	p=.01	12.58	p<0.0001	6		
	HDX 100 sec pulse (b2AR) at RT	rANOVA	372-381	p=.01	2.887	p=0.0210	4		
	HDX 10 sec pulse (A2A) at RT	rANOVA	382-390	p=.01	24.09	p<0.0001	5		
	HDX 10 sec pulse (b2AR) at RT	rANOVA	382-390	p=.01	83.52	p<0.0001	4		
	Figure 2D	HDX 10 sec pulse (A2A) on ice	rANOVA	46-59	p=.01	25.63	p<0.0001	3	
		HDX 10 sec pulse (b2AR) on ice	rANOVA	46-59	p=.01	34.77	p<0.0001	3	
HDX 10 sec pulse (A2A) on ice		rANOVA	367-371	p=.01	19.39	p=0.0004	3		
HDX 10 sec pulse (b2AR) on ice		rANOVA	367-371	p=.01	13.89	p=0.0003	3		
HDX 100 sec pulse (A2A) on ice		rANOVA	372-381	p=.01	7.501	p=0.0004	5		
HDX 100 sec pulse (b2AR) on ice		rANOVA	372-381	p=.01	3.464	p=0.0280	4		
HDX 10 sec pulse (A2A) on ice		rANOVA	382-390	p=.01	1.565	p=0.2552	3		
HDX 10 sec pulse (b2AR) on ice		rANOVA	382-390	p=.01	4.445	p=0.0216	3		
Figure S4A	HDX 100 sec pulse (A2A) at RT	rANOVA	46-59	p=.01	54.63	p<0.0001	6		
	HDX 100 sec pulse (b2AR) at RT	rANOVA	46-59	p=.01	146.6	p<0.0001	5		
	HDX 100 sec pulse (A2A) at RT	rANOVA	367-371	p=.01	16.65	p<0.0001	6		
	HDX 100 sec pulse (b2AR) at RT	rANOVA	367-371	p=.01	7.764	p<0.0001	4		
	HDX 100 sec pulse (A2A) at RT	rANOVA	382-390	p=.01	42.17	p<0.0001	6		
	HDX 100 sec pulse (b2AR) at RT	rANOVA	382-390	p=.01	32.44	p<0.0001	5		
Figure S4B	HDX 10 sec pulse (A2A) at RT	rANOVA	8-31	p=.01	7.787	p=0.0003	3		
	HDX 10 sec pulse (b2AR) at RT	rANOVA	8-31	p=.01	4.698	p=0.0042	3		
	HDX 100 sec pulse (A2A) at RT	rANOVA	8-31	p=.01	11.32	p<0.0001	5		
	HDX 100 sec pulse (b2AR) at RT	rANOVA	8-31	p=.01	28.32	p<0.0001	4		
	HDX 10 sec pulse (A2A) on ice	rANOVA	8-31	p=.01	0.3516	p=0.8699	3		
	HDX 10 sec pulse (b2AR) on ice	rANOVA	8-31	p=.01	0.9648	p=0.4829	3		
	HDX 10 sec pulse (A2A) at RT	rANOVA	256-272	p=.01	17.14	p<0.0001	5		
	HDX 10 sec pulse (b2AR) at RT	rANOVA	256-272					Note 1	

	HDX 100 sec pulse (A2A) at RT	rANOVA	256-272	p=.01	15.97	p<0.0001	5	
	HDX 100 sec pulse (b2AR) at RT	rANOVA	256-272	p=.01	28.42	p<0.0001	3	
	HDX 10 sec pulse (A2A) on ice	rANOVA	256-272	p=.01	3.835	p=0.0336	3	
	HDX 10 sec pulse (b2AR) on ice	rANOVA	256-272	p=.01	9.759	p=0.0013	3	
	HDX 10 sec pulse (A2A) at RT	rANOVA	297-315	p=.01	8.252	p<0.0001	5	
	HDX 10 sec pulse (b2AR) at RT	rANOVA	297-315	p=.01	15.08	p<0.0001	4	
	HDX 100 sec pulse (A2A) at RT	rANOVA	297-315	p=.01	33.73	p<0.0001	6	
	HDX 100 sec pulse (b2AR) at RT	rANOVA	297-315	p=.01	90.68	p<0.0001	5	
	HDX 10 sec pulse (A2A) on ice	rANOVA	297-315	p=.01	0.6923	p=0.6409	3	
	HDX 10 sec pulse (b2AR) on ice	rANOVA	297-315	p=.01	1.477	p=0.2798	3	
Figure 3	HRF	rANOVA	130-140	p=.01	5.69	p<0.0001	4	
	HRF	rANOVA	217-222	p=.01	2.93	p=0.007	4	
	HRF	rANOVA	368-377	p=.01	2.89	p=0.008	4	
	HRF	rANOVA	381-394	p=.05	1.7	p=0.110	4	Note 2

“Note 1” indicated in the Table: No data obtained.

“Note 2” indicated in the Table: While this time series does not meet the threshold of significance by rANOVA at  $\alpha=0.01$ , this is due to the surface exposed nature of this residue in the absence of being bound to the GPCR; this adds significantly to the experimental variability associated with this residue across the entire time series due to background oxidation. An unpaired t-test indicates that the observed differences between the 20 ms and 800 ms are significant to  $p=.03$ .