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(54) Title: ANTIBODY DESIGN USING ANTI-LIPID ANTIBODY CRYSTAL STRUCTURES

(57) Abstract: The present invention provides crystalline forms of an anti-lipid antibody or fragment thereof, which may further comprise a lipid ligand of said antibody and/or salts, metals, or co-factors. Methods for making such crystals and co-crystals are provided. The lipid may be a bioactive lipid, including sphingolipids such as S1P. X-ray coordinates of such a crystal are provided, as are methods of using this information in antibody design or optimization. Methods for designing a humanized antibody to a lipid are provided. These methods may be performed in silico and may be intended to enhance binding affinity of an antibody to its original target lipid, and/or to alter binding specificity. Antibodies produced by these methods are also provided.



WO 2010/065921 A2

ANTIBODY DESIGN USING ANTI-LIPID ANTIBODY CRYSTAL STRUCTURES

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Background of the Invention

1. Field of the Invention.

The present invention relates to crystalline forms of anti-lipid antibodies, methods of making them, and methods of using data derived therefrom in antibody design and optimization. Methods for designing antibodies or antibody fragments are provided, wherein the antibody target is a lipid, such as a bioactive lipid.

The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein, or any publication specifically or implicitly referenced herein, is prior art, or even particularly relevant, to the presently claimed invention.

2. Background.

Bioactive signaling lipids

Lipids and their derivatives are now recognized as important targets for medical research, not as just simple structural elements in cell membranes or as a source of energy for β -oxidation, glycolysis or other metabolic processes. In particular, certain bioactive lipids function as signaling mediators important in animal and human disease. Although most of the lipids of the plasma membrane play an exclusively structural role, a small proportion of them are involved in relaying extracellular stimuli into cells. "Lipid signaling" refers to any of a number of cellular signal transduction pathways that use cell membrane lipids as second messengers, as well as referring to direct interaction of a lipid signaling molecule with its own specific receptor. Lipid signaling pathways are activated by a variety of extracellular stimuli, ranging from growth factors to inflammatory cytokines, and regulate cell fate decisions such as apoptosis, differentiation and proliferation. Research into bioactive lipid signaling is an area of intense scientific investigation as more and more bioactive lipids are identified and their actions characterized.

Examples of bioactive lipids include the eicosanoids (including the cannabinoids, leukotrienes, prostaglandins, lipoxins, epoxyeicosatrienoic acids, and isoeicosanoids) such as the hydroxyeicosatetraenoic acids (HETEs, including 5-HETE, 12-HETE, 15-HETE and 20-HETE), non-eicosanoid cannabinoid mediators, phospholipids and their derivatives such as phosphatidic acid (PA) and phosphatidylglycerol (PG), platelet activating factor (PAF) and cardiolipins as well as lysophospholipids such as lysophosphatidyl choline (LPC) and various lysophosphatidic acids (LPA). Bioactive signaling lipid mediators also include the sphingolipids such as sphingomyelin, ceramide, ceramide-1-phosphate, sphingosine, sphingosylphosphoryl choline, sphinganine, sphinganine-1-phosphate (Dihydro-S1P) and sphingosine-1-phosphate. Sphingolipids and their derivatives represent a group of extracellular and intracellular signaling molecules with pleiotropic effects on important cellular processes. Other examples of bioactive signaling lipids include phosphatidylserine (PS), phosphatidylinositol (PI), phosphatidylethanolamine (PEA), diacylglyceride (DG), sulfatides, gangliosides, and cerebroside.

Sphingolipids are a unique class of lipids that were named, due to their initially mysterious nature, after the Sphinx. Sphingolipids were initially characterized as primary structural components of cell membranes, but recent studies indicate that sphingolipids also serve as cellular signaling and regulatory molecules (Hannun, et al., *Adv. Lipid Res.* 25:27-41, 1993; Spiegel, et al., *FASEB J.* 10:1388-1397, 1996; Igarashi, J. *Biochem* 122:1080-1087, 1997; Hla, T. (2004). *Semin Cell Dev Biol*, **15**, 513-2; Gardell, S.E., Dubin, A.E. & Chun, J. (2006). *Trends Mol Med*, **12**, 65-75). Sphingolipids are primary structural components of cell membranes that also serve as cellular signaling and regulatory molecules (Hannun and Bell, *Adv. Lipid Res.* 25: 27-41, 1993; Igarashi, J. *Biochem* 122: 1080-1087, 1997). The sphingolipid signaling mediators, ceramide (CER), sphingosine (SPH) and sphingosine-1-phosphate (S1P), have been most widely studied and have recently been appreciated for their roles in the cardiovascular system, angiogenesis and tumor biology (Claus, et al., *Curr Drug Targets* 1: 185-205, 2000; Levade, et al., *Circ. Res.* 89: 957-968, 2001; Wang, et al., *J. Biol. Chem.* 274: 35343-50, 1999; Wascholowski and Giannis, *Drug News Perspect.* 14: 581-90, 2001; Spiegel, S. & Milstien, S. (2003). Sphingosine-1-phosphate: an enigmatic signaling lipid. *Nat Rev Mol Cell Biol*, **4**, 397-407).

For a review of sphingolipid metabolism, see Liu, et al., *Crit Rev. Clin. Lab. Sci.* 36:511-573, 1999. For reviews of the sphingomyelin signaling pathway, see Hannun, et al., *Adv. Lipid Res.* 25:27-41, 1993; Liu, et al., *Crit. Rev. Clin. Lab. Sci.* 36:511-573, 1999; Igarashi, J. *Biochem.* 122:1080-1087, 1997; Oral, et al., *J. Biol. Chem.* 272:4836-4842, 1997; and Spiegel et al., *Biochemistry (Moscow)* 63:69-83, 1998.

Sphingosine-1-Phosphate (S1P)

S1P is a mediator of cell proliferation and protects from apoptosis through the activation of survival pathways (Maceyka, et al. (2002), *BBA*, vol. 1585): 192-201, and Spiegel, et al. (2003), *Nature Reviews Molecular Cell Biology*, vol. 4: 397-407). It has been proposed that the balance between

CER/SPH levels and S1P provides a rheostat mechanism that decides whether a cell is directed into the death pathway or is protected from apoptosis. The key regulatory enzyme of the rheostat mechanism is sphingosine kinase (SPHK) whose role is to convert the death-promoting bioactive signaling lipids (CER/SPH) into the growth-promoting S1P. S1P has two fates: S1P can be degraded by S1P lyase, an enzyme that cleaves S1P to phosphoethanolamine and hexadecanal, or, less common, hydrolyzed by S1P phosphatase to SPH.

The pleiotropic biological activities of S1P are mediated via a family of G protein-coupled receptors (GPCRs) originally known as Endothelial Differentiation Genes (EDG). Five GPCRs have been identified as high-affinity S1P receptors (S1PRs): S1P₁/EDG-1, S1P₂/EDG-5, S1P₃/EDG-3, S1P₄/EDG-6, and S1P₅/EDG-8 only identified as late as 1998 (Lee, et al., 1998). Many responses evoked by S1P are coupled to different heterotrimeric G proteins (G_q, G_i, G₁₂₋₁₃) and the small GTPases of the Rho family (Gardell, et al., 2006).

In the adult, S1P is released from platelets (Murata et al., 2000) and mast cells to create a local pulse of free S1P (sufficient enough to exceed the K_d of the S1PRs) for promoting wound healing and participating in the inflammatory response. Under normal conditions, the total S1P in the plasma is quite high (300-500 nM); however, it has been hypothesized that most of the S1P may be 'buffered' by serum proteins, particularly lipoproteins (e.g., HDL>LDL>VLDL) and albumin, so that the bio-available S1P (or the free fraction of S1P) is not sufficient to appreciably activate S1PRs (Murata et al., 2000). If this were not the case, inappropriate angiogenesis and inflammation would result. Intracellular actions of S1P have also been suggested (see, e.g., Spiegel S, Kolesnick R (2002), *Leukemia*, vol. 16: 1596-602; Suomalainen, *et al* (2005), *Am J Pathol*, vol. 166: 773-81).

Widespread expression of the cell surface S1P receptors allows S1P to influence a diverse spectrum of cellular responses, including proliferation, adhesion, contraction, motility, morphogenesis, differentiation, and survival. This spectrum of response appears to depend upon the overlapping or distinct expression patterns of the S1P receptors within the cell and tissue systems. In addition, crosstalk between S1P and growth factor signaling pathways, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and basic fibroblastic growth factor (bFGF), have recently been demonstrated (see, e.g., Baudhuin, et al. (2004), *FASEB J*, vol. 18: 341-3). The regulation of various cellular processes involving S1P has particular impact on neuronal signaling, vascular tone, wound healing, immune cell trafficking, reproduction, and cardiovascular function, among others. Alterations of endogenous levels of S1P within these systems can have detrimental effects, eliciting several pathophysiological conditions, including cancer, inflammation, angiogenesis, heart disease, asthma, and autoimmune diseases.

A recent novel approach to the treatment of various diseases and disorders, including cardiovascular diseases, cerebrovascular diseases, and various cancers, involves reducing levels of biologically available S1P, either alone or in combination with other treatments. While sphingolipid-based treatment strategies that target key enzymes of the sphingolipid metabolic pathway, such as SPHK,

have been proposed, interference with the lipid mediator S1P itself has not until recently been emphasized, largely because of difficulties in directly mitigating this lipid target, in particular because of the difficulty first in raising and then in detecting antibodies against the S1P target.

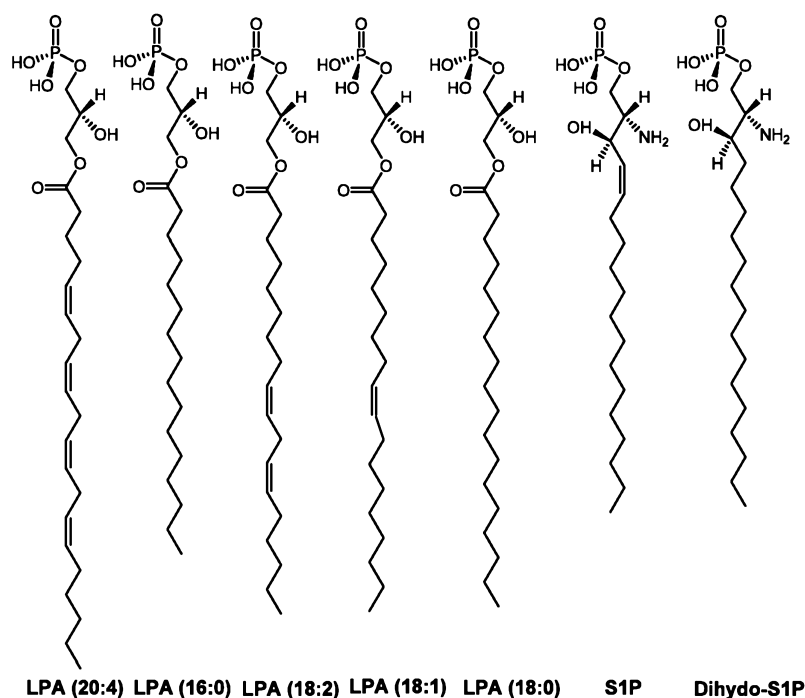
Recently, the generation of antibodies specific for S1P has been described. See, e.g., commonly owned, U.S. patent application Serial No. 20070148168; WO2007/053447. Such antibodies, which can, for example, selectively adsorb S1P from serum, act as molecular sponges to neutralize extracellular S1P. See also commonly owned U.S. patent numbers 6,881,546 and 6,858,383 and U.S. patent application serial number 10/029,372. SPHINGOMAB™, the murine monoclonal antibody (mAb) developed by Lpath, Inc. and described in certain patents or patent applications listed above, has been shown to be effective in models of human disease. In some situations, a humanized antibody may be preferable to a murine antibody, particularly for therapeutic uses in humans, where human-anti-mouse antibody (HAMA) response may occur. Such a response may reduce the effectiveness of the antibody by neutralizing the binding activity and/or by rapidly clearing the antibody from circulation in the body. The HAMA response can also cause toxicities with subsequent administrations of mouse antibodies.

A first-in-class humanized anti-S1P antibody (Sonepcizumab, LT1009) has now been developed and is described herein. This antibody is expected to have all the advantages of the murine mAb in terms of efficacy in binding S1P, neutralizing S1P and modulating disease states related to S1P, but with none of the potential disadvantages of the murine mAb when used in a human context. As described in the examples hereinbelow, this humanized antibody has in fact shown activity greater than that of the parent (murine) antibody in animal models of disease. Sonepcizumab is currently in clinical trials for cancer and age-related macular degeneration.

Lysolipids

Lysolipids are low molecular weight lipids that contain a polar head group and a single hydrocarbon backbone, due to the absence of an acyl group at one or both possible positions of acylation. Relative to the polar head group at sn-3, the hydrocarbon chain can be at the sn-2 and/or sn-1 position(s) (the term “lyso,” which originally related to hemolysis, has been redefined by IUPAC to refer to deacylation). See “Nomenclature of Lipids, www.chem.qmul.ac.uk/iupac/lipid/lip1n2.html. These lipids are representative of signaling, bioactive lipids, and their biologic and medical importance highlight what can be achieved by targeting lipid signaling molecules for therapeutic, diagnostic/prognostic, or research purposes (Gardell, *et al.* (2006), Trends in Molecular Medicine, vol 12: 65-75). Two particular examples of medically important lysolipids are LPA (glycerol backbone) and S1P (sphingoid backbone). Other lysolipids include sphingosine, lysophosphatidylcholine (LPC), sphingosylphosphorylcholine (lysosphingomyelin), ceramide, ceramide-1-phosphate, sphinganine (dihydrosphingosine), dihydrosphingosine-1-phosphate and N-acetyl-ceramide-1-phosphate. In contrast, the plasmalogens, which contain an *O*-alkyl (-O-CH₂-) or *O*-alkenyl ether at the C-1 (*sn*1) and an acyl at C-2, are excluded from the lysolipid genus.

The structures of selected LPAs, S1P, and dihydro S1P are presented below.



LPA is not a single molecular entity but a collection of endogenous structural variants with fatty acids of varied lengths and degrees of saturation (Fujiwara, et al. (2005), J Biol Chem, vol. 280: 35038-35050). The structural backbone of the LPAs is derived from glycerol-based phospholipids such as phosphatidylcholine (PC) or phosphatidic acid (PA). In the case of lysosphingolipids such as S1P, the fatty acid of the ceramide backbone at sn-2 is missing. The structural backbone of S1P, dihydro S1P (DHS1P) and sphingosylphosphorylcholine (SPC) is based on sphingosine, which is derived from sphingomyelin.

LPA and S1P regulate various cellular signaling pathways by binding to the same class of multiple transmembrane domain G protein-coupled (GPCR) receptors (Chun J, Rosen H (2006), Current Pharm Des, vol. 12: 161-171, and Moolenaar, WH (1999), Experimental Cell Research, vol. 253: 230-238). The S1P receptors are designated as S1P₁, S1P₂, S1P₃, S1P₄ and S1P₅ (formerly EDG-1, EDG-5/AGR16, EDG-3, EDG-6 and EDG-8) and the LPA receptors designated as LPA₁, LPA₂, LPA₃ (formerly, EDG-2, EDG-4, and EDG-7). A fourth LPA receptor of this family has been identified for LPA (LPA₄), and other putative receptors for these lysophospholipids have also been reported.

Lysophosphatic Acids (LPA)

LPAs have long been known as precursors of phospholipid biosynthesis in both eukaryotic and prokaryotic cells, but LPAs have emerged only recently as signaling molecules that are rapidly produced and released by activated cells, notably platelets, to influence target cells by acting on specific cell-surface receptor (see, e.g., Moolenaar, *et al.* (2004), BioEssays, vol. 26: 870-881, and van Leewen *et al.* (2003), Biochem Soc Trans, vol 31: 1209-1212). Besides being synthesized and processed to more

complex phospholipids in the endoplasmic reticulum, LPA can be generated through the hydrolysis of pre-existing phospholipids following cell activation; for example, the sn-2 position is commonly missing a fatty acid residue due to deacylation, leaving only the sn-1 hydroxyl esterified to a fatty acid.

Moreover, a key enzyme in the production of LPA, autotoxin (lysoPLD/NPP2), may be the product of an oncogene, as many tumor types up-regulate autotoxin (Brindley, D. (2004), J Cell Biochem, vol. 92: 900-12). The concentrations of LPA in human plasma and serum have been reported, including determinations made using a sensitive and specific LC/MS procedure (Baker, *et al.* (2001), Anal Biochem, vol 292: 287-295). For example, in freshly prepared human serum allowed to sit at 25°C for one hour, LPA concentrations have been estimated to be approximately 1.2 μ M, with the LPA analogs 16:0, 18:1, 18:2, and 20:4 being the predominant species. Similarly, in freshly prepared human plasma allowed to sit at 25°C for one hour, LPA concentrations have been estimated to be approximately 0.7 μ M, with 18:1 and 18:2 LPA being the predominant species.

LPA influences a wide range of biological responses, ranging from induction of cell proliferation, stimulation of cell migration and neurite retraction, gap junction closure, and even slime mold chemotaxis (Goetzl, *et al.* (2002), Scientific World Journal, vol. 2: 324-338). The body of knowledge about the biology of LPA continues to grow as more and more cellular systems are tested for LPA responsiveness. For instance, it is now known that, in addition to stimulating cell growth and proliferation, LPA promote cellular tension and cell-surface fibronectin binding, which are important events in wound repair and regeneration (Moolenaar, *et al.* (2004), BioEssays, vol. 26: 870-881). Recently, anti-apoptotic activity has also been ascribed to LPA, and it has recently been reported that peroxisome proliferation receptor gamma is a receptor/target for LPA (Simon, *et al.* (2005), J Biol Chem, vol. 280: 14656-14662). LPA is now recognized as a key signaling molecule involved in the etiology of cancer. Murph, M and Mills, GB (2007) Expert Rev. Mol. Med. 9:1-18.

LPA has proven to be a difficult target for antibody production, although there has been a report in the scientific literature of the production of polyclonal murine antibodies against LPA (Chen *et al.* (2000) Med Chem Lett, vol 10: 1691-3).

Lpath has recently humanized a monoclonal antibody against LPA, disclosed in US Patent application US20080145360 (attorney docket no. LPT-3100-UT4). The humanized anti-LPA antibody, LT3015, exhibits picomolar binding affinity as demonstrated using surface plasmon resonance and is highly specific for LPA.

Structure and Design of Monoclonal Antibodies

Soluble antibodies of the Immunoglobulin G (IgG) class consist of a pair of heavy and light chains that are held together by intra- and interchain disulfide bonds to generate the characteristic Y-shaped structure (Figure 1). In terms of protein tertiary structure, antibodies consist entirely of the immunoglobulin domain—a fold that is common to many effector molecules of the immune system. Heavy chains begin with one variable domain (Vh) followed by three constant domains (Ch1-3) while

kappa light chains consist of one variable domain (Vk) followed by one constant domain (Ck). Epitope binding specificity results from variability within the amino-terminal Vh and Vk domains, particularly within six loops (CDR H1, H2, H3, L1, L2 and L3) also known as hypervariable regions.

Treatment of purified whole IgG preparations with the protease papain separates a Fab fragment consisting of both variable domains and the Ck and constant domains from the Fc domain, which contains a pair of Ch2 and Ch3 domains. The Fab fragment retains one entire variable region and, therefore, serves as a useful tool for biochemical characterization of a 1:1 interaction between the antibody and epitope. Furthermore, because it lacks the flexibility and, generally, the glycosylation inherent in native purified whole IgG, the Fab fragment is generally an excellent platform for structural studies via single crystal x-ray diffraction.

Currently, there are over 20 therapeutic antibodies on the market. It is the fastest growing segment of therapeutics largely because humanized mAbs have a high safety profile. The huge success of antibody molecular sponges like Avastin, Lucentis, Humira and Remicade have demonstrated that the use of antibody therapeutics in this mode can also be effective in the treatment of cancer, AMD, inflammatory and autoimmune disorders by neutralizing the target (in the cited cases, protein growth factors) in the extracellular space and depriving receptors of their ligand.

Lpath's ImmuneY2TM technology allows generation of monoclonal antibodies (mAb) against extracellular lipid signaling mediators. Lpath has developed a first-in-class therapeutic agent, a humanized monoclonal antibody SonepcizumabTM (LT1009; the names Sonepcizumab and LT1009 are herein used interchangeably), which was derived from the murine form of the antibody, SphingomabTM. Sonepcizumab neutralizes the bioactive lipid signaling mediator, sphingosine-1-phosphate (S1P). S1P contributes to disease in cancer, multiple sclerosis, inflammatory disease and ocular diseases that involve dysregulated angiogenesis. A systemic formulation of Sonepcizumab, ASONEPTM, is currently in Phase 1 trials for cancer while an ocular formulation of the same mAb, iSONEPTM, is in Phase 1 clinical trials for Age-related Macular Degeneration (AMD). Lpath has also recently developed the humanized mAb LpathomabTM (LT3015; the names Lpathomab and LT3015 are herein used interchangeably), a mAb against the bioactive lipid mediator, lysophosphatidic acid (LPA). In addition to regulating physiological responses such as cell adhesion, motility, cytoskeletal changes, proliferation, angiogenesis, neurite retraction, and cell survival, LPA has been implicated in the pathogenesis and progression of severe diseases including cancer, fibrosis, neuropathic pain, and inflammatory diseases.

3. Definitions

Before describing the instant invention in detail, several terms used in the context of the present invention will be defined. In addition to these terms, others are defined elsewhere in the specification, as necessary. Unless otherwise expressly defined herein, terms of art used in this specification will have their art-recognized meanings.

The term “antibody” (“Ab”) or “immunoglobulin” (Ig) refers to any form of a peptide, polypeptide derived from, modeled after or encoded by, an immunoglobulin gene, or fragment thereof, that is capable of binding an antigen or epitope. See, e.g., IMMUNOBIOLOGY, Fifth Edition, C. A. Janeway, P. Travers, M., Walport, M.J. Shlomchik, ed. Garland Publishing (2001). The term “antibody” is used herein in the broadest sense, and encompasses monoclonal, polyclonal or multispecific antibodies, minibodies, heteroconjugates, diabodies, triabodies, chimeric, antibodies, synthetic antibodies, antibody fragments, and binding agents that employ the complementarity determining regions (CDRs) of the parent antibody, or variants thereof that retain antigen binding activity. Antibodies are defined herein as retaining at least one desired activity of the parent antibody. Desired activities can include the ability to bind the antigen specifically, the ability to inhibit proliferation in vitro, the ability to inhibit angiogenesis in vivo, and the ability to alter cytokine profile(s) in vitro.

Native antibodies (native immunoglobulins) are usually heterotetrameric glycoproteins of about 150,000 Daltons, typically composed of two identical light (L) chains and two identical heavy (H) chains. The heavy chain is approximately 50 kDa in size, and the light chain is approximately 25 kDa. Each light chain is typically linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain at one end (V_L) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light-chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light- and heavy-chain variable domains.

The light chains of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains. The ratio of the two types of light chain varies from species to species. As a way of example, the average κ to λ ratio is 20:1 in mice, whereas in humans it is 2:1 and in cattle it is 1:20.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2. The heavy-chain constant domains that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

An “antibody derivative” is an immune-derived moiety, i.e., a molecule that is derived from an antibody. This includes any antibody (Ab) or immunoglobulin (Ig), and refers to any form of a peptide, polypeptide derived from, modeled after or encoded by, an immunoglobulin gene, or a fragment of such

peptide or polypeptide that is capable of binding an antigen or epitope. This comprehends, for example, antibody variants, antibody fragments, chimeric antibodies, humanized antibodies, multivalent antibodies, antibody conjugates and the like, which retain a desired level of binding activity for antigen.

As used herein, "antibody fragment" refers to a portion of an intact antibody that includes the antigen binding site or variable regions of an intact antibody, wherein the portion can be free of the constant heavy chain domains (e.g., CH2, CH3, and CH4) of the Fc region of the intact antibody. Alternatively, portions of the constant heavy chain domains (e.g., CH2, CH3, and CH4) can be included in the "antibody fragment". Antibody fragments retain antigen-binding and include Fab, Fab', F(ab')₂, Fd, and Fv fragments; diabodies; triabodies; single-chain antibody molecules (sc-Fv); minibodies, nanobodies, and multispecific antibodies formed from antibody fragments. Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an F(ab')₂ fragment that has two antigen-combining sites and is still capable of cross-linking antigen. By way of example, a Fab fragment also contains the constant domain of a light chain and the first constant domain (CH1) of a heavy chain. "Fv" is the minimum antibody fragment that contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy chain and one light chain variable domain in tight, non-covalent association. It is in this configuration that the three hypervariable regions of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six hypervariable regions confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three hypervariable regions specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site. "Single-chain Fv" or "sFv" antibody fragments comprise the V_H and V_L domains of antibody, wherein these domains are present in a single polypeptide chain. Generally, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains that enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds. Springer-Verlag, New York, pp. 269-315 (1994).

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxyl terminus of the heavy chain CH1 domain including one or more cysteine(s) from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

An "antibody variant" refers herein to a molecule which differs in amino acid sequence from the amino acid sequence of a native or parent antibody that is directed to the same antigen by virtue of addition, deletion and/or substitution of one or more amino acid residue(s) in the antibody sequence and

which retains at least one desired activity of the parent anti-binding antibody. Desired activities can include the ability to bind the antigen specifically, the ability to inhibit proliferation in vitro, the ability to inhibit angiogenesis in vivo, and the ability to alter cytokine profile in vitro. The amino acid change(s) in an antibody variant may be within a variable region or a constant region of a light chain and/or a heavy chain, including in the Fc region, the Fab region, the CH₁ domain, the CH₂ domain, the CH₃ domain, and the hinge region. In one embodiment, the variant comprises one or more amino acid substitution(s) in one or more hypervariable region(s) of the parent antibody. For example, the variant may comprise at least one, e.g. from about one to about ten, and preferably from about two to about five, substitutions in one or more hypervariable regions of the parent antibody. Ordinarily, the variant will have an amino acid sequence having at least 50% amino acid sequence identity with the parent antibody heavy or light chain variable domain sequences, more preferably at least 65%, more preferably at 80%, more preferably at least 85%, more preferably at least 90%, and most preferably at least 95%. Identity or homology with respect to this sequence is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the parent antibody residues, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. None of N-terminal, C-terminal, or internal extensions, deletions, or insertions into the antibody sequence shall be construed as affecting sequence identity or homology. The variant retains the ability to bind LPA and preferably has desired activities which are superior to those of the parent antibody. For example, the variant may have a stronger binding affinity, enhanced ability to reduce angiogenesis and/or halt tumor progression. To analyze such desired properties (for example less immunogenic, longer half-life, enhanced stability, enhanced potency), one should compare a Fab form of the variant to a Fab form of the parent antibody or a full length form of the variant to a full length form of the parent antibody, for example, since it has been found that the format of the anti-sphingolipid antibody impacts its activity in the biological activity assays disclosed herein. The variant antibody of particular interest herein can be one which displays at least about 10 fold, preferably at least about % 5, 25, 59, or more of at least one desired activity. The preferred variant is one that has superior biophysical properties as measured in vitro or superior activities biological as measured in vitro or in vivo when compared to the parent antibody.

An “anti-LPA agent” refers to any therapeutic agent that binds LPA, and includes antibodies, antibody variants, antibody-derived molecules or non-antibody-derived moieties that bind LPA and its variants.

An “anti-LPA antibody” or an “immune-derived moiety reactive against LPA” refers to any antibody or antibody-derived molecule that binds LPA. As will be understood from these definitions, antibodies or immune-derived moieties may be polyclonal or monoclonal and may be generated through a variety of means, and/or may be isolated from an animal, including a human subject.

An “anti-SIP agent” refers to any therapeutic agent that binds SIP, and includes antibodies, antibody variants, antibody-derived molecules or non-antibody-derived moieties that bind LPA and its variants.

An “anti-S1P antibody” or an “immune-derived moiety reactive against S1P” refers to any antibody or antibody-derived molecule that binds S1P. As will be understood from these definitions, antibodies or immune-derived moieties may be polyclonal or monoclonal and may be generated through a variety of means, and/or may be isolated from an animal, including a human subject.

A “bioactive lipid” refers to a lipid signaling molecule. Bioactive lipids are distinguished from structural lipids (e.g., membrane-bound phospholipids) in that they mediate extracellular and/or intracellular signaling and thus are involved in controlling the function of many types of cells by modulating differentiation, migration, proliferation, secretion, survival, and other processes. In vivo, bioactive lipids can be found in extracellular fluids, where they can be complexed with other molecules, for example serum proteins such as albumin and lipoproteins, or in “free” form, i.e., not complexed with another molecule species. As extracellular mediators, some bioactive lipids alter cell signaling by activating membrane-bound ion channels or GPCRs or enzymes or factors that, in turn, activate complex signaling systems that result in changes in cell function or survival. As intracellular mediators, bioactive lipids can exert their actions by directly interacting with intracellular components such as enzymes, ion channels or structural elements such as actin.

Examples of bioactive lipids include sphingolipids such as ceramide, ceramide-1-phosphate (C1P), sphingosine, sphinganine, sphingosylphosphorylcholine (SPC) and sphingosine-1-phosphate (S1P). Sphingolipids and their derivatives and metabolites are characterized by a sphingoid backbone (derived from sphingomyelin). Sphingolipids and their derivatives and metabolites represent a group of extracellular and intracellular signaling molecules with pleiotropic effects on important cellular processes. They include sulfatides, gangliosides and cerebroside. Other bioactive lipids are characterized by a glycerol-based backbone; for example, lysophospholipids such as lysophosphatidylcholine (LPC) and various lysophosphatidic acids (LPA), as well as phosphatidylinositol (PI), phosphatidylethanolamine (PEA), phosphatidic acid, platelet activating factor (PAF), cardiolipin, phosphatidylglycerol (PG) and diacylglyceride (DG). Yet other bioactive lipids are derived from arachidonic acid; these include the eicosanoids (including the eicosanoid metabolites such as the HETEs, cannabinoids, leukotrienes, prostaglandins, lipoxins, epoxyeicosatrienoic acids, and isoeicosanoids), non-eicosanoid cannabinoid mediators. Other bioactive lipids, including other phospholipids and their derivatives, may also be used according to the instant invention.

In some embodiments of the invention it may be preferable to target glycerol-based bioactive lipids (those having a glycerol-derived backbone, such as the LPAs) for antibody production, as opposed to sphingosine-based bioactive lipids (those having a sphingoid backbone, such as sphingosine and S1P). In other embodiments it may be desired to target arachidonic acid-derived bioactive lipids for antibody generation, and in other embodiments arachidonic acid-derived and glycerol-derived bioactive lipids but not sphingoid-derived bioactive lipids are preferred. Together the arachidonic acid-derived and glycerol-derived bioactive lipids may be referred to in the context of this invention as “non-sphingoid bioactive lipids.”

Specifically excluded from the class of bioactive lipids according to the invention are phosphatidylcholine and phosphatidylserine, as well as their metabolites and derivatives that function primarily as structural members of the inner and/or outer leaflet of cellular membranes.

The term "biologically active," in the context of an antibody or antibody fragment or variant, refers to an antibody or antibody fragment or antibody variant that is capable of binding the desired epitope and in some ways exerting a biologic effect. Biological effects include, but are not limited to, the modulation of a growth signal, the modulation of an anti-apoptotic signal, the modulation of an apoptotic signal, the modulation of the effector function cascade, and modulation of other ligand interactions.

A "biomarker" is a specific biochemical in the body which has a particular molecular feature that makes it useful for measuring the progress of disease or the effects of treatment. For example, S1P is a biomarker for certain hyperproliferative and/or cardiovascular conditions.

The term "cardiotherapeutic agent" refers to an agent that is therapeutic to diseases and disorders caused by or associated with cardiac and myocardial diseases and disorders.

"Cardiovascular therapy" encompasses cardiac therapy (treatment of myocardial ischemia and/or heart failure) as well as the prevention and/or treatment of other diseases associated with the cardiovascular system, such as heart disease. The term "heart disease" encompasses any type of disease, disorder, trauma or surgical treatment that involves the heart or myocardial tissue. Of particular interest are conditions associated with tissue remodeling. The term "cardiotherapeutic agent" refers to an agent that is therapeutic to diseases and disorders caused by or associated with cardiac and myocardial diseases and disorders.

A "carrier" refers to a moiety adapted for conjugation to a hapten, thereby rendering the hapten immunogenic. A representative, non-limiting class of carriers is proteins, examples of which include albumin, keyhole limpet hemocyanin, hemagglutinin, tetanus, and diphtheria toxoid. Other classes and examples of carriers suitable for use in accordance with the invention are known in the art. These, as well as later discovered or invented naturally occurring or synthetic carriers, can be adapted for application in accordance with the invention.

As used herein, the expressions "cell," "cell line," and "cell culture" are used interchangeably and all such designations include progeny. Thus, the words "transformants" and "transformed cells" include the primary subject cell and cultures derived there from without regard for the number of transfers. It is also understood that all progeny may not be precisely identical in DNA content, due to deliberate or inadvertent mutations. Mutant progeny that have the same function or biological activity as screened for in the originally transformed cell are included. Where distinct designations are intended, it will be clear from the context.

"Cerebrovascular therapy" refers to therapy directed to the prevention and/or treatment of diseases and disorders associated with cerebral ischemia and/or hypoxia. Of particular interest is cerebral ischemia and/or hypoxia resulting from global ischemia resulting from a heart disease, including without limitation heart failure.

The term “chemotherapeutic agent” means anti-cancer and other anti-hyperproliferative agents. Thus chemotherapeutic agents are a subset of therapeutic agents in general. Chemotherapeutic agents include, but are not limited to: DNA damaging agents and agents that inhibit DNA synthesis: anthracyclines (doxorubicin, daunorubicin, epirubicin), alkylating agents (bendamustine, busulfan, carboplatin, carmustine, chlorambucil, cyclophosphamide, dacarbazine, hexamethylmelamine, ifosfamide, lomustine, mechlorethamine, melphalan, mitotane, mytomycin, pipobroman, procarbazine, streptozocin, thiotepa, and triethylenemelamine), platinum derivatives (cisplatin, carboplatin, cis diammine-dichloroplatinum), and topoisomerase inhibitors (Camptosar); anti-metabolites such as capecitabine, chlorodeoxyadenosine, cytarabine (and its activated form, ara-CMP), cytosine arabinoside, dacarbazine, floxuridine, fludarabine, 5-fluorouracil, 5-DFUR, gemcitabine, hydroxyurea, 6-mercaptopurine, methotrexate, pentostatin, trimetrexate, 6-thioguanine); anti-angiogenics (bevacizumab, thalidomide, sunitinib, lenalidomide, TNP-470, 2-methoxyestradiol, ranibizumab, sorafenib, erlotinib, bortezomib, pegaptanib, endostatin); vascular disrupting agents (flavonoids/flavones, DMXAA, combretastatin derivatives such as CA4DP, ZD6126, AVE8062A, etc.); biologics such as antibodies (Herceptin, Avastin, Panorex, Rituxin, Zevalin, Mylotarg, Campath, Bexxar, Erbitux); endocrine therapy: aromatase inhibitors (4-hydroandrostendione, exemestane, aminoglutethimide, anastrozole, letrozole), anti-estrogens (Tamoxifen, Toremifene, Raloxifene, Faslodex), steroids such as dexamethasone; immuno-modulators: cytokines such as IFN-beta and IL2), inhibitors to integrins, other adhesion proteins and matrix metalloproteinases); histone deacetylase inhibitors like suberoylanilide hydroxamic acid; inhibitors of signal transduction such as inhibitors of tyrosine kinases like imatinib (Gleevec); inhibitors of heat shock proteins like 17-N-allylamino-17-demethoxygeldanamycin; retinoids such as all trans retinoic acid; inhibitors of growth factor receptors or the growth factors themselves; anti-mitotic compounds and/or tubulin-depolymerizing agents such as the taxoids (paclitaxel, docetaxel, taxotere, BAY 59-8862), navelbine, vinblastine, vincristine, vindesine and vinorelbine; anti-inflammatories such as COX inhibitors and cell cycle regulators, e.g., check point regulators and telomerase inhibitors.

The term “chimeric” antibody (or immunoglobulin) refers to a molecule comprising a heavy and/or light chain which is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (Cabilly, *et al.*, *infra*; Morrison *et al.*, Proc. Natl. Acad. Sci. U.S.A., vol. 81:6851 (1984)).

The term “combination therapy” refers to a therapeutic regimen that involves the provision of at least two distinct therapies to achieve an indicated therapeutic effect. For example, a combination therapy may involve the administration of two or more chemically distinct active ingredients, for example, a fast-acting chemotherapeutic agent and an anti-lipid antibody, or two different antibodies.

Alternatively, a combination therapy may involve the administration of an anti-lipid antibody together with the delivery of another treatment, such as radiation therapy and/or surgery. Further, a combination therapy may involve administration of an anti-lipid antibody together with one or more other biological agents (e.g., anti-VEGF, TGF β , PDGF, or bFGF agent), chemotherapeutic agents and another treatment such as radiation and/or surgery. In the context of the administration of two or more chemically distinct active ingredients, it is understood that the active ingredients may be administered as part of the same composition or as different compositions. When administered as separate compositions, the compositions comprising the different active ingredients may be administered at the same or different times, by the same or different routes, using the same or different dosing regimens, all as the particular context requires and as determined by the attending physician. Similarly, when one or more anti-lipid antibody species, for example, an anti-LPA antibody, alone or in conjunction with one or more chemotherapeutic agents are combined with, for example, radiation and/or surgery, the drug(s) may be delivered before or after surgery or radiation treatment.

The term "constant domain" refers to the C-terminal region of an antibody heavy or light chain. Generally, the constant domains are not directly involved in the binding properties of an antibody molecule to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody-dependent cellular toxicity. Here, "effector functions" refer to the different physiological effects of antibodies (e.g., opsonization, cell lysis, mast cell, basophil and eosinophil degranulation, and other processes) mediated by the recruitment of immune cells by the molecular interaction between the Fc domain and proteins of the immune system. The isotype of the heavy chain determines the functional properties of the antibody. Their distinctive functional properties are conferred by the carboxy-terminal portions of the heavy chains, where they are not associated with light chains.

The expression "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

A "derivatized bioactive lipid" is a bioactive lipid, e.g., LPA, which has a polar head group and at least one hydrocarbon chain, wherein a carbon atom within the hydrocarbon chain is derivatized with a pendant reactive group [e.g., a sulfhydryl (thiol) group, a carboxylic acid group, a cyano group, an ester, a hydroxy group, an alkene, an alkyne, an acid chloride group or a halogen atom] that may or may not be protected. This derivatization serves to activate the bioactive lipid for reaction with a molecule, e.g., for conjugation to a carrier.

A "derivatized bioactive lipid conjugate" refers to a derivatized bioactive lipid that is covalently conjugated to a carrier. The carrier may be a protein molecule or may be a moiety such as polyethylene glycol, colloidal gold, adjuvants or silicone beads. A derivatized bioactive lipid conjugate may be used as an immunogen for generating an antibody response according to the instant invention, and the same or a different bioactive lipid conjugate may be used as a detection reagent for detecting the antibody thus

produced. In some embodiments the derivatized bioactive lipid conjugate is attached to a solid support when used for detection.

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy chain variable domain (V_H) connected to a light chain variable domain (V_L) in the same polypeptide chain ($V_H - V_L$). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993).

"Effective concentration" refers to the absolute, relative, and/or available concentration and/or activity, for example of certain undesired bioactive lipids. In other words, the effective concentration of a bioactive lipid is the amount of lipid available, and able, to perform its biological function. In the present invention, an immune-derived moiety such as, for example, a monoclonal antibody directed to a bioactive lipid (such as, for example, C1P) is able to reduce the effective concentration of the lipid by binding to the lipid and rendering it unable to perform its biological function. In this example, the lipid itself is still present (it is not degraded by the antibody, in other words) but can no longer bind its receptor or other targets to cause a downstream effect, so "effective concentration" rather than absolute concentration is the appropriate measurement. Methods and assays exist for directly and/or indirectly measuring the effective concentration of bioactive lipids.

An "epitope" or "antigenic determinant" refers to that portion of an antigen that reacts with an antibody antigen-binding portion derived from an antibody.

The term "expression cassette" refers to a nucleotide molecule capable of affecting expression of a structural gene (i.e., a protein coding sequence, such as an antibody of the invention) in a host compatible with such sequences. Expression cassettes include at least a promoter operably linked with the polypeptide-coding sequence, and, optionally, with other sequences, e.g., transcription termination signals. Additional regulatory elements necessary or helpful in effecting expression may also be used, e.g., enhancers. Thus, expression cassettes include plasmids, expression vectors, recombinant viruses, any form of recombinant "naked DNA" vector, and the like.

A "fully human antibody" can refer to an antibody produced in a genetically engineered (i.e., transgenic) mouse (e.g. from Medarex) that, when presented with an immunogen, can produce a human antibody that does not necessarily require CDR grafting. These antibodies are fully human (100% human protein sequences) from animals such as mice in which the non-human antibody genes are suppressed and replaced with human antibody gene expression. The applicants believe that antibodies could be generated against bioactive lipids when presented to these genetically engineered mice or other animals who might be able to produce human frameworks for the relevant CDRs.

A "hapten" is a substance that is non-immunogenic but can react with an antibody or antigen-binding portion derived from an antibody. In other words, haptens have the property of antigenicity but not immunogenicity. A hapten is generally a small molecule that can, under most circumstances, elicit

an immune response (i.e., act as an antigen) only when attached to a carrier, for example, a protein, polyethylene glycol (PEG), colloidal gold, silicone beads, or the like. The carrier may be one that also does not elicit an immune response by itself. A representative, non-limiting class of hapten molecules is proteins, examples of which include albumin, keyhole limpet hemocyanin, hemagglutinin, tetanus, and diphtheria toxoid. Other classes and examples of hapten molecules are known in the art. These, as well as later discovered or invented naturally occurring or synthetic haptens, can be adapted for application in accordance with the invention.

The term "heteroconjugate antibody" can refer to two covalently joined antibodies. Such antibodies can be prepared using known methods in synthetic protein chemistry, including using crosslinking agents. As used herein, the term "conjugate" refers to molecules formed by the covalent attachment of one or more antibody fragment(s) or binding moieties to one or more polymer molecule(s).

"Humanized" forms of non-human (e.g., murine) antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. Or, looked at another way, a humanized antibody is a human antibody that also contains selected sequences from non-human (e.g., murine) antibodies in place of the human sequences. A humanized antibody can include conservative amino acid substitutions or non-natural residues from the same or different species that do not significantly alter its binding and/or biologic activity. Such antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulins. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary-determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, camel, bovine, goat, or rabbit having the desired properties. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues.

Furthermore, humanized antibodies can comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and maximize antibody performance. Thus, in general, a humanized antibody will comprise all of at least one, and in one aspect two, variable domains, in which all or all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), or that of a human immunoglobulin. See, e.g., Cabilly, *et al.*, U.S. Pat. No. 4,816,567; Cabilly, *et al.*, European Patent No. 0,125,023 B1; Boss, *et al.*, U.S. Pat. No. 4,816,397; Boss, *et al.*, European Patent No. 0,120,694 B1; Neuberger, *et al.*, WO 86/01533; Neuberger, *et al.*, European Patent No. 0,194,276 B1; Winter, U.S. Pat. No. 5,225,539; Winter, European Patent No. 0,239,400 B1; Padlan, *et al.*, European Patent Application No. 0,519,596 A1; Queen, *et al.* (1989), Proc. Nat'l Acad. Sci. USA, vol. 86:10029-10033). For further details, see Jones *et al.*, Nature 321:522-525 (1986); Reichmann *et al.*, Nature 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol. 2:593-596 (1992) and Hansen, WO2006105062.

The term “hyperproliferative disorder” refers to diseases and disorders associated with, the uncontrolled proliferation of cells, including but not limited to uncontrolled growth of organ and tissue cells resulting in cancers and benign tumors. Hyperproliferative disorders associated with endothelial cells can result in diseases of angiogenesis such as angiomas, endometriosis, obesity, age-related macular degeneration and various retinopathies, as well as the proliferation of endothelial cells and smooth muscle cells that cause restenosis as a consequence of stenting in the treatment of atherosclerosis. Hyperproliferative disorders involving fibroblasts (i.e., fibrogenesis) include but are not limited to disorders of excessive scarring (i.e., fibrosis) such as age-related macular degeneration, cardiac remodeling and failure associated with myocardial infarction, excessive wound healing such as commonly occurs as a consequence of surgery or injury, keloids, and fibroid tumors and stenting.

An “immune-derived moiety” includes any antibody (Ab) or immunoglobulin (Ig), and refers to any form of a peptide, polypeptide derived from, modeled after or encoded by, an immunoglobulin gene, or a fragment of such peptide or polypeptide that is capable of binding an antigen or epitope (see, e.g., Immunobiology, 5th Edition, Janeway, Travers, Walport, Shlomchik. (editors), Garland Publishing (2001)). In the present invention, the antigen is a lipid molecule, such as a bioactive lipid molecule.

An “immunogen” is a molecule capable of inducing a specific immune response, particularly an antibody response in an animal to whom the immunogen has been administered. In the instant invention, the immunogen is a derivatized bioactive lipid conjugated to a carrier, i.e., a “derivatized bioactive lipid conjugate”. The derivatized bioactive lipid conjugate used as the immunogen may be used as capture material for detection of the antibody generated in response to the immunogen. Thus the immunogen may also be used as a detection reagent. Alternatively, the derivatized bioactive lipid conjugate used as capture material may have a different linker and/or carrier moiety from that in the immunogen.

The phrase “in silico” refers to computer simulations that model natural or laboratory processes

To “inhibit,” particularly in the context of a biological phenomenon, means to decrease, suppress or delay. For example, a treatment yielding “inhibition of tumorigenesis” may mean that tumors do not form at all, or that they form more slowly, or are fewer in number than in the untreated control.

An “isolated” antibody is one that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of

the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

The word "label" when used herein refers to a detectable compound or composition, such as one that is conjugated directly or indirectly to the antibody. The label may itself be detectable by itself (e.g., radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition that is detectable.

A "ligand" is a substance that is able to bind to and form a complex with a biomolecule to serve a biological purpose. Thus an antigen may be described as a ligand of the antibody to which it binds.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant that is useful for delivery of a drug (such as the anti-sphingolipid antibodies disclosed herein and, optionally, a chemotherapeutic agent) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes. An "isolated" nucleic acid molecule is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the antibody nucleic acid. An isolated nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated nucleic acid molecules therefore are distinguished from the nucleic acid molecule as it exists in natural cells. However, an isolated nucleic acid molecule includes a nucleic acid molecule contained in cells that ordinarily express the antibody where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

In the context of this invention, a "liquid composition" refers to one that, in its filled and finished form as provided from a manufacturer to an end user (e.g., a doctor or nurse), is a liquid or solution, as opposed to a solid. Here, "solid" refers to compositions that are not liquids or solutions. For example, solids include dried compositions prepared by lyophilization, freeze-drying, precipitation, and similar procedures.

The expression "linear antibodies" when used throughout this application refers to the antibodies described in Zapata et al. Protein Eng. 8(10):1057-1062 (1995). Briefly, these antibodies comprise a pair of tandem Fd segments (V_H - C_H1 - V_H - C_H1) that form a pair of antigen binding regions. Linear antibodies can be bispecific or monospecific.

The term "metabolites" refers to compounds from which LPAs are made, as well as those that result from the degradation of LPAs; that is, compounds that are involved in the lysophospholipid metabolic pathways. The term "metabolic precursors" may be used to refer to compounds from which sphingolipids are made.

The term "monoclonal antibody" (mAb) as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, or to said population of antibodies. The individual antibodies comprising the population are essentially identical, except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody

preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler et al., *Nature* 256:495 (1975), or may be made by recombinant DNA methods (see, e.g., U.S. Pat. No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., *Nature* 352:624-628 (1991) and Marks et al., *J. Mol. Biol.* 222:581-597 (1991), for example, or by other methods known in the art. The monoclonal antibodies herein specifically include chimeric antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Pat. No. 4,816,567; and Morrison et al., *Proc. Natl. Acad. Sci. USA* 81:6851-6855 (1984)).

"Monotherapy" refers to a treatment regimen based on the delivery of one therapeutically effective compound, whether administered as a single dose or several doses over time.

The term "multispecific antibody" can refer to an antibody, or a monoclonal antibody, having binding properties for at least two different epitopes. In one embodiment, the epitopes are from the same antigen. In another embodiment, the epitopes are from two or more different antigens. Methods for making multispecific antibodies are known in the art. Multispecific antibodies include bispecific antibodies (having binding properties for two epitopes), trispecific antibodies (three epitopes) and so on. For example, multispecific antibodies can be produced recombinantly using the co-expression of two or more immunoglobulin heavy chain/light chain pairs. Alternatively, multispecific antibodies can be prepared using chemical linkage. One of skill can produce multispecific antibodies using these or other methods as may be known in the art. Multispecific antibodies include multispecific antibody fragments. One example of a multispecific (in this case, bispecific) antibody comprehended by this invention is an antibody having binding properties for an S1P epitope and a C1P epitope, which thus is able to recognize and bind to both S1P and C1P. Another example of a bispecific antibody comprehended by this invention is an antibody having binding properties for an epitope from a bioactive lipid and an epitope from a cell surface antigen. Thus the antibody is able to recognize and bind the bioactive lipid and is able to recognize and bind to cells, e.g., for targeting purposes.

"Neoplasia" or "cancer" refers to abnormal and uncontrolled cell growth. A "neoplasm", or tumor or cancer, is an abnormal, unregulated, and disorganized proliferation of cell growth, and is generally referred to as cancer. A neoplasm may be benign or malignant. A neoplasm is malignant, or cancerous, if it has properties of destructive growth, invasiveness, and metastasis. Invasiveness refers to

the local spread of a neoplasm by infiltration or destruction of surrounding tissue, typically breaking through the basal laminas that define the boundaries of the tissues, thereby often entering the body's circulatory system. Metastasis typically refers to the dissemination of tumor cells by lymphatics or blood vessels. Metastasis also refers to the migration of tumor cells by direct extension through serous cavities, or subarachnoid or other spaces. Through the process of metastasis, tumor cell migration to other areas of the body establishes neoplasms in areas away from the site of initial appearance.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

The "parent" antibody herein is one that is encoded by an amino acid sequence used for the preparation of the variant. The parent antibody may be a native antibody or may already be a variant, e.g., a chimeric antibody. For example, the parent antibody may be a humanized or human antibody.

A "patentable" composition, process, machine, or article of manufacture according to the invention means that the subject matter satisfies all statutory requirements for patentability at the time the analysis is performed. For example, with regard to novelty, non-obviousness, or the like, if later investigation reveals that one or more claims encompass one or more embodiments that would negate novelty, non-obviousness, *etc.*, the claim(s), being limited by definition to "patentable" embodiments, specifically exclude the non-patentable embodiment(s). Also, the claims appended hereto are to be interpreted both to provide the broadest reasonable scope, as well as to preserve their validity. Furthermore, the claims are to be interpreted in a way that (1) preserves their validity and (2) provides the broadest reasonable interpretation under the circumstances, if one or more of the statutory requirements for patentability are amended or if the standards change for assessing whether a particular statutory requirement for patentability is satisfied from the time this application is filed or issues as a patent to a time the validity of one or more of the appended claims is questioned.

The term "pharmaceutically acceptable salt" refers to a salt, such as used in formulation, which retains the biological effectiveness and properties of the agents and compounds of this invention and which are is biologically or otherwise undesirable. In many cases, the agents and compounds of this invention are capable of forming acid and/or base salts by virtue of the presence of charged groups, for example, charged amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids,

while pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. For a review of pharmaceutically acceptable salts (see Berge, *et al.* (1977) J. Pharm. Sci., vol. 66, 1-19).

A "plurality" means more than one.

The term "promoter" includes all sequences capable of driving transcription of a coding sequence in a cell. Thus, promoters used in the constructs of the invention include cis-acting transcriptional control elements and regulatory sequences that are involved in regulating or modulating the timing and/or rate of transcription of a gene. For example, a promoter can be a cis-acting transcriptional control element, including an enhancer, a promoter, a transcription terminator, an origin of replication, a chromosomal integration sequence, 5' and 3' untranslated regions, or an intronic sequence, which are involved in transcriptional regulation. Transcriptional regulatory regions suitable for use in the present invention include but are not limited to the human cytomegalovirus (CMV) immediate-early enhancer/promoter, the SV40 early enhancer/promoter, the E. coli lac or trp promoters, and other promoters known to control expression of genes in prokaryotic or eukaryotic cells or their viruses.

The term "recombinant DNA" refers to nucleic acids and gene products expressed therefrom that have been engineered, created, or modified by man. "Recombinant" polypeptides or proteins are polypeptides or proteins produced by recombinant DNA techniques, for example, from cells transformed by an exogenous DNA construct encoding the desired polypeptide or protein. "Synthetic" polypeptides or proteins are those prepared by chemical synthesis.

The terms "separated", "purified", "isolated", and the like mean that one or more components of a sample contained in a sample-holding vessel are or have been physically removed from, or diluted in the presence of, one or more other sample components present in the vessel. Sample components that may be removed or diluted during a separating or purifying step include, chemical reaction products, non-reacted chemicals, proteins, carbohydrates, lipids, and unbound molecules.

By "solid phase" is meant a non-aqueous matrix such as one to which the antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g. controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g. an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Pat. No. 4,275,149.

The term "species" is used herein in various contexts, *e.g.*, a particular species of chemotherapeutic agent. In each context, the term refers to a population of chemically indistinct molecules of the sort referred in the particular context.

The term "specific" or "specificity" in the context of antibody-antigen interactions refers to the selective, non-random interaction between an antibody and its target epitope. Here, the term "antigen" refers to a molecule that is recognized and bound by an antibody molecule or other immune-

derived moiety. The specific portion of an antigen that is bound by an antibody is termed the “epitope”. This interaction depends on the presence of structural, hydrophobic/hydrophilic, and/or electrostatic features that allow appropriate chemical or molecular interactions between the molecules. Thus an antibody is commonly said to “bind” (or “specifically bind”) or be “reactive with” (or “specifically reactive with), or, equivalently, “reactive against” (or “specifically reactive against”) the epitope of its target antigen. Antibodies are commonly described in the art as being “against” or “to” their antigens as shorthand for antibody binding to the antigen. Thus an “antibody that binds C1P,” an “antibody reactive against C1P,” an “antibody reactive with C1P,” an “antibody to C1P” and an “anti-C1P antibody” all have the same meaning in the art. Antibody molecules can be tested for specificity of binding by comparing binding to the desired antigen to binding to unrelated antigen or analogue antigen or antigen mixture under a given set of conditions. Preferably, an antibody according to the invention will lack significant binding to unrelated antigens, or even analogs of the target antigen. “Specifically associate” and “specific association” and the like refer to a specific, non-random interaction between two molecules, which interaction depends on the presence of structural, hydrophobic/hydrophilic, and/or electrostatic features that allow appropriate chemical or molecular interactions between the molecules.

The term “sphingolipid” as used herein refers to the class of compounds in the art known as sphingolipids, including, but not limited to the following compounds (see <http://www.lipidmaps.org> for chemical formulas, structural information, etc. for the corresponding compounds):

- Sphingoid bases [SP01]
- Sphing-4-enines (Sphingosines) [SP0101]
- Sphinganine [SP0102]
- 4-Hydroxysphinganine (Phytosphingosine) [SP0103]
- Sphingoid base homologs and variants [SP0104]
- Sphingoid base 1-phosphates [SP0105]
- Lysosphingomyelins and lysoglycosphingolipids [SP0106]
- N-methylated sphingoid bases [SP0107]
- Sphingoid base analogs [SP0108]
- Ceramides [SP02]
- N-acylsphingosines (ceramides) [SP0201]
- N-acylsphinganine (dihydroceramides) [SP0202]
- N-acyl-4-hydroxysphinganine (phytoceramides) [SP0203]
- Acylceramides [SP0204]
- Ceramide 1-phosphates [SP0205]
- Phosphosphingolipids [SP03]
- Ceramide phosphocholines (sphingomyelins) [SP0301]
- Ceramide phosphoethanolamines [SP0302]
- Ceramide phosphoinositols [SP0303]
- Phosphosphingolipids [SP04]
- Neutral glycosphingolipids [SP05]
- Simple Glc series (GlcCer, LacCer, etc) [SP0501]
- GalNAc1-3Gal1-4Gal1-4Glc- (Globo series) [SP0502]
- GalNAc1-4Gal1-4Glc- (Ganglio series) [SP0503]
- Gal1-3GlcNAc1-3Gal1-4Glc- (Lacto series) [SP0504]
- Gal1-4GlcNAc1-3Gal1-4Glc- (Neolacto series) [SP0505]
- GalNAc1-3Gal1-3Gal1-4Glc- (Isoglobo series) [SP0506]

GlcNAc1-2Man1-3Man1-4Glc- (Mollu series) [SP0507]
 GalNAc1-4GlcNAc1-3Man1-4Glc- (Arthro series) [SP0508]
 Gal- (Gala series) [SP0509]
 Other [SP0510]
 Acidic glycosphingolipids [SP06]
 Gangliosides [SP0601]
 Sulfoglycosphingolipids (sulfatides) [SP0602]
 Glucuronosphingolipids [SP0603]
 Phosphoglycosphingolipids [SP0604]
 Other [SP0600]
 Basic glycosphingolipids [SP07]
 Amphoteric glycosphingolipids [SP08]
 Arsenosphingolipids [SP09]

The present invention relates to anti-lipid agents, including anti-sphingolipid antibodies, that are useful for treating or preventing hyperproliferative disorders such as cancer and cardiovascular or cerebrovascular diseases and disorders and various ocular disorders, as described in greater detail below. The invention relates, among others, to antibodies to S1P and its variants including but are not limited to sphingosine-1-phosphate [sphingene-1-phosphate; D-erythro-sphingosine-1-phosphate; sphing-4-enine-1-phosphate; (E,2S,3R)-2-amino-3-hydroxy-octadec-4-enoyl]phosphonic acid (AS 26993-30-6), DHS1P is defined as dihydrosphingosine-1-phosphate [sphinganine-1-phosphate; [(2S,3R)-2-amino-3-hydroxy-octadecoyl]phosphonic acid; D-Erythro-dihydro-D-sphingosine-1-phosphate (CAS 19794-97-9); SPC is sphingosylphosphoryl choline, lysosphingomyelin, sphingosylphosphocholine, sphingosine phosphorylcholine, ethanaminium; 2-((((2-amino-3-hydroxy-4-octadecenyl)oxy)hydroxyphosphinyl)oxy)-N,N,N-trimethyl-, chloride, (R-(R*,S*-(E))), 2-[(E,2R,3S)-2-amino-3-hydroxy-octadec-4-enoyl]-hydroxy-phosphoryl]oxyethyl 1-trimethyl-azanium chloride (CAS 10216-23-6).

The term "sphingolipid metabolite" refers to a compound from which a sphingolipid is made, as well as a that results from the degradation of a particular sphingolipid. In other words, a "sphingolipid metabolite" is a compound that is involved in the sphingolipid metabolic pathways. Metabolites include metabolic precursors and metabolic products. The term "metabolic precursors" refers to compounds from which sphingolipids are made. Metabolic precursors of particular interest include but are not limited to SPC, sphingomyelin, dihydrosphingosine, dihydroceramide, and 3-ketosphinganine. The term "metabolic products" refers to compounds that result from the degradation of sphingolipids, such as phosphorylcholine (e.g., phosphocholine, choline phosphate), fatty acids, including free fatty acids, and hexadecanal (e.g., palmitaldehyde).

Herein, "stable" refers to an interaction between two molecules (e.g., a peptide and a TLR molecule) that is sufficiently stable such that the molecules can be maintained for the desired purpose or manipulation. For example, a "stable" interaction between a peptide and a TLR molecule refers to one wherein the peptide becomes and remains associated with a TLR molecule for a period sufficient to achieve the desired effect.

A “subject” or “patient” refers to an animal in need of treatment that can be effected by molecules of the invention. Animals that can be treated in accordance with the invention include vertebrates, with mammals such as bovine, canine, equine, feline, ovine, porcine, and primate (including humans and non-human primates) animals being particularly preferred examples.

A “surrogate marker” refers to laboratory measurement of biological activity within the body that indirectly indicates the effect of treatment on disease state. Examples of surrogate markers for hyperproliferative and/or cardiovascular conditions include SPHK and/or S1PRs.

A “therapeutic agent” refers to a drug or compound that is intended to provide a therapeutic effect including, but not limited to: anti-inflammatory drugs including COX inhibitors and other NSAIDS, anti-angiogenic drugs, chemotherapeutic drugs as defined above, cardiovascular agents, immunomodulatory agents, agents that are used to treat neurodegenerative disorders, ophthalmic drugs, anti-fibrotics, etc.

A “therapeutically effective amount” (or “effective amount”) refers to an amount of an active ingredient, *e.g.*, an agent according to the invention, sufficient to effect treatment when administered to a subject in need of such treatment. Accordingly, what constitutes a therapeutically effective amount of a composition according to the invention may be readily determined by one of ordinary skill in the art. In the context of cancer therapy, a “therapeutically effective amount” is one that produces an objectively measured change in one or more parameters associated with cancer cell survival or metabolism, including an increase or decrease in the expression of one or more genes correlated with the particular cancer, reduction in tumor burden, cancer cell lysis, the detection of one or more cancer cell death markers in a biological sample (*e.g.*, a biopsy and an aliquot of a bodily fluid such as whole blood, plasma, serum, urine, *etc.*), induction of apoptosis or other cell death pathways, *etc.* Of course, the therapeutically effective amount will vary depending upon the particular subject and condition being treated, the weight and age of the subject, the severity of the disease condition, the particular compound chosen, the dosing regimen to be followed, timing of administration, the manner of administration and the like, all of which can readily be determined by one of ordinary skill in the art. It will be appreciated that in the context of combination therapy, what constitutes a therapeutically effective amount of a particular active ingredient may differ from what constitutes a therapeutically effective amount of the active ingredient when administered as a monotherapy (*i.e.*, a therapeutic regimen that employs only one chemical entity as the active ingredient).

The compositions of the invention are used in methods of bioactive lipid-based therapy. As used herein, the terms “therapy” and “therapeutic” encompasses the full spectrum of prevention and/or treatments for a disease, disorder or physical trauma. A “therapeutic” agent of the invention may act in a manner that is prophylactic or preventive, including those that incorporate procedures designed to target individuals that can be identified as being at risk (pharmacogenetics); or in a manner that is ameliorative or curative in nature; or may act to slow the rate or extent of the progression of at least one symptom of a disease or disorder being treated; or may act to minimize the time required, the occurrence or extent of

any discomfort or pain, or physical limitations associated with recuperation from a disease, disorder or physical trauma; or may be used as an adjuvant to other therapies and treatments. The term "treatment" or "treating" means any treatment of a disease or disorder, including preventing or protecting against the disease or disorder (that is, causing the clinical symptoms not to develop); inhibiting the disease or disorder (*i.e.*, arresting, delaying or suppressing the development of clinical symptoms; and/or relieving the disease or disorder (*i.e.*, causing the regression of clinical symptoms). As will be appreciated, it is not always possible to distinguish between "preventing" and "suppressing" a disease or disorder because the ultimate inductive event or events may be unknown or latent. Those "in need of treatment" include those already with the disorder as well as those in which the disorder is to be prevented. Accordingly, the term "prophylaxis" will be understood to constitute a type of "treatment" that encompasses both "preventing" and "suppressing". The term "protection" thus includes "prophylaxis".

The term "therapeutic regimen" means any treatment of a disease or disorder using chemotherapeutic and cytotoxic agents, radiation therapy, surgery, gene therapy, DNA vaccines and therapy, siRNA therapy, anti-angiogenic therapy, immunotherapy, bone marrow transplants, aptamers and other biologics such as antibodies and antibody variants, receptor decoys and other protein-based therapeutics.

The "variable" region of an antibody comprises framework and complementarity determining regions (CDRs, otherwise known as hypervariable regions). The variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in six CDR segments, three in each of the light chain and the heavy chain variable domains. The more highly conserved portions of variable domains are called the framework region (FR). The variable domains of native heavy and light chains each comprise four FRs (FR1, FR2, FR3 and FR4, respectively), largely adopting a β -sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the beta-sheet structure. The term "hypervariable region" when used herein refers to the amino acid residues of an antibody which are responsible for antigen binding. The hypervariable region comprises amino acid residues from a "complementarity determining region" or "CDR" (for example residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the light chain variable domain and 31-35 (H1), 50-65 (H2) and 95-102 (H3) in the heavy chain variable domain; Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)) and/or those residues from a "hypervariable loop" (for example residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the light chain variable domain and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the heavy chain variable domain; Chothia and Lesk J. Mol. Biol. 196:901-917 (1987)). "Framework" or "FR" residues are those variable domain residues other than the hypervariable region residues as herein defined.

It should be noted that, in the art, more than one system for numbering of amino acid residues is commonly used. The CDRs above are described and numbered according to the Kabat numbering

scheme (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)) but sequential numbering may also be used. Sequential and Kabat numbering are identical for the entire LT1009 light chain, and up to position 52 in the LT1009 heavy chain. In the heavy chain (VH), according to Kabat numbering there is a single residue insertion after position 52, a three-residue insertion after position 82 and a four residue insertion after position 100. Thus residues may at times be seen to be numbered 52A, 100A, 100C etc. to reflect these insertions according to the Kabat system.

The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991), pages 647-669). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody-dependent cellular toxicity.

A “vector” or “plasmid” or “expression vector” refers to a nucleic acid that can be maintained transiently or stably in a cell to effect expression of one or more recombinant genes. A vector can comprise nucleic acid, alone or complexed with other compounds. A vector optionally comprises viral or bacterial nucleic acids and/or proteins, and/or membranes. Vectors include, but are not limited, to replicons (e.g., RNA replicons, bacteriophages) to which fragments of DNA may be attached and become replicated. Thus, vectors include, but are not limited to, RNA, autonomous self-replicating circular or linear DNA or RNA and include both the expression and non-expression plasmids. Plasmids can be commercially available, publicly available on an unrestricted basis, or can be constructed from available plasmids as reported with published protocols. In addition, the expression vectors may also contain a gene to provide a phenotypic trait for selection of transformed host cells such as dihydrofolate reductase or neomycin resistance for eukaryotic cell culture, or such as tetracycline or ampicillin resistance in *E. coli*.

Summary of the Invention

The present invention provides patentable crystalline forms of an anti-lipid antibody or fragment thereof, which may further comprise a lipid ligand of said antibody and/or salts, metals, and/or co-factors. Methods for making such crystals are provided. The lipid may be a bioactive lipid, such as a sphingolipid including SIP. X-ray coordinates of one such crystal are provided, as are methods of using this information in antibody design or optimization.

Methods for designing a humanized antibody to a lipid are provided, which may be performed in silico. These methods may result in enhanced binding affinity of an antibody to its original target lipid, or may be intended to alter binding specificity.

These and other aspects and embodiments of the invention are discussed in greater detail in the sections that follow. The foregoing and other aspects of the invention will become more apparent from the following detailed description, accompanying drawings, and the claims. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In addition, the materials, methods, and examples below are illustrative only and not intended to be limiting.

Brief Description of the Drawings

This application contains at least one figure executed in color. Copies of this application with color drawing(s) will be provided upon request and payment of the necessary fee. A brief summary of each of the figures is provided below.

Figure 1: Purification, crystallization, x-ray diffraction, and structure of the anti-S1P Fab/S1P complex. Figure 1a shows the result of an SDS- PAGE analysis showing purity of the antibody Fab fragment and its separation from the Fc fragment contaminant. Figure 1b is a photograph of a hanging drop containing Fab/S1P complex co-crystals viewed through the eyepiece of a stereomicroscope. Figure 1c is a one-degree oscillation image of x-rays diffracted by the Fab/S1P crystals. Data were collected at 100K on an R-AxisIV++ image plate detector at the SDSU MXCF. Figure 1d is a ribbon diagram structure depicting the antibody Fab/S1P complex crystal structure. The heavy chain is depicted in dark orange while the light chain is represented in light orange. S1P is in a stick representation with cpk atom coloring. The two grey spheres are Ca^{2+} ions.

Figure 2: S1P binding of LT1009 variants. Figure 2a is a bar graph showing the calculated concentrations of LT1009 variants and WT that produce half-maximal S1P binding using the direct-binding ELISA. Figure 2b is a colored structure diagram showing the structure of the LT1009Fab/S1P complex. Atoms in the light (green) and heavy (blue) chains are drawn as spheres. The atoms in the amino acid side chains substituted in the LT1009 variants are colored magenta. The carbon, oxygen and phosphorus atoms of the bound S1P are colored grey, red, and yellow, respectively.

Figure 3: Effect of metal chelators and mutations on S1P binding by LT1009. Figure 3a is a ribbon model showing the interaction of S1P (gray) with key amino acid residues in the anti-S1P antibody. The calcium atoms are shown in purple. Figure 3b is a line graph showing the negative effect of chelators EGTA and EDTA on LT1009-S1P binding. Figure 3c is a line graph showing the effect of mutation of certain amino acid residues on LT1009-S1P binding. Numbering of amino acid residues is sequential.

Figure 4: Conversion of antibody specificity. A single amino acid at position 50 of the light chain of LT1009 was mutated (GluL50 to GlnL50). The figure is a line graph showing that the resulting antibody variant has significantly higher affinity for LPA conjugate than for S1P conjugate, as shown by direct ELISA.

DETAILED DESCRIPTION OF THE INVENTION1. Antibody Compounds.

Antibody molecules or immunoglobulins are large glycoprotein molecules with a molecular weight of approximately 150 kDa, usually composed of two different kinds of polypeptide chain. The heavy chain (H) is approximately 50 kDa. The light chain (L), is approximately 25 kDa. Each immunoglobulin molecule usually consists of two heavy chains and two light chains. The two heavy chains are linked to each other by disulfide bonds, the number of which varies between the heavy chains of different immunoglobulin isotypes. Each light chain is linked to a heavy chain by one covalent disulfide bond. In any given naturally occurring antibody molecule, the two heavy chains and the two light chains are identical, harboring two identical antigen-binding sites, and are thus said to be divalent, i.e., having the capacity to bind simultaneously to two identical molecules.

The light chains of antibody molecules from any vertebrate species can be assigned to one of two clearly distinct types, kappa (k) and lambda (l), based on the amino acid sequences of their constant domains. The ratio of the two types of light chain varies from species to species. As a way of example, the average k to l ratio is 20:1 in mice, whereas in humans it is 2:1 and in cattle it is 1:20.

The heavy chains of antibody molecules from any vertebrate species can be assigned to one of five clearly distinct types, called isotypes, based on the amino acid sequences of their constant domains. Some isotypes have several subtypes. The five major classes of immunoglobulin are immunoglobulin M (IgM), immunoglobulin D (IgD), immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin E (IgE). IgG is the most abundant isotype and has several subclasses (IgG1, 2, 3, and 4 in humans). The Fc fragment and hinge regions differ in antibodies of different isotypes, thus determining their functional properties. However, the overall organization of the domains is similar in all isotypes.

Sources of antibody are not limited to those exemplified herein (e.g., murine and humanized murine antibody). Antibodies may be raised in many species including mammalian species (for example, mouse, rat, camel, bovine, goat, horse, guinea pig, hamster, sheep and rabbit) and birds (duck, chicken). Antibodies raised may derive from a different species from the animal in which they are raised. For example, the XenoMouse™ (Abgenix, Inc., Fremont CA) produces fully human monoclonal antibodies. For certain purposes, native human antibodies, such as autoantibodies to S1P isolated from individuals who may show a titer of such S1P autoantibody may be used. Alternatively, a human antibody sequence library may be used to generate antibodies comprising a human sequence.

2. Antibody Applications.

Therapeutic agents that alter the activity or concentration of one or more undesired bioactive lipids, or precursors or metabolites thereof, are therapeutically useful. These agents, including antibodies, act by changing the effective concentration, i.e., the absolute, relative, effective and/or available concentration and/or activities, of certain undesired bioactive lipids. Lowering the effective

concentration of the bioactive lipid may be said to “neutralize” the target lipid or its undesired effects, including downstream effects. Here, “undesired” refers to a bioactive lipid that is unwanted due to its involvement in a disease process, for example, as a signaling molecule, or to an unwanted amount of a bioactive lipid which contributes to disease when present in excess.

Without wishing to be bound by any particular theory, it is believed that inappropriate concentrations of bioactive lipids, such as S1P and/or its metabolites or downstream effectors, may cause or contribute to the development of various diseases and disorders. As such, the compositions and methods can be used to treat these diseases and disorders, particularly by decreasing the effective in vivo concentration of a particular target lipid, for example, S1P or its variants. In particular, it is believed that the compositions and methods of the invention are useful in treating diseases characterized, at least in part, by aberrant neovascularization, angiogenesis, fibrogenesis, fibrosis, scarring, inflammation, and immune response.

Examples of diseases that may be treated with antibodies targeted to bioactive lipid are described below in applicant’s pending patent applications and issued patents. See, for example, WO 2008/070344 (Attorney docket no. LPT-3010-PC) and WO 2008/055072 (Attorney docket no. LPT-3020-PC), which are hereby incorporated by reference in their entirety and for all purposes.

One way to control the amount of undesirable sphingolipids or other bioactive lipids in a patient is by providing a composition that comprises one or more humanized anti-sphingolipid antibodies to bind one or more sphingolipids, thereby acting as therapeutic “sponges” that reduce the level of free undesirable sphingolipids. When a compound is referred to as “free”, the compound is not in any way restricted from reaching the site or sites where it exerts its undesirable effects. Typically, a free compound is present in blood and tissue, which either is or contains the site(s) of action of the free compound, or from which a compound can freely migrate to its site(s) of action. A free compound may also be available to be acted upon by any enzyme that converts the compound into an undesirable compound.

Without wishing to be bound by any particular theory, it is believed that the level of undesirable sphingolipids such as SPH or S1P, and/or one or more of their metabolites, cause or contribute to the development of cardiac and myocardial diseases and disorders.

Because sphingolipids are also involved in fibrogenesis and wound healing of liver tissue (Davaile, et al., J. Biol. Chem. 275:34268-34633, 2000; Ikeda, et al., Am J. Physiol. Gastrointest. Liver Physiol 279:G304-G310, 2000), healing of wounded vasculatures (Lee, et al., Am. J. Physiol. Cell Physiol. 278:C612-C618, 2000), and other disease states or disorders, or events associated with such diseases or disorders, such as cancer, angiogenesis, various ocular diseases associate with excessive fibrosis and inflammation (Pyne et al., Biochem. J. 349:385-402, 2000), the compositions and methods of the present disclosure may be applied to treat these diseases and disorders as well as cardiac and myocardial diseases and disorders.

One form of sphingolipid-based therapy involves manipulating the metabolic pathways of sphingolipids in order to decrease the actual, relative and/or available in vivo concentrations of undesirable, toxic sphingolipids. The invention provides compositions and methods for treating or preventing diseases, disorders or physical trauma, in which humanized anti-sphingolipid antibodies are administered to a patient to bind undesirable, toxic sphingolipids, or metabolites thereof.

Such humanized anti-sphingolipid antibodies may be formulated in a pharmaceutical composition and are useful for a variety of purposes, including the treatment of diseases, disorders or physical trauma. Pharmaceutical compositions comprising one or more humanized anti-sphingolipid antibodies of the invention may be incorporated into kits and medical devices for such treatment. Medical devices may be used to administer the pharmaceutical compositions of the invention to a patient in need thereof, and according to one embodiment of the invention, kits are provided that include such devices. Such devices and kits may be designed for routine administration, including self-administration, of the pharmaceutical compositions of the invention. Such devices and kits may also be designed for emergency use, for example, in ambulances or emergency rooms, or during surgery, or in activities where injury is possible but where full medical attention may not be immediately forthcoming (for example, hiking and camping, or combat situations).

3. Methods of Administration.

The treatment for diseases and conditions discussed herein can be achieved by administering agents and compositions of the invention by various routes employing different formulations and devices. Suitable pharmaceutically acceptable diluents, carriers, and excipients are well known in the art. One skilled in the art will appreciate that the amounts to be administered for any particular treatment protocol can readily be determined. Suitable amounts might be expected to fall within the range of 10 µg/dose to 10 g/dose, preferably within 10 mg/dose to 1 g/dose.

Drug substances may be administered by techniques known in the art, including but not limited to systemic, subcutaneous, intradermal, mucosal, including by inhalation, and topical administration. The mucosa refers to the epithelial tissue that lines the internal cavities of the body. For example, the mucosa comprises the alimentary canal, including the mouth, esophagus, stomach, intestines, and anus; the respiratory tract, including the nasal passages, trachea, bronchi, and lungs; and the genitalia. For the purpose of this specification, the mucosa also includes the external surface of the eye, i.e., the cornea and conjunctiva. Local administration (as opposed to systemic administration) may be advantageous because this approach can limit potential systemic side effects, but still allow therapeutic effect.

Pharmaceutical compositions used in the present invention include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions may be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids.

The pharmaceutical formulations used in the present invention may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). Preferred carriers include those that are pharmaceutically acceptable, particularly when the composition is intended for therapeutic use in humans. For non-human therapeutic applications (e.g., in the treatment of companion animals, livestock, fish, or poultry), veterinarily acceptable carriers may be employed. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

The compositions of the present invention may be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions of the present invention may also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

In one embodiment the pharmaceutical compositions may be formulated and used as foams. Pharmaceutical foams include formulations such as, but not limited to, emulsions, microemulsions, creams, jellies, and liposomes.

While basically similar in nature these formulations vary in the components and the consistency of the final product. The know-how on the preparation of such compositions and formulations is generally known to those skilled in the pharmaceutical and formulation arts and may be applied to the formulation of the compositions of the present invention.

In one embodiment, an immune-derived moiety can be delivered to the eye via, for example, topical drops or ointment, periocular injection, intracamerally into the anterior chamber or vitreous, via an implanted depot, or systemically by injection or oral administration. The quantity of antibody used can be readily determined by one skilled in the art.

The traditional approaches to delivering therapeutics to the eye include topical application, redistribution into the eye following systemic administration or direct intraocular/periocular injections [Sultana, et al. (2006), *Current Drug Delivery*, vol 3: 207-217; Ghate and Edelhauser (2006), *Expert Opinion*, vol 3: 275-287; and Kaur and Kanwar (2002), *Drug Develop Industrial Pharmacy*, vol 28: 473-493]. Anti-S1P or other anti-bioactive lipid antibody therapeutics would likely be used with any of these approaches although all have certain perceived advantages and disadvantages. Topical drops are convenient, but wash away primarily because of nasolacrimal drainage often delivering less than 5% of the applied drug into the anterior section of the eye and an even smaller fraction of that dose to the posterior segment of the globe. Besides drops, sprays afford another mode for topical administration. A third mode is ophthalmic ointments or emulsions can be used to prolong the contact time of the formulation with the ocular surface although blurring of vision and matting of the eyelids can be

troublesome. Such topical approaches are still preferable, since systemic administration of therapeutics to treat ocular disorders exposes the whole body to the potential toxicity of the drug.

Treatment of the posterior segment of the eye is medically important because age-related macular degeneration, diabetic retinopathy, posterior uveitis, and glaucoma are the leading causes of vision loss in the United States and other developed countries. Myles, et al. (2005), *Adv Drug Deliv Rev*; 57: 2063-79. The most efficient mode of drug delivery to the posterior segment is intravitreal injection through the pars plana. However, direct injections require a skilled medical practitioner to effect the delivery and can cause treatment-limiting anxiety in many patients. Periocular injections, an approach that includes subconjunctival, retrobulbar, peribulbar and posterior subtenon injections, are somewhat less invasive than intravitreal injections. Repeated and long-term intravitreal injections may cause complications, such as vitreous hemorrhage, retinal detachment, or endophthalmitis.

The anti-bioactive lipid antibody treatment might also be administered using one of the newer ocular delivery systems [Sultana, et al. (2006), *Current Drug Delivery*, vol 3: 207-217; and Ghate and Edelhauser (2006), *Expert Opinion*, vol 3: 275-287], including sustained or controlled release systems, such as (a) ocular inserts (soluble, erodible, non-erodible or hydrogel-based), corneal shields, eg, collagen-based bandage and contact lenses that provide controlled delivery of drug to the eye, (b) in situ gelling systems that provide ease of administration as drops that get converted to gel form in the eye, thereby providing some sustained effect of drug in the eye, (c) vesicular systems such as liposomes, niosomes/discomes, etc., that offers advantages of targeted delivery, bio-compatibility and freedom from blurring of vision, (d) mucoadhesive systems that provide better retention in the eye, (e) prodrugs (f) penetration enhancers, (g) lyophilized carrier systems, (h) particulates, (i) submicron emulsions, (j) iontophoresis, (k) dendrimers, (l) microspheres including bioadhesive microspheres, (m) nanospheres and other nanoparticles, (n) collasomes, and (o) drug delivery systems that combine one or more of the above stated systems to provide an additive, or even synergistic, beneficial effect. Most of these approaches target the anterior segment of the eye and may be beneficial for treating anterior segment disease. However, one or more of these approaches still may be useful affecting bioactive lipid concentrations in the posterior region of the eye because the relatively low molecular weights of the lipids will likely permit considerable movement of the lipid within the eye. In addition, the antibody introduced in the anterior region of the eye may be able to migrate throughout the eye especially if it is manufactured in a lower weight antibody variant such as a Fab fragment. Sustained drug delivery systems for the posterior segment such as those approved or under development (see references, supra) could also be employed.

As previously mentioned, the treatment of disease of the posterior retina, choroids, and macula is medically very important. In this regard, transscleral iontophoresis [Eljarrat-Binstock and Domb (2006), *Control Release*, 110: 479-89] is an important advance and may offer an effective way to deliver antibodies to the posterior segment of the eye.

Various excipients might also be added to the formulated antibody to improve performance of the therapy, make the therapy more convenient or to clearly ensure that the formulated antibody is used only for its intended, approved purpose. Examples of excipients include chemicals to control pH, antimicrobial agents, preservatives to prevent loss of antibody potency, dyes to identify the formulation for ocular use only, solubilizing agents to increase the concentration of antibody in the formulation, penetration enhancers and the use of agents to adjust isotonicity and/or viscosity. Inhibitors of, e.g., proteases, could be added to prolong the half life of the antibody. In one embodiment, the antibody is delivered to the eye by intravitreal injection in a solution comprising phosphate-buffered saline at a suitable pH for the eye.

The anti-S1P agent (e.g., a humanized antibody) can also be chemically modified to yield a pro-drug that is administered in one of the formulations or devices previously described above. The active form of the antibody is then released by action of an endogenous enzyme. Possible ocular enzymes to be considered in this application are the various cytochrome p450s, aldehyde reductases, ketone reductases, esterases or N-acetyl- β -glucosamidases. Other chemical modifications to the antibody could increase its molecular weight, and as a result, increase the residence time of the antibody in the eye. An example of such a chemical modification is pegylation [Harris and Chess (2003), Nat Rev Drug Discov; 2: 214-21], a process that can be general or specific for a functional group such as disulfide [Shaunak, et al. (2006), Nat Chem Biol ; 2:312-3] or a thiol [Doherty, et al. (2005), Bioconjug Chem; 16: 1291-8].

4. Conventional antibody generation and characterization

Antibody affinities may be determined as described in the examples herein below. Preferred humanized or variant antibodies are those which bind a sphingolipid with a K_d value of no more than about 1×10^{-7} M, preferably no more than about 1×10^{-8} M, and most preferably no more than about 5×10^{-9} M.

Aside from antibodies with strong binding affinity for sphingolipids, it is also desirable to select humanized or variant antibodies that have other beneficial properties from a therapeutic perspective. For example, the antibody may be one that reduce angiogenesis and alter tumor progression. Preferably, the antibody has an effective concentration 50 (EC50) value of no more than about 10 μ g/ml, preferably no more than about 1 μ g/ml, and most preferably no more than about 0.1 μ g/ml, as measured in a direct binding ELISA assay. Preferably, the antibody has an effective concentration value of no more than about 10 μ g/ml, preferably no more than about 1 μ g/ml, and most preferably no more than about 0.1 μ g/ml, as measured in cell assays in presence of 1 μ M of S1P, for example, at these concentrations the antibody is able to inhibit sphingolipid-induced IL-8 release in vitro by at least 10%. Preferably, the antibody has an effective concentration value of no more than about 10 μ g/ml, preferably no more than about 1 μ g/ml, and most preferably no more than about 0.1 μ g/ml, as measured in the CNV animal model after laser burn, for example, at these concentrations the antibody is able to inhibit sphingolipid-induced neovascularization in vivo by at least 50%.

Assays for determining the activity of the anti-sphingolipid antibodies of the invention include ELISA assays as shown in the examples hereinbelow.

Preferably the humanized or variant antibody fails to elicit an immunogenic response upon administration of a therapeutically effective amount of the antibody to a human patient. If an immunogenic response is elicited, preferably the response will be such that the antibody still provides a therapeutic benefit to the patient treated therewith.

According to one embodiment of the invention, humanized anti-sphingolipid antibodies bind the "epitope" as herein defined. To screen for antibodies that bind to the epitope on a sphingolipid bound by an antibody of interest (e.g., those that block binding of the antibody to sphingolipid), a routine cross-blocking assay such as that described in *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. Alternatively, epitope mapping, e.g., as described in Champe, et al. [*J. Biol. Chem.* 270:1388-1394 (1995)], can be performed to determine whether the antibody binds an epitope of interest.

The antibodies of the invention have a heavy chain variable domain comprising an amino acid sequence represented by the formula: FR1-CDRH1-FR2-CDRH2-FR3-CDRH3-FR4, wherein "FR1-4" represents the four framework regions and "CDRH1-3" represents the three hypervariable regions of an anti-sphingolipid antibody variable heavy domain. FR1-4 may be derived from a "consensus sequence" (for example the most common amino acids of a class, subclass or subgroup of heavy or light chains of human immunoglobulins) as in the examples below or may be derived from an individual human antibody framework region or from a combination of different framework region sequences. Many human antibody framework region sequences are compiled in Kabat, et al., *supra*, for example. In one embodiment, the variable heavy FR is provided by a consensus sequence of a human immunoglobulin subgroup as compiled by Kabat, et al., *above*.

The human variable heavy FR sequence preferably has one or more substitutions therein, e.g., wherein the human FR residue is replaced by a corresponding nonhuman residue (by "corresponding nonhuman residue" is meant the nonhuman residue with the same Kabat positional numbering as the human residue of interest when the human and nonhuman sequences are aligned), but replacement with the nonhuman residue is not necessary. For example, a replacement FR residue other than the corresponding nonhuman residue can be selected by phage display. Exemplary variable heavy FR residues which may be substituted include any one or more of FR residue numbers: 37H, 49H, 67H, 69H, 71H, 73H, 75H, 76H, 78H, and 94H (Kabat residue numbering employed here). Preferably at least two, or at least three, or at least four of these residues are substituted. A particularly preferred combination of FR substitutions is: 49H, 69H, 71H, 73H, 76H, 78H, and 94H. With respect to the heavy chain hypervariable regions, these preferably have amino acid sequences listed in Table 2, below.

The antibodies of the preferred embodiment herein have a light chain variable domain comprising an amino acid sequence represented by the formula: FR1-CDRL1-FR2-CDRL2-FR3-CDRL3-FR4, wherein "FR1-4" represents the four framework regions and "CDRL1-3" represents the

three hypervariable regions of an anti-sphingolipid antibody variable heavy domain. FR1-4 may be derived from a “consensus sequence” (for example, the most common amino acids of a class, subclass or subgroup of heavy or light chains of human immunoglobulins) as in the examples below or may be derived from an individual human antibody framework region or from a combination of different framework region sequences. In one preferred embodiment, the variable light FR is provided by a consensus sequence of a human immunoglobulin subgroup as compiled by Kabat, et al., above.

The human variable light FR sequence preferably has substitutions therein, e.g., wherein a human FR residue is replaced by a corresponding mouse residue, but replacement with the nonhuman residue is not necessary. For example, a replacement residue other than the corresponding nonhuman residue may be selected by phage display. Exemplary variable light FR residues that may be substituted include any one or more of FR residue numbers, including, but not limited to, F4, Y36, Y49, G64, S67.

Methods for generating humanized anti-sphingolipid antibodies of interest herein are elaborated in more detail below.

A. Antibody Preparation

Methods for humanizing nonhuman anti-sphingolipid antibodies and generating variants of anti-sphingolipid antibodies are described in the Examples below. In order to humanize an anti-sphingolipid antibody, the nonhuman antibody starting material is prepared. Where a variant is to be generated, the parent antibody is prepared. Exemplary techniques for generating such nonhuman antibody starting material and parent antibodies will be described in the following sections.

(i) Antigen Preparation.

The sphingolipid antigen to be used for production of antibodies may be, e.g., intact sphingolipid or a portion of a sphingolipid (e.g., a sphingolipid fragment comprising an “epitope”). Other forms of antigens useful for generating antibodies will be apparent to those skilled in the art. The sphingolipid antigen used to generate the antibody, is described in the examples below. In one embodiment, the antigen is a derivatized form of the sphingolipid, and may be associated with a carrier protein.

(ii) Polyclonal Antibodies.

Polyclonal antibodies are preferably raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. It may be useful to conjugate the relevant antigen to a protein that is immunogenic in the species to be immunized, e.g., keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor using a bifunctional or derivatizing agent, for example, maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, SOCl_2 , or $\text{R}^1\text{N}=\text{C}=\text{NR}$, where R and R^1 are different alkyl groups.

Animals are immunized against the antigen, immunogenic conjugates, or derivatives by combining, e.g., 100 ug or 5 ug of the protein or conjugate (for rabbits or mice, respectively) with three volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One month later the animals are boosted with 0.1 to 0.2 times the original amount of peptide or conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to 14 days later the animals are bled and the serum is assayed for antibody titer. Animals are boosted until the titer plateaus. Preferably, the animal is boosted with the conjugate of the same antigen, but conjugated to a different protein and/or through a different cross-linking reagent. Conjugates also can be made in recombinant cell culture as protein fusions. Also, aggregating agents such as alum may be suitably used to enhance the immune response.

(iii) Monoclonal Antibodies.

Monoclonal antibodies may be made using the hybridoma method first described by Kohler, et al., Nature, 256:495 (1975), or by other suitable methods, including by recombinant DNA methods (see, e.g., U.S. Pat. No. 4,816,567). In the hybridoma method, a mouse or other appropriate host animal, such as a hamster or macaque monkey, is immunized as hereinabove described to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized in vitro. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)).

The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

Preferred myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium.

Among these, preferred myeloma cell lines are murine myeloma lines, such as those derived from MOP-21 and M.C.-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, Calif. USA, and SP-2 or X63-Ag8-653 cells available from the American Type Culture Collection, Rockville, Md. USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, J. Immunol., 133:3001 (1984); Brodeur, et al., Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbant assay (ELISA).

The binding affinity of a monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson, et al., Anal. Biochem., 107:220 (1980).

After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown in vivo as ascites tumors in an animal.

The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as E. coli cells, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Recombinant production of antibodies will be described in more detail below.

(iv) Humanization and Amino Acid Sequence Variants.

General methods for antibody humanization are described in, for example, US5861155, US19960652558, US6479284, US20000660169, US6407213, US19930146206, US6639055, US20000705686, US6500931, US19950435516, US5530101, US5585089, US19950477728, US5693761, US19950474040, US5693762, US19950487200, US6180370, US19950484537, US2003229208, US20030389155, US5714350, US19950372262, US6350861, US19970862871,

US5777085, US19950458516, US5834597, US19960656586, US5882644, US19960621751, US5932448, US19910801798, US6013256, US19970934841, US6129914, US19950397411, US6210671, US6329511, US19990450520, US2003166871, US20020078757, US5225539, US19910782717, US6548640, US19950452462, US5624821, and US19950479752. In certain embodiments, it may be desirable to generate amino acid sequence variants of these humanized antibodies, particularly where these improve the binding affinity or other biological properties of the humanized antibody. Examples hereinbelow describe methodologies for generating amino acid sequence variants of an anti-sphingolipid antibody with enhanced affinity relative to the parent antibody.

Amino acid sequence variants of the anti-sphingolipid antibody are prepared by introducing appropriate nucleotide changes into the anti-sphingolipid antibody DNA, or by peptide synthesis. Such variants include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the anti-sphingolipid antibodies of the examples herein. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics. The amino acid changes also may alter post-translational processes of the humanized or variant anti-sphingolipid antibody, such as changing the number or position of glycosylation sites.

A useful method for identification of certain residues or regions of the anti-sphingolipid antibody that are preferred locations for mutagenesis is called "alanine scanning mutagenesis," as described by Cunningham and Wells Science, 244:1081-1085 (1989). Here, a residue or group of target residues are identified (e.g., charged residues such as arg, asp, his, lys, and glu) and replaced by a neutral or negatively charged amino acid (most preferably alanine or polyalanine) to affect the interaction of the amino acids with sphingolipid antigen. Those amino acid locations demonstrating functional sensitivity to the substitutions then are refined by introducing further or other variants at, or for, the sites of substitution. Thus, while the site for introducing an amino acid sequence variation is predetermined, the nature of the mutation per se need not be predetermined. For example, to analyze the performance of a mutation at a given site, ala scanning or random mutagenesis is conducted at the target codon or region and the expressed anti-sphingolipid antibody variants are screened for the desired activity. Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an anti-sphingolipid antibody with an N-terminal methionyl residue or the antibody fused to an epitope tag. Other insertional variants of the anti-sphingolipid antibody molecule include the fusion to the N- or C-terminus of the anti-sphingolipid antibody of an enzyme or a polypeptide which increases the serum half-life of the antibody.

Another type of variant is an amino acid substitution variant. These variants have at least one amino acid residue in the anti-sphingolipid antibody molecule removed and a different residue inserted in its place. The sites of greatest interest for substitutional mutagenesis include the hypervariable regions, but FR alterations are also contemplated. Conservative substitutions are preferred substitutions. If such

substitutions result in a change in biological activity, then more substantial changes, denominated “exemplary” substitutions listed below, or as further described below in reference to amino acid classes, may be introduced and the products screened.

Table 1: Exemplary Amino Acid Residue Substitutions

Amino acid residue (symbol)	Exemplary substitutions
Ala (A)	val; leu; ile val
Arg (R)	lys; gln; asn lys
Asn (N)	gln; his; asp, lys; gln arg
Asp (D)	glu; asn glu
Cys (C)	ser; ala ser
Gln (Q)	asn; glu asn
Glu (E)	asp; gln asp
Gly (G)	ala ala
His (H)	asn; gln; lys; arg arg
Ile (I)	leu; val; met; ala; leu phe; norleucine
Leu (L)	norleucine; ile; val; ile met; ala; phe
Lys (K)	arg; gln; asn arg
Met (M)	leu; phe; ile leu
Phe (F)	leu; val; ile; ala; tyr tyr
Pro (P)	ala ala
Ser (S)	thr thr
Thr (T)	ser ser
Trp (W)	tyr; phe tyr
Tyr (Y)	trp; phe; thr; ser phe
Val (V)	ile; leu; met; phe; leu ala; norleucine

Substantial modifications in the biological properties of the antibody are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- (1) hydrophobic: norleucine, met, ala, val, leu, ile;
- (2) neutral hydrophilic: cys, ser, thr;
- (3) acidic: asp, glu;
- (4) basic: asn, gln, his, lys, arg;
- (5) residues that influence chain orientation: gly, pro; and
- (6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

Any cysteine residue not involved in maintaining the proper conformation of the humanized or variant anti-sphingolipid antibody also may be substituted, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the antibody to improve its stability (particularly where the antibody is an antibody fragment such as an Fv fragment).

One type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (e.g., a humanized or human antibody). Generally, the resulting variant(s) selected for further development will have improved biological properties relative to the parent antibody from which they are generated. A convenient way for generating such substitutional variants is affinity maturation using phage display. Briefly, several hypervariable region sites (e.g., 6-7 sites) are mutated to generate all possible amino substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the gene III product of M13 packaged within each particle. The phage-displayed variants are then screened for their biological activity (e.g., binding affinity) as herein disclosed. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or in addition, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the antibody and sphingolipid. Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Crystals (co-crystals) of the antigen – antibody complex include co-crystals of the antigen and the Fab or other fragment of the antibody, along with any salts, metals (including divalent metals), cofactors and the like. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development.

Another type of amino acid variant of the antibody alters the original glycosylation pattern of the antibody. By altering is meant deleting one or more carbohydrate moieties found in the antibody, and/or adding one or more glycosylation sites that are not present in the antibody.

Glycosylation of antibodies is typically either N-linked and/or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the most common recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

Addition of glycosylation sites to the antibody is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original antibody (for O-linked glycosylation sites).

Nucleic acid molecules encoding amino acid sequence variants of the anti-sphingolipid antibody are prepared by a variety of methods known in the art. These methods include, but are not limited to, isolation from a natural source (in the case of naturally occurring amino acid sequence variants) or

preparation by oligonucleotide-mediated (or site-directed) mutagenesis, PCR mutagenesis, and cassette mutagenesis of an earlier prepared variant or a non-variant version of the anti-sphingolipid antibody.

(v) Human Antibodies.

As an alternative to humanization, human antibodies can be generated. For example, it is now possible to produce transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (J_H) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. See, e.g., Jakobovits, et al., Proc. Natl. Acad. Sci. USA, 90:2551 (1993); Jakobovits, et al., Nature, 362:255-258(1993); Bruggermann, et al., Year in Immuno., 7:33 (1993); and U.S. Pat. Nos. 5,591,669, 5,589,369 and 5,545,807. Human antibodies can also be derived from phage-display libraries (Hoogenboom, et al., J. Mol. Biol., 227:381 (1991); Marks, et al., J. Mol. Biol., 222:581-597 (1991); and U.S. Pat. Nos. 5,565,332 and 5,573,905). As discussed above, human antibodies may also be generated by in vitro activated B cells (see, e.g., U.S. Pat. Nos. 5,567,610 and 5,229,275) or by other suitable methods.

(vi) Antibody Fragments.

In certain embodiments, the humanized or variant anti-sphingolipid antibody is an antibody fragment. Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see, e.g., Morimoto, et al., Journal of Biochemical and Biophysical Methods 24:107-117(1992); and Brennan, et al., Science 229:81 (1985)). However, these fragments can now be produced directly by recombinant host cells. For example, Fab'-SH fragments can be directly recovered from E. coli and chemically coupled to form $F(ab')_2$ fragments (Carter, et al., Bio/Technology 10:163-167 (1992)). In another embodiment, the $F(ab')_2$ is formed using the leucine zipper GCN4 to promote assembly of the $F(ab')_2$ molecule. According to another approach, Fv, Fab or $F(ab')_2$ fragments can be isolated directly from recombinant host cell culture. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner.

(vii) Multispecific Antibodies.

In some embodiments, it may be desirable to generate multispecific (e.g., bispecific) humanized or variant anti-sphingolipid antibodies having binding specificities for at least two different epitopes. Exemplary bispecific antibodies may bind to two different epitopes of the sphingolipid. Alternatively, an anti-sphingolipid arm may be combined with an arm which binds to a different molecule. Bispecific

antibodies can be prepared as full length antibodies or antibody fragments (e.g., F(ab')₂ bispecific antibodies).

According to another approach for making bispecific antibodies, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers that are recovered from recombinant cell culture. The preferred interface comprises at least a part of the C_H3 domain of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g., tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g., alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers. See, e.g., U.S. patent no. 5,731,168.

Bispecific antibodies include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in, for example, U.S. Pat. No. 4,676,980, along with a number of cross-linking techniques.

Techniques for generating bispecific antibodies from antibody fragments have also been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan, et al., Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')₂ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes. In yet a further embodiment, Fab'-SH fragments directly recovered from *E. coli* can be chemically coupled in vitro to form bispecific antibodies. Shalaby, et al., J. Exp. Med. 175:217-225 (1992).

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny, et al., J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger, et al., Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain

variable domain (V_L) by a linker that is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, e.g., Gruber, et al., *J. Immunol.* 152:5368 (1994). Alternatively, the bispecific antibody may be a "linear antibody" produced as described in, for example, Zapata, et al. *Protein Eng.* 8(10):1057-1062 (1995).

Antibodies with more than two valencies are also contemplated. For example, trispecific antibodies can be prepared. Tutt et al., *J. Immunol.* 147:60 (1991).

An antibody (or polymer or polypeptide) of the invention comprising one or more binding sites per arm or fragment thereof will be referred to herein as "multivalent" antibody. For example a "bivalent" antibody of the invention comprises two binding sites per Fab or fragment thereof whereas a "trivalent" polypeptide of the invention comprises three binding sites per Fab or fragment thereof. In a multivalent polymer of the invention, the two or more binding sites per Fab may be binding to the same or different antigens. For example, the two or more binding sites in a multivalent polypeptide of the invention may be directed against the same antigen, for example against the same parts or epitopes of said antigen or against two or more same or different parts or epitopes of said antigen; and/or may be directed against different antigens; or a combination thereof. Thus, a bivalent polypeptide of the invention for example may comprise two identical binding sites, may comprise a first binding sites directed against a first part or epitope of an antigen and a second binding site directed against the same part or epitope of said antigen or against another part or epitope of said antigen; or may comprise a first binding sites directed against a first part or epitope of an antigen and a second binding site directed against the a different antigen. However, as will be clear from the description hereinabove, the invention is not limited thereto, in the sense that a multivalent polypeptide of the invention may comprise any number of binding sites directed against the same or different antigens.

An antibody (or polymer or polypeptide) of the invention that contains at least two binding sites per Fab or fragment thereof, in which at least one binding site is directed against a first antigen and a second binding site directed against a second antigen different from the first antigen, will also be referred to as "multispecific". Thus, a "bispecific" polymer comprises at least one site directed against a first antigen and at least one a second site directed against a second antigen, whereas a "trispecific" is a polymer that comprises at least one binding site directed against a first antigen, at least one further binding site directed against a second antigen, and at least one further binding site directed against a third antigen, etc. Accordingly, in their simplest form, a bispecific polypeptide of the invention is a bivalent polypeptide (per Fab) of the invention. However, as will be clear from the description hereinabove, the invention is not limited thereto, in the sense that a multispecific polypeptide of the invention may comprise any number of binding sites directed against two or more different antigens.

(viii) Other Modifications.

Other modifications of the humanized or variant anti-sphingolipid antibody are contemplated. For example, the invention also pertains to immunoconjugates comprising the antibody described herein conjugated to a cytotoxic agent such as a toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant or animal origin, or fragments thereof), or a radioactive isotope (for example, a radioconjugate). Conjugates are made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl)hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene).

The anti-sphingolipid antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688 (1985); Hwang, et al., Proc. Natl Acad. Sci. USA 77:4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Pat. No. 5,013,556. For example, liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidyl choline, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin, et al., J. Biol. Chem. 257:286-288 (1982) via a disulfide interchange reaction. Another active ingredient is optionally contained within the liposome.

Enzymes or other polypeptides can be covalently bound to the anti-sphingolipid antibodies by techniques well known in the art such as the use of the heterobifunctional crosslinking reagents discussed above. Alternatively, fusion proteins comprising at least the antigen binding region of an antibody of the invention linked to at least a functionally active portion of an enzyme of the invention can be constructed using recombinant DNA techniques well known in the art (see, e.g., Neuberger, et al., Nature 312:604-608 (1984)).

It may be desirable to use an antibody fragment, rather than an intact antibody, to increase penetration of target tissues and cells, for example. In this case, it may be desirable to modify the antibody fragment in order to increase its serum half life. This may be achieved, for example, by incorporation of a salvage receptor binding epitope into the antibody fragment (e.g., by mutation of the appropriate region in the antibody fragment or by incorporating the epitope into a peptide tag that is then fused to the antibody fragment at either end or in the middle, e.g., by DNA or peptide synthesis). See, e.g., U.S. patent no. 6,096,871.

Covalent modifications of the humanized or variant anti-sphingolipid antibody are also included within the scope of this invention. They may be made by chemical synthesis or by enzymatic or chemical cleavage of the antibody, if applicable. Other types of covalent modifications of the antibody

are introduced into the molecule by reacting targeted amino acid residues of the antibody with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues. Exemplary covalent modifications of polypeptides are described in U.S. Pat. No. 5,534,615, specifically incorporated herein by reference. A preferred type of covalent modification of the antibody comprises linking the antibody to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol, polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Pat. Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

B. Vectors, Host Cells and Recombinant Methods

The invention also provides isolated nucleic acid encoding the humanized or variant anti-sphingolipid antibody, vectors and host cells comprising the nucleic acid, and recombinant techniques for the production of the antibody.

For recombinant production of the antibody, the nucleic acid encoding it may be isolated and inserted into a replicable vector for further cloning (amplification of the DNA) or for expression. In another embodiment, the antibody may be produced by homologous recombination, e.g., as described in U.S. Pat. No. 5,204,244. DNA encoding the monoclonal antibody is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody). Many vectors are available. The vector components generally include, but are not limited to, one or more of the following: a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence, as described, for example, in U.S. Pat. No. 5,534,615.

Suitable host cells for cloning or expressing the DNA in the vectors herein are the prokaryote, yeast, or higher eukaryote cells described above. Suitable prokaryotes for this purpose include eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescens*, and *Shigella*, as well as Bacilli such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. One preferred *E. coli* cloning host is *E. coli* 294 (ATCC 31,446), although other strains such as *E. coli* B, *E. coli* X1776 (ATCC 31,537), and *E. coli* W3110 (ATCC 27,325) are suitable. These examples are illustrative rather than limiting.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for anti-sphingolipid antibody-encoding vectors. *Saccharomyces cerevisiae*, or common baker's yeast, is the most commonly used among lower eukaryotic host microorganisms. However, a number of other genera, species, and strains are commonly available and useful herein, such as *Schizosaccharomyces pombe*; *Kluyveromyces* hosts such as, e.g., *K. lactis*, *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilarum* (ATCC 36,906), *K. thermotolerans*, and *K. marxianus*; *Yarrowia* (EP 402,226); *Pichia*

pastoris (EP 183,070); *Candida*; *Trichoderma reesia* (EP 244,234); *Neurospora crassa*; *Schwanniomyces* such as *Schwanniomyces occidentalis*; and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium*, and *Aspergillus* hosts such as *A. nidulans* and *A. niger*.

Suitable host cells for the expression of glycosylated anti-sphingolipid antibodies are derived from multicellular organisms. Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as *Spodoptera frugiperda* (caterpillar), *Aedes aegypti* (mosquito), *Aedes albopictus* (mosquito), *Drosophila melanogaster* (fruitfly), and *Bombyx mori* have been identified. A variety of viral strains for transfection are publicly available, e.g., the L-1 variant of *Autographa californica* NPV and the Bm-5 strain of *Bombyx mori* NPV, and such viruses may be used as the virus herein according to the present invention, particularly for transfection of *Spodoptera frugiperda* cells. Plant cell cultures of cotton, corn, potato, soybean, petunia, tomato, and tobacco can also be utilized as hosts.

However, interest has been greatest in vertebrate cells, and propagation of vertebrate cells in culture (tissue culture) has become a routine procedure. Examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham, et al., *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK, ATCC CCL 10); Chinese hamster ovary cells/-DHFR (CHO, Urlaub, et al., *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); mouse Sertoli cells (TM4, Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); mouse mammary tumor (MMT 060562, ATCC CCL51); TRI cells (Mather, et al., *Annals N.Y. Acad. Sci.* 383:44-68 (1982)); MRC 5 cells; FS4 cells; and a human hepatoma line (Hep G2).

Host cells are transformed with the above-described expression or cloning vectors for anti-sphingolipid antibody production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences.

The host cells used to produce the anti-sphingolipid antibody of this invention may be cultured in a variety of media. Commercially available media such as Ham's F10 (Sigma), Minimal Essential Medium ((MEM), (Sigma), RPMI-1640 (Sigma), and Dulbecco's Modified Eagle's Medium ((DMEM), Sigma) are suitable for culturing the host cells. In addition, any of the media described in Ham, et al., *Meth. Enz.* 58:44 (1979), Barnes, et al., *Anal. Biochem.* 102:255 (1980), U.S. Pat. Nos. 4,767,704; 4,657,866; 4,927,762; 4,560,655; or 5,122,469; WO 90/03430; WO 87/00195; or U.S. Pat. Re. 30,985 may be used as culture media for the host cells. Any of these media may be supplemented as necessary with hormones and/or other growth factors (such as insulin, transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics (such as GENTAMYCIN™ drug), trace elements (defined

as inorganic compounds usually present at final concentrations in the micromolar range), and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art. The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

When using recombinant techniques, the antibody can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, is removed, for example, by centrifugation or ultrafiltration. Carter, et al., *Bio/Technology* 10:163-167 (1992) describe a procedure for isolating antibodies that are secreted to the periplasmic space of *E. coli*. Briefly, cell paste is thawed in the presence of sodium acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 min. Cell debris can be removed by centrifugation. Where the antibody is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious contaminants.

The antibody composition prepared from the cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being the preferred purification technique. The suitability of protein A as an affinity ligand depends on the species and isotype of any immunoglobulin Fc domain that is present in the antibody. Protein A can be used to purify antibodies that are based on human heavy chains (Lindmark, et al., *J. Immunol. Meth.* 62:1-13 (1983)). Protein G is recommended for all mouse isotypes and for human $\gamma 3$ (Guss, et al., *EMBO J.* 5:1567-1575 (1986)). The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly(styrenedivinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the antibody comprises a C_{H3} domain, the Bakerbond ABX™ resin (J. T. Baker, Phillipsburg, N.J.) is useful for purification. Other techniques for protein purification, such as fractionation on an ion-exchange column, ethanol precipitation, Reverse Phase HPLC, chromatography on silica, chromatography on heparin SEPHAROSE™, chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also available depending on the antibody to be recovered.

Following any preliminary purification step(s), the mixture comprising the antibody of interest and contaminants may be subjected to low pH hydrophobic interaction chromatography using an elution buffer at a pH between about 2.5-4.5, preferably performed at low salt concentrations (e.g., from about 0-0.25M salt).

C. Pharmaceutical Formulations

Therapeutic formulations of an antibody or immune-derived moiety of the invention are prepared for storage by mixing the antibody having the desired degree of purity with optional physiologically acceptable carriers, excipients, or stabilizers (see, e.g., Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEENTM, PLURONICSTM or polyethylene glycol (PEG).

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsule prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsule and poly-(methylmethacrylate) microcapsule, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, 16th edition, Osol, A. Ed. (1980).

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished for instance by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, or microcapsule. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinyl alcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ -ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the Lupron DepotTM (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels

release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

A preferred formulation for systemic administration of the antibodies of the invention is disclosed in provisional patent application US 61/042,736, "Pharmaceutical Compositions for Binding Sphingosine-1-Phosphate", filed April 5, 2008, and commonly owned with the instant invention. This formulation is described in Example 12 hereinbelow.

D. Non-therapeutic Uses for the Antibodies

Antibodies to bioactive lipids may be used as affinity purification agents. In this process, the antibodies are immobilized on a solid phase such as a Sephadex resin or filter paper, using methods well known in the art. The immobilized antibody is contacted with a sample containing the sphingolipid to be purified, and thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the sphingolipid, which is bound to the immobilized antibody. Finally, the support is washed with another suitable solvent, such as glycine buffer, for instance between pH 3 to pH 5.0, that will release the sphingolipid from the antibody.

Anti-lipid antibodies may also be useful in diagnostic assays for the target lipid, e.g., detecting its expression in specific cells, tissues (such as biopsy samples), or bodily fluids. Such diagnostic methods may be useful in diagnosis of a cardiovascular or cerebrovascular disease or disorder.

For diagnostic applications, the antibody typically will be labeled with a detectable moiety. Numerous labels are available which can be generally grouped into the following categories:

(a) Radioisotopes, such as ^{35}S , ^{14}C , ^{125}I , ^3H , and ^{131}I . The antibody can be labeled with the radioisotope using the techniques described in Current Protocols in Immunology, Volumes 1 and 2, Coligen et al., Ed. Wiley-Interscience, New York, N.Y., Pubs. (1991), for example, and radioactivity can be measured using scintillation counting.

(b) Fluorescent labels such as rare earth chelates (europium chelates) or fluorescein and its derivatives, rhodamine and its derivatives, dansyl, Lissamine, phycoerythrin and Texas Red are available. The fluorescent labels can be conjugated to the antibody using the techniques disclosed in Current Protocols in Immunology, supra, for example. Fluorescence can be quantified using a fluorimeter.

(c) Various enzyme-substrate labels are available. For example, U.S. Pat. No. 4,275,149 provides a review of some of these. The enzyme generally catalyzes a chemical alteration of the chromogenic substrate that can be measured using various techniques. For example, the enzyme may

catalyze a color change in a substrate, which can be measured spectrophotometrically. Alternatively, the enzyme may alter the fluorescence or chemiluminescence of the substrate. Techniques for quantifying a change in fluorescence are described above. The chemiluminescent substrate becomes electronically excited by a chemical reaction and may then emit light that can be measured (using a chemiluminometer, for example) or donates energy to a fluorescent acceptor. Examples of enzymatic labels include luciferases (e.g., firefly luciferase and bacterial luciferase; U.S. Pat. No. 4,737,456), luciferin, 2,3-dihydrophthalazinediones, malate dehydrogenase, urease, peroxidase such as horseradish peroxidase (HRPO), alkaline phosphatase, beta-galactosidase, glucoamylase, lysozyme, saccharide oxidases (e.g., glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase), heterocyclic oxidases (such as uricase and xanthine oxidase), lactoperoxidase, microperoxidase, and the like. Techniques for conjugating enzymes to antibodies are described in O'Sullivan, et al., *Methods for the Preparation of Enzyme-Antibody Conjugates for use in Enzyme Immunoassay*, in *Methods in Enzym.* (ed J. Langone & H. Van Vunakis), Academic press, New York, 73:147-166 (1981).

Examples of enzyme-substrate combinations include, for example:

- (i) Horseradish peroxidase (HRPO) with hydrogen peroxidase as a substrate, wherein the hydrogen peroxidase oxidizes a dye precursor (e.g., orthophenylene diamine (OPD) or 3,3',5,5'-tetramethyl benzidine hydrochloride (TMB));
- (ii) alkaline phosphatase (AP) with para-Nitrophenyl phosphate as chromogenic substrate; and
- (iii) β -D-galactosidase (β -D-Gal) with a chromogenic substrate (e.g., p-nitrophenyl- β -D-galactosidase) or fluorogenic substrate 4-methylumbelliferyl- β -D-galactosidase.

Numerous other enzyme-substrate combinations are available to those skilled in the art. For a general review of these, see U.S. Pat. Nos. 4,275,149 and 4,318,980.

Sometimes, the label is indirectly conjugated with the antibody. The skilled artisan will be aware of various techniques for achieving this. For example, the antibody can be conjugated with biotin and any of the three broad categories of labels mentioned above can be conjugated with avidin, or vice versa. Biotin binds selectively to avidin and thus, the label can be conjugated with the antibody in this indirect manner. Alternatively, to achieve indirect conjugation of the label with the antibody, the antibody is conjugated with a small hapten (e.g., digoxin) and one of the different types of labels mentioned above is conjugated with an anti-hapten antibody (e.g., anti-digoxin antibody). Thus, indirect conjugation of the label with the antibody can be achieved.

In another embodiment of the invention, the antibody need not be labeled, and the presence thereof can be detected using a labeled secondary antibody which binds to the anti-lipid antibody.

The antibodies of the present invention may be employed in any known assay method, such as competitive binding assays, direct and indirect sandwich assays, and immunoprecipitation assays. See, e.g., Zola, *Monoclonal Antibodies: A Manual of Techniques*, pp.147-158 (CRC Press, Inc. 1987).

Competitive binding assays rely on the ability of a labeled standard to compete with the test sample analyte for binding with a limited amount of antibody. The amount of bioactive lipid in the test

sample is inversely proportional to the amount of standard that becomes bound to the antibodies. To facilitate determining the amount of standard that becomes bound, the antibodies generally are insoluble before or after the competition, so that the standard and analyte that are bound to the antibodies may conveniently be separated from the standard and analyte that remain unbound.

Sandwich assays involve the use of two antibodies, each capable of binding to a different immunogenic portion, or epitope, of the protein to be detected. In a sandwich assay, the test sample analyte is bound by a first antibody that is immobilized on a solid support, and thereafter a second antibody binds to the analyte, thus forming an insoluble three-part complex. See, e.g., U.S. Pat. No. 4,376,110. The second antibody may itself be labeled with a detectable moiety (direct sandwich assays) or may be measured using an anti-immunoglobulin antibody that is labeled with a detectable moiety (indirect sandwich assay). For example, one type of sandwich assay is an ELISA assay, in which case the detectable moiety is an enzyme.

For immunohistochemistry, the blood or tissue sample may be fresh or frozen or may be embedded in paraffin and fixed with a preservative such as formalin, for example.

The antibodies may also be used for in vivo diagnostic assays. Generally, the antibody is labeled with a radionuclide (such as ^{111}In , ^{99}Tc , ^{14}C , ^{131}I , ^{125}I , ^3H , ^{32}P , or ^{35}S) so that the bound target molecule can be localized using immunoscintillography.

E. Diagnostic Kits

As a matter of convenience, antibodies to bioactive lipids can be provided in a kit, for example, a packaged combination of reagents in predetermined amounts with instructions for performing the diagnostic assay. Where the antibody is labeled with an enzyme, the kit will include substrates and cofactors required by the enzyme (e.g., a substrate precursor which provides the detectable chromophore or fluorophore). In addition, other additives may be included such as stabilizers, buffers (e.g., a block buffer or lysis buffer) and the like. The relative amounts of the various reagents may be varied widely to provide for concentrations in solution of the reagents which substantially optimize the sensitivity of the assay. Particularly, the reagents may be provided as dry powders, usually lyophilized, including excipients which on dissolution will provide a reagent solution having the appropriate concentration.

F. Therapeutic Uses for the Antibody

For therapeutic applications, antibodies to bioactive lipids are administered to a mammal, preferably a human, in a pharmaceutically acceptable dosage form such as those discussed above, including those that may be administered to a human intravenously as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intra-cerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes.

For the prevention or treatment of disease, the appropriate dosage of antibody will depend on the type of disease to be treated, as defined above, the severity and course of the disease, whether the

antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, and the discretion of the attending physician. The antibody is suitably administered to the patient at one time or over a series of treatments.

Depending on the type and severity of the disease, about 1 $\mu\text{g/kg}$ to about 50 mg/kg (e.g., 0.1-20 mg/kg) of antibody is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A typical daily or weekly dosage might range from about 1 $\mu\text{g/kg}$ to about 20 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is repeated until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays, including, for example, radiographic imaging.

According to another embodiment of the invention, the effectiveness of the antibody in preventing or treating disease may be improved by administering the antibody serially or in combination with another agent that is effective for those purposes, such as chemotherapeutic anti-cancer drugs, for example. Such other agents may be present in the composition being administered or may be administered separately. The antibody is suitably administered serially or in combination with the other agent.

G. Articles of Manufacture

In another embodiment of the invention, an article of manufacture containing materials useful for the treatment of the disorders described above is provided. The article of manufacture comprises a container and a label. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The active agent in the composition is the anti-sphingolipid antibody. The label on, or associated with, the container indicates that the composition is used for treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

H. Structure-based Design of Humanized Monoclonal Antibodies to Recognize Bioactive Lipids: Platform for Drug Discovery

Lpath's proprietary Immune Y2™ technology allows the generation of monoclonal antibodies against bioactive lipids, including sphingolipids. Lpath's mAbs Sonpcizumab and Lpathomab (also

referred to as LT1009 and LT3015, targeted to S1P and LPA, respectively) are first-in-class examples of antibody drugs against bioactive lipids.

Because of similarities in the structural framework of LT1009 and LT3015, and aided by recently derived x-ray diffraction data on LT1009 Fab fragment-S1P co-crystals, it is believed that in silico modeling can be used to generate new mAbs against different bioactive lipid targets without the need to immunize mice. This is facilitated by the relatively small sequence/structure space of sphingolipids and similar bioactive lipids compared to that of proteinaceous antigens. It is believed that the expensive and complicated process of humanization can also be avoided by using this in silico method. It is proposed to use structure activity relationship (SAR) assays unique to the Immune Y2 platform to make mutations in the humanized framework and CDRs of LT3015 and/or LT1009, to alter their affinity and/or specificity for their respective ligands. Ultimately it is believed that mutations can be made to alter the specificity to such a point that the binding specificity of the antibody can be converted to a different ligand entirely; e.g., from LPA or S1P (depending on whether LT3015 or LT1009 was the starting point) to another bioactive lipid.

The invention will be better understood by reference to the following Examples, which are intended to merely illustrate the best mode now known for practicing the invention. The scope of the invention is not to be considered limited thereto.

EXAMPLES

Example 1: Murine Monoclonal Antibody to S1P (Sphingomab™; LT1002)

One type of therapeutic antibody specifically binds undesirable sphingolipids to achieve beneficial effects such as, e.g., (1) lowering the effective concentration of undesirable, toxic sphingolipids (and/or the concentration of their metabolic precursors) that would promote an undesirable effect such as a cardiotoxic, tumorigenic, or angiogenic effect; (2) to inhibit the binding of an undesirable, toxic, tumorigenic, or angiogenic sphingolipids to a cellular receptor therefore, and/or to lower the concentration of a sphingolipid that is available for binding to such a receptor. Examples of such therapeutic effects include, but are not limited to, the use of anti-S1P antibodies to lower the effective *in vivo* serum concentration of available S1P, thereby blocking or at least limiting S1P's tumorigenic and angiogenic effects and its role in post-MI heart failure, cancer, or fibronogenic diseases.

Thiolated S1P was synthesized to contain a reactive group capable of cross-linking the essential structural features of S1P to a carrier molecule such as KLH. Prior to immunization, the thio-S1P analog was conjugated via IOA or SMCC cross-linking to protein carriers (e.g., KLH) using standard protocols. SMCC is a heterobifunctional crosslinker that reacts with primary amines and sulfhydryl groups, and represents a preferred crosslinker.

Swiss Webster or BALB-C mice were immunized four times over a two month period with 50µg of immunogen (SMCC facilitated conjugate of thiolated-S1P and KLH) per injection. Serum samples

were collected two weeks after the second, third, and fourth immunizations and screened by direct ELISA for the presence of anti-S1P antibodies. Spleens from animals that displayed high titers of the antibody were subsequently used to generate hybridomas per standard fusion procedures. The resulting hybridomas were grown to confluency, after which the cell supernatant was collected for ELISA analysis. Of the 55 mice that were immunized, 8 were good responders, showing significant serum titers of antibodies reactive to S1P. Fusions were subsequently carried out using the spleens of these mice and myeloma cells according to established procedures. The resulting 1,500 hybridomas were then screened by direct ELISA, yielding 287 positive hybridomas. Of these 287 hybridomas screened by direct ELISA, 159 showed significant titers. Each of the 159 hybridomas was then expanded into 24-well plates. The cell-conditioned media of the expanded hybridomas were then re-screened to identify stable hybridomas capable of secreting antibodies of interest. Competitive ELISAs were performed on the 60 highest titer stable hybridomas.

Of the 55 mice and almost 1,500 hybridomas screened, one hybridoma was discovered that displayed performance characteristics that justified limited dilution cloning, as is required to ultimately generate a true monoclonal antibody. This process yielded 47 clones, the majority of which were deemed positive for producing S1P antibodies. Of these 47 clones, 6 were expanded into 24-well plates and subsequently screened by competitive ELISA. From the 4 clones that remained positive, one was chosen to initiate large-scale production of the S1P monoclonal antibody. SCID mice were injected with these cells and the resulting ascites was protein A-purified (50% yield) and analyzed for endotoxin levels (<3 EU/mg). For one round of ascites production, 50 mice were injected, producing a total of 125mL of ascites. The antibodies were isotyped as IgG1 kappa, and were deemed >95% pure by HPLC. The antibody was prepared in 20mM sodium phosphate with 150 mM sodium chloride (pH 7.2) and stored at -70°C. This antibody is designated LT1002 or Sphingomab™.

The positive hybridoma clone (designated as clone 306D326.26) was deposited with the ATCC (safety deposit storage number SD-5362), and represents the first murine mAb directed against S1P. The clone also contains the variable regions of the antibody heavy and light chains that could be used for the generation of a “humanized” antibody variant, as well as the sequence information needed to construct a chimeric antibody.

Screening of serum and cell supernatant for S1P-specific antibodies was by direct ELISA using a thiolated S1P analog as the antigen. A standard ELISA was performed, as described below, except that 50ul of sample (serum or cell supernatant) was diluted with an equal volume of PBS/0.1% Tween-20 (PBST) during the primary incubation. ELISAs were performed in 96-well high binding ELISA plates (Costar) coated with 0.1 µg of chemically-synthesized thiolated-S1P conjugated to BSA in binding buffer (33.6mM Na₂CO₃, 100mM NaHCO₃; pH 9.5). The thiolated-S1P-BSA was incubated at 37°C for 1 hr. at 4°C overnight in the ELISA plate wells. The plates were then washed four times with PBS (137mM NaCl, 2.68mM KCl, 10.14mM Na₂HPO₄, 1.76mM KH₂PO₄; pH 7.4) and blocked with PBST for 1 hr. at room temperature. For the primary incubation step, 75uL of the sample (containing the S1P

to be measured), was incubated with 25uL of 0.1ug/mL anti-S1P mAb diluted in PBST and added to a well of the ELISA plate. Each sample was performed in triplicate wells. Following a 1 hr. incubation at room temperature, the ELISA plates were washed four times with PBS and incubated with 100ul per well of 0.1ug/mL HRP goat anti-mouse secondary (Jackson ImmunoResearch) for 1 hr. at room temperature. Plates were then washed four times with PBS and exposed to tetramethylbenzidine (Sigma) for 1-10 minutes. The detection reaction was stopped by the addition of an equal volume of 1M H₂SO₄. Optical density of the samples was determined by measurement at 450nm using an EL- X-800 ELISA plate reader (Bio-Tech).

For cross reactivity, a competitive ELISA was performed as described above, except for the following alterations. The primary incubation consisted of the competitor (S1P, SPH, LPA, etc.) and a biotin-conjugated anti-S1P mAb. Biotinylation of the purified monoclonal antibody was performed using the EZ-Link Sulfo-NHS-Biotinylation kit (Pierce). Biotin incorporation was determined as per kit protocol and ranged from 7 to 11 biotin molecules per antibody. The competitor was prepared as follows: lipid stocks were sonicated and dried under argon before reconstitution in DPBS/BSA [1mg/ml fatty acid free BSA (Calbiochem) in DPBS (Invitrogen 14040-133)]. Purified anti-S1P mAb was diluted as necessary in PBS/0.5% Triton X-100. Competitor and antibody solutions were mixed together so to generate 3 parts competitor to 1 part antibody. A HRP-conjugated streptavidin secondary antibody (Jackson ImmunoResearch) was used to generate signal.

Another aspect of the competitive ELISA data is that it shows that the anti-S1P mAb was unable to distinguish the thiolated-S1P analog from the natural S1P that was added in the competition experiment. It also demonstrates that the antibody does not recognize any oxidation products since the analog was constructed without any double bonds. The anti-S1P mAb was also tested against natural product containing the double bond that was allowed to sit at room temperature for 48 hours. Reverse phase HPLC of the natural S1P was performed according to methods reported previously (Deutschman, et al. (July 2003), *Am Heart J.*, vol. 146(1):62-8), and the results showed no difference in retention time. Further, a comparison of the binding characteristics of the monoclonal antibody to various lipids indicates that the epitope recognized by the antibody do not involve the hydrocarbon chain in the region of the double bond of natural S1P. On the other hand, the epitope recognized by the monoclonal antibody is the region containing the amino alcohol on the sphingosine base backbone plus the free phosphate. If the free phosphate is linked with a choline (as is the case with SPC), then the binding was somewhat reduced. If the amino group is esterified to a fatty acid (as is the case with C1P), no antibody binding was observed. If the sphingosine amino alcohol backbone was replaced by a glycerol backbone (as is the case with LPA), there the S1P-specific monoclonal exhibited no binding. These epitope mapping data indicate that there is only one epitope on S1P recognized by the monoclonal antibody, and that this epitope is defined by the unique polar headgroup of S1P.

In a similar experiment using ELISA measurements, suitable control materials were evaluated to ensure that this anti-S1P monoclonal antibody did not recognize either the protein carrier or the

crosslinking agent. For example, the normal crosslinker SMCC was exchanged for IOA in conjugating the thiolated-S1P to BSA as the laydown material in the ELISA. When IOA was used, the antibody's binding characteristics were nearly identical to when BSA-SMCC-thiolated-S1P was used. Similarly, KLH was exchanged for BSA as the protein that was complexed with thiolated-S1P as the laydown material. In this experiment, there was also no significant difference in the binding characteristics of the antibody.

Binding kinetics: The binding kinetics of S1P to its receptor or other moieties has, traditionally, been problematic because of the nature of lipids. Many problems have been associated with the insolubility of lipids. For BIAcore measurements, these problems were overcome by directly immobilizing S1P to a BIAcore chip. Antibody was then flowed over the surface of the chip and alterations in optical density were measured to determine the binding characteristics of the antibody to S1P. To circumvent the bivalent binding nature of antibodies, S1P was coated on the chip at low densities. Additionally, the chip was coated with various densities of S1P (7, 20, and 1000 RU) and antibody binding data was globally fit to a 1:1 interaction model. The results demonstrate the changes in optical density due to the binding of the monoclonal antibody to S1P at three different densities of S1P. Overall, the affinity of the monoclonal antibody to S1P was determined to be very high, in the range of approximately 88 picomolar (pM) to 99 nM, depending on whether a monovalent or bivalent binding model was used to analyze the binding data.

Example 2: ELISA assays

1. Quantitative ELISAs

Microtiter ELISA plates (Costar, Cat No. 3361) were coated with rabbit anti-mouse IgG, F(ab')₂ fragment specific antibody (Jackson, 315-005-047) diluted in 1M Carbonate Buffer (pH 9.5) at 37°C for 1 h. Plates were washed with PBS and blocked with PBS/BSA/Tween-20 for 1 hr at 37°C. For the primary incubation, dilutions of non-specific mouse IgG or human IgG, whole molecule (used for calibration curve) and samples to be measured were added to the wells. Plates were washed and incubated with 100 ul per well of HRP conjugated goat anti-mouse (H+L) diluted 1:40,000 (Jackson, cat No 115-035-146) for 1 hr at 37°C. After washing, the enzymatic reaction was detected with tetramethylbenzidine (Sigma, cat No T0440) and stopped by adding 1 M H₂SO₄. The optical density (OD) was measured at 450 nm using a Thermo Multiskan EX. Raw data were transferred to GraphPad software for analysis.

2. Direct ELISAs

Microtiter ELISA plates (Costar, Cat No. 3361) were coated with LPA-BSA diluted in 1M Carbonate Buffer (pH 9.5) at 37 °C for 1 h. Plates were washed with PBS (137 mM NaCl, 2.68 mM KCl, 10.1 mM Na₂HPO₄, 1.76 mM KH₂PO₄; pH 7.4) and blocked with PBS/BSA/Tween-20 for 1 h at room temperature or overnight at 4°C. The samples to be tested were diluted at 0.4 ug/mL, 0.2 ug/mL, 0.1 ug/mL, 0.05 ug/mL, 0.0125 ug/mL, and 0 ug/mL and 100 ul added to each well. Plates were washed and incubated with 100 ul per well of HRP conjugated goat anti-mouse (1:20,000 dilution) (Jackson, cat. no.

115-035-003) for 1 h at room temperature. After washing, the enzymatic reaction was detected with tetramethylbenzidine (Sigma, cat. no. T0440) and stopped by adding 1 M H₂SO₄. The optical density (OD) was measured at 450nm using a Thermo Multiskan EX. Raw data were transferred to GraphPad software for analysis.

3. Competition assays

The specificity of mAbs was tested in ELISA assays. Microtiter plates ELISA plates (Costar, Cat No. 3361) were coated with 18:0 LPA-BSA diluted in 1M Carbonate Buffer (pH 9.5) at 37 °C for 1 h. Plates were washed with PBS (137 mM NaCl, 2.68 mM KCl, 10.1 mM Na₂HPO₄, 1.76 mM KH₂PO₄; pH 7.4) and blocked with PBS/BSA/Tween-20 at 37 °C for 1 h or overnight at room temperature. For the primary incubation 0.4 ug/mL anti-LPA mAb and designated amounts of (14:0, 16:0, 18:0, 18:1, 18:2 and 20:4) LPA, DSPA, 18:1 LPC (lysophosphatidylcholine), S1P, ceramide and ceramide-1-phosphate were added to wells of the ELISA plates and incubated at 37 °C for 1 h. Plates were washed and incubated with 100 ul per well of HRP conjugated goat anti-mouse (1:20,000 dilution) (Jackson, cat No 115-035-003) or HRP conjugated goat anti-human(H +L) diluted 1:50,000 (Jackson, cat No109-035-003) at 37 °C for 1h. After washing, the enzymatic reaction was detected with tetramethylbenzidine and stopped by adding 1 M H₂SO₄. The optical density (OD) was measured at 450nm using a Thermo Multiskan EX. Raw data were transferred to GraphPad software for analysis.

Example 3: SPHINGOMAB murine mAb is highly specific for S1P

A competitive ELISA demonstrates SPHINGOMAB's specificity for S1P compared to other bioactive lipids. SPHINGOMAB demonstrated no cross-reactivity to sphingosine (SPH), the immediate metabolic precursor of S1P or lysophosphatidic acid (LPA), an important extracellular signaling molecule that is structurally and functionally similar to S1P. SPHINGOMAB did not recognize other structurally similar lipids and metabolites, including ceramide-1-phosphate (C1P), dihydrosphingosine (DH-SPH), phosphatidyl serine (PS), phosphatidyl ethanolamine (PE), or sphingomyelin (SM). SPHINGOMAB did cross react with dihydrosphingosine-1-phosphate (DH-S1P) and, to a lesser extent, sphingosylphorylcholine (SPC).

Example 4: Biological activity of SPHINGOMAB

SPHINGOMAB has been shown to significantly reduce choroidal neovascularization (CNV) and scar formation in the eye in a murine model of CNV, and inhibits cardiac scar formation in mice as well. These results and others are disclosed in US patent application serial no. 11/924,890 (attorney docket no. LPT-3010-UT), filed on October 26, 2007, entitled "Compositions and Methods for Binding Sphingosine-1-Phosphate," which is incorporated herein in its entirety.

Example 5: Cloning and Characterization of the variable domains of an S1P murine monoclonal antibody (LT1002; Sphingomab)

This example reports the cloning of the murine mAb against S1P. The overall strategy consisted of cloning the murine variable domains of both the light chain (VL) and the heavy chain (VH). The consensus sequence of 306D VH shows that the constant region fragment is consistent with a gamma 2b isotype. The murine variable domains were cloned together with the constant domain of the light chain (CL) and with the constant domain of the heavy chain (CH1, CH2, and CH3), resulting in a chimeric antibody construct.

1. Cloning of the murine mAb

A clone from the anti-S1P hybridoma cell line 306D326.1 (ATCC#SD-5362) was grown in DMEM (Dulbecco's Dulbecco's Modified Eagle Medium with GlutaMAX™ I, 4500mg/L D-Glucose, Sodium Puruvate; Gibco/Invitrogen, Carlsbad, CA, 111-035-003), 10% FBS (Sterile Fetal Clone I, Perbio Science), and 1X glutamine/Penicillin/Streptomycin (Gibco/Invitrogen). Total RNA was isolated from 10⁷ hybridoma cells using a procedure based on the RNeasy Mini kit (Qiagen, Hilden Germany). The RNA was used to generate first strand cDNA following the manufacturer's protocol (1st strand synthesis kit, Amersham Biosciences).

The immunoglobulin heavy chain variable region (VH) cDNA was amplified by PCR using an MHV7 primer (MHV7: 5'-ATGGRATGGAGCKGGRTCTTTMTCTT-3' [SEQ ID NO: 1]) in combination with a IgG2b constant region primer MHCG1/2a/2b/3 mixture (MHCG1: 5'-CAGTGGATAGACAGATGGGGG-3' [SEQ ID NO: 2]; MHCG2a: 5'-CAGTGGATAGACCGATGGGGC-3' [SEQ ID NO: 3]; MHCG2b: 5'-CAGTGGATAGACTGATGGGGG-3' [SEQ ID NO: 4]; MHCG3: 5'-CAAGGGATAGACAGATGGGGC-3' [SEQ ID NO: 5]). The product of the reaction was ligated into the pCR2.1®-TOPO® vector (Invitrogen) using the TOPO-TA cloning® kit and sequence. The variable domain of the heavy chain was then amplified by PCR from this vector and inserted as a Hind III and Apa I fragment and ligated into the expression vector pG1D200 (see U.S. patent no. 7,060,808) or pG4D200 (id.) containing the HCMVi promoter, a leader sequence, and the gamma-1 constant region to generate the plasmid pG1D200306DVH. The consensus sequence of 306D V_H (shown below) showed that the constant region fragment was consistent with a gamma 2b isotype.

Similarly, the immunoglobulin kappa chain variable region (VK) was amplified using the MKV 20 primer (5'- GTCTCTGATTCTAGGGCA-3' [SEQ ID NO: 6]) in combination with the kappa constant region primer MKC (5'- ACTGGATGGTGGGAAGATGG-3' [SEQ ID NO: 7]). The product of this reaction was ligated into the pCR2.1®-TOPO® vector using the TOPO-TA cloning® kit and sequence. The variable domain of the light chain was then amplified by PCR and then inserted as a Bam HI and Hind III fragment into the expression vector pKN100 (see U.S. patent no. 7,060,808) containing

the HCMV promoter, a leader sequence, and the human kappa constant domain, generating plasmid pKN100306DVK.

The heavy and light chain plasmids pG1D200306DVH plus pKN100306DVK were transformed into DH4a bacteria and stocked in glycerol. Large-scale plasmid DNA was prepared as described by the manufacturer (Qiagen, endotoxin-free MAXIPREP™ kit). DNA samples, purified using Qiagen's QIAprep Spin Miniprep Kit or EndoFree Plasmid Mega/Maxi Kit, were sequenced using an ABI 3730xl automated sequencer, which also translates the fluorescent signals into their corresponding nucleobase sequence. Primers were designed at the 5' and 3' ends so that the sequence obtained would overlap. The length of the primers was 18-24 bases, and preferably they contained 50% GC content and no predicted dimers or secondary structure. The amino acid sequences for the mouse V_H and V_L domains from Sphingomab™ are SEQ ID NOS: 8 and 9, respectively (Table 2). The CDR residues (see Kabat, EA (1982), Pharmacol Rev, vol. 34: 23-38) are underlined in Table 2, and are shown separately below in Table 3.

Table 2: V_H and V_L domains from the murine mAb, Sphingomab™

mouse V _H domains	Q A H L Q Q S D A E L V K P G A S V K I S C K V S G F I F I <u>D H T I H W M K Q R P E Q G L E W I</u> <u>G C I S P R H D I T K Y N E M F R G K A T L T A D K S S T T A Y I Q V N S L T F E D S A V Y F C</u> <u>A R G G F Y G S T I W F D F W G Q G T T L T V S</u>	SEQ ID NO: 8
mouse V _L domains	E T T V T Q S P A S L S M A I G E K V T I R C I T T T D I D D D M N W F Q Q K P G E P P N L L I <u>S E G N I L</u> <u>R P G V P S R F S S S G Y G T D F L F T I E N M L S E D V A D Y Y C L Q S D N L P F T F G S G T K L E I K</u>	SEQ ID NO: 9

Table 3: Mouse Sphingomab™ CDR sequences of the mouse V_H and V_L domains

V _L CDR	CDR
ITTTDIDDDMN (SEQ ID NO: 10)	CDR1
EGNILRP (SEQ ID NO: 11)	CDR2
LQSDNLPFT (SEQ ID NO: 12)	CDR3
V _H CDR	CDR
DHTIH (SEQ ID NO: 13)	CDR1
CISPRHDITKYNEMFRG (SEQ ID NO: 14)	CDR2
GGFYGSTIWFD (SEQ ID NO: 15)	CDR3

The amino acid sequences of several chimeric antibody variable (V_H and V_L) domains are compared in Table 4. These variants were cloned into expression vectors behind germ line leader sequences. The germ line leader sequences are underlined in Table 4 on the pATH200 (first 19 amino acids) and pATH300 sequences (first 22 amino acids). The CDRs are shown in bold. Amino acids that follow the C-terminus of each of the heavy and light chain sequences in Table 4 are shown in italics. These are the first few amino acids of the constant domain and not part of the variable domain.

It should be noted that while the pATH200 and pATH300 series numbers usually refer to a vector containing a particular variable domain variant sequence, for convenience this nomenclature may be used herein to refer to and distinguish the variant variable domains per se.

Sequences of the murine V_H and V_L domains were used to construct a molecular model to determine which framework residues should be incorporated into the humanized antibody.

Table 4: Amino acid sequences of the humanized V_H (pATH200 series) and V_L (pATH300 series) domains from the humanized anti-S1P antibody variants. Leaders are underlined, CDRs are in bold.

V _H Variants	
pATH200 SEQ ID NO: 16	<u>mgstailalallavlggv</u> cvseqqlvqsgaevkkpgeslkiscqsfgyifi dhtih wvrqmpggglewmg cisprhdi tkyn
pATH201	m.....
pATH202	f.....i.....
pATH203	m.....i.....
pATH204	f.....f.....
pATH205	f.....m.....i.....
pATH206	a.....f.....m.....i.....
pATH207	m.....m.....a.....
Sequences Continue:	
pATH200 continued	emfrg qvtisadkssstaylqwssllkasdtamfcar ggfygsti w fdf wgggtmvtvssastkgps
pATH201	
pATH202	
pATH203	
pATH204	
pATH205	a.l.....
pATH206	a.l.....
pATH207	

Table 4 continued	
V ₁ Variants	
pATH300 (SEQ ID NO: 17)	mdmr ~~v~~ paql ~~l~~ g ~~l~~ l ~~l~~ l ~~l~~ wlp ~~g~~ arcet ~~t~~ l ~~t~~ q ~~s~~ p ~~s~~ f ~~l~~ s ~~a~~ v ~~g~~ d ~~r~~ v ~~t~~ i ~~t~~ c ~~i~~ tttdiddm nwyq ~~q~~ e ~~p~~ g ~~k~~ ap ~~k~~ l ~~l~~ i ~~y~~ egn l ~~r~~ p ~~g~~ v
pATH301	s.....
pATH302	f.....
pATH303	v.....s.....
pATH304	f.....s.....
pATH305	v.....f.....s.....
pATH306	v.....f.....s.....
pATH308	v.....f.....s.....
pATH309	s.....
Sequences continue	
pATH300 continued	psr ~~f~~ sgsg ~~s~~ g ~~t~~ d ~~f~~ t ~~t~~ i ~~s~~ k ~~l~~ q ~~p~~ e ~~d~~ f ~~a~~ t ~~y~~ y ~~c~~ lqsdnl p ~~f~~ t ~~f~~ g ~~q~~ g ~~t~~ k ~~e~~ i ~~k~~ r ~~e~~ w ~~i~~ p
pATH301	
pATH302	
pATH303	-
pATH304	
pATH305	--
pATH306	s.....--
pATH308	s.y.....
pATH309	s.y.....

2. Expression and binding properties of the chimeric antibody

The heavy and light chain plasmids of both pG1D200306DVH plus pKN100306DVK were transformed into DH4a bacteria and stocked in glycerol. Large scale plasmid DNA was prepared as described by the manufacturer (Qiagen, endotoxin-free MAXIPREP™ kit Cat. No.12362).

For antibody expression in a non-human mammalian system, plasmids were transfected into the African green monkey kidney fibroblast cell line COS 7 by electroporation (0.7ml at 10^7 cells/ml) using 10 ug of each plasmid. Transfected cells were plated in 8 ml of growth medium for 4 days. The chimeric 306DH1 x 306DVK-2 antibody was expressed at 1.5µg/ml in transiently co-transfected COS cell conditioned medium. The binding of this antibody to S1P was measured using the S1P ELISA.

The expression level of the chimeric antibody was determined in a quantitative ELISA as follows. Microtiter plates (Nunc MaxiSorp immunoplate, Invitrogen) were coated with 100 µl aliquots of 0.4 µg/ml goat anti-human IgG antibody (Sigma, St. Louis, MO) diluted in PBS and incubate overnight at 4°C. The plates were then washed three times with 200 µl/well of washing buffer (1 x PBS, 0.1% TWEEN). Aliquots of 200 µL of each diluted serum sample or fusion supernatant were transferred to the toxin-coated plates and incubated for 37°C for 1 hr. Following 6 washes with washing buffer, the goat anti-human kappa light chain peroxidase conjugate (Jackson Immuno Research) was added to each well at a 1:5000 dilution. The reaction was carried out for 1 hr at room temperature, plates were washed 6 times with the washing buffer, and 150 µL of the K-BLUE substrate (Sigma) was added to each well, incubated in the dark at room temperature for 10 min. The reaction was stopped by adding 50 µl of RED STOP solution (SkyBio Ltd.) and the absorption was determined at 655 nm using a Microplater Reader 3550 (Bio-Rad Laboratories Ltd.).

3. 293F Expression

The heavy and light chain plasmids were transformed into Top 10 E. coli (One Shot Top 10 chemically competent E.coli cells (Invitrogen, C4040-10)) and stocked in glycerol. Large scale plasmid DNA was prepared as described by the manufacturer (Qiagen, endotoxin-free MAXIPREP™ kit CatNo12362).

For antibody expression in a human system, plasmids were transfected into the human embryonic kidney cell line 293F (Invitrogen) using 293fectin (Invitrogen) and using 293F-FreeStyle Media (Invitrogen) for culture. Light and heavy chain plasmids were both transfected at 0.5 g/mL. Transfections were performed at a cell density of 10^6 cells/mL. Supernatants were collected by centrifugation at 1100 rpm for 5 minutes at 25°C 3 days after transfection. Expression levels were quantified by quantitative ELISA (see previous examples) and varied from ~0.25-0.5 g/mL for the chimeric antibody.

4. Antibody purification

Monoclonal antibodies were purified from culture supernatants by passing culture supernatants over protein A/G columns (Pierce, Cat.No 53133) at 0.5 mL/min. Mobile phases consisted of 1X Pierce IgG binding Buffer (Cat.No 21001) and 0.1 M glycine pH 2.7 (Pierce, Elution Buffer, Cat.No 21004). Antibody collections in 0.1 M glycine were diluted 10 % (v/v) with 1 M Phosphate Buffer, pH 8.0, to neutralize the pH. IgG₁ collections were pooled and dialyzed exhaustively against 1X PBS (Pierce Slide-A-Lyzer Cassette, 3,500 MWCO, Cat.No 66382). Eluates were concentrated using Centricon YM-3(10,000 MWCO Amicon Cat.No 4203) by centrifugation for 1 h at 2,500 rcf. The antibody concentration was determined by quantitative ELISA as described above using a commercial myeloma IgG₁ stock solution as a standard. Heavy chain types of mAbs were determined by ELISA using Monoclonal Antibody Isotyping Kit (Sigma, ISO-2).

5. Comparative binding of antibody variants to S1P

Table 5, below, shows a comparative analysis of mutants with the chimeric antibody. To generate these results, bound antibody was detected by a second antibody, specific for the mouse or human IgG, conjugated with HRP. The chromogenic reaction was measured and reported as optical density (OD). The concentration of the panel of antibodies was 0.1 ug/ml. No interaction of the second antibody with S1P-coated matrix alone was detected.

Table 5: Comparative binding to S1P on variants of the chimeric anti-S1P antibody.

Variable Domain	Mutation	Plasmids	Binding
HC	Chimeric	pATH50 + pATH10	1.5
	CysAla	pATH50 + pATH11	2
	CysSer	pATH50 + pATH 12	0.6
	CysArg	pATH50 + pATH14	0.4
	CysPhe	pATH50 + pATH16	2
LC	MetLeu	pATH53 + pATH10	1.6

6. Determination of Binding Kinetics by Surface Plasmon Resonance (SPR)

All binding data were collected on a Biacore 2000 optical biosensor (Biacore AB, Uppsala Sweden). S1P was coupled to a maleimide CM5 sensor chip. First the CM5 chip was activated with an equal mixture of NHS/EDC for seven minutes followed by a 7 minute blocking step with ethyldiamine. Next sulfo-MBS (Pierce Co.) was passed over the surfaces at a concentration of 0.5 mM in HBS running buffer (10 mM HEPES, 150 mM NaCl, 0.005% p20, pH 7.4). S1P was diluted into the HBS running buffer to a concentration of 0.1 mM and injected for different lengths of time producing 2 different density S1P surfaces (305 and 470 RU). Next, binding data for the mAb was collected using a 3-fold dilution series starting with 16.7 nM, 50.0nM, 50.0nM, 16.7 nM, and 16.7 nM for the mouse, 201308, 201309, and 207308 antibodies respectively.

Each concentration was tested in duplicate. Surfaces were regenerated with 50 mM NaOH. All data were collected at 25°C. Responses data were processed using a reference surface as well as blank injections. The data sets (responses from two surfaces and each variant tested twice were fit to

interaction models to obtain binding parameters. Data from the different mAb concentrations were globally fitted using a 1:1 (mouse) or 1:2 (variants) interaction model to determine apparent binding rate constants. The number in parentheses indicates the error in the last digit.

Example 6: Chimeric mAb to S1P

As used herein, the term “chimeric” antibody (or “immunoglobulin”) refers to a molecule comprising a heavy and/or light chain which is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (Cabilly, et al., supra; Morrison et al., Proc. Natl. Acad. Sci. U.S.A. 81:6851 (1984)).

A chimeric antibody to S1P was generated using the variable regions (Fv) containing the active S1P binding regions of the murine antibody from a particular hybridoma (ATCC safety deposit storage number SD-5362) with the Fc region of a human IgG1 immunoglobulin. The Fc regions contained the CL, ChL, and Ch3 domains of the human antibody. Without being limited to a particular method, chimeric antibodies could also have been generated from Fc regions of human IgG1, IgG2, IgG3, IgG4, IgA, or IgM. As those in the art will appreciate, “humanized” antibodies can be generated by grafting the complementarity determining regions (CDRs, e.g. CDR1-3) of the murine anti-S1P mAb with a human antibody framework regions (e.g., Fr1, Fr4, etc.) such as the framework regions of an IgG1.

For the direct ELISA experiments, the chimeric antibody to S1P had similar binding characteristics to the fully murine monoclonal antibody. ELISAs were performed in 96-well high-binding ELISA plates (Costar) coated with 0.1 µg of chemically-synthesized, thiolated S1P conjugated to BSA in binding buffer (33.6mM Na₂CO₃, 100mM NaHCO₃; pH 9.5). The thiolated S1P-BSA was incubated at 37°C for 1 hr. or at 4°C overnight in the ELISA plate. Plates were then washed four times with PBS (137mM NaCl, 2.68mM KCl, 10.14mM Na₂HPO₄, 1.76mM KH₂PO₄; pH 7.4) and blocked with PBST for 1 hr. at room temperature. For the primary incubation step, 75 µL of the sample (containing the S1P to be measured), was incubated with 25 µL of 0.1 µg/mL anti-S1P monoclonal antibody diluted in PBST and added to a well of the ELISA plate. Each sample was performed in triplicate wells. Following a 1 hr. incubation at room temperature, the ELISA plates were washed four times with PBS and incubated with 100 µL per well of 0.1 µg/mL HRP goat anti-mouse secondary (Jackson ImmunoResearch) for 1 hr. at room temperature. Plates were then washed four times with PBS and exposed to tetramethylbenzidine (Sigma) for 1-10 minutes. The detection reaction was stopped by the addition of an equal volume of 1M H₂SO₄. Optical density of the samples was determined by measurement at 450nm using an EL- X-800 ELISA plate reader (Bio-Tech).

Again, the preferred method of measuring either antibody titer in the serum of an immunized animal or in cell-conditioned media (for example, supernatant) of an antibody-producing cell such as a

hybridoma, involves coating the ELISA plate with a target ligand (e.g., a thiolated analog of S1P, LPA, etc.) that has been covalently linked to a protein carrier such as BSA.

Without being limited to particular method or example, chimeric antibodies could be generated against other lipid targets such as LPA, PAF, ceramides, sulfatides, cerebroside, cardiolipins, phosphatidylserines, phosphatidylinositols, phosphatidic acids, phosphatidylcholines, phosphatidylethanolamines, eicosinoids, and other leukotrienes, etc. Further, many of these lipids could also be glycosylated and/or acetylated, if desired.

Example 7: Generation and characterization of humanized anti-S1P monoclonal antibody LT1009 (Sonepcizumab)

The murine anti-S1P monoclonal antibody 306D (LT1002; Sphingomab™), which specifically binds S1P, has been shown to potently suppress angiogenesis and tumor growth in various animal models. As discussed below, LT1002 was humanized using sequence identity and homology searches for human frameworks into which to graft the murine CDRs and a computer-generated model to guide some framework backmutations. Two variants, HuMAbHCLC₃ (LT1004) (with 3 backmutations in the light chain) and HuMAbHCLC₅ (LT1006) (with 5 backmutations in the light chain) exhibited binding affinity in the nanomolar range. Further engineering was performed in an effort to improve the biophysical and biological properties of the humanized variants. The humanized variants HuMAbHC_{CysAla}LC₃ (LT1007) and HuMAbHC_{CysAla}LC₅ (LT1009) in which a free-cysteine residue in HCDR2 was replaced with alanine exhibited a binding affinity in the picomolar range. All humanized variants inhibited angiogenesis in the choroid neovascularization (CNV) model of age-related macular degeneration (AMD), with HuMAbHC_{CysAla}LC₅ (LT1009) exhibiting superior stability and *in vivo* efficacy compared to the parent murine antibody. The variant huMAbHCcysalaLC₅ (LT1009) was designated Sonepcizumab™.

1. Humanization design for the anti-S1P antibody

The variable domains of murine mAb LT1002 (Sphingomab™) were humanized via CDR grafting (Winter U.S. Pat. No. 5,225,539). The CDR residues were identified based on sequence hypervariability as described by Kabat et al. 1991.

In this study, suitable acceptor structures were selected based on a homology search of human antibodies in the IMGT and Kabat databases using a structural alignment program (SR v7.6). The initial step was to query these human heavy variable (VH) and light variable (VL) sequence databases with LT1002 VH and VL protein sequences respectively, to identify human frameworks (FR) with high sequence identity in the FR, at Vernier (Foote, J. & Winter, G. Antibody framework residues affecting the conformation of the hypervariable loops. *J Mol. Biol.* **224**, 487-499 (1992)), Canonical (Morea, et al., Antibody modeling: implications for engineering and design, *Methods* **20**, 267-279 (2000) and VH-VL interface (Chothia, C., Novotny, J., Brucoleri, R., & Karplus, M. Domain association in immunoglobulin molecules. The packing of variable domains. *J Mol. Biol.* **186**, 651-663 (1985)) residues and with CDRs

of identical canonical class and/or length. The identity of each member of this library to individual aligned residues of the mouse antibody was calculated using the program. Those human sequences with FR sequence most identical to the mouse FR were identified, producing an initial shortlist of human "acceptor" sequences. Those sequences with most identity to the mouse antibody, at Vernier, Canonical and VH-VL Interface (VCI) residues, were also calculated. Differences at these positions between human and mouse were classified into conservative and non-conservative substitutions, so that the best framework choice would have the lowest number of non-conservative VCI differences from LT1002. The CDR loops L3 and H1 of LT1002 could be classified into canonical structures. These L3 and H1 structures were used to select human antibody FRs with identical canonical structures. For unclassified CDRs, an attempt was made to select human frameworks with CDR lengths identical to the mouse antibody. The rationale is that CDR loop structures are dependent not only on the CDR loop sequence itself, but also on the underlying framework residues (canonical residues). Therefore a human framework with matching canonical CDR structures and/or CDR lengths is likely to hold the grafted mouse CDRs in the most appropriate orientation to maintain antigen binding affinity. This was achieved for all CDRs except CDR H3, by the choice of human framework sequences. Additionally, frameworks with unusual cysteine or proline residues were excluded where possible. These calculations were performed separately for the heavy and light chain sequences. Finally, individual sequence differences, throughout the framework region, in the best matching sequences were compared. Of the human antibodies that best fit the above comparative calculations, the antibodies AY050707 and AJ002773 were selected as the most appropriate human framework provider for the light chain and the heavy chain respectively. The AY050707 framework was described by van den Brink, et al. (Blood, 15 April 2002, Vol. 99, No. 8, pp 2828-2834) and its sequence is available via Genbank (accession no. AY050707; Homo sapiens clone WR3VL immunoglobulin light chain variable region mRNA, partial cds.; submitted Nov 13, 2001, last revision April 8, 2002).

Similarly, the AJ002773 antibody framework was described by Snow, et al. [Eur. J. Immunol. 28 (10), 3354-3361 (1998)], and its sequence is available via Genbank (accession no. AJ002772; Homo sapiens mRNA for variable region 5 of immunoglobulin G4 heavy chain patient 2,2; submitted Nov. 6, 1998, last revision October 16, 2006).

Both the AY050707 (light chain) and the AJ002773 (heavy chain) sequences are also found in IMGT/LIGM, a comprehensive database of immunoglobulin (IG) and T cell receptor (TR) nucleotide sequences from human and other vertebrate species. This database was created in 1989 by Marie-Paule Lefranc, LIGM, Montpellier, France, and has been available online since July 1995.

The second step was to generate a molecular model of the variable regions of LT1002 and to identify FR residues which might affect antigen binding but were not included in the group of Vernier, Canonical and Interface residues. Many structural features of the graft donor and acceptor variable domains were examined in order to better understand how various FR residues influence the conformation of the CDR loops and vice versa. Non-conserved FR residues in LT1002 that were likely

to impact the CDRs were identified from the Vernier and Canonical definitions (see above) and thus several residues of the human FR were restored to the original murine amino acids (backmutated).

2. Mutagenesis

Mutations within the variable domain sequences were created using the QuikChange Site-Directed Mutagenesis Kit (Stratagene, Catalog #200524). Individual reactions were carried out with 50 ng of double-stranded DNA template, 2.5 U of PfuUltre HF DNA polymerase and its corresponding buffer (Stratagene, Catalog #200524), 10 mM dNTP mix and 125 ng of each of the mutagenic oligonucleotides resuspended in 5 mM Tris-HCl (pH 8.0), and 0.1 mM EDTA. The initial denaturation was carried out at 95°C for 30 s, followed by 16 cycles of amplification: 95°C for 30 s, 55°C for 60 s and 68°C for 8 min. Following temperature cycling, the final reaction was then digested with DpnI digest at 37°C for 1 h to remove methylated parental DNA. The resultant mutant was transformed into competent XL1-Blue E.coli and plated on LB-agar containing 50 µg/ml Ampicillin. The colonies were then checked by sequencing. Each of the mutants were then cultured in 1 liter shake flasks and purified using the EndoFree Plasmid Purification Kit from Qiagen, catalog #12362.

3. Generation of the humanized antibody variants

A mouse-human chimeric antibody (chMAb S1P) was constructed by cloning the variable domains of LT1002 into a vector that contained the human constant regions of the kappa and heavy chains to allow expression of the full length antibody into mammalian cells. The generation of the humanized heavy chain was the result of the graft of the Kabat CDRs 1, 2 and 3 from LT1002 V_H into the acceptor framework of AJ002773. The nearest germ line gene to AJ002773 was VH5-51, whose leader sequence was incorporated, as a leader sequence, into the humanized heavy chain variant. The protein sequence of pATH200, the first humanized version of LT1002 V_H, with the VH5-51 leader sequence, is shown in Table 4. In the case of the V_H domain of LT1002, residues at position 2, 27, 37, 48, 67 and 69 were Vernier residues or at the interface of the V_H and V_L domains and likely to influence CDR orientation. Position 37 appeared to be critical for the interface between the V_H and V_L domains. The residues at these positions in the human framework were backmutated with the murine residue found at the corresponding position. The mutations, V37M, M48I and Y27F, were tested individually. One version (pATH205) contained all 3 mutations together with V67A plus I69L and another version (pATH206) contained all 5 mutations plus V2A.

The generation of the humanized light chain was the result of the graft of the Kabat CDRs 1, 2 and 3 from LT1002 V_L into the acceptor framework of AY050707. The nearest germ line gene to AY050707 was L11, whose leader sequence was incorporated into the humanized light chain construct. The protein sequence of pATH300 (LT1002 light chain) is shown in Table 4. Germline leader sequences are indicated by underlining in Table 4. In the case of V_L, four non-conserved Vernier positions 4, 36, 49, 64 were selected for backmutation to murine residues as they are involved in supporting the structure of the CDR loops. Inspection of the molecular model of LT1002 suggested that Tyr 67 is close to the

CDR surface and oriented towards the antigen binding plane and could interact with S1P. Therefore the S67Y backmutation was also added to later humanized versions. Two mutations were introduced separately to generate two versions containing either Y49S or Y36F. Several versions were created with the following combinations of mutations: (Y49S, F4V), (Y49S,Y36F), (Y49S,Y36F,F4V), (Y49S, G64S), (Y49S, Y36F, F4V,G64S), (Y49S, Y36F, F4V, G64S, S67Y), (Y49S, G64S,S67Y).

4. Selection of the humanized lead candidates

The variable regions of the basic grafted versions (pATH 200 and pATH 300) and all the variants containing backmutations were cloned into expression vectors containing the human V_H or V_L constant regions. All the humanized variants were produced in mammalian cells under the same conditions as the chimeric (chMAb) antibody and were tested for binding to S1P by ELISA. The yield was approximately 10-20 mg /l for the humanized variants and 0.3-0.5 mg/l for chMAb S1P. SDS-PAGE under reducing conditions revealed two bands at 25 kDa and 50 kDa with high purity (>98%), consistent with the expected masses of the light and heavy chains. A single band was observed under non-reducing conditions with the expected mass of ~ 150k. chMAb was used as a standard in the humanized antibody binding assays because it contained the same variable regions as the parent mouse antibody and bore the same constant regions as the humanized antibodies and therefore could be detected using the same ELISA protocol.

The initial humanized antibody, in which the six murine CDRs were grafted into unmutated human frameworks, did not show any detectable binding to S1P. The kappa light chain containing the 4 backmutations (Y49S, Y36F, F4V and G64S), in association with chimeric heavy chain, exhibited suboptimal binding to S1P as measured by ELISA. The incorporation of an additional mutation at position Y67 significantly improved the binding. Version pATH308 which contained backmutations Y49S, Y36F, F4V, G64S and S67Y and version pATH309 which contained the backmutations Y49S, G64S and S67Y, in association with chimeric heavy chain, both generated antibodies which bound S1P similarly to the chimeric antibody as determined by ELISA. The 2 mutations Y36F and F4V were not considered necessary backmutations from the viewpoint of S1P binding. The engineering of 3 to 5 backmutations in the VL framework was required to restore activity.

The incorporation of the Vernier backmutation V37M into the human framework of the heavy chain, in association with the chimeric light chain, was sufficient to restore a binding behavior similar to the chimeric antibody .

In summary, humanization of the LT1002 V_H domain required only one amino acid from the murine framework sequence whereas the murine V_L framework domain, three or five murine residues had to be retained to achieve binding equivalent to the murine parent LT1002.

5. Optimization of a humanized lead candidate

The murine anti-S1P antibody contains a free cysteine residue in CDR2 (Cys50) of the heavy chain that could potentially cause some instability of the antibody molecule. Using site directed mutagenesis, variants of pATH201 were created with substitution of the cysteine residue with alanine (huMAbHCcysalaLC₃) (pATH207), glycine (huMAbHCcysalaLC₃), serine (huMAbHCcysserLC₃), and phenylalanine (huMAbHCcyspheLC₃). The cysteine mutant heavy chain was also tested with the humanized light chain (pATH 308) containing 5 backmutations (huMAbHCcysalaLC₅ = LT1009). The variants were expressed in mammalian cells and then characterized in a panel of *in vitro* assays. Importantly, the expression rate of the humanized variants was significantly higher than for chMAb S1P.

6. In-depth characterization of the humanized lead candidate

i. Specificity. The humanized variants were tested for specificity in a competitive ELISA assay against S1P and several other biolipids. This assay has the added benefit to allow for epitope mapping. The humanized antibody LT1009 demonstrated no cross-reactivity to sphingosine (SPH), the immediate metabolic precursor of S1P, or LPA (lysophosphatidic acid), an important extracellular signaling molecule that is structurally and functionally similar to S1P. Moreover, rhuMAb S1P did not recognize other structurally similar lipids and metabolites, including ceramide (CER), ceramide-1-phosphate (C1P). However as expected LT1009 did cross react with sphingosyl phosphocholine (SPC), a lipid in which the free phosphate group of S1P is tied up with a choline residue. Importantly, all the humanized variants exhibited a specificity profile comparable to the mouse antibody.

ii. Binding affinity. Biacore measurements of IgG binding to a S1P coated chip showed that the variants LT1004 or LT1006 exhibited binding affinity in the low nanomolar range similar to chMAb S1P. The humanized variants LT1007 and LT1009 in which the cysteine residue was replaced with alanine exhibited a binding affinity in the picomolar range similar to the murine parent LT1002 (Sphingomab™).

iii. Stability. The humanized variants were tested for stability after challenge at high temperature. The approximate midpoints of the thermal unfolding transitions (T_M) were determined for every humanized variant by subjecting the supernatants to temperatures ranging from 60 to 74°C. These temperatures were chosen based on the denaturation profile observed for the murine antibody molecule after thermochallenging between a broad range of temperatures between 50 and 80°C. The binding properties of each variant were determined before and after thermochallenge. The murine antibody exhibited a T_M of 65°C. The variant huMAbHCcysalaLC₅ (LT1009) exhibited superior T_M compared to all other variants. Table 6 shows the lead humanized candidates and their characteristics.

Table 6: Lead humanized S1P mAb candidates and characteristics

The number of mutations in the heavy and light chains are indicated. The description column gives the identity of the heavy and light chains.

mAb	Description	Mutations in the Heavy Chain		Mutations in the Light Chain		In vitro Activity	
		CDR	Frame-work	CDR	Frame-work	Binding Affinity (K_{DI})	Specificity (ELISA)
LT1002	Murine mAb Sphingomab	N/A	N/A	N/A	N/A	0.026 ± 0.000 nM	High
LT1004	HuHCLC ₃ pATH201HC pATH309LC	0	1	0	3	1.060 ± 0.010 nM	High
LT1006	HuHCLC ₅ pATH201HC pATH308LC	0	1	0	5	0.690 ± 0.010 nM	High
LT1007	HuHCcysalaLC ₃ pATH207HC pATH309LC	1	1	0	3	0.0414 ± 0.0004 nM	
LT1009	HuHCcysalaLC ₅ pATH207HC pATH308LC	1	1	0	5	0.056 ± 0.001 nM	High

iv. Sequences

As with naturally occurring antibodies, LT1009 includes three complementarity determining regions (each a “CDR”) in each of the two light chain polypeptides and each of the two heavy chain polypeptides that comprise each antibody molecule. The amino acid sequences for each of these six CDRs is provided immediately below (“VL” designates the variable region of the immunoglobulin light chain, whereas “VH” designates the variable region of the immunoglobulin heavy chain):

CDR1 VL: ITTTDIDDDMN [SEQ ID NO: 10]
 CDR2 VL: EGNILRP [SEQ ID NO: 11]
 CDR3 VL: LQSDNLPFT [SEQ ID NO: 12]
 CDR1 VH: DHTIH [SEQ ID NO: 13]
 CDR2 VH: AISPRHDITKYNEMFRG [SEQ ID NO: 18]
 CDR3 VH: GGFYGSTIWFD [SEQ ID NO: 15]

Example 8: Humanized S1P mAb production and purification

This example describes the production of a recombinant humanized monoclonal antibody (LT1009) that binds with high affinity to the bioactive lipid sphingosine-1-phosphate (S1P). LT1009 is a full-length IgG1k isotype antibody composed of two identical light chains and two identical heavy chains with a total molecular weight of approximately 150kDa. The heavy chain contains an N-linked glycosylation site. The nature of the oligosaccharide structure has not yet been determined but is

anticipated to be a complex biantennary structure with a core fucose. The nature of the glycoform that will be predominant is not known at this stage. Some C-terminal heterogeneity is expected because of the presence of lysine residues in the constant domain of the heavy chain. The two heavy chains are covalently coupled to each other through two inter-chain disulfide bonds, which is consistent with the structure of a human IgG1.

LT1009 was originally derived from a murine monoclonal antibody (LT1002; Sphingomab™) that was produced using hybridomas generated from mice immunized with S1P. The humanization of the murine antibody involved the insertion of the six murine CDRs in place of those of a human antibody framework selected for its structure similarity to the murine parent antibody. A series of substitutions were made in the framework to engineer the humanized antibody. These substitutions are called back mutations and replace human with murine residues that play a significant role in the interaction of the antibody with the antigen. The final humanized version contains one murine back mutation in the human framework of variable domain of the heavy chain and five murine back mutations in the human framework of the variable domain of the light chain. In addition, one residue present in the CDR #2 of the heavy chain was substituted to an alanine residue. This substitution was shown to increase stability and potency of the antibody molecule.

The humanized variable domains (both heavy and light chain) were cloned into the Lonza's GS gene expression system to generate the plasmid pATH1009. The Lonza GS expression system consists of an expression vector carrying the constant domains of the antibody genes and the selectable marker glutamine synthetase (GS). GS is the enzyme responsible for the biosynthesis of glutamine from glutamate and ammonia. The vector carrying both the antibody genes and the selectable marker is transfected into a proprietary Chinese hamster ovary host cell line (CHOK1SV) adapted for growth in serum-free medium and provides sufficient glutamine for the cell to survive without exogenous glutamine. In addition, the specific GS inhibitor, methionine sulfoximine (MSX), is supplemented in the medium to inhibit endogenous GS activity such that only the cell lines with GS activity provided by the vector can survive. The resulting CHO cell line transfected with pATH1009 is named LH1.

It should be noted that the natural germ line gene leader sequences described in the above examples are replaced by leader sequences in the GS expression vector backbone used to produce the plasmid pATH1009. The latter leader sequences can be seen as 19 amino acids beginning "mewswv," at the N-terminus of the LT1009 heavy chain (SEQ ID NO: 19 and 24), and the LC leader is 20 amino acids beginning "msvpt" (as shown at the N-terminus of SEQ ID NO: 20 and 26).

The transfected CHO LH1 cells were selected for their ability to grow in glutamine-free medium in the presence of MSX and isolates (clones) were selected for high level of secretion of active LT1009. LH1 275 is the name given to the lead clone of the LH1 CHO cell line containing the pATH1009 vector selected for the creation of a Master Cell Bank (MCB) for production of all lots of LT1009 antibody

product. Material for toxicology studies and clinical development were then produced for tox and clinical development.

ATCC deposits: E. coli StB12 containing the pATH1009 plasmid has been deposited with the American Type Culture Collection (deposit number PTA-8421). CHO cell line LH1 275, which contains the pATH1009 vector has also been deposited with the American Type Culture Collection (deposit number PTA-8422).

Sequences:

The nucleotide and amino acid sequences for the heavy and light chain polypeptides of LT1009 are listed immediately below. Leader sequences (from Lonza GS expression vector) are underlined; CDRs are in bold.

LT1009 HC amino acid sequence of the variable domain [SEQ ID NO: 19]:

```
1  mewswvflfflsvttgvhsevqlvqsgaevkkpgeslkiscqsfgyifid
51  htihwmrqmpggglewmgaisprhdi tkynemfrgqvtisadkssstayl
101  qwsslkasdtamyfcargggyfystiwfdfwgggtmvtvss
```

LT1009 LC amino acid sequence of the variable domain [SEQ ID NO: 20]:

```
1  msvptqvlgl llllwltdarcettvtqspflsasvgdrvtitcitttdid
51  ddmnwfqepgkpkllisegnrlrgvpsrfsssgygtdftltisklqp
101  edfatyyclqsdnlpftfgggtkleik
```

Corresponding nucleotide sequences encoding the heavy and light chain variable domains are listed immediately below. Leader sequences (from Lonza GS expression vector) are underlined; sequences preceding the leader are HindIII cut site (aagctt) and Kozak consensus sequence (gccgccacc), which plays a major role in the initiation of translation process; CDRs are in bold:

LT1009 HC nucleotide sequence of the variable domain [SEQ ID NO: 21]

```
1  aagcttgccg ccaccatgga atggagctgg gtgttcctgt tctttctgtc
51  cgtgaccaca ggcgtgcatt ctgaggtgca gctggtgcag tctggagcag
101  aggtgaaaaa gcccggggag tctctgaaga tctcctgtca gagttttgga
151  tacatcttta tcgaccatac tattcactgg atgcgccaga tgcccgggca
201  aggcttgag tggatggggg ctatttctcc cagacatgat attactaaat
251  acaatgagat gttcaggggc caggtcacca tctcagccga caagtccagc
301  agcaccgcct acttgcaagt gagcagcctg aaggcctcgg acaccgccat
351  gtatttctgt gcgagagggg ggttctacgg tagtactatc tggtttgact
401  ttgggggcca agggacaatg gtcaccgtct cttca
```

LT1009 LC nucleotide sequence of the variable domain [SEQ ID NO. 22]

```

1  aagcttgccg ccaccatgtc tgtgcctacc caggtgctgg gactgctgct
51 gctgtggctg acagacgccc gctgtgaaac gacagtgacg cagtctccat
101 ccttcctgtc tgcattctgta ggagacagag tcaccatcac ttgcataacc
151 accactgata ttgatgatga tatgaactgg ttccagcagg aaccagggaa
201 agcccctaag ctcttgatct ccgaaggcaa tattcttcgt cctgggggtcc
251 catcaagatt cagcagcagt ggatatggca cagatttcac tctcaccatc
301 agcaaattgc agcctgaaga ttttgcaact tattactgtt tgcagagtga
351 taacttacca ttcactttcg gccaaaggac caagctggag atcaaa

```

LT1009 full length HC nucleotide (cDNA) sequence [SEQ ID NO: 23] with CDRs in bold and leader region underlined; hinge region is in italics. Sequences preceding the leader are HindIII cut site (aagctt) and Kozak sequence (gccgccacc):

```

aagcttgccgccaccatggaatggagctgggtgttctgttctttctgtccgtgaccacagggcgtgcatt
ctgaggtgcagctggtgcagctctggagcagaggtgaaaaagccccgggagtgctctgaagatctcctgtca
gagttttggatacatctttatcgaccatactattcactggatgcgccagatgcccgggcaaggcctggag
tggatgggggctatttctcccagacatgatattactaaatacaatgagatgttcaggggccaggtcacca
tctcagccgacaagtccagcagcaccgcctacttgacgtggagcagcctgaaggcctcgacaccgccat
gtatttctgtgcgagaggggggttctacggtagtactatctgggttgacttttggggccaagggacaatg
gtcaccgtctcttcagcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacct
ctgggggacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaa
ctcaggcgccctgaccagcggcgtgcacaccttccccggtgtcctacagtcctcaggactctactccctc
agcagcgtggtgaccgtgcctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagc
ccagcaacaccaaggtggacaagagagttgagcccaaatcttgtagacaaaactcacacatgccaccggtg
cccagcacctgaactcctgggggggaccgtcagtccttcttcttccccccaaaaccaaggacaccctcatg
atctccccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagacccctgaggtcaagttca
actggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaacagcac
gtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgaag
gtctccaacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaac
cacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctggt
caaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaag
accacgcctcccgtgctggactccgacggctccttcttctctatagcaagctcacctgggacaagagca
ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaa
gagcctctcctgtctccgggtaaatag

```

LT1009 HC amino acid sequence, with leader (underlined) and minus the hinge region. CDRs are shown in bold. [SEQ ID NO: 24]:

```

1  mewswvflff lsvttgvhse vqlvqsgaev kkpgeslkis cqsfgyifid
51 htihwmrqmp ggglewmgai sprhditkyn emfrgqvtis adkssstayl
101 qwsslkasdt amyfcargggf ygstiwfdfw gggtmvtvss astkgpsvfp
151 lapsskstsg gtaalgclvk dyfpepvtvs wnsгалtsgv htfpavlgss
201 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvap ellggpsvfl
251 fppkpkdtlm isrtpevtcv vvdvshedpe vkfnwyvdgv evhnaktkpr
301 eeqynstyrv vsvltvlhqd wlngkeykck vsnkalpapi ektiskakgg
351 prepqvytlp psreemtknq vsltclvkgf ypsdiavewe sngqpennyk
401 ttppvldsdg sfflyskltv dksrwqqgnv fscsvmheal hnhytqksls
451 lspgk

```

LT1009 LC full length nucleotide sequence [SEQ ID NO: 25] with leader underlined and CDRs in bold; sequences preceding the leader are HindIII cut site (aagctt) and Kozak sequence (gccgccacc):

```

1  aagcttgccg ccaccatgtc tgtgcctacc caggtgctgg gactgctgct
51 gctgtggctg acagacgccc gctgtgaaac gacagtgacg cagtctccat
101 ccttctgtgc tgcattctgta ggagacagag tcaccatcac ttgcataacc
151 accactgata ttgatgatga tatgaactgg ttccagcagg aaccagggaa
201 agcccctaag ctctctgatct ccgaaggcaa tattcttcgt cctgggggtcc
251 catcaagatt cagcagcagt ggatatggca cagatttcac tctcaccatc
301 agcaaattgc agcctgaaga ttttgcaact tattactgtt tgcagagtga
351 taacttacca ttcacttttcg gccaaaggac caagctggag atcaaacgta
401 cggtggctgc accatctgtc ttcattcttc cgccatctga tgagcagttg
451 aaatctggaa ctgcctctgt tgtgtgcctg ctgaataact tctatcccag
501 agaggccaaa gtacagtgga aggtggataa cgccctccaa tcgggtaact
551 ccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc
601 agcagcacc tgacgtgag caaagcagac tacgagaaac acaaagtcta
651 cgctgcgaa gtcacccatc agggcctgag ctgcgccgctc acaaagagct
701 tcaacagggg agagtgttag

```

LT1009 LC amino acid sequence with leader underlined and CDRs in bold [SEQ ID NO: 26]:

```

1  msvptqvlgl lllwltdarc ettvtqpsf lsasvgdrvt itcitttdid
51 ddmnwfqpep gkapkllise gnilrpgvps rfsssgygtf ftltisklqp
101 edfatyyclq sdnlpftfgg gtkleikrtv aapsvfifpp sdeqlksgta
151 svvcllnfy preakvqwkvnalqsgnsq esvteqdskd styslsstlt
201 lskadyekhk vyacevthqg lsspvtksfn rgec

```

Sequences of the LT1009 heavy and light chains without leader sequences (and without preceding nuclease cut sites and Kozak sequences) are as follows. CDRs are shown in bold.

LT1009 HC amino acid sequence of the variable domain [SEQ ID NO: 27]:

evqlvqsgaevkkpgeslkiscqsfgyifi**dhtih**wmrqmpggglewmga**aisprhdi**tkynem**frg**qvti
sadkssstaylqwsslkasdtamyfcarg**gfygsti**w**fdf**wgggtmvtvss

Corresponding LT1009 HC nucleotide sequence encoding the variable domain [SEQ ID NO: 28]:

gaggtgcagctggtgcagtcctggagcagaggtgaaaaagcccgaggagtcctgaagatctcctgtcaga
gttttggatacatctttatc**gaccatactattcact**ggatgcgccagatgcccgggcaaggcctggagtg
gatgggg**gctatttctcccagacatgatattactaaatacaatgagatggttcaggggc**caggtcaccatc
tcagccgacaagtcagcagcaccgcctacttgagtcggagcagcctgaaggcctcgacaccgcatgt
atttctgtgcgagag**ggggggttctacggtagtactatctggtttgactttt**ggggccaagggaacaatggt
cacggtctcttca

LT1009 LC amino acid sequence of the variable domain [SEQ ID NO: 29]:

ettvtqspfsflsasvgrvtitc**itttdiddmn**wfqepgkpkllis**egnilrp**gvps
rfsssgygtdflltisklqpedfatyycl**qsdnlpft**fgggtkleik

Corresponding LT1009 LC nucleotide sequence encoding the variable domain [SEQ ID NO: 30]:

gaaacgacagtgcagcagtcctccatccttctgtctgcacatctgtaggagacagagtcaccatcacttgca
taaccaccactgatattgatgatgatatgaactggttcagcaggaaccagggaaagcccctaagtcct
gatctcc**gaaggcaatatcttctcgctcct**gggtcccatcaagattcagcagcagtgatggcacagat
ttcactctcaccatcagcaaattgcagcctgaagattttgcaacttattactgt**ttgcagagtgataact**
taccattcactttcggccaagggaaccaagctggagatcaaa

The amino acid sequences of the full length LT1009 heavy and light chains without leaders are as follows (CDRs are in bold):

LT1009 full length heavy chain amino acid sequence without leader (and without preceding nuclease cleavage site and Kozak sequence) and including hinge (underlined) (SEQ ID NO: 31) :

evqlvqsgaevkkpgeslkiscqsfgyifi**dhtih**wmrqmpggglewmga**aisprhdi**tkynem**frg**qvti
sadkssstaylqwsslkasdtamyfcarg**gfygsti**w**fdf**wgggtmvtvssastkgpsvfplapssksts
ggtaalglclvkdyfpepvtvswngaltsgvhtfpavllqssglyslssvvtvpssslgtqtyicnvnhkp
sntkvdkrvepkscdktht**cp**pcapellggpsvflfpkpkdtlmisrtpevtcvvdvshedpevkfn
wyvdgvevhnaktkpreeqynstyrvsvltvlhqdwlngkeykckvsnkalpapiektiskakgpprep
qvytlppsreemtknqvsltclvkgyfypsdiavewesngqpennykttpvldsdgsfflyskltvdksr
wqggnvfscsvmhealhnhytqkslsispkg

LT1009 full length light chain amino acid sequence without leader. [SEQ ID NO 32]:

ettvtqspflsasvgdrvtitc**itttdiddm**nwfqgepgkapkllis**egnilr**p^gvpsrfsssgygt
ftltisklqpedfatyy**clqsdnlpft**fgqgkcleikrtvaapsvfifppsdeqlksgtasvvcllnnfy
preakvqwkvdnalqsgnsqesvteqdsdstyslsstltlskadyekhkvyacevthqglsspvtksfn
rgec

The corresponding nucleotide sequences (without leaders or preceding nuclease or Kozak sites) are below. It will be understood that due to the degeneracy of the genetic code, alternative nucleotide sequences also may encode virtually any given amino acid sequence.

LT1009 full length heavy chain nucleotide (cDNA) sequence [SEQ ID NO: 33]:

gaggtgcagctggtgcagtcctggagcagaggtgaaaaagcccgaggagtcctgaagatctcctgtcaga
gttttggatacatctttatc**gaccatactattcac**tggatgcgccagatgcccggaaggcctggagtg
gatgggg**gctatttctcc**cagacatgatattactaaatacaatgagatg**ttcaggggc**caggtcaccatc
tcagccgacaagtccagcagcaccgcctacttgagtgagcagcctgaaggcctcggacaccgcatgt
atctctgtgcgagag**ggggggttctac**ggtagtactatctg**gtttgacttt**tggggccaagggaacaatggt
cacgctctcttcagcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctct
gggggcacagcggccctgggctgcttggtcaaggactacttccccgaaccggtgacggtgtcgtggaact
caggcgccctgaccagcggcgtgcacaccttcccggtgtcctacagtcctcaggactctactccctcag
cagcgtggtgacgctgcccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagccc
agcaacaccaaggtggacaagagagttgagcccaaatcttg**tgacaaaactcac**acatgcccaccgtg**cc**
cagcacctgaactcctggggggacgctcagtccttcttccccccaaaacccaaggacaccctcatgat
ctcccgacccctgaggtcacatgcgtggtggtgacgtgagccacgaagaccctgaggtcaagttcaac
tggtacgtggacggcgtggaggtgcataatgccaaagacaagccgaggagagcagtagacaacagcacgt
accgtgtggtcagcgtcctcacgctcctgcaccaggactggctgaatggcaaggagtacaagtgaagggt
ctccaacaaagccctccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaacca
caggtgtacacctgcccccatcccgaggagatgaccaagaaccaggtcagcctgacctgcctggtca
aaggcttctatccagcgacatcgccgtggagtgaggagcaatgggcagccggagaaactacaagac
cacgcctcccggtgctggactccgacggctccttcttctctatagcaagctcacggtggacaagagcagg
tggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaaga
gcctctccctgtctccgggtaaatag

LT1009 full length light chain nucleotide sequence [SEQ ID NO 34]:

gaaacgacagtgacgcagtcctccatccttctgtctgcacatctgtaggagacagagtcaccatcacttg**ca**
taaccaccactgatattgatgatgatatgaactgggtccagcaggaaccagggaagccctaagctcct
gatctcc**gaaggcaatattctt**cgctcctgggggtcccatcaagattcagcagcagtgatattggcacagat
ttcactctcaccatcagcaattgcagcctgaagattttgcaacttattactgt**ttgcagagtgataact**
taccattcactttcggccaagggaaccaagctggagatcaaacgtacggtggtgcaccatctgtcttcat

cttcccgccatctgatgagcagttgaaatctggaactgcctctgttggtgcctgctgaataacttctat
 cccagagaggccaaagtacagtggaaggtggataacgccctccaatcggttaactcccaggagagtgtca
 cagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacga
 gaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaac
 aggggagagtgttag

The C-terminal lysine on the LT1009 heavy chain may not always be present on the mature heavy chain protein.

While the nucleotide and amino acid sequences for LT1009 heavy chain reveal a lysine as the last (most C-terminal) amino acid residue of the protein, LT1009 when expressed, for example, in CHO cell clone LH1 275, does not contain the C-terminal lysine. This is shown by peptide mapping and, while not wishing to be bound by theory, is believed to result from posttranslational modification of the protein in mammalian systems. Again not wishing to be bound by theory, it is believed that in other expression systems, particularly nonmammalian systems, the C-terminal lysine is present on the mature LT1009 heavy chain.

The LT1009 heavy chain amino acid sequence as expressed in CHO cells (i.e., without leaders and without the C-terminal lysine) is shown below (CDRs are in bold, hinge in italics) [SEQ ID NO 35]:

evqlvqsgaevkpkgeslkiscqsfgyifi**dhtih**wmrqmpggglewmga**aisprhdi***tkynem***frg**qvti
 sadkssstaylqwsslkasdtamyfcar**ggfygsti****wfdf**wggqtmvtvssastkgpsvfplapssksts
 ggtaalglcvkdyfpepvtvswngaltsgvhtfpavlgssglyslssvvtvpssslgtqtyicnvnhkp
 sntkvdkrvepks**cdktht***cp*pcpapellggpsvflfpkpkdltmisrtpevtcvvvdvshedpevkfn
 wyvdgvevhnaktkpreeqynstyrvvsvltvlhqdwlngkeykckvsnkalpapiektiskakggprep
 qvytlppsreemtknqvsltclvkgyfypsdiavewesngqpennykttpvldsdgsfflyskltvdksr
 wqggnvfscsvmhealhnhytqkslsisp

An example of a nucleotide sequence that could encode this amino acid sequence is shown below as SEQ ID NO: 36. It will be understood that, due to the degeneracy of the genetic code, multiple nucleotide sequences may encode the same amino acid sequence, and for this reason, these and other nucleotide sequences shown herein as encoding amino acid sequences are recognized to be for purposes of exemplification. CDRs are shown in bold and the hinge region is in italics:

gaggtgcagctggtgcagctctggagcagaggtgaaaaagcccgaggagctctgaagatctcctgtcaga
 gttttggatacatctttatc**gaccatactattc**actggatgcgccagatgcccgaggcaaggcctggagtg
 gatgggg**gctat****ttctcccagacatgata****tactaaatacaatgagatgttcaggggc**caggtcaccatc
 tcagccgacaagtcagcagcaccgcctacttgagtgaggagcagcctgaaggcctcgacaccgccatgt
 atttctgtgcgagag**ggggggttctacggtagtactatctggtttgactttt**ggggccaagggaacaatggt
 caccgtctcttcagcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctct
 gggggcacagcggccctgggctgcctgggtcaaggactacttccccgaaccggtgacgggtgctgtggaact

caggcgccctgaccagcggcggtgcacaccttcccggctgtcctacagtcctcaggactctactccctcag
cagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagccc
agcaacaccaaggtggacaagagagttggtgagaggccagcacaggaggagggtgtctgctggaagcc
aggctcagcgctcctgacctggacgcacccggctatgcagtcctcagtcagggcagcaaggcaggccccc
tctgcctcttcacccggaggcctctgcccgcctcactcatgctcaggagagggtcttctggctttttcc
ccaggctctgggcaggcacaggctaggtgccctaacccaggccctgcacacaaaggggcagggtgctggg
ctcagacctgccaagagccatatccgggaggaccctgcccctgacctaaagccaccccaaaggccaaact
ctccactccctcagctcggacaccttctctcctcccagattccagtaactcccaatcttctctctgcaga
gccccaaatcttgtgacaaaaactcacacatgccaccgtgccaggtaagccagcccaggcctcgccctcc
agctcaaggcgggacagggtgccctagagtagcctgcatccaggggacaggccccagccgggtgctgacacg
tccacctccatctcttccctcagcacctgaactcctggggggaccgtcagtccttcttccccccaaaac
ccaaggacacctcatgatctcccgaccctgaggtcacatgcgtggtggtggacgtgagccacgaaga
ccctgagggtcaagttcaactggtacgtggacggcggtggaggtgcataatgccaagacaaagccgaggag
gagcagtacaacagcacgtaccgtgtggtcagcgctcctcacgctcctgcaccaggactggctgaatggca
aggagtacaagtgaagggtctccaacaaagccctcccagcccccatcgagaaaaccatctccaaagccaa
aggtgggaccctggtgggtgagggccacatggacagaggccggctcgcccaccctctgcctgagagt
gaccgtgtaccaacctctgtccctacagggcagccccgagaaccacagggtgtacacctgcccccatcc
cgggaggagatgaccaagaaccagggtcagcctgacctgctggtcaaaggcttctatcccagcgacatcg
ccgtggagtgaggaggaatgggcagccggagaacaactacaagaccacgcctcccgctgctggactccga
cggctccttcttctctatagcaagctcacctggacaagagcagggtggcagcagggggaacgtcttctca
tgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggttag

Peptide mapping of LT1009

Peptide mapping of LT1009 (four different lots, all expressed in CHO cell line LH1 275) was able to confirm >99% of the protein sequence. The only peptides not observed were single amino acids. Evidence of a deglycosylation reaction was present in fragment T23 of the heavy chain, wherein asparagine (N) was converted to aspartic acid (D) upon deglycosylation. This indicates prior glycosylation at this site, which corresponds to amino acid 301 (N) of the heavy chain amino acid sequence (as shown in, for example, SEQ ID NO: 31). It was also shown by peptide mapping that the C-terminal lysine was not present in the LT1009 heavy chain as expressed in CHO cell line LH1 275.

Example 9: In vivo efficacy of murine mAb (Sphingomab) vs, humanized mAb (Sonepcizumab)

Sphingomab (LT1002) and Sonepcizumab (LT1009) were compared in an assortment of animal and in vitro models as disclosed in US patent application serial no. 11/924,890 (attorney docket no. LPT-3010-UT), filed on October 26, 2007, entitled "Compositions and Methods for Binding Sphingosine-1-Phosphate," which is incorporated herein in its entirety.

The humanized antibody variants and the murine antibody were compared for their ability to inhibit neo-vascularization in the CNV animal model of AMD. Three of the humanized variants inhibited angiogenesis essentially equivalently to the murine antibody as assessed by measurement of CNV area. Both the murine mAb LT1002 (Sphingomab™) and the humanized mAb LT1009 (Sonepcizumab™) significantly decreased lesion size in this mouse model of CNV. All mAbs tested showed approximately 80-98% reduction of lesion size, which was significant ($p < 0.001$ vs. saline) in all cases. In addition, LT1007 and LT1009 also showed significant inhibition ($p < 0.05$) compared to non-specific antibody control. Percent inhibition of lesion size was approximately 80% for LT1002 (murine), 82% for LT1004 (humanized), 81% for LT1006 and 99% for LT1009. Thus, LT1009 was most active in this in vivo model of neovascularization.

LT1009 was also effective in reducing the development of retinal neovascularization in murine model of retinopathy of prematurity [US patent application serial no. 11/924,890 (attorney docket no. LPT-3010-UT), filed on October 26, 2007, entitled "Compositions and Methods for Binding Sphingosine-1-Phosphate," which is incorporated herein in its entirety]. Intravitreal administration of LT1009 (5.0 µg/eye) resulted in a nearly 4-fold reduction in retinal neovascularization compared to saline control.

LT1009 also blocked nearly 80% of VEGF-induced Angiogenesis in a Matrigel plug assay. This reduction is significant ($p < 0.05$ compared to VEGF alone) and confirms the potent anti-angiogenic activity of LT1009 and strongly suggest that LT1009 is capable of significantly inhibiting VEGF induced angiogenesis. This finding is consistent with data from Lpath's oncology program whereby that S1P antibody reduced serum levels of several angiogenic factors, including VEGF, in a murine orthotopic breast cancer model.

LT1009 also significantly reduces choroidal neovascularization and vascular leakage following laser rupture of Bruch's membrane. The area of choroidal neovascularization (stained by PECAM-1) was approximately 0.015 mm² for animals treated with LT1009 and approximately 0.03 mm² for saline-treated control animals. This is a 50% reduction in neovascularization ($p = 0.018$). The area of leakage from choroidal neovascularization (stained by fluorescein) was approximately 0.125 mm² for animals treated with LT1009 and approximately 0.2 mm² for saline-treated control animals. This is approximately a 38% reduction ($p = 0.017$) in blood vessel leakage.

These and other results showing efficacy of LT1009 (Sonepcizumab) in models e.g. for angiogenesis and cancer, are disclosed in US patent application serial no. 11/924,890 (attorney docket no. LPT-3010-UT), filed on October 26, 2007, entitled "Compositions and Methods for Binding Sphingosine-1-Phosphate," which is incorporated herein in its entirety.

Example 10 : Anti-S1P antibodies LT1002 and LT1009 decrease lymphocyte counts when administered to c57/bl6 mice or cynomolgous monkeys, respectively

Murine studies with LT1002

The purpose of this study was to determine the toxicity and toxicokinetic profile of the murine anti-S1P monoclonal antibody, LT1002, following daily administration to C57/BL6 mice. The study was conducted by an independent contract laboratory organization, LAB Research, Inc. The LT1002 dosing solutions were administered for 28 consecutive days to animals in each group by bolus intravenous injection via the tail vein (Days 1-14) and then by bolus intraperitoneal injection (Days 15-28), over a period of approximately 0.5-1.0 minute. The treated group animals were dosed with LT1002 at 30, 75 or 200 mg/kg (n=6 per group) and compared to animals treated with PBS as a saline (vehicle) control group.

During the study, animals were monitored for effects on mortality, clinical condition, body weight and food consumption. Blood samples were collected from a subgroup of animals at necropsy for assessment of hematology, coagulation and clinical chemistry. Study animals were euthanized and subjected to a necropsy examination. Selected organs were weighed and a full list of tissues was retained. A histopathology examination was performed on the full tissue list from all control and high dose animals (200 mg/kg/day) and all abnormalities, while target organs were examined on lower dose groups. Blood samples were collected from the toxicokinetic animals (3 animals/sex/group/time point) on Days 1, 14 and 28 and the animals were euthanized and discarded without examination.

Mean lymphocyte counts were significantly ($p < 0.001$) reduced in all LT1002-treated dosing groups with a weak dose-response effect. The average lymphocyte counts (10^9 cells/L $\pm$ SD) for the control, untreated group were 2.9 ± 1.3 (n=6), which were reduced in the 30, 75 and 200 mg/kg groups, respectively to 0.856 ± 0.426 (n=6), 0.902 ± 0.269 (n=5) and 0.638 ± 0.262 (n=4). These data are consistent with those in the example above, showing that, in the murine EAE model of multiple sclerosis, LT1002 caused substantial reductions in lymphocyte counts correlated with reductions in axonal degeneration, demyelination and infiltration of inflammatory cells.

Non-human primate studies

The purpose of this study was to determine the toxicity and toxicokinetic profile of LT1009 when administered to Cynomolgus monkeys in a GLP 28-day safety toxicology study conducted by an independent contract laboratory organization, LAB Research, Inc. LT1009 was administered by 30-minute intravenous infusion every third day for 28 days (10 doses). LT1009 was formulated in vehicle containing 20 mM sodium phosphate, 148 mM sodium chloride, 0.02% polysorbate-80, pH=6.5 for i.v. administration at doses of 3, 10, 30 and 100 mg/kg; For toxicological assessment, blood samples were collected from all animals at several timepoints on Days 1, 16 and 28. In addition, blood was collected from recovery animals 48, 72, 144 and 240 hours following the end of the last dose. Parameters monitored during this study included mortality, clinical signs, body weight, qualitative evaluation of the food consumption, ophthalmology, electrocardiography, and clinical pathology (hematology, clinical chemistry, coagulation and urinalysis). Blood samples were also collected for immunophenotyping assessments, at pre-treatment, on the last day of treatment, and on days 35, 42 and at the end of the recovery period. At termination, a macroscopic examination was performed and selected organs were weighed. Histological evaluation of tissues was conducted on all animals.

There was no mortality, treatment-related adverse clinical signs, or toxicologically-significant effects on body weight, ophthalmology or electrocardiography results, or clinical pathology (hematology, coagulation, clinical chemistry and urinalysis) during this study. There were no organ weight changes or macroscopic or microscopic findings to indicate an adverse effect of LT1009. LT1009 formulation every third day over 28 days (10 treatments) to Cynomolgus monkeys, at dose levels of 3, 10, 30 and 100 mg/kg was well tolerated and did not result in any toxicologically significant changes. As such, the No Observed Toxic Effect Level (NOTEL) for LT1009 in this study was considered to be 100 mg/kg.

However, there were significant ($p < 0.001$) reductions in peripheral blood lymphocyte counts at the high dose only (100 mg/kg). Of the 10 animals in the 100 mg/kg cohort, the mean lymphocyte counts (10^9 cells/L $\pm$ SD) were 5.61 ± 2.24 before treatment, and were significantly ($p < 0.001$) reduced to 3.18 ± 1.25 ($n=10$) when males ($n=5$) and females ($n=5$) were combined for the analysis. This change was reversed during 7 days of recovery and was not considered adverse under the conditions of the study. No test-article related effect was observed on lymphocyte subpopulations following administration of LT1009 at dose level up to and including 30 mg/kg, or apparent relationship between the LT1009 administration and the absolute number of B and NK cells at any of the dose levels tested. On Day 28, the absolute number of T cells showed a statistically significant decrease following administration of 100 mg/kg LT1009 formulation in both males and females, consistent with the reductions in lymphocyte counts. Analysis of the two main T-cell subsets, T-helper (CD4) and T-cytotoxic (CD8), indicated that the observed reduction in T cells was correlated with a decrease in the absolute number of T-helper cells, whereas the T cytotoxic cells were not affected.

These mouse and primate studies indicate that anti-S1P antibody treatment can reduce lymphocyte counts.. These findings are consistent with the scientific literature suggesting that S1P is involved in lymphocyte trafficking and egress from primary and secondary lymphoid tissue into the peripheral circulation. Consequently in humans, it is possible that changes in lymphocyte counts could be a pharmacodynamic marker that could indicate in vivo biological activity of the humanized LT1009 drug candidate formulated for systemic administration. Further, it is possible that systemic administration of LT1009 could be used to alter lymphocyte trafficking with resulting lymphopenia necessary for the treatment of multiple sclerosis or other disorders which might benefit from reduced peripheral blood lymphocyte counts.

Example 11: Purification of LT1009 antibody with low S1P carry-over

Generating highly pure, highly qualified antibodies for pre-clinical or clinical use is of paramount importance for therapeutic drug development. In addition to being free of cellular proteins, DNA and viruses, the antibody preparation should also not contain any of the antigen, so the antibody is fully active and able to bind its target when administered to a patient. Normally, purification and formulation of an antibody removes the antigen, but after purification of the anti-sphingosine-1-phosphate (S1P) monoclonal antibody, LT1009, Lpath sometimes observes significant levels of S1P carried over from the antibody production. S1P is a bioactive lipid that is synthesized by mammalian

cells, including Chinese Hamster Ovary (CHO) cells. During production of LT1009, e.g., from the transfected CHO cell line LH1 275 (ATCC Accession No. PTA-8422), intracellular pools of S1P can be released into the media as a result of normal cellular signaling and/or as a consequence of cell rupture after cell death. The LT1009 antibody expressed in the cell-conditioned medium (supernatant) is able to bind to this S1P. As production continues, more S1P may be released and accumulate in the supernatant as a complex with LT1009. While not wishing to be bound by theory, it is believed that the more time the antibody has in contact with the S1P in the medium, the more of that extracellular S1P would be bound to the LT1009 and carried over into the antibody preparation. When produced in CHO cells, LT1009 antibody preparations may contain in excess of 0.5 moles (50 mole percent, mol%) of S1P per mole of antibody. Thus in order to reduce the amount of S1P carry-over, steps must be taken in both upstream and downstream processing to minimize the amount of S1P in the crude harvest and to promote removal of that S1P during purification.

S1P quantification methods:

The S1P concentrations in various preparations of the LT1009 antibody were measured at WindRose Analytica by RP-HPLC-MS-MS method. Mass spectrometry is rapid and sensitive and, if applied properly, can quantify picogram amounts of analyte. The approach taken in this analytical method is to introduce the S1P into an electrospray mass spectrometer source by reversed phase liquid chromatography (RPC). The RPC step separates the S1P from protein, salts and other contaminants. Following the chromatographic step the S1P is ionized in the source and passed onto an ion trap mass analyzer. All ions except those of the appropriate mass-to-charge ratio ($m/z = 380$) are ejected from the trap. The remaining ions are fragmented in the ion trap and a specific daughter ion ($m/z = 264$) is monitored. The results verify sample identity in three dimensions of analysis: RPC retention time, parent ion m/z of 380, and daughter ion m/z of 264. It is unlikely that any other compound would satisfy all three of these criteria. Additionally, the MS-MS step maximizes signal-to-noise and therefore increases sensitivity significantly. Since there is no extraction step required there is no need for an internal standard. Additionally, the direct injection of sample into the HPLC-MS increases recovery and sensitivity and decreases complexity and analysis time.

For comparison, the concentration of S1P in extracts of selected antibody preparations was determined using a S1P-quantification ELISA. A 4-fold excess of 1:2 chloroform:methanol was added to 1 mg/ml antibody samples to extract the S1P. The aqueous/organic solution was extensively vortexed and sonicated to disrupt antibody-lipid complexes and incubated on ice. After centrifugation, the soluble fraction was evaporated using a speed-vac, and the dried S1P was resuspended in delipidated human serum. The S1P concentration in the resuspended sample was determined by a competitive ELISA using an anti-S1P antibody and a S1P-coating conjugate. The coating conjugate, a covalently linked S1P-BSA, was prepared by coupling a chemically synthesized thiolated S1P with maleimide-activated BSA. For the S1P standard, mono-layer S1P was solubilized in 1 % BSA in PBS (137 mM NaCl, 2.68 mM KCl, 10.1 mM Na₂HPO₄, 1.76 mM KH₂PO₄; pH 7.4) by sonication to obtain 10 uM S1P (S1P-BSA complex).

The S1P-BSA complex solution was further diluted with delipidated human serum to appropriate concentrations (up to 2 uM). Microtiter ELISA plates (Costar, high-binding plate) were coated with S1P-coating material diluted in 0.1M sodium carbonate buffer (pH 9.5) at 37 °C for 1 hour. Plates were washed with PBS and blocked with PBS/1 % BSA/0.1 % Tween-20 for 1 hr at room temperature. For the primary incubation, 0.4 ug/mL biotin-labeled anti-S1P antibody, designated amounts of S1P-BSA complex and samples to be tested were added to wells of the ELISA plates. After 1 hour-incubation at room temperature, plates were washed followed by incubation with 100 ul per well of HRP conjugated streptavidin (1:20,000 dilution) for 1 hour at room temperature. After washing, the peroxidase reaction was developed with TMB substrate and stopped by adding 1 M H₂SO₄. The optical density was measured at 450 nm using a Thermo Multiskan EX.

Upstream processing to minimize S1P:

For upstream processing, culturing the CHO cells in serum-free medium (Invitrogen, Cat # 10743-029) is essential because serum contains contaminating S1P that could add to that produced by the CHO cells themselves. In addition to use of serum-free medium, harvesting the antibody from the bioreactor prior to extensive cell death will prevent intracellular pools of S1P to be released into the medium. Finally, initiating the downstream processing immediately after harvest minimizes the time the LT1009 spends in the presence of S1P and the amount of lipid carried over to the final preparation. Despite attempts to minimize the S1P levels during upstream processing, significant S1P often remains in the crude harvest which typically ranges between 0.1 – 0.2 molar ratio (10-20 mol%) of bound S1P per mol of antibody .

Therefore, Lpath developed downstream methods to remove lipids from antibody preparations in order to generate LT1009 material with very low S1P carry-over levels. These methods (described immediately below) were developed by Lpath and transferred to Laureate Pharma, Inc. to incorporate into their processing methods. As a result, the final drug product produced by Laureate has very low levels of bound S1P (<0.4 mol % measured by HPLC-MS-MS).

Downstream processing to reduce S1P:

Traditionally, purification of antibodies from cultured supernatant or ascites fluid involves affinity chromatography. This one-step methods uses recombinant protein-A covalently bond to highly cross-linked agarose (GE healthcare, Cat No 17-5199-04). The protein-A acts as a ligand for Fc domains of monoclonal antibodies. Since the protein-A and S1P binding sites are distinct, S1P does not displace when LT1009 binds the protein-A resin. The high affinity for LT1009 and low solubility in aqueous buffers ensures that S1P remains associated with LT1009 even through extensive washes with high salt buffers (see below). Therefore, conventional antibody purification process that included: Protein A Chromatography, Low pH Viral Inactivation, followed by Neutralization, Q Anion Exchange Chromatography, Viral Nanofiltration and Final Ultrafiltration/ Diafiltration did not remove co-purified

(bound to LT1009) S1P. In order to dissociate S1P from the bound LT1009, Lpath exploits a special feature in the mechanism of binding.

Lpath in-house research demonstrated that S1P binding activity of LT1009 was reduced at pH < 4.0, or at pH > 8.5. However, conducting Protein A chromatography at pH < 4.0 in order to reduce bound S1P was not feasible because antibody will not bind to Protein A resin at such low pH. Therefore, high salt, pH 8.5 wash step was incorporated in protein A chromatography to reduce S1P bound to LT1009. Further studies demonstrated that the high salt buffer (650 mM NaCl) and 50 mM Sodium Phosphate buffer pH 8.5 did not effectively remove S1P from LT1009. Further increasing of salt concentration from 0.65 M to 1 M (pH 8.5) and extending of the high salt wash step from four column volumes to five column volumes did not yield product with lower bound S1P.

Use of metal chelators to remove S1P: Lpath developed a method that involved premixing of two volumes of crude LT1009 antibody harvest, produced from CHO cells bioreactor campaign, with one volume of Protein A IgG binding buffer ("Pierce binding buffer," Pierce Protein Research Products, Thermo Fisher Scientific, Rockford IL), containing 50 mM Potassium Phosphate, 1M NaCl, 2 mM EDTA and 5% glycerol, pH 8.0. According to this procedure the Protein A column was equilibrated with Pierce binding buffer, loaded with premixed crude harvest and washed with 10 column volumes of the same binding buffer. The resulting purified LT1009 contained 2-fold less mole percent of S1P as judged by the S1P-quantification ELISA.

It is currently believed that a metal chelator (e.g., EDTA) is important or even essential for effective reduction of S1P carryover in LT1009 antibody preparations. Indeed, titration of LT1009 with EDTA, which chelates divalent metal cations, abrogates S1P binding. The ability of EDTA to dissociate S1P from LT1009 is believed to facilitate removal of S1P during purification of LT1009. Addition of 2 mM EDTA in the binding and washing buffers effectively lowered the S1P carryover twofold in the eluted antibody fractions. It should be noted that the S1P levels in this study are relatively low initially, and including EDTA should produce greater reduction in lipid carryover in samples with higher initial S1P levels. Without being limited by the following examples, other metal chelators such as EGTA, histidine, malate and phytochelatin may be useful in dissociating S1P from the antibody. EGTA and EDTA are presently preferred divalent metal chelators for separating S1P from anti-S1P antibodies.

Based on these results, a new high salt buffer was developed by Lpath that was comparable in pH and conductivity to the Pierce buffer, and the new premixing step was incorporated in the LT1009 manufacturing process.

Current Downstream Purification Process includes:

- Premixing of crude harvest with 4X potassium high salt EDTA buffer (200 mM KPi, 4M NaCl, 8 mM EDTA, 20% glycerol, pH 8.0) in ratio of 2L crude harvest to 0.182L KPi high salt-EDTA buffer. This step is intended to disrupt and dissociate S1P from LT1009
- Capture of Crude Harvest-High Salt mix on Protein A column and washing the column with 10 column volumes of High Salt-EDTA buffer to remove S1P
- Elution of LT1009 from Protein A resin at low pH (3.6 – 3.8)

- Low pH hold of Protein A Eluate at pH 3.6 – 3.8 for a viral inactivation followed by neutralization of the eluate to neutral pH
- Sartobind Q anion exchange chromatography to remove residual host cell proteins and nucleotides, as well as any leached protein A.
- Nanofiltration using Virosart CPV nanofilter as an additional step for virus removal
- Final UF/DF filtration for protein concentration and final formulation

Use of low pH and C8 resins to remove S1P: In addition to the use of metal chelators such as EDTA during the purification, one can also exploit the hydrophobic nature of S1P to remove the lipid from purified antibody preparations. This method involves a two-step process: 1) dissociation of the lipid from the antibody, and 2) physical separation of the lipid from the aqueous environment. The applicant employs a pH induced Lipid removal (pHiL) treatment as an easy, robust method to promote dissociation from antibody preparations. Antibodies generally exhibit markedly reduced antigen-binding affinity at low pH. Antibodies generated against phospholipids (e.g. S1P and LPA) fail to bind lipids at pH 3.0-3.5, depending on the specific antibody and the lipid. In determining the correct pH to promote dissociation, a pH titration experiment should be performed to determine the pH that abrogates binding yet maintains an intact IgG, such that binding activity is restored once the pH is increased. In other words the antibody should not be irreversibly inactivated. Once this pH has been determined, the antibody is dialyzed against buffer below the critical pH (e.g. 50 mM sodium acetate, pH 3.0-3.5) at 4 °C. Under these conditions, both the lipid and antibody exist as isolated components in solution. The dialyzed solution is passed through a material, such as C8 silica resin (e.g., SepPak cartridges, Waters, Cat no WAT036775), that binds the lipid and facilitates separation of the protein free of lipid. As a consequence, the free lipid irreversibly binds the hydrophobic resin (in the case of C8 silica resin) while the antibody flows through without significant loss (~90% recovery). Most of the lipid can be removed with one pass through the cartridge, but modest gains in lipid removal can be achieved with an additional pass (Table 7).

The metal chelation and pHiL methods described above can easily be incorporated into a single purification procedure. EDTA is compatible with most buffers and does not adversely affect antibody stability, solubility or protein-A binding. During purification, washing the bound IgG with copious amount of EDTA-containing buffer will remove a portion of the S1P from the S1P-LT1009 complex as well as potentially dissociate other metal-dependant antigens-antibody complexes. If the EDTA wash does not sufficiently remove the lipid, the eluate from the protein-A column can be treated using the pHiL method. Elution of bound IgG from protein-A is typically achieved using low pH buffers (pH<3.0). If the anti-lipid antibody elutes from the column at a pH or below the critical pH for lipid binding, the sample can simply be applied to the C8 silica resin to remove the lipid. If necessary, the pH can be easily adjusted prior to applying it to the resin.

Table 7. Lipid removal using pHIL method

Monoclonal Antibody	Mole percent of lipid in sample (relative to amount of antibody)			Antibody Recovery
	Before treatment	After 1 st treatment	After 2 nd treatment	
Murine Anti-S1P	60 %	6.3 %	0.97 %	88 %
Humanized Anti-S1P	46 %	4.3 %	0.81 %	89 %
Humanized Anti-LPA	14	4.5	6.0	91 %

Example 12: Formulations containing the humanized monoclonal antibody LT1009**1. Introduction**

This example describes experiments to assess the stability of several formulations containing the humanized monoclonal antibody LT1009, which is reactive against the bioactive signaling lipid sphingosine 1-phosphate (S1P). LT1009 is an engineered full-length IgG1k isotype antibody that contains two identical light chains and two identical heavy chains, and has a total molecular weight of about 150 kDa. The complementarity determining regions (CDRs) of the light and heavy chains were derived from a murine monoclonal antibody generated against S1P, and further include a Cys to Ala substitution in one of the CDRs. In LT1009, human framework regions contribute approximately 95% of the total amino acid sequences in the antibody, which binds S1P with high affinity and specificity.

The purpose of the testing described in this example was to develop one or more preferred formulations suitable for systemic administration that are capable of maintaining stability and bioactivity of LT1009 over time. As is known, maintenance of molecular conformation, and hence stability, is dependent at least in part on the molecular environment of the protein and on storage conditions. Preferred formulations should not only stabilize the antibody, but also be tolerated by patients when injected. Accordingly, in this study the various formulations tested included either 11 mg/mL or 42 mg/mL of LT1009, as well as different pH, salt, and nonionic surfactant concentrations. Additionally, three different storage temperatures (5°C, 25°C, and 40°C) were also examined (representing actual, accelerated, and temperature stress conditions, respectively). Stability was assessed using representative samples taken from the various formulations at five different time points: at study initiation and after two weeks, 1 month, 2 months, and 3 months. At each time point, testing involved visual inspection, syringeability (by pulling through a 30-gauge needle), and size exclusion high performance liquid chromatography (SE-HPLC). Circular dichroism (CD) spectroscopy was also used to assess protein stability since above a certain temperature, proteins undergo denaturation, followed by some degree of

aggregate formation. The observed transition is referred to as an apparent denaturation or “melting” temperature (T_m) and indicate the relative stability of a protein.

2. Materials and Methods

a. LT1009

The formulation samples (~0.6 mL each) were generated from an aqueous stock solution containing 42 mg/mL LT1009 in 24 mM sodium phosphate, 148 mM NaCl, pH 6.5. Samples containing 11 mg/mL LT1009 were prepared by diluting a volume of aqueous stock solution to the desired concentration using a 24 mM sodium phosphate, 148 mM NaCl, pH 6.5, solution. To prepare samples having the different pH values, the pH of each concentration of LT1009 (11 mg/mL and 42 mg/mL) was adjusted to 6.0 or 7.0 with 0.1 M HCl or 0.1 M NaOH, respectively, from the original 6.5 value. To prepare samples having different NaCl concentrations, 5 M NaCl was added to the samples to bring the salt concentration to either 300 mM or 450 mM from the original 148 mM. To prepare samples having different concentrations of nonionic surfactant, polysorbate-80 was added to the samples to a final concentration of either 200 ppm or 500 ppm. All samples were aseptically filtered through 0.22 μ m PVDF membrane syringe filters into sterile, depyrogenated 10 mL serum vials. The vials were each then sealed with a non-shedding PTFE-lined stopper that was secured in place and protected from contamination with a crimped on cap. Prior to placement into stability chambers, the vials were briefly stored at 2-8°C; thereafter, they were placed upright in a stability chamber adjusted to one of three specified storage conditions: 40°C($\pm$ 2°C)/75%($\pm$ 5%) relative humidity (RH); 25°C($\pm$ 2°C)/60%($\pm$ 5%) RH; or 5°C($\pm$ 3°C)/ambient RH. A summary of the formulation variables tested appears in Table 8, below.

Table 8. Formulation Summary

LT1009, 11 mg/mL			LT1009, 42 mg/mL		
Polysorbate 80	NaCl	pH	Polysorbate 80	NaCl	pH
0.02 % Polysorbate	148 mM NaCl	7	0.02 % Polysorbate	148 mM NaCl	7
		6.5			6.5
		6			6
	300 mM NaCl	7		300 mM NaCl	7
		6.5			6.5
		6			6
	450 mM NaCl	7		450 mM NaCl	7
		6.5			6.5
		6			6
0.05 % Polysorbate	148 mM NaCl	7	0.05 % Polysorbate	148 mM NaCl	7
		6.5			6.5
		6			6
	300 mM NaCl	7		300 mM NaCl	7
		6.5			6.5
		6			6
	450 mM NaCl	7		450 mM NaCl	7
		6.5			6.5
		6			6

		6			6
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b. Taking of Samples

Samples of each formulation were analyzed according to the schedule listed in Table 9, below. One vial was used for each storage condition for all time points. On a date when samples were to be taken, vials were pulled from each stability chamber and 150 μ L of each sample were transferred into correspondingly labeled separate vials that were placed on the bench for 1 hour prior to testing. The original vial was immediately placed back into the specified stability chamber after withdrawing the aliquot to be tested.

Table 9. Drug Product Formulation Study Stability Matrix

Protein Concentration	LT1009, 11 mg/mL				
Storage Conditions	Intervals (months)				
	T=0	0.5	1	2	3
40°C	x, y	x, y	x	x	x, y
25°C		x, y	x	x	x, y
5°C		x, y	x	x	x, y
Protein Concentration	LT1009, 42 mg/mL				
Storage Conditions	Intervals (months)				
	T=0	0.5	1	2	3
40°C	x, y	x, y	x	x	x, y
25°C		x, y	x	x	x, y
5°C		x, y	x	x	x, y

x=Appearance, pH, SDS-PAGE, SE-HPLC, UV OD-280, IEF

y = Syringeability (performed by aseptically drawing 200 μ L of a sample with a 30-gauge needle connected to a disposable 1-mL syringe)

c. Analytical Procedures

For a given time point, aliquots from each sample were subjected to a series of standard analyses, including visual inspection, syringeability, pH, SDS-PAGE (under both reducing and non-reducing conditions), SE-HPLC, and IEF. Protein concentrations were determined by UV spectroscopy (OD-280). Circular dichroism (CD) studies were also performed.

Circular dichroism spectroscopy was performed separately from the formulation studies. An Aviv 202 CD spectrophotometer was used to perform these analyses. Near UV CD spectra were collected from 400 nm to 250 nm. In this region, the disulfides and aromatic side chains contribute to the CD signals. In the far UV wavelength region (250-190 nm), the spectra are dominated by the peptide backbone. Thermal denaturation curves were generated by monitoring at 205 nm, a wavelength commonly used for β -sheet proteins. Data was collected using 0.1 mg/ml samples with heating from

25°C to 85°C. Data were collected in 1°C increments. The total time for such a denaturation scan was between 70 and 90 minutes. The averaging time was 2 seconds.

3. Results and Discussion

For all samples analyzed, visual appearance did not change over time. Likewise, syringeability testing demonstrated that samples could be pulled into a syringe equipped with a 30-gauge needle without difficulty. The results of the various analytical tests were consistent, and SE-HPLC was determined to be an excellent stability-indicating method for LT1009. These results showed that increasing salt concentration reduced both the generation of aggregates and the generation of smaller non-aggregate impurities. It was also found that decreasing pH also reduced aggregate and impurity formation. In addition, it was determined that increasing the polysorbate-80 concentration above 200 ppm did not further stabilize LT1009. The SE-HPLC experiments were performed on samples containing 11mg/mL LT1009, and comparable results were obtained for samples containing 42mg/mL LT1009, although lower LT1009 concentrations showed less potential for aggregate formation as compared to the higher concentration, indicating that the antibody appeared to be slightly less stable under all conditions tested at the higher concentration.

From the circular dichroism studies, it was found that LT1009 adopts a well-defined tertiary structure in aqueous solution, with well-ordered environments around both Tyr and Trp residues. It also appeared that at least some of the disulfides in antibody molecules experience some degree of bond strain, although this is not uncommon when both intra- and inter-chain disulfides are present. The secondary structure of LT1009 was found to be unremarkable, and exhibited a far UV CD spectrum consistent with β -sheet structure. The observed transition is referred to as an apparent denaturation or “melting” temperature (T_m). Upon heating, LT1009 displayed an apparent T_m of approximately 73°C at pH 7.2. The apparent T_m increased to about 77°C at pH 6.0. These results indicate that a slightly acidic pH could enhance long-term stability of aqueous formulations of LT1009. Addition of NaCl and/or polysorbate-80 also provided additional stabilization.

Together, the data from these experiments indicate that LT1009 is most stable around pH 6 and 450 mM NaCl independent of antibody concentration. Indeed, SE-HPLC testing indicated that increasing the salt concentration to 450 mM and decreasing the pH to 6.0 while maintaining the polysorbate-80 concentration at 200 ppm had a very beneficial effect on the stability of LT1009. Inclusion of polysorbate-80 above 200 ppm had no further mitigating effect against aggregate formation, probably because it was already above its critical micelle concentration at 200 ppm. While not wishing to be bound by any particular theory, the fact that aggregate formation in LT1009 was reduced with increasing salt concentration under the studied conditions could indicate that aggregate formation is at least in part based more on ionic interactions between molecules rather than hydrophobic interactions. The observation that lowering the pH from 7 to 6 also reduces aggregate formation could be explained by reduced hydrophobicity of the amino acid histidine at the lower pH. Finally, the observed increased

tendency of aggregate formation at increased LT11009 concentration can simply be explained by the greater chance of molecules hitting each other at the right time at the right place for aggregate formation.

As these experiments show, a preferred aqueous LT1009 formulation is one having 24 mM phosphate, 450 mM NaCl, 200 ppm polysorbate-80, pH 6.1. The relatively high tonicity of this formulation should not pose a problem for systemic applications since the drug product will likely be diluted by injection into iv-bags containing a larger volume of PBS prior to administration to a patient.

Example 13: Production and purification of anti-S1P and anti-LPA antibodies

Because X-ray crystallography requires substantial amounts of material, a stable CHO cell line that produces >0.5 mg/L of anti-S1P antibody is used. While maintaining a viability of $\geq 95\%$, cells are seeded at a density of 0.4×10^6 cells/ml into 1 liter shaker flasks with 500 ml of CD-CHO medium (Invitrogen, San Diego, cat. No. 10743-029) containing 25 μ M L-methionine sulfoximine (Sigma, St. Louis MO, Cat. No. M5379). Cells are grown in an atmosphere of 7.5% CO₂ for ten days or until the viability dropped to 45-50%. Supernatants are then harvested by centrifugation at 1500 rpm for 10 minutes and sterile-filtered through a 0.22 micron filter system (Corning, Lowell MA, cat no. 431098). The clarified supernatants are concentrated tenfold using a Labscale Tangential Flow Filtration system installed with a Pellicon XL Biomax 50 cartridge (Millipore, Billerica MA, Cat. no PXB050A50) according to manufacturer's protocol assuring that all tubing and vessels were cleaned prior to use with 0.5% NaOH and thoroughly rinsed with DNase and RNase-free distilled water (Invitrogen, San Diego CA, cat no. 10977-015).

Clarified, concentrated supernatants were diluted with equal volume IgG binding buffer (Pierce, Rockford IL, cat. no. 21001) and applied to a gravity-flow column packed with ProSep-vA-Ultra resin (Millipore, cat. no. 115115827) equilibrated with 5 column volumes of binding buffer. The flow through was collected and the bound IgG was washed with 10-15 column volumes of binding buffer. The bound IgG was eluted with elution buffer (Pierce, cat no. 21004) and collected in 40 ml fractions containing 5 ml of binding buffer to neutralize the pH. Fractions with an absorption at 280 nm (A₂₈₀) of greater than 0.1 were pooled and concentrated using an Amicon stirred cell equipped with a 50 kDa molecular weight cut off (MWCO) filter (Millipore, Cat No PBQK07610). The concentrated antibody was extensively dialyzed against 1X PBS (Cellgro, Manassas VA, Cat No 21-040), filtered through a 0.22 μ m syringe-driven filter unit (Millipore, Cat No SLGP033RS) and stored at 4°C.

Anti-LPA antibody is produced and purified in substantially the same manner as the S1P antibody.

Example 14: Isolation of Fab Fragments from Anti-S1P and Anti-LPA Monoclonal Antibodies.

Treatment of purified whole IgG preparations with the protease papain separates a Fab fragment consisting of both variable domains and the Ck and Ch1 constant domains from the Fc domain, which contains a pair of Ch2 and Ch3 domains. The Fab fragment retains one entire variable region and,

therefore, serves as a useful tool for biochemical characterization of a 1:1 interaction between the antibody and epitope. Furthermore, because it lacks the flexibility and, generally, the glycosylation inherent in native purified whole IgG, the Fab fragment is generally an excellent platform for structure studies via single crystal x-ray diffraction.

Purified, intact anti-S1P IgG was digested with activated papain (incubated 10 mg/ml papain in 5.5 mM cysteine-HCL, 1 mM EDTA, 70 μ M 2-mercaptoethanol for 0.5 hours at 37 °C) in digestion buffer (100:1 LT1009:papain in 50 mM sodium phosphate pH 7.2, 2 mM EDTA). After 2 hours at 37 °C, the protease reaction was quenched with 50 mM iodoacetamide, dialyzed against 20 mM TRIS pH 9, and loaded onto 2 x 5ml HiTrap Q columns. The bound protein was eluted with a linear gradient of 20 mM TRIS pH 8, 0.5 M NaCl and collected in 4 ml fractions. The fractions containing the anti-S1P Fab fragment were pooled and loaded onto a protein A column equilibrated with 20 mM TRIS pH 8. The intact antibody and the Fc fragment bound to the resin, while the Fab fragment was present in the flow through fraction. The Fab fragment was concentrated using a centricon-YM30 centrifugal concentrator (Millipore, Cat No 4209), dialyzed against 25 mM HEPES pH 7, and stored at 4 °C.

The anti-LPA Fab fragment is prepared similarly.

Example 15: Formation of the Fab/lipid complexes

The concentration of the isolated Fab fragment was calculated from the A_{280} value using an extinction coefficient of 1.4 ml/mg. A 5-fold molar excess of 1 mM S1P (Avanti, Cat No 860429P) suspended in methanol was dried in 13x100 mm borosilicate glass tubes by holding in a low vacuum for three hours. The lipids were resuspended in 500 μ L of purified anti-S1P Fab by pipetting and filtered through a 0.22 μ m Costar Spin-X centrifugal cellulose acetate filter (Corning, Cat No 8160). The complex is concentrated to approximately 12 mg/ml using the centrprep-10 centrifugal concentrator (Millipore). The concentrated Fab/lipid complexes were stored at 4 °C. Similarly, Fab/LPA complexes are prepared using LPA (Avanti, Cat No 857120X) and isolated LPA Fab.

Example 16: Crystallization of the Fab/lipid complexes. For both Fab/lipid complexes, initial crystallization conditions were determined by the use of a sparse matrix screen (Hampton Research, Aliso Viejo CA) and the hanging drop vapor diffusion method. In the case of the Fab/S1P complex, single crystals suitable for diffraction studies were grown at room temperature. 1 microliter of 12 mg/ml Fab/S1P complex was mixed with 1 microliter of reservoir solution containing 22% (w/v) polyethylene glycol 3350, 100 mM $MgSO_4$, 100 mM sodium citrate (pH 6.0) and 10% (v/v) ethylene glycol and sealed over 1 milliliter of reservoir solution. Crystals grew to a final size of 0.2 x 0.2 x 0.2 mm in two days. The crystals were harvested from the crystallization drop with nylon loops and flash cooled directly in liquid nitrogen.

Example 17: X-ray crystallography

X-ray crystallography is a powerful tool that enables researchers to visualize the mechanisms of molecular recognition at the atomic level. This information is extremely valuable to understand the mode of action for therapeutic antibodies as well as engineer antibodies for enhanced binding characteristics or novel antigen specificities. A combination of x-ray crystallography with innovative biochemical methods is used herein to study two monoclonal antibodies that specifically recognize two bioactive lipids. In addition, these techniques will be used to engineer antibodies with novel specificities for other lipids. This technology grants researchers new tools for studying lipid pathways, metabolism and signaling and hopefully arms clinicians with powerful new weapons against lipid-based pathologies. As lipidomics emerges as an important field in medicine and as more bioactive lipids become implicated in human disease, antibodies that recognize lipids and other non-proteinaceous targets will likely play a significant role in biomedical research.

Due to the structural flexibility and heterogeneity in glycosylation of intact IgGs, the structural studies proposed here focus on the isolated Fab fragments from the anti-S1P and anti-LPA antibodies. High-resolution structures comprising the Fab domain in complex with the lipid target contain sufficient information to elucidate the structural basis for S1P and LPA recognition by their cognate antibodies.

1. X-ray Diffraction Data Collection and Processing. For the Fab/S1P complex, complete X-ray diffraction data was collected at 100 K on an R-Axis IV++ image plate detector (Rigaku, The Woodlands, TX) at the San Diego State University Macromolecular X-ray Crystallography Facility (MXCF). X-rays were produced by an RU-H3R rotating anode x-ray generator functioning at 100 mA and 50 kV with Osmic Blue confocal optics (Rigaku). Data indexing and scaling were carried out using HKL2000. Otwinowski, Z. and W. Minor (1997) *Methods Enzymol.* 276:307-326. Cryo-cooled crystals were tested on the San Diego State University Macromolecular X-ray Crystallography Facility and were observed to diffract x-rays to beyond 2.7 Å resolution (Figure 1c). The data coordinates for this crystal are shown in Table 10, below. Data of this quality are suitable for structure determination and a complete set of diffraction intensities have been collected (93.1% completeness overall, 86.2% in highest resolution shell; greater than 3.3-fold redundancy on average throughout all data shells; overall I/sigma 8.7, I/sigma for highest resolution shell 2.7; overall R_{sym} 12.9%, R_{sym} in highest resolution shell 47.1%).

Table 10
Fab/S1P co-crystal x-ray coordinates at 2.7Å resolution

```

HEADER ---- XX-XXX-XX xxxx
COMPND ---
REMARK 3
REMARK 3 REFINEMENT.
REMARK 3 PROGRAM : REFMAC 5.2.0019
REMARK 3 AUTHORS : MURSHUDOV,VAGIN,DODSON
REMARK 3

```

REMARK 3 REFINEMENT TARGET : MAXIMUM LIKELIHOOD
REMARK 3
REMARK 3 DATA USED IN REFINEMENT.
REMARK 3 RESOLUTION RANGE HIGH (ANGSTROMS) : 2.69
REMARK 3 RESOLUTION RANGE LOW (ANGSTROMS) : 68.84
REMARK 3 DATA CUTOFF (SIGMA(F)) : NONE
REMARK 3 COMPLETENESS FOR RANGE (%) : 92.94
REMARK 3 NUMBER OF REFLECTIONS : 16273
REMARK 3
REMARK 3 FIT TO DATA USED IN REFINEMENT.
REMARK 3 CROSS-VALIDATION METHOD : THROUGHOUT
REMARK 3 FREE R VALUE TEST SET SELECTION : RANDOM
REMARK 3 R VALUE (WORKING + TEST SET) : 0.22432
REMARK 3 R VALUE (WORKING SET) : 0.22098
REMARK 3 FREE R VALUE : 0.28587
REMARK 3 FREE R VALUE TEST SET SIZE (%) : 5.1
REMARK 3 FREE R VALUE TEST SET COUNT : 866
REMARK 3
REMARK 3 FIT IN THE HIGHEST RESOLUTION BIN.
REMARK 3 TOTAL NUMBER OF BINS USED : 20
REMARK 3 BIN RESOLUTION RANGE HIGH : 2.692
REMARK 3 BIN RESOLUTION RANGE LOW : 2.762
REMARK 3 REFLECTION IN BIN (WORKING SET) : 1068
REMARK 3 BIN COMPLETENESS (WORKING+TEST) (%) : 83.54
REMARK 3 BIN R VALUE (WORKING SET) : 0.325
REMARK 3 BIN FREE R VALUE SET COUNT : 54
REMARK 3 BIN FREE R VALUE : 0.357
REMARK 3
REMARK 3 NUMBER OF NON-HYDROGEN ATOMS USED IN REFINEMENT.
REMARK 3 ALL ATOMS : 3396
REMARK 3
REMARK 3 B VALUES.
REMARK 3 FROM WILSON PLOT (A**2) : NULL
REMARK 3 MEAN B VALUE (OVERALL, A**2) : 22.369
REMARK 3 OVERALL ANISOTROPIC B VALUE.
REMARK 3 B11 (A**2) : 1.20
REMARK 3 B22 (A**2) : -1.04
REMARK 3 B33 (A**2) : -0.16
REMARK 3 B12 (A**2) : 0.00
REMARK 3 B13 (A**2) : 0.00
REMARK 3 B23 (A**2) : 0.00
REMARK 3
REMARK 3 ESTIMATED OVERALL COORDINATE ERROR.
REMARK 3 ESU BASED ON R VALUE (A): 0.697
REMARK 3 ESU BASED ON FREE R VALUE (A): 0.367
REMARK 3 ESU BASED ON MAXIMUM LIKELIHOOD (A): 0.256
REMARK 3 ESU FOR B VALUES BASED ON MAXIMUM LIKELIHOOD (A**2): 12.155
REMARK 3
REMARK 3 CORRELATION COEFFICIENTS.
REMARK 3 CORRELATION COEFFICIENT FO-FC : 0.904
REMARK 3 CORRELATION COEFFICIENT FO-FC FREE : 0.847
REMARK 3
REMARK 3 RMS DEVIATIONS FROM IDEAL VALUES COUNT RMS WEIGHT
REMARK 3 BOND LENGTHS REFINED ATOMS (A): 3426 ; 0.013 ; 0.022
REMARK 3 BOND ANGLES REFINED ATOMS (DEGREES): 4654 ; 1.687 ; 1.955
REMARK 3 TORSION ANGLES, PERIOD 1 (DEGREES): 429 ; 8.447 ; 5.000
REMARK 3 TORSION ANGLES, PERIOD 2 (DEGREES): 137 ; 38.749 ; 24.672

REMARK 3 TORSION ANGLES, PERIOD 3 (DEGREES): 553 ;21.579 ;15.000
 REMARK 3 TORSION ANGLES, PERIOD 4 (DEGREES): 11 ;17.989 ;15.000
 REMARK 3 CHIRAL-CENTER RESTRAINTS (A**3): 521 ; 0.160 ; 0.200
 REMARK 3 GENERAL PLANES REFINED ATOMS (A): 2560 ; 0.004 ; 0.020
 REMARK 3 NON-BONDED CONTACTS REFINED ATOMS (A): 1450 ; 0.228 ; 0.200
 REMARK 3 NON-BONDED TORSION REFINED ATOMS (A): 2266 ; 0.311 ; 0.200
 REMARK 3 H-BOND (X...Y) REFINED ATOMS (A): 136 ; 0.151 ; 0.200
 REMARK 3 SYMMETRY VDW REFINED ATOMS (A): 23 ; 0.182 ; 0.200
 REMARK 3 SYMMETRY H-BOND REFINED ATOMS (A): 1 ; 0.016 ; 0.200
 REMARK 3
 REMARK 3 ISOTROPIC THERMAL FACTOR RESTRAINTS. COUNT RMS WEIGHT
 REMARK 3 MAIN-CHAIN BOND REFINED ATOMS (A**2): 2196 ; 0.600 ; 1.500
 REMARK 3 MAIN-CHAIN ANGLE REFINED ATOMS (A**2): 3491 ; 1.067 ; 2.000
 REMARK 3 SIDE-CHAIN BOND REFINED ATOMS (A**2): 1406 ; 1.453 ; 3.000
 REMARK 3 SIDE-CHAIN ANGLE REFINED ATOMS (A**2): 1163 ; 2.396 ; 4.500
 REMARK 3
 REMARK 3 NCS RESTRAINTS STATISTICS
 REMARK 3 NUMBER OF NCS GROUPS : NULL
 REMARK 3
 REMARK 3
 REMARK 3 TLS DETAILS
 REMARK 3 NUMBER OF TLS GROUPS : NULL
 REMARK 3
 REMARK 3
 REMARK 3 BULK SOLVENT MODELLING.
 REMARK 3 METHOD USED : MASK
 REMARK 3 PARAMETERS FOR MASK CALCULATION
 REMARK 3 VDW PROBE RADIUS : 1.40
 REMARK 3 ION PROBE RADIUS : 0.80
 REMARK 3 SHRINKAGE RADIUS : 0.80
 REMARK 3
 REMARK 3 OTHER REFINEMENT REMARKS:
 REMARK 3 HYDROGENS HAVE BEEN ADDED IN THE RIDING POSITIONS
 REMARK 3
 SSBOND 1 CYS A 23 CYS A 88
 SSBOND 2 CYS A 134 CYS A 194
 SSBOND 3 CYS B 22 CYS B 96
 SSBOND 4 CYS B 148 CYS B 204
 CISPEP 1 SER A 7 PRO A 8 0.00
 CISPEP 2 LEU A 94 PRO A 95 0.00
 CISPEP 3 TYR A 140 PRO A 141 0.00
 LINK SER B 136 SER B 140 gap
 CISPEP 4 LEU B 146 GLY B 147 0.00
 CISPEP 5 CYS B 148 LEU B 149 0.00
 CISPEP 6 PHE B 154 PRO B 155 0.00
 CISPEP 7 GLU B 156 PRO B 157 0.00
 CISPEP 8 SER B 188 VAL B 189 0.00
 CISPEP 9 LEU B 197 GLY B 198 0.00
 LINK PRO B 134 GLY B 141 gap
 LINK GLY B 126 PRO B 134 gap
 CRYST1 65.713 70.789 137.686 90.00 90.00 90.00 P 21 21 21
 SCALE1 0.015218 0.000000 0.000000 0.000000
 SCALE2 0.000000 0.014126 0.000000 0.000000
 SCALE3 0.000000 0.000000 0.007263 0.000000
 ATOM 1 N GLU A 1 8.631 8.985 23.274 1.00 19.26 N
 ATOM 2 CA GLU A 1 7.514 8.609 24.190 1.00 19.69 C
 ATOM 3 CB GLU A 1 6.265 8.130 23.404 1.00 19.65 C

ATOM	4	CG	GLU	A	1	6.516	6.962	22.410	1.00	20.81	C
ATOM	5	CD	GLU	A	1	5.233	6.262	21.895	1.00	21.73	C
ATOM	6	OE1	GLU	A	1	5.247	5.003	21.826	1.00	24.36	O
ATOM	7	OE2	GLU	A	1	4.226	6.948	21.549	1.00	23.44	O
ATOM	8	C	GLU	A	1	7.990	7.524	25.140	1.00	18.84	C
ATOM	9	O	GLU	A	1	8.933	6.797	24.839	1.00	18.71	O
ATOM	10	N	THR	A	2	7.346	7.401	26.291	1.00	18.11	N
ATOM	11	CA	THR	A	2	7.646	6.259	27.111	1.00	17.63	C
ATOM	12	CB	THR	A	2	7.656	6.570	28.612	1.00	17.81	C
ATOM	13	OG1	THR	A	2	6.871	5.594	29.317	1.00	17.77	O
ATOM	14	CG2	THR	A	2	7.136	7.962	28.884	1.00	17.18	C
ATOM	15	C	THR	A	2	6.711	5.134	26.723	1.00	17.58	C
ATOM	16	O	THR	A	2	5.508	5.328	26.574	1.00	17.59	O
ATOM	17	N	THR	A	3	7.300	3.965	26.517	1.00	17.33	N
ATOM	18	CA	THR	A	3	6.609	2.823	25.971	1.00	17.05	C
ATOM	19	CB	THR	A	3	7.593	1.975	25.144	1.00	17.36	C
ATOM	20	OG1	THR	A	3	8.161	2.810	24.125	1.00	17.45	O
ATOM	21	CG2	THR	A	3	6.914	0.730	24.513	1.00	16.34	C
ATOM	22	C	THR	A	3	6.077	2.044	27.143	1.00	16.99	C
ATOM	23	O	THR	A	3	6.731	1.981	28.190	1.00	16.95	O
ATOM	24	N	VAL	A	4	4.881	1.479	26.994	1.00	16.67	N
ATOM	25	CA	VAL	A	4	4.329	0.661	28.068	1.00	16.45	C
ATOM	26	CB	VAL	A	4	3.264	1.390	28.986	1.00	16.36	C
ATOM	27	CG1	VAL	A	4	2.752	2.689	28.373	1.00	16.63	C
ATOM	28	CG2	VAL	A	4	2.134	0.476	29.417	1.00	15.26	C
ATOM	29	C	VAL	A	4	3.951	-0.722	27.589	1.00	16.70	C
ATOM	30	O	VAL	A	4	3.082	-0.914	26.723	1.00	17.24	O
ATOM	31	N	THR	A	5	4.667	-1.677	28.166	1.00	16.11	N
ATOM	32	CA	THR	A	5	4.543	-3.071	27.853	1.00	15.96	C
ATOM	33	CB	THR	A	5	5.933	-3.740	27.927	1.00	16.04	C
ATOM	34	OG1	THR	A	5	6.869	-2.929	27.207	1.00	15.78	O
ATOM	35	CG2	THR	A	5	5.907	-5.146	27.356	1.00	14.31	C
ATOM	36	C	THR	A	5	3.609	-3.713	28.856	1.00	15.82	C
ATOM	37	O	THR	A	5	3.905	-3.753	30.049	1.00	16.13	O
ATOM	38	N	GLN	A	6	2.486	-4.217	28.361	1.00	15.61	N
ATOM	39	CA	GLN	A	6	1.510	-4.909	29.188	1.00	15.44	C
ATOM	40	CB	GLN	A	6	0.125	-4.386	28.839	1.00	15.12	C
ATOM	41	CG	GLN	A	6	-1.008	-4.897	29.689	1.00	14.24	C
ATOM	42	CD	GLN	A	6	-2.243	-4.043	29.530	1.00	12.79	C
ATOM	43	OE1	GLN	A	6	-2.199	-3.026	28.838	1.00	14.64	O
ATOM	44	NE2	GLN	A	6	-3.353	-4.442	30.164	1.00	9.72	N
ATOM	45	C	GLN	A	6	1.587	-6.407	28.913	1.00	15.76	C
ATOM	46	O	GLN	A	6	1.696	-6.809	27.760	1.00	16.55	O
ATOM	47	N	SER	A	7	1.578	-7.232	29.955	1.00	15.90	N
ATOM	48	CA	SER	A	7	1.316	-8.655	29.777	1.00	16.21	C
ATOM	49	CB	SER	A	7	2.577	-9.499	29.581	1.00	16.30	C
ATOM	50	OG	SER	A	7	3.679	-8.950	30.236	1.00	17.77	O
ATOM	51	C	SER	A	7	0.486	-9.192	30.903	1.00	16.53	C
ATOM	52	O	SER	A	7	0.456	-8.605	31.968	1.00	16.86	O
ATOM	53	N	PRO	A	8	-0.231	-10.301	30.653	1.00	17.03	N
ATOM	54	CA	PRO	A	8	-0.274	-10.969	29.343	1.00	17.11	C
ATOM	55	CB	PRO	A	8	-0.706	-12.379	29.714	1.00	16.71	C
ATOM	56	CG	PRO	A	8	-1.614	-12.164	30.892	1.00	16.99	C
ATOM	57	CD	PRO	A	8	-1.086	-10.976	31.647	1.00	16.42	C
ATOM	58	C	PRO	A	8	-1.307	-10.286	28.411	1.00	17.78	C
ATOM	59	O	PRO	A	8	-2.111	-9.468	28.874	1.00	17.61	O
ATOM	60	N	SER	A	9	-1.289	-10.608	27.117	1.00	18.39	N

ATOM	61	CA	SER A	9	-2.237	-9.993	26.181	1.00	18.58	C
ATOM	62	CB	SER A	9	-1.835	-10.240	24.744	1.00	18.37	C
ATOM	63	OG	SER A	9	-0.531	-9.758	24.516	1.00	20.25	O
ATOM	64	C	SER A	9	-3.600	-10.554	26.394	1.00	18.47	C
ATOM	65	O	SER A	9	-4.586	-9.849	26.245	1.00	18.93	O
ATOM	66	N	PHE A	10	-3.630	-11.834	26.745	1.00	18.53	N
ATOM	67	CA	PHE A	10	-4.841	-12.640	26.800	1.00	18.48	C
ATOM	68	CB	PHE A	10	-5.004	-13.467	25.506	1.00	19.29	C
ATOM	69	CG	PHE A	10	-6.277	-14.314	25.458	1.00	21.14	C
ATOM	70	CD1	PHE A	10	-7.469	-13.786	24.941	1.00	21.90	C
ATOM	71	CE1	PHE A	10	-8.641	-14.555	24.881	1.00	21.65	C
ATOM	72	CZ	PHE A	10	-8.632	-15.877	25.338	1.00	22.35	C
ATOM	73	CE2	PHE A	10	-7.447	-16.432	25.866	1.00	23.32	C
ATOM	74	CD2	PHE A	10	-6.276	-15.645	25.919	1.00	23.25	C
ATOM	75	C	PHE A	10	-4.667	-13.556	27.989	1.00	17.58	C
ATOM	76	O	PHE A	10	-3.573	-14.046	28.232	1.00	17.42	O
ATOM	77	N	LEU A	11	-5.752	-13.784	28.721	1.00	16.83	N
ATOM	78	CA	LEU A	11	-5.707	-14.512	29.968	1.00	15.84	C
ATOM	79	CB	LEU A	11	-5.325	-13.563	31.105	1.00	15.57	C
ATOM	80	CG	LEU A	11	-5.151	-14.110	32.521	1.00	14.76	C
ATOM	81	CD1	LEU A	11	-4.102	-15.204	32.589	1.00	13.18	C
ATOM	82	CD2	LEU A	11	-4.780	-12.961	33.435	1.00	15.07	C
ATOM	83	C	LEU A	11	-7.050	-15.175	30.244	1.00	16.19	C
ATOM	84	O	LEU A	11	-8.110	-14.542	30.140	1.00	16.06	O
ATOM	85	N	SER A	12	-7.001	-16.459	30.591	1.00	16.35	N
ATOM	86	CA	SER A	12	-8.213	-17.217	30.888	1.00	16.11	C
ATOM	87	CB	SER A	12	-8.243	-18.531	30.105	1.00	15.90	C
ATOM	88	OG	SER A	12	-8.207	-18.303	28.710	1.00	15.26	O
ATOM	89	C	SER A	12	-8.259	-17.521	32.365	1.00	16.33	C
ATOM	90	O	SER A	12	-7.265	-17.952	32.958	1.00	16.17	O
ATOM	91	N	ALA A	13	-9.418	-17.305	32.961	1.00	16.55	N
ATOM	92	CA	ALA A	13	-9.594	-17.655	34.353	1.00	17.42	C
ATOM	93	CB	ALA A	13	-9.030	-16.551	35.275	1.00	17.30	C
ATOM	94	C	ALA A	13	-11.060	-17.936	34.635	1.00	17.74	C
ATOM	95	O	ALA A	13	-11.922	-17.562	33.851	1.00	17.99	O
ATOM	96	N	SER A	14	-11.325	-18.611	35.744	1.00	18.31	N
ATOM	97	CA	SER A	14	-12.671	-19.018	36.091	1.00	19.42	C
ATOM	98	CB	SER A	14	-12.638	-20.298	36.931	1.00	19.44	C
ATOM	99	OG	SER A	14	-11.584	-21.166	36.512	1.00	20.85	O
ATOM	100	C	SER A	14	-13.270	-17.919	36.910	1.00	19.74	C
ATOM	101	O	SER A	14	-12.538	-17.192	37.583	1.00	20.76	O
ATOM	102	N	VAL A	15	-14.596	-17.811	36.882	1.00	19.85	N
ATOM	103	CA	VAL A	15	-15.324	-16.876	37.738	1.00	19.31	C
ATOM	104	CB	VAL A	15	-16.856	-17.012	37.536	1.00	19.58	C
ATOM	105	CG1	VAL A	15	-17.651	-16.103	38.508	1.00	19.33	C
ATOM	106	CG2	VAL A	15	-17.242	-16.722	36.073	1.00	18.75	C
ATOM	107	C	VAL A	15	-14.947	-17.159	39.185	1.00	19.32	C
ATOM	108	O	VAL A	15	-14.921	-18.313	39.613	1.00	19.68	O
ATOM	109	N	GLY A	16	-14.621	-16.104	39.924	1.00	19.33	N
ATOM	110	CA	GLY A	16	-14.247	-16.217	41.333	1.00	18.83	C
ATOM	111	C	GLY A	16	-12.741	-16.226	41.538	1.00	18.78	C
ATOM	112	O	GLY A	16	-12.275	-16.162	42.672	1.00	19.04	O
ATOM	113	N	ASP A	17	-11.977	-16.299	40.446	1.00	18.42	N
ATOM	114	CA	ASP A	17	-10.523	-16.316	40.535	1.00	18.38	C
ATOM	115	CB	ASP A	17	-9.905	-16.857	39.246	1.00	18.77	C
ATOM	116	CG	ASP A	17	-9.908	-18.357	39.187	1.00	20.45	C
ATOM	117	OD1	ASP A	17	-9.398	-18.925	38.195	1.00	22.62	O

ATOM	118	OD2 ASP A 17	-10.431	-18.974	40.134	1.00	23.50	O
ATOM	119	C ASP A 17	-9.928	-14.951	40.825	1.00	17.91	C
ATOM	120	O ASP A 17	-10.611	-13.935	40.762	1.00	17.66	O
ATOM	121	N ARG A 18	-8.637	-14.959	41.141	1.00	17.91	N
ATOM	122	CA ARG A 18	-7.817	-13.758	41.245	1.00	17.94	C
ATOM	123	CB ARG A 18	-7.237	-13.617	42.655	1.00	18.09	C
ATOM	124	CG ARG A 18	-5.764	-13.163	42.763	1.00	21.31	C
ATOM	125	CD ARG A 18	-5.501	-12.525	44.121	1.00	27.48	C
ATOM	126	NE ARG A 18	-6.583	-12.862	45.048	1.00	32.32	N
ATOM	127	CZ ARG A 18	-6.748	-12.332	46.255	1.00	34.75	C
ATOM	128	NH1 ARG A 18	-5.885	-11.423	46.705	1.00	36.05	N
ATOM	129	NH2 ARG A 18	-7.784	-12.712	47.005	1.00	34.44	N
ATOM	130	C ARG A 18	-6.727	-13.812	40.183	1.00	17.43	C
ATOM	131	O ARG A 18	-6.245	-14.884	39.812	1.00	17.22	O
ATOM	132	N VAL A 19	-6.322	-12.640	39.720	1.00	17.10	N
ATOM	133	CA VAL A 19	-5.495	-12.530	38.538	1.00	16.62	C
ATOM	134	CB VAL A 19	-6.442	-12.563	37.302	1.00	16.77	C
ATOM	135	CG1 VAL A 19	-6.569	-11.197	36.591	1.00	17.26	C
ATOM	136	CG2 VAL A 19	-6.061	-13.689	36.370	1.00	16.60	C
ATOM	137	C VAL A 19	-4.644	-11.255	38.666	1.00	16.28	C
ATOM	138	O VAL A 19	-5.027	-10.326	39.367	1.00	15.91	O
ATOM	139	N THR A 20	-3.469	-11.223	38.051	1.00	16.13	N
ATOM	140	CA THR A 20	-2.648	-10.011	38.098	1.00	16.44	C
ATOM	141	CB THR A 20	-1.518	-10.069	39.168	1.00	16.40	C
ATOM	142	OG1 THR A 20	-2.091	-10.104	40.474	1.00	16.55	O
ATOM	143	CG2 THR A 20	-0.623	-8.846	39.088	1.00	16.12	C
ATOM	144	C THR A 20	-2.067	-9.711	36.727	1.00	16.84	C
ATOM	145	O THR A 20	-1.353	-10.534	36.141	1.00	16.51	O
ATOM	146	N ILE A 21	-2.409	-8.523	36.238	1.00	17.43	N
ATOM	147	CA ILE A 21	-2.037	-8.030	34.924	1.00	18.08	C
ATOM	148	CB ILE A 21	-3.171	-7.138	34.358	1.00	18.18	C
ATOM	149	CG1 ILE A 21	-4.393	-7.966	33.990	1.00	18.71	C
ATOM	150	CD1 ILE A 21	-5.642	-7.089	33.802	1.00	20.31	C
ATOM	151	CG2 ILE A 21	-2.732	-6.336	33.137	1.00	18.88	C
ATOM	152	C ILE A 21	-0.852	-7.151	35.202	1.00	18.20	C
ATOM	153	O ILE A 21	-0.792	-6.540	36.258	1.00	18.95	O
ATOM	154	N THR A 22	0.073	-7.068	34.260	1.00	18.48	N
ATOM	155	CA THR A 22	1.338	-6.380	34.482	1.00	19.00	C
ATOM	156	CB THR A 22	2.504	-7.416	34.440	1.00	19.25	C
ATOM	157	OG1 THR A 22	3.200	-7.402	35.688	1.00	20.82	O
ATOM	158	CG2 THR A 22	3.489	-7.204	33.252	1.00	19.39	C
ATOM	159	C THR A 22	1.515	-5.258	33.451	1.00	18.88	C
ATOM	160	O THR A 22	1.041	-5.388	32.321	1.00	19.01	O
ATOM	161	N CYS A 23	2.168	-4.156	33.840	1.00	18.69	N
ATOM	162	CA CYS A 23	2.571	-3.092	32.881	1.00	18.14	C
ATOM	163	CB CYS A 23	1.558	-1.951	32.811	1.00	17.87	C
ATOM	164	SG CYS A 23	0.222	-2.255	31.654	1.00	18.51	S
ATOM	165	C CYS A 23	3.931	-2.530	33.229	1.00	17.82	C
ATOM	166	O CYS A 23	4.183	-2.198	34.384	1.00	18.76	O
ATOM	167	N ILE A 24	4.800	-2.414	32.232	1.00	17.19	N
ATOM	168	CA ILE A 24	6.176	-1.988	32.453	1.00	16.72	C
ATOM	169	CB ILE A 24	7.150	-3.210	32.370	1.00	16.82	C
ATOM	170	CG1 ILE A 24	6.963	-4.089	33.610	1.00	16.90	C
ATOM	171	CD1 ILE A 24	6.988	-5.567	33.311	1.00	19.35	C
ATOM	172	CG2 ILE A 24	8.626	-2.789	32.250	1.00	15.92	C
ATOM	173	C ILE A 24	6.553	-0.827	31.527	1.00	16.66	C
ATOM	174	O ILE A 24	6.419	-0.907	30.304	1.00	16.68	O

ATOM	175	N	THR	A	25	7.019	0.260	32.125	1.00	16.59	N
ATOM	176	CA	THR	A	25	7.357	1.470	31.370	1.00	16.50	C
ATOM	177	CB	THR	A	25	6.881	2.712	32.118	1.00	16.33	C
ATOM	178	OG1	THR	A	25	7.446	2.714	33.427	1.00	16.11	O
ATOM	179	CG2	THR	A	25	5.355	2.724	32.240	1.00	15.78	C
ATOM	180	C	THR	A	25	8.860	1.589	31.074	1.00	16.60	C
ATOM	181	O	THR	A	25	9.692	1.108	31.853	1.00	16.88	O
ATOM	182	N	THR	A	26	9.204	2.216	29.949	1.00	16.28	N
ATOM	183	CA	THR	A	26	10.606	2.401	29.565	1.00	16.28	C
ATOM	184	CB	THR	A	26	10.781	2.652	28.051	1.00	16.76	C
ATOM	185	OG1	THR	A	26	9.910	3.723	27.632	1.00	17.73	O
ATOM	186	CG2	THR	A	26	10.504	1.385	27.241	1.00	16.56	C
ATOM	187	C	THR	A	26	11.262	3.558	30.300	1.00	15.91	C
ATOM	188	O	THR	A	26	12.475	3.711	30.273	1.00	16.54	O
ATOM	189	N	THR	A	27	10.472	4.394	30.945	1.00	15.67	N
ATOM	190	CA	THR	A	27	11.036	5.472	31.745	1.00	15.47	C
ATOM	191	CB	THR	A	27	10.917	6.857	31.049	1.00	15.55	C
ATOM	192	OG1	THR	A	27	9.541	7.170	30.830	1.00	14.51	O
ATOM	193	CG2	THR	A	27	11.663	6.885	29.721	1.00	14.30	C
ATOM	194	C	THR	A	27	10.299	5.515	33.066	1.00	15.87	C
ATOM	195	O	THR	A	27	9.167	5.040	33.170	1.00	15.85	O
ATOM	196	N	ASP	A	28	10.948	6.082	34.079	1.00	16.16	N
ATOM	197	CA	ASP	A	28	10.351	6.215	35.409	1.00	15.68	C
ATOM	198	CB	ASP	A	28	11.413	6.706	36.384	1.00	15.63	C
ATOM	199	CG	ASP	A	28	10.997	6.558	37.835	1.00	16.94	C
ATOM	200	OD1	ASP	A	28	9.845	6.927	38.198	1.00	15.98	O
ATOM	201	OD2	ASP	A	28	11.853	6.090	38.621	1.00	18.81	O
ATOM	202	C	ASP	A	28	9.132	7.162	35.378	1.00	15.30	C
ATOM	203	O	ASP	A	28	9.265	8.374	35.210	1.00	15.63	O
ATOM	204	N	ILE	A	29	7.941	6.605	35.530	1.00	14.60	N
ATOM	205	CA	ILE	A	29	6.728	7.408	35.497	1.00	13.50	C
ATOM	206	CB	ILE	A	29	5.667	6.779	34.570	1.00	13.40	C
ATOM	207	CG1	ILE	A	29	5.249	5.397	35.064	1.00	12.45	C
ATOM	208	CD1	ILE	A	29	3.792	5.090	34.832	1.00	11.19	C
ATOM	209	CG2	ILE	A	29	6.201	6.671	33.158	1.00	12.93	C
ATOM	210	C	ILE	A	29	6.183	7.596	36.910	1.00	13.63	C
ATOM	211	O	ILE	A	29	4.981	7.826	37.111	1.00	13.16	O
ATOM	212	N	ASP	A	30	7.088	7.534	37.887	1.00	13.69	N
ATOM	213	CA	ASP	A	30	6.722	7.603	39.310	1.00	14.02	C
ATOM	214	CB	ASP	A	30	6.716	9.050	39.884	1.00	13.72	C
ATOM	215	CG	ASP	A	30	5.899	10.026	39.058	1.00	12.99	C
ATOM	216	OD1	ASP	A	30	6.431	10.573	38.075	1.00	11.40	O
ATOM	217	OD2	ASP	A	30	4.733	10.287	39.409	1.00	13.93	O
ATOM	218	C	ASP	A	30	5.442	6.810	39.623	1.00	14.15	C
ATOM	219	O	ASP	A	30	5.467	5.603	39.540	1.00	14.53	O
ATOM	220	N	ASP	A	31	4.342	7.460	39.970	1.00	14.33	N
ATOM	221	CA	ASP	A	31	3.128	6.726	40.306	1.00	14.71	C
ATOM	222	CB	ASP	A	31	2.626	7.127	41.693	1.00	14.78	C
ATOM	223	CG	ASP	A	31	2.305	8.615	41.783	1.00	15.81	C
ATOM	224	OD1	ASP	A	31	2.747	9.382	40.885	1.00	14.71	O
ATOM	225	OD2	ASP	A	31	1.609	9.018	42.745	1.00	17.29	O
ATOM	226	C	ASP	A	31	2.045	7.026	39.286	1.00	14.66	C
ATOM	227	O	ASP	A	31	0.861	6.808	39.551	1.00	14.81	O
ATOM	228	N	ASP	A	32	2.450	7.527	38.126	1.00	14.76	N
ATOM	229	CA	ASP	A	32	1.503	7.967	37.108	1.00	15.12	C
ATOM	230	CB	ASP	A	32	2.117	9.099	36.250	1.00	15.19	C
ATOM	231	CG	ASP	A	32	2.651	10.274	37.103	1.00	15.97	C

ATOM	232	OD1 ASP A 32	1.990	10.650	38.113	1.00	15.30	O
ATOM	233	OD2 ASP A 32	3.727	10.824	36.764	1.00	14.32	O
ATOM	234	C ASP A 32	0.982	6.797	36.249	1.00	14.93	C
ATOM	235	O ASP A 32	1.075	6.811	35.031	1.00	15.31	O
ATOM	236	N MET A 33	0.399	5.801	36.898	1.00	14.65	N
ATOM	237	CA MET A 33	-0.208	4.689	36.201	1.00	14.38	C
ATOM	238	CB MET A 33	0.368	3.355	36.684	1.00	14.32	C
ATOM	239	CG MET A 33	-0.114	2.155	35.877	1.00	14.45	C
ATOM	240	SD MET A 33	0.215	2.332	34.104	1.00	17.56	S
ATOM	241	CE MET A 33	1.867	1.681	33.998	1.00	16.73	C
ATOM	242	C MET A 33	-1.712	4.708	36.406	1.00	14.39	C
ATOM	243	O MET A 33	-2.199	4.987	37.506	1.00	14.61	O
ATOM	244	N ASN A 34	-2.443	4.393	35.339	1.00	13.98	N
ATOM	245	CA ASN A 34	-3.890	4.419	35.350	1.00	13.07	C
ATOM	246	CB ASN A 34	-4.384	5.606	34.528	1.00	13.00	C
ATOM	247	CG ASN A 34	-3.822	6.941	35.008	1.00	12.00	C
ATOM	248	OD1 ASN A 34	-4.507	7.690	35.704	1.00	14.10	O
ATOM	249	ND2 ASN A 34	-2.580	7.244	34.636	1.00	8.79	N
ATOM	250	C ASN A 34	-4.343	3.126	34.715	1.00	13.15	C
ATOM	251	O ASN A 34	-3.651	2.609	33.838	1.00	13.38	O
ATOM	252	N TRP A 35	-5.477	2.583	35.147	1.00	12.37	N
ATOM	253	CA TRP A 35	-5.941	1.334	34.575	1.00	12.36	C
ATOM	254	CB TRP A 35	-5.884	0.189	35.598	1.00	12.51	C
ATOM	255	CG TRP A 35	-4.511	-0.132	36.004	1.00	12.61	C
ATOM	256	CD1 TRP A 35	-3.797	0.455	37.008	1.00	14.73	C
ATOM	257	NE1 TRP A 35	-2.529	-0.089	37.083	1.00	14.63	N
ATOM	258	CE2 TRP A 35	-2.411	-1.047	36.112	1.00	13.00	C
ATOM	259	CD2 TRP A 35	-3.641	-1.096	35.407	1.00	13.60	C
ATOM	260	CE3 TRP A 35	-3.783	-2.009	34.351	1.00	13.46	C
ATOM	261	CZ3 TRP A 35	-2.713	-2.818	34.036	1.00	13.65	C
ATOM	262	CH2 TRP A 35	-1.503	-2.743	34.756	1.00	13.82	C
ATOM	263	CZ2 TRP A 35	-1.337	-1.863	35.796	1.00	12.70	C
ATOM	264	C TRP A 35	-7.343	1.541	34.108	1.00	12.34	C
ATOM	265	O TRP A 35	-8.119	2.184	34.807	1.00	12.75	O
ATOM	266	N PHE A 36	-7.668	1.000	32.933	1.00	12.42	N
ATOM	267	CA PHE A 36	-9.009	1.123	32.357	1.00	12.45	C
ATOM	268	CB PHE A 36	-8.985	1.976	31.089	1.00	11.97	C
ATOM	269	CG PHE A 36	-8.543	3.389	31.291	1.00	11.42	C
ATOM	270	CD1 PHE A 36	-9.481	4.411	31.422	1.00	12.86	C
ATOM	271	CE1 PHE A 36	-9.065	5.742	31.592	1.00	13.06	C
ATOM	272	CZ PHE A 36	-7.697	6.038	31.606	1.00	11.07	C
ATOM	273	CE2 PHE A 36	-6.775	5.020	31.455	1.00	9.45	C
ATOM	274	CD2 PHE A 36	-7.197	3.716	31.289	1.00	9.70	C
ATOM	275	C PHE A 36	-9.607	-0.224	31.971	1.00	13.02	C
ATOM	276	O PHE A 36	-8.891	-1.206	31.707	1.00	13.53	O
ATOM	277	N GLN A 37	-10.926	-0.239	31.872	1.00	13.13	N
ATOM	278	CA GLN A 37	-11.653	-1.399	31.411	1.00	13.56	C
ATOM	279	CB GLN A 37	-12.543	-1.891	32.542	1.00	13.26	C
ATOM	280	CG GLN A 37	-13.456	-3.039	32.179	1.00	12.26	C
ATOM	281	CD GLN A 37	-14.512	-3.253	33.233	1.00	10.26	C
ATOM	282	OE1 GLN A 37	-15.522	-2.563	33.242	1.00	7.55	O
ATOM	283	NE2 GLN A 37	-14.277	-4.212	34.138	1.00	8.29	N
ATOM	284	C GLN A 37	-12.506	-1.027	30.197	1.00	14.40	C
ATOM	285	O GLN A 37	-13.179	-0.001	30.212	1.00	14.84	O
ATOM	286	N GLN A 38	-12.492	-1.858	29.161	1.00	15.13	N
ATOM	287	CA GLN A 38	-13.339	-1.640	27.994	1.00	16.28	C
ATOM	288	CB GLN A 38	-12.482	-1.179	26.798	1.00	16.16	C

ATOM	289	CG	GLN A 38	-13.279	-0.901	25.509	1.00	16.03	C
ATOM	290	CD	GLN A 38	-12.470	-0.185	24.427	1.00	16.51	C
ATOM	291	OE1	GLN A 38	-11.364	-0.601	24.074	1.00	17.78	O
ATOM	292	NE2	GLN A 38	-13.037	0.881	23.878	1.00	15.62	N
ATOM	293	C	GLN A 38	-14.131	-2.900	27.631	1.00	16.97	C
ATOM	294	O	GLN A 38	-13.552	-3.944	27.388	1.00	16.99	O
ATOM	295	N	GLU A 39	-15.451	-2.798	27.600	1.00	18.40	N
ATOM	296	CA	GLU A 39	-16.302	-3.854	27.030	1.00	19.86	C
ATOM	297	CB	GLU A 39	-17.687	-3.837	27.670	1.00	20.03	C
ATOM	298	CG	GLU A 39	-17.668	-4.015	29.181	1.00	25.24	C
ATOM	299	CD	GLU A 39	-18.996	-4.533	29.733	1.00	32.12	C
ATOM	300	OE1	GLU A 39	-19.012	-5.092	30.861	1.00	33.29	O
ATOM	301	OE2	GLU A 39	-20.030	-4.393	29.032	1.00	37.20	O
ATOM	302	C	GLU A 39	-16.424	-3.592	25.525	1.00	20.08	C
ATOM	303	O	GLU A 39	-16.300	-2.435	25.102	1.00	19.57	O
ATOM	304	N	PRO A 40	-16.674	-4.648	24.709	1.00	20.52	N
ATOM	305	CA	PRO A 40	-16.705	-4.474	23.245	1.00	20.95	C
ATOM	306	CB	PRO A 40	-17.047	-5.870	22.731	1.00	20.93	C
ATOM	307	CG	PRO A 40	-16.688	-6.783	23.821	1.00	20.83	C
ATOM	308	CD	PRO A 40	-16.950	-6.042	25.087	1.00	20.29	C
ATOM	309	C	PRO A 40	-17.748	-3.446	22.754	1.00	21.50	C
ATOM	310	O	PRO A 40	-18.916	-3.482	23.177	1.00	21.38	O
ATOM	311	N	GLY A 41	-17.300	-2.534	21.882	1.00	21.82	N
ATOM	312	CA	GLY A 41	-18.134	-1.467	21.333	1.00	22.01	C
ATOM	313	C	GLY A 41	-18.604	-0.435	22.348	1.00	22.34	C
ATOM	314	O	GLY A 41	-19.638	0.216	22.148	1.00	22.65	O
ATOM	315	N	LYS A 42	-17.858	-0.293	23.444	1.00	22.18	N
ATOM	316	CA	LYS A 42	-18.127	0.732	24.460	1.00	21.81	C
ATOM	317	CB	LYS A 42	-18.648	0.106	25.755	1.00	21.81	C
ATOM	318	CG	LYS A 42	-20.130	-0.272	25.738	1.00	23.19	C
ATOM	319	CD	LYS A 42	-20.592	-0.730	27.134	1.00	24.08	C
ATOM	320	CE	LYS A 42	-22.028	-1.276	27.104	1.00	29.18	C
ATOM	321	NZ	LYS A 42	-23.080	-0.192	27.064	1.00	29.23	N
ATOM	322	C	LYS A 42	-16.885	1.563	24.740	1.00	20.44	C
ATOM	323	O	LYS A 42	-15.780	1.188	24.366	1.00	20.27	O
ATOM	324	N	ALA A 43	-17.067	2.704	25.393	1.00	19.77	N
ATOM	325	CA	ALA A 43	-15.928	3.547	25.776	1.00	18.57	C
ATOM	326	CB	ALA A 43	-16.409	4.947	26.131	1.00	18.17	C
ATOM	327	C	ALA A 43	-15.175	2.922	26.951	1.00	17.41	C
ATOM	328	O	ALA A 43	-15.794	2.354	27.836	1.00	17.35	O
ATOM	329	N	PRO A 44	-13.839	3.042	26.976	1.00	16.69	N
ATOM	330	CA	PRO A 44	-13.112	2.636	28.182	1.00	16.20	C
ATOM	331	CB	PRO A 44	-11.675	3.107	27.905	1.00	15.84	C
ATOM	332	CG	PRO A 44	-11.560	3.196	26.459	1.00	15.57	C
ATOM	333	CD	PRO A 44	-12.931	3.563	25.938	1.00	16.51	C
ATOM	334	C	PRO A 44	-13.656	3.313	29.462	1.00	16.15	C
ATOM	335	O	PRO A 44	-14.075	4.479	29.439	1.00	15.60	O
ATOM	336	N	LYS A 45	-13.653	2.569	30.560	1.00	16.47	N
ATOM	337	CA	LYS A 45	-14.036	3.091	31.868	1.00	17.23	C
ATOM	338	CB	LYS A 45	-15.106	2.184	32.487	1.00	17.25	C
ATOM	339	CG	LYS A 45	-15.532	2.547	33.912	1.00	18.50	C
ATOM	340	CD	LYS A 45	-16.781	1.760	34.323	1.00	19.10	C
ATOM	341	CE	LYS A 45	-17.345	2.261	35.663	1.00	22.55	C
ATOM	342	NZ	LYS A 45	-16.856	1.488	36.849	1.00	21.57	N
ATOM	343	C	LYS A 45	-12.804	3.203	32.783	1.00	16.64	C
ATOM	344	O	LYS A 45	-12.044	2.237	32.929	1.00	17.21	O
ATOM	345	N	LEU A 46	-12.593	4.376	33.380	1.00	15.81	N

ATOM	346	CA	LEU A 46	-11.477	4.556	34.318	1.00	15.19	C
ATOM	347	CB	LEU A 46	-11.204	6.039	34.589	1.00	15.01	C
ATOM	348	CG	LEU A 46	-10.155	6.358	35.654	1.00	13.46	C
ATOM	349	CD1	LEU A 46	-8.769	5.867	35.277	1.00	10.70	C
ATOM	350	CD2	LEU A 46	-10.142	7.831	35.901	1.00	12.65	C
ATOM	351	C	LEU A 46	-11.719	3.828	35.635	1.00	14.96	C
ATOM	352	O	LEU A 46	-12.766	4.023	36.265	1.00	14.97	O
ATOM	353	N	LEU A 47	-10.733	3.013	36.037	1.00	14.52	N
ATOM	354	CA	LEU A 47	-10.806	2.152	37.227	1.00	13.86	C
ATOM	355	CB	LEU A 47	-10.336	0.737	36.891	1.00	13.45	C
ATOM	356	CG	LEU A 47	-11.057	-0.114	35.863	1.00	13.92	C
ATOM	357	CD1	LEU A 47	-10.183	-1.323	35.541	1.00	15.44	C
ATOM	358	CD2	LEU A 47	-12.449	-0.558	36.307	1.00	13.40	C
ATOM	359	C	LEU A 47	-9.923	2.661	38.361	1.00	13.82	C
ATOM	360	O	LEU A 47	-10.336	2.695	39.526	1.00	13.50	O
ATOM	361	N	ILE A 48	-8.686	3.002	38.019	1.00	13.59	N
ATOM	362	CA	ILE A 48	-7.714	3.437	38.997	1.00	13.77	C
ATOM	363	CB	ILE A 48	-6.771	2.281	39.396	1.00	13.59	C
ATOM	364	CG1	ILE A 48	-7.484	1.323	40.344	1.00	13.18	C
ATOM	365	CD1	ILE A 48	-6.830	-0.057	40.486	1.00	13.25	C
ATOM	366	CG2	ILE A 48	-5.500	2.805	40.063	1.00	12.96	C
ATOM	367	C	ILE A 48	-6.931	4.565	38.363	1.00	14.51	C
ATOM	368	O	ILE A 48	-6.524	4.451	37.210	1.00	15.02	O
ATOM	369	N	SER A 49	-6.725	5.654	39.100	1.00	15.18	N
ATOM	370	CA	SER A 49	-5.937	6.776	38.586	1.00	15.56	C
ATOM	371	CB	SER A 49	-6.747	8.064	38.650	1.00	15.69	C
ATOM	372	OG	SER A 49	-7.296	8.274	39.932	1.00	14.40	O
ATOM	373	C	SER A 49	-4.638	6.934	39.346	1.00	16.38	C
ATOM	374	O	SER A 49	-4.463	6.319	40.412	1.00	16.95	O
ATOM	375	N	GLU A 50	-3.743	7.772	38.817	1.00	17.09	N
ATOM	376	CA	GLU A 50	-2.404	8.010	39.400	1.00	17.97	C
ATOM	377	CB	GLU A 50	-1.856	9.388	39.017	1.00	18.08	C
ATOM	378	CG	GLU A 50	-2.050	9.834	37.576	1.00	18.57	C
ATOM	379	CD	GLU A 50	-1.444	11.206	37.337	1.00	18.70	C
ATOM	380	OE1	GLU A 50	-1.121	11.531	36.174	1.00	18.96	O
ATOM	381	OE2	GLU A 50	-1.276	11.959	38.324	1.00	20.10	O
ATOM	382	C	GLU A 50	-2.335	7.886	40.926	1.00	18.15	C
ATOM	383	O	GLU A 50	-3.135	8.490	41.650	1.00	18.38	O
ATOM	384	N	GLY A 51	-1.356	7.119	41.397	1.00	18.50	N
ATOM	385	CA	GLY A 51	-1.179	6.859	42.829	1.00	18.79	C
ATOM	386	C	GLY A 51	-2.182	5.859	43.386	1.00	18.76	C
ATOM	387	O	GLY A 51	-2.642	6.024	44.506	1.00	18.51	O
ATOM	388	N	ASN A 52	-2.524	4.838	42.588	1.00	18.81	N
ATOM	389	CA	ASN A 52	-3.411	3.730	42.985	1.00	18.69	C
ATOM	390	CB	ASN A 52	-2.674	2.693	43.853	1.00	18.47	C
ATOM	391	CG	ASN A 52	-1.353	2.258	43.251	1.00	18.25	C
ATOM	392	OD1	ASN A 52	-0.297	2.614	43.762	1.00	18.89	O
ATOM	393	ND2	ASN A 52	-1.399	1.507	42.162	1.00	16.11	N
ATOM	394	C	ASN A 52	-4.714	4.165	43.658	1.00	18.83	C
ATOM	395	O	ASN A 52	-5.139	3.589	44.660	1.00	18.74	O
ATOM	396	N	ILE A 53	-5.353	5.180	43.096	1.00	19.13	N
ATOM	397	CA	ILE A 53	-6.579	5.684	43.685	1.00	19.49	C
ATOM	398	CB	ILE A 53	-6.604	7.240	43.725	1.00	19.81	C
ATOM	399	CG1	ILE A 53	-5.489	7.756	44.659	1.00	19.16	C
ATOM	400	CD1	ILE A 53	-5.154	9.238	44.460	1.00	19.19	C
ATOM	401	CG2	ILE A 53	-7.982	7.758	44.164	1.00	19.30	C
ATOM	402	C	ILE A 53	-7.766	5.092	42.945	1.00	19.80	C

ATOM	403	O	ILE A 53	-7.952	5.316	41.747	1.00	19.85	O
ATOM	404	N	LEU A 54	-8.537	4.297	43.676	1.00	20.21	N
ATOM	405	CA	LEU A 54	-9.704	3.618	43.148	1.00	20.37	C
ATOM	406	CB	LEU A 54	-10.198	2.627	44.186	1.00	20.07	C
ATOM	407	CG	LEU A 54	-10.525	1.176	43.872	1.00	20.40	C
ATOM	408	CD1	LEU A 54	-11.889	0.858	44.468	1.00	19.50	C
ATOM	409	CD2	LEU A 54	-10.531	0.914	42.405	1.00	21.38	C
ATOM	410	C	LEU A 54	-10.777	4.665	42.942	1.00	20.86	C
ATOM	411	O	LEU A 54	-11.150	5.357	43.886	1.00	21.66	O
ATOM	412	N	ARG A 55	-11.279	4.800	41.726	1.00	21.07	N
ATOM	413	CA	ARG A 55	-12.335	5.775	41.465	1.00	21.64	C
ATOM	414	CB	ARG A 55	-12.679	5.811	39.974	1.00	21.42	C
ATOM	415	CG	ARG A 55	-11.482	5.967	39.047	1.00	19.91	C
ATOM	416	CD	ARG A 55	-10.578	7.108	39.478	1.00	18.82	C
ATOM	417	NE	ARG A 55	-11.357	8.279	39.877	1.00	18.81	N
ATOM	418	CZ	ARG A 55	-10.941	9.203	40.741	1.00	18.14	C
ATOM	419	NH1	ARG A 55	-9.735	9.110	41.304	1.00	14.26	N
ATOM	420	NH2	ARG A 55	-11.743	10.226	41.038	1.00	18.29	N
ATOM	421	C	ARG A 55	-13.585	5.458	42.294	1.00	22.56	C
ATOM	422	O	ARG A 55	-13.830	4.293	42.591	1.00	22.86	O
ATOM	423	N	PRO A 56	-14.351	6.491	42.715	1.00	23.46	N
ATOM	424	CA	PRO A 56	-15.643	6.240	43.382	1.00	23.74	C
ATOM	425	CB	PRO A 56	-16.313	7.630	43.419	1.00	23.70	C
ATOM	426	CG	PRO A 56	-15.405	8.568	42.691	1.00	23.91	C
ATOM	427	CD	PRO A 56	-14.044	7.933	42.664	1.00	23.69	C
ATOM	428	C	PRO A 56	-16.511	5.287	42.580	1.00	23.75	C
ATOM	429	O	PRO A 56	-16.543	5.402	41.354	1.00	24.34	O
ATOM	430	N	GLY A 57	-17.186	4.355	43.253	1.00	23.64	N
ATOM	431	CA	GLY A 57	-18.103	3.415	42.591	1.00	23.79	C
ATOM	432	C	GLY A 57	-17.453	2.163	41.999	1.00	24.07	C
ATOM	433	O	GLY A 57	-18.146	1.248	41.539	1.00	24.50	O
ATOM	434	N	VAL A 58	-16.125	2.113	41.997	1.00	23.61	N
ATOM	435	CA	VAL A 58	-15.419	0.982	41.412	1.00	23.33	C
ATOM	436	CB	VAL A 58	-14.072	1.413	40.765	1.00	23.48	C
ATOM	437	CG1	VAL A 58	-13.235	0.205	40.359	1.00	23.08	C
ATOM	438	CG2	VAL A 58	-14.330	2.288	39.543	1.00	23.41	C
ATOM	439	C	VAL A 58	-15.204	-0.062	42.495	1.00	22.99	C
ATOM	440	O	VAL A 58	-14.676	0.266	43.560	1.00	22.86	O
ATOM	441	N	PRO A 59	-15.609	-1.323	42.228	1.00	22.57	N
ATOM	442	CA	PRO A 59	-15.507	-2.359	43.254	1.00	22.07	C
ATOM	443	CB	PRO A 59	-15.921	-3.635	42.514	1.00	21.74	C
ATOM	444	CG	PRO A 59	-16.785	-3.164	41.406	1.00	22.39	C
ATOM	445	CD	PRO A 59	-16.173	-1.857	40.971	1.00	22.62	C
ATOM	446	C	PRO A 59	-14.083	-2.493	43.788	1.00	21.80	C
ATOM	447	O	PRO A 59	-13.117	-2.376	43.032	1.00	21.85	O
ATOM	448	N	SER A 60	-13.973	-2.732	45.091	1.00	21.43	N
ATOM	449	CA	SER A 60	-12.693	-2.926	45.775	1.00	21.08	C
ATOM	450	CB	SER A 60	-12.937	-2.951	47.272	1.00	21.23	C
ATOM	451	OG	SER A 60	-14.323	-3.143	47.516	1.00	22.54	O
ATOM	452	C	SER A 60	-11.926	-4.185	45.346	1.00	20.63	C
ATOM	453	O	SER A 60	-10.746	-4.336	45.668	1.00	20.76	O
ATOM	454	N	ARG A 61	-12.575	-5.079	44.602	1.00	19.55	N
ATOM	455	CA	ARG A 61	-11.886	-6.263	44.109	1.00	18.56	C
ATOM	456	CB	ARG A 61	-12.882	-7.319	43.636	1.00	18.76	C
ATOM	457	CG	ARG A 61	-13.763	-6.873	42.514	1.00	19.31	C
ATOM	458	CD	ARG A 61	-14.562	-8.038	41.973	1.00	18.48	C
ATOM	459	NE	ARG A 61	-15.264	-7.651	40.757	1.00	17.39	N

ATOM	460	CZ	ARG	A	61	-16.437	-7.028	40.729	1.00	17.17	C
ATOM	461	NH1	ARG	A	61	-17.065	-6.717	41.869	1.00	15.74	N
ATOM	462	NH2	ARG	A	61	-16.980	-6.721	39.555	1.00	14.52	N
ATOM	463	C	ARG	A	61	-10.839	-5.920	43.037	1.00	17.89	C
ATOM	464	O	ARG	A	61	-10.032	-6.776	42.630	1.00	17.56	O
ATOM	465	N	PHE	A	62	-10.855	-4.651	42.615	1.00	16.82	N
ATOM	466	CA	PHE	A	62	-9.831	-4.059	41.761	1.00	15.53	C
ATOM	467	CB	PHE	A	62	-10.462	-3.051	40.771	1.00	15.00	C
ATOM	468	CG	PHE	A	62	-11.374	-3.686	39.748	1.00	12.96	C
ATOM	469	CD1	PHE	A	62	-10.854	-4.235	38.578	1.00	10.71	C
ATOM	470	CE1	PHE	A	62	-11.674	-4.838	37.654	1.00	10.19	C
ATOM	471	CZ	PHE	A	62	-13.037	-4.896	37.883	1.00	11.43	C
ATOM	472	CE2	PHE	A	62	-13.566	-4.348	39.037	1.00	10.27	C
ATOM	473	CD2	PHE	A	62	-12.737	-3.750	39.964	1.00	10.03	C
ATOM	474	C	PHE	A	62	-8.858	-3.336	42.664	1.00	15.53	C
ATOM	475	O	PHE	A	62	-9.269	-2.537	43.495	1.00	15.94	O
ATOM	476	N	SER	A	63	-7.574	-3.628	42.528	1.00	15.43	N
ATOM	477	CA	SER	A	63	-6.537	-2.870	43.232	1.00	15.64	C
ATOM	478	CB	SER	A	63	-6.276	-3.428	44.623	1.00	15.66	C
ATOM	479	OG	SER	A	63	-5.838	-4.772	44.531	1.00	18.38	O
ATOM	480	C	SER	A	63	-5.269	-2.944	42.407	1.00	15.59	C
ATOM	481	O	SER	A	63	-5.136	-3.833	41.534	1.00	15.80	O
ATOM	482	N	SER	A	64	-4.345	-2.024	42.677	1.00	14.49	N
ATOM	483	CA	SER	A	64	-3.167	-1.872	41.844	1.00	14.12	C
ATOM	484	CB	SER	A	64	-3.348	-0.674	40.906	1.00	14.45	C
ATOM	485	OG	SER	A	64	-3.651	0.501	41.655	1.00	15.61	O
ATOM	486	C	SER	A	64	-1.979	-1.625	42.719	1.00	13.39	C
ATOM	487	O	SER	A	64	-2.131	-1.332	43.881	1.00	13.84	O
ATOM	488	N	SER	A	65	-0.788	-1.731	42.169	1.00	12.71	N
ATOM	489	CA	SER	A	65	0.388	-1.379	42.924	1.00	12.45	C
ATOM	490	CB	SER	A	65	0.819	-2.542	43.824	1.00	12.29	C
ATOM	491	OG	SER	A	65	1.764	-3.383	43.180	1.00	13.79	O
ATOM	492	C	SER	A	65	1.470	-1.024	41.924	1.00	12.36	C
ATOM	493	O	SER	A	65	1.325	-1.304	40.717	1.00	12.13	O
ATOM	494	N	GLY	A	66	2.537	-0.408	42.422	1.00	12.06	N
ATOM	495	CA	GLY	A	66	3.717	-0.132	41.626	1.00	12.73	C
ATOM	496	C	GLY	A	66	4.177	1.308	41.677	1.00	13.37	C
ATOM	497	O	GLY	A	66	3.400	2.203	41.979	1.00	13.96	O
ATOM	498	N	TYR	A	67	5.451	1.519	41.369	1.00	14.02	N
ATOM	499	CA	TYR	A	67	6.083	2.837	41.319	1.00	14.41	C
ATOM	500	CB	TYR	A	67	6.462	3.310	42.726	1.00	14.09	C
ATOM	501	CG	TYR	A	67	6.794	4.786	42.815	1.00	14.66	C
ATOM	502	CD1	TYR	A	67	5.861	5.718	43.303	1.00	14.12	C
ATOM	503	CE1	TYR	A	67	6.177	7.080	43.384	1.00	13.24	C
ATOM	504	CZ	TYR	A	67	7.438	7.505	42.967	1.00	14.84	C
ATOM	505	OH	TYR	A	67	7.817	8.834	43.002	1.00	15.81	O
ATOM	506	CE2	TYR	A	67	8.362	6.600	42.483	1.00	14.48	C
ATOM	507	CD2	TYR	A	67	8.044	5.257	42.415	1.00	14.59	C
ATOM	508	C	TYR	A	67	7.332	2.744	40.423	1.00	15.08	C
ATOM	509	O	TYR	A	67	7.982	1.689	40.366	1.00	15.70	O
ATOM	510	N	GLY	A	68	7.657	3.824	39.715	1.00	15.20	N
ATOM	511	CA	GLY	A	68	8.845	3.848	38.888	1.00	15.52	C
ATOM	512	C	GLY	A	68	8.572	3.313	37.499	1.00	16.41	C
ATOM	513	O	GLY	A	68	8.142	4.064	36.613	1.00	16.95	O
ATOM	514	N	THR	A	69	8.820	2.016	37.297	1.00	16.51	N
ATOM	515	CA	THR	A	69	8.667	1.396	35.975	1.00	16.13	C
ATOM	516	CB	THR	A	69	10.023	1.044	35.350	1.00	15.74	C

ATOM	517	OG1 THR A 69	10.496	-0.168	35.933	1.00	16.79	O
ATOM	518	CG2 THR A 69	11.024	2.107	35.612	1.00	15.22	C
ATOM	519	C THR A 69	7.835	0.115	35.986	1.00	16.11	C
ATOM	520	O THR A 69	7.474	-0.396	34.935	1.00	16.42	O
ATOM	521	N ASP A 70	7.557	-0.419	37.168	1.00	15.98	N
ATOM	522	CA ASP A 70	6.905	-1.719	37.276	1.00	15.77	C
ATOM	523	CB ASP A 70	7.752	-2.674	38.105	1.00	15.39	C
ATOM	524	CG ASP A 70	9.094	-2.921	37.489	1.00	16.21	C
ATOM	525	OD1 ASP A 70	10.093	-2.729	38.195	1.00	18.97	O
ATOM	526	OD2 ASP A 70	9.165	-3.291	36.298	1.00	16.57	O
ATOM	527	C ASP A 70	5.557	-1.572	37.919	1.00	15.77	C
ATOM	528	O ASP A 70	5.455	-1.036	39.031	1.00	15.81	O
ATOM	529	N PHE A 71	4.519	-2.043	37.233	1.00	15.33	N
ATOM	530	CA PHE A 71	3.172	-1.761	37.695	1.00	15.63	C
ATOM	531	CB PHE A 71	2.578	-0.529	36.971	1.00	15.74	C
ATOM	532	CG PHE A 71	3.353	0.739	37.221	1.00	15.35	C
ATOM	533	CD1 PHE A 71	4.432	1.085	36.404	1.00	14.98	C
ATOM	534	CE1 PHE A 71	5.178	2.220	36.636	1.00	14.99	C
ATOM	535	CZ PHE A 71	4.865	3.039	37.702	1.00	16.51	C
ATOM	536	CE2 PHE A 71	3.781	2.707	38.545	1.00	16.89	C
ATOM	537	CD2 PHE A 71	3.044	1.550	38.298	1.00	15.84	C
ATOM	538	C PHE A 71	2.282	-2.965	37.595	1.00	15.64	C
ATOM	539	O PHE A 71	2.519	-3.841	36.786	1.00	16.65	O
ATOM	540	N THR A 72	1.235	-2.977	38.408	1.00	15.49	N
ATOM	541	CA THR A 72	0.467	-4.172	38.680	1.00	14.88	C
ATOM	542	CB THR A 72	1.053	-4.832	39.959	1.00	14.94	C
ATOM	543	OG1 THR A 72	1.888	-5.922	39.563	1.00	15.85	O
ATOM	544	CG2 THR A 72	-0.009	-5.296	40.934	1.00	14.06	C
ATOM	545	C THR A 72	-0.992	-3.818	38.870	1.00	14.58	C
ATOM	546	O THR A 72	-1.306	-2.837	39.550	1.00	14.35	O
ATOM	547	N LEU A 73	-1.870	-4.595	38.238	1.00	14.25	N
ATOM	548	CA LEU A 73	-3.313	-4.585	38.534	1.00	14.38	C
ATOM	549	CB LEU A 73	-4.145	-4.166	37.309	1.00	14.04	C
ATOM	550	CG LEU A 73	-5.682	-4.166	37.431	1.00	13.55	C
ATOM	551	CD1 LEU A 73	-6.121	-3.027	38.302	1.00	13.43	C
ATOM	552	CD2 LEU A 73	-6.381	-4.047	36.089	1.00	13.68	C
ATOM	553	C LEU A 73	-3.704	-6.002	38.938	1.00	14.95	C
ATOM	554	O LEU A 73	-3.333	-6.977	38.257	1.00	15.51	O
ATOM	555	N THR A 74	-4.431	-6.141	40.039	1.00	15.01	N
ATOM	556	CA THR A 74	-4.973	-7.444	40.356	1.00	15.49	C
ATOM	557	CB THR A 74	-4.134	-8.230	41.468	1.00	15.68	C
ATOM	558	OG1 THR A 74	-4.908	-8.485	42.643	1.00	14.16	O
ATOM	559	CG2 THR A 74	-2.786	-7.537	41.818	1.00	14.82	C
ATOM	560	C THR A 74	-6.479	-7.347	40.584	1.00	16.41	C
ATOM	561	O THR A 74	-6.957	-6.385	41.178	1.00	16.78	O
ATOM	562	N ILE A 75	-7.227	-8.293	40.027	1.00	17.70	N
ATOM	563	CA ILE A 75	-8.677	-8.323	40.203	1.00	19.03	C
ATOM	564	CB ILE A 75	-9.477	-8.378	38.880	1.00	18.77	C
ATOM	565	CG1 ILE A 75	-8.923	-7.360	37.866	1.00	18.42	C
ATOM	566	CD1 ILE A 75	-9.360	-7.592	36.418	1.00	18.02	C
ATOM	567	CG2 ILE A 75	-10.953	-8.129	39.157	1.00	17.11	C
ATOM	568	C ILE A 75	-8.971	-9.530	41.055	1.00	21.06	C
ATOM	569	O ILE A 75	-8.412	-10.605	40.848	1.00	20.92	O
ATOM	570	N SER A 76	-9.847	-9.349	42.030	1.00	23.61	N
ATOM	571	CA SER A 76	-9.715	-10.164	43.208	1.00	25.78	C
ATOM	572	CB SER A 76	-9.885	-9.358	44.471	1.00	25.63	C
ATOM	573	OG SER A 76	-9.376	-10.144	45.513	1.00	28.14	O

ATOM	574	C	SER A 76	-10.583	-11.376	43.250	1.00	26.82	C
ATOM	575	O	SER A 76	-10.074	-12.460	43.509	1.00	28.04	O
ATOM	576	N	LYS A 77	-11.884	-11.225	43.059	1.00	27.56	N
ATOM	577	CA	LYS A 77	-12.697	-12.428	42.935	1.00	28.34	C
ATOM	578	CB	LYS A 77	-13.319	-12.933	44.260	1.00	28.71	C
ATOM	579	CG	LYS A 77	-14.257	-12.012	45.019	1.00	29.72	C
ATOM	580	CD	LYS A 77	-15.236	-12.864	45.876	1.00	30.52	C
ATOM	581	CE	LYS A 77	-16.392	-12.008	46.482	1.00	32.83	C
ATOM	582	NZ	LYS A 77	-17.680	-12.776	46.634	1.00	32.50	N
ATOM	583	C	LYS A 77	-13.635	-12.263	41.758	1.00	27.68	C
ATOM	584	O	LYS A 77	-14.842	-12.006	41.883	1.00	27.96	O
ATOM	585	N	LEU A 78	-12.972	-12.383	40.608	1.00	26.88	N
ATOM	586	CA	LEU A 78	-13.483	-12.225	39.263	1.00	25.35	C
ATOM	587	CB	LEU A 78	-12.690	-13.162	38.365	1.00	25.06	C
ATOM	588	CG	LEU A 78	-11.901	-12.617	37.183	1.00	25.68	C
ATOM	589	CD1	LEU A 78	-11.659	-11.115	37.267	1.00	25.99	C
ATOM	590	CD2	LEU A 78	-10.594	-13.379	37.072	1.00	25.52	C
ATOM	591	C	LEU A 78	-14.966	-12.499	39.155	1.00	24.77	C
ATOM	592	O	LEU A 78	-15.438	-13.580	39.485	1.00	24.33	O
ATOM	593	N	GLN A 79	-15.691	-11.488	38.701	1.00	24.44	N
ATOM	594	CA	GLN A 79	-17.128	-11.553	38.514	1.00	24.24	C
ATOM	595	CB	GLN A 79	-17.720	-10.293	39.113	1.00	24.55	C
ATOM	596	CG	GLN A 79	-18.999	-10.498	39.834	1.00	27.19	C
ATOM	597	CD	GLN A 79	-18.766	-10.735	41.280	1.00	30.93	C
ATOM	598	OE1	GLN A 79	-18.562	-9.780	42.052	1.00	33.59	O
ATOM	599	NE2	GLN A 79	-18.778	-12.008	41.678	1.00	29.18	N
ATOM	600	C	GLN A 79	-17.379	-11.591	36.998	1.00	23.42	C
ATOM	601	O	GLN A 79	-16.553	-11.076	36.258	1.00	23.37	O
ATOM	602	N	PRO A 80	-18.484	-12.224	36.528	1.00	22.87	N
ATOM	603	CA	PRO A 80	-18.762	-12.318	35.064	1.00	22.22	C
ATOM	604	CB	PRO A 80	-20.219	-12.808	35.004	1.00	22.22	C
ATOM	605	CG	PRO A 80	-20.397	-13.595	36.287	1.00	22.78	C
ATOM	606	CD	PRO A 80	-19.507	-12.937	37.329	1.00	22.78	C
ATOM	607	C	PRO A 80	-18.589	-11.006	34.279	1.00	21.45	C
ATOM	608	O	PRO A 80	-17.877	-10.967	33.273	1.00	20.98	O
ATOM	609	N	GLU A 81	-19.212	-9.935	34.750	1.00	20.98	N
ATOM	610	CA	GLU A 81	-19.018	-8.594	34.165	1.00	20.32	C
ATOM	611	CB	GLU A 81	-19.855	-7.528	34.916	1.00	20.65	C
ATOM	612	CG	GLU A 81	-19.633	-7.461	36.451	1.00	23.24	C
ATOM	613	CD	GLU A 81	-20.434	-8.532	37.267	1.00	28.04	C
ATOM	614	OE1	GLU A 81	-20.499	-9.728	36.846	1.00	28.06	O
ATOM	615	OE2	GLU A 81	-20.987	-8.173	38.347	1.00	28.18	O
ATOM	616	C	GLU A 81	-17.539	-8.162	34.057	1.00	18.89	C
ATOM	617	O	GLU A 81	-17.216	-7.347	33.207	1.00	18.49	O
ATOM	618	N	ASP A 82	-16.653	-8.701	34.901	1.00	17.78	N
ATOM	619	CA	ASP A 82	-15.214	-8.323	34.886	1.00	17.00	C
ATOM	620	CB	ASP A 82	-14.482	-8.785	36.155	1.00	17.17	C
ATOM	621	CG	ASP A 82	-15.111	-8.289	37.439	1.00	16.58	C
ATOM	622	OD1	ASP A 82	-15.840	-7.284	37.457	1.00	14.92	O
ATOM	623	OD2	ASP A 82	-14.840	-8.934	38.461	1.00	18.22	O
ATOM	624	C	ASP A 82	-14.413	-8.862	33.688	1.00	16.30	C
ATOM	625	O	ASP A 82	-13.234	-8.551	33.523	1.00	15.40	O
ATOM	626	N	PHE A 83	-15.051	-9.685	32.872	1.00	15.89	N
ATOM	627	CA	PHE A 83	-14.360	-10.330	31.779	1.00	15.97	C
ATOM	628	CB	PHE A 83	-14.933	-11.724	31.562	1.00	15.83	C
ATOM	629	CG	PHE A 83	-14.467	-12.700	32.576	1.00	15.18	C
ATOM	630	CD1	PHE A 83	-13.257	-13.344	32.417	1.00	14.82	C

ATOM	631	CE1 PHE A	83	-12.819	-14.246	33.357	1.00	15.24	C
ATOM	632	CZ PHE A	83	-13.585	-14.492	34.481	1.00	15.49	C
ATOM	633	CE2 PHE A	83	-14.788	-13.833	34.658	1.00	14.67	C
ATOM	634	CD2 PHE A	83	-15.219	-12.949	33.707	1.00	14.79	C
ATOM	635	C PHE A	83	-14.380	-9.499	30.501	1.00	16.13	C
ATOM	636	O PHE A	83	-15.312	-9.590	29.693	1.00	16.36	O
ATOM	637	N ALA A	84	-13.337	-8.694	30.329	1.00	15.79	N
ATOM	638	CA ALA A	84	-13.305	-7.693	29.269	1.00	15.27	C
ATOM	639	CB ALA A	84	-13.999	-6.435	29.730	1.00	15.07	C
ATOM	640	C ALA A	84	-11.852	-7.424	28.919	1.00	15.28	C
ATOM	641	O ALA A	84	-10.980	-8.286	29.163	1.00	15.64	O
ATOM	642	N THR A	85	-11.574	-6.265	28.335	1.00	14.74	N
ATOM	643	CA THR A	85	-10.193	-5.919	28.018	1.00	14.82	C
ATOM	644	CB THR A	85	-10.039	-5.517	26.538	1.00	14.39	C
ATOM	645	OG1 THR A	85	-10.640	-6.528	25.719	1.00	14.32	O
ATOM	646	CG2 THR A	85	-8.571	-5.384	26.140	1.00	13.48	C
ATOM	647	C THR A	85	-9.709	-4.838	28.972	1.00	15.28	C
ATOM	648	O THR A	85	-10.466	-3.956	29.328	1.00	15.83	O
ATOM	649	N TYR A	86	-8.463	-4.924	29.418	1.00	15.85	N
ATOM	650	CA TYR A	86	-7.938	-3.925	30.345	1.00	16.12	C
ATOM	651	CB TYR A	86	-7.564	-4.571	31.677	1.00	15.87	C
ATOM	652	CG TYR A	86	-8.779	-5.064	32.424	1.00	16.63	C
ATOM	653	CD1 TYR A	86	-9.312	-6.342	32.174	1.00	16.68	C
ATOM	654	CE1 TYR A	86	-10.445	-6.793	32.830	1.00	15.99	C
ATOM	655	CZ TYR A	86	-11.067	-5.956	33.748	1.00	16.53	C
ATOM	656	OH TYR A	86	-12.194	-6.390	34.410	1.00	16.89	O
ATOM	657	CE2 TYR A	86	-10.562	-4.683	34.007	1.00	16.72	C
ATOM	658	CD2 TYR A	86	-9.432	-4.244	33.347	1.00	16.60	C
ATOM	659	C TYR A	86	-6.750	-3.202	29.730	1.00	16.63	C
ATOM	660	O TYR A	86	-5.854	-3.837	29.148	1.00	16.74	O
ATOM	661	N TYR A	87	-6.765	-1.870	29.835	1.00	16.62	N
ATOM	662	CA TYR A	87	-5.624	-1.045	29.406	1.00	16.19	C
ATOM	663	CB TYR A	87	-6.023	-0.064	28.289	1.00	15.65	C
ATOM	664	CG TYR A	87	-6.547	-0.745	27.047	1.00	14.82	C
ATOM	665	CD1 TYR A	87	-5.672	-1.228	26.061	1.00	13.49	C
ATOM	666	CE1 TYR A	87	-6.160	-1.844	24.924	1.00	13.82	C
ATOM	667	CZ TYR A	87	-7.542	-1.995	24.772	1.00	14.43	C
ATOM	668	OH TYR A	87	-8.068	-2.621	23.662	1.00	14.97	O
ATOM	669	CE2 TYR A	87	-8.413	-1.529	25.741	1.00	12.85	C
ATOM	670	CD2 TYR A	87	-7.915	-0.904	26.856	1.00	12.83	C
ATOM	671	C TYR A	87	-4.996	-0.288	30.578	1.00	16.10	C
ATOM	672	O TYR A	87	-5.700	0.198	31.475	1.00	15.84	O
ATOM	673	N CYS A	88	-3.670	-0.215	30.567	1.00	15.67	N
ATOM	674	CA CYS A	88	-2.973	0.651	31.480	1.00	16.05	C
ATOM	675	CB CYS A	88	-1.832	-0.105	32.173	1.00	16.01	C
ATOM	676	SG CYS A	88	-0.458	-0.416	31.124	1.00	17.37	S
ATOM	677	C CYS A	88	-2.470	1.880	30.728	1.00	15.97	C
ATOM	678	O CYS A	88	-2.153	1.809	29.552	1.00	16.04	O
ATOM	679	N LEU A	89	-2.394	3.009	31.415	1.00	16.50	N
ATOM	680	CA LEU A	89	-2.002	4.278	30.807	1.00	16.62	C
ATOM	681	CB LEU A	89	-3.229	5.185	30.730	1.00	16.60	C
ATOM	682	CG LEU A	89	-3.025	6.671	30.449	1.00	17.20	C
ATOM	683	CD1 LEU A	89	-2.670	6.930	28.985	1.00	17.31	C
ATOM	684	CD2 LEU A	89	-4.265	7.438	30.830	1.00	16.26	C
ATOM	685	C LEU A	89	-0.954	4.962	31.668	1.00	16.89	C
ATOM	686	O LEU A	89	-1.120	5.057	32.892	1.00	17.83	O
ATOM	687	N GLN A	90	0.124	5.444	31.062	1.00	16.49	N

ATOM	688	CA	GLN	A	90	1.002	6.342	31.801	1.00	16.13	C
ATOM	689	CB	GLN	A	90	2.481	6.158	31.447	1.00	16.25	C
ATOM	690	CG	GLN	A	90	2.867	6.600	30.030	1.00	16.77	C
ATOM	691	CD	GLN	A	90	3.225	8.073	29.911	1.00	16.36	C
ATOM	692	OE1	GLN	A	90	3.382	8.785	30.904	1.00	14.59	O
ATOM	693	NE2	GLN	A	90	3.365	8.530	28.679	1.00	17.54	N
ATOM	694	C	GLN	A	90	0.543	7.775	31.583	1.00	15.77	C
ATOM	695	O	GLN	A	90	0.123	8.148	30.494	1.00	15.48	O
ATOM	696	N	SER	A	91	0.604	8.565	32.644	1.00	15.72	N
ATOM	697	CA	SER	A	91	0.217	9.966	32.577	1.00	15.24	C
ATOM	698	CB	SER	A	91	-1.163	10.183	33.201	1.00	15.09	C
ATOM	699	OG	SER	A	91	-1.195	9.696	34.524	1.00	14.66	O
ATOM	700	C	SER	A	91	1.290	10.786	33.267	1.00	14.97	C
ATOM	701	O	SER	A	91	0.998	11.738	33.977	1.00	15.50	O
ATOM	702	N	ASP	A	92	2.539	10.386	33.044	1.00	14.61	N
ATOM	703	CA	ASP	A	92	3.716	11.135	33.461	1.00	14.15	C
ATOM	704	CB	ASP	A	92	4.905	10.197	33.639	1.00	14.00	C
ATOM	705	CG	ASP	A	92	6.143	10.919	34.108	1.00	15.15	C
ATOM	706	OD1	ASP	A	92	7.187	10.834	33.420	1.00	17.45	O
ATOM	707	OD2	ASP	A	92	6.067	11.593	35.158	1.00	15.09	O
ATOM	708	C	ASP	A	92	4.098	12.260	32.490	1.00	13.57	C
ATOM	709	O	ASP	A	92	4.402	13.369	32.926	1.00	14.00	O
ATOM	710	N	ASN	A	93	4.091	11.979	31.191	1.00	12.85	N
ATOM	711	CA	ASN	A	93	4.588	12.930	30.190	1.00	12.72	C
ATOM	712	CB	ASN	A	93	6.106	12.842	30.125	1.00	11.96	C
ATOM	713	CG	ASN	A	93	6.586	11.518	29.564	1.00	11.80	C
ATOM	714	OD1	ASN	A	93	7.121	10.689	30.292	1.00	14.91	O
ATOM	715	ND2	ASN	A	93	6.395	11.308	28.275	1.00	9.04	N
ATOM	716	C	ASN	A	93	3.999	12.749	28.767	1.00	13.08	C
ATOM	717	O	ASN	A	93	3.502	11.664	28.415	1.00	13.85	O
ATOM	718	N	LEU	A	94	4.088	13.792	27.940	1.00	12.45	N
ATOM	719	CA	LEU	A	94	3.518	13.749	26.590	1.00	11.42	C
ATOM	720	CB	LEU	A	94	3.235	15.159	26.062	1.00	11.36	C
ATOM	721	CG	LEU	A	94	1.839	15.759	26.292	1.00	11.82	C
ATOM	722	CD1	LEU	A	94	0.947	15.009	27.329	1.00	11.22	C
ATOM	723	CD2	LEU	A	94	1.970	17.246	26.622	1.00	12.40	C
ATOM	724	C	LEU	A	94	4.448	13.033	25.654	1.00	10.82	C
ATOM	725	O	LEU	A	94	5.665	13.212	25.737	1.00	10.93	O
ATOM	726	N	PRO	A	95	3.886	12.195	24.765	1.00	10.45	N
ATOM	727	CA	PRO	A	95	2.447	11.873	24.690	1.00	9.93	C
ATOM	728	CB	PRO	A	95	2.294	11.323	23.278	1.00	9.94	C
ATOM	729	CG	PRO	A	95	3.655	10.766	22.927	1.00	9.73	C
ATOM	730	CD	PRO	A	95	4.679	11.497	23.731	1.00	9.96	C
ATOM	731	C	PRO	A	95	2.022	10.793	25.683	1.00	9.78	C
ATOM	732	O	PRO	A	95	2.804	9.887	25.986	1.00	9.05	O
ATOM	733	N	PHE	A	96	0.789	10.895	26.184	1.00	9.62	N
ATOM	734	CA	PHE	A	96	0.182	9.803	26.939	1.00	9.26	C
ATOM	735	CB	PHE	A	96	-1.293	10.068	27.146	1.00	9.27	C
ATOM	736	CG	PHE	A	96	-1.580	11.267	28.005	1.00	9.59	C
ATOM	737	CD1	PHE	A	96	-1.659	11.147	29.386	1.00	8.25	C
ATOM	738	CE1	PHE	A	96	-1.926	12.250	30.196	1.00	8.69	C
ATOM	739	CZ	PHE	A	96	-2.128	13.503	29.626	1.00	10.64	C
ATOM	740	CE2	PHE	A	96	-2.045	13.650	28.237	1.00	11.86	C
ATOM	741	CD2	PHE	A	96	-1.766	12.523	27.432	1.00	11.07	C
ATOM	742	C	PHE	A	96	0.354	8.528	26.134	1.00	9.18	C
ATOM	743	O	PHE	A	96	0.194	8.550	24.916	1.00	9.99	O
ATOM	744	N	THR	A	97	0.752	7.438	26.783	1.00	8.80	N

ATOM	745	CA	THR	A	97	0.875	6.162	26.093	1.00	8.48	C
ATOM	746	CB	THR	A	97	2.343	5.762	25.736	1.00	8.33	C
ATOM	747	OG1	THR	A	97	3.128	5.634	26.916	1.00	8.17	O
ATOM	748	CG2	THR	A	97	3.020	6.770	24.783	1.00	7.51	C
ATOM	749	C	THR	A	97	0.158	5.057	26.856	1.00	9.23	C
ATOM	750	O	THR	A	97	0.046	5.082	28.084	1.00	9.50	O
ATOM	751	N	PHE	A	98	-0.337	4.088	26.099	1.00	10.01	N
ATOM	752	CA	PHE	A	98	-1.175	3.029	26.607	1.00	10.39	C
ATOM	753	CB	PHE	A	98	-2.436	2.957	25.771	1.00	9.87	C
ATOM	754	CG	PHE	A	98	-3.458	3.988	26.133	1.00	10.77	C
ATOM	755	CD1	PHE	A	98	-3.436	5.258	25.545	1.00	11.66	C
ATOM	756	CE1	PHE	A	98	-4.419	6.222	25.879	1.00	12.01	C
ATOM	757	CZ	PHE	A	98	-5.420	5.907	26.808	1.00	10.74	C
ATOM	758	CE2	PHE	A	98	-5.436	4.653	27.395	1.00	10.32	C
ATOM	759	CD2	PHE	A	98	-4.459	3.697	27.058	1.00	10.06	C
ATOM	760	C	PHE	A	98	-0.459	1.710	26.519	1.00	11.13	C
ATOM	761	O	PHE	A	98	0.487	1.575	25.755	1.00	11.57	O
ATOM	762	N	GLY	A	99	-0.905	0.744	27.319	1.00	12.06	N
ATOM	763	CA	GLY	A	99	-0.477	-0.647	27.188	1.00	12.77	C
ATOM	764	C	GLY	A	99	-1.320	-1.282	26.114	1.00	13.05	C
ATOM	765	O	GLY	A	99	-2.424	-0.805	25.853	1.00	13.09	O
ATOM	766	N	GLN	A	100	-0.794	-2.342	25.491	1.00	13.76	N
ATOM	767	CA	GLN	A	100	-1.447	-3.029	24.365	1.00	14.60	C
ATOM	768	CB	GLN	A	100	-0.552	-4.130	23.787	1.00	15.19	C
ATOM	769	CG	GLN	A	100	0.803	-3.638	23.207	1.00	18.95	C
ATOM	770	CD	GLN	A	100	1.998	-3.824	24.168	1.00	23.16	C
ATOM	771	OE1	GLN	A	100	3.016	-4.418	23.780	1.00	24.58	O
ATOM	772	NE2	GLN	A	100	1.873	-3.328	25.423	1.00	21.52	N
ATOM	773	C	GLN	A	100	-2.790	-3.624	24.756	1.00	14.49	C
ATOM	774	O	GLN	A	100	-3.661	-3.812	23.909	1.00	14.79	O
ATOM	775	N	GLY	A	101	-2.951	-3.915	26.041	1.00	14.05	N
ATOM	776	CA	GLY	A	101	-4.193	-4.445	26.538	1.00	14.43	C
ATOM	777	C	GLY	A	101	-4.098	-5.890	26.989	1.00	14.80	C
ATOM	778	O	GLY	A	101	-3.138	-6.593	26.680	1.00	14.61	O
ATOM	779	N	THR	A	102	-5.109	-6.313	27.739	1.00	15.06	N
ATOM	780	CA	THR	A	102	-5.226	-7.682	28.214	1.00	15.52	C
ATOM	781	CB	THR	A	102	-4.786	-7.814	29.688	1.00	15.20	C
ATOM	782	OG1	THR	A	102	-3.394	-7.519	29.799	1.00	14.05	O
ATOM	783	CG2	THR	A	102	-5.039	-9.210	30.183	1.00	15.03	C
ATOM	784	C	THR	A	102	-6.690	-8.090	28.117	1.00	16.13	C
ATOM	785	O	THR	A	102	-7.543	-7.511	28.821	1.00	16.26	O
ATOM	786	N	LYS	A	103	-6.979	-9.045	27.229	1.00	16.14	N
ATOM	787	CA	LYS	A	103	-8.299	-9.649	27.156	1.00	16.45	C
ATOM	788	CB	LYS	A	103	-8.565	-10.157	25.742	1.00	16.97	C
ATOM	789	CG	LYS	A	103	-10.042	-10.454	25.400	1.00	17.27	C
ATOM	790	CD	LYS	A	103	-10.238	-10.298	23.863	1.00	21.41	C
ATOM	791	CE	LYS	A	103	-11.590	-10.848	23.336	1.00	22.10	C
ATOM	792	NZ	LYS	A	103	-12.728	-9.853	23.390	1.00	23.67	N
ATOM	793	C	LYS	A	103	-8.445	-10.790	28.182	1.00	16.44	C
ATOM	794	O	LYS	A	103	-7.763	-11.831	28.094	1.00	15.74	O
ATOM	795	N	LEU	A	104	-9.347	-10.582	29.142	1.00	16.21	N
ATOM	796	CA	LEU	A	104	-9.752	-11.626	30.083	1.00	16.21	C
ATOM	797	CB	LEU	A	104	-10.271	-11.003	31.367	1.00	15.77	C
ATOM	798	CG	LEU	A	104	-9.353	-10.892	32.561	1.00	16.04	C
ATOM	799	CD1	LEU	A	104	-10.147	-10.328	33.730	1.00	16.13	C
ATOM	800	CD2	LEU	A	104	-8.782	-12.265	32.903	1.00	17.75	C
ATOM	801	C	LEU	A	104	-10.856	-12.523	29.539	1.00	16.44	C

ATOM	802	O	LEU A 104	-11.935	-12.053	29.190	1.00	16.83	O
ATOM	803	N	GLU A 105	-10.606	-13.818	29.521	1.00	16.75	N
ATOM	804	CA	GLU A 105	-11.591	-14.770	29.034	1.00	17.35	C
ATOM	805	CB	GLU A 105	-11.005	-15.542	27.852	1.00	17.25	C
ATOM	806	CG	GLU A 105	-11.947	-16.528	27.204	1.00	17.86	C
ATOM	807	CD	GLU A 105	-11.247	-17.798	26.771	1.00	17.96	C
ATOM	808	OE1	GLU A 105	-11.353	-18.149	25.585	1.00	19.36	O
ATOM	809	OE2	GLU A 105	-10.597	-18.454	27.612	1.00	16.75	O
ATOM	810	C	GLU A 105	-12.075	-15.734	30.141	1.00	17.36	C
ATOM	811	O	GLU A 105	-11.344	-16.045	31.084	1.00	17.98	O
ATOM	812	N	ILE A 106	-13.311	-16.199	30.015	1.00	16.99	N
ATOM	813	CA	ILE A 106	-13.893	-17.122	30.970	1.00	16.72	C
ATOM	814	CB	ILE A 106	-15.447	-16.988	30.970	1.00	17.47	C
ATOM	815	CG1	ILE A 106	-15.862	-15.500	31.063	1.00	17.01	C
ATOM	816	CD1	ILE A 106	-17.324	-15.228	31.483	1.00	16.88	C
ATOM	817	CG2	ILE A 106	-16.105	-17.923	32.044	1.00	17.20	C
ATOM	818	C	ILE A 106	-13.467	-18.568	30.657	1.00	16.39	C
ATOM	819	O	ILE A 106	-13.773	-19.120	29.607	1.00	16.22	O
ATOM	820	N	LYS A 107	-12.738	-19.162	31.582	1.00	16.10	N
ATOM	821	CA	LYS A 107	-12.325	-20.544	31.487	1.00	15.65	C
ATOM	822	CB	LYS A 107	-11.266	-20.830	32.563	1.00	15.72	C
ATOM	823	CG	LYS A 107	-10.560	-22.190	32.499	1.00	16.00	C
ATOM	824	CD	LYS A 107	-9.567	-22.369	33.672	1.00	16.06	C
ATOM	825	CE	LYS A 107	-8.356	-21.422	33.577	1.00	17.92	C
ATOM	826	NZ	LYS A 107	-7.760	-21.312	32.161	1.00	19.37	N
ATOM	827	C	LYS A 107	-13.549	-21.432	31.685	1.00	15.32	C
ATOM	828	O	LYS A 107	-14.424	-21.138	32.499	1.00	14.77	O
ATOM	829	N	ARG A 108	-13.605	-22.509	30.913	1.00	15.23	N
ATOM	830	CA	ARG A 108	-14.626	-23.517	31.072	1.00	15.55	C
ATOM	831	CB	ARG A 108	-15.953	-23.085	30.428	1.00	15.59	C
ATOM	832	CG	ARG A 108	-15.924	-22.813	28.918	1.00	16.15	C
ATOM	833	CD	ARG A 108	-16.357	-24.017	28.110	1.00	15.69	C
ATOM	834	NE	ARG A 108	-17.806	-24.217	28.134	1.00	16.78	N
ATOM	835	CZ	ARG A 108	-18.416	-25.408	28.092	1.00	17.79	C
ATOM	836	NH1	ARG A 108	-17.721	-26.552	28.052	1.00	15.20	N
ATOM	837	NH2	ARG A 108	-19.746	-25.451	28.116	1.00	18.37	N
ATOM	838	C	ARG A 108	-14.147	-24.862	30.543	1.00	15.79	C
ATOM	839	O	ARG A 108	-13.057	-24.982	29.992	1.00	15.96	O
ATOM	840	N	THR A 109	-14.968	-25.874	30.767	1.00	16.21	N
ATOM	841	CA	THR A 109	-14.745	-27.237	30.315	1.00	16.08	C
ATOM	842	CB	THR A 109	-16.001	-28.048	30.748	1.00	16.01	C
ATOM	843	OG1	THR A 109	-15.837	-28.443	32.112	1.00	15.77	O
ATOM	844	CG2	THR A 109	-16.285	-29.270	29.897	1.00	16.37	C
ATOM	845	C	THR A 109	-14.552	-27.232	28.798	1.00	16.35	C
ATOM	846	O	THR A 109	-15.242	-26.496	28.088	1.00	17.13	O
ATOM	847	N	VAL A 110	-13.613	-28.026	28.294	1.00	15.95	N
ATOM	848	CA	VAL A 110	-13.500	-28.238	26.846	1.00	15.48	C
ATOM	849	CB	VAL A 110	-12.329	-29.172	26.474	1.00	15.23	C
ATOM	850	CG1	VAL A 110	-12.637	-30.602	26.842	1.00	14.34	C
ATOM	851	CG2	VAL A 110	-12.019	-29.063	25.007	1.00	14.12	C
ATOM	852	C	VAL A 110	-14.813	-28.726	26.201	1.00	16.02	C
ATOM	853	O	VAL A 110	-15.509	-29.602	26.725	1.00	15.85	O
ATOM	854	N	ALA A 111	-15.142	-28.124	25.064	1.00	16.72	N
ATOM	855	CA	ALA A 111	-16.312	-28.490	24.275	1.00	16.77	C
ATOM	856	CB	ALA A 111	-17.391	-27.427	24.417	1.00	16.64	C
ATOM	857	C	ALA A 111	-15.894	-28.645	22.813	1.00	16.79	C
ATOM	858	O	ALA A 111	-15.332	-27.708	22.222	1.00	16.85	O

ATOM	859	N	ALA A 112	-16.154	-29.828	22.247	1.00	16.60	N
ATOM	860	CA	ALA A 112	-15.907	-30.092	20.827	1.00	16.27	C
ATOM	861	CB	ALA A 112	-16.000	-31.560	20.542	1.00	16.08	C
ATOM	862	C	ALA A 112	-16.886	-29.319	19.952	1.00	16.24	C
ATOM	863	O	ALA A 112	-18.044	-29.125	20.326	1.00	16.11	O
ATOM	864	N	PRO A 113	-16.419	-28.843	18.790	1.00	16.46	N
ATOM	865	CA	PRO A 113	-17.342	-28.120	17.916	1.00	16.67	C
ATOM	866	CB	PRO A 113	-16.411	-27.404	16.911	1.00	16.67	C
ATOM	867	CG	PRO A 113	-15.094	-28.066	17.002	1.00	16.23	C
ATOM	868	CD	PRO A 113	-15.052	-28.928	18.239	1.00	16.50	C
ATOM	869	C	PRO A 113	-18.279	-29.061	17.180	1.00	16.69	C
ATOM	870	O	PRO A 113	-17.897	-30.177	16.861	1.00	16.83	O
ATOM	871	N	SER A 114	-19.508	-28.618	16.950	1.00	16.94	N
ATOM	872	CA	SER A 114	-20.373	-29.238	15.957	1.00	16.94	C
ATOM	873	CB	SER A 114	-21.837	-29.001	16.288	1.00	16.86	C
ATOM	874	OG	SER A 114	-22.310	-30.041	17.101	1.00	19.32	O
ATOM	875	C	SER A 114	-20.052	-28.589	14.612	1.00	16.67	C
ATOM	876	O	SER A 114	-20.069	-27.361	14.467	1.00	16.27	O
ATOM	877	N	VAL A 115	-19.764	-29.423	13.630	1.00	16.27	N
ATOM	878	CA	VAL A 115	-19.381	-28.928	12.334	1.00	15.91	C
ATOM	879	CB	VAL A 115	-18.082	-29.603	11.886	1.00	15.83	C
ATOM	880	CG1	VAL A 115	-17.479	-28.866	10.719	1.00	15.57	C
ATOM	881	CG2	VAL A 115	-17.114	-29.641	13.051	1.00	15.11	C
ATOM	882	C	VAL A 115	-20.518	-29.150	11.336	1.00	15.79	C
ATOM	883	O	VAL A 115	-21.147	-30.215	11.342	1.00	15.70	O
ATOM	884	N	PHE A 116	-20.778	-28.133	10.509	1.00	15.36	N
ATOM	885	CA	PHE A 116	-21.741	-28.207	9.406	1.00	14.98	C
ATOM	886	CB	PHE A 116	-23.026	-27.474	9.755	1.00	14.78	C
ATOM	887	CG	PHE A 116	-23.661	-27.926	11.027	1.00	15.25	C
ATOM	888	CD1	PHE A 116	-24.497	-29.056	11.048	1.00	15.21	C
ATOM	889	CE1	PHE A 116	-25.110	-29.470	12.234	1.00	15.93	C
ATOM	890	CZ	PHE A 116	-24.887	-28.752	13.425	1.00	16.24	C
ATOM	891	CE2	PHE A 116	-24.052	-27.621	13.405	1.00	16.11	C
ATOM	892	CD2	PHE A 116	-23.450	-27.216	12.209	1.00	14.36	C
ATOM	893	C	PHE A 116	-21.150	-27.549	8.166	1.00	15.10	C
ATOM	894	O	PHE A 116	-20.472	-26.531	8.251	1.00	15.19	O
ATOM	895	N	ILE A 117	-21.412	-28.129	7.007	1.00	15.30	N
ATOM	896	CA	ILE A 117	-20.926	-27.553	5.759	1.00	15.32	C
ATOM	897	CB	ILE A 117	-19.892	-28.488	5.037	1.00	15.20	C
ATOM	898	CG1	ILE A 117	-19.292	-27.801	3.807	1.00	14.21	C
ATOM	899	CD1	ILE A 117	-17.985	-28.408	3.341	1.00	14.16	C
ATOM	900	CG2	ILE A 117	-20.479	-29.882	4.750	1.00	14.25	C
ATOM	901	C	ILE A 117	-22.130	-27.211	4.899	1.00	16.43	C
ATOM	902	O	ILE A 117	-23.081	-27.997	4.803	1.00	16.36	O
ATOM	903	N	PHE A 118	-22.110	-26.019	4.319	1.00	17.40	N
ATOM	904	CA	PHE A 118	-23.231	-25.527	3.542	1.00	18.52	C
ATOM	905	CB	PHE A 118	-23.745	-24.206	4.124	1.00	18.66	C
ATOM	906	CG	PHE A 118	-24.409	-24.331	5.478	1.00	18.82	C
ATOM	907	CD1	PHE A 118	-25.711	-24.811	5.591	1.00	17.71	C
ATOM	908	CE1	PHE A 118	-26.334	-24.917	6.830	1.00	16.99	C
ATOM	909	CZ	PHE A 118	-25.673	-24.530	7.975	1.00	17.86	C
ATOM	910	CE2	PHE A 118	-24.373	-24.037	7.892	1.00	19.87	C
ATOM	911	CD2	PHE A 118	-23.743	-23.934	6.638	1.00	19.81	C
ATOM	912	C	PHE A 118	-22.760	-25.292	2.122	1.00	19.52	C
ATOM	913	O	PHE A 118	-21.903	-24.433	1.903	1.00	20.12	O
ATOM	914	N	PRO A 119	-23.294	-26.063	1.148	1.00	20.45	N
ATOM	915	CA	PRO A 119	-22.996	-25.801	-0.271	1.00	20.73	C

ATOM	916	CB	PRO A 119	-23.771	-26.906	-1.008	1.00	20.58	C
ATOM	917	CG	PRO A 119	-24.786	-27.403	-0.040	1.00	20.33	C
ATOM	918	CD	PRO A 119	-24.193	-27.226	1.317	1.00	20.49	C
ATOM	919	C	PRO A 119	-23.514	-24.434	-0.692	1.00	21.10	C
ATOM	920	O	PRO A 119	-24.482	-23.962	-0.096	1.00	20.92	O
ATOM	921	N	PRO A 120	-22.883	-23.797	-1.704	1.00	21.71	N
ATOM	922	CA	PRO A 120	-23.402	-22.532	-2.229	1.00	22.41	C
ATOM	923	CB	PRO A 120	-22.456	-22.203	-3.391	1.00	22.44	C
ATOM	924	CG	PRO A 120	-21.745	-23.448	-3.700	1.00	21.83	C
ATOM	925	CD	PRO A 120	-21.668	-24.217	-2.415	1.00	21.70	C
ATOM	926	C	PRO A 120	-24.788	-22.751	-2.767	1.00	23.27	C
ATOM	927	O	PRO A 120	-25.069	-23.832	-3.255	1.00	23.91	O
ATOM	928	N	SER A 121	-25.650	-21.749	-2.667	1.00	24.73	N
ATOM	929	CA	SER A 121	-27.029	-21.850	-3.156	1.00	26.00	C
ATOM	930	CB	SER A 121	-27.898	-20.759	-2.524	1.00	26.11	C
ATOM	931	OG	SER A 121	-27.402	-19.462	-2.831	1.00	25.84	O
ATOM	932	C	SER A 121	-27.097	-21.724	-4.671	1.00	26.83	C
ATOM	933	O	SER A 121	-26.219	-21.124	-5.276	1.00	26.59	O
ATOM	934	N	ASP A 122	-28.152	-22.270	-5.275	1.00	28.54	N
ATOM	935	CA	ASP A 122	-28.354	-22.154	-6.722	1.00	30.21	C
ATOM	936	CB	ASP A 122	-29.549	-22.998	-7.190	1.00	30.65	C
ATOM	937	CG	ASP A 122	-29.272	-24.511	-7.144	1.00	32.31	C
ATOM	938	OD1	ASP A 122	-30.253	-25.275	-7.282	1.00	33.19	O
ATOM	939	OD2	ASP A 122	-28.099	-24.938	-6.972	1.00	32.88	O
ATOM	940	C	ASP A 122	-28.527	-20.692	-7.149	1.00	30.88	C
ATOM	941	O	ASP A 122	-28.008	-20.282	-8.205	1.00	31.05	O
ATOM	942	N	GLU A 123	-29.234	-19.908	-6.324	1.00	31.50	N
ATOM	943	CA	GLU A 123	-29.425	-18.471	-6.594	1.00	32.16	C
ATOM	944	CB	GLU A 123	-30.505	-17.841	-5.709	1.00	32.00	C
ATOM	945	CG	GLU A 123	-30.509	-18.296	-4.254	1.00	34.07	C
ATOM	946	CD	GLU A 123	-31.421	-19.499	-3.975	1.00	35.55	C
ATOM	947	OE1	GLU A 123	-31.078	-20.641	-4.394	1.00	37.00	O
ATOM	948	OE2	GLU A 123	-32.464	-19.296	-3.303	1.00	33.87	O
ATOM	949	C	GLU A 123	-28.122	-17.647	-6.593	1.00	32.40	C
ATOM	950	O	GLU A 123	-27.989	-16.719	-7.400	1.00	32.63	O
ATOM	951	N	GLN A 124	-27.158	-17.988	-5.730	1.00	32.47	N
ATOM	952	CA	GLN A 124	-25.840	-17.331	-5.794	1.00	32.58	C
ATOM	953	CB	GLN A 124	-24.958	-17.621	-4.573	1.00	32.58	C
ATOM	954	CG	GLN A 124	-23.754	-16.663	-4.492	1.00	31.78	C
ATOM	955	CD	GLN A 124	-22.659	-17.116	-3.556	1.00	31.35	C
ATOM	956	OE1	GLN A 124	-22.696	-18.223	-3.011	1.00	32.12	O
ATOM	957	NE2	GLN A 124	-21.663	-16.256	-3.368	1.00	30.32	N
ATOM	958	C	GLN A 124	-25.087	-17.695	-7.067	1.00	32.84	C
ATOM	959	O	GLN A 124	-24.535	-16.819	-7.752	1.00	32.86	O
ATOM	960	N	LEU A 125	-25.062	-18.989	-7.369	1.00	33.03	N
ATOM	961	CA	LEU A 125	-24.482	-19.473	-8.615	1.00	33.46	C
ATOM	962	CB	LEU A 125	-24.719	-20.980	-8.780	1.00	33.23	C
ATOM	963	CG	LEU A 125	-23.664	-22.006	-8.336	1.00	32.56	C
ATOM	964	CD1	LEU A 125	-22.291	-21.355	-8.047	1.00	32.77	C
ATOM	965	CD2	LEU A 125	-24.131	-22.860	-7.170	1.00	29.91	C
ATOM	966	C	LEU A 125	-25.005	-18.692	-9.837	1.00	34.01	C
ATOM	967	O	LEU A 125	-24.231	-18.385	-10.753	1.00	34.01	O
ATOM	968	N	LYS A 126	-26.300	-18.359	-9.826	1.00	34.40	N
ATOM	969	CA	LYS A 126	-26.914	-17.549	-10.879	1.00	35.11	C
ATOM	970	CB	LYS A 126	-28.321	-17.082	-10.473	1.00	35.82	C
ATOM	971	CG	LYS A 126	-29.466	-18.125	-10.605	1.00	37.85	C
ATOM	972	CD	LYS A 126	-29.841	-18.428	-12.059	1.00	41.85	C

ATOM	973	CE	LYS A 126	-29.969	-17.149	-12.913	1.00	44.36	C
ATOM	974	NZ	LYS A 126	-29.917	-17.443	-14.385	1.00	45.76	N
ATOM	975	C	LYS A 126	-26.086	-16.320	-11.242	1.00	34.94	C
ATOM	976	O	LYS A 126	-26.060	-15.910	-12.409	1.00	35.15	O
ATOM	977	N	SER A 127	-25.410	-15.736	-10.250	1.00	34.49	N
ATOM	978	CA	SER A 127	-24.678	-14.486	-10.456	1.00	33.78	C
ATOM	979	CB	SER A 127	-25.040	-13.463	-9.387	1.00	33.77	C
ATOM	980	OG	SER A 127	-24.790	-13.993	-8.094	1.00	35.03	O
ATOM	981	C	SER A 127	-23.171	-14.666	-10.521	1.00	33.26	C
ATOM	982	O	SER A 127	-22.433	-13.681	-10.461	1.00	33.68	O
ATOM	983	N	GLY A 128	-22.709	-15.910	-10.638	1.00	32.28	N
ATOM	984	CA	GLY A 128	-21.323	-16.168	-11.044	1.00	31.17	C
ATOM	985	C	GLY A 128	-20.305	-16.388	-9.945	1.00	30.54	C
ATOM	986	O	GLY A 128	-19.088	-16.347	-10.183	1.00	30.88	O
ATOM	987	N	THR A 129	-20.794	-16.640	-8.739	1.00	29.57	N
ATOM	988	CA	THR A 129	-19.926	-16.790	-7.581	1.00	28.22	C
ATOM	989	CB	THR A 129	-19.779	-15.444	-6.817	1.00	28.56	C
ATOM	990	OG1	THR A 129	-19.386	-14.422	-7.739	1.00	29.03	O
ATOM	991	CG2	THR A 129	-18.727	-15.535	-5.708	1.00	28.12	C
ATOM	992	C	THR A 129	-20.474	-17.874	-6.671	1.00	26.85	C
ATOM	993	O	THR A 129	-21.682	-18.054	-6.566	1.00	26.39	O
ATOM	994	N	ALA A 130	-19.565	-18.591	-6.025	1.00	25.51	N
ATOM	995	CA	ALA A 130	-19.917	-19.658	-5.105	1.00	24.37	C
ATOM	996	CB	ALA A 130	-19.399	-20.954	-5.629	1.00	24.59	C
ATOM	997	C	ALA A 130	-19.334	-19.395	-3.727	1.00	23.33	C
ATOM	998	O	ALA A 130	-18.129	-19.239	-3.573	1.00	23.78	O
ATOM	999	N	SER A 131	-20.174	-19.343	-2.712	1.00	21.87	N
ATOM	1000	CA	SER A 131	-19.633	-19.249	-1.376	1.00	20.64	C
ATOM	1001	CB	SER A 131	-20.256	-18.085	-0.617	1.00	20.42	C
ATOM	1002	OG	SER A 131	-19.969	-16.857	-1.256	1.00	19.93	O
ATOM	1003	C	SER A 131	-19.881	-20.574	-0.684	1.00	19.94	C
ATOM	1004	O	SER A 131	-21.026	-21.053	-0.646	1.00	19.84	O
ATOM	1005	N	VAL A 132	-18.810	-21.184	-0.179	1.00	18.74	N
ATOM	1006	CA	VAL A 132	-18.954	-22.395	0.616	1.00	18.27	C
ATOM	1007	CB	VAL A 132	-18.027	-23.537	0.132	1.00	18.39	C
ATOM	1008	CG1	VAL A 132	-18.500	-24.905	0.691	1.00	18.26	C
ATOM	1009	CG2	VAL A 132	-17.995	-23.582	-1.371	1.00	17.83	C
ATOM	1010	C	VAL A 132	-18.691	-22.078	2.093	1.00	18.03	C
ATOM	1011	O	VAL A 132	-17.595	-21.620	2.447	1.00	17.73	O
ATOM	1012	N	VAL A 133	-19.694	-22.329	2.942	1.00	17.36	N
ATOM	1013	CA	VAL A 133	-19.600	-21.998	4.365	1.00	16.91	C
ATOM	1014	CB	VAL A 133	-20.811	-21.178	4.842	1.00	17.16	C
ATOM	1015	CG1	VAL A 133	-20.725	-20.907	6.356	1.00	16.19	C
ATOM	1016	CG2	VAL A 133	-20.921	-19.848	4.033	1.00	16.57	C
ATOM	1017	C	VAL A 133	-19.436	-23.215	5.252	1.00	16.75	C
ATOM	1018	O	VAL A 133	-20.103	-24.218	5.069	1.00	16.74	O
ATOM	1019	N	CYS A 134	-18.523	-23.115	6.211	1.00	16.87	N
ATOM	1020	CA	CYS A 134	-18.324	-24.158	7.203	1.00	16.47	C
ATOM	1021	CB	CYS A 134	-16.930	-24.755	7.094	1.00	16.60	C
ATOM	1022	SG	CYS A 134	-16.657	-26.197	8.179	1.00	17.52	S
ATOM	1023	C	CYS A 134	-18.522	-23.559	8.579	1.00	16.23	C
ATOM	1024	O	CYS A 134	-17.927	-22.530	8.905	1.00	16.40	O
ATOM	1025	N	LEU A 135	-19.372	-24.201	9.372	1.00	15.91	N
ATOM	1026	CA	LEU A 135	-19.751	-23.717	10.694	1.00	15.74	C
ATOM	1027	CB	LEU A 135	-21.269	-23.711	10.818	1.00	15.58	C
ATOM	1028	CG	LEU A 135	-21.942	-23.381	12.141	1.00	15.54	C
ATOM	1029	CD1	LEU A 135	-21.502	-22.001	12.663	1.00	16.93	C

ATOM	1030	CD2 LEU A 135	-23.444	-23.435	11.983	1.00	15.12	C
ATOM	1031	C LEU A 135	-19.159	-24.622	11.766	1.00	15.93	C
ATOM	1032	O LEU A 135	-19.279	-25.843	11.693	1.00	16.32	O
ATOM	1033	N LEU A 136	-18.493	-24.021	12.738	1.00	15.63	N
ATOM	1034	CA LEU A 136	-18.058	-24.739	13.907	1.00	15.85	C
ATOM	1035	CB LEU A 136	-16.572	-24.532	14.159	1.00	15.69	C
ATOM	1036	CG LEU A 136	-15.491	-25.215	13.336	1.00	15.21	C
ATOM	1037	CD1 LEU A 136	-15.580	-24.832	11.883	1.00	15.63	C
ATOM	1038	CD2 LEU A 136	-14.151	-24.779	13.896	1.00	15.57	C
ATOM	1039	C LEU A 136	-18.861	-24.146	15.044	1.00	16.51	C
ATOM	1040	O LEU A 136	-18.661	-22.985	15.408	1.00	16.50	O
ATOM	1041	N ASN A 137	-19.777	-24.936	15.595	1.00	17.01	N
ATOM	1042	CA ASN A 137	-20.744	-24.415	16.537	1.00	17.68	C
ATOM	1043	CB ASN A 137	-22.133	-24.860	16.128	1.00	18.46	C
ATOM	1044	CG ASN A 137	-23.181	-23.861	16.517	1.00	22.06	C
ATOM	1045	OD1 ASN A 137	-23.175	-22.720	16.021	1.00	26.03	O
ATOM	1046	ND2 ASN A 137	-24.078	-24.254	17.438	1.00	23.76	N
ATOM	1047	C ASN A 137	-20.488	-24.788	17.994	1.00	17.52	C
ATOM	1048	O ASN A 137	-20.234	-25.959	18.300	1.00	18.04	O
ATOM	1049	N ASN A 138	-20.555	-23.779	18.870	1.00	16.80	N
ATOM	1050	CA ASN A 138	-20.406	-23.905	20.336	1.00	16.26	C
ATOM	1051	CB ASN A 138	-21.703	-24.370	21.006	1.00	16.15	C
ATOM	1052	CG ASN A 138	-22.918	-23.558	20.572	1.00	17.29	C
ATOM	1053	OD1 ASN A 138	-22.804	-22.419	20.107	1.00	17.14	O
ATOM	1054	ND2 ASN A 138	-24.096	-24.160	20.702	1.00	19.41	N
ATOM	1055	C ASN A 138	-19.215	-24.711	20.844	1.00	16.01	C
ATOM	1056	O ASN A 138	-19.373	-25.768	21.460	1.00	15.79	O
ATOM	1057	N PHE A 139	-18.015	-24.194	20.611	1.00	15.85	N
ATOM	1058	CA PHE A 139	-16.797	-24.886	21.041	1.00	15.56	C
ATOM	1059	CB PHE A 139	-15.931	-25.280	19.828	1.00	14.91	C
ATOM	1060	CG PHE A 139	-15.540	-24.123	18.966	1.00	14.01	C
ATOM	1061	CD1 PHE A 139	-16.353	-23.714	17.924	1.00	13.35	C
ATOM	1062	CE1 PHE A 139	-15.997	-22.640	17.132	1.00	13.14	C
ATOM	1063	CZ PHE A 139	-14.817	-21.951	17.387	1.00	14.27	C
ATOM	1064	CE2 PHE A 139	-13.994	-22.354	18.426	1.00	13.43	C
ATOM	1065	CD2 PHE A 139	-14.361	-23.435	19.203	1.00	13.73	C
ATOM	1066	C PHE A 139	-15.978	-24.084	22.061	1.00	15.85	C
ATOM	1067	O PHE A 139	-16.151	-22.855	22.217	1.00	15.53	O
ATOM	1068	N TYR A 140	-15.098	-24.805	22.758	1.00	15.83	N
ATOM	1069	CA TYR A 140	-14.113	-24.208	23.654	1.00	15.72	C
ATOM	1070	CB TYR A 140	-14.734	-23.879	25.015	1.00	15.19	C
ATOM	1071	CG TYR A 140	-13.796	-23.128	25.902	1.00	14.37	C
ATOM	1072	CD1 TYR A 140	-12.876	-23.807	26.699	1.00	13.65	C
ATOM	1073	CE1 TYR A 140	-11.983	-23.119	27.501	1.00	12.57	C
ATOM	1074	CZ TYR A 140	-12.018	-21.745	27.513	1.00	12.83	C
ATOM	1075	OH TYR A 140	-11.127	-21.077	28.305	1.00	14.69	O
ATOM	1076	CE2 TYR A 140	-12.918	-21.041	26.727	1.00	12.09	C
ATOM	1077	CD2 TYR A 140	-13.797	-21.733	25.927	1.00	13.30	C
ATOM	1078	C TYR A 140	-12.942	-25.179	23.801	1.00	16.03	C
ATOM	1079	O TYR A 140	-13.166	-26.382	23.869	1.00	15.68	O
ATOM	1080	N PRO A 141	-11.693	-24.670	23.833	1.00	16.64	N
ATOM	1081	CA PRO A 141	-11.310	-23.264	23.759	1.00	17.59	C
ATOM	1082	CB PRO A 141	-9.897	-23.265	24.329	1.00	17.04	C
ATOM	1083	CG PRO A 141	-9.348	-24.547	23.854	1.00	17.41	C
ATOM	1084	CD PRO A 141	-10.505	-25.536	23.933	1.00	16.64	C
ATOM	1085	C PRO A 141	-11.327	-22.726	22.326	1.00	18.67	C
ATOM	1086	O PRO A 141	-11.770	-23.404	21.413	1.00	19.06	O

ATOM	1087	N	ARG A 142	-10.817	-21.520	22.157	1.00	20.24	N
ATOM	1088	CA	ARG A 142	-10.993	-20.727	20.962	1.00	21.90	C
ATOM	1089	CB	ARG A 142	-10.693	-19.266	21.304	1.00	22.27	C
ATOM	1090	CG	ARG A 142	-11.456	-18.265	20.501	1.00	23.81	C
ATOM	1091	CD	ARG A 142	-10.537	-17.548	19.539	1.00	27.99	C
ATOM	1092	NE	ARG A 142	-11.012	-16.181	19.306	1.00	30.48	N
ATOM	1093	CZ	ARG A 142	-10.511	-15.361	18.395	1.00	30.02	C
ATOM	1094	NH1	ARG A 142	-9.512	-15.762	17.616	1.00	29.87	N
ATOM	1095	NH2	ARG A 142	-11.016	-14.143	18.266	1.00	29.56	N
ATOM	1096	C	ARG A 142	-10.149	-21.178	19.777	1.00	22.63	C
ATOM	1097	O	ARG A 142	-10.578	-21.036	18.634	1.00	22.72	O
ATOM	1098	N	GLU A 143	-8.953	-21.696	20.032	1.00	23.76	N
ATOM	1099	CA	GLU A 143	-8.120	-22.214	18.948	1.00	25.89	C
ATOM	1100	CB	GLU A 143	-6.810	-22.794	19.475	1.00	25.58	C
ATOM	1101	CG	GLU A 143	-5.690	-21.792	19.636	1.00	28.77	C
ATOM	1102	CD	GLU A 143	-4.299	-22.459	19.702	1.00	29.83	C
ATOM	1103	OE1	GLU A 143	-4.022	-23.406	18.904	1.00	32.56	O
ATOM	1104	OE2	GLU A 143	-3.476	-22.016	20.549	1.00	35.18	O
ATOM	1105	C	GLU A 143	-8.855	-23.284	18.135	1.00	25.55	C
ATOM	1106	O	GLU A 143	-9.429	-24.227	18.691	1.00	25.41	O
ATOM	1107	N	ALA A 144	-8.836	-23.116	16.816	1.00	25.87	N
ATOM	1108	CA	ALA A 144	-9.448	-24.057	15.891	1.00	25.80	C
ATOM	1109	CB	ALA A 144	-10.955	-23.831	15.817	1.00	25.58	C
ATOM	1110	C	ALA A 144	-8.803	-23.897	14.517	1.00	26.01	C
ATOM	1111	O	ALA A 144	-8.782	-22.804	13.949	1.00	26.05	O
ATOM	1112	N	LYS A 145	-8.251	-24.994	14.009	1.00	26.21	N
ATOM	1113	CA	LYS A 145	-7.709	-25.058	12.663	1.00	26.62	C
ATOM	1114	CB	LYS A 145	-6.540	-26.042	12.643	1.00	26.96	C
ATOM	1115	CG	LYS A 145	-5.716	-26.128	11.354	1.00	27.62	C
ATOM	1116	CD	LYS A 145	-4.638	-27.232	11.509	1.00	28.06	C
ATOM	1117	CE	LYS A 145	-3.890	-27.519	10.195	1.00	30.39	C
ATOM	1118	NZ	LYS A 145	-3.039	-28.765	10.211	1.00	29.79	N
ATOM	1119	C	LYS A 145	-8.816	-25.512	11.710	1.00	26.22	C
ATOM	1120	O	LYS A 145	-9.406	-26.569	11.879	1.00	26.51	O
ATOM	1121	N	VAL A 146	-9.120	-24.684	10.723	1.00	25.92	N
ATOM	1122	CA	VAL A 146	-10.021	-25.073	9.649	1.00	25.13	C
ATOM	1123	CB	VAL A 146	-11.200	-24.102	9.515	1.00	24.89	C
ATOM	1124	CG1	VAL A 146	-12.060	-24.486	8.354	1.00	24.53	C
ATOM	1125	CG2	VAL A 146	-12.026	-24.109	10.768	1.00	24.98	C
ATOM	1126	C	VAL A 146	-9.238	-25.097	8.346	1.00	24.89	C
ATOM	1127	O	VAL A 146	-8.574	-24.132	7.984	1.00	25.24	O
ATOM	1128	N	GLN A 147	-9.297	-26.214	7.649	1.00	24.59	N
ATOM	1129	CA	GLN A 147	-8.736	-26.281	6.314	1.00	24.22	C
ATOM	1130	CB	GLN A 147	-7.535	-27.210	6.283	1.00	24.33	C
ATOM	1131	CG	GLN A 147	-6.318	-26.586	6.901	1.00	26.64	C
ATOM	1132	CD	GLN A 147	-5.179	-27.569	7.045	1.00	30.78	C
ATOM	1133	OE1	GLN A 147	-5.401	-28.780	7.236	1.00	31.83	O
ATOM	1134	NE2	GLN A 147	-3.939	-27.061	6.953	1.00	30.78	N
ATOM	1135	C	GLN A 147	-9.787	-26.711	5.312	1.00	23.13	C
ATOM	1136	O	GLN A 147	-10.559	-27.628	5.564	1.00	22.91	O
ATOM	1137	N	TRP A 148	-9.815	-26.014	4.186	1.00	22.41	N
ATOM	1138	CA	TRP A 148	-10.661	-26.382	3.072	1.00	21.44	C
ATOM	1139	CB	TRP A 148	-11.163	-25.146	2.351	1.00	20.14	C
ATOM	1140	CG	TRP A 148	-12.178	-24.344	3.071	1.00	18.29	C
ATOM	1141	CD1	TRP A 148	-11.965	-23.205	3.779	1.00	16.54	C
ATOM	1142	NE1	TRP A 148	-13.151	-22.728	4.274	1.00	15.89	N
ATOM	1143	CE2	TRP A 148	-14.162	-23.560	3.879	1.00	15.52	C

ATOM	1144	CD2 TRP A 148	-13.584	-24.592	3.118	1.00	16.65	C
ATOM	1145	CE3 TRP A 148	-14.411	-25.594	2.594	1.00	16.13	C
ATOM	1146	CZ3 TRP A 148	-15.758	-25.529	2.841	1.00	16.92	C
ATOM	1147	CH2 TRP A 148	-16.308	-24.482	3.608	1.00	17.22	C
ATOM	1148	CZ2 TRP A 148	-15.524	-23.498	4.136	1.00	16.53	C
ATOM	1149	C TRP A 148	-9.858	-27.231	2.096	1.00	22.04	C
ATOM	1150	O TRP A 148	-8.647	-27.053	1.921	1.00	21.82	O
ATOM	1151	N LYS A 149	-10.555	-28.165	1.466	1.00	22.91	N
ATOM	1152	CA LYS A 149	-9.975	-29.041	0.473	1.00	23.35	C
ATOM	1153	CB LYS A 149	-9.652	-30.402	1.088	1.00	23.29	C
ATOM	1154	CG LYS A 149	-8.232	-30.475	1.602	1.00	24.64	C
ATOM	1155	CD LYS A 149	-7.923	-31.793	2.267	1.00	27.56	C
ATOM	1156	CE LYS A 149	-7.905	-31.629	3.779	1.00	29.36	C
ATOM	1157	NZ LYS A 149	-7.225	-32.760	4.469	1.00	30.66	N
ATOM	1158	C LYS A 149	-10.962	-29.166	-0.665	1.00	23.69	C
ATOM	1159	O LYS A 149	-12.154	-29.397	-0.440	1.00	23.85	O
ATOM	1160	N VAL A 150	-10.467	-28.957	-1.882	1.00	24.12	N
ATOM	1161	CA VAL A 150	-11.257	-29.160	-3.095	1.00	24.15	C
ATOM	1162	CB VAL A 150	-11.305	-27.893	-3.969	1.00	24.13	C
ATOM	1163	CG1 VAL A 150	-12.164	-28.134	-5.195	1.00	23.73	C
ATOM	1164	CG2 VAL A 150	-11.864	-26.729	-3.184	1.00	23.58	C
ATOM	1165	C VAL A 150	-10.592	-30.287	-3.847	1.00	24.43	C
ATOM	1166	O VAL A 150	-9.413	-30.196	-4.191	1.00	24.65	O
ATOM	1167	N ASP A 151	-11.324	-31.372	-4.069	1.00	25.01	N
ATOM	1168	CA ASP A 151	-10.739	-32.569	-4.689	1.00	25.53	C
ATOM	1169	CB ASP A 151	-10.677	-32.431	-6.221	1.00	25.31	C
ATOM	1170	CG ASP A 151	-12.067	-32.403	-6.884	1.00	25.56	C
ATOM	1171	OD1 ASP A 151	-13.022	-33.011	-6.341	1.00	25.86	O
ATOM	1172	OD2 ASP A 151	-12.193	-31.769	-7.962	1.00	24.59	O
ATOM	1173	C ASP A 151	-9.341	-32.835	-4.110	1.00	26.09	C
ATOM	1174	O ASP A 151	-8.410	-33.198	-4.831	1.00	26.25	O
ATOM	1175	N ASN A 152	-9.215	-32.632	-2.799	1.00	26.65	N
ATOM	1176	CA ASN A 152	-7.959	-32.800	-2.063	1.00	27.23	C
ATOM	1177	CB ASN A 152	-7.392	-34.198	-2.269	1.00	27.79	C
ATOM	1178	CG ASN A 152	-8.102	-35.216	-1.417	1.00	30.90	C
ATOM	1179	OD1 ASN A 152	-9.197	-35.691	-1.770	1.00	33.40	O
ATOM	1180	ND2 ASN A 152	-7.511	-35.532	-0.259	1.00	32.30	N
ATOM	1181	C ASN A 152	-6.871	-31.729	-2.210	1.00	26.84	C
ATOM	1182	O ASN A 152	-5.745	-31.898	-1.720	1.00	26.99	O
ATOM	1183	N ALA A 153	-7.206	-30.612	-2.845	1.00	26.05	N
ATOM	1184	CA ALA A 153	-6.265	-29.518	-2.899	1.00	25.32	C
ATOM	1185	CB ALA A 153	-6.327	-28.832	-4.240	1.00	25.10	C
ATOM	1186	C ALA A 153	-6.529	-28.544	-1.755	1.00	25.05	C
ATOM	1187	O ALA A 153	-7.606	-27.948	-1.667	1.00	25.00	O
ATOM	1188	N LEU A 154	-5.546	-28.391	-0.873	1.00	24.54	N
ATOM	1189	CA LEU A 154	-5.622	-27.401	0.194	1.00	24.42	C
ATOM	1190	CB LEU A 154	-4.306	-27.363	0.970	1.00	24.65	C
ATOM	1191	CG LEU A 154	-4.259	-27.280	2.512	1.00	25.46	C
ATOM	1192	CD1 LEU A 154	-3.129	-26.322	2.914	1.00	24.84	C
ATOM	1193	CD2 LEU A 154	-5.582	-26.856	3.176	1.00	24.36	C
ATOM	1194	C LEU A 154	-5.882	-26.011	-0.378	1.00	24.18	C
ATOM	1195	O LEU A 154	-5.393	-25.658	-1.453	1.00	24.70	O
ATOM	1196	N GLN A 155	-6.639	-25.201	0.336	1.00	23.75	N
ATOM	1197	CA GLN A 155	-6.784	-23.825	-0.084	1.00	23.06	C
ATOM	1198	CB GLN A 155	-8.236	-23.522	-0.379	1.00	23.12	C
ATOM	1199	CG GLN A 155	-8.532	-23.544	-1.867	1.00	24.64	C
ATOM	1200	CD GLN A 155	-8.960	-24.883	-2.297	1.00	25.07	C

ATOM	1201	OE1 GLN A 155	-9.853	-25.451	-1.684	1.00	27.06	O
ATOM	1202	NE2 GLN A 155	-8.328	-25.426	-3.330	1.00	24.39	N
ATOM	1203	C GLN A 155	-6.226	-22.843	0.920	1.00	22.58	C
ATOM	1204	O GLN A 155	-6.698	-22.786	2.056	1.00	22.97	O
ATOM	1205	N SER A 156	-5.210	-22.084	0.520	1.00	21.82	N
ATOM	1206	CA SER A 156	-4.805	-20.931	1.319	1.00	21.94	C
ATOM	1207	CB SER A 156	-3.364	-21.010	1.827	1.00	22.06	C
ATOM	1208	OG SER A 156	-2.479	-21.414	0.817	1.00	23.50	O
ATOM	1209	C SER A 156	-5.051	-19.647	0.579	1.00	21.49	C
ATOM	1210	O SER A 156	-4.929	-19.594	-0.634	1.00	21.74	O
ATOM	1211	N GLY A 157	-5.449	-18.625	1.325	1.00	21.32	N
ATOM	1212	CA GLY A 157	-5.682	-17.305	0.768	1.00	20.98	C
ATOM	1213	C GLY A 157	-7.061	-17.016	0.212	1.00	20.80	C
ATOM	1214	O GLY A 157	-7.345	-15.875	-0.123	1.00	20.80	O
ATOM	1215	N ASN A 158	-7.919	-18.026	0.100	1.00	20.70	N
ATOM	1216	CA ASN A 158	-9.267	-17.813	-0.430	1.00	20.87	C
ATOM	1217	CB ASN A 158	-9.414	-18.487	-1.794	1.00	21.14	C
ATOM	1218	CG ASN A 158	-9.004	-19.950	-1.774	1.00	22.36	C
ATOM	1219	OD1 ASN A 158	-9.000	-20.610	-2.810	1.00	22.46	O
ATOM	1220	ND2 ASN A 158	-8.654	-20.464	-0.592	1.00	23.26	N
ATOM	1221	C ASN A 158	-10.401	-18.227	0.509	1.00	21.01	C
ATOM	1222	O ASN A 158	-11.468	-18.648	0.065	1.00	20.75	O
ATOM	1223	N SER A 159	-10.143	-18.111	1.809	1.00	21.58	N
ATOM	1224	CA SER A 159	-11.123	-18.364	2.873	1.00	21.93	C
ATOM	1225	CB SER A 159	-10.799	-19.647	3.654	1.00	21.69	C
ATOM	1226	OG SER A 159	-9.905	-20.492	2.954	1.00	23.67	O
ATOM	1227	C SER A 159	-11.047	-17.190	3.851	1.00	21.90	C
ATOM	1228	O SER A 159	-9.987	-16.592	4.031	1.00	22.16	O
ATOM	1229	N GLN A 160	-12.154	-16.875	4.500	1.00	21.59	N
ATOM	1230	CA GLN A 160	-12.133	-15.862	5.528	1.00	21.75	C
ATOM	1231	CB GLN A 160	-12.668	-14.535	5.000	1.00	21.59	C
ATOM	1232	CG GLN A 160	-11.754	-13.839	4.001	1.00	20.90	C
ATOM	1233	CD GLN A 160	-12.211	-12.422	3.733	1.00	21.80	C
ATOM	1234	OE1 GLN A 160	-13.171	-12.201	2.978	1.00	23.40	O
ATOM	1235	NE2 GLN A 160	-11.550	-11.448	4.366	1.00	18.67	N
ATOM	1236	C GLN A 160	-12.978	-16.339	6.681	1.00	22.26	C
ATOM	1237	O GLN A 160	-14.048	-16.920	6.477	1.00	22.51	O
ATOM	1238	N GLU A 161	-12.498	-16.087	7.896	1.00	22.51	N
ATOM	1239	CA GLU A 161	-13.173	-16.565	9.097	1.00	22.55	C
ATOM	1240	CB GLU A 161	-12.213	-17.330	9.993	1.00	22.45	C
ATOM	1241	CG GLU A 161	-11.695	-18.617	9.417	1.00	24.73	C
ATOM	1242	CD GLU A 161	-10.722	-19.263	10.352	1.00	25.51	C
ATOM	1243	OE1 GLU A 161	-10.112	-18.513	11.126	1.00	25.37	O
ATOM	1244	OE2 GLU A 161	-10.573	-20.504	10.325	1.00	27.78	O
ATOM	1245	C GLU A 161	-13.701	-15.405	9.890	1.00	22.31	C
ATOM	1246	O GLU A 161	-13.273	-14.268	9.710	1.00	22.36	O
ATOM	1247	N SER A 162	-14.616	-15.723	10.792	1.00	22.09	N
ATOM	1248	CA SER A 162	-15.212	-14.761	11.681	1.00	22.06	C
ATOM	1249	CB SER A 162	-16.475	-14.197	11.039	1.00	21.61	C
ATOM	1250	OG SER A 162	-17.128	-13.313	11.914	1.00	21.93	O
ATOM	1251	C SER A 162	-15.551	-15.556	12.932	1.00	22.26	C
ATOM	1252	O SER A 162	-16.132	-16.643	12.835	1.00	22.77	O
ATOM	1253	N VAL A 163	-15.183	-15.038	14.101	1.00	22.06	N
ATOM	1254	CA VAL A 163	-15.473	-15.730	15.357	1.00	21.69	C
ATOM	1255	CB VAL A 163	-14.170	-16.098	16.111	1.00	22.05	C
ATOM	1256	CG1 VAL A 163	-14.464	-17.063	17.267	1.00	22.13	C
ATOM	1257	CG2 VAL A 163	-13.146	-16.725	15.166	1.00	21.12	C

ATOM	1258	C	VAL A 163	-16.386	-14.886	16.246	1.00	21.59	C
ATOM	1259	O	VAL A 163	-16.160	-13.688	16.410	1.00	21.33	O
ATOM	1260	N	THR A 164	-17.428	-15.502	16.802	1.00	21.72	N
ATOM	1261	CA	THR A 164	-18.319	-14.796	17.732	1.00	22.04	C
ATOM	1262	CB	THR A 164	-19.563	-15.598	18.076	1.00	21.84	C
ATOM	1263	OG1	THR A 164	-19.170	-16.905	18.510	1.00	22.20	O
ATOM	1264	CG2	THR A 164	-20.520	-15.680	16.886	1.00	21.40	C
ATOM	1265	C	THR A 164	-17.631	-14.495	19.054	1.00	22.74	C
ATOM	1266	O	THR A 164	-16.721	-15.221	19.472	1.00	22.48	O
ATOM	1267	N	GLU A 165	-18.070	-13.412	19.697	1.00	23.66	N
ATOM	1268	CA	GLU A 165	-17.678	-13.069	21.063	1.00	24.63	C
ATOM	1269	CB	GLU A 165	-18.400	-11.774	21.459	1.00	24.78	C
ATOM	1270	CG	GLU A 165	-17.637	-10.819	22.381	1.00	28.48	C
ATOM	1271	CD	GLU A 165	-16.358	-10.220	21.755	1.00	32.38	C
ATOM	1272	OE1	GLU A 165	-15.341	-10.071	22.479	1.00	33.14	O
ATOM	1273	OE2	GLU A 165	-16.375	-9.882	20.551	1.00	33.65	O
ATOM	1274	C	GLU A 165	-18.083	-14.259	21.977	1.00	24.72	C
ATOM	1275	O	GLU A 165	-19.102	-14.916	21.735	1.00	25.20	O
ATOM	1276	N	GLN A 166	-17.289	-14.566	22.996	1.00	24.81	N
ATOM	1277	CA	GLN A 166	-17.601	-15.694	23.896	1.00	25.19	C
ATOM	1278	CB	GLN A 166	-16.574	-15.723	25.044	1.00	24.59	C
ATOM	1279	CG	GLN A 166	-16.701	-16.888	25.989	1.00	24.78	C
ATOM	1280	CD	GLN A 166	-15.530	-17.015	26.957	1.00	26.07	C
ATOM	1281	OE1	GLN A 166	-14.962	-16.017	27.414	1.00	27.74	O
ATOM	1282	NE2	GLN A 166	-15.180	-18.258	27.297	1.00	27.35	N
ATOM	1283	C	GLN A 166	-19.071	-15.646	24.410	1.00	25.29	C
ATOM	1284	O	GLN A 166	-19.495	-14.639	24.970	1.00	25.34	O
ATOM	1285	N	ASP A 167	-19.846	-16.712	24.195	1.00	25.67	N
ATOM	1286	CA	ASP A 167	-21.280	-16.729	24.562	1.00	26.49	C
ATOM	1287	CB	ASP A 167	-21.911	-18.085	24.263	1.00	26.19	C
ATOM	1288	CG	ASP A 167	-23.418	-18.061	24.360	1.00	25.77	C
ATOM	1289	OD1	ASP A 167	-23.966	-18.449	25.408	1.00	27.07	O
ATOM	1290	OD2	ASP A 167	-24.067	-17.656	23.382	1.00	26.10	O
ATOM	1291	C	ASP A 167	-21.520	-16.402	26.032	1.00	27.56	C
ATOM	1292	O	ASP A 167	-20.827	-16.925	26.915	1.00	27.88	O
ATOM	1293	N	SER A 168	-22.512	-15.554	26.292	1.00	28.35	N
ATOM	1294	CA	SER A 168	-22.797	-15.097	27.655	1.00	28.98	C
ATOM	1295	CB	SER A 168	-23.743	-13.897	27.625	1.00	29.08	C
ATOM	1296	OG	SER A 168	-24.932	-14.239	26.930	1.00	30.27	O
ATOM	1297	C	SER A 168	-23.375	-16.193	28.557	1.00	29.28	C
ATOM	1298	O	SER A 168	-23.071	-16.228	29.747	1.00	29.27	O
ATOM	1299	N	LYS A 169	-24.202	-17.082	27.998	1.00	29.46	N
ATOM	1300	CA	LYS A 169	-24.823	-18.153	28.789	1.00	29.51	C
ATOM	1301	CB	LYS A 169	-26.047	-18.738	28.071	1.00	29.93	C
ATOM	1302	CG	LYS A 169	-27.259	-17.769	27.874	1.00	31.79	C
ATOM	1303	CD	LYS A 169	-28.086	-18.172	26.589	1.00	31.72	C
ATOM	1304	CE	LYS A 169	-29.508	-17.566	26.529	1.00	33.25	C
ATOM	1305	NZ	LYS A 169	-29.499	-16.107	26.144	1.00	34.57	N
ATOM	1306	C	LYS A 169	-23.842	-19.277	29.125	1.00	28.36	C
ATOM	1307	O	LYS A 169	-23.784	-19.733	30.266	1.00	28.52	O
ATOM	1308	N	ASP A 170	-23.071	-19.729	28.137	1.00	26.96	N
ATOM	1309	CA	ASP A 170	-22.313	-20.968	28.290	1.00	25.25	C
ATOM	1310	CB	ASP A 170	-23.024	-22.094	27.539	1.00	25.08	C
ATOM	1311	CG	ASP A 170	-22.889	-21.985	26.031	1.00	25.54	C
ATOM	1312	OD1	ASP A 170	-22.144	-21.128	25.497	1.00	25.96	O
ATOM	1313	OD2	ASP A 170	-23.535	-22.794	25.353	1.00	27.63	O
ATOM	1314	C	ASP A 170	-20.834	-20.898	27.895	1.00	24.40	C

ATOM	1315	O	ASP A 170	-20.151	-21.922	27.852	1.00	24.57	O
ATOM	1316	N	SER A 171	-20.362	-19.699	27.568	1.00	23.31	N
ATOM	1317	CA	SER A 171	-18.925	-19.405	27.416	1.00	22.33	C
ATOM	1318	CB	SER A 171	-18.172	-19.607	28.750	1.00	22.34	C
ATOM	1319	OG	SER A 171	-18.756	-18.829	29.789	1.00	21.65	O
ATOM	1320	C	SER A 171	-18.211	-20.105	26.246	1.00	21.75	C
ATOM	1321	O	SER A 171	-16.975	-20.192	26.210	1.00	21.46	O
ATOM	1322	N	THR A 172	-18.977	-20.575	25.270	1.00	21.05	N
ATOM	1323	CA	THR A 172	-18.348	-21.079	24.053	1.00	20.45	C
ATOM	1324	CB	THR A 172	-19.026	-22.352	23.464	1.00	20.32	C
ATOM	1325	OG1	THR A 172	-20.440	-22.161	23.343	1.00	19.93	O
ATOM	1326	CG2	THR A 172	-18.733	-23.568	24.334	1.00	20.71	C
ATOM	1327	C	THR A 172	-18.182	-20.027	22.957	1.00	19.93	C
ATOM	1328	O	THR A 172	-18.537	-18.856	23.108	1.00	19.02	O
ATOM	1329	N	TYR A 173	-17.575	-20.496	21.873	1.00	19.71	N
ATOM	1330	CA	TYR A 173	-17.439	-19.773	20.642	1.00	19.17	C
ATOM	1331	CB	TYR A 173	-15.963	-19.587	20.307	1.00	19.23	C
ATOM	1332	CG	TYR A 173	-15.186	-18.790	21.314	1.00	19.40	C
ATOM	1333	CD1	TYR A 173	-14.393	-19.428	22.268	1.00	20.47	C
ATOM	1334	CE1	TYR A 173	-13.661	-18.699	23.206	1.00	20.08	C
ATOM	1335	CZ	TYR A 173	-13.714	-17.308	23.178	1.00	20.86	C
ATOM	1336	OH	TYR A 173	-12.995	-16.584	24.107	1.00	21.42	O
ATOM	1337	CE2	TYR A 173	-14.481	-16.647	22.223	1.00	19.23	C
ATOM	1338	CD2	TYR A 173	-15.220	-17.395	21.306	1.00	19.30	C
ATOM	1339	C	TYR A 173	-18.120	-20.559	19.514	1.00	18.86	C
ATOM	1340	O	TYR A 173	-18.222	-21.792	19.542	1.00	18.79	O
ATOM	1341	N	SER A 174	-18.595	-19.820	18.524	1.00	18.24	N
ATOM	1342	CA	SER A 174	-19.001	-20.390	17.273	1.00	17.22	C
ATOM	1343	CB	SER A 174	-20.496	-20.172	17.073	1.00	17.63	C
ATOM	1344	OG	SER A 174	-21.239	-20.916	18.036	1.00	17.30	O
ATOM	1345	C	SER A 174	-18.154	-19.665	16.243	1.00	16.87	C
ATOM	1346	O	SER A 174	-17.704	-18.545	16.488	1.00	16.66	O
ATOM	1347	N	LEU A 175	-17.880	-20.333	15.128	1.00	16.67	N
ATOM	1348	CA	LEU A 175	-17.065	-19.782	14.049	1.00	16.53	C
ATOM	1349	CB	LEU A 175	-15.592	-20.171	14.254	1.00	16.47	C
ATOM	1350	CG	LEU A 175	-14.516	-20.616	13.227	1.00	16.91	C
ATOM	1351	CD1	LEU A 175	-14.738	-20.238	11.793	1.00	13.87	C
ATOM	1352	CD2	LEU A 175	-13.107	-20.154	13.684	1.00	16.36	C
ATOM	1353	C	LEU A 175	-17.606	-20.203	12.677	1.00	16.82	C
ATOM	1354	O	LEU A 175	-18.116	-21.318	12.516	1.00	16.67	O
ATOM	1355	N	SER A 176	-17.532	-19.290	11.708	1.00	17.03	N
ATOM	1356	CA	SER A 176	-17.886	-19.597	10.324	1.00	17.45	C
ATOM	1357	CB	SER A 176	-19.086	-18.763	9.856	1.00	17.22	C
ATOM	1358	OG	SER A 176	-18.674	-17.607	9.132	1.00	18.42	O
ATOM	1359	C	SER A 176	-16.671	-19.350	9.435	1.00	17.56	C
ATOM	1360	O	SER A 176	-15.942	-18.377	9.640	1.00	18.34	O
ATOM	1361	N	SER A 177	-16.430	-20.248	8.484	1.00	17.49	N
ATOM	1362	CA	SER A 177	-15.413	-20.026	7.453	1.00	17.63	C
ATOM	1363	CB	SER A 177	-14.259	-21.025	7.591	1.00	17.66	C
ATOM	1364	OG	SER A 177	-13.566	-21.188	6.364	1.00	17.24	O
ATOM	1365	C	SER A 177	-16.045	-20.085	6.050	1.00	17.87	C
ATOM	1366	O	SER A 177	-16.748	-21.036	5.713	1.00	17.39	O
ATOM	1367	N	THR A 178	-15.804	-19.040	5.262	1.00	18.51	N
ATOM	1368	CA	THR A 178	-16.306	-18.932	3.898	1.00	19.15	C
ATOM	1369	CB	THR A 178	-17.022	-17.575	3.636	1.00	18.96	C
ATOM	1370	OG1	THR A 178	-18.202	-17.486	4.435	1.00	19.25	O
ATOM	1371	CG2	THR A 178	-17.443	-17.472	2.190	1.00	19.02	C

ATOM	1372	C	THR A 178	-15.159	-19.081	2.912	1.00	19.63	C
ATOM	1373	O	THR A 178	-14.171	-18.345	2.978	1.00	19.78	O
ATOM	1374	N	LEU A 179	-15.297	-20.054	2.015	1.00	20.34	N
ATOM	1375	CA	LEU A 179	-14.411	-20.213	0.869	1.00	21.02	C
ATOM	1376	CB	LEU A 179	-14.015	-21.679	0.732	1.00	20.58	C
ATOM	1377	CG	LEU A 179	-13.340	-22.214	-0.529	1.00	20.28	C
ATOM	1378	CD1	LEU A 179	-11.848	-21.858	-0.621	1.00	19.22	C
ATOM	1379	CD2	LEU A 179	-13.536	-23.724	-0.587	1.00	20.51	C
ATOM	1380	C	LEU A 179	-15.151	-19.722	-0.371	1.00	22.07	C
ATOM	1381	O	LEU A 179	-16.283	-20.142	-0.634	1.00	22.23	O
ATOM	1382	N	THR A 180	-14.534	-18.805	-1.113	1.00	23.71	N
ATOM	1383	CA	THR A 180	-15.172	-18.235	-2.317	1.00	25.12	C
ATOM	1384	CB	THR A 180	-15.299	-16.696	-2.255	1.00	25.21	C
ATOM	1385	OG1	THR A 180	-15.929	-16.315	-1.023	1.00	25.82	O
ATOM	1386	CG2	THR A 180	-16.137	-16.188	-3.435	1.00	24.60	C
ATOM	1387	C	THR A 180	-14.464	-18.609	-3.609	1.00	25.79	C
ATOM	1388	O	THR A 180	-13.274	-18.319	-3.772	1.00	25.99	O
ATOM	1389	N	LEU A 181	-15.204	-19.252	-4.514	1.00	26.60	N
ATOM	1390	CA	LEU A 181	-14.735	-19.487	-5.879	1.00	27.55	C
ATOM	1391	CB	LEU A 181	-14.505	-20.980	-6.154	1.00	27.63	C
ATOM	1392	CG	LEU A 181	-14.141	-22.005	-5.081	1.00	28.05	C
ATOM	1393	CD1	LEU A 181	-15.364	-22.816	-4.715	1.00	29.11	C
ATOM	1394	CD2	LEU A 181	-13.075	-22.941	-5.594	1.00	27.99	C
ATOM	1395	C	LEU A 181	-15.710	-18.932	-6.930	1.00	28.19	C
ATOM	1396	O	LEU A 181	-16.918	-18.803	-6.693	1.00	28.15	O
ATOM	1397	N	SER A 182	-15.175	-18.620	-8.104	1.00	28.98	N
ATOM	1398	CA	SER A 182	-16.002	-18.345	-9.271	1.00	29.68	C
ATOM	1399	CB	SER A 182	-15.107	-17.999	-10.471	1.00	29.92	C
ATOM	1400	OG	SER A 182	-14.214	-19.062	-10.803	1.00	30.07	O
ATOM	1401	C	SER A 182	-16.850	-19.586	-9.580	1.00	29.80	C
ATOM	1402	O	SER A 182	-16.421	-20.709	-9.298	1.00	29.64	O
ATOM	1403	N	LYS A 183	-18.043	-19.380	-10.144	1.00	29.98	N
ATOM	1404	CA	LYS A 183	-18.864	-20.475	-10.673	1.00	30.46	C
ATOM	1405	CB	LYS A 183	-20.020	-19.905	-11.493	1.00	30.87	C
ATOM	1406	CG	LYS A 183	-21.024	-20.922	-12.037	1.00	32.19	C
ATOM	1407	CD	LYS A 183	-21.587	-20.433	-13.378	1.00	35.62	C
ATOM	1408	CE	LYS A 183	-23.129	-20.393	-13.401	1.00	37.97	C
ATOM	1409	NZ	LYS A 183	-23.816	-21.729	-13.367	1.00	37.79	N
ATOM	1410	C	LYS A 183	-18.006	-21.382	-11.555	1.00	30.67	C
ATOM	1411	O	LYS A 183	-18.108	-22.602	-11.486	1.00	30.42	O
ATOM	1412	N	ALA A 184	-17.153	-20.766	-12.376	1.00	31.02	N
ATOM	1413	CA	ALA A 184	-16.177	-21.489	-13.186	1.00	31.26	C
ATOM	1414	CB	ALA A 184	-15.158	-20.525	-13.801	1.00	31.17	C
ATOM	1415	C	ALA A 184	-15.475	-22.573	-12.368	1.00	31.42	C
ATOM	1416	O	ALA A 184	-15.643	-23.763	-12.654	1.00	31.71	O
ATOM	1417	N	ASP A 185	-14.715	-22.161	-11.349	1.00	31.29	N
ATOM	1418	CA	ASP A 185	-13.937	-23.093	-10.539	1.00	31.24	C
ATOM	1419	CB	ASP A 185	-13.004	-22.352	-9.573	1.00	31.66	C
ATOM	1420	CG	ASP A 185	-11.679	-21.948	-10.219	1.00	32.83	C
ATOM	1421	OD1	ASP A 185	-11.101	-22.760	-10.980	1.00	34.71	O
ATOM	1422	OD2	ASP A 185	-11.205	-20.822	-9.951	1.00	32.81	O
ATOM	1423	C	ASP A 185	-14.823	-24.068	-9.775	1.00	31.09	C
ATOM	1424	O	ASP A 185	-14.475	-25.243	-9.637	1.00	31.15	O
ATOM	1425	N	TYR A 186	-15.967	-23.586	-9.292	1.00	30.81	N
ATOM	1426	CA	TYR A 186	-16.876	-24.426	-8.520	1.00	30.77	C
ATOM	1427	CB	TYR A 186	-17.960	-23.600	-7.800	1.00	29.68	C
ATOM	1428	CG	TYR A 186	-18.945	-24.457	-7.028	1.00	28.36	C

ATOM	1429	CD1 TYR A 186	-18.539	-25.172	-5.910	1.00	27.75	C
ATOM	1430	CE1 TYR A 186	-19.424	-25.987	-5.203	1.00	26.60	C
ATOM	1431	CZ TYR A 186	-20.736	-26.083	-5.609	1.00	26.82	C
ATOM	1432	OH TYR A 186	-21.593	-26.883	-4.897	1.00	26.15	O
ATOM	1433	CE2 TYR A 186	-21.180	-25.377	-6.721	1.00	26.83	C
ATOM	1434	CD2 TYR A 186	-20.278	-24.570	-7.429	1.00	28.07	C
ATOM	1435	C TYR A 186	-17.502	-25.537	-9.365	1.00	31.74	C
ATOM	1436	O TYR A 186	-17.712	-26.635	-8.854	1.00	32.25	O
ATOM	1437	N GLU A 187	-17.800	-25.253	-10.639	1.00	32.58	N
ATOM	1438	CA GLU A 187	-18.319	-26.262	-11.572	1.00	33.40	C
ATOM	1439	CB GLU A 187	-18.878	-25.615	-12.842	1.00	33.98	C
ATOM	1440	CG GLU A 187	-20.017	-24.595	-12.672	1.00	36.17	C
ATOM	1441	CD GLU A 187	-21.336	-25.202	-12.207	1.00	39.05	C
ATOM	1442	OE1 GLU A 187	-22.387	-24.838	-12.785	1.00	38.92	O
ATOM	1443	OE2 GLU A 187	-21.326	-26.022	-11.256	1.00	40.11	O
ATOM	1444	C GLU A 187	-17.262	-27.296	-11.982	1.00	33.48	C
ATOM	1445	O GLU A 187	-17.601	-28.418	-12.365	1.00	33.55	O
ATOM	1446	N LYS A 188	-15.990	-26.907	-11.907	1.00	33.40	N
ATOM	1447	CA LYS A 188	-14.870	-27.750	-12.334	1.00	33.47	C
ATOM	1448	CB LYS A 188	-13.674	-26.862	-12.721	1.00	34.01	C
ATOM	1449	CG LYS A 188	-13.607	-26.507	-14.219	1.00	37.23	C
ATOM	1450	CD LYS A 188	-12.688	-27.487	-15.017	1.00	41.68	C
ATOM	1451	CE LYS A 188	-13.342	-27.961	-16.366	1.00	43.18	C
ATOM	1452	NZ LYS A 188	-14.096	-29.288	-16.198	1.00	42.76	N
ATOM	1453	C LYS A 188	-14.409	-28.799	-11.313	1.00	32.62	C
ATOM	1454	O LYS A 188	-13.453	-29.519	-11.568	1.00	32.44	O
ATOM	1455	N HIS A 189	-15.071	-28.890	-10.162	1.00	31.83	N
ATOM	1456	CA HIS A 189	-14.577	-29.736	-9.075	1.00	30.87	C
ATOM	1457	CB HIS A 189	-13.753	-28.903	-8.090	1.00	30.86	C
ATOM	1458	CG HIS A 189	-12.488	-28.341	-8.664	1.00	30.62	C
ATOM	1459	ND1 HIS A 189	-12.360	-27.014	-9.023	1.00	30.03	N
ATOM	1460	CE1 HIS A 189	-11.141	-26.802	-9.486	1.00	30.06	C
ATOM	1461	NE2 HIS A 189	-10.472	-27.941	-9.435	1.00	30.13	N
ATOM	1462	CD2 HIS A 189	-11.291	-28.920	-8.923	1.00	30.13	C
ATOM	1463	C HIS A 189	-15.701	-30.443	-8.325	1.00	30.36	C
ATOM	1464	O HIS A 189	-16.812	-29.949	-8.281	1.00	30.12	O
ATOM	1465	N LYS A 190	-15.382	-31.574	-7.694	1.00	30.08	N
ATOM	1466	CA LYS A 190	-16.389	-32.503	-7.164	1.00	29.60	C
ATOM	1467	CB LYS A 190	-16.077	-33.931	-7.637	1.00	29.93	C
ATOM	1468	CG LYS A 190	-17.070	-35.006	-7.214	1.00	32.02	C
ATOM	1469	CD LYS A 190	-18.231	-35.113	-8.197	1.00	37.00	C
ATOM	1470	CE LYS A 190	-18.735	-36.560	-8.302	1.00	39.58	C
ATOM	1471	NZ LYS A 190	-19.789	-36.679	-9.357	1.00	40.78	N
ATOM	1472	C LYS A 190	-16.520	-32.472	-5.643	1.00	28.70	C
ATOM	1473	O LYS A 190	-17.575	-32.131	-5.119	1.00	28.64	O
ATOM	1474	N VAL A 191	-15.455	-32.842	-4.940	1.00	27.75	N
ATOM	1475	CA VAL A 191	-15.496	-32.922	-3.476	1.00	26.70	C
ATOM	1476	CB VAL A 191	-14.632	-34.081	-2.947	1.00	26.40	C
ATOM	1477	CG1 VAL A 191	-14.540	-34.044	-1.421	1.00	25.75	C
ATOM	1478	CG2 VAL A 191	-15.176	-35.410	-3.426	1.00	26.03	C
ATOM	1479	C VAL A 191	-15.061	-31.613	-2.802	1.00	26.33	C
ATOM	1480	O VAL A 191	-13.937	-31.123	-3.010	1.00	26.42	O
ATOM	1481	N TYR A 192	-15.960	-31.065	-1.990	1.00	25.32	N
ATOM	1482	CA TYR A 192	-15.667	-29.894	-1.176	1.00	24.32	C
ATOM	1483	CB TYR A 192	-16.663	-28.788	-1.487	1.00	24.39	C
ATOM	1484	CG TYR A 192	-16.505	-28.281	-2.895	1.00	24.46	C
ATOM	1485	CD1 TYR A 192	-17.060	-28.969	-3.968	1.00	24.73	C

ATOM	1486	CE1 TYR A 192	-16.904	-28.507	-5.281	1.00	25.31	C
ATOM	1487	CZ TYR A 192	-16.168	-27.346	-5.520	1.00	25.50	C
ATOM	1488	OH TYR A 192	-16.010	-26.872	-6.811	1.00	25.13	O
ATOM	1489	CE2 TYR A 192	-15.601	-26.650	-4.461	1.00	25.10	C
ATOM	1490	CD2 TYR A 192	-15.770	-27.127	-3.158	1.00	24.54	C
ATOM	1491	C TYR A 192	-15.683	-30.277	0.290	1.00	23.55	C
ATOM	1492	O TYR A 192	-16.669	-30.835	0.788	1.00	23.45	O
ATOM	1493	N ALA A 193	-14.572	-30.015	0.971	1.00	22.67	N
ATOM	1494	CA ALA A 193	-14.401	-30.521	2.330	1.00	22.16	C
ATOM	1495	CB ALA A 193	-13.508	-31.772	2.343	1.00	21.89	C
ATOM	1496	C ALA A 193	-13.908	-29.493	3.345	1.00	21.81	C
ATOM	1497	O ALA A 193	-12.980	-28.720	3.085	1.00	21.44	O
ATOM	1498	N CYS A 194	-14.552	-29.504	4.506	1.00	21.10	N
ATOM	1499	CA CYS A 194	-14.134	-28.709	5.630	1.00	21.03	C
ATOM	1500	CB CYS A 194	-15.326	-27.943	6.187	1.00	20.83	C
ATOM	1501	SG CYS A 194	-14.873	-26.847	7.518	1.00	20.55	S
ATOM	1502	C CYS A 194	-13.532	-29.614	6.707	1.00	21.33	C
ATOM	1503	O CYS A 194	-14.234	-30.412	7.335	1.00	21.21	O
ATOM	1504	N GLU A 195	-12.230	-29.485	6.921	1.00	21.86	N
ATOM	1505	CA GLU A 195	-11.558	-30.249	7.960	1.00	22.43	C
ATOM	1506	CB GLU A 195	-10.271	-30.848	7.423	1.00	22.70	C
ATOM	1507	CG GLU A 195	-9.635	-31.808	8.410	1.00	25.29	C
ATOM	1508	CD GLU A 195	-8.298	-32.335	7.942	1.00	29.06	C
ATOM	1509	OE1 GLU A 195	-7.825	-33.317	8.555	1.00	31.48	O
ATOM	1510	OE2 GLU A 195	-7.728	-31.785	6.967	1.00	29.18	O
ATOM	1511	C GLU A 195	-11.252	-29.384	9.181	1.00	22.10	C
ATOM	1512	O GLU A 195	-10.606	-28.350	9.058	1.00	22.38	O
ATOM	1513	N VAL A 196	-11.703	-29.814	10.357	1.00	21.64	N
ATOM	1514	CA VAL A 196	-11.493	-29.041	11.579	1.00	21.32	C
ATOM	1515	CB VAL A 196	-12.820	-28.405	12.122	1.00	21.19	C
ATOM	1516	CG1 VAL A 196	-14.004	-29.150	11.624	1.00	21.43	C
ATOM	1517	CG2 VAL A 196	-12.848	-28.298	13.651	1.00	21.07	C
ATOM	1518	C VAL A 196	-10.696	-29.775	12.655	1.00	21.47	C
ATOM	1519	O VAL A 196	-11.014	-30.912	13.024	1.00	21.36	O
ATOM	1520	N THR A 197	-9.633	-29.120	13.119	1.00	21.65	N
ATOM	1521	CA THR A 197	-8.864	-29.592	14.246	1.00	22.45	C
ATOM	1522	CB THR A 197	-7.347	-29.538	13.966	1.00	22.75	C
ATOM	1523	OG1 THR A 197	-7.064	-30.141	12.701	1.00	22.84	O
ATOM	1524	CG2 THR A 197	-6.585	-30.297	15.054	1.00	23.57	C
ATOM	1525	C THR A 197	-9.195	-28.748	15.483	1.00	22.60	C
ATOM	1526	O THR A 197	-9.126	-27.512	15.443	1.00	22.32	O
ATOM	1527	N HIS A 198	-9.555	-29.432	16.572	1.00	22.85	N
ATOM	1528	CA HIS A 198	-9.879	-28.788	17.846	1.00	23.07	C
ATOM	1529	CB HIS A 198	-11.377	-28.516	17.940	1.00	22.91	C
ATOM	1530	CG HIS A 198	-11.763	-27.715	19.140	1.00	22.36	C
ATOM	1531	ND1 HIS A 198	-11.646	-26.342	19.186	1.00	22.15	N
ATOM	1532	CE1 HIS A 198	-12.043	-25.906	20.367	1.00	21.66	C
ATOM	1533	NE2 HIS A 198	-12.413	-26.948	21.091	1.00	22.75	N
ATOM	1534	CD2 HIS A 198	-12.244	-28.093	20.348	1.00	22.04	C
ATOM	1535	C HIS A 198	-9.461	-29.680	18.992	1.00	23.43	C
ATOM	1536	O HIS A 198	-9.563	-30.892	18.899	1.00	24.04	O
ATOM	1537	N GLN A 199	-9.019	-29.093	20.092	1.00	24.10	N
ATOM	1538	CA GLN A 199	-8.509	-29.902	21.210	1.00	24.65	C
ATOM	1539	CB GLN A 199	-7.664	-29.061	22.170	1.00	24.70	C
ATOM	1540	CG GLN A 199	-6.176	-29.076	21.784	1.00	26.86	C
ATOM	1541	CD GLN A 199	-5.430	-27.778	22.138	1.00	30.72	C
ATOM	1542	OE1 GLN A 199	-5.929	-26.659	21.900	1.00	30.67	O

ATOM	1543	NE2 GLN A 199	-4.214	-27.927	22.695	1.00	31.50	N
ATOM	1544	C GLN A 199	-9.532	-30.791	21.937	1.00	24.22	C
ATOM	1545	O GLN A 199	-9.139	-31.684	22.679	1.00	23.92	O
ATOM	1546	N GLY A 200	-10.822	-30.573	21.680	1.00	24.18	N
ATOM	1547	CA GLY A 200	-11.894	-31.408	22.247	1.00	24.24	C
ATOM	1548	C GLY A 200	-12.294	-32.524	21.306	1.00	24.40	C
ATOM	1549	O GLY A 200	-13.209	-33.296	21.583	1.00	23.78	O
ATOM	1550	N LEU A 201	-11.588	-32.577	20.176	1.00	25.05	N
ATOM	1551	CA LEU A 201	-11.713	-33.614	19.153	1.00	25.17	C
ATOM	1552	CB LEU A 201	-11.837	-32.952	17.781	1.00	24.55	C
ATOM	1553	CG LEU A 201	-13.168	-32.931	17.004	1.00	24.83	C
ATOM	1554	CD1 LEU A 201	-14.423	-33.406	17.753	1.00	23.50	C
ATOM	1555	CD2 LEU A 201	-13.398	-31.566	16.366	1.00	25.61	C
ATOM	1556	C LEU A 201	-10.483	-34.527	19.199	1.00	25.81	C
ATOM	1557	O LEU A 201	-9.328	-34.056	19.198	1.00	25.71	O
ATOM	1558	N SER A 202	-10.722	-35.833	19.267	1.00	26.46	N
ATOM	1559	CA SER A 202	-9.617	-36.797	19.371	1.00	27.52	C
ATOM	1560	CB SER A 202	-10.129	-38.125	19.924	1.00	27.43	C
ATOM	1561	OG SER A 202	-11.390	-38.430	19.362	1.00	28.18	O
ATOM	1562	C SER A 202	-8.903	-36.981	18.023	1.00	28.04	C
ATOM	1563	O SER A 202	-7.705	-37.275	17.966	1.00	28.00	O
ATOM	1564	N SER A 203	-9.673	-36.796	16.949	1.00	28.72	N
ATOM	1565	CA SER A 203	-9.180	-36.739	15.576	1.00	28.85	C
ATOM	1566	CB SER A 203	-9.538	-38.033	14.831	1.00	29.11	C
ATOM	1567	OG SER A 203	-8.596	-39.054	15.103	1.00	29.90	O
ATOM	1568	C SER A 203	-9.848	-35.559	14.867	1.00	28.59	C
ATOM	1569	O SER A 203	-10.967	-35.173	15.236	1.00	28.54	O
ATOM	1570	N PRO A 204	-9.165	-34.975	13.857	1.00	28.13	N
ATOM	1571	CA PRO A 204	-9.784	-34.029	12.930	1.00	27.81	C
ATOM	1572	CB PRO A 204	-8.778	-33.973	11.792	1.00	27.71	C
ATOM	1573	CG PRO A 204	-7.472	-34.128	12.491	1.00	27.71	C
ATOM	1574	CD PRO A 204	-7.728	-35.142	13.569	1.00	28.09	C
ATOM	1575	C PRO A 204	-11.108	-34.542	12.408	1.00	27.52	C
ATOM	1576	O PRO A 204	-11.216	-35.711	12.062	1.00	27.89	O
ATOM	1577	N VAL A 205	-12.110	-33.674	12.389	1.00	27.07	N
ATOM	1578	CA VAL A 205	-13.419	-33.987	11.833	1.00	26.37	C
ATOM	1579	CB VAL A 205	-14.569	-33.507	12.768	1.00	26.46	C
ATOM	1580	CG1 VAL A 205	-15.812	-33.064	11.981	1.00	26.51	C
ATOM	1581	CG2 VAL A 205	-14.917	-34.580	13.779	1.00	25.99	C
ATOM	1582	C VAL A 205	-13.517	-33.345	10.446	1.00	26.17	C
ATOM	1583	O VAL A 205	-13.124	-32.188	10.256	1.00	25.44	O
ATOM	1584	N THR A 206	-14.017	-34.130	9.489	1.00	25.92	N
ATOM	1585	CA THR A 206	-14.180	-33.710	8.109	1.00	25.71	C
ATOM	1586	CB THR A 206	-13.341	-34.596	7.135	1.00	25.69	C
ATOM	1587	OG1 THR A 206	-11.969	-34.171	7.151	1.00	25.27	O
ATOM	1588	CG2 THR A 206	-13.856	-34.501	5.690	1.00	25.77	C
ATOM	1589	C THR A 206	-15.658	-33.752	7.752	1.00	25.98	C
ATOM	1590	O THR A 206	-16.345	-34.747	8.000	1.00	25.58	O
ATOM	1591	N LYS A 207	-16.138	-32.652	7.178	1.00	26.48	N
ATOM	1592	CA LYS A 207	-17.522	-32.527	6.750	1.00	27.09	C
ATOM	1593	CB LYS A 207	-18.221	-31.459	7.590	1.00	26.99	C
ATOM	1594	CG LYS A 207	-19.509	-31.916	8.260	1.00	27.04	C
ATOM	1595	CD LYS A 207	-19.303	-33.021	9.299	1.00	27.78	C
ATOM	1596	CE LYS A 207	-20.615	-33.313	10.026	1.00	29.48	C
ATOM	1597	NZ LYS A 207	-20.486	-34.385	11.063	1.00	30.87	N
ATOM	1598	C LYS A 207	-17.537	-32.178	5.269	1.00	27.53	C
ATOM	1599	O LYS A 207	-16.851	-31.254	4.851	1.00	27.44	O

ATOM	1600	N	SER A 208	-18.314	-32.927	4.481	1.00	28.72	N
ATOM	1601	CA	SER A 208	-18.168	-32.939	3.006	1.00	29.53	C
ATOM	1602	CB	SER A 208	-17.373	-34.167	2.579	1.00	29.38	C
ATOM	1603	OG	SER A 208	-16.097	-33.766	2.150	1.00	31.01	O
ATOM	1604	C	SER A 208	-19.430	-32.921	2.161	1.00	30.07	C
ATOM	1605	O	SER A 208	-20.512	-33.250	2.624	1.00	30.16	O
ATOM	1606	N	PHE A 209	-19.260	-32.558	0.894	1.00	31.27	N
ATOM	1607	CA	PHE A 209	-20.247	-32.841	-0.141	1.00	31.87	C
ATOM	1608	CB	PHE A 209	-21.378	-31.810	-0.151	1.00	31.12	C
ATOM	1609	CG	PHE A 209	-20.947	-30.424	-0.523	1.00	30.43	C
ATOM	1610	CD1	PHE A 209	-20.945	-30.014	-1.849	1.00	29.46	C
ATOM	1611	CE1	PHE A 209	-20.563	-28.734	-2.196	1.00	28.36	C
ATOM	1612	CZ	PHE A 209	-20.191	-27.831	-1.212	1.00	29.76	C
ATOM	1613	CE2	PHE A 209	-20.191	-28.214	0.118	1.00	29.79	C
ATOM	1614	CD2	PHE A 209	-20.571	-29.511	0.458	1.00	30.31	C
ATOM	1615	C	PHE A 209	-19.584	-32.950	-1.506	1.00	33.21	C
ATOM	1616	O	PHE A 209	-18.399	-32.627	-1.651	1.00	32.77	O
ATOM	1617	N	ASN A 210	-20.364	-33.428	-2.483	1.00	35.34	N
ATOM	1618	CA	ASN A 210	-20.010	-33.418	-3.901	1.00	37.29	C
ATOM	1619	CB	ASN A 210	-20.139	-34.819	-4.503	1.00	37.18	C
ATOM	1620	CG	ASN A 210	-19.458	-35.887	-3.688	1.00	37.65	C
ATOM	1621	OD1	ASN A 210	-18.263	-35.814	-3.415	1.00	37.56	O
ATOM	1622	ND2	ASN A 210	-20.216	-36.914	-3.321	1.00	37.47	N
ATOM	1623	C	ASN A 210	-20.973	-32.550	-4.688	1.00	38.92	C
ATOM	1624	O	ASN A 210	-22.171	-32.615	-4.434	1.00	39.52	O
ATOM	1625	N	ARG A 211	-20.461	-31.739	-5.624	1.00	40.91	N
ATOM	1626	CA	ARG A 211	-21.223	-31.307	-6.831	1.00	42.83	C
ATOM	1627	CB	ARG A 211	-22.752	-31.316	-6.639	1.00	42.65	C
ATOM	1628	CG	ARG A 211	-23.424	-32.538	-7.247	1.00	43.52	C
ATOM	1629	CD	ARG A 211	-24.903	-32.590	-6.904	1.00	45.90	C
ATOM	1630	NE	ARG A 211	-25.173	-33.457	-5.756	1.00	48.28	N
ATOM	1631	CZ	ARG A 211	-26.191	-33.289	-4.908	1.00	49.86	C
ATOM	1632	NH1	ARG A 211	-27.031	-32.271	-5.070	1.00	50.60	N
ATOM	1633	NH2	ARG A 211	-26.367	-34.125	-3.883	1.00	48.86	N
ATOM	1634	C	ARG A 211	-20.766	-30.078	-7.642	1.00	44.27	C
ATOM	1635	O	ARG A 211	-21.158	-28.943	-7.373	1.00	44.08	O
ATOM	1636	N	GLY A 212	-19.955	-30.334	-8.670	1.00	46.22	N
ATOM	1637	CA	GLY A 212	-19.782	-29.398	-9.775	1.00	47.96	C
ATOM	1638	C	GLY A 212	-21.033	-29.544	-10.624	1.00	49.57	C
ATOM	1639	O	GLY A 212	-21.034	-30.285	-11.611	1.00	49.46	O
ATOM	1640	N	GLU A 213	-22.109	-28.867	-10.195	1.00	51.01	N
ATOM	1641	CA	GLU A 213	-23.415	-28.857	-10.883	1.00	52.30	C
ATOM	1642	CB	GLU A 213	-24.467	-29.667	-10.102	1.00	52.37	C
ATOM	1643	CG	GLU A 213	-25.858	-29.698	-10.777	1.00	53.37	C
ATOM	1644	CD	GLU A 213	-27.013	-29.914	-9.789	1.00	53.29	C
ATOM	1645	OE1	GLU A 213	-27.248	-31.079	-9.387	1.00	54.07	O
ATOM	1646	OE2	GLU A 213	-27.695	-28.920	-9.433	1.00	53.86	O
ATOM	1647	C	GLU A 213	-23.917	-27.422	-11.067	1.00	52.50	C
ATOM	1648	O	GLU A 213	-24.012	-26.656	-10.097	1.00	52.81	O
ATOM	1649	N	GLU B 1	-25.173	15.398	36.080	1.00	35.84	N
ATOM	1650	CA	GLU B 1	-24.357	14.254	35.562	1.00	36.29	C
ATOM	1651	CB	GLU B 1	-25.267	13.095	35.144	1.00	36.33	C
ATOM	1652	CG	GLU B 1	-24.535	11.770	34.914	1.00	37.88	C
ATOM	1653	CD	GLU B 1	-25.454	10.686	34.337	1.00	38.89	C
ATOM	1654	OE1	GLU B 1	-25.160	9.476	34.550	1.00	42.59	O
ATOM	1655	OE2	GLU B 1	-26.467	11.041	33.674	1.00	40.91	O
ATOM	1656	C	GLU B 1	-23.435	14.651	34.397	1.00	34.92	C

ATOM	1657	O	GLU	B	1	-23.865	15.280	33.427	1.00	34.40	O
ATOM	1658	N	VAL	B	2	-22.165	14.270	34.508	1.00	33.93	N
ATOM	1659	CA	VAL	B	2	-21.184	14.571	33.468	1.00	32.86	C
ATOM	1660	CB	VAL	B	2	-19.716	14.527	34.010	1.00	33.01	C
ATOM	1661	CG1	VAL	B	2	-18.699	14.540	32.873	1.00	32.36	C
ATOM	1662	CG2	VAL	B	2	-19.460	15.699	34.963	1.00	32.28	C
ATOM	1663	C	VAL	B	2	-21.385	13.656	32.254	1.00	32.10	C
ATOM	1664	O	VAL	B	2	-21.366	12.433	32.371	1.00	32.16	O
ATOM	1665	N	GLN	B	3	-21.580	14.267	31.091	1.00	30.95	N
ATOM	1666	CA	GLN	B	3	-21.868	13.530	29.884	1.00	30.04	C
ATOM	1667	CB	GLN	B	3	-23.345	13.647	29.584	1.00	30.40	C
ATOM	1668	CG	GLN	B	3	-24.050	12.336	29.416	1.00	32.78	C
ATOM	1669	CD	GLN	B	3	-25.547	12.528	29.281	1.00	35.96	C
ATOM	1670	OE1	GLN	B	3	-26.160	13.339	30.003	1.00	35.65	O
ATOM	1671	NE2	GLN	B	3	-26.150	11.794	28.339	1.00	36.53	N
ATOM	1672	C	GLN	B	3	-21.078	14.139	28.743	1.00	28.98	C
ATOM	1673	O	GLN	B	3	-21.072	15.366	28.582	1.00	29.14	O
ATOM	1674	N	LEU	B	4	-20.388	13.285	27.976	1.00	27.47	N
ATOM	1675	CA	LEU	B	4	-19.731	13.689	26.723	1.00	25.48	C
ATOM	1676	CB	LEU	B	4	-18.248	13.332	26.725	1.00	25.27	C
ATOM	1677	CG	LEU	B	4	-17.272	13.737	27.832	1.00	24.80	C
ATOM	1678	CD1	LEU	B	4	-15.879	13.846	27.235	1.00	24.51	C
ATOM	1679	CD2	LEU	B	4	-17.629	15.034	28.499	1.00	24.57	C
ATOM	1680	C	LEU	B	4	-20.434	13.016	25.534	1.00	24.53	C
ATOM	1681	O	LEU	B	4	-20.485	11.794	25.443	1.00	24.21	O
ATOM	1682	N	VAL	B	5	-20.993	13.827	24.641	1.00	23.34	N
ATOM	1683	CA	VAL	B	5	-21.796	13.324	23.538	1.00	22.06	C
ATOM	1684	CB	VAL	B	5	-23.228	13.900	23.562	1.00	22.09	C
ATOM	1685	CG1	VAL	B	5	-24.028	13.418	22.375	1.00	22.31	C
ATOM	1686	CG2	VAL	B	5	-23.939	13.510	24.840	1.00	21.94	C
ATOM	1687	C	VAL	B	5	-21.094	13.689	22.240	1.00	21.51	C
ATOM	1688	O	VAL	B	5	-20.799	14.863	21.993	1.00	21.12	O
ATOM	1689	N	GLN	B	6	-20.817	12.658	21.434	1.00	20.66	N
ATOM	1690	CA	GLN	B	6	-20.091	12.788	20.177	1.00	19.40	C
ATOM	1691	CB	GLN	B	6	-18.987	11.758	20.092	1.00	19.08	C
ATOM	1692	CG	GLN	B	6	-17.930	11.861	21.141	1.00	17.26	C
ATOM	1693	CD	GLN	B	6	-16.878	10.812	20.945	1.00	15.78	C
ATOM	1694	OE1	GLN	B	6	-16.285	10.726	19.884	1.00	16.18	O
ATOM	1695	NE2	GLN	B	6	-16.642	10.001	21.963	1.00	15.50	N
ATOM	1696	C	GLN	B	6	-21.025	12.546	19.023	1.00	19.51	C
ATOM	1697	O	GLN	B	6	-22.057	11.900	19.183	1.00	19.76	O
ATOM	1698	N	SER	B	7	-20.648	13.058	17.854	1.00	19.44	N
ATOM	1699	CA	SER	B	7	-21.470	12.983	16.649	1.00	19.02	C
ATOM	1700	CB	SER	B	7	-20.983	14.008	15.617	1.00	18.73	C
ATOM	1701	OG	SER	B	7	-19.573	13.958	15.435	1.00	17.94	O
ATOM	1702	C	SER	B	7	-21.513	11.562	16.066	1.00	19.37	C
ATOM	1703	O	SER	B	7	-20.673	10.712	16.409	1.00	19.81	O
ATOM	1704	N	GLY	B	8	-22.497	11.317	15.197	1.00	19.36	N
ATOM	1705	CA	GLY	B	8	-22.795	9.988	14.666	1.00	18.94	C
ATOM	1706	C	GLY	B	8	-21.731	9.434	13.738	1.00	19.33	C
ATOM	1707	O	GLY	B	8	-20.721	10.093	13.456	1.00	19.44	O
ATOM	1708	N	ALA	B	9	-21.962	8.212	13.263	1.00	19.18	N
ATOM	1709	CA	ALA	B	9	-20.995	7.489	12.452	1.00	19.01	C
ATOM	1710	CB	ALA	B	9	-21.459	6.056	12.233	1.00	18.70	C
ATOM	1711	C	ALA	B	9	-20.745	8.181	11.117	1.00	19.13	C
ATOM	1712	O	ALA	B	9	-21.667	8.671	10.480	1.00	18.96	O
ATOM	1713	N	GLU	B	10	-19.490	8.198	10.692	1.00	19.55	N

ATOM	1714	CA	GLU	B	10	-19.115	8.863	9.464	1.00	20.19	C
ATOM	1715	CB	GLU	B	10	-18.088	9.971	9.743	1.00	19.81	C
ATOM	1716	CG	GLU	B	10	-18.650	11.163	10.500	1.00	20.77	C
ATOM	1717	CD	GLU	B	10	-19.519	12.113	9.634	1.00	23.62	C
ATOM	1718	OE1	GLU	B	10	-20.108	13.052	10.226	1.00	24.97	O
ATOM	1719	OE2	GLU	B	10	-19.609	11.943	8.389	1.00	20.17	O
ATOM	1720	C	GLU	B	10	-18.574	7.866	8.451	1.00	20.91	C
ATOM	1721	O	GLU	B	10	-17.694	7.048	8.765	1.00	21.42	O
ATOM	1722	N	VAL	B	11	-19.109	7.926	7.235	1.00	21.36	N
ATOM	1723	CA	VAL	B	11	-18.580	7.131	6.138	1.00	21.94	C
ATOM	1724	CB	VAL	B	11	-19.585	6.085	5.633	1.00	21.99	C
ATOM	1725	CG1	VAL	B	11	-18.925	5.197	4.566	1.00	21.77	C
ATOM	1726	CG2	VAL	B	11	-20.082	5.235	6.796	1.00	22.22	C
ATOM	1727	C	VAL	B	11	-18.113	8.046	5.010	1.00	22.26	C
ATOM	1728	O	VAL	B	11	-18.881	8.853	4.488	1.00	22.18	O
ATOM	1729	N	LYS	B	12	-16.840	7.913	4.657	1.00	22.58	N
ATOM	1730	CA	LYS	B	12	-16.181	8.865	3.781	1.00	22.75	C
ATOM	1731	CB	LYS	B	12	-15.427	9.918	4.613	1.00	22.78	C
ATOM	1732	CG	LYS	B	12	-16.319	11.002	5.288	1.00	23.05	C
ATOM	1733	CD	LYS	B	12	-17.187	11.752	4.266	1.00	24.05	C
ATOM	1734	CE	LYS	B	12	-17.376	13.241	4.592	1.00	24.20	C
ATOM	1735	NZ	LYS	B	12	-18.724	13.512	5.135	1.00	24.40	N
ATOM	1736	C	LYS	B	12	-15.246	8.180	2.783	1.00	23.11	C
ATOM	1737	O	LYS	B	12	-14.852	7.011	2.948	1.00	23.09	O
ATOM	1738	N	LYS	B	13	-14.896	8.912	1.731	1.00	23.34	N
ATOM	1739	CA	LYS	B	13	-13.987	8.384	0.719	1.00	23.28	C
ATOM	1740	CB	LYS	B	13	-14.537	8.691	-0.677	1.00	23.60	C
ATOM	1741	CG	LYS	B	13	-15.882	8.004	-0.945	1.00	25.84	C
ATOM	1742	CD	LYS	B	13	-16.155	7.787	-2.422	1.00	29.71	C
ATOM	1743	CE	LYS	B	13	-14.969	7.112	-3.112	1.00	33.07	C
ATOM	1744	NZ	LYS	B	13	-14.773	7.572	-4.534	1.00	35.26	N
ATOM	1745	C	LYS	B	13	-12.581	8.937	0.958	1.00	22.34	C
ATOM	1746	O	LYS	B	13	-12.449	9.989	1.574	1.00	22.05	O
ATOM	1747	N	PRO	B	14	-11.533	8.205	0.540	1.00	21.99	N
ATOM	1748	CA	PRO	B	14	-10.164	8.702	0.698	1.00	22.48	C
ATOM	1749	CB	PRO	B	14	-9.322	7.641	-0.019	1.00	22.39	C
ATOM	1750	CG	PRO	B	14	-10.127	6.399	0.075	1.00	21.62	C
ATOM	1751	CD	PRO	B	14	-11.551	6.863	-0.066	1.00	22.00	C
ATOM	1752	C	PRO	B	14	-9.985	10.049	0.014	1.00	23.26	C
ATOM	1753	O	PRO	B	14	-10.322	10.179	-1.167	1.00	23.63	O
ATOM	1754	N	GLY	B	15	-9.500	11.050	0.757	1.00	23.66	N
ATOM	1755	CA	GLY	B	15	-9.315	12.399	0.215	1.00	23.25	C
ATOM	1756	C	GLY	B	15	-10.273	13.463	0.716	1.00	23.41	C
ATOM	1757	O	GLY	B	15	-10.033	14.652	0.516	1.00	23.87	O
ATOM	1758	N	GLU	B	16	-11.351	13.063	1.379	1.00	23.46	N
ATOM	1759	CA	GLU	B	16	-12.385	14.014	1.792	1.00	23.66	C
ATOM	1760	CB	GLU	B	16	-13.755	13.354	1.753	1.00	23.57	C
ATOM	1761	CG	GLU	B	16	-14.003	12.524	0.540	1.00	24.57	C
ATOM	1762	CD	GLU	B	16	-15.476	12.246	0.352	1.00	28.03	C
ATOM	1763	OE1	GLU	B	16	-16.058	11.403	1.095	1.00	28.27	O
ATOM	1764	OE2	GLU	B	16	-16.053	12.888	-0.552	1.00	29.42	O
ATOM	1765	C	GLU	B	16	-12.158	14.630	3.176	1.00	23.82	C
ATOM	1766	O	GLU	B	16	-11.377	14.117	3.969	1.00	23.95	O
ATOM	1767	N	SER	B	17	-12.852	15.733	3.453	1.00	24.00	N
ATOM	1768	CA	SER	B	17	-12.742	16.428	4.729	1.00	24.18	C
ATOM	1769	CB	SER	B	17	-13.197	17.877	4.595	1.00	24.14	C
ATOM	1770	OG	SER	B	17	-12.366	18.592	3.714	1.00	26.06	O

ATOM	1771	C	SER B	17	-13.657	15.774	5.729	1.00	24.13	C
ATOM	1772	O	SER B	17	-14.667	15.164	5.354	1.00	24.75	O
ATOM	1773	N	LEU B	18	-13.343	15.941	7.006	1.00	23.48	N
ATOM	1774	CA	LEU B	18	-14.253	15.501	8.046	1.00	23.16	C
ATOM	1775	CB	LEU B	18	-14.165	13.970	8.259	1.00	22.76	C
ATOM	1776	CG	LEU B	18	-15.001	13.320	9.373	1.00	23.12	C
ATOM	1777	CD1	LEU B	18	-16.494	13.544	9.169	1.00	22.06	C
ATOM	1778	CD2	LEU B	18	-14.689	11.841	9.576	1.00	22.78	C
ATOM	1779	C	LEU B	18	-13.990	16.280	9.335	1.00	23.04	C
ATOM	1780	O	LEU B	18	-12.847	16.567	9.670	1.00	22.67	O
ATOM	1781	N	LYS B	19	-15.075	16.629	10.019	1.00	22.99	N
ATOM	1782	CA	LYS B	19	-15.039	17.287	11.305	1.00	23.29	C
ATOM	1783	CB	LYS B	19	-15.400	18.766	11.139	1.00	23.16	C
ATOM	1784	CG	LYS B	19	-15.497	19.606	12.430	1.00	24.28	C
ATOM	1785	CD	LYS B	19	-15.356	21.104	12.049	1.00	24.86	C
ATOM	1786	CE	LYS B	19	-15.577	22.057	13.219	1.00	27.64	C
ATOM	1787	NZ	LYS B	19	-15.133	23.437	12.853	1.00	28.83	N
ATOM	1788	C	LYS B	19	-16.030	16.582	12.227	1.00	22.55	C
ATOM	1789	O	LYS B	19	-17.239	16.725	12.080	1.00	22.92	O
ATOM	1790	N	ILE B	20	-15.522	15.808	13.170	1.00	22.02	N
ATOM	1791	CA	ILE B	20	-16.390	15.208	14.174	1.00	21.50	C
ATOM	1792	CB	ILE B	20	-16.015	13.727	14.411	1.00	21.78	C
ATOM	1793	CG1	ILE B	20	-14.649	13.592	15.074	1.00	20.63	C
ATOM	1794	CD1	ILE B	20	-14.323	12.157	15.439	1.00	20.50	C
ATOM	1795	CG2	ILE B	20	-16.039	12.958	13.079	1.00	21.26	C
ATOM	1796	C	ILE B	20	-16.411	16.048	15.473	1.00	21.20	C
ATOM	1797	O	ILE B	20	-15.505	16.855	15.708	1.00	21.03	O
ATOM	1798	N	SER B	21	-17.437	15.869	16.302	1.00	20.52	N
ATOM	1799	CA	SER B	21	-17.616	16.728	17.472	1.00	20.02	C
ATOM	1800	CB	SER B	21	-18.798	17.671	17.238	1.00	20.17	C
ATOM	1801	OG	SER B	21	-20.025	16.964	17.169	1.00	19.81	O
ATOM	1802	C	SER B	21	-17.794	16.003	18.812	1.00	19.91	C
ATOM	1803	O	SER B	21	-18.122	14.821	18.855	1.00	19.99	O
ATOM	1804	N	CYS B	22	-17.590	16.739	19.901	1.00	19.37	N
ATOM	1805	CA	CYS B	22	-17.753	16.228	21.259	1.00	19.51	C
ATOM	1806	CB	CYS B	22	-16.382	15.786	21.809	1.00	19.05	C
ATOM	1807	SG	CYS B	22	-16.307	15.243	23.535	1.00	17.97	S
ATOM	1808	C	CYS B	22	-18.393	17.319	22.139	1.00	19.84	C
ATOM	1809	O	CYS B	22	-17.780	18.342	22.399	1.00	19.70	O
ATOM	1810	N	GLN B	23	-19.632	17.104	22.572	1.00	20.38	N
ATOM	1811	CA	GLN B	23	-20.300	18.049	23.453	1.00	21.20	C
ATOM	1812	CB	GLN B	23	-21.753	18.259	23.058	1.00	21.00	C
ATOM	1813	CG	GLN B	23	-21.966	19.514	22.284	1.00	22.41	C
ATOM	1814	CD	GLN B	23	-23.294	20.175	22.565	1.00	22.33	C
ATOM	1815	OE1	GLN B	23	-23.344	21.274	23.110	1.00	22.21	O
ATOM	1816	NE2	GLN B	23	-24.373	19.521	22.185	1.00	22.16	N
ATOM	1817	C	GLN B	23	-20.251	17.651	24.913	1.00	21.90	C
ATOM	1818	O	GLN B	23	-20.580	16.507	25.267	1.00	21.79	O
ATOM	1819	N	SER B	24	-19.860	18.613	25.753	1.00	22.59	N
ATOM	1820	CA	SER B	24	-19.846	18.437	27.201	1.00	23.72	C
ATOM	1821	CB	SER B	24	-18.605	19.086	27.792	1.00	23.83	C
ATOM	1822	OG	SER B	24	-17.425	18.438	27.331	1.00	24.89	O
ATOM	1823	C	SER B	24	-21.100	19.005	27.863	1.00	24.40	C
ATOM	1824	O	SER B	24	-21.557	20.093	27.495	1.00	24.51	O
ATOM	1825	N	PHE B	25	-21.651	18.249	28.821	1.00	24.94	N
ATOM	1826	CA	PHE B	25	-22.824	18.649	29.604	1.00	25.66	C
ATOM	1827	CB	PHE B	25	-24.069	17.856	29.204	1.00	25.68	C

ATOM	1828	CG	PHE	B	25	-24.496	18.034	27.777	1.00	27.09	C
ATOM	1829	CD1	PHE	B	25	-25.459	18.997	27.437	1.00	28.43	C
ATOM	1830	CE1	PHE	B	25	-25.882	19.158	26.107	1.00	27.58	C
ATOM	1831	CZ	PHE	B	25	-25.347	18.329	25.102	1.00	26.83	C
ATOM	1832	CE2	PHE	B	25	-24.401	17.355	25.433	1.00	26.54	C
ATOM	1833	CD2	PHE	B	25	-23.982	17.208	26.770	1.00	26.96	C
ATOM	1834	C	PHE	B	25	-22.576	18.373	31.088	1.00	26.18	C
ATOM	1835	O	PHE	B	25	-21.894	17.401	31.441	1.00	26.27	O
ATOM	1836	N	GLY	B	26	-23.161	19.212	31.948	1.00	26.40	N
ATOM	1837	CA	GLY	B	26	-23.159	18.997	33.395	1.00	26.24	C
ATOM	1838	C	GLY	B	26	-21.868	19.307	34.144	1.00	26.19	C
ATOM	1839	O	GLY	B	26	-21.659	18.791	35.235	1.00	26.33	O
ATOM	1840	N	TYR	B	27	-20.993	20.126	33.564	1.00	26.00	N
ATOM	1841	CA	TYR	B	27	-19.775	20.596	34.257	1.00	25.85	C
ATOM	1842	CB	TYR	B	27	-18.667	19.514	34.333	1.00	25.49	C
ATOM	1843	CG	TYR	B	27	-17.897	19.235	33.038	1.00	24.82	C
ATOM	1844	CD1	TYR	B	27	-18.340	18.269	32.139	1.00	24.17	C
ATOM	1845	CE1	TYR	B	27	-17.651	18.003	30.952	1.00	24.17	C
ATOM	1846	CZ	TYR	B	27	-16.493	18.699	30.649	1.00	25.04	C
ATOM	1847	OH	TYR	B	27	-15.827	18.413	29.470	1.00	23.90	O
ATOM	1848	CE2	TYR	B	27	-16.017	19.674	31.528	1.00	25.25	C
ATOM	1849	CD2	TYR	B	27	-16.723	19.930	32.724	1.00	25.10	C
ATOM	1850	C	TYR	B	27	-19.277	21.834	33.542	1.00	25.94	C
ATOM	1851	O	TYR	B	27	-19.732	22.128	32.440	1.00	26.13	O
ATOM	1852	N	ILE	B	28	-18.344	22.550	34.153	1.00	26.15	N
ATOM	1853	CA	ILE	B	28	-17.827	23.782	33.552	1.00	26.74	C
ATOM	1854	CB	ILE	B	28	-17.231	24.748	34.610	1.00	26.94	C
ATOM	1855	CG1	ILE	B	28	-18.351	25.276	35.537	1.00	27.83	C
ATOM	1856	CD1	ILE	B	28	-17.882	25.779	36.925	1.00	27.47	C
ATOM	1857	CG2	ILE	B	28	-16.489	25.901	33.923	1.00	27.02	C
ATOM	1858	C	ILE	B	28	-16.805	23.437	32.483	1.00	26.42	C
ATOM	1859	O	ILE	B	28	-15.717	22.926	32.781	1.00	26.37	O
ATOM	1860	N	PHE	B	29	-17.166	23.716	31.233	1.00	26.16	N
ATOM	1861	CA	PHE	B	29	-16.350	23.303	30.088	1.00	25.62	C
ATOM	1862	CB	PHE	B	29	-16.989	23.760	28.783	1.00	25.75	C
ATOM	1863	CG	PHE	B	29	-16.276	23.273	27.548	1.00	26.74	C
ATOM	1864	CD1	PHE	B	29	-15.982	21.919	27.380	1.00	26.20	C
ATOM	1865	CE1	PHE	B	29	-15.341	21.460	26.243	1.00	26.09	C
ATOM	1866	CZ	PHE	B	29	-14.998	22.350	25.240	1.00	27.40	C
ATOM	1867	CE2	PHE	B	29	-15.298	23.715	25.379	1.00	28.46	C
ATOM	1868	CD2	PHE	B	29	-15.927	24.167	26.533	1.00	28.06	C
ATOM	1869	C	PHE	B	29	-14.904	23.785	30.162	1.00	25.01	C
ATOM	1870	O	PHE	B	29	-13.967	23.014	29.914	1.00	25.13	O
ATOM	1871	N	ILE	B	30	-14.735	25.052	30.525	1.00	24.10	N
ATOM	1872	CA	ILE	B	30	-13.432	25.700	30.503	1.00	23.24	C
ATOM	1873	CB	ILE	B	30	-13.588	27.231	30.321	1.00	23.43	C
ATOM	1874	CG1	ILE	B	30	-14.584	27.822	31.330	1.00	22.61	C
ATOM	1875	CD1	ILE	B	30	-14.171	29.174	31.872	1.00	18.95	C
ATOM	1876	CG2	ILE	B	30	-14.088	27.545	28.914	1.00	23.32	C
ATOM	1877	C	ILE	B	30	-12.558	25.328	31.725	1.00	23.10	C
ATOM	1878	O	ILE	B	30	-11.415	25.783	31.851	1.00	22.47	O
ATOM	1879	N	ASP	B	31	-13.104	24.477	32.601	1.00	22.87	N
ATOM	1880	CA	ASP	B	31	-12.383	23.958	33.770	1.00	22.50	C
ATOM	1881	CB	ASP	B	31	-13.357	23.650	34.900	1.00	22.90	C
ATOM	1882	CG	ASP	B	31	-13.697	24.868	35.727	1.00	24.41	C
ATOM	1883	OD1	ASP	B	31	-13.003	25.910	35.585	1.00	27.88	O
ATOM	1884	OD2	ASP	B	31	-14.659	24.779	36.523	1.00	24.82	O

ATOM	1885	C	ASP B 31	-11.559	22.708	33.497	1.00	21.87	C
ATOM	1886	O	ASP B 31	-10.853	22.235	34.379	1.00	22.00	O
ATOM	1887	N	HIS B 32	-11.650	22.167	32.285	1.00	21.15	N
ATOM	1888	CA	HIS B 32	-10.965	20.918	31.946	1.00	20.01	C
ATOM	1889	CB	HIS B 32	-11.919	19.747	32.151	1.00	19.95	C
ATOM	1890	CG	HIS B 32	-12.388	19.582	33.566	1.00	20.91	C
ATOM	1891	ND1	HIS B 32	-13.548	20.160	34.040	1.00	21.35	N
ATOM	1892	CE1	HIS B 32	-13.717	19.833	35.309	1.00	21.38	C
ATOM	1893	NE2	HIS B 32	-12.713	19.054	35.674	1.00	21.71	N
ATOM	1894	CD2	HIS B 32	-11.865	18.883	34.605	1.00	21.13	C
ATOM	1895	C	HIS B 32	-10.401	20.932	30.507	1.00	19.05	C
ATOM	1896	O	HIS B 32	-10.639	21.872	29.756	1.00	18.84	O
ATOM	1897	N	THR B 33	-9.634	19.905	30.151	1.00	17.58	N
ATOM	1898	CA	THR B 33	-9.182	19.719	28.784	1.00	16.51	C
ATOM	1899	CB	THR B 33	-7.694	19.362	28.711	1.00	16.45	C
ATOM	1900	OG1	THR B 33	-7.401	18.364	29.695	1.00	16.97	O
ATOM	1901	CG2	THR B 33	-6.792	20.597	28.890	1.00	15.58	C
ATOM	1902	C	THR B 33	-9.935	18.559	28.139	1.00	16.25	C
ATOM	1903	O	THR B 33	-10.325	17.609	28.820	1.00	16.38	O
ATOM	1904	N	ILE B 34	-10.131	18.631	26.825	1.00	15.50	N
ATOM	1905	CA	ILE B 34	-10.718	17.526	26.084	1.00	14.92	C
ATOM	1906	CB	ILE B 34	-11.887	17.994	25.192	1.00	14.75	C
ATOM	1907	CG1	ILE B 34	-13.017	18.551	26.048	1.00	13.74	C
ATOM	1908	CD1	ILE B 34	-13.721	17.510	26.891	1.00	14.88	C
ATOM	1909	CG2	ILE B 34	-12.424	16.850	24.338	1.00	14.22	C
ATOM	1910	C	ILE B 34	-9.616	16.855	25.267	1.00	14.88	C
ATOM	1911	O	ILE B 34	-8.774	17.548	24.698	1.00	15.37	O
ATOM	1912	N	HIS B 35	-9.611	15.519	25.242	1.00	14.34	N
ATOM	1913	CA	HIS B 35	-8.548	14.746	24.585	1.00	14.13	C
ATOM	1914	CB	HIS B 35	-7.731	13.919	25.584	1.00	13.75	C
ATOM	1915	CG	HIS B 35	-7.105	14.717	26.682	1.00	11.36	C
ATOM	1916	ND1	HIS B 35	-5.739	14.816	26.838	1.00	9.39	N
ATOM	1917	CE1	HIS B 35	-5.477	15.562	27.895	1.00	9.64	C
ATOM	1918	NE2	HIS B 35	-6.623	15.952	28.425	1.00	9.37	N
ATOM	1919	CD2	HIS B 35	-7.656	15.421	27.696	1.00	8.90	C
ATOM	1920	C	HIS B 35	-9.173	13.783	23.610	1.00	14.55	C
ATOM	1921	O	HIS B 35	-10.270	13.298	23.849	1.00	14.94	O
ATOM	1922	N	TRP B 36	-8.464	13.502	22.522	1.00	14.98	N
ATOM	1923	CA	TRP B 36	-8.961	12.635	21.473	1.00	15.16	C
ATOM	1924	CB	TRP B 36	-8.946	13.343	20.119	1.00	15.36	C
ATOM	1925	CG	TRP B 36	-10.042	14.333	19.976	1.00	15.59	C
ATOM	1926	CD1	TRP B 36	-9.947	15.683	20.134	1.00	16.43	C
ATOM	1927	NE1	TRP B 36	-11.167	16.271	19.932	1.00	16.56	N
ATOM	1928	CE2	TRP B 36	-12.089	15.299	19.652	1.00	15.76	C
ATOM	1929	CD2	TRP B 36	-11.411	14.059	19.671	1.00	15.69	C
ATOM	1930	CE3	TRP B 36	-12.131	12.885	19.404	1.00	16.61	C
ATOM	1931	CZ3	TRP B 36	-13.495	12.992	19.123	1.00	16.89	C
ATOM	1932	CH2	TRP B 36	-14.140	14.258	19.110	1.00	16.52	C
ATOM	1933	CZ2	TRP B 36	-13.453	15.411	19.364	1.00	15.35	C
ATOM	1934	C	TRP B 36	-8.129	11.381	21.399	1.00	15.30	C
ATOM	1935	O	TRP B 36	-6.893	11.445	21.307	1.00	15.15	O
ATOM	1936	N	MET B 37	-8.826	10.249	21.440	1.00	15.21	N
ATOM	1937	CA	MET B 37	-8.211	8.936	21.327	1.00	15.41	C
ATOM	1938	CB	MET B 37	-8.523	8.076	22.559	1.00	15.43	C
ATOM	1939	CG	MET B 37	-7.356	7.796	23.487	1.00	14.95	C
ATOM	1940	SD	MET B 37	-6.800	9.225	24.409	1.00	15.11	S
ATOM	1941	CE	MET B 37	-8.328	9.814	25.155	1.00	14.73	C

ATOM	1942	C	MET B 37	-8.732	8.231	20.096	1.00	15.57	C
ATOM	1943	O	MET B 37	-9.941	8.248	19.803	1.00	15.35	O
ATOM	1944	N	ARG B 38	-7.798	7.612	19.387	1.00	15.75	N
ATOM	1945	CA	ARG B 38	-8.099	6.728	18.279	1.00	15.82	C
ATOM	1946	CB	ARG B 38	-7.082	6.957	17.172	1.00	15.58	C
ATOM	1947	CG	ARG B 38	-7.294	6.078	15.981	1.00	14.65	C
ATOM	1948	CD	ARG B 38	-6.418	6.494	14.848	1.00	14.15	C
ATOM	1949	NE	ARG B 38	-5.081	5.930	14.974	1.00	13.82	N
ATOM	1950	CZ	ARG B 38	-4.172	5.979	14.006	1.00	13.97	C
ATOM	1951	NH1	ARG B 38	-4.479	6.558	12.854	1.00	12.44	N
ATOM	1952	NH2	ARG B 38	-2.965	5.447	14.189	1.00	13.53	N
ATOM	1953	C	ARG B 38	-8.008	5.267	18.730	1.00	16.38	C
ATOM	1954	O	ARG B 38	-7.100	4.900	19.498	1.00	16.69	O
ATOM	1955	N	GLN B 39	-8.941	4.447	18.254	1.00	16.48	N
ATOM	1956	CA	GLN B 39	-8.802	3.007	18.337	1.00	17.03	C
ATOM	1957	CB	GLN B 39	-9.729	2.430	19.394	1.00	16.85	C
ATOM	1958	CG	GLN B 39	-9.388	1.003	19.762	1.00	15.46	C
ATOM	1959	CD	GLN B 39	-10.192	0.512	20.947	1.00	15.15	C
ATOM	1960	OE1	GLN B 39	-11.292	0.995	21.197	1.00	15.45	O
ATOM	1961	NE2	GLN B 39	-9.647	-0.454	21.681	1.00	13.32	N
ATOM	1962	C	GLN B 39	-9.107	2.366	17.000	1.00	17.97	C
ATOM	1963	O	GLN B 39	-10.279	2.242	16.604	1.00	17.62	O
ATOM	1964	N	MET B 40	-8.044	1.959	16.308	1.00	19.04	N
ATOM	1965	CA	MET B 40	-8.166	1.205	15.056	1.00	19.97	C
ATOM	1966	CB	MET B 40	-6.821	1.113	14.347	1.00	19.77	C
ATOM	1967	CG	MET B 40	-6.356	2.463	13.808	1.00	20.35	C
ATOM	1968	SD	MET B 40	-4.678	2.443	13.165	1.00	21.95	S
ATOM	1969	CE	MET B 40	-3.778	1.477	14.395	1.00	21.06	C
ATOM	1970	C	MET B 40	-8.737	-0.175	15.347	1.00	20.16	C
ATOM	1971	O	MET B 40	-8.400	-0.771	16.370	1.00	19.60	O
ATOM	1972	N	PRO B 41	-9.614	-0.678	14.449	1.00	20.88	N
ATOM	1973	CA	PRO B 41	-10.457	-1.864	14.700	1.00	21.05	C
ATOM	1974	CB	PRO B 41	-11.117	-2.139	13.348	1.00	20.85	C
ATOM	1975	CG	PRO B 41	-10.359	-1.311	12.355	1.00	21.42	C
ATOM	1976	CD	PRO B 41	-9.835	-0.131	13.100	1.00	20.83	C
ATOM	1977	C	PRO B 41	-9.672	-3.073	15.177	1.00	21.27	C
ATOM	1978	O	PRO B 41	-8.727	-3.494	14.505	1.00	20.71	O
ATOM	1979	N	GLY B 42	-10.069	-3.577	16.356	1.00	21.73	N
ATOM	1980	CA	GLY B 42	-9.426	-4.700	17.036	1.00	22.10	C
ATOM	1981	C	GLY B 42	-8.045	-4.408	17.609	1.00	22.83	C
ATOM	1982	O	GLY B 42	-7.322	-5.332	17.976	1.00	23.07	O
ATOM	1983	N	GLN B 43	-7.690	-3.130	17.755	1.00	23.36	N
ATOM	1984	CA	GLN B 43	-6.283	-2.753	17.877	1.00	23.12	C
ATOM	1985	CB	GLN B 43	-5.823	-2.173	16.521	1.00	24.06	C
ATOM	1986	CG	GLN B 43	-4.323	-1.959	16.293	1.00	27.07	C
ATOM	1987	CD	GLN B 43	-3.538	-3.239	16.369	1.00	32.58	C
ATOM	1988	OE1	GLN B 43	-3.252	-3.742	17.465	1.00	36.00	O
ATOM	1989	NE2	GLN B 43	-3.173	-3.786	15.208	1.00	34.09	N
ATOM	1990	C	GLN B 43	-5.866	-1.845	19.054	1.00	21.99	C
ATOM	1991	O	GLN B 43	-4.725	-1.403	19.087	1.00	22.94	O
ATOM	1992	N	GLY B 44	-6.712	-1.560	20.032	1.00	20.38	N
ATOM	1993	CA	GLY B 44	-6.181	-0.765	21.170	1.00	19.25	C
ATOM	1994	C	GLY B 44	-6.041	0.757	21.026	1.00	18.45	C
ATOM	1995	O	GLY B 44	-6.395	1.332	19.998	1.00	18.43	O
ATOM	1996	N	LEU B 45	-5.520	1.422	22.060	1.00	18.00	N
ATOM	1997	CA	LEU B 45	-5.710	2.887	22.222	1.00	17.11	C
ATOM	1998	CB	LEU B 45	-6.255	3.213	23.620	1.00	16.99	C

ATOM	1999	CG	LEU	B	45	-7.660	2.687	23.973	1.00	16.66	C
ATOM	2000	CD1	LEU	B	45	-7.877	2.595	25.485	1.00	14.57	C
ATOM	2001	CD2	LEU	B	45	-8.762	3.504	23.306	1.00	15.37	C
ATOM	2002	C	LEU	B	45	-4.502	3.775	21.943	1.00	16.71	C
ATOM	2003	O	LEU	B	45	-3.376	3.419	22.275	1.00	16.53	O
ATOM	2004	N	GLU	B	46	-4.752	4.937	21.331	1.00	16.28	N
ATOM	2005	CA	GLU	B	46	-3.700	5.938	21.083	1.00	15.59	C
ATOM	2006	CB	GLU	B	46	-3.250	5.938	19.620	1.00	15.69	C
ATOM	2007	CG	GLU	B	46	-2.610	4.653	19.133	1.00	16.96	C
ATOM	2008	CD	GLU	B	46	-2.752	4.488	17.626	1.00	19.85	C
ATOM	2009	OE1	GLU	B	46	-3.910	4.457	17.140	1.00	20.12	O
ATOM	2010	OE2	GLU	B	46	-1.711	4.398	16.925	1.00	20.64	O
ATOM	2011	C	GLU	B	46	-4.158	7.335	21.455	1.00	14.60	C
ATOM	2012	O	GLU	B	46	-5.241	7.775	21.056	1.00	15.03	O
ATOM	2013	N	TRP	B	47	-3.336	8.039	22.222	1.00	13.29	N
ATOM	2014	CA	TRP	B	47	-3.634	9.421	22.497	1.00	11.88	C
ATOM	2015	CB	TRP	B	47	-2.981	9.870	23.797	1.00	10.90	C
ATOM	2016	CG	TRP	B	47	-3.239	11.327	24.159	1.00	9.67	C
ATOM	2017	CD1	TRP	B	47	-4.324	11.829	24.825	1.00	8.66	C
ATOM	2018	NE1	TRP	B	47	-4.196	13.193	24.982	1.00	8.27	N
ATOM	2019	CE2	TRP	B	47	-3.014	13.595	24.414	1.00	8.02	C
ATOM	2020	CD2	TRP	B	47	-2.383	12.445	23.889	1.00	7.08	C
ATOM	2021	CE3	TRP	B	47	-1.143	12.583	23.261	1.00	7.29	C
ATOM	2022	CZ3	TRP	B	47	-0.574	13.854	23.166	1.00	8.96	C
ATOM	2023	CH2	TRP	B	47	-1.229	14.988	23.707	1.00	8.97	C
ATOM	2024	CZ2	TRP	B	47	-2.440	14.876	24.334	1.00	8.67	C
ATOM	2025	C	TRP	B	47	-3.165	10.250	21.299	1.00	11.93	C
ATOM	2026	O	TRP	B	47	-1.984	10.224	20.925	1.00	11.26	O
ATOM	2027	N	MET	B	48	-4.117	10.965	20.703	1.00	12.05	N
ATOM	2028	CA	MET	B	48	-3.874	11.846	19.563	1.00	12.14	C
ATOM	2029	CB	MET	B	48	-5.114	11.907	18.671	1.00	12.09	C
ATOM	2030	CG	MET	B	48	-5.635	10.550	18.257	1.00	12.40	C
ATOM	2031	SD	MET	B	48	-7.095	10.683	17.216	1.00	12.11	S
ATOM	2032	CE	MET	B	48	-6.335	11.364	15.729	1.00	12.80	C
ATOM	2033	C	MET	B	48	-3.471	13.270	19.952	1.00	12.30	C
ATOM	2034	O	MET	B	48	-2.532	13.819	19.376	1.00	12.49	O
ATOM	2035	N	GLY	B	49	-4.175	13.864	20.919	1.00	12.41	N
ATOM	2036	CA	GLY	B	49	-3.950	15.265	21.285	1.00	12.60	C
ATOM	2037	C	GLY	B	49	-5.025	15.832	22.197	1.00	13.14	C
ATOM	2038	O	GLY	B	49	-5.984	15.141	22.549	1.00	13.17	O
ATOM	2039	N	ALA	B	50	-4.884	17.099	22.577	1.00	13.48	N
ATOM	2040	CA	ALA	B	50	-5.803	17.698	23.543	1.00	13.91	C
ATOM	2041	CB	ALA	B	50	-5.322	17.430	24.941	1.00	13.85	C
ATOM	2042	C	ALA	B	50	-5.953	19.193	23.335	1.00	14.49	C
ATOM	2043	O	ALA	B	50	-5.084	19.823	22.717	1.00	14.84	O
ATOM	2044	N	ILE	B	51	-7.046	19.751	23.861	1.00	14.61	N
ATOM	2045	CA	ILE	B	51	-7.281	21.190	23.826	1.00	15.16	C
ATOM	2046	CB	ILE	B	51	-8.348	21.585	22.752	1.00	15.27	C
ATOM	2047	CG1	ILE	B	51	-8.339	23.089	22.492	1.00	13.50	C
ATOM	2048	CD1	ILE	B	51	-8.646	23.437	21.125	1.00	10.08	C
ATOM	2049	CG2	ILE	B	51	-9.770	21.163	23.189	1.00	15.13	C
ATOM	2050	C	ILE	B	51	-7.763	21.699	25.175	1.00	15.99	C
ATOM	2051	O	ILE	B	51	-8.489	21.006	25.886	1.00	15.42	O
ATOM	2052	N	SER	B	52	-7.373	22.929	25.499	1.00	17.35	N
ATOM	2053	CA	SER	B	52	-7.942	23.659	26.625	1.00	18.64	C
ATOM	2054	CB	SER	B	52	-6.839	24.252	27.500	1.00	18.49	C
ATOM	2055	OG	SER	B	52	-7.401	25.081	28.502	1.00	18.58	O

ATOM	2056	C	SER B 52	-8.827	24.781	26.108	1.00	19.64	C
ATOM	2057	O	SER B 52	-8.338	25.817	25.693	1.00	19.90	O
ATOM	2058	N	PRO B 53	-10.143	24.599	26.150	1.00	20.86	N
ATOM	2059	CA	PRO B 53	-10.968	25.772	25.837	1.00	22.08	C
ATOM	2060	CB	PRO B 53	-12.389	25.201	25.869	1.00	22.10	C
ATOM	2061	CG	PRO B 53	-12.281	23.990	26.792	1.00	21.39	C
ATOM	2062	CD	PRO B 53	-10.935	23.418	26.534	1.00	20.61	C
ATOM	2063	C	PRO B 53	-10.735	26.783	26.978	1.00	23.28	C
ATOM	2064	O	PRO B 53	-10.565	26.366	28.133	1.00	24.63	O
ATOM	2065	N	ARG B 54	-10.671	28.077	26.718	1.00	24.09	N
ATOM	2066	CA	ARG B 54	-10.049	28.957	27.746	1.00	24.86	C
ATOM	2067	CB	ARG B 54	-10.517	28.630	29.194	1.00	25.09	C
ATOM	2068	CG	ARG B 54	-9.527	29.062	30.320	1.00	24.86	C
ATOM	2069	CD	ARG B 54	-9.734	28.357	31.658	1.00	24.57	C
ATOM	2070	NE	ARG B 54	-10.571	29.137	32.577	1.00	24.72	N
ATOM	2071	CZ	ARG B 54	-11.064	28.686	33.733	1.00	23.37	C
ATOM	2072	NH1	ARG B 54	-10.832	27.438	34.139	1.00	24.13	N
ATOM	2073	NH2	ARG B 54	-11.814	29.473	34.479	1.00	20.39	N
ATOM	2074	C	ARG B 54	-8.580	28.645	27.654	1.00	24.78	C
ATOM	2075	O	ARG B 54	-8.166	27.557	28.045	1.00	25.17	O
ATOM	2076	N	HIS B 55	-7.809	29.589	27.137	1.00	24.77	N
ATOM	2077	CA	HIS B 55	-6.382	29.394	26.809	1.00	24.97	C
ATOM	2078	CB	HIS B 55	-5.686	28.309	27.659	1.00	24.28	C
ATOM	2079	CG	HIS B 55	-5.564	28.671	29.110	1.00	25.27	C
ATOM	2080	ND1	HIS B 55	-6.010	27.850	30.126	1.00	25.53	N
ATOM	2081	CE1	HIS B 55	-5.791	28.435	31.291	1.00	24.99	C
ATOM	2082	NE2	HIS B 55	-5.226	29.608	31.067	1.00	25.00	N
ATOM	2083	CD2	HIS B 55	-5.072	29.781	29.714	1.00	25.33	C
ATOM	2084	C	HIS B 55	-6.100	29.184	25.325	1.00	24.98	C
ATOM	2085	O	HIS B 55	-4.998	29.505	24.870	1.00	25.43	O
ATOM	2086	N	ASP B 56	-7.104	28.718	24.575	1.00	25.09	N
ATOM	2087	CA	ASP B 56	-6.898	28.087	23.264	1.00	24.95	C
ATOM	2088	CB	ASP B 56	-6.381	29.071	22.193	1.00	25.61	C
ATOM	2089	CG	ASP B 56	-7.259	29.090	20.914	1.00	27.04	C
ATOM	2090	OD1	ASP B 56	-8.280	28.358	20.856	1.00	27.47	O
ATOM	2091	OD2	ASP B 56	-6.925	29.854	19.968	1.00	27.15	O
ATOM	2092	C	ASP B 56	-5.902	26.977	23.568	1.00	24.14	C
ATOM	2093	O	ASP B 56	-6.210	26.106	24.360	1.00	24.39	O
ATOM	2094	N	ILE B 57	-4.699	27.026	23.015	1.00	23.21	N
ATOM	2095	CA	ILE B 57	-3.686	25.974	23.289	1.00	22.64	C
ATOM	2096	CB	ILE B 57	-3.030	26.092	24.698	1.00	22.22	C
ATOM	2097	CG1	ILE B 57	-2.299	27.429	24.831	1.00	22.52	C
ATOM	2098	CD1	ILE B 57	-1.704	27.674	26.196	1.00	22.30	C
ATOM	2099	CG2	ILE B 57	-2.048	24.938	24.930	1.00	21.59	C
ATOM	2100	C	ILE B 57	-4.098	24.502	23.022	1.00	22.13	C
ATOM	2101	O	ILE B 57	-5.021	23.964	23.622	1.00	21.67	O
ATOM	2102	N	THR B 58	-3.369	23.871	22.112	1.00	22.02	N
ATOM	2103	CA	THR B 58	-3.571	22.482	21.794	1.00	21.95	C
ATOM	2104	CB	THR B 58	-4.148	22.311	20.369	1.00	21.86	C
ATOM	2105	OG1	THR B 58	-3.214	22.821	19.411	1.00	22.43	O
ATOM	2106	CG2	THR B 58	-5.449	23.065	20.206	1.00	21.50	C
ATOM	2107	C	THR B 58	-2.226	21.768	21.886	1.00	22.14	C
ATOM	2108	O	THR B 58	-1.174	22.351	21.605	1.00	22.37	O
ATOM	2109	N	LYS B 59	-2.272	20.509	22.294	1.00	22.33	N
ATOM	2110	CA	LYS B 59	-1.132	19.628	22.224	1.00	22.76	C
ATOM	2111	CB	LYS B 59	-0.799	19.089	23.614	1.00	23.50	C
ATOM	2112	CG	LYS B 59	0.449	19.721	24.278	1.00	25.33	C

ATOM	2113	CD	LYS	B	59	0.389	21.253	24.461	1.00	26.73	C
ATOM	2114	CE	LYS	B	59	1.809	21.806	24.640	1.00	27.90	C
ATOM	2115	NZ	LYS	B	59	1.850	23.300	24.806	1.00	31.09	N
ATOM	2116	C	LYS	B	59	-1.459	18.495	21.257	1.00	22.73	C
ATOM	2117	O	LYS	B	59	-2.626	18.113	21.086	1.00	22.87	O
ATOM	2118	N	TYR	B	60	-0.434	17.976	20.602	1.00	22.20	N
ATOM	2119	CA	TYR	B	60	-0.627	16.884	19.678	1.00	22.00	C
ATOM	2120	CB	TYR	B	60	-0.503	17.365	18.237	1.00	21.59	C
ATOM	2121	CG	TYR	B	60	-1.570	18.329	17.805	1.00	21.32	C
ATOM	2122	CD1	TYR	B	60	-2.781	17.871	17.275	1.00	21.43	C
ATOM	2123	CE1	TYR	B	60	-3.764	18.760	16.863	1.00	19.82	C
ATOM	2124	CZ	TYR	B	60	-3.532	20.111	16.978	1.00	19.83	C
ATOM	2125	OH	TYR	B	60	-4.488	21.004	16.590	1.00	21.01	O
ATOM	2126	CE2	TYR	B	60	-2.347	20.583	17.497	1.00	19.99	C
ATOM	2127	CD2	TYR	B	60	-1.372	19.698	17.902	1.00	20.03	C
ATOM	2128	C	TYR	B	60	0.419	15.827	19.930	1.00	22.23	C
ATOM	2129	O	TYR	B	60	1.544	16.142	20.297	1.00	22.20	O
ATOM	2130	N	ASN	B	61	0.038	14.570	19.740	1.00	22.44	N
ATOM	2131	CA	ASN	B	61	0.993	13.500	19.670	1.00	22.88	C
ATOM	2132	CB	ASN	B	61	0.238	12.172	19.591	1.00	22.64	C
ATOM	2133	CG	ASN	B	61	1.139	10.945	19.734	1.00	20.80	C
ATOM	2134	OD1	ASN	B	61	2.313	10.953	19.354	1.00	19.86	O
ATOM	2135	ND2	ASN	B	61	0.565	9.867	20.248	1.00	17.61	N
ATOM	2136	C	ASN	B	61	1.811	13.743	18.412	1.00	23.87	C
ATOM	2137	O	ASN	B	61	1.253	14.071	17.375	1.00	23.36	O
ATOM	2138	N	GLU	B	62	3.131	13.598	18.518	1.00	25.70	N
ATOM	2139	CA	GLU	B	62	4.055	13.774	17.387	1.00	27.51	C
ATOM	2140	CB	GLU	B	62	5.497	13.372	17.767	1.00	28.02	C
ATOM	2141	CG	GLU	B	62	6.159	14.211	18.912	1.00	31.13	C
ATOM	2142	CD	GLU	B	62	5.747	13.769	20.335	1.00	33.16	C
ATOM	2143	OE1	GLU	B	62	4.848	14.404	20.929	1.00	32.69	O
ATOM	2144	OE2	GLU	B	62	6.324	12.778	20.855	1.00	35.49	O
ATOM	2145	C	GLU	B	62	3.619	13.000	16.148	1.00	28.33	C
ATOM	2146	O	GLU	B	62	3.671	13.531	15.041	1.00	28.91	O
ATOM	2147	N	MET	B	63	3.185	11.749	16.314	1.00	29.21	N
ATOM	2148	CA	MET	B	63	2.833	10.926	15.145	1.00	30.32	C
ATOM	2149	CB	MET	B	63	2.890	9.407	15.461	1.00	29.95	C
ATOM	2150	CG	MET	B	63	1.542	8.706	15.741	1.00	31.66	C
ATOM	2151	SD	MET	B	63	1.423	6.905	15.320	1.00	33.85	S
ATOM	2152	CE	MET	B	63	1.847	6.802	13.564	1.00	31.65	C
ATOM	2153	C	MET	B	63	1.507	11.384	14.497	1.00	29.46	C
ATOM	2154	O	MET	B	63	1.073	10.828	13.494	1.00	29.00	O
ATOM	2155	N	PHE	B	64	0.893	12.420	15.066	1.00	29.52	N
ATOM	2156	CA	PHE	B	64	-0.377	12.953	14.567	1.00	29.64	C
ATOM	2157	CB	PHE	B	64	-1.501	12.738	15.590	1.00	29.68	C
ATOM	2158	CG	PHE	B	64	-1.964	11.317	15.693	1.00	29.43	C
ATOM	2159	CD1	PHE	B	64	-2.874	10.800	14.767	1.00	29.07	C
ATOM	2160	CE1	PHE	B	64	-3.305	9.483	14.847	1.00	28.96	C
ATOM	2161	CZ	PHE	B	64	-2.819	8.667	15.867	1.00	30.11	C
ATOM	2162	CE2	PHE	B	64	-1.904	9.182	16.805	1.00	29.03	C
ATOM	2163	CD2	PHE	B	64	-1.489	10.494	16.711	1.00	28.16	C
ATOM	2164	C	PHE	B	64	-0.360	14.425	14.141	1.00	29.86	C
ATOM	2165	O	PHE	B	64	-1.328	14.883	13.548	1.00	29.70	O
ATOM	2166	N	ARG	B	65	0.706	15.168	14.454	1.00	30.20	N
ATOM	2167	CA	ARG	B	65	0.801	16.560	14.003	1.00	31.02	C
ATOM	2168	CB	ARG	B	65	2.078	17.266	14.496	1.00	30.92	C
ATOM	2169	CG	ARG	B	65	1.929	18.034	15.826	1.00	32.57	C

ATOM	2170	CD	ARG B 65	2.834	19.302	15.976	1.00	33.22	C
ATOM	2171	NE	ARG B 65	4.068	19.283	15.174	1.00	38.25	N
ATOM	2172	CZ	ARG B 65	5.113	18.468	15.367	1.00	40.31	C
ATOM	2173	NH1	ARG B 65	5.108	17.548	16.344	1.00	40.59	N
ATOM	2174	NH2	ARG B 65	6.169	18.561	14.559	1.00	40.44	N
ATOM	2175	C	ARG B 65	0.740	16.592	12.484	1.00	30.29	C
ATOM	2176	O	ARG B 65	1.361	15.768	11.821	1.00	30.18	O
ATOM	2177	N	GLY B 66	-0.034	17.525	11.941	1.00	29.97	N
ATOM	2178	CA	GLY B 66	-0.135	17.673	10.501	1.00	29.24	C
ATOM	2179	C	GLY B 66	-1.322	16.964	9.880	1.00	28.97	C
ATOM	2180	O	GLY B 66	-1.873	17.454	8.881	1.00	29.45	O
ATOM	2181	N	GLN B 67	-1.723	15.821	10.448	1.00	27.96	N
ATOM	2182	CA	GLN B 67	-2.864	15.063	9.911	1.00	27.02	C
ATOM	2183	CB	GLN B 67	-2.715	13.556	10.132	1.00	27.45	C
ATOM	2184	CG	GLN B 67	-1.970	12.823	9.011	1.00	30.51	C
ATOM	2185	CD	GLN B 67	-0.457	12.824	9.218	1.00	33.16	C
ATOM	2186	OE1	GLN B 67	0.098	13.712	9.881	1.00	34.38	O
ATOM	2187	NE2	GLN B 67	0.214	11.818	8.662	1.00	33.20	N
ATOM	2188	C	GLN B 67	-4.213	15.513	10.431	1.00	25.58	C
ATOM	2189	O	GLN B 67	-5.220	15.307	9.766	1.00	25.61	O
ATOM	2190	N	VAL B 68	-4.244	16.086	11.631	1.00	24.23	N
ATOM	2191	CA	VAL B 68	-5.511	16.504	12.243	1.00	22.67	C
ATOM	2192	CB	VAL B 68	-6.049	15.470	13.309	1.00	22.71	C
ATOM	2193	CG1	VAL B 68	-6.158	14.071	12.725	1.00	22.14	C
ATOM	2194	CG2	VAL B 68	-5.193	15.456	14.572	1.00	21.21	C
ATOM	2195	C	VAL B 68	-5.403	17.891	12.872	1.00	21.99	C
ATOM	2196	O	VAL B 68	-4.305	18.385	13.140	1.00	21.62	O
ATOM	2197	N	THR B 69	-6.549	18.514	13.100	1.00	21.26	N
ATOM	2198	CA	THR B 69	-6.601	19.717	13.914	1.00	21.00	C
ATOM	2199	CB	THR B 69	-6.884	21.000	13.049	1.00	21.14	C
ATOM	2200	OG1	THR B 69	-5.808	21.201	12.126	1.00	20.20	O
ATOM	2201	CG2	THR B 69	-7.016	22.246	13.914	1.00	20.10	C
ATOM	2202	C	THR B 69	-7.663	19.519	14.986	1.00	21.01	C
ATOM	2203	O	THR B 69	-8.776	19.066	14.705	1.00	21.01	O
ATOM	2204	N	ILE B 70	-7.300	19.836	16.221	1.00	21.17	N
ATOM	2205	CA	ILE B 70	-8.253	19.831	17.328	1.00	21.34	C
ATOM	2206	CB	ILE B 70	-7.631	19.222	18.621	1.00	21.11	C
ATOM	2207	CG1	ILE B 70	-7.219	17.769	18.358	1.00	20.53	C
ATOM	2208	CD1	ILE B 70	-6.339	17.175	19.389	1.00	19.18	C
ATOM	2209	CG2	ILE B 70	-8.610	19.274	19.795	1.00	20.67	C
ATOM	2210	C	ILE B 70	-8.649	21.280	17.528	1.00	21.71	C
ATOM	2211	O	ILE B 70	-7.810	22.166	17.427	1.00	22.36	O
ATOM	2212	N	SER B 71	-9.927	21.526	17.770	1.00	21.86	N
ATOM	2213	CA	SER B 71	-10.415	22.882	17.968	1.00	22.11	C
ATOM	2214	CB	SER B 71	-10.834	23.517	16.631	1.00	21.85	C
ATOM	2215	OG	SER B 71	-12.088	23.013	16.191	1.00	22.26	O
ATOM	2216	C	SER B 71	-11.574	22.835	18.964	1.00	22.42	C
ATOM	2217	O	SER B 71	-11.967	21.753	19.398	1.00	22.02	O
ATOM	2218	N	ALA B 72	-12.097	24.004	19.338	1.00	23.21	N
ATOM	2219	CA	ALA B 72	-13.197	24.085	20.296	1.00	23.82	C
ATOM	2220	CB	ALA B 72	-12.681	23.986	21.709	1.00	24.15	C
ATOM	2221	C	ALA B 72	-14.044	25.332	20.148	1.00	24.20	C
ATOM	2222	O	ALA B 72	-13.666	26.289	19.473	1.00	23.91	O
ATOM	2223	N	ASP B 73	-15.197	25.293	20.811	1.00	24.86	N
ATOM	2224	CA	ASP B 73	-16.178	26.349	20.776	1.00	25.51	C
ATOM	2225	CB	ASP B 73	-17.298	25.914	19.861	1.00	25.85	C
ATOM	2226	CG	ASP B 73	-18.191	27.051	19.458	1.00	28.68	C

ATOM	2227	OD1 ASP B 73	-19.306	27.186	20.029	1.00	31.01	O
ATOM	2228	OD2 ASP B 73	-17.766	27.816	18.565	1.00	32.44	O
ATOM	2229	C ASP B 73	-16.735	26.518	22.178	1.00	25.80	C
ATOM	2230	O ASP B 73	-17.610	25.742	22.572	1.00	25.96	O
ATOM	2231	N LYS B 74	-16.251	27.505	22.939	1.00	26.02	N
ATOM	2232	CA LYS B 74	-16.731	27.654	24.321	1.00	26.77	C
ATOM	2233	CB LYS B 74	-15.888	28.591	25.214	1.00	27.01	C
ATOM	2234	CG LYS B 74	-15.049	29.655	24.540	1.00	29.87	C
ATOM	2235	CD LYS B 74	-13.546	29.374	24.710	1.00	33.55	C
ATOM	2236	CE LYS B 74	-12.732	30.685	24.851	1.00	34.43	C
ATOM	2237	NZ LYS B 74	-13.131	31.410	26.099	1.00	34.57	N
ATOM	2238	C LYS B 74	-18.214	27.971	24.453	1.00	26.61	C
ATOM	2239	O LYS B 74	-18.844	27.561	25.423	1.00	26.76	O
ATOM	2240	N SER B 75	-18.781	28.659	23.470	1.00	26.74	N
ATOM	2241	CA SER B 75	-20.185	29.052	23.549	1.00	26.87	C
ATOM	2242	CB SER B 75	-20.548	30.026	22.424	1.00	26.67	C
ATOM	2243	OG SER B 75	-20.229	29.477	21.158	1.00	28.20	O
ATOM	2244	C SER B 75	-21.119	27.841	23.572	1.00	26.78	C
ATOM	2245	O SER B 75	-22.202	27.899	24.155	1.00	26.91	O
ATOM	2246	N SER B 76	-20.688	26.738	22.962	1.00	26.77	N
ATOM	2247	CA SER B 76	-21.489	25.499	22.943	1.00	26.36	C
ATOM	2248	CB SER B 76	-21.751	25.078	21.497	1.00	26.36	C
ATOM	2249	OG SER B 76	-20.532	24.803	20.827	1.00	25.86	O
ATOM	2250	C SER B 76	-20.875	24.305	23.696	1.00	26.20	C
ATOM	2251	O SER B 76	-21.352	23.174	23.543	1.00	26.37	O
ATOM	2252	N SER B 77	-19.830	24.548	24.493	1.00	25.68	N
ATOM	2253	CA SER B 77	-19.062	23.478	25.160	1.00	25.20	C
ATOM	2254	CB SER B 77	-19.828	22.933	26.360	1.00	25.28	C
ATOM	2255	OG SER B 77	-20.112	23.958	27.281	1.00	27.12	O
ATOM	2256	C SER B 77	-18.648	22.301	24.249	1.00	24.56	C
ATOM	2257	O SER B 77	-18.658	21.141	24.683	1.00	24.51	O
ATOM	2258	N THR B 78	-18.277	22.589	23.002	1.00	23.44	N
ATOM	2259	CA THR B 78	-17.975	21.516	22.062	1.00	22.46	C
ATOM	2260	CB THR B 78	-18.850	21.589	20.803	1.00	22.23	C
ATOM	2261	OG1 THR B 78	-20.221	21.594	21.192	1.00	21.72	O
ATOM	2262	CG2 THR B 78	-18.623	20.379	19.922	1.00	22.65	C
ATOM	2263	C THR B 78	-16.510	21.467	21.686	1.00	22.01	C
ATOM	2264	O THR B 78	-15.878	22.502	21.465	1.00	22.46	O
ATOM	2265	N ALA B 79	-15.969	20.257	21.631	1.00	21.34	N
ATOM	2266	CA ALA B 79	-14.625	20.050	21.116	1.00	21.12	C
ATOM	2267	CB ALA B 79	-13.794	19.215	22.079	1.00	20.96	C
ATOM	2268	C ALA B 79	-14.714	19.376	19.759	1.00	20.88	C
ATOM	2269	O ALA B 79	-15.638	18.589	19.501	1.00	20.79	O
ATOM	2270	N TYR B 80	-13.744	19.673	18.904	1.00	20.56	N
ATOM	2271	CA TYR B 80	-13.795	19.234	17.530	1.00	20.69	C
ATOM	2272	CB TYR B 80	-14.044	20.418	16.588	1.00	20.95	C
ATOM	2273	CG TYR B 80	-15.447	20.987	16.682	1.00	21.22	C
ATOM	2274	CD1 TYR B 80	-16.524	20.305	16.117	1.00	21.74	C
ATOM	2275	CE1 TYR B 80	-17.810	20.805	16.196	1.00	21.89	C
ATOM	2276	CZ TYR B 80	-18.045	22.008	16.845	1.00	21.58	C
ATOM	2277	OH TYR B 80	-19.340	22.468	16.894	1.00	21.85	O
ATOM	2278	CE2 TYR B 80	-17.002	22.715	17.427	1.00	20.34	C
ATOM	2279	CD2 TYR B 80	-15.700	22.200	17.340	1.00	20.76	C
ATOM	2280	C TYR B 80	-12.518	18.559	17.163	1.00	20.74	C
ATOM	2281	O TYR B 80	-11.448	18.989	17.563	1.00	20.89	O
ATOM	2282	N LEU B 81	-12.648	17.488	16.400	1.00	21.22	N
ATOM	2283	CA LEU B 81	-11.519	16.845	15.759	1.00	21.98	C

ATOM	2284	CB	LEU	B	81	-11.372	15.404	16.262	1.00	22.06	C
ATOM	2285	CG	LEU	B	81	-10.356	14.471	15.595	1.00	21.41	C
ATOM	2286	CD1	LEU	B	81	-8.944	14.842	16.005	1.00	21.72	C
ATOM	2287	CD2	LEU	B	81	-10.647	13.027	15.968	1.00	21.96	C
ATOM	2288	C	LEU	B	81	-11.777	16.866	14.255	1.00	22.46	C
ATOM	2289	O	LEU	B	81	-12.895	16.598	13.821	1.00	22.80	O
ATOM	2290	N	GLN	B	82	-10.754	17.179	13.464	1.00	22.76	N
ATOM	2291	CA	GLN	B	82	-10.951	17.305	12.034	1.00	23.19	C
ATOM	2292	CB	GLN	B	82	-11.448	18.705	11.690	1.00	23.48	C
ATOM	2293	CG	GLN	B	82	-10.351	19.741	11.672	1.00	26.24	C
ATOM	2294	CD	GLN	B	82	-10.797	21.029	11.035	1.00	29.49	C
ATOM	2295	OE1	GLN	B	82	-11.589	21.785	11.611	1.00	30.35	O
ATOM	2296	NE2	GLN	B	82	-10.285	21.297	9.836	1.00	29.64	N
ATOM	2297	C	GLN	B	82	-9.735	16.950	11.169	1.00	23.19	C
ATOM	2298	O	GLN	B	82	-8.570	17.127	11.583	1.00	22.99	O
ATOM	2299	N	TRP	B	83	-10.046	16.483	9.953	1.00	23.01	N
ATOM	2300	CA	TRP	B	83	-9.067	16.123	8.942	1.00	22.95	C
ATOM	2301	CB	TRP	B	83	-9.284	14.675	8.562	1.00	21.66	C
ATOM	2302	CG	TRP	B	83	-8.879	13.666	9.555	1.00	20.27	C
ATOM	2303	CD1	TRP	B	83	-7.698	12.994	9.589	1.00	19.07	C
ATOM	2304	NE1	TRP	B	83	-7.698	12.097	10.623	1.00	18.52	N
ATOM	2305	CE2	TRP	B	83	-8.897	12.172	11.278	1.00	18.20	C
ATOM	2306	CD2	TRP	B	83	-9.673	13.144	10.625	1.00	18.28	C
ATOM	2307	CE3	TRP	B	83	-10.963	13.403	11.093	1.00	18.02	C
ATOM	2308	CZ3	TRP	B	83	-11.428	12.706	12.198	1.00	18.44	C
ATOM	2309	CH2	TRP	B	83	-10.635	11.747	12.831	1.00	19.49	C
ATOM	2310	CZ2	TRP	B	83	-9.363	11.465	12.387	1.00	19.67	C
ATOM	2311	C	TRP	B	83	-9.191	16.948	7.645	1.00	23.96	C
ATOM	2312	O	TRP	B	83	-10.278	17.415	7.296	1.00	24.16	O
ATOM	2313	N	SER	B	84	-8.072	17.112	6.937	1.00	24.92	N
ATOM	2314	CA	SER	B	84	-8.085	17.498	5.518	1.00	25.90	C
ATOM	2315	CB	SER	B	84	-7.033	18.560	5.227	1.00	25.58	C
ATOM	2316	OG	SER	B	84	-7.356	19.761	5.890	1.00	27.38	O
ATOM	2317	C	SER	B	84	-7.729	16.259	4.716	1.00	26.37	C
ATOM	2318	O	SER	B	84	-6.592	15.777	4.782	1.00	27.15	O
ATOM	2319	N	SER	B	85	-8.683	15.728	3.968	1.00	26.31	N
ATOM	2320	CA	SER	B	85	-8.426	14.511	3.191	1.00	25.96	C
ATOM	2321	CB	SER	B	85	-7.440	14.768	2.022	1.00	25.96	C
ATOM	2322	OG	SER	B	85	-6.092	14.661	2.418	1.00	25.67	O
ATOM	2323	C	SER	B	85	-8.057	13.273	4.046	1.00	25.55	C
ATOM	2324	O	SER	B	85	-6.905	13.071	4.467	1.00	24.91	O
ATOM	2325	N	LEU	B	86	-9.078	12.454	4.287	1.00	25.49	N
ATOM	2326	CA	LEU	B	86	-8.954	11.203	5.024	1.00	25.04	C
ATOM	2327	CB	LEU	B	86	-10.346	10.621	5.226	1.00	24.89	C
ATOM	2328	CG	LEU	B	86	-11.253	10.948	6.414	1.00	24.38	C
ATOM	2329	CD1	LEU	B	86	-10.467	11.549	7.533	1.00	24.15	C
ATOM	2330	CD2	LEU	B	86	-12.393	11.823	6.042	1.00	23.24	C
ATOM	2331	C	LEU	B	86	-8.125	10.192	4.241	1.00	25.20	C
ATOM	2332	O	LEU	B	86	-8.131	10.205	3.002	1.00	25.31	O
ATOM	2333	N	LYS	B	87	-7.412	9.325	4.952	1.00	24.99	N
ATOM	2334	CA	LYS	B	87	-6.757	8.183	4.323	1.00	25.40	C
ATOM	2335	CB	LYS	B	87	-5.281	8.052	4.739	1.00	25.35	C
ATOM	2336	CG	LYS	B	87	-4.474	9.360	4.815	1.00	27.71	C
ATOM	2337	CD	LYS	B	87	-2.949	9.155	4.648	1.00	26.99	C
ATOM	2338	CE	LYS	B	87	-2.598	8.895	3.165	1.00	30.49	C
ATOM	2339	NZ	LYS	B	87	-1.130	8.734	2.870	1.00	30.67	N
ATOM	2340	C	LYS	B	87	-7.548	6.945	4.753	1.00	24.86	C

ATOM	2341	O	LYS	B	87	-8.266	6.994	5.753	1.00	25.17	O
ATOM	2342	N	ALA	B	88	-7.430	5.839	4.021	1.00	23.90	N
ATOM	2343	CA	ALA	B	88	-8.133	4.617	4.416	1.00	23.16	C
ATOM	2344	CB	ALA	B	88	-7.903	3.503	3.393	1.00	23.17	C
ATOM	2345	C	ALA	B	88	-7.747	4.142	5.829	1.00	22.52	C
ATOM	2346	O	ALA	B	88	-8.586	3.624	6.583	1.00	21.88	O
ATOM	2347	N	SER	B	89	-6.484	4.324	6.191	1.00	21.81	N
ATOM	2348	CA	SER	B	89	-6.023	3.846	7.485	1.00	21.57	C
ATOM	2349	CB	SER	B	89	-4.504	3.642	7.497	1.00	21.63	C
ATOM	2350	OG	SER	B	89	-3.827	4.848	7.213	1.00	22.16	O
ATOM	2351	C	SER	B	89	-6.495	4.732	8.646	1.00	21.11	C
ATOM	2352	O	SER	B	89	-6.108	4.523	9.795	1.00	21.02	O
ATOM	2353	N	ASP	B	90	-7.341	5.714	8.341	1.00	20.60	N
ATOM	2354	CA	ASP	B	90	-7.984	6.524	9.382	1.00	20.03	C
ATOM	2355	CB	ASP	B	90	-8.225	7.968	8.909	1.00	19.97	C
ATOM	2356	CG	ASP	B	90	-6.936	8.759	8.782	1.00	21.21	C
ATOM	2357	OD1	ASP	B	90	-5.964	8.442	9.493	1.00	23.46	O
ATOM	2358	OD2	ASP	B	90	-6.870	9.698	7.969	1.00	24.03	O
ATOM	2359	C	ASP	B	90	-9.264	5.874	9.877	1.00	19.17	C
ATOM	2360	O	ASP	B	90	-9.889	6.363	10.795	1.00	19.41	O
ATOM	2361	N	THR	B	91	-9.643	4.762	9.270	1.00	18.79	N
ATOM	2362	CA	THR	B	91	-10.738	3.948	9.771	1.00	18.76	C
ATOM	2363	CB	THR	B	91	-10.927	2.707	8.889	1.00	19.19	C
ATOM	2364	OG1	THR	B	91	-11.290	3.122	7.561	1.00	19.20	O
ATOM	2365	CG2	THR	B	91	-11.986	1.744	9.484	1.00	18.10	C
ATOM	2366	C	THR	B	91	-10.456	3.517	11.215	1.00	18.62	C
ATOM	2367	O	THR	B	91	-9.443	2.861	11.501	1.00	18.61	O
ATOM	2368	N	ALA	B	92	-11.345	3.908	12.120	1.00	18.07	N
ATOM	2369	CA	ALA	B	92	-11.169	3.622	13.531	1.00	17.85	C
ATOM	2370	CB	ALA	B	92	-9.877	4.264	14.041	1.00	18.08	C
ATOM	2371	C	ALA	B	92	-12.356	4.138	14.327	1.00	17.67	C
ATOM	2372	O	ALA	B	92	-13.237	4.783	13.781	1.00	18.00	O
ATOM	2373	N	MET	B	93	-12.377	3.852	15.622	1.00	17.40	N
ATOM	2374	CA	MET	B	93	-13.300	4.521	16.514	1.00	17.01	C
ATOM	2375	CB	MET	B	93	-13.741	3.594	17.650	1.00	17.88	C
ATOM	2376	CG	MET	B	93	-14.994	4.067	18.371	1.00	18.61	C
ATOM	2377	SD	MET	B	93	-16.307	3.404	17.379	1.00	26.75	S
ATOM	2378	CE	MET	B	93	-17.660	3.214	18.554	1.00	23.50	C
ATOM	2379	C	MET	B	93	-12.562	5.713	17.092	1.00	15.92	C
ATOM	2380	O	MET	B	93	-11.406	5.598	17.487	1.00	15.64	O
ATOM	2381	N	TYR	B	94	-13.221	6.858	17.146	1.00	15.01	N
ATOM	2382	CA	TYR	B	94	-12.625	7.996	17.829	1.00	14.18	C
ATOM	2383	CB	TYR	B	94	-12.456	9.189	16.892	1.00	14.09	C
ATOM	2384	CG	TYR	B	94	-11.523	8.864	15.758	1.00	13.74	C
ATOM	2385	CD1	TYR	B	94	-11.985	8.191	14.627	1.00	13.89	C
ATOM	2386	CE1	TYR	B	94	-11.133	7.870	13.588	1.00	14.34	C
ATOM	2387	CZ	TYR	B	94	-9.805	8.204	13.691	1.00	14.23	C
ATOM	2388	OH	TYR	B	94	-8.955	7.876	12.669	1.00	15.43	O
ATOM	2389	CE2	TYR	B	94	-9.315	8.857	14.815	1.00	12.94	C
ATOM	2390	CD2	TYR	B	94	-10.172	9.184	15.831	1.00	12.31	C
ATOM	2391	C	TYR	B	94	-13.357	8.356	19.105	1.00	14.02	C
ATOM	2392	O	TYR	B	94	-14.600	8.423	19.153	1.00	12.84	O
ATOM	2393	N	PHE	B	95	-12.547	8.559	20.147	1.00	14.18	N
ATOM	2394	CA	PHE	B	95	-13.035	8.875	21.475	1.00	13.87	C
ATOM	2395	CB	PHE	B	95	-12.585	7.795	22.434	1.00	13.85	C
ATOM	2396	CG	PHE	B	95	-13.305	6.489	22.274	1.00	13.24	C
ATOM	2397	CD1	PHE	B	95	-14.612	6.341	22.728	1.00	11.83	C

ATOM	2398	CE1 PHE B 95	-15.269	5.135	22.603	1.00	11.68	C
ATOM	2399	CZ PHE B 95	-14.614	4.051	22.037	1.00	12.23	C
ATOM	2400	CE2 PHE B 95	-13.313	4.184	21.587	1.00	12.50	C
ATOM	2401	CD2 PHE B 95	-12.658	5.397	21.715	1.00	12.04	C
ATOM	2402	C PHE B 95	-12.509	10.198	21.994	1.00	13.91	C
ATOM	2403	O PHE B 95	-11.307	10.459	21.941	1.00	13.95	O
ATOM	2404	N CYS B 96	-13.419	11.025	22.498	1.00	14.03	N
ATOM	2405	CA CYS B 96	-13.038	12.162	23.326	1.00	14.19	C
ATOM	2406	CB CYS B 96	-13.855	13.422	22.995	1.00	13.46	C
ATOM	2407	SG CYS B 96	-15.577	13.309	23.486	1.00	15.73	S
ATOM	2408	C CYS B 96	-13.180	11.743	24.804	1.00	14.25	C
ATOM	2409	O CYS B 96	-14.120	11.011	25.177	1.00	14.05	O
ATOM	2410	N ALA B 97	-12.232	12.186	25.631	1.00	14.13	N
ATOM	2411	CA ALA B 97	-12.295	11.965	27.074	1.00	14.21	C
ATOM	2412	CB ALA B 97	-11.368	10.821	27.481	1.00	13.90	C
ATOM	2413	C ALA B 97	-11.926	13.262	27.788	1.00	13.89	C
ATOM	2414	O ALA B 97	-11.279	14.115	27.192	1.00	14.74	O
ATOM	2415	N ARG B 98	-12.343	13.415	29.044	1.00	13.31	N
ATOM	2416	CA ARG B 98	-11.996	14.595	29.853	1.00	12.77	C
ATOM	2417	CB ARG B 98	-13.131	14.942	30.825	1.00	12.54	C
ATOM	2418	CG ARG B 98	-13.023	16.348	31.381	1.00	12.76	C
ATOM	2419	CD ARG B 98	-14.195	16.703	32.243	1.00	15.44	C
ATOM	2420	NE ARG B 98	-14.042	16.132	33.582	1.00	20.13	N
ATOM	2421	CZ ARG B 98	-14.940	16.196	34.567	1.00	20.76	C
ATOM	2422	NH1 ARG B 98	-14.660	15.618	35.721	1.00	22.02	N
ATOM	2423	NH2 ARG B 98	-16.108	16.810	34.410	1.00	21.15	N
ATOM	2424	C ARG B 98	-10.655	14.490	30.618	1.00	12.69	C
ATOM	2425	O ARG B 98	-10.264	13.416	31.099	1.00	12.15	O
ATOM	2426	N GLY B 99	-9.965	15.622	30.730	1.00	12.88	N
ATOM	2427	CA GLY B 99	-8.686	15.702	31.429	1.00	13.05	C
ATOM	2428	C GLY B 99	-8.514	16.983	32.229	1.00	13.21	C
ATOM	2429	O GLY B 99	-9.472	17.729	32.435	1.00	13.70	O
ATOM	2430	N GLY B 100	-7.282	17.225	32.674	1.00	13.10	N
ATOM	2431	CA GLY B 100	-6.928	18.378	33.490	1.00	12.90	C
ATOM	2432	C GLY B 100	-5.760	19.108	32.859	1.00	13.01	C
ATOM	2433	O GLY B 100	-5.657	19.170	31.645	1.00	13.25	O
ATOM	2434	N PHE B 101	-4.881	19.662	33.682	1.00	13.09	N
ATOM	2435	CA PHE B 101	-3.784	20.498	33.210	1.00	13.66	C
ATOM	2436	CB PHE B 101	-4.044	21.972	33.611	1.00	13.74	C
ATOM	2437	CG PHE B 101	-5.386	22.527	33.127	1.00	13.84	C
ATOM	2438	CD1 PHE B 101	-6.590	22.204	33.787	1.00	13.93	C
ATOM	2439	CE1 PHE B 101	-7.824	22.697	33.341	1.00	11.66	C
ATOM	2440	CZ PHE B 101	-7.865	23.546	32.225	1.00	12.27	C
ATOM	2441	CE2 PHE B 101	-6.691	23.893	31.582	1.00	11.17	C
ATOM	2442	CD2 PHE B 101	-5.449	23.382	32.037	1.00	12.41	C
ATOM	2443	C PHE B 101	-2.447	19.996	33.780	1.00	13.95	C
ATOM	2444	O PHE B 101	-2.410	19.008	34.500	1.00	13.50	O
ATOM	2445	N TYR B 102	-1.347	20.670	33.460	1.00	14.88	N
ATOM	2446	CA TYR B 102	-0.074	20.376	34.097	1.00	15.69	C
ATOM	2447	CB TYR B 102	1.009	21.335	33.603	1.00	16.07	C
ATOM	2448	CG TYR B 102	1.464	21.027	32.187	1.00	16.43	C
ATOM	2449	CD1 TYR B 102	0.721	21.438	31.084	1.00	15.95	C
ATOM	2450	CE1 TYR B 102	1.124	21.126	29.778	1.00	16.82	C
ATOM	2451	CZ TYR B 102	2.290	20.403	29.560	1.00	17.20	C
ATOM	2452	OH TYR B 102	2.699	20.087	28.266	1.00	16.69	O
ATOM	2453	CE2 TYR B 102	3.049	19.983	30.646	1.00	17.84	C
ATOM	2454	CD2 TYR B 102	2.630	20.296	31.955	1.00	17.92	C

ATOM	2455	C	TYR B 102	-0.296	20.504	35.591	1.00	16.51	C
ATOM	2456	O	TYR B 102	-0.814	21.535	36.068	1.00	17.43	O
ATOM	2457	N	GLY B 103	0.019	19.437	36.328	1.00	16.77	N
ATOM	2458	CA	GLY B 103	-0.260	19.403	37.760	1.00	16.75	C
ATOM	2459	C	GLY B 103	-1.422	18.516	38.177	1.00	16.91	C
ATOM	2460	O	GLY B 103	-1.422	18.002	39.292	1.00	16.54	O
ATOM	2461	N	SER B 104	-2.413	18.328	37.298	1.00	17.17	N
ATOM	2462	CA	SER B 104	-3.536	17.420	37.617	1.00	17.20	C
ATOM	2463	CB	SER B 104	-4.825	17.735	36.852	1.00	17.16	C
ATOM	2464	OG	SER B 104	-4.586	18.641	35.816	1.00	18.18	O
ATOM	2465	C	SER B 104	-3.222	15.932	37.547	1.00	16.89	C
ATOM	2466	O	SER B 104	-2.281	15.486	36.886	1.00	16.29	O
ATOM	2467	N	THR B 105	-4.095	15.180	38.208	1.00	17.06	N
ATOM	2468	CA	THR B 105	-3.773	13.888	38.771	1.00	16.41	C
ATOM	2469	CB	THR B 105	-3.671	14.096	40.309	1.00	16.20	C
ATOM	2470	OG1	THR B 105	-2.353	13.780	40.754	1.00	16.32	O
ATOM	2471	CG2	THR B 105	-4.781	13.407	41.141	1.00	15.04	C
ATOM	2472	C	THR B 105	-4.802	12.834	38.347	1.00	16.70	C
ATOM	2473	O	THR B 105	-4.659	11.662	38.661	1.00	17.40	O
ATOM	2474	N	ILE B 106	-5.830	13.263	37.621	1.00	16.63	N
ATOM	2475	CA	ILE B 106	-6.899	12.383	37.164	1.00	17.06	C
ATOM	2476	CB	ILE B 106	-8.234	12.690	37.858	1.00	17.08	C
ATOM	2477	CG1	ILE B 106	-8.166	12.311	39.355	1.00	17.13	C
ATOM	2478	CD1	ILE B 106	-9.107	13.131	40.275	1.00	14.56	C
ATOM	2479	CG2	ILE B 106	-9.379	11.969	37.138	1.00	15.82	C
ATOM	2480	C	ILE B 106	-7.093	12.532	35.668	1.00	17.59	C
ATOM	2481	O	ILE B 106	-7.314	13.622	35.174	1.00	17.87	O
ATOM	2482	N	TRP B 107	-7.006	11.438	34.924	1.00	18.64	N
ATOM	2483	CA	TRP B 107	-7.055	11.606	33.479	1.00	18.89	C
ATOM	2484	CB	TRP B 107	-5.747	11.230	32.784	1.00	18.59	C
ATOM	2485	CG	TRP B 107	-4.692	12.149	33.346	1.00	18.84	C
ATOM	2486	CD1	TRP B 107	-3.875	11.900	34.415	1.00	19.16	C
ATOM	2487	NE1	TRP B 107	-3.086	12.998	34.681	1.00	19.47	N
ATOM	2488	CE2	TRP B 107	-3.402	13.997	33.797	1.00	19.44	C
ATOM	2489	CD2	TRP B 107	-4.429	13.505	32.951	1.00	18.83	C
ATOM	2490	CE3	TRP B 107	-4.935	14.340	31.947	1.00	18.26	C
ATOM	2491	CZ3	TRP B 107	-4.411	15.623	31.823	1.00	19.06	C
ATOM	2492	CH2	TRP B 107	-3.383	16.084	32.679	1.00	18.46	C
ATOM	2493	CZ2	TRP B 107	-2.867	15.288	33.663	1.00	18.30	C
ATOM	2494	C	TRP B 107	-8.353	11.235	32.810	1.00	19.15	C
ATOM	2495	O	TRP B 107	-9.339	11.957	32.942	1.00	20.64	O
ATOM	2496	N	PHE B 108	-8.430	10.126	32.121	1.00	18.55	N
ATOM	2497	CA	PHE B 108	-9.606	10.018	31.269	1.00	17.84	C
ATOM	2498	CB	PHE B 108	-9.217	9.348	29.970	1.00	16.87	C
ATOM	2499	CG	PHE B 108	-8.004	9.980	29.362	1.00	15.75	C
ATOM	2500	CD1	PHE B 108	-6.882	9.231	29.069	1.00	13.87	C
ATOM	2501	CE1	PHE B 108	-5.755	9.840	28.526	1.00	14.97	C
ATOM	2502	CZ	PHE B 108	-5.743	11.228	28.310	1.00	14.18	C
ATOM	2503	CE2	PHE B 108	-6.850	11.983	28.633	1.00	11.83	C
ATOM	2504	CD2	PHE B 108	-7.965	11.368	29.160	1.00	14.18	C
ATOM	2505	C	PHE B 108	-10.797	9.442	32.031	1.00	18.09	C
ATOM	2506	O	PHE B 108	-11.110	8.248	31.960	1.00	18.26	O
ATOM	2507	N	ASP B 109	-11.430	10.322	32.797	1.00	17.80	N
ATOM	2508	CA	ASP B 109	-12.413	9.884	33.765	1.00	18.17	C
ATOM	2509	CB	ASP B 109	-12.321	10.655	35.108	1.00	18.10	C
ATOM	2510	CG	ASP B 109	-12.385	12.172	34.960	1.00	18.16	C
ATOM	2511	OD1	ASP B 109	-12.138	12.721	33.860	1.00	18.83	O

ATOM	2512	OD2 ASP B 109	-12.666	12.825	35.988	1.00	17.33	O
ATOM	2513	C ASP B 109	-13.818	9.847	33.212	1.00	18.19	C
ATOM	2514	O ASP B 109	-14.662	9.141	33.755	1.00	18.69	O
ATOM	2515	N PHE B 110	-14.056	10.593	32.136	1.00	17.96	N
ATOM	2516	CA PHE B 110	-15.327	10.573	31.428	1.00	17.75	C
ATOM	2517	CB PHE B 110	-16.150	11.808	31.760	1.00	18.06	C
ATOM	2518	CG PHE B 110	-16.749	11.770	33.111	1.00	20.04	C
ATOM	2519	CD1 PHE B 110	-16.065	12.322	34.212	1.00	22.90	C
ATOM	2520	CE1 PHE B 110	-16.625	12.287	35.504	1.00	21.72	C
ATOM	2521	CZ PHE B 110	-17.867	11.677	35.695	1.00	21.14	C
ATOM	2522	CE2 PHE B 110	-18.555	11.125	34.598	1.00	22.55	C
ATOM	2523	CD2 PHE B 110	-17.992	11.175	33.315	1.00	21.41	C
ATOM	2524	C PHE B 110	-15.066	10.530	29.939	1.00	17.46	C
ATOM	2525	O PHE B 110	-14.212	11.281	29.431	1.00	17.37	O
ATOM	2526	N TRP B 111	-15.791	9.654	29.240	1.00	16.70	N
ATOM	2527	CA TRP B 111	-15.631	9.528	27.792	1.00	16.30	C
ATOM	2528	CB TRP B 111	-15.140	8.124	27.414	1.00	15.35	C
ATOM	2529	CG TRP B 111	-13.811	7.754	28.006	1.00	14.43	C
ATOM	2530	CD1 TRP B 111	-13.485	7.717	29.333	1.00	12.67	C
ATOM	2531	NE1 TRP B 111	-12.174	7.339	29.489	1.00	12.73	N
ATOM	2532	CE2 TRP B 111	-11.624	7.103	28.257	1.00	13.38	C
ATOM	2533	CD2 TRP B 111	-12.630	7.351	27.293	1.00	13.88	C
ATOM	2534	CE3 TRP B 111	-12.325	7.172	25.935	1.00	13.50	C
ATOM	2535	CZ3 TRP B 111	-11.015	6.761	25.582	1.00	13.86	C
ATOM	2536	CH2 TRP B 111	-10.041	6.524	26.573	1.00	13.59	C
ATOM	2537	CZ2 TRP B 111	-10.331	6.685	27.909	1.00	13.49	C
ATOM	2538	C TRP B 111	-16.919	9.845	27.055	1.00	16.60	C
ATOM	2539	O TRP B 111	-17.987	9.982	27.657	1.00	16.61	O
ATOM	2540	N GLY B 112	-16.804	9.984	25.741	1.00	17.20	N
ATOM	2541	CA GLY B 112	-17.974	10.001	24.861	1.00	17.45	C
ATOM	2542	C GLY B 112	-18.215	8.577	24.415	1.00	17.38	C
ATOM	2543	O GLY B 112	-17.353	7.728	24.603	1.00	17.39	O
ATOM	2544	N GLN B 113	-19.384	8.314	23.843	1.00	17.81	N
ATOM	2545	CA GLN B 113	-19.758	6.964	23.412	1.00	18.46	C
ATOM	2546	CB GLN B 113	-21.267	6.880	23.117	1.00	18.32	C
ATOM	2547	CG GLN B 113	-21.704	7.432	21.761	1.00	19.38	C
ATOM	2548	CD GLN B 113	-21.815	8.963	21.689	1.00	20.48	C
ATOM	2549	OE1 GLN B 113	-21.091	9.708	22.373	1.00	20.00	O
ATOM	2550	NE2 GLN B 113	-22.727	9.437	20.836	1.00	19.11	N
ATOM	2551	C GLN B 113	-18.918	6.500	22.216	1.00	18.84	C
ATOM	2552	O GLN B 113	-18.930	5.336	21.841	1.00	18.87	O
ATOM	2553	N GLY B 114	-18.169	7.430	21.640	1.00	19.69	N
ATOM	2554	CA GLY B 114	-17.326	7.147	20.492	1.00	20.17	C
ATOM	2555	C GLY B 114	-18.051	7.444	19.202	1.00	20.45	C
ATOM	2556	O GLY B 114	-19.272	7.317	19.127	1.00	20.35	O
ATOM	2557	N THR B 115	-17.291	7.868	18.200	1.00	21.13	N
ATOM	2558	CA THR B 115	-17.791	7.954	16.829	1.00	21.91	C
ATOM	2559	CB THR B 115	-17.969	9.415	16.345	1.00	21.81	C
ATOM	2560	OG1 THR B 115	-17.639	9.505	14.956	1.00	22.14	O
ATOM	2561	CG2 THR B 115	-17.097	10.346	17.111	1.00	22.51	C
ATOM	2562	C THR B 115	-16.939	7.115	15.860	1.00	21.91	C
ATOM	2563	O THR B 115	-15.749	7.381	15.684	1.00	21.75	O
ATOM	2564	N MET B 116	-17.564	6.093	15.268	1.00	22.35	N
ATOM	2565	CA MET B 116	-16.915	5.251	14.256	1.00	22.21	C
ATOM	2566	CB MET B 116	-17.707	3.937	14.026	1.00	22.51	C
ATOM	2567	CG MET B 116	-17.098	2.924	13.015	1.00	23.67	C
ATOM	2568	SD MET B 116	-15.428	2.274	13.384	1.00	29.60	S

ATOM	2569	CE	MET B 116	-15.842	0.739	14.240	1.00	31.29	C
ATOM	2570	C	MET B 116	-16.726	6.034	12.956	1.00	21.86	C
ATOM	2571	O	MET B 116	-17.636	6.722	12.483	1.00	21.48	O
ATOM	2572	N	VAL B 117	-15.528	5.937	12.398	1.00	21.70	N
ATOM	2573	CA	VAL B 117	-15.215	6.580	11.129	1.00	21.94	C
ATOM	2574	CB	VAL B 117	-14.189	7.723	11.294	1.00	22.15	C
ATOM	2575	CG1	VAL B 117	-13.698	8.203	9.922	1.00	21.51	C
ATOM	2576	CG2	VAL B 117	-14.768	8.881	12.143	1.00	20.34	C
ATOM	2577	C	VAL B 117	-14.681	5.537	10.158	1.00	22.45	C
ATOM	2578	O	VAL B 117	-13.710	4.828	10.446	1.00	22.57	O
ATOM	2579	N	THR B 118	-15.336	5.436	9.011	1.00	23.06	N
ATOM	2580	CA	THR B 118	-14.968	4.455	8.005	1.00	23.62	C
ATOM	2581	CB	THR B 118	-16.131	3.493	7.720	1.00	23.55	C
ATOM	2582	OG1	THR B 118	-16.889	3.299	8.918	1.00	23.55	O
ATOM	2583	CG2	THR B 118	-15.612	2.166	7.238	1.00	23.77	C
ATOM	2584	C	THR B 118	-14.547	5.186	6.727	1.00	24.31	C
ATOM	2585	O	THR B 118	-15.257	6.082	6.235	1.00	24.06	O
ATOM	2586	N	VAL B 119	-13.382	4.808	6.211	1.00	24.80	N
ATOM	2587	CA	VAL B 119	-12.826	5.438	5.032	1.00	25.65	C
ATOM	2588	CB	VAL B 119	-11.553	6.268	5.373	1.00	25.92	C
ATOM	2589	CG1	VAL B 119	-11.093	7.087	4.167	1.00	24.55	C
ATOM	2590	CG2	VAL B 119	-11.819	7.190	6.582	1.00	26.05	C
ATOM	2591	C	VAL B 119	-12.506	4.372	3.996	1.00	26.32	C
ATOM	2592	O	VAL B 119	-11.546	3.604	4.170	1.00	26.37	O
ATOM	2593	N	SER B 120	-13.310	4.344	2.924	1.00	26.67	N
ATOM	2594	CA	SER B 120	-13.195	3.346	1.841	1.00	26.96	C
ATOM	2595	CB	SER B 120	-14.163	2.187	2.098	1.00	26.76	C
ATOM	2596	OG	SER B 120	-13.828	1.024	1.357	1.00	26.72	O
ATOM	2597	C	SER B 120	-13.511	3.970	0.478	1.00	27.30	C
ATOM	2598	O	SER B 120	-14.099	5.052	0.396	1.00	28.04	O
ATOM	2599	N	SER B 121	-13.131	3.296	-0.597	1.00	26.97	N
ATOM	2600	CA	SER B 121	-13.549	3.735	-1.919	1.00	26.51	C
ATOM	2601	CB	SER B 121	-12.567	3.249	-2.959	1.00	26.23	C
ATOM	2602	OG	SER B 121	-11.372	3.960	-2.758	1.00	27.20	O
ATOM	2603	C	SER B 121	-14.958	3.275	-2.263	1.00	26.32	C
ATOM	2604	O	SER B 121	-15.590	3.823	-3.173	1.00	26.91	O
ATOM	2605	N	ALA B 122	-15.455	2.283	-1.531	1.00	25.43	N
ATOM	2606	CA	ALA B 122	-16.714	1.654	-1.869	1.00	24.89	C
ATOM	2607	CB	ALA B 122	-17.006	0.521	-0.925	1.00	24.94	C
ATOM	2608	C	ALA B 122	-17.848	2.655	-1.860	1.00	24.53	C
ATOM	2609	O	ALA B 122	-17.715	3.760	-1.351	1.00	24.30	O
ATOM	2610	N	SER B 123	-18.963	2.258	-2.446	1.00	24.51	N
ATOM	2611	CA	SER B 123	-20.154	3.082	-2.464	1.00	24.48	C
ATOM	2612	CB	SER B 123	-20.561	3.400	-3.904	1.00	24.31	C
ATOM	2613	OG	SER B 123	-19.576	4.210	-4.527	1.00	23.96	O
ATOM	2614	C	SER B 123	-21.235	2.290	-1.774	1.00	24.53	C
ATOM	2615	O	SER B 123	-21.145	1.066	-1.673	1.00	24.17	O
ATOM	2616	N	THR B 124	-22.256	2.978	-1.285	1.00	24.84	N
ATOM	2617	CA	THR B 124	-23.350	2.271	-0.649	1.00	25.30	C
ATOM	2618	CB	THR B 124	-24.456	3.218	-0.237	1.00	24.84	C
ATOM	2619	OG1	THR B 124	-23.865	4.296	0.489	1.00	25.11	O
ATOM	2620	CG2	THR B 124	-25.439	2.524	0.668	1.00	24.69	C
ATOM	2621	C	THR B 124	-23.834	1.166	-1.588	1.00	25.95	C
ATOM	2622	O	THR B 124	-23.959	1.370	-2.793	1.00	26.25	O
ATOM	2623	N	LYS B 125	-24.026	-0.024	-1.029	1.00	26.49	N
ATOM	2624	CA	LYS B 125	-24.475	-1.192	-1.782	1.00	26.73	C
ATOM	2625	CB	LYS B 125	-23.276	-1.970	-2.329	1.00	26.77	C

ATOM	2626	CG	LYS B 125	-23.354	-2.349	-3.806	1.00	28.48	C
ATOM	2627	CD	LYS B 125	-24.437	-3.403	-4.142	1.00	32.39	C
ATOM	2628	CE	LYS B 125	-23.891	-4.831	-4.127	1.00	32.33	C
ATOM	2629	NZ	LYS B 125	-22.536	-4.852	-4.725	1.00	32.13	N
ATOM	2630	C	LYS B 125	-25.266	-2.076	-0.823	1.00	26.39	C
ATOM	2631	O	LYS B 125	-24.760	-2.438	0.244	1.00	26.12	O
ATOM	2632	N	GLY B 126	-26.518	-2.365	-1.185	1.00	25.95	N
ATOM	2633	CA	GLY B 126	-27.342	-3.329	-0.473	1.00	25.04	C
ATOM	2634	C	GLY B 126	-26.769	-4.726	-0.645	1.00	24.99	C
ATOM	2635	O	GLY B 126	-25.982	-4.975	-1.571	1.00	24.94	O
ATOM	2636	N	PRO B 127	-27.117	-5.644	0.272	1.00	24.86	N
ATOM	2637	CA	PRO B 127	-26.622	-7.008	0.197	1.00	24.81	C
ATOM	2638	CB	PRO B 127	-26.643	-7.443	1.652	1.00	24.68	C
ATOM	2639	CG	PRO B 127	-27.804	-6.733	2.209	1.00	24.49	C
ATOM	2640	CD	PRO B 127	-27.943	-5.438	1.471	1.00	24.71	C
ATOM	2641	C	PRO B 127	-27.510	-7.957	-0.592	1.00	24.79	C
ATOM	2642	O	PRO B 127	-28.725	-7.785	-0.652	1.00	24.98	O
ATOM	2643	N	SER B 128	-26.886	-8.961	-1.183	1.00	24.50	N
ATOM	2644	CA	SER B 128	-27.597	-10.137	-1.620	1.00	24.37	C
ATOM	2645	CB	SER B 128	-26.796	-10.844	-2.698	1.00	24.47	C
ATOM	2646	OG	SER B 128	-26.387	-9.928	-3.703	1.00	25.31	O
ATOM	2647	C	SER B 128	-27.709	-11.028	-0.398	1.00	23.99	C
ATOM	2648	O	SER B 128	-26.767	-11.102	0.396	1.00	24.61	O
ATOM	2649	N	VAL B 129	-28.852	-11.691	-0.238	1.00	23.33	N
ATOM	2650	CA	VAL B 129	-29.063	-12.631	0.865	1.00	22.20	C
ATOM	2651	CB	VAL B 129	-30.285	-12.252	1.727	1.00	22.03	C
ATOM	2652	CG1	VAL B 129	-30.378	-13.170	2.950	1.00	21.20	C
ATOM	2653	CG2	VAL B 129	-30.227	-10.793	2.150	1.00	20.54	C
ATOM	2654	C	VAL B 129	-29.302	-14.025	0.308	1.00	22.26	C
ATOM	2655	O	VAL B 129	-30.276	-14.239	-0.405	1.00	22.63	O
ATOM	2656	N	PHE B 130	-28.427	-14.973	0.635	1.00	22.12	N
ATOM	2657	CA	PHE B 130	-28.578	-16.359	0.169	1.00	21.91	C
ATOM	2658	CB	PHE B 130	-27.339	-16.798	-0.616	1.00	21.66	C
ATOM	2659	CG	PHE B 130	-26.934	-15.846	-1.702	1.00	20.51	C
ATOM	2660	CD1	PHE B 130	-27.773	-15.604	-2.786	1.00	18.80	C
ATOM	2661	CE1	PHE B 130	-27.414	-14.722	-3.794	1.00	18.36	C
ATOM	2662	CZ	PHE B 130	-26.188	-14.069	-3.744	1.00	20.03	C
ATOM	2663	CE2	PHE B 130	-25.329	-14.294	-2.659	1.00	21.33	C
ATOM	2664	CD2	PHE B 130	-25.710	-15.198	-1.647	1.00	20.61	C
ATOM	2665	C	PHE B 130	-28.838	-17.330	1.318	1.00	22.19	C
ATOM	2666	O	PHE B 130	-28.452	-17.062	2.448	1.00	21.94	O
ATOM	2667	N	PRO B 131	-29.506	-18.464	1.036	1.00	23.00	N
ATOM	2668	CA	PRO B 131	-29.765	-19.441	2.097	1.00	23.37	C
ATOM	2669	CB	PRO B 131	-30.974	-20.226	1.572	1.00	23.12	C
ATOM	2670	CG	PRO B 131	-30.861	-20.151	0.088	1.00	22.70	C
ATOM	2671	CD	PRO B 131	-30.084	-18.896	-0.256	1.00	23.24	C
ATOM	2672	C	PRO B 131	-28.607	-20.386	2.336	1.00	23.86	C
ATOM	2673	O	PRO B 131	-27.921	-20.790	1.399	1.00	24.23	O
ATOM	2674	N	LEU B 132	-28.392	-20.708	3.604	1.00	24.57	N
ATOM	2675	CA	LEU B 132	-27.497	-21.766	4.016	1.00	25.27	C
ATOM	2676	CB	LEU B 132	-26.537	-21.277	5.107	1.00	24.96	C
ATOM	2677	CG	LEU B 132	-25.684	-20.053	4.724	1.00	24.08	C
ATOM	2678	CD1	LEU B 132	-25.298	-19.214	5.938	1.00	23.95	C
ATOM	2679	CD2	LEU B 132	-24.462	-20.485	3.974	1.00	21.96	C
ATOM	2680	C	LEU B 132	-28.465	-22.810	4.516	1.00	26.10	C
ATOM	2681	O	LEU B 132	-28.986	-22.717	5.621	1.00	25.51	O
ATOM	2682	N	ALA B 133	-28.737	-23.780	3.648	1.00	27.87	N

ATOM	2683	CA	ALA B 133	-29.848	-24.708	3.833	1.00	29.33	C
ATOM	2684	CB	ALA B 133	-30.480	-25.038	2.494	1.00	28.90	C
ATOM	2685	C	ALA B 133	-29.413	-25.976	4.560	1.00	30.72	C
ATOM	2686	O	ALA B 133	-28.275	-26.446	4.370	1.00	31.09	O
ATOM	2687	N	PRO B 134	-30.314	-26.531	5.395	1.00	32.09	N
ATOM	2688	CA	PRO B 134	-30.066	-27.773	6.143	1.00	33.42	C
ATOM	2689	CB	PRO B 134	-31.165	-27.759	7.206	1.00	33.41	C
ATOM	2690	CG	PRO B 134	-32.308	-26.999	6.548	1.00	32.74	C
ATOM	2691	CD	PRO B 134	-31.658	-25.974	5.667	1.00	32.01	C
ATOM	2692	C	PRO B 134	-30.196	-29.034	5.273	1.00	34.75	C
ATOM	2693	O	PRO B 134	-30.902	-29.014	4.261	1.00	34.91	O
ATOM	2694	N	SER B 135	-29.507	-30.102	5.686	1.00	36.45	N
ATOM	2695	CA	SER B 135	-29.494	-31.429	5.033	1.00	38.03	C
ATOM	2696	CB	SER B 135	-28.944	-31.373	3.587	1.00	38.24	C
ATOM	2697	OG	SER B 135	-27.753	-30.598	3.479	1.00	38.36	O
ATOM	2698	C	SER B 135	-28.670	-32.395	5.898	1.00	38.80	C
ATOM	2699	O	SER B 135	-28.859	-32.432	7.117	1.00	38.96	O
ATOM	2700	N	SER B 136	-27.768	-33.153	5.256	1.00	39.78	N
ATOM	2701	CA	SER B 136	-26.803	-34.094	5.896	1.00	40.20	C
ATOM	2702	CB	SER B 136	-25.341	-33.772	5.466	1.00	40.61	C
ATOM	2703	OG	SER B 136	-24.760	-32.714	6.225	1.00	39.90	O
ATOM	2704	C	SER B 136	-26.912	-34.253	7.427	1.00	40.11	C
ATOM	2705	O	SER B 136	-25.912	-34.230	8.150	1.00	39.83	O
ATOM	2706	N	SER B 140	-33.465	-39.250	11.718	1.00	47.15	N
ATOM	2707	CA	SER B 140	-32.771	-37.963	11.660	1.00	47.10	C
ATOM	2708	CB	SER B 140	-33.775	-36.808	11.818	1.00	47.30	C
ATOM	2709	OG	SER B 140	-34.648	-37.008	12.924	1.00	47.48	O
ATOM	2710	C	SER B 140	-31.633	-37.846	12.695	1.00	46.83	C
ATOM	2711	O	SER B 140	-31.702	-38.449	13.787	1.00	46.79	O
ATOM	2712	N	GLY B 141	-30.598	-37.071	12.336	1.00	46.09	N
ATOM	2713	CA	GLY B 141	-29.435	-36.805	13.218	1.00	44.73	C
ATOM	2714	C	GLY B 141	-29.626	-35.600	14.142	1.00	43.58	C
ATOM	2715	O	GLY B 141	-29.885	-34.492	13.668	1.00	43.54	O
ATOM	2716	N	GLY B 142	-29.500	-35.831	15.455	1.00	42.37	N
ATOM	2717	CA	GLY B 142	-29.694	-34.821	16.510	1.00	40.47	C
ATOM	2718	C	GLY B 142	-30.288	-33.472	16.105	1.00	39.33	C
ATOM	2719	O	GLY B 142	-31.515	-33.283	16.120	1.00	39.31	O
ATOM	2720	N	THR B 143	-29.406	-32.538	15.736	1.00	37.43	N
ATOM	2721	CA	THR B 143	-29.781	-31.148	15.478	1.00	35.34	C
ATOM	2722	CB	THR B 143	-29.181	-30.184	16.550	1.00	35.66	C
ATOM	2723	OG1	THR B 143	-28.024	-29.525	16.023	1.00	34.92	O
ATOM	2724	CG2	THR B 143	-28.814	-30.930	17.849	1.00	35.39	C
ATOM	2725	C	THR B 143	-29.371	-30.673	14.071	1.00	33.83	C
ATOM	2726	O	THR B 143	-28.454	-31.223	13.466	1.00	33.65	O
ATOM	2727	N	ALA B 144	-30.047	-29.637	13.577	1.00	31.87	N
ATOM	2728	CA	ALA B 144	-29.820	-29.103	12.245	1.00	30.18	C
ATOM	2729	CB	ALA B 144	-31.080	-29.214	11.464	1.00	30.20	C
ATOM	2730	C	ALA B 144	-29.342	-27.644	12.270	1.00	29.35	C
ATOM	2731	O	ALA B 144	-29.573	-26.934	13.251	1.00	28.95	O
ATOM	2732	N	ALA B 145	-28.699	-27.196	11.181	1.00	28.38	N
ATOM	2733	CA	ALA B 145	-28.225	-25.800	11.050	1.00	27.02	C
ATOM	2734	CB	ALA B 145	-26.705	-25.753	11.206	1.00	26.87	C
ATOM	2735	C	ALA B 145	-28.674	-25.049	9.773	1.00	26.65	C
ATOM	2736	O	ALA B 145	-28.719	-25.638	8.709	1.00	26.85	O
ATOM	2737	N	LEU B 146	-29.013	-23.755	9.924	1.00	26.39	N
ATOM	2738	CA	LEU B 146	-29.342	-22.743	8.852	1.00	25.60	C
ATOM	2739	CB	LEU B 146	-30.841	-22.474	8.821	1.00	25.24	C

ATOM	2740	CG	LEU B 146	-31.710	-23.432	9.637	1.00	25.94	C
ATOM	2741	CD1	LEU B 146	-33.013	-22.799	10.058	1.00	26.06	C
ATOM	2742	CD2	LEU B 146	-31.954	-24.694	8.879	1.00	26.47	C
ATOM	2743	C	LEU B 146	-28.616	-21.441	9.276	1.00	24.66	C
ATOM	2744	O	LEU B 146	-28.190	-21.400	10.429	1.00	24.91	O
ATOM	2745	N	GLY B 147	-28.513	-20.355	8.484	1.00	23.79	N
ATOM	2746	CA	GLY B 147	-29.396	-19.963	7.387	1.00	23.02	C
ATOM	2747	C	GLY B 147	-28.988	-18.914	6.347	1.00	22.77	C
ATOM	2748	O	GLY B 147	-29.059	-19.218	5.176	1.00	23.33	O
ATOM	2749	N	CYS B 148	-28.606	-17.687	6.716	1.00	22.30	N
ATOM	2750	CA	CYS B 148	-28.293	-16.615	5.707	1.00	21.94	C
ATOM	2751	CB	CYS B 148	-29.331	-15.499	5.857	1.00	21.56	C
ATOM	2752	SG	CYS B 148	-31.079	-16.064	5.745	1.00	19.66	S
ATOM	2753	C	CYS B 148	-26.892	-16.096	6.029	1.00	21.92	C
ATOM	2754	O	CYS B 148	-26.745	-15.519	7.088	1.00	22.91	O
ATOM	2755	N	LEU B 149	-25.833	-16.197	5.219	1.00	21.50	N
ATOM	2756	CA	LEU B 149	-25.487	-15.605	3.909	1.00	20.83	C
ATOM	2757	CB	LEU B 149	-25.056	-16.587	2.816	1.00	20.90	C
ATOM	2758	CG	LEU B 149	-23.790	-16.056	2.078	1.00	21.19	C
ATOM	2759	CD1	LEU B 149	-22.740	-15.394	2.977	1.00	20.62	C
ATOM	2760	CD2	LEU B 149	-23.096	-17.111	1.215	1.00	20.88	C
ATOM	2761	C	LEU B 149	-25.903	-14.189	3.417	1.00	20.47	C
ATOM	2762	O	LEU B 149	-26.626	-14.037	2.440	1.00	20.58	O
ATOM	2763	N	VAL B 150	-25.337	-13.182	4.079	1.00	19.73	N
ATOM	2764	CA	VAL B 150	-25.582	-11.779	3.752	1.00	18.82	C
ATOM	2765	CB	VAL B 150	-25.969	-10.994	4.987	1.00	18.65	C
ATOM	2766	CG1	VAL B 150	-26.091	-9.529	4.664	1.00	17.82	C
ATOM	2767	CG2	VAL B 150	-27.279	-11.549	5.564	1.00	18.74	C
ATOM	2768	C	VAL B 150	-24.327	-11.189	3.131	1.00	18.89	C
ATOM	2769	O	VAL B 150	-23.344	-10.922	3.827	1.00	17.76	O
ATOM	2770	N	LYS B 151	-24.370	-10.999	1.811	1.00	19.04	N
ATOM	2771	CA	LYS B 151	-23.146	-10.813	1.045	1.00	19.45	C
ATOM	2772	CB	LYS B 151	-22.923	-12.041	0.163	1.00	19.37	C
ATOM	2773	CG	LYS B 151	-21.500	-12.200	-0.297	1.00	20.46	C
ATOM	2774	CD	LYS B 151	-21.328	-13.348	-1.265	1.00	21.68	C
ATOM	2775	CE	LYS B 151	-19.838	-13.594	-1.555	1.00	22.65	C
ATOM	2776	NZ	LYS B 151	-19.274	-12.582	-2.506	1.00	22.31	N
ATOM	2777	C	LYS B 151	-23.062	-9.510	0.223	1.00	19.47	C
ATOM	2778	O	LYS B 151	-24.072	-8.975	-0.222	1.00	19.54	O
ATOM	2779	N	ASP B 152	-21.834	-9.033	0.039	1.00	19.52	N
ATOM	2780	CA	ASP B 152	-21.507	-7.831	-0.736	1.00	19.67	C
ATOM	2781	CB	ASP B 152	-21.379	-8.154	-2.227	1.00	19.40	C
ATOM	2782	CG	ASP B 152	-20.450	-9.326	-2.498	1.00	19.50	C
ATOM	2783	OD1	ASP B 152	-20.967	-10.404	-2.828	1.00	20.57	O
ATOM	2784	OD2	ASP B 152	-19.209	-9.192	-2.389	1.00	19.30	O
ATOM	2785	C	ASP B 152	-22.443	-6.631	-0.472	1.00	19.94	C
ATOM	2786	O	ASP B 152	-23.363	-6.334	-1.265	1.00	20.52	O
ATOM	2787	N	TYR B 153	-22.207	-5.976	0.665	1.00	19.33	N
ATOM	2788	CA	TYR B 153	-22.869	-4.735	1.042	1.00	18.93	C
ATOM	2789	CB	TYR B 153	-23.992	-4.993	2.069	1.00	18.65	C
ATOM	2790	CG	TYR B 153	-23.489	-5.453	3.418	1.00	18.84	C
ATOM	2791	CD1	TYR B 153	-23.296	-6.815	3.689	1.00	18.44	C
ATOM	2792	CE1	TYR B 153	-22.802	-7.246	4.930	1.00	17.60	C
ATOM	2793	CZ	TYR B 153	-22.506	-6.316	5.901	1.00	18.09	C
ATOM	2794	OH	TYR B 153	-22.039	-6.741	7.108	1.00	18.02	O
ATOM	2795	CE2	TYR B 153	-22.686	-4.956	5.666	1.00	18.25	C
ATOM	2796	CD2	TYR B 153	-23.182	-4.530	4.429	1.00	18.29	C

ATOM	2797	C	TYR B 153	-21.832	-3.751	1.612	1.00	19.23	C
ATOM	2798	O	TYR B 153	-20.751	-4.158	2.092	1.00	19.32	O
ATOM	2799	N	PHE B 154	-22.159	-2.460	1.559	1.00	19.12	N
ATOM	2800	CA	PHE B 154	-21.313	-1.425	2.149	1.00	18.95	C
ATOM	2801	CB	PHE B 154	-20.173	-1.084	1.198	1.00	18.60	C
ATOM	2802	CG	PHE B 154	-19.302	0.010	1.689	1.00	19.20	C
ATOM	2803	CD1	PHE B 154	-19.639	1.342	1.458	1.00	19.23	C
ATOM	2804	CE1	PHE B 154	-18.835	2.376	1.935	1.00	18.72	C
ATOM	2805	CZ	PHE B 154	-17.688	2.082	2.647	1.00	18.79	C
ATOM	2806	CE2	PHE B 154	-17.341	0.750	2.889	1.00	19.38	C
ATOM	2807	CD2	PHE B 154	-18.151	-0.276	2.413	1.00	19.79	C
ATOM	2808	C	PHE B 154	-22.137	-0.166	2.486	1.00	19.15	C
ATOM	2809	O	PHE B 154	-23.025	0.210	1.713	1.00	19.18	O
ATOM	2810	N	PRO B 155	-21.867	0.486	3.645	1.00	19.19	N
ATOM	2811	CA	PRO B 155	-20.901	0.177	4.697	1.00	19.01	C
ATOM	2812	CB	PRO B 155	-20.697	1.541	5.353	1.00	19.01	C
ATOM	2813	CG	PRO B 155	-22.059	2.151	5.315	1.00	18.33	C
ATOM	2814	CD	PRO B 155	-22.638	1.707	3.982	1.00	19.06	C
ATOM	2815	C	PRO B 155	-21.510	-0.784	5.719	1.00	19.15	C
ATOM	2816	O	PRO B 155	-22.493	-1.448	5.412	1.00	19.28	O
ATOM	2817	N	GLU B 156	-20.938	-0.834	6.922	1.00	19.36	N
ATOM	2818	CA	GLU B 156	-21.564	-1.466	8.084	1.00	19.49	C
ATOM	2819	CB	GLU B 156	-20.498	-1.706	9.157	1.00	19.41	C
ATOM	2820	CG	GLU B 156	-19.437	-2.753	8.821	1.00	19.48	C
ATOM	2821	CD	GLU B 156	-19.707	-4.086	9.500	1.00	21.35	C
ATOM	2822	OE1	GLU B 156	-20.817	-4.644	9.317	1.00	22.27	O
ATOM	2823	OE2	GLU B 156	-18.811	-4.580	10.229	1.00	21.47	O
ATOM	2824	C	GLU B 156	-22.663	-0.522	8.624	1.00	19.80	C
ATOM	2825	O	GLU B 156	-22.707	0.652	8.258	1.00	19.96	O
ATOM	2826	N	PRO B 157	-23.566	-1.015	9.487	1.00	20.08	N
ATOM	2827	CA	PRO B 157	-23.789	-2.367	9.943	1.00	20.53	C
ATOM	2828	CB	PRO B 157	-24.203	-2.145	11.396	1.00	20.38	C
ATOM	2829	CG	PRO B 157	-25.001	-0.861	11.350	1.00	19.38	C
ATOM	2830	CD	PRO B 157	-24.480	-0.075	10.170	1.00	20.11	C
ATOM	2831	C	PRO B 157	-24.954	-3.017	9.209	1.00	21.13	C
ATOM	2832	O	PRO B 157	-25.697	-2.344	8.496	1.00	20.92	O
ATOM	2833	N	VAL B 158	-25.126	-4.316	9.424	1.00	21.78	N
ATOM	2834	CA	VAL B 158	-26.326	-5.003	8.999	1.00	22.26	C
ATOM	2835	CB	VAL B 158	-26.005	-6.016	7.873	1.00	22.39	C
ATOM	2836	CG1	VAL B 158	-25.184	-7.183	8.405	1.00	22.91	C
ATOM	2837	CG2	VAL B 158	-27.265	-6.520	7.222	1.00	23.22	C
ATOM	2838	C	VAL B 158	-26.950	-5.664	10.236	1.00	22.54	C
ATOM	2839	O	VAL B 158	-26.253	-6.197	11.091	1.00	22.10	O
ATOM	2840	N	THR B 159	-28.268	-5.574	10.331	1.00	23.30	N
ATOM	2841	CA	THR B 159	-29.048	-6.201	11.384	1.00	23.90	C
ATOM	2842	CB	THR B 159	-30.196	-5.270	11.770	1.00	23.75	C
ATOM	2843	OG1	THR B 159	-29.676	-4.262	12.627	1.00	24.51	O
ATOM	2844	CG2	THR B 159	-31.321	-5.996	12.507	1.00	25.04	C
ATOM	2845	C	THR B 159	-29.603	-7.526	10.850	1.00	24.37	C
ATOM	2846	O	THR B 159	-30.159	-7.558	9.738	1.00	24.88	O
ATOM	2847	N	VAL B 160	-29.430	-8.611	11.607	1.00	24.09	N
ATOM	2848	CA	VAL B 160	-30.084	-9.873	11.267	1.00	24.20	C
ATOM	2849	CB	VAL B 160	-29.106	-11.012	10.866	1.00	24.12	C
ATOM	2850	CG1	VAL B 160	-29.885	-12.248	10.435	1.00	22.78	C
ATOM	2851	CG2	VAL B 160	-28.190	-10.571	9.752	1.00	24.05	C
ATOM	2852	C	VAL B 160	-30.934	-10.343	12.430	1.00	24.72	C
ATOM	2853	O	VAL B 160	-30.544	-10.231	13.592	1.00	25.29	O

ATOM	2854	N	SER B 161	-32.089	-10.902	12.105	1.00	24.91	N
ATOM	2855	CA	SER B 161	-33.036	-11.329	13.099	1.00	24.83	C
ATOM	2856	CB	SER B 161	-33.992	-10.179	13.372	1.00	24.72	C
ATOM	2857	OG	SER B 161	-35.277	-10.662	13.681	1.00	26.95	O
ATOM	2858	C	SER B 161	-33.749	-12.540	12.512	1.00	24.65	C
ATOM	2859	O	SER B 161	-33.712	-12.737	11.299	1.00	25.03	O
ATOM	2860	N	TRP B 162	-34.381	-13.356	13.355	1.00	24.36	N
ATOM	2861	CA	TRP B 162	-35.046	-14.576	12.887	1.00	24.02	C
ATOM	2862	CB	TRP B 162	-34.313	-15.812	13.381	1.00	23.01	C
ATOM	2863	CG	TRP B 162	-33.009	-16.011	12.708	1.00	22.18	C
ATOM	2864	CD1	TRP B 162	-31.794	-15.518	13.100	1.00	20.62	C
ATOM	2865	NE1	TRP B 162	-30.816	-15.917	12.211	1.00	20.90	N
ATOM	2866	CE2	TRP B 162	-31.391	-16.676	11.226	1.00	21.11	C
ATOM	2867	CD2	TRP B 162	-32.776	-16.754	11.504	1.00	21.82	C
ATOM	2868	CE3	TRP B 162	-33.604	-17.484	10.632	1.00	21.00	C
ATOM	2869	CZ3	TRP B 162	-33.032	-18.103	9.528	1.00	20.50	C
ATOM	2870	CH2	TRP B 162	-31.657	-18.001	9.276	1.00	21.11	C
ATOM	2871	CZ2	TRP B 162	-30.818	-17.298	10.115	1.00	21.28	C
ATOM	2872	C	TRP B 162	-36.505	-14.639	13.294	1.00	24.72	C
ATOM	2873	O	TRP B 162	-36.867	-14.245	14.407	1.00	25.17	O
ATOM	2874	N	ASN B 163	-37.328	-15.171	12.392	1.00	25.22	N
ATOM	2875	CA	ASN B 163	-38.782	-15.082	12.491	1.00	25.90	C
ATOM	2876	CB	ASN B 163	-39.364	-16.320	13.162	1.00	25.82	C
ATOM	2877	CG	ASN B 163	-38.997	-17.604	12.419	1.00	27.28	C
ATOM	2878	OD1	ASN B 163	-38.427	-17.557	11.324	1.00	27.27	O
ATOM	2879	ND2	ASN B 163	-39.316	-18.758	13.014	1.00	27.47	N
ATOM	2880	C	ASN B 163	-39.237	-13.775	13.138	1.00	26.17	C
ATOM	2881	O	ASN B 163	-39.841	-13.754	14.204	1.00	25.93	O
ATOM	2882	N	SER B 164	-38.905	-12.676	12.470	1.00	26.82	N
ATOM	2883	CA	SER B 164	-39.289	-11.336	12.915	1.00	27.64	C
ATOM	2884	CB	SER B 164	-40.665	-10.932	12.338	1.00	27.72	C
ATOM	2885	OG	SER B 164	-41.478	-12.061	12.063	1.00	27.43	O
ATOM	2886	C	SER B 164	-39.256	-11.188	14.435	1.00	27.63	C
ATOM	2887	O	SER B 164	-40.202	-10.684	15.035	1.00	28.13	O
ATOM	2888	N	GLY B 165	-38.171	-11.657	15.047	1.00	27.48	N
ATOM	2889	CA	GLY B 165	-37.987	-11.549	16.500	1.00	27.21	C
ATOM	2890	C	GLY B 165	-38.176	-12.811	17.329	1.00	26.56	C
ATOM	2891	O	GLY B 165	-37.544	-12.963	18.363	1.00	26.59	O
ATOM	2892	N	ALA B 166	-39.024	-13.715	16.855	1.00	26.33	N
ATOM	2893	CA	ALA B 166	-39.538	-14.837	17.647	1.00	26.32	C
ATOM	2894	CB	ALA B 166	-40.788	-15.422	16.972	1.00	26.38	C
ATOM	2895	C	ALA B 166	-38.553	-15.963	17.960	1.00	26.53	C
ATOM	2896	O	ALA B 166	-38.736	-16.683	18.943	1.00	27.09	O
ATOM	2897	N	LEU B 167	-37.542	-16.145	17.112	1.00	26.35	N
ATOM	2898	CA	LEU B 167	-36.538	-17.188	17.311	1.00	25.65	C
ATOM	2899	CB	LEU B 167	-36.411	-18.036	16.055	1.00	25.08	C
ATOM	2900	CG	LEU B 167	-35.240	-19.002	15.904	1.00	25.01	C
ATOM	2901	CD1	LEU B 167	-35.416	-20.271	16.726	1.00	24.66	C
ATOM	2902	CD2	LEU B 167	-35.098	-19.364	14.446	1.00	24.48	C
ATOM	2903	C	LEU B 167	-35.206	-16.524	17.673	1.00	25.90	C
ATOM	2904	O	LEU B 167	-34.634	-15.773	16.875	1.00	26.27	O
ATOM	2905	N	THR B 168	-34.736	-16.777	18.890	1.00	25.66	N
ATOM	2906	CA	THR B 168	-33.493	-16.195	19.386	1.00	25.44	C
ATOM	2907	CB	THR B 168	-33.770	-15.148	20.472	1.00	25.55	C
ATOM	2908	OG1	THR B 168	-34.708	-15.690	21.410	1.00	26.69	O
ATOM	2909	CG2	THR B 168	-34.343	-13.873	19.869	1.00	24.44	C
ATOM	2910	C	THR B 168	-32.529	-17.262	19.933	1.00	25.32	C

ATOM	2911	O	THR B 168	-31.319	-17.038	19.979	1.00	24.95	O
ATOM	2912	N	SER B 169	-33.070	-18.416	20.329	1.00	25.17	N
ATOM	2913	CA	SER B 169	-32.268	-19.538	20.841	1.00	25.26	C
ATOM	2914	CB	SER B 169	-33.170	-20.594	21.495	1.00	25.41	C
ATOM	2915	OG	SER B 169	-33.492	-20.248	22.828	1.00	27.17	O
ATOM	2916	C	SER B 169	-31.404	-20.221	19.776	1.00	24.90	C
ATOM	2917	O	SER B 169	-31.912	-20.734	18.755	1.00	24.74	O
ATOM	2918	N	GLY B 170	-30.102	-20.256	20.035	1.00	24.31	N
ATOM	2919	CA	GLY B 170	-29.162	-20.927	19.136	1.00	24.10	C
ATOM	2920	C	GLY B 170	-28.747	-20.094	17.929	1.00	23.62	C
ATOM	2921	O	GLY B 170	-28.056	-20.585	17.034	1.00	23.42	O
ATOM	2922	N	VAL B 171	-29.164	-18.831	17.911	1.00	22.90	N
ATOM	2923	CA	VAL B 171	-28.796	-17.914	16.833	1.00	22.39	C
ATOM	2924	CB	VAL B 171	-29.807	-16.738	16.738	1.00	22.26	C
ATOM	2925	CG1	VAL B 171	-29.341	-15.692	15.758	1.00	20.70	C
ATOM	2926	CG2	VAL B 171	-31.198	-17.261	16.378	1.00	22.05	C
ATOM	2927	C	VAL B 171	-27.374	-17.369	17.035	1.00	21.92	C
ATOM	2928	O	VAL B 171	-27.047	-16.854	18.097	1.00	21.72	O
ATOM	2929	N	HIS B 172	-26.532	-17.503	16.019	1.00	21.36	N
ATOM	2930	CA	HIS B 172	-25.243	-16.823	16.013	1.00	20.98	C
ATOM	2931	CB	HIS B 172	-24.069	-17.801	16.067	1.00	21.24	C
ATOM	2932	CG	HIS B 172	-23.997	-18.581	17.345	1.00	22.26	C
ATOM	2933	ND1	HIS B 172	-23.544	-18.034	18.525	1.00	22.95	N
ATOM	2934	CE1	HIS B 172	-23.609	-18.944	19.481	1.00	22.74	C
ATOM	2935	NE2	HIS B 172	-24.081	-20.062	18.963	1.00	21.71	N
ATOM	2936	CD2	HIS B 172	-24.330	-19.864	17.628	1.00	22.28	C
ATOM	2937	C	HIS B 172	-25.154	-15.968	14.775	1.00	20.51	C
ATOM	2938	O	HIS B 172	-25.254	-16.474	13.651	1.00	20.59	O
ATOM	2939	N	THR B 173	-24.996	-14.665	14.990	1.00	19.62	N
ATOM	2940	CA	THR B 173	-24.761	-13.741	13.902	1.00	18.67	C
ATOM	2941	CB	THR B 173	-25.786	-12.597	13.930	1.00	18.82	C
ATOM	2942	OG1	THR B 173	-27.095	-13.159	13.722	1.00	18.68	O
ATOM	2943	CG2	THR B 173	-25.510	-11.576	12.840	1.00	18.34	C
ATOM	2944	C	THR B 173	-23.300	-13.309	13.951	1.00	18.00	C
ATOM	2945	O	THR B 173	-22.854	-12.693	14.906	1.00	17.85	O
ATOM	2946	N	PHE B 174	-22.543	-13.689	12.926	1.00	17.55	N
ATOM	2947	CA	PHE B 174	-21.095	-13.471	12.926	1.00	16.71	C
ATOM	2948	CB	PHE B 174	-20.418	-14.427	11.952	1.00	15.79	C
ATOM	2949	CG	PHE B 174	-20.519	-15.841	12.377	1.00	14.96	C
ATOM	2950	CD1	PHE B 174	-21.595	-16.622	11.984	1.00	14.06	C
ATOM	2951	CE1	PHE B 174	-21.711	-17.929	12.417	1.00	13.44	C
ATOM	2952	CZ	PHE B 174	-20.752	-18.467	13.284	1.00	14.75	C
ATOM	2953	CE2	PHE B 174	-19.692	-17.695	13.699	1.00	13.90	C
ATOM	2954	CD2	PHE B 174	-19.577	-16.383	13.246	1.00	15.14	C
ATOM	2955	C	PHE B 174	-20.704	-12.024	12.674	1.00	16.71	C
ATOM	2956	O	PHE B 174	-21.356	-11.336	11.907	1.00	16.95	O
ATOM	2957	N	PRO B 175	-19.662	-11.543	13.362	1.00	16.92	N
ATOM	2958	CA	PRO B 175	-19.080	-10.274	12.981	1.00	17.03	C
ATOM	2959	CB	PRO B 175	-17.754	-10.272	13.742	1.00	16.33	C
ATOM	2960	CG	PRO B 175	-18.039	-11.034	14.929	1.00	16.79	C
ATOM	2961	CD	PRO B 175	-18.972	-12.123	14.530	1.00	17.07	C
ATOM	2962	C	PRO B 175	-18.813	-10.310	11.481	1.00	17.34	C
ATOM	2963	O	PRO B 175	-18.430	-11.368	10.962	1.00	17.27	O
ATOM	2964	N	ALA B 176	-19.033	-9.188	10.791	1.00	17.57	N
ATOM	2965	CA	ALA B 176	-18.784	-9.126	9.337	1.00	17.93	C
ATOM	2966	CB	ALA B 176	-19.441	-7.917	8.731	1.00	18.12	C
ATOM	2967	C	ALA B 176	-17.304	-9.163	8.966	1.00	17.80	C

ATOM	2968	O	ALA B 176	-16.440	-8.670	9.692	1.00	18.33	O
ATOM	2969	N	VAL B 177	-17.031	-9.743	7.813	1.00	17.69	N
ATOM	2970	CA	VAL B 177	-15.681	-9.876	7.288	1.00	17.54	C
ATOM	2971	CB	VAL B 177	-15.450	-11.374	6.970	1.00	17.73	C
ATOM	2972	CG1	VAL B 177	-14.880	-11.600	5.605	1.00	17.61	C
ATOM	2973	CG2	VAL B 177	-14.641	-12.061	8.094	1.00	16.10	C
ATOM	2974	C	VAL B 177	-15.515	-8.919	6.087	1.00	18.18	C
ATOM	2975	O	VAL B 177	-16.463	-8.709	5.311	1.00	18.01	O
ATOM	2976	N	LEU B 178	-14.352	-8.287	5.957	1.00	18.79	N
ATOM	2977	CA	LEU B 178	-14.139	-7.338	4.850	1.00	19.82	C
ATOM	2978	CB	LEU B 178	-13.193	-6.204	5.257	1.00	19.82	C
ATOM	2979	CG	LEU B 178	-13.452	-4.752	4.817	1.00	19.72	C
ATOM	2980	CD1	LEU B 178	-12.242	-3.857	5.111	1.00	19.13	C
ATOM	2981	CD2	LEU B 178	-13.852	-4.642	3.371	1.00	17.91	C
ATOM	2982	C	LEU B 178	-13.532	-8.084	3.681	1.00	20.58	C
ATOM	2983	O	LEU B 178	-12.470	-8.680	3.822	1.00	20.90	O
ATOM	2984	N	GLN B 179	-14.189	-8.067	2.530	1.00	21.86	N
ATOM	2985	CA	GLN B 179	-13.705	-8.869	1.399	1.00	23.37	C
ATOM	2986	CB	GLN B 179	-14.865	-9.342	0.538	1.00	23.15	C
ATOM	2987	CG	GLN B 179	-15.810	-10.235	1.287	1.00	23.15	C
ATOM	2988	CD	GLN B 179	-17.075	-10.483	0.527	1.00	24.29	C
ATOM	2989	OE1	GLN B 179	-17.925	-9.594	0.401	1.00	26.14	O
ATOM	2990	NE2	GLN B 179	-17.226	-11.697	0.020	1.00	23.49	N
ATOM	2991	C	GLN B 179	-12.665	-8.107	0.578	1.00	24.46	C
ATOM	2992	O	GLN B 179	-12.453	-6.909	0.815	1.00	24.52	O
ATOM	2993	N	SER B 180	-12.005	-8.788	-0.367	1.00	25.46	N
ATOM	2994	CA	SER B 180	-10.968	-8.135	-1.183	1.00	26.01	C
ATOM	2995	CB	SER B 180	-10.232	-9.146	-2.053	1.00	26.39	C
ATOM	2996	OG	SER B 180	-10.894	-9.318	-3.300	1.00	28.18	O
ATOM	2997	C	SER B 180	-11.585	-7.036	-2.047	1.00	25.93	C
ATOM	2998	O	SER B 180	-10.931	-6.050	-2.393	1.00	26.07	O
ATOM	2999	N	SER B 181	-12.852	-7.214	-2.398	1.00	26.04	N
ATOM	3000	CA	SER B 181	-13.643	-6.113	-2.895	1.00	26.34	C
ATOM	3001	CB	SER B 181	-15.019	-6.610	-3.305	1.00	26.08	C
ATOM	3002	OG	SER B 181	-15.820	-6.874	-2.164	1.00	25.65	O
ATOM	3003	C	SER B 181	-13.771	-5.139	-1.718	1.00	27.17	C
ATOM	3004	O	SER B 181	-13.657	-5.530	-0.542	1.00	27.55	O
ATOM	3005	N	ASP B 182	-14.029	-3.875	-1.992	1.00	26.98	N
ATOM	3006	CA	ASP B 182	-14.206	-2.948	-0.867	1.00	27.15	C
ATOM	3007	CB	ASP B 182	-14.342	-1.497	-1.408	1.00	28.31	C
ATOM	3008	CG	ASP B 182	-13.647	-1.295	-2.784	1.00	30.84	C
ATOM	3009	OD1	ASP B 182	-14.290	-0.700	-3.689	1.00	34.07	O
ATOM	3010	OD2	ASP B 182	-12.475	-1.735	-2.960	1.00	32.18	O
ATOM	3011	C	ASP B 182	-15.397	-3.348	0.075	1.00	25.59	C
ATOM	3012	O	ASP B 182	-15.742	-2.617	1.011	1.00	25.20	O
ATOM	3013	N	LEU B 183	-15.971	-4.531	-0.152	1.00	24.02	N
ATOM	3014	CA	LEU B 183	-17.310	-4.872	0.344	1.00	22.90	C
ATOM	3015	CB	LEU B 183	-18.158	-5.365	-0.830	1.00	23.13	C
ATOM	3016	CG	LEU B 183	-18.261	-4.460	-2.069	1.00	22.59	C
ATOM	3017	CD1	LEU B 183	-18.837	-5.237	-3.248	1.00	21.02	C
ATOM	3018	CD2	LEU B 183	-19.092	-3.214	-1.782	1.00	20.29	C
ATOM	3019	C	LEU B 183	-17.400	-5.878	1.515	1.00	21.98	C
ATOM	3020	O	LEU B 183	-16.500	-6.696	1.728	1.00	21.62	O
ATOM	3021	N	TYR B 184	-18.499	-5.812	2.263	1.00	20.64	N
ATOM	3022	CA	TYR B 184	-18.642	-6.629	3.462	1.00	19.82	C
ATOM	3023	CB	TYR B 184	-19.172	-5.808	4.629	1.00	20.00	C
ATOM	3024	CG	TYR B 184	-18.246	-4.753	5.195	1.00	19.34	C

ATOM	3025	CD1 TYR B 184	-18.305	-3.442	4.740	1.00	19.94	C
ATOM	3026	CE1 TYR B 184	-17.491	-2.460	5.271	1.00	20.99	C
ATOM	3027	CZ TYR B 184	-16.609	-2.779	6.296	1.00	21.30	C
ATOM	3028	OH TYR B 184	-15.802	-1.783	6.819	1.00	20.81	O
ATOM	3029	CE2 TYR B 184	-16.545	-4.075	6.777	1.00	19.42	C
ATOM	3030	CD2 TYR B 184	-17.366	-5.048	6.226	1.00	19.08	C
ATOM	3031	C TYR B 184	-19.567	-7.817	3.249	1.00	19.25	C
ATOM	3032	O TYR B 184	-20.373	-7.832	2.328	1.00	19.29	O
ATOM	3033	N SER B 185	-19.452	-8.799	4.137	1.00	18.33	N
ATOM	3034	CA SER B 185	-20.141	-10.074	4.010	1.00	17.51	C
ATOM	3035	CB SER B 185	-19.399	-10.966	3.005	1.00	17.23	C
ATOM	3036	OG SER B 185	-20.003	-12.238	2.886	1.00	16.40	O
ATOM	3037	C SER B 185	-20.219	-10.754	5.379	1.00	17.23	C
ATOM	3038	O SER B 185	-19.226	-10.824	6.107	1.00	17.02	O
ATOM	3039	N LEU B 186	-21.406	-11.231	5.737	1.00	17.12	N
ATOM	3040	CA LEU B 186	-21.574	-11.987	6.965	1.00	17.28	C
ATOM	3041	CB LEU B 186	-21.971	-11.077	8.132	1.00	17.56	C
ATOM	3042	CG LEU B 186	-23.335	-10.438	8.343	1.00	16.45	C
ATOM	3043	CD1 LEU B 186	-24.434	-11.431	8.674	1.00	13.38	C
ATOM	3044	CD2 LEU B 186	-23.145	-9.473	9.491	1.00	15.93	C
ATOM	3045	C LEU B 186	-22.560	-13.108	6.837	1.00	17.69	C
ATOM	3046	O LEU B 186	-23.237	-13.240	5.820	1.00	18.24	O
ATOM	3047	N SER B 187	-22.638	-13.919	7.884	1.00	18.46	N
ATOM	3048	CA SER B 187	-23.563	-15.032	7.930	1.00	19.15	C
ATOM	3049	CB SER B 187	-22.811	-16.320	7.662	1.00	19.44	C
ATOM	3050	OG SER B 187	-21.686	-16.367	8.520	1.00	20.70	O
ATOM	3051	C SER B 187	-24.217	-15.105	9.288	1.00	19.51	C
ATOM	3052	O SER B 187	-23.762	-14.478	10.248	1.00	19.44	O
ATOM	3053	N SER B 188	-25.272	-15.914	9.347	1.00	20.33	N
ATOM	3054	CA SER B 188	-26.136	-16.103	10.499	1.00	20.55	C
ATOM	3055	CB SER B 188	-26.858	-14.771	10.747	1.00	20.16	C
ATOM	3056	OG SER B 188	-27.969	-14.895	11.630	1.00	20.00	O
ATOM	3057	C SER B 188	-27.150	-17.140	10.020	1.00	21.13	C
ATOM	3058	O SER B 188	-27.524	-17.079	8.858	1.00	21.18	O
ATOM	3059	N VAL B 189	-27.624	-18.133	10.765	1.00	22.08	N
ATOM	3060	CA VAL B 189	-27.060	-19.157	11.652	1.00	22.81	C
ATOM	3061	CB VAL B 189	-25.588	-19.651	11.506	1.00	23.00	C
ATOM	3062	CG1 VAL B 189	-25.033	-19.406	10.094	1.00	22.94	C
ATOM	3063	CG2 VAL B 189	-24.690	-19.168	12.648	1.00	24.13	C
ATOM	3064	C VAL B 189	-27.772	-19.533	12.942	1.00	23.26	C
ATOM	3065	O VAL B 189	-27.698	-18.837	13.954	1.00	23.42	O
ATOM	3066	N VAL B 190	-28.529	-20.615	12.845	1.00	23.83	N
ATOM	3067	CA VAL B 190	-29.292	-21.121	13.964	1.00	24.72	C
ATOM	3068	CB VAL B 190	-30.719	-20.480	14.022	1.00	24.43	C
ATOM	3069	CG1 VAL B 190	-31.428	-20.527	12.676	1.00	25.06	C
ATOM	3070	CG2 VAL B 190	-31.558	-21.111	15.079	1.00	24.94	C
ATOM	3071	C VAL B 190	-29.299	-22.644	13.918	1.00	25.43	C
ATOM	3072	O VAL B 190	-29.540	-23.240	12.872	1.00	25.77	O
ATOM	3073	N THR B 191	-28.956	-23.265	15.040	1.00	26.40	N
ATOM	3074	CA THR B 191	-29.167	-24.693	15.223	1.00	27.47	C
ATOM	3075	CB THR B 191	-28.194	-25.293	16.243	1.00	27.32	C
ATOM	3076	OG1 THR B 191	-28.337	-24.603	17.495	1.00	27.61	O
ATOM	3077	CG2 THR B 191	-26.767	-25.168	15.758	1.00	26.90	C
ATOM	3078	C THR B 191	-30.593	-24.883	15.734	1.00	28.49	C
ATOM	3079	O THR B 191	-31.063	-24.122	16.581	1.00	28.08	O
ATOM	3080	N VAL B 192	-31.279	-25.887	15.196	1.00	30.17	N
ATOM	3081	CA VAL B 192	-32.669	-26.186	15.548	1.00	31.74	C

ATOM	3082	CB	VAL B 192	-33.663	-25.636	14.495	1.00	31.76	C
ATOM	3083	CG1	VAL B 192	-33.670	-24.107	14.477	1.00	30.79	C
ATOM	3084	CG2	VAL B 192	-33.364	-26.227	13.108	1.00	31.38	C
ATOM	3085	C	VAL B 192	-32.839	-27.704	15.614	1.00	33.22	C
ATOM	3086	O	VAL B 192	-31.991	-28.438	15.092	1.00	33.12	O
ATOM	3087	N	PRO B 193	-33.933	-28.187	16.242	1.00	34.61	N
ATOM	3088	CA	PRO B 193	-34.139	-29.644	16.251	1.00	35.73	C
ATOM	3089	CB	PRO B 193	-35.406	-29.835	17.100	1.00	35.28	C
ATOM	3090	CG	PRO B 193	-36.085	-28.522	17.078	1.00	35.58	C
ATOM	3091	CD	PRO B 193	-35.005	-27.472	16.959	1.00	34.73	C
ATOM	3092	C	PRO B 193	-34.353	-30.179	14.841	1.00	36.86	C
ATOM	3093	O	PRO B 193	-35.186	-29.658	14.087	1.00	36.88	O
ATOM	3094	N	SER B 194	-33.597	-31.213	14.498	1.00	38.16	N
ATOM	3095	CA	SER B 194	-33.696	-31.816	13.191	1.00	39.64	C
ATOM	3096	CB	SER B 194	-32.808	-33.046	13.122	1.00	39.83	C
ATOM	3097	OG	SER B 194	-32.767	-33.548	11.800	1.00	41.68	O
ATOM	3098	C	SER B 194	-35.134	-32.183	12.853	1.00	40.42	C
ATOM	3099	O	SER B 194	-35.514	-32.155	11.690	1.00	40.58	O
ATOM	3100	N	SER B 195	-35.930	-32.501	13.873	1.00	41.65	N
ATOM	3101	CA	SER B 195	-37.309	-32.976	13.690	1.00	42.80	C
ATOM	3102	CB	SER B 195	-37.870	-33.547	14.997	1.00	42.75	C
ATOM	3103	OG	SER B 195	-38.124	-32.512	15.926	1.00	42.49	O
ATOM	3104	C	SER B 195	-38.265	-31.924	13.135	1.00	43.49	C
ATOM	3105	O	SER B 195	-38.899	-32.146	12.105	1.00	43.95	O
ATOM	3106	N	SER B 196	-38.372	-30.790	13.820	1.00	44.31	N
ATOM	3107	CA	SER B 196	-39.285	-29.715	13.417	1.00	45.11	C
ATOM	3108	CB	SER B 196	-39.546	-28.772	14.601	1.00	45.51	C
ATOM	3109	OG	SER B 196	-38.428	-27.917	14.827	1.00	46.27	O
ATOM	3110	C	SER B 196	-38.736	-28.929	12.216	1.00	45.10	C
ATOM	3111	O	SER B 196	-38.282	-27.794	12.361	1.00	45.15	O
ATOM	3112	N	LEU B 197	-38.813	-29.541	11.039	1.00	45.26	N
ATOM	3113	CA	LEU B 197	-38.064	-29.130	9.854	1.00	45.65	C
ATOM	3114	CB	LEU B 197	-36.577	-29.011	10.212	1.00	45.12	C
ATOM	3115	CG	LEU B 197	-35.420	-28.935	9.217	1.00	44.52	C
ATOM	3116	CD1	LEU B 197	-34.401	-27.949	9.742	1.00	43.84	C
ATOM	3117	CD2	LEU B 197	-34.757	-30.282	8.970	1.00	42.98	C
ATOM	3118	C	LEU B 197	-38.287	-30.227	8.796	1.00	46.45	C
ATOM	3119	O	LEU B 197	-37.729	-31.325	8.914	1.00	47.34	O
ATOM	3120	N	GLY B 198	-39.131	-29.981	7.793	1.00	46.56	N
ATOM	3121	CA	GLY B 198	-39.922	-28.770	7.677	1.00	46.41	C
ATOM	3122	C	GLY B 198	-41.272	-28.875	8.367	1.00	46.16	C
ATOM	3123	O	GLY B 198	-42.196	-29.537	7.879	1.00	45.85	O
ATOM	3124	N	THR B 199	-41.368	-28.215	9.518	1.00	45.76	N
ATOM	3125	CA	THR B 199	-42.650	-27.979	10.149	1.00	45.10	C
ATOM	3126	CB	THR B 199	-43.022	-29.086	11.159	1.00	45.35	C
ATOM	3127	OG1	THR B 199	-44.403	-29.399	10.985	1.00	46.29	O
ATOM	3128	CG2	THR B 199	-42.768	-28.664	12.622	1.00	45.42	C
ATOM	3129	C	THR B 199	-42.691	-26.584	10.756	1.00	44.16	C
ATOM	3130	O	THR B 199	-43.729	-25.934	10.744	1.00	44.29	O
ATOM	3131	N	GLN B 200	-41.567	-26.127	11.293	1.00	43.13	N
ATOM	3132	CA	GLN B 200	-41.419	-24.710	11.596	1.00	42.18	C
ATOM	3133	CB	GLN B 200	-40.610	-24.467	12.875	1.00	42.68	C
ATOM	3134	CG	GLN B 200	-41.458	-24.113	14.109	1.00	44.84	C
ATOM	3135	CD	GLN B 200	-42.117	-25.339	14.762	1.00	47.67	C
ATOM	3136	OE1	GLN B 200	-41.546	-25.958	15.671	1.00	48.85	O
ATOM	3137	NE2	GLN B 200	-43.313	-25.695	14.294	1.00	47.79	N
ATOM	3138	C	GLN B 200	-40.751	-24.058	10.400	1.00	40.71	C

ATOM	3139	O	GLN B 200	-39.781	-24.577	9.857	1.00	40.62	O
ATOM	3140	N	THR B 201	-41.305	-22.940	9.962	1.00	38.96	N
ATOM	3141	CA	THR B 201	-40.718	-22.194	8.877	1.00	37.13	C
ATOM	3142	CB	THR B 201	-41.773	-21.387	8.102	1.00	37.27	C
ATOM	3143	OG1	THR B 201	-42.365	-20.425	8.986	1.00	37.93	O
ATOM	3144	CG2	THR B 201	-42.862	-22.301	7.546	1.00	36.41	C
ATOM	3145	C	THR B 201	-39.672	-21.263	9.482	1.00	35.86	C
ATOM	3146	O	THR B 201	-39.858	-20.718	10.580	1.00	35.38	O
ATOM	3147	N	TYR B 202	-38.567	-21.106	8.763	1.00	34.33	N
ATOM	3148	CA	TYR B 202	-37.449	-20.284	9.214	1.00	32.81	C
ATOM	3149	CB	TYR B 202	-36.196	-21.157	9.457	1.00	33.09	C
ATOM	3150	CG	TYR B 202	-36.400	-22.210	10.535	1.00	32.85	C
ATOM	3151	CD1	TYR B 202	-36.412	-21.861	11.888	1.00	33.52	C
ATOM	3152	CE1	TYR B 202	-36.617	-22.819	12.887	1.00	34.44	C
ATOM	3153	CZ	TYR B 202	-36.811	-24.148	12.532	1.00	35.04	C
ATOM	3154	OH	TYR B 202	-37.012	-25.109	13.514	1.00	35.25	O
ATOM	3155	CE2	TYR B 202	-36.803	-24.515	11.189	1.00	34.09	C
ATOM	3156	CD2	TYR B 202	-36.600	-23.543	10.203	1.00	33.10	C
ATOM	3157	C	TYR B 202	-37.182	-19.152	8.223	1.00	31.33	C
ATOM	3158	O	TYR B 202	-36.856	-19.387	7.054	1.00	31.29	O
ATOM	3159	N	ILE B 203	-37.364	-17.928	8.703	1.00	29.39	N
ATOM	3160	CA	ILE B 203	-37.161	-16.732	7.916	1.00	27.56	C
ATOM	3161	CB	ILE B 203	-38.461	-15.919	7.780	1.00	27.50	C
ATOM	3162	CG1	ILE B 203	-39.545	-16.748	7.081	1.00	26.72	C
ATOM	3163	CD1	ILE B 203	-40.953	-16.236	7.303	1.00	26.23	C
ATOM	3164	CG2	ILE B 203	-38.193	-14.582	7.055	1.00	26.63	C
ATOM	3165	C	ILE B 203	-36.145	-15.869	8.622	1.00	26.84	C
ATOM	3166	O	ILE B 203	-36.281	-15.625	9.815	1.00	27.05	O
ATOM	3167	N	CYS B 204	-35.127	-15.413	7.893	1.00	25.89	N
ATOM	3168	CA	CYS B 204	-34.174	-14.448	8.420	1.00	24.75	C
ATOM	3169	CB	CYS B 204	-32.741	-14.813	8.020	1.00	24.41	C
ATOM	3170	SG	CYS B 204	-32.236	-14.471	6.323	1.00	23.29	S
ATOM	3171	C	CYS B 204	-34.565	-13.058	7.939	1.00	24.63	C
ATOM	3172	O	CYS B 204	-34.925	-12.890	6.788	1.00	24.50	O
ATOM	3173	N	ASN B 205	-34.536	-12.077	8.839	1.00	24.70	N
ATOM	3174	CA	ASN B 205	-34.852	-10.690	8.504	1.00	24.65	C
ATOM	3175	CB	ASN B 205	-35.844	-10.093	9.499	1.00	24.54	C
ATOM	3176	CG	ASN B 205	-36.900	-11.084	9.924	1.00	25.23	C
ATOM	3177	OD1	ASN B 205	-36.868	-11.583	11.045	1.00	26.19	O
ATOM	3178	ND2	ASN B 205	-37.827	-11.399	9.022	1.00	24.22	N
ATOM	3179	C	ASN B 205	-33.593	-9.848	8.471	1.00	24.72	C
ATOM	3180	O	ASN B 205	-32.922	-9.665	9.487	1.00	24.58	O
ATOM	3181	N	VAL B 206	-33.288	-9.337	7.284	1.00	24.86	N
ATOM	3182	CA	VAL B 206	-32.080	-8.580	7.034	1.00	24.60	C
ATOM	3183	CB	VAL B 206	-31.342	-9.142	5.800	1.00	24.45	C
ATOM	3184	CG1	VAL B 206	-30.095	-8.361	5.517	1.00	24.68	C
ATOM	3185	CG2	VAL B 206	-30.994	-10.602	6.003	1.00	24.13	C
ATOM	3186	C	VAL B 206	-32.492	-7.139	6.798	1.00	24.94	C
ATOM	3187	O	VAL B 206	-33.454	-6.871	6.074	1.00	24.68	O
ATOM	3188	N	ASN B 207	-31.783	-6.223	7.450	1.00	25.56	N
ATOM	3189	CA	ASN B 207	-31.972	-4.792	7.275	1.00	25.96	C
ATOM	3190	CB	ASN B 207	-32.734	-4.187	8.462	1.00	25.94	C
ATOM	3191	CG	ASN B 207	-33.147	-2.712	8.240	1.00	26.68	C
ATOM	3192	OD1	ASN B 207	-32.827	-2.088	7.221	1.00	28.22	O
ATOM	3193	ND2	ASN B 207	-33.860	-2.158	9.210	1.00	25.84	N
ATOM	3194	C	ASN B 207	-30.601	-4.155	7.132	1.00	26.54	C
ATOM	3195	O	ASN B 207	-29.727	-4.347	7.970	1.00	26.26	O

ATOM	3196	N	HIS B 208	-30.412	-3.434	6.035	1.00	27.71	N
ATOM	3197	CA	HIS B 208	-29.212	-2.658	5.810	1.00	29.08	C
ATOM	3198	CB	HIS B 208	-28.414	-3.239	4.636	1.00	29.08	C
ATOM	3199	CG	HIS B 208	-27.294	-2.367	4.165	1.00	29.38	C
ATOM	3200	ND1	HIS B 208	-26.137	-2.178	4.889	1.00	30.05	N
ATOM	3201	CE1	HIS B 208	-25.335	-1.362	4.228	1.00	30.69	C
ATOM	3202	NE2	HIS B 208	-25.929	-1.016	3.100	1.00	30.29	N
ATOM	3203	CD2	HIS B 208	-27.156	-1.632	3.038	1.00	29.65	C
ATOM	3204	C	HIS B 208	-29.686	-1.225	5.566	1.00	30.20	C
ATOM	3205	O	HIS B 208	-29.939	-0.816	4.429	1.00	30.28	O
ATOM	3206	N	LYS B 209	-29.817	-0.472	6.660	1.00	31.48	N
ATOM	3207	CA	LYS B 209	-30.436	0.853	6.621	1.00	32.64	C
ATOM	3208	CB	LYS B 209	-30.640	1.444	8.035	1.00	33.23	C
ATOM	3209	CG	LYS B 209	-29.382	2.035	8.669	1.00	36.11	C
ATOM	3210	CD	LYS B 209	-29.571	3.508	9.107	1.00	39.87	C
ATOM	3211	CE	LYS B 209	-28.294	4.337	8.832	1.00	40.46	C
ATOM	3212	NZ	LYS B 209	-27.086	3.694	9.449	1.00	41.53	N
ATOM	3213	C	LYS B 209	-29.759	1.864	5.680	1.00	32.45	C
ATOM	3214	O	LYS B 209	-30.468	2.659	5.053	1.00	33.14	O
ATOM	3215	N	PRO B 210	-28.408	1.844	5.569	1.00	32.09	N
ATOM	3216	CA	PRO B 210	-27.723	2.811	4.692	1.00	31.86	C
ATOM	3217	CB	PRO B 210	-26.245	2.422	4.824	1.00	31.77	C
ATOM	3218	CG	PRO B 210	-26.147	1.727	6.106	1.00	31.83	C
ATOM	3219	CD	PRO B 210	-27.436	0.975	6.255	1.00	32.07	C
ATOM	3220	C	PRO B 210	-28.134	2.776	3.217	1.00	31.78	C
ATOM	3221	O	PRO B 210	-27.942	3.754	2.503	1.00	31.88	O
ATOM	3222	N	SER B 211	-28.682	1.655	2.765	1.00	31.97	N
ATOM	3223	CA	SER B 211	-29.125	1.523	1.385	1.00	31.94	C
ATOM	3224	CB	SER B 211	-28.413	0.348	0.730	1.00	32.07	C
ATOM	3225	OG	SER B 211	-28.850	-0.865	1.329	1.00	32.00	O
ATOM	3226	C	SER B 211	-30.621	1.267	1.339	1.00	31.91	C
ATOM	3227	O	SER B 211	-31.161	0.914	0.284	1.00	31.88	O
ATOM	3228	N	ASN B 212	-31.278	1.444	2.484	1.00	31.80	N
ATOM	3229	CA	ASN B 212	-32.688	1.087	2.664	1.00	32.25	C
ATOM	3230	CB	ASN B 212	-33.602	2.203	2.148	1.00	32.77	C
ATOM	3231	CG	ASN B 212	-34.042	3.164	3.251	1.00	34.32	C
ATOM	3232	OD1	ASN B 212	-35.243	3.406	3.415	1.00	36.37	O
ATOM	3233	ND2	ASN B 212	-33.078	3.703	4.020	1.00	33.42	N
ATOM	3234	C	ASN B 212	-33.080	-0.269	2.060	1.00	31.98	C
ATOM	3235	O	ASN B 212	-34.125	-0.400	1.406	1.00	32.36	O
ATOM	3236	N	THR B 213	-32.225	-1.265	2.277	1.00	31.15	N
ATOM	3237	CA	THR B 213	-32.473	-2.627	1.839	1.00	30.44	C
ATOM	3238	CB	THR B 213	-31.182	-3.268	1.326	1.00	30.49	C
ATOM	3239	OG1	THR B 213	-30.652	-2.464	0.270	1.00	30.85	O
ATOM	3240	CG2	THR B 213	-31.422	-4.683	0.826	1.00	29.90	C
ATOM	3241	C	THR B 213	-32.974	-3.445	3.013	1.00	30.06	C
ATOM	3242	O	THR B 213	-32.299	-3.530	4.035	1.00	30.00	O
ATOM	3243	N	LYS B 214	-34.165	-4.019	2.854	1.00	29.72	N
ATOM	3244	CA	LYS B 214	-34.760	-4.973	3.794	1.00	29.45	C
ATOM	3245	CB	LYS B 214	-35.990	-4.378	4.486	1.00	29.13	C
ATOM	3246	CG	LYS B 214	-35.714	-3.672	5.810	1.00	29.96	C
ATOM	3247	CD	LYS B 214	-37.020	-3.425	6.597	1.00	30.77	C
ATOM	3248	CE	LYS B 214	-36.869	-3.777	8.108	1.00	33.33	C
ATOM	3249	NZ	LYS B 214	-36.747	-5.277	8.420	1.00	33.09	N
ATOM	3250	C	LYS B 214	-35.157	-6.233	3.021	1.00	28.98	C
ATOM	3251	O	LYS B 214	-35.815	-6.141	1.973	1.00	29.33	O
ATOM	3252	N	VAL B 215	-34.747	-7.398	3.524	1.00	28.32	N

ATOM	3253	CA	VAL B 215	-35.061	-8.687	2.900	1.00	27.42	C
ATOM	3254	CB	VAL B 215	-33.846	-9.280	2.174	1.00	27.45	C
ATOM	3255	CG1	VAL B 215	-34.179	-10.659	1.612	1.00	26.97	C
ATOM	3256	CG2	VAL B 215	-33.345	-8.345	1.074	1.00	26.85	C
ATOM	3257	C	VAL B 215	-35.510	-9.709	3.934	1.00	27.52	C
ATOM	3258	O	VAL B 215	-34.842	-9.915	4.954	1.00	27.61	O
ATOM	3259	N	ASP B 216	-36.648	-10.342	3.675	1.00	27.23	N
ATOM	3260	CA	ASP B 216	-37.085	-11.465	4.482	1.00	26.96	C
ATOM	3261	CB	ASP B 216	-38.539	-11.306	4.914	1.00	26.27	C
ATOM	3262	CG	ASP B 216	-38.736	-10.161	5.891	1.00	25.31	C
ATOM	3263	OD1	ASP B 216	-37.874	-9.958	6.778	1.00	24.58	O
ATOM	3264	OD2	ASP B 216	-39.758	-9.461	5.780	1.00	22.77	O
ATOM	3265	C	ASP B 216	-36.925	-12.665	3.593	1.00	27.63	C
ATOM	3266	O	ASP B 216	-37.600	-12.775	2.582	1.00	28.05	O
ATOM	3267	N	LYS B 217	-35.997	-13.543	3.947	1.00	28.45	N
ATOM	3268	CA	LYS B 217	-35.707	-14.720	3.147	1.00	29.42	C
ATOM	3269	CB	LYS B 217	-34.230	-14.728	2.723	1.00	29.36	C
ATOM	3270	CG	LYS B 217	-33.688	-16.076	2.259	1.00	29.81	C
ATOM	3271	CD	LYS B 217	-34.201	-16.472	0.883	1.00	30.52	C
ATOM	3272	CE	LYS B 217	-33.128	-16.384	-0.170	1.00	30.29	C
ATOM	3273	NZ	LYS B 217	-33.576	-17.114	-1.379	1.00	30.42	N
ATOM	3274	C	LYS B 217	-36.071	-15.992	3.903	1.00	30.14	C
ATOM	3275	O	LYS B 217	-35.757	-16.141	5.077	1.00	30.05	O
ATOM	3276	N	ARG B 218	-36.750	-16.897	3.211	1.00	31.24	N
ATOM	3277	CA	ARG B 218	-37.085	-18.203	3.738	1.00	32.23	C
ATOM	3278	CB	ARG B 218	-38.349	-18.702	3.059	1.00	32.64	C
ATOM	3279	CG	ARG B 218	-38.901	-19.995	3.612	1.00	34.29	C
ATOM	3280	CD	ARG B 218	-40.389	-19.978	3.445	1.00	36.99	C
ATOM	3281	NE	ARG B 218	-40.975	-21.291	3.630	1.00	40.51	N
ATOM	3282	CZ	ARG B 218	-42.286	-21.518	3.641	1.00	43.95	C
ATOM	3283	NH1	ARG B 218	-42.733	-22.760	3.820	1.00	45.16	N
ATOM	3284	NH2	ARG B 218	-43.152	-20.506	3.478	1.00	42.95	N
ATOM	3285	C	ARG B 218	-35.940	-19.145	3.439	1.00	32.52	C
ATOM	3286	O	ARG B 218	-35.398	-19.126	2.337	1.00	32.49	O
ATOM	3287	N	VAL B 219	-35.570	-19.954	4.430	1.00	33.15	N
ATOM	3288	CA	VAL B 219	-34.527	-20.966	4.285	1.00	33.58	C
ATOM	3289	CB	VAL B 219	-33.487	-20.872	5.413	1.00	33.12	C
ATOM	3290	CG1	VAL B 219	-32.290	-21.754	5.117	1.00	32.72	C
ATOM	3291	CG2	VAL B 219	-33.049	-19.449	5.624	1.00	32.94	C
ATOM	3292	C	VAL B 219	-35.196	-22.337	4.336	1.00	34.78	C
ATOM	3293	O	VAL B 219	-35.702	-22.753	5.371	1.00	34.93	O
ATOM	3294	N	GLU B 220	-35.235	-23.034	3.214	1.00	36.20	N
ATOM	3295	CA	GLU B 220	-35.828	-24.354	3.214	1.00	37.67	C
ATOM	3296	CB	GLU B 220	-36.869	-24.463	2.098	1.00	37.58	C
ATOM	3297	CG	GLU B 220	-38.305	-24.421	2.627	1.00	38.80	C
ATOM	3298	CD	GLU B 220	-39.355	-24.108	1.560	1.00	38.78	C
ATOM	3299	OE1	GLU B 220	-39.171	-24.516	0.393	1.00	40.22	O
ATOM	3300	OE2	GLU B 220	-40.379	-23.461	1.902	1.00	40.32	O
ATOM	3301	C	GLU B 220	-34.762	-25.448	3.116	1.00	38.24	C
ATOM	3302	O	GLU B 220	-33.678	-25.201	2.591	1.00	38.07	O
ATOM	3303	N	PRO B 221	-35.050	-26.647	3.668	1.00	39.25	N
ATOM	3304	CA	PRO B 221	-34.274	-27.859	3.348	1.00	39.91	C
ATOM	3305	CB	PRO B 221	-35.146	-28.979	3.912	1.00	39.70	C
ATOM	3306	CG	PRO B 221	-35.900	-28.341	5.025	1.00	39.32	C
ATOM	3307	CD	PRO B 221	-36.109	-26.912	4.663	1.00	39.11	C
ATOM	3308	C	PRO B 221	-34.153	-28.004	1.828	1.00	40.78	C
ATOM	3309	O	PRO B 221	-35.078	-27.615	1.111	1.00	40.82	O

ATOM	3310	N	LYS B 222	-33.045	-28.550	1.328	1.00	41.84	N
ATOM	3311	CA	LYS B 222	-32.761	-28.440	-0.120	1.00	42.82	C
ATOM	3312	CB	LYS B 222	-31.265	-28.178	-0.386	1.00	43.17	C
ATOM	3313	CG	LYS B 222	-30.310	-29.399	-0.243	1.00	45.07	C
ATOM	3314	CD	LYS B 222	-30.156	-30.192	-1.577	1.00	48.01	C
ATOM	3315	CE	LYS B 222	-29.948	-29.268	-2.804	1.00	48.25	C
ATOM	3316	NZ	LYS B 222	-30.358	-29.916	-4.076	1.00	48.65	N
ATOM	3317	C	LYS B 222	-33.332	-29.551	-1.020	1.00	42.79	C
ATOM	3318	O	LYS B 222	-33.363	-30.725	-0.650	1.00	42.87	O
ATOM	3319	MG	MG M 301	2.841	11.391	39.790	1.00	8.56	MG
ATOM	3320	MG	MG M 302	5.388	12.268	36.963	1.00	18.93	MG
ATOM	3321	MG	MG M 303	-5.933	-18.358	36.217	1.00	21.89	MG
ATOM	3322	O25	S1P S 401	3.817	13.000	38.270	1.00	16.16	O
ATOM	3323	P22	S1P S 401	3.655	14.241	39.119	1.00	13.18	P
ATOM	3324	O23	S1P S 401	3.754	13.948	40.575	1.00	15.50	O
ATOM	3325	O24	S1P S 401	4.460	15.415	38.652	1.00	15.05	O
ATOM	3326	O1	S1P S 401	2.092	14.603	38.970	1.00	13.56	O
ATOM	3327	C1	S1P S 401	1.636	15.415	37.900	1.00	14.35	C
ATOM	3328	C2	S1P S 401	1.331	14.595	36.642	1.00	15.91	C
ATOM	3329	N2	S1P S 401	1.053	13.159	36.959	1.00	13.57	N
ATOM	3330	C3	S1P S 401	0.155	15.223	35.858	1.00	15.55	C
ATOM	3331	O3	S1P S 401	-0.017	16.639	36.204	1.00	12.84	O
ATOM	3332	C4	S1P S 401	0.301	14.960	34.334	1.00	15.87	C
ATOM	3333	C5	S1P S 401	1.474	14.826	33.661	1.00	14.59	C
ATOM	3334	C6	S1P S 401	1.345	14.559	32.129	1.00	13.79	C
ATOM	3335	C7	S1P S 401	1.875	15.700	31.195	1.00	15.17	C
ATOM	3336	C8	S1P S 401	1.066	17.100	31.114	1.00	16.31	C
ATOM	3337	C9	S1P S 401	-0.506	16.916	30.812	1.00	15.46	C
ATOM	3338	C10	S1P S 401	-0.991	18.201	30.160	1.00	16.66	C
ATOM	3339	C11	S1P S 401	-2.469	17.863	29.502	1.00	17.84	C
ATOM	3340	C12	S1P S 401	-2.393	18.695	27.985	1.00	17.29	C
ATOM	3341	C13	S1P S 401	-3.547	19.687	27.832	1.00	19.49	C
ATOM	3342	C14	S1P S 401	-3.284	20.566	26.751	1.00	20.27	C
ATOM	3343	C15	S1P S 401	-3.587	22.102	27.308	1.00	19.06	C
ATOM	3344	C16	S1P S 401	-2.345	22.906	28.099	1.00	17.62	C
ATOM	3345	C17	S1P S 401	-3.003	23.690	29.282	1.00	18.69	C
ATOM	3346	C18	S1P S 401	-2.805	25.197	29.120	1.00	18.34	C

2. Structure determination and refinement. Complete x-ray diffraction data was collected for a single Fab/S1P complex co-crystal and the x-ray crystal structure has been solved. Data collection is complete. Coordinates for the Q425 monoclonal antibody Fab fragment (pdb code 2ADG) (T. Zhou et al., 2005 PNAS 102: 14575) with water molecules and Ca^{2+} removed was prepared for use as a probe and molecular replacement was carried out against all data between 10.0 and 4.0 Å using the program Phaser (McCoy, A.J., et al., Phaser Crystallography Software. J. Appl Crystallogr., 2007. 40: p. 658-674).

Rigid body refinement by the program Refmac5 (Murshudov, G.N., A.A. Vagin, and E.J. Dodson (1997) Acta Crystallogr D Biol Crystallogr. **53**: 240-55) using all data to 3.50 Å with each of the four immunoglobulin domains treated as a separate body lowered R-factor to 45.7% (R-free 45.3%). Restrained refinement against all data further lowered the R-factor to 36.1% (R-free 41.0%). At this point, amino acid side chains were changed to the anti-S1P sequence and some loop

rebuilding was carried out in $2|F_O - F_C|$ difference electron density maps in the program Xtalview (McRee, D.E. (1999) J Struct Biol., **125**: 156-65). Upon further refinement, a clear positive electron density was observed in $F_O - F_C$ difference maps within the epitope binding site of the antibody Fab fragment.

Coordinates for sphingosine-1-phosphate were prepared by adding a phosphate group to the 3-hydroxyl group of sphingosine taken from the Hic-up server (Hetero-compound Information Centre – Uppsala). Kleywegt, G.J. and T.A. Jones (1998) Acta Crystallogr D Biol Crystallogr. **54**: 1119-31. A library for the resulting lipid structure was prepared in the Monomer Library Sketcher program (Collaborative Computational Project, Number 4, Acta Crystallogr D Biol Crystallogr, 1994. **50**(Pt 5): 760-3.) and introduced into positive peak electron density. Additionally, two Ca^{2+} , one Mg^{2+} , one ethylene glycol molecule and 20 H_2O molecules were added. Our current Anti-S1P Fab/S1P complex crystallographic model exhibits excellent stereochemistry and a final crystallographic *R*-factor of 20% and *R*-free of 26% (Figure 1d).

In addition to the nearly completed x-ray crystal structure of the LT1009Fab/S1P complex at 2.7 Å reported here, we have also recently succeeded in recording a complete set of x-ray reflection intensities refined to 1.9 Å resolution using high energy synchrotron radiation on an ADSC 200 CCD detector at the Advanced Light Source beamline 5.0.1 at Berkeley National Laboratory.

The coordinates at 1.9 Å resolution are shown below as Table 11 and have been submitted to the RCSB Protein Data Bank. The refined pdb file in Table 11 clarifies that the bridging metals in the antibody fragment- antigen crystal are calcium. In addition, 5 magnesium atoms and 64 water atoms were added to the refined model and proper stereochemistry of S1P was considered.

Table 11 Fab/S1P co-crystal x-ray coordinates at 1.9 Å resolution

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HEADER    ----                XX-XXX-XX  xxxx
COMPND    ---
REMARK    3
REMARK    3 REFINEMENT.
REMARK    3 PROGRAM      : REFMAC 5.2.0019
REMARK    3 AUTHORS      : MURSHUDOV,VAGIN,DODSON
REMARK    3
REMARK    3 REFINEMENT TARGET : MAXIMUM LIKELIHOOD
REMARK    3
REMARK    3 DATA USED IN REFINEMENT.
REMARK    3 RESOLUTION RANGE HIGH (ANGSTROMS) : 1.90
REMARK    3 RESOLUTION RANGE LOW  (ANGSTROMS) : 69.34
REMARK    3 DATA CUTOFF          (SIGMA(F)) : NONE
REMARK    3 COMPLETENESS FOR RANGE (%) : 96.96
REMARK    3 NUMBER OF REFLECTIONS      : 47882
REMARK    3
REMARK    3 FIT TO DATA USED IN REFINEMENT.
REMARK    3 CROSS-VALIDATION METHOD      : THROUGHOUT
REMARK    3 FREE R VALUE TEST SET SELECTION : RANDOM
REMARK    3 R VALUE    (WORKING + TEST SET) : 0.19159
REMARK    3 R VALUE    (WORKING SET) : 0.19016

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REMARK 3 FREE R VALUE : 0.21902
REMARK 3 FREE R VALUE TEST SET SIZE (%) : 5.1
REMARK 3 FREE R VALUE TEST SET COUNT : 2548
REMARK 3
REMARK 3 FIT IN THE HIGHEST RESOLUTION BIN.
REMARK 3 TOTAL NUMBER OF BINS USED : 20
REMARK 3 BIN RESOLUTION RANGE HIGH : 1.901
REMARK 3 BIN RESOLUTION RANGE LOW : 1.951
REMARK 3 REFLECTION IN BIN (WORKING SET): 2601
REMARK 3 BIN COMPLETENESS (WORKING+TEST) (%): 72.83
REMARK 3 BIN R VALUE (WORKING SET): 0.257
REMARK 3 BIN FREE R VALUE SET COUNT : 147
REMARK 3 BIN FREE R VALUE : 0.276
REMARK 3
REMARK 3 NUMBER OF NON-HYDROGEN ATOMS USED IN REFINEMENT.
REMARK 3 ALL ATOMS : 3676
REMARK 3
REMARK 3 B VALUES.
REMARK 3 FROM WILSON PLOT (A**2) : NULL
REMARK 3 MEAN B VALUE (OVERALL, A**2) : 28.232
REMARK 3 OVERALL ANISOTROPIC B VALUE.
REMARK 3 B11 (A**2) : 0.54
REMARK 3 B22 (A**2) : -1.26
REMARK 3 B33 (A**2) : 0.72
REMARK 3 B12 (A**2) : 0.00
REMARK 3 B13 (A**2) : 0.00
REMARK 3 B23 (A**2) : 0.00
REMARK 3
REMARK 3 ESTIMATED OVERALL COORDINATE ERROR.
REMARK 3 ESU BASED ON R VALUE (A): 0.124
REMARK 3 ESU BASED ON FREE R VALUE (A): 0.119
REMARK 3 ESU BASED ON MAXIMUM LIKELIHOOD (A): 0.082
REMARK 3 ESU FOR B VALUES BASED ON MAXIMUM LIKELIHOOD (A**2): 2.810
REMARK 3
REMARK 3 CORRELATION COEFFICIENTS.
REMARK 3 CORRELATION COEFFICIENT FO-FC : 0.958
REMARK 3 CORRELATION COEFFICIENT FO-FC FREE : 0.943
REMARK 3
REMARK 3 RMS DEVIATIONS FROM IDEAL VALUES COUNT RMS WEIGHT
REMARK 3 BOND LENGTHS REFINED ATOMS (A): 3471 ; 0.013 ; 0.022
REMARK 3 BOND ANGLES REFINED ATOMS (DEGREES): 4715 ; 1.542 ; 1.954
REMARK 3 TORSION ANGLES, PERIOD 1 (DEGREES): 433 ; 8.849 ; 5.000
REMARK 3 TORSION ANGLES, PERIOD 2 (DEGREES): 141 ; 35.921 ; 24.752
REMARK 3 TORSION ANGLES, PERIOD 3 (DEGREES): 567 ; 15.264 ; 15.000
REMARK 3 TORSION ANGLES, PERIOD 4 (DEGREES): 11 ; 21.612 ; 15.000
REMARK 3 CHIRAL-CENTER RESTRAINTS (A**3): 527 ; 0.106 ; 0.200
REMARK 3 GENERAL PLANES REFINED ATOMS (A): 2595 ; 0.005 ; 0.020
REMARK 3 NON-BONDED CONTACTS REFINED ATOMS (A): 1442 ; 0.194 ; 0.200
REMARK 3 NON-BONDED TORSION REFINED ATOMS (A): 2341 ; 0.299 ; 0.200
REMARK 3 H-BOND (X...Y) REFINED ATOMS (A): 287 ; 0.137 ; 0.200
REMARK 3 POTENTIAL METAL-ION REFINED ATOMS (A): 12 ; 0.223 ; 0.200
REMARK 3 SYMMETRY VDW REFINED ATOMS (A): 27 ; 0.110 ; 0.200
REMARK 3 SYMMETRY H-BOND REFINED ATOMS (A): 13 ; 0.153 ; 0.200
REMARK 3
REMARK 3 ISOTROPIC THERMAL FACTOR RESTRAINTS. COUNT RMS WEIGHT
REMARK 3 MAIN-CHAIN BOND REFINED ATOMS (A**2): 2235 ; 0.913 ; 1.500
REMARK 3 MAIN-CHAIN ANGLE REFINED ATOMS (A**2): 3527 ; 1.506 ; 2.000

REMARK 3 SIDE-CHAIN BOND REFINED ATOMS (A**2): 1431 ; 2.102 ; 3.000
 REMARK 3 SIDE-CHAIN ANGLE REFINED ATOMS (A**2): 1188 ; 3.370 ; 4.500
 REMARK 3
 REMARK 3 NCS RESTRAINTS STATISTICS
 REMARK 3 NUMBER OF NCS GROUPS : NULL
 REMARK 3
 REMARK 3
 REMARK 3 TLS DETAILS
 REMARK 3 NUMBER OF TLS GROUPS : NULL
 REMARK 3
 REMARK 3
 REMARK 3 BULK SOLVENT MODELLING.
 REMARK 3 METHOD USED : MASK
 REMARK 3 PARAMETERS FOR MASK CALCULATION
 REMARK 3 VDW PROBE RADIUS : 1.40
 REMARK 3 ION PROBE RADIUS : 0.80
 REMARK 3 SHRINKAGE RADIUS : 0.80
 REMARK 3
 REMARK 3 OTHER REFINEMENT REMARKS:
 REMARK 3 HYDROGENS HAVE BEEN ADDED IN THE RIDING POSITIONS
 REMARK 3
 REMARK 40
 REMARK 40 MOLPROBITY STRUCTURE VALIDATION
 REMARK 40 PROGRAMS : MOLPROBITY (KING, REDUCE, AND PROBE)
 REMARK 40 AUTHORS : I.W.DAVIS,V.B.CHEN,
 REMARK 40 : R.M.IMMORMINO,J.J.HEADD,W.B.ARENDALL,J.M.WORD
 REMARK 40 URL : HTTP://KINEMAGE.BIOCHEM.DUKE.EDU/MOLPROBITY/
 REMARK 40 AUTHORS : I.W.DAVIS,A.LEAVER-FAY,V.B.CHEN,J.N.BLOCK,
 REMARK 40 : G.J.KAPRAL,X.WANG,L.W.MURRAY,W.B.ARENDALL,
 REMARK 40 : J.SNOEYINK,J.S.RICHARDSON,D.C.RICHARDSON
 REMARK 40 REFERENCE : MOLPROBITY: ALL-ATOM CONTACTS AND STRUCTURE
 REMARK 40 : VALIDATION FOR PROTEINS AND NUCLEIC ACIDS
 REMARK 40 : NUCLEIC ACIDS RESEARCH. 2007;35:W375-83.
 REMARK 40 MOLPROBITY OUTPUT SCORES:
 REMARK 40 ALL-ATOM CLASHSCORE : 8.01
 REMARK 40 BAD ROTAMERS : 2.9% 11/380 (TARGET 0-1%)
 REMARK 40 RAMACHANDRAN OUTLIERS : 0.2% 1/431 (TARGET 0.2%)
 REMARK 40 RAMACHANDRAN FAVORED : 96.5% 416/431 (TARGET 98.0%)
 SSBOND 1 CYS H 140 CYS H 196
 SSBOND 2 CYS L 23 CYS L 88
 SSBOND 3 CYS L 134 CYS L 194
 SSBOND 4 CYS H 22 CYS H 92
 CISPEP 1 GLN H 105 GLY H 106 0.00
 CISPEP 2 PHE H 146 PRO H 147 0.00
 CISPEP 3 GLU H 148 PRO H 149 0.00
 CISPEP 4 SER H 173 GLY H 174 0.00
 CISPEP 5 GLY H 174 LEU H 175 0.00
 CISPEP 6 SER H 188 LEU H 189 0.00
 CISPEP 7 LEU H 189 GLY H 190 0.00
 CISPEP 8 SER L 7 PRO L 8 0.00
 CISPEP 9 LEU L 94 PRO L 95 0.00
 CISPEP 10 TYR L 140 PRO L 141 0.00
 CRYST1 66.052 70.889 138.719 90.00 90.00 90.00 P 21 21 21 0
 SCALE1 0.015140 0.000000 0.000000 0.000000
 SCALE2 0.000000 0.014107 0.000000 0.000000
 SCALE3 0.000000 0.000000 0.007209 0.000000
 ATOM 1 N GLU H 1 -25.584 14.762 35.504 1.00 42.70 N

ATOM	2	CA	GLU	H	1	-24.140	14.508	35.738	1.00	42.38	C
ATOM	3	CB	GLU	H	1	-23.924	13.093	36.291	1.00	43.50	C
ATOM	4	CG	GLU	H	1	-23.011	13.058	37.553	1.00	47.73	C
ATOM	5	CD	GLU	H	1	-21.512	12.964	37.237	1.00	51.40	C
ATOM	6	OE1	GLU	H	1	-21.144	12.225	36.301	1.00	53.87	O
ATOM	7	OE2	GLU	H	1	-20.698	13.611	37.939	1.00	53.58	O
ATOM	8	C	GLU	H	1	-23.337	14.731	34.457	1.00	40.58	C
ATOM	9	O	GLU	H	1	-23.872	15.201	33.442	1.00	40.25	O
ATOM	10	N	VAL	H	2	-22.047	14.422	34.525	1.00	38.73	N
ATOM	11	CA	VAL	H	2	-21.122	14.671	33.432	1.00	36.63	C
ATOM	12	CB	VAL	H	2	-19.648	14.455	33.881	1.00	36.74	C
ATOM	13	CG1	VAL	H	2	-18.693	14.651	32.712	1.00	36.33	C
ATOM	14	CG2	VAL	H	2	-19.285	15.392	35.036	1.00	36.09	C
ATOM	15	C	VAL	H	2	-21.464	13.748	32.258	1.00	35.63	C
ATOM	16	O	VAL	H	2	-21.556	12.532	32.423	1.00	35.55	O
ATOM	17	N	GLN	H	3	-21.684	14.332	31.085	1.00	33.92	N
ATOM	18	CA	GLN	H	3	-21.805	13.548	29.866	1.00	33.06	C
ATOM	19	CB	GLN	H	3	-23.252	13.444	29.398	1.00	33.60	C
ATOM	20	CG	GLN	H	3	-24.234	12.931	30.418	1.00	37.43	C
ATOM	21	CD	GLN	H	3	-25.648	12.977	29.871	1.00	42.54	C
ATOM	22	OE1	GLN	H	3	-25.916	12.486	28.766	1.00	43.38	O
ATOM	23	NE2	GLN	H	3	-26.556	13.591	30.626	1.00	44.39	N
ATOM	24	C	GLN	H	3	-21.015	14.206	28.765	1.00	31.21	C
ATOM	25	O	GLN	H	3	-21.075	15.422	28.602	1.00	30.88	O
ATOM	26	N	LEU	H	4	-20.293	13.385	28.007	1.00	29.21	N
ATOM	27	CA	LEU	H	4	-19.610	13.801	26.787	1.00	27.36	C
ATOM	28	CB	LEU	H	4	-18.136	13.378	26.826	1.00	26.77	C
ATOM	29	CG	LEU	H	4	-17.151	14.334	27.538	1.00	26.93	C
ATOM	30	CD1	LEU	H	4	-17.563	14.680	28.967	1.00	26.48	C
ATOM	31	CD2	LEU	H	4	-15.724	13.789	27.510	1.00	26.44	C
ATOM	32	C	LEU	H	4	-20.352	13.115	25.645	1.00	27.52	C
ATOM	33	O	LEU	H	4	-20.476	11.886	25.641	1.00	26.87	O
ATOM	34	N	VAL	H	5	-20.892	13.906	24.718	1.00	26.33	N
ATOM	35	CA	VAL	H	5	-21.694	13.352	23.619	1.00	26.62	C
ATOM	36	CB	VAL	H	5	-23.160	13.890	23.613	1.00	26.60	C
ATOM	37	CG1	VAL	H	5	-23.993	13.170	22.554	1.00	27.97	C
ATOM	38	CG2	VAL	H	5	-23.790	13.710	24.987	1.00	26.56	C
ATOM	39	C	VAL	H	5	-21.038	13.583	22.274	1.00	26.22	C
ATOM	40	O	VAL	H	5	-20.810	14.730	21.863	1.00	26.22	O
ATOM	41	N	GLN	H	6	-20.742	12.480	21.586	1.00	25.02	N
ATOM	42	CA	GLN	H	6	-20.087	12.537	20.307	1.00	24.44	C
ATOM	43	CB	GLN	H	6	-19.005	11.445	20.195	1.00	24.68	C
ATOM	44	CG	GLN	H	6	-17.894	11.575	21.273	1.00	23.01	C
ATOM	45	CD	GLN	H	6	-16.725	10.626	21.059	1.00	24.34	C
ATOM	46	OE1	GLN	H	6	-16.373	9.856	21.951	1.00	24.47	O
ATOM	47	NE2	GLN	H	6	-16.121	10.669	19.881	1.00	24.70	N
ATOM	48	C	GLN	H	6	-21.072	12.474	19.142	1.00	24.51	C
ATOM	49	O	GLN	H	6	-22.188	11.976	19.286	1.00	24.52	O
ATOM	50	N	SER	H	7	-20.626	12.973	17.999	1.00	24.55	N
ATOM	51	CA	SER	H	7	-21.401	12.991	16.770	1.00	24.74	C
ATOM	52	CB	SER	H	7	-20.842	14.031	15.797	1.00	24.69	C
ATOM	53	OG	SER	H	7	-19.459	13.832	15.528	1.00	25.46	O
ATOM	54	C	SER	H	7	-21.428	11.586	16.159	1.00	25.32	C
ATOM	55	O	SER	H	7	-20.657	10.702	16.583	1.00	25.24	O
ATOM	56	N	GLY	H	8	-22.323	11.379	15.190	1.00	24.82	N
ATOM	57	CA	GLY	H	8	-22.606	10.035	14.649	1.00	24.98	C
ATOM	58	C	GLY	H	8	-21.567	9.453	13.716	1.00	25.25	C

ATOM	59	O	GLY H	8	-20.640	10.158	13.278	1.00	25.03	O
ATOM	60	N	ALA H	9	-21.729	8.159	13.393	1.00	24.59	N
ATOM	61	CA	ALA H	9	-20.777	7.435	12.565	1.00	25.05	C
ATOM	62	CB	ALA H	9	-21.230	5.976	12.335	1.00	24.99	C
ATOM	63	C	ALA H	9	-20.581	8.128	11.232	1.00	25.21	C
ATOM	64	O	ALA H	9	-21.511	8.714	10.702	1.00	25.34	O
ATOM	65	N	GLU H	10	-19.374	8.042	10.698	1.00	25.39	N
ATOM	66	CA	GLU H	10	-19.040	8.690	9.439	1.00	26.02	C
ATOM	67	CB	GLU H	10	-17.981	9.778	9.670	1.00	26.03	C
ATOM	68	CG	GLU H	10	-18.455	10.898	10.595	1.00	27.77	C
ATOM	69	CD	GLU H	10	-19.276	11.985	9.878	1.00	30.78	C
ATOM	70	OE1	GLU H	10	-19.411	11.959	8.624	1.00	31.23	O
ATOM	71	OE2	GLU H	10	-19.780	12.879	10.588	1.00	32.65	O
ATOM	72	C	GLU H	10	-18.504	7.677	8.459	1.00	26.07	C
ATOM	73	O	GLU H	10	-17.748	6.777	8.826	1.00	25.43	O
ATOM	74	N	VAL H	11	-18.901	7.828	7.204	1.00	26.26	N
ATOM	75	CA	VAL H	11	-18.352	7.024	6.135	1.00	26.79	C
ATOM	76	CB	VAL H	11	-19.383	5.983	5.599	1.00	27.14	C
ATOM	77	CG1	VAL H	11	-18.728	5.104	4.551	1.00	26.07	C
ATOM	78	CG2	VAL H	11	-19.944	5.122	6.750	1.00	26.92	C
ATOM	79	C	VAL H	11	-17.869	7.960	5.025	1.00	27.42	C
ATOM	80	O	VAL H	11	-18.633	8.775	4.518	1.00	27.77	O
ATOM	81	N	LYS H	12	-16.600	7.833	4.660	1.00	28.18	N
ATOM	82	CA	LYS H	12	-15.936	8.782	3.775	1.00	29.27	C
ATOM	83	CB	LYS H	12	-15.092	9.766	4.606	1.00	29.50	C
ATOM	84	CG	LYS H	12	-15.924	10.639	5.523	1.00	29.78	C
ATOM	85	CD	LYS H	12	-16.455	11.830	4.741	1.00	34.08	C
ATOM	86	CE	LYS H	12	-17.610	12.450	5.445	1.00	34.63	C
ATOM	87	NZ	LYS H	12	-17.926	13.743	4.802	1.00	36.50	N
ATOM	88	C	LYS H	12	-15.037	8.073	2.794	1.00	30.18	C
ATOM	89	O	LYS H	12	-14.688	6.908	2.991	1.00	30.40	O
ATOM	90	N	LYS H	13	-14.663	8.792	1.738	1.00	30.69	N
ATOM	91	CA	LYS H	13	-13.685	8.336	0.764	1.00	32.21	C
ATOM	92	CB	LYS H	13	-14.113	8.787	-0.634	1.00	32.87	C
ATOM	93	CG	LYS H	13	-14.722	7.705	-1.488	1.00	35.72	C
ATOM	94	CD	LYS H	13	-16.200	7.808	-1.550	1.00	38.02	C
ATOM	95	CE	LYS H	13	-16.685	7.002	-2.718	1.00	38.58	C
ATOM	96	NZ	LYS H	13	-18.158	6.895	-2.636	1.00	41.40	N
ATOM	97	C	LYS H	13	-12.303	8.912	1.065	1.00	32.26	C
ATOM	98	O	LYS H	13	-12.206	10.005	1.618	1.00	32.37	O
ATOM	99	N	PRO H	14	-11.235	8.196	0.679	1.00	32.82	N
ATOM	100	CA	PRO H	14	-9.898	8.768	0.839	1.00	33.44	C
ATOM	101	CB	PRO H	14	-8.977	7.741	0.178	1.00	33.65	C
ATOM	102	CG	PRO H	14	-9.764	6.460	0.163	1.00	33.39	C
ATOM	103	CD	PRO H	14	-11.203	6.848	0.082	1.00	32.65	C
ATOM	104	C	PRO H	14	-9.786	10.117	0.129	1.00	33.97	C
ATOM	105	O	PRO H	14	-10.321	10.283	-0.983	1.00	34.04	O
ATOM	106	N	GLY H	15	-9.110	11.064	0.783	1.00	33.80	N
ATOM	107	CA	GLY H	15	-8.945	12.423	0.267	1.00	33.42	C
ATOM	108	C	GLY H	15	-9.993	13.413	0.742	1.00	33.33	C
ATOM	109	O	GLY H	15	-9.806	14.619	0.584	1.00	33.64	O
ATOM	110	N	GLU H	16	-11.103	12.930	1.302	1.00	32.65	N
ATOM	111	CA	GLU H	16	-12.174	13.817	1.765	1.00	32.37	C
ATOM	112	CB	GLU H	16	-13.509	13.085	1.848	1.00	33.21	C
ATOM	113	CG	GLU H	16	-14.016	12.555	0.508	1.00	33.94	C
ATOM	114	CD	GLU H	16	-15.461	12.105	0.551	1.00	38.29	C
ATOM	115	OE1	GLU H	16	-16.122	12.222	-0.505	1.00	40.04	O

ATOM	116	OE2	GLU	H	16	-15.944	11.622	1.609	1.00	37.08	O
ATOM	117	C	GLU	H	16	-11.831	14.406	3.127	1.00	32.13	C
ATOM	118	O	GLU	H	16	-10.989	13.864	3.841	1.00	32.05	O
ATOM	119	N	SER	H	17	-12.485	15.502	3.490	1.00	31.67	N
ATOM	120	CA	SER	H	17	-12.224	16.136	4.783	1.00	31.67	C
ATOM	121	CB	SER	H	17	-12.124	17.662	4.644	1.00	31.54	C
ATOM	122	OG	SER	H	17	-13.409	18.231	4.467	1.00	34.51	O
ATOM	123	C	SER	H	17	-13.321	15.751	5.748	1.00	30.76	C
ATOM	124	O	SER	H	17	-14.395	15.287	5.333	1.00	31.35	O
ATOM	125	N	LEU	H	18	-13.066	15.922	7.042	1.00	29.23	N
ATOM	126	CA	LEU	H	18	-14.022	15.491	8.052	1.00	27.95	C
ATOM	127	CB	LEU	H	18	-13.929	13.957	8.252	1.00	27.91	C
ATOM	128	CG	LEU	H	18	-14.707	13.332	9.427	1.00	26.77	C
ATOM	129	CD1	LEU	H	18	-16.197	13.438	9.192	1.00	26.43	C
ATOM	130	CD2	LEU	H	18	-14.293	11.862	9.651	1.00	27.87	C
ATOM	131	C	LEU	H	18	-13.780	16.198	9.379	1.00	27.37	C
ATOM	132	O	LEU	H	18	-12.641	16.346	9.802	1.00	27.23	O
ATOM	133	N	LYS	H	19	-14.862	16.607	10.026	1.00	27.05	N
ATOM	134	CA	LYS	H	19	-14.812	17.161	11.347	1.00	27.65	C
ATOM	135	CB	LYS	H	19	-15.040	18.687	11.325	1.00	28.06	C
ATOM	136	CG	LYS	H	19	-15.181	19.333	12.724	1.00	30.76	C
ATOM	137	CD	LYS	H	19	-14.609	20.766	12.772	1.00	34.77	C
ATOM	138	CE	LYS	H	19	-15.520	21.786	12.160	1.00	37.70	C
ATOM	139	NZ	LYS	H	19	-15.028	23.170	12.446	1.00	39.11	N
ATOM	140	C	LYS	H	19	-15.848	16.443	12.198	1.00	27.22	C
ATOM	141	O	LYS	H	19	-17.048	16.398	11.866	1.00	27.13	O
ATOM	142	N	ILE	H	20	-15.370	15.834	13.279	1.00	25.36	N
ATOM	143	CA	ILE	H	20	-16.260	15.212	14.240	1.00	24.49	C
ATOM	144	CB	ILE	H	20	-15.888	13.701	14.495	1.00	24.49	C
ATOM	145	CG1	ILE	H	20	-14.527	13.554	15.189	1.00	23.69	C
ATOM	146	CD1	ILE	H	20	-14.163	12.053	15.516	1.00	24.14	C
ATOM	147	CG2	ILE	H	20	-15.912	12.911	13.182	1.00	22.81	C
ATOM	148	C	ILE	H	20	-16.245	16.036	15.522	1.00	24.86	C
ATOM	149	O	ILE	H	20	-15.338	16.858	15.724	1.00	24.16	O
ATOM	150	N	SER	H	21	-17.228	15.815	16.386	1.00	24.93	N
ATOM	151	CA	SER	H	21	-17.410	16.659	17.549	1.00	25.93	C
ATOM	152	CB	SER	H	21	-18.507	17.703	17.277	1.00	25.57	C
ATOM	153	OG	SER	H	21	-19.782	17.087	17.197	1.00	27.68	O
ATOM	154	C	SER	H	21	-17.751	15.892	18.822	1.00	25.98	C
ATOM	155	O	SER	H	21	-18.177	14.739	18.782	1.00	26.02	O
ATOM	156	N	CYS	H	22	-17.567	16.574	19.946	1.00	26.41	N
ATOM	157	CA	CYS	H	22	-17.794	16.061	21.280	1.00	25.98	C
ATOM	158	CB	CYS	H	22	-16.462	15.549	21.873	1.00	25.90	C
ATOM	159	SG	CYS	H	22	-16.480	15.066	23.619	1.00	29.58	S
ATOM	160	C	CYS	H	22	-18.338	17.216	22.117	1.00	26.37	C
ATOM	161	O	CYS	H	22	-17.628	18.202	22.383	1.00	25.92	O
ATOM	162	N	GLN	H	23	-19.588	17.094	22.539	1.00	26.72	N
ATOM	163	CA	GLN	H	23	-20.224	18.139	23.328	1.00	27.85	C
ATOM	164	CB	GLN	H	23	-21.585	18.522	22.722	1.00	27.62	C
ATOM	165	CG	GLN	H	23	-22.251	19.716	23.433	1.00	28.84	C
ATOM	166	CD	GLN	H	23	-23.440	20.260	22.654	1.00	29.75	C
ATOM	167	OE1	GLN	H	23	-24.180	19.505	22.014	1.00	31.53	O
ATOM	168	NE2	GLN	H	23	-23.638	21.566	22.721	1.00	29.67	N
ATOM	169	C	GLN	H	23	-20.387	17.741	24.787	1.00	27.91	C
ATOM	170	O	GLN	H	23	-20.912	16.669	25.090	1.00	27.65	O
ATOM	171	N	SER	H	24	-19.940	18.623	25.686	1.00	28.29	N
ATOM	172	CA	SER	H	24	-19.937	18.362	27.121	1.00	29.03	C

ATOM	173	CB	SER	H	24	-18.694	18.964	27.770	1.00	28.96	C
ATOM	174	OG	SER	H	24	-17.536	18.268	27.352	1.00	30.05	O
ATOM	175	C	SER	H	24	-21.159	18.936	27.807	1.00	29.93	C
ATOM	176	O	SER	H	24	-21.588	20.046	27.484	1.00	30.30	O
ATOM	177	N	PHE	H	25	-21.700	18.171	28.754	1.00	30.53	N
ATOM	178	CA	PHE	H	25	-22.838	18.578	29.581	1.00	30.91	C
ATOM	179	CB	PHE	H	25	-24.113	17.822	29.175	1.00	31.55	C
ATOM	180	CG	PHE	H	25	-24.494	17.988	27.722	1.00	32.15	C
ATOM	181	CD1	PHE	H	25	-23.952	17.156	26.742	1.00	33.62	C
ATOM	182	CE1	PHE	H	25	-24.299	17.303	25.390	1.00	33.50	C
ATOM	183	CZ	PHE	H	25	-25.216	18.290	25.006	1.00	34.10	C
ATOM	184	CE2	PHE	H	25	-25.769	19.128	25.976	1.00	33.96	C
ATOM	185	CD2	PHE	H	25	-25.408	18.973	27.330	1.00	34.42	C
ATOM	186	C	PHE	H	25	-22.516	18.265	31.035	1.00	31.14	C
ATOM	187	O	PHE	H	25	-21.734	17.339	31.319	1.00	31.16	O
ATOM	188	N	GLY	H	26	-23.096	19.051	31.946	1.00	30.56	N
ATOM	189	CA	GLY	H	26	-23.089	18.739	33.375	1.00	30.56	C
ATOM	190	C	GLY	H	26	-21.873	19.188	34.170	1.00	30.54	C
ATOM	191	O	GLY	H	26	-21.704	18.798	35.317	1.00	30.59	O
ATOM	192	N	TYR	H	27	-21.028	20.018	33.567	1.00	30.77	N
ATOM	193	CA	TYR	H	27	-19.856	20.561	34.260	1.00	30.70	C
ATOM	194	CB	TYR	H	27	-18.720	19.510	34.351	1.00	30.09	C
ATOM	195	CG	TYR	H	27	-17.959	19.253	33.046	1.00	29.59	C
ATOM	196	CD1	TYR	H	27	-16.778	19.952	32.761	1.00	29.68	C
ATOM	197	CE1	TYR	H	27	-16.082	19.744	31.579	1.00	27.94	C
ATOM	198	CZ	TYR	H	27	-16.559	18.807	30.659	1.00	27.90	C
ATOM	199	OH	TYR	H	27	-15.860	18.600	29.488	1.00	27.86	O
ATOM	200	CE2	TYR	H	27	-17.724	18.095	30.913	1.00	27.86	C
ATOM	201	CD2	TYR	H	27	-18.429	18.331	32.100	1.00	29.32	C
ATOM	202	C	TYR	H	27	-19.402	21.823	33.517	1.00	31.13	C
ATOM	203	O	TYR	H	27	-19.917	22.127	32.439	1.00	31.42	O
ATOM	204	N	ILE	H	28	-18.431	22.538	34.081	1.00	31.17	N
ATOM	205	CA	ILE	H	28	-17.920	23.753	33.466	1.00	31.31	C
ATOM	206	CB	ILE	H	28	-17.407	24.768	34.549	1.00	31.56	C
ATOM	207	CG1	ILE	H	28	-18.533	25.109	35.540	1.00	32.47	C
ATOM	208	CD1	ILE	H	28	-18.049	25.662	36.901	1.00	33.38	C
ATOM	209	CG2	ILE	H	28	-16.885	26.046	33.887	1.00	32.01	C
ATOM	210	C	ILE	H	28	-16.816	23.374	32.486	1.00	29.91	C
ATOM	211	O	ILE	H	28	-15.756	22.892	32.894	1.00	29.97	O
ATOM	212	N	PHE	H	29	-17.091	23.581	31.201	1.00	29.12	N
ATOM	213	CA	PHE	H	29	-16.219	23.185	30.077	1.00	28.42	C
ATOM	214	CB	PHE	H	29	-16.855	23.708	28.787	1.00	28.86	C
ATOM	215	CG	PHE	H	29	-16.195	23.253	27.519	1.00	28.68	C
ATOM	216	CD1	PHE	H	29	-15.932	21.901	27.282	1.00	27.96	C
ATOM	217	CE1	PHE	H	29	-15.359	21.490	26.077	1.00	27.89	C
ATOM	218	CZ	PHE	H	29	-15.061	22.425	25.091	1.00	28.95	C
ATOM	219	CE2	PHE	H	29	-15.349	23.799	25.316	1.00	27.14	C
ATOM	220	CD2	PHE	H	29	-15.906	24.187	26.513	1.00	24.67	C
ATOM	221	C	PHE	H	29	-14.783	23.720	30.220	1.00	28.33	C
ATOM	222	O	PHE	H	29	-13.808	22.975	30.051	1.00	26.93	O
ATOM	223	N	ILE	H	30	-14.661	25.008	30.561	1.00	27.01	N
ATOM	224	CA	ILE	H	30	-13.352	25.652	30.684	1.00	26.37	C
ATOM	225	CB	ILE	H	30	-13.465	27.204	30.574	1.00	26.33	C
ATOM	226	CG1	ILE	H	30	-14.304	27.782	31.718	1.00	27.61	C
ATOM	227	CD1	ILE	H	30	-14.087	29.319	31.894	1.00	27.16	C
ATOM	228	CG2	ILE	H	30	-14.037	27.586	29.216	1.00	25.65	C
ATOM	229	C	ILE	H	30	-12.535	25.231	31.924	1.00	25.33	C

ATOM	230	O	ILE H 30	-11.359	25.579	32.051	1.00	25.01	O
ATOM	231	N	ASP H 31	-13.149	24.466	32.823	1.00	25.20	N
ATOM	232	CA	ASP H 31	-12.429	23.912	33.983	1.00	24.86	C
ATOM	233	CB	ASP H 31	-13.377	23.664	35.155	1.00	25.23	C
ATOM	234	CG	ASP H 31	-13.737	24.946	35.901	1.00	29.57	C
ATOM	235	OD1	ASP H 31	-13.174	26.014	35.582	1.00	30.60	O
ATOM	236	OD2	ASP H 31	-14.576	24.873	36.809	1.00	32.57	O
ATOM	237	C	ASP H 31	-11.606	22.646	33.698	1.00	23.97	C
ATOM	238	O	ASP H 31	-10.888	22.173	34.574	1.00	23.45	O
ATOM	239	N	HIS H 32	-11.694	22.120	32.483	1.00	23.34	N
ATOM	240	CA	HIS H 32	-10.995	20.870	32.119	1.00	22.80	C
ATOM	241	CB	HIS H 32	-11.970	19.684	32.245	1.00	22.13	C
ATOM	242	CG	HIS H 32	-12.519	19.518	33.627	1.00	24.88	C
ATOM	243	ND1	HIS H 32	-11.863	18.806	34.609	1.00	27.98	N
ATOM	244	CE1	HIS H 32	-12.562	18.856	35.728	1.00	27.73	C
ATOM	245	NE2	HIS H 32	-13.654	19.566	35.506	1.00	26.42	N
ATOM	246	CD2	HIS H 32	-13.649	19.994	34.202	1.00	25.80	C
ATOM	247	C	HIS H 32	-10.355	20.913	30.737	1.00	21.79	C
ATOM	248	O	HIS H 32	-10.504	21.897	29.993	1.00	22.35	O
ATOM	249	N	THR H 33	-9.627	19.850	30.379	1.00	20.36	N
ATOM	250	CA	THR H 33	-9.121	19.696	29.014	1.00	19.25	C
ATOM	251	CB	THR H 33	-7.609	19.437	28.977	1.00	19.51	C
ATOM	252	OG1	THR H 33	-7.297	18.362	29.880	1.00	18.58	O
ATOM	253	CG2	THR H 33	-6.786	20.731	29.336	1.00	18.51	C
ATOM	254	C	THR H 33	-9.873	18.534	28.313	1.00	18.79	C
ATOM	255	O	THR H 33	-10.449	17.679	28.975	1.00	18.97	O
ATOM	256	N	ILE H 34	-9.924	18.555	26.987	1.00	18.85	N
ATOM	257	CA	ILE H 34	-10.583	17.480	26.228	1.00	19.29	C
ATOM	258	CB	ILE H 34	-11.761	17.988	25.347	1.00	19.49	C
ATOM	259	CG1	ILE H 34	-12.913	18.528	26.203	1.00	19.49	C
ATOM	260	CD1	ILE H 34	-13.678	17.504	27.074	1.00	23.13	C
ATOM	261	CG2	ILE H 34	-12.286	16.879	24.386	1.00	20.74	C
ATOM	262	C	ILE H 34	-9.527	16.836	25.363	1.00	19.11	C
ATOM	263	O	ILE H 34	-8.775	17.521	24.692	1.00	18.91	O
ATOM	264	N	HIS H 35	-9.495	15.498	25.368	1.00	18.46	N
ATOM	265	CA	HIS H 35	-8.428	14.756	24.727	1.00	17.90	C
ATOM	266	CB	HIS H 35	-7.716	13.907	25.785	1.00	17.38	C
ATOM	267	CG	HIS H 35	-7.101	14.713	26.881	1.00	17.80	C
ATOM	268	ND1	HIS H 35	-5.740	14.798	27.056	1.00	17.25	N
ATOM	269	CE1	HIS H 35	-5.483	15.581	28.092	1.00	18.91	C
ATOM	270	NE2	HIS H 35	-6.633	16.018	28.581	1.00	17.02	N
ATOM	271	CD2	HIS H 35	-7.661	15.469	27.855	1.00	16.01	C
ATOM	272	C	HIS H 35	-9.075	13.842	23.703	1.00	17.93	C
ATOM	273	O	HIS H 35	-10.204	13.457	23.895	1.00	18.34	O
ATOM	274	N	TRP H 36	-8.364	13.520	22.625	1.00	18.68	N
ATOM	275	CA	TRP H 36	-8.895	12.627	21.603	1.00	19.05	C
ATOM	276	CB	TRP H 36	-8.920	13.299	20.215	1.00	19.08	C
ATOM	277	CG	TRP H 36	-10.011	14.321	20.081	1.00	19.92	C
ATOM	278	CD1	TRP H 36	-9.896	15.687	20.278	1.00	22.72	C
ATOM	279	NE1	TRP H 36	-11.114	16.291	20.091	1.00	23.04	N
ATOM	280	CE2	TRP H 36	-12.048	15.331	19.769	1.00	22.42	C
ATOM	281	CD2	TRP H 36	-11.391	14.076	19.770	1.00	22.13	C
ATOM	282	CE3	TRP H 36	-12.137	12.918	19.473	1.00	22.63	C
ATOM	283	CZ3	TRP H 36	-13.505	13.050	19.181	1.00	22.29	C
ATOM	284	CH2	TRP H 36	-14.127	14.324	19.189	1.00	21.94	C
ATOM	285	CZ2	TRP H 36	-13.417	15.462	19.486	1.00	21.57	C
ATOM	286	C	TRP H 36	-8.048	11.366	21.541	1.00	18.64	C

ATOM	287	O	TRP H 36	-6.835	11.452	21.434	1.00	18.10	O
ATOM	288	N	MET H 37	-8.724	10.215	21.563	1.00	19.06	N
ATOM	289	CA	MET H 37	-8.100	8.889	21.479	1.00	19.29	C
ATOM	290	CB	MET H 37	-8.577	8.012	22.657	1.00	19.69	C
ATOM	291	CG	MET H 37	-7.510	7.697	23.732	1.00	20.61	C
ATOM	292	SD	MET H 37	-6.920	9.209	24.563	1.00	23.44	S
ATOM	293	CE	MET H 37	-8.380	9.748	25.420	1.00	22.21	C
ATOM	294	C	MET H 37	-8.524	8.204	20.180	1.00	19.55	C
ATOM	295	O	MET H 37	-9.672	8.366	19.758	1.00	20.05	O
ATOM	296	N	ARG H 38	-7.589	7.471	19.557	1.00	19.27	N
ATOM	297	CA	ARG H 38	-7.890	6.628	18.389	1.00	19.91	C
ATOM	298	CB	ARG H 38	-6.843	6.822	17.288	1.00	19.47	C
ATOM	299	CG	ARG H 38	-7.186	6.105	15.992	1.00	20.48	C
ATOM	300	CD	ARG H 38	-6.249	6.428	14.848	1.00	21.31	C
ATOM	301	NE	ARG H 38	-4.920	5.858	15.042	1.00	24.22	N
ATOM	302	CZ	ARG H 38	-3.952	5.896	14.137	1.00	25.20	C
ATOM	303	NH1	ARG H 38	-4.156	6.502	12.972	1.00	27.06	N
ATOM	304	NH2	ARG H 38	-2.766	5.359	14.411	1.00	25.31	N
ATOM	305	C	ARG H 38	-7.855	5.176	18.845	1.00	20.28	C
ATOM	306	O	ARG H 38	-6.990	4.815	19.633	1.00	19.65	O
ATOM	307	N	GLN H 39	-8.787	4.356	18.347	1.00	20.70	N
ATOM	308	CA	GLN H 39	-8.700	2.909	18.537	1.00	20.82	C
ATOM	309	CB	GLN H 39	-9.681	2.440	19.609	1.00	20.48	C
ATOM	310	CG	GLN H 39	-9.599	0.926	19.913	1.00	20.32	C
ATOM	311	CD	GLN H 39	-10.284	0.568	21.201	1.00	20.03	C
ATOM	312	OE1	GLN H 39	-11.397	1.003	21.455	1.00	22.57	O
ATOM	313	NE2	GLN H 39	-9.616	-0.215	22.039	1.00	21.68	N
ATOM	314	C	GLN H 39	-8.990	2.252	17.189	1.00	21.74	C
ATOM	315	O	GLN H 39	-10.146	2.175	16.763	1.00	21.34	O
ATOM	316	N	MET H 40	-7.925	1.842	16.508	1.00	22.94	N
ATOM	317	CA	MET H 40	-8.058	1.143	15.231	1.00	26.12	C
ATOM	318	CB	MET H 40	-6.714	1.071	14.510	1.00	25.56	C
ATOM	319	CG	MET H 40	-6.274	2.448	13.955	1.00	27.70	C
ATOM	320	SD	MET H 40	-4.707	2.341	13.123	1.00	32.83	S
ATOM	321	CE	MET H 40	-3.597	1.865	14.455	1.00	30.11	C
ATOM	322	C	MET H 40	-8.697	-0.224	15.446	1.00	26.15	C
ATOM	323	O	MET H 40	-8.629	-0.771	16.570	1.00	25.78	O
ATOM	324	N	PRO H 41	-9.411	-0.736	14.414	1.00	27.21	N
ATOM	325	CA	PRO H 41	-10.146	-1.995	14.578	1.00	27.56	C
ATOM	326	CB	PRO H 41	-10.642	-2.298	13.156	1.00	27.98	C
ATOM	327	CG	PRO H 41	-10.834	-0.921	12.557	1.00	28.03	C
ATOM	328	CD	PRO H 41	-9.619	-0.165	13.063	1.00	26.90	C
ATOM	329	C	PRO H 41	-9.267	-3.122	15.132	1.00	27.39	C
ATOM	330	O	PRO H 41	-8.196	-3.407	14.589	1.00	26.96	O
ATOM	331	N	GLY H 42	-9.722	-3.701	16.240	1.00	27.74	N
ATOM	332	CA	GLY H 42	-9.014	-4.790	16.903	1.00	28.12	C
ATOM	333	C	GLY H 42	-7.757	-4.385	17.664	1.00	27.88	C
ATOM	334	O	GLY H 42	-7.051	-5.259	18.178	1.00	27.93	O
ATOM	335	N	GLN H 43	-7.471	-3.079	17.740	1.00	26.29	N
ATOM	336	CA	GLN H 43	-6.238	-2.600	18.384	1.00	26.35	C
ATOM	337	CB	GLN H 43	-5.460	-1.656	17.476	1.00	27.00	C
ATOM	338	CG	GLN H 43	-5.502	-2.008	16.031	1.00	32.32	C
ATOM	339	CD	GLN H 43	-4.221	-2.577	15.569	1.00	38.12	C
ATOM	340	OE1	GLN H 43	-3.507	-1.948	14.779	1.00	41.64	O
ATOM	341	NE2	GLN H 43	-3.887	-3.767	16.062	1.00	39.21	N
ATOM	342	C	GLN H 43	-6.526	-1.878	19.685	1.00	24.36	C
ATOM	343	O	GLN H 43	-7.683	-1.791	20.115	1.00	23.60	O

ATOM	344	N	GLY	H	44	-5.457	-1.383	20.302	1.00	23.49	N
ATOM	345	CA	GLY	H	44	-5.534	-0.683	21.584	1.00	22.70	C
ATOM	346	C	GLY	H	44	-5.786	0.804	21.390	1.00	22.77	C
ATOM	347	O	GLY	H	44	-6.223	1.229	20.315	1.00	22.66	O
ATOM	348	N	LEU	H	45	-5.467	1.581	22.420	1.00	21.61	N
ATOM	349	CA	LEU	H	45	-5.763	3.023	22.464	1.00	21.24	C
ATOM	350	CB	LEU	H	45	-6.370	3.353	23.820	1.00	20.85	C
ATOM	351	CG	LEU	H	45	-7.746	2.728	24.090	1.00	21.38	C
ATOM	352	CD1	LEU	H	45	-7.980	2.585	25.584	1.00	21.24	C
ATOM	353	CD2	LEU	H	45	-8.885	3.556	23.463	1.00	21.32	C
ATOM	354	C	LEU	H	45	-4.520	3.873	22.215	1.00	21.14	C
ATOM	355	O	LEU	H	45	-3.434	3.521	22.644	1.00	20.40	O
ATOM	356	N	GLU	H	46	-4.692	4.972	21.482	1.00	21.10	N
ATOM	357	CA	GLU	H	46	-3.620	5.924	21.205	1.00	21.00	C
ATOM	358	CB	GLU	H	46	-3.268	5.919	19.730	1.00	21.08	C
ATOM	359	CG	GLU	H	46	-2.715	4.610	19.204	1.00	23.69	C
ATOM	360	CD	GLU	H	46	-2.851	4.518	17.711	1.00	26.08	C
ATOM	361	OE1	GLU	H	46	-1.839	4.723	17.025	1.00	26.27	O
ATOM	362	OE2	GLU	H	46	-3.972	4.254	17.232	1.00	27.93	O
ATOM	363	C	GLU	H	46	-4.095	7.333	21.529	1.00	20.37	C
ATOM	364	O	GLU	H	46	-5.160	7.734	21.064	1.00	19.66	O
ATOM	365	N	TRP	H	47	-3.304	8.076	22.303	1.00	19.97	N
ATOM	366	CA	TRP	H	47	-3.628	9.473	22.599	1.00	19.08	C
ATOM	367	CB	TRP	H	47	-2.934	9.886	23.899	1.00	19.31	C
ATOM	368	CG	TRP	H	47	-3.146	11.339	24.306	1.00	18.27	C
ATOM	369	CD1	TRP	H	47	-4.204	11.862	24.999	1.00	18.96	C
ATOM	370	NE1	TRP	H	47	-4.014	13.227	25.190	1.00	18.10	N
ATOM	371	CE2	TRP	H	47	-2.824	13.589	24.617	1.00	18.50	C
ATOM	372	CD2	TRP	H	47	-2.250	12.423	24.051	1.00	18.26	C
ATOM	373	CE3	TRP	H	47	-1.008	12.520	23.411	1.00	16.45	C
ATOM	374	CZ3	TRP	H	47	-0.373	13.772	23.352	1.00	20.21	C
ATOM	375	CH2	TRP	H	47	-0.975	14.912	23.912	1.00	18.14	C
ATOM	376	CZ2	TRP	H	47	-2.190	14.842	24.559	1.00	18.88	C
ATOM	377	C	TRP	H	47	-3.184	10.371	21.417	1.00	19.51	C
ATOM	378	O	TRP	H	47	-2.014	10.365	21.013	1.00	19.44	O
ATOM	379	N	MET	H	48	-4.130	11.112	20.840	1.00	19.18	N
ATOM	380	CA	MET	H	48	-3.830	11.916	19.662	1.00	20.22	C
ATOM	381	CB	MET	H	48	-5.046	11.980	18.727	1.00	19.65	C
ATOM	382	CG	MET	H	48	-5.526	10.613	18.191	1.00	20.25	C
ATOM	383	SD	MET	H	48	-7.103	10.767	17.325	1.00	21.59	S
ATOM	384	CE	MET	H	48	-6.496	11.433	15.792	1.00	22.51	C
ATOM	385	C	MET	H	48	-3.422	13.352	20.020	1.00	19.82	C
ATOM	386	O	MET	H	48	-2.567	13.932	19.364	1.00	20.50	O
ATOM	387	N	GLY	H	49	-4.069	13.921	21.030	1.00	19.62	N
ATOM	388	CA	GLY	H	49	-3.839	15.335	21.379	1.00	19.20	C
ATOM	389	C	GLY	H	49	-4.916	15.829	22.303	1.00	18.84	C
ATOM	390	O	GLY	H	49	-5.830	15.094	22.635	1.00	18.62	O
ATOM	391	N	ALA	H	50	-4.821	17.095	22.718	1.00	18.40	N
ATOM	392	CA	ALA	H	50	-5.733	17.657	23.686	1.00	18.14	C
ATOM	393	CB	ALA	H	50	-5.247	17.391	25.142	1.00	17.40	C
ATOM	394	C	ALA	H	50	-5.851	19.160	23.466	1.00	17.98	C
ATOM	395	O	ALA	H	50	-5.010	19.753	22.802	1.00	18.59	O
ATOM	396	N	ILE	H	51	-6.901	19.728	24.034	1.00	18.98	N
ATOM	397	CA	ILE	H	51	-7.151	21.188	23.995	1.00	19.51	C
ATOM	398	CB	ILE	H	51	-8.209	21.591	22.902	1.00	19.52	C
ATOM	399	CG1	ILE	H	51	-8.291	23.133	22.772	1.00	20.57	C
ATOM	400	CD1	ILE	H	51	-8.726	23.604	21.416	1.00	21.15	C

ATOM	401	CG2 ILE H 51	-9.619	20.977	23.204	1.00	19.78	C
ATOM	402	C ILE H 51	-7.635	21.660	25.345	1.00	19.52	C
ATOM	403	O ILE H 51	-8.419	20.975	26.003	1.00	19.63	O
ATOM	404	N SER H 52	-7.153	22.845	25.756	1.00	19.90	N
ATOM	405	CA SER H 52	-7.757	23.605	26.844	1.00	20.20	C
ATOM	406	CB SER H 52	-6.671	24.272	27.721	1.00	19.83	C
ATOM	407	OG SER H 52	-7.265	25.104	28.725	1.00	21.34	O
ATOM	408	C SER H 52	-8.633	24.692	26.212	1.00	20.90	C
ATOM	409	O SER H 52	-8.097	25.660	25.654	1.00	20.66	O
ATOM	410	N PRO H 52A	-9.967	24.525	26.266	1.00	21.94	N
ATOM	411	CA PRO H 52A	-10.844	25.599	25.768	1.00	22.43	C
ATOM	412	CB PRO H 52A	-12.258	25.053	25.986	1.00	22.92	C
ATOM	413	CG PRO H 52A	-12.120	23.841	26.882	1.00	22.95	C
ATOM	414	CD PRO H 52A	-10.716	23.349	26.757	1.00	21.85	C
ATOM	415	C PRO H 52A	-10.650	26.953	26.498	1.00	23.25	C
ATOM	416	O PRO H 52A	-10.780	27.995	25.863	1.00	22.08	O
ATOM	417	N ARG H 53	-10.340	26.922	27.799	1.00	23.83	N
ATOM	418	CA ARG H 53	-10.078	28.143	28.585	1.00	25.36	C
ATOM	419	CB ARG H 53	-9.788	27.798	30.055	1.00	24.39	C
ATOM	420	CG ARG H 53	-9.525	29.012	30.954	1.00	25.38	C
ATOM	421	CD ARG H 53	-9.151	28.618	32.369	1.00	26.50	C
ATOM	422	NE ARG H 53	-10.290	28.140	33.155	1.00	29.56	N
ATOM	423	CZ ARG H 53	-11.072	28.915	33.904	1.00	31.94	C
ATOM	424	NH1 ARG H 53	-10.871	30.229	33.965	1.00	32.57	N
ATOM	425	NH2 ARG H 53	-12.069	28.374	34.596	1.00	31.70	N
ATOM	426	C ARG H 53	-8.917	28.955	28.000	1.00	25.47	C
ATOM	427	O ARG H 53	-9.023	30.172	27.855	1.00	26.34	O
ATOM	428	N HIS H 54	-7.814	28.284	27.668	1.00	25.20	N
ATOM	429	CA HIS H 54	-6.591	28.956	27.221	1.00	25.28	C
ATOM	430	CB HIS H 54	-5.377	28.375	27.955	1.00	25.10	C
ATOM	431	CG HIS H 54	-5.506	28.431	29.443	1.00	26.18	C
ATOM	432	ND1 HIS H 54	-5.359	29.605	30.154	1.00	24.75	N
ATOM	433	CE1 HIS H 54	-5.539	29.363	31.442	1.00	25.53	C
ATOM	434	NE2 HIS H 54	-5.796	28.076	31.591	1.00	27.14	N
ATOM	435	CD2 HIS H 54	-5.776	27.468	30.355	1.00	25.07	C
ATOM	436	C HIS H 54	-6.329	28.945	25.722	1.00	25.76	C
ATOM	437	O HIS H 54	-5.335	29.533	25.265	1.00	25.49	O
ATOM	438	N ASP H 55	-7.199	28.259	24.973	1.00	25.84	N
ATOM	439	CA ASP H 55	-7.044	28.022	23.541	1.00	27.14	C
ATOM	440	CB ASP H 55	-7.384	29.275	22.700	1.00	28.37	C
ATOM	441	CG ASP H 55	-7.526	28.968	21.202	1.00	33.43	C
ATOM	442	OD1 ASP H 55	-7.271	29.882	20.387	1.00	40.89	O
ATOM	443	OD2 ASP H 55	-7.885	27.826	20.829	1.00	38.48	O
ATOM	444	C ASP H 55	-5.668	27.475	23.210	1.00	26.39	C
ATOM	445	O ASP H 55	-5.001	27.940	22.279	1.00	26.74	O
ATOM	446	N ILE H 56	-5.246	26.483	23.993	1.00	25.14	N
ATOM	447	CA ILE H 56	-3.962	25.833	23.799	1.00	24.78	C
ATOM	448	CB ILE H 56	-3.087	25.971	25.071	1.00	24.55	C
ATOM	449	CG1 ILE H 56	-2.476	27.385	25.119	1.00	24.60	C
ATOM	450	CD1 ILE H 56	-1.727	27.697	26.396	1.00	25.61	C
ATOM	451	CG2 ILE H 56	-1.987	24.921	25.110	1.00	24.01	C
ATOM	452	C ILE H 56	-4.185	24.351	23.437	1.00	23.99	C
ATOM	453	O ILE H 56	-4.974	23.684	24.074	1.00	23.30	O
ATOM	454	N THR H 57	-3.482	23.881	22.418	1.00	23.55	N
ATOM	455	CA THR H 57	-3.577	22.492	21.969	1.00	23.91	C
ATOM	456	CB THR H 57	-3.972	22.384	20.497	1.00	23.75	C
ATOM	457	OG1 THR H 57	-3.122	23.237	19.727	1.00	26.43	O

ATOM	458	CG2 THR H 57	-5.383	22.808	20.285	1.00	20.62	C
ATOM	459	C THR H 57	-2.226	21.824	22.126	1.00	24.19	C
ATOM	460	O THR H 57	-1.171	22.466	22.013	1.00	24.02	O
ATOM	461	N LYS H 58	-2.260	20.526	22.400	1.00	23.98	N
ATOM	462	CA LYS H 58	-1.057	19.717	22.429	1.00	24.31	C
ATOM	463	CB LYS H 58	-0.759	19.312	23.880	1.00	25.72	C
ATOM	464	CG LYS H 58	-0.289	20.498	24.785	1.00	27.05	C
ATOM	465	CD LYS H 58	1.240	20.599	24.767	1.00	33.87	C
ATOM	466	CE LYS H 58	1.747	22.003	24.462	1.00	39.38	C
ATOM	467	NZ LYS H 58	1.499	23.077	25.486	1.00	42.38	N
ATOM	468	C LYS H 58	-1.326	18.506	21.536	1.00	24.26	C
ATOM	469	O LYS H 58	-2.452	17.993	21.519	1.00	23.62	O
ATOM	470	N TYR H 59	-0.330	18.088	20.758	1.00	23.87	N
ATOM	471	CA TYR H 59	-0.495	16.924	19.883	1.00	24.59	C
ATOM	472	CB TYR H 59	-0.445	17.326	18.413	1.00	24.48	C
ATOM	473	CG TYR H 59	-1.539	18.267	17.967	1.00	22.65	C
ATOM	474	CD1 TYR H 59	-1.370	19.659	18.048	1.00	24.35	C
ATOM	475	CE1 TYR H 59	-2.387	20.539	17.630	1.00	22.93	C
ATOM	476	CZ TYR H 59	-3.569	20.023	17.114	1.00	24.21	C
ATOM	477	OH TYR H 59	-4.568	20.862	16.700	1.00	23.71	O
ATOM	478	CE2 TYR H 59	-3.764	18.636	17.019	1.00	23.44	C
ATOM	479	CD2 TYR H 59	-2.743	17.771	17.430	1.00	22.27	C
ATOM	480	C TYR H 59	0.582	15.878	20.123	1.00	25.43	C
ATOM	481	O TYR H 59	1.727	16.201	20.449	1.00	25.60	O
ATOM	482	N ASN H 60	0.206	14.618	19.951	1.00	25.86	N
ATOM	483	CA ASN H 60	1.170	13.544	19.830	1.00	26.42	C
ATOM	484	CB ASN H 60	0.404	12.218	19.823	1.00	25.58	C
ATOM	485	CG ASN H 60	1.303	10.992	19.856	1.00	25.68	C
ATOM	486	OD1 ASN H 60	2.436	11.005	19.371	1.00	26.23	O
ATOM	487	ND2 ASN H 60	0.772	9.902	20.411	1.00	23.21	N
ATOM	488	C ASN H 60	1.911	13.771	18.510	1.00	28.01	C
ATOM	489	O ASN H 60	1.282	13.996	17.474	1.00	26.72	O
ATOM	490	N GLU H 61	3.241	13.720	18.556	1.00	30.75	N
ATOM	491	CA GLU H 61	4.100	13.916	17.376	1.00	34.52	C
ATOM	492	CB GLU H 61	5.566	13.610	17.733	1.00	34.43	C
ATOM	493	CG GLU H 61	6.576	13.753	16.584	1.00	38.56	C
ATOM	494	CD GLU H 61	8.013	13.309	16.965	1.00	39.74	C
ATOM	495	OE1 GLU H 61	8.233	12.872	18.132	1.00	46.54	O
ATOM	496	OE2 GLU H 61	8.921	13.394	16.093	1.00	46.38	O
ATOM	497	C GLU H 61	3.644	13.071	16.184	1.00	35.00	C
ATOM	498	O GLU H 61	3.698	13.524	15.032	1.00	34.51	O
ATOM	499	N METH 62	3.168	11.853	16.443	1.00	36.28	N
ATOM	500	CA METH 62	2.731	11.007	15.323	1.00	38.37	C
ATOM	501	CB METH 62	2.710	9.505	15.680	1.00	38.91	C
ATOM	502	CG METH 62	1.509	8.958	16.440	1.00	40.52	C
ATOM	503	SD METH 62	1.330	7.150	16.117	1.00	44.64	S
ATOM	504	CE METH 62	0.603	6.541	17.654	1.00	43.64	C
ATOM	505	C METH 62	1.448	11.506	14.637	1.00	36.77	C
ATOM	506	O METH 62	1.172	11.125	13.509	1.00	36.60	O
ATOM	507	N PHE H 63	0.696	12.387	15.297	1.00	35.74	N
ATOM	508	CA PHE H 63	-0.534	12.942	14.702	1.00	35.04	C
ATOM	509	CB PHE H 63	-1.742	12.750	15.630	1.00	34.49	C
ATOM	510	CG PHE H 63	-2.121	11.315	15.823	1.00	33.12	C
ATOM	511	CD1 PHE H 63	-1.637	10.608	16.910	1.00	31.83	C
ATOM	512	CE1 PHE H 63	-1.964	9.261	17.100	1.00	32.15	C
ATOM	513	CZ PHE H 63	-2.779	8.612	16.181	1.00	32.86	C
ATOM	514	CE2 PHE H 63	-3.272	9.314	15.060	1.00	32.78	C

ATOM	515	CD2 PHE H	63	-2.934	10.663	14.888	1.00	33.26	C
ATOM	516	C PHE H	63	-0.433	14.408	14.297	1.00	35.24	C
ATOM	517	O PHE H	63	-1.314	14.917	13.618	1.00	34.45	O
ATOM	518	N ARG H	64	0.621	15.090	14.731	1.00	35.62	N
ATOM	519	CA ARG H	64	0.770	16.509	14.399	1.00	36.77	C
ATOM	520	CB ARG H	64	1.971	17.107	15.130	1.00	37.06	C
ATOM	521	CG ARG H	64	1.979	18.637	15.182	1.00	40.15	C
ATOM	522	CD ARG H	64	2.893	19.166	16.294	1.00	45.47	C
ATOM	523	NE ARG H	64	4.102	18.351	16.448	1.00	49.47	N
ATOM	524	CZ ARG H	64	4.454	17.691	17.557	1.00	50.64	C
ATOM	525	NH1 ARG H	64	3.707	17.746	18.659	1.00	49.02	N
ATOM	526	NH2 ARG H	64	5.577	16.979	17.561	1.00	51.00	N
ATOM	527	C ARG H	64	0.879	16.687	12.877	1.00	36.31	C
ATOM	528	O ARG H	64	1.615	15.964	12.217	1.00	36.49	O
ATOM	529	N GLY H	65	0.119	17.627	12.328	1.00	36.56	N
ATOM	530	CA GLY H	65	0.085	17.833	10.876	1.00	36.53	C
ATOM	531	C GLY H	65	-0.944	17.002	10.125	1.00	36.27	C
ATOM	532	O GLY H	65	-1.191	17.242	8.938	1.00	36.71	O
ATOM	533	N GLN H	66	-1.547	16.028	10.811	1.00	35.35	N
ATOM	534	CA GLN H	66	-2.563	15.149	10.222	1.00	34.31	C
ATOM	535	CB GLN H	66	-2.360	13.706	10.691	1.00	35.43	C
ATOM	536	CG GLN H	66	-0.928	13.224	10.682	1.00	39.28	C
ATOM	537	CD GLN H	66	-0.407	13.007	9.291	1.00	45.86	C
ATOM	538	OE1 GLN H	66	-1.034	12.315	8.478	1.00	48.61	O
ATOM	539	NE2 GLN H	66	0.749	13.599	8.996	1.00	48.43	N
ATOM	540	C GLN H	66	-3.953	15.568	10.639	1.00	32.49	C
ATOM	541	O GLN H	66	-4.919	15.377	9.898	1.00	31.84	O
ATOM	542	N VAL H	67	-4.051	16.125	11.846	1.00	30.26	N
ATOM	543	CA VAL H	67	-5.330	16.507	12.432	1.00	28.34	C
ATOM	544	CB VAL H	67	-5.835	15.451	13.483	1.00	28.58	C
ATOM	545	CG1 VAL H	67	-6.095	14.090	12.822	1.00	26.58	C
ATOM	546	CG2 VAL H	67	-4.857	15.313	14.643	1.00	25.70	C
ATOM	547	C VAL H	67	-5.259	17.876	13.117	1.00	27.39	C
ATOM	548	O VAL H	67	-4.183	18.344	13.469	1.00	27.12	O
ATOM	549	N THR H	68	-6.421	18.484	13.307	1.00	26.62	N
ATOM	550	CA THR H	68	-6.552	19.694	14.093	1.00	25.79	C
ATOM	551	CB THR H	68	-6.890	20.927	13.196	1.00	26.17	C
ATOM	552	OG1 THR H	68	-5.866	21.070	12.219	1.00	27.51	O
ATOM	553	CG2 THR H	68	-6.956	22.200	14.010	1.00	25.71	C
ATOM	554	C THR H	68	-7.625	19.517	15.130	1.00	24.83	C
ATOM	555	O THR H	68	-8.741	19.069	14.835	1.00	24.40	O
ATOM	556	N ILE H	69	-7.287	19.907	16.353	1.00	23.61	N
ATOM	557	CA ILE H	69	-8.213	19.878	17.455	1.00	23.03	C
ATOM	558	CB ILE H	69	-7.566	19.203	18.705	1.00	22.67	C
ATOM	559	CG1 ILE H	69	-7.236	17.730	18.369	1.00	22.16	C
ATOM	560	CD1 ILE H	69	-6.231	17.042	19.348	1.00	21.67	C
ATOM	561	CG2 ILE H	69	-8.498	19.278	19.893	1.00	22.81	C
ATOM	562	C ILE H	69	-8.592	21.327	17.731	1.00	23.85	C
ATOM	563	O ILE H	69	-7.728	22.203	17.695	1.00	23.84	O
ATOM	564	N SER H	70	-9.873	21.564	17.976	1.00	23.98	N
ATOM	565	CA SER H	70	-10.371	22.906	18.235	1.00	25.09	C
ATOM	566	CB SER H	70	-10.766	23.566	16.904	1.00	25.50	C
ATOM	567	OG SER H	70	-11.852	22.870	16.315	1.00	25.49	O
ATOM	568	C SER H	70	-11.546	22.810	19.202	1.00	25.59	C
ATOM	569	O SER H	70	-11.982	21.704	19.533	1.00	24.80	O
ATOM	570	N ALA H	71	-12.058	23.953	19.668	1.00	25.99	N
ATOM	571	CA ALA H	71	-13.178	23.992	20.616	1.00	27.17	C

ATOM	572	CB	ALA	H	71	-12.676	23.979	22.050	1.00	26.99	C
ATOM	573	C	ALA	H	71	-14.034	25.232	20.401	1.00	28.64	C
ATOM	574	O	ALA	H	71	-13.547	26.243	19.916	1.00	28.68	O
ATOM	575	N	ASP	H	72	-15.302	25.140	20.775	1.00	29.78	N
ATOM	576	CA	ASP	H	72	-16.198	26.281	20.774	1.00	31.70	C
ATOM	577	CB	ASP	H	72	-17.315	26.066	19.738	1.00	32.28	C
ATOM	578	CG	ASP	H	72	-18.367	27.191	19.733	1.00	36.32	C
ATOM	579	OD1	ASP	H	72	-19.538	26.910	19.394	1.00	40.31	O
ATOM	580	OD2	ASP	H	72	-18.038	28.346	20.051	1.00	39.31	O
ATOM	581	C	ASP	H	72	-16.748	26.385	22.192	1.00	31.78	C
ATOM	582	O	ASP	H	72	-17.543	25.540	22.623	1.00	31.34	O
ATOM	583	N	LYS	H	73	-16.305	27.413	22.919	1.00	32.21	N
ATOM	584	CA	LYS	H	73	-16.736	27.644	24.297	1.00	32.98	C
ATOM	585	CB	LYS	H	73	-15.997	28.847	24.911	1.00	33.75	C
ATOM	586	CG	LYS	H	73	-14.515	28.628	25.175	1.00	35.44	C
ATOM	587	CD	LYS	H	73	-13.962	29.671	26.140	1.00	39.58	C
ATOM	588	CE	LYS	H	73	-13.656	31.014	25.479	1.00	41.99	C
ATOM	589	NZ	LYS	H	73	-12.319	31.023	24.818	1.00	46.35	N
ATOM	590	C	LYS	H	73	-18.229	27.874	24.423	1.00	33.30	C
ATOM	591	O	LYS	H	73	-18.834	27.466	25.418	1.00	33.09	O
ATOM	592	N	SER	H	74	-18.828	28.531	23.426	1.00	33.94	N
ATOM	593	CA	SER	H	74	-20.250	28.895	23.500	1.00	34.69	C
ATOM	594	CB	SER	H	74	-20.663	29.844	22.361	1.00	35.24	C
ATOM	595	OG	SER	H	74	-20.528	29.242	21.079	1.00	37.48	O
ATOM	596	C	SER	H	74	-21.176	27.678	23.579	1.00	34.41	C
ATOM	597	O	SER	H	74	-22.167	27.698	24.320	1.00	34.61	O
ATOM	598	N	SER	H	75	-20.832	26.614	22.847	1.00	33.51	N
ATOM	599	CA	SER	H	75	-21.626	25.373	22.852	1.00	32.85	C
ATOM	600	CB	SER	H	75	-21.825	24.897	21.424	1.00	33.09	C
ATOM	601	OG	SER	H	75	-20.566	24.769	20.794	1.00	34.11	O
ATOM	602	C	SER	H	75	-21.001	24.229	23.666	1.00	32.29	C
ATOM	603	O	SER	H	75	-21.533	23.112	23.666	1.00	32.16	O
ATOM	604	N	SER	H	76	-19.895	24.516	24.358	1.00	31.01	N
ATOM	605	CA	SER	H	76	-19.108	23.512	25.094	1.00	30.01	C
ATOM	606	CB	SER	H	76	-19.837	23.051	26.352	1.00	30.17	C
ATOM	607	OG	SER	H	76	-20.098	24.143	27.195	1.00	30.59	O
ATOM	608	C	SER	H	76	-18.756	22.306	24.219	1.00	29.30	C
ATOM	609	O	SER	H	76	-18.927	21.164	24.636	1.00	28.66	O
ATOM	610	N	THR	H	77	-18.258	22.571	23.013	1.00	28.30	N
ATOM	611	CA	THR	H	77	-17.980	21.501	22.046	1.00	28.11	C
ATOM	612	CB	THR	H	77	-18.857	21.643	20.758	1.00	28.16	C
ATOM	613	OG1	THR	H	77	-20.242	21.663	21.119	1.00	27.56	O
ATOM	614	CG2	THR	H	77	-18.639	20.478	19.808	1.00	27.91	C
ATOM	615	C	THR	H	77	-16.501	21.494	21.671	1.00	27.52	C
ATOM	616	O	THR	H	77	-15.923	22.549	21.422	1.00	27.43	O
ATOM	617	N	ALA	H	78	-15.901	20.304	21.651	1.00	26.15	N
ATOM	618	CA	ALA	H	78	-14.560	20.090	21.106	1.00	25.60	C
ATOM	619	CB	ALA	H	78	-13.730	19.240	22.092	1.00	25.33	C
ATOM	620	C	ALA	H	78	-14.665	19.368	19.764	1.00	24.99	C
ATOM	621	O	ALA	H	78	-15.617	18.620	19.559	1.00	25.17	O
ATOM	622	N	TYR	H	79	-13.682	19.561	18.884	1.00	24.68	N
ATOM	623	CA	TYR	H	79	-13.717	19.024	17.522	1.00	25.32	C
ATOM	624	CB	TYR	H	79	-14.007	20.126	16.474	1.00	26.65	C
ATOM	625	CG	TYR	H	79	-15.297	20.880	16.698	1.00	28.05	C
ATOM	626	CD1	TYR	H	79	-16.515	20.423	16.174	1.00	28.19	C
ATOM	627	CE1	TYR	H	79	-17.707	21.117	16.408	1.00	29.27	C
ATOM	628	CZ	TYR	H	79	-17.672	22.302	17.154	1.00	31.24	C

ATOM	629	OH	TYR	H	79	-18.812	23.025	17.425	1.00	30.75	O
ATOM	630	CE2	TYR	H	79	-16.476	22.768	17.674	1.00	31.16	C
ATOM	631	CD2	TYR	H	79	-15.300	22.061	17.437	1.00	29.27	C
ATOM	632	C	TYR	H	79	-12.387	18.381	17.179	1.00	24.83	C
ATOM	633	O	TYR	H	79	-11.345	18.785	17.682	1.00	23.84	O
ATOM	634	N	LEU	H	80	-12.441	17.387	16.300	1.00	24.37	N
ATOM	635	CA	LEU	H	80	-11.264	16.768	15.727	1.00	24.57	C
ATOM	636	CB	LEU	H	80	-11.087	15.321	16.244	1.00	24.32	C
ATOM	637	CG	LEU	H	80	-9.958	14.446	15.682	1.00	23.62	C
ATOM	638	CD1	LEU	H	80	-8.576	15.003	15.989	1.00	22.28	C
ATOM	639	CD2	LEU	H	80	-10.081	12.999	16.239	1.00	23.71	C
ATOM	640	C	LEU	H	80	-11.472	16.759	14.224	1.00	25.52	C
ATOM	641	O	LEU	H	80	-12.514	16.305	13.744	1.00	25.36	O
ATOM	642	N	GLN	H	81	-10.489	17.241	13.473	1.00	26.70	N
ATOM	643	CA	GLN	H	81	-10.675	17.336	12.032	1.00	27.87	C
ATOM	644	CB	GLN	H	81	-11.206	18.721	11.597	1.00	28.22	C
ATOM	645	CG	GLN	H	81	-10.238	19.862	11.703	1.00	30.77	C
ATOM	646	CD	GLN	H	81	-10.907	21.212	11.412	1.00	31.42	C
ATOM	647	OE1	GLN	H	81	-11.422	21.433	10.314	1.00	37.62	O
ATOM	648	NE2	GLN	H	81	-10.907	22.102	12.395	1.00	33.52	N
ATOM	649	C	GLN	H	81	-9.483	16.922	11.213	1.00	27.02	C
ATOM	650	O	GLN	H	81	-8.337	17.121	11.609	1.00	27.62	O
ATOM	651	N	TRP	H	82	-9.790	16.344	10.053	1.00	26.86	N
ATOM	652	CA	TRP	H	82	-8.814	15.973	9.048	1.00	26.74	C
ATOM	653	CB	TRP	H	82	-8.977	14.510	8.672	1.00	25.81	C
ATOM	654	CG	TRP	H	82	-8.683	13.502	9.751	1.00	24.27	C
ATOM	655	CD1	TRP	H	82	-7.538	12.778	9.896	1.00	24.74	C
ATOM	656	NE1	TRP	H	82	-7.654	11.926	10.979	1.00	24.05	N
ATOM	657	CE2	TRP	H	82	-8.893	12.082	11.540	1.00	23.91	C
ATOM	658	CD2	TRP	H	82	-9.579	13.056	10.785	1.00	23.94	C
ATOM	659	CE3	TRP	H	82	-10.890	13.388	11.149	1.00	24.81	C
ATOM	660	CZ3	TRP	H	82	-11.467	12.736	12.248	1.00	24.47	C
ATOM	661	CH2	TRP	H	82	-10.755	11.787	12.967	1.00	24.28	C
ATOM	662	CZ2	TRP	H	82	-9.474	11.435	12.624	1.00	24.65	C
ATOM	663	C	TRP	H	82	-9.136	16.772	7.797	1.00	28.23	C
ATOM	664	O	TRP	H	82	-10.318	16.959	7.456	1.00	27.86	O
ATOM	665	N	SER	H	82A	-8.113	17.201	7.074	1.00	29.58	N
ATOM	666	CA	SER	H	82A	-8.393	17.887	5.815	1.00	31.68	C
ATOM	667	CB	SER	H	82A	-7.438	19.063	5.584	1.00	31.62	C
ATOM	668	OG	SER	H	82A	-6.117	18.594	5.416	1.00	33.95	O
ATOM	669	C	SER	H	82A	-8.352	16.901	4.655	1.00	32.04	C
ATOM	670	O	SER	H	82A	-8.986	17.130	3.641	1.00	32.80	O
ATOM	671	N	SER	H	82B	-7.642	15.787	4.831	1.00	32.68	N
ATOM	672	CA	SER	H	82B	-7.540	14.761	3.797	1.00	33.19	C
ATOM	673	CB	SER	H	82B	-6.352	15.064	2.889	1.00	33.52	C
ATOM	674	OG	SER	H	82B	-6.265	14.130	1.841	1.00	35.84	O
ATOM	675	C	SER	H	82B	-7.409	13.349	4.383	1.00	32.57	C
ATOM	676	O	SER	H	82B	-6.304	12.898	4.706	1.00	32.57	O
ATOM	677	N	LEU	H	82C	-8.543	12.656	4.486	1.00	32.02	N
ATOM	678	CA	LEU	H	82C	-8.606	11.323	5.092	1.00	31.67	C
ATOM	679	CB	LEU	H	82C	-10.061	10.904	5.295	1.00	30.73	C
ATOM	680	CG	LEU	H	82C	-10.871	11.625	6.358	1.00	30.44	C
ATOM	681	CD1	LEU	H	82C	-12.331	11.356	6.103	1.00	27.28	C
ATOM	682	CD2	LEU	H	82C	-10.456	11.174	7.763	1.00	29.03	C
ATOM	683	C	LEU	H	82C	-7.892	10.250	4.285	1.00	32.21	C
ATOM	684	O	LEU	H	82C	-7.807	10.321	3.055	1.00	32.92	O
ATOM	685	N	LYS	H	83	-7.380	9.249	4.991	1.00	32.79	N

ATOM	686	CA	LYS	H	83	-6.767	8.084	4.376	1.00	33.09	C
ATOM	687	CB	LYS	H	83	-5.290	8.009	4.767	1.00	33.66	C
ATOM	688	CG	LYS	H	83	-4.369	8.913	3.948	1.00	37.58	C
ATOM	689	CD	LYS	H	83	-3.372	9.656	4.837	1.00	43.21	C
ATOM	690	CE	LYS	H	83	-2.239	8.766	5.344	1.00	46.43	C
ATOM	691	NZ	LYS	H	83	-1.539	9.373	6.540	1.00	47.70	N
ATOM	692	C	LYS	H	83	-7.517	6.834	4.859	1.00	32.46	C
ATOM	693	O	LYS	H	83	-8.169	6.877	5.908	1.00	31.45	O
ATOM	694	N	ALA	H	84	-7.423	5.731	4.106	1.00	32.09	N
ATOM	695	CA	ALA	H	84	-8.094	4.470	4.493	1.00	31.70	C
ATOM	696	CB	ALA	H	84	-7.794	3.350	3.466	1.00	31.55	C
ATOM	697	C	ALA	H	84	-7.657	4.045	5.899	1.00	31.04	C
ATOM	698	O	ALA	H	84	-8.452	3.521	6.691	1.00	31.31	O
ATOM	699	N	SER	H	85	-6.396	4.307	6.210	1.00	30.94	N
ATOM	700	CA	SER	H	85	-5.813	3.918	7.488	1.00	31.17	C
ATOM	701	CB	SER	H	85	-4.281	3.969	7.404	1.00	31.91	C
ATOM	702	OG	SER	H	85	-3.847	5.269	7.054	1.00	34.04	O
ATOM	703	C	SER	H	85	-6.317	4.745	8.682	1.00	29.89	C
ATOM	704	O	SER	H	85	-5.980	4.435	9.822	1.00	30.07	O
ATOM	705	N	ASP	H	86	-7.103	5.793	8.410	1.00	28.95	N
ATOM	706	CA	ASP	H	86	-7.806	6.566	9.446	1.00	27.90	C
ATOM	707	CB	ASP	H	86	-8.141	7.978	8.948	1.00	28.08	C
ATOM	708	CG	ASP	H	86	-6.905	8.831	8.756	1.00	29.88	C
ATOM	709	OD1	ASP	H	86	-6.869	9.630	7.792	1.00	31.11	O
ATOM	710	OD2	ASP	H	86	-5.953	8.692	9.554	1.00	30.83	O
ATOM	711	C	ASP	H	86	-9.074	5.876	9.937	1.00	26.85	C
ATOM	712	O	ASP	H	86	-9.720	6.347	10.872	1.00	25.17	O
ATOM	713	N	THR	H	87	-9.428	4.753	9.302	1.00	25.73	N
ATOM	714	CA	THR	H	87	-10.552	3.944	9.752	1.00	24.79	C
ATOM	715	CB	THR	H	87	-10.786	2.729	8.817	1.00	24.62	C
ATOM	716	OG1	THR	H	87	-11.123	3.212	7.512	1.00	24.59	O
ATOM	717	CG2	THR	H	87	-11.933	1.836	9.342	1.00	24.65	C
ATOM	718	C	THR	H	87	-10.296	3.471	11.188	1.00	24.56	C
ATOM	719	O	THR	H	87	-9.323	2.760	11.450	1.00	24.89	O
ATOM	720	N	ALA	H	88	-11.163	3.902	12.098	1.00	23.72	N
ATOM	721	CA	ALA	H	88	-11.004	3.645	13.526	1.00	23.95	C
ATOM	722	CB	ALA	H	88	-9.712	4.300	14.056	1.00	23.27	C
ATOM	723	C	ALA	H	88	-12.203	4.172	14.290	1.00	23.32	C
ATOM	724	O	ALA	H	88	-13.050	4.896	13.737	1.00	24.31	O
ATOM	725	N	MET	H	89	-12.282	3.805	15.563	1.00	22.27	N
ATOM	726	CA	MET	H	89	-13.170	4.444	16.510	1.00	21.63	C
ATOM	727	CB	MET	H	89	-13.566	3.470	17.624	1.00	21.36	C
ATOM	728	CG	MET	H	89	-14.638	4.031	18.581	1.00	24.67	C
ATOM	729	SD	MET	H	89	-16.300	4.186	17.875	1.00	31.34	S
ATOM	730	CE	MET	H	89	-16.745	2.473	17.607	1.00	29.47	C
ATOM	731	C	MET	H	89	-12.408	5.611	17.130	1.00	21.29	C
ATOM	732	O	MET	H	89	-11.233	5.466	17.476	1.00	21.53	O
ATOM	733	N	TYR	H	90	-13.091	6.739	17.298	1.00	20.67	N
ATOM	734	CA	TYR	H	90	-12.489	7.931	17.922	1.00	20.55	C
ATOM	735	CB	TYR	H	90	-12.431	9.104	16.928	1.00	20.48	C
ATOM	736	CG	TYR	H	90	-11.474	8.805	15.817	1.00	19.73	C
ATOM	737	CD1	TYR	H	90	-11.908	8.166	14.647	1.00	20.39	C
ATOM	738	CE1	TYR	H	90	-11.013	7.850	13.632	1.00	20.43	C
ATOM	739	CZ	TYR	H	90	-9.685	8.153	13.791	1.00	21.46	C
ATOM	740	OH	TYR	H	90	-8.770	7.840	12.819	1.00	19.76	O
ATOM	741	CE2	TYR	H	90	-9.234	8.782	14.949	1.00	21.51	C
ATOM	742	CD2	TYR	H	90	-10.133	9.087	15.949	1.00	19.44	C

ATOM	743	C	TYR	H	90	-13.252	8.279	19.173	1.00	20.31	C
ATOM	744	O	TYR	H	90	-14.483	8.346	19.173	1.00	20.79	O
ATOM	745	N	PHE	H	91	-12.510	8.457	20.268	1.00	20.49	N
ATOM	746	CA	PHE	H	91	-13.106	8.809	21.545	1.00	19.39	C
ATOM	747	CB	PHE	H	91	-12.697	7.804	22.613	1.00	19.61	C
ATOM	748	CG	PHE	H	91	-13.276	6.427	22.421	1.00	19.67	C
ATOM	749	CD1	PHE	H	91	-14.601	6.164	22.768	1.00	21.37	C
ATOM	750	CE1	PHE	H	91	-15.143	4.884	22.610	1.00	22.01	C
ATOM	751	CZ	PHE	H	91	-14.341	3.860	22.110	1.00	19.12	C
ATOM	752	CE2	PHE	H	91	-13.015	4.108	21.761	1.00	19.65	C
ATOM	753	CD2	PHE	H	91	-12.486	5.399	21.918	1.00	21.93	C
ATOM	754	C	PHE	H	91	-12.607	10.169	22.017	1.00	19.75	C
ATOM	755	O	PHE	H	91	-11.446	10.459	21.870	1.00	19.38	O
ATOM	756	N	CYS	H	92	-13.491	10.959	22.619	1.00	20.54	N
ATOM	757	CA	CYS	H	92	-13.067	12.111	23.416	1.00	21.81	C
ATOM	758	CB	CYS	H	92	-13.952	13.351	23.126	1.00	22.19	C
ATOM	759	SG	CYS	H	92	-15.684	13.126	23.574	1.00	27.12	S
ATOM	760	C	CYS	H	92	-13.124	11.703	24.898	1.00	21.09	C
ATOM	761	O	CYS	H	92	-13.922	10.826	25.288	1.00	21.10	O
ATOM	762	N	ALA	H	93	-12.271	12.315	25.727	1.00	20.26	N
ATOM	763	CA	ALA	H	93	-12.276	12.056	27.158	1.00	19.21	C
ATOM	764	CB	ALA	H	93	-11.305	10.882	27.479	1.00	19.04	C
ATOM	765	C	ALA	H	93	-11.833	13.312	27.921	1.00	19.60	C
ATOM	766	O	ALA	H	93	-11.046	14.095	27.395	1.00	18.50	O
ATOM	767	N	ARG	H	94	-12.300	13.471	29.154	1.00	18.93	N
ATOM	768	CA	ARG	H	94	-11.955	14.664	29.967	1.00	19.56	C
ATOM	769	CB	ARG	H	94	-13.138	15.024	30.878	1.00	19.56	C
ATOM	770	CG	ARG	H	94	-13.121	16.441	31.427	1.00	20.98	C
ATOM	771	CD	ARG	H	94	-14.304	16.669	32.373	1.00	21.44	C
ATOM	772	NE	ARG	H	94	-14.153	15.986	33.654	1.00	24.69	N
ATOM	773	CZ	ARG	H	94	-14.933	16.197	34.709	1.00	28.00	C
ATOM	774	NH1	ARG	H	94	-14.710	15.540	35.837	1.00	28.57	N
ATOM	775	NH2	ARG	H	94	-15.940	17.067	34.641	1.00	28.31	N
ATOM	776	C	ARG	H	94	-10.665	14.481	30.784	1.00	19.16	C
ATOM	777	O	ARG	H	94	-10.364	13.383	31.274	1.00	18.67	O
ATOM	778	N	GLY	H	95	-9.871	15.553	30.894	1.00	18.36	N
ATOM	779	CA	GLY	H	95	-8.692	15.558	31.758	1.00	19.06	C
ATOM	780	C	GLY	H	95	-8.437	16.913	32.422	1.00	19.30	C
ATOM	781	O	GLY	H	95	-9.297	17.812	32.417	1.00	18.33	O
ATOM	782	N	GLY	H	96	-7.237	17.058	32.975	1.00	19.80	N
ATOM	783	CA	GLY	H	96	-6.851	18.288	33.677	1.00	19.40	C
ATOM	784	C	GLY	H	96	-5.694	18.994	32.983	1.00	19.08	C
ATOM	785	O	GLY	H	96	-5.578	18.971	31.745	1.00	18.73	O
ATOM	786	N	PHE	H	97	-4.830	19.604	33.794	1.00	18.91	N
ATOM	787	CA	PHE	H	97	-3.744	20.447	33.310	1.00	20.23	C
ATOM	788	CB	PHE	H	97	-4.012	21.915	33.742	1.00	20.27	C
ATOM	789	CG	PHE	H	97	-5.352	22.437	33.290	1.00	20.73	C
ATOM	790	CD1	PHE	H	97	-6.496	22.181	34.028	1.00	21.65	C
ATOM	791	CE1	PHE	H	97	-7.742	22.646	33.590	1.00	23.51	C
ATOM	792	CZ	PHE	H	97	-7.841	23.376	32.421	1.00	20.05	C
ATOM	793	CE2	PHE	H	97	-6.724	23.633	31.675	1.00	22.58	C
ATOM	794	CD2	PHE	H	97	-5.469	23.168	32.114	1.00	22.91	C
ATOM	795	C	PHE	H	97	-2.404	19.962	33.866	1.00	20.81	C
ATOM	796	O	PHE	H	97	-2.347	18.892	34.484	1.00	21.28	O
ATOM	797	N	TYR	H	98	-1.322	20.723	33.668	1.00	20.56	N
ATOM	798	CA	TYR	H	98	-0.038	20.362	34.311	1.00	20.77	C
ATOM	799	CB	TYR	H	98	1.112	21.262	33.831	1.00	20.27	C

ATOM	800	CG TYR H 98	1.516	21.025	32.397	1.00	21.12	C
ATOM	801	CD1 TYR H 98	2.607	20.212	32.089	1.00	20.22	C
ATOM	802	CE1 TYR H 98	2.981	19.976	30.775	1.00	19.05	C
ATOM	803	CZ TYR H 98	2.251	20.550	29.731	1.00	19.82	C
ATOM	804	OH TYR H 98	2.638	20.311	28.424	1.00	20.79	O
ATOM	805	CE2 TYR H 98	1.154	21.350	30.003	1.00	20.25	C
ATOM	806	CD2 TYR H 98	0.783	21.583	31.336	1.00	19.94	C
ATOM	807	C TYR H 98	-0.201	20.418	35.823	1.00	21.37	C
ATOM	808	O TYR H 98	-0.651	21.429	36.368	1.00	21.85	O
ATOM	809	N GLY H 99	0.081	19.303	36.502	1.00	20.56	N
ATOM	810	CA GLY H 99	-0.216	19.179	37.914	1.00	19.82	C
ATOM	811	C GLY H 99	-1.441	18.372	38.311	1.00	18.93	C
ATOM	812	O GLY H 99	-1.549	17.964	39.457	1.00	20.35	O
ATOM	813	N SER H 100	-2.366	18.138	37.386	1.00	18.70	N
ATOM	814	CA SER H 100	-3.575	17.355	37.670	1.00	18.54	C
ATOM	815	CB SER H 100	-4.612	17.574	36.574	1.00	18.95	C
ATOM	816	OG SER H 100	-4.993	18.935	36.564	1.00	20.38	O
ATOM	817	C SER H 100	-3.263	15.846	37.742	1.00	18.25	C
ATOM	818	O SER H 100	-2.323	15.378	37.101	1.00	17.20	O
ATOM	819	N THR H 100A	-4.078	15.117	38.489	1.00	19.15	N
ATOM	820	CA THR H 100A	-3.743	13.722	38.831	1.00	19.94	C
ATOM	821	CB THR H 100A	-3.451	13.565	40.341	1.00	20.49	C
ATOM	822	OG1 THR H 100A	-4.590	13.970	41.100	1.00	21.87	O
ATOM	823	CG2 THR H 100A	-2.230	14.406	40.770	1.00	19.59	C
ATOM	824	C THR H 100A	-4.814	12.727	38.376	1.00	20.37	C
ATOM	825	O THR H 100A	-4.717	11.533	38.661	1.00	20.82	O
ATOM	826	N ILE H 100B	-5.858	13.228	37.713	1.00	20.20	N
ATOM	827	CA ILE H 100B	-6.967	12.375	37.253	1.00	20.92	C
ATOM	828	CB ILE H 100B	-8.320	12.656	37.969	1.00	21.22	C
ATOM	829	CG1 ILE H 100B	-8.207	12.473	39.484	1.00	21.37	C
ATOM	830	CD1 ILE H 100B	-9.414	12.953	40.252	1.00	22.49	C
ATOM	831	CG2 ILE H 100B	-9.454	11.786	37.417	1.00	20.48	C
ATOM	832	C ILE H 100B	-7.115	12.593	35.764	1.00	21.04	C
ATOM	833	O ILE H 100B	-7.264	13.746	35.315	1.00	21.10	O
ATOM	834	N TRP H 100C	-7.083	11.494	34.996	1.00	19.74	N
ATOM	835	CA TRP H 100C	-7.073	11.549	33.530	1.00	19.44	C
ATOM	836	CB TRP H 100C	-5.676	11.228	32.961	1.00	18.83	C
ATOM	837	CG TRP H 100C	-4.687	12.205	33.489	1.00	19.56	C
ATOM	838	CD1 TRP H 100C	-3.885	12.058	34.584	1.00	19.01	C
ATOM	839	NE1 TRP H 100C	-3.168	13.214	34.809	1.00	20.07	N
ATOM	840	CE2 TRP H 100C	-3.517	14.143	33.857	1.00	19.91	C
ATOM	841	CD2 TRP H 100C	-4.495	13.541	33.018	1.00	18.56	C
ATOM	842	CE3 TRP H 100C	-5.049	14.289	31.963	1.00	18.55	C
ATOM	843	CZ3 TRP H 100C	-4.581	15.614	31.757	1.00	18.91	C
ATOM	844	CH2 TRP H 100C	-3.605	16.182	32.612	1.00	18.30	C
ATOM	845	CZ2 TRP H 100C	-3.069	15.474	33.672	1.00	17.75	C
ATOM	846	C TRP H 100C	-8.106	10.597	32.948	1.00	20.31	C
ATOM	847	O TRP H 100C	-8.112	9.399	33.274	1.00	19.85	O
ATOM	848	N PHE H 100D	-8.980	11.154	32.109	1.00	20.09	N
ATOM	849	CA PHE H 100D	-9.959	10.392	31.307	1.00	20.47	C
ATOM	850	CB PHE H 100D	-9.270	9.411	30.317	1.00	19.92	C
ATOM	851	CG PHE H 100D	-8.035	9.956	29.657	1.00	20.69	C
ATOM	852	CD1 PHE H 100D	-6.963	9.112	29.368	1.00	18.73	C
ATOM	853	CE1 PHE H 100D	-5.800	9.600	28.743	1.00	21.25	C
ATOM	854	CZ PHE H 100D	-5.697	10.966	28.438	1.00	20.72	C
ATOM	855	CE2 PHE H 100D	-6.766	11.817	28.740	1.00	17.41	C
ATOM	856	CD2 PHE H 100D	-7.917	11.323	29.336	1.00	19.27	C

ATOM	857	C	PHE H 100D	-10.955	9.698	32.241	1.00	21.17	C
ATOM	858	O	PHE H 100D	-11.239	8.483	32.151	1.00	20.42	O
ATOM	859	N	ASP H 101	-11.495	10.487	33.163	1.00	21.62	N
ATOM	860	CA	ASP H 101	-12.515	9.983	34.059	1.00	22.26	C
ATOM	861	CB	ASP H 101	-12.570	10.757	35.389	1.00	22.69	C
ATOM	862	CG	ASP H 101	-12.701	12.270	35.221	1.00	23.79	C
ATOM	863	OD1	ASP H 101	-12.966	12.930	36.258	1.00	25.89	O
ATOM	864	OD2	ASP H 101	-12.550	12.791	34.105	1.00	23.90	O
ATOM	865	C	ASP H 101	-13.886	9.859	33.392	1.00	22.80	C
ATOM	866	O	ASP H 101	-14.648	8.970	33.742	1.00	22.68	O
ATOM	867	N	PHE H 102	-14.197	10.752	32.447	1.00	22.56	N
ATOM	868	CA	PHE H 102	-15.399	10.629	31.611	1.00	22.88	C
ATOM	869	CB	PHE H 102	-16.405	11.762	31.893	1.00	23.70	C
ATOM	870	CG	PHE H 102	-16.864	11.798	33.320	1.00	25.81	C
ATOM	871	CD1	PHE H 102	-16.164	12.550	34.273	1.00	26.95	C
ATOM	872	CE1	PHE H 102	-16.575	12.579	35.612	1.00	28.40	C
ATOM	873	CZ	PHE H 102	-17.693	11.835	36.003	1.00	28.10	C
ATOM	874	CE2	PHE H 102	-18.395	11.079	35.054	1.00	29.27	C
ATOM	875	CD2	PHE H 102	-17.973	11.060	33.722	1.00	28.21	C
ATOM	876	C	PHE H 102	-15.019	10.596	30.154	1.00	22.43	C
ATOM	877	O	PHE H 102	-14.091	11.312	29.728	1.00	22.22	O
ATOM	878	N	TRP H 103	-15.715	9.739	29.401	1.00	21.58	N
ATOM	879	CA	TRP H 103	-15.459	9.507	27.982	1.00	21.43	C
ATOM	880	CB	TRP H 103	-15.033	8.056	27.759	1.00	21.24	C
ATOM	881	CG	TRP H 103	-13.707	7.677	28.313	1.00	20.04	C
ATOM	882	CD1	TRP H 103	-13.351	7.569	29.642	1.00	20.11	C
ATOM	883	NE1	TRP H 103	-12.039	7.183	29.741	1.00	18.15	N
ATOM	884	CE2	TRP H 103	-11.523	7.035	28.483	1.00	15.71	C
ATOM	885	CD2	TRP H 103	-12.555	7.333	27.558	1.00	18.44	C
ATOM	886	CE3	TRP H 103	-12.292	7.225	26.181	1.00	17.68	C
ATOM	887	CZ3	TRP H 103	-11.014	6.838	25.777	1.00	19.23	C
ATOM	888	CH2	TRP H 103	-10.005	6.543	26.732	1.00	19.56	C
ATOM	889	CZ2	TRP H 103	-10.247	6.635	28.083	1.00	19.53	C
ATOM	890	C	TRP H 103	-16.738	9.694	27.196	1.00	21.67	C
ATOM	891	O	TRP H 103	-17.826	9.398	27.705	1.00	21.52	O
ATOM	892	N	GLY H 104	-16.618	10.177	25.957	1.00	22.19	N
ATOM	893	CA	GLY H 104	-17.738	10.121	25.019	1.00	22.32	C
ATOM	894	C	GLY H 104	-17.950	8.669	24.588	1.00	23.75	C
ATOM	895	O	GLY H 104	-17.154	7.779	24.921	1.00	22.16	O
ATOM	896	N	GLN H 105	-18.990	8.423	23.806	1.00	23.82	N
ATOM	897	CA	GLN H 105	-19.347	7.046	23.472	1.00	25.56	C
ATOM	898	CB	GLN H 105	-20.883	6.979	23.368	1.00	25.05	C
ATOM	899	CG	GLN H 105	-21.485	7.424	21.980	1.00	25.43	C
ATOM	900	CD	GLN H 105	-21.552	8.960	21.748	1.00	25.95	C
ATOM	901	OE1	GLN H 105	-21.002	9.756	22.516	1.00	22.95	O
ATOM	902	NE2	GLN H 105	-22.225	9.361	20.662	1.00	23.46	N
ATOM	903	C	GLN H 105	-18.822	6.339	22.211	1.00	25.66	C
ATOM	904	O	GLN H 105	-18.844	5.135	22.133	1.00	26.16	O
ATOM	905	N	GLY H 106	-18.405	6.995	21.151	1.00	26.76	N
ATOM	906	CA	GLY H 106	-17.143	7.443	20.731	1.00	24.57	C
ATOM	907	C	GLY H 106	-17.733	7.484	19.289	1.00	24.36	C
ATOM	908	O	GLY H 106	-18.957	7.344	19.129	1.00	24.17	O
ATOM	909	N	THR H 107	-16.926	7.705	18.257	1.00	24.35	N
ATOM	910	CA	THR H 107	-17.423	7.932	16.881	1.00	23.67	C
ATOM	911	CB	THR H 107	-17.213	9.428	16.453	1.00	23.39	C
ATOM	912	OG1	THR H 107	-18.047	10.264	17.259	1.00	22.54	O
ATOM	913	CG2	THR H 107	-17.547	9.646	14.977	1.00	22.82	C

ATOM	914	C	THR	H 107	-16.684	7.044	15.897	1.00	23.79	C
ATOM	915	O	THR	H 107	-15.465	7.154	15.750	1.00	23.39	O
ATOM	916	N	MET	H 108	-17.419	6.178	15.193	1.00	24.11	N
ATOM	917	CA	MET	H 108	-16.785	5.312	14.216	1.00	24.68	C
ATOM	918	CB	MET	H 108	-17.620	4.034	13.982	1.00	25.31	C
ATOM	919	CG	MET	H 108	-16.957	3.074	13.013	1.00	25.67	C
ATOM	920	SD	MET	H 108	-15.480	2.352	13.765	1.00	31.04	S
ATOM	921	CE	MET	H 108	-14.576	1.930	12.285	1.00	26.79	C
ATOM	922	C	MET	H 108	-16.582	6.064	12.892	1.00	24.93	C
ATOM	923	O	MET	H 108	-17.521	6.644	12.355	1.00	25.08	O
ATOM	924	N	VAL	H 109	-15.361	6.017	12.372	1.00	24.94	N
ATOM	925	CA	VAL	H 109	-15.031	6.603	11.082	1.00	24.92	C
ATOM	926	CB	VAL	H 109	-13.972	7.754	11.226	1.00	24.82	C
ATOM	927	CG1	VAL	H 109	-13.561	8.305	9.851	1.00	24.84	C
ATOM	928	CG2	VAL	H 109	-14.527	8.887	12.152	1.00	23.50	C
ATOM	929	C	VAL	H 109	-14.521	5.513	10.149	1.00	25.01	C
ATOM	930	O	VAL	H 109	-13.536	4.852	10.435	1.00	25.29	O
ATOM	931	N	THR	H 110	-15.204	5.333	9.024	1.00	25.18	N
ATOM	932	CA	THR	H 110	-14.780	4.392	8.006	1.00	25.22	C
ATOM	933	CB	THR	H 110	-15.946	3.451	7.607	1.00	25.30	C
ATOM	934	OG1	THR	H 110	-16.431	2.796	8.784	1.00	26.93	O
ATOM	935	CG2	THR	H 110	-15.478	2.401	6.590	1.00	26.14	C
ATOM	936	C	THR	H 110	-14.347	5.180	6.787	1.00	25.26	C
ATOM	937	O	THR	H 110	-15.093	6.030	6.298	1.00	25.33	O
ATOM	938	N	VAL	H 111	-13.150	4.890	6.306	1.00	25.59	N
ATOM	939	CA	VAL	H 111	-12.637	5.521	5.108	1.00	26.34	C
ATOM	940	CB	VAL	H 111	-11.347	6.337	5.354	1.00	26.10	C
ATOM	941	CG1	VAL	H 111	-10.950	7.063	4.077	1.00	26.10	C
ATOM	942	CG2	VAL	H 111	-11.534	7.333	6.511	1.00	26.25	C
ATOM	943	C	VAL	H 111	-12.363	4.450	4.067	1.00	26.72	C
ATOM	944	O	VAL	H 111	-11.513	3.577	4.257	1.00	26.43	O
ATOM	945	N	SER	H 112	-13.092	4.531	2.959	1.00	27.44	N
ATOM	946	CA	SER	H 112	-12.956	3.533	1.899	1.00	28.07	C
ATOM	947	CB	SER	H 112	-13.873	2.342	2.210	1.00	27.61	C
ATOM	948	OG	SER	H 112	-13.890	1.410	1.151	1.00	27.46	O
ATOM	949	C	SER	H 112	-13.298	4.119	0.531	1.00	28.87	C
ATOM	950	O	SER	H 112	-14.120	5.028	0.441	1.00	28.96	O
ATOM	951	N	SER	H 113	-12.682	3.565	-0.515	1.00	30.38	N
ATOM	952	CA	SER	H 113	-13.043	3.862	-1.916	1.00	32.37	C
ATOM	953	CB	SER	H 113	-12.031	3.230	-2.866	1.00	32.26	C
ATOM	954	OG	SER	H 113	-10.758	3.822	-2.700	1.00	37.30	O
ATOM	955	C	SER	H 113	-14.406	3.311	-2.293	1.00	32.51	C
ATOM	956	O	SER	H 113	-14.996	3.755	-3.274	1.00	33.02	O
ATOM	957	N	ALA	H 114	-14.902	2.341	-1.527	1.00	32.59	N
ATOM	958	CA	ALA	H 114	-16.164	1.677	-1.843	1.00	32.67	C
ATOM	959	CB	ALA	H 114	-16.388	0.473	-0.922	1.00	31.96	C
ATOM	960	C	ALA	H 114	-17.343	2.625	-1.768	1.00	32.93	C
ATOM	961	O	ALA	H 114	-17.279	3.651	-1.096	1.00	33.11	O
ATOM	962	N	SER	H 115	-18.410	2.283	-2.484	1.00	33.22	N
ATOM	963	CA	SER	H 115	-19.659	3.036	-2.441	1.00	33.87	C
ATOM	964	CB	SER	H 115	-20.079	3.488	-3.855	1.00	34.54	C
ATOM	965	OG	SER	H 115	-19.090	4.331	-4.451	1.00	37.30	O
ATOM	966	C	SER	H 115	-20.761	2.199	-1.819	1.00	33.28	C
ATOM	967	O	SER	H 115	-20.668	0.971	-1.785	1.00	33.30	O
ATOM	968	N	THR	H 116	-21.803	2.876	-1.343	1.00	33.15	N
ATOM	969	CA	THR	H 116	-22.969	2.241	-0.735	1.00	32.83	C
ATOM	970	CB	THR	H 116	-24.034	3.269	-0.391	1.00	33.36	C

ATOM	971	OG1 THR H 116	-23.449	4.287	0.432	1.00	34.31	O
ATOM	972	CG2 THR H 116	-25.226	2.623	0.347	1.00	33.36	C
ATOM	973	C THR H 116	-23.562	1.168	-1.641	1.00	32.82	C
ATOM	974	O THR H 116	-23.754	1.385	-2.841	1.00	32.60	O
ATOM	975	N LYS H 117	-23.812	0.000	-1.053	1.00	31.88	N
ATOM	976	CA LYS H 117	-24.313	-1.152	-1.788	1.00	31.29	C
ATOM	977	CB LYS H 117	-23.160	-1.879	-2.471	1.00	31.25	C
ATOM	978	CG LYS H 117	-23.628	-3.047	-3.326	1.00	34.57	C
ATOM	979	CD LYS H 117	-22.496	-3.714	-4.053	1.00	36.80	C
ATOM	980	CE LYS H 117	-22.988	-5.038	-4.614	1.00	41.23	C
ATOM	981	NZ LYS H 117	-22.609	-5.216	-6.050	1.00	45.90	N
ATOM	982	C LYS H 117	-25.063	-2.070	-0.820	1.00	30.69	C
ATOM	983	O LYS H 117	-24.535	-2.413	0.244	1.00	30.16	O
ATOM	984	N GLY H 118	-26.306	-2.415	-1.162	1.00	29.56	N
ATOM	985	CA GLY H 118	-27.098	-3.367	-0.380	1.00	28.50	C
ATOM	986	C GLY H 118	-26.624	-4.811	-0.545	1.00	28.00	C
ATOM	987	O GLY H 118	-26.021	-5.157	-1.557	1.00	27.57	O
ATOM	988	N PRO H 119	-26.888	-5.676	0.454	1.00	27.79	N
ATOM	989	CA PRO H 119	-26.423	-7.051	0.295	1.00	27.73	C
ATOM	990	CB PRO H 119	-26.459	-7.583	1.728	1.00	27.35	C
ATOM	991	CG PRO H 119	-27.572	-6.837	2.362	1.00	27.58	C
ATOM	992	CD PRO H 119	-27.580	-5.471	1.735	1.00	27.46	C
ATOM	993	C PRO H 119	-27.333	-7.916	-0.577	1.00	27.79	C
ATOM	994	O PRO H 119	-28.502	-7.593	-0.764	1.00	28.10	O
ATOM	995	N SER H 120	-26.774	-8.998	-1.106	1.00	28.21	N
ATOM	996	CA SER H 120	-27.550	-10.141	-1.573	1.00	27.55	C
ATOM	997	CB SER H 120	-26.804	-10.846	-2.688	1.00	28.20	C
ATOM	998	OG SER H 120	-26.735	-10.014	-3.830	1.00	30.35	O
ATOM	999	C SER H 120	-27.666	-11.077	-0.389	1.00	26.87	C
ATOM	1000	O SER H 120	-26.720	-11.198	0.395	1.00	26.59	O
ATOM	1001	N VAL H 121	-28.821	-11.716	-0.227	1.00	25.47	N
ATOM	1002	CA VAL H 121	-29.026	-12.635	0.895	1.00	23.54	C
ATOM	1003	CB VAL H 121	-30.213	-12.212	1.808	1.00	23.53	C
ATOM	1004	CG1 VAL H 121	-30.308	-13.118	3.029	1.00	21.62	C
ATOM	1005	CG2 VAL H 121	-30.063	-10.746	2.256	1.00	22.73	C
ATOM	1006	C VAL H 121	-29.225	-14.032	0.302	1.00	24.51	C
ATOM	1007	O VAL H 121	-30.157	-14.241	-0.496	1.00	23.74	O
ATOM	1008	N PHE H 122	-28.329	-14.964	0.650	1.00	23.39	N
ATOM	1009	CA PHE H 122	-28.404	-16.344	0.148	1.00	23.23	C
ATOM	1010	CB PHE H 122	-27.089	-16.719	-0.539	1.00	23.67	C
ATOM	1011	CG PHE H 122	-26.736	-15.819	-1.693	1.00	24.08	C
ATOM	1012	CD1 PHE H 122	-25.559	-15.081	-1.678	1.00	25.45	C
ATOM	1013	CE1 PHE H 122	-25.229	-14.234	-2.756	1.00	27.82	C
ATOM	1014	CZ PHE H 122	-26.099	-14.138	-3.851	1.00	25.47	C
ATOM	1015	CE2 PHE H 122	-27.289	-14.861	-3.856	1.00	24.66	C
ATOM	1016	CD2 PHE H 122	-27.600	-15.699	-2.792	1.00	24.63	C
ATOM	1017	C PHE H 122	-28.714	-17.329	1.280	1.00	23.57	C
ATOM	1018	O PHE H 122	-28.275	-17.107	2.400	1.00	23.32	O
ATOM	1019	N PRO H 123	-29.475	-18.419	0.995	1.00	23.83	N
ATOM	1020	CA PRO H 123	-29.785	-19.372	2.076	1.00	23.97	C
ATOM	1021	CB PRO H 123	-30.986	-20.160	1.527	1.00	24.41	C
ATOM	1022	CG PRO H 123	-30.773	-20.163	0.010	1.00	24.21	C
ATOM	1023	CD PRO H 123	-30.058	-18.832	-0.308	1.00	23.34	C
ATOM	1024	C PRO H 123	-28.608	-20.303	2.325	1.00	24.91	C
ATOM	1025	O PRO H 123	-27.863	-20.618	1.402	1.00	24.63	O
ATOM	1026	N LEU H 124	-28.423	-20.682	3.582	1.00	25.76	N
ATOM	1027	CA LEU H 124	-27.495	-21.727	3.975	1.00	26.78	C

ATOM	1028	CB	LEU	H 124	-26.572	-21.240	5.108	1.00	26.61	C
ATOM	1029	CG	LEU	H 124	-25.548	-20.138	4.765	1.00	25.91	C
ATOM	1030	CD1	LEU	H 124	-24.905	-19.550	6.025	1.00	25.76	C
ATOM	1031	CD2	LEU	H 124	-24.466	-20.656	3.839	1.00	24.98	C
ATOM	1032	C	LEU	H 124	-28.446	-22.828	4.426	1.00	27.92	C
ATOM	1033	O	LEU	H 124	-28.929	-22.832	5.546	1.00	26.89	O
ATOM	1034	N	ALA	H 125	-28.752	-23.742	3.509	1.00	30.27	N
ATOM	1035	CA	ALA	H 125	-29.903	-24.634	3.690	1.00	32.38	C
ATOM	1036	CB	ALA	H 125	-30.486	-25.048	2.316	1.00	32.30	C
ATOM	1037	C	ALA	H 125	-29.536	-25.855	4.526	1.00	33.90	C
ATOM	1038	O	ALA	H 125	-28.438	-26.398	4.374	1.00	34.04	O
ATOM	1039	N	PRO	H 126	-30.447	-26.291	5.417	1.00	35.72	N
ATOM	1040	CA	PRO	H 126	-30.135	-27.487	6.189	1.00	38.01	C
ATOM	1041	CB	PRO	H 126	-31.188	-27.481	7.306	1.00	37.37	C
ATOM	1042	CG	PRO	H 126	-32.342	-26.737	6.743	1.00	36.75	C
ATOM	1043	CD	PRO	H 126	-31.778	-25.743	5.747	1.00	35.68	C
ATOM	1044	C	PRO	H 126	-30.252	-28.749	5.316	1.00	40.39	C
ATOM	1045	O	PRO	H 126	-31.063	-28.805	4.384	1.00	40.40	O
ATOM	1046	N	SER	H 127	-29.407	-29.727	5.604	1.00	43.54	N
ATOM	1047	CA	SER	H 127	-29.399	-31.003	4.887	1.00	46.65	C
ATOM	1048	CB	SER	H 127	-28.566	-30.913	3.586	1.00	46.79	C
ATOM	1049	OG	SER	H 127	-27.160	-30.904	3.832	1.00	47.72	O
ATOM	1050	C	SER	H 127	-28.842	-32.041	5.854	1.00	48.58	C
ATOM	1051	O	SER	H 127	-28.900	-31.835	7.079	1.00	49.22	O
ATOM	1052	N	SER	H 128	-28.326	-33.153	5.321	1.00	50.65	N
ATOM	1053	CA	SER	H 128	-27.627	-34.161	6.146	1.00	52.23	C
ATOM	1054	CB	SER	H 128	-27.617	-35.533	5.451	1.00	52.16	C
ATOM	1055	OG	SER	H 128	-27.435	-35.400	4.049	1.00	53.02	O
ATOM	1056	C	SER	H 128	-26.202	-33.715	6.537	1.00	52.97	C
ATOM	1057	O	SER	H 128	-25.747	-33.979	7.661	1.00	53.12	O
ATOM	1058	N	LYS	H 129	-25.528	-33.027	5.608	1.00	53.97	N
ATOM	1059	CA	LYS	H 129	-24.178	-32.460	5.809	1.00	54.80	C
ATOM	1060	CB	LYS	H 129	-23.629	-31.908	4.480	1.00	54.91	C
ATOM	1061	CG	LYS	H 129	-22.903	-32.931	3.600	1.00	55.44	C
ATOM	1062	CD	LYS	H 129	-23.859	-33.880	2.847	1.00	56.96	C
ATOM	1063	CE	LYS	H 129	-23.106	-34.844	1.922	1.00	56.54	C
ATOM	1064	NZ	LYS	H 129	-22.134	-35.739	2.636	1.00	56.65	N
ATOM	1065	C	LYS	H 129	-24.169	-31.362	6.892	1.00	55.40	C
ATOM	1066	O	LYS	H 129	-23.096	-30.889	7.338	1.00	54.26	O
ATOM	1067	N	SER	H 130	-25.382	-30.967	7.291	1.00	56.23	N
ATOM	1068	CA	SER	H 130	-25.597	-30.001	8.363	1.00	57.08	C
ATOM	1069	CB	SER	H 130	-25.859	-28.585	7.797	1.00	56.98	C
ATOM	1070	OG	SER	H 130	-27.207	-28.396	7.405	1.00	57.41	O
ATOM	1071	C	SER	H 130	-26.698	-30.477	9.337	1.00	57.51	C
ATOM	1072	O	SER	H 130	-27.629	-29.732	9.660	1.00	57.43	O
ATOM	1073	N	THR	H 131	-26.565	-31.731	9.787	1.00	58.11	N
ATOM	1074	CA	THR	H 131	-27.422	-32.325	10.829	1.00	58.78	C
ATOM	1075	CB	THR	H 131	-28.639	-33.135	10.232	1.00	58.97	C
ATOM	1076	OG1	THR	H 131	-29.546	-32.248	9.560	1.00	59.44	O
ATOM	1077	CG2	THR	H 131	-29.407	-33.906	11.328	1.00	58.69	C
ATOM	1078	C	THR	H 131	-26.571	-33.215	11.754	1.00	58.96	C
ATOM	1079	O	THR	H 131	-26.413	-34.414	11.507	1.00	59.33	O
ATOM	1080	N	SER	H 132	-26.026	-32.614	12.814	1.00	59.12	N
ATOM	1081	CA	SER	H 132	-25.125	-33.309	13.753	1.00	58.99	C
ATOM	1082	CB	SER	H 132	-24.565	-32.327	14.801	1.00	59.18	C
ATOM	1083	OG	SER	H 132	-23.524	-32.917	15.575	1.00	59.96	O
ATOM	1084	C	SER	H 132	-25.787	-34.533	14.419	1.00	58.41	C

ATOM	1085	O	SER H 132	-25.517	-35.679	14.031	1.00	58.99	O
ATOM	1086	N	GLY H 133	-26.645	-34.302	15.412	1.00	57.26	N
ATOM	1087	CA	GLY H 133	-27.368	-35.404	16.051	1.00	55.37	C
ATOM	1088	C	GLY H 133	-28.810	-35.332	15.601	1.00	53.80	C
ATOM	1089	O	GLY H 133	-29.123	-35.561	14.415	1.00	54.40	O
ATOM	1090	N	GLY H 134	-29.688	-35.004	16.547	1.00	51.66	N
ATOM	1091	CA	GLY H 134	-31.030	-34.536	16.211	1.00	48.65	C
ATOM	1092	C	GLY H 134	-31.014	-33.016	16.069	1.00	46.25	C
ATOM	1093	O	GLY H 134	-32.036	-32.360	16.270	1.00	45.87	O
ATOM	1094	N	THR H 135	-29.839	-32.465	15.742	1.00	43.80	N
ATOM	1095	CA	THR H 135	-29.645	-31.014	15.568	1.00	41.05	C
ATOM	1096	CB	THR H 135	-28.542	-30.461	16.509	1.00	41.28	C
ATOM	1097	OG1	THR H 135	-29.012	-30.492	17.859	1.00	42.36	O
ATOM	1098	CG2	THR H 135	-28.182	-29.015	16.164	1.00	40.80	C
ATOM	1099	C	THR H 135	-29.283	-30.682	14.136	1.00	38.89	C
ATOM	1100	O	THR H 135	-28.346	-31.251	13.573	1.00	39.04	O
ATOM	1101	N	ALA H 136	-30.035	-29.759	13.551	1.00	35.97	N
ATOM	1102	CA	ALA H 136	-29.757	-29.264	12.212	1.00	33.42	C
ATOM	1103	CB	ALA H 136	-31.023	-29.310	11.374	1.00	33.23	C
ATOM	1104	C	ALA H 136	-29.241	-27.817	12.317	1.00	31.47	C
ATOM	1105	O	ALA H 136	-29.617	-27.106	13.236	1.00	31.03	O
ATOM	1106	N	ALA H 137	-28.382	-27.407	11.386	1.00	29.29	N
ATOM	1107	CA	ALA H 137	-28.006	-25.994	11.247	1.00	27.40	C
ATOM	1108	CB	ALA H 137	-26.491	-25.788	11.382	1.00	26.67	C
ATOM	1109	C	ALA H 137	-28.509	-25.409	9.943	1.00	26.14	C
ATOM	1110	O	ALA H 137	-28.531	-26.064	8.903	1.00	25.00	O
ATOM	1111	N	LEU H 138	-28.907	-24.147	10.013	1.00	25.43	N
ATOM	1112	CA	LEU H 138	-29.295	-23.402	8.823	1.00	25.36	C
ATOM	1113	CB	LEU H 138	-30.802	-23.554	8.555	1.00	25.53	C
ATOM	1114	CG	LEU H 138	-31.771	-23.383	9.724	1.00	28.73	C
ATOM	1115	CD1	LEU H 138	-32.461	-22.045	9.629	1.00	31.80	C
ATOM	1116	CD2	LEU H 138	-32.800	-24.500	9.700	1.00	32.31	C
ATOM	1117	C	LEU H 138	-28.888	-21.930	8.996	1.00	24.48	C
ATOM	1118	O	LEU H 138	-28.525	-21.511	10.090	1.00	23.70	O
ATOM	1119	N	GLY H 139	-28.924	-21.163	7.915	1.00	23.93	N
ATOM	1120	CA	GLY H 139	-28.555	-19.752	8.020	1.00	23.64	C
ATOM	1121	C	GLY H 139	-28.786	-18.956	6.756	1.00	23.58	C
ATOM	1122	O	GLY H 139	-29.409	-19.438	5.807	1.00	23.16	O
ATOM	1123	N	CYS H 140	-28.290	-17.722	6.777	1.00	22.59	N
ATOM	1124	CA	CYS H 140	-28.300	-16.839	5.641	1.00	23.05	C
ATOM	1125	CB	CYS H 140	-29.312	-15.702	5.878	1.00	23.73	C
ATOM	1126	SG	CYS H 140	-31.061	-16.224	5.597	1.00	29.99	S
ATOM	1127	C	CYS H 140	-26.914	-16.268	5.483	1.00	22.44	C
ATOM	1128	O	CYS H 140	-26.285	-15.891	6.475	1.00	21.56	O
ATOM	1129	N	LEU H 141	-26.443	-16.230	4.246	1.00	21.47	N
ATOM	1130	CA	LEU H 141	-25.220	-15.529	3.878	1.00	21.78	C
ATOM	1131	CB	LEU H 141	-24.445	-16.343	2.831	1.00	20.93	C
ATOM	1132	CG	LEU H 141	-23.193	-15.744	2.173	1.00	21.83	C
ATOM	1133	CD1	LEU H 141	-22.117	-15.397	3.195	1.00	20.96	C
ATOM	1134	CD2	LEU H 141	-22.655	-16.701	1.114	1.00	22.94	C
ATOM	1135	C	LEU H 141	-25.591	-14.126	3.355	1.00	22.20	C
ATOM	1136	O	LEU H 141	-26.324	-13.977	2.374	1.00	22.36	O
ATOM	1137	N	VAL H 142	-25.115	-13.094	4.035	1.00	22.88	N
ATOM	1138	CA	VAL H 142	-25.456	-11.722	3.689	1.00	23.58	C
ATOM	1139	CB	VAL H 142	-25.869	-10.903	4.950	1.00	23.67	C
ATOM	1140	CG1	VAL H 142	-26.188	-9.455	4.593	1.00	22.88	C
ATOM	1141	CG2	VAL H 142	-27.070	-11.565	5.668	1.00	23.57	C

ATOM	1142	C	VAL H 142	-24.201	-11.188	3.008	1.00	24.52	C
ATOM	1143	O	VAL H 142	-23.223	-10.823	3.675	1.00	24.73	O
ATOM	1144	N	LYS H 143	-24.204	-11.167	1.681	1.00	25.01	N
ATOM	1145	CA	LYS H 143	-22.940	-10.982	0.969	1.00	26.70	C
ATOM	1146	CB	LYS H 143	-22.698	-12.167	0.012	1.00	27.16	C
ATOM	1147	CG	LYS H 143	-21.213	-12.371	-0.325	1.00	28.83	C
ATOM	1148	CD	LYS H 143	-20.982	-13.419	-1.382	1.00	29.13	C
ATOM	1149	CE	LYS H 143	-19.504	-13.414	-1.799	1.00	32.32	C
ATOM	1150	NZ	LYS H 143	-19.220	-12.338	-2.761	1.00	34.54	N
ATOM	1151	C	LYS H 143	-22.857	-9.631	0.238	1.00	26.53	C
ATOM	1152	O	LYS H 143	-23.856	-9.152	-0.289	1.00	26.26	O
ATOM	1153	N	ASP H 144	-21.660	-9.031	0.230	1.00	26.61	N
ATOM	1154	CA	ASP H 144	-21.342	-7.871	-0.630	1.00	26.77	C
ATOM	1155	CB	ASP H 144	-21.441	-8.250	-2.118	1.00	26.82	C
ATOM	1156	CG	ASP H 144	-20.407	-9.271	-2.531	1.00	27.55	C
ATOM	1157	OD1	ASP H 144	-19.395	-9.477	-1.815	1.00	28.59	O
ATOM	1158	OD2	ASP H 144	-20.611	-9.891	-3.591	1.00	30.09	O
ATOM	1159	C	ASP H 144	-22.125	-6.584	-0.357	1.00	26.60	C
ATOM	1160	O	ASP H 144	-22.850	-6.073	-1.223	1.00	26.70	O
ATOM	1161	N	TYR H 145	-21.978	-6.052	0.848	1.00	25.29	N
ATOM	1162	CA	TYR H 145	-22.623	-4.796	1.198	1.00	24.21	C
ATOM	1163	CB	TYR H 145	-23.741	-5.013	2.239	1.00	23.46	C
ATOM	1164	CG	TYR H 145	-23.240	-5.473	3.604	1.00	23.37	C
ATOM	1165	CD1	TYR H 145	-23.099	-6.840	3.893	1.00	22.28	C
ATOM	1166	CE1	TYR H 145	-22.616	-7.266	5.118	1.00	22.34	C
ATOM	1167	CZ	TYR H 145	-22.286	-6.333	6.093	1.00	22.18	C
ATOM	1168	OH	TYR H 145	-21.821	-6.795	7.288	1.00	22.39	O
ATOM	1169	CE2	TYR H 145	-22.392	-4.972	5.852	1.00	21.10	C
ATOM	1170	CD2	TYR H 145	-22.884	-4.541	4.602	1.00	22.24	C
ATOM	1171	C	TYR H 145	-21.562	-3.801	1.691	1.00	24.46	C
ATOM	1172	O	TYR H 145	-20.449	-4.187	2.097	1.00	24.17	O
ATOM	1173	N	PHE H 146	-21.919	-2.521	1.648	1.00	25.18	N
ATOM	1174	CA	PHE H 146	-21.084	-1.450	2.169	1.00	24.65	C
ATOM	1175	CB	PHE H 146	-19.966	-1.055	1.183	1.00	25.03	C
ATOM	1176	CG	PHE H 146	-19.088	0.060	1.698	1.00	25.06	C
ATOM	1177	CD1	PHE H 146	-19.443	1.398	1.486	1.00	24.96	C
ATOM	1178	CE1	PHE H 146	-18.655	2.451	1.999	1.00	24.91	C
ATOM	1179	CZ	PHE H 146	-17.511	2.164	2.708	1.00	25.23	C
ATOM	1180	CE2	PHE H 146	-17.151	0.820	2.951	1.00	26.49	C
ATOM	1181	CD2	PHE H 146	-17.945	-0.224	2.441	1.00	24.62	C
ATOM	1182	C	PHE H 146	-21.998	-0.264	2.455	1.00	24.74	C
ATOM	1183	O	PHE H 146	-22.878	0.037	1.672	1.00	24.97	O
ATOM	1184	N	PRO H 147	-21.812	0.413	3.596	1.00	25.06	N
ATOM	1185	CA	PRO H 147	-20.865	0.129	4.669	1.00	24.93	C
ATOM	1186	CB	PRO H 147	-20.602	1.528	5.238	1.00	24.58	C
ATOM	1187	CG	PRO H 147	-21.964	2.187	5.139	1.00	25.08	C
ATOM	1188	CD	PRO H 147	-22.594	1.640	3.875	1.00	25.14	C
ATOM	1189	C	PRO H 147	-21.520	-0.744	5.733	1.00	24.94	C
ATOM	1190	O	PRO H 147	-22.688	-1.138	5.594	1.00	24.43	O
ATOM	1191	N	GLU H 148	-20.798	-1.000	6.814	1.00	24.72	N
ATOM	1192	CA	GLU H 148	-21.415	-1.546	8.018	1.00	25.52	C
ATOM	1193	CB	GLU H 148	-20.318	-1.837	9.052	1.00	25.67	C
ATOM	1194	CG	GLU H 148	-19.460	-3.043	8.719	1.00	27.14	C
ATOM	1195	CD	GLU H 148	-20.036	-4.306	9.335	1.00	31.59	C
ATOM	1196	OE1	GLU H 148	-21.166	-4.737	8.946	1.00	31.31	O
ATOM	1197	OE2	GLU H 148	-19.368	-4.857	10.235	1.00	27.87	O
ATOM	1198	C	GLU H 148	-22.440	-0.547	8.576	1.00	25.79	C

ATOM	1199	O	GLU H 148	-22.347	0.637	8.286	1.00	25.98	O
ATOM	1200	N	PRO H 149	-23.409	-1.011	9.393	1.00	26.18	N
ATOM	1201	CA	PRO H 149	-23.732	-2.373	9.777	1.00	26.60	C
ATOM	1202	CB	PRO H 149	-24.129	-2.196	11.239	1.00	26.52	C
ATOM	1203	CG	PRO H 149	-24.914	-0.911	11.206	1.00	26.38	C
ATOM	1204	CD	PRO H 149	-24.242	-0.055	10.144	1.00	26.37	C
ATOM	1205	C	PRO H 149	-24.940	-2.945	9.042	1.00	27.43	C
ATOM	1206	O	PRO H 149	-25.697	-2.200	8.398	1.00	27.58	O
ATOM	1207	N	VAL H 150	-25.123	-4.258	9.169	1.00	27.96	N
ATOM	1208	CA	VAL H 150	-26.402	-4.905	8.857	1.00	29.00	C
ATOM	1209	CB	VAL H 150	-26.312	-6.004	7.742	1.00	29.30	C
ATOM	1210	CG1	VAL H 150	-25.951	-5.400	6.412	1.00	29.80	C
ATOM	1211	CG2	VAL H 150	-25.342	-7.098	8.107	1.00	30.66	C
ATOM	1212	C	VAL H 150	-26.947	-5.524	10.136	1.00	29.02	C
ATOM	1213	O	VAL H 150	-26.176	-5.891	11.025	1.00	29.11	O
ATOM	1214	N	THR H 151	-28.269	-5.618	10.246	1.00	29.10	N
ATOM	1215	CA	THR H 151	-28.865	-6.393	11.329	1.00	29.20	C
ATOM	1216	CB	THR H 151	-29.813	-5.554	12.230	1.00	29.53	C
ATOM	1217	OG1	THR H 151	-30.879	-5.017	11.449	1.00	31.39	O
ATOM	1218	CG2	THR H 151	-29.048	-4.408	12.915	1.00	30.40	C
ATOM	1219	C	THR H 151	-29.611	-7.594	10.758	1.00	28.59	C
ATOM	1220	O	THR H 151	-30.147	-7.531	9.643	1.00	28.31	O
ATOM	1221	N	VAL H 152	-29.613	-8.677	11.530	1.00	27.93	N
ATOM	1222	CA	VAL H 152	-30.303	-9.914	11.196	1.00	27.73	C
ATOM	1223	CB	VAL H 152	-29.322	-11.059	10.789	1.00	27.98	C
ATOM	1224	CG1	VAL H 152	-30.112	-12.271	10.220	1.00	28.34	C
ATOM	1225	CG2	VAL H 152	-28.319	-10.579	9.758	1.00	27.70	C
ATOM	1226	C	VAL H 152	-31.124	-10.380	12.393	1.00	27.92	C
ATOM	1227	O	VAL H 152	-30.614	-10.470	13.510	1.00	27.83	O
ATOM	1228	N	SER H 153	-32.398	-10.674	12.160	1.00	26.86	N
ATOM	1229	CA	SER H 153	-33.173	-11.429	13.118	1.00	27.23	C
ATOM	1230	CB	SER H 153	-34.299	-10.572	13.710	1.00	27.54	C
ATOM	1231	OG	SER H 153	-35.178	-10.128	12.695	1.00	29.43	O
ATOM	1232	C	SER H 153	-33.703	-12.677	12.411	1.00	26.62	C
ATOM	1233	O	SER H 153	-33.549	-12.827	11.185	1.00	25.68	O
ATOM	1234	N	TRP H 154	-34.287	-13.579	13.192	1.00	26.51	N
ATOM	1235	CA	TRP H 154	-34.900	-14.794	12.675	1.00	27.06	C
ATOM	1236	CB	TRP H 154	-34.152	-16.032	13.179	1.00	25.80	C
ATOM	1237	CG	TRP H 154	-32.849	-16.207	12.455	1.00	24.10	C
ATOM	1238	CD1	TRP H 154	-31.636	-15.636	12.779	1.00	24.00	C
ATOM	1239	NE1	TRP H 154	-30.676	-16.008	11.854	1.00	22.56	N
ATOM	1240	CE2	TRP H 154	-31.260	-16.813	10.911	1.00	22.86	C
ATOM	1241	CD2	TRP H 154	-32.631	-16.960	11.261	1.00	22.95	C
ATOM	1242	CE3	TRP H 154	-33.458	-17.756	10.445	1.00	23.01	C
ATOM	1243	CZ3	TRP H 154	-32.904	-18.371	9.331	1.00	22.96	C
ATOM	1244	CH2	TRP H 154	-31.541	-18.206	9.006	1.00	24.04	C
ATOM	1245	CZ2	TRP H 154	-30.701	-17.442	9.786	1.00	22.72	C
ATOM	1246	C	TRP H 154	-36.374	-14.838	13.057	1.00	28.56	C
ATOM	1247	O	TRP H 154	-36.730	-14.607	14.215	1.00	28.46	O
ATOM	1248	N	ASN H 155	-37.221	-15.142	12.075	1.00	30.38	N
ATOM	1249	CA	ASN H 155	-38.669	-15.218	12.284	1.00	32.42	C
ATOM	1250	CB	ASN H 155	-39.046	-16.516	13.015	1.00	32.19	C
ATOM	1251	CG	ASN H 155	-38.751	-17.764	12.199	1.00	32.74	C
ATOM	1252	OD1	ASN H 155	-38.377	-17.689	11.039	1.00	33.50	O
ATOM	1253	ND2	ASN H 155	-38.916	-18.928	12.820	1.00	31.79	N
ATOM	1254	C	ASN H 155	-39.203	-13.982	13.028	1.00	33.72	C
ATOM	1255	O	ASN H 155	-39.903	-14.101	14.052	1.00	34.03	O

ATOM	1256	N	SER H 156	-38.834	-12.801	12.518	1.00	34.89	N
ATOM	1257	CA	SER H 156	-39.251	-11.502	13.074	1.00	36.49	C
ATOM	1258	CB	SER H 156	-40.740	-11.235	12.774	1.00	36.85	C
ATOM	1259	OG	SER H 156	-40.950	-11.197	11.374	1.00	38.09	O
ATOM	1260	C	SER H 156	-38.956	-11.334	14.563	1.00	36.85	C
ATOM	1261	O	SER H 156	-39.666	-10.611	15.269	1.00	37.32	O
ATOM	1262	N	GLY H 157	-37.905	-11.998	15.038	1.00	37.07	N
ATOM	1263	CA	GLY H 157	-37.482	-11.875	16.434	1.00	36.78	C
ATOM	1264	C	GLY H 157	-38.020	-12.954	17.358	1.00	37.00	C
ATOM	1265	O	GLY H 157	-37.614	-13.039	18.521	1.00	36.44	O
ATOM	1266	N	ALA H 158	-38.925	-13.780	16.845	1.00	36.81	N
ATOM	1267	CA	ALA H 158	-39.451	-14.919	17.606	1.00	37.33	C
ATOM	1268	CB	ALA H 158	-40.712	-15.480	16.928	1.00	37.16	C
ATOM	1269	C	ALA H 158	-38.424	-16.042	17.842	1.00	37.33	C
ATOM	1270	O	ALA H 158	-38.555	-16.802	18.801	1.00	37.67	O
ATOM	1271	N	LEU H 159	-37.430	-16.165	16.957	1.00	36.62	N
ATOM	1272	CA	LEU H 159	-36.380	-17.187	17.094	1.00	35.76	C
ATOM	1273	CB	LEU H 159	-36.163	-17.909	15.764	1.00	35.56	C
ATOM	1274	CG	LEU H 159	-35.727	-19.374	15.688	1.00	35.63	C
ATOM	1275	CD1	LEU H 159	-35.003	-19.629	14.370	1.00	33.48	C
ATOM	1276	CD2	LEU H 159	-34.902	-19.861	16.875	1.00	35.23	C
ATOM	1277	C	LEU H 159	-35.069	-16.540	17.551	1.00	35.53	C
ATOM	1278	O	LEU H 159	-34.440	-15.792	16.796	1.00	35.00	O
ATOM	1279	N	THR H 160	-34.665	-16.825	18.788	1.00	35.10	N
ATOM	1280	CA	THR H 160	-33.458	-16.239	19.359	1.00	34.87	C
ATOM	1281	CB	THR H 160	-33.771	-15.249	20.518	1.00	35.28	C
ATOM	1282	OG1	THR H 160	-34.591	-15.902	21.498	1.00	36.53	O
ATOM	1283	CG2	THR H 160	-34.474	-13.988	20.009	1.00	35.84	C
ATOM	1284	C	THR H 160	-32.493	-17.302	19.876	1.00	34.30	C
ATOM	1285	O	THR H 160	-31.289	-17.105	19.837	1.00	33.96	O
ATOM	1286	N	SER H 161	-33.021	-18.428	20.349	1.00	33.97	N
ATOM	1287	CA	SER H 161	-32.183	-19.510	20.872	1.00	33.69	C
ATOM	1288	CB	SER H 161	-33.029	-20.586	21.546	1.00	34.09	C
ATOM	1289	OG	SER H 161	-33.140	-20.321	22.929	1.00	37.94	O
ATOM	1290	C	SER H 161	-31.358	-20.158	19.780	1.00	32.36	C
ATOM	1291	O	SER H 161	-31.888	-20.495	18.715	1.00	32.47	O
ATOM	1292	N	GLY H 162	-30.068	-20.329	20.054	1.00	31.17	N
ATOM	1293	CA	GLY H 162	-29.159	-21.010	19.136	1.00	29.93	C
ATOM	1294	C	GLY H 162	-28.750	-20.186	17.930	1.00	28.48	C
ATOM	1295	O	GLY H 162	-28.099	-20.702	17.020	1.00	28.64	O
ATOM	1296	N	VAL H 163	-29.128	-18.907	17.915	1.00	27.49	N
ATOM	1297	CA	VAL H 163	-28.711	-17.989	16.848	1.00	25.70	C
ATOM	1298	CB	VAL H 163	-29.685	-16.770	16.677	1.00	25.45	C
ATOM	1299	CG1	VAL H 163	-29.173	-15.821	15.600	1.00	25.34	C
ATOM	1300	CG2	VAL H 163	-31.055	-17.231	16.316	1.00	23.76	C
ATOM	1301	C	VAL H 163	-27.271	-17.484	17.053	1.00	25.30	C
ATOM	1302	O	VAL H 163	-26.908	-17.064	18.141	1.00	25.63	O
ATOM	1303	N	HIS H 164	-26.464	-17.543	15.999	1.00	24.50	N
ATOM	1304	CA	HIS H 164	-25.150	-16.898	15.970	1.00	24.02	C
ATOM	1305	CB	HIS H 164	-23.989	-17.917	15.961	1.00	24.13	C
ATOM	1306	CG	HIS H 164	-23.879	-18.736	17.215	1.00	26.21	C
ATOM	1307	ND1	HIS H 164	-23.709	-18.175	18.464	1.00	28.31	N
ATOM	1308	CE1	HIS H 164	-23.646	-19.133	19.372	1.00	28.81	C
ATOM	1309	NE2	HIS H 164	-23.741	-20.298	18.756	1.00	29.74	N
ATOM	1310	CD2	HIS H 164	-23.873	-20.078	17.405	1.00	28.23	C
ATOM	1311	C	HIS H 164	-25.055	-16.040	14.730	1.00	23.43	C
ATOM	1312	O	HIS H 164	-24.983	-16.554	13.609	1.00	23.11	O

ATOM	1313	N	THR	H	165	-25.027	-14.728	14.930	1.00	22.98	N
ATOM	1314	CA	THR	H	165	-24.730	-13.823	13.834	1.00	23.01	C
ATOM	1315	CB	THR	H	165	-25.696	-12.621	13.803	1.00	23.29	C
ATOM	1316	OG1	THR	H	165	-27.029	-13.121	13.614	1.00	23.59	O
ATOM	1317	CG2	THR	H	165	-25.376	-11.690	12.638	1.00	23.34	C
ATOM	1318	C	THR	H	165	-23.263	-13.429	13.946	1.00	23.12	C
ATOM	1319	O	THR	H	165	-22.825	-12.862	14.952	1.00	23.09	O
ATOM	1320	N	PHE	H	166	-22.501	-13.754	12.912	1.00	22.38	N
ATOM	1321	CA	PHE	H	166	-21.051	-13.541	12.946	1.00	22.68	C
ATOM	1322	CB	PHE	H	166	-20.345	-14.523	11.997	1.00	22.38	C
ATOM	1323	CG	PHE	H	166	-20.430	-15.933	12.476	1.00	22.94	C
ATOM	1324	CD1	PHE	H	166	-21.489	-16.763	12.074	1.00	23.27	C
ATOM	1325	CE1	PHE	H	166	-21.591	-18.088	12.566	1.00	22.41	C
ATOM	1326	CZ	PHE	H	166	-20.630	-18.552	13.465	1.00	23.84	C
ATOM	1327	CE2	PHE	H	166	-19.577	-17.712	13.874	1.00	24.19	C
ATOM	1328	CD2	PHE	H	166	-19.487	-16.423	13.378	1.00	24.13	C
ATOM	1329	C	PHE	H	166	-20.663	-12.096	12.658	1.00	23.11	C
ATOM	1330	O	PHE	H	166	-21.378	-11.400	11.927	1.00	22.52	O
ATOM	1331	N	PRO	H	167	-19.556	-11.625	13.272	1.00	23.52	N
ATOM	1332	CA	PRO	H	167	-18.975	-10.361	12.832	1.00	23.45	C
ATOM	1333	CB	PRO	H	167	-17.666	-10.277	13.636	1.00	23.99	C
ATOM	1334	CG	PRO	H	167	-17.913	-11.084	14.864	1.00	24.08	C
ATOM	1335	CD	PRO	H	167	-18.798	-12.228	14.384	1.00	23.52	C
ATOM	1336	C	PRO	H	167	-18.658	-10.438	11.327	1.00	23.28	C
ATOM	1337	O	PRO	H	167	-18.160	-11.475	10.843	1.00	22.33	O
ATOM	1338	N	ALA	H	168	-18.944	-9.356	10.603	1.00	22.81	N
ATOM	1339	CA	ALA	H	168	-18.684	-9.295	9.176	1.00	23.55	C
ATOM	1340	CB	ALA	H	168	-19.268	-8.013	8.575	1.00	23.33	C
ATOM	1341	C	ALA	H	168	-17.206	-9.353	8.882	1.00	23.60	C
ATOM	1342	O	ALA	H	168	-16.396	-8.915	9.701	1.00	23.54	O
ATOM	1343	N	VAL	H	169	-16.856	-9.908	7.725	1.00	23.65	N
ATOM	1344	CA	VAL	H	169	-15.475	-9.824	7.211	1.00	24.63	C
ATOM	1345	CB	VAL	H	169	-14.886	-11.192	6.771	1.00	24.34	C
ATOM	1346	CG1	VAL	H	169	-14.740	-12.130	7.977	1.00	25.01	C
ATOM	1347	CG2	VAL	H	169	-15.738	-11.850	5.653	1.00	26.18	C
ATOM	1348	C	VAL	H	169	-15.407	-8.842	6.041	1.00	25.60	C
ATOM	1349	O	VAL	H	169	-16.384	-8.677	5.307	1.00	24.83	O
ATOM	1350	N	LEU	H	170	-14.251	-8.196	5.886	1.00	26.00	N
ATOM	1351	CA	LEU	H	170	-14.042	-7.246	4.810	1.00	27.19	C
ATOM	1352	CB	LEU	H	170	-13.209	-6.050	5.288	1.00	27.10	C
ATOM	1353	CG	LEU	H	170	-12.898	-4.955	4.260	1.00	27.23	C
ATOM	1354	CD1	LEU	H	170	-14.179	-4.444	3.669	1.00	25.96	C
ATOM	1355	CD2	LEU	H	170	-12.150	-3.807	4.951	1.00	27.54	C
ATOM	1356	C	LEU	H	170	-13.320	-8.006	3.734	1.00	27.45	C
ATOM	1357	O	LEU	H	170	-12.226	-8.514	3.966	1.00	27.65	O
ATOM	1358	N	GLN	H	171	-13.957	-8.129	2.577	1.00	28.52	N
ATOM	1359	CA	GLN	H	171	-13.425	-8.929	1.482	1.00	30.60	C
ATOM	1360	CB	GLN	H	171	-14.574	-9.405	0.585	1.00	30.11	C
ATOM	1361	CG	GLN	H	171	-15.636	-10.214	1.335	1.00	30.75	C
ATOM	1362	CD	GLN	H	171	-16.910	-10.441	0.505	1.00	31.57	C
ATOM	1363	OE1	GLN	H	171	-17.238	-11.570	0.138	1.00	34.21	O
ATOM	1364	NE2	GLN	H	171	-17.625	-9.372	0.219	1.00	32.56	N
ATOM	1365	C	GLN	H	171	-12.431	-8.079	0.698	1.00	31.73	C
ATOM	1366	O	GLN	H	171	-12.404	-6.849	0.865	1.00	31.62	O
ATOM	1367	N	SER	H	172	-11.618	-8.709	-0.152	1.00	33.24	N
ATOM	1368	CA	SER	H	172	-10.647	-7.950	-0.951	1.00	34.93	C
ATOM	1369	CB	SER	H	172	-9.672	-8.858	-1.699	1.00	35.41	C

ATOM	1370	OG	SER H 172	-10.356	-9.735	-2.561	1.00	37.40	O
ATOM	1371	C	SER H 172	-11.303	-6.938	-1.890	1.00	34.85	C
ATOM	1372	O	SER H 172	-10.656	-5.978	-2.289	1.00	35.77	O
ATOM	1373	N	SER H 173	-12.588	-7.140	-2.195	1.00	35.02	N
ATOM	1374	CA	SER H 173	-13.414	-6.158	-2.936	1.00	34.53	C
ATOM	1375	CB	SER H 173	-14.791	-6.723	-3.297	1.00	34.58	C
ATOM	1376	OG	SER H 173	-15.469	-7.191	-2.155	1.00	34.22	O
ATOM	1377	C	SER H 173	-13.545	-4.738	-2.323	1.00	34.51	C
ATOM	1378	O	SER H 173	-13.851	-3.815	-3.071	1.00	34.55	O
ATOM	1379	N	GLY H 174	-13.508	-4.522	-1.001	1.00	34.27	N
ATOM	1380	CA	GLY H 174	-14.368	-5.153	-0.009	1.00	34.47	C
ATOM	1381	C	GLY H 174	-15.377	-4.032	0.218	1.00	32.34	C
ATOM	1382	O	GLY H 174	-15.061	-2.960	0.716	1.00	32.92	O
ATOM	1383	N	LEU H 175	-16.641	-4.228	-0.068	1.00	31.28	N
ATOM	1384	CA	LEU H 175	-17.554	-5.237	0.375	1.00	28.56	C
ATOM	1385	CB	LEU H 175	-18.235	-5.869	-0.834	1.00	28.36	C
ATOM	1386	CG	LEU H 175	-18.378	-4.855	-2.004	1.00	28.86	C
ATOM	1387	CD1	LEU H 175	-19.296	-5.425	-3.075	1.00	28.60	C
ATOM	1388	CD2	LEU H 175	-18.841	-3.442	-1.603	1.00	27.38	C
ATOM	1389	C	LEU H 175	-17.336	-6.160	1.578	1.00	27.01	C
ATOM	1390	O	LEU H 175	-16.459	-7.018	1.610	1.00	26.58	O
ATOM	1391	N	TYR H 176	-18.215	-5.947	2.549	1.00	25.66	N
ATOM	1392	CA	TYR H 176	-18.375	-6.814	3.707	1.00	24.79	C
ATOM	1393	CB	TYR H 176	-19.039	-6.039	4.830	1.00	24.80	C
ATOM	1394	CG	TYR H 176	-18.178	-4.932	5.358	1.00	25.13	C
ATOM	1395	CD1	TYR H 176	-18.285	-3.637	4.842	1.00	25.33	C
ATOM	1396	CE1	TYR H 176	-17.480	-2.599	5.326	1.00	24.56	C
ATOM	1397	CZ	TYR H 176	-16.559	-2.875	6.316	1.00	25.61	C
ATOM	1398	OH	TYR H 176	-15.761	-1.869	6.795	1.00	26.81	O
ATOM	1399	CE2	TYR H 176	-16.421	-4.167	6.835	1.00	25.47	C
ATOM	1400	CD2	TYR H 176	-17.240	-5.185	6.345	1.00	24.82	C
ATOM	1401	C	TYR H 176	-19.276	-7.981	3.386	1.00	24.37	C
ATOM	1402	O	TYR H 176	-20.117	-7.911	2.486	1.00	24.36	O
ATOM	1403	N	SER H 177	-19.148	-9.025	4.193	1.00	24.26	N
ATOM	1404	CA	SER H 177	-19.999	-10.176	4.089	1.00	24.06	C
ATOM	1405	CB	SER H 177	-19.394	-11.124	3.066	1.00	24.17	C
ATOM	1406	OG	SER H 177	-20.007	-12.388	3.099	1.00	27.52	O
ATOM	1407	C	SER H 177	-20.094	-10.797	5.475	1.00	24.01	C
ATOM	1408	O	SER H 177	-19.109	-10.823	6.217	1.00	23.61	O
ATOM	1409	N	LEU H 178	-21.295	-11.225	5.855	1.00	23.33	N
ATOM	1410	CA	LEU H 178	-21.464	-12.000	7.082	1.00	22.78	C
ATOM	1411	CB	LEU H 178	-21.914	-11.124	8.268	1.00	22.71	C
ATOM	1412	CG	LEU H 178	-23.272	-10.436	8.386	1.00	22.99	C
ATOM	1413	CD1	LEU H 178	-24.447	-11.398	8.670	1.00	20.96	C
ATOM	1414	CD2	LEU H 178	-23.150	-9.469	9.542	1.00	23.86	C
ATOM	1415	C	LEU H 178	-22.453	-13.126	6.886	1.00	22.24	C
ATOM	1416	O	LEU H 178	-23.203	-13.145	5.902	1.00	21.47	O
ATOM	1417	N	SER H 179	-22.451	-14.043	7.851	1.00	22.00	N
ATOM	1418	CA	SER H 179	-23.411	-15.131	7.925	1.00	22.90	C
ATOM	1419	CB	SER H 179	-22.692	-16.466	7.860	1.00	23.69	C
ATOM	1420	OG	SER H 179	-22.340	-16.732	6.511	1.00	28.09	O
ATOM	1421	C	SER H 179	-24.122	-15.065	9.242	1.00	21.75	C
ATOM	1422	O	SER H 179	-23.540	-14.659	10.244	1.00	21.26	O
ATOM	1423	N	SER H 180	-25.382	-15.474	9.243	1.00	21.46	N
ATOM	1424	CA	SER H 180	-26.119	-15.669	10.476	1.00	21.23	C
ATOM	1425	CB	SER H 180	-27.262	-14.662	10.589	1.00	21.34	C
ATOM	1426	OG	SER H 180	-27.965	-14.844	11.814	1.00	21.68	O

ATOM	1427	C	SER H 180	-26.655	-17.098	10.446	1.00	21.87	C
ATOM	1428	O	SER H 180	-27.256	-17.507	9.448	1.00	21.98	O
ATOM	1429	N	VAL H 181	-26.405	-17.849	11.515	1.00	21.95	N
ATOM	1430	CA	VAL H 181	-26.792	-19.255	11.583	1.00	22.58	C
ATOM	1431	CB	VAL H 181	-25.586	-20.217	11.577	1.00	22.14	C
ATOM	1432	CG1	VAL H 181	-24.727	-20.029	10.316	1.00	22.00	C
ATOM	1433	CG2	VAL H 181	-24.760	-20.079	12.898	1.00	22.75	C
ATOM	1434	C	VAL H 181	-27.649	-19.532	12.819	1.00	23.10	C
ATOM	1435	O	VAL H 181	-27.616	-18.785	13.801	1.00	22.90	O
ATOM	1436	N	VAL H 182	-28.441	-20.596	12.744	1.00	23.77	N
ATOM	1437	CA	VAL H 182	-29.178	-21.064	13.901	1.00	25.42	C
ATOM	1438	CB	VAL H 182	-30.605	-20.414	13.998	1.00	25.27	C
ATOM	1439	CG1	VAL H 182	-31.437	-20.676	12.765	1.00	26.02	C
ATOM	1440	CG2	VAL H 182	-31.346	-20.885	15.229	1.00	25.86	C
ATOM	1441	C	VAL H 182	-29.179	-22.594	13.910	1.00	26.26	C
ATOM	1442	O	VAL H 182	-29.241	-23.222	12.857	1.00	26.30	O
ATOM	1443	N	THR H 183	-29.026	-23.190	15.089	1.00	27.87	N
ATOM	1444	CA	THR H 183	-29.200	-24.638	15.222	1.00	28.84	C
ATOM	1445	CB	THR H 183	-28.126	-25.305	16.112	1.00	29.13	C
ATOM	1446	OG1	THR H 183	-28.050	-24.620	17.366	1.00	28.39	O
ATOM	1447	CG2	THR H 183	-26.773	-25.281	15.449	1.00	28.25	C
ATOM	1448	C	THR H 183	-30.590	-24.906	15.782	1.00	30.38	C
ATOM	1449	O	THR H 183	-31.053	-24.218	16.701	1.00	30.73	O
ATOM	1450	N	VAL H 184	-31.254	-25.894	15.197	1.00	32.38	N
ATOM	1451	CA	VAL H 184	-32.648	-26.227	15.513	1.00	34.13	C
ATOM	1452	CB	VAL H 184	-33.635	-25.649	14.450	1.00	33.81	C
ATOM	1453	CG1	VAL H 184	-33.512	-24.113	14.353	1.00	34.01	C
ATOM	1454	CG2	VAL H 184	-33.420	-26.290	13.079	1.00	33.12	C
ATOM	1455	C	VAL H 184	-32.784	-27.754	15.571	1.00	36.08	C
ATOM	1456	O	VAL H 184	-31.926	-28.477	15.033	1.00	36.49	O
ATOM	1457	N	PRO H 185	-33.852	-28.257	16.226	1.00	37.79	N
ATOM	1458	CA	PRO H 185	-34.101	-29.704	16.173	1.00	39.05	C
ATOM	1459	CB	PRO H 185	-35.397	-29.874	16.986	1.00	38.63	C
ATOM	1460	CG	PRO H 185	-35.430	-28.702	17.894	1.00	38.98	C
ATOM	1461	CD	PRO H 185	-34.845	-27.563	17.072	1.00	37.92	C
ATOM	1462	C	PRO H 185	-34.298	-30.182	14.735	1.00	40.06	C
ATOM	1463	O	PRO H 185	-35.041	-29.565	13.970	1.00	40.30	O
ATOM	1464	N	SER H 186	-33.623	-31.267	14.373	1.00	41.68	N
ATOM	1465	CA	SER H 186	-33.769	-31.868	13.055	1.00	43.78	C
ATOM	1466	CB	SER H 186	-32.915	-33.118	12.953	1.00	44.04	C
ATOM	1467	OG	SER H 186	-32.673	-33.425	11.597	1.00	46.55	O
ATOM	1468	C	SER H 186	-35.227	-32.200	12.737	1.00	44.80	C
ATOM	1469	O	SER H 186	-35.658	-32.091	11.594	1.00	44.87	O
ATOM	1470	N	SER H 187	-35.988	-32.591	13.753	1.00	46.21	N
ATOM	1471	CA	SER H 187	-37.417	-32.839	13.584	1.00	47.74	C
ATOM	1472	CB	SER H 187	-37.983	-33.545	14.826	1.00	47.71	C
ATOM	1473	OG	SER H 187	-37.929	-32.720	15.982	1.00	47.83	O
ATOM	1474	C	SER H 187	-38.214	-31.559	13.249	1.00	48.84	C
ATOM	1475	O	SER H 187	-39.450	-31.589	13.219	1.00	49.25	O
ATOM	1476	N	SER H 188	-37.496	-30.461	12.968	1.00	49.89	N
ATOM	1477	CA	SER H 188	-38.081	-29.116	12.750	1.00	50.75	C
ATOM	1478	CB	SER H 188	-37.040	-27.996	12.840	1.00	50.68	C
ATOM	1479	OG	SER H 188	-37.068	-27.422	14.130	1.00	51.37	O
ATOM	1480	C	SER H 188	-38.981	-28.920	11.532	1.00	50.95	C
ATOM	1481	O	SER H 188	-40.007	-28.297	11.696	1.00	51.41	O
ATOM	1482	N	LEU H 189	-38.593	-29.254	10.301	1.00	51.40	N
ATOM	1483	CA	LEU H 189	-37.377	-28.834	9.624	1.00	51.55	C

ATOM	1484	CB	LEU	H 189	-36.297	-29.912	9.523	1.00	51.29	C
ATOM	1485	CG	LEU	H 189	-34.834	-29.462	9.752	1.00	50.01	C
ATOM	1486	CD1	LEU	H 189	-33.884	-30.148	8.780	1.00	48.53	C
ATOM	1487	CD2	LEU	H 189	-34.621	-27.943	9.704	1.00	48.60	C
ATOM	1488	C	LEU	H 189	-37.809	-28.379	8.210	1.00	52.29	C
ATOM	1489	O	LEU	H 189	-37.139	-27.516	7.621	1.00	53.20	O
ATOM	1490	N	GLY	H 190	-38.912	-28.897	7.648	1.00	51.91	N
ATOM	1491	CA	GLY	H 190	-39.791	-29.914	8.237	1.00	51.50	C
ATOM	1492	C	GLY	H 190	-41.220	-29.405	8.394	1.00	51.16	C
ATOM	1493	O	GLY	H 190	-42.037	-29.488	7.469	1.00	51.69	O
ATOM	1494	N	THR	H 191	-41.507	-28.856	9.569	1.00	50.10	N
ATOM	1495	CA	THR	H 191	-42.825	-28.339	9.906	1.00	48.99	C
ATOM	1496	CB	THR	H 191	-43.522	-29.236	10.966	1.00	49.54	C
ATOM	1497	OG1	THR	H 191	-44.908	-28.876	11.060	1.00	51.93	O
ATOM	1498	CG2	THR	H 191	-42.864	-29.118	12.357	1.00	49.24	C
ATOM	1499	C	THR	H 191	-42.785	-26.883	10.389	1.00	47.47	C
ATOM	1500	O	THR	H 191	-43.821	-26.212	10.433	1.00	47.72	O
ATOM	1501	N	GLN	H 192	-41.595	-26.402	10.755	1.00	45.31	N
ATOM	1502	CA	GLN	H 192	-41.404	-25.017	11.200	1.00	43.36	C
ATOM	1503	CB	GLN	H 192	-40.595	-24.971	12.507	1.00	44.02	C
ATOM	1504	CG	GLN	H 192	-40.151	-23.578	12.977	1.00	45.57	C
ATOM	1505	CD	GLN	H 192	-41.293	-22.671	13.420	1.00	47.90	C
ATOM	1506	OE1	GLN	H 192	-41.986	-22.948	14.401	1.00	49.12	O
ATOM	1507	NE2	GLN	H 192	-41.475	-21.566	12.708	1.00	48.35	N
ATOM	1508	C	GLN	H 192	-40.743	-24.176	10.102	1.00	41.32	C
ATOM	1509	O	GLN	H 192	-39.785	-24.606	9.466	1.00	40.65	O
ATOM	1510	N	THR	H 193	-41.290	-22.988	9.877	1.00	39.22	N
ATOM	1511	CA	THR	H 193	-40.782	-22.065	8.870	1.00	37.26	C
ATOM	1512	CB	THR	H 193	-41.926	-21.205	8.287	1.00	37.67	C
ATOM	1513	OG1	THR	H 193	-42.755	-22.042	7.468	1.00	37.42	O
ATOM	1514	CG2	THR	H 193	-41.391	-20.040	7.436	1.00	37.11	C
ATOM	1515	C	THR	H 193	-39.645	-21.219	9.454	1.00	35.67	C
ATOM	1516	O	THR	H 193	-39.759	-20.704	10.573	1.00	35.71	O
ATOM	1517	N	TYR	H 194	-38.547	-21.114	8.700	1.00	33.96	N
ATOM	1518	CA	TYR	H 194	-37.375	-20.329	9.110	1.00	31.82	C
ATOM	1519	CB	TYR	H 194	-36.143	-21.233	9.262	1.00	31.97	C
ATOM	1520	CG	TYR	H 194	-36.322	-22.237	10.376	1.00	30.73	C
ATOM	1521	CD1	TYR	H 194	-36.583	-23.581	10.101	1.00	31.27	C
ATOM	1522	CE1	TYR	H 194	-36.777	-24.501	11.143	1.00	32.22	C
ATOM	1523	CZ	TYR	H 194	-36.737	-24.061	12.461	1.00	32.29	C
ATOM	1524	OH	TYR	H 194	-36.931	-24.943	13.511	1.00	33.59	O
ATOM	1525	CE2	TYR	H 194	-36.502	-22.725	12.746	1.00	32.05	C
ATOM	1526	CD2	TYR	H 194	-36.294	-21.827	11.704	1.00	29.34	C
ATOM	1527	C	TYR	H 194	-37.098	-19.205	8.123	1.00	30.84	C
ATOM	1528	O	TYR	H 194	-36.844	-19.454	6.947	1.00	30.77	O
ATOM	1529	N	ILE	H 195	-37.172	-17.974	8.615	1.00	29.22	N
ATOM	1530	CA	ILE	H 195	-36.957	-16.779	7.803	1.00	28.56	C
ATOM	1531	CB	ILE	H 195	-38.281	-15.985	7.601	1.00	27.86	C
ATOM	1532	CG1	ILE	H 195	-39.284	-16.814	6.788	1.00	29.42	C
ATOM	1533	CD1	ILE	H 195	-40.731	-16.295	6.878	1.00	29.78	C
ATOM	1534	CG2	ILE	H 195	-38.026	-14.656	6.864	1.00	27.86	C
ATOM	1535	C	ILE	H 195	-35.924	-15.868	8.472	1.00	27.51	C
ATOM	1536	O	ILE	H 195	-36.069	-15.521	9.644	1.00	26.80	O
ATOM	1537	N	CYS	H 196	-34.891	-15.471	7.730	1.00	27.43	N
ATOM	1538	CA	CYS	H 196	-33.969	-14.445	8.246	1.00	27.17	C
ATOM	1539	CB	CYS	H 196	-32.501	-14.750	7.896	1.00	27.16	C
ATOM	1540	SG	CYS	H 196	-32.137	-14.555	6.176	1.00	30.36	S

ATOM	1541	C	CYS H 196	-34.405	-13.063	7.749	1.00	26.68	C
ATOM	1542	O	CYS H 196	-34.697	-12.878	6.562	1.00	27.52	O
ATOM	1543	N	ASN H 197	-34.472	-12.110	8.670	1.00	26.00	N
ATOM	1544	CA	ASN H 197	-34.842	-10.734	8.362	1.00	26.11	C
ATOM	1545	CB	ASN H 197	-35.850	-10.206	9.391	1.00	26.22	C
ATOM	1546	CG	ASN H 197	-36.861	-11.268	9.815	1.00	27.02	C
ATOM	1547	OD1	ASN H 197	-36.835	-11.755	10.956	1.00	27.64	O
ATOM	1548	ND2	ASN H 197	-37.749	-11.638	8.896	1.00	26.54	N
ATOM	1549	C	ASN H 197	-33.590	-9.882	8.382	1.00	25.77	C
ATOM	1550	O	ASN H 197	-32.966	-9.715	9.425	1.00	25.48	O
ATOM	1551	N	VAL H 198	-33.226	-9.359	7.217	1.00	25.74	N
ATOM	1552	CA	VAL H 198	-31.972	-8.644	7.027	1.00	26.22	C
ATOM	1553	CB	VAL H 198	-31.156	-9.251	5.842	1.00	25.83	C
ATOM	1554	CG1	VAL H 198	-29.874	-8.441	5.561	1.00	26.31	C
ATOM	1555	CG2	VAL H 198	-30.818	-10.739	6.104	1.00	25.53	C
ATOM	1556	C	VAL H 198	-32.285	-7.167	6.772	1.00	26.99	C
ATOM	1557	O	VAL H 198	-33.129	-6.855	5.934	1.00	26.38	O
ATOM	1558	N	ASN H 199	-31.613	-6.275	7.505	1.00	27.84	N
ATOM	1559	CA	ASN H 199	-31.777	-4.825	7.333	1.00	28.76	C
ATOM	1560	CB	ASN H 199	-32.523	-4.235	8.529	1.00	29.42	C
ATOM	1561	CG	ASN H 199	-33.097	-2.828	8.264	1.00	31.43	C
ATOM	1562	OD1	ASN H 199	-32.934	-2.233	7.191	1.00	33.84	O
ATOM	1563	ND2	ASN H 199	-33.789	-2.304	9.262	1.00	34.83	N
ATOM	1564	C	ASN H 199	-30.416	-4.141	7.154	1.00	29.04	C
ATOM	1565	O	ASN H 199	-29.559	-4.185	8.050	1.00	29.05	O
ATOM	1566	N	HIS H 200	-30.212	-3.545	5.984	1.00	28.83	N
ATOM	1567	CA	HIS H 200	-29.051	-2.709	5.726	1.00	29.91	C
ATOM	1568	CB	HIS H 200	-28.297	-3.189	4.484	1.00	29.32	C
ATOM	1569	CG	HIS H 200	-27.005	-2.473	4.238	1.00	28.76	C
ATOM	1570	ND1	HIS H 200	-26.734	-1.813	3.059	1.00	29.38	N
ATOM	1571	CE1	HIS H 200	-25.524	-1.284	3.119	1.00	30.12	C
ATOM	1572	NE2	HIS H 200	-25.000	-1.579	4.296	1.00	27.90	N
ATOM	1573	CD2	HIS H 200	-25.904	-2.322	5.014	1.00	27.09	C
ATOM	1574	C	HIS H 200	-29.558	-1.284	5.527	1.00	30.90	C
ATOM	1575	O	HIS H 200	-29.920	-0.897	4.416	1.00	30.89	O
ATOM	1576	N	LYS H 201	-29.587	-0.518	6.614	1.00	32.56	N
ATOM	1577	CA	LYS H 201	-30.141	0.847	6.601	1.00	34.28	C
ATOM	1578	CB	LYS H 201	-30.252	1.408	8.016	1.00	34.79	C
ATOM	1579	CG	LYS H 201	-31.217	0.625	8.891	1.00	37.62	C
ATOM	1580	CD	LYS H 201	-31.823	1.505	9.965	1.00	42.65	C
ATOM	1581	CE	LYS H 201	-32.820	0.732	10.832	1.00	44.13	C
ATOM	1582	NZ	LYS H 201	-32.228	0.341	12.151	1.00	45.56	N
ATOM	1583	C	LYS H 201	-29.418	1.831	5.667	1.00	34.72	C
ATOM	1584	O	LYS H 201	-30.081	2.639	5.005	1.00	35.59	O
ATOM	1585	N	PRO H 202	-28.070	1.777	5.597	1.00	35.03	N
ATOM	1586	CA	PRO H 202	-27.364	2.644	4.647	1.00	35.19	C
ATOM	1587	CB	PRO H 202	-25.918	2.168	4.774	1.00	35.02	C
ATOM	1588	CG	PRO H 202	-25.817	1.698	6.162	1.00	34.64	C
ATOM	1589	CD	PRO H 202	-27.116	0.998	6.413	1.00	34.59	C
ATOM	1590	C	PRO H 202	-27.832	2.602	3.172	1.00	35.98	C
ATOM	1591	O	PRO H 202	-27.798	3.624	2.477	1.00	36.11	O
ATOM	1592	N	SER H 203	-28.255	1.439	2.682	1.00	35.85	N
ATOM	1593	CA	SER H 203	-28.749	1.342	1.301	1.00	35.70	C
ATOM	1594	CB	SER H 203	-28.119	0.143	0.592	1.00	35.66	C
ATOM	1595	OG	SER H 203	-28.561	-1.066	1.215	1.00	33.45	O
ATOM	1596	C	SER H 203	-30.265	1.182	1.279	1.00	36.22	C
ATOM	1597	O	SER H 203	-30.847	0.932	0.223	1.00	36.35	O

ATOM	1598	N	ASN H 204	-30.887	1.315	2.446	1.00	36.69	N
ATOM	1599	CA	ASN H 204	-32.310	1.026	2.639	1.00	37.81	C
ATOM	1600	CB	ASN H 204	-33.188	2.174	2.102	1.00	39.13	C
ATOM	1601	CG	ASN H 204	-33.033	3.452	2.912	1.00	41.72	C
ATOM	1602	OD1	ASN H 204	-33.357	3.496	4.108	1.00	45.33	O
ATOM	1603	ND2	ASN H 204	-32.542	4.505	2.261	1.00	45.42	N
ATOM	1604	C	ASN H 204	-32.749	-0.324	2.056	1.00	37.46	C
ATOM	1605	O	ASN H 204	-33.819	-0.433	1.435	1.00	37.90	O
ATOM	1606	N	THR H 205	-31.912	-1.344	2.255	1.00	35.89	N
ATOM	1607	CA	THR H 205	-32.201	-2.700	1.798	1.00	34.41	C
ATOM	1608	CB	THR H 205	-30.939	-3.369	1.222	1.00	34.53	C
ATOM	1609	OG1	THR H 205	-30.427	-2.555	0.165	1.00	33.48	O
ATOM	1610	CG2	THR H 205	-31.240	-4.765	0.673	1.00	34.29	C
ATOM	1611	C	THR H 205	-32.756	-3.522	2.954	1.00	33.72	C
ATOM	1612	O	THR H 205	-32.111	-3.654	4.000	1.00	32.92	O
ATOM	1613	N	LYS H 206	-33.965	-4.046	2.761	1.00	32.67	N
ATOM	1614	CA	LYS H 206	-34.629	-4.931	3.724	1.00	32.11	C
ATOM	1615	CB	LYS H 206	-35.831	-4.256	4.380	1.00	32.79	C
ATOM	1616	CG	LYS H 206	-35.527	-3.315	5.517	1.00	35.73	C
ATOM	1617	CD	LYS H 206	-36.670	-3.306	6.533	1.00	39.56	C
ATOM	1618	CE	LYS H 206	-37.933	-2.654	5.968	1.00	42.60	C
ATOM	1619	NZ	LYS H 206	-39.093	-2.802	6.928	1.00	43.56	N
ATOM	1620	C	LYS H 206	-35.114	-6.171	2.974	1.00	30.93	C
ATOM	1621	O	LYS H 206	-35.785	-6.046	1.951	1.00	30.29	O
ATOM	1622	N	VAL H 207	-34.754	-7.352	3.480	1.00	29.36	N
ATOM	1623	CA	VAL H 207	-35.021	-8.628	2.815	1.00	27.90	C
ATOM	1624	CB	VAL H 207	-33.753	-9.200	2.109	1.00	27.96	C
ATOM	1625	CG1	VAL H 207	-33.992	-10.662	1.614	1.00	27.56	C
ATOM	1626	CG2	VAL H 207	-33.303	-8.315	0.950	1.00	27.15	C
ATOM	1627	C	VAL H 207	-35.477	-9.639	3.850	1.00	27.74	C
ATOM	1628	O	VAL H 207	-34.873	-9.754	4.928	1.00	26.70	O
ATOM	1629	N	ASP H 208	-36.557	-10.358	3.532	1.00	27.30	N
ATOM	1630	CA	ASP H 208	-36.992	-11.496	4.336	1.00	27.46	C
ATOM	1631	CB	ASP H 208	-38.460	-11.374	4.748	1.00	27.50	C
ATOM	1632	CG	ASP H 208	-38.715	-10.220	5.708	1.00	29.18	C
ATOM	1633	OD1	ASP H 208	-37.883	-9.968	6.611	1.00	31.64	O
ATOM	1634	OD2	ASP H 208	-39.773	-9.559	5.583	1.00	30.26	O
ATOM	1635	C	ASP H 208	-36.747	-12.746	3.495	1.00	27.25	C
ATOM	1636	O	ASP H 208	-37.361	-12.923	2.447	1.00	27.66	O
ATOM	1637	N	LYS H 209	-35.812	-13.585	3.934	1.00	27.14	N
ATOM	1638	CA	LYS H 209	-35.406	-14.755	3.178	1.00	27.94	C
ATOM	1639	CB	LYS H 209	-33.887	-14.731	2.923	1.00	28.16	C
ATOM	1640	CG	LYS H 209	-33.294	-16.000	2.281	1.00	29.27	C
ATOM	1641	CD	LYS H 209	-33.922	-16.322	0.937	1.00	30.53	C
ATOM	1642	CE	LYS H 209	-32.956	-16.176	-0.188	1.00	33.59	C
ATOM	1643	NZ	LYS H 209	-33.549	-16.855	-1.380	1.00	33.42	N
ATOM	1644	C	LYS H 209	-35.843	-16.025	3.920	1.00	28.87	C
ATOM	1645	O	LYS H 209	-35.387	-16.305	5.025	1.00	27.96	O
ATOM	1646	N	ARG H 210	-36.765	-16.759	3.301	1.00	29.84	N
ATOM	1647	CA	ARG H 210	-37.165	-18.085	3.754	1.00	31.09	C
ATOM	1648	CB	ARG H 210	-38.425	-18.512	2.992	1.00	32.15	C
ATOM	1649	CG	ARG H 210	-38.770	-19.977	3.127	1.00	35.45	C
ATOM	1650	CD	ARG H 210	-39.997	-20.138	3.956	1.00	42.75	C
ATOM	1651	NE	ARG H 210	-40.618	-21.427	3.675	1.00	47.70	N
ATOM	1652	CZ	ARG H 210	-41.929	-21.640	3.659	1.00	50.55	C
ATOM	1653	NH1	ARG H 210	-42.785	-20.645	3.902	1.00	52.48	N
ATOM	1654	NH2	ARG H 210	-42.380	-22.853	3.384	1.00	52.35	N

ATOM	1655	C	ARG H 210	-36.048	-19.088	3.468	1.00	30.67	C
ATOM	1656	O	ARG H 210	-35.538	-19.152	2.357	1.00	30.42	O
ATOM	1657	N	VAL H 211	-35.674	-19.867	4.474	1.00	31.05	N
ATOM	1658	CA	VAL H 211	-34.626	-20.882	4.319	1.00	31.81	C
ATOM	1659	CB	VAL H 211	-33.464	-20.703	5.353	1.00	30.81	C
ATOM	1660	CG1	VAL H 211	-32.404	-21.798	5.182	1.00	30.96	C
ATOM	1661	CG2	VAL H 211	-32.831	-19.320	5.222	1.00	29.65	C
ATOM	1662	C	VAL H 211	-35.260	-22.279	4.463	1.00	33.24	C
ATOM	1663	O	VAL H 211	-35.775	-22.624	5.516	1.00	32.57	O
ATOM	1664	N	GLU H 212	-35.211	-23.051	3.386	1.00	35.77	N
ATOM	1665	CA	GLU H 212	-35.830	-24.373	3.322	1.00	38.55	C
ATOM	1666	CB	GLU H 212	-36.797	-24.429	2.143	1.00	39.17	C
ATOM	1667	CG	GLU H 212	-37.985	-23.514	2.328	1.00	42.95	C
ATOM	1668	CD	GLU H 212	-39.132	-23.873	1.434	1.00	47.77	C
ATOM	1669	OE1	GLU H 212	-38.988	-23.728	0.200	1.00	48.74	O
ATOM	1670	OE2	GLU H 212	-40.178	-24.302	1.974	1.00	51.82	O
ATOM	1671	C	GLU H 212	-34.781	-25.469	3.164	1.00	39.73	C
ATOM	1672	O	GLU H 212	-33.757	-25.242	2.522	1.00	39.19	O
ATOM	1673	N	PRO H 213	-35.043	-26.662	3.747	1.00	41.42	N
ATOM	1674	CA	PRO H 213	-34.185	-27.846	3.655	1.00	42.98	C
ATOM	1675	CB	PRO H 213	-35.027	-28.937	4.316	1.00	42.91	C
ATOM	1676	CG	PRO H 213	-35.894	-28.227	5.245	1.00	42.25	C
ATOM	1677	CD	PRO H 213	-36.223	-26.922	4.593	1.00	41.53	C
ATOM	1678	C	PRO H 213	-33.827	-28.274	2.234	1.00	44.79	C
ATOM	1679	O	PRO H 213	-34.559	-27.972	1.284	1.00	45.13	O
ATOM	1680	N	LYS H 214	-32.702	-28.984	2.121	1.00	46.74	N
ATOM	1681	CA	LYS H 214	-32.151	-29.490	0.850	1.00	48.38	C
ATOM	1682	CB	LYS H 214	-32.860	-30.790	0.388	1.00	48.81	C
ATOM	1683	CG	LYS H 214	-34.216	-30.622	-0.328	1.00	50.48	C
ATOM	1684	CD	LYS H 214	-34.077	-30.595	-1.854	1.00	53.36	C
ATOM	1685	CE	LYS H 214	-34.040	-32.004	-2.438	1.00	54.86	C
ATOM	1686	NZ	LYS H 214	-33.445	-32.008	-3.803	1.00	55.56	N
ATOM	1687	C	LYS H 214	-32.100	-28.423	-0.252	1.00	48.81	C
ATOM	1688	O	LYS H 214	-31.126	-27.675	-0.350	1.00	49.46	O
ATOM	1689	N	GLU L 1	8.876	8.780	23.421	1.00	27.08	N
ATOM	1690	CA	GLU L 1	7.742	8.546	24.354	1.00	27.71	C
ATOM	1691	CB	GLU L 1	6.462	8.207	23.574	1.00	27.12	C
ATOM	1692	CG	GLU L 1	6.486	6.892	22.796	1.00	29.33	C
ATOM	1693	CD	GLU L 1	5.153	6.555	22.128	1.00	30.55	C
ATOM	1694	OE1	GLU L 1	4.429	7.470	21.675	1.00	32.02	O
ATOM	1695	OE2	GLU L 1	4.816	5.351	22.054	1.00	34.53	O
ATOM	1696	C	GLU L 1	8.089	7.429	25.343	1.00	26.22	C
ATOM	1697	O	GLU L 1	8.988	6.612	25.089	1.00	26.80	O
ATOM	1698	N	THR L 2	7.378	7.395	26.461	1.00	25.01	N
ATOM	1699	CA	THR L 2	7.512	6.304	27.426	1.00	23.33	C
ATOM	1700	CB	THR L 2	6.922	6.712	28.768	1.00	23.52	C
ATOM	1701	OG1	THR L 2	7.706	7.790	29.299	1.00	21.93	O
ATOM	1702	CG2	THR L 2	6.940	5.547	29.767	1.00	23.00	C
ATOM	1703	C	THR L 2	6.743	5.126	26.843	1.00	23.38	C
ATOM	1704	O	THR L 2	5.575	5.273	26.467	1.00	22.88	O
ATOM	1705	N	THR L 3	7.407	3.978	26.727	1.00	22.46	N
ATOM	1706	CA	THR L 3	6.739	2.780	26.206	1.00	22.28	C
ATOM	1707	CB	THR L 3	7.719	1.903	25.400	1.00	21.89	C
ATOM	1708	OG1	THR L 3	8.106	2.604	24.229	1.00	24.94	O
ATOM	1709	CG2	THR L 3	7.101	0.540	25.004	1.00	24.71	C
ATOM	1710	C	THR L 3	6.186	2.030	27.398	1.00	20.96	C
ATOM	1711	O	THR L 3	6.833	1.956	28.446	1.00	20.94	O

ATOM	1712	N	VAL L	4	4.972	1.509	27.247	1.00	20.65	N
ATOM	1713	CA	VAL L	4	4.292	0.774	28.314	1.00	20.40	C
ATOM	1714	CB	VAL L	4	2.919	1.400	28.642	1.00	20.59	C
ATOM	1715	CG1	VAL L	4	2.276	0.662	29.789	1.00	20.06	C
ATOM	1716	CG2	VAL L	4	3.033	2.939	28.990	1.00	20.26	C
ATOM	1717	C	VAL L	4	4.096	-0.681	27.816	1.00	20.94	C
ATOM	1718	O	VAL L	4	3.478	-0.885	26.770	1.00	21.08	O
ATOM	1719	N	THR L	5	4.650	-1.651	28.548	1.00	20.75	N
ATOM	1720	CA	THR L	5	4.548	-3.078	28.212	1.00	20.66	C
ATOM	1721	CB	THR L	5	5.940	-3.768	28.212	1.00	21.68	C
ATOM	1722	OG1	THR L	5	6.804	-3.084	27.296	1.00	23.52	O
ATOM	1723	CG2	THR L	5	5.829	-5.244	27.767	1.00	22.68	C
ATOM	1724	C	THR L	5	3.620	-3.781	29.196	1.00	18.96	C
ATOM	1725	O	THR L	5	3.944	-3.941	30.376	1.00	18.57	O
ATOM	1726	N	GLN L	6	2.465	-4.203	28.694	1.00	18.67	N
ATOM	1727	CA	GLN L	6	1.432	-4.827	29.498	1.00	17.97	C
ATOM	1728	CB	GLN L	6	0.059	-4.284	29.093	1.00	17.74	C
ATOM	1729	CG	GLN L	6	-1.063	-4.767	29.978	1.00	19.63	C
ATOM	1730	CD	GLN L	6	-2.356	-4.002	29.803	1.00	21.45	C
ATOM	1731	OE1	GLN L	6	-2.410	-2.960	29.126	1.00	20.03	O
ATOM	1732	NE2	GLN L	6	-3.413	-4.505	30.425	1.00	19.37	N
ATOM	1733	C	GLN L	6	1.467	-6.342	29.268	1.00	18.81	C
ATOM	1734	O	GLN L	6	1.557	-6.785	28.121	1.00	18.70	O
ATOM	1735	N	SER L	7	1.376	-7.120	30.347	1.00	19.47	N
ATOM	1736	CA	SER L	7	1.285	-8.578	30.199	1.00	20.51	C
ATOM	1737	CB	SER L	7	2.656	-9.249	30.010	1.00	21.92	C
ATOM	1738	OG	SER L	7	3.597	-8.799	30.929	1.00	28.65	O
ATOM	1739	C	SER L	7	0.451	-9.253	31.280	1.00	19.99	C
ATOM	1740	O	SER L	7	0.306	-8.723	32.382	1.00	19.25	O
ATOM	1741	N	PRO L	8	-0.167	-10.411	30.942	1.00	19.92	N
ATOM	1742	CA	PRO L	8	-0.159	-11.036	29.620	1.00	20.04	C
ATOM	1743	CB	PRO L	8	-0.632	-12.471	29.927	1.00	19.38	C
ATOM	1744	CG	PRO L	8	-1.637	-12.245	31.045	1.00	19.90	C
ATOM	1745	CD	PRO L	8	-0.987	-11.168	31.908	1.00	19.90	C
ATOM	1746	C	PRO L	8	-1.168	-10.360	28.686	1.00	20.14	C
ATOM	1747	O	PRO L	8	-2.029	-9.627	29.146	1.00	21.71	O
ATOM	1748	N	SER L	9	-1.097	-10.621	27.390	1.00	20.48	N
ATOM	1749	CA	SER L	9	-2.093	-10.062	26.460	1.00	21.45	C
ATOM	1750	CB	SER L	9	-1.590	-10.200	25.029	1.00	21.99	C
ATOM	1751	OG	SER L	9	-0.329	-9.553	24.927	1.00	27.19	O
ATOM	1752	C	SER L	9	-3.459	-10.725	26.595	1.00	20.76	C
ATOM	1753	O	SER L	9	-4.492	-10.141	26.271	1.00	18.97	O
ATOM	1754	N	PHE L	10	-3.458	-11.975	27.050	1.00	20.80	N
ATOM	1755	CA	PHE L	10	-4.682	-12.772	27.105	1.00	21.21	C
ATOM	1756	CB	BPHE L	10	-4.812	-13.680	25.866	0.35	21.35	C
ATOM	1757	CB	APHE L	10	-4.839	-13.601	25.823	0.65	21.85	C
ATOM	1758	CG	BPHE L	10	-4.797	-12.949	24.550	0.35	21.60	C
ATOM	1759	CG	APHE L	10	-6.138	-14.366	25.731	0.65	22.87	C
ATOM	1760	CD1	BPHE L	10	-3.622	-12.838	23.815	0.35	21.89	C
ATOM	1761	CD1	APHE L	10	-7.283	-13.769	25.204	0.65	24.22	C
ATOM	1762	CE1	BPHE L	10	-3.600	-12.168	22.597	0.35	21.49	C
ATOM	1763	CE1	APHE L	10	-8.480	-14.485	25.091	0.65	25.65	C
ATOM	1764	CZ	BPHE L	10	-4.772	-11.614	22.093	0.35	22.42	C
ATOM	1765	CZ	APHE L	10	-8.526	-15.810	25.495	0.65	24.88	C
ATOM	1766	CE2	BPHE L	10	-5.954	-11.727	22.811	0.35	22.42	C
ATOM	1767	CE2	APHE L	10	-7.393	-16.415	26.028	0.65	25.21	C
ATOM	1768	CD2	BPHE L	10	-5.965	-12.396	24.030	0.35	21.84	C

ATOM	1769	CD2APHE L 10	-6.203 -15.696 26.137 0.65 24.67	C
ATOM	1770	C PHE L 10	-4.576 -13.651 28.332 1.00 21.08	C
ATOM	1771	O PHE L 10	-3.499 -14.195 28.615 1.00 20.83	O
ATOM	1772	N LEU L 11	-5.671 -13.783 29.069 1.00 21.19	N
ATOM	1773	CA LEU L 11	-5.665 -14.609 30.272 1.00 21.96	C
ATOM	1774	CB LEU L 11	-5.279 -13.761 31.507 1.00 22.05	C
ATOM	1775	CG LEU L 11	-5.044 -14.418 32.868 1.00 22.21	C
ATOM	1776	CD1 LEU L 11	-3.890 -15.412 32.806 1.00 24.75	C
ATOM	1777	CD2 LEU L 11	-4.756 -13.295 33.857 1.00 23.72	C
ATOM	1778	C LEU L 11	-7.024 -15.256 30.481 1.00 21.79	C
ATOM	1779	O LEU L 11	-8.060 -14.580 30.439 1.00 21.15	O
ATOM	1780	N SER L 12	-7.021 -16.575 30.708 1.00 21.32	N
ATOM	1781	CA SER L 12	-8.254 -17.288 31.081 1.00 21.02	C
ATOM	1782	CB SER L 12	-8.357 -18.628 30.337 1.00 20.95	C
ATOM	1783	OG SER L 12	-8.120 -18.431 28.948 1.00 21.75	O
ATOM	1784	C SER L 12	-8.288 -17.512 32.574 1.00 20.92	C
ATOM	1785	O SER L 12	-7.271 -17.838 33.190 1.00 21.26	O
ATOM	1786	N ALA L 13	-9.452 -17.306 33.156 1.00 21.02	N
ATOM	1787	CA ALA L 13	-9.653 -17.527 34.561 1.00 21.50	C
ATOM	1788	CB ALA L 13	-9.293 -16.246 35.376 1.00 21.43	C
ATOM	1789	C ALA L 13	-11.087 -17.920 34.806 1.00 21.78	C
ATOM	1790	O ALA L 13	-11.989 -17.636 34.002 1.00 21.20	O
ATOM	1791	N SER L 14	-11.318 -18.573 35.936 1.00 22.43	N
ATOM	1792	CA SER L 14	-12.670 -18.952 36.300 1.00 23.23	C
ATOM	1793	CB SER L 14	-12.670 -20.250 37.130 1.00 23.08	C
ATOM	1794	OG SER L 14	-12.042 -21.288 36.381 1.00 24.09	O
ATOM	1795	C SER L 14	-13.327 -17.826 37.062 1.00 23.67	C
ATOM	1796	O SER L 14	-12.645 -17.055 37.747 1.00 23.18	O
ATOM	1797	N VAL L 15	-14.650 -17.727 36.946 1.00 23.78	N
ATOM	1798	CA VAL L 15	-15.417 -16.868 37.840 1.00 25.03	C
ATOM	1799	CB VAL L 15	-16.947 -17.029 37.652 1.00 25.36	C
ATOM	1800	CG1 VAL L 15	-17.714 -16.289 38.744 1.00 27.37	C
ATOM	1801	CG2 VAL L 15	-17.380 -16.530 36.281 1.00 27.27	C
ATOM	1802	C VAL L 15	-15.011 -17.206 39.276 1.00 25.06	C
ATOM	1803	O VAL L 15	-14.900 -18.387 39.633 1.00 24.98	O
ATOM	1804	N GLY L 16	-14.748 -16.172 40.079 1.00 24.59	N
ATOM	1805	CA GLY L 16	-14.293 -16.350 41.457 1.00 24.25	C
ATOM	1806	C GLY L 16	-12.789 -16.362 41.676 1.00 23.83	C
ATOM	1807	O GLY L 16	-12.352 -16.242 42.805 1.00 24.48	O
ATOM	1808	N ASP L 17	-12.000 -16.513 40.610 1.00 23.46	N
ATOM	1809	CA ASP L 17	-10.527 -16.547 40.693 1.00 23.35	C
ATOM	1810	CB ASP L 17	-9.919 -16.978 39.367 1.00 23.63	C
ATOM	1811	CG ASP L 17	-9.922 -18.475 39.173 1.00 25.79	C
ATOM	1812	OD1 ASP L 17	-9.485 -18.931 38.083 1.00 27.09	O
ATOM	1813	OD2 ASP L 17	-10.379 -19.180 40.094 1.00 26.70	O
ATOM	1814	C ASP L 17	-9.956 -15.160 40.975 1.00 23.97	C
ATOM	1815	O ASP L 17	-10.646 -14.161 40.809 1.00 23.45	O
ATOM	1816	N ARG L 18	-8.680 -15.122 41.341 1.00 23.32	N
ATOM	1817	CA ARG L 18	-7.949 -13.873 41.475 1.00 24.25	C
ATOM	1818	CB ARG L 18	-7.345 -13.753 42.878 1.00 24.17	C
ATOM	1819	CG ARG L 18	-6.256 -12.655 43.011 1.00 27.71	C
ATOM	1820	CD ARG L 18	-5.772 -12.508 44.452 1.00 28.35	C
ATOM	1821	NE ARG L 18	-6.929 -12.343 45.326 1.00 38.39	N
ATOM	1822	CZ ARG L 18	-6.961 -12.671 46.611 1.00 42.62	C
ATOM	1823	NH1 ARG L 18	-5.873 -13.163 47.202 1.00 44.40	N
ATOM	1824	NH2 ARG L 18	-8.087 -12.503 47.305 1.00 43.69	N
ATOM	1825	C ARG L 18	-6.871 -13.899 40.415 1.00 22.95	C

ATOM	1826	O	ARG L 18	-6.256	-14.944	40.190	1.00	22.28	O
ATOM	1827	N	VAL L 19	-6.652	-12.763	39.747	1.00	21.44	N
ATOM	1828	CA	VAL L 19	-5.608	-12.635	38.741	1.00	20.28	C
ATOM	1829	CB	VAL L 19	-6.159	-12.638	37.277	1.00	21.25	C
ATOM	1830	CG1	VAL L 19	-7.223	-11.531	37.072	1.00	20.25	C
ATOM	1831	CG2	VAL L 19	-6.721	-14.052	36.852	1.00	19.58	C
ATOM	1832	C	VAL L 19	-4.797	-11.346	38.963	1.00	20.28	C
ATOM	1833	O	VAL L 19	-5.309	-10.392	39.532	1.00	19.64	O
ATOM	1834	N	THR L 20	-3.559	-11.338	38.485	1.00	20.33	N
ATOM	1835	CA	THR L 20	-2.690	-10.137	38.525	1.00	20.70	C
ATOM	1836	CB	THR L 20	-1.590	-10.215	39.606	1.00	20.07	C
ATOM	1837	OG1	THR L 20	-2.202	-10.391	40.885	1.00	19.52	O
ATOM	1838	CG2	THR L 20	-0.757	-8.912	39.626	1.00	21.16	C
ATOM	1839	C	THR L 20	-2.085	-9.910	37.154	1.00	21.02	C
ATOM	1840	O	THR L 20	-1.488	-10.830	36.560	1.00	20.99	O
ATOM	1841	N	ILE L 21	-2.260	-8.675	36.665	1.00	20.03	N
ATOM	1842	CA	ILE L 21	-1.775	-8.200	35.374	1.00	21.34	C
ATOM	1843	CB	ILE L 21	-2.871	-7.368	34.634	1.00	21.76	C
ATOM	1844	CG1	ILE L 21	-4.128	-8.167	34.342	1.00	25.48	C
ATOM	1845	CD1	ILE L 21	-5.215	-7.256	33.708	1.00	23.52	C
ATOM	1846	CG2	ILE L 21	-2.320	-6.727	33.334	1.00	25.60	C
ATOM	1847	C	ILE L 21	-0.690	-7.179	35.681	1.00	20.49	C
ATOM	1848	O	ILE L 21	-0.771	-6.487	36.699	1.00	19.49	O
ATOM	1849	N	THR L 22	0.304	-7.074	34.810	1.00	20.33	N
ATOM	1850	CA	THR L 22	1.459	-6.207	35.061	1.00	21.79	C
ATOM	1851	CB	THR L 22	2.770	-7.024	35.312	1.00	21.81	C
ATOM	1852	OG1	THR L 22	3.132	-7.755	34.132	1.00	22.26	O
ATOM	1853	CG2	THR L 22	2.603	-8.009	36.472	1.00	23.05	C
ATOM	1854	C	THR L 22	1.656	-5.221	33.910	1.00	22.18	C
ATOM	1855	O	THR L 22	1.248	-5.491	32.785	1.00	21.29	O
ATOM	1856	N	CYS L 23	2.252	-4.064	34.214	1.00	23.53	N
ATOM	1857	CA	CYS L 23	2.715	-3.095	33.213	1.00	23.89	C
ATOM	1858	CB	CYS L 23	1.737	-1.891	33.053	1.00	25.47	C
ATOM	1859	SG	CYS L 23	0.303	-2.344	32.026	1.00	32.49	S
ATOM	1860	C	CYS L 23	4.100	-2.598	33.619	1.00	23.22	C
ATOM	1861	O	CYS L 23	4.327	-2.285	34.788	1.00	23.22	O
ATOM	1862	N	ILE L 24	5.008	-2.541	32.651	1.00	22.42	N
ATOM	1863	CA	ILE L 24	6.370	-2.090	32.862	1.00	22.72	C
ATOM	1864	CB	ILE L 24	7.413	-3.218	32.527	1.00	22.83	C
ATOM	1865	CG1	ILE L 24	7.178	-4.528	33.331	1.00	24.94	C
ATOM	1866	CD1	ILE L 24	6.710	-4.403	34.760	1.00	26.97	C
ATOM	1867	CG2	ILE L 24	8.856	-2.735	32.688	1.00	24.27	C
ATOM	1868	C	ILE L 24	6.594	-0.890	31.933	1.00	22.12	C
ATOM	1869	O	ILE L 24	6.271	-0.947	30.744	1.00	22.40	O
ATOM	1870	N	THR L 25	7.158	0.189	32.466	1.00	21.29	N
ATOM	1871	CA	THR L 25	7.422	1.365	31.641	1.00	20.80	C
ATOM	1872	CB	THR L 25	6.862	2.629	32.312	1.00	20.74	C
ATOM	1873	OG1	THR L 25	7.514	2.790	33.571	1.00	19.13	O
ATOM	1874	CG2	THR L 25	5.359	2.455	32.563	1.00	20.69	C
ATOM	1875	C	THR L 25	8.912	1.531	31.369	1.00	20.80	C
ATOM	1876	O	THR L 25	9.735	1.115	32.186	1.00	20.68	O
ATOM	1877	N	THR L 26	9.256	2.131	30.223	1.00	20.61	N
ATOM	1878	CA	THR L 26	10.655	2.350	29.858	1.00	20.88	C
ATOM	1879	CB	THR L 26	10.850	2.554	28.345	1.00	21.29	C
ATOM	1880	OG1	THR L 26	9.974	3.604	27.891	1.00	21.39	O
ATOM	1881	CG2	THR L 26	10.584	1.260	27.574	1.00	22.20	C
ATOM	1882	C	THR L 26	11.283	3.560	30.563	1.00	21.17	C

ATOM	1883	O	THR L 26	12.494	3.752	30.488	1.00	21.66	O
ATOM	1884	N	THR L 27	10.473	4.376	31.232	1.00	20.85	N
ATOM	1885	CA	THR L 27	11.017	5.473	32.033	1.00	20.99	C
ATOM	1886	CB	THR L 27	10.839	6.860	31.346	1.00	20.61	C
ATOM	1887	OG1	THR L 27	9.454	7.173	31.272	1.00	22.68	O
ATOM	1888	CG2	THR L 27	11.402	6.846	29.922	1.00	21.16	C
ATOM	1889	C	THR L 27	10.332	5.438	33.384	1.00	20.10	C
ATOM	1890	O	THR L 27	9.264	4.837	33.529	1.00	19.06	O
ATOM	1891	N	ASPL 28	10.967	6.057	34.385	1.00	20.01	N
ATOM	1892	CA	ASPL 28	10.407	6.112	35.716	1.00	20.13	C
ATOM	1893	CB	ASPL 28	11.478	6.565	36.715	1.00	20.17	C
ATOM	1894	CG	ASPL 28	11.023	6.484	38.166	1.00	19.36	C
ATOM	1895	OD1	ASPL 28	9.907	6.911	38.499	1.00	22.39	O
ATOM	1896	OD2	ASPL 28	11.808	6.008	39.005	1.00	20.42	O
ATOM	1897	C	ASPL 28	9.253	7.108	35.660	1.00	20.48	C
ATOM	1898	O	ASPL 28	9.470	8.327	35.449	1.00	20.73	O
ATOM	1899	N	ILE L 29	8.042	6.598	35.861	1.00	19.02	N
ATOM	1900	CA	ILE L 29	6.831	7.414	35.845	1.00	18.34	C
ATOM	1901	CB	ILE L 29	5.729	6.790	34.931	1.00	18.13	C
ATOM	1902	CG1	ILE L 29	5.297	5.398	35.454	1.00	17.25	C
ATOM	1903	CD1	ILE L 29	3.869	5.027	35.027	1.00	17.99	C
ATOM	1904	CG2	ILE L 29	6.196	6.737	33.506	1.00	17.51	C
ATOM	1905	C	ILE L 29	6.250	7.665	37.230	1.00	17.91	C
ATOM	1906	O	ILE L 29	5.075	8.000	37.368	1.00	17.09	O
ATOM	1907	N	ASPL 30	7.080	7.506	38.259	1.00	18.12	N
ATOM	1908	CA	ASPL 30	6.654	7.628	39.645	1.00	17.89	C
ATOM	1909	CB	ASPL 30	6.690	9.113	40.164	1.00	17.52	C
ATOM	1910	CG	ASPL 30	5.756	10.049	39.404	1.00	15.64	C
ATOM	1911	OD1	ASPL 30	4.615	10.203	39.823	1.00	15.15	O
ATOM	1912	OD2	ASPL 30	6.200	10.662	38.422	1.00	17.54	O
ATOM	1913	C	ASPL 30	5.380	6.822	39.949	1.00	19.49	C
ATOM	1914	O	ASPL 30	5.385	5.587	39.726	1.00	19.56	O
ATOM	1915	N	ASPL 31	4.311	7.447	40.449	1.00	18.32	N
ATOM	1916	CA	ASPL 31	3.046	6.750	40.663	1.00	18.41	C
ATOM	1917	CB	ASPL 31	2.451	7.110	42.040	1.00	18.82	C
ATOM	1918	CG	ASPL 31	2.090	8.593	42.158	1.00	22.01	C
ATOM	1919	OD1	ASPL 31	2.222	9.328	41.154	1.00	21.36	O
ATOM	1920	OD2	ASPL 31	1.657	9.030	43.235	1.00	22.69	O
ATOM	1921	C	ASPL 31	1.985	7.007	39.577	1.00	18.02	C
ATOM	1922	O	ASPL 31	0.813	6.798	39.822	1.00	18.49	O
ATOM	1923	N	ASPL 32	2.376	7.484	38.394	1.00	17.60	N
ATOM	1924	CA	ASPL 32	1.373	7.943	37.417	1.00	15.50	C
ATOM	1925	CB	ASPL 32	1.978	8.980	36.493	1.00	15.07	C
ATOM	1926	CG	ASPL 32	2.466	10.208	37.255	1.00	15.08	C
ATOM	1927	OD1	ASPL 32	1.914	10.486	38.330	1.00	15.52	O
ATOM	1928	OD2	ASPL 32	3.402	10.831	36.773	1.00	16.22	O
ATOM	1929	C	ASPL 32	0.830	6.806	36.541	1.00	16.08	C
ATOM	1930	O	ASPL 32	0.826	6.917	35.326	1.00	15.37	O
ATOM	1931	N	MET L 33	0.383	5.730	37.173	1.00	16.24	N
ATOM	1932	CA	MET L 33	-0.199	4.626	36.425	1.00	16.98	C
ATOM	1933	CB	MET L 33	0.439	3.302	36.896	1.00	17.04	C
ATOM	1934	CG	MET L 33	-0.114	2.040	36.232	1.00	19.44	C
ATOM	1935	SD	MET L 33	-0.045	2.093	34.463	1.00	23.58	S
ATOM	1936	CE	MET L 33	1.668	2.229	34.036	1.00	22.42	C
ATOM	1937	C	MET L 33	-1.704	4.663	36.636	1.00	16.02	C
ATOM	1938	O	MET L 33	-2.182	4.938	37.729	1.00	17.68	O
ATOM	1939	N	ASN L 34	-2.449	4.399	35.570	1.00	15.94	N

ATOM	1940	CA	ASN	L	34	-3.894	4.457	35.585	1.00	15.86	C
ATOM	1941	CB	ASN	L	34	-4.396	5.675	34.778	1.00	14.74	C
ATOM	1942	CG	ASN	L	34	-3.754	6.997	35.237	1.00	14.84	C
ATOM	1943	OD1	ASN	L	34	-4.308	7.701	36.074	1.00	15.00	O
ATOM	1944	ND2	ASN	L	34	-2.572	7.316	34.685	1.00	14.94	N
ATOM	1945	C	ASN	L	34	-4.413	3.180	34.916	1.00	15.88	C
ATOM	1946	O	ASN	L	34	-3.774	2.682	33.996	1.00	16.56	O
ATOM	1947	N	TRP	L	35	-5.550	2.687	35.371	1.00	16.04	N
ATOM	1948	CA	TRP	L	35	-6.116	1.436	34.825	1.00	16.65	C
ATOM	1949	CB	TRP	L	35	-6.058	0.306	35.868	1.00	16.50	C
ATOM	1950	CG	TRP	L	35	-4.659	-0.088	36.260	1.00	17.69	C
ATOM	1951	CD1	TRP	L	35	-3.913	0.429	37.299	1.00	19.42	C
ATOM	1952	NE1	TRP	L	35	-2.682	-0.180	37.351	1.00	17.50	N
ATOM	1953	CE2	TRP	L	35	-2.598	-1.099	36.332	1.00	19.15	C
ATOM	1954	CD2	TRP	L	35	-3.833	-1.074	35.628	1.00	18.86	C
ATOM	1955	CE3	TRP	L	35	-4.019	-1.952	34.539	1.00	18.41	C
ATOM	1956	CZ3	TRP	L	35	-2.968	-2.826	34.194	1.00	18.31	C
ATOM	1957	CH2	TRP	L	35	-1.757	-2.827	34.928	1.00	17.50	C
ATOM	1958	CZ2	TRP	L	35	-1.545	-1.963	35.978	1.00	18.60	C
ATOM	1959	C	TRP	L	35	-7.538	1.633	34.338	1.00	16.02	C
ATOM	1960	O	TRP	L	35	-8.358	2.270	35.015	1.00	16.74	O
ATOM	1961	N	PHE	L	36	-7.823	1.060	33.164	1.00	16.78	N
ATOM	1962	CA	PHE	L	36	-9.125	1.163	32.493	1.00	16.46	C
ATOM	1963	CB	PHE	L	36	-8.960	1.913	31.156	1.00	16.50	C
ATOM	1964	CG	PHE	L	36	-8.540	3.360	31.330	1.00	16.76	C
ATOM	1965	CD1	PHE	L	36	-7.190	3.700	31.430	1.00	16.05	C
ATOM	1966	CE1	PHE	L	36	-6.804	5.055	31.640	1.00	17.36	C
ATOM	1967	CZ	PHE	L	36	-7.788	6.048	31.737	1.00	16.63	C
ATOM	1968	CE2	PHE	L	36	-9.148	5.713	31.631	1.00	16.21	C
ATOM	1969	CD2	PHE	L	36	-9.513	4.360	31.424	1.00	17.83	C
ATOM	1970	C	PHE	L	36	-9.664	-0.223	32.161	1.00	17.14	C
ATOM	1971	O	PHE	L	36	-8.875	-1.125	31.902	1.00	16.40	O
ATOM	1972	N	GLN	L	37	-10.991	-0.334	32.127	1.00	17.23	N
ATOM	1973	CA	GLN	L	37	-11.691	-1.529	31.640	1.00	18.66	C
ATOM	1974	CB	GLN	L	37	-12.673	-1.983	32.697	1.00	17.96	C
ATOM	1975	CG	GLN	L	37	-13.460	-3.246	32.394	1.00	20.47	C
ATOM	1976	CD	GLN	L	37	-14.555	-3.413	33.420	1.00	25.35	C
ATOM	1977	OE1	GLN	L	37	-15.521	-2.643	33.439	1.00	26.60	O
ATOM	1978	NE2	GLN	L	37	-14.391	-4.383	34.319	1.00	24.91	N
ATOM	1979	C	GLN	L	37	-12.467	-1.122	30.410	1.00	20.01	C
ATOM	1980	O	GLN	L	37	-13.081	-0.033	30.398	1.00	19.85	O
ATOM	1981	N	GLN	L	38	-12.453	-1.970	29.377	1.00	20.10	N
ATOM	1982	CA	GLN	L	38	-13.237	-1.707	28.198	1.00	21.15	C
ATOM	1983	CB	GLN	L	38	-12.361	-1.210	27.044	1.00	20.42	C
ATOM	1984	CG	GLN	L	38	-13.196	-0.699	25.866	1.00	21.30	C
ATOM	1985	CD	GLN	L	38	-12.358	-0.288	24.655	1.00	20.60	C
ATOM	1986	OE1	GLN	L	38	-11.258	-0.805	24.425	1.00	22.27	O
ATOM	1987	NE2	GLN	L	38	-12.877	0.651	23.878	1.00	22.43	N
ATOM	1988	C	GLN	L	38	-13.966	-2.962	27.738	1.00	22.95	C
ATOM	1989	O	GLN	L	38	-13.334	-3.998	27.488	1.00	21.53	O
ATOM	1990	N	GLU	L	39	-15.285	-2.848	27.615	1.00	25.02	N
ATOM	1991	CA	GLU	L	39	-16.104	-3.914	27.015	1.00	28.73	C
ATOM	1992	CB	GLU	L	39	-17.452	-3.983	27.714	1.00	29.15	C
ATOM	1993	CG	GLU	L	39	-17.334	-4.042	29.222	1.00	35.04	C
ATOM	1994	CD	GLU	L	39	-18.677	-4.183	29.899	1.00	43.08	C
ATOM	1995	OE1	GLU	L	39	-19.709	-4.009	29.206	1.00	45.79	O
ATOM	1996	OE2	GLU	L	39	-18.705	-4.468	31.124	1.00	48.21	O

ATOM	1997	C	GLU	L	39	-16.283	-3.669	25.521	1.00	29.81	C
ATOM	1998	O	GLU	L	39	-16.154	-2.519	25.067	1.00	29.85	O
ATOM	1999	N	PRO	L	40	-16.565	-4.744	24.733	1.00	31.26	N
ATOM	2000	CA	PRO	L	40	-16.678	-4.571	23.280	1.00	31.55	C
ATOM	2001	CB	PRO	L	40	-16.986	-5.995	22.789	1.00	31.89	C
ATOM	2002	CG	PRO	L	40	-16.411	-6.886	23.854	1.00	31.69	C
ATOM	2003	CD	PRO	L	40	-16.739	-6.160	25.119	1.00	31.35	C
ATOM	2004	C	PRO	L	40	-17.785	-3.561	22.896	1.00	31.44	C
ATOM	2005	O	PRO	L	40	-18.873	-3.565	23.474	1.00	31.30	O
ATOM	2006	N	GLY	L	41	-17.468	-2.657	21.982	1.00	31.84	N
ATOM	2007	CA	GLY	L	41	-18.422	-1.630	21.564	1.00	31.95	C
ATOM	2008	C	GLY	L	41	-18.635	-0.464	22.514	1.00	32.06	C
ATOM	2009	O	GLY	L	41	-19.452	0.414	22.233	1.00	32.62	O
ATOM	2010	N	LYS	L	42	-17.907	-0.434	23.636	1.00	30.95	N
ATOM	2011	CA	LYS	L	42	-18.063	0.640	24.616	1.00	29.82	C
ATOM	2012	CB	LYS	L	42	-18.487	0.075	25.975	1.00	29.52	C
ATOM	2013	CG	LYS	L	42	-19.867	-0.619	26.017	1.00	31.69	C
ATOM	2014	CD	LYS	L	42	-20.129	-1.093	27.448	1.00	33.02	C
ATOM	2015	CE	LYS	L	42	-21.550	-1.635	27.679	1.00	38.79	C
ATOM	2016	NZ	LYS	L	42	-21.745	-1.893	29.160	1.00	39.88	N
ATOM	2017	C	LYS	L	42	-16.794	1.485	24.782	1.00	27.72	C
ATOM	2018	O	LYS	L	42	-15.698	1.071	24.408	1.00	26.74	O
ATOM	2019	N	ALA	L	43	-16.954	2.673	25.356	1.00	25.53	N
ATOM	2020	CA	ALA	L	43	-15.806	3.489	25.751	1.00	24.41	C
ATOM	2021	CB	ALA	L	43	-16.267	4.891	26.126	1.00	24.05	C
ATOM	2022	C	ALA	L	43	-15.097	2.835	26.947	1.00	23.21	C
ATOM	2023	O	ALA	L	43	-15.742	2.150	27.753	1.00	23.80	O
ATOM	2024	N	PRO	L	44	-13.779	3.045	27.074	1.00	22.34	N
ATOM	2025	CA	PRO	L	44	-13.117	2.630	28.314	1.00	22.53	C
ATOM	2026	CB	PRO	L	44	-11.644	3.010	28.076	1.00	21.83	C
ATOM	2027	CG	PRO	L	44	-11.491	3.037	26.579	1.00	22.43	C
ATOM	2028	CD	PRO	L	44	-12.815	3.585	26.090	1.00	22.09	C
ATOM	2029	C	PRO	L	44	-13.680	3.298	29.571	1.00	22.53	C
ATOM	2030	O	PRO	L	44	-14.322	4.368	29.516	1.00	22.45	O
ATOM	2031	N	LYS	L	45	-13.484	2.631	30.696	1.00	21.67	N
ATOM	2032	CA	LYS	L	45	-13.952	3.108	31.971	1.00	21.39	C
ATOM	2033	CB	LYS	L	45	-14.988	2.110	32.510	1.00	22.55	C
ATOM	2034	CG	LYS	L	45	-15.409	2.299	33.952	1.00	26.71	C
ATOM	2035	CD	LYS	L	45	-16.303	1.125	34.329	1.00	31.95	C
ATOM	2036	CE	LYS	L	45	-17.238	1.437	35.478	1.00	36.74	C
ATOM	2037	NZ	LYS	L	45	-16.473	1.551	36.738	1.00	40.13	N
ATOM	2038	C	LYS	L	45	-12.769	3.201	32.922	1.00	20.31	C
ATOM	2039	O	LYS	L	45	-12.039	2.226	33.100	1.00	19.19	O
ATOM	2040	N	LEU	L	46	-12.595	4.346	33.578	1.00	19.16	N
ATOM	2041	CA	LEU	L	46	-11.477	4.505	34.501	1.00	18.87	C
ATOM	2042	CB	LEU	L	46	-11.225	5.994	34.790	1.00	18.78	C
ATOM	2043	CG	LEU	L	46	-10.118	6.372	35.779	1.00	19.15	C
ATOM	2044	CD1	LEU	L	46	-8.739	5.959	35.264	1.00	17.38	C
ATOM	2045	CD2	LEU	L	46	-10.157	7.903	36.086	1.00	17.89	C
ATOM	2046	C	LEU	L	46	-11.735	3.757	35.818	1.00	18.84	C
ATOM	2047	O	LEU	L	46	-12.763	3.969	36.477	1.00	20.15	O
ATOM	2048	N	LEU	L	47	-10.802	2.893	36.199	1.00	18.71	N
ATOM	2049	CA	LEU	L	47	-10.927	2.124	37.425	1.00	18.42	C
ATOM	2050	CB	LEU	L	47	-10.455	0.677	37.214	1.00	18.71	C
ATOM	2051	CG	LEU	L	47	-11.191	-0.124	36.127	1.00	19.97	C
ATOM	2052	CD1	LEU	L	47	-10.426	-1.412	35.872	1.00	22.84	C
ATOM	2053	CD2	LEU	L	47	-12.647	-0.410	36.501	1.00	22.27	C

ATOM	2054	C	LEU	L	47	-10.102	2.747	38.541	1.00	17.85	C
ATOM	2055	O	LEU	L	47	-10.582	2.883	39.657	1.00	17.07	O
ATOM	2056	N	ILE	L	48	-8.849	3.062	38.222	1.00	17.42	N
ATOM	2057	CA	ILE	L	48	-7.843	3.493	39.198	1.00	18.01	C
ATOM	2058	CB	ILE	L	48	-6.912	2.297	39.601	1.00	18.44	C
ATOM	2059	CG1	ILE	L	48	-7.695	1.242	40.411	1.00	17.84	C
ATOM	2060	CD1	ILE	L	48	-6.945	-0.086	40.550	1.00	19.90	C
ATOM	2061	CG2	ILE	L	48	-5.676	2.799	40.395	1.00	17.71	C
ATOM	2062	C	ILE	L	48	-6.994	4.604	38.590	1.00	17.80	C
ATOM	2063	O	ILE	L	48	-6.509	4.454	37.482	1.00	17.32	O
ATOM	2064	N	SER	L	49	-6.815	5.709	39.317	1.00	18.59	N
ATOM	2065	CA	SER	L	49	-6.024	6.850	38.828	1.00	18.36	C
ATOM	2066	CB	SER	L	49	-6.822	8.161	38.992	1.00	17.90	C
ATOM	2067	OG	SER	L	49	-7.138	8.389	40.349	1.00	17.81	O
ATOM	2068	C	SER	L	49	-4.665	6.940	39.552	1.00	18.56	C
ATOM	2069	O	SER	L	49	-4.401	6.165	40.483	1.00	18.55	O
ATOM	2070	N	GLU	L	50	-3.796	7.851	39.106	1.00	18.18	N
ATOM	2071	CA	GLU	L	50	-2.453	8.027	39.693	1.00	18.71	C
ATOM	2072	CB	GLU	L	50	-1.845	9.406	39.342	1.00	18.24	C
ATOM	2073	CG	GLU	L	50	-1.919	9.817	37.887	1.00	16.78	C
ATOM	2074	CD	GLU	L	50	-1.319	11.224	37.650	1.00	18.34	C
ATOM	2075	OE1	GLU	L	50	-1.140	11.600	36.474	1.00	17.75	O
ATOM	2076	OE2	GLU	L	50	-0.992	11.920	38.645	1.00	18.88	O
ATOM	2077	C	GLU	L	50	-2.425	7.888	41.213	1.00	19.24	C
ATOM	2078	O	GLU	L	50	-3.271	8.451	41.916	1.00	18.42	O
ATOM	2079	N	GLY	L	51	-1.449	7.125	41.702	1.00	19.64	N
ATOM	2080	CA	GLY	L	51	-1.279	6.900	43.144	1.00	20.27	C
ATOM	2081	C	GLY	L	51	-2.168	5.794	43.683	1.00	21.29	C
ATOM	2082	O	GLY	L	51	-2.504	5.772	44.875	1.00	20.74	O
ATOM	2083	N	ASN	L	52	-2.526	4.850	42.806	1.00	22.05	N
ATOM	2084	CA	ASN	L	52	-3.385	3.713	43.167	1.00	22.95	C
ATOM	2085	CB	ASN	L	52	-2.642	2.760	44.125	1.00	23.85	C
ATOM	2086	CG	ASN	L	52	-1.323	2.349	43.574	1.00	24.82	C
ATOM	2087	OD1	ASN	L	52	-1.257	1.728	42.519	1.00	25.35	O
ATOM	2088	ND2	ASN	L	52	-0.245	2.740	44.250	1.00	28.10	N
ATOM	2089	C	ASN	L	52	-4.707	4.108	43.765	1.00	23.54	C
ATOM	2090	O	ASN	L	52	-5.185	3.452	44.700	1.00	24.81	O
ATOM	2091	N	ILE	L	53	-5.337	5.145	43.218	1.00	22.73	N
ATOM	2092	CA	ILE	L	53	-6.580	5.616	43.801	1.00	23.29	C
ATOM	2093	CB	ILE	L	53	-6.665	7.168	43.819	1.00	23.41	C
ATOM	2094	CG1	ILE	L	53	-5.526	7.747	44.682	1.00	23.24	C
ATOM	2095	CD1	ILE	L	53	-5.427	9.273	44.629	1.00	25.04	C
ATOM	2096	CG2	ILE	L	53	-8.040	7.619	44.309	1.00	24.68	C
ATOM	2097	C	ILE	L	53	-7.756	4.996	43.060	1.00	22.93	C
ATOM	2098	O	ILE	L	53	-7.931	5.200	41.867	1.00	22.21	O
ATOM	2099	N	LEU	L	54	-8.535	4.196	43.778	1.00	23.67	N
ATOM	2100	CA	LEU	L	54	-9.710	3.566	43.211	1.00	24.31	C
ATOM	2101	CB	LEU	L	54	-10.238	2.510	44.184	1.00	24.58	C
ATOM	2102	CG	LEU	L	54	-11.303	1.512	43.747	1.00	25.63	C
ATOM	2103	CD1	LEU	L	54	-10.802	0.696	42.590	1.00	26.10	C
ATOM	2104	CD2	LEU	L	54	-11.668	0.586	44.930	1.00	26.03	C
ATOM	2105	C	LEU	L	54	-10.758	4.644	42.973	1.00	24.73	C
ATOM	2106	O	LEU	L	54	-11.052	5.418	43.871	1.00	24.75	O
ATOM	2107	N	ARG	L	55	-11.343	4.691	41.786	1.00	24.95	N
ATOM	2108	CA	ARG	L	55	-12.362	5.715	41.511	1.00	26.09	C
ATOM	2109	CB	ARG	L	55	-12.618	5.876	40.004	1.00	26.02	C
ATOM	2110	CG	ARG	L	55	-11.373	6.171	39.152	1.00	24.85	C

ATOM	2111	CD	ARG L	55	-10.477	7.317	39.695	1.00	26.09	C
ATOM	2112	NE	ARG L	55	-11.258	8.499	40.082	1.00	26.24	N
ATOM	2113	CZ	ARG L	55	-10.854	9.408	40.966	1.00	26.22	C
ATOM	2114	NH1	ARG L	55	-9.650	9.314	41.542	1.00	25.54	N
ATOM	2115	NH2	ARG L	55	-11.657	10.429	41.257	1.00	27.29	N
ATOM	2116	C	ARG L	55	-13.671	5.428	42.263	1.00	27.35	C
ATOM	2117	O	ARG L	55	-13.997	4.258	42.527	1.00	26.75	O
ATOM	2118	N	PRO L	56	-14.435	6.490	42.612	1.00	28.76	N
ATOM	2119	CA	PRO L	56	-15.701	6.284	43.332	1.00	29.63	C
ATOM	2120	CB	PRO L	56	-16.305	7.702	43.390	1.00	30.26	C
ATOM	2121	CG	PRO L	56	-15.131	8.603	43.340	1.00	30.06	C
ATOM	2122	CD	PRO L	56	-14.194	7.925	42.352	1.00	29.53	C
ATOM	2123	C	PRO L	56	-16.622	5.331	42.566	1.00	29.80	C
ATOM	2124	O	PRO L	56	-16.701	5.411	41.337	1.00	30.16	O
ATOM	2125	N	GLY L	57	-17.253	4.396	43.278	1.00	29.78	N
ATOM	2126	CA	GLY L	57	-18.151	3.420	42.646	1.00	29.98	C
ATOM	2127	C	GLY L	57	-17.494	2.177	42.041	1.00	30.42	C
ATOM	2128	O	GLY L	57	-18.190	1.246	41.613	1.00	31.07	O
ATOM	2129	N	VAL L	58	-16.164	2.156	41.979	1.00	29.04	N
ATOM	2130	CA	VAL L	58	-15.460	0.979	41.459	1.00	28.45	C
ATOM	2131	CB	VAL L	58	-14.090	1.354	40.810	1.00	28.13	C
ATOM	2132	CG1	VAL L	58	-13.420	0.112	40.189	1.00	28.19	C
ATOM	2133	CG2	VAL L	58	-14.296	2.405	39.736	1.00	26.29	C
ATOM	2134	C	VAL L	58	-15.314	-0.039	42.597	1.00	28.16	C
ATOM	2135	O	VAL L	58	-14.876	0.333	43.691	1.00	27.62	O
ATOM	2136	N	PRO L	59	-15.696	-1.322	42.352	1.00	27.80	N
ATOM	2137	CA	PRO L	59	-15.601	-2.357	43.395	1.00	27.99	C
ATOM	2138	CB	PRO L	59	-16.009	-3.646	42.649	1.00	27.88	C
ATOM	2139	CG	PRO L	59	-16.868	-3.189	41.560	1.00	28.13	C
ATOM	2140	CD	PRO L	59	-16.249	-1.877	41.101	1.00	27.66	C
ATOM	2141	C	PRO L	59	-14.197	-2.506	44.005	1.00	27.89	C
ATOM	2142	O	PRO L	59	-13.196	-2.386	43.302	1.00	27.28	O
ATOM	2143	N	SER L	60	-14.131	-2.783	45.305	1.00	28.03	N
ATOM	2144	CA	SER L	60	-12.848	-2.904	45.989	1.00	28.35	C
ATOM	2145	CB	SER L	60	-13.032	-2.740	47.500	1.00	28.93	C
ATOM	2146	OG	SER L	60	-14.115	-3.542	47.921	1.00	32.55	O
ATOM	2147	C	SER L	60	-12.118	-4.210	45.667	1.00	27.57	C
ATOM	2148	O	SER L	60	-11.005	-4.433	46.149	1.00	27.42	O
ATOM	2149	N	ARG L	61	-12.728	-5.068	44.840	1.00	26.41	N
ATOM	2150	CA	ARG L	61	-12.007	-6.237	44.325	1.00	24.85	C
ATOM	2151	CB	ARG L	61	-12.972	-7.301	43.768	1.00	24.62	C
ATOM	2152	CG	ARG L	61	-13.795	-6.897	42.557	1.00	25.03	C
ATOM	2153	CD	ARG L	61	-14.641	-8.087	42.057	1.00	24.66	C
ATOM	2154	NE	ARG L	61	-15.414	-7.752	40.864	1.00	24.65	N
ATOM	2155	CZ	ARG L	61	-16.573	-7.095	40.875	1.00	24.74	C
ATOM	2156	NH1	ARG L	61	-17.121	-6.724	42.023	1.00	28.72	N
ATOM	2157	NH2	ARG L	61	-17.197	-6.816	39.736	1.00	26.65	N
ATOM	2158	C	ARG L	61	-10.905	-5.840	43.321	1.00	24.22	C
ATOM	2159	O	ARG L	61	-10.035	-6.642	43.010	1.00	22.43	O
ATOM	2160	N	PHE L	62	-10.949	-4.591	42.833	1.00	23.38	N
ATOM	2161	CA	PHE L	62	-9.875	-4.045	41.994	1.00	22.83	C
ATOM	2162	CB	PHE L	62	-10.454	-3.035	40.987	1.00	22.43	C
ATOM	2163	CG	PHE L	62	-11.340	-3.654	39.974	1.00	21.87	C
ATOM	2164	CD1	PHE L	62	-10.811	-4.128	38.785	1.00	20.70	C
ATOM	2165	CE1	PHE L	62	-11.631	-4.746	37.839	1.00	20.27	C
ATOM	2166	CZ	PHE L	62	-12.997	-4.901	38.091	1.00	20.37	C
ATOM	2167	CE2	PHE L	62	-13.531	-4.447	39.285	1.00	21.98	C

ATOM	2168	CD2 PHE L 62	-12.699	-3.828	40.228	1.00	21.98	C
ATOM	2169	C PHE L 62	-8.876	-3.333	42.898	1.00	23.18	C
ATOM	2170	O PHE L 62	-9.285	-2.490	43.681	1.00	23.24	O
ATOM	2171	N SER L 63	-7.596	-3.692	42.818	1.00	23.05	N
ATOM	2172	CA SER L 63	-6.538	-2.977	43.543	1.00	24.41	C
ATOM	2173	CB SER L 63	-6.194	-3.660	44.875	1.00	24.76	C
ATOM	2174	OG SER L 63	-5.739	-4.974	44.633	1.00	27.73	O
ATOM	2175	C SER L 63	-5.304	-2.926	42.666	1.00	23.98	C
ATOM	2176	O SER L 63	-5.154	-3.747	41.761	1.00	24.23	O
ATOM	2177	N SER L 64	-4.416	-1.971	42.930	1.00	23.63	N
ATOM	2178	CA SER L 64	-3.188	-1.859	42.157	1.00	22.90	C
ATOM	2179	CB SER L 64	-3.351	-0.758	41.086	1.00	23.14	C
ATOM	2180	OG SER L 64	-3.493	0.522	41.688	1.00	24.38	O
ATOM	2181	C SER L 64	-1.987	-1.582	43.052	1.00	23.03	C
ATOM	2182	O SER L 64	-2.136	-1.221	44.220	1.00	22.98	O
ATOM	2183	N SER L 65	-0.795	-1.757	42.510	1.00	22.60	N
ATOM	2184	CA SER L 65	0.411	-1.400	43.230	1.00	23.12	C
ATOM	2185	CB SER L 65	0.893	-2.587	44.087	1.00	22.93	C
ATOM	2186	OG SER L 65	1.359	-3.616	43.228	1.00	25.96	O
ATOM	2187	C SER L 65	1.477	-1.011	42.245	1.00	22.36	C
ATOM	2188	O SER L 65	1.360	-1.284	41.024	1.00	22.65	O
ATOM	2189	N GLY L 66	2.537	-0.389	42.761	1.00	22.22	N
ATOM	2190	CA GLY L 66	3.715	-0.122	41.963	1.00	21.69	C
ATOM	2191	C GLY L 66	4.132	1.330	41.979	1.00	22.54	C
ATOM	2192	O GLY L 66	3.287	2.221	42.138	1.00	22.79	O
ATOM	2193	N TYR L 67	5.431	1.555	41.812	1.00	22.87	N
ATOM	2194	CA TYR L 67	6.016	2.896	41.787	1.00	23.02	C
ATOM	2195	CB TYR L 67	6.347	3.382	43.210	1.00	23.92	C
ATOM	2196	CG TYR L 67	6.711	4.849	43.250	1.00	23.40	C
ATOM	2197	CD1 TYR L 67	5.741	5.796	43.537	1.00	24.77	C
ATOM	2198	CE1 TYR L 67	6.043	7.163	43.562	1.00	25.31	C
ATOM	2199	CZ TYR L 67	7.315	7.590	43.273	1.00	26.13	C
ATOM	2200	OH TYR L 67	7.535	8.962	43.313	1.00	28.95	O
ATOM	2201	CE2 TYR L 67	8.317	6.683	42.970	1.00	24.96	C
ATOM	2202	CD2 TYR L 67	8.010	5.295	42.961	1.00	24.61	C
ATOM	2203	C TYR L 67	7.284	2.838	40.965	1.00	23.46	C
ATOM	2204	O TYR L 67	8.136	1.982	41.204	1.00	24.90	O
ATOM	2205	N GLY L 68	7.428	3.733	39.996	1.00	21.87	N
ATOM	2206	CA GLY L 68	8.671	3.843	39.276	1.00	20.81	C
ATOM	2207	C GLY L 68	8.502	3.302	37.874	1.00	20.95	C
ATOM	2208	O GLY L 68	8.026	4.013	36.988	1.00	20.05	O
ATOM	2209	N THR L 69	8.887	2.037	37.675	1.00	19.38	N
ATOM	2210	CA THR L 69	8.755	1.381	36.365	1.00	19.90	C
ATOM	2211	CB THR L 69	10.128	1.035	35.757	1.00	20.15	C
ATOM	2212	OG1 THR L 69	10.840	0.162	36.659	1.00	21.15	O
ATOM	2213	CG2 THR L 69	10.949	2.318	35.525	1.00	18.64	C
ATOM	2214	C THR L 69	7.907	0.091	36.364	1.00	20.22	C
ATOM	2215	O THR L 69	7.593	-0.423	35.299	1.00	21.12	O
ATOM	2216	N ASP L 70	7.560	-0.439	37.533	1.00	20.53	N
ATOM	2217	CA ASP L 70	6.853	-1.747	37.598	1.00	20.13	C
ATOM	2218	CB ASP L 70	7.692	-2.815	38.321	1.00	19.79	C
ATOM	2219	CG ASP L 70	9.088	-2.966	37.744	1.00	23.13	C
ATOM	2220	OD1 ASP L 70	9.218	-3.266	36.551	1.00	29.38	O
ATOM	2221	OD2 ASP L 70	10.074	-2.789	38.493	1.00	29.24	O
ATOM	2222	C ASP L 70	5.534	-1.598	38.312	1.00	19.08	C
ATOM	2223	O ASP L 70	5.495	-1.114	39.438	1.00	18.82	O
ATOM	2224	N PHE L 71	4.461	-2.063	37.674	1.00	17.66	N

ATOM	2225	CA	PHE	L	71	3.101	-1.857	38.159	1.00	17.61	C
ATOM	2226	CB	PHE	L	71	2.452	-0.677	37.399	1.00	17.22	C
ATOM	2227	CG	PHE	L	71	3.246	0.605	37.522	1.00	16.65	C
ATOM	2228	CD1	PHE	L	71	4.264	0.887	36.625	1.00	15.00	C
ATOM	2229	CE1	PHE	L	71	5.039	2.070	36.763	1.00	16.19	C
ATOM	2230	CZ	PHE	L	71	4.760	2.939	37.825	1.00	14.90	C
ATOM	2231	CE2	PHE	L	71	3.736	2.675	38.714	1.00	16.55	C
ATOM	2232	CD2	PHE	L	71	2.983	1.498	38.567	1.00	17.41	C
ATOM	2233	C	PHE	L	71	2.225	-3.097	38.000	1.00	17.97	C
ATOM	2234	O	PHE	L	71	2.418	-3.881	37.070	1.00	18.64	O
ATOM	2235	N	THR	L	72	1.240	-3.242	38.879	1.00	17.97	N
ATOM	2236	CA	THR	L	72	0.291	-4.365	38.782	1.00	18.22	C
ATOM	2237	CB	THR	L	72	0.605	-5.478	39.838	1.00	18.49	C
ATOM	2238	OG1	THR	L	72	0.297	-4.999	41.157	1.00	19.60	O
ATOM	2239	CG2	THR	L	72	2.058	-5.907	39.782	1.00	17.17	C
ATOM	2240	C	THR	L	72	-1.128	-3.925	39.044	1.00	17.86	C
ATOM	2241	O	THR	L	72	-1.368	-2.914	39.732	1.00	17.44	O
ATOM	2242	N	LEU	L	73	-2.060	-4.693	38.502	1.00	16.35	N
ATOM	2243	CA	LEU	L	73	-3.459	-4.627	38.846	1.00	17.12	C
ATOM	2244	CB	LEU	L	73	-4.299	-4.216	37.620	1.00	16.00	C
ATOM	2245	CG	LEU	L	73	-5.831	-4.190	37.716	1.00	19.07	C
ATOM	2246	CD1	LEU	L	73	-6.435	-4.145	36.285	1.00	18.15	C
ATOM	2247	CD2	LEU	L	73	-6.379	-3.039	38.601	1.00	18.19	C
ATOM	2248	C	LEU	L	73	-3.870	-6.035	39.241	1.00	17.83	C
ATOM	2249	O	LEU	L	73	-3.629	-6.978	38.482	1.00	17.67	O
ATOM	2250	N	THR	L	74	-4.521	-6.146	40.386	1.00	19.15	N
ATOM	2251	CA	THR	L	74	-5.079	-7.406	40.850	1.00	20.68	C
ATOM	2252	CB	THR	L	74	-4.493	-7.775	42.250	1.00	19.81	C
ATOM	2253	OG1	THR	L	74	-3.074	-7.962	42.114	1.00	19.75	O
ATOM	2254	CG2	THR	L	74	-5.156	-9.058	42.837	1.00	21.02	C
ATOM	2255	C	THR	L	74	-6.592	-7.279	40.879	1.00	21.38	C
ATOM	2256	O	THR	L	74	-7.131	-6.310	41.404	1.00	22.39	O
ATOM	2257	N	ILE	L	75	-7.283	-8.254	40.294	1.00	22.17	N
ATOM	2258	CA	ILE	L	75	-8.721	-8.384	40.472	1.00	23.46	C
ATOM	2259	CB	ILE	L	75	-9.472	-8.464	39.118	1.00	22.97	C
ATOM	2260	CG1	ILE	L	75	-8.967	-7.372	38.159	1.00	22.33	C
ATOM	2261	CD1	ILE	L	75	-9.284	-7.610	36.685	1.00	23.37	C
ATOM	2262	CG2	ILE	L	75	-11.025	-8.421	39.335	1.00	23.12	C
ATOM	2263	C	ILE	L	75	-8.990	-9.654	41.282	1.00	25.21	C
ATOM	2264	O	ILE	L	75	-8.612	-10.743	40.870	1.00	25.50	O
ATOM	2265	N	SER	L	76	-9.633	-9.500	42.430	1.00	27.09	N
ATOM	2266	CA	SER	L	76	-9.982	-10.639	43.277	1.00	29.49	C
ATOM	2267	CB	SER	L	76	-9.858	-10.257	44.737	1.00	29.18	C
ATOM	2268	OG	SER	L	76	-8.538	-9.829	44.967	1.00	33.93	O
ATOM	2269	C	SER	L	76	-11.398	-11.060	42.996	1.00	29.71	C
ATOM	2270	O	SER	L	76	-12.202	-10.270	42.484	1.00	30.82	O
ATOM	2271	N	LYS	L	77	-11.699	-12.320	43.284	1.00	30.01	N
ATOM	2272	CA	LYS	L	77	-13.053	-12.808	43.187	1.00	30.21	C
ATOM	2273	CB	LYS	L	77	-13.837	-12.461	44.457	1.00	31.27	C
ATOM	2274	CG	LYS	L	77	-13.525	-13.407	45.621	1.00	35.66	C
ATOM	2275	CD	LYS	L	77	-14.729	-13.608	46.577	1.00	42.78	C
ATOM	2276	CE	LYS	L	77	-16.086	-13.843	45.851	1.00	45.82	C
ATOM	2277	NZ	LYS	L	77	-16.145	-15.052	44.954	1.00	46.66	N
ATOM	2278	C	LYS	L	77	-13.747	-12.305	41.916	1.00	28.75	C
ATOM	2279	O	LYS	L	77	-14.796	-11.671	41.968	1.00	29.45	O
ATOM	2280	N	LEU	L	78	-13.154	-12.645	40.776	1.00	27.18	N
ATOM	2281	CA	LEU	L	78	-13.663	-12.282	39.454	1.00	25.61	C

ATOM	2282	CB	LEU	L	78	-12.896	-13.045	38.375	1.00	24.54	C
ATOM	2283	CG	LEU	L	78	-11.552	-12.467	37.958	1.00	24.62	C
ATOM	2284	CD1	LEU	L	78	-10.740	-13.520	37.201	1.00	20.19	C
ATOM	2285	CD2	LEU	L	78	-11.785	-11.175	37.101	1.00	22.38	C
ATOM	2286	C	LEU	L	78	-15.148	-12.548	39.305	1.00	25.90	C
ATOM	2287	O	LEU	L	78	-15.619	-13.659	39.609	1.00	25.00	O
ATOM	2288	N	GLN	L	79	-15.892	-11.527	38.869	1.00	25.29	N
ATOM	2289	CA	GLN	L	79	-17.327	-11.669	38.584	1.00	25.75	C
ATOM	2290	CB	GLN	L	79	-18.134	-10.511	39.201	1.00	26.42	C
ATOM	2291	CG	BGLN	L	79	-18.098	-10.543	40.748	0.35	25.94	C
ATOM	2292	CG	AGLN	L	79	-18.007	-10.362	40.695	0.65	28.63	C
ATOM	2293	CD	BGLN	L	79	-19.127	-9.654	41.453	0.35	25.72	C
ATOM	2294	CD	AGLN	L	79	-18.639	-11.512	41.427	0.65	31.43	C
ATOM	2295	OE1	BGLN	L	79	-19.973	-9.022	40.830	0.35	25.51	O
ATOM	2296	OE1	AGLN	L	79	-19.778	-11.889	41.145	0.65	34.39	O
ATOM	2297	NE2	BGLN	L	79	-19.046	-9.617	42.778	0.35	25.40	N
ATOM	2298	NE2	AGLN	L	79	-17.904	-12.088	42.371	0.65	33.43	N
ATOM	2299	C	GLN	L	79	-17.507	-11.729	37.068	1.00	25.60	C
ATOM	2300	O	GLN	L	79	-16.628	-11.259	36.345	1.00	25.41	O
ATOM	2301	N	PRO	L	80	-18.632	-12.306	36.565	1.00	25.66	N
ATOM	2302	CA	PRO	L	80	-18.791	-12.392	35.107	1.00	25.63	C
ATOM	2303	CB	PRO	L	80	-20.230	-12.920	34.942	1.00	26.02	C
ATOM	2304	CG	PRO	L	80	-20.444	-13.743	36.176	1.00	26.40	C
ATOM	2305	CD	PRO	L	80	-19.779	-12.920	37.267	1.00	26.19	C
ATOM	2306	C	PRO	L	80	-18.606	-11.059	34.349	1.00	25.47	C
ATOM	2307	O	PRO	L	80	-18.025	-11.049	33.262	1.00	24.76	O
ATOM	2308	N	GLU	L	81	-19.077	-9.953	34.924	1.00	25.14	N
ATOM	2309	CA	GLU	L	81	-18.932	-8.634	34.289	1.00	25.55	C
ATOM	2310	CB	GLU	L	81	-19.855	-7.596	34.962	1.00	26.22	C
ATOM	2311	CG	GLU	L	81	-19.606	-7.384	36.468	1.00	29.13	C
ATOM	2312	CD	GLU	L	81	-20.380	-8.347	37.367	1.00	34.46	C
ATOM	2313	OE1	GLU	L	81	-20.665	-7.933	38.521	1.00	36.81	O
ATOM	2314	OE2	GLU	L	81	-20.693	-9.506	36.944	1.00	33.00	O
ATOM	2315	C	GLU	L	81	-17.471	-8.142	34.244	1.00	24.50	C
ATOM	2316	O	GLU	L	81	-17.161	-7.181	33.524	1.00	24.82	O
ATOM	2317	N	ASP	L	82	-16.572	-8.802	34.990	1.00	22.57	N
ATOM	2318	CA	ASP	L	82	-15.147	-8.442	34.986	1.00	21.79	C
ATOM	2319	CB	ASP	L	82	-14.442	-8.925	36.265	1.00	21.58	C
ATOM	2320	CG	ASP	L	82	-15.033	-8.331	37.522	1.00	22.64	C
ATOM	2321	OD1	ASP	L	82	-15.699	-7.264	37.444	1.00	23.05	O
ATOM	2322	OD2	ASP	L	82	-14.846	-8.944	38.600	1.00	23.81	O
ATOM	2323	C	ASP	L	82	-14.381	-8.937	33.764	1.00	20.90	C
ATOM	2324	O	ASP	L	82	-13.229	-8.539	33.535	1.00	19.72	O
ATOM	2325	N	PHE	L	83	-14.997	-9.825	32.979	1.00	20.38	N
ATOM	2326	CA	PHE	L	83	-14.269	-10.430	31.868	1.00	20.97	C
ATOM	2327	CB	PHE	L	83	-14.750	-11.870	31.584	1.00	19.85	C
ATOM	2328	CG	PHE	L	83	-14.362	-12.828	32.665	1.00	18.63	C
ATOM	2329	CD1	PHE	L	83	-13.179	-13.566	32.572	1.00	17.92	C
ATOM	2330	CE1	PHE	L	83	-12.795	-14.444	33.623	1.00	17.93	C
ATOM	2331	CZ	PHE	L	83	-13.590	-14.554	34.749	1.00	19.25	C
ATOM	2332	CE2	PHE	L	83	-14.777	-13.798	34.864	1.00	19.98	C
ATOM	2333	CD2	PHE	L	83	-15.138	-12.925	33.812	1.00	18.75	C
ATOM	2334	C	PHE	L	83	-14.347	-9.522	30.652	1.00	21.87	C
ATOM	2335	O	PHE	L	83	-15.308	-9.584	29.884	1.00	24.46	O
ATOM	2336	N	ALA	L	84	-13.332	-8.675	30.503	1.00	22.54	N
ATOM	2337	CA	ALA	L	84	-13.314	-7.584	29.516	1.00	22.16	C
ATOM	2338	CB	ALA	L	84	-13.929	-6.312	30.140	1.00	22.71	C

ATOM	2339	C	ALA L 84	-11.852	-7.356	29.162	1.00	22.12	C
ATOM	2340	O	ALA L 84	-11.001	-8.205	29.471	1.00	22.07	O
ATOM	2341	N	THR L 85	-11.529	-6.229	28.524	1.00	20.20	N
ATOM	2342	CA	THR L 85	-10.140	-5.926	28.218	1.00	19.52	C
ATOM	2343	CB	THR L 85	-9.963	-5.509	26.749	1.00	19.95	C
ATOM	2344	OG1	THR L 85	-10.379	-6.589	25.906	1.00	20.14	O
ATOM	2345	CG2	THR L 85	-8.508	-5.171	26.406	1.00	19.02	C
ATOM	2346	C	THR L 85	-9.685	-4.818	29.171	1.00	19.80	C
ATOM	2347	O	THR L 85	-10.442	-3.880	29.413	1.00	20.61	O
ATOM	2348	N	TYR L 86	-8.484	-4.962	29.718	1.00	19.00	N
ATOM	2349	CA	TYR L 86	-7.907	-3.967	30.646	1.00	18.46	C
ATOM	2350	CB	TYR L 86	-7.484	-4.658	31.962	1.00	17.71	C
ATOM	2351	CG	TYR L 86	-8.704	-5.122	32.710	1.00	17.62	C
ATOM	2352	CD1	TYR L 86	-9.271	-6.386	32.448	1.00	18.11	C
ATOM	2353	CE1	TYR L 86	-10.444	-6.789	33.073	1.00	17.58	C
ATOM	2354	CZ	TYR L 86	-11.057	-5.937	33.978	1.00	18.35	C
ATOM	2355	OH	TYR L 86	-12.211	-6.326	34.605	1.00	18.91	O
ATOM	2356	CE2	TYR L 86	-10.544	-4.656	34.220	1.00	16.44	C
ATOM	2357	CD2	TYR L 86	-9.370	-4.265	33.583	1.00	17.42	C
ATOM	2358	C	TYR L 86	-6.738	-3.266	29.983	1.00	18.94	C
ATOM	2359	O	TYR L 86	-5.955	-3.901	29.270	1.00	19.50	O
ATOM	2360	N	TYR L 87	-6.616	-1.949	30.207	1.00	18.80	N
ATOM	2361	CA	TYR L 87	-5.514	-1.165	29.644	1.00	18.44	C
ATOM	2362	CB	TYR L 87	-6.028	-0.144	28.597	1.00	18.80	C
ATOM	2363	CG	TYR L 87	-6.527	-0.759	27.324	1.00	19.61	C
ATOM	2364	CD1	TYR L 87	-5.632	-1.179	26.344	1.00	18.37	C
ATOM	2365	CE1	TYR L 87	-6.070	-1.734	25.157	1.00	18.72	C
ATOM	2366	CZ	TYR L 87	-7.431	-1.867	24.936	1.00	17.38	C
ATOM	2367	OH	TYR L 87	-7.819	-2.426	23.758	1.00	20.42	O
ATOM	2368	CE2	TYR L 87	-8.359	-1.479	25.883	1.00	18.25	C
ATOM	2369	CD2	TYR L 87	-7.908	-0.905	27.083	1.00	18.72	C
ATOM	2370	C	TYR L 87	-4.870	-0.373	30.779	1.00	18.65	C
ATOM	2371	O	TYR L 87	-5.578	0.181	31.614	1.00	18.32	O
ATOM	2372	N	CYS L 88	-3.539	-0.344	30.820	1.00	18.87	N
ATOM	2373	CA	CYS L 88	-2.851	0.605	31.694	1.00	19.40	C
ATOM	2374	CB	CYS L 88	-1.601	-0.032	32.348	1.00	21.18	C
ATOM	2375	SG	CYS L 88	-0.446	-0.635	31.157	1.00	25.43	S
ATOM	2376	C	CYS L 88	-2.532	1.875	30.902	1.00	18.65	C
ATOM	2377	O	CYS L 88	-2.578	1.890	29.686	1.00	17.56	O
ATOM	2378	N	LEU L 89	-2.242	2.965	31.610	1.00	18.11	N
ATOM	2379	CA	LEU L 89	-1.963	4.234	30.962	1.00	17.42	C
ATOM	2380	CB	LEU L 89	-3.256	5.066	30.869	1.00	17.84	C
ATOM	2381	CG	LEU L 89	-2.992	6.587	30.641	1.00	19.53	C
ATOM	2382	CD1	LEU L 89	-2.638	6.842	29.180	1.00	19.40	C
ATOM	2383	CD2	LEU L 89	-4.136	7.460	31.142	1.00	19.28	C
ATOM	2384	C	LEU L 89	-0.970	4.964	31.865	1.00	16.60	C
ATOM	2385	O	LEU L 89	-1.223	5.071	33.058	1.00	17.07	O
ATOM	2386	N	GLN L 90	0.154	5.401	31.307	1.00	16.69	N
ATOM	2387	CA	GLN L 90	1.050	6.332	32.006	1.00	16.66	C
ATOM	2388	CB	GLN L 90	2.539	6.075	31.671	1.00	15.44	C
ATOM	2389	CG	GLN L 90	3.018	6.542	30.255	1.00	17.44	C
ATOM	2390	CD	GLN L 90	3.326	8.062	30.141	1.00	19.63	C
ATOM	2391	OE1	GLN L 90	3.546	8.763	31.155	1.00	19.07	O
ATOM	2392	NE2	GLN L 90	3.365	8.562	28.898	1.00	16.42	N
ATOM	2393	C	GLN L 90	0.607	7.794	31.736	1.00	16.20	C
ATOM	2394	O	GLN L 90	0.341	8.191	30.585	1.00	17.09	O
ATOM	2395	N	SER L 91	0.513	8.566	32.817	1.00	17.31	N

ATOM	2396	CA	SER L 91	0.183	9.987	32.748	1.00	17.49	C
ATOM	2397	CB	SER L 91	-1.177	10.235	33.374	1.00	16.54	C
ATOM	2398	OG	SER L 91	-1.215	9.722	34.691	1.00	18.45	O
ATOM	2399	C	SER L 91	1.265	10.794	33.451	1.00	18.11	C
ATOM	2400	O	SER L 91	0.964	11.758	34.151	1.00	19.57	O
ATOM	2401	N	ASP L 92	2.515	10.391	33.245	1.00	18.29	N
ATOM	2402	CA	ASP L 92	3.667	11.110	33.735	1.00	19.55	C
ATOM	2403	CB	ASP L 92	4.862	10.175	33.928	1.00	18.06	C
ATOM	2404	CG	ASP L 92	6.123	10.920	34.336	1.00	17.32	C
ATOM	2405	OD1	ASP L 92	7.087	10.973	33.528	1.00	16.35	O
ATOM	2406	OD2	ASP L 92	6.145	11.461	35.465	1.00	17.82	O
ATOM	2407	C	ASP L 92	4.100	12.228	32.789	1.00	19.47	C
ATOM	2408	O	ASP L 92	4.561	13.272	33.236	1.00	20.64	O
ATOM	2409	N	ASN L 93	4.045	11.965	31.492	1.00	20.11	N
ATOM	2410	CA	ASN L 93	4.639	12.871	30.523	1.00	20.10	C
ATOM	2411	CB	ASN L 93	6.165	12.698	30.476	1.00	19.89	C
ATOM	2412	CG	ASN L 93	6.598	11.390	29.829	1.00	20.90	C
ATOM	2413	OD1	ASN L 93	6.756	11.308	28.602	1.00	21.42	O
ATOM	2414	ND2	ASN L 93	6.806	10.365	30.657	1.00	19.08	N
ATOM	2415	C	ASN L 93	4.010	12.714	29.155	1.00	20.68	C
ATOM	2416	O	ASN L 93	3.462	11.654	28.839	1.00	19.82	O
ATOM	2417	N	LEU L 94	4.087	13.768	28.339	1.00	20.43	N
ATOM	2418	CA	LEU L 94	3.526	13.708	26.974	1.00	20.22	C
ATOM	2419	CB	LEU L 94	3.108	15.120	26.470	1.00	20.02	C
ATOM	2420	CG	LEU L 94	1.980	15.844	27.212	1.00	19.15	C
ATOM	2421	CD1	LEU L 94	1.596	17.153	26.449	1.00	17.92	C
ATOM	2422	CD2	LEU L 94	0.744	14.956	27.433	1.00	17.16	C
ATOM	2423	C	LEU L 94	4.489	13.061	25.997	1.00	20.14	C
ATOM	2424	O	LEU L 94	5.710	13.290	26.083	1.00	20.31	O
ATOM	2425	N	PRO L 95	3.961	12.243	25.053	1.00	19.65	N
ATOM	2426	CA	PRO L 95	2.538	11.890	24.893	1.00	19.50	C
ATOM	2427	CB	PRO L 95	2.475	11.352	23.458	1.00	19.45	C
ATOM	2428	CG	PRO L 95	3.824	10.771	23.200	1.00	19.35	C
ATOM	2429	CD	PRO L 95	4.812	11.619	24.017	1.00	19.50	C
ATOM	2430	C	PRO L 95	2.073	10.818	25.901	1.00	19.43	C
ATOM	2431	O	PRO L 95	2.877	9.964	26.271	1.00	19.93	O
ATOM	2432	N	PHE L 96	0.819	10.905	26.350	1.00	18.63	N
ATOM	2433	CA	PHE L 96	0.161	9.825	27.110	1.00	18.11	C
ATOM	2434	CB	PHE L 96	-1.329	10.094	27.303	1.00	17.84	C
ATOM	2435	CG	PHE L 96	-1.631	11.240	28.266	1.00	20.04	C
ATOM	2436	CD1	PHE L 96	-1.695	11.029	29.630	1.00	21.59	C
ATOM	2437	CE1	PHE L 96	-1.982	12.096	30.526	1.00	23.75	C
ATOM	2438	CZ	PHE L 96	-2.193	13.376	30.029	1.00	20.58	C
ATOM	2439	CE2	PHE L 96	-2.156	13.597	28.686	1.00	21.07	C
ATOM	2440	CD2	PHE L 96	-1.882	12.525	27.788	1.00	21.43	C
ATOM	2441	C	PHE L 96	0.319	8.550	26.288	1.00	17.87	C
ATOM	2442	O	PHE L 96	0.176	8.580	25.057	1.00	16.11	O
ATOM	2443	N	THR L 97	0.636	7.442	26.959	1.00	17.19	N
ATOM	2444	CA	THR L 97	0.823	6.185	26.235	1.00	17.72	C
ATOM	2445	CB	THR L 97	2.318	5.850	25.958	1.00	17.26	C
ATOM	2446	OG1	THR L 97	3.091	6.029	27.144	1.00	19.75	O
ATOM	2447	CG2	THR L 97	2.896	6.711	24.823	1.00	18.85	C
ATOM	2448	C	THR L 97	0.166	5.081	27.021	1.00	17.29	C
ATOM	2449	O	THR L 97	0.171	5.102	28.250	1.00	16.17	O
ATOM	2450	N	PHE L 98	-0.440	4.143	26.290	1.00	18.46	N
ATOM	2451	CA	PHE L 98	-1.224	3.060	26.868	1.00	18.45	C
ATOM	2452	CB	PHE L 98	-2.588	2.934	26.163	1.00	19.06	C

ATOM	2453	CG PHE L 98	-3.571	4.062	26.434	1.00	19.04	C
ATOM	2454	CD1 PHE L 98	-3.573	5.223	25.641	1.00	19.54	C
ATOM	2455	CE1 PHE L 98	-4.525	6.254	25.868	1.00	18.85	C
ATOM	2456	CZ PHE L 98	-5.476	6.117	26.869	1.00	19.62	C
ATOM	2457	CE2 PHE L 98	-5.495	4.942	27.658	1.00	20.56	C
ATOM	2458	CD2 PHE L 98	-4.543	3.925	27.418	1.00	19.01	C
ATOM	2459	C PHE L 98	-0.491	1.727	26.628	1.00	18.37	C
ATOM	2460	O PHE L 98	0.205	1.575	25.631	1.00	18.13	O
ATOM	2461	N GLY L 99	-0.657	0.786	27.553	1.00	18.97	N
ATOM	2462	CA GLY L 99	-0.297	-0.616	27.326	1.00	19.34	C
ATOM	2463	C GLY L 99	-1.190	-1.213	26.253	1.00	20.02	C
ATOM	2464	O GLY L 99	-2.249	-0.654	25.914	1.00	18.81	O
ATOM	2465	N GLN L 100	-0.750	-2.341	25.696	1.00	20.93	N
ATOM	2466	CA GLN L 100	-1.448	-2.956	24.562	1.00	22.35	C
ATOM	2467	CB GLN L 100	-0.488	-3.851	23.763	1.00	23.80	C
ATOM	2468	CG GLN L 100	-0.705	-5.377	23.946	1.00	31.56	C
ATOM	2469	CD GLN L 100	0.095	-6.036	25.085	1.00	38.44	C
ATOM	2470	OE1 GLN L 100	1.328	-6.135	25.019	1.00	44.12	O
ATOM	2471	NE2 GLN L 100	-0.611	-6.544	26.096	1.00	36.58	N
ATOM	2472	C GLN L 100	-2.717	-3.710	24.962	1.00	21.83	C
ATOM	2473	O GLN L 100	-3.462	-4.155	24.097	1.00	21.94	O
ATOM	2474	N GLY L 101	-2.970	-3.849	26.259	1.00	20.20	N
ATOM	2475	CA GLY L 101	-4.202	-4.449	26.715	1.00	20.28	C
ATOM	2476	C GLY L 101	-4.077	-5.895	27.186	1.00	19.66	C
ATOM	2477	O GLY L 101	-3.176	-6.631	26.755	1.00	19.71	O
ATOM	2478	N THR L 102	-4.974	-6.270	28.091	1.00	19.91	N
ATOM	2479	CA THR L 102	-5.118	-7.657	28.553	1.00	20.05	C
ATOM	2480	CB THR L 102	-4.672	-7.829	30.027	1.00	19.53	C
ATOM	2481	OG1 THR L 102	-3.289	-7.475	30.157	1.00	18.74	O
ATOM	2482	CG2 THR L 102	-4.871	-9.300	30.466	1.00	19.61	C
ATOM	2483	C THR L 102	-6.576	-8.067	28.429	1.00	20.31	C
ATOM	2484	O THR L 102	-7.435	-7.509	29.108	1.00	20.34	O
ATOM	2485	N LYS L 103	-6.862	-9.060	27.583	1.00	20.65	N
ATOM	2486	CA LYS L 103	-8.209	-9.564	27.467	1.00	21.50	C
ATOM	2487	CB LYS L 103	-8.512	-9.933	26.000	1.00	22.54	C
ATOM	2488	CG LYS L 103	-9.802	-10.765	25.732	1.00	26.83	C
ATOM	2489	CD LYS L 103	-11.058	-10.254	26.426	1.00	28.72	C
ATOM	2490	CE LYS L 103	-12.279	-11.177	26.175	1.00	29.90	C
ATOM	2491	NZ LYS L 103	-13.350	-11.081	27.246	1.00	26.67	N
ATOM	2492	C LYS L 103	-8.391	-10.764	28.423	1.00	21.55	C
ATOM	2493	O LYS L 103	-7.651	-11.761	28.326	1.00	20.54	O
ATOM	2494	N LEU L 104	-9.367	-10.649	29.319	1.00	21.15	N
ATOM	2495	CA LEU L 104	-9.706	-11.725	30.262	1.00	22.74	C
ATOM	2496	CB LEU L 104	-10.128	-11.180	31.616	1.00	22.06	C
ATOM	2497	CG LEU L 104	-9.152	-10.459	32.521	1.00	25.59	C
ATOM	2498	CD1 LEU L 104	-9.761	-10.523	33.893	1.00	26.70	C
ATOM	2499	CD2 LEU L 104	-7.742	-11.075	32.515	1.00	28.39	C
ATOM	2500	C LEU L 104	-10.888	-12.512	29.731	1.00	22.63	C
ATOM	2501	O LEU L 104	-11.938	-11.935	29.437	1.00	22.42	O
ATOM	2502	N GLU L 105	-10.714	-13.825	29.643	1.00	22.55	N
ATOM	2503	CA GLU L 105	-11.702	-14.722	29.090	1.00	22.33	C
ATOM	2504	CB GLU L 105	-11.042	-15.540	27.961	1.00	23.24	C
ATOM	2505	CG GLU L 105	-11.918	-16.659	27.525	1.00	26.51	C
ATOM	2506	CD GLU L 105	-11.208	-17.874	27.028	1.00	26.94	C
ATOM	2507	OE1 GLU L 105	-11.357	-18.139	25.825	1.00	27.79	O
ATOM	2508	OE2 GLU L 105	-10.551	-18.584	27.829	1.00	26.69	O
ATOM	2509	C GLU L 105	-12.182	-15.690	30.197	1.00	22.04	C

ATOM	2510	O	GLU L 105	-11.392	-16.056	31.069	1.00	21.35	O
ATOM	2511	N	ILE L 106	-13.452	-16.101	30.162	1.00	21.49	N
ATOM	2512	CA	ILE L 106	-13.980	-17.050	31.152	1.00	22.66	C
ATOM	2513	CB	ILE L 106	-15.531	-17.001	31.268	1.00	22.90	C
ATOM	2514	CG1	ILE L 106	-15.994	-15.615	31.743	1.00	24.68	C
ATOM	2515	CD1	ILE L 106	-17.514	-15.370	31.703	1.00	24.18	C
ATOM	2516	CG2	ILE L 106	-16.058	-18.081	32.243	1.00	23.54	C
ATOM	2517	C	ILE L 106	-13.505	-18.461	30.794	1.00	22.30	C
ATOM	2518	O	ILE L 106	-13.728	-18.959	29.684	1.00	21.43	O
ATOM	2519	N	LYS L 107	-12.841	-19.091	31.748	1.00	22.40	N
ATOM	2520	CA	LYS L 107	-12.394	-20.471	31.596	1.00	22.77	C
ATOM	2521	CB	LYS L 107	-11.230	-20.750	32.568	1.00	23.17	C
ATOM	2522	CG	LYS L 107	-10.814	-22.210	32.643	1.00	24.37	C
ATOM	2523	CD	LYS L 107	-9.481	-22.494	33.338	1.00	25.57	C
ATOM	2524	CE	LYS L 107	-8.838	-21.378	34.174	1.00	27.57	C
ATOM	2525	NZ	LYS L 107	-7.948	-22.032	35.229	1.00	25.71	N
ATOM	2526	C	LYS L 107	-13.571	-21.432	31.834	1.00	21.76	C
ATOM	2527	O	LYS L 107	-14.327	-21.283	32.782	1.00	21.01	O
ATOM	2528	N	ARG L 108	-13.721	-22.418	30.961	1.00	20.77	N
ATOM	2529	CA	ARG L 108	-14.719	-23.465	31.170	1.00	20.09	C
ATOM	2530	CB	ARG L 108	-16.005	-23.142	30.394	1.00	20.55	C
ATOM	2531	CG	ARG L 108	-15.802	-22.904	28.895	1.00	19.59	C
ATOM	2532	CD	ARG L 108	-17.013	-23.350	28.035	1.00	21.22	C
ATOM	2533	NE	ARG L 108	-17.198	-24.805	28.109	1.00	24.50	N
ATOM	2534	CZ	ARG L 108	-18.367	-25.450	28.135	1.00	25.15	C
ATOM	2535	NH1	ARG L 108	-18.371	-26.788	28.234	1.00	23.76	N
ATOM	2536	NH2	ARG L 108	-19.528	-24.787	28.082	1.00	22.95	N
ATOM	2537	C	ARG L 108	-14.138	-24.798	30.713	1.00	20.25	C
ATOM	2538	O	ARG L 108	-12.969	-24.868	30.329	1.00	19.46	O
ATOM	2539	N	THR L 109	-14.952	-25.857	30.739	1.00	20.12	N
ATOM	2540	CA	THR L 109	-14.470	-27.175	30.290	1.00	20.72	C
ATOM	2541	CB	THR L 109	-15.377	-28.325	30.812	1.00	20.85	C
ATOM	2542	OG1	THR L 109	-16.730	-28.075	30.424	1.00	20.32	O
ATOM	2543	CG2	THR L 109	-15.320	-28.389	32.317	1.00	20.82	C
ATOM	2544	C	THR L 109	-14.335	-27.288	28.761	1.00	20.71	C
ATOM	2545	O	THR L 109	-14.996	-26.583	27.978	1.00	20.60	O
ATOM	2546	N	VAL L 110	-13.471	-28.186	28.320	1.00	20.70	N
ATOM	2547	CA	VAL L 110	-13.335	-28.392	26.890	1.00	21.26	C
ATOM	2548	CB	VAL L 110	-12.164	-29.362	26.560	1.00	21.56	C
ATOM	2549	CG1	VAL L 110	-12.406	-30.753	27.139	1.00	22.47	C
ATOM	2550	CG2	VAL L 110	-11.932	-29.431	25.053	1.00	22.20	C
ATOM	2551	C	VAL L 110	-14.699	-28.820	26.283	1.00	21.86	C
ATOM	2552	O	VAL L 110	-15.455	-29.596	26.897	1.00	20.95	O
ATOM	2553	N	ALA L 111	-15.042	-28.237	25.134	1.00	21.33	N
ATOM	2554	CA	ALA L 111	-16.225	-28.606	24.360	1.00	22.14	C
ATOM	2555	CB	ALA L 111	-17.357	-27.603	24.547	1.00	22.56	C
ATOM	2556	C	ALA L 111	-15.841	-28.681	22.896	1.00	22.25	C
ATOM	2557	O	ALA L 111	-15.446	-27.679	22.308	1.00	22.17	O
ATOM	2558	N	ALA L 112	-15.973	-29.865	22.302	1.00	21.89	N
ATOM	2559	CA	ALA L 112	-15.734	-30.038	20.864	1.00	21.96	C
ATOM	2560	CB	ALA L 112	-15.753	-31.547	20.509	1.00	22.19	C
ATOM	2561	C	ALA L 112	-16.786	-29.292	20.036	1.00	21.42	C
ATOM	2562	O	ALA L 112	-17.919	-29.204	20.456	1.00	22.07	O
ATOM	2563	N	PRO L 113	-16.411	-28.735	18.866	1.00	21.24	N
ATOM	2564	CA	PRO L 113	-17.431	-28.107	18.010	1.00	22.05	C
ATOM	2565	CB	PRO L 113	-16.602	-27.387	16.941	1.00	21.89	C
ATOM	2566	CG	PRO L 113	-15.304	-28.147	16.877	1.00	21.57	C

ATOM	2567	CD PRO L 113	-15.065	-28.666	18.272	1.00	21.31	C
ATOM	2568	C PRO L 113	-18.320	-29.139	17.306	1.00	22.70	C
ATOM	2569	O PRO L 113	-17.855	-30.245	17.023	1.00	22.79	O
ATOM	2570	N SER L 114	-19.585	-28.792	17.069	1.00	23.78	N
ATOM	2571	CA SER L 114	-20.383	-29.470	16.049	1.00	23.90	C
ATOM	2572	CB SER L 114	-21.864	-29.336	16.332	1.00	24.70	C
ATOM	2573	OG SER L 114	-22.136	-29.770	17.643	1.00	28.55	O
ATOM	2574	C SER L 114	-20.053	-28.761	14.752	1.00	23.86	C
ATOM	2575	O SER L 114	-20.015	-27.527	14.691	1.00	23.00	O
ATOM	2576	N VAL L 115	-19.800	-29.545	13.714	1.00	23.19	N
ATOM	2577	CA VAL L 115	-19.328	-29.010	12.452	1.00	22.82	C
ATOM	2578	CB VAL L 115	-17.938	-29.613	12.056	1.00	22.35	C
ATOM	2579	CG1 VAL L 115	-17.409	-28.983	10.771	1.00	21.20	C
ATOM	2580	CG2 VAL L 115	-16.918	-29.422	13.195	1.00	22.74	C
ATOM	2581	C VAL L 115	-20.370	-29.239	11.367	1.00	23.29	C
ATOM	2582	O VAL L 115	-20.937	-30.343	11.256	1.00	22.15	O
ATOM	2583	N PHE L 116	-20.623	-28.198	10.576	1.00	22.29	N
ATOM	2584	CA PHE L 116	-21.595	-28.257	9.489	1.00	23.04	C
ATOM	2585	CB PHE L 116	-22.874	-27.481	9.842	1.00	23.27	C
ATOM	2586	CG PHE L 116	-23.482	-27.875	11.157	1.00	24.06	C
ATOM	2587	CD1 PHE L 116	-24.484	-28.837	11.214	1.00	26.12	C
ATOM	2588	CE1 PHE L 116	-25.064	-29.207	12.436	1.00	26.52	C
ATOM	2589	CZ PHE L 116	-24.629	-28.622	13.599	1.00	26.50	C
ATOM	2590	CE2 PHE L 116	-23.619	-27.655	13.557	1.00	26.75	C
ATOM	2591	CD2 PHE L 116	-23.050	-27.293	12.341	1.00	24.59	C
ATOM	2592	C PHE L 116	-20.994	-27.625	8.264	1.00	23.12	C
ATOM	2593	O PHE L 116	-20.236	-26.661	8.374	1.00	22.63	O
ATOM	2594	N ILE L 117	-21.328	-28.163	7.094	1.00	22.30	N
ATOM	2595	CA ILE L 117	-20.859	-27.576	5.831	1.00	23.13	C
ATOM	2596	CB ILE L 117	-19.797	-28.488	5.088	1.00	22.45	C
ATOM	2597	CG1 ILE L 117	-19.147	-27.751	3.902	1.00	22.47	C
ATOM	2598	CD1 ILE L 117	-17.880	-28.460	3.342	1.00	24.39	C
ATOM	2599	CG2 ILE L 117	-20.397	-29.869	4.672	1.00	22.05	C
ATOM	2600	C ILE L 117	-22.077	-27.221	4.957	1.00	23.87	C
ATOM	2601	O ILE L 117	-23.073	-27.974	4.918	1.00	24.10	O
ATOM	2602	N PHE L 118	-22.000	-26.067	4.296	1.00	23.61	N
ATOM	2603	CA PHE L 118	-23.055	-25.579	3.420	1.00	24.06	C
ATOM	2604	CB PHE L 118	-23.635	-24.255	3.936	1.00	24.30	C
ATOM	2605	CG PHE L 118	-24.214	-24.337	5.322	1.00	25.05	C
ATOM	2606	CD1 PHE L 118	-25.514	-24.819	5.524	1.00	26.42	C
ATOM	2607	CE1 PHE L 118	-26.061	-24.890	6.802	1.00	25.99	C
ATOM	2608	CZ PHE L 118	-25.321	-24.467	7.893	1.00	26.35	C
ATOM	2609	CE2 PHE L 118	-24.030	-23.979	7.711	1.00	27.55	C
ATOM	2610	CD2 PHE L 118	-23.484	-23.916	6.420	1.00	26.30	C
ATOM	2611	C PHE L 118	-22.512	-25.374	2.012	1.00	24.93	C
ATOM	2612	O PHE L 118	-21.614	-24.526	1.794	1.00	24.11	O
ATOM	2613	N PRO L 119	-23.060	-26.128	1.030	1.00	25.52	N
ATOM	2614	CA PRO L 119	-22.677	-25.868	-0.363	1.00	25.94	C
ATOM	2615	CB PRO L 119	-23.425	-26.962	-1.159	1.00	25.76	C
ATOM	2616	CG PRO L 119	-23.841	-27.965	-0.174	1.00	26.94	C
ATOM	2617	CD PRO L 119	-24.041	-27.224	1.133	1.00	25.38	C
ATOM	2618	C PRO L 119	-23.190	-24.502	-0.789	1.00	26.50	C
ATOM	2619	O PRO L 119	-24.079	-23.947	-0.131	1.00	26.05	O
ATOM	2620	N PRO L 120	-22.630	-23.942	-1.873	1.00	26.69	N
ATOM	2621	CA PRO L 120	-23.206	-22.696	-2.365	1.00	27.49	C
ATOM	2622	CB PRO L 120	-22.308	-22.310	-3.550	1.00	27.24	C
ATOM	2623	CG PRO L 120	-21.480	-23.495	-3.840	1.00	27.50	C

ATOM	2624	CD PRO L 120	-21.476	-24.403	-2.665	1.00	27.38	C
ATOM	2625	C PRO L 120	-24.637	-22.922	-2.829	1.00	28.36	C
ATOM	2626	O PRO L 120	-24.973	-24.013	-3.341	1.00	28.05	O
ATOM	2627	N SER L 121	-25.478	-21.916	-2.638	1.00	28.83	N
ATOM	2628	CA SER L 121	-26.858	-21.963	-3.144	1.00	29.93	C
ATOM	2629	CB SER L 121	-27.704	-20.895	-2.443	1.00	29.83	C
ATOM	2630	OG SER L 121	-27.347	-19.602	-2.898	1.00	29.22	O
ATOM	2631	C SER L 121	-26.946	-21.776	-4.674	1.00	30.86	C
ATOM	2632	O SER L 121	-26.083	-21.138	-5.303	1.00	30.69	O
ATOM	2633	N ASP L 122	-28.009	-22.310	-5.271	1.00	32.08	N
ATOM	2634	CA ASP L 122	-28.214	-22.168	-6.715	1.00	33.72	C
ATOM	2635	CB ASP L 122	-29.399	-23.024	-7.190	1.00	34.76	C
ATOM	2636	CG ASP L 122	-29.114	-24.521	-7.097	1.00	37.92	C
ATOM	2637	OD1 ASP L 122	-30.028	-25.283	-6.696	1.00	41.61	O
ATOM	2638	OD2 ASP L 122	-27.971	-24.935	-7.403	1.00	42.08	O
ATOM	2639	C ASP L 122	-28.400	-20.707	-7.114	1.00	33.38	C
ATOM	2640	O ASP L 122	-27.908	-20.272	-8.157	1.00	32.72	O
ATOM	2641	N GLU L 123	-29.081	-19.949	-6.256	1.00	33.79	N
ATOM	2642	CA GLU L 123	-29.265	-18.510	-6.478	1.00	33.78	C
ATOM	2643	CB BGLU L 123	-30.133	-17.912	-5.370	0.35	33.73	C
ATOM	2644	CB AGLU L 123	-30.218	-17.888	-5.451	0.65	34.30	C
ATOM	2645	CG BGLU L 123	-30.710	-16.533	-5.690	0.35	33.71	C
ATOM	2646	CG AGLU L 123	-30.206	-18.510	-4.061	0.65	36.42	C
ATOM	2647	CD BGLU L 123	-31.178	-15.777	-4.455	0.35	33.62	C
ATOM	2648	CD AGLU L 123	-31.223	-19.634	-3.881	0.65	38.00	C
ATOM	2649	OE1BGLU L 123	-31.297	-14.538	-4.546	0.35	33.38	O
ATOM	2650	OE1AGLU L 123	-30.926	-20.791	-4.267	0.65	38.11	O
ATOM	2651	OE2BGLU L 123	-31.422	-16.405	-3.396	0.35	33.54	O
ATOM	2652	OE2AGLU L 123	-32.305	-19.354	-3.320	0.65	38.28	O
ATOM	2653	C GLU L 123	-27.928	-17.765	-6.557	1.00	33.46	C
ATOM	2654	O GLU L 123	-27.739	-16.927	-7.437	1.00	33.40	O
ATOM	2655	N GLN L 124	-26.983	-18.091	-5.672	1.00	33.06	N
ATOM	2656	CA GLN L 124	-25.670	-17.459	-5.736	1.00	32.67	C
ATOM	2657	CB GLN L 124	-24.831	-17.741	-4.481	1.00	31.91	C
ATOM	2658	CG GLN L 124	-23.532	-16.953	-4.509	1.00	30.33	C
ATOM	2659	CD GLN L 124	-22.550	-17.306	-3.425	1.00	26.60	C
ATOM	2660	OE1 GLN L 124	-22.586	-18.397	-2.838	1.00	24.14	O
ATOM	2661	NE2 GLN L 124	-21.629	-16.380	-3.169	1.00	26.85	N
ATOM	2662	C GLN L 124	-24.901	-17.892	-6.988	1.00	33.66	C
ATOM	2663	O GLN L 124	-24.252	-17.068	-7.641	1.00	33.15	O
ATOM	2664	N LEU L 125	-24.959	-19.186	-7.304	1.00	34.80	N
ATOM	2665	CA LEU L 125	-24.291	-19.706	-8.502	1.00	36.98	C
ATOM	2666	CB LEU L 125	-24.476	-21.227	-8.626	1.00	36.73	C
ATOM	2667	CG LEU L 125	-23.673	-22.079	-7.624	1.00	36.84	C
ATOM	2668	CD1 LEU L 125	-23.987	-23.581	-7.727	1.00	36.94	C
ATOM	2669	CD2 LEU L 125	-22.178	-21.823	-7.786	1.00	37.70	C
ATOM	2670	C LEU L 125	-24.733	-18.963	-9.775	1.00	38.12	C
ATOM	2671	O LEU L 125	-23.923	-18.716	-10.666	1.00	38.53	O
ATOM	2672	N LYS L 126	-26.002	-18.562	-9.821	1.00	39.88	N
ATOM	2673	CA LYS L 126	-26.536	-17.782	-10.945	1.00	41.95	C
ATOM	2674	CB LYS L 126	-28.029	-17.489	-10.757	1.00	41.95	C
ATOM	2675	CG LYS L 126	-28.953	-18.683	-10.996	1.00	43.66	C
ATOM	2676	CD LYS L 126	-30.404	-18.333	-10.634	1.00	43.80	C
ATOM	2677	CE LYS L 126	-31.195	-19.596	-10.250	1.00	47.81	C
ATOM	2678	NZ LYS L 126	-32.381	-19.288	-9.398	1.00	49.05	N
ATOM	2679	C LYS L 126	-25.800	-16.467	-11.182	1.00	42.22	C
ATOM	2680	O LYS L 126	-25.812	-15.947	-12.300	1.00	42.59	O

ATOM	2681	N	SER L 127	-25.167	-15.929	-10.138	1.00	42.21	N
ATOM	2682	CA	SER L 127	-24.519	-14.623	-10.232	1.00	42.14	C
ATOM	2683	CB	SER L 127	-24.770	-13.800	-8.965	1.00	42.53	C
ATOM	2684	OG	SER L 127	-24.309	-14.483	-7.802	1.00	44.06	O
ATOM	2685	C	SER L 127	-23.025	-14.707	-10.537	1.00	41.75	C
ATOM	2686	O	SER L 127	-22.369	-13.670	-10.687	1.00	42.36	O
ATOM	2687	N	GLY L 128	-22.487	-15.924	-10.635	1.00	40.45	N
ATOM	2688	CA	GLY L 128	-21.096	-16.119	-11.063	1.00	39.09	C
ATOM	2689	C	GLY L 128	-20.068	-16.411	-9.978	1.00	37.99	C
ATOM	2690	O	GLY L 128	-18.871	-16.560	-10.268	1.00	37.88	O
ATOM	2691	N	THR L 129	-20.528	-16.502	-8.732	1.00	36.92	N
ATOM	2692	CA	THR L 129	-19.647	-16.780	-7.588	1.00	35.62	C
ATOM	2693	CB	THR L 129	-19.430	-15.497	-6.732	1.00	36.15	C
ATOM	2694	OG1	THR L 129	-18.860	-14.484	-7.559	1.00	37.35	O
ATOM	2695	CG2	THR L 129	-18.478	-15.740	-5.543	1.00	35.54	C
ATOM	2696	C	THR L 129	-20.185	-17.928	-6.733	1.00	34.08	C
ATOM	2697	O	THR L 129	-21.394	-18.170	-6.693	1.00	33.70	O
ATOM	2698	N	ALA L 130	-19.273	-18.643	-6.078	1.00	32.60	N
ATOM	2699	CA	ALA L 130	-19.627	-19.737	-5.174	1.00	31.58	C
ATOM	2700	CB	ALA L 130	-19.173	-21.041	-5.754	1.00	31.72	C
ATOM	2701	C	ALA L 130	-18.995	-19.542	-3.787	1.00	30.97	C
ATOM	2702	O	ALA L 130	-17.762	-19.493	-3.657	1.00	31.59	O
ATOM	2703	N	SER L 131	-19.829	-19.437	-2.755	1.00	28.80	N
ATOM	2704	CA	SER L 131	-19.316	-19.382	-1.393	1.00	27.33	C
ATOM	2705	CB	SER L 131	-19.955	-18.231	-0.613	1.00	26.83	C
ATOM	2706	OG	SER L 131	-19.756	-17.002	-1.275	1.00	25.85	O
ATOM	2707	C	SER L 131	-19.633	-20.681	-0.694	1.00	26.24	C
ATOM	2708	O	SER L 131	-20.806	-21.074	-0.631	1.00	26.15	O
ATOM	2709	N	VAL L 132	-18.604	-21.344	-0.168	1.00	25.09	N
ATOM	2710	CA	VAL L 132	-18.803	-22.554	0.637	1.00	24.54	C
ATOM	2711	CB	VAL L 132	-17.881	-23.721	0.195	1.00	24.90	C
ATOM	2712	CG1	VAL L 132	-18.381	-25.050	0.781	1.00	24.94	C
ATOM	2713	CG2	VAL L 132	-17.797	-23.792	-1.341	1.00	25.49	C
ATOM	2714	C	VAL L 132	-18.544	-22.209	2.106	1.00	24.89	C
ATOM	2715	O	VAL L 132	-17.516	-21.607	2.429	1.00	24.41	O
ATOM	2716	N	VAL L 133	-19.483	-22.571	2.983	1.00	23.98	N
ATOM	2717	CA	VAL L 133	-19.395	-22.185	4.388	1.00	23.55	C
ATOM	2718	CB	VAL L 133	-20.605	-21.319	4.824	1.00	23.05	C
ATOM	2719	CG1	VAL L 133	-20.512	-20.957	6.346	1.00	23.64	C
ATOM	2720	CG2	VAL L 133	-20.718	-20.062	3.935	1.00	23.79	C
ATOM	2721	C	VAL L 133	-19.264	-23.401	5.304	1.00	23.72	C
ATOM	2722	O	VAL L 133	-19.984	-24.389	5.161	1.00	23.80	O
ATOM	2723	N	CYS L 134	-18.342	-23.310	6.245	1.00	24.14	N
ATOM	2724	CA	CYS L 134	-18.186	-24.309	7.277	1.00	23.96	C
ATOM	2725	CB	CYS L 134	-16.789	-24.911	7.181	1.00	24.69	C
ATOM	2726	SG	CYS L 134	-16.411	-26.240	8.326	1.00	27.59	S
ATOM	2727	C	CYS L 134	-18.404	-23.631	8.618	1.00	23.61	C
ATOM	2728	O	CYS L 134	-17.810	-22.573	8.892	1.00	23.50	O
ATOM	2729	N	LEU L 135	-19.281	-24.224	9.428	1.00	22.01	N
ATOM	2730	CA	LEU L 135	-19.646	-23.707	10.734	1.00	21.09	C
ATOM	2731	CB	LEU L 135	-21.172	-23.606	10.849	1.00	20.96	C
ATOM	2732	CG	LEU L 135	-21.779	-23.342	12.226	1.00	22.14	C
ATOM	2733	CD1	LEU L 135	-21.416	-21.911	12.722	1.00	22.27	C
ATOM	2734	CD2	LEU L 135	-23.292	-23.567	12.206	1.00	21.66	C
ATOM	2735	C	LEU L 135	-19.121	-24.643	11.828	1.00	21.34	C
ATOM	2736	O	LEU L 135	-19.356	-25.860	11.787	1.00	20.12	O
ATOM	2737	N	LEU L 136	-18.404	-24.072	12.791	1.00	20.33	N

ATOM	2738	CA	LEU L 136	-18.020	-24.791	14.018	1.00	20.91	C
ATOM	2739	CB	LEU L 136	-16.542	-24.581	14.337	1.00	20.66	C
ATOM	2740	CG	LEU L 136	-15.487	-25.322	13.499	1.00	21.16	C
ATOM	2741	CD1	LEU L 136	-15.578	-25.001	12.006	1.00	20.51	C
ATOM	2742	CD2	LEU L 136	-14.088	-24.968	14.046	1.00	21.49	C
ATOM	2743	C	LEU L 136	-18.831	-24.176	15.126	1.00	21.70	C
ATOM	2744	O	LEU L 136	-18.698	-22.970	15.425	1.00	21.62	O
ATOM	2745	N	ASN L 137	-19.679	-24.979	15.741	1.00	21.40	N
ATOM	2746	CA	ASN L 137	-20.637	-24.434	16.673	1.00	22.97	C
ATOM	2747	CB	ASN L 137	-22.049	-24.913	16.321	1.00	23.60	C
ATOM	2748	CG	ASN L 137	-23.104	-24.003	16.867	1.00	27.83	C
ATOM	2749	OD1	ASN L 137	-23.132	-22.817	16.539	1.00	34.20	O
ATOM	2750	ND2	ASN L 137	-23.957	-24.527	17.741	1.00	30.09	N
ATOM	2751	C	ASN L 137	-20.315	-24.804	18.118	1.00	22.77	C
ATOM	2752	O	ASN L 137	-20.059	-25.977	18.419	1.00	23.33	O
ATOM	2753	N	ASN L 138	-20.327	-23.786	18.987	1.00	22.81	N
ATOM	2754	CA	ASN L 138	-20.305	-23.937	20.455	1.00	22.41	C
ATOM	2755	CB	ASN L 138	-21.626	-24.510	20.999	1.00	23.47	C
ATOM	2756	CG	ASN L 138	-22.850	-23.631	20.708	1.00	26.82	C
ATOM	2757	OD1	ASN L 138	-22.758	-22.479	20.277	1.00	27.15	O
ATOM	2758	ND2	ASN L 138	-24.019	-24.205	20.937	1.00	32.67	N
ATOM	2759	C	ASN L 138	-19.115	-24.743	21.003	1.00	21.76	C
ATOM	2760	O	ASN L 138	-19.289	-25.799	21.623	1.00	21.36	O
ATOM	2761	N	PHE L 139	-17.914	-24.230	20.783	1.00	20.42	N
ATOM	2762	CA	PHE L 139	-16.700	-24.935	21.181	1.00	19.93	C
ATOM	2763	CB	PHE L 139	-15.889	-25.331	19.943	1.00	19.63	C
ATOM	2764	CG	PHE L 139	-15.388	-24.166	19.114	1.00	19.05	C
ATOM	2765	CD1	PHE L 139	-16.111	-23.702	18.025	1.00	18.43	C
ATOM	2766	CE1	PHE L 139	-15.646	-22.636	17.232	1.00	16.08	C
ATOM	2767	CZ	PHE L 139	-14.427	-22.031	17.538	1.00	19.19	C
ATOM	2768	CE2	PHE L 139	-13.681	-22.496	18.627	1.00	17.61	C
ATOM	2769	CD2	PHE L 139	-14.162	-23.556	19.413	1.00	18.36	C
ATOM	2770	C	PHE L 139	-15.852	-24.133	22.180	1.00	20.58	C
ATOM	2771	O	PHE L 139	-16.031	-22.907	22.336	1.00	19.55	O
ATOM	2772	N	TYR L 140	-14.940	-24.841	22.850	1.00	19.48	N
ATOM	2773	CA	TYR L 140	-14.026	-24.241	23.813	1.00	18.82	C
ATOM	2774	CB	TYR L 140	-14.719	-23.967	25.168	1.00	19.04	C
ATOM	2775	CG	TYR L 140	-13.783	-23.200	26.081	1.00	19.03	C
ATOM	2776	CD1	TYR L 140	-12.827	-23.873	26.855	1.00	19.31	C
ATOM	2777	CE1	TYR L 140	-11.909	-23.175	27.645	1.00	19.23	C
ATOM	2778	CZ	TYR L 140	-11.953	-21.771	27.655	1.00	19.12	C
ATOM	2779	OH	TYR L 140	-11.065	-21.085	28.435	1.00	20.17	O
ATOM	2780	CE2	TYR L 140	-12.890	-21.069	26.886	1.00	19.20	C
ATOM	2781	CD2	TYR L 140	-13.788	-21.797	26.084	1.00	17.94	C
ATOM	2782	C	TYR L 140	-12.853	-25.222	23.980	1.00	19.36	C
ATOM	2783	O	TYR L 140	-13.102	-26.438	24.136	1.00	19.41	O
ATOM	2784	N	PRO L 141	-11.589	-24.728	23.952	1.00	19.60	N
ATOM	2785	CA	PRO L 141	-11.145	-23.330	23.896	1.00	19.50	C
ATOM	2786	CB	PRO L 141	-9.667	-23.414	24.300	1.00	19.78	C
ATOM	2787	CG	PRO L 141	-9.218	-24.778	23.715	1.00	19.50	C
ATOM	2788	CD	PRO L 141	-10.435	-25.664	23.961	1.00	19.79	C
ATOM	2789	C	PRO L 141	-11.304	-22.723	22.492	1.00	20.63	C
ATOM	2790	O	PRO L 141	-11.763	-23.390	21.556	1.00	19.61	O
ATOM	2791	N	ARG L 142	-10.942	-21.450	22.375	1.00	20.97	N
ATOM	2792	CA	ARG L 142	-11.153	-20.670	21.159	1.00	21.99	C
ATOM	2793	CB	ARG L 142	-10.885	-19.185	21.483	1.00	21.82	C
ATOM	2794	CG	ARG L 142	-11.302	-18.196	20.395	1.00	22.19	C

ATOM	2795	CD	ARG L 142	-10.963	-16.773	20.855	1.00	25.11	C
ATOM	2796	NE	ARG L 142	-11.437	-15.759	19.905	1.00	30.07	N
ATOM	2797	CZ	ARG L 142	-10.819	-15.449	18.767	1.00	32.56	C
ATOM	2798	NH1	ARG L 142	-9.703	-16.076	18.414	1.00	30.59	N
ATOM	2799	NH2	ARG L 142	-11.327	-14.509	17.969	1.00	33.48	N
ATOM	2800	C	ARG L 142	-10.285	-21.150	19.988	1.00	22.33	C
ATOM	2801	O	ARG L 142	-10.692	-21.039	18.827	1.00	21.74	O
ATOM	2802	N	GLU L 143	-9.098	-21.696	20.289	1.00	22.92	N
ATOM	2803	CA	GLU L 143	-8.161	-22.165	19.260	1.00	24.07	C
ATOM	2804	CB	BGLU L 143	-6.831	-22.555	19.928	0.35	23.44	C
ATOM	2805	CB	AGLU L 143	-6.796	-22.605	19.840	0.65	23.86	C
ATOM	2806	CG	BGLU L 143	-6.300	-21.505	20.951	0.35	22.55	C
ATOM	2807	CG	AGLU L 143	-5.745	-23.003	18.765	0.65	25.27	C
ATOM	2808	CD	BGLU L 143	-6.801	-21.719	22.388	0.35	20.74	C
ATOM	2809	CD	AGLU L 143	-4.485	-23.709	19.327	0.65	27.91	C
ATOM	2810	OE1	BGLU L 143	-6.384	-22.718	23.023	0.35	22.80	O
ATOM	2811	OE1	AGLU L 143	-4.294	-23.761	20.567	0.65	33.84	O
ATOM	2812	OE2	BGLU L 143	-7.568	-20.874	22.899	0.35	16.18	O
ATOM	2813	OE2	AGLU L 143	-3.673	-24.221	18.522	0.65	32.44	O
ATOM	2814	C	GLU L 143	-8.767	-23.339	18.460	1.00	24.18	C
ATOM	2815	O	GLU L 143	-9.191	-24.342	19.036	1.00	22.92	O
ATOM	2816	N	ALA L 144	-8.801	-23.182	17.144	1.00	24.59	N
ATOM	2817	CA	ALA L 144	-9.375	-24.180	16.231	1.00	26.27	C
ATOM	2818	CB	ALA L 144	-10.896	-24.009	16.114	1.00	25.73	C
ATOM	2819	C	ALA L 144	-8.693	-23.991	14.880	1.00	27.19	C
ATOM	2820	O	ALA L 144	-8.425	-22.857	14.479	1.00	27.17	O
ATOM	2821	N	LYS L 145	-8.370	-25.091	14.208	1.00	27.34	N
ATOM	2822	CA	LYS L 145	-7.778	-25.031	12.874	1.00	29.29	C
ATOM	2823	CB	LYS L 145	-6.510	-25.894	12.823	1.00	29.17	C
ATOM	2824	CG	LYS L 145	-5.887	-26.075	11.438	1.00	31.91	C
ATOM	2825	CD	LYS L 145	-4.879	-27.229	11.459	1.00	32.92	C
ATOM	2826	CE	LYS L 145	-3.999	-27.220	10.213	1.00	39.49	C
ATOM	2827	NZ	LYS L 145	-2.867	-28.217	10.294	1.00	42.65	N
ATOM	2828	C	LYS L 145	-8.799	-25.543	11.861	1.00	28.38	C
ATOM	2829	O	LYS L 145	-9.305	-26.648	12.002	1.00	27.75	O
ATOM	2830	N	VAL L 146	-9.077	-24.745	10.836	1.00	28.25	N
ATOM	2831	CA	VAL L 146	-10.005	-25.144	9.766	1.00	28.60	C
ATOM	2832	CB	VAL L 146	-11.218	-24.164	9.679	1.00	29.16	C
ATOM	2833	CG1	VAL L 146	-12.122	-24.477	8.472	1.00	28.60	C
ATOM	2834	CG2	VAL L 146	-12.013	-24.196	10.977	1.00	29.61	C
ATOM	2835	C	VAL L 146	-9.250	-25.205	8.440	1.00	28.97	C
ATOM	2836	O	VAL L 146	-8.659	-24.207	8.010	1.00	29.29	O
ATOM	2837	N	GLN L 147	-9.232	-26.373	7.808	1.00	28.34	N
ATOM	2838	CA	GLN L 147	-8.615	-26.497	6.488	1.00	29.09	C
ATOM	2839	CB	GLN L 147	-7.434	-27.475	6.505	1.00	29.70	C
ATOM	2840	CG	GLN L 147	-6.272	-27.006	7.378	1.00	34.13	C
ATOM	2841	CD	GLN L 147	-4.935	-27.614	6.965	1.00	39.58	C
ATOM	2842	OE1	GLN L 147	-3.925	-26.910	6.887	1.00	42.82	O
ATOM	2843	NE2	GLN L 147	-4.925	-28.920	6.688	1.00	41.24	N
ATOM	2844	C	GLN L 147	-9.614	-26.883	5.389	1.00	28.49	C
ATOM	2845	O	GLN L 147	-10.399	-27.831	5.545	1.00	28.45	O
ATOM	2846	N	TRP L 148	-9.564	-26.138	4.284	1.00	27.00	N
ATOM	2847	CA	TRP L 148	-10.397	-26.403	3.129	1.00	26.51	C
ATOM	2848	CB	TRP L 148	-10.803	-25.095	2.457	1.00	26.15	C
ATOM	2849	CG	TRP L 148	-11.894	-24.353	3.171	1.00	26.57	C
ATOM	2850	CD1	TRP L 148	-11.766	-23.211	3.930	1.00	25.46	C
ATOM	2851	NE1	TRP L 148	-13.009	-22.830	4.412	1.00	25.63	N

ATOM	2852	CE2 TRP L 148	-13.951	-23.726	3.966	1.00	24.89	C
ATOM	2853	CD2 TRP L 148	-13.283	-24.703	3.192	1.00	24.60	C
ATOM	2854	CE3 TRP L 148	-14.032	-25.738	2.605	1.00	25.27	C
ATOM	2855	CZ3 TRP L 148	-15.389	-25.777	2.813	1.00	24.65	C
ATOM	2856	CH2 TRP L 148	-16.032	-24.792	3.604	1.00	25.90	C
ATOM	2857	CZ2 TRP L 148	-15.330	-23.765	4.186	1.00	25.47	C
ATOM	2858	C TRP L 148	-9.615	-27.252	2.145	1.00	26.90	C
ATOM	2859	O TRP L 148	-8.425	-26.998	1.892	1.00	25.41	O
ATOM	2860	N LYS L 149	-10.290	-28.261	1.599	1.00	27.06	N
ATOM	2861	CA LYS L 149	-9.724	-29.112	0.562	1.00	29.06	C
ATOM	2862	CB LYS L 149	-9.318	-30.480	1.120	1.00	28.83	C
ATOM	2863	CG LYS L 149	-7.949	-30.469	1.808	1.00	31.53	C
ATOM	2864	CD LYS L 149	-7.680	-31.760	2.578	1.00	33.56	C
ATOM	2865	CE LYS L 149	-7.742	-31.521	4.103	1.00	41.96	C
ATOM	2866	NZ LYS L 149	-8.069	-32.769	4.899	1.00	45.19	N
ATOM	2867	C LYS L 149	-10.736	-29.245	-0.565	1.00	28.83	C
ATOM	2868	O LYS L 149	-11.928	-29.492	-0.327	1.00	28.33	O
ATOM	2869	N VAL L 150	-10.263	-29.013	-1.786	1.00	28.53	N
ATOM	2870	CA VAL L 150	-11.090	-29.136	-2.976	1.00	29.43	C
ATOM	2871	CB VAL L 150	-11.187	-27.787	-3.714	1.00	29.25	C
ATOM	2872	CG1 VAL L 150	-11.993	-27.917	-4.998	1.00	30.38	C
ATOM	2873	CG2 VAL L 150	-11.794	-26.714	-2.802	1.00	28.89	C
ATOM	2874	C VAL L 150	-10.418	-30.195	-3.844	1.00	30.11	C
ATOM	2875	O VAL L 150	-9.288	-29.993	-4.303	1.00	29.56	O
ATOM	2876	N ASP L 151	-11.097	-31.329	-4.043	1.00	31.20	N
ATOM	2877	CA ASP L 151	-10.485	-32.490	-4.695	1.00	32.15	C
ATOM	2878	CB ASP L 151	-10.457	-32.312	-6.230	1.00	32.16	C
ATOM	2879	CG ASP L 151	-11.826	-32.526	-6.881	1.00	32.91	C
ATOM	2880	OD1 ASP L 151	-12.698	-33.185	-6.273	1.00	35.01	O
ATOM	2881	OD2 ASP L 151	-12.027	-32.052	-8.018	1.00	32.85	O
ATOM	2882	C ASP L 151	-9.078	-32.762	-4.139	1.00	32.88	C
ATOM	2883	O ASP L 151	-8.117	-32.938	-4.904	1.00	33.53	O
ATOM	2884	N ASN L 152	-8.967	-32.769	-2.807	1.00	33.13	N
ATOM	2885	CA ASN L 152	-7.708	-33.021	-2.070	1.00	34.01	C
ATOM	2886	CB ASN L 152	-7.085	-34.365	-2.461	1.00	35.33	C
ATOM	2887	CG ASN L 152	-8.043	-35.507	-2.303	1.00	39.37	C
ATOM	2888	OD1 ASN L 152	-8.594	-35.721	-1.216	1.00	43.68	O
ATOM	2889	ND2 ASN L 152	-8.256	-36.263	-3.391	1.00	43.06	N
ATOM	2890	C ASN L 152	-6.639	-31.928	-2.133	1.00	32.77	C
ATOM	2891	O ASN L 152	-5.551	-32.092	-1.589	1.00	33.09	O
ATOM	2892	N ALA L 153	-6.941	-30.823	-2.796	1.00	31.31	N
ATOM	2893	CA ALA L 153	-5.995	-29.724	-2.875	1.00	30.43	C
ATOM	2894	CB ALA L 153	-6.118	-28.994	-4.224	1.00	30.03	C
ATOM	2895	C ALA L 153	-6.271	-28.777	-1.724	1.00	29.70	C
ATOM	2896	O ALA L 153	-7.379	-28.256	-1.605	1.00	29.20	O
ATOM	2897	N LEU L 154	-5.265	-28.556	-0.882	1.00	29.33	N
ATOM	2898	CA LEU L 154	-5.381	-27.627	0.237	1.00	29.29	C
ATOM	2899	CB LEU L 154	-4.154	-27.740	1.153	1.00	29.60	C
ATOM	2900	CG LEU L 154	-4.084	-26.718	2.296	1.00	30.79	C
ATOM	2901	CD1 LEU L 154	-5.134	-27.003	3.413	1.00	31.48	C
ATOM	2902	CD2 LEU L 154	-2.657	-26.635	2.868	1.00	30.52	C
ATOM	2903	C LEU L 154	-5.532	-26.187	-0.251	1.00	29.07	C
ATOM	2904	O LEU L 154	-4.694	-25.692	-1.013	1.00	28.17	O
ATOM	2905	N GLN L 155	-6.579	-25.504	0.208	1.00	28.15	N
ATOM	2906	CA GLN L 155	-6.831	-24.125	-0.228	1.00	28.02	C
ATOM	2907	CB GLN L 155	-8.328	-23.826	-0.292	1.00	27.75	C
ATOM	2908	CG GLN L 155	-9.121	-24.811	-1.134	1.00	27.58	C

ATOM	2909	CD	GLN	L 155	-8.681	-24.807	-2.587	1.00	28.17	C
ATOM	2910	OE1	GLN	L 155	-8.170	-25.806	-3.102	1.00	29.00	O
ATOM	2911	NE2	GLN	L 155	-8.880	-23.689	-3.250	1.00	25.79	N
ATOM	2912	C	GLN	L 155	-6.157	-23.166	0.735	1.00	28.21	C
ATOM	2913	O	GLN	L 155	-6.357	-23.251	1.947	1.00	28.29	O
ATOM	2914	N	SER	L 156	-5.363	-22.251	0.196	1.00	27.99	N
ATOM	2915	CA	SER	L 156	-4.612	-21.311	1.031	1.00	28.54	C
ATOM	2916	CB	SER	L 156	-3.128	-21.705	1.031	1.00	28.68	C
ATOM	2917	OG	SER	L 156	-2.402	-21.001	2.023	1.00	29.28	O
ATOM	2918	C	SER	L 156	-4.797	-19.888	0.504	1.00	28.49	C
ATOM	2919	O	SER	L 156	-4.511	-19.640	-0.661	1.00	28.93	O
ATOM	2920	N	GLY	L 157	-5.304	-18.978	1.344	1.00	28.21	N
ATOM	2921	CA	GLY	L 157	-5.523	-17.570	0.965	1.00	28.30	C
ATOM	2922	C	GLY	L 157	-6.861	-17.292	0.297	1.00	28.96	C
ATOM	2923	O	GLY	L 157	-7.124	-16.186	-0.168	1.00	28.46	O
ATOM	2924	N	ASN	L 158	-7.697	-18.326	0.301	1.00	28.71	N
ATOM	2925	CA	ASN	L 158	-8.932	-18.470	-0.433	1.00	29.31	C
ATOM	2926	CB	ASN	L 158	-8.945	-19.928	-0.930	1.00	29.71	C
ATOM	2927	CG	ASN	L 158	-8.907	-20.033	-2.398	1.00	34.57	C
ATOM	2928	OD1	ASN	L 158	-9.470	-20.972	-2.969	1.00	38.68	O
ATOM	2929	ND2	ASN	L 158	-8.256	-19.061	-3.057	1.00	38.94	N
ATOM	2930	C	ASN	L 158	-10.168	-18.311	0.455	1.00	27.91	C
ATOM	2931	O	ASN	L 158	-11.309	-18.360	-0.036	1.00	27.25	O
ATOM	2932	N	SER	L 159	-9.932	-18.177	1.761	1.00	27.11	N
ATOM	2933	CA	SER	L 159	-10.998	-18.241	2.751	1.00	26.33	C
ATOM	2934	CB	SER	L 159	-11.043	-19.620	3.416	1.00	26.30	C
ATOM	2935	OG	SER	L 159	-9.800	-19.964	4.011	1.00	26.52	O
ATOM	2936	C	SER	L 159	-10.851	-17.151	3.794	1.00	26.14	C
ATOM	2937	O	SER	L 159	-9.757	-16.588	3.977	1.00	25.94	O
ATOM	2938	N	GLN	L 160	-11.959	-16.845	4.459	1.00	25.42	N
ATOM	2939	CA	GLN	L 160	-11.984	-15.883	5.553	1.00	25.49	C
ATOM	2940	CB	GLN	L 160	-12.589	-14.568	5.080	1.00	25.52	C
ATOM	2941	CG	GLN	L 160	-11.655	-13.803	4.155	1.00	27.30	C
ATOM	2942	CD	GLN	L 160	-12.153	-12.415	3.881	1.00	28.83	C
ATOM	2943	OE1	GLN	L 160	-13.082	-12.234	3.107	1.00	29.83	O
ATOM	2944	NE2	GLN	L 160	-11.548	-11.424	4.518	1.00	29.23	N
ATOM	2945	C	GLN	L 160	-12.801	-16.464	6.697	1.00	25.85	C
ATOM	2946	O	GLN	L 160	-13.811	-17.134	6.458	1.00	25.87	O
ATOM	2947	N	GLU	L 161	-12.345	-16.224	7.923	1.00	25.41	N
ATOM	2948	CA	GLU	L 161	-12.976	-16.745	9.142	1.00	25.97	C
ATOM	2949	CB	GLU	L 161	-11.968	-17.459	10.055	1.00	26.37	C
ATOM	2950	CG	GLU	L 161	-11.485	-18.799	9.628	1.00	28.84	C
ATOM	2951	CD	GLU	L 161	-10.599	-19.443	10.674	1.00	28.32	C
ATOM	2952	OE1	GLU	L 161	-10.351	-20.655	10.547	1.00	36.41	O
ATOM	2953	OE2	GLU	L 161	-10.143	-18.757	11.628	1.00	31.01	O
ATOM	2954	C	GLU	L 161	-13.511	-15.599	9.962	1.00	25.01	C
ATOM	2955	O	GLU	L 161	-12.946	-14.489	9.966	1.00	24.52	O
ATOM	2956	N	SER	L 162	-14.558	-15.894	10.717	1.00	23.90	N
ATOM	2957	CA	SER	L 162	-15.080	-14.965	11.686	1.00	23.34	C
ATOM	2958	CB	SER	L 162	-16.302	-14.264	11.087	1.00	23.46	C
ATOM	2959	OG	SER	L 162	-16.910	-13.454	12.051	1.00	25.24	O
ATOM	2960	C	SER	L 162	-15.457	-15.753	12.945	1.00	22.84	C
ATOM	2961	O	SER	L 162	-15.977	-16.870	12.843	1.00	21.62	O
ATOM	2962	N	VAL	L 163	-15.215	-15.164	14.122	1.00	21.34	N
ATOM	2963	CA	VAL	L 163	-15.460	-15.842	15.398	1.00	21.39	C
ATOM	2964	CB	VAL	L 163	-14.106	-16.193	16.125	1.00	20.89	C
ATOM	2965	CG1	VAL	L 163	-14.326	-17.027	17.386	1.00	20.69	C

ATOM	2966	CG2 VAL L 163	-13.161	-16.930	15.183	1.00	22.08	C
ATOM	2967	C VAL L 163	-16.338	-14.956	16.268	1.00	21.41	C
ATOM	2968	O VAL L 163	-16.121	-13.747	16.347	1.00	21.54	O
ATOM	2969	N THR L 164	-17.340	-15.539	16.902	1.00	21.57	N
ATOM	2970	CA THR L 164	-18.186	-14.801	17.835	1.00	22.33	C
ATOM	2971	CB THR L 164	-19.481	-15.579	18.207	1.00	23.01	C
ATOM	2972	OG1 THR L 164	-19.130	-16.867	18.727	1.00	23.86	O
ATOM	2973	CG2 THR L 164	-20.428	-15.750	16.990	1.00	21.95	C
ATOM	2974	C THR L 164	-17.454	-14.491	19.141	1.00	22.98	C
ATOM	2975	O THR L 164	-16.451	-15.139	19.489	1.00	23.56	O
ATOM	2976	N GLU L 165	-17.971	-13.509	19.881	1.00	23.44	N
ATOM	2977	CA GLU L 165	-17.548	-13.302	21.252	1.00	24.34	C
ATOM	2978	CB GLU L 165	-18.116	-12.007	21.841	1.00	25.72	C
ATOM	2979	CG GLU L 165	-17.645	-10.714	21.125	1.00	30.45	C
ATOM	2980	CD GLU L 165	-16.210	-10.261	21.476	1.00	37.95	C
ATOM	2981	OE1 GLU L 165	-15.789	-9.190	20.968	1.00	40.37	O
ATOM	2982	OE2 GLU L 165	-15.503	-10.942	22.260	1.00	41.28	O
ATOM	2983	C GLU L 165	-18.017	-14.487	22.081	1.00	23.73	C
ATOM	2984	O GLU L 165	-18.991	-15.179	21.732	1.00	22.11	O
ATOM	2985	N GLN L 166	-17.314	-14.721	23.183	1.00	22.99	N
ATOM	2986	CA GLN L 166	-17.640	-15.817	24.090	1.00	23.46	C
ATOM	2987	CB GLN L 166	-16.666	-15.736	25.269	1.00	23.14	C
ATOM	2988	CG GLN L 166	-16.755	-16.830	26.215	1.00	23.53	C
ATOM	2989	CD GLN L 166	-15.549	-16.926	27.115	1.00	22.84	C
ATOM	2990	OE1 GLN L 166	-15.012	-15.905	27.602	1.00	20.06	O
ATOM	2991	NE2 GLN L 166	-15.136	-18.167	27.393	1.00	20.24	N
ATOM	2992	C GLN L 166	-19.104	-15.728	24.531	1.00	24.41	C
ATOM	2993	O GLN L 166	-19.557	-14.670	24.979	1.00	24.42	O
ATOM	2994	N ASP L 167	-19.856	-16.821	24.400	1.00	25.11	N
ATOM	2995	CA ASP L 167	-21.286	-16.820	24.719	1.00	27.28	C
ATOM	2996	CB ASP L 167	-21.926	-18.178	24.412	1.00	26.92	C
ATOM	2997	CG ASP L 167	-23.449	-18.151	24.520	1.00	30.45	C
ATOM	2998	OD1 ASP L 167	-23.976	-18.608	25.547	1.00	33.41	O
ATOM	2999	OD2 ASP L 167	-24.123	-17.642	23.596	1.00	30.83	O
ATOM	3000	C ASP L 167	-21.540	-16.447	26.178	1.00	28.49	C
ATOM	3001	O ASP L 167	-20.897	-16.985	27.083	1.00	27.86	O
ATOM	3002	N SER L 168	-22.485	-15.533	26.408	1.00	29.98	N
ATOM	3003	CA SER L 168	-22.772	-15.075	27.773	1.00	31.83	C
ATOM	3004	CB SER L 168	-23.712	-13.874	27.756	1.00	32.34	C
ATOM	3005	OG SER L 168	-24.979	-14.291	27.275	1.00	34.96	O
ATOM	3006	C SER L 168	-23.389	-16.176	28.640	1.00	32.45	C
ATOM	3007	O SER L 168	-23.329	-16.104	29.865	1.00	33.37	O
ATOM	3008	N LYS L 169	-24.000	-17.182	28.019	1.00	32.79	N
ATOM	3009	CA LYS L 169	-24.595	-18.268	28.793	1.00	33.43	C
ATOM	3010	CB LYS L 169	-25.961	-18.678	28.221	1.00	34.08	C
ATOM	3011	CG LYS L 169	-27.052	-17.608	28.428	1.00	36.65	C
ATOM	3012	CD LYS L 169	-28.368	-17.974	27.713	1.00	36.89	C
ATOM	3013	CE LYS L 169	-29.535	-17.026	28.095	1.00	40.13	C
ATOM	3014	NZ LYS L 169	-29.880	-17.083	29.562	1.00	44.24	N
ATOM	3015	C LYS L 169	-23.673	-19.481	28.996	1.00	31.60	C
ATOM	3016	O LYS L 169	-23.514	-19.940	30.120	1.00	31.53	O
ATOM	3017	N ASP L 170	-23.060	-19.999	27.931	1.00	29.59	N
ATOM	3018	CA ASP L 170	-22.254	-21.216	28.091	1.00	28.40	C
ATOM	3019	CB ASP L 170	-22.789	-22.356	27.203	1.00	28.85	C
ATOM	3020	CG ASP L 170	-22.572	-22.115	25.720	1.00	30.98	C
ATOM	3021	OD1 ASP L 170	-21.851	-21.166	25.330	1.00	30.86	O
ATOM	3022	OD2 ASP L 170	-23.114	-22.907	24.913	1.00	34.32	O

ATOM	3023	C	ASP L 170	-20.735	-21.013	27.910	1.00	26.33	C
ATOM	3024	O	ASP L 170	-19.971	-21.972	27.988	1.00	26.05	O
ATOM	3025	N	SER L 171	-20.323	-19.764	27.676	1.00	24.41	N
ATOM	3026	CA	SER L 171	-18.912	-19.386	27.547	1.00	22.90	C
ATOM	3027	CB	SER L 171	-18.170	-19.594	28.884	1.00	23.85	C
ATOM	3028	OG	SER L 171	-18.784	-18.857	29.940	1.00	25.39	O
ATOM	3029	C	SER L 171	-18.177	-20.067	26.364	1.00	21.58	C
ATOM	3030	O	SER L 171	-16.950	-20.172	26.355	1.00	21.73	O
ATOM	3031	N	THR L 172	-18.924	-20.527	25.362	1.00	19.82	N
ATOM	3032	CA	THR L 172	-18.302	-21.127	24.176	1.00	19.46	C
ATOM	3033	CB	THR L 172	-19.121	-22.335	23.619	1.00	19.47	C
ATOM	3034	OG1	THR L 172	-20.403	-21.877	23.152	1.00	18.98	O
ATOM	3035	CG2	THR L 172	-19.288	-23.456	24.684	1.00	19.85	C
ATOM	3036	C	THR L 172	-18.161	-20.078	23.062	1.00	19.85	C
ATOM	3037	O	THR L 172	-18.654	-18.955	23.202	1.00	19.88	O
ATOM	3038	N	TYR L 173	-17.500	-20.482	21.975	1.00	19.71	N
ATOM	3039	CA	TYR L 173	-17.280	-19.693	20.782	1.00	20.14	C
ATOM	3040	CB	TYR L 173	-15.775	-19.610	20.496	1.00	20.26	C
ATOM	3041	CG	TYR L 173	-14.999	-18.850	21.546	1.00	21.14	C
ATOM	3042	CD1	TYR L 173	-14.395	-19.515	22.629	1.00	19.67	C
ATOM	3043	CE1	TYR L 173	-13.683	-18.805	23.610	1.00	21.70	C
ATOM	3044	CZ	TYR L 173	-13.573	-17.414	23.488	1.00	21.40	C
ATOM	3045	OH	TYR L 173	-12.894	-16.681	24.424	1.00	22.53	O
ATOM	3046	CE2	TYR L 173	-14.165	-16.741	22.414	1.00	21.71	C
ATOM	3047	CD2	TYR L 173	-14.869	-17.460	21.456	1.00	20.32	C
ATOM	3048	C	TYR L 173	-17.922	-20.450	19.630	1.00	20.29	C
ATOM	3049	O	TYR L 173	-18.117	-21.688	19.705	1.00	19.17	O
ATOM	3050	N	SER L 174	-18.257	-19.713	18.573	1.00	20.09	N
ATOM	3051	CA	SER L 174	-18.590	-20.319	17.296	1.00	20.51	C
ATOM	3052	CB	SER L 174	-20.096	-20.264	17.018	1.00	20.44	C
ATOM	3053	OG	SER L 174	-20.811	-20.942	18.055	1.00	20.85	O
ATOM	3054	C	SER L 174	-17.769	-19.618	16.226	1.00	20.67	C
ATOM	3055	O	SER L 174	-17.303	-18.487	16.441	1.00	20.88	O
ATOM	3056	N	LEU L 175	-17.550	-20.301	15.111	1.00	19.89	N
ATOM	3057	CA	LEU L 175	-16.679	-19.830	14.058	1.00	20.97	C
ATOM	3058	CB	LEU L 175	-15.260	-20.431	14.216	1.00	20.77	C
ATOM	3059	CG	LEU L 175	-14.163	-20.174	13.153	1.00	20.94	C
ATOM	3060	CD1	LEU L 175	-12.782	-20.282	13.761	1.00	22.60	C
ATOM	3061	CD2	LEU L 175	-14.258	-21.123	11.953	1.00	21.72	C
ATOM	3062	C	LEU L 175	-17.268	-20.211	12.711	1.00	22.46	C
ATOM	3063	O	LEU L 175	-17.769	-21.335	12.530	1.00	22.42	O
ATOM	3064	N	SER L 176	-17.221	-19.278	11.765	1.00	22.98	N
ATOM	3065	CA	SER L 176	-17.539	-19.617	10.404	1.00	24.31	C
ATOM	3066	CB	SER L 176	-18.752	-18.833	9.900	1.00	24.93	C
ATOM	3067	OG	SER L 176	-18.348	-17.523	9.616	1.00	28.67	O
ATOM	3068	C	SER L 176	-16.313	-19.379	9.514	1.00	24.68	C
ATOM	3069	O	SER L 176	-15.503	-18.448	9.746	1.00	24.63	O
ATOM	3070	N	SER L 177	-16.151	-20.255	8.532	1.00	23.12	N
ATOM	3071	CA	SER L 177	-15.112	-20.116	7.544	1.00	23.22	C
ATOM	3072	CB	SER L 177	-14.088	-21.243	7.674	1.00	23.40	C
ATOM	3073	OG	SER L 177	-13.073	-21.121	6.676	1.00	22.81	O
ATOM	3074	C	SER L 177	-15.791	-20.172	6.179	1.00	23.55	C
ATOM	3075	O	SER L 177	-16.546	-21.100	5.896	1.00	23.97	O
ATOM	3076	N	THR L 178	-15.526	-19.170	5.352	1.00	23.53	N
ATOM	3077	CA	THR L 178	-16.115	-19.085	4.038	1.00	23.66	C
ATOM	3078	CB	THR L 178	-16.883	-17.769	3.864	1.00	24.17	C
ATOM	3079	OG1	THR L 178	-17.922	-17.709	4.848	1.00	24.46	O

ATOM	3080	CG2 THR L 178	-17.500	-17.681	2.477	1.00	24.14	C
ATOM	3081	C THR L 178	-15.043	-19.207	2.971	1.00	24.08	C
ATOM	3082	O THR L 178	-14.110	-18.408	2.939	1.00	23.83	O
ATOM	3083	N LEU L 179	-15.191	-20.208	2.108	1.00	24.06	N
ATOM	3084	CA LEU L 179	-14.307	-20.418	0.963	1.00	25.23	C
ATOM	3085	CB LEU L 179	-14.070	-21.918	0.755	1.00	24.42	C
ATOM	3086	CG LEU L 179	-13.273	-22.343	-0.484	1.00	25.12	C
ATOM	3087	CD1 LEU L 179	-11.787	-22.041	-0.283	1.00	25.30	C
ATOM	3088	CD2 LEU L 179	-13.484	-23.816	-0.773	1.00	24.69	C
ATOM	3089	C LEU L 179	-14.978	-19.831	-0.275	1.00	26.28	C
ATOM	3090	O LEU L 179	-16.117	-20.195	-0.594	1.00	25.88	O
ATOM	3091	N THR L 180	-14.303	-18.908	-0.953	1.00	27.54	N
ATOM	3092	CA THR L 180	-14.893	-18.257	-2.133	1.00	30.50	C
ATOM	3093	CB THR L 180	-14.918	-16.698	-2.003	1.00	31.23	C
ATOM	3094	OG1 THR L 180	-15.640	-16.332	-0.817	1.00	33.71	O
ATOM	3095	CG2 THR L 180	-15.614	-16.058	-3.204	1.00	33.01	C
ATOM	3096	C THR L 180	-14.157	-18.664	-3.403	1.00	30.72	C
ATOM	3097	O THR L 180	-12.928	-18.534	-3.469	1.00	30.94	O
ATOM	3098	N LEU L 181	-14.912	-19.188	-4.372	1.00	31.24	N
ATOM	3099	CA LEU L 181	-14.403	-19.523	-5.713	1.00	32.23	C
ATOM	3100	CB LEU L 181	-14.430	-21.044	-5.961	1.00	32.36	C
ATOM	3101	CG LEU L 181	-13.904	-22.149	-5.046	1.00	34.23	C
ATOM	3102	CD1 LEU L 181	-14.934	-22.436	-3.986	1.00	36.95	C
ATOM	3103	CD2 LEU L 181	-13.671	-23.424	-5.851	1.00	32.77	C
ATOM	3104	C LEU L 181	-15.301	-18.900	-6.784	1.00	32.18	C
ATOM	3105	O LEU L 181	-16.469	-18.602	-6.524	1.00	31.69	O
ATOM	3106	N SER L 182	-14.773	-18.750	-8.004	1.00	32.75	N
ATOM	3107	CA SER L 182	-15.612	-18.433	-9.167	1.00	33.05	C
ATOM	3108	CB SER L 182	-14.758	-18.126	-10.415	1.00	33.21	C
ATOM	3109	OG SER L 182	-13.994	-19.261	-10.837	1.00	32.93	O
ATOM	3110	C SER L 182	-16.567	-19.600	-9.447	1.00	33.75	C
ATOM	3111	O SER L 182	-16.258	-20.750	-9.107	1.00	33.11	O
ATOM	3112	N LYS L 183	-17.722	-19.304	-10.055	1.00	34.47	N
ATOM	3113	CA LYS L 183	-18.632	-20.361	-10.516	1.00	35.91	C
ATOM	3114	CB LYS L 183	-19.846	-19.778	-11.244	1.00	35.76	C
ATOM	3115	CG LYS L 183	-20.854	-20.821	-11.788	1.00	37.36	C
ATOM	3116	CD LYS L 183	-21.819	-20.148	-12.775	1.00	38.16	C
ATOM	3117	CE LYS L 183	-23.106	-20.944	-12.998	1.00	43.87	C
ATOM	3118	NZ LYS L 183	-23.033	-21.891	-14.158	1.00	46.94	N
ATOM	3119	C LYS L 183	-17.882	-21.356	-11.414	1.00	35.43	C
ATOM	3120	O LYS L 183	-18.033	-22.568	-11.253	1.00	35.32	O
ATOM	3121	N ALA L 184	-17.061	-20.825	-12.325	1.00	35.48	N
ATOM	3122	CA ALA L 184	-16.240	-21.624	-13.222	1.00	35.69	C
ATOM	3123	CB ALA L 184	-15.418	-20.730	-14.161	1.00	35.96	C
ATOM	3124	C ALA L 184	-15.345	-22.601	-12.473	1.00	35.66	C
ATOM	3125	O ALA L 184	-15.355	-23.794	-12.789	1.00	35.59	O
ATOM	3126	N ASP L 185	-14.593	-22.117	-11.474	1.00	35.48	N
ATOM	3127	CA ASP L 185	-13.737	-23.007	-10.676	1.00	35.66	C
ATOM	3128	CB ASP L 185	-12.787	-22.236	-9.746	1.00	36.33	C
ATOM	3129	CG ASP L 185	-11.511	-21.775	-10.446	1.00	39.58	C
ATOM	3130	OD1 ASP L 185	-11.065	-22.429	-11.424	1.00	41.74	O
ATOM	3131	OD2 ASP L 185	-10.952	-20.740	-10.010	1.00	42.57	O
ATOM	3132	C ASP L 185	-14.543	-24.016	-9.861	1.00	34.76	C
ATOM	3133	O ASP L 185	-14.172	-25.190	-9.789	1.00	34.58	O
ATOM	3134	N TYR L 186	-15.635	-23.552	-9.249	1.00	33.92	N
ATOM	3135	CA TYR L 186	-16.500	-24.423	-8.450	1.00	33.62	C
ATOM	3136	CB TYR L 186	-17.692	-23.635	-7.881	1.00	32.18	C

ATOM	3137	CG	TYR	L	186	-18.666	-24.493	-7.103	1.00	30.92	C
ATOM	3138	CD1	TYR	L	186	-18.297	-25.069	-5.887	1.00	28.61	C
ATOM	3139	CE1	TYR	L	186	-19.165	-25.872	-5.182	1.00	29.15	C
ATOM	3140	CZ	TYR	L	186	-20.444	-26.097	-5.663	1.00	29.73	C
ATOM	3141	OH	TYR	L	186	-21.296	-26.884	-4.925	1.00	29.28	O
ATOM	3142	CE2	TYR	L	186	-20.855	-25.534	-6.866	1.00	29.69	C
ATOM	3143	CD2	TYR	L	186	-19.959	-24.735	-7.584	1.00	30.68	C
ATOM	3144	C	TYR	L	186	-17.001	-25.631	-9.255	1.00	34.55	C
ATOM	3145	O	TYR	L	186	-17.013	-26.765	-8.769	1.00	33.88	O
ATOM	3146	N	GLU	L	187	-17.412	-25.367	-10.489	1.00	36.04	N
ATOM	3147	CA	GLU	L	187	-17.991	-26.401	-11.345	1.00	37.76	C
ATOM	3148	CB	GLU	L	187	-18.950	-25.757	-12.346	1.00	38.15	C
ATOM	3149	CG	GLU	L	187	-20.063	-25.051	-11.593	1.00	40.93	C
ATOM	3150	CD	GLU	L	187	-21.248	-24.684	-12.432	1.00	45.06	C
ATOM	3151	OE1	GLU	L	187	-22.385	-24.767	-11.895	1.00	46.94	O
ATOM	3152	OE2	GLU	L	187	-21.043	-24.304	-13.608	1.00	46.70	O
ATOM	3153	C	GLU	L	187	-16.996	-27.379	-11.996	1.00	38.14	C
ATOM	3154	O	GLU	L	187	-17.400	-28.397	-12.553	1.00	38.44	O
ATOM	3155	N	LYS	L	188	-15.701	-27.100	-11.885	1.00	38.77	N
ATOM	3156	CA	LYS	L	188	-14.704	-28.036	-12.398	1.00	39.42	C
ATOM	3157	CB	LYS	L	188	-13.588	-27.311	-13.164	1.00	39.73	C
ATOM	3158	CG	LYS	L	188	-12.595	-26.549	-12.314	1.00	41.75	C
ATOM	3159	CD	LYS	L	188	-11.265	-26.291	-13.051	1.00	42.10	C
ATOM	3160	CE	LYS	L	188	-10.467	-27.594	-13.267	1.00	45.93	C
ATOM	3161	NZ	LYS	L	188	-8.987	-27.427	-13.075	1.00	47.19	N
ATOM	3162	C	LYS	L	188	-14.160	-28.986	-11.319	1.00	38.50	C
ATOM	3163	O	LYS	L	188	-13.240	-29.764	-11.572	1.00	38.20	O
ATOM	3164	N	HIS	L	189	-14.759	-28.946	-10.128	1.00	37.01	N
ATOM	3165	CA	HIS	L	189	-14.329	-29.809	-9.041	1.00	35.78	C
ATOM	3166	CB	HIS	L	189	-13.535	-29.006	-8.016	1.00	36.11	C
ATOM	3167	CG	HIS	L	189	-12.237	-28.487	-8.544	1.00	36.79	C
ATOM	3168	ND1	HIS	L	189	-12.065	-27.179	-8.941	1.00	38.51	N
ATOM	3169	CE1	HIS	L	189	-10.827	-27.012	-9.374	1.00	38.99	C
ATOM	3170	NE2	HIS	L	189	-10.194	-28.167	-9.281	1.00	39.06	N
ATOM	3171	CD2	HIS	L	189	-11.055	-29.109	-8.773	1.00	37.42	C
ATOM	3172	C	HIS	L	189	-15.502	-30.511	-8.392	1.00	35.27	C
ATOM	3173	O	HIS	L	189	-16.634	-30.065	-8.509	1.00	34.62	O
ATOM	3174	N	LYS	L	190	-15.217	-31.615	-7.711	1.00	34.96	N
ATOM	3175	CA	LYS	L	190	-16.258	-32.471	-7.150	1.00	34.68	C
ATOM	3176	CB	LYS	L	190	-16.108	-33.914	-7.658	1.00	35.49	C
ATOM	3177	CG	LYS	L	190	-17.239	-34.857	-7.188	1.00	38.15	C
ATOM	3178	CD	LYS	L	190	-17.374	-36.079	-8.099	1.00	43.36	C
ATOM	3179	CE	LYS	L	190	-18.119	-37.238	-7.422	1.00	45.94	C
ATOM	3180	NZ	LYS	L	190	-17.190	-38.203	-6.749	1.00	46.63	N
ATOM	3181	C	LYS	L	190	-16.328	-32.468	-5.625	1.00	33.43	C
ATOM	3182	O	LYS	L	190	-17.383	-32.172	-5.066	1.00	33.31	O
ATOM	3183	N	VAL	L	191	-15.228	-32.818	-4.961	1.00	32.24	N
ATOM	3184	CA	VAL	L	191	-15.243	-32.983	-3.502	1.00	31.62	C
ATOM	3185	CB	VAL	L	191	-14.379	-34.173	-3.027	1.00	31.68	C
ATOM	3186	CG1	VAL	L	191	-14.483	-34.348	-1.508	1.00	31.10	C
ATOM	3187	CG2	VAL	L	191	-14.802	-35.452	-3.745	1.00	32.55	C
ATOM	3188	C	VAL	L	191	-14.818	-31.709	-2.768	1.00	30.64	C
ATOM	3189	O	VAL	L	191	-13.691	-31.236	-2.928	1.00	30.33	O
ATOM	3190	N	TYR	L	192	-15.741	-31.175	-1.969	1.00	29.80	N
ATOM	3191	CA	TYR	L	192	-15.488	-30.004	-1.098	1.00	28.19	C
ATOM	3192	CB	TYR	L	192	-16.534	-28.921	-1.368	1.00	28.22	C
ATOM	3193	CG	TYR	L	192	-16.341	-28.344	-2.737	1.00	27.90	C

ATOM	3194	CD1 TYR L 192	-16.814	-29.011	-3.877	1.00	26.64	C
ATOM	3195	CE1 TYR L 192	-16.596	-28.494	-5.148	1.00	26.72	C
ATOM	3196	CZ TYR L 192	-15.885	-27.319	-5.287	1.00	28.00	C
ATOM	3197	OH TYR L 192	-15.653	-26.792	-6.529	1.00	28.70	O
ATOM	3198	CE2 TYR L 192	-15.394	-26.644	-4.178	1.00	27.75	C
ATOM	3199	CD2 TYR L 192	-15.617	-27.162	-2.913	1.00	27.48	C
ATOM	3200	C TYR L 192	-15.509	-30.435	0.349	1.00	27.63	C
ATOM	3201	O TYR L 192	-16.527	-30.944	0.819	1.00	26.78	O
ATOM	3202	N ALA L 193	-14.380	-30.251	1.039	1.00	26.50	N
ATOM	3203	CA ALA L 193	-14.200	-30.711	2.416	1.00	26.99	C
ATOM	3204	CB ALA L 193	-13.257	-31.916	2.472	1.00	26.82	C
ATOM	3205	C ALA L 193	-13.689	-29.608	3.346	1.00	27.17	C
ATOM	3206	O ALA L 193	-12.814	-28.826	2.964	1.00	26.56	O
ATOM	3207	N CYS L 194	-14.252	-29.561	4.549	1.00	27.30	N
ATOM	3208	CA CYS L 194	-13.793	-28.701	5.627	1.00	27.24	C
ATOM	3209	CB CYS L 194	-14.988	-27.892	6.173	1.00	27.54	C
ATOM	3210	SG CYS L 194	-14.599	-26.894	7.601	1.00	32.30	S
ATOM	3211	C CYS L 194	-13.254	-29.647	6.697	1.00	26.65	C
ATOM	3212	O CYS L 194	-14.009	-30.476	7.206	1.00	26.06	O
ATOM	3213	N GLU L 195	-11.962	-29.537	7.020	1.00	26.33	N
ATOM	3214	CA GLU L 195	-11.332	-30.334	8.080	1.00	27.36	C
ATOM	3215	CB GLU L 195	-10.061	-31.060	7.580	1.00	26.96	C
ATOM	3216	CG GLU L 195	-9.535	-32.078	8.640	1.00	29.95	C
ATOM	3217	CD GLU L 195	-8.227	-32.768	8.258	1.00	33.25	C
ATOM	3218	OE1 GLU L 195	-8.108	-34.002	8.500	1.00	39.87	O
ATOM	3219	OE2 GLU L 195	-7.321	-32.078	7.726	1.00	39.79	O
ATOM	3220	C GLU L 195	-11.000	-29.508	9.339	1.00	26.21	C
ATOM	3221	O GLU L 195	-10.289	-28.500	9.257	1.00	26.12	O
ATOM	3222	N VAL L 196	-11.492	-29.960	10.491	1.00	24.96	N
ATOM	3223	CA VAL L 196	-11.416	-29.213	11.745	1.00	24.53	C
ATOM	3224	CB VAL L 196	-12.831	-28.969	12.328	1.00	24.30	C
ATOM	3225	CG1 VAL L 196	-12.775	-28.313	13.738	1.00	23.51	C
ATOM	3226	CG2 VAL L 196	-13.657	-28.139	11.353	1.00	23.54	C
ATOM	3227	C VAL L 196	-10.576	-29.950	12.774	1.00	24.95	C
ATOM	3228	O VAL L 196	-10.830	-31.121	13.078	1.00	24.81	O
ATOM	3229	N THR L 197	-9.596	-29.237	13.308	1.00	25.03	N
ATOM	3230	CA THR L 197	-8.743	-29.717	14.387	1.00	25.61	C
ATOM	3231	CB THR L 197	-7.256	-29.617	13.965	1.00	25.91	C
ATOM	3232	OG1 THR L 197	-7.078	-30.331	12.742	1.00	27.13	O
ATOM	3233	CG2 THR L 197	-6.324	-30.193	15.048	1.00	27.09	C
ATOM	3234	C THR L 197	-9.006	-28.851	15.621	1.00	25.53	C
ATOM	3235	O THR L 197	-9.003	-27.613	15.547	1.00	25.03	O
ATOM	3236	N HIS L 198	-9.233	-29.511	16.755	1.00	25.16	N
ATOM	3237	CA HIS L 198	-9.585	-28.833	17.988	1.00	24.90	C
ATOM	3238	CB HIS L 198	-11.070	-28.513	17.979	1.00	24.07	C
ATOM	3239	CG HIS L 198	-11.503	-27.674	19.135	1.00	22.88	C
ATOM	3240	ND1 HIS L 198	-12.056	-28.210	20.277	1.00	20.71	N
ATOM	3241	CE1 HIS L 198	-12.329	-27.236	21.127	1.00	20.71	C
ATOM	3242	NE2 HIS L 198	-11.969	-26.088	20.578	1.00	19.69	N
ATOM	3243	CD2 HIS L 198	-11.444	-26.335	19.333	1.00	20.93	C
ATOM	3244	C HIS L 198	-9.271	-29.757	19.160	1.00	25.81	C
ATOM	3245	O HIS L 198	-9.382	-30.969	19.031	1.00	26.26	O
ATOM	3246	N GLN L 199	-8.905	-29.178	20.301	1.00	26.36	N
ATOM	3247	CA GLN L 199	-8.419	-29.949	21.463	1.00	27.04	C
ATOM	3248	CB GLN L 199	-7.668	-29.033	22.475	1.00	26.71	C
ATOM	3249	CG BGLN L 199	-6.280	-28.577	22.009	0.35	26.30	C
ATOM	3250	CG AGLN L 199	-6.264	-28.598	21.936	0.65	26.26	C

ATOM	3251	CD BGLN L 199	-5.167	-29.573	22.314	0.35	26.46	C
ATOM	3252	CD AGLN L 199	-5.722	-27.246	22.460	0.65	27.86	C
ATOM	3253	OE1BGLN L 199	-5.407	-30.769	22.494	0.35	26.15	O
ATOM	3254	OE1AGLN L 199	-6.338	-26.181	22.289	0.65	26.63	O
ATOM	3255	NE2BGLN L 199	-3.934	-29.076	22.368	0.35	26.85	N
ATOM	3256	NE2AGLN L 199	-4.535	-27.293	23.067	0.65	27.07	N
ATOM	3257	C GLN L 199	-9.512	-30.800	22.106	1.00	27.56	C
ATOM	3258	O GLN L 199	-9.209	-31.726	22.870	1.00	28.27	O
ATOM	3259	N GLY L 200	-10.770	-30.508	21.770	1.00	27.20	N
ATOM	3260	CA GLY L 200	-11.909	-31.302	22.219	1.00	28.09	C
ATOM	3261	C GLY L 200	-12.204	-32.531	21.363	1.00	28.90	C
ATOM	3262	O GLY L 200	-13.085	-33.325	21.703	1.00	28.94	O
ATOM	3263	N LEU L 201	-11.473	-32.667	20.257	1.00	29.50	N
ATOM	3264	CA LEU L 201	-11.586	-33.803	19.328	1.00	30.26	C
ATOM	3265	CB LEU L 201	-11.779	-33.281	17.893	1.00	29.52	C
ATOM	3266	CG LEU L 201	-12.961	-32.365	17.541	1.00	28.35	C
ATOM	3267	CD1 LEU L 201	-12.746	-31.648	16.179	1.00	26.71	C
ATOM	3268	CD2 LEU L 201	-14.293	-33.111	17.548	1.00	26.81	C
ATOM	3269	C LEU L 201	-10.321	-34.688	19.396	1.00	31.44	C
ATOM	3270	O LEU L 201	-9.183	-34.182	19.326	1.00	30.91	O
ATOM	3271	N SER L 202	-10.514	-36.005	19.535	1.00	33.15	N
ATOM	3272	CA SER L 202	-9.369	-36.941	19.577	1.00	34.45	C
ATOM	3273	CB SER L 202	-9.786	-38.337	20.054	1.00	34.80	C
ATOM	3274	OG SER L 202	-10.962	-38.780	19.399	1.00	37.15	O
ATOM	3275	C SER L 202	-8.632	-37.026	18.246	1.00	34.82	C
ATOM	3276	O SER L 202	-7.399	-37.186	18.210	1.00	35.35	O
ATOM	3277	N SER L 203	-9.379	-36.899	17.151	1.00	34.66	N
ATOM	3278	CA SER L 203	-8.772	-36.670	15.840	1.00	34.62	C
ATOM	3279	CB SER L 203	-8.627	-38.000	15.078	1.00	34.64	C
ATOM	3280	OG SER L 203	-9.907	-38.546	14.825	1.00	36.77	O
ATOM	3281	C SER L 203	-9.593	-35.639	15.025	1.00	34.09	C
ATOM	3282	O SER L 203	-10.763	-35.379	15.348	1.00	33.57	O
ATOM	3283	N PRO L 204	-8.983	-35.051	13.975	1.00	33.65	N
ATOM	3284	CA PRO L 204	-9.688	-34.095	13.114	1.00	33.17	C
ATOM	3285	CB PRO L 204	-8.713	-33.885	11.960	1.00	33.38	C
ATOM	3286	CG PRO L 204	-7.367	-34.127	12.564	1.00	33.79	C
ATOM	3287	CD PRO L 204	-7.581	-35.235	13.549	1.00	33.78	C
ATOM	3288	C PRO L 204	-11.018	-34.616	12.560	1.00	32.86	C
ATOM	3289	O PRO L 204	-11.147	-35.799	12.231	1.00	32.89	O
ATOM	3290	N VAL L 205	-11.992	-33.721	12.459	1.00	31.83	N
ATOM	3291	CA VAL L 205	-13.298	-34.025	11.894	1.00	31.12	C
ATOM	3292	CB VAL L 205	-14.445	-33.557	12.832	1.00	31.12	C
ATOM	3293	CG1 VAL L 205	-15.757	-33.414	12.088	1.00	31.97	C
ATOM	3294	CG2 VAL L 205	-14.605	-34.539	13.988	1.00	31.94	C
ATOM	3295	C VAL L 205	-13.398	-33.388	10.512	1.00	30.52	C
ATOM	3296	O VAL L 205	-13.047	-32.219	10.335	1.00	29.60	O
ATOM	3297	N THR L 206	-13.843	-34.179	9.535	1.00	29.77	N
ATOM	3298	CA THR L 206	-14.026	-33.705	8.166	1.00	29.75	C
ATOM	3299	CB THR L 206	-13.208	-34.528	7.122	1.00	29.74	C
ATOM	3300	OG1 THR L 206	-11.805	-34.375	7.377	1.00	30.25	O
ATOM	3301	CG2 THR L 206	-13.461	-34.023	5.714	1.00	28.67	C
ATOM	3302	C THR L 206	-15.508	-33.733	7.832	1.00	30.13	C
ATOM	3303	O THR L 206	-16.198	-34.747	8.047	1.00	30.02	O
ATOM	3304	N LYS L 207	-15.997	-32.605	7.336	1.00	29.68	N
ATOM	3305	CA LYS L 207	-17.314	-32.519	6.729	1.00	30.21	C
ATOM	3306	CB LYS L 207	-18.105	-31.388	7.370	1.00	30.49	C
ATOM	3307	CG LYS L 207	-19.242	-31.824	8.234	1.00	33.26	C

ATOM	3308	CD	LYS	L 207	-18.779	-32.640	9.384	1.00	36.76	C
ATOM	3309	CE	LYS	L 207	-19.846	-33.625	9.777	1.00	38.45	C
ATOM	3310	NZ	LYS	L 207	-19.558	-34.208	11.117	1.00	40.08	N
ATOM	3311	C	LYS	L 207	-17.140	-32.231	5.252	1.00	30.17	C
ATOM	3312	O	LYS	L 207	-16.412	-31.304	4.885	1.00	29.53	O
ATOM	3313	N	SER	L 208	-17.802	-33.009	4.399	1.00	30.22	N
ATOM	3314	CA	SER	L 208	-17.666	-32.811	2.964	1.00	30.66	C
ATOM	3315	CB	SER	L 208	-16.543	-33.681	2.403	1.00	31.17	C
ATOM	3316	OG	SER	L 208	-16.820	-35.050	2.599	1.00	31.75	O
ATOM	3317	C	SER	L 208	-18.950	-33.035	2.183	1.00	31.13	C
ATOM	3318	O	SER	L 208	-19.921	-33.567	2.710	1.00	31.35	O
ATOM	3319	N	PHE	L 209	-18.941	-32.617	0.922	1.00	31.74	N
ATOM	3320	CA	PHE	L 209	-20.014	-32.926	-0.027	1.00	31.70	C
ATOM	3321	CB	PHE	L 209	-21.133	-31.867	0.018	1.00	30.83	C
ATOM	3322	CG	PHE	L 209	-20.712	-30.485	-0.445	1.00	29.65	C
ATOM	3323	CD1	PHE	L 209	-20.839	-30.112	-1.782	1.00	26.17	C
ATOM	3324	CE1	PHE	L 209	-20.449	-28.833	-2.224	1.00	27.96	C
ATOM	3325	CZ	PHE	L 209	-19.957	-27.904	-1.305	1.00	28.37	C
ATOM	3326	CE2	PHE	L 209	-19.833	-28.266	0.045	1.00	27.10	C
ATOM	3327	CD2	PHE	L 209	-20.218	-29.549	0.468	1.00	28.25	C
ATOM	3328	C	PHE	L 209	-19.407	-33.063	-1.420	1.00	32.95	C
ATOM	3329	O	PHE	L 209	-18.310	-32.566	-1.670	1.00	31.62	O
ATOM	3330	N	ASN	L 210	-20.101	-33.778	-2.314	1.00	34.95	N
ATOM	3331	CA	ASN	L 210	-19.754	-33.749	-3.739	1.00	36.94	C
ATOM	3332	CB	ASN	L 210	-19.838	-35.133	-4.378	1.00	37.48	C
ATOM	3333	CG	ASN	L 210	-19.135	-36.188	-3.560	1.00	39.50	C
ATOM	3334	OD1	ASN	L 210	-17.962	-36.046	-3.206	1.00	41.41	O
ATOM	3335	ND2	ASN	L 210	-19.855	-37.251	-3.234	1.00	42.09	N
ATOM	3336	C	ASN	L 210	-20.688	-32.808	-4.441	1.00	37.62	C
ATOM	3337	O	ASN	L 210	-21.896	-32.854	-4.215	1.00	38.08	O
ATOM	3338	N	ARG	L 211	-20.132	-31.940	-5.278	1.00	39.23	N
ATOM	3339	CA	ARG	L 211	-20.932	-31.006	-6.037	1.00	41.18	C
ATOM	3340	CB	ARG	L 211	-20.051	-30.112	-6.904	1.00	40.66	C
ATOM	3341	CG	ARG	L 211	-20.826	-29.105	-7.721	1.00	39.54	C
ATOM	3342	CD	ARG	L 211	-19.930	-28.393	-8.710	1.00	40.28	C
ATOM	3343	NE	ARG	L 211	-19.116	-29.341	-9.468	1.00	41.53	N
ATOM	3344	CZ	ARG	L 211	-19.511	-29.952	-10.583	1.00	42.42	C
ATOM	3345	NH1	ARG	L 211	-20.709	-29.711	-11.100	1.00	42.22	N
ATOM	3346	NH2	ARG	L 211	-18.698	-30.803	-11.184	1.00	42.61	N
ATOM	3347	C	ARG	L 211	-21.927	-31.785	-6.895	1.00	43.42	C
ATOM	3348	O	ARG	L 211	-21.576	-32.817	-7.486	1.00	43.21	O
ATOM	3349	N	GLY	L 212	-23.162	-31.288	-6.944	1.00	45.79	N
ATOM	3350	CA	GLY	L 212	-24.246	-31.957	-7.653	1.00	49.09	C
ATOM	3351	C	GLY	L 212	-25.109	-32.735	-6.681	1.00	51.14	C
ATOM	3352	O	GLY	L 212	-26.285	-32.410	-6.489	1.00	51.91	O
ATOM	3353	N	GLU	L 213	-24.509	-33.751	-6.058	1.00	52.80	N
ATOM	3354	CA	GLU	L 213	-25.175	-34.604	-5.066	1.00	54.32	C
ATOM	3355	CB	GLU	L 213	-24.240	-35.749	-4.659	1.00	54.45	C
ATOM	3356	CG	GLU	L 213	-23.579	-36.464	-5.849	1.00	55.42	C
ATOM	3357	CD	GLU	L 213	-22.446	-37.401	-5.440	1.00	55.62	C
ATOM	3358	OE1	GLU	L 213	-21.577	-37.686	-6.302	1.00	57.08	O
ATOM	3359	OE2	GLU	L 213	-22.417	-37.847	-4.264	1.00	56.94	O
ATOM	3360	C	GLU	L 213	-25.617	-33.827	-3.818	1.00	54.71	C
ATOM	3361	O	GLU	L 213	-26.800	-33.828	-3.450	1.00	55.34	O
ATOM	3362	CAA	CA	M 301	2.809	11.227	40.181	1.00	30.07	CA
ATOM	3363	CAA	CA	M 302	5.052	12.087	37.218	1.00	31.38	CA
ATOM	3364	MG	MG	M 303	-6.126	-19.192	35.780	1.00	54.37	MG

ATOM	3365	MG	MG M 304	-4.969	-16.621	44.481	1.00	49.90	MG
ATOM	3366	MG	MG M 305	-1.899	-14.872	49.621	1.00	49.83	MG
ATOM	3367	MG	MG M 306	-20.983	-17.017	33.275	1.00	62.74	MG
ATOM	3368	MG	MG M 307	-9.444	-23.948	-7.001	1.00	66.32	MG
ATOM	3369	O25	S1P S 401	3.775	12.880	38.888	1.00	20.25	O
ATOM	3370	P22	S1P S 401	3.627	14.289	39.455	1.00	20.86	P
ATOM	3371	O23	S1P S 401	3.053	14.337	40.809	1.00	19.18	O
ATOM	3372	O24	S1P S 401	4.897	15.019	39.186	1.00	18.76	O
ATOM	3373	O1	S1P S 401	2.576	15.024	38.468	1.00	18.31	O
ATOM	3374	C1	S1P S 401	1.176	14.756	38.557	1.00	17.79	C
ATOM	3375	C2	S1P S 401	0.688	14.320	37.182	1.00	19.53	C
ATOM	3376	N2	S1P S 401	1.387	13.099	36.758	1.00	20.13	N
ATOM	3377	C3	S1P S 401	0.926	15.438	36.154	1.00	21.30	C
ATOM	3378	O3	S1P S 401	0.042	16.520	36.452	1.00	21.66	O
ATOM	3379	C4	S1P S 401	0.619	14.958	34.749	1.00	21.02	C
ATOM	3380	C5	S1P S 401	1.576	15.002	33.828	1.00	23.12	C
ATOM	3381	C6	S1P S 401	1.297	14.528	32.422	1.00	23.95	C
ATOM	3382	C7	S1P S 401	1.727	15.648	31.470	1.00	28.61	C
ATOM	3383	C8	S1P S 401	0.517	16.100	30.691	1.00	32.59	C
ATOM	3384	C9	S1P S 401	-0.211	17.316	31.203	1.00	30.96	C
ATOM	3385	C10	S1P S 401	-0.685	18.029	29.949	1.00	30.95	C
ATOM	3386	C11	S1P S 401	-2.190	17.987	29.693	1.00	32.47	C
ATOM	3387	C12	S1P S 401	-2.461	18.528	28.287	1.00	34.85	C
ATOM	3388	C13	S1P S 401	-3.474	19.662	28.391	1.00	36.76	C
ATOM	3389	C14	S1P S 401	-3.533	20.629	27.190	1.00	38.45	C
ATOM	3390	C15	S1P S 401	-2.735	21.920	27.414	1.00	37.32	C
ATOM	3391	C16	S1P S 401	-3.160	22.741	28.632	1.00	37.31	C
ATOM	3392	C17	S1P S 401	-2.258	23.951	28.796	1.00	35.54	C
ATOM	3393	C18	S1P S 401	-2.816	24.962	29.780	1.00	36.84	C
ATOM	3394	O	HOH W 501	0.824	11.943	40.612	1.00	19.98	O
ATOM	3395	O	HOH W 502	4.276	13.744	36.006	1.00	17.28	O
ATOM	3396	O	HOH W 503	6.607	13.568	38.001	1.00	17.68	O
ATOM	3397	O	HOH W 504	3.756	11.938	42.195	1.00	23.46	O
ATOM	3398	O	HOH W 505	4.574	17.517	38.814	1.00	29.12	O
ATOM	3399	O	HOH W 506	1.020	15.426	42.199	1.00	35.02	O
ATOM	3400	O	HOH W 507	-9.825	24.571	29.761	1.00	22.69	O
ATOM	3401	O	HOH W 508	-6.828	8.879	35.739	1.00	16.34	O
ATOM	3402	O	HOH W 509	-5.205	10.170	41.045	1.00	18.48	O
ATOM	3403	O	HOH W 510	-5.387	1.967	17.917	1.00	25.09	O
ATOM	3404	O	HOH W 511	-12.291	0.183	17.113	1.00	28.82	O
ATOM	3405	O	HOH W 512	-0.471	4.572	23.400	1.00	21.49	O
ATOM	3406	O	HOH W 513	-0.545	7.168	22.885	1.00	20.71	O
ATOM	3407	O	HOH W 514	5.571	9.590	26.750	1.00	19.94	O
ATOM	3408	O	HOH W 515	3.193	2.037	24.991	1.00	28.25	O
ATOM	3409	O	HOH W 516	3.017	-0.609	24.036	1.00	40.97	O
ATOM	3410	O	HOH W 517	8.253	-1.176	28.438	1.00	26.15	O
ATOM	3411	O	HOH W 518	-18.258	0.166	7.283	1.00	30.32	O
ATOM	3412	O	HOH W 519	-18.316	4.293	10.146	1.00	27.68	O
ATOM	3413	O	HOH W 520	-20.244	5.981	15.650	1.00	24.44	O
ATOM	3414	O	HOH W 521	-20.993	8.014	17.362	1.00	22.96	O
ATOM	3415	O	HOH W 522	-20.756	10.161	6.876	1.00	32.93	O
ATOM	3416	O	HOH W 523	-19.354	12.496	13.382	1.00	27.56	O
ATOM	3417	O	HOH W 524	2.460	-10.578	34.042	1.00	30.01	O
ATOM	3418	O	HOH W 525	4.462	-6.240	31.647	1.00	27.29	O
ATOM	3419	O	HOH W 526	-2.599	-16.724	29.170	1.00	27.65	O
ATOM	3420	O	HOH W 527	13.354	3.893	38.562	1.00	22.17	O
ATOM	3421	O	HOH W 528	-1.272	4.316	40.264	1.00	18.91	O

ATOM	3422	O	HOH W 529	0.467	2.310	40.847	1.00	35.93	O
ATOM	3423	O	HOH W 530	-0.466	0.297	39.306	1.00	20.31	O
ATOM	3424	O	HOH W 531	-14.744	6.267	33.346	1.00	20.98	O
ATOM	3425	O	HOH W 532	-16.352	-0.367	28.680	1.00	24.47	O
ATOM	3426	O	HOH W 533	-13.595	9.174	38.721	1.00	28.77	O
ATOM	3427	O	HOH W 534	9.092	9.341	32.872	1.00	24.35	O
ATOM	3428	O	HOH W 535	5.268	16.241	29.120	1.00	22.45	O
ATOM	3429	O	HOH W 536	4.748	18.694	28.001	1.00	19.24	O
ATOM	3430	O	HOH W 537	-24.818	-19.204	-1.634	1.00	29.30	O
ATOM	3431	O	HOH W 538	-25.007	-19.612	0.792	1.00	34.66	O
ATOM	3432	O	HOH W 539	-22.858	-21.381	1.033	1.00	27.49	O
ATOM	3433	O	HOH W 540	-20.275	-28.261	20.948	1.00	39.95	O
ATOM	3434	O	HOH W 541	-17.948	-15.353	-0.198	1.00	41.26	O
ATOM	3435	O	HOH W 542	-17.456	-13.708	1.762	1.00	41.05	O
ATOM	3436	O	HOH W 543	-20.860	-20.138	20.977	1.00	24.33	O
ATOM	3437	O	HOH W 544	-20.528	-17.362	20.937	1.00	27.11	O
ATOM	3438	O	HOH W 545	-26.282	-22.684	17.905	1.00	32.97	O
ATOM	3439	O	HOH W 546	-13.832	-14.132	20.099	1.00	25.48	O
ATOM	3440	O	HOH W 547	-9.977	-20.125	24.696	1.00	25.93	O
ATOM	3441	O	HOH W 548	-8.297	-26.459	20.521	1.00	23.39	O
ATOM	3442	O	HOH W 549	-7.631	-23.918	4.194	1.00	29.20	O
ATOM	3443	O	HOH W 550	-8.198	-21.011	2.169	1.00	27.95	O
ATOM	3444	O	HOH W 551	-19.140	-13.334	8.959	1.00	27.09	O
ATOM	3445	O	HOH W 552	-19.410	-16.353	29.047	1.00	31.43	O
ATOM	3446	O	HOH W 553	-16.792	-16.600	7.315	1.00	31.10	O
ATOM	3447	O	HOH W 554	-13.859	-16.124	1.240	1.00	35.96	O
ATOM	3448	O	HOH W 555	-16.994	-18.094	-13.080	1.00	40.00	O
ATOM	3449	O	HOH W 556	-11.331	-32.574	-1.047	1.00	31.45	O
ATOM	3450	O	HOH W 557	-19.026	6.675	0.750	1.00	43.84	O
ATOM	3451	O	HOH W 558	-3.228	0.342	23.623	1.00	25.25	O
ATOM	3452	O	HOH W 559	-7.873	16.179	36.237	1.00	33.99	O
ATOM	3453	O	HOH W 560	-6.301	8.483	12.206	1.00	29.35	O
ATOM	3454	O	HOH W 561	1.231	-11.726	36.069	1.00	23.25	O
ATOM	3455	O	HOH W 562	-28.446	-5.885	-4.728	1.00	49.36	O
ATOM	3456	O	HOH W 563	-7.799	-17.674	42.640	1.00	28.44	O
ATOM	3457	O	HOH W 564	7.378	14.971	27.581	1.00	33.35	O
ATOM	3458	O	HOH W 565	-4.536	-19.044	33.036	1.00	24.34	O
ATOM	3459	O	HOH W 566	-40.151	-8.655	10.415	1.00	38.88	O
ATOM	3460	O	HOH W 567	-38.280	-22.624	6.174	1.00	31.53	O
ATOM	3461	O	HOH W 568	-33.750	-22.096	1.050	1.00	43.85	O
ATOM	3462	O	HOH W 569	-28.207	-1.296	9.210	1.00	32.67	O
ATOM	3463	O	HOH W 570	-33.819	-0.072	5.884	1.00	40.20	O
ATOM	3464	O	HOH W 571	-38.113	-25.517	7.865	1.00	42.85	O
ATOM	3465	O	HOH W 572	-39.835	-19.298	15.903	1.00	35.56	O
ATOM	3466	O	HOH W 573	-44.311	-22.483	10.239	1.00	46.07	O
ATOM	3467	O	HOH W 574	-32.828	-22.855	18.112	1.00	32.73	O
ATOM	3468	O	HOH W 575	-13.971	-1.059	2.058	1.00	24.89	O
ATOM	3469	O	HOH W 576	-14.364	-0.525	4.876	1.00	26.88	O
ATOM	3470	O	HOH W 577	-28.920	-11.799	15.040	1.00	34.67	O
ATOM	3471	O	HOH W 578	-35.957	-18.794	20.455	1.00	34.68	O
ATOM	3472	O	HOH W 579	-34.023	-13.306	15.964	1.00	32.81	O
ATOM	3473	O	HOH W 580	-9.769	-12.387	6.634	1.00	50.80	O
ATOM	3474	O	HOH W 581	-19.543	-15.571	5.702	1.00	41.67	O
ATOM	3475	O	HOH W 582	-9.812	-14.909	8.065	1.00	34.14	O
ATOM	3476	O	HOH W 583	-8.192	-22.074	10.960	1.00	31.57	O
ATOM	3477	O	HOH W 584	-11.724	-15.239	0.211	1.00	48.80	O
ATOM	3478	O	HOH W 585	-20.055	-6.988	11.780	1.00	33.34	O

ATOM	3479	O	HOH W 586	-22.910	-5.728	10.984	1.00	38.73	O
ATOM	3480	O	HOH W 587	-27.847	-8.424	14.011	1.00	32.64	O
ATOM	3481	O	HOH W 588	-25.526	-13.352	17.553	1.00	32.04	O
ATOM	3482	O	HOH W 589	-33.108	-7.029	10.784	1.00	42.66	O
ATOM	3483	O	HOH W 590	-24.544	-8.862	-4.697	1.00	46.11	O
ATOM	3484	O	HOH W 591	-27.644	-1.480	-3.674	1.00	37.77	O
ATOM	3485	O	HOH W 592	-16.854	5.112	1.280	1.00	31.89	O
ATOM	3486	O	HOH W 593	-19.280	6.717	27.118	1.00	37.56	O
ATOM	3487	O	HOH W 594	-20.471	4.238	19.223	1.00	40.76	O
ATOM	3488	O	HOH W 595	-19.645	10.773	29.084	1.00	32.87	O
ATOM	3489	O	HOH W 596	-15.020	5.372	36.660	1.00	32.03	O
ATOM	3490	O	HOH W 597	-17.561	5.304	34.813	1.00	59.51	O
ATOM	3491	O	HOH W 598	-23.216	-11.554	-4.085	1.00	41.82	O
ATOM	3492	O	HOH W 599	-23.414	7.532	18.732	1.00	31.24	O
ATOM	3493	O	HOH W 600	-17.999	2.943	29.181	1.00	35.33	O
ATOM	3494	O	HOH W 601	-19.561	3.698	25.916	1.00	36.44	O
ATOM	3495	O	HOH W 602	-10.961	15.521	34.703	1.00	40.08	O
ATOM	3496	O	HOH W 603	-5.861	12.210	42.585	1.00	24.72	O
ATOM	3497	O	HOH W 604	-8.955	11.465	43.451	1.00	34.28	O
ATOM	3498	O	HOH W 605	3.221	22.746	27.353	1.00	27.64	O
ATOM	3499	O	HOH W 606	-16.226	5.757	30.752	1.00	34.40	O
ATOM	3500	O	HOH W 607	-6.721	19.447	38.399	1.00	43.41	O
ATOM	3501	O	HOH W 608	-11.898	0.766	5.528	1.00	41.85	O
ATOM	3502	O	HOH W 609	-5.066	11.504	7.144	1.00	37.24	O
ATOM	3503	O	HOH W 610	-22.369	25.575	26.590	1.00	44.69	O
ATOM	3504	O	HOH W 611	-10.219	26.177	19.149	1.00	29.52	O
ATOM	3505	O	HOH W 612	-1.609	19.413	14.017	1.00	33.56	O
ATOM	3506	O	HOH W 613	4.700	13.529	20.901	1.00	30.87	O
ATOM	3507	O	HOH W 614	3.107	15.182	22.806	1.00	36.91	O
ATOM	3508	O	HOH W 615	-3.991	23.412	16.797	1.00	33.21	O
ATOM	3509	O	HOH W 616	4.807	-3.394	40.896	1.00	26.91	O
ATOM	3510	O	HOH W 617	1.697	7.155	20.800	1.00	30.08	O
ATOM	3511	O	HOH W 618	-11.564	-2.380	18.140	1.00	39.20	O
ATOM	3512	O	HOH W 619	-13.459	0.701	19.759	1.00	32.30	O
ATOM	3513	O	HOH W 620	-21.929	16.425	19.619	1.00	43.86	O
ATOM	3514	O	HOH W 621	-18.995	18.796	13.183	1.00	38.42	O
ATOM	3515	O	HOH W 622	-17.500	16.957	8.479	1.00	39.20	O
ATOM	3516	O	HOH W 623	-18.584	10.462	0.984	1.00	49.75	O
ATOM	3517	O	HOH W 624	-1.689	7.637	46.558	1.00	44.24	O
ATOM	3518	O	HOH W 625	-5.544	0.360	44.496	1.00	26.11	O
ATOM	3519	O	HOH W 626	-1.845	-5.706	42.625	1.00	28.22	O
ATOM	3520	O	HOH W 627	-7.810	-7.058	44.426	1.00	26.36	O
ATOM	3521	O	HOH W 628	-9.091	-1.938	46.371	1.00	32.33	O
ATOM	3522	O	HOH W 629	-8.079	3.917	46.830	1.00	32.07	O
ATOM	3523	O	HOH W 630	-8.978	-24.957	32.160	1.00	25.73	O
ATOM	3524	O	HOH W 631	1.918	-3.343	25.978	1.00	23.98	O
ATOM	3525	O	HOH W 632	-6.787	16.620	39.445	1.00	25.33	O
ATOM	3526	O	HOH W 633	0.099	11.308	42.995	1.00	23.18	O
ATOM	3527	O	HOH W 634	-16.388	-4.863	36.397	1.00	25.88	O
ATOM	3528	O	HOH W 635	10.290	8.659	40.738	1.00	23.30	O
ATOM	3529	O	HOH W 636	-7.725	-29.211	10.406	1.00	26.70	O
ATOM	3530	O	HOH W 637	-17.712	-25.639	32.105	1.00	29.88	O
ATOM	3531	O	HOH W 638	2.701	0.440	45.518	1.00	29.53	O
ATOM	3532	O	HOH W 639	-15.151	-12.957	23.893	1.00	29.76	O
ATOM	3533	O	HOH W 640	-35.626	-20.012	0.086	1.00	45.54	O
ATOM	3534	O	HOH W 641	-9.469	-19.060	6.461	1.00	45.91	O
ATOM	3535	O	HOH W 642	-17.551	-14.320	6.704	1.00	42.38	O

ATOM	3536	O	HOH W 643	-2.631	22.940	37.209	1.00	30.23	O
ATOM	3537	O	HOH W 644	-20.337	-12.020	18.768	1.00	30.14	O
ATOM	3538	O	HOH W 645	-23.313	-15.294	18.757	1.00	37.24	O
ATOM	3539	O	HOH W 646	-10.698	-21.036	7.766	1.00	38.06	O
ATOM	3540	O	HOH W 647	-2.682	-5.162	44.835	1.00	39.66	O
ATOM	3541	O	HOH W 648	-19.591	-35.121	5.603	1.00	32.03	O
ATOM	3542	O	HOH W 649	9.307	9.691	27.931	1.00	28.31	O
ATOM	3543	O	HOH W 650	-1.605	25.746	21.137	1.00	29.95	O
ATOM	3544	O	HOH W 651	-17.148	-9.099	-3.068	1.00	36.38	O
ATOM	3545	O	HOH W 652	-17.242	17.832	37.024	1.00	32.96	O
ATOM	3546	O	HOH W 653	-6.518	-2.554	12.665	1.00	41.45	O
ATOM	3547	O	HOH W 654	-16.701	12.587	17.808	1.00	28.83	O
ATOM	3548	O	HOH W 655	-5.608	-19.638	4.184	1.00	39.47	O
ATOM	3549	O	HOH W 656	11.330	5.299	26.474	1.00	32.36	O
ATOM	3550	O	HOH W 657	-16.439	-2.000	36.299	1.00	38.09	O
ATOM	3551	O	HOH W 658	-6.485	-18.160	37.598	1.00	39.80	O
ATOM	3552	O	HOH W 659	3.939	-3.916	43.300	1.00	31.13	O
ATOM	3553	O	HOH W 660	-15.384	-31.429	28.890	1.00	27.37	O
ATOM	3554	O	HOH W 661	-40.328	-13.398	9.658	1.00	36.21	O
ATOM	3555	O	HOH W 662	-9.574	-21.769	37.452	1.00	38.86	O
ATOM	3556	O	HOH W 663	-4.216	10.859	9.937	1.00	45.15	O
ATOM	3557	O	HOH W 664	-6.764	-32.872	22.648	1.00	39.27	O
ATOM	3558	O	HOH W 665	4.766	9.437	19.966	1.00	35.94	O
ATOM	3559	O	HOH W 666	7.455	-0.935	41.916	1.00	41.42	O
ATOM	3560	O	HOH W 667	11.790	-0.488	32.706	1.00	39.38	O
ATOM	3561	O	HOH W 668	-17.547	7.966	31.049	1.00	30.71	O
ATOM	3562	O	HOH W 669	-22.145	9.870	26.121	1.00	38.43	O
ATOM	3563	O	HOH W 670	-20.898	9.657	31.006	1.00	45.35	O
ATOM	3564	O	HOH W 671	-24.162	6.650	14.644	1.00	37.63	O
ATOM	3565	O	HOH W 672	-19.626	14.215	7.115	1.00	43.28	O
ATOM	3566	O	HOH W 673	-19.184	15.532	10.260	1.00	43.63	O
ATOM	3567	O	HOH W 674	-24.099	13.420	14.560	1.00	35.98	O
ATOM	3568	O	HOH W 675	-24.487	9.116	23.719	1.00	42.28	O
ATOM	3569	O	HOH W 676	-7.220	1.614	10.311	1.00	39.24	O
ATOM	3570	O	HOH W 677	-13.735	11.957	38.568	1.00	37.02	O
ATOM	3571	O	HOH W 678	-24.709	-6.787	-3.065	1.00	44.50	O
ATOM	3572	O	HOH W 679	-30.963	-8.326	-1.786	1.00	38.52	O
ATOM	3573	O	HOH W 680	-28.011	-23.355	0.538	1.00	46.03	O
ATOM	3574	O	HOH W 681	6.256	3.141	22.428	1.00	34.50	O
ATOM	3575	O	HOH W 682	8.269	11.757	25.666	1.00	35.57	O
ATOM	3576	O	HOH W 683	1.533	7.650	45.463	1.00	36.83	O
ATOM	3577	O	HOH W 684	-10.929	20.884	14.703	1.00	27.30	O
ATOM	3578	O	HOH W 685	-16.687	-1.227	31.322	1.00	34.49	O
ATOM	3579	O	HOH W 686	-10.594	-3.458	23.819	1.00	34.73	O
ATOM	3580	O	HOH W 687	-10.076	-3.266	20.053	1.00	31.57	O
ATOM	3581	O	HOH W 688	-6.341	-4.252	22.649	1.00	38.67	O
ATOM	3582	O	HOH W 689	-14.206	-2.269	8.985	1.00	39.01	O
ATOM	3583	O	HOH W 690	-17.017	-3.292	46.868	1.00	45.86	O
ATOM	3584	O	HOH W 691	-9.047	-6.104	46.557	1.00	39.86	O
ATOM	3585	O	HOH W 692	-12.587	-14.066	24.333	1.00	35.27	O
ATOM	3586	O	HOH W 693	-15.903	-20.078	35.287	1.00	34.71	O
ATOM	3587	O	HOH W 694	-17.853	-30.531	30.440	1.00	38.13	O
ATOM	3588	O	HOH W 695	-16.901	-32.067	23.836	1.00	36.27	O
ATOM	3589	O	HOH W 696	-14.639	-33.038	24.369	1.00	42.76	O
ATOM	3590	O	HOH W 697	-17.861	-32.991	15.916	1.00	43.00	O
ATOM	3591	O	HOH W 698	-19.710	-32.451	14.184	1.00	36.07	O
ATOM	3592	O	HOH W 699	-1.805	10.726	43.920	1.00	37.85	O

ATOM	3593	O	HOH W 700	0.245	17.607	41.383	1.00	40.42	O
ATOM	3594	O	HOH W 701	-24.478	15.410	15.865	1.00	51.66	O
ATOM	3595	O	HOH W 702	-23.107	3.151	8.887	1.00	41.69	O
ATOM	3596	O	HOH W 703	-13.372	20.361	29.208	1.00	36.79	O
ATOM	3597	O	HOH W 704	-20.277	2.830	10.049	1.00	41.79	O
ATOM	3598	O	HOH W 705	-26.251	-4.626	-4.755	1.00	44.59	O
ATOM	3599	O	HOH W 706	-23.181	-16.517	21.345	1.00	34.78	O
ATOM	3600	O	HOH W 707	-15.088	-14.195	2.651	1.00	37.47	O
ATOM	3601	O	HOH W 708	9.096	10.280	42.002	1.00	38.22	O
ATOM	3602	O	HOH W 709	-31.375	-10.882	-1.954	1.00	39.23	O
ATOM	3603	O	HOH W 710	-22.875	-34.970	-1.453	1.00	38.62	O
ATOM	3604	O	HOH W 711	12.023	1.583	39.188	1.00	35.24	O
ATOM	3605	O	HOH W 712	-8.539	-19.832	-10.528	1.00	43.05	O
ATOM	3606	O	HOH W 713	-14.847	29.667	21.417	1.00	38.57	O
ATOM	3607	O	HOH W 714	-17.487	26.781	30.405	1.00	35.07	O
ATOM	3608	O	HOH W 715	9.817	0.134	39.814	1.00	33.47	O
ATOM	3609	O	HOH W 716	-3.304	21.603	39.371	1.00	56.99	O
ATOM	3610	O	HOH W 717	-13.510	-12.755	14.071	1.00	33.66	O
ATOM	3611	O	HOH W 718	-14.555	-8.812	26.160	1.00	32.65	O
ATOM	3612	O	HOH W 719	-26.444	-22.733	20.513	1.00	41.61	O
ATOM	3613	O	HOH W 720	-21.920	-13.798	-4.676	1.00	42.42	O
ATOM	3614	O	HOH W 721	-10.602	-14.788	44.542	1.00	39.52	O
ATOM	3615	O	HOH W 722	-12.133	-8.492	8.067	1.00	38.14	O
ATOM	3616	O	HOH W 723	-14.469	-31.919	33.144	1.00	33.64	O
ATOM	3617	O	HOH W 724	-36.342	-7.658	6.870	1.00	36.83	O
ATOM	3618	O	HOH W 725	-0.639	23.471	19.643	1.00	38.79	O
ATOM	3619	O	HOH W 726	-8.338	-22.755	28.821	1.00	37.08	O
ATOM	3620	O	HOH W 727	-11.025	-36.039	9.326	1.00	46.76	O
ATOM	3621	O	HOH W 728	-11.744	-19.152	-7.938	1.00	38.97	O
ATOM	3622	O	HOH W 729	-15.402	-13.197	27.634	1.00	38.55	O
ATOM	3623	O	HOH W 730	-10.296	-24.819	30.039	1.00	41.80	O
ATOM	3624	O	HOH W 731	-12.921	-19.822	41.188	1.00	33.00	O
ATOM	3625	O	HOH W 732	13.393	7.336	33.798	1.00	35.87	O
ATOM	3626	O	HOH W 733	-27.293	-18.355	20.786	1.00	41.24	O
ATOM	3627	O	HOH W 734	-6.448	19.350	9.844	1.00	44.49	O
ATOM	3628	O	HOH W 735	-19.860	-5.245	42.361	1.00	41.62	O
ATOM	3629	O	HOH W 736	-30.306	-14.500	19.382	1.00	41.32	O
ATOM	3630	O	HOH W 737	-16.918	30.827	21.795	1.00	50.39	O
ATOM	3631	O	HOH W 738	-13.221	-25.401	34.257	1.00	38.89	O
ATOM	3632	O	HOH W 739	-27.161	-26.802	2.573	1.00	33.63	O
ATOM	3633	O	HOH W 740	-11.449	12.710	42.956	1.00	36.60	O
ATOM	3634	O	HOH W 741	-10.838	27.330	22.536	1.00	47.83	O
ATOM	3635	O	HOH W 742	-9.659	-19.612	16.326	1.00	46.80	O
ATOM	3636	O	HOH W 743	-21.049	5.899	-1.234	1.00	45.30	O
ATOM	3637	O	HOH W 744	-6.418	26.814	34.285	1.00	39.41	O
ATOM	3638	O	HOH W 745	-36.117	-6.079	8.649	1.00	47.81	O
ATOM	3639	O	HOH W 746	-18.235	0.901	38.751	1.00	39.64	O
ATOM	3640	O	HOH W 747	-10.474	1.692	0.133	1.00	40.40	O
ATOM	3641	O	HOH W 748	-11.850	-11.777	-0.062	1.00	44.61	O
ATOM	3642	O	HOH W 749	-14.284	16.866	1.353	1.00	40.34	O
ATOM	3643	O	HOH W 750	-0.652	-13.819	26.307	1.00	37.72	O
ATOM	3644	O	HOH W 751	-16.718	18.776	24.986	1.00	35.76	O
ATOM	3645	O	HOH W 752	1.865	25.663	24.649	1.00	47.61	O
ATOM	3646	O	HOH W 753	-13.737	24.546	15.075	1.00	37.78	O
ATOM	3647	O	HOH W 754	-9.395	-6.980	23.658	1.00	37.95	O
ATOM	3648	O	HOH W 755	-7.242	-17.338	3.484	1.00	35.71	O
ATOM	3649	O	HOH W 756	-14.551	7.995	36.684	1.00	42.33	O

ATOM	3650	O	HOH W 757	6.004	-10.173	33.271	1.00	43.20	O
ATOM	3651	O	HOH W 758	-22.433	-25.916	24.612	1.00	44.28	O
ATOM	3652	O	HOH W 759	-11.987	33.018	34.560	1.00	45.59	O
ATOM	3653	O	HOH W 760	-34.763	-33.480	16.275	1.00	41.73	O
ATOM	3654	O	HOH W 761	-19.578	24.676	30.283	1.00	41.97	O
ATOM	3655	O	HOH W 762	-11.338	15.011	37.069	1.00	44.56	O
ATOM	3656	O	HOH W 763	-24.696	21.287	30.967	1.00	42.14	O
ATOM	3657	O	HOH W 764	-16.602	15.421	38.319	1.00	45.73	O
ATOM	3658	O	HOH W 765	-19.820	-5.270	39.671	1.00	45.41	O
ATOM	3659	O	HOH W 766	-15.889	-6.150	45.231	1.00	40.67	O
ATOM	3660	O	HOH W 767	10.088	4.184	24.167	1.00	37.00	O
ATOM	3661	O	HOH W 768	5.869	-2.731	24.759	1.00	44.55	O
ATOM	3662	O	HOH W 769	-13.598	-13.136	-1.207	1.00	43.50	O
ATOM	3663	O	HOH W 770	-16.943	-12.615	-4.052	1.00	42.67	O
ATOM	3664	O	HOH W 771	-19.506	-15.461	8.721	1.00	34.82	O
ATOM	3665	O	HOH W 772	-6.812	24.654	17.245	1.00	38.59	O
ATOM	3666	O	HOH W 773	-6.135	26.262	19.363	1.00	43.16	O
ATOM	3667	O	HOH W 774	-3.497	26.708	19.343	1.00	42.73	O
ATOM	3668	O	HOH W 775	6.433	11.419	20.694	1.00	38.53	O
ATOM	3669	O	HOH W 776	8.201	11.377	22.722	1.00	44.78	O
ATOM	3670	O	HOH W 777	-22.217	20.942	19.327	1.00	45.24	O
ATOM	3671	O	HOH W 778	-4.105	12.384	2.883	1.00	47.83	O
ATOM	3672	O	HOH W 779	-11.571	-1.576	1.513	1.00	40.69	O
ATOM	3673	O	HOH W 780	-36.583	-21.486	19.922	1.00	47.00	O
ATOM	3674	O	HOH W 781	-3.029	-33.084	-1.044	1.00	42.25	O
ATOM	3675	O	HOH W 782	7.916	-2.787	43.504	1.00	52.20	O
ATOM	3676	O	HOH W 783	-20.356	3.411	23.314	1.00	39.22	O

3. Overall complex structure:

The LT1009 Fab fragment structure exhibits the standard immunoglobulin domain folds. The structural novelty of the antibody derives from its high affinity binding of the bioactive lipid ($K_D = 10$ -5-nM) and the direct participation of a pair of Ca^{2+} ions in S1P binding, as shown in Figure 3a. This is believed to be the first known example of metal ions bridging an antibody and its epitope in a crystal structure.

In its complex-bound state the S1P ligand adopts a slightly curled conformation as it perfectly fits the refined electron density with near ideal stereochemistry, bond lengths, and angles. In addition to the two bridging metal ions, the most striking feature of the S1P:LT1009Fab complex structure is the extent (approx. 70%) to which the ligand is almost completely engulfed by its antibody. The exposed portions include most of the phosphate head group and the terminal carbon atom of the hydrocarbon tail, which was the point of attachment when the derivatized S1P hapten was prepared for immunization. Thus, the LT1009 Fab intimately contacts nearly all of the S1P atoms.

In an effort to determine the source of the metal ions in our refined structure, we have carried out inductively coupled plasma (ICP) spectroscopy on the complexes in solution. These studies reveal the presence of Ca^{2+} at roughly a 2:1 stoichiometric ratio to the complex in the proteins prior to crystallization. No Mg^{2+} or Mn^{2+} ions are present in these complexes. This result indicates that the two ions or Ca^{2+} that we observe in the x-ray structure are inherent to the antibody/ligand complex, while the

Mg²⁺ ion and ethylene glycol molecule observed in the electron density appear almost certainly as a consequence of the conditions under which the crystals were grown.

Strikingly, these two calcium atoms appear to mediate interactions between side chains of the antibody light chain and the phosphate group of the lipid. This type of metal bridge is extremely unusual in antibody-antigen interactions. Notably, the calcium atoms remain bound throughout the purification of the intact IgG, proteolytic digestion, Fab purification and extensive dialysis, all of which were performed in buffers without calcium added. This apparent strong affinity of LT1009 for calcium is consistent with the crystal structure; all the distances between the calcium atoms and the coordinating oxygen atoms in LT1009 are less than 2.3 Å and exhibit good geometry. In the structure, the metal atoms are coordinated by the side chains of four aspartic acid residues, including two bivalent interactions from aspartic acids D30 and D32 of the CDR L1. (Figure 3a). Interestingly, when either unbound whole LT1009 IgG or Fab fragments were analyzed by ICP, the amount of detected Ca²⁺ corresponded to less than one metal ion per binding site.

The role of calcium in the LT1009-S1P interaction has been investigated using metal chelating agents. Titration of LT1009 with EDTA, which chelates divalent metals nonspecifically, or EGTA, which chelates Ca²⁺ specifically, reveals that ~100-fold excess of either chelator abrogates S1P binding (Figure 3b). While not wishing to be bound by theory, this is likely due to EDTA/EGTA competing with S1P for the bound Ca²⁺ rather than displacement of the bound metal, since extensive dialysis of LT1009 after spiking the antibody with high concentrations of EDTA does not render the antibody inactive. When whole LT1009 IgG was first pre-incubated with 50µM EDTA or EGTA, S1P binding could be rescued by the addition of either Mg²⁺ or Ca²⁺. These results suggest that both Mg²⁺ and Ca²⁺ are capable of bridging the LT1009 antibody and its S1P epitope, and illustrate the extremely stable binding of Ca²⁺ in the complex.

The coordination sphere is made up of both amino acid side chains from the LT1009 light chain and the phosphate group of S1P. Both Ca²⁺ are octahedrally coordinated through one terminal *syn* η¹ bond from either aspartic acid D31 in the antibody light chain to one calcium (designated Ca1) and from aspartic acid D92 in the antibody light chain to the other calcium (designated Ca2). Two bridging interactions with the side chains of aspartic acids at positions 30 and 32 in the light chain provide another pair of bonds to each metal ion. Two separate pairs of water molecules occupy symmetrically similar positions about the ions providing the fourth and fifth ligands. Finally, an oxygen atom from the phosphate head group of S1P completes the coordination of both ions via a bridge. This ligand arrangement allows the two Ca²⁺ to come within 3.81 Å of each other without any linking atoms directly between them.

In addition to this electrostatic interaction between the two bound Ca²⁺ atoms and the oxygen from the phosphate head group, there are also hydrogen bonds between LT1009 and the amino alcohol region of the S1P. Both the C2-amino and C3-hydroxyl groups of S1P participate in two hydrogen bonds. Only the hydrogen bond between the carboxylic acid group of glutamic acid E50 in the LT1009 light chain and the amino group of S1P involves an amino acid side chain. This interaction is believed to be

critical for specificity. The C3-hydroxyl moiety forms hydrogen bonds with the backbone amides of glycine 99 and serine 100, both from CDR-H3.

The remaining contacts between S1P and the LT1009 Fab are hydrophobic in nature. These include amino acid residues leucine L94 and phenylalanine F96 from the light chain and threonine T33, histidine H35, alanine A50, serine S52, histidine H54, isoleucine I56, lysine K58, phenylalanine F97, tyrosine Y98, threonine T100A and tryptophan W100C from the antibody heavy chain (Kabat numbering). Although some of these contain polar or charged side chains, each contributes to create a network of closely packed carbon atoms and create a hydrophobic channel that surrounds the lipid aliphatic tail. The CDR-H3 loop of the heavy chain appears to fold over the top of the lipid upon S1P binding to the antibody, with tyrosine Y98 thought to function as a “gate” or “latch” that passes over the bound S1P molecule and fastens to the side chains of leucine at position 94 of the light chain and lysine at position 58 of the heavy chain through van der Waals forces.

In order to demonstrate a gain of function role for divalent metals in the Fab-S1P interaction, LT1009 Fab binding to an immobilized S1P derivative was measured using Surface Plasmon Resonance (SPR) in the presence and absence of calcium. LT1009 Fab was passed over C18 thiolated S1P (S1P-SH) coated on a ProteOn GLM sensor chip using sulfo-MBS coupling. The results show that the presence of 50 μM CaCl_2 significantly promotes complex formation by decreasing the equilibrium dissociation binding constant (K_D) over 100 fold (Table 12). These data are entirely consistent with the crystal structure, mutagenesis, and binding studies in the presence of chelators demonstrating that divalent metals, including calcium, play a major role in formation of the LT1009 Fab-S1P complex.

Table 12 LT1009 binding to S1P in presence and absence of calcium

<u>Buffer</u> 10 mM HEPES pH 7.4, 150 mM NaCl, 0.005% tween-20, 0.1 mg/ml BSA	S1P-SH density (RU)	k_a ($\text{M}^{-1}\text{s}^{-1}$)	k_d (s^{-1})	K_D (nM)
without CaCl_2	600	5.5E+4	7.03E-3	131
+ 50 μM CaCl_2	900	3.03E+5	3.00E-4	0.99

Example 18: Mutagenesis and Biochemical Characterization of the Antibody- Lipid

Complexes

Lpath's Immune Y2 technology provides a powerful, sensitive and robust method for rapidly analyzing the lipid-binding characteristics of many antibody variants. This platform is disclosed in Lpath's patent applications US20070281320 (attorney docket no. LPT-3100-UT1), US20080138334 (attorney docket no. LPT-3100-UT2) and US20080090303A1 (attorney docket no. LPT-3100-UT3), all of which are herein incorporated in their entirety for all purposes.

The Immune Y2 platform relies upon a derivatized bioactive lipid for immunogen preparation and for detection and characterization methods. The highly reactive sulfhydryl group covalently attached to the terminal carbon of the aliphatic lipid chain enables the thiolated S1P and LPA (including C12 and C18 isoforms) to be directly coupled to a surface plasma resonance (SPR) chip or conjugated with a protein (e.g., albumin) to serve as the coating material for enzyme-linked immunosorbent assays (ELISA). With this technology, the antibody-lipid interactions can be studied either directly or via competition between the lipid coated on a plate and other lipids presented in solution. This competition ELISA measures the crossreactivity of either wild type (WT) or mutant antibodies to a variety of structurally related lipids. ELISAs are described in Examples 1 and 2, and below. The ELISA results confirm that the anti-S1P and anti-LPA antibodies LT1009 and LT3015 are highly specific for their lipid targets. The direct-binding ELISA, competition ELISA and SPR methods are used to determine the effect of mutating amino acids in the variable domains of the anti-S1P and anti-LPA antibodies on the ability of those variants to recognize and bind lipids.

1. Production of Antibody Variants

These techniques have several practical advantages, such as the relatively small amounts of material required to perform the experiment. SPR requires only microgram quantities while the direct-binding and competition ELISA use mere nanograms of a particular antibody. Therefore, antibodies harboring essentially any desired mutation can be produced by transiently transfecting HEK 293 cells. These cultures typically produce 10-50 ug/ml of antibody, thereby requiring small quantities of reagents and providing a cost-effective, efficient method to generate sufficient material to fully characterize each antibody variant. Another advantage of these experiments is that binding studies can be performed using the clarified supernatant, thereby eliminating the purification step. However, antibody secreted into the supernatant is easily purified using protein-A affinity chromatography, if desired. Using this production method, several antibody variants can be studied simultaneously. A comprehensive analysis of the amino acids that contact the lipid in the crystal structure can be evaluated to determine their affect on lipid binding and specificity.

a. Mutagenesis. Plasmid constructs containing mutations within the variable domains of the heavy and light chains are created using the QuikChange Site-Directed Mutagenesis Kit (Stratagene, San Diego CA, Cat. No 200524). Individual reactions are carried out with 50 ng of double-stranded DNA template, 2.5 U of Pfu Ultra HF DNA polymerase and its corresponding buffer (Stratagene, Cat. No 200524), 10 mM dNTP mix and 125 ng of each of the mutagenic oligonucleotides (provided in kit) resuspended in 5 mM Tris-HCl (pH 8.0), and 0.1 mM EDTA. The initial denaturation is carried out at 95 °C for 30 seconds, followed by 16 cycles of amplification: 95 °C for 30 seconds, 55 °C for 1 minute and 68 °C for 8 minutes. Following temperature cycling, the final reaction was then digested with DpnI digest at 37°C for 1 h to remove methylated parental DNA. The resultant mutants are transformed into competent XL1-Blue E.coli and plated on LB-agar containing 50µg/ml ampicillin. The colonies are

screened by DNA sequencing to confirm the presence of the mutation. Each mutant is cultured in 1 liter shake flasks and purified using the EndoFree Plasmid Purification Kit from Qiagen, Valencia CA (Cat. No 12362).

b. Expression and Production of Mutant Antibodies in Mammalian Cells. Purified plasmids containing the mutations are transfected into the human embryonic kidney cell line 293F using 293fectin and using 293F-FreeStyle Media (Invitrogen) for culture. Light and heavy chain plasmids are both transfected at 0.5 µg/mL following manufacturer's instructions. The purity and structural integrity is judged using SDS-PAGE. Under reducing conditions, the expected masses of the heavy and light chains are 25 kDa and 50 kDa, while a single band is observed under non-reducing conditions with the expected mass of ~ 150 kDa.

c. Purification of Mutant Antibodies. Mutant antibodies expressed from transient transfections are purified using protein-A affinity chromatography as described for the wild-type antibodies. The antibody concentration is determined using quantitative ELISA.

d. Quantitative ELISA. Goat-anti human IgG-Fc antibody (Bethyl, Montgomery TX, Cat no. A80-104A, 1 mg/ml) is diluted 1:100 in carbonate buffer (100 mM NaHCO₃, 33.6 mM Na₂CO₃, pH 9.5). Plates are coated with 100 µl/well of coating solution and incubated at 37°C for 1 hour. The plates are then washed 4X with TBS-T (50 mM Tris, 0.14 M NaCl, 0.05% Tween-20, pH 8.0) and blocked with 200 µl/well TBS/BSA (50mM Tris, 0.14 M NaCl, + 1% BSA, pH 8.0) for 1 hour at 37°C. Samples and standards are prepared on non-binding plates with enough volume to run in duplicate.

The standard is prepared by diluting human reference serum (Bethyl RS10-110; 4 mg/ml) in TBS-T/BSA (50 mM Tris, 0.14 NaCl, 1% BSA, 0.05 % Tween-20, pH 8.0) to the following dilutions: 500 ng/ml, 250 ng/ml, 125 ng/ml, 62.5 ng/ml, 31.25 ng/ml, 15.625 ng/ml, 7.8125 ng/ml, and 0.0 ng/ml. The samples are prepared by making appropriate dilutions in TBS-T/BSA so that the samples OD fall within the range of this standard curve, the most linear range being from 125 ng/ml to 15.625 ng/ml. After washing the plates 4 times with TBS-T, 100 µl of the standard/samples preparation is added to each well and incubated at 37°C for 1 hour. Next, the plates are washed 4 times with TBS-T and then incubated for 1 hour at 37 °C with 100 µl/well of HRP-goat anti-human IgG antibody (Bethyl A80-104P, 1 mg/ml) diluted 1:150,000 in TBS-T/BSA. The plates are washed 4 additional times with TBS-T and developed using 100 µl/well TMB substrate at 4 °C. After 7 minutes, the reaction is stopped by adding 100 µl/well of 1 M H₂SO₄. The OD is measured at 450 nm. Data is analyzed using Graphpad Prism software.

e. Direct-Binding ELISA. Microtiter ELISA plates (Costar, Corning Inc., Lowell MA, Cat No. 3361) are coated overnight with either S1P or LPA conjugated to delipidated BSA diluted in 0.1M Carbonate Buffer (pH 9.5) at 37 °C for 1 h. Plates are washed with PBS (137 mM NaCl, 2.68 mM KCl,

10.1 mM Na₂HPO₄, 1.76 mM KH₂PO₄; pH 7.4) and blocked with PBS/BSA/Tween-20 for 1 hour at room temp or overnight at 4 °C. For the primary incubation (1 hour at room temp.), a dilution curve (0.4 µg/mL, 0.2 µg/mL, 0.1 µg/mL, 0.05 µg/mL, 0.0125 µg/mL, and 0 µg/mL) of the wild-type or mutant antibody is built (100 µl/well). Plates are washed and incubated with 100 µl/well of HRP conjugated goat anti-mouse (1:20,000 dilution) (Jackson ImmunoResearch, West Grove PA, Cat No 115-035-003) or HRP conjugated goat anti-human (H+L) diluted 1:50,000 (Jackson, Cat No 109-035-003) for 1 hour at room temperature. After washing, the peroxidase is developed with Tetramethylbenzidine substrate (Sigma, cat No T0440) and quenched by addition of 1 M H₂SO₄. The optical density (OD) is measured at 450nm using a Thermo Multiskan EX. The raw data is transferred to the GraphPad software and the concentration of lipid that produced half maximal effect (EC₅₀) and the maximum binding absorbance (V_{max}) is calculated using a 4-parameter nonlinear least squares fit of the saturation binding curves.

f. Lipid Competition Assay. The ability of various lipids in solution to inhibit direct-S1P or direct-LPA binding by the WT/mutant antibodies is tested using an ELISA assay format. Microtiter ELISA plates (Costar, Cat No. 3361) are coated with S1P diluted in 0.1 M Carbonate Buffer (pH 9.5) at 37 °C for 1 hour. Plates are washed with PBS (137 mM NaCl, 2.68 mM KCl, 10.1 mM Na₂HPO₄, 1.76 mM KH₂PO₄; pH 7.4) and blocked with PBS/BSA/Tween-20 for 1 hour at room temp or overnight at 4 °C. For the primary incubation, 0.4 µg/mL of antibody and designated amounts of lipid are added to wells of the ELISA plates and incubated at room temp for 1 hr. Plates are washed and incubated with 100 µ per well of HRP conjugated goat anti-mouse (1:20,000 dilution) (Jackson, cat No 115-035-003) or HRP conjugated goat anti-human (H +L) diluted 1:50,000 (Jackson, cat No 109-035-003) for 1 hour at room temperature. After washing, the peroxidase reaction is developed with Tetramethylbenzidine substrate and stopped by adding 1 M H₂SO₄. The optical density (OD) is measured at 450nm using a Thermo Multiskan EX. The maximum binding absorbance (V_{max}) and percent inhibition are calculated by linear regression of the Lineweaver-Burke plots using Excel software.

g. Surface Plasmon Resonance. All binding data is collected on a ProteOn optical biosensor (BioRad, Hercules CA). Thiolated lipids are coupled to a maleimide modified GLC sensor chip (Cat. No 176-5011). First, the GLC chip is activated with an equal mixture of sulfo-NHS/EDC for seven minutes followed by a 7 minute blocking step with ethyldiamine. Next sulfo-MBS (Pierce Co Rockford, IL, cat #22312) is passed over the surfaces at a concentration of 0.5 mM in HBS running buffer (10 mM HEPES, 150 mM NaCl, 0.005% tween-20, pH 7.4). The thiolated lipid is diluted into the HBS running buffer to a concentration of 10, 1 and 0.1 µM and injected for 7 minutes producing different lipid density surfaces (~100, ~300 and ~1400 RU). Next, binding data for the WT and mutant antibodies is collected using a 3-fold dilution series starting with 25 nM as the highest concentration. Surfaces are regenerated with a 10 second pulse of 100 mM HCl. All data is collected at 25 °C. Controls are processed using a reference surface as well as blank injections. In order to extract binding parameters, the data is globally fit using 1-site and 2-site models.

2. Mutations Designed to Abrogate Lipid Binding

Initially, mutations in the anti-S1P and anti-LPA antibodies are designed to test the x-ray structures with biochemical techniques. Amino acids in the variable domains that directly contact the lipids in the complex are substituted with amino acids designed to reduce binding in the SPR and direct-binding ELISA. The importance of the electrostatic charge, polarity and hydrophobicity of the amino acids are thus investigated. Based on preliminary data, it is presently believed that amino acids recognize the S1P head group using electrostatic and hydrogen bonding interactions, whereas hydrophobic residues stabilize the aliphatic carbon chain of S1P. Therefore, it is believed that mutating residues that contact the lipid head groups to alanine or a residue with opposite charge will abrogate lipid binding. In addition, select residues that form the hydrophobic pocket are substituted with charged, polar residues (such as glutamic acid) designed to dramatically alter the electrostatic surface of the variable domain and sequester water into the hydrophobic binding pocket and dramatically reduce stability of the complex.

These experiments also identify positions in the variable domains that influence lipid binding and specificity. It is currently believed that a limited number of positions in the variable domains provide the major determinants for lipid recognition. At these positions subtle amino acid substitutions (such as glutamine to asparagine) are believed to cause a dramatic effect in lipid binding or specificity. Here, investigations are designed to probe the size of the side chains as well as the role of the framework residues that support the position and orientation of the residues that directly contact the lipids. By 'fine-tuning' the antibody-lipid interaction through conservative mutagenesis, it is believed to be possible to improve the overall affinity of the antibodies for their cognate lipids, or improve the lifetime of the complex. This is believed to enhance the therapeutic potential of the antibody by increasing its ability to sequester and neutralize the bioactive lipid target.

During development of the humanized monoclonal anti-S1P antibody LT1009, numerous biochemical studies were initiated to characterize S1P binding, crossreactivity, thermostability and solubility, as described above. Several variants of the antibody were designed with point mutations located within the antigen-binding surfaces in the heavy and light chains. These variants were produced, purified and their S1P-binding affinities were measured using the direct-binding ELISA as described above. Mutating several solvent-exposed arginine residues (R55 in CDRL2, R54 in CDRH2, and R65 in CDRH2, using sequential numbering) did not affect the S1P binding affinities (Figure 2a). However, mutation of histidine H35 in the CDR H1, resulted in markedly altered S1P binding compared to wildtype. Mutation of this residue to an alanine does not significantly change S1P binding, while a variant containing a glutamine substitution at this position exhibits a twofold increase in EC₅₀ (from approximately 80 ng/ml for wildtype to approximately 160 ng/ml for H35Q), indicating decreased S1P binding, and mutation to glutamic acid at this position (H35E) eliminates measurable S1P binding altogether (Figure 2a). While not wishing to be bound by theory, these data suggest that position 35 in CDR H1 likely forms hydrophobic contacts with S1P in the complex. Indeed, when the positions of the mutations are mapped onto the initial X-ray structures, histidine H35 in the heavy chain appears to pack

tightly against the hydrophobic tail of S1P, and substitution to a glutamic acid dramatically alters the electrostatic environment to create an unfavorable binding pocket (Figure 2b). This is consistent with the observations that the alanine variant, which forms energetically favorable hydrophobic interactions, retains S1P binding. Mutation of tyrosine 98 in the heavy chain to alanine also resulted in a significant decrease in binding. The other LT1009 variants containing arginine mutations (R55 in CDR L2, R54 in CDR H2 and R65 in CDR H2), which do not show significant differences in S1P binding compared to WT, are far removed from the bound S1P in the LT1009Fab/S1P complex. These data demonstrate that the structural and biochemical data are in excellent agreement and suggest that the crystal structures of the LT1009Fab/S1P and LT3015Fab/LPA complexes will provide a reliable structural basis for the understanding of, and manipulation of, particular amino acid residues in the antibodies that serve as the major determinants for lipid recognition.

An interesting feature detected in the LT1009Fab/S1P structure is the position of Y102 in the CDR H3. In the S1P-bound conformation, the side chain of this tyrosine residue appears to fold over the hydrocarbon tail of S1P, clamping down on the lipid. In this conformation, the lipid is unable to freely dissociate from the antibody. Based on the structure, a conformational change in the CDR H3 or the Y102 side chain rotamer position is believed to take place which allows the lipid to dissociate. While not wishing to be bound by theory, this is believed to play an important role in the lifetime of the LT1009-S1P complex.

To further investigate this ‘tyrosine gate’ mechanism, position 102 in the CDRH3 was mutated to an alanine and S1P binding of the mutant was measured. The equilibrium S1P binding constant of the Y102A mutant was ~4-fold higher than WT, indicating that the affinity of the mutant for the lipid was significantly reduced. However, the loss of binding was not absolute as with the mutation in the calcium binding site (Figure 3c). Future experiments using surface plasmon resonance (SPR) are planned to determine whether the kinetic effect of mutating Y102 is greater than at equilibrium. While again not wishing to be bound by theory, it is anticipated that the off-rate of the mutant will be much faster than the wild type antibody.

Finally, the effect of mutating glutamic acid E50 in the LT1009 CDR L2 was investigated; this amino acid has been predicted to form a specific interaction with S1P. Computational studies suggest that the ammonium group in S1P likely contains a +1 charge in the “free” lipid. This is consistent with the observed structure, which shows the ammonium ion forming an electrostatic interaction with the negatively charged side chain of E50 in the CDR L2. We hypothesize that this interaction is likely a major determinant of S1P specificity, and mutating this position would dramatically reduce S1P binding. As expected, mutating this position to an alanine abrogates S1P binding (Figure 3c). Altogether, these studies validate the LT1009Fab/S1P crystal structure and elucidate the positions in LT1009 that are important for lipid binding.

3. Mutations Designed to Modulate Lipid Specificity

Once the major determinants that govern lipid recognition have been identified, antibody variants are generated and cross-reactivity with other lipids is measured using the competition ELISA. Using molecular modeling software to morph S1P and LPA into structurally related lipid, positions in the variable domains to be substituted are identified. Eventually, libraries of variants will be built up, providing rapid analysis of a variety of lipids. Because the structure space of lipids, including bioactive lipids, is small, the task of modulating the lipid specificity of an antibody is a manageable one, unlike the case for antibodies against protein antigens, which are much larger and more variable in secondary and tertiary structure.

Previous modeling studies on S1P₁ identified a single glutamic acid residue that when mutated to glutamine causes the receptor to become activated and internalized by LPA. Wang, D.A., et al.(2001) *J Biol Chem*, 2001. 276: 49213-20. The same research group also identified a single position in the LPA receptors, LPA₁₋₃, where a single glutamine to glutamic acid substitution enables the receptor to become more responsive to S1P. Valentine, W.J., et al. (2008) *J Biol Chem*. 283: 12175-87. The modeling studies predict the glutamic acid/glutamine residue interacts with the primary amine group of S1P. Interesting, in the LT1009Fab/S1P complex this moiety forms an analogous electrostatic interaction with glutamic acid E50 in the CDR L2 light chain. Therefore, it is believed that mutating glutamic acid E50 in CDR L2 to a glutamine will cause LT1009 to gain LPA-binding activity. Alternatively, we can substitute the entire CDR L2 from the anti-LPA mAb, since glutamic acid E50 is the only position in CDR L2 that directly contacts the lipid. We believe that the CDRs from either LT1009 or LT3015, or a combination thereof, that contact the lipid phosphate group may be used to design an antibody against other bioactive lipids, particularly lysolipids.

It is also believed that the Vh framework may present a favorable, universal binding pocket for lysolipids. The LT1009 and LT3015 Vh sequences are 93% identical outside the CDRs (as expected, the CDRs have lower identity, in this case 46%). The Vk sequences are 59% identical outside the CDRs (19% identity within the CDRs). In the LT1009Fab/S1P structure, the less conserved Vk domain exclusively contacts the head group of S1P, which is dissimilar to LPA, whereas the highly conserved Vh domain primarily contacts the hydrocarbon chain, which is chemically conserved between S1P and LPA. The fact that the homology among variable domains directly relates to the chemical similarity among lipid regions suggests common mechanisms in antibody-lipid interactions, which we may be able to exploit to generate libraries of CDRs that specifically recognize the various structural and functional groups that distinguish bioactive lipids. By using different combinations of CDRs, it is believed to be possible to develop novel antibodies, *in silico*, against a wide range of therapeutic targets. The crystal structure disclosed herein for S1P-LT1009 will be used as a template for direction of *in silico* modeling. Different bioactive lipids are docked in the S1P binding pocket and the antibody will be morphed *in silico* such that the new antibodies form stabilizing interactions analogous or similar to the ones described herein for LT1009 and S1P. Once additional cocrystals are available (e.g., humanized anti-LPA antibody and LPA), it is envisioned that information from multiple co-crystals, particularly bioactive lipid-antibody co-crystals, may be used together in the design of new anti-lipid antibodies.

It has now been demonstrated that mutating glutamic acid at position 50 of the light chain to a glutamine changes the antibody specificity. While not wishing to be bound by theory, the crystal structure of sphingosine-1-phosphate (S1P) in complex with the Fab fragment of LT1009 suggests that S1P specificity of the antibody may be governed by an interaction with the ammonium group located at the C2 position of the lipid. Under physiological conditions, this moiety is likely positively charged in both in S1P and dihydro S1P, which show high affinity for the Fab, and neutral in sphingosine and sphingosylphosphorylcholine, which have relatively lower affinities for the Fab. In the S1P structure, the ammonium group forms a single, electrostatic interaction with side chain of glutamic acid at position 50, which protrudes from the antibody light chain. These observations invited speculation that changing the amino acid at this position may modulate the antibody's specificity for other lipid targets, such as lysophosphatidic acid (LPA).

To test this idea, this glutamic acid (GluL50) was mutated to glutamine (GlnL50) and binding of these antibodies to either S1P or LPA was assayed using a direct ELISA. As expected, the wild-type (WT) LT1009 shows high affinity for the S1P-BSA coating material, while no binding activity was observed for C12 LPA-BSA coated on the plate. In contrast, the LT1009 GlnL50 mutant antibody shows significantly higher affinity for the C12 LPA-BSA conjugate compared to S1P-BSA (Figure 4), suggesting that this amino acid plays a significant role in S1P specificity and changes at this position alters target specificity.

While not wishing to be bound by theory, these results are consistent with the chemical nature of the amino acid side chains and the functional groups in the lipid targets. In the Fab-S1P crystal structure, the positively charged ammonium group of S1P forms an electrostatic interaction with the negatively charged GluL50 side chain. In LPA, the ammonium group is replaced with an uncharged hydroxyl group, so the favorable electrostatic interaction is not available for binding to the WT antibody. The GlnL50 mutation introduces a neutral, polar side chain capable of forming a hydrogen bond with the hydroxyl group of LPA. The presence of this interaction apparently stabilizes binding of the mutant LT1009 to LPA and destabilizes binding to S1P. Thus antibody *in silico* antibody design has been used here to convert an anti-S1P antibody to an antibody that binds LPA better than it binds S1P.

4. Mutations to disrupt the calcium binding site:

The effect of the bound calcium in S1P binding was further investigated using site-directed mutagenesis. Aspartic acids D30 and D32 in the CDR L1 were changed to alanine to disrupt the calcium-binding site. Antibodies harboring either of these mutations did not bind any S1P (Figure 3c). Inductively coupled plasma (ICP) spectroscopy will be used to compare the metal content of the wildtype LT1009 antibody, which measures a 2:1 Ca²⁺:LT1009 stoichiometry, with the D30A and D32A mutants to confirm the absence of calcium.

Example 19: Purification and production of anti-LPA antibodies

Applicant has recently developed a mammalian cell line (CHO CK1sv) that expresses >0.5 mg/ml of the humanized, anti-LPA mAb, LT3015. This stable cell line was utilized in a 50 liter bioreactor campaign to produce large quantities of non-GMP material. Purification of LT3015 from the bioreactor supernatant resulted in >10 grams of antibody material. LT3015 was formulated at 18 mg/ml in 24 mM PBS, 148 mM NaCl, pH 6.5, and this preparation meets strict specifications for purity, aggregation and LPA-binding properties. Therefore, suitable material is available for papain digestion, isolation of the Fab fragment, complex formation with LPA, and crystallization of the LT3015Fab/LPA complex.

Example 20: Information gained from comparison of anti-S1P and anti-LPA humanized antibodies

Based on primary structure (amino acid sequence) and three-dimensional (crystal) structure, LT1009 and LT3015 are compared. The relatively minor differences in the amino acid sequences of the antibody hypervariable regions function to discriminate between LPA and S1P, two bioactive lipids with such high structural and chemical identity. The anti-LPA and anti-S1P VH sequences (heavy chain variable domain) are 93% identical outside the CDRs (as expected, the CDRs have lower identity, in this case 46%). The Vk sequences (light chain variable domain) are 59% identical outside the CDRs (19% identity within the CDRs). Information on the locations and nature (e.g., size and/or charge of amino acid side chain) of differences between the two antibody sequences will be used to aid in design of variants for SAR testing.

More information about this discrimination is based on the LT1009Fab/S1P complex crystal structure refined at 2.7 Å resolution. A similar approach is used to determine the structure of the LT3015Fab/LPA complex crystal structure, as described in the Examples above. The amino acid composition of the Ch1-3 domains is identical between LT1009 and LT3015, and thus it is believed that the methods used for cocrystallization of LT1009Fab and S1P will also yield cocrystals of LT3015Fab and LPA.

* * *

All of the compositions and methods described and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and methods. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit and scope of the invention as defined by the appended claims.

All patents, patent applications, and publications mentioned in the specification are indicative of the levels of those of ordinary skill in the art to which the invention pertains. All patents, patent applications, and publications, including those to which priority or another benefit is claimed, are herein

incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

The invention illustratively described herein suitably may be practiced in the absence of any element(s) not specifically disclosed herein. Thus, for example, in each instance herein any of the terms “comprising”, “consisting essentially of”, and “consisting of” may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

WHAT IS CLAIMED IS:

1. A crystalline composition comprising an anti-lipid antibody or fragment thereof, wherein the lipid is a bioactive lipid, optionally a sphingolipid or a lysolipid, and wherein the anti-lipid antibody or fragment thereof optionally is a monoclonal anti-lipid antibody or fragment thereof, wherein the fragment optionally is a Fab fragment.
2. A crystalline composition according to claim 1 that further comprises a lipid ligand of the antibody.
3. A crystalline composition according to claim 1 that further comprises at least one co-factor, salt, or metal.
4. A crystalline composition according to claim 1 that comprises an anti-lipid antibody defined by a set of structure coordinates as presented in Table 10 or Table 11.
5. A crystalline composition according to claim 1 that comprises a co-crystal of an antibody Fab fragment and its bioactive lipid ligand.
6. A computer-readable storage medium comprising a data storage medium storing computer-readable data, wherein the data comprises structural coordinates of all or a selected portion of an anti-lipid antibody or fragment thereof derived from a crystalline composition according to claim 1, wherein the data optionally comprises all or a selected portion of the structural coordinates shown in Table 10 or Table 11.
7. Use of a crystalline composition according to claim 1 in:
 - a. determining the structure of the antibody;
 - b. determining the ligand-binding characteristics of the antibody or fragment thereof, or of a variant or fragment of variant of the antibody;
 - c. designing an antibody, or fragment thereof, specifically reactive with a lipid, optionally a bioactive lipid; and/or
 - d. optimizing or altering the affinity of a monoclonal antibody for a lipid,
8. A method of preparing a crystalline composition according to claim 2 comprising co-crystals comprising the antibody or antibody fragment and its lipid ligand, comprising:
 - a. providing an anti-lipid monoclonal antibody or fragment thereof, optionally a Fab fragment;

- b. combining the antibody or fragment thereof with an excess of the lipid ligand under conditions in which antibody-ligand or antibody fragment-ligand complexes form; and
 - c. incubating the antibody-ligand or antibody fragment-ligand complexes under conditions in which antibody-ligand or antibody fragment-ligand co-crystals form, thereby preparing a co-crystal of antibody or antibody fragment and its lipid ligand.
9. A co-crystal of an antibody or antibody fragment and its lipid ligand prepared according to claim 8, wherein the lipid is optionally a bioactive lipid, optionally a sphingolipid or a lysolipid.
10. A method of designing an optimized antibody to a lipid comprising:
- a. providing an amino acid sequence of at least one variable region of a heavy or light chain of a first humanized anti-lipid antibody, wherein the anti-lipid antibody is specific for a first lipid, optionally a sphingolipid or a lysolipid, and wherein optionally at least one complementarity-determining region within the variable region is identified;
 - b. replacing one or more amino acids within the at least one variable region with a different amino acid to yield a variant amino acid sequence, wherein the amino acid replacement(s) is(are) within a complementarity-determining region;
 - c. preparing a second humanized anti-lipid antibody containing the variant amino acid sequence, wherein the amino acid sequences of the first and second humanized anti-lipid antibodies differ only in the variant amino acid sequence;
 - d. determining one or more activity criteria of the second humanized antibody, optionally by molecular modeling, ELISA or surface plasmon resonance, wherein at least one of the activity criteria is optionally binding affinity for the first lipid, binding affinity for a second lipid, or specificity for the first lipid or specificity for a second lipid, wherein the first and second lipids are different lipid species; and
 - e. selecting an optimized antibody based on one or more of the activity criteria, wherein the optimized antibody is the second humanized antibody, wherein the method is optionally performed in silico.
11. A method according to claim 10 further comprising use of three-dimensional structural information about the binding of the first antibody and the first lipid to select a location and/or identity of the amino acid replacement(s), optionally wherein the three-dimensional structural information is molecular modeling data or x-ray crystallography data.
12. An optimized antibody made according to claim 15.
13. A method according to claim 10 wherein the first humanized anti-lipid antibody is LT1009, optionally wherein the one or more amino acids replaced is/are selected from the group consisting of:

aspartic acid at positions 30, 31 and 32, glutamic acid at position 50, aspartic acid at position 92, leucine at position 94 and phenylalanine at position 96, all of the light chain; and threonine at position 33, histidine at position 35, alanine at position 50, serine at position 52, histidine at position 54, isoleucine at position 56, lysine at position 58, phenylalanine at position 97, tyrosine at position 98, threonine at position 100A or tryptophan at position 100C, all of the heavy chain.

14. An optimized antibody variant of LT1009 prepared according to claim 13, optionally wherein one or more amino acids within one or more of the variable regions of LT1009 is replaced with a different amino acid to yield a variant amino acid sequence, and wherein the one or more replaced amino acids is selected from the group consisting of: aspartic acid at positions 30, 31 and 32, glutamic acid at position 50, aspartic acid at position 92, leucine at position 94 and phenylalanine at position 96, all of the light chain; and threonine at position 33, histidine at position 35, alanine at position 50, serine at position 52, histidine at position 54, isoleucine at position 56, lysine at position 58, phenylalanine at position 97, tyrosine at position 98, glycine at position 99, serine at position 100, threonine at position 100A or tryptophan at position 100C, all of the heavy chain.

15. A method selected from the group consisting of:

a. a method of designing a consensus anti-lipid antibody specifically reactive with a target bioactive lipid, comprising:

(i) identifying at least a first CDR amino acid sequence from a first parent antibody species specifically reactive with a target bioactive lipid and at least a second CDR amino acid sequence from a second parent antibody species specifically reactive with the target bioactive lipid, wherein the first and second CDR amino acid sequences are both CDRH1, both CDRH2, both CDRH3, both CDRL1, both CDRL2 or both CDRL3 CDR amino acid sequences;

(ii) aligning the first CDR amino acid sequence and second CDR amino acid sequence to determine a consensus CDR amino acid sequence; and

(iii) engineering a nucleic acid sequence that encodes the consensus CDR amino acid sequence into a gene comprising a variable region of an antibody heavy or light chain, thereby designing a consensus anti-lipid antibody specifically reactive with a target bioactive lipid, and, optionally; and

(iv) producing an antibody or antibody fragment that binds the target bioactive lipid;

b. a method of designing an antibody variant or antibody fragment variant specifically reactive with a target bioactive lipid, comprising:

(i) providing a first structural representation comprising an initial representation of a target bioactive lipid in binding association with an antibody or antibody fragment specifically reactive with a source bioactive lipid, wherein the target bioactive lipid and the source bioactive lipid are the same or a different bioactive lipid species, wherein the initial representation comprises three-dimensional structural information for the antibody or antibody fragment optionally derived from molecular modeling data or x-ray crystallography data; and

(ii) substituting at least one amino acid residue represented in the first structural representation with a different amino acid residue in order to identify a second structural representation comprising a subsequent representation of the target bioactive lipid in modified binding association with the modified antibody or antibody fragment, thereby designing an antibody variant or antibody fragment variant that is specifically reactive with the target bioactive lipid, wherein the antibody variant or antibody fragment optionally has a modified binding association, optionally an improved binding association, for the bioactive lipid.

16. A method according to claim 15 performed in silico.

17. An antibody or antibody fragment, optionally a humanized antibody or fragment thereof, produced according to claim 15(a).

18. A method according to claim 15(b) wherein the target bioactive lipid is (i) the same as the source bioactive lipid or (ii) different than the source bioactive lipid, wherein in either case the target bioactive lipid optionally is SIP.

19. A method according to claim 15(b) further comprising engineering one or more nucleotide sequences that encode the antibody variant or antibody fragment variant that binds the target bioactive lipid, and optionally further comprising producing the antibody variant or antibody fragment variant.

20. An antibody or antibody fragment specifically reactive with a target bioactive lipid, or a composition comprising such an antibody or antibody fragment, wherein in either case the antibody or antibody fragment is produced in accordance with claim 19.

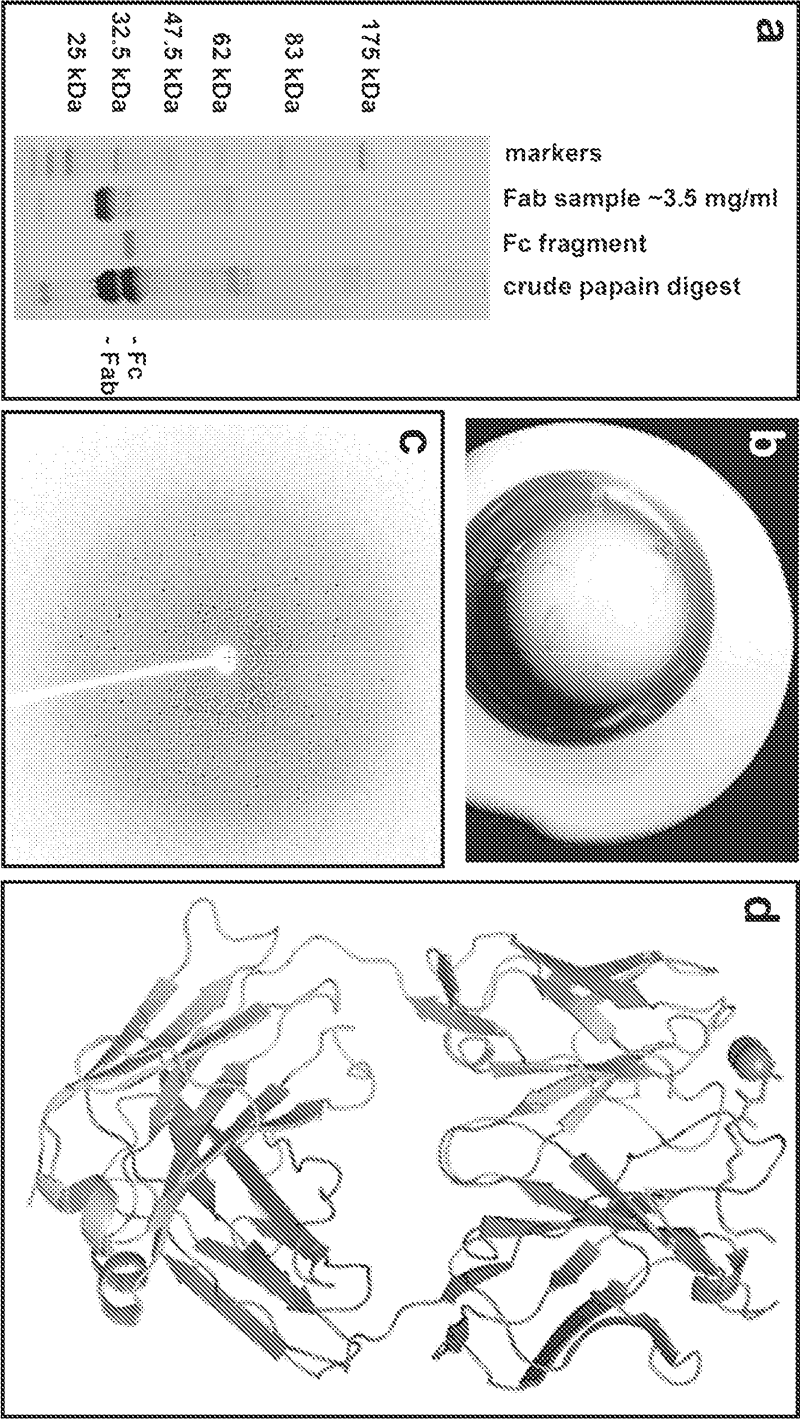
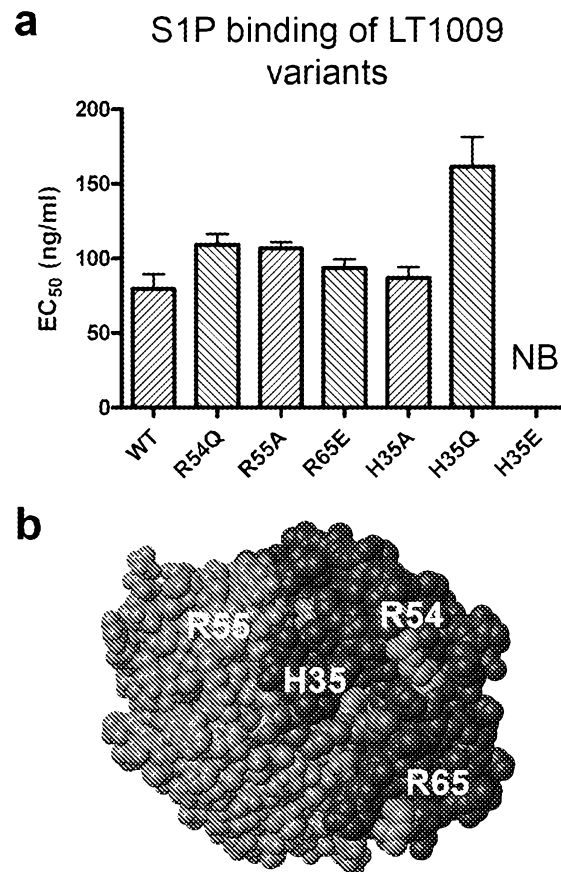


Figure 1

**Figure 2**

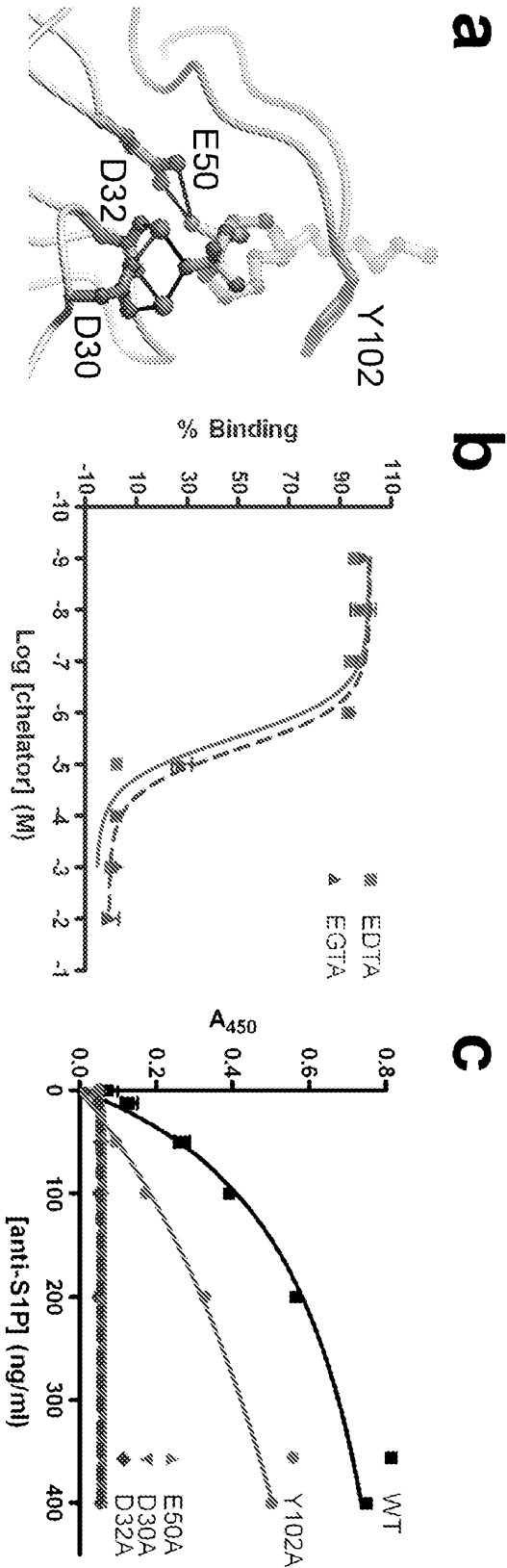


Figure 3

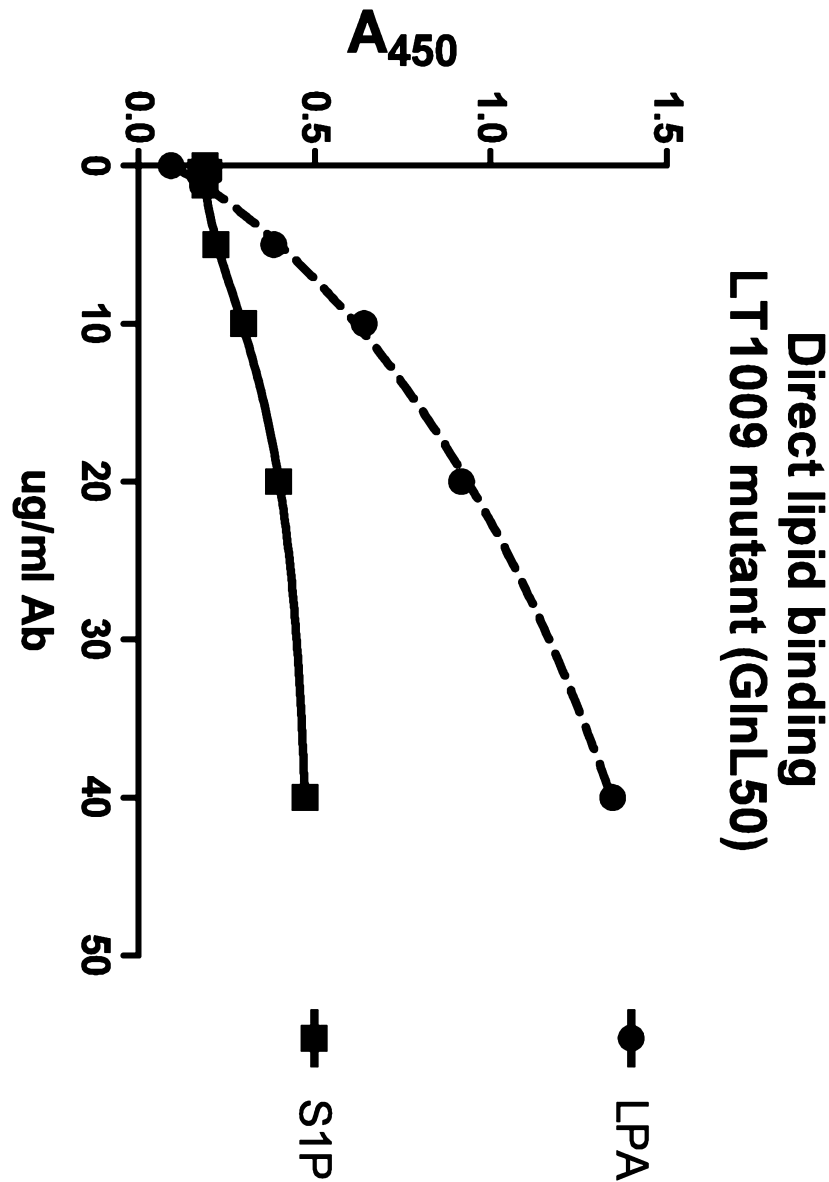


Figure 4

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Huxford, Tom

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<400> 13

Asp His Thr Ile His

1 5

<210> 14

<211> 17

<212> PRT

<213> Mus musculus

<400> 14

Cys Ile Ser Pro Arg His Asp Ile Thr Lys Tyr Asn Glu Met Phe Arg

1 5 10 15

Gly

<210> 15

<211> 12

<212> PRT

<213> Mus musculus

<400> 15

Gly Gly Phe Tyr Gly Ser Thr Ile Trp Phe Asp Phe

1 5 10

<210> 16

<211> 147

<212> PRT

<213> Mus musculus

<400> 16

Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Gln Gly

1 5 10 15

Val Cys Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys

20

25

30

Pro Gly Glu Ser Leu Lys Ile Ser Cys Gln Ser Phe Gly Tyr Ile Phe

35

40

45

Ile Asp His Thr Ile His Trp Val Arg Gln Met Pro Gly Gln Gly Leu

50

55

60

Glu Trp Met Gly Cys Ile Ser Pro Arg His Asp Ile Thr Lys Tyr Asn

65

70

75

80

Glu Met Phe Arg Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ser Ser

85

90

95

Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met

100

105

110

Tyr Phe Cys Ala Arg Gly Gly Phe Tyr Gly Ser Thr Ile Trp Phe Asp

115

120

125

Phe Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys

130

135

140

Gly Pro Ser

145

<210> 17

<211> 134

<212> PRT

<213> Mus musculus

<400> 17

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp

1

5

10

15

Leu Pro Gly Ala Arg Cys Glu Thr Thr Leu Thr Gln Ser Pro Ser Phe

20

25

30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ile Thr Thr

35 40 45

Thr Asp Ile Asp Asp Asp Met Asn Trp Tyr Gln Gln Glu Pro Gly Lys

50 55 60

Ala Pro Lys Leu Leu Ile Tyr Glu Gly Asn Ile Leu Arg Pro Gly Val

65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr

85 90 95

Ile Ser Lys Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln

100 105 110

Ser Asp Asn Leu Pro Phe Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile

115 120 125

Lys Arg Glu Trp Ile Pro

130

<210> 18

<211> 17

<212> PRT

<213> Mus musculus

<400> 18

Ala Ile Ser Pro Arg His Asp Ile Thr Lys Tyr Asn Glu Met Phe Arg

1 5 10 15

Gly

<210> 19

<211> 140

<212> PRT

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 19

Met Glu Trp Ser Trp Val Phe Leu Phe Phe Leu Ser Val Thr Thr Gly

1 5 10 15

Val His Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys

20 25 30

Pro Gly Glu Ser Leu Lys Ile Ser Cys Gln Ser Phe Gly Tyr Ile Phe

35 40 45

Ile Asp His Thr Ile His Trp Met Arg Gln Met Pro Gly Gln Gly Leu

50 55 60

Glu Trp Met Gly Ala Ile Ser Pro Arg His Asp Ile Thr Lys Tyr Asn

65 70 75 80

Glu Met Phe Arg Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ser Ser

85

90

95

Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met

100

105

110

Tyr Phe Cys Ala Arg Gly Gly Phe Tyr Gly Ser Thr Ile Trp Phe Asp

115

120

125

Phe Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser

130

135

140

<210> 20

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 20

Met Ser Val Pro Thr Gln Val Leu Gly Leu Leu Leu Leu Trp Leu Thr

1 5 10 15

Asp Ala Arg Cys Glu Thr Thr Val Thr Gln Ser Pro Ser Phe Leu Ser

20 25 30

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ile Thr Thr Thr Asp

35 40 45

Ile Asp Asp Asp Met Asn Trp Phe Gln Gln Glu Pro Gly Lys Ala Pro

50 55 60

Lys Leu Leu Ile Ser Glu Gly Asn Ile Leu Arg Pro Gly Val Pro Ser

65 70 75 80

Arg Phe Ser Ser Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser

85 90 95

Lys Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Ser Asp

100

105

110

Asn Leu Pro Phe Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys

115

120

125

<210> 21

<211> 435

<212> DNA

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 21

aagcttgccg ccacatgga atggagctgg gtgttcctgt tctttctgtc cgtgaccaca 60

ggcgtgcatt ctgaggtgca gctggtgcag tctggagcag aggtgaaaaa gcccggggag 120

tctctgaaga tctcctgtca gagttttgga tacatcttta tcgaccatac tattcactgg 180

atgcgccaga tgcccgggca aggcctggag tggatggggg ctatttctcc cagacatgat 240

attactaaat acaatgagat gttcaggggc caggtcacca tctcagccga caagtcacgc 300

agcacgcctt acttgacgtg gagcagcctg aaggcctcgg acaccgcat gtatttctgt 360

gcgagagggg ggttctacgg tagtactatc tggttgact ttggggcca agggacaatg 420

gtcacgtct cttca 435

<210> 22

<211> 396

<212> DNA

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 22

aagcttgccg ccaccatgtc tgtgcctacc caggtgctgg gactgctgct gctgtggctg 60

acagacgccc gctgtgaaac gacagtgaac cagtctccat ccttctgtc tgcattctga 120

ggagacagag tcaccatcac ttgcataacc accactgata ttgatgatga tatgaactgg 180

ttccagcagg aaccagggaa agcccctaag ctctgatct ccgaaggcaa tattcttctg 240

cctgggggtcc catcaagatt cagcagcagt ggatatggca cagatttcac tctcaccatc 300

agcaaattgc agcctgaaga ttttgcaact tattactgtt tgcagagtga taacttacca 360

ttcactttcg gccaaaggac caagctggag atcaaa 396

<210> 23

<211> 1428

<212> DNA

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 23

aagcttgccg ccacatgga atggagctgg gtgttcctgt tctttctgtc cgtgaccaca 60

ggcgtgcatt ctgaggtgca gctggtgcag tctggagcag aggtgaaaaa gcccggggag 120

tctctgaaga tctcctgtca gagttttgga tacatcttta tcgaccatac tattcactgg 180

atgcgccaga tgcccgggca aggcctggag tggatggggg ctatttctcc cagacatgat 240

attactaaat acaatgagat gttcaggggc caggtcacca tctcagccga caagtcacgc 300

agcaccgcct acttgacgtg gagcagcctg aaggcctcgg acaccgcat gtatttctgt 360

gcgagagggg ggttctacgg tagtactatc tggttgact tttggggcca agggacaatg 420

gtcaccgtct cttcagcctc caccaagggc ccatcggctt tccccctggc accctcctcc 480

aagagcacct ctgggggcac agcggccctg ggctgcctgg tcaaggacta cttccccgaa 540

ccggtgacgg tgtcgtggaa ctcaggcgcc ctgaccagcg gcgtgcacac cttcccggt 600

gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcagc 660

ttgggcaccc agacctacat ctgcaacgtg aatcacaagc ccagcaacac caaggtggac 720

aagagagttg agcccaaate ttgtgacaaa actcacacat gccaccgtg cccagcacct 780

gaactcctgg ggggaccgtc agtcttctc tccccccaa aaccaagga caccctcatg 840

atctcccgga cccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag 900

gtcaagtca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 960

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 1020

tggctgaatg gcaaggagta caagtgaag gtctccaaca aagccctccc agcccccatc 1080

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta caccctgccc 1140

ccatcccggg aggagatgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 1200

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1260

accacgcctc ccgtgctgga ctccgacggc tccttcttcc tctatagcaa gtcaccgtg 1320

gacaagagca ggtggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1380

cacaaccact acacgcagaa gaggcctctcc ctgtctccgg gtaaatag 1428

<210> 24

<211> 455

<212> PRT

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 24

Met Glu Trp Ser Trp Val Phe Leu Phe Phe Leu Ser Val Thr Thr Gly

1 5 10 15

Val His Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys

20 25 30

Pro Gly Glu Ser Leu Lys Ile Ser Cys Gln Ser Phe Gly Tyr Ile Phe

35 40 45

Ile Asp His Thr Ile His Trp Met Arg Gln Met Pro Gly Gln Gly Leu

50 55 60

Glu Trp Met Gly Ala Ile Ser Pro Arg His Asp Ile Thr Lys Tyr Asn

65 70 75 80

Glu Met Phe Arg Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ser Ser

85 90 95

Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met

100

105

110

Tyr Phe Cys Ala Arg Gly Gly Phe Tyr Gly Ser Thr Ile Trp Phe Asp

115

120

125

Phe Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys

130

135

140

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly

145

150

155

160

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro

165

170

175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr

180

185

190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val

195 200 205

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn

210 215 220

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Ala Pro

225 230 235 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys

245 250 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val

260 265 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp

275 280 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr

290 295 300

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp

305 310 315 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu

325 330 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg

340 345 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys

355 360 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp

370 375 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys

385 390 395 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser

405

410

415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser

420

425

430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser

435

440

445

Leu Ser Leu Ser Pro Gly Lys

450

455

<210> 25

<211> 720

<212> DNA

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 25

aagcttgccg ccacatgtc tgtgcctacc caggtgctgg gactgctgct gctgtggctg 60

acagacgccc gctgtgaaac gacagtgacg cagtctccat ccttcctgtc tgcattctga 120

ggagacagag tcacatcac ttgcataacc accactgata ttgatgatga tatgaactgg 180

ttccagcagg aaccagggaa agcccctaag ctctgatct cccaaggcaa tattcttctg 240

cctggggctc catcaagatt cagcagcagt ggatatggca cagatttcac ttcaccatc 300

agcaaattgc agcctgaaga tttgcaact tattactgtt tgcagagtga taacttacca 360

ttcactttcg gccaaaggac caagctggag atcaaacgta cggtaggctgc accatctgtc 420

ttcatctcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 480

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 540

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagctc 600

agcagcacc tgacgtgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 660

gtcaccatc agggcctgag ctgcccgtc acaaagagct tcaacagggg agagtgttag 720

<210> 26

<211> 234

<212> PRT

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 26

Met Ser Val Pro Thr Gln Val Leu Gly Leu Leu Leu Leu Trp Leu Thr

1 5 10 15

Asp Ala Arg Cys Glu Thr Thr Val Thr Gln Ser Pro Ser Phe Leu Ser

20 25 30

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ile Thr Thr Thr Asp

35 40 45

Ile Asp Asp Asp Met Asn Trp Phe Gln Gln Glu Pro Gly Lys Ala Pro

50 55 60

Lys Leu Leu Ile Ser Glu Gly Asn Ile Leu Arg Pro Gly Val Pro Ser

65 70 75 80

Arg Phe Ser Ser Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser

85 90 95

Lys Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Ser Asp

100 105 110

Asn Leu Pro Phe Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg

115 120 125

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln

130 135 140

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr

145 150 155 160

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser

165

170

175

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr

180

185

190

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys

195

200

205

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro

210

215

220

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

225

230

<210> 27

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 27

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

Ser Leu Lys Ile Ser Cys Gln Ser Phe Gly Tyr Ile Phe Ile Asp His

20 25 30

Thr Ile His Trp Met Arg Gln Met Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

Gly Ala Ile Ser Pro Arg His Asp Ile Thr Lys Tyr Asn Glu Met Phe

50 55 60

Arg Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ser Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys

85

90

95

Ala Arg Gly Gly Phe Tyr Gly Ser Thr Ile Trp Phe Asp Phe Trp Gly

100

105

110

Gln Gly Thr Met Val Thr Val Ser Ser

115

120

<210> 28

<211> 363

<212> DNA

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 28

gaggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc ccgggggagtc tctgaagatc 60

tcctgtcaga gttttggata catctttatc gaccatacta ttactggat gcgccagatg 120

cccggaag gcctggagt gatggggct attctcca gacatgatat tactaaatac 180

aatgagatgt tcaggggcca ggtcaccatc tcagccgaca agtccagcag caccgcctac 240

ttgcagtga gcagcctgaa ggccctggac accgcatgt attctgtgc gagagggggg 300

ttctacggtg gtactatctg gtttgacttt tggggccaag ggacaatggt caccgtctct 360

tca 363

<210> 29

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 29

Glu Thr Thr Val Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly

1

5

10

15

Asp Arg Val Thr Ile Thr Cys Ile Thr Thr Thr Asp Ile Asp Asp Asp

20

25

30

Met Asn Trp Phe Gln Gln Glu Pro Gly Lys Ala Pro Lys Leu Leu Ile

35

40

45

Ser Glu Gly Asn Ile Leu Arg Pro Gly Val Pro Ser Arg Phe Ser Ser

50

55

60

Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Lys Leu Gln Pro

65

70

75

80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Ser Asp Asn Leu Pro Phe

85

90

95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys

100

105

<210> 30

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 30

gaaacgacag tgacgcagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgca taaccaccac tgatattgat gatgatatga actggttcca gcaggaacca 120

gggaaagccc ctaagctcct gatctccgaa ggcaatattc ttcgtcctgg ggtcccatca 180

agattcagca gcagtggata tggcacagat ttactctca ccatcagcaa attgcagcct 240

gaagattttg caacttatta ctgtttgcag agtgataact taccattcac ttctggccaa 300

gggaccaagc tggagatcaa a 321

<210> 31

<211> 451

<212> PRT

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 31

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

Ser Leu Lys Ile Ser Cys Gln Ser Phe Gly Tyr Ile Phe Ile Asp His

20 25 30

Thr Ile His Trp Met Arg Gln Met Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

Gly Ala Ile Ser Pro Arg His Asp Ile Thr Lys Tyr Asn Glu Met Phe

50 55 60

Arg Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ser Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys

85

90

95

Ala Arg Gly Gly Phe Tyr Gly Ser Thr Ile Trp Phe Asp Phe Trp Gly

100

105

110

Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser

115

120

125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala

130

135

140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val

145

150

155

160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala

165

170

175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val

180

185

190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His

195

200

205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys

210

215

220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly

225

230

235

240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met

245

250

255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His

260

265

270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val

275

280

285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr

290

295

300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly

305

310

315

320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile

325

330

335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val

340

345

350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser

355

360

365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu

370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro

385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val

405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met

420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser

435 440 445

Pro Gly Lys

450

<210> 32

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 32

Glu Thr Thr Val Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ile Thr Thr Thr Asp Ile Asp Asp Asp

20 25 30

Met Asn Trp Phe Gln Gln Glu Pro Gly Lys Ala Pro Lys Leu Leu Ile

35 40 45

Ser Glu Gly Asn Ile Leu Arg Pro Gly Val Pro Ser Arg Phe Ser Ser

50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Lys Leu Gln Pro

65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Ser Asp Asn Leu Pro Phe

85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala

100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly

115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala

130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln

145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser

165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr

180

185

190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser

195

200

205

Phe Asn Arg Gly Glu Cys

210

<210> 33

<211> 1356

<212> DNA

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 33

gaggtgcagc tgggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60

tcctgtcaga gttttggata catctttatc gaccatacta ttactggat gcgccagatg 120

ccccggcaag gcctggagtg gatgggggct atttctcca gacatgatat tactaaatac 180

aatgagatgt tcaggggcca ggtcaccatc tcagccgaca agtccagcag caccgcctac 240

ttgcagtgga gcagcctgaa ggcctcggac accgccatgt atttctgtgc gagagggggg 300

ttctacgga gtactatctg gtttgacttt tggggccaag ggacaatggc caccgtctct 360

tcagcctcca ccaagggccc atcggtcttc cccctggcac cctcctcaa gagcacctct 420

gggggcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480

tcgtggaact caggcgcctt gaccagcggc gtgcacacct tcccggtgt cctacagtcc 540

tcaggactct actccctcag cagcgtggtg accgtgccct ccagcagctt gggcaccag 600

acctacatct gcaacgtgaa tcacaagccc agcaacacca aggtggacaa gagagttgag 660

cccaaatttt gtgacaaaac tcacacatgc ccaccgtgcc cagcacctga actcctgggg 720

ggaccgtcag tcttctctt cccccaaaa cccaaggaca cctcatgat ctcccgacc 780

cctgagggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 840

tggtacgtgg acggcgtgga ggtgcataat gccaaagaaa agccgcggga ggagcagtac 900

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 960

aaggagtaca agtgcaaggt ctccaacaaa gccctcccag ccccatcga gaaaaccatc 1020

tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgcccc atcccgggag 1080

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac 1140

atgcccgtag agtgggagag caatgggcag ccgagaaca actacaagac cagcctccc 1200

gtgctggact ccgacggctc cttctcctc tatagcaagc tcaccgtgga caagagcagg 1260

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1320

acgcagaaga gcctctccct gtctccgggt aaatag 1356

<210> 34

<211> 645

<212> DNA

<213> Artificial Sequence

<220>

<223> humanized antibody sequence

<400> 34

gaaacgacag tgacgcagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgca taaccaccac tgatattgat gatgatatga actggttcca gcaggaacca 120

gggaaagccc ctaagctcct gatctccgaa ggcaatattc ttcgtcctgg ggtcccatca 180

agattcagca gcagtggata tggcacagat ttactctca ccatcagcaa attgcagcct 240

gaagatttg caacttatta ctgtttgcag agtgataact taccattcac ttccggccaa 300

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Arg Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ser Ser Thr Ala Tyr

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Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Phe Cys

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Ala Arg Gly Gly Phe Tyr Gly Ser Thr Ile Trp Phe Asp Phe Trp Gly

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Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser

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Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala

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Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val

145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala

165

170

175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val

180

185

190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His

195

200

205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys

210

215

220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly

225

230

235

240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met

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Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val

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280

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His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr

290

295

300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly

305

310

315

320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile

325

330

335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val

340

345

350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser

355

360

365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu

370

375

380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro

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390

395

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Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val

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Pro Gly

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