**Supplementary Information**

**Table S1**. Table for the data presented in Figure 2.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Amino acid in trypsin | Participation in hydrogen bonding interaction (in %) in tryosin | Amino acid in trypsin | Participation in non-bonded interaction (in %) in trypsin | Amino acid in inhibitors | Participation in hydrogen bonding interaction (in %) | Amino acid in inhibitors | Participation in non-bonded interaction (in %) in inhibitor |
| SER | 33.7 | SER | 23.3 | ARG | 39.3 | ARG | 26.9 |
| GLY | 23.8 | GLY | 15.6 | LYS | 20.5 | LYS | 16.6 |
| ASP | 9.8 | GLN | 11.8 | CYS | 6.5 | CYS | 7.3 |
| HIS | 7.3 | HIS | 9.9 | PRO | 4.7 | ILE | 5.8 |
| PHE | 6.3 | TYR | 9.4 | ILE | 4.2 | PRO | 5.7 |
| GLN | 6.2 | TRP | 6.8 | SER | 2.8 | ALA | 5.4 |
| ASN | 5.8 | PHE | 5.2 | GLY | 2.5 | LEU | 4.3 |
| TYR | 4.8 | CYS | 5.2 | LEU | 2.5 | SER | 4 |
| ARG | 1 | ASP | 4.9 | GLN | 2.3 | THR | 3.7 |
| LYS | 0.8 | LEU | 2.5 | HIS | 2 | GLY | 3.4 |
| THR | 0.4 | ASN | 2.3 | ASP | 1.9 | VAL | 2.7 |
| GLU | 0.1 | LYS | 1.1 | VAL | 1.9 | PHE | 2.5 |
| ALA | 0.1 | ARG | 0.7 | THR | 1.8 | ASP | 1.9 |
|  |  | THR | 0.4 | GLU | 1.5 | GLN | 1.9 |
|  |  | PRO | 0.3 | TRP | 1.4 | HIS | 1.8 |
|  |  | VAL | 0.2 | PHE | 1.1 | TYR | 1.7 |
|  |  | ILE | 0.2 | ALA | 1.1 | GLU | 1.5 |
|  |  | ALA | 0.1 | TYR | 0.9 | TRP | 1.3 |
|  |  | GLU | 0.1 | MET | 0.8 | MET | 1.1 |
|  |  |  |  | ASN | 0.3 | ASN | 0.4 |

**Table S2**. Table for the data presented in Figure 3.

|  |  |  |  |
| --- | --- | --- | --- |
| Residues | Participation in hydrogen bonding interactions (in %) | Residues  | Participation in non-bonded interactions (in %) |
| SER195 | 14.4 | SER195 | 11.4 |
| GLY216 | 8.9 | GLN192 | 8.9 |
| SER190 | 7.5 | GLY193 | 6.4 |
| GLY193 | 7.4 | HIS57 | 6.2 |
| ASP189 | 6.1 | TRP215 | 5.4 |
| HIS40 | 5.8 | GLY216 | 5.1 |
| SER214 | 5.6 | SER190 | 4.9 |
| PHE41 | 5.5 | PHE41 | 4.3 |
| ASN97 | 5.3 | TYR39 | 4.2 |
| GLN192 | 5.1 | CYS191 | 3.6 |
| GLY219 | 4.4 | TYR151 | 3.5 |
| TYR39 | 3.9 | ASP189 | 3.3 |
| ASP194 | 3.6 | SER214 | 2.8 |
| SER217 | 1.8 | LEU99 | 2.2 |
| SER200 | 1.1 | HIS40 | 1.9 |
| SER96 | 1 | ASN97 | 1.7 |
| ARG64 | 0.9 | ASP194 | 1.4 |
| HIS57 | 0.9 | GLY219 | 1.3 |
| GLY217 | 0.9 | GLN197 | 1.3 |
| GLY212 | 0.8 | SER217 | 1.2 |
| SER215 | 0.6 | SER200 | 0.9 |
| GLY198 | 0.6 | TRP216 | 0.7 |
| GLN197 | 0.6 | GLN175 | 0.7 |
| PHE42 | 0.5 | HIS58 | 0.7 |
| HIS46 | 0.4 | CYS42 | 0.6 |
| GLY214 | 0.4 | ARG64 | 0.6 |
| SER210 | 0.4 | HIS63 | 0.6 |
| SER192 | 0.4 | GLY226 | 0.6 |
| ASN102 | 0.4 | LYS60 | 0.6 |
| GLY209 | 0.4 | GLY217 | 0.5 |
| THR144 | 0.4 | TYR154 | 0.5 |
| SER187 | 0.3 | SER96 | 0.5 |
| TYR45 | 0.3 | PHE42 | 0.4 |
| LYS60 | 0.3 | GLY198 | 0.4 |
| PHE47 | 0.3 | GLY212 | 0.4 |
| SER213 | 0.3 | CYS196 | 0.4 |
| HIS58 | 0.3 | TRP211 | 0.3 |
| SER207 | 0.3 | TYR45 | 0.3 |
| TYR40 | 0.3 | GLN214 | 0.3 |
| GLY190 | 0.3 | GLN189 | 0.3 |
| GLN214 | 0.3 | PHE47 | 0.3 |
| LYS224 | 0.3 | ASN102 | 0.3 |
| GLN189 | 0.1 | TYR40 | 0.3 |
| PHE39 | 0.1 | HIS55 | 0.3 |
| ASN95 | 0.1 | SER192 | 0.3 |
| LYS97 | 0.1 | SER210 | 0.3 |
| LYS58 | 0.1 | TRP208 | 0.2 |
| ALA66 | 0.1 | TYR37 | 0.2 |
| ARG92 | 0.1 | GLY190 | 0.2 |
| LYS215 | 0.1 | HIS46 | 0.2 |
| SER142 | 0.1 | VAL213 | 0.2 |
| SER61 | 0.1 | SER215 | 0.2 |
| TYR59 | 0.1 | CYS220 | 0.2 |
| GLU151 | 0.1 | TYR149 | 0.2 |
| TYR37 | 0.1 | GLY209 | 0.2 |
|  |  | SER213 | 0.2 |
|  |  | LYS224 | 0.2 |
|  |  | SER142 | 0.2 |
|  |  | PHE39 | 0.2 |
|  |  | LEU104 | 0.2 |
|  |  | ILE65 | 0.2 |
|  |  | CYS188 | 0.1 |
|  |  | GLN178 | 0.1 |
|  |  | ASN94 | 0.1 |
|  |  | GLY214 | 0.1 |
|  |  | SER187 | 0.1 |
|  |  | ALA66 | 0.1 |
|  |  | PRO62 | 0.1 |
|  |  | PRO63 | 0.1 |
|  |  | LEU115 | 0.1 |
|  |  | SER207 | 0.1 |
|  |  | THR149 | 0.1 |
|  |  | LYS58 | 0.1 |
|  |  | TYR146 | 0.1 |
|  |  | SER61 | 0.1 |
|  |  | CYS48 | 0.1 |
|  |  | ASN13 | 0.1 |
|  |  | GLN173 | 0.1 |
|  |  | THR98 | 0.1 |
|  |  | LYS97 | 0.1 |
|  |  | LYS215 | 0.1 |
|  |  | THR144 | 0.1 |
|  |  | ARG92 | 0.1 |
|  |  | TYR94 | 0.1 |
|  |  | GLY227 | 0.1 |
|  |  | SER141 | 0.1 |
|  |  | ASN146 | 0.1 |
|  |  | ASP199 | 0.1 |
|  |  | CYS43 | 0.1 |
|  |  | PHE116 | 0.1 |
|  |  | LYS61 | 0.1 |
|  |  | THR103 | 0.1 |
|  |  | GLY143 | 0.1 |
|  |  | GLU151 | 0.1 |
|  |  | GLY222 | 0.04 |
|  |  | ARG12 | 0.04 |
|  |  | THR152 | 0.04 |
|  |  | HIS41 | 0.04 |
|  |  | PRO173 | 0.04 |
|  |  | TYR59 | 0.04 |
|  |  | ILE10 | 0.04 |
|  |  | ASP102 | 0.04 |
|  |  | SER218 | 0.04 |
|  |  | TRP60 | 0.03 |
|  |  | ASP186 | 0.03 |
|  |  | GLN170 | 0.03 |
|  |  | GLY14 | 0.03 |
|  |  | VAL206 | 0.03 |
|  |  | GLY15 | 0.03 |
|  |  | SER101 | 0.03 |
|  |  | LEU96 | 0.03 |
|  |  | ILE67 | 0.03 |
|  |  | HIS114 | 0.03 |
|  |  | GLY211 | 0.01 |
|  |  | GLY174 | 0.01 |
|  |  | THR16 | 0.01 |
|  |  | ASP191 | 0.01 |
|  |  | CYS64 | 0.01 |
|  |  | HIS38 | 0.01 |
|  |  | THR147 | 0.01 |
|  |  | ASN95 | 0.01 |
|  |  | TYR65 | 0.01 |
|  |  | TYR60 | 0.01 |
|  |  | SER43 | 0.01 |
|  |  | CYS40 | 0.01 |
|  |  | CYS215 | 0.01 |
|  |  | SER37 | 0.01 |
|  |  | ILE58 | 0.01 |
|  |  | TYR172 | 0.01 |
|  |  | ARG96 | 0.01 |