| **Table S1: Dataset: Pdb (21) codes of 232 proteins used in this analysis** |
|---|
| **119l 153l 16pk 1a12 1a2p 1a2z 1a3a 1a68 1a6m 1a8d 1a8e 1a8i 1aay 1aba** |
| **1ads 1agj 1ajs 1ako 1amm 1aoh 1aqb 1arb 1aru 1atg 1atl 1atz 1avm 1axn** |
| **1ay7 1b0y 1b3a 1b4v 1b5e 1b8o 1bd8 1bdo 1beb 1bfd 1bfg 1bgf 1bj7 1bkf** |
| **1bkr 1bm8 1bs9 1bup 1bx7 1bxa 1byq 1c52 1c8k 1cem 1cex 1chd 1cjc 1cjw** |
| **1cka 1cmb 1cnv 1cnz 1cor 1cse 1csh 1ctf 1cv8 1cyo 1dci 1dhn 1din 1dmr** |
| **1dps 1dpt 1e7u 1eca 1edg 1epw 1eul 1ezm 1fgl 1flt 1fna 1fnc 1ftr 1fvk** |
| **1g8k 1gdo 1gof 1gpe 1gte 1guq 1h3n 1h5u 1h7w 1hfc 1hfe 1hxn 1hyp 1iab** |
| **1ida 1iib 1isu 1ixh 1jer 1jhg 1jz8 1k06 1k32 1kbl 1kcw 1kek 1kid 1koe** |
| **1kpe 1kpt 1kqf 1kuh 1kve 1l58 1l8a 1lam 1lcl 1lfa 1lkk 1lmb 1mfm 1mla** |
| **1mml 1mof 1mol 1moq 1mpg 1mrj 1msi 1msk 1mty 1mug 1nbc 1nkd 1nox 1npk** |
| **1nwp 1oaa 1one 1opd 1pcf 1pdo 1pgs 1pj5 1pmi 1poa 1pot 1ppn 1psr 1q16** |
| **1qcx 1qdd 1qhf 1qnf 1qre 1r27 1ra9 1rcf 1rge 1rie 1ryc 1rzl 1sbp 1smd** |
| **1svf 1tag 1tca 1thv 1tif 1tph 1tvx 1tx4 1ubi 1unk 1uro 1vfa 1vfb 1vfy** |
| **1vhh 1vie 1vqb 1wap 1whi 1xnb 1yac 1yge 1zin 256b 2a0b 2acy 2ayh 2baa** |
| **2bbk 2ccy 2cpl 2ctc 2dri 2end 2hbg 2igd 2ilk 2mcm 2myr 2nac 2ohx 2olb** |
| **2por 2pth 2pvi 2rn2 2sak 2sic 2sn3 2sns 2tgi 2tps 2utg 3chb 3cyr 3grs** |
| **3pte 3seb 3vub 4pga 5hpg 5pti 6gsv 8abp** |

**Table S2: Normalization values of amino acid residues (17)**

| Amino Acid | Normalization Values ($N_i$)[1] |
|---|---|
| Ala | 55.76 |
| Arg | 93.79 |
| Asn | 73.41 |
| Asp | 75.15 |
| Cys | 54.95 |
| Gln | 78.13 |
| Glu | 78.83 |
| Gly | 47.31 |
| His | 83.74 |
| Ile | 67.95 |
| Leu | 72.25 |
| Lys | 69.61 |
| Met | 69.26 |
| Phe | 93.31 |
| Pro | 51.33 |
| Ser | 61.39 |
| Thr | 63.71 |
| Trp | 106.70 |
| Tyr | 100.72 |
| Val | 62.37 |

[1]: The normalization values of the 20 amino acids ($N_i$) are given here. The combinations of these values like $sqrt(N_i \times N_j)$, $(N_i+N_j)/2$ and $min(N_i,N_j)$, which have been used in the analysis, can be obtained from these values.

Figure S1a

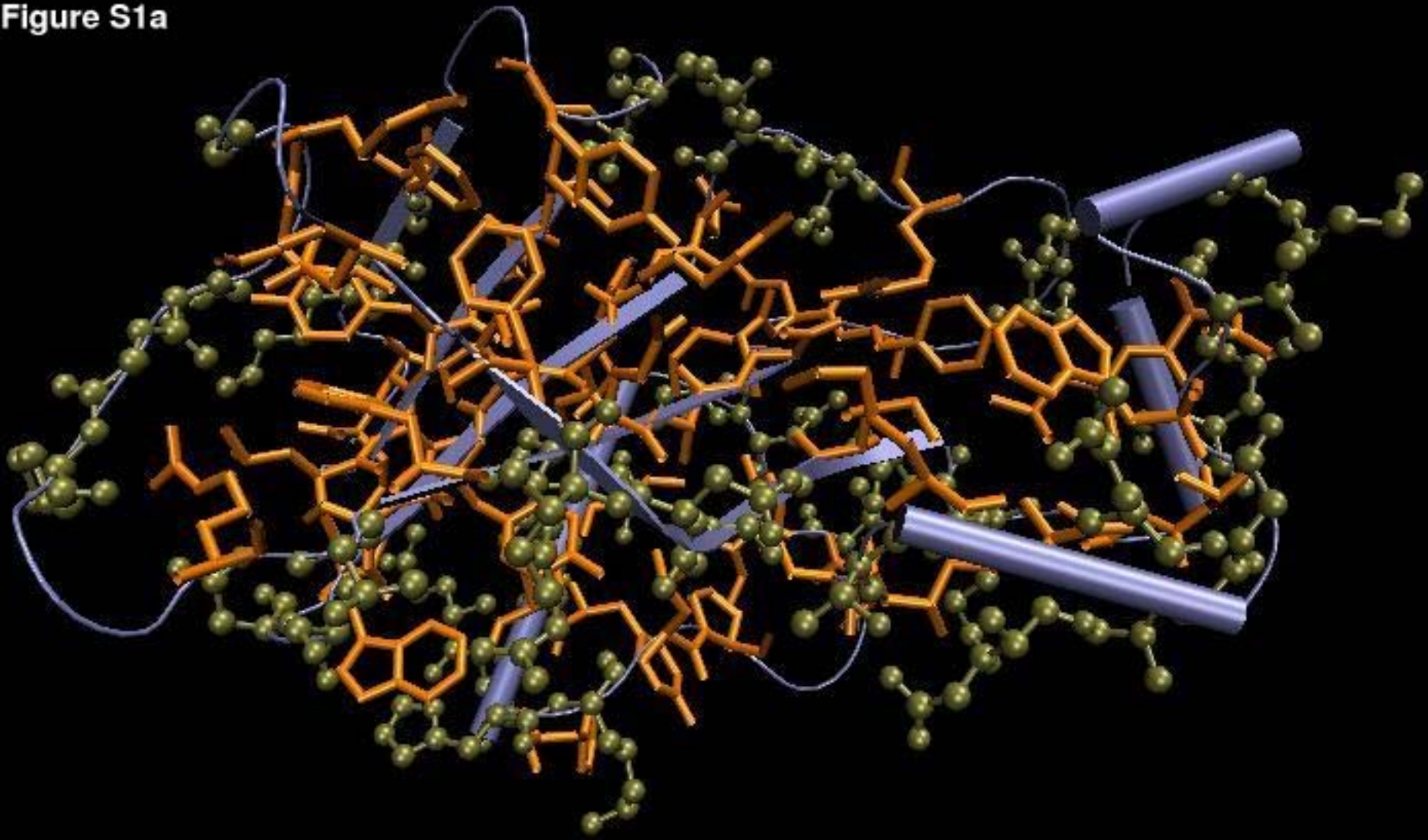

Figure S1b

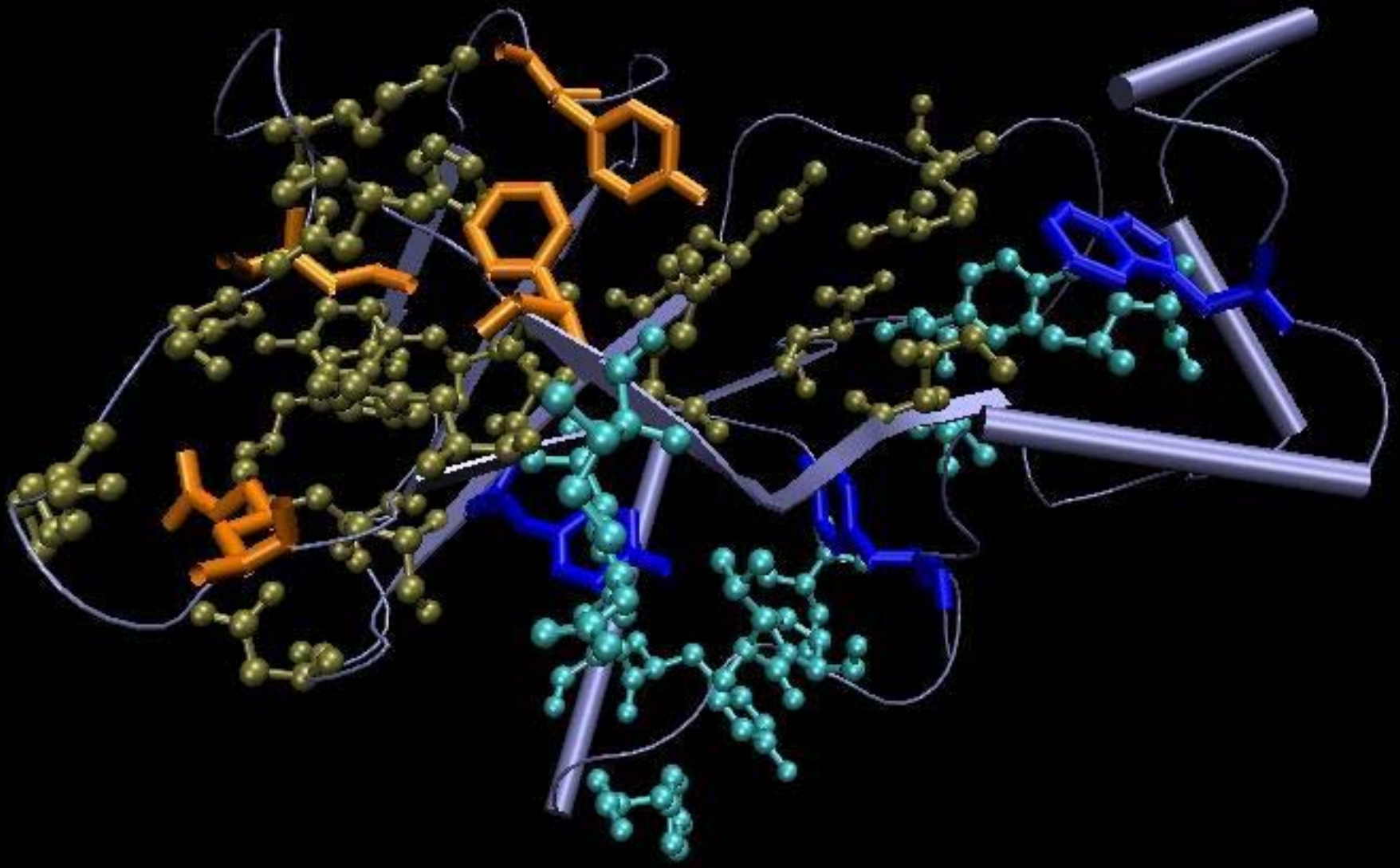

**Figure S2: Multiple sequence alignment of Carboxypeptidases:**

```
2CTC          TYHTLDEIYDFMDLLVAEHPQLVSKLQIGRSYEGRPIYVLKFS---TGGSNRPAIWIDLG 67
1PCA          TYHTLEEIYDFMDILVAEHPALVSKLQIGRSYEGRPIYVLKFS---TGGSNRPAIWIDSG 162
1DTD          AYHTLEEISQEMDNLVAEHPGLVSKVNIGSSFENRPMNVLKFS---TGG-DKPAIWLDAG 60
1NSA          KYNNWETIEAWTEQVTSKNPDLISRSAIGTTFDGDNIYLLKVG---KPGSNKPAIFMDCG 153
1OBR          GYHNYNEMVNKINTVASNYPNIVKKFSIGKSYEGRELWAVKISDNVGTDENEPEVLYTAL 67
1JQG          KIHSYEEVDAYLQELAKEFPNVVTVVEGGKSFEGRSIKYLRISTTNFQDASKPVVMMQSL 179

2CTC          IHSREWITQATGVWFAKKFTEDYGQDPSFTAILDSMDIFLEIVTNPDG--FAFTHSQNRL 125
1PCA          IHSREWITQASGVWFAKKITENYGQNSSFTAILDSMDIFLEIVTNPNG--FAFTHSDNRL 220
1DTD          IHAREWVTQATALWTANKIVSDYGKDPSITSILDALDIFLLPVTNPDG--YVFSQTKNRM 118
1NSA          FHAREWISQAFCQWFVRDAVRTYGYEAHMTEFLDNLDFYVLPVLNIDG--YIYTWTKNRM 211
1OBR          HHAREHLTVEMALYTLDLFTQNYNLDSRITNLVNNREIYIVFNINPDGGEYDISSGSYKS 127
1JQG          LHCREWVTLPATLYAIHKLVIDVTES----DLINNIDWIILPVANPDG--YVHTFGGDRY 233
                NE

2CTC          WRKTRSVTSS--SLCVGVDANRNWDAGFGKAGASS-SPCSETYHGKYANSEVEVKSIVDF 182
1PCA          WRKTRSKASG--SLCVGSDSNRNWDAGFGGAGASS-SPCAETYHGKYPNSEVEVKSITDF 277
1DTD          WRKTRSKVSAG-SLCVGVDPNRNWDAGFGGPGASS-NPCSDSYHGPSANSEVEVKSIVDF 176
1NSA          WRKTRSTNAG--SSCTGTDPNRNFNAGWCTVGASV-NPCNETYCGSAAESEKETKALADF 268
1OBR          WRKNRQPNSG--SSYVGTDLNRNYGYKWGCCGGSSGSPSSETYRGRSAFSAPETAAMRDF 185
1JQG          WRKNRATGYMAGNLCMGVDLNRNFGMNWGTASSSS--VCSDTFHGRSAFSEPESSVIRDI 291

2CTC          VKDH-----GNFKAFLSIHSYSQLLLYPYGYTTQSIPDKTELNQVAKSAVEALKSLYGTS 237
1PCA          VKNN-----GNIKAFISIHSYSQLLLYPYGYKTQSPADKSELNQIAKSAVAALKSLYGTS 332
1DTD          IKSH-----GKVKAFIILHSYSQLLMFPYGYKCTKLDDFDELSEVAQKAAQSLSRLHGTK 231
1NSA          IRNNL----SSIKAYLTIHSYSQMILYPYSYDYKLPENDAELNSLAKGAVKELASLYGTS 324
1OBR          INSRVVGGKQQIKTLITFHTYSELILYPYGYTYTDVPSDMTQDDFNVFKTMANTMAQTNG 245
1JQG          IAEHR----NRMALYLDIHSFGSMILYGYG-NGVLPSNALQLHLIGVQMAQAIDRVKWSS 346
                          NC    C                          E

2CTC          ---YKYGSIITTIYQASGGSIDWSYNQGIKYSFTFEL---RDTGR-YGFLLPASQIIPTA 290
1PCA          ---YKYGSIITVIYQASGGVIDWTYNQGIKYSFSFEL---RDTGR-RGFLLPASQIIPTA 385
1DTD          ---YKVGPICSVIYQASGGSIDWSYDYGIKYSFAFEL---RDTGR-YGFLLPARQILPTA 284
1NSA          ---YSYGPGSTTIYPAAGGSDDWAYNQGIKYSFTFEL---RDKGR-FGFVLPESQIQATC 377
1OBR          ---YTP-QQASDLYITDGDMTDWAYGQHKIFAFTFEM---YPTSYNPGFYPPDEVIGRET 298
1JQG          NKDYIVGNIFHVLYAASGGASDYAMQAAAPFSYTYELPAYRNSVWFDGFLVDPDFIEQAG 406
                                                    E
2CTC           QETWLGVLTIMEHTLNN----------- 307
1PCA           QETWLALLTIMEHTLNNS---------- 403
1DTD           EETWLGLKAIMEHVRDHPY--------- 303
1NSA           QETMLAVKYVTNYTLEHL---------- 395
1OBR           SRNKEAVLYVAEKADCPYSVIGKSCSTK 326
1JQG           FETWEGIKVGARAAAAAAKELKKLNTA- 433
```

**Figure Legend:**

Multiple sequence alignments of carboxypeptidases obtained from Homstrad (29). Only those proteins with known structures are shown here in the alignment. 2ctc, 1pca, 1dtd, 1nsa, 1jqg are mesophilic carboxypeptidases. 1obr is a thermophilic carboxypeptidase. All the hub residues identified in 2ctc and 1obr (protein considered in the present study) at $I_{min}$=4% are highlighted in blue. The conservation profile of the hubs can be identified from the figure. An example each of *common* (**C**), *exclusive* (**E**), *non-exclusive* (**NE**) and *non-conserved* (**NC**) hubs (definitions are given in the text) are indicated below the corresponding residue in the alignment.

Figure Caption for Supplementary Figures:

1. Figure S1: Clusters and hubs in Barnase (1RNB) at (a) $I_{min}$ = 0% and (b) $I_{min}$ = 6%. In both the figures, the protein tertiary structure is shown in blue colored cartoon representation. The hubs are shown in bond representation and other residues, which form clusters, are shown in ball and stick representation. Figure S1a shows a single big cluster in Barnase at $I_{min}$=0% (shown in tan colored ball and stick) with a large number of hubs (orange bonds). The big cluster splits up into two disjoint clusters at $I_{min}$ = 6%, which are shown in tan and cyan colored ball and stick representation respectively in Figure S1b. The hubs in these two clusters are shown in orange and blue bonds respectively. There are three other smaller clusters with 3-4 residues in each occurring at $I_{min}$=6% in Barnase, which are not shown here in the interest of clarity. The hubs in both the Figures S1a and S1b are predominantly the aromatic residues. However, the hydrophobic residues also can be seen as hubs in Figure S1a, which have lost many interactions at $I_{min}$=6%, as can be seen by their absence in Figure S1b.

2. Figure S2: Multiple sequence alignments of carboxypeptidases obtained from Homstrad (29). Only those proteins with known structures are shown here in the alignment. 2ctc, 1pca, 1dtd, 1nsa, 1jqg are mesophilic carboxypeptidases. 1obr is a thermophilic carboxypeptidase. All the hub residues identified in 2ctc and 1obr (protein considered in the present study) at $I_{min}$=4% are highlighted in blue. The conservation profile of the hubs can be identified from the figure. An example each of *common* (**C**), *exclusive* (**E**), *non-exclusive* (**NE**) and *non-conserved* (**NC**) hubs (definitions are given in the text) are indicated below the corresponding residue in the alignment.