molecules

MDPI

Supplementary Materials

How different substitution positions of F, Cl atoms in benzene ring of 5-methylpyrimidine pyridine derivatives affect the inhibition ability of $EGFR^{L858R/T790M/C797S}$ Inhibitors: A Molecular Dynamics Simulation Study

Jingwen E[1], Ye Liu[2], Shanshan Guan[3,4], Zhijian Luo[1], Fei Han[1], Weiwei Han[2], Song Wang[1*] and Hao Zhang[1*]

[1] Laboratory of Theoretical and Computational Chemistry, Institute of Theoretical Chemistry, Jilin University, Changchun 130023, People's Republic of China
[2] Key Laboratory for Molecular Enzymology and Engineering of Ministry of Education, School of Life Science, Jilin
[3] College of Food Engineering, Jilin Engineering Normal University, Changchun, Jilin 130052, China
[4] Key Laboratory of Molecular Nutrition at Universities of Jilin Province, Changchun, Jilin 130052, China
* Correspondence: ws@jlu.edu.cn (S. Wang); stringbell@jlu.edu.cn (H. Zhang); Tel.: +86-27-88498761

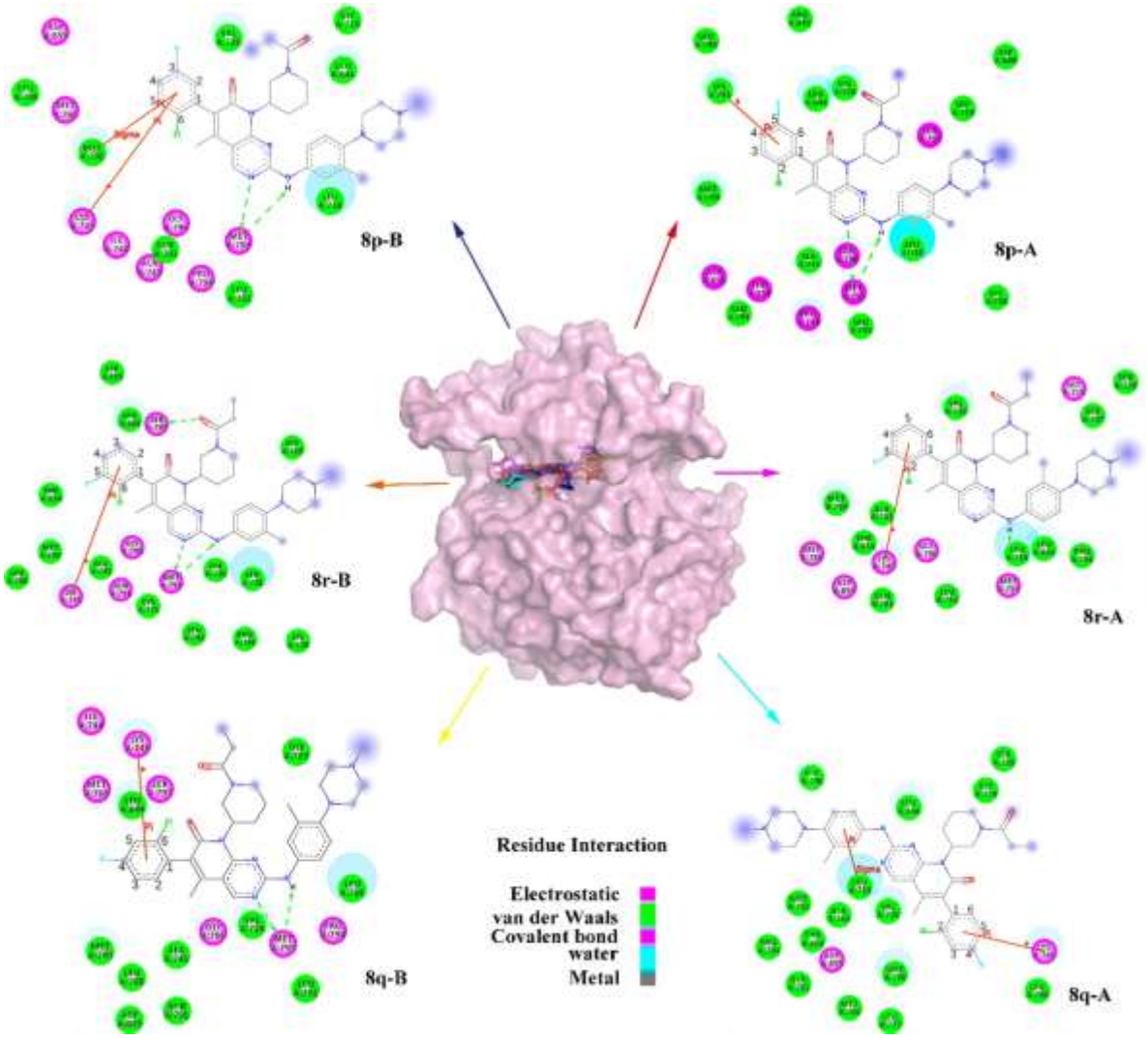

Figure S1. Optimal docking models of the six complexes: compound (**a**) 8r-B, (**b**) 8r-A (**c**) 8p-B (**d**) 8p-A (**e**) 8q-B and (**f**) 8q-A docked to EGFR™. Key residues and ligands are represented by stick models.

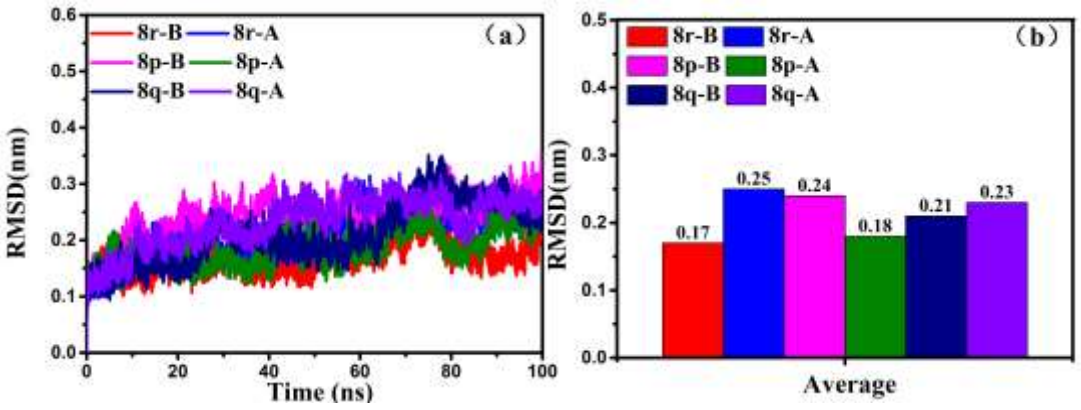

Figure S2. Stability analyses for EGFR™_8r-B(red), EGFR™_8r-A(blue), EGFR™_8p-B(magenta), EGFR™_8p-A(olive), EGFR™_8q-B(navy), EGFR™_8q-A(violet) complexes during the 100ns simulation. (**a**) RMSDs of the protein backbone, (**b**) Average RMSD values for the six systems.

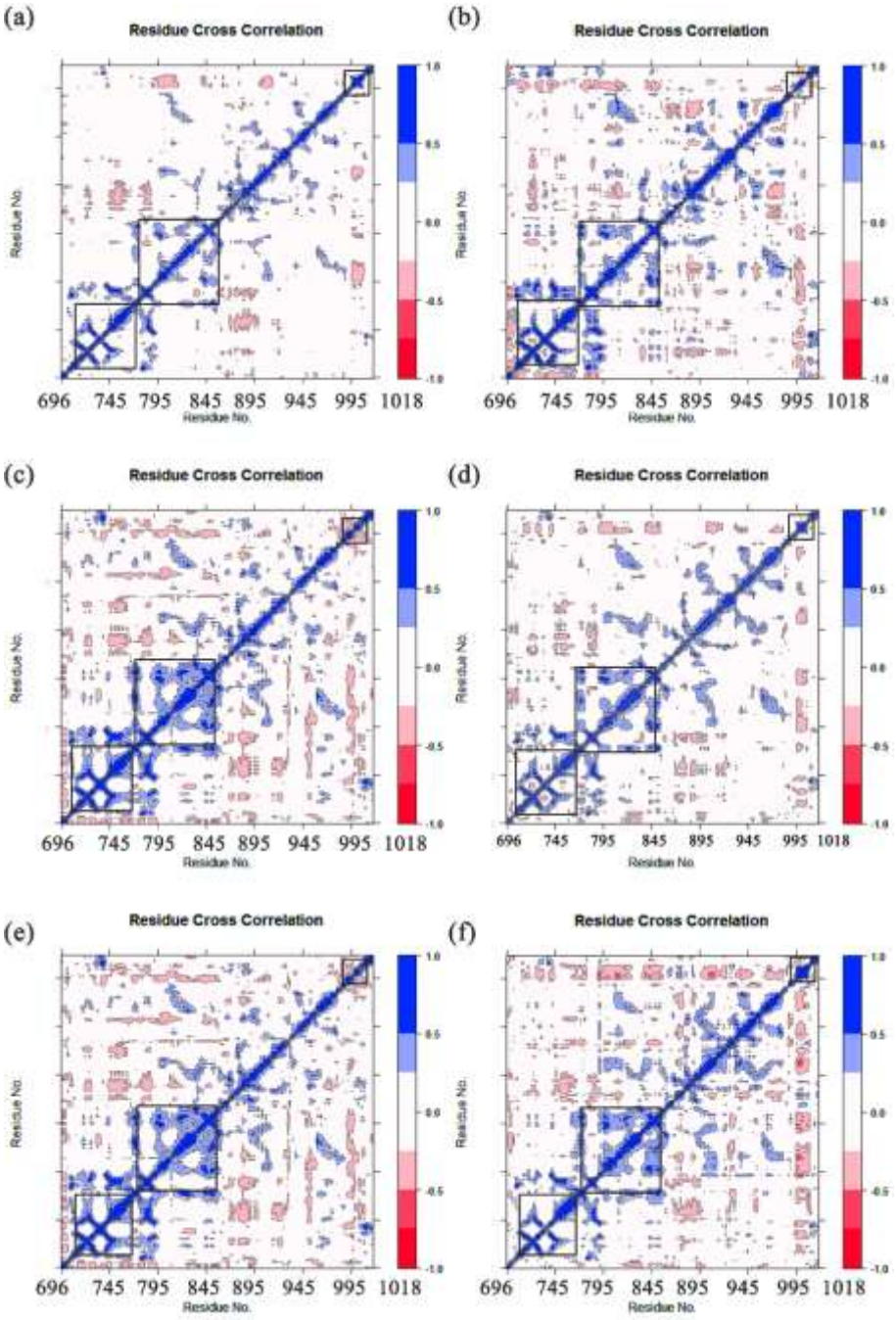

Figure S3. Cross-correlation matrix maps for the complex. (**a**) EGFR™-8r-B, (**b**) EGFR™-8r-A, (**c**) EGFR™-8p-B, (**d**) EGFR™-8p-A, (**e**) EGFR™-8q-B, and (**f**) EGFR™-8q-A.

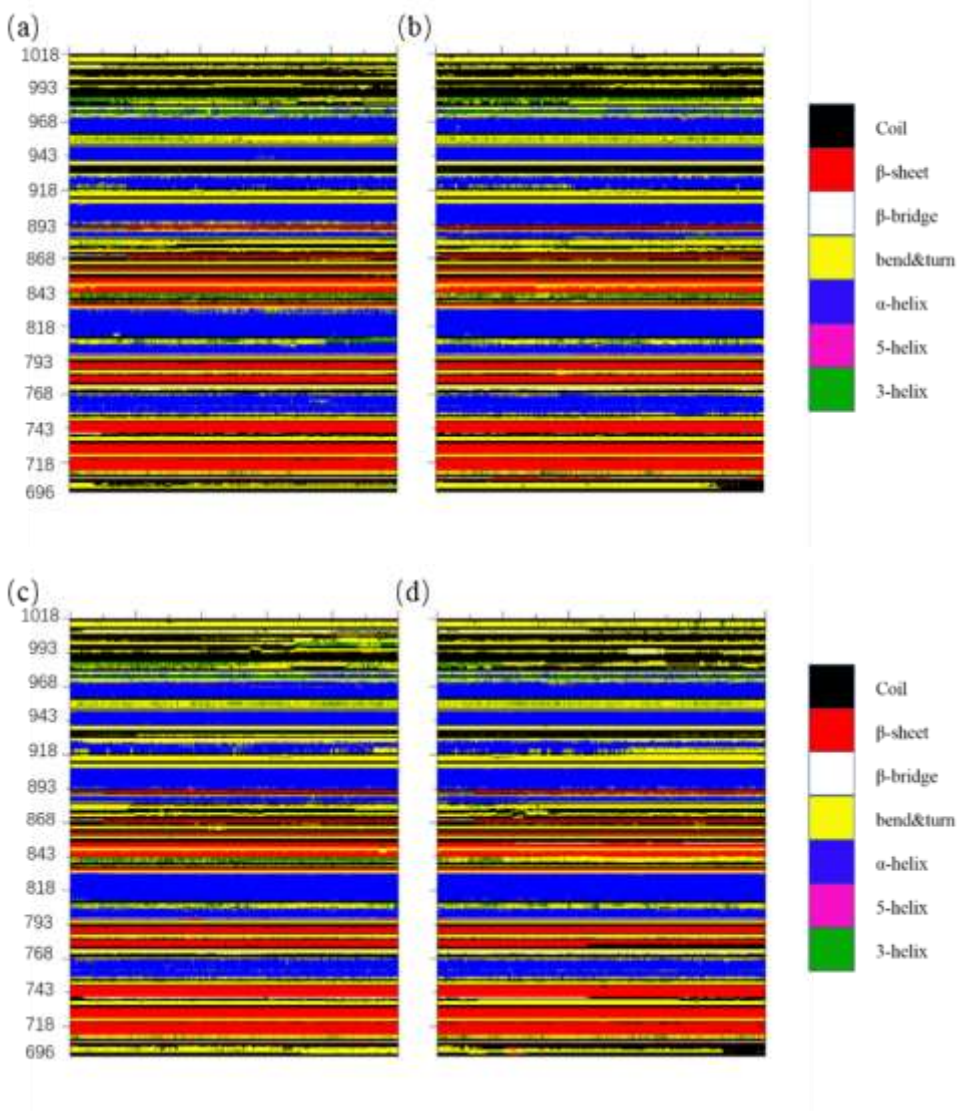

Figure S4. Comparison the differences of secondary structural differences between (a) 8p-B-bound, (b) 8p-A-bound, (c) 8q-B-bound, (d) 8q-A-bound proteins.

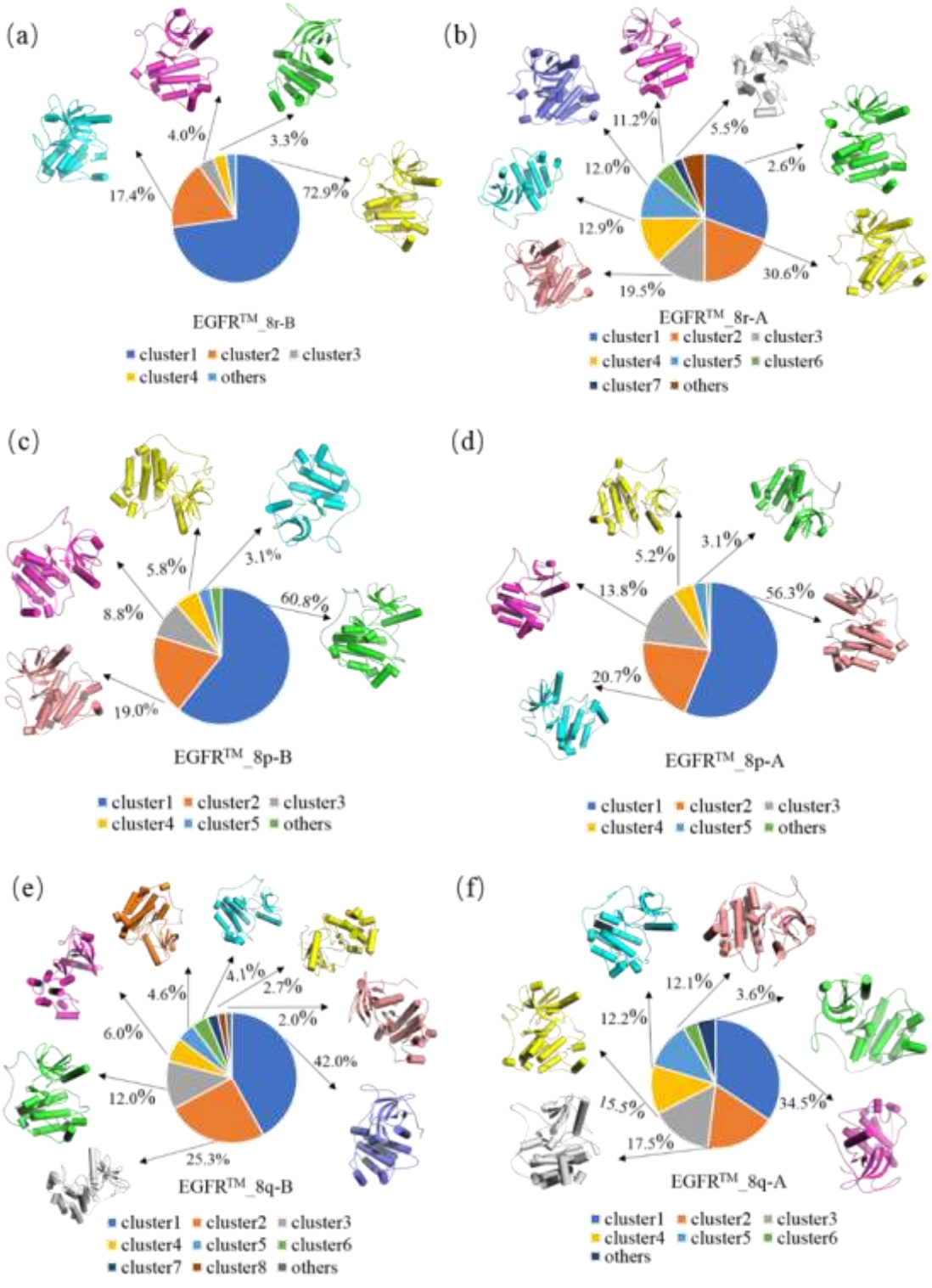

Figure S5. Structure based clustering analysis on equalized trajectory. Cluster centroids are shown and labeled. The clusters are shown others which percentage population were lower than 2%. (**a**) Complex EGFR™_8r-B, (**b**) Complex EGFR™_8r-A, (**c**) Complex EGFR™_8p-B, (**d**) Complex EGFR™_8p-A, (**e**) Complex EGFR™_8q-B, (**f**) Complex EGFR™_8q-A.

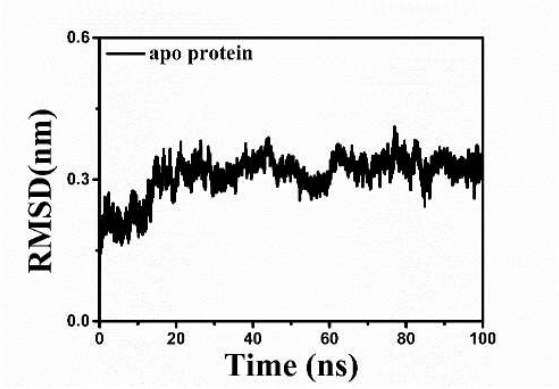

Figure S6. The optimized protein backbone atoms' RMSDs.

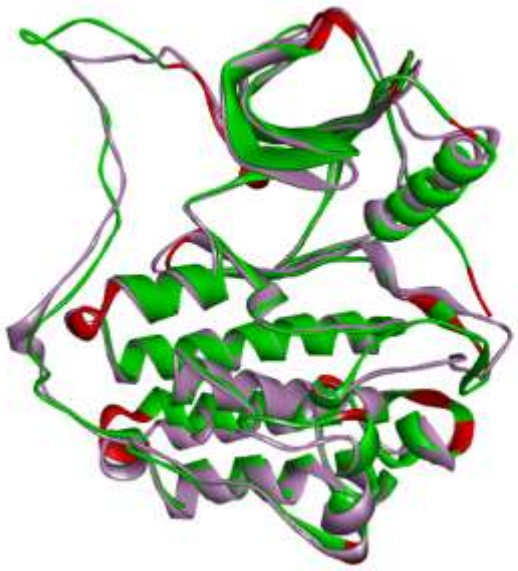

Figure S7. The comparison between the protein in 5EDP.pdb (green) and the optimized protein (purple). Different for two structure show as red region.

```
696     GEAPNQALLR ILKETEFKKI KVLGSGAFGT VYKGLWIPEG EKVKIPVAIK ELREATSPKA NKEILDEAYV MASVDNPHVC RLLGICLTST VQLIMQLMPF  795
5EDP              B  GGG EEE EEEEEE  SSEEEEEEEE    TTSBEEEEEE EE      HHH HHHHHHHHHH HHT   TTB   EEEEEESSS EEEEEE  TT
Opt     TTT       B  TTS EEE EEEEEE  SSEEEEEEEE    TTSEEEEEEE EE     TTH HHHHHHHHHH HHS   TTB   EEEEE  SS  EEEEE  TT
796     GCLLDYVREN KDNIGSQYLL NWCVQIAKGM NYLEDRRLVH RDLAARNVLV KTPQHVKITD FGLAKLLGAE EKEYHAEGGK VPIKWMALES ILHRIYTHQS  895
5EDP     BHHHHHHHH GGG  HHHHH HHHHHHHHHH HHHHHTTEE  S   GGGEEE SSSS EEE    TT EE  SS  S EE  S     GGGS HHH HHH EE HHH
Opt      BHHHHHHHS TTT  HHHHH HHHHHHHHHH HHHHHTTEE  S   GGGEEE EETT EEE    TT EE  TT     B  S     TTTS THH HHT B  HHH
896     DVWSYGVTVW ELMTFGSKPY DGIPASEISS ILEKGERLPQ PPICTIDVYM IMVKCWMIDA DSRPKFRELI IEFSKMARDP QRYLVIQGDE RMHLPSPTDS  995
5EDP    HHHHHHHHHH HHHTTS  TT TT  HHHHHH HHHHT       TTB HHHHH HHHHHT SSG GGS  HHHHH HHHHHHHHSH HHHB  TTTT T
Opt     HHHHHHHHHH HHHTTS  TT TT  TTHHHH HHHTT       TTBTHHHHH HHHHHT SSG GGS  HHHHH HHHHHHTT G GGTB  TTTT T
996     NFYRALMDEE DMDDVVDADE YLI                                                                                1018
5EDP              TTB  GGG
Opt               SSSS TTT
```

Figure S8. Comparison of secondary structure for constructed structure. H=α-helix, B=residue in isolated β-bridge, E=extended strand, participates in β-ladder, G=3-helix (3/10helix), I=5-helix (pi helix), T=hydrogen bonded turn, S=bend, Blank=loop or irregular.

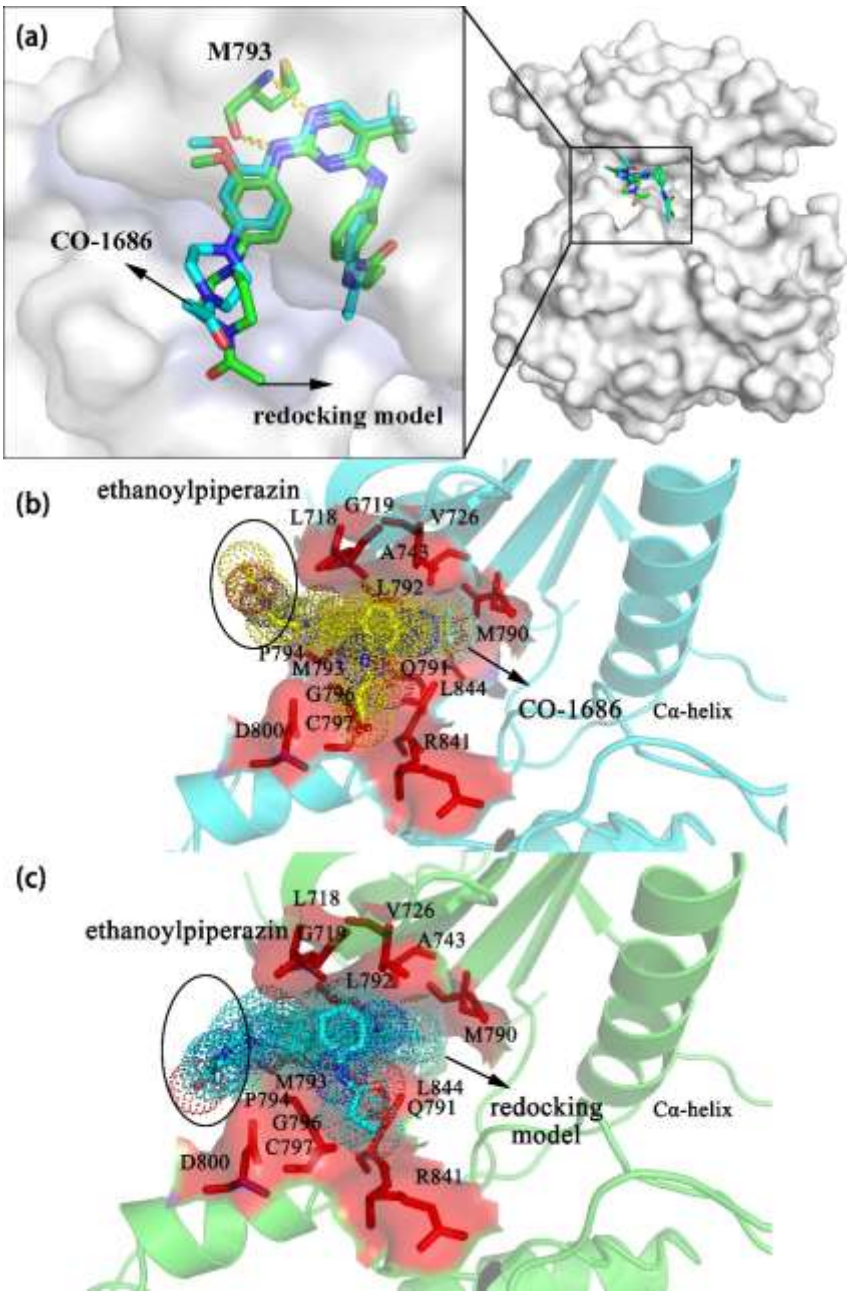

Figure S9. Redocking result for complex. (**a**) Overall comparison of crystal ligand CO-1686 (cyan stick) and redocking model (green stick). The main contributing residues (red stick and surface) of CO-1686-bound (**b**) and redocking model-bound (**c**) complexes during docking calculations.

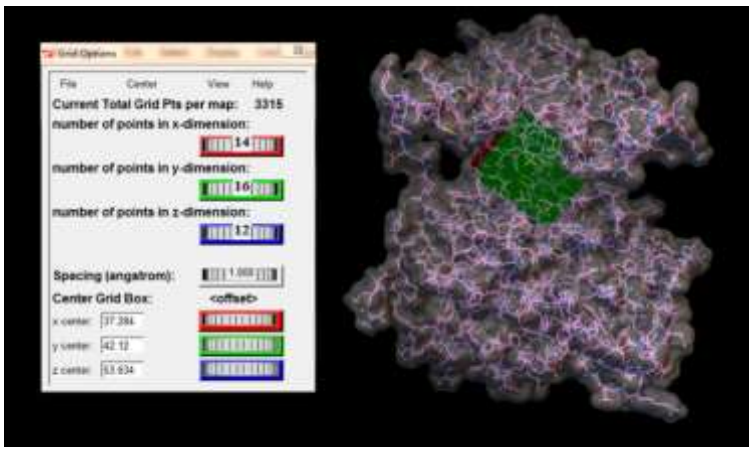

Figure S10. Docking grid for six inhibitors bound with EGFR™.