Supporting Information for

Structural and energetic study of cation–π–cation interactions in proteins

Silvana Pinheiro,[1] Ignacio Soteras,[2] Josep Lluis Gelpí,[3] François Dehez,[4] Christophe Chipot,[4,5] F. Javier Luque,[2] and Carles Curutchet[1,*]

[1]*Departament de Farmàcia i Tecnologia Farmacèutica i Fisicoquímica and Institut de Biomedicina (IBUB), Facultat de Farmàcia i Ciències de l'Alimentació, Universitat de Barcelona, Barcelona Spain*

[2]*Departament de Nutrició, Ciències de l'Alimentació i Gastronomia and Institut de Biomedicina (IBUB), Facultat de Farmàcia i Ciències de l'Alimentació, Universitat de Barcelona, Santa Coloma de Gramenet, Spain.*

[3]*Departament de Bioquímica i Biomedicina Molecular, Facultat de Biologia, Universitat de Barcelona, Spain*

[4]*Laboratoire International Associé Centre National de la Recherche Scientifique et University of Illinois at Urbana −Champaign, Unité Mixte de Recherche No. 7565, Université de Lorraine, Vandoeuvre-lès-Nancy cedex, France*

[5]*Beckman Institute for Advanced Science and Engineering, University of Illinois at Urbana — Champaign, Urbana, Illinois (USA).*

Table S1: Nature of X–Trp–Y interactions (in percent). The total number of interactions is 728.

X/Y	LYS	ARG	HIS	CU	CA	NA	MG	K	LI
LYS	11.95	28.02	16.35	0	0	0	0	0	0
ARG		20.33	17.99	0	0	0.14	0	0	0
HIS			4.95	0	0	0.14	0.14	0	0
CU				0	0	0	0	0	0
CA					0	0	0	0	0
NA						0	0	0	0
MG							0	0	0
K								0	0
LI									0

Table S2: Nature of X–Tyr–Y interactions (in percent). The total number of interactions is 1356.

X/Y	LYS	ARG	HIS	CU	CA	NA	MG	K	LI
LYS	19.25	26.47	17.7	0	0.07	0	0.15	0	0
ARG		13.57	16.96	0	0	0.07	0.07	0	0
HIS			5.68	0	0	0	0	0	0
CU				0	0	0	0	0	0
CA					0	0	0	0	0
NA						0	0	0	0
MG							0	0	0
K								0	0
LI									0

Table S3: Nature of X–Phe–Y interactions (in percent). The total number of interactions is 814.

X/Y	LYS	ARG	HIS	CU	CA	NA	MG	K	LI
LYS	13.39	22.97	17.08	0	0.12	0	0	0	0
ARG		15.6	20.88	0	0	0	0	0	0
HIS			9.95	0	0	0	0	0	0
CU				0	0	0	0	0	0
CA					0	0	0	0	0
NA						0	0	0	0
MG							0	0	0
K								0	0
LI									0

Table S4: Protein structures corresponding to the cation–π–cation interactions selected for the energetic analysis.

ID	Classification	Organism
1A22	Growth hormone bound to single receptor	Homo sapiens
1B35	Virus	Cricket paralysis virus
1CN4	Haematopoietic Cytokine	Homo sapiens
1EGJ	Immune System	Homo sapiens
1FG9	Immune System	Homo sapiens
1GQK	Hydrolase	Cellvibrio japonicus
1GXS	Lyase	Sorghum bicolor
1IWB	Lyase	Klebsiella oxytoca
1KXV	Hydrolase	Camelus dromedarius
1MDX	Transferase	Salmonella typhimurium
1SQV	Oxidoreductase	Bos taurus
1T72	Transport Protein	Aquifex aeolicus
1TJ0	Oxidoreductase	Escherichia coli
1TZ9	Lyase	Enterococcus faecalis v583
1UA4	Transferase	Pyrococcus furiosus
1VFF	Hydrolase	Pyrococcus horikoshii
2AK4	Immune System	Homo sapiens
2CQQ	Membrane Protein	Homo sapiens
2CVF	DNA Binding Protein	Thermococcus kodakarensis
2CYC	Ligase	Pyrococcus horikoshii ot3
2GRE	Hydrolase	Bacillus cereus
2H39	Transferase	Arabidopsis thaliana
2HCS	Transferase	Kunjin virus
2J47	Inhibitor	Bacteroides thetaiotaomicron
2J7A	Oxidoreductase	Desulfovibrio vulgaris
2JKV	Oxidoreductase	Human
2OT4	Oxidoreductase	Thioalkalivibrio nitratireducens
2PAM	Isomerase	Aneurinibacillus thermoaerophilus
2PI0	Transcription Activator/dna	Homo sapiens

2QOW	Ribosome	Escherichia coli
2QWN	Chaperone	Bos taurus
2VLR	Immune System	Homo sapiens
2YU9	Transcription	Saccharomyces cerevisiae
2ZTG	Ligase	Archaeoglobus fulgidus
3C5Z	Sugar Binding Protein/immune System	Mus musculus
3CES	RNA Binding Protein	Escherichia coli
3DGC	Cytokine/signaling Protein	Homo sapiens
3E0M	Oxidoreductase	Streptococcus pneumoniae
3FQD	Hydrolase/protein Binding	Schizosaccharomyces pombe
3G9V	Cytokine/cytokine Receptor	Homo sapiens
3GVP	Hydrolase	Homo sapiens
3HUJ	Immune System	Homo sapiens

Table S5: Amino acids corresponding to the cation–π–cation interactions selected for the energetic analysis.

ID	X		Ar		Y	
X-Trp-Y						
1A22-1	LYS	B379	TRP	B386	ARG	B411
1CN4-1	ARG	A197	TRP	A209	ARG	A199
1EGJ-1	ARG	A377	TRP	A383	ARG	A411
1EGJ-2	ARG	A413	TRP	A425	ARG	A415
1FG9-1	LYS	C47	TRP	C56	ARG	C84
1GXS-1	ARG	A215	TRP	A205	ARG	D368
1GXS-2	ARG	B368	TRP	C205	ARG	C215
1IWB-2	LYS	A395	TRP	A538	LYS	A542
1KXV-1	ARG	C45	TRP	C111	LYS	C96
1MDX-1	ARG	A110	TRP	A353	ARG	A357
1SQV-2	LYS	C311	TRP	C379	ARG	F33
1UA4-1	LYS	A37	TRP	A103	ARG	A47
1VFF-1	ARG	A75	TRP	A49	LYS	A90
2CQQ-1	ARG	A43	TRP	A11	LYS	A51
2HCS-1	ARG	A742	TRP	A800	ARG	A797
2PI0-1	LYS	A77	TRP	A38	LYS	A105
2QOW-1	ARG	I112	TRP	N100	ARG	J48
2ZTG-1	ARG	A89	TRP	A619	ARG	A679
3DGC-1	LYS	R58	TRP	R65	ARG	R95
3FQD-1	ARG	A853	TRP	B204	ARG	B271
3G9V-1	LYS	A65	TRP	A72	ARG	A102
3G9V-2	ARG	A102	TRP	A114	ARG	A104
3GVP-1	LYS	A228	TRP	A302	ARG	A254
X-Tyr-Y						
1A22-2	ARG	B413	TYR	B422	LYS	B415
1TJ0-1	ARG	A100	TYR	A99	ARG	A409
1TZ9-2	ARG	A80	TYR	A188	ARG	A192
2GRE-1	ARG	G171	TYR	A103	LYS	G181

2J47-1	ARG	A235	TYR	A230	LYS	A269
2J47-2	ARG	A219	TYR	A260	LYS	A264
2J47-4	ARG	A519	TYR	A523	LYS	A527
2JKV-1	LYS	B76	TYR	A481	LYS	B261
2JKV-2	ARG	C136	TYR	C137	LYS	F309
2PAM-1	LYS	A32	TYR	A113	LYS	B25
2PAM-2	LYS	A25	TYR	B113	LYS	B32
2QWN-1	ARG	A100	TYR	A115	LYS	A102
2YU9-1	ARG	C84	TYR	C82	LYS	C161
3E0M-1	ARG	A259	TYR	A246	ARG	B115
X-Phe-Y						
1A22-3	ARG	B411	PHE	B425	ARG	B413
1B35-1	ARG	B78	PHE	B75	LYS	B115
1GQK-2	ARG	A550	PHE	A558	ARG	A560
1T72-1	ARG	A107	PHE	A189	ARG	B192
1T72-2	ARG	A192	PHE	B189	ARG	B107
2AK4-1	ARG	E190	PHE	E124	ARG	E230
2CVF-1	LYS	A165	PHE	A157	ARG	A181
2CYC-1	LYS	A247	PHE	A243	ARG	A285
2H39-1	ARG	A26	PHE	A240	ARG	B116
2H39-2	ARG	A116	PHE	B240	ARG	B26
2J7A-1	ARG	A133	PHE	A111	LYS	A295
2OT4-1	ARG	A131	PHE	A109	LYS	A358
2VLR-1	ARG	E187	PHE	E121	ARG	E227
3C5Z-1	ARG	B183	PHE	B117	ARG	B223
3CES-1	LYS	A145	PHE	A2	ARG	A147
3HUJ-1	ARG	F190	PHE	F124	ARG	F230

Table S6: Distances, angles, and dihedral angles between the aromatic amino acid and the arginine guanidinium planes characterizing the cation–π–cation interactions selected for the energetic analysis.

ID	d_{XAr} (Å)	θ_{XAr} (˚)	d_{ArY} (Å)	θ_{ArY} (˚)	$\varphi_{XAr\ planes}$ (˚)	$\varphi_{ArY\ planes}$ (˚)
X-Trp-Y						
1A22-1	3.7	25.5	4.1	33.7		14.7
1CN4-1	3.6	15.2	3.8	20.6	25.8	74.0
1EGJ-1	3.8	19.6	3.7	15.0	42.3	9.4
1EGJ-2	3.8	14.7	3.7	20.2	18.9	44.4
1FG9-1	4.0	12.7	3.7	11.5		12.8
1GXS-1	3.9	16.0	3.7	26.0	36.9	13.3
1GXS-2	3.6	24.5	3.8	12.7	12.3	32.2
1IWB-2	3.6	11.7	3.5	16.3		
1KXV-1	3.5	20.2	4.0	6.4	15.3	
1MDX-1	3.7	13.3	3.6	23.5	32.4	5.4
1SQV-2	3.6	6.5	3.5	29.4		9.6
1UA4-1	3.3	8.4	3.6	28.3		22.0
1VFF-1	3.8	17.9	3.8	11.6	7.2	
2CQQ-1	4.2	17.4	3.6	21.5	37.5	
2HCS-1	3.6	10.9	4.4	19.8	10.5	6.2
2PI0-1	3.7	29.3	3.5	6.7		
2QOW-1	3.9	18.4	3.3	17.7	17.4	12.2
2ZTG-1	3.5	10.7	3.7	21.1	2.2	13.9
3DGC-1	4.6	17.5	3.2	7.4		13.2
3FQD-1	3.9	19.4	3.5	1.0	6.5	1.4
3G9V-1	4.2	19.2	3.4	8.2		14.9
3G9V-2	3.5	12.4	3.9	32.4	10.8	12.6
3GVP-1	4.3	30.4	3.5	8.7		57.4
X-Tyr-Y						
1A22-2	4.4	36.1	4.0	25.3	10.2	
1TJ0-1	3.9	7.3	3.6	19.9	26.2	16.2
1TZ9-2	3.4	2.9	3.5	21.1	5.2	28.7
2GRE-1	4.1	11.2	3.8	14.1	19.8	
2J47-1	3.6	21.7	4.0	4.2	10.3	
2J47-2	4.1	39.9	4.4	41.6	8.2	
2J47-4	4.2	24.1	4.4	24.8	9.9	
2JKV-1	3.7	16.7	3.6	12.9		
2JKV-2	5.0	28.1	3.6	6.9	10.4	
2PAM-1	3.9	37.7	4.7	14.7		
2PAM-2	4.1	8.5	3.8	27.2		
2QWN-1	3.9	27.3	3.7	3.1	14.8	
2YU9-1	3.7	14.5	4.0	23.2	23.6	
3E0M-1	3.5	3.5	3.6	24.3	5.0	12.7
X-Phe-Y						

1A22-3	4.1	29.0	4.7	43.4	21.4	24.9
1B35-1	3.8	1.4	3.7	18.2	23.0	
1GQK-2	3.7	19.4	3.6	19.8	76.2	3.4
1T72-1	4.2	31.8	3.7	25.6	3.4	20.0
1T72-2	3.9	23.1	3.9	14.6	23.3	18.9
2AK4-1	3.6	10.5	3.9	25.3	6.4	9.9
2CVF-1	3.8	20.9	4.0	18.8		53.7
2CYC-1	3.9	12.2	3.9	22.1		28.5
2H39-1	4.2	30.5	3.7	8.3	4.4	3.8
2H39-2	3.6	7.1	4.5	32.4	10.0	12.4
2J7A-1	4.1	22.5	3.9	8.6	5.2	
2OT4-1	4.0	17.2	3.5	14.6	33.7	
2VLR-1	3.8	15.8	4.0	23.7	4.1	10.1
3C5Z-1	3.6	16.6	3.6	19.5	39.4	14.2
3CES-1	3.8	23.4	3.6	11.6		13.0
3HUJ-1	3.5	5.8	3.9	27.2	9.2	8.7

Table S7: Conservation, residue variety, pKa and percent of buried surface computed using the PropKa and the ConSurf servers for the cation–π–cation interactions selected for energetic analysis.

ID	Residue	pKa	Buried (%)	Score	Residue variety
X-Trp-Y					
1A22-1	TRP B386			9	W,P
	LYS B379	11.2	0	7	S,Q,T,N,R,K
	ARG B411	11.5	0	8	H,Q,D,R,E,V
1CN4-1	TRP A209			7	W,P,R
	ARG A197	11.6	32	9	T,R,L
	ARG A199	11.0	38	8	H,Q,N,K,R,L
1EGJ-1	TRP A383			6	R,W,E,L
	ARG A377	11.6	8	6	W,K,T,R,M
	ARG A411	10.7	30	9	R,K
1EGJ-2	TRP A425			8	W,Y
	ARG A413	11.6	23	9	R
	ARG A415	11.8	10	5	E,M,R,K
1FG9-1	TRP C56			9	W
	LYS C47	10.5	30	8	K,I,L,M
	ARG C84	12.7	29	8	K,Q,R
1GXS-1	TRP A205			9	W
	ARG A215	12.5	62	5	N,R,A,Y,F,L,H,V,I
	ARG D368	10.2	100	8	M,K,I,R,Q
1GXS-2	TRP C205			9	W
	ARG B368	10.4	100	8	M,I,K,R,Q
	ARG C215	12.7	62	5	L,I,F,V,N,Y,R,H,A
1IWB-2	TRP A538			7	Q,W,R
	LYS A395	8.7	72	1	S,A,Q,M,R,K,G,E
	LYS A542	11.0	43	6	S,Q,D,N,I,K,E,V
1KXV-1	TRP C111			9	W
	ARG C45	11.0	31	9	R,P,L
	LYS C96	8.2	73	7	T,K,E,S,V,G,R,M,A
1MDX-1	TRP A353			1	L,F,V,D,S,T,R,H,E,W,K,N,A,Q
	ARG A110	13.1	1	2	Q,M,A,N,E,Y,S,R,D,L,K,G,I,P,H,V,C
	ARG A357	12.9	19	4	S,T,R,H,G,E,K,N,Q,A
1SQV-2	TRP C379			8	F,W
	LYS C311	9.4	60	8	N,K
	ARG F33	12.8	73	4	F,A,S,W,T,N,K,Y,H,Q,M,R,I,G,L
1UA4-1	TRP A103			2	A,S,F,T,W,N,K,E,Y,V,H,I,R,L
	LYS A37	9.0	45	5	A,T,N,K,Y,V,H,M,C,R,I
	ARG A47	13.9	28	7	F,M,I,R,Y,L,V
1VFF-1	TRP A49			8	F,W,R,Y
	ARG A75	13.8	96	9	S,T,R,G,L
	LYS A90	9.7	41	6	H,F,R,K,Y

2CQQ-1	TRP A11			9	W
	ARG A43	12.8	2	9	K,R,H
	LYS A51	10.1	0	7	K,F,V,R,H,A,Q,M
2HCS-1	TRP A800			8	W,E
	ARG A742	12.5	15	9	T,K,R
	ARG A797	11.7	20	9	K,R
2PI0-1	TRP A38			9	W
	LYS A77	9.8	75	9	K,E
	LYS A105	9.3	72	8	P,R,K,E
2QOW-1	TRP N100			9	W
	ARG I112	13.0	0	9	R
	ARG J48	12.0	0	1	H,I,K,R,L,V
2ZTG-1	TRP A619			4	A,S,T,W,N,K,E,V,H,Q,M,I,R,G,L
	ARG A89	9.1	100	9	K,R
	ARG A679	9.8	85	8	S,A,T,K,E,V,Q,M,D,C,R,I,G
3DGC-1	TRP R65			9	W
	LYS R58	10.2	26	6	F,A,S,T,N,K,Y,Q,M,I,L
	ARG R95	12.3	23	7	S,Q,D,N,K,R
3FQD-1	TRP B204			4	A,F,W,K,E,Y,V,Q,C,I,R,L
	ARG A853	10.4	98	4	A,S,N,K,P,E,V,H,Q,C,D,I,R
	ARG B271	10.9	66	6	A,T,N,K,Y,E,H,Q,D,R,I,L
3G9V-1	TRP A72			9	W
	LYS A65	8.9	52	9	S,K,F,L
	ARG A102	10.1	50	8	S,K,R
3G9V-2	TRP A114			8	C,T,W
	ARG A102	10.1	50	8	S,K,R
	ARG A104	11.9	14	3	S,K,T,M,R,H,Q
3GVP-1	TRP A302			1	A,W,K,P,E,D,G,L
	LYS A228	10.1	0	6	Q,T,N,R,K,V
	ARG A254	12.2	55	6	S,A,T,K,Y,V,Q,R,L
X-Tyr-Y					
1A22-2	TYR B422			6	A,F,W,R,K,Y
	ARG B413	12.8	0	9	S,H,Q,R
	LYS B415	10.3	1	6	A,T,N,K,V,Q,M,R,I
1TJ0-1	TYR A99			4	A,S,F,T,W,N,P,K,Y,H,M,C,R,I,G
	ARG A100	12.1	34	7	A,S,T,N,Y,V,H,Q,M,C,D,I,R,G,L
	ARG A409	10.7	89	9	S,R
1TZ9-2	TYR A188			2	A,F,W,E,Y,V,H,D,L
	ARG A80	12.0	22	6	A,F,W,C,R,Y
	ARG A192	12.7	11	2	A,Q,N,K,R,G,E
2GRE-1	TYR A103			8	S,T,N,P,K,E,Y,V,H,Q,D,C,R,G
	ARG G171	12.5	100	6	S,A,T,N,P,K,E,H,Q,M,C,D,R,G,L
	LYS G181	9.0	89	8	A,S,T,N,K,V,M,R,I,G,L
2J47-1	TYR A230			9	Y
	ARG A235	13.0	31	9	R
	LYS A269	11.4	0	9	H,K

2J47-2	TYR A260			6	R,Y,F,D,K
	ARG A219	13.1	0	8	M,Y,S,R
	LYS A264	10.5	0	4	V,T,R,A,E,K,H,N,Q
2J47-4	TYR A523			1	V,Y,S,R,T,K,G,E,L,F,A,N,H,D,Q
	ARG A519	12.7	0	1	Q,D,P,N,H,K,G,E,S,R
	LYS A527	10.7	15	1	Q,S,R,T,Y,V,N,I,H,G,K,L,A
2JKV-1	TYR A481			9	H,Y
	LYS B76	10.1	0	7	S,Q,T,M,R,K,E
	LYS B261	7.2	70	9	K
2JKV-2	TYR C137			1	F,W,T,N,K,E,Y,H,Q,M,I,R,L
	ARG C136	12.9	26	9	R,L
	LYS F309	11.5	0	1	F,S,T,N,K,E,V,Q,M,C,L,A,P,H,D,I,R,G
2PAM-1	TYR A113			1	S,F,T,N,K,E,Y,V,Q,M,L,A,P,H,D,I,R,G
	LYS A32	11.2	3	6	S,A,N,K,E,V,H,Q,C,R,L
	LYS B25	11.5	0	1	F,S,T,N,K,Y,E,V,Q,M,C,L,A,W,P,H,D,R,I,G
2PAM-2	TYR B113			1	S,F,T,N,K,E,Y,V,Q,M,L,A,P,H,D,I,R,G
	LYS A25	10.4	0	1	F,S,T,N,K,Y,E,V,Q,M,C,L,A,W,P,H,D,R,I,G
	LYS B32	11.5	13	6	S,A,N,K,E,V,H,Q,C,R,L
2QWN-1	TYR A115			5	A,S,F,T,N,K,Y,H,Q,R
	ARG A100	10.4	21	5	A,S,T,N,K,Y,E,V,Q,M,D,R,I,G,L
	LYS A102	10.4	11	1	S,A,W,T,N,K,E,Y,V,H,Q,M,D,R,I,G,L
2YU9-1	TYR C82			4	S,F,T,N,K,E,Y,M,L,A,W,P,H,D,R,I,G
	ARG C84	11.8	50	6	S,T,N,K,Y,E,V,Q,M,A,W,P,H,D,R,I,G
	LYS C161	9.2	57	9	M,P,R,K,L
3E0M-1	TYR A246			1	S,F,T,N,K,E,Y,V,Q,L,A,W,P,H,D,R,I
	ARG A259	13.0	60	8	S,T,I,K,R,L,V
	ARG B115	11.2	59	1	A,S,T,N,P,K,E,H,Q,D,R,G,L
X-Phe-Y					
1A22-3	PHE B425			9	F,W
	ARG B411	11.5	0	8	H,Q,D,R,E,V
	ARG B413	12.8	0	9	S,H,Q,R
1B35-1	PHE B75			8	F
	ARG B78	12.1	0	9	R
	LYS B115	10.2	0	9	K
1GQK-2	PHE A558			9	F,T,K,Y,V,M,C,R,I
	ARG A550	11.8	29	6	F,S,N,K,Y,H,Q,R,G
	ARG A560	12.4	100	9	R
1T72-1	PHE A189			5	S,F,T,N,Y,V,Q,M,C,L,A,W,H,D,R,I
	ARG A107	11.6	82	6	S,F,T,N,K,Y,E,V,Q,M,L,A,H,D,I,R,G
	ARG B192	9.6	100	8	S,N,K,E,H,Q,R,G,L
1T72-2	PHE B189			5	S,F,T,N,Y,V,Q,M,C,L,A,W,H,D,R,I
	ARG A192	12.5	100	8	S,N,K,E,H,Q,R,G,L
	ARG B107	10.5	76	6	S,F,T,N,K,Y,E,V,Q,M,L,A,H,D,I,R,G
2AK4-1	PHE E124			3	S,H,F,Q,T,N,I,R,K,E
	ARG E190	11.6	42	6	S,T,N,K,Y,V,H,Q,M,R,L
	ARG E230	11.3	17	7	S,W,N,I,R

2CVF-1	PHE A157			3	F,Y
	LYS A165	9.9	12	5	K,R
	ARG A181	12.1	44	9	R
2CYC-1	PHE A243			3	S,F,N,I,E,Y
	LYS A247	9.8	47	6	A,S,T,N,K,Y,V,Q,D,G,L
	ARG A285	12.8	0	3	A,S,F,N,P,K,E,Q,D,R,I,G
2H39-1	PHE A240			5	W,F,Y
	ARG A26	13.7	50	9	H,R
	ARG B116	11.6	36	5	N,C,M,D,Q,W,K,S,A,V,R,F,G,T,E,L
2H39-2	PHE B240			5	Y,F,W
	ARG A116	11.5	38	5	K,L,N,E,S,V,W,R,M,C,G,T,A,F,Q,D
	ARG B26	13.6	54	9	H,R
2J7A-1	PHE A111			9	A,F,M,Y
	ARG A133	11.3	100	9	S,P,R
	LYS A295	9.4	100	9	A,F,H,Q,K,Y
2OT4-1	PHE A109			9	F
	ARG A131	11.1	100	9	R
	LYS A358	9.6	100	9	K
2VLR-1	PHE E121			4	S,H,F,Q,I,L,K,E,R,T,N
	ARG E187	11.7	34	1	L,V,F,S,N,T,R,K
	ARG E227	11.3	15	6	N,G,R,T,E,W,S,D
3C5Z-1	PHE B117			5	A,S,F,T,N,P,K,E,V,H,Q,R,I,L
	ARG B183	11.6	33	6	S,T,N,K,Y,V,H,Q,M,R,L
	ARG B223	11.4	14	7	S,W,N,R
3CES-1	PHE A2			1	F,T,W,N,K,E,Y,H,Q,D,R,I,G,L
	LYS A145	9.6	51	1	S,F,T,N,K,Y,E,V,Q,M,C,L,A,P,H,D,R,I
	ARG A147	12.0	23	1	S,F,T,N,K,E,Y,Q,M,C,L,A,W,P,H,D,I,R,G
3HUJ-1	PHE F124			6	A,S,F,T,N,P,K,E,V,H,Q,R,I,L
	ARG F190	12.0	22	7	S,T,N,K,Y,V,H,Q,M,R,L
	ARG F230	11.3	17	7	S,W,N,R,E

Table S8: SCS-MP2/CBS interaction energies (kcal/mol) predicted for the cation–π–cation interactions in vacuum.

ID	ΔE_{XAr}	ΔE_{ArY}	ΔE_{XY}	ΔE_{XArY}	$\Delta E_{3\text{-}body}$
X-Trp-Y					
1A22-1	-5.5	-8.2	39.7	28.2	2.1
1CN4-1	-9.1	-8.7	43.9	32.1	5.9
1EGJ-1	-11.5	-8.5	41.9	26.3	4.4
1EGJ-2	-9.8	-4.2	40.5	30.4	4.0
1FG9-1	-6.6	-7.1	43.9	32.4	2.2
1GXS-1	-12.0	-7.1	42.4	27.0	3.6
1GXS-2	-6.9	-11.3	42.1	27.4	3.5
1IWB-2	-8.7	-4.5	45.8	33.8	1.2
1KXV-1	-11.9	-16.8	48.1	25.9	6.5
1MDX-1	-11.2	-6.9	42.5	28.0	3.6
1SQV-2	-8.3	-5.4	45.9	33.8	1.6
1UA4-1	-10.9	-4.1	48.0	34.2	1.2
1VFF-1	-11.0	-15.0	43.1	22.5	5.3
2CQQ-1	-12.0	-15.1	43.3	21.5	5.3
2HCS-1	-10.0	-8.8	38.5	23.3	3.7
2PI0-1	-4.9	-11.7	42.4	28.7	2.9
2QOW-1	-6.4	-10.5	42.7	29.4	3.6
2ZTG-1	-10.3	-8.6	42.3	27.4	4.0
3DGC-1	-3.8	-8.0	41.5	32.5	2.8
3FQD-1	-8.2	-9.6	41.0	26.5	3.4
3G9V-1	-8.7	-9.8	44.4	29.8	3.8
3G9V-2	-8.0	-6.0	41.5	30.2	2.6
3GVP-1	-8.2	-11.0	42.1	26.2	3.3
X-Tyr-Y					
1A22-2	-5.0	-4.7	34.0	27.0	2.7
1TJ0-1	-8.2	-5.5	40.7	30.6	3.5
1TZ9-2	-7.0	-6.0	44.1	35.4	4.4
2GRE-1	-7.2	-13.1	41.2	25.6	4.7
2J47-1	-8.5	-7.7	41.1	29.0	4.2
2J47-2	-7.2	-6.2	42.4	31.2	2.2
2J47-4	-5.9	-8.1	39.8	27.8	2.0
2JKV-1	-9.9	-8.9	39.9	26.5	5.4
2JKV-2	-4.7	-12.4	37.2	23.6	3.5
2PAM-1	-11.9	-7.2	39.4	25.0	4.7
2PAM-2	-7.9	-12.6	43.5	26.6	3.6
2QWN-1	-8.1	-8.1	38.9	26.9	4.1
2YU9-1	-7.6	-8.8	40.3	28.1	4.2
3E0M-1	-7.5	-7.6	42.4	31.0	3.7
X-Phe-Y					
1A22-3	-6.7	-5.0	39.5	30.4	2.6

1B35-1	-7.2	-9.5	41.7	28.5	3.6
1GQK-2	-7.9	-6.5	41.0	30.3	3.7
1T72-1	-6.7	-8.1	41.4	30.4	3.8
1T72-2	-7.6	-8.4	40.3	28.5	4.2
2AK4-1	-7.0	-6.3	41.1	30.9	3.1
2CVF-1	-12.5	-11.1	45.7	29.5	7.4
2CYC-1	-8.4	-5.3	39.5	29.5	3.9
2H39-1	-6.3	-6.9	39.5	29.4	3.1
2H39-2	-6.4	-6.7	38.8	28.8	3.2
2J7A-1	-6.4	-7.4	38.5	27.7	3.0
2OT4-1	-6.0	-11.9	40.4	27.2	4.8
2VLR-1	-6.9	-6.0	39.5	29.5	3.0
3C5Z-1	-8.9	-6.6	43.0	32.2	4.7
3CES-1	-7.2	-7.7	40.6	29.4	3.8
3HUJ-1	-7.0	-6.9	41.8	31.2	3.2

Table S9: Interaction energies (kcal/mol) predicted for the cation–π–cation interactions in vacuum, in a polar (water) and apolar (*n*-octanol) environments, and in the protein environment. Vacuum interaction energies were computed at the SCS-MP2/CBS level of theory, octanol and water solvation energies by MST-IEFPCM B3LYP/6-31G(d) calculations, and water to protein transfer free energies by classical MM-GBSA calculations.

ID	ΔE_{vac}	$\Delta\Delta G_{solv}^{oct}$	$\Delta\Delta G_{solv}^{wat}$	$\Delta G_{wat\rightarrow prot}$	ΔE_{oct}	ΔE_{wat}	ΔE_{prot}
X-Trp-Y							
1A22-1	28.2	-21.5	-26.6	-18.3	6.7	1.5	-16.7
1CN4-1	32.1	-20.2	-19.6	-2.8	11.9	12.5	9.7
1EGJ-1	26.3	-22.0	-22.8	1.3	4.3	3.6	4.8
1EGJ-2	30.4	-24.4	-27.2	30.1	6.1	3.2	33.3
1FG9-1	32.4	-24.1	-29.6	-10.5	8.2	2.7	-7.8
1GXS-1	27.0	-24.0	-25.3	-26.2	3.0	1.7	-24.5
1GXS-2	27.4	-24.0	-26.1	-26.2	3.3	1.2	-25.0
1IWB-2	33.8	-22.7	-28.8	-8.2	11.1	5.0	-3.3
1KXV-1	25.9	-19.3	-19.1	4.6	6.6	6.8	11.4
1MDX-1	28.0	-24.3	-26.2	-16.9	3.7	1.8	-15.2
1SQV-2	33.8	-25.4	-29.2	-3.9	8.4	4.6	0.7
1UA4-1	34.2	-25.6	-29.7	-10.7	8.6	4.5	-6.2
1VFF-1	22.5	-19.1	-20.0	-7.0	3.4	2.5	-4.5
2CQQ-1	21.5	-14.9	-15.5	13.9	6.6	6.1	20.0
2HCS-1	23.3	-21.7	-23.9	-1.0	1.7	-0.6	-1.6
2PI0-1	28.7	-18.7	-23.6	-12.2	9.9	5.0	-7.2
2QOW-1	29.4	-25.9	-28.1	-44.6	3.5	1.3	-43.3
2ZTG-1	27.4	-25.3	-27.2	-13.2	2.0	0.2	-13.0
3DGC-1	32.5	-23.2	-28.0	-1.0	9.3	4.5	3.5
3FQD-1	26.5	-24.5	-26.5	0.0	2.1	0.0	0.0
3G9V-1	29.8	-22.9	-25.5	9.0	6.9	4.3	13.2
3G9V-2	30.2	-26.6	-29.9	-3.8	3.5	0.3	-3.5
3GVP-1	26.2	-20.4	-22.2	-8.3	5.8	4.0	-4.3
X-Tyr-Y							
1A22-2	27.0	-20.8	-26.1	-1.9	6.1	0.9	-1.0
1TJ0-1	30.6	-27.1	-30.1	3.5	3.5	0.5	4.0
1TZ9-2	35.4	-26.9	-28.0	-11.3	8.6	7.5	-3.8
2GRE-1	25.6	-20.1	-21.7	-22.2	5.5	4.0	-18.3
2J47-1	29.0	-22.8	-27.6	-9.1	6.2	1.4	-7.7
2J47-2	31.2	-23.8	-27.8	-7.5	7.3	3.3	-4.1
2J47-4	27.8	-22.0	-26.2	0.7	5.8	1.6	2.3
2JKV-1	26.5	-17.3	-20.2	11.7	9.3	6.3	18.0
2JKV-2	23.6	-18.6	-20.4	-9.6	5.0	3.2	-6.4
2PAM-1	25.0	-14.5	-16.3	-2.9	10.5	8.7	5.8
2PAM-2	26.6	-17.0	-20.0	-4.5	9.5	6.6	2.0

2QWN-1	26.9	-20.3	-22.9	-4.6	6.6	4.0	-0.6
2YU9-1	28.1	-21.2	-24.8	-4.4	6.9	3.3	-1.0
3E0M-1	31.0	-28.3	-30.3	-27.0	2.7	0.7	-26.3
X-Phe-Y							
1A22-3	30.4	-25.8	-29.0	-9.2	4.6	1.4	-7.8
1B35-1	28.5	-22.5	-24.7	-1.7	6.0	3.9	2.2
1GQK-2	30.3	-28.0	-30.5	-22.3	2.3	-0.3	-22.6
1T72-1	30.4	-26.2	-28.6	-10.7	4.2	1.8	-8.9
1T72-2	28.5	-25.6	-27.8	-6.1	2.9	0.7	-5.4
2AK4-1	30.9	-28.4	-31.2	-10.5	2.5	-0.3	-10.8
2CVF-1	29.5	-19.3	-18.7	8.5	10.2	10.8	19.3
2CYC-1	29.5	-23.1	-27.0	12.0	6.4	2.5	14.5
2H39-1	29.4	-26.9	-29.7	-22.0	2.5	-0.3	-22.2
2H39-2	28.8	-25.7	-28.0	-23.0	3.1	0.8	-22.2
2J7A-1	27.7	-22.0	-26.2	6.3	5.7	1.5	7.7
2OT4-1	27.2	-21.6	-23.1	-7.4	5.6	4.1	-3.3
2VLR-1	29.5	-27.1	-30.8	-4.3	2.4	-1.3	-5.6
3C5Z-1	32.2	-26.7	-28.6	-8.0	5.6	3.6	-4.4
3CES-1	29.4	-23.5	-27.2	9.1	5.9	2.2	11.3
3HUJ-1	31.2	-28.5	-31.4	-9.2	2.7	-0.2	-9.4

Table S10: Comparison of SCS-MP2 and CCSD interaction energies (kcal/mol) predicted for the multiple cation–π–cation interactions identified in the human growth hormone receptor (PDB entry 1A22) in vacuum.

ID	Method	ΔE_{XAr}	ΔE_{ArY}	ΔE_{XY}	ΔE_{XArY}	$\Delta E_{3\text{-}body}$
1A22-1						
	SCS-MP2/aug-cc-pVDZ	-5.4	-7.6	39.7	28.8	2.2
	SCS-MP2/aug-cc-pVTZ	-5.4	-7.9	39.7	28.5	2.1
	SCS-MP2/CBS	-5.5	-8.2	39.7	28.2	2.1
	CCSD/aug-cc-pVDZ	-5.4	-7.4	39.7	29.0	2.2
1A22-2						
	SCS-MP2/aug-cc-pVDZ	-4.8	-4.6	34.0	27.3	2.7
	SCS-MP2/aug-cc-pVTZ	-4.9	-4.6	34.0	27.1	2.7
	SCS-MP2/CBS	-5.0	-4.7	34.0	27.0	2.7
	CCSD/aug-cc-pVDZ	-4.6	-4.6	34.0	27.4	2.7
1A22-3						
	SCS-MP2/aug-cc-pVDZ	-6.1	-4.7	39.5	31.3	2.6
	SCS-MP2/aug-cc-pVTZ	-6.5	-4.8	39.5	30.8	2.6
	SCS-MP2/CBS	-6.7	-5.0	39.5	30.4	2.6
	CCSD/aug-cc-pVDZ	-5.9	-4.5	39.5	31.6	2.6