Supporting information

Table S1: DLS data for RIα(98-381) at 22°C

RIα(98-381) (μM)	[cAMP] added (μM)	Hydrodynamic Radius (nm)	Mw	Polydispersity*	Intensity (%)**
cAMP-bound (740)	--	3.2	50	11.8	96.9
cAMP-bound (185)	--	3.3	55	8.0	95.4
cAMP-bound (23)	--	3.3	56	6.5	89.1
Apo (23)	--	3.8	74	33.7	85.6
Apo (23)	100	3.4	58	4.0	97.6

The cAMP bound protein was purified as the ligand-bound form while for the *apo*-protein cAMP was removed by unfolding/folding (see text).
*Higher numbers indicate the presence of aggregation
**Percentage of total scattered intensity in sample

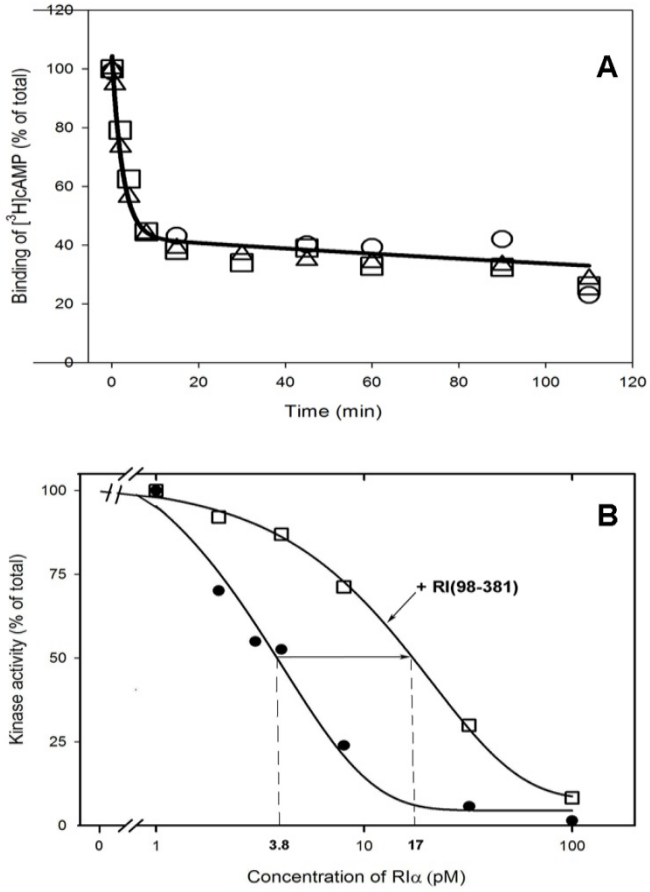

Figure S1. cAMP binding to RIα(98-381) and kinase activity of the C subunit of PKA. A, Exchange of [^{3}H]cAMP bound to wt-RIα (O), RIα(92-381) (△), or RIα(98-381) (□). Note, all RIα variants exhibited two distinct similar phases. B, Kinase activity of the C subunit of PKA (3.8 pM) in the absence (●) or presence (□) of 500 pM RIα(98-381). Note that 4.5-fold more wt-RIα was required to inhibit the kinase in the presence of RIα(98-381).

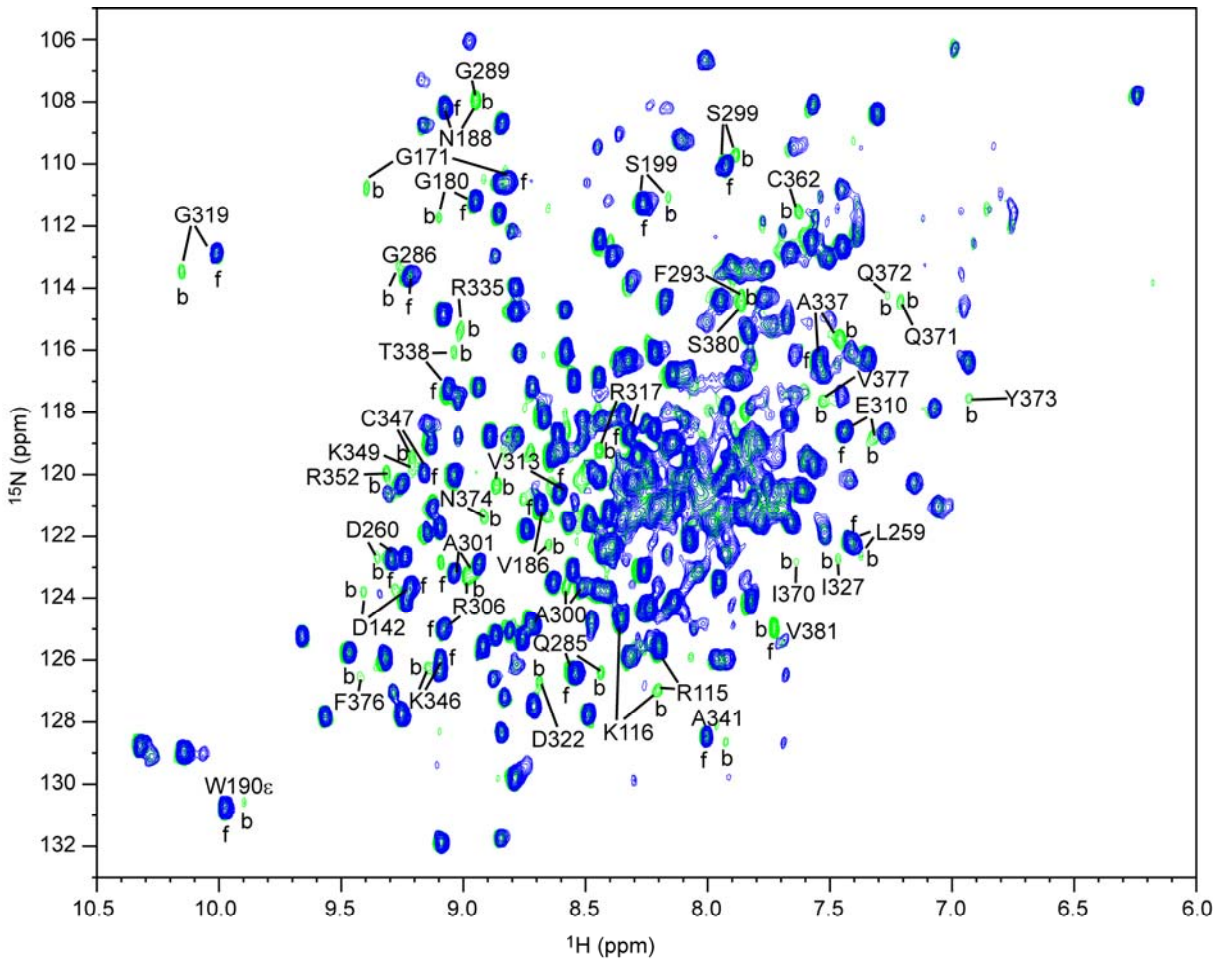

Figure S2. ^{1}H-^{15}N TROSY-HSQC spectra of RIα(98-381) in the presence of trace amounts of cAMP. Superpositions of the ^{1}H-^{15}N TROSY-HSQC spectra recorded on 50 μM U-[^{2}H/^{13}C/^{15}N]-labelled RIα(98-381) samples at 30°C in the absence (blue, identical to the spectrum shown in Figure 2A) and presence of trace amounts of cAMP (green). Assignments are given by residue name and number and the cAMP-free and cAMP-bound RIα(98-381) resonances are labeled by 'f' and 'b', respectively.