SUPPLEMENTARY MATERIAL

Network approach for capturing the ligand-induced subtle global changes in protein structures

Anshul Sukhwal[a], Moitrayee Bhattacharyya[b], Saraswathi Vishveshwara[b]*

[b]Molecular Biophysics Unit, Indian Institute of Science, Bangalore-560012, India

[a]Current Address: National Center for Biological Sciences, Bangalore-560065, India

Correspondence email: sv@mbu.iisc.ernet.in

Supplementary Figures

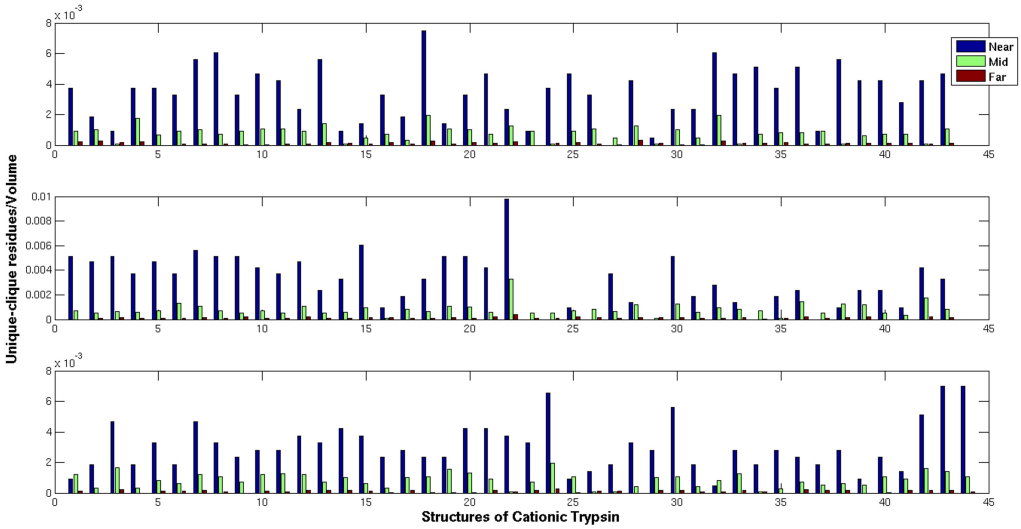

Figure S1a

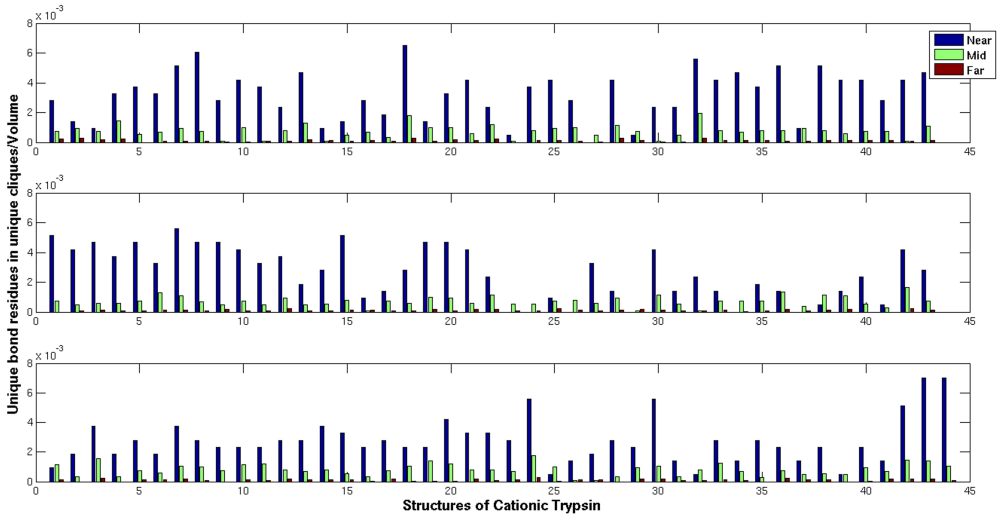

Figure S1b

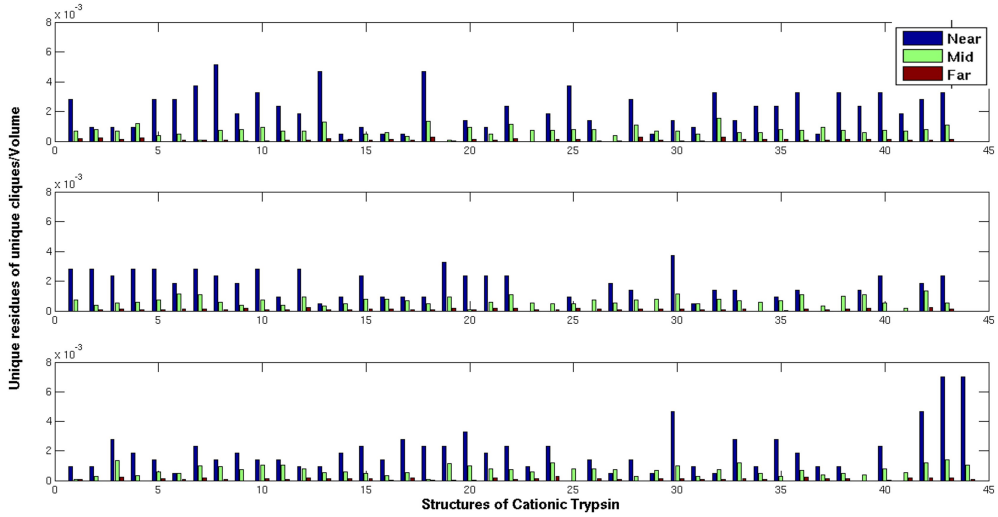

Figure S1c

Figure S1: Long-range effect of ligand induced conformational changes in 109 high resolution crystal structures of cationic trypsin (one native structure and 108 different ligand bound states). The effect is captured in terms of the number of residues participating in (a-c) unique cliques/edges/residues respectively [parameters are schematically detailed in Figure 1(c-e)] along the three tiers around the ligand binding site: 'near', 'mid' and 'far' with respect to a native structure.

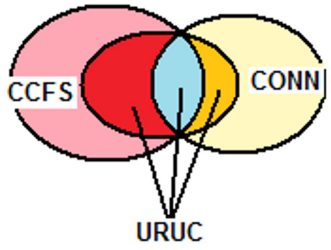

Figure S2: Venn diagram showing the overlap between the list of residues identified from increase in connectivity and clustering co-efficient and the URUC. The regions highlighted in blue, red and orange signify the URUC, clearly manifesting that the URUC forms a subset of the combined list of residues with Δconn/Δccfs > 0 or both.

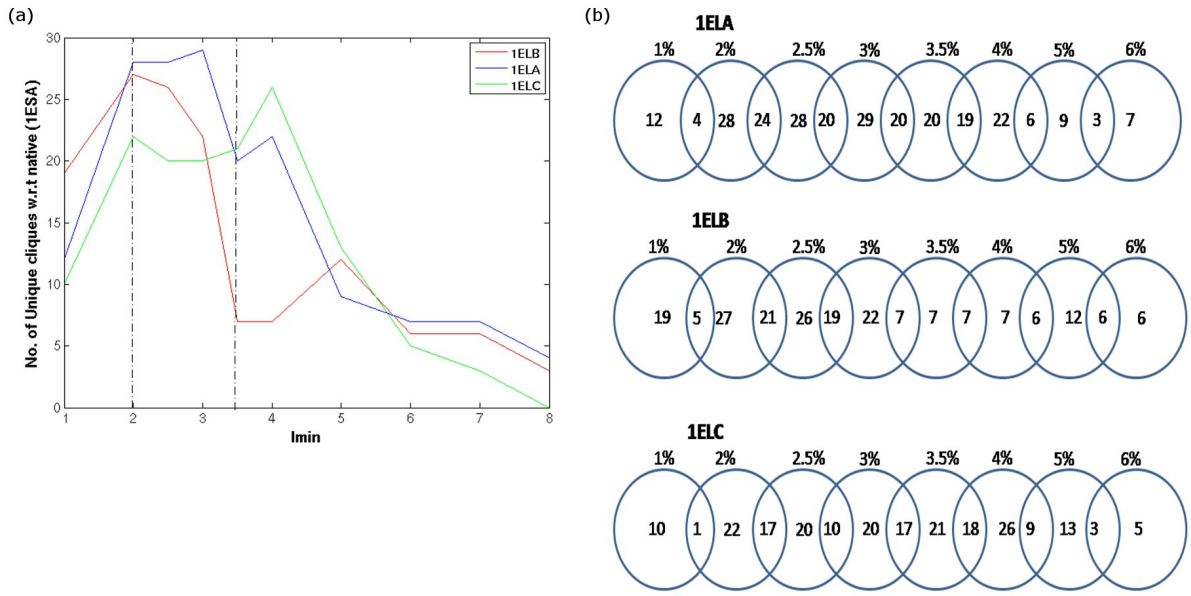

Figure S3: (a) Number of unique cliques in the three liganded structures of elastase w.r.t native as a function of I_{min}. The maximum number is seen in the range of ~2-3.5% for 1ELA, 1ELB, and 1ELC. (b) Venn diagram showing the overlap in the unique residues of unique cliques at different I_{min}s (1-6%). Significant overlaps are seen in the range of 2-4% for most of the structures of elastase.

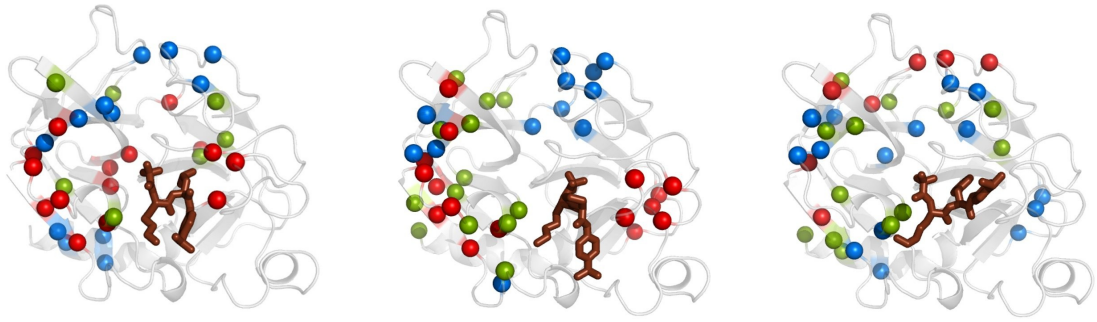

Figure S4: Effect of differential binding of three analogous inhibitors on global side-chain re-wiring in elastase at I_{min}=2% and 3%. The common URUC between the two I_{min}s are depicted as red van der Waals' spheres and the unique ones at each I_{min} are blue (2%) and green (3%). The protein backbone is represented as light gray cartoon and the unique clique residues are depicted as van der Waals' spheres. The ligands are shown in deep blue sticks representation.

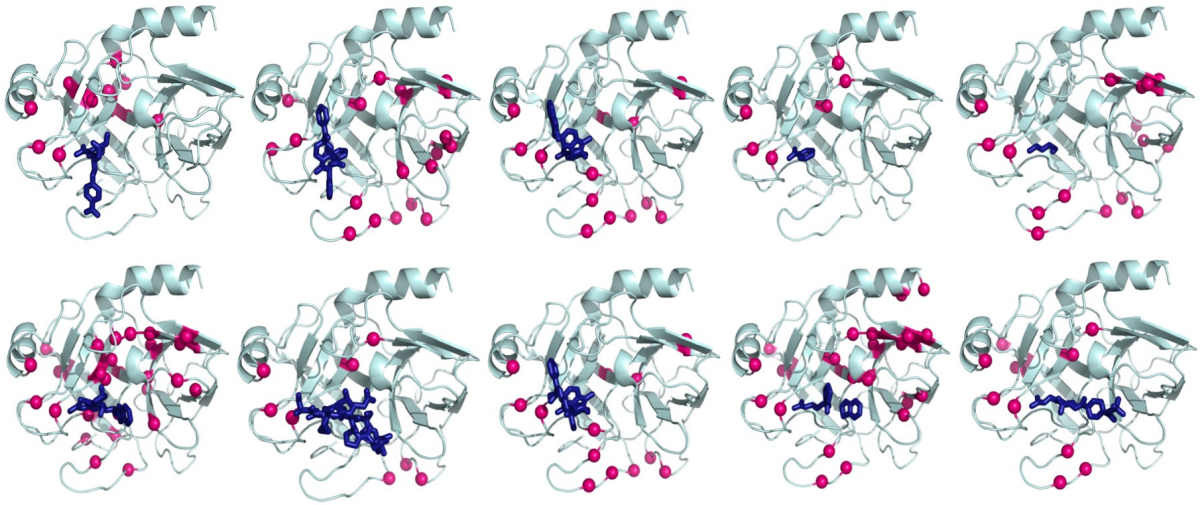

Figure S5: Effect of binding of ten different ligands on global side-chain re-wiring in cationic trypsin. Pictorial depiction of the unique residues in unique cliques with respect to the native structure (1S0Q) for the ten systems shows differences in their structural distribution, exhibiting conformational re-orientation at the level of side-chain interactions. The protein backbone is represented as light gray cartoon and the unique clique residues are depicted as van der Waals' spheres. The ligands are shown as deep blue sticks.

Supplementary Tables

Name of Protein (Native protein PDB – Resolution in Å) [R-fac.]	PDB Ids of chosen structures	Ligands (Ligand Identifier)	Resolution (in Å)	R-Factor	Function/s
Apolipoprotein a	1I71	-	1.45	0.173	'Injury-response' macromolecule in peripheral nerves. It can inhibit tissue-type plasminogen activator-mediated plasminogen activation on fibrin surfaces.(1,2)
	1KIV	-	2.10	0.178	
	3KIV	6-AMINO HEXANOIC ACID (ACA)	1.80	0.182	
	4KIV	-	2.20	0.162	
Complement Factor B (**1RRK** - 2.00) [0.220]	**1RTK**	4-GUANIDINOBENZOIC ACID (GBS)	2.30	0.208	It is cleaved by complement Factor D to yield Ba and Bb. Ba and Bb are two counteracting fragments involved in the regulatory mechanism of B-lymphocyte proliferation.(3,4)
Complement C2	2I6Q	-	2.1	0.189	It is a critical component of the lectin pathway. It also functions as a key regulator in the early activation phase of the classical pathway and participates in the formation of the classical pathway C3 convertase C4b2a. (5)
	2ODQ	-	2.30	0.217	
	2ODP	-	1.9	0.209	
Complement Factor D (**1DST** – 2.00) [n/a]	**1BIO**	ISATOIC ANHYDRIDE (SOA)	1.5	0.186	Adipsin (complement factor D) is one of several adipose tissue-derived complement components that are required for the enzymatic production of acylation stimulating protein (ASP), a complement protein that affects both lipid and glucose metabolism. (6)
	1DIC	3,4-DICHLOROISOCOUMARIN (DIC)	1.8	0.182	
	1HFD	-	2.3	0.174	
Kallikrein-6 (**1GVL** - 1.80) [0.185]	**1L2E**	BENZAMIDINE (BAM)	1.75	0.230	It may serve as a circulating tumor marker in ovarian cancers.(7)
	1LO6	BENZAMIDINE (BAM)	1.56	0.197	
Prostatin (**3E1X** - 1.70) [0.171]	3DFJ	-	1.45	0.191	It plays a critical role in the regulation of extracellular sodium ion transport via its activation of the epithelial cell sodium channel.(8)
	3DFL	4-GUANIDINOBENZOIC ACID (GBS)	2	0.176	
	3E0N	DEOXY-METHYL-ARGININE (ARM); D-PHENYLALANINE (DPN); PHENYLALANINE (PHE)	1.70	0.159	
	3E0P	benzyl [(1R)-1-({(2S,4R)-2-({(1S)-5-amino- 1-[(S)-1,3-benzoxazol-2-yl (hydroxy)methyl]pentyl}carbamoyl)- 4-[(4-methylbenzyl)oxy]pyrrolidin-1-yl}carbonyl)- 3 -phenylpropyl]carbamate (B3C)	1.70	0.179	
	3FVF	1-[4-(hydroxymethyl)phenyl]guanidine (1JZ)	1.60	0.160	
	3GYL	-	1.30	0.154	
Azurocidin	1A7S	-	1.12	0.159	It plays a central role in early capillary leakage and extravasation of neutrophils. (9)
	1AE5	-	2.30	n/a	
	1FY1	-	2.50	0.207	
	1FY3	-	1.89	0.182	
Ancrod	2AIP	-	1.65	0.171	It is a rapid acting defibrinogenating agent.(10)
	2AIQ	BENZAMIDINE (BAM)	1.54	0.169	
Plasma Kallikrein	2ANW	BENZAMIDINE (BAM) & Mutation:C122S	1.85	0.221	It helps in modulation of blood pressure, complement activation, and

	2ANY	BENZAMIDINE (BAM) & Mutation:C122S, N21E, N72E, N113E	1.40	0.190	mediation and maintenance of inflammatory responses.(11)
Chymase (**1NN6** - 1.75)	**1KLT**	phenylmethanesulfonic acid (PMS)	1.9	0.183	It plays important role in the airways, particularly in the regulation of neuropeptide activity, bronchomotor tone, and submucosal gland secretion. (12)
	1T31	2-(N-MORPHOLINO)-ETHANESULFONIC ACID (MES); 2-[3-({METHYL[1-(2-NAPHTHOYL)PIPERIDIN-4-YL]AMINO}CARBONYL)-2-NAPHTHYL]-1-(1 -NAPHTHYL)- 2-OXOETHYLPHOSPHONIC ACID (OHH)	1.9	0.198	
	1PJP	PEPTIDIC INHIBITOR (SUCCINYL-ALA-ALA-PRO-PHE-CHLOROMETHYLKETONE)	2.20	0.184	
Kallikrein-7	2QXH	N-(3-carboxypropanoyl)-L-alanyl-L-alanyl- N-[(1S,2R)-1-benzyl-2-hydroxypropyl]-L -prolinamide (K7J)	2.00	0.180	It plays a significant role in physiological and pathophysiological processes of the skin.(13)
	2QXJ	N-(3-carboxypropanoyl)-L-alanyl-L-alanyl- N-[(1S,2R)-1-benzyl-2-hydroxypropyl]-L -prolinamide (K7J)	2.10	0.214	
Trypsin-1 (**1UTK** - 1.53)	**1HJ8**	BENZAMIDINE (BAM)	1.00	0.118	Activates other pancreatic proteases. (14)
	1UTJ	BENZYLAMINE (ABN)	1.83	0.162	
	1UTL	3-PHENYLPROPYLAMINE (PRA)	1.70	0.176	
	1UTM	2-PHENYLETHYLAMINE (PEA)	1.50	0.189	
Urokinase-type Plasminogen Activator (**2O8T** - 1.45) [0.242]	**2O8U**	BENZAMIDINE (BEN) & Mutation:C122A/N145Q/S195A	1.70	0.218	It plays a crucial role in the regulation of plasminogen activation, tumor cell adhesion and migration. The inhibition of uPA activity is a promising mechanism for anti-cancer therapy. (15)
	2O8W	Mutation:C122A/N145Q/S195A	1.86	0.213	
	2R2W	1-[4-(2-oxo-2-phenylethyl)phenyl]guanidine (4PG)	2.01	0.199	
	1SQO	8-(PYRIMIDIN-2-YLAMINO)NAPHTHALENE-2-CARBOXIMIDAMIDE (UI2)	1.84	0.222	
Trypsin (**1OS8** - 1.55) [0.196]	**1OSS**	BENZAMIDINE (BEN)	1.93	0.167	Forms the functional principle of some large and highly specific proteases involved in blood clotting and complement binding.(16)
	1SGT	-	1.70	0.161	
	2FMJ	-	1.65	0.157	
Coagulation factor XI	1ZHM	BENZAMIDINE (BEN)	1.96	0.170	Activated Factor XI (FXIa) is a key enzyme in the amplification phase of the coagulation cascade.(17)
	1ZSJ	N-(7-CARBAMIMIDOYL-NAPHTHALEN-1-YL)-3-HYDROXY- 2-METHYL-BENZAMIDE (709)	1.90	0.188	
	2FDA	N~2~-(AMINOCARBONYL)-N~1~-{4-{[AMINO(IMINO)METHYL]AMINO}- 1-[HYDROXY(1,3-THIAZOL -2-YL)METHYL]BUTYL}VALINAMIDE	2.00	0.186	

		(682)			
Chymotrypsin-like Elastase Family Member 1	1B0E	1-{3-METHYL-2-[4-(MORPHOLINE-4-CARBONYL)-BENZOYLAMINO]-BUTYRYL}-PYRROLIDINE-2 -CARBOXYLIC ACID (3,3,4,4,4- PENTAFLUORO-1-ISOPROPYL-2-OXO-BUTYL)-AMIDE (SEI)	1.80	0.180	It is also known as Elastase 1. Elastase breaks down elastin, the specific protein of elastic fibers, and digests other proteins such as fibrin, hemoglobin, and albumin.(18)
	1L1G	-	1.50	0.173	
Anionic Trypsin-2	1AND	BENZAMIDINE (BEN) & Mutation:R96H	2.30	0.161	Anionic trypsinogen is one isoform of typsinogen found in bulk (~30-40%) in pancreatic juice and is a digestive proteolytic proenzyme.(19) Active form of enzyme is Anionic Trypsin.
	1J14	BENZAMIDINE (BEN) & Mutation:K97E, L99Y	2.40	0.193	
Cationic Trypsin	1AUJ	1-{[1-(2-AMINO-3-PHENYL-PROPIONYL)-PYRROLIDINE- 2-CARBONYL]-AMINO}-2-(3-CYANO-PHENYL)-ETHANEBORONIC ACID (PPB)	2.10	0.169	Trypsinogen (one isoform is Cationic Trypsinogen) is the most abundant digestive proteolytic proenzyme in the pancreatic juice.(19) Active form of enzyme is Cationic Trypsin.
	1AZ8	+/-METHYL 4-(AMINOIMINOMETHYL)-BETA-[3- INH (AMINOIMINO)PHENYL]BENZENE PENTANOATE (IN4)	1.80	0.188	
	1BJU	1-(4-AMIDINOPHENYL)-3-(4-CHLOROPHENYL)UREA (GP6)	1.80	0.171	
	1C1P	(5-AMIDINO-2-BENZIMIDAZOLYL)(2-BENZIMIDAZOLYL)METHANE (BAI)	1.37	0.178	
	1BTW	T-BUTOXY-ALA-VAL-BORO-LYS 1,3-PROPANEDIOL MONOESTER (Polypeptide)	1.70	0.164	
Cathepsin G	1CGH	PHOSPHONATE INHIBITOR SUC-VAL-PRO-PHEP-(OPH)2 (Polypeptide)	1.80	0.190	It induces platelet aggregation, serotonin release, and calcium mobilization.(20)
	1T32	2-[3-({METHYL[1-(2-NAPHTHOYL) PIPERIDIN-4-YL]AMINO}CARBONYL)-2-NAPHTHYL]-1-(1-NAPHTHYL)- 2-OXOETHYLPHOSPHONIC ACID (OHH)	1.85	0.172	
Human Leukocyte Elastase	1HNE	METHOXYSUCCINYL-ALA-ALA-PRO-ALA CHLOROMETHYL KETONE (Polypeptide)	1.84	0.164	It is released at the site of inflammation. Active Human Leukocyte Elastase is detectable on the surface of psoriatic lesions, correlates well with skin induration and disappears with successful therapy.(21)
	1PPG	MEO-SUCCINYL-ALA-ALA-PRO-VAL CHLOROMETHYLACETONE (Polypeptide)	2.30	0.145	
Granzyme M	2ZGC	-	1.96	0.212	Granzyme M initiates caspase-dependent apoptosis with typical apoptotic nuclear morphology. Granzyme M induces DNA fragmentation, not DNA nicking.(22)
	2ZGH	SSGKVPL (Polypeptide)	2.17	0.214	
	2ZGJ	SSGKVPLS (Polypeptide)	2.30	0.242	

Protein Elastase	1ELA	TRIFLUOROACETYL-L-LYSYL-L-PROLYL -P-ISOPROPYLANILID (Polypeptide)	2.00	0.185	It breaks down elastin that, together with collagen, determines the mechanical properties of connective tissues.(23)
	1QR3	FR901277 (Polypeptide)	1.60	0.197	

Table S1: Summary of Dataset I (72 structures) and reduced Dataset II (27 structures). The name of the protein and the structures included in dataset II are highlighted as bold.

Cationic Trypsin (Native protein PDB – Resolution in Å)	**PDB Ids of other chosen structures**	**Ligands (Ligand Identifier)**	**Resolution (in Å)**
Group-1 (1S0Q – 1.02)	1JRS	TRYPSIN (Polypeptide)	1.80
	1JRT	TRYPSIN (Polypeptide)	1.70
Group-2 (1S0Q – 1.02)	2ZFT	(S)-N-(4-CARBAMIMIDOYLBENZYL)-1-(2-(CYCLOPENTYLAMINO)ETHANOYL)PYRROLIDINE-2-CARBOXAMIDE (10U)	1.76
	2ZFS	N-CYCLOHEPTYLGLYCYL-N-(4-CARBAMIMIDOYLBENZYL)-L-PROLINAMIDE (12U)	1.51
	2ZQ1	(S)-N-(4-CARBAMIMIDOYLBENZYL)-1-(2-(CYCLOHEXYLAMINO)ETHANOYL)PYRROLIDINE-2-CARBOXAMIDE (11U)	1.68
	2ZQ2	N-CYCLOOCTYLGLYCYL-N-(4-CARBAMIMIDOYLBENZYL)-L-PROLINAMIDE (13U)	1.40
	2ZDM	(S)-N-(4-CARBAMIMIDOYLBENZYL)-1-(2-(CYCLOHEXYLOXY)ETHANOYL)PYRROLIDINE-2-CARBOXAMIDE (46U)	1.93
	2ZDN	(S)-N-(4-CARBAMIMIDOYLBENZYL)-1-(3-CYCLOPENTYLPROPANOYL)PYRROLIDINE-2-CARBOXAMIDE (49U)	1.98
	2ZDK	(S)-N-(4-CARBAMIMIDOYLBENZYL)-1-(3CYCLOHEXYLPROPANOYL)PYRROLIDINE-2-CARBOXAMIDE (50U)	1.67
	2ZDL	(S)-N-(4-CARBAMIMIDOYLBENZYL)-1-(2-(CYCLOPENTYLOXY)ETHANOYL)PYRROLIDINE-2-CARBOXAMIDE (45U)	1.80
Group-3 (1S0Q – 1.02)	1Y3U	(1R,3AS,4R,8AS,8BR)-4-(2-BENZO[1,3]DIOXOL-5-YLMETHYL-1-ISOPROPYL-3-OXO-DECAHYDRO-PYRROLO[3,4-A]PYRROLIZIN-4-YL)-BENZAMIDINE (UIQ)	1.80
	1Y3V	(1R,3AS,4R,8AS,8BR)-4-(2-BENZO[1,3]DIOXOL-5-YL-1-CYCLOPROPYL-3-OXO-DECAHYDRO-PYRROLO[3,4-A]PYRROLIZIN-4-YL)-BENZAMIDINE (UIR)	1.60
	1Y3W	(1R,3AS,4R,8AS,8BR)-4-(2-BENZO[1,3]DIOXOL-5-YLMETHYL-1-ETHYL-3-OXO-DECAHYDRO-PYRROLO[3,4-A]PYRROLIZIN-4-YL)-BENZAMIDINE (UIP)	1.80
	1Y3X	(1R,3AS,4R,8AS,8BR)-4-{5-(PHENYL[1,3]DIOXOL-5-YLMETHYL)-4-ETHYL-2,3,3-TRIMETHYL-6-OXO-OCTAHYDRO-PYRROLO[3,4-C]PYRROL-1-YL}-BENZAMIDINE	1.70

		(UIB)	
Group-4 (1S0Q – 1.02)	1UTP	4-PHENYLBUTYLAMINE (PBN)	1.3
	1UTO	2-PHENYLETHYLAMINE (PEA)	1.15
	1UTN	BENZYLAMINE (ABN)	1.150.97
Group-5 (1S0Q – 1.02)	1QB1	1-[2-[5-[AMINO(IMINO)METHYL]-2-HYDROXYPHENOXY]-6-[3-(4,5-DIHYDRO-1-METHYL-1H-IMIDAZOL-2-YL)PHENOXY]PYRIDIN-4-YL]PIPERIDINE-3-CARBOXYLIC ACID (974)	1.80
	1QB6	3,3'-[3,5-DIFLUORO-4-METHYL-2,6-PYRIDYLENEBIS(OXY)]-BIS(BENZENECARBOXIMIDAMIDE) (623)	1.80
	1QB9	7-[[2-[[1-(1-IMINOETHYL)PIPERIDIN-4-YL]OXY]-9H-CARBOZOL-9-YL]METHYL]NAPHTHALENE-2-CARBOXIMIDAMIDE) (806)	1.80
	1QBN	2-[AMINO(IMINO)METHYL]-2-HYDROXYPHENOXY]-6-[3-(4,5-DIHYDRO-1H-IMIDAZOL-2-YL)PHENOXY]PYRIDINE-4-CARBOXYLIC ACID (688)	1.80
	1QBO	7-[[6-[[1-(1-IMINOETHYL)PIPERIDIN-4-YL]OXY]-2-METHYL-BENZIMIDAZOL-1-YL]METHYL]NAPHTHALENE-2-CARBOXIMIDAMIDE) (711)	1.80
	1QA0	2H-BENZOIMIDAZOL-2-YLAMINE (270)	1.80
Group-6 (1S0Q – 1.02)	1O3D	3-{5-[AMINO(IMINIO)METHYL]-1H-BENZIMIDAZOL-2-YL}-1,1'-BIPHENYL-2-OLATE (780)	1.33
	1O3G	3-{5-[AMINO(IMINIO)METHYL]-1H-INDOL-2-YL}-1,1'-BIPHENYL-2-OLATE (696)	1.55
	1O35	2-{5-[AMINO(IMINIO)METHYL]-1H-BENZIMIDAZOL-2-YL}-4-802 FLUOROBENZENOLATE (802)	1.41
	1O36	2-(2'-AMINO-5-{5-[AMINO(IMINIO)METHYL]-1H-BENZIMIDAZOL-2-YL}-6-OXIDO-1,1'-BIPHENYL-3-YL)SUCCINATE (607)	1.70
	1O38	5-(2-AMINOETHYL)-3-{5-[AMINO(IMINIO)METHYL]-1H-BENZIMIDAZOL-2-YL}-1,1'-BIPHENYL-2-OLATE (653)	1.38
	1O33	2-{5-[AMINO(IMINIO)METHYL]-1H-BENZIMIDAZOL-2-YL}PYRIDIN-3-OLATE (801)	1.46
	1O30	2-(5-{5-[AMINO(IMINIO)METHYL]-1H-BENZIMIDAZOL-2-YL}-2'-FLUORO-6-OXIDO-1,1'-BIPHENYL-3-YL)SUCCINATE (693)	1.55
	1O3N	2-{5-[AMINO(IMINIO)METHYL]-1H-BENZIMIDAZOL-2-YL}-4-(TRIFLUOROMETHOXY)BENZENOLATE (785)	1.55
	1O3J	2-{5-[AMINO(IMINIO)METHYL]-1H-BENZIMIDAZOL-2-YL}-6-BROMO-4-METHYLBENZENOLATE (334)	1.40
	1O3I	2-{5-[AMINO(IMINIO)METHYL]-1H-INDOL-2-YL}-6-BROMO-4-METHYLBENZENOLATE (907)	1.51
	1O2O	2-{5-[AMINO(IMINIO)METHYL]-6-FLUORO-1H-BENZIMIDAZOL-	1.63

		2-YL}-6-ISOBUTOXYBENZENOLATE (950)	
	1O2P	2-{5-[AMINO(IMINIO)METHYL]-6-CHLORO-1H-BENZIMIDAZOL-2-YL}-6-ISOBUTOXYBENZENOLATE (972)	1.47
	1O2Q	2-{5-[AMINO(IMINIO)METHYL]-6-CHLORO-1H-INDOL-2-YL}-6-(CYCLOPENTYLOXY)BENZENOLATE (991)	1.50
	1O2R	2-{5-[AMINO(IMINIO)METHYL]-6-FLUORO-1H-BENZIMIDAZOL-2-YL}-6-[(2-METHYLCYCLOHEXYL)OXY]BENZENOLATE (CR9)	1.45
	1O2S	2-{5-[AMINO(IMINIO)METHYL]-1H-BENZIMIDAZOL-2-YL}BENZENOLATE (CR4)	1.65
	1O2T	3-{5-[AMINO(IMINIO)METHYL]-1H-INDOL-2-YL}-5-METHOXY-1,1'-BIPHENYL-2-OLATE (783)	1.62
	1O2U	2-(3-{5-[AMINO(IMINIO)METHYL]-1H-BENZIMIDAZOL-2-YL}-5-BROMO-4-OXIDOPHENYL)SUCCINATE (847)	1.41
	1O2Z	2-(5-{5-[AMINO(IMINIO)METHYL]-1H-BENZIMIDAZOL-2-YL}-2'-METHOXY-6-OXIDO-1,1'-BIPHENYL-3-YL)SUCCINATE (312)	1.65
	1O2N	3-{5-[AMINO(IMINIO)METHYL]-6-CHLORO-1H-BENZIMIDAZOL-2-YL}-1,1'-BIPHENYL-2-OLATE (762)	1.50
	1O2K	2-{5-[AMINO(IMINIO)METHYL]-1H-BENZIMIDAZOL-2-YL}-6-ISOBUTOXYBENZENOLATE (656)	1.63
	1O2H	2-{5-[AMINO(IMINIO)METHYL]-1H-INDOL-2-YL}-6(CYCLOPENTYLOXY)BENZENOLATE (CR3)	1.77
	1O2I	2-{5-[AMINO(IMINIO)METHYL]-1H-BENZIMIDAZOL-2-YL}-6-(CYCLOPENTYLOXY)BENZENOLATE (655)	1.50
Group-7 (1S0Q – 1.02)	1MTW	(2S)-3-(7-CARBAMIMIDOYLNAPHTHALEN-2-YL)-2-[4-({(3R)-1-[(1Z)-ETHANIMIDOYL]PYRROLIDIN-3-YL}OXY)PHENYL]PROPANOIC ACID (DX9)	1.90
	1MTV	(+)-2-[4-[(-1-ACETIMIDOYL-4-PIPERIDINYL)OXY]-3-(7-AMIDINO-2-NAPHTHYL)PROPIONIC ACID (BX3)	1.90
Group-8 (1S0Q – 1.02)	1K1N	[N-[N-(4-METHOXY-2,3,6-TRIMETHYLPHENYLSULFONYL)-L-ASPARTYL]-D-(4-AMIDINO-PHENYLALANYL)]-PIPERIDINE (CCR)	2.00
	1K1O	{[(1R)-2-((2S)-2-{[(3-{[AMINO(IMINO)METHYL]AMINO}PROPYL)AMINO]CARBONYL}PIPERIDINYL)-1-(CYCLOHEXYLMETHYL)-2-OXOETHYL]AMINO}ACETIC ACID (IGN)	2.00
	1K1P	[((1R)-2-{(2S)-2-[({4-[AMINO(IMINO)METHYL]BENZYL}AMINO)CARBONYL]AZETIDINYL}-1-CYCLOHEXYL-2-OXOETHYL)AMINO]ACETIC ACID (MEL)	1.90
Group-9 (1S0Q – 1.02)	1GI5	2-(2-HYDROXY-5-METHOXY-PHENYL)-1H-BENZOIMIDAZOLE-5-CARBOXAMIDINE (123)	1.60
	1GI6	2-(2-HYDROXY-PHENYL)-1H-INDOLE-5-CARBOXAMIDINE (124)	1.49

	1GJ6	6-CHLORO-2-(2-HYDROXY-BIPHENYL-3-YL)-1H-INDOLE-5-CARBOXAMIDINE (132)	1.50
	1GI4	2-(2-HYDROXY-PHENYL)-3H-BENZOIMIDAZOLE-5-CARBOXAMIDINE (122)	1.37
	1GI1	BMZ 2-(2-HYDROXY-PHENYL)-1H-BENZOIMIDAZOLE-5-CARBOXAMIDINE (BMZ)	1.42
	1GHZ	2-(2-OXO-1,2-DIHYDRO-PYRIDIN-3-YL)-1H-BENZOIMIDAZOLE-5-CARBOXAMIDINE (120)	1.39
Group-10 (1S0Q – 1.02)	1G3C	2-(4-CARBAMIMIDOYL-2-HYDROXY-BENZYLAMINO)-PROPIONIC ACID (109)	1.80
	1G3D	2-(5-CARBAMIMIDOYL-2-HYDROXY-BENZYLAMINO)-PROPIONIC ACID (108)	1.80
Group-11 (1S0Q – 1.02)	1C5T	THIENO[2,3-B]PYRIDINE-2-CARBOXAMIDINE (ESP)	1.37
	1C1T	BIS(5-AMIDINO-BENZIMIDAZOLYL)METHANE (BAB)	1.37
	1C5S	BENZO[B]THIOPHENE-2-CARBOXAMIDINE (ESX)	1.36
	1C5Q	-IODOBENZO[B]THIOPHENE-2-CARBOXAMIDINE (ESI)	1.43
	1C2H	BIS(5-AMIDINO-2-BENZIMIDAZOLYL)METHANE KETONE (BAK)	1.40
	1C2G	BIS(5-AMIDINO-2-BENZIMIDAZOLYL)METHANE KETONE HYDRATE (BAH)	1.65
	1C1Q	(5-AMIDINO-2-BENZIMIDAZOLYL)(2-BENZIMIDAZOLYL)METHANE (BAI)	1.37
Group-12 (1S0Q – 1.02)	1F0T	4-HYDROXY-3-[2-OXO-3-(THIENO[3,2-B]PYRIDINE-2-SULFONYLAMINO)-PYRROLIDIN-1-YLMETHYL]-BENZAMIDINE (PR1)	1.80
	1F0U	3-[(3'-AMINOMETHYL-BIPHENYL-4-CARBONYL)-AMINO]-2-(3-CARBAMIMIDOYL-BENZYL)-BUTYRIC ACID METHYL ESTER (RPR)	1.90
Group-13 (1S0Q – 1.02)	1BJU	1-(4-AMIDINOPHENYL)-3-(4-CHLOROPHENYL)UREA DMS DIMETHYL SULFOXIDE (GP6)	1.80
	1BJV	1-(2-AMIDINOPHENYL)-3-(PHENOXYPHENYL)UREA (GP8)	1.80
Group-14 (1S0Q – 1.02)	1BTX	DIETHYL [(1R)-1,5-DIAMINOPENTYL]BORONATE (0AY)	1.70
	1BTW	LYSINE BORONIC ACID PDO 1,3-PROPANDIOL (BLY)	1.70
Group-15 (1S0Q – 1.02)	1XUJ	BIS(5-AMIDINO-BENZIMIDAZOLYL)METHANONE (BOZ)	1.92
	1XUF	BIS(5-AMIDINO-BENZIMIDAZOLYL)METHANE (BAZ)	1.90
	1XUI	BIS(5-AMIDINO-2-BENZIMIDAZOLYL)METHANONE (BAO)	1.50
Group-16 (1S0Q – 1.02)	1TYN	CYCLOTHEONAMIDE A (CTA)	2.00

	1TPS	1-(SULFOGLYCOLOYL-LEUCYL-THREONYL-VALYL-N-METHYLTYROSYL-LEUCYL)-3-(ARGINYLANYLAMINO)-6-HYDROXY-2-PIPERIDONE (A9A)	1.90
	1TPP	AMIDO PHENYL PYRUVIC ACID (APA)	1.40
Group-17 (1S0Q – 1.02)	1TX8	4-(METHYLSULFONYL) BENZENECARBOXIMIDAMIDE (AM4)	1.70
	1TX7	(4-CARBAMIMIDOYLPHENYL)-METHYL-PHOSPHINIC ACID (4CM)	1.75
Group-18 (1S0Q – 1.02)	1TNL	TRANS-2-PHENYLCYCLOPROPYLAMINE (TPA)	1.90
	1TNK	3-PHENYLPROPYLAMINE (PRA)	1.80
	1TNH	4-FLUOROBENZYLAMINE (FBA)	1.80
	1TNG	AMINOMETHYLCYCLOHEXANE (AMC)	1.80
Group-19 (1S0Q – 1.02)	2G8T	2-(2-METHYLPHENYL)-1H-INDOLE-5-CARBOXIMIDAMIDE (MI2)	1.41
	2G5N	2-(3-METHYLPHENYL)-1H-INDOLE-5-CARBOXIMIDAMIDE (23M)	1.51
	2G5V	2-(2-METHYLPHENYL)-1H-INDOLE-6-CARBOXIMIDAMIDE (22M)	1.45
Group-20 (1S0Q – 1.02)	2AH4	4-GUANIDINOBENZOIC ACID (GBS)	1.13
	2AGE	Succinyl-Ala-Ala-Pro-Arg (Polypeptide)	1.15
	2AGG	Succinyl-Ala-Ala-Pro-Lys (Polypeptide)	1.28
	2AGI	Leupeptin	1.14
Group-21 (1S0Q – 1.02)	1PPH	M-AMIDINOPHENYL-3-ALANINE (APM)	1.90
	1PPC	P-AMIDINOPHENYL-3-ALANINE (APH)	1.80
Group-22 (1S0Q – 1.02)	1S0R	BENZAMIDINE (BEN)	1.02
	3ITI	5-AMINO-2,4,6-TRIBROMOBENZENE-1,3-DICARBOXYLIC ACID & BENZAMIDINE (BRV) & (BEN)	1.55
	2OTV	NICOTINAMIDE (NCA)	1.56
	2FX4	4-PIPERIDINEBUTYRATE (C1R)	1.65
	1G36	4-{[1-METHYL-5-(2-METHYL-BENZOIMIDAZOL-1-YLMETHYL)-1H-BENZOIMIDAZOL-2-YLMETHYL]-AMINO}-BENZAMIDINE (R11)	1.90
	1J8A	BENZAMIDINE (BEN)	1.21
	1ZZZ	NORVALINE & 3-(1-CARBAMIMIDOYL-PIPERIDIN-3-YL)-L-ALANINE (NVA) & (1PI)	1.90
	1RXP	1-(4-TERT-BUTYLCARBAMOYL-PIPERAZINE-1-CARBONYL)-3-(3-2 169 GUANIDINO-PROPYL)-4-OXO-AZETIDINE-2-CARBOXYLIC ACID (169)	1.70

	1NC6	(2S,4R)-1-ACETYL-N-[(1S)-4-[(AMINOIMINOMETHYL)AMINO]-1-(2-BENZOTHIAZOLYLCARBONYL)BUTYL]-4-HYDROXY-2-PYRROLIDINECARBOXAMIDE (ABB)	1.90
	1JIR	AMYLAMINE (AML)	2.00
	1EB2	3-[(Z)-AMINO(IMINO)METHYL]-N-[2-(4-BENZOYL-1-IPERIDINYL)-2-OXO-1-PHENYLETHYL]BENZAMIDE (BPO)	2
	1AZ8	+/-METHYL 4-(AMINOIMINOMETHYL)-BETA-[3-(AMINOIMINO)PHENYL]BENZENE PENTANOATE (IN4)	1.80
	1QCP	CYCLOPENTANECARBOXYLIC ACID [1-(BENZOTHIAZOLE-2-CARBONYL)-4-GUANIDINO-BUTYL]-AMIDE (RWJ)	1.80
	1OYQ	[(1-{2[(4-CARBAMIMIDOYL-PHENYLAMINO)-METHYL]-1-METHYL-1H-BENZOIMIDAZOL-5-YL}-CYCLOPROPYL)-PYRIDIN-2-YL-METHYLENEAMINOOXY]-ACETIC ACID ETHYL ESTER (T87)	1.90
	1OX1	11-mer peptide	2.00
	2AYW	2-[2-({[4-(DIAMINOMETHYL)PHENYL]AMINO}CARBONYL)-6-METHOXYPYRIDIN-3-YL]-5-{[(1-FORMYL-2,2-DIMETHYLPROPYL)AMINO]CARBONYL}BENZOIC ACID & BENZAMIDINE (ONO) & (BEN)	0.97

Table S2: Summary of the structures of cationic trypsin forming dataset III (109 structures). 1S0Q is selected as the native structure on the basis of resolution and R-factor [1.02 & 0.112 (obs.) respectively]. Various groups are created within cationic trypsin (from 1-21) according to depositing author name while all the remaining structures were grouped together (Group-22). All these structures were filtered using a resolution (<=2Å) and R-factor (<=0.200) cut-off.

Protein	**PDB – I**	**PDB – II**	**RMSD [Align] Atom-wise**	**RMSD [Align] C-Alpha**	**RMSD [Align] Backbone**	**% of Common Cliques [1%]**
Apolipoprotein A	1I71	1KIV	0.50030	0.50029	0.45518	66
	1I71	3KIV	0.37286	0.52571	0.41361	74
	1I71	4KIV	0.57329	0.50515	0.49742	62
	1KIV	3KIV	0.39410	0.30443	0.32055	74
	1KIV	4KIV	0.51462	0.38553	0.40979	87
	3KIV	4KIV	0.47331	0.35737	0.38801	69
Complement Factor B	1RRK	1RTK	0.19664	0.19935	0.19764	89
Complement C2	2I6Q	2ODP	0.48015	0.54141	0.50819	77
	2I6Q	2ODQ	0.42270	0.5039	0.47102	73

				2		
	2ODP	2ODQ	0.20122	0.19350	0.19427	88
Complement Factor D	1BIO	1DIC	0.33788	0.35562	0.33596	74
	1BIO	1DST	0.46534	0.46851	0.46145	61
	1BIO	1HFD	0.29663	0.27364	0.27562	77
	1DIC	1DST	0.32308	0.33377	0.30964	65
	1DIC	1HFD	0.24432	0.23591	0.23012	79
	1DST	1HFD	0.36890	0.36298	0.33879	63
Kallikrein-6	1GVL	1LO6	0.36130	0.45692	0.40538	57
	1GVL	1L2E	0.37817	0.43631	0.40048	60
	1LO6	1L2E	0.11731	0.09991	0.10129	94
Prostatin	3DFJ	3DFL	0.24688	0.26606	0.23506	82
	3DFJ	3E0N	0.51843	0.57470	0.52595	61
	3DFJ	3E0P	0.46330	0.49991	0.46285	80
	3DFJ	3E1X	0.26259	0.30240	0.26266	83
	3DFJ	3FVF	0.36289	0.39014	0.35273	78
	3DFJ	3GYL	0.24381	0.27992	0.26382	84
	3DFL	3E0N	0.46073	0.50570	0.46714	60
	3DFL	3E0P	0.35413	0.37488	0.35701	83
	3DFL	3E1X	0.23980	0.23508	0.22286	82
	3DFL	3FVF	0.24263	0.25134	0.23088	86
	3DFL	3GYL	0.25788	0.27082	0.25816	88
	3E0N	3E0P	0.46681	0.52773	0.48375	67
	3E0N	3E1X	0.44719	0.48124	0.44875	64
	3E0N	3FVF	0.40752	0.43936	0.42490	65
	3E0N	3GYL	0.48115	0.46945	0.45764	60

	3E0P	3E1X	0.34942	0.38351	0.35636	87
	3E0P	3FVF	0.25243	0.31720	0.28382	87
	3E0P	3GYL	0.45936	0.50665	0.47382	81
	3E1X	3FVF	0.17691	0.20861	0.18308	87
	3E1X	3GYL	0.19229	0.19020	0.18866	87
	3FVF	3GYL	0.22350	0.30811	0.27298	87
Azurocidin	1A7S	1AE5	0.31076	0.29597	0.28475	79
	1A7S	1FY1	0.40546	0.38360	0.38484	73
	1A7S	1FY3	0.17565	0.16946	0.16128	79
	1AE5	1FY1	0.32198	0.28893	0.28697	81
	1AE5	1FY3	0.28566	0.27893	0.25419	73
	1FY1	1FY3	0.40148	0.35318	0.38866	73
Ancrod	2AIP	2AIQ	0.09920	0.09399	0.09188	96
Plasma Kallikrein	2ANW	2ANY	0.29023	0.31461	0.27642	73
Chymase	1KLT	1NN6	0.55266	0.59752	0.56412	57
	1KLT	1T31	0.38898	0.38886	0.37155	67
	1KLT	1PJP	0.40465	0.37854	0.37188	66
	1NN6	1T31	0.53646	0.59824	0.55116	67
	1NN6	1PJP	0.46223	0.54109	0.48311	56
	1T31	1PJP	0.35180	0.34651	0.34291	67
Kallikrein-7	2QXH	2QXJ	0.26963	0.26916	0.26166	84
Trypsin-1	1HJ8	1UTJ	0.24283	0.22221	0.22864	83
	1HJ8	1UTK	0.19512	0.19161	0.18846	79
	1HJ8	1UTL	0.24750	0.23598	0.24113	80
	1HJ8	1UTM	0.44102	0.43047	0.42559	78
	1UTJ	1UTK	0.27245	0.27682	0.26437	75

	1UTJ	1UTL	0.10045	0.09560	0.09069	91
	1UTJ	1UTM	0.43659	0.42912	0.42135	80
	1UTK	1UTL	0.26476	0.26679	0.25415	77
	1UTK	1UTM	0.46317	0.44632	0.44035	74
	1UTL	1UTM	0.43349	0.42521	0.42380	80
Urokinase-Type Plasminogen Activator	2O8T	2O8U	0.16460	0.15049	0.14652	87
	2O8T	2O8W	0.14991	0.13843	0.13538	85
	2O8T	2R2W	0.32722	0.32300	0.30767	80
	2O8T	1SQO	0.45272	0.44192	0.41231	76
	2O8U	2O8W	0.16633	0.15397	0.15090	79
	2O8U	2R2W	0.33818	0.33588	0.31944	83
	2O8U	1SQO	0.45706	0.44972	0.42462	76
	2O8W	2R2W	0.37058	0.36142	0.35147	72
	2O8W	1SQO	0.48436	0.44804	0.43674	67
	2R2W	1SQO	0.41053	0.38648	0.37757	79
Trypsin	1OS8	1OSS	0.11240	0.11068	0.10250	96
	1OS8	1SGT	0.24290	0.22510	0.21869	84
	1OS8	2FMJ	0.25326	0.26151	0.25048	88
	1OSS	1SGT	0.26491	0.25110	0.24583	83
	1OSS	2FMJ	0.26485	0.26503	0.24893	87
	1SGT	2FMJ	0.26971	0.26697	0.25231	79
Coagulation Factor XI	1ZHM	1ZSJ	0.14082	0.14629	0.13674	96
	1ZHM	2FDA	0.20049	0.19662	0.19447	88
	1ZSJ	2FDA	0.14709	0.14181	0.14393	89
Chymotrypsin-Like Elastase Family Member 1	1B0E	1L1G	0.39479	0.42397	0.39028	84
Anionic Trypsin	1AND	1J14	0.18781	0.16940	0.16752	85
Cationic Trypsin	1AUJ	1AZ8	0.16915	0.1623	0.15694	88

				2		
	1AUJ	1BJU	0.18497	0.18343	0.17797	86
	1AUJ	1C1P	0.21548	0.22123	0.20482	94
	1AUJ	1BTW	0.29193	0.28584	0.27911	85
	1AZ8	1BJU	0.15586	0.15214	0.14840	90
	1AZ8	1C1P	0.17402	0.17914	0.15769	90
	1AZ8	1BTW	0.24572	0.24245	0.23140	83
	1BJU	1C1P	0.17461	0.18555	0.16332	89
	1BJU	1BTW	0.25307	0.27152	0.25076	89
	1C1P	1BTW	0.26784	0.29743	0.27129	89
Cathepsin G	1CGH	1T32	0.31477	0.32025	0.29727	81
Human Leucocyte Elastase	1HNE	1PPG	0.29240	0.25745	0.26119	69
Granzyme M	2ZGC	2ZGH	0.26463	0.25185	0.24252	78
	2ZGC	2ZGJ	0.28995	0.29957	0.26735	72
	2ZGH	2ZGJ	0.17492	0.15821	0.15909	77
Protein Elastase	1ELA	1QR3	0.21023	0.19914	0.19126	78

Table S3: Data for all atom RMSD, backbone RMSD, and Cα RMSD and percentage of common cliques at I_{min}=1% between the 72 structures in dataset I [data for Figure 3(a)]. The comparisons of RMSD and network parameters are done for all the structures of a particular protein.

Protein Name	**Radius$_{avg}$**	**Volume 'near'**	**Volume 'mid'**	**Volume 'far'**
Complement Factor B	25.949	2143.57	15005.02	56004.09
Trypsin	23.139	2143.57	15005.02	34719.73
Trypsin-1	23.914	2143.57	15005.02	40107.94
Complement Factor D	26.258	2143.57	15005.02	58648.64
Kallikrein-6	23.861	2143.57	15005.02	39728.10
Prostatin	24.174	2143.57	15005.02	41995.85
Chymase	23.596	2143.57	15005.02	37854.05
Urokinase Type Plasminogen Activator	24.280	2143.57	15005.02	42777.29

Table S4: Summary of the average radius of the structures (computed between His of the catalytic triad and different peripheral amino acid residues in 10 different directions) and volume of the three tiers: 'near', 'mid', and 'far' for structures in dataset II.

Protein Name	PDB-ID	Within 1/3rd d	Per Residue Volume for 1/3rd d	Between 1/3rd d & 2/3rd d	Per Residue Volume for Residues between 1/3rd d & 2/3rd d	Beyond	Per Residue Volume for Residues beyond
Complement Factor D	1BIO	4	0.001866	21	0.001400	14	0.000239
	1DIC	4	0.001866	15	0.001000	14	0.000239
	*1DST	7	0.003265	28	0.001866	14	0.000239
Trypsin-1	1HJ8	6	0.002799	13	0.000866	9	0.000224
	1UTJ	6	0.002799	14	0.000933	9	0.000224
	*1UTK	9	0.004199	31	0.002066	16	0.000399
	1UTL	8	0.003732	10	0.000666	7	0.000175
	1UTM	4	0.001866	5	0.000333	0	0.000000
Trypsin	*1OS8	1	0.000467	13	0.000866	9	0.000259
	1OSS	2	0.000933	15	0.001000	3	0.000086
Kallikrein-6	*1GVL	10	0.004665	18	0.001200	15	0.000378
	1L2E	7	0.003265	22	0.001466	12	0.000302
Prostatin	3DFL	5	0.002333	10	0.000666	1	0.000024
	3E0P	5	0.002333	6	0.000400	17	0.000405
	*3E1X	7	0.003265	23	0.001533	10	0.000238
	3FVF	0	0.000000	6	0.000400	12	0.000286
Chymase	1KLT	9	0.004199	24	0.001599	31	0.000819
	*1NN6	12	0.005598	29	0.001933	11	0.000291
	1T31	9	0.004199	27	0.001799	31	0.000819
	1PJP	13	0.006065	21	0.001400	28	0.000740
Urokinase-type plasminogen activator	*2O8T	13	0.006065	33	0.002199	12	0.000281
	2O8U	1	0.000467	11	0.000733	9	0.000210
	2O8W	9	0.004199	20	0.001333	18	0.000421
	2R2W	3	0.001400	2	0.000133	11	0.000257
	1SQO	4	0.001866	9	0.000600	11	0.000257
Complement Factor B	*1RRK	10	0.004665	6	0.000400	10	0.000179
	1RTK	4	0.001866	16	0.001066	12	0.000214

Table S5: Volume-wise statistics of the number of unique cliques residues in the three tiers: 'near', 'mid', and 'far' with respect to the native structures (highlighted by an *) [data for figure 4(c)]. The volume normalization ensures unbiased comparison across the three tiers.

Protein Name	PDB-ID	Within 1/3rd d	Per Residue Volume for 1/3rd d	Between 1/3rd d & 2/3rd d	Per Residue Volume for Residues between 1/3rd d & 2/3rd d	Beyond	Per Residue Volume for Residues beyond
Complement	1BIO	4	0.001866	21	0.001400	13	0.000222

Factor D							
	1DIC	4	0.001866	12	0.000800	12	0.000205
	*1DST	7	0.003265	26	0.001733	14	0.000239
Trypsin-1	1HJ8	6	0.002799	11	0.000733	9	0.000224
	1UTJ	6	0.002799	14	0.000933	9	0.000224
	*1UTK	9	0.004199	30	0.001999	16	0.000399
	1UTL	8	0.003732	10	0.000666	7	0.000175
	1UTM	2	0.000933	4	0.000267	0	0.000000
Trypsin	*1OS8	1	0.000467	13	0.000866	9	0.000259
	1OSS	2	0.000933	14	0.000933	0	0.000000
Kallikrein-6	*1GVL	10	0.004665	18	0.001200	15	0.000378
	1L2E	6	0.002799	22	0.001466	12	0.000302
Prostatin	3DFL	5	0.002333	10	0.000666	1	0.000024
	3E0P	5	0.002333	6	0.000400	17	0.000405
	*3E1X	7	0.003265	23	0.001533	10	0.000238
	3FVF	0	0.000000	6	0.000400	12	0.000286
Chymase	1KLT	8	0.003732	24	0.001599	26	0.000687
	*1NN6	12	0.005598	29	0.001933	11	0.000291
	1T31	9	0.004199	27	0.001799	26	0.000687
	1PJP	12	0.005598	21	0.001400	25	0.000660
Urokinase-type plasminogen activator	*2O8T	13	0.006065	33	0.002199	12	0.000281
	2O8U	1	0.000467	11	0.000733	9	0.000210
	2O8W	9	0.004199	20	0.001333	18	0.000421
	2R2W	3	0.001400	2	0.000133	11	0.000257
	1SQO	4	0.001866	9	0.000600	11	0.000257
Complement Factor B	*1RRK	10	0.004665	6	0.000400	10	0.000179
	1RTK	4	0.001866	16	0.001066	12	0.000214

Table S6: Volume-wise statistics of the number of unique pair of residues in unique cliques in the three tiers: ‘near’, ‘mid’, and ‘far’ with respect to the native structures (highlighted by an *) [data for figure 4(b)]. The volume normalization ensures unbiased comparison across the three tiers.

Protein Name	**PDB-ID**	**Within $1/3^{rd}$ d**	**Per Residue Volume for $1/3^{rd}$ d**	**Between $1/3^{rd}$ d & $2/3^{rd}$ d**	**Per Residue Volume for Residues between $1/3^{rd}$ d & $2/3^{rd}$ d**	**Beyond**	**Per Residue Volume for Residues beyond**
Complement Factor D	1BIO	2	0.000933	14	0.000933	11	0.000188
	1DIC	2	0.000933	9	0.000600	10	0.000171
	*1DST	5	0.002333	20	0.001333	11	0.000188
Trypsin-1	1HJ8	3	0.001400	7	0.000467	9	0.000224
	1UTJ	4	0.001866	12	0.000800	9	0.000224
	*1UTK	9	0.004199	29	0.001933	16	0.000399
	1UTL	6	0.002799	8	0.000533	7	0.000175
	1UTM	2	0.000933	1	0.000067	0	0.000000
Trypsin	*1OS8	1	0.000467	10	0.000666	6	0.000173
	1OSS	2	0.000933	12	0.000800	0	0.000000
Kallikrein-6	*1GVL	6	0.002799	12	0.000800	8	0.000201

	1L2E	3	0.001400	16	0.001066	5	0.000126
Prostatin	3DFL	5	0.002333	8	0.000533	1	0.000024
	3E0P	4	0.001866	3	0.000200	17	0.000405
	*3E1X	7	0.003265	23	0.001533	10	0.000238
	3FVF	0	0.000000	5	0.000333	12	0.000286
Chymase	1KLT	4	0.001866	18	0.001200	25	0.000660
	*1NN6	11	0.005132	24	0.001599	6	0.000159
	1T31	8	0.003732	23	0.001533	25	0.000660
	1PJP	6	0.002799	19	0.001266	23	0.000608
Urokinase-type plasminogen activator	*2O8T	13	0.006065	33	0.002199	9	0.000210
	2O8U	0	0.000000	10	0.000666	9	0.000210
	2O8W	8	0.003732	18	0.001200	15	0.000351
	2R2W	3	0.001400	1	0.000067	10	0.000234
	1SQO	4	0.001866	5	0.000333	8	0.000187
Complement Factor B	*1RRK	10	0.004665	5	0.000333	8	0.000143
	1RTK	4	0.001866	15	0.001000	10	0.000179

Table S7: Volume-wise statistics of the number of unique individual residues in unique cliques in the three tiers: 'near', 'mid', and 'far' with respect to the native structures (highlighted by an *) [data for figure 4(a)]. The volume normalization ensures unbiased comparison across the three tiers.

PDB_id	No. of residues from Δconn >0 or Δccfs >0	No. of URUC
1ELA	46	29
1ELB	45	22
1ELC	41	20

Table S8: Number of residues identified from increase in connectivity / clustering co-efficient and URUC for 1ELA, 1ELB, and 1ELC.

Structures	Common unique residues of unique cliques w.r.t 1ESA (native)
1ELA+1ELB+1ELC	26 45 74 77 97 109
1ELA+1ELB	20 26 44 45 49 51 74 77 79 97 109
1ELB+1ELC	12 26 45 74 77 97 109 128 147
1ELA+1ELC	19 26 43 45 54 57 70 74 77 97 109 240
	Exclusive unique residues of unique cliques w.r.t 1ESA (native)
1ELA	39 48 76 85 98 121 125 152 213 216 219
1ELB	33 35 41 183 193 200 209 214
1ELC	6 60 78 144 236

Table S9: List of common and exclusive unique residues of unique cliques among 1ELA, 1ELB, and 1ELC at 3% [the unique cliques for the three liganded system 1ELA, 1ELB, and 1ELC are computed with respect to the native structure (1ESA)].

Protein Name	PDB_ID	Within 1/3rd d	Per Residue Volume for 1/3rd d	Between 1/3rd d & 2/3rd d	Per Residue Volume for Residues between 1/3rd d & 2/3rd d	Beyond	Per Residue Volume for Residues beyond
Elastase	1ESA	6	0.002797	17	0.001132	18	0.000471
	1ELA	7	0.004195	14	0.000932	8	0.000209
	1ELB	5	0.003263	13	0.000999	4	0.000183
	1ELC	2	0.001398	9	0.000866	9	0.000236

Table S10: Volume-wise statistics of the number of unique individual residues in unique cliques in the three tiers: 'near', 'mid', and 'far' for the analogous ligand bound elastase structures (1ELA, 1ELB, and 1ELC) with respect to the native structure (1ESA). The volume normalization ensures unbiased comparison across the three tiers.

Group 1	Group 2
230N, **199C**, **197S**, 178Y, **223F**, 186S, 195V, 239T, **54W**	**22A**, **163A**, **142C, 209C**, 218H, 130P, 7**5H, 85Q**, 49**L, 111L**, 110A

Table S11: Groups of statistically coupled residues (from SCA analysis) in S1A family of serine proteases. The ones coinciding with URUC for 1ELA, 1ELB, and 1ELC (or the ones which are ±1 neighbours) are highlighted in bold.

References

1. Akaabourne, M., Villanova, M., Festoff, B.W., Verdiere-Sahuque, M. & Hantai, D. (1994). FEBS Letters, **351**, 246-248.
2. Feric, N.T., Boffa, M.B., Johnston, S.M., & Koschinsky, M.L. (2008). Journal of Thrombosis and Haemostasis, **6**, 2113–2120.
3. Seriramalu, R., Pang, W.W., Jayapalan, J.J., Mohamed, E., Abdul-Rehman, P.S., Bustam, A.Z., Khoo, A.S-B. & Hashim, O.H. (2010). Electrophoresis, **31**, 2388–2395.
4. Torreira, E., Tortajada, A., Montes, T., Cordoba, S. R.d. & Llorca, O. (2009). J Immunol, **183**, 7347-7351.
5. Martini, P.G.V, Cook, L.C., Alderucci, S., Norton, A.W., Lundberg, D.M., Fish, S.M., Langsetmo, K., Jönsson, G., Lood, C., Gullstrand, B., Zaleski, K.J., Savioli, N., Lottherand, J., Bedard, C., Gill, J., Concino, M.F., Heartlein, M.W., Truedsson, L., Powell, J.L. & Tzianabos, A.O. (2010). BMC Immunology, **11**:43.
6. Kershaw, E.E. & Flier, J.S. (2004). J. Clin. Endocrinol. Metab. **89**, 2548-2556.
7. Gomis-Ruth, F.X.,, Bayes, A., Sotiropoulou, G., Pampalakis, G., Tsetsenis, T., Villegas, V., Aviles, F.X. & Coll, M. (2002). J. Biol.Chem., **277**, 27273–27281.
8. Spraggon, G., Hornsby, M., Shipway, A., Tully, D.C., Bursulaya, B., Danahay, H., Harris, J.L. & Lesley, S.A. (2009). Protein Sci., **18**,1081—1094.
9. Lauritzen, B., Lykkesfeldt, J., Djurup, R., Flodgaard, H. & Svendsen, O. (2005). Pharmacological Research, **51**, 509-514.
10. Demers C., Ginsberg, J.S., Brill-Edwards, P, Panju, A., Warkentin, T.E., Anderson, D.R., Turner, C. and Kelton, J.G. (1991). Blood, **78**, 2194-2197.
11. Tang, J., Yu, C.L., Williams, S.R., Springman, E., Jeffery, D., Sprengeler, P.A., Estevez, A., Sampang, J., Shrader, W., Spencer, J., Young, W., McGrath, M. & Katz, B.A. (2005). THE J. Biol.Chem., **280**, 41077–41089.
12. Caughey, G.H. (1989). Am J Physiol Lung Cell Mol Physiol **257**: L39-L46, 1989

13. Debela, M., Hess, P., Magdolen, V., Schechter, N.M., Steiner, T., Huber, R., Bode, W. & Goettig, P. (2007). PNAS, **104**, 16086–16091.
14. Gaboriaud, C., Serre, L., Guy-Crotte, O., Forest, E., & Fontecilla-Camps, J-C. (1996). J. Mol. Biol. **259**, 995–1010.
15. Zhao, G., Yuan, C., Wind, T., Huang, Z., Andreasen, P.A. & Huang, M. (2007). Journal of Structural Biology, **160**, 1–10.
16. Huber, R. & Bode, W. (1978). Accounts of Chemical Research, **11,** 114-122.
17. Jin, L., Pandey, P., Babine, R.E., Gorga. J.C., Seidl, K.J., Gelfand, E., Weaver, D.T., Abdel-Meguid, S.S. & Strickler, J.E. (2005). J. Biol.Chem., **280**, 4704–4712.
18. Talas, U., Dunlop, J., Khalaf, S., Leigh, I.M. & Kelsell, D.P. (2000). Journal of Investigative Dermatology, **114**, 165-170.
19. Szmola, R. & Sahin-Toth, M. (2007). PNAS, **104**, 11227–11232.
20. Yamazaki, T. & Aoki, Y. (1997). Journal of Leukocyte Biology, **61**, 73-79.
21. Meyer-Hoffert, U., Wingertszahn, J. & Wiedow, O. (2004). J Invest Dermatol **123**, 338 – 345.
22. Lu, H., Hou, Q., Zhao, T., Zhang, H., Zhang, Q., Wu, L. & Fan, Z. (2006). The Journal of Immunology, **177**, 1171–1178.
23. Moon, J-Y., Yim, E-Y., Song, G., Lee, N.H. & Hyun, C-G. (2010). EurAsian Journal of BioSciences, **4**, 41-53.