

Table S3. Predicted binding free energy values (ΔG_{bin} , kcal/mol) and binding site contacts of synthesized cytotoxic hybrids with amino acids of MEK1, TPK, and EGFR.

Compounds	ΔG_{bin}	H-Bonds and Hydrophobic Contacts in the Binding Site*
MEK1 (mean ΔG_{bin} = -9.72 kcal/mol)		
5e	-9.2	Gly79, Lys97 , Ile99, Leu115, Leu118, Ile141, Arg189 , Asp190, Cys207, Asp208, Gly210, Val211, Leu215, Ile216, Met219*, Ala220, Gly225, Arg227, Met230, Arg234 , Tyr240
5f	-8.7	Leu74, Gly75, Ala76, Gly77, Asn78, Gly79 , Val82, Lys97 , Ile99, Ile141, Ser150, Asp190*, Lys192 , Ser194 , Asn195, Leu197, Asp208*, Phe209, Leu215, Met219*, Gly210, Ile216
6a	-10.5	Lys97 , Ile99, Leu115, Leu118*, Val127, Gly128, Phe129, Ile141, Met143*, Arg189, Cys207, Asp208, Phe209, Gly210, Val211, Ser212, Leu215*, Ile216, Met219*, Ala220
6b	-9.8	Lys97, Ile99, Leu118*, Gly128, Phe129, Ile141, Met143*, Arg189*, Asp190, Asp208*, Phe209*, Gly210, Val211, Ser212, Leu215, Ile216*, Met219*, Ala220, Gly225, Met230
6c	-10.2	Lys97, Leu115, Leu118, Val127, Phe129, Ile141*, Met143, Arg189*, Asp190, Cys207, Asp208, Phe209, Gly210, Val211 , Ser212 , Leu215, Ile216*, Met219, Met230
6e	-9.9	Lys97, Ile99, Leu115, Leu118, Val127, Phe129, Ile141, Met143, Arg189 , Asp190, Cys207, Asp208, Phe209, Gly210, Ser212, Val211, Leu215, Ile216, Met219, Ala220, Gly225, Thr226, met230, Arg234 , Tyr240
TPK (mean ΔG_{bin} = -9.62 kcal/mol)		
5e	-8.6	Leu881, Gly882, Glu883, Gly884 , His885, Phe886, Gly887, Lys888, Val889*, Lys908 , Ser963, Glu966, His918, Asp1003, Arg1007 , Asn1008, Leu1010, Gly1020, Asp1021*, Gly1023, Leu1024, Asp1039, Asp1042, Pro1044
5f	-8.2	Leu881, Gly882, Glu883, Gly884*, His885, Phe886, Gly887, Val889, Lys908 , Leu910, His918, Asp921, Ser963, Lys965, Asp1003, Arg1007 , Asn1008, Leu1010, Asp1021, Gly1023, Leu1024, Asp1039, Asp1042
6a	-10.3	Leu881*, Gly882, Glu883, Gly884*, His885, Phe886, Gly887, Lys888, Val889*, Ala906*, Lys908*, Leu910, His918, Asp921, Leu922, Met956*, Asp1003, Arg1007 , Asn1008, Leu1010*, Gly1020, Asp1021*
6b	-10.3	Leu881*, Gly882, Glu883, Gly884, His885, Phe886, Gly887, Lys888, Val889*, Ala906*, Lys908*, Leu910, Asp921, Leu922, Glu925, Met956*, Phe958*, Leu959*, Asp1003, Arg1007 , Asn1008, Leu1010*, Gly1020, Asp1021*, Gly1023
6c	-10.4	Leu881*, Gly882, Glu883, Gly884, His885, Phe886, Gly887, Lys888, Val889* , Ala906*, Ly908*, Met956, Phe958*, Leu959, Asp1003, Arg1007 , Asn1008 , Leu1010*, Gly1020, Asp1021*, Gly1023, Leu1024, Asp1042
6e	-9.9	Leu881, Gly882, Glu883, Gly884, Phe886, Gly887, Lys888, Val889*, Ala906, Lys908*, Leu910, His918, Asp921, Leu922, Glu925, Phe958, Leu959, Gly962, Ser963, Lys965, Glu966, Asp1003, Arg1007 , Asn1008, Leu1010*, Asp1021*, Gly1023
EGFR (mean ΔG_{bin} = -9.53 kcal/mol)		
5e	-7.2	Leu718, Gly719, Ser720, Val726*, Ala743*, Ile744, Lys745 , Met766*, Val769, Arg776, Leu777*, Leu788, Ile789, Met790*, Gln791, Met793, Gly796, Cys797, Arg841, Leu844*, Thr854 , Asp855, Phe856, Leu858
5f	-7.4	Leu718*, Gly719, Ser720, Gly721, Val726*, Ala743, Ile744, Lys745, Met766*, Cys775, Arg776, Leu777*, Leu788*, Met790*, Gln791, Leu792, Met793, Gly796, Cys797*, Asp800, Arg841 , Asn842, Leu844*, Asp855, Phe856, Leu858
6a	-10.6	Gly719, Ser720, Val726*, Ala743*, Ile744, Lys745* , Met766, Cys775, Arg776, Leu777, Leu788, Ile789, Met790*, Met793, Cys797, Arg841, Leu844, Thr854, Asp855, Phe856*, Leu858
6b	-10.6	Gly719, Ser720, Val726*, Ala743, Ile744, Lys745* , Met766, Cys775, Arg776, Leu777, Leu788, Ile789, Met790*, Met793, Cys797 Amino Acids, Asp800, Arg841, Leu844, Thr854, Asp855, Phe856, Leu858
6c	-11.1	Val726*, Ala743*, Ile744, Lys745* , Met766, Cys775, Arg776, Leu777, Leu788, Ile789, Met790*, Cys797, Gly719, Arg841, Leu844 Thr854, Asp855, Phe856, Leu858

6e

-10.0 Gly719, Ser720, Gly721, Val726*, Ala743*, Ile744, **Lys745***, Met766, Cys775, Arg776, Leu777, Leu788*,
Ile789, Met790*, Gly796, Cys797*, Asp800, Arg841, Asn842, Leu844, **Thr854**, Asp855, Phe856, Leu858

Bolded names correspond to those amino acids involved in H-bonds with the corresponding CBHQs and CNQs.

Residues with * correspond to amino acids that interact with the ligand by any type of Pi-interactions