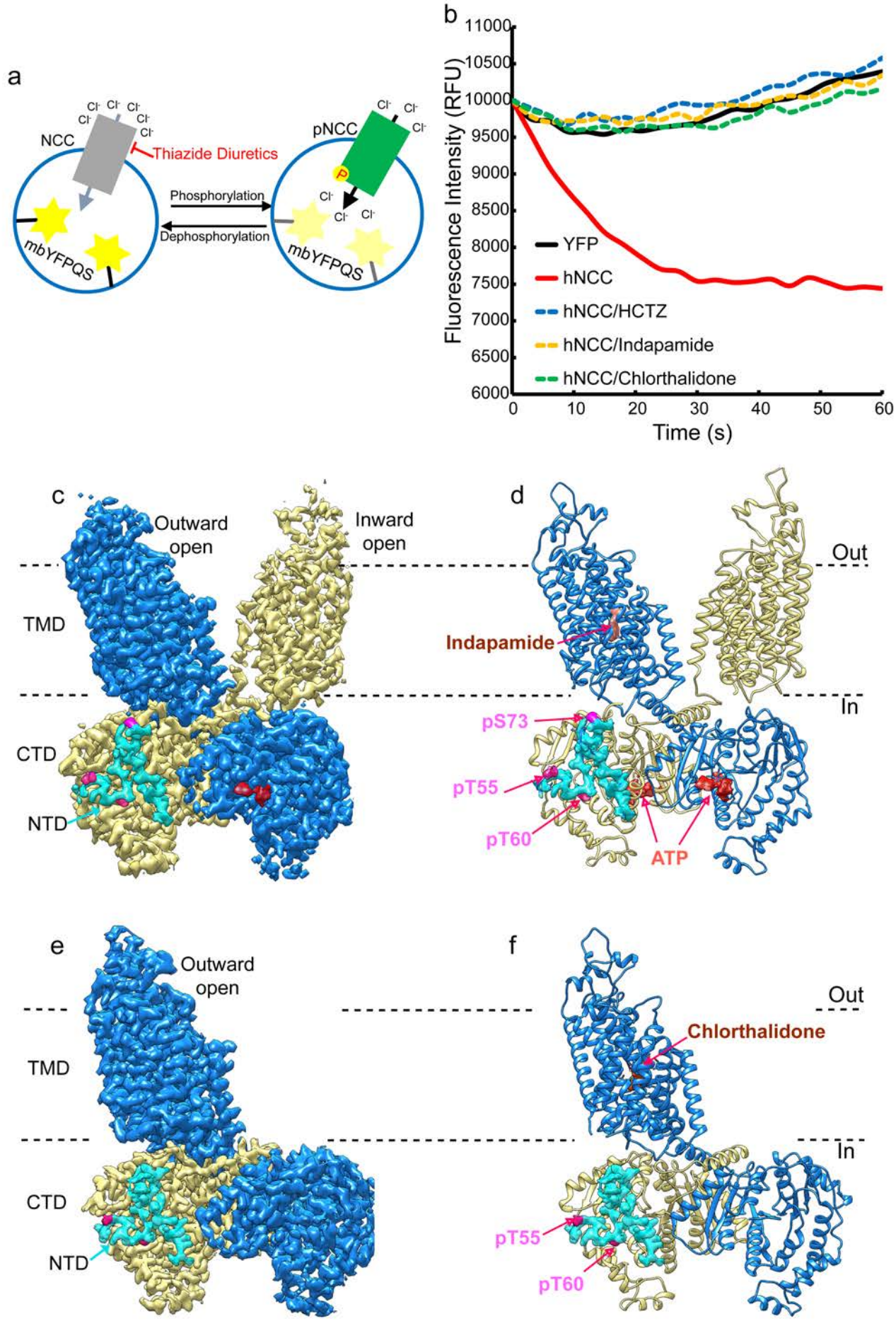

Structures and inhibition of human NCC by thiazide diuretics. (a) Schematics of cell-based Cl- flux assay for measuring NCC-mediated ion transport. In this assay, NCC is co-expressed with a membrane-anchored Cl--sensitive YFP in a HEK293 stable cell line where NCC-mediated Cl- influx quenches YFP fluorescence. (b) Average raw traces show that NCC activity is completely blocked by the thiazide-type drugs hydrochlorothiazide (HCTZ), indapamide, and chlorthalidone. (c-d) Overall structure of NCC bound with indapamide shown in map (c) and ribbon diagram (d). (e-f) overall structure of NCC bound with chlorthalidone shown in map (e) and ribbon diagram (f). Two NCC subunits are colored-coded blue and khaki. ATP, phosphoacceptors, indapamide, and chlorthalidone are highlighted. The N-terminal phosphoregulatory region is shown in cyan with the phosphorylation sites highlighted in red.