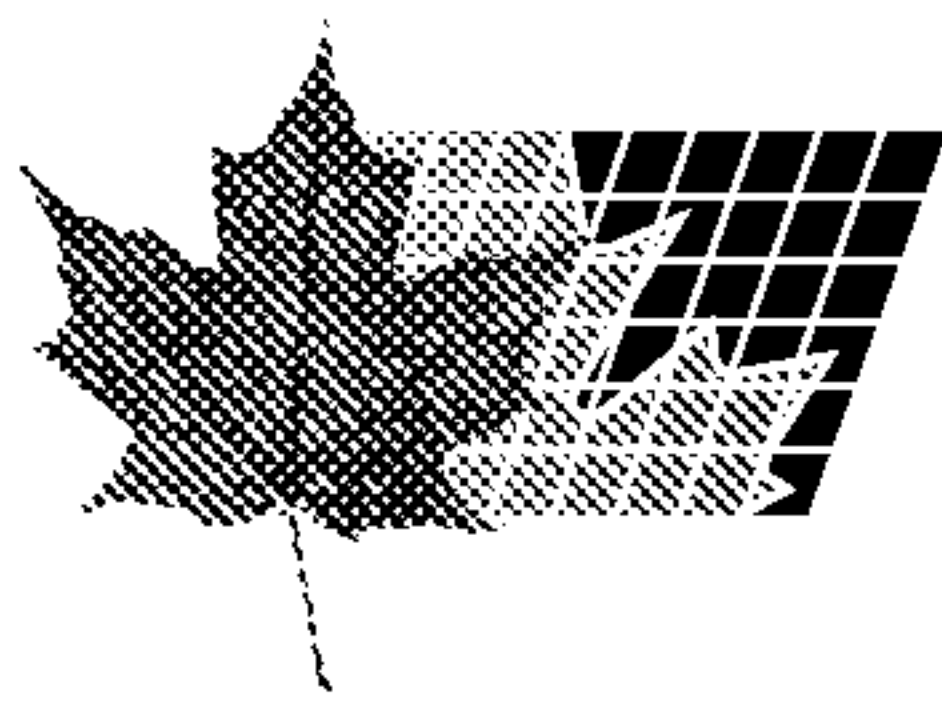




- (72) SHON, KI-JOON, US
(72) OLIVERA, BALDOMERO M., US
(72) RIVIER, JEAN E., US
(72) KOERBER, STEVEN C., US
(72) SHEN, GREGORY S., US
(72) MCINTOSH, J. MICHAEL, US
(72) CARTIER, G. EDWARD, US
(72) YOSHIKAMI, DOJU, US
(71) UNIVERSITY OF UTAH RESEARCH FOUNDATION, US
(71) CASE WESTERN RESERVE UNIVERSITY, US
(71) SALK INSTITUTE, US
(71) COGNETIX, INC., US
(51) Int.Cl.⁶ C07K 7/08, G01N 33/68, G06F 17/30, G01N 24/08, G06F 19/00
(30) 1997/10/24 (60/062,783) US
(30) 1997/11/14 (60/065,814) US
(54) **INTERACTION DE PEPTIDES D'ALPHA-CONOTOXINE AVEC
DES RECEPTEURS NEURAUX D'ACETYLCHOLINE
NICOTINIQUE**
(54) **INTERACTION OF ALPHA-CONOTOXIN PEPTIDES WITH
NEURONAL NICOTINIC ACETYLCHOLINE RECEPTORS**

(57) L'invention concerne des dérivés du conopeptide MII, peptide de conotoxine d' α 4/7, dans lequel des résidus aminoacides sont substitués, selon l'invention, tout en conservant l'activité de base de MII. Elle concerne également la découverte de la structure tridimensionnelle de MII et le rapport entre sa structure et sa spécificité pour le sous-type α 3 β 2 du récepteur neural d'acétylcholine nicotinique (nAChR). Elle concerne également des programmes informatisés servant à l'expression de la structure tridimensionnelle de MII et de ses analogues peptidiques, ses mimétiques peptidiques ou non peptidiques. On peut mettre en corrélation les caractéristiques structurales avec l'activité biologique afin de pouvoir élaborer des analogues et des mimétiques de peptide de conotoxine α -4/7 qui montrent la même spécificité pour nAChR neural. Ces analogues et ces mimétiques sont utiles en tant qu'agents cardio-vasculaires et servent également à traiter ou à détecter le carcinome pulmonaire à petites cellules (SCLC).

(57) This invention relates to derivatives of the conopeptide MII, an α -4/7 conotoxin peptide, in which amino acid residues are substituted as described herein while maintaining the basic activity of MII. The present invention also relates to the discovery of the 3-dimensional structure of MII, and the relationship of its structure to its specificity to the α 3 β 2 subtype of the neuronal nicotinic acetylcholine receptor (nAChR). The present invention also relates to computer based programs for the expression of the three-dimensional structure of MII and peptide analogs, peptide mimetics or non-peptide mimetics thereof. The structural characteristics may be correlated with biological activity to enable the design of α -4/7 conotoxin peptide analogs and peptide mimetics which demonstrate the same specificity to neuronal nAChR. Such analogs and peptide mimetics are useful as cardiovascular agents and for treating or detecting small-cell lung carcinoma (SCLC).



PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁶:**C07K 7/08, G01N 24/08, 33/68, G06F
17/30, 19/00****A1**

(11) International Publication Number:

WO 99/21878

(43) International Publication Date:

6 May 1999 (06.05.99)(21) International Application Number: **PCT/US98/22368**(22) International Filing Date: **23 October 1998 (23.10.98)**

(30) Priority Data:

60/062,783	24 October 1997 (24.10.97)	US
60/065,814	14 November 1997 (14.11.97)	US

(71) Applicants: UNIVERSITY OF UTAH RESEARCH FOUNDATION [US/US]; Suite 170, 421 Wakara Way, Salt Lake City, UT 84108 (US). CASE WESTERN RESERVE UNIVERSITY [US/US]; Office of University Attorney, Room 109, Delbert Hall, 10900 Euclid Avenue, Cleveland, OH 44106-7020 (US). SALK INSTITUTE [US/US]; 10010 North Torrey Pines Road, La Jolla, CA 92037 (US). COGNETIX, INC. [US/US]; Suite 201, 421 Wakara Way, Salt Lake City, UT 84108 (US).

(72) Inventors: SHON, Ki-Joon; 3136 Huntington Road, Shaker Heights, OH 44120 (US). OLIVERA, Baldomero, M.; 1370 Bryan Avenue, Salt Lake City, UT 84108 (US). RIVIER, Jean, E.; 9674 Blackgold Road, La Jolla, CA 92037 (US). KOERBER, Steven, C.; 818 Nardo Road, Encinitas, CA 92024 (US). SHEN, Gregory, S.; 2218 Lakeline Circle, Salt Lake City, UT 84109 (US). MCINTOSH, J., Michael; 1151 South 2000 East, Salt Lake City, UT 84108 (US). CARTIER, G., Edward; Apartment #B-216, 2629 East Stringham Avenue, Salt Lake City, UT 84109 (US). YOSHIKAMI, Doju; 1074 East 600 South, Salt Lake City, UT 84102 (US).

(74) Agents: IHNEN, Jeffrey, L. et al.; Rothwell, Figg, Ernst & Kurz, Suite 701 East, 555 13th Street N.W., Columbia Square, Washington, DC 20004 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published*With international search report.*(54) Title: **INTERACTION OF ALPHA-CONOTOXIN PEPTIDES WITH NEURONAL NICOTINIC ACETYLCHOLINE RECEPTORS**

(57) Abstract

This invention relates to derivatives of the conopeptide MII, an α -4/7 conotoxin peptide, in which amino acid residues are substituted as described herein while maintaining the basic activity of MII. The present invention also relates to the discovery of the 3-dimensional structure of MII, and the relationship of its structure to its specificity to the α 3 β 2 subtype of the neuronal nicotinic acetylcholine receptor (nAChR). The present invention also relates to computer based programs for the expression of the three-dimensional structure of MII and peptide analogs, peptide mimetics or non-peptide mimetics thereof. The structural characteristics may be correlated with biological activity to enable the design of α -4/7 conotoxin peptide analogs and peptide mimetics which demonstrate the same specificity to neuronal nAChR. Such analogs and peptide mimetics are useful as cardiovascular agents and for treating or detecting small-cell lung carcinoma (SCLC).

TITLE OF THE INVENTIONINTERACTION OF ALPHA-CONOTOXIN PEPTIDES WITH
NEURONAL NICOTINIC ACETYLCHOLINE RECEPTORS

5 This invention was made with Government support under Grant Nos. GM-54710, P01 48677
and MH-53631 awarded by the National Institutes of Health, Bethesda, Maryland. The United
States Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

10 The present invention relates to derivatives of the alpha conopeptide MII, an α -4/7 conotoxin
peptide, in which amino acid residues are substituted as described herein while maintaining activity
substantially similar to MII.

15 The present invention is further directed to the discovery of the 3-dimensional structure of
MII and the relationship of its structure to its specificity for the $\alpha 3\beta 2$ subtype of the neuronal
nicotinic acetylcholine receptor (nAChR). The discovery of the 3-dimensional structure enables the
design of α -4/7 conotoxin peptide analogs and peptide mimetics which will demonstrate the same
specificity to neuronal nAChR. Such analogs and peptide mimetics are useful as cardiovascular
agents and for treating or detecting small-cell lung carcinoma (SCLC). The present invention also
relates to computer based programs for the expression of the three-dimensional structure of MII and
peptide analogs, peptide mimetics or non-peptide mimetics thereof.

20 The publications and other materials used herein to illuminate the background of the
invention and, in particular cases, to provide additional details respecting the practice, are
incorporated by reference, and for convenience are numerically referenced in the following text and
respectively grouped in the appended bibliography.

25 The α -conopeptide MII has the amino acid sequence: Gly-Cys-Cys-Ser-Asn-Pro-Val-Cys-
His-Leu-Glu-His-Ser-Asn-Leu-Cys (SEQ ID NO:1). This peptide contains two disulfide bonds
between the first and third cysteine residues and between the second and fourth cysteine residues.
The C-terminal end may contain a carboxyl or amide group, preferably an amide group. The amino

acid at position 6 may be proline or 4-trans-hydroxyproline, preferably proline. The identification of MII is described in U.S. Patent No. 5,514,774, incorporated herein by reference.

5 A major challenge for neurobiology is to define the function of the multiple forms of nicotinic receptors and ion channels that have recently been discovered in the nervous system by molecular techniques. The use of gene knock-out organisms is one method for examining such function. A complementary approach is to use ligands that specifically inhibit a particular molecular form of receptor or ion channel. Such ligands must be able to discriminate between closely related members of receptor families.

10 Nicotinic acetylcholine receptors (nAChR) are ligand-gated ion channels which are key components of nervous systems. The classical role of these receptors was defined at the neuromuscular junction, nicotinic receptors concentrated on the muscle end plate serve as the key macromolecule that detects release of neurotransmitter from the presynaptic terminus of the motor axon. However, in addition to these skeletal muscle nicotinic receptors, many other molecular forms of nicotinic receptors exist; these are generally referred to as neuronal nicotinic receptors. In the
15 central nervous system (CNS), nAChRs play a prominent role in modulating the release of neurotransmitters including dopamine, norepinephrine, acetylcholine, GABA and glutamate.

The small peptide toxins (conotoxins) from the venom of fish-hunting cone snail, *Conus magus*, are a natural source of ligands that discriminate between closely related molecular forms of a single receptor or ion channel family. Alpha conopeptide MII is a small peptide with selective
20 action on neuronal nicotinic receptors. In the autonomic nervous system, MII was recently used to help pharmacologically dissect the nAChRs which mediate synaptic transmission in the parasympathetic ciliary ganglion. In frog sympathetic ganglia, MII discriminates between nAChRs in B versus C neurons. In the CNS, the specificity of MII enables identification of subunits of nAChRs which modulate nicotine-stimulated dopamine release. In retina, MII's selective block was
25 used to confirm the role of nAChRs in the development of visual circuitry. The use of MII for detecting the presence and location of small-cell lung carcinoma (SCLC) tumors, treating a patient having SCLC and inhibiting proliferation of SCLC tumors is described in U.S. Patent 5,595,972, incorporated herein by reference. The use of MII for treating disorders resulting from nicotine stimulated dopamine release is described in U.S. Patent 5,780,433, incorporated herein by reference.
30 The use of MII as a cardiovascular agent is described in copending provisional application Serial No. 60/031,141, filed 18 November 1996, incorporated herein by reference. To date, there have been no reports of the three-dimensional structure of MII and no systematic studies of the relationship of

the three-dimensional structure and function of the molecule, studies which are essential to the systematic design of MII analogs and mimetics.

It is desired to identify derivatives of MII, peptide analogs and peptide mimetics of α -conotoxins, generally, which are selective for specific subtypes of nAChRs and which have the uses described herein.

SUMMARY OF THE INVENTION

The present invention relates to derivatives of the alpha conopeptide MII, an α -4/7 conotoxin peptide, in which amino acid residues are substituted as described herein while maintaining activity substantially similar to MII. More specifically, the present invention is directed to the derivatives having the general formula (SEQ ID NO:2):

Xaa-Cys-Cys-Xaa-Xaa₁-Xaa₂-Xaa-Cys-Xaa₃-Xaa-Xaa₄-Xaa₅-Xaa-Xaa-Xaa-Cys,

wherein Xaa represents an amino acid selected from the group consisting of natural, modified or non-natural amino acids. The modifications may be by addition substitution or deletion of one or more amino acid residues. The modification may also include the addition or substitution of analogs of the amino acid themselves, such as peptidomimetics, or amino acids with altered side groups, or mimetics, e.g., organic molecules with similar space/structure/function relationships. Individual residue Xaa₁ is any amino acid, preferably Asn or His; Xaa₂ is any amino acid, preferably Pro or hydroxy-Pro; Xaa₃ is any amino acid, preferably His or Asn; Xaa₄ is any amino acid, preferably Glu; and Xaa₅ is any amino acid, preferably His or Asn. It is most preferred that Xaa₁ is Asn; Xaa₂ is Pro or hydroxy-Pro; and Xaa₅ is His. The C-terminal end may contain a carboxyl or amide group, preferably an amide group.

A second aspect of the present invention is directed to the discovery of the 3-dimensional structure of MII and the relationship of its structure to its specificity for the α 3 β 2 subtype of the neuronal nicotinic acetylcholine receptor (nAChR). Based on the correlation of structure to biological activity, the discovery of the 3-dimensional structure enables the design of α -4/7 conotoxin peptide analog, peptide mimetics and non-peptide mimetics which demonstrate specificity to different subtypes of neuronal nAChRs. In one embodiment, compounds are developed which demonstrate higher specificity to the α 3 β 2 subtype of neuronal nAChR than the α 3 β 4 subtype, such as evidence by MII. In a second embodiment, compounds are developed which demonstrate higher specificity to the α 3 β 4 subtype of neuronal nAChR than the α 3 β 2 subtype, such as evidence by several of the MII derivatives described herein.

The derivatives, peptide analogs, peptide mimetics and non-peptide mimetics of the present invention are useful as cardiovascular agents, gastric motility agents, urinary incontinence agents, anti-smoking agents and for treating or detecting small-cell lung carcinoma (SCLC) .

5 A third aspect of the present invention is directed to the synthesis of mimetics, e.g., organic molecules based on the three-dimensional structure of MII which demonstrates the same or different specificity to neuronal nAChRs.

10 A fourth aspect of the present invention is directed to the synthesis of peptide analogs and peptide mimetics of MII with altered nicotinic AChR subtype specificity based on the identification of peptide fragments which define the activity and selectivity of the conopeptide MII and on its three-dimensional structure.

A fifth aspect of the present invention is directed to synthesis of mimetics, e.g., organic molecules based upon the overall structural activity information relating to MII.

15 A sixth aspect of the present invention also provides for computer programs for the expression (such as visual display) of the three-dimensional structure of MII or a peptide analog or peptide mimetic thereof, and further, a computer program which expresses the identity of each constituent of MII and the precise location within the overall structure of that constituent, down to the atomic level. There are many currently available computer programs for the expression of the three-dimensional structure of a molecule. Generally, these programs provide for inputting of the coordinates for the three-dimensional structure of a molecule; means to express (such as visually
20 display) such coordinates, means to alter such coordinates and means to express an image of a molecule having such altered coordinates. In a further aspect, one may program NMR coordinates of the location of the atoms of an MII molecule in three dimension space, wherein such coordinates have been obtained from NMR analysis of said MII molecule, into such programs to perform comparative protein modeling of MII or a portion thereof, as described herein. Also provided,
25 therefore, is a computer program for the expression of the three-dimensional structure of a peptide analog or peptide mimetic of MII. Preferred is the computer program CAVEAT, available from Molecular Simulations, Inc. (Waltham, MA) with the coordinates as set forth in Figure 8 input.

BRIEF DESCRIPTION OF THE FIGURES

The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

5 Figure 1 shows the effect of alanine substitutions in the conopeptide MII on the ability of the analogs to block acetylcholine-gated currents in voltage-clamped *Xenopus* oocytes expressing cloned rat $\alpha 3$ and $\beta 2$ subunits.

Figure 2 shows the NOESY spectrum (250-ms mixing time) of α -CT_x MII in H₂O illustrating sequential NOE connectives between neighboring α and amide protons. The $d_{\alpha N}$ NOE cross peaks are connected by lines and are labeled by residue number. Two traces between residues
10 Cys² - Asn⁵ and Val⁷ - Cys¹⁶ are shown with their contiguous connectives broken at Pro⁶.

Figure 3 shows an amino acid sequence of α -CT_x MII with its disulfide bridges drawn to show its disulfide bridge pattern and a summary of short- to medium-range sequential NOE cross peaks as well as experimentally measured $^3J_{\text{NH-C}\alpha\text{H}}$ coupling constants. Arrows pointing down are
15 those with ^3J constants <5.0 Hz, and those pointing up are those with ^3J constants >8.0 Hz. Filled bars represent the NOE cross peaks with the thickness classifying NOE intensities from strong (thick) to weak (thin) and the width indicating short- to medium-range separation along the linear sequence. *** represents overlapped NOE cross peaks.

Figure 4 shows α proton chemical shift differences (ppm), between observed values from
20 α -CT_x MII in H₂O and random-coil values, plotted versus the residue.

Figures 5A-B show superimposition of the 14 lowest energy structures of α -CT_x MII calculated from simulated annealing.

Figure 6A-C show the angular order parameters for the backbone obtained from the 14 minimum energy structures, plotted versus the residue number. Figure 6A shows parameters for ϕ ,
25 Figure 6B for ψ ; and Figure 6C for χ .

Figure 7 shows surface (A,B) and backbone (C, D, E) representations of α -CT_{ss} MII, PnIA, and GI. Space-filling models of the X-ray crystal structure of α -CT_x PnIA (A) and the lowest energy structure of α -CT_x MII (B) are displayed in purple for hydrophobic residues, in yellow for polar side chains and in red (positive) and blue (negative) for charged side chains. Backbone conformations
30 of α -CT_x PnIA (C), α -CT_x MII (D), and α -CT_x GI (E) are displayed in ribbons and surface distributions in dots with the same color codes to illustrate their similarity and difference. Arrows indicate terminal residues, blue for carboxyl and yellow for amino.

Figure 8 lists the coordinates of α -conotoxin MII. These coordinates have been deposited in the Brookhaven Protein Data Bank, Upton, NY 19973, under accession code 1m2c.

Figure 9 shows selective block by α -Conotoxin MII of $\alpha 3\beta 2$ nAChRs. Oocytes expressing various nAChR subunit combinations were voltage-clamped and the response to ACh was measured at various α -Conotoxin MII concentrations. Data represent the mean $\pm$ S.E. for at least three oocytes at each concentration.

Figure 10 shows that block of $\alpha 3\beta 2$ nAChRs by α -Conotoxin MII is independent of the membrane potential. Oocytes expressing $\alpha 3\beta 2$ nAChRs were voltage-clamped and the response to ACh was measured over a range of membrane potentials. Peak-amplitude currents in the absence ($\circ$) and presence ($\blacktriangle$) of 500 pM α -Conotoxin MII are plotted against the membrane potential. Scaled toxin responses ($\blacktriangledown$) are also shown.

Figure 11A-C show that the competitive antagonist, Dihydro- β -Erythroidine (DH β E), protects $\alpha 3\beta 2$ nAChRs from blockade by α -Conotoxin MII. Oocytes expressing $\alpha 3\beta 2$ nAChRs were voltage-clamped and the response to ACh was measured. In Figure 11A, 500 μ M DH β E was applied for 5 min. The oocyte was then continuously perfused with buffer without DH β E. In Figure 11B, 500 μ M DH β E was applied for 5 min. followed by coapplication of 500 μ M DH β E and 20nM α -Conotoxin MII for 2 min. The oocyte was then continuously perfused with buffer without toxins. In Figure 11C, 20 nM α -Conotoxin MII was applied for 2 min. The oocyte was then continuously perfused with buffer without toxin.

Figure 12A and B show the kinetics of block of $\alpha 3\beta 2$ and $\alpha 3\beta 4$ nAChRs by α -Conotoxin MII. Figure 12A shows the response of voltage-clamped oocytes expressing $\alpha 3\beta 2$ nAChRs to ACh measured during application of 500 pM α -Conotoxin MII (first graph) and following washout from toxin (second graph). Figure 12B shows the response of voltage-clamped oocytes expressing $\alpha 3\beta 4$ nAChRs to ACh measured during application of 1 μ M α -Conotoxin MII (first graph) and following washout from toxin (second graph).

Figure 13A and B show the recovery kinetics of $\alpha 3\beta 2$ and $\alpha 3\beta 4$ nAChRs from block by saturating concentrations of α -Conotoxin MII. Figure 13A shows voltage-clamped oocytes expressing $\alpha 3\beta 2$ nAChRs and their response to ACh. 2 μ M α -conotoxin MII was applied for 5 min. The oocyte was then continuously perfused with buffer without toxin. Figure 13B shows oocytes expressing $\alpha 3\beta 4$ nAChRs, which were voltage-clamped and their response to ACh. 2.5 mM α -Conotoxin MII was applied for 5 min. The oocyte was then continuously perfused with buffer

without toxin. Data were fit to a 2-site model (solid lines). Dashed lines represent the expected single-exponential recovery kinetics.

Figures 14A-C show the MII "Dock & Lock" model of ligand/receptor interaction. In this illustration, MII binds at the interface between the α and β subunits. MII interacts with the β subunit with a very fast k_{on} and k_{off} and thus moderate affinity. Conversely, MII interacts with the α subunit with a very slow k_{on} and k_{off} and thus moderate affinity. As shown in Fig. 14A and 14B, MII approaches the receptor and very rapidly binds to the β subunit (docking interaction). However, this rapid binding to the β subunit in close proximity to the α subunit binding site leads to enhancement of the rate of MII's interaction with the α subunit and subsequent blockage of the receptor. Fig. 14C shows that once MII is bound to the α subunit, it has a very slow k_{off} (locking interaction). Thus, by targeting the subunit interface of the nicotinic receptor, MII is able to convert two relatively moderate binding interactions into a very potent and specific interaction with one molecular form of neuronal nAChR.

SUMMARY OF SEQUENCE LISTING

- SEQ ID NO:1 is the amino acid sequence for α -CT_x MII peptide.
 SEQ ID NO:2 is the amino acid sequence for derivatives of the alpha conopeptide MII.
 SEQ ID NO:3 is the amino acid sequence for the FATN chimera of MII.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. Derivatives of MII

The present invention relates to derivatives of MII, an α -4/7 conotoxinpeptide, in which amino acid residues are substituted as described herein while maintaining the basic activity of MII. More specifically, the present invention is directed to the derivatives having the general formula (SEQ ID NO:2):

Xaa-Cys-Cys-Xaa-Xaa₁-Xaa₂-Xaa-Cys-Xaa₃-Xaa-Xaa₄-Xaa₅-Xaa-Xaa-Xaa-Cys,

wherein Xaa represents an amino acid selected from the group consisting of natural, modified or non-natural amino acids. The modifications may be by addition substitution or deletion of one or more amino acid residues. The modification may also include the addition or substitution of analogs of the amino acid themselves, such as peptidomimetics, or amino acids with altered side groups, or mimetics, e.g., organic molecules with similar space/structure/function relationships. Individual residue Xaa₁ is any amino acid, preferably Asn or His; Xaa₂ is any amino acid, preferably Pro or

hydroxy-Pro; Xaa₃ is any amino acid, preferably His or Asn; Xaa₄ is any amino acid, preferably Glu; and Xaa₅ is preferably His or Asn. It is most preferred that Xaa₁ is Asn; Xaa₂ is Pro or hydroxy-Pro; and Xaa₅ is His. The derivatives contain two disulfide bonds between the first and third cysteine residues and between the second and fourth cysteine residues. The C-terminal end may contain a
5 carboxyl or amide group, preferably an amide group. The amino acid is an α -amino acid, which includes natural amino acids, including unusual amino acids such as γ -carboxyglutamic acid, as well as modified or non-natural amino acids, such as those described in, for example, Roberts et al. (1983).

10 The derivatives of the present invention are highly selective for either the $\alpha 3\beta 2$ or $\alpha 3\beta 4$ subtype of neuronal nAChRs which are present in the autonomic and central nervous systems. Thus, they are useful as cardiovascular agents, gastric motility agents, urinary incontinence agents and anti-smoking agents, as well as being useful against SCLC.

The conopeptides can be produced by recombinant DNA techniques well known in the art. Also, these conopeptide derivatives are sufficiently small to be chemically synthesized. General
15 chemical syntheses for preparing the foregoing conopeptide derivatives are described hereinafter, along with specific chemical synthesis of conopeptide derivatives and indications of biological activities of these synthetic products. The conopeptides of the present invention may be synthesized and/or substantially pure. By "substantially pure" is meant that the peptide is present in the substantial absence of other biological molecules of the same type; it is preferably present in an
20 amount of at least about 85% purity and preferably at least about 95% purity.

II. Preparation of recombinant and chemically synthesized derivatives.

The conopeptides of the present invention can be produced by recombinant DNA techniques well known in the art, such as those described in, for example, Sambrook et al. (1979). The peptides produced in this manner are isolated, reduced if necessary, and oxidized to form the correct
25 disulfide bonds, if present in the final molecule.

One method of forming disulfide bonds in the conopeptides of the present invention is the air oxidation of the linear peptides for prolonged periods under cold room temperatures or at room temperature. This procedure results in the creation of a substantial amount of the bioactive, disulfide-linked peptides. The oxidized peptides are fractionated using reverse-phase high
30 performance liquid chromatography (HPLC) or the like, to separate peptides having different linked configurations. Thereafter, either by comparing these fractions with the elution of the native material

or by using a simple assay, the particular fraction having the correct linkage for maximum biological potency is easily determined. It is also found that the linear peptide, or the oxidized product having more than one fraction, can sometimes be used for *in vivo* administration because the cross-linking and/or rearrangement which occurs *in vivo* has been found to create the biologically potent conopeptide molecule. However, because of the dilution resulting from the presence of other fractions of less biopotency, a somewhat higher dosage may be required.

It should be possible to prepare many, or even all, of these peptides using recombinant DNA technology. However, when peptides are not so prepared, they can be chemically synthesized by a suitable method, such as by exclusively solid-phase techniques, by partial solid-phase techniques, by fragment condensation or by classical solution couplings.

In conventional solution phase peptide synthesis, the peptide chain can be prepared by a series of coupling reactions in which constituent amino acids are added to the growing peptide chain in the desired sequence. Use of various coupling reagents, e.g., dicyclohexylcarbodiimide or diisopropylcarbonyldimidazole, various active esters, e.g., esters of N-hydroxyphthalimide or N-hydroxy-succinimide, and the various cleavage reagents, to carry out reaction in solution, with subsequent isolation and purification of intermediates, is well known classical peptide methodology. Classical solution synthesis is described in detail in the treatise, "Methoden der Organischen Chemie (Houben-Weyl): Synthese von Peptiden," (1974). Techniques of exclusively solid-phase synthesis are set forth in the textbook, "Solid-Phase Peptide Synthesis," (Stewart and Young, 1969), and are exemplified by the disclosure of U.S. Patent 4,105,603 (Vale et al., 1978). The fragment condensation method of synthesis is exemplified in U.S. Patent 3,972,859 (1976). Other available syntheses are exemplified by U.S. Patents No. 3,842,067 (1974) and 3,862,925 (1975). The synthesis of peptides containing γ -carboxyglutamic acid residues is exemplified by Rivier et al. (1987), Nishiuchi et al. (1993) and Zhou et al. (1996).

Common to such chemical syntheses is the protection of the labile side chain groups of the various amino acid moieties with suitable protecting groups which will prevent a chemical reaction from occurring at that site until the group is ultimately removed. Usually also common is the protection of an α -amino group on an amino acid or a fragment while that entity reacts at the carboxyl group, followed by the selective removal of the α -amino protecting group to allow subsequent reaction to take place at that location. Accordingly, it is common that, as a step in such a synthesis, an intermediate compound is produced which includes each of the amino acid residues

located in its desired sequence in the peptide chain with appropriate side-chain protecting groups linked to various ones of the residues having labile side chains.

As far as the selection of a side chain amino protecting group is concerned, generally one is chosen which is not removed during deprotection of the α -amino groups during the synthesis. However, for some amino acids, e.g., His, protection is not generally necessary. In selecting a particular side chain protecting group to be used in the synthesis of the peptides, the following general rules are followed: (a) the protecting group preferably retains its protecting properties and is not split off under coupling conditions, (b) the protecting group should be stable under the reaction conditions selected for removing the α -amino protecting group at each step of the synthesis, and © the side chain protecting group must be removable, upon the completion of the synthesis containing the desired amino acid sequence, under reaction conditions that will not undesirably alter the peptide chain.

While solution phase synthesis may be used, peptides are preferably prepared using the Merrifield solid-phase synthesis, although other equivalent chemical syntheses known in the art can also be used as previously mentioned. Solid-phase synthesis is commenced from the C-terminus of the peptide by coupling a protected α -amino acid to a suitable resin. Such a starting material can be prepared by attaching an α -amino-protected amino acid by an ester linkage to a chloromethylated resin or a hydroxymethyl resin, or by an amide bond to a benzhydrylamine (BHA) resin or paramethylbenzhydrylamine (MBHA) resin. Preparation of the hydroxymethyl resin is described by Bodansky et al. (1966). Chloromethylated resins are commercially available from Bio Rad Laboratories (Richmond, CA) and from Lab. Systems, Inc. The preparation of such a resin is described by Stewart and Young (1969). BHA and MBHA resin supports are commercially available, and are generally used when the desired polypeptide being synthesized has an unsubstituted amide at the C-terminus. Thus, solid resin supports may be any of those known in the art, such as one having the formulae $-O-CH_2$ -resin support, $-NH$ BHA resin support, or $-NH$ -MBHA resin support. When the unsubstituted amide is desired, use of a BHA or MBHA resin is preferred, because cleavage directly gives the amide. In case the N-methyl amide is desired, it can be generated from an N-methyl BHA resin. Should other substituted amides be desired, the teaching of U.S. Patent No. 4,569,967 (Kornreich et al., 1986) can be used, or should still other groups than the free acid be desired at the C-terminus, it may be preferable to synthesize the peptide using classical methods as set forth in the Houben-Weyl text (1974).

The C-terminal amino acid, protected by Boc or Fmoc and by a side-chain protecting group, if appropriate, can be first coupled to a chloromethylated resin according to the procedure set forth in Horiki et al. (1978), using KF in DMF at about 60° C for 24 hours with stirring, when a peptide having free acid at the C-terminus is to be synthesized. Following the coupling of the BOC-protected amino acid to the resin support, the α -amino protecting group is removed, as by using trifluoroacetic acid (TFA) in methylene chloride (CH_2Cl_2) or TFA alone. The deprotection is carried out at a temperature between about 0° C and room temperature. Other standard cleaving reagents, such as HCl in dioxane, and conditions for removal of specific α -amino protecting groups may be used as described in Schroder and Lubke (1965).

After removal of the α -amino-protecting group, the remaining α -amino- and side chain-protected amino acids are coupled step-wise in the desired order to obtain the intermediate compound defined hereinbefore, or as an alternative to adding each amino acid separately in the synthesis, some of them may be coupled to one another prior to addition to the solid phase reactor. Selection of an appropriate coupling reagent is within the skill of the art. Particularly suitable as a coupling reagent is N,N'-dicyclohexylcarbodiimide (DCC, DIC, HBTU, HATU, TBTU in the presence of HoBt or HoAt).

The activating reagents used in the solid phase synthesis of the peptides are well known in the peptide art. Examples of suitable activating reagents are carbodiimides, such as N,N'-diisopropylcarbodiimide and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide. Other activating reagents and their use in peptide coupling are described by Schroder and Lubke (1965) and Kapoor (1970).

Each protected amino acid or amino acid sequence is introduced into the solid-phase reactor in about a twofold or more excess, and the coupling may be carried out in a medium of dimethylformamide (DMF): CH_2Cl_2 (1:1) or in DMF or CH_2Cl_2 alone. In cases where intermediate coupling occurs, the coupling procedure is repeated before removal of the α -amino protecting group prior to the coupling of the next amino acid. The success of the coupling reaction at each stage of the synthesis, if performed manually, is preferably monitored by the ninhydrin reaction, as described by Kaiser et al. (1970). Coupling reactions can be performed automatically, as on a Beckman 990 automatic synthesizer, using a program such as that reported in Rivier et al. (1978).

After the desired amino acid sequence has been completed, the intermediate peptide can be removed from the resin support by treatment with a reagent, such as liquid hydrogen fluoride or TFA (if using Fmoc chemistry), which not only cleaves the peptide from the resin but also cleaves all

remaining side chain protecting groups and also the α -amino protecting group at the N-terminus if it was not previously removed to obtain the peptide in the form of the free acid. If Met is present in the sequence, the Boc protecting group is preferably first removed using trifluoroacetic acid (TFA)/ethanedithiol prior to cleaving the peptide from the resin with HF to eliminate potential S-alkylation. When using hydrogen fluoride or TFA for cleaving, one or more scavengers such as anisole, cresol, dimethyl sulfide and methylethyl sulfide are included in the reaction vessel.

Cyclization of the linear peptide is preferably affected, as opposed to cyclizing the peptide while a part of the peptido-resin, to create bonds between Cys residues. To effect such a disulfide cyclizing linkage, fully protected peptide can be cleaved from a hydroxymethylated resin or a chloromethylated resin support by ammonolysis, as is well known in the art, to yield the fully protected amide intermediate, which is thereafter suitably cyclized and deprotected. Alternatively, deprotection, as well as cleavage of the peptide from the above resins or a benzhydrylamine (BHA) resin or a methylbenzhydrylamine (MBHA), can take place at 0°C with hydrofluoric acid (HF) or TFA, followed by oxidation as described above.

The conopeptide derivatives of the present invention may possess biological activity different from MII or may demonstrate the same or varying degrees of the same biological activity as MII which is known to block native $\alpha 3\beta 2$ -containing nAChRs and with lower potencies, $\alpha 3\beta 4$ containing nAChRs (U.S. Patent 5,780,433 incorporated herein by reference), as well as other activities described herein.

III. Three-Dimensional Structure of MII

A. Overview

Another aspect of the present invention is directed to the discovery of the 3-dimensional structure of MII and the relationship of its structure to its specificity for the $\alpha 3\beta 2$ subtype of the neuronal nicotinic acetylcholine receptor (nAChR). The discovery of the 3-dimensional structure enables the design of α -4/7 conotoxin peptide analogs and peptide mimetics which will demonstrate the same specificity to neuronal nAChR. Such analogs and peptide mimetics are useful as cardiovascular agents and for treating or detecting small-cell lung carcinoma (SCLC).

II has the following amino acid sequence (SEQ ID NO:1):

Gly-Cys-Cys-Ser-Asn-Pro-Val-Cys-His-Leu-Glu-His-Ser-Asn-Leu-Cys.

The C-terminus may contain a carboxyl or amide group, preferably an amide group. The amino acid at position 6 may be proline or 4-trans-hydroxyproline, preferably proline.

The identification of MII is described in U.S. Patent 5,514,774 and U.S. Patent 5,780,433, incorporated herein by reference. The use of MII for: (a) treating a patient having small-cell lung carcinoma (SCLC); (b) inhibiting SCLC proliferation; (c) detecting the presence of SCLC tumors, and (d) detecting the location of SCLC tumors is described in application U.S. Patent 5,595,972, incorporated herein by reference. The use of MII to treat CNS disorders is described in U.S. Patent 5,780,433, incorporated herein by reference. The use of MII as a cardiovascular agent is described in U.S. Serial No. 60/031,141, filed 18 November 1996, incorporated herein by reference.

B. Determination of the peptide three-dimensional structures using NMR.

Different techniques give different and complementary information about protein structure. The primary structure is obtained by biochemical methods, either by direct determination of the amino acid sequence from the protein, or from the nucleotide sequence of the corresponding gene or cDNA. NMR methods may be employed to obtain the secondary and tertiary structure, which requires detailed information about the arrangement of atoms within a protein.

NMR methods use the magnetic properties of atomic nuclei. Certain atomic nuclei, such as ^1H , ^{13}C , ^{15}N , and ^{31}P have a magnetic moment or spin. The chemical environment of such nuclei can be probed by nuclear magnetic resonance, NMR, and this technique can be exploited to give information on the distances between atoms in a molecule. These distances can then be used to derive a three-dimensional model of the molecule. Most structure determinations of protein molecules by NMR have used the spin of ^1H , since hydrogen atoms are abundant in proteins.

When protein molecules are placed in a strong magnetic field, the spin of their hydrogen atoms aligns along the field. This equilibrium alignment can be changed to an excited state by applying radio frequency (RF) pulses to the sample. When the nuclei of the protein molecule revert to their equilibrium state, they emit RF radiation that can be measured. The exact frequency of the emitted radiation from each nucleus depends on the molecular environment of the nucleus and is different for each atom, unless they are chemically equivalent and have the same molecular environment. These different frequencies are obtained relative to a reference signal and are called chemical shifts. The nature, duration and combination of applied RF pulses can be varied enormously and different molecular properties of the sample can be probed by selecting the appropriate combination of pulses.

In principle, it is possible to obtain a unique signal (chemical shift) for each hydrogen atom in a protein molecule, except those that are chemically equivalent, for example, the protons on the CH_3 side chain of an alanine residue. In practice, however, such one-dimensional NMR spectra of

protein molecules contain overlapping signals from many hydrogen atoms because the differences in chemical shifts are often smaller than the resolving power of the instrument. This problem has been overcome by designing experimental conditions that yield a two-dimensional NMR spectrum, the results of which are usually plotted in a diagram. The diagonal in such a diagram corresponds to a normal one-dimensional NMR spectrum. The peaks off the diagonal result from interactions between hydrogen atoms that are close to each other in space. By varying the nature of the applied RF pulses, these off-diagonal peaks can reveal different types of interactions.

Two-dimensional experiments consist of discrete elements: a preparation period; an evolution period where spins are "labeled" as they process in the xy plane according to their chemical shift; a mixing period, during which correlations are made with other spins; and a detection period, where a free induction decay is recorded.

Experiments are distinguished by the nature of the correlation that are probed during the mixing period. A COSY (correlation spectroscopy) experiment gives peaks between hydrogen atoms that are covalently connected through one or two other atoms, for example, the hydrogen atoms attached to the nitrogen and C α atoms within the same amino acid residue. For amino acids with a single H β proton, a standard double quantum filtered COSY (DQF-COSY) recorded in D₂O may be used. However, for amino acids with a β -methylene group, modified COSY experiments such as P.E. COSY, is better suited. Nuclear overhauser effect spectroscopy (NOESY), on the other hand, gives peaks between pairs of hydrogen atoms that are close together in space even if they are from amino acid residues that are quite distant in the primary sequence. In total correlation spectroscopy (TOCSY), correlations are observed between all protons which share mutual coupling partners, whether or not they are directly coupled to each other.

Two dimensional NMR spectra of proteins are interpreted by the method of sequential assignment. Obviously, two-dimensional NOE spectra, by specifying which groups are close together in space, contain three-dimensional information about the protein molecule. It is far from trivial, however, to assign the observed peaks in the spectra to hydrogen atoms in specific residues along the polypeptide chain because the order of peaks along the diagonal has no simple relation to the order of amino acids along the polypeptide chain. This problem has in principle been solved in the laboratory of Kurt Wüthrich in the E.T.H., Zürich, where the method of sequential assignment was invented.

Sequential assignment is based on the differences in the number of hydrogen atoms and their covalent connectivity in the different amino acid residues. Each type of amino acid has a specific

set of covalently connected hydrogen atoms that will give a specific combination of cross-peaks, a "fingerprint," in a COSY spectrum. From the COSY spectrum, it is therefore possible to identify the H atoms that belong to each amino acid residue and, in addition, determine the nature of the side chain of that residue. However, the order of these fingerprints along the diagonal has no relation to the amino acid sequence of the protein.

The sequence-specific assignment, however, can be made from NOE spectra that record signals from H atoms that are close together in space. In addition to the interactions between H atoms that are far apart in the sequent, these spectra also record interactions between H atoms from sequentially adjacent residues. These signals in the NOE spectra therefore in principle make it possible to determine which fingerprint in the COSY spectrum comes from a residue adjacent to the one previously identified.

In practice, it is difficult to make unique assignments for longer pieces than di- or tri-peptides, since NOE signals also occur between residues close together in space but far apart in the sequence. Therefore, the peptide segments that have been uniquely identified by NMR are usually matched with corresponding segments in the independently determined amino acid sequence of the protein. NMR spectroscopy identifies H atoms in the protein that are close together in space, and this information is then used to derive, indirectly, a three-dimensional model of the protein.

Distance constraints can be used to derive possible structures of a protein molecule. The result of the sequence-specific assignment of NMR signals, preferably done using interactive computer graphics, is a list of distance constraints from specific hydrogen atoms in one residue to hydrogen atoms in a second residue. The list contains a large number of such distances, which are usually divided into three intervals within the region 1.8 Å to 5 Å, depending on the intensity of the NOE peak. This list immediately identifies the secondary structure elements of the peptide or protein molecules because both α helices and β sheets have very specific sets of interactions of less than 5 Å between their hydrogen atoms. It is also possible to derive models of the three-dimensional structure of the molecule. In order to obtain a more qualitative picture of conformations of a peptide and to generate three-dimensional structures compatible with NMR data, the principles of simulated annealing (Nilges, M. (1988)) may be employed. Simulated annealing calculations carry out an extensive search for all possible three-dimensional conformations that satisfy given experimental data (e.g., NOE-derived distances and dihedral angles) and root mean square (RMS) deviation (described herein) is used as a measure of degree of convergence among those calculated structures.

C. Description of MII Structure

Even though α -CT_x MII is a small peptide made of only 16 amino acid residues, it has a well-defined three-dimensional solution structure. In addition to two disulfide bridges which form a hydrophobic Cys knot, there are three helical regions in the structure which contribute to form a very tight conformation. The presence of such stable secondary structures and disulfide bridges allows the multidimensional NMR method to be effective in obtaining a very high resolution structure of the peptide. The amino-terminal region has almost a full turn of α -helix (Cys² - Ser⁴); this is followed by Asn⁵ which has backbone dihedral angles of $\phi = -89^\circ$ and $\psi = +132^\circ$ (measured from the minimum energy structure), thereby essentially making a 90° turn. The helix with almost two turns (Pro⁶ - Glu¹¹) is the major secondary structural component of the peptide. This helix is terminated by His¹² ($\phi = -136^\circ$, $\psi = +77^\circ$; measured from the minimum energy structure) which orients the remaining C-terminal distorted 3_{10} helix (Ser¹³-Cys¹⁶) toward the N-terminus. These two turns associated with Asn⁵ and His¹² are perhaps critical residues for the overall fold of the peptide and the presence of such turns is further supported by C α proton shift data presented in Figure 4 (positive shifts compare to the rest having negative shifts) as well as $^3J_{\text{NH-C}\alpha}$ coupling constants in Figure 2 (>8.0 Hz coupling constants compare to the rest having <5.0 Hz). A possible function of Asn⁵ is to induce a turn between the N-terminal segment and the main α -helix; this function is consistent with the survey by Richardson and Richardson (Richardson, J.S. (1988)) of 215 α -helices from 45 different globular protein structures. They reported a striking preference of 3.5:1 for Asn at the N-cap position and 2.6:1 for Pro at the N-cap + 1 position (helix initiator) for α -helices. With respect to the second turn around His¹², the function of His may be to bring Cys³ and Cys¹⁶ close together to form the second disulfide bridge.

The space-filling model of α -CT_x MII shown in Figure 7B is oriented to explore the surface distribution of hydrophobic and hydrophilic side chain groups of the molecule. Hydrophobic residues are colored purple to distinguish them from polar residues which are yellow, or charged residues which are red (positive) and blue (negative). A flat surface located on top of the molecule in purple is a distinct structural feature representing the cluster of hydrophobic residues exposed to solvent. This hydrophobic surface is formed largely by Gly¹ (excluding the N-terminal amino group), Cys², Cys³, Leu¹⁵, Cys¹⁶ and the disulfide bond between Cys³ and Cys¹⁶. This flat surface may be important for ligand-receptor binding through hydrophobic interactions. There is another very distinct surface that consists entirely of hydrophilic residues with both polar and charged groups. On the left side of the model, the cluster of red, blue and yellow represents a region of the

turn at His¹² (Glu¹¹-Asn¹⁴). This highly charged surface, almost perpendicular to the hydrophobic surface, could be responsible for its initial recognition by nAChR based on long-range electrostatic attractions. This potential receptor-binding interface is composed of sequential residues Glu¹¹, His¹², Ser¹³ and Asn¹⁴.

5 In view of the above analysis and the Examples which follow, the conceptually important structural features unique to nAChR targeting α -4/7 conotoxins can be summarized as follows:

(1) There are two disulfide bridges between the first and third cysteine and the second and fourth cysteine. Several isoforms generated with different disulfide pairings have been tested for their activity towards the nAChRs and shown *not* to retain the native activity.

10 (2) There is a central α -helix consisting of six residues starting precisely at the position $i+3$ where i is the second cysteine residue and ending at $j+3$ where j is the third cysteine residue. It is believed that this α -helix is essential for the overall backbone conformation and, in particular, its length (six amino acids in MII) and helical pitch are identified as critical features for targeting nAChRs. NMR data from an α -4/7 conotoxin MII mutant suggests that the mutation causes the
15 central helix to further extend beyond the $j+3$ position towards the C-terminal end and thereby causing its helical pitch to change. This structural change is associated with the loss of activity by three orders of magnitude.

(3) Two turns at both the N and C terminal ends (N- and C-caps) of the central helix are also unique structural features found in this class of conotoxins. They are intimately linked with the
20 central helix to dictate the three dimensional folding motif and their positions are $i+2$ for the N-cap where i is the second cysteine residue and $j+4$ for the C-cap where j is the third cysteine. Based on the primary sequence comparison among the sequenced α -4/7 conotoxins, there appears to be some preference for both N- and C-cap positions. These are asparagine, which is a good hydrogen bonding partner, and histidine and tyrosine, which are sterically bulky aromatic residues. For
25 example, there are 3.5:1 preference for Asn at the N-cap position from 215 α -helices subjected for studies by Richardson J.S. et al. (1988). It has been found that mutations at these positions in conotoxins results in the loss of their functions by three orders of magnitude.

(4) Proline residue at position $i+3$ where i is the second cysteine residue is conserved among all α -4/7 conotoxins. Its structural role is mostly likely to prevent continuation of the central
30 helix in the amino terminal direction due to its sterically hindering ring structure.

(5) Analysis of the kinetics of binding of MII indicate that this peptide has two distinct binding surfaces which interact with the α and β subunit of the nAChR. NMR analysis is consistent

with this and indicates that one MII face is hydrophobic in nature consisting of residues $i-2$, $i-1$, i (where i is the second cysteine residue), $j+7$ (where j is the third cysteine) and the fourth cysteine, and the disulfide bond between the second and fourth cysteine residues. The other face is hydrophilic in nature and consists of residues $j+3$, $j+4$, $j+5$ and $j+6$ where j is the third cysteine. Mutational analysis indicates that the hydrophilic face is particularly important for peptide on-rate (peptide docking) and the hydrophobic face is particularly important for peptide off-rate (peptide locking). The use of two physically distinct peptide surfaces to interact with adjacent α and β receptor subunits represents a specific strategy for designing ligands selective for receptors with different combinations of α and β subunits.

IV. Interaction of MII with nAChRs

MII achieves its remarkable subtype specificity through double-faced interacting with the receptor. MII's rank order of potency suggests that MII interacts with both α and non- α subunits of nAChRs. Block by MII is consistent with competitive inhibition as evidenced by voltage-independence of MII's activity and the ability of competitive antagonist dihydro- β -erythroidine to interfere with MII's ability to block the receptor. The shape of the time course recovery curve following block of $\alpha 3\beta 2$ and $\alpha 3\beta 4$ receptors by high concentrations of MII indicates that each of these receptors has two binding sites for MII, and occupancy of either site by toxin blocks receptor function. There appears to be a general pattern of two ligand binding sites for α /non- α subunit combinations of neuronal nAChRs. This is in contrast to $\alpha 7$ homomeric receptors which may have up to five Ach binding sites. Rates of recovery following block by MII are markedly longer for $\alpha 3$ -containing receptors than for receptors with no $\alpha 3$ subunits. However, the IC_{50} for MII's block of $\alpha 3\beta 2$ receptors is approximately 4 orders of magnitude lower than that of $\alpha 3\beta 4$ receptors. Remarkably, MII's off-rate is essentially the same for both receptor subtypes and the IC_{50} difference is almost entirely accounted for by a difference in MII's on-rate. Taken together, the data suggest that MII's on-rate is largely controlled by its interaction with the β subunit whereas interaction with the α subunit is primarily responsible for MII's off-rate. The kinetics of a synthetic chimera of MII support this conclusion (Example 10). MII's selective actions can be accounted for by a "dock and lock" model (Example 12).

The 3-dimensional solution structure of MII taken together with the data discussed in detail herein leads to a two-step dock-and-lock mechanism to explain the remarkable subtype specificity of MII. The NMR structure suggests that MII is a roughly wedge-shaped peptide with a hydrophilic

edge and a hydrophobic edge. The four amino-acids of α -conotoxin MII (HLEH) which were substituted to FATN are all located on the hydrophilic edge of the peptide. The results with the FATN analog, and the kinetic results obtained with wild-type toxin acting on the $\alpha 3\beta 2$ nicotinic receptor are thus suggestive that the docking face of the toxin is located on the hydrophilic side of the wedge, and that this hydrophilic face interacts with a fast on-time with the $\beta 2$ subunit. The other side of the wedge which is characterized by hydrophobic residues exposed to solvent, would be an attractive locus for the locking face of α -conotoxin MII, which is postulated to interact with high affinity on a site on the $\alpha 3$ subunit of nAChR targets of this peptide. A cartoon representation of α -conotoxin MII interacting with the $\alpha 3\beta 2$ and $\alpha 3\beta 4$ receptors, and of the FATN- α -conotoxin MII analog is shown in Figure 14.

The differential on and off rates for MII can be used to develop an assay to screen compounds for nAChR antagonistic activity and receptor subtype specificity. The on and off rates for the binding of MII and a compound to be screened to the $\alpha 3\beta 2$ and $\alpha 3\beta 4$ subunits are determined and compared. If the on rate for the compound is greater than or equal to the on rate for MII with respect to the $\alpha 3\beta 2$ subtype, the on rate for the compound is less than or equal to the on rate for MII with respect to the $\alpha 3\beta 4$ subtype and the off rates for the compound are greater than or equal to the off rates for MII, then the compound is a nAChR antagonist and specific for the $\alpha 3\beta 2$ subtype. If the on rate for the compound is less than or equal to the on rate for MII with respect to the $\alpha 3\beta 2$ subtype, the on rate for the compound is greater than or equal to the on rate for MII with respect to the $\alpha 3\beta 4$ subtype and the off rates for the compound are greater than or equal to the off rates for MII, then the compound is a nAChR antagonist and specific for the $\alpha 3\beta 4$ subtype.

In addition, compounds can be developed which modulate the activity of neuronal nAChRs having $\alpha 3\beta 2$ or $\alpha 3\beta 4$ subtype specificity based on the three dimensional structure of MII as disclosed herein, the structure/biological activity of MII disclosed herein and molecular modeling analysis. Thus, in accordance with the present invention, compounds are developed which modulate the activity of neuronal nAChRs and which have subtype specificity for either the $\alpha 3\beta 2$ or $\alpha 3\beta 4$ subtype.

V. Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptides or compounds with which they interact (agonists, antagonists, inhibitors, binding partners, etc.). By creating such analogs, it is possible to fashion drugs which are more active or

stable than the natural molecules, which have different susceptibility to alteration or which may affect the function of various other molecules. In one approach, one would generate a three-dimensional structure for MII, such as described herein, or by computer modeling, or by a combination of both approaches. An alternative approach, "alanine scan," involves the random replacement of residues throughout molecule with alanine, and the resulting affect on function determined.

It also is possible to isolate an MII specific antibody, selected by a functional assay, and then solve its crystal structure. In principle, this approach yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallograph altogether by generating anti-idiotypic antibodies to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of anti-idiotypic would be expected to be an analog of the original antigen. The anti-idiotypic could then be used to identify and isolate peptides from banks of chemically- or biologically-produced peptides. Selected peptides would then serve as the pharmacore. Anti-idiotypes may be generated using the methods described herein for producing antibodies, using an antibody as the antigen.

Thus, one may design drugs which have improved MII activity or which act as stimulators, inhibitors, agonists, antagonists or MII or molecules affected by MII function. In addition, knowledge of the polypeptide sequences permits computer employed predictions of structure-function relationships.

A substance identified as a modulator of polypeptide function may be peptide or non-peptide in nature. Non-peptide "small molecules" are often preferred for many *in vivo* pharmaceutical uses. Accordingly, a mimetic or mimic of the substance (particularly if a peptide) may be designed for pharmaceutical use.

The designing of mimetics to a known pharmaceutically active compound is a known approach to the development of pharmaceuticals based on a "lead" compound. This might be desirable where the active compound is difficult or expensive to synthesize or where it is unsuitable for a particular method of administration, e.g., pure peptides are unsuitable active agents for oral compositions as they tend to be quickly degraded by proteases in the alimentary canal. Mimetic design, synthesis and testing is generally used to avoid randomly screening large numbers of molecules for a target property.

There are several steps commonly taken in the design of a mimetic from a compound having a given target property. First, the particular parts of the compound that are critical and/or important

in determining the target property are determined. In the case of a peptide, this can be done by systematically varying the amino acid residues in the peptide, e.g., by substituting each residue in turn. Alanine scans of peptide are commonly used to refine such peptide motifs. These parts or residues constituting the active region of the compound are known as its "pharmacophore".

5 Once the pharmacophore has been found, its structure is modeled according to its physical properties, e.g., stereochemistry, bonding, size and/or charge, using data from a range of sources, e.g., spectroscopic techniques, x-ray diffraction data and NMR. Computational analysis, similarity mapping (which models the charge and/or volume of a pharmacophore, rather than the bonding between atoms) and other techniques can be used in this modeling process.

10 In a variant of this approach, the three-dimensional structure of the ligand and its binding partner are modeled. This can be especially useful where the ligand and/or binding partner change conformation on binding, allowing the model to take account of this in the design of the mimetic.

15 A template molecule is then selected onto which chemical groups which mimic the pharmacophore can be grafted. The template molecule and the chemical groups grafted onto it can conveniently be selected so that the mimetic is easy to synthesize, is likely to be pharmacologically acceptable, and does not degrade *in vivo*, while retaining the biological activity of the lead compound. Alternatively, where the mimetic is peptide-based, further stability can be achieved by cyclizing the peptide, increasing its rigidity. The mimetic or mimetics found by this approach can then be screened to see whether they have the target property, or to what extent they exhibit it.

20 Further optimization or modification can then be carried out to arrive at one or more final mimetics for *in vivo* or clinical testing.

VI. Designing Biologically Active Molecules Based on Structure of MII

A. Overview

25 In general, biologically active molecules exert their effect by binding to a receptor. The ability of a given molecule to bind to a receptor is determined by the presence of certain important functional groups and the three-dimensional (3D) presentation of these features by the molecule. A goal of molecular modeling in the context of designing bioactive molecules is to understand the determinants of receptor binding and to use this knowledge in the design or discovery of novel molecules with the desired activity. The availability of structure-activity data or the structure of a

30 receptor enables the proposal of a pharmacophoric pattern which, in the best case, would include the functionality required for activity and the relative orientation of the functional groups. (Gund,

1979). Recent advances in techniques for generating 3D molecular structures for typical drug-sized organic molecules and for searching databases of 3D structures combined with a 3D pharmacophore hypothesis give the medicinal chemist new tools that can assist in discovering novel active molecules. A 3D pharmacophore can be used as a query to search a database of molecules for those that are predicted to possess the desired activity if the pharmacophore hypothesis is correct. If a receptor structure or receptor site model is available, another type of 3D searching can be used. For this, molecules are selected based on their steric and chemical match to the receptor structure, without the need to propose which interactions might be most important. The methods are complementary and both have assisted in the discovery of active molecules.

10 The significance of the HLEH fragment of MII has been investigated and its biological activity and receptor binding has been correlated to its structural, chemical and physical attributes (features). These features are used to help understand the range of biological activity observed in a series of compounds, as well as to help guide the design of new compounds with potentially different affinities for nicotinic nAChRs, e.g., compounds with higher affinity for the $\alpha 3\beta 2$ subtype or compounds with higher affinity for the $\alpha 3\beta 4$ subtype.

15 A wide range of experimental and theoretical data is routinely used to develop patterns of such features. This process is generally referred to as pharmacophore mapping and involves three main aspects: finding the features required for biological activity; determining the molecular conformation required (i.e., the "bioactive" conformation); and developing a superposition or alignment rule for the series of compounds. The primary information used in pharmacophore mapping is derived naturally from the compounds synthesized in a series and their measured biological activity. From this, structure-activity relations emerge and rudimentary pharmacophore hypotheses can begin to be formulated. If the structure of the macromolecular target or target-ligand complex is known, either as determined experimentally or as computationally modeled, this information is obviously very useful to the pharmacophore-mapping process. A variety of molecular-modeling and computational chemistry techniques can then be applied, in conjunction with the experimental data, to develop pharmacophore models. These techniques range from simple, qualitative molecular graphics comparisons of several members in a series to sophisticated, quantitative methodologies for generating pharmacophore maps and measuring their ability to reproduce experimental results.

30 Pharmacophore mapping is largely a *qualitative* exercise. Allied with pharmacophore mapping is the field of three-dimensional *quantitative* structure-activity relations (3D-QSAR). 3D-

QSAR techniques attempt to derive and investigate quantitative models of biological activity; namely, models that fit the potency of the studied compounds and that can be used to predict the potency of compounds outside the study set. In fact, the application of many 3D-QSAR methods requires a proposed pharmacophore model.

5 Pharmacophore mapping has its roots in traditional medicinal chemistry and the structure-activity relations derived from the synthesis and biological testing of series of compounds. From the relative measured potencies of individual members of a series, a picture of the types of functionality, and perhaps their spatial relations that are important for activity, begins to emerge. More detailed molecular-modeling studies can then be used to formulate a more rigorous model but
10 even in their absence proposed pharmacophore hypotheses can begin to take shape.

 Many ligand-design studies employ molecular modeling as well as chemical synthesis to help elucidate pharmacophoric patterns. Structure-activity data and the conformational analysis results are used to propose a bioactive conformation and superposition rule for the series. This may be done by using molecular graphics.

15 Another common approach in pharmacophore mapping is the use of structurally rigid molecules to probe requirements for receptor binding. One of the advantages of using less conformationally flexible molecules is that they can more exactly define the bioactive conformation, provided that the rigid molecules selected show good affinity. Use of rigidification to better define pharmacophore space has been used successfully in generating active nonpeptidic compounds from
20 peptide leads. Ku, et al. (1995) and co-workers' recent work with nonpeptide compounds based on cyclic RGD peptide analogues is a good example of this.

 Receptor site mapping encompasses a variety of computational procedures that identify energetically favorable binding sites on macromolecules. The most straightforward procedures involve "painting" a solvent-accessible surface (or an otherwise generated cast) of the
25 macromolecular target according to empirically determined physical properties, such as electrostatic or lipophilic potential, degree of curvature, and hydrogen-bonding character. Such methods for thus characterizing the surface of a macromolecule are incorporated in programs such as Grasp (Columbia University), DelPhi (Biosym Technologies), MOLCAD (Tripos, Inc.), and Hint (Virginia Commonwealth University). Subsequent molecule design involves identification or design of
30 ligands that possess features complimentary to the identified surface characteristics. More advanced algorithms involve the actual calculation of interaction enthalpies between the target and potential ligands or fragments. In practice, the coordinates of the protein or protein fragment of interest

(which may be rotated or otherwise transformed) are stripped of any undesired ligand (or portion thereof) and/or of any undesired solvent molecules. The coordinates are then processed to attach molecular mechanics parameters to the atomic positions to provide a processed target for mapping. The target may be partitioned into discrete binding sites. The target or partitioned sites thereof are
5 flooded with given functional group fragments that are subsequently allowed to relax into desired locations, as in the program MCSS (Molecular Simulations, Inc.), or are encased within a regular lattice of site points on which single fragment probes are positioned sequentially; examples of programs that exploit the site-lattice algorithm include Grin/Grid (Molecular Discovery, Ltd.), Ludi (Biosym Technologies), Leapfrog (Tripos, Inc.), and Legend (University of Tokyo). In both
10 techniques, the enthalpic contribution to binding affinity is estimated with a molecular mechanics force-field, and appropriate positions of selected functional groups are determined systematically.

In the site-lattice approach, a box is defined enclosing a desired portion of the target within a defined lattice. The lattice resolution, i.e., the distance between lattice points, may be defined by the practitioner or may be set by the computer program. Likewise, the other parameters of points
15 within the lattice, such as hydrophobicity or other characteristics, may be similarly defined. Probes (i.e., computer models) of one or more selected moieties, functional groups, molecules or molecular fragments are positioned at lattice points and the interaction energy of the probe-target pair is determined for each such lattice point. The data for each selected moiety, functional group, etc. is collected and may be recovered as a data set, visualized on a computer monitor or printed out in
20 various text or graphic formats.

As an alternative to positioning a moiety at each of a set of lattice points, one may, as previously mentioned, flood the target (defined by the coordinates as described above) with multiple copies of a selected fragment, moiety, molecule, etc. by superimposing the multiple copies into the vicinity of the protein target. The model is then subjected to group minimization (i.e., molecular
25 mechanics minimization) calculations to identify points or areas of favorable interaction. Data may be handled as in the lattice approach.

Receptor site maps provide the seeds for ligand evolution via Database searches, which are described above, and for Grow/link methods for *de Novo* design of new chemical entities. Programs for ligand growth first access extensible fragment dictionaries in order to place appropriate
30 functional groups at site points. A genetic algorithm or a subgraph isomorphism protocol is then invoked to connect the fragments with small aliphatic chains or rings. Stochastic enhancements may be introduced by modification of internal degrees of freedom as well as translation and rotation of

the candidate model within the binding cavity. The resulting sets of molecules are scored and filtered by functions that consider the steric constraints of the binding site, the complementarity of electrostatic and hydrophobic interactions, and a solvation estimate. Programs of this type that could be applied include Ludi (Biosym Technologies), Leapfrog (Tripos, Inc.), Legend (University of Tokyo), Grow (Upjohn), Builder/Delegate (University of California, San Francisco), and Sprout (University of Leeds). Clique detection methods provide an alternative strategy to site mapping and ligand growth. DOCK (University of California, San Francisco) and similar programs fill a given binding site with the smallest set of atom-sized spheres possible; a database search then attempts to orient ligands such that the atoms superimpose onto the centers (or "nuclei") of the site-filling spheres. The shape complementarity of augmented by scoring functions that include the steric requirements of the cavity and a potential energy function.

Optimization of ligands (from any source) may be enhanced using the three dimensional structural of MII. Use of receptor site maps or hydrophobic profiles of MII may be used to identify preferred positions for functional group components of ligands, and can be used to filter or constrain conformational searches of ligand structures which would otherwise typically be controlled by minimal steric considerations of the ligand structures themselves. The availability of an explicit binding site also permits one to determine the mode of ligand binding to the target protein via methods that utilize force-fields directly in simulated annealing, distance geometry, Metropolis Monte Carlo, or stochastic searches for binding modes. Examples of programs that can be applied to rationalize ligand binding include Autodock (Scripps Clinic), DGEOM (QCPE #590), Sculpt (Interactive Simulations, Inc.), or any of the molecular dynamics programs described above. Once a tractable set of possible binding orientations is obtained, one can readily identify the appropriate mode of binding through modifications in test ligands designed to alter in a predictable fashion the binding affinity of each model under consideration. For instance, a ligand may be modified to contain a functional group at a position which is inconsistent with one binding model, yet consistent with another model. Binding data can then be used to weed out "disproven" models. Once iterative weeding of unlikely binding modes generates an appropriate model, possibilities for improvement of the lead become readily apparent from the local protein environment.

An alternative protocol for ligand optimization involves 3D database searching in conjunction with knowledge of the binding site. Modeling can reveal multiple candidates for the bioactive conformation of a given ligand. A probe for the correct conformation can include a 3D search to identify several constrained mimics of each possible conformer. Structure-activity

relationships of the unconstrained ligand would suggest which functional groups should be retained in the constrained mimics. Finally, the steric and electrostatic requirements of the binding site could constitute a filter for prioritizing the resultant possibilities.

The structure of MII permits accurate model-building of homologous peptides and their subsequent use in drug design. The MII structure may be readily used in the development of a reliable model by either knowledge-based template building methods, or by iterations of directed point mutations followed by local molecular mechanics minimizations. Examples of programs that can be applied in the development of a model of Syk-NC include Composer (Birbeck College), Modeler (MSI), and Homology (Biosym Technologies). The resultant model can then be subjected to any of the CADD techniques described above.

B. Utilization of the structure of the α -conotoxin MII in computer-aided drug design.

The availability of the three-dimensional structure of the α -conotoxin MII makes structure-based drug discovery approaches possible. Structure-based approaches include *de Novo* molecular design, computer-aided optimization of lead molecules, and computer-based selection of candidate drug structures based on structural criteria. New peptidomimetic modules may be developed directly from the structure of the peptide ligand by design or database searches for conformationally-restricted peptide replacements. Alternatively, structure-based lead discovery may be accomplished using the target protein structure, e.g. receptor, stripped of its ligand.

Multiple uncomplexed states of MII can be generated by several methods to provide additional target conformations. The experimental coordinates and the resulting uncomplexed models can be subjected to techniques such as receptor site mapping to identify sites of favorable interaction energies between the structure of the target protein and potential ligands or chemical moieties ("fragments" or "seeds"). Such evaluation may be followed by procedures such as fragment seed linking and growth. Fragment seed linking refers to methods for designing structures that contain "linked" "seeds," i.e. chemical structures comprising two or more of the mapped moieties appropriately spaced to reach the respective sites of favorable interactions. Growth refers to the design of structures which extend, based on receptor site mapping or to fill available space, a given molecule or moiety. Based on the receptor site mapping data, one may also select potential ligands from databases of chemical structures. Potential ligands, or suboptimal ligands, of whatever source, can be refined by using the receptor site maps to filter multiple ligand conformations and orientations according to energetic preferences. The structure of MII permits one to generate a high-quality model of MII by either knowledge-based homology template methods or iterative site-

mutations followed by minimizations. The generated structure of MII may then be treated as an additional protein target by the methods outlined above. These methods and their application to MII are described in the sections that follow.

5 The amino acid sequence of α -conotoxin MII has been determined (Cartier, et al., 1996) and the determinants for specificity (specific amino acid residues) for MII on $\alpha 3\beta 2$ neuronal nicotinic receptors have been identified (Harvey, et al., 1997, incorporated herein by reference). Knowledge of the determinants and the binding orientation of a peptide can suggest avenues for conformational restriction and peptide bond replacement. A less biased approach involves computer algorithms for searching databases of three-dimensional structures to identify replacements for one or more
10 portions of the peptide ligand, preferably non-peptidic replacement moieties. By this method, one can generate compounds for which the bioactive conformation is heavily populated, i.e., compounds which are based on particularly biologically relevant conformations of the peptide ligand. Algorithms for this purpose are implemented in programs such as Cast-3D (Chemical Abstracts Service), 3DB Unity (Tripos, Inc.) and MACCS/ISIS-3D (Molecular Design Limited). These
15 geometric searches can be augmented by steric searching, in which the size and shape requirements of the binding site are used to weed out hits that have prohibitive dimensions. Programs that may be used to synchronize the geometric and steric requirements in a search applied to MII include CAVEAT (University of California, Berkeley).

By way of illustration, a non-exclusive list of computer programs for performing rigid three-
20 dimensional searches include the following:

3Dsearch (Seridan, r.p. et al., J. Chen. Inf. Comput. Sci. 29:255. 1989)
Aladdin (Van Drie, J.H. et al., J. Comput. Aided Mol. Design 3:225. 1989)
UNITY (Tripos, Inc.)
MACCS-3D (MDL)
25 CATALYST (Biosyn/MSI, Inc.)

All of these searching protocols may be used in conjunction with existing corporate databases, the Cambridge Structural Database, or available chemical databases from chemical suppliers.

As practitioners in this art will appreciate, various computational analyses may be used to determine the degree of similarity between the three-dimensional structure of a given peptide and
30 MII (or a portion or complex thereof) or another α -conotoxin peptide or portion or complex thereof such as are described herein. Such analyses may be carried out with commercially available

software applications, such as CAVEAT (Molecular Simulations, Inc., Waltham, MA) as described by Lauri and Bartlott (1994).

CAVEAT is a program that uses a database search to assist in the design of novel molecules. It is a special-purpose program that was written to aid in the design of small molecules that could mimic a protein loop important in a protein-protein interaction. The basic assumption of the programs is that protein-protein recognition is based on specific positioning of amino acid side chains and that the backbone is not critical and could be replaced. The CAVEAT program attempts to find ring systems that can present the side chains in the desired orientation. A CAVEAT database consists of the distance and angle relations of vectors, defined by the exocyclic bonds of ring systems, and an index back to the 3D structure of the ring. A typical query might define the C α -C β vector relations that would be required to present the necessary side chain analogues. Such a vector search could be conducted by most generic database-searching programs discussed in this chapter; however, CAVEAT is optimized for this task. Although the initial CAVEAT applications were for protein mimicry, the program could be useful in any situation for which one needed a novel scaffold to present a set of functional groups in a defined orientation. The latest CAVEAT suite of programs includes the ability to cluster the hits, based on size or substructure similarity, and to rank hits by size, number of atoms at ring fusions, and whether the designed molecule would have eclipsing interactions. Two novel databases are available for use with CAVEAT: Triad, a computer-generated collection of all tricyclic hydrocarbons, and Iliad, a collection of acyclic molecules. Software is also available to create CAVEAT databases from the Cambridge Structural Database.

In addition to the retention of potential pharmacophoric elements that are present in the peptide explicitly, the incorporation into a ligand structure of hydrogen-bond donating or accepting groups that can displace ordered water molecules usually provides a significant entropic gain that leads to a favorable free energy of binding. Such ordered waters are identifiable from the structure, and other ordered waters may be located during computer simulations of a fully solvated structure.

Structural coordinates of the peptides of this invention may be stored in a machine-readable form on a machine-readable storage medium, e.g. a computer hard drive, diskette, DAT tape, etc., for display as a three-dimensional shape or for other uses involving computer-assisted manipulation of, or computation based on, the structural coordinates or the three-dimensional structures they define. In order to use the structural coordinates generated for MII as set forth in Figure 8, it is often necessary to display them as, or convert them to, a three-dimensional shape, or to otherwise manipulate them. This is typically accomplished by the use of commercially available software such

as a program which is capable of generating three-dimensional graphical representations of molecules or portions thereof from a set of structural coordinates. By way of illustration, a non-exclusive list of computer programs for viewing or otherwise manipulating protein or peptide structures include the following:

- 5 Midas (University of California, San Francisco)
- MidasPlus (University of California, San Francisco)
- MOIL (University of Illinois)
- Yummie (Yale University)
- Sybyl (Tripos, Inc.)
- 10 Insight/Discovery (Biosym Technologies)
- MacroModel (Columbia University)
- Quanta (Molecular Simulations, Inc.)
- Cerius (Molecular Simulations, Inc.)
- Alcherny (Tripos, Inc.)
- 15 LabVision (Tripos, Inc.)
- Rasmol (Glaxo Research and Development)
- Ribbon (University of Alabama)
- NAOMI (Oxford University)
- Explorer Eyechem (Silicon Graphics, Inc.)
- 20 Univision (Cray Research)
- Molscript (Uppsala University)
- Chem-3D (Cambridge Scientific)
- Chain (Baylor College of Medicine)
- O (Uppsala University)
- 25 GRASP (Columbia University)
- X-Plor (Molecular Simulations, Inc.; Yale University)
- Spartan (Wavefunction, Inc.)
- Catalyst (Molecular Simulations, Inc.)
- Molcadd (Tripos, Inc.)
- 30 VMD (University of Illinois/Beckman Institute)
- Sculpt (Interactive Simulations, Inc.)
- Procheck (Brookhaven National Laboratory)

DGEOM (QCPE)

RE_VIEW (Brunel University)

Modeller (Birbeck College, University of London)

Xmol (Minnesota Supercomputing Center)

5 Protein Expert (Cambridge Scientific)

HyperChem (Hypercube)

MD Display (University of Washington)

PKD (National Center for Biotechnology Information, NIH)

10 For example, data defining the three-dimensional structure of an α -conotoxin peptide, or portions or structurally similar homologs or analogs of MII, may be stored in a machine-readable storage medium and may be displayed as a graphical three-dimensional representation of the peptide structure, typically using a computer capable of reading the data from said storage medium and programmed with instructions for creating the representation from such data. This invention thus encompasses a machine, such as a computer, having a memory which contains data representing the

15 structural coordinates of a composition of this invention, e.g. the coordinates set forth in Example 8, together with additional optional data and instructions for manipulating such data. Such data may be used for a variety of purposes, such as the elucidation of other related structures and drug discovery (WO 97/08300).

20 In comparative protein modeling, a first set of such machine readable data may be combined with a second set of machine-readable data using a machine programmed with instructions for using the first data set and the second data set to determine at least a portion of the coordinates corresponding to the second set of machine-readable data. For instance, the first set of data may comprise a Fourier transform of at least a portion of the coordinates for MII set forth in Figure 8, while the second data set may comprise coordinates for a potential analog of MII. In this manner,

25 one may use molecular replacement to exploit a set of coordinates such as set forth in Figure 8 to determine the effect on the structure of such a replacement.

Therefore, another object of the invention is to provide a method for determining the three-dimensional structure of a peptide analog or peptide mimetic of MII using comparative protein modeling techniques and structural coordinates for a composition of this invention. Comparative

30 protein modeling involves constructing a model of an unknown structure using structural coordinates of one or more related peptides. Comparative protein modeling may be conducted by

fitting common or homologous portions of the protein or peptide whose three-dimensional structure is to be solved to the three-dimensional structure of known homologous structural elements. Comparative protein modeling can include rebuilding part or all of a three-dimensional structure with replacement of amino acids (or other components) by those of the related structure to be solved.

5 For example, using the structural coordinates of MII, one may determine the three dimensional structure of a peptide analog of MII using comparative protein modeling. Those coordinates may be stored, displayed, manipulated and otherwise used in like fashion as the MII coordinates of Example 8.

This invention further provides for the use of the structural coordinates of a peptide of this invention, or portions thereof, to identify reactive amino acids, such as cysteine residues, within the three-dimensional structure, preferably within or adjacent to a receptor binding site; to generate and visualize a molecular surface, such as a water-accessible surface or a surface comprising the space-filling van der Waals surface of all atoms; to calculate and visualize the size and shape of surface features of the peptide; to locate potential H-bond donors and acceptors within the three-dimensional structure, preferably within or adjacent to a receptor binding site and to calculate regions of hydrophobicity and hydrophilicity within the three-dimensional structure, preferably within or adjacent to a receptor binding site. One may use the foregoing approaches for characterizing the peptide and its interactions with a receptor to design or select compounds of complementary characteristics (e.g., size, shape, charge, hydrophobicity/hydrophilicity, receptor specificity, etc.) to surface features of the peptide, a set of which may be preselected. Using the structural coordinates, one may also predict or calculate the orientation, binding constant or relative affinity of the peptide to a given receptor subtype in the bound state, and use that information to design or select compounds of improved or altered affinity.

10
15
20

In such cases, the structural coordinates of the α -conotoxin peptide, or portion thereof, are entered in machine readable form into a machine programmed with instructions for carrying out the desired operation and containing any necessary additional data, e.g. data defining structural and/or functional characteristics of a potential analog, defining molecular characteristics of the various amino acids, etc.

25

Compounds of the structures selected or designed by any of the foregoing means may be tested for their ability to bind to an nAChR, inhibit the binding of an nAChR to a natural or non-natural ligand therefor, and/or inhibit a biological function mediated by an nAChR.

30

This invention also provides peptidomimetic and mimetic methods for designing a compound capable of binding to an nAChR. One such method involves graphically displaying a three-dimensional representation based on coordinates defining the three-dimensional structure of MII or a portion thereof bound to an nAChR. Interactions between portions of an MII and the receptor are characterized in order to identify candidate moieties for replacement. One or more portions of MII which interact with the receptor may be replaced with substitute moieties selected from a knowledge base of one or more candidate substitute moieties, and/or moieties may be added to MII to permit additional interactions with the receptor.

The computational approaches and structural insights disclosed herein, also permit the design or identification of molecules with *reduced* capacity, or substantial *inability*, to bind to an nAChR subtype. For example, one may apply the same modeling and computational methods to the data described herein, but with the opposite goal, i.e., to design or identify compounds which *lack* substantial binding affinity to one or more nAChR subtypes. Such information can be useful in research efforts aimed at identifying antagonists of a single subtype of nAChR. Compounds first identified by any such methods are also encompassed by this invention.

For storage, transfer and use with such programs of structural coordinates for a crystalline substance of this invention, a machine-readable storage medium is provided comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, e.g. a computer loaded with one or more programs of the sort identified above, is capable of displaying a graphical three-dimensional representation of any of the molecules or molecular complexes described herein. Machine-readable storage media comprising a data storage material include conventional computer hard drives, floppy disks, DAT tape, CD-ROM, and other magnetic, magneto-optical, optical, floptical and other media which may be adapted for use with a computer.

Even more preferred is a machine-readable data storage medium that is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex that is defined by the structural coordinates of MII or portion thereof, and in particular, structural coordinates of MII set forth in Fig. 8 $\pm$ a root mean square deviation from the backbone atoms of the amino acids of such protein of not more than 1.5 Å. An illustrative embodiment of this aspect of the invention is a conventional 3.5" diskette, DAT tape or hard drive encoded with a data set, preferably in PDB format, comprising the coordinates of Fig. 8.

In another 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 structural coordinates set forth in Appendix I, Appendix II or Appendix III (or again, a derivative thereof), and which, when using a machine programmed with instructions for 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 structural coordinates corresponding to the second set of machine readable data. Examples of systems useful for this aspect of the present invention are shown in WO/97/08300.

VII. Definitions

The present invention employs the following definitions.

"Biological Activity" is used herein to broadly denote function.

"Derivative" refers to an amino acid sequence wherein one or more residue of the natural sequence is substituted.

"Features" of a compound include any combination of structural, physical or chemical attributes of the compound which are required to elicit a certain biological activity.

A peptide **"fragment," "portion"** or **"segment"** is a stretch of amino acid residues of at least about two contiguous amino acids, typically at least about three contiguous amino acids and, most preferably, at least about four or more contiguous amino acids.

"Neuronal nAChR" refers to a natural nicotinic acetylcholine receptor found in the CNS.

"Peptide Analog(s)" refers to molecules which have more, fewer, different or modified residues from an α -conotoxin amino acid sequence. The modifications may be by addition, substitution or deletion of one or more amino acid residues. The modification may include the addition or substitution of analogs of the amino acids themselves, such as peptidomimetics or amino acids with altered moieties such as altered side groups. The analogs may possess functions different from natural α -conotoxin molecule, or may exhibit the same functions, or varying degrees of the same functions. For example, the analogs may be designed to have a higher or lower biological activity, have a longer shelf-life or increased stability or be easier to formulate. From time to time herein, the present analogs are referred to as proteins or peptides for convenience, but contemplated herein are other types of molecules, such as peptidomimetics or chemically modified peptides. A peptide analog may be referred to herein as a peptide for convenience.

"Peptide mimetic or mimetic" is intended to refer to a substance which has the essential biological activity of an α -conotoxin peptide. A peptide mimetic or mimetic may be a peptide-containing molecule that mimics elements of peptide secondary structure (Johnson et al., 1993). The underlying rationale behind the use of peptide mimetics or mimetics is that the peptide backbone exists chiefly to orient amino acid side chains in such a way as to facilitate molecular interactions, such as those of ligand and receptor. A peptide mimetic is designed to permit molecular interactions similar to the natural molecule. A mimetic may not be a peptide at all, but it will retain the essential biological activity of a natural conotoxin peptide.

"Related Composition" refers to compositions comprising a conotoxin peptide analog or peptide mimetic as an active ingredient.

"Simulated annealing" refers to a strategy for superimposing flexible molecules to investigate potential alignments.

"Substantially pure" refers to a peptide which is present in the substantial absence of other biological molecules of the same type; it is preferably present in an amount of at least about 85% purity and most preferably at least about 95% purity.

"Substantially similar activity" refers to the activity of a modified peptide, with reference to a natural α -conotoxin peptide. The modified peptide will have substantially similar activity. The modified peptide may have an altered amino acid sequence and/or may contain modified amino acids. In addition to the similarity of activity, the modified polypeptide may have other useful properties, such as a longer half-life. Alternatively, the similarity of activity of the modified peptide may be higher than the activity of the natural α -conopeptide. The modified peptide is synthesized using conventional techniques or is encoded by a modified nucleic acid and produced using conventional techniques. The modified nucleic acid is prepared by conventional techniques. A nucleic acid with an activity substantially similar to the natural α -conotoxin gene function may be used to produce the modified peptide described above.

"Subtype of nAChR" refers to different molecular forms of nicotinic acetylcholine receptors.

VIII. Preparation of peptide analogs and mimetics.

Peptide analogs and peptide mimetics of the present invention specific for the $\alpha 3\beta 2$ or $\alpha 3\beta 4$ subtypes of the nAChR, are prepared on the basis of procedures described herein, using conventional techniques, such as drug modeling, drug design and combinatorial chemistry. Suitable techniques

include, but are not limited to those described in U.S. Patent 5,571,698, U.S. Patent 5,514,774, WO 95/21193 (Ecker, et al. (1995); Persidis (1997); Johnson et al. (1993); Sun et al. (1993)) and the references cited therein which are all incorporated herein by reference. The development of peptide analogs and peptide mimetics are prepared using commercially available drug design software, including those set forth in Persidis et al. (1997). These peptide analogs and peptide mimetics have the substantially similar activities as an α -conotoxin described herein and in the published literature.

IX. Preparation of pharmaceutical compositions containing peptide analogs and mimetics

Pharmaceutical compositions containing a compound of the present invention as the active ingredient can be prepared according to conventional pharmaceutical compounding techniques, such as those in *Remington's Pharmaceutical Sciences* (1990). Typically, an antagonistic amount of the active ingredient will be admixed with a pharmaceutically acceptable carrier. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., intravenous, oral or parenteral.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions or emulsions. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, suspending agents, and the like in the case of oral liquid preparations (such as, for example, suspensions, elixirs and solutions); or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations (such as, for example, powders, capsules and tablets). Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques.

For parenteral administration, the compound may be dissolved in a pharmaceutical carrier and administered as either a solution or a suspension. Illustrative of suitable carriers are water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative or synthetic origin. The carrier may also contain other ingredients, for example, preservatives, suspending agents, solubilizing agents, buffers and the like. When the compounds are being administered intrathecally, they may also be dissolved in cerebrospinal fluid.

The active ingredients, which are peptides, can also be administered in a cell based delivery system in which a DNA sequence encoding an active agent is introduced into cells designed for implantation in the body of the patient, especially in the spinal cord region. Suitable delivery systems are described in U.S. Patent No. 5,550,050 and published PCT Application Nos. WO 92/19195, WO 94/25503, WO 95/01203, WO 95/05452, WO 96/02286, WO 96/02646, WO 96/40871, WO 96/40959 and WO 97/12635. Suitable DNA sequences can be prepared synthetically for each active ingredient on the basis of the developed sequences and the known genetic code.

The active ingredients of the present invention are administered in an amount sufficient to generate the desired effect. The dosage range at which these agents exhibit this effect can vary widely, depending upon the severity of the patient's defect, the patient, the route of administration and the presence of other underlying disease states within the patient. Typically, the active ingredients exhibit their therapeutic effect at a dosage range from about 0.05 mg/kg to about 250 mg/kg, and preferably from about 0.1 mg/kg to about 100 mg/kg of the active ingredient. A suitable dose can be administered in multiple sub-doses per day. Typically, a dose or sub-dose may contain from about 0.1 mg to about 500 mg of the active ingredient per unit dosage form. A more preferred dosage will contain from about 0.5 mg to about 100 mg of active ingredient per unit dosage form. Dosages are generally initiated at lower levels and increased until desired effects are achieved.

EXAMPLES

The present invention is further detailed in the following Examples, which are offered by way of illustration and are not intended to limit the invention in any manner. Standard techniques well known in the art of the techniques specifically described below are utilized.

EXAMPLE 1

Synthesis of α -Conotoxin MII and MII Derivatives

MII, originally isolated from *Conus magus*, was chemically synthesized using standard Fmoc chemistry on an ABI model 431 peptide synthesizer and properly folded to its biologically active conformation using two-step oxidation protocols (Monje et al., 1993). Once purified, the peptide's identity with the native MII was confirmed as described by Cartier et al., 1996.

MII derivatives were chemically synthesized and folded in the similar manner. Initial derivatives were prepared with alanine substitutions for each non-cysteine amino acid residue, (i.e., an alanine walk) in order to determine the effect of substitutions at each residue. Additional

derivatives or analogs are prepared in the similar manner by substituting any amino acid for the amino acid residues of MII except the cysteine and His₁₂ amino acid residues.

EXAMPLE 2

Biological Activity of α -Conotoxins MII and MII Derivatives, Peptide Analogs and Peptide Mimetics

Each of the MII derivatives, peptide analogs and peptide mimetics were tested for activity on neuronal nAChRs in *Xenopus laevis* oocytes containing the $\alpha 3$ and $\beta 2$ subunits of nAChRs as described by Cartier et al. (1996). Briefly, oocytes (1-2 days after harvesting) were injected with cRNA encoding the $\alpha 3$ and $\beta 2$ subunits of rat nAChRs and incubated at 25° C for 1-4 days prior to use. Electrophysiological currents were measured using conventional techniques, such as described in Cartier et al. (1996). Measurements were made for oocytes perfused with acetylcholine as controls and for oocytes incubated with either MII or the analogs prepared in Example 1.

Figure 1 shows the effect of alanine substitutions in the conopeptide MII on the ability of the analogs to block acetylcholine-gated currents in voltage-clamped *Xenopus* oocytes expressing cloned rat $\alpha 3$ and $\beta 2$ subunits. Most substitutions decreased MII's potency 4-fold or less. The notable exceptions are: Glu₁₁: 8-fold decrease; His₉: 25-fold decrease; His₁₂: >10⁴-fold decrease. In addition, it was seen that Asn₅ (which can be substituted with His) and Pro₆ along with His₁₂ (which can be substituted with Asn) were essential for high affinity binding to the $\alpha 3\beta 2$ nAChR. Similar effects are seen when other amino acids are substituted for the various residues of MII. The more conservative the substitution of amino acid residues in the analogs, the more similar the activity which is seen for the synthesized analogs. Sequences of several α -conotoxins and their biological activity is shown in Shon et al. (1997).

EXAMPLE 3

NMR Spectroscopy

NMR Spectroscopy. A sample containing 8 mg. of the peptide was dissolved in 500 μ L of 5mM sodium phosphate buffer made of 90% H₂O and 10% D₂O (Cambridge Isotope Laboratory). The final pH of the peptide solution was 3.3, and the peptide concentration was 9.4 mM. For experiments requiring "100%" replacement of labile amide hydrogens with deuterons, the sample was lyophilized and dissolved in D₂O (99.96% isotope enriched). After being allowed to sit

overnight at room temperature, the sample was again lyophilized and dissolved in D₂O (99.996% isotope enriched).

All NMR data were obtained with a Varian 600 MHz Unity Plus spectrometer equipped with a pulsed-field-gradient (z) unit. A set of 2-D ¹H NMR experiments were carried out at 275 K: these were NOESY (Jeener, J. (1979); Kumar, A. (1980); Macura, S. (1981)) with mixing times of 75, 150, 250 and 350 ms, TOCSY (Braunschweiler, L. (1983); Davis, D.G. (1985)) with a mixing time of 64 ms, DQF-COSY (Piantini, U. (1982); Rance, M. (1983)) and PE-COSY (Muller, L. (1987)). All spectra were recorded in a phase sensitive mode (States, D.J. (1982)) with a spectral width of 6600 Hz and 4K data points except for PE-COSY (8K data points). Eight to 32 scans were signal averaged for each free induction decay (FID) with a relaxation delay of 2 s; each 2-D experiment was completed with 400-512 FIDs. In NOESY experiments, the solvent signal was suppressed by gradient echo combined with the WATERGATE sequence (Piotto, M. (1992)). A "flip-back" pulse was inserted right after the mixing time to restore the residual magnetization along the z-axis. In TOCSY, a spin lock field of 7.7 kHz necessary for the coherence transfer among scalar-coupled ¹H spins was generated with the DIPSI-2 sequence (Rucker, S. (1989)), and water suppression was obtained using the WATERGATE sequence along with minimum presaturation set at the residual water signal during the relaxation delay. In PE-COSY, water suppression was not needed since the sample was prepared in 100% D₂O. A mixing pulse of 30° was used for PE-COSY, and each FID was recorded with 32 scans to compensation for the sensitivity loss due to the small mixing pulse.

2-D NMR data were transferred to an SGI workstation (Indigo²) and were processed using Felix 95.0 (MSI, San Diego) except for PE-COSY, which was processed using VNMR 5.10 (Varian). FIDs were apodized with a window function (90° and 135° shifted sine bell) in both dimensions prior to Fourier transformation. Each Fourier transformed FID was baseline corrected by applying a third-order polynomial, and each dimension was referenced to a chemical shift value of 4.76 ppm at the residual water signal.

Even though complete resonance assignments were easily obtained except for the C β protons of Ser¹³ (not observed), the 1-D spectrum of the peptide in the amide proton region had a few resonance overlaps. Starting with the unique residue Val⁷, identified on the basis of its spin type, sequential $d_{\alpha N}$ NOE connectivity was traced through the carboxyl terminal residue Cys¹⁶. Along the trace, resonance assignment for each residue was confirmed on the basis of its spin type obtained from the TOCSY experiment. The remaining N-terminal residues were also assigned on the basis of sequential $d_{\alpha N}$ NOE connectivity starting from Asn⁵, whose spin system was identified from NOE

cross peaks between its amide proton and β protons as well as its side chain γ NH2 protons. In addition, sequential NOEs arising from neighboring amide protons, d_{NN} , confirmed the above resonance assignments. Figure 2 depicts two traces of sequential NOE $d_{\alpha\text{N}}$ connectivities which extend from Cys² to Asn⁵ and from Val⁷ to Cys¹⁶.

5

EXAMPLE 4

Generation of Dihedral and Distance Restraints

NOE cross peak volumes were measured from NOESY data with four different mixing times using FELIX 95.0. NOE buildup curves were then fitted with a second-order polynomial and exact distances were generated for all assigned NOE cross peaks. A distance of 1.8 Å was used as an appropriate reference for nonoverlapping geminal C β proton cross peaks, as well as for lower distance bounds. Several volumes of nonoverlapping geminal C β proton cross peaks were averaged and used for calibrating measured NOE volumes. A pseudoatom correction of 1 Å (Wuthrich, K. (1983)) was added to the upper limits of those NOE cross peaks involving spectroscopically degenerate methyl and methylene protons. As for dihedral restraints, $^3J_{\text{HN-H}\alpha}$ coupling constants were measured from a 1-D ^1H spectrum recorded with 32K data points and converted to ϕ dihedral angles centered at $-120^\circ (\pm 30^\circ)$ for $^3J_{\text{HN-H}\alpha} > 8.0$ Hz and $-60^\circ (\pm 30^\circ)$ for $^3J_{\text{HN-H}\alpha} < 5.0$ Hz (Pardi, A., et al. (1984)). $^3J_{\alpha\beta}$ coupling constants were also measured from PE-COSY recorded from the sample whose amide protons were completely exchanged out with deuterons in "100%" D₂O. The measured $^3J_{\alpha\beta}$ coupling constants derived from those residues with an AMX spin system and with nonoverlapping geminal β protons were used for defining χ_1 dihedral angles in combination with the sequential $d_{\text{HN-H}\alpha}$ and $d_{\alpha\beta}$ NOE cross peak intensities (Hyberts, S. (1987); Wagner, G. (1987)).

Initially, 99 interresidue NOE cross peaks with a high level of confidence in their assignments were selected and corrected for those NOE cross peaks containing at least one pseudoatom. Fifteen chirality restraints and 11 ϕ and 5 χ_1 dihedral angles were also included in the restraint file for generating an initial set of 10 structures using the DGII (Havel, T. (1991)) module of the InsightII program (MSI, San Diego). All structures generated by the DGII calculations had similar overall backbone folding patterns, and thus the lowest energy structure with the minimum number of NOE violations was chosen and subjected to an iterative relaxation matrix approach (IRMA). This procedure improves the accuracy and precision of interproton NOE-derived distance restraints by evaluating the full relaxation network of spins in a molecule (Boelens, R. (1988)). At this stage, the total of 158 NOE-derived interproton distances (including intraresidue NOEs with

pseudoatom correction) along with 16 dihedral angle and 15 chirality restraints were subjected to IRMA and restrained molecular dynamics (RMD) followed by energy minimization steps. Any distances derived from NOEs containing at least one pseudoatom were not treated by IRMA, and therefore those were not refined by the process. Each cycle of IRMA took experimental NOE intensities measured as a function of mixing time and merged them with the calculated theoretical NOE intensity values for the model structure. A new set of distance restraints was then deduced from this mixed NOE intensity matrix. A rotational correlation time of 1.5 ns, estimated from NOE buildup curves of nonoverlapping geminal β protons, and diagonal leakage rate of 1.0 s were used in each IRMA cycle. After each cycle of IRMA, the structure was subjected to RMD and energy minimization steps using a Lennard-Jones potential with a 12.0 Å cutoff. Five cycles of 1,000 steps of RMD of 1.0 fs for a duration of 5 ps was calculated at 700 K followed by cooling over 5 ps at 500 k and another 5 ps at 300 K. The structure was minimized using 100 steps of steepest descents followed by 1500 steps of conjugated gradient minimization. Four IRMA/RMD cycles were carried out and the convergence was achieved with the final R -factors (a measure of the difference in the theoretical and experimental NOE intensities) reaching 0.407 for R_1 and 0.007 for R_6 (reflects $1/r^6$ relationship between NOE intensity and distance, r) (Gonzales, C. (1991)). This IRMA/RMD protocol is well documented in the manual provided by the InsightII software for refining distances converted from experimentally measured NOE cross peaks.

It was obvious from both $^3J_{\text{NH-C}\alpha}$ coupling constants recorded from a high-resolution 1-D spectrum and short- and medium-range NOE cross peaks from NOESY experiments that a large portion of the peptide was helical. Nine of 16 residues were determined to have $^3J_{\text{NH-C}\alpha}$ coupling constants of less than 5.0 Hz and among those nine residues we have identified short- and medium-range NOE cross peaks, d_{NN} , $d_{\text{NN}(1,1+2)}$, $d_{\alpha\text{N}}$, and $d_{\alpha\text{N}(1,1+2)}$, very typical of an α -helix (Wuthrich, K. et al. (1986)). Figure 2 displays those NOE cross peaks according to their intensities along with $^3J_{\text{NH-C}\alpha}$ coupling constants used to generate dihedral angle restraints. In addition to the observed NOE cross peaks, C α proton chemical shifts relative to random-coil values (Wuthrich, K. et al. (1986)) are a good assessments for identifying local helical components in peptides and proteins (Wishart, D.S. et al. (1991); Rothmund, S. et al. (1996)). The plot shown in Figure 4 strongly suggests that the peptide contains a large portion of helical conformation throughout the sequence except for residues Asn⁵ and His¹². The backbone conformation of these residues could deviate from a helical conformation on the basis of their positive shifts in the plot.

EXAMPLE 5

Molecular Modeling, Distance Geometry and Simulated Annealing

Computer models of α -CT_x MII were constructed and manipulated using the InsightII and Discover programs (MSI, San Diego) on a Silicon Graphics workstation. Simulated annealing (SA) computations were conducted on a Cray C-90 supercomputer at the San Diego Supercomputer Center. The consistent valence force field of Hagler and co-workers (Dauber-Osguthorpe, P. (1988)) was employed for both the DGII and simulated annealing calculations. An extended molecule with two disulfide bridges was constructed as the triply charged cation with full positive charges on the N-terminal nitrogen and the imidazole side chains of His⁹ and His¹².

A triangle inequality bound smoothing and four-dimensional embedding procedure followed by prospective metrication and majorization with a constant weighting scheme was used for DGII calculations with default settings except for an initial energy of 750 kcal/mol and 20,000 steps of built-in simulated annealing with a step size of 0.3 ps.

In order to develop a more qualitative picture of the conformation(s) of α -CT_x MII and to generate three-dimensional structures compatible with the NMR data, a protocol based generally on the principles of simulated annealing as developed by Clore and Gronenborn and co-workers (Nilges, M. (1988)) was employed. The calculations incorporated two notable departures from previous work. First, the interproton distances were introduced in a biphasic manner during high-temperature molecular dynamics (MD); initially they involved only backbone protons, but then subsequently they involved side chain protons. Second, transition from a quartic to a Lennard-Jones nonbonded potential was achieved in a final dynamics phase concomitant with final maturation of the nonbond energy factor. A total of 50 rounds of SA were conducted in order to sample as large a conformational space as practical given computer processor and disk limitations. A final minimization with a convergence criterion of the large derivative not exceeding 0.01 kcal mol⁻¹ Å⁻¹ was conducted.

A total of 50 structures resulted from the SA calculations were described using 154 distance (85 intraresidue, 42 sequential, 22 medium range and 5 long range), 14 dihedral and 15 chirality restraints. An RMS deviation-based family clustering scheme was used which resulted in the grouping of these structures into 30 families spanning the energy range 396-5360 kcal/mol with the two families of lowest energy encompassing 18 of the 50 structures. Structural statistics of these five families, with minimum energy structure (MES) energies within 22 kcal/mol of the overall MES are given in Table 1. The next lowest energy family (family 3) was at 79 kcal/mol relative to the

overall MES. By interactive graphical inspection, we have observed that many of the higher energy family representatives (families 3-30) contained unusually high internal energy terms or pathological features (e.g., broken bonds, knots involving backbone and cystine bridges). An interesting structural pathology is observed in structure 8 of family 1 (PDB accession code 1m2c) wherein L - α -Cys⁸ is inverted to D - α -Cys⁸. This structure is included because it fits the criterion used for classifying family 1 but in no way influenced the final model and underscores the importance of maintaining proper chirality constraints during SA.

In Figure 5, the structures of family 1 were superimposed to demonstrate how well they converge in the structural calculations with a given set of experimentally determined and refined restraints. As shown in Table 1, the pairwise backbone and heavy atom RMS deviations among those 14 structures in family 1 calculated over residues Cys²-Cys¹⁶ (Gly¹ is excluded due to its mobility) are 0.76 ± 0.31 and 1.35 ± 0.34 Å, respectively. In the SA procedure, no particular restraints were employed to force backbone amide bonds to the trans configuration. All amide bonds in all residues of all structures in this family are trans, and all 14 structures in family 1 have almost the same backbone dihedral angles with the exception of Gly¹, as seen from high values of the backbone angular order parameters (Hyberts, S. et al (1992); Pallaghy, P. et al (1993)). In Figure 6A,B. However, this consistency of the backbone dihedral angles is not maintained at the level of the χ_1 side chain dihedral. High angular order parameters as seen in Figure 6C for residues 2, 5, 9 and 10 indicate that all structures of family 1 have equivalent side chain rotameric states. All other residues have multiple side chain rotameric states which generally fall into the *gauche*⁻, *gauche*⁺, or *trans* classification. The structures of family 1 are well built as judged by the range and magnitude of the energetic contributions detailed in Table 1. Clearly, important energetic contributions to the maintenance of these structures are found in the nonbonded terms, both van der Waals and Coulombic. These modeling studies were conducted *in vacua*, and any modulation of the effective dielectric constant by either empirical solvation methods or explicit solvent inclusion should serve only to decrease the net effect of electrostatics for this simple constrained peptide.

TABLE 1

Structural Statistics for the Two Lowest Energy
Families of MII Resulting from Simulated Annealing

	family	1	2
5	no. of structures	14	4
	energy components ^a		
	E_{total}	453±30	476±48
	E_{bond}	28±2	28±1
	E_{angle}	161±12	165±14
10	E_{torsion}	50±6	63±14
	$E_{\text{out of plane}}$	4±1	4±1
	$E_{\text{van der Waals}}$	75±8	84±17
	E_{Coulomb}	135±9	132±9
	E_{force}	75±20	77±21
15	$E_{\text{total+force}}$	527±47	553±68
	pairwise RMS ^b		
	backbone (2-16)	0.76±0.31	0.99±0.25
	heavy atoms (2-16)	1.35±0.34	1.61±0.25
	NMR violations >0.2Å ^b		
20	av no. of violations per structure	16.64±3.13	16.50±3.64
	av violation	0.30±0.11	0.31±0.11
	dihedral violations >10°	1/14 ^c (Cys ² χ_1)	1/4 ^d (Cys ² χ_1) 2/4 ^d (His ⁹ χ_1)
	minimum energy structure		
	E_{total}	396	418
25	$E_{\text{total+force}}$	440	463
	no. of violations >0.2 Å	13	21
	av violation >0.2 Å ^b	0.25±0.04	0.32±0.12
	max violation ^b	0.35	0.66
30	^a All energies in kcal/mol. ^b All distance in Å. ^c Number of structures in family 1. ^d Number of structures of a family 2.		

EXAMPLE 6

Three Dimensional Solution Structure

Even though α -CT_x MII is a small peptide made of only 16 amino acid residues, it has a well-defined three-dimensional solution structure. In addition to two disulfide bridges which form a hydrophobic Cys knot, there are three helical regions in the structure which contribute to form a very tight conformation. The presence of such stable secondary structures and disulfide bridges allows the multidimensional NMR method to be effective in obtaining a very high resolution structure of the peptide. The amino-terminal region has almost a full turn of α -helix (Cys² - Ser⁴); this is followed by Asn⁵ which has backbone dihedral angles of $\phi = -89^\circ$ and $\psi = +132^\circ$ (measured from the minimum energy structure), thereby essentially making a 90° turn. The helix with almost two turns (Pro⁶ - Glu¹¹) is the major secondary structural component of the peptide. This helix is terminated by His¹² ($\phi = -136^\circ$, $\psi = +77^\circ$; measured from the minimum energy structure) which orients the remaining C-terminal distorted 3₁₀ helix (Ser¹³-Cys¹⁶) toward the N-terminus. These two turns associated with Asn⁵ and His¹² are perhaps critical residues for the overall fold of the peptide and the presence of such turns is further supported by C α proton shift data presented in Figure 4 (positive shifts compare to the rest having negative shifts) as well as $^3J_{\text{NH-C}\alpha}$ coupling constants in Figure 2 (>8.0 Hz coupling constants compare to the rest having <5.0 Hz). A possible function of Asn⁵ is to induce a turn between the N-terminal segment and the main α -helix; this function is consistent with the survey by Richardson and Richardson (Richardson, J.S. et al (1988)) of 215 α -helices from 45 different globular protein structures. They reported a striking preference of 3,5:1 for Asn at the N-cap position and 2.6:1 for Pro at the N-cap + 1 position (helix initiator) for α -helices. With respect to the second turn around His¹², the function of His may be to bring Cys³ and Cys¹⁶ close together to form the second disulfide bridge.

The space-filling model of α -CT_x MII shown in Figure 7B is oriented to explore the surface distribution of hydrophobic and hydrophilic side chain groups of the molecule. Hydrophobic residues are colored purple to distinguish them from polar residues which are yellow, or charged residues which are red (positive) and blue (negative). A flat surface located on top of the molecule in purple is a distinct structural feature representing the cluster of hydrophobic residues exposed to solvent. This hydrophobic surface is formed largely by Gly¹ (excluding the N-terminal amino group), Cys², Cys³, Leu¹⁵, Cys¹⁶ and the disulfide bond between Cys³ and Cys¹⁶. This flat surface may be important for ligand-receptor binding through hydrophobic interactions. There is another very distinct surface that consists entirely of hydrophilic residues with both polar and charged

groups. On the left side of the model, the cluster of red, blue and yellow represents a region of the turn at His¹² (Glu¹¹-Asn¹⁴). This highly charged surface, almost perpendicular to the hydrophobic surface, could be responsible for its initial recognition by nAChR based on long-range electrostatic attractions. This potential receptor-binding interface is composed of sequential residues Glu¹¹, His¹², Ser¹³ and Asn¹⁴.

EXAMPLE 7

Electrophysiology

cDNA clones encoding nAChR subunits were provided by S. Heinemann and D. Johnson (Salk Institute, San Diego, CA). cRNA was transcribed using RiboMAX™ large scale RNA production systems (Promega, Madison, WI). Diguanosine triphosphate (Sigma, St. Louis, MO) was used for synthesis of capped cRNA transcripts according to the protocol of the manufacturer. Plasmid constructs of mouse and rat nAChR subunits were as conventionally described: $\alpha 1$, $\beta 1$, γ , δ ; $\alpha 2$; $\alpha 3$; $\alpha 4$; $\alpha 7$; $\alpha 9$; $\beta 2$; $\beta 4$.

cRNA was injected with a Drummond 10 μ l microdispenser (Drummond Scientific, Broomall, PA) using conventional techniques. It was fitted with micropipettes pulled from glass capillaries provided for the microdispenser. The pipette tips were broken to an OD of 22-25 μ m and back-filled with paraffin before mounting on the microdispenser. cRNA were drawn into the micropipette and 50 nl, containing 5 ng cRNA subunit, was injected into each oocyte. In the case of muscle subunits, 0.5-5 ng of each subunit was injected.

Oocytes were harvested from *Xenopus* frogs, cut into clumps of 20-50 oocytes, and placed in a 50 ml polypropylene tube (Sarstedt) containing 580 U/ml type 1 collagenase (Worthington Biochemical, Freehold, NJ) in OR-2 (82.5 mM NaCl, 2.0 mM KCl, 1.0 mM MgCl₂ and 5mM HEPES, pH ~7.3). The tube was incubated for 1-2 hr on a rotary shaker rotating at 50 rpm. Halfway through the incubation, the solution was exchanged with fresh collagenase solution. The oocytes were then washed with six to eight ~50 ml volumes of OR-2, transferred to a 60 mm x 15 mm petri dish containing ND-96 (96.0 mM NaCl, 2.0 mM KCl, 1.8 mM CaCl₂, 1.0 mM MgCl₂, 5mM HEPES, pH = 7.1-7.5)/Pen/Strep/Gen (100 U/ml penicillin G (Sigma), 100 μ g/ml streptomycin (Sigma), and 100 μ g/ml gentamycin (Gibco BRL, Grand Island, NY). The oocytes were visually examined and only healthy appearing oocytes were transferred to a second dish containing ND96 and antibiotics. Oocytes were injected 1-2 days after harvesting and recordings were made 1-7 days after injection.

An injected oocyte was placed in a $\sim 30 \mu\text{l}$ recording chamber consisting of a cylindrical well ($\sim 4 \text{ mm}$ dia x 2 mm deep) fabricated from Sylgard, and gravity-perfused with either ND96 or ND96 containing $1 \mu\text{M}$ atropine (ND96A) at a rate of $\sim 1 \text{ ml/min}$. All toxin solutions also containing 0.1 mg/ml bovine serum albumin (BSA) to reduce nonspecific adsorption of peptide. The perfusion medium could be switched to one containing peptide or acetylcholine (ACh) by use of a distributor valve (SmartValve, Cavro Scientific Instruments, Sunnyvale, CA) and a series of three-way solenoid valves (model 161T031, Neptune Research, Northboro, MA). ACh-gated currents were obtained with a two-electrode voltage-clamp amplifier (model OC-725B, Warner Instrument Corp., Hamden, CT) set for "fast" clamp and with clamp gain at maximum ($\times 2000$). Glass microelectrodes, pulled from fiber-filled borosilicate capillaries (1 mm OD x 0.75 mm ID, WPI Inc., Sarasota, FL) and filled with 3 M KCl, served as voltage and current electrodes. Resistances were $0.5 - 5 \text{ M}\Omega$ for voltage, and $0.5 - 2 \text{ M}\Omega$ for current, electrodes. The membrane potential was clamped at -70 mV , and the current signal, recorded through virtual ground, was low-pass filtered (5 Hz cut-off) and digitized at a sampling frequency of 20 Hz . The solenoid perfusion valves were controlled with solid state relays (model ODC5 in a PB16HC digital I/O backplane, Opto 22, Temecula, CA). A/D conversion and digital control of solenoid valves were performed with a Lab-LC or Lab-NB board (National Instruments, Austin, TX) in a Macintosh (Quadra 630 or IICx) computer. The computer communicated with the distributor valve via its serial port. Data acquisition and activities of the distributor and solenoid valves were automatically controlled by a home-made virtual instrument constructed with the graphical programming language LabVIEW (National Instruments, Austin, TX).

To apply a pulse of ACh to the oocyte, the perfusion fluid was switched to one containing ACh for 1 sec . This was automatically done in intervals of $1-5 \text{ min}$. The shortest time interval was chosen such that reproducible control responses were obtained with no observable rundown. This time interval was dependent upon the nAChR subtypes being tested. The concentration of ACh was $1 \mu\text{M}$ for oocytes expressing $\alpha 1\beta\gamma\delta$, 1 mM for $\alpha 7$, and $300 \mu\text{M}$ for all others. The ACh was diluted in ND96A for all except $\alpha 7$, in which case the diluent was ND96. For control responses, the ACh pulse was preceded by perfusion with ND96 (for $\alpha 7$) or ND96A (all others). No atropine was used with oocytes expressing $\alpha 7$, since it has been demonstrated to be an antagonist of these receptors. (Gerzanich, 1994) For responses in toxin (test responses), the perfusion solution was switched to one containing toxin while maintaining the interval pulses of ACh. Toxin was continuously perfused until equilibrium was reached. All ACh pulses contained no toxin, for it was assumed that

little, if any, bound toxin would have washed away in the brief time (<2 sec) it takes for the responses to peak. The peak amplitudes of the ACh-gated current responses were measured by the virtual instrument. All recordings were made at room temperature (~22° C).

An injected oocyte was voltage-clamped at a membrane potential of -70 mV and response to ACh was measured every 5 min. After several control responses were determined at -70 mV, the membrane potential was stepped to the test potential for 1 min. beginning 10 sec. before application of ACh. The membrane potential was returned to -70 mV between each test. The test potential was varied, in sequence, from -90 mV to -10 mV in steps of 10 mV followed by a final test at a membrane potential of +10mV. After the test sequence, the perfusion solution was switched to one containing toxin. After equilibrium was achieved, the test sequence was repeated.

All data analysis was performed with Prism software (GraphPad Software Inc., San Diego, CA) running on an Apple Power Macintosh 6100/66 equip with a 486 Intel processor and Windows 3.1™. The average of three control responses just preceding a test response was used to normalize the test response to obtain "% response" or "% block."

Each data point of a dose response curve represents the average $\pm$ standard error of at least three oocytes. Dose response curves were fit to the equation: $\% \text{Response} = 100 / (1 + (\text{toxin}) / \text{IC}_{50})^{n_H}$, where n_H is the Hill coefficient.

Kinetic traces represent the data from one experiment only. All experiments were repeated on at least three oocytes. Reported kinetic parameters are the average from all experiments performed on that subtype. The data describing the time course of toxin inhibition were fit to an equation describing a simple exponential association of the form: $Y = (1 - e^{-kt})$. The data describing the time course of recovery from toxin inhibition at low toxin concentrations were fit to an equation describing a simple exponential dissociation of the form: $Y = e^{-kt}$. The data describing the time course of recovery from toxin inhibition at high toxin concentrations were fit to an equation describing a complex exponential dissociation of the form: $Y = (1 - (1 - e^{-kt})^2)$.

EXAMPLE 8

Subtype specificity of MII

nAChR subunits expressed in *Xenopus* oocytes were used to quantitate the potency of MII at various nAChR combinations. Each subtype was inhibited in a dose-dependent manner by MII but with widely differing potencies (Fig. 9). α -conotoxin MII most potently inhibited the $\alpha 3\beta 2$ combination with 200-fold to > 10,000-fold less potency at other subtypes (Table 2).

TABLE 2

Inhibition of nAChR Subtypes by Alpha-conotoxin MII

nAChR	IC ₅₀	Hillslope
$\alpha 3\beta 2$	4.9×10^{-10}	0.8
$\alpha 7$	1.3×10^{-7}	0.9
$\alpha 4\beta 2$	4.3×10^{-7}	0.9
$\alpha 2\beta 2$	9.8×10^{-7}	1.0
$\alpha 3\beta 4$	1.1×10^{-6}	1.1
muscle	3.7×10^{-6}	0.7
$\alpha 4\beta 4$	$>4.0 \times 10^{-6}$	N.D.
$\alpha 2\beta 4$	$>4.0 \times 10^{-6}$	N.D.

Many small molecules act as non-competitive inhibitors of nAChRs by blocking the open channel. Open channel block of nAChRs is generally dependent upon membrane potential. We examined whether MII block of the $\alpha 3\beta 2$ nAChR was voltage-dependent. To accomplish this, acetylcholine response of $\alpha 3\beta 2$ nAChRs to acetylcholine was measured over a range of membrane potentials both in the presence and absence of MII at its approximate IC₅₀ (500 pM). As shown in Fig. 2, blockade by α -conotoxin MII shows no voltage dependence over the range tested (-100 mV to +10 mV).

To further examine the mechanism of action of MII, the differing off-rates of dihydro- β -erythroidine (DH β E) and α -conotoxin MII were utilized. DH β E has been shown to be a competitive antagonist of nAChRs. Blockade of $\alpha 3\beta 2$ nAChRs expressed in oocytes by DH β E is fully reversed after four minutes of washout (Fig. 11A). In contrast, the $\alpha 3\beta 2$ nAChR recovers relatively slowly from MII block after toxin washout (Fig. 11C). To test whether α -conotoxin MII was acting at the same site as DH β E, we pre-applied DH β E to $\alpha 3\beta 2$ nAChRs. We then co-applied DH β E and α -conotoxin MII. If α -conotoxin MII and DH β E act at the same site, pre-application of the DH β E should protect the receptors from block by α -conotoxin MII. In this case, the recovery from block would follow the faster time course of block by DH β E alone. If preapplication of Dh β E does not prevent the binding of α -conotoxin MII to the receptor, then the recovery from blockade by the co-applied Dh β E and MII would be expected to follow the slower time course of block by α -conotoxin MII alone. As shown in Fig. 11B, the time course of recovery following washout of DH β E and α -

conotoxin MII is similar to that of washout of DH β E alone, indicating that DH β E prevents the binding of MII.

At low concentrations (e.g., near the IC₅₀) of α -conotoxin MII, recovery from block following toxin washout has a time course that is well fit by a single exponential decay function consistent with simple bi-molecular dissociation (Fig. 12). However, as the concentration of α -conotoxin MII approaches saturation, an initial lag in recovery after toxin washout occurs. This lag is maximal at fully saturated concentrations of α -conotoxin MII (data not shown). The time course of recovery from blockade with saturating concentrations MII is inconsistent with the simple bi-molecular dissociation (See dash lines in Fig. 13). Instead the time course is well fit by a model in which each receptor is assumed to have two binding sites which can either be occupied by ACh or α -conotoxin MII. Also in this model, occupation of either binding site by α -conotoxin MII is sufficient to block against induced opening of the receptor. Thus, at saturating concentrations, both binding sites are occupied by MII. Upon toxin washout each binding site becomes unoccupied following a time course of simple bi-molecular dissociation. Since both binding sites must be unoccupied by toxin for a receptor activation by agonist to occur, an initial lag in functional recovery following saturating toxin block is observed. The values of K_{off} calculated using this model under saturating toxin concentration matched those calculated under non-saturated condition validating the model. (Table 3).

TABLE 3

Equilibrium and Kinetic Constants of the Functional Block of nAChR by Variants of Class a A-Conotoxins

Peptide	Target	K _d (nM)	k _{off} (min ⁻¹)	k _{on} (min ⁻¹ M ⁻¹)
MII	$\alpha 3\beta 2$	0.33	0.13	400 x 10 ⁶
	$\alpha 3\beta 4$	2600	0.13	0.057 x 10 ⁶
Chimera	$\alpha 3\beta 2$	500	0.23	0.46 x 10 ⁶
	$\alpha 3\beta 4$	620	0.32	0.52 x 10 ⁶
Aul	$\alpha 3\beta 2$	>10,000	ND	ND
	$\alpha 3\beta 4$	1500	0.33	0.23 x 10 ⁶

EXAMPLE 9

Kinetics of Interaction with Receptor Subtypes

The affinity of a ligand is determined by its microscopic rates of association (k_{on}) and dissociation (k_{off}). As judged by measurements on voltage-clamped *Xenopus* oocytes expressing nAChRs, when MII blocks currents of $\alpha 3\beta 2$ receptors, its on rate is relatively rapid ($k_{on} = 4 \times 10^8$ min⁻¹ M⁻¹); its off rate is slow ($k_{off} = 0.13$ min⁻¹). This results in a high affinity interaction between α -conotoxin MII and $\alpha 3\beta 2$ nAChRs. ($K_d = 3.3 \times 10^{-10}$ M). A substantially lower affinity is observed if either the $\alpha 3$ or $\beta 2$ subunit is replaced with a different subunit. That is when the $\alpha 3$ subunit is switched to $\alpha 4$, the resulting $\alpha 4\beta 2$ receptor is blocked by MII with a K_d that is 800-fold higher. If the $\beta 2$ subunit is switched (to yield $\alpha 3\beta 4$) an 8,000-fold decrease in MII potency is seen. Furthermore, when the k_{on} and k_{off} values of MII for these two types of receptors ($\alpha 3\beta 4$ and $\alpha 3\beta 2$) are measured, a most striking result is obtained. Despite a decrease of nearly 4-orders of magnitude in potency, when α -conotoxin blocks the $\alpha 3\beta 4$ versus $\alpha 3\beta 2$ receptor, k_{off} is changed little if any. Thus, the difference in potency is essentially accounted for by a corresponding decrease in toxin k_{on} .

Conversely, when the α subunit is changed (i.e., to yield $\alpha 2\beta 2$ or $\alpha 4\beta 2$ a marked increase in k_{off} for MII is found, the quantitation of which is presently beyond our assay capabilities). These results suggest that the k_{on} of the toxin is largely controlled by determinants on the $\beta 2$ subunit whereas the $\alpha 3$ subunit may have the major determinants that control k_{off} .

EXAMPLE 10

Affinity of Chimera for $\alpha 3/\beta 2$ Subtype

To further examine the kinetic interactions of toxin with receptor, a chimera of α -conotoxin MII was constructed. A series of peptides from the venom *Conus aulicus* was isolated that, unlike α -conotoxin MII, prefer the $\alpha 3/\beta 4$ interface over that of the $\alpha 3/\beta 2$. One of these peptides is α -conotoxin AuIA. The presence of either histidine or asparagine at position 12 is highly conserved in all conopeptides. A conserved sequence of each of the *aulicus* peptides was used in the design of the MII chimera indicated in Table 4 in which a string of four amino acids (9-12) of MII are replaced by FATN. In general, substitution of these four amino acids results in a change in selectivity and affinity for the nicotinic receptors. Compared to MII, the affinity of the chimera for the $\alpha 3/\beta 2$ interface was more than 1,000-fold lower (K_d has changed from 330 pM for the wild-type to 500 nM for the chimera) but k_{off} was changed by a factor of less than two. Thus, the four amino

acid substitution does not affect toxin residues which determine off-rate (which must be elsewhere on the peptide), but clearly effects residues which determine on-rate. Other chimeras were synthesized in which amino acid fragment 9-12 was substituted from one peptide into another.

EXAMPLE 11

5 Cyclic Peptides Based on MII Motif

In order to test the significance of the HLEH fragment of MII (amino acid residues 9-12 of SEQ ID NO:1), several cyclic peptides based on this structure were constructed utilizing standard FMOC chemistry. These include: cyclic cys-HLEH-cys (SEQ ID NO:4), cyclic A-HLEH-A (SEQ ID NO:5) connected through an amide bond, and cyclic HLEH (amino acid residues 9-12 of SEQ ID NO:1) connected through an amide bond. These small peptides are screened for biological activity by the procedures of Example 8.

TABLE 4

Sequences of MII, Aul and a Chimera of the Two

Peptide	Sequence (ID NO:)
MII	GCCSNPVCHLEHSNLC* (1)
Chimera (MII HLEH[(9-12] FATN	GCCSNPVCFATNSNLC* (3)
Aul	GCCSYPPCFATNSGYC* (6)
The FATN sequence (amino acid residues 9-12 of SEQ ID NO:6) shown in bold is a conserved feature of at least three different $\alpha 3\beta 4$ -preferring α -conotoxins from <i>C. aulicus</i> venom.	

EXAMPLE 12

Dock and Lock Model

Comparison of the data for interactions between MII and nAChRs (Examples 9 and 10) emerges as a two-step "dock and lock" mechanism to explain the remarkable subtype specificity of MII. The data suggest that two putative "faces" of the MII interacts with its respective binding sites on the receptor, and that the dual interaction may provide a general mechanism for the observed high receptor subtype specificity and affinity. Thus, it is proposed that α -conotoxin MII has two interaction surfaces, which are referred to as the "docking face" and the "locking face." The docking face interacts relatively rapidly with a site on the $\beta 2$ subunit, which is referred to as the "docking

site." The second phase of toxin interaction involves a different surface of the toxin, the "locking face." This locking face binds to a site on the $\alpha 3$ subunit which is referred to as the "locking site." In the absence of docking interactions, the k_{on} for the "locking face- locking site" interaction may be quite slow. However, if the peptide is already docked (through the $\beta 2$ docking site), the locking phase then proceeds much more rapidly (Figs 14A and 7B).

The data discussed above demonstrate that a switch in receptor subunits can cause a decrease in MII's affinity of several orders of magnitude, without affecting its k_{off} (implying that the locking site remains intact and that the change in affinity is primarily due to changes in docking interactions). The results with the FATN- α MII analog (Example 11; SEQ ID NO:3) and the kinetic results obtained with wild-type toxin acting on the $\alpha 3\beta 4$ nicotinic receptor are thus suggestive that the docking face of the toxin is located on the hydrophilic side of the wedge and that this hydrophilic face interacts with a fast on-time with the $\beta 2$ subunit. The other side of the wedge which is characterized by hydrophobic residues exposed to solvent, would be an attractive locus for the locking face of α -conotoxin MII, which is postulated to interact with high affinity on a site on the $\alpha 3$ subunit of neuronal nicotinic receptor targets of this peptide. A cartoon representation of α -conotoxin MII interacting with the $\alpha 3\beta 2$ and $\alpha 3\beta 4$ receptors and of the FATN- α -conotoxin MII analog (SEQ ID NO:3) is shown in Fig. 14.

The presence of two distinct interaction faces, which lead to distinguishable docking-and-locking interactions as described herein may be a general design feature of many *Conus* peptides and may represent a novel paradigm for achieving subtype selective interaction with multisubunit receptors. The term "Janus-ligands" is suggested to refer to binding molecules that have two distinct interaction faces (from Janus, the two-faced Roman god of beginnings). α -Conotoxin MII would be a prototype Janus ligand.

EXAMPLE 13

Synthesis of Organic Molecules as Ligands

The HLEH fragment of MII appears essential in determining activity and selectivity of the MII conopeptide. Computational examinations of the HLEH fragment are undertaken in order to develop an organic scaffold for use in developing small molecules. The spacial arrangement of the HLEH fragment is studied computationally using a vector analysis. Databases are then be searched to find organic fragments that have the proper spatial requirements and geometry to be used as a scaffold from which organic models are synthesized. The presence of two physically distinct

peptide surfaces (hydrophilic and hydrophobic) on the MII conopeptide and their interaction with α and β receptor subunits presents a specific strategy for designing ligands selective for receptors with different combinations of α and β subunits.

It will be appreciated that the methods and compositions of the instant invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent to the artisan that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

LIST OF REFERENCES

- 10 Bodansky et al. (1966). *Chem. Ind.* **38**:1597-98.
- Boelens, R. (1988). *Mol. Struct.* **173**:299.
- Braunschweiler, L. et al. (1983). *J. Magn. Reson.* **53**:521-528.
- Cartier, G.E. et al. (1996). *J. Biol. Chem.* **271**:7522-7528.
- Dauber-Osguthorpe, P. et al. (1988). *Proteins* **4**:31-47.
- 15 Davis, D.G. et al. (1985). *J. Am. Chem. Soc.* **107**:2820-2821.
- Davis, J. et al. (1993). *Biochemistry* **32**:7396-7405.
- DesJarlais, R.L. (1997) "Generation and use of Three-Dimensional Databases for Drug Discovery" in *Practical Application of Computer-Aided Drug Design*, Charifson, ed., Marcel Dekker, New York.
- 20 Ecker, et al. (1995). *Bio/Technology* **13**:351-360.
- Fainzilber, M. et al. (1994). *Biochemistry* **33**:9523-9529.
- Gerzanich, V. et al. (1994). *Mol. Pharmacol.* **45**:212-220.
- Gonzales, C. et al. (1991). *J. Magn. Reson.* **91**:659-664.
- Gray, W.R., et al. (1981). *J. Biol Chem.* **256**:4734-4740.
- 25 Gray, W.R. et al. (1983). *J. Biol Chem.* **258**:12247-12251.
- Guddat, L.W. et al.(1996). *Biochemistry* **33**:11329-11335.
- Gund, P., Pharmacophoric pattern searching and receptor mapping, *Ann. Rep. Med. Chem.* **14**:288 (1979).
- Hann, R.M. et al. (1994). *Biochemistry* **33**:14058-14063.
- 30 Harvey, S.C. et al. (1997). *Mol. Pharmacol.* **51**:336-342.
- Havel, T. (1991). *Prog. Mol. Biol. Biophys.* **56**:43-78.

- Horiki, K. et al. (1978). *Chemistry Letters* 165-68.
- Hu, S.H. et al. (1996). *Structure* 4:417-423.
- Hyberts, S. et al. (1987). *Eur. J. Biochem.* 164:625-635.
- Hyberts, S. et al. (1992). *Protein Sci.* 1:736-751.
- 5 Jeener, J. et al. (1979). *J. Chem. Phys.* 71:4546-4553.
- Johnson, et al. (1993). "Peptide Turn Mimetics" in *Biotechnology and Pharmacy*, Pezutto et al., eds., Chapman and Hall, New York.
- Kaiser et al. (1970). *Anal. Biochem.* 34:595.
- Kapoor (1970). *J. Pharm. Sci.* 59:1-27.
- 10 Kobayashi, Y. et al. (1989). *Biochemistry* 28:4853-4860.
- Kohn, T. et al. (1995). *Biochemistry* 34:10256-10265.
- Kornreich, W.D. et al. (1986). U.S. Patent No. 4,569,967.
- Kreienkamp, H.J. et al. (1994). *J. Biol. Chem.* 269:8108-8114.
- Ku, T.W. et al. (1995). *J. Med. Chem.* 38:9-12.
- 15 Kumar, A. et al. (1980). *Biochem., Biophys, Res. Commun.* 95:1-6.
- Kutak, J.M., et al. (1997). *J. Neurosci.* 17:5263-5470.
- Lauri, G. and P.A. Bartlott (1994). *J. Comp. Aid. Mol. Des.* 8:51-66.
- Macura, S. et al. (1981). *J. Magn. Reson.* 43:259-281.
- Martinez, J.S. et al. (1995). *Biochemistry* 34:14519-14526.
- 20 McIntosh, J.M. et al. (1982). *Arch. Biochem. Biophys.* 218:329-334.
- McIntosh, J.M. et al. (1994). *J. Biol. Chem.* 269:16733-16739.
- Methoden der Organischen Chemie (Houben-Weyl): Synthese von Peptiden*, E. Wunsch (Ed.), Georg Thieme Verlag, Stuttgart, Ger. (1974).
- Monje, V.D. et al. (1993). *Neuropharmacology* 32:1141-1149.
- 25 Muller, L. (1987). *J. Magn. Reson.* 72:191-196.
- Myers, R.A. et al. (1991). *Biochemistry* 30:9370-9377.
- Nilges, M. et al. (1988). *FEBS Lett.* 239:129-136.
- Nishiuchi, Y. et al. (1993). Synthesis of gamma-carboxyglutamic acid-containing peptides by the Boc strategy. *Int. J. Pept. Protein Res.* 42:533-538.
- 30 Pallaghy, P. et al. (1993). *J. Mol. Biol.* 234:405-420.
- Pardi, A. et al. (1984). *J. Mol. Biol.* 180:741-751.
- Pardi, A. et al. (1989). *Biochemistry* 28:5494-5501.
- Persidis et al. (1997). *Bio/Technology* 15:1035-1036.

- Piantini, U. et al. (1982). *J. Am. Chem. Soc.* **104**:6800-6801.
- Piotto, M. et al. (1992). *J. Biomol. NMR* **2**:661-665.
- Rance, M. et al. (1983). *Biochem. Biophys. Res. Commun.* **117**:479-485.
- Remington's Pharmaceutical Sciences*, 18th Ed., Mack Publishing Co., Easton, PA (1990).
- 5 Richardson, J.S. et al. (1988). *Science* **240**:1648-1652.
- Rivier, J.R. et al. (1978). *Biopolymers* **17**:1927-38.
- Rivier, J.R. et al. (1987). Total synthesis and further characterization of the gamma-carboxyglutamate-containing 'sleeper' peptide from *Conus geographus*. *Biochem.* **26**:8508-8512.
- 10 Roberts et al. (1983). *The Peptides* **5**:342-429.
- Rothmund, S. et al. (1996). *Biopolymers* **39**:207-219.
- Rucker, S. (1989). *Mol Phys.* **68**:509-517.
- Sambrook, J. et al. (1979). *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.
- 15 Sargent, P.B. (1993). *Annu. Rev. Neurosci.* **16**:403-443.
- Schroder & Lubke (1965). *The Peptides* **1**:72-75, Academic Press, NY.
- Shon, K.J. et al. (1997). *Biochemistry* **36**:15693-15700.
- Sine, S.M. et al. (1995). *Neuron* **15**:205-21.
- Skalicky, J. et al. (1993). *Protein Sci.* **2**:1591-1603.
- 20 States, D.J. et al. (1982). *J. Magn. Reson.* **48**:286-292.
- Stewart and Young, *Solid-Phase Peptide Synthesis*, Freeman & Co., San Francisco, CA (1969).
- Sun et al. (1993). *Gene* **137**:127-132.
- Tegenfeldt, J. et al. (1979). *J. Magn. Reson.* **36**:453-457.
- Ullian, E.M. et al. (1997). *J. Neurosci.* (in press).
- 25 Utkin, Y.N. et al. (1994). *Toxicon* **32**:1153-1157.
- Vale et al. (1978). U.S. Patent 4,105,603.
- Wagner, G. et al. (1987). *J. Mol. Biol.* **196**:611-639.
- Wilshart, D.S., et al. (1991). *J. Mol. Biol.* **222**:311-333.
- Wuthrich, K. et al. (1983). *J. Mol. Biol.* **169**:949-961.
- 30 Wuthrich, K. et al. (1986). *NMR of Proteins and Nucleic Acids*, Wiley-Interscience, New York.
- Zafaralla, G.C. et al. (1988). *Biochemistry* **27**:7102-7105.
- Zhou L.M., et al. (1996a). Synthetic Analogues of Contryphan-G: NMDA Antagonists Acting Through a Novel Polyamine-Coupled Site. *J. Neurochem.* **66**:620-628.

- U.S. Patent 3,972,859 (1976).
U.S. Patent 3,842,067 (1974).
U.S. Patent 3,862,925 (1975).
U.S. Patent No. 4,105,603.
5 U.S. Patent 5,514,774 (1996).
U.S. Patent 5,550,050 (1996).
U.S. Patent 5,571,698 (1996).
U.S. Patent No. 5,595,972 (1997).
U.S. Patent No. 5,780,433 (1998).
10 PCT Application No. WO 92/19195.
PCT Application No. WO 94/25503.
PCT Application No. WO 95/01203.
PCT Application No. WO 95/05452.
PCT Application No. WO 95/21193.
15 PCT Application No. WO 96/02286.
PCT Application No. WO 96/02646.
PCT Application No. WO 96/40871.
PCT Application No. WO 96/40959.
PCT Application No. WO 97/12635.
20 PCT Application No. WO 97/08300.

WO 99/21878

PCT/US98/22368

1

SEQUENCE LISTING

<110> Shon, Ki-Joon
 Olivera, Baldomero M.
 Rivier, Jean E.
 Koerber, Steven C.
 Shen, Gregory S.
 McIntosh, J. Michael
 Cartier, G. Edward
 Yoshikami, Doju

<120> Interaction of Alpha-Conotoxin Peptides with Neuronal
 Nicotinic Acetylcholine Receptors

<130> MII Interaction with nAChR

<140>
 <141>

<150> U.S. 60/062,783
 <151> 1997-10-24

<150> U.S. 60/065,814
 <151> 1997-11-14

<160> 6

<170> PatentIn Ver. 2.0

<210> 1
 <211> 16
 <212> PRT
 <213> Conus magus

<220>
 <221> DISULFID
 <222> (2)..(8)

<220>
 <221> DISULFID
 <222> (3)..(16)

<400> 1
 Gly Cys Cys Ser Asn Pro Val Cys His Leu Glu His Ser Asn Leu Cys
 1 5 10 15

<210> 2
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: generic
 alpha-conotoxin sequence based on MII

<220>
 <221> VARIANT
 <222> (1)..(15)
 <223> Xaa at positions 1, 4, 7, 10, 13, 14, 15 may be
 any amino acid.

<220>
 <221> VARIANT
 <222> (5)
 <223> Xaa at position 5 may be any amino acid,
 preferably Asn or His.

```
<220>
<221> VARIANT
<222> (9)
<223> Xaa at position 9 may be any amino acid,
        preferably His or Asn.
```

```
<220>
<221> VARIANT
<222> (11)
<223> Xaa at position 11 may be any amino acid,
preferably Glu.
```

```
<220>
<221> VARIANT
<222> (12)
<223> Xaa at position 12 may be any amino acid,
        preferably His or Asn.
```

<220>
<221> DISULFID
<222> (2) . . (8)

```
<220>
<221> DISULFID
<222> (3) .. (16)
```

<400> 2
Xaa Cys Cys Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
1 5 10 15

```
<210> 3
<211> 16
<212> PRT
<213> Artificial Sequence
```

<220>
<223> Description of Artificial Sequence: MII Chimera

<220>
<221> DISULFID
<222> (3) . . (8)

```
<220>
<221> DISULFID
<222> (2) .. (16)
```

<400> 3
Gly Cys Cys Ser Asn Pro Val Cys Phe Ala Thr Asn Ser Asn Leu Cys
1 5 10 15

```
<210> 4
<211> 6
<212> PRT
<213> Artificial Sequence
```

<220>
<223> Description of Artificial Sequence: cyclic analog
of MII 9-12 residues

```
<400> 4
Cys His Leu Glu His Cys
  1             5
```

WO 99/21878

PCT/US98/22368

3

<210> 5
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: cyclic analog
of MII residues 9-12

<400> 5
Ala His Leu Glu His Ala
1 5

<210> 6
<211> 16
<212> PRT
<213> Conus aulicus

<400> 6
Gly Cys Cys Ser Tyr Pro Pro Cys Phe Ala Thr Asn Ser Gly Tyr Cys
1 5 10 15

WHAT IS CLAIMED IS:

1. A substantially pure peptide having the general formula:
Xaa-Cys-Cys-Xaa-Xaa₁-Xaa₂-Xaa-Cys-Xaa₃-Xaa-Xaa₄-Xaa₅-Xaa-Xaa-Xaa-Cys,
wherein Xaa, Xaa₁, Xaa₂, Xaa₃ and Xaa₄ each is an amino acid selected from the group
5 consisting of natural, modified or non-natural amino acids and Xaa₅ is His or Asn.
2. The peptide of claim 1 wherein the C-terminus is amidated.
3. The peptide of claim 1 wherein Xaa₁ is Asn or His.
4. The peptide of claim 1 wherein Xaa₂ is Pro or hydroxy-Pro.
5. The peptide of claim 1 wherein Xaa₃ is His.
- 10 6. The peptide of claim 1 wherein Xaa₄ is Glu.
7. The peptide of claim 1 wherein Xaa₁ is Asn or His and Xaa₂ is Pro or hydroxy-Pro.
8. The peptide of claim 7 wherein Xaa₁ is Asn.
9. The peptide of claim 7 wherein Xaa₄ is Glu and Xaa₅ is His.
10. The peptide of claim 7 wherein Xaa₃ is and Xaa₄ is Glu.
- 15 11. The peptide of claim 1 wherein the biological activity of the peptide is substantially the same
as the biological activity of α -conotoxin MII.
12. The peptide of claim 7 wherein the biological activity of the peptide is substantially the same
as the biological activity of α -conotoxin MII.

13. The peptide of claim 10 wherein the biological activity of the peptide is substantially the same as the biological activity of α -conotoxin MII.
14. A peptide analog, peptide mimetic or mimetic of α -conotoxin MII specific for one or more subtypes of neuronal nicotinic acetylcholine receptor (neuronal nAChR).
- 5 15. The peptide analog, peptide mimetic or mimetic of claim 14 wherein the specificity is for the $\alpha 3 \beta 2$ subtype of neuronal nAChR.
16. The peptide analog, peptide mimetic or mimetic of claim 14 wherein the specificity is for the $\alpha 3 \beta 4$ subtype of neuronal nAChR.
- 10 17. The peptide analog, peptide mimetic or mimetic of claim 14 wherein the specificity is for the $\alpha 2 \beta 2$ subtype of neuronal nAChR.
18. A method for screening compounds for neuronal nicotinic acetylcholine (nAChR) receptor antagonistic activity and receptor subtype which comprises determining the on and off rates for the binding of α -conotoxin MII and a compound to be screened to different subunits of nAChR and comparing said on and off rates.
- 15 19. The method of claim 18 wherein the subunits of nAChR are the $\alpha 3 \beta 2$ and $\alpha 3 \beta 4$ subunits.
20. A derivative, peptide analog, peptide mimetic or mimetic of α -conotoxin MII which selectively modulates biological activity at nAChRs.
21. A method for determining the three-dimensional structure of an alpha-conotoxin, analog which comprises:
 - 20 (a) obtaining NMR spectroscopy data for the peptide;
 - (b) providing three-dimensional structural coordinates for a composition of MII; and
 - (c) determining the three-dimensional structure of the alpha-conotoxin by analyzing the data with reference to the previous structural coordinates using molecular replacement.

22. A method of claim 21 which further comprises testing a compound so identified for its ability to:
- (a) bind to a neuronal nicotinic acetylcholine receptor (nAChR);
 - (b) inhibit the binding of a ligand to a neuronal nAChR; and/or
 - (c) inhibit a biological function mediated by a natural ligand of an nAChR.
23. A method for selecting a compound capable of binding to a neuronal nicotinic acetylcholine receptor (NACHR) which comprises:
- (a) providing coordinates defining the three dimensional structure of MII or a portion thereof;
 - (b) characterizing points associated with that three dimensional structure with respect to the favorability of interactions with one or more selected functional groups;
 - (c) providing database of one or more dandidate compounds; and
 - (d) identifying from the database those compounds having structures which best fit the points of favorable interaction with the three dimensional structure.
24. A method of claim 23 which further comprises testing a compound so identified for its ability to:
- (a) bind to neuronal nAChR,
 - (b) inhibit the binding of MII to a natural or non-natural ligand therefor, and/or
 - (c) inhibit a biological function mediated by MII.
25. 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 a molecule comprising a MII peptide or a portion thereof.
26. 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 an α -cono-toxin or portion thereof based on the coordinates of Fig. 8, or based on coordinates having

a root mean square deviation therefrom with respect to conserved protein backbone atoms of not more than 1.5 Å.

27. 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 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 coordinates according to Fig. 8; and said second set of data comprises coordinates of a molecule or molecular complex.
28. A method for displaying a three dimensional representation of a composition of MII which comprises:
- a) providing a machine capable of reading data stored on a machine-readable storage medium of claim 25, programmed with instructions for using said data to display a graphical three-dimensional representation of a protein or protein ligand complex or portion thereof defined by said data, and loaded with a machine-readable storage medium of claim 25; and
 - b) permitting the machine to read said data and display the three-dimensional representation.
29. A method for designing a compound capable of binding to a neuronal nicotinic acetylcholine receptor (nAChR) which comprises:
- (a) graphically displaying a three-dimensional representation based on coordinates defining the three-dimensional structure of MII or a portion thereof;
 - (b) characterizing the interactions between portions of a ligand that is known to bind to the protein to identify candidate moieties for replacement;
 - (c) providing a knowledge base of one or more candidate substitute moieties; and
 - (d) identifying from the knowledge base one or more substitute moieties which may be used to replace one or more selected portions of the ligand and retain at least a portion of the ligand's binding affinity for the protein.

30. The method of claim 29 which further comprises testing the compound for its modulating activity of said neuronal nAChR.
31. A method for designing a compound capable of binding to a neuronal nicotinic acetylcholine receptor (nAChR) which comprises:
- 5 (a) providing coordinates defining the three-dimensional structure of MII or a portion thereof;
- (b) characterizing points associated with that three-dimensional structure to identify preferred points with respect to the favorability of interactions of one or more selected functional groups with the protein;
- 10 (c) characterizing one or more portions of a ligand that is known to bind to the protein that are proximal to the characterized points;
- (d) providing a knowledge base of one or more molecular fragments or molecules;
- (e) identifying from the knowledge base one or more fragments or molecules that permit connection of preferred points identified in (b) to portions of the ligand; and
- 15 (f) modifying the structure of the ligand by the covalent attachment thereto of one or more such fragments or molecules so identified in an orientation and location selected to permit the modified ligand to bind to the protein.
32. The method of claim 31 which further comprises testing the compound for its modulating activity of said neuronal nAChR.

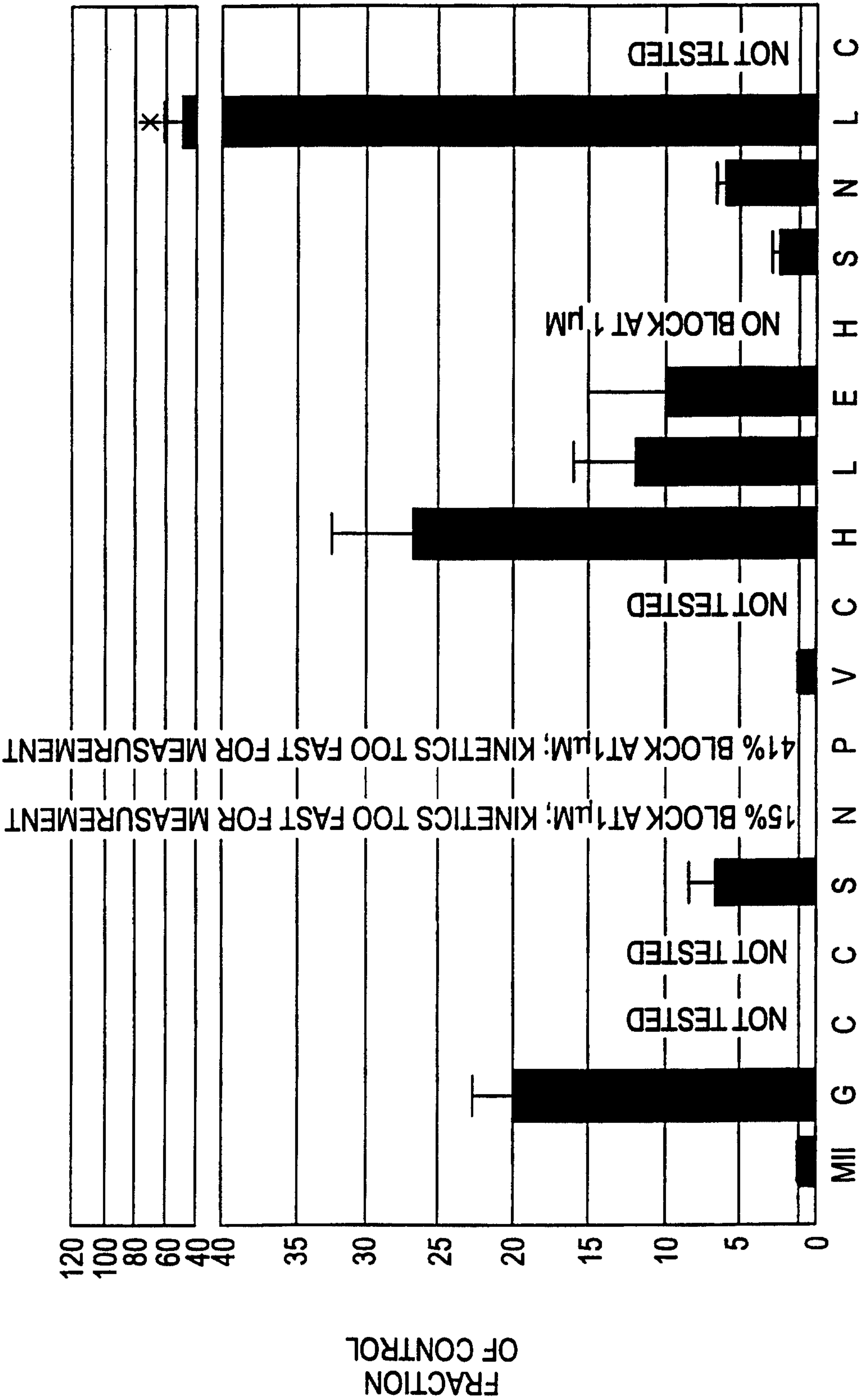
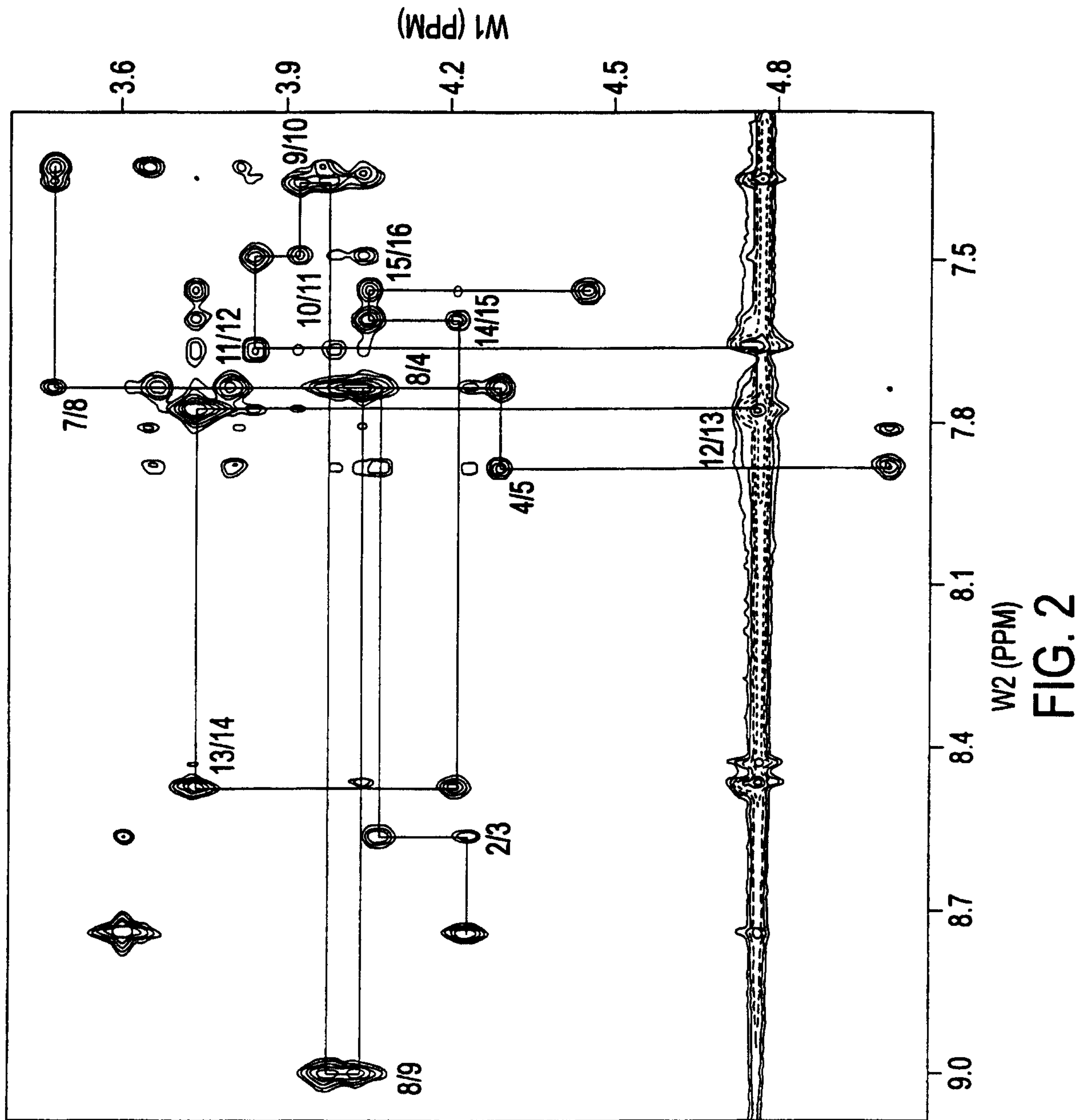


FIG. 1

2/107



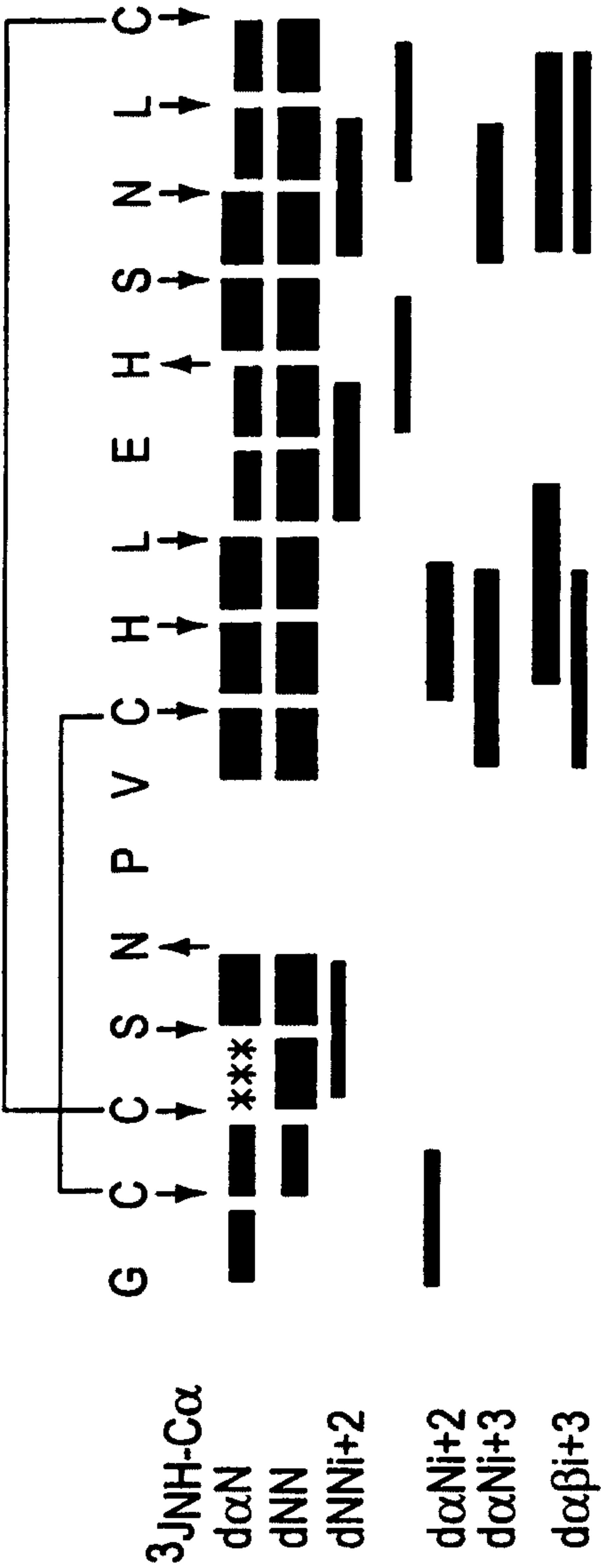


FIG. 3

4/107

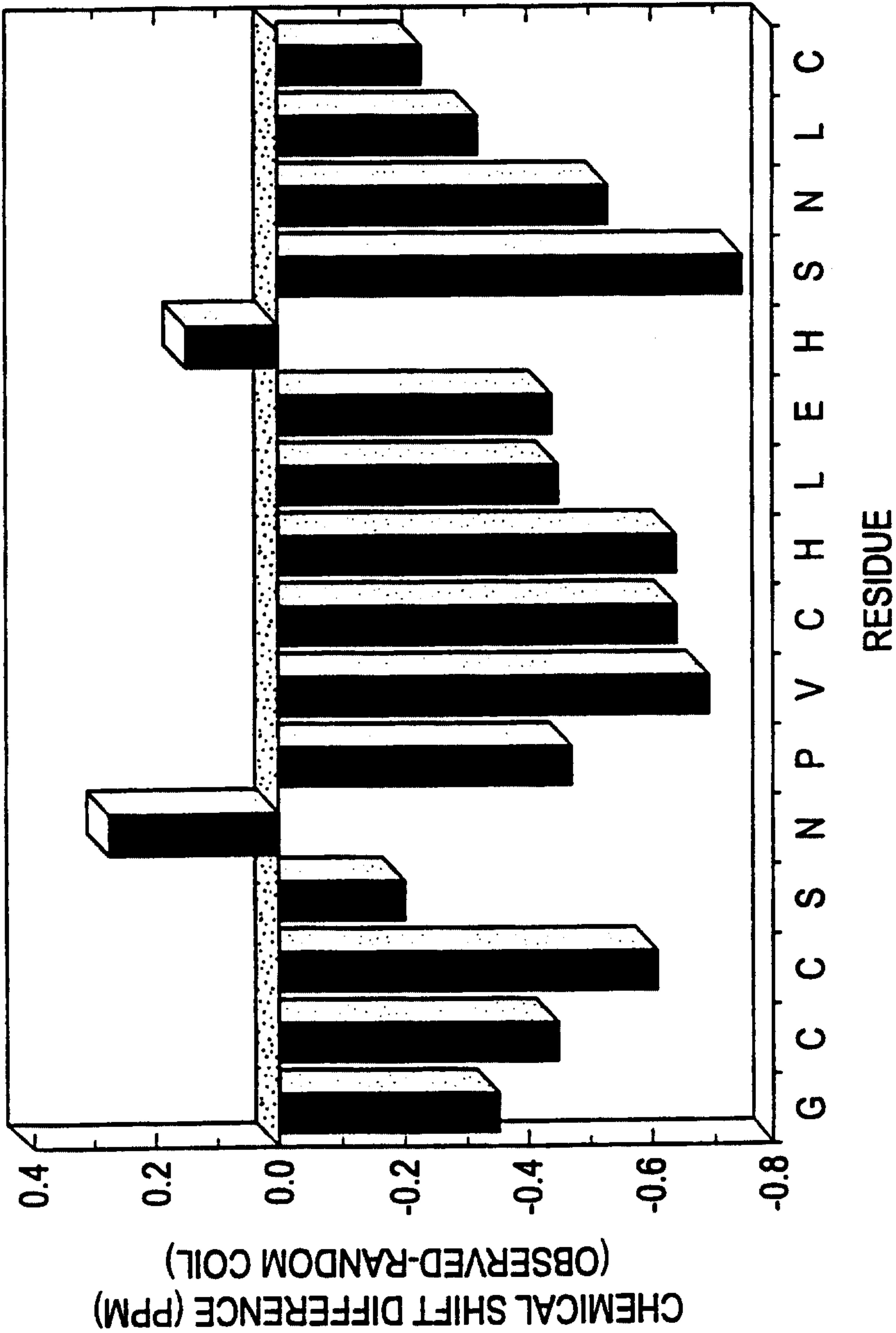


FIG. 4

5/107

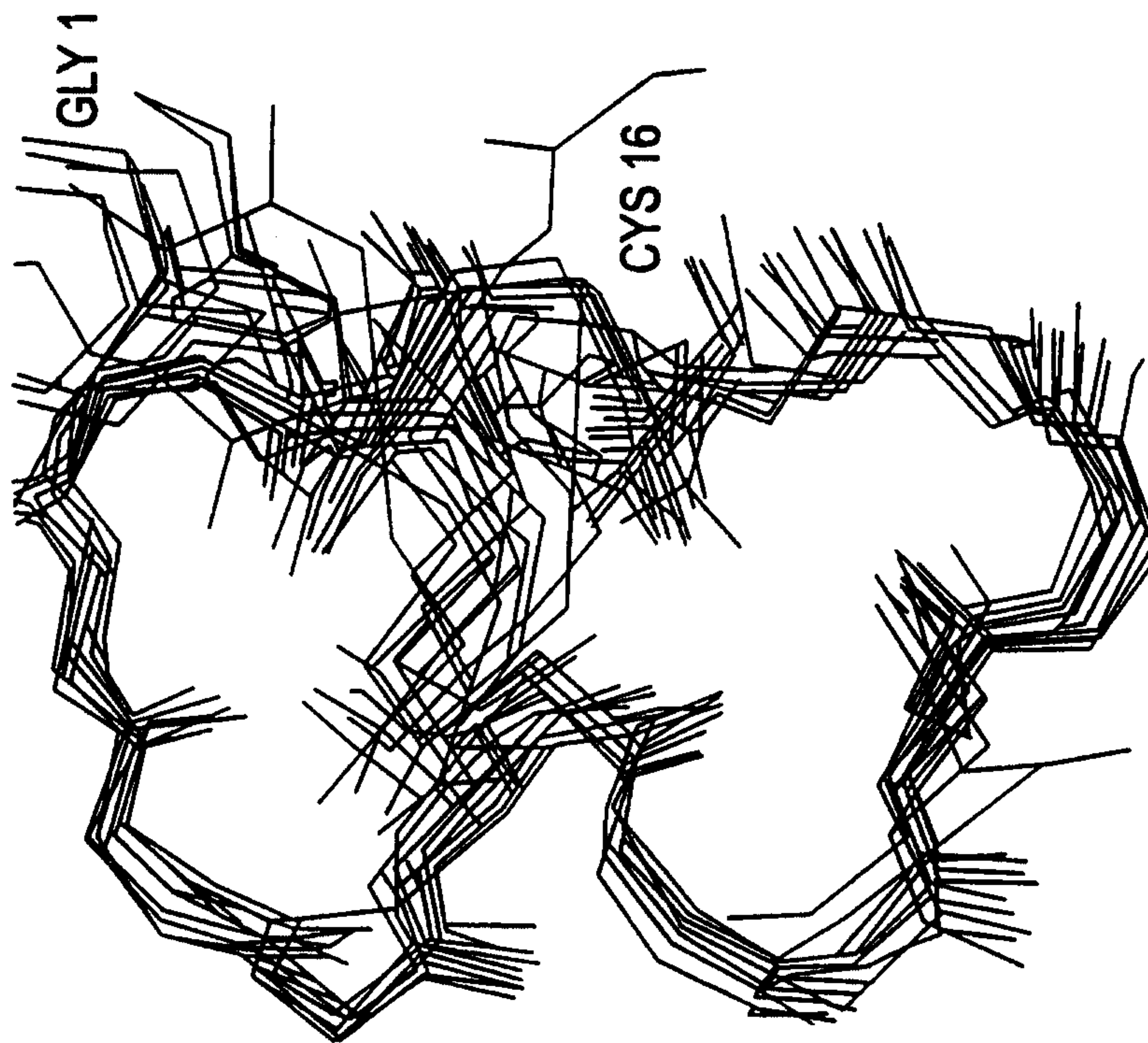


FIG. 5B

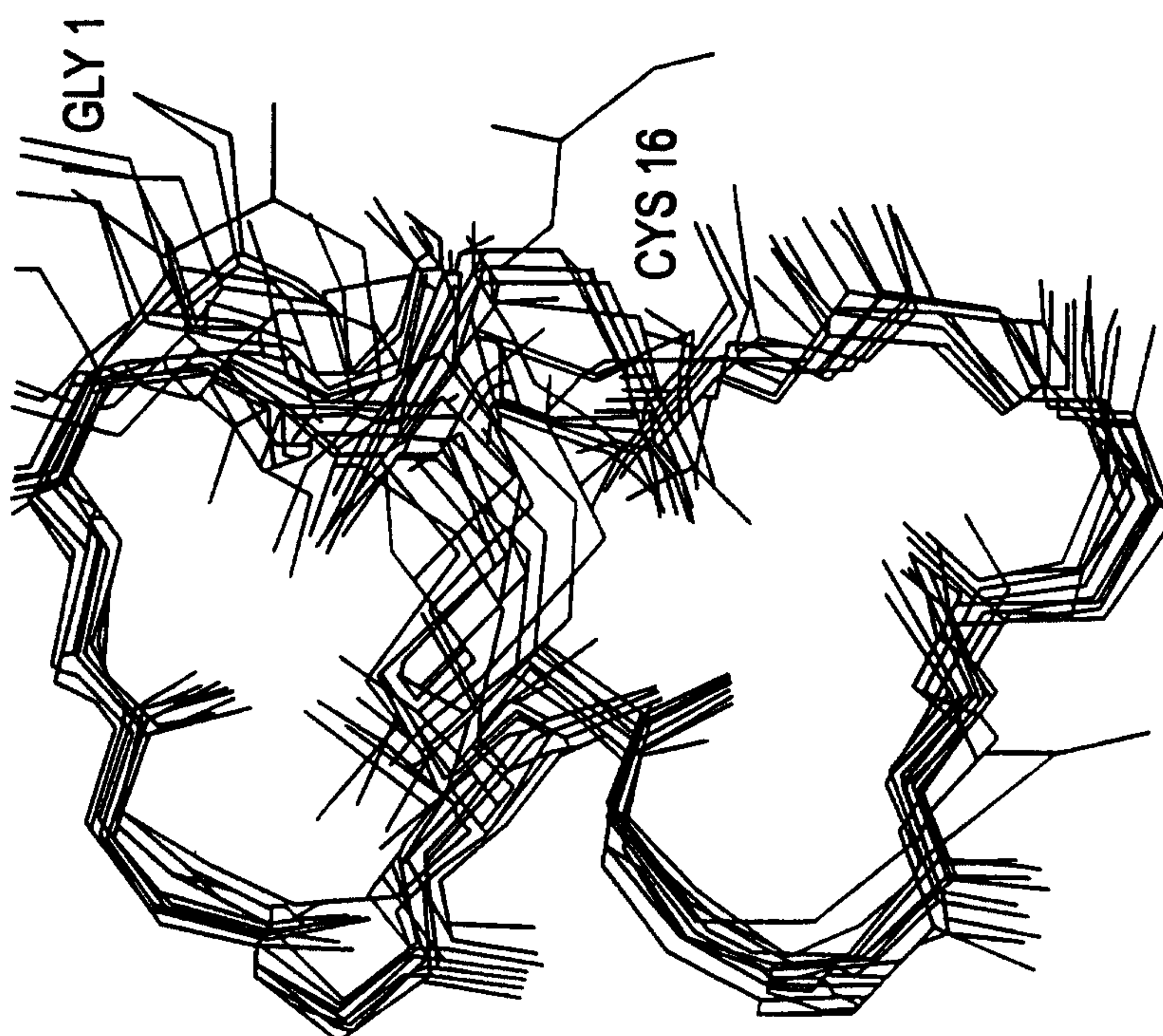


FIG. 5A

6/107

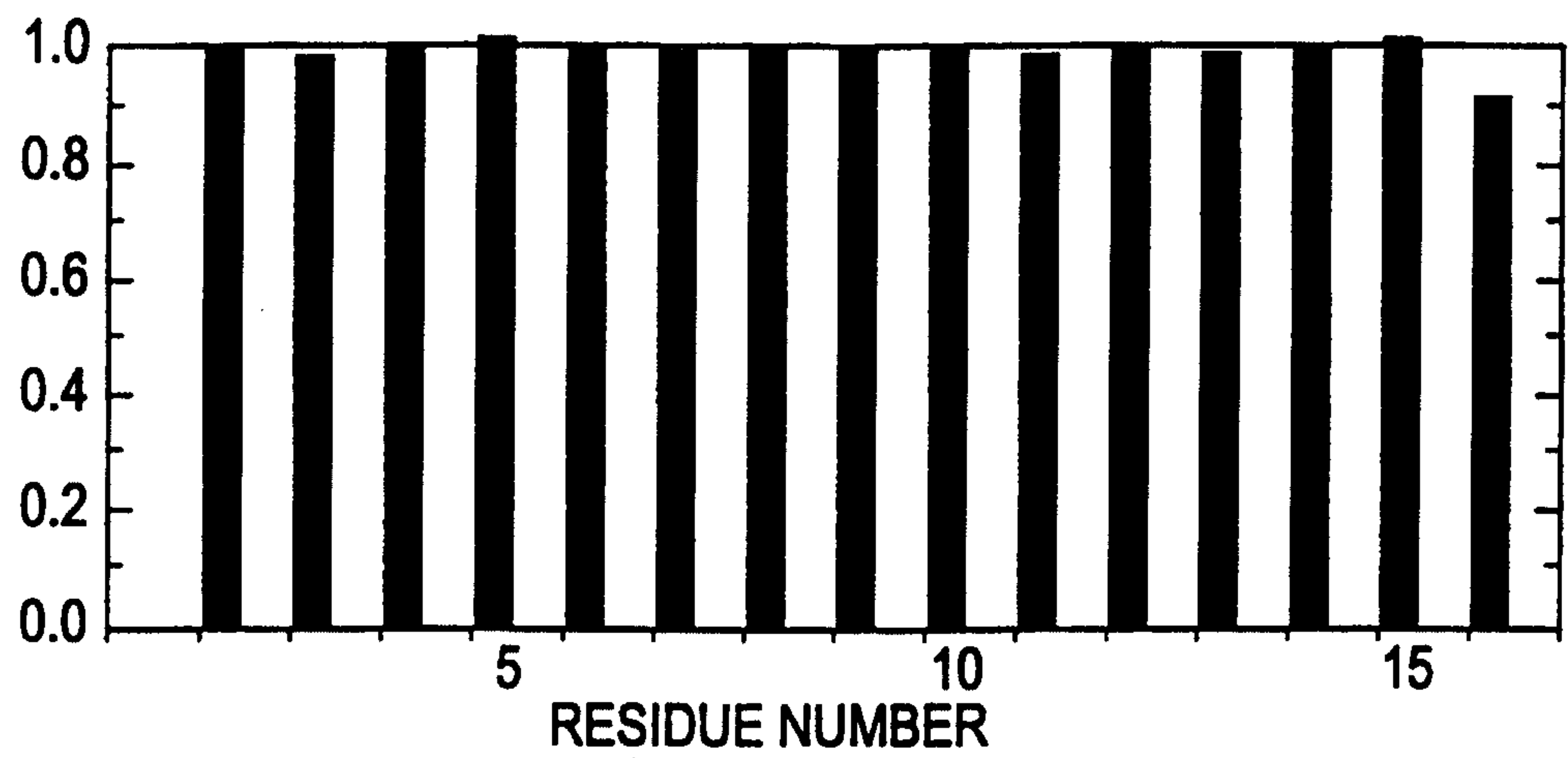


FIG. 6A

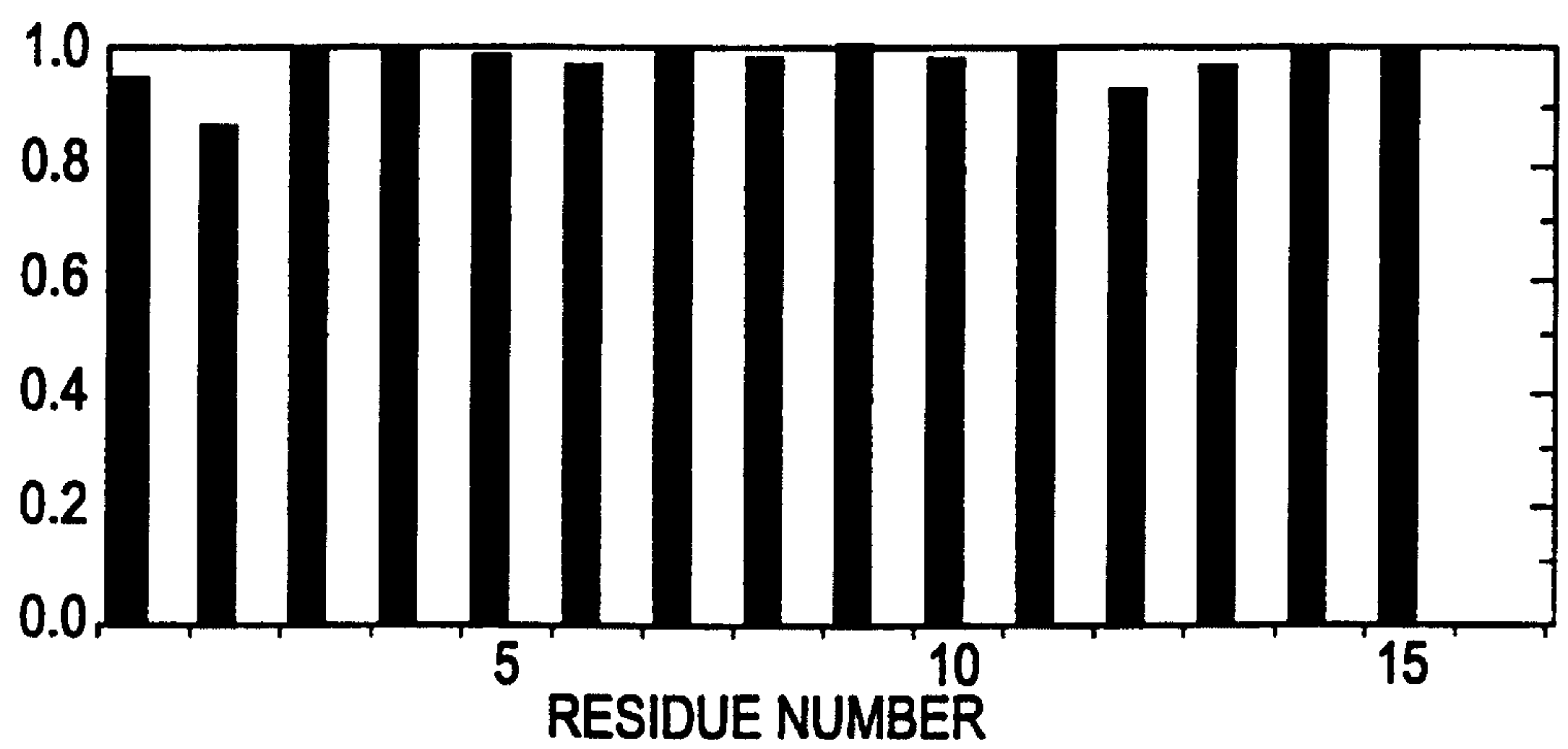


FIG. 6B

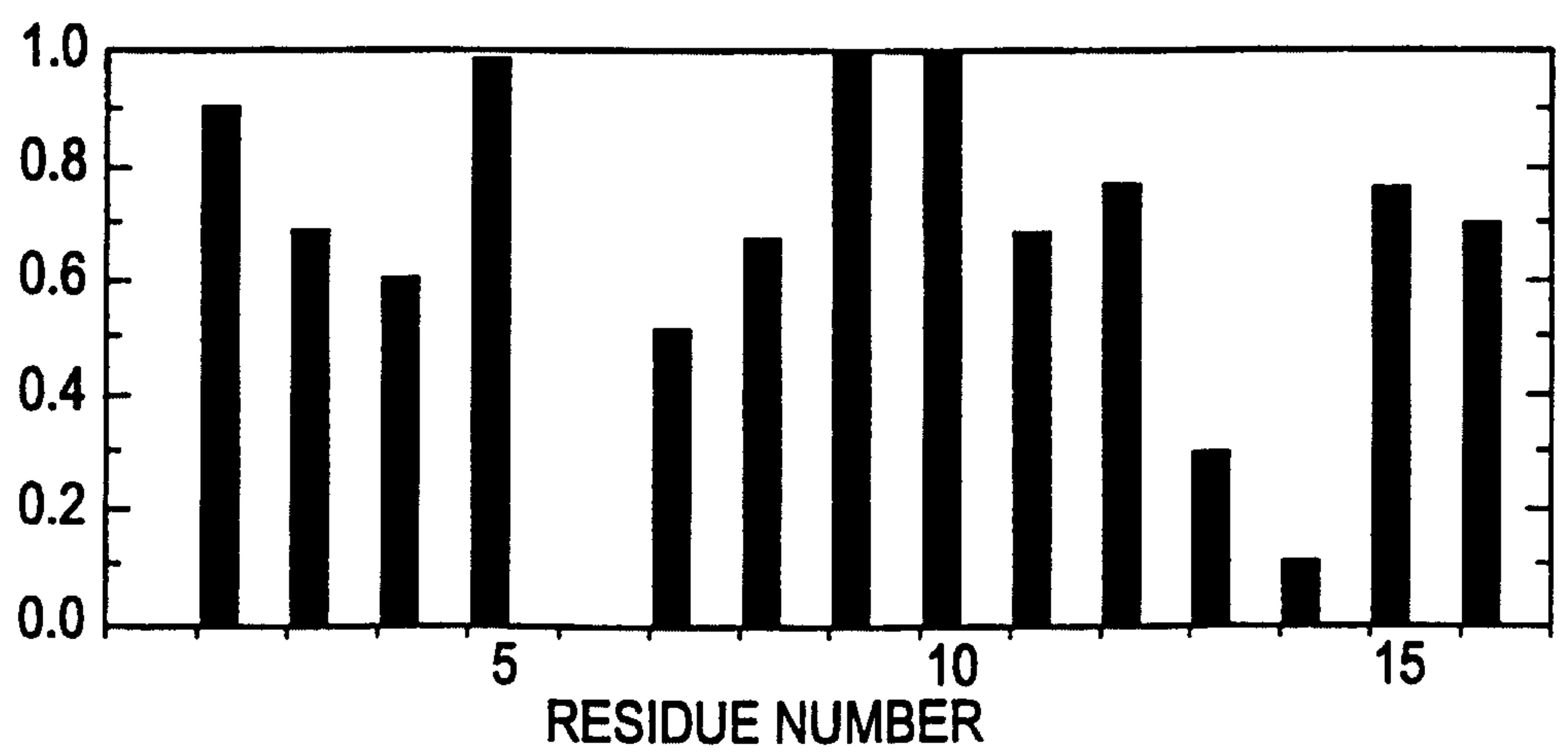


FIG. 6C

7/107

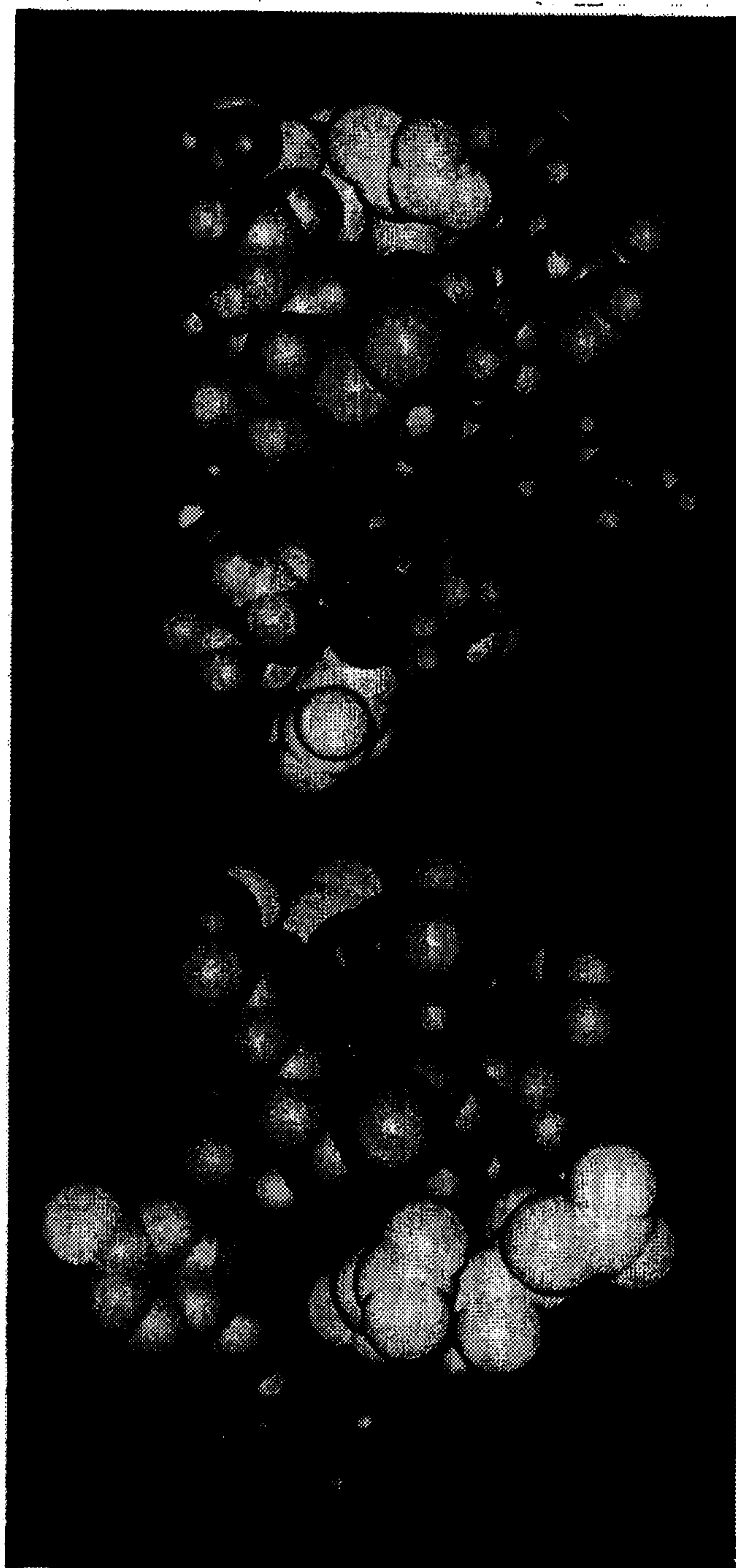


FIG. 7B

FIG. 7A

8/107

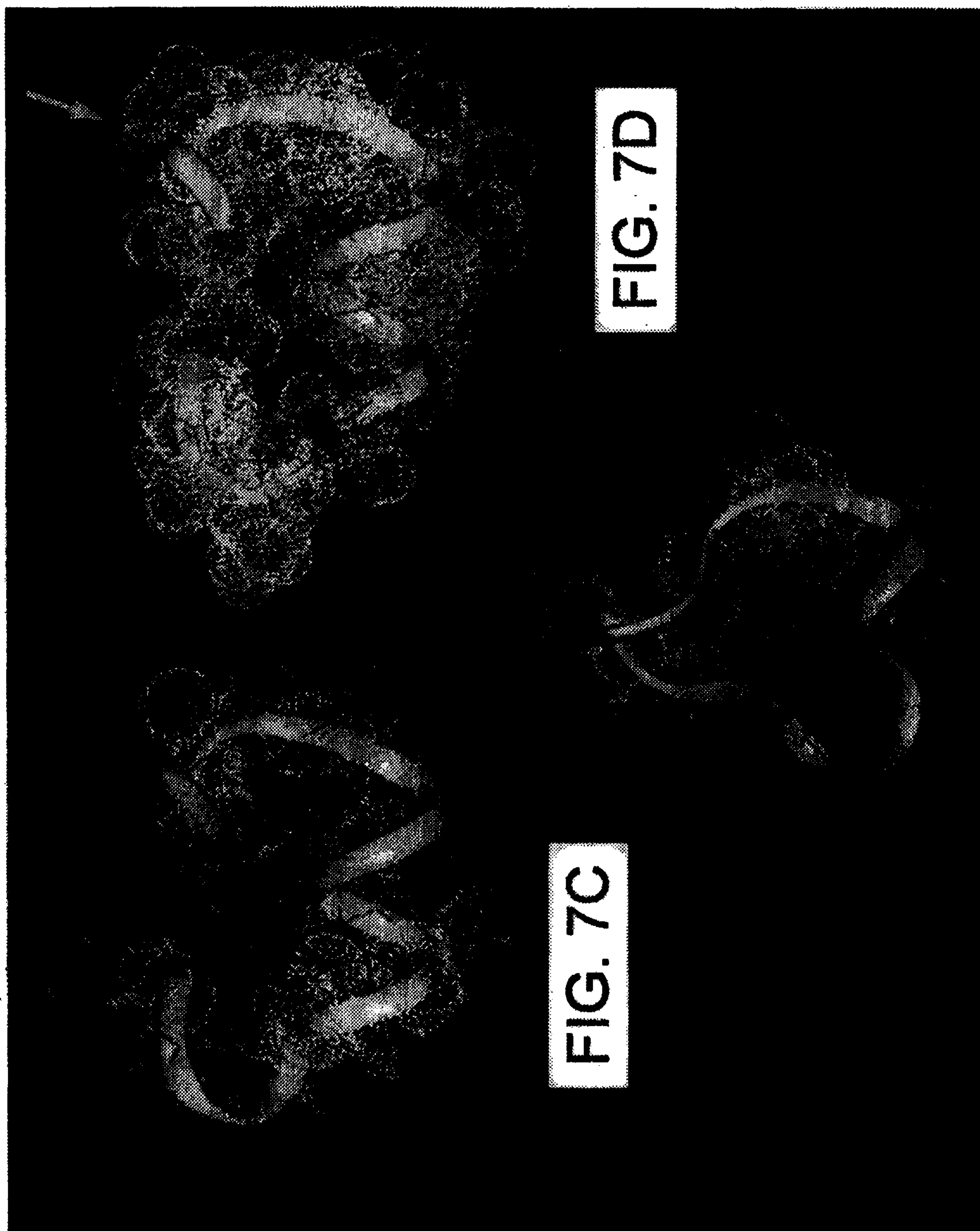


FIG. 8 - 1

ATOM	1	N	GLY	1	15.634	14.616	-13.035	0.00	0.00		N
ATOM	2	CA	GLY	1	16.374	15.823	-12.552	0.00	0.00		C
ATOM	3	C	GLY	1	16.601	16.957	-13.565	0.00	0.00		C
ATOM	4	O	GLY	1	16.407	16.772	-14.760	0.00	0.00		O
ATOM	5	1H	GLY	1	16.149	14.188	-13.818	1.00	0.00		H
ATOM	6	2H	GLY	1	15.549	13.935	-12.267	1.00	0.00		H
ATOM	7	3H	GLY	1	14.695	14.893	-13.353	1.00	0.00		H
ATOM	8	1HA	GLY	1	15.844	16.270	-11.694	0.00	0.00		H
ATOM	9	2HA	GLY	1	17.384	15.550	-12.193	0.00	0.00		H
ATOM	10	N	CYS	2	17.044	18.164	-13.217	0.00	0.00		N
ATOM	11	CA	CYS	2	17.260	18.675	-11.832	0.00	0.00		C
ATOM	12	C	CYS	2	15.966	19.090	-11.049	0.00	0.00		C
ATOM	13	O	CYS	2	15.593	18.382	-10.113	0.00	0.00		O
ATOM	14	CB	CYS	2	18.371	19.733	-11.934	0.00	0.00		C
ATOM	15	SG	CYS	2	19.281	19.941	-10.382	0.00	0.00		S
ATOM	16	H	CYS	2	17.281	18.712	-14.041	0.00	0.00		H
ATOM	17	HA	CYS	2	17.745	17.875	-11.249	0.00	0.00		H
ATOM	18	1HB	CYS	2	19.143	19.397	-12.649	0.00	0.00		H
ATOM	19	2HB	CYS	2	17.996	20.698	-12.322	0.00	0.00		H
ATOM	20	N	CYS	3	15.243	20.139	-11.483	0.00	0.00		N
ATOM	21	CA	CYS	3	13.872	20.523	-10.994	0.00	0.00		C
ATOM	22	C	CYS	3	12.795	19.383	-10.799	0.00	0.00		C
ATOM	23	O	CYS	3	11.986	19.455	-9.871	0.00	0.00		O
ATOM	24	CB	CYS	3	13.438	21.551	-12.071	0.00	0.00		C
ATOM	25	SG	CYS	3	11.902	22.446	-11.718	0.00	0.00		S
ATOM	26	H	CYS	3	15.586	20.503	-12.376	0.00	0.00		H
ATOM	27	HA	CYS	3	13.961	21.072	-10.017	0.00	0.00		H
ATOM	28	1HB	CYS	3	14.209	22.336	-12.216	0.00	0.00		H
ATOM	29	2HB	CYS	3	13.317	21.074	-13.063	0.00	0.00		H
ATOM	30	N	SER	4	12.820	18.327	-11.633	0.00	0.00		N
ATOM	31	CA	SER	4	11.986	17.111	-11.503	0.00	0.00		C
ATOM	32	C	SER	4	12.408	16.016	-10.457	0.00	0.00		C
ATOM	33	O	SER	4	11.576	15.193	-10.077	0.00	0.00		O
ATOM	34	CB	SER	4	11.936	16.580	-12.956	0.00	0.00		C

FIG. 8-2

ATOM	35	OG	SER	4	13.209	16.259	-13.539	0.00	0.00	O
ATOM	36	H	SER	4	13.571	18.289	-12.320	0.00	0.00	H
ATOM	37	HA	SER	4	10.956	17.405	-11.220	0.00	0.00	H
ATOM	38	1HB	SER	4	11.311	15.686	-12.964	0.00	0.00	H
ATOM	39	2HB	SER	4	11.395	17.301	-13.604	0.00	0.00	H
ATOM	40	HG	SER	4	13.078	16.330	-14.497	0.00	0.00	H
ATOM	41	N	ASN	5	13.648	16.019	-9.934	0.00	0.00	N
ATOM	42	CA	ASN	5	13.964	15.396	-8.631	0.00	0.00	C
ATOM	43	C	ASN	5	13.755	16.434	-7.481	0.00	0.00	C
ATOM	44	O	ASN	5	14.339	17.517	-7.578	0.00	0.00	O
ATOM	45	CB	ASN	5	15.467	15.027	-8.649	0.00	0.00	C
ATOM	46	CG	ASN	5	15.811	13.698	-9.280	0.00	0.00	C
ATOM	47	OD1	ASN	5	16.114	13.557	-10.457	0.00	0.00	O
ATOM	48	ND2	ASN	5	15.822	12.717	-8.434	0.00	0.00	N
ATOM	49	H	ASN	5	14.222	16.819	-10.206	0.00	0.00	H
ATOM	50	HA	ASN	5	13.348	14.497	-8.433	0.00	0.00	H
ATOM	51	1HB	ASN	5	16.100	15.832	-9.065	0.00	0.00	H
ATOM	52	2HB	ASN	5	15.814	14.978	-7.611	0.00	0.00	H
ATOM	53	1HD2	ASN	5	16.367	11.911	-8.732	0.00	0.00	H
ATOM	54	2HD2	ASN	5	15.707	13.088	-7.487	0.00	0.00	H
ATOM	55	N	PRO	6	13.055	16.153	-6.351	0.00	0.00	N
ATOM	56	CA	PRO	6	12.951	17.126	-5.223	0.00	0.00	C
ATOM	57	C	PRO	6	14.266	17.584	-4.506	0.00	0.00	C
ATOM	58	O	PRO	6	14.367	18.716	-4.040	0.00	0.00	O
ATOM	59	CB	PRO	6	11.867	16.477	-4.360	0.00	0.00	C
ATOM	60	CG	PRO	6	11.976	14.970	-4.613	0.00	0.00	C
ATOM	61	CD	PRO	6	12.445	14.838	-6.065	0.00	0.00	C
ATOM	62	HA	PRO	6	12.524	18.059	-5.584	0.00	0.00	H
ATOM	63	1HB	PRO	6	11.966	16.777	-3.306	0.00	0.00	H
ATOM	64	2HB	PRO	6	10.866	16.831	-4.679	0.00	0.00	H
ATOM	65	1HG	PRO	6	12.710	14.520	-3.924	0.00	0.00	H
ATOM	66	2HG	PRO	6	11.034	14.432	-4.417	0.00	0.00	H
ATOM	67	1HD	PRO	6	13.153	13.999	-6.168	0.00	0.00	H
ATOM	68	2HD	PRO	6	11.641	14.619	-6.788	0.00	0.00	H

11/107

FIG. 8-3

ATOM	69	N	VAL	7	15.297	16.745	-4.539	0.00	0.00	N
ATOM	70	CA	VAL	7	16.659	17.036	-4.017	0.00	0.00	C
ATOM	71	C	VAL	7	17.510	17.915	-4.975	0.00	0.00	C
ATOM	72	O	VAL	7	17.948	19.001	-4.584	0.00	0.00	O
ATOM	73	CB	VAL	7	17.269	15.639	-3.622	0.00	0.00	C
ATOM	74	CG1	VAL	7	18.794	15.639	-3.351	0.00	0.00	C
ATOM	75	CG2	VAL	7	16.615	15.033	-2.355	0.00	0.00	C
ATOM	76	H	VAL	7	15.093	15.928	-5.110	0.00	0.00	H
ATOM	77	HA	VAL	7	16.567	17.703	-3.149	0.00	0.00	H
ATOM	78	HB	VAL	7	17.068	14.940	-4.473	0.00	0.00	H
ATOM	79	1HG1	VAL	7	19.070	16.317	-2.520	0.00	0.00	H
ATOM	80	2HG1	VAL	7	19.171	14.633	-3.080	0.00	0.00	H
ATOM	81	3HG1	VAL	7	19.383	15.954	-4.233	0.00	0.00	H
ATOM	82	1HG2	VAL	7	15.520	14.920	-2.458	0.00	0.00	H
ATOM	83	2HG2	VAL	7	17.007	14.024	-2.120	0.00	0.00	H
ATOM	84	3HG2	VAL	7	16.784	15.658	-1.456	0.00	0.00	H
ATOM	85	N	CYS	8	17.723	17.496	-6.234	0.00	0.00	N
ATOM	86	CA	CYS	8	18.426	18.331	-7.241	0.00	0.00	C
ATOM	87	C	CYS	8	17.810	19.697	-7.633	0.00	0.00	C
ATOM	88	O	CYS	8	18.496	20.703	-7.829	0.00	0.00	O
ATOM	89	CB	CYS	8	18.832	17.434	-8.435	0.00	0.00	C
ATOM	90	SG	CYS	8	19.989	18.228	-9.590	0.00	0.00	S
ATOM	91	H	CYS	8	17.355	16.575	-6.422	0.00	0.00	H
ATOM	92	HA	CYS	8	19.259	18.670	-6.659	0.00	0.00	H
ATOM	93	1HB	CYS	8	19.325	16.510	-8.074	0.00	0.00	H
ATOM	94	2HB	CYS	8	17.940	17.112	-8.997	0.00	0.00	H
ATOM	95	N	HIS	9	16.490	19.730	-7.577	0.00	0.00	N
ATOM	96	CA	HIS	9	15.672	20.954	-7.520	0.00	0.00	C
ATOM	97	C	HIS	9	16.116	21.946	-6.408	0.00	0.00	C
ATOM	98	O	HIS	9	16.152	23.143	-6.649	0.00	0.00	O
ATOM	99	CB	HIS	9	14.212	20.441	-7.372	0.00	0.00	C
ATOM	100	CG	HIS	9	12.988	21.178	-6.837	0.00	0.00	C
ATOM	101	ND1	HIS	9	11.743	20.871	-7.343	0.00	0.00	C
ATOM	102	CD2	HIS	9	12.933	22.419	-6.207	0.00	0.00	C

12/107

FIG. 8 - 4

ATOM	103	CE1	HIS	9	11.061	22.027	-7.066	0.00	0.00	C
ATOM	104	NE2	HIS	9	11.665	22.970	-6.286	0.00	0.00	N
ATOM	105	H	HIS	9	16.122	18.799	-7.387	0.00	0.00	H
ATOM	106	HA	HIS	9	15.792	21.444	-8.470	0.00	0.00	H
ATOM	107	1HB	HIS	9	13.964	19.804	-8.230	0.00	0.00	H
ATOM	108	2HB	HIS	9	14.310	19.747	-6.514	0.00	0.00	H
ATOM	109	HD1	HIS	9	11.556	20.209	-8.116	0.00	0.00	H
ATOM	110	HD2	HIS	9	13.833	22.948	-5.987	0.00	0.00	H
ATOM	111	HE1	HIS	9	10.350	22.380	-7.807	0.00	0.00	H
ATOM	112	HE2	HIS	9	11.288	23.837	-5.876	1.00	0.00	H
ATOM	113	N	LEU	10	16.348	21.442	-5.199	0.00	0.00	N
ATOM	114	CA	LEU	10	16.543	22.306	-3.982	0.00	0.00	C
ATOM	115	C	LEU	10	18.003	22.749	-3.677	0.00	0.00	C
ATOM	116	O	LEU	10	18.247	23.915	-3.362	0.00	0.00	O
ATOM	117	CB	LEU	10	15.796	21.702	-2.764	0.00	0.00	C
ATOM	118	CG	LEU	10	14.248	21.705	-2.866	0.00	0.00	C
ATOM	119	CD1	LEU	10	13.632	20.894	-1.719	0.00	0.00	C
ATOM	120	CD2	LEU	10	13.634	23.120	-2.848	0.00	0.00	C
ATOM	121	H	LEU	10	16.639	20.446	-5.325	0.00	0.00	H
ATOM	122	HA	LEU	10	16.061	23.277	-4.172	0.00	0.00	H
ATOM	123	1HB	LEU	10	16.160	20.668	-2.601	0.00	0.00	H
ATOM	124	2HB	LEU	10	16.085	22.244	-1.841	0.00	0.00	H
ATOM	125	HG	LEU	10	13.977	21.199	-3.814	0.00	0.00	H
ATOM	126	1HD1	LEU	10	14.009	19.855	-1.706	0.00	0.00	H
ATOM	127	2HD1	LEU	10	13.853	21.334	-0.729	0.00	0.00	H
ATOM	128	3HD1	LEU	10	12.532	20.826	-1.811	0.00	0.00	H
ATOM	129	1HD2	LEU	10	13.884	23.667	-1.919	0.00	0.00	H
ATOM	130	2HD2	LEU	10	13.976	23.750	-3.687	0.00	0.00	H
ATOM	131	3HD2	LEU	10	12.530	23.089	-2.916	0.00	0.00	H
ATOM	132	N	GLU	11	18.974	21.867	-3.920	0.00	0.00	N
ATOM	133	CA	GLU	11	20.366	22.222	-4.268	0.00	0.00	C
ATOM	134	C	GLU	11	20.637	23.448	-5.202	0.00	0.00	C
ATOM	135	O	GLU	11	21.614	24.177	-5.020	0.00	0.00	O
ATOM	136	CB	GLU	11	20.855	20.906	-4.919	0.00	0.00	C

FIG. 8 - 5

ATOM	137	CG	GLU	11	21.268	19.744	-3.980	0.00	0.00	C
ATOM	138	CD	GLU	11	21.627	18.433	-4.686	0.00	0.00	C
ATOM	139	OE1	GLU	11	21.653	18.290	-5.906	0.00	0.00	O
ATOM	140	OE2	GLU	11	21.898	17.438	-3.795	0.00	0.00	O
ATOM	141	H	GLU	11	18.737	20.866	-3.861	1.00	0.00	H
ATOM	142	HA	GLU	11	20.934	22.422	-3.357	0.00	0.00	H
ATOM	143	1HB	GLU	11	20.142	20.545	-5.688	0.00	0.00	H
ATOM	144	2HB	GLU	11	21.713	21.169	-5.515	0.00	0.00	H
ATOM	145	1HG	GLU	11	22.118	20.050	-3.342	0.00	0.00	H
ATOM	146	2HG	GLU	11	20.433	19.538	-3.293	0.00	0.00	H
ATOM	147	HE2	GLU	11	22.110	16.618	-4.241	0.00	0.00	H
ATOM	148	N	HIS	12	19.798	23.633	-6.226	0.00	0.00	N
ATOM	149	CA	HIS	12	19.786	24.867	-7.040	0.00	0.00	C
ATOM	150	C	HIS	12	18.309	25.290	-7.270	0.00	0.00	C
ATOM	151	O	HIS	12	17.726	25.056	-8.328	0.00	0.00	O
ATOM	152	CB	HIS	12	20.582	24.609	-8.333	0.00	0.00	C
ATOM	153	CG	HIS	12	22.101	24.523	-8.182	0.00	0.00	C
ATOM	154	ND1	HIS	12	22.784	23.322	-8.090	0.00	0.00	N
ATOM	155	CD2	HIS	12	22.965	25.594	-7.876	0.00	0.00	C
ATOM	156	CE1	HIS	12	24.015	23.756	-7.667	0.00	0.00	C
ATOM	157	NE2	HIS	12	24.231	25.108	-7.557	0.00	0.00	N
ATOM	158	H	HIS	12	18.960	23.046	-6.147	0.00	0.00	H
ATOM	159	HA	HIS	12	20.270	25.707	-6.517	0.00	0.00	H
ATOM	160	1HB	HIS	12	20.164	23.686	-8.773	0.00	0.00	H
ATOM	161	2HB	HIS	12	20.351	25.426	-9.036	0.00	0.00	H
ATOM	162	HD1	HIS	12	22.391	22.375	-8.064	0.00	0.00	H
ATOM	163	HD2	HIS	12	22.639	26.626	-7.782	0.00	0.00	H
ATOM	164	HE1	HIS	12	24.768	23.040	-7.334	0.00	0.00	H
ATOM	165	HE2	HIS	12	25.090	25.620	-7.308	1.00	0.00	H
ATOM	166	N	SER	13	17.697	25.882	-6.236	0.00	0.00	N
ATOM	167	CA	SER	13	16.263	26.271	-6.249	0.00	0.00	C
ATOM	168	C	SER	13	15.832	27.466	-7.148	0.00	0.00	C
ATOM	169	O	SER	13	14.759	27.460	-7.748	0.00	0.00	O
ATOM	170	CB	SER	13	15.756	26.384	-4.793	0.00	0.00	C

FIG. 8 - 6

ATOM	171	OG	SER	13	14.332	26.272	-4.752	0.00	0.00	O
ATOM	172	H	SER	13	18.036	25.446	-5.395	0.00	0.00	H
ATOM	173	HA	SER	13	15.796	25.412	-6.707	0.00	0.00	H
ATOM	174	1HB	SER	13	16.191	25.599	-4.142	0.00	0.00	H
ATOM	175	2HB	SER	13	16.082	27.346	-4.346	0.00	0.00	H
ATOM	176	HG	SER	13	14.016	26.867	-4.059	0.00	0.00	H
ATOM	177	N	ASN	14	16.773	28.383	-7.341	0.00	0.00	N
ATOM	178	CA	ASN	14	16.901	29.190	-8.591	0.00	0.00	C
ATOM	179	C	ASN	14	16.718	28.475	-9.975	0.00	0.00	C
ATOM	180	O	ASN	14	16.103	29.023	-10.889	0.00	0.00	O
ATOM	181	CB	ASN	14	18.264	29.935	-8.516	0.00	0.00	C
ATOM	182	CG	ASN	14	19.577	29.139	-8.682	0.00	0.00	C
ATOM	183	OD1	ASN	14	19.814	28.095	-8.080	0.00	0.00	O
ATOM	184	ND2	ASN	14	20.472	29.600	-9.517	0.00	0.00	N
ATOM	185	H	ASN	14	17.588	27.967	-6.878	0.00	0.00	H
ATOM	186	HA	ASN	14	16.101	29.953	-8.559	0.00	0.00	H
ATOM	187	1HB	ASN	14	18.219	30.728	-9.282	0.00	0.00	H
ATOM	188	2HB	ASN	14	18.332	30.463	-7.551	0.00	0.00	H
ATOM	189	1HD2	ASN	14	21.324	29.044	-9.601	0.00	0.00	H
ATOM	190	2HD2	ASN	14	20.214	30.432	-10.057	0.00	0.00	H
ATOM	191	N	LEU	15	17.269	27.262	-10.102	0.00	0.00	N
ATOM	192	CA	LEU	15	17.117	26.420	-11.323	0.00	0.00	C
ATOM	193	C	LEU	15	15.850	25.494	-11.396	0.00	0.00	C
ATOM	194	O	LEU	15	15.600	24.903	-12.450	0.00	0.00	O
ATOM	195	CB	LEU	15	18.428	25.623	-11.576	0.00	0.00	C
ATOM	196	CG	LEU	15	19.755	26.418	-11.723	0.00	0.00	C
ATOM	197	CD1	LEU	15	20.920	25.447	-11.952	0.00	0.00	C
ATOM	198	CD2	LEU	15	19.730	27.443	-12.869	0.00	0.00	C
ATOM	199	H	LEU	15	17.588	26.893	-9.195	0.00	0.00	H
ATOM	200	HA	LEU	15	16.999	27.101	-12.177	0.00	0.00	H
ATOM	201	1HB	LEU	15	18.533	24.872	-10.772	0.00	0.00	H
ATOM	202	2HB	LEU	15	18.284	25.024	-12.497	0.00	0.00	H
ATOM	203	HG	LEU	15	19.943	26.970	-10.782	0.00	0.00	H
ATOM	204	1HD1	LEU	15	20.978	24.671	-11.170	0.00	0.00	H

FIG. 8 - 7

ATOM	205	2HD1	LEU	15	20.824	24.921	-12.921	0.00	0.00	H
ATOM	206	3HD1	LEU	15	21.890	25.977	-11.960	0.00	0.00	H
ATOM	207	1HD2	LEU	15	19.502	26.978	-13.847	0.00	0.00	H
ATOM	208	2HD2	LEU	15	18.970	28.229	-12.701	0.00	0.00	H
ATOM	209	3HD2	LEU	15	20.696	27.971	-12.978	0.00	0.00	H
ATOM	210	N	CYS	16	15.032	25.367	-10.333	0.00	0.00	N
ATOM	211	CA	CYS	16	13.605	24.985	-10.483	0.00	0.00	C
ATOM	212	C	CYS	16	12.591	26.176	-10.521	0.00	0.00	C
ATOM	213	O	CYS	16	11.707	26.224	-11.368	0.00	0.00	O
ATOM	214	CB	CYS	16	13.268	24.001	-9.358	0.00	0.00	C
ATOM	215	SG	CYS	16	11.802	23.053	-9.808	0.00	0.00	S
ATOM	216	H	CYS	16	15.380	25.854	-9.498	0.00	0.00	H
ATOM	217	HA	CYS	16	13.461	24.447	-11.437	0.00	0.00	H
ATOM	218	1HB	CYS	16	14.020	23.224	-9.193	0.00	0.00	H
ATOM	219	2HB	CYS	16	13.215	24.552	-8.399	0.00	0.00	H
TER	220		CYS	16						
HETATM	221	N	NH2	17H	12.608	27.130	-9.608	0.00	0.00	N
HETATM	222	1HN	NH2	17H	13.333	27.130	-8.876	1.00	0.00	H
HETATM	223	2HN	NH2	17H	11.896	27.874	-9.628	1.00	0.00	H
ENDMDL										
MODEL	2									
ATOM	224	N	GLY	1	14.267	17.154	-16.168	0.00	0.00	N
ATOM	225	CA	GLY	1	15.718	17.213	-15.794	0.00	0.00	C
ATOM	226	C	GLY	1	15.977	17.230	-14.264	0.00	0.00	C
ATOM	227	O	GLY	1	15.276	16.529	-13.537	0.00	0.00	O
ATOM	228	1H	GLY	1	13.780	17.978	-15.788	1.00	0.00	H
ATOM	229	2H	GLY	1	14.176	17.146	-17.194	1.00	0.00	H
ATOM	230	3H	GLY	1	13.846	16.297	-15.781	1.00	0.00	H
ATOM	231	1HA	GLY	1	16.245	16.323	-16.195	0.00	0.00	H
ATOM	232	2HA	GLY	1	16.206	18.082	-16.280	0.00	0.00	H
ATOM	233	N	CYS	2	16.947	17.998	-13.736	0.00	0.00	N
ATOM	234	CA	CYS	2	17.280	17.912	-12.279	0.00	0.00	C
ATOM	235	C	CYS	2	16.307	18.759	-11.354	0.00	0.00	C
ATOM	236	O	CYS	2	15.915	18.300	-10.283	0.00	0.00	O

FIG. 8 - 8

ATOM	237	CB	CYS	2	18.750	18.346	-12.154	0.00	0.00	C
ATOM	238	SG	CYS	2	19.069	18.878	-10.463	0.00	0.00	S
ATOM	239	H	CYS	2	17.697	18.283	-14.376	0.00	0.00	H
ATOM	240	HA	CYS	2	17.217	16.863	-11.923	0.00	0.00	H
ATOM	241	1HB	CYS	2	19.444	17.562	-12.506	0.00	0.00	H
ATOM	242	2HB	CYS	2	18.928	19.245	-12.774	0.00	0.00	H
ATOM	243	N	CYS	3	15.877	19.965	-11.766	0.00	0.00	N
ATOM	244	CA	CYS	3	14.608	20.610	-11.289	0.00	0.00	C
ATOM	245	C	CYS	3	13.303	19.715	-11.225	0.00	0.00	C
ATOM	246	O	CYS	3	12.479	19.936	-10.337	0.00	0.00	O
ATOM	247	CB	CYS	3	14.460	21.831	-12.226	0.00	0.00	C
ATOM	248	SG	CYS	3	12.912	22.710	-11.945	0.00	0.00	S
ATOM	249	H	CYS	3	16.327	20.233	-12.647	0.00	0.00	H
ATOM	250	HA	CYS	3	14.740	21.021	-10.252	0.00	0.00	H
ATOM	251	1HB	CYS	3	15.285	22.556	-12.082	0.00	0.00	H
ATOM	252	2HB	CYS	3	14.477	21.547	-13.296	0.00	0.00	H
ATOM	253	N	SER	4	13.123	18.690	-12.085	0.00	0.00	N
ATOM	254	CA	SER	4	12.080	17.647	-11.888	0.00	0.00	C
ATOM	255	C	SER	4	12.391	16.468	-10.886	0.00	0.00	C
ATOM	256	O	SER	4	11.554	15.583	-10.718	0.00	0.00	O
ATOM	257	CB	SER	4	11.690	17.171	-13.307	0.00	0.00	C
ATOM	258	OG	SER	4	12.630	16.273	-13.903	0.00	0.00	O
ATOM	259	H	SER	4	13.953	18.411	-12.605	0.00	0.00	H
ATOM	260	HA	SER	4	11.170	18.126	-11.471	0.00	0.00	H
ATOM	261	1HB	SER	4	10.731	16.655	-13.216	0.00	0.00	H
ATOM	262	2HB	SER	4	11.478	18.024	-13.982	0.00	0.00	H
ATOM	263	HG	SER	4	12.671	15.500	-13.317	0.00	0.00	H
ATOM	264	N	ASN	5	13.518	16.484	-10.152	0.00	0.00	N
ATOM	265	CA	ASN	5	13.727	15.715	-8.918	0.00	0.00	C
ATOM	266	C	ASN	5	13.257	16.443	-7.608	0.00	0.00	C
ATOM	267	O	ASN	5	13.005	17.652	-7.625	0.00	0.00	O
ATOM	268	CB	ASN	5	15.248	15.453	-8.868	0.00	0.00	C
ATOM	269	CG	ASN	5	15.815	14.162	-9.386	0.00	0.00	C
ATOM	270	OD1	ASN	5	15.531	13.678	-10.472	0.00	0.00	O

FIG. 8 - 9

ATOM	271	ND2	ASN	5	16.768	13.664	-8.665	0.00	0.00	N
ATOM	272	H	ASN	5	14.288	17.138	-10.338	0.00	0.00	H
ATOM	273	HA	ASN	5	13.260	14.728	-8.976	0.00	0.00	H
ATOM	274	1HB	ASN	5	15.763	16.040	-9.603	0.00	0.00	H
ATOM	275	2HB	ASN	5	15.710	15.930	-8.009	0.00	0.00	H
ATOM	276	1HD2	ASN	5	17.365	13.107	-9.271	0.00	0.00	H
ATOM	277	2HD2	ASN	5	17.030	14.217	-7.846	0.00	0.00	H
ATOM	278	N	PRO	6	13.219	15.766	-6.432	0.00	0.00	N
ATOM	279	CA	PRO	6	13.046	16.445	-5.115	0.00	0.00	C
ATOM	280	C	PRO	6	14.257	17.306	-4.627	0.00	0.00	C
ATOM	281	O	PRO	6	14.159	18.505	-4.368	0.00	0.00	O
ATOM	282	CB	PRO	6	12.647	15.247	-4.238	0.00	0.00	C
ATOM	283	CG	PRO	6	13.429	14.074	-4.834	0.00	0.00	C
ATOM	284	CD	PRO	6	13.367	14.298	-6.333	0.00	0.00	C
ATOM	285	HA	PRO	6	12.197	17.119	-5.110	0.00	0.00	H
ATOM	286	1HB	PRO	6	12.850	15.433	-3.173	0.00	0.00	H
ATOM	287	2HB	PRO	6	11.557	15.056	-4.313	0.00	0.00	H
ATOM	288	1HG	PRO	6	14.474	14.066	-4.483	0.00	0.00	H
ATOM	289	2HG	PRO	6	13.061	13.093	-4.561	0.00	0.00	H
ATOM	290	1HD	PRO	6	14.278	13.884	-6.779	0.00	0.00	H
ATOM	291	2HD	PRO	6	12.540	13.796	-6.867	0.00	0.00	H
ATOM	292	N	VAL	7	15.412	16.657	-4.561	0.00	0.00	N
ATOM	293	CA	VAL	7	16.610	17.124	-3.820	0.00	0.00	C
ATOM	294	C	VAL	7	17.524	18.017	-4.681	0.00	0.00	C
ATOM	295	O	VAL	7	17.855	19.138	-4.293	0.00	0.00	O
ATOM	296	CB	VAL	7	17.305	15.801	-3.328	0.00	0.00	C
ATOM	297	CG1	VAL	7	18.715	15.985	-2.741	0.00	0.00	C
ATOM	298	CG2	VAL	7	16.502	15.043	-2.257	0.00	0.00	C
ATOM	299	H	VAL	7	15.273	15.661	-4.749	0.00	0.00	H
ATOM	300	HA	VAL	7	16.319	17.791	-2.987	0.00	0.00	H
ATOM	301	HB	VAL	7	17.399	15.124	-4.210	0.00	0.00	H
ATOM	302	1HG1	VAL	7	18.703	16.661	-1.865	0.00	0.00	H
ATOM	303	2HG1	VAL	7	19.150	15.022	-2.417	0.00	0.00	H
ATOM	304	3HG1	VAL	7	19.416	16.412	-3.481	0.00	0.00	H

18/107

FIG. 8 - 10

ATOM	305	1HG2	VAL	7	15.476	14.815	-2.595	0.00	0.00	H
ATOM	306	2HG2	VAL	7	16.976	14.076	-2.011	0.00	0.00	H
ATOM	307	3HG2	VAL	7	16.415	15.634	-1.328	0.00	0.00	H
ATOM	308	N	CYS	8	17.945	17.519	-5.852	0.00	0.00	N
ATOM	309	CA	CYS	8	18.800	18.310	-6.774	0.00	0.00	C
ATOM	310	C	CYS	8	18.200	19.595	-7.433	0.00	0.00	C
ATOM	311	O	CYS	8	18.901	20.560	-7.755	0.00	0.00	O
ATOM	312	CB	CYS	8	19.585	17.408	-7.744	0.00	0.00	C
ATOM	313	SG	CYS	8	18.676	17.283	-9.293	0.00	0.00	S
ATOM	314	H	CYS	8	17.652	16.545	-5.925	0.00	0.00	H
ATOM	315	HA	CYS	8	19.478	18.741	-6.057	0.00	0.00	H
ATOM	316	1HB	CYS	8	20.579	17.844	-7.956	0.00	0.00	H
ATOM	317	2HB	CYS	8	19.785	16.400	-7.330	0.00	0.00	H
ATOM	318	N	HIS	9	16.872	19.603	-7.516	0.00	0.00	N
ATOM	319	CA	HIS	9	16.022	20.810	-7.579	0.00	0.00	C
ATOM	320	C	HIS	9	16.327	21.879	-6.487	0.00	0.00	C
ATOM	321	O	HIS	9	16.337	23.069	-6.777	0.00	0.00	O
ATOM	322	CB	HIS	9	14.563	20.257	-7.547	0.00	0.00	C
ATOM	323	CG	HIS	9	13.278	20.974	-7.119	0.00	0.00	C
ATOM	324	ND1	HIS	9	12.032	20.482	-7.452	0.00	0.00	N
ATOM	325	CD2	HIS	9	13.125	22.225	-6.531	0.00	0.00	C
ATOM	326	CE1	HIS	9	11.216	21.519	-7.082	0.00	0.00	C
ATOM	327	NE2	HIS	9	11.787	22.598	-6.466	0.00	0.00	N
ATOM	328	H	HIS	9	16.502	18.717	-7.185	0.00	0.00	H
ATOM	329	HA	HIS	9	16.215	21.262	-8.533	0.00	0.00	H
ATOM	330	1HB	HIS	9	14.396	19.611	-8.422	0.00	0.00	H
ATOM	331	2HB	HIS	9	14.586	19.572	-6.681	0.00	0.00	H
ATOM	332	HD1	HIS	9	11.832	19.638	-8.011	0.00	0.00	H
ATOM	333	HD2	HIS	9	13.978	22.826	-6.296	0.00	0.00	H
ATOM	334	HE1	HIS	9	10.181	21.570	-7.416	0.00	0.00	H
ATOM	335	HE2	HIS	9	11.353	23.443	-6.068	1.00	0.00	H
ATOM	336	N	LEU	10	16.461	21.442	-5.238	0.00	0.00	N
ATOM	337	CA	LEU	10	16.551	22.359	-4.048	0.00	0.00	C
ATOM	338	C	LEU	10	17.980	22.858	-3.652	0.00	0.00	C

FIG. 8 - 11

ATOM	339	O	LEU	10	18.166	24.025	-3.307	0.00	0.00	O
ATOM	340	CB	LEU	10	15.731	21.762	-2.874	0.00	0.00	C
ATOM	341	CG	LEU	10	14.193	21.697	-3.089	0.00	0.00	C
ATOM	342	CD1	LEU	10	13.532	20.881	-1.974	0.00	0.00	C
ATOM	343	CD2	LEU	10	13.533	23.090	-3.152	0.00	0.00	C
ATOM	344	H	LEU	10	16.686	20.422	-5.257	0.00	0.00	H
ATOM	345	HA	LEU	10	16.057	23.307	-4.309	0.00	0.00	H
ATOM	346	1HB	LEU	10	16.122	20.751	-2.645	0.00	0.00	H
ATOM	347	2HB	LEU	10	15.929	22.343	-1.952	0.00	0.00	H
ATOM	348	HG	LEU	10	13.986	21.158	-4.033	0.00	0.00	H
ATOM	349	1HD1	LEU	10	13.933	19.852	-1.936	0.00	0.00	H
ATOM	350	2HD1	LEU	10	13.681	21.334	-0.976	0.00	0.00	H
ATOM	351	3HD1	LEU	10	12.441	20.783	-2.133	0.00	0.00	H
ATOM	352	1HD2	LEU	10	13.703	23.671	-2.225	0.00	0.00	H
ATOM	353	2HD2	LEU	10	13.910	23.708	-3.986	0.00	0.00	H
ATOM	354	3HD2	LEU	10	12.438	23.019	-3.290	0.00	0.00	H
ATOM	355	N	GLU	11	19.005	22.036	-3.865	0.00	0.00	N
ATOM	356	CA	GLU	11	20.372	22.479	-4.230	0.00	0.00	C
ATOM	357	C	GLU	11	20.553	23.589	-5.329	0.00	0.00	C
ATOM	358	O	GLU	11	21.516	24.355	-5.322	0.00	0.00	O
ATOM	359	CB	GLU	11	20.965	21.149	-4.750	0.00	0.00	C
ATOM	360	CG	GLU	11	21.455	20.100	-3.724	0.00	0.00	C
ATOM	361	CD	GLU	11	22.052	18.829	-4.335	0.00	0.00	C
ATOM	362	OE1	GLU	11	22.158	18.618	-5.542	0.00	0.00	O
ATOM	363	OE2	GLU	11	22.453	17.953	-3.377	0.00	0.00	O
ATOM	364	H	GLU	11	18.838	21.024	-3.769	1.00	0.00	H
ATOM	365	HA	GLU	11	20.916	22.823	-3.343	0.00	0.00	H
ATOM	366	1HB	GLU	11	20.300	20.674	-5.496	0.00	0.00	H
ATOM	367	2HB	GLU	11	21.806	21.427	-5.359	0.00	0.00	H
ATOM	368	1HG	GLU	11	22.204	20.543	-3.042	0.00	0.00	H
ATOM	369	2HG	GLU	11	20.611	19.803	-3.084	0.00	0.00	H
ATOM	370	HE2	GLU	11	22.820	17.169	-3.788	0.00	0.00	H
ATOM	371	N	HIS	12	19.668	23.583	-6.329	0.00	0.00	N
ATOM	372	CA	HIS	12	19.632	24.590	-7.415	0.00	0.00	C

FIG. 8 - 12

20/107

ATOM	373	C	HIS	12	18.228	25.279	-7.467	0.00	0.00	C
ATOM	374	O	HIS	12	17.504	25.191	-8.458	0.00	0.00	O
ATOM	375	CB	HIS	12	20.050	23.866	-8.721	0.00	0.00	C
ATOM	376	CG	HIS	12	21.465	23.272	-8.765	0.00	0.00	C
ATOM	377	ND1	HIS	12	21.705	21.925	-8.557	0.00	0.00	N
ATOM	378	CD2	HIS	12	22.683	23.982	-8.781	0.00	0.00	C
ATOM	379	CE1	HIS	12	23.072	21.918	-8.425	0.00	0.00	C
ATOM	380	NE2	HIS	12	23.746	23.104	-8.581	0.00	0.00	N
ATOM	381	H	HIS	12	18.854	23.028	-6.071	0.00	0.00	H
ATOM	382	HA	HIS	12	20.356	25.393	-7.231	0.00	0.00	H
ATOM	383	1HB	HIS	12	19.305	23.072	-8.900	0.00	0.00	H
ATOM	384	2HB	HIS	12	19.922	24.566	-9.561	0.00	0.00	H
ATOM	385	HD1	HIS	12	21.013	21.211	-8.287	0.00	0.00	H
ATOM	386	HD2	HIS	12	22.761	25.064	-8.831	0.00	0.00	H
ATOM	387	HE1	HIS	12	23.605	21.006	-8.146	0.00	0.00	H
ATOM	388	HE2	HIS	12	24.759	23.292	-8.556	1.00	0.00	H
ATOM	389	N	SER	13	17.836	25.928	-6.362	0.00	0.00	N
ATOM	390	CA	SER	13	16.441	26.361	-6.091	0.00	0.00	C
ATOM	391	C	SER	13	15.868	27.547	-6.898	0.00	0.00	C
ATOM	392	O	SER	13	14.771	27.472	-7.441	0.00	0.00	O
ATOM	393	CB	SER	13	16.240	26.544	-4.566	0.00	0.00	C
ATOM	394	OG	SER	13	17.091	27.570	-4.045	0.00	0.00	O
ATOM	395	H	SER	13	18.337	25.569	-5.566	0.00	0.00	H
ATOM	396	HA	SER	13	15.859	25.510	-6.412	0.00	0.00	H
ATOM	397	1HB	SER	13	15.182	26.797	-4.347	0.00	0.00	H
ATOM	398	2HB	SER	13	16.425	25.600	-4.025	0.00	0.00	H
ATOM	399	HG	SER	13	16.898	27.680	-3.106	0.00	0.00	H
ATOM	400	N	ASN	14	16.711	28.553	-7.058	0.00	0.00	N
ATOM	401	CA	ASN	14	16.737	29.460	-8.249	0.00	0.00	C
ATOM	402	C	ASN	14	16.410	28.835	-9.656	0.00	0.00	C
ATOM	403	O	ASN	14	15.664	29.413	-10.445	0.00	0.00	O
ATOM	404	CB	ASN	14	18.130	30.154	-8.143	0.00	0.00	C
ATOM	405	CG	ASN	14	18.511	31.133	-9.251	0.00	0.00	C
ATOM	406	OD1	ASN	14	18.145	32.298	-9.248	0.00	0.00	O

FIG. 8 - 13

ATOM	407	ND2	ASN	14	19.273	30.693	-10.222	0.00	0.00	N
ATOM	408	H	ASN	14	17.533	28.211	-6.552	0.00	0.00	H
ATOM	409	HA	ASN	14	15.958	30.222	-8.103	0.00	0.00	H
ATOM	410	1HB	ASN	14	18.169	30.739	-7.203	0.00	0.00	H
ATOM	411	2HB	ASN	14	18.940	29.408	-8.032	0.00	0.00	H
ATOM	412	1HD2	ASN	14	19.438	31.380	-10.959	0.00	0.00	H
ATOM	413	2HD2	ASN	14	19.395	29.682	-10.278	0.00	0.00	H
ATOM	414	N	LEU	15	16.962	27.653	-9.949	0.00	0.00	N
ATOM	415	CA	LEU	15	16.741	26.927	-11.229	0.00	0.00	C
ATOM	416	C	LEU	15	15.509	25.946	-11.288	0.00	0.00	C
ATOM	417	O	LEU	15	15.205	25.390	-12.345	0.00	0.00	O
ATOM	418	CB	LEU	15	18.105	26.267	-11.585	0.00	0.00	C
ATOM	419	CG	LEU	15	19.301	27.263	-11.704	0.00	0.00	C
ATOM	420	CD1	LEU	15	20.233	27.331	-10.482	0.00	0.00	C
ATOM	421	CD2	LEU	15	20.137	26.987	-12.949	0.00	0.00	C
ATOM	422	H	LEU	15	17.505	27.222	-9.199	0.00	0.00	H
ATOM	423	HA	LEU	15	16.537	27.672	-12.014	0.00	0.00	H
ATOM	424	1HB	LEU	15	18.333	25.449	-10.882	0.00	0.00	H
ATOM	425	2HB	LEU	15	17.954	25.747	-12.552	0.00	0.00	H
ATOM	426	HG	LEU	15	18.858	28.275	-11.796	0.00	0.00	H
ATOM	427	1HD1	LEU	15	19.680	27.495	-9.541	0.00	0.00	H
ATOM	428	2HD1	LEU	15	20.851	26.426	-10.371	0.00	0.00	H
ATOM	429	3HD1	LEU	15	20.936	28.183	-10.576	0.00	0.00	H
ATOM	430	1HD2	LEU	15	19.510	27.042	-13.859	0.00	0.00	H
ATOM	431	2HD2	LEU	15	20.941	27.736	-13.066	0.00	0.00	H
ATOM	432	3HD2	LEU	15	20.599	25.985	-12.915	0.00	0.00	H
ATOM	433	N	CYS	16	14.777	25.764	-10.178	0.00	0.00	N
ATOM	434	CA	CYS	16	13.314	25.476	-10.211	0.00	0.00	C
ATOM	435	C	CYS	16	12.402	26.741	-10.052	0.00	0.00	C
ATOM	436	O	CYS	16	11.558	27.025	-10.893	0.00	0.00	O
ATOM	437	CB	CYS	16	13.014	24.354	-9.201	0.00	0.00	C
ATOM	438	SG	CYS	16	12.506	22.810	-9.987	0.00	0.00	S
ATOM	439	H	CYS	16	15.221	26.270	-9.398	0.00	0.00	H
ATOM	440	HA	CYS	16	13.008	25.068	-11.181	0.00	0.00	H

FIG. 8 - 14

22/107

ATOM	441	1HB	CYS	16	13.838	24.189	-8.482	0.00	0.00	H
ATOM	442	2HB	CYS	16	12.139	24.641	-8.605	0.00	0.00	H
TER	443		CYS	16						
HETATM	444	N	NH2	17H	12.467	27.507	-8.982	0.00	0.00	N
HETATM	445	1HN	NH2	17H	11.921	28.368	-9.091	0.00	0.00	H
HETATM	446	2HN	NH2	17H	13.302	27.373	-8.381	0.00	0.00	H
ENDMDL										
MODEL	3									
ATOM	447	N	GLY	1	14.339	14.763	-15.648	0.00	0.00	N
ATOM	448	CA	GLY	1	15.501	15.674	-15.380	0.00	0.00	C
ATOM	449	C	GLY	1	15.797	15.944	-13.877	0.00	0.00	C
ATOM	450	O	GLY	1	15.122	15.395	-13.008	0.00	0.00	O
ATOM	451	1H	GLY	1	14.514	13.846	-15.214	1.00	0.00	H
ATOM	452	2H	GLY	1	13.482	15.173	-15.250	1.00	0.00	H
ATOM	453	3H	GLY	1	14.223	14.645	-16.665	1.00	0.00	H
ATOM	454	1HA	GLY	1	16.418	15.264	-15.850	0.00	0.00	H
ATOM	455	2HA	GLY	1	15.328	16.651	-15.876	0.00	0.00	H
ATOM	456	N	CYS	2	16.776	16.803	-13.541	0.00	0.00	N
ATOM	457	CA	CYS	2	17.170	17.004	-12.112	0.00	0.00	C
ATOM	458	C	CYS	2	16.202	17.965	-11.305	0.00	0.00	C
ATOM	459	O	CYS	2	15.843	17.666	-10.165	0.00	0.00	O
ATOM	460	CB	CYS	2	18.629	17.503	-12.156	0.00	0.00	C
ATOM	461	SG	CYS	2	19.008	18.386	-10.634	0.00	0.00	S
ATOM	462	H	CYS	2	17.487	16.987	-14.258	0.00	0.00	H
ATOM	463	HA	CYS	2	17.172	16.036	-11.572	0.00	0.00	H
ATOM	464	1HB	CYS	2	19.337	16.682	-12.370	0.00	0.00	H
ATOM	465	2HB	CYS	2	18.758	18.253	-12.959	0.00	0.00	H
ATOM	466	N	CYS	3	15.761	19.098	-11.885	0.00	0.00	N
ATOM	467	CA	CYS	3	14.518	19.828	-11.470	0.00	0.00	C
ATOM	468	C	CYS	3	13.220	18.988	-11.158	0.00	0.00	C
ATOM	469	O	CYS	3	12.535	19.264	-10.171	0.00	0.00	O
ATOM	470	CB	CYS	3	14.242	20.788	-12.652	0.00	0.00	C
ATOM	471	SG	CYS	3	15.309	22.251	-12.667	0.00	0.00	S
ATOM	472	H	CYS	3	16.193	19.251	-12.802	0.00	0.00	H

FIG. 8 - 15

23/107

ATOM	473	HA	CYS	3	14.710	20.428	-10.545	0.00	0.00	H
ATOM	474	1HB	CYS	3	14.297	20.289	-13.638	0.00	0.00	H
ATOM	475	2HB	CYS	3	13.196	21.138	-12.602	0.00	0.00	H
ATOM	476	N	SER	4	12.896	17.981	-11.985	0.00	0.00	N
ATOM	477	CA	SER	4	11.833	16.981	-11.696	0.00	0.00	C
ATOM	478	C	SER	4	12.098	15.927	-10.557	0.00	0.00	C
ATOM	479	O	SER	4	11.175	15.210	-10.172	0.00	0.00	O
ATOM	480	CB	SER	4	11.493	16.321	-13.054	0.00	0.00	C
ATOM	481	OG	SER	4	12.458	15.352	-13.475	0.00	0.00	O
ATOM	482	H	SER	4	13.623	17.767	-12.661	0.00	0.00	H
ATOM	483	HA	SER	4	10.925	17.528	-11.374	0.00	0.00	H
ATOM	484	1HB	SER	4	10.520	15.823	-12.947	0.00	0.00	H
ATOM	485	2HB	SER	4	11.325	17.075	-13.848	0.00	0.00	H
ATOM	486	HG	SER	4	12.587	14.760	-12.717	0.00	0.00	H
ATOM	487	N	ASN	5	13.298	15.890	-9.954	0.00	0.00	N
ATOM	488	CA	ASN	5	13.520	15.271	-8.631	0.00	0.00	C
ATOM	489	C	ASN	5	13.249	16.320	-7.492	0.00	0.00	C
ATOM	490	O	ASN	5	13.496	17.514	-7.700	0.00	0.00	O
ATOM	491	CB	ASN	5	15.027	14.909	-8.516	0.00	0.00	C
ATOM	492	CG	ASN	5	15.650	13.872	-9.436	0.00	0.00	C
ATOM	493	OD1	ASN	5	15.196	13.528	-10.518	0.00	0.00	O
ATOM	494	ND2	ASN	5	16.748	13.339	-8.977	0.00	0.00	N
ATOM	495	H	ASN	5	14.052	16.431	-10.390	0.00	0.00	H
ATOM	496	HA	ASN	5	12.876	14.376	-8.486	0.00	0.00	H
ATOM	497	1HB	ASN	5	15.673	15.813	-8.516	0.00	0.00	H
ATOM	498	2HB	ASN	5	15.157	14.500	-7.513	0.00	0.00	H
ATOM	499	1HD2	ASN	5	16.916	12.434	-9.409	0.00	0.00	H
ATOM	500	2HD2	ASN	5	16.959	13.603	-8.009	0.00	0.00	H
ATOM	501	N	PRO	6	12.853	15.946	-6.246	0.00	0.00	N
ATOM	502	CA	PRO	6	12.790	16.921	-5.117	0.00	0.00	C
ATOM	503	C	PRO	6	14.122	17.558	-4.592	0.00	0.00	C
ATOM	504	O	PRO	6	14.104	18.620	-3.975	0.00	0.00	O
ATOM	505	CB	PRO	6	11.974	16.138	-4.077	0.00	0.00	C
ATOM	506	CG	PRO	6	12.134	14.661	-4.400	0.00	0.00	C

FIG. 8 - 16

24/107

ATOM	507	CD	PRO	6	12.460	14.569	-5.892	0.00	0.00	C
ATOM	508	HA	PRO	6	12.198	17.787	-5.426	0.00	0.00	H
ATOM	509	1HB	PRO	6	12.237	16.397	-3.035	0.00	0.00	H
ATOM	510	2HB	PRO	6	10.906	16.346	-4.172	0.00	0.00	H
ATOM	511	1HG	PRO	6	12.949	14.294	-3.782	0.00	0.00	H
ATOM	512	2HG	PRO	6	11.258	14.055	-4.114	0.00	0.00	H
ATOM	513	1HD	PRO	6	13.254	13.829	-6.078	0.00	0.00	H
ATOM	514	2HD	PRO	6	11.608	14.236	-6.509	0.00	0.00	H
ATOM	515	N	VAL	7	15.274	16.948	-4.875	0.00	0.00	N
ATOM	516	CA	VAL	7	16.521	17.139	-4.081	0.00	0.00	C
ATOM	517	C	VAL	7	17.575	17.995	-4.822	0.00	0.00	C
ATOM	518	O	VAL	7	17.963	19.052	-4.324	0.00	0.00	O
ATOM	519	CB	VAL	7	16.989	15.709	-3.620	0.00	0.00	C
ATOM	520	CG1	VAL	7	18.420	15.642	-3.030	0.00	0.00	C
ATOM	521	CG2	VAL	7	16.065	15.088	-2.543	0.00	0.00	C
ATOM	522	H	VAL	7	15.101	16.079	-5.379	0.00	0.00	H
ATOM	523	HA	VAL	7	16.306	17.787	-3.217	0.00	0.00	H
ATOM	524	HB	VAL	7	16.958	15.048	-4.522	0.00	0.00	H
ATOM	525	1HG1	VAL	7	18.532	16.285	-2.135	0.00	0.00	H
ATOM	526	2HG1	VAL	7	18.699	14.615	-2.721	0.00	0.00	H
ATOM	527	3HG1	VAL	7	19.193	15.960	-3.755	0.00	0.00	H
ATOM	528	1HG2	VAL	7	15.013	15.025	-2.874	0.00	0.00	H
ATOM	529	2HG2	VAL	7	16.366	14.057	-2.274	0.00	0.00	H
ATOM	530	3HG2	VAL	7	16.063	15.676	-1.604	0.00	0.00	H
ATOM	531	N	CYS	8	18.035	17.582	-6.014	0.00	0.00	N
ATOM	532	CA	CYS	8	18.938	18.422	-6.846	0.00	0.00	C
ATOM	533	C	CYS	8	18.366	19.678	-7.571	0.00	0.00	C
ATOM	534	O	CYS	8	19.057	20.660	-7.856	0.00	0.00	O
ATOM	535	CB	CYS	8	19.809	17.525	-7.738	0.00	0.00	C
ATOM	536	SG	CYS	8	18.825	17.034	-9.159	0.00	0.00	S
ATOM	537	H	CYS	8	17.562	16.755	-6.347	0.00	0.00	H
ATOM	538	HA	CYS	8	19.520	18.894	-6.080	0.00	0.00	H
ATOM	539	1HB	CYS	8	20.710	18.063	-8.085	0.00	0.00	H
ATOM	540	2HB	CYS	8	20.183	16.631	-7.200	0.00	0.00	H

FIG. 8 - 17
25/107

ATOM	541	N	HIS	9	17.051	19.656	-7.725	0.00	0.00	N
ATOM	542	CA	HIS	9	16.148	20.838	-7.697	0.00	0.00	C
ATOM	543	C	HIS	9	16.469	21.904	-6.631	0.00	0.00	C
ATOM	544	O	HIS	9	16.546	23.092	-6.899	0.00	0.00	O
ATOM	545	CB	HIS	9	14.734	20.263	-7.519	0.00	0.00	C
ATOM	546	CG	HIS	9	13.407	20.846	-7.036	0.00	0.00	C
ATOM	547	ND1	HIS	9	12.224	20.266	-7.455	0.00	0.00	N
ATOM	548	CD2	HIS	9	13.209	22.204	-6.911	0.00	0.00	C
ATOM	549	CE1	HIS	9	11.446	21.377	-7.666	0.00	0.00	C
ATOM	550	NE2	HIS	9	11.929	22.588	-7.275	0.00	0.00	N
ATOM	551	H	HIS	9	16.703	18.728	-7.484	0.00	0.00	H
ATOM	552	HA	HIS	9	16.114	21.253	-8.669	0.00	0.00	H
ATOM	553	1HB	HIS	9	14.624	19.560	-8.258	0.00	0.00	H
ATOM	554	2HB	HIS	9	14.899	19.593	-6.691	0.00	0.00	H
ATOM	555	HD1	HIS	9	12.170	19.386	-7.993	0.00	0.00	H
ATOM	556	HD2	HIS	9	14.088	22.797	-6.943	0.00	0.00	H
ATOM	557	HE1	HIS	9	10.657	21.358	-8.411	0.00	0.00	H
ATOM	558	HE2	HIS	9	11.478	23.514	-7.257	1.00	0.00	H
ATOM	559	N	LEU	10	16.510	21.400	-5.416	0.00	0.00	N
ATOM	560	CA	LEU	10	16.570	22.253	-4.174	0.00	0.00	C
ATOM	561	C	LEU	10	17.979	22.645	-3.618	0.00	0.00	C
ATOM	562	O	LEU	10	18.136	23.712	-3.025	0.00	0.00	O
ATOM	563	CB	LEU	10	15.554	21.758	-3.114	0.00	0.00	C
ATOM	564	CG	LEU	10	14.053	21.915	-3.487	0.00	0.00	C
ATOM	565	CD1	LEU	10	13.157	21.366	-2.376	0.00	0.00	C
ATOM	566	CD2	LEU	10	13.618	23.365	-3.798	0.00	0.00	C
ATOM	567	H	LEU	10	16.467	20.363	-5.592	0.00	0.00	H
ATOM	568	HA	LEU	10	16.207	23.258	-4.449	0.00	0.00	H
ATOM	569	1HB	LEU	10	15.773	20.698	-2.875	0.00	0.00	H
ATOM	570	2HB	LEU	10	15.731	22.300	-2.164	0.00	0.00	H
ATOM	571	HG	LEU	10	13.860	21.281	-4.370	0.00	0.00	H
ATOM	572	1HD1	LEU	10	13.400	20.312	-2.145	0.00	0.00	H
ATOM	573	2HD1	LEU	10	13.255	21.943	-1.438	0.00	0.00	H
ATOM	574	3HD1	LEU	10	12.092	21.384	-2.670	0.00	0.00	H

26/107

FIG. 8 - 18

ATOM	575	1HD2	LEU	10	13.811	24.049	-2.951	0.00	0.00	H
ATOM	576	2HD2	LEU	10	14.133	23.792	-4.676	0.00	0.00	H
ATOM	577	3HD2	LEU	10	12.537	23.430	-4.028	0.00	0.00	H
ATOM	578	N	GLU	11	19.031	21.902	-3.966	0.00	0.00	N
ATOM	579	CA	GLU	11	20.375	22.455	-4.234	0.00	0.00	C
ATOM	580	C	GLU	11	20.491	23.666	-5.226	0.00	0.00	C
ATOM	581	O	GLU	11	21.376	24.511	-5.104	0.00	0.00	O
ATOM	582	CB	GLU	11	21.076	21.236	-4.876	0.00	0.00	C
ATOM	583	CG	GLU	11	21.574	20.070	-3.990	0.00	0.00	C
ATOM	584	CD	GLU	11	22.277	18.962	-4.782	0.00	0.00	C
ATOM	585	OE1	GLU	11	22.450	18.994	-6.002	0.00	0.00	O
ATOM	586	OE2	GLU	11	22.675	17.938	-3.979	0.00	0.00	O
ATOM	587	H	GLU	11	18.899	20.884	-4.054	1.00	0.00	H
ATOM	588	HA	GLU	11	20.867	22.751	-3.302	0.00	0.00	H
ATOM	589	1HB	GLU	11	20.482	20.839	-5.720	0.00	0.00	H
ATOM	590	2HB	GLU	11	21.935	21.634	-5.387	0.00	0.00	H
ATOM	591	1HG	GLU	11	22.256	20.449	-3.207	0.00	0.00	H
ATOM	592	2HG	GLU	11	20.713	19.633	-3.461	0.00	0.00	H
ATOM	593	HE2	GLU	11	23.106	17.244	-4.479	0.00	0.00	H
ATOM	594	N	HIS	12	19.661	23.658	-6.276	0.00	0.00	N
ATOM	595	CA	HIS	12	19.662	24.699	-7.333	0.00	0.00	C
ATOM	596	C	HIS	12	18.259	25.379	-7.429	0.00	0.00	C
ATOM	597	O	HIS	12	17.553	25.276	-8.431	0.00	0.00	O
ATOM	598	CB	HIS	12	20.149	24.048	-8.654	0.00	0.00	C
ATOM	599	CG	HIS	12	21.537	23.388	-8.644	0.00	0.00	C
ATOM	600	ND1	HIS	12	21.694	22.016	-8.527	0.00	0.00	N
ATOM	601	CD2	HIS	12	22.786	24.026	-8.503	0.00	0.00	C
ATOM	602	CE1	HIS	12	23.042	21.920	-8.284	0.00	0.00	C
ATOM	603	NE2	HIS	12	23.784	23.076	-8.286	0.00	0.00	N
ATOM	604	H	HIS	12	18.898	22.991	-6.129	0.00	0.00	H
ATOM	605	HA	HIS	12	20.366	25.499	-7.078	0.00	0.00	H
ATOM	606	1HB	HIS	12	19.390	23.298	-8.934	0.00	0.00	H
ATOM	607	2HB	HIS	12	20.103	24.812	-9.453	0.00	0.00	H
ATOM	608	HD1	HIS	12	20.950	21.320	-8.367	0.00	0.00	H

FIG. 8 - 19

27/107

ATOM	609	HD2	HIS	12	22.921	25.104	-8.459	0.00	0.00	H
ATOM	610	HE1	HIS	12	23.498	20.961	-8.028	0.00	0.00	H
ATOM	611	HE2	HIS	12	24.798	23.206	-8.161	1.00	0.00	H
ATOM	612	N	SER	13	17.833	26.009	-6.331	0.00	0.00	N
ATOM	613	CA	SER	13	16.403	26.311	-6.059	0.00	0.00	C
ATOM	614	C	SER	13	15.718	27.474	-6.816	0.00	0.00	C
ATOM	615	O	SER	13	14.613	27.336	-7.338	0.00	0.00	O
ATOM	616	CB	SER	13	16.189	26.389	-4.527	0.00	0.00	C
ATOM	617	OG	SER	13	16.891	27.498	-3.959	0.00	0.00	O
ATOM	618	H	SER	13	18.343	25.629	-5.549	0.00	0.00	H
ATOM	619	HA	SER	13	15.909	25.433	-6.445	0.00	0.00	H
ATOM	620	1HB	SER	13	15.108	26.478	-4.299	0.00	0.00	H
ATOM	621	2HB	SER	13	16.516	25.458	-4.029	0.00	0.00	H
ATOM	622	HG	SER	13	16.656	27.563	-3.024	0.00	0.00	H
ATOM	623	N	ASN	14	16.478	28.547	-6.968	0.00	0.00	N
ATOM	624	CA	ASN	14	16.319	29.509	-8.097	0.00	0.00	C
ATOM	625	C	ASN	14	16.196	28.900	-9.538	0.00	0.00	C
ATOM	626	O	ASN	14	15.449	29.428	-10.362	0.00	0.00	O
ATOM	627	CB	ASN	14	17.433	30.582	-7.913	0.00	0.00	C
ATOM	628	CG	ASN	14	17.510	31.688	-8.972	0.00	0.00	C
ATOM	629	OD1	ASN	14	16.857	32.717	-8.883	0.00	0.00	O
ATOM	630	ND2	ASN	14	18.299	31.511	-10.004	0.00	0.00	D
ATOM	631	H	ASN	14	17.359	28.256	-6.537	0.00	0.00	N
ATOM	632	HA	ASN	14	15.350	29.999	-7.960	0.00	0.00	H
ATOM	633	1HB	ASN	14	17.269	31.099	-6.949	0.00	0.00	H
ATOM	634	2HB	ASN	14	18.427	30.117	-7.799	0.00	0.00	H
ATOM	635	1HD2	ASN	14	18.192	32.224	-10.730	0.00	0.00	H
ATOM	636	2HD2	ASN	14	18.688	30.575	-10.121	0.00	0.00	H
ATOM	637	N	LEU	15	16.899	27.804	-9.844	0.00	0.00	N
ATOM	638	CA	LEU	15	16.899	27.204	-11.194	0.00	0.00	C
ATOM	639	C	LEU	15	15.745	26.168	-11.474	0.00	0.00	C
ATOM	640	O	LEU	15	15.452	25.855	-12.628	0.00	0.00	O
ATOM	641	CB	LEU	15	18.308	26.575	-11.310	0.00	0.00	C
ATOM	642	CG	LEU	15	19.596	27.407	-11.027	0.00	0.00	C

FIG. 8 - 20

28/107

ATOM	643	CD1	LEU	15	19.847	28.470	-12.110	0.00	0.00	C
ATOM	644	CD2	LEU	15	19.880	28.024	-9.646	0.00	0.00	C
ATOM	645	H	LEU	15	17.547	27.387	-9.148	0.00	0.00	H
ATOM	646	HA	LEU	15	16.807	27.999	-11.955	0.00	0.00	H
ATOM	647	1HB	LEU	15	18.335	25.661	-10.691	0.00	0.00	H
ATOM	648	2HB	LEU	15	18.393	26.174	-12.340	0.00	0.00	H
ATOM	649	HG	LEU	15	20.330	26.619	-11.036	0.00	0.00	H
ATOM	650	1HD1	LEU	15	19.819	28.049	-13.131	0.00	0.00	H
ATOM	651	2HD1	LEU	15	19.082	29.271	-12.079	0.00	0.00	H
ATOM	652	3HD1	LEU	15	20.828	28.970	-11.997	0.00	0.00	H
ATOM	653	1HD2	LEU	15	19.668	27.333	-8.816	0.00	0.00	H
ATOM	654	2HD2	LEU	15	20.941	28.329	-9.548	0.00	0.00	H
ATOM	655	3HD2	LEU	15	19.291	28.937	-9.474	0.00	0.00	H
ATOM	656	N	CYS	16	15.133	25.607	-10.417	0.00	0.00	N
ATOM	657	CA	CYS	16	13.992	24.663	-10.501	0.00	0.00	C
ATOM	658	C	CYS	16	12.652	25.054	-9.780	0.00	0.00	C
ATOM	659	O	CYS	16	11.655	24.340	-9.888	0.00	0.00	O
ATOM	660	CB	CYS	16	14.550	23.376	-9.879	0.00	0.00	C
ATOM	661	SG	CYS	16	15.932	22.694	-10.819	0.00	0.00	S
ATOM	662	H	CYS	16	15.599	25.875	-9.541	0.00	0.00	H
ATOM	663	HA	CYS	16	13.717	24.466	-11.556	0.00	0.00	H
ATOM	664	1HB	CYS	16	14.829	23.538	-8.822	0.00	0.00	H
ATOM	665	2HB	CYS	16	13.759	22.619	-9.861	0.00	0.00	H
TER	666		CYS	16						
HETATM	667	N	NH2	17H	12.537	26.071	-8.951	0.00	0.00	N
HETATM	668	1HN	NH2	17H	11.572	26.337	-8.734	0.00	0.00	H
HETATM	669	2HN	NH2	17H	13.382	26.635	-8.774	0.00	0.00	H
ENDMDL										
MODEL	4									
ATOM	670	N	GLY	1	15.059	14.027	-13.141	0.00	0.00	N
ATOM	671	CA	GLY	1	16.088	14.977	-12.615	0.00	0.00	C
ATOM	672	C	GLY	1	16.607	16.088	-13.554	0.00	0.00	C
ATOM	673	O	GLY	1	16.438	16.002	-14.763	0.00	0.00	O
ATOM	674	1H	GLY	1	15.438	13.528	-13.958	1.00	0.00	H

29/107

FIG. 8 - 21

ATOM	675	2H	GLY	1	14.811	13.347	-12.408	1.00	0.00	H
ATOM	676	3H	GLY	1	14.217	14.552	-13.420	1.00	0.00	H
ATOM	677	1HA	GLY	1	15.688	15.490	-11.727	0.00	0.00	H
ATOM	678	2HA	GLY	1	16.985	14.427	-12.274	0.00	0.00	H
ATOM	679	N	CYS	2	17.317	17.140	-13.128	0.00	0.00	N
ATOM	680	CA	CYS	2	17.660	17.441	-11.707	0.00	0.00	C
ATOM	681	C	CYS	2	16.577	18.357	-11.003	0.00	0.00	C
ATOM	682	O	CYS	2	16.057	17.970	-9.960	0.00	0.00	O
ATOM	683	CB	CYS	2	19.087	18.023	-11.778	0.00	0.00	C
ATOM	684	SG	CYS	2	19.488	19.059	-10.356	0.00	0.00	S
ATOM	685	H	CYS	2	17.952	17.439	-13.870	0.00	0.00	H
ATOM	686	HA	CYS	2	17.739	16.520	-11.099	0.00	0.00	H
ATOM	687	1HB	CYS	2	19.835	17.233	-11.962	0.00	0.00	H
ATOM	688	2HB	CYS	2	19.192	18.713	-12.639	0.00	0.00	H
ATOM	689	N	CYS	3	16.172	19.501	-11.591	0.00	0.00	N
ATOM	690	CA	CYS	3	14.858	20.181	-11.315	0.00	0.00	C
ATOM	691	C	CYS	3	13.556	19.293	-11.198	0.00	0.00	C
ATOM	692	O	CYS	3	12.729	19.511	-10.314	0.00	0.00	O
ATOM	693	CB	CYS	3	14.701	21.143	-12.519	0.00	0.00	C
ATOM	694	SG	CYS	3	15.742	22.618	-12.416	0.00	0.00	S
ATOM	695	H	CYS	3	16.653	19.656	-12.483	0.00	0.00	H
ATOM	696	HA	CYS	3	14.900	20.786	-10.365	0.00	0.00	H
ATOM	697	1HB	CYS	3	14.874	20.648	-13.495	0.00	0.00	H
ATOM	698	2HB	CYS	3	13.652	21.479	-12.589	0.00	0.00	H
ATOM	699	N	SER	4	13.380	18.294	-12.069	0.00	0.00	N
ATOM	700	CA	SER	4	12.337	17.247	-11.953	0.00	0.00	C
ATOM	701	C	SER	4	12.583	16.081	-10.925	0.00	0.00	C
ATOM	702	O	SER	4	11.776	15.161	-10.816	0.00	0.00	O
ATOM	703	CB	SER	4	12.180	16.771	-13.416	0.00	0.00	C
ATOM	704	OG	SER	4	13.362	16.213	-14.006	0.00	0.00	O
ATOM	705	H	SER	4	14.140	18.118	-12.711	0.00	0.00	H
ATOM	706	HA	SER	4	11.376	17.710	-11.649	0.00	0.00	H
ATOM	707	1HB	SER	4	11.392	16.022	-13.435	0.00	0.00	H
ATOM	708	2HB	SER	4	11.793	17.598	-14.050	0.00	0.00	H

FIG. 8 - 22

30/107

ATOM	709	HG	SER	4	13.280	16.362	-14.961	0.00	0.00	H
ATOM	710	N	ASN	5	13.663	16.130	-10.132	0.00	0.00	N
ATOM	711	CA	ASN	5	13.771	15.482	-8.819	0.00	0.00	C
ATOM	712	C	ASN	5	13.274	16.354	-7.604	0.00	0.00	C
ATOM	713	O	ASN	5	13.227	17.582	-7.725	0.00	0.00	O
ATOM	714	CB	ASN	5	15.272	15.177	-8.665	0.00	0.00	C
ATOM	715	CG	ASN	5	15.813	13.824	-9.019	0.00	0.00	C
ATOM	716	OD1	ASN	5	15.655	13.286	-10.110	0.00	0.00	O
ATOM	717	ND2	ASN	5	16.627	13.356	-8.136	0.00	0.00	N
ATOM	718	H	ASN	5	14.351	16.885	-10.257	0.00	0.00	H
ATOM	719	HA	ASN	5	13.279	14.509	-8.837	0.00	0.00	H
ATOM	720	1HB	ASN	5	15.839	15.643	-9.453	0.00	0.00	H
ATOM	721	2HB	ASN	5	15.718	15.760	-7.862	0.00	0.00	H
ATOM	722	1HD2	ASN	5	17.292	12.729	-8.579	0.00	0.00	H
ATOM	723	2HD2	ASN	5	16.770	13.982	-7.339	0.00	0.00	H
ATOM	724	N	PRO	6	13.033	15.795	-6.384	0.00	0.00	N
ATOM	725	CA	PRO	6	12.918	16.608	-5.133	0.00	0.00	C
ATOM	726	C	PRO	6	14.176	17.432	-4.697	0.00	0.00	C
ATOM	727	O	PRO	6	14.142	18.652	-4.532	0.00	0.00	O
ATOM	728	CB	PRO	6	12.462	15.536	-4.132	0.00	0.00	C
ATOM	729	CG	PRO	6	13.138	14.255	-4.628	0.00	0.00	C
ATOM	730	CD	PRO	6	12.950	14.337	-6.142	0.00	0.00	C
ATOM	731	HA	PRO	6	12.111	17.331	-5.196	0.00	0.00	H
ATOM	732	1HB	PRO	6	12.706	15.819	-3.096	0.00	0.00	H
ATOM	733	2HB	PRO	6	11.358	15.424	-4.160	0.00	0.00	H
ATOM	734	1HG	PRO	6	14.207	14.219	-4.357	0.00	0.00	H
ATOM	735	2HG	PRO	6	12.724	13.350	-4.179	0.00	0.00	H
ATOM	736	1HD	PRO	6	13.686	13.735	-6.697	0.00	0.00	H
ATOM	737	2HD	PRO	6	11.963	13.945	-6.447	0.00	0.00	H
ATOM	738	N	VAL	7	15.287	16.727	-4.527	0.00	0.00	N
ATOM	739	CA	VAL	7	16.473	17.203	-3.754	0.00	0.00	C
ATOM	740	C	VAL	7	17.494	17.972	-4.639	0.00	0.00	C
ATOM	741	O	VAL	7	17.908	19.082	-4.298	0.00	0.00	O
ATOM	742	CB	VAL	7	17.035	15.938	-3.008	0.00	0.00	C

FIG. 8 - 23

31/107

ATOM	743	CG1	VAL	7	18.444	16.107	-2.391	0.00	0.00	C
ATOM	744	CG2	VAL	7	16.123	15.465	-1.846	0.00	0.00	C
ATOM	745	H	VAL	7	15.073	15.735	-4.666	0.00	0.00	H
ATOM	746	HA	VAL	7	16.163	17.974	-3.025	0.00	0.00	H
ATOM	747	HB	VAL	7	17.084	15.114	-3.759	0.00	0.00	H
ATOM	748	1HG1	VAL	7	18.477	16.921	-1.640	0.00	0.00	H
ATOM	749	2HG1	VAL	7	18.791	15.188	-1.879	0.00	0.00	H
ATOM	750	3HG1	VAL	7	19.215	16.339	-3.150	0.00	0.00	H
ATOM	751	1HG2	VAL	7	15.092	15.246	-2.175	0.00	0.00	H
ATOM	752	2HG2	VAL	7	16.496	14.537	-1.371	0.00	0.00	H
ATOM	753	3HG2	VAL	7	16.043	16.224	-1.042	0.00	0.00	H
ATOM	754	N	CYS	8	17.872	17.417	-5.801	0.00	0.00	N
ATOM	755	CA	CYS	8	18.690	18.144	-6.806	0.00	0.00	C
ATOM	756	C	CYS	8	18.141	19.445	-7.453	0.00	0.00	C
ATOM	757	O	CYS	8	18.886	20.369	-7.801	0.00	0.00	O
ATOM	758	CB	CYS	8	19.262	17.142	-7.829	0.00	0.00	C
ATOM	759	SG	CYS	8	20.430	17.943	-8.964	0.00	0.00	S
ATOM	760	H	CYS	8	17.471	16.494	-5.905	0.00	0.00	H
ATOM	761	HA	CYS	8	19.446	18.554	-6.162	0.00	0.00	H
ATOM	762	1HB	CYS	8	19.796	16.318	-7.316	0.00	0.00	H
ATOM	763	2HB	CYS	8	18.456	16.672	-8.422	0.00	0.00	H
ATOM	764	N	HIS	9	16.820	19.532	-7.478	0.00	0.00	N
ATOM	765	CA	HIS	9	16.058	20.785	-7.639	0.00	0.00	C
ATOM	766	C	HIS	9	16.432	21.874	-6.583	0.00	0.00	C
ATOM	767	O	HIS	9	16.545	23.049	-6.912	0.00	0.00	O
ATOM	768	CB	HIS	9	14.568	20.330	-7.633	0.00	0.00	C
ATOM	769	CG	HIS	9	13.315	21.162	-7.325	0.00	0.00	C
ATOM	770	ND1	HIS	9	12.106	20.860	-7.921	0.00	0.00	N
ATOM	771	CD2	HIS	9	13.245	22.449	-6.805	0.00	0.00	C
ATOM	772	CE1	HIS	9	11.426	22.044	-7.783	0.00	0.00	C
ATOM	773	NE2	HIS	9	12.016	23.041	-7.059	0.00	0.00	N
ATOM	774	H	HIS	9	16.398	18.684	-7.112	0.00	0.00	H
ATOM	775	HA	HIS	9	16.314	21.166	-8.612	0.00	0.00	H
ATOM	776	1HB	HIS	9	14.400	19.630	-8.462	0.00	0.00	H

FIG. 8 - 24

32/107

ATOM	777	2HB	HIS	9	14.521	19.702	-6.724	0.00	0.00	H
ATOM	778	HD1	HIS	9	11.953	20.120	-8.627	0.00	0.00	H
ATOM	779	HD2	HIS	9	14.140	22.947	-6.513	0.00	0.00	H
ATOM	780	HE1	HIS	9	10.553	22.263	-8.397	0.00	0.00	H
ATOM	781	HE2	HIS	9	11.653	23.964	-6.782	1.00	0.00	H
ATOM	782	N	LEU	10	16.546	21.463	-5.324	0.00	0.00	N
ATOM	783	CA	LEU	10	16.623	22.400	-4.150	0.00	0.00	C
ATOM	784	C	LEU	10	18.044	22.887	-3.719	0.00	0.00	C
ATOM	785	O	LEU	10	18.250	24.063	-3.425	0.00	0.00	O
ATOM	786	CB	LEU	10	15.738	21.856	-2.997	0.00	0.00	C
ATOM	787	CG	LEU	10	14.210	21.820	-3.281	0.00	0.00	C
ATOM	788	CD1	LEU	10	13.479	21.043	-2.182	0.00	0.00	C
ATOM	789	CD2	LEU	10	13.585	23.223	-3.405	0.00	0.00	C
ATOM	790	H	LEU	10	16.738	20.438	-5.338	0.00	0.00	H
ATOM	791	HA	LEU	10	16.171	23.354	-4.450	0.00	0.00	H
ATOM	792	1HB	LEU	10	16.096	20.843	-2.724	0.00	0.00	H
ATOM	793	2HB	LEU	10	15.908	22.460	-2.084	0.00	0.00	H
ATOM	794	HG	LEU	10	14.032	21.269	-4.225	0.00	0.00	H
ATOM	795	1HD1	LEU	10	13.852	20.005	-2.103	0.00	0.00	H
ATOM	796	2HD1	LEU	10	13.592	21.515	-1.188	0.00	0.00	H
ATOM	797	3HD1	LEU	10	12.394	20.969	-2.390	0.00	0.00	H
ATOM	798	1HD2	LEU	10	13.717	23.821	-2.483	0.00	0.00	H
ATOM	799	2HD2	LEU	10	14.019	23.816	-4.230	0.00	0.00	H
ATOM	800	3HD2	LEU	10	12.498	23.174	-3.604	0.00	0.00	H
ATOM	801	N	GLU	11	19.064	22.049	-3.869	0.00	0.00	N
ATOM	802	CA	GLU	11	20.407	22.421	-4.348	0.00	0.00	C
ATOM	803	C	GLU	11	20.611	23.577	-5.381	0.00	0.00	C
ATOM	804	O	GLU	11	21.633	24.262	-5.396	0.00	0.00	O
ATOM	805	CB	GLU	11	20.904	21.063	-4.913	0.00	0.00	C
ATOM	806	CG	GLU	11	22.043	20.408	-4.142	0.00	0.00	C
ATOM	807	CD	GLU	11	23.392	21.124	-4.207	0.00	0.00	C
ATOM	808	OE1	GLU	11	23.970	21.378	-5.261	0.00	0.00	O
ATOM	809	OE2	GLU	11	23.864	21.448	-2.976	0.00	0.00	O
ATOM	810	H	GLU	11	18.903	21.059	-3.632	1.00	0.00	H

FIG. 8 - 25

ATOM	811	HA	GLU	11	20.992	22.636	-3.467	0.00	0.00	H
ATOM	812	1HB	GLU	11	20.136	20.298	-4.896	0.00	0.00	H
ATOM	813	2HB	GLU	11	21.058	21.108	-5.979	0.00	0.00	H
ATOM	814	1HG	GLU	11	21.626	20.358	-3.123	0.00	0.00	H
ATOM	815	2HG	GLU	11	22.187	19.361	-4.460	0.00	0.00	H
ATOM	816	HE2	GLU	11	24.707	21.898	-3.059	0.00	0.00	H
ATOM	817	N	HIS	12	19.654	23.710	-6.305	0.00	0.00	N
ATOM	818	CA	HIS	12	19.621	24.795	-7.314	0.00	0.00	C
ATOM	819	C	HIS	12	18.222	25.501	-7.324	0.00	0.00	C
ATOM	820	O	HIS	12	17.531	25.513	-8.342	0.00	0.00	O
ATOM	821	CB	HIS	12	20.018	24.166	-8.678	0.00	0.00	C
ATOM	822	CG	HIS	12	21.374	23.448	-8.768	0.00	0.00	C
ATOM	823	ND1	HIS	12	21.457	22.077	-8.581	0.00	0.00	N
ATOM	824	CD2	HIS	12	22.641	24.039	-8.569	0.00	0.00	C
ATOM	825	CE1	HIS	12	22.760	21.953	-8.167	0.00	0.00	C
ATOM	826	NE2	HIS	12	23.566	23.062	-8.204	0.00	0.00	N
ATOM	827	H	HIS	12	18.833	23.143	-6.077	0.00	0.00	H
ATOM	828	HA	HIS	12	20.351	25.575	-7.065	0.00	0.00	H
ATOM	829	1HB	HIS	12	19.212	23.457	-8.930	0.00	0.00	H
ATOM	830	2HB	HIS	12	19.957	24.955	-9.448	0.00	0.00	H
ATOM	831	HD1	HIS	12	20.664	21.458	-8.363	0.00	0.00	H
ATOM	832	HD2	HIS	12	22.804	25.108	-8.488	0.00	0.00	H
ATOM	833	HE1	HIS	12	23.070	21.065	-7.611	0.00	0.00	H
ATOM	834	HE2	HIS	12	24.575	23.149	-8.014	1.00	0.00	H
ATOM	835	N	SER	13	17.780	26.039	-6.174	0.00	0.00	N
ATOM	836	CA	SER	13	16.350	26.389	-5.936	0.00	0.00	C
ATOM	837	C	SER	13	15.727	27.559	-6.737	0.00	0.00	C
ATOM	838	O	SER	13	14.673	27.435	-7.361	0.00	0.00	O
ATOM	839	CB	SER	13	16.065	26.504	-4.420	0.00	0.00	C
ATOM	840	OG	SER	13	14.660	26.423	-4.173	0.00	0.00	O
ATOM	841	H	SER	13	18.257	25.574	-5.415	0.00	0.00	H
ATOM	842	HA	SER	13	15.839	25.519	-6.308	0.00	0.00	H
ATOM	843	1HB	SER	13	16.566	25.711	-3.840	0.00	0.00	H
ATOM	844	2HB	SER	13	16.469	27.457	-4.021	0.00	0.00	H

FIG. 8-25

FIG. 8 - 26

34/107

ATOM	845	HG	SER	13	14.469	26.944	-3.383	0.00	0.00	H
ATOM	846	N	ASN	14	16.510	28.624	-6.799	0.00	0.00	N
ATOM	847	CA	ASN	14	16.400	29.677	-7.858	0.00	0.00	C
ATOM	848	C	ASN	14	16.297	29.171	-9.339	0.00	0.00	C
ATOM	849	O	ASN	14	15.594	29.761	-10.159	0.00	0.00	O
ATOM	850	CB	ASN	14	17.594	30.671	-7.749	0.00	0.00	C
ATOM	851	CG	ASN	14	17.847	31.339	-6.396	0.00	0.00	C
ATOM	852	OD1	ASN	14	16.947	31.797	-5.707	0.00	0.00	O
ATOM	853	ND2	ASN	14	19.081	31.412	-5.971	0.00	0.00	N
ATOM	854	H	ASN	14	17.368	28.309	-6.340	0.00	0.00	H
ATOM	855	HA	ASN	14	15.465	30.229	-7.676	0.00	0.00	H
ATOM	856	1HB	ASN	14	18.516	30.175	-8.109	0.00	0.00	H
ATOM	857	2HB	ASN	14	17.428	31.499	-8.464	0.00	0.00	H
ATOM	858	1HD2	ASN	14	19.174	31.992	-5.131	0.00	0.00	H
ATOM	859	2HD2	ASN	14	19.807	31.146	-6.641	0.00	0.00	H
ATOM	860	N	LEU	15	17.010	28.082	-9.666	0.00	0.00	N
ATOM	861	CA	LEU	15	17.026	27.483	-11.024	0.00	0.00	C
ATOM	862	C	LEU	15	15.940	26.374	-11.308	0.00	0.00	C
ATOM	863	O	LEU	15	15.836	25.890	-12.437	0.00	0.00	O
ATOM	864	CB	LEU	15	18.485	26.990	-11.264	0.00	0.00	C
ATOM	865	CG	LEU	15	19.634	28.013	-10.984	0.00	0.00	C
ATOM	866	CD1	LEU	15	20.288	27.907	-9.590	0.00	0.00	C
ATOM	867	CD2	LEU	15	20.730	27.927	-12.045	0.00	0.00	C
ATOM	868	H	LEU	15	17.481	27.598	-8.889	0.00	0.00	H
ATOM	869	HA	LEU	15	16.835	28.284	-11.757	0.00	0.00	H
ATOM	870	1HB	LEU	15	18.654	26.053	-10.715	0.00	0.00	H
ATOM	871	2HB	LEU	15	18.524	26.675	-12.327	0.00	0.00	H
ATOM	872	HG	LEU	15	19.177	29.022	-11.030	0.00	0.00	H
ATOM	873	1HD1	LEU	15	19.549	27.930	-8.770	0.00	0.00	H
ATOM	874	2HD1	LEU	15	20.900	26.999	-9.470	0.00	0.00	H
ATOM	875	3HD1	LEU	15	20.961	28.769	-9.407	0.00	0.00	H
ATOM	876	1HD2	LEU	15	20.316	28.106	-13.055	0.00	0.00	H
ATOM	877	2HD2	LEU	15	21.512	28.692	-11.883	0.00	0.00	H
ATOM	878	3HD2	LEU	15	21.219	26.935	-12.055	0.00	0.00	H

35/107

FIG. 8 - 27

ATOM	879	N	CYS	16	15.159	25.949	-10.297	0.00	0.00	N
ATOM	880	CA	CYS	16	14.105	24.914	-10.420	0.00	0.00	C
ATOM	881	C	CYS	16	12.694	25.245	-9.812	0.00	0.00	C
ATOM	882	O	CYS	16	11.714	24.559	-10.098	0.00	0.00	O
ATOM	883	CB	CYS	16	14.692	23.688	-9.705	0.00	0.00	C
ATOM	884	SG	CYS	16	16.173	23.049	-10.512	0.00	0.00	S
ATOM	885	H	CYS	16	15.494	26.285	-9.387	0.00	0.00	H
ATOM	886	HA	CYS	16	13.918	24.662	-11.483	0.00	0.00	H
ATOM	887	1HB	CYS	16	14.895	23.907	-8.643	0.00	0.00	H
ATOM	888	2HB	CYS	16	13.942	22.890	-9.705	0.00	0.00	H
TER	889		CYS	16						
HETATM	890	N	NH2	17H	12.497	26.173	-8.893	0.00	0.00	N
HETATM	891	1HN	NH2	17H	11.516	26.453	-8.801	0.00	0.00	H
HETATM	892	2HN	NH2	17H	13.319	26.738	-8.629	0.00	0.00	H
ENDMDL										
MODEL	5									
ATOM	893	N	GLY	1	15.082	13.884	-12.916	0.00	0.00	N
ATOM	894	CA	GLY	1	16.136	14.869	-12.526	0.00	0.00	C
ATOM	895	C	GLY	1	16.474	16.001	-13.521	0.00	0.00	C
ATOM	896	O	GLY	1	16.209	15.876	-14.710	0.00	0.00	O
ATOM	897	1H	GLY	1	15.364	13.403	-13.782	1.00	0.00	H
ATOM	898	2H	GLY	1	14.963	13.191	-12.162	1.00	0.00	H
ATOM	899	3H	GLY	1	14.191	14.377	-13.072	1.00	0.00	H
ATOM	900	1HA	GLY	1	15.848	15.354	-11.578	0.00	0.00	H
ATOM	901	2HA	GLY	1	17.093	14.354	-12.320	0.00	0.00	H
ATOM	902	N	CYS	2	17.112	17.122	-13.166	0.00	0.00	N
ATOM	903	CA	CYS	2	17.567	17.453	-11.785	0.00	0.00	C
ATOM	904	C	CYS	2	16.449	18.211	-10.967	0.00	0.00	C
ATOM	905	O	CYS	2	16.043	17.702	-9.923	0.00	0.00	O
ATOM	906	CB	CYS	2	18.896	18.213	-11.980	0.00	0.00	C
ATOM	907	SG	CYS	2	19.281	19.275	-10.573	0.00	0.00	S
ATOM	908	H	CYS	2	17.652	17.467	-13.961	0.00	0.00	H
ATOM	909	HA	CYS	2	17.826	16.545	-11.208	0.00	0.00	H
ATOM	910	1HB	CYS	2	19.716	17.521	-12.237	0.00	0.00	H

FIG. 8 - 28
36/107

ATOM	911	2HB	CYS	2	18.840	18.911	-12.839	0.00	0.00	H
ATOM	912	N	CYS	3	15.885	19.332	-11.469	0.00	0.00	N
ATOM	913	CA	CYS	3	14.546	19.879	-11.054	0.00	0.00	C
ATOM	914	C	CYS	3	13.364	18.871	-10.769	0.00	0.00	C
ATOM	915	O	CYS	3	12.642	19.013	-9.780	0.00	0.00	O
ATOM	916	CB	CYS	3	14.152	20.800	-12.237	0.00	0.00	C
ATOM	917	SG	CYS	3	15.130	22.318	-12.370	0.00	0.00	S
ATOM	918	H	CYS	3	16.273	19.567	-12.388	0.00	0.00	H
ATOM	919	HA	CYS	3	14.634	20.513	-10.136	0.00	0.00	H
ATOM	920	1HB	CYS	3	14.186	20.273	-13.212	0.00	0.00	H
ATOM	921	2HB	CYS	3	13.093	21.095	-12.140	0.00	0.00	H
ATOM	922	N	SER	4	13.180	17.871	-11.643	0.00	0.00	N
ATOM	923	CA	SER	4	12.209	16.760	-11.468	0.00	0.00	C
ATOM	924	C	SER	4	12.602	15.587	-10.501	0.00	0.00	C
ATOM	925	O	SER	4	11.791	14.692	-10.261	0.00	0.00	O
ATOM	926	CB	SER	4	11.886	16.286	-12.906	0.00	0.00	C
ATOM	927	OG	SER	4	13.012	15.768	-13.627	0.00	0.00	O
ATOM	928	H	SER	4	13.887	17.821	-12.370	0.00	0.00	H
ATOM	929	HA	SER	4	11.267	17.167	-11.049	0.00	0.00	H
ATOM	930	1HB	SER	4	11.103	15.516	-12.855	0.00	0.00	H
ATOM	931	2HB	SER	4	11.421	17.115	-13.481	0.00	0.00	H
ATOM	932	HG	SER	4	12.782	15.844	-14.567	0.00	0.00	H
ATOM	933	N	ASN	5	13.792	15.610	-9.877	0.00	0.00	N
ATOM	934	CA	ASN	5	13.986	15.032	-8.530	0.00	0.00	C
ATOM	935	C	ASN	5	13.677	16.139	-7.456	0.00	0.00	C
ATOM	936	O	ASN	5	14.216	17.242	-7.607	0.00	0.00	O
ATOM	937	CB	ASN	5	15.486	14.688	-8.382	0.00	0.00	C
ATOM	938	CG	ASN	5	16.072	13.527	-9.162	0.00	0.00	C
ATOM	939	OD1	ASN	5	15.560	13.003	-10.144	0.00	0.00	O
ATOM	940	ND2	ASN	5	17.223	13.130	-8.710	0.00	0.00	N
ATOM	941	H	ASN	5	14.376	16.423	-10.107	0.00	0.00	H
ATOM	942	HA	ASN	5	13.363	14.128	-8.371	0.00	0.00	H
ATOM	943	1HB	ASN	5	16.122	15.583	-8.534	0.00	0.00	H
ATOM	944	2HB	ASN	5	15.637	14.439	-7.329	0.00	0.00	H

FIG. 8 - 29

37/107

ATOM	945	1HD2	ASN	5	17.397	12.149	-8.926	0.00	0.00	H
ATOM	946	2HD2	ASN	5	17.466	13.612	-7.838	0.00	0.00	H
ATOM	947	N	PRO	6	12.941	15.919	-6.333	0.00	0.00	N
ATOM	948	CA	PRO	6	12.804	16.952	-5.258	0.00	0.00	C
ATOM	949	C	PRO	6	14.084	17.597	-4.627	0.00	0.00	C
ATOM	950	O	PRO	6	14.104	18.780	-4.289	0.00	0.00	O
ATOM	951	CB	PRO	6	11.845	16.282	-4.265	0.00	0.00	C
ATOM	952	CG	PRO	6	11.813	14.800	-4.593	0.00	0.00	C
ATOM	953	CD	PRO	6	12.291	14.635	-6.013	0.00	0.00	C
ATOM	954	HA	PRO	6	12.288	17.810	-5.680	0.00	0.00	H
ATOM	955	1HB	PRO	6	12.099	16.499	-3.213	0.00	0.00	H
ATOM	956	2HB	PRO	6	10.819	16.634	-4.398	0.00	0.00	H
ATOM	957	1HG	PRO	6	12.502	14.277	-3.972	0.00	0.00	H
ATOM	958	2HG	PRO	6	10.832	14.329	-4.400	0.00	0.00	H
ATOM	959	1HD	PRO	6	12.945	13.756	-6.146	0.00	0.00	H
ATOM	960	2HD	PRO	6	11.407	14.435	-6.603	0.00	0.00	H
ATOM	961	N	VAL	7	15.163	16.828	-4.561	0.00	0.00	N
ATOM	962	CA	VAL	7	16.453	17.200	-3.940	0.00	0.00	C
ATOM	963	C	VAL	7	17.330	18.055	-4.875	0.00	0.00	C
ATOM	964	O	VAL	7	17.677	19.181	-4.527	0.00	0.00	O
ATOM	965	CB	VAL	7	17.105	15.830	-3.529	0.00	0.00	C
ATOM	966	CG1	VAL	7	18.549	15.947	-3.014	0.00	0.00	C
ATOM	967	CG2	VAL	7	16.328	15.047	-2.452	0.00	0.00	C
ATOM	968	H	VAL	7	15.060	15.928	-5.016	0.00	0.00	H
ATOM	969	HA	VAL	7	16.276	17.884	-3.093	0.00	0.00	H
ATOM	970	HB	VAL	7	17.128	15.187	-4.439	0.00	0.00	H
ATOM	971	1HG1	VAL	7	19.221	16.381	-3.775	0.00	0.00	H
ATOM	972	2HG1	VAL	7	18.602	16.587	-2.113	0.00	0.00	H
ATOM	973	3HG1	VAL	7	18.968	14.958	-2.752	0.00	0.00	H
ATOM	974	1HG2	VAL	7	15.296	14.824	-2.777	0.00	0.00	H
ATOM	975	2HG2	VAL	7	16.804	14.074	-2.233	0.00	0.00	H
ATOM	976	3HG2	VAL	7	16.261	15.618	-1.508	0.00	0.00	H
ATOM	977	N	CYS	8	17.692	17.538	-6.058	0.00	0.00	N
ATOM	978	CA	CYS	8	18.505	18.311	-7.037	0.00	0.00	C

FIG. 8 - 30

38/107

ATOM	979	C	CYS	8	17.930	19.620	-7.651	0.00	0.00	C
ATOM	980	O	CYS	8	18.644	20.560	-8.009	0.00	0.00	O
ATOM	981	CB	CYS	8	19.132	17.343	-8.059	0.00	0.00	C
ATOM	982	SG	CYS	8	20.270	18.203	-9.180	0.00	0.00	S
ATOM	983	H	CYS	8	17.500	16.540	-6.066	0.00	0.00	H
ATOM	984	HA	CYS	8	19.241	18.738	-6.376	0.00	0.00	H
ATOM	985	1HB	CYS	8	19.705	16.550	-7.542	0.00	0.00	H
ATOM	986	2HB	CYS	8	18.354	16.836	-8.658	0.00	0.00	H
ATOM	987	N	HIS	9	16.613	19.709	-7.594	0.00	0.00	N
ATOM	988	CA	HIS	9	15.829	20.966	-7.622	0.00	0.00	C
ATOM	989	C	HIS	9	16.313	22.029	-6.596	0.00	0.00	C
ATOM	990	O	HIS	9	16.459	23.204	-6.893	0.00	0.00	O
ATOM	991	CB	HIS	9	14.357	20.533	-7.434	0.00	0.00	C
ATOM	992	CG	HIS	9	13.062	21.206	-7.022	0.00	0.00	C
ATOM	993	ND1	HIS	9	11.875	20.890	-7.656	0.00	0.00	N
ATOM	994	CD2	HIS	9	13.008	22.497	-6.579	0.00	0.00	C
ATOM	995	CE1	HIS	9	11.207	22.088	-7.580	0.00	0.00	C
ATOM	996	NE2	HIS	9	11.803	23.110	-6.894	0.00	0.00	N
ATOM	997	H	HIS	9	16.214	18.808	-7.327	0.00	0.00	H
ATOM	998	HA	HIS	9	15.878	21.364	-8.592	0.00	0.00	H
ATOM	999	1HB	HIS	9	14.231	19.530	-7.657	0.00	0.00	H
ATOM	1000	2HB	HIS	9	14.526	20.220	-6.414	0.00	0.00	H
ATOM	1001	HD1	HIS	9	11.746	20.133	-8.348	0.00	0.00	H
ATOM	1002	HD2	HIS	9	13.974	22.917	-6.473	0.00	0.00	H
ATOM	1003	HE1	HIS	9	10.344	22.294	-8.214	0.00	0.00	H
ATOM	1004	HE2	HIS	9	11.459	24.056	-6.675	1.00	0.00	H
ATOM	1005	N	LEU	10	16.420	21.548	-5.369	0.00	0.00	N
ATOM	1006	CA	LEU	10	16.582	22.410	-4.148	0.00	0.00	C
ATOM	1007	C	LEU	10	18.038	22.815	-3.751	0.00	0.00	O
ATOM	1008	O	LEU	10	18.301	23.969	-3.412	0.00	0.00	C
ATOM	1009	CB	LEU	10	15.718	21.858	-2.983	0.00	0.00	C
ATOM	1010	CG	LEU	10	14.178	21.911	-3.196	0.00	0.00	C
ATOM	1011	CD1	LEU	10	13.455	21.184	-2.059	0.00	0.00	C
ATOM	1012	CD2	LEU	10	13.623	23.345	-3.307	0.00	0.00	C

FIG. 8 - 31

39/107

ATOM	1013	H	LEU	10	16.417	20.498	-5.496	0.00	0.00	H
ATOM	1014	HA	LEU	10	16.166	23.398	-4.383	0.00	0.00	H
ATOM	1015	1HB	LEU	10	16.031	20.818	-2.770	0.00	0.00	H
ATOM	1016	2HB	LEU	10	15.958	22.412	-2.054	0.00	0.00	H
ATOM	1017	HG	LEU	10	13.932	21.363	-4.124	0.00	0.00	H
ATOM	1018	1HD1	LEU	10	13.784	20.131	-1.979	0.00	0.00	H
ATOM	1019	2HD1	LEU	10	13.631	21.663	-1.078	0.00	0.00	H
ATOM	1020	3HD1	LEU	10	12.362	21.159	-2.224	0.00	0.00	H
ATOM	1021	1HD2	LEU	10	13.845	23.949	-2.407	0.00	0.00	H
ATOM	1022	2HD2	LEU	10	14.035	23.899	-4.169	0.00	0.00	H
ATOM	1023	3HD2	LEU	10	12.524	23.352	-3.440	0.00	0.00	H
ATOM	1024	N	GLU	11	19.012	21.934	-3.962	0.00	0.00	N
ATOM	1025	CA	GLU	11	20.391	22.280	-4.358	0.00	0.00	C
ATOM	1026	C	GLU	11	20.649	23.471	-5.340	0.00	0.00	C
ATOM	1027	O	GLU	11	21.649	24.182	-5.234	0.00	0.00	O
ATOM	1028	CB	GLU	11	20.836	20.951	-5.020	0.00	0.00	C
ATOM	1029	CG	GLU	11	21.004	19.711	-4.119	0.00	0.00	C
ATOM	1030	CD	GLU	11	21.969	18.646	-4.628	0.00	0.00	C
ATOM	1031	OE1	GLU	11	21.794	18.014	-5.665	0.00	0.00	O
ATOM	1032	OE2	GLU	11	23.035	18.477	-3.804	0.00	0.00	O
ATOM	1033	H	GLU	11	18.786	20.936	-3.841	1.00	0.00	H
ATOM	1034	HA	GLU	11	20.986	22.488	-3.459	0.00	0.00	H
ATOM	1035	1HB	GLU	11	20.180	20.682	-5.861	0.00	0.00	H
ATOM	1036	2HB	GLU	11	21.768	21.165	-5.512	0.00	0.00	H
ATOM	1037	1HG	GLU	11	21.249	20.053	-3.109	0.00	0.00	H
ATOM	1038	2HG	GLU	11	20.033	19.222	-3.992	0.00	0.00	H
ATOM	1039	HE2	GLU	11	23.611	17.799	-4.162	0.00	0.00	H
ATOM	1040	N	HIS	12	19.767	23.635	-6.331	0.00	0.00	N
ATOM	1041	CA	HIS	12	19.742	24.844	-7.192	0.00	0.00	C
ATOM	1042	C	HIS	12	18.316	25.480	-7.231	0.00	0.00	C
ATOM	1043	O	HIS	12	17.642	25.479	-8.261	0.00	0.00	O
ATOM	1044	CB	HIS	12	20.337	24.461	-8.565	0.00	0.00	C
ATOM	1045	CG	HIS	12	21.854	24.244	-8.603	0.00	0.00	C
ATOM	1046	ND1	HIS	12	22.445	23.004	-8.427	0.00	0.00	N

FIG. 8 - 32

40/107

ATOM	1047	CD2	HIS	12	22.845	25.248	-8.632	0.00	0.00	C
ATOM	1048	CE1	HIS	12	23.767	23.359	-8.306	0.00	0.00	C
ATOM	1049	NE2	HIS	12	24.104	24.680	-8.455	0.00	0.00	N
ATOM	1050	H	HIS	12	18.959	23.015	-6.188	0.00	0.00	H
ATOM	1051	HA	HIS	12	20.385	25.630	-6.778	0.00	0.00	H
ATOM	1052	1HB	HIS	12	19.796	23.564	-8.919	0.00	0.00	H
ATOM	1053	2HB	HIS	12	20.086	25.263	-9.276	0.00	0.00	H
ATOM	1054	HD1	HIS	12	21.987	22.116	-8.195	0.00	0.00	H
ATOM	1055	HD2	HIS	12	22.637	26.312	-8.698	0.00	0.00	H
ATOM	1056	HE1	HIS	12	24.520	22.618	-8.029	0.00	0.00	H
ATOM	1057	HE2	HIS	12	25.031	25.128	-8.440	1.00	0.00	H
ATOM	1058	N	SER	13	17.856	25.996	-6.080	0.00	0.00	N
ATOM	1059	CA	SER	13	16.426	26.340	-5.842	0.00	0.00	C
ATOM	1060	C	SER	13	15.797	27.491	-6.673	0.00	0.00	C
ATOM	1061	O	SER	13	14.748	27.348	-7.299	0.00	0.00	O
ATOM	1062	CB	SER	13	16.170	26.508	-4.325	0.00	0.00	C
ATOM	1063	OG	SER	13	14.769	26.465	-4.051	0.00	0.00	O
ATOM	1064	H	SER	13	18.324	25.522	-5.322	0.00	0.00	H
ATOM	1065	HA	SER	13	15.916	25.446	-6.164	0.00	0.00	H
ATOM	1066	1HB	SER	13	16.665	25.719	-3.731	0.00	0.00	H
ATOM	1067	2HB	SER	13	16.600	27.462	-3.961	0.00	0.00	H
ATOM	1068	HG	SER	13	14.622	26.889	-3.195	0.00	0.00	H
ATOM	1069	N	ASN	14	16.571	28.563	-6.751	0.00	0.00	N
ATOM	1070	CA	ASN	14	16.469	29.589	-7.836	0.00	0.00	C
ATOM	1071	C	ASN	14	16.367	29.063	-9.312	0.00	0.00	C
ATOM	1072	O	ASN	14	15.690	29.684	-10.132	0.00	0.00	O
ATOM	1073	CB	ASN	14	17.670	30.553	-7.611	0.00	0.00	C
ATOM	1074	CG	ASN	14	17.676	31.827	-8.458	0.00	0.00	C
ATOM	1075	OD1	ASN	14	17.103	32.843	-8.095	0.00	0.00	O
ATOM	1076	ND2	ASN	14	18.319	31.822	-9.599	0.00	0.00	N
ATOM	1077	H	ASN	14	17.433	28.239	-6.305	0.00	0.00	H
ATOM	1078	HA	ASN	14	15.535	30.150	-7.666	0.00	0.00	H
ATOM	1079	1HB	ASN	14	17.677	30.902	-6.560	0.00	0.00	H
ATOM	1080	2HB	ASN	14	18.633	30.021	-7.735	0.00	0.00	H

FIG. 8 - 33

41/107

ATOM	1081	1HD2	ASN	14	18.158	32.675	-10.143	0.00	0.00	H
ATOM	1082	2HD2	ASN	14	18.587	30.907	-9.960	0.00	0.00	H
ATOM	1083	N	LEU	15	17.027	27.943	-9.649	0.00	0.00	N
ATOM	1084	CA	LEU	15	16.908	27.324	-11.003	0.00	0.00	C
ATOM	1085	C	LEU	15	15.749	26.276	-11.218	0.00	0.00	C
ATOM	1086	O	LEU	15	15.544	25.822	-12.347	0.00	0.00	O
ATOM	1087	CB	LEU	15	18.298	26.763	-11.422	0.00	0.00	C
ATOM	1088	CG	LEU	15	19.535	27.704	-11.332	0.00	0.00	C
ATOM	1089	CD1	LEU	15	20.795	26.962	-11.794	0.00	0.00	C
ATOM	1090	CD2	LEU	15	19.379	28.993	-12.158	0.00	0.00	C
ATOM	1091	H	LEU	15	17.367	27.407	-8.836	0.00	0.00	H
ATOM	1092	HA	LEU	15	16.678	28.125	-11.719	0.00	0.00	H
ATOM	1093	1HB	LEU	15	18.487	25.848	-10.833	0.00	0.00	H
ATOM	1094	2HB	LEU	15	18.210	26.404	-12.467	0.00	0.00	H
ATOM	1095	HG	LEU	15	19.683	27.998	-10.274	0.00	0.00	H
ATOM	1096	1HD1	LEU	15	20.963	26.030	-11.231	0.00	0.00	H
ATOM	1097	2HD1	LEU	15	20.732	26.688	-12.865	0.00	0.00	H
ATOM	1098	3HD1	LEU	15	21.698	27.589	-11.672	0.00	0.00	H
ATOM	1099	1HD2	LEU	15	19.217	28.790	-13.234	0.00	0.00	H
ATOM	1100	2HD2	LEU	15	18.518	29.601	-11.820	0.00	0.00	H
ATOM	1101	3HD2	LEU	15	20.265	29.650	-12.083	0.00	0.00	H
ATOM	1102	N	CYS	16	15.005	25.869	-10.171	0.00	0.00	N
ATOM	1103	CA	CYS	16	13.876	24.908	-10.270	0.00	0.00	C
ATOM	1104	C	CYS	16	12.524	25.301	-9.571	0.00	0.00	C
ATOM	1105	O	CYS	16	11.492	24.684	-9.821	0.00	0.00	O
ATOM	1106	CB	CYS	16	14.421	23.618	-9.640	0.00	0.00	C
ATOM	1107	SG	CYS	16	15.790	22.911	-10.579	0.00	0.00	S
ATOM	1108	H	CYS	16	15.385	26.161	-9.268	0.00	0.00	H
ATOM	1109	HA	CYS	16	13.612	24.709	-11.329	0.00	0.00	H
ATOM	1110	1HB	CYS	16	14.721	23.789	-8.592	0.00	0.00	H
ATOM	1111	2HB	CYS	16	13.622	22.870	-9.604	0.00	0.00	H
TER	1112		CYS	16						
HETATM	1113	N	NH2	17H	12.434	26.204	-8.613	0.00	0.00	N
HETATM	1114	1HN	NH2	17H	11.480	26.549	-8.471	0.00	0.00	H

FIG. 8 - 34

42/107

HETATM	1115	2HN	NH2	17H	13.304	26.706	-8.373	0.00	0.00	H
ENDMDL										
MODEL	6									
ATOM	1116	N	GLY	1	14.719	14.941	-15.415	0.00	0.00	N
ATOM	1117	CA	GLY	1	15.699	16.059	-15.219	0.00	0.00	C
ATOM	1118	C	GLY	1	16.046	16.375	-13.735	0.00	0.00	C
ATOM	1119	O	GLY	1	15.733	15.583	-12.847	0.00	0.00	O
ATOM	1120	1H	GLY	1	15.101	14.075	-15.010	1.00	0.00	H
ATOM	1121	2H	GLY	1	13.832	15.176	-14.948	1.00	0.00	H
ATOM	1122	3H	GLY	1	14.551	14.804	-16.422	1.00	0.00	H
ATOM	1123	1HA	GLY	1	16.644	15.832	-15.752	0.00	0.00	H
ATOM	1124	2HA	GLY	1	15.308	16.981	-15.693	0.00	0.00	H
ATOM	1125	N	CYS	2	16.680	17.524	-13.443	0.00	0.00	N
ATOM	1126	CA	CYS	2	17.113	17.846	-12.049	0.00	0.00	C
ATOM	1127	C	CYS	2	16.008	18.625	-11.227	0.00	0.00	C
ATOM	1128	O	CYS	2	15.642	18.187	-10.136	0.00	0.00	O
ATOM	1129	CB	CYS	2	18.465	18.570	-12.235	0.00	0.00	C
ATOM	1130	SG	CYS	2	18.896	19.621	-10.838	0.00	0.00	S
ATOM	1131	H	CYS	2	17.228	17.934	-14.208	0.00	0.00	H
ATOM	1132	HA	CYS	2	17.328	16.923	-11.474	0.00	0.00	H
ATOM	1133	1HB	CYS	2	19.269	17.860	-12.493	0.00	0.00	H
ATOM	1134	2HB	CYS	2	18.418	19.280	-13.084	0.00	0.00	H
ATOM	1135	N	CYS	3	15.425	19.719	-11.766	0.00	0.00	N
ATOM	1136	CA	CYS	3	14.112	20.302	-11.320	0.00	0.00	C
ATOM	1137	C	CYS	3	12.890	19.323	-11.127	0.00	0.00	C
ATOM	1138	O	CYS	3	12.071	19.555	-10.237	0.00	0.00	O
ATOM	1139	CB	CYS	3	13.805	21.352	-12.415	0.00	0.00	C
ATOM	1140	SG	CYS	3	12.295	22.321	-12.128	0.00	0.00	S
ATOM	1141	H	CYS	3	15.808	19.952	-12.687	0.00	0.00	H
ATOM	1142	HA	CYS	3	14.244	20.856	-10.351	0.00	0.00	H
ATOM	1143	1HB	CYS	3	14.636	22.079	-12.513	0.00	0.00	H
ATOM	1144	2HB	CYS	3	13.701	20.882	-13.412	0.00	0.00	H
ATOM	1145	N	SER	4	12.768	18.236	-11.914	0.00	0.00	N
ATOM	1146	CA	SER	4	11.796	17.143	-11.668	0.00	0.00	C

FIG. 8 - 35

43/107

ATOM	1147	C	SER	4	12.018	16.211	-10.426	0.00	0.00	C
ATOM	1148	O	SER	4	11.072	15.575	-9.963	0.00	0.00	O
ATOM	1149	CB	SER	4	11.798	16.349	-12.992	0.00	0.00	C
ATOM	1150	OG	SER	4	12.972	15.552	-13.182	0.00	0.00	O
ATOM	1151	H	SER	4	13.538	18.017	-12.543	0.00	0.00	H
ATOM	1152	HA	SER	4	10.793	17.588	-11.535	0.00	0.00	H
ATOM	1153	1HB	SER	4	10.928	15.693	-12.973	0.00	0.00	H
ATOM	1154	2HB	SER	4	11.618	17.006	-13.868	0.00	0.00	H
ATOM	1155	HG	SER	4	13.114	15.057	-12.358	0.00	0.00	H
ATOM	1156	N	ASN	5	13.239	16.143	-9.876	0.00	0.00	N
ATOM	1157	CA	ASN	5	13.530	15.427	-8.616	0.00	0.00	C
ATOM	1158	C	ASN	5	13.322	16.362	-7.371	0.00	0.00	C
ATOM	1159	O	ASN	5	13.540	17.572	-7.492	0.00	0.00	O
ATOM	1160	CB	ASN	5	15.038	15.047	-8.653	0.00	0.00	C
ATOM	1161	CG	ASN	5	15.526	14.030	-9.674	0.00	0.00	C
ATOM	1162	OD1	ASN	5	14.906	13.695	-10.676	0.00	0.00	O
ATOM	1163	ND2	ASN	5	16.674	13.481	-9.392	0.00	0.00	N
ATOM	1164	H	ASN	5	13.962	16.717	-10.318	0.00	0.00	H
ATOM	1165	HA	ASN	5	12.892	14.522	-8.510	0.00	0.00	H
ATOM	1166	1HB	ASN	5	15.692	15.944	-8.681	0.00	0.00	H
ATOM	1167	2HB	ASN	5	15.264	14.591	-7.688	0.00	0.00	H
ATOM	1168	1HD2	ASN	5	16.762	12.586	-9.864	0.00	0.00	H
ATOM	1169	2HD2	ASN	5	17.036	13.716	-8.462	0.00	0.00	H
ATOM	1170	N	PRO	6	13.015	15.870	-6.141	0.00	0.00	N
ATOM	1171	CA	PRO	6	13.007	16.740	-4.926	0.00	0.00	C
ATOM	1172	C	PRO	6	14.354	17.360	-4.424	0.00	0.00	C
ATOM	1173	O	PRO	6	14.358	18.349	-3.696	0.00	0.00	O
ATOM	1174	CB	PRO	6	12.261	15.855	-3.915	0.00	0.00	C
ATOM	1175	CG	PRO	6	12.418	14.416	-4.376	0.00	0.00	C
ATOM	1176	CD	PRO	6	12.658	14.461	-5.886	0.00	0.00	C
ATOM	1177	HA	PRO	6	12.390	17.619	-5.127	0.00	0.00	H
ATOM	1178	1HB	PRO	6	12.583	16.027	-2.872	0.00	0.00	H
ATOM	1179	2HB	PRO	6	11.188	16.056	-3.929	0.00	0.00	H
ATOM	1180	1HG	PRO	6	13.268	14.005	-3.836	0.00	0.00	H

FIG. 8 - 36

ATOM	1181	2HG	PRO	6	11.564	13.776	-4.095	0.00	0.00	H
ATOM	1182	1HD	PRO	6	13.446	13.752	-6.185	0.00	0.00	H
ATOM	1183	2HD	PRO	6	11.772	14.172	-6.478	0.00	0.00	H
ATOM	1184	N	VAL	7	15.492	16.818	-4.851	0.00	0.00	N
ATOM	1185	CA	VAL	7	16.818	17.054	-4.230	0.00	0.00	C
ATOM	1186	C	VAL	7	17.675	17.990	-5.105	0.00	0.00	C
ATOM	1187	O	VAL	7	18.032	19.091	-4.682	0.00	0.00	C
ATOM	1188	CB	VAL	7	17.431	15.623	-4.010	0.00	0.00	C
ATOM	1189	CG1	VAL	7	18.895	15.634	-3.536	0.00	0.00	C
ATOM	1190	CG2	VAL	7	16.658	14.747	-3.007	0.00	0.00	C
ATOM	1191	H	VAL	7	15.332	15.947	-5.349	0.00	0.00	H
ATOM	1192	HA	VAL	7	16.717	17.631	-3.294	0.00	0.00	H
ATOM	1193	HB	VAL	7	17.397	15.090	-4.988	0.00	0.00	H
ATOM	1194	1HG1	VAL	7	19.557	16.139	-4.262	0.00	0.00	H
ATOM	1195	2HG1	VAL	7	18.997	16.154	-2.566	0.00	0.00	H
ATOM	1196	3HG1	VAL	7	19.288	14.608	-3.415	0.00	0.00	H
ATOM	1197	1HG2	VAL	7	15.610	14.597	-3.323	0.00	0.00	H
ATOM	1198	2HG2	VAL	7	17.106	13.740	-2.917	0.00	0.00	H
ATOM	1199	3HG2	VAL	7	16.638	15.205	-2.002	0.00	0.00	H
ATOM	1200	N	CYS	8	17.999	17.574	-6.338	0.00	0.00	N
ATOM	1201	CA	CYS	8	18.726	18.441	-7.296	0.00	0.00	C
ATOM	1202	C	CYS	8	18.083	19.776	-7.751	0.00	0.00	C
ATOM	1203	O	CYS	8	18.756	20.785	-7.989	0.00	0.00	O
ATOM	1204	CB	CYS	8	19.282	17.585	-8.452	0.00	0.00	C
ATOM	1205	SG	CYS	8	20.175	18.602	-9.658	0.00	0.00	S
ATOM	1206	H	CYS	8	17.686	16.619	-6.492	0.00	0.00	H
ATOM	1207	HA	CYS	8	19.498	18.819	-6.651	0.00	0.00	H
ATOM	1208	1HB	CYS	8	19.970	16.807	-8.068	0.00	0.00	H
ATOM	1209	2HB	CYS	8	18.469	17.053	-8.981	0.00	0.00	H
ATOM	1210	N	HIS	9	16.763	19.766	-7.728	0.00	0.00	N
ATOM	1211	CA	HIS	9	15.902	20.956	-7.678	0.00	0.00	C
ATOM	1212	C	HIS	9	16.252	21.937	-6.517	0.00	0.00	C
ATOM	1213	O	HIS	9	16.286	23.142	-6.729	0.00	0.00	O
ATOM	1214	CB	HIS	9	14.464	20.367	-7.620	0.00	0.00	C

45/107

FIG. 8 - 37

ATOM	1215	CG	HIS	9	13.181	21.026	-7.124	0.00	0.00	C
ATOM	1216	ND1	HIS	9	11.969	20.593	-7.613	0.00	0.00	N
ATOM	1217	CD2	HIS	9	13.037	22.317	-6.631	0.00	0.00	C
ATOM	1218	CE1	HIS	9	11.225	21.734	-7.506	0.00	0.00	C
ATOM	1219	NE2	HIS	9	11.743	22.785	-6.805	0.00	0.00	N
ATOM	1220	H	HIS	9	16.424	18.832	-7.509	0.00	0.00	H
ATOM	1221	HA	HIS	9	16.040	21.472	-8.610	0.00	0.00	H
ATOM	1222	1HB	HIS	9	14.287	19.728	-8.496	0.00	0.00	H
ATOM	1223	2HB	HIS	9	14.539	19.668	-6.766	0.00	0.00	H
ATOM	1224	HD1	HIS	9	11.849	19.859	-8.331	0.00	0.00	H
ATOM	1225	HD2	HIS	9	13.902	22.910	-6.443	0.00	0.00	H
ATOM	1226	HE1	HIS	9	10.573	21.978	-8.339	0.00	0.00	H
ATOM	1227	HE2	HIS	9	11.304	23.665	-6.498	1.00	0.00	H
ATOM	1228	N	LEU	10	16.386	21.410	-5.303	0.00	0.00	N
ATOM	1229	CA	LEU	10	16.451	22.245	-4.049	0.00	0.00	C
ATOM	1230	C	LEU	10	17.855	22.700	-3.558	0.00	0.00	C
ATOM	1231	O	LEU	10	18.024	23.830	-3.104	0.00	0.00	O
ATOM	1232	CB	LEU	10	15.562	21.628	-2.938	0.00	0.00	C
ATOM	1233	CG	LEU	10	14.037	21.642	-3.222	0.00	0.00	C
ATOM	1234	CD1	LEU	10	13.272	20.932	-2.099	0.00	0.00	C
ATOM	1235	CD2	LEU	10	13.444	23.061	-3.361	0.00	0.00	C
ATOM	1236	H	LEU	10	16.718	20.427	-5.418	0.00	0.00	H
ATOM	1237	HA	LEU	10	16.006	23.226	-4.274	0.00	0.00	H
ATOM	1238	1HB	LEU	10	15.896	20.589	-2.745	0.00	0.00	H
ATOM	1239	2HB	LEU	10	15.743	22.157	-1.981	0.00	0.00	H
ATOM	1240	HG	LEU	10	13.881	21.067	-4.157	0.00	0.00	H
ATOM	1241	1HD1	LEU	10	13.649	19.910	-1.920	0.00	0.00	H
ATOM	1242	2HD1	LEU	10	13.346	21.472	-1.137	0.00	0.00	H
ATOM	1243	3HD1	LEU	10	12.196	20.833	-2.338	0.00	0.00	H
ATOM	1244	1HD2	LEU	10	13.592	23.663	-2.444	0.00	0.00	H
ATOM	1245	2HD2	LEU	10	13.887	23.643	-4.188	0.00	0.00	H
ATOM	1246	3HD2	LEU	10	12.354	23.035	-3.555	0.00	0.00	H
ATOM	1247	N	GLU	11	18.880	21.879	-3.779	0.00	0.00	N
ATOM	1248	CA	GLU	11	20.245	22.318	-4.082	0.00	0.00	C

46/107

FIG. 8 - 38

ATOM	1249	C	GLU	11	20.493	23.583	-4.964	0.00	0.00	C
ATOM	1250	O	GLU	11	21.467	24.316	-4.792	0.00	0.00	O
ATOM	1251	CB	GLU	11	20.791	21.037	-4.731	0.00	0.00	C
ATOM	1252	CG	GLU	11	21.444	19.943	-3.873	0.00	0.00	C
ATOM	1253	CD	GLU	11	22.001	18.769	-4.686	0.00	0.00	C
ATOM	1254	OE1	GLU	11	22.176	18.803	-5.906	0.00	0.00	O
ATOM	1255	OE2	GLU	11	22.273	17.688	-3.903	0.00	0.00	O
ATOM	1256	H	GLU	11	18.702	20.866	-3.734	1.00	0.00	H
ATOM	1257	HA	GLU	11	20.786	22.441	-3.184	0.00	0.00	H
ATOM	1258	1HB	GLU	11	20.036	20.569	-5.334	0.00	0.00	H
ATOM	1259	2HB	GLU	11	21.465	21.324	-5.500	0.00	0.00	H
ATOM	1260	1HG	GLU	11	22.246	20.392	-3.277	0.00	0.00	H
ATOM	1261	2HG	GLU	11	20.692	19.573	-3.160	0.00	0.00	H
ATOM	1262	HE2	GLU	11	22.616	16.958	-4.419	0.00	0.00	H
ATOM	1263	N	HIS	12	19.663	23.745	-5.997	0.00	0.00	N
ATOM	1264	CA	HIS	12	19.795	24.738	-7.034	0.00	0.00	C
ATOM	1265	C	HIS	12	18.371	25.312	-7.326	0.00	0.00	C
ATOM	1266	O	HIS	12	17.772	25.069	-8.374	0.00	0.00	O
ATOM	1267	CB	HIS	12	20.393	23.956	-8.187	0.00	0.00	C
ATOM	1268	CG	HIS	12	21.692	23.137	-8.104	0.00	0.00	C
ATOM	1269	ND1	HIS	12	21.700	21.763	-8.263	0.00	0.00	N
ATOM	1270	CD2	HIS	12	22.952	23.581	-7.658	0.00	0.00	C
ATOM	1271	CE1	HIS	12	22.977	21.459	-7.857	0.00	0.00	C
ATOM	1272	NE2	HIS	12	23.812	22.493	-7.510	0.00	0.00	N
ATOM	1273	H	HIS	12	19.001	23.031	-6.247	0.00	0.00	H
ATOM	1274	HA	HIS	12	20.477	25.537	-6.812	0.00	0.00	H
ATOM	1275	1HB	HIS	12	19.564	23.416	-8.609	0.00	0.00	H
ATOM	1276	2HB	HIS	12	20.513	24.720	-8.897	0.00	0.00	H
ATOM	1277	HD1	HIS	12	20.876	21.151	-8.337	0.00	0.00	H
ATOM	1278	HD2	HIS	12	23.163	24.601	-7.346	0.00	0.00	H
ATOM	1279	HE1	HIS	12	23.276	20.421	-7.691	0.00	0.00	H
ATOM	1280	HE2	HIS	12	24.800	22.470	-7.220	1.00	0.00	H
ATOM	1281	N	SER	13	17.775	25.970	-6.339	0.00	0.00	N
ATOM	1282	CA	SER	13	16.348	26.376	-6.377	0.00	0.00	C

47/107

FIG. 8 - 39

ATOM	1283	C	SER	13	15.968	27.531	-7.346	0.00	0.00	C
ATOM	1284	O	SER	13	14.904	27.518	-7.963	0.00	0.00	O
ATOM	1285	CB	SER	13	15.834	26.584	-4.933	0.00	0.00	C
ATOM	1286	OG	SER	13	16.463	27.697	-4.292	0.00	0.00	O
ATOM	1287	H	SER	13	18.132	25.566	-5.494	0.00	0.00	H
ATOM	1288	HA	SER	13	15.872	25.484	-6.786	0.00	0.00	H
ATOM	1289	1HB	SER	13	14.735	26.724	-4.927	0.00	0.00	H
ATOM	1290	2HB	SER	13	16.011	25.676	-4.323	0.00	0.00	H
ATOM	1291	HG	SER	13	16.095	28.512	-4.653	0.00	0.00	H
ATOM	1292	N	ASN	14	16.947	28.406	-7.567	0.00	0.00	N
ATOM	1293	CA	ASN	14	17.176	29.086	-8.873	0.00	0.00	C
ATOM	1294	C	ASN	14	16.881	28.323	-10.193	0.00	0.00	C
ATOM	1295	O	ASN	14	16.213	28.825	-11.097	0.00	0.00	O
ATOM	1296	CB	ASN	14	18.619	29.676	-8.881	0.00	0.00	C
ATOM	1297	CG	ASN	14	19.834	28.729	-8.942	0.00	0.00	C
ATOM	1298	OD1	ASN	14	20.154	28.014	-8.001	0.00	0.00	O
ATOM	1299	ND2	ASN	14	20.541	28.643	-10.046	0.00	0.00	N
ATOM	1300	H	ASN	14	17.724	27.985	-7.044	0.00	0.00	H
ATOM	1301	HA	ASN	14	16.470	29.917	-8.909	0.00	0.00	H
ATOM	1302	1HB	ASN	14	18.681	30.384	-9.726	0.00	0.00	H
ATOM	1303	2HB	ASN	14	18.752	30.292	-7.978	0.00	0.00	H
ATOM	1304	1HD2	ASN	14	21.409	28.123	-9.897	0.00	0.00	H
ATOM	1305	2HD2	ASN	14	20.018	28.676	-10.935	0.00	0.00	H
ATOM	1306	N	LEU	15	17.450	27.127	-10.306	0.00	0.00	N
ATOM	1307	CA	LEU	15	17.465	26.335	-11.512	0.00	0.00	C
ATOM	1308	C	LEU	15	16.251	25.338	-11.667	0.00	0.00	C
ATOM	1309	O	LEU	15	16.055	24.796	-12.757	0.00	0.00	O
ATOM	1310	CB	LEU	15	18.924	25.801	-11.283	0.00	0.00	C
ATOM	1311	CG	LEU	15	19.360	24.759	-12.261	0.00	0.00	C
ATOM	1312	CD1	LEU	15	19.494	25.432	-13.633	0.00	0.00	C
ATOM	1313	CD2	LEU	15	20.669	24.037	-11.901	0.00	0.00	C
ATOM	1314	H	LEU	15	17.907	26.626	-9.528	0.00	0.00	H
ATOM	1315	HA	LEU	15	17.444	26.993	-12.402	0.00	0.00	H
ATOM	1316	1HB	LEU	15	19.670	26.615	-11.317	0.00	0.00	H

48/107

FIG. 8 - 40

ATOM	1317	2HB	LEU	15	19.045	25.327	-10.298	0.00	0.00	H
ATOM	1318	HG	LEU	15	18.495	24.107	-12.090	0.00	0.00	H
ATOM	1319	1HD1	LEU	15	20.218	26.273	-13.583	0.00	0.00	H
ATOM	1320	2HD1	LEU	15	19.835	24.737	-14.410	0.00	0.00	H
ATOM	1321	3HD1	LEU	15	18.538	25.874	-13.969	0.00	0.00	H
ATOM	1322	1HD2	LEU	15	21.520	24.740	-11.808	0.00	0.00	H
ATOM	1323	2HD2	LEU	15	20.588	23.472	-10.959	0.00	0.00	H
ATOM	1324	3HD2	LEU	15	20.947	23.302	-12.682	0.00	0.00	H
ATOM	1325	N	CYS	16	15.419	25.107	-10.630	0.00	0.00	N
ATOM	1326	CA	CYS	16	13.995	24.752	-10.839	0.00	0.00	C
ATOM	1327	C	CYS	16	13.006	25.959	-10.966	0.00	0.00	C
ATOM	1328	O	CYS	16	12.157	25.980	-11.850	0.00	0.00	O
ATOM	1329	CB	CYS	16	13.583	23.811	-9.701	0.00	0.00	C
ATOM	1330	SG	CYS	16	12.114	22.898	-10.210	0.00	0.00	S
ATOM	1331	H	CYS	16	15.717	25.614	-9.788	0.00	0.00	H
ATOM	1332	HA	CYS	16	13.901	24.193	-11.786	0.00	0.00	H
ATOM	1333	1HB	CYS	16	14.291	23.004	-9.495	0.00	0.00	H
ATOM	1334	2HB	CYS	16	13.513	24.383	-8.752	0.00	0.00	H
TER	1335		CYS	16						
HETATM	1336	N	NH2	17H	13.003	26.957	-10.100	0.00	0.00	N
HETATM	1337	1HN	NH2	17H	12.396	27.730	-10.391	0.00	0.00	H
HETATM	1338	2HN	NH2	17H	13.772	26.998	-9.412	0.00	0.00	H
ENDMDL										
MODEL	7									
ATOM	1339	N	GLY	1	15.155	24.544	-15.190	0.00	0.00	N
ATOM	1340	CA	GLY	1	15.819	23.221	-15.430	0.00	0.00	C
ATOM	1341	C	GLY	1	15.274	22.088	-14.544	0.00	0.00	C
ATOM	1342	O	GLY	1	14.062	21.875	-14.577	0.00	0.00	O
ATOM	1343	1H	GLY	1	15.295	24.827	-14.210	1.00	0.00	H
ATOM	1344	2H	GLY	1	15.566	25.253	-15.814	1.00	0.00	H
ATOM	1345	3H	GLY	1	14.146	24.462	-15.383	1.00	0.00	H
ATOM	1346	1HA	GLY	1	15.658	22.889	-16.472	0.00	0.00	H
ATOM	1347	2HA	GLY	1	16.912	23.301	-15.283	0.00	0.00	H
ATOM	1348	N	CYS	2	16.114	21.366	-13.767	0.00	0.00	N

49/107

FIG. 8 - 41

ATOM	1349	CA	CYS	2	15.626	20.295	-12.909	0.00	0.00	C
ATOM	1350	C	CYS	2	14.792	20.665	-11.648	0.00	0.00	C
ATOM	1351	O	CYS	2	15.215	20.910	-10.526	0.00	0.00	O
ATOM	1352	CB	CYS	2	16.751	19.310	-12.674	0.00	0.00	C
ATOM	1353	SG	CYS	2	17.644	19.532	-11.107	0.00	0.00	S
ATOM	1354	H	CYS	2	16.824	20.853	-14.280	0.00	0.00	H
ATOM	1355	HA	CYS	2	14.997	19.697	-13.613	0.00	0.00	H
ATOM	1356	1HB	CYS	2	16.137	18.416	-12.647	0.00	0.00	H
ATOM	1357	2HB	CYS	2	17.428	19.169	-13.534	0.00	0.00	H
ATOM	1358	N	CYS	3	13.539	20.634	-11.987	0.00	0.00	N
ATOM	1359	CA	CYS	3	12.379	20.624	-11.063	0.00	0.00	C
ATOM	1360	C	CYS	3	11.834	19.220	-10.613	0.00	0.00	C
ATOM	1361	O	CYS	3	11.402	19.067	-9.471	0.00	0.00	O
ATOM	1362	CB	CYS	3	11.278	21.375	-11.838	0.00	0.00	C
ATOM	1363	SG	CYS	3	11.556	23.161	-11.884	0.00	0.00	S
ATOM	1364	H	CYS	3	13.660	20.271	-12.944	0.00	0.00	H
ATOM	1365	HA	CYS	3	12.642	21.191	-10.135	0.00	0.00	H
ATOM	1366	1HB	CYS	3	11.177	21.011	-12.881	0.00	0.00	H
ATOM	1367	2HB	CYS	3	10.295	21.142	-11.401	0.00	0.00	H
ATOM	1368	N	SER	4	11.798	18.233	-11.513	0.00	0.00	N
ATOM	1369	CA	SER	4	11.212	16.880	-11.284	0.00	0.00	C
ATOM	1370	C	SER	4	11.900	15.953	-10.226	0.00	0.00	C
ATOM	1371	O	SER	4	11.291	15.001	-9.737	0.00	0.00	O
ATOM	1372	CB	SER	4	11.102	16.202	-12.653	0.00	0.00	C
ATOM	1373	OG	SER	4	10.313	16.945	-13.588	0.00	0.00	O
ATOM	1374	H	SER	4	12.257	18.450	-12.384	0.00	0.00	H
ATOM	1375	HA	SER	4	10.171	16.982	-10.986	0.00	0.00	H
ATOM	1376	1HB	SER	4	12.112	16.058	-13.027	0.00	0.00	H
ATOM	1377	2HB	SER	4	10.676	15.192	-12.534	0.00	0.00	H
ATOM	1378	HG	SER	4	9.989	16.329	-14.257	0.00	0.00	H
ATOM	1379	N	ASN	5	13.126	16.294	-9.806	0.00	0.00	N
ATOM	1380	CA	ASN	5	13.766	15.691	-8.624	0.00	0.00	C
ATOM	1381	C	ASN	5	13.379	16.460	-7.309	0.00	0.00	C
ATOM	1382	O	ASN	5	13.321	17.696	-7.339	0.00	0.00	O

FIG. 8 - 42

ATOM	1383	CB	ASN	5	15.296	15.867	-8.797	0.00	0.00	C
ATOM	1384	CG	ASN	5	15.978	15.043	-9.867	0.00	0.00	C
ATOM	1385	OD1	ASN	5	16.076	15.412	-11.030	0.00	0.00	O
ATOM	1386	ND2	ASN	5	16.554	13.958	-9.443	0.00	0.00	N
ATOM	1387	H	ASN	5	13.581	17.005	-10.386	0.00	0.00	H
ATOM	1388	HA	ASN	5	13.509	14.617	-8.561	0.00	0.00	H
ATOM	1389	1HB	ASN	5	15.586	16.928	-8.913	0.00	0.00	H
ATOM	1390	2HB	ASN	5	15.776	15.600	-7.857	0.00	0.00	H
ATOM	1391	1HD2	ASN	5	17.207	13.570	-10.115	0.00	0.00	H
ATOM	1392	2HD2	ASN	5	16.566	13.873	-8.424	0.00	0.00	H
ATOM	1393	N	PRO	6	13.248	15.824	-6.111	0.00	0.00	N
ATOM	1394	CA	PRO	6	13.315	16.565	-4.810	0.00	0.00	C
ATOM	1395	C	PRO	6	14.632	17.365	-4.542	0.00	0.00	C
ATOM	1396	O	PRO	6	14.643	18.566	-4.276	0.00	0.00	O
ATOM	1397	CB	PRO	6	13.030	15.433	-3.802	0.00	0.00	C
ATOM	1398	CG	PRO	6	13.620	14.193	-4.479	0.00	0.00	C
ATOM	1399	CD	PRO	6	13.228	14.352	-5.944	0.00	0.00	C
ATOM	1400	HA	PRO	6	12.514	17.299	-4.753	0.00	0.00	H
ATOM	1401	1HB	PRO	6	13.454	15.627	-2.798	0.00	0.00	H
ATOM	1402	2HB	PRO	6	11.937	15.311	-3.658	0.00	0.00	H
ATOM	1403	1HG	PRO	6	14.716	14.152	-4.376	0.00	0.00	H
ATOM	1404	2HG	PRO	6	13.289	13.257	-4.036	0.00	0.00	H
ATOM	1405	1HD	PRO	6	13.915	13.793	-6.597	0.00	0.00	H
ATOM	1406	2HD	PRO	6	12.222	13.946	-6.148	0.00	0.00	H
ATOM	1407	N	VAL	7	15.742	16.658	-4.688	0.00	0.00	N
ATOM	1408	CA	VAL	7	17.093	17.079	-4.256	0.00	0.00	C
ATOM	1409	C	VAL	7	17.730	18.083	-5.231	0.00	0.00	C
ATOM	1410	O	VAL	7	18.088	19.193	-4.834	0.00	0.00	O
ATOM	1411	CB	VAL	7	17.886	15.728	-4.112	0.00	0.00	C
ATOM	1412	CG1	VAL	7	19.409	15.878	-3.946	0.00	0.00	C
ATOM	1413	CG2	VAL	7	17.422	14.872	-2.921	0.00	0.00	C
ATOM	1414	H	VAL	7	15.531	15.687	-4.926	0.00	0.00	H
ATOM	1415	HA	VAL	7	17.024	17.649	-3.310	0.00	0.00	H
ATOM	1416	HB	VAL	7	17.713	15.129	-5.039	0.00	0.00	H

FIG. 8 - 43

ATOM	1417	1HG1	VAL	7	19.659	16.478	-3.051	0.00	0.00	H
ATOM	1418	2HG1	VAL	7	19.905	14.895	-3.844	0.00	0.00	H
ATOM	1419	3HG1	VAL	7	19.867	16.371	-4.822	0.00	0.00	H
ATOM	1420	1HG2	VAL	7	16.339	14.674	-2.956	0.00	0.00	H
ATOM	1421	2HG2	VAL	7	17.926	13.887	-2.917	0.00	0.00	H
ATOM	1422	3HG2	VAL	7	17.631	15.375	-1.960	0.00	0.00	H
ATOM	1423	N	CYS	8	17.876	17.700	-6.509	0.00	0.00	N
ATOM	1424	CA	CYS	8	18.484	18.600	-7.528	0.00	0.00	C
ATOM	1425	C	CYS	8	17.786	19.937	-7.876	0.00	0.00	C
ATOM	1426	O	CYS	8	18.420	20.950	-8.184	0.00	0.00	O
ATOM	1427	CB	CYS	8	19.013	17.847	-8.772	0.00	0.00	C
ATOM	1428	SG	CYS	8	17.768	17.790	-10.095	0.00	0.00	S
ATOM	1429	H	CYS	8	17.543	16.742	-6.603	0.00	0.00	H
ATOM	1430	HA	CYS	8	19.291	18.993	-6.930	0.00	0.00	H
ATOM	1431	1HB	CYS	8	19.906	18.359	-9.176	0.00	0.00	H
ATOM	1432	2HB	CYS	8	19.346	16.820	-8.529	0.00	0.00	H
ATOM	1433	N	HIS	9	16.477	19.926	-7.681	0.00	0.00	N
ATOM	1434	CA	HIS	9	15.651	21.129	-7.532	0.00	0.00	C
ATOM	1435	C	HIS	9	16.063	22.015	-6.330	0.00	0.00	C
ATOM	1436	O	HIS	9	16.098	23.228	-6.459	0.00	0.00	O
ATOM	1437	CB	HIS	9	14.198	20.586	-7.494	0.00	0.00	C
ATOM	1438	CG	HIS	9	12.943	21.249	-6.940	0.00	0.00	C
ATOM	1439	ND1	HIS	9	11.711	20.824	-7.379	0.00	0.00	N
ATOM	1440	CD2	HIS	9	12.831	22.562	-6.502	0.00	0.00	C
ATOM	1441	CE1	HIS	9	10.992	21.982	-7.327	0.00	0.00	C
ATOM	1442	NE2	HIS	9	11.553	23.063	-6.710	0.00	0.00	N
ATOM	1443	H	HIS	9	16.155	19.012	-7.380	0.00	0.00	H
ATOM	1444	HA	HIS	9	15.802	21.717	-8.414	0.00	0.00	H
ATOM	1445	1HB	HIS	9	13.998	20.013	-8.412	0.00	0.00	H
ATOM	1446	2HB	HIS	9	14.275	19.844	-6.679	0.00	0.00	H
ATOM	1447	HD1	HIS	9	11.523	19.983	-7.958	0.00	0.00	H
ATOM	1448	HD2	HIS	9	13.710	23.124	-6.297	0.00	0.00	H
ATOM	1449	HE1	HIS	9	10.240	22.154	-8.091	0.00	0.00	H
ATOM	1450	HE2	HIS	9	11.149	23.979	-6.470	1.00	0.00	H

FIG. 8 - 44

ATOM	1451	N	LEU	10	16.266	21.423	-5.162	0.00	0.00	N
ATOM	1452	CA	LEU	10	16.336	22.200	-3.872	0.00	0.00	C
ATOM	1453	C	LEU	10	17.740	22.697	-3.410	0.00	0.00	C
ATOM	1454	O	LEU	10	17.901	23.851	-3.008	0.00	0.00	O
ATOM	1455	CB	LEU	10	15.445	21.515	-2.803	0.00	0.00	C
ATOM	1456	CG	LEU	10	13.921	21.539	-3.121	0.00	0.00	C
ATOM	1457	CD1	LEU	10	13.144	20.672	-2.128	0.00	0.00	C
ATOM	1458	CD2	LEU	10	13.306	22.955	-3.130	0.00	0.00	C
ATOM	1459	H	LEU	10	16.565	20.437	-5.352	0.00	0.00	H
ATOM	1460	HA	LEU	10	15.853	23.177	-4.037	0.00	0.00	H
ATOM	1461	1HB	LEU	10	15.789	20.470	-2.670	0.00	0.00	H
ATOM	1462	2HB	LEU	10	15.614	21.988	-1.817	0.00	0.00	H
ATOM	1463	HG	LEU	10	13.776	21.078	-4.117	0.00	0.00	H
ATOM	1464	1HD1	LEU	10	13.514	19.631	-2.128	0.00	0.00	H
ATOM	1465	2HD1	LEU	10	13.219	21.053	-1.094	0.00	0.00	H
ATOM	1466	3HD1	LEU	10	12.070	20.622	-2.390	0.00	0.00	H
ATOM	1467	1HD2	LEU	10	13.431	23.469	-2.159	0.00	0.00	H
ATOM	1468	2HD2	LEU	10	13.750	23.615	-3.895	0.00	0.00	H
ATOM	1469	3HD2	LEU	10	12.221	22.930	-3.347	0.00	0.00	H
ATOM	1470	N	GLU	11	18.774	21.884	-3.619	0.00	0.00	N
ATOM	1471	CA	GLU	11	20.172	22.330	-3.801	0.00	0.00	C
ATOM	1472	C	GLU	11	20.470	23.502	-4.793	0.00	0.00	C
ATOM	1473	O	GLU	11	21.407	24.281	-4.611	0.00	0.00	O
ATOM	1474	CB	GLU	11	20.839	21.016	-4.293	0.00	0.00	C
ATOM	1475	CG	GLU	11	21.326	20.027	-3.212	0.00	0.00	C
ATOM	1476	CD	GLU	11	22.604	20.452	-2.487	0.00	0.00	C
ATOM	1477	OE1	GLU	11	23.633	20.783	-3.070	0.00	0.00	O
ATOM	1478	OE2	GLU	11	22.472	20.422	-1.136	0.00	0.00	O
ATOM	1479	H	GLU	11	18.586	20.872	-3.656	1.00	0.00	H
ATOM	1480	HA	GLU	11	20.610	22.632	-2.848	0.00	0.00	H
ATOM	1481	1HB	GLU	11	20.226	20.477	-5.044	0.00	0.00	H
ATOM	1482	2HB	GLU	11	21.686	21.315	-4.886	0.00	0.00	H
ATOM	1483	1HG	GLU	11	20.504	19.866	-2.496	0.00	0.00	H
ATOM	1484	2HG	GLU	11	21.522	19.037	-3.661	0.00	0.00	H

FIG. 8-44

FIG. 8 - 45

ATOM	1485	HE2	GLU	11	23.298	20.695	-0.733	0.00	0.00	H
ATOM	1486	N	HIS	12	19.735	23.535	-5.906	0.00	0.00	N
ATOM	1487	CA	HIS	12	19.922	24.514	-6.991	0.00	0.00	C
ATOM	1488	C	HIS	12	18.521	25.072	-7.409	0.00	0.00	C
ATOM	1489	O	HIS	12	17.989	24.766	-8.472	0.00	0.00	O
ATOM	1490	CB	HIS	12	20.755	23.800	-8.086	0.00	0.00	C
ATOM	1491	CG	HIS	12	22.215	23.450	-7.743	0.00	0.00	C
ATOM	1492	ND1	HIS	12	22.673	22.147	-7.631	0.00	0.00	N
ATOM	1493	CD2	HIS	12	23.219	24.344	-7.309	0.00	0.00	C
ATOM	1494	CE1	HIS	12	23.923	22.348	-7.094	0.00	0.00	C
ATOM	1495	NE2	HIS	12	24.346	23.637	-6.897	0.00	0.00	N
ATOM	1496	H	HIS	12	18.881	22.984	-5.810	0.00	0.00	H
ATOM	1497	HA	HIS	12	20.503	25.381	-6.649	0.00	0.00	H
ATOM	1498	1HB	HIS	12	20.193	22.896	-8.379	0.00	0.00	H
ATOM	1499	2HB	HIS	12	20.761	24.433	-8.980	0.00	0.00	H
ATOM	1500	HD1	HIS	12	22.161	21.270	-7.782	0.00	0.00	H
ATOM	1501	HD2	HIS	12	23.080	25.414	-7.199	0.00	0.00	H
ATOM	1502	HE1	HIS	12	24.546	21.507	-6.783	0.00	0.00	H
ATOM	1503	HE2	HIS	12	25.247	23.986	-6.541	1.00	0.00	H
ATOM	1504	N	SER	13	17.921	25.863	-6.509	0.00	0.00	N
ATOM	1505	CA	SER	13	16.491	26.279	-6.562	0.00	0.00	C
ATOM	1506	C	SER	13	16.009	27.341	-7.576	0.00	0.00	C
ATOM	1507	O	SER	13	14.955	27.195	-8.200	0.00	0.00	O
ATOM	1508	CB	SER	13	16.013	26.552	-5.115	0.00	0.00	C
ATOM	1509	OG	SER	13	16.675	27.694	-4.563	0.00	0.00	O
ATOM	1510	H	SER	13	18.213	25.528	-5.602	0.00	0.00	H
ATOM	1511	HA	SER	13	15.984	25.406	-6.930	0.00	0.00	H
ATOM	1512	1HB	SER	13	14.918	26.716	-5.099	0.00	0.00	H
ATOM	1513	2HB	SER	13	16.189	25.669	-4.468	0.00	0.00	H
ATOM	1514	HG	SER	13	16.292	27.883	-3.697	0.00	0.00	H
ATOM	1515	N	ASN	14	16.887	28.295	-7.830	0.00	0.00	N
ATOM	1516	CA	ASN	14	16.931	29.039	-9.130	0.00	0.00	C
ATOM	1517	C	ASN	14	16.988	28.153	-10.428	0.00	0.00	C
ATOM	1518	O	ASN	14	16.420	28.498	-11.464	0.00	0.00	O

FIG. 8 - 46

ATOM	1519	CB	ASN	14	18.123	30.038	-9.133	0.00	0.00	C
ATOM	1520	CG	ASN	14	18.129	31.105	-8.037	0.00	0.00	C
ATOM	1521	OD1	ASN	14	17.144	31.781	-7.777	0.00	0.00	O
ATOM	1522	ND2	ASN	14	19.237	31.299	-7.371	0.00	0.00	N
ATOM	1523	H	ASN	14	17.682	28.043	-7.236	0.00	0.00	H
ATOM	1524	HA	ASN	14	15.996	29.614	-9.211	0.00	0.00	H
ATOM	1525	1HB	ASN	14	19.077	29.480	-9.141	0.00	0.00	H
ATOM	1526	2HB	ASN	14	18.117	30.598	-10.086	0.00	0.00	H
ATOM	1527	1HD2	ASN	14	19.181	32.098	-6.730	0.00	0.00	H
ATOM	1528	2HD2	ASN	14	20.070	30.813	-7.710	0.00	0.00	H
ATOM	1529	N	LEU	15	17.672	27.002	-10.353	0.00	0.00	N
ATOM	1530	CA	LEU	15	17.873	26.068	-11.480	0.00	0.00	C
ATOM	1531	C	LEU	15	16.774	24.953	-11.639	0.00	0.00	C
ATOM	1532	O	LEU	15	16.617	24.441	-12.747	0.00	0.00	O
ATOM	1533	CB	LEU	15	19.339	25.555	-11.398	0.00	0.00	C
ATOM	1534	CG	LEU	15	20.437	26.670	-11.332	0.00	0.00	C
ATOM	1535	CD1	LEU	15	20.934	27.055	-9.923	0.00	0.00	C
ATOM	1536	CD2	LEU	15	21.647	26.316	-12.197	0.00	0.00	C
ATOM	1537	H	LEU	15	18.075	26.786	-9.437	0.00	0.00	H
ATOM	1538	HA	LEU	15	17.817	26.655	-12.415	0.00	0.00	H
ATOM	1539	1HB	LEU	15	19.441	24.839	-10.569	0.00	0.00	H
ATOM	1540	2HB	LEU	15	19.501	24.930	-12.297	0.00	0.00	H
ATOM	1541	HG	LEU	15	19.973	27.590	-11.738	0.00	0.00	H
ATOM	1542	1HD1	LEU	15	20.114	27.186	-9.195	0.00	0.00	H
ATOM	1543	2HD1	LEU	15	21.652	26.334	-9.501	0.00	0.00	H
ATOM	1544	3HD1	LEU	15	21.466	28.028	-9.953	0.00	0.00	H
ATOM	1545	1HD2	LEU	15	21.352	26.151	-13.249	0.00	0.00	H
ATOM	1546	2HD2	LEU	15	22.393	27.132	-12.201	0.00	0.00	H
ATOM	1547	3HD2	LEU	15	22.152	25.399	-11.842	0.00	0.00	H
ATOM	1548	N	CYS	16	15.902	24.687	-10.637	0.00	0.00	N
ATOM	1549	CA	CYS	16	14.447	24.472	-10.924	0.00	0.00	C
ATOM	1550	C	CYS	16	13.798	25.765	-11.533	0.00	0.00	C
ATOM	1551	O	CYS	16	13.518	25.816	-12.729	0.00	0.00	O
ATOM	1552	CB	CYS	16	13.661	23.955	-9.687	0.00	0.00	C

FIG. 8 - 47

S	H	H	H	H	N	H	H	N	C	C	O	H	H	H	H	N	C	C	O	C	S	H	H	H	H	N	C	C	O
11.886	23.916	-10.051	0.00	0.00	13.607	26.834	-10.777	0.00	0.00	15.059	13.097	-14.332	0.00	0.00	15.485	15.135	-14.893	0.00	0.00	17.213	15.836	-12.811	0.00	0.00	17.832	16.210	-11.496	0.00	0.00
16.215	25.198	-9.796	0.00	0.00	13.331	27.672	-11.299	0.00	0.00	15.949	14.309	-14.317	0.00	0.00	17.006	17.347	-10.772	0.00	0.00	17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
14.354	23.684	-11.698	0.00	0.00	14.065	26.808	-9.844	0.00	0.00	16.291	14.867	-12.909	0.00	0.00	16.538	17.131	-9.659	0.00	0.00	17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
13.919	22.928	-9.378	0.00	0.00						15.714	14.437	-11.915	0.00	0.00	19.321	16.437	-11.885	0.00	0.00	17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
13.846	24.608	-8.812	0.00	0.00						15.514	12.330	-13.817	1.00	0.00	20.425	17.454	-10.867	0.00	0.00	17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										14.160	13.325	-13.883	1.00	0.00	17.770	15.985	-13.661	0.00	0.00	17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										14.892	12.806	-15.306	1.00	0.00	17.823	15.346	-10.798	0.00	0.00	17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										16.900	14.089	-14.841	0.00	0.00	19.820	15.480	-12.128	0.00	0.00	17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										15.485	15.135	-14.893	0.00	0.00	19.337	17.030	-12.824	0.00	0.00	17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										17.213	15.836	-12.811	0.00	0.00	16.700	18.500	-11.400	0.00	0.00	17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										17.832	16.210	-11.496	0.00	0.00	15.475	19.311	-11.108	0.00	0.00	17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										16.538	17.131	-9.659	0.00	0.00	14.057	18.627	-11.218	0.00	0.00	17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										19.321	16.437	-11.885	0.00	0.00	13.104	19.118	-10.607	0.00	0.00	17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										20.425	17.454	-10.867	0.00	0.00						17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										17.770	15.985	-13.661	0.00	0.00						17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										17.823	15.346	-10.798	0.00	0.00						17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										19.820	15.480	-12.128	0.00	0.00						17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										19.337	17.030	-12.824	0.00	0.00						17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										16.700	18.500	-11.400	0.00	0.00						17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										15.475	19.311	-11.108	0.00	0.00						17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										14.057	18.627	-11.218	0.00	0.00						17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00
										13.104	19.118	-10.607	0.00	0.00						17.832	16.210	-11.496	0.00	0.00	17.006	17.347	-10.772	0.00	0.00

FIG. 8 - 48

ATOM	1585	CB	CYS	3	15.714	20.442	-12.118	0.00	0.00	C
ATOM	1586	SG	CYS	3	16.874	21.609	-11.379	0.00	0.00	S
ATOM	1587	H	CYS	3	17.037	18.582	-12.364	0.00	0.00	H
ATOM	1588	HA	CYS	3	15.467	19.806	-10.100	0.00	0.00	H
ATOM	1589	1HB	CYS	3	16.043	20.132	-13.133	0.00	0.00	H
ATOM	1590	2HB	CYS	3	14.777	20.947	-12.316	0.00	0.00	H
ATOM	1591	N	SER	4	13.926	17.499	-11.937	0.00	0.00	N
ATOM	1592	CA	SER	4	12.776	16.552	-11.773	0.00	0.00	C
ATOM	1593	C	SER	4	12.750	15.630	-10.495	0.00	0.00	C
ATOM	1594	O	SER	4	11.677	15.133	-10.148	0.00	0.00	O
ATOM	1595	CB	SER	4	12.567	15.841	-13.121	0.00	0.00	C
ATOM	1596	OG	SER	4	11.800	14.639	-13.029	0.00	0.00	O
ATOM	1597	H	SER	4	14.830	17.182	-12.295	0.00	0.00	H
ATOM	1598	HA	SER	4	11.864	17.140	-11.695	0.00	0.00	H
ATOM	1599	1HB	SER	4	12.092	16.532	-13.848	0.00	0.00	H
ATOM	1600	2HB	SER	4	13.537	15.611	-13.545	0.00	0.00	H
ATOM	1601	HG	SER	4	11.077	14.794	-12.402	0.00	0.00	H
ATOM	1602	N	ASN	5	13.854	15.481	-9.746	0.00	0.00	N
ATOM	1603	CA	ASN	5	13.825	15.066	-8.328	0.00	0.00	C
ATOM	1604	C	ASN	5	13.679	16.328	-7.403	0.00	0.00	C
ATOM	1605	O	ASN	5	14.295	17.363	-7.698	0.00	0.00	O
ATOM	1606	CB	ASN	5	15.213	14.467	-7.982	0.00	0.00	C
ATOM	1607	CG	ASN	5	15.604	13.090	-8.478	0.00	0.00	C
ATOM	1608	OD1	ASN	5	15.111	12.523	-9.443	0.00	0.00	O
ATOM	1609	ND2	ASN	5	16.541	12.529	-7.764	0.00	0.00	N
ATOM	1610	H	ASN	5	14.730	15.832	-10.131	0.00	0.00	H
ATOM	1611	HA	ASN	5	13.009	14.339	-8.127	0.00	0.00	H
ATOM	1612	1HB	ASN	5	16.026	15.166	-8.249	0.00	0.00	H
ATOM	1613	2HB	ASN	5	15.262	14.397	-6.889	0.00	0.00	H
ATOM	1614	1HD2	ASN	5	16.559	11.520	-7.892	0.00	0.00	H
ATOM	1615	2HD2	ASN	5	16.775	13.053	-6.910	0.00	0.00	H
ATOM	1616	N	PRO	6	12.997	16.274	-6.225	0.00	0.00	N
ATOM	1617	CA	PRO	6	12.988	17.412	-5.263	0.00	0.00	C
ATOM	1618	C	PRO	6	14.359	17.956	-4.757	0.00	0.00	C

FIG. 8 - 49

ATOM	1619	O	PRO	6	14.585	19.158	-4.734	0.00	0.00
ATOM	1620	CB	PRO	6	11.993	16.949	-4.189	0.00	0.00
ATOM	1621	CG	PRO	6	11.829	15.445	-4.336	0.00	0.00
ATOM	1622	CD	PRO	6	12.277	15.077	-5.751	0.00	0.00
ATOM	1623	HA	PRO	6	12.543	18.273	-5.754	0.00	0.00
ATOM	1624	1HB	PRO	6	12.289	17.264	-3.172	0.00	0.00
ATOM	1625	2HB	PRO	6	11.000	17.378	-4.349	0.00	0.00
ATOM	1626	1HG	PRO	6	12.454	14.982	-3.573	0.00	0.00
ATOM	1627	2HG	PRO	6	10.806	15.099	-4.110	0.00	0.00
ATOM	1628	1HD	PRO	6	12.903	14.170	-5.741	0.00	0.00
ATOM	1629	2HD	PRO	6	11.442	14.834	-6.432	0.00	0.00
ATOM	1630	N	VAL	7	15.290	17.064	-4.458	0.00	0.00
ATOM	1631	CA	VAL	7	16.576	17.374	-3.758	0.00	0.00
ATOM	1632	C	VAL	7	17.714	17.925	-4.675	0.00	0.00
ATOM	1633	O	VAL	7	18.391	18.877	-4.320	0.00	0.00
ATOM	1634	CB	VAL	7	16.943	16.044	-2.997	0.00	0.00
ATOM	1635	CG1	VAL	7	18.350	16.028	-2.346	0.00	0.00
ATOM	1636	CG2	VAL	7	15.962	15.676	-1.854	0.00	0.00
ATOM	1637	H	VAL	7	14.934	16.119	-4.590	0.00	0.00
ATOM	1638	HA	VAL	7	16.393	18.231	-3.079	0.00	0.00
ATOM	1639	HB	VAL	7	16.901	15.227	-3.762	0.00	0.00
ATOM	1640	1HG1	VAL	7	19.160	16.214	-3.075	0.00	0.00
ATOM	1641	2HG1	VAL	7	18.453	16.795	-1.552	0.00	0.00
ATOM	1642	3HG1	VAL	7	18.584	15.052	-1.879	0.00	0.00
ATOM	1643	1HG2	VAL	7	14.920	15.564	-2.206	0.00	0.00
ATOM	1644	2HG2	VAL	7	16.225	14.716	-1.369	0.00	0.00
ATOM	1645	3HG2	VAL	7	15.944	16.442	-1.054	0.00	0.00
ATOM	1646	N	CYS	8	17.896	17.370	-5.866	0.00	0.00
ATOM	1647	CA	CYS	8	18.291	18.144	-7.057	0.00	0.00
ATOM	1648	C	CYS	8	17.820	19.591	-7.382	0.00	0.00
ATOM	1649	O	CYS	8	18.590	20.542	-7.483	0.00	0.00
ATOM	1650	CB	CYS	8	19.557	17.670	-7.794	0.00	0.00
ATOM	1651	SG	CYS	8	19.558	18.491	-9.413	0.00	0.00
ATOM	1652	H	CYS	8	17.159	16.662	-5.968	0.00	0.00

O C C C H H H H H H H N C C O C C C H H H H H H H N C C O C S H

FIG. 8 - 50

ATOM	1653	HA	CYS	8	17.492	17.708	-7.595	0.00	0.00	H
ATOM	1654	1HB	CYS	8	20.468	17.938	-7.226	0.00	0.00	H
ATOM	1655	2HB	CYS	8	19.569	16.571	-7.922	0.00	0.00	H
ATOM	1656	N	HIS	9	16.514	19.732	-7.646	0.00	0.00	N
ATOM	1657	CA	HIS	9	15.806	21.026	-7.866	0.00	0.00	C
ATOM	1658	C	HIS	9	16.177	22.061	-6.771	0.00	0.00	C
ATOM	1659	O	HIS	9	16.500	23.214	-7.025	0.00	0.00	O
ATOM	1660	CB	HIS	9	14.312	20.632	-7.956	0.00	0.00	C
ATOM	1661	CG	HIS	9	13.007	21.391	-7.825	0.00	0.00	C
ATOM	1662	ND1	HIS	9	12.014	21.276	-8.780	0.00	0.00	N
ATOM	1663	CD2	HIS	9	12.941	22.618	-7.238	0.00	0.00	C
ATOM	1664	CE1	HIS	9	11.445	22.526	-8.711	0.00	0.00	C
ATOM	1665	NE2	HIS	9	11.913	23.392	-7.760	0.00	0.00	N
ATOM	1666	H	HIS	9	16.006	18.837	-7.624	0.00	0.00	H
ATOM	1667	HA	HIS	9	16.027	21.422	-8.827	0.00	0.00	H
ATOM	1668	1HB	HIS	9	14.187	19.622	-8.196	0.00	0.00	H
ATOM	1669	2HB	HIS	9	14.266	20.336	-6.918	0.00	0.00	H
ATOM	1670	HD1	HIS	9	11.954	20.579	-9.539	0.00	0.00	H
ATOM	1671	HD2	HIS	9	13.914	22.898	-6.925	0.00	0.00	H
ATOM	1672	HE1	HIS	9	10.845	22.914	-9.537	0.00	0.00	H
ATOM	1673	HE2	HIS	9	11.596	24.338	-7.506	1.00	0.00	H
ATOM	1674	N	LEU	10	16.090	21.515	-5.570	0.00	0.00	N
ATOM	1675	CA	LEU	10	16.401	22.225	-4.305	0.00	0.00	C
ATOM	1676	C	LEU	10	17.889	22.281	-3.854	0.00	0.00	C
ATOM	1677	O	LEU	10	18.229	23.109	-3.010	0.00	0.00	O
ATOM	1678	CB	LEU	10	15.379	21.786	-3.223	0.00	0.00	C
ATOM	1679	CG	LEU	10	13.872	22.022	-3.547	0.00	0.00	C
ATOM	1680	CD1	LEU	10	12.982	21.431	-2.453	0.00	0.00	C
ATOM	1681	CD2	LEU	10	13.529	23.504	-3.758	0.00	0.00	C
ATOM	1682	H	LEU	10	16.128	20.478	-5.801	0.00	0.00	H
ATOM	1683	HA	LEU	10	16.224	23.291	-4.483	0.00	0.00	H
ATOM	1684	1HB	LEU	10	15.550	20.715	-3.000	0.00	0.00	H
ATOM	1685	2HB	LEU	10	15.625	22.301	-2.275	0.00	0.00	H
ATOM	1686	HG	LEU	10	13.613	21.483	-4.477	0.00	0.00	H

FIG. 8 - 51

ATOM	1687	1HD1	LEU	10	13.181	21.885	-1.465	0.00	0.00	H
ATOM	1688	2HD1	LEU	10	11.909	21.579	-2.676	0.00	0.00	H
ATOM	1689	3HD1	LEU	10	13.138	20.340	-2.356	0.00	0.00	H
ATOM	1690	1HD2	LEU	10	13.834	24.128	-2.897	0.00	0.00	H
ATOM	1691	2HD2	LEU	10	14.034	23.922	-4.648	0.00	0.00	H
ATOM	1692	3HD2	LEU	10	12.448	23.672	-3.917	0.00	0.00	H
ATOM	1693	N	GLU	11	18.812	21.595	-4.546	0.00	0.00	N
ATOM	1694	CA	GLU	11	20.223	21.983	-4.645	0.00	0.00	C
ATOM	1695	C	GLU	11	20.517	23.347	-5.351	0.00	0.00	C
ATOM	1696	O	GLU	11	21.509	24.018	-5.079	0.00	0.00	O
ATOM	1697	CB	GLU	11	20.849	20.761	-5.350	0.00	0.00	C
ATOM	1698	CG	GLU	11	21.657	19.817	-4.467	0.00	0.00	C
ATOM	1699	CD	GLU	11	22.982	20.363	-3.944	0.00	0.00	C
ATOM	1700	OE1	GLU	11	23.932	20.633	-4.671	0.00	0.00	O
ATOM	1701	OE2	GLU	11	22.983	20.526	-2.595	0.00	0.00	O
ATOM	1702	H	GLU	11	18.511	20.743	-5.039	1.00	0.00	H
ATOM	1703	HA	GLU	11	20.630	22.007	-3.647	0.00	0.00	H
ATOM	1704	1HB	GLU	11	20.102	20.092	-5.750	0.00	0.00	H
ATOM	1705	2HB	GLU	11	21.315	21.050	-6.271	0.00	0.00	H
ATOM	1706	1HG	GLU	11	20.944	19.574	-3.662	0.00	0.00	H
ATOM	1707	2HG	GLU	11	21.853	18.865	-4.988	0.00	0.00	H
ATOM	1708	HE2	GLU	11	23.835	20.878	-2.329	0.00	0.00	H
ATOM	1709	N	HIS	12	19.646	23.728	-6.299	0.00	0.00	N
ATOM	1710	CA	HIS	12	19.691	25.027	-7.006	0.00	0.00	C
ATOM	1711	C	HIS	12	18.287	25.650	-7.211	0.00	0.00	C
ATOM	1712	O	HIS	12	17.746	25.705	-8.312	0.00	0.00	O
ATOM	1713	CB	HIS	12	20.675	24.904	-8.185	0.00	0.00	C
ATOM	1714	CG	HIS	12	20.560	23.817	-9.250	0.00	0.00	C
ATOM	1715	ND1	HIS	12	21.628	22.979	-9.519	0.00	0.00	N
ATOM	1716	CD2	HIS	12	19.362	23.138	-9.437	0.00	0.00	C
ATOM	1717	CE1	HIS	12	20.978	21.794	-9.708	0.00	0.00	C
ATOM	1718	NE2	HIS	12	19.607	21.805	-9.759	0.00	0.00	N
ATOM	1719	H	HIS	12	18.865	23.079	-6.376	0.00	0.00	H
ATOM	1720	HA	HIS	12	20.170	25.744	-6.361	0.00	0.00	H

60/107

FIG. 8 - 52

ATOM	1721	1HB	HIS	12	20.830	25.893	-8.648	0.00	0.00	H
ATOM	1722	2HB	HIS	12	21.556	24.631	-7.595	0.00	0.00	H
ATOM	1723	HD1	HIS	12	22.610	23.123	-9.240	0.00	0.00	H
ATOM	1724	HD2	HIS	12	18.550	23.512	-8.820	0.00	0.00	H
ATOM	1725	HE1	HIS	12	21.501	20.859	-9.492	0.00	0.00	H
ATOM	1726	HE2	HIS	12	18.947	21.045	-9.975	1.00	0.00	H
ATOM	1727	N	SER	13	17.691	26.036	-6.081	0.00	0.00	N
ATOM	1728	CA	SER	13	16.249	26.349	-5.974	0.00	0.00	C
ATOM	1729	C	SER	13	15.708	27.608	-6.698	0.00	0.00	C
ATOM	1730	O	SER	13	14.712	27.558	-7.420	0.00	0.00	O
ATOM	1731	CB	SER	13	15.885	26.343	-4.468	0.00	0.00	C
ATOM	1732	OG	SER	13	14.471	26.433	-4.292	0.00	0.00	O
ATOM	1733	H	SER	13	18.082	25.458	-5.350	0.00	0.00	H
ATOM	1734	HA	SER	13	15.801	25.510	-6.492	0.00	0.00	H
ATOM	1735	1HB	SER	13	16.258	25.440	-3.949	0.00	0.00	H
ATOM	1736	2HB	SER	13	16.375	27.194	-3.951	0.00	0.00	H
ATOM	1737	HG	SER	13	14.303	27.039	-3.558	0.00	0.00	H
ATOM	1738	N	ASN	14	16.489	28.672	-6.585	0.00	0.00	N
ATOM	1739	CA	ASN	14	16.473	29.812	-7.558	0.00	0.00	C
ATOM	1740	C	ASN	14	16.517	29.426	-9.077	0.00	0.00	C
ATOM	1741	O	ASN	14	15.874	30.064	-9.909	0.00	0.00	O
ATOM	1742	CB	ASN	14	17.637	30.802	-7.261	0.00	0.00	C
ATOM	1743	CG	ASN	14	17.717	31.430	-5.868	0.00	0.00	C
ATOM	1744	OD1	ASN	14	16.728	31.695	-5.199	0.00	0.00	O
ATOM	1745	ND2	ASN	14	18.906	31.704	-5.400	0.00	0.00	N
ATOM	1746	H	ASN	14	17.304	28.297	-6.096	0.00	0.00	H
ATOM	1747	HA	ASN	14	15.519	30.344	-7.424	0.00	0.00	H
ATOM	1748	1HB	ASN	14	18.599	30.315	-7.508	0.00	0.00	H
ATOM	1749	2HB	ASN	14	17.565	31.654	-7.964	0.00	0.00	H
ATOM	1750	1HD2	ASN	14	18.877	32.254	-4.535	0.00	0.00	H
ATOM	1751	2HD2	ASN	14	19.690	31.583	-6.045	0.00	0.00	H
ATOM	1752	N	LEU	15	17.281	28.377	-9.419	0.00	0.00	N
ATOM	1753	CA	LEU	15	17.453	27.899	-10.811	0.00	0.00	C
ATOM	1754	C	LEU	15	16.429	26.809	-11.303	0.00	0.00	C

FIG. 8 - 53

ATOM	1755	O	LEU	15	16.447	26.440	-12.479	0.00	0.00	O
ATOM	1756	CB	LEU	15	18.956	27.495	-10.905	0.00	0.00	C
ATOM	1757	CG	LEU	15	19.958	28.657	-10.599	0.00	0.00	C
ATOM	1758	CD1	LEU	15	20.620	28.628	-9.208	0.00	0.00	C
ATOM	1759	CD2	LEU	15	21.040	28.757	-11.669	0.00	0.00	C
ATOM	1760	H	LEU	15	17.716	27.853	-8.649	0.00	0.00	H
ATOM	1761	HA	LEU	15	17.308	28.751	-11.496	0.00	0.00	H
ATOM	1762	1HB	LEU	15	19.167	26.614	-10.275	0.00	0.00	H
ATOM	1763	2HB	LEU	15	19.115	27.121	-11.936	0.00	0.00	H
ATOM	1764	HG	LEU	15	19.368	29.595	-10.613	0.00	0.00	H
ATOM	1765	1HD1	LEU	15	19.900	28.429	-8.394	0.00	0.00	H
ATOM	1766	2HD1	LEU	15	21.443	27.898	-9.135	0.00	0.00	H
ATOM	1767	3HD1	LEU	15	21.074	29.613	-8.978	0.00	0.00	H
ATOM	1768	1HD2	LEU	15	20.590	28.889	-12.670	0.00	0.00	H
ATOM	1769	2HD2	LEU	15	21.697	29.628	-11.493	0.00	0.00	H
ATOM	1770	3HD2	LEU	15	21.670	27.849	-11.697	0.00	0.00	H
ATOM	1771	N	CYS	16	15.545	26.290	-10.427	0.00	0.00	N
ATOM	1772	CA	CYS	16	14.463	25.336	-10.785	0.00	0.00	C
ATOM	1773	C	CYS	16	13.027	25.602	-10.206	0.00	0.00	C
ATOM	1774	O	CYS	16	12.068	24.944	-10.603	0.00	0.00	O
ATOM	1775	CB	CYS	16	15.012	23.961	-10.369	0.00	0.00	C
ATOM	1776	SG	CYS	16	16.243	23.486	-11.612	0.00	0.00	S
ATOM	1777	H	CYS	16	15.787	26.528	-9.458	0.00	0.00	H
ATOM	1778	HA	CYS	16	14.308	25.329	-11.884	0.00	0.00	H
ATOM	1779	1HB	CYS	16	15.396	23.966	-9.326	0.00	0.00	H
ATOM	1780	2HB	CYS	16	14.203	23.225	-10.383	0.00	0.00	H
TER	1781		CYS	16						
HETATM	1782	N	NH2	17H	12.765	26.462	-9.243	0.00	0.00	N
HETATM	1783	1HN	NH2	17H	11.781	26.742	-9.205	0.00	0.00	H
HETATM	1784	2HN	NH2	17H	13.561	27.023	-8.899	0.00	0.00	H
ENDMDL										
MODEL		9								
ATOM	1785	N	GLY	1	14.562	17.015	-16.324	0.00	0.00	N
ATOM	1786	CA	GLY	1	15.859	17.600	-15.842	0.00	0.00	C

FIG. 8 - 54

ATOM	1787	C	GLY	1	16.143	17.408	-14.324	0.00	0.00	C
ATOM	1788	O	GLY	1	15.460	16.619	-13.674	0.00	0.00	O
ATOM	1789	1H	GLY	1	13.778	17.454	-15.820	1.00	0.00	H
ATOM	1790	2H	GLY	1	14.460	17.190	-17.334	1.00	0.00	H
ATOM	1791	3H	GLY	1	14.557	16.000	-16.150	1.00	0.00	H
ATOM	1792	1HA	GLY	1	16.706	17.160	-16.407	0.00	0.00	H
ATOM	1793	2HA	GLY	1	15.885	18.685	-16.071	0.00	0.00	H
ATOM	1794	N	CYS	2	17.111	18.125	-13.724	0.00	0.00	N
ATOM	1795	CA	CYS	2	17.437	17.922	-12.275	0.00	0.00	C
ATOM	1796	C	CYS	2	16.471	18.711	-11.299	0.00	0.00	C
ATOM	1797	O	CYS	2	16.000	18.158	-10.307	0.00	0.00	O
ATOM	1798	CB	CYS	2	18.911	18.333	-12.112	0.00	0.00	C
ATOM	1799	SG	CYS	2	19.241	18.754	-10.390	0.00	0.00	S
ATOM	1800	H	CYS	2	17.863	18.469	-14.331	0.00	0.00	H
ATOM	1801	HA	CYS	2	17.364	16.850	-11.999	0.00	0.00	H
ATOM	1802	1HB	CYS	2	19.599	17.573	-12.519	0.00	0.00	H
ATOM	1803	2HB	CYS	2	19.096	19.273	-12.669	0.00	0.00	H
ATOM	1804	N	CYS	3	16.127	19.980	-11.588	0.00	0.00	N
ATOM	1805	CA	CYS	3	14.826	20.600	-11.235	0.00	0.00	C
ATOM	1806	C	CYS	3	13.487	19.762	-11.375	0.00	0.00	C
ATOM	1807	O	CYS	3	12.507	20.103	-10.714	0.00	0.00	O
ATOM	1808	CB	CYS	3	14.880	21.721	-12.293	0.00	0.00	C
ATOM	1809	SG	CYS	3	16.179	22.947	-11.997	0.00	0.00	S
ATOM	1810	H	CYS	3	16.530	20.353	-12.450	0.00	0.00	H
ATOM	1811	HA	CYS	3	14.839	21.061	-10.203	0.00	0.00	H
ATOM	1812	1HB	CYS	3	14.936	21.357	-13.339	0.00	0.00	H
ATOM	1813	2HB	CYS	3	13.940	22.263	-12.269	0.00	0.00	H
ATOM	1814	N	SER	4	13.420	18.686	-12.185	0.00	0.00	N
ATOM	1815	CA	SER	4	12.322	17.678	-12.114	0.00	0.00	C
ATOM	1816	C	SER	4	12.332	16.659	-10.912	0.00	0.00	C
ATOM	1817	O	SER	4	11.322	16.001	-10.662	0.00	0.00	O
ATOM	1818	CB	SER	4	12.262	16.958	-13.467	0.00	0.00	C
ATOM	1819	OG	SER	4	12.267	17.813	-14.620	0.00	0.00	O
ATOM	1820	H	SER	4	14.301	18.380	-12.596	0.00	0.00	H

63/107

FIG. 8 - 55

ATOM	1821	HA	SER	4	11.365	18.182	-12.053	0.00	0.00	H
ATOM	1822	1HB	SER	4	13.091	16.258	-13.487	0.00	0.00	H
ATOM	1823	2HB	SER	4	11.370	16.320	-13.484	0.00	0.00	H
ATOM	1824	HG	SER	4	11.461	18.347	-14.562	0.00	0.00	H
ATOM	1825	N	ASN	5	13.423	16.565	-10.141	0.00	0.00	N
ATOM	1826	CA	ASN	5	13.518	15.810	-8.887	0.00	0.00	C
ATOM	1827	C	ASN	5	13.099	16.594	-7.592	0.00	0.00	C
ATOM	1828	O	ASN	5	13.054	17.828	-7.618	0.00	0.00	O
ATOM	1829	CB	ASN	5	15.006	15.397	-8.796	0.00	0.00	C
ATOM	1830	CG	ASN	5	15.453	14.037	-9.250	0.00	0.00	C
ATOM	1831	OD1	ASN	5	15.174	13.550	-10.336	0.00	0.00	O
ATOM	1832	ND2	ASN	5	16.300	13.461	-8.458	0.00	0.00	N
ATOM	1833	H	ASN	5	14.271	17.096	-10.359	0.00	0.00	H
ATOM	1834	HA	ASN	5	12.969	14.872	-8.977	0.00	0.00	H
ATOM	1835	1HB	ASN	5	15.578	15.875	-9.579	0.00	0.00	H
ATOM	1836	2HB	ASN	5	15.518	15.883	-7.969	0.00	0.00	H
ATOM	1837	1HD2	ASN	5	16.865	12.822	-9.013	0.00	0.00	H
ATOM	1838	2HD2	ASN	5	16.570	14.001	-7.632	0.00	0.00	H
ATOM	1839	N	PRO	6	12.920	15.946	-6.408	0.00	0.00	N
ATOM	1840	CA	PRO	6	12.932	16.658	-5.095	0.00	0.00	C
ATOM	1841	C	PRO	6	14.249	17.411	-4.715	0.00	0.00	C
ATOM	1842	O	PRO	6	14.277	18.623	-4.508	0.00	0.00	O
ATOM	1843	CB	PRO	6	12.519	15.524	-4.145	0.00	0.00	C
ATOM	1844	CG	PRO	6	13.109	14.267	-4.793	0.00	0.00	C
ATOM	1845	CD	PRO	6	12.800	14.476	-6.275	0.00	0.00	C
ATOM	1846	HA	PRO	6	12.147	17.406	-5.037	0.00	0.00	H
ATOM	1847	1HB	PRO	6	12.851	15.717	-3.113	0.00	0.00	H
ATOM	1848	2HB	PRO	6	11.413	15.445	-4.094	0.00	0.00	H
ATOM	1849	1HG	PRO	6	14.194	14.179	-4.620	0.00	0.00	H
ATOM	1850	2HG	PRO	6	12.703	13.341	-4.384	0.00	0.00	H
ATOM	1851	1HD	PRO	6	13.463	13.896	-6.938	0.00	0.00	H
ATOM	1852	2HD	PRO	6	11.777	14.144	-6.526	0.00	0.00	H
ATOM	1853	N	VAL	7	15.344	16.665	-4.645	0.00	0.00	N
ATOM	1854	CA	VAL	7	16.539	17.031	-3.829	0.00	0.00	C

FIG. 8 - 56

ATOM	1855	C	VAL	7	17.586	17.841	-4.634	0.00	0.00	C
ATOM	1856	O	VAL	7	17.982	18.935	-4.218	0.00	0.00	O
ATOM	1857	CB	VAL	7	17.053	15.688	-3.188	0.00	0.00	C
ATOM	1858	CG1	VAL	7	18.468	15.753	-2.564	0.00	0.00	C
ATOM	1859	CG2	VAL	7	16.125	15.159	-2.065	0.00	0.00	C
ATOM	1860	H	VAL	7	15.090	15.693	-4.842	0.00	0.00	H
ATOM	1861	HA	VAL	7	16.248	17.751	-3.042	0.00	0.00	H
ATOM	1862	HB	VAL	7	17.072	14.926	-4.005	0.00	0.00	H
ATOM	1863	1HG1	VAL	7	18.533	16.500	-1.749	0.00	0.00	H
ATOM	1864	2HG1	VAL	7	18.779	14.781	-2.130	0.00	0.00	H
ATOM	1865	3HG1	VAL	7	19.247	16.014	-3.305	0.00	0.00	H
ATOM	1866	1HG2	VAL	7	15.088	15.000	-2.409	0.00	0.00	H
ATOM	1867	2HG2	VAL	7	16.466	14.183	-1.666	0.00	0.00	H
ATOM	1868	3HG2	VAL	7	16.071	15.852	-1.204	0.00	0.00	H
ATOM	1869	N	CYS	8	18.013	17.345	-5.806	0.00	0.00	N
ATOM	1870	CA	CYS	8	18.874	18.128	-6.728	0.00	0.00	C
ATOM	1871	C	CYS	8	18.308	19.418	-7.392	0.00	0.00	C
ATOM	1872	O	CYS	8	19.043	20.354	-7.731	0.00	0.00	O
ATOM	1873	CB	CYS	8	19.661	17.215	-7.691	0.00	0.00	C
ATOM	1874	SG	CYS	8	18.806	17.128	-9.277	0.00	0.00	S
ATOM	1875	H	CYS	8	17.529	16.484	-6.028	0.00	0.00	H
ATOM	1876	HA	CYS	8	19.543	18.563	-6.011	0.00	0.00	H
ATOM	1877	1HB	CYS	8	20.672	17.625	-7.871	0.00	0.00	H
ATOM	1878	2HB	CYS	8	19.821	16.197	-7.286	0.00	0.00	H
ATOM	1879	N	HIS	9	16.978	19.488	-7.453	0.00	0.00	N
ATOM	1880	CA	HIS	9	16.208	20.736	-7.602	0.00	0.00	C
ATOM	1881	C	HIS	9	16.562	21.788	-6.505	0.00	0.00	C
ATOM	1882	O	HIS	9	16.679	22.972	-6.799	0.00	0.00	O
ATOM	1883	CB	HIS	9	14.705	20.315	-7.638	0.00	0.00	C
ATOM	1884	CG	HIS	9	13.498	21.237	-7.347	0.00	0.00	C
ATOM	1885	ND1	HIS	9	12.448	21.322	-8.241	0.00	0.00	N
ATOM	1886	CD2	HIS	9	13.438	22.355	-6.512	0.00	0.00	C
ATOM	1887	CE1	HIS	9	11.905	22.544	-7.934	0.00	0.00	C
ATOM	1888	NE2	HIS	9	12.388	23.200	-6.842	0.00	0.00	N

65/107

FIG. 8 - 57

ATOM	1889	H	HIS	9	16.544	18.625	-7.139	0.00	0.00	H
ATOM	1890	HA	HIS	9	16.472	21.160	-8.548	0.00	0.00	H
ATOM	1891	1HB	HIS	9	14.536	19.651	-8.499	0.00	0.00	H
ATOM	1892	2HB	HIS	9	14.624	19.629	-6.769	0.00	0.00	H
ATOM	1893	HD1	HIS	9	12.279	20.746	-9.087	0.00	0.00	H
ATOM	1894	HD2	HIS	9	14.311	22.656	-5.992	0.00	0.00	H
ATOM	1895	HE1	HIS	9	11.435	23.142	-8.716	0.00	0.00	H
ATOM	1896	HE2	HIS	9	12.068	24.070	-6.392	1.00	0.00	H
ATOM	1897	N	LEU	10	16.601	21.348	-5.248	0.00	0.00	N
ATOM	1898	CA	LEU	10	16.649	22.250	-4.046	0.00	0.00	C
ATOM	1899	C	LEU	10	18.035	22.865	-3.693	0.00	0.00	C
ATOM	1900	O	LEU	10	18.161	24.071	-3.484	0.00	0.00	O
ATOM	1901	CB	LEU	10	15.921	21.586	-2.847	0.00	0.00	C
ATOM	1902	CG	LEU	10	14.374	21.492	-2.958	0.00	0.00	C
ATOM	1903	CD1	LEU	10	13.820	20.581	-1.857	0.00	0.00	C
ATOM	1904	CD2	LEU	10	13.678	22.862	-2.867	0.00	0.00	C
ATOM	1905	H	LEU	10	16.792	20.326	-5.278	0.00	0.00	H
ATOM	1906	HA	LEU	10	16.075	23.150	-4.292	0.00	0.00	H
ATOM	1907	1HB	LEU	10	16.351	20.578	-2.684	0.00	0.00	H
ATOM	1908	2HB	LEU	10	16.162	22.134	-1.913	0.00	0.00	H
ATOM	1909	HG	LEU	10	14.108	21.029	-3.927	0.00	0.00	H
ATOM	1910	1HD1	LEU	10	14.248	19.563	-1.916	0.00	0.00	H
ATOM	1911	2HD1	LEU	10	14.032	20.969	-0.842	0.00	0.00	H
ATOM	1912	3HD1	LEU	10	12.723	20.461	-1.940	0.00	0.00	H
ATOM	1913	1HD2	LEU	10	13.901	23.380	-1.915	0.00	0.00	H
ATOM	1914	2HD2	LEU	10	13.974	23.546	-3.680	0.00	0.00	H
ATOM	1915	3HD2	LEU	10	12.577	22.767	-2.930	0.00	0.00	H
ATOM	1916	N	GLU	11	19.097	22.074	-3.805	0.00	0.00	N
ATOM	1917	CA	GLU	11	20.422	22.493	-4.284	0.00	0.00	C
ATOM	1918	C	GLU	11	20.588	23.645	-5.323	0.00	0.00	C
ATOM	1919	O	GLU	11	21.575	24.379	-5.312	0.00	0.00	O
ATOM	1920	CB	GLU	11	20.985	21.146	-4.812	0.00	0.00	C
ATOM	1921	CG	GLU	11	22.132	20.545	-4.001	0.00	0.00	C
ATOM	1922	CD	GLU	11	23.464	21.293	-4.099	0.00	0.00	C

FIG. 8 - 58

ATOM	1923	OE1	GLU	11	23.989	21.571	-5.174	0.00	0.00	O
ATOM	1924	OE2	GLU	11	23.985	21.606	-2.880	0.00	0.00	O
ATOM	1925	H	GLU	11	18.982	21.086	-3.534	1.00	0.00	H
ATOM	1926	HA	GLU	11	20.989	22.752	-3.406	0.00	0.00	H
ATOM	1927	1HB	GLU	11	20.244	20.358	-4.817	0.00	0.00	H
ATOM	1928	2HB	GLU	11	21.171	21.189	-5.873	0.00	0.00	H
ATOM	1929	1HG	GLU	11	21.703	20.512	-2.987	0.00	0.00	H
ATOM	1930	2HG	GLU	11	22.312	19.494	-4.291	0.00	0.00	H
ATOM	1931	HE2	GLU	11	24.818	22.073	-2.949	0.00	0.00	H
ATOM	1932	N	HIS	12	19.642	23.740	-6.267	0.00	0.00	N
ATOM	1933	CA	HIS	12	19.603	24.832	-7.272	0.00	0.00	C
ATOM	1934	C	HIS	12	18.182	25.479	-7.383	0.00	0.00	C
ATOM	1935	O	HIS	12	17.603	25.552	-8.465	0.00	0.00	O
ATOM	1936	CB	HIS	12	20.114	24.245	-8.617	0.00	0.00	C
ATOM	1937	CG	HIS	12	21.494	23.567	-8.642	0.00	0.00	C
ATOM	1938	ND1	HIS	12	21.606	22.191	-8.514	0.00	0.00	N
ATOM	1939	CD2	HIS	12	22.730	24.180	-8.342	0.00	0.00	C
ATOM	1940	CE1	HIS	12	22.890	22.081	-8.041	0.00	0.00	C
ATOM	1941	NE2	HIS	12	23.663	23.211	-7.976	0.00	0.00	N
ATOM	1942	H	HIS	12	18.841	23.129	-6.066	0.00	0.00	H
ATOM	1943	HA	HIS	12	20.266	25.652	-6.968	0.00	0.00	H
ATOM	1944	1HB	HIS	12	19.349	23.509	-8.918	0.00	0.00	H
ATOM	1945	2HB	HIS	12	20.071	25.045	-9.379	0.00	0.00	H
ATOM	1946	HD1	HIS	12	20.829	21.530	-8.372	0.00	0.00	H
ATOM	1947	HD2	HIS	12	22.856	25.248	-8.191	0.00	0.00	H
ATOM	1948	HE1	HIS	12	23.193	21.175	-7.510	0.00	0.00	H
ATOM	1949	HE2	HIS	12	24.657	23.315	-7.727	1.00	0.00	H
ATOM	1950	N	SER	13	17.592	25.911	-6.257	0.00	0.00	N
ATOM	1951	CA	SER	13	16.129	26.183	-6.159	0.00	0.00	C
ATOM	1952	C	SER	13	15.555	27.406	-6.926	0.00	0.00	C
ATOM	1953	O	SER	13	14.523	27.328	-7.592	0.00	0.00	O
ATOM	1954	CB	SER	13	15.676	26.175	-4.680	0.00	0.00	C
ATOM	1955	OG	SER	13	14.266	25.960	-4.598	0.00	0.00	O
ATOM	1956	H	SER	13	18.030	25.452	-5.473	0.00	0.00	H

67/107

FIG. 8 - 59

ATOM	1957	HA	SER	13	15.700	25.314	-6.640	0.00	0.00	H
ATOM	1958	1HB	SER	13	16.186	25.394	-4.091	0.00	0.00	H
ATOM	1959	2HB	SER	13	15.949	27.130	-4.185	0.00	0.00	H
ATOM	1960	HG	SER	13	13.942	26.453	-3.832	0.00	0.00	H
ATOM	1961	N	ASN	14	16.334	28.477	-6.887	0.00	0.00	N
ATOM	1962	CA	ASN	14	16.254	29.595	-7.870	0.00	0.00	C
ATOM	1963	C	ASN	14	16.476	29.228	-9.382	0.00	0.00	C
ATOM	1964	O	ASN	14	15.951	29.930	-10.245	0.00	0.00	O
ATOM	1965	CB	ASN	14	17.219	30.706	-7.366	0.00	0.00	C
ATOM	1966	CG	ASN	14	16.919	32.108	-7.895	0.00	0.00	C
ATOM	1967	OD1	ASN	14	16.133	32.850	-7.325	0.00	0.00	O
ATOM	1968	ND2	ASN	14	17.517	32.530	-8.979	0.00	0.00	N
ATOM	1969	H	ASN	14	17.186	28.126	-6.444	0.00	0.00	H
ATOM	1970	HA	ASN	14	15.222	29.984	-7.820	0.00	0.00	H
ATOM	1971	1HB	ASN	14	17.154	30.804	-6.265	0.00	0.00	H
ATOM	1972	2HB	ASN	14	18.273	30.439	-7.561	0.00	0.00	H
ATOM	1973	1HD2	ASN	14	17.172	33.448	-9.274	0.00	0.00	H
ATOM	1974	2HD2	ASN	14	17.957	31.818	-9.566	0.00	0.00	H
ATOM	1975	N	LEU	15	17.204	28.141	-9.718	0.00	0.00	N
ATOM	1976	CA	LEU	15	17.171	27.571	-11.102	0.00	0.00	C
ATOM	1977	C	LEU	15	16.031	26.521	-11.412	0.00	0.00	C
ATOM	1978	O	LEU	15	15.972	25.971	-12.515	0.00	0.00	O
ATOM	1979	CB	LEU	15	18.585	27.019	-11.451	0.00	0.00	C
ATOM	1980	CG	LEU	15	19.802	27.979	-11.329	0.00	0.00	C
ATOM	1981	CD1	LEU	15	21.109	27.217	-11.592	0.00	0.00	C
ATOM	1982	CD2	LEU	15	19.709	29.172	-12.296	0.00	0.00	C
ATOM	1983	H	LEU	15	17.459	27.540	-8.918	0.00	0.00	H
ATOM	1984	HA	LEU	15	16.970	28.389	-11.803	0.00	0.00	H
ATOM	1985	1HB	LEU	15	18.760	26.122	-10.834	0.00	0.00	H
ATOM	1986	2HB	LEU	15	18.558	26.636	-12.491	0.00	0.00	H
ATOM	1987	HG	LEU	15	19.848	28.381	-10.297	0.00	0.00	H
ATOM	1988	1HD1	LEU	15	21.252	26.381	-10.887	0.00	0.00	H
ATOM	1989	2HD1	LEU	15	21.143	26.801	-12.616	0.00	0.00	H
ATOM	1990	3HD1	LEU	15	21.989	27.881	-11.483	0.00	0.00	H

68/107

FIG. 8 - 60

ATOM	1991	1HD2	LEU	15	19.640	28.855	-13.353	0.00	0.00	H
ATOM	1992	2HD2	LEU	15	18.824	29.802	-12.088	0.00	0.00	H
ATOM	1993	3HD2	LEU	15	20.587	29.841	-12.214	0.00	0.00	H
ATOM	1994	N	CYS	16	15.146	26.209	-10.448	0.00	0.00	N
ATOM	1995	CA	CYS	16	14.210	25.087	-10.488	0.00	0.00	C
ATOM	1996	C	CYS	16	12.707	25.378	-10.166	0.00	0.00	C
ATOM	1997	O	CYS	16	11.817	24.719	-10.691	0.00	0.00	O
ATOM	1998	CB	CYS	16	14.875	24.209	-9.443	0.00	0.00	C
ATOM	1999	SG	CYS	16	16.333	23.318	-10.035	0.00	0.00	S
ATOM	2000	H	CYS	16	15.548	26.241	-9.507	0.00	0.00	H
ATOM	2001	HA	CYS	16	14.267	24.522	-11.403	0.00	0.00	H
ATOM	2002	1HB	CYS	16	15.050	24.770	-8.551	0.00	0.00	H
ATOM	2003	2HB	CYS	16	14.187	23.538	-9.012	0.00	0.00	H
TER	2004		CYS	16						
HETATM	2005	N	NH2	17H	12.344	26.224	-9.219	0.00	0.00	N
HETATM	2006	1HN	NH2	17H	11.364	26.516	-9.291	0.00	0.00	H
HETATM	2007	2HN	NH2	17H	13.117	26.763	-8.793	0.00	0.00	H
ENDMDL										
MODEL	10									
ATOM	2008	N	GLY	1	14.432	13.271	-13.202	0.00	0.00	N
ATOM	2009	CA	GLY	1	15.517	14.193	-12.746	0.00	0.00	C
ATOM	2010	C	GLY	1	16.063	15.239	-13.751	0.00	0.00	C
ATOM	2011	O	GLY	1	15.808	15.141	-14.945	0.00	0.00	O
ATOM	2012	1H	GLY	1	13.609	13.821	-13.484	1.00	0.00	H
ATOM	2013	2H	GLY	1	14.766	12.717	-14.004	1.00	0.00	H
ATOM	2014	3H	GLY	1	14.174	12.637	-12.433	1.00	0.00	H
ATOM	2015	1HA	GLY	1	15.167	14.765	-11.870	0.00	0.00	H
ATOM	2016	2HA	GLY	1	16.397	13.615	-12.405	0.00	0.00	H
ATOM	2017	N	CYS	2	16.864	16.247	-13.386	0.00	0.00	N
ATOM	2018	CA	CYS	2	17.331	16.492	-11.994	0.00	0.00	C
ATOM	2019	C	CYS	2	16.351	17.440	-11.195	0.00	0.00	C
ATOM	2020	O	CYS	2	15.954	17.099	-10.087	0.00	0.00	O
ATOM	2021	CB	CYS	2	18.754	17.067	-12.108	0.00	0.00	C
ATOM	2022	SG	CYS	2	19.146	17.973	-10.596	0.00	0.00	S

69/107

FIG. 8 - 61

ATOM	2023	H	CYS	2	17.482	16.490	-14.163	0.00	0.00	H
ATOM	2024	HA	CYS	2	17.423	15.555	-11.414	0.00	0.00	H
ATOM	2025	1HB	CYS	2	19.488	16.286	-12.371	0.00	0.00	H
ATOM	2026	2HB	CYS	2	18.802	17.823	-12.917	0.00	0.00	H
ATOM	2027	N	CYS	3	15.940	18.608	-11.714	0.00	0.00	N
ATOM	2028	CA	CYS	3	14.788	19.392	-11.211	0.00	0.00	C
ATOM	2029	C	CYS	3	13.371	18.710	-11.150	0.00	0.00	C
ATOM	2030	O	CYS	3	12.558	19.085	-10.304	0.00	0.00	O
ATOM	2031	CB	CYS	3	14.913	20.601	-12.145	0.00	0.00	C
ATOM	2032	SG	CYS	3	16.186	21.689	-11.467	0.00	0.00	S
ATOM	2033	H	CYS	3	16.269	18.871	-12.647	0.00	0.00	H
ATOM	2034	HA	CYS	3	14.975	19.778	-10.184	0.00	0.00	H
ATOM	2035	1HB	CYS	3	15.096	20.369	-13.215	0.00	0.00	H
ATOM	2036	2HB	CYS	3	13.973	21.134	-12.169	0.00	0.00	H
ATOM	2037	N	SER	4	13.097	17.671	-11.957	0.00	0.00	N
ATOM	2038	CA	SER	4	12.028	16.680	-11.702	0.00	0.00	C
ATOM	2039	C	SER	4	12.317	15.546	-10.640	0.00	0.00	C
ATOM	2040	O	SER	4	11.478	14.671	-10.433	0.00	0.00	O
ATOM	2041	CB	SER	4	11.704	16.154	-13.119	0.00	0.00	C
ATOM	2042	OG	SER	4	12.809	15.582	-13.833	0.00	0.00	O
ATOM	2043	H	SER	4	13.821	17.372	-12.604	0.00	0.00	H
ATOM	2044	HA	SER	4	11.119	17.198	-11.331	0.00	0.00	H
ATOM	2045	1HB	SER	4	10.925	15.399	-13.021	0.00	0.00	H
ATOM	2046	2HB	SER	4	11.240	16.960	-13.726	0.00	0.00	H
ATOM	2047	HG	SER	4	12.656	15.783	-14.769	0.00	0.00	H
ATOM	2048	N	ASN	5	13.442	15.588	-9.904	0.00	0.00	N
ATOM	2049	CA	ASN	5	13.521	15.080	-8.516	0.00	0.00	C
ATOM	2050	C	ASN	5	13.137	16.199	-7.474	0.00	0.00	C
ATOM	2051	O	ASN	5	13.196	17.395	-7.788	0.00	0.00	O
ATOM	2052	CB	ASN	5	15.016	14.734	-8.245	0.00	0.00	C
ATOM	2053	CG	ASN	5	15.689	13.570	-8.946	0.00	0.00	C
ATOM	2054	OD1	ASN	5	15.290	13.040	-9.976	0.00	0.00	O
ATOM	2055	ND2	ASN	5	16.776	13.161	-8.352	0.00	0.00	N
ATOM	2056	H	ASN	5	14.126	16.304	-10.173	0.00	0.00	H

70/107

FIG. 8 - 62

ATOM	2057	HA	ASN	5	12.847	14.208	-8.327	0.00	0.00	H
ATOM	2058	1HB	ASN	5	15.664	15.624	-8.324	0.00	0.00	H
ATOM	2059	2HB	ASN	5	15.103	14.503	-7.184	0.00	0.00	H
ATOM	2060	1HD2	ASN	5	16.997	12.194	-8.585	0.00	0.00	H
ATOM	2061	2HD2	ASN	5	16.926	13.620	-7.446	0.00	0.00	H
ATOM	2062	N	PRO	6	12.865	15.864	-6.187	0.00	0.00	N
ATOM	2063	CA	PRO	6	12.805	16.876	-5.088	0.00	0.00	C
ATOM	2064	C	PRO	6	14.139	17.612	-4.737	0.00	0.00	C
ATOM	2065	O	PRO	6	14.192	18.831	-4.583	0.00	0.00	O
ATOM	2066	CB	PRO	6	12.226	16.023	-3.941	0.00	0.00	C
ATOM	2067	CG	PRO	6	12.797	14.632	-4.222	0.00	0.00	C
ATOM	2068	CD	PRO	6	12.696	14.470	-5.727	0.00	0.00	C
ATOM	2069	HA	PRO	6	12.094	17.664	-5.336	0.00	0.00	H
ATOM	2070	1HB	PRO	6	12.483	16.408	-2.936	0.00	0.00	H
ATOM	2071	2HB	PRO	6	11.119	16.003	-3.992	0.00	0.00	H
ATOM	2072	1HG	PRO	6	13.849	14.562	-3.898	0.00	0.00	H
ATOM	2073	2HG	PRO	6	12.323	13.818	-3.692	0.00	0.00	H
ATOM	2074	1HD	PRO	6	13.461	13.753	-6.045	0.00	0.00	H
ATOM	2075	2HD	PRO	6	11.756	14.056	-6.132	0.00	0.00	H
ATOM	2076	N	VAL	7	15.217	16.844	-4.627	0.00	0.00	N
ATOM	2077	CA	VAL	7	16.438	17.235	-3.866	0.00	0.00	C
ATOM	2078	C	VAL	7	17.480	17.991	-4.722	0.00	0.00	C
ATOM	2079	O	VAL	7	17.900	19.088	-4.349	0.00	0.00	O
ATOM	2080	CB	VAL	7	16.958	15.921	-3.170	0.00	0.00	C
ATOM	2081	CG1	VAL	7	18.411	15.969	-2.634	0.00	0.00	C
ATOM	2082	CG2	VAL	7	16.089	15.512	-1.953	0.00	0.00	C
ATOM	2083	H	VAL	7	14.924	15.867	-4.742	0.00	0.00	H
ATOM	2084	HA	VAL	7	16.172	18.010	-3.120	0.00	0.00	H
ATOM	2085	HB	VAL	7	16.913	15.105	-3.937	0.00	0.00	H
ATOM	2086	1HG1	VAL	7	18.553	16.771	-1.883	0.00	0.00	H
ATOM	2087	2HG1	VAL	7	18.711	15.021	-2.147	0.00	0.00	H
ATOM	2088	3HG1	VAL	7	19.153	16.144	-3.434	0.00	0.00	H
ATOM	2089	1HG2	VAL	7	15.015	15.435	-2.193	0.00	0.00	H
ATOM	2090	2HG2	VAL	7	16.386	14.528	-1.538	0.00	0.00	H

71/107

FIG. 8 - 63

ATOM	2091	3HG2	VAL	7	16.165	16.240	-1.122	0.00	0.00	H
ATOM	2092	N	CYS	8	17.896	17.441	-5.872	0.00	0.00	N
ATOM	2093	CA	CYS	8	18.840	18.150	-6.784	0.00	0.00	C
ATOM	2094	C	CYS	8	18.348	19.404	-7.580	0.00	0.00	C
ATOM	2095	O	CYS	8	19.099	20.312	-7.945	0.00	0.00	O
ATOM	2096	CB	CYS	8	19.680	17.158	-7.605	0.00	0.00	C
ATOM	2097	SG	CYS	8	18.762	16.704	-9.078	0.00	0.00	S
ATOM	2098	H	CYS	8	17.375	16.592	-6.065	0.00	0.00	H
ATOM	2099	HA	CYS	8	19.470	18.622	-6.055	0.00	0.00	H
ATOM	2100	1HB	CYS	8	20.640	17.616	-7.911	0.00	0.00	H
ATOM	2101	2HB	CYS	8	19.952	16.254	-7.026	0.00	0.00	H
ATOM	2102	N	HIS	9	17.032	19.479	-7.703	0.00	0.00	N
ATOM	2103	CA	HIS	9	16.227	20.727	-7.819	0.00	0.00	C
ATOM	2104	C	HIS	9	16.624	21.855	-6.823	0.00	0.00	C
ATOM	2105	O	HIS	9	16.788	23.015	-7.177	0.00	0.00	O
ATOM	2106	CB	HIS	9	14.763	20.256	-7.651	0.00	0.00	C
ATOM	2107	CG	HIS	9	13.443	20.918	-7.294	0.00	0.00	C
ATOM	2108	ND1	HIS	9	12.247	20.457	-7.805	0.00	0.00	N
ATOM	2109	CD2	HIS	9	13.344	22.259	-7.060	0.00	0.00	C
ATOM	2110	CE1	HIS	9	11.538	21.628	-7.902	0.00	0.00	C
ATOM	2111	NE2	HIS	9	12.095	22.761	-7.389	0.00	0.00	N
ATOM	2112	H	HIS	9	16.613	18.615	-7.362	0.00	0.00	H
ATOM	2113	HA	HIS	9	16.271	21.075	-8.813	0.00	0.00	H
ATOM	2114	1HB	HIS	9	14.649	19.276	-7.962	0.00	0.00	H
ATOM	2115	2HB	HIS	9	14.896	19.917	-6.638	0.00	0.00	H
ATOM	2116	HD1	HIS	9	12.130	19.621	-8.402	0.00	0.00	H
ATOM	2117	HD2	HIS	9	14.281	22.747	-7.032	0.00	0.00	H
ATOM	2118	HE1	HIS	9	10.736	21.735	-8.629	0.00	0.00	H
ATOM	2119	HE2	HIS	9	11.703	23.707	-7.279	1.00	0.00	H
ATOM	2120	N	LEU	10	16.617	21.435	-5.568	0.00	0.00	N
ATOM	2121	CA	LEU	10	16.638	22.341	-4.368	0.00	0.00	C
ATOM	2122	C	LEU	10	18.027	22.739	-3.781	0.00	0.00	C
ATOM	2123	O	LEU	10	18.188	23.850	-3.278	0.00	0.00	O
ATOM	2124	CB	LEU	10	15.630	21.863	-3.289	0.00	0.00	C

72/107

FIG. 8 - 64

ATOM	2125	CG	LEU	10	14.128	21.969	-3.659	0.00	0.00	C
ATOM	2126	CD1	LEU	10	13.257	21.341	-2.569	0.00	0.00	C
ATOM	2127	CD2	LEU	10	13.651	23.415	-3.911	0.00	0.00	C
ATOM	2128	H	LEU	10	16.593	20.389	-5.655	0.00	0.00	H
ATOM	2129	HA	LEU	10	16.278	23.327	-4.699	0.00	0.00	H
ATOM	2130	1HB	LEU	10	15.876	20.820	-3.008	0.00	0.00	H
ATOM	2131	2HB	LEU	10	15.790	22.441	-2.357	0.00	0.00	H
ATOM	2132	HG	LEU	10	13.954	21.370	-4.567	0.00	0.00	H
ATOM	2133	1HD1	LEU	10	13.528	20.283	-2.395	0.00	0.00	H
ATOM	2134	2HD1	LEU	10	13.350	21.873	-1.603	0.00	0.00	H
ATOM	2135	3HD1	LEU	10	12.187	21.348	-2.850	0.00	0.00	H
ATOM	2136	1HD2	LEU	10	13.817	24.068	-3.035	0.00	0.00	H
ATOM	2137	2HD2	LEU	10	14.162	23.892	-4.766	0.00	0.00	H
ATOM	2138	3HD2	LEU	10	12.570	23.456	-4.147	0.00	0.00	H
ATOM	2139	N	GLU	11	19.069	21.938	-4.007	0.00	0.00	N
ATOM	2140	CA	GLU	11	20.399	22.416	-4.408	0.00	0.00	C
ATOM	2141	C	GLU	11	20.555	23.700	-5.281	0.00	0.00	C
ATOM	2142	O	GLU	11	21.500	24.473	-5.140	0.00	0.00	O
ATOM	2143	CB	GLU	11	20.954	21.167	-5.114	0.00	0.00	C
ATOM	2144	CG	GLU	11	21.840	20.196	-4.329	0.00	0.00	C
ATOM	2145	CD	GLU	11	22.508	19.118	-5.190	0.00	0.00	C
ATOM	2146	OE1	GLU	11	22.471	19.103	-6.421	0.00	0.00	O
ATOM	2147	OE2	GLU	11	23.142	18.182	-4.430	0.00	0.00	O
ATOM	2148	H	GLU	11	18.933	20.923	-3.895	1.00	0.00	H
ATOM	2149	HA	GLU	11	20.982	22.550	-3.534	0.00	0.00	H
ATOM	2150	1HB	GLU	11	20.163	20.573	-5.529	0.00	0.00	H
ATOM	2151	2HB	GLU	11	21.427	21.465	-6.025	0.00	0.00	H
ATOM	2152	1HG	GLU	11	22.603	20.766	-3.785	0.00	0.00	H
ATOM	2153	2HG	GLU	11	21.193	19.725	-3.574	0.00	0.00	H
ATOM	2154	HE2	GLU	11	23.556	17.508	-4.970	0.00	0.00	H
ATOM	2155	N	HIS	12	19.653	23.856	-6.252	0.00	0.00	N
ATOM	2156	CA	HIS	12	19.614	24.970	-7.171	0.00	0.00	C
ATOM	2157	C	HIS	12	18.198	25.620	-7.181	0.00	0.00	C
ATOM	2158	O	HIS	12	17.517	25.648	-8.208	0.00	0.00	O

73/107

FIG. 8 - 65

ATOM	2159	CB	HIS	12	19.987	24.338	-8.497	0.00	0.00	C
ATOM	2160	CG	HIS	12	21.260	23.496	-8.717	0.00	0.00	C
ATOM	2161	ND1	HIS	12	21.235	22.113	-8.786	0.00	0.00	N
ATOM	2162	CD2	HIS	12	22.590	23.946	-8.584	0.00	0.00	C
ATOM	2163	CE1	HIS	12	22.567	21.817	-8.640	0.00	0.00	C
ATOM	2164	NE2	HIS	12	23.460	22.856	-8.554	0.00	0.00	N
ATOM	2165	H	HIS	12	18.949	23.151	-6.428	0.00	0.00	H
ATOM	2166	HA	HIS	12	20.338	25.733	-6.969	0.00	0.00	H
ATOM	2167	1HB	HIS	12	19.070	23.909	-8.859	0.00	0.00	H
ATOM	2168	2HB	HIS	12	20.015	25.190	-9.108	0.00	0.00	H
ATOM	2169	HD1	HIS	12	20.431	21.483	-8.629	0.00	0.00	H
ATOM	2170	HD2	HIS	12	22.868	24.979	-8.397	0.00	0.00	H
ATOM	2171	HE1	HIS	12	22.890	20.787	-8.465	0.00	0.00	H
ATOM	2172	HE2	HIS	12	24.487	22.836	-8.487	1.00	0.00	H
ATOM	2173	N	SER	13	17.704	26.045	-6.021	0.00	0.00	N
ATOM	2174	CA	SER	13	16.270	26.382	-5.845	0.00	0.00	C
ATOM	2175	C	SER	13	15.747	27.643	-6.596	0.00	0.00	C
ATOM	2176	O	SER	13	14.666	27.653	-7.178	0.00	0.00	O
ATOM	2177	CB	SER	13	15.918	26.402	-4.338	0.00	0.00	C
ATOM	2178	OG	SER	13	16.581	27.464	-3.647	0.00	0.00	O
ATOM	2179	H	SER	13	18.202	25.605	-5.263	0.00	0.00	H
ATOM	2180	HA	SER	13	15.806	25.516	-6.322	0.00	0.00	H
ATOM	2181	1HB	SER	13	14.822	26.491	-4.195	0.00	0.00	H
ATOM	2182	2HB	SER	13	16.190	25.446	-3.853	0.00	0.00	H
ATOM	2183	HG	SER	13	16.050	28.266	-3.728	0.00	0.00	H
ATOM	2184	N	ASN	14	16.631	28.630	-6.666	0.00	0.00	N
ATOM	2185	CA	ASN	14	16.617	29.686	-7.714	0.00	0.00	C
ATOM	2186	C	ASN	14	16.649	29.229	-9.214	0.00	0.00	C
ATOM	2187	O	ASN	14	16.140	29.970	-10.055	0.00	0.00	O
ATOM	2188	CB	ASN	14	17.764	30.675	-7.366	0.00	0.00	C
ATOM	2189	CG	ASN	14	17.580	32.098	-7.894	0.00	0.00	C
ATOM	2190	OD1	ASN	14	17.027	32.959	-7.226	0.00	0.00	O
ATOM	2191	ND2	ASN	14	18.027	32.409	-9.083	0.00	0.00	N
ATOM	2192	H	ASN	14	17.469	28.208	-6.256	0.00	0.00	H

74/107

FIG. 8 - 66

ATOM	2193	HA	ASN	14	15.652	30.205	-7.612	0.00	0.00	H
ATOM	2194	1HB	ASN	14	17.858	30.795	-6.270	0.00	0.00	H
ATOM	2195	2HB	ASN	14	18.744	30.273	-7.686	0.00	0.00	H
ATOM	2196	1HD2	ASN	14	17.766	33.363	-9.347	0.00	0.00	H
ATOM	2197	2HD2	ASN	14	18.212	31.626	-9.713	0.00	0.00	H
ATOM	2198	N	LEU	15	17.196	28.048	-9.578	0.00	0.00	N
ATOM	2199	CA	LEU	15	16.978	27.488	-10.947	0.00	0.00	C
ATOM	2200	C	LEU	15	15.620	26.732	-11.192	0.00	0.00	C
ATOM	2201	O	LEU	15	15.232	26.553	-12.349	0.00	0.00	O
ATOM	2202	CB	LEU	15	18.203	26.629	-11.380	0.00	0.00	C
ATOM	2203	CG	LEU	15	19.612	27.283	-11.352	0.00	0.00	C
ATOM	2204	CD1	LEU	15	20.667	26.280	-11.838	0.00	0.00	C
ATOM	2205	CD2	LEU	15	19.705	28.551	-12.221	0.00	0.00	C
ATOM	2206	H	LEU	15	17.494	27.415	-8.810	0.00	0.00	H
ATOM	2207	HA	LEU	15	16.936	28.332	-11.647	0.00	0.00	H
ATOM	2208	1HB	LEU	15	18.214	25.707	-10.772	0.00	0.00	H
ATOM	2209	2HB	LEU	15	18.013	26.276	-12.414	0.00	0.00	H
ATOM	2210	HG	LEU	15	19.853	27.570	-10.309	0.00	0.00	H
ATOM	2211	1HD1	LEU	15	20.644	25.332	-11.275	0.00	0.00	H
ATOM	2212	2HD1	LEU	15	20.522	26.023	-12.905	0.00	0.00	H
ATOM	2213	3HD1	LEU	15	21.688	26.693	-11.743	0.00	0.00	H
ATOM	2214	1HD2	LEU	15	19.439	28.358	-13.278	0.00	0.00	H
ATOM	2215	2HD2	LEU	15	19.030	29.350	-11.862	0.00	0.00	H
ATOM	2216	3HD2	LEU	15	20.722	28.987	-12.218	0.00	0.00	H
ATOM	2217	N	CYS	16	14.934	26.226	-10.147	0.00	0.00	N
ATOM	2218	CA	CYS	16	13.785	25.290	-10.291	0.00	0.00	C
ATOM	2219	C	CYS	16	12.516	25.503	-9.392	0.00	0.00	C
ATOM	2220	O	CYS	16	11.554	24.743	-9.480	0.00	0.00	O
ATOM	2221	CB	CYS	16	14.428	23.909	-10.052	0.00	0.00	C
ATOM	2222	SG	CYS	16	15.528	23.569	-11.455	0.00	0.00	S
ATOM	2223	H	CYS	16	15.438	26.334	-9.266	0.00	0.00	H
ATOM	2224	HA	CYS	16	13.387	25.317	-11.325	0.00	0.00	H
ATOM	2225	1HB	CYS	16	14.926	23.857	-9.057	0.00	0.00	H
ATOM	2226	2HB	CYS	16	13.649	23.138	-10.044	0.00	0.00	H

SUBSTITUTE SHEET (RULE 26)

76/107

FIG. 8 - 68

ATOM	2259	2HB	CYS	3	14.913	20.901	-13.420	0.00	0.00	H
ATOM	2260	N	SER	4	13.643	18.272	-12.026	0.00	0.00	N
ATOM	2261	CA	SER	4	12.575	17.241	-11.933	0.00	0.00	C
ATOM	2262	C	SER	4	12.717	16.123	-10.834	0.00	0.00	C
ATOM	2263	O	SER	4	11.845	15.261	-10.729	0.00	0.00	O
ATOM	2264	CB	SER	4	12.459	16.673	-13.369	0.00	0.00	C
ATOM	2265	OG	SER	4	13.652	16.046	-13.863	0.00	0.00	O
ATOM	2266	H	SER	4	14.490	18.046	-12.542	0.00	0.00	H
ATOM	2267	HA	SER	4	11.608	17.735	-11.710	0.00	0.00	H
ATOM	2268	1HB	SER	4	11.634	15.947	-13.393	0.00	0.00	H
ATOM	2269	2HB	SER	4	12.141	17.476	-14.067	0.00	0.00	H
ATOM	2270	HG	SER	4	13.568	16.053	-14.829	0.00	0.00	H
ATOM	2271	N	ASN	5	13.753	16.142	-9.976	0.00	0.00	N
ATOM	2272	CA	ASN	5	13.712	15.477	-8.648	0.00	0.00	C
ATOM	2273	C	ASN	5	13.159	16.428	-7.516	0.00	0.00	C
ATOM	2274	O	ASN	5	13.225	17.653	-7.670	0.00	0.00	O
ATOM	2275	CB	ASN	5	15.185	15.140	-8.295	0.00	0.00	C
ATOM	2276	CG	ASN	5	15.843	13.954	-8.973	0.00	0.00	C
ATOM	2277	OD1	ASN	5	15.415	13.394	-9.974	0.00	0.00	O
ATOM	2278	ND2	ASN	5	16.937	13.541	-8.406	0.00	0.00	N
ATOM	2279	H	ASN	5	14.434	16.894	-10.132	0.00	0.00	H
ATOM	2280	HA	ASN	5	13.105	14.549	-8.669	0.00	0.00	H
ATOM	2281	1HB	ASN	5	15.834	16.032	-8.363	0.00	0.00	H
ATOM	2282	2HB	ASN	5	15.211	14.889	-7.231	0.00	0.00	H
ATOM	2283	1HD2	ASN	5	17.101	12.554	-8.604	0.00	0.00	H
ATOM	2284	2HD2	ASN	5	17.118	14.008	-7.514	0.00	0.00	H
ATOM	2285	N	PRO	6	12.762	15.938	-6.307	0.00	0.00	N
ATOM	2286	CA	PRO	6	12.725	16.787	-5.079	0.00	0.00	C
ATOM	2287	C	PRO	6	14.041	17.516	-4.651	0.00	0.00	C
ATOM	2288	O	PRO	6	14.085	18.734	-4.500	0.00	0.00	O
ATOM	2289	CB	PRO	6	12.080	15.845	-4.057	0.00	0.00	C
ATOM	2290	CG	PRO	6	12.367	14.420	-4.542	0.00	0.00	C
ATOM	2291	CD	PRO	6	12.458	14.514	-6.047	0.00	0.00	C
ATOM	2292	HA	PRO	6	12.022	17.599	-5.197	0.00	0.00	H

77/107

FIG. 8 - 69

ATOM	2293	1HB	PRO	6	12.422	16.065	-3.035	0.00	0.00	H
ATOM	2294	2HB	PRO	6	10.983	16.006	-4.040	0.00	0.00	H
ATOM	2295	1HG	PRO	6	13.320	14.028	-4.221	0.00	0.00	H
ATOM	2296	2HG	PRO	6	11.618	13.687	-4.194	0.00	0.00	H
ATOM	2297	1HD	PRO	6	13.176	13.802	-6.487	0.00	0.00	H
ATOM	2298	2HD	PRO	6	11.488	14.212	-6.414	0.00	0.00	H
ATOM	2299	N	VAL	7	15.123	16.766	-4.520	0.00	0.00	N
ATOM	2300	CA	VAL	7	16.361	17.176	-3.800	0.00	0.00	C
ATOM	2301	C	VAL	7	17.403	17.839	-4.733	0.00	0.00	C
ATOM	2302	O	VAL	7	17.901	18.932	-4.463	0.00	0.00	O
ATOM	2303	CB	VAL	7	16.877	15.851	-3.130	0.00	0.00	C
ATOM	2304	CG1	VAL	7	18.244	15.984	-2.437	0.00	0.00	C
ATOM	2305	CG2	VAL	7	15.926	15.247	-2.080	0.00	0.00	C
ATOM	2306	H	VAL	7	14.914	15.780	-4.630	0.00	0.00	H
ATOM	2307	HA	VAL	7	16.143	17.969	-3.059	0.00	0.00	H
ATOM	2308	HB	VAL	7	16.978	15.094	-3.939	0.00	0.00	H
ATOM	2309	1HG1	VAL	7	19.036	16.293	-3.142	0.00	0.00	H
ATOM	2310	2HG1	VAL	7	18.211	16.729	-1.621	0.00	0.00	H
ATOM	2311	3HG1	VAL	7	18.574	15.022	-1.999	0.00	0.00	H
ATOM	2312	1HG2	VAL	7	14.935	15.012	-2.509	0.00	0.00	H
ATOM	2313	2HG2	VAL	7	16.320	14.297	-1.675	0.00	0.00	H
ATOM	2314	3HG2	VAL	7	15.763	15.940	-1.236	0.00	0.00	H
ATOM	2315	N	CYS	8	17.720	17.182	-5.856	0.00	0.00	N
ATOM	2316	CA	CYS	8	18.599	17.767	-6.903	0.00	0.00	C
ATOM	2317	C	CYS	8	18.168	19.114	-7.559	0.00	0.00	C
ATOM	2318	O	CYS	8	18.976	19.958	-7.940	0.00	0.00	O
ATOM	2319	CB	CYS	8	18.951	16.635	-7.903	0.00	0.00	C
ATOM	2320	SG	CYS	8	20.346	16.984	-9.013	0.00	0.00	S
ATOM	2321	H	CYS	8	17.357	16.233	-5.799	0.00	0.00	H
ATOM	2322	HA	CYS	8	19.428	18.095	-6.293	0.00	0.00	H
ATOM	2323	1HB	CYS	8	19.221	15.705	-7.364	0.00	0.00	H
ATOM	2324	2HB	CYS	8	18.075	16.381	-8.524	0.00	0.00	H
ATOM	2325	N	HIS	9	16.870	19.352	-7.546	0.00	0.00	N
ATOM	2326	CA	HIS	9	16.223	20.669	-7.713	0.00	0.00	C

FIG. 8 - 70

ATOM	2327	C	HIS	9	16.683	21.767	-6.697	0.00	0.00	C
ATOM	2328	O	HIS	9	16.869	22.928	-7.055	0.00	0.00	O
ATOM	2329	CB	HIS	9	14.712	20.290	-7.654	0.00	0.00	C
ATOM	2330	CG	HIS	9	13.514	21.175	-7.315	0.00	0.00	C
ATOM	2331	ND1	HIS	9	12.258	20.879	-7.804	0.00	0.00	N
ATOM	2332	CD2	HIS	9	13.498	22.443	-6.747	0.00	0.00	C
ATOM	2333	CE1	HIS	9	11.586	22.045	-7.538	0.00	0.00	C
ATOM	2334	NE2	HIS	9	12.240	23.026	-6.847	0.00	0.00	N
ATOM	2335	H	HIS	9	16.385	18.565	-7.123	0.00	0.00	H
ATOM	2336	HA	HIS	9	16.478	21.009	-8.700	0.00	0.00	H
ATOM	2337	1HB	HIS	9	14.473	19.599	-8.475	0.00	0.00	H
ATOM	2338	2HB	HIS	9	14.658	19.678	-6.730	0.00	0.00	H
ATOM	2339	HD1	HIS	9	12.013	20.122	-8.463	0.00	0.00	H
ATOM	2340	HD2	HIS	9	14.410	22.916	-6.457	0.00	0.00	H
ATOM	2341	HE1	HIS	9	10.669	22.285	-8.070	0.00	0.00	H
ATOM	2342	HE2	HIS	9	11.900	23.935	-6.501	1.00	0.00	H
ATOM	2343	N	LEU	10	16.765	21.369	-5.432	0.00	0.00	N
ATOM	2344	CA	LEU	10	16.835	22.294	-4.251	0.00	0.00	C
ATOM	2345	C	LEU	10	18.247	22.752	-3.769	0.00	0.00	C
ATOM	2346	O	LEU	10	18.412	23.870	-3.285	0.00	0.00	O
ATOM	2347	CB	LEU	10	15.971	21.736	-3.086	0.00	0.00	C
ATOM	2348	CG	LEU	10	14.437	21.708	-3.312	0.00	0.00	C
ATOM	2349	CD1	LEU	10	13.751	20.917	-2.192	0.00	0.00	C
ATOM	2350	CD2	LEU	10	13.800	23.108	-3.378	0.00	0.00	C
ATOM	2351	H	LEU	10	17.004	20.358	-5.442	0.00	0.00	H
ATOM	2352	HA	LEU	10	16.375	23.241	-4.558	0.00	0.00	H
ATOM	2353	1HB	LEU	10	16.334	20.719	-2.836	0.00	0.00	H
ATOM	2354	2HB	LEU	10	16.166	22.324	-2.166	0.00	0.00	H
ATOM	2355	HG	LEU	10	14.237	21.178	-4.262	0.00	0.00	H
ATOM	2356	1HD1	LEU	10	14.143	19.886	-2.120	0.00	0.00	H
ATOM	2357	2HD1	LEU	10	13.886	21.390	-1.201	0.00	0.00	H
ATOM	2358	3HD1	LEU	10	12.662	20.825	-2.367	0.00	0.00	H
ATOM	2359	1HD2	LEU	10	13.975	23.687	-2.451	0.00	0.00	H
ATOM	2360	2HD2	LEU	10	14.194	23.716	-4.209	0.00	0.00	H

79/107

FIG. 8 - 71

ATOM	2361	3HD2	LEU	10	12.705	23.056	-3.524	0.00	0.00	H
ATOM	2362	N	GLU	11	19.293	21.969	-4.048	0.00	0.00	N
ATOM	2363	CA	GLU	11	20.569	22.428	-4.615	0.00	0.00	C
ATOM	2364	C	GLU	11	20.706	23.839	-5.257	0.00	0.00	C
ATOM	2365	O	GLU	11	21.649	24.588	-5.018	0.00	0.00	O
ATOM	2366	CB	GLU	11	20.851	21.278	-5.640	0.00	0.00	C
ATOM	2367	CG	GLU	11	22.210	20.622	-5.488	0.00	0.00	C
ATOM	2368	CD	GLU	11	23.381	21.455	-6.010	0.00	0.00	C
ATOM	2369	OE1	GLU	11	23.430	21.855	-7.172	0.00	0.00	O
ATOM	2370	OE2	GLU	11	24.329	21.697	-5.065	0.00	0.00	O
ATOM	2371	H	GLU	11	19.197	20.963	-3.851	1.00	0.00	H
ATOM	2372	HA	GLU	11	21.292	22.346	-3.813	0.00	0.00	H
ATOM	2373	1HB	GLU	11	20.189	20.416	-5.526	0.00	0.00	H
ATOM	2374	2HB	GLU	11	20.641	21.586	-6.667	0.00	0.00	H
ATOM	2375	1HG	GLU	11	22.201	20.404	-4.410	0.00	0.00	H
ATOM	2376	2HG	GLU	11	22.236	19.643	-6.000	0.00	0.00	H
ATOM	2377	HE2	GLU	11	25.057	22.220	-5.398	0.00	0.00	H
ATOM	2378	N	HIS	12	19.750	24.127	-6.144	0.00	0.00	N
ATOM	2379	CA	HIS	12	19.674	25.376	-6.921	0.00	0.00	C
ATOM	2380	C	HIS	12	18.211	25.828	-7.155	0.00	0.00	C
ATOM	2381	O	HIS	12	17.701	25.791	-8.267	0.00	0.00	O
ATOM	2382	CB	HIS	12	20.679	25.261	-8.090	0.00	0.00	C
ATOM	2383	CG	HIS	12	20.646	24.114	-9.096	0.00	0.00	C
ATOM	2384	ND1	HIS	12	21.761	23.324	-9.317	0.00	0.00	N
ATOM	2385	CD2	HIS	12	19.490	23.369	-9.294	0.00	0.00	C
ATOM	2386	CE1	HIS	12	21.175	22.107	-9.507	0.00	0.00	C
ATOM	2387	NE2	HIS	12	19.807	22.049	-9.598	0.00	0.00	N
ATOM	2388	H	HIS	12	19.058	23.385	-6.204	0.00	0.00	H
ATOM	2389	HA	HIS	12	20.067	26.174	-6.319	0.00	0.00	H
ATOM	2390	1HB	HIS	12	20.781	26.228	-8.609	0.00	0.00	H
ATOM	2391	2HB	HIS	12	21.585	25.087	-7.498	0.00	0.00	H
ATOM	2392	HD1	HIS	12	22.705	23.477	-8.930	0.00	0.00	H
ATOM	2393	HD2	HIS	12	18.642	23.717	-8.714	0.00	0.00	H
ATOM	2394	HE1	HIS	12	21.732	21.209	-9.228	0.00	0.00	H

FIG. 8 - 72

ATOM	2395	HE2	HIS	12	19.191	21.255	-9.825	1.00	0.00	H
ATOM	2396	N	SER	13	17.523	26.185	-6.068	0.00	0.00	N
ATOM	2397	CA	SER	13	16.046	26.357	-6.045	0.00	0.00	C
ATOM	2398	C	SER	13	15.403	27.496	-6.865	0.00	0.00	C
ATOM	2399	O	SER	13	14.404	27.297	-7.553	0.00	0.00	O
ATOM	2400	CB	SER	13	15.549	26.451	-4.576	0.00	0.00	C
ATOM	2401	OG	SER	13	16.041	25.406	-3.743	0.00	0.00	O
ATOM	2402	H	SER	13	17.917	25.664	-5.293	0.00	0.00	H
ATOM	2403	HA	SER	13	15.710	25.459	-6.555	0.00	0.00	H
ATOM	2404	1HB	SER	13	15.848	27.426	-4.139	0.00	0.00	H
ATOM	2405	2HB	SER	13	14.441	26.450	-4.540	0.00	0.00	H
ATOM	2406	HG	SER	13	16.085	25.742	-2.837	0.00	0.00	H
ATOM	2407	N	ASN	14	16.087	28.628	-6.837	0.00	0.00	N
ATOM	2408	CA	ASN	14	15.978	29.687	-7.890	0.00	0.00	C
ATOM	2409	C	ASN	14	16.141	29.192	-9.368	0.00	0.00	C
ATOM	2410	O	ASN	14	15.446	29.652	-10.272	0.00	0.00	O
ATOM	2411	CB	ASN	14	17.003	30.825	-7.614	0.00	0.00	C
ATOM	2412	CG	ASN	14	16.955	31.519	-6.250	0.00	0.00	C
ATOM	2413	OD1	ASN	14	15.923	31.659	-5.609	0.00	0.00	O
ATOM	2414	ND2	ASN	14	18.080	31.976	-5.766	0.00	0.00	N
ATOM	2415	H	ASN	14	16.935	28.369	-6.325	0.00	0.00	H
ATOM	2416	HA	ASN	14	14.964	30.108	-7.832	0.00	0.00	H
ATOM	2417	1HB	ASN	14	18.025	30.447	-7.804	0.00	0.00	H
ATOM	2418	2HB	ASN	14	16.854	31.625	-8.364	0.00	0.00	H
ATOM	2419	1HD2	ASN	14	17.952	32.539	-4.918	0.00	0.00	H
ATOM	2420	2HD2	ASN	14	18.893	31.941	-6.386	0.00	0.00	H
ATOM	2421	N	LEU	15	17.056	28.237	-9.587	0.00	0.00	N
ATOM	2422	CA	LEU	15	17.346	27.646	-10.917	0.00	0.00	C
ATOM	2423	C	LEU	15	16.491	26.380	-11.307	0.00	0.00	C
ATOM	2424	O	LEU	15	16.506	25.951	-12.460	0.00	0.00	O
ATOM	2425	CB	LEU	15	18.891	27.447	-10.955	0.00	0.00	C
ATOM	2426	CG	LEU	15	19.728	28.743	-10.689	0.00	0.00	C
ATOM	2427	CD1	LEU	15	20.301	28.891	-9.265	0.00	0.00	C
ATOM	2428	CD2	LEU	15	20.862	28.896	-11.699	0.00	0.00	C

81/107

FIG. 8 - 73

ATOM	2429	H	LEU	15	17.521	27.858	-8.751	0.00	0.00	H
ATOM	2430	HA	LEU	15	17.106	28.398	-11.688	0.00	0.00	H
ATOM	2431	1HB	LEU	15	19.197	26.636	-10.274	0.00	0.00	H
ATOM	2432	2HB	LEU	15	19.127	27.049	-11.962	0.00	0.00	H
ATOM	2433	HG	LEU	15	19.035	29.599	-10.813	0.00	0.00	H
ATOM	2434	1HD1	LEU	15	19.566	28.646	-8.478	0.00	0.00	H
ATOM	2435	2HD1	LEU	15	21.206	28.285	-9.095	0.00	0.00	H
ATOM	2436	3HD1	LEU	15	20.605	29.941	-9.078	0.00	0.00	H
ATOM	2437	1HD2	LEU	15	20.469	28.910	-12.731	0.00	0.00	H
ATOM	2438	2HD2	LEU	15	21.407	29.846	-11.548	0.00	0.00	H
ATOM	2439	3HD2	LEU	15	21.589	28.067	-11.624	0.00	0.00	H
ATOM	2440	N	CYS	16	15.705	25.803	-10.377	0.00	0.00	N
ATOM	2441	CA	CYS	16	14.406	25.168	-10.709	0.00	0.00	C
ATOM	2442	C	CYS	16	13.208	26.159	-10.909	0.00	0.00	C
ATOM	2443	O	CYS	16	12.504	26.115	-11.910	0.00	0.00	O
ATOM	2444	CB	CYS	16	14.116	24.099	-9.660	0.00	0.00	C
ATOM	2445	SG	CYS	16	13.079	22.775	-10.326	0.00	0.00	S
ATOM	2446	H	CYS	16	15.878	26.220	-9.455	0.00	0.00	H
ATOM	2447	HA	CYS	16	14.494	24.599	-11.627	0.00	0.00	H
ATOM	2448	1HB	CYS	16	15.012	23.693	-9.163	0.00	0.00	H
ATOM	2449	2HB	CYS	16	13.559	24.594	-8.876	0.00	0.00	H
TER	2450		CYS	16						
HETATM	2451	N	NH2	17H	12.890	27.026	-9.963	0.00	0.00	N
HETATM	2452	1HN	NH2	17H	12.218	27.733	-10.275	0.00	0.00	H
HETATM	2453	2HN	NH2	17H	13.533	27.077	-9.151	0.00	0.00	H
ENDMDL										
MODEL	12									
ATOM	2454	N	GLY	1	13.354	14.572	-15.326	0.00	0.00	N
ATOM	2455	CA	GLY	1	14.650	15.326	-15.254	0.00	0.00	C
ATOM	2456	C	GLY	1	15.107	15.718	-13.821	0.00	0.00	C
ATOM	2457	O	GLY	1	14.525	15.253	-12.844	0.00	0.00	O
ATOM	2458	1H	GLY	1	13.437	13.694	-14.794	1.00	0.00	H
ATOM	2459	2H	GLY	1	12.600	15.147	-14.924	1.00	0.00	H
ATOM	2460	3H	GLY	1	13.135	14.358	-16.309	1.00	0.00	H

82/107

FIG. 8 - 74

ATOM	2461	1HA	GLY	1	15.460	14.728	-15.718	0.00	0.00	H
ATOM	2462	2HA	GLY	1	14.578	16.248	-15.866	0.00	0.00	H
ATOM	2463	N	CYS	2	16.119	16.588	-13.668	0.00	0.00	N
ATOM	2464	CA	CYS	2	16.688	16.913	-12.319	0.00	0.00	C
ATOM	2465	C	CYS	2	15.766	17.849	-11.440	0.00	0.00	C
ATOM	2466	O	CYS	2	15.508	17.548	-10.277	0.00	0.00	O
ATOM	2467	CB	CYS	2	18.081	17.504	-12.618	0.00	0.00	C
ATOM	2468	SG	CYS	2	18.692	18.566	-11.292	0.00	0.00	S
ATOM	2469	H	CYS	2	16.711	16.753	-14.489	0.00	0.00	H
ATOM	2470	HA	CYS	2	16.838	15.983	-11.733	0.00	0.00	H
ATOM	2471	1HB	CYS	2	18.812	16.724	-12.897	0.00	0.00	H
ATOM	2472	2HB	CYS	2	18.010	18.197	-13.478	0.00	0.00	H
ATOM	2473	N	CYS	3	15.199	18.934	-11.999	0.00	0.00	N
ATOM	2474	CA	CYS	3	13.934	19.557	-11.543	0.00	0.00	C
ATOM	2475	C	CYS	3	12.694	18.648	-11.179	0.00	0.00	C
ATOM	2476	O	CYS	3	11.913	19.029	-10.304	0.00	0.00	O
ATOM	2477	CB	CYS	3	13.681	20.386	-12.822	0.00	0.00	C
ATOM	2478	SG	CYS	3	14.895	21.703	-13.054	0.00	0.00	S
ATOM	2479	H	CYS	3	15.438	19.131	-12.973	0.00	0.00	H
ATOM	2480	HA	CYS	3	14.106	20.251	-10.671	0.00	0.00	H
ATOM	2481	1HB	CYS	3	13.585	19.784	-13.748	0.00	0.00	H
ATOM	2482	2HB	CYS	3	12.718	20.874	-12.731	0.00	0.00	H
ATOM	2483	N	SER	4	12.517	17.469	-11.811	0.00	0.00	N
ATOM	2484	CA	SER	4	11.561	16.421	-11.349	0.00	0.00	C
ATOM	2485	C	SER	4	11.879	15.671	-10.001	0.00	0.00	C
ATOM	2486	O	SER	4	10.982	15.068	-9.412	0.00	0.00	O
ATOM	2487	CB	SER	4	11.352	15.420	-12.497	0.00	0.00	C
ATOM	2488	OG	SER	4	11.215	15.987	-13.809	0.00	0.00	O
ATOM	2489	H	SER	4	13.295	17.164	-12.394	0.00	0.00	H
ATOM	2490	HA	SER	4	10.580	16.864	-11.213	0.00	0.00	H
ATOM	2491	1HB	SER	4	12.183	14.721	-12.457	0.00	0.00	H
ATOM	2492	2HB	SER	4	10.471	14.809	-12.267	0.00	0.00	H
ATOM	2493	HG	SER	4	10.444	16.572	-13.773	0.00	0.00	H
ATOM	2494	N	ASN	5	13.116	15.749	-9.489	0.00	0.00	N

FIG. 8 - 75

ATOM	2495	CA	ASN	5	13.502	15.214	-8.170	0.00	0.00	C
ATOM	2496	C	ASN	5	13.265	16.250	-7.015	0.00	0.00	C
ATOM	2497	O	ASN	5	13.267	17.464	-7.256	0.00	0.00	O
ATOM	2498	CB	ASN	5	15.039	14.979	-8.240	0.00	0.00	C
ATOM	2499	CG	ASN	5	15.570	13.842	-9.092	0.00	0.00	C
ATOM	2500	OD1	ASN	5	15.547	13.842	-10.314	0.00	0.00	O
ATOM	2501	ND2	ASN	5	16.174	12.897	-8.432	0.00	0.00	N
ATOM	2502	H	ASN	5	13.833	16.147	-10.100	0.00	0.00	H
ATOM	2503	HA	ASN	5	12.962	14.274	-7.919	0.00	0.00	H
ATOM	2504	1HB	ASN	5	15.569	15.900	-8.535	0.00	0.00	H
ATOM	2505	2HB	ASN	5	15.409	14.806	-7.225	0.00	0.00	H
ATOM	2506	1HD2	ASN	5	16.707	12.280	-9.034	0.00	0.00	H
ATOM	2507	2HD2	ASN	5	16.358	13.135	-7.454	0.00	0.00	H
ATOM	2508	N	PRO	6	13.172	15.822	-5.727	0.00	0.00	N
ATOM	2509	CA	PRO	6	13.241	16.757	-4.567	0.00	0.00	C
ATOM	2510	C	PRO	6	14.606	17.500	-4.419	0.00	0.00	C
ATOM	2511	O	PRO	6	14.713	18.717	-4.530	0.00	0.00	O
ATOM	2512	CB	PRO	6	12.825	15.823	-3.410	0.00	0.00	C
ATOM	2513	CG	PRO	6	13.365	14.455	-3.838	0.00	0.00	C
ATOM	2514	CD	PRO	6	13.132	14.396	-5.337	0.00	0.00	C
ATOM	2515	HA	PRO	6	12.497	17.544	-4.667	0.00	0.00	H
ATOM	2516	1HB	PRO	6	13.205	16.154	-2.425	0.00	0.00	H
ATOM	2517	2HB	PRO	6	11.719	15.790	-3.321	0.00	0.00	H
ATOM	2518	1HG	PRO	6	14.439	14.365	-3.606	0.00	0.00	H
ATOM	2519	2HG	PRO	6	12.926	13.603	-3.336	0.00	0.00	H
ATOM	2520	1HD	PRO	6	13.907	13.762	-5.783	0.00	0.00	H
ATOM	2521	2HD	PRO	6	12.179	13.944	-5.663	0.00	0.00	H
ATOM	2522	N	VAL	7	15.657	16.709	-4.279	0.00	0.00	N
ATOM	2523	CA	VAL	7	17.050	17.147	-4.030	0.00	0.00	C
ATOM	2524	C	VAL	7	17.682	17.887	-5.228	0.00	0.00	C
ATOM	2525	O	VAL	7	18.138	19.025	-5.096	0.00	0.00	O
ATOM	2526	CB	VAL	7	17.789	15.814	-3.635	0.00	0.00	C
ATOM	2527	CG1	VAL	7	19.321	15.925	-3.548	0.00	0.00	C
ATOM	2528	CG2	VAL	7	17.336	15.221	-2.287	0.00	0.00	C

84/107

FIG. 8 - 76

ATOM	2529	H	VAL	7	15.398	15.726	-4.369	0.00	0.00	H
ATOM	2530	HA	VAL	7	17.061	17.912	-3.232	0.00	0.00	H
ATOM	2531	HB	VAL	7	17.558	15.055	-4.422	0.00	0.00	H
ATOM	2532	1HG1	VAL	7	19.627	16.676	-2.795	0.00	0.00	H
ATOM	2533	2HG1	VAL	7	19.782	14.959	-3.271	0.00	0.00	H
ATOM	2534	3HG1	VAL	7	19.764	16.217	-4.517	0.00	0.00	H
ATOM	2535	1HG2	VAL	7	16.249	15.031	-2.269	0.00	0.00	H
ATOM	2536	2HG2	VAL	7	17.828	14.251	-2.087	0.00	0.00	H
ATOM	2537	3HG2	VAL	7	17.564	15.904	-1.450	0.00	0.00	H
ATOM	2538	N	CYS	8	17.712	17.245	-6.401	0.00	0.00	N
ATOM	2539	CA	CYS	8	18.297	17.863	-7.622	0.00	0.00	C
ATOM	2540	C	CYS	8	17.652	19.136	-8.237	0.00	0.00	C
ATOM	2541	O	CYS	8	18.298	19.955	-8.894	0.00	0.00	O
ATOM	2542	CB	CYS	8	18.685	16.783	-8.651	0.00	0.00	C
ATOM	2543	SG	CYS	8	19.739	17.468	-9.962	0.00	0.00	S
ATOM	2544	H	CYS	8	17.410	16.284	-6.251	0.00	0.00	H
ATOM	2545	HA	CYS	8	19.166	18.324	-7.181	0.00	0.00	H
ATOM	2546	1HB	CYS	8	19.243	15.955	-8.171	0.00	0.00	H
ATOM	2547	2HB	CYS	8	17.791	16.330	-9.116	0.00	0.00	H
ATOM	2548	N	HIS	9	16.420	19.382	-7.848	0.00	0.00	N
ATOM	2549	CA	HIS	9	15.751	20.684	-7.982	0.00	0.00	C
ATOM	2550	C	HIS	9	16.288	21.736	-6.932	0.00	0.00	C
ATOM	2551	O	HIS	9	16.554	22.898	-7.243	0.00	0.00	O
ATOM	2552	CB	HIS	9	14.251	20.284	-7.886	0.00	0.00	C
ATOM	2553	CG	HIS	9	13.055	21.163	-7.546	0.00	0.00	C
ATOM	2554	ND1	HIS	9	11.791	20.822	-7.985	0.00	0.00	N
ATOM	2555	CD2	HIS	9	13.086	22.519	-7.255	0.00	0.00	C
ATOM	2556	CE1	HIS	9	11.162	22.041	-7.965	0.00	0.00	C
ATOM	2557	NE2	HIS	9	11.853	23.116	-7.481	0.00	0.00	N
ATOM	2558	H	HIS	9	16.024	18.603	-7.329	0.00	0.00	H
ATOM	2559	HA	HIS	9	15.955	21.034	-8.974	0.00	0.00	H
ATOM	2560	1HB	HIS	9	14.005	19.522	-8.638	0.00	0.00	H
ATOM	2561	2HB	HIS	9	14.256	19.741	-6.916	0.00	0.00	H
ATOM	2562	HD1	HIS	9	11.531	19.975	-8.518	0.00	0.00	H

85/107

FIG. 8 - 77

ATOM	2563	HD2	HIS	9	14.030	23.009	-7.124	0.00	0.00	H
ATOM	2564	HE1	HIS	9	10.220	22.192	-8.488	0.00	0.00	H
ATOM	2565	HE2	HIS	9	11.548	24.088	-7.328	1.00	0.00	H
ATOM	2566	N	LEU	10	16.311	21.289	-5.679	0.00	0.00	N
ATOM	2567	CA	LEU	10	16.377	22.144	-4.445	0.00	0.00	C
ATOM	2568	C	LEU	10	17.760	22.473	-3.820	0.00	0.00	C
ATOM	2569	O	LEU	10	17.890	23.482	-3.129	0.00	0.00	O
ATOM	2570	CB	LEU	10	15.351	21.636	-3.398	0.00	0.00	C
ATOM	2571	CG	LEU	10	13.864	21.683	-3.834	0.00	0.00	C
ATOM	2572	CD1	LEU	10	12.967	20.942	-2.840	0.00	0.00	C
ATOM	2573	CD2	LEU	10	13.324	23.116	-4.004	0.00	0.00	C
ATOM	2574	H	LEU	10	16.722	20.341	-5.756	0.00	0.00	H
ATOM	2575	HA	LEU	10	16.040	23.155	-4.728	0.00	0.00	H
ATOM	2576	1HB	LEU	10	15.630	20.602	-3.117	0.00	0.00	H
ATOM	2577	2HB	LEU	10	15.460	22.214	-2.460	0.00	0.00	H
ATOM	2578	HG	LEU	10	13.796	21.140	-4.797	0.00	0.00	H
ATOM	2579	1HD1	LEU	10	13.290	19.894	-2.705	0.00	0.00	H
ATOM	2580	2HD1	LEU	10	12.969	21.420	-1.843	0.00	0.00	H
ATOM	2581	3HD1	LEU	10	11.919	20.907	-3.191	0.00	0.00	H
ATOM	2582	1HD2	LEU	10	13.416	23.712	-3.076	0.00	0.00	H
ATOM	2583	2HD2	LEU	10	13.857	23.672	-4.790	0.00	0.00	H
ATOM	2584	3HD2	LEU	10	12.258	23.127	-4.297	0.00	0.00	H
ATOM	2585	N	GLU	11	18.818	21.722	-4.151	0.00	0.00	N
ATOM	2586	CA	GLU	11	20.192	22.246	-4.286	0.00	0.00	C
ATOM	2587	C	GLU	11	20.452	23.699	-4.747	0.00	0.00	C
ATOM	2588	O	GLU	11	21.407	24.357	-4.335	0.00	0.00	O
ATOM	2589	CB	GLU	11	20.855	21.223	-5.225	0.00	0.00	C
ATOM	2590	CG	GLU	11	20.374	21.058	-6.666	0.00	0.00	C
ATOM	2591	CD	GLU	11	21.342	20.441	-7.665	0.00	0.00	C
ATOM	2592	OE1	GLU	11	21.674	19.157	-7.352	0.00	0.00	O
ATOM	2593	OE2	GLU	11	21.773	21.058	-8.633	0.00	0.00	O
ATOM	2594	H	GLU	11	18.664	20.718	-4.321	1.00	0.00	H
ATOM	2595	HA	GLU	11	20.702	22.154	-3.341	0.00	0.00	H
ATOM	2596	1HB	GLU	11	21.906	21.464	-5.251	0.00	0.00	H

FIG. 8 - 78

ATOM	2597	2HB	GLU	11	20.744	20.261	-4.757	0.00	0.00	H
ATOM	2598	1HG	GLU	11	19.428	20.512	-6.677	0.00	0.00	H
ATOM	2599	2HG	GLU	11	20.124	22.058	-6.983	0.00	0.00	H
ATOM	2600	HE1	GLU	11	22.291	18.796	-7.989	0.00	0.00	H
ATOM	2601	N	HIS	12	19.626	24.107	-5.707	0.00	0.00	N
ATOM	2602	CA	HIS	12	19.818	25.374	-6.428	0.00	0.00	C
ATOM	2603	C	HIS	12	18.733	26.484	-6.333	0.00	0.00	C
ATOM	2604	O	HIS	12	19.042	27.663	-6.454	0.00	0.00	O
ATOM	2605	CB	HIS	12	20.277	24.968	-7.827	0.00	0.00	C
ATOM	2606	CG	HIS	12	21.792	24.962	-8.073	0.00	0.00	C
ATOM	2607	ND1	HIS	12	22.510	23.780	-8.091	0.00	0.00	N
ATOM	2608	CD2	HIS	12	22.679	26.050	-7.905	0.00	0.00	C
ATOM	2609	CE1	HIS	12	23.778	24.226	-7.847	0.00	0.00	C
ATOM	2610	NE2	HIS	12	23.986	25.580	-7.769	0.00	0.00	N
ATOM	2611	H	HIS	12	19.186	23.263	-6.127	0.00	0.00	H
ATOM	2612	HA	HIS	12	20.646	25.870	-6.000	0.00	0.00	H
ATOM	2613	1HB	HIS	12	19.871	24.005	-8.071	0.00	0.00	H
ATOM	2614	2HB	HIS	12	19.701	25.532	-8.524	0.00	0.00	H
ATOM	2615	HD1	HIS	12	22.195	22.809	-8.254	0.00	0.00	H
ATOM	2616	HD2	HIS	12	22.355	27.074	-7.739	0.00	0.00	H
ATOM	2617	HE1	HIS	12	24.554	23.506	-7.580	0.00	0.00	H
ATOM	2618	HE2	HIS	12	24.864	26.105	-7.645	1.00	0.00	H
ATOM	2619	N	SER	13	17.502	26.066	-6.092	0.00	0.00	N
ATOM	2620	CA	SER	13	16.275	26.291	-6.922	0.00	0.00	C
ATOM	2621	C	SER	13	16.016	27.519	-7.866	0.00	0.00	C
ATOM	2622	O	SER	13	14.946	27.637	-8.466	0.00	0.00	O
ATOM	2623	CB	SER	13	15.085	26.087	-5.953	0.00	0.00	C
ATOM	2624	OG	SER	13	13.888	25.783	-6.677	0.00	0.00	O
ATOM	2625	H	SER	13	17.824	25.106	-6.087	0.00	0.00	H
ATOM	2626	HA	SER	13	16.259	25.417	-7.601	0.00	0.00	H
ATOM	2627	1HB	SER	13	15.275	25.276	-5.225	0.00	0.00	H
ATOM	2628	2HB	SER	13	14.934	26.990	-5.326	0.00	0.00	H
ATOM	2629	HG	SER	13	13.655	26.591	-7.161	0.00	0.00	H
ATOM	2630	N	ASN	14	17.065	28.268	-8.166	0.00	0.00	N

87/107

FIG. 8 - 79

ATOM	2631	CA	ASN	14	17.267	28.960	-9.478	0.00	0.00	C
ATOM	2632	C	ASN	14	16.981	28.145	-10.777	0.00	0.00	C
ATOM	2633	O	ASN	14	16.450	28.632	-11.772	0.00	0.00	O
ATOM	2634	CB	ASN	14	18.711	29.560	-9.501	0.00	0.00	C
ATOM	2635	CG	ASN	14	19.898	28.649	-9.888	0.00	0.00	C
ATOM	2636	OD1	ASN	14	20.367	27.822	-9.118	0.00	0.00	O
ATOM	2637	ND2	ASN	14	20.329	28.664	-11.129	0.00	0.00	N
ATOM	2638	H	ASN	14	17.839	27.949	-7.552	0.00	0.00	H
ATOM	2639	HA	ASN	14	16.538	29.780	-9.510	0.00	0.00	H
ATOM	2640	1HB	ASN	14	18.691	30.416	-10.194	0.00	0.00	H
ATOM	2641	2HB	ASN	14	18.947	29.985	-8.512	0.00	0.00	H
ATOM	2642	1HD2	ASN	14	20.827	27.815	-11.424	0.00	0.00	H
ATOM	2643	2HD2	ASN	14	19.856	29.331	-11.747	0.00	0.00	H
ATOM	2644	N	LEU	15	17.434	26.894	-10.735	0.00	0.00	N
ATOM	2645	CA	LEU	15	17.465	25.958	-11.833	0.00	0.00	C
ATOM	2646	C	LEU	15	16.094	25.226	-12.112	0.00	0.00	C
ATOM	2647	O	LEU	15	15.892	24.667	-13.190	0.00	0.00	O
ATOM	2648	CB	LEU	15	18.645	25.153	-11.154	0.00	0.00	C
ATOM	2649	CG	LEU	15	19.027	23.885	-11.860	0.00	0.00	C
ATOM	2650	CD1	LEU	15	19.644	24.197	-13.232	0.00	0.00	C
ATOM	2651	CD2	LEU	15	19.959	22.970	-11.051	0.00	0.00	C
ATOM	2652	H	LEU	15	17.818	26.478	-9.879	0.00	0.00	H
ATOM	2653	HA	LEU	15	17.789	26.452	-12.767	0.00	0.00	H
ATOM	2654	1HB	LEU	15	19.574	25.759	-11.047	0.00	0.00	H
ATOM	2655	2HB	LEU	15	18.371	24.803	-10.132	0.00	0.00	H
ATOM	2656	HG	LEU	15	18.016	23.473	-11.871	0.00	0.00	H
ATOM	2657	1HD1	LEU	15	18.960	24.783	-13.875	0.00	0.00	H
ATOM	2658	2HD1	LEU	15	20.568	24.802	-13.127	0.00	0.00	H
ATOM	2659	3HD1	LEU	15	19.909	23.284	-13.788	0.00	0.00	H
ATOM	2660	1HD2	LEU	15	19.521	22.672	-10.081	0.00	0.00	H
ATOM	2661	2HD2	LEU	15	20.167	22.028	-11.593	0.00	0.00	H
ATOM	2662	3HD2	LEU	15	20.939	23.443	-10.850	0.00	0.00	H
ATOM	2663	N	CYS	16	15.198	25.175	-11.109	0.00	0.00	N
ATOM	2664	CA	CYS	16	13.936	24.408	-11.131	0.00	0.00	C

88/107

FIG. 8 - 80

ATOM	2665	C	CYS	16	12.679	25.064	-10.450	0.00	0.00	C
ATOM	2666	O	CYS	16	11.597	24.482	-10.447	0.00	0.00	O
ATOM	2667	CB	CYS	16	14.330	23.126	-10.385	0.00	0.00	C
ATOM	2668	SG	CYS	16	15.612	22.205	-11.261	0.00	0.00	S
ATOM	2669	H	CYS	16	15.573	25.599	-10.260	0.00	0.00	H
ATOM	2670	HA	CYS	16	13.634	24.165	-12.170	0.00	0.00	H
ATOM	2671	1HB	CYS	16	14.651	23.335	-9.351	0.00	0.00	H
ATOM	2672	2HB	CYS	16	13.446	22.487	-10.298	0.00	0.00	H
TER	2673		CYS	16						
HETATM	2674	N	NH2	17H	12.720	26.210	-9.795	0.00	0.00	N
HETATM	2675	1HN	NH2	17H	11.793	26.617	-9.632	0.00	0.00	H
HETATM	2676	2HN	NH2	17H	13.621	26.710	-9.784	0.00	0.00	H
ENDMDL										
MODEL	13									
ATOM	2677	N	GLY	1	13.947	15.282	-15.007	0.00	0.00	N
ATOM	2678	CA	GLY	1	14.855	16.076	-14.121	0.00	0.00	C
ATOM	2679	C	GLY	1	15.276	17.463	-14.665	0.00	0.00	C
ATOM	2680	O	GLY	1	15.034	17.768	-15.827	0.00	0.00	O
ATOM	2681	1H	GLY	1	14.412	15.111	-15.910	1.00	0.00	H
ATOM	2682	2H	GLY	1	13.728	14.382	-14.558	1.00	0.00	H
ATOM	2683	3H	GLY	1	13.075	15.808	-15.165	1.00	0.00	H
ATOM	2684	1HA	GLY	1	14.399	16.227	-13.125	0.00	0.00	H
ATOM	2685	2HA	GLY	1	15.801	15.525	-13.947	0.00	0.00	H
ATOM	2686	N	CYS	2	15.995	18.343	-13.968	0.00	0.00	N
ATOM	2687	CA	CYS	2	16.391	18.195	-12.539	0.00	0.00	C
ATOM	2688	C	CYS	2	15.351	18.836	-11.527	0.00	0.00	C
ATOM	2689	O	CYS	2	15.104	18.264	-10.468	0.00	0.00	O
ATOM	2690	CB	CYS	2	17.788	18.838	-12.462	0.00	0.00	C
ATOM	2691	SG	CYS	2	18.125	19.304	-10.761	0.00	0.00	S
ATOM	2692	H	CYS	2	16.588	18.881	-14.600	0.00	0.00	H
ATOM	2693	HA	CYS	2	16.515	17.136	-12.247	0.00	0.00	H
ATOM	2694	1HB	CYS	2	18.566	18.201	-12.915	0.00	0.00	H
ATOM	2695	2HB	CYS	2	17.801	19.797	-13.017	0.00	0.00	H
ATOM	2696	N	CYS	3	14.728	19.991	-11.837	0.00	0.00	N

89/107

FIG. 8 - 81

ATOM	2697	CA	CYS	3	13.427	20.481	-11.242	0.00	0.00	C
ATOM	2698	C	CYS	3	12.310	19.434	-10.890	0.00	0.00	C
ATOM	2699	O	CYS	3	11.642	19.526	-9.862	0.00	0.00	O
ATOM	2700	CB	CYS	3	12.860	21.392	-12.366	0.00	0.00	C
ATOM	2701	SG	CYS	3	11.666	22.648	-11.823	0.00	0.00	S
ATOM	2702	H	CYS	3	15.119	20.408	-12.691	0.00	0.00	H
ATOM	2703	HA	CYS	3	13.640	21.077	-10.314	0.00	0.00	H
ATOM	2704	1HB	CYS	3	13.659	21.902	-12.916	0.00	0.00	H
ATOM	2705	2HB	CYS	3	12.370	20.804	-13.168	0.00	0.00	H
ATOM	2706	N	SER	4	12.144	18.432	-11.759	0.00	0.00	N
ATOM	2707	CA	SER	4	11.306	17.231	-11.497	0.00	0.00	C
ATOM	2708	C	SER	4	11.834	16.185	-10.443	0.00	0.00	C
ATOM	2709	O	SER	4	11.126	15.225	-10.136	0.00	0.00	O
ATOM	2710	CB	SER	4	10.973	16.615	-12.882	0.00	0.00	C
ATOM	2711	OG	SER	4	11.744	15.450	-13.192	0.00	0.00	O
ATOM	2712	H	SER	4	12.844	18.506	-12.498	0.00	0.00	H
ATOM	2713	HA	SER	4	10.341	17.587	-11.086	0.00	0.00	H
ATOM	2714	1HB	SER	4	9.909	16.340	-12.868	0.00	0.00	H
ATOM	2715	2HB	SER	4	11.020	17.351	-13.707	0.00	0.00	H
ATOM	2716	HG	SER	4	11.445	14.769	-12.567	0.00	0.00	H
ATOM	2717	N	ASN	5	13.041	16.364	-9.884	0.00	0.00	N
ATOM	2718	CA	ASN	5	13.514	15.626	-8.696	0.00	0.00	C
ATOM	2719	C	ASN	5	13.111	16.353	-7.355	0.00	0.00	C
ATOM	2720	O	ASN	5	12.963	17.583	-7.358	0.00	0.00	O
ATOM	2721	CB	ASN	5	15.072	15.620	-8.728	0.00	0.00	C
ATOM	2722	CG	ASN	5	15.831	14.958	-9.870	0.00	0.00	C
ATOM	2723	OD1	ASN	5	15.471	14.943	-11.044	0.00	0.00	O
ATOM	2724	ND2	ASN	5	16.967	14.425	-9.515	0.00	0.00	N
ATOM	2725	H	ASN	5	13.633	17.096	-10.297	0.00	0.00	H
ATOM	2726	HA	ASN	5	13.123	14.590	-8.709	0.00	0.00	H
ATOM	2727	1HB	ASN	5	15.504	16.628	-8.559	0.00	0.00	H
ATOM	2728	2HB	ASN	5	15.369	15.080	-7.826	0.00	0.00	H
ATOM	2729	1HD2	ASN	5	17.285	13.705	-10.159	0.00	0.00	H
ATOM	2730	2HD2	ASN	5	17.140	14.472	-8.505	0.00	0.00	H

FIG. 8 - 82

ATOM	2731	N	PRO	6	13.076	15.692	-6.165	0.00	0.00	N
ATOM	2732	CA	PRO	6	13.180	16.409	-4.855	0.00	0.00	C
ATOM	2733	C	PRO	6	14.464	17.274	-4.613	0.00	0.00	C
ATOM	2734	O	PRO	6	14.415	18.470	-4.332	0.00	0.00	O
ATOM	2735	CB	PRO	6	12.982	15.249	-3.869	0.00	0.00	C
ATOM	2736	CG	PRO	6	13.594	14.045	-4.592	0.00	0.00	C
ATOM	2737	CD	PRO	6	13.107	14.217	-6.027	0.00	0.00	C
ATOM	2738	HA	PRO	6	12.350	17.088	-4.702	0.00	0.00	H
ATOM	2739	1HB	PRO	6	13.421	15.474	-2.884	0.00	0.00	H
ATOM	2740	2HB	PRO	6	11.901	15.077	-3.685	0.00	0.00	H
ATOM	2741	1HG	PRO	6	14.694	14.052	-4.557	0.00	0.00	H
ATOM	2742	2HG	PRO	6	13.327	13.089	-4.144	0.00	0.00	H
ATOM	2743	1HD	PRO	6	13.758	13.689	-6.739	0.00	0.00	H
ATOM	2744	2HD	PRO	6	12.101	13.788	-6.171	0.00	0.00	H
ATOM	2745	N	VAL	7	15.614	16.630	-4.752	0.00	0.00	N
ATOM	2746	CA	VAL	7	16.898	17.062	-4.142	0.00	0.00	C
ATOM	2747	C	VAL	7	17.678	18.042	-5.029	0.00	0.00	C
ATOM	2748	O	VAL	7	18.019	19.148	-4.602	0.00	0.00	O
ATOM	2749	CB	VAL	7	17.664	15.717	-3.854	0.00	0.00	C
ATOM	2750	CG1	VAL	7	19.152	15.869	-3.486	0.00	0.00	C
ATOM	2751	CG2	VAL	7	17.042	14.894	-2.714	0.00	0.00	C
ATOM	2752	H	VAL	7	15.443	15.638	-4.927	0.00	0.00	H
ATOM	2753	HA	VAL	7	16.711	17.662	-3.231	0.00	0.00	H
ATOM	2754	HB	VAL	7	17.623	15.102	-4.786	0.00	0.00	H
ATOM	2755	1HG1	VAL	7	19.287	16.497	-2.587	0.00	0.00	H
ATOM	2756	2HG1	VAL	7	19.627	14.889	-3.288	0.00	0.00	H
ATOM	2757	3HG1	VAL	7	19.732	16.330	-4.306	0.00	0.00	H
ATOM	2758	1HG2	VAL	7	15.968	14.707	-2.875	0.00	0.00	H
ATOM	2759	2HG2	VAL	7	17.528	13.906	-2.624	0.00	0.00	H
ATOM	2760	3HG2	VAL	7	17.135	15.416	-1.746	0.00	0.00	H
ATOM	2761	N	CYS	8	17.973	17.627	-6.266	0.00	0.00	N
ATOM	2762	CA	CYS	8	18.732	18.485	-7.211	0.00	0.00	C
ATOM	2763	C	CYS	8	18.075	19.816	-7.675	0.00	0.00	C
ATOM	2764	O	CYS	8	18.722	20.849	-7.866	0.00	0.00	O

91/107

FIG. 8 - 83

ATOM	2765	CB	CYS	8	19.327	17.663	-8.371	0.00	0.00	C
ATOM	2766	SG	CYS	8	18.102	17.597	-9.689	0.00	0.00	S
ATOM	2767	H	CYS	8	17.640	16.671	-6.383	0.00	0.00	H
ATOM	2768	HA	CYS	8	19.500	18.850	-6.554	0.00	0.00	H
ATOM	2769	1HB	CYS	8	20.240	18.150	-8.762	0.00	0.00	H
ATOM	2770	2HB	CYS	8	19.633	16.645	-8.063	0.00	0.00	H
ATOM	2771	N	HIS	9	16.746	19.764	-7.731	0.00	0.00	N
ATOM	2772	CA	HIS	9	15.848	20.926	-7.638	0.00	0.00	C
ATOM	2773	C	HIS	9	16.214	21.926	-6.506	0.00	0.00	C
ATOM	2774	O	HIS	9	16.217	23.124	-6.739	0.00	0.00	O
ATOM	2775	CB	HIS	9	14.420	20.313	-7.514	0.00	0.00	C
ATOM	2776	CG	HIS	9	13.162	20.966	-6.936	0.00	0.00	C
ATOM	2777	ND1	HIS	9	11.920	20.488	-7.277	0.00	0.00	N
ATOM	2778	CD2	HIS	9	13.019	22.252	-6.425	0.00	0.00	C
ATOM	2779	CE1	HIS	9	11.148	21.600	-7.096	0.00	0.00	C
ATOM	2780	NE2	HIS	9	11.701	22.677	-6.468	0.00	0.00	N
ATOM	2781	H	HIS	9	16.445	18.835	-7.449	0.00	0.00	H
ATOM	2782	HA	HIS	9	15.935	21.445	-8.574	0.00	0.00	H
ATOM	2783	1HB	HIS	9	14.201	19.700	-8.401	0.00	0.00	H
ATOM	2784	2HB	HIS	9	14.548	19.601	-6.681	0.00	0.00	H
ATOM	2785	HD1	HIS	9	11.741	19.710	-7.935	0.00	0.00	H
ATOM	2786	HD2	HIS	9	13.875	22.867	-6.277	0.00	0.00	H
ATOM	2787	HE1	HIS	9	10.364	21.792	-7.821	0.00	0.00	H
ATOM	2788	HE2	HIS	9	11.268	23.547	-6.128	1.00	0.00	H
ATOM	2789	N	LEU	10	16.404	21.430	-5.289	0.00	0.00	N
ATOM	2790	CA	LEU	10	16.469	22.294	-4.058	0.00	0.00	C
ATOM	2791	C	LEU	10	17.879	22.815	-3.657	0.00	0.00	C
ATOM	2792	O	LEU	10	18.050	24.001	-3.372	0.00	0.00	O
ATOM	2793	CB	LEU	10	15.678	21.634	-2.897	0.00	0.00	C
ATOM	2794	CG	LEU	10	14.144	21.551	-3.108	0.00	0.00	C
ATOM	2795	CD1	LEU	10	13.494	20.685	-2.026	0.00	0.00	C
ATOM	2796	CD2	LEU	10	13.455	22.933	-3.117	0.00	0.00	C
ATOM	2797	H	LEU	10	16.743	20.448	-5.388	0.00	0.00	H
ATOM	2798	HA	LEU	10	15.947	23.239	-4.273	0.00	0.00	H

FIG. 8 - 84

ATOM	2799	1HB	LEU	10	16.090	20.622	-2.717	0.00	0.00	H
ATOM	2800	2HB	LEU	10	15.871	22.184	-1.954	0.00	0.00	H
ATOM	2801	HG	LEU	10	13.964	21.041	-4.074	0.00	0.00	H
ATOM	2802	1HD1	LEU	10	13.924	19.666	-2.011	0.00	0.00	H
ATOM	2803	2HD1	LEU	10	13.620	21.114	-1.015	0.00	0.00	H
ATOM	2804	3HD1	LEU	10	12.408	20.563	-2.202	0.00	0.00	H
ATOM	2805	1HD2	LEU	10	13.604	23.478	-2.166	0.00	0.00	H
ATOM	2806	2HD2	LEU	10	13.825	23.598	-3.918	0.00	0.00	H
ATOM	2807	3HD2	LEU	10	12.363	22.846	-3.272	0.00	0.00	H
ATOM	2808	N	GLU	11	18.899	21.965	-3.780	0.00	0.00	N
ATOM	2809	CA	GLU	11	20.306	22.361	-4.001	0.00	0.00	C
ATOM	2810	C	GLU	11	20.630	23.571	-4.940	0.00	0.00	C
ATOM	2811	O	GLU	11	21.568	24.332	-4.694	0.00	0.00	O
ATOM	2812	CB	GLU	11	20.898	21.046	-4.564	0.00	0.00	C
ATOM	2813	CG	GLU	11	21.265	19.933	-3.550	0.00	0.00	C
ATOM	2814	CD	GLU	11	21.750	18.620	-4.172	0.00	0.00	C
ATOM	2815	OE1	GLU	11	21.709	18.369	-5.374	0.00	0.00	O
ATOM	2816	OE2	GLU	11	22.213	17.754	-3.228	0.00	0.00	O
ATOM	2817	H	GLU	11	18.691	20.959	-3.717	1.00	0.00	H
ATOM	2818	HA	GLU	11	20.777	22.604	-3.047	0.00	0.00	H
ATOM	2819	1HB	GLU	11	20.272	20.635	-5.383	0.00	0.00	H
ATOM	2820	2HB	GLU	11	21.796	21.325	-5.090	0.00	0.00	H
ATOM	2821	1HG	GLU	11	22.029	20.301	-2.841	0.00	0.00	H
ATOM	2822	2HG	GLU	11	20.375	19.703	-2.946	0.00	0.00	H
ATOM	2823	HE2	GLU	11	22.501	16.929	-3.619	0.00	0.00	H
ATOM	2824	N	HIS	12	19.881	23.705	-6.039	0.00	0.00	N
ATOM	2825	CA	HIS	12	19.904	24.915	-6.883	0.00	0.00	C
ATOM	2826	C	HIS	12	18.435	25.270	-7.235	0.00	0.00	C
ATOM	2827	O	HIS	12	17.937	24.935	-8.308	0.00	0.00	O
ATOM	2828	CB	HIS	12	20.801	24.640	-8.106	0.00	0.00	C
ATOM	2829	CG	HIS	12	22.305	24.561	-7.838	0.00	0.00	C
ATOM	2830	ND1	HIS	12	22.988	23.363	-7.720	0.00	0.00	N
ATOM	2831	CD2	HIS	12	23.141	25.632	-7.464	0.00	0.00	C
ATOM	2832	CE1	HIS	12	24.190	23.798	-7.221	0.00	0.00	C

93/107

FIG. 8 - 85

ATOM	2833	NE2	HIS	12	24.389	25.148	-7.075	0.00	0.00	N
ATOM	2834	H	HIS	12	19.054	23.097	-6.018	0.00	0.00	H
ATOM	2835	HA	HIS	12	20.322	25.783	-6.350	0.00	0.00	H
ATOM	2836	1HB	HIS	12	20.425	23.706	-8.559	0.00	0.00	H
ATOM	2837	2HB	HIS	12	20.622	25.440	-8.844	0.00	0.00	H
ATOM	2838	HD1	HIS	12	22.608	22.411	-7.767	0.00	0.00	H
ATOM	2839	HD2	HIS	12	22.808	26.663	-7.385	0.00	0.00	H
ATOM	2840	HE1	HIS	12	24.934	23.081	-6.871	0.00	0.00	H
ATOM	2841	HE2	HIS	12	25.227	25.661	-6.765	1.00	0.00	H
ATOM	2842	N	SER	13	17.723	25.904	-6.292	0.00	0.00	N
ATOM	2843	CA	SER	13	16.284	26.242	-6.453	0.00	0.00	C
ATOM	2844	C	SER	13	15.884	27.393	-7.422	0.00	0.00	C
ATOM	2845	O	SER	13	14.791	27.391	-7.988	0.00	0.00	O
ATOM	2846	CB	SER	13	15.618	26.349	-5.064	0.00	0.00	C
ATOM	2847	OG	SER	13	14.197	26.238	-5.181	0.00	0.00	O
ATOM	2848	H	SER	13	17.982	25.485	-5.414	0.00	0.00	H
ATOM	2849	HA	SER	13	15.889	25.354	-6.930	0.00	0.00	H
ATOM	2850	1HB	SER	13	15.976	25.553	-4.382	0.00	0.00	H
ATOM	2851	2HB	SER	13	15.892	27.301	-4.564	0.00	0.00	H
ATOM	2852	HG	SER	13	13.867	27.089	-5.497	0.00	0.00	H
ATOM	2853	N	ASN	14	16.846	28.263	-7.701	0.00	0.00	N
ATOM	2854	CA	ASN	14	16.983	28.941	-9.025	0.00	0.00	C
ATOM	2855	C	ASN	14	16.874	28.065	-10.323	0.00	0.00	C
ATOM	2856	O	ASN	14	16.255	28.470	-11.305	0.00	0.00	O
ATOM	2857	CB	ASN	14	18.314	29.744	-8.991	0.00	0.00	C
ATOM	2858	CG	ASN	14	19.660	28.989	-8.998	0.00	0.00	C
ATOM	2859	OD1	ASN	14	19.897	28.030	-8.268	0.00	0.00	O
ATOM	2860	ND2	ASN	14	20.586	29.387	-9.832	0.00	0.00	N
ATOM	2861	H	ASN	14	17.661	27.885	-7.206	0.00	0.00	H
ATOM	2862	HA	ASN	14	16.155	29.670	-9.101	0.00	0.00	H
ATOM	2863	1HB	ASN	14	18.278	30.433	-9.853	0.00	0.00	H
ATOM	2864	2HB	ASN	14	18.318	30.390	-8.099	0.00	0.00	H
ATOM	2865	1HD2	ASN	14	21.462	28.865	-9.796	0.00	0.00	H
ATOM	2866	2HD2	ASN	14	20.335	30.145	-10.474	0.00	0.00	H

94/107

FIG. 8 - 86

ATOM	2867	N	LEU	15	17.483	26.875	-10.296	0.00	0.00	N
ATOM	2868	CA	LEU	15	17.425	25.893	-11.416	0.00	0.00	C
ATOM	2869	C	LEU	15	16.208	24.898	-11.429	0.00	0.00	C
ATOM	2870	O	LEU	15	16.036	24.170	-12.411	0.00	0.00	O
ATOM	2871	CB	LEU	15	18.782	25.143	-11.528	0.00	0.00	C
ATOM	2872	CG	LEU	15	20.076	25.982	-11.710	0.00	0.00	C
ATOM	2873	CD1	LEU	15	21.296	25.054	-11.772	0.00	0.00	C
ATOM	2874	CD2	LEU	15	20.057	26.867	-12.968	0.00	0.00	C
ATOM	2875	H	LEU	15	17.778	26.621	-9.342	0.00	0.00	H
ATOM	2876	HA	LEU	15	17.311	26.467	-12.347	0.00	0.00	H
ATOM	2877	1HB	LEU	15	18.887	24.492	-10.640	0.00	0.00	H
ATOM	2878	2HB	LEU	15	18.708	24.437	-12.378	0.00	0.00	H
ATOM	2879	HG	LEU	15	20.192	26.647	-10.833	0.00	0.00	H
ATOM	2880	1HD1	LEU	15	21.357	24.386	-10.897	0.00	0.00	H
ATOM	2881	2HD1	LEU	15	21.270	24.409	-12.670	0.00	0.00	H
ATOM	2882	3HD1	LEU	15	22.239	25.631	-11.809	0.00	0.00	H
ATOM	2883	1HD2	LEU	15	19.902	26.281	-13.894	0.00	0.00	H
ATOM	2884	2HD2	LEU	15	19.253	27.624	-12.926	0.00	0.00	H
ATOM	2885	3HD2	LEU	15	21.001	27.430	-13.095	0.00	0.00	H
ATOM	2886	N	CYS	16	15.331	24.873	-10.408	0.00	0.00	N
ATOM	2887	CA	CYS	16	13.895	24.574	-10.641	0.00	0.00	C
ATOM	2888	C	CYS	16	13.015	25.822	-10.985	0.00	0.00	C
ATOM	2889	O	CYS	16	12.259	25.813	-11.950	0.00	0.00	O
ATOM	2890	CB	CYS	16	13.342	23.815	-9.426	0.00	0.00	C
ATOM	2891	SG	CYS	16	11.765	23.044	-9.854	0.00	0.00	S
ATOM	2892	H	CYS	16	15.632	25.474	-9.631	0.00	0.00	H
ATOM	2893	HA	CYS	16	13.806	23.901	-11.512	0.00	0.00	H
ATOM	2894	1HB	CYS	16	13.961	22.968	-9.097	0.00	0.00	H
ATOM	2895	2HB	CYS	16	13.297	24.504	-8.561	0.00	0.00	H
TER	2896		CYS	16						
HETATM	2897	N	NH2	17H	13.017	26.902	-10.225	0.00	0.00	N
HETATM	2898	1HN	NH2	17H	12.498	27.685	-10.637	0.00	0.00	H
HETATM	2899	2HN	NH2	17H	13.720	26.943	-9.469	0.00	0.00	H
ENDMDL.										

95/107

FIG. 8-87

[illegible]

96/107

FIG. 8 - 88

ATOM	2933	CB	SER	4	12.449	16.342	-13.223	0.00	0.00	C
ATOM	2934	OG	SER	4	13.464	15.341	-13.336	0.00	0.00	O
ATOM	2935	H	SER	4	14.431	17.722	-12.734	0.00	0.00	H
ATOM	2936	HA	SER	4	11.605	17.769	-11.841	0.00	0.00	H
ATOM	2937	1HB	SER	4	11.475	15.857	-13.245	0.00	0.00	H
ATOM	2938	2HB	SER	4	12.437	17.000	-14.117	0.00	0.00	H
ATOM	2939	HG	SER	4	13.499	14.884	-12.480	0.00	0.00	H
ATOM	2940	N	ASN	5	13.587	16.223	-9.839	0.00	0.00	N
ATOM	2941	CA	ASN	5	13.626	15.552	-8.520	0.00	0.00	C
ATOM	2942	C	ASN	5	13.108	16.479	-7.352	0.00	0.00	C
ATOM	2943	O	ASN	5	13.045	17.703	-7.517	0.00	0.00	O
ATOM	2944	CB	ASN	5	15.132	15.263	-8.259	0.00	0.00	C
ATOM	2945	CG	ASN	5	15.818	14.138	-9.015	0.00	0.00	C
ATOM	2946	OD1	ASN	5	15.444	13.703	-10.095	0.00	0.00	O
ATOM	2947	ND2	ASN	5	16.853	13.619	-8.411	0.00	0.00	N
ATOM	2948	H	ASN	5	14.410	16.700	-10.230	0.00	0.00	H
ATOM	2949	HA	ASN	5	13.050	14.605	-8.525	0.00	0.00	H
ATOM	2950	1HB	ASN	5	15.738	16.180	-8.356	0.00	0.00	H
ATOM	2951	2HB	ASN	5	15.235	14.989	-7.205	0.00	0.00	H
ATOM	2952	1HD2	ASN	5	17.047	12.689	-8.773	0.00	0.00	H
ATOM	2953	2HD2	ASN	5	16.995	13.945	-7.450	0.00	0.00	H
ATOM	2954	N	PRO	6	12.860	15.981	-6.106	0.00	0.00	N
ATOM	2955	CA	PRO	6	12.911	16.842	-4.885	0.00	0.00	C
ATOM	2956	C	PRO	6	14.262	17.591	-4.624	0.00	0.00	C
ATOM	2957	O	PRO	6	14.346	18.817	-4.600	0.00	0.00	O
ATOM	2958	CB	PRO	6	12.479	15.843	-3.801	0.00	0.00	C
ATOM	2959	CG	PRO	6	13.016	14.499	-4.302	0.00	0.00	C
ATOM	2960	CD	PRO	6	12.706	14.540	-5.798	0.00	0.00	C
ATOM	2961	HA	PRO	6	12.154	17.618	-4.907	0.00	0.00	H
ATOM	2962	1HB	PRO	6	12.838	16.146	-2.806	0.00	0.00	H
ATOM	2963	2HB	PRO	6	11.372	15.810	-3.725	0.00	0.00	H
ATOM	2964	1HG	PRO	6	14.098	14.393	-4.120	0.00	0.00	H
ATOM	2965	2HG	PRO	6	12.580	13.643	-3.785	0.00	0.00	H
ATOM	2966	1HD	PRO	6	13.351	13.863	-6.380	0.00	0.00	H

97/107

FIG. 8 - 89

ATOM	2967	2HD	PRO	6	11.674	14.207	-6.007	0.00	0.00	H
ATOM	2968	N	VAL	7	15.323	16.811	-4.475	0.00	0.00	N
ATOM	2969	CA	VAL	7	16.608	17.250	-3.861	0.00	0.00	C
ATOM	2970	C	VAL	7	17.567	17.920	-4.877	0.00	0.00	C
ATOM	2971	O	VAL	7	18.063	19.021	-4.627	0.00	0.00	O
ATOM	2972	CB	VAL	7	17.184	15.982	-3.128	0.00	0.00	C
ATOM	2973	CG1	VAL	7	18.653	16.106	-2.653	0.00	0.00	C
ATOM	2974	CG2	VAL	7	16.372	15.579	-1.870	0.00	0.00	C
ATOM	2975	H	VAL	7	15.040	15.829	-4.548	0.00	0.00	H
ATOM	2976	HA	VAL	7	16.414	18.073	-3.148	0.00	0.00	H
ATOM	2977	HB	VAL	7	17.128	15.141	-3.861	0.00	0.00	H
ATOM	2978	1HG1	VAL	7	18.791	16.937	-1.934	0.00	0.00	H
ATOM	2979	2HG1	VAL	7	19.010	15.186	-2.150	0.00	0.00	H
ATOM	2980	3HG1	VAL	7	19.354	16.285	-3.488	0.00	0.00	H
ATOM	2981	1HG2	VAL	7	15.305	15.394	-2.092	0.00	0.00	H
ATOM	2982	2HG2	VAL	7	16.753	14.650	-1.405	0.00	0.00	H
ATOM	2983	3HG2	VAL	7	16.399	16.361	-1.087	0.00	0.00	H
ATOM	2984	N	CYS	8	17.804	17.290	-6.039	0.00	0.00	N
ATOM	2985	CA	CYS	8	18.587	17.917	-7.135	0.00	0.00	C
ATOM	2986	C	CYS	8	18.062	19.181	-7.879	0.00	0.00	C
ATOM	2987	O	CYS	8	18.794	19.958	-8.496	0.00	0.00	O
ATOM	2988	CB	CYS	8	19.138	16.835	-8.078	0.00	0.00	C
ATOM	2989	SG	CYS	8	20.308	17.598	-9.223	0.00	0.00	S
ATOM	2990	H	CYS	8	17.324	16.401	-6.077	0.00	0.00	H
ATOM	2991	HA	CYS	8	19.363	18.371	-6.551	0.00	0.00	H
ATOM	2992	1HB	CYS	8	19.656	16.030	-7.524	0.00	0.00	H
ATOM	2993	2HB	CYS	8	18.325	16.358	-8.657	0.00	0.00	H
ATOM	2994	N	HIS	9	16.797	19.450	-7.654	0.00	0.00	N
ATOM	2995	CA	HIS	9	16.153	20.767	-7.851	0.00	0.00	C
ATOM	2996	C	HIS	9	16.658	21.847	-6.851	0.00	0.00	C
ATOM	2997	O	HIS	9	16.904	22.999	-7.184	0.00	0.00	O
ATOM	2998	CB	HIS	9	14.650	20.448	-7.763	0.00	0.00	C
ATOM	2999	CG	HIS	9	13.383	21.243	-7.511	0.00	0.00	C
ATOM	3000	ND1	HIS	9	12.195	20.898	-8.121	0.00	0.00	N

98/107

FIG. 8 - 90

ATOM	3001	CD2	HIS	9	13.419	22.594	-7.323	0.00	0.00	C
ATOM	3002	CE1	HIS	9	11.636	22.135	-8.324	0.00	0.00	C
ATOM	3003	NE2	HIS	9	12.284	23.225	-7.813	0.00	0.00	N
ATOM	3004	H	HIS	9	16.322	18.669	-7.209	0.00	0.00	H
ATOM	3005	HA	HIS	9	16.306	21.078	-8.843	0.00	0.00	H
ATOM	3006	1HB	HIS	9	14.482	19.479	-8.083	0.00	0.00	H
ATOM	3007	2HB	HIS	9	14.682	20.128	-6.733	0.00	0.00	H
ATOM	3008	HD1	HIS	9	12.050	20.042	-8.680	0.00	0.00	H
ATOM	3009	HD2	HIS	9	14.407	22.959	-7.222	0.00	0.00	H
ATOM	3010	HE1	HIS	9	10.850	22.277	-9.061	0.00	0.00	H
ATOM	3011	HE2	HIS	9	12.010	24.218	-7.796	1.00	0.00	H
ATOM	3012	N	LEU	10	16.627	21.420	-5.603	0.00	0.00	N
ATOM	3013	CA	LEU	10	16.595	22.317	-4.396	0.00	0.00	C
ATOM	3014	C	LEU	10	17.943	22.748	-3.740	0.00	0.00	C
ATOM	3015	O	LEU	10	18.033	23.823	-3.150	0.00	0.00	O
ATOM	3016	CB	LEU	10	15.516	21.838	-3.389	0.00	0.00	C
ATOM	3017	CG	LEU	10	14.041	21.975	-3.858	0.00	0.00	C
ATOM	3018	CD1	LEU	10	13.087	21.336	-2.847	0.00	0.00	C
ATOM	3019	CD2	LEU	10	13.594	23.429	-4.107	0.00	0.00	C
ATOM	3020	H	LEU	10	16.631	20.375	-5.733	0.00	0.00	H
ATOM	3021	HA	LEU	10	16.240	23.300	-4.744	0.00	0.00	H
ATOM	3022	1HB	LEU	10	15.729	20.785	-3.114	0.00	0.00	H
ATOM	3023	2HB	LEU	10	15.626	22.396	-2.438	0.00	0.00	H
ATOM	3024	HG	LEU	10	13.923	21.398	-4.791	0.00	0.00	H
ATOM	3025	1HD1	LEU	10	13.338	20.273	-2.671	0.00	0.00	H
ATOM	3026	2HD1	LEU	10	13.111	21.850	-1.869	0.00	0.00	H
ATOM	3027	3HD1	LEU	10	12.043	21.354	-3.210	0.00	0.00	H
ATOM	3028	1HD2	LEU	10	13.707	24.062	-3.207	0.00	0.00	H
ATOM	3029	2HD2	LEU	10	14.164	23.918	-4.916	0.00	0.00	H
ATOM	3030	3HD2	LEU	10	12.533	23.487	-4.415	0.00	0.00	H
ATOM	3031	N	GLU	11	19.030	22.016	-3.980	0.00	0.00	N
ATOM	3032	CA	GLU	11	20.388	22.583	-4.144	0.00	0.00	C
ATOM	3033	C	GLU	11	20.604	23.880	-4.977	0.00	0.00	C
ATOM	3034	O	GLU	11	21.453	24.729	-4.709	0.00	0.00	O

FIG. 8 - 91

ATOM	3035	CB	GLU	11	21.133	21.382	-4.740	0.00	0.00	C
ATOM	3036	CG	GLU	11	20.842	20.879	-6.152	0.00	0.00	C
ATOM	3037	CD	GLU	11	21.906	19.994	-6.792	0.00	0.00	C
ATOM	3038	OE1	GLU	11	21.904	18.730	-6.296	0.00	0.00	O
ATOM	3039	OE2	GLU	11	22.678	20.395	-7.658	0.00	0.00	O
ATOM	3040	H	GLU	11	18.920	20.995	-4.055	1.00	0.00	H
ATOM	3041	HA	GLU	11	20.843	22.762	-3.178	0.00	0.00	H
ATOM	3042	1HB	GLU	11	22.164	21.666	-4.714	0.00	0.00	H
ATOM	3043	2HB	GLU	11	20.986	20.540	-4.077	0.00	0.00	H
ATOM	3044	1HG	GLU	11	19.866	20.388	-6.164	0.00	0.00	H
ATOM	3045	2HG	GLU	11	20.728	21.778	-6.738	0.00	0.00	H
ATOM	3046	HE1	GLU	11	22.592	18.220	-6.730	0.00	0.00	H
ATOM	3047	N	HIS	12	19.830	23.933	-6.051	0.00	0.00	N
ATOM	3048	CA	HIS	12	19.793	25.084	-6.983	0.00	0.00	C
ATOM	3049	C	HIS	12	18.341	25.604	-7.183	0.00	0.00	C
ATOM	3050	O	HIS	12	17.769	25.550	-8.271	0.00	0.00	O
ATOM	3051	CB	HIS	12	20.550	24.711	-8.277	0.00	0.00	C
ATOM	3052	CG	HIS	12	22.072	24.549	-8.146	0.00	0.00	C
ATOM	3053	ND1	HIS	12	22.710	23.323	-8.216	0.00	0.00	N
ATOM	3054	CD2	HIS	12	22.998	25.539	-7.743	0.00	0.00	C
ATOM	3055	CE1	HIS	12	23.971	23.649	-7.790	0.00	0.00	C
ATOM	3056	NE2	HIS	12	24.247	24.965	-7.520	0.00	0.00	N
ATOM	3057	H	HIS	12	19.252	23.067	-6.020	0.00	0.00	H
ATOM	3058	HA	HIS	12	20.325	25.928	-6.536	0.00	0.00	H
ATOM	3059	1HB	HIS	12	20.089	23.792	-8.679	0.00	0.00	H
ATOM	3060	2HB	HIS	12	20.333	25.497	-9.021	0.00	0.00	H
ATOM	3061	HD1	HIS	12	22.327	22.376	-8.347	0.00	0.00	H
ATOM	3062	HD2	HIS	12	22.738	26.571	-7.533	0.00	0.00	H
ATOM	3063	HE1	HIS	12	24.703	22.866	-7.586	0.00	0.00	H
ATOM	3064	HE2	HIS	12	25.132	25.406	-7.232	1.00	0.00	H
ATOM	3065	N	SER	13	17.740	26.070	-6.084	0.00	0.00	N
ATOM	3066	CA	SER	13	16.270	26.177	-5.937	0.00	0.00	C
ATOM	3067	C	SER	13	15.509	27.232	-6.765	0.00	0.00	C
ATOM	3068	O	SER	13	14.557	26.928	-7.482	0.00	0.00	O

100/107

FIG. 8 - 92

ATOM	3069	CB	SER	13	15.911	26.254	-4.427	0.00	0.00	C
ATOM	3070	OG	SER	13	16.462	27.427	-3.817	0.00	0.00	O
ATOM	3071	H	SER	13	18.232	25.724	-5.272	0.00	0.00	H
ATOM	3072	HA	SER	13	15.954	25.236	-6.359	0.00	0.00	H
ATOM	3073	1HB	SER	13	14.812	26.255	-4.295	0.00	0.00	H
ATOM	3074	2HB	SER	13	16.266	25.364	-3.879	0.00	0.00	H
ATOM	3075	HG	SER	13	16.109	27.500	-2.922	0.00	0.00	H
ATOM	3076	N	ASN	14	16.058	28.429	-6.710	0.00	0.00	N
ATOM	3077	CA	ASN	14	15.841	29.503	-7.728	0.00	0.00	C
ATOM	3078	C	ASN	14	16.029	29.089	-9.228	0.00	0.00	C
ATOM	3079	O	ASN	14	15.333	29.594	-10.106	0.00	0.00	O
ATOM	3080	CB	ASN	14	16.759	30.722	-7.420	0.00	0.00	C
ATOM	3081	CG	ASN	14	16.656	31.342	-6.024	0.00	0.00	C
ATOM	3082	OD1	ASN	14	15.592	31.699	-5.541	0.00	0.00	O
ATOM	3083	ND2	ASN	14	17.757	31.486	-5.333	0.00	0.00	N
ATOM	3084	H	ASN	14	16.864	28.291	-6.091	0.00	0.00	H
ATOM	3085	HA	ASN	14	14.792	29.826	-7.648	0.00	0.00	H
ATOM	3086	1HB	ASN	14	17.809	30.464	-7.654	0.00	0.00	H
ATOM	3087	2HB	ASN	14	16.511	31.538	-8.124	0.00	0.00	H
ATOM	3088	1HD2	ASN	14	17.614	32.011	-4.465	0.00	0.00	H
ATOM	3089	2HD2	ASN	14	18.633	31.290	-5.823	0.00	0.00	H
ATOM	3090	N	LEU	15	16.973	28.176	-9.508	0.00	0.00	N
ATOM	3091	CA	LEU	15	17.317	27.750	-10.888	0.00	0.00	C
ATOM	3092	C	LEU	15	16.441	26.583	-11.474	0.00	0.00	C
ATOM	3093	O	LEU	15	16.268	26.480	-12.689	0.00	0.00	O
ATOM	3094	CB	LEU	15	18.848	27.469	-10.907	0.00	0.00	C
ATOM	3095	CG	LEU	15	19.771	28.613	-10.375	0.00	0.00	C
ATOM	3096	CD1	LEU	15	20.170	28.506	-8.888	0.00	0.00	C
ATOM	3097	CD2	LEU	15	21.044	28.737	-11.214	0.00	0.00	C
ATOM	3098	H	LEU	15	17.437	27.739	-8.697	0.00	0.00	H
ATOM	3099	HA	LEU	15	17.143	28.606	-11.559	0.00	0.00	H
ATOM	3100	1HB	LEU	15	19.060	26.519	-10.394	0.00	0.00	H
ATOM	3101	2HB	LEU	15	19.101	27.255	-11.965	0.00	0.00	H
ATOM	3102	HG	LEU	15	19.192	29.555	-10.466	0.00	0.00	H

FIG. 8 - 93

ATOM	3103	1HD1	LEU	15	19.299	28.404	-8.217	0.00	0.00	H
ATOM	3104	2HD1	LEU	15	20.850	27.666	-8.689	0.00	0.00	H
ATOM	3105	3HD1	LEU	15	20.691	29.426	-8.555	0.00	0.00	H
ATOM	3106	1HD2	LEU	15	20.803	28.926	-12.277	0.00	0.00	H
ATOM	3107	2HD2	LEU	15	21.671	29.586	-10.881	0.00	0.00	H
ATOM	3108	3HD2	LEU	15	21.663	27.823	-11.171	0.00	0.00	H
ATOM	3109	N	CYS	16	15.890	25.713	-10.614	0.00	0.00	N
ATOM	3110	CA	CYS	16	14.827	24.744	-10.972	0.00	0.00	C
ATOM	3111	C	CYS	16	13.345	25.158	-10.666	0.00	0.00	C
ATOM	3112	O	CYS	16	12.414	24.661	-11.292	0.00	0.00	O
ATOM	3113	CB	CYS	16	15.199	23.478	-10.188	0.00	0.00	C
ATOM	3114	SG	CYS	16	16.698	22.717	-10.841	0.00	0.00	S
ATOM	3115	H	CYS	16	16.165	25.920	-9.647	0.00	0.00	H
ATOM	3116	HA	CYS	16	14.860	24.509	-12.056	0.00	0.00	H
ATOM	3117	1HB	CYS	16	15.302	23.693	-9.107	0.00	0.00	H
ATOM	3118	2HB	CYS	16	14.391	22.736	-10.273	0.00	0.00	H
TER	3119		CYS	16						
HETATM	3120	N	NH2	17H	13.008	25.950	-9.665	0.00	0.00	N
HETATM	3121	1HN	NH2	17H	12.082	26.370	-9.800	0.00	0.00	H
HETATM	3122	2HN	NH2	17H	13.785	26.359	-9.118	0.00	0.00	H

102/107

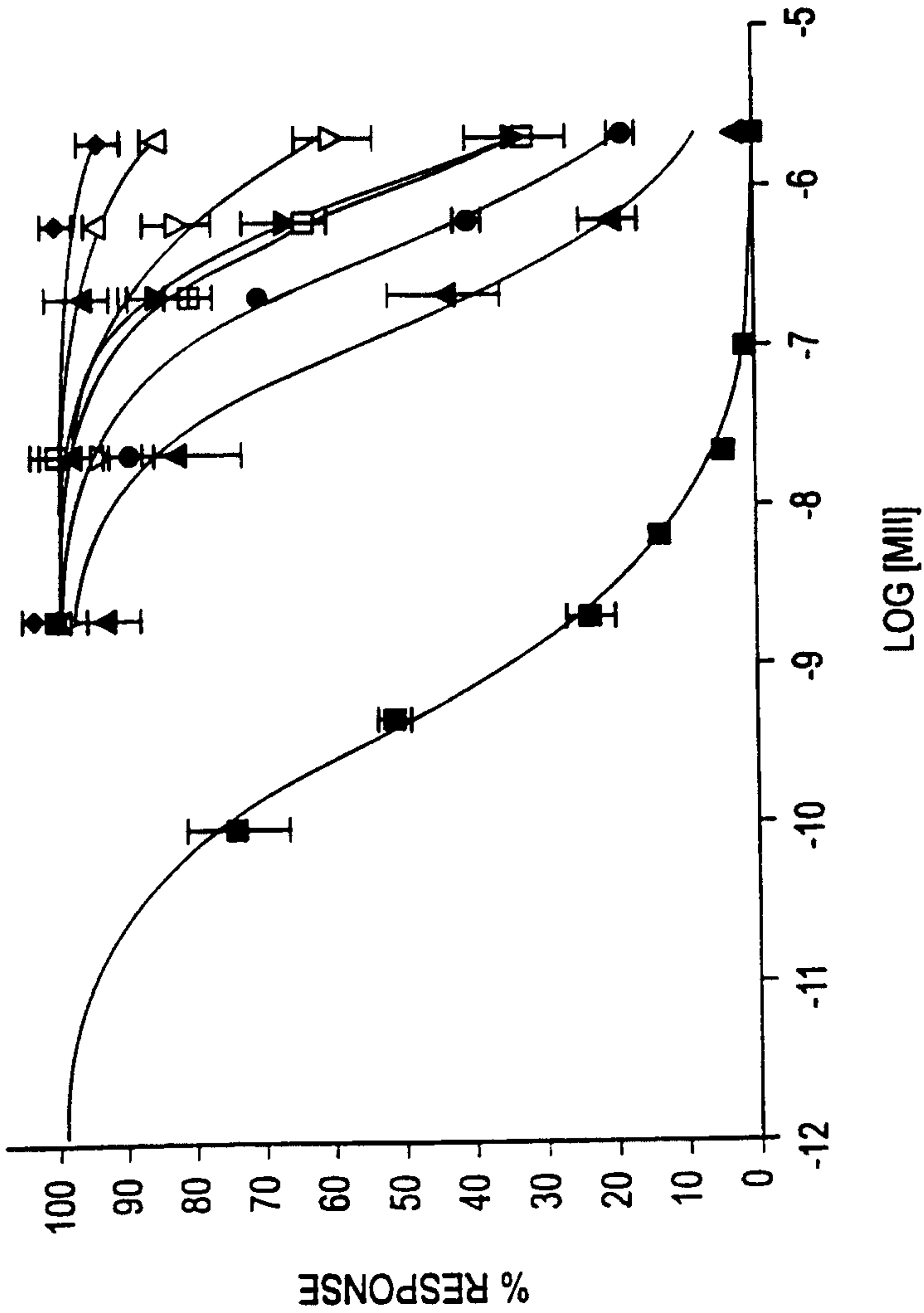


FIG. 9

103/107

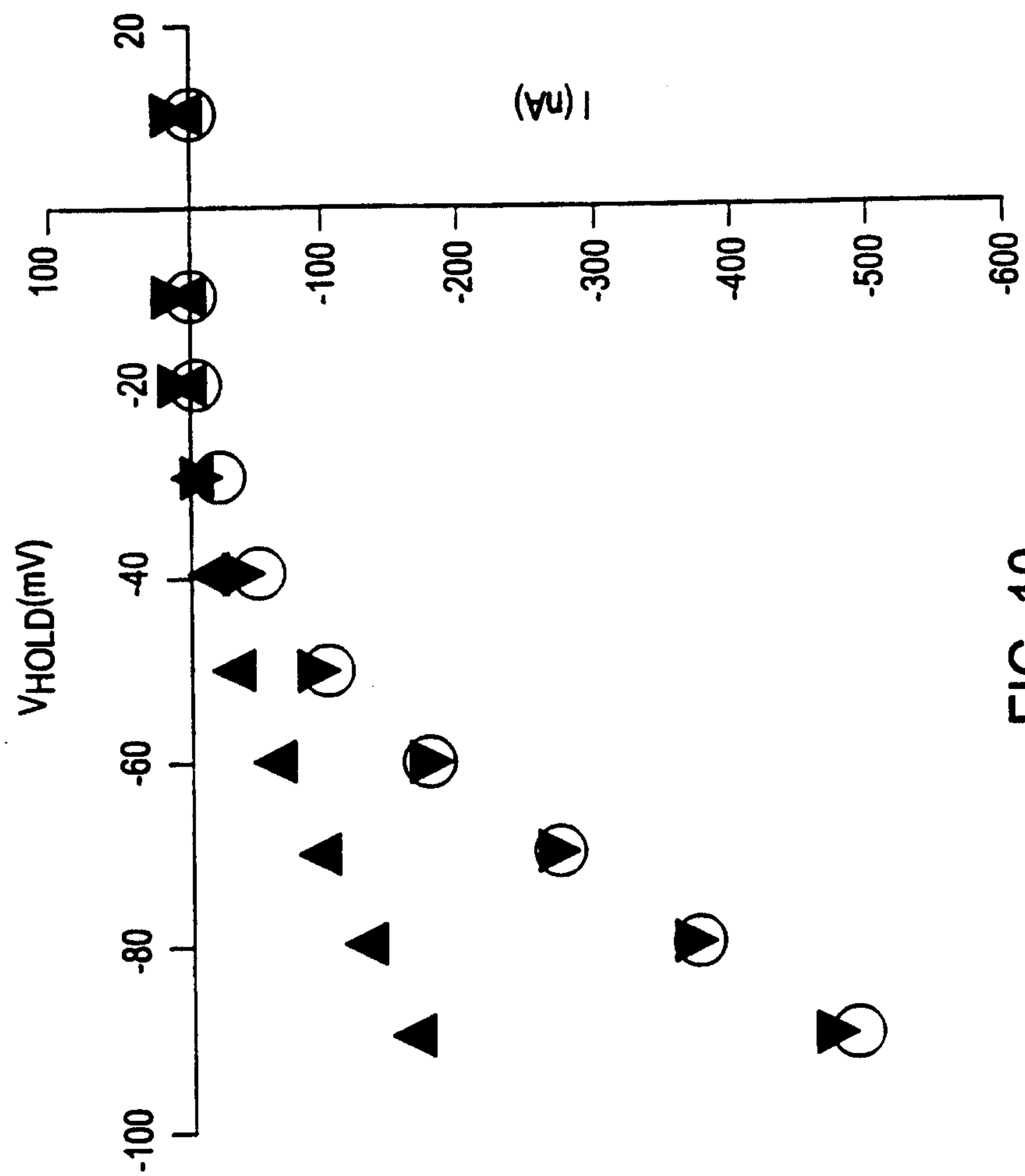


FIG. 10

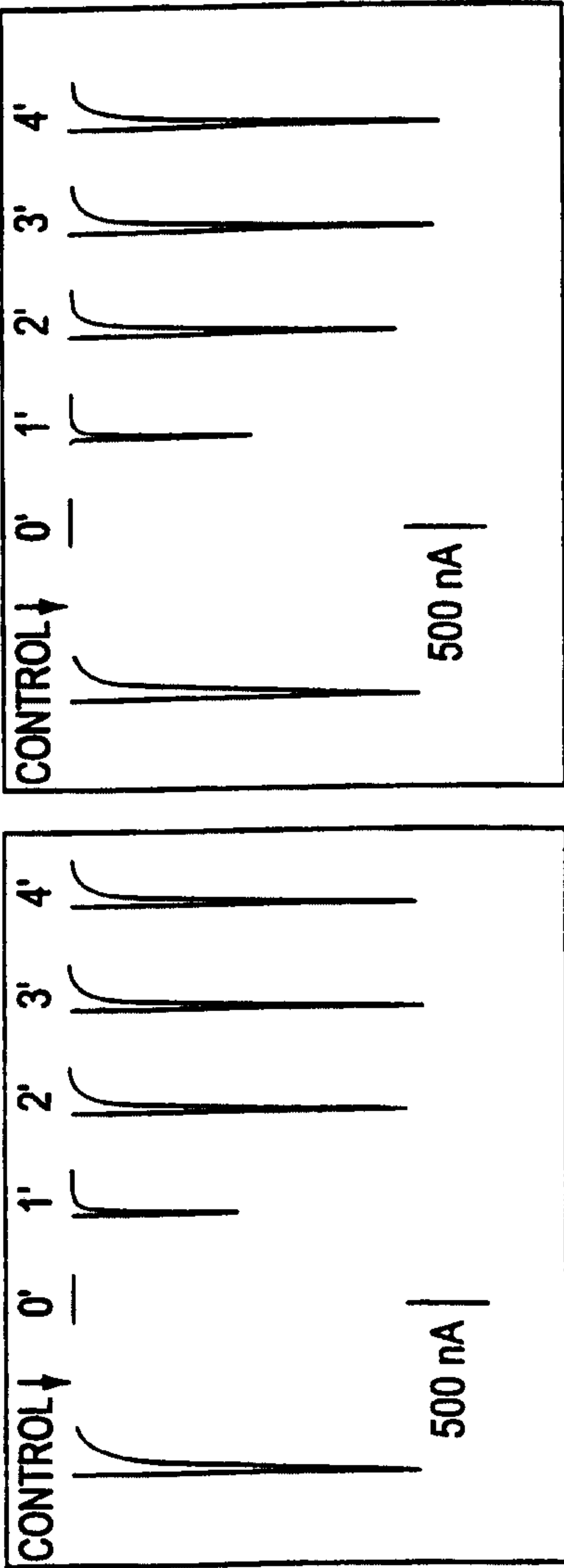


FIG. 11B

FIG. 11A

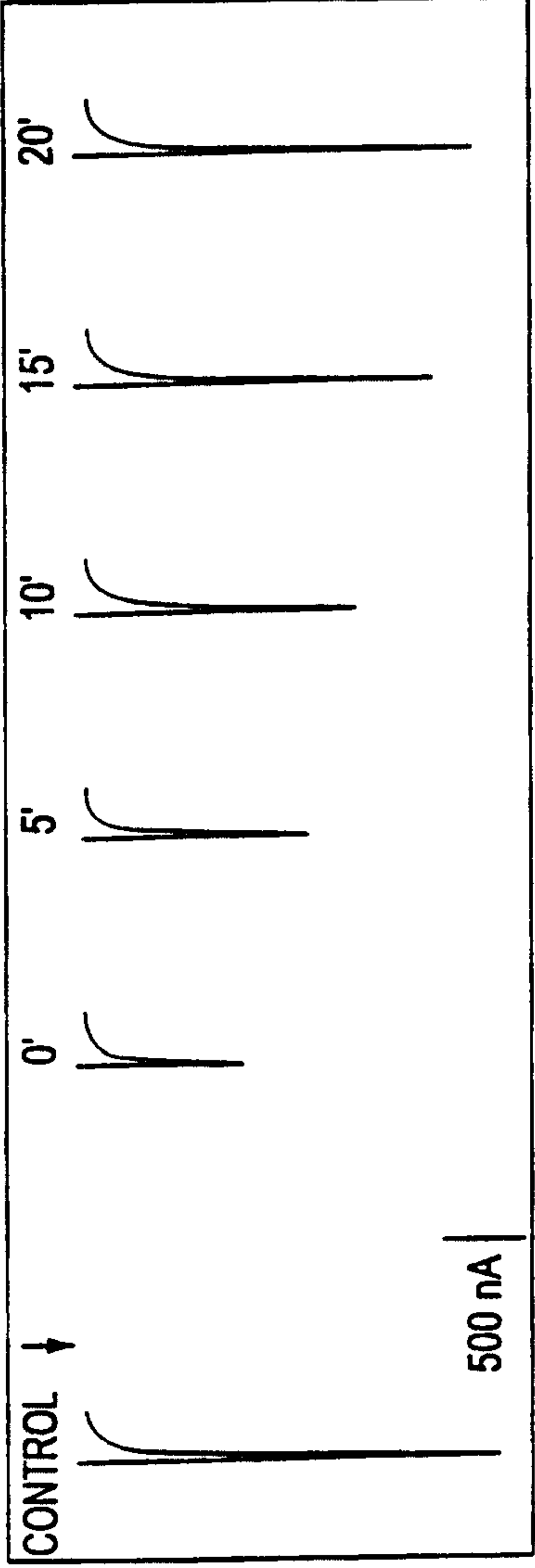


FIG. 11C

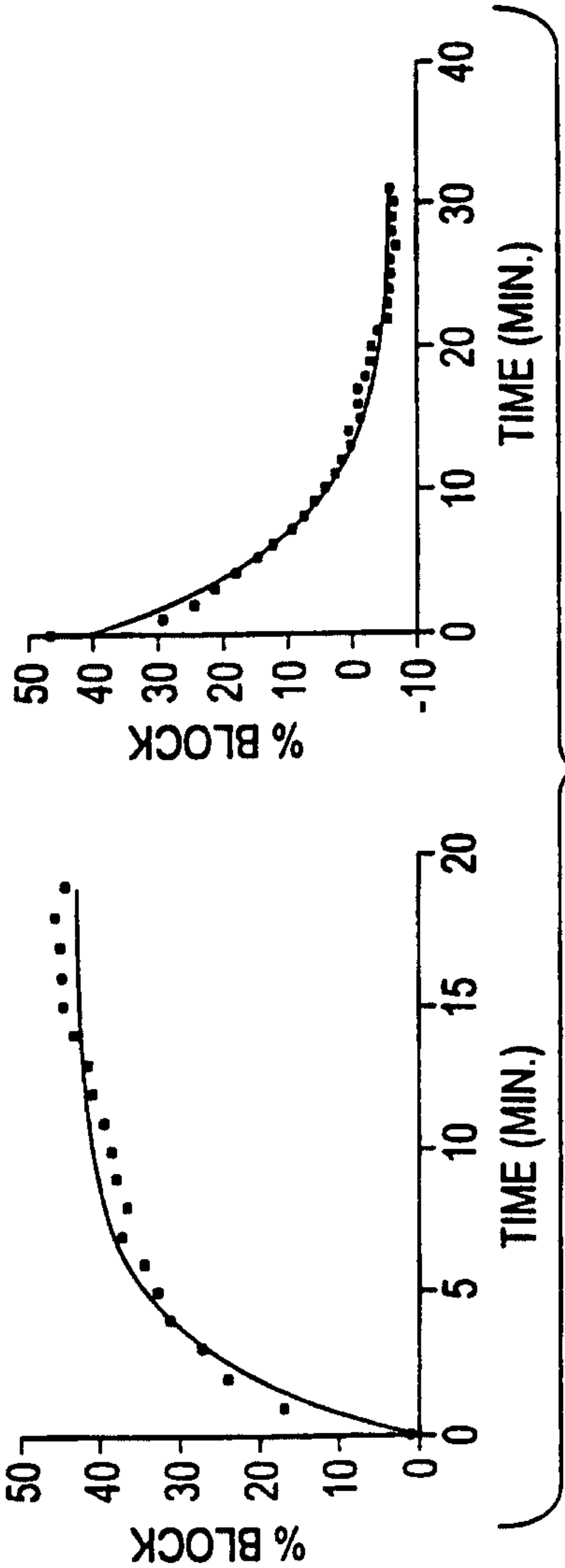


FIG. 12A

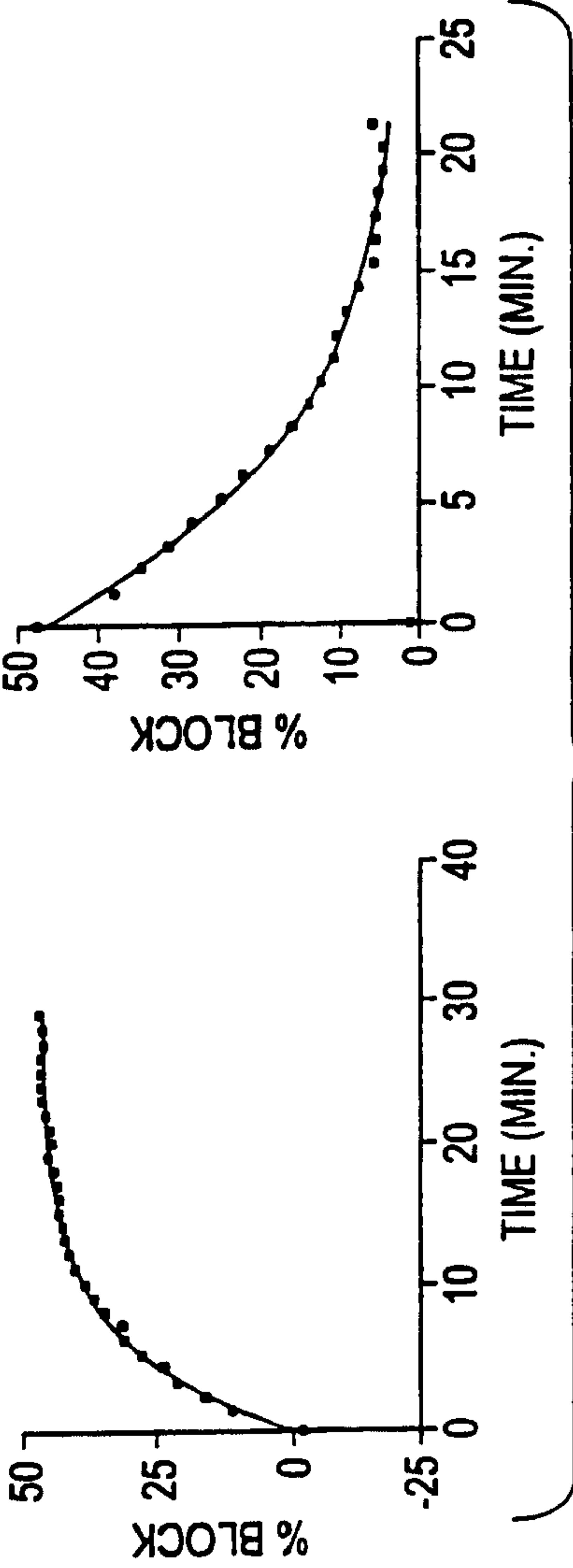
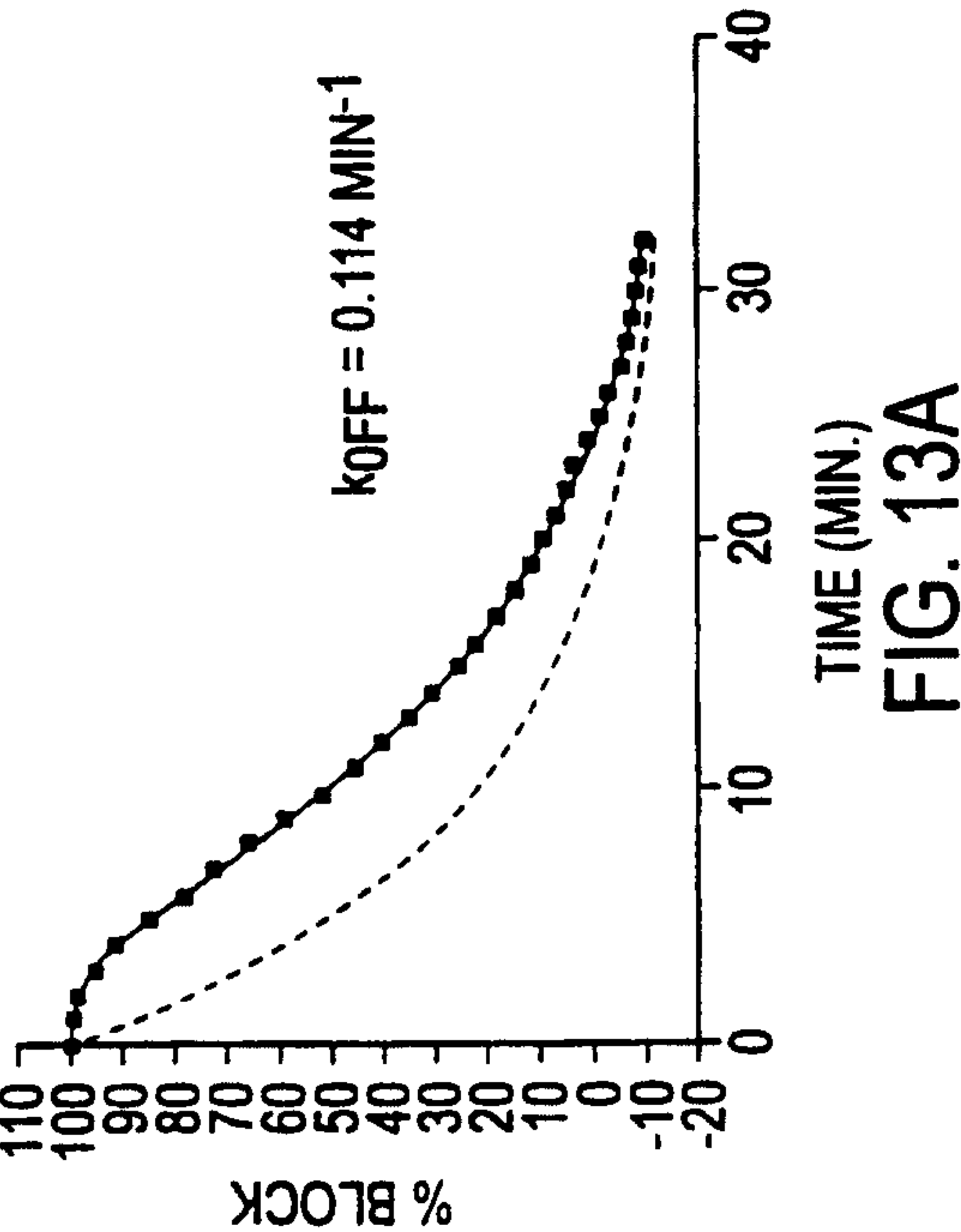
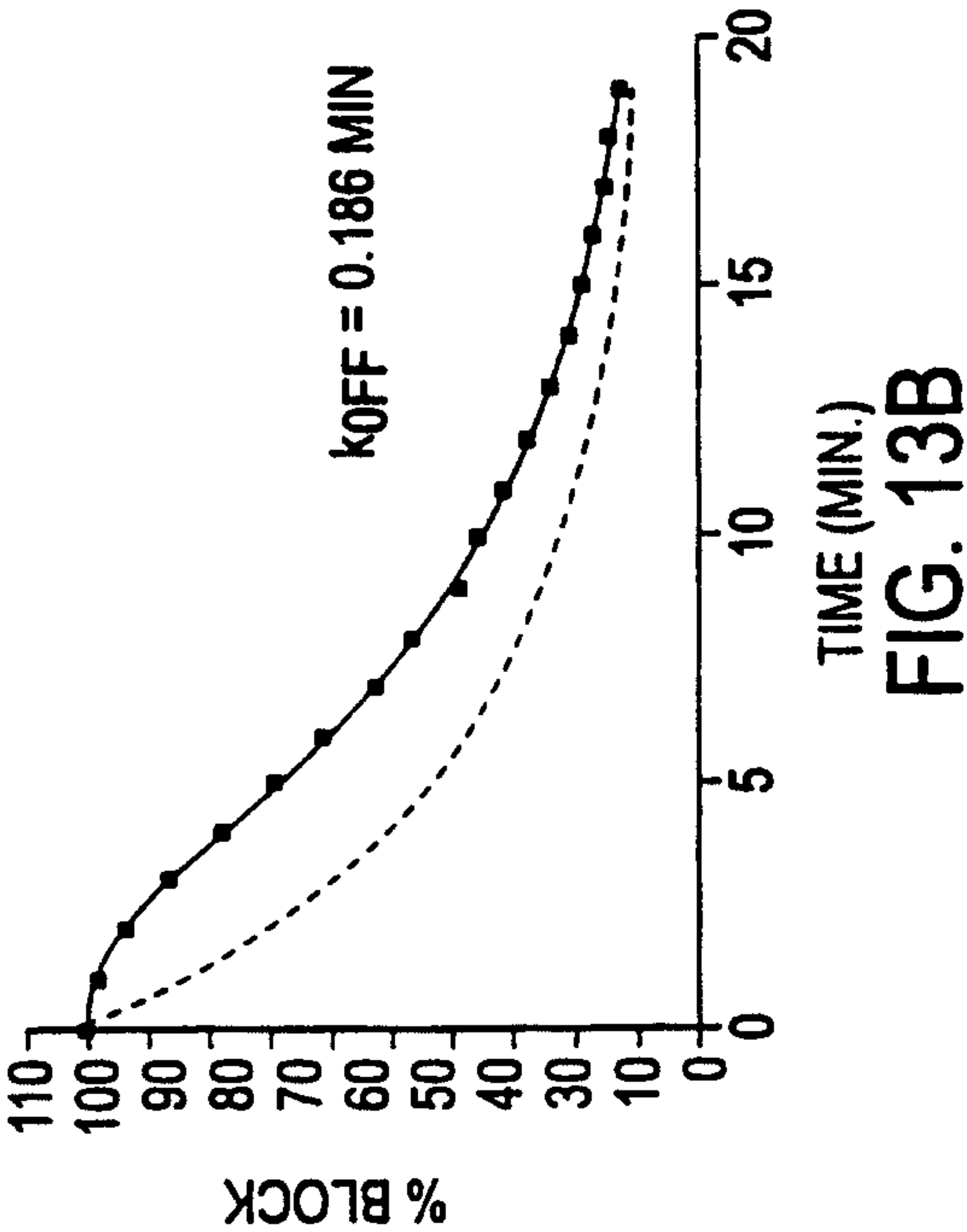


FIG. 12B



107/107

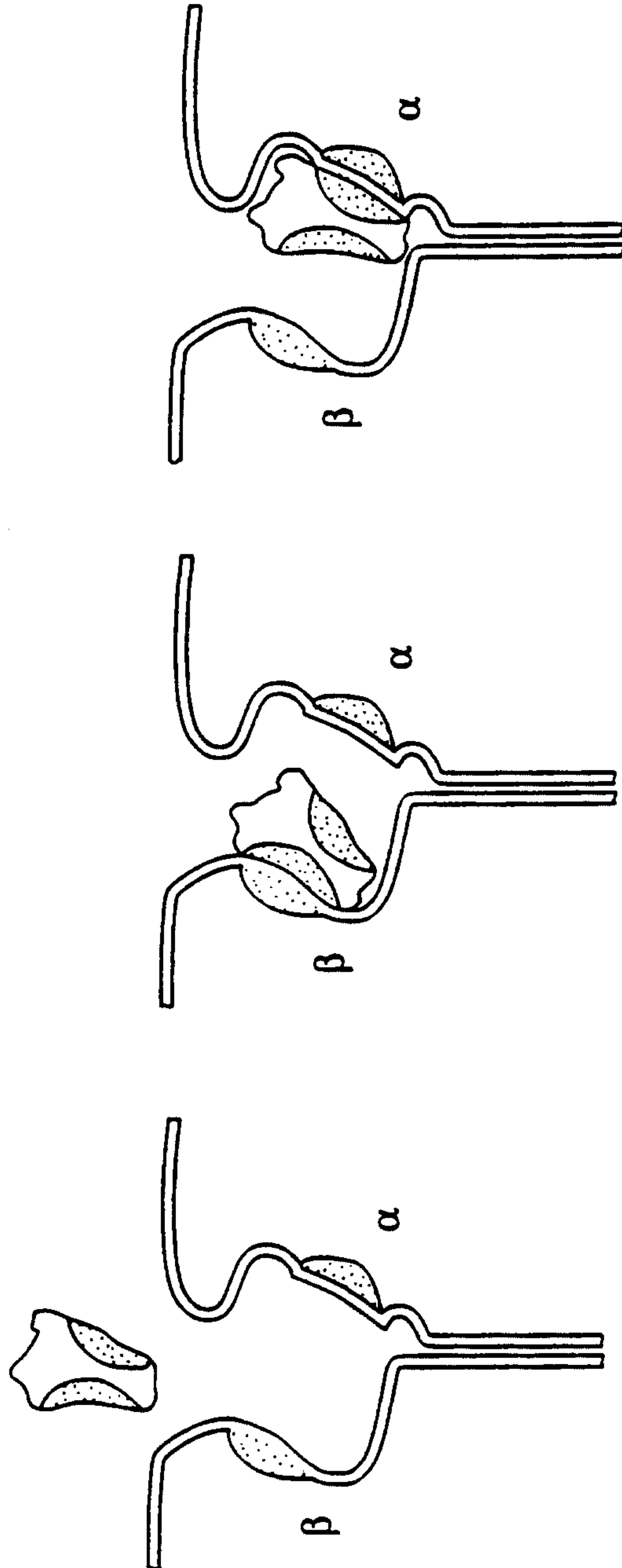


FIG. 14C

FIG. 14B

FIG. 14A