**Legends to supplementary Figures**

**Supplementary Figure 1** Asp496 – Ser317 distance in ligand-free human DPP III (PDB: 3FVY).

Structure was generated by PyMOL ([www.pymol.org](http://www.pymol.org)). Amino acid residues (Asp496 and Ser317) are given in black, by the ball-and-stick representation.

**Supplementary Figure 2**  Multiple sequence alignment (MSA) of a selection of M49 family peptidases.

MSA was obtained using ClustalO (UniProt) ([www.uniprot.org./align](http://www.uniprot.org./align)). Presented is a region comprising five constituents of the S2 subsite, which are bolded in human sequence (Trp495, Asp496, Ser504, Glu507 and Glu508), and ETGE motif (italic font in human DPP III sequence). Aligned were amino acid sequences from: *Homo sapiens* (Q9NY33), *Felis catus* (M3WB74), *Pelodiscus sinensis* (K7F547), *Salmo salar* (B5X435), *Caenorhabditis elegans* (G5ECW7), *Giardia intestinalis* (A8B3Q8), *Apis mellifera* (A0A088A023), *Trichoplax adhaerens* (B3S0Q5), *Bombyx mori* (H9J598), *Nematostella vectensis* (A7RZW4), *Aspergillus niger* (A2QHM6), *Saccharomyces cerevisiae* (Q08225), *Bacteroides thetaiotaomicron* (Q8A6N1), *Croceibacter atlanticus* (A3U8C5), *Flavobacterium frigoris* (H7FU07), and *Stigmatella aurantiaca* (Q08U85).