

a

3QAQ: 0001 SEESQAFQRLTALIGYDVTDVSNVHDELEFTRFGLVTPRMAEIVASRTP-----
 PI3K α : 0107 NREEKILNREIIGFALGMPVCFEFDMLKLPVQDFRENILLNVCKEADLRRLNSPHS

3QAQ: 0051 -KLYAMHEWWTSKP--LPEYLWKKIANNCIFIVLHRSTTS-----QTIKVSPTDT
 PI3K α : 0162 RAMYVYPENVESSEELPKHIYNKLDKQQLVVIWVIVSPNNDKQKYTLKINHDCV

3QAQ: 0098 FGATILQS-----FDVLRVCGRDEYLVGETPIKNFQ
 PI3K α : 0217 EEQVIAEAIRKKTRSMLLSSEQLKLCVLEYQGKYILKVGCCDEYFLEKYPLISQYK

3QAQ: 0129 WVRHCLKNSEEIHVVIDT-----EP-----D-PALDEVKRET--VS
 PI3K α : 0272 YIRSCIMLGRMPNLMIMAKESLYSQLEMDCFMPSYSRRISTATPYMNGETSTKS

3QAQ: 0162 LWDCDRKFRVKIRG---IDIPVLDIT-VFVEANIQHCQVLCQRRTPKPFTEEV
 PI3K α : 0327 LWVINSALRIKILCATYVNVNTRIDKIYVIRGTYHCGEPVLCNDVNTQVRVPCSNP

3QAQ: 0213 LWNVWLEFSIKIKDLPKGALENNQTY--CGKVQL--LY----YVNIILLIDHRFLI
 PI3K α : 0382 RFNENLNYDIYTPDLPRARRCSLCSVKGRKGAKEEHCPVWGNINLEFDYDITL

3QAQ: 0260 RRGEYVILHMWQISSFNALKIT----SATNPKEN-SMSTSLLDNHPVIALPKHQV
 PI3K α : 0437 VSGKMAINLWPVPHGLELLNPIGVTIGSNENKHTPCLELEFDWFSVVKFVDMSTV

3QAQ: 0310 RAEMP-----NQLR---R-QIEAIIATDPIINPLIAE
 PI3K α : 0492 IEEHANWSVSREAGFSYSHAGLSNRLARDNELFENDNEQLKATSTRDPISEIEEQ

3QAQ: 0337 DKELLWHFRYESLKHFKAYPKLFSVVKWQQQEIIVAKTYQLLARREVWQOSALDVG
 PI3K α : 0547 EKDFLWSHRHVCVTIPEIILPKLILSVKWNSTRDEVAQMYCLVK-----IWPPIKPE

3QAQ: 0392 LTMQLLDCNFSLENVRAIAVQKLES-LEDVDLHYLLQLVQAVKFPVHSAIAR
 PI3K α : 0597 QAMELLDCNYPVPMVRFVAVRCLEKYLTDDKLSQYLIQLVQVLYKYQLLNLLVVR

3QAQ: 0446 FLLKRGLRNKRIGHFLFWFLRSEIAQSRHYQREAVILEAVLFGCCTAMLDFTQ
 PI3K α : 0652 FLLKKALTNQRIGHFFFWHLKSEMHN-KTVSQRGLLLESYCRACQMYKTI-LNR

3QAQ: 0501 QVQVIEMQKVTILDIKSLSAIVSSQVISQLKQKLENLQNS---QLPESRVEFYDF
 PI3K α : 0705 QVEAMEKTIINLTDILKQEKKEETQKV--QMKFLVEQMRPDMFALQGLSILNR

3QAQ: 0553 GLKAGALAEIKCKVMASKKPKLWLEFKCAEPT-AISNETIGIIFKHGDDLQDML
 PI3K α : 0758 AHQLGNLRLEECRIMSSAKRPLWLNWENPIMSEILFQNETIIFKNGDDLQDML

3QAQ: 0607 ILQILRIMESIWEETESLDICLLPYGCIETGDKIGMIEIVKDATPIAKIQQS---T
 PI3K α : 0813 TLQIIRIMENIWQNQGLDRLMLPYGCLSIGDCVGLIEVVRNSHTIMQIQCKGGLK

3QAQ: 0659 VGGAFKDEVLNHWLKEKSPTEKFKQAAVEREVYSCAGYCVATFVLGIGDRHNDNI
 PI3K α : 0868 GALQENSHTLHQWLKDKN-KGHIYDAAIDLSTRSCAGYCVATFILGIGDRHNSNI

3QAQ: 0714 MITETGNLFHIDFG----H-----KERVPPVLTIPDFLIVMGTSGKK--TS
 PI3K α : 0922 MVKDDGQLFHIDFGHFLDHEKKKKFGYKRERVPPVLTIPDFLIVISKGAQECTKIRE

3QAQ: 0755 FQKFQDICVKAYLALRHHTNLLIILFSMMLMTGMPQITSKEDIYIRDALTVGKN
 PI3K α : 0977 FERFQEMCYKAYLAIROHANLEINLFSMMLGSGMPELQSFDDIAYIRKTLALDKT

3QAQ: 0810 EEDAKKYFLDQIEVCRDKGWTIVQFNWFL-----
 PI3K α : 1032 EQEALEYFMKOMNDAHGGWTITKMDWIEHTIKQHALN

b

3QAQ: 0001 SEESQAFQRLTALIGYDVTDVSNVHDELEFTRFGLVTPRMAEIVASRTP-----
 mTOR: 1577 AMAGESYSRAYGAMVSCMMLSELEEVIQYKLVPERREIIRQIWWVRLQGCQRIVE

3QAQ: 0048 RDPKLIYAMHPWTSKPLPEYLNKRIANN--IF-IVIHRSITSQTIKVSFDDTPG
 mTOR: 1632 DWQKILMVRSLVVSYPHEDMRTNLYASLGGKSGRLALAHKILVLLLGIDFSRQLD

3QAQ: 0100 AILQSDFVLRVCGRDEYLVGETPKNFWVRCLKNGEHIHVLDTPPP-ALD
 mTOR: 1687 HPLPTVHPQVTYAYMKNMWKSARKIDAFQHMQHFVQTMQQQAHAIAATEQQHKQ

3QAQ: 0154 EVRKETVSLWDCDRKFRVKIRGIDIPVLDLTVFVEANTIQHGQQVLCQRRTSPKPF
 mTOR: 1742 ELHKLMARCEFLKLGEWQLNLOGIN-----ESTIPKVLQYYSAAATEHDRSWYKAW

3QAQ: 0209 TEEVLWVWLEFSIKIKDLPKGALLNLQIYCKVQLLYYVNLLLIDHRFLLRRGE
 mTOR: 1791 HAWAVMFEAVLHYKHQHQARDEKKLRHASSANITNATTAATTAATATTTASTE

3QAQ: 0264 YVLHMWQISSFNADKLTSATNPDKENSMSISILLDNHIALPKHVRRAEMP-NQL
 mTOR: 1846 GSNSESEAESTENSPTSPPLQKKVTEDDLKTLMLYTVFAVQGFERSISLSRGNL

3QAQ: 0318 RKQLEAIIATDPLNPLTAEDKELLWHFRYESLK-HPKAYFKLFSVVKWGOQETVA
 mTOR: 1901 QDTRVLTTLWFQYGHWPDVNEAVEGVKAIQIDTWLQVLPOLARIDTPRPVLR

3QAQ: 0372 KTYQLIARREVVDQSALDVGELTMQLLDCNFSDEVRAIAVQKLESLE----D-DD
 mTOR: 1956 LIHQLLTIDIGRYHPQALIYPLTVASKSTTTARHAAANKILKNMCEHSNTLVQAM

3QAQ: 0422 VLHYLLQLVQAVKFPYPYHDSALARFLKRLRNKRIGHFLWFVRSEREAQS----
 mTOR: 2011 MVSEELIRVAAILWHEMWHEGLEEASRLYFGERNVKGMFEVLEPHAMMERGPQTL

3QAQ: 0473 -R-HYQCRFAVILEAYLRGGTANLH-DFTQQVVIEMLQKVTLDKSLSDADVSS
 mTOR: 2066 KETSFNQAYGRDMEAQEWARKYKSGNVKDLTCAWDLYYHWFRRISKQLPQLTS

3QAQ: 0525 QVTSQIKQKIENLQNSQLPESFRVPYDPLKAGALAIKCKVMASKKKLWLEFK
 mTOR: 2121 LELQYVSPKILMCRDLELAVPGTYDPNQPIIRIQSIAPSLQVITSKQRERKTLM

3QAQ: 0580 CADPTALSNETIGIIFKPHGDDLRLQMLILQILRIMESIWETE-S---LDICLLPF
 mTOR: 2176 GSN-----GHEFVFLKKGHEDLRLQERVMQLEGLVNTLLANDPTSLRKNLSIQRY

3QAQ: 0631 GCI STGDKIGMIEIVKDATIIAKIQOST-----VGGAF-----
 mTOR: 2226 AVIPLSTNSGLIGWPHCDILHALIRDYREKKKILLNIEHRIMLRMAPDYDHLTL

3QAQ: 0664 KD--EVLNHWLK-----EKSPTEKKEQAAVERFVYSCAGYCVATFVLG
 mTOR: 2281 MOKVEVFEHAVNNTAGDDLAKLLWLKSPSSVWFDRRTNYTRLLVMSVGYILG

3QAQ: 0705 IGDRLNDNIMIT-ETGNLFHIDFGHKERVPFV---L---TDFLFWVGTSGKKT
 mTOR: 2336 LGDRHPSNMLDRLSGKILHIDFGDCFVAMTREKPEKIFRTRLLNAMEVT

3QAQ: 0753 PHFQKFQDIQVKAYLALRHHTNLLIILFSMMLMTGMP--QLTSKEDI EYIRDALT
 mTOR: 2391 GLDGNRYRITGHTVMEVLEKESVMAVLEAFVYDPLLNWRIMDTNTKGNKSRTR

3QAQ: 0806 VGKNEEDAKKYFLDQIEVCRDKGWTVQFNWFL-----
 mTOR: 2446 TDSYSAGQSVEILLGVELGEPAAHKKTGTTVPESIHSFIGDGLVKPEALNKKAIQ

Figure S1. Multi-sequence alignment of PI3Ka, mTOR and the template PI3K γ (a: PI3Ka and PI3K γ ; b: mTOR and PI3K γ).

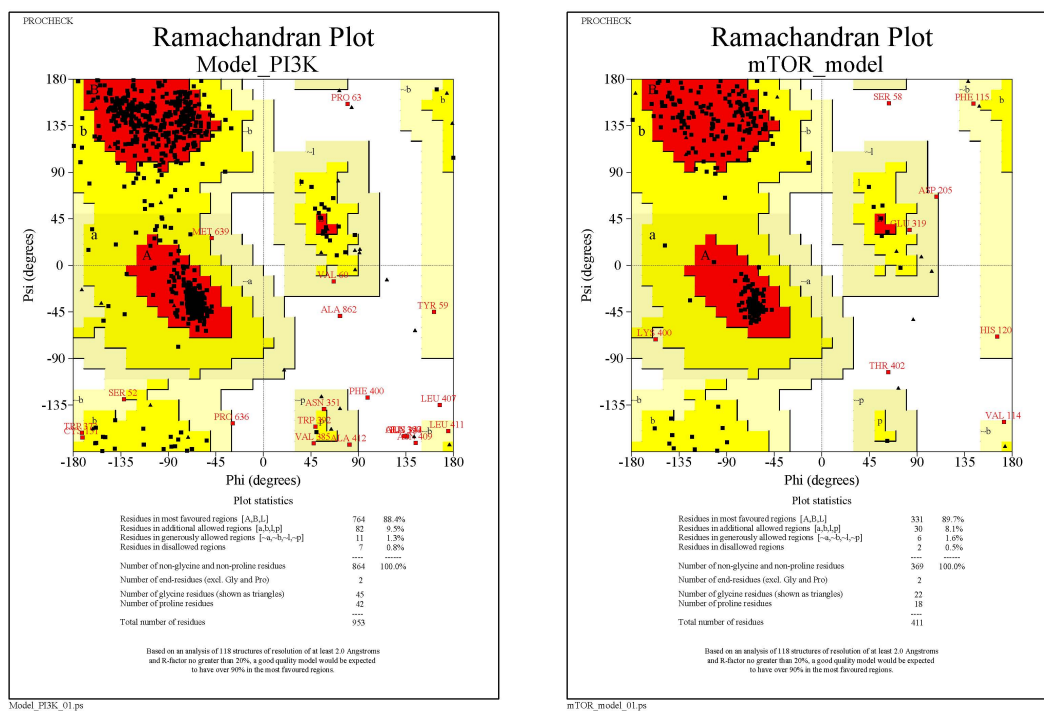


Figure S2. Ramachandran plot of homology models by PROCHECK



Figure S3. Superimposition of homology models and the template (green: PI3K γ ; yellow: PI3K α ; blue: mTOR).

Table S1. Binding free energy contribution of the key binding-site residues calculated from the binding energy decomposition (kcal/mol).

Compound **25** with mTOR

Residue	ΔE_{vdw}	ΔE_{ele}	ΔG_{GB}	ΔG_{SA}	ΔG_{bind}
L2185	-0.871	-0.106	0.051	-0.14	-1.066
K2187	-0.217	2.451	-2.215	-0.093	-0.074
D2195	-0.098	-1.932	0.281	-0.018	-1.767
Y2225	-1.151	-0.649	-0.33	-0.29	-2.42
I2237	-0.87	0.049	-0.114	-0.187	-1.122
W2239	-6.34	-0.262	-0.282	-0.595	-7.479
V2240	-1.494	-4.4	0.808	-0.256	-5.342
P2241	-0.761	-1.154	0.531	-0.106	-1.49
C2243	-1.883	-2.362	-0.018	-0.264	-4.527
M2345	-1.493	0.056	-0.062	-0.172	-1.671
I2356	-2.927	-0.707	-0.113	-0.309	-4.056
D2357	-1.226	-0.934	-0.89	-0.215	-3.265

Compound **65** with mTOR

Residue	ΔE_{vdw}	ΔE_{ele}	ΔG_{GB}	ΔG_{SA}	ΔG_{bind}
Q2161	-0.149	-0.253	0.262	-0.006	-0.146
I2163	-0.014	0.047	-0.05	0	-0.017
T2164	-0.004	-0.05	0.05	0	-0.004
K2187	-0.926	3.075	-2.051	-0.259	-0.161
E2190	-0.091	1.673	-1.588	-0.002	-0.008
D2195	-0.367	0.112	-0.614	-0.16	-1.029
Y2225	-1.769	-1.041	0.634	-0.345	-2.521
V2227	-0.291	-0.081	0.028	-0.073	-0.417
I2237	-1.739	-0.218	0.051	-0.22	-2.126
W2239	-5.659	-0.825	0.698	-0.509	-6.295
V2240	-1.087	-4.026	0.687	-0.271	-4.697
P2241	-0.189	-2.136	-0.12	-0.037	-2.482
A2248	-0.29	0.014	-0.142	-0.086	-0.504
M2345	-1.75	-0.091	0.081	-0.236	-1.996
I2356	-2.996	-0.065	-0.328	-0.322	-3.711
D2357	-2.35	3.565	-3.11	-0.26	-2.155
F2358	-0.337	0.069	0.134	-0.047	-0.181

Compound **25** with PI3K α

Residue	ΔE_{vdw}	ΔE_{ele}	ΔG_{GB}	ΔG_{SA}	ΔG_{bind}
I800	-0.853	-0.148	0.089	-0.168	-1.08
K802	-0.408	2.113	-1.772	-0.159	-0.226
D810	-0.124	-2.269	0.258	-0.149	-2.284
Y836	-1.179	-1.784	1.04	-0.309	-2.232
I848	-1.285	-0.012	-0.078	-0.204	-1.579
V850	-4.902	0.201	-0.314	-0.195	-5.21
V851	-1.545	-4.037	0.956	-0.228	-4.854
R852	-0.656	-0.401	-0.005	-0.107	-1.169
S854	-0.485	-0.419	0.037	-0.208	-1.075
M922	-1.626	0.086	-0.099	-0.186	-1.825

I932	-2.957	-0.846	-0.123	-0.297	-4.223
D933	-1.795	-0.481	-1.278	-0.228	-3.782

Compound **65** with PI3K α

Residue	ΔE_{vdw}	ΔE_{ele}	ΔG_{GB}	ΔG_{SA}	ΔG_{bind}
R770	-1.062	-4.156	2.312	-0.286	-3.192
M772	-0.989	-0.292	0.306	-0.325	-1.3
S773	-1.609	-1.112	0.164	-0.254	-2.811
K802	-0.879	-6.857	3.696	-0.243	-4.283
D805	-0.114	2.661	-2.346	-0.003	0.198
D810	-0.657	-2.89	2.034	-0.169	-1.682
Y836	-1.785	0.246	-0.233	-0.33	-2.102
C838	-0.345	0.109	-0.158	-0.073	-0.467
I848	-1.839	0.248	-0.317	-0.275	-2.183
V850	-1.769	-0.694	-0.409	-0.217	-3.089
V851	-2.034	-3.967	0.578	-0.243	-5.666
R852	-0.166	-2.804	-0.825	-0.033	-3.828
Q859	-1.086	-0.693	0.231	-0.246	-1.794
M922	-1.761	0.269	-0.288	-0.205	-1.985
I932	-2.825	0.057	-0.485	-0.293	-3.546
D933	-2.171	4.378	-3.625	-0.253	-1.671
F934	-0.233	0.161	-0.051	-0.019	-0.142