Supplementary Material

Structural Basis for Tailor-Made Selective PI3K α/β inhibitors :A computational perspective

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P42338|PK3CB_HUMAN      MCFSFIMPPAMADILDIWAVDSQIASDGSIPVDFLLPTGIYIQLEVPREATISYIKQMLW   60
Q8BTI9|PK3CB_MOUSE      ------MPPAMADNLDIWAVDSQIASDGAISVDFLLPTGIYIQLEVPREATISYIKQMLW   54
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P42338|PK3CB_HUMAN      TELLCKTIVSSEVSGKNDHIWNEPLEFDINICDLPRMARLCFAVYAVLDKVKTKKSTKTI   420
Q8BTI9|PK3CB_MOUSE      TELLCKTVVSSEISGKNDHIWNEQLEFDINICDLPRMARLCFAVYAVLDKVKTKKSTKTI   414
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P42338|PK3CB_HUMAN      FTLSCAGYCVASYVLGIGDRHSDNIMVKKTGQLFHIDFGHILGNFKSKFGIKRERVPFIL   960
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P42338|PK3CB_HUMAN      IQYLKDSLALGKSEEEALKQFKQKFDEALRESWTTKVNWMAHTVRKDYRS             1070
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Identical positions	1020
Identity	95.86%
Similar positions	33
Program	CLUSTALO

Figure S1. UniProt Align results of human PI3Kβ and mouse PI3Kβ protein sequence.

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P42336|PK3CA_HUMAN      MPPR-PSSGELWGIHL---MPPRILVECLLPNGMIVTLECLREATLITIKHELFKEARKY   56
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P42336|PK3CA_HUMAN      PLHQLLQDESSYIFVSVTQEAEREEFFDETRRLCDLRLFQPFLKVIEPVGNREEKILNRE   116
Q8BTI9|PK3CB_MOUSE      PMFNLLMDIDSYMFACVNQTAVYEELEDETRRLCDVRPFLPVLKLVTRSCDPAE-KLDSK   119
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P42336|PK3CA_HUMAN      IGFAIGMPVCEFDMVKDPEVQDFRRNILNVCKEAVDLRDLNSPHSRAMYVYPPNVESSPE   176
Q8BTI9|PK3CB_MOUSE      IGVLIGKGLHEFDALKDPEVNEFRRKMRKFSEAKIQSLVGLSWIDWLKHTYPPEHE--PS   177
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P42336|PK3CA_HUMAN      EQLKLCVLEYQGKYILKVCGCDEYFLEKYPLSQYKYIRSCIMLGRMPNLMLMAKESLYSQ   296
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P42336|PK3CA_HUMAN      ------------------KGAKEEHCPLAWGNINLFDYTDTLVSGKMALNLWP-VPHGLE   453
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P42336|PK3CA_HUMAN      DLLNPIGVTGSNPNKETPC-LELEFDWFS-SVVKFPDMSV-IEEHANWSVSREAGFSYSH   510
Q8BTI9|PK3CB_MOUSE      EMLNPMGTVQTNPYAENATALHITFPENKKQPCYYPPFDKIIEKAAELASGDSAN-----   519
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P42336|PK3CA_HUMAN      ALQFNSHTLHQWLKDKNKGEIYDAAIDLFTRSCAGYCVATFILGIGDRHNSNIMVKDDGQ   928
Q8BTI9|PK3CB_MOUSE      TAAFNKDALLNWLKEYNSGDDLDRAIEEFTLSCAGYCVASYVLGIGDRHSDNIMVKKTGQ   926
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Q8BTI9|PK3CB_MOUSE      LFHIDFGHILGNFKSKFGIKRERVPFILTYDFIHVIQQGKTG--NTEKFGRFRQCCEDAY   984
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P42336|PK3CA_HUMAN      GGWTTKMDWIFHTIKQHALN          1068
Q8BTI9|PK3CB_MOUSE      ESWTTKVNWMAHTVRKDYRS          1064
                         .****::*: **:::.  .
```

Identical positions	426
Identity	41.28%
Similar positions	348
Program	CLUSTALO

Figure S2. UniProt Align results of human PI3Kα and mouse PI3Kβ protein sequence.

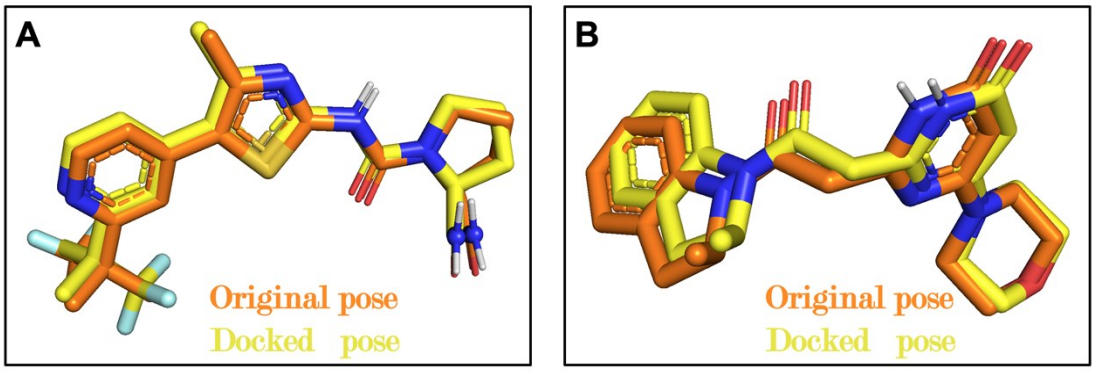

Figure S3. Comparison of the predicted and experimental poses for (A) PI3Kα, RMSD=0.637 Å (PDB ID:4JPS) and (B) PI3Kβ, RMSD =0.260 Å (PDB ID:4BFR). Orange sticks represent the experimental pose extracted from X-ray structure and yellow sticks represent docked poses.

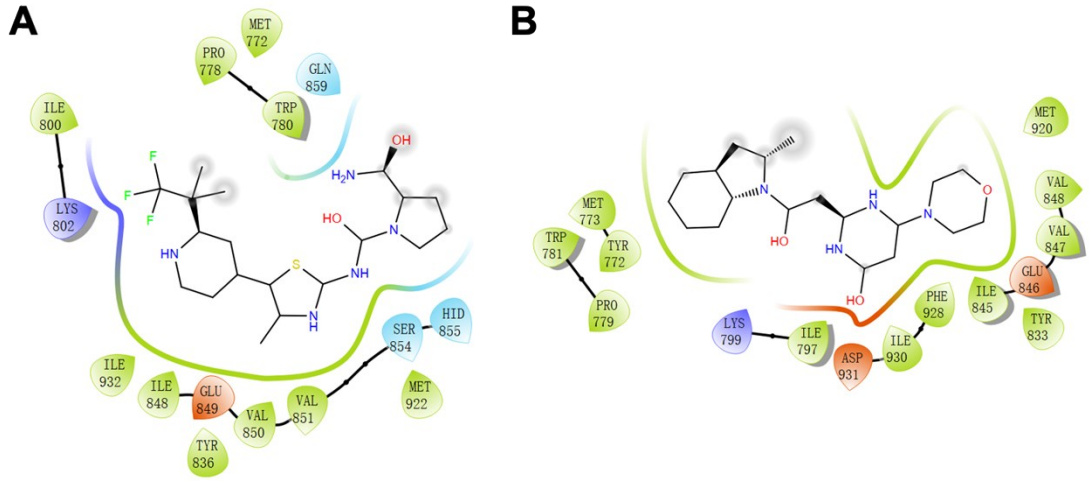

Figure S4. The docking results for the crystal ligands (A) PI3Kα (PDB ID:4JPS) and (B) PI3Kβ (PDB ID:4BFR).

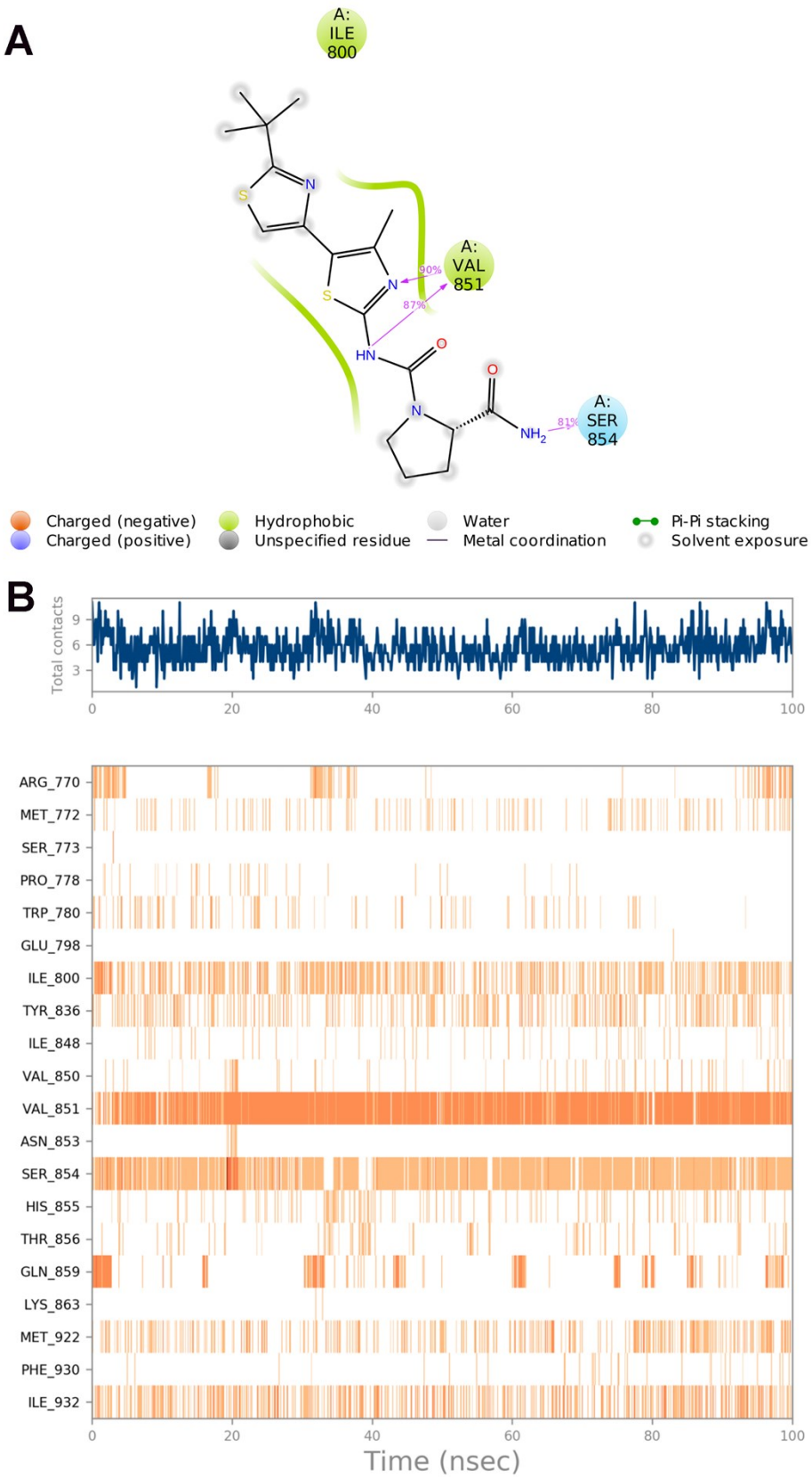

Figure S5. Ligand-Protein contacts of PI3Kα/Compd**1** complex.

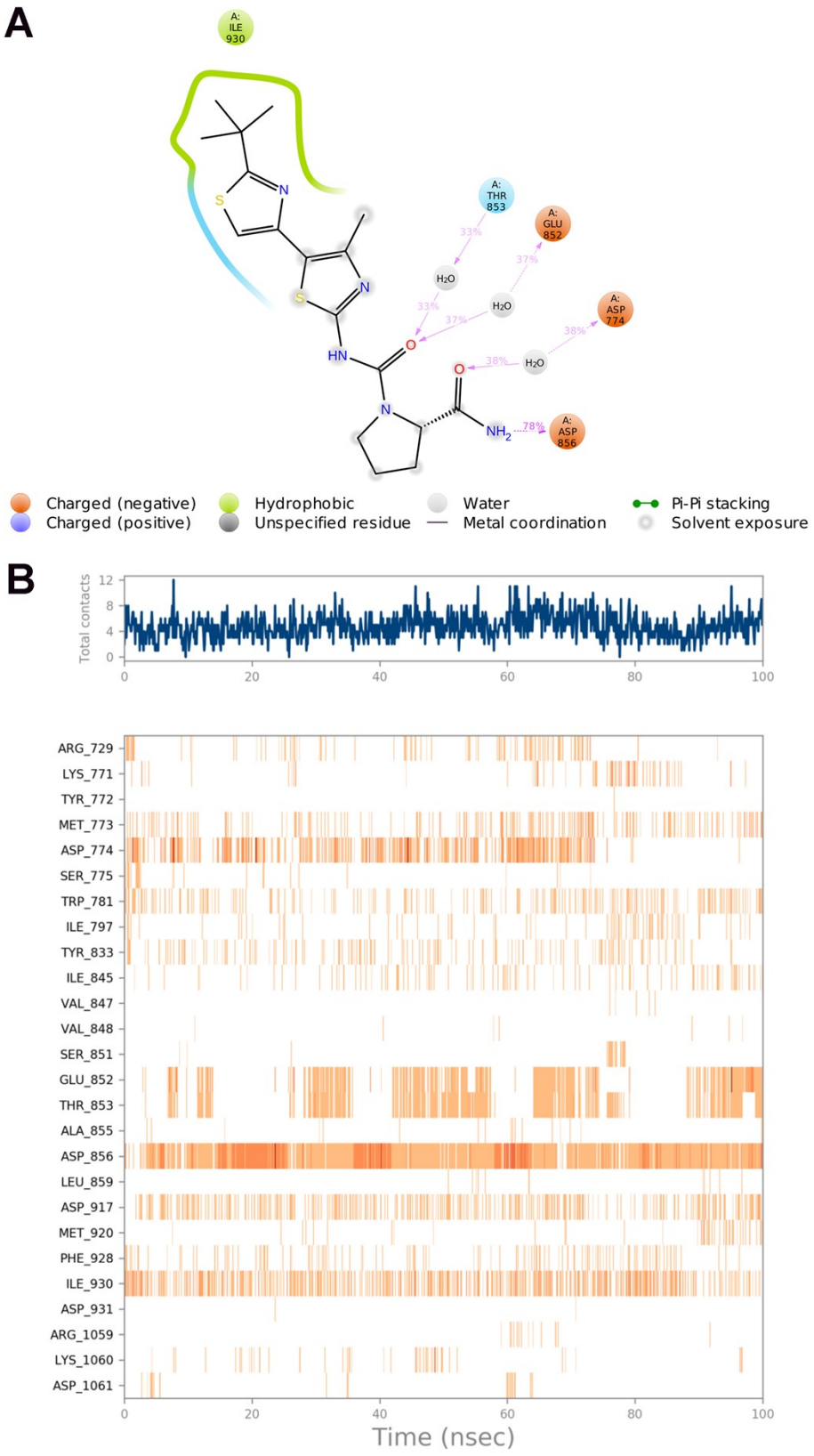

Figure S6. Ligand-Protein contacts of PI3Kβ/Compd**1** complex.

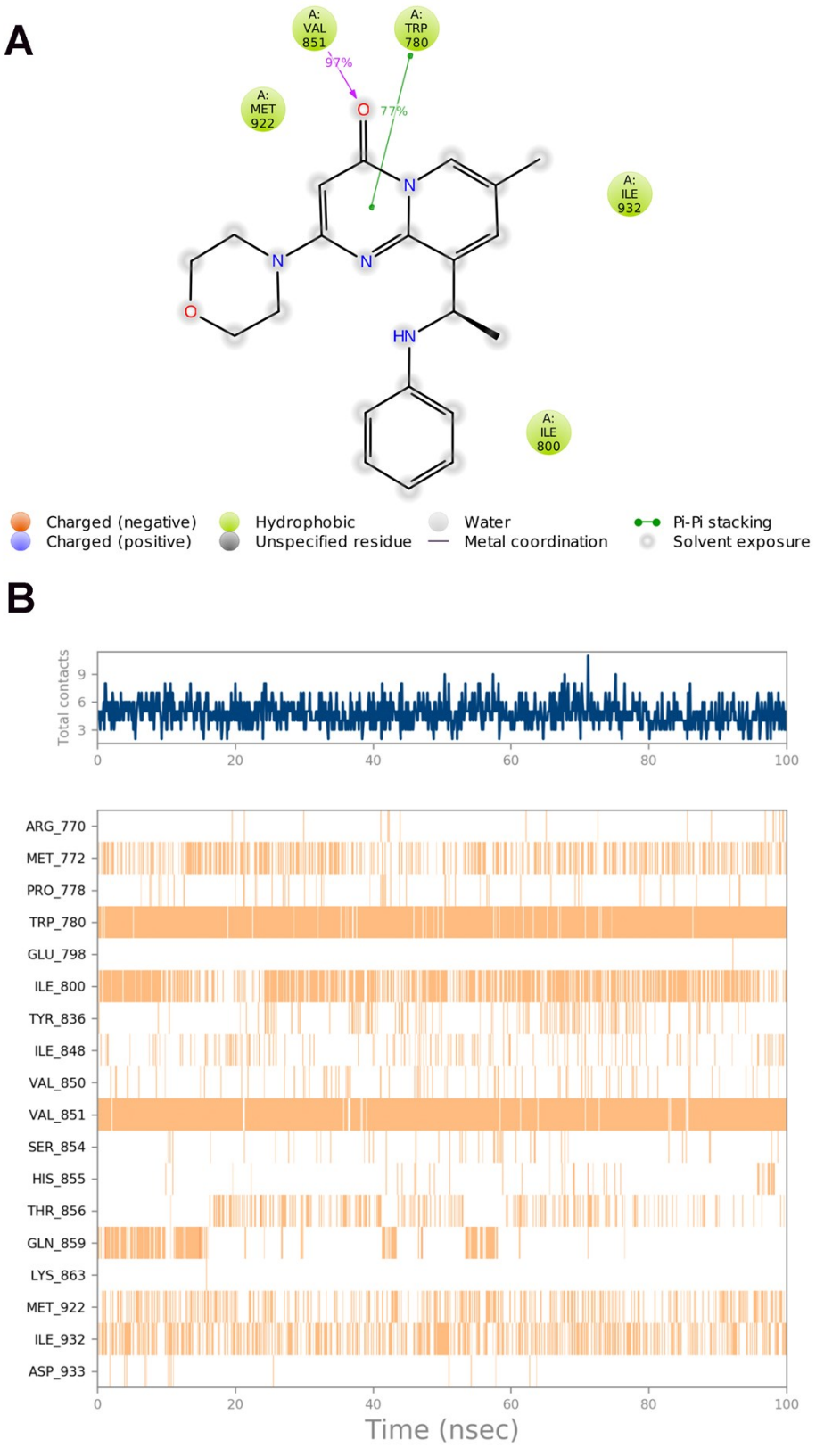

Figure S7. Ligand-Protein contacts of PI3Kα/Compd**2** complex.

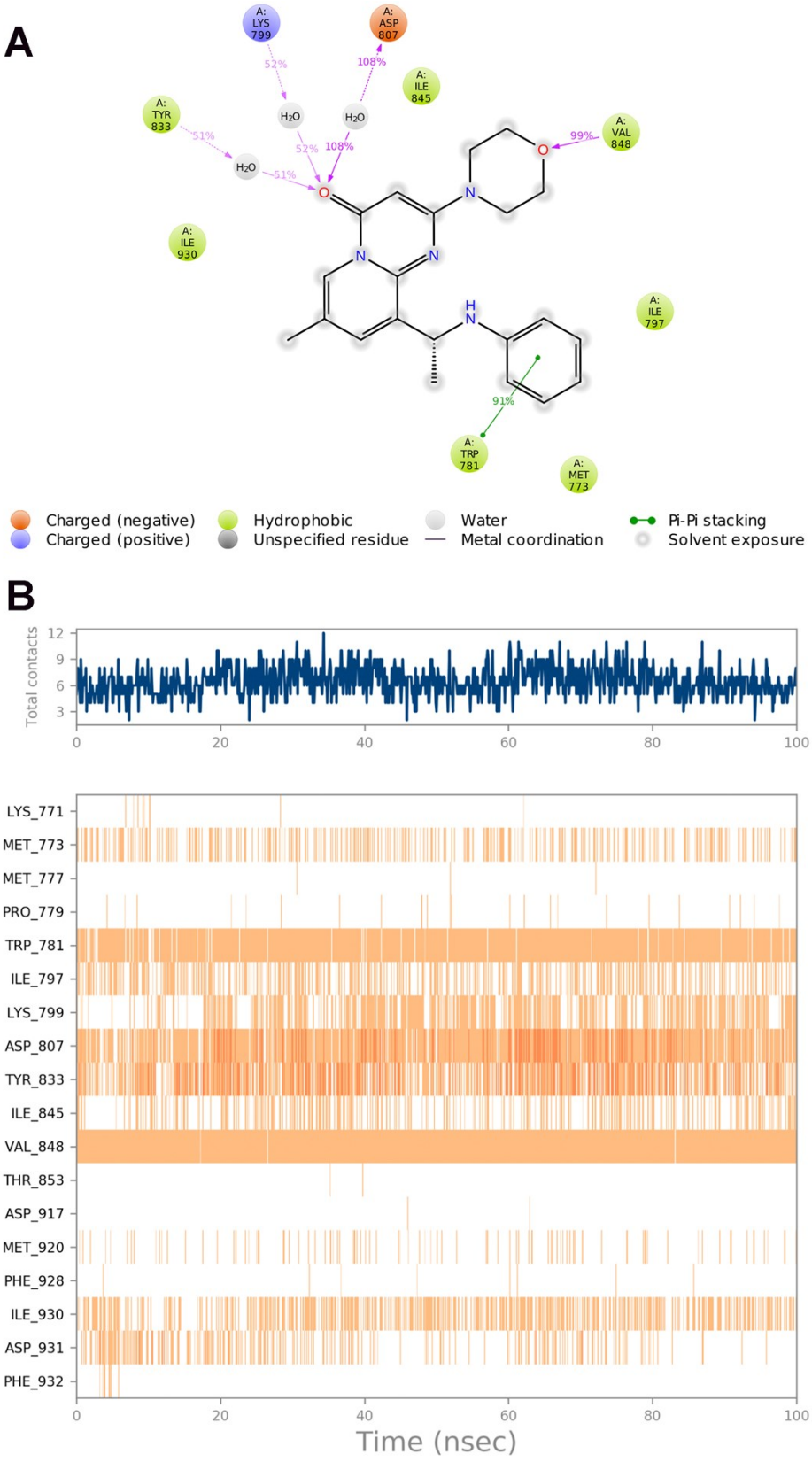

Figure S8. Ligand-Protein contacts of PI3Kβ/Compd**2** complex.

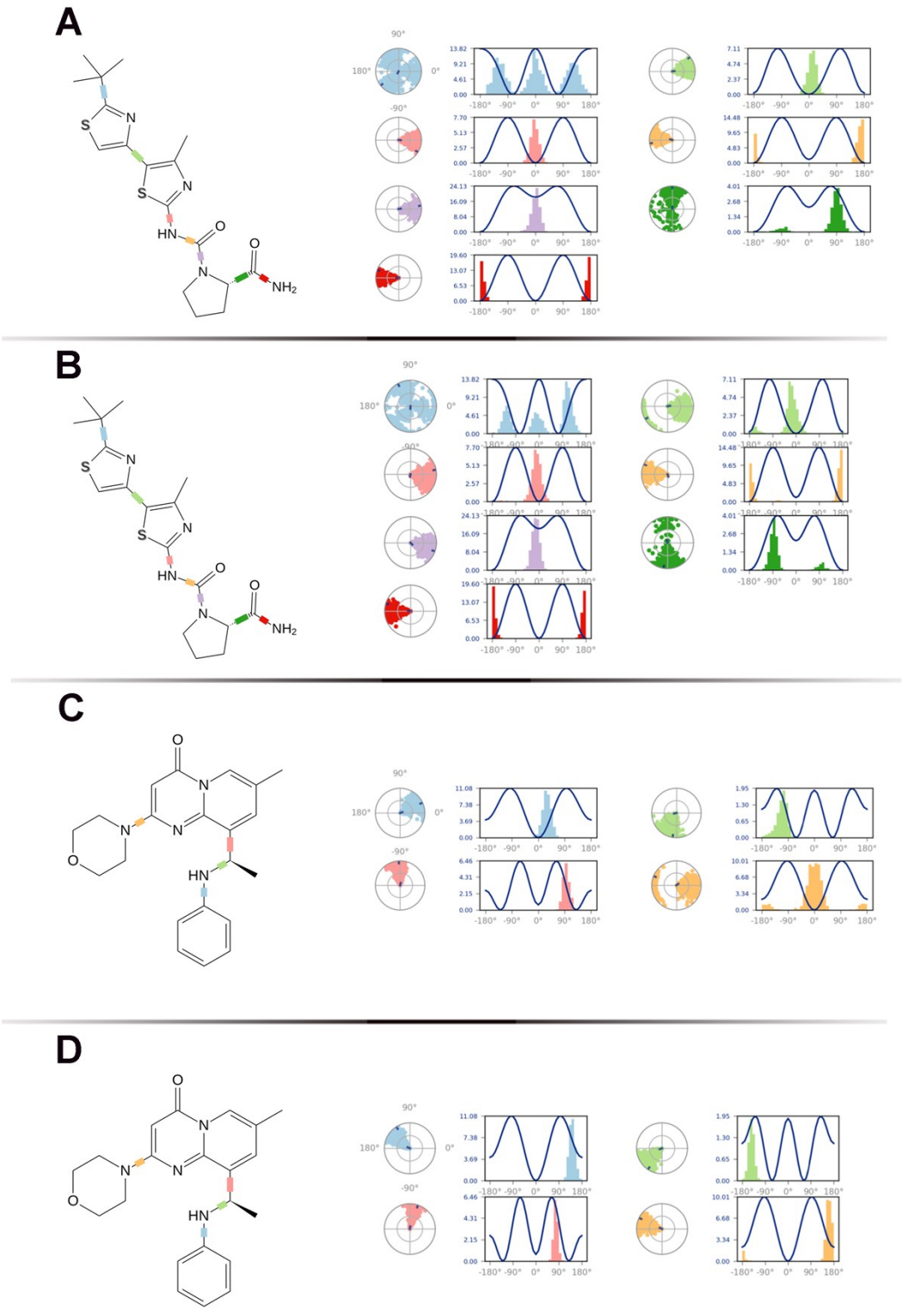

Figure S9. Ligand Torsion Profile of four complexes. (A) PI3Kα/Compd**1**. (B) PI3Kβ/Compd**1**. (C) PI3Kα/Compd**2**. (D) PI3Kβ/Compd**2**.

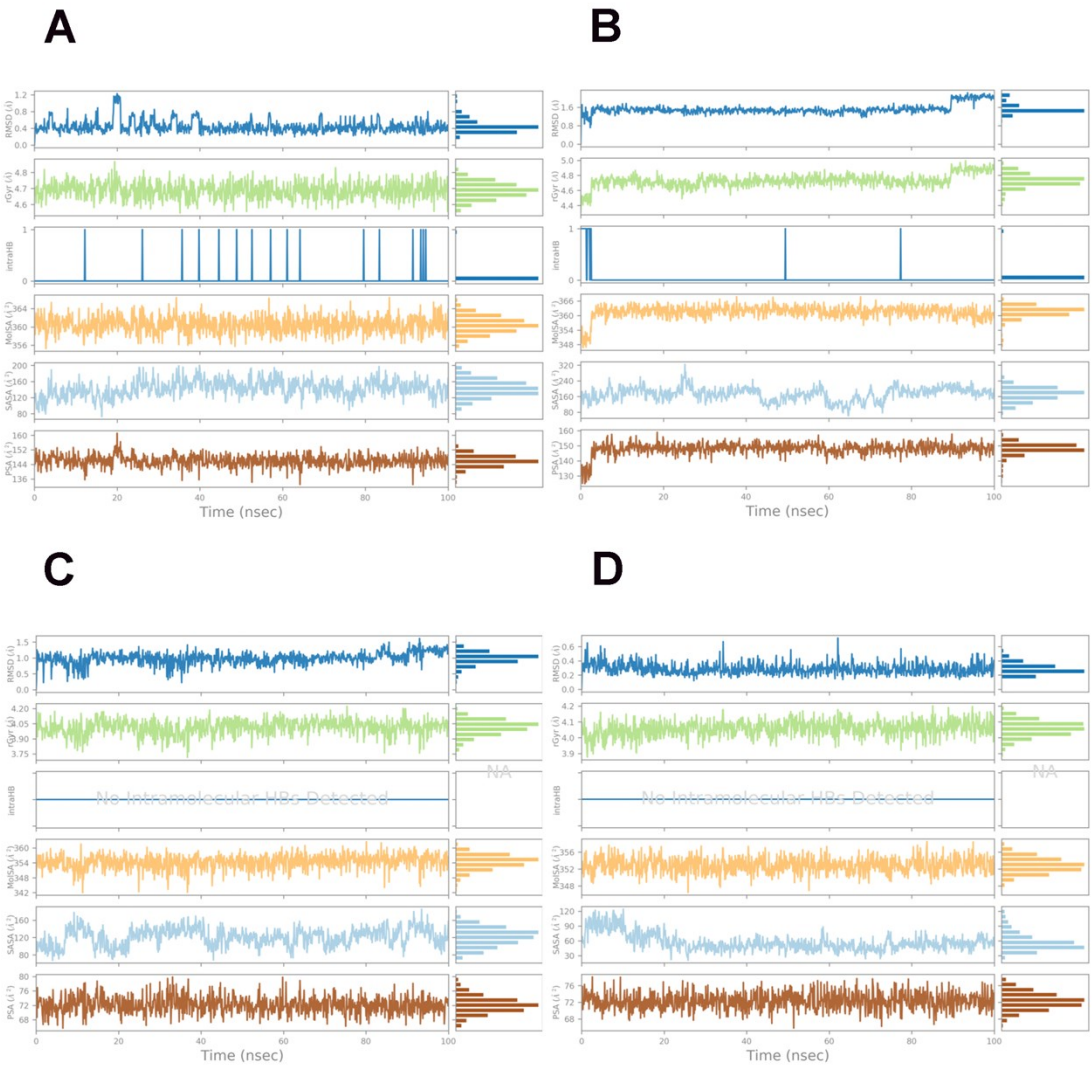

Figure S10. Variation in the ligand's properties w.r.t time during the 100 ns MD simulation. (A) PI3Kα/Compd**1**. (B) PI3Kβ/Compd**1**. (C) PI3Kα/Compd**2**. (D) PI3Kβ/Compd**2**.

Table S1 Key residues of docking results based on PI3Kα/β.

Entry	Hydrogen bonds	Surrounding residues
α		
Compd**1**	VAL851,SER854, GLN859	ARG770,MET772,SER774,PRO778,TRP780,ILE800,LYS802 ,TYR836,ILE848,GLU849,VAL850,VAL851,ARG852,ASN853 ,SER854,HIS855,THR856,GLN859,MET922, PHE930,ILE932,ASP933
Compd**2**	GLN859	MET772,TRP780,GLU798,ILE800 ,TYR836,ILE848,GLU849,VAL850,VAL851,ARG852,ASN853 ,SER854,HIS855,THR856,GLN859,MET922,PHE930,ILE932 ,ASP933
Co-ligand	VAL851,SER854, GLN859	ARG770,MET772,SER774,PRO778,TRP780,ILE800,LYS802 ,TYR836,GLU849,VAL850,VAL851,ARG852,ASN853,SER85 4,HIS855,THR856,GLN859,MET922,PHE930,ILE932, ASP933
β		
Compd**1**	LYS771, ARG729, ASP856	ARG729,LYS771,TYR772,MET773,PRO779,TRP781, ILE797,LYS799,ILE845,ASP856,MET920,ILE930,ASP931
Compd**2**	VAL848,ASP931	LYS771,TYR772,MET773,PRO779,LEU780,TRP781,LYS79 9,TYR833,ILE845,GLU846,VAL847,VAL848,SER851,THR85 3,MET920,ILE930,ASP931
Co-ligand	LYS799,TYR833, VAL848, ASP931	LYS771,TYR772,MET773,PRO779,LEU780,TRP781,ILE797, LYS799,ASP807,TYR833,ILE845,GLU846,VAL847,VAL848, SER851,MET920,PHE928,ILE930,ASP931

Table S2 MM/GBSA calculation score of PI3Kα/β complexes.

Energy	PI3Kα (kcal/mol)		PI3Kβ (kcal/mol)	
	Compd**1**	Compd**2**	Compd**1**	Compd**2**
Total	-70.77±1.02	-39.46±0.74	-30.87±0.77	-52.45±0.94
Coulomb	-26.16±0.62	-15.48±0.36	-20.13±0.35	-13.05±0.26
Covalent	0.22±0.03	8.00±0.12	7.78±0.16	8.04±0.14
Hbond	-3.05±0.06	-1.01±0.03	-1.74±0.05	-0.84±0.02
Lipo	-22.56±0.33	-17.81±0.17	-20.12±0.19	-22.76±0.24
Packing	-0.75±0.06	-0.68±0.04	-0.66±0.05	-0.94±0.06
SolvGB	-35.05±0.32	27.32±0.25	35.05±0.31	24.75±0.26
vdW	-53.52±0.52	-39.78±0.52	-31.05±0.53	-47.65±0.34