

Supplementary information

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PI3Kbeta      .VGHMKVLSKQVEALNKILKTLN.SLIKNAVKLNRA.KGKEAMHTCLKQSAVREALSDLQ
PI3Kdelta    .THHMKVLMKQGEALSKLKAALN.DFVKLSSQKTPKP.QTKELMHLCMRQEAYLEALSHLQ
PI3Kalpha    .GMYLKHLNRQVEAMEKLIINLT.DILKQEKKDETPK.VQMKFLVEQMRRPDMFMDALQGF
PI3Kgamma    GTAMLHDFTOQVQVIEMLQKVTLDIKSLSAEKYDVSSQVLSQLKQKLENLQNSQLPESFR
PI3K2alpha   GKRLREELLKQTKLVQLLGGVAEKVROASGSA.....RQVVLQRSMERVQSFQKN.KCR
PI3K2beta    GKGLREEFNRCQWLVNALAKLAQVREAPSA.....RQGIILRTGLEEVKQFFALNGSCR
PI3K2gamma   GKALNDEFKKEQKLIKILGDLIGERVKSAASHQ.....RQEVLKKEIGRLEEFDQDVNTCH
vsp34        .....ESGNRKKKNERLQALLGDNK.....MNLSDVELIP
    
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PI3Kbeta      SPLNFCVITSELYVEKCKYMDSKMKPLWTVYNNKVFGEED...SVGVIFKNGDDLRODML
PI3Kdelta    SPLDPSTLLAEVCEQCTFMDSKMKPLWIMYSNEEAGSGG...SVGIIFKNGDDLRODML
PI3Kalpha    SPLNPAHQGLGNLRLEECRIMSSAKRPLWLNWENPDIMSELLFQNNIEIFKNGDDLRODML
PI3Kgamma    VPYDPGLKAGALAEKCKVMASSKKKPLWLEFKCADPTALSN.ETIGIIFKNGDDLRODML
PI3K2alpha   LPLKPSLVAKELNLIKSCSFFSNNAVPLKVTMVNADPMGEE...INVVFKNGDDLRODML
PI3K2beta    LPLSPSLLVKGIVPRDCSYFNSNAVPLKLSFQNVDP LGEN...IRVIFKNGDDLRODML
PI3K2gamma   LPLNPAALCIKGIIDHDCSYFTSNALPLKIIITFINANPMGKN...ISIIIFKNGDDLRODML
vsp34        LPLEPOVKIRGIIPETATLFRKSAALMPALFFKTEDGGKYP...VIFKNGDDLRODML
    
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P-loop

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PI3Kbeta      TLOMLRLMDLWKEAGLDLRLPYGCLATGDRSGLIEVVSTSETIADIQLNSSNVAAAAA
PI3Kdelta    TLOMIQLMDVWVKQEGLDLRLTPYGCLPTGDRTGLIEVVLRSDTIANIQLNKSNMAATAA
PI3Kalpha    TLOIRIRIMENIWQNGLDLRLPYGCLSIGDCVGLIEVVRNSHTIMQIQCKGG.LKGALQ
PI3Kgamma    LLOILRIMESIWETESLDLCLLPYGCISTGDKIGMIEIVKDATTIAKIQ..QSTVGNLGA
PI3K2alpha   ALOMIKIMDKIWLKELGLDLRMVIFKCLSTGRDRGMVELVPAASDTLRKIQVEYG...VTGS
PI3K2beta    TLOMIRIMSKIWVQEGLDMRMVIIFRCFSTGRGRGMVEMIPNAETLRKIQVEHG...VTGS
PI3K2gamma   VLQLIQVMDNIWLOEGLDQMIIYRCLSTGKQDGLVQMVPAVDTLAKIHRHSG...LIGP
vsp34        LLOIISLMDKLLRKENLDLKLTPYKVLATS TKHGFMQFIQSVFVAEVLDTTEGS.....
    
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Hinge loop

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PI3Kbeta      FNKDALLNWLKEYN.SGDDLDRATEEFTLSCAGYCVASYVVLGIGDRHSDNIMVKKTGQLF
PI3Kdelta    FNKDALLNWLKSKN.PGEALDRATEEFTLSCAGYCVATYVVLGIGDRHSDNIMIRESGQLF
PI3Kalpha    FNSHTLHQWLKDKN.KGEIYDAADIDLTRSCAGYCVATFVLGIGDRHSDNIMVKDDGQLF
PI3Kgamma    FKDEVLNHLKESPTKEKFAAVERFVYSCAGYCVATFVLGIGDRHSDNIMITETGNLF
PI3K2alpha   FKDKPLAENLRKYNPSEEEYKASENFYIYSCAGYCVATYVVLGIGDRHSDNIMLRSTGHMF
PI3K2beta    FKDRPLADWLQKHNPEDEYEKAVENFIYSCAGYCVATYVVLGIGDRHSDNIMLKTGHMF
PI3K2gamma   LKENTIKKWFVQHNHLKADYEKALRNFIYSCAGYCVVTFVLGIGDRHSDNIMLTKSGHMF
vsp34        .IQNFERRYAPSENGPNGISAEVMDTYVKSCAGYCVITYIYLVGIGDRHSDNIMLTKSGHMF
    
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Catalytic loop

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PI3Kbeta      HIDFGHILGNFKSKFGIKRERVVFILTYDFIHVIOQGKTGNTEK..FGRFRQCEDAYLTI
PI3Kdelta    HIDFGHFLGNFKTKFGINRRVVFILTYDFVHVIOQGKTNNSEK..FERFRGYCERAYTI
PI3Kalpha    HIDFGHFLDHKKKFGYKRRVVFVLTQDFLIVISKGAQECTKTREFERFQEMCYKAYLA
PI3Kgamma    HIDFGHILGNYSKFLGINKERVVFVLTQDFLFLVMGTSGKKTSPH..FQKQFQDICVAYLA
PI3K2alpha   HIDFGKFLGHAQMFSGFKRDRAPFVLTSDMAYVINGGKPTIR..FQLFVDLCCQAYNL
PI3K2beta    HIDFGKFLGHAQMFSGIKRDRAPFVLTSDMAYVINGGDKP.SSR..FHFVDLCCQAYNL
PI3K2gamma   HIDFGKFLGHAQTFGGIKRDRAPFIFTSEMAYFITEGGKN.PQH..FQDFVELCCRAYNI
vsp34        HIDFGYILGRDP.....KPLPPMKLNLKEMVEGMSGG.....TQSEQVQEFKQCYTAFHLH
    
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Activation loop

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PI3Kbeta      IRRHGNLFTTLFALMLTAGLPELTSVKDITQYLKDSLALGKSEEALKQFKQKQFDEALRES
PI3Kdelta    IRRHGLFLHLFLALMRAAGLPELTSCKSDITQYLKDSLALGKTEEALKHFVRVKFNALRES
PI3Kalpha    IRQHANLFINLFSMMLGSGMPELQSFDDIAYIRKTLALDKTEQEALEYFMKQMNDAHHGG
PI3Kgamma    IRRHTNLILILFSMMLMTGMPQLTSKEDIYIIRDALTVGKNEEDAKKYFLDQIEVCRDKG
PI3K2alpha   IRKQTNLFLNLLSLMIPSGLPELTSIQDLKYVVDALQPQTDAEATIFFTRLIESSLG.S
PI3K2beta    IRKHTHLFLNLLGLMLSCGIPELSDLEDLKYVVDALRPQDTEANATTYFTRLIESSLG.S
PI3K2gamma   IRKHSQLLNLNLEMMLYAGLPELTSIQDLKYVYNNLRPQDTELEATSHFTKKIKESLE.C
vsp34        IRRYSNLILN.....KPLPPMKLNLKEMVEGMSGG.....TQSEQVQEFKQCYTAFHLH
    
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PI3Kbeta      WTKVNWMAH
PI3Kdelta    WTKVNWLAH
PI3Kalpha    WTKMDWIFH
PI3Kgamma    WTVQFNWFLH
PI3K2alpha   IATKFNFFIH
PI3K2beta    VATKLNFFIH
PI3K2gamma   FPVKLNNLIH
vsp34        .....
    
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Fig. S1: Sequence alignment of kinase domain of all classes of PI3K showing important regions.

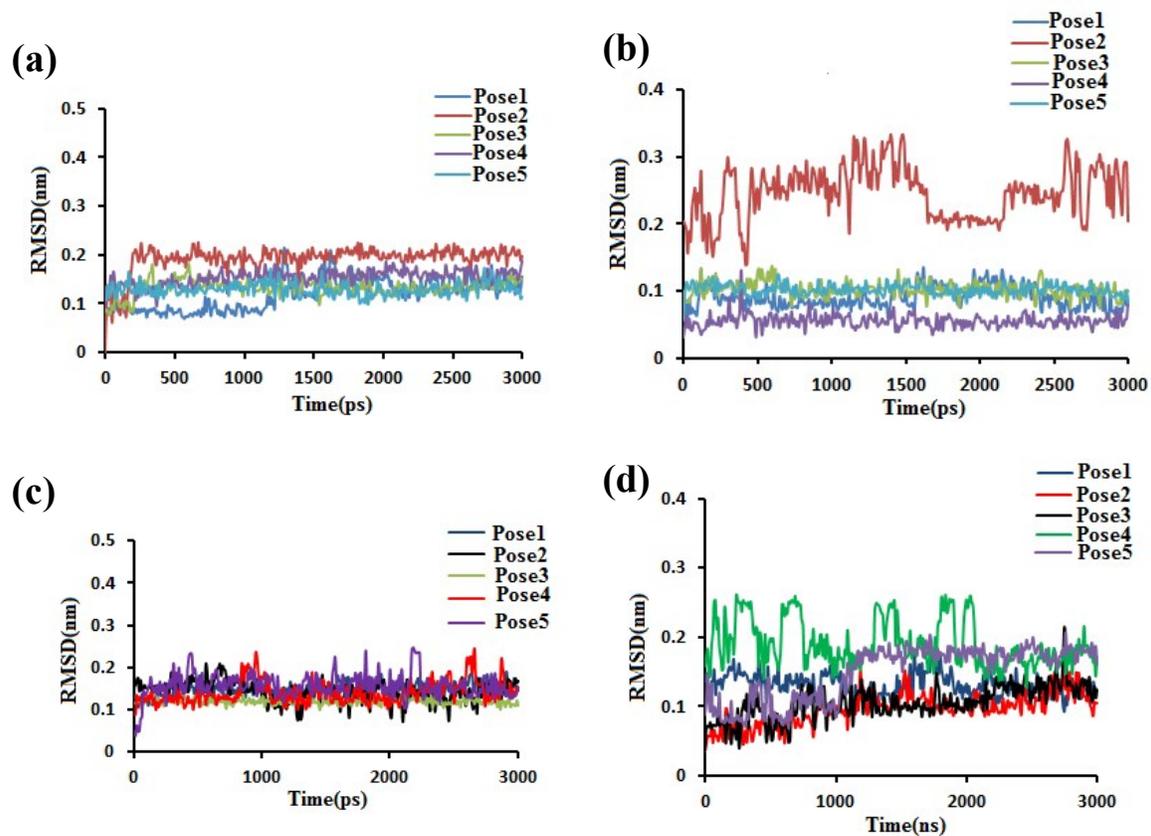


Fig.S2: RMSD profiles of top 5 poses of (a) PI-701 in complex with PI3KC2 α (b) PI-702 in complex with PI3KC2 α (c) PI-701 in complex with PI3KC2 γ and (d) PI-702 in complex with PI3KC2 γ .

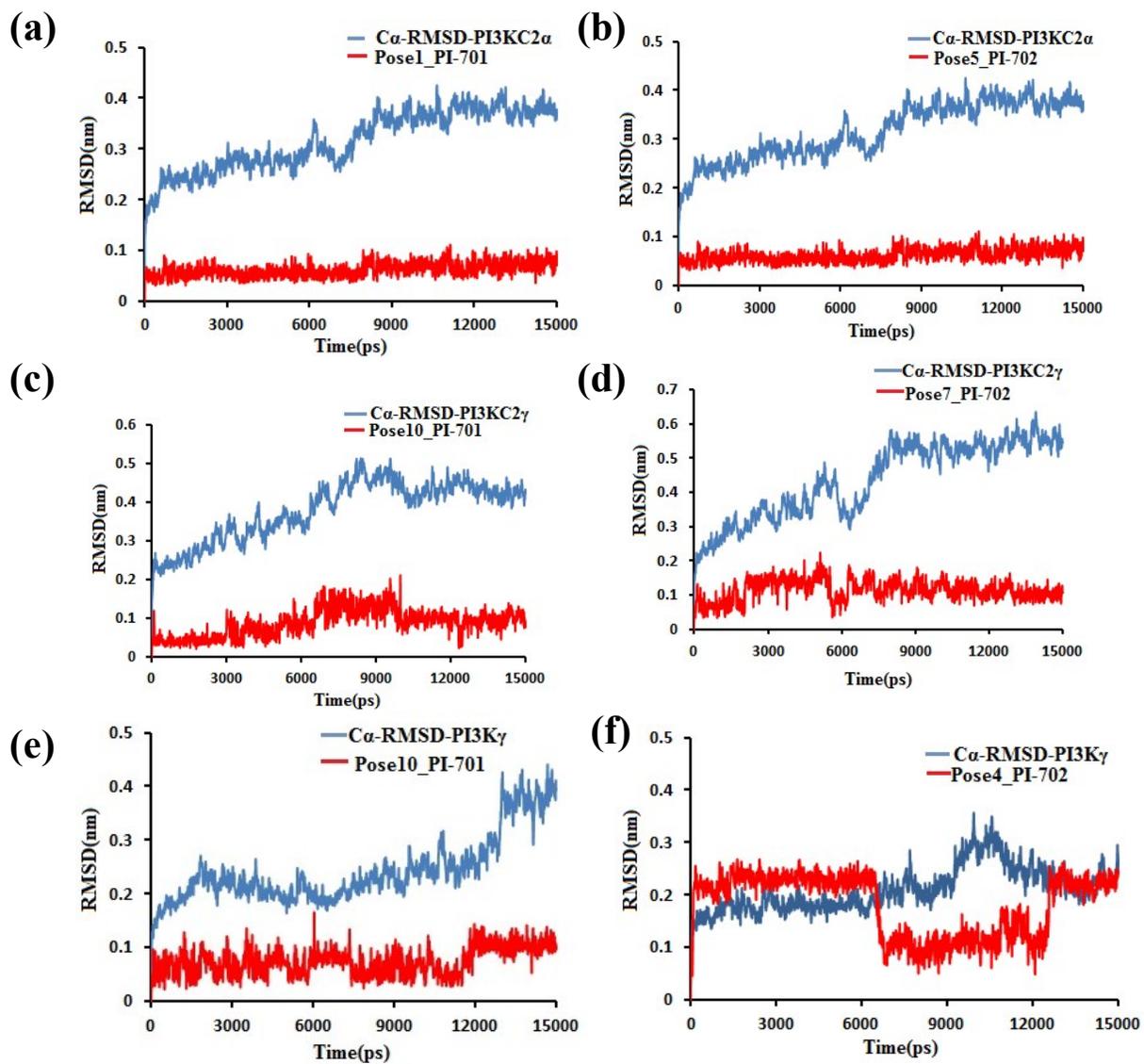


Fig.S3: RMSD of C α and selected pose of (a) PI3KC2 α -PI-701 complex (b) PI3KC2 α -PI-702 complex (c) PI3KC2 γ -PI-701 complex (d) PI3KC2 γ -PI-702 complex (e) PI3K γ -PI-701 complex and (f) PI3K γ -PI-702 complex.

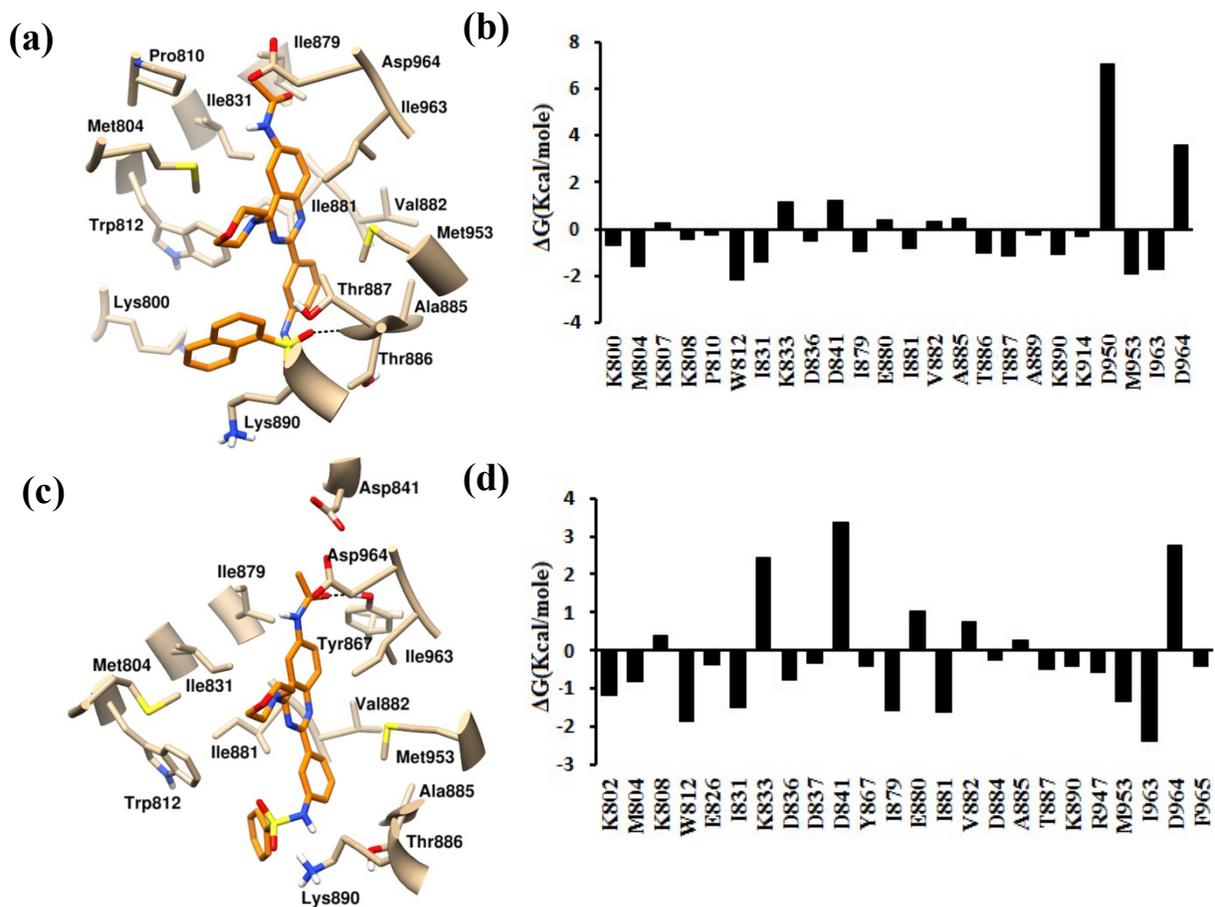


Fig.S4: (a) Binding mode of PI-701 in PI3K γ (b) residue wise decomposition of binding free energy of PI3K γ -PI-701 complex (c) binding mode of PI-702 in PI3K γ and (d) residue wise decomposition of binding free energy of PI3K γ -PI-702 complex. In case of PI3K γ -PI-702 complex, interaction analysis was carried out on frame obtained at 8.5ns and residue wise free energy decomposition was carried out on frame obtained between 8 and 8.5ns of MD simulation.

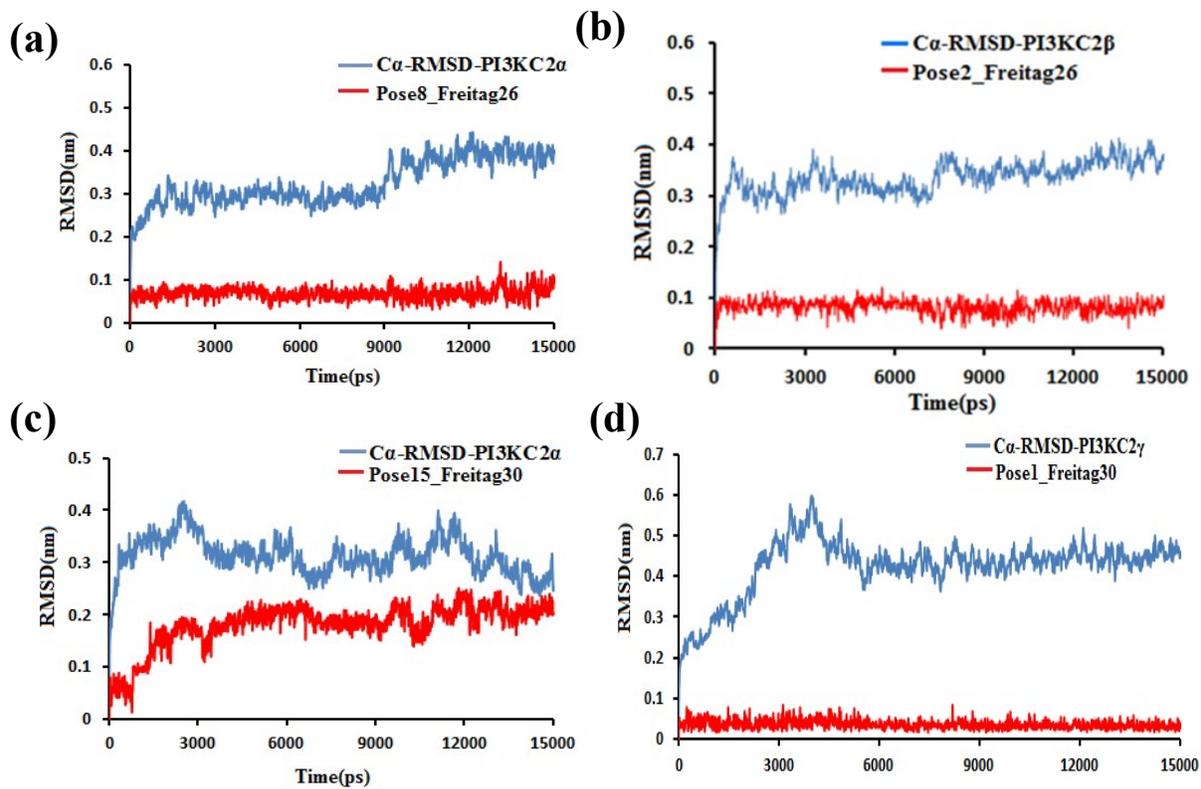


Fig.S5: RMSD of $C\alpha$ and selected pose of (a) PI3KC2 α -Freitag26 complex (b) PI3KC2 β -Freitag26 complex (c) PI3KC2 α -Freitag30 complex and (d) PI3KC2 γ -Freitag30 complex.

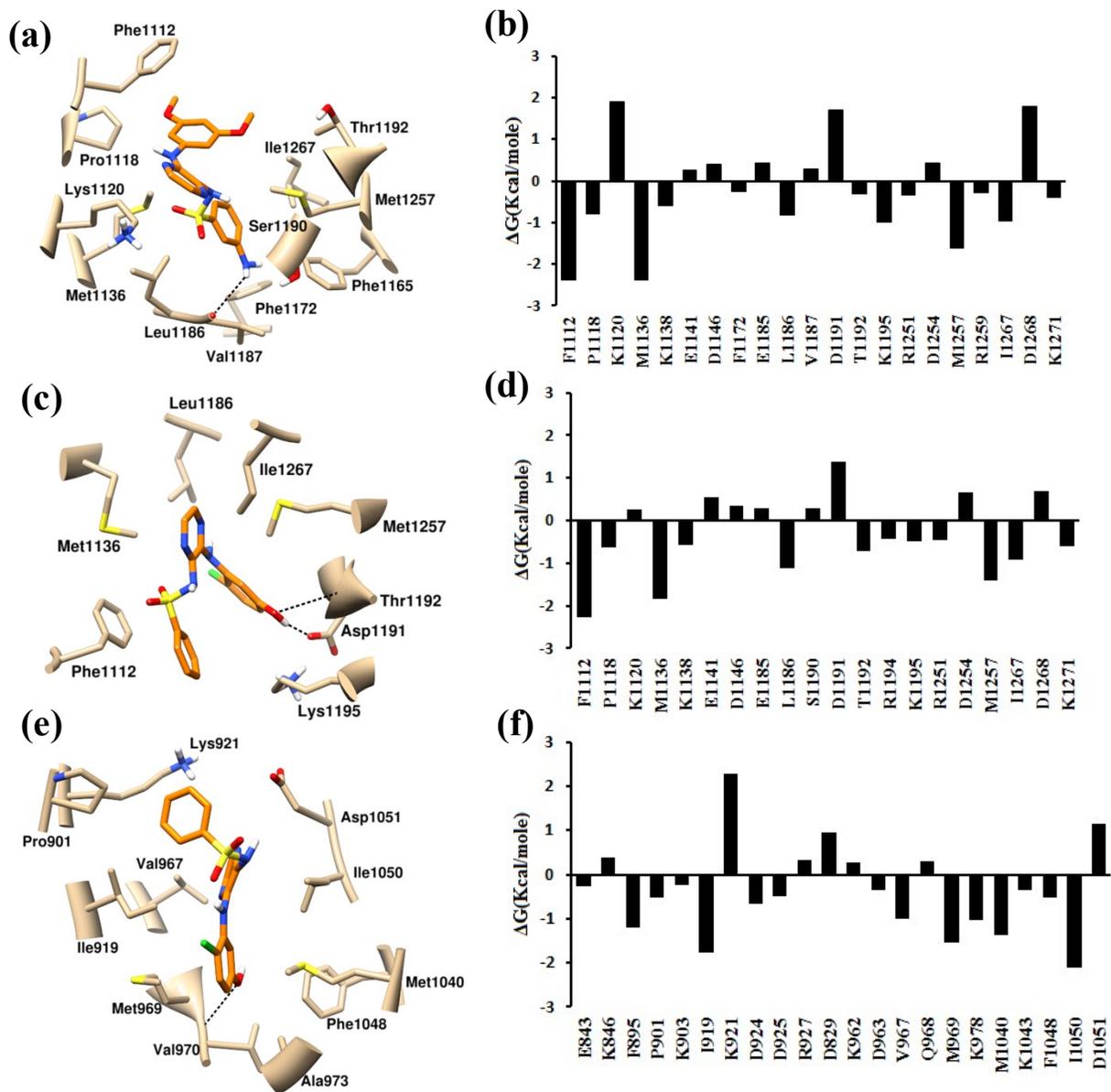


Fig.S6: (a) Binding mode of Freitag26 in PI3KC2 α (b) residue wise decomposition of binding free energy of PI3KC2 α -Freitag26 complex (c) binding mode of Freitag30 in PI3KC2 α and (d) residue wise decomposition of binding free energy of PI3KC2 α -Freitag30 complex (e) binding mode of Freitag30 in PI3KC2 γ and (f) residue wise free energy decomposition of PI3KC2 γ -Freitag30 complex.