Table S2. Intra- and inter- molecular restraints used in the MD simulation of AcCYS_DL/papain complex structure*

Distance restraints1

| number | residue | atom name | number | residue | atom name | distance(Å) |
|--------|---------|-----------|--------|---------|-----------|-------------|
| 47     | TYR     | HN        | 88     | GLU     | HN        | 3.03        |
| 49     | ALA     | HB1       | 86     | ALA     | HB2       | 2.52        |
| 62     | LEU     | HD22      | 98     | LEU     | HD11      | 3.62        |
| 62     | LEU     | HD22      | 98     | LEU     | HD12      | 2.57        |
| 62     | LEU     | HD22      | 98     | LEU     | HD21      | 4.54        |
| 62     | LEU     | HD11      | 115    | VAL     | HB        | 2.88        |
| 62     | LEU     | HD11      | 115    | VAL     | HG11      | 2.68        |
| 62     | LEU     | HD11      | 115    | VAL     | HG21      | 3.00        |
| 63     | ALA     | HB1       | 80     | PHE     | HD2       | 2.63        |
| 63     | ALA     | HB1       | 80     | PHE     | HE2       | 2.96        |
| 63     | ALA     | HB1       | 83     | VAL     | HG11      | 2.44        |
| 63     | ALA     | HB1       | 83     | VAL     | HG12      | 2.57        |
| 63     | ALA     | HB1       | 100    | VAL     | HG11      | 2.42        |
| 63     | ALA     | HB1       | 100    | VAL     | HG21      | 3.31        |
| 66     | ALA     | HB1       | 126    | LEU     | HD12      | 2.93        |
| 66     | ALA     | HB1       | 126    | LEU     | HD13      | 2.27        |
| 66     | ALA     | HB1       | 129    | PHE     | HD2       | 3.36        |
| 66     | ALA     | HB1       | 129    | PHE     | HE2       | 3.78        |
| 67     | VAL     | HG11      | 80     | PHE     | HN        | 2.94        |
| 67     | VAL     | HG21      | 80     | PHE     | HB2       | 2.27        |
| 67     | VAL     | HG23      | 129    | PHE     | HE2       | 2.24        |
| 70     | TYR     | HH        | 78     | LEU     | HD11      | 3.54        |
| 70     | TYR     | HH        | 78     | LEU     | HD21      | 2.61        |

Hydrogen bond restraints2

| Atom 1 | Atom 2 | distance(Å) |
|--------|--------|-------------|
| 59     | LYS    | O           | 63     | ALA    | HN        | 2.38        |
| 60     | GLU    | O           | 64     | ARG    | HN        | 1.88        |
| 61     | ASP    | O           | 65     | PHE    | HN        | 2.12        |
| 62     | LEU    | O           | 66     | ALA    | HN        | 1.95        |
| 63     | ALA    | O           | 67     | VAL    | HN        | 2.05        |
| 64     | ARG    | O           | 68     | ARG    | HN        | 1.81        |
| 65     | PHE    | O           | 69     | GLU    | HN        | 1.89        |
| 66     | ALA    | O           | 70     | TYR    | HN        | 2.22        |
| Atom 1 (papain) | Atom 2 (AcCYS) | distance(Å) |
|-----------------|----------------|-------------|
| 67 VAL          | 71 ASN         | O 1.9       |
| 68 ARG          | 72 ASN         | O 1.89      |
| 79 GLU          | 103 ASN        | O 1.92      |
| 79 GLU          | 103 ASN        | HN 1.92     |
| 81 VAL          | 101 GLU        | HN 1.89     |
| 82 ARG          | 101 GLU        | O 1.93      |
| 87 LYS          | 97 TYR         | O 1.92      |
| 89 GLN          | 95 MET         | O 1.97      |
| 89 GLN          | 95 MET         | HN 1.97     |
| 84 VAL          | 99 THR         | HN 2.02     |
| 85 LYS          | 99 THR         | O 1.98      |
| 96 HIS          | 115 VAL        | HN 1.93     |
| 98 LEU          | 113 ALA        | O 1.92      |
| 98 LEU          | 113 ALA        | HN 2.03     |
| 100 VAL         | 111 TYR        | O 1.99      |
| 102 VAL         | 109 LYS        | HN 1.94     |
| 102 VAL         | 109 LYS        | O 1.97      |
| 104 ASP         | 107 LYS        | O 2.04      |
| 110 LEU         | 132 LEU        | O 1.99      |
| 112 GLU         | 130 THR        | O 1.99      |
| 114 LYS         | 130 THR        | O 1.94      |
| 114 LYS         | 127 GLN        | HN 2.02     |
| 114 LYS         | 127 GLN        | O 2.15      |
| 116 TRP         | 125 GLN        | HN 2.03     |
| 116 TRP         | 125 GLN        | O 2.17      |
| 118 GLN         | 123 PHE        | O 2.02      |

**Intermolecular restraints**

| Atom 1 (papain) | Atom 2 (AcCYS) | distance(Å) |
|-----------------|----------------|-------------|
| 159 HIS         | 90 VAL         | HD1 1.50    |
| 177 TRP         | 91 VAL         | HE1 3.55    |

*Intramolecular and intermolecular distance restraints used in the MD simulation of AcCYS-DL/papain complex. These restraints were derived from hydrogen exchange and CSI plot, H/D exchange, and chemical shift perturbation in the NMR experiments.*

*Intramolecular distance restraints of hydrophobic clusters in AcCYS.*

*Hydrogen bond distance restraints derived from the hydrogen exchange and CSI data.*

*Intermolecular distance restraints between AcCYS and papain, derived from the dock structure of AcCYS/papain.*