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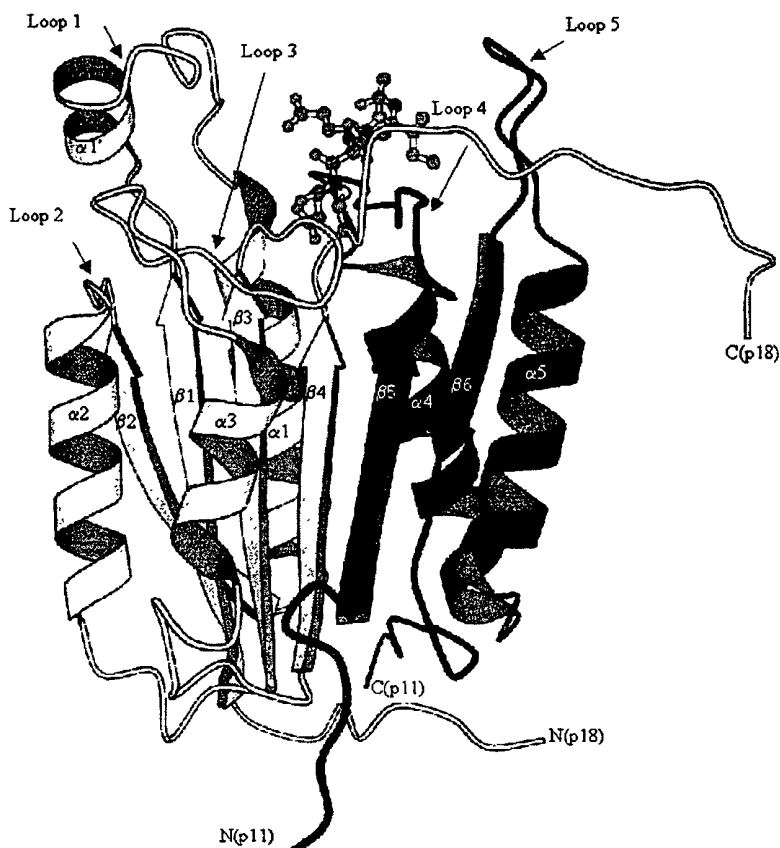
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(54) Title: CASPASE-8 CRYSTALS, MODELS AND METHODS



(57) Abstract: A caspase-8/inhibitor complex has been crystallized, and the three dimensional x-ray crystal structure of a recombinant human caspase-8 has been solved at atomic resolution (1.2Å), and substrate binding pocket has been identified. The x-ray crystal structure is useful for solving the structure of other molecules or molecular complexes, and designing modulators of caspase-8 activity.



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CASPASE-8 CRYSTALS, MODELS AND METHODS

5 Background of the Invention

The caspases are a family of related cysteine proteases that play important intracellular roles in inflammation and apoptosis. Members of this protease family, which currently number more than a dozen, share various features in common, but are structurally unrelated to the papain superfamily of

10 cysteine proteases. They all employ a conserved cysteine residue as the nucleophile for attack on peptide bonds, and the sites of cleavage all show aspartate in the P1 position of the peptide substrates. The caspase catalytic domain has a mass of roughly 30 kDa and comprises two polypeptide chains, a 17-20 kDa N-terminal (α -subunit) fragment which contains the active site

15 cysteine, and a 10-12 kDa C-terminal (β -subunit) which contributes to the formation of the active site. These chains arise by internal cleavage of a single-chain zymogen precursor, and are tightly associated in an $\alpha\beta$ heterodimer. Proteolytic processing which gives rise to these component polypeptides is either autocatalytic, or is mediated by other caspases or enzymes of similar specificity

20 (e.g. granzyme B). The $\alpha\beta$ dimeric protein associates further to form a $\alpha_2\beta_2$ heterotetramer that appears to be required for catalytic activity. Three-dimensional structures of enzyme/ligand complexes have been reported for both caspase-1 (interleukin converting enzyme; ICE) (Walker et al., Cell 78:343-352 (1994); Wilson et al., Nature 370:270-275 (1994)) and caspase-3 (CPP32, apopain, Yama) (Rotonda et al., Nat. Struct. Biol. 3:619-625 (1996); Mittl et al.,

25 J. Biol. Chem. 272:6539-6547 (1997)) from 2.3 to 2.5 Å resolution.

As with all proteolytic enzymes, the caspases exist as inactive precursors, or proenzymes. The length of the N-terminal prodomains of the caspases varies considerably depending on how activation is regulated. Our interest has been

30 focused on those caspases which are involved in apoptosis, principally caspase-8 and one of its natural substrates, caspase-3. The catalytic regions of caspase-3 and caspase-8 correspond closely with regard to length, placement of the active

site cysteine, and pattern of processing required for activation. The remarkable distinction between the two is in the greater length of the N-terminal prodomain in caspase-8, a region that contains two death-effector domains (DED).

Immunoprecipitation experiments of activated death-initiation signaling

5 complexes (DISC) show that procaspase-8 is a component of the activated receptor complexes. Because of sequence homology between the DED's of procaspase-8 and the death domains (DD) of FADD and TRADD, the death domain proteins associated with TNF and Fas receptors (Medema et al., EMBO J. 16:2794-2804 (1997)), the DED's are thought to result in association or
10 recruitment of procaspase-8 to the activated receptors. Therefore, as a component of activated DISC, procaspase-8 is positioned in the direct line of signal transduction induced by a variety of effectors such as TNF- α . Activation of the Fas or TNF receptors with Fas ligand or TNF- α results in the autocatalytic activation of procaspase-8. Activated caspase-8 is then thought to activate other
15 downstream caspases like caspase-3 which have prosegments that are shorter and whose intracellular concentrations are not high enough to support their autocatalytic processing and activation. Thus, caspase-8 has been designated as an "upstream" caspase and it is believed to sit at the apex of the Fas or TNF mediated apoptotic cascade. Its likely role is to serve as the prime mover for
20 activation of downstream caspases such as caspase-3, the "executioners" of apoptosis, whose function is to destroy critical cellular proteins in programmed cell death.

Because of its initiating role in Fas or TNF mediated apoptosis, caspase-8 is a likely target in blockade of the undesirable cell death that occurs in a variety
25 of diseases. Drugs that will inhibit this activity selectively could well find important therapeutic application, and one avenue toward drug design is via a well defined three dimensional structure of an enzyme/inhibitor complex.

Summary of the Invention

30 Structural knowledge of a protein provides a means of investigating the mechanism of action of the protein in the body. It is an object of this invention to provide information on the three-dimensional structure of caspase-8, and

further to enable rational drug design of small molecules that specifically inhibit or otherwise affect the activity of caspase-8 or caspase-8 mutants with altered catalytic activity. For example, computer models can predict binding of caspase proteins to various receptor molecules. Upon discovering that such binding in
5 fact takes place, knowledge of the protein structure then allows chemists to design and synthesize chemical entities that mimic the functional binding of caspase-8 to its receptor, in what has become known as rational drug design.

A caspase-8/inhibitor complex has been crystallized, and the three dimensional x-ray crystal structure of a recombinant human caspase-8 has been
10 solved at atomic resolution (1.2 Å). A substrate binding pocket has been identified, and structure coordinates are set forth in Figure 10. The invention thus provides a molecule or molecular complex that includes least a portion of a caspase-8 or caspase-8-like substrate binding pocket. The substrate binding pocket includes backbone atoms defined by a set of points having a root mean
15 square deviation from the backbone atoms of caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp 420, as represented by structure coordinates according to Fig. 10, of less than about 2.0 Å. The positions of these backbone atoms within the molecule or molecular complex are preferably represented by
20 the structure coordinates according to Fig. 10, essentially without any root mean square deviation. The substrate binding pocket can be further defined by a set of points having a root mean square deviation from the nonhydrogen side chain atoms of caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp 420, as
25 represented by structure coordinates according to Fig. 10, of less than about 2.0 Å. Alternatively, the substrate binding pocket can be defined as including backbone atoms characterized by interatomic distances having a root-mean-square deviation from the interatomic distances characterizing the backbone atoms of caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317,
30 Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp 420, as represented by structure coordinates according to Fig. 10, of less than about 2.0 Å; or as including backbone atoms defined by a set of points having a root mean

square deviation from the backbone atoms of caspase-8 amino acids as represented by structure coordinates according to Fig. 10 situated within a sphere having a radius of about 10 Å and centered on the coordinates representing the alpha carbon atom of residue 360, of less than about 2.0 Å. Also provided is a molecule or molecular complex that is structurally homologous to a caspase-8 molecule or molecular complex.

The high quality of the caspase-8 x-ray crystal structure serves as an important basis for evaluating detailed interactions between ligands and the enzyme subsites and for development of inhibitors with optimized binding properties. Accordingly, in one aspect the present invention relates to the three-dimensional structure of caspase-8, as determined by X-ray crystallography and represented by the structure coordinates shown in Figure 10. The invention further relates to models of caspase-8 and a computer readable form having stored thereon a model of caspase-8. Also included are methods of using the three-dimensional structure and models of caspase-8. For example, the structure coordinates of caspase-8 can be used to solve the crystal structures of caspase-8 homologues and other crystal forms of caspase-8, mutants and co-complexes of caspase-8 or structurally related proteins. The structure coordinates can also serve as the starting point for modeling the structure of other members of the caspase family of proteins, or other structurally related proteins. Use of the structure coordinates of caspase-8 in "rational drug design" is also contemplated. Specifically, the invention provides a scalable three dimensional configuration of points that includes selected points derived from the structure coordinates according to Fig. 10 representing the backbone atoms of a plurality of caspase-8 amino acids defining at least a portion of a caspase-8 substrate binding pocket and having a root mean square deviation of less than about 2.0 Å from said structure coordinates. Preferably, the caspase-8 substrate binding pocket comprises amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp 420, and the scalable three dimensional configuration of points include selected points derived from the structure coordinates according to Fig. 10 representing the backbone atoms of caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261,

His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp 420. More preferably, the selected points represent at least 50 contiguous backbone atoms of caspase-8 and having a root mean square deviation of less than about 2.0 Å from said structure coordinates. The invention further includes
5 a scalable three dimensional configuration of points that includes selected points derived from the structure coordinates of at least a portion of a molecule or a molecular complex that is structurally homologous to a caspase-8 molecule or molecular complex as represented by the structure coordinates according to Fig. 10, wherein the selected points have a root mean square deviation of less than
10 about 2.0 Å from the structure coordinates of said structurally homologous molecule or molecular complex. Advantageously, the scalable three-dimensional configuration of points of claim 8 displayed as a physical model, a computer-displayed image, a holographic image, or a stereodiagram.

The invention also provides a machine-readable data storage medium
15 comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of any molecule or molecular complex of the invention, or portion thereof.

The invention further provides a computer-assisted method for obtaining
20 structural information about a molecule or a molecular complex of unknown structure. The method utilizes the technique of molecular replacement, and includes:

crystallizing the molecule or molecular complex;
generating an x-ray diffraction pattern from the crystallized molecule or
25 molecular complex; and
applying at least a portion of the structure coordinates set forth in Fig. 10 to the x-ray diffraction pattern to generate a three-dimensional electron density map of at least a portion of the molecule or molecular complex whose structure is unknown.

30 Also provided is a computer-assisted method for homology modeling a caspase-8 homolog. The amino acid sequence of the caspase-8 homolog is aligned with the amino acid sequence of caspase-8 (SEQ ID NO:1) to yield an

amino acid alignment, then used to incorporate the sequence of the caspase-8 homolog into a model of caspase-8 derived from the structure coordinates set forth in Fig. 10 to yield a preliminary model of the caspase-8 homolog. The preliminary model is subjected to energy minimization to yield an energy
5 minimized model, and regions of the energy minimized model where stereochemistry restraints are violated are remodeled to yield a final model of the caspase-8 homolog.

A method for solving a crystal structure of a crystal of a caspase-8 molecule or molecular complex is also provided, wherein the crystal is
10 characterized by the trigonal space group $P3_121$ and having unit cell dimensions of $a = b = 62.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $c = 129.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 120^\circ$. The method includes

generating an x-ray diffraction pattern from the crystal,
collecting diffraction data, and
15 analyzing the data to generate the structure coordinates for the caspase-8 molecule or molecular complex.

The invention further provides computer-assisted methods for identifying a modulator of caspase-8 activity. In one embodiment, the method involves:

supplying a computer modeling application with a set of structure
20 coordinates of a molecule or molecular complex, the molecule or molecular complex comprising at least a portion of a caspase-8 or caspase-8-like substrate binding pocket;

supplying the computer modeling application with a set of structure coordinates of a chemical entity; and
25 determining whether the chemical entity is expected to bind to the molecule or molecular complex at the substrate binding pocket, wherein binding to the molecule or molecular complex is indicative of potential modulation of caspase-8 activity.

In another embodiment, the method involves:
30 supplying a computer modeling application with a set of structure coordinates of a molecule or molecular complex, the molecule or molecular

complex comprising at least a portion of a caspase-8 or caspase-8-like substrate binding pocket;

supplying the computer modeling application with a set of structure coordinates for a chemical entity;

5 evaluating the potential binding interactions between the chemical entity and substrate binding pocket of the molecule or molecular complex;

structurally modifying the chemical entity to yield a set of structure coordinates for a modified chemical entity; and

determining whether the chemical entity is expected to bind to the molecule or molecular complex at the substrate binding pocket, wherein binding to the molecule or molecular complex is indicative of potential modulation of caspase-8 activity.

The set of structure coordinates for the chemical entity can be obtained from a chemical fragment library, and either of the methods can be performed a multiplicity of times to screen a library of chemical entities.

15 The invention also provides for *de novo* design a modulator of caspase-8 activity. The method involves:

supplying a computer modeling application with a set of structure coordinates of a molecule or molecular complex, the molecule or molecular complex comprising at least a portion of a caspase-8 or caspase-8-like substrate binding pocket;

20 computationally building a chemical entity represented by set of structure coordinates; and

determining whether the chemical entity is expected to bind to the molecule or molecular complex at the substrate binding pocket, wherein binding to the molecule or molecular complex is indicative of potential modulation of caspase-8 activity.

The methods optionally include assaying the potential modulator to determine whether it modulates caspase-8 activity. A modulator of caspase-8 activity identified using a method of the invention is preferably an inhibitor of caspase-8 activity.

Preferably, determining whether the chemical entity is expected to bind to the molecule or molecular complex at the substrate binding pocket involves performing a fitting operation between the chemical entity and the substrate binding pocket, followed by computationally analyzing the results of the fitting operation to quantify the association between the chemical entity and the substrate binding pocket.

Also provided by the invention is a method for making a modulator of caspase-8 activity that involves chemically or enzymatically synthesizing a chemical entity to yield a modulator of caspase-8 activity, wherein the chemical entity has been designed or identified during a computer-assisted process as described herein.

It should be understood that the invention further encompasses a modulator of caspase-8 activity identified or designed according to any embodiment of the methods of the invention, as well as a composition that includes such modulator of caspase-8 activity. A pharmaceutical composition that includes a modulator of caspase-8 activity as identified or designed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier is also included in the invention.

The invention further provides a method for treating a patient having an injury or disease that is accompanied by or associated with abnormal caspase-8 activity. The method involves administering to the patient an effective amount of a pharmaceutical composition comprising a modulator of caspase-8 activity identified or designed according to the method of any of claims 21, 22 or 25, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. The composition can be used to Parkinson's disease, Alzheimer's disease, Huntington's disease, stroke, cancer, spinal cord injury, cardiovascular disease and neurological disease.

In another aspect the invention relates to caspase-8 in crystallized form and to a method of preparing caspase-8 crystals. Preferred crystals of caspase-8 are of sufficient quality to determine the three dimensional structure of the protein by X-ray diffraction methods are provided. Obtaining such crystals is in fact very much an unexpected result. It is well known in the protein

crystallographic art that obtaining crystals of quality sufficient for determining the structure of caspase-8 has not been achievable until the present application.

Accordingly, the invention provides a method for crystallizing a caspase-8 molecule that involves growing a crystal by hanging and sitting drop vapor
5 diffusion from a precipitant solution. The precipitant solution includes about 2 to about 5 mg/ml purified caspase-8, a buffer and a salt, and is buffered to a pH of about 7 to about 8. A caspase-8/ligand complex can be grown by including a ligand, such as a modulator of caspase-8 activity, in the precipitant solution. The modulator is preferably an inhibitor of caspase-8 activity, more preferably it is a
10 peptide or a peptidomimetic compound and is covalently bound to caspase-8. Crystallized caspase-8, and crystallized caspase-8/ligand complex are also included in the invention.

A composition comprising crystalline caspase-8 or crystalline caspase-8 complexed with a small molecule ligand is also provided.

15

Brief Description of the Drawings

Figure 1 shows the amino acid sequences of caspase-8 (SEQ ID NO:1), caspase-3 (SEQ ID NO:2) and caspase-1 (SEQ ID NO:3) with spatially aligned α helix and β -sheet secondary structural elements indicated. Alignment of the
20 ends and loop (L) regions of the subunits is not implied. The first 12 residues of p18 (the α -subunit of caspase-8) and first 4 residues of p11 (the β -subunit of caspase-8) are disordered. Vertical arrows indicate cleavage sites as follows: D210↓S211 at the beginning and D375↓S376 at the end of the α -subunit in caspase-8. The cleavage site D384↓L385 produces the β -subunit in caspase-8.

25 Figure 2 is a schematic diagram with labeling of the heterodimer with the p18 subunit shown in light shades and the p11 subunit shown in dark shades. β -strands are arrows; α -helices, coils. The N and C termini of the subunits are labeled. The Ac-IETD-H (SEQ ID NO:4) inhibitor is shown as a ball and stick model.

30 Figure 3 is a backbone drawing of the superimposed structures of caspase-8 shown in light shades, caspase-3 medium shades and caspase-1 in dark shades. The dyad related caspase-8 dimer is shown as a white cord. Strands of

the protein surrounding the substrate-binding pocket and the approximate location of the binding subsites are indicated. Orientation is similar to that of Figure 2.

Figure 4 presents a table of hydrogen bond contacts between
5 heterodimers along the dimer-dimer interface. The asterisk denotes the symmetry-related molecule.

Figure 5 shows the molecular surface of (A) caspase-8 and (B) caspase-3 generated by GRASP (Nicholls et al., *J. Appl. Cryst.* 24:946-950 (1991)) and viewed down the two-fold axis. The surface is seen approximately parallel to
10 the 2-fold axis. The central cavities are outlined in black. The tetrapeptide inhibitors and dithiane-diol molecules are shown as stick models. (C) Close-up of the electron-density of the dithiane-diol molecule located in the central cavity of caspase-8.

Figure 6 shows a schematic of the hydrogen bonding scheme in the Ac-IETD-caspase-8 complex. The ligand is covalently linked to the active site
15 nucleophilic Cys-360 through a thiohemiacetal bond. The hydrogen bonds are represented by dashed lines.

Figure 7 is shows the following: (A) Electron density of the substrate binding pocket using Amber parameters (Weiner et al., *J. Comp. Chem.* 7:230-
20 252 (1986)) for electrostatic surface of the protein. (B) Electron density of the catalytic triad region.

Figure 8 presents a summary of data collection and processing parameters.

Figure 9 presents refinement statistics for the Ac-IETD-caspase-8
25 complex.

Figure 10 lists the atomic structure coordinates for the Ac-IETD-caspase-8 complex as derived by X-ray diffraction from a crystal of that complex. The following abbreviations are used in Figure 10:

"Atom type" refers to the element whose coordinates are measured. The
30 first letter in the column defines the element.

"X, Y, Z" crystallographically define the atomic position of the element measured.

"B" is a thermal factor that measures movement of the atom around its atomic center.

"Occ" is an occupancy factor that refers to the fraction of the molecules in which each atom occupies the position specified by the coordinates. A value of "1" indicates that each atom has the same conformation, i.e., the same position, in all molecules of the crystal.

Detailed Description of the Invention

The following abbreviations are used throughout the application:

A = Ala = Alanine

V = Val = Valine

L = Leu = Leucine

I = Ile = Isoleucine

P = Pro = Proline

F = Phe = Phenylalanine

W = Trp = Tryptophan

M = Met = Methionine

G = Gly = Glycine

S = Ser = Serine

T = Thr = Threonine

C = Cys = Cysteine

Y = Tyr = Tyrosine

N = Asn = Asparagine

Q = Gln = Glutamine

D = Asp = Aspartic Acid

E = Glu = Glutamic Acid

K = Lys = Lysine

R = Arg = Arginine

H = His = Histidine

10

The caspase-8 structure described herein is the third caspase to be solved crystallographically, and can be compared to those of caspase-1, an enzyme associated with inflammation, and caspase-3, the downstream executioner of apoptosis. Fig. 1 shows structurally aligned secondary structure elements for these three proteins, and Fig. 3 shows their superimposed tertiary structures. The high resolution of the caspase-8 structure has also helped to clarify some issues regarding the enzyme mechanism and binding of substrate.

15

10 subunits of procaspases 8, 3, and 1 (Cohen, Biochem. J. 326:1-16 (1997)):

15 p11-----D⁴⁷⁹

20 Prosegment with CARD Domains-----↓S¹⁰⁴-----p20-----D²⁹⁷ A³¹⁷-----

25 to the activity of the enzyme: R258, D259, R260, N261, H317, Q358, Y365,

30 and caspase-8 fusion proteins (e.g. Histidine-tagged caspase-8). A "mutant"

preferably replacement of one or more selected amino acids. An example of a caspase-8 mutant is the caspase-8 mutant C360A, wherein the cysteine at position 360 in SEQ ID NO:1 is replaced with an alanine.

Crystalline form(s) and method of making

5 One embodiment of the invention provides a caspase-8 crystal (crystalline caspase-8). Optionally, the crystal additionally comprises a low molecular weight compound associated with caspase-8. Preferably, the low molecular weight compound is an inhibitor, such as an irreversible inhibitor, of caspase-8 activity, yielding a caspase-8/inhibitor complex. It should be
10 understood that the words "complex," "molecular complex," and "co-complex" are used herein interchangeably to refer to a covalent or noncovalent complex of caspase-8 and a small molecule ligand, such as a substrate, substrate analog, modulator, inhibitor and the like. Protease inhibition is readily determinable by assays known to the field; a representative assay is described herein in Example
15 4. The inhibitor is preferably a peptide or a peptidomimetic compound. A "peptidomimetic" compound is a compound that functionally and/or structurally mimics a peptide, but that lacks one or more of the peptide bonds that characterize the peptide. Peptidomimetic compounds therefore not typically do not serve as substrate for proteases and are likely to be active *in vivo* for a longer
20 period of time as compared to the analogous peptides. Unless otherwise specified, the term "peptide" when used herein in the context of an inhibitor peptide or inhibitor molecule includes peptides and peptidomimetic compounds.

 An irreversible cysteine protease inhibitor is typically, although not necessarily, characterized by a functional group capable of reacting with the
25 thiol group of the active site caspase-8 cysteine (C360) resulting in a covalent bond. Thus, in a preferred embodiment, the crystal includes a low molecular weight compound is covalently bound to the active site cysteine (C360) of caspase-8. Usually this functional group is located at the P₁ amino acid of a peptide inhibitor. The amino acid residues of a caspase-8 substrate are
30 designated P₁, P₂, etc., for those extending towards the N-terminus from the scissile bond of the substrate. Likewise, the residues designated P₁', P₂', etc., extend toward the C-terminus from the scissile bond of the substrate. A

particularly preferred irreversible inhibitor is a derivative of the tetrapeptide Ile-Glu-Thr-Asp, for example Ac-Ile-Glu-Thr-Asp-H (also referred to herein as Ac-IETD-H) (SEQ ID NO:4). The amino acids in SEQ ID NO:4 are referred to, from left to right, as substrate P₄ to P₁ amino acids (i.e., starting from the N-terminal Ile, thus Ile being P₄, Glu being P₃, Thr being P₂ and Asp being P₁).

The crystallization process typically begins with the isolation and purification of caspase-8. Caspase-8 is "isolated" if it has been removed from its natural environment, produced using recombinant techniques, or chemically or enzymatically synthesized. "Purified" caspase-8 is essentially free from any other biomolecules and associated cellular products or other impurities. Preferably, purified recombinant caspase-8 is used for crystallization. If needed or desired, the enzyme is deactivated, for example, by adding a suitable low molecular weight compound to form a complex of caspase-8 and the low molecular weight compound. The enzyme or enzyme complex is then crystallized from a solution using a suitable precipitating agent and, preferably, by a vapor diffusion technique. The crystallization buffer is prepared by mixing a caspase-8 complex solution with a "reservoir buffer", preferably in a 1:1 ratio, such that the crystallization buffer has a lower concentration of the precipitating agent necessary for crystal formation than the reservoir buffer. To form crystals, the concentration of the precipitating agent in the crystallization buffer is increased by allowing the concentration of the precipitating agent to balance through diffusion between the crystallization buffer and the reservoir buffer. In the crystallization buffer, caspase-8 has a concentration of about 2 to about 5 mg/ml. Diffusion occurs along a vapor gradient through a "hanging drop" or a "sitting drop". For example, in the "sitting drop" method, a 1:1 mixture of the crystallization buffer containing the protein is placed in a micro-bridge that is placed in a larger pool of reservoir buffer. The micro-bridge prevents the protein from being diluted into the reservoir buffer. The crystals are typically stable for three to four weeks, if kept at 4°C in a buffer of 1.4M sodium citrate, 0.1M HEPES, pH 7.9.

Formation of caspase-8 crystals depends upon the following parameters: pH, presence of salts, presence of additives, temperature, protein concentration,

and precipitating agent. The pH of the crystallization buffer is preferably about pH 7.0 to about pH 8.0. The concentration/type of buffer is relatively unimportant, and can be varied considerably. Suitable buffers included HEPES, MES, Tris, citrate, acetate and phosphate. Some useful salts and additives
 5 include chlorides, sulfates and some low molecular weight organic solvents, such as ethanol. Suitable precipitating agents include water miscible organic solvents, like a polyethylene glycol that has a molecular weight between about 100 and about 20,000, preferably between about 2,000 and about 8,000; and salts, such as ammonium sulfate, chloride, citrate or tartrate.

10 Prior to crystallization, caspase-8 may be equilibrated with a low molecular weight compound as described above. The low molecular compound may bind, covalently or noncovalently, and may stabilize caspase-8. Preferably the low molecular weight compound inhibits caspase-8 activity.

A particularly preferred crystal comprises caspase-8 belonging to the
 15 trigonal space group $P3_121$ with unit cell dimensions of $a = b = 62.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $c = 129.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 120^\circ$, preferably having one (p18/p11) heterodimer and one inhibitor molecule in the asymmetric unit. The invention further includes caspase-8 complexes that are characterized by having the same space group and cell dimensions of $a = b = 62.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $c = 129.4$
 20 $\text{ \AA} \pm 3.0 \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 120^\circ$.

X-ray crystallographic analysis

Applicants have solved the three-dimensional structure of a caspase-8/inhibitor complex using high resolution x-ray crystallography. Preferably, the crystallized enzyme or enzyme/ligand complex has the trigonal space group
 25 $P3_121$. The unit cell of the crystal preferably has the dimensions of $a = b = 62.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $c = 129.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 120^\circ$. The crystallized enzyme or enzyme/ligand complex is preferably a heterotetramer, with one (p18/p11) heterodimer (or, in the case of the co-complex, one heterodimer and one inhibitor molecule) in the asymmetric unit.

30 Each of the constituent amino acids of caspase-8 is defined by a set of structure coordinates as set forth in Fig. 10. The term "structure coordinates" refers to Cartesian coordinates derived from mathematical equations related to

the patterns obtained on diffraction of a monochromatic beam of x-rays by the atoms (scattering centers) of a caspase-8 complex in crystal form. The diffraction data are used to calculate an electron density map of the repeating unit of the crystal. The electron density maps are then used to establish the positions of the individual atoms of the caspase-8 protein or protein/ligand complex.

Slight variations in structure coordinates can be generated by mathematically manipulating the caspase-8 or caspase-8/ligand structure coordinates. For example, the structure coordinates set forth in Fig. 10 could be manipulated by crystallographic permutations of the structure coordinates, fractionalization of the structure coordinates, integer additions or subtractions to sets of the structure coordinates, inversion of the structure coordinates or any combination of the above. Alternatively, modifications in the crystal structure due to mutations, additions, substitutions, and/or deletions of amino acids, or other changes in any of the components that make up the crystal, could also yield variations in structure coordinates. Such slight variations in the individual coordinates will have little effect on overall shape. If such variations are within an acceptable standard error as compared to the original coordinates, the resulting three-dimensional shape is considered to be structurally equivalent. Structural equivalence is described in more detail below.

It should be noted that slight variations in individual structure coordinates of the caspase-8 or caspase-8/ligand complex, as defined above, would not be expected to significantly alter the nature of ligands that could associate with the substrate binding pocket. Thus, for example, a ligand that bound to the substrate binding pocket of caspase-8 would also be expected to bind to another substrate binding pocket whose structure coordinates define a shape that falls within the acceptable error.

Substrate binding pocket, active site, and other structural features

Applicants' invention has provided, for the first time, detailed information about the shape and structure of the substrate binding pocket of caspase-8.

Binding pockets are of significant utility in fields such as drug discovery. The association of natural ligands or substrates with the binding pockets of their corresponding receptors or enzymes is the basis of many biological mechanisms of action. Similarly, many drugs exert their biological effects through
5 association with the binding pockets of receptors and enzymes. Such associations may occur with all or any parts of the binding pocket. An understanding of such associations helps lead to the design of drugs having more favorable associations with their target, and thus improved biological effects. Therefore, this information is valuable in designing potential inhibitors of
10 caspase-8-like binding pockets, as discussed in more detail below.

The term "binding pocket," as used herein, refers to a region of a molecule or molecular complex, that, as a result of its shape, favorably associates with another chemical entity or compound. The substrate binding pocket of caspase-8 preferably comprises those amino acids whose backbone
15 atoms are situated within about 3.5 Å, more preferably within about 5.0 Å, most preferably within about 7.0 Å, of one or more constituent atoms of a bound substrate or inhibitor, as determined from the structure coordinates in Fig. 10. Preferably, the substrate binding pocket of caspase-8 includes amino Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr
20 412, Arg 413, Pro 415, and Trp 420. It will be readily apparent to those of skill in the art that the numbering of amino acids in other isoforms of caspase-8 may be different than that of human caspase-8. Alternatively, the substrate binding pocket is defined as including those amino acids whose backbone atoms are situated within a sphere centered on the coordinates representing the alpha
25 carbon atom of residue 360, the sphere having a radius of about 10 Å, preferably having a radius of about 15 Å. Another way of defining the substrate binding pocket of caspase-8 is in terms of pairwise interatomic distances. Thus, the substrate binding pocket of caspase-8 includes the amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Ser 411, Tyr 412, and Arg 413; more
30 preferably Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415, and Trp 420, wherein the constituent

atoms are positioned in space according pairwise interatomic distances readily determinable from the structure coordinates listed in Fig. 10.

The substrate binding pocket of caspase-8 is capable of binding a tetrapeptide (N-terminus-P4-P3-P2-P1-C-terminus), such that Arg 413, Arg 260, 5 Gln 358, and His 317 comprise the S1 binding site; Val 410, Tyr 412 and Tyr 365 comprise the S2 binding site; Arg 413, Arg 258, Pro 415 and Asn 261 comprise the S3 binding site; and Trp 420 and Tyr 412 comprise the S4 site.

The amino acid constituents of a caspase-8 substrate binding pocket as defined herein, as well as selected constituent atoms thereof, are positioned in 10 three dimensions in accordance with the structure coordinates listed in Fig. 10. In one aspect, the structure coordinates of the substrate binding pocket of caspase-8 includes structure coordinates of all atoms in the constituent amino acids as thus identified; in another aspect, the structure coordinates of the substrate binding pocket of caspase-8 includes the structure coordinates of just 15 the backbone atoms of the constituent atoms.

The term "caspase-8-like binding pocket" refers to a portion of a molecule or molecular complex whose shape is sufficiently similar to at least a portion of the substrate binding pocket of caspase-8 as to be expected to bind a common ligand. A structurally equivalent binding pocket is defined by a root 20 mean square deviation from the structure coordinates of the backbone atoms of the amino acids that make up the substrate binding pocket of caspase-8 (as set forth in Fig. 1) of at most about 2.0 Å, preferably at most about 1.5 Å. How this calculation is obtained is described below.

The term "associating with" refers to a condition of proximity between a 25 chemical entity or compound, such as a ligand or substrate, or portions thereof, and a caspase-8 molecule or portions thereof. The association may be non-covalent, wherein the juxtaposition is energetically favored by hydrogen bonding, van der Waals forces, or electrostatic interactions, or it may be covalent.

30 Accordingly, the invention thus provides molecules or molecular complexes comprising an caspase-8 substrate binding pocket or caspase-8-like

substrate binding pocket, as defined by the sets of structure coordinates described above.

The asymmetric unit of caspase-8 contains the p18/p11 heterodimer (Fig. 2). The overall topology is similar to that of caspase-1 and caspase-3, with the p18 and p11 subunits folded into a compact cylinder of approximately 28Å x 37Å x 48Å in size. The protein has a typical of an α/β folding motif with a central 6-strand β -sheet with five parallel strands (β 1, residues 231-241; β 2, 278-285; β 3, 308-316; β 4, 351-358; β 5, 397-404) and one antiparallel strand (β 6, residues 462-467). These structural elements are defined for caspase-8 in Fig. 1. The antiparallel strand lies on the edge of the sheet, perpendicular and adjacent to the crystallographic 2-fold axis. Also identified in Fig. 1 are the six α -helices (α 1', residues 244-250, within a large loop 1; α 1, residues 261-276; α 2, 289-302; α 3, 332-341; α 4, 419-435; and α 5, 438-452), three on one side of the main β -sheet and two on the other side. There is a turn of helix (α 1', residues 244-250) that is part of loop 1 that occurs along the binding pocket region of the p18 subunit. There is also a two-stranded antiparallel sheet made up of contributions from loop 3 (residues 317-320) and loop 4 (residues 408-415) at the top of the main β -sheet that forms the base of the pocket. In the heterotetramer, the first segment (residues 385-396) of the p11 subunits and the last segment (residues 363-374) of the p18 extend from the compact structure in an antiparallel fashion and interact across the crystallographic two-fold with the other heterodimer.

There are many differences observed among caspase-1, caspase-3 and caspase-8 in the loop regions near the active site; these are indicated structurally in Fig. 3 and in terms of amino acid sequence in Fig. 1. When compared to caspase-3, caspase-8 has an insertion of seven residues, designated as loop 1, between β -strand 1 and α -helix. In comparison with caspase-1, this loop is even bigger (10 residues) and this larger sized loop in caspase-8 is clearly seen in the structural overlay. This insertion includes a helical segment, α 1', which has not been observed in either caspase-1 or caspase-3. In caspase-1, loop 3 is six residues longer than in caspases-3 and 8, again, clearly evident in Fig. 3. Loop 4 is identical in length in all 3 caspases, and this is seen in the coincidence of fold in this region. Loop 5 is intermediate in length between caspases 3 and 8. All

three caspases can adopt different conformations and these differences have an important bearing on the specificity of the S₄ pocket.

Two p18/p11 heterodimers form a tetramer around a crystallographic 2-fold axis (Fig. 3). This extends the 6 strands of the β -sheet per dimer to twelve strands with the two-fold axis perpendicular to the middle of the β -sheet. Besides the extended β -sheet there are other interactions around the 2-fold axis, which influence the substrate-binding region. Residues Lys-367 through Asp-374 of one heterodimer extend into the 2-fold related molecule to form interactions with residues Thr-390 through Asp-395.

Crystal structures of caspase-1 in two crystal forms and caspase-3 in two crystal forms show similar tetrameric interactions to that found in caspase-8. The structural and mutagenic studies indicate that this tetramer and the dimer/dimer interface are necessary for biological activity. The formation of the heterotetramer probably modifies the neighboring tertiary structure resulting in the activation of the catalytic and substrate binding site. The approximate area of the solvent accessible interface between the two dimers is 2100 Å² in caspase-8. Both hydrophobic and hydrophilic interactions are important in forming a strong dimer-dimer interface. This interface contains twenty-three hydrogen bonds (or twelve per dimer) with main chain and side chain atoms involved (Fig. 5). A deep cavity of 17 x 15 x 11 Å³ is present on the crystallographic 2-fold axis (Figure 5A). This cavity is larger than those are in caspase-3 (Figure 5B) and caspase-1 (17 x 7 x 11 Å³ and 9 x 5 x 11 Å³, respectively) (Mittl et al., *J. Biol. Chem.* 272:6539-6547 (1997)). There is a clearly identifiable oxidized dithiothreitol molecule (1,2-dithiane-4,5-diol) (Figure 5C) and its symmetric-related pair in this cavity. These dithiane-diol molecules are separated by ~ 13 Å and are approximately 19 Å from the P₁-P₄ substrate binding pocket. Another dithiane-diol molecule is located elsewhere on the surface of the protein. Examination of other data sets indicate that these dithiane-diol molecules are not always present in crystals of caspase-8, but depend on the concentration of dithiothreitol and age of crystals. It is possible that ligand binding in the central cavity could effect that catalytic activity of the enzyme and further work is planned to study effects of ligand binding in the cavity.

Fig. 6 is a schematic of the hydrogen bonding of the inhibitor, acetyl-Ile-Glu-Thr-Asp-aldehyde, to caspase-8. Fig. 7A shows the electrostatic surface of the protein and the quality of the electron density map for the inhibitor bound in caspase-8. The inhibitor binds in an extended conformation and with the
5 aldehyde forming a thiohemiacetal bond to S γ of Cys-360 (Fig. 7B). In caspase-8, the main chain of the inhibitor, like in many other proteases, is antiparallel with respect to residues lining the binding pocket (411-413). P₁-P₃ residues form a β -sheet type hydrogen-bonding network. The active site cysteine (Cys-360) resides on a long C-terminal segment of p18 (Fig. 1) which interacts with the N-
10 terminal portion of the p11 unit in the 2-fold related heterodimer (Fig. 2). The acetyl end of the inhibitor is situated near loop 4.

The carboxyl group of the P₁ Asp forms salt bridges with Arg-413 and Arg-260 and hydrogen bonds to Gln-358 in a pattern similar to that found in caspase-1 and caspase-3. All these residues are conserved. The P₁ α -carbonyl
15 rotates and rehybridizes (sp^2 to sp^3) to become a hydroxyl and form a hydrogen bond with the imidazole group of His-317 (Fig. 7B). Mittl et al. (J. Biol. Chem. 272:6539-6547 (1997)) suggested that the CED3/ICE-like proteases have a catalytic Cys/His dyad rather than the classical (Cys/His/Asn) triad as seen in papain and most other cysteine proteases. Wilson et al. (Nature 370:270-275
20 (1994)) have also proposed the Cys/His catalytic dyad for caspase-1, but they indicated the possible involvement of a putative third component, the backbone carbonyl oxygen of Pro-177, that could affect the basicity of the histidine imidazole. In fact, Rotonda et al. (Nat. Struct. Biol. 3:619-625 (1996)) later invoked the existence of the same carbonyl oxygen in caspase-3, this time from
25 the spatially equivalent Thr-62 in an interaction with the catalytic imidazole ring. No one has provided evidence that this backbone carbonyl oxygen might play a role as the third member of a catalytic triad. Based upon our high-resolution structure of caspase-8, a clear interaction exists between the carbonyl oxygen of Arg-258, equivalent to Pro-177 in caspase-1 and Thr-62 in caspase-3, and the N ϵ
30 of His-317. We would infer, therefore, that irrespective of the nature of the amino acid at this position, the carbonyl oxygen could serve as a member of a catalytic triad in the caspases.

The tetrahedral nature of the thiohemiacetal C is clearly evident in the 1.2 Å resolution map. This is the same conformation as was modeled for the aldehyde inhibitor models of caspase-1 and caspase-3 (Rotonda et al., Nat. Struct. Biol. 3:619-625 (1996)), but different from those modeled for the methyl ketone inhibitors in which the carbonyl oxygen extends into the "oxyanion" pocket. There was some uncertainty regarding the different interpretation of the conformation in this region because the other caspase structures were determined with ~ 2.5 Å resolution data. Our data at high resolution clearly establishes the interaction between the thiohemiacetal OH group and N_δ of His-317. In the case of the caspase-3/Ac-DVAD-fluoromethyl ketone structure (Mittl et al., J. Biol. Chem. 272:6539-6547)), the carbonyl oxygen points directly into the presumptive "oxyanion hole" to form a hydrogen bond with a peptide NH group in a highly conserved region of these enzymes (a Gly residue in caspases 8, 3, and 1; residues 350, 122, and 238, respectively, Fig. 1). We would agree with earlier interpretations that the thiohemiacetal can, and in this case does, bind in a non-transition state conformation.

The C_γ of the Thr side chain at P₂ lies in a hydrophobic pocket formed by the side chains of Val-410 and Tyr-412 (Tyr-204 and Trp-206 in caspase-3). The O_γ is surrounded by water molecules, one of which forms a bridge to O_η of Tyr-365.

The Glu at P₃ sits in a cleft defined by Arg-413, Arg-258, Pro-415, and Asn-261. All interactions with these residues are mediated through solvent molecules with the exception of that to Arg-413. The residue forms salt bridges to both P₃ Glu and P₁ Asp side chains. Besides these salt bridges, Arg-413 is a crucial residue forming hydrogen-bonding interactions between its main chain atoms and the peptide inhibitors main chain. In caspase-8, the preference for Glu in the S₃ pocket is enhanced by the proximity of Arg-258 and Asn-261. For example, Arg-258 is homologous to Thr-62 and Asn-258 to Ser-65 in caspase-3.

Comparing the specificities of the different caspases suggests that the size and nature of the S₄ pocket is especially important in selectivity (Thornberry et al., J. Biol. Chem. 272:17907-17911 (1997)). Caspase-3 prefers an Asp in P₄ while caspase-1 and caspase-8 prefer hydrophobic groups. In caspase-8, the

acetyl hydrogen bonds through a water bridge to the carboxyl of the P₃ Glu. The S₄ pocket differs from that of caspase-3 with the hydrogen bond participants moving away to accommodate a nonpolar residue. The faces of the aromatic groups, Trp-420 and Tyr-412 form a hydrophobic S₄ pocket. It is fairly open and additional functional groups might be substituted onto the side group.

Three-dimensional configurations

The structure coordinates listed in Fig. 10 for the caspase-8/substrate complex or a portion thereof, such as its substrate binding pocket, define a unique configuration of points in space. Those of skill in the art understand that a set of structure coordinates for protein or an protein/ligand complex, or a portion thereof, define a relative set of points that, in turn, define a configuration in three dimensions. A similar or identical configuration can be defined by an entirely different set of coordinates, provided the distances and angles between coordinates remain essentially the same.

The present invention thus includes the three-dimensional configuration of points derived from the structure coordinates of at least a portion of a caspase-8 molecule or molecular complex, as shown in Fig. 10, as well as structurally equivalent configurations, as described below. Preferably, the three-dimensional configuration includes points derived from structure coordinates representing the locations of a plurality of the amino acids defining the caspase-8 substrate binding pocket. In one embodiment, the three-dimensional configuration includes points derived from structure coordinates representing the locations the backbone atoms of a plurality of amino acids defining the caspase-8 substrate binding pocket, preferably Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415, and Trp 420; in another embodiment, the three-dimensional configuration includes points derived from structure coordinates representing the locations of the side chain and the backbone atoms (other than hydrogens) of a plurality of the amino acids defining the caspase-8 substrate binding pocket. In yet another embodiment, the three-dimensional configuration includes points derived from structure coordinates representing the locations the backbone atoms of at least 50 amino acids that are contiguous in the amino acid sequence of human caspase-8 (SEQ

ID NO:1). In still another embodiment, the three-dimensional configuration includes points derived from structure coordinates representing the locations the side chain atoms and the backbone atoms of at least 50 amino acids that are contiguous in the amino acid sequence of caspase-8 (SEQ ID NO:1).

5 Likewise, the invention also includes the three-dimensional configuration of points derived from structure coordinates of molecules or molecular complexes that are structurally homologous to caspase-8, as well as structurally equivalent configurations. Structurally homologous molecules or molecular complexes are defined below. Advantageously, structurally homologous
10 molecules can be identified using the structure coordinates of the caspase-8/ligand complex (Fig. 10) according to a method of the invention.

 The configurations of points in space derived from structure coordinates according to the invention can be visualized as, for example, a holographic image, a stereodiagram, a model or a computer-displayed image, and the
15 invention thus includes such images, diagrams or models.

Structurally equivalent crystal structures

 Various computational analyses can be used to determine whether a molecule or the binding pocket portion thereof is "structurally equivalent," defined in terms of its three-dimensional structure, to all or part of caspase-8 or
20 its substrate binding pocket. Such analyses may be carried out in current software applications, such as the Molecular Similarity application of QUANTA (Molecular Simulations Inc., San Diego, CA) version 4.1, and as described in the accompanying User's Guide.

 The Molecular Similarity application permits comparisons between
25 different structures, different conformations of the same structure, and different parts of the same structure. The procedure used in Molecular Similarity to compare structures is divided into four steps: (1) load the structures to be compared; (2) define the atom equivalences in these structures; (3) perform a fitting operation; and (4) analyze the results.

30 Each structure is identified by a name. One structure is identified as the target (i.e., the fixed structure); all remaining structures are working structures (i.e., moving structures). Since atom equivalency within QUANTA is defined

by user input, for the purpose of this invention equivalent atoms are defined as protein backbone atoms (N, C α , C, and O) for all conserved residues between the two structures being compared. For this purpose, conserved residues are defined as a set of atoms with the same interatomic connectivity. Only rigid fitting operations are considered.

When a rigid fitting method is used, the working structure is translated and rotated to obtain an optimum fit with the target structure. The fitting operation uses an algorithm that computes the optimum translation and rotation to be applied to the moving structure, such that the root mean square difference of the fit over the specified pairs of equivalent atom is an absolute minimum. This number, given in angstroms, is reported by QUANTA.

For the purpose of this invention, any molecule or molecular complex or binding pocket thereof, or any portion thereof, that has a root mean square deviation of conserved residue backbone atoms (N, C α , C, O) of less than about 2.0 Å, preferably less than about 1.5 Å, when superimposed on the relevant backbone atoms described by the reference structure coordinates listed in Fig. 10, is considered "structurally equivalent" to the reference molecule. That is to say, the crystal structures of those portions of the two molecules are substantially identical, within acceptable error. Particularly preferred structurally equivalent molecules or molecular complexes are those that are defined by the entire set of structure coordinates in Fig. 10, $\pm$ a root mean square deviation from the conserved backbone atoms of those amino acids of not more than about 2.0 Å. More preferably, the root mean square deviation is less than about 1.5 Å, most preferably less than about 1.0 Å.

The term "root mean square deviation" means the square root of the arithmetic mean of the squares of the deviations from the mean. It is a way to express the deviation or variation from a trend or object. For purposes of this invention, the "root mean square deviation" defines the variation in the backbone of a protein from the backbone of caspase-8 or a portion thereof, such as its substrate binding pocket, as defined by the structure coordinates of caspase-8 described herein.

Computers and machine readable storage media

Transformation of the structure coordinates for all or a portion of caspase-8 or the caspase-8/ligand complex or one its substrate binding pocket, for structurally homologous molecules as defined below, or for the structural
5 equivalents of any of these molecules or molecular complexes as defined above, into three-dimensional graphical representations of the molecule or complex can be conveniently achieved through the use of computer-assisted methods utilizing commercially-available software.

The invention thus further provides a machine-readable storage medium
10 comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of any of the molecule or molecular complexes of this invention that have been described above. In a preferred embodiment, the machine-readable data storage medium
15 comprises a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex comprising all or any parts of the caspase-8 substrate binding pocket or an caspase-8-like binding pocket, as defined above. In another
20 preferred embodiment, the machine-readable data storage medium is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex defined by the structure coordinates of all of the amino acids in Fig. 10, $\pm$ a root mean square deviation from the backbone atoms of said amino acids of not more than about 2.0 Å, preferably of not more than about 1.5
25 Å

In an alternative embodiment, the machine-readable data storage medium comprises a data storage material encoded with a first set of machine readable data which comprises the Fourier transform of the structure coordinates set forth in Fig. 10, and which, when using a machine programmed with instructions for
30 using said data, can be combined with a second set of machine readable data comprising the x-ray diffraction pattern of a molecule or molecular complex to

determine at least a portion of the structure coordinates corresponding to the second set of machine readable data.

The invention further includes, and computer-assisted methods of the invention advantageously utilize, a system that includes a computer comprising a central processing unit ("CPU"), a working memory which may be, e.g., RAM (random access memory) or "core" memory, mass storage memory (such as one or more disk drives or CD-ROM drives), one or more cathode-ray tube ("CRT") display terminals, one or more keyboards, one or more input lines, and one or more output lines, all of which are interconnected by a conventional bidirectional system bus. Machine-readable data of the invention may be inputted in a variety of ways, for example via the use of one or more modems connected by a telephone line or dedicated data line. Alternatively or additionally, the input hardware may comprise CD-ROM drives or disk drives. In conjunction with the display terminal, the keyboard may also be used as an input device. Output hardware may include a CRT display terminal for displaying a graphical representation of a caspase-8 molecule, or a portion thereof such as a substrate binding pocket, using a program such as QUANTA as described herein. Output hardware can also include a printer, so that hard copy output may be produced, or a disk drive, to store system output for later use.

In operation, the CPU coordinates the use of the various input and output devices, coordinates data accesses from mass storage and accesses to and from working memory, and determines the sequence of data processing steps. A number of programs may be used to process the machine-readable data of this invention. Such programs are discussed in reference to the computational methods of drug discovery as described herein. Specific references to components of the hardware system are included as appropriate throughout the following description of the data storage medium.

The machine-readable data storage medium encoded with machine-readable data or set of instructions can be, for example, a magnetic data storage medium, an optically-readable data storage medium, or magneto-optical data storage medium. Examples of a magnetic data storage medium include a conventional floppy diskette or hard disk, having a suitable substrate and coating

on one or both sides containing magnetic domains whose polarity or orientation can be altered magnetically. The magnetic medium optionally contains a opening for receiving the spindle of a disk drive or other data storage device. The magnetic domains of the medium coating are polarized or oriented so as to
5 encode machine readable data such as that described herein, for execution by the system.

Examples of an optically-readable data storage medium encoded with machine-readable data or set of instructions include a conventional compact disk read only memory (CD-ROM) or a rewritable medium such as a magneto-optical
10 disk which is optically readable and magneto-optically writable. The optically-readable medium typically contains a suitable substrate and a coating on at least one side of the substrate. In the case of CD-ROM, as is well known, the coating is reflective and is impressed with a plurality of pits to encode the machine-readable data or instructions. The arrangement of pits is read by reflecting laser
15 light off the surface of the coating. A protective coating, which preferably is substantially transparent, is provided on top of the reflective coating. In the case of a magneto-optical disk, as is also well known, the coating has no pits but has a plurality of magnetic domains whose polarity or orientation can be changed magnetically when heated above a certain temperature, as by a laser. The
20 orientation of the domains can be read by measuring the polarization of laser light reflected from coating. The arrangement of the domains encodes the data as described above.

Structurally homologous molecules, molecular complexes, and crystal structures

The structure coordinates set forth in Fig. 10 can be used to aid in
25 obtaining structural information about another crystallized molecule or molecular complex. A "molecular complex" means a protein in covalent or non-covalent association with a chemical entity or compound. The method of the invention allows determination of at least a portion of the three-dimensional structure of molecules or molecular complexes which contain one or more
30 structural features that are similar to structural features of caspase-8. These molecules are referred to herein as "structurally homologous" to caspase-8. Similar structural features can include, for example, regions of amino acid

identity, conserved active site or binding site motifs, and similarly arranged secondary structural elements (e.g., α helices and β sheets). Optionally, structural homology is determined by aligning the residues of the two amino acid sequences to optimize the number of identical amino acids along the lengths of their sequences; gaps in either or both sequences are permitted in making the alignment in order to optimize the number of identical amino acids, although the amino acids in each sequence must nonetheless remain in their proper order. Preferably, two amino acid sequences are compared using the Blastp program, version 2.0.9, of the BLAST 2 search algorithm, as described by Tatusova et al., FEMS Microbiol. Lett. 174:247-250 (1999)), and available at <http://www.ncbi.nlm.nih.gov/gorf/bl2.html>. Preferably, the default values for all BLAST 2 search parameters are used, including matrix = BLOSUM62; open gap penalty = 11, extension gap penalty = 1, gap x_dropoff = 50, expect = 10, wordsize = 3, and filter on. In the comparison of two amino acid sequences using the BLAST search algorithm, structural similarity is referred to as "identity." Preferably, a structurally homologous molecule is a protein that has an amino acid sequence sharing at least 65% identity with the amino acid sequence of caspase-8 (SEQ ID NO:1). More preferably, a protein that is structurally homologous to caspase-8 includes at least one contiguous stretch of at least 50 amino acids that shares at least 80% amino acid sequence identity with the analogous portion of caspase-8. Methods for generating structural information about the structurally homologous molecule or molecular complex are well-known and include, for example, molecular replacement techniques.

Therefore, in another embodiment this invention provides a method of utilizing molecular replacement to obtain structural information about a molecule or molecular complex whose structure is unknown comprising the steps of:

- (a) crystallizing the molecule or molecular complex of unknown structure;
- (b) generating an x-ray diffraction pattern from said crystallized molecule or molecular complex; and

(c) applying at least a portion of the structure coordinates set forth in Fig. 10 to the x-ray diffraction pattern to generate a three-dimensional electron density map of the molecule or molecular complex whose structure is unknown.

By using molecular replacement, all or part of the structure coordinates of caspase-8 or the caspase-8/ligand complex as provided by this invention (and set forth in Fig. 10) can be used to determine the structure of a crystallized molecule or molecular complex whose structure is unknown more quickly and efficiently than attempting to determine such information *ab initio*.

Molecular replacement provides an accurate estimation of the phases for an unknown structure. Phases are a factor in equations used to solve crystal structures that cannot be determined directly. Obtaining accurate values for the phases, by methods other than molecular replacement, is a time-consuming process that involves iterative cycles of approximations and refinements and greatly hinders the solution of crystal structures. However, when the crystal structure of a protein containing at least a structurally homologous portion has been solved, the phases from the known structure provide a satisfactory estimate of the phases for the unknown structure.

Thus, this method involves generating a preliminary model of a molecule or molecular complex whose structure coordinates are unknown, by orienting and positioning the relevant portion of caspase-8 or the caspase-8/ligand complex according to Fig. 10 within the unit cell of the crystal of the unknown molecule or molecular complex so as best to account for the observed x-ray diffraction pattern of the crystal of the molecule or molecular complex whose structure is unknown. Phases can then be calculated from this model and combined with the observed x-ray diffraction pattern amplitudes to generate an electron density map of the structure whose coordinates are unknown. This, in turn, can be subjected to any well-known model building and structure refinement techniques to provide a final, accurate structure of the unknown crystallized molecule or molecular complex (E. Lattman, "Use of the Rotation and Translation Functions," in Meth. Enzymol., 115, pp. 55-77 (1985); M.G. Rossman, ed., "The Molecular Replacement Method," Int. Sci. Rev. Ser., No. 13, Gordon & Breach, New York (1972)).

Structural information about a portion of any crystallized molecule or molecular complex that is sufficiently structurally homologous to a portion of caspase-8 can be resolved by this method. In addition to a molecule that shares one or more structural features with caspase-8 as described above, a molecule
5 that has similar bioactivity, such as the same catalytic activity, substrate specificity or ligand binding activity as caspase-8, may also be sufficiently structurally homologous to caspase-8 to permit use of the structure coordinates of caspase-8 to solve its crystal structure.

In a preferred embodiment, the method of molecular replacement is
10 utilized to obtain structural information about a molecule or molecular complex, wherein the molecule or molecular complex comprises at least one caspase-8 subunit or homolog. A "subunit" of caspase-8 is a caspase-8 molecule that has been truncated at the N-terminus or the C-terminus, or both. In the context of the present invention, a "homolog" of caspase-8 is a protein that contains one or
15 more amino acid substitutions, deletions, additions, or rearrangements with respect to the amino acid sequence of caspase-8, but that, when folded into its native conformation, exhibits or is reasonably expected to exhibit at least a portion of the tertiary (three-dimensional) structure of caspase-8. For example, structurally homologous molecules can contain deletions or additions of one or
20 more contiguous or noncontiguous amino acids, such as a loop or a domain. A preferred caspase-8 homolog comprises an amino acid other than the native arginine 258, as it has been discovered that the backbone carbonyl of Arg 258 helps form the active site of caspase-8, not the arginine side chain. Structurally homologous molecules also include "modified" caspase-8 molecules that have
25 been chemically or enzymatically derivatized at one or more constituent amino acid, including side chain modifications, backbone modifications, and N- and C-terminal modifications including acetylation, hydroxylation, methylation, amidation, and the attachment of carbohydrate or lipid moieties, cofactors, and the like.

30 A heavy atom derivative of caspase-8 is also included as a caspase-8 homolog. The term "heavy atom derivative" refers to derivatives of caspase-8 produced by chemically modifying a crystal of caspase-8. In practice, a crystal

is soaked in a solution containing heavy metal atom salts, or organometallic compounds, e.g., lead chloride, gold thiomalate, thiomersal or uranyl acetate, which can diffuse through the crystal and bind to the surface of the protein. The location(s) of the bound heavy metal atom(s) can be determined by x-ray

5 diffraction analysis of the soaked crystal. This information, in turn, is used to generate the phase information used to construct three-dimensional structure of the protein (T.L. Blundell and N.L. Johnson, Protein Crystallography, Academic Press (1976)).

Because it is expected that caspase-8 can crystallize in more than one
10 crystal form, the structure coordinates of caspase-8 as provided by this invention are particularly useful in solving the structure of other crystal forms of caspase-8 or caspase-8/substrate complexes.

The structure coordinates of caspase-8 as provided by this invention are particularly useful in solving the structure of caspase-8 mutants. Mutants may
15 be prepared, for example, by expression of caspase-8 cDNA previously altered in its coding sequence by oligonucleotide-directed mutagenesis.

The structure coordinates of caspase-8 in Fig. 10 are also particularly useful to solve the structure of crystals of caspase-8, caspase-8 mutants or caspase-8 homologs co-complexed with a variety of chemical entities. This
20 approach enables the determination of the optimal sites for interaction between chemical entities, including candidate caspase-8 inhibitors and caspase-8. Potential sites for modification within the various binding site of the molecule can also be identified. This information provides an additional tool for determining the most efficient binding interactions, for example, increased
25 hydrophobic interactions, between caspase-8 and a chemical entity. For example, high resolution x-ray diffraction data collected from crystals exposed to different types of solvent allows the determination of where each type of solvent molecule resides. Small molecules that bind tightly to those sites can then be designed and synthesized and assayed for their caspase-8 inhibition activity.

30 All of the complexes referred to above may be studied using well-known x-ray diffraction techniques and may be refined versus 1.5-3.0 Å resolution x-ray data to an R value of about 0.20 or less using computer software, such as X-

PLOR (Yale University, ©1992, distributed by Molecular Simulations, Inc.; see, e.g., Blundell & Johnson, *supra*; *Meth. Enzymol.*, Vol. 114 & 115, H.W. Wyckoff et al., eds., Academic Press (1985)). This information may thus be used to optimize known caspase-8 inhibitors, and more importantly, to design
5 new caspase-8 inhibitors.

The invention also includes the unique three-dimensional configuration defined by a set of points defined by the structure coordinates for a molecule or molecular complex structurally homologous to caspase-8 as determined using the method of the present invention, structurally equivalent configurations, and
10 magnetic storage media comprising such set of structure coordinates.

Further, the invention includes structurally homologous molecules as identified using the method of the invention.

Homology modeling

Using homology modeling, a computer model of a caspase-8 homolog
15 can be built or refined without crystallizing the homolog. First, a preliminary model of the caspase-8 homolog is created by sequence alignment with caspase-8, secondary structure prediction, the screening of structural libraries, or any combination of those techniques. Computational software may be used to carry out the sequence alignments and the secondary structure predictions. Structural
20 incoherences, e.g., structural fragments around insertions and deletions, can be modeled by screening a structural library for peptides of the desired length and with a suitable conformation. For prediction of the side chain conformation, a side chain rotamer library may be employed. Where the caspase-8 homolog has been crystallized, the final homology model can be used to solve the crystal
25 structure of the homolog by molecular replacement, as described above. Next, the preliminary model is subjected to energy minimization to yield an energy minimized model. The energy minimized model may contain regions where stereochemistry restraints are violated, in which case such regions are remodeled to obtain a final homology model. The homology model is positioned according
30 to the results of molecular replacement, and subjected to further refinement comprising molecular dynamics calculations.

Rational drug design

Computational techniques can be used to screen, identify, select and design chemical entities capable of associating with caspase-8 or structurally homologous molecules. Knowledge of the structure coordinates for caspase-8 permits the design and/or identification of synthetic compounds and/or other molecules which have a shape complementary to the conformation of the caspase-8 substrate binding site. In particular, computational techniques can be used to identify or design chemical entities, such as inhibitors, agonists and antagonists, that associate with a caspase-8 substrate binding pocket or a caspase-8 -like substrate binding pocket. Inhibitors may bind to all or a portion of the active site of caspase-8, and can be competitive, non-competitive, or uncompetitive inhibitors; or interfere with dimerization by binding at the interface between the two monomers. Once identified and screened for biological activity, these inhibitors may be used therapeutically or prophylactically to block caspase-8 activity and, thus, inhibit cell death. Structure-activity data for analogs of ligands bind to caspase-8 or caspase-8 -like binding pockets can also be obtained computationally.

The term "chemical entity," as used herein, refers to chemical compounds, complexes of two or more chemical compounds, and fragments of such compounds or complexes. Chemical entities that are determined to associate with caspase-8 are potential drug candidates.

Data stored in a machine-readable storage medium that is capable of displaying a graphical three-dimensional representation of the structure of caspase-8 or a structurally homologous molecule, as identified herein, or portions thereof may thus be advantageously used for drug discovery. The structure coordinates of the chemical entity are used to generate a three-dimensional image that can be computationally fit to the three-dimensional image of caspase-8 or a structurally homologous molecule. The three-dimensional molecular structure encoded by the data in the magnetic storage medium can then be computationally evaluated for its ability to associate with chemical entities. When the molecular structures encoded by the data is displayed in a graphical three-dimensional representation on a computer screen,

the protein structure can also be visually inspected for potential association with chemical entities.

One embodiment of the method of drug design involves evaluating the potential association of a known chemical entity with caspase-8 or a structurally homologous molecule, particularly with a caspase-8 substrate binding pocket or caspase-8 -like substrate binding pocket. The method of drug design thus includes computationally evaluating the potential of a selected chemical entity to associate with any of the molecules or molecular complexes set forth above. This method comprises the steps of: (a) employing computational means to perform a fitting operation between the selected chemical entity and the substrate binding pocket of the molecule or molecular complex; and (b) analyzing the results of said fitting operation to quantify the association between the chemical entity and the substrate binding pocket.

In another embodiment, the method of drug design involves computer-assisted design of chemical entities that associate with caspase-8, its homologs, or portions thereof. Chemical entities can be designed in a step-wise fashion, one fragment at a time, or may be designed as a whole or "*de novo*."

To be a viable drug candidate, the chemical entity identified or designed according to the method must be capable of structurally associating with at least part of a caspase-8 or caspase-8 -like binding pockets, and must be able, sterically and energetically, to assume a conformation that allows it to associate with the caspase-8 or caspase-8 -like binding pocket. Non-covalent molecular interactions important in this association include hydrogen bonding, van der Waals interactions, hydrophobic interactions, and electrostatic interactions. Conformational considerations include the overall three-dimensional structure and orientation of the chemical entity in relation to the binding pocket, and the spacing between various functional groups of an entity that directly interact with the caspase-8 -like binding pocket or homologs thereof.

Optionally, the potential binding of a chemical entity to a caspase-8 substrate binding pocket or a caspase-8-like substrate binding pocket is analyzed using computer modeling techniques prior to the actual synthesis and testing of the chemical entity. If these computational experiments suggest insufficient

interaction and association between it and the caspase-8 substrate binding pocket or caspase-8-like binding pocket, testing of the entity is obviated. However, if computer modeling indicates a strong interaction, the molecule may then be synthesized and tested for its ability to bind to a caspase-8 substrate binding pocket or caspase-8-like substrate binding pocket. Binding assays to determine if a compound actually binds to and inhibits the activity of caspase-8 can also be performed and are well known in the art; see, for example, Example IV herein.

One skilled in the art may use one of several methods to screen chemical entities or fragments for their ability to associate with a caspase-8 or caspase-8-like binding pocket. This process may begin by visual inspection of, for example, a caspase-8 or caspase-8-like binding pocket on the computer screen based on the caspase-8 structure coordinates in Fig. 10 or other coordinates which define a similar shape generated from the machine-readable storage medium. Selected fragments or chemical entities may then be positioned in a variety of orientations, or docked, within the binding pocket. Docking may be accomplished using software such as QUANTA and SYBYL, followed by energy minimization and molecular dynamics with standard molecular mechanics forcefields, such as CHARMM and AMBER.

Specialized computer programs may also assist in the process of selecting fragments or chemical entities. Examples include GRID (P.J. Goodford, J. Med. Chem. 28:849-857 (1985); available from Oxford University, Oxford, UK); MCSS (A. Miranker et al., Proteins: Struct. Funct. Gen., 11:29-34 (1991); available from Molecular Simulations, San Diego, CA); AUTODOCK (D.S. Goodsell et al., Proteins: Struct. Funct. Genet. 8:195-202 (1990); available from Scripps Research Institute, La Jolla, CA); and DOCK (I.D. Kuntz et al., J. Mol. Biol. 161:269-288 (1982); available from University of California, San Francisco, CA)

Once suitable chemical entities or fragments have been selected, they can be assembled into a single compound or complex. Assembly may be preceded by visual inspection of the relationship of the fragments to each other on the three-dimensional image displayed on a computer screen in relation to the structure coordinates of caspase-8. This would be followed by manual model

building using software such as QUANTA or SYBYL (Tripos Associates, St. Louis, MO).

Useful programs to aid one of skill in the art in connecting the individual chemical entities or fragments include, without limitation, CAVEAT (P.A.

- 5 Bartlett et al., in Molecular Recognition in Chemical and Biological Problems," Special Publ., Royal Chem. Soc., 78:182-196 (1989); G. Lauri et al., J. Comput. Aided Mol. Des. 8:51-66 (1994); available from the University of California, Berkeley, CA); 3D database systems such as ISIS (available from MDL Information Systems, San Leandro, CA; reviewed in Y.C. Martin, J. Med. Chem. 35:2145-2154 (1992)); and HOOK (M.B. Eisen et al., Proteins: Struct., Funct., Genet. 19:199-221 (1994); available from Molecular Simulations, San Diego, CA).

Caspase-8 inhibitors may be designed "de novo" using either an empty binding site or optionally including some portion(s) of a known inhibitor(s).

- 15 There are many de novo ligand design methods including, without limitation, LUDI (H.-J. Bohm, J. Comp. Aid. Molec. Design. 6:61-78 (1992); available from Molecular Simulations Inc., San Diego, CA); LEGEND (Y. Nishibata et al., Tetrahedron, 47:8985 (1991); available from Molecular Simulations Inc., San Diego, CA); LeapFrog (available from Tripos Associates, St. Louis, MO); and SPROUT (V. Gillet et al., J. Comput. Aided Mol. Design 7:127-153 (1993); available from the University of Leeds, UK).

- Once a compound has been designed or selected by the above methods, the efficiency with which that entity may bind to a caspase-8 substrate binding pocket or caspase-8-like substrate binding pocket may be tested and optimized
- 25 by computational evaluation. For example, an effective inhibitor must preferably demonstrate a relatively small difference in energy between its bound and free states (i.e., a small deformation energy of binding). Thus, the most efficient inhibitors should preferably be designed with a deformation energy of binding of not greater than about 10 kcal/mole; more preferably, not greater than
- 30 7 kcal/mole. Caspase-8 inhibitors may interact with the binding pocket in more than one conformation that is similar in overall binding energy. In those cases, the deformation energy of binding is taken to be the difference between the

energy of the free entity and the average energy of the conformations observed when the inhibitor binds to the protein.

An entity designed or selected as binding to a caspase-8 substrate binding pocket or caspase-8-like binding pocket may be further computationally
5 optimized so that in its bound state it would preferably lack repulsive electrostatic interaction with the target enzyme and with the surrounding water molecules. Such non-complementary electrostatic interactions include repulsive charge-charge, dipole-dipole, and charge-dipole interactions.

Specific computer software is available in the art to evaluate compound
10 deformation energy and electrostatic interactions. Examples of programs designed for such uses include: Gaussian 94, revision C (M.J. Frisch, Gaussian, Inc., Pittsburgh, PA ©1995); AMBER, version 4.1 (P.A. Kollman, University of California at San Francisco, ©1995); QUANTA/CHARMM (Molecular Simulations, Inc., San Diego, CA ©1995); Insight II/Discover (Molecular
15 Simulations, Inc., San Diego, CA ©1995); DelPhi (Molecular Simulations, Inc., San Diego, CA ©1995); and AMSOL (Quantum Chemistry Program Exchange, Indiana University). These programs may be implemented, for instance, using a Silicon Graphics workstation such as an Indigo² with "IMPACT" graphics. Other hardware systems and software packages will be known to those skilled in
20 the art.

Another approach encompassed by this invention is the computational screening of small molecule databases for chemical entities or compounds that can bind in whole, or in part, to a caspase-8 or caspase-8-like substrate binding pocket. In this screening, the quality of fit of such entities to the binding site
25 may be judged either by shape complementarity or by estimated interaction energy (E.C. Meng et al., *J. Comp. Chem.* 13:505-524 (1992)).

This invention also enables the development of chemical entities that can isomerize to short-lived reaction intermediates in the chemical reaction of a substrate or other compound that binds to or with caspase-8. Time-dependent
30 analysis of structural changes in caspase-8 during its interaction with other molecules is carried out. The reaction intermediates of caspase-8 can also be deduced from the reaction product in co-complex with caspase-8. Such

information is useful to design improved analogs of known caspase-8 inhibitors or to design novel classes of inhibitors based on the reaction intermediates of the caspase-8 and inhibitor co-complex. This provides a novel route for designing caspase-8 inhibitors with both high specificity and stability.

5 Yet another approach to rational drug design involves probing the caspase-8 crystal of the invention with molecules comprising a variety of different functional groups to determine optimal sites for interaction between candidate caspase-8 inhibitors and the protein. For example, high resolution x-ray diffraction data collected from crystals soaked in or co-crystallized with
10 other molecules allows the determination of where each type of solvent molecule sticks. Molecules that bind tightly to those sites can then be further modified and synthesized and tested for their herpes protease inhibitor activity [J. Travis, *Science*, 262:1374 (1993)].

In a related approach, iterative drug design is used to identify inhibitors
15 of caspase-8 activity. Iterative drug design is a method for optimizing associations between a protein and a compound by determining and evaluating the three-dimensional structures of successive sets of protein/compound complexes. In iterative drug design, crystals of a series of protein/compound complexes are obtained and then the three-dimensional structures of each
20 complex is solved. Such an approach provides insight into the association between the proteins and compounds of each complex. This is accomplished by selecting compounds with inhibitory activity, obtaining crystals of this new protein/compound complex, solving the three dimensional structure of the complex, and comparing the associations between the new protein/compound
25 complex and previously solved protein/compound complexes. By observing how changes in the compound affected the protein/compound associations, these associations may be optimized.

Ligands and inhibitors

Included in the invention are compounds that modulate, and preferably
30 inhibit, the activity of caspase-8 or homologs thereof by associating directly with the binding site, for example as identified in the method of rational drug design above. Therapeutic uses of such compounds are also envisioned. In one

embodiment, an inhibitor compound is a peptide or a peptidomimetic compound, preferably one that comprises at least three amino acids. In a particularly preferred embodiment, an inhibitor of caspase-8 activity is a peptide or a peptidomimetic compound comprising at least four amino acids, wherein the amino acid at the P4 position is a hydrophobic amino acid. More preferably, the amino acids at the P3 and/or P1 positions of the peptide or peptidomimetic inhibitor are negatively charged amino acids. Positions P1, P2, P3 and P4 preferably associate with caspase-8 binding sites S1, S2, S3 and S4, respectively. Peptide and peptidomimetic inhibitors are optionally derivatized at one or both of the N- and C-termini. For example, the inhibitor can be derivatized with an acetyl group on the N-terminus and/or an aldehyde, fluoromethylketone, or the like on the C-terminus.

Pharmaceutical compositions

Pharmaceutical compositions of this invention comprise an inhibitor of caspase-8 activity identified according to the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The term "pharmaceutically acceptable carrier" refers to a carrier(s) that is "acceptable" in the sense of being compatible with the other ingredients of a composition and not deleterious to the recipient thereof. Optionally, the pH of the formulation is adjusted with pharmaceutically acceptable acids, bases, or buffers to enhance the stability of the formulated compound or its delivery form.

Methods of making and using such pharmaceutical compositions are also included in the invention. The pharmaceutical compositions of the invention can be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally, or via an implanted reservoir. Oral administration or administration by injection is preferred. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, and intracranial injection or infusion techniques.

Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 0.5 and about 75 mg/kg body weight per day

of a caspase-8 inhibitor are expected to be useful for the prevention and treatment of diseases associated with abnormal caspase-8 activity, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, stroke, cancer, spinal cord injury, cardiovascular and neurological diseases. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

EXAMPLES

The present invention is illustrated by the following examples. It is to be understood that the particular examples, materials, amounts, and procedures are to be interpreted broadly in accordance with the scope and spirit of the invention as set forth herein.

Example 1: Gene Construction and Protein Expression

The gene for the procaspase-8 construct was cloned into the BamHI and HindIII sites of vector pQE30 (Qiagen) and transformed into M15 (pREP4) cells (Qiagen) for propagation and expression in *E. coli*, using standard protocols. Cell cultures were grown in LB broth with 100 µg/ml ampicillin and 25 µg/ml kanamycin. At $A_{550} = 0.7$ to 0.8, expression was induced by addition of IPTG to 1 mM. Cells were harvested after 30 minutes, resuspended in 10 mM Tris, pH 8.0, 1 mM EDTA and frozen at -70 degrees C. The presence of inclusion bodies was determined by light microscopy. Cells were disrupted by sonication and the inclusion bodies were separated from soluble proteins and cell debris by low speed centrifugation (Sorvall SS34; 3000 rpm, 30 minutes).

Example 2: Refolding Protocol

E. coli inclusion bodies harboring the procaspase-8 were resuspended in 10 mM Tris buffer, pH 8.0, containing 1mM EDTA, washed in the same buffer, and finally collected by centrifugation at 1074 x g. The inclusion bodies were
5 then dissolved in 6M guanidinium chloride, 0.1 M Tris, pH 8.0, containing 5 mM DTT, and insoluble material was removed by centrifugation.

The solution of procaspase-8 in 6M guanidinium chloride (2-3 mg protein/ml) was treated with an equal volume of glacial acetic acid, followed by dialysis against 50% acetic acid. This solution was added rapidly to nine
10 volumes of water to produce a clear solution of protein in 5% acetic acid. The pH was brought rapidly to 8.0 by addition of this solution to nine volumes of 1.0 M Tris buffer, pH 8, containing 5 mM DTT. This resulted in a clear solution of procaspase-8 at neutral pH. SDS-PAGE showed a single band corresponding to a mass of 33 kDa.

15 The solution of protein was concentrated by ultrafiltration in an Amicon stirred cell concentrator. This concentration step led to autocatalytic processing of all of the 33 kDa procaspase-8 to the p18 and p11 species that are characteristic of the activated caspase. Sequence and mass spectrometric analysis of the activated caspase-8 established that the p18 subunit begins at Ser-
20 211 and extends on to Asp-374, while the p11 subunit starts at Leu-285 and continues on to the C-terminal Asp-479 (Fig. 1).

Example 3: Analytical Methods

Protein quantitation was afforded by amino acid analysis employing a
25 Beckman Model 6300 ion-exchange instrument. Protein sequencing was performed using a Perkin Elmer/Applied Biosystems Procise™ Sequencer. The masses of major procaspase processing fragments and intermediates were determined with electrospray ionization on a Micromass Quattro II MS and MALDI ionization on a Perseptive Biosystems Voyager Elite time-of-flight MS.
30 Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) was carried out using Novex 16 % Tris-glycine or 10% NuPage Bis-Tris (with MES running buffer) precast mini-gels and a Novex Xcell II mini-cell apparatus.

Example 4: Assay of caspase-8

Enzyme activity of caspase-8 preparations was monitored using the chromogenic substrates Ac-DEVD-pNA (SEQ ID NO:5) or Ac-IETD-pNA (SEQ ID NO:6) (California Peptide Research, Inc.). Kinetic release of para-nitroaniline (pNA) was followed spectrophotometrically at 405 nm in reactions maintained at pH 7.50 and 37 degrees C. The autocatalytically processed caspase-8 preparations (Example 2) readily cleaved the chromogenic caspase-8 (Ac-IETD-pNA) (SEQ ID NO:5) or caspase-3 (Ac-DEVD-pNA) (SEQ ID NO:6) substrates, but exhibited no measurable activity toward the caspase-1 (ICE) substrate Ac-YVAD-AMC (SEQ ID NO:7). For the optimal substrate, Ac-IETD-pNA (SEQ ID NO:6), $K_m = 66 \pm 5 \mu\text{M}$, $V_{\text{max}} = 8.43 \pm 0.18 \mu\text{mol/min/mg}$.

Example 5: Preparation of the Caspase-8/Ligand Complex

To a volume of 2.5 ml of a 8.4 mg/ml solution of caspase-8 (0.7 μmol) in 20 mM Tris, 100 mM DTT, pH 8.0 was added 140 μl of a 10 mM stock solution of the peptide inhibitor Ac-IETD-H (SEQ ID NO:4) in DMSO (1.4 μmol , 2 fold molar excess). Ac-IETD-aldehyde (SEQ ID NO:4) is a substrate mimic which covalently modifies the active-site Cys360 ($\text{IC}_{50} = 50 \text{ nM}$). The solution was stirred on ice for 30 minutes.

Example 6: Crystallization and Data Collection

The caspase-8:Ac-IETD complex was crystallized by hanging and sitting drop vapor diffusion according to the method of McPherson (in Preparation and Analysis of Protein Crystals, McPherson, A., ed., pp. 94-97, Kreiger Publishing Co., Malabar, FL (1989)). Drops (3 μl) of protein-inhibitor solution (8.4 mg/ml in 20 mM Tris, pH 8.0, 100 mM DTT) were mixed with an equal volume of reservoir buffer (1.4M sodium citrate, 0.1M HEPES, pH 8.0) and incubated at 4°C. The average size of the crystals was 0.20 x 0.30 x 0.40 mm.

The crystals were mounted in nylon loops and frozen directly in the nitrogen stream just prior to measurement of the data. In the first data set, X-ray diffraction data were measured using a rotating anode Cu $K\alpha$ source (50 kV, 100 mA) equipped with a Bruker Dual Hi-Star area detector system. A 100% complete data set to 2.07 Å was used to solve and refine the structure during the early rebuilding stages. The second data set was measured at the Advanced Photon Source (Argonne National Laboratory, Argonne, IL) IMCA-CAT beamline ID-17 using a wavelength of 1.03 Å and a Bruker Mosaic CCD area detector system. Data collection and processing for both crystals were carried out using *SMART* and *SAINT* software (SMART software reference manual and SAINT software reference manual; Bruker Analytical X-ray Systems, Madison, WI (1998)). The data collection statistics are given in Fig. 8.

Example 7: Structure Solution and Refinement

The structure was solved by molecular replacement using the program *AMoRe* in the *CCP4* program suite (Collaborative Computational Project No. 4, "The CCP4 Suite: programs for protein crystallography," *Acta Crystallogr. D* 50:760-763 (1994); Nazava, *Acta Crystallogr. A* 50:157-163 (1994)) using the diffraction data (Data set I) from the Bruker Dual Hi-Star system. A truncated p10/p20 poly-alanine search model based on the caspase-3 (1CP3 in the Brookhaven Data Bank) structure (Mittl et al., *J. Biol. Chem.* 272:6539-6547 (1997)) was used. A peak was found in the cross-rotation function with the rotation angles $\alpha=8.18$, $\beta=62.21$ and $\gamma=150.08$ (peak height = 7σ), in the resolution range 8 - 4.0 Å with an integration radius of 25 Å. The two-dimensional translation function, calculated with the search model rotated according to the above angles in the resolution 8 - 3 Å, yielded a solution for the translation $a = 0.2479$, $b = 0.5195$, and $c = 0.1947$ (correlation coefficient = 19.8%, $R_F = 0.519$). Initial refinement was carried out with data set I and PROFFT (Finzel, *J. Appl. Crystallogr.* 20:53-55 (1987)). The high-resolution refinement was carried out using the synchrotron radiation data set II. The structure was refined by alternating rounds of restrained least squares using *SHELXL97* (Sheldrick et al., *Methods Enzymol.* 277:319-343 (1997)) with

manual interventions on the graphic terminal (*CHAIN*; Sack et al., *J. Mol. Graphics* 6:224-225 (1998) and *LORE* (Finzel, *Acta Crystallogr. D* 51:450-457 (1995)). The R_F converged at 0.147 for all the data greater than $2\sigma_F$ between 10-1.2 Å resolution. 340 water molecules, the inhibitor and two dithiane-diol
5 molecules were included in the final model. Hydrogen parameters for the non-solvent atoms were included in the model but not refined. The root mean square deviations for bond lengths and angles are 0.024 Å and 2.14°, respectively. Not all of the residues could be assigned because the electron density was too weak. In the p18 and p11 dimers, twelve and four N-terminal residues, respectively,
10 could not be located due to disorder. Final refinement and *PROCHECK* (Laskowski et al., *J. Appl. Crystallogr.* 26:283-291 (1993)) statistics are included in Fig. 9.

The atomic coordinates and structure factors of the caspase-8:Ac-IETD-aldehyde complex (accession code 1QTN) were deposited in the RCSB Protein
15 Data Bank (PDB®) located at Rutgers University (<http://www.csb.org/pdb/>) on 28 June 1999 ("hold" status) and are scheduled to be publicly released 15 September 2000.

The complete disclosures of all patents, patent applications including
20 provisional patent applications, and publications, and electronically available material (e.g., GenBank amino acid and nucleotide sequence submissions; RCSB and Brookhaven Protein Data Bank atomic coordinate submissions) cited herein are incorporated by reference. The foregoing detailed description and examples have been provided for clarity of understanding only. No unnecessary
25 limitations are to be understood therefrom. The invention is not limited to the exact details shown and described; many variations will be apparent to one skilled in the art and are intended to be included within the invention defined by the claims.

WHAT IS CLAIMED IS:

1. A molecule or molecular complex comprising at least a portion of a caspase-8 or caspase-8-like substrate binding pocket, the substrate binding pocket
5 comprising backbone atoms defined by a set of points having a root mean square deviation from the backbone atoms of caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp 420, as represented by structure coordinates according to Fig. 10, of less than about 2.0 Å.
10
2. The molecule or molecular complex of claim 1 wherein the substrate binding pocket is further defined by a set of points having a root mean square deviation from the nonhydrogen side chain atoms of caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412,
15 Arg 413, Pro 415 and Trp 420, as represented by structure coordinates according to Fig. 10, of less than about 2.0 Å.
3. The molecule or molecular complex of claim 1 that is structurally homologous to a caspase-8 molecule or molecular complex.
20
4. The molecule or molecular complex of claim 1 wherein the substrate binding pocket comprises backbone atoms defined by a set of points representing the backbone atoms of caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp
25 420, as represented by structure coordinates according to Fig. 10.
5. A molecule or molecular complex comprising at least a portion of a caspase-8 or caspase-8-like substrate binding pocket, the substrate binding pocket comprising backbone atoms characterized by interatomic distances having a
30 root-mean-square deviation from the interatomic distances characterizing the backbone atoms of caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp

420, as represented by structure coordinates according to Fig. 10, of less than about 2.0 Å.

6. A molecule or molecular complex comprising at least a portion of a caspase-8 or caspase-8-like substrate binding pocket, the substrate binding pocket
- 5 comprising backbone atoms defined by a set of points having a root mean square deviation from the backbone atoms of caspase-8 amino acids as represented by structure coordinates according to Fig. 10 situated within a sphere having a radius of about 10 Å and centered on the coordinates representing the alpha carbon atom of residue 360, of less than about 2.0 Å.

10

7. A scalable three dimensional configuration of points comprising selected points derived from the structure coordinates according to Fig. 10 representing the backbone atoms of a plurality of caspase-8 amino acids defining at least a portion of a caspase-8 substrate binding pocket and having a root mean square
- 15 deviation of less than about 2.0 Å from said structure coordinates.

8. The scalable three dimensional configuration of points wherein the caspase-8 substrate binding pocket comprises amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415
- 20 and Trp 420.

9. The scalable three dimensional configuration of points of claim 8 wherein the selected points are defined by the structure coordinates according to Fig. 10 representing the backbone atoms of caspase-8 amino acids Arg 258, Asp 259,
- 25 Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp 420.

- 10 The scalable three dimensional configuration of points of claim 10 further comprising selected points derived from the structure coordinates according to
- 30 Fig. 10 representing at least 50 contiguous backbone atoms of caspase-8 and having a root mean square deviation of less than about 2.0 Å from said structure coordinates.

11. The scalable three-dimensional configuration of points of claim 8 displayed as a physical model, a computer-displayed image, a holographic image, or a stereodiagram.

5

12. A scalable three dimensional configuration of points comprising selected points derived from the structure coordinates of at least a portion of a molecule or a molecular complex that is structurally homologous to a caspase-8 molecule or molecular complex as represented by the structure coordinates according to Fig. 10, wherein the selected points have a root mean square deviation of less than about 2.0 Å from the structure coordinates of said structurally homologous molecule or molecular complex.

13. The scalable three-dimensional configuration of points of claim 12 displayed as a physical model, a computer-displayed image, a holographic image, or a stereodiagram.

14. A machine-readable data storage medium comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of

(i) a molecule or molecular complex comprising at least a portion of a caspase-8-like substrate binding pocket, the caspase-8-like substrate binding pocket comprising backbone atoms defined by a set of points having a root mean square deviation from the backbone atoms of caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp 420, as represented by structure coordinates according to Fig. 10, of less than about 2.0 Å;

(ii) a molecule or molecular complex comprising at least a portion of a caspase-8-like substrate binding pocket, the caspase-8-like substrate binding pocket comprising backbone atoms defined by a set of points having a root mean square deviation from the backbone atoms and nonhydrogen side chain atoms of

caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Ser 411, Tyr 412 and Arg 413, as represented by structure coordinates according to Fig. 10, of less than about 2.0 Å;

(iii) a molecule or molecular complex comprising at least a portion of a
5 caspase-8-like substrate binding pocket, the caspase-8-like substrate binding pocket comprising backbone atoms characterized by interatomic distances having a root-mean-square deviation from the interatomic distances characterizing the backbone atoms of caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg
10 413, Pro 415 and Trp 420, as represented by structure coordinates according to Fig. 10, of less than about 2.0 Å;

(iv) a molecule or molecular complex that is structurally homologous to a molecule or molecular complex comprising at least a portion of a caspase-8-like substrate binding pocket, the caspase-8-like substrate binding pocket
15 comprising backbone atoms defined by a set of points having a root mean square deviation from the backbone atoms of caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp 420, as represented by structure coordinates according to Fig. 10, of less than about 2.0 Å; or

(v) a molecule or molecular complex comprising at least a portion of a
20 caspase-8-like substrate binding pocket, the caspase-8-like substrate binding pocket comprising backbone atoms defined by a set of points having a root mean square deviation from the backbone atoms of caspase-8 amino acids as represented by structure coordinates according to Fig. 10 situated within a sphere
25 having a radius of about 10 Å and centered on the coordinates representing the alpha carbon atom of residue 360, of less than about 2.0 Å.

15. A machine-readable data storage medium comprising a data storage material encoded with structure coordinates as shown in Fig. 10 representing at least the
30 backbone atoms of at least a portion of caspase-8 molecule comprising a caspase-8 substrate binding pocket.

16. The machine-readable data storage medium of claim 15 wherein the data storage material is encoded with structure coordinates as shown in Fig. 10 representing at least the backbone atoms of at least amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp 420.
17. A machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data, wherein said first set of data comprises a Fourier transform of at least a portion of the structural coordinates for caspase-8 according to Fig. 10; and said second set of data comprises an x-ray diffraction pattern of a molecule or molecular complex of unknown structure.
18. A computer-assisted method for obtaining structural information about a molecule or a molecular complex of unknown structure using the technique of molecular replacement, the method comprising:
- crystallizing the molecule or molecular complex;
 - generating an x-ray diffraction pattern from the crystallized molecule or molecular complex;
 - applying at least a portion of the structure coordinates set forth in Fig. 10 to the x-ray diffraction pattern to generate a three-dimensional electron density map of at least a portion of the molecule or molecular complex whose structure is unknown.
19. The method of claim 18 wherein the molecule or molecular complex of unknown structure is structurally homologous to a caspase-8 molecule or molecular complex.

20. A computer-assisted method for homology modeling a caspase-8 homolog comprising:

aligning the amino acid sequence of the caspase-8 homolog with the amino acid sequence of caspase-8 (SEQ ID NO:1) to yield an amino acid alignment;

utilizing the amino acid alignment to incorporate the sequence of the caspase-8 homolog into a model of caspase-8 derived from the structure coordinates set forth in Fig. 10 to yield a preliminary model of the caspase-8 homolog;

subjecting the preliminary model to energy minimization to yield an energy minimized model;

remodeling regions of the energy minimized model where stereochemistry restraints are violated to yield a final model of the caspase-8 homolog.

21. A computer-assisted method for identifying a modulator of caspase-8 activity comprising:

supplying a computer modeling application with a set of structure coordinates of a molecule or molecular complex, the molecule or molecular complex comprising at least a portion of a caspase-8 or caspase-8-like substrate binding pocket;

supplying the computer modeling application with a set of structure coordinates of a chemical entity; and

determining whether the chemical entity is expected to bind to the molecule or molecular complex at the substrate binding pocket, wherein binding to the molecule or molecular complex is indicative of potential modulation of caspase-8 activity.

22. A computer-assisted method for designing a modulator of caspase-8 activity comprising:

supplying a computer modeling application with a set of structure coordinates of a molecule or molecular complex, the molecule or molecular

complex comprising at least a portion of a caspase-8 or caspase-8-like substrate binding pocket;

supplying the computer modeling application with a set of structure coordinates for a chemical entity;

5 evaluating the potential binding interactions between the chemical entity and substrate binding pocket of the molecule or molecular complex;

structurally modifying the chemical entity to yield a set of structure coordinates for a modified chemical entity; and

determining whether the chemical entity is expected to bind to the
10 molecule or molecular complex at the substrate binding pocket, wherein binding to the molecule or molecular complex is indicative of potential modulation of caspase-8 activity.

23. The method of claims 22 wherein the set of structure coordinates for the
15 chemical entity is obtained from a chemical fragment library.

24. The method of claim 21 or 22 performed a multiplicity of times to screen a library of chemical entities.

20 25. A computer-assisted method for designing a modulator of caspase-8 activity *de novo* comprising:

supplying a computer modeling application with a set of structure coordinates of a molecule or molecular complex, the molecule or molecular complex comprising at least a portion of a caspase-8 or caspase-8-like substrate

25 binding pocket;

computationally building a chemical entity represented by set of structure coordinates; and

determining whether the chemical entity is expected to bind to the
molecule or molecular complex at the substrate binding pocket, wherein binding
30 to the molecule or molecular complex is indicative of potential modulation of caspase-8 activity.

26. The method of any of claims 21, 22 or 25 wherein the modulator is an inhibitor of caspase-8 activity.
27. The method of any of claims 21, 22 or 25 further comprising supplying or
5 synthesizing the potential modulator, then assaying the potential modulator to determine whether it modulates caspase-8 activity.
28. The method of any of claims 21, 22 or 25 wherein the substrate binding
10 pocket is defined by a scalable set of points in three dimensions having a root mean square deviation from the backbone atoms of caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp 420, as represented by structure coordinates according to Fig. 10, of less than about 2.0 Å.
- 15 29. The method of claim 28 wherein the substrate binding pocket is further defined by a scalable set of points in three dimensions having a root mean square deviation from the nonhydrogen side chain atoms of caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp 420, as represented by structure coordinates
20 according to Fig. 10, of less than about 2.0 Å.
30. The method of claim 28 wherein the substrate binding pocket is defined by a scalable set of points in three dimensions representing the backbone atoms of caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358,
25 Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp 420, as represented by structure coordinates according to Fig. 10.
31. The method of any of claims 21, 22 or 25 wherein the substrate binding
30 pocket is defined by a scalable set of points in three dimensions characterized by pairwise distances having a root-mean-square deviation from the interatomic distances characterizing the backbone atoms of caspase-8 amino acids Arg 258, Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr

412, Arg 413, Pro 415 and Trp 420, as represented by structure coordinates according to Fig. 10, of less than about 2.0 Å.

32. The method of any of claims 21, 22, or 25 wherein the substrate binding pocket is defined by a scalable set of points having a root mean square deviation from the backbone atoms of caspase-8 amino acids as represented by structure coordinates according to Fig. 10 situated within a sphere having a radius of about 10 Å and centered on the coordinates representing the alpha carbon atom of residue 360, of less than about 2.0 Å.

10

33. The method of any of claims 21, 22 or 25 wherein the determining step comprises performing a fitting operation between the chemical entity and the substrate binding pocket, followed by computationally analyzing the results of the fitting operation to quantify the association between the chemical entity and the substrate binding pocket.

15

34. The method of any of claims 21, 22 or 25 further comprising chemically or enzymatically synthesizing the chemical entity to yield a modulator of caspase-8 activity.

20

35. The method of claim 34 wherein the modulator of caspase-8 activity is an inhibitor of caspase-8 activity.

36. A method for making a modulator of caspase-8 activity, the method comprising chemically or enzymatically synthesizing a chemical entity to yield a modulator of caspase-8 activity, the chemical entity having been identified during a computer-assisted process comprising supplying a computer modeling application with a set of structure coordinates of a molecule or molecular complex, the molecule or molecular complex comprising at least a portion of a caspase-8 or caspase-8-like substrate binding pocket; supplying the computer modeling application with a set of structure coordinates of a chemical entity; and determining whether the chemical entity is expected to bind to the molecule or

25
30

molecular complex at the substrate binding pocket, wherein binding to the molecule or molecular complex is indicative of potential modulation of caspase-8 activity.

- 5 37. A method for making a modulator of caspase-8 activity, the method comprising chemically or enzymatically synthesizing a chemical entity to yield a modulator of caspase-8 activity, the chemical entity having been designed during a computer-assisted process comprising supplying a computer modeling application with a set of structure coordinates of a molecule or molecular
10 complex, the molecule or molecular complex comprising at least a portion of a caspase-8 or caspase-8-like substrate binding pocket; supplying the computer modeling application with a set of structure coordinates for a chemical entity; evaluating the potential binding interactions between the chemical entity and substrate binding pocket of the molecule or molecular complex; structurally
15 modifying the chemical entity to yield a set of structure coordinates for a modified chemical entity; and determining whether the chemical entity is expected to bind to the molecule or molecular complex at the substrate binding pocket, wherein binding to the molecule or molecular complex is indicative of potential modulation of caspase-8 activity.

- 20 38. A method for making a modulator of caspase-8 activity, the method comprising chemically or enzymatically synthesizing a chemical entity to yield a modulator of caspase-8 activity, the chemical entity having been designed during a computer-assisted process comprising supplying a computer modeling
25 application with a set of structure coordinates of a molecule or molecular complex, the molecule or molecular complex comprising at least a portion of a caspase-8 or caspase-8-like substrate binding pocket; computationally building a chemical entity represented by set of structure coordinates; and determining whether the chemical entity is expected to bind to the molecule or molecular
30 complex at the substrate binding pocket, wherein binding to the molecule or molecular complex is indicative of potential modulation of caspase-8 activity.

39. A modulator of caspase-8 activity identified or designed according to the method of any of claims 21, 22, 25, 36, 37 or 38.
40. A composition comprising a modulator of caspase-8 activity identified or
5 designed according to the method of any of claims 21, 22, 25, 36, 37 or 38.
41. A pharmaceutical composition comprising a modulator of caspase-8 activity identified or designed according to the method of any of 21, 22, 25, 36, 37 or 38, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable
10 carrier.
42. A method for treating patient having an injury or disease that is accompanied by or associated with abnormal caspase-8 activity, the method comprising administering to the patient an effective amount of a pharmaceutical
15 composition comprising a modulator of caspase-8 activity identified or designed according to the method of any of claims 21, 22 or 25, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
43. The method of claim 42 wherein the injury or disease is selected from the
20 group consisting of Parkinson's disease, Alzheimer's disease, Huntington's disease, stroke, cancer, spinal cord injury, cardiovascular disease and neurological disease.
44. A method for crystallizing a caspase-8 molecule comprising growing a
25 crystal by hanging and sitting drop vapor diffusion from a precipitant solution buffered to a pH of about 7 to about 8, the precipitant solution comprising about 2 to about 5 mg/ml purified caspase-8, a buffer and a salt.
45. A method for crystallizing a caspase-8/modulator complex comprising
30 growing a crystal by hanging and sitting drop vapor diffusion from a precipitant solution buffered to a pH of about 7 to about 8, the precipitant solution

comprising about 2 to about 5 mg/ml purified caspase-8, a modulator of caspase-8 activity, a buffer and a salt.

46. The method of claim 45 wherein the modulator is an inhibitor of caspase-8 activity.

47. The method of claim 45 wherein the inhibitor is a peptide or a peptidomimetic compound.

48. The method of claim 45 wherein the inhibitor is Acetyl-Ile-Glu-Thr-Asp-H.

49. The method of claim 45 wherein the inhibitor is covalently bound to caspase-8.

50. The method of claim 45 wherein the salt comprises at least one anion selected from the group consisting of sulfate, chloride, citrate and tartrate.

51. The method of claim 45 wherein the precipitant solution further comprises polyethylene glycol having a molecular weight of about 2000 to about 8000.

52. Crystalline caspase-8.

53. Crystalline caspase-8 complexed with a small molecule ligand.

54. Crystalline caspase-8 of claim 53 wherein the small molecule ligand is a peptide or a peptidomimetic compound that binds to the substrate binding pocket.

55. Crystalline caspase-8 of claim 53 wherein the small molecule ligand is Acetyl-Ile-Glu-Thr-Asp-H.

56. Crystalline caspase-8 characterized by the trigonal space group $P3_121$.

57. Crystalline caspase-8 of claim 56 further characterized by having unit cell dimensions of $a = b = 62.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $c = 129.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 120^\circ$.

5

58. Crystalline caspase-8 complexed with Acetyl-Ile-Glu-Thr-Asp-H characterized by the trigonal space group $P3_121$ and having unit cell dimensions of $a = b = 62.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $c = 129.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 120^\circ$ with one (p18/p11) heterodimer and one inhibitor molecule in the asymmetric unit.

10

59. Crystalline caspase-8 or crystalline caspase-8 complexed with a small molecule ligand wherein the amino acid sequence of the caspase-8 is represented in Fig. 1.

15 60. A composition comprising crystalline caspase-8 or crystalline caspase-8 complexed with a small molecule ligand.

61. A method for solving a crystal structure of a crystal of a caspase-8 molecule or molecular complex characterized by the trigonal space group $P3_121$ and
20 having unit cell dimensions of $a = b = 62.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $c = 129.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 120^\circ$, the method comprising:

generating an x-ray diffraction pattern from the crystal,

collecting diffraction data, and

analyzing the data to generate the structure coordinates for the caspase-8

25 molecule or molecular complex.

62. The method of claims 61 wherein the amino acid sequence of the caspase-8 is represented in Fig. 1.

AMENDED CLAIMS

[received by the International Bureau on 1 December 2000 (01.12.00) ;
original claims 1-7, 8-11, 13-62 replaced by amended claims 1-7, 8-11, 13-62
new claims 63-66 added; remaining claims unchanged (4 pages)]

420, as represented by structure coordinates according to Fig. 10, of less than
about 2.0 Å.

6. A molecule or molecular complex comprising at least a portion of a caspase-8
or caspase-8-like substrate binding pocket, the substrate binding pocket

5 comprising backbone atoms defined by a set of points having a root mean square
deviation from the backbone atoms of caspase-8 amino acids as represented by
structure coordinates according to Fig. 10 situated within a sphere having a
radius of about 10 Å and centered on the coordinates representing the alpha
carbon atom of residue 360, of less than about 2.0 Å.

10

7. A scalable three dimensional configuration of points comprising selected
points derived from the structure coordinates according to Fig. 10 representing
the backbone atoms of a plurality of caspase-8 amino acids defining at least a
portion of a caspase-8 substrate binding pocket and having a root mean square
15 deviation of less than about 2.0 Å from said structure coordinates.

8. The scalable three dimensional configuration of points of claim 7 wherein the
caspase-8 substrate binding pocket comprises amino acids Arg 258, Asp 259,
Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg
20 413, Pro 415 and Trp 420.

9. The scalable three dimensional configuration of points of claim 7 wherein the
selected points are defined by the structure coordinates according to Fig. 10
representing the backbone atoms of caspase-8 amino acids Arg 258, Asp 259,
25 Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg
413, Pro 415 and Trp 420.

10. The scalable three dimensional configuration of points of claim 7 further
comprising selected points derived from the structure coordinates according to
30 Fig. 10 representing at least 50 contiguous backbone atoms of caspase-8 and
having a root mean square deviation of less than about 2.0 Å from said structure
coordinates.

11. The scalable three-dimensional configuration of points of claim 7 displayed as a physical model, a computer-displayed image, a holographic image, or a stereodiagram.
- 5 12. A scalable three dimensional configuration of points comprising selected points derived from the structure coordinates of at least a portion of a molecule or a molecular complex that is structurally homologous to a caspase-8 molecule or molecular complex as represented by the structure coordinates according to Fig. 10, wherein the selected points have a root mean square deviation of less
10 than about 2.0 Å from the structure coordinates of said structurally homologous molecule or molecular complex.
13. The scalable three-dimensional configuration of points of claim 12 displayed as a physical model, a computer-displayed image, a holographic
15 image, or a stereodiagram.
14. A machine-readable data storage medium comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-
20 dimensional representation of
- (i) a molecule or molecular complex comprising at least a portion of a caspase-8-like substrate binding pocket, the caspase-8-like substrate binding pocket comprising backbone atoms defined by a set of points having a root mean square deviation from the backbone atoms of caspase-8 amino acids Arg 258,
25 Asp 259, Arg 260, Asn 261, His 317, Gln 358, Tyr 365, Val 410, Ser 411, Tyr 412, Arg 413, Pro 415 and Trp 420, as represented by structure coordinates according to Fig. 10, of less than about 2.0 Å;
- (ii) a molecule or molecular complex comprising at least a portion of a caspase-8-like substrate binding pocket, the caspase-8-like substrate binding
30 pocket comprising backbone atoms defined by a set of points having a root mean square deviation from the backbone atoms and nonhydrogen side chain atoms of

57. Crystalline caspase-8 of claim 56 further characterized by having unit cell dimensions of $a = b = 62.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $c = 129.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 120^\circ$.
- 5 58. Crystalline caspase-8 complexed with Acetyl-Ile-Glu-Thr-Asp-H characterized by the trigonal space group $P3_121$ and having unit cell dimensions of $a = b = 62.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $c = 129.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 120^\circ$ with one (p18/p11) heterodimer and one inhibitor molecule in the asymmetric unit.
- 10 59. Crystalline caspase-8 or crystalline caspase-8 complexed with a small molecule ligand wherein the amino acid sequence of the caspase-8 is represented in Fig. 1.
60. A composition comprising crystalline caspase-8 or crystalline caspase-8
15 complexed with a small molecule ligand.
61. A method for solving a crystal structure of a crystal of a caspase-8 molecule or molecular complex characterized by the trigonal space group $P3_121$ and having unit cell dimensions of $a = b = 62.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $c = 129.4 \text{ \AA} \pm 3.0 \text{ \AA}$, $\alpha =$
20 90° , $\beta = 90^\circ$, $\gamma = 120^\circ$, the method comprising:
generating an x-ray diffraction pattern from the crystal,
collecting diffraction data, and
analyzing the data to generate the structure coordinates for the caspase-8 molecule or molecular complex.
- 25 62. The method of claims 61 wherein the amino acid sequence of the caspase-8 is represented in Fig. 1.
63. A method for preparing caspase-8 comprising:
30 expressing recombinant procaspase-8 in *E. coli* to yield inclusion bodies comprising procaspase-8;

contacting the inclusion bodies with a chaotropic agent and a reducing agent to yield a mixture comprising reduced procaspase-8;
acidifying the mixture; and
concentrating the mixture so as to cause autocatalytic processing of the
5 procaspase-8 to activated caspase-8 comprising α and β subunits.

64. The method of claim 63 wherein the chaotropic agent is guanadinium chloride.

10 65. The method of claim 63 wherein the reducing agent is dithiothreitol.

66. The method of claim 63 wherein the mixture is acidified with glacial acetic acid.

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Caspase-8 (MRGSHHHHHHGS)MTISD↓SPREQDSESQTLDKVYQMK229
Caspase-3 ..DNSYKMD40
Caspase-1 ..AEIYPIM156

|<---β1--->|<---α1'--->|<---L1--->|<---α1
Caspase-8 S....KPRGYCLIIINNHNFAKAREKVPKLHSIRDNRNGTHLD266
Caspase-3 Y....PEMGLCIIINNKNF.H.KS....TGMTSRSGTDVD70
Caspase-1 .DKSSRT.RLALIICNEEFDS.....IPRRTGAEVD185

---α1--->|<---β2--->|L2|<---α2--->|
Caspase-8 AGALTTFEELHFEIKPHDDCTVEQIYEILKIYQLMD.HSN306
Caspase-3 AANLRETFRNLKYEVNRKNDLTREEIVELMRDVSKEH.HSK110
Caspase-1 ITGMTMLLQNLGYSDVKKNLTASDMTTELEAFARPEHKT226

|<---β3--->|<---L3--->|<---α3--->|
Caspase-8 MDCFICCILSHGDKGIYGTD.....GQEAPIYELTSQFT341
Caspase-3 RSSFVVCVLLSHGEEGIIFGTN.....GP.VDLKKITNFFR144
Caspase-1 SDSTFLVFMMSGIREGICGKKHSEQVPDI.LQLNAIFNMLN266

|<---β4--->|<---end of p18--->|<---linker
Caspase-8 GLKCPSLAGKPKVFFIQACQGDNYQKGIPVETD↓SEEQPYL381
Caspase-3 GDRCRSLTGKPKLFIIQACRGTELDCCI..ETD↓S.G...V178
Caspase-1 TKNCPSLKDKPKVIIIIQACRGDSPGVVW..FKD↓SVG...V301

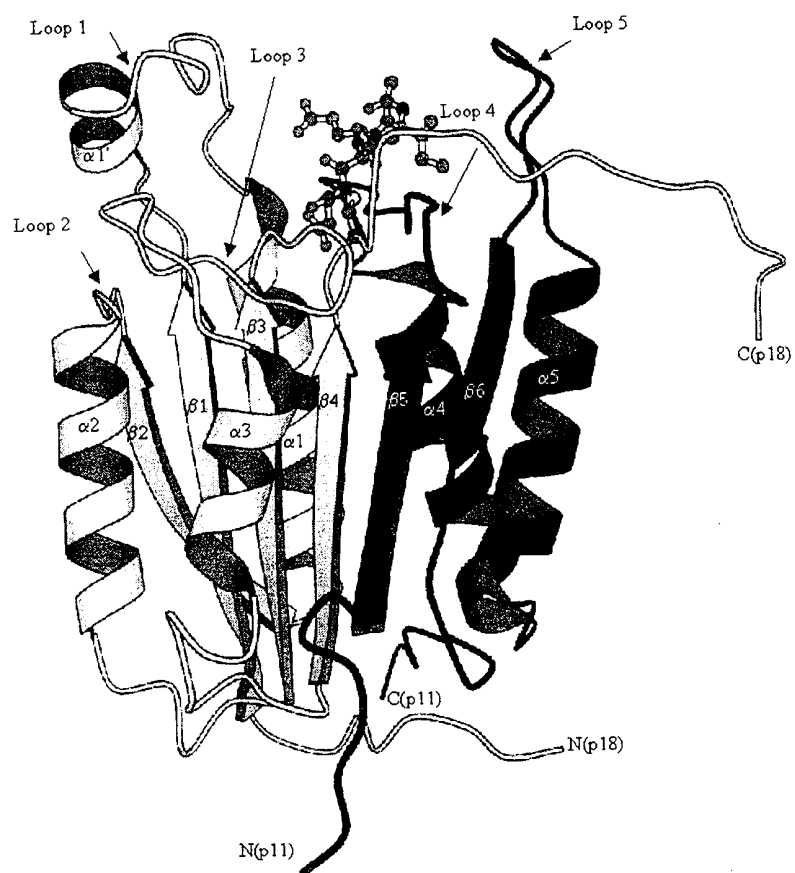
-->|<---beginning of p11--->|<---β5--->|<---L4---
Caspase-8 EMD↓L.....SSPQTRYIPDEADFLGMATVNNCV410
Caspase-3 DDD M.....ACHK...IPVDADFLYAYSTAPGY204
Caspase-1 SGNLSLPTTEEFEDD↓AIKK...AHIEKDFIAFCSSTPDNV338

---L4--->|<---α4--->|<---α5--->|
Caspase-8 SYRNPAEGTWYIQSLCQSLRERCPRGDDILTILTEVNVEV450
Caspase-3 SWRNSKDGSWFIQSLCAMLKQ.YADKLEFMHILTRVNRKV242
Caspase-1 SWRHPTMGSVFIGRLIEHMQE.YACSCDVEEIFRKVRFSF376

->|<---L5--->|<β6>|
Caspase-8 SN..KDDKK.....NMGKQMPQPTFTLRKKLVFSPD479
Caspase-3 ATTEFESFSFDATFHAKKQIPCIIVSM.LTKELYFYH277
Caspase-1 EQQPDGR.....AQMPPTTERVTLTRCFYLFPGH404

```

Fig. 1

**Figure 2**

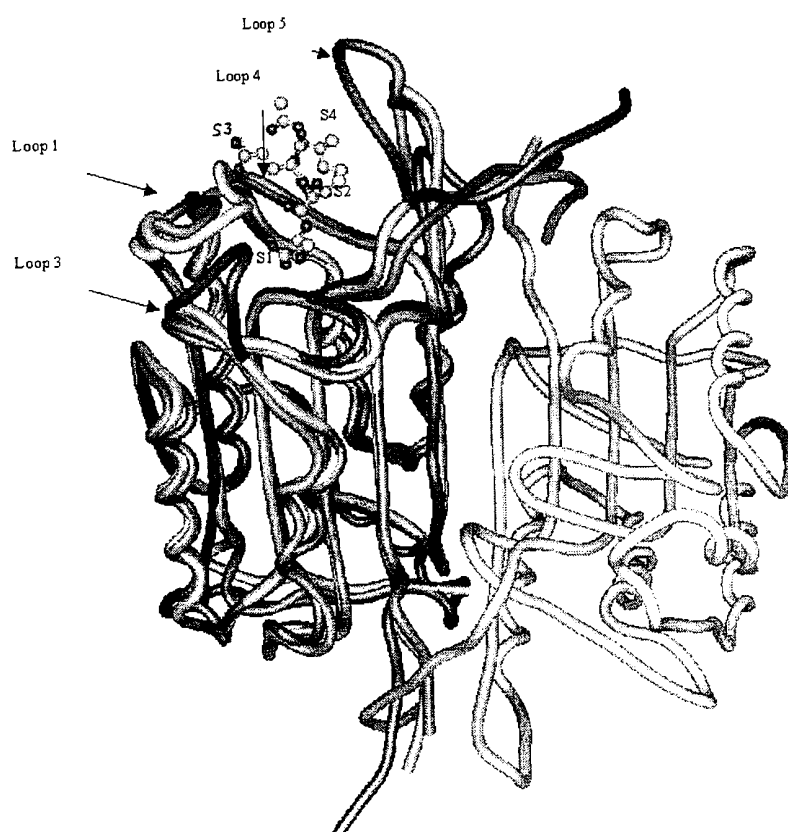
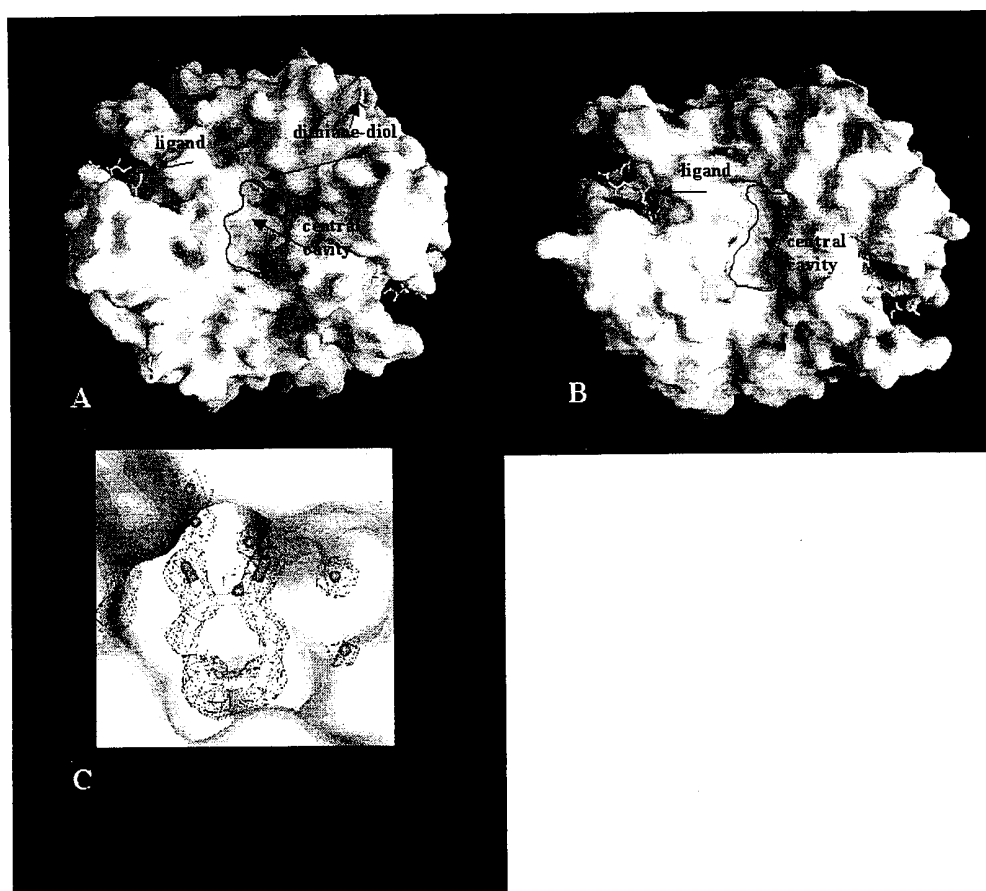


Figure 3.

Hydrogen-bond contacts between heterodimers along the dimer-dimer interface.

Atom	Residue	Atom*	Residue*	Distance (Å)
Oδ1	D223	Nη1	R432	2.60
Ne2	N366	N	E396	2.97
O	K367	N	D395	2.92
N	I369	O	I393	2.87
O	I369	N	I393	3.01
N	V371	O	R391	2.91
Oδ2	D374	Nζ	K472	2.90
O	Y392	Nζ	K461	2.88
Oγ1	T441	Nζ	K473	2.91
Oδ1	N447	O	L470	2.83
O	P466	N	F468	3.01
Oγ1	T467	Oγ1	T467	2.90
Nη1	R432	Oδ1	D223	2.60
N	E396	Ne2	N366	2.97
N	D395	O	K367	2.92
O	I393	N	I369	2.87
N	I393	O	I369	3.01
O	R391	N	V371	2.91
Nζ	K472	Oδ2	D374	2.90
Nζ	K461	O	Y392	2.88
Nζ	K473	Oγ1	T441	2.91
O	L470	Oδ1	N447	2.83
N	F468	O	P466	3.01

Fig. 4

**Figure 5**

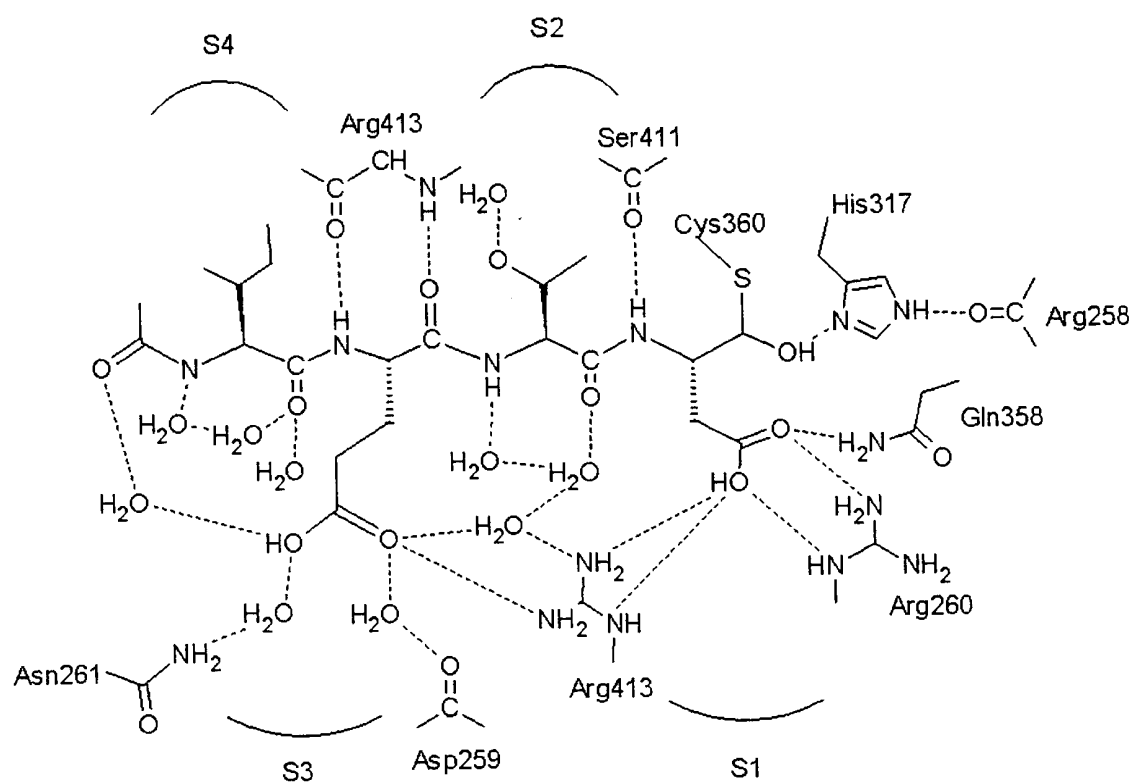
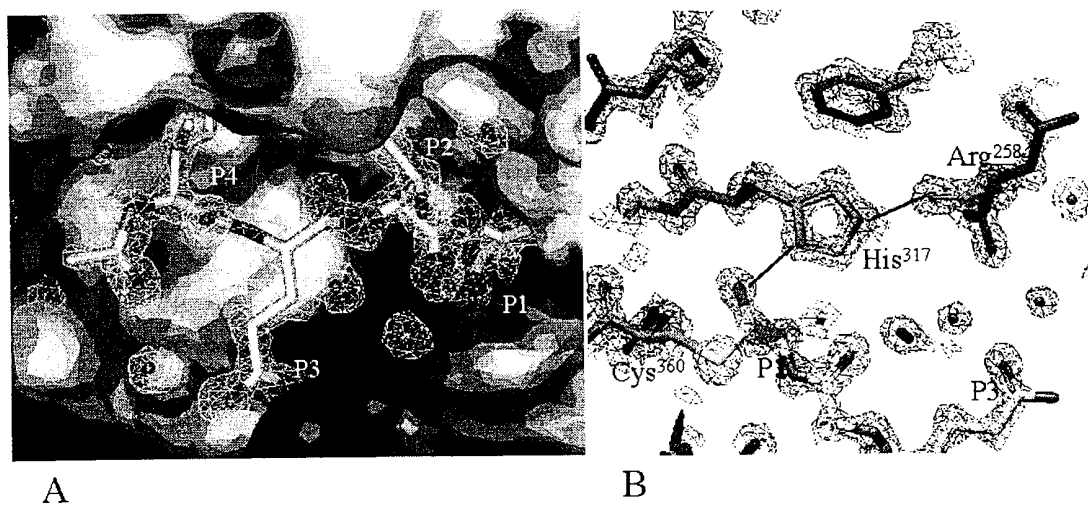


Figure 6

**Figure 7**

Summary of data collection and processing statistics.

Data set	I	II
Data collection method	Dual Hi-Star	Synchrotron
Resolution (Å)	40–2.07	40–1.20
Wavelength (Å)	1.54178	1.03321
Total reflections	107,109	298,890
Unique reflections	29,882	79,843
I/σ(I) (last shell)	5.49 (2.14–2.07)	2.35 (1.24–1.20)
R _{merge} (F ²)*	0.051	0.068
Redundancy	3.80	3.73
Completeness (%)	100	87
Temperature (K)	100	105
Space group	P3 ₁ 21	P3 ₁ 21
Cell parameters (Å)		
a,b	62.45	62.40
c	129.16	129.25

$$*R_{\text{merge}} = \frac{\sum_{hkl} \sum_i |F_i^2(hkl) - \langle F^2(hkl) \rangle|}{\sum_{hkl} \sum_i F_i^2(hkl)}.$$

Fig. 8

Refinement statistics for data set II.

Resolution range (Å)	8.0–1.20
R factor ($F_o > 4\sigma$)	0.143
R factor (all reflections within range)	0.166
R _{free} ($F_o > 4\sigma$)	0.165
Total reflections	75,433
Total reflections ($F_o > 4\sigma$)	60,671
Number of protein atoms (including alternate sites)	1945
Number of substrate atoms	51
Number of solvent atoms	334
Average B values (Å ²)	
mainchain	7.83
sidechain	14.18
solvent (full occupancy)	29.67
Stereochemistry	
Bond distances	
mainchain atoms/overall (Å)	0.014/0.017
Bond angles	
mainchain atoms/overall (°)	1.8/1.8
Phi–Psi torsion angles	
most favored regions (%)	89.0
Phi–Psi torsion angles	
additional allowed regions (%)	11.0
Phi–Psi torsion angles	
generous or disallowed (%)	0.0

Fig. 9

Fig. 10A

```

TITLE   HUMAN CASPASE-8 ATOMIC COORDINATES (SET = LS16)
CRYST1  62.400  62.400  129.250  90.00  90.00  120.00
REMARK  SPACE GROUP P3(1)21
SCALE1  0.016026  0.009252  0.000000  0.000000
SCALE2  0.000000  0.018505  0.000000  0.000000
SCALE3  0.000000  0.000000  0.007737  0.000000
REMARK  ATM RES. NO. X Y Z OCC. B
ATOM    1 N ASP 223 -1.759 6.850 12.431 1.000 32.45
ATOM    2 CA ASP 223 -2.313 8.208 12.577 1.000 25.64
ATOM    3 C ASP 223 -1.257 9.230 12.105 1.000 20.93
ATOM    4 O ASP 223 -0.076 9.121 12.452 1.000 21.08
ATOM    5 CB ASP 223 -2.534 8.474 14.094 1.000 29.34
ATOM    6 CG ASP 223 -3.802 7.848 14.626 1.000 33.36
ATOM    7 OD1 ASP 223 -4.662 7.444 13.830 1.000 36.01
ATOM    8 OD2 ASP 223 -3.946 7.764 15.876 1.000 41.02
ATOM    9 N LYS 224 -1.713 10.270 11.426 1.000 15.51
ATOM   10 CA LYS 224 -0.807 11.350 11.050 1.000 11.97
ATOM   11 C LYS 224 -0.482 12.181 12.301 1.000 11.01
ATOM   12 O LYS 224 -1.340 12.360 13.168 1.000 10.29
ATOM   13 CB LYS 224 -1.388 12.236 9.967 1.000 18.84
ATOM   14 CG LYS 224 -1.833 11.449 8.727 1.000 26.89
ATOM   15 CD LYS 224 -2.771 12.265 7.850 1.000 33.34
ATOM   16 CE LYS 224 -4.206 12.167 8.342 1.000 43.14
ATOM   17 NZ LYS 224 -5.094 11.372 7.485 1.000 49.23
ATOM   18 N VAL 225 0.736 12.634 12.361 1.000 10.15
ATOM   19 CA VAL 225 1.278 13.408 13.479 1.000 7.67
ATOM   20 C VAL 225 1.990 14.628 12.959 1.000 7.97
ATOM   21 O VAL 225 2.730 14.523 11.957 1.000 8.53
ATOM   22 CB VAL 225 2.272 12.535 14.293 1.000 10.76
ATOM   23 CG1 VAL 225 2.841 13.326 15.459 1.000 12.82
ATOM   24 CG2 VAL 225 1.648 11.241 14.727 1.000 17.93
ATOM   25 N TYR 226 1.799 15.814 13.540 1.000 5.44
ATOM   26 CA TYR 226 2.526 16.978 13.117 1.000 5.14
ATOM   27 C TYR 226 4.038 16.757 13.329 1.000 5.89
ATOM   28 O TYR 226 4.501 16.262 14.348 1.000 5.99
ATOM   29 CB TYR 226 2.135 18.221 13.924 1.000 5.02
ATOM   30 CG TYR 226 0.765 18.746 13.651 1.000 5.07
ATOM   31 CD1 TYR 226 0.479 19.466 12.505 1.000 5.02
ATOM   32 CD2 TYR 226 -0.288 18.569 14.551 1.000 5.16
ATOM   33 CE1 TYR 226 -0.779 19.947 12.240 1.000 4.05
ATOM   34 CE2 TYR 226 -1.534 19.060 14.306 1.000 4.44
ATOM   35 CZ TYR 226 -1.786 19.771 13.164 1.000 5.26
ATOM   36 OH TYR 226 -3.047 20.271 12.928 1.000 5.05
ATOM   37 N GLN 227 4.787 17.256 12.330 1.000 6.90
ATOM   38 CA GLN 227 6.248 17.261 12.456 1.000 6.70
ATOM   39 C GLN 227 6.648 18.085 13.675 1.000 7.07
ATOM   40 O GLN 227 6.148 19.183 13.896 1.000 6.87
ATOM   41 CB GLN 227 6.855 17.876 11.183 1.000 11.84
ATOM   42 CG GLN 227 8.372 18.041 11.257 1.000 13.31
ATOM   43 CD GLN 227 8.945 18.502 9.923 1.000 19.49
ATOM   44 OE1 GLN 227 9.035 17.724 8.983 1.000 20.56
ATOM   45 NE2 GLN 227 9.295 19.783 9.838 1.000 19.13
ATOM   46 N MET 228 7.554 17.542 14.493 1.000 7.22
ATOM   47 CA MET 228 7.964 18.256 15.712 1.000 6.78
ATOM   48 C MET 228 9.409 17.844 16.044 1.000 8.16
ATOM   49 O MET 228 9.653 17.046 16.924 1.000 10.72
ATOM   50 CB MET 228 7.036 17.906 16.868 1.000 7.89
ATOM   51 CG MET 228 7.135 18.836 18.054 1.000 8.50
ATOM   52 SD MET 228 6.580 20.523 17.721 1.000 9.37
ANISOU 52 SD MET 228 1001 1221 1337 84 206 109
ATOM   53 CE MET 228 4.948 20.224 17.154 1.000 9.02
ATOM   54 N LYS 229 10.299 18.316 15.179 1.000 8.14

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Fig. 10B

ATOM	55	CA	LYS	229	11.713	17.914	15.252	1.000	11.79
ATOM	56	C	LYS	229	12.639	19.107	15.347	1.000	10.88
ATOM	57	O	LYS	229	13.829	18.947	15.663	1.000	10.45
ATOM	58	CB	LYS	229	12.080	17.121	13.971	1.000	18.00
ATOM	59	CG	LYS	229	11.375	15.798	13.842	1.000	32.21
ATOM	60	CD	LYS	229	11.493	15.266	12.410	1.000	41.37
ATOM	61	CE	LYS	229	10.917	13.845	12.329	1.000	50.20
ATOM	62	NZ	LYS	229	9.908	13.743	11.215	1.000	56.49
ATOM	63	N	SER	230	12.174	20.317	15.039	1.000	8.43
ATOM	64	CA	SER	230	13.043	21.473	15.052	1.000	7.26
ATOM	65	C	SER	230	13.552	21.769	16.463	1.000	8.60
ATOM	66	O	SER	230	12.881	21.474	17.450	1.000	7.34
ATOM	67	CB	SER	230	12.453	22.675	14.387	1.000	7.61
ATOM	68	OG	SER	230	11.324	23.202	15.105	1.000	7.96
ATOM	69	N	LYS	231	14.704	22.401	16.556	1.000	7.42
ATOM	70	CA	LYS	231	15.323	22.793	17.808	1.000	7.18
ATOM	71	C	LYS	231	15.825	24.206	17.712	1.000	8.35
ATOM	72	O	LYS	231	16.861	24.429	17.057	1.000	8.58
ATOM	73	CB	LYS	231	16.446	21.820	18.219	1.000	10.62
ATOM	74	CG	LYS	231	15.895	20.483	18.671	1.000	15.44
ATOM	75	CD	LYS	231	16.699	19.816	19.742	1.000	24.38
ATOM	76	CE	LYS	231	15.960	18.580	20.277	1.000	21.04
ATOM	77	NZ	LYS	231	16.927	17.562	20.739	1.000	22.47
ATOM	78	N	PRO	232	15.123	25.179	18.225	1.000	7.16
ATOM	79	CA	PRO	232	13.928	25.036	19.050	1.000	6.87
ATOM	80	C	PRO	232	12.694	24.644	18.260	1.000	6.02
ATOM	81	O	PRO	232	12.641	24.773	17.033	1.000	6.22
ATOM	82	CB	PRO	232	13.732	26.486	19.565	1.000	9.03
ATOM	83	CG	PRO	232	14.319	27.326	18.477	1.000	12.03
ATOM	84	CD	PRO	232	15.539	26.542	18.016	1.000	7.43
ATOM	85	N	ARG	233	11.704	24.116	18.966	1.000	6.56
ATOM	86	CA	ARG	233	10.437	23.742	18.325	1.000	6.23
ATOM	87	C	ARG	233	9.736	24.978	17.778	1.000	6.11
ATOM	88	O	ARG	233	8.991	24.876	16.775	1.000	5.84
ATOM	89	CB	ARG	233	9.491	23.157	19.392	1.000	7.23
ATOM	90	CG	ARG	233	9.928	21.924	20.033	1.000	8.65
ATOM	91	CD	ARG	233	10.178	20.786	19.042	1.000	10.08
ATOM	92	NE	ARG	233	10.438	19.548	19.774	1.000	7.49
ATOM	93	CZ	ARG	233	11.395	18.695	19.554	1.000	9.39
ATOM	94	NH1	ARG	233	12.307	18.841	18.590	1.000	10.30
ATOM	95	NH2	ARG	233	11.491	17.604	20.331	1.000	10.82
ATOM	96	N	GLY	234	9.880	26.095	18.462	1.000	5.53
ATOM	97	CA	GLY	234	9.199	27.318	18.119	1.000	6.44
ATOM	98	C	GLY	234	9.257	28.284	19.304	1.000	5.47
ATOM	99	O	GLY	234	9.887	27.936	20.320	1.000	5.49
ATOM	100	N	TYR	235	8.596	29.398	19.166	1.000	4.76
ATOM	101	CA	TYR	235	8.474	30.371	20.255	1.000	5.42
ATOM	102	C	TYR	235	7.294	29.981	21.164	1.000	5.41
ATOM	103	O	TYR	235	6.300	29.436	20.685	1.000	5.93
ATOM	104	CB	TYR	235	8.231	31.767	19.743	1.000	6.05
ATOM	105	CG	TYR	235	9.351	32.297	18.888	1.000	7.08
ATOM	106	CD1	TYR	235	10.576	32.585	19.474	1.000	8.58
ATOM	107	CD2	TYR	235	9.163	32.476	17.526	1.000	7.82
ATOM	108	CE1	TYR	235	11.607	33.087	18.670	1.000	11.08
ATOM	109	CE2	TYR	235	10.191	32.942	16.733	1.000	9.64
ATOM	110	CZ	TYR	235	11.390	33.245	17.328	1.000	10.57
ATOM	111	OH	TYR	235	12.437	33.707	16.519	1.000	15.58
ATOM	112	N	CYS	236	7.464	30.230	22.440	1.000	4.75
ATOM	113	CA	CYS	236	6.408	30.081	23.419	1.000	4.03
ATOM	114	C	CYS	236	6.249	31.451	24.100	1.000	4.03
ATOM	115	O	CYS	236	7.111	31.787	24.934	1.000	5.55
ATOM	116	CB	CYS	236	6.671	28.996	24.404	1.000	5.04

Fig. 10C

ATOM	117	SG	CYS	236	5.413	28.869	25.737	1.000	6.25	
ANISOU	117	SG	CYS	236	624	970	782	-53	47	133
ATOM	118	N	LEU	237	5.302	32.258	23.702	1.000	4.50	
ATOM	119	CA	LEU	237	5.063	33.555	24.316	1.000	4.81	
ATOM	120	C	LEU	237	4.339	33.380	25.649	1.000	6.66	
ATOM	121	O	LEU	237	3.456	32.523	25.790	1.000	6.63	
ATOM	122	CB	LEU	237	4.140	34.435	23.444	1.000	7.25	
ATOM	123	CG	LEU	237	4.499	34.628	22.022	1.000	8.78	
ATOM	124	CD1	LEU	237	3.655	35.728	21.378	1.000	9.81	
ATOM	125	CD2	LEU	237	5.963	34.821	21.750	1.000	11.08	
ATOM	126	N	ILE	238	4.737	34.200	26.630	1.000	5.31	
ATOM	127	CA	ILE	238	3.964	34.195	27.887	1.000	5.54	
ATOM	128	C	ILE	238	3.604	35.636	28.218	1.000	7.39	
ATOM	129	O	ILE	238	4.529	36.440	28.437	1.000	11.12	
ATOM	130	CB	ILE	238	4.747	33.580	29.059	1.000	7.02	
ATOM	131	CG1	ILE	238	5.190	32.167	28.754	1.000	7.28	
ATOM	132	CG2	ILE	238	3.873	33.615	30.319	1.000	8.75	
ATOM	133	CD1	ILE	238	6.122	31.574	29.818	1.000	8.23	
ATOM	134	N	ILE	239	2.350	35.974	28.201	1.000	6.16	
ATOM	135	CA	ILE	239	1.862	37.307	28.604	1.000	6.09	
ATOM	136	C	ILE	239	1.328	37.162	30.018	1.000	5.05	
ATOM	137	O	ILE	239	0.363	36.427	30.264	1.000	6.19	
ATOM	138	CB	ILE	239	0.732	37.771	27.659	1.000	7.26	
ATOM	139	CG1	ILE	239	1.165	37.825	26.207	1.000	13.35	
ATOM	140	CG2	ILE	239	0.131	39.071	28.145	1.000	9.43	
ATOM	141	CD1AILE	239	0.203	38.336	25.205	0.400	18.14		
ATOM	142	CD1BILE	239	1.988	38.697	25.778	0.600	12.64		
ATOM	143	N	ASN	240	2.072	37.753	30.955	1.000	5.51	
ATOM	144	CA	ASN	240	1.825	37.523	32.378	1.000	5.64	
ATOM	145	C	ASN	240	1.371	38.800	33.070	1.000	5.58	
ATOM	146	O	ASN	240	2.159	39.709	33.390	1.000	6.80	
ATOM	147	CB	ASN	240	3.204	37.079	32.961	1.000	5.93	
ATOM	148	CG	ASN	240	3.167	36.824	34.431	1.000	9.18	
ATOM	149	OD1	ASN	240	4.183	37.132	35.143	1.000	14.11	
ATOM	150	ND2	ASN	240	2.114	36.310	34.917	1.000	6.68	
ATOM	151	N	ASN	241	0.059	38.929	33.250	1.000	5.08	
ATOM	152	CA	ASN	241	-0.538	40.138	33.768	1.000	4.85	
ATOM	153	C	ASN	241	-0.815	40.055	35.252	1.000	4.75	
ATOM	154	O	ASN	241	-1.645	39.275	35.701	1.000	4.92	
ATOM	155	CB	ASN	241	-1.815	40.494	33.002	1.000	4.93	
ATOM	156	CG	ASN	241	-1.497	41.113	31.655	1.000	5.55	
ATOM	157	OD1	ASN	241	-0.356	41.352	31.313	1.000	5.11	
ATOM	158	ND2	ASN	241	-2.555	41.372	30.885	1.000	5.75	
ATOM	159	N	HIS	242	-0.129	40.900	36.015	1.000	5.40	
ATOM	160	CA	HIS	242	-0.262	40.969	37.449	1.000	5.50	
ATOM	161	C	HIS	242	-0.977	42.212	37.977	1.000	5.01	
ATOM	162	O	HIS	242	-1.829	42.115	38.823	1.000	5.67	
ATOM	163	CB	HIS	242	1.112	40.854	38.136	1.000	5.40	
ATOM	164	CG	HIS	242	1.067	41.112	39.589	1.000	6.56	
ATOM	165	ND1	HIS	242	1.355	42.348	40.149	1.000	8.69	
ATOM	166	CD2	HIS	242	0.667	40.321	40.601	1.000	6.48	
ATOM	167	CE1	HIS	242	1.162	42.261	41.439	1.000	8.88	
ATOM	168	NE2	HIS	242	0.742	41.046	41.758	1.000	8.42	
ATOM	169	N	ASN	243	-0.493	43.380	37.545	1.000	6.14	
ATOM	170	CA	ASN	243	-0.854	44.665	38.117	1.000	6.25	
ATOM	171	C	ASN	243	-2.000	45.347	37.386	1.000	5.22	
ATOM	172	O	ASN	243	-1.826	45.804	36.263	1.000	7.66	
ATOM	173	CB	ASN	243	0.387	45.585	38.046	1.000	8.86	
ATOM	174	CG	ASN	243	0.133	46.928	38.687	1.000	9.83	
ATOM	175	OD1	ASN	243	-0.941	47.279	39.117	1.000	10.27	
ATOM	176	ND2	ASN	243	1.234	47.696	38.809	1.000	23.38	
ATOM	177	N	PHE	244	-3.156	45.403	38.012	1.000	6.86	

Fig. 10D

ATOM	178	CA	PHE	244	-4.354	45.971	37.449	1.000	6.09
ATOM	179	C	PHE	244	-4.722	47.319	38.032	1.000	9.04
ATOM	180	O	PHE	244	-5.877	47.772	37.942	1.000	8.78
ATOM	181	CB	PHE	244	-5.522	44.961	37.594	1.000	8.26
ATOM	182	CG	PHE	244	-5.371	43.802	36.604	1.000	6.23
ATOM	183	CD1	PHE	244	-4.519	42.762	36.866	1.000	5.29
ATOM	184	CD2	PHE	244	-6.052	43.826	35.389	1.000	6.71
ATOM	185	CE1	PHE	244	-4.304	41.763	35.931	1.000	5.76
ATOM	186	CE2	PHE	244	-5.854	42.812	34.483	1.000	5.77
ATOM	187	CZ	PHE	244	-4.963	41.809	34.736	1.000	5.79
ATOM	188	N	ALA	245	-3.718	48.037	38.527	1.000	10.62
ATOM	189	CA	ALA	245	-4.003	49.400	39.036	1.000	11.62
ATOM	190	C	ALA	245	-4.585	50.283	37.930	1.000	13.45
ATOM	191	O	ALA	245	-5.506	51.087	38.218	1.000	17.73
ATOM	192	CB	ALA	245	-2.675	49.967	39.528	1.000	11.15
ATOM	193	N	LYS	246	-4.109	50.197	36.711	1.000	11.81
ATOM	194	CA	LYS	246	-4.617	51.051	35.621	1.000	13.99
ATOM	195	C	LYS	246	-6.106	50.790	35.395	1.000	17.21
ATOM	196	O	LYS	246	-6.895	51.693	35.176	1.000	15.38
ATOM	197	CB	LYS	246	-3.840	50.949	34.382	1.000	15.16
ATOM	198	CG	LYS	246	-2.447	51.492	34.250	1.000	20.03
ATOM	199	CD	LYS	246	-1.812	51.037	32.942	1.000	24.17
ATOM	200	CE	LYS	246	-0.299	51.099	32.976	1.000	26.04
ATOM	201	NZ	LYS	246	0.259	50.921	31.599	1.000	29.77
ATOM	202	N	ALA	247	-6.488	49.503	35.447	1.000	11.79
ATOM	203	CA	ALA	247	-7.913	49.167	35.271	1.000	12.45
ATOM	204	C	ALA	247	-8.746	49.735	36.414	1.000	13.66
ATOM	205	O	ALA	247	-9.843	50.279	36.193	1.000	14.42
ATOM	206	CB	ALA	247	-8.066	47.661	35.207	1.000	10.04
ATOM	207	N	ARG	248	-8.245	49.600	37.641	1.000	11.89
ATOM	208	CA	ARG	248	-8.968	50.127	38.785	1.000	14.27
ATOM	209	C	ARG	248	-9.130	51.646	38.670	1.000	16.12
ATOM	210	O	ARG	248	-10.179	52.170	39.062	1.000	21.73
ATOM	211	CB	ARG	248	-8.258	49.781	40.098	1.000	14.38
ATOM	212	CG	ARG	248	-8.345	48.303	40.456	1.000	14.91
ATOM	213	CD	ARG	248	-7.863	48.058	41.878	1.000	15.50
ATOM	214	NE	ARG	248	-6.429	48.235	42.016	1.000	13.96
ATOM	215	CZ	ARG	248	-5.495	47.336	41.763	1.000	10.36
ATOM	216	NH1	ARG	248	-5.857	46.128	41.308	1.000	11.60
ATOM	217	NH2	ARG	248	-4.209	47.577	41.940	1.000	13.87
ATOM	218	N	GLU	249	-8.127	52.316	38.137	1.000	14.41
ATOM	219	CA	GLU	249	-8.175	53.742	37.941	1.000	20.65
ATOM	220	C	GLU	249	-9.005	54.227	36.791	1.000	25.44
ATOM	221	O	GLU	249	-9.584	55.339	36.874	1.000	27.13
ATOM	222	CB	GLU	249	-6.802	54.397	37.953	1.000	20.02
ATOM	223	CG	GLU	249	-6.833	55.886	38.280	1.000	34.77
ATOM	224	CD	GLU	249	-6.998	56.780	37.081	1.000	44.19
ATOM	225	OE1	GLU	249	-6.207	56.677	36.123	1.000	55.90
ATOM	226	OE2	GLU	249	-7.958	57.590	37.073	1.000	59.17
ATOM	227	N	LYS	250	-9.055	53.520	35.654	1.000	20.74
ATOM	228	CA	LYS	250	-9.702	54.030	34.477	1.000	20.46
ATOM	229	C	LYS	250	-11.076	53.471	34.165	1.000	22.04
ATOM	230	O	LYS	250	-11.834	54.107	33.397	1.000	20.81
ATOM	231	CB	LYS	250	-8.834	53.904	33.232	1.000	24.11
ATOM	232	CG	LYS	250	-7.351	53.980	33.374	1.000	33.83
ATOM	233	CD	LYS	250	-6.625	52.994	32.449	1.000	44.61
ATOM	234	CE	LYS	250	-6.053	53.669	31.223	1.000	49.63
ATOM	235	NZ	LYS	250	-6.607	53.129	29.949	1.000	54.83
ATOM	236	N	VAL	251	-11.369	52.249	34.563	1.000	15.80
ATOM	237	CA	VAL	251	-12.629	51.615	34.152	1.000	15.33
ATOM	238	C	VAL	251	-13.551	51.466	35.337	1.000	16.49
ATOM	239	O	VAL	251	-13.312	50.695	36.256	1.000	15.46

Fig. 10 E

ATOM	240	CB	VAL	251	-12.372	50.258	33.480	1.000	15.25
ATOM	241	CG1	VAL	251	-13.677	49.660	32.942	1.000	14.86
ATOM	242	CG2	VAL	251	-11.337	50.370	32.374	1.000	17.97
ATOM	243	N	PRO	252	-14.613	52.305	35.368	1.000	18.93
ATOM	244	CA	PRO	252	-15.504	52.296	36.523	1.000	21.43
ATOM	245	C	PRO	252	-15.956	50.981	37.021	1.000	18.31
ATOM	246	O	PRO	252	-15.952	50.664	38.225	1.000	22.39
ATOM	247	CB	PRO	252	-16.685	53.167	36.052	1.000	27.23
ATOM	248	CG	PRO	252	-16.029	54.149	35.121	1.000	26.66
ATOM	249	CD	PRO	252	-15.011	53.315	34.366	1.000	25.95
ATOM	250	N	LYS	253	-16.374	50.058	36.124	1.000	19.95
ATOM	251	CA	LYS	253	-16.875	48.793	36.658	1.000	17.92
ATOM	252	C	LYS	253	-15.781	47.936	37.263	1.000	17.60
ATOM	253	O	LYS	253	-16.039	46.941	37.935	1.000	17.78
ATOM	254	CB	LYS	253	-17.643	47.998	35.613	1.000	21.68
ATOM	255	CG	LYS	253	-16.796	47.556	34.419	1.000	25.26
ATOM	256	CD	LYS	253	-17.568	46.544	33.583	1.000	25.53
ATOM	257	CE	LYS	253	-16.780	46.070	32.381	1.000	25.14
ATOM	258	NZ	LYS	253	-17.705	45.459	31.360	1.000	41.75
ATOM	259	N	LEU	254	-14.537	48.272	36.946	1.000	16.21
ATOM	260	CA	LEU	254	-13.410	47.472	37.416	1.000	14.75
ATOM	261	C	LEU	254	-12.728	48.128	38.595	1.000	15.74
ATOM	262	O	LEU	254	-11.568	47.872	38.907	1.000	14.94
ATOM	263	CB	LEU	254	-12.430	47.241	36.276	1.000	10.93
ATOM	264	CG	LEU	254	-12.937	46.530	35.024	1.000	14.08
ATOM	265	CD1	LEU	254	-11.795	46.340	34.024	1.000	11.92
ATOM	266	CD2	LEU	254	-13.559	45.190	35.328	1.000	14.69
ATOM	267	N	HIS	255	-13.488	48.987	39.309	1.000	16.78
ATOM	268	CA	HIS	255	-12.942	49.650	40.463	1.000	17.91
ATOM	269	C	HIS	255	-12.296	48.710	41.459	1.000	14.66
ATOM	270	O	HIS	255	-11.345	49.150	42.153	1.000	17.46
ATOM	271	CB	HIS	255	-14.008	50.500	41.183	1.000	22.22
ATOM	272	CG	HIS	255	-15.229	49.710	41.528	1.000	23.05
ATOM	273	ND1	HIS	255	-15.340	48.985	42.691	1.000	28.12
ATOM	274	CD2	HIS	255	-16.351	49.468	40.811	1.000	29.11
ATOM	275	CE1	HIS	255	-16.504	48.355	42.702	1.000	31.31
ATOM	276	NE2	HIS	255	-17.142	48.644	41.582	1.000	33.11
ATOM	277	N	SER	256	-12.775	47.491	41.603	1.000	12.42
ATOM	278	CA	SER	256	-12.228	46.565	42.568	1.000	20.13
ATOM	279	C	SER	256	-11.546	45.341	42.010	1.000	15.28
ATOM	280	O	SER	256	-11.303	44.353	42.712	1.000	18.37
ATOM	281	CB	SER	256	-13.327	46.151	43.583	1.000	31.09
ATOM	282	OG	SER	256	-13.503	47.240	44.514	1.000	37.00
ATOM	283	N	ILE	257	-11.224	45.356	40.716	1.000	13.95
ATOM	284	CA	ILE	257	-10.499	44.208	40.128	1.000	13.37
ATOM	285	C	ILE	257	-9.171	44.060	40.826	1.000	14.37
ATOM	286	O	ILE	257	-8.479	45.054	41.098	1.000	14.98
ATOM	287	CB	ILE	257	-10.347	44.338	38.629	1.000	16.14
ATOM	288	CG1	ILE	257	-10.114	43.033	37.877	1.000	15.57
ATOM	289	CG2	ILE	257	-9.392	45.413	38.192	1.000	16.68
ATOM	290	CD1	ILE	257	-10.056	43.217	36.363	1.000	13.32
ATOM	291	N	ARG	258	-8.807	42.847	41.213	1.000	11.32
ATOM	292	CA	ARG	258	-7.613	42.657	42.006	1.000	10.43
ATOM	293	C	ARG	258	-6.383	42.317	41.210	1.000	9.77
ATOM	294	O	ARG	258	-6.421	41.705	40.135	1.000	9.47
ATOM	295	CB	ARG	258	-7.863	41.525	43.033	1.000	13.26
ATOM	296	CG	ARG	258	-8.819	41.922	44.151	1.000	18.51
ATOM	297	CD	ARG	258	-8.999	40.755	45.127	1.000	29.04
ATOM	298	NE	ARG	258	-9.607	41.176	46.379	1.000	51.07
ATOM	299	CZ	ARG	258	-10.877	41.511	46.546	1.000	64.55
ATOM	300	NH1	ARG	258	-11.723	41.486	45.521	1.000	82.39
ATOM	301	NH2	ARG	258	-11.323	41.879	47.745	1.000	73.14

Fig. 10F

ATOM	302	N	ASP	259	-5.225	42.630	41.794	1.000	7.68
ATOM	303	CA	ASP	259	-3.964	42.217	41.202	1.000	8.47
ATOM	304	C	ASP	259	-3.861	40.695	41.272	1.000	8.61
ATOM	305	O	ASP	259	-4.388	40.070	42.210	1.000	11.29
ATOM	306	CB	ASP	259	-2.783	42.829	41.961	1.000	7.67
ATOM	307	CG	ASP	259	-2.654	44.308	41.748	1.000	9.75
ATOM	308	OD1	ASP	259	-3.288	44.914	40.894	1.000	8.00
ATOM	309	OD2	ASP	259	-1.843	44.925	42.508	1.000	12.55
ATOM	310	N	ARG	260	-3.179	40.079	40.327	1.000	5.63
ATOM	311	CA	ARG	260	-3.164	38.633	40.210	1.000	5.21
ATOM	312	C	ARG	260	-2.029	37.975	40.934	1.000	4.92
ATOM	313	O	ARG	260	-1.147	37.362	40.363	1.000	5.24
ATOM	314	CB	ARG	260	-3.278	38.214	38.748	1.000	4.85
ATOM	315	CG	ARG	260	-4.574	38.732	38.099	1.000	5.22
ATOM	316	CD	ARG	260	-4.701	38.261	36.632	1.000	4.62
ATOM	317	NE	ARG	260	-4.666	36.830	36.548	1.000	4.67
ATOM	318	CZ	ARG	260	-3.638	36.040	36.251	1.000	3.91
ATOM	319	NH1	ARG	260	-2.499	36.536	35.830	1.000	4.47
ATOM	320	NH2	ARG	260	-3.777	34.732	36.394	1.000	4.95
ATOM	321	N	ASN	261	-2.020	38.172	42.261	1.000	5.85
ATOM	322	CA	ASN	261	-0.929	37.633	43.077	1.000	5.01
ATOM	323	C	ASN	261	-0.751	36.147	42.824	1.000	4.52
ATOM	324	O	ASN	261	-1.646	35.355	42.801	1.000	5.64
ATOM	325	CB	ASN	261	-1.185	37.921	44.545	1.000	6.51
ATOM	326	CG	ASN	261	-1.105	39.410	44.892	1.000	7.99
ATOM	327	OD1	ASN	261	-0.317	40.145	44.294	1.000	11.57
ATOM	328	ND2	ASN	261	-1.844	39.784	45.907	1.000	13.60
ATOM	329	N	GLY	262	0.535	35.764	42.637	1.000	5.50
ATOM	330	CA	GLY	262	0.897	34.421	42.361	1.000	6.65
ATOM	331	C	GLY	262	1.087	34.063	40.909	1.000	4.86
ATOM	332	O	GLY	262	1.504	32.957	40.587	1.000	5.75
ATOM	333	N	THR	263	0.690	34.949	39.996	1.000	5.10
ATOM	334	CA	THR	263	0.783	34.648	38.575	1.000	4.72
ATOM	335	C	THR	263	2.176	34.325	38.115	1.000	4.23
ATOM	336	O	THR	263	2.369	33.494	37.209	1.000	4.29
ATOM	337	CB	THR	263	0.131	35.762	37.750	1.000	4.03
ATOM	338	OG1	THR	263	0.075	35.353	36.387	1.000	4.78
ATOM	339	CG2	THR	263	0.863	37.080	37.848	1.000	5.80
ATOM	340	N	HIS	264	3.212	34.856	38.760	1.000	4.01
ATOM	341	CA	HIS	264	4.574	34.521	38.369	1.000	3.50
ATOM	342	C	HIS	264	4.849	33.048	38.575	1.000	3.22
ATOM	343	O	HIS	264	5.702	32.474	37.870	1.000	4.90
ATOM	344	CB	HIS	264	5.599	35.362	39.129	1.000	6.17
ATOM	345	CG	HIS	264	5.658	35.059	40.605	1.000	5.40
ATOM	346	ND1	HIS	264	4.668	35.496	41.459	1.000	4.98
ATOM	347	CD2	HIS	264	6.590	34.374	41.331	1.000	4.96
ATOM	348	CE1	HIS	264	5.018	35.076	42.697	1.000	5.96
ATOM	349	NE2	HIS	264	6.143	34.415	42.621	1.000	6.28
ATOM	350	N	LEU	265	4.166	32.353	39.474	1.000	3.52
ATOM	351	CA	LEU	265	4.387	30.920	39.656	1.000	4.09
ATOM	352	C	LEU	265	3.941	30.124	38.428	1.000	3.98
ATOM	353	O	LEU	265	4.511	29.103	38.086	1.000	4.54
ATOM	354	CB	LEU	265	3.626	30.415	40.904	1.000	4.04
ATOM	355	CG	LEU	265	4.111	31.051	42.232	1.000	4.62
ATOM	356	CD1	LEU	265	3.225	30.480	43.371	1.000	6.32
ATOM	357	CD2	LEU	265	5.539	30.817	42.525	1.000	5.54
ATOM	358	N	ASP	266	2.918	30.652	37.749	1.000	3.62
ATOM	359	CA	ASP	266	2.455	30.018	36.479	1.000	3.37
ATOM	360	C	ASP	266	3.436	30.353	35.366	1.000	3.29
ATOM	361	O	ASP	266	3.764	29.481	34.557	1.000	3.85
ATOM	362	CB	ASP	266	1.086	30.564	36.117	1.000	3.63
ATOM	363	CG	ASP	266	-0.086	29.967	36.825	1.000	4.13

Fig. 10 G

ATOM	364	OD1	ASP	266	0.068	28.999	37.593	1.000	4.89
ATOM	365	OD2	ASP	266	-1.219	30.397	36.453	1.000	6.12
ATOM	366	N	ALA	267	3.889	31.589	35.283	1.000	3.67
ATOM	367	CA	ALA	267	4.867	31.940	34.231	1.000	3.94
ATOM	368	C	ALA	267	6.091	31.070	34.388	1.000	4.90
ATOM	369	O	ALA	267	6.673	30.617	33.392	1.000	5.37
ATOM	370	CB	ALA	267	5.207	33.399	34.279	1.000	6.35
ATOM	371	N	GLY	268	6.535	30.880	35.628	1.000	5.57
ATOM	372	CA	GLY	268	7.712	30.050	35.857	1.000	5.40
ATOM	373	C	GLY	268	7.489	28.611	35.498	1.000	5.27
ATOM	374	O	GLY	268	8.345	27.947	34.882	1.000	4.64
ATOM	375	N	ALA	269	6.333	28.054	35.885	1.000	4.29
ATOM	376	CA	ALA	269	6.018	26.672	35.553	1.000	4.23
ATOM	377	C	ALA	269	5.970	26.466	34.034	1.000	4.02
ATOM	378	O	ALA	269	6.468	25.461	33.511	1.000	4.67
ATOM	379	CB	ALA	269	4.732	26.241	36.194	1.000	4.89
ATOM	380	N	LEU	270	5.357	27.414	33.320	1.000	3.87
ATOM	381	CA	LEU	270	5.285	27.293	31.859	1.000	4.90
ATOM	382	C	LEU	270	6.683	27.406	31.250	1.000	5.44
ATOM	383	O	LEU	270	6.999	26.712	30.257	1.000	4.44
ATOM	384	CB	LEU	270	4.394	28.435	31.311	1.000	4.53
ATOM	385	CG	LEU	270	2.884	28.207	31.582	1.000	3.88
ATOM	386	CD1	LEU	270	2.152	29.533	31.388	1.000	5.68
ATOM	387	CD2	LEU	270	2.323	27.140	30.674	1.000	4.64
ATOM	388	N	THR	271	7.504	28.258	31.808	1.000	5.17
ATOM	389	CA	THR	271	8.887	28.397	31.292	1.000	5.53
ATOM	390	C	THR	271	9.625	27.096	31.472	1.000	5.89
ATOM	391	O	THR	271	10.260	26.581	30.531	1.000	7.15
ATOM	392	CB	THR	271	9.584	29.556	32.002	1.000	5.35
ATOM	393	OG1	THR	271	8.939	30.765	31.714	1.000	6.57
ATOM	394	CG2	THR	271	11.054	29.647	31.595	1.000	6.32
ATOM	395	N	THR	272	9.618	26.527	32.669	1.000	5.86
ATOM	396	CA	THR	272	10.291	25.286	32.935	1.000	7.47
ATOM	397	C	THR	272	9.819	24.184	31.989	1.000	5.44
ATOM	398	O	THR	272	10.614	23.442	31.378	1.000	6.79
ATOM	399	CB	THR	272	9.983	24.796	34.411	1.000	8.02
ATOM	400	OG1	THR	272	10.647	25.698	35.306	1.000	12.63
ATOM	401	CG2	THR	272	10.601	23.412	34.572	1.000	18.81
ATOM	402	N	THR	273	8.499	24.066	31.883	1.000	5.05
ATOM	403	CA	THR	273	7.860	23.010	31.112	1.000	5.23
ATOM	404	C	THR	273	8.185	23.103	29.641	1.000	4.72
ATOM	405	O	THR	273	8.637	22.145	29.017	1.000	5.79
ATOM	406	CB	THR	273	6.328	23.036	31.339	1.000	6.05
ATOM	407	OG1	THR	273	6.056	22.843	32.723	1.000	7.52
ATOM	408	CG2	THR	273	5.625	21.978	30.539	1.000	7.39
ATOM	409	N	PHE	274	7.998	24.277	29.072	1.000	4.99
ATOM	410	CA	PHE	274	8.209	24.448	27.650	1.000	5.20
ATOM	411	C	PHE	274	9.650	24.559	27.246	1.000	4.20
ATOM	412	O	PHE	274	10.055	24.150	26.148	1.000	5.49
ATOM	413	CB	PHE	274	7.314	25.528	27.047	1.000	4.40
ATOM	414	CG	PHE	274	5.870	25.053	26.931	1.000	4.86
ATOM	415	CD1	PHE	274	5.546	24.038	26.039	1.000	7.04
ATOM	416	CD2	PHE	274	4.851	25.566	27.720	1.000	5.71
ATOM	417	CE1	PHE	274	4.262	23.567	25.906	1.000	8.16
ATOM	418	CE2	PHE	274	3.575	25.053	27.615	1.000	5.98
ATOM	419	CZ	PHE	274	3.269	24.038	26.750	1.000	6.28
ATOM	420	N	GLU	275	10.541	24.982	28.156	1.000	5.71
ATOM	421	CA	GLU	275	11.977	24.914	27.842	1.000	6.03
ATOM	422	C	GLU	275	12.419	23.458	27.827	1.000	7.45
ATOM	423	O	GLU	275	13.207	23.075	26.941	1.000	7.49
ATOM	424	CB	GLU	275	12.774	25.686	28.917	1.000	8.30
ATOM	425	CG	GLU	275	12.752	27.166	28.610	1.000	10.18

Fig. 10 H

ATOM	426	CD	GLU	275	13.735	27.998	29.395	1.000	14.02
ATOM	427	OE1	GLU	275	14.193	27.524	30.466	1.000	13.58
ATOM	428	OE2	GLU	275	14.003	29.153	28.988	1.000	13.41
ATOM	429	N	GLU	276	11.952	22.644	28.704	1.000	6.39
ATOM	430	CA	GLU	276	12.232	21.215	28.744	1.000	8.23
ATOM	431	C	GLU	276	11.769	20.561	27.446	1.000	10.38
ATOM	432	O	GLU	276	12.415	19.608	26.968	1.000	10.97
ATOM	433	CB	GLU	276	11.496	20.621	29.931	1.000	12.98
ATOM	434	CG	GLU	276	11.738	19.223	30.345	1.000	24.10
ATOM	435	CD	GLU	276	11.178	19.000	31.776	1.000	22.88
ATOM	436	OE1	GLU	276	11.835	19.476	32.712	1.000	32.40
ATOM	437	OE2	GLU	276	10.070	18.472	31.863	1.000	23.50
ATOM	438	N	LEU	277	10.697	21.092	26.861	1.000	6.23
ATOM	439	CA	LEU	277	10.142	20.627	25.612	1.000	8.49
ATOM	440	C	LEU	277	10.749	21.269	24.397	1.000	6.22
ATOM	441	O	LEU	277	10.231	21.091	23.278	1.000	7.20
ATOM	442	CB	LEU	277	8.626	20.664	25.634	1.000	7.76
ATOM	443	CG	LEU	277	7.947	19.789	26.678	1.000	9.62
ATOM	444	CD1	LEU	277	6.496	20.098	26.873	1.000	11.76
ATOM	445	CD2	LEU	277	8.170	18.317	26.407	1.000	14.67
ATOM	446	N	HIS	278	11.792	22.059	24.553	1.000	5.89
ATOM	447	CA	HIS	278	12.564	22.604	23.478	1.000	6.09
ATOM	448	C	HIS	278	12.017	23.835	22.825	1.000	5.64
ATOM	449	O	HIS	278	12.387	24.167	21.689	1.000	6.63
ATOM	450	CB	HIS	278	13.001	21.555	22.472	1.000	7.52
ATOM	451	CG	HIS	278	13.648	20.361	23.086	1.000	7.88
ATOM	452	ND1	HIS	278	14.912	20.440	23.650	1.000	9.40
ATOM	453	CD2	HIS	278	13.226	19.109	23.265	1.000	8.41
ATOM	454	CE1	HIS	278	15.207	19.225	24.140	1.000	10.67
ATOM	455	NE2	HIS	278	14.205	18.424	23.940	1.000	11.52
ATOM	456	N	PHE	279	11.158	24.587	23.497	1.000	5.48
ATOM	457	CA	PHE	279	10.668	25.832	23.016	1.000	5.11
ATOM	458	C	PHE	279	11.534	27.008	23.477	1.000	5.33
ATOM	459	O	PHE	279	12.168	26.904	24.553	1.000	7.03
ATOM	460	CB	PHE	279	9.211	26.103	23.435	1.000	4.58
ATOM	461	CG	PHE	279	8.219	25.239	22.640	1.000	5.75
ATOM	462	CD1	PHE	279	8.037	23.910	22.955	1.000	5.37
ATOM	463	CD2	PHE	279	7.509	25.789	21.593	1.000	4.93
ATOM	464	CE1	PHE	279	7.177	23.111	22.217	1.000	6.34
ATOM	465	CE2	PHE	279	6.661	24.982	20.837	1.000	6.55
ATOM	466	CZ	PHE	279	6.486	23.676	21.158	1.000	6.18
ATOM	467	N	GLU	280	11.542	28.082	22.753	1.000	5.34
ATOM	468	CA	GLU	280	12.211	29.337	23.095	1.000	6.24
ATOM	469	C	GLU	280	11.189	30.254	23.746	1.000	5.48
ATOM	470	O	GLU	280	10.226	30.696	23.089	1.000	5.97
ATOM	471	CB	GLU	280	12.826	29.982	21.858	1.000	8.11
ATOM	472	CG	GLU	280	13.704	31.193	22.136	1.000	15.33
ATOM	473	CD	GLU	280	14.357	31.760	20.887	1.000	24.81
ATOM	474	OE1	GLU	280	14.853	30.979	20.047	1.000	25.89
ATOM	475	OE2	GLU	280	14.377	33.005	20.731	1.000	36.17
ATOM	476	N	ILE	281	11.351	30.517	25.021	1.000	6.00
ATOM	477	CA	ILE	281	10.381	31.258	25.796	1.000	4.92
ATOM	478	C	ILE	281	10.537	32.751	25.682	1.000	6.32
ATOM	479	O	ILE	281	11.688	33.230	25.789	1.000	9.33
ATOM	480	CB	ILE	281	10.442	30.848	27.283	1.000	6.80
ATOM	481	CG1	ILE	281	10.554	29.381	27.545	1.000	9.07
ATOM	482	CG2	ILE	281	9.319	31.543	28.054	1.000	10.03
ATOM	483	CD1	ILE	281	9.510	28.511	26.873	1.000	10.06
ATOM	484	N	LYS	282	9.481	33.496	25.478	1.000	5.52
ATOM	485	CA	LYS	282	9.445	34.934	25.307	1.000	7.65
ATOM	486	C	LYS	282	8.406	35.532	26.256	1.000	6.54
ATOM	487	O	LYS	282	7.240	35.669	25.946	1.000	6.92

Fig. 10 I

ATOM	488	CB	LYS	282	9.063	35.286	23.851	1.000	7.89
ATOM	489	CG	LYS	282	10.004	34.704	22.815	1.000	8.84
ATOM	490	CD	LYS	282	11.377	35.400	22.899	1.000	13.03
ATOM	491	CE	LYS	282	12.155	35.167	21.610	1.000	20.93
ATOM	492	NZ	LYS	282	13.557	35.684	21.757	1.000	27.67
ATOM	493	N	PRO	283	8.855	35.885	27.450	1.000	7.20
ATOM	494	CA	PRO	283	7.964	36.438	28.465	1.000	7.40
ATOM	495	C	PRO	283	7.739	37.926	28.355	1.000	7.62
ATOM	496	O	PRO	283	8.652	38.683	27.969	1.000	9.99
ATOM	497	CB	PRO	283	8.700	36.073	29.775	1.000	11.66
ATOM	498	CG	PRO	283	10.137	36.199	29.396	1.000	12.65
ATOM	499	CD	PRO	283	10.236	35.685	27.981	1.000	10.56
ATOM	500	N	HIS	284	6.560	38.399	28.704	1.000	6.76
ATOM	501	CA	HIS	284	6.185	39.804	28.728	1.000	7.87
ATOM	502	C	HIS	284	5.239	40.020	29.914	1.000	9.39
ATOM	503	O	HIS	284	4.220	39.339	29.998	1.000	11.56
ATOM	504	CB	HIS	284	5.414	40.166	27.436	1.000	9.22
ATOM	505	CG	HIS	284	6.289	40.037	26.227	1.000	11.22
ATOM	506	ND1	HIS	284	7.145	41.063	25.838	1.000	16.33
ATOM	507	CD2	HIS	284	6.500	39.012	25.360	1.000	14.92
ATOM	508	CE1	HIS	284	7.805	40.672	24.774	1.000	16.33
ATOM	509	NE2	HIS	284	7.438	39.453	24.458	1.000	12.97
ATOM	510	N	ASP	285	5.628	40.874	30.845	1.000	9.91
ATOM	511	CA	ASP	285	4.859	41.096	32.049	1.000	8.00
ATOM	512	C	ASP	285	4.015	42.356	31.965	1.000	7.93
ATOM	513	O	ASP	285	4.485	43.381	31.431	1.000	9.89
ATOM	514	CB	ASP	285	5.797	41.195	33.253	1.000	9.46
ATOM	515	CG	ASP	285	6.538	39.972	33.647	1.000	15.17
ATOM	516	OD1	ASP	285	6.195	38.840	33.246	1.000	15.23
ATOM	517	OD2	ASP	285	7.491	40.096	34.503	1.000	20.04
ATOM	518	N	ASP	286	2.839	42.357	32.541	1.000	6.91
ATOM	519	CA	ASP	286	2.003	43.531	32.754	1.000	5.59
ATOM	520	C	ASP	286	1.711	44.300	31.511	1.000	8.05
ATOM	521	O	ASP	286	2.173	45.448	31.286	1.000	9.61
ATOM	522	CB	ASP	286	2.641	44.402	33.842	1.000	6.91
ATOM	523	CG	ASP	286	2.496	43.816	35.190	1.000	9.09
ATOM	524	OD1	ASP	286	1.568	43.059	35.464	1.000	7.47
ATOM	525	OD2	ASP	286	3.351	44.169	36.077	1.000	10.41
ATOM	526	N	CYS	287	0.911	43.712	30.626	1.000	5.81
ATOM	527	CA	CYS	287	0.589	44.201	29.338	1.000	6.79
ATOM	528	C	CYS	287	-0.816	44.777	29.205	1.000	5.70
ATOM	529	O	CYS	287	-1.783	44.098	29.542	1.000	5.98
ATOM	530	CB	CYS	287	0.790	43.148	28.248	1.000	6.09
ATOM	531	SG	CYS	287	2.445	42.490	28.083	1.000	9.66
ANISOU	531	SG	CYS	287	915	1355	1401	133	18 -249
ATOM	532	N	THR	288	-0.932	45.987	28.675	1.000	6.79
ATOM	533	CA	THR	288	-2.245	46.550	28.321	1.000	6.46
ATOM	534	C	THR	288	-2.699	45.870	27.021	1.000	7.62
ATOM	535	O	THR	288	-1.919	45.185	26.353	1.000	6.35
ATOM	536	CB	THR	288	-2.094	48.064	28.024	1.000	7.15
ATOM	537	OG1	THR	288	-1.239	48.191	26.896	1.000	7.72
ATOM	538	CG2	THR	288	-1.532	48.810	29.215	1.000	9.44
ATOM	539	N	VAL	289	-3.968	46.091	26.654	1.000	6.92
ATOM	540	CA	VAL	289	-4.434	45.492	25.406	1.000	7.63
ATOM	541	C	VAL	289	-3.620	45.916	24.220	1.000	6.97
ATOM	542	O	VAL	289	-3.227	45.082	23.392	1.000	7.66
ATOM	543	CB	VAL	289	-5.938	45.792	25.162	1.000	9.91
ATOM	544	CG1	VAL	289	-6.327	45.303	23.769	1.000	11.00
ATOM	545	CG2	VAL	289	-6.768	45.078	26.221	1.000	9.09
ATOM	546	N	GLU	290	-3.327	47.213	24.078	1.000	8.17
ATOM	547	CA	GLU	290	-2.526	47.664	22.933	1.000	10.31
ATOM	548	C	GLU	290	-1.154	47.022	22.936	1.000	8.52

Fig. 10 J

ATOM	549	O	GLU	290	-0.591	46.689	21.898	1.000	7.97
ATOM	550	CB	GLU	290	-2.379	49.201	22.974	1.000	13.43
ATOM	551	CG	GLU	290	-3.586	49.946	22.447	1.000	27.89
ATOM	552	CD	GLU	290	-3.438	51.458	22.579	1.000	43.01
ATOM	553	OE1	GLU	290	-2.399	51.995	22.146	1.000	49.63
ATOM	554	OE2	GLU	290	-4.363	52.092	23.136	1.000	66.94
ATOM	555	N	GLN	291	-0.572	46.862	24.116	1.000	6.68
ATOM	556	CA	GLN	291	0.735	46.201	24.194	1.000	8.34
ATOM	557	C	GLN	291	0.654	44.743	23.776	1.000	6.75
ATOM	558	O	GLN	291	1.566	44.216	23.136	1.000	7.09
ATOM	559	CB	GLN	291	1.320	46.368	25.591	1.000	7.77
ATOM	560	CG	GLN	291	1.714	47.816	25.896	1.000	8.64
ATOM	561	CD	GLN	291	1.794	48.191	27.319	1.000	9.44
ATOM	562	OE1	GLN	291	1.932	49.417	27.683	1.000	13.00
ATOM	563	NE2	GLN	291	1.776	47.253	28.228	1.000	6.53
ATOM	564	N	ILE	292	-0.418	44.062	24.157	1.000	6.82
ATOM	565	CA	ILE	292	-0.609	42.680	23.705	1.000	6.51
ATOM	566	C	ILE	292	-0.709	42.587	22.203	1.000	6.72
ATOM	567	O	ILE	292	-0.060	41.777	21.560	1.000	6.56
ATOM	568	CB	ILE	292	-1.841	42.060	24.380	1.000	6.02
ATOM	569	CG1	ILE	292	-1.634	41.865	25.889	1.000	7.10
ATOM	570	CG2	ILE	292	-2.148	40.711	23.712	1.000	8.77
ATOM	571	CD1	ILE	292	-2.859	41.419	26.634	1.000	8.36
ATOM	572	N	TYR	293	-1.481	43.485	21.599	1.000	8.00
ATOM	573	CA	TYR	293	-1.580	43.454	20.132	1.000	8.31
ATOM	574	C	TYR	293	-0.259	43.736	19.482	1.000	7.82
ATOM	575	O	TYR	293	0.075	43.173	18.429	1.000	9.28
ATOM	576	CB	TYR	293	-2.664	44.423	19.687	1.000	9.06
ATOM	577	CG	TYR	293	-4.088	44.040	19.984	1.000	12.79
ATOM	578	CD1	TYR	293	-4.488	42.715	20.110	1.000	24.02
ATOM	579	CD2	TYR	293	-5.062	45.018	20.150	1.000	16.92
ATOM	580	CE1	TYR	293	-5.795	42.395	20.404	1.000	25.77
ATOM	581	CE2	TYR	293	-6.381	44.718	20.401	1.000	17.18
ATOM	582	CZ	TYR	293	-6.737	43.385	20.523	1.000	16.85
ATOM	583	OH	TYR	293	-8.054	43.063	20.760	1.000	17.86
ATOM	584	N	GLU	294	0.527	44.645	20.077	1.000	9.18
ATOM	585	CA	GLU	294	1.833	44.936	19.512	1.000	9.05
ATOM	586	C	GLU	294	2.734	43.694	19.522	1.000	8.78
ATOM	587	O	GLU	294	3.414	43.380	18.562	1.000	9.02
ATOM	588	CB	GLU	294	2.526	46.082	20.238	1.000	12.16
ATOM	589	CG	GLU	294	3.826	46.508	19.596	1.000	22.65
ATOM	590	CD	GLU	294	4.864	47.102	20.505	1.000	30.45
ATOM	591	OE1	GLU	294	4.663	47.257	21.722	1.000	32.65
ATOM	592	OE2	GLU	294	5.961	47.451	19.956	1.000	43.26
ATOM	593	N	ILE	295	2.750	42.999	20.662	1.000	8.34
ATOM	594	CA	ILE	295	3.601	41.786	20.779	1.000	8.50
ATOM	595	C	ILE	295	3.162	40.743	19.784	1.000	6.66
ATOM	596	O	ILE	295	3.972	40.115	19.082	1.000	8.09
ATOM	597	CB	ILE	295	3.505	41.265	22.227	1.000	8.50
ATOM	598	CG1	ILE	295	4.133	42.227	23.245	1.000	9.19
ATOM	599	CG2	ILE	295	4.043	39.866	22.358	1.000	11.61
ATOM	600	CD1	ILE	295	3.688	42.060	24.661	1.000	11.60
ATOM	601	N	LEU	296	1.856	40.526	19.652	1.000	7.24
ATOM	602	CA	LEU	296	1.384	39.544	18.695	1.000	7.61
ATOM	603	C	LEU	296	1.750	39.924	17.263	1.000	7.49
ATOM	604	O	LEU	296	2.071	39.051	16.449	1.000	8.78
ATOM	605	CB	LEU	296	-0.107	39.282	18.814	1.000	7.97
ATOM	606	CG	LEU	296	-0.554	38.690	20.152	1.000	8.53
ATOM	607	CD1	LEU	296	-2.053	38.426	20.159	1.000	13.91
ATOM	608	CD2	LEU	296	0.234	37.521	20.600	1.000	8.46
ATOM	609	N	LYS	297	1.628	41.212	16.954	1.000	8.22
ATOM	610	CA	LYS	297	1.989	41.692	15.609	1.000	8.82

Fig. 10K

ATOM	611	C	LYS	297	3.454	41.379	15.305	1.000	9.09
ATOM	612	O	LYS	297	3.803	40.954	14.213	1.000	9.68
ATOM	613	CB	LYS	297	1.698	43.164	15.463	1.000	9.86
ATOM	614	CG	LYS	297	2.003	43.761	14.087	1.000	14.25
ATOM	615	CD	LYS	297	1.440	45.189	14.035	1.000	26.97
ATOM	616	CE	LYS	297	1.741	45.834	12.694	1.000	40.62
ATOM	617	NZ	LYS	297	3.096	46.473	12.681	1.000	60.19
ATOM	618	N	ILE	298	4.331	41.590	16.271	1.000	7.75
ATOM	619	CA	ILE	298	5.746	41.244	16.080	1.000	9.67
ATOM	620	C	ILE	298	5.948	39.814	15.702	1.000	9.16
ATOM	621	O	ILE	298	6.632	39.450	14.754	1.000	9.64
ATOM	622	CB	ILE	298	6.570	41.653	17.307	1.000	9.45
ATOM	623	CG1	ILE	298	6.736	43.167	17.431	1.000	15.21
ATOM	624	CG2	ILE	298	7.901	40.937	17.357	1.000	12.68
ATOM	625	CD1	ILE	298	7.265	43.637	18.766	1.000	18.33
ATOM	626	N	TYR	299	5.264	38.899	16.434	1.000	7.93
ATOM	627	CA	TYR	299	5.376	37.505	16.082	1.000	6.83
ATOM	628	C	TYR	299	4.643	37.106	14.849	1.000	7.19
ATOM	629	O	TYR	299	5.082	36.160	14.135	1.000	10.33
ATOM	630	CB	TYR	299	4.967	36.633	17.344	1.000	9.60
ATOM	631	CG	TYR	299	6.157	36.722	18.308	1.000	7.18
ATOM	632	CD1	TYR	299	7.255	35.899	18.157	1.000	11.37
ATOM	633	CD2	TYR	299	6.215	37.735	19.248	1.000	8.93
ATOM	634	CE1	TYR	299	8.348	36.015	18.987	1.000	9.51
ATOM	635	CE2	TYR	299	7.320	37.881	20.067	1.000	8.69
ATOM	636	CZ	TYR	299	8.375	37.009	19.927	1.000	10.21
ATOM	637	OH	TYR	299	9.495	37.145	20.714	1.000	10.57
ATOM	638	N	GLN	300	3.559	37.747	14.504	1.000	6.62
ATOM	639	CA	GLN	300	2.859	37.431	13.251	1.000	8.29
ATOM	640	C	GLN	300	3.761	37.742	12.051	1.000	9.74
ATOM	641	O	GLN	300	3.670	37.060	11.049	1.000	10.30
ATOM	642	CB	GLN	300	1.609	38.304	13.202	1.000	11.24
ATOM	643	CG	AGLN	300	0.927	38.412	11.853	0.900	12.68
ATOM	644	CD	AGLN	300	-0.151	39.492	11.902	0.500	15.89
ATOM	645	OE1	AGLN	300	-1.290	39.180	12.195	0.500	11.59
ATOM	646	NE2	AGLN	300	0.276	40.730	11.736	0.500	15.55
ATOM	647	CG'	BGLN	300	-1.737	38.916	11.879	0.100	8.83
ATOM	648	CD'	BGLN	300	1.015	40.101	10.535	0.500	21.84
ATOM	649	OE1	BGLN	300	0.439	40.869	11.896	0.500	14.50
ATOM	650	NE2	BGLN	300	0.872	39.236	9.977	0.500	19.25
ATOM	651	N	LEU	301	4.565	38.784	12.188	1.000	9.31
ATOM	652	CA	LEU	301	5.441	39.240	11.096	1.000	9.95
ATOM	653	C	LEU	301	6.761	38.526	11.067	1.000	15.06
ATOM	654	O	LEU	301	7.566	38.645	10.111	1.000	15.22
ATOM	655	CB	LEU	301	5.640	40.753	11.206	1.000	13.13
ATOM	656	CG	LEU	301	4.413	41.628	10.983	1.000	11.84
ATOM	657	CD1	LEU	301	4.751	43.089	11.340	1.000	15.92
ATOM	658	CD2	LEU	301	3.866	41.556	9.587	1.000	23.09
ATOM	659	N	MET	302	7.104	37.793	12.092	1.000	12.65
ATOM	660	CA	MET	302	8.345	37.052	12.193	1.000	13.54
ATOM	661	C	MET	302	8.357	35.846	11.229	1.000	10.22
ATOM	662	O	MET	302	7.345	35.346	10.823	1.000	12.95
ATOM	663	CB	MET	302	8.451	36.476	13.608	1.000	16.44
ATOM	664	CG	MET	302	9.855	36.218	14.085	1.000	31.44
ATOM	665	SD	MET	302	10.028	36.312	15.875	1.000	39.71
ANISOU	665	SD	MET	302	4367	7335	3387	245	185 -343
ATOM	666	CE	MET	302	9.435	37.944	16.225	1.000	11.01
ATOM	667	N	ASP	303	9.598	35.415	10.944	1.000	11.09
ATOM	668	CA	ASP	303	9.791	34.244	10.104	1.000	12.07
ATOM	669	C	ASP	303	9.846	32.986	10.954	1.000	11.57
ATOM	670	O	ASP	303	10.788	32.796	11.733	1.000	15.11
ATOM	671	CB	ASP	303	11.074	34.378	9.286	1.000	14.92

Fig. 10 L

ATOM	672	CG	ASP	303	11.399	33.133	8.495	1.000	23.47	
ATOM	673	OD1	ASP	303	10.492	32.379	8.128	1.000	14.45	
ATOM	674	OD2	ASP	303	12.619	32.900	8.255	1.000	51.47	
ATOM	675	N	HIS	304	8.826	32.139	10.861	1.000	8.35	
ATOM	676	CA	HIS	304	8.766	30.914	11.624	1.000	7.04	
ATOM	677	C	HIS	304	9.113	29.713	10.763	1.000	6.08	
ATOM	678	O	HIS	304	8.838	28.579	11.110	1.000	6.91	
ATOM	679	CB	HIS	304	7.348	30.688	12.212	1.000	5.95	
ATOM	680	CG	HIS	304	6.877	31.745	13.146	1.000	6.53	
ATOM	681	ND1	HIS	304	6.813	31.579	14.535	1.000	6.46	
ATOM	682	CD2	HIS	304	6.399	32.998	12.889	1.000	6.91	
ATOM	683	CE1	HIS	304	6.331	32.683	15.035	1.000	6.14	
ATOM	684	NE2	HIS	304	6.076	33.562	14.076	1.000	7.16	
ATOM	685	N	SER	305	9.739	29.965	9.582	1.000	7.14	
ATOM	686	CA	SER	305	10.028	28.895	8.660	1.000	7.93	
ATOM	687	C	SER	305	10.820	27.746	9.242	1.000	8.15	
ATOM	688	O	SER	305	10.618	26.582	8.885	1.000	11.47	
ATOM	689	CB	SER	305	10.711	29.408	7.380	1.000	10.79	
ATOM	690	OG	ASER	305	11.912	30.007	7.544	0.500	9.18	
ATOM	691	OG'	BSER	305	10.075	30.315	6.558	0.500	9.52	
ATOM	692	N	ASN	306	11.729	28.036	10.169	1.000	7.91	
ATOM	693	CA	ASN	306	12.540	27.023	10.793	1.000	7.67	
ATOM	694	C	ASN	306	11.946	26.454	12.066	1.000	7.53	
ATOM	695	O	ASN	306	12.629	25.672	12.753	1.000	8.91	
ATOM	696	CB	ASN	306	13.956	27.541	11.092	1.000	13.62	
ATOM	697	CG	ASN	306	14.653	27.970	9.795	1.000	19.61	
ATOM	698	OD1	ASN	306	14.591	27.218	8.823	1.000	20.42	
ATOM	699	ND2	ASN	306	15.258	29.130	9.814	1.000	21.31	
ATOM	700	N	MET	307	10.717	26.838	12.380	1.000	6.31	
ATOM	701	CA	MET	307	10.000	26.323	13.547	1.000	5.35	
ATOM	702	C	MET	307	8.943	25.314	13.122	1.000	6.46	
ATOM	703	O	MET	307	8.408	25.394	11.990	1.000	7.33	
ATOM	704	CB	MET	307	9.287	27.477	14.273	1.000	5.91	
ATOM	705	CG	MET	307	10.173	28.640	14.613	1.000	7.29	
ATOM	706	SD	MET	307	11.621	28.184	15.559	1.000	9.33	
ANISOU	706	SD	MET	307	784	1456	1304	-104	22	-96
ATOM	707	CE	MET	307	12.025	29.783	16.287	1.000	15.23	
ATOM	708	N	ASP	308	8.590	24.421	14.032	1.000	5.40	
ATOM	709	CA	ASP	308	7.557	23.433	13.794	1.000	5.19	
ATOM	710	C	ASP	308	6.250	23.777	14.528	1.000	5.24	
ATOM	711	O	ASP	308	5.242	23.142	14.273	1.000	5.54	
ATOM	712	CB	ASP	308	8.038	22.043	14.172	1.000	6.07	
ATOM	713	CG	ASP	308	8.967	21.422	13.127	1.000	8.78	
ATOM	714	OD1	ASP	308	8.928	21.886	11.966	1.000	9.91	
ATOM	715	OD2	ASP	308	9.707	20.490	13.466	1.000	8.77	
ATOM	716	N	CYS	309	6.261	24.747	15.425	1.000	4.82	
ATOM	717	CA	CYS	309	5.056	25.037	16.246	1.000	5.16	
ATOM	718	C	CYS	309	5.169	26.467	16.789	1.000	5.06	
ATOM	719	O	CYS	309	6.239	27.078	16.779	1.000	6.18	
ATOM	720	CB	CYS	309	5.126	24.047	17.460	1.000	7.10	
ATOM	721	SG	CYS	309	3.695	23.953	18.537	1.000	6.34	
ANISOU	721	SG	CYS	309	657	1045	707	-27	127	94
ATOM	722	N	PHE	310	4.070	26.989	17.284	1.000	4.67	
ATOM	723	CA	PHE	310	4.032	28.286	17.961	1.000	4.33	
ATOM	724	C	PHE	310	3.040	28.163	19.160	1.000	4.34	
ATOM	725	O	PHE	310	1.971	27.597	18.982	1.000	5.69	
ATOM	726	CB	PHE	310	3.475	29.346	17.015	1.000	5.10	
ATOM	727	CG	PHE	310	3.237	30.698	17.653	1.000	4.73	
ATOM	728	CD1	PHE	310	4.314	31.474	18.056	1.000	6.88	
ATOM	729	CD2	PHE	310	1.965	31.185	17.873	1.000	4.91	
ATOM	730	CE1	PHE	310	4.110	32.694	18.656	1.000	7.31	
ATOM	731	CE2	PHE	310	1.772	32.422	18.428	1.000	7.11	

Fig. 10M

ATOM	732	CZ	PHE	310	2.826	33.186	18.837	1.000	7.07	
ATOM	733	N	ILE	311	3.451	28.660	20.312	1.000	4.49	
ATOM	734	CA	ILE	311	2.601	28.643	21.505	1.000	3.05	
ATOM	735	C	ILE	311	2.483	30.048	22.050	1.000	3.72	
ATOM	736	O	ILE	311	3.471	30.795	22.076	1.000	4.65	
ATOM	737	CB	ILE	311	3.174	27.705	22.599	1.000	4.19	
ATOM	738	CG1	ILE	311	2.249	27.674	23.823	1.000	4.86	
ATOM	739	CG2	ILE	311	3.351	26.304	22.021	1.000	8.07	
ATOM	740	CD1	ILE	311	2.421	26.428	24.654	1.000	39.16	
ATOM	741	N	CYS	312	1.305	30.416	22.503	1.000	3.68	
ATOM	742	CA	CYS	312	1.053	31.681	23.172	1.000	3.97	
ATOM	743	C	CYS	312	0.204	31.433	24.427	1.000	3.33	
ATOM	744	O	CYS	312	-0.889	30.906	24.327	1.000	4.28	
ATOM	745	CB	CYS	312	0.330	32.651	22.243	1.000	4.90	
ATOM	746	SG	CYS	312	-0.069	34.252	22.970	1.000	6.82	
ANISOU	746	SG	CYS	312	857	727	1009	90	110	255
ATOM	747	N	CYS	313	0.743	31.800	25.572	1.000	3.19	
ATOM	748	CA	CYS	313	0.064	31.648	26.860	1.000	3.64	
ATOM	749	C	CYS	313	-0.306	33.029	27.387	1.000	5.08	
ATOM	750	O	CYS	313	0.566	33.915	27.443	1.000	6.47	
ATOM	751	CB	CYS	313	1.065	31.029	27.871	1.000	4.09	
ATOM	752	SG	CYS	313	1.711	29.425	27.364	1.000	5.62	
ANISOU	752	SG	CYS	313	639	866	631	-74	-58	-12
ATOM	753	N	ILE	314	-1.558	33.210	27.765	1.000	4.23	
ATOM	754	CA	ILE	314	-2.043	34.448	28.328	1.000	4.28	
ATOM	755	C	ILE	314	-2.540	34.213	29.746	1.000	4.00	
ATOM	756	O	ILE	314	-3.420	33.357	29.936	1.000	5.38	
ATOM	757	CB	ILE	314	-3.167	35.071	27.468	1.000	5.93	
ATOM	758	CG1	ILE	314	-2.751	35.247	26.036	1.000	9.89	
ATOM	759	CG2	ILE	314	-3.727	36.325	28.112	1.000	8.24	
ATOM	760	CD1A	ILE	314	-3.662	35.876	25.063	0.500	9.64	
ATOM	761	CD1B	ILE	314	-1.969	36.023	25.763	0.500	6.92	
ATOM	762	N	LEU	315	-1.980	34.920	30.672	1.000	3.53	
ATOM	763	CA	LEU	315	-2.338	34.844	32.105	1.000	4.45	
ATOM	764	C	LEU	315	-2.915	36.196	32.497	1.000	3.81	
ATOM	765	O	LEU	315	-2.186	37.218	32.578	1.000	4.50	
ATOM	766	CB	LEU	315	-1.073	34.552	32.928	1.000	4.02	
ATOM	767	CG	LEU	315	-0.139	33.475	32.410	1.000	4.55	
ATOM	768	CD1	LEU	315	1.099	33.393	33.297	1.000	4.90	
ATOM	769	CD2	LEU	315	-0.816	32.142	32.289	1.000	6.99	
ATOM	770	N	SER	316	-4.225	36.281	32.704	1.000	3.76	
ATOM	771	CA	SER	316	-4.830	37.576	32.967	1.000	3.14	
ATOM	772	C	SER	316	-6.219	37.418	33.548	1.000	3.76	
ATOM	773	O	SER	316	-6.702	36.323	33.791	1.000	4.40	
ATOM	774	CB	SER	316	-4.937	38.406	31.659	1.000	4.41	
ATOM	775	OG	SER	316	-5.106	39.774	31.978	1.000	4.86	
ATOM	776	N	HIS	317	-6.870	38.549	33.821	1.000	4.33	
ATOM	777	CA	HIS	317	-8.281	38.577	34.078	1.000	4.17	
ATOM	778	C	HIS	317	-9.025	38.472	32.727	1.000	5.55	
ATOM	779	O	HIS	317	-8.447	38.694	31.666	1.000	4.71	
ATOM	780	CB	HIS	317	-8.712	39.843	34.804	1.000	4.95	
ATOM	781	CG	HIS	317	-8.424	39.806	36.266	1.000	5.95	
ATOM	782	ND1	HIS	317	-8.966	38.805	37.069	1.000	5.44	
ATOM	783	CD2	HIS	317	-7.665	40.614	37.047	1.000	6.05	
ATOM	784	CE1	HIS	317	-8.547	39.036	38.301	1.000	6.37	
ATOM	785	NE2	HIS	317	-7.796	40.137	38.325	1.000	6.05	
ATOM	786	N	GLY	318	-10.300	38.135	32.784	1.000	4.91	
ATOM	787	CA	GLY	318	-11.133	38.086	31.606	1.000	6.14	
ATOM	788	C	GLY	318	-12.613	38.075	31.959	1.000	4.95	
ATOM	789	O	GLY	318	-12.994	38.114	33.118	1.000	6.63	
ATOM	790	N	ASP	319	-13.405	38.019	30.921	1.000	5.58	
ATOM	791	CA	ASP	319	-14.864	37.991	30.976	1.000	6.46	

Fig. 10 N

ATOM	792	C	ASP	319	-15.325	37.191	29.761	1.000	6.50
ATOM	793	O	ASP	319	-14.479	36.681	29.019	1.000	6.23
ATOM	794	CB	ASP	319	-15.490	39.344	31.047	1.000	9.30
ATOM	795	CG	ASP	319	-16.888	39.417	31.603	1.000	14.29
ATOM	796	OD1	ASP	319	-17.621	38.418	31.695	1.000	11.30
ATOM	797	OD2	ASP	319	-17.340	40.572	31.834	1.000	41.80
ATOM	798	N	LYS	320	-16.626	37.090	29.512	1.000	7.34
ATOM	799	CA	LYS	320	-17.116	36.242	28.432	1.000	8.44
ATOM	800	C	LYS	320	-16.451	36.525	27.106	1.000	8.24
ATOM	801	O	LYS	320	-16.631	37.616	26.538	1.000	10.32
ATOM	802	CB	LYS	320	-18.631	36.440	28.289	1.000	12.60
ATOM	803	CG	LYS	320	-19.500	36.005	29.438	1.000	17.35
ATOM	804	CD	LYS	320	-20.983	36.315	29.087	1.000	28.41
ATOM	805	CE	LYS	320	-21.499	37.467	29.926	1.000	39.51
ATOM	806	NZ	LYS	320	-22.584	37.020	30.884	1.000	60.54
ATOM	807	N	GLY	321	-15.714	35.582	26.572	1.000	7.72
ATOM	808	CA	GLY	321	-15.071	35.689	25.296	1.000	7.58
ATOM	809	C	GLY	321	-13.911	36.607	25.189	1.000	6.93
ATOM	810	O	GLY	321	-13.392	36.831	24.088	1.000	7.96
ATOM	811	N	ILE	322	-13.458	37.197	26.295	1.000	5.94
ATOM	812	CA	ILE	322	-12.427	38.204	26.248	1.000	6.52
ATOM	813	C	ILE	322	-11.361	37.984	27.329	1.000	5.86
ATOM	814	O	ILE	322	-11.615	37.341	28.332	1.000	5.81
ATOM	815	CB	ILE	322	-12.985	39.641	26.388	1.000	7.68
ATOM	816	CG1	ILE	322	-13.530	39.971	27.781	1.000	8.59
ATOM	817	CG2	ILE	322	-14.072	39.884	25.326	1.000	7.87
ATOM	818	CD1	ILE	322	-12.540	40.678	28.689	1.000	12.42
ATOM	819	N	ILE	323	-10.222	38.647	27.133	1.000	5.27
ATOM	820	CA	ILE	323	-9.236	38.807	28.192	1.000	4.53
ATOM	821	C	ILE	323	-9.046	40.302	28.412	1.000	6.69
ATOM	822	O	ILE	323	-9.267	41.124	27.486	1.000	7.21
ATOM	823	CB	ILE	323	-7.917	38.095	27.969	1.000	7.45
ATOM	824	CG1	ILE	323	-7.124	38.571	26.774	1.000	8.41
ATOM	825	CG2	ILE	323	-8.141	36.566	27.910	1.000	8.22
ATOM	826	CD1	ILE	323	-6.144	39.670	26.989	1.000	10.12
ATOM	827	N	TYR	324	-8.678	40.692	29.609	1.000	5.90
ATOM	828	CA	TYR	324	-8.436	42.091	29.927	1.000	5.85
ATOM	829	C	TYR	324	-6.928	42.372	29.861	1.000	6.25
ATOM	830	O	TYR	324	-6.091	41.606	30.321	1.000	6.53
ATOM	831	CB	TYR	324	-8.896	42.382	31.363	1.000	7.68
ATOM	832	CG	TYR	324	-10.362	42.561	31.558	1.000	6.39
ATOM	833	CD1	TYR	324	-11.038	43.650	30.976	1.000	9.32
ATOM	834	CD2	TYR	324	-11.107	41.685	32.336	1.000	7.99
ATOM	835	CE1	TYR	324	-12.390	43.818	31.159	1.000	10.76
ATOM	836	CE2	TYR	324	-12.466	41.858	32.523	1.000	8.36
ATOM	837	CZ	TYR	324	-13.092	42.917	31.932	1.000	10.28
ATOM	838	OH	TYR	324	-14.461	43.116	32.114	1.000	13.34
ATOM	839	N	GLY	325	-6.603	43.552	29.359	1.000	6.20
ATOM	840	CA	GLY	325	-5.263	44.076	29.549	1.000	6.92
ATOM	841	C	GLY	325	-5.171	44.633	30.976	1.000	5.85
ATOM	842	O	GLY	325	-6.182	44.796	31.651	1.000	6.38
ATOM	843	N	THR	326	-3.973	44.965	31.430	1.000	6.37
ATOM	844	CA	THR	326	-3.787	45.558	32.744	1.000	6.54
ATOM	845	C	THR	326	-4.518	46.896	32.864	1.000	7.79
ATOM	846	O	THR	326	-4.741	47.312	34.009	1.000	7.85
ATOM	847	CB	THR	326	-2.292	45.793	33.045	1.000	7.90
ATOM	848	OG1	THR	326	-1.736	46.510	31.943	1.000	8.65
ATOM	849	CG2	THR	326	-1.546	44.510	33.233	1.000	8.08
ATOM	850	N	ASP	327	-4.837	47.526	31.762	1.000	7.07
ATOM	851	CA	ASP	327	-5.569	48.779	31.695	1.000	7.68
ATOM	852	C	ASP	327	-7.057	48.592	31.741	1.000	10.41
ATOM	853	O	ASP	327	-7.838	49.562	31.760	1.000	11.05

Fig 10 0

ATOM	854	CB	ASP	327	-5.172	49.570	30.450	1.000	8.87
ATOM	855	CG	ASP	327	-5.350	48.889	29.142	1.000	10.66
ATOM	856	OD1	ASP	327	-5.501	47.656	29.048	1.000	9.41
ATOM	857	OD2	ASP	327	-5.297	49.624	28.077	1.000	10.00
ATOM	858	N	GLY	328	-7.523	47.347	31.767	1.000	7.82
ATOM	859	CA	GLY	328	-8.974	47.121	31.824	1.000	9.69
ATOM	860	C	GLY	328	-9.661	47.185	30.488	1.000	8.01
ATOM	861	O	GLY	328	-10.892	47.080	30.440	1.000	9.40
ATOM	862	N	GLN	329	-8.922	47.385	29.416	1.000	8.49
ATOM	863	CA	GLN	329	-9.515	47.293	28.064	1.000	8.52
ATOM	864	C	GLN	329	-9.676	45.810	27.708	1.000	8.65
ATOM	865	O	GLN	329	-9.049	44.945	28.351	1.000	7.83
ATOM	866	CB	GLN	329	-8.620	48.011	27.070	1.000	11.22
ATOM	867	CG	GLN	329	-8.567	49.526	27.284	1.000	15.65
ATOM	868	CD	GLN	329	-9.942	50.165	27.203	1.000	19.22
ATOM	869	OE1	GLN	329	-10.405	50.837	28.121	1.000	25.05
ATOM	870	NE2	GLN	329	-10.613	49.955	26.074	1.000	29.98
ATOM	871	N	GLU	330	-10.573	45.493	26.810	1.000	8.28
ATOM	872	CA	GLU	330	-10.914	44.142	26.425	1.000	8.25
ATOM	873	C	GLU	330	-10.249	43.725	25.115	1.000	8.74
ATOM	874	O	GLU	330	-10.214	44.538	24.168	1.000	9.51
ATOM	875	CB	GLU	330	-12.421	43.984	26.253	1.000	10.19
ATOM	876	CG	GLU	330	-13.311	44.344	27.378	1.000	16.05
ATOM	877	CD	GLU	330	-14.790	44.010	27.142	1.000	25.66
ATOM	878	OE1	GLU	330	-15.127	43.524	26.027	1.000	21.83
ATOM	879	OE2	GLU	330	-15.597	44.212	28.061	1.000	24.27
ATOM	880	N	ALA	331	-9.818	42.509	25.031	1.000	8.19
ATOM	881	CA	ALA	331	-9.316	41.874	23.840	1.000	8.70
ATOM	882	C	ALA	331	-10.134	40.599	23.595	1.000	8.06
ATOM	883	O	ALA	331	-10.017	39.633	24.362	1.000	8.08
ATOM	884	CB	ALA	331	-7.837	41.579	23.909	1.000	9.91
ATOM	885	N	PRO	332	-10.983	40.586	22.571	1.000	7.73
ATOM	886	CA	PRO	332	-11.694	39.320	22.272	1.000	6.96
ATOM	887	C	PRO	332	-10.638	38.255	21.966	1.000	7.15
ATOM	888	O	PRO	332	-9.666	38.489	21.260	1.000	7.59
ATOM	889	CB	PRO	332	-12.460	39.647	20.992	1.000	11.11
ATOM	890	CG	PRO	332	-12.655	41.130	21.061	1.000	10.96
ATOM	891	CD	PRO	332	-11.395	41.676	21.657	1.000	9.57
ATOM	892	N	ILE	333	-10.889	37.046	22.468	1.000	7.40
ATOM	893	CA	ILE	333	-9.985	35.956	22.226	1.000	7.41
ATOM	894	C	ILE	333	-9.746	35.704	20.759	1.000	6.77
ATOM	895	O	ILE	333	-8.629	35.416	20.334	1.000	7.45
ATOM	896	CB	ILE	333	-10.283	34.741	23.074	1.000	8.66
ATOM	897	CG1	ILE	333	-10.098	35.037	24.604	1.000	9.89
ATOM	898	CG2	ILE	333	-9.448	33.536	22.701	1.000	10.78
ATOM	899	CD1	ILE	333	-10.849	34.078	25.482	1.000	11.98
ATOM	900	N	TYR	334	-10.806	35.818	19.953	1.000	7.61
ATOM	901	CA	TYR	334	-10.649	35.607	18.511	1.000	8.17
ATOM	902	C	TYR	334	-9.733	36.621	17.894	1.000	8.41
ATOM	903	O	TYR	334	-9.032	36.274	16.901	1.000	10.73
ATOM	904	CB	TYR	334	-12.061	35.749	17.840	1.000	12.37
ATOM	905	CG	TYR	334	-11.927	35.612	16.315	1.000	17.83
ATOM	906	CD1	TYR	334	-11.714	34.353	15.771	1.000	20.81
ATOM	907	CD2	TYR	334	-12.017	36.698	15.473	1.000	21.79
ATOM	908	CE1	TYR	334	-11.582	34.183	14.394	1.000	20.07
ATOM	909	CE2	TYR	334	-11.906	36.539	14.081	1.000	25.95
ATOM	910	CZ	TYR	334	-11.690	35.276	13.569	1.000	21.59
ATOM	911	OH	TYR	334	-11.576	35.103	12.195	1.000	25.80
ATOM	912	N	GLU	335	-9.690	37.847	18.356	1.000	9.36
ATOM	913	CA	GLU	335	-8.758	38.855	17.838	1.000	11.24
ATOM	914	C	GLU	335	-7.318	38.475	18.138	1.000	13.66
ATOM	915	O	GLU	335	-6.381	38.933	17.442	1.000	16.51

Fig. 10 P

ATOM	916	CB	GLU	335	-9.046	40.234	18.419	1.000	16.71
ATOM	917	CG	GLU	335	-10.376	40.823	18.059	1.000	23.14
ATOM	918	CD	GLU	335	-10.552	40.998	16.556	1.000	30.98
ATOM	919	OE1	GLU	335	-9.544	41.358	15.920	1.000	30.64
ATOM	920	OE2	GLU	335	-11.663	40.733	16.067	1.000	48.39
ATOM	921	N	LEU	336	-7.083	37.675	19.160	1.000	8.87
ATOM	922	CA	LEU	336	-5.703	37.241	19.465	1.000	8.20
ATOM	923	C	LEU	336	-5.297	36.079	18.586	1.000	7.13
ATOM	924	O	LEU	336	-4.253	36.103	17.924	1.000	7.26
ATOM	925	CB	LEU	336	-5.577	36.924	20.946	1.000	10.57
ATOM	926	CG	LEU	336	-6.002	37.986	21.949	1.000	11.57
ATOM	927	CD1	LEU	336	-6.026	37.493	23.366	1.000	16.26
ATOM	928	CD2	LEU	336	-5.231	39.264	21.809	1.000	15.31
ATOM	929	N	THR	337	-6.143	35.025	18.547	1.000	5.88
ATOM	930	CA	THR	337	-5.791	33.853	17.775	1.000	5.40
ATOM	931	C	THR	337	-5.748	34.140	16.278	1.000	5.62
ATOM	932	O	THR	337	-4.910	33.575	15.581	1.000	6.76
ATOM	933	CB	THR	337	-6.742	32.677	18.055	1.000	7.69
ATOM	934	OG1	THR	337	-8.075	33.064	17.742	1.000	7.59
ATOM	935	CG2	THR	337	-6.730	32.311	19.547	1.000	7.32
ATOM	936	N	SER	338	-6.628	34.995	15.794	1.000	5.47
ATOM	937	CA	SER	338	-6.755	35.299	14.392	1.000	6.27
ATOM	938	C	SER	338	-5.528	35.944	13.812	1.000	5.53
ATOM	939	O	SER	338	-5.368	35.996	12.576	1.000	7.47
ATOM	940	CB	SER	338	-8.038	36.022	14.071	1.000	8.93
ATOM	941	OG	SER	338	-8.000	37.379	14.487	1.000	11.25
ATOM	942	N	GLN	339	-4.603	36.448	14.637	1.000	6.39
ATOM	943	CA	GLN	339	-3.383	37.036	14.111	1.000	5.65
ATOM	944	C	GLN	339	-2.439	35.988	13.571	1.000	5.69
ATOM	945	O	GLN	339	-1.460	36.321	12.875	1.000	7.37
ATOM	946	CB	GLN	339	-2.675	37.898	15.154	1.000	8.16
ATOM	947	CG	GLN	339	-3.486	38.977	15.796	1.000	9.16
ATOM	948	CD	GLN	339	-4.326	39.770	14.819	1.000	13.95
ATOM	949	OE1	GLN	339	-5.518	39.991	15.024	1.000	25.60
ATOM	950	NE2	GLN	339	-3.678	40.213	13.750	1.000	12.01
ATOM	951	N	PHE	340	-2.726	34.695	13.777	1.000	4.97
ATOM	952	CA	PHE	340	-1.875	33.626	13.393	1.000	3.82
ATOM	953	C	PHE	340	-2.439	32.631	12.400	1.000	4.47
ATOM	954	O	PHE	340	-1.926	31.538	12.214	1.000	5.10
ATOM	955	CB	PHE	340	-1.248	32.891	14.600	1.000	4.74
ATOM	956	CG	PHE	340	-0.438	33.880	15.459	1.000	5.22
ATOM	957	CD1	PHE	340	0.916	34.059	15.168	1.000	7.10
ATOM	958	CD2	PHE	340	-1.035	34.607	16.449	1.000	5.50
ATOM	959	CE1	PHE	340	1.642	35.014	15.905	1.000	7.49
ATOM	960	CE2	PHE	340	-0.312	35.553	17.181	1.000	7.79
ATOM	961	CZ	PHE	340	1.015	35.752	16.871	1.000	9.00
ATOM	962	N	THR	341	-3.500	33.068	11.722	1.000	4.90
ATOM	963	CA	THR	341	-4.072	32.237	10.653	1.000	4.38
ATOM	964	C	THR	341	-3.006	32.060	9.561	1.000	4.50
ATOM	965	O	THR	341	-1.996	32.753	9.499	1.000	5.04
ATOM	966	CB	THR	341	-5.306	32.906	10.035	1.000	5.87
ATOM	967	OG1	THR	341	-4.939	34.113	9.432	1.000	7.62
ATOM	968	CG2	THR	341	-6.431	33.103	10.994	1.000	8.16
ATOM	969	N	GLY	342	-3.276	31.103	8.686	1.000	3.84
ATOM	970	CA	GLY	342	-2.297	30.825	7.634	1.000	4.89
ATOM	971	C	GLY	342	-2.085	32.013	6.718	1.000	3.68
ATOM	972	O	GLY	342	-0.950	32.172	6.203	1.000	5.64
ATOM	973	N	LEU	343	-3.083	32.817	6.471	1.000	3.99
ATOM	974	CA	LEU	343	-2.897	33.998	5.609	1.000	4.23
ATOM	975	C	LEU	343	-2.076	35.059	6.312	1.000	5.27
ATOM	976	O	LEU	343	-1.293	35.791	5.678	1.000	6.07
ATOM	977	CB	LEU	343	-4.215	34.560	5.147	1.000	4.86

Fig. 10 Q

ATOM	978	CG	LEU	343	-5.041	33.648	4.212	1.000	5.32
ATOM	979	CD1	LEU	343	-6.453	34.170	4.065	1.000	6.14
ATOM	980	CD2	LEU	343	-4.380	33.497	2.843	1.000	5.01
ATOM	981	N	LYS	344	-2.313	35.233	7.605	1.000	5.41
ATOM	982	CA	LYS	344	-1.639	36.335	8.345	1.000	5.47
ATOM	983	C	LYS	344	-0.250	35.954	8.727	1.000	8.64
ATOM	984	O	LYS	344	0.597	36.871	8.904	1.000	10.27
ATOM	985	CB	LYS	344	-2.518	36.739	9.539	1.000	8.57
ATOM	986	CG	LYS	344	-3.844	37.325	9.062	1.000	12.74
ATOM	987	CD	LYS	344	-4.378	38.389	9.976	1.000	22.63
ATOM	988	CE	LYS	344	-5.448	39.235	9.294	1.000	28.67
ATOM	989	NZ	LYS	344	-4.877	40.460	8.655	1.000	48.97
ATOM	990	N	CYS	345	0.028	34.676	8.897	1.000	5.69
ATOM	991	CA	CYS	345	1.349	34.185	9.238	1.000	6.11
ATOM	992	C	CYS	345	1.671	32.933	8.449	1.000	5.74
ATOM	993	O	CYS	345	1.615	31.792	8.884	1.000	5.01
ATOM	994	CB	CYS	345	1.472	33.938	10.733	1.000	6.93
ATOM	995	SG	CYS	345	3.147	33.571	11.278	1.000	8.59
ANISOU	995	SG	CYS	345	1031	1198	1035	-275	-283 175
ATOM	996	N	PRO	346	2.037	33.156	7.154	1.000	6.15
ATOM	997	CA	PRO	346	2.274	32.060	6.256	1.000	5.45
ATOM	998	C	PRO	346	3.350	31.097	6.634	1.000	4.63
ATOM	999	O	PRO	346	3.290	29.908	6.308	1.000	5.19
ATOM	1000	CB	PRO	346	2.556	32.704	4.878	1.000	6.82
ATOM	1001	CG	PRO	346	1.906	34.059	5.009	1.000	11.22
ATOM	1002	CD	PRO	346	2.102	34.464	6.456	1.000	7.23
ATOM	1003	N	SER	347	4.381	31.569	7.361	1.000	5.40
ATOM	1004	CA	SER	347	5.426	30.689	7.800	1.000	7.38
ATOM	1005	C	SER	347	5.009	29.725	8.905	1.000	5.92
ATOM	1006	O	SER	347	5.831	28.838	9.237	1.000	6.99
ATOM	1007	CB	SER	347	6.713	31.432	8.183	1.000	8.36
ATOM	1008	OG	SER	347	6.555	32.278	9.235	1.000	8.38
ATOM	1009	N	LEU	348	3.812	29.828	9.441	1.000	4.63
ATOM	1010	CA	LEU	348	3.232	28.839	10.330	1.000	4.04
ATOM	1011	C	LEU	348	2.135	28.052	9.626	1.000	4.93
ATOM	1012	O	LEU	348	1.471	27.220	10.257	1.000	4.71
ATOM	1013	CB	LEU	348	2.715	29.450	11.621	1.000	4.66
ATOM	1014	CG	LEU	348	3.764	29.962	12.603	1.000	5.38
ATOM	1015	CD1	LEU	348	3.082	30.784	13.707	1.000	6.42
ATOM	1016	CD2	LEU	348	4.569	28.798	13.181	1.000	5.80
ATOM	1017	N	ALA	349	1.914	28.228	8.322	1.000	6.11
ATOM	1018	CA	ALA	349	0.876	27.467	7.633	1.000	5.41
ATOM	1019	C	ALA	349	1.131	25.997	7.700	1.000	5.63
ATOM	1020	O	ALA	349	2.261	25.511	7.448	1.000	6.71
ATOM	1021	CB	ALA	349	0.733	27.939	6.190	1.000	7.31
ATOM	1022	N	GLY	350	0.116	25.200	8.080	1.000	5.29
ATOM	1023	CA	GLY	350	0.229	23.777	8.242	1.000	6.06
ATOM	1024	C	GLY	350	0.870	23.337	9.558	1.000	4.75
ATOM	1025	O	GLY	350	1.022	22.130	9.760	1.000	5.96
ATOM	1026	N	LYS	351	1.261	24.285	10.389	1.000	4.66
ATOM	1027	CA	LYS	351	1.908	24.006	11.657	1.000	4.07
ATOM	1028	C	LYS	351	0.958	24.338	12.821	1.000	4.74
ATOM	1029	O	LYS	351	0.194	25.298	12.750	1.000	4.69
ATOM	1030	CB	LYS	351	3.187	24.814	11.809	1.000	5.29
ATOM	1031	CG	LYS	351	4.166	24.615	10.645	1.000	5.91
ATOM	1032	CD	LYS	351	5.372	25.517	10.789	1.000	5.97
ATOM	1033	CE	LYS	351	6.288	25.404	9.601	1.000	7.50
ATOM	1034	NZ	LYS	351	7.353	26.454	9.641	1.000	6.29
ATOM	1035	N	PRO	352	1.061	23.562	13.903	1.000	4.31
ATOM	1036	CA	PRO	352	0.202	23.793	15.056	1.000	4.89
ATOM	1037	C	PRO	352	0.467	25.082	15.731	1.000	5.48
ATOM	1038	O	PRO	352	1.644	25.466	15.987	1.000	7.35

Fig. 10 R

ATOM	1039	CB	PRO	352	0.494	22.574	15.936	1.000	6.80
ATOM	1040	CG	PRO	352	1.794	22.046	15.488	1.000	8.25
ATOM	1041	CD	PRO	352	1.947	22.429	14.062	1.000	6.18
ATOM	1042	N	LYS	353	-0.594	25.764	16.089	1.000	5.19
ATOM	1043	CA	LYS	353	-0.617	27.014	16.821	1.000	4.96
ATOM	1044	C	LYS	353	-1.485	26.776	18.067	1.000	4.42
ATOM	1045	O	LYS	353	-2.662	26.446	17.958	1.000	4.37
ATOM	1046	CB	LYS	353	-1.178	28.142	15.986	1.000	5.68
ATOM	1047	CG	LYS	353	-0.259	28.344	14.760	1.000	10.92
ATOM	1048	CD	LYS	353	-0.856	29.007	13.630	1.000	8.07
ATOM	1049	CE	LYS	353	-1.749	28.185	12.727	1.000	5.42
ATOM	1050	NZ	LYS	353	-0.962	27.528	11.649	1.000	4.63
ATOM	1051	N	VAL	354	-0.827	26.912	19.210	1.000	3.87
ATOM	1052	CA	VAL	354	-1.448	26.554	20.491	1.000	4.13
ATOM	1053	C	VAL	354	-1.564	27.759	21.393	1.000	3.88
ATOM	1054	O	VAL	354	-0.571	28.475	21.627	1.000	5.09
ATOM	1055	CB	VAL	354	-0.599	25.458	21.166	1.000	5.11
ATOM	1056	CG1	VAL	354	-1.220	24.992	22.462	1.000	7.54
ATOM	1057	CG2	VAL	354	-0.366	24.286	20.225	1.000	6.62
ATOM	1058	N	PHE	355	-2.751	28.042	21.878	1.000	3.33
ATOM	1059	CA	PHE	355	-3.022	29.136	22.776	1.000	3.74
ATOM	1060	C	PHE	355	-3.578	28.566	24.104	1.000	3.67
ATOM	1061	O	PHE	355	-4.512	27.779	24.080	1.000	5.23
ATOM	1062	CB	PHE	355	-4.098	30.094	22.216	1.000	3.74
ATOM	1063	CG	PHE	355	-3.506	30.891	21.042	1.000	7.25
ATOM	1064	CD1	PHE	355	-3.376	30.182	19.836	1.000	10.88
ATOM	1065	CD2	PHE	355	-3.103	32.170	21.142	1.000	10.90
ATOM	1066	CE1	PHE	355	-2.876	30.791	18.688	1.000	11.93
ATOM	1067	CE2	PHE	355	-2.549	32.806	19.964	1.000	10.95
ATOM	1068	CZ	PHE	355	-2.395	32.067	18.865	1.000	11.05
ATOM	1069	N	PHE	356	-2.959	28.959	25.206	1.000	3.19
ATOM	1070	CA	PHE	356	-3.459	28.592	26.547	1.000	4.09
ATOM	1071	C	PHE	356	-3.916	29.886	27.220	1.000	3.64
ATOM	1072	O	PHE	356	-3.118	30.836	27.335	1.000	5.54
ATOM	1073	CB	PHE	356	-2.379	27.902	27.359	1.000	4.20
ATOM	1074	CG	PHE	356	-1.974	26.538	26.839	1.000	4.24
ATOM	1075	CD1	PHE	356	-2.883	25.486	26.865	1.000	4.81
ATOM	1076	CD2	PHE	356	-0.724	26.291	26.333	1.000	4.77
ATOM	1077	CE1	PHE	356	-2.551	24.253	26.375	1.000	5.89
ATOM	1078	CE2	PHE	356	-0.377	25.051	25.863	1.000	5.39
ATOM	1079	CZ	PHE	356	-1.291	24.023	25.883	1.000	5.94
ATOM	1080	N	ILE	357	-5.170	29.948	27.627	1.000	3.70
ATOM	1081	CA	ILE	357	-5.722	31.145	28.238	1.000	4.11
ATOM	1082	C	ILE	357	-6.171	30.862	29.655	1.000	3.95
ATOM	1083	O	ILE	357	-7.149	30.140	29.905	1.000	4.45
ATOM	1084	CB	ILE	357	-6.955	31.651	27.441	1.000	5.41
ATOM	1085	CG1	ILE	357	-6.624	31.817	25.959	1.000	8.78
ATOM	1086	CG2	ILE	357	-7.444	32.959	28.067	1.000	6.63
ATOM	1087	CD1	ILE	357	-5.690	32.880	25.611	1.000	10.61
ATOM	1088	N	GLN	358	-5.421	31.418	30.595	1.000	2.87
ATOM	1089	CA	GLN	358	-5.710	31.330	32.010	1.000	2.99
ATOM	1090	C	GLN	358	-6.312	32.705	32.406	1.000	3.47
ATOM	1091	O	GLN	358	-5.583	33.667	32.570	1.000	4.29
ATOM	1092	CB	GLN	358	-4.431	31.057	32.801	1.000	4.21
ATOM	1093	CG	GLN	358	-4.593	31.211	34.321	1.000	4.20
ATOM	1094	CD	GLN	358	-5.824	30.506	34.847	1.000	3.90
ATOM	1095	OE1	GLN	358	-5.996	29.293	34.649	1.000	4.53
ATOM	1096	NE2	GLN	358	-6.709	31.230	35.520	1.000	5.45
ATOM	1097	N	ALA	359	-7.620	32.742	32.452	1.000	3.51
ATOM	1098	CA	ALA	359	-8.393	33.922	32.782	1.000	4.09
ATOM	1099	C	ALA	359	-9.794	33.498	33.208	1.000	4.21
ATOM	1100	O	ALA	359	-10.202	32.365	32.917	1.000	5.09

Fig. 10 S

ATOM	1101	CB	ALA	359	-8.535	34.829	31.544	1.000	4.67
ATOM	1102	N	CYS	360	-10.525	34.335	33.887	1.000	4.30
ATOM	1103	CA	CYS	360	-11.951	34.078	34.076	1.000	4.09
ATOM	1104	C	CYS	360	-12.664	34.390	32.713	1.000	5.78
ATOM	1105	O	CYS	360	-12.109	35.093	31.892	1.000	4.90
ATOM	1106	CB	CYS	360	-12.524	35.048	35.117	1.000	5.49
ATOM	1107	SG	CYS	360	-11.892	34.731	36.799	1.000	5.35
ANISOU	1107	SG	CYS	360	564	826	642	-111	-83 -27
ATOM	1108	N	GLN	361	-13.845	33.808	32.583	1.000	4.37
ATOM	1109	CA	GLN	361	-14.720	34.025	31.436	1.000	4.88
ATOM	1110	C	GLN	361	-16.084	34.526	31.901	1.000	4.94
ATOM	1111	O	GLN	361	-17.070	34.385	31.168	1.000	6.10
ATOM	1112	CB	GLN	361	-14.823	32.839	30.526	1.000	4.40
ATOM	1113	CG	GLN	361	-13.491	32.545	29.799	1.000	5.10
ATOM	1114	CD	GLN	361	-13.212	33.605	28.742	1.000	5.60
ATOM	1115	OE1	GLN	361	-13.841	33.596	27.661	1.000	6.55
ATOM	1116	NE2	GLN	361	-12.310	34.512	29.017	1.000	6.33
ATOM	1117	N	GLY	362	-16.105	35.149	33.038	1.000	5.90
ATOM	1118	CA	GLY	362	-17.324	35.666	33.671	1.000	7.88
ATOM	1119	C	GLY	362	-17.170	35.604	35.175	1.000	7.48
ATOM	1120	O	GLY	362	-16.097	35.278	35.696	1.000	8.67
ATOM	1121	N	ASP	363	-18.240	35.945	35.890	1.000	7.23
ATOM	1122	CA	ASP	363	-18.142	36.036	37.339	1.000	9.40
ATOM	1123	C	ASP	363	-18.921	34.968	38.070	1.000	10.70
ATOM	1124	O	ASP	363	-19.021	34.976	39.323	1.000	11.40
ATOM	1125	CB	ASP	363	-18.605	37.432	37.796	1.000	15.69
ATOM	1126	CG	ASP	363	-20.059	37.697	37.446	1.000	20.75
ATOM	1127	OD1	ASP	363	-20.802	36.777	37.105	1.000	23.80
ATOM	1128	OD2	ASP	363	-20.450	38.897	37.505	1.000	55.07
ATOM	1129	N	ASN	364	-19.476	34.003	37.346	1.000	9.10
ATOM	1130	CA	ASN	364	-20.227	32.949	38.028	1.000	10.29
ATOM	1131	C	ASN	364	-19.314	31.845	38.554	1.000	9.56
ATOM	1132	O	ASN	364	-18.304	31.494	37.947	1.000	7.64
ATOM	1133	CB	ASN	364	-21.249	32.325	37.063	1.000	12.62
ATOM	1134	CG	ASN	364	-22.248	33.388	36.601	1.000	16.42
ATOM	1135	OD1	ASN	364	-22.267	33.749	35.433	1.000	20.19
ATOM	1136	ND2	ASN	364	-22.983	33.930	37.545	1.000	16.68
ATOM	1137	N	TYR	365	-19.712	31.263	39.687	1.000	8.54
ATOM	1138	CA	TYR	365	-19.032	30.081	40.192	1.000	7.95
ATOM	1139	C	TYR	365	-19.708	28.862	39.523	1.000	12.46
ATOM	1140	O	TYR	365	-20.913	28.693	39.623	1.000	15.61
ATOM	1141	CB	TYR	365	-19.266	29.965	41.730	1.000	10.90
ATOM	1142	CG	TYR	365	-18.529	31.046	42.493	1.000	11.27
ATOM	1143	CD1	TYR	365	-17.160	31.076	42.585	1.000	11.68
ATOM	1144	CD2	TYR	365	-19.254	32.072	43.124	1.000	14.79
ATOM	1145	CE1	TYR	365	-16.478	32.080	43.279	1.000	14.73
ATOM	1146	CE2	TYR	365	-18.578	33.078	43.804	1.000	19.54
ATOM	1147	CZ	TYR	365	-17.210	33.071	43.878	1.000	22.77
ATOM	1148	OH	TYR	365	-16.544	34.082	44.569	1.000	30.65
ATOM	1149	N	GLN	366	-18.925	28.027	38.884	1.000	7.90
ATOM	1150	CA	GLN	366	-19.424	26.775	38.314	1.000	6.19
ATOM	1151	C	GLN	366	-19.854	25.876	39.472	1.000	5.23
ATOM	1152	O	GLN	366	-19.113	25.618	40.407	1.000	5.28
ATOM	1153	CB	GLN	366	-18.292	26.168	37.500	1.000	6.50
ATOM	1154	CG	GLN	366	-18.505	24.825	36.923	1.000	9.02
ATOM	1155	CD	GLN	366	-19.390	24.806	35.682	1.000	6.64
ATOM	1156	OE1	GLN	366	-19.765	25.813	35.082	1.000	11.16
ATOM	1157	NE2	GLN	366	-19.756	23.631	35.344	1.000	4.45
ATOM	1158	N	LYS	367	-21.072	25.349	39.370	1.000	5.49
ATOM	1159	CA	LYS	367	-21.589	24.482	40.420	1.000	6.32
ATOM	1160	C	LYS	367	-21.087	23.068	40.275	1.000	5.83
ATOM	1161	O	LYS	367	-20.639	22.671	39.187	1.000	5.59

Fig. 10 T

ATOM	1162	CB	LYS	367	-23.123	24.485	40.382	1.000	7.72
ATOM	1163	CG	LYS	367	-23.742	25.834	40.741	1.000	8.46
ATOM	1164	CD	LYS	367	-25.230	25.823	40.430	1.000	12.60
ATOM	1165	CE	LYS	367	-25.934	27.116	40.782	1.000	15.81
ATOM	1166	NZ	LYS	367	-25.670	28.208	39.813	1.000	32.53
ATOM	1167	N	GLY	368	-21.191	22.307	41.356	1.000	5.58
ATOM	1168	CA	GLY	368	-20.804	20.913	41.348	1.000	4.83
ATOM	1169	C	GLY	368	-22.015	19.975	41.305	1.000	5.09
ATOM	1170	O	GLY	368	-23.118	20.400	41.644	1.000	6.11
ATOM	1171	N	ILE	369	-21.773	18.770	40.860	1.000	5.40
ATOM	1172	CA	ILE	369	-22.728	17.691	40.761	1.000	5.93
ATOM	1173	C	ILE	369	-22.134	16.426	41.367	1.000	7.64
ATOM	1174	O	ILE	369	-20.958	16.136	41.202	1.000	6.45
ATOM	1175	CB	ILE	369	-23.124	17.388	39.279	1.000	7.48
ATOM	1176	CG1	ILE	369	-21.914	17.081	38.385	1.000	7.84
ATOM	1177	CG2	ILE	369	-23.887	18.583	38.729	1.000	6.44
ATOM	1178	CD1	ILE	369	-22.258	16.715	36.954	1.000	8.23
ATOM	1179	N	PRO	370	-22.973	15.665	42.117	1.000	7.96
ATOM	1180	CA	PRO	370	-22.471	14.446	42.739	1.000	8.52
ATOM	1181	C	PRO	370	-22.380	13.275	41.794	1.000	8.04
ATOM	1182	O	PRO	370	-23.284	13.020	40.976	1.000	11.83
ATOM	1183	CB	PRO	370	-23.531	14.169	43.831	1.000	10.22
ATOM	1184	CG	PRO	370	-24.788	14.705	43.250	1.000	10.13
ATOM	1185	CD	PRO	370	-24.397	15.950	42.466	1.000	9.23
ATOM	1186	N	VAL	371	-21.277	12.550	41.865	1.000	9.30
ATOM	1187	CA	VAL	371	-21.072	11.362	41.049	1.000	10.60
ATOM	1188	C	VAL	371	-20.352	10.290	41.861	1.000	11.97
ATOM	1189	O	VAL	371	-19.786	10.583	42.903	1.000	15.40
ATOM	1190	CB	VAL	371	-20.257	11.658	39.786	1.000	10.52
ATOM	1191	CG1	VAL	371	-20.999	12.531	38.823	1.000	11.69
ATOM	1192	CG2	VAL	371	-18.872	12.186	40.115	1.000	11.82
ATOM	1193	N	GLU	372	-20.459	9.058	41.368	1.000	18.65
ATOM	1194	CA	GLU	372	-19.794	7.950	42.076	1.000	27.79
ATOM	1195	C	GLU	372	-18.289	8.048	41.866	1.000	30.20
ATOM	1196	O	GLU	372	-17.835	8.558	40.841	1.000	26.48
ATOM	1197	CB	GLU	372	-20.334	6.614	41.601	1.000	42.16
ATOM	1198	CG	GLU	372	-21.338	5.995	42.594	1.000	52.56
ATOM	1199	CD	GLU	372	-21.906	4.699	42.038	1.000	63.36
ATOM	1200	OE1	GLU	372	-21.762	4.472	40.812	1.000	73.97
ATOM	1201	OE2	GLU	372	-22.486	3.919	42.824	1.000	73.02
ATOM	1202	N	THR	373	-17.524	7.627	42.865	1.000	31.65
ATOM	1203	CA	THR	373	-16.061	7.718	42.794	1.000	30.88
ATOM	1204	C	THR	373	-15.499	6.639	41.873	1.000	30.93
ATOM	1205	O	THR	373	-15.946	5.489	41.924	1.000	30.02
ATOM	1206	CB	THR	373	-15.468	7.500	44.219	1.000	32.72
ATOM	1207	OG1	THR	373	-16.123	8.447	45.106	1.000	33.13
ATOM	1208	CG2	THR	373	-13.994	7.908	44.212	1.000	33.30
ATOM	1209	N	ASP	374	-14.535	7.002	41.024	1.000	25.07
ATOM	1210	CA	ASP	374	-13.947	6.023	40.106	1.000	24.10
ATOM	1211	C	ASP	374	-13.093	4.984	40.876	1.000	33.45
ATOM	1212	O	ASP	374	-12.624	5.323	41.978	1.000	33.81
ATOM	1213	CB	ASP	374	-13.037	6.688	39.093	1.000	18.76
ATOM	1214	CG	ASP	374	-13.745	7.486	38.021	1.000	17.37
ATOM	1215	OD1	ASP	374	-13.164	8.513	37.620	1.000	17.89
ATOM	1216	OD2	ASP	374	-14.851	7.095	37.595	1.000	20.07
ATOM	1217	OXT	ASP	374	-12.800	3.929	40.279	1.000	41.40
ATOM	1218	N	THR	390	-0.915	23.802	-6.005	1.000	52.92
ATOM	1219	CA	THR	390	-0.476	23.131	-4.770	1.000	36.64
ATOM	1220	C	THR	390	-1.680	22.611	-4.008	1.000	26.97
ATOM	1221	O	THR	390	-2.796	22.653	-4.547	1.000	27.88
ATOM	1222	CB	THR	390	0.387	24.034	-3.897	1.000	43.62
ATOM	1223	OG1	THR	390	-0.346	25.129	-3.357	1.000	25.59

Fig 10U

ATOM	1224	CG2	THR	390	1.555	24.623	-4.685	1.000	48.36
ATOM	1225	N	ARG	391	-1.506	22.132	-2.765	1.000	23.21
ATOM	1226	CA	ARG	391	-2.740	21.722	-2.022	1.000	14.14
ATOM	1227	C	ARG	391	-3.092	22.828	-1.045	1.000	8.66
ATOM	1228	O	ARG	391	-2.212	23.521	-0.537	1.000	12.14
ATOM	1229	CB	ARG	391	-2.485	20.419	-1.261	1.000	19.97
ATOM	1230	CG	ARG	391	-2.192	19.240	-2.201	1.000	31.11
ATOM	1231	CD	ARG	391	-3.486	18.495	-2.523	1.000	40.39
ATOM	1232	NE	ARG	391	-3.245	17.423	-3.486	1.000	54.05
ATOM	1233	CZ	ARG	391	-3.021	17.641	-4.781	1.000	66.48
ATOM	1234	NH1	ARG	391	-3.022	18.882	-5.253	1.000	76.01
ATOM	1235	NH2	ARG	391	-2.801	16.620	-5.599	1.000	81.74
ATOM	1236	N	TYR	392	-4.399	22.967	-0.781	1.000	8.01
ATOM	1237	CA	TYR	392	-4.900	24.001	0.101	1.000	5.71
ATOM	1238	C	TYR	392	-5.679	23.408	1.291	1.000	5.23
ATOM	1239	O	TYR	392	-6.388	22.436	1.153	1.000	6.12
ATOM	1240	CB	TYR	392	-5.822	24.980	-0.655	1.000	7.53
ATOM	1241	CG	TYR	392	-5.016	25.742	-1.722	1.000	7.16
ATOM	1242	CD1	TYR	392	-4.717	25.136	-2.932	1.000	10.60
ATOM	1243	CD2	TYR	392	-4.562	27.010	-1.488	1.000	7.55
ATOM	1244	CE1	TYR	392	-3.999	25.849	-3.915	1.000	10.79
ATOM	1245	CE2	TYR	392	-3.810	27.711	-2.433	1.000	8.91
ATOM	1246	CZ	TYR	392	-3.514	27.086	-3.616	1.000	11.78
ATOM	1247	OH	TYR	392	-2.765	27.801	-4.580	1.000	14.42
ATOM	1248	N	ILE	393	-5.496	24.070	2.440	1.000	5.23
ATOM	1249	CA	ILE	393	-6.268	23.730	3.667	1.000	4.76
ATOM	1250	C	ILE	393	-6.903	25.005	4.169	1.000	3.83
ATOM	1251	O	ILE	393	-6.627	26.113	3.680	1.000	4.55
ATOM	1252	CB	ILE	393	-5.356	23.093	4.729	1.000	4.87
ATOM	1253	CG1	ILE	393	-4.222	23.992	5.181	1.000	4.77
ATOM	1254	CG2	ILE	393	-4.879	21.736	4.220	1.000	6.62
ATOM	1255	CD1	ILE	393	-3.368	23.413	6.318	1.000	7.45
ATOM	1256	N	PRO	394	-7.810	24.952	5.141	1.000	3.76
ATOM	1257	CA	PRO	394	-8.436	26.158	5.637	1.000	3.30
ATOM	1258	C	PRO	394	-7.500	27.119	6.356	1.000	4.22
ATOM	1259	O	PRO	394	-6.575	26.696	7.059	1.000	4.05
ATOM	1260	CB	PRO	394	-9.501	25.630	6.619	1.000	3.53
ATOM	1261	CG	PRO	394	-9.795	24.233	6.092	1.000	4.23
ATOM	1262	CD	PRO	394	-8.448	23.717	5.676	1.000	3.62
ATOM	1263	N	ASP	395	-7.746	28.421	6.202	1.000	3.14
ATOM	1264	CA	ASP	395	-7.029	29.475	6.875	1.000	4.60
ATOM	1265	C	ASP	395	-6.933	29.238	8.384	1.000	4.01
ATOM	1266	O	ASP	395	-5.895	29.566	8.977	1.000	4.32
ATOM	1267	CB	ASP	395	-7.806	30.791	6.604	1.000	4.68
ATOM	1268	CG	ASP	395	-7.064	32.012	7.114	1.000	5.85
ATOM	1269	OD1	ASP	395	-5.845	32.074	6.980	1.000	6.13
ATOM	1270	OD2	ASP	395	-7.753	32.928	7.603	1.000	7.94
ATOM	1271	N	GLU	396	-7.941	28.697	9.007	1.000	3.54
ATOM	1272	CA	GLU	396	-8.075	28.507	10.436	1.000	2.41
ATOM	1273	C	GLU	396	-7.734	27.122	10.882	1.000	2.91
ATOM	1274	O	GLU	396	-8.063	26.744	12.025	1.000	3.95
ATOM	1275	CB	GLU	396	-9.421	28.996	10.941	1.000	3.82
ATOM	1276	CG	GLU	396	-9.602	30.498	10.810	1.000	6.68
ATOM	1277	CD	GLU	396	-10.951	31.000	11.256	1.000	6.72
ATOM	1278	OE1	GLU	396	-11.438	30.658	12.343	1.000	6.82
ATOM	1279	OE2	GLU	396	-11.596	31.704	10.420	1.000	12.32
ATOM	1280	N	ALA	397	-7.048	26.337	10.074	1.000	3.03
ATOM	1281	CA	ALA	397	-6.627	25.008	10.463	1.000	3.58
ATOM	1282	C	ALA	397	-5.492	25.051	11.473	1.000	3.60
ATOM	1283	O	ALA	397	-4.748	26.026	11.638	1.000	4.44
ATOM	1284	CB	ALA	397	-6.141	24.246	9.210	1.000	4.24
ATOM	1285	N	ASP	398	-5.327	23.913	12.169	1.000	3.31

Fig. 10 V

ATOM	1286	CA	ASP	398	-4.170	23.684	12.989	1.000	2.90
ATOM	1287	C	ASP	398	-4.061	24.475	14.235	1.000	3.49
ATOM	1288	O	ASP	398	-2.945	24.722	14.731	1.000	4.55
ATOM	1289	CB	ASP	398	-2.864	23.723	12.162	1.000	4.17
ATOM	1290	CG	ASP	398	-2.984	22.912	10.872	1.000	4.87
ATOM	1291	OD1	ASP	398	-3.372	21.739	10.924	1.000	5.01
ATOM	1292	OD2	ASP	398	-2.709	23.488	9.776	1.000	5.60
ATOM	1293	N	PHE	399	-5.143	24.922	14.839	1.000	3.12
ATOM	1294	CA	PHE	399	-5.176	25.612	16.084	1.000	2.97
ATOM	1295	C	PHE	399	-5.657	24.662	17.222	1.000	3.08
ATOM	1296	O	PHE	399	-6.483	23.793	17.048	1.000	3.40
ATOM	1297	CB	PHE	399	-6.171	26.787	16.065	1.000	4.09
ATOM	1298	CG	PHE	399	-5.649	28.047	15.414	1.000	4.20
ATOM	1299	CD1	PHE	399	-5.626	28.170	14.027	1.000	4.21
ATOM	1300	CD2	PHE	399	-5.241	29.131	16.171	1.000	5.25
ATOM	1301	CE1	PHE	399	-5.190	29.325	13.432	1.000	5.38
ATOM	1302	CE2	PHE	399	-4.786	30.292	15.574	1.000	7.67
ATOM	1303	CZ	PHE	399	-4.778	30.398	14.193	1.000	5.71
ATOM	1304	N	LEU	400	-5.095	24.978	18.387	1.000	3.32
ATOM	1305	CA	LEU	400	-5.557	24.374	19.647	1.000	2.80
ATOM	1306	C	LEU	400	-5.703	25.538	20.644	1.000	3.72
ATOM	1307	O	LEU	400	-4.735	26.268	20.868	1.000	4.75
ATOM	1308	CB	LEU	400	-4.594	23.346	20.144	1.000	4.38
ATOM	1309	CG	LEU	400	-4.795	22.801	21.566	1.000	4.77
ATOM	1310	CD1	LEU	400	-6.117	22.117	21.689	1.000	5.19
ATOM	1311	CD2	LEU	400	-3.641	21.862	21.907	1.000	7.23
ATOM	1312	N	LEU	401	-6.890	25.683	21.200	1.000	3.00
ATOM	1313	CA	LEU	401	-7.143	26.723	22.219	1.000	3.66
ATOM	1314	C	LEU	401	-7.519	25.989	23.521	1.000	3.94
ATOM	1315	O	LEU	401	-8.527	25.304	23.594	1.000	4.46
ATOM	1316	CB	LEU	401	-8.313	27.584	21.778	1.000	5.14
ATOM	1317	CG	LEU	401	-8.828	28.614	22.802	1.000	6.42
ATOM	1318	CD1	LEU	401	-7.716	29.605	23.118	1.000	9.29
ATOM	1319	CD2	LEU	401	-10.055	29.311	22.226	1.000	9.85
ATOM	1320	N	GLY	402	-6.658	26.140	24.508	1.000	3.21
ATOM	1321	CA	GLY	402	-6.869	25.552	25.832	1.000	3.81
ATOM	1322	C	GLY	402	-7.412	26.615	26.767	1.000	3.94
ATOM	1323	O	GLY	402	-6.638	27.480	27.198	1.000	4.25
ATOM	1324	N	MET	403	-8.704	26.590	27.063	1.000	3.30
ATOM	1325	CA	MET	403	-9.272	27.565	28.007	1.000	4.54
ATOM	1326	C	MET	403	-9.292	26.927	29.419	1.000	4.02
ATOM	1327	O	MET	403	-9.591	25.770	29.621	1.000	4.03
ATOM	1328	CB	MET	403	-10.725	27.880	27.623	1.000	4.23
ATOM	1329	CG	MET	403	-10.912	28.564	26.282	1.000	5.55
ATOM	1330	SD	MET	403	-10.203	30.225	26.239	1.000	7.19
ANISOU	1330	SD	MET	403	921	915	896	-19	141 323
ATOM	1331	CE	MET	403	-11.253	31.073	27.412	1.000	8.87
ATOM	1332	N	ALA	404	-8.965	27.774	30.416	1.000	3.37
ATOM	1333	CA	ALA	404	-9.026	27.342	31.800	1.000	3.70
ATOM	1334	C	ALA	404	-10.454	27.122	32.287	1.000	3.21
ATOM	1335	O	ALA	404	-10.633	26.365	33.257	1.000	3.55
ATOM	1336	CB	ALA	404	-8.392	28.450	32.652	1.000	3.63
ATOM	1337	N	THR	405	-11.429	27.709	31.656	1.000	2.70
ATOM	1338	CA	THR	405	-12.821	27.566	32.042	1.000	3.64
ATOM	1339	C	THR	405	-13.740	27.680	30.830	1.000	3.93
ATOM	1340	O	THR	405	-13.450	28.451	29.901	1.000	4.79
ATOM	1341	CB	THR	405	-13.218	28.631	33.079	1.000	4.52
ATOM	1342	OG1	THR	405	-14.615	28.532	33.411	1.000	4.49
ATOM	1343	CG2	THR	405	-12.950	30.035	32.607	1.000	5.35
ATOM	1344	N	VAL	406	-14.863	27.023	30.936	1.000	3.53
ATOM	1345	CA	VAL	406	-16.023	27.236	30.105	1.000	4.87
ATOM	1346	C	VAL	406	-16.487	28.699	30.279	1.000	4.03

Fig. 10 W

ATOM	1347	O	VAL	406	-16.173	29.391	31.252	1.000	4.86
ATOM	1348	CB	VAL	406	-17.194	26.304	30.502	1.000	4.62
ATOM	1349	CG1	VAL	406	-16.911	24.871	30.181	1.000	5.63
ATOM	1350	CG2	VAL	406	-17.652	26.536	31.924	1.000	6.57
ATOM	1351	N	ASN	407	-17.262	29.164	29.310	1.000	4.79
ATOM	1352	CA	ASN	407	-17.762	30.540	29.322	1.000	5.89
ATOM	1353	C	ASN	407	-18.633	30.813	30.548	1.000	5.55
ATOM	1354	O	ASN	407	-19.237	29.903	31.100	1.000	5.97
ATOM	1355	CB	ASN	407	-18.644	30.783	28.078	1.000	7.43
ATOM	1356	CG	ASN	407	-18.714	32.259	27.752	1.000	13.12
ATOM	1357	OD1	ASN	407	-17.800	33.033	28.021	1.000	13.49
ATOM	1358	ND2	ASN	407	-19.838	32.646	27.160	1.000	23.25
ATOM	1359	N	ASN	408	-18.681	32.086	30.940	1.000	4.97
ATOM	1360	CA	ASN	408	-19.492	32.640	31.982	1.000	6.80
ATOM	1361	C	ASN	408	-18.956	32.475	33.388	1.000	6.27
ATOM	1362	O	ASN	408	-19.552	33.047	34.318	1.000	8.36
ATOM	1363	CB	ASN	408	-20.912	32.000	32.027	1.000	10.82
ATOM	1364	CG	ASN	408	-21.658	32.027	30.744	1.000	21.76
ATOM	1365	OD1	ASN	408	-22.256	31.003	30.335	1.000	38.33
ATOM	1366	ND2	ASN	408	-21.609	33.140	30.054	1.000	22.74
ATOM	1367	N	CYS	409	-17.925	31.704	33.584	1.000	6.10
ATOM	1368	CA	CYS	409	-17.434	31.321	34.877	1.000	5.69
ATOM	1369	C	CYS	409	-16.040	31.771	35.207	1.000	4.29
ATOM	1370	O	CYS	409	-15.200	32.018	34.352	1.000	4.67
ATOM	1371	CB	CYS	409	-17.571	29.811	35.102	1.000	5.66
ATOM	1372	SG	CYS	409	-19.276	29.214	34.947	1.000	8.03
ANISOU	1372	SG	CYS	409	575	1015	1460	-134	12 -62
ATOM	1373	N	VAL	410	-15.747	31.766	36.514	1.000	4.89
ATOM	1374	CA	VAL	410	-14.433	32.069	37.018	1.000	4.29
ATOM	1375	C	VAL	410	-13.475	30.907	36.812	1.000	4.38
ATOM	1376	O	VAL	410	-13.878	29.741	36.638	1.000	4.83
ATOM	1377	CB	VAL	410	-14.474	32.419	38.524	1.000	6.44
ATOM	1378	CG1	VAL	410	-15.349	33.619	38.785	1.000	6.43
ATOM	1379	CG2	VAL	410	-14.885	31.233	39.387	1.000	6.71
ATOM	1380	N	SER	411	-12.195	31.210	36.895	1.000	4.71
ATOM	1381	CA	SER	411	-11.167	30.219	37.087	1.000	4.65
ATOM	1382	C	SER	411	-10.356	30.619	38.343	1.000	4.02
ATOM	1383	O	SER	411	-10.400	31.802	38.723	1.000	4.92
ATOM	1384	CB	SER	411	-10.262	29.944	35.927	1.000	5.41
ATOM	1385	OG	SER	411	-9.583	31.074	35.486	1.000	5.74
ATOM	1386	N	TYR	412	-9.672	29.661	38.923	1.000	3.52
ATOM	1387	CA	TYR	412	-9.043	29.829	40.191	1.000	4.06
ATOM	1388	C	TYR	412	-7.539	29.978	40.172	1.000	3.86
ATOM	1389	O	TYR	412	-6.823	29.324	39.414	1.000	4.19
ATOM	1390	CB	TYR	412	-9.450	28.738	41.147	1.000	5.41
ATOM	1391	CG	TYR	412	-10.908	28.775	41.557	1.000	4.77
ATOM	1392	CD1	TYR	412	-11.290	29.663	42.559	1.000	6.55
ATOM	1393	CD2	TYR	412	-11.855	27.974	40.974	1.000	5.99
ATOM	1394	CE1	TYR	412	-12.601	29.730	42.975	1.000	7.10
ATOM	1395	CE2	TYR	412	-13.165	27.997	41.404	1.000	7.62
ATOM	1396	CZ	TYR	412	-13.524	28.885	42.400	1.000	6.67
ATOM	1397	OH	TYR	412	-14.830	28.938	42.837	1.000	11.20
ATOM	1398	N	ARG	413	-7.089	30.841	41.101	1.000	4.38
ATOM	1399	CA	ARG	413	-5.694	31.120	41.305	1.000	5.15
ATOM	1400	C	ARG	413	-5.361	31.032	42.816	1.000	5.84
ATOM	1401	O	ARG	413	-5.957	31.754	43.588	1.000	5.23
ATOM	1402	CB	ARG	413	-5.303	32.491	40.792	1.000	4.60
ATOM	1403	CG	ARG	413	-3.890	32.951	41.014	1.000	5.42
ATOM	1404	CD	ARG	413	-3.488	34.178	40.182	1.000	6.10
ATOM	1405	NE	ARG	413	-4.623	35.088	40.105	1.000	6.86
ATOM	1406	CZ	ARG	413	-5.156	35.749	41.109	1.000	6.22
ATOM	1407	NH1	ARG	413	-4.510	35.845	42.273	1.000	6.91

Fig. 10 X

ATOM	1408	NH2	ARG	413	-6.311	36.410	40.950	1.000	7.97
ATOM	1409	N	ASN	414	-4.468	30.125	43.136	1.000	4.99
ATOM	1410	CA	ASN	414	-3.981	30.091	44.561	1.000	5.25
ATOM	1411	C	ASN	414	-2.737	30.994	44.590	1.000	5.13
ATOM	1412	O	ASN	414	-1.741	30.686	43.924	1.000	5.31
ATOM	1413	CB	ASN	414	-3.632	28.647	44.874	1.000	6.87
ATOM	1414	CG	ASN	414	-3.162	28.396	46.276	1.000	9.66
ATOM	1415	OD1	ASN	414	-3.219	27.247	46.795	1.000	14.57
ATOM	1416	ND2	ASN	414	-2.751	29.411	46.954	1.000	7.60
ATOM	1417	N	PRO	415	-2.771	32.103	45.333	1.000	5.27
ATOM	1418	CA	PRO	415	-1.616	33.000	45.354	1.000	6.33
ATOM	1419	C	PRO	415	-0.301	32.363	45.742	1.000	4.98
ATOM	1420	O	PRO	415	0.771	32.883	45.385	1.000	6.23
ATOM	1421	CB	PRO	415	-2.005	34.094	46.355	1.000	7.92
ATOM	1422	CG	PRO	415	-3.508	34.088	46.297	1.000	10.33
ATOM	1423	CD	PRO	415	-3.892	32.632	46.141	1.000	6.30
ATOM	1424	N	ALA	416	-0.324	31.296	46.489	1.000	6.27
ATOM	1425	CA	ALA	416	0.777	30.535	46.962	1.000	7.38
ATOM	1426	C	ALA	416	1.244	29.380	46.144	1.000	5.86
ATOM	1427	O	ALA	416	2.286	28.760	46.409	1.000	7.04
ATOM	1428	CB	ALA	416	0.633	30.177	48.424	1.000	8.80
ATOM	1429	N	GLU	417	0.523	29.011	45.068	1.000	6.43
ATOM	1430	CA	GLU	417	0.861	27.895	44.227	1.000	6.62
ATOM	1431	C	GLU	417	0.720	28.152	42.725	1.000	5.95
ATOM	1432	O	GLU	417	1.378	27.411	41.970	1.000	7.77
ATOM	1433	CB	GLU	417	-0.057	26.686	44.567	1.000	8.23
ATOM	1434	CG	GLU	417	0.123	26.221	45.993	1.000	13.15
ATOM	1435	CD	GLU	417	1.345	25.371	46.190	1.000	20.59
ATOM	1436	OE1	GLU	417	2.090	25.114	45.225	1.000	19.88
ATOM	1437	OE2	GLU	417	1.578	24.919	47.345	1.000	26.28
ATOM	1438	N	GLY	418	-0.082	29.100	42.308	1.000	5.08
ATOM	1439	CA	GLY	418	-0.384	29.243	40.870	1.000	4.51
ATOM	1440	C	GLY	418	-1.845	28.879	40.616	1.000	4.05
ATOM	1441	O	GLY	418	-2.625	28.606	41.538	1.000	5.18
ATOM	1442	N	THR	419	-2.218	28.852	39.321	1.000	4.21
ATOM	1443	CA	THR	419	-3.619	28.551	38.993	1.000	4.00
ATOM	1444	C	THR	419	-3.851	27.071	38.898	1.000	3.28
ATOM	1445	O	THR	419	-3.003	26.260	38.547	1.000	4.24
ATOM	1446	CB	THR	419	-4.056	29.268	37.723	1.000	4.87
ATOM	1447	OG1	THR	419	-3.298	28.808	36.584	1.000	3.78
ATOM	1448	CG2	THR	419	-3.939	30.774	37.843	1.000	3.95
ATOM	1449	N	TRP	420	-5.102	26.679	39.145	1.000	3.73
ATOM	1450	CA	TRP	420	-5.466	25.267	39.037	1.000	4.62
ATOM	1451	C	TRP	420	-5.136	24.756	37.619	1.000	4.78
ATOM	1452	O	TRP	420	-4.567	23.694	37.467	1.000	4.62
ATOM	1453	CB	TRP	420	-6.982	25.121	39.270	1.000	4.25
ATOM	1454	CG	TRP	420	-7.436	25.291	40.678	1.000	5.13
ATOM	1455	CD1	TRP	420	-6.695	25.623	41.771	1.000	5.68
ATOM	1456	CD2	TRP	420	-8.785	25.067	41.163	1.000	5.11
ATOM	1457	NE1	TRP	420	-7.502	25.636	42.903	1.000	5.64
ATOM	1458	CE2	TRP	420	-8.764	25.319	42.558	1.000	5.39
ATOM	1459	CE3	TRP	420	-9.970	24.714	40.543	1.000	5.20
ATOM	1460	CZ2	TRP	420	-9.949	25.199	43.309	1.000	6.64
ATOM	1461	CZ3	TRP	420	-11.129	24.596	41.298	1.000	7.34
ATOM	1462	CH2	TRP	420	-11.085	24.854	42.669	1.000	6.88
ATOM	1463	N	TYR	421	-5.537	25.533	36.602	1.000	3.55
ATOM	1464	CA	TYR	421	-5.340	25.101	35.230	1.000	3.73
ATOM	1465	C	TYR	421	-3.900	25.004	34.823	1.000	3.56
ATOM	1466	O	TYR	421	-3.436	23.980	34.292	1.000	3.47
ATOM	1467	CB	TYR	421	-6.170	25.928	34.284	1.000	3.71
ATOM	1468	CG	TYR	421	-6.035	25.589	32.824	1.000	3.13
ATOM	1469	CD1	TYR	421	-6.574	24.412	32.328	1.000	3.30

Fig. 10 Y

ATOM	1470	CD2	TYR	421	-5.426	26.454	31.926	1.000	3.76
ATOM	1471	CE1	TYR	421	-6.473	24.084	30.995	1.000	3.14
ATOM	1472	CE2	TYR	421	-5.346	26.158	30.589	1.000	3.99
ATOM	1473	CZ	TYR	421	-5.874	24.961	30.131	1.000	3.37
ATOM	1474	OH	TYR	421	-5.783	24.694	28.771	1.000	4.35
ATOM	1475	N	ILE	422	-3.142	26.090	34.980	1.000	3.41
ATOM	1476	CA	ILE	422	-1.751	26.063	34.495	1.000	3.02
ATOM	1477	C	ILE	422	-0.916	25.090	35.241	1.000	3.40
ATOM	1478	O	ILE	422	-0.067	24.388	34.671	1.000	4.17
ATOM	1479	CB	ILE	422	-1.161	27.466	34.455	1.000	4.47
ATOM	1480	CG1	ILE	422	-1.940	28.404	33.538	1.000	4.47
ATOM	1481	CG2	ILE	422	0.326	27.423	34.120	1.000	4.03
ATOM	1482	CD1	ILE	422	-1.889	28.057	32.051	1.000	4.99
ATOM	1483	N	GLN	423	-1.072	25.006	36.563	1.000	3.72
ATOM	1484	CA	GLN	423	-0.281	24.042	37.325	1.000	4.20
ATOM	1485	C	GLN	423	-0.590	22.617	36.905	1.000	4.10
ATOM	1486	O	GLN	423	0.313	21.783	36.788	1.000	5.23
ATOM	1487	CB	GLN	423	-0.378	24.282	38.814	1.000	4.31
ATOM	1488	CG	GLN	423	0.096	25.647	39.270	1.000	5.26
ATOM	1489	CD	GLN	423	1.584	25.867	39.036	1.000	5.71
ATOM	1490	OE1	GLN	423	2.407	24.982	39.325	1.000	7.83
ATOM	1491	NE2	GLN	423	1.944	27.020	38.534	1.000	5.87
ATOM	1492	N	SER	424	-1.869	22.291	36.700	1.000	4.99
ATOM	1493	CA	SER	424	-2.243	20.956	36.262	1.000	4.12
ATOM	1494	C	SER	424	-1.723	20.683	34.863	1.000	4.06
ATOM	1495	O	SER	424	-1.218	19.591	34.597	1.000	5.31
ATOM	1496	CB	SER	424	-3.749	20.793	36.309	1.000	5.31
ATOM	1497	OG	ASER	424	-4.203	20.847	37.668	0.400	8.52
ATOM	1498	OG'	BSER	424	-4.164	19.552	35.733	0.600	7.57
ATOM	1499	N	LEU	425	-1.863	21.668	33.969	1.000	3.66
ATOM	1500	CA	LEU	425	-1.352	21.538	32.601	1.000	3.92
ATOM	1501	C	LEU	425	0.122	21.214	32.599	1.000	4.47
ATOM	1502	O	LEU	425	0.567	20.297	31.909	1.000	4.71
ATOM	1503	CB	LEU	425	-1.632	22.820	31.839	1.000	4.51
ATOM	1504	CG	LEU	425	-1.020	22.936	30.447	1.000	4.26
ATOM	1505	CD1	LEU	425	-1.669	21.932	29.484	1.000	5.96
ATOM	1506	CD2	LEU	425	-1.182	24.353	29.917	1.000	5.49
ATOM	1507	N	CYS	426	0.912	21.994	33.345	1.000	4.11
ATOM	1508	CA	CYS	426	2.367	21.760	33.348	1.000	4.90
ATOM	1509	C	CYS	426	2.732	20.427	33.956	1.000	5.29
ATOM	1510	O	CYS	426	3.602	19.712	33.422	1.000	6.01
ATOM	1511	CB	CYS	426	3.067	22.896	34.075	1.000	4.91
ATOM	1512	SG	CYS	426	3.022	24.458	33.165	1.000	6.10
ANISOU	1512	SG	CYS	426	590	875	853	-25	37
ATOM	1513	N	GLN	427	2.062	20.027	35.026	1.000	5.13
ATOM	1514	CA	GLN	427	2.371	18.696	35.604	1.000	5.82
ATOM	1515	C	GLN	427	2.074	17.591	34.612	1.000	6.09
ATOM	1516	O	GLN	427	2.887	16.658	34.430	1.000	8.95
ATOM	1517	CB	GLN	427	1.540	18.527	36.873	1.000	9.35
ATOM	1518	CG	GLN	427	1.590	17.119	37.468	1.000	18.44
ATOM	1519	CD	GLN	427	1.416	17.162	38.977	1.000	32.21
ATOM	1520	OE1	GLN	427	0.772	18.070	39.508	1.000	45.92
ATOM	1521	NE2	GLN	427	2.011	16.186	39.643	1.000	56.23
ATOM	1522	N	SER	428	0.945	17.655	33.934	1.000	5.97
ATOM	1523	CA	SER	428	0.557	16.633	32.975	1.000	5.57
ATOM	1524	C	SER	428	1.485	16.598	31.783	1.000	5.80
ATOM	1525	O	SER	428	1.858	15.519	31.310	1.000	6.47
ATOM	1526	CB	SER	428	-0.883	16.779	32.564	1.000	7.41
ATOM	1527	OG	ASER	428	-1.301	15.841	31.600	0.400	12.01
ATOM	1528	OG'	BSER	428	-1.781	16.566	33.735	0.600	9.42
ATOM	1529	N	LEU	429	1.869	17.763	31.258	1.000	5.45
ATOM	1530	CA	LEU	429	2.820	17.786	30.148	1.000	5.98

Fig. 10 Z

ATOM	1531	C	LEU	429	4.144	17.174	30.543	1.000	7.65
ATOM	1532	O	LEU	429	4.772	16.401	29.813	1.000	6.98
ATOM	1533	CB	LEU	429	3.008	19.239	29.694	1.000	5.41
ATOM	1534	CG	LEU	429	1.857	19.909	28.963	1.000	5.03
ATOM	1535	CD1	LEU	429	2.019	21.420	28.926	1.000	6.86
ATOM	1536	CD2	LEU	429	1.675	19.364	27.564	1.000	8.82
ATOM	1537	N	ARG	430	4.670	17.588	31.712	1.000	7.67
ATOM	1538	CA	ARG	430	5.959	17.075	32.133	1.000	8.90
ATOM	1539	C	ARG	430	5.977	15.592	32.330	1.000	10.66
ATOM	1540	O	ARG	430	6.984	14.939	31.985	1.000	11.39
ATOM	1541	CB	ARG	430	6.469	17.812	33.382	1.000	11.51
ATOM	1542	CG	ARG	430	6.742	19.291	33.101	1.000	12.18
ATOM	1543	CD	ARG	430	7.396	19.981	34.296	1.000	14.24
ATOM	1544	NE	ARG	430	8.829	19.675	34.352	1.000	18.29
ATOM	1545	CZ	ARG	430	9.589	19.893	35.430	1.000	18.67
ATOM	1546	NH1	ARG	430	9.056	20.397	36.522	1.000	20.84
ATOM	1547	NH2	ARG	430	10.880	19.620	35.385	1.000	20.90
ATOM	1548	N	GLU	431	4.907	15.014	32.827	1.000	9.11
ATOM	1549	CA	GLU	431	4.799	13.587	33.045	1.000	10.46
ATOM	1550	C	GLU	431	4.544	12.796	31.776	1.000	10.06
ATOM	1551	O	GLU	431	5.042	11.679	31.606	1.000	12.70
ATOM	1552	CB	GLU	431	3.632	13.310	34.023	1.000	13.74
ATOM	1553	CG	GLU	431	3.210	11.842	34.028	1.000	32.67
ATOM	1554	CD	GLU	431	4.092	11.000	34.929	1.000	47.87
ATOM	1555	OE1	GLU	431	3.971	11.136	36.166	1.000	61.17
ATOM	1556	OE2	GLU	431	4.897	10.204	34.394	1.000	64.04
ATOM	1557	N	ARG	432	3.660	13.312	30.893	1.000	7.52
ATOM	1558	CA	ARG	432	3.201	12.549	29.765	1.000	6.42
ATOM	1559	C	ARG	432	3.855	12.779	28.462	1.000	7.96
ATOM	1560	O	ARG	432	3.831	11.916	27.566	1.000	8.24
ATOM	1561	CB	ARG	432	1.659	12.729	29.624	1.000	9.05
ATOM	1562	CG	ARG	432	0.964	12.275	30.910	1.000	12.03
ATOM	1563	CD	ARG	432	-0.521	12.246	30.736	1.000	15.33
ATOM	1564	NE	ARG	432	-0.991	11.193	29.882	1.000	24.03
ATOM	1565	CZ	ARG	432	-1.931	10.297	30.084	1.000	24.21
ATOM	1566	NH1	ARG	432	-2.633	10.236	31.213	1.000	32.54
ATOM	1567	NH2	ARG	432	-2.176	9.422	29.113	1.000	25.64
ATOM	1568	N	CYS	433	4.399	13.964	28.212	1.000	7.38
ATOM	1569	CA	CYS	433	5.125	14.142	26.955	1.000	8.85
ATOM	1570	C	CYS	433	6.259	13.143	26.823	1.000	8.31
ATOM	1571	O	CYS	433	6.450	12.628	25.691	1.000	12.56
ATOM	1572	CB	CYS	433	5.604	15.563	26.814	1.000	9.07
ATOM	1573	SG	CYS	433	4.241	16.747	26.559	1.000	10.23
ANISOU	1573	SG	CYS	433	2028	934	924	-233	167
ATOM	1574	N	PRO	434	7.026	12.813	27.827	1.000	11.66
ATOM	1575	CA	PRO	434	8.066	11.775	27.676	1.000	15.19
ATOM	1576	C	PRO	434	7.516	10.421	27.290	1.000	16.14
ATOM	1577	O	PRO	434	8.282	9.593	26.739	1.000	17.78
ATOM	1578	CB	PRO	434	8.732	11.717	29.042	1.000	20.14
ATOM	1579	CG	PRO	434	8.481	13.073	29.633	1.000	16.26
ATOM	1580	CD	PRO	434	7.191	13.546	29.089	1.000	12.86
ATOM	1581	N	ARG	435	6.273	10.156	27.560	1.000	14.23
ATOM	1582	CA	ARG	435	5.589	8.909	27.241	1.000	17.09
ATOM	1583	C	ARG	435	5.025	8.918	25.819	1.000	15.31
ATOM	1584	O	ARG	435	4.514	7.875	25.370	1.000	18.41
ATOM	1585	CB	ARG	435	4.498	8.629	28.242	1.000	18.38
ATOM	1586	CG	ARG	435	4.812	8.657	29.699	1.000	33.53
ATOM	1587	CD	ARG	435	6.268	8.530	30.071	1.000	52.48
ATOM	1588	NE	ARG	435	6.510	7.441	31.019	1.000	65.68
ATOM	1589	CZ	ARG	435	6.572	6.161	30.687	1.000	74.36
ATOM	1590	NH1	ARG	435	6.418	5.785	29.421	1.000	89.03
ATOM	1591	NH2	ARG	435	6.792	5.241	31.615	1.000	84.16

-6

Fig. 10 AA

ATOM	1592	N	GLY	436	5.112	10.027	25.116	1.000	11.98
ATOM	1593	CA	GLY	436	4.624	10.145	23.761	1.000	12.33
ATOM	1594	C	GLY	436	3.146	10.423	23.650	1.000	11.94
ATOM	1595	O	GLY	436	2.583	10.372	22.533	1.000	11.36
ATOM	1596	N	ASP	437	2.485	10.747	24.746	1.000	9.22
ATOM	1597	CA	ASP	437	1.060	11.044	24.724	1.000	9.90
ATOM	1598	C	ASP	437	0.785	12.336	23.969	1.000	7.00
ATOM	1599	O	ASP	437	1.558	13.294	24.040	1.000	7.66
ATOM	1600	CB	ASP	437	0.471	11.132	26.118	1.000	9.26
ATOM	1601	CG	ASP	437	0.437	9.813	26.862	1.000	16.13
ATOM	1602	OD1	ASP	437	0.420	8.756	26.202	1.000	19.00
ATOM	1603	OD2	ASP	437	0.419	9.834	28.103	1.000	16.80
ATOM	1604	N	ASP	438	-0.341	12.385	23.274	1.000	6.73
ATOM	1605	CA	ASP	438	-0.673	13.566	22.500	1.000	6.86
ATOM	1606	C	ASP	438	-1.375	14.610	23.339	1.000	6.35
ATOM	1607	O	ASP	438	-1.880	14.330	24.458	1.000	6.57
ATOM	1608	CB	ASP	438	-1.516	13.225	21.278	1.000	7.77
ATOM	1609	CG	ASP	438	-2.940	12.885	21.667	1.000	10.13
ATOM	1610	OD1	ASP	438	-3.153	11.730	22.147	1.000	16.36
ATOM	1611	OD2	ASP	438	-3.848	13.703	21.515	1.000	13.48
ATOM	1612	N	ILE	439	-1.436	15.822	22.841	1.000	5.23
ATOM	1613	CA	ILE	439	-1.966	16.933	23.612	1.000	5.64
ATOM	1614	C	ILE	439	-3.423	16.815	23.967	1.000	4.94
ATOM	1615	O	ILE	439	-3.823	17.329	25.031	1.000	5.00
ATOM	1616	CB	ILE	439	-1.690	18.281	22.941	1.000	7.01
ATOM	1617	CG1	ILE	439	-1.812	19.466	23.891	1.000	8.07
ATOM	1618	CG2	ILE	439	-2.743	18.466	21.778	1.000	13.44
ATOM	1619	CD1	ILE	439	-0.914	19.415	25.095	1.000	20.61
ATOM	1620	N	LEU	440	-4.244	16.231	23.126	1.000	5.20
ATOM	1621	CA	LEU	440	-5.665	16.066	23.448	1.000	6.64
ATOM	1622	C	LEU	440	-5.862	15.095	24.566	1.000	6.72
ATOM	1623	O	LEU	440	-6.718	15.277	25.460	1.000	6.52
ATOM	1624	CB	LEU	440	-6.459	15.691	22.199	1.000	8.51
ATOM	1625	CG	LEU	440	-6.449	16.709	21.060	1.000	7.99
ATOM	1626	CD1	LEU	440	-7.359	16.232	19.932	1.000	10.01
ATOM	1627	CD2	LEU	440	-6.892	18.085	21.530	1.000	10.37
ATOM	1628	N	THR	441	-5.057	14.050	24.609	1.000	7.28
ATOM	1629	CA	THR	441	-5.087	13.103	25.733	1.000	8.53
ATOM	1630	C	THR	441	-4.625	13.797	26.998	1.000	7.53
ATOM	1631	O	THR	441	-5.268	13.684	28.072	1.000	7.06
ATOM	1632	CB	THR	441	-4.094	11.937	25.383	1.000	11.04
ATOM	1633	OG1	THR	441	-4.667	11.304	24.213	1.000	14.61
ATOM	1634	CG2	THR	441	-4.075	10.931	26.496	1.000	11.96
ATOM	1635	N	ILE	442	-3.563	14.581	26.916	1.000	5.39
ATOM	1636	CA	ILE	442	-3.105	15.354	28.057	1.000	5.09
ATOM	1637	C	ILE	442	-4.149	16.314	28.552	1.000	3.92
ATOM	1638	O	ILE	442	-4.398	16.418	29.756	1.000	5.46
ATOM	1639	CB	ILE	442	-1.758	16.013	27.760	1.000	7.42
ATOM	1640	CG1	ILE	442	-0.656	14.963	27.587	1.000	8.92
ATOM	1641	CG2	ILE	442	-1.352	17.056	28.768	1.000	10.14
ATOM	1642	CD1	ILE	442	0.622	15.423	26.979	1.000	10.36
ATOM	1643	N	LEU	443	-4.812	17.034	27.645	1.000	4.07
ATOM	1644	CA	LEU	443	-5.826	17.984	28.024	1.000	3.81
ATOM	1645	C	LEU	443	-7.054	17.349	28.627	1.000	3.92
ATOM	1646	O	LEU	443	-7.740	17.973	29.452	1.000	4.39
ATOM	1647	CB	LEU	443	-6.146	18.983	26.930	1.000	2.96
ATOM	1648	CG	LEU	443	-5.059	20.008	26.599	1.000	4.45
ATOM	1649	CD1	LEU	443	-5.388	20.717	25.295	1.000	5.92
ATOM	1650	CD2	LEU	443	-4.908	21.061	27.703	1.000	8.45
ATOM	1651	N	THR	444	-7.342	16.112	28.222	1.000	3.95
ATOM	1652	CA	THR	444	-8.414	15.333	28.848	1.000	4.75
ATOM	1653	C	THR	444	-8.057	15.063	30.320	1.000	3.98

Fig. 10 BB

ATOM	1654	O	THR	444	-8.913	15.194	31.205	1.000	4.52
ATOM	1655	CB	THR	444	-8.623	14.009	28.075	1.000	5.12
ATOM	1656	OG1	THR	444	-9.143	14.370	26.748	1.000	5.63
ATOM	1657	CG2	THR	444	-9.744	13.192	28.708	1.000	5.43
ATOM	1658	N	GLU	445	-6.816	14.708	30.582	1.000	4.02
ATOM	1659	CA	GLU	445	-6.338	14.513	31.951	1.000	4.52
ATOM	1660	C	GLU	445	-6.423	15.800	32.739	1.000	4.21
ATOM	1661	O	GLU	445	-6.828	15.757	33.924	1.000	5.29
ATOM	1662	CB	GLU	445	-4.924	13.951	31.971	1.000	6.08
ATOM	1663	CG	GLU	445	-4.306	13.889	33.374	1.000	8.57
ATOM	1664	CD	GLU	445	-3.060	13.046	33.442	1.000	15.38
ATOM	1665	OE1	GLU	445	-3.175	11.799	33.546	1.000	33.54
ATOM	1666	OE2	GLU	445	-1.938	13.612	33.398	1.000	17.66
ATOM	1667	N	VAL	446	-6.074	16.930	32.153	1.000	4.38
ATOM	1668	CA	VAL	446	-6.214	18.206	32.862	1.000	4.12
ATOM	1669	C	VAL	446	-7.682	18.424	33.220	1.000	4.32
ATOM	1670	O	VAL	446	-8.004	18.855	34.320	1.000	4.23
ATOM	1671	CB	VAL	446	-5.665	19.370	32.035	1.000	3.93
ATOM	1672	CG1	VAL	446	-5.918	20.709	32.664	1.000	5.23
ATOM	1673	CG2	VAL	446	-4.146	19.174	31.851	1.000	6.30
ATOM	1674	N	ASN	447	-8.596	18.145	32.276	1.000	3.86
ATOM	1675	CA	ASN	447	-10.027	18.235	32.599	1.000	3.67
ATOM	1676	C	ASN	447	-10.371	17.393	33.811	1.000	3.40
ATOM	1677	O	ASN	447	-11.114	17.850	34.703	1.000	4.16
ATOM	1678	CB	ASN	447	-10.890	17.874	31.404	1.000	3.53
ATOM	1679	CG	ASN	447	-10.973	18.906	30.320	1.000	4.35
ATOM	1680	OD1	ASN	447	-11.540	18.558	29.202	1.000	6.21
ATOM	1681	ND2	ASN	447	-10.509	20.083	30.502	1.000	1.99
ATOM	1682	N	TYR	448	-9.917	16.169	33.824	1.000	3.51
ATOM	1683	CA	TYR	448	-10.220	15.243	34.932	1.000	3.55
ATOM	1684	C	TYR	448	-9.653	15.806	36.245	1.000	4.94
ATOM	1685	O	TYR	448	-10.369	15.820	37.258	1.000	4.68
ATOM	1686	CB	TYR	448	-9.631	13.881	34.627	1.000	4.02
ATOM	1687	CG	TYR	448	-9.929	12.842	35.688	1.000	6.03
ATOM	1688	CD1	TYR	448	-9.125	12.648	36.797	1.000	7.60
ATOM	1689	CD2	TYR	448	-11.067	12.053	35.530	1.000	7.02
ATOM	1690	CE1	TYR	448	-9.484	11.672	37.733	1.000	9.04
ATOM	1691	CE2	TYR	448	-11.406	11.084	36.455	1.000	9.50
ATOM	1692	CZ	TYR	448	-10.597	10.912	37.540	1.000	7.77
ATOM	1693	OH	TYR	448	-10.938	9.930	38.494	1.000	12.76
ATOM	1694	N	GLU	449	-8.403	16.229	36.247	1.000	4.42
ATOM	1695	CA	GLU	449	-7.761	16.681	37.480	1.000	4.85
ATOM	1696	C	GLU	449	-8.385	17.923	38.007	1.000	4.57
ATOM	1697	O	GLU	449	-8.718	18.045	39.212	1.000	5.15
ATOM	1698	CB	GLU	449	-6.244	16.848	37.263	1.000	6.18
ATOM	1699	CG	GLU	449	-5.540	15.535	37.000	1.000	14.18
ATOM	1700	CD	GLU	449	-5.540	14.616	38.219	1.000	23.06
ATOM	1701	OE1	GLU	449	-5.299	15.102	39.350	1.000	22.34
ATOM	1702	OE2	GLU	449	-5.829	13.414	38.045	1.000	27.67
ATOM	1703	N	VAL	450	-8.586	18.937	37.169	1.000	4.34
ATOM	1704	CA	VAL	450	-9.196	20.178	37.577	1.000	4.41
ATOM	1705	C	VAL	450	-10.623	19.978	38.050	1.000	4.00
ATOM	1706	O	VAL	450	-11.053	20.608	39.032	1.000	4.68
ATOM	1707	CB	VAL	450	-9.063	21.285	36.517	1.000	3.87
ATOM	1708	CG1	VAL	450	-9.743	22.572	36.956	1.000	4.17
ATOM	1709	CG2	VAL	450	-7.578	21.580	36.248	1.000	5.19
ATOM	1710	N	SER	451	-11.354	19.056	37.442	1.000	4.13
ATOM	1711	CA	SER	451	-12.710	18.732	37.856	1.000	4.50
ATOM	1712	C	SER	451	-12.779	18.178	39.266	1.000	5.24
ATOM	1713	O	SER	451	-13.899	18.217	39.848	1.000	5.62
ATOM	1714	CB	SER	451	-13.344	17.725	36.882	1.000	5.05
ATOM	1715	OG	SER	451	-13.686	18.347	35.649	1.000	5.73

Fig. 10 CC

ATOM	1716	N	ASN	452	-11.706	17.668	39.799	1.000	5.28
ATOM	1717	CA	ASN	452	-11.736	17.120	41.178	1.000	5.86
ATOM	1718	C	ASN	452	-11.421	18.150	42.209	1.000	6.73
ATOM	1719	O	ASN	452	-11.635	17.904	43.429	1.000	9.43
ATOM	1720	CB	ASN	452	-10.794	15.923	41.278	1.000	7.91
ATOM	1721	CG	ASN	452	-11.314	14.743	40.472	1.000	7.51
ATOM	1722	OD1	ASN	452	-12.520	14.607	40.266	1.000	8.71
ATOM	1723	ND2	ASN	452	-10.395	13.925	39.989	1.000	11.11
ATOM	1724	N	LYS	453	-10.950	19.326	41.859	1.000	5.84
ATOM	1725	CA	LYS	453	-10.635	20.385	42.805	1.000	6.29
ATOM	1726	C	LYS	453	-11.877	21.148	43.209	1.000	6.16
ATOM	1727	O	LYS	453	-12.882	21.212	42.481	1.000	6.79
ATOM	1728	CB	LYS	453	-9.637	21.371	42.167	1.000	6.37
ATOM	1729	CG	LYS	453	-8.330	20.679	41.759	1.000	9.11
ATOM	1730	CD	LYS	453	-7.384	21.709	41.158	1.000	11.21
ATOM	1731	CE	LYS	453	-6.229	21.068	40.418	1.000	24.15
ATOM	1732	NZ	LYS	453	-5.408	20.211	41.332	1.000	43.71
ATOM	1733	N	ASP	454	-11.858	21.763	44.384	1.000	7.06
ATOM	1734	CA	ASP	454	-12.993	22.577	44.767	1.000	9.22
ATOM	1735	C	ASP	454	-12.611	23.786	45.594	1.000	7.48
ATOM	1736	O	ASP	454	-11.520	23.814	46.214	1.000	9.41
ATOM	1737	CB	ASP	454	-14.107	21.791	45.420	1.000	15.97
ATOM	1738	CG	ASP	454	-13.597	20.914	46.513	1.000	12.60
ATOM	1739	OD1	ASP	454	-12.688	21.404	47.256	1.000	17.72
ATOM	1740	OD2	ASP	454	-14.010	19.748	46.646	1.000	21.61
ATOM	1741	N	ASP	455	-13.502	24.730	45.570	1.000	8.50
ATOM	1742	CA	ASP	455	-13.434	25.972	46.368	1.000	9.54
ATOM	1743	C	ASP	455	-14.518	25.807	47.470	1.000	10.18
ATOM	1744	O	ASP	455	-15.688	25.980	47.186	1.000	9.35
ATOM	1745	CB	ASP	455	-13.740	27.146	45.471	1.000	11.61
ATOM	1746	CG	ASP	455	-14.138	28.425	46.151	1.000	10.26
ATOM	1747	OD1	ASP	455	-13.920	28.503	47.402	1.000	16.32
ATOM	1748	OD2	ASP	455	-14.640	29.336	45.485	1.000	10.90
ATOM	1749	N	LYS	456	-14.088	25.397	48.646	1.000	11.89
ATOM	1750	CA	LYS	456	-14.995	25.142	49.759	1.000	13.58
ATOM	1751	C	LYS	456	-15.459	26.405	50.442	1.000	15.87
ATOM	1752	O	LYS	456	-16.258	26.323	51.415	1.000	18.08
ATOM	1753	CB	LYS	456	-14.427	24.154	50.749	1.000	18.25
ATOM	1754	CG	LYS	456	-13.929	22.860	50.149	1.000	25.86
ATOM	1755	CD	LYS	456	-14.970	21.772	50.154	1.000	38.95
ATOM	1756	CE	LYS	456	-14.406	20.394	49.868	1.000	42.42
ATOM	1757	NZ	LYS	456	-12.930	20.308	50.010	1.000	43.79
ATOM	1758	N	LYS	457	-15.053	27.569	49.983	1.000	13.15
ATOM	1759	CA	LYS	457	-15.631	28.811	50.497	1.000	13.28
ATOM	1760	C	LYS	457	-16.921	29.152	49.793	1.000	14.63
ATOM	1761	O	LYS	457	-17.925	29.518	50.411	1.000	18.28
ATOM	1762	CB	LYS	457	-14.661	29.953	50.504	1.000	18.43
ATOM	1763	CG	LYS	457	-13.598	29.940	51.569	1.000	36.23
ATOM	1764	CD	LYS	457	-14.152	29.995	52.981	1.000	45.69
ATOM	1765	CE	LYS	457	-13.475	28.979	53.888	1.000	47.28
ATOM	1766	NZ	LYS	457	-13.867	27.577	53.566	1.000	53.94
ATOM	1767	N	ASN	458	-16.949	29.066	48.448	1.000	10.86
ATOM	1768	CA	ASN	458	-18.111	29.396	47.668	1.000	13.01
ATOM	1769	C	ASN	458	-18.770	28.140	47.041	1.000	9.87
ATOM	1770	O	ASN	458	-19.673	28.350	46.215	1.000	16.71
ATOM	1771	CB	ASN	458	-17.736	30.316	46.493	1.000	15.66
ATOM	1772	CG	ASN	458	-17.112	31.606	47.022	1.000	21.52
ATOM	1773	OD1	ASN	458	-17.804	32.386	47.669	1.000	20.29
ATOM	1774	ND2	ASN	458	-15.829	31.779	46.757	1.000	20.58
ATOM	1775	N	MET	459	-18.337	26.988	47.393	1.000	8.94
ATOM	1776	CA	MET	459	-18.846	25.737	46.785	1.000	9.71
ATOM	1777	C	MET	459	-18.702	25.818	45.269	1.000	9.96

Fig. 10 DD

ATOM	1778	O	MET	459	-19.670	25.658	44.525	1.000	14.38	
ATOM	1779	CB	MET	459	-20.314	25.548	47.187	1.000	11.57	
ATOM	1780	CG	MET	459	-20.456	25.462	48.712	1.000	14.12	
ATOM	1781	SD	MET	459	-19.359	24.200	49.400	1.000	23.52	
ANISOU	1781	SD	MET	459	4375	3080	1480	-478	1421	42
ATOM	1782	CE	MET	459	-19.398	24.596	51.135	1.000	18.15	
ATOM	1783	N	GLY	460	-17.500	26.181	44.833	1.000	7.42	
ATOM	1784	CA	GLY	460	-17.195	26.341	43.436	1.000	5.40	
ATOM	1785	C	GLY	460	-16.341	25.228	42.871	1.000	5.74	
ATOM	1786	O	GLY	460	-15.541	24.582	43.510	1.000	6.27	
ATOM	1787	N	LYS	461	-16.545	25.030	41.556	1.000	5.06	
ATOM	1788	CA	LYS	461	-15.783	24.063	40.771	1.000	4.29	
ATOM	1789	C	LYS	461	-15.206	24.836	39.570	1.000	4.48	
ATOM	1790	O	LYS	461	-15.481	26.018	39.392	1.000	5.16	
ATOM	1791	CB	LYS	461	-16.722	22.966	40.260	1.000	4.83	
ATOM	1792	CG	LYS	461	-17.363	22.144	41.355	1.000	5.01	
ATOM	1793	CD	LYS	461	-16.420	21.327	42.179	1.000	5.68	
ATOM	1794	CE	LYS	461	-15.995	20.046	41.458	1.000	6.05	
ATOM	1795	NZ	LYS	461	-14.951	19.306	42.212	1.000	6.24	
ATOM	1796	N	GLN	462	-14.413	24.140	38.761	1.000	3.50	
ATOM	1797	CA	GLN	462	-13.848	24.750	37.556	1.000	3.35	
ATOM	1798	C	GLN	462	-13.770	23.656	36.454	1.000	3.30	
ATOM	1799	O	GLN	462	-13.291	22.590	36.725	1.000	3.60	
ATOM	1800	CB	GLN	462	-12.438	25.277	37.824	1.000	3.15	
ATOM	1801	CG	GLN	462	-11.856	25.999	36.598	1.000	3.94	
ATOM	1802	CD	GLN	462	-10.505	26.568	36.903	1.000	3.89	
ATOM	1803	OE1	GLN	462	-10.209	27.024	38.009	1.000	3.86	
ATOM	1804	NE2	GLN	462	-9.601	26.512	35.928	1.000	3.69	
ATOM	1805	N	MET	463	-14.283	24.036	35.291	1.000	3.04	
ATOM	1806	CA	MET	463	-14.302	23.110	34.148	1.000	3.60	
ATOM	1807	C	MET	463	-13.521	23.700	32.963	1.000	3.29	
ATOM	1808	O	MET	463	-14.028	24.555	32.256	1.000	3.73	
ATOM	1809	CB	MET	463	-15.756	22.888	33.703	1.000	3.08	
ATOM	1810	CG	MET	463	-15.867	21.782	32.619	1.000	4.55	
ATOM	1811	SD	MET	463	-15.476	20.164	33.266	1.000	4.83	
ANISOU	1811	SD	MET	463	658	677	499	-231	185	-30
ATOM	1812	CE	MET	463	-13.923	19.758	32.501	1.000	4.65	
ATOM	1813	N	PRO	464	-12.297	23.246	32.754	1.000	2.87	
ATOM	1814	CA	PRO	464	-11.527	23.710	31.573	1.000	2.86	
ATOM	1815	C	PRO	464	-12.189	23.189	30.298	1.000	3.99	
ATOM	1816	O	PRO	464	-12.988	22.263	30.309	1.000	4.03	
ATOM	1817	CB	PRO	464	-10.143	23.175	31.799	1.000	3.93	
ATOM	1818	CG	PRO	464	-10.054	22.908	33.290	1.000	4.12	
ATOM	1819	CD	PRO	464	-11.464	22.404	33.624	1.000	3.65	
ATOM	1820	N	GLN	465	-11.724	23.758	29.168	1.000	2.98	
ATOM	1821	CA	GLN	465	-12.349	23.406	27.889	1.000	3.69	
ATOM	1822	C	GLN	465	-11.448	23.689	26.713	1.000	3.12	
ATOM	1823	O	GLN	465	-11.260	24.855	26.298	1.000	4.54	
ATOM	1824	CB	GLN	465	-13.606	24.293	27.789	1.000	5.47	
ATOM	1825	CG	GLN	465	-14.380	24.067	26.478	1.000	5.65	
ATOM	1826	CD	GLN	465	-15.195	25.342	26.212	1.000	10.23	
ATOM	1827	OE1	GLN	465	-14.574	26.299	25.689	1.000	27.00	
ATOM	1828	NE2	GLN	465	-16.356	25.418	26.727	1.000	15.04	
ATOM	1829	N	PRO	466	-10.929	22.645	26.087	1.000	3.17	
ATOM	1830	CA	PRO	466	-10.179	22.853	24.825	1.000	4.37	
ATOM	1831	C	PRO	466	-11.142	22.910	23.621	1.000	3.98	
ATOM	1832	O	PRO	466	-12.204	22.319	23.626	1.000	4.29	
ATOM	1833	CB	PRO	466	-9.325	21.577	24.694	1.000	5.36	
ATOM	1834	CG	PRO	466	-9.329	20.995	26.057	1.000	5.48	
ATOM	1835	CD	PRO	466	-10.677	21.309	26.627	1.000	4.04	
ATOM	1836	N	THR	467	-10.661	23.623	22.629	1.000	3.73	
ATOM	1837	CA	THR	467	-11.289	23.707	21.312	1.000	3.39	

Fig. 10 EE

ATOM	1838	C	THR	467	-10.197	23.558	20.260	1.000	3.32
ATOM	1839	O	THR	467	-9.089	24.031	20.484	1.000	4.23
ATOM	1840	CB	THR	467	-11.947	25.066	21.106	1.000	5.72
ATOM	1841	OG1	THR	467	-12.884	25.358	22.089	1.000	11.20
ATOM	1842	CG2	THR	467	-12.723	25.020	19.793	1.000	8.51
ATOM	1843	N	PHE	468	-10.461	22.883	19.144	1.000	3.69
ATOM	1844	CA	PHE	468	-9.356	22.649	18.215	1.000	2.96
ATOM	1845	C	PHE	468	-9.802	22.500	16.766	1.000	3.16
ATOM	1846	O	PHE	468	-10.906	22.013	16.458	1.000	3.95
ATOM	1847	CB	PHE	468	-8.559	21.423	18.635	1.000	3.69
ATOM	1848	CG	PHE	468	-9.231	20.094	18.581	1.000	4.03
ATOM	1849	CD1	PHE	468	-9.989	19.603	19.637	1.000	3.97
ATOM	1850	CD2	PHE	468	-9.101	19.245	17.466	1.000	4.84
ATOM	1851	CE1	PHE	468	-10.590	18.380	19.585	1.000	4.81
ATOM	1852	CE2	PHE	468	-9.678	18.012	17.420	1.000	4.55
ATOM	1853	CZ	PHE	468	-10.417	17.542	18.519	1.000	4.98
ATOM	1854	N	THR	469	-8.883	22.886	15.893	1.000	2.82
ATOM	1855	CA	THR	469	-8.973	22.664	14.449	1.000	2.85
ATOM	1856	C	THR	469	-7.767	21.863	13.983	1.000	3.03
ATOM	1857	O	THR	469	-7.442	21.792	12.786	1.000	3.58
ATOM	1858	CB	THR	469	-9.171	23.942	13.647	1.000	2.77
ATOM	1859	OG1	THR	469	-8.058	24.790	13.901	1.000	3.62
ATOM	1860	CG2	THR	469	-10.436	24.669	14.035	1.000	3.71
ATOM	1861	N	LEU	470	-7.086	21.204	14.917	1.000	3.12
ATOM	1862	CA	LEU	470	-5.978	20.313	14.615	1.000	3.78
ATOM	1863	C	LEU	470	-6.427	19.213	13.641	1.000	3.98
ATOM	1864	O	LEU	470	-7.529	18.669	13.782	1.000	4.23
ATOM	1865	CB	LEU	470	-5.455	19.628	15.881	1.000	3.97
ATOM	1866	CG	LEU	470	-4.894	20.545	16.964	1.000	3.62
ATOM	1867	CD1	LEU	470	-4.410	19.645	18.112	1.000	5.73
ATOM	1868	CD2	LEU	470	-3.757	21.405	16.447	1.000	4.43
ATOM	1869	N	ARG	471	-5.580	18.891	12.699	1.000	3.69
ATOM	1870	CA	ARG	471	-5.821	17.904	11.650	1.000	4.32
ATOM	1871	C	ARG	471	-4.924	16.688	11.792	1.000	5.20
ATOM	1872	O	ARG	471	-5.120	15.715	11.034	1.000	5.19
ATOM	1873	CB	ARG	471	-5.573	18.518	10.274	1.000	5.53
ATOM	1874	CG	ARG	471	-6.431	19.670	9.878	1.000	5.27
ATOM	1875	CD	ARG	471	-5.984	20.334	8.569	1.000	6.81
ATOM	1876	NE	ARG	471	-4.589	20.641	8.604	1.000	7.98
ATOM	1877	CZ	ARG	471	-3.579	20.114	7.939	1.000	5.76
ATOM	1878	NH1	ARG	471	-3.715	19.193	7.007	1.000	8.44
ATOM	1879	NH2	ARG	471	-2.368	20.518	8.231	1.000	7.31
ATOM	1880	N	LYS	472	-4.013	16.692	12.735	1.000	4.52
ATOM	1881	CA	LYS	472	-3.126	15.581	13.019	1.000	5.89
ATOM	1882	C	LYS	472	-2.958	15.463	14.546	1.000	5.05
ATOM	1883	O	LYS	472	-3.339	16.392	15.252	1.000	4.93
ATOM	1884	CB	LYS	472	-1.737	15.858	12.388	1.000	6.28
ATOM	1885	CG	LYS	472	-1.778	16.165	10.896	1.000	5.50
ATOM	1886	CD	LYS	472	-0.392	16.399	10.319	1.000	6.33
ATOM	1887	CE	LYS	472	-0.439	16.594	8.819	1.000	8.79
ATOM	1888	NZ	LYS	472	0.909	17.007	8.283	1.000	10.66
ATOM	1889	N	LYS	473	-2.396	14.366	14.979	1.000	5.58
ATOM	1890	CA	LYS	473	-2.010	14.232	16.395	1.000	7.06
ATOM	1891	C	LYS	473	-0.890	15.228	16.702	1.000	5.32
ATOM	1892	O	LYS	473	0.024	15.405	15.887	1.000	6.25
ATOM	1893	CB	LYS	473	-1.505	12.804	16.646	1.000	10.79
ATOM	1894	CG	LYS	473	-2.590	11.747	16.500	1.000	23.76
ATOM	1895	CD	LYS	473	-2.570	10.774	17.680	1.000	37.47
ATOM	1896	CE	LYS	473	-3.967	10.212	17.966	1.000	38.68
ATOM	1897	NZ	LYS	473	-3.983	9.533	19.302	1.000	50.66
ATOM	1898	N	LEU	474	-0.963	15.843	17.880	1.000	5.57
ATOM	1899	CA	LEU	474	0.044	16.790	18.310	1.000	6.26

Fig. 10 FF

ATOM	1900	C	LEU	474	0.815	16.211	19.491	1.000	5.58
ATOM	1901	O	LEU	474	0.211	16.034	20.575	1.000	6.58
ATOM	1902	CB	LEU	474	-0.584	18.127	18.697	1.000	6.02
ATOM	1903	CG	LEU	474	0.350	19.199	19.205	1.000	5.69
ATOM	1904	CD1	LEU	474	1.411	19.582	18.173	1.000	8.09
ATOM	1905	CD2	LEU	474	-0.445	20.455	19.599	1.000	11.02
ATOM	1906	N	VAL	475	2.067	15.954	19.316	1.000	5.34
ATOM	1907	CA	VAL	475	2.969	15.484	20.348	1.000	5.86
ATOM	1908	C	VAL	475	4.128	16.445	20.492	1.000	6.91
ATOM	1909	O	VAL	475	4.558	17.061	19.502	1.000	8.30
ATOM	1910	CB	VAL	475	3.513	14.074	20.060	1.000	7.46
ATOM	1911	CG1	VAL	475	4.352	14.061	18.799	1.000	13.03
ATOM	1912	CG2	VAL	475	2.414	13.051	20.023	1.000	10.26
ATOM	1913	N	PHE	476	4.671	16.588	21.687	1.000	7.61
ATOM	1914	CA	PHE	476	5.838	17.387	21.998	1.000	8.20
ATOM	1915	C	PHE	476	6.953	16.456	22.498	1.000	7.30
ATOM	1916	O	PHE	476	7.044	16.208	23.703	1.000	9.07
ATOM	1917	CB	PHE	476	5.578	18.428	23.085	1.000	9.57
ATOM	1918	CG	PHE	476	4.547	19.483	22.709	1.000	9.48
ATOM	1919	CD1	PHE	476	4.560	20.106	21.478	1.000	9.99
ATOM	1920	CD2	PHE	476	3.560	19.813	23.618	1.000	12.17
ATOM	1921	CE1	PHE	476	3.617	21.076	21.175	1.000	12.03
ATOM	1922	CE2	PHE	476	2.665	20.824	23.352	1.000	15.98
ATOM	1923	CZ	PHE	476	2.686	21.449	22.107	1.000	12.38
ATOM	1924	N	PRO	477	7.714	15.894	21.596	1.000	9.85
ATOM	1925	CA	PRO	477	8.729	14.909	22.025	1.000	13.88
ATOM	1926	C	PRO	477	9.745	15.546	22.938	1.000	13.05
ATOM	1927	O	PRO	477	10.106	16.708	22.802	1.000	12.51
ATOM	1928	CB	PRO	477	9.332	14.413	20.729	1.000	15.29
ATOM	1929	CG	PRO	477	8.248	14.710	19.692	1.000	14.13
ATOM	1930	CD	PRO	477	7.714	16.061	20.127	1.000	10.52
ATOM	1931	N	SER	478	10.185	14.787	23.955	1.000	21.27
ATOM	1932	CA	SER	478	11.135	15.345	24.905	1.000	21.99
ATOM	1933	C	SER	478	12.552	15.265	24.441	1.000	19.79
ATOM	1934	O	SER	478	13.468	15.835	25.036	1.000	21.48
ATOM	1935	CB	SER	478	10.927	14.912	26.328	1.000	25.29
ATOM	1936	OG	SER	478	10.664	13.539	26.449	1.000	35.36
ATOM	1937	N	ASP	479	12.793	14.570	23.308	1.000	29.67
ATOM	1938	CA	ASP	479	14.158	14.491	22.820	1.000	37.02
ATOM	1939	C	ASP	479	14.335	15.155	21.473	1.000	39.29
ATOM	1940	O	ASP	479	13.349	15.305	20.732	1.000	30.56
ATOM	1941	CB	ASP	479	14.719	13.094	22.870	1.000	46.26
ATOM	1942	CG	ASP	479	14.921	12.564	24.279	1.000	57.69
ATOM	1943	OD1	ASP	479	15.432	13.306	25.151	1.000	52.02
ATOM	1944	OD2	ASP	479	14.552	11.386	24.524	1.000	76.63
ATOM	1945	OXT	ASP	479	15.463	15.578	21.149	1.000	48.45
ATOM	1946	C	ACE	500	-7.173	31.990	48.894	1.000	16.49
ATOM	1947	O	ACE	500	-6.443	32.774	48.294	1.000	17.02
ATOM	1948	CA	ACE	500	-7.200	31.976	50.413	1.000	22.31
ATOM	1949	N	ILE	501	-7.942	31.102	48.291	1.000	15.20
ATOM	1950	CA	ILE	501	-8.001	31.032	46.811	1.000	11.20
ATOM	1951	CB	ILE	501	-8.805	29.785	46.395	1.000	14.39
ATOM	1952	CG2	ILE	501	-10.288	29.988	46.519	1.000	21.38
ATOM	1953	CG1	ILE	501	-8.403	29.246	45.025	1.000	18.69
ATOM	1954	CD1	ILE	501	-9.268	28.082	44.609	1.000	38.74
ATOM	1955	C	ILE	501	-8.677	32.279	46.277	1.000	9.36
ATOM	1956	O	ILE	501	-9.498	32.925	46.922	1.000	10.81
ATOM	1957	N	GLU	502	-8.235	32.706	45.098	1.000	6.87
ATOM	1958	CA	GLU	502	-8.734	33.902	44.437	1.000	6.39
ATOM	1959	C	GLU	502	-9.261	33.562	43.037	1.000	5.45
ATOM	1960	O	GLU	502	-8.905	32.491	42.503	1.000	6.91
ATOM	1961	CB	GLU	502	-7.617	34.948	44.318	1.000	7.14

Fig. 10 GG

ATOM	1962	CG	GLU	502	-7.090	35.362	45.700	1.000	6.61
ATOM	1963	CD	GLU	502	-6.067	36.438	45.669	1.000	8.30
ATOM	1964	OE1	GLU	502	-5.604	36.933	44.640	1.000	8.36
ATOM	1965	OE2	GLU	502	-5.700	36.916	46.826	1.000	10.04
ATOM	1966	N	THR	503	-10.059	34.422	42.477	1.000	5.65
ATOM	1967	CA	THR	503	-10.579	34.208	41.146	1.000	5.07
ATOM	1968	C	THR	503	-9.904	35.121	40.137	1.000	4.78
ATOM	1969	O	THR	503	-9.515	36.239	40.438	1.000	6.54
ATOM	1970	CB	THR	503	-12.104	34.434	41.084	1.000	7.25
ATOM	1971	OG1	THR	503	-12.422	35.737	41.536	1.000	8.86
ATOM	1972	CG2	THR	503	-12.840	33.420	41.889	1.000	8.58
ATOM	1973	N	AS2	504	-9.800	34.631	38.909	1.000	4.92
ATOM	1974	CA	AS2	504	-9.374	35.448	37.784	1.000	4.36
ATOM	1975	C	AS2	504	-10.579	35.867	36.994	1.000	5.24
ATOM	1976	O	AS2	504	-10.285	36.755	35.966	1.000	5.80
ATOM	1977	CB	AS2	504	-8.472	34.589	36.839	1.000	4.94
ATOM	1978	CG	AS2	504	-7.044	34.533	37.348	1.000	4.35
ATOM	1979	OD1	AS2	504	-6.638	35.388	38.154	1.000	5.44
ATOM	1980	OD2	AS2	504	-6.282	33.619	36.937	1.000	6.31
ATOM	1981	C1	DTT	505	-9.475	28.068	15.516	1.000	16.01
ATOM	1982	S2	DTT	505	-9.928	26.893	16.790	1.000	19.11
ANISOU	1982	S2	DTT	505	1496	2241	3526	-434	843 -1121
ATOM	1983	S3	DTT	505	-9.719	27.950	18.422	1.000	19.45
ANISOU	1983	S3	DTT	505	2592	3098	1700	-426	-388 351
ATOM	1984	C4	DTT	505	-10.803	29.344	17.998	1.000	19.73
ATOM	1985	C5	DTT	505	-10.297	30.115	16.781	1.000	18.16
ATOM	1986	O5	DTT	505	-11.159	31.253	16.680	1.000	27.39
ATOM	1987	C6	DTT	505	-10.382	29.313	15.474	1.000	16.26
ATOM	1988	O6	DTT	505	-9.916	30.116	14.406	1.000	17.15
ATOM	1989	C1	DTT	506	2.985	50.148	20.875	1.000	20.33
ATOM	1990	S2	DTT	506	1.893	49.247	21.967	1.000	33.24
ANISOU	1990	S2	DTT	506	7345	2843	2442	-2751	732 -458
ATOM	1991	S3	DTT	506	0.933	50.739	22.859	1.000	32.46
ANISOU	1991	S3	DTT	506	3445	5689	3197	-1221	-31 -628
ATOM	1992	C4	DTT	506	0.298	51.691	21.477	1.000	17.70
ATOM	1993	C5	DTT	506	1.542	52.267	20.695	1.000	26.73
ATOM	1994	O5	DTT	506	1.043	53.200	19.790	1.000	54.64
ATOM	1995	C6	DTT	506	2.304	51.167	19.995	1.000	25.32
ATOM	1996	O6	DTT	506	3.315	51.723	19.172	1.000	26.58
ATOM	1997	O	HOH	607	-7.179	28.001	36.747	1.000	4.00
ATOM	1998	O	HOH	608	-15.926	28.146	37.575	1.000	7.45
ATOM	1999	O	HOH	609	-2.157	26.109	9.420	1.000	6.30
ATOM	2000	O	HOH	612	-15.547	26.617	35.207	1.000	6.00
ATOM	2001	O	HOH	613	-8.155	20.966	29.490	1.000	4.92
ATOM	2002	O	HOH	614	1.059	35.590	46.010	1.000	5.62
ATOM	2003	O	HOH	616	-1.540	33.030	36.144	1.000	7.74
ATOM	2004	O	HOH	617	14.248	25.913	14.986	1.000	9.74
ATOM	2005	O	HOH	622	-0.363	30.091	10.336	1.000	5.23
ATOM	2006	O	HOH	624	-12.824	14.389	37.525	1.000	7.21
ATOM	2007	O	HOH	626	-3.313	26.044	42.321	1.000	13.54
ATOM	2008	O	HOH	628	-14.426	29.093	27.326	1.000	8.41
ATOM	2009	O	HOH	629	-22.860	26.207	37.247	1.000	11.35
ATOM	2010	O	HOH	631	7.962	42.319	30.389	1.000	24.28
ATOM	2011	O	HOH	632	-15.432	31.550	26.740	1.000	17.87
ATOM	2012	O	HOH	633	3.581	14.898	23.747	1.000	15.82
ATOM	2013	O	HOH	635	8.497	41.084	13.599	1.000	17.69
ATOM	2014	O	HOH	637	7.211	29.672	16.637	1.000	6.14
ATOM	2015	O	HOH	639	-3.621	55.110	35.262	1.000	34.33
ATOM	2016	O	HOH	640	3.297	51.622	29.118	1.000	15.92
ATOM	2017	O	HOH	641	-10.095	30.703	30.538	1.000	14.68
ATOM	2018	O	HOH	644	-9.784	45.306	45.463	1.000	38.21
ATOM	2019	O	HOH	645	-5.518	19.757	0.813	1.000	11.66

Fig. 10 HH

ATOM	2020	O	HOH	646	-1.137	47.321	41.862	1.000	18.79
ATOM	2021	O	HOH	647	13.548	26.231	32.626	1.000	17.43
ATOM	2022	O	HOH	649	10.056	23.866	10.012	1.000	24.07
ATOM	2023	O	HOH	651	-5.318	21.804	-4.840	1.000	26.32
ATOM	2024	O	HOH	653	-3.925	28.055	10.196	1.000	7.86
ATOM	2025	O	HOH	656	5.204	34.243	7.780	1.000	11.86
ATOM	2026	O	HOH	662	-6.150	21.460	-2.477	1.000	12.16
ATOM	2027	O	HOH	669	-0.905	50.973	26.570	1.000	14.22
ATOM	2028	O	HOH	671	16.582	30.301	28.856	1.000	37.67
ATOM	2029	O	HOH	673	-5.243	16.072	17.404	1.000	9.13
ATOM	2030	O	HOH	674	-13.499	21.739	39.864	1.000	5.09
ATOM	2031	O	HOH	675	8.992	25.342	37.548	1.000	30.43
ATOM	2032	O	HOH	676	2.480	38.569	43.080	1.000	12.77
ATOM	2033	O	HOH	678	15.071	23.012	30.087	1.000	24.55
ATOM	2034	O	HOH	681	-7.069	43.249	51.076	1.000	54.47
ATOM	2035	O	HOH	682	-0.962	47.846	19.263	1.000	19.18
ATOM	2036	O	HOH	684	-12.222	39.810	36.386	1.000	20.58
ATOM	2037	O	HOH	691	4.985	25.099	39.829	1.000	29.55
ATOM	2038	O	HOH	694	-8.204	23.482	28.242	1.000	3.78
ATOM	2039	O	HOH	695	-3.371	15.591	19.456	1.000	7.88
ATOM	2040	O	HOH	696	8.800	19.105	22.070	1.000	8.87
ATOM	2041	O	HOH	697	3.426	16.825	16.892	1.000	7.42
ATOM	2042	O	HOH	698	-0.599	30.883	3.798	1.000	8.17
ATOM	2043	O	HOH	699	-3.185	37.706	47.421	1.000	11.41
ATOM	2044	O	HOH	701	13.944	29.869	26.328	1.000	10.41
ATOM	2045	O	HOH	702	3.306	36.787	44.934	1.000	8.08
ATOM	2046	O	HOH	704	3.354	18.012	9.920	1.000	8.56
ATOM	2047	O	HOH	710	4.834	21.060	12.483	1.000	8.58
ATOM	2048	O	HOH	711	-23.562	25.428	34.640	1.000	11.33
ATOM	2049	O	HOH	714	3.989	26.948	42.303	1.000	22.31
ATOM	2050	O	HOH	715	-14.656	46.360	40.410	1.000	26.26
ATOM	2051	O	HOH	716	-13.496	47.498	29.830	1.000	22.63
ATOM	2052	O	HOH	717	-3.101	51.872	25.316	1.000	20.32
ATOM	2053	O	HOH	720	4.765	42.917	42.559	1.000	26.97
ATOM	2054	O	HOH	722	-14.660	43.262	23.356	1.000	26.62
ATOM	2055	O	HOH	724	1.166	42.481	45.035	1.000	18.74
ATOM	2056	O	HOH	727	6.697	22.010	10.495	1.000	15.09
ATOM	2057	O	HOH	730	3.377	20.698	10.247	1.000	8.59
ATOM	2058	O	HOH	731	9.044	16.788	29.709	1.000	29.70
ATOM	2059	O	HOH	732	-2.973	30.522	49.603	1.000	21.81
ATOM	2060	O	HOH	735	3.306	41.174	44.074	1.000	17.40
ATOM	2061	O	HOH	736	10.070	33.184	31.211	1.000	20.15
ATOM	2062	O	HOH	737	15.275	28.476	14.811	1.000	16.20
ATOM	2063	O	HOH	740	-6.904	35.449	7.852	1.000	9.05
ATOM	2064	O	HOH	742	1.301	29.201	2.977	1.000	12.06
ATOM	2065	O	HOH	743	3.490	43.726	38.760	1.000	12.67
ATOM	2066	O	HOH	744	-4.805	49.264	25.516	1.000	13.07
ATOM	2067	O	HOH	745	0.431	19.918	8.169	1.000	12.10
ATOM	2068	O	HOH	746	4.376	38.798	37.975	1.000	11.74
ATOM	2069	O	HOH	747	-16.615	28.161	40.706	1.000	14.62
ATOM	2070	O	HOH	748	-13.780	31.693	13.296	1.000	9.49
ATOM	2071	O	HOH	749	-17.785	27.621	26.913	1.000	11.20
ATOM	2072	O	HOH	750	-1.930	48.544	35.821	1.000	10.61
ATOM	2073	O	HOH	751	-21.848	23.971	43.796	1.000	12.54
ATOM	2074	O	HOH	752	7.194	28.554	39.176	1.000	14.58
ATOM	2075	O	HOH	753	3.046	37.521	40.556	1.000	12.45
ATOM	2076	O	HOH	754	-8.269	31.948	14.074	1.000	15.70
ATOM	2077	O	HOH	755	-9.389	21.099	45.972	1.000	17.47
ATOM	2078	O	HOH	756	3.478	28.336	48.963	1.000	12.88
ATOM	2079	O	HOH	758	6.050	44.656	35.370	1.000	19.56
ATOM	2080	O	HOH	759	-18.048	22.455	45.668	1.000	14.78
ATOM	2081	O	HOH	760	-5.283	43.746	44.516	1.000	17.25

Fig. 10 II

ATOM	2082	O	HOH	761	-10.720	36.645	44.490	1.000	18.26
ATOM	2083	O	HOH	762	-20.542	36.415	34.236	1.000	19.05
ATOM	2084	O	HOH	763	8.364	19.383	30.247	1.000	17.59
ATOM	2085	O	HOH	764	4.970	21.248	36.753	1.000	19.34
ATOM	2086	O	HOH	765	-1.227	18.246	5.902	1.000	15.72
ATOM	2087	O	HOH	766	13.252	23.428	32.079	1.000	14.92
ATOM	2088	O	HOH	767	-6.124	12.474	20.278	1.000	17.65
ATOM	2089	O	HOH	768	-13.767	33.338	10.540	1.000	19.33
ATOM	2090	O	HOH	769	-9.587	38.135	42.267	1.000	19.08
ATOM	2091	O	HOH	770	11.338	14.857	17.465	1.000	22.03
ATOM	2092	O	HOH	771	-1.898	35.950	49.077	1.000	16.54
ATOM	2093	O	HOH	772	-4.753	39.432	44.724	1.000	19.70
ATOM	2094	O	HOH	773	-22.226	32.257	40.837	1.000	20.77
ATOM	2095	O	HOH	774	-7.252	17.319	41.461	1.000	18.51
ATOM	2096	O	HOH	775	4.101	45.922	23.540	1.000	17.32
ATOM	2097	O	HOH	776	-7.072	38.324	42.694	1.000	17.03
ATOM	2098	O	HOH	777	4.552	26.633	6.386	1.000	20.73
ATOM	2099	O	HOH	778	3.891	28.390	3.989	1.000	19.37
ATOM	2100	O	HOH	779	-8.680	51.703	30.090	1.000	22.91
ATOM	2101	O	HOH	780	7.673	26.307	39.166	1.000	32.23
ATOM	2102	O	HOH	781	-7.101	18.937	-1.415	1.000	20.07
ATOM	2103	O	HOH	782	-7.714	14.213	40.700	1.000	18.65
ATOM	2104	O	HOH	783	-12.262	47.561	25.970	1.000	23.37
ATOM	2105	O	HOH	784	5.374	36.431	9.273	1.000	20.33
ATOM	2106	O	HOH	785	-15.510	18.821	44.821	1.000	17.82
ATOM	2107	O	HOH	786	8.318	31.025	39.614	1.000	19.81
ATOM	2108	O	HOH	787	-11.574	28.078	48.924	1.000	22.49
ATOM	2109	O	HOH	788	-9.713	44.978	21.494	1.000	32.54
ATOM	2110	O	HOH	789	-5.365	52.422	40.616	1.000	22.27
ATOM	2111	O	HOH	790	14.856	24.140	11.767	1.000	22.06
ATOM	2112	O	HOH	791	-4.011	25.203	44.753	1.000	26.70
ATOM	2113	O	HOH	792	12.240	33.905	13.730	1.000	26.02
ATOM	2114	O	HOH	793	-1.847	42.136	16.641	1.000	20.71
ATOM	2115	O	HOH	794	1.266	26.728	49.757	1.000	23.89
ATOM	2116	O	HOH	795	2.592	14.996	9.122	1.000	22.52
ATOM	2117	O	HOH	796	9.332	15.707	31.667	1.000	31.43
ATOM	2118	O	HOH	797	4.359	9.598	20.298	1.000	19.76
ATOM	2119	O	HOH	798	8.161	14.702	14.242	1.000	21.04
ATOM	2120	O	HOH	800	-10.337	32.049	19.008	1.000	18.94
ATOM	2121	O	HOH	801	-4.301	41.381	11.648	1.000	28.87
ATOM	2122	O	HOH	802	0.310	12.606	34.367	1.000	27.43
ATOM	2123	O	HOH	803	-25.185	27.783	34.677	1.000	25.40
ATOM	2124	O	HOH	805	-12.634	52.349	38.278	1.000	23.37
ATOM	2125	O	HOH	806	-17.723	40.055	27.482	1.000	29.02
ATOM	2126	O	HOH	807	-23.774	26.302	44.297	1.000	19.59
ATOM	2127	O	HOH	808	-17.080	50.855	33.510	1.000	35.77
ATOM	2128	O	HOH	810	0.698	47.657	32.361	1.000	20.18
ATOM	2129	O	HOH	811	-10.545	40.668	40.950	1.000	21.05
ATOM	2130	O	HOH	812	14.307	25.358	25.212	1.000	21.30
ATOM	2131	O	HOH	813	-6.329	25.396	45.608	1.000	19.18
ATOM	2132	O	HOH	816	11.866	20.393	11.576	1.000	20.91
ATOM	2133	O	HOH	817	-0.384	44.610	44.515	1.000	36.34
ATOM	2134	O	HOH	819	-22.077	8.560	39.191	1.000	33.06
ATOM	2135	O	HOH	820	-5.435	12.938	10.701	1.000	25.38
ATOM	2136	O	HOH	821	10.948	25.557	6.372	1.000	36.96
ATOM	2137	O	HOH	822	3.213	47.108	36.318	1.000	25.66
ATOM	2138	O	HOH	823	-13.992	43.856	39.020	1.000	29.04
ATOM	2139	O	HOH	824	12.471	33.255	30.136	1.000	28.65
ATOM	2140	O	HOH	825	-18.510	26.597	22.886	1.000	33.62
ATOM	2141	O	HOH	826	-13.731	38.129	36.616	1.000	22.55
ATOM	2142	O	HOH	827	-23.035	29.635	34.589	1.000	23.97
ATOM	2143	O	HOH	828	-0.205	47.079	17.122	1.000	25.73

Fig. 10 JJ

ATOM	2144	O	HOH	829	9.273	12.160	23.981	1.000	28.31
ATOM	2145	O	HOH	830	-5.250	41.507	46.185	1.000	29.94
ATOM	2146	O	HOH	831	2.470	11.541	10.357	1.000	23.80
ATOM	2147	O	HOH	832	6.011	36.318	31.308	1.000	22.17
ATOM	2148	O	HOH	833	6.226	34.416	5.316	1.000	31.68
ATOM	2149	O	HOH	834	10.274	17.019	33.942	1.000	34.53
ATOM	2150	O	HOH	836	0.447	9.767	20.825	1.000	27.76
ATOM	2151	O	HOH	837	11.974	37.677	19.103	1.000	24.01
ATOM	2152	O	HOH	838	-3.618	22.313	39.808	1.000	19.49
ATOM	2153	O	HOH	839	4.939	46.341	31.827	1.000	37.82
ATOM	2154	O	HOH	840	-4.229	29.665	-6.816	1.000	27.70
ATOM	2155	O	HOH	841	-7.756	17.460	44.012	1.000	41.04
ATOM	2156	O	HOH	842	9.706	32.694	34.637	1.000	38.02
ATOM	2157	O	HOH	843	-2.218	26.771	-6.995	1.000	21.77
ATOM	2158	O	HOH	844	7.635	29.830	5.044	1.000	27.65
ATOM	2159	O	HOH	845	-22.684	29.215	41.020	1.000	34.34
ATOM	2160	O	HOH	846	-4.458	39.343	49.931	1.000	29.51
ATOM	2161	O	HOH	847	15.255	31.773	17.310	1.000	44.62
ATOM	2162	O	HOH	848	5.550	27.265	40.069	1.000	34.19
ATOM	2163	O	HOH	849	-25.695	27.587	37.418	1.000	24.48
ATOM	2164	O	HOH	850	-5.682	13.156	17.595	1.000	24.06
ATOM	2165	O	HOH	851	1.674	7.246	24.284	1.000	28.71
ATOM	2166	O	HOH	852	11.839	33.303	33.342	1.000	56.13
ATOM	2167	O	HOH	853	13.627	35.973	18.323	1.000	42.17
ATOM	2168	O	HOH	854	4.261	45.957	28.187	1.000	50.63
ATOM	2169	O	HOH	856	-13.519	35.755	21.260	1.000	19.16
ATOM	2170	O	HOH	857	-10.680	22.444	47.859	1.000	13.84
ATOM	2171	O	HOH	858	-6.475	35.757	49.159	1.000	25.01
ATOM	2172	O	HOH	859	-20.281	27.157	27.230	1.000	19.41
ATOM	2173	O	HOH	860	-4.202	11.941	12.936	1.000	24.78
ATOM	2174	O	HOH	861	13.628	16.309	18.344	1.000	23.86
ATOM	2175	O	HOH	862	-4.754	50.704	43.017	1.000	40.54
ATOM	2176	O	HOH	863	5.129	17.206	7.967	1.000	25.90
ATOM	2177	O	HOH	864	-1.748	9.718	23.529	1.000	26.53
ATOM	2178	O	HOH	866	-17.147	36.144	41.118	1.000	23.78
ATOM	2179	O	HOH	867	3.828	10.149	17.741	1.000	24.56
ATOM	2180	O	HOH	868	11.984	37.254	11.380	1.000	24.92
ATOM	2181	O	HOH	869	-3.060	32.701	50.244	1.000	45.79
ATOM	2182	O	HOH	872	-7.260	36.552	10.390	1.000	12.29
ATOM	2183	O	HOH	873	5.813	31.178	4.361	1.000	26.34
ATOM	2184	O	HOH	874	-13.767	41.455	36.282	1.000	28.92
ATOM	2185	O	HOH	875	14.152	31.938	32.570	1.000	23.65
ATOM	2186	O	HOH	876	-4.168	9.993	10.524	1.000	45.05
ATOM	2187	O	HOH	877	1.165	50.465	39.930	1.000	41.22
ATOM	2188	O	HOH	879	13.995	21.383	33.857	1.000	25.83
ATOM	2189	O	HOH	880	-22.343	29.493	28.623	1.000	47.73
ATOM	2190	O	HOH	881	7.956	43.850	13.265	1.000	36.32
ATOM	2191	O	HOH	882	-19.313	20.822	44.933	1.000	10.09
ATOM	2192	O	HOH	883	8.369	47.144	19.169	1.000	42.47
ATOM	2193	O	HOH	884	6.417	11.805	21.030	1.000	29.34
ATOM	2194	O	HOH	885	-11.732	24.357	49.307	1.000	31.03
ATOM	2195	O	HOH	887	16.099	29.034	21.500	1.000	40.66
ATOM	2196	O	HOH	888	-21.583	8.666	36.766	1.000	21.89
ATOM	2197	O	HOH	889	-10.549	52.055	42.480	1.000	34.28
ATOM	2198	O	HOH	890	-12.161	32.039	46.100	1.000	47.45
ATOM	2199	O	HOH	891	-21.383	30.336	46.722	1.000	29.93
ATOM	2200	O	HOH	892	-15.427	26.720	21.542	0.500	22.02
ATOM	2201	O	HOH	894	-6.440	10.914	29.434	1.000	22.32
ATOM	2202	O	HOH	895	13.829	31.463	29.822	1.000	31.42
ATOM	2203	O	HOH	896	-16.934	28.949	24.186	1.000	30.90
ATOM	2204	O	HOH	897	-13.257	31.021	23.815	1.000	44.32
ATOM	2205	O	HOH	901	-0.115	50.492	36.679	1.000	36.40

Fig. 10 KK

ATOM	2206	O	HOH	903	-20.114	20.199	46.937	1.000	32.15
ATOM	2207	O	HOH	904	1.969	49.353	30.773	1.000	36.45
ATOM	2208	O	HOH	905	7.799	44.290	22.412	1.000	33.53
ATOM	2209	O	HOH	906	10.507	38.137	25.804	1.000	23.57
ATOM	2210	O	HOH	907	3.950	46.052	40.059	1.000	27.57
ATOM	2211	O	HOH	908	-19.926	38.755	33.004	1.000	34.98
ATOM	2212	O	HOH	909	-14.819	45.422	30.327	1.000	43.94
ATOM	2213	O	HOH	911	-6.782	49.611	23.981	1.000	27.91
ATOM	2214	O	HOH	913	-0.936	53.177	36.543	1.000	36.83
ATOM	2215	O	HOH	914	-12.496	26.338	24.317	1.000	13.86
ATOM	2216	O	HOH	916	-12.018	38.336	43.644	1.000	50.92
ATOM	2217	O	HOH	919	-1.845	23.943	41.968	1.000	26.70
ATOM	2218	O	HOH	920	12.202	30.379	11.774	1.000	14.82
ATOM	2219	O	HOH	921	14.385	30.545	13.255	1.000	21.57
ATOM	2220	O	HOH	922	3.301	22.636	37.905	1.000	28.40
ATOM	2221	O	HOH	923	4.561	15.912	36.349	1.000	35.01
ATOM	2222	O	HOH	924	6.781	46.206	37.412	1.000	30.11
ATOM	2223	O	HOH	925	-4.495	52.104	28.461	1.000	25.87
ATOM	2224	O	HOH	926	-2.373	17.251	36.286	1.000	31.14
ATOM	2225	O	HOH	927	-21.205	34.872	25.582	1.000	41.14
ATOM	2226	O	HOH	928	-13.908	10.164	41.692	1.000	28.83
ATOM	2227	O	HOH	930	-13.428	55.057	36.927	1.000	44.46
ATOM	2228	O	HOH	931	-6.602	40.027	47.271	1.000	38.71
ATOM	2229	O	HOH	932	-1.860	26.774	49.365	1.000	31.35
ATOM	2230	O	HOH	933	0.533	10.602	17.876	1.000	35.97
ATOM	2231	O	HOH	934	-8.081	53.535	41.749	1.000	29.52
ATOM	2232	O	HOH	935	-20.189	32.399	47.695	1.000	26.35
ATOM	2233	O	HOH	937	7.378	26.969	6.715	1.000	21.70
ATOM	2234	O	HOH	938	-16.873	43.179	30.317	1.000	38.27
ATOM	2235	O	HOH	939	5.918	42.189	39.509	1.000	42.67
ATOM	2236	O	HOH	941	-12.713	45.073	22.199	1.000	36.72
ATOM	2237	O	HOH	942	2.483	13.475	36.740	1.000	35.57
ATOM	2238	O	HOH	943	-6.941	39.978	50.564	1.000	38.23
ATOM	2239	O	HOH	944	-10.674	30.602	49.658	1.000	42.61
ATOM	2240	O	HOH	945	-1.028	41.328	13.816	1.000	25.15
ATOM	2241	O	HOH	946	8.827	34.766	32.725	1.000	35.94
ATOM	2242	O	HOH	947	-12.324	37.948	39.765	1.000	28.86
ATOM	2243	O	HOH	949	-14.159	28.467	25.112	1.000	43.18
ATOM	2244	O	HOH	950	5.954	44.949	14.155	1.000	32.26
ATOM	2245	O	HOH	952	10.925	41.335	15.107	1.000	38.92
ATOM	2246	O	HOH	953	4.324	45.532	16.216	1.000	44.59
ATOM	2247	O	HOH	954	15.157	29.102	32.431	1.000	19.88
ATOM	2248	O	HOH	955	1.041	21.856	-2.157	1.000	45.53
ATOM	2249	O	HOH	956	7.793	47.257	25.120	1.000	25.73
ATOM	2250	O	HOH	957	9.589	11.745	18.787	1.000	55.31
ATOM	2251	O	HOH	959	6.815	46.145	28.989	1.000	60.00
ATOM	2252	O	HOH	960	-10.328	34.814	51.148	1.000	29.35
ATOM	2253	O	HOH	961	-26.935	31.351	40.608	1.000	49.07
ATOM	2254	O	HOH	963	-22.698	28.826	37.213	1.000	34.52
ATOM	2255	O	HOH	964	-7.326	45.498	44.930	1.000	37.38
ATOM	2256	O	HOH	965	17.312	30.447	31.765	1.000	42.46
ATOM	2257	O	HOH	967	8.451	44.145	32.558	1.000	52.39
ATOM	2258	O	HOH	968	-21.875	27.625	44.250	1.000	29.05
ATOM	2259	O	HOH	969	6.428	21.678	8.084	1.000	36.88
ATOM	2260	O	HOH	970	-21.702	30.184	26.072	1.000	41.70
ATOM	2261	O	HOH	971	7.129	43.700	27.119	1.000	30.85
ATOM	2262	O	HOH	972	-13.957	34.182	48.091	1.000	38.32
ATOM	2263	O	HOH	973	-1.524	14.906	35.532	1.000	38.96
ATOM	2264	O	HOH	974	5.460	14.007	11.470	1.000	37.60
ATOM	2265	O	HOH	976	11.409	41.032	18.573	1.000	58.73
ATOM	2266	O	HOH	978	7.814	36.886	33.878	1.000	38.95
ATOM	2267	O	HOH	979	11.214	39.351	10.877	1.000	54.37

Fig. 10 LL

ATOM	2268	O	HOH	980	5.493	49.569	28.976	1.000	41.62
ATOM	2269	O	HOH	981	2.117	20.340	5.973	1.000	42.61
ATOM	2270	O	HOH	982	14.389	20.065	11.911	1.000	42.46
ATOM	2271	O	HOH	983	9.521	38.955	22.585	1.000	16.12
ATOM	2272	O	HOH	984	-13.853	38.967	17.671	1.000	54.68
ATOM	2273	O	HOH	985	5.811	13.190	23.111	1.000	22.41
ATOM	2274	O	HOH	986	7.324	10.340	32.631	1.000	35.62
ATOM	2275	O	HOH	987	0.938	23.568	42.002	1.000	34.05
ATOM	2276	O	HOH	988	13.730	35.802	7.258	1.000	45.12
ATOM	2277	O	HOH	990	-18.792	34.735	24.475	1.000	34.93
ATOM	2278	O	HOH	991	3.010	46.013	42.159	1.000	49.74
ATOM	2279	O	HOH	992	-7.336	10.393	7.043	1.000	35.61
ATOM	2280	O	HOH	993	-18.233	37.629	23.787	1.000	41.95
ATOM	2281	O	HOH	995	-14.472	34.674	45.374	1.000	37.56
ATOM	2282	O	HOH	996	0.314	8.716	6.600	1.000	41.28
ATOM	2283	O	HOH	999	0.550	42.867	10.524	1.000	23.58
ATOM	2284	O	HOH	1000	1.817	8.818	32.776	1.000	41.30
ATOM	2285	O	HOH	1001	-2.554	19.953	39.554	1.000	33.73
ATOM	2286	O	HOH	1002	-15.172	42.220	34.486	1.000	51.58
ATOM	2287	O	HOH	1003	0.883	7.971	30.093	1.000	32.55
ATOM	2288	O	HOH	1007	12.429	13.213	28.652	1.000	38.67
ATOM	2289	O	HOH	1008	1.064	48.138	34.563	1.000	47.15
ATOM	2290	O	HOH	1009	-16.375	41.852	22.768	1.000	46.49
ATOM	2291	O	HOH	1010	6.675	22.716	36.916	1.000	36.52
ATOM	2292	O	HOH	1012	-24.397	31.582	39.313	1.000	46.34
ATOM	2293	O	HOH	1013	-3.138	37.009	50.687	1.000	50.71
ATOM	2294	O	HOH	1014	14.070	32.748	24.770	1.000	64.75
ATOM	2295	O	HOH	1015	-20.943	26.682	22.425	1.000	70.34
ATOM	2296	O	HOH	1016	-15.843	35.165	42.714	1.000	67.16
ATOM	2297	O	HOH	1017	2.184	45.761	9.947	1.000	45.43
ATOM	2298	O	HOH	1018	8.820	32.623	37.967	1.000	64.48
ATOM	2299	O	HOH	1019	11.171	11.278	24.844	1.000	157.91
ATOM	2300	O	HOH	1020	-11.349	18.463	46.244	1.000	45.06
ATOM	2301	O	HOH	1021	-1.259	49.160	43.227	1.000	65.61
ATOM	2302	O	HOH	1022	13.342	36.089	31.751	1.000	81.65
ATOM	2303	O	HOH	1023	-2.636	54.126	26.761	1.000	63.89
ATOM	2304	O	HOH	1024	-7.354	41.347	13.489	1.000	53.70
ATOM	2305	O	HOH	1025	-17.546	42.173	25.620	1.000	46.42
ATOM	2306	O	HOH	1026	9.791	45.924	16.732	1.000	107.86
ATOM	2307	O	HOH	1027	-0.588	52.423	29.574	1.000	43.14
ATOM	2308	O	HOH	1028	11.745	39.461	23.759	1.000	46.18
ATOM	2309	O	HOH	1029	15.218	17.052	16.372	1.000	49.94
ATOM	2310	O	HOH	1030	13.354	36.792	26.203	1.000	86.88
ATOM	2311	O	HOH	1031	-9.460	39.219	12.887	1.000	43.47
ATOM	2312	O	HOH	1032	-9.813	35.885	10.955	1.000	74.66
ATOM	2313	O	HOH	1033	0.794	25.227	-7.467	1.000	43.61
ATOM	2314	O	HOH	1034	-6.761	11.472	40.091	1.000	50.68
ATOM	2315	O	HOH	1035	-2.430	7.743	6.630	1.000	90.86
ATOM	2316	O	HOH	1036	10.590	21.262	7.652	1.000	41.48
ATOM	2317	O	HOH	1037	12.833	16.684	27.343	1.000	61.39
ATOM	2318	O	HOH	1038	-18.876	5.705	45.134	1.000	79.91
ATOM	2319	O	HOH	1039	-4.622	18.024	40.059	1.000	57.07
ATOM	2320	O	HOH	1040	-1.051	8.259	16.907	1.000	46.76
ATOM	2321	O	HOH	1041	-2.329	41.926	9.883	1.000	51.34
ATOM	2322	O	HOH	1042	-1.659	42.834	45.450	1.000	51.03
ATOM	2323	O	HOH	1043	3.525	24.656	-0.644	1.000	62.40
ATOM	2324	O	HOH	1044	4.075	40.555	36.548	1.000	61.36
ATOM	2325	O	HOH	1045	-16.160	38.159	22.579	1.000	61.20
ATOM	2326	O	HOH	1046	-0.693	50.564	19.120	1.000	55.33
ATOM	2327	O	HOH	1047	-3.796	54.598	39.107	1.000	122.73
ATOM	2328	O	HOH	1048	-17.829	20.770	47.901	1.000	78.20
ATOM	2329	O	HOH	1049	-10.980	33.320	48.960	1.000	59.10

Fig. 10 MM

ATOM	2330	O	HOH	1050	-5.408	10.334	4.741	1.000	43.80
ATOM	2331	O	HOH	1051	17.268	14.039	19.503	1.000	59.75
ATOM	2332	O	HOH	1052	-3.265	18.108	38.221	1.000	36.85
ATOM	2333	O	HOH	1053	-8.137	56.811	40.536	1.000	83.67
ATOM	2334	O	HOH	1054	-13.090	36.361	44.130	1.000	53.30
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SEQUENCE LISTING

<110> WATT, WILLIAM
WATENPAUGH, KEITH D.

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<151> 1999-06-10

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<151> 1999-08-20

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Tyr	Gln	Met	Lys	Ser	Lys	Pro	Arg	Gly	Tyr	Cys	Leu	Ile	Ile	Asn	Asn	35	40	45	
His	Asn	Phe	Ala	Lys	Ala	Arg	Glu	Lys	Val	Pro	Lys	Leu	His	Ser	Ile	50	55	60	
Arg	Asp	Arg	Asn	Gly	Thr	His	Leu	Asp	Ala	Gly	Ala	Leu	Thr	Thr	Thr	65	70	75	80
Phe	Glu	Glu	Leu	His	Phe	Glu	Ile	Lys	Pro	His	Asp	Asp	Cys	Thr	Val	85	90	95	
Glu	Gln	Ile	Tyr	Glu	Ile	Leu	Lys	Ile	Tyr	Gln	Leu	Met	Asp	His	Ser	100	105	110	

Asn Met Asp Cys Phe Ile Cys Cys Ile Leu Ser His Gly Asp Lys Gly
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Ile Ile Tyr Gly Thr Asp Gly Gln Glu Ala Pro Ile Tyr Glu Leu Thr
 130 135 140

Ser Gln Phe Thr Gly Leu Lys Cys Pro Ser Leu Ala Gly Lys Pro Lys
 145 150 155 160

Val Phe Phe Ile Gln Ala Cys Gln Gly Asp Asn Tyr Gln Lys Gly Ile
 165 170 175

Pro Val Glu Thr Asp Ser Glu Glu Gln Pro Tyr Leu Glu Met Asp Leu
 180 185 190

Ser Ser Pro Gln Thr Arg Tyr Ile Pro Asp Glu Ala Asp Phe Leu Leu
 195 200 205

Gly Met Ala Thr Val Asn Asn Cys Val Ser Tyr Arg Asn Pro Ala Glu
 210 215 220

Gly Thr Trp Tyr Ile Gln Ser Leu Cys Gln Ser Leu Arg Glu Arg Cys
 225 230 235 240

Pro Arg Gly Asp Asp Ile Leu Thr Ile Leu Thr Glu Val Asn Tyr Glu
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Val Ser Asn Lys Asp Asp Lys Lys Asn Met Gly Lys Gln Met Pro Gln
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Pro Thr Phe Thr Leu Arg Lys Lys Leu Val Phe Pro Ser Asp
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 Lys Tyr Glu Val Arg Asn Lys Asn Asp Leu Thr Arg Glu Glu Ile Val
 50 55 60
 Glu Leu Met Arg Asp Val Ser Lys Glu Asp His Ser Lys Arg Ser Ser
 65 70 75 80
 Phe Val Cys Val Leu Leu Ser His Gly Glu Glu Gly Ile Ile Phe Gly
 85 90 95
 Thr Asn Gly Pro Val Asp Leu Lys Lys Ile Thr Asn Phe Phe Arg Gly
 100 105 110
 Asp Arg Cys Arg Ser Leu Thr Gly Lys Pro Lys Leu Phe Ile Ile Gln
 115 120 125
 Ala Cys Arg Gly Thr Glu Leu Asp Cys Gly Ile Glu Thr Asp Ser Gly
 130 135 140
 Val Asp Asp Asp Met Ala Cys His Lys Ile Pro Val Asp Ala Asp Phe
 145 150 155 160
 Leu Tyr Ala Tyr Ser Thr Ala Pro Gly Tyr Tyr Ser Trp Arg Asn Ser
 165 170 175
 Lys Asp Gly Ser Trp Phe Ile Gln Ser Leu Cys Ala Met Leu Lys Gln
 180 185 190
 Tyr Ala Asp Lys Leu Glu Phe Met His Ile Leu Thr Arg Val Asn Arg
 195 200 205
 Lys Val Ala Thr Thr Glu Phe Glu Ser Phe Ser Phe Asp Ala Thr Phe
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<212> PRT

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 35 40 45
 Tyr Ser Val Asp Val Lys Lys Asn Leu Thr Ala Ser Asp Met Thr Thr
 50 55 60
 Glu Leu Glu Ala Phe Ala His Arg Pro Glu His Lys Thr Ser Asp Ser
 65 70 75 80
 Thr Phe Leu Val Phe Met Ser His Gly Ile Arg Glu Gly Ile Cys Gly
 85 90 95
 Lys Lys His Ser Glu Gln Val Pro Asp Ile Leu Gln Leu Asn Ala Ile
 100 105 110
 Phe Asn Met Leu Asn Thr Lys Asn Cys Pro Ser Leu Lys Asp Lys Pro
 115 120 125
 Lys Val Ile Ile Ile Gln Ala Cys Arg Gly Asp Ser Pro Gly Val Val
 130 135 140
 Trp Phe Lys Asp Ser Val Gly Val Ser Gly Asn Leu Ser Leu Pro Thr
 145 150 155 160
 Thr Glu Glu Phe Glu Asp Asp Ala Ile Lys Lys Ala His Ile Glu Lys
 165 170 175
 Asp Phe Ile Ala Phe Cys Ser Ser Thr Pro Asp Asn Val Ser Trp Arg
 180 185 190
 His Pro Thr Met Gly Ser Val Phe Ile Gly Arg Leu Ile Glu His Met
 195 200 205
 Gln Glu Tyr Ala Cys Ser Cys Asp Val Glu Glu Ile Phe Arg Lys Val
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/15882

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N9/64 C12Q1/37 C07K5/103 A61K38/07

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EP0-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MUZIO M ET AL: "FLICE, A NOVEL FADD-HOMOLOGOUS ICE/CED-3-LIKE PROTEASE, IS RECRUITED TO THE CD95 (FAS/APO-1) DEATH-INDUCING SIGNALING COMPLEX" CELL,US,CELL PRESS, CAMBRIDGE, NA, vol. 85, no. 6, 14 June 1996 (1996-06-14), pages 817-827, XP002035464 ISSN: 0092-8674	1-17, 52-54, 56,57, 59-62
Y	the whole document	18-38, 44-51, 55,58
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

18 October 2000

Date of mailing of the international search report

08.11.00

Name and mailing address of the ISA

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Authorized officer

VAN DER SCHAAL C.A.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/15882

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 35020 A (ALNEMRI EMAD S ;LITWACK GERALD (US); TOMASELLI KEVIN (US); UNIV JE) 25 September 1997 (1997-09-25)	1-17, 52-54, 56,57, 59-62
Y	the whole document	18-38, 41-51, 55,58
X	--- CHOU KUO-CHEN ET AL: "Prediction of the tertiary structure and substrate binding site of caspase-8." FEBS LETTERS, vol. 419, no. 1, 8 December 1997 (1997-12-08), pages 49-54, XP002150240 ISSN: 0014-5793	1-20,39, 40, 52-54, 56,57, 59-62
Y	the whole document	21-38, 41-51, 55,58
A	--- WO 95 35367 A (VERTEX PHARMA) 28 December 1995 (1995-12-28)	1-17, 52-62
Y	the whole document	18-38, 44-51
A	--- WO 97 31018 A (MERCK & CO INC ;MERCK FROSST CANADA INC (CA); NICHOLSON DONALD W () 28 August 1997 (1997-08-28)	1-17, 52-62
Y	the whole document	18-38, 44-51
X	--- MARGOLIN NARA ET AL: "Substrate and inhibitor specificity of interleukin-1-beta-converting enzyme and related caspases." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 11, 1997, pages 7223-7228, XP002150241 ISSN: 0021-9258 the whole document	39,40
X	--- DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; June 1999 (1999-06) FELDENBERG L RICHARD ET AL: "Partial ATP depletion induces Fas- and caspase-mediated apoptosis in MDCK cells." Database accession no. PREV199900368459 XP002150244	39,40
Y	abstract	41-43, 48,55,58
	& AMERICAN JOURNAL OF PHYSIOLOGY, vol. 276, no. 6 PART 2, June 1999 (1999-06), pages F837-F846, ISSN: 0002-9513 --- -/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/15882

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WATT WILLIAM ET AL: "The atomic-resolution structure of human caspase-8, a key activator of apoptosis." STRUCTURE (LONDON), vol. 7, no. 9, pages 1135-1143, XP000946989 ISSN: 0969-2126 the whole document ---	1-40, 44-62
P,X	BLANCHARD HELEN ET AL: "The three-dimensional structure of caspase-8: An initiator enzyme in apoptosis." STRUCTURE (LONDON), vol. 7, no. 9, pages 1125-1133, XP000946945 ISSN: 0969-2126 the whole document -----	1-40, 44-47, 49-54, 56,57, 59-62

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/15882

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 42 and 43 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 7-17 could be considered as a mere presentation of information or a computer program, Rule 39.1 (v and vi) PCT, search has been carried out as far as possible in our systematic documentation

Continuation of Box I.2

Present claims 39-41 relate to a product defined by reference to a desirable characteristic or property, namely modulation of caspase 8.

The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the inhibitor of caspase 8 derived from SEQ ID NO 4

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/15882

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W0 9735020 A	25-09-1997	US 5851815 A	22-12-1998
		US 5786173 A	28-07-1998
		AU 2333197 A	10-10-1997
		EP 0906434 A	07-04-1999

W0 9535367 A	28-12-1995	AU 701759 B	04-02-1999
		AU 2705595 A	15-01-1996
		AU 9611398 A	04-03-1999
		CA 2192485 A	28-12-1995
		EP 0765388 A	02-04-1997
		JP 10504447 T	06-05-1998
		US 5856116 A	05-01-1999
		US 6057119 A	02-05-2000

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		EP 0885243 A	23-12-1998
		JP 2000505457 T	09-05-2000
