

Figure S1

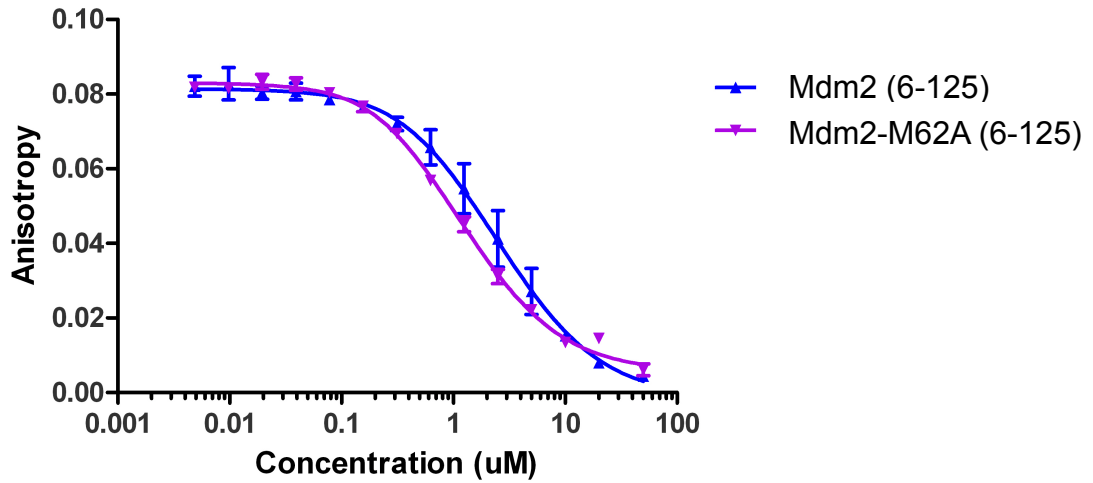


Figure S2

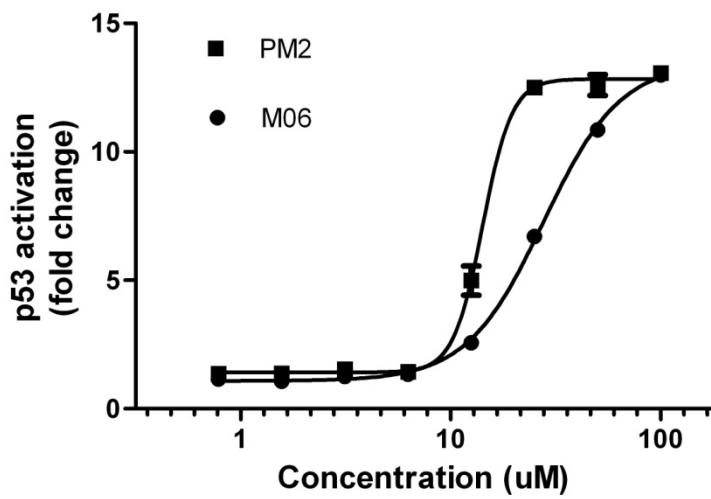


Figure S3

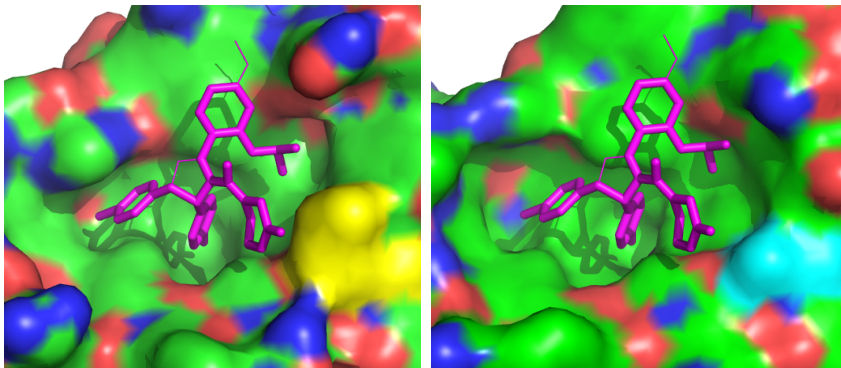


Figure **S1**, Comparative binding of MO6 stapled peptide to Mdm2 (6-125) and Mdm2-M62A (6-125) as measured by fluorescence anisotropy assay. Competition titrations of MO6 stapled peptide against FAM-labelled p53-binding peptide 12.1 for binding to Mdm2 (6-125) (blue) and Mdm2-M62A (6-125) (purple). Values represent mean  $\pm$  SD (n=2) of a representative experiment. Final  $K_d$  values determined from average of 3-5 independent experiments. Figure **S2**, T22 reporter assay measuring p53 transactivation. Cells were treated with indicated Mdm2 ligands and p53 activity determined by measuring  $\beta$  galactosidase levels. Activity is expressed as fold increase over cells treated with vehicle only. Values represent average  $\pm$  SD (n=2). Figure **S3**, Nutlin binding comprised by M62A mutation in Mdm2. Structure of Nutlin (magenta) bound to Mdm2 (left) with M62 highlighted in yellow (adapted from 1YCR). When docked onto the structure of Mdm2-M62A (right), mutation to alanine (depicted in cyan) results in loss of significant packing interface and weak binding.