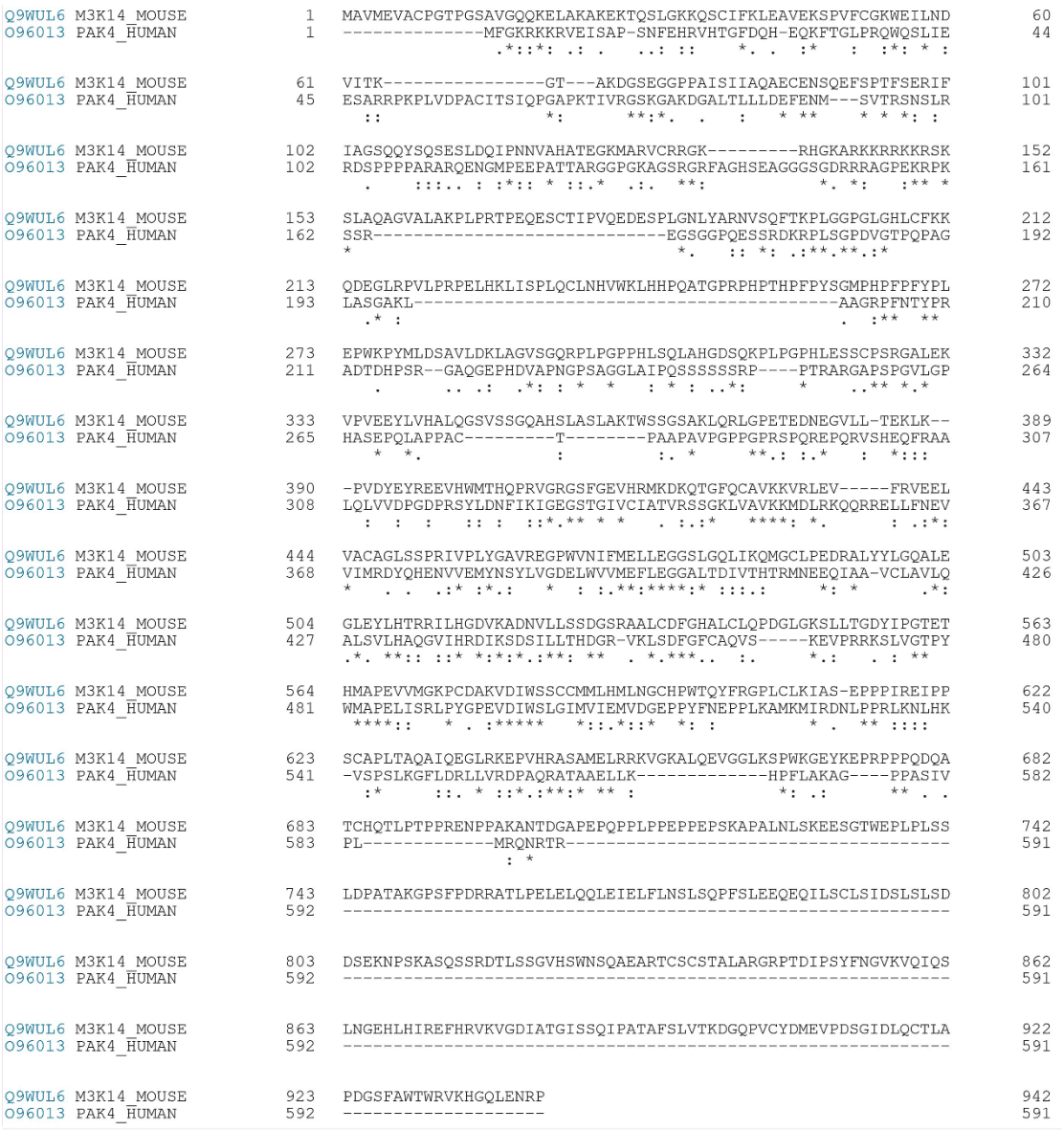
Support information

```
Q9WUL6 M3K14_MOUSE          1   MAVMEVACPGTPGSAVGQQKELAKAKEKTQSLGKKQSCIFKLEAVEKSPVFCGKWEILND      60
Q99558 M3K14_HUMAN          1   MAVMEMACPGAPGSAVGQQKELPKAKEKTPPLGKKQSSVYKLEAVEKSPVFCGKWEILND      60
                                ******:****:*********** ******  ******.::********************

Q9WUL6 M3K14_MOUSE         61   VITKGTAKDGSEGGPPAISIIAQAECENSQEFSPTFSERIFIAGSQQYSQSESLDQIPNN      120
Q99558 M3K14_HUMAN         61   VITKGTAKEGSEAGPAAISIIAQAECENSQEFSPTFSERIFIAGSKQYSQSESLDQIPNN      120
                                ********:***.** ****************************:***************

Q9WUL6 M3K14_MOUSE        121   VAHATEGKMARVCRRGKRHGKARKKRRKKRSKSLAQAGVALAKPLPRTPEQESCTIPVQE      180
Q99558 M3K14_HUMAN        121   VAHATEGKMARVCWKGKRRSKARKKRKKKSSKSLAHAGVALAKPLPRTPEQESCTIPVQE      180
                                ************* :***:.******:** *****:************************

Q9WUL6 M3K14_MOUSE        181   DESPLGNLYARNVSQFTKPLGGPGLGHLCFKKQDEGLRPVLPRPELHKLISPLQCLNHVW      240
Q99558 M3K14_HUMAN        181   DESPLGAPYVRNTPQFTKPLKEPGLGQLCFKQLGEGLRPALPRSELHKLISPLQCLNHVW      240
                                ******  *.**. ******  ****:****: .*****.*** ****************

Q9WUL6 M3K14_MOUSE        241   KLHHPQATGPRPHPTHPFPYSGMPHPFPFYPLEPWKPYMLDSAVLDKLAGVSGQRPLPGP      300
Q99558 M3K14_HUMAN        241   KLHHPQDGGPLPLPTHPFPYSRLPHPFPFHPLQPWKPHPLES-FLGKLACVDSQKPLPD-      298
                                ******  ** * ******** :******:**:****: *:* .*.*** *..*:***.

Q9WUL6 M3K14_MOUSE        301   PHLSQLAHGDSQKPLPGPHLESSCPSRGALEKVPVEEYLVHALQGSVSSGQAHSLASLAK      360
Q99558 M3K14_HUMAN        299   PHLSKLACVDSPKPLPGPHLEPSCLSRGAHEKFSVEEYLVHALQGSVSSGQAHSLTSLAK      358
                                ****:**  ** ********* ** **** **. **********************:****

Q9WUL6 M3K14_MOUSE        361   TWSSGSAKLQRLGPETEDNEGVLLTEKLKPVDYEYREEVHWMTHQPRVGRGSFGEVHRMK      420
Q99558 M3K14_HUMAN        359   TWAARGSRSREPSPKTEDNEGVLLTEKLKPVDYEYREEVHWATHQLRLGRGSFGEVHRME      418
                                **:: .:: :. .*:************************** *** *:************:

Q9WUL6 M3K14_MOUSE        421   DKQTGFQCAVKKVRLEVFRVEELVACAGLSSPRIVPLYGAVREGPWVNIFMELLEGGSLG      480
Q99558 M3K14_HUMAN        419   DKQTGFQCAVKKVRLEVFRAEELMACAGLTSPRIVPLYGAVREGPWVNIFMELLEGGSLG      478
                                ******************.***:*****:********************************

Q9WUL6 M3K14_MOUSE        481   QLIKQMGCLPEDRALYYLGQALEGLEYLHTRRILHGDVKADNVLLSSDGSRAALCDFGHA      540
Q99558 M3K14_HUMAN        479   QLVKEQGCLPEDRALYYLGQALEGLEYLHSRRILHGDVKADNVLLSSDGSHAALCDFGHA      538
                                **:*: ************************:**********************:**********

Q9WUL6 M3K14_MOUSE        541   LCLQPDGLGKSLLTGDYIPGTETHMAPEVVMGKPCDAKVDIWSSCCMMLHMLNGCHPWTQ      600
Q99558 M3K14_HUMAN        539   VCLQPDGLGKSLLTGDYIPGTETHMAPEVVLGRSCDAKVDVWSSCCMMLHMLNGCHPWTQ      598
                                :*******************************:*: ******:********************

Q9WUL6 M3K14_MOUSE        601   YFRGPLCLKIASEPPPIREIPPSCAPLTAQAIQEGLRKEPVHRASAMELRRKVGKALQEV      660
Q99558 M3K14_HUMAN        599   FFRGPLCLKIASEPPPVREIPPSCAPLTAQAIQEGLRKEPIHRVSAAELGGKVNRALQQV      658
                                :****************:************************:**.** **  **.:***:*

Q9WUL6 M3K14_MOUSE        661   GGLKSPWKGEYKEPRPPPQDQATCHQTLPTPPRENPP-------AKANTDGAPEPQPPLP      713
Q99558 M3K14_HUMAN        659   GGLKSPWRGEYKEPRHPPPNQANYHQTLHAQPRELSPRAPGPRPAEETTGRAPKLQPPLP      718
                                *******:******* ** :**. **** : ***  *       *: .*. **: *****

Q9WUL6 M3K14_MOUSE        714   PEPPEPSKAPALNLSKEESGTWEPLPLSSLDPATAKGPSFPDRRATLPELELQQLEIELF      773
Q99558 M3K14_HUMAN        719   PEPPEPNKSPPLTLSKEESGMWEPLPLSSLEPAPARNPSSPERKATVPEQELQQLEIELF      778
                                ******.*:* *.******* *********:** *:.** *:*:**:** **********

Q9WUL6 M3K14_MOUSE        774   LNSLSQPFSLEEQEQILSCLSIDSLSLSDDSEKNPSKASQSSRDTLSSGVHSWNSQAEAR      833
Q99558 M3K14_HUMAN        779   LNSLSQPFSLEEQEQILSCLSIDSLSLSDDSEKNPSKASQSSRDTLSSGVHSWSSQAEAR      838
                                ************************************************.******

Q9WUL6 M3K14_MOUSE        834   TCSCSTALARGRPTDIPSYFNGVKVQIQSLNGEHLHIREFHRVKVGDIATGISSQIPATA      893
Q99558 M3K14_HUMAN        839   SSSWNMVLARGRPTDTPSYFNGVKVQIQSLNGEHLHIREFHRVKVGDIATGISSQIPAAA      898
                                :.* . .******** ****************************************:*

Q9WUL6 M3K14_MOUSE        894   FSLVTKDGQPVCYDMEVPDSGIDLQCTLAPDGSFAWTWRVKHGQLENRP                942
Q99558 M3K14_HUMAN        899   FSLVTKDGQPVRYDMEVPDSGIDLQCTLAPDGSFAWSWRVKHGQLENRP                947
                                *********** ************************:************
```

Identical positions	798
Identity	84.089%
Similar positions	86
Program	CLUSTALO

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



Identical positions	129
Identity	13.163%
Similar positions	181
Program	CLUSTALO

Figure S2: UniProt Align results of human PAK4 and mouse NIK protein sequence.

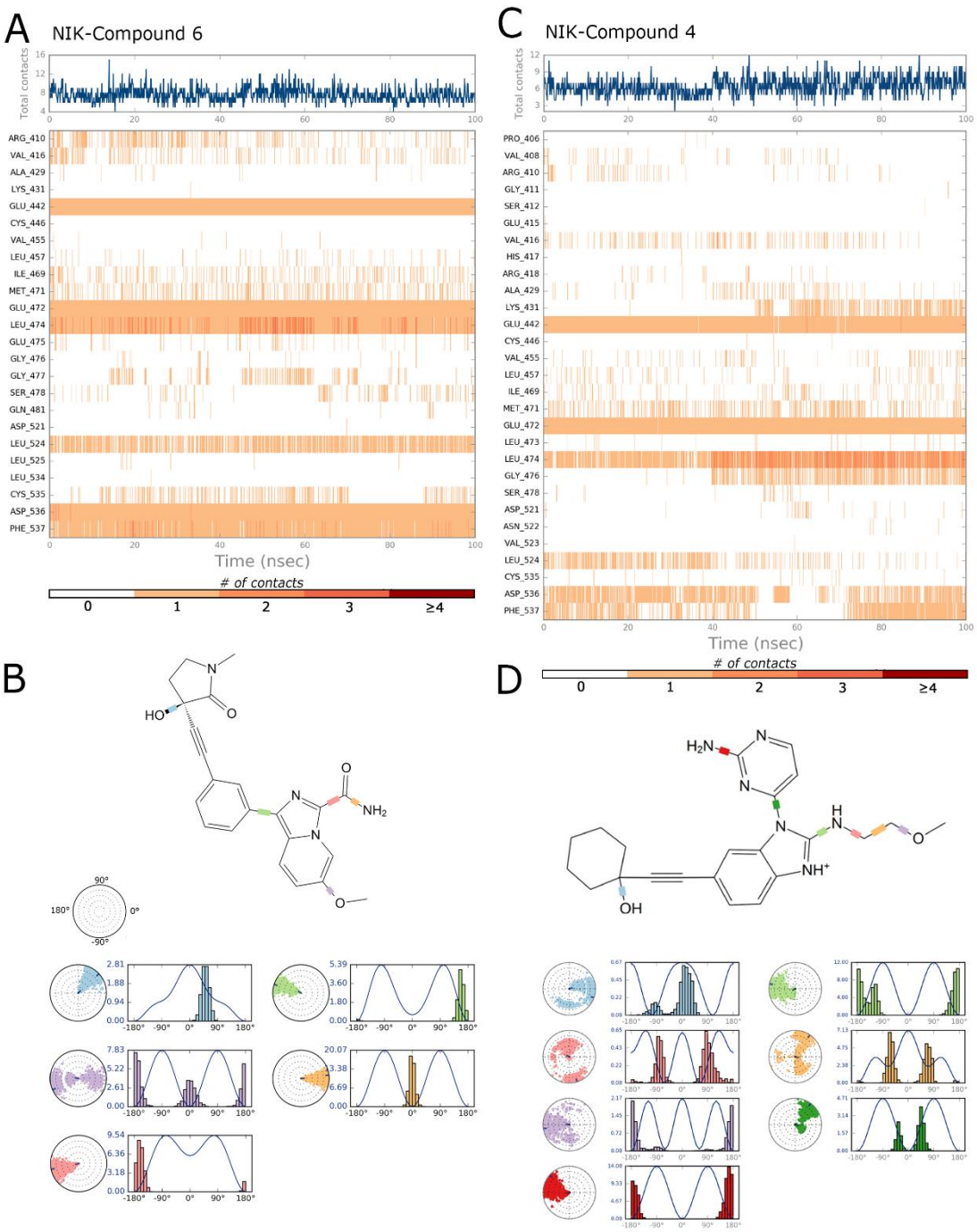


Figure S3: (A) Timeline of protein-ligand contacts of NIK with compound **6 (B)** Ligand torsion profile of compound **6** in NIK. It summarized the conformational evolution of every rotatable bond in the ligand throughout the simulation trajectory **(C)** Timeline of protein-ligand contacts of NIK with compound **4 (D)** Ligand torsion profile of compound **4** in NIK.

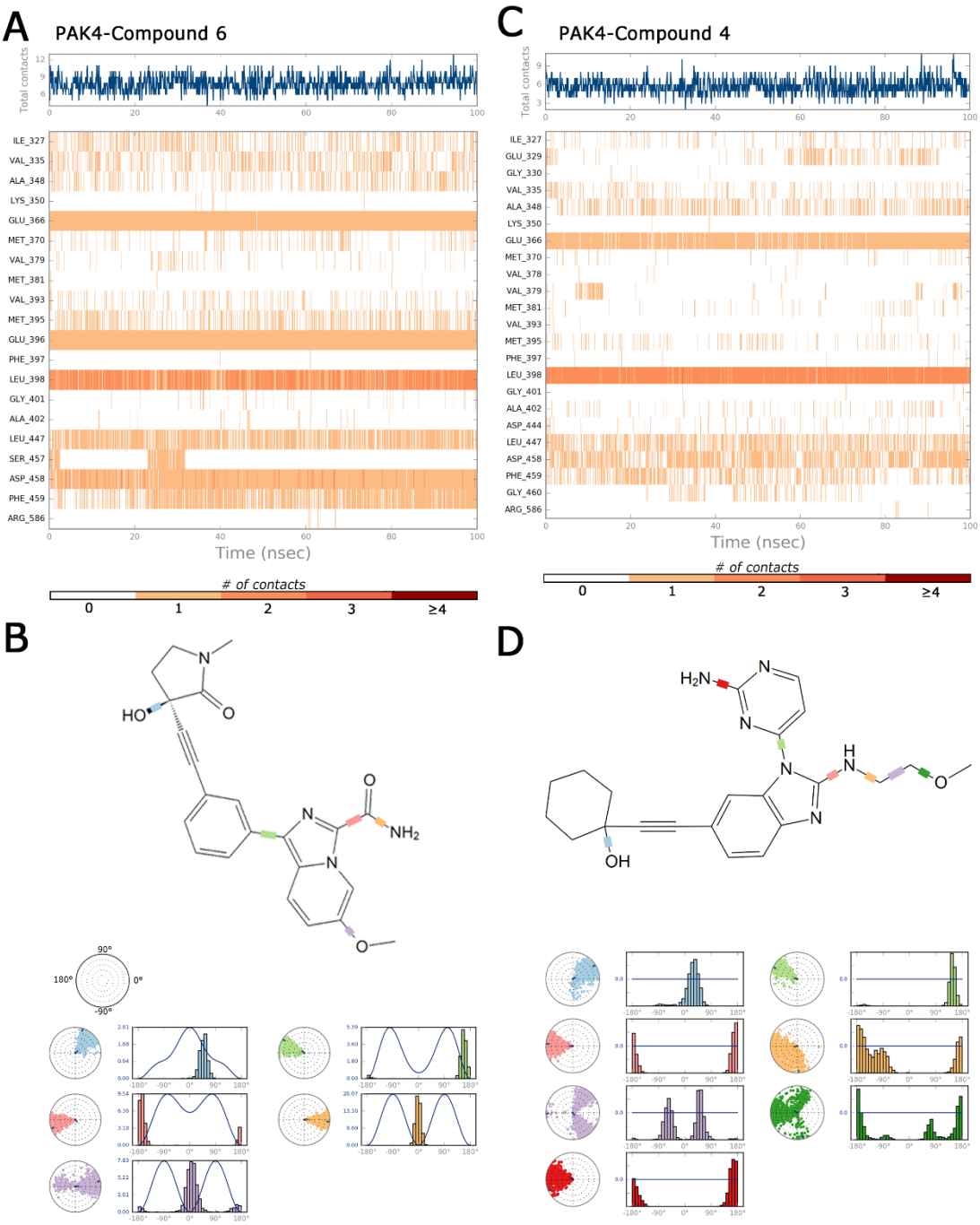


Figure S4: (A) Timeline of protein-ligand contacts of PAK4 with compound **6 (B)** Ligand torsion profile of compound **6** in PAK4. It summarized the conformational evolution of every rotatable bond in the ligand throughout the simulation trajectory **(C)** Timeline of protein-ligand contacts of PAK4 with compound **4 (D)** Ligand torsion profile of compound **4** in PAK4.

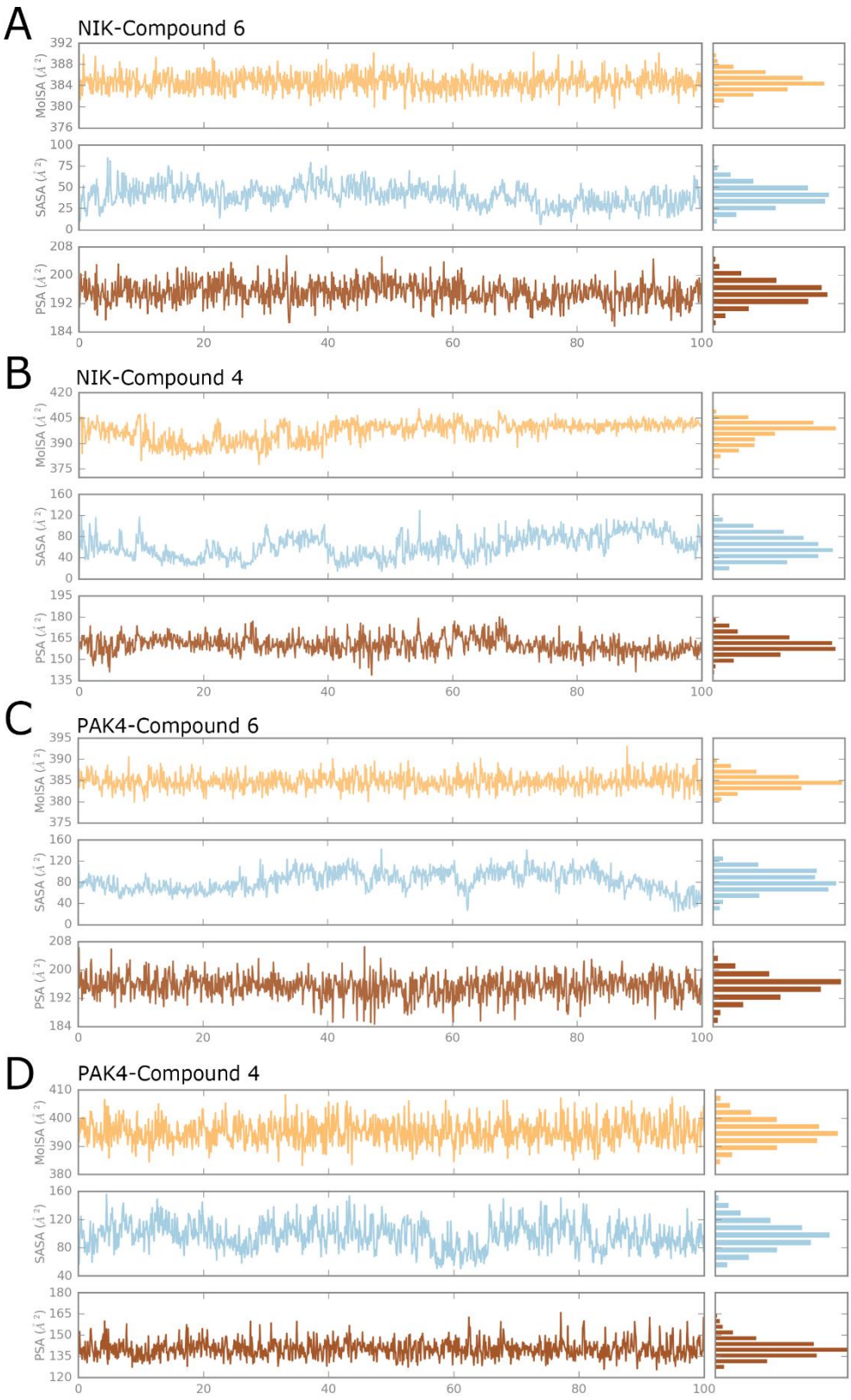


Figure S5: (A) (B) (C) (D) Molecular surface area, solvent accessible surface area, polar surface area ligand properties of complexes in the simulation

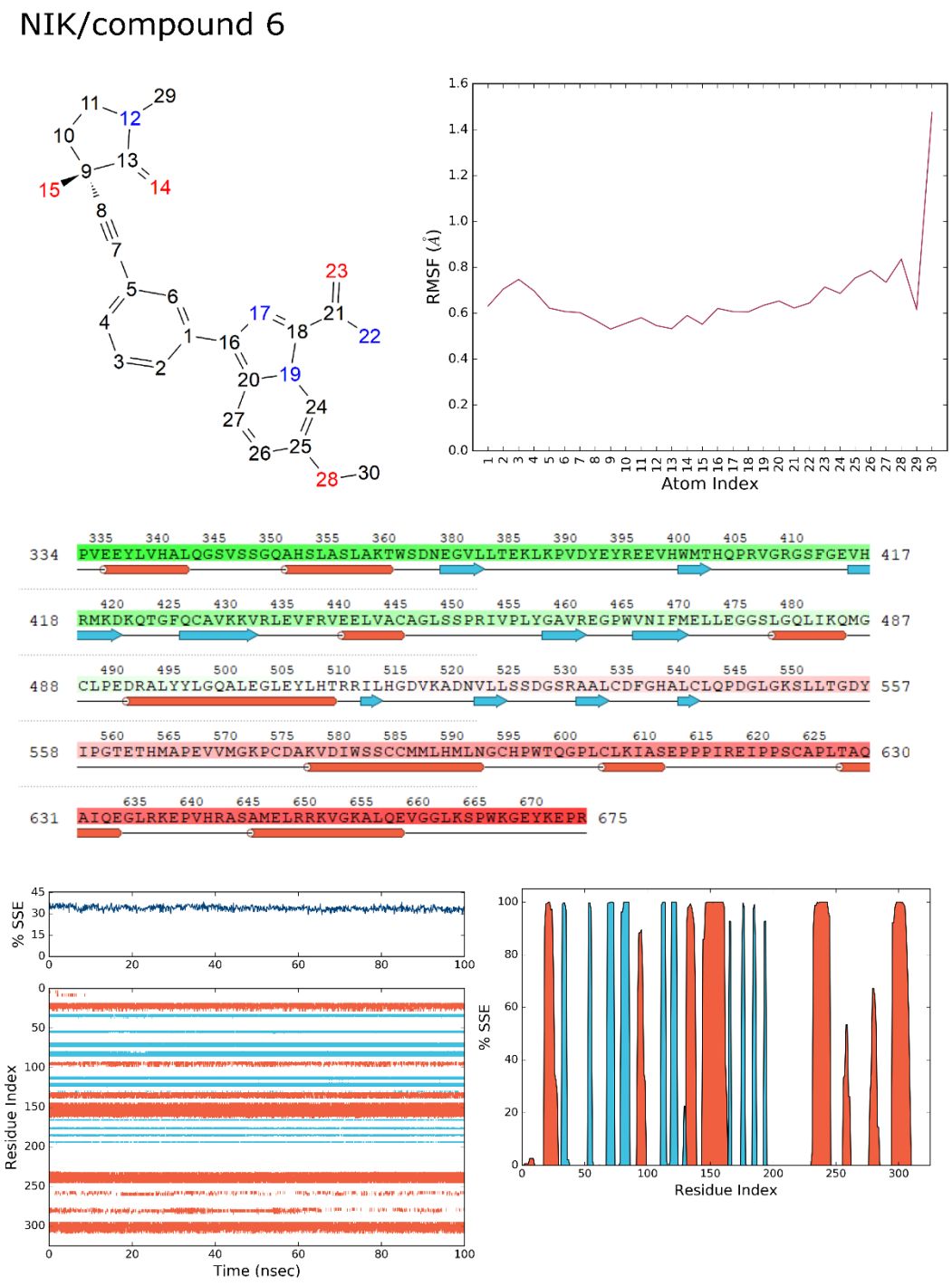


Figure S6: Ligand PMSF and protein secondary structure changing plots of NIK/compound 6 complex during Desmond MD simulations.

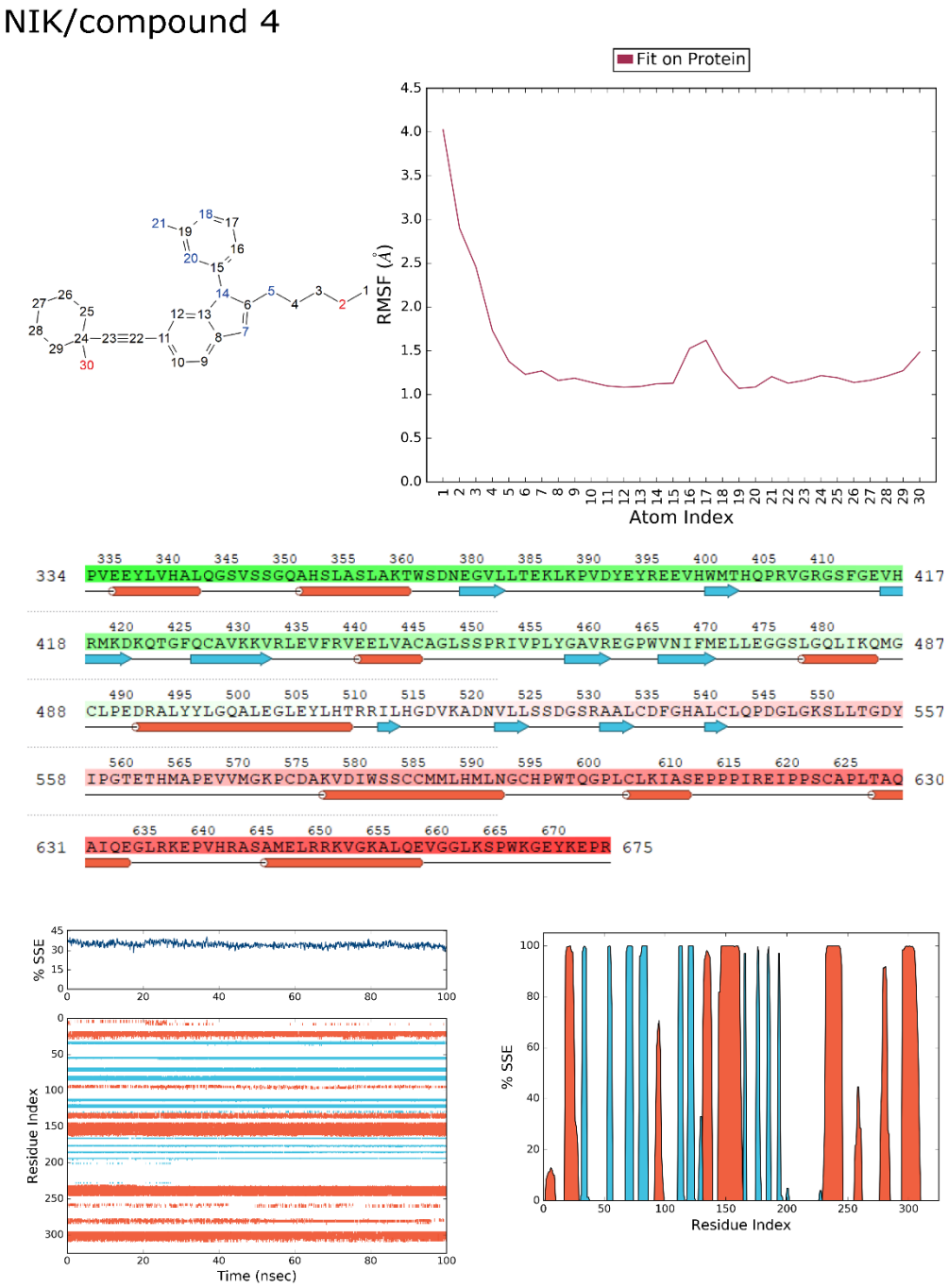


Figure S7: Ligand RMSF and protein secondary structure changing plots of NIK/compound 4 complex during Desmond MD simulations.

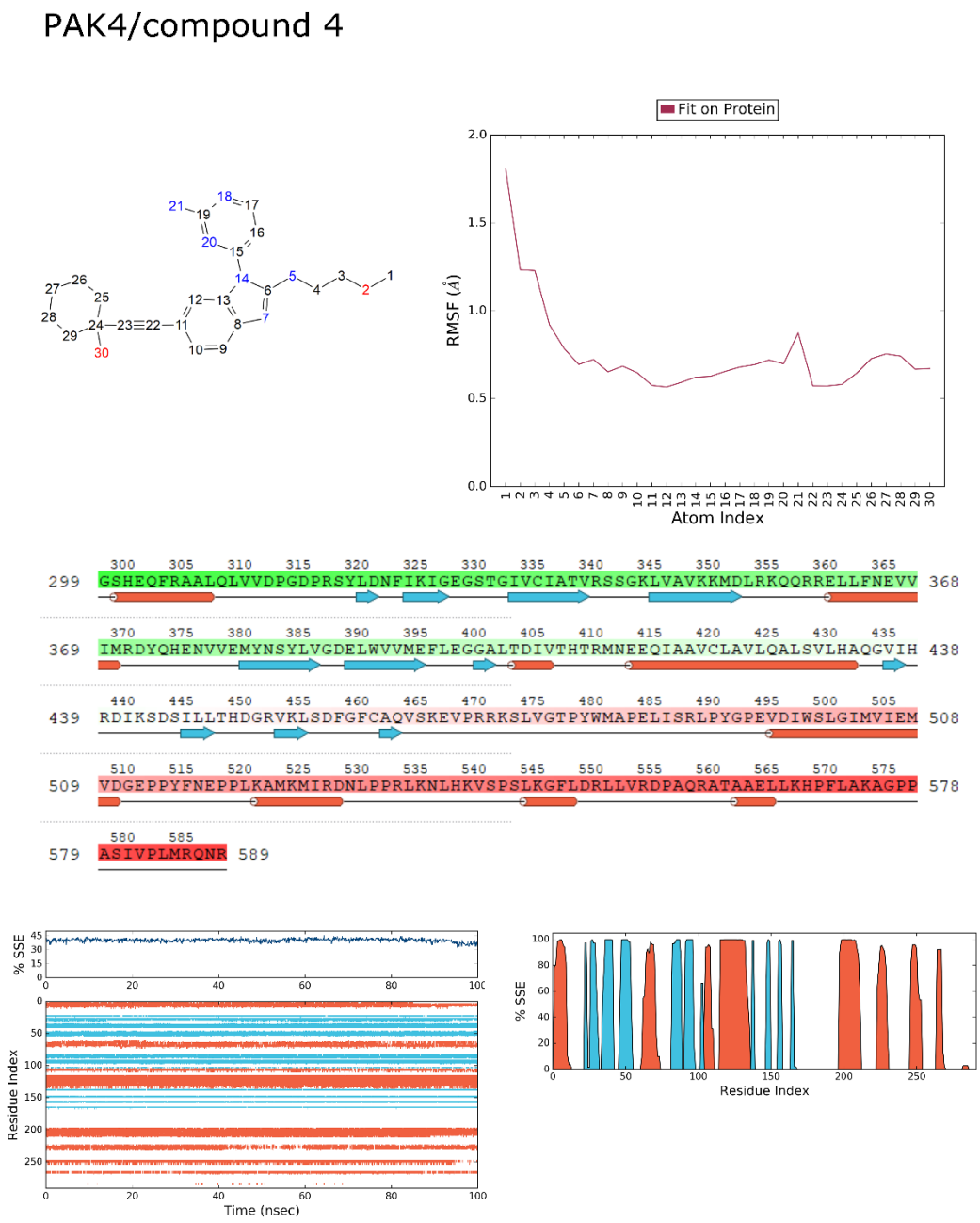


Figure S8: Ligand RMSF and protein secondary structure changing plots of PAK4/compound 4 complex during Desmond MD simulations.

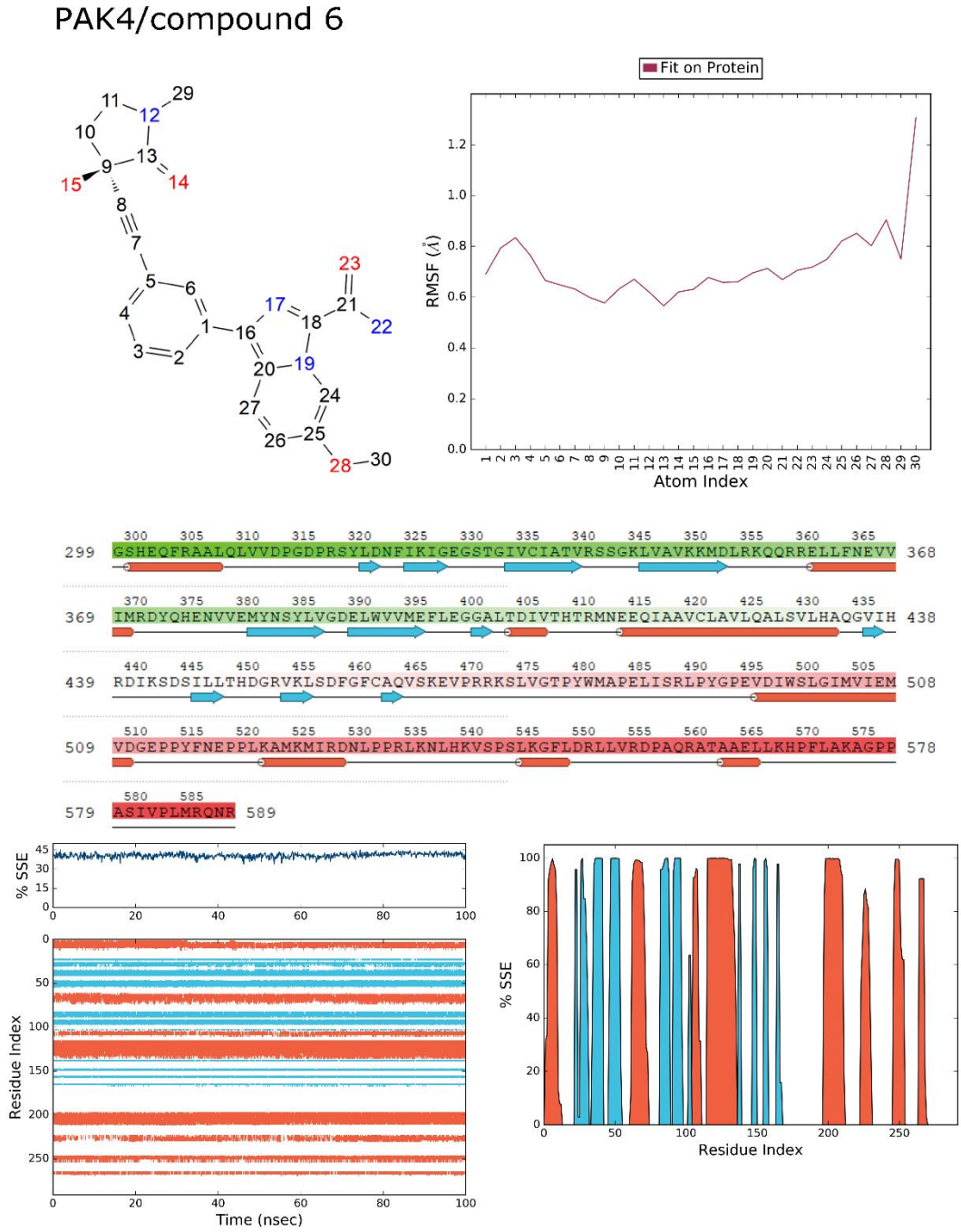


Figure S9: Ligand RMSF and protein secondary structure changing plots of PAK4/compound 6 complex during Desmond MD simulations.

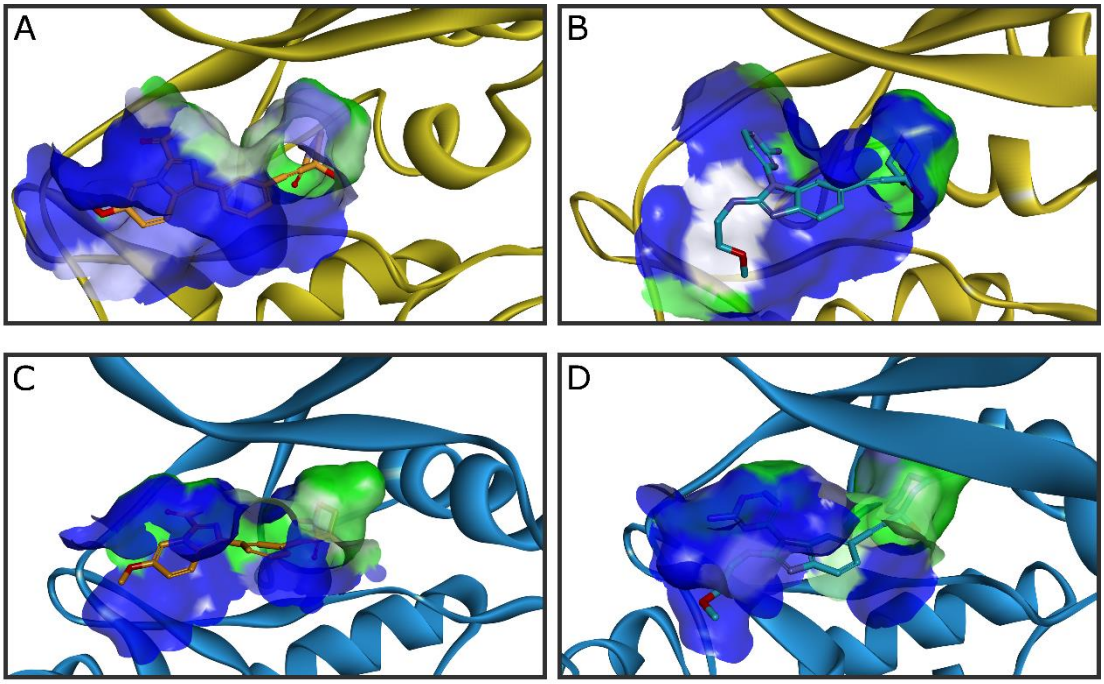


Figure S10: Illustration of solvent accessible surface of ligand-receptor complexes that extracted from the last frame of MD results. The surface was colored with blue and green corresponding to solvent exposing degree of receptor atoms in binding pockets. **(A)** NIK protein (yellow ribbon) complex with compound **6** (orange stick). **(B)** NIK protein complex with compound **4** (blue stick). **(C)** PAK4 protein (blue ribbon) complex with compound **4**. **(D)** PAK4 protein complex with compound

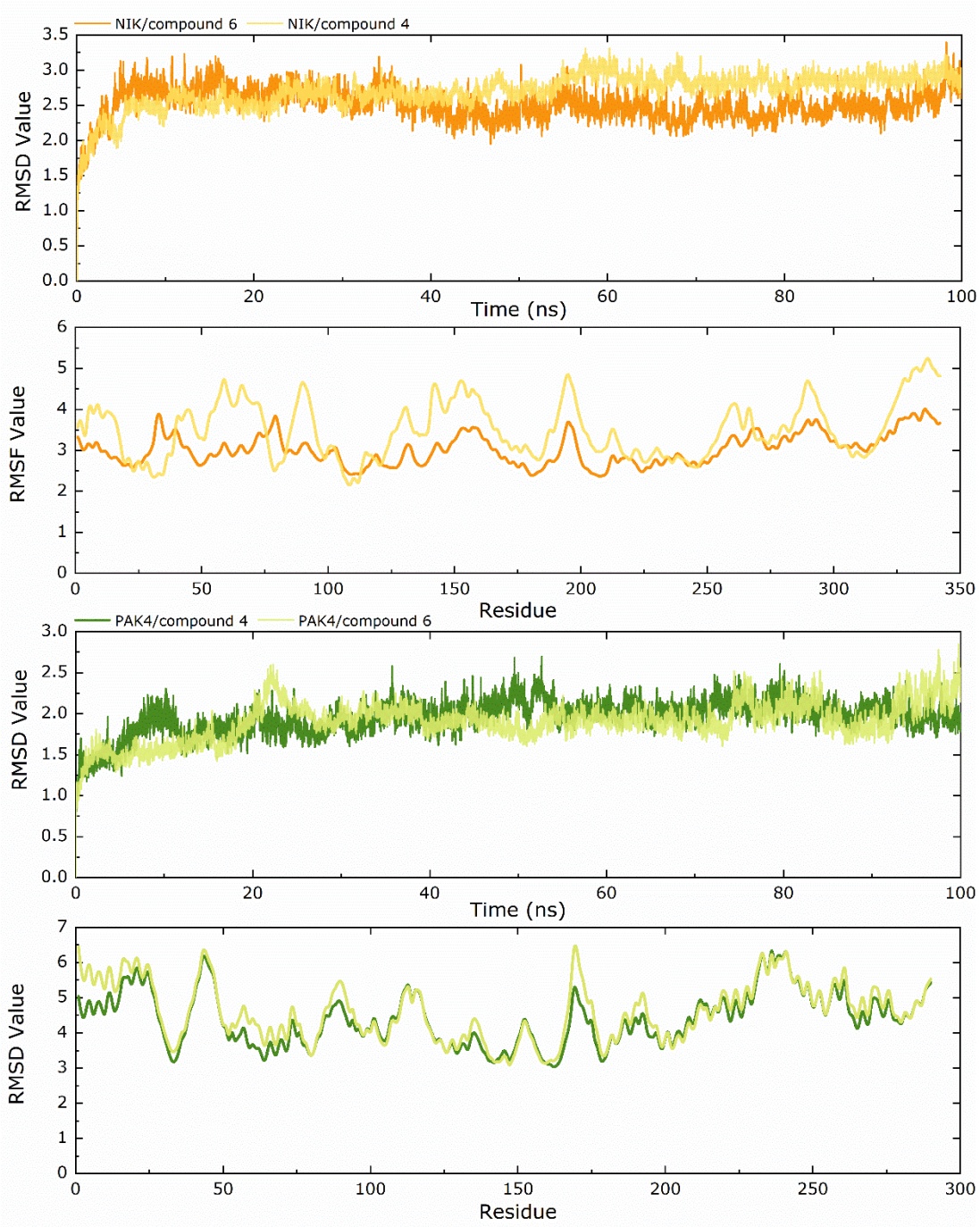


Figure S11: RMSD and RMSF plots of four complexes in Amber MD

Table S1: Distance-similarity analysis of human NIK and mouse NIK protein binding pocket

Distance/ Å	Identity (%)	Similarity (%)	Homology (%)
3	100	100	100
4	98.3333	100	100
5	98.4615	100	100
6	95.122	98.7805	98.7805
7	92.6316	97.8947	96.8421
8	92.3077	98.0769	97.1154
9	90.8333	96.6667	96.6667
10	91.9118	97.0588	97.0588

Table S2: Distance-similarity Analysis of human PAK4 and mouse NIK protein binding pocket

Distance/ Å	Identity (%)	Similarity (%)	Homology (%)
3	53.8462	71.7949	69.2308
4	46.6667	65	61.6667
5	43.0769	61.5385	60
6	39.0244	56.0976	59.7561
7	35.7895	52.6316	57.8947
8	33.6538	50	55.7692
9	30.8333	47.5	51.6667
10	30.8824	47.7941	50.7353

Table S3: Ligand single point energy results of QM/MM minimized complexes

Entry	Complex	HOMO (eV)	LUMO (eV)	HOMO-LUMO energy gap (eV)
1	NIK/Compound 6	-0.1924	-0.0477	0.1447
2	NIK/Compound 4	-0.3269	-0.1883	0.1386
3	PAK4/Compound 6	-0.1896	-0.0539	0.1357
4	PAK4/Compound 4	-0.1898	-0.0478	0.1420