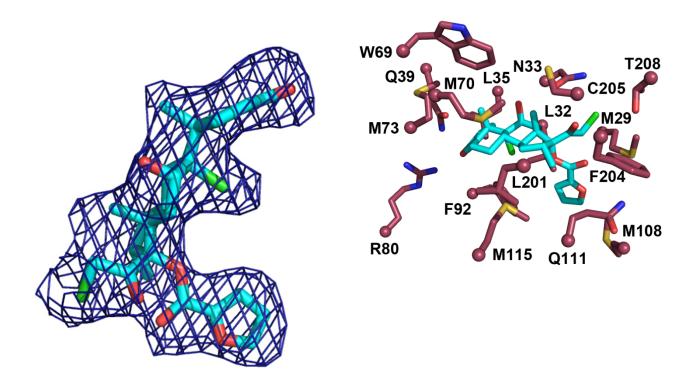
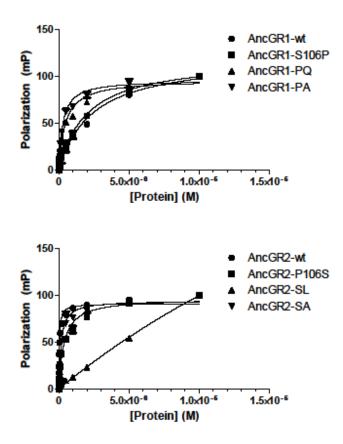
## **Supporting Information**

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**Fig. S1.** (*Left*)  $F_0$ - $F_c$  omission map of MOF in the AncGR2 ligand binding pocket. (*Right*) MOF inside the AncGR2 ligand binding pocket with contacting residues shown.



**Fig. S2.** Binding of dexamethasone-fluorescein (DM) to AncGR1 (*top*) and AncGR2 (*bottom*) wild-type and mutants were measured by fluorescence polarization in a buffer containing 12 nM DM, 150 mM NaCl, 10 mM HEPES pH 7.4, 5 mM DTT 3 mM EDTA and 0.005% Tween-20, and variable protein concentration of  $10^{-10} - 10^{-5}$  M.