STRUCTURE OF A FREE REGULATOR OF G-PROTEIN SIGNALING (RGS4) AND METHODS OF IDENTIFYING AGONISTS AND ANTAGONISTS USING SAME

BACKGROUND OF THE INVENTION

A variety of biochemical processes, particularly those involving protein-protein interactions, are believed to be mediated by an induced conformational change in the protein target. The resulting structural change in the protein is then used to explain a modification in its function (e.g., enzymatic activity) or its affinity for another protein in the biological system. Conformational change has been proposed to occur in the cascade of steps associated with certain signal transduction pathways in eukaryotic cells. A ubiquitous component of such signal transduction pathways is a heterotrimeric guanine nucleotide-binding protein (G-protein) coupled to a cell surface receptor (for reviews see references 1-4 and 72). G-proteins relay signals initiated by various stimuli including photons, odorants, and a number of hormones and neurotransmitters. A variety of diseases are caused by defects in G-protein activity. G-proteins exist as heterotrimeric complexes of α, β, and γ subunits. The α-subunit (Gα) is weakly bound to a dimer (G$\beta\gamma$) in which the β-subunit is tightly bound to the γ-subunit. Gα is also associated with the intracellular carboxy terminal tail of a seven-helical transmembrane receptor. G-proteins transfer signals from more than 1000 receptors with various Gα subtypes regulating a variety of distinct downstream signaling pathways. Guanine nucleotide binding and GTPase function within the Gα domain to regulate the activity of G-proteins.

The G-protein signaling process is typically initiated by the binding of an agonist to the cell surface receptor resulting in an induced conformational change in the G-protein. The G-protein structural change affects the guanine nucleotide affinity of Gα, so that it preferentially binds GTP and Mg^{2+} over GDP. Numerous x-ray structures for $G_{i\alpha1}$ during the various stages of the GTPase cycle have been used to identify regions of induced conformational change (5-8). In particular, the Gα guanine nucleotide binding site is composed of three distinct "switch" regions: residues V179-V185 in switch I, residues Q204-H213 in switch II and residues A235-N237 in switch III, which undergo conformational changes upon GTP hydrolysis. The Gα surface that binds the G$\beta\gamma$ dimer contains switch I and switch II regions. In the active Gα-GTP-Mg^{2+} complex, a conformational change in switch I is associated with binding Mg^{2+}, and switch II and switch III regions become

well ordered due to ionic interactions between the two switch regions. As a result of the formation of the Gα-GTP-Mg^2 complex, modifications in the structure of the three "switch" regions facilitate dissociation of Gα from Gβγ. The released subunits are then available to interact with a variety of target proteins to elicit the desired response. Termination of the signal results when the process is reversed by the hydrolysis of GTP bound to Gα. Reassociation of Gα with Gβγ results in the inactivation of the G-protein. Therefore the duration of the G-protein signal is directly dependent on the GTPase activity of the Gα protein.

Regulators of G-protein signaling (RGS) affect the intensity and duration of the G-protein signal cascade by binding to the active Gα-GTP-Mg^2 complex and inducing a 50-fold increase in the rate of GTP hydrolysis (For reviews see references 9-13). Conversely, RGS proteins have little or no affinity for the inactive Gα-GDP complex. Thus, RGS proteins act as attenuators of the induced G-protein signal by increasing the rate of inactivation of the G-protein and termination of the signal. RGS proteins may exhibit additional biological function, e.g., RGS4 is reported to block activation of GTP-Gα by effectors (83). The RGS family, including RGS4, GAIP (human Gα-interacting protein), RGS1, RGS10, and RGS16, among others, contains more than 20 known members where specificity for Gα subtypes has been demonstrated and appears to be associated with subtle sequence differences (8, 14). The RGS family contains significant structural diversity, however, all RGS proteins are characterized by a conserved domain of about 130 amino acids which may be separated by linker regions of varying lengths. Recently, the RGS family has been reported to comprise at least six separate subfamilies designated A-F with unique structural features (Zheng, B. et al. (1999) (86). RGS4 exhibits structural features of RGS subfamily A. Subfamily-specific structural features may be associated with subfamily-specific functions, e.g., differences in Gα binding specificity among RGS proteins, membrane association of RGS protein, or functions exhibited by RGS proteins in addition to GAP activity. RGS4 is believed to function to attenuate induced G-protein by stabilizing the transition.

RGS proteins are widely expressed in eukaryotic cells, including human cells (13). At least one RGS protein is found in tissue of each human organ and many tissues express multiple RGS proteins. Additionally, members of the RGS family are specifically expressed in the human brain, where RGS4 is perhaps the most widely distributed and highly expressed RGS subtype (15, 16). RGS expression has been correlated with a response

to induced seizures, which indicates that regulation of RGS expression is an adaptive response in the brain signal transduction pathway to compensate for desensitization and sensitization of G-protein-coupled receptor function (16). In addition to regulation of the response to neurotransmiters, RGS activity has been associated with a variety of cellular functions including: cell proliferation, cell differentiation, membrane trafficking and embryonic development (9, 10, 12, 17).

An x-ray structure of RGS4 bound to Giα1 [8], site-directed mutagenesis [18-20] and biochemical studies [17, 21] suggest that RGS4 binds preferentially to the Gα-GTP-Mg^{2+} complex and stabilizes the transition state structure of the switch regions facilitating hydrolysis of GTP. Since the functional result of RGS4 binding to Giα1 is induction of GTP hydrolysis by Giα1, it is reasonable to anticipate that the conformational change upon complex formation with RGS4 primarily occurs in $G_{i\alpha 1}$. However, the x-ray crystal structure of Giα1 in the RGS4-Giα1 complex exhibits only a 0.6 Å rms difference from that of Giα1 in Giα1–AIΦ_4 which is trapped in the proposed transition state for GTP hydrolysis. This comparison indicates that there is no significant conformational change in Giα1. On the other hand, analysis of the RGS4-Giα1 complex x-ray structure indicates that RGS4 binding to Giα1 induces a decrease in the mobility of the switch regions of Giα1. In these regions, critical interactions occur between N82 of RGS4 (employing the numbering of Figure 1) with the switch regions I and II of Giα1 and between T182 of Giα1 with a Gα binding pocket on RGS4. The RGS4 residue N82 has been identified as critical for facilitating the intrinsic Giα1 GTPase activity presumably by stabilizing the switch regions and substrate binding (19, 20). Similar changes in the switch regions are observed between the Gα-GTP-Mg^2 complex and the Gα-GDP complex (2), suggesting that a conformational change in RGS4 may contribute to regulation of G-protein signaling.

de Alba, E. et al. (1999) (87) reports the solution structure of human GAIP as determined by NMR techniques. The structure calculation used dipolar couplings of the oriented protein in two different liquid crystal media. The GAIP solution structure was compared to that of the rat RGS4-$G_i\alpha_1$ x-ray structure (8). The reference suggests that GAIP-L187 participates in Gα-RGS binding and may also be important in the folding and stability of the RGS protein. It is also suggested that GAIP-S156 plays a role in GAIP stability. GAIP-S156 has been identified as a subfamily-specific residue for

the RGS subfamily A [GAIP, Ret-RGS1, RGS21] (86) and Wang et al. (89). In RGS subfamily B which includes RGS4, the core amino acid corresponding to GAIP S156 is RGS N82 (as numbered in Fig. 1 and N128 as numbered in Tesmer et al. (8)). The core region of GAIP is reported to have only 60% sequence identity to the core of RGS4. Any differences observed between these two structures are at least in part due to the differences in amino acid sequence.

It is thus desirable to provide structural information for free RGS4 to better understand the mechanism of the regulation of G-protein signaling. More specifically, such structural information allows a direct comparison between the solution structure of RGS4 and the x-ray structure of the RGS4-Gα complex to determine which conformational changes occur in RGS proteins on binding to Gα. The structural information and comparison can be employed to identify factors (chemical or biochemical species) that affect G- protein signaling by interaction with RGS proteins or their complexes with Gα. The structurally information can be of particular use in the identification and rational design of agonists and antagonists of free RGS and RGS/Gα complex activity.

SUMMARY OF THE INVENTION

The present invention provides the three-dimensional solution structure of a free (i.e., not complexed) RGS protein of subfamily B, specifically that of free RGS4, as determined by NMR (nuclear magnetic resonance) spectroscopy. Particularly, the invention provides the three-dimensional solution structure of a Gα binding site of an RGS subfamily B protein. The Gα binding site of RGS subfamily B is exemplified by the three-dimensional structure of the RGS4 Giα1 binding site comprising the RGS4 protein residues D117, S118 and R121. The invention also provides the three-dimensional structure of the α6 - α7 region of a free RGS subclass B which region exhibits a significant conformational change on binding of RGS to Gα. Binding at the α6 - α7 region of RGS protein can effect the function of RGS protein in G-protein signaling. Further, the invention identifies and provided the three-dimensional structure of an allosteric binding site in an RGS protein. Binding at this allosteric site can affect the regulation of G-protein signaling. An allosteric binding site in the RGS protein is exemplified by the allosteric binding site in RGS4 located in the α1 and α2 helical regions of free RGS4 and in the tight turn located between

the two helical regions. More specifically, the allosteric binding site in RGS4 comprises the residues V10, W13, L17, I20, H23, E24, C25 and T132.

The three dimensional structure of free RGS4 in solution, including the Gα binding site, the C-terminus α_6 - α_7 region of free RGS4, and the allosteric binding site in free RGS4 are provided by the relative atomic structural coordinates given in Table 2 as obtained by NMR spectroscopy. Also provided are the ^{15}N, ^{13}C, ^{13}CO and ^{1}H NMR assignments for free RGS4 (Table 1) which are employed in the determination of its secondary and three-dimensional structure. These assignments are also useful in methods for identifying or detecting chemical and biochemical species that bind to RGS and which can affect RGS function or RGS-Gα function and are particularly useful for identifying or detecting species that bind to RGS subclass B which can affect its function or RGS subfamily B-Gα function.

The invention further provides a representation or model of all or part of the three-dimensional structure of a free RGS subfamily B protein comprising a data set of relative atomic structural coordinates embodying the three-dimensional structure of free RGS4 protein. The invention also provides a data set of relative atomic structural coordinates embodying the three-dimensional structure of the Gα binding site in an RGS subfamily B protein. The invention further provides a data set of relative atomic structural coordinates embodying the α_6 - α_7 region of an RGS subfamily protein. In addition, the invention provides a data set of relative atomic structural coordinates embodying an allosteric binding site in an RGS subfamily B protein. The data set and any structural representation or model of a free RGS subfamily B, its Gα binding site its α_6 - α_7 region or the allosteric binding site in RGS subfamily B created or generated using the data set provided herein can be employed to identify, select or rationally design factors, e.g., chemical or biochemical species, which affect RGS function or activity or RGS/Gα complex activity or function. Further, the data set, structural representation or model of the Gα binding site can also be used to identify, select or rationally design species which affect Gα function by binding to Gα. The data set and structural representations and models provided by this invention are particularly useful for the identification of agonists or antagonists of RGS function or RGS/Gα complex function or activity.

The data set, including subsets of data embodying the Gα binding site, the α6 - α7 region and the allosteric binding site, provided herein was determined by NMR analysis. However, any known method can be

employed to provide the structural data. In one embodiment, the data set embodies the structure of free RGS4 in solution. In certain embodiments, the data set comprises one or more portions of the structure of free RGS4. Of particular interest are those portions of the structure of RSG4 which function in RSG-regulation of G-protein signaling or more specifically which affect binding of RGS to Gα or which affect the biological function or activity of the RGS-Gα complex. Also of interest are those portions of the structure of RSG4 to which candidate agonists and antagonists of RSG bind to affect its biological function.

Any available method may be used to construct a structural representation or model from the NMR-derived data disclosed herein or from data obtained from an independent structural analysis of free RGS4. Such a model or representation can be generated or constructed from the available analytical data points using software packages such as HKL, CHARMM, MOSFILM, XDS, CCP4, SHARP, PHASES, HEAVY, XPLOR, TNT, NMRCOMPASS, NMRPIPE, DIANA, NMRDRAW, FELIX, VNMR, MADIGRAS, QUANTA, BUSTER, SOLVE, O, FRODO, XPLOR, RASMOL, and CHAIN, all of which are well-known and available to those in the art. A structural representation or model can be generated from these data using available systems, including, for example, Silicon Graphics, Evans and Sutherland, SUN, Hewlett Packard, Apple Macintosh, DEC, IBM, and Compaq systems. The structural representation or model can be displayed or generated in any two-dimensional or three-dimensional form known in the art for viewing, analyzing, modeling or otherwise representing the structure. The structural representation can be transmitted, conveyed or stored in any known graphic, digital or analog form. Structural representations or models generated with the RGS data provided herein can be combined with structural representations of other chemical and biochemical species (e.g., candidate antagonists or agonists) including x-ray data of RGS-complexes, in order to analyze potential interactions between RGS, particularly RGS subfamily B proteins, and Gα and those species. The data provided herein may also be combined, as illustrated herein, with structural information (including x-ray data) of RGS-complexes, particularly RGS subclass B protein-complexes and particularly those complexes believed to be or believed to model biologically functional complexes.

The present invention relates to the structural data for free RGS4, the Gα binding site of RGS4, the α6 - α7 region whose conformation changes on binding of RGS4 to Gα, and allosteric binding sites in RGS4 in any form

(for example in digital, tabular, graphic, or pictorial form or as embodied in any representation or model or as embodied in a computer storage medium) and the use of the data (in whatever form) for generating a structural representation or model of free RGS, particularly an RGS subfamily B protein, more particularly RGS4, or of the interaction of RGS, an RGS subfamily B protein, and RGS4, with any other chemical or biochemical species, including structural representations or models of RGS interaction with G-protein subunits and of RGS interaction with potential agonists or antagonists of RGS function.

The present invention also provides for a computer system which comprises the structural representation or model of the invention and hardware used for construction, processing and/or visualization of the model of the invention. The solution structural coordinates of RGS4 or portions thereof as provided herein can be stored in or on an appropriate medium for introduction into or use with any computer program or system for generating a representation or model of the structure of an RGS protein, an RGS subclass B protein or RGS4, or for analysis of the interaction of RGS with other chemical or biochemcial species.

The structural coordinates can be stored in a machine-readable form on a machine-readable storage medium, for example, 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. By way of example, the data defining the three dimensional structure of RGS4 of the present invention, or of a portion of RGS4 as disclosed herein, may be stored in a machine-readable storage medium, and may be displayed as a graphical three-dimensional representation of the relevant structural coordinates, typically using a computer capable of reading the data from said storage medium and programmed with instructions for creating the representation from such data.

Accordingly, the present invention provides a machine, such as a computer, programmed in memory with the coordinates of the RGS4 or RGS subfamily B protein, or portions thereof (such as, by way of example, the coordinates of the RSG4 Gα binding site, the α6 - α7 region of RGS4, or the allosteric binding site in the α1-α2 region of RGS4), together with a program capable of converting the coordinates into a three dimensional graphical representation of the structural coordinates on a display connected to the machine. A machine having a memory containing such data aids in the

rational design or selection of inhibitors or activators of RGS, Gα or RGS-Gα complex activity, including the evaluation of the ability of a particular chemical or biochemical species to favorably associate with RGS, particularly an RGS subclass B protein, as well as in the modeling of compounds, proteins, complexes, etc. related by significant structural or sequence homology to RGS4 or other RGS proteins.

The present invention is additionally directed to a method of determining the three dimensional solution structure of a compound, e.g., a protein or peptide or other chemical or biochemical species (including RGS proteins or portions thereof, or more specifically, RGS subfamily B proteins or portions thereof that are not RGS4) whose structure is unknown, comprising the steps of first obtaining a solution of the protein or peptide whose structure is unknown, and then generating NMR data from this solution. The NMR data from the protein or peptide can then be compared with the known three dimensional structure of RGS4 (or portion thereof, e.g., the Gα binding site) as disclosed herein, and the three dimensional structure of the protein or peptide whose structure is unknown conformed to the known RGS4 structure using standard techniques, such as 2D, 3D and 4D isotope filtering, editing and triple resonance NMR techniques, computer homology modeling as well an adaptation of molecular replacement techniques as applied to NMR data. Alternatively, a three dimensional model of a protein or peptide of unknown structure, but related by sequence similarity to RGS4, may be generated by initial sequence alignment between RGS4 and the protein or peptide, based on any or all amino acid sequence identity, secondary structure elements or tertiary folds, and then generating by computer modeling a three dimensional structure for the molecule using the known three dimensional structure of, and sequence alignment with, RGS4.

Methods are also provided for identifying a species which is an agonist or antagonist of RGS activity, RGS binding to Gα, Gα binding to RGS, or RGS/Gα complex activity, particularly for RGS subfamily B proteins. The method comprises the steps of using a three dimensional structure of free RGS subfamily B protein or a portion (e.g., an RGS4 core protein) thereof as defined by the relative structural coordinates of amino acids encoding the RGS4-core protein to design or select a potential agonist or antagonist, and synthesizing or otherwise obtaining the potential agonist or antagonist. The potential agonist or antagonist may be selected by screening an appropriate database, may be designed *de novo* by analyzing

the steric configurations and charge potentials of the RGS4 Gα binding site, the α_6 - α_7 region of RGS4, or an allosteric binding site of RGS4 in conjunction with the appropriate software programs, or may be designed using characteristics of known agonists or antagonists of RGS4, RGS subfamily B, or other RGS proteins in order to create "hybrid" agonists or antagonists. The method of the present invention is preferably used to design or select inhibitors of RGS subfamily B proteins, or RGS subclass B-Gα complex activity, and specifically RGS4 or RGS4-Giα1complex activity. In a specific embodiment, the potential agonist or antagonist is identified, selected or designed by studying the interaction of candidate species with a three-dimensional model of RGS4 (or a portion thereof) or a three-dimensional model of another RGS subfamily B protein (or model thereof) and selecting a species which is predicted by its interaction with the RGS protein or a portion of an RGS protein to act as an agonist or antagonist. Potential antagonists and agonists can be readily tested using various procedures disclosed herein or known in the art to confirm their antagonist or agonist function. Species identified in accordance with such methods are also provided.

Other specific embodiments provide: (1) a process of identifying a substance that inhibits RGS4 activity, RGS4 binding to Giα1, Giα1 binding to RGS4 or RGS4/Giα1 complex activity comprising determining the interaction between a candidate substance and a model of all of part of the structure of free RGS4, or (2) a process of identifying a substance that mimics or promotes RGS4 activity, RGS4 binding to Giα1, Giα1 binding to RGS4 or RGS4/Gα complex activity comprising determining the interaction between a candidate substance and a model of all or part of the structure of free RGS4 by analyzing the steric configuration and charge potential of free RGS4 and comparing these properties to those of a candidate substance. Substances identified in accordance with such processes are also provided.

Other embodiments provide a method of identifying antagonists or agonists of RGS activity, RGS binding to Gα, Gα binding to RGS or RGS/Gα complex activity by rational drug design comprising: (a) designing a potential antagonist or agonist that will form a reversible or non-reversible complex with one or more amino acids in the RGS Gα binding site based upon the structure coordinates of free RGS4; (b) synthesizing or otherwise obtaining the antagonist or agonist; and (c) determining whether the potential antagonist or agonist inhibits or promotes the activity or binding of RGS or the activity of the RGS-Gα complex. In other preferred embodiments, the

antagonist or agonist is designed to interact with one or more atoms of one or more amino acids in the RGS4-Giα1binding site. More specifically, the antagonist or agonist is designed to interact with amino acids selected from the group consisting of D117, S118, or R121 of RGS4, other amino acids associated with the Gα binding site and other amino acids revealed by the determined structure. Yet more specifically, the antagonist or agonist is designed to interact with amino acids selected from the group consisting of S39, E41, N42, L113, D117, S118, R121 or N82 of RGS4. Substances identified in accordance with such processes are also provided. The agonist or antagonist may form a covalent or non-covalent bond with an RGS protein. This method is specifically applicable to identifying antagonists or agonists of RGS subfamily B proteins.

Other specific embodiments provide a method of identifying antagonists or agonists of RGS activity or RGS/Gα complex activity by rational drug design comprising: (a) designing a potential antagonist or agonist that will form a reversible or non-reversible complex with one or more amino acids in a α6 - α7 region of RGS based upon the structure co-ordinates of free RGS4; (b) synthesizing the antagonist or agonist; and (c) determining whether the potential antagonist or agonist inhibits or promotes the activity of RGS or RGS/Gα complex. In preferred embodiments, the antagonist or agonist is designed to prevent or facilitate conformation change in these regions on binding to Gα. This method is specifically applicable to identifying antagonists or agonists of RGS subfamily B protein activity or RGS subfamily B/Gα complex activity.

Other specific embodiments provide a method of identifying antagonists or agonists of RGS activity or RGS/Gα complex activity by rational drug design comprising: (a) designing a potential antagonist or agonist that will form a reversible or non-reversible complex with one or more amino acids in an RGS4 allosteric binding site based upon the structure co-ordinates of free RGS4; (b) synthesizing the antagonist or agonist; and (c) determining whether the potential antagonist or agonist inhibits or promotes the activity of RGS or RGS/Gα complex. In preferred embodiments, the antagonist or agonist is designed to interact with the allosteric binding site in the α_1-α_2 region of RGS4. In yet other preferred embodiments, the antagonist or agonist is designed to interact with one or more atoms of one or more amino acids in the allosteric binding site in the α_1 and α_2 region of RGS4, and particularly with one or more atoms of amino acids V10, W13, L17, L20, H23, E24, C25, or T132 of RGS4. Substances identified in

accordance with such processes are also provided. This method is specifically applicable to identifying antagonists or agonists of RGS subclass B protein activity or RGS subclass B/Gα complex activity.

Candidate agonists and antagonists of RGS, RGS-Gα complexes can be selected from any type of small molecule, dimer, multimer, oligomer, or polymer of natural or non-natural origin that is obtained from any source and may be isolated from a natural source or chemically or biologically synthesized. Candidate antagonists and agonists can include nucleic acids, peptides, polypeptides, proteins, and various small organic molecules.

The study of the interaction of the candidate species with the three-dimensional structure of RGS and/or portions of that structure can be performed using available software platforms, including QUANTA, RASMOL, O, CHAIN, FRODO, INSIGHT, DOCK, MCSS/HOOK, CHARMM, LEAPFROG, CAVEAT(UC Berkley), CAVEAT(MSI), MODELLER, CATALYST, and ISIS.

The invention also provides a method for identifying the presence of and determining the location of allosteric binding sites in RGS4. The method comprises the steps of contacting free RGS4-core in solution with test compounds that are members of a library of chemical species which encompass a range of structural features or which are known to inhibit RGS function; measuring the ^{1}H, ^{15}N, and/or ^{13}C NMR spectra of the RGS4-core in the presence of test compounds of the library to detect any perturbations in the chemical shifts of RGS4-core that are induced by binding of a test compound to RGS4-core, and determining if binding of the test compound affects RGS activity. This can be done, for example, by assessing the affect of the test compound on RGS induced Gα GTPase activity. The amino acid residues of RGS4-core that are affected by binding of the test compound define the binding site of the test compound. If the test compound is found to affect RGS4-core activity and the location to which the test compound binds in RGS4-core is not the Gα binding site, then the location to which the test compound binds is an allosteric binding site. One such allosteric binding site in the α1-α2 region of RGS4-core has been identified using this method.

The three-dimensional structure of any allosteric binding site identified by this method can then be employed in methods described herein to identify, select and design candidate agonists and antagonists of RGS activity and specifically of RGS subclass B activity. Test compounds for assessing the presence of allosteric sites in RGS can be members of a library

that exhibit a range of structural feature (e.g., alicyclic rings, heterocyclic rings, aromatic rings, aliphatic, alicyclic compounds or aromatic compounds displaying various substituent groups (e.g., OH, -CO-,- NHCO-, etc.). Test compounds can also be selected in screens for compounds that are known to exhibit an affect on RGS activity (e.g., that enhance or retard the rate of RGS4-induced Gα GTPase). Initial screens can be performed by assessing mixtures containing a plurality of test compounds for an affect on RGS activity. In cases in which an affect is observed with the mixture of test compounds, the individual compounds can be re-tested individually to determine which test compound(s) affect RGS activity.

In a specific embodiment, the invention provides a method in which the three dimensional structure of free RGS4-core is employed to identify chemical or biochemical species or fragments thereof capable of binding to an RGS protein. Once identified the species or fragments capable of binding to RGS are assembled (using well-known computer modeling techniques) into a single molecule to provide a structure of a potential antagonist or agonist. The molecule assembled can contain additional species or fragments (e.g., a backbone) for desired orientation of the species or fragments capable of binding to RGS. This method is particularly applicable to RGS subfamily B proteins.

The invention further provides a method for identifying mutants of RGS4 proteins in which the activity of the mutant protein is different from that of RGS4. In this method the three-dimensional structure of free RGS4 is employed to identify amino acids that are involved in the regulation of G-protein signaling. One or more of the amino acid residues identified are then modified to generate a mutant RGS4. Mutants identified in this method are expected to exhibit altered function in the regulation of G-protein signaling.

Other objects of the invention will be readily apparent from the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the secondary structure of RGS4. The figure provides a summary of the sequential and medium range NOEs involving the NH, Hα and Hβ protons, the amide exchange and ^{3}JHNα coupling constant data, and the ^{13}Cα and ^{13}Cβ secondary chemical shifts observed for RGS4 with the secondary structure deduced from this data. The thickness of the lines reflects the strength of the NOEs. Amide protons still present after exchange to D2O are indicated by closed circles. The open boxes represent

potential sequential assignments NOEs which are obscured by resonance overlap and could therefore not be assigned unambiguously. The gray boxes on the same line as the Hα(i)-NH(i+1) NOEs represents the sequential NOE between the Hα proton of residue i and the CδH proton of the i+1 proline and is indicative of a trans proline. Seven alpha helical regions are indicated (α1-α7).

Figures 2A and 2B are ribbon diagrams of the (A) x-ray structure of RGS4 from the RGS4-Giαl complex, (B) NMR structure of free RGS4 for residues V5 to P134. The residues which exhibit a significant structural change between the RGS4-Giαl x-ray structure and the free RGS4 NMR structure are numbered. Residues K116-Y119 correspond to key residues involved in the interaction with Giα1 and the location of a structural change between the free and complexed forms of RGS are indicated. The C- and N-terminal regions which exhibit a change in secondary structure and helical packing are also indicated. The RGS4-Giαl x-ray structure is that of Tesmer et al. (8). The C- and N-terminal regions which incur a change in secondary structure and helical packing are indicated. The observed helical regions of the RGS4 structure are labeled.

DETAILED DESCRIPTION OF THE INVENTION

RGS proteins are regulators of G-protein signaling which affect the intensity and duration of the G-protein signal cascade by binding to the active Gα-GTP-Mg^2 complex to increase the rate of GTP hydrolysis. RGS proteins act as attenuators of the induced G-protein signal by increasing the rate of inactivation of the G-protein and termination of the signal. RGS proteins have been identified in a wide range of eukaryotes, including humans. RGS proteins are highly diverse, multifunctional proteins characterized by the presence of a core region of approximately 130 amino acid residues (sometimes identified as having 120 amino acids), which may be separated by linker regions of varying lengths (79, 80, 9), that is conserved in all RGS proteins that have so far been identified. All RGS proteins that have been identified bind to members of the Giα class of G protein α subunits. The family of RGS proteins include RGS4, GAIP (human Gα-interacting protein), RGS1, RGS10, RGS11, RGS12, RGS13, RGS14, and RGS16 (also called RGSr), Axin, Conductin, p115-RhoGEF, PD2-RhoGEF and LSC (86), among others, and contains more than 20 known members where specificity for Gα subtypes has been demonstrated and appears to be associated with subtle sequence differences (8, 14). RGS4

is believed to stabilize the transition state for GTP hydrolysis (17, 57, 21). The conserved region of RGS provides for binding to Gα and can thus be used to identify species that affect (as agonists or antagonists) RGS binding to Gα and the activity of RGS as an attenuator of G-protein signaling. RGS proteins of this invention function in G-protein regulation by binding to the Gα subunit of a G-protein. RGS proteins may, but need not, exhibit other biological functions. References 89 and 91 provided reviews of additional biological functions exhibited by RGS proteins.

The term "RGS protein" as used herein, including its use for specific RGS proteins and RGS protein subfamilies, includes native RGS proteins (and native RGS core proteins) isolated from or otherwise obtained from (e.g., by expression of cloned genes) from any natural sources, recombinant RGS proteins which may contain portions of RGS sequence and non-RGS sequence (e.g., RGS-core sequence with the hexahis pro-tag), variant RGS proteins which contain conservative amino acid sequence differences from a native RGS protein or in which sequences non-functional in RGS activity are deleted, mutant RGS proteins in which one or more amino acids have been modified by expression from a mutant RGS coding sequence. Mutants include, among others, those having one or more site specific mutations, those having one or more deletions and those having one or more insertions compared to a native RGS protein (or RGS-core) or variant RGS (or variant RGS-core). The term mutant RGS refers in particular to those proteins having the described mutations, insertions or deletions in the RGS core region. Variant RGS proteins are expected to have biological function for G-protein regulation substantially the same as that of the native RGS protein from which they are derived. Mutant RGS proteins include those which have biological function substantially the same as or modified from that of a native or variant RGS protein from which they are derived. Variant, derivative, recombinant and mutant RGS proteins do not necessarily represent mutually exclusive subsets of proteins.

As noted herein, the RGS-core region is involved with RGS function in G-protein regulation, the term RGS proteins as used herein include RGS proteins in which non-functional regions are absent, e.g., RGS-core regions of native, recombinant, variant or mutant RGS proteins. The RGS core region of a native RGS has been found to retain full native RGS activity (8). The core region of RGS4 is approximately 130 amino acids in length. (References may also refer to conserved or core regions of RGS as having a length of approximately 120 amino acid) RGS cores from other RGS

proteins can differ in length from that of RGS4. RGS proteins of this invention can be obtained by *in vitro* or *in vivo* expression of an RGS coding sequence by isolation from natural sources or any other means known in the art.

Known RGS proteins are categorized into six or seven subfamilies on the basis of a phylo-genetic analysis of 61 mammalian and invertebrate RGS proteins (86). Mammalian RGS proteins are composed of at least six subfamilies designated A-F as follows: A (GAIP, Ret-RGS1, RGS21); B (RGS1, RGS2, RGS3, RGS4, RGS5, RGS8, RGS13 and RGS16 [also called RGS-r]; C (RGS6, RGS7, RGS9 and RGS11); D (RGS12, RGS14); E (Axin and Conductin); and F (p115-RhoGEF, PD2-RhoGEF and Lsc). Two other RGS proteins TGS10 and D-AKAP2 are structurally diverse from those of subfamilies A-F and may represent a separate subfamily. Subfamilies B, C and D all have characteristic residue Asn (N82 in RGS4 as numbered herein, or N128 as numbered in Tesmer et al. [8]), which is associated with Gα binding at least in RGS subfamily B proteins. RGS proteins of subfamily A are substituted at this position in the RGS core with a serine (S156 in GAIP). Additionally, the B subfamily of RGS proteins is reported to have another characteristic residue, a serine (at position 57 in RGS4 as numbered herein and S103 as numbered in Tesmer et al. [8]). RGS4 represents the B subfamily of RGS proteins and is structurally more similar to and believed to have biological activity and function more similar to other members of the B subfamily, including RGS1, RGS2, RGS3, RGS5, RGS8, RGS13 and RGS16. GAIP, for example, is representative of the A subfamily of RGS proteins and is structurally more similar to and believed to have biological activity and function more similar to other members of the A subfamily including Ret-RGS1 and RGSZ1. Thus, the term RGS subfamily B refers to RGS1, RGS2, RGS3, RGS4, RGS5, RGS8, RGS13, RGS16 and other, as yet uncharacterized, RGS proteins that exhibit structural features characteristic of the B subfamily and which are classifiable into the B subfamily by phylogenetic analysis as described in Zheng, B. et al. (1999) supra. Analogously, the term RGS subfamily A refers to GAIP, Ret-RGS1 and RGS21 and other RGS proteins as yet uncharacterized that exhibit structural characteristics of the A subfamily and which are classified as RGS subfamily A proteins by phylogenetic analysis. RGS subfamilies C-F have analogous definitions.

The term RGS4 refers to RGS4 exemplified by RGS4 of rat (Tesmer et al. (1997) supra) and homologs thereof including, among others, human

RGS4 and mouse RGS4. The RGS core region of human, rat and mouse RGS4 differ from one another by 2-4 amino acids (representing about 97% or more sequence identify in the 130 amino acid core). Homologs of GAIP can exhibit as low as about 85% sequence identity in the RGS core region. An RGS4 homolog may, thus, exhibit RGS4 core sequence identify as low as about 85% with rat RGS4.

RGS protein NMR studies and structural determinations herein were performed using an RGS4 -core protein consisting of the conserved region of RGS4 (specifically that derived from rat) with a N-terminal methionine and a C-terminal hexahistidine tail. The three-dimensional solution structure determined for the RGS4-core protein, assuming the possibility of conservative amino acids changes and within ± a root mean square deviation of the relative structural coordinates of the backbone atoms listed in Table 2 of not more than 1.5Å (or more preferably, not more than 1.0Å, or most preferably, not more than 0.5Å), model the three-dimensional solution structures of other RGS4 proteins of any eukaryotic origin, including human RGS4. Further, because of the significant conservation of this domain among different RGS proteins, the three-dimensional structure of RGS4-core provided herein, again assuming conservative amino acids changes, and within ± a root mean square deviation of the relative structural coordinates of the backbone atoms of the structure of not more than 1.5Å (or more preferably, not more than 1.0Å, or most preferably, not more than 0.5Å), models the structures of the conserved region in other RGS proteins of all origins.

"Structural coordinates" are the Cartesian coordinates corresponding to an atom's spatial relationship to other atoms in a molecule or molecular complex. Structural coordinates may be obtained using NMR techniques, as described herein or as known in the art, or using x-ray crystallography as is known in the art. Alternatively, structural coordinates can be derived using molecular replacement analysis or homology modeling. Various software programs allow for the graphical representation of a set of structural coordinates to obtain a three dimensional representation of a molecule or molecular complex. The structural coordinates of the present invention may be modified from the original sets provided in Table 2 by mathematical manipulation, such as by inversion or integer additions or subtractions. As such, it is recognized that the structural coordinates of the present invention are relative, and are in no way specifically limited by the actual x, y, z coordinates of Table 2. The structural coordinates of Table 2 ± a root mean

square deviation from the conserved backbone atoms of the amino acids therein(or conservative substitutions thereof) of not more than 1.5Å (or more preferably, not more than 1.0Å, or most preferably, not more than 0.5Å) define or embody the three-dimensional structure of free RGS4 (i.e., not complexed with another molecule) in solution. The RGS4 core conserved region contains a Gα binding site and an allosteric binding site. Amino acid sequences can be inserted between the helical regions of the RGS core region without significantly altering the biological function of the RGS protein. RGS proteins of lower eukaryotes contain such insertions.

"Root mean square deviation" is the square root of the arithmetic mean of the squares of the deviations from the mean, and is a way of expressing deviation or variation from the structural coordinates described herein.

As used herein, "RGS activity," "activity of RGS" and other similar terms refer to the ability of RGS to bind to an active Gα-GTP-Mg^2 complex and induce a change in the rate of GTP hydrolysis. Any other biological function or activity of an individual RGS protein will be specifically defined herein. References 89 and 91 are incorporated by reference herein for their review of the additional biological functions of certain RGS proteins. Any assay which measures the rate of GTP hydrolysis in a Gα-GTP-Mg^2 complex in the presence and absence of RGS (or portions thereof) can be used to measure such activity. A preferred assay method measures precipitated radiolabeled phosphate that results from hydrolysis of Gα-[γ-^{32}P]-GTP-Mg^2 as described in the Examples herein.

Table 2 lists the atomic structure coordinates for the restrained minimized mean structure of free RSG4 as derived by NMR spectroscopy. The first two columns in Table 2 list atom number, the third column identifies the atom type using standard nomenclature, the fourth and fifth columns list the amino acid and its number in the sequence. The sixth, seventh and eighth columns of the table are relative coordinate values (in three dimensions).

It will be obvious to the skilled practitioner that the numbering of the amino acid residues in the RGS4 and other RSG proteins covered by the present invention may be different than that set forth herein. The RGS4 core protein used herein contains an RGS core domain with an N-terminal Met and a six residue histidine tag at the C-terminus. In Fig. 1 the amino acid sequence of the RGS4 core protein used is numbered beginning at the N-terminal Met. For comparison to the full-length RGS4 sequence (for

example, as numbered in Tesmer et al. (1997) (8)) add 46 to the numbering used herein.

It will also be obvious to the skilled practitioner that RGS proteins and portions thereof covered by this invention may contain certain conservative amino acid substitutions that yield the same three dimensional structures as those defined by the structural coordinates provided herein ± a root mean square deviation from the conserved backbone atoms of the amino acids therein(or conservative substitutions thereof) of not more than 1.5Å. Amino acids in other RGS proteins or peptides corresponding to those in RGS4 and conservative substitutions in other RGS proteins or peptides are readily identified by visual inspection of the relevant amino acid sequences or by using commercially available homology software programs. "Conservative substitutions" are those amino acid substitutions which are functionally equivalent to the substituted amino acid residue, either by way of having similar polarity, steric arrangement, or by belonging to the same class as the substituted residue (e.g., hydrophobic, acidic or basic), and includes substitutions having an inconsequential effect on the three dimensional structure of RGS with respect to the use of said structure for the identification and design of RGS antagonists or agonists, and for molecular replacement analyses and/or for homology modeling.

The structural coordinates of the present invention permit the use of various molecular design and analysis techniques in order to (i) solve the three dimensional structures of related RGS proteins, peptides or complexes thereof, and particularly RGS subfamily B proteins, peptides or complexes thereof and (ii) to select, design and synthesize or otherwise obtain chemical and biochemical species capable of associating, binding or interacting with RGS potentially having function as antagonists or agonists of an RGS, Gα or an RGS-Gα complex.

Molecular replacement analysis is a well-known technique employed in x-ray crystallography which uses the x-ray structure of a molecule having as a starting point to model a molecule whose crystal structure is unknown. This technique is based on the principle that two molecules which have similar structures, orientations and positions will diffract x-rays similarly. A corresponding approach to molecular replacement is applicable to modeling an unknown solution structure using NMR technology. The NMR spectra and resulting analysis of the NMR data for two similar structures will be essentially identical for regions of the molecules that are structurally conserved, where the NMR analysis consists of obtaining the NMR

resonance assignments and the structural constraint assignments, which may contain hydrogen bond, distance, dihedral angle, coupling constant, chemical shift and dipolar coupling constant constraints. Appropriate NMR spectra are accumulated for a solution of the species of unknown structure and compared to NMR of the species of known structure. The observed differences in the NMR spectra of the two structures will highlight the differences (and similarities) between the two structures and identify the corresponding differences in the structural constraints. The structure determination process for the unknown structure is then based on modifying the NMR constraints from the known structure to be consistent with the observed spectral differences. This method is applicable to the determination of three-dimensional solution structures of any RGS protein or peptide using the structural information for RGS4 provided herein. The method is most appropriate for determining the structures of RGS proteins that are expected to have significant structural similarity with RGS4. For example, this invention specifically provides the three-dimensional structure of a rat RGS4-core region in solution. The replacement method described above can be employed to determine the three-dimensional structure of the human RGS4-core which differs from that of rat by 2 amino acids in the 130 RGS core (at positions 22 N (rat) >S (human), and 132 T(rat) > V(human), referring to the rat sequence given in Fig. 1.

Accordingly, in one nonlimiting embodiment of the invention, the NMR resonance assignments for RGS4 provide the starting point for resonance assignments of other RGS family proteins (or portions thereof), that are expected to be structurally similar to RGS4, e.g., RGS4 homologs from different organisms or more generally RGS proteins of the subfamily B. Chemical shift perturbations can be detected using one or two dimensionalspectra (e.g., $^{15}N/^{1}H$, $^{13}C/^{1}H$ spectra) or using other methods well known in the art and compared between RGS4 and another RGS protein. In this way, the affected residues may be correlated with the three dimensional structure of RGS4 as provided by the relevant residues of Table 2. This effectively identifies the region of the other RGS protein or peptide that has a structural change relative to the RGS4 protein. The ^{1}H, ^{15}N, ^{13}C and ^{13}CO NMR resonance assignments corresponding to both the sequential backbone and side-chain amino acid assignments of the other RGS protein, or portion thereof, can then be obtained and the three dimensional structure of this protein, or portion thereof, can be generated using standard 2D, 3D and 4D triple resonance NMR techniques and NMR assignment methodology, using

the RGS4 structure, resonance assignments and structural constraints as a reference. Various computer fitting analyses of the other RGS protein or peptide with the three dimensional model of RGS4 can be performed in order to generate an initial three dimensional model of the other RGS protein or peptide, and the resulting three dimensional model may be refined using standard experimental constraints and energy minimization techniques in order to position and orient the other RGS in association with the three dimensional structure of RGS4. The present invention further provides that the structural coordinates of the present invention can be used with standard homology modeling techniques in order to determine the unknown three-dimensional structure of an RGS protein or portion thereof. Homology modeling, as is known in the art, involves constructing a model of an unknown structure using structural coordinates of one or more related protein molecules, molecular complexes or parts thereof (i.e., active sites). Homology modeling may be conducted by fitting common or homologous portions of the protein whose three dimensional structure is to be solved to the three dimensional structure of homologous structural elements in the molecule of known three-dimensional structure, specifically using the relevant (i.e., homologous) structural coordinates provided by Table 2. Homology can be determined a variety of known methods, for example, using amino acid sequence identity, homologous secondary structure elements, and/or homologous tertiary folds. Tesmer et al. (1997) (8) and Druey and Kehrl (1997) (88) provide examples of multiple sequence alignments of RSG protein sequences. Homology 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. Molecular replacement analysis as adapted and applied to NMR structural data (as discussed above) and homology modeling are techniques that are well known in the art which can be readily applied or adapted to the determination of the three dimensional structures of other proteins of the RGS family (and portions thereof, e.g., Gα binding sites and/or allosteric binding sites). These methods are particularly useful for determining RGS solution structure within the conserved region of the protein based on the RGS4 three-dimensional solution structure. These methods are applicable to presently known members of the RGS family of proteins as well as to proteins, particularly those of RGS sub-family B, as yet unidentified as RGS proteins, and particularly those that exhibit significant sequence identity above 60% or more, preferably 85% or more sequence identity in the RGS-

core region. NMR assignments, structural coordinates and three-dimensional structures of RGS proteins or peptides, determined using molecular replacement analysis and homology modeling based on the structural coordinated and NMR assignments provided herein and optionally refined using a number of techniques well known in the art, can be employed in a similar fashion to the structural coordinates of Table 2 for identifying, selecting or designing chemical species that are antagonists or agonists of RGS, Gα or RGS Gα complexes.

Description of the Structure of RGS4

The primary amino acid sequence of several RGS4 proteins are known. The amino acid sequence of RGS4-core (from rat) with attached hexahis pro tail is listed in Fig. 1 (as SEQ ID No. 1). The regular secondary structure elements of free RGS4 were identified from a qualitative analysis of sequential and inter-strand NOEs, NH exchange rates, $^{3}J_{HN\alpha}$ coupling constants and the $^{13}C\alpha$ and $^{13}C\beta$ secondary chemical shifts (*47, 48*). The sequential and medium NOEs were obtained from a qualitative analysis of the ^{15}N-edited NOESY and ^{13}C-edited NOESY spectra. $^{3}J_{HN\alpha}$ coupling constants were obtained from the relative intensity of Hα crosspeaks to the NH diagonal in the HNHA experiment (*18*). Slowly exchanging NH protons were identified by recording an HSQC spectra two hours after exchanging an RGS4 sample from H2O to D2O. These data, together with the deduced secondary structure elements are summarized in Fig. 1.

The overall structure of RGS4 is composed of seven helical regions corresponding to residues 7-12 (α_1); 17-36 (α_2); 40-53 (α_3); 61-71 (α_4); 86-95 (α_5); 105-125 (α_6) and 128-132 (α_7). A simple description of the RGS4 topology is that the protein consists of two pseudo 4-helix bundles with an up-down-up-down arrangement where helical region six is part of both bundles. An unusual feature of the RGS4 structure occurs in the second helical region. There is a one residue (H23) ~90° bend in the helix which effectively divides this helical region into two separate helices (as described in the RGS4 x-ray structure (*5*)). This one residue bend was not obvious from the NMR analysis of the secondary structure data (Fig. 1) where it appears to be a continual helical stretch. The bend only became apparent during the structure refinement process. Some observable NOEs that contribute to the bend at H23 occur between residues L20, I21, and residues G26, L27, A29, and F30. The bend at H23 effectively allows for appropriate packing of these hydrophobic side-chains.

Additional bends or turns occur throughout the RGS4 structure. Helical regions α_1 and α_2 are connected by residue S16 that adopts an extended conformation allowing these two helices to be essentially parallel. This is very similar to the turns connecting helical regions α_3 and α_4 and helical regions α_5 and α_6. Conversely, helical regions α_2 and α_3 are connected by Y38 that has a positive ϕ torsion angle, suggesting a β type turn. The conformation of Y38 results in an angle between helical regions α_2 and α_3 of ~45°, which also represents a transition point between the two pseudo 4-helix bundles. The longest loop in the structure occurs between helical regions α_4 and α_5. This loop region is well ordered based on high order parameters ($S^2 > 0.6$). The low mobility for this loop results from interactions with helical regions α_3 and α_6. The observed bend between the longest helical region α_6 and the shortest helical region α_7 is suggestive of a distortion in this helical segment to achieve an optimal packing interaction between helical regions α_1 and α_7. The end result of these local conformations on the overall topology of RGS4 is to create an elongated structure where the two pseudo 4-helix bundles are nearly perpendicular. The interface between these the two pseudo 4-helix bundles is predominately hydrophobic in nature (L17, I21, L27, F30, L34, W46, I47, I110, F111, L113, M114) consistent with the general packing of hydrophobic residues in the core of the protein with charged residues on the protein surface.

As previously described, the primary biological function for RGS4 is to bind $G_{i\alpha1}$ and stimulate its intrinsic GTPase activity. Key residues in the RGS4 structure that are involved in the interaction of RGS4 with $G_{i\alpha1}$ correspond to RGS4 residues S39, E41, N42, L113, D117, S118, and R121 that form the binding pocket for T182 from $G_{i\alpha1}$. Similarly, N82 from RGS4 binds into the $G_{i\alpha1}$ active site interacting with residues Q204, S206 and E207 (8) of $G_{i\alpha}$. RGS4 mutational work support the functional importance of these residues in the binding and activity of RGS4 with $G_{i\alpha1}$ while identifying N82 to be critical in facilitating GTP hydrolysis (18-20). RGS4 residues S39, E41 and N42 are located in the N-terminal end of helical region α_3 while L113, D117, S118, and R121 are located directly opposite at the C-terminal end of helical region α_6. N82 is located approximately in the center of the structured loop region between helical regions α_4 and α_5 which is positioned relatively above the T182 binding pocket on RGS4.

Another feature of the RGS4 structure is the observation that residues M1-S4 and P134-H166 are completely disordered and dynamically flexible. Structure coordinates for these atoms are not included in Table 2. This is

evident by the sharp line-widths and the minimal number of observable NOEs. The flexible nature of these residues are further supported by ^{15}N T1, T2 and NOE measurements which indicate low order-parameters ($S^2 < 0.6$)

RGS4 Structure Determination

The final 30 simulated annealing structures were calculated on the basis of 2871 experimental NMR restraints consisting of 1960 approximate interproton distance restraints, 78 distance restraints for 39 backbone hydrogen bonds, 431 torsion angle restraints comprised of 151 ϕ, 154 ψ, 97 $\chi 1$, and 29 $\chi 2$ torsion angle restraints, 132 $^3J_{NH\alpha}$ restraints and 136 Cα and 134 Cβ chemical shift restraints. Stereospecific assignments were obtained for 58 of the 125 residues with β-methylene protons, for the methyl groups of 3 of the 5 Val residues, and for the methyl groups of 9 of the 12 Leu residues. In addition, 7 out of the 8 Phe residues and 4 out of the 5 Tyr residues were well defined making it possible to assign NOE restraints to only one of the pair of CδH and CεH protons and to assign a $\chi 2$ torsion angle restraint.

Comparison of the Free RGS4 NMR Structure with the RGS4 $G_{i\alpha 1}$ Bound Structure

Figs. 2A and 2B are ribbon diagrams of (A) the x-ray structure of RGS4 complexed to Giα1 (8) and (B) the solution structure of RGS4 as determined by NMR methods. Residues that effect significant structural change between the two structures are indicated. An unexpected result from determining the solution structure of RGS4 in the absence of $G_{i\alpha 1}$ was the observation of a significant change in the conformation for free RGS4 relative to RGS4 in the complex (*5*). A fundamental factor in the difference between the two structures is a perturbation in the secondary structure elements. Consistent with the RGS4-$G_{i\alpha 1}$ x-ray structure, the NMR structure of free RGS4 is an α-helical protein comprised of two peudo 4-helix bundles. The NMR data shows that free RGS4 is composed of seven helical regions and a majority of this data is consistent with the RGS4-$G_{i\alpha 1}$ x-ray structure. The significant difference between the two secondary structures occurs within the C-terminal helical regions α_6 and α_7. In the RGS4-$G_{i\alpha 1}$ x-ray structure residues V5 to T132 are observed in (i.e., they are ordered) and residues 104-116 and 119-129 are helical. This contrasts with the free RGS4 NMR structure where residues 5-133, 105-125 (α_6) and 128-132 (α_7) are helical. There is a significant shift in the helical structure in this region containing residues 104-133.

The observed structural change between the free RGS4 NMR structure and the RGS4-$G_{i\alpha1}$ x-ray structure is a movement of a kink between helical regions α_6 and α_7 towards the C-terminus. The movement of this kink results in α_6 being longer by nine residues and α_7 being shorter by six residues in the free RGS4 NMR structure. Additionally, α_7 of free RGS4 extends three residues beyond what was observed as a structural region in the RGS4-$G_{i\alpha1}$ x-ray structure.

The observed change in the secondary structure, although only involving a few C-terminal residues, has far-reaching effect, since it results in a significant modification in the overall fold for RGS4. This is evident from a 1.94 Å backbone rms difference between the RGS4-$G_{i\alpha1}$ x-ray structure and the free RGS4 NMR structure for residues 5-134. The major effect of the alteration in secondary structures is a reorganization of the packing of the N-terminal and C-terminal helix as is evident from per-residue backbone atomic rms differences between the free RGS4 NMR structure and the bound RGS4 x-ray structure. Therefore, the accuracy of the secondary structure interpretation is important for proper analysis of the free RGS4 structure. The reliability of the NMR secondary structure is demonstrated by the extensive data summarized in Fig. 1. Residues 105-125 and 128-132 show a continual stretch of NMR data consistent with an α-helical definition with an abrupt break in this information for residues 125-128. Furthermore, the significant differences between the – and C-terminal regions of the free RGS4 NMR structure and the bound RGS4 x-ray structure are indicated by a large number of interproton distance (145) and torsion angle (39) violations and by the corresponding very high values for the NOE and torsion angle restraint energies exhibited by the bound RGS4 x-ray structure. The self-consistency of the NMR data using NOEs, coupling constants, NH exchange rates and secondary carbon chemical shifts and the large number of restraint violations with the bound structure, demonstrate the accuracy of the RGS4 NMR structure provided. Comparisons of the free RGS4 structure of this invention with the structure of the RGS4-Giαl complex should then provide an accurate description of the conformational changes that occur in on RGS4 on binding to Giα1.

Relevance to Activity for the RGS4 Conformational Change

RGS4 is involved in the regulation of the $G_{i\alpha1}$ GTPase cycle having a modest affinity for GTP-Gα, but not binding to GDP-Gα. It is believed that the observed conformational changes for free RGS4 are related to modulating its affinity to $G_{i\alpha1}$ to allow for perpetuation of the GTPase cycle.

This role for the RGS4 conformational change is evident by the fact that the RGS4 Gα binding site is the location of the $G_{i\alpha1}$ induced structural perturbation. The pronounced kink between helical regions α_6 and α_7 observed in the bound RGS4 x-ray structure occurs at residues D117 and S118. RGS4 molecular surfaces for both the free RGS4 NMR structure and the RGS4-$G_{i\alpha1}$ x-ray structure in the vicinity of the $G_{i\alpha1}$ T182 binding pocket were calculated. A comparison of the two RGS4 molecular surfaces, shows that the $G_{i\alpha1}$ T182 binding pocket is larger and more accessible in the free RGS4 NMR structure. Also, in the RGS4-$G_{i\alpha1}$ x-ray structure there appears to be a molecular surface "wall" composed of the RGS4 sidechains from residues D117, S118 and R121 which surround the $G_{i\alpha1}$ T182 binding pocket. These residues form an important hydrogen-bonding network which is critical for the binding of RGS4 with $G_{i\alpha1}$ where D117 forms a hydrogen bond with R121 and the backbone nitrogen of $G_{i\alpha1}$ T182. The critical nature of these residues is further supported by mutagenesis. Alanine mutations of D117 and R121 diminishes RGS4 activity and binding to $G_{i\alpha1}$. Since the helical kink at residues D117 and S118 is less pronounced in the free RGS4 NMR structure and a disruption in the helix occurs instead between residues 125-128, the sidechains for D117, S118 and R121 are well beyond hydrogen-bonding distance. It is evident from the free RGS4 NMR structure that the network of sidechain interactions with $G_{i\alpha1}$ T182 in the absence of $G_{i\alpha1}$ is not pre-formed.

The observation that RGS4 undergoes a significant structural change in the presence of $G_{i\alpha1}$ where the focal point of this change occurs at key residues in the RGS4- $G_{i\alpha1}$ interface creates a different explanation for the process of RGS4 activation of $G_{i\alpha1}$ GTPase activity. This information suggests a two-stage process composed of a binding and locking step. Because the $G_{i\alpha1}$ T182 binding pocket is clearly more accessible in the free RGS4 NMR structure, the binding step appears to be driven by the fit of T182 into this pocket. The locking step then results from the induced conformational change in the RGS4 structure where the pronounced kink in the helix between residues D117 and S118 brings these residues into close contact with R121 and $G_{i\alpha1}$ T182 to form the hydrogen bonding network observed in the RGS4-$G_{i\alpha1}$ x-ray structure. T182 in the binding pocket induces the formation of a hydrogen bonding network and the resulting RGS4 conformational change as opposed to a pre-formed binding site suggested from the RGS4-$G_{i\alpha1}$ x-ray structure. The release of RGS4 from $G_{i\alpha1}$ would then require the removal of $G_{i\alpha1}$ T182 from the RGS4 binding

pocket which presumably occurs during GTP hydrolysis. This mechanism is consistent with a local perturbation in the vicinity of T182 seen between the GDP- $G_{i\alpha1}$ (*2*) and RGS4- $G_{i\alpha1}$ x-ray structures where this localized movement appears to be sufficient to remove T182 from the RGS4 binding site and disrupt the hydrogen-bonding network resulting in dissociation of the complex. Comparison of the T182 $G_{i\alpha1}$ region between the RGS4- $G_{i\alpha1}$ and the GDP-AlF_4-$G_{i\alpha1}$ x-ray structures (*4*) indicate that these two structures are essentially identical in this region of $G_{i\alpha1}$. Since the GDP-AlF_4-$G_{i\alpha1}$ structure corresponds to the active form of GDP-AlF_4-$G_{i\alpha1}$ as well as the conformation that RGS4 preferentially binds, the similarity between these two structures is also consistent with the proposed mechanism for the activity of RGS4.

The x-ray structure of RGS4 complexed with $G_{i\alpha1}$ in conjunction with other Gα conformers suggest that the role of RGS4 in stimulating Gα GTPase activity is accomplished by stabilizing the GTP hydrolysis transition state. The NMR structure of free RGS4 reported here expands this mechanism suggesting that the RGS4 induced conformation in the presence of $G_{i\alpha1}$ may be related to its GTP-$G_{i\alpha1}$ specificity which facilitates binding turnover that is critical for perpetuating the GTPase cycle. The described structural change in RGS4 provides an elegant mechanism for the observed binding selectivity between the various Gα conformers despite the close similarity in these structures.

Detection of an Allosteric binding site in RGS4

Several small molecule inhibitors of the RGS4-Gα interaction were identified in a large scale screening based on detection of inhibition of Gα GTPase function which implies inhibition of the binding of RGS4 to Gα. One of these compounds (designated compound **1** for convenience) exhibited 100% inhibition of binding. The nature of the activity of compound **1** and its ability to inhibit RGS4 binding to Gα was further investigated by ^{1}H-^{15}N HSQC chemical shift perturbation experiments. A total of five compounds, three that had exhibited inhibition of RGS4 binding in the screen and two controls that showed no activity in the screen were examined. 2D ^{1}H-^{15}N HSQC spectra were collected for a ^{15}N-enriched RGS4 sample and a series of ^{15}N-enriched RGS4 samples titrated with one of the three test compounds and two controls. Comparison of the HSQC spectra of a free RGS4 sample and each of the samples titrated with a potential inhibitor allowed the identification of any chemical shift changes for RGS4 in the presence of the test and control compounds. In such an

analysis the observation of a change in the position shape or intensity of a resonance indicates perturbation. With the NMR instrumentation employed a shift of half a line width in peak position could be reliably detected. Only in NMR spectra taken of RGS4 in the presence of compound **1** were any chemical shift perturbations observed indicating that compound **1** directly binds to RGS4. Employing the chemical shift assignments for free RGS4 (Table 1), the binding site of compound **1** in RGS4 was identified. RGS4 amino acid residues V10, W13, I17, I20, H23, E24, C25 and T125 exhibited a chemical shift perturbation in the presence of compound **1**.

The observed chemical shift perturbations did not arise from a pH change caused by addition of compound **1** to the RGS4 solution. (^{1}H-^{15}N HSQC spectra of free RGS4 taken over a pH range of 5.5-6.5 indicate that none of the amino acid residues listed above was sensitive to pH changes over this range). The binding site for compound **1** corresponds to residues in the α1-α2 region of RGS4 (where the α1-α2 region includes the tight turn between the two helices). In the three-dimensional structure of RGS4, the binding region is positioned on the opposite surface from the Gα binding site. No amino acids residues associated with the Gα binding site exhibited any chemical shift perturbation in the presence of compound **1.** This indicates that the structure of the RGS4 Gα binding site is unchanged in the presence of compound **1**. Compound **1** was found to significantly decrease the expected GTPase activity of Gα which combined with the fact that compound **1** binds at a site distal from the Gα binding site indicates that compound **1** is an allosteric inhibitor of RGS4 and that there is an allosteric binding site in the α1-α2 region of RGS4.

It is believed that binding of compound **1** at the allosteric binding site stabilizes RGS4 in the free form and effectively locks the RGS4 protein in free form. Compound **1** prevents the formation of a hydrogen-bonding network around the Gα T182 binding pocket.

The solution structural information provided herein, including the secondary and tertiary structure of RGS4-core, the RGS4 Gα binding site, the α6 - α7 region, and the allosteric binding site in the α1-α2 region of RGS4 can all be employed in methods described herein and methods well known in the art to identify, select or design candidate agonists and antagonists of RGS4 activity which in turn affects G-protein signaling functions in various eukaryotic cells and organisms.

The following examples are provided to further illustrate the invention and are not intended to limit the invention.

EXAMPLES

The following abbreviations are used herein:

G-proteins, heterotrimeric guanine nucleotide-binding proteins; RGS4, Regulators of G-protein Signaling; $G_{i\alpha1}$, Gα subunit of heterotrimeric G proteins, $G_{i\alpha1}$-AlF_4^-, Gα subunit of heterotrimeric G proteins complexed with Mg^{2+}, GDP and AlF_4^- stabilized in the transition state for GTP hydrolysis, DTT, DL-1,4-Dithiothreitol; GTP, guanosine triphosphate; GDP, guanosine diphosphate; NMR, nuclear magnetic resonance; 2D, two-dimensional; 3D, three-dimensional; HSQC, heteronuclear single-quantum coherence spectroscopy; HMQC, heteronuclear multiple-quantum coherence spectroscopy; TPPI, time-proportional phase incrementation; NOE, nuclear Overhauser effect; NOESY, nuclear Overhauser enhanced spectroscopy; COSY, correlated spectroscopy; HNHA, amide proton to nitrogen to CαH proton correlation; HNHB, amide proton to nitrogen to CβH proton correlation; CT-HCACO, constant time CαH proton to α-carbon to carbonyl correlation; HACAHB, CαH proton to α-carbon to CβH proton correlation.

Example 1: Assignment of NMR Peaks and Secondary Structure Determination

The RGS core domain of RGS4 was expressed in *Escherichia coli* (J109) using the prokaryotic expression vector pQE50 (Qiagin, Valencia, CA). PCR was used to amplify and add a C-terminal hexahis -pro tag to the RGS core (here residues 51-206 of RGS4) and the product was ligated between the BamH1 and Sal1 sites of pQE50 to give plasmid pRGS4. *E. coli* (BL21(DE3)) containing pRGS4 were grown in LB broth supplemented with 100 μg/mL ampicillin. An overnight culture was diluted 1:20 and grown at 37 °C to an A_{600} of 0.6 - 0.8 with vigorous shaking. Isopropyl β-D-galactoside (1PTG) was added to a final concentration of 1 mM and cultures were shaken for 3 h at 37 °C. The cells were harvested by centrifugation (7000 x g) for 15 min. at 4 °C, washed with PBS and stored at -70 °C.

Uniformly (>95%) ^{15}– and ^{13}C-labeled recombinant RGS4-core (containing the 166 amino acid core domain of RGS4 with an N-terminal methionine and C-terminal hexahis-pro tag) was obtained by growing BL21 (DE3) *E. coli* in defined medium containing 2.0 g/L [^{13}C6, 98% +] D-glucose and 1.0 g/L [^{15}N, 98%+] ammonium chloride as sole carbon and nitrogen sources, respectively. In addition, the defined medium contained

M9 salts, trace elements, vitamins and 100 μg/L ampicillin. Conditions for induction and growth are as described above. The recombinant RGS4-core protein was purified using affinity chromatography on a 10 mL Ni^{2+} column and purified to homogeneity following ion-exchange chromatography on Resource S at pH 5.5. Protein was desalted into appropriate buffer prior to use. N-terminal amino acid sequencing was performed to confirm protein identity and uniform labeling of RGS4-core was confirmed by MALDI-TO mass spectrometry (Perceptive Biosystems).

The NMR samples contained 1 mM of RGS4 manually purified-core protein in a buffer containing 50mM K_2PO_4, 2mM NaN_3, and 50 mM deuterated DTT, in either 90% H2O/ 10% D2O or 100% D2O at pH 6.0.

All spectra were recorded at 30 – 35° C on a Brucker AMX-2 600 spectrometer using a gradient enhanced triple-resonance $^{1}H/^{13}C/^{15}N$ probe. For spectra recorded in H_2O, water suppression was achieved with the WATERGATE sequence and water-flip back pulses (23, 24). Quadrature detection in the indirectly detected dimensions were recorded with States-TPPI hypercomplex phase increment (25). Spectra were collected with appropriate refocusing delays to allow for 0,0 or -90,180 phase correction. Spectra were processed using the NMRPipe software package (*28*) and analyzed with PIPP (*29*), NMR Pipe and in a peak sorting program--on a Sun Ultra10 Workstation. When appropriate, data processing included a solvent filter, zero-padding data to a power of two, linear predicting back one data point of indirectly acquired data to obtain zero phase corrections, linear prediction of additional points for the indirectly acquired dimensions to increase resolution. linear prediction by the means of the mirror image technique was used only for constant-time experiments (38). In all cases data was processed with a skewed sine-bell apodization function and one zero-filling was used in all dimensions.

The assignments of the ^{1}H, ^{15}N, ^{13}CO, and ^{13}C resonances were based on the following experiments: CBCA(CO)NH (62), CBCANH (63), C(CO)NH (64), HC(CO)NH (64), HBHA(CO)NH (65), HNCO (66), HCACO (29), HNHA (26), HNCA (67), HCCH-COSY (68) and HCCH-TOCSY (69) (for reviews see: Bax et al 1994 and Clore and Gronenborm, 1994). The resonance assignments of RGS4 essentially followed the semi-automated protocol described previously (37, 70, 71). The accuracy of RGS4-core assignment was further confirmed by sequential NOEs in the 15 N-edited NOESY-HMQC spectra. Because the RGS4 structure is exclusively α–helical, the sequential NH_i–NH_{i+1} NOEs were extremely

useful in completing the RGS4 backbone assignments. ^{1}H, ^{15}N, ^{13}C AND ^{13}CO assignments for RGS4-core are summarized in Table 1.

The backbone ^{1}H, ^{15}N, ^{13}CO, and ^{13}C assignments in Table 1 are essentially complete for the RGS4-core. As noted above, the native core sequence was appended to six histidines. The last five histidines were the only unassigned residues in the protein. The ability to obtain the complete assignments for RGS4-core implies a well-packed ordered structure. The side-chain assignments are also nearly complete; the majority of missing information is in residues with long side-chains which are potentially solvent exposed.

The secondary structure of the RGS4-core (summarized in Fig. 1) is based on characteristic NOE data involving the NH, Hα and Hβ protons from ^{15}N-edited NOESY-HMQC and ^{13}C-edited NOESY-HMQC spectra, $^{3J}HN\alpha$ coupling constants from HNHA, slowly exchanging NH protons and $^{13}C\alpha$ and $^{13}C\beta$ secondary chemical shifts (for reviews see: (56) and (78). It was determined that the RGS4-core solution NMR was composed of seven helical regions corresponding to residues 7-12(α1);17-36(α2); 40-53(α3); 61-71(α4); 86-95 (α5); 105-125 (α6); and 128-132 (α7). The RGS4-core overall fold is essentially comprised of two 4-helix bundles with the long helical region α6 part of both bundles. A distinct difference in the RGS4-core secondary structure in solution from the x-ray structure of the RGS4-Giα1 complex was unexpectedly observed at the C-terminus. The x-ray structure indicates that residues 104-116 and 119-129 are helical where only residues V5 to T132 are observed. The solution NMR structure indicates that residues 105-125 and 128-132 are helical and residues P134-H166 appear, in view of the sharp line-widths observed, to be extremely mobile. The differences in secondary structure between the x-ray crystal structure and that of free RGS4-core suggest a conformational change in RGS4 on binding to Gα.

Example 2: Three-Dimensional Structure Determination for RGS4-core

RGS4-core was prepared, purified and uniformly labeled as in Example 1. NMR samples were prepared and spectral data accumulated as indicated in Example 1.

The RGS4 structure is based on the following series of spectra: HNHA (26), HNHB (27), 3D long-range ^{13}C-^{13}C correlation (28), coupled CT-HCACO (29, 30), HACAHB-COSY (31), 3D ^{15}N– (32, 33) and ^{13}C-edited NOESY (35, 37) experiments. The ^{15}N-edited NOESY, and ^{13}C-

edited NOESY experiments were collected with 100 msec and 120 msec and mixing times, respectively.

Spectra were processed using the NMRPipe software package (36) and analyzed with PIPP (37) on a Sun Ultra10 Workstation. When appropriate, data processing included a solvent filter, zero-padding data to a power of two, linear predicting back one data point of indirectly acquired data to obtain zero phase corrections, linear prediction of additional points for the indirectly acquired dimensions to increase resolution. Linear prediction by the means of the mirror image technique was used only for constant-time experiments (38). In all cases, data were processed with a skewed sine-bell apodization function and one zero-filling was used in all dimensions.

Interproton Distance Restraints.

The NOEs assigned from 3D ^{13}C-edited NOESY and 3D ^{15}N-edited NOESY experiments were classified into strong, medium, weak and very weak corresponding to interproton distance restraints of 1.8-2.7 Å (1.8-2.9 Å for NOEs involving NH protons), 1.8-3.3 Å (1.8-3.5 Å for NOEs involving NH protons), 1.8-5.0 Å, and 3.0-6.0 Å, respectively (39, 40). Upper distance limits for distances involving methyl protons and non-stereospecifically assigned methylene protons were corrected appropriately for center averaging (41).

Torsion Angle Restraints and Stereospecific Assignments.

The β-methylene stereospecific assignments and $\chi 1$ torsion angle restraints were obtained primarily from a qualitative estimate of the magnitude of $^{3}J\alpha\beta$ coupling constants from the HACAHB-COSY experiment (31) and $^{3}JN\beta$ coupling constants from the HNHB experiment (27). Further support for the assignments was obtained from approximate distance restraints for intraresidue NOEs involving NH, CαH, and CβH protons (42).

The ϕ and ψ torsion angle restraints were obtained from $^{3}JNH\alpha$ coupling constants measured from the relative intensity of Hα crosspeaks to the NH diagonal in the HNHA experiment (26), from chemical shift analysis using the TALOS program (43) and from consistency with distance restraints for intraresidue and sequential NOEs involving NH, CαH, and CβH protons. $^{1}JC\alpha H\alpha$ coupling constants obtained from a coupled 3D CT-HCACO spectrum were used to ascertain the presence of non-glycine residues with positive ϕ backbone torsion angles (30). The presence of a $^{1}JC\ \alpha H\alpha$

coupling constant greater then 130 Hz allowed for a minimum ϕ restraint of -2° to -178°.

The Ile and Leu $\chi 2$ torsion angle restraints and the stereospecific assignments for leucine methyl groups were determined from $^{3}JC\alpha C\delta$ coupling constants obtained from the relative intensity of Cα and Cδ cross peaks in a 3D long-range ^{13}C-^{13}C NMR correlation spectrum (44), in conjunction with the relative intensities of intraresidue NOEs (45). Stereospecific assignments for valine methyl groups were determined based on the relative intensity of intraresidue NH-CγH and CαH-CγH NOEs as described by Zuiderweg et al. (1985) (46). The minimum ranges employed for the ϕ, ψ, and χ torsion angle restraints were ± 30°, ± 50°, and ± 20° respectively (47).

Structure Calculations

The structures were calculated using the hybrid distance geometry-dynamical simulated annealing method of Nilges et al. (1988) (48) with minor modifications (49) using the program XPLOR (50), adapted to incorporate pseudopotentials for $^{3}J_{NH\alpha}$ coupling constants (51), secondary $^{13}C\alpha/^{13}C\beta$ chemical shift restraints (52) and a conformational database potential (53, 54). The target function that is minimized during restrained minimization and simulated annealing comprises only quadratic harmonic terms for covalent geometry, $^{3}J_{NH\alpha}$ coupling constants and secondary $^{13}C\alpha/^{13}C\beta$ chemical shift restraints, square-well quadratic potentials for the experimental distance and torsion angle restraints, and a quartic van der Waals term for non-bonded contacts. All peptide bonds were constrained to be planar and trans. There were no hydrogen-bonding, electrostatic, or 6-12 Lennard-Jones empirical potential energy terms in the target function.

Analysis of a T-182 Binding Site on RGS4-core.

The overall appearance of the NMR structure in the area of the proposed T182 (of Gα) binding site is one of great interest. To obtain a more quantitative measurement of the differences in accessibility between the free RGS4 NMR structure and the x-ray structure of the RGS4-$G_{i\alpha 1}$ complex, MOLCAD (commercially available from TRIPOST) surfaces were calculated for both structures and the surface area of each was measured.

The x-ray structure of the RGS4-$G_{i\alpha 1}$ complex (AGR1) was read into SYBYL (Tripos) and all substructures except chain E (RGS4) were deleted. Additionally, all waters were deleted. Polar hydrogens were added and optimized using the Kollman United Atom force field. This was followed by

addition of all the remaining hydrogens. MOLCAD was then used to generate a surface for all residues thought to be involved in binding of T182 (Gα-binding site). These RGS4-core residues include, I21, I27, F30, F33, L34, E37, S39, N42, I43, W46, I110, L113, M114, D117, S118, R121. The surface area was calculated based on the MOLCAD surface. MOLCAD was also used to calculate the surface area for the identical residues of the free RGS4 NMR structure. The surface area for the free RGS4 NMR structure was calculated to be 404.56 $Å^2$. The surface area for the crystal structure was calculated to be 321.88 $Å^2$. The difference in surface area of 82.67 $Å^2$, is an approximate 20% change in surface area between the two structures. A MOLCAD surface generated on the methyl and hydroxyl groups of T182 of Gα has a surface area of 57.72 $Å^2$.

Example 3: Identification of an Allosteric Binding Site in RGS4-Core

Bead Precipitation Assay for Inhibition of RGS Binding to Gα

Radiolabled [^{35}S]-Gαi1was synthesized in a rabbit reticulocyte lysate *in vitro* translation reaaction (Promega, Madison, WI Cat. NO. 14960) programmed with *in vitro* transcribed cRNA preparations (Promega, Cat. No. P1290). Affinity-purified GST-RGS4 core (100ng, about 25 nM final concentration) is incubated with 17.5 µL glutathione-Sepharose 4B bead (Amersham Pharmacia, Piscataway, NJ, Cat. NO. 17-0756-01) slurry in 100µL binding buffer (1X PBS, 1mM $MgCl_2$, 1mM DTT, 1% BSA) in a 96-well microtube assay plate. Approximately 300µM of test compound (about 0.1mg/mL final concentration, either as a mixture or individual compound) is added to each well and incubated at 4°C for 30 min. Approximately 50,000-100,000 cpm (?) ^{35}S]-Gαi1 in 100µL assay buffer (1X PBS, 1mM $MgCl_2$, 10µM GDP, 1mM DTT, 30 µM $AlCl_3$, 1% BSA, 500 µM NaF) is added to the reaction and incubated at 4°C for 30 min. The resulting assay sample has a final concentration of about 1-3 nM activated Gαi1. Reaction plates were centrifuged at 1000xg for 3 min, and the supernatant aspirated. Beads were washed 2x by resuspension in 200 µL binding buffer followed by centrifugation. Bound [^{35}S]-Gαi1is eluted from the bead pellets by resuspending them in 100µL 1% SDS. Elutates are either counted in 4 mL scintillation fluid or subjected to gel electrophoresis. Random small molecules can be evaluated in the assay described using a compressed library wherein a plurality of test compounds are combined in a single well (e.g., 10 compounds/well for 3000 primary assays tests 30,000 test compounds). Mixtures of test compounds that exhibited a greater than 50% decrease in precipitated radioactivity were confirmed by re-screening in an

identical format. Combi-wells (here 10 test compounds/well) that tested positive in both assays were deconvoluted and the individual compounds were tested individually in an identical bead precipitation assay. Compounds that demonstrated the requisite decrease (about 50% or more) in precipitated radioactivity were further tested to confirm that the decrease in precipitated radioactivity was dependent on the RGS4-Gα interaction and not due to spurious activity of the test compound. In these cases, the assay precipitate was analyzed by gel electrophoresis to confirm the presence of RGS4 in the precipitate.

^{1}H-^{15}N HSQC Chemical Shift Perturbation

The RGS4 NMR samples contained 0.3mM of RGS4-core protein in a sample buffer (50mM KPO_4, 2mM NaN_3, and 50mM deuterated DTT in 90% H_2O/10%D_2O at pH 6.0). Test compounds were added to the sample in 10-fold molar excess. 2D 1H-15N HSQC spectra for free RGS4 and RGS4 in the presence of test compounds were collected over a pH titration range of 5.5-6.5. The spectral width in the indirectly detected ^{15}N dimension was 30.00 ppm with the carrier position at 119.1 ppm. Spectral width in the acquisition dimension was 13.44 ppm with the carrier at the water frequency (4.73 ppm). The number of points acquired in the two dimensions was 256 complex in F1(^{15}N) and 1024 real in F2(^{1}H).

All spectra were recorded at 35°C on a Brucker AMX-2 600 spectrometer using a gradient enhanced triple resonance $^{1}H/^{13}C/^{15}N$ probe. Water suppression was achieved in the indirectly detected dimension with the WATERGATE sequence and water-flip back pulses (23, 24). Quadrature detection in the indirectly detected dimensions were recorded with States-TPPI hypercomplex phase increment (25). Spectra were collected with appropriate refocusing delays to allow for 0,0 phase correction, processed using the NMRPipe software package (36)) and analyzed with PIPP (37) on a Sun Ultra 10 Workstation. Data processing included a solvent filter, a skewed sine-bell apodization function and one zero-filing in all dimensions.

GTPase Functional Assay. A single-turnover GTP-ase assay of G-protein α subunits was used. In this assay GTPase-induced hydrolysis of [γ-^{32}P]-GTP results in precipitation of radiolabel as ^{32}Pi. Unhydrolyzed [γ-^{32}P]-GTP is separated from precipitated label which is then counted. Precipitated label ^{32}Pi is directly proportional to the amount of [γ-^{32}P]-GTP hydrolyzed and to the activity of the Gα GTPase .

Purified [γ-32P]-GTP bound Gα is prepared by incubating Gα (2μM) with [γ-32P]-GTP (2μM) in a reaction buffer (total volume 30 μL), 10mM Hepes (pH 8.0), 5 mM EDTA, 2mM DTT, 0.05% C12E10 (Lubrol, ICN Biomedicals, Inc., Aurora, OH), 10 μg /mL BSA) for 30 min at 30° C. Unbound [γ-^{32}P]GTP is removed using a gel filtration column (Centri-Sep, Princeton Separations, Princeton, NJ) according to the manufacturers directions. The eluate containing [γ-^{32}P]GTP bound Gα is collected and the protein is recovered (typically up to about 80-90%) after centrifugation at 2000rpm for 2 min at 4° C.

All steps of the assay are performed at 4° C. The purified [γ-^{32}P]GTP bound Gα obtained above is added to 500 μL of reaction buffer (as above) and separated in to eight 50μL samples (a zero time control (no initiation) and seven assay time points). The reaction is initiated by adding 10μL of 1M $MgCl_2$ and 10μL of 10mM GTP to the seven assay samples. After 10, 20, 30, 40, 60, 90, and 120 seconds, respectively, 750 μL of stop buffer (50 mM $NaPO_4$ (pH 3.0), 5% activated charcoal) is added to one of the assay samples. The control and samples are then centrifuged at 100,000 rpm for 10 min to precipitate the charcoal and 500 μL of supernatant is remove to assay radiolabel present. GTPase activity is expressed as the amount of free [^{32}P]-phosphate released from [γ-^{32}P]GTP. Phosphate release (fmol) = radioactivity (zero time control- time assay) (counts)/specific activity of [γ-^{32}P]GTP.

GTPase activity of Gαi in the presence of RGS4-GST fusion protein was determined as described above where GTP hydrolysis by 100 nM Gαi was initiated by the addition of $MgCl_2$ in the presence and absence of 100nM RGS4-GST protein. GTP hydrolysis at the indicated time points was calculated as the amount of ^{32}Pi released (in fmol). The dose-dependent effect of RGS4-GST protein on the hydrolysis of GTP-Gαi was measured as described above in the presence or absence of 10 nM or 100nM RGS4-GST protein.

The effects of test compounds are evaluated for modification of the activity of the RGS4 core domain. The RGS4 core protein was generated as a GST-RGS4core fusion using standard molecular techniques. Briefly, the core region of RGS4 was obtained using PCR to generate a cDNA fragment encoding amino acid 51 (val) to the C-terminal end of the protein, amino acid 206 (ala). The 5' forward amplification primer contained an embedded BamHI restriction site, followed by nucleotides encoding a flexible linker, Gly-Ser-Gly-Ser, prior to the Val residue of rat RGS4. The

3' reverse amplification primer contained a stop codon, followed by an embedded BamHI site. The amplimers were used with pWE2RGS4 (Shuey et al., 1998 (84)) as template to generate a PCR product of approximately 625 base pairs. This PCR product was BamHI digested, purified and ligated in the BamHI site of pGEX-2T (Ammersham Pharmacia, Piscataway NJ) to generate pGST-RGS4c recombinant plasmid. Plasmid was tranfected into bacterial cells, and DNA prepared by standard methods, and confirmed by sequence analysis. GST-RGS4c fusion protein was generated and purified according to manufacturer suggestions for expression using the pGEX-2T vector.

To measure the effect of test compounds on the activity of RGS4 core domain, RGS4-GST fusion protein (1.6 μM) is incubated with test compound (or mixtures of test compounds) (30μM-40μM each) or DMSO for 1 hr at 30°C. Thereafter, GTPase activity of Gαi (100nM) is measured in the presence or absence of the RGS4-GST treated with the test compound (100nM). Each assay is replicated at least three-times. RGS4-GST was treated with Compound **1** at 30 μM and inhibited the GTPase activity of RGS by 30%; while RGS4-GST treated with Compound **1** at 300 μM inhibited GTPase activity in comparison to a DMSO control.

Those of ordinary skill in the art will appreciate that reagents, methods, procedures and techniques other than those specifically disclosed herein are known in the art and can be readily employed or adapted to the practice of this invention to achieve the results of this invention. All such art-known functionally equivalent reagents, methods, procedures and techniques are intended to be encompassed by this invention. All references cited herein are incorporated by reference herein in their entirety to the extent that they are not inconsistent with the disclosure herein.

Table 1 ^{15}N, ^{13}C, ^{13}CO and ^{1}H resonance assignments for RGS4 at pH 6.0 and 30°C.[a]

Residue	N	CO	Cα	Cβ	Others
M1	- (-)	176.1	55.9 (4.30)	29.4 (2.10,2.00)	Cγ 33.9 (2.38);Cε 21.7 (0.36)
R2	123.0 (8.34)	177.2	56.7 (4.29)	33.0 (1.84,1.77)	Cγ 24.8 (1.45);Cδ 29.2 (1.71);Cε 42.2 (3.00)
G3	110.4 (8.40)	173.7	45.3 (4.00)		
S4	115.7 (8.23)	174.0	58.1 (4.59)	64.2 (3.90)	
V5	121.6 (8.20)	174.9	61.2 (4.38)	33.6 (1.99)	Cγ 21.7 (0.98);21.9 (0.89)
S6	122.3 (8.56)	175.1	57.5 (4.51)	65.3 (4.33,4.02)	
Q7	121.5 (8.95)	178.2	58.5 (3.80)	28.3 (2.02)	Cγ 34.3 (2.39)
E8	118.9 (8.48)	178.8	59.7 (3.85)	29.1 (2.01,1.94)	Cγ 36.6 (2.29)
E9	120.5 (7.43)	177.0	58.9 (3.77)	29.4 (2.04,1.72)	Cγ 36.4 (2.23)
V10	116.8 (7.16)	180.8	65.0 (3.89)	31.4 (1.54)	Cγ 22.1 (0.34);22.6 (0.34)
K11	122.0 (7.86)	179.6	59.9 (3.92)	32.1 (1.82)	Cγ 25.4 (1.52,1.37);Cδ 29.4 (1.62); Cε 42.1 (2.91,2.79)
K12	120.0 (7.39)	180.4	59.1 (4.09)	31.7 (2.12,1.93)	Cγ 25.4 (1.52,1.45); Cδ 29.2 (1.68); Cε 42.0 (2.99)
W13	120.7 (7.84)	176.7	57.2 (4.63)	29.8 (3.46)	Cδ1 126.4 (6.67); Nε1 129.3(9.69); Cζ2 113.9(6.25); Cη2 124.0(6.81); Cζ3 121.3(7.18)
A14	117.5 (7.48)	176.9	52.3 (4.36)	18.6 (1.52)	
E15	117.5 (7.80)	177.1	57.6 (4.29)	30.9 (2.16)	Cγ 36.6 (2.48,2.25)
S16	111.6 (7.02)	173.6	57.5 (4.50)	65.0 (4.22,3.93)	
L17	125.4 (8.36)	177.5	57.1 (3.17)	39.5 (0.97)	Cγ 26.2 (0.65);Cδ 25.9 (-0.48);23.9 (-0.08)
E18	117.2 (8.68)	177.7	60.1 (3.63)	29.3 (1.98,1.91)	Cγ 36.5 (2.19)
N19	116.0 (7.53)	176.9	55.3 (4.37)	38.4 (3.20,2.78)	
L20	119.5 (7.01)	176.4	58.2 (3.50)	41.8 (1.79,1.63)	Cγ 24.7 (0.52);Cδ 26.9 (-0.03);24.9 (0.33)
I21	105.6 (7.37)	175.1	63.3 (3.65)	37.1 (1.61)	Cγm 19.2(0.33);Cγ (0.70,0.81); Cδ 12.3(-0.62)
N22	115.7 (7.10)	173.8	53.9 (4.76)	39.5 (2.88)	
H23	121.6 (7.32)	176.0	56.4 (4.71)	33.9 (3.31,2.98)	Cδ2 138.6 (8.15)
E24	128.2 (9.04)	179.5	60.6 (4.07)	29.8 (2.09)	Cγ 36.1 (2.44,2.34)
C25	121.4 (10.57)	176.9	61.8 (4.46)	27.3 (3.37)	
G26	114.1 (7.36)	-	46.6 (2.86,2.45)		
L27	122.8 (8.66)	178.3	58.2 (3.76)	41.4 (1.72,1.65)	Cγ 27.1 (1.60);Cδ 25.6 (1.05); 23.5 (1.04)
A28	118.3 (7.29)	180.8	55.3 (4.06)	18.4 (1.60)	
A29	122.8 (7.85)	178.9	55.3 (4.51)	18.2 (1.84)	

Table 1 continued

F30	120.0 (8.51)	177.8	59.1 (3.94)	39.5 (2.62,2.38)	Cδ - (6.34)
K31	118.9 (9.02)	177.5	60.6 (3.59)	32.4 (1.94,1.74)	Cγ 26.0 (1.70,1.44);Cδ - (1.63);Cε - (2.96)
A32	121.6 (7.82)	180.3	55.3 (3.98)	17.8 (1.61)	
F33	121.5 (7.82)	177.8	59.9 (4.39)	39.2 (3.18,2.00)	Cδ - (6.78);Cε - (7.18)
L34	122.0 (8.57)	180.0	57.6 (3.34)	40.2 (0.88)	Cγ 26.2 (1.01);Cδ 21.8 (0.57); 26.3 (0.19)
K35	120.9 (8.60)	180.1	59.6 (3.90)	32.1 (1.79)	Cγ 24.9 (1.54,1.39);Cε - (2.93)
S36	116.7 (7.43)	174.1	61.1 (4.09)	63.1 (4.04,2.38)	
E37	118.0 (6.86)	175.3	55.3 (4.28)	29.9 (1.98,1.45)	Cγ 35.9 (1.66)
Y38	118.8 (7.60)	175.8	58.7 (4.37)	35.5 (3.27,3.09)	Cδ 133.4 (7.04);Cε 118.2 (6.84)
S39	113.0 (8.05)	175.5	57.0 (5.04)	64.5 (3.83,3.71)	
E40	122.2 (9.07)	175.9	58.2 (3.86)	30.2 (1.96,1.75)	Cγ 36.9 (2.20)
E41	122.3 (10.22)	177.2	60.9 (4.25)	27.7 (2.13,1.98)	Cγ 35.6 (2.37)
N42	116.4 (7.67)	176.9	56.7 (4.52)	38.8 (2.68)	
I43	117.6 (6.99)	176.2	58.9 (4.52)	38.3 (1.58)	Cγm 20.7 (1.05); Cδ 14.6 (0.92)
D44	126.2 (8.38)	179.6	57.6 (4.59)	39.1 (2.85)	
F45	123.8 (8.40)	176.5	60.2 (4.37)	39.0 (2.98,2.50)	Cδ - (6.67)
W46	122.3 (7.98)	177.7	64.9 (4.39)	29.9 (3.78,3.21)	Nε1 130.7 (10.68);Cζ2 115.1 (7.25); Cη2 125.8 (7.01);Cζ3 122.9(7.01); Cε3 119.9 (7.35)
I47	118.2 (9.04)	178.4	65.1 (3.37)	38.6 (2.02)	Cγm 17.0 (0.95);Cγ 29.4 (2.24,1.46); Cδ 14.3 (1.07)
S48	117.4 (7.91)	176.6	62.8 (4.22)	- (3.89,3.67)	
C49	120.4 (7.53)	179.6	64.0 (3.90)	- (3.61)	
E50	120.1 (7.39)	179.1	58.8 (3.58)	29.0 (1.65)	Cγ 35.2 (-)
E51	118.3 (7.93)	180.0	59.0 (3.84)	29.7 (2.21,1.95)	Cγ 36.3 (2.15)
Y52	123.0 (8.11)	175.6	61.2 (3.95)	38.7 (3.30,2.95)	Cδ - (7.03);Cε 118.5 (7.15)
K53	112.6 (7.43)	177.1	58.2 (3.89)	32.2 (1.86,1.76)	Cγ - (1.54,1.39)
K54	117.5 (7.18)	176.9	56.1 (4.17)	33.1 (1.98,1.71)	Cγ 25.4 (-);Cδ 29.4 (1.60);Cε 42.2 (-)
I55	123.1 (7.39)	176.8	64.0 (3.58)	37.2 (1.74)	Cγm 19.4 (0.75);Cγ 23.3 (0.35)
K56	126.5 (8.39)	176.7	56.3 (4.34)	33.6 (1.95,1.72)	Cγ 24.6 (1.40);Cδ 28.7 (1.64);Cε 42.1 (3.00)
S57	116.2 (7.35)	-	54.6 (4.98)	64.0 (3.79)	
P58	- (-)	178.8	65.0 (4.19)	32.1 (2.45,2.06)	Cγ 27.5 (2.17,2.06);Cδ 51.4 (4.11,3.98)
S59	112.3 (8.15)	175.5	60.5 (4.32)	62.7 (3.90)	
K60	119.7 (7.77)	177.6	56.3 (4.36)	33.2 (2.03,1.89)	Cγ 25.7 (-);Cδ 29.0 (-);Cε 42.4 (-)
L61	120.4 (7.49)	178.5	58.7 (4.12)	41.3 (1.82,1.71)	Cγ 26.8 (1.67);Cδ 25.9 (0.74);23.2 (0.35)
S62	112.7 (8.67)	-	64.0 (4.38)	60.8 (4.08)	
P63	- (-)	180.0	66.0 (4.39)	30.8 (2.42,1.95)	
K64	118.0 (7.08)	178.0	57.9 (4.36)	31.9 (2.26)	
A65	122.5 (9.23)	179.9	55.5 (4.19)	17.7 (1.76)	
K66	116.9 (8.40)	178.4	60.2 (3.99)	32.4 (1.93)	Cγ 25.8 (1.43);Cδ 29.2 (1.68);Cε 42.1 (3.00)
K67	119.5 (7.52)	179.6	59.9 (4.14)	32.7 (2.09)	Cγ 25.2 (1.66,1.52)
I68	120.9 (8.24)	178.4	65.9 (3.87)	38.3 (2.08)	Cγm 18.3 (0.93); Cδ - 0.30
Y69	120.8 (9.15)	178.6	62.4 (3.99)	39.5 (3.52,3.26)	Cδ 133.4 (7.07);Cε 117.9 (6.78)
N70	117.5 (8.77)	176.0	55.7 (4.42)	38.4 (2.99,2.78)	Nγ 112.0 (7.59,6.97)
E71	118.4 (7.88)	176.4	58.8 (4.00)	30.6 (1.76,1.37)	Cγ 35.9 (1.80,1.09)

Table 1 continued

F72	110.4 (7.76)	175.1	58.5 (4.95)	43.4 (2.77)	Cδ 133.6 (7.75);Cε 133.1 (7.19);Cζ - (6.89)
I73	116.5 (7.59)	175.3	61.3 (4.05)	38.0 (1.59)	Cγ 27.2 (1.43,1.03);Cγm 18.5 (0.79); Cδ 12.0 (0.76)
S74	113.4 (7.43)	174.6	57.7 (3.89)	64.1 (3.44)	
V75	120.6 (8.20)	177.1	64.4 (3.99)	31.3 (2.18)	Cγ 20.3 (1.02);21.1 (1.02)
Q76	118.6 (8.10)	175.4	55.7 (4.29)	28.2 (2.23,1.87)	Cγ 34.6 (2.30)
A77	124.1 (7.54)	178.7	52.8 (4.11)	18.8 (1.10)	
T78	114.8 (7.99)	175.6	64.0 (4.05)	68.8 (4.11)	Cγ 22.6 (1.27)
K79	123.8 (7.89)	173.4	54.6 (4.47)	33.1 (1.76,1.39)	Cγ 25.2 (1.27);Cδ 29.7 (1.64,1.51); Cε 42.0 (2.84)
E80	117.8 (7.16)	176.2	56.6 (3.97)	30.0 (1.82)	Cγ 34.5 (2.69,2.19)
V81	119.3 (8.22)	176.3	59.5 (4.56)	33.4 (2.01)	Cγ 22.5 (0.89);17.5 (0.34)
N82	122.5 (9.09)	173.7	53.2 (4.64)	37.5 (2.89,2.63)	
L83	122.7 (7.43)	176.1	53.1 (4.52)	46.3 (1.49,1.34)	Cγ 26.4 (-); Cδ 24.3 (0.94) - (0.73)
D84	120.3 (8.27)	176.3	53.2 (4.66)	41.7 (3.03,2.79)	
S85	116.6 (8.93)	176.7	62.5 (4.00)	- (4.01)	
C86	121.4 (8.36)	177.9	62.4 (4.30)	26.1 (3.07)	
T87	120.2 (8.35)	178.5	67.0 (4.06)	67.0 (4.06)	Cγ 22.7 (1.22)
R88	125.5 (8.55)	178.2	61.6 (3.73)	29.9 (1.98,1.91)	Cγ - (1.51,1.67); Cδ 43.3 (3.10)
E89	121.1 (8.49)	179.5	59.6 (4.12)	29.2 (2.17,2.08)	Cγ 36.2 (2.39)
E90	121.2 (8.44)	178.5	59.5 (4.01)	29.4 (2.17)	Cγ 35.6 (2.40)
T91	115.1 (8.10)	175.8	67.8 (3.91)	68.4 (4.42)	Cγ 22.3 (1.43)
S92	116.6 (8.32)	176.6	62.4 (3.90)	62.7 (4.09,3.99)	
R93	122.3 (7.84)	179.6	59.3 (4.05)	29.9 (1.95,1.91)	Cγ 27.9 (1.82,1.60);Cδ 43.5 (3.23)
N94	121.6 (8.10)	176.7	54.9 (4.33)	38.6 (3.18)	
M95	115.7 (7.40)	176.9	55.1 (4.07)	31.3 (1.83,1.77)	Cγ 31.7 (2.29,1.94); Cε 15.3 (1.67)
L96	119.8 (7.29)	178.4	57.7 (4.02)	41.5 (1.80,1.55)	Cγ 27.0 (1.80);Cδ 23.0 (0.85); 24.8 (0.95)
E97	116.6 (7.20)	-	53.8 (4.52)	30.1 (1.92,1.85)	Cγ 36.1 (2.10)
P98	- (-)	176.9	64.4 (4.34)	32.1 (2.26,1.93)	Cγ 27.9 (2.08);Cδ 49.9 (3.59)
T99	113.7 (8.43)	179.1	59.6 (4.79)	72.5 (4.60)	Cγ 21.1 (1.30)
I100	123.2 (9.19)	176.1	63.2 (4.22)	39.6 (1.97)	Cγm 19.1 (1.04);Cγ 28.5 (1.47,1.39); Cδ 14.8 (0.90)
T101	109.8 (7.61)	176.2	61.5 (4.57)	69.3 (4.63)	Cγ 21.7 (1.20)
C102	122.7 (7.48)	174.5	62.6 (3.85)	28.9 (3.15,2.31)	
F103	112.8 (8.78)	175.2	57.8 (4.95)	40.7 (3.71,2.57)	Cδ - (6.76)
D104	122.0 (7.72)	179.1	58.9 (4.28)	39.8 (2.82,2.59)	
E105	119.9 (8.75)	175.0	59.4 (4.16)	28.6 (2.44,2.12)	Cγ 35.9 (2.42)
A106	122.9 (8.66)	178.8	55.4 (4.03)	18.6 (1.65)	
Q107	118.7 (9.58)	178.3	60.3 (3.90)	27.9 (-)	Cγ 35.2 (-)
K108	120.1 (8.11)	179.3	59.6 (4.21)	32.4 (2.18,2.02)	Cγ 25.2 (1.46);Cδ 29.8 (1.69);Cε 42.2 (3.00)
K109	118.8 (8.08)	180.4	59.0 (4.27)	31.8 (2.22,2.04)	Cγ 24.9 (1.44);Cδ 29.1 (1.71, 1.81); Cε 42.0 (3.00)
I110	121.3 (8.30)	177.9	61.5 (4.22)	36.0 (2.44)	Cγ 29.0 (2.06,1.43);Cγm 19.6 (1.38); Cδ 10.0 (0.76)
F111	124.5 (9.22)	176.8	63.2 (3.80)	39.2 (3.51,3.21)	Cδ 131.9 (6.87);Cε - (7.04)

Table 1 continued

N112	117.2 (8.51)	177.5	56.3 (4.50)	38.6 (3.08,2.90)	
L113	121.5 (7.95)	180.3	58.3 (4.21)	42.3 (1.99)	Cγ 27.1 (1.83);Cδ 24.9 (1.06)
M114	118.6 (8.22)	177.0	60.0 (4.28)	35.0 (1.82,1.68)	Cγ 32.0 (2.38,2.26);Cε 15.9 (1.73)
E115	120.2 (8.46)	177.3	60.4 (3.49)	29.6 (1.58)	Cγ 37.3 (2.07)
K116	143.5 (7.57)	176.9	57.5 (4.26)	33.1 (1.98)	Cγ 24.7 (1.59);Cδ 29.5 (1.72);Cε 42.3 (3.04)
D117	116.6 (7.62)	176.6	55.8 (5.08)	42.8 (2.92,2.84)	
S118	117.2 (8.45)	176.2	63.0 (4.52)	63.6 (4.33,4.02)	
Y119	121.8 (8.95)	175.5	60.4 (4.27)	39.2 (2.81,2.00)	Cδ - (6.72);Cε 117.2 (6.58)
R120	114.4 (7.11)	179.8	58.3 (3.52)	28.7 (1.96,1.80)	Cγ 27.0 (1.87,1.64);Cδ 42.9 (3.16,3.10)
R121	117.5 (7.63)	179.4	59.6 (3.97)	30.3 (2.07)	Cδ 43.1 (-)
F122	124.0 (8.57)	178.4	60.0 (3.32)	38.3 (2.89,2.76)	Cδ - (6.77)
L123	117.7 (7.05)	176.3	56.3 (3.27)	41.4 (1.11,1.06)	Cγ 25.6 (1.31);Cδ 25.2 (0.32);19.6 (-0.09)
K124	114.3 (6.72)	175.5	54.8 (4.42)	33.0 (2.09,1.63)	Cγ 24.8 (1.46);Cδ 28.9 (1.70);Cε 42.2 (2.97)
S125	118.2 (7.83)	175.6	57.9 (4.79)	67.1 (4.52)	
R126	121.1 (9.39)	176.5	58.2 (3.92)	28.4 (1.81)	Cγ 25.5 (1.60,1.43); Cδ 42.5 (3.05,2.97)
F127	115.5 (7.47)	176.0	60.7 (4.21)	39.5 (3.42,3.27)	Cδ - (7.18)
Y128	114.2 (6.68)	177.2	59.3 (4.40)	39.8 (2.39)	Cδ 133.0 (7.17);Cε 117.6 (6.91)
L129	116.8 (8.34)	180.4	57.6 (3.71)	41.7 (1.41,1.37)	Cγ 26.8 (1.76);Cδ 25.6 (0.74);22.4 (0.89)
D130	119.0 (8.61)	177.8	56.8 (4.38)	39.8 (2.63)	
L131	117.5 (7.46)	177.8	55.7 (4.18)	42.1 (1.83,1.43)	Cγ 22.9 (1.27);Cδ 22.4 (0.94);22.6 (0.33)
T132	108.3 (7.24)	173.9	61.6 (4.26)	70.1 (4.09)	Cγ 21.6 (0.73)
N133	119.8 (7.60)	173.0	51.3 (4.95)	38.8 (2.78,2.62)	
P134	- (-)	177.4	63.7 (4.43)	32.1 (2.27,1.96)	Cγ 27.2 (1.97);Cδ 50.6 (3.67,3.50)
S135	115.5 (8.32)	174.9	58.8 (4.44)	63.7 (4.42,3.88)	
S136	117.6 (8.22)	174.7	58.5 (4.47)	63.8 (3.90,3.13)	
C137	120.7 (8.27)	175.1	58.7 (4.55)	28.1 (2.95)	
G138	111.5 (8.43)	173.8	45.4 (3.96)	- (-)	
A139	124.0 (8.10)	178.0	52.6 (4.30)	19.4 (1.43)	
E140	120.0 (8.48)	176.8	57.0 (4.22)	30.0 (2.01)	Cγ 36.2 (2.28)
K141	122.1 (8.23)	176.7	56.5 (4.27)	32.9 (1.80)	Cγ 24.9 (1.44);Cδ 29.0 (1.71);Cε 42.2 (3.00)
Q142	121.1 (8.27)	173.1	55.0 (4.16)	33.1 (2.21)	Cγ 30.9 (2.64)
K143	120.7 (8.27)	176.3	56.7 (4.42)	30.8 (1.92,1.86)	Cγ 24.7 (-);Cδ 27.1 (1.71);Cε 43.5 (3.25)
G144	111.1 (8.57)	176.1	45.4 (3.97)	- (-)	
A145	124.0 (8.15)	177.9	52.7 (4.30)	19.5 (1.43)	
K146	120.9 (8.35)	179.9	56.3 (4.35)	33.1 (1.81,1.45)	Cγ 24.8 (1.46);Cδ 29.1 (1.71,1.84); Cε 42.2 (3.01)
S147	117.3 (8.39)	174.8	58.2 (3.94)	64.1 (4.50,3.90)	
S148	118.3 (8.39)	174.5	58.5 (4.47)	63.9 (3.90)	
A149	125.7 (8.30)	177.5	52.8 (4.29)	19.3 (1.38)	
D150	119.3 (8.18)	176.5	54.4 (4.61)	41.2 (2.70)	
C151	119.8 (8.28)	175.1	58.8 (4.58)	27.9 (2.98)	
T152	116.4 (8.28)	174.7	62.5 (4.33)	69.7 (4.27)	Cγ 21.7 (1.24)
S153	118.0 (8.20)	174.2	58.4 (4.47)	63.8 (3.93,3.87)	
L154	124.3 (8.18)	177.0	55.2 (4.37)	42.4 (1.61)	Cγ 27.0 (1.61);Cδ 23.5 (0.86);24.9 (0.90)
V155	122.4 (8.01)	174.4	59.9 (4.39)	32.6 (2.06)	Cγ 21.0 (0.94);20.4 (0.94)

Table 1 continued

P156	- (-)	177.0	63.3 (4.39)	32.2 (2.30,1.90)	Cγ 27.5 (2.03,1.94);Cδ 51.1 (3.86,3.69)
Q157	120.9 (8.49)	176.1	56.1 (4.29)	29.5 (2.06,2.00)	Cγ 33.9 (2.41)
C158	120.2 (8.31)	174.1	58.2 (4.45)	28.2 (2.88)	
A159	126.3 (8.32)	177.3	52.6 (4.25)	19.3 (1.30)	
H160	117.9 (8.24)	-	55.5 (4.62)	29.8 (3.15,3.06)	Cδ2 119.5 (7.13)

Footnotes to Table S1

[a]In each column, ^{15}N and ^{13}C shifts are listed first, and the corresponding ^{1}H shifts are given in parentheses. ^{1}H and ^{13}C chemical shifts are reported relative to 3-(trimethylsily)propionic-d_4 acid and ^{15}N shifts relative to external liguid NH_3.

Table 2

Restrained Minimized NMR Coordinates for Free RGS4

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The structural coordinates herein are deposited with Brookhaven Protein Database. (Brookhaven National Laboratory)

Deposit No. _____

ATOM	7[illegible]	[illegible]	VAL	10	-10.061	2.62[illegible]	-5.566	1.00	0.50
ATOM	7[illegible]	[illegible]	VAL	10	-11.126	4.26	6.559	1.00	0.50
ATOM	80	HB	VAL	10	-10.787	4.993	-5.906	1.00	0.53
ATOM	81	CG1	VAL	10	-10.216	4.132	-7.790	1.00	0.67
ATOM	82	HG11	VAL	10	-9.970	5.133	-8.114	1.00	1.32
ATOM	83	HG12	VAL	10	-10.729	3.613	-8.587	1.00	1.27
ATOM	84	HG13	VAL	10	-9.309	3.602	-7.542	1.00	1.13
ATOM	85	CG2	VAL	10	-12.552	4.486	-7.011	1.00	0.58
ATOM	86	HG21	VAL	10	-13.164	4.719	-6.153	1.00	1.12
ATOM	87	HG22	VAL	10	-12.938	3.615	-7.506	1.00	1.22
ATOM	88	HG23	VAL	10	-12.556	5.321	-7.695	1.00	1.18
ATOM	89	C	VAL	10	-11.887	2.964	-4.504	1.00	0.45
ATOM	90	O	VAL	10	-11.340	3.243	-3.457	1.00	0.46
ATOM	91	N	LYS	11	-13.173	2.730	-4.545	1.00	0.47
ATOM	92	HN	LYS	11	-13.607	2.498	-5.393	1.00	0.48
ATOM	93	CA	LYS	11	-13.973	2.807	-3.285	1.00	0.50
ATOM	94	HA	LYS	11	-13.867	3.795	-2.864	1.00	0.52
ATOM	95	CB	LYS	11	-15.456	2.528	-3.561	1.00	0.56
ATOM	96	HB1	LYS	11	-15.979	2.413	-2.623	1.00	0.59
ATOM	97	HB2	LYS	11	-15.547	1.618	-4.135	1.00	0.56
ATOM	98	CG	LYS	11	-16.077	3.690	-4.348	1.00	0.63
ATOM	99	HG1	LYS	11	-15.820	3.597	-5.391	1.00	0.93
ATOM	100	HG2	LYS	11	-15.705	4.631	-3.967	1.00	1.22
ATOM	101	CD	LYS	11	-17.599	3.646	-4.195	1.00	1.17
ATOM	102	HD1	LYS	11	-17.870	4.006	-3.214	1.00	1.77
ATOM	103	HD2	LYS	11	-17.942	2.628	-4.311	1.00	1.80
ATOM	104	CE	LYS	11	-18.255	4.531	-5.257	1.00	1.66
ATOM	105	HE1	LYS	11	-19.306	4.640	-5.034	1.00	2.16
ATOM	106	HE2	LYS	11	-18.140	4.073	-6.228	1.00	2.08
ATOM	107	NZ	LYS	11	-17.608	5.874	-5.261	1.00	2.39
ATOM	108	HZ1	LYS	11	-16.668	5.805	-5.699	1.00	2.84
ATOM	109	HZ2	LYS	11	-17.512	6.215	-4.282	1.00	2.78
ATOM	110	HZ3	LYS	11	-18.193	6.539	-5.805	1.00	2.81
ATOM	111	C	LYS	11	-13.432	1.788	-2.279	1.00	0.48
ATOM	112	O	LYS	11	-13.402	2.035	-1.090	1.00	0.50
ATOM	113	N	LYS	12	-12.989	0.650	-2.743	1.00	0.47
ATOM	114	HN	LYS	12	-13.009	0.470	-3.705	1.00	0.47
ATOM	115	CA	LYS	12	-12.436	-0.366	-1.802	1.00	0.49
ATOM	116	HA	LYS	12	-13.193	-0.650	-1.084	1.00	0.55
ATOM	117	CB	LYS	12	-11.966	-1.601	-2.576	1.00	0.51
ATOM	118	HB1	LYS	12	-11.411	-2.249	-1.913	1.00	0.52
ATOM	119	HB2	LYS	12	-11.328	-1.292	-3.390	1.00	0.51
ATOM	120	CG	LYS	12	-13.169	-2.363	-3.135	1.00	0.64
ATOM	121	HG1	LYS	12	-13.724	-1.723	-3.803	1.00	1.06
ATOM	122	HG2	LYS	12	-13.807	-2.679	-2.321	1.00	1.06
ATOM	123	CD	LYS	12	-12.669	-3.590	-3.902	1.00	0.82
ATOM	124	HD1	LYS	12	-12.111	-4.229	-3.234	1.00	1.47
ATOM	125	HD2	LYS	12	-12.029	-3.270	-4.711	1.00	1.51
ATOM	126	CE	LYS	12	-13.858	-4.367	-4.469	1.00	1.39
ATOM	127	HE1	LYS	12	-13.611	-4.733	-5.455	1.00	1.89
ATOM	128	HE2	LYS	12	-14.718	-3.717	-4.531	1.00	1.86
ATOM	129	NZ	LYS	12	-14.168	-5.517	-3.574	1.00	2.37
ATOM	130	HZ1	LYS	12	-14.867	-5.226	-2.863	1.00	2.74
ATOM	131	HZ2	LYS	12	-13.297	-5.829	-3.097	1.00	2.90
ATOM	132	HZ3	LYS	12	-14.555	-6.301	-4.137	1.00	2.83
ATOM	133	C	LYS	12	-11.244	0.252	-1.076	1.00	0.43
ATOM	134	O	LYS	12	-11.026	0.019	0.097	1.00	0.45
ATOM	135	N	TRP	13	-10.476	1.049	-1.766	1.00	0.39
ATOM	136	HN	TRP	13	-10.677	1.228	-2.708	1.00	0.41
ATOM	137	CA	TRP	13	-9.305	1.696	-1.119	1.00	0.37
ATOM	138	HA	TRP	13	-8.624	0.943	-0.750	1.00	0.37
ATOM	139	CB	TRP	13	-8.587	2.598	-2.125	1.00	0.38
ATOM	140	HB1	TRP	13	-7.711	3.023	-1.656	1.00	0.41
ATOM	141	HB2	TRP	13	-9.248	3.395	-2.426	1.00	0.39
ATOM	142	CG	TRP	13	-8.172	1.813	-3.333	1.00	0.41
ATOM	143	CD1	TRP	13	-8.276	0.468	-3.480	1.00	0.44
ATOM	144	HD1	TRP	13	-8.672	-0.220	-2.749	1.00	0.44
ATOM	145	CD2	TRP	13	-7.587	2.312	-4.571	1.00	0.47
ATOM	146	NE1	TRP	13	-7.788	0.117	-4.726	1.00	0.50
ATOM	147	HE1	TRP	13	-7.748	-0.796	-5.080	1.00	0.54
ATOM	148	CE2	TRP	13	-7.353	1.217	-5.435	1.00	0.52
ATOM	149	CE3	TRP	13	-7.240	3.599	-5.022	1.00	0.51
ATOM	150	HE3	TRP	13	-7.408	4.454	-4.384	1.00	0.50
ATOM	151	CZ2	TRP	13	-6.793	1.392	-6.702	1.00	0.61
ATOM	152	HZ2	TRP	13	-6.623	0.540	-7.343	1.00	0.67
ATOM	153	CZ3	TRP	13	-6.677	3.779	-6.296	1.00	0.60
ATOM	154	HZ3	TRP	13	-6.414	4.771	-6.632	1.00	0.65

ATOM	1'	:H2	TRP	13	-6.454	2.6	-7.134	1.00	0.65
ATOM	15.	HH2	TRP	13	-6.021	2.8	-8.112	1.00	0.73
ATOM	157	C	TRP	13	-9.803	2.548	0.044	1.00	0.38
ATOM	158	O	TRP	13	-9.119	2.739	1.021	1.00	0.39
ATOM	159	N	ALA	14	-10.994	3.061	-0.050	1.00	0.42
ATOM	160	HN	ALA	14	-11.540	2.896	-0.847	1.00	0.45
ATOM	161	CA	ALA	14	-11.527	3.892	1.062	1.00	0.48
ATOM	162	HA	ALA	14	-10.739	4.509	1.466	1.00	0.48
ATOM	163	CB	ALA	14	-12.658	4.779	0.536	1.00	0.55
ATOM	164	HB1	ALA	14	-12.555	5.774	0.943	1.00	1.11
ATOM	165	HB2	ALA	14	-13.610	4.365	0.835	1.00	1.21
ATOM	166	HB3	ALA	14	-12.608	4.824	-0.542	1.00	1.14
ATOM	167	C	ALA	14	-12.072	2.970	2.156	1.00	0.49
ATOM	168	O	ALA	14	-12.450	3.412	3.223	1.00	0.55
ATOM	169	N	GLU	15	-12.134	1.691	1.886	1.00	0.47
ATOM	170	HN	GLU	15	-11.839	1.362	1.011	1.00	0.45
ATOM	171	CA	GLU	15	-12.679	0.736	2.894	1.00	0.52
ATOM	172	HA	GLU	15	-13.328	1.268	3.572	1.00	0.58
ATOM	173	CB	GLU	15	-13.494	-0.334	2.168	1.00	0.58
ATOM	174	HB1	GLU	15	-13.766	-1.114	2.863	1.00	0.64
ATOM	175	HB2	GLU	15	-12.904	-0.753	1.365	1.00	0.55
ATOM	176	CG	GLU	15	-14.762	0.302	1.596	1.00	0.70
ATOM	177	HG1	GLU	15	-14.491	1.108	0.930	1.00	1.24
ATOM	178	HG2	GLU	15	-15.365	0.691	2.404	1.00	1.12
ATOM	179	CD	GLU	15	-15.560	-0.748	0.823	1.00	1.35
ATOM	180	OE1	GLU	15	-16.609	-0.403	0.305	1.00	1.94
ATOM	181	OE2	GLU	15	-15.108	-1.880	0.763	1.00	2.17
ATOM	182	C	GLU	15	-11.556	0.062	3.698	1.00	0.47
ATOM	183	O	GLU	15	-11.765	-0.345	4.824	1.00	0.51
ATOM	184	N	SER	16	-10.375	-0.080	3.150	1.00	0.42
ATOM	185	HN	SER	16	-10.207	0.238	2.238	1.00	0.42
ATOM	186	CA	SER	16	-9.291	-0.751	3.933	1.00	0.42
ATOM	187	HA	SER	16	-9.188	-0.259	4.889	1.00	0.44
ATOM	188	CB	SER	16	-9.670	-2.214	4.165	1.00	0.48
ATOM	189	HB1	SER	16	-10.416	-2.272	4.947	1.00	0.54
ATOM	190	HB2	SER	16	-8.798	-2.771	4.462	1.00	0.50
ATOM	191	OG	SER	16	-10.186	-2.761	2.959	1.00	0.53
ATOM	192	HG	SER	16	-9.619	-2.476	2.238	1.00	0.96
ATOM	193	C	SER	16	-7.949	-0.693	3.192	1.00	0.38
ATOM	194	O	SER	16	-7.879	-0.820	1.986	1.00	0.37
ATOM	195	N	LEU	17	-6.884	-0.511	3.930	1.00	0.37
ATOM	196	HN	LEU	17	-6.984	-0.421	4.901	1.00	0.40
ATOM	197	CA	LEU	17	-5.518	-0.442	3.327	1.00	0.37
ATOM	198	HA	LEU	17	-5.470	0.385	2.639	1.00	0.36
ATOM	199	CB	LEU	17	-4.507	-0.218	4.456	1.00	0.40
ATOM	200	HB1	LEU	17	-4.570	-1.038	5.156	1.00	0.44
ATOM	201	HB2	LEU	17	-4.743	0.704	4.967	1.00	0.43
ATOM	202	CG	LEU	17	-3.082	-0.138	3.902	1.00	0.45
ATOM	203	HG	LEU	17	-2.848	-1.047	3.375	1.00	0.54
ATOM	204	CD1	LEU	17	-2.945	1.053	2.952	1.00	0.57
ATOM	205	HD11	LEU	17	-3.281	0.771	1.966	1.00	1.30
ATOM	206	HD12	LEU	17	-1.909	1.356	2.905	1.00	1.08
ATOM	207	HD13	LEU	17	-3.542	1.874	3.318	1.00	1.17
ATOM	208	CD2	LEU	17	-2.109	0.039	5.066	1.00	0.49
ATOM	209	HD21	LEU	17	-2.302	-0.716	5.809	1.00	1.13
ATOM	210	HD22	LEU	17	-2.248	1.014	5.503	1.00	1.06
ATOM	211	HD23	LEU	17	-1.095	-0.057	4.708	1.00	1.17
ATOM	212	C	LEU	17	-5.184	-1.744	2.587	1.00	0.38
ATOM	213	O	LEU	17	-4.592	-1.725	1.526	1.00	0.39
ATOM	214	N	GLU	18	-5.533	-2.872	3.141	1.00	0.40
ATOM	215	HN	GLU	18	-5.986	-2.874	4.007	1.00	0.41
ATOM	216	CA	GLU	18	-5.205	-4.162	2.470	1.00	0.43
ATOM	217	HA	GLU	18	-4.136	-4.299	2.461	1.00	0.45
ATOM	218	CB	GLU	18	-5.860	-5.314	3.239	1.00	0.49
ATOM	219	HB1	GLU	18	-5.772	-6.225	2.665	1.00	0.53
ATOM	220	HB2	GLU	18	-6.904	-5.091	3.402	1.00	0.48
ATOM	221	CG	GLU	18	-5.159	-5.495	4.587	1.00	0.53
ATOM	222	HG1	GLU	18	-5.243	-4.586	5.163	1.00	0.76
ATOM	223	HG2	GLU	18	-4.116	-5.721	4.419	1.00	0.70
ATOM	224	CD	GLU	18	-5.812	-6.646	5.355	1.00	0.92
ATOM	225	OE1	GLU	18	-6.853	-7.108	4.920	1.00	1.64
ATOM	226	OE2	GLU	18	-5.260	-7.044	6.368	1.00	1.49
ATOM	227	C	GLU	18	-5.730	-4.151	1.034	1.00	0.42
ATOM	228	O	GLU	18	-5.077	-4.625	0.126	1.00	0.44
ATOM	229	N	ASN	19	-6.896	-3.618	0.813	1.00	0.41
ATOM	230	HN	ASN	19	-7.412	-3.238	1.554	1.00	0.41
ATOM	231	CA	ASN	19	-7.439	-3.588	-0.575	1.00	0.41

ATOM	23[illegible]	HA	ASN	19	-7.504	-4.5[illegible]	-0.959	1.00	0.45
ATOM	2[illegible]	HB	ASN	19	-8.832	-2.9	-0.560	1.00	0.42
ATOM	234	HB1	ASN	19	-9.146	-2.755	-1.573	1.00	0.42
ATOM	235	HB2	ASN	19	-8.801	-2.032	-0.001	1.00	0.41
ATOM	236	CG	ASN	19	-9.822	-3.918	0.097	1.00	0.48
ATOM	237	OD1	ASN	19	-9.650	-4.301	1.237	1.00	1.22
ATOM	238	ND2	ASN	19	-10.862	-4.324	-0.578	1.00	1.19
ATOM	239	HD21	ASN	19	-11.003	-4.011	-1.496	1.00	1.98
ATOM	240	HD22	ASN	19	-11.503	-4.941	-0.167	1.00	1.21
ATOM	241	C	ASN	19	-6.518	-2.755	-1.470	1.00	0.38
ATOM	242	O	ASN	19	-6.220	-3.127	-2.589	1.00	0.40
ATOM	243	N	LEU	20	-6.061	-1.633	-0.986	1.00	0.35
ATOM	244	HN	LEU	20	-6.312	-1.353	-0.080	1.00	0.35
ATOM	245	CA	LEU	20	-5.159	-0.777	-1.807	1.00	0.34
ATOM	246	HA	LEU	20	-5.655	-0.512	-2.728	1.00	0.37
ATOM	247	CB	LEU	20	-4.827	0.494	-1.013	1.00	0.34
ATOM	248	HB1	LEU	20	-4.340	0.215	-0.090	1.00	0.35
ATOM	249	HB2	LEU	20	-5.742	1.019	-0.783	1.00	0.37
ATOM	250	CG	LEU	20	-3.896	1.418	-1.814	1.00	0.35
ATOM	251	HG	LEU	20	-3.027	0.870	-2.147	1.00	0.38
ATOM	252	CD1	LEU	20	-4.633	1.986	-3.032	1.00	0.39
ATOM	253	HD11	LEU	20	-4.627	1.260	-3.828	1.00	1.05
ATOM	254	HD12	LEU	20	-4.136	2.885	-3.365	1.00	1.12
ATOM	255	HD13	LEU	20	-5.653	2.219	-2.765	1.00	1.10
ATOM	256	CD2	LEU	20	-3.453	2.573	-0.913	1.00	0.38
ATOM	257	HD21	LEU	20	-2.688	3.147	-1.412	1.00	0.99
ATOM	258	HD22	LEU	20	-3.061	2.177	0.012	1.00	1.12
ATOM	259	HD23	LEU	20	-4.300	3.210	-0.702	1.00	1.05
ATOM	260	C	LEU	20	-3.877	-1.558	-2.117	1.00	0.36
ATOM	261	O	LEU	20	-3.353	-1.506	-3.212	1.00	0.41
ATOM	262	N	ILE	21	-3.373	-2.284	-1.156	1.00	0.36
ATOM	263	HN	ILE	21	-3.816	-2.310	-0.282	1.00	0.36
ATOM	264	CA	ILE	21	-2.129	-3.075	-1.379	1.00	0.41
ATOM	265	HA	ILE	21	-1.429	-2.488	-1.955	1.00	0.43
ATOM	266	CB	ILE	21	-1.505	-3.430	-0.013	1.00	0.47
ATOM	267	HB	ILE	21	-2.206	-4.021	0.554	1.00	1.27
ATOM	268	CG1	ILE	21	-1.189	-2.148	0.759	1.00	1.31
ATOM	269	HG11	ILE	21	-2.105	-1.621	0.977	1.00	2.03
ATOM	270	HG12	ILE	21	-0.541	-1.518	0.166	1.00	1.83
ATOM	271	CG2	ILE	21	-0.199	-4.221	-0.176	1.00	1.28
ATOM	272	HG21	ILE	21	-0.199	-4.759	-1.105	1.00	1.89
ATOM	273	HG22	ILE	21	-0.105	-4.922	0.641	1.00	1.82
ATOM	274	HG23	ILE	21	0.636	-3.538	-0.159	1.00	1.86
ATOM	275	CD1	ILE	21	-0.490	-2.517	2.070	1.00	1.34
ATOM	276	HD11	ILE	21	-0.759	-1.812	2.837	1.00	1.53
ATOM	277	HD12	ILE	21	0.581	-2.499	1.926	1.00	1.73
ATOM	278	HD13	ILE	21	-0.796	-3.505	2.372	1.00	1.71
ATOM	279	C	ILE	21	-2.480	-4.358	-2.148	1.00	0.44
ATOM	280	O	ILE	21	-1.670	-4.901	-2.874	1.00	0.47
ATOM	281	N	ASN	22	-3.671	-4.861	-1.981	1.00	0.44
ATOM	282	HN	ASN	22	-4.310	-4.423	-1.382	1.00	0.43
ATOM	283	CA	ASN	22	-4.044	-6.125	-2.681	1.00	0.48
ATOM	284	HA	ASN	22	-3.166	-6.745	-2.779	1.00	0.52
ATOM	285	CB	ASN	22	-5.089	-6.872	-1.850	1.00	0.53
ATOM	286	HB1	ASN	22	-5.476	-7.703	-2.420	1.00	0.58
ATOM	287	HB2	ASN	22	-5.897	-6.199	-1.599	1.00	0.51
ATOM	288	CG	ASN	22	-4.440	-7.394	-0.567	1.00	0.59
ATOM	289	OD1	ASN	22	-3.376	-7.980	-0.605	1.00	1.15
ATOM	290	ND2	ASN	22	-5.040	-7.206	0.576	1.00	1.33
ATOM	291	HD21	ASN	22	-5.898	-6.732	0.607	1.00	2.10
ATOM	292	HD22	ASN	22	-4.634	-7.538	1.403	1.00	1.37
ATOM	293	C	ASN	22	-4.612	-5.840	-4.075	1.00	0.46
ATOM	294	O	ASN	22	-4.958	-6.752	-4.800	1.00	0.50
ATOM	295	N	HIS	23	-4.701	-4.598	-4.470	1.00	0.42
ATOM	296	HN	HIS	23	-4.410	-3.871	-3.880	1.00	0.41
ATOM	297	CA	HIS	23	-5.236	-4.292	-5.831	1.00	0.44
ATOM	298	HA	HIS	23	-5.874	-5.101	-6.157	1.00	0.48
ATOM	299	CB	HIS	23	-6.043	-2.995	-5.795	1.00	0.44
ATOM	300	HB1	HIS	23	-5.376	-2.159	-5.684	1.00	0.42
ATOM	301	HB2	HIS	23	-6.730	-3.021	-4.962	1.00	0.46
ATOM	302	CG	HIS	23	-6.814	-2.856	-7.078	1.00	0.54
ATOM	303	ND1	HIS	23	-6.275	-2.251	-8.203	1.00	0.89
ATOM	304	HD1	HIS	23	-5.378	-1.863	-8.278	1.00	1.50
ATOM	305	CD2	HIS	23	-8.081	-3.246	-7.433	1.00	1.13
ATOM	306	HD2	HIS	23	-8.781	-3.751	-6.784	1.00	1.83
ATOM	307	CE1	HIS	23	-7.207	-2.294	-9.172	1.00	0.77
ATOM	308	HE1	HIS	23	-7.066	-1.897	-10.166	1.00	1.14

ATOM	309	NE2	HIS	23	-8.328	-2.890	-8.756	1.00	0.94
ATOM	310	C	HIS	23	-4.063	-4.14.	-6.808	1.00	0.45
ATOM	311	O	HIS	23	-3.062	-3.529	-6.506	1.00	0.41
ATOM	312	N	GLU	24	-4.171	-4.741	-7.968	1.00	0.54
ATOM	313	HN	GLU	24	-4.980	-5.251	-8.180	1.00	0.58
ATOM	314	CA	GLU	24	-3.056	-4.671	-8.960	1.00	0.59
ATOM	315	HA	GLU	24	-2.168	-5.109	-8.529	1.00	0.60
ATOM	316	CB	GLU	24	-3.447	-5.458	-10.214	1.00	0.72
ATOM	317	HB1	GLU	24	-4.340	-5.028	-10.642	1.00	0.74
ATOM	318	HB2	GLU	24	-3.635	-6.487	-9.947	1.00	0.76
ATOM	319	CG	GLU	24	-2.312	-5.394	-11.240	1.00	0.78
ATOM	320	HG1	GLU	24	-1.390	-5.715	-10.778	1.00	1.02
ATOM	321	HG2	GLU	24	-2.204	-4.380	-11.596	1.00	1.07
ATOM	322	CD	GLU	24	-2.637	-6.315	-12.417	1.00	1.39
ATOM	323	OE1	GLU	24	-3.745	-6.232	-12.921	1.00	1.95
ATOM	324	OE2	GLU	24	-1.774	-7.093	-12.791	1.00	2.12
ATOM	325	C	GLU	24	-2.764	-3.216	-9.343	1.00	0.56
ATOM	326	O	GLU	24	-1.620	-2.822	-9.488	1.00	0.57
ATOM	327	N	CYS	25	-3.773	-2.406	-9.507	1.00	0.56
ATOM	328	HN	CYS	25	-4.692	-2.727	-9.389	1.00	0.57
ATOM	329	CA	CYS	25	-3.512	-0.991	-9.885	1.00	0.58
ATOM	330	HA	CYS	25	-2.650	-0.947	-10.536	1.00	0.62
ATOM	331	CB	CYS	25	-4.725	-0.402	-10.606	1.00	0.66
ATOM	332	HB1	CYS	25	-5.469	-0.107	-9.881	1.00	0.59
ATOM	333	HB2	CYS	25	-5.143	-1.142	-11.273	1.00	0.74
ATOM	334	SG	CYS	25	-4.206	1.045	-11.562	1.00	0.90
ATOM	335	HG	CYS	25	-4.416	1.830	-11.051	1.00	1.39
ATOM	336	C	CYS	25	-3.227	-0.193	-8.619	1.00	0.49
ATOM	337	O	CYS	25	-2.470	0.757	-8.631	1.00	0.50
ATOM	338	N	GLY	26	-3.796	-0.588	-7.514	1.00	0.44
ATOM	339	HN	GLY	26	-4.384	-1.372	-7.510	1.00	0.46
ATOM	340	CA	GLY	26	-3.507	0.141	-6.253	1.00	0.39
ATOM	341	HA1	GLY	26	-4.035	-0.312	-5.433	1.00	0.38
ATOM	342	HA2	GLY	26	-3.799	1.178	-6.354	1.00	0.44
ATOM	343	C	GLY	26	-2.007	0.042	-6.009	1.00	0.36
ATOM	344	O	GLY	26	-1.351	1.009	-5.687	1.00	0.37
ATOM	345	N	LEU	27	-1.455	-1.127	-6.196	1.00	0.38
ATOM	346	HN	LEU	27	-2.003	-1.889	-6.480	1.00	0.40
ATOM	347	CA	LEU	27	0.010	-1.292	-6.016	1.00	0.40
ATOM	348	HA	LEU	27	0.283	-1.029	-5.006	1.00	0.38
ATOM	349	CB	LEU	27	0.401	-2.746	-6.304	1.00	0.47
ATOM	350	HB1	LEU	27	1.474	-2.821	-6.397	1.00	0.54
ATOM	351	HB2	LEU	27	-0.060	-3.060	-7.230	1.00	0.51
ATOM	352	CG	LEU	27	-0.081	-3.653	-5.165	1.00	0.45
ATOM	353	HG	LEU	27	-1.060	-3.332	-4.839	1.00	0.42
ATOM	354	CD1	LEU	27	-0.158	-5.096	-5.665	1.00	0.52
ATOM	355	HD11	LEU	27	0.780	-5.368	-6.127	1.00	1.23
ATOM	356	HD12	LEU	27	-0.955	-5.185	-6.389	1.00	1.16
ATOM	357	HD13	LEU	27	-0.353	-5.756	-4.832	1.00	1.05
ATOM	358	CD2	LEU	27	0.902	-3.589	-3.988	1.00	0.48
ATOM	359	HD21	LEU	27	1.549	-2.732	-4.093	1.00	1.12
ATOM	360	HD22	LEU	27	1.500	-4.488	-3.973	1.00	1.17
ATOM	361	HD23	LEU	27	0.350	-3.512	-3.064	1.00	1.06
ATOM	362	C	LEU	27	0.720	-0.364	-7.000	1.00	0.43
ATOM	363	O	LEU	27	1.618	0.371	-6.641	1.00	0.43
ATOM	364	N	ALA	28	0.310	-0.384	-8.242	1.00	0.48
ATOM	365	HN	ALA	28	-0.424	-0.981	-8.510	1.00	0.49
ATOM	366	CA	ALA	28	0.952	0.508	-9.248	1.00	0.53
ATOM	367	HA	ALA	28	2.004	0.281	-9.312	1.00	0.56
ATOM	368	CB	ALA	28	0.298	0.297	-10.615	1.00	0.61
ATOM	369	HB1	ALA	28	-0.756	0.525	-10.549	1.00	1.18
ATOM	370	HB2	ALA	28	0.425	-0.731	-10.920	1.00	1.16
ATOM	371	HB3	ALA	28	0.762	0.948	-11.340	1.00	1.21
ATOM	372	C	ALA	28	0.770	1.964	-8.819	1.00	0.50
ATOM	373	O	ALA	28	1.709	2.736	-8.784	1.00	0.50
ATOM	374	N	ALA	29	-0.433	2.344	-8.491	1.00	0.49
ATOM	375	HN	ALA	29	-1.173	1.703	-8.526	1.00	0.50
ATOM	376	CA	ALA	29	-0.684	3.748	-8.063	1.00	0.49
ATOM	377	HA	ALA	29	-0.283	4.429	-8.799	1.00	0.53
ATOM	378	CB	ALA	29	-2.192	3.974	-7.924	1.00	0.52
ATOM	379	HB1	ALA	29	-2.496	3.756	-6.910	1.00	1.18
ATOM	380	HB2	ALA	29	-2.719	3.322	-8.605	1.00	1.21
ATOM	381	HB3	ALA	29	-2.426	5.002	-8.156	1.00	1.00
ATOM	382	C	ALA	29	-0.015	3.997	-6.712	1.00	0.43
ATOM	383	O	ALA	29	0.552	5.044	-6.471	1.00	0.45
ATOM	384	N	PHE	30	-0.089	3.045	-5.824	1.00	0.39
ATOM	385	HN	PHE	30	-0.558	2.212	-6.038	1.00	0.40

ATOM	386	[illegible]	PHE	30	0.530	3.227	1.484	1.00	0.37
ATOM	387	[illegible]A	PHE	30	0.165	4.146	1.051	1.00	0.41
ATOM	388	CB	PHE	30	0.147	2.055	-3.576	1.00	0.38
ATOM	389	HB1	PHE	30	0.545	1.138	-3.984	1.00	0.43
ATOM	390	HB2	PHE	30	-0.929	1.984	-3.513	1.00	0.40
ATOM	391	CG	PHE	30	0.716	2.282	-2.197	1.00	0.48
ATOM	392	CD1	PHE	30	0.267	3.363	-1.428	1.00	0.64
ATOM	393	HD1	PHE	30	-0.486	4.031	-1.821	1.00	0.71
ATOM	394	CD2	PHE	30	1.690	1.416	-1.685	1.00	0.59
ATOM	395	HD2	PHE	30	2.035	0.580	-2.275	1.00	0.64
ATOM	396	CE1	PHE	30	0.793	3.580	-0.151	1.00	0.82
ATOM	397	HE1	PHE	30	0.446	4.412	0.440	1.00	1.00
ATOM	398	CE2	PHE	30	2.213	1.633	-0.406	1.00	0.76
ATOM	399	HE2	PHE	30	2.963	0.964	-0.009	1.00	0.90
ATOM	400	CZ	PHE	30	1.765	2.715	0.360	1.00	0.86
ATOM	401	HZ	PHE	30	2.171	2.887	1.344	1.00	1.03
ATOM	402	C	PHE	30	2.054	3.309	-4.615	1.00	0.36
ATOM	403	O	PHE	30	2.691	4.134	-3.992	1.00	0.37
ATOM	404	N	LYS	31	2.650	2.468	-5.421	1.00	0.38
ATOM	405	HN	LYS	31	2.126	1.808	-5.922	1.00	0.40
ATOM	406	CA	LYS	31	4.132	2.527	-5.573	1.00	0.40
ATOM	407	HA	LYS	31	4.598	2.360	-4.613	1.00	0.41
ATOM	408	CB	LYS	31	4.607	1.457	-6.562	1.00	0.47
ATOM	409	HB1	LYS	31	5.586	1.721	-6.932	1.00	0.52
ATOM	410	HB2	LYS	31	3.914	1.402	-7.389	1.00	0.49
ATOM	411	CG	LYS	31	4.680	0.094	-5.869	1.00	0.51
ATOM	412	HG1	LYS	31	3.699	-0.184	-5.513	1.00	0.80
ATOM	413	HG2	LYS	31	5.364	0.157	-5.035	1.00	0.72
ATOM	414	CD	LYS	31	5.173	-0.953	-6.878	1.00	0.73
ATOM	415	HD1	LYS	31	6.052	-0.577	-7.380	1.00	1.40
ATOM	416	HD2	LYS	31	4.398	-1.137	-7.607	1.00	1.34
ATOM	417	CE	LYS	31	5.521	-2.270	-6.168	1.00	1.20
ATOM	418	HE1	LYS	31	5.814	-2.074	-5.148	1.00	1.85
ATOM	419	HE2	LYS	31	6.339	-2.748	-6.687	1.00	1.74
ATOM	420	NZ	LYS	31	4.337	-3.174	-6.180	1.00	1.97
ATOM	421	HZ1	LYS	31	4.363	-3.788	-5.342	1.00	2.46
ATOM	422	HZ2	LYS	31	4.357	-3.759	-7.041	1.00	2.37
ATOM	423	HZ3	LYS	31	3.467	-2.607	-6.165	1.00	2.48
ATOM	424	C	LYS	31	4.535	3.905	-6.099	1.00	0.41
ATOM	425	O	LYS	31	5.483	4.509	-5.632	1.00	0.42
ATOM	426	N	ALA	32	3.819	4.413	-7.063	1.00	0.45
ATOM	427	HN	ALA	32	3.056	3.915	-7.425	1.00	0.46
ATOM	428	CA	ALA	32	4.164	5.751	-7.611	1.00	0.51
ATOM	429	HA	ALA	32	5.213	5.777	-7.868	1.00	0.53
ATOM	430	CB	ALA	32	3.324	6.024	-8.860	1.00	0.62
ATOM	431	HB1	ALA	32	2.389	5.487	-8.790	1.00	1.11
ATOM	432	HB2	ALA	32	3.863	5.694	-9.736	1.00	1.10
ATOM	433	HB3	ALA	32	3.126	7.083	-8.937	1.00	1.24
ATOM	434	C	ALA	32	3.872	6.814	-6.554	1.00	0.48
ATOM	435	O	ALA	32	4.627	7.748	-6.372	1.00	0.49
ATOM	436	N	PHE	33	2.784	6.676	-5.847	1.00	0.48
ATOM	437	HN	PHE	33	2.189	5.912	-6.003	1.00	0.49
ATOM	438	CA	PHE	33	2.454	7.675	-4.796	1.00	0.53
ATOM	439	HA	PHE	33	2.365	8.648	-5.253	1.00	0.60
ATOM	440	CB	PHE	33	1.133	7.316	-4.120	1.00	0.60
ATOM	441	HB1	PHE	33	1.205	6.334	-3.677	1.00	0.56
ATOM	442	HB2	PHE	33	0.335	7.331	-4.848	1.00	0.66
ATOM	443	CG	PHE	33	0.863	8.336	-3.046	1.00	0.76
ATOM	444	CD1	PHE	33	0.371	9.600	-3.389	1.00	0.93
ATOM	445	HD1	PHE	33	0.170	9.841	-4.422	1.00	0.97
ATOM	446	CD2	PHE	33	1.125	8.023	-1.708	1.00	0.84
ATOM	447	HD2	PHE	33	1.502	7.046	-1.446	1.00	0.82
ATOM	448	CE1	PHE	33	0.143	10.554	-2.391	1.00	1.11
ATOM	449	HE1	PHE	33	-0.236	11.530	-2.653	1.00	1.27
ATOM	450	CE2	PHE	33	0.893	8.974	-0.711	1.00	1.05
ATOM	451	HE2	PHE	33	1.093	8.733	0.323	1.00	1.16
ATOM	452	CZ	PHE	33	0.404	10.239	-1.052	1.00	1.16
ATOM	453	HZ	PHE	33	0.233	10.974	-0.283	1.00	1.33
ATOM	454	C	PHE	33	3.567	7.717	-3.748	1.00	0.47
ATOM	455	O	PHE	33	3.965	8.770	-3.297	1.00	0.52
ATOM	456	N	LEU	34	4.073	6.583	-3.355	1.00	0.42
ATOM	457	HN	LEU	34	3.740	5.741	-3.729	1.00	0.43
ATOM	458	CA	LEU	34	5.160	6.574	-2.335	1.00	0.44
ATOM	459	HA	LEU	34	4.810	7.052	-1.436	1.00	0.53
ATOM	460	CB	LEU	34	5.587	5.135	-2.027	1.00	0.51
ATOM	461	HB1	LEU	34	6.490	5.150	-1.434	1.00	0.57
ATOM	462	HB2	LEU	34	5.781	4.618	-2.955	1.00	0.50

ATOM	463	G	LEU	34	4.483	4.395	-1.257	1.00	0.62
ATOM	464	.G	LEU	34	3.562	4.450	-1.822	1.00	0.53
ATOM	465	CD1	LEU	34	4.900	2.919	-1.119	1.00	0.82
ATOM	466	HD11	LEU	34	5.962	2.832	-1.296	1.00	1.31
ATOM	467	HD12	LEU	34	4.369	2.329	-1.851	1.00	1.24
ATOM	468	HD13	LEU	34	4.672	2.548	-0.134	1.00	1.37
ATOM	469	CD2	LEU	34	4.280	5.051	0.129	1.00	0.81
ATOM	470	HD21	LEU	34	5.215	5.455	0.477	1.00	1.25
ATOM	471	HD22	LEU	34	3.916	4.330	0.840	1.00	1.37
ATOM	472	HD23	LEU	34	3.557	5.848	0.044	1.00	1.35
ATOM	473	C	LEU	34	6.352	7.356	-2.877	1.00	0.38
ATOM	474	O	LEU	34	7.016	8.074	-2.156	1.00	0.41
ATOM	475	N	LYS	35	6.629	7.228	-4.142	1.00	0.39
ATOM	476	HN	LYS	35	6.081	6.644	-4.711	1.00	0.41
ATOM	477	CA	LYS	35	7.779	7.971	-4.724	1.00	0.47
ATOM	478	HA	LYS	35	8.702	7.612	-4.294	1.00	0.48
ATOM	479	CB	LYS	35	7.798	7.765	-6.239	1.00	0.60
ATOM	480	HB1	LYS	35	7.495	8.677	-6.730	1.00	1.08
ATOM	481	HB2	LYS	35	7.115	6.970	-6.501	1.00	0.93
ATOM	482	CG	LYS	35	9.211	7.393	-6.688	1.00	1.34
ATOM	483	HG1	LYS	35	9.485	6.440	-6.262	1.00	1.84
ATOM	484	HG2	LYS	35	9.905	8.151	-6.355	1.00	1.85
ATOM	485	CD	LYS	35	9.248	7.297	-8.213	1.00	1.48
ATOM	486	HD1	LYS	35	9.686	8.196	-8.620	1.00	1.59
ATOM	487	HD2	LYS	35	8.242	7.183	-8.591	1.00	1.64
ATOM	488	CE	LYS	35	10.091	6.091	-8.627	1.00	2.33
ATOM	489	HE1	LYS	35	11.059	6.148	-8.153	1.00	2.75
ATOM	490	HE2	LYS	35	10.214	6.088	-9.700	1.00	2.70
ATOM	491	NZ	LYS	35	9.402	4.839	-8.202	1.00	3.09
ATOM	492	HZ1	LYS	35	9.038	4.955	-7.235	1.00	3.47
ATOM	493	HZ2	LYS	35	10.076	4.047	-8.227	1.00	3.33
ATOM	494	HZ3	LYS	35	8.610	4.643	-8.846	1.00	3.60
ATOM	495	C	LYS	35	7.606	9.461	-4.413	1.00	0.50
ATOM	496	O	LYS	35	8.552	10.155	-4.099	1.00	0.55
ATOM	497	N	SER	36	6.399	9.952	-4.493	1.00	0.54
ATOM	498	HN	SER	36	5.652	9.369	-4.743	1.00	0.52
ATOM	499	CA	SER	36	6.148	11.392	-4.196	1.00	0.66
ATOM	500	HA	SER	36	6.722	12.002	-4.877	1.00	0.73
ATOM	501	CB	SER	36	4.661	11.704	-4.365	1.00	0.75
ATOM	502	HB1	SER	36	4.479	12.737	-4.100	1.00	0.88
ATOM	503	HB2	SER	36	4.081	11.066	-3.722	1.00	0.71
ATOM	504	OG	SER	36	4.282	11.475	-5.716	1.00	0.81
ATOM	505	HG	SER	36	4.052	10.548	-5.807	1.00	1.17
ATOM	506	C	SER	36	6.570	11.704	-2.758	1.00	0.65
ATOM	507	O	SER	36	7.065	12.774	-2.467	1.00	0.75
ATOM	508	N	GLU	37	6.364	10.781	-1.856	1.00	0.59
ATOM	509	HN	GLU	37	5.953	9.929	-2.115	1.00	0.55
ATOM	510	CA	GLU	37	6.736	11.025	-0.431	1.00	0.66
ATOM	511	HA	GLU	37	6.817	12.086	-0.251	1.00	0.77
ATOM	512	CB	GLU	37	5.658	10.433	0.482	1.00	0.72
ATOM	513	HB1	GLU	37	6.004	10.451	1.504	1.00	0.80
ATOM	514	HB2	GLU	37	5.458	9.413	0.187	1.00	0.65
ATOM	515	CG	GLU	37	4.375	11.259	0.366	1.00	0.86
ATOM	516	HG1	GLU	37	4.043	11.267	-0.661	1.00	0.89
ATOM	517	HG2	GLU	37	4.568	12.271	0.691	1.00	1.11
ATOM	518	CD	GLU	37	3.288	10.638	1.245	1.00	1.09
ATOM	519	OE1	GLU	37	3.179	9.423	1.249	1.00	1.61
ATOM	520	OE2	GLU	37	2.582	11.388	1.899	1.00	1.69
ATOM	521	C	GLU	37	8.076	10.349	-0.132	1.00	0.58
ATOM	522	O	GLU	37	8.509	10.281	1.001	1.00	0.65
ATOM	523	N	TYR	38	8.737	9.860	-1.145	1.00	0.49
ATOM	524	HN	TYR	38	8.369	9.936	-2.049	1.00	0.47
ATOM	525	CA	TYR	38	10.057	9.200	-0.937	1.00	0.48
ATOM	526	HA	TYR	38	10.389	8.762	-1.866	1.00	0.47
ATOM	527	CB	TYR	38	11.075	10.242	-0.473	1.00	0.62
ATOM	528	HB1	TYR	38	12.041	9.775	-0.354	1.00	0.65
ATOM	529	HB2	TYR	38	10.758	10.661	0.469	1.00	0.69
ATOM	530	CG	TYR	38	11.171	11.338	-1.507	1.00	0 72
ATOM	531	CD1	TYR	38	10.437	12.519	-1.340	1.00	0.83
ATOM	532	HD1	TYR	38	9.807	12.645	-0.472	1.00	0.89
ATOM	533	CD2	TYR	38	11.988	11.173	-2.631	1.00	0.77
ATOM	534	HD2	TYR	38	12.553	10.262	-2.760	1.00	0.78
ATOM	535	CE1	TYR	38	10.520	13.535	-2.298	1.00	0.95
ATOM	536	HE1	TYR	38	9.954	14.446	-2.170	1.00	1.07
ATOM	537	CE2	TYR	38	12.071	12.191	-3.590	1.00	0.89
ATOM	538	HE2	TYR	38	12.702	12.065	-4.457	1.00	0.98
ATOM	539	CZ	TYR	38	11.338	13.372	-3.423	1.00	0.96

ATOM	540	HH	TYR	38	11.420	14.374	-4.368	1.00	1.10
ATOM	541	OH	TYR	38	10.671	14.284	-4.961	1.00	1.26
ATOM	542	C	TYR	38	9.923	8.105	0.122	1.00	0.45
ATOM	543	O	TYR	38	10.871	7.770	0.804	1.00	0.53
ATOM	544	N	SER	39	8.753	7.544	0.253	1.00	0.41
ATOM	545	HN	SER	39	8.009	7.832	-0.316	1.00	0.41
ATOM	546	CA	SER	39	8.539	6.463	1.257	1.00	0.44
ATOM	547	HA	SER	39	9.338	6.481	1.984	1.00	0.51
ATOM	548	CB	SER	39	7.201	6.687	1.965	1.00	0.52
ATOM	549	HB1	SER	39	7.369	7.244	2.877	1.00	1.14
ATOM	550	HB2	SER	39	6.750	5.741	2.208	1.00	1.14
ATOM	551	OG	SER	39	6.333	7.417	1.106	1.00	1.45
ATOM	552	HG	SER	39	5.440	7.094	1.244	1.00	1.88
ATOM	553	C	SER	39	8.544	5.114	0.532	1.00	0.37
ATOM	554	O	SER	39	7.896	4.168	0.936	1.00	0.37
ATOM	555	N	GLU	40	9.276	5.026	-0.546	1.00	0.36
ATOM	556	HN	GLU	40	9.787	5.803	-0.853	1.00	0.40
ATOM	557	CA	GLU	40	9.331	3.751	-1.314	1.00	0.35
ATOM	558	HA	GLU	40	8.330	3.447	-1.581	1.00	0.35
ATOM	559	CB	GLU	40	10.156	3.962	-2.584	1.00	0.41
ATOM	560	HB1	GLU	40	9.749	4.789	-3.146	1.00	0.45
ATOM	561	HB2	GLU	40	10.122	3.065	-3.185	1.00	0.42
ATOM	562	CG	GLU	40	11.606	4.270	-2.204	1.00	0.46
ATOM	563	HG1	GLU	40	12.083	3.370	-1.847	1.00	0.91
ATOM	564	HG2	GLU	40	11.622	5.020	-1.426	1.00	0.86
ATOM	565	CD	GLU	40	12.356	4.789	-3.431	1.00	1.09
ATOM	566	OE1	GLU	40	11.780	4.769	-4.506	1.00	1.76
ATOM	567	OE2	GLU	40	13.496	5.196	-3.276	1.00	1.77
ATOM	568	C	GLU	40	9.982	2.668	-0.455	1.00	0.37
ATOM	569	O	GLU	40	9.820	1.494	-0.694	1.00	0.37
ATOM	570	N	GLU	41	10.709	3.045	0.551	1.00	0.43
ATOM	571	HN	GLU	41	10.830	3.999	0.745	1.00	0.47
ATOM	572	CA	GLU	41	11.341	2.018	1.420	1.00	0.50
ATOM	573	HA	GLU	41	11.954	1.361	0.822	1.00	0.54
ATOM	574	CB	GLU	41	12.203	2.712	2.476	1.00	0.63
ATOM	575	HB1	GLU	41	12.956	3.314	1.989	1.00	0.75
ATOM	576	HB2	GLU	41	12.682	1.968	3.096	1.00	0.65
ATOM	577	CG	GLU	41	11.320	3.611	3.346	1.00	0.65
ATOM	578	HG1	GLU	41	10.948	3.045	4.186	1.00	0.98
ATOM	579	HG2	GLU	41	10.489	3.975	2.760	1.00	0.79
ATOM	580	CD	GLU	41	12.143	4.794	3.857	1.00	1.10
ATOM	581	OE1	GLU	41	11.545	5.789	4.231	1.00	1.72
ATOM	582	OE2	GLU	41	13.358	4.687	3.862	1.00	1.73
ATOM	583	C	GLU	41	10.232	1.212	2.104	1.00	0.45
ATOM	584	O	GLU	41	10.379	0.040	2.387	1.00	0.45
ATOM	585	N	ASN	42	9.124	1.849	2.378	1.00	0.42
ATOM	586	HN	ASN	42	9.040	2.797	2.143	1.00	0.44
ATOM	587	CA	ASN	42	7.990	1.153	3.053	1.00	0.41
ATOM	588	HA	ASN	42	8.316	0.797	4.018	1.00	0.45
ATOM	589	CB	ASN	42	6.842	2.144	3.250	1.00	0.44
ATOM	590	HB1	ASN	42	5.959	1.613	3.574	1.00	0.46
ATOM	591	HB2	ASN	42	6.638	2.646	2.316	1.00	0.41
ATOM	592	CG	ASN	42	7.231	3.176	4.308	1.00	0.51
ATOM	593	OD1	ASN	42	8.056	2.910	5.159	1.00	1.00
ATOM	594	ND2	ASN	42	6.667	4.352	4.291	1.00	1.28
ATOM	595	HD21	ASN	42	6.002	4.566	3.604	1.00	2.00
ATOM	596	HD22	ASN	42	6.907	5.020	4.965	1.00	1.32
ATOM	597	C	ASN	42	7.485	-0.035	2.223	1.00	0.36
ATOM	598	O	ASN	42	7.276	-1.113	2.744	1.00	0.36
ATOM	599	N	ILE	43	7.260	0.145	0.946	1.00	0.36
ATOM	600	HN	ILE	43	7.413	1.021	0.534	1.00	0.38
ATOM	601	CA	ILE	43	6.741	-0.993	0.129	1.00	0.35
ATOM	602	HA	ILE	43	5.915	-1.439	0.665	1.00	0.36
ATOM	603	CB	ILE	43	6.224	-0.485	-1.234	1.00	0.36
ATOM	604	HB	ILE	43	5.556	0.347	-1.071	1.00	0.40
ATOM	605	CG1	ILE	43	5.472	-1.611	-1.958	1.00	0.46
ATOM	606	HG11	ILE	43	6.092	-2.494	-1.985	1.00	0.55
ATOM	607	HG12	ILE	43	5.255	-1.297	-2.969	1.00	0.49
ATOM	608	CG2	ILE	43	7.383	-0.019	-2.115	1.00	0.45
ATOM	609	HG21	ILE	43	7.549	-0.739	-2.902	1.00	1.14
ATOM	610	HG22	ILE	43	8.269	0.075	-1.524	1.00	1.12
ATOM	611	HG23	ILE	43	7.139	0.938	-2.552	1.00	1.10
ATOM	612	CD1	ILE	43	4.154	-1.937	-1.238	1.00	0.59
ATOM	613	HD11	ILE	43	4.247	-2.890	-0.737	1.00	1.19
ATOM	614	HD12	ILE	43	3.354	-1.991	-1.962	1.00	1.22
ATOM	615	HD13	ILE	43	3.928	-1.171	-0.513	1.00	1.18
ATOM	616	C	ILE	43	7.829	-2.063	-0.035	1.00	0.36

ATOM	617		ILE	43	7.550	-3.244	0.022	1.00	0.36
ATOM	618	N	ASP	44	9.067	-1.678	-0.210	1.00	0.38
ATOM	619	HN	ASP	44	9.291	-0.724	-0.235	1.00	0.39
ATOM	620	CA	ASP	44	10.137	-2.707	-0.339	1.00	0.42
ATOM	621	HA	ASP	44	9.903	-3.382	-1.149	1.00	0.44
ATOM	622	CB	ASP	44	11.481	-2.023	-0.601	1.00	0.48
ATOM	623	HB1	ASP	44	12.277	-2.749	-0.521	1.00	0.52
ATOM	624	HB2	ASP	44	11.635	-1.239	0.126	1.00	0.48
ATOM	625	CG	ASP	44	11.483	-1.423	-2.008	1.00	0.53
ATOM	626	OD1	ASP	44	10.684	-1.862	-2.819	1.00	0.98
ATOM	627	OD2	ASP	44	12.282	-0.533	-2.250	1.00	0.85
ATOM	628	C	ASP	44	10.205	-3.480	0.978	1.00	0.38
ATOM	629	O	ASP	44	10.286	-4.692	1.005	1.00	0.40
ATOM	630	N	PHE	45	10.144	-2.771	2.072	1.00	0.36
ATOM	631	HN	PHE	45	10.059	-1.797	2.012	1.00	0.37
ATOM	632	CA	PHE	45	10.172	-3.426	3.408	1.00	0.34
ATOM	633	HA	PHE	45	11.069	-4.019	3.505	1.00	0.36
ATOM	634	CB	PHE	45	10.154	-2.333	4.482	1.00	0.35
ATOM	635	HB1	PHE	45	9.259	-1.739	4.371	1.00	0.36
ATOM	636	HB2	PHE	45	11.019	-1.699	4.358	1.00	0.40
ATOM	637	CG	PHE	45	10.180	-2.942	5.864	1.00	0.34
ATOM	638	CD1	PHE	45	8.979	-3.176	6.545	1.00	0.35
ATOM	639	HD1	PHE	45	8.037	-2.931	6.077	1.00	0.38
ATOM	640	CD2	PHE	45	11.402	-3.260	6.469	1.00	0.38
ATOM	641	HD2	PHE	45	12.328	-3.080	5.944	1.00	0.43
ATOM	642	CE1	PHE	45	8.998	-3.727	7.832	1.00	0.39
ATOM	643	HE1	PHE	45	8.070	-3.904	8.358	1.00	0.44
ATOM	644	CE2	PHE	45	11.422	-3.814	7.756	1.00	0.41
ATOM	645	HE2	PHE	45	12.364	-4.060	8.223	1.00	0.47
ATOM	646	CZ	PHE	45	10.220	-4.047	8.437	1.00	0.40
ATOM	647	HZ	PHE	45	10.236	-4.472	9.430	1.00	0.45
ATOM	648	C	PHE	45	8.942	-4.325	3.546	1.00	0.32
ATOM	649	O	PHE	45	9.010	-5.420	4.068	1.00	0.33
ATOM	650	N	TRP	46	7.816	-3.863	3.074	1.00	0.32
ATOM	651	HN	TRP	46	7.791	-2.977	2.656	1.00	0.33
ATOM	652	CA	TRP	46	6.569	-4.673	3.164	1.00	0.33
ATOM	653	HA	TRP	46	6.353	-4.885	4.201	1.00	0.34
ATOM	654	CB	TRP	46	5.409	-3.882	2.553	1.00	0.36
ATOM	655	HB1	TRP	46	5.625	-3.672	1.516	1.00	0.36
ATOM	656	HB2	TRP	46	5.287	-2.953	3.089	1.00	0.38
ATOM	657	CG	TRP	46	4.147	-4.679	2.647	1.00	0.38
ATOM	658	CD1	TRP	46	3.381	-4.785	3.758	1.00	0.47
ATOM	659	HD1	TRP	46	3.586	-4.316	4.709	1.00	0.55
ATOM	660	CD2	TRP	46	3.487	-5.471	1.618	1.00	0.42
ATOM	661	NE1	TRP	46	2.295	-5.593	3.477	1.00	0.50
ATOM	662	HE1	TRP	46	1.587	-5.830	4.112	1.00	0.58
ATOM	663	CE2	TRP	46	2.315	-6.041	2.171	1.00	0.47
ATOM	664	CE3	TRP	46	3.787	-5.750	0.273	1.00	0.50
ATOM	665	HE3	TRP	46	4.674	-5.331	-0.177	1.00	0.52
ATOM	666	CZ2	TRP	46	1.471	-6.856	1.417	1.00	0.54
ATOM	667	HZ2	TRP	46	0.582	-7.278	1.863	1.00	0.58
ATOM	668	CZ3	TRP	46	2.939	-6.571	-0.490	1.00	0.61
ATOM	669	HZ3	TRP	46	3.179	-6.779	-1.522	1.00	0.73
ATOM	670	CH2	TRP	46	1.784	-7.123	0.082	1.00	0.61
ATOM	671	HH2	TRP	46	1.136	-7.753	-0.509	1.00	0.70
ATOM	672	C	TRP	46	6.758	-5.991	2.403	1.00	0.34
ATOM	673	O	TRP	46	6.316	-7.037	2.836	1.00	0.36
ATOM	674	N	ILE	47	7.406	-5.948	1.266	1.00	0.35
ATOM	675	HN	ILE	47	7.750	-5.094	0.930	1.00	0.35
ATOM	676	CA	ILE	47	7.613	-7.199	0.476	1.00	0.39
ATOM	677	HA	ILE	47	6.659	-7.670	0.292	1.00	0.41
ATOM	678	CB	ILE	47	8.280	-6.857	-0.859	1.00	0.44
ATOM	679	HB	ILE	47	9.177	-6.286	-0.669	1.00	0.44
ATOM	680	CG1	ILE	47	7.308	-6.033	-1.715	1.00	0.46
ATOM	681	HG11	ILE	47	6.922	-5.214	-1.127	1.00	0.43
ATOM	682	HG12	ILE	47	6.488	-6.663	-2.030	1.00	0.48
ATOM	683	CG2	ILE	47	8.643	-8.149	-1.595	1.00	0.50
ATOM	684	HG21	ILE	47	9.497	-8.607	-1.119	1.00	1.26
ATOM	685	HG22	ILE	47	8.882	-7.924	-2.623	1.00	1.09
ATOM	686	HG23	ILE	47	7.805	-8.830	-1.561	1.00	1.06
ATOM	687	CD1	ILE	47	8.023	-5.475	-2.954	1.00	0.53
ATOM	688	HD11	ILE	47	7.886	-6.152	-3.783	1.00	1.12
ATOM	689	HD12	ILE	47	9.077	-5.362	-2.752	1.00	1.14
ATOM	690	HD13	ILE	47	7.602	-4.513	-3.206	1.00	1.18
ATOM	691	C	ILE	47	8.512	-8.157	1.260	1.00	0.38
ATOM	692	O	ILE	47	8.271	-9.347	1.309	1.00	0.39
ATOM	693	N	SER	48	9.538	-7.649	1.884	1.00	0.38

ATOM	694	H	SER	48	9.713	-6.686	1.842	1.00	0.38
ATOM	695	HA	SER	48	10.435	-8.537	2.672	1.00	0.41
ATOM	696	HA	SER	48	10.745	-9.373	2.060	1.00	0.43
ATOM	697	CB	SER	48	11.666	-7.753	3.131	1.00	0.43
ATOM	698	HB1	SER	48	12.173	-7.343	2.267	1.00	0.45
ATOM	699	HB2	SER	48	12.337	-8.409	3.659	1.00	0.46
ATOM	700	OG	SER	48	11.257	-6.703	3.998	1.00	0.43
ATOM	701	HG	SER	48	11.122	-7.077	4.872	1.00	0.98
ATOM	702	C	SER	48	9.666	-9.051	3.888	1.00	0.41
ATOM	703	O	SER	48	9.778	-10.198	4.272	1.00	0.42
ATOM	704	N	CYS	49	8.879	-8.204	4.493	1.00	0.41
ATOM	705	HN	CYS	49	8.803	-7.285	4.160	1.00	0.41
ATOM	706	CA	CYS	49	8.088	-8.628	5.681	1.00	0.44
ATOM	707	HA	CYS	49	8.752	-9.033	6.431	1.00	0.45
ATOM	708	CB	CYS	49	7.347	-7.420	6.253	1.00	0.49
ATOM	709	HB1	CYS	49	6.369	-7.726	6.595	1.00	1.07
ATOM	710	HB2	CYS	49	7.241	-6.666	5.487	1.00	1.09
ATOM	711	SG	CYS	49	8.285	-6.738	7.642	1.00	1.57
ATOM	712	HG	CYS	49	7.704	-6.155	8.136	1.00	1.99
ATOM	713	C	CYS	49	7.073	-9.695	5.262	1.00	0.44
ATOM	714	O	CYS	49	6.812	-10.635	5.987	1.00	0.45
ATOM	715	N	GLU	50	6.497	-9.556	4.097	1.00	0.46
ATOM	716	HN	GLU	50	6.722	-8.791	3.529	1.00	0.46
ATOM	717	CA	GLU	50	5.498	-10.563	3.636	1.00	0.49
ATOM	718	HA	GLU	50	4.673	-10.598	4.332	1.00	0.52
ATOM	719	CB	GLU	50	4.980	-10.171	2.250	1.00	0.52
ATOM	720	HB1	GLU	50	4.419	-10.991	1.829	1.00	0.93
ATOM	721	HB2	GLU	50	5.817	-9.938	1.607	1.00	0.86
ATOM	722	CG	GLU	50	4.074	-8.945	2.371	1.00	0.83
ATOM	723	HG1	GLU	50	4.303	-8.247	1.580	1.00	1.28
ATOM	724	HG2	GLU	50	4.236	-8.471	3.329	1.00	1.55
ATOM	725	CD	GLU	50	2.611	-9.379	2.257	1.00	1.44
ATOM	726	OE1	GLU	50	1.829	-8.989	3.108	1.00	2.08
ATOM	727	OE2	GLU	50	2.298	-10.094	1.319	1.00	2.13
ATOM	728	C	GLU	50	6.162	-11.937	3.561	1.00	0.46
ATOM	729	O	GLU	50	5.635	-12.918	4.047	1.00	0.48
ATOM	730	N	GLU	51	7.325	-12.014	2.976	1.00	0.43
ATOM	731	HN	GLU	51	7.744	-11.209	2.604	1.00	0.43
ATOM	732	CA	GLU	51	8.025	-13.325	2.899	1.00	0.43
ATOM	733	HA	GLU	51	7.408	-14.035	2.367	1.00	0.47
ATOM	734	CB	GLU	51	9.363	-13.157	2.175	1.00	0.44
ATOM	735	HB1	GLU	51	9.941	-14.064	2.274	1.00	0.46
ATOM	736	HB2	GLU	51	9.907	-12.333	2.612	1.00	0.42
ATOM	737	CG	GLU	51	9.114	-12.874	0.692	1.00	0.51
ATOM	738	HG1	GLU	51	8.465	-12.018	0.592	1.00	0.73
ATOM	739	HG2	GLU	51	8.649	-13.736	0.235	1.00	0.69
ATOM	740	CD	GLU	51	10.446	-12.585	-0.002	1.00	0.63
ATOM	741	OE1	GLU	51	10.431	-12.357	-1.200	1.00	1.41
ATOM	742	OE2	GLU	51	11.460	-12.595	0.678	1.00	1.24
ATOM	743	C	GLU	51	8.272	-13.822	4.321	1.00	0.40
ATOM	744	O	GLU	51	8.141	-14.992	4.619	1.00	0.41
ATOM	745	N	TYR	52	8.633	-12.928	5.197	1.00	0.37
ATOM	746	HN	TYR	52	8.731	-11.992	4.924	1.00	0.37
ATOM	747	CA	TYR	52	8.899	-13.316	6.607	1.00	0.35
ATOM	748	HA	TYR	52	9.696	-14.043	6.639	1.00	0.34
ATOM	749	CB	TYR	52	9.312	-12.067	7.390	1.00	0.36
ATOM	750	HB1	TYR	52	8.442	-11.454	7.573	1.00	0.40
ATOM	751	HB2	TYR	52	10.032	-11.505	6.814	1.00	0.38
ATOM	752	CG	TYR	52	9.929	-12.468	8.708	1.00	0.31
ATOM	753	CD1	TYR	52	11.322	-12.552	8.828	1.00	0.30
ATOM	754	HD1	TYR	52	11.951	-12.330	7.979	1.00	0.33
ATOM	755	CD2	TYR	52	9.113	-12.755	9.807	1.00	0.30
ATOM	756	HD2	TYR	52	8.039	-12.690	9.715	1.00	0.33
ATOM	757	CE1	TYR	52	11.899	-12.921	10.048	1.00	0.28
ATOM	758	HE1	TYR	52	12.973	-12.986	10.139	1.00	0.29
ATOM	759	CE2	TYR	52	9.690	-13.125	11.027	1.00	0.29
ATOM	760	HE2	TYR	52	9.061	-13.347	11.875	1.00	0.31
ATOM	761	CZ	TYR	52	11.083	-13.209	11.148	1.00	0.28
ATOM	762	OH	TYR	52	11.652	-13.575	12.351	1.00	0.29
ATOM	763	HH	TYR	52	11.898	-12.774	12.819	1.00	0.88
ATOM	764	C	TYR	52	7.627	-13.919	7.220	1.00	0.38
ATOM	765	O	TYR	52	7.678	-14.896	7.941	1.00	0.38
ATOM	766	N	LYS	53	6.485	-13.343	6.940	1.00	0.43
ATOM	767	HN	LYS	53	6.464	-12.555	6.358	1.00	0.44
ATOM	768	CA	LYS	53	5.212	-13.884	7.508	1.00	0.48
ATOM	769	HA	LYS	53	5.331	-14.019	8.573	1.00	0.49
ATOM	770	CB	LYS	53	4.060	-12.909	7.256	1.00	0.58

ATOM	771	"B1	LYS	53	3.121	-13.421	-7.407	1.00	0.64
ATOM	772	32	LYS	53	4.112	-12.549	6.239	1.00	0.58
ATOM	773	CG	LYS	53	4.152	-11.724	8.219	1.00	0.66
ATOM	774	HG1	LYS	53	5.045	-11.156	8.008	1.00	0.79
ATOM	775	HG2	LYS	53	4.187	-12.088	9.236	1.00	0.94
ATOM	776	CD	LYS	53	2.923	-10.826	8.033	1.00	0.81
ATOM	777	HD1	LYS	53	2.035	-11.438	7.968	1.00	1.25
ATOM	778	HD2	LYS	53	3.032	-10.255	7.122	1.00	1.23
ATOM	779	CE	LYS	53	2.791	-9.870	9.220	1.00	1.12
ATOM	780	HE1	LYS	53	2.836	-10.430	10.142	1.00	1.54
ATOM	781	HE2	LYS	53	1.844	-9.356	9.164	1.00	1.59
ATOM	782	NZ	LYS	53	3.902	-8.878	9.186	1.00	2.03
ATOM	783	HZ1	LYS	53	4.149	-8.668	8.198	1.00	2.49
ATOM	784	HZ2	LYS	53	4.733	-9.271	9.675	1.00	2.51
ATOM	785	HZ3	LYS	53	3.602	-8.003	9.659	1.00	2.52
ATOM	786	C	LYS	53	4.859	-15.231	6.872	1.00	0.48
ATOM	787	O	LYS	53	4.084	-15.991	7.417	1.00	0.52
ATOM	788	N	LYS	54	5.394	-15.537	5.722	1.00	0.46
ATOM	789	HN	LYS	54	6.008	-14.915	5.278	1.00	0.46
ATOM	790	CA	LYS	54	5.041	-16.836	5.083	1.00	0.50
ATOM	791	HA	LYS	54	4.020	-17.089	5.331	1.00	0.53
ATOM	792	CB	LYS	54	5.178	-16.721	3.562	1.00	0.56
ATOM	793	HB1	LYS	54	5.090	-17.700	3.117	1.00	0.60
ATOM	794	HB2	LYS	54	6.142	-16.298	3.318	1.00	0.54
ATOM	795	CG	LYS	54	4.068	-15.816	3.021	1.00	0.62
ATOM	796	HG1	LYS	54	4.154	-14.836	3.466	1.00	0.60
ATOM	797	HG2	LYS	54	3.105	-16.240	3.269	1.00	0.66
ATOM	798	CD	LYS	54	4.197	-15.695	1.502	1.00	0.71
ATOM	799	HD1	LYS	54	4.109	-16.674	1.054	1.00	0.84
ATOM	800	HD2	LYS	54	5.160	-15.271	1.254	1.00	0.88
ATOM	801	CE	LYS	54	3.086	-14.790	0.965	1.00	0.89
ATOM	802	HE1	LYS	54	2.472	-14.449	1.785	1.00	1.34
ATOM	803	HE2	LYS	54	2.478	-15.343	0.265	1.00	1.45
ATOM	804	NZ	LYS	54	3.693	-13.617	0.277	1.00	1.70
ATOM	805	HZ1	LYS	54	4.116	-13.922	-0.622	1.00	2.20
ATOM	806	HZ2	LYS	54	4.429	-13.202	0.885	1.00	2.24
ATOM	807	HZ3	LYS	54	2.958	-12.906	0.088	1.00	2.18
ATOM	808	C	LYS	54	5.970	-17.929	5.606	1.00	0.47
ATOM	809	O	LYS	54	5.586	-19.077	5.721	1.00	0.52
ATOM	810	N	ILE	55	7.178	-17.586	5.954	1.00	0.43
ATOM	811	HN	ILE	55	7.468	-16.654	5.877	1.00	0.43
ATOM	812	CA	ILE	55	8.102	-18.616	6.501	1.00	0.44
ATOM	813	HA	ILE	55	8.062	-19.504	5.886	1.00	0.49
ATOM	814	CB	ILE	55	9.531	-18.067	6.523	1.00	0.42
ATOM	815	HB	ILE	55	9.545	-17.129	7.057	1.00	0.40
ATOM	816	CG1	ILE	55	10.012	-17.858	5.077	1.00	0.43
ATOM	817	HG11	ILE	55	9.228	-17.386	4.505	1.00	0.44
ATOM	818	HG12	ILE	55	10.244	-18.818	4.637	1.00	0.47
ATOM	819	CG2	ILE	55	10.446	-19.072	7.229	1.00	0.44
ATOM	820	HG21	ILE	55	11.472	-18.778	7.096	1.00	1.12
ATOM	821	HG22	ILE	55	10.297	-20.055	6.805	1.00	1.10
ATOM	822	HG23	ILE	55	10.214	-19.096	8.283	1.00	1.11
ATOM	823	CD1	ILE	55	11.267	-16.972	5.041	1.00	0.43
ATOM	824	HD11	ILE	55	11.181	-16.182	5.772	1.00	1.04
ATOM	825	HD12	ILE	55	11.368	-16.536	4.058	1.00	1.11
ATOM	826	HD13	ILE	55	12.141	-17.568	5.256	1.00	1.07
ATOM	827	C	ILE	55	7.654	-18.956	7.925	1.00	0.46
ATOM	828	O	ILE	55	7.679	-18.117	8.803	1.00	0.45
ATOM	829	N	LYS	56	7.242	-20.173	8.159	1.00	0.53
ATOM	830	HN	LYS	56	7.228	-20.831	7.433	1.00	0.57
ATOM	831	CA	LYS	56	6.786	-20.564	9.526	1.00	0.60
ATOM	832	HA	LYS	56	6.530	-19.676	10.084	1.00	0.60
ATOM	833	CB	LYS	56	5.549	-21.450	9.410	1.00	0.71
ATOM	834	HB1	LYS	56	5.320	-21.883	10.372	1.00	0.76
ATOM	835	HB2	LYS	56	5.739	-22.235	8.693	1.00	0.72
ATOM	836	CG	LYS	56	4.372	-20.592	8.941	1.00	0.76
ATOM	837	HG1	LYS	56	4.605	-20.155	7.982	1.00	0.92
ATOM	838	HG2	LYS	56	4.196	-19.804	9.660	1.00	1.08
ATOM	839	CD	LYS	56	3.113	-21.450	8.815	1.00	1.01
ATOM	840	HD1	LYS	56	2.896	-21.918	9.763	1.00	1.45
ATOM	841	HD2	LYS	56	3.269	-22.210	8.062	1.00	1.34
ATOM	842	CE	LYS	56	1.938	-20.558	8.407	1.00	1.20
ATOM	843	HE1	LYS	56	2.278	-19.819	7.696	1.00	1.51
ATOM	844	HE2	LYS	56	1.546	-20.060	9.282	1.00	1.81
ATOM	845	NZ	LYS	56	0.867	-21.388	7.789	1.00	1.88
ATOM	846	HZ1	LYS	56	0.749	-21.115	6.793	1.00	2.37
ATOM	847	HZ2	LYS	56	-0.027	-21.236	8.299	1.00	2.42

ATOM	848	Z3	LYS	56	1.131	-22.392	7.842	1.00	2.24
ATOM	849	-	LYS	56	7.899	-21.308	10.259	1.00	0.59
ATOM	850	O	LYS	56	7.723	-21.765	11.369	1.00	0.66
ATOM	851	N	SER	57	9.044	-21.421	9.651	1.00	0.54
ATOM	852	HN	SER	57	9.159	-21.038	8.757	1.00	0.52
ATOM	853	CA	SER	57	10.182	-22.120	10.314	1.00	0.56
ATOM	854	HA	SER	57	9.802	-22.839	11.018	1.00	0.62
ATOM	855	CB	SER	57	11.010	-22.840	9.251	1.00	0.60
ATOM	856	HB1	SER	57	11.904	-23.245	9.707	1.00	0.61
ATOM	857	HB2	SER	57	11.291	-22.142	8.479	1.00	0.57
ATOM	858	OG	SER	57	10.235	-23.883	8.677	1.00	0.69
ATOM	859	HG	SER	57	9.561	-23.481	8.123	1.00	1.15
ATOM	860	C	SER	57	11.078	-21.070	11.006	1.00	0.50
ATOM	861	O	SER	57	11.730	-20.304	10.328	1.00	0.45
ATOM	862	N	PRO	58	11.127	-21.000	12.328	1.00	0.51
ATOM	863	CA	PRO	58	11.984	-19.977	12.992	1.00	0.48
ATOM	864	HA	PRO	58	11.693	-18.986	12.685	1.00	0.44
ATOM	865	CB	PRO	58	11.659	-20.165	14.475	1.00	0.55
ATOM	866	HB1	PRO	58	11.180	-19.277	14.857	1.00	0.57
ATOM	867	HB2	PRO	58	12.572	-20.350	15.025	1.00	0.58
ATOM	868	CG	PRO	58	10.713	-21.360	14.630	1.00	0.60
ATOM	869	HG1	PRO	58	9.810	-21.045	15.129	1.00	0.64
ATOM	870	HG2	PRO	58	11.198	-22.132	15.211	1.00	0.64
ATOM	871	CD	PRO	58	10.366	-21.902	13.241	1.00	0.59
ATOM	872	HD2	PRO	58	10.699	-22.928	13.144	1.00	0.63
ATOM	873	HD1	PRO	58	9.309	-21.820	13.057	1.00	0.61
ATOM	874	C	PRO	58	13.479	-20.198	12.738	1.00	0.47
ATOM	875	O	PRO	58	14.312	-19.439	13.194	1.00	0.48
ATOM	876	N	SER	59	13.829	-21.230	12.020	1.00	0.49
ATOM	877	HN	SER	59	13.146	-21.836	11.663	1.00	0.51
ATOM	878	CA	SER	59	15.273	-21.490	11.752	1.00	0.52
ATOM	879	HA	SER	59	15.856	-21.166	12.601	1.00	0.54
ATOM	880	CB	SER	59	15.491	-22.987	11.535	1.00	0.59
ATOM	881	HB1	SER	59	15.026	-23.539	12.341	1.00	0.97
ATOM	882	HB2	SER	59	16.547	-23.200	11.520	1.00	1.14
ATOM	883	OG	SER	59	14.920	-23.368	10.291	1.00	1.30
ATOM	884	HG	SER	59	14.343	-22.658	9.999	1.00	1.81
ATOM	885	C	SER	59	15.726	-20.723	10.506	1.00	0.48
ATOM	886	O	SER	59	16.876	-20.346	10.389	1.00	0.51
ATOM	887	N	LYS	60	14.844	-20.487	9.571	1.00	0.46
ATOM	888	HN	LYS	60	13.920	-20.797	9.674	1.00	0.46
ATOM	889	CA	LYS	60	15.257	-19.746	8.344	1.00	0.45
ATOM	890	HA	LYS	60	16.288	-19.968	8.117	1.00	0.49
ATOM	891	CB	LYS	60	14.372	-20.154	7.165	1.00	0.49
ATOM	892	HB1	LYS	60	14.552	-19.487	6.335	1.00	0.51
ATOM	893	HB2	LYS	60	13.338	-20.085	7.460	1.00	0.46
ATOM	894	CG	LYS	60	14.671	-21.589	6.731	1.00	0.57
ATOM	895	HG1	LYS	60	14.342	-22.275	7.496	1.00	0.82
ATOM	896	HG2	LYS	60	15.734	-21.705	6.570	1.00	1.07
ATOM	897	CD	LYS	60	13.917	-21.874	5.428	1.00	1.20
ATOM	898	HD1	LYS	60	14.502	-21.522	4.592	1.00	1.80
ATOM	899	HD2	LYS	60	12.968	-21.357	5.444	1.00	1.78
ATOM	900	CE	LYS	60	13.675	-23.376	5.280	1.00	1.67
ATOM	901	HE1	LYS	60	13.104	-23.560	4.381	1.00	2.00
ATOM	902	HE2	LYS	60	13.124	-23.739	6.135	1.00	2.17
ATOM	903	NZ	LYS	60	14.981	-24.086	5.191	1.00	2.48
ATOM	904	HZ1	LYS	60	14.935	-24.804	4.441	1.00	2.80
ATOM	905	HZ2	LYS	60	15.187	-24.546	6.101	1.00	3.08
ATOM	906	HZ3	LYS	60	15.732	-23.403	4.968	1.00	2.81
ATOM	907	C	LYS	60	15.086	-18.242	8.570	1.00	0.39
ATOM	908	O	LYS	60	15.656	-17.432	7.867	1.00	0.40
ATOM	909	N	LEU	61	14.295	-17.862	9.535	1.00	0.34
ATOM	910	HN	LEU	61	13.833	-18.532	10.085	1.00	0.35
ATOM	911	CA	LEU	61	14.080	-16.406	9.787	1.00	0.30
ATOM	912	HA	LEU	61	13.695	-15.937	8.895	1.00	0.30
ATOM	913	CB	LEU	61	13.082	-16.224	10.935	1.00	0.28
ATOM	914	HB1	LEU	61	12.898	-15.171	11.086	1.00	0.26
ATOM	915	HB2	LEU	61	13.496	-16.648	11.836	1.00	0.30
ATOM	916	CG	LEU	61	11.760	-16.926	10.607	1.00	0.29
ATOM	917	HG	LEU	61	11.939	-17.985	10.500	1.00	0.32
ATOM	918	CD1	LEU	61	10.767	-16.695	11.747	1.00	0.31
ATOM	919	HD11	LEU	61	11.298	-16.675	12.688	1.00	1.07
ATOM	920	HD12	LEU	61	10.041	-17.495	11.761	1.00	1.07
ATOM	921	HD13	LEU	61	10.262	-15.753	11.599	1.00	1.02
ATOM	922	CD2	LEU	61	11.175	-16.374	9.305	1.00	0.29
ATOM	923	HD21	LEU	61	11.610	-16.894	8.466	1.00	1.05
ATOM	924	HD22	LEU	61	11.395	-15.322	9.228	1.00	1.00

ATOM	925	[illegible]23	LEU	61	10.105	-16.519	9.302	1.00	1.00
ATOM	926	[illegible]	LEU	61	15.406	-15.745	10.173	1.00	0.32
ATOM	927	O	LEU	61	15.699	-14.637	9.772	1.00	0.32
ATOM	928	N	SER	62	16.202	-16.411	10.963	1.00	0.35
ATOM	929	HN	SER	62	15.939	-17.299	11.284	1.00	0.37
ATOM	930	CA	SER	62	17.501	-15.819	11.396	1.00	0.40
ATOM	931	HA	SER	62	17.295	-14.972	12.033	1.00	0.39
ATOM	932	CB	SER	62	18.288	-16.854	12.204	1.00	0.46
ATOM	933	HB1	SER	62	19.339	-16.786	11.954	1.00	0.81
ATOM	934	HB2	SER	62	17.925	-17.842	11.979	1.00	0.76
ATOM	935	OG	SER	62	18.101	-16.602	13.590	1.00	0.90
ATOM	936	HG	SER	62	18.764	-15.966	13.869	1.00	1.29
ATOM	937	C	SER	62	18.326	-15.333	10.188	1.00	0.43
ATOM	938	O	SER	62	18.585	-14.153	10.065	1.00	0.43
ATOM	939	N	PRO	63	18.749	-16.208	9.298	1.00	0.46
ATOM	940	CA	PRO	63	19.553	-15.775	8.121	1.00	0.51
ATOM	941	HA	PRO	63	20.579	-15.618	8.406	1.00	0.56
ATOM	942	CB	PRO	63	19.467	-16.990	7.197	1.00	0.56
ATOM	943	HB1	PRO	63	20.459	-17.291	6.900	1.00	0.66
ATOM	944	HB2	PRO	63	18.885	-16.738	6.321	1.00	0.58
ATOM	945	CG	PRO	63	18.790	-18.137	7.955	1.00	0.52
ATOM	946	HG1	PRO	63	19.453	-18.988	7.993	1.00	0.57
ATOM	947	HG2	PRO	63	17.876	-18.411	7.450	1.00	0.50
ATOM	948	CD	PRO	63	18.476	-17.669	9.379	1.00	0.48
ATOM	949	HD2	PRO	63	17.445	-17.871	9.625	1.00	0.43
ATOM	950	HD1	PRO	63	19.145	-18.138	10.080	1.00	0.52
ATOM	951	C	PRO	63	18.998	-14.526	7.425	1.00	0.47
ATOM	952	O	PRO	63	19.684	-13.534	7.280	1.00	0.48
ATOM	953	N	LYS	64	17.773	-14.567	6.977	1.00	0.44
ATOM	954	HN	LYS	64	17.233	-15.377	7.089	1.00	0.45
ATOM	955	CA	LYS	64	17.205	-13.380	6.277	1.00	0.44
ATOM	956	HA	LYS	64	17.910	-13.040	5.532	1.00	0.48
ATOM	957	CB	LYS	64	15.891	-13.762	5.589	1.00	0.48
ATOM	958	HB1	LYS	64	16.029	-14.687	5.051	1.00	0.57
ATOM	959	HB2	LYS	64	15.617	-12.982	4.895	1.00	0.50
ATOM	960	CG	LYS	64	14.782	-13.937	6.639	1.00	0.47
ATOM	961	HG1	LYS	64	14.491	-12.969	7.019	1.00	0.52
ATOM	962	HG2	LYS	64	15.153	-14.543	7.452	1.00	0.65
ATOM	963	CD	LYS	64	13.554	-14.620	6.017	1.00	0.65
ATOM	964	HD1	LYS	64	12.944	-15.036	6.804	1.00	1.34
ATOM	965	HD2	LYS	64	13.871	-15.413	5.356	1.00	1.14
ATOM	966	CE	LYS	64	12.726	-13.599	5.228	1.00	1.10
ATOM	967	HE1	LYS	64	13.339	-12.750	4.972	1.00	1.80
ATOM	968	HE2	LYS	64	11.893	-13.270	5.831	1.00	1.66
ATOM	969	NZ	LYS	64	12.214	-14.237	3.982	1.00	1.78
ATOM	970	HZ1	LYS	64	11.179	-14.312	4.032	1.00	2.21
ATOM	971	HZ2	LYS	64	12.627	-15.187	3.885	1.00	2.30
ATOM	972	HZ3	LYS	64	12.478	-13.657	3.161	1.00	2.22
ATOM	973	C	LYS	64	16.958	-12.252	7.282	1.00	0.37
ATOM	974	O	LYS	64	17.022	-11.087	6.942	1.00	0.37
ATOM	975	N	ALA	65	16.675	-12.578	8.515	1.00	0.35
ATOM	976	HN	ALA	65	16.623	-13.522	8.781	1.00	0.37
ATOM	977	CA	ALA	65	16.426	-11.505	9.517	1.00	0.31
ATOM	978	HA	ALA	65	15.572	-10.919	9.210	1.00	0.31
ATOM	979	CB	ALA	65	16.150	-12.132	10.884	1.00	0.33
ATOM	980	HB1	ALA	65	16.918	-12.856	11.109	1.00	1.02
ATOM	981	HB2	ALA	65	15.187	-12.621	10.868	1.00	1.03
ATOM	982	HB3	ALA	65	16.150	-11.362	11.640	1.00	1.02
ATOM	983	C	ALA	65	17.658	-10.602	9.606	1.00	0.32
ATOM	984	O	ALA	65	17.550	-9.392	9.575	1.00	0.31
ATOM	985	N	LYS	66	18.830	-11.172	9.710	1.00	0.36
ATOM	986	HN	LYS	66	18.903	-12.149	9.728	1.00	0.38
ATOM	987	CA	LYS	66	20.054	-10.325	9.790	1.00	0.39
ATOM	988	HA	LYS	66	19.992	-9.685	10.656	1.00	0.39
ATOM	989	CB	LYS	66	21.302	-11.208	9.901	1.00	0.47
ATOM	990	HB1	LYS	66	22.180	-10.612	9.704	1.00	0.50
ATOM	991	HB2	LYS	66	21.240	-12.006	9.176	1.00	0.49
ATOM	992	CG	LYS	66	21.403	-11.808	11.305	1.00	0.50
ATOM	993	HG1	LYS	66	20.530	-12.412	11.506	1.00	0.47
ATOM	994	HG2	LYS	66	21.467	-11.011	12.033	1.00	0.50
ATOM	995	CD	LYS	66	22.658	-12.684	11.385	1.00	0.60
ATOM	996	HD1	LYS	66	23.521	-12.100	11.100	1.00	0.89
ATOM	997	HD2	LYS	66	22.553	-13.522	10.711	1.00	0.79
ATOM	998	CE	LYS	66	22.847	-13.201	12.814	1.00	0.91
ATOM	999	HE1	LYS	66	22.576	-12.429	13.518	1.00	1.53
ATOM	1000	HE2	LYS	66	23.881	-13.474	12.962	1.00	1.37
ATOM	1001	NZ	LYS	66	21.985	-14.396	13.031	1.00	1.77

ATOM	1002	?1	LYS	66	22.475	-15.068	3.655	1.00	2.25
ATOM	1003	aZ2	LYS	66	21.787	-14.852	2.117	1.00	2.26
ATOM	1004	HZ3	LYS	66	21.092	-14.104	13.474	1.00	2.32
ATOM	1005	C	LYS	66	20.169	-9.465	8.533	1.00	0.39
ATOM	1006	O	LYS	66	20.497	-8.298	8.599	1.00	0.39
ATOM	1007	N	LYS	67	19.911	-10.030	7.385	1.00	0.40
ATOM	1008	HN	LYS	67	19.653	-10.975	7.348	1.00	0.42
ATOM	1009	CA	LYS	67	20.019	-9.233	6.133	1.00	0.42
ATOM	1010	HA	LYS	67	21.007	-8.801	6.069	1.00	0.46
ATOM	1011	CB	LYS	67	19.789	-10.150	4.931	1.00	0.47
ATOM	1012	HB1	LYS	67	19.743	-9.560	4.028	1.00	0.51
ATOM	1013	HB2	LYS	67	18.860	-10.688	5.059	1.00	0.45
ATOM	1014	CG	LYS	67	20.949	-11.143	4.832	1.00	0.54
ATOM	1015	HG1	LYS	67	20.996	-11.732	5.735	1.00	0.73
ATOM	1016	HG2	LYS	67	21.876	-10.601	4.708	1.00	0.88
ATOM	1017	CD	LYS	67	20.737	-12.070	3.634	1.00	1.02
ATOM	1018	HD1	LYS	67	20.694	-11.484	2.728	1.00	1.58
ATOM	1019	HD2	LYS	67	19.811	-12.612	3.758	1.00	1.44
ATOM	1020	CE	LYS	67	21.902	-13.058	3.543	1.00	1.16
ATOM	1021	HE1	LYS	67	21.922	-13.672	4.432	1.00	1.68
ATOM	1022	HE2	LYS	67	22.831	-12.514	3.461	1.00	1.61
ATOM	1023	NZ	LYS	67	21.726	-13.925	2.344	1.00	1.81
ATOM	1024	HZ1	LYS	67	20.813	-13.714	1.894	1.00	2.28
ATOM	1025	HZ2	LYS	67	21.749	-14.925	2.633	1.00	2.30
ATOM	1026	HZ3	LYS	67	22.494	-13.742	1.668	1.00	2.26
ATOM	1027	C	LYS	67	18.977	-8.113	6.147	1.00	0.38
ATOM	1028	O	LYS	67	19.294	-6.962	5.928	1.00	0.40
ATOM	1029	N	ILE	68	17.740	-8.430	6.425	1.00	0.34
ATOM	1030	HN	ILE	68	17.500	-9.361	6.616	1.00	0.34
ATOM	1031	CA	ILE	68	16.700	-7.363	6.471	1.00	0.33
ATOM	1032	HA	ILE	68	16.701	-6.825	5.535	1.00	0.36
ATOM	1033	CB	ILE	68	15.318	-7.985	6.700	1.00	0.34
ATOM	1034	HB	ILE	68	15.379	-8.690	7.516	1.00	0.34
ATOM	1035	CG1	ILE	68	14.877	-8.706	5.415	1.00	0.38
ATOM	1036	HG11	ILE	68	15.722	-9.227	4.992	1.00	0.39
ATOM	1037	HG12	ILE	68	14.517	-7.976	4.705	1.00	0.40
ATOM	1038	CG2	ILE	68	14.317	-6.879	7.055	1.00	0.37
ATOM	1039	HG21	ILE	68	13.310	-7.250	6.944	1.00	1.13
ATOM	1040	HG22	ILE	68	14.462	-6.036	6.399	1.00	1.06
ATOM	1041	HG23	ILE	68	14.472	-6.569	8.079	1.00	1.06
ATOM	1042	CD1	ILE	68	13.757	-9.716	5.710	1.00	0.41
ATOM	1043	HD11	ILE	68	13.980	-10.259	6.615	1.00	1.07
ATOM	1044	HD12	ILE	68	13.681	-10.412	4.888	1.00	1.07
ATOM	1045	HD13	ILE	68	12.818	-9.196	5.822	1.00	1.16
ATOM	1046	C	ILE	68	17.025	-6.398	7.608	1.00	0.31
ATOM	1047	O	ILE	68	16.998	-5.194	7.443	1.00	0.32
ATOM	1048	N	TYR	69	17.336	-6.917	8.762	1.00	0.30
ATOM	1049	HN	TYR	69	17.354	-7.890	8.874	1.00	0.31
ATOM	1050	CA	TYR	69	17.665	-6.032	9.908	1.00	0.30
ATOM	1051	HA	TYR	69	16.818	-5.405	10.128	1.00	0.31
ATOM	1052	CB	TYR	69	17.999	-6.888	11.129	1.00	0.32
ATOM	1053	HB1	TYR	69	18.840	-7.526	10.902	1.00	0.34
ATOM	1054	HB2	TYR	69	17.143	-7.496	11.384	1.00	0.34
ATOM	1055	CG	TYR	69	18.346	-5.995	12.296	1.00	0.32
ATOM	1056	CD1	TYR	69	19.645	-5.490	12.428	1.00	0.35
ATOM	1057	HD1	TYR	69	20.395	-5.731	11.689	1.00	0.38
ATOM	1058	CD2	TYR	69	17.374	-5.683	13.253	1.00	0.34
ATOM	1059	HD2	TYR	69	16.372	-6.074	13.152	1.00	0.36
ATOM	1060	CE1	TYR	69	19.972	-4.672	13.515	1.00	0.38
ATOM	1061	HE1	TYR	69	20.974	-4.283	13.617	1.00	0.42
ATOM	1062	CE2	TYR	69	17.699	-4.864	14.340	1.00	0.37
ATOM	1063	HE2	TYR	69	16.949	-4.623	15.078	1.00	0.41
ATOM	1064	CZ	TYR	69	18.999	-4.359	14.472	1.00	0.38
ATOM	1065	OH	TYR	69	19.320	-3.553	15.544	1.00	0.42
ATOM	1066	HH	TYR	69	20.265	-3.385	15.516	1.00	1.03
ATOM	1067	C	TYR	69	18.875	-5.168	9.555	1.00	0.31
ATOM	1068	O	TYR	69	18.864	-3.965	9.721	1.00	0.33
ATOM	1069	N	ASN	70	19.922	-5.778	9.072	1.00	0.33
ATOM	1070	HN	ASN	70	19.910	-6.750	8.950	1.00	0.34
ATOM	1071	CA	ASN	70	21.137	-4.999	8.710	1.00	0.36
ATOM	1072	HA	ASN	70	21.424	-4.381	9.545	1.00	0.39
ATOM	1073	CB	ASN	70	22.282	-5.958	8.376	1.00	0.40
ATOM	1074	HB1	ASN	70	23.104	-5.403	7.950	1.00	0.43
ATOM	1075	HB2	ASN	70	21.938	-6.695	7.665	1.00	0.39
ATOM	1076	CG	ASN	70	22.752	-6.658	9.653	1.00	0.44
ATOM	1077	OD1	ASN	70	22.635	-6.116	10.734	1.00	1.05
ATOM	1078	ND2	ASN	70	23.282	-7.847	9.573	1.00	0.99

ATOM	1079	21	ASN	70	23.376	-8.285	8.702	1.00	1.65
ATOM	1080	22	ASN	70	23.586	-8.303	0.386	1.00	0.99
ATOM	1081	C	ASN	70	20.846	-4.115	7.497	1.00	0.36
ATOM	1082	O	ASN	70	21.461	-3.088	7.305	1.00	0.41
ATOM	1083	N	GLU	71	19.934	-4.518	6.659	1.00	0.34
ATOM	1084	HN	GLU	71	19.460	-5.361	6.816	1.00	0.33
ATOM	1085	CA	GLU	71	19.631	-3.703	5.451	1.00	0.37
ATOM	1086	HA	GLU	71	20.542	-3.239	5.103	1.00	0.41
ATOM	1087	CB	GLU	71	19.089	-4.618	4.347	1.00	0.42
ATOM	1088	HB1	GLU	71	18.117	-4.990	4.633	1.00	0.89
ATOM	1089	HB2	GLU	71	19.766	-5.448	4.204	1.00	0.65
ATOM	1090	CG	GLU	71	18.967	-3.832	3.039	1.00	1.01
ATOM	1091	HG1	GLU	71	19.928	-3.418	2.777	1.00	1.38
ATOM	1092	HG2	GLU	71	18.251	-3.033	3.165	1.00	1.52
ATOM	1093	CD	GLU	71	18.496	-4.768	1.923	1.00	1.15
ATOM	1094	OE1	GLU	71	18.168	-4.270	0.858	1.00	1.71
ATOM	1095	OE2	GLU	71	18.475	-5.967	2.151	1.00	1.57
ATOM	1096	C	GLU	71	18.599	-2.605	5.760	1.00	0.37
ATOM	1097	O	GLU	71	18.784	-1.461	5.395	1.00	0.56
ATOM	1098	N	PHE	72	17.492	-2.951	6.376	1.00	0.36
ATOM	1099	HN	PHE	72	17.343	-3.887	6.625	1.00	0.50
ATOM	1100	CA	PHE	72	16.426	-1.926	6.640	1.00	0.38
ATOM	1101	HA	PHE	72	16.558	-1.101	5.959	1.00	0.42
ATOM	1102	CB	PHE	72	15.065	-2.563	6.364	1.00	0.41
ATOM	1103	HB1	PHE	72	14.283	-1.905	6.712	1.00	0.45
ATOM	1104	HB2	PHE	72	14.998	-3.508	6.884	1.00	0.43
ATOM	1105	CG	PHE	72	14.904	-2.793	4.880	1.00	0.39
ATOM	1106	CD1	PHE	72	14.338	-1.798	4.075	1.00	0.45
ATOM	1107	HD1	PHE	72	14.019	-0.865	4.514	1.00	0.51
ATOM	1108	CD2	PHE	72	15.318	-4.003	4.311	1.00	0.39
ATOM	1109	HD2	PHE	72	15.757	-4.768	4.931	1.00	0.42
ATOM	1110	CE1	PHE	72	14.185	-2.014	2.700	1.00	0.47
ATOM	1111	HE1	PHE	72	13.748	-1.246	2.078	1.00	0.54
ATOM	1112	CE2	PHE	72	15.166	-4.218	2.936	1.00	0.40
ATOM	1113	HE2	PHE	72	15.485	-5.152	2.497	1.00	0.43
ATOM	1114	CZ	PHE	72	14.599	-3.224	2.131	1.00	0.43
ATOM	1115	HZ	PHE	72	14.480	-3.391	1.070	1.00	0.46
ATOM	1116	C	PHE	72	16.428	-1.382	8.083	1.00	0.37
ATOM	1117	O	PHE	72	16.004	-0.265	8.308	1.00	0.45
ATOM	1118	N	ILE	73	16.844	-2.144	9.065	1.00	0.33
ATOM	1119	HN	ILE	73	17.154	-3.056	8.887	1.00	0.31
ATOM	1120	CA	ILE	73	16.790	-1.622	10.476	1.00	0.35
ATOM	1121	HA	ILE	73	16.040	-0.850	10.543	1.00	0.39
ATOM	1122	CB	ILE	73	16.417	-2.762	11.430	1.00	0.34
ATOM	1123	HB	ILE	73	17.183	-3.521	11.381	1.00	0.33
ATOM	1124	CG1	ILE	73	15.064	-3.376	11.022	1.00	0.35
ATOM	1125	HG11	ILE	73	14.816	-4.175	11.706	1.00	0.40
ATOM	1126	HG12	ILE	73	15.145	-3.778	10.024	1.00	0.35
ATOM	1127	CG2	ILE	73	16.343	-2.234	12.869	1.00	0.39
ATOM	1128	HG21	ILE	73	17.257	-2.477	13.389	1.00	1.05
ATOM	1129	HG22	ILE	73	15.507	-2.691	13.378	1.00	1.11
ATOM	1130	HG23	ILE	73	16.212	-1.162	12.854	1.00	1.12
ATOM	1131	CD1	ILE	73	13.944	-2.324	11.048	1.00	0.40
ATOM	1132	HD11	ILE	73	14.174	-1.548	11.760	1.00	1.07
ATOM	1133	HD12	ILE	73	13.015	-2.799	11.330	1.00	1.09
ATOM	1134	HD13	ILE	73	13.838	-1.890	10.065	1.00	1.13
ATOM	1135	C	ILE	73	18.141	-1.048	10.913	1.00	0.38
ATOM	1136	O	ILE	73	18.235	-0.385	11.928	1.00	0.40
ATOM	1137	N	SER	74	19.188	-1.295	10.182	1.00	0.45
ATOM	1138	HN	SER	74	19.108	-1.837	9.370	1.00	0.51
ATOM	1139	CA	SER	74	20.516	-0.755	10.599	1.00	0.50
ATOM	1140	HA	SER	74	20.767	-1.142	11.576	1.00	0.55
ATOM	1141	CB	SER	74	21.586	-1.181	9.600	1.00	0.65
ATOM	1142	HB1	SER	74	21.160	-1.205	8.610	1.00	1.28
ATOM	1143	HB2	SER	74	21.953	-2.158	9.857	1.00	1.25
ATOM	1144	OG	SER	74	22.663	-0.254	9.645	1.00	1.39
ATOM	1145	HG	SER	74	23.480	-0.752	9.720	1.00	1.87
ATOM	1146	C	SER	74	20.479	0.771	10.656	1.00	0.43
ATOM	1147	O	SER	74	20.057	1.428	9.725	1.00	0.43
ATOM	1148	N	VAL	75	20.949	1.341	11.731	1.00	0.44
ATOM	1149	HN	VAL	75	21.307	0.793	12.460	1.00	0.48
ATOM	1150	CA	VAL	75	20.976	2.824	11.832	1.00	0.47
ATOM	1151	HA	VAL	75	19.974	3.213	11.719	1.00	0.47
ATOM	1152	CB	VAL	75	21.543	3.241	13.191	1.00	0.55
ATOM	1153	HB	VAL	75	21.665	4.314	13.216	1.00	0.65
ATOM	1154	CG1	VAL	75	20.580	2.811	14.300	1.00	0.58
ATOM	1155	HG11	VAL	75	20.495	1.735	14.307	1.00	1.22

ATOM	1156	12	VAL	75	19.609	3.248	4.122	1.00	1.13
ATOM	1157	13	VAL	75	20.957	3.149	5.254	1.00	1.18
ATOM	1158	CG2	VAL	75	22.898	2.565	13.405	1.00	0.62
ATOM	1159	HG21	VAL	75	23.659	3.319	13.546	1.00	1.17
ATOM	1160	HG22	VAL	75	23.142	1.964	12.541	1.00	1.22
ATOM	1161	HG23	VAL	75	22.851	1.933	14.280	1.00	1.19
ATOM	1162	C	VAL	75	21.865	3.363	10.711	1.00	0.51
ATOM	1163	O	VAL	75	21.825	4.529	10.374	1.00	0.58
ATOM	1164	N	GLN	76	22.672	2.511	10.135	1.00	0.53
ATOM	1165	HN	GLN	76	22.683	1.576	10.431	1.00	0.51
ATOM	1166	CA	GLN	76	23.575	2.948	9.032	1.00	0.64
ATOM	1167	HA	GLN	76	23.706	4.019	9.069	1.00	0.69
ATOM	1168	CB	GLN	76	24.932	2.257	9.185	1.00	0.75
ATOM	1169	HB1	GLN	76	25.538	2.460	8.316	1.00	0.85
ATOM	1170	HB2	GLN	76	24.782	1.191	9.279	1.00	0.74
ATOM	1171	CG	GLN	76	25.643	2.783	10.434	1.00	0.81
ATOM	1172	HG1	GLN	76	25.021	2.617	11.300	1.00	0.85
ATOM	1173	HG2	GLN	76	25.831	3.841	10.322	1.00	1.02
ATOM	1174	CD	GLN	76	26.971	2.043	10.613	1.00	1.29
ATOM	1175	OE1	GLN	76	27.267	1.119	9.882	1.00	1.74
ATOM	1176	NE2	GLN	76	27.786	2.408	11.564	1.00	1.77
ATOM	1177	HE21	GLN	76	27.546	3.151	12.157	1.00	1.99
ATOM	1178	HE22	GLN	76	28.638	1.940	11.686	1.00	2.18
ATOM	1179	C	GLN	76	22.959	2.549	7.688	1.00	0.61
ATOM	1180	O	GLN	76	23.519	2.798	6.639	1.00	0.71
ATOM	1181	N	ALA	77	21.812	1.927	7.712	1.00	0.52
ATOM	1182	HN	ALA	77	21.379	1.733	8.570	1.00	0.46
ATOM	1183	CA	ALA	77	21.160	1.506	6.438	1.00	0.53
ATOM	1184	HA	ALA	77	21.728	0.704	5.991	1.00	0.62
ATOM	1185	CB	ALA	77	19.736	1.022	6.723	1.00	0.51
ATOM	1186	HB1	ALA	77	19.207	1.775	7.288	1.00	1.18
ATOM	1187	HB2	ALA	77	19.772	0.106	7.290	1.00	1.14
ATOM	1188	HB3	ALA	77	19.223	0.848	5.789	1.00	1.09
ATOM	1189	C	ALA	77	21.098	2.688	5.471	1.00	0.57
ATOM	1190	O	ALA	77	20.834	3.808	5.860	1.00	0.58
ATOM	1191	N	THR	78	21.329	2.445	4.210	1.00	0.64
ATOM	1192	HN	THR	78	21.531	1.533	3.916	1.00	0.68
ATOM	1193	CA	THR	78	21.269	3.553	3.218	1.00	0.71
ATOM	1194	HA	THR	78	21.864	4.385	3.566	1.00	0.78
ATOM	1195	CB	THR	78	21.807	3.063	1.871	1.00	0.82
ATOM	1196	HB	THR	78	21.908	3.900	1.197	1.00	0.89
ATOM	1197	OG1	THR	78	20.904	2.115	1.320	1.00	0.80
ATOM	1198	HG1	THR	78	20.897	1.344	1.891	1.00	1.14
ATOM	1199	CG2	THR	78	23.175	2.409	2.071	1.00	0.94
ATOM	1200	HG21	THR	78	23.866	3.135	2.475	1.00	1.58
ATOM	1201	HG22	THR	78	23.545	2.050	1.122	1.00	1.33
ATOM	1202	HG23	THR	78	23.081	1.581	2.758	1.00	1.29
ATOM	1203	C	THR	78	19.814	3.993	3.055	1.00	0.66
ATOM	1204	O	THR	78	19.532	5.083	2.597	1.00	0.74
ATOM	1205	N	LYS	79	18.891	3.145	3.431	1.00	0.58
ATOM	1206	HN	LYS	79	19.153	2.274	3.796	1.00	0.57
ATOM	1207	CA	LYS	79	17.443	3.488	3.310	1.00	0.59
ATOM	1208	HA	LYS	79	17.336	4.545	3.119	1.00	0.67
ATOM	1209	CB	LYS	79	16.826	2.697	2.150	1.00	0.64
ATOM	1210	HB1	LYS	79	17.139	3.132	1.213	1.00	0.72
ATOM	1211	HB2	LYS	79	15.749	2.738	2.223	1.00	0.67
ATOM	1212	CG	LYS	79	17.285	1.236	2.210	1.00	0.62
ATOM	1213	HG1	LYS	79	16.974	0.793	3.143	1.00	0.58
ATOM	1214	HG2	LYS	79	18.362	1.194	2.134	1.00	0.63
ATOM	1215	CD	LYS	79	16.664	0.456	1.049	1.00	0.75
ATOM	1216	HD1	LYS	79	16.979	0.892	0.113	1.00	1.13
ATOM	1217	HD2	LYS	79	15.586	0.499	1.122	1.00	1.16
ATOM	1218	CE	LYS	79	17.122	-1.002	1.109	1.00	1.04
ATOM	1219	HE1	LYS	79	16.646	-1.495	1.943	1.00	1.68
ATOM	1220	HE2	LYS	79	18.195	-1.038	1.235	1.00	1.62
ATOM	1221	NZ	LYS	79	16.747	-1.694	-0.157	1.00	1.61
ATOM	1222	HZ1	LYS	79	15.881	-1.268	-0.541	1.00	2.15
ATOM	1223	HZ2	LYS	79	16.583	-2.703	0.037	1.00	2.00
ATOM	1224	HZ3	LYS	79	17.517	-1.594	-0.848	1.00	2.07
ATOM	1225	C	LYS	79	16.723	3.139	4.616	1.00	0.51
ATOM	1226	O	LYS	79	15.948	2.207	4.682	1.00	0.50
ATOM	1227	N	GLU	80	16.969	3.886	5.657	1.00	0.51
ATOM	1228	HN	GLU	80	17.594	4.638	5.585	1.00	0.55
ATOM	1229	CA	GLU	80	16.296	3.598	6.955	1.00	0.47
ATOM	1230	HA	GLU	80	16.552	2.602	7.282	1.00	0.47
ATOM	1231	CB	GLU	80	16.743	4.615	8.006	1.00	0.55
ATOM	1232	HB1	GLU	80	16.129	4.512	8.888	1.00	0.55

ATOM	1233	[illegible]2	GLU	80	16.638	5.614	7.608	1.00	0.60
ATOM	1234	[illegible]	GLU	80	18.205	4.365	3.377	1.00	0.62
ATOM	1235	HG1	GLU	80	18.822	4.451	7.496	1.00	0.93
ATOM	1236	HG2	GLU	80	18.306	3.373	8.794	1.00	0.82
ATOM	1237	CD	GLU	80	18.646	5.402	9.410	1.00	1.22
ATOM	1238	OE1	GLU	80	19.839	5.528	9.622	1.00	1.84
ATOM	1239	OE2	GLU	80	17.781	6.050	9.976	1.00	1.91
ATOM	1240	C	GLU	80	14.783	3.704	6.770	1.00	0.43
ATOM	1241	O	GLU	80	14.298	4.526	6.019	1.00	0.49
ATOM	1242	N	VAL	81	14.035	2.882	7.451	1.00	0.39
ATOM	1243	HN	VAL	81	14.449	2.228	8.052	1.00	0.41
ATOM	1244	CA	VAL	81	12.552	2.933	7.317	1.00	0.37
ATOM	1245	HA	VAL	81	12.286	3.377	6.369	1.00	0.41
ATOM	1246	CB	VAL	81	11.986	1.514	7.394	1.00	0.38
ATOM	1247	HB	VAL	81	10.927	1.560	7.604	1.00	0.40
ATOM	1248	CG1	VAL	81	12.211	0.801	6.060	1.00	0.43
ATOM	1249	HG11	VAL	81	12.464	-0.233	6.243	1.00	1.14
ATOM	1250	HG12	VAL	81	13.019	1.280	5.527	1.00	1.05
ATOM	1251	HG13	VAL	81	11.309	0.851	5.468	1.00	1.13
ATOM	1252	CG2	VAL	81	12.698	0.745	8.508	1.00	0.38
ATOM	1253	HG21	VAL	81	12.756	1.363	9.392	1.00	0.98
ATOM	1254	HG22	VAL	81	13.696	0.484	8.186	1.00	1.17
ATOM	1255	HG23	VAL	81	12.146	-0.156	8.734	1.00	1.05
ATOM	1256	C	VAL	81	11.974	3.772	8.457	1.00	0.37
ATOM	1257	O	VAL	81	12.532	3.837	9.535	1.00	0.38
ATOM	1258	N	ASN	82	10.865	4.420	8.231	1.00	0.41
ATOM	1259	HN	ASN	82	10.429	4.361	7.355	1.00	0.44
ATOM	1260	CA	ASN	82	10.267	5.255	9.309	1.00	0.45
ATOM	1261	HA	ASN	82	11.035	5.861	9.765	1.00	0.47
ATOM	1262	CB	ASN	82	9.188	6.160	8.713	1.00	0.55
ATOM	1263	HB1	ASN	82	9.652	7.005	8.228	1.00	0.63
ATOM	1264	HB2	ASN	82	8.536	6.510	9.501	1.00	0.61
ATOM	1265	CG	ASN	82	8.373	5.370	7.689	1.00	0.56
ATOM	1266	OD1	ASN	82	8.264	4.164	7.781	1.00	1.10
ATOM	1267	ND2	ASN	82	7.790	6.004	6.709	1.00	1.18
ATOM	1268	HD21	ASN	82	7.876	6.977	6.634	1.00	1.85
ATOM	1269	HD22	ASN	82	7.264	5.507	6.049	1.00	1.22
ATOM	1270	C	ASN	82	9.641	4.343	10.364	1.00	0.42
ATOM	1271	O	ASN	82	8.602	3.750	10.153	1.00	0.45
ATOM	1272	N	LEU	83	10.273	4.228	11.498	1.00	0.40
ATOM	1273	HN	LEU	83	11.110	4.717	11.640	1.00	0.41
ATOM	1274	CA	LEU	83	9.733	3.357	12.580	1.00	0.42
ATOM	1275	HA	LEU	83	8.664	3.264	12.468	1.00	0.46
ATOM	1276	CB	LEU	83	10.381	1.969	12.510	1.00	0.41
ATOM	1277	HB1	LEU	83	10.164	1.424	13.417	1.00	0.43
ATOM	1278	HB2	LEU	83	11.451	2.083	12.413	1.00	0.40
ATOM	1279	CG	LEU	83	9.846	1.190	11.302	1.00	0.45
ATOM	1280	HG	LEU	83	9.973	1.781	10.408	1.00	0.46
ATOM	1281	CD1	LEU	83	10.631	-0.114	11.154	1.00	0.49
ATOM	1282	HD11	LEU	83	10.352	-0.599	10.230	1.00	1.04
ATOM	1283	HD12	LEU	83	10.407	-0.765	11.985	1.00	1.16
ATOM	1284	HD13	LEU	83	11.689	0.103	11.141	1.00	1.14
ATOM	1285	CD2	LEU	83	8.358	0.868	11.496	1.00	0.51
ATOM	1286	HD21	LEU	83	8.129	0.810	12.549	1.00	1.21
ATOM	1287	HD22	LEU	83	8.132	-0.079	11.028	1.00	1.10
ATOM	1288	HD23	LEU	83	7.761	1.644	11.042	1.00	1.06
ATOM	1289	C	LEU	83	10.050	3.988	13.935	1.00	0.45
ATOM	1290	O	LEU	83	10.908	4.840	14.048	1.00	0.48
ATOM	1291	N	ASP	84	9.366	3.575	14.965	1.00	0.49
ATOM	1292	HN	ASP	84	8.679	2.886	14.853	1.00	0.50
ATOM	1293	CA	ASP	84	9.632	4.152	16.310	1.00	0.55
ATOM	1294	HA	ASP	84	9.636	5.231	16.247	1.00	0.61
ATOM	1295	CB	ASP	84	8.542	3.700	17.283	1.00	0.64
ATOM	1296	HB1	ASP	84	8.735	4.117	18.260	1.00	1.28
ATOM	1297	HB2	ASP	84	8.541	2.621	17.345	1.00	1.26
ATOM	1298	CG	ASP	84	7.178	4.184	16.786	1.00	1.25
ATOM	1299	OD1	ASP	84	6.183	3.793	17.374	1.00	2.03
ATOM	1300	OD2	ASP	84	7.152	4.927	15.819	1.00	2.00
ATOM	1301	C	ASP	84	10.994	3.662	16.807	1.00	0.50
ATOM	1302	O	ASP	84	11.517	2.672	16.335	1.00	0.46
ATOM	1303	N	SER	85	11.575	4.349	17.752	1.00	0.55
ATOM	1304	HN	SER	85	11.139	5.146	18.118	1.00	0.61
ATOM	1305	CA	SER	85	12.905	3.922	18.273	1.00	0.56
ATOM	1306	HA	SER	85	13.579	3.757	17.445	1.00	0.55
ATOM	1307	CB	SER	85	13.475	5.012	19.182	1.00	0.68
ATOM	1308	HB1	SER	85	14.435	4.693	19.566	1.00	1.19
ATOM	1309	HB2	SER	85	12.802	5.186	20.005	1.00	1.27

ATOM	1310		SER	85	13.624	6.213	18.437	1.00	1.48
ATOM	1311		SER	85	14.112	6.007	17.637	1.00	1.97
ATOM	1312	C	SER	85	12.749	2.625	19.067	1.00	0.51
ATOM	1313	O	SER	85	13.688	1.874	19.239	1.00	0.51
ATOM	1314	N	CYS	86	11.569	2.354	19.553	1.00	0.53
ATOM	1315	HN	CYS	86	10.824	2.972	19.403	1.00	0.56
ATOM	1316	CA	CYS	86	11.355	1.104	20.334	1.00	0.54
ATOM	1317	HA	CYS	86	12.225	0.903	20.940	1.00	0.58
ATOM	1318	CB	CYS	86	10.129	1.272	21.236	1.00	0.64
ATOM	1319	HB1	CYS	86	9.326	0.650	20.869	1.00	1.29
ATOM	1320	HB2	CYS	86	9.816	2.306	21.228	1.00	1.16
ATOM	1321	SG	CYS	86	10.548	0.782	22.927	1.00	1.74
ATOM	1322	HG	CYS	86	9.773	0.922	23.476	1.00	2.26
ATOM	1323	C	CYS	86	11.120	-0.061	19.371	1.00	0.48
ATOM	1324	O	CYS	86	11.554	-1.171	19.606	1.00	0.47
ATOM	1325	N	THR	87	10.433	0.183	18.290	1.00	0.45
ATOM	1326	HN	THR	87	10.091	1.086	18.122	1.00	0.48
ATOM	1327	CA	THR	87	10.167	-0.910	17.314	1.00	0.42
ATOM	1328	HA	THR	87	9.615	-1.701	17.800	1.00	0.46
ATOM	1329	CB	THR	87	9.344	-0.356	16.145	1.00	0.45
ATOM	1330	HB	THR	87	9.912	0.401	15.628	1.00	0.45
ATOM	1331	OG1	THR	87	8.140	0.208	16.647	1.00	0.50
ATOM	1332	HG1	THR	87	7.466	-0.476	16.638	1.00	0.94
ATOM	1333	CG2	THR	87	9.000	-1.485	15.169	1.00	0.48
ATOM	1334	HG21	THR	87	9.908	-1.938	14.800	1.00	1.14
ATOM	1335	HG22	THR	87	8.439	-1.083	14.340	1.00	1.02
ATOM	1336	HG23	THR	87	8.406	-2.231	15.677	1.00	1.19
ATOM	1337	C	THR	87	11.496	-1.463	16.789	1.00	0.38
ATOM	1338	O	THR	87	11.717	-2.658	16.771	1.00	0.38
ATOM	1339	N	ARG	88	12.383	-0.606	16.354	1.00	0.37
ATOM	1340	HN	ARG	88	12.188	0.354	16.370	1.00	0.39
ATOM	1341	CA	ARG	88	13.689	-1.094	15.825	1.00	0.37
ATOM	1342	HA	ARG	88	13.517	-1.748	14.983	1.00	0.37
ATOM	1343	CB	ARG	88	14.545	0.094	15.382	1.00	0.41
ATOM	1344	HB1	ARG	88	15.533	-0.253	15.118	1.00	0.45
ATOM	1345	HB2	ARG	88	14.619	0.805	16.192	1.00	0.43
ATOM	1346	CG	ARG	88	13.907	0.771	14.169	1.00	0.47
ATOM	1347	HG1	ARG	88	13.000	1.271	14.470	1.00	0.85
ATOM	1348	HG2	ARG	88	13.678	0.026	13.420	1.00	0.82
ATOM	1349	CD	ARG	88	14.885	1.795	13.590	1.00	0.93
ATOM	1350	HD1	ARG	88	15.525	1.310	12.867	1.00	1.47
ATOM	1351	HD2	ARG	88	15.489	2.206	14.384	1.00	1.51
ATOM	1352	NE	ARG	88	14.123	2.890	12.929	1.00	1.81
ATOM	1353	HE	ARG	88	13.166	2.783	12.748	1.00	2.38
ATOM	1354	CZ	ARG	88	14.728	4.002	12.610	1.00	2.49
ATOM	1355	NH1	ARG	88	14.055	4.979	12.068	1.00	3.58
ATOM	1356	HH11	ARG	88	13.075	4.877	11.896	1.00	3.99
ATOM	1357	HH12	ARG	88	14.519	5.831	11.825	1.00	4.19
ATOM	1358	NH2	ARG	88	16.008	4.134	12.829	1.00	2.58
ATOM	1359	HH21	ARG	88	16.524	3.383	13.241	1.00	2.27
ATOM	1360	HH22	ARG	88	16.472	4.985	12.585	1.00	3.35
ATOM	1361	C	ARG	88	14.433	-1.857	16.921	1.00	0.37
ATOM	1362	O	ARG	88	14.927	-2.947	16.707	1.00	0.36
ATOM	1363	N	GLU	89	14.521	-1.292	18.094	1.00	0.40
ATOM	1364	HN	GLU	89	14.119	-0.412	18.247	1.00	0.42
ATOM	1365	CA	GLU	89	15.238	-1.987	19.199	1.00	0.43
ATOM	1366	HA	GLU	89	16.263	-2.158	18.911	1.00	0.44
ATOM	1367	CB	GLU	89	15.198	-1.120	20.459	1.00	0.49
ATOM	1368	HB1	GLU	89	15.560	-1.691	21.301	1.00	0.53
ATOM	1369	HB2	GLU	89	14.182	-0.806	20.648	1.00	0.50
ATOM	1370	CG	GLU	89	16.086	0.110	20.262	1.00	0.53
ATOM	1371	HG1	GLU	89	15.724	0.684	19.422	1.00	0.73
ATOM	1372	HG2	GLU	89	17.102	-0.206	20.073	1.00	0.73
ATOM	1373	CD	GLU	89	16.046	0.975	21.523	1.00	0.95
ATOM	1374	OE1	GLU	89	16.839	1.898	21.609	1.00	1.64
ATOM	1375	OE2	GLU	89	15.223	0.700	22.380	1.00	1.54
ATOM	1376	C	GLU	89	14.559	-3.325	19.479	1.00	0.41
ATOM	1377	O	GLU	89	15.207	-4.326	19.711	1.00	0.42
ATOM	1378	N	GLU	90	13.257	-3.352	19.456	1.00	0.42
ATOM	1379	HN	GLU	90	12.753	-2.535	19.265	1.00	0.42
ATOM	1380	CA	GLU	90	12.542	-4.628	19.717	1.00	0.44
ATOM	1381	HA	GLU	90	12.802	-4.990	20.701	1.00	0.48
ATOM	1382	CB	GLU	90	11.032	-4.395	19.645	1.00	0.49
ATOM	1383	HB1	GLU	90	10.749	-4.177	18.626	1.00	0.75
ATOM	1384	HB2	GLU	90	10.766	-3.563	20.280	1.00	0.91
ATOM	1385	CG	GLU	90	10.301	-5.653	20.116	1.00	1.00
ATOM	1386	HG1	GLU	90	10.670	-5.941	21.090	1.00	1.59

ATOM	1387	G2	GLU	90	10.474	-6.455	9.413	1.00	1.45
ATOM	1388	D	GLU	90	8.802	-5.368	0.207	1.00	1.19
ATOM	1389	OE1	GLU	90	8.052	-6.305	20.424	1.00	1.64
ATOM	1390	OE2	GLU	90	8.429	-4.215	20.058	1.00	1.85
ATOM	1391	C	GLU	90	12.958	-5.663	18.671	1.00	0.40
ATOM	1392	O	GLU	90	13.167	-6.820	18.979	1.00	0.43
ATOM	1393	N	THR	91	13.085	-5.259	17.433	1.00	0.37
ATOM	1394	HN	THR	91	12.916	-4.321	17.199	1.00	0.36
ATOM	1395	CA	THR	91	13.492	-6.227	16.378	1.00	0.36
ATOM	1396	HA	THR	91	12.808	-7.063	16.370	1.00	0.39
ATOM	1397	CB	THR	91	13.482	-5.543	15.009	1.00	0.35
ATOM	1398	HB	THR	91	14.321	-4.868	14.934	1.00	0.34
ATOM	1399	OG1	THR	91	12.267	-4.824	14.849	1.00	0.43
ATOM	1400	HG1	THR	91	12.455	-4.032	14.340	1.00	1.03
ATOM	1401	CG2	THR	91	13.591	-6.600	13.910	1.00	0.39
ATOM	1402	HG21	THR	91	14.000	-6.151	13.017	1.00	1.03
ATOM	1403	HG22	THR	91	12.610	-6.998	13.695	1.00	1.06
ATOM	1404	HG23	THR	91	14.239	-7.398	14.240	1.00	1.18
ATOM	1405	C	THR	91	14.904	-6.726	16.678	1.00	0.36
ATOM	1406	O	THR	91	15.208	-7.887	16.506	1.00	0.41
ATOM	1407	N	SER	92	15.770	-5.850	17.119	1.00	0.35
ATOM	1408	HN	SER	92	15.498	-4.916	17.243	1.00	0.34
ATOM	1409	CA	SER	92	17.170	-6.263	17.422	1.00	0.39
ATOM	1410	HA	SER	92	17.634	-6.646	16.526	1.00	0.41
ATOM	1411	CB	SER	92	17.957	-5.050	17.920	1.00	0.42
ATOM	1412	HB1	SER	92	17.820	-4.227	17.231	1.00	0.43
ATOM	1413	HB2	SER	92	19.004	-5.296	17.977	1.00	0.51
ATOM	1414	OG	SER	92	17.490	-4.685	19.212	1.00	0.40
ATOM	1415	HG	SER	92	16.642	-5.112	19.353	1.00	0.98
ATOM	1416	C	SER	92	17.170	-7.345	18.505	1.00	0.41
ATOM	1417	O	SER	92	17.917	-8.300	18.443	1.00	0.47
ATOM	1418	N	ARG	93	16.344	-7.202	19.502	1.00	0.40
ATOM	1419	HN	ARG	93	15.750	-6.424	19.541	1.00	0.39
ATOM	1420	CA	ARG	93	16.305	-8.228	20.580	1.00	0.45
ATOM	1421	HA	ARG	93	17.314	-8.430	20.906	1.00	0.50
ATOM	1422	CB	ARG	93	15.486	-7.706	21.767	1.00	0.49
ATOM	1423	HB1	ARG	93	15.348	-8.502	22.482	1.00	0.52
ATOM	1424	HB2	ARG	93	14.523	-7.360	21.419	1.00	0.47
ATOM	1425	CG	ARG	93	16.249	-6.545	22.426	1.00	0.55
ATOM	1426	HG1	ARG	93	16.224	-5.689	21.768	1.00	0.81
ATOM	1427	HG2	ARG	93	17.276	-6.837	22.589	1.00	0.95
ATOM	1428	CD	ARG	93	15.616	-6.163	23.771	1.00	1.01
ATOM	1429	HD1	ARG	93	16.381	-5.752	24.417	1.00	1.67
ATOM	1430	HD2	ARG	93	15.192	-7.035	24.239	1.00	1.59
ATOM	1431	NE	ARG	93	14.544	-5.150	23.560	1.00	1.59
ATOM	1432	HE	ARG	93	14.468	-4.684	22.702	1.00	2.15
ATOM	1433	CZ	ARG	93	13.713	-4.876	24.530	1.00	2.23
ATOM	1434	NH1	ARG	93	12.783	-3.976	24.363	1.00	3.17
ATOM	1435	HH11	ARG	93	12.705	-3.492	23.491	1.00	3.53
ATOM	1436	HH12	ARG	93	12.149	-3.768	25.109	1.00	3.77
ATOM	1437	NH2	ARG	93	13.817	-5.502	25.671	1.00	2.56
ATOM	1438	HH21	ARG	93	14.532	-6.189	25.800	1.00	2.42
ATOM	1439	HH22	ARG	93	13.182	-5.294	26.415	1.00	3.34
ATOM	1440	C	ARG	93	15.696	-9.526	20.034	1.00	0.44
ATOM	1441	O	ARG	93	16.049	-10.611	20.450	1.00	0.46
ATOM	1442	N	ASN	94	14.781	-9.419	19.108	1.00	0.43
ATOM	1443	HN	ASN	94	14.510	-8.533	18.790	1.00	0.44
ATOM	1444	CA	ASN	94	14.142	-10.642	18.535	1.00	0.46
ATOM	1445	HA	ASN	94	13.738	-11.243	19.336	1.00	0.48
ATOM	1446	CB	ASN	94	13.012	-10.233	17.589	1.00	0.52
ATOM	1447	HB1	ASN	94	12.667	-11.099	17.045	1.00	0.56
ATOM	1448	HB2	ASN	94	13.376	-9.491	16.893	1.00	0.53
ATOM	1449	CG	ASN	94	11.854	-9.648	18.399	1.00	0.57
ATOM	1450	OD1	ASN	94	11.720	-9.922	19.575	1.00	1.33
ATOM	1451	ND2	ASN	94	11.005	-8.848	17.814	1.00	1.12
ATOM	1452	HD21	ASN	94	11.114	-8.628	16.865	1.00	1.88
ATOM	1453	HD22	ASN	94	10.258	-8.469	18.323	1.00	1.13
ATOM	1454	C	ASN	94	15.176	-11.461	17.758	1.00	0.47
ATOM	1455	O	ASN	94	14.989	-12.637	17.513	1.00	0.47
ATOM	1456	N	MET	95	16.261	-10.856	17.362	1.00	0.55
ATOM	1457	HN	MET	95	16.396	-9.907	17.564	1.00	0.59
ATOM	1458	CA	MET	95	17.292	-11.613	16.597	1.00	0.63
ATOM	1459	HA	MET	95	16.860	-11.996	15.684	1.00	0.66
ATOM	1460	CB	MET	95	18.466	-10.691	16.267	1.00	0.78
ATOM	1461	HB1	MET	95	19.130	-11.185	15.573	1.00	0.83
ATOM	1462	HB2	MET	95	19.003	-10.451	17.173	1.00	0.87
ATOM	1463	CG	MET	95	17.932	-9.409	15.632	1.00	0.92

ATOM	1464	CG1	MET	95	18.755	-8.745	15.415	1.00	1.48
ATOM	1465	G2	MET	95	17.259	-8.930	6.317	1.00	1.45
ATOM	1466	SD	MET	95	17.048	-9.799	14.104	1.00	1.27
ATOM	1467	CE	MET	95	18.402	-9.445	12.963	1.00	0.68
ATOM	1468	HE1	MET	95	18.054	-9.569	11.950	1.00	1.31
ATOM	1469	HE2	MET	95	19.218	-10.123	13.148	1.00	1.10
ATOM	1470	HE3	MET	95	18.740	-8.429	13.110	1.00	1.19
ATOM	1471	C	MET	95	17.781	-12.773	17.462	1.00	0.62
ATOM	1472	O	MET	95	18.093	-13.840	16.973	1.00	0.65
ATOM	1473	N	LEU	96	17.838	-12.570	18.749	1.00	0.62
ATOM	1474	HN	LEU	96	17.573	-11.702	19.118	1.00	0.60
ATOM	1475	CA	LEU	96	18.290	-13.657	19.660	1.00	0.69
ATOM	1476	HA	LEU	96	19.238	-14.044	19.324	1.00	0.79
ATOM	1477	CB	LEU	96	18.420	-13.104	21.084	1.00	0.74
ATOM	1478	HB1	LEU	96	18.755	-13.891	21.744	1.00	0.91
ATOM	1479	HB2	LEU	96	17.458	-12.743	21.417	1.00	0.71
ATOM	1480	CG	LEU	96	19.434	-11.953	21.114	1.00	0.88
ATOM	1481	HG	LEU	96	19.332	-11.359	20.217	1.00	1.46
ATOM	1482	CD1	LEU	96	19.165	-11.078	22.339	1.00	1.14
ATOM	1483	HD11	LEU	96	18.289	-10.471	22.164	1.00	1.78
ATOM	1484	HD12	LEU	96	20.016	-10.438	22.519	1.00	1.69
ATOM	1485	HD13	LEU	96	18.999	-11.707	23.201	1.00	1.48
ATOM	1486	CD2	LEU	96	20.860	-12.508	21.207	1.00	1.41
ATOM	1487	HD21	LEU	96	21.562	-11.688	21.231	1.00	1.93
ATOM	1488	HD22	LEU	96	21.068	-13.131	20.352	1.00	1.80
ATOM	1489	HD23	LEU	96	20.961	-13.091	22.111	1.00	1.98
ATOM	1490	C	LEU	96	17.244	-14.774	19.639	1.00	0.63
ATOM	1491	O	LEU	96	17.546	-15.930	19.858	1.00	0.72
ATOM	1492	N	GLU	97	16.013	-14.426	19.374	1.00	0.54
ATOM	1493	HN	GLU	97	15.802	-13.484	19.200	1.00	0.51
ATOM	1494	CA	GLU	97	14.925	-15.445	19.329	1.00	0.52
ATOM	1495	HA	GLU	97	15.348	-16.429	19.201	1.00	0.57
ATOM	1496	CB	GLU	97	14.134	-15.397	20.638	1.00	0.61
ATOM	1497	HB1	GLU	97	13.340	-16.127	20.606	1.00	1.01
ATOM	1498	HB2	GLU	97	13.713	-14.411	20.769	1.00	1.07
ATOM	1499	CG	GLU	97	15.066	-15.714	21.810	1.00	1.37
ATOM	1500	HG1	GLU	97	15.579	-14.814	22.116	1.00	1.99
ATOM	1501	HG2	GLU	97	15.790	-16.455	21.504	1.00	1.89
ATOM	1502	CD	GLU	97	14.246	-16.254	22.984	1.00	1.82
ATOM	1503	OE1	GLU	97	13.579	-17.259	22.801	1.00	2.29
ATOM	1504	OE2	GLU	97	14.300	-15.654	24.044	1.00	2.43
ATOM	1505	C	GLU	97	13.987	-15.114	18.160	1.00	0.43
ATOM	1506	O	GLU	97	12.921	-14.565	18.357	1.00	0.44
ATOM	1507	N	PRO	98	14.382	-15.427	16.946	1.00	0.40
ATOM	1508	CA	PRO	98	13.539	-15.121	15.757	1.00	0.41
ATOM	1509	HA	PRO	98	13.400	-14.057	15.660	1.00	0.45
ATOM	1510	CB	PRO	98	14.397	-15.630	14.595	1.00	0.49
ATOM	1511	HB1	PRO	98	14.543	-14.838	13.874	1.00	0.56
ATOM	1512	HB2	PRO	98	13.906	-16.467	14.121	1.00	0.54
ATOM	1513	CG	PRO	98	15.758	-16.073	15.146	1.00	0.50
ATOM	1514	HG1	PRO	98	16.520	-15.374	14.838	1.00	0.52
ATOM	1515	HG2	PRO	98	15.996	-17.060	14.774	1.00	0.57
ATOM	1516	CD	PRO	98	15.680	-16.102	16.674	1.00	0.47
ATOM	1517	HD2	PRO	98	15.669	-17.124	17.029	1.00	0.53
ATOM	1518	HD1	PRO	98	16.492	-15.547	17.114	1.00	0.50
ATOM	1519	C	PRO	98	12.183	-15.832	15.800	1.00	0.38
ATOM	1520	O	PRO	98	12.106	-17.045	15.811	1.00	0.42
ATOM	1521	N	THR	99	11.118	-15.073	15.829	1.00	0.37
ATOM	1522	HN	THR	99	11.220	-14.098	15.823	1.00	0.38
ATOM	1523	CA	THR	99	9.748	-15.668	15.878	1.00	0.38
ATOM	1524	HA	THR	99	9.809	-16.742	15.786	1.00	0.43
ATOM	1525	CB	THR	99	9.076	-15.304	17.205	1.00	0.45
ATOM	1526	HB	THR	99	8.084	-15.727	17.233	1.00	0.46
ATOM	1527	OG1	THR	99	8.989	-13.891	17.316	1.00	0.49
ATOM	1528	HG1	THR	99	9.097	-13.517	16.438	1.00	0.85
ATOM	1529	CG2	THR	99	9.892	-15.861	18.374	1.00	0.58
ATOM	1530	HG21	THR	99	9.862	-15.163	19.198	1.00	1.21
ATOM	1531	HG22	THR	99	10.915	-16.007	18.064	1.00	1.22
ATOM	1532	HG23	THR	99	9.473	-16.806	18.687	1.00	1.10
ATOM	1533	C	THR	99	8.914	-15.104	14.728	1.00	0.34
ATOM	1534	O	THR	99	9.319	-14.181	14.051	1.00	0.30
ATOM	1535	N	ILE	100	7.751	-15.649	14.503	1.00	0.37
ATOM	1536	HN	ILE	100	7.443	-16.392	15.063	1.00	0.41
ATOM	1537	CA	ILE	100	6.890	-15.143	13.398	1.00	0.38
ATOM	1538	HA	ILE	100	7.470	-15.079	12.489	1.00	0.38
ATOM	1539	CB	ILE	100	5.713	-16.102	13.190	1.00	0.46
ATOM	1540	HB	ILE	100	6.080	-17.117	13.135	1.00	0.49

ATOM	1541	[illegible]1	ILE	100	4.970	-15.744	[illegible]1.895	1.00	0.53
ATOM	1542	[illegible]i	ILE	100	4.707	-14.697	.910	1.00	0.54
ATOM	1543	HG12	ILE	100	4.070	-16.337	11.826	1.00	0.59
ATOM	1544	CG2	ILE	100	4.749	-15.978	14.371	1.00	0.50
ATOM	1545	HG21	ILE	100	4.105	-16.844	14.403	1.00	1.03
ATOM	1546	HG22	ILE	100	4.149	-15.087	14.253	1.00	1.14
ATOM	1547	HG23	ILE	100	5.312	-15.913	15.290	1.00	1.17
ATOM	1548	CD1	ILE	100	5.857	-16.026	10.675	1.00	0.59
ATOM	1549	HD11	ILE	100	6.567	-16.804	10.910	1.00	1.22
ATOM	1550	HD12	ILE	100	6.388	-15.127	10.402	1.00	1.15
ATOM	1551	HD13	ILE	100	5.238	-16.342	9.848	1.00	1.11
ATOM	1552	C	ILE	100	6.365	-13.754	13.767	1.00	0.38
ATOM	1553	O	ILE	100	5.956	-12.988	12.917	1.00	0.41
ATOM	1554	N	THR	101	6.377	-13.419	15.031	1.00	0.39
ATOM	1555	HN	THR	101	6.714	-14.050	15.701	1.00	0.40
ATOM	1556	CA	THR	101	5.881	-12.078	15.452	1.00	0.44
ATOM	1557	HA	THR	101	5.174	-11.718	14.727	1.00	0.48
ATOM	1558	CB	THR	101	5.200	-12.181	16.820	1.00	0.53
ATOM	1559	HB	THR	101	4.849	-11.206	17.120	1.00	0.59
ATOM	1560	OG1	THR	101	6.134	-12.661	17.777	1.00	0.54
ATOM	1561	HG1	THR	101	6.977	-12.235	17.608	1.00	0.89
ATOM	1562	CG2	THR	101	4.011	-13.139	16.736	1.00	0.58
ATOM	1563	HG21	THR	101	3.336	-12.807	15.961	1.00	1.20
ATOM	1564	HG22	THR	101	3.493	-13.153	17.684	1.00	1.20
ATOM	1565	HG23	THR	101	4.364	-14.133	16.505	1.00	1.14
ATOM	1566	C	THR	101	7.058	-11.104	15.546	1.00	0.41
ATOM	1567	O	THR	101	6.926	-9.998	16.031	1.00	0.46
ATOM	1568	N	CYS	102	8.211	-11.513	15.095	1.00	0.34
ATOM	1569	HN	CYS	102	8.295	-12.412	14.714	1.00	0.31
ATOM	1570	CA	CYS	102	9.406	-10.622	15.163	1.00	0.34
ATOM	1571	HA	CYS	102	9.591	-10.353	16.192	1.00	0.42
ATOM	1572	CB	CYS	102	10.622	-11.368	14.611	1.00	0.34
ATOM	1573	HB1	CYS	102	10.377	-11.795	13.650	1.00	0.33
ATOM	1574	HB2	CYS	102	10.901	-12.157	15.295	1.00	0.40
ATOM	1575	SG	CYS	102	12.004	-10.214	14.425	1.00	0.37
ATOM	1576	HG	CYS	102	11.669	-9.415	14.013	1.00	0.89
ATOM	1577	C	CYS	102	9.179	-9.348	14.340	1.00	0.32
ATOM	1578	O	CYS	102	9.273	-8.248	14.848	1.00	0.32
ATOM	1579	N	PHE	103	8.906	-9.484	13.068	1.00	0.33
ATOM	1580	HN	PHE	103	8.852	-10.379	12.673	1.00	0.36
ATOM	1581	CA	PHE	103	8.704	-8.276	12.210	1.00	0.34
ATOM	1582	HA	PHE	103	9.226	-7.437	12.643	1.00	0.34
ATOM	1583	CB	PHE	103	9.272	-8.554	10.816	1.00	0.37
ATOM	1584	HB1	PHE	103	8.966	-7.770	10.140	1.00	0.41
ATOM	1585	HB2	PHE	103	8.900	-9.503	10.459	1.00	0.36
ATOM	1586	CG	PHE	103	10.780	-8.599	10.881	1.00	0.38
ATOM	1587	CD1	PHE	103	11.430	-9.774	11.273	1.00	0.40
ATOM	1588	HD1	PHE	103	10.854	-10.647	11.537	1.00	0.45
ATOM	1589	CD2	PHE	103	11.526	-7.466	10.540	1.00	0.47
ATOM	1590	HD2	PHE	103	11.022	-6.561	10.233	1.00	0.56
ATOM	1591	CE1	PHE	103	12.829	-9.815	11.328	1.00	0.45
ATOM	1592	HE1	PHE	103	13.331	-10.722	11.630	1.00	0.52
ATOM	1593	CE2	PHE	103	12.924	-7.506	10.594	1.00	0.52
ATOM	1594	HE2	PHE	103	13.500	-6.630	10.333	1.00	0.62
ATOM	1595	CZ	PHE	103	13.576	-8.680	10.989	1.00	0.48
ATOM	1596	HZ	PHE	103	14.655	-8.712	11.030	1.00	0.53
ATOM	1597	C	PHE	103	7.216	-7.935	12.081	1.00	0.35
ATOM	1598	O	PHE	103	6.856	-6.949	11.469	1.00	0.35
ATOM	1599	N	ASP	104	6.344	-8.728	12.637	1.00	0.37
ATOM	1600	HN	ASP	104	6.640	-9.525	13.126	1.00	0.38
ATOM	1601	CA	ASP	104	4.890	-8.415	12.516	1.00	0.41
ATOM	1602	HA	ASP	104	4.618	-8.378	11.471	1.00	0.43
ATOM	1603	CB	ASP	104	4.063	-9.488	13.220	1.00	0.47
ATOM	1604	HB1	ASP	104	3.027	-9.184	13.243	1.00	0.52
ATOM	1605	HB2	ASP	104	4.423	-9.613	14.228	1.00	0.45
ATOM	1606	CG	ASP	104	4.186	-10.807	12.454	1.00	0.52
ATOM	1607	OD1	ASP	104	4.780	-10.796	11.388	1.00	1.11
ATOM	1608	OD2	ASP	104	3.673	-11.803	12.938	1.00	1.20
ATOM	1609	C	ASP	104	4.607	-7.058	13.162	1.00	0.39
ATOM	1610	O	ASP	104	3.833	-6.268	12.659	1.00	0.41
ATOM	1611	N	GLU	105	5.229	-6.784	14.275	1.00	0.38
ATOM	1612	HN	GLU	105	5.847	-7.438	14.663	1.00	0.38
ATOM	1613	CA	GLU	105	4.997	-5.483	14.959	1.00	0.39
ATOM	1614	HA	GLU	105	3.942	-5.367	15.160	1.00	0.42
ATOM	1615	CB	GLU	105	5.771	-5.448	16.279	1.00	0.43
ATOM	1616	HB1	GLU	105	6.831	-5.442	16.075	1.00	0.85
ATOM	1617	HB2	GLU	105	5.522	-6.320	16.867	1.00	1.05

ATOM	1618	CG	GLU	105	5.398	-4.183	17.056	1.00	1.06
ATOM	1619	1	GLU	105	4.325	-4.131	[illegible].164	1.00	1.73
ATOM	1620	HG2	GLU	105	5.750	-3.314	[illegible].519	1.00	1.61
ATOM	1621	CD	GLU	105	6.044	-4.225	18.441	1.00	1.50
ATOM	1622	OE1	GLU	105	5.950	-3.235	19.148	1.00	2.16
ATOM	1623	OE2	GLU	105	6.621	-5.248	18.771	1.00	2.05
ATOM	1624	C	GLU	105	5.470	-4.343	14.056	1.00	0.36
ATOM	1625	O	GLU	105	4.862	-3.292	13.997	1.00	0.38
ATOM	1626	N	ALA	106	6.557	-4.535	13.359	1.00	0.35
ATOM	1627	HN	ALA	106	7.039	-5.386	13.425	1.00	0.35
ATOM	1628	CA	ALA	106	7.070	-3.453	12.472	1.00	0.36
ATOM	1629	HA	ALA	106	7.149	-2.536	13.034	1.00	0.37
ATOM	1630	CB	ALA	106	8.450	-3.844	11.939	1.00	0.39
ATOM	1631	HB1	ALA	106	9.160	-3.066	12.176	1.00	1.00
ATOM	1632	HB2	ALA	106	8.400	-3.972	10.868	1.00	1.12
ATOM	1633	HB3	ALA	106	8.764	-4.770	12.399	1.00	1.10
ATOM	1634	C	ALA	106	6.110	-3.247	11.296	1.00	0.36
ATOM	1635	O	ALA	106	5.792	-2.130	10.939	1.00	0.36
ATOM	1636	N	GLN	107	5.632	-4.304	10.698	1.00	0.41
ATOM	1637	HN	GLN	107	5.886	-5.201	11.000	1.00	0.44
ATOM	1638	CA	GLN	107	4.683	-4.135	9.560	1.00	0.45
ATOM	1639	HA	GLN	107	5.162	-3.559	8.780	1.00	0.46
ATOM	1640	CB	GLN	107	4.263	-5.498	9.004	1.00	0.54
ATOM	1641	HB1	GLN	107	3.737	-6.053	9.766	1.00	0.64
ATOM	1642	HB2	GLN	107	5.141	-6.048	8.697	1.00	0.68
ATOM	1643	CG	GLN	107	3.339	-5.289	7.798	1.00	0.70
ATOM	1644	HG1	GLN	107	3.863	-4.733	7.035	1.00	0.87
ATOM	1645	HG2	GLN	107	2.461	-4.740	8.105	1.00	0.82
ATOM	1646	CD	GLN	107	2.913	-6.643	7.233	1.00	0.81
ATOM	1647	OE1	GLN	107	2.352	-7.455	7.936	1.00	1.35
ATOM	1648	NE2	GLN	107	3.158	-6.922	5.982	1.00	1.26
ATOM	1649	HE21	GLN	107	3.612	-6.265	5.414	1.00	1.89
ATOM	1650	HE22	GLN	107	2.888	-7.788	5.611	1.00	1.28
ATOM	1651	C	GLN	107	3.455	-3.378	10.063	1.00	0.43
ATOM	1652	O	GLN	107	2.921	-2.520	9.389	1.00	0.44
ATOM	1653	N	LYS	108	3.008	-3.688	11.249	1.00	0.44
ATOM	1654	HN	LYS	108	3.458	-4.381	11.776	1.00	0.44
ATOM	1655	CA	LYS	108	1.819	-2.986	11.805	1.00	0.47
ATOM	1656	HA	LYS	108	0.959	-3.170	11.178	1.00	0.53
ATOM	1657	CB	LYS	108	1.551	-3.505	13.223	1.00	0.51
ATOM	1658	HB1	LYS	108	2.414	-3.313	13.843	1.00	0.47
ATOM	1659	HB2	LYS	108	1.366	-4.568	13.185	1.00	0.55
ATOM	1660	CG	LYS	108	0.331	-2.798	13.823	1.00	0.58
ATOM	1661	HG1	LYS	108	-0.536	-2.991	13.209	1.00	0.64
ATOM	1662	HG2	LYS	108	0.513	-1.734	13.867	1.00	0.56
ATOM	1663	CD	LYS	108	0.080	-3.329	15.236	1.00	0.66
ATOM	1664	HD1	LYS	108	1.000	-3.300	15.801	1.00	1.17
ATOM	1665	HD2	LYS	108	-0.275	-4.348	15.180	1.00	0.97
ATOM	1666	CE	LYS	108	-0.969	-2.459	15.931	1.00	1.17
ATOM	1667	HE1	LYS	108	-1.535	-1.917	15.189	1.00	1.70
ATOM	1668	HE2	LYS	108	-0.476	-1.760	16.590	1.00	1.60
ATOM	1669	NZ	LYS	108	-1.889	-3.324	16.724	1.00	2.14
ATOM	1670	HZ1	LYS	108	-2.836	-2.895	16.744	1.00	2.66
ATOM	1671	HZ2	LYS	108	-1.527	-3.413	17.696	1.00	2.61
ATOM	1672	HZ3	LYS	108	-1.945	-4.264	16.286	1.00	2.59
ATOM	1673	C	LYS	108	2.117	-1.489	11.852	1.00	0.43
ATOM	1674	O	LYS	108	1.274	-0.668	11.548	1.00	0.47
ATOM	1675	N	LYS	109	3.314	-1.128	12.216	1.00	0.37
ATOM	1676	HN	LYS	109	3.983	-1.806	12.448	1.00	0.35
ATOM	1677	CA	LYS	109	3.668	0.315	12.266	1.00	0.38
ATOM	1678	HA	LYS	109	2.945	0.838	12.867	1.00	0.43
ATOM	1679	CB	LYS	109	5.068	0.483	12.867	1.00	0.38
ATOM	1680	HB1	LYS	109	5.348	1.525	12.835	1.00	0.66
ATOM	1681	HB2	LYS	109	5.776	-0.096	12.293	1.00	0.65
ATOM	1682	CG	LYS	109	5.076	0.000	14.326	1.00	0.71
ATOM	1683	HG1	LYS	109	6.091	-0.217	14.623	1.00	1.11
ATOM	1684	HG2	LYS	109	4.482	-0.898	14.406	1.00	1.07
ATOM	1685	CD	LYS	109	4.496	1.075	15.256	1.00	0.60
ATOM	1686	HD1	LYS	109	3.471	1.278	14.994	1.00	0.54
ATOM	1687	HD2	LYS	109	5.076	1.981	15.167	1.00	0.70
ATOM	1688	CE	LYS	109	4.549	0.574	16.701	1.00	1.05
ATOM	1689	HE1	LYS	109	4.897	-0.449	16.714	1.00	1.64
ATOM	1690	HE2	LYS	109	3.561	0.623	17.134	1.00	1.55
ATOM	1691	NZ	LYS	109	5.480	1.426	17.493	1.00	1.71
ATOM	1692	HZ1	LYS	109	5.381	1.202	18.503	1.00	2.20
ATOM	1693	HZ2	LYS	109	5.251	2.429	17.334	1.00	2.20
ATOM	1694	HZ3	LYS	109	6.458	1.241	17.194	1.00	2.19

ATOM	1695	C	LYS	109	3.631	0.880	10.845	1.00	0.37
ATOM	1696		LYS	109	3.171	1.983	9.622	1.00	0.39
ATOM	1697	N	ILE	110	4.099	0.135	9.876	1.00	0.35
ATOM	1698	HN	ILE	110	4.459	-0.758	10.068	1.00	0.34
ATOM	1699	CA	ILE	110	4.064	0.646	8.478	1.00	0.36
ATOM	1700	HA	ILE	110	4.532	1.618	8.431	1.00	0.37
ATOM	1701	CB	ILE	110	4.791	-0.332	7.549	1.00	0.38
ATOM	1702	HB	ILE	110	4.301	-1.294	7.601	1.00	0.39
ATOM	1703	CG1	ILE	110	6.258	-0.485	7.991	1.00	0.40
ATOM	1704	HG11	ILE	110	6.766	-1.157	7.315	1.00	0.42
ATOM	1705	HG12	ILE	110	6.283	-0.902	8.987	1.00	0.41
ATOM	1706	CG2	ILE	110	4.725	0.180	6.106	1.00	0.41
ATOM	1707	HG21	ILE	110	5.675	0.018	5.620	1.00	1.14
ATOM	1708	HG22	ILE	110	4.498	1.237	6.109	1.00	1.15
ATOM	1709	HG23	ILE	110	3.954	-0.352	5.570	1.00	1.01
ATOM	1710	CD1	ILE	110	6.982	0.871	7.997	1.00	0.43
ATOM	1711	HD11	ILE	110	6.630	1.485	7.183	1.00	1.15
ATOM	1712	HD12	ILE	110	8.044	0.708	7.886	1.00	1.09
ATOM	1713	HD13	ILE	110	6.795	1.374	8.933	1.00	1.08
ATOM	1714	C	ILE	110	2.600	0.762	8.050	1.00	0.36
ATOM	1715	O	ILE	110	2.194	1.741	7.457	1.00	0.37
ATOM	1716	N	PHE	111	1.798	-0.223	8.367	1.00	0.37
ATOM	1717	HN	PHE	111	2.144	-0.998	8.858	1.00	0.38
ATOM	1718	CA	PHE	111	0.353	-0.160	8.002	1.00	0.39
ATOM	1719	HA	PHE	111	0.256	-0.074	6.931	1.00	0.40
ATOM	1720	CB	PHE	111	-0.357	-1.434	8.478	1.00	0.41
ATOM	1721	HB1	PHE	111	-1.317	-1.174	8.897	1.00	0.43
ATOM	1722	HB2	PHE	111	0.245	-1.919	9.232	1.00	0.43
ATOM	1723	CG	PHE	111	-0.556	-2.375	7.310	1.00	0.44
ATOM	1724	CD1	PHE	111	0.521	-2.699	6.477	1.00	0.47
ATOM	1725	HD1	PHE	111	1.499	-2.283	6.670	1.00	0.50
ATOM	1726	CD2	PHE	111	-1.823	-2.918	7.056	1.00	0.46
ATOM	1727	HD2	PHE	111	-2.656	-2.671	7.698	1.00	0.49
ATOM	1728	CE1	PHE	111	0.330	-3.563	5.390	1.00	0.52
ATOM	1729	HE1	PHE	111	1.161	-3.813	4.749	1.00	0.58
ATOM	1730	CE2	PHE	111	-2.011	-3.781	5.969	1.00	0.50
ATOM	1731	HE2	PHE	111	-2.984	-4.196	5.767	1.00	0.54
ATOM	1732	CZ	PHE	111	-0.940	-4.102	5.139	1.00	0.52
ATOM	1733	HZ	PHE	111	-1.096	-4.766	4.303	1.00	0.56
ATOM	1734	C	PHE	111	-0.286	1.060	8.672	1.00	0.39
ATOM	1735	O	PHE	111	-0.997	1.821	8.049	1.00	0.40
ATOM	1736	N	ASN	112	-0.047	1.252	9.940	1.00	0.40
ATOM	1737	HN	ASN	112	0.527	0.627	10.434	1.00	0.41
ATOM	1738	CA	ASN	112	-0.645	2.425	10.638	1.00	0.43
ATOM	1739	HA	ASN	112	-1.713	2.431	10.473	1.00	0.44
ATOM	1740	CB	ASN	112	-0.369	2.322	12.139	1.00	0.49
ATOM	1741	HB1	ASN	112	-0.478	3.295	12.592	1.00	0.51
ATOM	1742	HB2	ASN	112	0.638	1.963	12.294	1.00	0.49
ATOM	1743	CG	ASN	112	-1.363	1.350	12.777	1.00	0.54
ATOM	1744	OD1	ASN	112	-2.285	1.763	13.452	1.00	1.23
ATOM	1745	ND2	ASN	112	-1.218	0.067	12.587	1.00	1.22
ATOM	1746	HD21	ASN	112	-0.477	-0.267	12.039	1.00	2.00
ATOM	1747	HD22	ASN	112	-1.850	-0.562	12.992	1.00	1.25
ATOM	1748	C	ASN	112	-0.044	3.729	10.100	1.00	0.42
ATOM	1749	O	ASN	112	-0.734	4.712	9.922	1.00	0.43
ATOM	1750	N	LEU	113	1.241	3.755	9.861	1.00	0.42
ATOM	1751	HN	LEU	113	1.788	2.959	10.025	1.00	0.42
ATOM	1752	CA	LEU	113	1.877	5.011	9.361	1.00	0.45
ATOM	1753	HA	LEU	113	1.674	5.806	10.058	1.00	0.48
ATOM	1754	CB	LEU	113	3.396	4.800	9.246	1.00	0.51
ATOM	1755	HB1	LEU	113	3.592	4.029	8.516	1.00	0.58
ATOM	1756	HB2	LEU	113	3.784	4.487	10.204	1.00	0.65
ATOM	1757	CG	LEU	113	4.107	6.097	8.812	1.00	0.66
ATOM	1758	HG	LEU	113	3.530	6.596	8.049	1.00	1.18
ATOM	1759	CD1	LEU	113	4.272	7.037	10.015	1.00	1.30
ATOM	1760	HD11	LEU	113	4.845	7.905	9.721	1.00	1.71
ATOM	1761	HD12	LEU	113	4.789	6.519	10.808	1.00	1.92
ATOM	1762	HD13	LEU	113	3.304	7.355	10.366	1.00	1.86
ATOM	1763	CD2	LEU	113	5.487	5.740	8.249	1.00	1.24
ATOM	1764	HD21	LEU	113	5.868	4.867	8.757	1.00	1.64
ATOM	1765	HD22	LEU	113	6.166	6.566	8.396	1.00	1.80
ATOM	1766	HD23	LEU	113	5.401	5.531	7.193	1.00	1.86
ATOM	1767	C	LEU	113	1.302	5.379	7.993	1.00	0.42
ATOM	1768	O	LEU	113	0.782	6.460	7.801	1.00	0.44
ATOM	1769	N	MET	114	1.390	4.497	7.038	1.00	0.42
ATOM	1770	HN	MET	114	1.814	3.630	7.205	1.00	0.44
ATOM	1771	CA	MET	114	0.847	4.820	5.692	1.00	0.44

ATOM	1	[illegible]	VAL	5	-8.546	2.447	3.971	1.00	0.99
ATOM	2	HN	VAL	5	-8.477	3.418	4.081	1.00	1.07
ATOM	3	CA	VAL	5	-9.109	1.878	-12.714	1.00	0.86
ATOM	4	HA	VAL	5	-8.922	0.815	-12.685	1.00	0.89
ATOM	5	CB	VAL	5	-8.442	2.546	-11.509	1.00	0.82
ATOM	6	HB	VAL	5	-8.686	3.599	-11.500	1.00	1.23
ATOM	7	CG1	VAL	5	-8.941	1.895	-10.217	1.00	1.02
ATOM	8	HG11	VAL	5	-10.011	2.014	-10.143	1.00	1.62
ATOM	9	HG12	VAL	5	-8.467	2.368	-9.370	1.00	1.48
ATOM	10	HG13	VAL	5	-8.695	0.844	-10.226	1.00	1.53
ATOM	11	CG2	VAL	5	-6.925	2.373	-11.609	1.00	1.37
ATOM	12	HG21	VAL	5	-6.540	2.024	-10.663	1.00	1.93
ATOM	13	HG22	VAL	5	-6.470	3.321	-11.855	1.00	1.76
ATOM	14	HG23	VAL	5	-6.696	1.652	-12.380	1.00	1.88
ATOM	15	C	VAL	5	-10.617	2.132	-12.671	1.00	0.82
ATOM	16	O	VAL	5	-11.079	3.227	-12.927	1.00	0.84
ATOM	17	N	SER	6	-11.389	1.130	-12.350	1.00	0.82
ATOM	18	HN	SER	6	-10.997	0.255	-12.147	1.00	0.83
ATOM	19	CA	SER	6	-12.866	1.318	-12.292	1.00	0.83
ATOM	20	HA	SER	6	-13.194	1.870	-13.160	1.00	0.89
ATOM	21	CB	SER	6	-13.550	-0.049	-12.268	1.00	0.89
ATOM	22	HB1	SER	6	-13.181	-0.650	-13.089	1.00	0.95
ATOM	23	HB2	SER	6	-14.615	0.077	-12.370	1.00	0.93
ATOM	24	OG	SER	6	-13.271	-0.692	-11.031	1.00	0.87
ATOM	25	HG	SER	6	-12.543	-0.228	-10.613	1.00	1.20
ATOM	26	C	SER	6	-13.234	2.093	-11.025	1.00	0.74
ATOM	27	O	SER	6	-12.494	2.113	-10.061	1.00	0.68
ATOM	28	N	GLN	7	-14.375	2.727	-11.017	1.00	0.75
ATOM	29	HN	GLN	7	-14.960	2.695	-11.803	1.00	0.82
ATOM	30	CA	GLN	7	-14.792	3.496	-9.810	1.00	0.70
ATOM	31	HA	GLN	7	-13.973	4.129	-9.505	1.00	0.66
ATOM	32	CB	GLN	7	-15.999	4.376	-10.139	1.00	0.76
ATOM	33	HB1	GLN	7	-16.404	4.793	-9.230	1.00	0.75
ATOM	34	HB2	GLN	7	-16.754	3.780	-10.633	1.00	0.82
ATOM	35	CG	GLN	7	-15.551	5.508	-11.067	1.00	0.83
ATOM	36	HG1	GLN	7	-15.175	5.090	-11.988	1.00	1.37
ATOM	37	HG2	GLN	7	-14.768	6.077	-10.585	1.00	1.26
ATOM	38	CD	GLN	7	-16.733	6.428	-11.375	1.00	1.51
ATOM	39	OE1	GLN	7	-17.840	5.972	-11.578	1.00	2.25
ATOM	40	NE2	GLN	7	-16.540	7.720	-11.412	1.00	2.18
ATOM	41	HE21	GLN	7	-15.646	8.086	-11.243	1.00	2.33
ATOM	42	HE22	GLN	7	-17.288	8.322	-11.606	1.00	2.90
ATOM	43	C	GLN	7	-15.130	2.533	-8.666	1.00	0.66
ATOM	44	O	GLN	7	-15.090	2.888	-7.507	1.00	0.65
ATOM	45	N	GLU	8	-15.470	1.317	-8.979	1.00	0.69
ATOM	46	HN	GLU	8	-15.504	1.043	-9.919	1.00	0.73
ATOM	47	CA	GLU	8	-15.800	0.339	-7.904	1.00	0.69
ATOM	48	HA	GLU	8	-16.529	0.773	-7.237	1.00	0.71
ATOM	49	CB	GLU	8	-16.377	-0.935	-8.526	1.00	0.78
ATOM	50	HB1	GLU	8	-16.450	-1.702	-7.770	1.00	0.81
ATOM	51	HB2	GLU	8	-15.725	-1.273	-9.319	1.00	0.79
ATOM	52	CG	GLU	8	-17.768	-0.652	-9.096	1.00	0.87
ATOM	53	HG1	GLU	8	-17.707	0.150	-9.816	1.00	1.11
ATOM	54	HG2	GLU	8	-18.435	-0.368	-8.294	1.00	1.22
ATOM	55	CD	GLU	8	-18.300	-1.912	-9.781	1.00	1.57
ATOM	56	OE1	GLU	8	-19.406	-1.864	-10.292	1.00	2.30
ATOM	57	OE2	GLU	8	-17.590	-2.905	-9.784	1.00	2.12
ATOM	58	C	GLU	8	-14.535	-0.020	-7.113	1.00	0.62
ATOM	59	O	GLU	8	-14.569	-0.196	-5.911	1.00	0.61
ATOM	60	N	GLU	9	-13.429	-0.178	-7.793	1.00	0.61
ATOM	61	HN	GLU	9	-13.439	-0.064	-8.766	1.00	0.64
ATOM	62	CA	GLU	9	-12.163	-0.582	-7.106	1.00	0.59
ATOM	63	HA	GLU	9	-12.353	-1.452	-6.496	1.00	0.63
ATOM	64	CB	GLU	9	-11.123	-0.939	-8.169	1.00	0.67
ATOM	65	HB1	GLU	9	-10.158	-1.063	-7.701	1.00	0.68
ATOM	66	HB2	GLU	9	-11.069	-0.145	-8.900	1.00	0.67
ATOM	67	CG	GLU	9	-11.524	-2.244	-8.860	1.00	0.81
ATOM	68	HG1	GLU	9	-12.552	-2.179	-9.180	1.00	1.46
ATOM	69	HG2	GLU	9	-11.411	-3.068	-8.170	1.00	1.11
ATOM	70	CD	GLU	9	-10.628	-2.471	-10.080	1.00	1.55
ATOM	71	OE1	GLU	9	-10.815	-3.474	-10.749	1.00	2.28
ATOM	72	OE2	GLU	9	-9.772	-1.636	-10.325	1.00	2.22
ATOM	73	C	GLU	9	-11.603	0.542	-6.221	1.00	0.52
ATOM	74	O	GLU	9	-11.118	0.290	-5.135	1.00	0.51
ATOM	75	N	VAL	10	-11.644	1.770	-6.659	1.00	0.50
ATOM	76	HN	VAL	10	-12.027	1.971	-7.539	1.00	0.53
ATOM	77	CA	VAL	10	-11.087	2.865	-5.808	1.00	0.47

ATOM	1772	HA	MET	114	1.306	5.729	5.332	1.00	0.50
ATOM	1773	)	MET	114	1.161	3.676	1.722	1.00	0.48
ATOM	1774	_B1	MET	114	2.228	3.512	4.691	1.00	0.64
ATOM	1775	HB2	MET	114	0.808	3.935	3.734	1.00	0.55
ATOM	1776	CG	MET	114	0.468	2.400	5.192	1.00	0.41
ATOM	1777	HG1	MET	114	-0.487	2.307	4.697	1.00	0.53
ATOM	1778	HG2	MET	114	0.316	2.451	6.256	1.00	0.70
ATOM	1779	SD	MET	114	1.500	0.965	4.795	1.00	0.90
ATOM	1780	CE	MET	114	1.183	0.924	3.014	1.00	0.53
ATOM	1781	HE1	MET	114	0.647	1.815	2.721	1.00	1.23
ATOM	1782	HE2	MET	114	0.592	0.059	2.773	1.00	1.18
ATOM	1783	HE3	MET	114	2.124	0.871	2.484	1.00	1.20
ATOM	1784	C	MET	114	-0.664	5.028	5.798	1.00	0.41
ATOM	1785	O	MET	114	-1.228	5.884	5.149	1.00	0.46
ATOM	1786	N	GLU	115	-1.325	4.254	6.615	1.00	0.38
ATOM	1787	HN	GLU	115	-0.854	3.569	7.135	1.00	0.37
ATOM	1788	CA	GLU	115	-2.799	4.417	6.757	1.00	0.43
ATOM	1789	HA	GLU	115	-3.252	4.361	5.780	1.00	0.46
ATOM	1790	CB	GLU	115	-3.367	3.300	7.635	1.00	0.47
ATOM	1791	HB1	GLU	115	-2.950	3.371	8.627	1.00	0.88
ATOM	1792	HB2	GLU	115	-3.119	2.342	7.205	1.00	0.93
ATOM	1793	CG	GLU	115	-4.889	3.443	7.711	1.00	0.84
ATOM	1794	HG1	GLU	115	-5.295	3.505	6.712	1.00	1.29
ATOM	1795	HG2	GLU	115	-5.138	4.341	8.257	1.00	1.25
ATOM	1796	CD	GLU	115	-5.483	2.229	8.426	1.00	0.86
ATOM	1797	OE1	GLU	115	-4.716	1.370	8.829	1.00	1.35
ATOM	1798	OE2	GLU	115	-6.695	2.174	8.551	1.00	1.34
ATOM	1799	C	GLU	115	-3.123	5.777	7.390	1.00	0.49
ATOM	1800	O	GLU	115	-4.069	6.436	7.016	1.00	0.60
ATOM	1801	N	LYS	116	-2.365	6.202	8.359	1.00	0.48
ATOM	1802	HN	LYS	116	-1.609	5.661	8.671	1.00	0.45
ATOM	1803	CA	LYS	116	-2.668	7.513	9.001	1.00	0.58
ATOM	1804	HA	LYS	116	-3.739	7.614	9.108	1.00	0.66
ATOM	1805	CB	LYS	116	-2.021	7.571	10.386	1.00	0.65
ATOM	1806	HB1	LYS	116	-2.103	8.573	10.781	1.00	0.73
ATOM	1807	HB2	LYS	116	-0.978	7.298	10.308	1.00	0.62
ATOM	1808	CG	LYS	116	-2.739	6.596	11.321	1.00	0.72
ATOM	1809	HG1	LYS	116	-2.662	5.595	10.928	1.00	1.06
ATOM	1810	HG2	LYS	116	-3.779	6.877	11.391	1.00	1.02
ATOM	1811	CD	LYS	116	-2.096	6.649	12.711	1.00	1.27
ATOM	1812	HD1	LYS	116	-2.210	7.642	13.120	1.00	1.84
ATOM	1813	HD2	LYS	116	-1.045	6.414	12.629	1.00	1.69
ATOM	1814	CE	LYS	116	-2.775	5.637	13.643	1.00	1.56
ATOM	1815	HE1	LYS	116	-2.724	5.998	14.660	1.00	2.10
ATOM	1816	HE2	LYS	116	-2.264	4.689	13.574	1.00	1.73
ATOM	1817	NZ	LYS	116	-4.202	5.459	13.252	1.00	2.20
ATOM	1818	HZ1	LYS	116	-4.268	4.755	12.489	1.00	2.55
ATOM	1819	HZ2	LYS	116	-4.587	6.367	12.921	1.00	2.66
ATOM	1820	HZ3	LYS	116	-4.748	5.129	14.072	1.00	2.60
ATOM	1821	C	LYS	116	-2.141	8.665	8.139	1.00	0.59
ATOM	1822	O	LYS	116	-2.447	9.815	8.391	1.00	0.74
ATOM	1823	N	ASP	117	-1.347	8.373	7.135	1.00	0.56
ATOM	1824	HN	ASP	117	-1.108	7.439	6.957	1.00	0.57
ATOM	1825	CA	ASP	117	-0.794	9.464	6.268	1.00	0.63
ATOM	1826	HA	ASP	117	-1.212	10.412	6.564	1.00	0.74
ATOM	1827	CB	ASP	117	0.727	9.518	6.428	1.00	0.74
ATOM	1828	HB1	ASP	117	1.182	9.719	5.470	1.00	1.35
ATOM	1829	HB2	ASP	117	1.083	8.570	6.804	1.00	1.02
ATOM	1830	CG	ASP	117	1.103	10.629	7.410	1.00	1.44
ATOM	1831	OD1	ASP	117	2.187	11.172	7.271	1.00	2.14
ATOM	1832	OD2	ASP	117	0.304	10.917	8.286	1.00	2.15
ATOM	1833	C	ASP	117	-1.125	9.214	4.795	1.00	0.55
ATOM	1834	O	ASP	117	-1.718	10.045	4.136	1.00	0.67
ATOM	1835	N	SER	118	-0.719	8.096	4.258	1.00	0.45
ATOM	1836	HN	SER	118	-0.219	7.445	4.794	1.00	0.48
ATOM	1837	CA	SER	118	-0.987	7.832	2.816	1.00	0.42
ATOM	1838	HA	SER	118	-0.515	8.600	2.221	1.00	0.45
ATOM	1839	CB	SER	118	-0.410	6.472	2.424	1.00	0.46
ATOM	1840	HB1	SER	118	0.552	6.339	2.900	1.00	0.53
ATOM	1841	HB2	SER	118	-0.287	6.429	1.355	1.00	0.47
ATOM	1842	OG	SER	118	-1.303	5.445	2.834	1.00	0.47
ATOM	1843	HG	SER	118	-1.809	5.168	2.067	1.00	0.87
ATOM	1844	C	SER	118	-2.489	7.836	2.540	1.00	0.39
ATOM	1845	O	SER	118	-2.950	8.491	1.634	1.00	0.41
ATOM	1846	N	TYR	119	-3.257	7.113	3.309	1.00	0.40
ATOM	1847	HN	TYR	119	-2.865	6.587	4.037	1.00	0.43
ATOM	1848	CA	TYR	119	-4.730	7.075	3.069	1.00	0.41

ATOM	1849	A	TYR	119	-4.924	6.667	2.090	1.00	0.41
ATOM	1850	CB	TYR	119	-5.388	6.195	4.123	1.00	0.46
ATOM	1851	HB1	TYR	119	-6.210	6.728	4.576	1.00	0.51
ATOM	1852	HB2	TYR	119	-4.663	5.949	4.874	1.00	0.53
ATOM	1853	CG	TYR	119	-5.892	4.929	3.487	1.00	0.43
ATOM	1854	CD1	TYR	119	-5.050	4.165	2.669	1.00	0.61
ATOM	1855	HD1	TYR	119	-4.032	4.481	2.497	1.00	0.83
ATOM	1856	CD2	TYR	119	-7.207	4.521	3.711	1.00	0.46
ATOM	1857	HD2	TYR	119	-7.854	5.113	4.343	1.00	0.65
ATOM	1858	CE1	TYR	119	-5.529	2.994	2.075	1.00	0.63
ATOM	1859	HE1	TYR	119	-4.883	2.405	1.445	1.00	0.87
ATOM	1860	CE2	TYR	119	-7.683	3.349	3.118	1.00	0.45
ATOM	1861	HE2	TYR	119	-8.696	3.031	3.289	1.00	0.61
ATOM	1862	CZ	TYR	119	-6.845	2.586	2.300	1.00	0.45
ATOM	1863	OH	TYR	119	-7.318	1.434	1.711	1.00	0.50
ATOM	1864	HH	TYR	119	-7.406	1.597	0.769	1.00	0.86
ATOM	1865	C	TYR	119	-5.316	8.478	3.150	1.00	0.41
ATOM	1866	O	TYR	119	-6.093	8.885	2.309	1.00	0.43
ATOM	1867	N	ARG	120	-4.951	9.228	4.143	1.00	0.43
ATOM	1868	HN	ARG	120	-4.324	8.885	4.813	1.00	0.43
ATOM	1869	CA	ARG	120	-5.494	10.606	4.252	1.00	0.47
ATOM	1870	HA	ARG	120	-6.569	10.582	4.338	1.00	0.51
ATOM	1871	CB	ARG	120	-4.874	11.295	5.474	1.00	0.52
ATOM	1872	HB1	ARG	120	-5.257	12.301	5.549	1.00	0.58
ATOM	1873	HB2	ARG	120	-3.800	11.330	5.356	1.00	0.50
ATOM	1874	CG	ARG	120	-5.218	10.524	6.754	1.00	0.60
ATOM	1875	HG1	ARG	120	-4.491	10.758	7.518	1.00	1.00
ATOM	1876	HG2	ARG	120	-5.192	9.464	6.550	1.00	1.23
ATOM	1877	CD	ARG	120	-6.614	10.911	7.250	1.00	1.18
ATOM	1878	HD1	ARG	120	-7.354	10.608	6.528	1.00	1.78
ATOM	1879	HD2	ARG	120	-6.661	11.983	7.392	1.00	1.85
ATOM	1880	NE	ARG	120	-6.886	10.223	8.543	1.00	1.72
ATOM	1881	HE	ARG	120	-6.355	9.442	8.804	1.00	2.17
ATOM	1882	CZ	ARG	120	-7.838	10.654	9.325	1.00	2.45
ATOM	1883	NH1	ARG	120	-8.089	10.036	10.447	1.00	3.29
ATOM	1884	HH11	ARG	120	-7.552	9.234	10.707	1.00	3.50
ATOM	1885	HH12	ARG	120	-8.818	10.366	11.048	1.00	3.98
ATOM	1886	NH2	ARG	120	-8.532	11.708	8.991	1.00	2.92
ATOM	1887	HH21	ARG	120	-8.334	12.186	8.136	1.00	2.75
ATOM	1888	HH22	ARG	120	-9.260	12.037	9.592	1.00	3.77
ATOM	1889	C	ARG	120	-5.079	11.366	2.992	1.00	0.46
ATOM	1890	O	ARG	120	-5.863	12.066	2.375	1.00	0.49
ATOM	1891	N	ARG	121	-3.844	11.218	2.603	1.00	0.44
ATOM	1892	HN	ARG	121	-3.239	10.641	3.115	1.00	0.43
ATOM	1893	CA	ARG	121	-3.347	11.910	1.386	1.00	0.45
ATOM	1894	HA	ARG	121	-3.618	12.955	1.429	1.00	0.49
ATOM	1895	CB	ARG	121	-1.825	11.783	1.313	1.00	0.47
ATOM	1896	HB1	ARG	121	-1.470	12.338	0.460	1.00	0.49
ATOM	1897	HB2	ARG	121	-1.559	10.741	1.202	1.00	0.48
ATOM	1898	CG	ARG	121	-1.185	12.341	2.594	1.00	0.56
ATOM	1899	HG1	ARG	121	-0.442	11.645	2.952	1.00	1.20
ATOM	1900	HG2	ARG	121	-1.947	12.468	3.349	1.00	1.08
ATOM	1901	CD	ARG	121	-0.518	13.695	2.321	1.00	1.18
ATOM	1902	HD1	ARG	121	-1.275	14.440	2.130	1.00	1.73
ATOM	1903	HD2	ARG	121	0.136	13.615	1.465	1.00	1.91
ATOM	1904	NE	ARG	121	0.284	14.091	3.513	1.00	1.81
ATOM	1905	HE	ARG	121	0.159	13.622	4.364	1.00	2.29
ATOM	1906	CZ	ARG	121	1.164	15.050	3.420	1.00	2.47
ATOM	1907	NH1	ARG	121	1.886	15.375	4.458	1.00	3.36
ATOM	1908	HH11	ARG	121	1.765	14.889	5.324	1.00	3.67
ATOM	1909	HH12	ARG	121	2.561	16.110	4.387	1.00	3.97
ATOM	1910	NH2	ARG	121	1.321	15.686	2.292	1.00	2.78
ATOM	1911	HH21	ARG	121	0.766	15.438	1.497	1.00	2.59
ATOM	1912	HH22	ARG	121	1.995	16.421	2.222	1.00	3.55
ATOM	1913	C	ARG	121	-3.959	11.273	0.131	1.00	0.42
ATOM	1914	O	ARG	121	-4.306	11.957	-0.806	1.00	0.44
ATOM	1915	N	PHE	122	-4.079	9.967	0.099	1.00	0.39
ATOM	1916	HN	PHE	122	-3.782	9.429	0.861	1.00	0.40
ATOM	1917	CA	PHE	122	-4.647	9.296	-1.114	1.00	0.40
ATOM	1918	HA	PHE	122	-4.008	9.489	-1.963	1.00	0.42
ATOM	1919	CB	PHE	122	-4.746	7.783	-0.886	1.00	0.40
ATOM	1920	HB1	PHE	122	-5.785	7.498	-0.826	1.00	0.54
ATOM	1921	HB2	PHE	122	-4.253	7.523	0.032	1.00	0.48
ATOM	1922	CG	PHE	122	-4.092	7.041	-2.028	1.00	0.38
ATOM	1923	CD1	PHE	122	-2.709	6.825	-2.025	1.00	0.49
ATOM	1924	HD1	PHE	122	-2.106	7.196	-1.210	1.00	0.67
ATOM	1925	CD2	PHE	122	-4.874	6.559	-3.085	1.00	0.69

ATOM	192[illegible]	HD2	PHE	122	-5.941	6.72[illegible]	-3.087	1.00	0.92
ATOM	192	CE1	PHE	122	-2.108	6.12[illegible]	-3.079	1.00	0.68
ATOM	192[illegible]	HE1	PHE	122	-1.041	5.959	-3.077	1.00	0.90
ATOM	1929	CE2	PHE	122	-4.272	5.863	-4.140	1.00	0.85
ATOM	1930	HE2	PHE	122	-4.876	5.492	-4.955	1.00	1.15
ATOM	1931	CZ	PHE	122	-2.889	5.646	-4.137	1.00	0.78
ATOM	1932	HZ	PHE	122	-2.426	5.107	-4.950	1.00	0.98
ATOM	1933	C	PHE	122	-6.043	9.836	-1.397	1.00	0.41
ATOM	1934	O	PHE	122	-6.356	10.202	-2.507	1.00	0.47
ATOM	1935	N	LEU	123	-6.886	9.892	-0.410	1.00	0.39
ATOM	1936	HN	LEU	123	-6.620	9.593	0.484	1.00	0.38
ATOM	1937	CA	LEU	123	-8.258	10.411	-0.648	1.00	0.43
ATOM	1938	HA	LEU	123	-8.748	9.803	-1.394	1.00	0.46
ATOM	1939	CB	LEU	123	-9.052	10.359	0.659	1.00	0.45
ATOM	1940	HB1	LEU	123	-10.028	10.794	0.509	1.00	0.49
ATOM	1941	HB2	LEU	123	-8.524	10.916	1.420	1.00	0.45
ATOM	1942	CG	LEU	123	-9.200	8.897	1.104	1.00	0.45
ATOM	1943	HG	LEU	123	-8.224	8.433	1.124	1.00	0.42
ATOM	1944	CD1	LEU	123	-9.809	8.845	2.505	1.00	0.50
ATOM	1945	HD11	LEU	123	-9.851	7.818	2.840	1.00	1.17
ATOM	1946	HD12	LEU	123	-10.807	9.256	2.480	1.00	1.13
ATOM	1947	HD13	LEU	123	-9.199	9.420	3.185	1.00	1.05
ATOM	1948	CD2	LEU	123	-10.106	8.131	0.130	1.00	0.49
ATOM	1949	HD21	LEU	123	-10.854	8.796	-0.276	1.00	1.11
ATOM	1950	HD22	LEU	123	-10.593	7.324	0.656	1.00	1.18
ATOM	1951	HD23	LEU	123	-9.510	7.725	-0.674	1.00	1.11
ATOM	1952	C	LEU	123	-8.158	11.851	-1.156	1.00	0.45
ATOM	1953	O	LEU	123	-8.878	12.256	-2.046	1.00	0.54
ATOM	1954	N	LYS	124	-7.262	12.625	-0.605	1.00	0.43
ATOM	1955	HN	LYS	124	-6.683	12.277	0.110	1.00	0.41
ATOM	1956	CA	LYS	124	-7.109	14.035	-1.069	1.00	0.48
ATOM	1957	HA	LYS	124	-8.060	14.386	-1.441	1.00	0.53
ATOM	1958	CB	LYS	124	-6.675	14.918	0.102	1.00	0.55
ATOM	1959	HB1	LYS	124	-6.390	15.892	-0.267	1.00	0.60
ATOM	1960	HB2	LYS	124	-5.834	14.462	0.603	1.00	0.55
ATOM	1961	CG	LYS	124	-7.836	15.068	1.086	1.00	0.64
ATOM	1962	HG1	LYS	124	-8.123	14.096	1.457	1.00	0.81
ATOM	1963	HG2	LYS	124	-8.677	15.524	0.581	1.00	1.05
ATOM	1964	CD	LYS	124	-7.401	15.953	2.257	1.00	1.08
ATOM	1965	HD1	LYS	124	-7.103	16.921	1.885	1.00	1.62
ATOM	1966	HD2	LYS	124	-6.566	15.490	2.764	1.00	1.52
ATOM	1967	CE	LYS	124	-8.564	16.120	3.238	1.00	1.26
ATOM	1968	HE1	LYS	124	-9.495	15.905	2.734	1.00	1.66
ATOM	1969	HE2	LYS	124	-8.581	17.135	3.604	1.00	1.84
ATOM	1970	NZ	LYS	124	-8.393	15.184	4.384	1.00	1.82
ATOM	1971	HZ1	LYS	124	-9.095	15.405	5.119	1.00	2.26
ATOM	1972	HZ2	LYS	124	-7.435	15.287	4.776	1.00	2.35
ATOM	1973	HZ3	LYS	124	-8.533	14.207	4.058	1.00	2.23
ATOM	1974	C	LYS	124	-6.069	14.124	-2.195	1.00	0.47
ATOM	1975	O	LYS	124	-5.784	15.194	-2.695	1.00	0.52
ATOM	1976	N	SER	125	-5.491	13.022	-2.596	1.00	0.46
ATOM	1977	HN	SER	125	-5.724	12.165	-2.182	1.00	0.49
ATOM	1978	CA	SER	125	-4.466	13.076	-3.684	1.00	0.49
ATOM	1979	HA	SER	125	-3.780	13.886	-3.486	1.00	0.54
ATOM	1980	CB	SER	125	-3.689	11.759	-3.739	1.00	0.55
ATOM	1981	HB1	SER	125	-3.181	11.598	-2.800	1.00	1.13
ATOM	1982	HB2	SER	125	-2.961	11.804	-4.531	1.00	1.15
ATOM	1983	OG	SER	125	-4.591	10.691	-3.997	1.00	1.34
ATOM	1984	HG	SER	125	-4.433	10.380	-4.892	1.00	1.80
ATOM	1985	C	SER	125	-5.144	13.310	-5.035	1.00	0.46
ATOM	1986	O	SER	125	-6.282	12.941	-5.246	1.00	0.47
ATOM	1987	N	ARG	126	-4.443	13.914	-5.955	1.00	0.52
ATOM	1988	HN	ARG	126	-3.525	14.196	-5.761	1.00	0.56
ATOM	1989	CA	ARG	126	-5.027	14.172	-7.302	1.00	0.58
ATOM	1990	HA	ARG	126	-5.954	14.715	-7.189	1.00	0.58
ATOM	1991	CB	ARG	126	-4.052	15.009	-8.132	1.00	0.71
ATOM	1992	HB1	ARG	126	-4.391	15.050	-9.156	1.00	1.12
ATOM	1993	HB2	ARG	126	-3.069	14.560	-8.095	1.00	1.28
ATOM	1994	CG	ARG	126	-3.989	16.427	-7.561	1.00	1.29
ATOM	1995	HG1	ARG	126	-3.651	16.388	-6.536	1.00	1.89
ATOM	1996	HG2	ARG	126	-4.973	16.872	-7.598	1.00	1.94
ATOM	1997	CD	ARG	126	-3.016	17.274	-8.384	1.00	1.86
ATOM	1998	HD1	ARG	126	-3.016	18.288	-8.009	1.00	2.13
ATOM	1999	HD2	ARG	126	-3.324	17.274	-9.418	1.00	2.26
ATOM	2000	NE	ARG	126	-1.644	16.705	-8.277	1.00	2.80
ATOM	2001	HE	ARG	126	-1.438	16.050	-7.577	1.00	3.15
ATOM	2002	CZ	ARG	126	-0.715	17.081	-9.112	1.00	3.67

ATOM	2003	NH1	ARG	126	0.490	16.589	-9.016	1.00	4.70
ATOM	2004	11	ARG	126	0.702	15.922	-8.301	1.00	4.91
ATOM	2005	12	ARG	126	1.201	16.878	-9.657	1.00	5.46
ATOM	2006	NH2	ARG	126	-0.991	17.952	-10.045	1.00	3.92
ATOM	2007	HH21	ARG	126	-1.914	18.330	-10.118	1.00	3.48
ATOM	2008	HH22	ARG	126	-0.280	18.241	-10.685	1.00	4.82
ATOM	2009	C	ARG	126	-5.305	12.846	-8.015	1.00	0.58
ATOM	2010	O	ARG	126	-6.275	12.714	-8.734	1.00	0.60
ATOM	2011	N	PHE	127	-4.460	11.863	-7.838	1.00	0.60
ATOM	2012	HN	PHE	127	-3.675	11.984	-7.264	1.00	0.61
ATOM	2013	CA	PHE	127	-4.693	10.563	-8.531	1.00	0.65
ATOM	2014	HA	PHE	127	-4.690	10.713	-9.600	1.00	0.72
ATOM	2015	CB	PHE	127	-3.592	9.570	-8.147	1.00	0.73
ATOM	2016	HB1	PHE	127	-3.856	8.587	-8.507	1.00	0.80
ATOM	2017	HB2	PHE	127	-3.495	9.543	-7.071	1.00	0.69
ATOM	2018	CG	PHE	127	-2.276	9.989	-8.755	1.00	0.84
ATOM	2019	CD1	PHE	127	-1.398	10.804	-8.031	1.00	0.85
ATOM	2020	HD1	PHE	127	-1.665	11.137	-7.038	1.00	0.82
ATOM	2021	CD2	PHE	127	-1.930	9.557	-10.041	1.00	0.98
ATOM	2022	HD2	PHE	127	-2.607	8.929	-10.601	1.00	1.03
ATOM	2023	CE1	PHE	127	-0.174	11.187	-8.592	1.00	0.98
ATOM	2024	HE1	PHE	127	0.503	11.815	-8.032	1.00	1.03
ATOM	2025	CE2	PHE	127	-0.706	9.941	-10.603	1.00	1.10
ATOM	2026	HE2	PHE	127	-0.439	9.609	-11.595	1.00	1.23
ATOM	2027	CZ	PHE	127	0.172	10.756	-9.878	1.00	1.09
ATOM	2028	HZ	PHE	127	1.116	11.051	-10.310	1.00	1.19
ATOM	2029	C	PHE	127	-6.041	9.987	-8.093	1.00	0.58
ATOM	2030	O	PHE	127	-6.859	9.611	-8.907	1.00	0.59
ATOM	2031	N	TYR	128	-6.280	9.920	-6.813	1.00	0.52
ATOM	2032	HN	TYR	128	-5.609	10.233	-6.171	1.00	0.54
ATOM	2033	CA	TYR	128	-7.578	9.373	-6.327	1.00	0.48
ATOM	2034	HA	TYR	128	-7.701	8.362	-6.679	1.00	0.51
ATOM	2035	CB	TYR	128	-7.602	9.392	-4.801	1.00	0.48
ATOM	2036	HB1	TYR	128	-7.542	10.415	-4.463	1.00	0.48
ATOM	2037	HB2	TYR	128	-6.762	8.832	-4.417	1.00	0.51
ATOM	2038	CG	TYR	128	-8.892	8.779	-4.309	1.00	0.48
ATOM	2039	CD1	TYR	128	-8.961	7.403	-4.059	1.00	0.51
ATOM	2040	HD1	TYR	128	-8.093	6.781	-4.220	1.00	0.53
ATOM	2041	CD2	TYR	128	-10.017	9.586	-4.100	1.00	0.51
ATOM	2042	HD2	TYR	128	-9.964	10.647	-4.292	1.00	0.52
ATOM	2043	CE1	TYR	128	-10.155	6.834	-3.601	1.00	0.56
ATOM	2044	HE1	TYR	128	-10.208	5.772	-3.408	1.00	0.61
ATOM	2045	CE2	TYR	128	-11.211	9.016	-3.642	1.00	0.55
ATOM	2046	HE2	TYR	128	-12.079	9.638	-3.482	1.00	0.61
ATOM	2047	CZ	TYR	128	-11.280	7.640	-3.393	1.00	0.58
ATOM	2048	OH	TYR	128	-12.458	7.079	-2.942	1.00	0.66
ATOM	2049	HH	TYR	128	-12.323	6.797	-2.034	1.00	1.10
ATOM	2050	C	TYR	128	-8.721	10.241	-6.847	1.00	0.45
ATOM	2051	O	TYR	128	-9.718	9.751	-7.336	1.00	0.47
ATOM	2052	N	LEU	129	-8.581	11.531	-6.724	1.00	0.45
ATOM	2053	HN	LEU	129	-7.770	11.894	-6.312	1.00	0.46
ATOM	2054	CA	LEU	129	-9.656	12.453	-7.181	1.00	0.49
ATOM	2055	HA	LEU	129	-10.566	12.245	-6.638	1.00	0.49
ATOM	2056	CB	LEU	129	-9.218	13.896	-6.916	1.00	0.53
ATOM	2057	HB1	LEU	129	-9.912	14.578	-7.383	1.00	0.60
ATOM	2058	HB2	LEU	129	-8.233	14.046	-7.335	1.00	0.55
ATOM	2059	CG	LEU	129	-9.177	14.156	-5.402	1.00	0.50
ATOM	2060	HG	LEU	129	-8.561	13.403	-4.930	1.00	0.45
ATOM	2061	CD1	LEU	129	-8.578	15.539	-5.127	1.00	0.59
ATOM	2062	HD11	LEU	129	-7.762	15.725	-5.810	1.00	1.16
ATOM	2063	HD12	LEU	129	-8.212	15.576	-4.112	1.00	1.16
ATOM	2064	HD13	LEU	129	-9.339	16.293	-5.262	1.00	1.20
ATOM	2065	CD2	LEU	129	-10.593	14.094	-4.814	1.00	0.55
ATOM	2066	HD21	LEU	129	-11.317	14.343	-5.574	1.00	1.20
ATOM	2067	HD22	LEU	129	-10.673	14.796	-3.998	1.00	1.06
ATOM	2068	HD23	LEU	129	-10.785	13.096	-4.448	1.00	1.16
ATOM	2069	C	LEU	129	-9.901	12.261	-8.678	1.00	0.55
ATOM	2070	O	LEU	129	-11.027	12.146	-9.119	1.00	0.61
ATOM	2071	N	ASP	130	-8.863	12.218	-9.467	1.00	0.59
ATOM	2072	HN	ASP	130	-7.959	12.306	-9.100	1.00	0.60
ATOM	2073	CA	ASP	130	-9.063	12.023	-10.930	1.00	0.67
ATOM	2074	HA	ASP	130	-9.667	12.828	-11.323	1.00	0.75
ATOM	2075	CB	ASP	130	-7.705	12.003	-11.636	1.00	0.76
ATOM	2076	HB1	ASP	130	-7.838	11.690	-12.661	1.00	0.81
ATOM	2077	HB2	ASP	130	-7.048	11.311	-11.130	1.00	0.74
ATOM	2078	CG	ASP	130	-7.091	13.403	-11.609	1.00	0.87
ATOM	2079	OD1	ASP	130	-7.835	14.351	-11.416	1.00	1.23

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ATOM   2080  OD2 ASP   130      -5.888  13.504 -11.783  1.00  1.58
ATOM   2081  C   ASP   130      -9.778  10.693 -11.158  1.00  0.65
ATOM   2082  O   ASP   130     -10.766  10.615 -11.859  1.00  0.72
ATOM   2083  N   LEU   131      -9.292   9.645 -10.556  1.00  0.61
ATOM   2084  HN  LEU   131      -8.499   9.731  -9.986  1.00  0.59
ATOM   2085  CA  LEU   131      -9.949   8.321 -10.719  1.00  0.66
ATOM   2086  HA  LEU   131     -10.108   8.123 -11.768  1.00  0.73
ATOM   2087  CB  LEU   131      -9.066   7.221 -10.112  1.00  0.70
ATOM   2088  HB1 LEU   131      -9.501   6.255 -10.319  1.00  0.78
ATOM   2089  HB2 LEU   131      -9.011   7.363  -9.042  1.00  0.65
ATOM   2090  CG  LEU   131      -7.649   7.280 -10.701  1.00  0.76
ATOM   2091  HG  LEU   131      -7.339   8.308 -10.805  1.00  0.74
ATOM   2092  CD1 LEU   131      -6.686   6.551  -9.763  1.00  0.85
ATOM   2093 HD11 LEU   131      -5.747   6.382 -10.270  1.00  1.47
ATOM   2094 HD12 LEU   131      -7.114   5.603  -9.472  1.00  1.25
ATOM   2095 HD13 LEU   131      -6.516   7.154  -8.883  1.00  1.30
ATOM   2096  CD2 LEU   131      -7.619   6.591 -12.073  1.00  0.85
ATOM   2097 HD21 LEU   131      -8.623   6.483 -12.452  1.00  1.38
ATOM   2098 HD22 LEU   131      -7.167   5.616 -11.974  1.00  1.27
ATOM   2099 HD23 LEU   131      -7.038   7.187 -12.760  1.00  1.36
ATOM   2100  C   LEU   131     -11.296   8.339  -9.994  1.00  0.67
ATOM   2101  O   LEU   131     -12.196   7.593 -10.325  1.00  0.82
ATOM   2102  N   THR   132     -11.426   9.177  -8.992  1.00  0.58
ATOM   2103  HN  THR   132     -10.679   9.756  -8.743  1.00  0.52
ATOM   2104  CA  THR   132     -12.702   9.242  -8.217  1.00  0.65
ATOM   2105  HA  THR   132     -13.392   8.501  -8.588  1.00  0.79
ATOM   2106  CB  THR   132     -12.417   8.962  -6.735  1.00  0.60
ATOM   2107  HB  THR   132     -13.350   8.813  -6.214  1.00  0.74
ATOM   2108  OG1 THR   132     -11.734  10.071  -6.169  1.00  0.53
ATOM   2109  HG1 THR   132     -10.823  10.044  -6.471  1.00  1.02
ATOM   2110  CG2 THR   132     -11.555   7.703  -6.592  1.00  0.79
ATOM   2111 HG21 THR   132     -12.092   6.965  -6.013  1.00  1.38
ATOM   2112 HG22 THR   132     -10.634   7.953  -6.088  1.00  1.32
ATOM   2113 HG23 THR   132     -11.332   7.299  -7.567  1.00  1.28
ATOM   2114  C   THR   132     -13.339  10.629  -8.348  1.00  0.77
ATOM   2115  O   THR   132     -13.331  11.414  -7.421  1.00  0.84
ATOM   2116  N   ASN   133     -13.911  10.931  -9.481  1.00  0.97
ATOM   2117  HN  ASN   133     -13.917  10.281 -10.213  1.00  1.04
ATOM   2118  CA  ASN   133     -14.569  12.260  -9.651  1.00  1.21
ATOM   2119  HA  ASN   133     -14.028  13.005  -9.086  1.00  1.15
ATOM   2120  CB  ASN   133     -14.583  12.652 -11.131  1.00  1.44
ATOM   2121  HB1 ASN   133     -15.359  13.383 -11.301  1.00  1.70
ATOM   2122  HB2 ASN   133     -14.778  11.775 -11.732  1.00  1.60
ATOM   2123  CG  ASN   133     -13.231  13.247 -11.522  1.00  1.35
ATOM   2124  OD1 ASN   133     -13.027  14.440 -11.414  1.00  1.57
ATOM   2125  ND2 ASN   133     -12.292  12.464 -11.972  1.00  1.89
ATOM   2126 HD21 ASN   133     -12.455  11.502 -12.057  1.00  2.51
ATOM   2127 HD22 ASN   133     -11.422  12.839 -12.225  1.00  1.97
ATOM   2128  C   ASN   133     -16.010  12.179  -9.142  1.00  1.48
ATOM   2129  O   ASN   133     -16.515  11.115  -8.847  1.00  1.63
END
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CLAIMS

1. A representation of the three-dimensional solution structure of an RGS protein or portion thereof generated using the structural coordinates for RGS4-core protein.

2. The representation of claim 1 that is a representation of an RGS subfamily B protein.

3. The representation of claim 1 that is a representation of an RGS4.

4. The representation of claim 1 that is a representation of rat RGS4 .

5. The representation of claim 1 that is a representation of the Gα binding site of an RGS protein.

6. The representation of claim 1 that is a representation of the α_6-α_7 region of an RGS protein.

7. The representation of claim 1 that is a representation of the allosteric binding site in the α1-α2 region of an RGS protein.

8. The representation of claim 1 which comprises the entire core region of an RGS protein.

9. The representation of claim 1 that is generated using the structural coordinates for RGS4-core protein as determined by NMR spectroscopy.

10. A method for identifying, selecting or designing a chemical or biochemical species which is an agonist or antagonist of RGS activity, RGS binding or RGS-Gα complex activity which comprised the steps:

(a) studying the interaction of one or more chemical or biochemical test species with the three-dimensional solution structure of an RGS4 protein or a portion thereof; and

(b) selecting a chemical or biochemical test species, which is predicted by its interaction with the three-dimensional structure

of RGS4 to act as an agonist or antagonist of an RGS protein to thereby identify, select or design the agonist or antagonist.

11. The method of claim 10 wherein the agonist or antagonist is identified, selected or designed based on its predicted interaction with a Gα binding site of a free RGS4 protein.

12. The method of claim 10 wherein the agonist or antagonist is identified, selected or designed based on its predicted interaction with an allosteric binding site of a free RGS protein.

13. The method of claim 12 wherein the allosteric binding site is located in the α_1-α_2 region of a free RGS4 protein.

14. The method of claim 10 wherein the agonist or antagonist is identified, selected or designed based on its predicted interaction with the α_6-α_7 region of a free RGS4 protein.

15. The method of claim 10 wherein the test species are selected from small organic molecules.

16. The method of claim 10 further comprising the steps of:

(a) obtaining the selected test species and

(b) assaying the test species to measure its activity as an agonist or antagonist of RGS activity, RGS binding or RGS-Gα complex activity.

17. An agonist or antagonist identified, selected or designed by the method of claim 10.

18. A process for identifying a substance that inhibits RGS activity, RGS binding or RGS-Gα complex activity comprising the step of determining the interaction between a candidate species and the structure of free RGS using a representation of the three-dimensional solution structure of RGS4.

19. A process for identifying a substance that mimics or promotes RGS activity, RGS binding or RGS-Gα complex activity comprising the step of determining the interaction between a candidate species and a representation of the three-dimensional structure of free RGS4.

20. A method of identifying antagonist or agonists of RGS activity, RGS binding or RGS4/Gα complex activity by rational drug design comprising the steps:

(a) designing a potential antagonist or agonist that will form a reversible or non-reversible bond with one or more amino acids in the RGS4 Gα binding site based upon the NMR structure coordinates of free RGS;

(b) synthesizing or otherwise obtaining the antagonist or agonist; and

(c) determining whether the potential antagonist or agonist inhibits or promotes the activity of RGS or RGS4/G_α complex.

21. The method of claim 20 wherein said antagonist or agonist is designed to interact with one or more atoms of said one or more amino acids in the RGS4 Gα binding site and wherein said one or more amino acids is selected from the group of D117, S118 or R121.

22. The method of claim 20 wherein the amino acids are selected from S39, E41, N42, L113, D117, S118, R121 or N82

23. A method for identifying antagonist or agonists of RGS activity, RGS binding or RGS4/Gα complex activity by rational drug design comprising the steps:

(a) designing a potential antagonist or agonist that will form a reversible or non-reversible bond with one or more amino acids in the allosteric binding site in the α1-α2 region of RGS based upon the NMR structure coordinates of free RGS4;

(b) synthesizing or otherwise obtaining the antagonist or agonist; and

(c) determining whether the potential antagonist or agonist inhibits or promotes the activity of RGS or RGS4/G_α complex.

24. The method of claim 23 wherein said antagonist or agonist is designed to interact with one or more atoms of said one or more amino acids in the allosteric binding site and wherein said one or more atoms is selected from the group of RGS residues V10, W13, L17, I20, H23, E24, C25 and T132.

25. An agonist or antagonist identified by the method of claim 23.

26. A method of identifying antagonist or agonists of RGS activity, RGS binding or RGS4/Gα complex activity by rational drug design comprising the steps:

(a) designing a potential antagonist or agonist that will form a reversible or non-reversible bond with one or more amino acids in the α_6-α_7 region of RGS4;

(b) synthesizing or otherwise obtaining the antagonist or agonist; and

(c) determining whether the potential antagonist or agonist inhibits or promotes the activity of RGS or RGS4-G_α complex.

27. The method of claim 26 wherein the antagonist or agonist activity is assesses using an enzyme assay.

28. A method for identifying a potential antagonist or agonist of RGS activity, RGS binding or RGS-Gα complex activity by rational drug design comprising the steps:

(a) providing a three dimensional structure of a free RGS;

(b) employing the three dimensional structure of step (a) to design or select a potential antagonist or agonist; and

(c) synthesizing or otherwise obtaining the potential antagonist or agonist.

29. The method of claim 28 further comprising the step of testing the potential antagonist or agonist for biological activity as an antagonist or agonist of RGS activity, RGS binding or RGS-Gα complex activity.

30. The method of claim 28 wherein the three dimensional structure of step (a) is that of free RGS4 as defined by the relative structural coordinates of RGS4-core protein according to Table 2, ± a root mean square deviation of not more than 1.5Å from the conserved backbone atoms of the amino acids of RGS4-core.

31. An agonist or antagonist identified by the method of claim 28.

32. The method of claim 28 wherein the three dimensional structure of step (a) is that of an RGS protein other than RGS4 and wherein the three dimensional structure of the RGS protein other than RGS4 is obtained by molecular replacement analysis or homology modeling techniques employing the relative structural coordinates of RGS4-core protein according to Table 2, ± a root mean square deviation of not more than 1.5Å from the conserved backbone atoms of the amino acids of RGS4-core.

33. The method of claim 32 wherein the RGS protein other than RGS4 is an RGS subfamily B protein.

34. The method of claim 28 wherein the step of employing the three dimensional structure to designing or select the potential inhibitor comprises the steps of:

(a) identifying chemical or biochemical species or fragments thereof capable of binding to an RGS4 protein; and

(a) assembling the identified chemical entities or fragments into a single molecule to provide the structure of a potential inhibitor.

35. The method of claim 34 wherein in step (a) the chemical or biochemical species or fragments thereof capable of binding to the Gα binding site of a free RGS-core is a protein.

36. The method of claim 34 wherein in step (a) the chemical or biochemical species or fragments thereof capable of binding to the allosteric binding site in the α_1-α_2 region of a free RGS core protein are identified.

37. The method of claim 34 wherein in step (a) the chemical or biochemical species or fragments thereof capable of binding to α_6-α_7 region of a free RGS core protein are identified.

38. The method of claim 34 further comprising the step of testing the potential inhibitor designed or selected in step (b) as an antagonist or agonist of an RGS protein.

39. An agonist or antagonist identified by the method of claim 34.

40. A method for identifying a mutant of RGS4 where the biological activity of the derivative is different from that of RGS4 comprising the steps of:

(a) identifying amino acid residues of RGS4 protein that are involved in the function of the protein for regulation of G-protein signaling from the three dimensional structure of free RGS4;

(b) modifying one or more of the RGS4 amino acid residues identified in step (a) to generate the derivative of RGS4.

41. The method of claim 40 wherein the amino acid residues of RGS4 are modified by site directed mutagenesis of an RGS4 coding sequences

after which the derivative RGS4 protein is expressed from the mutagenized RGS4 coding sequence.

42. The method of claim 40 wherein the amino acids modified are in the Gα binding site of RGS4.

43. The method of claim 40 wherein the amino acids modified are in an allosteric binding site of RGS4.

44. The method of claim 40 wherein the amino acids modified are in the α_6-α_7 region of RGS4.

45. A method for identifying potential agonists and antagonists of an RGS protein which comprises the steps of:

(a) identifying an RGS binding site by detecting perturbations of the NMR resonances in NMR spectra of RGS4 core protein in the presence and absence of chemical and biochemcial species that potential bind to RGS4;

(a) employing the three dimensional structure of free RGS4 at the binding site identified in step (b) to select or design chemical or biochemical species that are predicted to bind at the binding site;

(a) testing the chemical or biochemical species that are predicted to bind at the binding site for function as an antagonist or agonist of RGS activity or RGS-Gα complex activity.