Supplementary Information

In Silico Studies of Tumor Targeted Peptide- Conjugated Natural Products for Targeting Over-Expressed Receptors in Breast Cancer Cells using Molecular Docking, Molecular Dynamics and MMGBSA Calculations

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Table S1. Binding Energies based on FireDock Analysis of each of the ligands with ERα; PPARα and EGFR

(a) ERα

	Polyphenol	**Polyphenol**	**Polyphenol**	**Polyphenol**	
Peptide Sequence Conjugated	Carnosic Acid	Chlorogenic Acid	Gallic Acid	Rosmarinic Acid	Neat Peptide (unconjugated)
YHWYGYTPQN (original)	-64.23	-66.23	-73.15	-73.36	-61.63
FHWYGYTPQN (Mut1)	-57.61	-67.98	-73.56	-62.90	-68.13
Y**I**WYGYTPQN (Mut2)	-79.12	-73.56	-70.11	-66.24	-64.23
YHWYGYT**H**QN (Mut3)	-63.70	-78.09	-64.63	-69.61	-70.49
YHWYGYTPQ**D** (Mut4)	-68.57	-70.26	-80.98	-42.37	-70.45

(b) PPARα

	Polyphenol	**Polyphenol**	**Polyphenol**	**Polyphenol**	
Peptide Sequence Conjugated	Carnosic Acid	Chlorogenic Acid	Gallic Acid	Rosmarinic Acid	Neat Peptide (unconjugated)
YHWYGYTPQN (original)	-56.18	-61.56	-59.00	-57.70	-49.68
FHWYGYTPQN (Mut1)	-67.12	-55.23	-62.95	-57.97	-49.55
Y**I**WYGYTPQN (Mut2)	-48.47	-55.14	-59.82	-52.45	-63.27
YHWYGYT**H**QN (Mut3)	-65.81	-57.02	-58.52	-60.65	-52.99
YHWYGYTPQ**D** (Mut4)	-59.40	-62.66	-61.28	-54.42	-54.18

(c) EGFR

	Polyphenol	**Polyphenol**	**Polyphenol**	**Polyphenol**	
Peptide Sequence Conjugated	Carnosic Acid	Chlorogenic Acid	Gallic Acid	Rosmarinic Acid	Neat Peptide (unconjugated)
YHWYGYTPQN (original)	-59.96	-63.18	-57.78	-52.97	-60.12
FHWYGYTPQN (Mut1)	-64.38	-63.59	-61.86	-62.51	-61.48
Y**I**WYGYTPQN (Mut2)	-62.73	-60.99	-67.08	-56.35	-60.53
YHWYGYT**H**QN (Mut3)	-69.03	-65.33	-65.84	-66.65	-55.70

YHWYGYTPQ**D** (Mut4)	-61.12	-57.41	-60.71	-72.15	-55.23

Table S2. Peptide Interactions with ERα Using PLIP

a. Neat Peptide (Y-H-W-Y-G-Y-T-P-Q-N)

Hydrogen Bonding		**Hydrophobic Interactions**		**Stacking Interactions**		**Salt Bridges**	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS377B	2.79	GLU432D	3.92	TYR537A	4.97	HIS516D	5.34
GLU380B	2.76	THR460B	3.78			LYS520D	3.59
GLU380B	2.14	SER463B	3.77				
ASP426D	2.95	MET522B	3.81				
LEU462B	2.15	TYR537B	3.68				
SER463B	3.05	TYR537B	3.62				
SER464B	2.63	TYR537B	3.49				
HIS516D	3.6	ASP538A	3.76				
HIS516D	2.14						
SER518B	3.07						
SER518B	2.76						
ASN519B	2.9						
LYS520D	3.06						
TYR526B	2.33						
VAL534A	1.92						
SER536A	2.26						
ASP538A	2.65						
ASP538A	2.28						

S2b. Mutation 1 (F-H-W-Y-G-Y-T-P-Q-N)

Hydrogen Bonding		**Hydrophobic Interactions**		**Stacking Interactions**		**Cation Interactions**		**Salt Bridges**	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS377B	2.59	HIS377B	3.5	-	-	-	-	-	-
ARG412D	2.39	VAL422D	3.75						
GLY420D	2.77	GLU432D	3.83						
GLU423D	2.7	TYR526A	3.74						
THR460B	2	TYR526A	3.46						
SER464B	2.95	LYS531A	3.72						
ASN532A	2.46	VAL534A	3.97						
PRO535A	2.13	TYR537A	3.7						
SER536A	2.17	TYR537B	3.61						
SER536A	1.84	TYR537B	3.63						
SER536A	2.48	ASP538A	3.75						
SER536A	3.46								
ASP538A	2.06								
ASP538A	3.23								
GLU542A	2.53								

S2c. Mutation 2 (Y-I-W-Y-G-Y-T-P-Q-N) with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS373A	2.91	GLU423D	3.61	TYR526A	4.95	-	-	-	-
HIS373B	3.01	THR460B	3.52	TYR537A	4.22				
HIS377A	3.24	VAL534A	3.54						
GLU380B	2.77	TYR537A	3.99						
GLU380B	2.15	TYR537B	3.45						
GLU380B	1.83								
TRP383B	2.69								
ARG412D	2.5								
GLU423D	2.19								
ASP426D	2.03								
VAL533A	3.14								
TYR537A	2.26								
TYR537B	2.37								
ASP538B	2.65								

S2d. Mutation 3 (Y-H-W-Y-G-Y-T-H-Q-N) with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
THR371B	3.26	VAL422D	3.68	TYR537A	5.06	ARG412D	5.36	-	-
ARG412D	2.83	GLU423D	3.64						
GLU419D	2.6	ASP426D	3.77						
ASP426D	2.29	LEU462B	3.68						
LEU462B	2.6	SER463B	3.72						
MET528A	2.26	TYR526A	3.39						
LYS531A	2.76	TYR537A	3.83						
VAL533A	2.54	TYR537B	3.66						
VAL534A	2.74	TYR537B	3.84						
SER536A	2.26	TYR537B	3.63						
TYR537A	2.63	LEU 514A	3.84						
ASP538A	2.55								
ASP538A	3.01								
ASP538A	2.15								
ASP538B	3.73								
LEU539A	3.6								
GLU542A	2.66								
GLU542A	2.65								

S2e. Mutation 4 (Y-H-W-Y-G-Y-T-P-Q-D) with ER

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS373A	3.51	GLU423C	3.73	Tyr 537B	4.81	LYS520C	3.58	ARG515A	5.03
HIS373B	2.27	ASP426C	3.69					HIS516C	4.16
HIS377A	2.35	ASN519A	3.99					LYS520C	5.47
GLU380A	3.45	LYS520C	3.89						
GLU380A	3.37	MET522A	3.83						
GLU423C	1.91	TYR526A	3.79						
THR460A	2.26	TYR526B	3.47						
THR460A	2.45	VAL534B	3.38						
GLU523C	2.9	TYR537A	3.48						
TYR526A	2.8	TYR537A	3.96						
TYR526A	3.02	TYR537A	3.75						
LYS531B	2.43								
TYR537A	3.05								
ASP538A	3.08								

Table S3. Polyphenol-Peptide (Y-H-W-Y-G-Y-T-P-Q-N) Conjugate Interactions with ERα

a. Chlorogenate-Pep

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS373A	2.23	GLU380B	3.65	TYR526A	4.85	ARG412D	4.47	HIS516D	5.23
HIS377B	2.18	VAL422D	3.9	TYR537A	4.2				
GLU380A	2.4	GLU423D	3.96						
GLU380A	2.83	LEU462B	3.75						
GLU380B	2.56	SER463B	3.41						
ARG412D	2.99	LYS531A	3.55						
GLU423D	2.86	VAL534A	3.91						
ASP426D	3.09	VAL534A	3.53						
ASN519B	2.23	TYR537A	3.84						
LYS520D	2.1	TYR537B	3.34						
TYR526A	2.45								
TYR526B	2.86								
TYR526B	2.88								
TYR526B	3.05								
MET528A	3.11								
VAL533A	2.72								
VAL534A	3.11								
SER536A	3.23								
TYR537A	2.31								
ASP538A	3.66								

S3b. Carnosate-Pep

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS377B	3.45	ASP426D	3.53	TYR526A	4.58	-	-	-	-
ARG412D	2.03	SER463B	3.12	TYR526A	5.15				
ARG412D	2.25	TYR526A	3.88	TYR526A	3.94				
GLU423D	2.85	ASN532A	3.71						
THR460B	2.76	VAL534A	3.79						
LEU462B	3.22	VAL534A	3.59						
LEU462B	2.4	TYR537A	3.69						
ASN532A	2.75	TYR537B	3.63						
VAL533A	2.67	TYR537B	3.4						
VAL534A	3.02								
SER536A	2.44								
5SER36A	3.11								

S3c. Gallate-Pep

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS377B	2.81	THR465B	3.44	-	-	ARG412D	4.94	-	-
ARG412D	3.44	TYR537A	3.95						
ARG412D	2.13	LEU539A	3.69						
ARG412D	3.29	LEU539A	3.5						
GLU423D	2.22	LEU539A	3.84						
GLU423D	2.5	LEU541A	3.6						
PHE461B	3.28	GLU542A	3.73						
LEU462B	3.39								
SER464B	3.35								
SER464B	3.21								
TYR526B	2.98								
ASN532A	2.49								
SER536A	2.1								
SER536A	2.94								
ASP538A	3.14								
ASP538A	2.94								

S3d. Rosmarinate-Pep

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
GLU380A	2.19	VAL422D	3.87	TYR526A	4.91	-	-	HIS377B	5.24
GLU380B	3.05	VAL422D	3.47	TYR537A	4.29			LYS520D	3.45
CYS381B	2.17	GLU423D	3.36						
TRP383B	1.94	THR460B	3.75						
ARG412D	2.53	LEU462B	3.44						
MET427D	3.54	TYR526A	3.63						
THR460B	3.39	TYR526A	3.67						
HIS516D	2.34	TYR537A	3.43						
ASN519B	3.3	TYR537B	3.44						
LYS520D	3.31	TYR537B	3.68						
TYR526B	1.99								
ASN532A	2.86								
VAL534A	2.16								
VAL534A	2.25								
SER536A	2.27								
TYR537A	1.99								
TYR537B	3.08								
ASP538A	3.12								

Table S3e. Chlorogenate-Mut1 (F-H-W-Y-G-Y-T-P-Q-N) conjugate with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
THR371B	3.01	GLU423D	3.6	TYR526A	4.87	HIS373B	4.65	-	-
HIS373B	3.09	ASP426D	3.82	TYR537B	4.29				
ASP374B	2.22	TYR526A	3.88						
GLU380A	2.48	VAL534A	3.56						
GLU380B	2.67	TYR537A	3.65						
TRP383A	2.2	TYR537B	3.37						
ARG412D	2.84	ASP538A	3.73						
ASP426D	2.02	GLU542A	3.74						
LEU462B	2.79								
SER468B	2.53								
TYR526A	2.44								
TYR526A	2.41								
ASN532A	3.45								
VAL534A	2.53								
VAL534A	2.53								
SER536A	2.95								
SER536A	2.75								
TYR537A	2.38								
ASP538A	2.24								
ASP538A	3.02								

S3f. Carnosate--Mut1 (F-H-W-Y-G-Y-T-P-Q-N) conjugate with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS377A	2.34	VAL422C	3.84	TYR526A	4.69	-	-	HIS377A	5.34
HIS377B	3.21	TYR526A	3.9						
ARG412C	2.78	TYR526B	3.57						
ARG412D	2.94	LYS531B	3.61						
GLU423C	2.23	TYR537B	3.99						
GLU423C	3.57	ASP538A	4						
LEU462A	2.46								
ASN519A	2.61								
TYR526A	2.55								
SER536A	3.25								
SER536B	3.25								
SER536B	3.42								
ASP538B	3.43								

S3g. Gallate-Mut1 (F-H-W-Y-G-Y-T-P-Q-N) conjugate with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS373A	2.09	GLU423C	3.62	TYR526B	4.86	-	-	HIS516C	4.82
GLU380A	2.59	GLU423C	3.83					LYS520C	3.49
TRP383A	2.28	THR460A	3.7						
ARG412C	3.26	MET522A	3.42						
GLU419C	2.36	TYR526A	3.64						
HIS516C	2.01	TYR526B	3.83						
SER518A	2.9	VAL534B	3.83						
ASN519A	2.48	VAL534B	3.62						
LYS520C	3.26	TYR537B	3.77						
LEU525B	2.92								
TYR526A	2.58								
TYR526A	2.55								
ASP538B	2.33								

S3h. Rosmarinate- Mut1 (F-H-W-Y-G-Y-T-P-Q-N) conjugate with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS373B	2.63	ASP426D	3.67	TYR526A	4.8	-	-	-	-
HIS377B	3.16	THR460B	3.83						
GLU380A	2.51	TYR526A	3.81						
GLU380B	1.87	TYR526A	3.61						
TRP383B	2.72	LYS531A	3.52						
GLU423D	2.93	VAL534A	3.55						
GLU423D	2.47	VAL534A	3.37						
GLU423D	2.62	VAL534B	3.75						
ASN519B	3.2	TYR537A	3.4						
LYS520D	2.15	TYR537A	3.83						
LEU525A	2.52	TYR537B	3.64						
TYR526B	2.28								
TYR526B	2.29								
MET528A	3.25								
TYR537A	2.19								
TYR537B	3.19								
ASP538A	2.71								
ASP538A	2.92								
ASP538A	2.77								
ASP538B	2.92								

Table S3i. Chlorogenate-Mut 2 (Y-I-W-Y-G-Y-T-P-Q-N) Conjugate with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS373B	2.17	GLU380B	3.66	TYR526B	3.87	LYS520C	3.51	LYS520C	5.49
HIS377A	3.04	ASP426C	3.65						
GLU380A	3.11	ASN519A	3.88						
GLU423C	1.97	LYS520C	3.88						
ASP426C	3.31	TYR526A	3.78						
THR460A	2.42	TYR526B	3.78						
THR460A	2.73	VAL534A	3.75						
THR460A	3.52	TYR537A	3.86						
PHE461B	2.7	TYR537A	4						
HIS516C	3.43	TYR537B	3.45						
ASN519A	2.13	TYR537B	3.3						
LYS520D	2.4								
TYR526B	3.48								
TYR526B	3.19								
SER536A	2.99								
ASP538A	2.08								
ASP538A	2.17								

S3j. Carnosate-Mut 2 (Y-I-W-Y-G-Y-T-P-Q-N) Conjugate with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS377A	2.96	TYR526A	3.74	-	-	-	-	ARG412C	4.45
GLU380B	3.23	TYR526A	3.92						
TRP383A	2.94	VAL534A	3.66						
ARG412C	3.44	TYR537A	3.67						
GLU423C	2.32	TYR537B	3.5						
GLU423C	3.69	TYR537B	3.27						
GLU423C	3.52								
THR460A	2.15								
THR460A	3.18								
THR460A	2.83								
LYS520C	2.65								
LYS531B	3.41								
LYS531B	2.15								
SER536B	2.34								
SER536B	2.18								
LEU539B	3.56								

S3k. Gallate-Mut2 (Y-I-W-Y-G-Y-T-P-Q-N) Conjugate with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS373B	3.32	GLU380A	3.95	TYR537A	4.25	-	-	-	-
HIS377B	2.6	VAL422D	3.25						
GLU380A	2.02	GLU423D	3.65						
ARG412D	2.03	TYR526A	3.62						
ARG412D	1.92	TYR526A	3.68						
ARG412D	2.19	LYS531A	3.83						
PHE461B	2.06	ASN532A	3.52						
SER464B	2.84	VAL534A	3.84						
HIS516C	2.1	TYR537A	3.38						
LYS520C	2.52	TYR537A	3.88						
TYR526A	2.78	LEU539A	3.62						
MET528A	3.13								
MET528A	2.17								
SER536A	2.69								
SER536A	3.46								
TYR537A	2.03								
ASP538A	2.45								
ASP538A	2.78								
ASP538A	2.52								

S3l. Rosmarinate-Mut2 (Y-I-W-Y-G-Y-T-P-Q-N) Conjugate with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
CYS381B	3.25	ASP426D	3.43	-	-	-	-	HIS377A	4.89
GLU423D	2.43	THR460B	3.99						
GLU423D	2.01	TYR526B	3.97						
TYR459B	3.19	TYR537B	3.67						
PHE461B	3.3	ASP538A	3.92						
LEU462A	2.47								
LEU462B	1.83								
LEU462B	3.6								
SER463B	3.06								
HIS516D	3.52								
LYS520D	2.1								
TYR526B	2.38								
TYR526B	2.31								
TYR526B	2.31								
SER536A	3.02								
SER536B	2.39								
TYR537B	3								
ASP538A	3.51								
ASP538B	2.01								

Table S3m. Chlorogenate-Mut3 (Y-H-W-Y-G-Y-T-H-Q-N) Conjugates with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
GLU380A	3.08	VAL422D	3.51	TYR526A	4.7	-	-	HIS377B	4.93
ARG412C	2.48	VAL534A	3.85	TYR526B	4.99				
ARG412D	2.07	VAL534A	3.36						
GLU423D	3.4	VAL534B	3.42						
ASP426C	2.79	TYR537A	3.68						
ASP426C	2.09	TYR537B	3.49						
ASP426D	3.08								
THR460A	1.88								
LEU462B	2.83								
TYR526A	2.88								
LYS531A	2.51								
LYS531B	2.55								
SER536A	3.05								
SER536A	2.53								
ASP538A	3.59								

Table S3n. Carnosate-Mut3 (Y-H-W-Y-G-Y-T-H-Q-N) Conjugates with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
GLU380A	2.77	HIS377A	3.63	-	-	-	-	ARG412D	4.6
ARG412D	3.06	VAL422D	3.56						
ARG412D	2.82	GLU423C	3.63						
GLU423D	2.49	GLU423D	3.42						
THR460B	2.08	TYR526A	3.96						
TYR526A	2.5	TYR526A	3.97						
ASN532A	3.69	VAL534A	3.33						
VAL534A	3.26	VAL534A	3.44						
SER536A	2.55	TYR537A	3.59						
SER536A	2.65	TYR537A	3.5						
TYR537B	3.13	TYR537A	3.69						
ASP538A	2.36	TYR537B	3.35						
		ASP538A	3.92						

Table S3o. Gallate-Mut 3 (Y-H-W-Y-G-Y-T-H-Q-N) Conjugates with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS377A	2.42	TYR537A	3.36	TYR537A	5.13	-	-	ARG412C	4.26
GLU380A	2.42	TYR537B	3.68						
GLU380A	3.3	TYR537B	3.54						
GLU380B	2.67	LEU539B	3.65						
ARG412C	2.42								
GLU423C	1.72								
LEU462A	2.31								
SER463A	3.53								
VAL533B	2.86								
SER536B	3.06								
SER536B	2.55								
TYR537A	2.5								
TYR537B	2.55								
ASP538A	2.73								
ASP538B	3.09								
ASP538B	2.8								

Table S3p. Rosmarinate-Mut 3 (Y-H-W-Y-G-Y-T-H-Q-N) Conjugates with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS373A	2.31	GLU380A	3.57	TYR526B	5.12	-	-	HIS377A	4.61
HIS373B	2.33	VAL534B	3.81	TYR537A	4.24				
GLU380B	2.46	TYR537A	3.71						
GLU380B	3.03	TYR537B	3.56						
ARG412C	2.36								
VAL422C	3.28								
GLU423C	2.21								
GLU423C	2.46								
GLU423C	2.99								
THR460B	2.23								
HIS516C	2.47								
HIS516D	2.26								
LYS520C	2.94								
TYR526A	2.94								
TYR526A	3.23								
TYR537B	2.69								
ASP538A	1.89								
ASP538A	3.05								
ASP538B	3								

Table S3q. Chlorogenate-Mut 4 (Y-H-W-Y-G-Y-T-P-Q-D) Conjugates with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
THR371B	3	VAL422C	3.5	-	-	-	-	HIS377A	4.19
HIS373B	2.87	GLU423D	3.95					HIS377A	5.09
ASP374B	2.35	GLU423D	3.44						
ASP374B	2.88	TYR526B	3.81						
GLU380A	3.08	TYR526B	3.77						
GLU380A	2.01	LYS531B	3.88						
ARG412C	2.58	VAL534B	3.46						
ARG412D	2.8	VAL534B	3.49						
ARG412D	2.59	TYR537B	3.56						
GLU423D	2.82	ASP538B	3.96						
THR460A	2.2	LEU541A	4						
TYR526B	2.58	GLU542A	3.66						
LYS531B	3.09								
SER536B	2.05								
SER536B	2.14								
TYR537B	2.43								
ASP538A	2.63								
ASP538B	2.16								

Table S3r. Carnosate-Mut 4 (Y-H-W-Y-G-Y-T-P-Q-D) Conjugates with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
ARG412D	3.35	GLU423D	3.15	-	-	ARG412D	4.74	-	-
GLU423D	2.09	ASP426D	3.21						
GLU423D	2.67	THR460B	3.82						
GLU423D	2.36	LEU462B	3.96						
HIS516D	2.29	TYR537A	3.63						
LYS520D	2.24	TYR537B	3.4						
TYR526A	2.48	TYR537B	3.71						
TYR526B	2.47	LEU539A	3.54						
TYR526B	3.22	LEU539A	3.97						
SER536A	2.26								
SER536A	3.53								
TYR537A	2.47								
TYR537B	2.93								
ASP538A	3.65								

Table S3s. Gallate- Mut 4 (Y-H-W-Y-G-Y-T-P-Q-D) Conjugates with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
GLU380A	3.31	GLU380A	3.42	TYR537B	4.12	HIS516C	4.48	-	-
GLU380B	3.54	VAL422D	3.57						
ARG412D	3.25	GLU423C	3.98						
ASP426C	3.01	TYR526A	3.94						
ASP426D	3.49	TYR526A	3.79						
MET427D	3.59	VAL534A	3.44						
THR460A	2.64	VAL534A	3.63						
THR460A	2.61	TYR537A	3.37						
LEU462B	2.55	TYR537A	3.73						
SER463B	2.95	TYR537B	3.53						
HIS516C	2.54	TYR538A	3.53						
LYS520C	2.6								
TYR526A	2.04								
LYS531A	2.5								
LYS531A	2.11								
SER536A	3.14								
ASP538A	2.65								
ASP538A	2.45								
GLU542A	2.67								

Table S3t. Rosmarinate-Mut 4 (Y-H-W-Y-G-Y-T-P-Q-D) Conjugates with ERα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS377A	2.92	GLU380B	3.75	HIS516D	4.6	HIS377B	5.45	ARG412D	4.86
CYS381B	2.22	GLU423D	3.66	TYR537A	4.22			LYS520D	3.84
TRP383B	2.67	THR460B	3.77						
ARG412D	2.63	SER463B	3.36						
ARG412D	2.21	TYR526B	3.84						
ARG412D	2.26	VAL534A	3.6						
ASP426D	3	TYR537A	3.91						
ASP426D	2.54	TYR537B	3.32						
HIS516D	2.55	TYR537B	3.91						
SER518B	2.73								
ASN519B	1.97								
TYR526B	3.27								
ASN532A	2.15								
ASN532A	3.4								
VAL534B	2.46								
PRO535B	2.98								
SER536A	2.86								
SER536A	2.19								
SER536A	1.91								
ASP538A	2.36								
ASP538A	3.46								
ASP538A	2.62								

Table S4. **Peptide Interactions with PPARα Using PLIP**

(a) Pep (Y-H-W-Y-G-Y-T-P-Q-N)

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
ALA256A	3.25	MET220A	3.62	-	-	-	-	-	-
LYS257A	2.35	ILE241A	3.57						
HIS274A	2.43	LYS257A	3.57						
HIS274A	2.2	THR279A	3.28						
THR279A	2.81	VAL281A	3.59						
LEU331A	2.53	LEU321A	3.74						
ALA333A	2.09	VAL332A	3.75						
TYR334A	2.87	VAL332A	3.99						
TYR334A	2.77	ALA333A	3.7						
GLY335A	2.84	TYR334A	3.61						
ALA455A	2.76								
HIS457A	3.23								

(b) Mutation 1 (**F**-H-W-Y-G-Y-T-P-Q-N)

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LEU254A	2.44	MET220A	3.89	TYR334A	5.05	-	-	-	-
ALA256A	2.4	ILE241A	3.54						
LYS257A	2.61	LYS257A	3.68						
HIS274A	2.27	THR279A	3.43						
THR279A	2.68	THR283A	3.82						
THR283A	2.57	MET320A	3.91						
THR285A	2.1	LEU321A	3.97						
ALA333A	2.18	VAL324A	3.53						
TYR334A	3.23	VAL324A	3.31						
GLY335A	2.71	VAL332A	3.91						
HIS457A	3.16	VAL332A	3.77						
HIS457A	2.36	ALA333A	3.68						
		TYR334A	3.6						

(c) Mutation 2 (Y-**I**-W-Y-G-Y-T-P-Q-N)

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
TYR214A	2.27	MET220A	3.81	TYR334A	4.5	-	-	-	-
LYS222A	3.29	ILE241A	3.78						
LEU254A	2.72	LYS257A	3.72						
LEU254A	2.31	THR279A	2.92						
ALA256A	2.37	GLU282A	3.36						
THR279A	2.26	GLU282A	3.88						
GLU282A	2.01	MET320A	3.56						
THR283A	3.59	LEU321A	3.78						
SER323A	2.17	VAL332A	3.8						
ALA333A	2.16	ALA333A	3.38						
TYR334A	2.35	TYR334A	3.69						
TYR334A	2.3								
TYR334A	2.33								
GLY335A	3.08								

(d) **Mutation 3 (Y-H-W-Y-G-Y-T-H-Q-N)**

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
ASN217A	2.66	MET220A	3.75	-	-	-	-	-	-
ASN219A	2.7	ILE241A	3.75						
ASN219A	2.25	VAL255A	3.97						
MET220A	2.33	VAL255A	3.69						
HIS274A	2.92	THR283A	3.95						
THR279A	2.3	THR285A	3.76						
THR279A	2.76	GLU286A	3.84						
GLU282A	2.55	GLU289A	3.84						
GLU282A	3.37	VAL324A	3.49						
THR283A	2.45	ALA333A	3.44						
GLU286A	2.73	TYR334A	3.45						
GLU289A	3.41	TYR334A	3.98						
ALA333A	2.08	TYR334A	3.69						
TYR334A	3.14								
TYR334A	2.38								
TYR334A	3.44								

(e) **Mutation 4 (Y-H-W-Y-G-Y-T-P-Q-D)**

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LYS224A	2.33	LYS224A	3.88	-	-	-	-	LYS224A	4.34
SER234A	2.5	ASN236A	3.87						
THR253A	2.2	ILE241A	3.72						
HIS274A	2.13	LEU254A	3.61						
THR279A	3.15	THR279A	3.6						
THR283A	2.28	VAL324A	3.5						
ALA333A	2.07	ALA333A	3.48						
TYR334A	3.2	TYR334A	3.48						
TYR334A	3.23	TYR334A	3.87						
TYR334A	2.25	TYR334A	3.72						

Table S5. PLIP results for Polyphenol peptide conjugates with PPARα

S5. (a) Chlorogenate-Y-H-W-Y-G-Y-T-P-Q-N (original peptide).

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LYS216A	2.04	VAL255A	3.65	TYR334A	3.96	-	-	-	-
ASN219A	2.32	VAL255A	3.72	TYR334A	3.69				
LEU254A	2.16	LYS257A	3.31						
CYS278A	2.74	LEU258A	3.77						
THR279A	3.28	THR279A	3.58						
THR279A	3.68	VAL281A	3.8						
THR279A	2.26	GLU282A	3.9						
THR279A	2.2	GLU282A	3.22						
GLU282A	2.11	VAL332A	3.49						
GLU282A	1.98	VAL332A	3.3						
GLU282A	1.9	TYR334A	3.68						
GLU282A	3.23	ILE339A	3.88						
2GLU82A	2.49	ILE339A	3.97						
THR285A	3.18	LEU693B	3.78						
TYR334A	3.25								
TYR334A	2.22								
GLU696B	3.03								

S5. (b) Carnosate- Y-H-W-Y-G-Y-T-P-Q-N (original peptide).

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LYS224A	2.41	VAL255A	3.62	TYR334A	4.08	-	-	-	-
LYS224A	2.21	VAL255A	3.78						
THR279A	2.33	VAL281A	3.64						
GLU282A	2.89	GLU282A	3.89						
GLU282A	2.87	THR285A	3.43						
TYR334A	3.35	GLU286A	3.74						
ASN336A	1.96	GLU289A	3.74						
ASN336A	2.47	TYR334A	3.8						
		TYR334A	3.78						

S5. (c) Gallate- Y-H-W-Y-G-Y-T-P-Q-N (original peptide).

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
ASN219A	3.13	ASN219A	3.44	-	-	-	-	-	-
LYS224A	2.2	LYS224A	3.47						
SER234A	3.02	ILE228A	3.68						
ASN236A	3.38	ASN236A	3.7						
ASN236A	2.38	LEU254A	3.87						
LYS257A	2.7	VAL255A	3.27						
ILE272A	2.54	LYS257A	3.86						
ILE272A	3.31	GLU282A	3.77						
CYS275A	3.22	VAL332A	3.77						
THR279A	3.35	ALA333A	3.41						
GLU282A	1.99	TYR334A	3.49						
ALA333A	2.24	TYR334A	3.54						
ASN336A	2.35	ILE339A	3.85						
ASN336A	2.91								

S5. (d) Rosmarinate-Y-H-W-Y-G-Y-T-P-Q-N (original peptide).

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
ASN219A	2.84	MET220A	3.29	TYR334A	3.93	-	-	-	-
ASN219A	2.15	LEU254A	3.55	TYR334A	4.71				
MET220A	2.56	VAL255A	3.72						
CYS275A	3.49	VAL255A	3.78						
THR279A	3.42	LYS257A	3.76						
THR279A	2.97	LYS257A	3.54						
THR279A	3.37	THR279A	3.44						
GLU282A	2.06	ILE317A	3.51						
THR285A	2.35	PHE318A	3.56						
GLU286A	3.12	MET320A	3.87						
GLU286A	3.45	LEU321A	3.31						
ALA333A	2.42	VAL324A	3.34						
TYR334A	2.4	VAL324A	3.79						
ARG692B	2.52	TYR334A	3.8						
		TYR334A	3.17						
		TYR334A	3.47						
		LEU693B	3.76						

S5. (e) Chlorogenate-Mut1 (F-H-W-Y-G-Y-T-P-Q-N) Conjugate with PPARα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
ASN219A	2.93	LEU254A	3.51	-	-	-	-	-	-
ASN219A	2.27	VAL255A	3.43						
HIS274A	3.02	VAL255A	3.43						
CYS275A	2.68	LYS257A	3.59						
THR279A	2.12	LYS257A	3.31						
THR279A	2.92	LEU258A	3.68						
GLU282A	2.28	GLU282A	3.66						
THR285A	3.37	THR285A	3.63						
GLU289A	2.28	GLU286A	3.81						
GLU289A	2.14	GLU289A	3.53						
ALA333A	2.07	ALA333A	3.3						
		TYR334A	2.9						
		TYR334A	3.81						
		TYR334A	3.72						

S5. (f) Carnosate-Mut1 (**F**-H-W-Y-G-Y-T-P-Q-N) Conjugate with PPARα

Hydrogen Bonding		**Hydrophobic Interactions**		**Stacking Interactions**		**Cation Interactions**		**Salt Bridges**	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS274A	3.29	GLU286A	3.57	TYR334A	4.15	-	-	-	-
GLU282A	2.53	GLU289A	3.87						
GLU282A	2.54	TYR334A	3.95						
GLU289A	2.97	TYR334A	3.63						
GLU289A	2.8	LEU459A	3.76						
HIS457A	2.68	ILE689B	3.95						
ARG692B	1.88	LEU693B	3.96						
ARG692B	2.87	LEU693B	3.79						
GLU696B	2.24								

S5. (g) Gallate-Mut1 (**F**-H-W-Y-G-Y-T-P-Q-N) Conjugate with PPARα

Hydrogen Bonding		**Hydrophobic Interactions**		**Stacking Interactions**		**Cation Interactions**		**Salt Bridges**	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
ALA256A	2.42	MET220A	3.6	-	-	-	-	HIS457A	4.95
LYS257A	2.02	ILE241A	3.6						
HIS274A	3.25	LEU247A	3.56						
THR279A	1.92	GLU251A	3.86						
THR283A	1.96	VAL255A	3.63						
THR285A	2.31	LYS257A	3.75						
THR285A	2	THR279A	3						
LEU331A	1.86	VAL281A	3.92						
ALA333A	3.19	VAL324A	3.93						
TYR334A	1.9	VAL324A	3.68						
		VAL332A	3.13						
		ALA333A	3.12						
		TYR334A	3.68						

S5. (h) Rosmarinate-Mut1 (**F**-H-W-Y-G-Y-T-P-Q-N) Conjugate with PPARα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
THR279A	2.48	ILE241A	3.41	TYR334A	4.61	HIS274A	4.42	-	-
THR279A	3.54	LEU247A	3.78						
SER280A	3.24	VAL255A	3.56						
SER280A	3.24	ILE272A	3.4						
GLU282A	2.15	ILE272A	3.59						
GLU282A	2.73	THR279A	3.07						
GLU282A	2.62	THR283A	3.76						
THR285A	2.34	THR285A	3.77						
MET320A	2.11	PHE318A	3.25						
ALA333A	2.71	MET320A	3.37						
TYR334A	3.16	LEU321A	3.51						
HIS440A	2.53	LEU321A	3.37						
HIS457A	2.03	VAL332A	3.41						
ARG692B	2.18	VAL332A	3.79						
ARG692B	2.04	VAL332A	3.47						
		ALA333A	3.52						
		TYR334A	4						
		ILE339A	3.42						
		HIS457A	3.64						
		LEU693B	3.57						

S5. (i) Chlorogenate-Mut2 (Y-**I**-W-Y-G-Y-T-P-Q-N) Conjugate with PPARα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
ASN219A	2.18	LEU254A	3.76	TYR334A	5	-	-	HIS274A	5.18
ASN236A	2.31	VAL281A	3.56					HIS457A	3.87
THR279A	3.35	GLU282A	3.95						
THR279A	3.2	THR285A	3.38						
GLU282A	2.22	GLU286A	3.71						
GLU289A	2.94	GLU289A	3.79						
ALA333A	2.37	TYR334A	3.71						
TYR334A	2.38	TYR334A	3.84						
ASN336A	2.09	TYR334A	3.49						
ASN336A	3.11	TYR334A	3.83						
ARG692B	1.96	LEU459A	3.61						
ARG692B	3.37								

S5. (j) Carnosate-Mut2 (Y-**I**-W-Y-G-Y-T-P-Q-N) Conjugate with PPARα

Hydrogen Bonding		**Hydrophobic Interactions**		**Stacking Interactions**		**Cation Interactions**		**Salt Bridges**	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
ASN217A	2.38	VAL281A	3.74	HIS457A	4.53	ARG692B	4.23	-	-
ASN219A	2.05	THR285A	3.95						
LYS257A	2	GLU289A	3.74						
GLU282A	3.14	TYR334A	3.65						
THR285A	2.48	ILE689B	3.84						
GLU289A	3.55	LEU693B	3.93						
HIS457A	2.29								
ARG692B	2.72								

S5. (k) Gallate-Mut2 (Y-**I**-W-Y-G-Y-T-P-Q-N) Conjugate with PPARα

Hydrogen Bonding		**Hydrophobic Interactions**		**Stacking Interactions**		**Cation Interactions**		**Salt Bridges**	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
MET220A	2.86	MET220A	3.97	TYR334A	4.16	-	-	HIS457A	3.97
ILE272A	2.05	ILE241A	3.07						
HIS274A	2.69	LEU247A	3.58						
CYS276A	3.73	LEU254A	3.9						
CYS278A	2.54	VAL255A	3.73						
THR279A	2.81	VAL255A	3.59						
THR283A	2.48	ILE272A	3.64						
THR285A	1.93	THR279A	3.55						
THR285A	2.29	LEU321A	3.45						
GLU286A	2.47	VAL324A	3.41						
LEU331A	3.18	VAL324A	3.63						
ALA333A	2.34	VAL332A	3.12						
TYR334A	2.16	VAL332A	3.3						
TYR334A	3.31	VAL332A	3.45						
		VAL332A	3.38						
		ALA333A	3.35						
		ILE339A	3.41						

S5. (l) Rosmarinate-Mut2 (Y-**I**-W-Y-G-Y-T-P-Q-N) Conjugate with PPARα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LEU215A	2.53	ASN219A	3.63	-	-	-	-	-	-
PHE218A	2.42	LYS224A	3.85						
ASN219A	1.92	LYS224A	3.4						
ASN221A	2.54	ILE228A	3.59						
LYS224A	2.18	ASN236A	3.34						
THR253A	2.75	LEU254A	3.97						
GLY335A	2.76	TYR334A	3.45						
ASN336A	1.77	TYR334A	3.6						
		TYR334A	3.71						

S5. (m) Chlorogenate-Mut3 (Y-H-W-Y-G-Y-T-**H**-Q-N) Conjugate with PPARα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
ASN217A	2.49	LYS224A	3.67	-	-	-	-	-	-
ASN219A	3.09	ILE228A	3.66						
SER234A	2.16	ILE228A	3.67						
CYS275A	2.6	LEU254A	3.73						
THR279A	2.17	VAL255A	3.48						
TYR334A	3.06	VAL281A	3.84						
TYR334A	2.72	GLU282A	3.7						
ASN336A	2.09	GLU286A	3.36						
ASN336A	2.28	TYR334A	3.78						
HIS457A	1.89	TYR334A	3.93						
ARG692B	3.46								

S5. (n) Carnosate-Mut3 (Y-H-W-Y-G-Y-T-**H**-Q-N) Conjugate with PPARα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LYS224A	2.11	ASN219A	3.77	TYR334A	5.4	LYS224A	4.07	-	-
ASN236A	2.53	LYS224A	3.66						
LEU254A	2.83	VAL227A	3.52						
ALA256A	2.11	ILE228A	3.76						
HIS274A	2.22	ASN236A	3.58						
TYR334A	3.17	VAL255A	3.33						
ASN336A	2.54	VAL255A	3.67						
ASN336A	3.07	LYS257A	3.93						
		ALA333A	3.24						
		TYR334A	3.71						
		TYR334A	3.61						
		TYR334A	3.85						

S5. (o) Gallate-Mut3 (Y-H-W-Y-G-Y-T-**H**-Q-N) Conjugate with PPARα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
HIS274A	3.09	VAL255A	3.31	HIS274A	4.7	-	-	ARG692B	4.42
THR279A	2.95	VAL255A	3.93						
GLU282A	2.4	LYS257A	3.54						
THR285A	2.34	THR279A	3.61						
HIS457A	2.38	VAL281A	3.94						
ARG692B	2.57	GLU282A	3.79						
		TYR334A	3.21						
		HIS457A	3.63						
		LEU693B	3.78						

S5. (p) Rosmarinate-Mut3 (Y-H-W-Y-G-Y-T-**H**-Q-N) Conjugate with PPARα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
MET220A	3.09	MET220A	3.9	TYR334A	4.36	-	-	ARG692B	4.39
ALA250A	2.71	LEU254A	3.54	TYR334A	3.99				
ALA256A	2.59	VAL255A	3.44	TYR334A	3.76				
LYS257A	2.53	VAL255A	3.2	HIS457A	4.34				
THR279A	3.22	LYS257A	3.79						
THR279A	2.33	LEU258A	3.89						
GLU282A	2.15	THR279A	3.65						
GLU282A	2.88	VAL281A	3.94						
THR283A	2.34	GLU282A	3.71						
THR285A	2.21	ALA333A	3.41						
HIS457A	2.36	TYR334A	3.31						
HIS457A	2.34								
ARG692B	2.61								

S5. (q) Chlorogenate-Mut 4 (Y-H-W-Y-G-Y-T-P-Q-**D**) Conjugates with PPARα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
ASN219A	3.16	MET220A	3.19	TYR334A	4.2	-	-	HIS274A	4.88
MET220A	2.47	THR279A	3.68						
LEU254A	3.77	VAL281A	3.67						
HIS274A	2.23	TYR334A	3.31						
GLU282A	2.35	TYR334A	3.42						
GLU282A	2.37	PRO458A	3.5						
GLU282A	2.66	ILE689B	3.73						
GLU282A	3.57								
THR285A	2.02								
THR285A	2.15								
GLU286A	2.95								
GLU286A	2.47								
ALA333A	2.25								
HIS457A	2.18								
ARG692B	2.15								
ARG692B	2.41								

S5. (r) Carnosate-Mut 4 (Y-H-W-Y-G-Y-T-P-Q-**D**) Conjugates with PPARα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LYS222A	2.9	VAL223A	3.65	-	-	-	-	-	-
ARG226A	2.42	VAL223A	3.45						
ARG226A	2.12	ARG226A	3.46						
ARG226A	3.35	ARG226A	3.8						
ARG226A	3.16	VAL227A	3.63						
VAL227A	3.15	ILE228A	3.85						
SER230A	2.43	LEU229A	3.67						
SER234A	2.42	LYS232A	3.64						
ASN236A	3.11	ASN326A	3.84						
ASN236A	2.39								
ASN326A	1.99								
LEU370A	2.47								

S5. (s) Gallate-Mut4 (Y-H-W-Y-G-Y-T-P-Q-**D**) Conjugates with PPARα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
TYR214A	2.72	PHE218A	3.72	TYR334A	4.02	-	-	-	-
LYS222A	3.48	VAL255A	3.51						
LEU254A	2.14	ILE272A	3.62						
ALA256A	2.78	THR279A	3.52						
CYS275A	3.24	THR283A	3.46						
CYS275A	2.65	MET320A	3.64						
THR279A	2.27	LEU321A	3.91						
GLU282A	3.42	VAL332A	3.55						
THR283A	2.85	VAL332A	3.49						
THR283A	3.03	ILE354A	3.63						
THR283A	2.96								
THR283A	3.39								
SER323A	2.49								
SER323A	2.44								
ALA333A	2.23								
TYR334A	1.8								
TYR334A	3.5								
TYR334A	3.41								
GLY335A	2.26								

S5. (t) Rosmarinate-Mut 4 (Y-H-W-Y-G-Y-T-P-Q-**D**) Conjugates with PPARα

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LEU254A	2.06	LYS257A	3.69	TYR334A	4.18	HIS457A	5.19	ARG692B	5.25
ALA256A	3.27	LYS257A	3.58					ARG692B	4.56
HIS274A	2.68	THR279A	3.35						
THR279A	2.42	VAL324A	3.34						
GLU282A	2.46	VAL332A	3.7						
GLU282A	2.26	ALA333A	3.84						
THR283A	3.1	ILE689B	3.78						
THR283A	2.26								
THR285A	1.85								
ALA333A	1.91								
HIS457A	3.57								
ARG692B	3.01								
ARG692B	2.26								

Table S6. Peptide Interactions with EGFR Using PLIP

(a) **Pep** (Y-H-W-Y-G-Y-T-P-Q-N)

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LYS745A	3.41	VAL726A	2.19	-	-	-	-	-	-
ASP800A	2.78	ALA743A	3.93						
ASP800A	3.35	LEU799A	2.68						
ARG803A	2.96	ASP800A	2.92						
ARG803A	3.16	ARG841A	2.77						
THR854A	2.8	ARG841A	2.16						
LYS913A	2.47	LEU844A	3.42						
		LEU844A	2.88						

S6. (b) Mut 1 (**F**-H-W-Y-G-Y-T-P-Q-N)

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LYS745A	1.51	LEU718A	3.9	-	-	-	-	LYS745A	4.47
MET793A	3.16	GLY719A	2.22						
GLY796A	2.79	ASP800A	3.89						
ASP800A	2.1	ARG841A	3.64						
ASP855A	3.72	ARG841A	3.97						
ASN996A	2.24	LEU844A	3.61						

S6. (c) Mut 2 (Y-**I**-W-Y-G-Y-T-P-Q-N)

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LEU718A	2.72	LEU718A	3.78	-	-	-	-	LYS745A	4.75
SER720A	3.53	GLY719A	3.63						
SER720A	2.1	VAL726A	3.97						
LYS745A	1.51	MET793A	3.47						
MET793A	1.87	GLU804A	2.97						
ASN842A	2.31	ARG841A	3.87						
ASN842A	2.56	LEU844A	2.03						
THR854A	3.16	LEU844A	2.85						
ASP855A	2.07	THR854A	3.56						
ASN996A	3.17	ASP855A	3.89						
		LEU1001A	3.58						

S6. (d) Mut 3 (Y-H-W-Y-G-Y-T-**H**-Q-N)

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
CYS797A	2.74	GLU804A	3.48	-	-	-	-	-	-
ARG803A	2.88	ARG841A	3.03						
ARG803A	3.08								
ASN842A	3.55								
LYS913A	2.56								

S6. (e) Mut 4 (Y-H-W-Y-G-Y-T-P-Q-**D**)

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LYS745A	2.59	VAL726A	3.27	-	-	-	-	ASP800A	3.2
ARG803A	3.19	VAL726A	3.4						
ASP855A	2.6	LEU844A	3.81						
LYS913A	2.92	LEU844A	2.61						
		LEU1001A	3.4						
		LEU1001A	3.38						

Table S7. Ligand-Residue Interactions using PLIP for Polyphenol-Peptide Conjugate Interactions with EGFR

a. Chlorogenate-Y-H-W-Y-G-Y-T-P-Q-N (Pep) conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
GLY719A	2.81	SER720A	2.87	-	-	ARG803A	4.67	-	-
SER720A	2.75	ALA722A	3.44						
GLY721A	1.35	LEU799A	2.84						
CYS797A	3.4	ASP800A	3.83						
ASP800A	2.81	VAL876A	3.24						
ARG803A	3.64	PRO877A	2.94						
ARG841A	3.41								
VAL876A	2.76								

S7b. Carnosate-Y-H-W-Y-G-Y-T-P-Q-N (Pep) conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
VAL717A	2.66	SER720A	3.16	-	-	-	-	-	-
LEU718A	1.31	LEU799A	2.96						
SER720A	3.11	ASP800A	1.3						
SER720A	2.73	ARG841A	2.86						
SER720A	3.43	LEU844A	2.46						
LYS745A	3.04	THR854A	3.95						
CYS797A	2.15	TRP880A	3.8						
		LYS913A	3.54						

S7c. Gallate-Y-H-W-Y-G-Y-T-P-Q-N (Pep) conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
CYS797A	3.1	LEU718A	2.47	-	-	ARG841A	3.07	-	-
ASP800A	2.79	VAL726A	3.43						
ASP800A	3.21	ARG841A	2.5						
ARG803A	2.98	ARG841A	3.09						
ARG803A	3.42	TRP880A	3.62						
ARG841A	3	LEU1001A	3.84						

S7d. Rosmarinate-Y-H-W-Y-G-Y-T-P-Q-N (Pep) conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
SER720A	2.57	LEU718A	2.17	-	-	-	-	-	-
SER720A	3.06	SER720A	3.96						
SER720A	3.13	ALA722A	3.73						
SER720A	3.11	VAL726A	3.95						
LYS745A	3.08	ARG803A	3.84						
ARG803A	1.87	ARG803A	3.22						
GLU804A	2.31	GLU804A	2.06						
PHE910A	2.81	ASN996A	3.37						
ASN996A	3.11	LEU1001A	2.9						
PHE997A	3.09								

S7e. Chlorogenate-**F**-H-W-Y-G-Y-T-P-Q-N Mut1 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LEU718A	2.92	SER720A	3.09	-	-	-	-	LYS913A	4.36
SER720A	1.96	VAL726A	3.72						
ALA722A	2.12	ASP855A	3.92						
ALA722A	3.19	TRP880A	3.24						
GLY724A	1.29	TRP880A	3.44						
ARG803A	2.85	LYS913A	1.3						
ARG841A	1.98	LYS913A	3.31						
LYS913A	2.3								
LYS913A	2.8								
ASP916A	2.17								

S7f. Carnosate-**F**-H-W-Y-G-Y-T-P-Q-N Mut1 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
CYS797A	1.82	LEU718A	2.95	-	-	-	-	-	-
ASP800A	2.14	LEU718A	3.48						
ASP800A	2.14	GLY719A	3.6						
ARG803A	2.33	SER720A	3.59						
ARG803A	2.6	VAL726A	2.68						
ARG841A	3.17	VAL726A	3.84						
ARG841A	1.56	ALA743A	3.84						
VAL876A	3.35	LEU799A	2.77						
ALA920A	1.8	ASN842A	3.93						
SER921A	2.5	LEU844A	3.04						
		THR854A	2.79						
		ASP855A	3.9						
		VAL876A	3.9						
		LYS879A	3.31						
		TRP880A	3.31						

S7g. Gallate-**F**-H-W-Y-G-Y-T-P-Q-N Mut 1 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
SER720A	2.98	LEU718A	3.24	TRP880A	4.9	ARG841A	3.54	-	-
LYS745A	3.23	LEU718A	3.26	TRP880A	2.8				
MET793A	2.73	VAL726A	3.51						
MET793A	2.4	LEU844A	3.83						
THR854A	3.1	LEU844A	1.86						
THR854A	2.71	THR854A	3.42						
THR854A	2.26	TRP880A	3.86						
ASP855A	2.88	PRO914A	3.91						
ASP855A	2.85								

S7h. Rosmarinate-**F**-H-W-Y-G-Y-T-P-Q-N Mut1 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LEU718A	2.31	GLY719A	3.66	-	-	LYS879A	2.47	LYS879A	5.47
SER720A	1.95	GLY721A	3.44						
GLY721A	3.27	GLY721A	3.63						
CYS797A	2.95	ALA722A	1.31						
ASP800A	3.51	PHE723A	2.75						
ASP800A	3.65	VAL726A	2.61						
LYS879A	3.1	LEU799A	3.75						
GLY911A	2.42	ASP800A	3.01						
LYS913A	3.17	ARG841A	3.79						
ALA920A	1.45	LEU844A	3.56						
		THR854A	3.51						
		LYS879A	3.23						
		ALA920A	3						

S7i. Chlorogenate-Y-**I**-W-Y-G-Y-T-P-Q-N Mut2 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
VAL717A	2.65	VAL717A	3.25	-	-	-	-	ARG841A	4.41
SER720A	2.26	LEU718A	3.08						
SER720A	2.16	LEU718A	2.86						
SER720A	1.79	ASP800A	3.65						
ALA722A	2.84	ARG841A	3.99						
ARG841A	2.93	ARG841A	3.59						
ARG841A	1.21	LEU1001A	2.96						
ARG841A	1.34								

LYS913A	3.3								

S7j. Carnosate-Y-**I**-W-Y-G-Y-T-P-Q-N Mut2 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LEU718A	2.59	LEU718A	2.21					ARG841A	5.38
SER720A	3.02	SER720A	3.44						
SER720A	3.13	ALA722A	3.83						
ARG841A	2.92	VAL726A	3.97						
		LEU799A	3.89						
		ASP800A	3.6						
		LEU844A	3.07						
		TRP880A	3.18						
		LEU1001A	3.56						
		LEU1001A	2.49						

S7k. Gallate-Y-**I**-W-Y-G-Y-T-P-Q-N Mut 2 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
TYR801A	3.2	PRO794A	3.6	-	-	-	-	-	-
LYS846A	3.04	PHE795A	3.41						
GLN849A	3.27	ASN808A	3.05						
MET987A	2.02	TYR813A	2.36						
MET987A	3.43	LYS846A	3.63						
ASN996A	1.83	THR847A	2.7						
		PHE997A	3.94						
		PHE997A	3.48						
		TYR998A	4						
		ARG999A	3.58						
		ASP1012A	3.13						

S7l. Rosmarinate-Y-**I**-W-Y-G-Y-T-P-Q-N Mut 2 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
ALA722A	2.44	SER720A	2.6					ARG803A	4.23
ASP800A	3.12	ALA722A	3.52					LYS879A	5.43
ARG841A	2.96	ARG803A	3.26						
VAL876A	1.6	ARG841A	3.31						
LYS879A	2.42	TRP880A	2.27						
GLY917A	2.62	TRP880A	3.23						
GLY917A	2.83								
ALA920A	1.33								

Table S7m. Chlorogenate-Y-H-W-Y-G-Y-T-**H**-Q-N Mut 3 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
SER720A	3	LEU718A	3.11	-	-	-	-	ARG841A	4.25
SER720A	3.12	GLY719A	3.28						
ALA722A	2.99	SER720A	3.82						
LYS745A	2.9	LEU799A	3.32						
ASP800A	3	ASP800A	3.68						
ARG803A	2.04	GLU804A	3.37						
ARG803A	1.87	ASN996A	3.94						
ARG803A	2.12								
ASN842A	3.3								
ASN996A	3.1								

S7n. Carnosate-Y-H-W-Y-G-Y-T-**H**-Q-N Mut 3 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LYS745A	2.99	ALA722A	1.49	PHE723A	4.7	-	-	-	-
ARG841A	3.05	VAL726A	3.79						
ARG841A	3.34	VAL726A	1.97						
ARG841A	2.78	ARG841A	3.84						
VAL876A	3.09	LEU844A	2.67						
LYS879A	3.21	LEU844A	2.8						
ILE918A	3.08	THR854A	2.56						
ALA920A	2.36	VAL876A	2.05						
		ILE878A	4						
		TRP880A	3.19						

S7o. Gallate-Y-H-W-Y-G-Y-T-**H**-Q-N Mut 3 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
LEU718A	1.74	LEU718A	3.83	-	-	-	-	-	-
CYS797A	2.64	VAL726A	3.81						
ASP800A	1.96	VAL726A	3.99						
ASP800A	2.98	ASP800A	3.19						
ARG841A	2.85	ARG841A	3.84						
ARG841A	1.89	ARG841A	3.06						
ASN842A	2.97	LEU844A	3.72						
ASN842A	2.63	TRP880A	2.31						
		TRP880A	3.55						

S7p. Rosmarinate-Y-H-W-Y-G-Y-T-**H**-Q-N Mut3 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
VAL717A	0.81	LEU718A	3.88	-	-	-	-	-	-
VAL717A	1.03	GLY719A	3.76						
GLY719A	3.01	LEU799A	3.38						
SER720A	1.65	ASP800A	3.47						
ARG803A	2.85	LYS879A	3.13						
ARG803A	2.89	TRP880A	3.68						
VAL876A	1.41	TRP880A	3.93						
LYS913A	1.17								

S7q. Chlorogenate-Y-H-W-Y-G-Y-T-P-Q-**D** Mut4 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
VAL717A	2.57	LYS716A	3.42	-	-	-	-	LYS745A	3.49
VAL717A	2.22	LEU718A	3.69						
LEU718A	2.56	LEU718A	3.48						
GLY719A	3.33	GLY719A	2.62						
GLY719A	3.34	LEU844A	3.43						
SER720A	3.33	LEU1001A	3.8						
SER720A	2.5	LEU1001A	2.55						
GLY721A	2.88								
LYS728A	3.23								
ASP800A	2.1								
ALA1000A	2.39								
ASP1003A	0.97								
ASP1003A	0.87								

S7r. Carnosate-Y-H-W-Y-G-Y-T-P-Q-**D** Mutation 4 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
ALA722A	2.76	GLY719A	3.12	-	-	-	-	-	-
PHE723A	3.22	GLY719A	3.38						
LYS745A	3.72	PHE723A	3.68						
ARG748A	3.5	VAL726A	1.5						
ARG841A	2.88	ALA743A	2.84						
THR854A	3.26	THR854A	3.73						
GLY863A	3.1	GLU866A	3.87						
GLY863A	2.73	PRO877A	2.89						
VAL876A	2.28								
VAL876A	3.6								
ARG889A	3.29								
ARG889A	1.78								

S7s. Gallate-Y-H-W-Y-G-Y-T-P-Q-**D** Mut4 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
GLY719A	1.92	PHE723A	3.46	-	-	-	-	ARG841A	4.05
SER720A	2.37	VAL726A	2.93						
SER720A	1.24	VAL726A	3.94						
GLY721A	3.39	LEU844A	3.08						
GLY721A	2.16	LEU844A	2.85						
ALA722A	1.97								
ALA722A	2.62								
ALA722A	2.87								
PHE723A	1.64								
GLY724A	2.33								
LYS745A	2.89								
ASP800A	2.8								
ARG803A	1.9								
GLU804A	3.63								
ASN842A	2.31								
ASN842A	3.24								
ASN996A	3.11								

S7t. Rosmarinate-Y-H-W-Y-G-Y-T-P-Q-**D** Mut4 conjugate

Hydrogen Bonding		Hydrophobic Interactions		Stacking Interactions		Cation Interactions		Salt Bridges	
Residue	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**	**Residue**	**Distance (A°)**
GLY719A	2.39	LEU718A	3.91	-	-	-	-	-	-
SER720A	2.63	VAL726A	3.55						
GLY721A	3.4	ALA743A	3.37						
PHE723A	2.3	ASP800A	3.58						
VAL726A	3.1	ARG841A	2.82						
GLN791A	3.22	ARG841A	3.31						
MET793A	2.37	LEU844A	2.55						
CYS797A	1.37	TYR998A	3.73						
ASP800A	3.28	LEU1001A	3.2						
ASP800A	2.23								
ARG803A	3.17								
GLU804A	2.56								
GLU804A	2.76								
ASN996A	2.6								

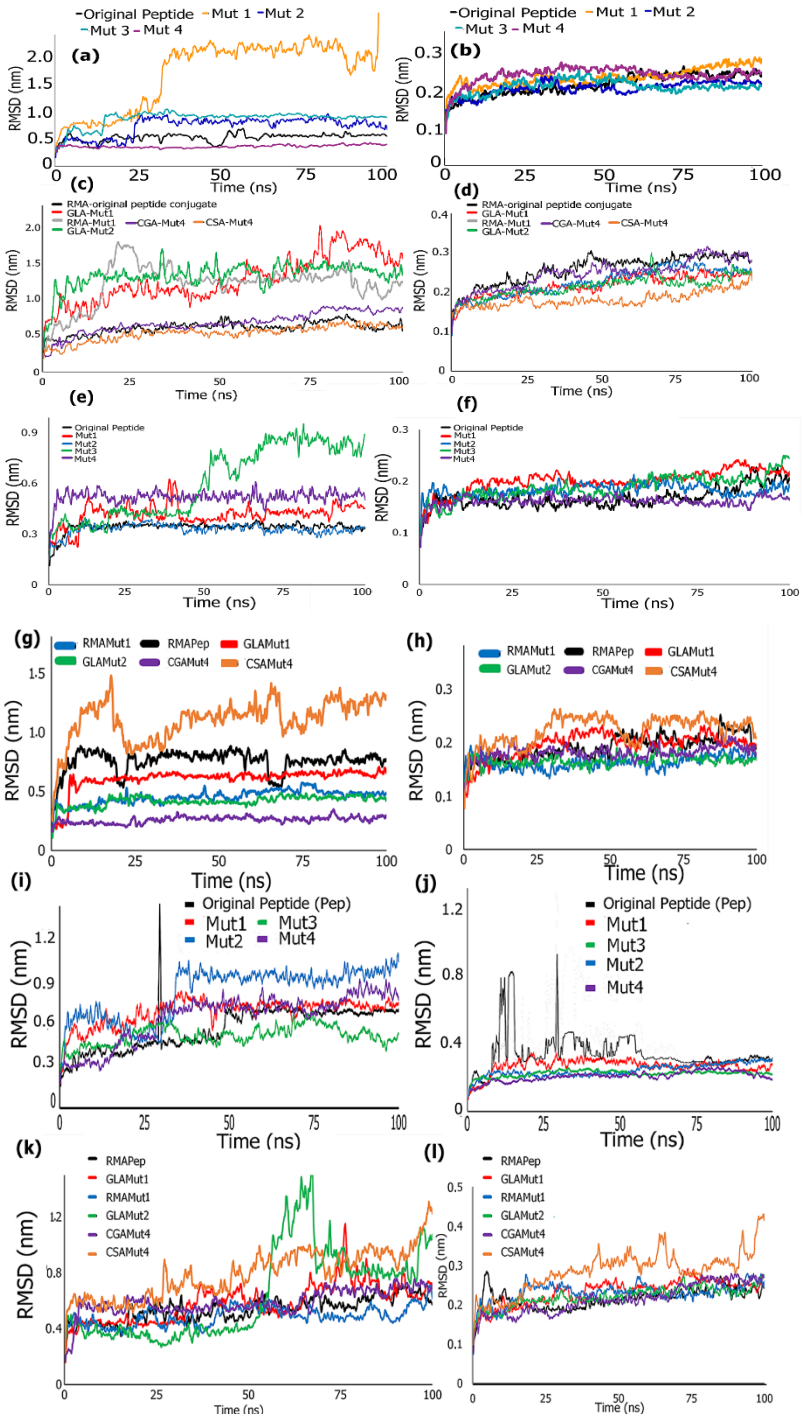


Figure S1. (a) RMSD plots of various peptides with ER-α receptor. (b) Corresponding Cα plots of ER-α receptor. (c) RMSD plots of various peptide-polyphenol conjugates with ER-α receptor; (d) Corresponding Cα plots of ER-α receptor.(e) RMSD plots of various peptides with PPAR-α receptor. (f) Corresponding Cα plots of PPAR-α receptor. (g) RMSD plots of various peptide-polyphenol conjugates with PPAR-α receptor; (h) Corresponding Cα plots of PPAR-α receptor; (i) RMSD plots of various peptides with EGFR receptor. (b) Corresponding Cα plots of EGFR receptor. (c) RMSD plots of various peptide-polyphenol conjugates with EGFR receptor; (d) Corresponding Cα plots of EGFR receptor

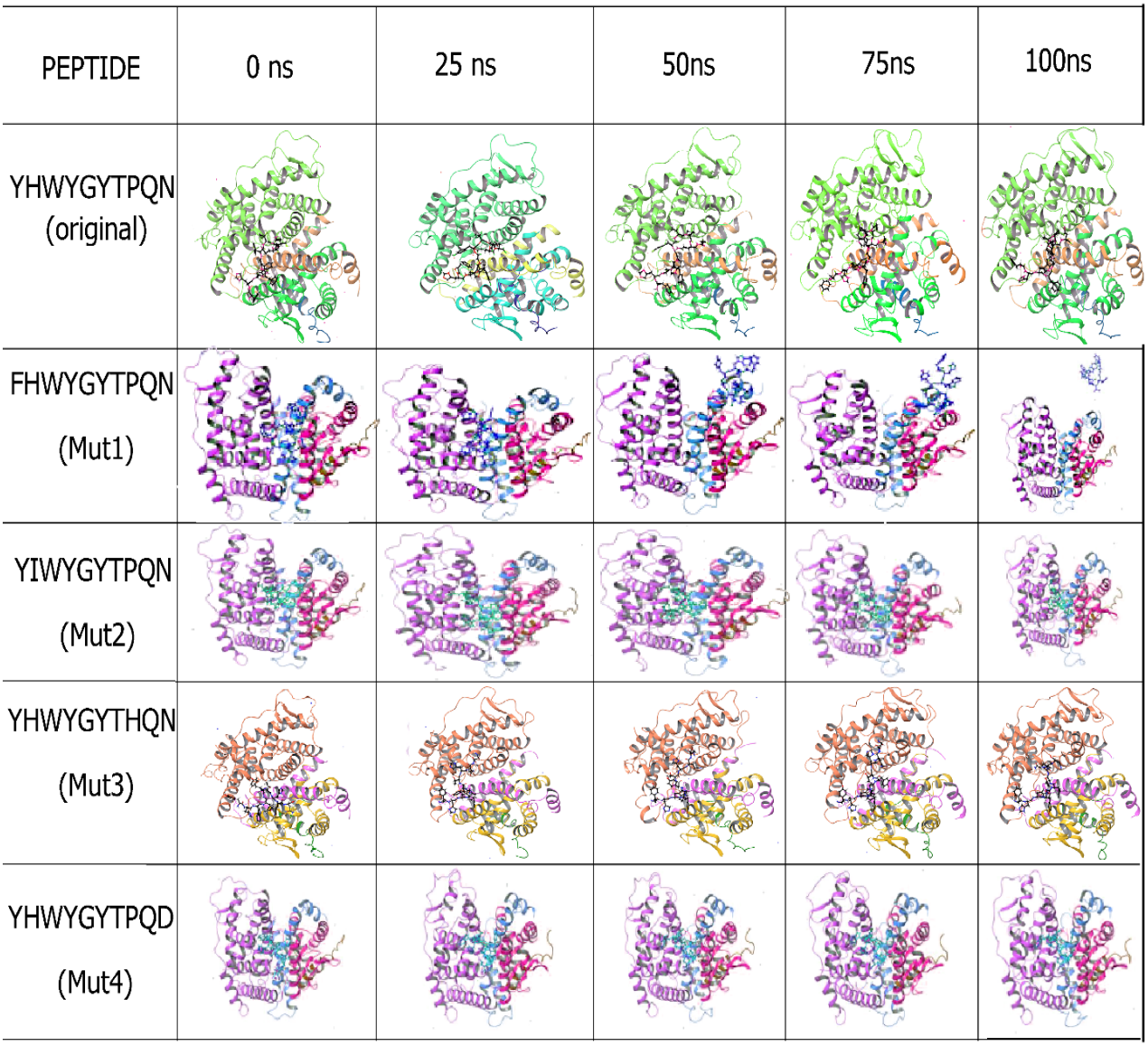


Figure S2. Trajectory images obtained during MD simulation of original peptide and the four mutated peptides at 0, 25, 50, 75 and 100 ns showing interactions of the peptides with the ERα receptor.

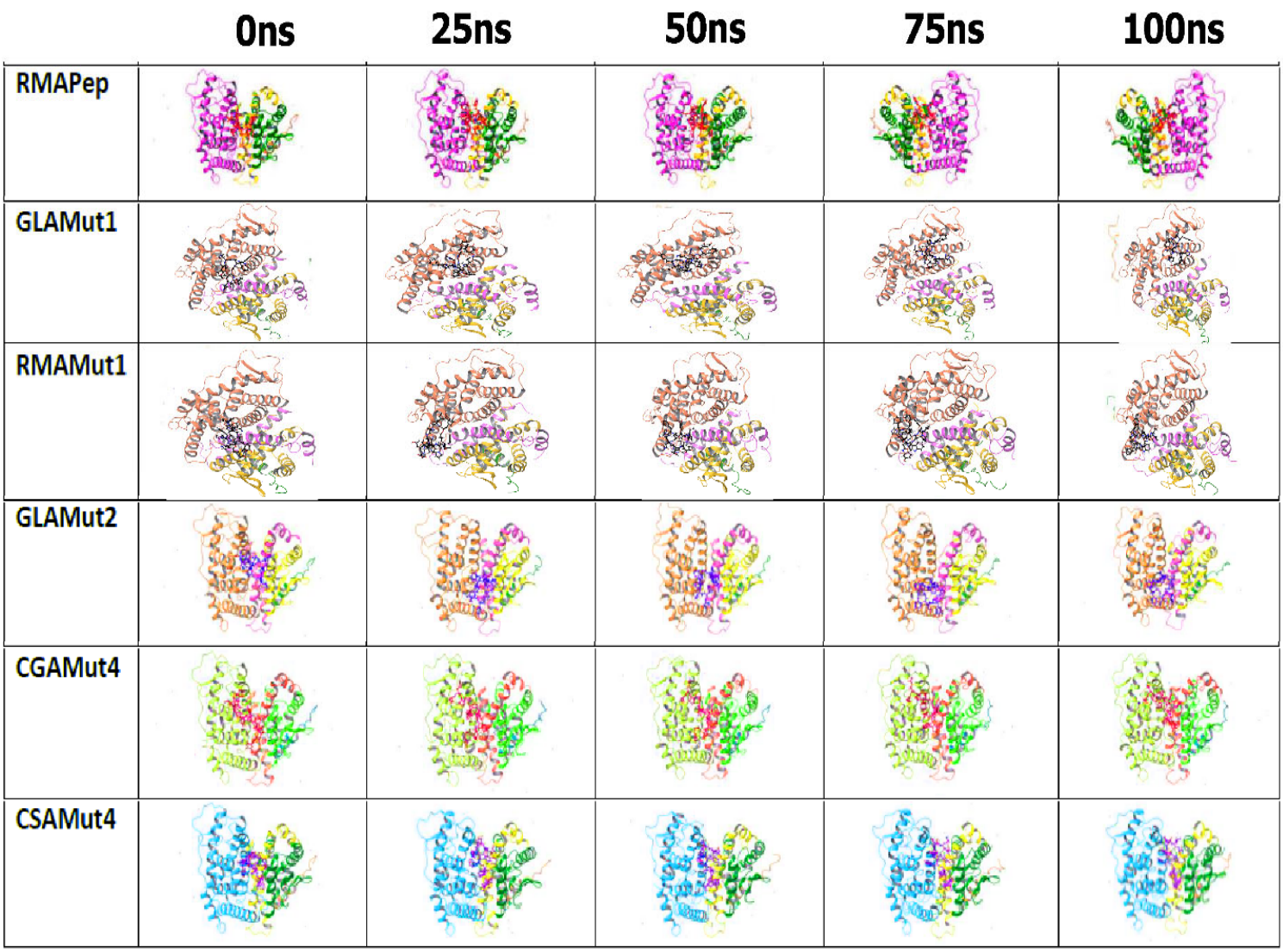


Figure S3. Trajectory images obtained during MD simulation of peptide-polyphenol conjugates at 0, 25, 50, 75 and 100 ns showing interactions of the peptides with the ERα receptor

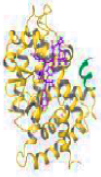
PEPTIDE	0 (ns)	25 (ns)	50 (ns)	75 (ns)	100 (ns)
YHWYGYTPQN (original)					
FHWYGYTPQN (Mut1)					
YIWYGYTPQN (Mut2)					
YHWYGYTHQN (Mut3)					
YHWYGYTPQD (Mut4)					

Figure S4. Trajectory images over 100 ns molecular dynamics simulation of peptide complexes with PPARα.

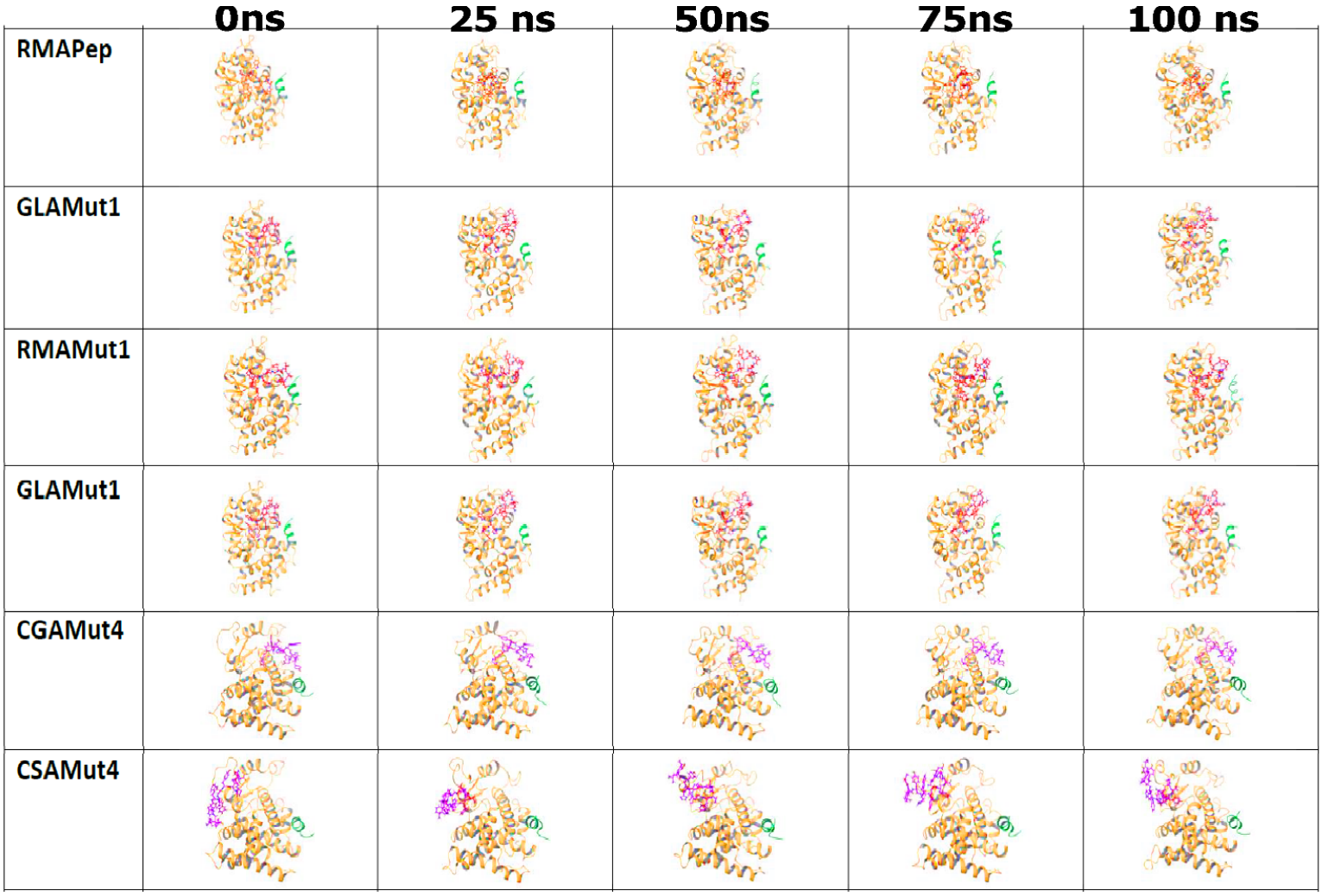


Figure S5. Trajectory images over 100 ns molecular dynamics simulation of polyphenol-peptide conjugate complexes with PPARα. The ligand is shown in pink.

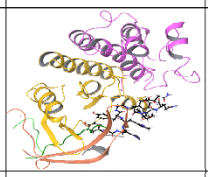
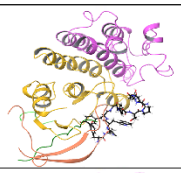
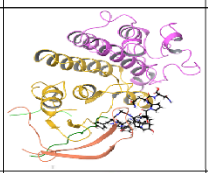
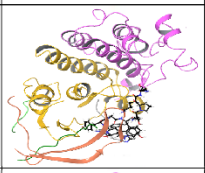
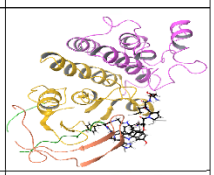
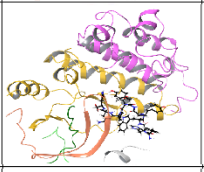
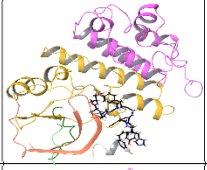
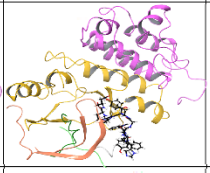
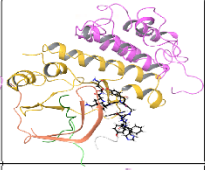
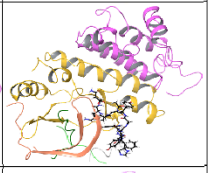
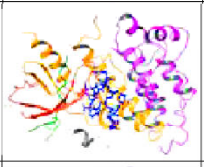
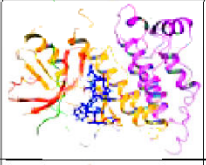
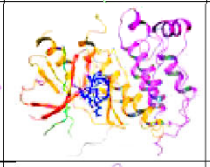
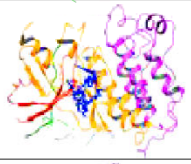
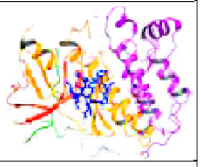
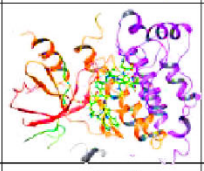
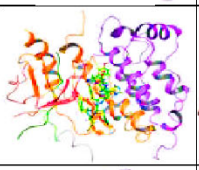
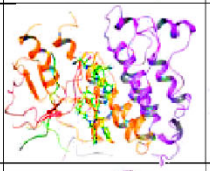
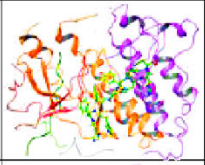
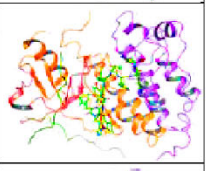
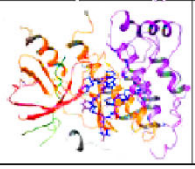
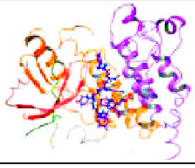
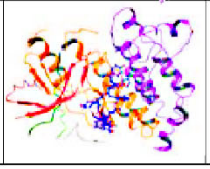
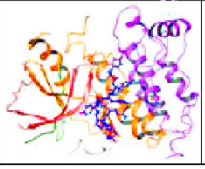
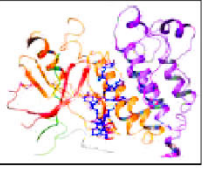
PEPTIDE	0 (ns)	25 (ns)	50 (ns)	75 (ns)	100 (ns)
YHWYGYTPQN (original)					
FHWYGYTPQN (Mut1)					
YIWYGYTPQN (Mut2)					
YHWYGYTHQN (Mut3)					
YHWYGYTPQD (Mut4)					

Figure S6. Trajectory images over 100 ns molecular dynamics simulation of peptide complexes with EGFR.

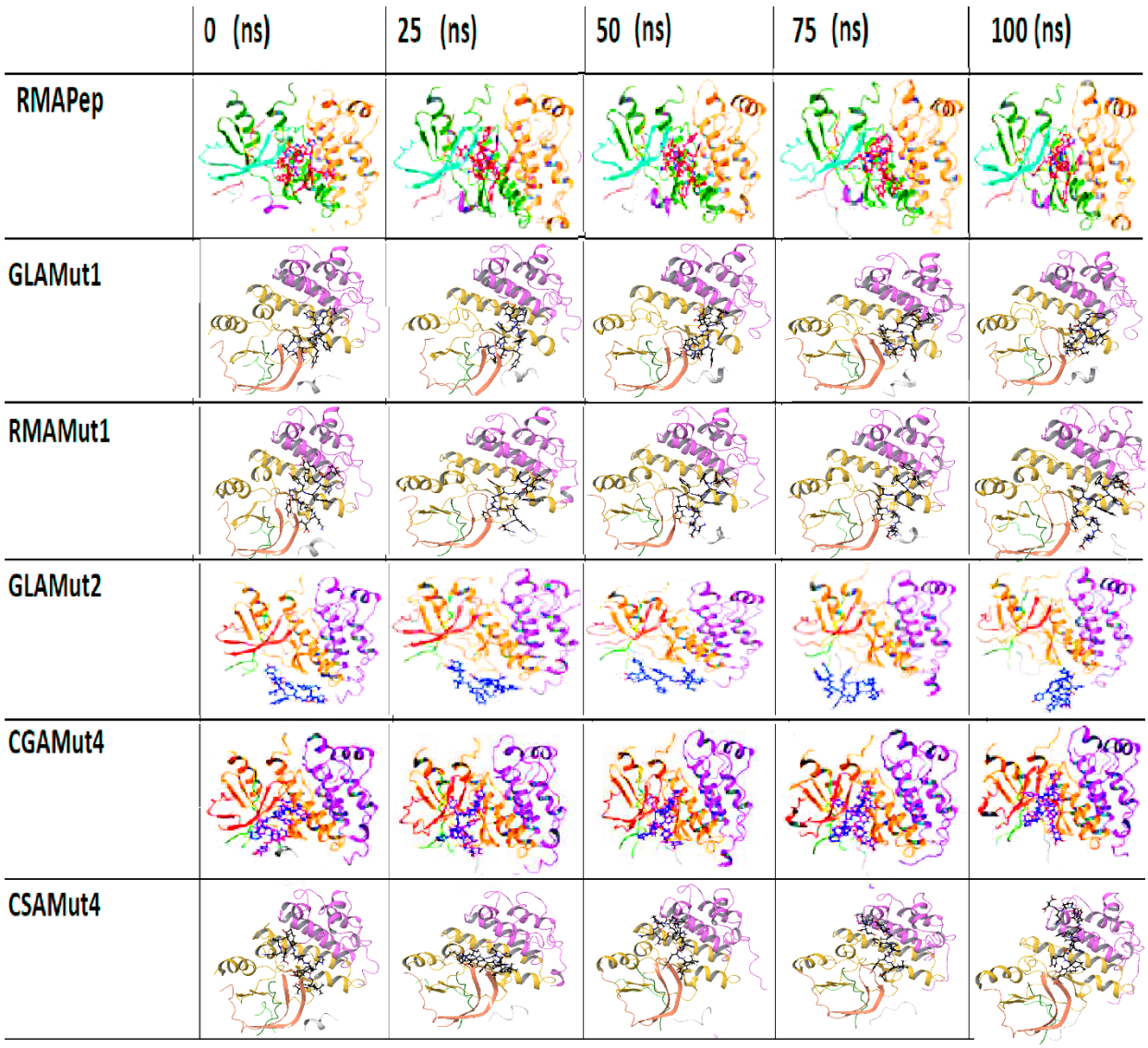


Figure S7. Trajectory images over 100 ns molecular dynamics simulation of polyphenol-peptide conjugate complexes with EGFR.

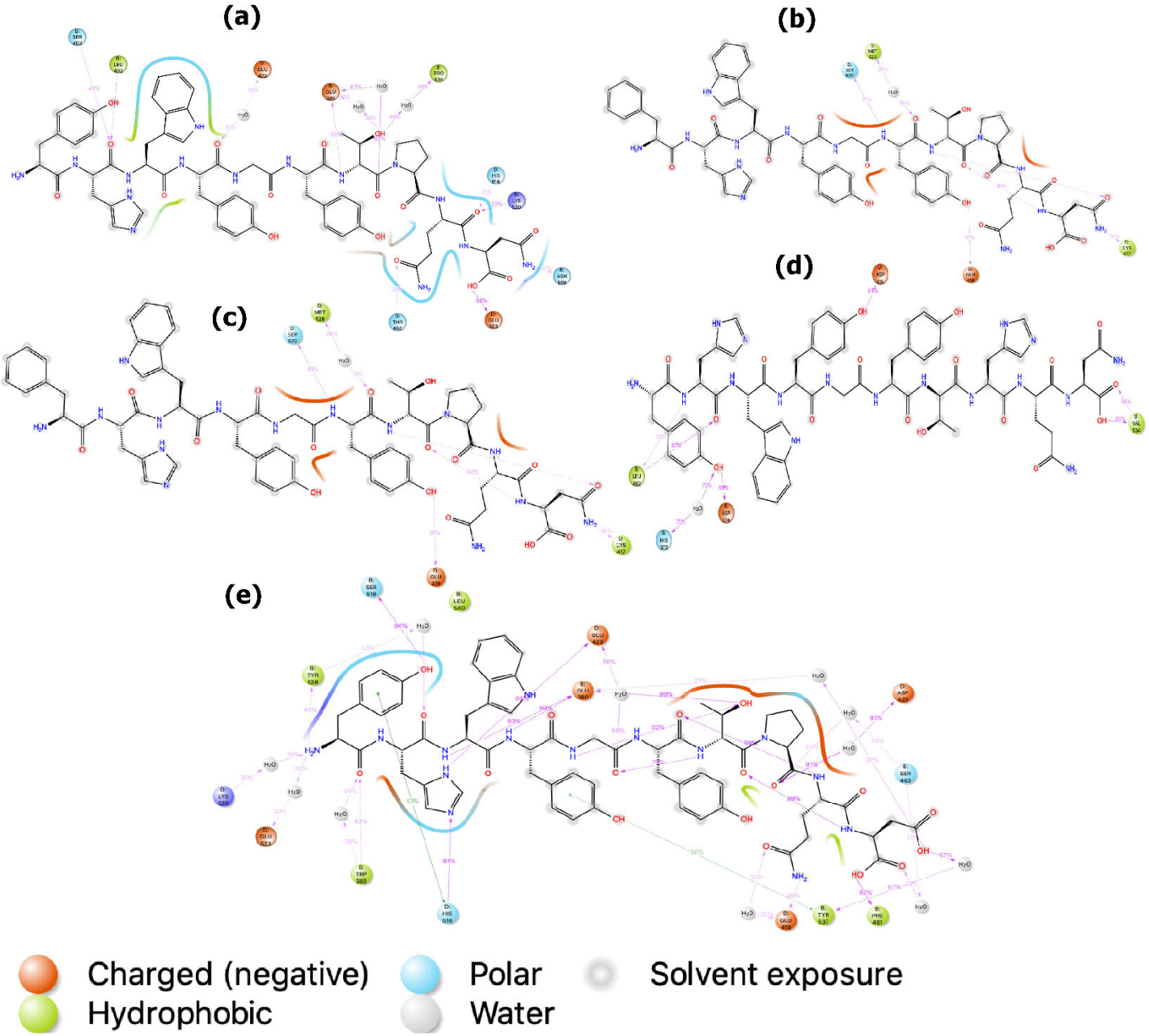


Figure S8. Schematic of ligand atom interactions with the ERα receptor protein residues. Interactions that occur more than **30.0%** of the simulation time are shown. (a) Pep; (b) Mut1; (c) Mut2; (d) Mut3; (e) Mut4

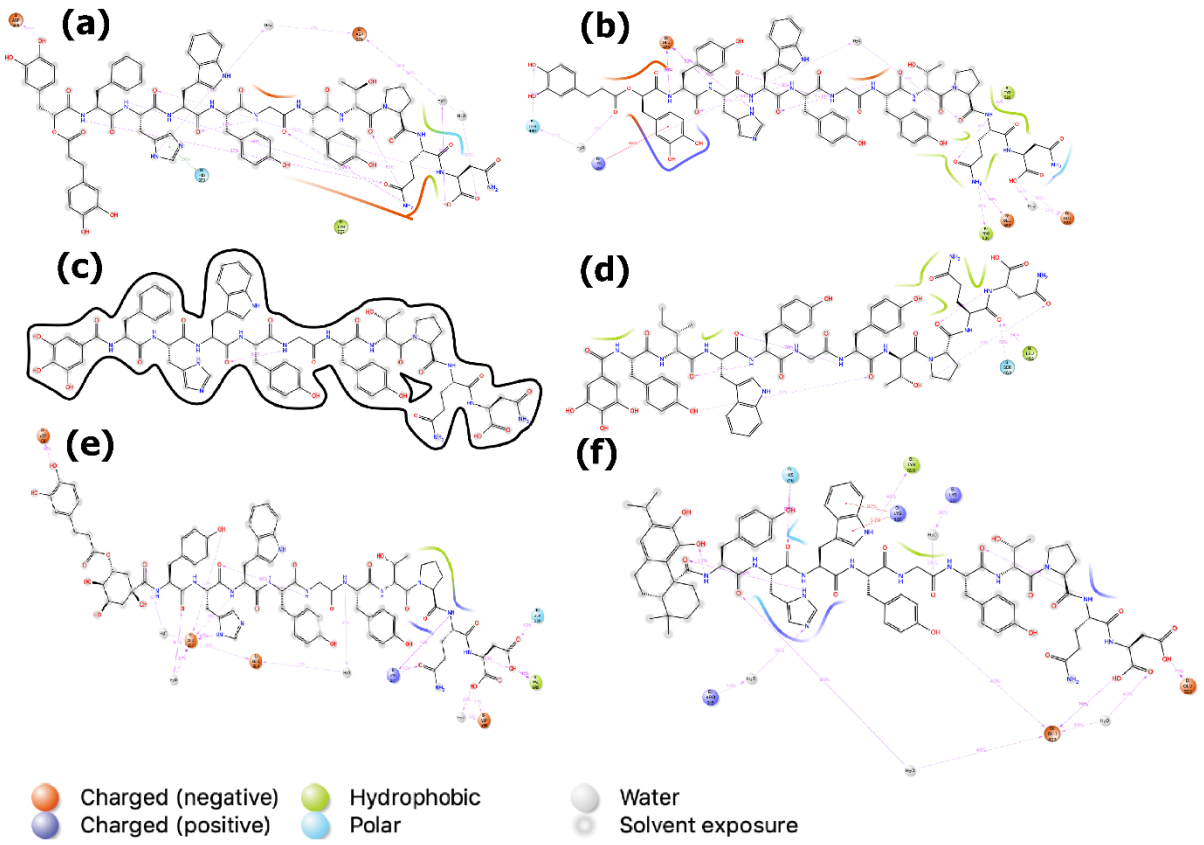


Figure S9. Schematic of ligand atom interactions with the ERα receptor protein residues. Interactions that occur more than **30.0%** of the simulation time are shown. (a) RMA-Mut1; (b) RMA-Pep; (c) GLA-Mut1; (d) GLA-Mut2; (e) CGA-Mut4; (f) CSA-Mut4

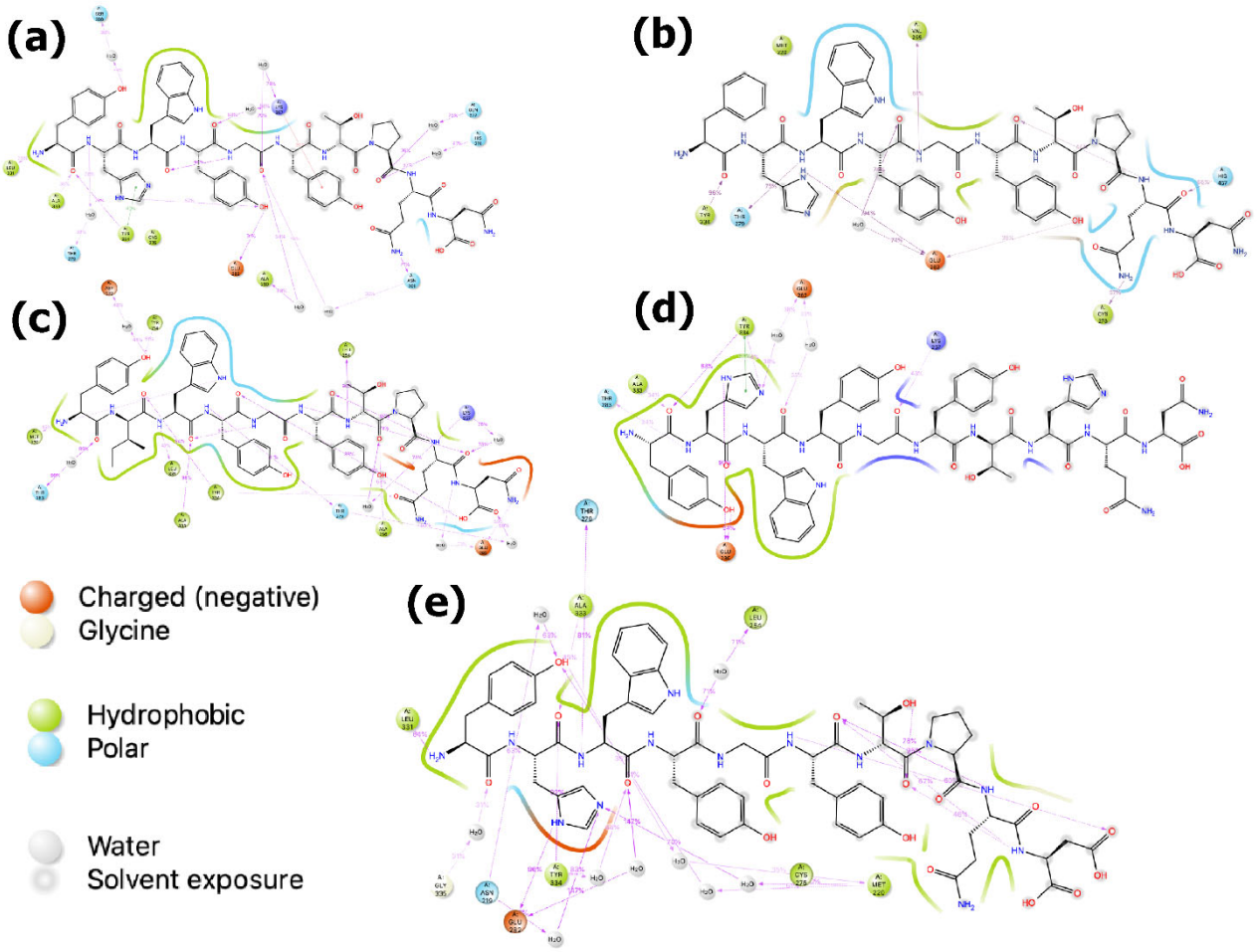


Figure S10. Schematic of ligand atom interactions with the PPARαreceptor protein residues. Interactions that occur more than **30.0%** of the simulation time are shown. (a) Pep; (b) Mut1; (c) Mut2; (d) Mut3; (e) Mut4

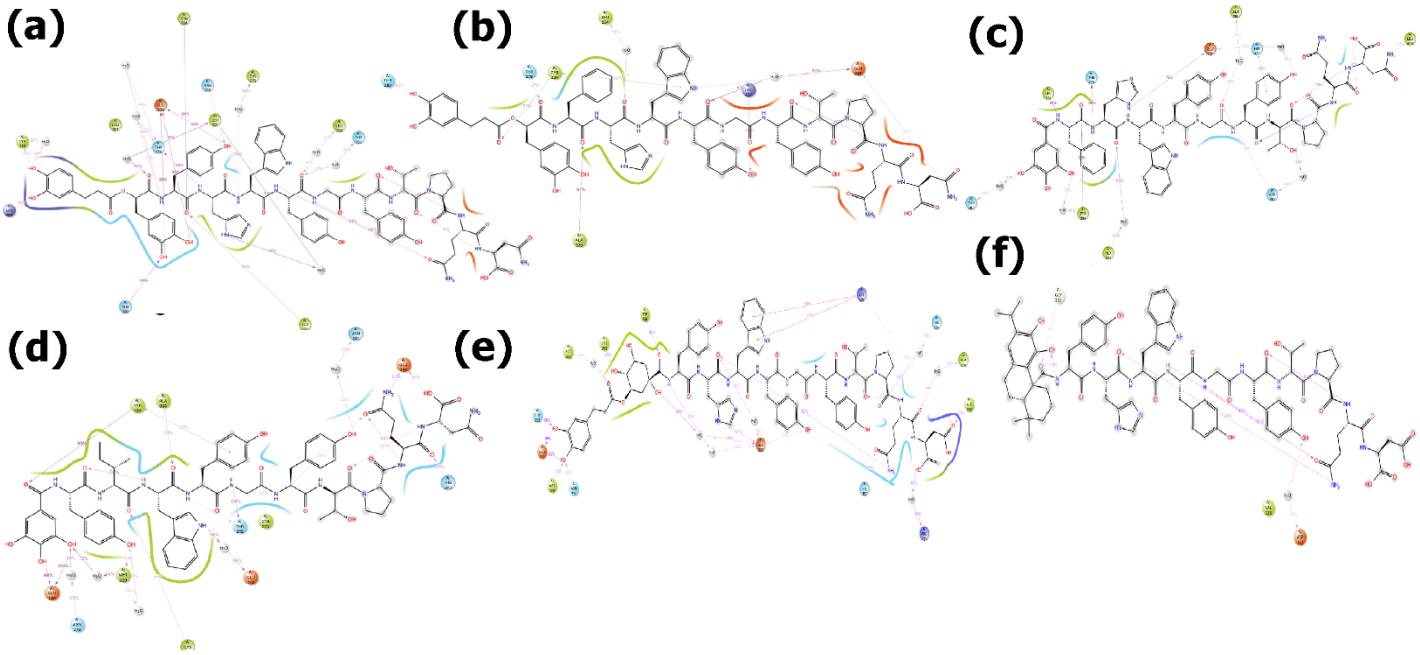


Figure S11. Schematic of ligand atom interactions with the PPARα receptor protein residues. Interactions that occur more than **30.0%** of the simulation time are shown (a) with RMA-Pep conjugate; (b) with RMA-Mut1 conjugate; (c) with GLA-Mut1 conjugate (d) with GLA-Mut2 conjugate; (e) with CGA-Mut4 conjugate; (f) with CSA-Mut4 conjugate

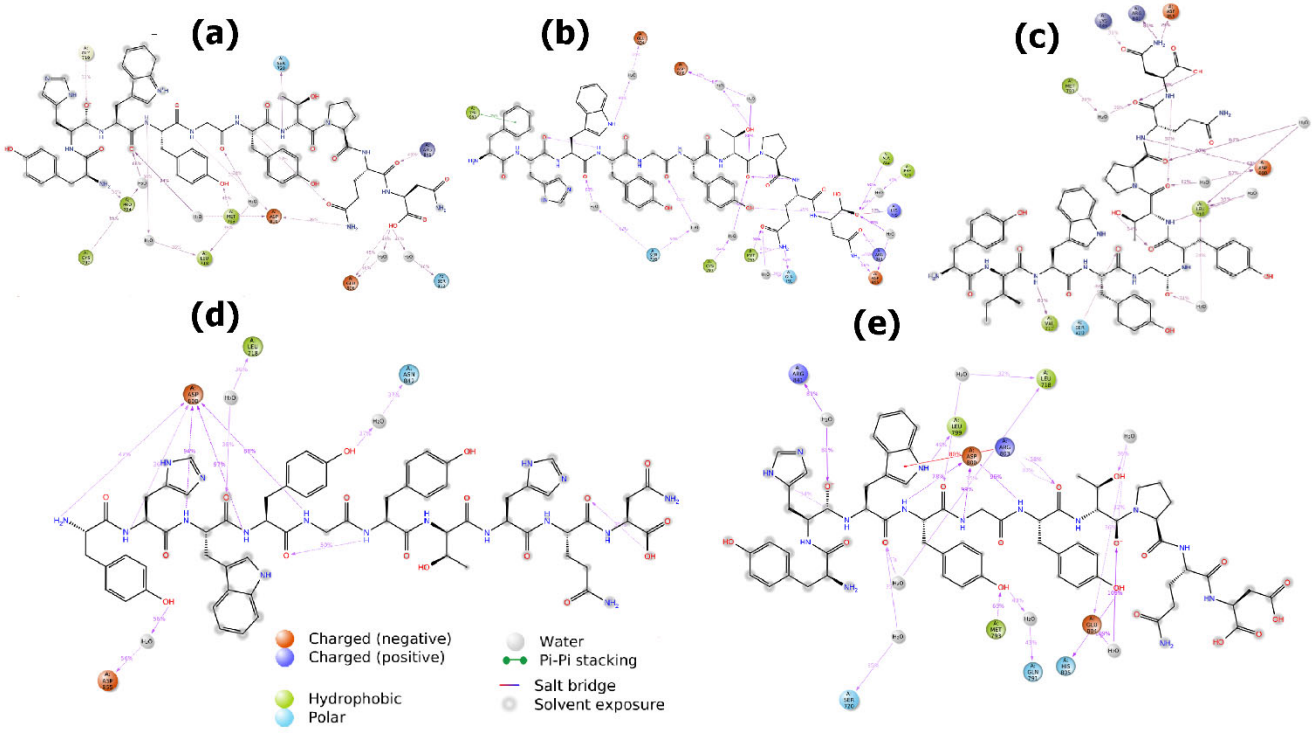


Figure S12. Schematic of ligand atom interactions with the EGFR receptor protein residues. Interactions that occur more than **30.0%** of the simulation time are shown. (a) Pep; (b) Mut1; (c) Mut2; (d) Mut3; (e) Mut4

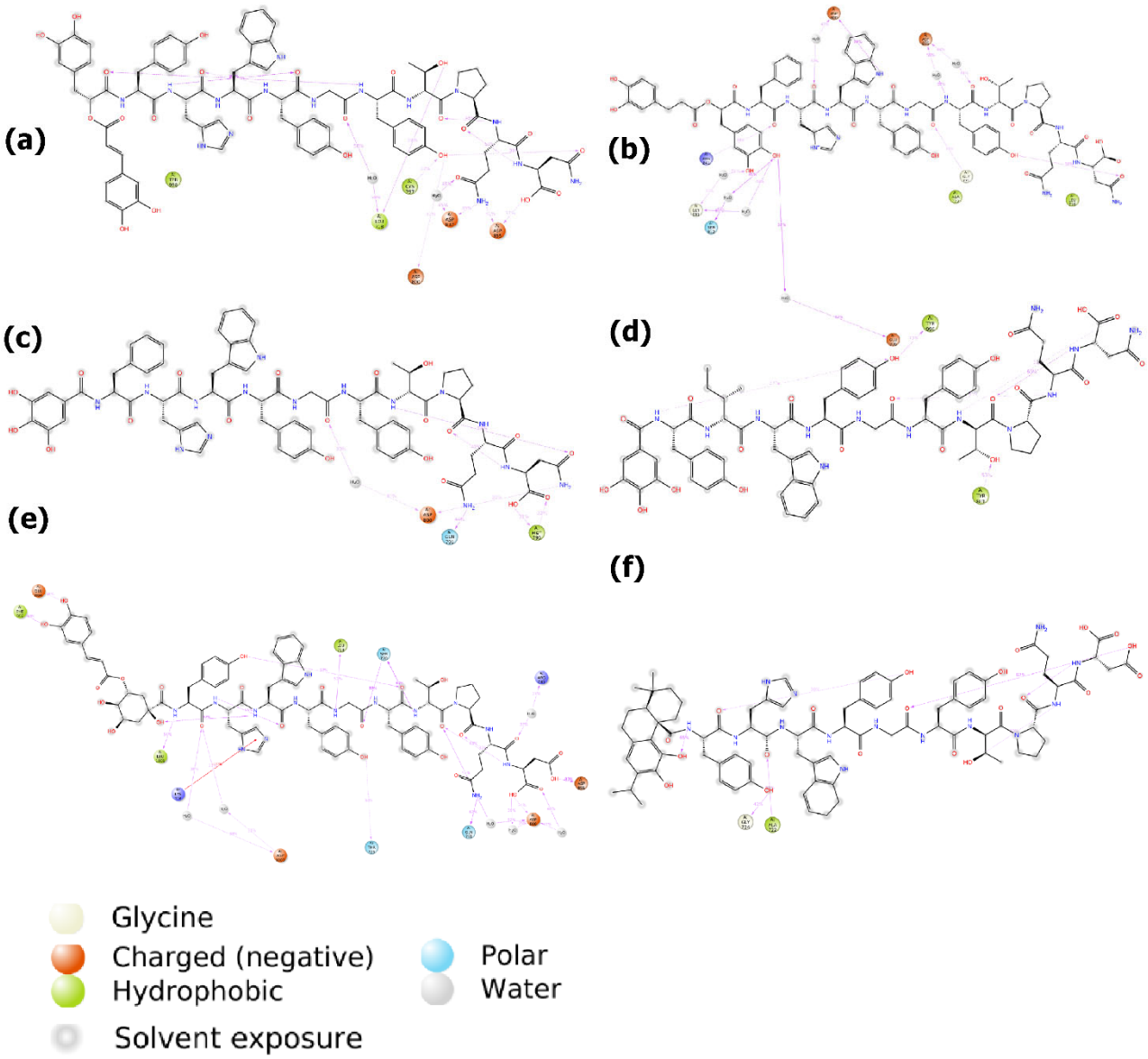


Figure S13. Schematic of ligand atom interactions with the EGFR receptor protein residues. Interactions that occur more than **30.0%** of the simulation time are shown. (a) with RMA-Pep; (b) with RMA-Mut1 conjugate (c) with GLA-Mut1 conjugate; (d) with GLA-Mut2 conjugate; (e) with CGA-Mut4 conjugate; (f) with CSA-Mut4 conjugate