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Supplementary Materials

Mechanism of the dual activities of CYP17A1 and binding to anti-prostate cancer drug abiraterone revealed by a novel V366M mutation causing 17,20 lyase deficiency.

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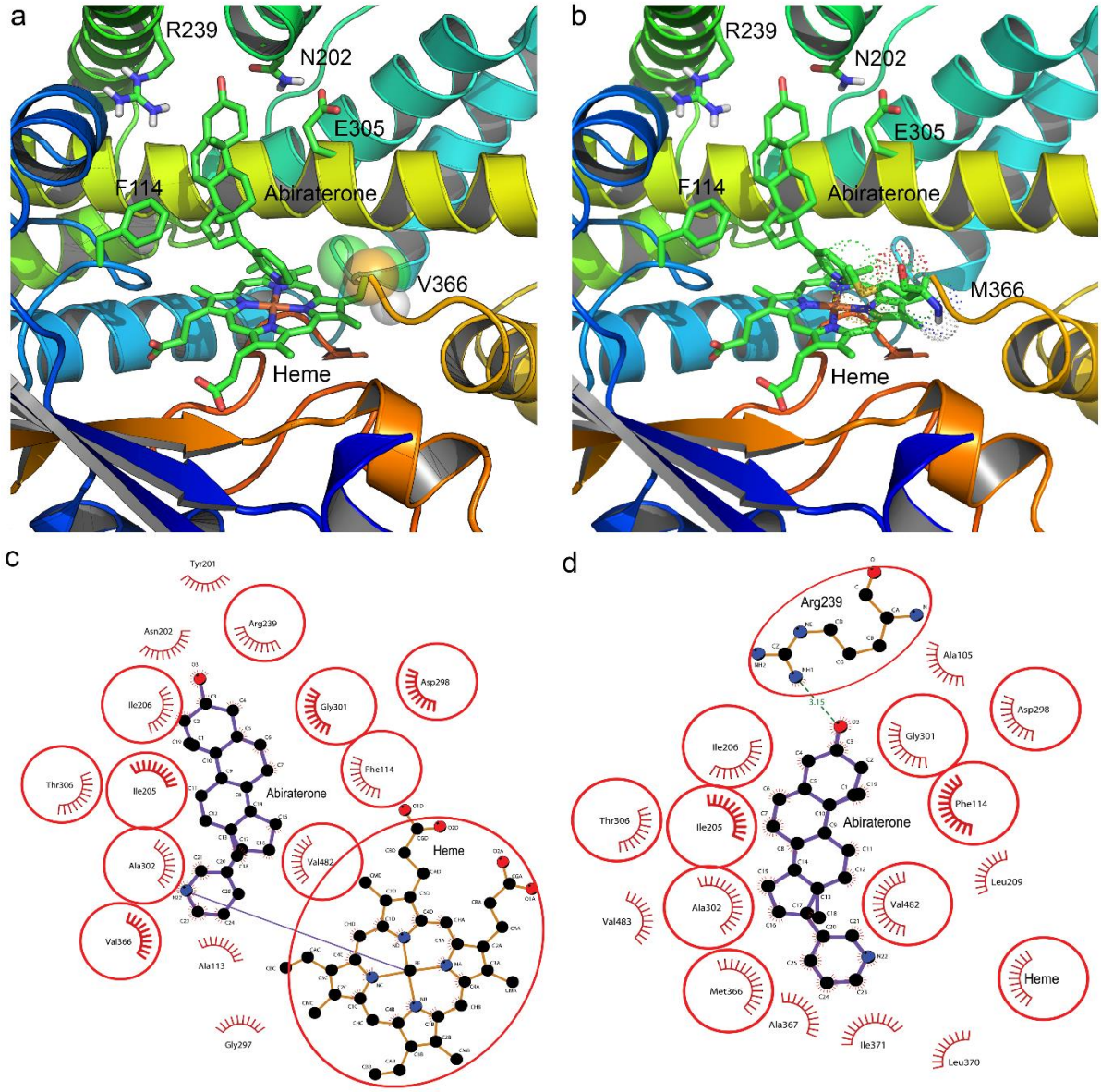
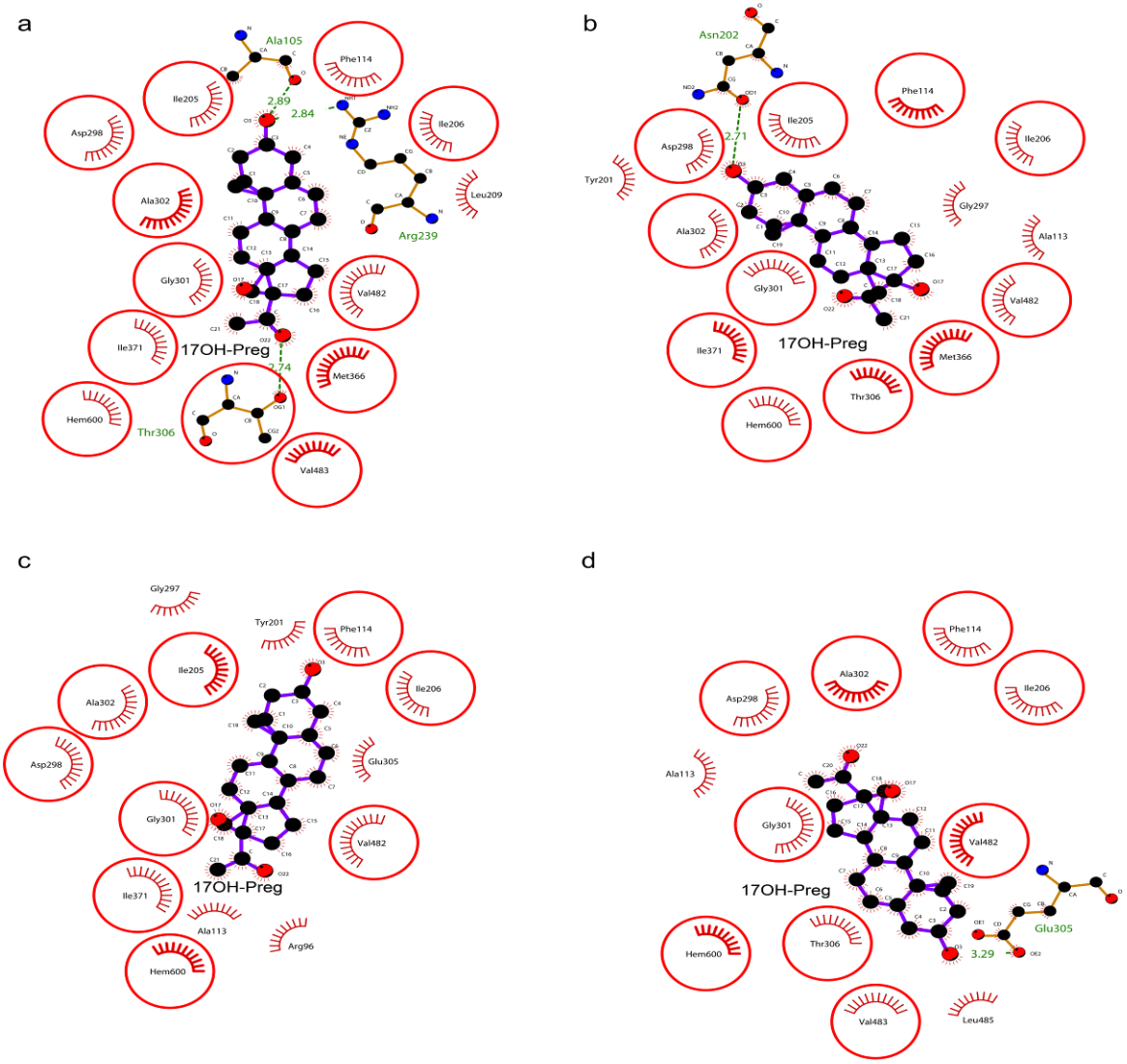


Supplementary Fig. 1: Details of abiraterone interaction with the WT and V366M variant of CYP17A1. In the WT CYP17A1 abiraterone binds by forming a nitrogen-iron co-ordination with the central heme (a and c). In the V366M mutant, the larger methionine side chain protrudes towards the heme iron and creates a steric hindrance for the binding of abiraterone (b and d). As a result, abiraterone is ineffective towards the residual 17hydroxylation reaction of the mutant enzyme. Panels a and b show the ribbons diagram of the active site of CYP17A1 while panels c and d show the ligand interactions depicted by LIGPLOT analysis.



Supplementary Fig. 2: Details of 17OH-PREG interaction with the V366M variant of CYP17A1.There are differences in optimal binding poses for PREG/PROG and 17OH-PREG and while interaction with N202 seems to benefit in orienting the steroids for 17hydroxylase reaction, this increases the distance between C17 and heme iron. The multiple additional interactions observed here for 17OH-PREG and V366M mutant of CYP17A1 indicate nonoptimal binding and explain the loss of 17,20 lyase activity.