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(54) **Title**: PROTEIN ENGINEERING OF MONOACYLGLYCEROL LIPASE (MGLL)

(57) **Abstract**: A number of soluble engineered forms of MGLL that are suitable for high-throughput screening and protein crystallization, as well as a crystallized form of monoacylglycerol lipase protein (MGLL) and descriptions of the X-ray diffraction patterns are disclosed. The engineered constructs of MGLL permit the expression and purification of protein suitable for crystallography or high-throughput screening and identification of ligands, which can function as active agents to MGLL. The X-ray diffraction patterns allow the three dimensional structure of MGLL to be determined at atomic resolution so that ligand binding sites on MGLL can be identified and the interactions of ligands with MGLL amino acid residues can be modeled. Models prepared using such maps permit the design of ligands which can function as active agents which include, but are not limited to, those that function as inhibitors of MGLL.

PROTEIN ENGINEERING OF MONOACYLGLYCEROL LIPASE (MGLL)

TECHNICAL FIELD

[0001] The present invention generally pertains to the fields of molecular biology, protein purification, high-throughput screening, protein crystallization, X-ray diffraction analysis, three-dimensional structural determination, molecular modelling, and structure based rational drug design. The present invention provides a number of soluble engineered forms of MGLL that are suitable for high-throughput screening and protein crystallization, as well as a crystallized form of monoacylglycerol lipase protein (MGLL) and descriptions of the X-ray diffraction patterns.

[0002] The forms of MGLL provided by the present invention permit the expression and purification of protein suitable for high-throughput screening and crystallography. Thus forms of MGLL of the present invention have applications to the screening of MGLL to identify active agents which include, but are not limited to, those that find use as inhibitors of MGLL.

[0003] The X-ray diffraction patterns of the crystal of the present invention are of sufficient resolution so that the three-dimensional structure of MGLL can be determined at atomic resolution, ligand-binding sites on MGLL can be identified, and the interactions of ligands with amino acid residues of MGLL can be modeled. The high resolution maps provided by the present invention and the models prepared using such maps permit the design of ligands which can function as active agents. Thus, the three-dimensional structure of MGLL of the present invention has applications to the design of active agents, which include, but are not limited to, those that find use as inhibitors of MGLL.

BACKGROUND OF THE INVENTION

[0004] Various publications, which may include patents, published applications, technical articles and scholarly articles, are cited throughout the specification in parentheses, and full citations of each may be found at the end of the specification. Each of these cited publications is incorporated by reference herein, in its entirety.

[0005] Δ^9-Tetrahydrocannabinol (THC) is the main psychoactive substance found in the cannabis plant. THC activates two distinct G protein-coupled receptors, cannabinoid 1

receptor (CB1) and cannabinoid 2 receptor (CB2) (Matsuda et al. 1990; Munro et al. 1993). CB1 is primarily expressed in the central nervous system (CNS) (Hohmann and Herkenham 1999; Farquhar-Smith et al. 2000; Rice et al. 2002; Walczak et al. 2005). CB2 expression, however, seems to be restricted to only peripheral tissues (Munro et al. 1993; Galiegue et al. 1995).

[0006] CNS mediated analgesic effects of cannabinoids have been well documented, but there is also accumulating evidence suggesting that cannabinoids can produce antinociception through peripheral mechanisms involving CB1 or CB2 (Hohmann 2002) (Malan et al. 2002). Richardson et al. demonstrated that cannabinoid antihyperalgesic effects were predominantly mediated by CB1 (Richardson et al. 1998; Richardson 2000). Hanus et al. showed that intraperitoneal injection of a CB2 selective agonist could suppress the late-phase response in the formalin test (Hanus et al. 1999). It was also shown that a CB2 selective agonist could attenuate thermal nociception and hyperalgesia (Malan et al. 2001; Malan et al. 2002; Quartilho et al. 2003) or suppress hyperalgesia evoked by intradermal administration of capsaicin (Hohmann et al. 2004). Ibrahim et al. showed that activation of CB2 with a selective CB2 agonist inhibited experimental neuropathic pain (Ibrahim et al. 2006). Taken together, the accumulating evidence clearly suggests great potential therapeutic value in targeting CB2 as a peripheral target for the treatment of pain. It should be noted that a significant advantage of this approach is that it would preclude unwanted CNS side effects caused by targeting CB1.

[0007] An arachidonic acid derivative, 2-arachidonyl glycerol (2-AG), is one of the two major and most well studied endogenous ligands for CB1 and CB2 (Gonsiorek et al. 2000). It has been shown that 2-AG acts as a potent and full-efficacy agonist of CB2 (Gonsiorek et al. 2000; Sugiura et al. 2000; Maresz et al. 2005) and that 2-AG is primarily hydrolysed by monoacylglycerol lipase (MGLL) (Dinh et al. 2002; Dinh et al. 2004; Saario et al. 2004). A non-competitive MGLL inhibitor that blocked 2-AG hydrolysis was found to enhance 2-AG levels and antinociception in stress models (Hohmann et al. 2005; Makara et al. 2005). It was also demonstrated that local administration of either 2-AG or a selective MGLL inhibitor induced a dose-dependent antinociceptive effect in an inflammatory pain model. Furthermore, local administration of the selective MGLL inhibitor in combination with 2-AG produced an additive antinociceptive effect (Guindon

et al. 2007). Thus selective inhibition of MGLL may provide a novel therapeutic approach for the treatment of pain. Hitting this target, however, is inconceivable without good knowledge of the enzyme (Vandevoorde and Lambert 2005).

[0008] Lipases are lipolytic enzymes that have been differentiated from carboxylesterases by the fact that lipases have improved kinetics of hydrolysis for emulsions formed in oversaturated solutions. Carboxylesterases have been shown to have maximal activity using solutions of short-chain esters, with half-maximal activity at substrate concentrations far below the solubility limit. Exceeding the solubility limit was shown to have no effect on carboxylesterase activity. Lipases, on the other hand, were shown to have maximal activity using emulsified substrates, with half-maximal activity at substrate concentrations near the solubility limit (Chahinian et al. 2002). Early work with porcine pancreatic lipase showed that activity was low using a solution of ester substrates and abruptly increased as soon as an emulsion was formed. It was speculated that the porcine pancreatic lipase was activated by a conformational change of the enzyme as it bound to its water-insoluble substrate. The work with porcine pancreatic lipase was reviewed by Nini et al. (Nini et al. 2001).

[0009] In general, lipases share a similar α/β hydrolase fold with a catalytic Ser-His-Asp triad buried beneath a flexible cap-domain which is also referred to as a "lid" or "flap" (Brady et al. 1990; Winkler et al. 1990; Schrag et al. 1991). Although there is little conservation in the primary sequence of the cap-domain, it is generally formed of loops and one or more amphipathic helices. The cap-domains of human and dog gastric lipase are composed of intricate mixtures of 8 helices, turns, and random coils (Roussel et al. 1999; Roussel et al. 2002). In the crystal structure of human pancreatic lipase the lid adopts a helix-turn helix motif composed of two short amphipathic helices (van Tilbeurgh et al. 1992).

[0010] It has long been proposed that higher lipase activity for substrates presented as multimolecular aggregates (interfacial activation) is due to a conformational change in the cap-domain. It has also been proposed that changes from a closed to an open conformation of the lid is triggered by interaction with the substrate or lipid membrane (Brzozowski et al. 1991; van den Berg et al. 1995; van den Berg et al. 1995; Nini et al. 2001). Several other reports have also indicated that the loop covering the active site

mediates lipase substrate specificity (Dugi et al. 1992; Dugi et al. 1995). It was demonstrated that movement of the helical lid results in a change in the hydrophobic-hydrophilic balance of the exterior surface of the lipase with the hydrophobic side of the lid becoming completely exposed in the active enzyme (Faustinella et al. 1992). Some lipases, such as guinea pig pancreatic lipase and bile salt-activated lipase, do not have a lid domain. Their active sites are freely accessible to solvent. As expected, based on the lack of the a cap-domain, these lipases are not activated by a lipid/water interface (Wang et al. 1997) (Carriere et al. 1997).

[0011] Although much has been learned about the structure of lipases through determination of three-dimensional structures of several microbial lipases and mammalian lipases, the three-dimensional structure of MGLL is unknown and its mechanism of action is not well understood. Furthermore, MGLL shows very little sequence similarity with other mammalian lipases and is unique among lipases in having monoglycerides as its only substrates. MGLL seems to be only distantly related to microbial proteins that include esterases, lysophospholipases, and haloperoxidases (Karlsson et al. 1997). A virtual molecular model of MGLL was built based on the crystal structure of chloroperoxidase (Saario et al. 2005; Saario et al. 2006). The model shows an alpha beta hydrolase fold with a lid domain comprised of four helices. The model, however, is only a virtual model and gives little insight into the actual mechanism of action of MGLL.

[0012] A crystal structure of MGLL would greatly facilitate the effort to discover MGLL selective inhibitors. A potential problem for crystallization experiments with MGLL is that detergents have been required to purify and stabilize MGLL in solution for both recombinant MGLL and MGLL from endogenous sources. (Tornqvist and Belfrage 1976; Somma-Delpero et al. 1995; Karlsson et al. 2000). Without detergent the purified MGLL protein was prone to aggregation. Crystallizing a detergent-solubilized protein into a structure of sufficient regularity to enable high-resolution X-ray crystallography can be problematic because well-ordered protein crystals can be difficult to obtain (US6172262B1).

[0013] The present invention provides a number of soluble engineered forms of monoacylglycerol lipase protein (MGLL) that do not require detergent for purification. The forms of MGLL provided by the present invention permit the expression and

purification of protein suitable for identifying active agents in high-throughput screening and for crystallography. The present invention also provides a crystallized form of MGLL and descriptions of the X-ray diffraction patterns. Selective point mutations of hydrophobic residues in the cap-domain of MGLL generated soluble protein that did not require detergent for purification and stability. The protein displayed monomeric behaviour by gel filtration and was suitable for crystallization and high-throughput screening. In addition, selective mutation of surface lysine residues produced protein that generated crystals of improved quality. The crystal structure of MGLL was determined at atomic resolution. The forms of MGLL provide protein that can be used to identify inhibitors in high-throughput screens and the crystal structure of MGLL provides an important tool for structure-based drug design of MGLL inhibitors.

SUMMARY OF THE INVENTION

[0014] According to a first aspect of the present invention, there is provided a composition comprising a form of MGLL, or a fragment, or target structural motif or derivative thereof, wherein one or more hydrophobic residues of the cap-domain is mutated to improve solubility.

[0015] The present invention also provides a composition comprising a form of MGLL, or a fragment, or target structural motif or derivative thereof, wherein one or more hydrophobic Leucine residues of the cap-domain is mutated to improve solubility.

[0016] The present invention further provides a composition comprising a form of MGLL comprising one or more mutated hydrophobic Leucine residues of the cap-domain, wherein said one or more mutated hydrophobic Leucine residues of the cap-domain is selected from the group consisting of Leucine 162, Leucine 167, Leucine 169, Leucine 171, Leucine174, Leucine 176, and Leucine 184, numbering based on the reference sequence for human MGLL Isoform 2 (SEQ ID NO: 1).

[0017] The present invention provides a composition comprising a form of MGLL, comprising one or more mutated hydrophobic residues of the cap-domain, wherein said one or more hydrophobic residues of the cap-domain is mutated to Serine, Glutamine, or Arginine.

[0018] In another aspect of the invention, the present invention includes a form of MGLL comprising one or more mutated hydrophobic Leucine residues of the cap-domain further comprising a Lysine mutated to an Alanine.

[0019] The present invention also includes a form of MGLL comprising one or more mutated hydrophobic Leucine residues of the cap-domain further comprising a Lysine mutated to an Alanine, wherein said Lysine residue is selected from the group consisting of Lysine 36, Lysine 160, Lysine 165, Lysine 188, Lysine 206, Lysine 226, Lysine 259 and Lysine 269, numbering based on the reference sequence for human MGLL Isoform 2.

[0020] The present invention further includes a method of identifying an agent that binds to the forms of MGLL of the present invention, comprising the steps of contacting the form of MGLL with the agent; measuring the binding of the agent to the form of MGLL; and, determining that the agent binds to the form of MGLL; thereby identifying an agent that binds to the form of MGLL.

[0021] In a preferred embodiment, the present invention includes a method of identifying an agent that binds to the forms of MGLL, wherein the form of MGLL has an amino acid sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7.

[0022] In another preferred embodiment, the present invention includes a method of identifying an agent that binds to the forms of MGLL, wherein the binding is measured by the thermal stability of the form of MGLL.

[0023] The present invention further includes a method of identifying an agent that inhibits the activity of the forms of MGLL of the present invention comprising the steps of contacting the form of MGLL with the agent; measuring the biological activity of the form of MGLL in the presence of the agent; measuring the biological activity of the form of MGLL without the agent; and, comparing the biological activity of the form of MGLL measured in the presence of the agent and without the agent; thereby identifying the agent that decreases the biological activity the biological activity of the form of MGLL, when the activity measured in the presence of the agent is less than the activity measured without the agent.

[0024] In a preferred embodiment, the present invention includes a method of identifying an agent that inhibits the activity of the forms of MGLL, wherein the form of MGLL has an amino acid sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7.

[0025] In another preferred embodiment, the present invention includes a method of identifying an agent that inhibits the activity of the forms of MGLL of the present invention, wherein the biological activity is measured with an enzyme assay.

[0026] The present invention further includes methods of producing and using three-dimensional structure information derived from the crystal structure of monoacylglycerol lipase protein (MGLL).

[0027] The present invention also includes specific crystallization conditions to obtain crystals of the inhibitor-MGLL complex. The crystals are subsequently used to obtain a 3-dimensional structure of the complex using X-ray crystallography. The obtained data is used for rational drug discovery with the aim to design compounds that are inhibitors of MGLL.

[0028] The present invention includes a crystal comprising monoacylglycerol lipase (MGLL), or a fragment, or target structural motif or derivative thereof, and a ligand, wherein the ligand is a small molecule inhibitor. In another embodiment, the crystal has a spacegroup of $C222_1$.

[0029] In another aspect of the invention, the present invention includes a crystal comprising a form of MGLL which comprises a peptide having at least 95% sequence identity to SEQ ID NO: 7.

[0030] In another aspect of the invention, the invention includes a computer system comprising: (a) a database containing information on the three dimensional structure of a crystal comprising MGLL, or a fragment or a target structural motif or derivative thereof, and a ligand, wherein the ligand is a small molecule inhibitor, stored on a computer readable storage medium; and, (b) a user interface to view the information.

[0031] The present invention also includes a method of evaluating the potential of an agent to associate with MGLL comprising: (a) exposing MGLL to the agent; and (b) detecting the association of said agent to MGLL amino acid residues SER48-HIS54,

ARG57, TYR58, HIS77, HIS80, MET88, PHE93, PHE96, GLY120-ILE127, ILE145-VAL161, ALA163, SER176-ASN195, ASP197, ILE200, CYS201, ALA203, LEU205-VAL207, PHE209-SER218, ASP239-ASP243, TYR268-LEU275, THR279 thereby evaluating the potential of the agent.

[0032] The invention further includes a method of evaluating the potential of an agent to associate with the peptide having the sequence of SEQ ID NO: 7, comprising: (a) exposing SEQ ID NO: 7 to the agent; and (b) detecting the level of association of the agent to SEQ ID NO: 7, thereby evaluating the potential of the agent.

[0033] Further included in the present invention is a method of identifying a potential agonist or antagonist against monoacylglycerol lipase comprising: (a) employing the three dimensional structure of MGLL cocrystallized with a small molecule inhibitor to design or select said potential agonist or antagonist.

[0034] The invention comprises a method of locating the attachment site of an inhibitor to monoacylglycerol lipase, comprising: (a) obtaining X-ray diffraction data for a crystal of MGLL; (b) obtaining X-ray diffraction data for a complex of MGLL and an inhibitor; (c) subtracting the X-ray diffraction data obtained in step (a) from the X-ray diffraction data obtained in step (b) to obtain the difference in the X-ray diffraction data; (d) obtaining phases that correspond to X-ray diffraction data obtained in step (a); (e) utilizing the phases obtained in step (d) and the difference in the X-ray diffraction data obtained in step (c) to compute a difference Fourier image of the inhibitor; and, (f) locating the attachment site of the inhibitor to MGLL based on the computations obtained in step (e).

[0035] The present invention further comprises a method of obtaining a modified inhibitor comprising: (a) obtaining a crystal comprising MGLL and an inhibitor; (b) obtaining the atomic coordinates of the crystal; (c) using the atomic coordinates and one or more molecular modelling techniques to determine how to modify the interaction of the inhibitor with MGLL; and, (d) modifying the inhibitor based on the determinations obtained in step (c) to produce a modified inhibitor.

[0036] In another aspect of the invention, the invention includes an isolated protein fragment comprising a binding pocket or active site defined by structure coordinates of

MGLL amino acid residues SER48-HIS54, ARG57, TYR58, HIS77, HIS80, MET88, PHE93, PHE96, GLY120-ILE127, ILE145-VAL161, ALA163, SER176-ASN195, ASP197, ILE200, CYS201, ALA203, LEU205-VAL207, PHE209-SER218, ASP239-ASP243, TYR268-LEU275, THR279.

[0037] In another aspect of the invention, the invention includes an isolated nucleic acid molecule encoding the fragment which comprises a binding pocket or active site defined by structure coordinates of MGLL amino acid residues SER48-HIS54, ARG57, TYR58, HIS77, HIS80, MET88, PHE93, PHE96, GLY120-ILE127, ILE145-VAL161, ALA163, SER176-ASN195, ASP197, ILE200, CYS201, ALA203, LEU205-VAL207, PHE209-SER218, ASP239-ASP243, TYR268-LEU275, THR279. In another aspect of the invention, the invention includes a method of screening for an agent that associates with MGLL, comprising: (a) exposing a protein molecule fragment to the agent; and (b) detecting the level of association of the agent to the fragment. In another aspect of the invention, the invention includes a kit comprising a protein molecule fragment.

[0038] The invention additionally comprises a method for the production of a crystal complex comprising a MGLL polypeptide-ligand comprising: (a) contacting the MGLL polypeptide with said ligand in a suitable solution comprising PEG MME 5K, Na Citrate pH5.5 and n-Octyl-Beta-D-Glucopyranoside; and b) crystallizing said resulting complex of MGLL polypeptide-ligand from said solution.

[0039] The invention further includes a method for the production of a crystal comprising MGLL and a ligand wherein the ligand is a small molecule inhibitor comprising crystallizing a peptide comprising SEQ ID NO: 7 with a potential inhibitor.

[0040] The invention includes a method for identifying a potential inhibitor of monoacylglycerol lipase comprising: a) using a three dimensional structure of MGLL as defined by atomic coordinates according to Table 5; b) replacing one or more MGLL amino acids selected from SER48-HIS54, ARG57, TYR58, HIS77, HIS80, MET88, PHE93, PHE96, GLY120-ILE127, ILE145-VAL161, ALA163, SER176-ASN195, ASP197, ILE200, CYS201, ALA203, LEU205-VAL207, PHE209-SER218, ASP239-ASP243, TYR268-LEU275, THR279 in said three-dimensional structure with a different amino acid to produce a modified MGLL; c) using said three-dimensional structure to design or select said potential inhibitor; d) synthesizing said potential inhibitor; and, e)

contacting said potential inhibitor with said modified MGLL in the presence of a substrate to test the ability of said potential inhibitor to inhibit MGLL or said modified MGLL. Also included in the invention is an inhibitor identified by the method.

BRIEF DESCRIPTION OF THE DRAWINGS

[0041] A preferred embodiment of the present invention will now be described, by way of an example only, with reference to the accompanying drawings wherein:

[0042] **Figure 1: A.** Shown is SEQ ID NO: 1, the amino acid sequence of human monoglyceride lipase isoform 2 (Karlsson et al. 2001), accession NP_001003794, version NP_001003794.1, GI:51242953. **B.** Shown is SEQ ID NO: 2, the amino acid sequence of human monoglyceride lipase isoform 1 (Wall et al. 1997), Accession NP_009214, Version NP_009214.1, GI:6005786. **C.** Shown is the sequence alignment for SEQ ID NO: 1 and SEQ ID NO: 2, which are human monoglyceride lipase isoform 2 and isoform 1, respectively. Sequence alignment was done with the online BLAST 2 SEQUENCES software (Tatusova and Madden 1999).

[0043] **Figure 2: A.** Shown is the sequence alignment of human MGLL isoform 2 (SEQ ID NO: 1) and crystallized RsbQ (RsbQ, PDB 1WOM). Sequence alignment was done with the ClustalW software. Homologous residues are shown in black. Identical residues are shown in green. Position of helices and β sheets are indicated by red stars and green columns, respectively. The active site residues are highlighted in red. Leu 169 and Leu 176 are indicated by blue arrows. **B.** Shown is ribbon diagram representation of a homology model of human MGLL isoform 2 based on RsbQ (Pdb 1bro). Leu 169 and Leu 176 are shown in magenta. The active site residues are shown in green. **C.** Shown is surface representation of a homology model of human MGLL isoform 2 based on RsbQ (Pdb 1bro). Leu 169 and Leu 176 are shown in magenta. The active site residues are shown in green.

[0044] **Figure 3: A.** Shown is SEQ ID NO: 3, the amino acid sequence of the construct used to express wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) . The N-terminal His tag is shown in non-capitalized text and the TEV cleavage site is shown in bold non-capitalized text with an arrow over the site of cleavage. **B.** Shown is SEQ ID NO: 4, the amino acid sequence of the construct used to express a form of mut-MGLL (hMGLL 1-

303 L169S, L176S). The N-terminal His tag is shown in non-capitalized text, the TEV cleavage site is shown in bold non-capitalized text with an arrow over the site of cleavage, and the mutations are shown in bold non-capitalized text. **C**. Shown is SEQ ID NO: 5, the amino acid sequence of mut-MGLL (hMGLL 1-303 L169S, L176S) after TEV cleavage of the N-terminal His tag. The one amino acid from the TEV cleavage site that remains after TEV cleavage is shown in bold non-capitalized text and the mutations are shown in bold non-capitalized text. **D**. Shown is SEQ ID NO: 6, the amino acid sequence of the construct used to express a form of mut-MGLL (hMGLL 1-303 L169S, L176S, K36A). The N-terminal His tag is shown in non-capitalized text, the TEV cleavage site is shown in bold non-capitalized text with an arrow over the site of cleavage, and the mutations are shown in bold non-capitalized text. **E**. Shown is SEQ ID NO: 7, the amino acid sequence of mut-MGLL (hMGLL 1-303 L169S, L176S, K36A) after TEV cleavage of the N-terminal His tag. The one amino acid from the TEV cleavage site that remains after TEV cleavage is shown in bold non-capitalized text and the mutations are shown in bold non-capitalized text.

[0045] **Figure 4: A.** Shown are size exclusion elution profiles for wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) (magenta dotted lines) and TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S) (SEQ ID NO: 5) (blue solid line) purified in the absence of detergent showing 100% aggregation for wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) and 90% monomer for TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S) (SEQ ID NO: 5). **B.** Shown is circular dichroism structural analysis of wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) and TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S) (SEQ ID NO: 5). Far UV scans from 200 to 260 nm are shown in **(i)** and temperature melts from 25 to 80 °C monitored at 210 nm are shown in **(ii)**.

[0046] **Figure 5:** Shown are duplicate Michaelis-Menten curves for the hydrolysis of TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S) (SEQ ID NO: 5).

[0047] **Figure 6:** Shown are thermal shift data of the melting transitions for wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) (green line) and TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S) (SEQ ID NO: 5) (red line). The midpoint of the melting transition was 58 °C for wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) and 56.7 °C for TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S) (SEQ ID NO: 5).

[0048] **Figure 7: A.** Shown is the structure of Compound 1. **B.** Shown is the structure of Compound 2.

[0049] **Figure 8:** Shown is a ribbon diagram of the structure of the complex of TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S, K36A) (SEQ ID NO: 7) and Compound 2. Color-coding is according to secondary structure (α-helices: magenta, β-sheets: yellow). The ligand (Compound 2) is drawn in ball-and-stick representation (green). The protein adopts a typical α/β hydrolase fold comprised of 8 β-sheets, with β2 being antiparallel to the other sheets. The inhibitor is located in the active site, which is capped by loops connecting α4 to α6.

[0050] **Figure 9:** Shown is a surface representation of the structure for the complex of TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S, K36A) (SEQ ID NO: 7) and Compound 2.

[0051] **Figure 10: A.** Shown is a ribbon diagram of MGLL with the cap-domain (residues 145-206) colored cyan to illustrate the location of the cap-domain. **B.** Shown is an overlay of the ribbon diagram of MGLL (orange) onto Bromoperoxidase A1 (salmon) and Chloroperoxidase L (green); **C.** Shown is an overlay of the ribbon diagram of MGLL (orange) onto *P.putida* Esterase (grey) and Gamma Lactamase (yellow). The cap-domain was omitted for clarity to show the good alignment between the core α/β-hydrolase in all structures. **D.** Shown is a ribbon diagram of the MGLL cap-domain. Superposition of different cap-domains highlighting the different arrangement between MGLL and other hydrolases. **E.** Shown is an overlay of the ribbon diagrams of the cap-domains of Bromoperoxidase A1 (salmon) and Chloroperoxidase L (green); **F.** Shown is an overlay of the ribbon diagrams of the cap-domains of *P.putida* Esterase (grey) and GammaLactamase (yellow).

[0052] **Figure 11:** Shown is a ribbon diagram of MGLL showing the location of mutations L169S and L176S in the cap-domain that prevented protein aggregation and K36A on the loop between β2 and β4 that would make interactions with a symmetry mate if present in the wild-type protein.

[0053] **Table 1:** Shown is a table of the forms of MGLL of the present invention and the purification yield in mg/liter.

[0054] **Table 2:** Shown is a table of the kinetic constants of the various MGLL constructs using 4MC-B or C-A as substrates. Values for the 4MC-B substrate are the average of 2 or 4 separate assays. The k_{cat}/ K_M values for the C-A substrate are the average values for the hydrolysis of five different substrate concentrations at $[S]<<K_M$.

[0055] **Table 3:** Shown are the data collection and refinement statistics for the complex of TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S, K36A) (SEQ ID NO: 7) and Compound 2.

[0056] **Table 4:** Shown is are the superposition statistics for selected α/β hydrolases without the cap-domain superimposed onto MGLL without the cap-domain

[0057] **Table 5:** Shown are the coordinates for the complex of TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S, K36A) (SEQ ID NO: 7) and Compound 2.

DEFINITIONS

[0058] As is generally the case in biotechnology and chemistry, the description of the present invention has required the use of a number of terms of art. Although it is not practical to do so exhaustively, definitions for some of these terms are provided here for ease of reference. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Definitions for other terms may also appear elsewhere herein. However, the definitions provided here and elsewhere herein should always be considered in determining the intended scope and meaning of the defined terms. Although any methods and materials similar or equivalent to those described herein can be used in the practice of the present invention, the preferred methods and materials are described.

[0059] The term “comprising” means “including principally, but not necessarily solely”. Furthermore, variations of the word “comprising”, such as “comprise” and “comprises”, have correspondingly varied meanings.

[0060] As used herein, the terms "containing", “having” and “including” are used in their open, non-limiting sense.

[0061] As used herein, “sequence” means the linear order in which monomers occur in a polymer, for example, the order of amino acids in a polypeptide or the order of nucleotides in a polynucleotide.

[0062] The terms "polypeptide," "protein," and "peptide" are used herein interchangeably to refer to amino acid chains in which the amino acid residues are linked by peptide bonds or modified peptide bonds. The amino acid chains can be of any length of greater than two amino acids. Unless otherwise specified, the terms "polypeptide," "protein," and "peptide" also encompass various modified forms thereof. Such modified forms may be naturally occurring modified forms or chemically modified forms. Examples of modified forms include, but are not limited to, glycosylated forms, phosphorylated forms, myristoylated forms, palmitoylated forms, ribosylated forms, acetylated forms, ubiquitinated forms, etc. Modifications also include intra-molecular crosslinking and covalent attachment to various moieties such as lipids, flavin, biotin, polyethylene glycol or derivatives thereof, etc. In addition, modifications may also include cyclization, branching and cross-linking. Further, amino acids other than the conventional twenty amino acids encoded by the codons of genes may also be included in a polypeptide.

[0063] As used herein, a protein or nucleic acid molecule is said to be "isolated" when the protein or nucleic acid molecule is substantially separated from contaminants from the source of the protein or nucleic acid.

[0064] As used herein, the term "native protein" refers to a protein comprising an amino acid sequence identical to that of a protein isolated from its natural source or organism.

[0065] As used herein, the term "amino acids" refers to the L-isomers of the naturally occurring amino acids. The naturally occurring amino acids are glycine, alanine, valine, leucine, isoleucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, γ-carboxylglutamic acid, arginine, ornithine, and lysine. Unless specifically indicated, all amino acids are referred to in this application are in the L-form.

[0066] As used herein, the term "nonnatural amino acids" refers to amino acids that are not naturally found in proteins. For example, selenomethionine.

[0067] As used herein, the term "positively charged amino acid" includes any amino acids having a positively charged side chain under normal physiological conditions. Examples of positively charged naturally occurring amino acids are arginine, lysine, and histidine.

[0068] As used herein, the term "negatively charged amino acid" includes any amino acids having a negatively charged side chains under normal physiological conditions. Examples of negatively charged naturally occurring amino acids are aspartic acid and glutamic acid.

[0069] As used herein, the term "hydrophobic amino acid" includes any amino acids having an uncharged, nonpolar side chain that is relatively insoluble in water. Examples of naturally occurring hydrophobic amino acids are alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine.

[0070] As used herein, the term "hydrophilic amino acid" refers to any amino acids having an uncharged, polar side chain that is relatively soluble in water. Examples of naturally occurring hydrophilic amino acids are serine, threonine, tyrosine, asparagine, glutamine and cysteine.

[0071] As used herein, "nucleic acid" is defined as RNA or DNA that encodes a protein or peptide as defined herein, or is complementary to nucleic acid sequence encoding such peptides, or hybridizes to such nucleic acid and remains stably bound to it under appropriate stringency conditions. Nucleic acid sequences can be composed of natural nucleotides of the following bases: thymidine, adenine, cytosine, guanine, and uracil; abbreviated T, A, C, G, and U, respectively, and/or synthetic analogs of the natural nucleotides.

[0072] The term “oligonucleotide” or “oligo” refers to a single-stranded DNA or RNA sequence of a relatively short length, for example, less than 100 residues long. For many methods, oligonucleotides of about 16-25 nucleotides in length are useful, although longer oligonucleotides of greater than about 25 nucleotides may sometimes be utilized. Some oligonucleotides can be used as “primers” for the synthesis of complimentary

nucleic acid strands. For example, DNA primers can hybridize to a complimentary nucleic acid sequence to prime the synthesis of a complimentary DNA strand in reactions using DNA polymerases. Oligonucleotides are also useful for hybridization in several methods of nucleic acid detection, for example, in Northern blotting or in situ hybridization.

[0073] "Recombinant" refers to a nucleic acid, a protein encoded by a nucleic acid, a cell, or a viral particle, that has been modified using molecular biology techniques to something other than its natural state. For example, recombinant cells can contain nucleotide sequence that is not found within the native (non-recombinant) form of the cell or can express native genes that are otherwise abnormally, under- expressed, or not expressed at all. Recombinant cells can also contain genes found in the native form of the cell wherein the genes are modified and re-introduced into the cell by artificial means. The term also encompasses cells that contain an endogenous nucleic acid that has been modified without removing the nucleic acid from the cell; such modifications include those obtained, for example, by gene replacement, and site-specific mutation.

[0074] The term "high stringency" as used herein refers to the conditions under which two nucleic acids may be hybridized, and may include, for example, the concentration of salts and/or detergents in a solution, the temperature of a solution that is used during the hybridization of the two nucleic acids and time period of the hybridization. Accordingly, the term "high stringency" as used herein refers to conditions in a solution that are conducive to hybridization of two nucleic acids only where such nucleic acids share a high degree of complementarity. The degree of complementarity may include, but not be limited to, a range of from about 90% to 100%. Thus, "high stringency" conditions may involve, but are not limited to, the use of a varying temperature and a buffer comprising various concentrations of detergents, salts, and divalent cations.

[0075] As used herein, "vector" refers to a nucleic acid molecule into which a heterologous nucleic acid can be or is inserted. Some vectors can be introduced into a host cell allowing for replication of the vector or for expression of a protein that is encoded by the vector or construct. Vectors typically have selectable markers, for example, genes that encode proteins allowing for drug resistance, origins of replication sequences, and multiple cloning sites that allow for insertion of a heterologous sequence.

Vectors are typically plasmid-based and are designated by a lower case “p” followed by a combination of letters and/or numbers. Starting plasmids disclosed herein are either commercially available, publicly available on an unrestricted basis, or can be constructed from available plasmids by application of procedures known in the art. Many plasmids and other cloning and expression vectors that can be used in accordance with the present invention are well-known and readily available to those of skill in the art. Moreover, those of skill readily may construct any number of other plasmids suitable for use in the invention. The properties, construction and use of such plasmids, as well as other vectors, in the present invention will be readily apparent to those of skill from the present disclosure.

[0076] As used herein, the term “activity” refers to an activity exerted by MGLL as determined in vivo or in vitro, according to standard techniques. Examples of such activity include, but are not limited to, direct activity such as the ability to bind to a ligand or an analog thereof, enzymatic activity, or functional changes of cell physiology that result from changes in activity.

[0077] The term “high-throughput assay” or “high-throughput screening” refers to assay designs that allow easy screening of multiple samples simultaneously and/or in rapid succession, and may include the capacity for robotic manipulation. Another desired feature of high-throughput assays is an assay design that is optimized to reduce reagent usage, or minimize the number of manipulations in order to achieve the analysis desired. Examples of high-throughput assay formats include, but are not limited to, formats that utilize 96-well, 384-well, and 1536-well plates, or “lab on a chip” microchannel chips used for liquid handling experiments. It is well known by those in the art that as miniaturization of plastic molds and liquid handling devices are advanced, or as improved assay devices are designed, greater numbers of samples can be processed using the forms of the present invention. Any high-throughput screening may be utilized to test new compounds, which are identified or designed for their ability to interact with MGLL. For general information on high-throughput screening see, for example, (Devlin (editor) 1998); and U.S. Pat. No. (US5763263).

[0078] By the term "selecting” or "select” compounds it is intended to encompass both (a) choosing compounds from a group previously unknown to be modulators of a protein

complex or interacting protein members thereof; and (b) testing compounds that are known to be capable of binding, or modulating the functions and activities of, a protein complex or interacting protein members thereof. The compounds encompass numerous chemical classes, including but not limited to, small organic or inorganic compounds, natural or synthetic molecules, such as antibodies, proteins or fragments thereof, antisense nucleotides, interfering RNA (iRNA) and ribozymes, and derivatives, mimetics and analogs thereof. Preferably, they are small organic compounds, i.e., those having a molecular weight of no greater than 10,000 daltons, more preferably less than 5,000 daltons.

[0079] As used herein, the term "atomic coordinates" or "structure coordinates" refers to mathematical coordinates that describe the positions of atoms in crystals of MGLL in Protein Data Bank (PDB) format, including X, Y, Z and B, for each atom. The diffraction data obtained from the crystals are used to calculate an electron density map of the repeating unit of the crystal. The electron density maps may be used to establish the positions (i.e. coordinates X, Y and Z) of the individual atoms within the crystal. Those of skill in the art understand that a set of structure coordinates determined by X-ray crystallography is not without standard error. For the purpose of this invention, any set of structure coordinates for MGLL from any source having a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 5 are considered substantially identical or homologous. In a more preferred embodiment, any set of structure coordinates for MGLL from any source having a root mean square deviation of non-hydrogen atoms of less than about 0.75 Å. when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 5 are considered substantially identical or homologous.

[0080] The term "atom type" refers to the chemical element whose coordinates are measured. The abbreviations in column 3 of Table 5 identifies the element.

[0081] The terms "X," "Y" and "Z" refer to the crystallographically-defined atomic position of the element measured with respect to the chosen crystallographic origin. The term "B" refers to a thermal factor that measures the mean variation of an atom's position with respect to its average position.

[0082] As used herein, the term "crystal" refers to any three-dimensional ordered array of molecules that diffracts X-rays.

[0083] As used herein, the term "carrier" in a composition refers to a diluent, adjuvant, excipient, or vehicle with which the product is mixed.

[0084] As used herein, the term "composition" refers to the combining of distinct elements or ingredients to form a whole. A composition comprises more than one element or ingredient. For the purposes of this invention, a composition will often, but not always comprise a carrier.

[0085] As used herein, "MGLL" is used to mean a protein obtained as a result of expression of monoacylglycerol lipase. Within the meaning of this term, it will be understood that human MGLL encompasses all proteins encoded by monoacylglycerol lipase, mutants thereof, conservative amino acid substitutions, alternative splice proteins thereof, and phosphorylated proteins thereof. Additionally, as used herein, it will be understood that the term "MGLL" includes monoacylglycerol lipase and homologues from other animals. As an example, MGLL includes the protein comprising SEQ ID NO: 7 and variants thereof comprising at least about 70% amino acid sequence identity to SEQ ID NO: 7, or preferably 80%, 85%, 90% and 95% sequence identity to SEQ ID NO: 7, or more preferably, at least about 95% or more sequence identity to SEQ ID NO: 7.

[0086] As used herein, the term "SAR," an abbreviation for Structure-Activity Relationships, collectively refers to the structure-activity/structure property relationships pertaining to the relationship(s) between a compound's activity/properties and its chemical structure.

[0087] As used herein, the term "molecular structure" refers to the three dimensional arrangement of molecules of a particular compound or complex of molecules (e.g., the three dimensional structure of MGLL and ligands that interact with MGLL.

[0088] As used herein, the term "molecular modeling" refers to the use of computational methods, preferably computer assisted methods, to draw realistic models of what molecules look like and to make predictions about structure activity relationships of ligands. The methods used in molecular modeling range from molecular graphics to computational chemistry.

[0089] As used herein, the term "molecular model" refers to the three dimensional arrangement of the atoms of a molecule connected by covalent bonds or the three dimensional arrangement of the atoms of a complex comprising more than one molecule, e.g., a protein-ligand complex.

[0090] As used herein, the term "molecular graphics" refers to three dimensional (3D) representations of the molecules; for instance, a 3D representation produced using computer assisted computational methods.

[0091] As used herein, "computer readable medium" refers to any medium, which can be read and accessed directly by a computer. Such media include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage media, and magnetic tape; optical storage media such as optical discs or CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media.

[0092] As used herein, "recorded" refers to a process for storing information on computer readable media. A skilled artisan can readily adopt any of the presently known methods for recording information on computer readable media to generate manufactures comprising an amino acid sequence and/or atomic coordinate/X-ray diffraction data information of the present invention.

[0093] As used herein, "a computer-based system" refers to the hardware means, software means, and data storage means used to analyze the sequence and/or X-ray diffraction data of the present invention. The minimum hardware means of the computer-based systems of the present invention comprises a central processing unit (CPU), input means, output means, and data storage means. A skilled artisan can readily appreciate which of the currently available computer-based systems are suitable for use in the present invention. A visualization device, such as a monitor, is optionally provided to visualize structure data.

[0094] As stated above, the computer-based systems of the present invention comprise a data storage means having stored therein sequence and/or atomic coordinate/X-ray diffraction data of the present invention and the necessary hardware means and software means for supporting and implementing an analysis means. As used herein, "data storage means" refers to memory which can store sequence or atomic coordinate/X-ray diffraction

data of the present invention, or a memory access means which can access manufactures having recorded thereon the sequence or X-ray data of the present invention.

[0095] As used herein, "search means" or "analysis means" refers to one or more programs which are implemented on the computer-based system to compare a target sequence or target structural motif with the sequence or X-ray data stored within the data storage means. Search means are used to identify fragments or regions of a protein which match a particular target sequence or target motif. A variety of known algorithms are disclosed publicly and a variety of commercially available software for conducting search means are and can be used in the computer-based systems of the present invention. A skilled artisan can readily recognize that any one of the available algorithms or implementing software packages for conducting computer analyses can be adapted for use in the present computer-based systems.

[0096] As used herein, "a target structural motif," or "target motif," refers to any rationally selected sequence or combination of sequences in which the sequence(s) are chosen based on a three-dimensional configuration or electron density map which is formed upon the folding of the target motif. There are a variety of target motifs known in the art. Protein target motifs include, but are not limited to, enzymatic active sites, inhibitor binding sites, structural subdomains, epitopes, functional domains and signal sequences. Similar motifs are known for RNA. A variety of structural formats for the input and output means can be used to input and output the information in the computer-based systems of the present invention.

[0097] As used herein, the term "computational chemistry" refers to calculations of the physical and chemical properties of the molecules.

[0098] As used herein, the term "molecular replacement" refers to a method that involves generating a preliminary model of a crystal of MGLL whose coordinates are unknown, by orienting and positioning the said atomic coordinates described in the present invention so as best to account for the observed diffraction pattern of the unknown crystal. Phases can then be calculated from this model and combined with the observed amplitudes to give an approximate Fourier synthesis of the structure whose coordinates are unknown. (Rossmann 1972)

[0099] As used herein, the term "homolog" refers to the MGLL protein molecule or the nucleic acid molecule which encodes the protein, or a functional domain from said protein from a first source having at least about 70% or 75% sequence identity, or at least about 80% sequence identity, or more preferably at least about 85% sequence identity, or even more preferably at least about 90% sequence identity, and most preferably at least about 95%, 97% or 99% amino acid or nucleotide sequence identity, with the protein, encoding nucleic acid molecule or any functional domain thereof, from a second source. The second source may be a version of the molecule from the first source that has been genetically altered by any available means to change the primary amino acid or nucleotide sequence or may be from the same or a different species than that of the first source.

[00100] As used herein, the term "active site" refers to regions on MGLL or a structural motif of MGLL that are directly involved in the function or activity of human MGLL.

[00101] As used herein, the terms "binding site" or "binding pocket" refer to a region of human MGLL or a molecular complex comprising MGLL that, as a result of the primary amino acid sequence of human MGLL and/or its three-dimensional shape, favourably associates with another chemical entity or compound including ligands, cofactors, or inhibitors. For the purpose of this invention, any active site, binding site or binding pocket defined by a set of structure coordinates for MGLL or for a homolog of MGLL from any source having a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å. when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 5 are considered substantially identical or homologous. In a more preferred embodiment, any set of structure coordinates for MGLL or a homolog of MGLL from any source having a root mean square deviation of non-hydrogen atoms of less than about 0.75 Å. when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 5 are considered substantially identical or homologous.

[00102] The tem "root mean square deviation" means the square root of the arithmetic mean of the squares of the deviations from the mean.

[00103] As used herein, the term "hydrogen bond" refers to two hydrophilic atoms (either O or N), which share a hydrogen that is covalently bonded to only one atom, while interacting with the other.

[00104] As used herein, the term "hydrophobic interaction" refers to interactions made by two hydrophobic residues or atoms (such as C).

[00105] As used herein, the term "conjugated system" refers to more than two double bonds adjacent to each other, in which electrons are completely delocalized with the entire system. This also includes aromatic residues.

[00106] As used herein, the term "aromatic residue" refers to amino acids with side chains having a delocalized conjugated system. Examples of aromatic residues are phenylalanine, tryptophan, and tyrosine.

[00107] As used herein, the phrase "inhibiting the binding" refers to preventing or reducing the direct or indirect association of one or more molecules, peptides, proteins, enzymes, or receptors, or preventing or reducing the normal activity of one or more molecules, peptides, proteins, enzymes or receptors, e.g., preventing or reducing the direct or indirect association with human MGLL.

[00108] As used herein, the term "competitive inhibitor" refers to inhibitors that bind to human MGLL, thus directly competing with them. Competitive inhibition may, in some instances, be reversed completely by increasing the substrate concentration.

[00109] As used herein, the term "uncompetitive inhibitor" refers to one that inhibits the functional activity of human MGLL by binding to a different site than does its substrate(s). As used herein, the term "non-competitive inhibitor" refers to one that can bind to either the free or bound form of MGLL. Those of skill in the art may identify inhibitors as competitive, uncompetitive, or non-competitive by computer fitting enzyme kinetic data using standard methods. See, for example, (Segel 1975)

[00110] As used herein, the term "R or S-isomer" refers to two possible stereoisomers of a chiral carbon according to the Cahn-Ingold-Prelog system adopted by International Union of Pure and Applied Chemistry (IUPAC). Each group attached to the chiral carbon is first assigned to a preference or priority a, b, c, or d on the basis of the atomic number of the atom that is directly attached to the chiral carbon. The group with the highest

atomic number is given the highest preference a, the group with next highest atomic number is given the next highest preference b, and so on. The group with the lowest preference (d) is then directed away from the viewer. If the trace of a path from a to b to c is counter clockwise, the isomer is designated (S); in the opposite direction, clockwise, the isomer is designated (R).

[00111] As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

[00112] As used herein, the term "chiral center" refers to a carbon atom to which four different groups are attached.

[00113] As used herein, the term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposable on its mirror image and hence optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

[00114] As used herein, the term "racemic" refers to a mixture of equal parts of enantiomers and which is optically active.

[00115] As used herein, the term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule. In the context of this application. The term "resolution" also refers to the amount of detail, which can be resolved by the diffraction experiment. Or in other terms, since the inherent disorder of a protein crystal diffraction pattern fades away at some diffraction angle $theta_{max}$, the corresponding distance d_{min} of the reciprocal lattices is determined by Bragg's law. In practice in protein crystallography it is usual to quote the nominal resolution of a protein electron density in terms of d_{min}, the minimum lattice distance to which data is included in the calculation of the map.

[00116] As used herein, the term "ligand" refers to any molecule, or chemical entity, which binds with or to MGLL, a subunit of MGLL, a domain of MGLL, a target structural motif of MGLL, or a fragment of MGLL. Thus, ligands include, but are not limited to, small molecule inhibitors, for example.

[00117] As used herein, the term "small molecule inhibitor" refers to compounds useful in the present invention having measurable MGLL inhibiting activity. In addition to small organic molecules, peptides, antibodies, cyclic peptides and peptidomimetics are contemplated as being useful in the disclosed methods. Preferred inhibitors are small molecules, preferably less than 10,000 daltons, and more preferably less than 5,000 daltons.

[00118] As used herein the terms "bind," "binding," "bond," or "bonded" when used in reference to the association of atoms, molecules, or chemical groups, refer to any physical contact or association of two or more atoms, molecules, or chemical groups.

[00119] As used herein, the terms "covalent bond" or "valence bond" refer to a chemical bond between two atoms in a molecule created by the sharing of electrons, usually in pairs, by the bonded atoms.

[00120] As used herein, "noncovalent bond" refers to an interaction between atoms and/or molecules that does not involve the formation of a covalent bond between them.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[00121] It is to be understood at the outset, that the figures and examples provided herein are to exemplify, and not to limit the invention and its various embodiments.

[00122] The present invention includes a crystal comprising the monoacylglycerol lipase (MGLL), or a fragment, or target structural motif or derivative thereof, and a ligand, wherein the ligand is a small molecule inhibitor. In one embodiment, the fragment or derivative thereof is a peptide comprising SEQ ID NO: 7

[00123] In another embodiment, the crystal has a spacegroup of $C222_1$. In a different embodiment, the crystal effectively diffracts X-rays for determination of atomic coordinates to a resolution of at least about 3.2 Å. In a preferred embodiment, the ligand is in crystalline form. In a highly preferred embodiment, the ligand is the structure depicted in Figure 7A or Figure 7B, and, derivatives thereof.

[00124] The present invention also includes a crystal comprising MGLL, which comprises a peptide having at least 95% sequence identity to SEQ ID NO. 6. In a preferred embodiment, the crystal comprising SEQ ID NO: 7 comprises an atomic

structure characterized by the coordinates of Table 5. In another preferred embodiment, the crystal comprises a unit cell selected from the group consisting of: a cell having dimensions of a = 93.95, b = 128.45, c = 60.6.

[00125] In another aspect of the invention, the invention includes a computer system comprising: (a) a database containing information on the three dimensional structure of a crystal comprising MGLL, or a fragment or a target structural motif or derivative thereof, and a ligand, wherein the ligand is a small molecule inhibitor, stored on a computer readable storage medium; and, (b) a user interface to view the information. In one embodiment, the information comprises diffraction data obtained from a crystal comprising SEQ ID NO: 7.

[00126] In another embodiment, the information comprises an electron density map of a crystal form comprising SEQ ID NO: 7. In a different embodiment, the information comprises the structure coordinates of Table 5 or homologous structure coordinates comprising a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 5. In a preferred embodiment, the information comprises structure coordinates comprising a root mean square deviation of non-hydrogen atoms of less than about 0.75 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 5. In a highly preferred embodiment, the information comprises the structure coordinates for amino acids SER48-HIS54, ARG57, TYR58, HIS77, HIS80, MET88, PHE93, PHE96, GLY120-ILE127, ILE145-VAL161, ALA163, SER176-ASN195, ASP197, ILE200, CYS201, ALA203, LEU205-VAL207, PHE209-SER218, ASP239-ASP243, TYR268-LEU275, THR279 according to Table 5 or similar structure coordinates for said amino acids comprising a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å to 0.75 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 5.

[00127] The present invention also includes a method of evaluating the potential of an agent to associate with MGLL comprising: (a) exposing MGLL to the agent; and (b) detecting the association of said agent to MGLL amino acid residues SER48-HIS54, ARG57, TYR58, HIS77, HIS80, MET88, PHE93, PHE96, GLY120-ILE127, ILE145-VAL161, ALA163, SER176-ASN195, ASP197, ILE200, CYS201, ALA203, LEU205-

VAL207, PHE209-SER218, ASP239-ASP243, TYR268-LEU275, THR279 thereby evaluating the potential. In one embodiment of the invention, the agent is a virtual compound. In another embodiment of the invention, step (a) comprises comparing the atomic structure of the compound to the three dimensional structure of MGLL. In a different embodiment, the comparing of step (a) comprises employing a computational means to perform a fitting operation between the compound and at least one binding site of MGLL. In a preferred embodiment, the binding site is defined by structure coordinates for amino acids SER48-HIS54, ARG57, TYR58, HIS77, HIS80, MET88, PHE93, PHE96, GLY120-ILE127, ILE145-VAL161, ALA163, SER176-ASN195, ASP197, ILE200, CYS201, ALA203, LEU205-VAL207, PHE209-SER218, ASP239-ASP243, TYR268-LEU275, THR279 according to Table 5 or similar structure coordinates for said amino acids comprising a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 5. In a highly preferred embodiment, step (a) comprise exposing the agent to crystalline SEQ ID NO: 7 and the detecting of step (b) comprises determining the three dimensional structure of the agent-SEQ ID NO: 7 complex.

[00128] The present invention includes a method of identifying a potential agonist or antagonist against MGLL comprising: (a) employing the three dimensional structure of MGLL cocrystallized with a small molecule inhibitor to design or select said potential agonist or antagonist. In one embodiment, the three dimensional structure corresponds to the atomic structure characterized by the coordinates of Table 5 or similar structure coordinates comprising a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 5. In a different embodiment, the method further comprises the steps of: (b) synthesizing the potential agonist or antagonist; and (c) contacting the potential agonist or antagonist with MGLL.

[00129] The instant invention comprises a method of locating the attachment site of an inhibitor to MGLL, comprising: (a) obtaining X-ray diffraction data for a crystal of MGLL; (b) obtaining X-ray diffraction data for a complex of MGLL and an inhibitor; (c) subtracting the X-ray diffraction data obtained in step (a) from the X-ray diffraction data obtained in step (b) to obtain the difference in the X-ray diffraction data; (d) obtaining

phases that correspond to X-ray diffraction data obtained in step (a); (e) utilizing the phases obtained in step (d) and the difference in the X-ray diffraction data obtained in step (c) to compute a difference Fourier image of the inhibitor; and, (f) locating the attachment site of the inhibitor to MGLL based on the computations obtained in step (e).

[00130] The present invention further comprises a method of obtaining a modified inhibitor comprising: (a) obtaining a crystal comprising MGLL and an inhibitor; (b) obtaining the atomic coordinates of the crystal; (c) using the atomic coordinates and one or more molecular modeling techniques to determine how to modify the interaction of the inhibitor with MGLL; and, (d) modifying the inhibitor based on the determinations obtained in step (c) to produce a modified inhibitor. In one embodiment, the crystal comprises a peptide having a sequence comprising SEQ ID NO: 7. In a different embodiment, the one or more molecular modeling techniques are selected from the group consisting of graphic molecular modeling and computational chemistry. In a preferred embodiment, step (a) comprises detecting the interaction of the inhibitor to MGLL amino acid residues SER48-HIS54, ARG57, TYR58, HIS77, HIS80, MET88, PHE93, PHE96, GLY120-ILE127, ILE145-VAL161, ALA163, SER176-ASN195, ASP197, ILE200, CYS201, ALA203, LEU205-VAL207, PHE209-SER218, ASP239-ASP243, TYR268-LEU275, THR279. In another embodiment of the invention, the invention includes an MGLL inhibitor identified by this method.

[00131] In another aspect of the invention, the invention includes an isolated protein fragment comprising a binding pocket or active site defined by structure coordinates of MGLL amino acid residues SER48-HIS54, ARG57, TYR58, HIS77, HIS80, MET88, PHE93, PHE96, GLY120-ILE127, ILE145-VAL161, ALA163, SER176-ASN195, ASP197, ILE200, CYS201, ALA203, LEU205-VAL207, PHE209-SER218, ASP239-ASP243, TYR268-LEU275, THR279. In one embodiment, the isolated fragment is linked to a solid support.

[00132] In another aspect of the invention, the invention includes an isolated nucleic acid molecule encoding the fragment, which comprises a binding pocket or active site defined by structure coordinates of MGLL. In one embodiment, a vector comprises the nucleic acid molecule. In another embodiment, a host cell comprises the vector. In yet another aspect of the invention, the invention includes a method of producing a protein

fragment, comprising culturing the host cell under conditions in which the fragment is expressed. In another aspect of the invention, the invention includes a method of screening for an agent that associates with MGLL, comprising: (a) exposing a protein molecule fragment to the agent; and (b) detecting the level of association of the agent to the fragment. In another aspect of the invention, the invention includes a kit comprising a protein molecule fragment.

[00133] In another aspect of the invention, the invention includes a method for the production of a crystal complex comprising an MGLL polypeptide-ligand comprising: (a) contacting the MGLL polypeptide with said ligand in a suitable solution comprising PEG MME 5K, M Na Citrate pH 5.5, and n-Octyl-Beta-D-Glucopyranoside; and, b) crystallizing said resulting complex of MGLL polypeptide-ligand from said solution. In one embodiment, the MGLL polypeptide is a polypeptide SEQ ID NO: 7. In another embodiment, PEG MME has an average molecular weight range from 2000 to 10000, wherein said PEG MME is present in solution at a range from about 1% w/v to about 5% w/v and said n-Octyl-Beta-D-Glucopyranoside is present in solution at a range of from about 0.2% to 2%. In a preferred embodiment, PEG MME has an average molecular weight of about 5000 and is present in solution at about 2.4% w/v and said n-Octyl-Beta-D-Glucopyranoside is present in solution at about 0.6%.

[00134] The invention further includes a method for the production of a crystal comprising MGLL and a ligand wherein the ligand is a small molecule inhibitor comprising crystallizing a peptide comprising SEQ ID NO: 7 with a potential inhibitor.

[00135] The invention includes a method for identifying a potential inhibitor of MGLL comprising: a) using a three dimensional structure of MGLL as defined by atomic coordinates according to Table 5; b) replacing one or more MGLL amino acids selected from SER48-HIS54, ARG57, TYR58, HIS77, HIS80, MET88, PHE93, PHE96, GLY120-ILE127, ILE145-VAL161, ALA163, SER176-ASN195, ASP197, ILE200, CYS201, ALA203, LEU205-VAL207, PHE209-SER218, ASP239-ASP243, TYR268-LEU275, THR279 in said three-dimensional structure with a different amino acid to produce a modified MGLL; c) using said three-dimensional structure to design or select said potential inhibitor; d) synthesizing said potential inhibitor; and, e) contacting said potential inhibitor with said modified MGLL in the presence of a substrate to test the

ability of said potential inhibitor to inhibit MGLL or said modified MGLL. In another embodiment, the potential inhibitor is selected from a database. In a preferred embodiment, the potential inhibitor is designed de novo. In another preferred embodiment, the potential inhibitor is designed from a known inhibitor. In a highly preferred embodiment, the step of employing said three-dimensional structure to design or select said potential inhibitor comprises the steps of: a) identifying chemical entities or fragments capable of associating with modified MGLL; and b) assembling the identified chemical entities or fragments into a single molecule to provide the structure of said potential inhibitor. In one embodiment, the potential inhibitor is a competitive inhibitor of SEQ ID NO: 7. In a different embodiment, the potential inhibitor is a non-competitive or uncompetitive inhibitor of SEQ ID NO: 7. In yet another embodiment, an inhibitor is identified by the method.

Engineered Forms and Fragments

[00136] Engineered forms of MGLL or fragments thereof, for instance engineered forms or fragments comprising active sites defined by two or more amino acids selected from the group consisting of: SER48-HIS54, ARG57, TYR58, HIS77, HIS80, MET88, PHE93, PHE96, GLY120-ILE127, ILE145-VAL161, ALA163, SER176-ASN195, ASP197, ILE200, CYS201, ALA203, LEU205-VAL207, PHE209-SER218, ASP239-ASP243, TYR268-LEU275, THR279 may be prepared by any available means including synthetic or recombinant means. Such fragments may then be used in the assays as described herein, for example, but not limited to, high-throughput assays to detect interactions between prospective agents and the active site within the fragment.

[00137] For recombinant expression or production of the forms or fragments of the invention, nucleic acid molecules encoding the form or fragment may be prepared. Nucleic acid molecules encoding engineered forms or fragments of the invention may differ in sequence because of the degeneracy in the genetic code or may differ in sequence as they encode proteins or protein fragments that differ in amino acid sequence. Homology or sequence identity between two or more such nucleic acid molecules is determined by BLAST (Basic Local Alignment Search Tool) analysis using the algorithm employed by the programs blastp, blastn, blastx, tblastn and tblastx (Karlin and Altschul

1990) and (Altschul 1993), fully incorporated by reference, which are tailored for sequence similarity searching.

[00138] The approach used by the BLAST program is to first consider similar segments between a query sequence and a database sequence, then to evaluate the statistical significance of all matches that are identified and finally to summarize only those matches which satisfy a preselected threshold of significance. For a discussion of basic issues in similarity searching of sequence databases, see (Altschul et al. 1994) which is fully incorporated by reference. The search parameters for histogram, descriptions, alignments, expect (i.e., the statistical significance threshold for reporting matches against database sequences), cutoff, matrix and filter are at the default settings. For a discussion of default scoring matrix used by blastp, blastx, tblastn, and tblastx, see (Henikoff 1992).

[00139] The encoding nucleic acid molecules of the present invention or fragments thereof (i.e., synthetic oligonucleotides) and those that are used as probes or specific primers for polymerase chain reaction (PCR) or to synthesize gene sequences encoding proteins of the invention can easily be synthesized by chemical techniques, for example, the phosphotriester method of (Matteucci and Caruthers 1981) or using automated synthesis methods. In addition, larger DNA segments can readily be prepared by well-known methods, such as synthesis of a group of oligonucleotides that define various modular segments of the gene, followed by ligation of oligonucleotides to build the complete modified gene.

[00140] The encoding nucleic acid molecules of the present invention may further be modified so as to contain a detectable label for diagnostic and probe purposes. A variety of such labels are known in the art and can readily be employed with the encoding molecules herein described. Suitable labels include, but are not limited to, biotin, radiolabeled nucleotides and the like. A skilled artisan can employ any of the art-known labels to obtain a labeled encoding nucleic acid molecule.

[00141] The present invention further provides recombinant DNA molecules (rDNA) that contain a coding sequence for a protein or protein fragment as described herein. As used herein, an rDNA molecule is a DNA molecule that has been subjected to molecular manipulation. Methods for generating rDNA molecules are well known in the art, for

example, see (Sambrook et al. 1989). In the preferred rDNA molecules, a coding DNA sequence is operably linked to expression control sequences and/or vector sequences.

[00142] The choice of vector and expression control sequences to which one of the protein encoding sequences of the present invention is operably linked depends directly, as is well known in the art, on the functional properties desired (e.g., protein expression, and the host cell to be transformed). A vector of the present invention may be capable of directing the replication or insertion into the host chromosome, and preferably also expression, of the structural gene included in the rDNA molecule.

[00143] Expression control elements that are used for regulating the expression of an operably linked protein encoding sequence are known in the art and include, but are not limited to, inducible promoters, constitutive promoters, secretion signals, and other regulatory elements. Preferably, the inducible promoter is readily controlled, such as being responsive to a nutrient in the host cell's medium.

[00144] The present invention further provides host cells transformed with a nucleic acid molecule that encodes a protein or protein fragment of the present invention. The host cell can be either prokaryotic or eukaryotic. Eukaryotic cells useful for expression of a protein of the invention are not limited, so long as the cell line is compatible with cell culture methods and compatible with the propagation of the expression vector and expression of the gene product. Preferred eukaryotic host cells include, but are not limited to, insect, yeast, and mammalian cells. Preferred eukaryotic host cells include *Spodoptera frugiperda* (Sf9or Sf21) insect cells.

[00145] Transformed host cells of the invention may be cultured under conditions that allow the production of the recombinant protein. Optionally the recombinant protein is isolated from the medium or from the cells; recovery and purification of the protein may not be necessary in some instances where some impurities may be tolerated.

[00146] Kits may also be prepared with any of the above described nucleic acid molecules, proteins, protein fragments, vector and/or host cells optionally packaged with the reagents needed for a specific assay, such as those described above. In such kits, the protein, protein fragments, or other reagents may be attached to a solid support, such as glass or plastic beads.

High-throughput Assays

[00147] Compound identification methods can be performed using conventional laboratory assay formats or in high-throughput assays, including, but not limited to, those described below.

[00148] Immunoassays are a group of techniques used for the measurement of specific biochemical substances, commonly at low concentrations in complex mixtures such as biological fluids. The assays depend upon suitably prepared and selected antibodies with specificity and high affinity for their complementary antigens. A substance to be measured must, of necessity, be antigenic, either an immunogenic macromolecule or a haptenic small molecule. To each sample a known limited amount of specific antibody is added and the fraction of the antigen combining with it, often expressed as the bound:free ratio, is estimated by quantifying the signal from the antibody. Quantification can be achieved with a number of readily identifiable labels and used for various types of assays, including, but not limited to, radioisotopes for radioimmunoassays (RIA), fluorescent molecules for fluoroimmunoassays (FIA), stable free radicals for spin immunoassays, chemiluminescent molecules for chemiluminescent immunoassays (CLIA), colloidal gold particles for immunogold assays, and enzymes for enzyme-linked immunosorbent assays (ELISA).

[00149] A common immunoassay format is the ELISA, which avoids the hazards of radiochemicals and the expense of fluorescence detection systems. Instead, an ELISA is a form of quantitative immunoassay based on the use of antibodies (or antigens) that may be linked to an insoluble carrier surface, which is then used to "capture" the relevant antigen (or antibody) the test solution. The antigen-antibody complex is then detected by measuring the activity of an appropriate enzyme that can be covalently attached to the capture antigen (or antibody) or to a subsequent “detection” antibody (or antigen). For more information on ELISA techniques, see, for example, (Crowther 1995); (Kemeny (editor) and Challacombe (editor) 1988), (Kemeny 1991), and (Ishikawa 1999).

[00150] Colorimetric assays for enzymes are methods of quantitative chemical analysis in which the concentration or amount of a compound is determined by comparing the color produced by the reaction of a reagent with both standard and test amounts of the compound, often using a colorimeter. A colorimeter is a device for measuring color

intensity or differences in color intensity, either visually or photoelectrically. Standard colorimetric assays of beta-galactosidase enzymatic activity are well known to those skilled in the art, see for example, (Norton and Coffin 1985). A colorimetric assay can be performed on whole cell lysates using O-nitrophenyl-beta-D-galacto-pyranoside (ONPG, Sigma) as the substrate in a standard colorimetric beta-galactosidase assay (Sambrook et al. 1989). Automated colorimetric assays are also available for the detection of beta-galactosidase activity, as described in U.S. Patent Number (US5733720).

[00151] Enzymatic substrates that become fluorescent after being acted upon by an enzyme generally are well known. Such fluorescent substrates typically have two components that are bound to one another through, for example, a covalent chemical bond. One component is a fluorescent molecule that is capable of fluorescing by first accepting light energy and then emitting light energy. The other component is an entity that prevents the fluorescent molecule from accepting or emitting light energy when the two components are covalently bound to one another. In the presence of an appropriate enzyme, the enzyme cleaves the covalent bond between the two components and separates one component from the other to permit the fluorescent molecule to accept and emit light energy. In other words, the enzyme frees the fluorescent molecule and allows it to fluoresce. Ideally, fluorescent substrates should be soluble and stable in aqueous buffers, should have a high affinity for the enzymes that act upon them, and should yield a strong signal upon enzymatic action (US5998593A).

[00152] Detecting fluorescence emitted from the fluorescent component of a fluorescent enzyme substrate is typically achieved in two steps. In particular, the fluorescent molecule is first excited with light energy and subsequently the fluorescence emitted from the fluorescent component is then detected. Generally, fluorescent molecules can be excited with light energy from, for example, a laser or another suitable light source. Fluorescence is detected with a device designed to detect light energy of a wavelength that is emitted by the fluorescent molecule. Such excitation and emission detection systems generally are designed to operate at particular wavelength ranges (US5998593A).

[00153] Thermofluor® assays detect small changes in the intrinsic melting temperature of proteins based on binding of ligands. Compounds that interact

preferentially with the native form of the protein will increase the T_m, the temperature at which half of the protein is unfolded (Pantoliano et al. 2001). The technique monitors changes in the fluorescent intensity of dyes such as 1-anilinonaphthalene-8-sulfonic acid (1,8-ANS). The fluorescent dyes are quenched in aqueous environments but increase in fluorescence on binding to the hydrophobic core of denatured proteins.

Modeling the Three-Dimensional Structure of MGLL

[00154] The atomic coordinate data provided in Table 5, or the coordinate data derived from homologous proteins may be used to build a three-dimensional model of MGLL. Any available computational methods may be used to build the three dimensional model. As a starting point, the X-ray diffraction pattern obtained from the assemblage of the molecules or atoms in a crystalline version of MGLL or an MGLL homolog can be used to build an electron density map using tools well known to those skilled in the art of crystallography and X-ray diffraction techniques. Additional phase information extracted either from the diffraction data and available in the published literature and/or from supplementing experiments may then be used to complete the reconstruction.

[00155] For basic concepts and procedures of collecting, analyzing, and utilizing X-ray diffraction data for the construction of electron densities see, for example, (Campbell 1984), (Cantor and Schimmel 1980), (Brunger 1993), (Woolfson 1997), (Drenth 1999), (Tsirelson and Ozerov 1996), and U.S. Patent Numbers (US5942428A); (US6037117A); (US5200910A); and (US5365456A), each of which is herein specifically incorporated by reference in their entirety.

[00156] For basic information on molecular modeling, see, for example, (Schlecht 1998); (Gans et al. 1996); (Cohen (editor) 1996); and (Smith 1996). U.S. Patents which provide detailed information on molecular modeling include U.S. Patent Numbers (US4906122A; US5030103A; US5583973A; US5612894A; US5994503A; US6071700A; US6075014A; US6075123A; US6080576A; US6093573A), each of which are incorporated by reference herein in their entirety.

Methods of Using the Atomic Coordinates to Identify and Design Ligands of Interest

[00157] The atomic coordinates of the invention, such as those described in Table 5, or coordinates substantially identical to or homologous to those of Table 5 may be used with

any available methods to prepare three dimensional models of MGLL as well as to identify and design MGLL ligands, inhibitors or antagonists or agonist molecules. Such a method provides the amino acid sequence and/or X-ray diffraction data in a form which allows a skilled artisan to analyze and molecular model the three-dimensional structure of MGLL or related molecules, including a subdomain thereof.

[00158] For instance, three-dimensional modeling may be performed using the experimentally determined coordinates derived from X-ray diffraction patterns, such as those in Table 5, for example, wherein such modeling includes, but is not limited to, drawing pictures of the actual structures, building physical models of the actual structures, and determining the structures of related subunits and MGLL/ligand and MGLL subunit/ligand complexes using the coordinates. Such molecular modeling can utilize known X-ray diffraction molecular modeling algorithms or molecular modeling software to generate atomic coordinates corresponding to the three-dimensional structure of MGLL.

[00159] As described above, molecular modeling involves the use of computational methods, preferably computer assisted methods, to build realistic models of molecules that are identifiably related in sequence to the known crystal structure. It also involves modeling new small molecule inhibitors bound to MGLL starting with the structures of MGLL and or MGLL complexed with known ligands or inhibitors. The methods utilized in ligand modeling range from molecular graphics (i.e., 3D representations) to computational chemistry (i.e., calculations of the physical and chemical properties) to make predictions about the binding of ligands or activities of ligands; to design new ligands; and to predict novel molecules, including ligands such as drugs, for chemical synthesis, collectively referred to as rational drug design.

[00160] One approach to rational drug design is to search for known molecular structures that might bind to an active site. Using molecular modeling, rational drug design programs can look at a range of different molecular structures of drugs that may fit into the active site of an enzyme, and by moving them in a three-dimensional environment it can be decided which structures actually fit the site well.

[00161] An alternative but related rational drug design approach starts with the known structure of a complex with a small molecule ligand and models modifications of that small molecule in an effort to make additional favourable interactions with MGLL.

[00162] The present invention includes the use of molecular and computer modeling techniques to design and select and design ligands, such as small molecule agonists or antagonists or other therapeutic agents that interact with MGLL. For example, the invention as herein described includes the design of ligands that act as competitive inhibitors of at least one MGLL function by binding to all, or a portion of, the active sites or other regions of MGLL.

[00163] This invention also includes the design of compounds that act as uncompetitive inhibitors of at least one function of MGLL. These inhibitors may bind to all, or a portion of, the active sites or other regions of MGLL already bound to its substrate and may be more potent and less non-specific than competitive inhibitors that compete for MGLL active sites. Similarly, non-competitive inhibitors that bind to and inhibit at least one function of MGLL whether or not it is bound to another chemical entity may be designed using the atomic coordinates of MGLL or complexes comprising MGLL of this invention.

[00164] The atomic coordinates of the present invention also provide the needed information to probe a crystal of MGLL with molecules composed of a variety of different chemical features to determine optimal sites for interaction between candidate inhibitors and/or activators and MGLL. For example, high resolution X-ray diffraction data collected from crystals saturated with solvent allows the determination of where each type of solvent molecule sticks. Small molecules that bind to those sites can then be designed and synthesized and tested for their inhibitory activity (Travis 1993).

[00165] The present invention also includes methods for computationally screening small molecule databases and libraries for chemical entities, agents, ligands, or compounds that can bind in whole, or in part, to MGLL. In this screening, the quality of fit of such entities or compounds to the binding site or sites may be judged either by shape complementarity or by estimated interaction energy (Meng et al. 1992).

[00166] The design of compounds that bind to, promote or inhibit the functional activity of MGLL according to this invention generally involves consideration of two factors. First, the compound must be capable of physically and structurally associating with MGLL. Non-covalent molecular interactions important in the association of MGLL with the compound include hydrogen bonding, van der Waals and hydrophobic interactions. Second, the compound must be able to assume a conformation that allows it to associate with MGLL. Although certain portions of the compound may not directly participate in the association with MGLL, those portions may still influence the overall conformation of the molecule. This, in turn, may have a significant impact on binding affinities, therapeutic efficacy, drug-like qualities and potency. Such conformational requirements include the overall three-dimensional structure and orientation of the chemical entity or compound in relation to all or a portion of the active site or other region of MGLL, or the spacing between functional groups of a compound comprising several chemical entities that directly interact with MGLL.

[00167] The potential, predicted, inhibitory agonist, antagonist or binding effect of a ligand or other compound on MGLL may be analyzed prior to its actual synthesis and testing by the use of computer modeling techniques. If the theoretical structure of the given compound suggests insufficient interaction and association between it and MGLL, synthesis and testing of the compound may be obviated. However, if computer modeling indicates a strong interaction, the molecule may then be synthesized and tested for its ability to interact with MGLL. In this manner, synthesis of inoperative compounds may be avoided. In some cases, inactive compounds are synthesized predicted on modeling and then tested to develop a SAR (structure-activity relationship) for compounds interacting with a specific region of MGLL.

[00168] One skilled in the art may use one of several methods to screen chemical entities fragments, compounds, or agents for their ability to associate with MGLL and more particularly with the individual binding pockets or active sites of MGLL. This process may begin by visual inspection of, for example, the active site on the computer screen based on the atomic coordinates of MGLL or MGLL complexed with a ligand. Selected chemical entities, compounds, or agents may then be positioned in a variety of orientations, or docked within an individual binding pocket of MGLL. Docking may be

accomplished using software such as QUANTA, available from Accelrys, Inc., San Diego, CA.; and SYBYL, available for Tripos, St. Louis, Missouri; followed by energy minimization and molecular dynamics with standard molecular mechanics forcefields, such as CHARMm; available from Accelrys, Inc., San Diego, CA; and AMBER, University of California, San Francisco.

[00169] Specialized computer programs may also assist in the process of selecting chemical entities. These include but are not limited to: GRID (Goodford 1985), available from Oxford University, Oxford, UK); MCSS (Miranker and Karplus 1991), available from Molecular Simulations, Burlington, Mass.; AUTODOCK (Goodsell and Olsen 1990), available from Scripps Research Institute, La Jolla, CA; and DOCK (Kuntz et al. 1982), available from University of California, San Francisco, California.

[00170] The use of software such as GRID, a program that determines probable interaction sites between probes with various functional group characteristics and the macromolecular surface, is used to analyze the surface sites to determine structures of similar inhibiting proteins or compounds. The GRID calculations, with suitable inhibiting groups on molecules (e.g., protonated primary amines) as the probe, are used to identify potential hotspots around accessible positions at suitable energy contour levels. The program DOCK may be used to analyze an active site or ligand-binding site and suggest ligands with complementary steric properties.

[00171] Once suitable chemical entities, compounds, or agents have been selected, they can be assembled into a single ligand or compound or inhibitor or activator. Assembly may proceed by visual inspection of the relationship of the fragments to each other on the three-dimensional image. This may be followed by manual model building using software such as QUANTA or SYBYL.

[00172] Useful programs to aid in connecting the individual chemical entities, compounds, or agents include but are not limited to: CAVEAT (Bartlett et al. 1989); 3D Database systems such as MACCS-3D (Martin 1992), available from MDL Information Systems, San Leandro, CA; and HOOK, available from Molecular Simulations, Burlington, Massachusetts.

[00173] Several methodologies for searching three-dimensional databases to test pharmacophore hypotheses and select compounds for screening are available. These include the program CAVEAT (Bacon and Moult 1992). For instance, CAVEAT uses databases of cyclic compounds which can act as "spacers" to connect any number of chemical fragments already positioned in the active site. This allows one skilled in the art to quickly generate hundreds of possible ways to connect the fragments already known or suspected to be necessary for tight binding.

[00174] Instead of proceeding to build an inhibitor activator, agonist or antagonist of MGLL in a step-wise fashion one chemical entity at a time as described above, such compounds may be designed as a whole or "*de novo*" using either an empty active site or optionally including some portion(s) of a known molecule(s). These methods include: LUDI (Bohm 1992), available from Biosym Technologies, San Diego, CA; LEGEND (Nishibata and Itai 1991), available from Molecular Simulations, Burlington, Mass.; and LeapFrog, available from Tripos Associates, St. Louis, Mo,. USA.

[00175] For instance, the program LUDI can determine a list of interaction sites into which to place both hydrogen bonding and hydrophobic fragments. LUDI then uses a library of linkers to connect up to four different interaction sites into fragments. Then smaller "bridging" groups such as --CH2- and --COO-- are used to connect these fragments. For example, for the enzyme DHFR, the placements of key functional groups in the well-known inhibitor methotrexate were reproduced by LUDI. See also, (Rotstein and Murcko 1993).

[00176] Other molecular modeling techniques may also be employed in accordance with this invention. See, e.g., (Cohen et al. 1990). See also, (Navia and Murcko 1992).

[00177] Once a compound has been designed or selected by the above methods, the affinity with which that compound may bind or associate with MGLL may be tested and optimized by computational evaluation and/or by testing biological activity after synthesizing the compound. Inhibitors or compounds may interact with the MGLL in more than one conformation that is similar in overall binding energy. In those cases, the deformation energy of binding is taken to be the difference between the energy of the free compound and the average energy of the conformations observed when the compound binds to MGLL.

[00178] A compound designed or selected as binding or associating with MGLL may be further computationally optimized so that in its bound state it would preferably lack repulsive electrostatic interaction with MGLL. Such non-complementary (e.g., electrostatic) interactions include repulsive charge-charge, dipole-dipole and charge-dipole interactions. Specifically, the sum of all electrostatic interactions between the inhibitor and MGLL when the inhibitor is bound, preferably make a neutral or favourable contribution to the enthalpy of binding. Weak binding compounds will also be designed by these methods so as to determine SAR.

[00179] Specific computer software is available in the art to evaluate compound deformation energy and electrostatic interaction. Examples of programs designed for such uses include: Gaussian 92, revision C (Frisch et al. 1992); AMBER, University of California, San Francisco; QUANTA and CHARMm, available from Accelrys, Inc., San Diego, CA.; and Insight II/Discover, from Biosysm Technologies Inc., San Diego, CA, USA. Other hardware systems and software packages will be known to those skilled in the art.

[00180] Once a compound that associates with MGLL has been optimally selected or designed, as described above, substitutions may then be made in some of its atoms or side groups in order to improve or modify its binding properties. Generally, initial substitutions are conservative, i.e., the replacement group will have approximately the same size, shape, hydrophobicity and charge as the original group. It should, of course, be understood that components known in the art to alter conformation may be avoided. Such substituted chemical compounds may then be analyzed for efficiency of fit to MGLL by the same computer methods described in detail, above.

Use of Homology Structure Modeling to Design Ligands with Modulated Binding or Activity to MGLL.

[00181] The present invention includes the use of the atomic coordinates and structures of MGLL and/or MGLL complexed with an inhibitor to design modifications to starting compounds and derivatives thereof that will bind more tightly or interact more specifically to the target enzyme.

[00182] The structure of a complex between the MGLL and the starting compound can be used to guide the modification of that compound to produce new compounds that have

other desirable properties for applicable industrial and other uses (e.g., as pharmaceuticals), such as chemical stability, solubility or membrane permeability. (Lipinski et al. 1997).

[00183] Binding compounds, agonists, antagonists and such that are known in the art. Such compounds can be diffused into or soaked with the stabilized crystals of MGLL to form a complex for collecting X-ray diffraction data. Alternatively, the compounds, known and unknown in the art, can be cocrystallized with MGLL by mixing the compound with MGLL before precipitation.

[00184] To produce custom high affinity and very specific compounds, the structure of MGLL can be compared to the structure of a selected non-targeted molecule and a hybrid constructed by changing the structure of residues at the binding site for a ligand for the residues at the same positions of the non-target molecule. The process whereby this modeling is achieved is referred to as homology structure modeling. This is done computationally by removing the side chains from the molecule or target of known structure and replacing them with the side chains of the unknown structure put in sterically plausible positions. In this way it can be understood how the shapes of the active site cavities of the targeted and non-targeted molecules differ. This process, therefore, provides information concerning how a bound ligand can be chemically altered in order to produce compounds that will bind tightly and specifically to the desired target but will simultaneously be sterically prevented from binding to the non-targeted molecule. Likewise, knowledge of portions of the bound ligands that are facing to the solvent would allow introduction of other functional groups for additional pharmaceutical purposes. The use of homology structure modeling to design molecules (ligands) that bind more tightly to the target enzyme than to the non-target enzyme has wide spread applicability.

Databases and Computer Systems

[00185] An amino acid sequence or nucleotide sequence of MGLL and/or X-ray diffraction data, useful for computer molecular modeling of MGLL or a portion thereof, can be provided in a variety of mediums to facilitate use thereof. In one application of this embodiment, databases comprising data pertaining to MGLL, or at least one subdomain thereof, amino acid and nucleic acid sequence and/or X-ray diffraction data of the present

invention is recorded on computer readable medium. A skilled artisan can readily appreciate how any of the presently known computer readable media can be used to create a manufacture comprising computer readable medium having recorded thereon an amino acid sequence and/or X-ray diffraction data of the present invention.

[00186] A variety of data storage structures are available to a skilled artisan for creating a computer readable medium having recorded thereon an amino acid sequence and/or atomic coordinate/X-ray diffraction data of the present invention. The choice of the data storage structure will generally be based on the means chosen to access the stored information. In addition, a variety of data processor programs and formats can be used to store the sequence and X-ray data information of the present invention on computer readable media. The sequence information can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and MICROSOFT Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like. A skilled artisan can readily adapt any number of dataprocessor structuring formats (e.g., text file or database) in order to obtain computer readable media having recorded thereon the information of the present invention.

[00187] By providing computer readable media having sequence and/or atomic coordinates based on X-ray diffraction data, a skilled artisan can routinely access the sequence and atomic coordinate or X-ray diffraction data to model a related molecule, a subdomain, mimetic, or a ligand thereof. Computer algorithms are publicly and commercially available which allow a skilled artisan to access this data provided in a computer readable medium and analyze it for molecular modeling and/or RDD (rational drug design). See, e.g., (Mary Ann Liebert (Publishers) 1995).

[00188] The present invention further provides systems, particularly computer-based systems, which contain the sequence and/or diffraction data described herein. Such systems are designed to do structure determination and RDD for MGLL or at least one subdomain thereof. Non-limiting examples are microcomputer workstations available from Silicon Graphics Incorporated and Sun Microsystems running UNIX based, Windows NT or IBM OS/2 operating systems.

[00189] A variety of comparing means can also be used to compare a target sequence or target motif with the data storage means to identify structural motifs or electron density maps derived in part from the atomic coordinate/X-ray diffraction data. A skilled artisan can readily recognize that any one of the publicly available computer modeling programs can be used as the search means for the computer-based systems of the present invention.

Integrated Procedures Which Utilize the Present Invention

[00190] Molecular modeling is provided by the present invention for rational drug design (RDD) of mimetics and ligands of MGLL. As described above, the drug design paradigm uses computer-modeling programs to determine potential mimetics and ligands which are expected to interact with sites on the protein. The potential mimetics or ligands are then screened for activity and/or binding and/or interaction. For MGLL-related mimetics or ligands, screening methods can be selected from assays for at least one biological activity of MGLL, e.g., such as hydrolysis by MGLL.

[00191] Thus, the tools and methodologies provided by the present invention may be used in procedures for identifying and designing ligands which bind in desirable ways with the target. Such procedures utilize an iterative process whereby ligands are synthesized, tested and characterized. New ligands can be designed based on the information gained in the testing and characterization of the initial ligands and then such newly identified ligands can themselves be tested and characterized. This series of processes may be repeated as many times as necessary to obtain ligands with the desirable binding properties.

The following steps (1-7) serve as an example of the overall procedure:

1. A biological activity of a target is selected (e.g., hydrolysis by MGLL).

2. A ligand is identified that appears to be in some way associated with the chosen biological activity (e.g., the ligand may be an inhibitor of a known activity). The activity of the ligand may be tested by in vivo and/or in vitro methods. A ligand of the present invention can be, but is not limited to, at least one selected from a lipid, a nucleic acid, a compound, a protein, an element, an antibody, a saccharide, an isotope, a carbohydrate, an imaging agent, a lipoprotein, a glycoprotein, an enzyme, a detectable probe, and antibody or fragment thereof, or any combination thereof, which

can be detectably labeled as for labeling antibodies. Such labels include, but are not limited to, enzymatic labels, radioisotope or radioactive compounds or elements, fluorescent compounds or metals, chemiluminescent compounds and bioluminescent compounds. Alternatively, any other known diagnostic or therapeutic agent can be used in a method of the invention. Suitable compounds are then tested for activities in relationship to the target. Complexes between MGLL and ligands are made either by co-crystallization or more commonly by diffusing the small molecule ligand into the crystal. X-ray diffraction data from the complex crystal are measured and a difference electron density map is calculated. This process provides the precise location of the bound ligand on the target molecule. The difference Fourier is calculated using measure diffraction amplitudes and the phases of these reflections calculated from the coordinates.

3. Using the methods of the present invention, X-ray crystallography is utilized to create electron density maps and/or molecular models of the interaction of the ligand with the target molecule. The entry of the coordinates of the target into the computer programs discussed above results in the calculation of most probable structure of the macromolecule. These structures are combined and refined by additional calculations using such programs to determine the probable or actual three-dimensional structure of the target including potential or actual active or binding sites of ligands. Such molecular modeling (and related) programs useful for rational drug design of ligands or mimetics are also provided by the present invention.

4. The electron density maps and/or molecular models obtained in Step 3 are compared to the electron density maps and/or molecular models of a non-ligand containing target and the observed/calculated differences are used to specifically locate the binding of the ligand on the target or subunit.

5. Modeling tools, such as computational chemistry and computer modeling, are used to adjust or modify the structure of the ligand so that it can make additional or different interactions with the target. The ligand design uses computer-modeling programs which calculate how different molecules interact with the various sites of the target, subunit, or a fragment thereof. Thus, this procedure determines potential ligands or ligand mimetics.

6. The newly designed ligand from Step 5 can be tested for its biological activity using appropriate in vivo or in vitro tests, including the high-throughput screening methods discussed above. The potential ligands or mimetics are then screened for activity relating to MGLL, or at least a fragment thereof. Such screening methods are selected from assays for at least one biological activity of the native target. The resulting ligands or mimetics, provided by methods of the present invention, are useful for treating, screening or preventing diseases in animals, such as mammals (including humans).

7. Of course, each of the above steps can be modified as desired by those of skill in the art so as to refine the procedure for the particular goal in mind. Also, additional X-ray diffraction data may be collected on MGLL, MGLL/ligand complexes, MGLL structural target motifs and MGLL subunit/ligand complexes at any step or phase of the procedure. Such additional diffraction data can be used to reconstruct electron density maps and molecular models, which may further assist in the design and selection of ligands with the desirable binding attributes.

[00192] It is to be understood that the present invention is considered to include stereoisomers as well as optical isomers, e.g., mixtures of enantiomers as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in selected compounds, ligands or mimetics of the present series.

[00193] Some of the compounds or agents disclosed or discovered by the methods herein may contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass all such possible forms as well as their racemic and resolved forms and mixtures thereof. When the compounds described or discovered herein contain olefinic double bonds or other centers of geometric asymmetry, and unless otherwise specified, it is intended to include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well.

Examples

[00194] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the present invention and practice the claimed methods. The following working

examples therefore, specifically point out preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

BLAST search and sequence alignment

[00195] The reference sequences for MGLL Isoform 2 (Karlsson et al. 2001) and Isoform 1 (Wall et al. 1997) are shown in Figure 1: A and Figure 1: B, respectively . Note that the sequences of MGLL Isoform 2 and MGLL Isoform 1 are 100% identical, except that MGLL Isoform 1 has an additional 10 amino acids at the N-terminus. The alignment for MGLL Isoform 2 and MGLL Isoform 1 is shown in Figure 1: C. The numbering of amino acids for MGLL Isoform 2 (SEQ ID NO: 1) was used throughout the following description to refer to amino acids in the engineered constructs of the present invention.

[00196] A BLAST search (Altschul et al. 1990) against the sequence data set deposited in the Protein Data Bank (Sussman et al. 1998) was conducted to identify a protein of known crystal structure with reasonable sequence homology to MGLL. The closest relative to MGLL found in the Protein Data Bank was RsbQ, a stress-response regulator in Bacillus subtilis (Kaneko et al. 2005). RsbQ shares 25 % sequence identity with human MGLL. RsbQ also had the highest sequence identity and smallest insertions and deletions relative to MGLL of any structure available in the PDB at the time of this work. The protein RsbQ, PDB ID 1wom (Kaneko et al. 2005), was used as a template. The sequences of RsbQ and MGLL isoform 2 were aligned using the ClustalW software (Thompson et al. 1994; Higgins et al. 1996). RsbQ is a α/β hydrolase with a catalytic triad composed of Ser96, His247 and Asp219. The Asp-His-Ser catalytic triad of MGLL matched the corresponding residues in RsbQ. This alignment was duplicated within the GeneMine software (Lee and Irizarry 2001) and adjusted to eliminate insertions or deletions within elements of secondary structure without disturbing the alignment of the catalytic residues. The final alignment of human MGLL isoform 2 and RsbQ is shown in Figure 2A. Although the sequence identity between MGLL and RsbQ is low for generating a homology model for MGLL, it was estimated that a low accuracy model would be sufficient to identify hydrophobic residues in the outside of the molecule that could trigger aggregation.

Homology model

[00197] A homology model of MGLL was created using RsbQ as a template and the "quick refine" option in GeneMine software (Figure 2A) (Levitt 1992) (Lee and Irizarry 2001). The model shows a α/β hydrolase domain and a cap-domain composed of 4 helices. Helix 151-185 of the cap-domain shows amphiphilic properties, characteristic of proteins involved in lipid binding. The helix contains a slight bend due to the presence of a proline residue at position 172. 14 out of the 32 residues constituting the helix are hydrophobic (Figure 2A). 7 of the hydrophobic residues are Leucines (Leu 152, 157, 159, 171, 174, 176, 184). In the model, the side chains of Leu 159 and 176 point towards the solvent, possibly constituting a recognition site for the interaction of MGLL with the membrane. It should be noted that because of the low accuracy of the model, other Leucine residues, whose side chains appear to point toward the core of the molecule in the homology model, may also contribute to the hydrophobic properties of MGLL and trigger the need for detergent.

Construct design

[00198] A library of constructs was designed in an effort to generate MGLL protein that would be less prone to aggregation, not require detergent for purification, and be more suitable for high-throughput screening and crystallization. A total of 52 mut-MGLL constructs were generated by mixing and matching the cap-domain mutations, surface mutations, and truncations (Table 1). Seven different hydrophobic Leucine residues (designated as Leu or L) of the cap-domain were selected for mutations (Leu 162, 167, 169, 171, 174, 176, and 184). The Leucine residues were replaced by Serine (designated as Ser or S), Glutamine (designated as Gln, or Q), or Arginine (designated as Arg or R). In addition, eight Lysine residues (designated as Lys or K) were identified at the surface of the MGLL homology model (Lys 36, 160, 165, 188, 206, 226, 259 and 269) and were mutated to Alanine (designated as Ala or A) to increase crystal contacts, promote crystallization, and improve crystal quality. The surface mutations were introduced into the mut-MGLL (hMGLL 1-303 L169S, 176S) double cap-domain mutant construct either independently or in combination with other surface mutations. N-terminal and C-terminal truncation constructs were also designed (Table 1). The N-terminus was truncated at amino acid 9, 19, 26, and 33. The C-terminus was truncated at 297 and 292. The N-

terminal and C-terminal truncations were introduced independently or combined with other truncations and were introduced into the mut-MGLL (hMGLL 1-303 L169S, 176S) double cap-domain mutant construct (Table 1). All constructs, including the wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) construct, were engineered with an N-terminal histidine tag (His tag) followed by a TEV protease cleavage site so that the tag could be cleaved after purification. TEV is highly site-specific protease that is found in the Tobacco Etch Virus (Invitrogen).

Cloning

[00199] The cDNA for MGLL was cloned from human brain DNA and used as a template to generate a PCR fragment of full-length wt-MGLL corresponding to amino acids 1-303 of the reference sequence for human MGLL Isoform 2 (SEQ ID NO: 1) The sequences for the 3' and 5' PCR primers are shown below.

5' primer: gagaatttggtattttcaaggtatgccagaggaaagttcccc

3' primer: tggatgtgtatgtttctatcagggtggggacgaagttcc

[00200] The PCR product was purified (GENECLEAN SPIN kits, Qbiogene, Inc), treated with T4 polymerase (New England Biolabs), ligated into the modified pENTR.11cLIC vector, and transformed into TOP10 one shot competent cells (Invitrogen). After sequence confirmation, the mutations were added by Quickchange mutagenesis, (Stratagene). The sequence confirmed plasmids were purified for transfection into insect cells using the BaculoDirect Baculovirus Expression System (Invitrogen). All of the resulting proteins contained an N-terminal His tag followed by a TEV cleavage site and the amino acids of the different MGLL constructs. Viral stock was propagated for two more amplifications at a low multiplicity of infection (MOI) to render a P2 virus stock.

Recombinant production of wt-MGLL and mut-MGLL

[00201] Large-scale expression was carried out in 2-liter shake flasks or WAVE bioreactors (WAVE Products Group, GE Healthcare). The P2 virus was expanded to generate a high titer P3 stock by infecting Sf9 cells in suspension at MOI of 0.3 and harvesting the virus after 72 hours. Cell paste for wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) and mut-MGLL were obtained by infecting Sf9 cells at a density of 1.5×10^6

cells/ml with a MOI of 1. Infected cultures were maintained at 27 °C under constant shaking at 140 rpm. Cells were harvested 65-72 hours post-infection by centrifugation at 1000 X g for 10 minutes at 4°C. Cell viability were determined by Guava ViaCount or Trypan Blue and routinely were between 60 and 80% at time of harvest. Cell pellets were washed once in phosphate-buffered saline with broad range protease inhibitors and stored at –80 °C.

Purification of wild-type MGLL (wt-MGLL)

[00202] A pilot purification of wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3), performed in the complete absence of detergent, generated no protein (data not shown). A second purification of wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) was done with detergent in the lysis buffer only. Frozen cell pellets for wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) were thawed, resuspended, and lysed in Bugbuster® lysis buffer for 1 hour at 4 °C. Bugbuster® lysis buffer is a proprietary lysis buffer from Invitrogen that contains detergent. The lysate was clarified by centrifugation at 40,000 x g for 1 hr. No detergent was added at this point or during the rest of the purification. From this point forward, the purification protocol and buffers were the same as described below for mut-MGLL. An average of 2.2 mg of wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) per liter of cell culture was obtained. Further analysis by size exclusion chromatography showed complete aggregation of the purified wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3), which confirmed the need for detergent for wt-MGLL purification as previously described in the literature.

Purification of mut-MGLL

[00203] Mutant MGLL (mut-MGLL) constructs were purified in the absence of detergent. Frozen cell pellets were thawed and resuspended in buffer A (50 mM Hepes buffer pH 7.5, 400 mM NaCl, 5 % glycerol, 0.05% BME, 1 X Complete EDTA-free protease inhibitor cocktail tablets (Roche)), dounce homogenized and mechanically lysed with a microfluidizer processor (Microfluidics). The extract was clarified by centrifugation at 40,000 x g for 1 hr. The cleared lysate was loaded on a 1 ml His-Trap FF Crude column (GE-Healthcare) at 4°C using the AktaXpress system. For larger preparations, a 5 ml His-Trap FF Crude column was used. The column was washed with 10-15 column volumes (CV) of buffer A containing 30 mM imidazole and mut-MGLL

was eluted with 5 CV of 50 mM Hepes buffer pH 7.5, 400 mM NaCl, 5 % glycerol, 0.05% BME, 400 mM imidazole. In most preparations, 30 mM imidazole was included in Buffer A from the beginning of thepreparation to reduce non-specific binding on the His-Trap column. In addition, a slightly lower imidazole concentration of 350 mM was used in the final elution during later preparations to further improve purity. Glycerol concentration was also reduced to 4% to avoid back pressure problems on the AktaXpress, afer it wasdetermined that mut-MGLL constructs were stable in 2% glycerol. The elution peak was directly loaded on a Superdex 200 HR 16/60 preequilibrated with 50 mM Hepes pH7.5 buffer containing 200 mM NaCl, 2 % glycerol, 2mM DDT, 2mM EDTA.DTT. Fractions were analysed by SDS-PAGE. Fractions containing mut-MGLL were pooled. Purification yields were determined by Bradford assay using the protein assay kit from BioRad according to manufacturer's instruction with BSA as a standard (Bradford 1976).

[00204] The majority of constructs containing N-terminal and/or C-terminal truncations did not have high enough expression to allow for purification of soluble protein (Table 1).

[00205] Constructs that were evaluated containing just the cap-domain mutations generated between 0.7 and 4.5 mg/L, except the mut-MGLL construct containing the L174Q mutation, which showed no expression (Table1). Analysis by size exclusion chromatography showed that the purified mut-MGLL proteins were 90% monomeric and only 10% aggregated compared to 100% aggregation for wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) (Figure 1A), which indicated that the mutations significantly improved protein solubility and eliminated the need for detergent during purification.

[00206] Constructs that were evaluated with a combination of cap-domain and surface mutations showed expression levels between 0.5 and 3.6 mg/L and were also ~ 90% monomeric on SDS Page as well (data not shown).

TEV Cleavage

[00207] To remove the N-terminal His tag, 0.2 units of TEV Protease for each ug of mut-MGLL were added to the mut-MGLL pool. The reaction was done overnight at 4°C. Cleavage of the histidine tag was monitored by SDS-PAGE.

Complex formation

[00208] For crystallization trials, compounds were added in a 1:2 molar ratio (mut-MGLL: compound). TEV cleaved mut-MGLL was first diluted to 0.3 mg/ml with buffer containing 50 mM Hepes pH 7.5, 200mM NaCl, 2% Glycerol, 2 mM DTT, and 2 mM EDTA. Compounds were added to the diluted protein and the mixture was incubated overnight at 4°C. After the overnight incubation, the mixture was concentrated to a final protein concentration of 6.0 mg/ml using a Ultrafree membrane (10KDa cut-off). At this stage the purity was > 98% as determined by SDS-PAGE and the protein was ready for crystallization trials.

Circular Dichroism (CD)

[00209] One construct, TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S) (SEQ ID NO: 5), was selected for further characterization by CD to ensure that the mutations introduced did not adversely affect protein conformation and activity. Circular dichroism experiments were performed on a Circular Dichroism Spectrometer Model 202 from Aviv Instruments Inc. The CD scans of wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) and TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S) (SEQ ID NO: 5) (5 μM protein in 10 mM cacodylic acid pH 7 and 140 mM NaCl) were measured from 200 to 260 nm. Temperature melts were monitored at 210 nm. The CD spectra were converted to molar ellipticity and are shown in Figure 1B.

[00210] The CD scans for the wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) purified in the presence of detergent and TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S) (SEQ ID NO: 5) were similar indicating that the two enzymes had a similar conformation (Figure 1B). The scans were characteristic of proteins with high alpha-helical content as expected for a lipase.

Kinetic Analysis

[00211] To ensure that the mutations engineered did not adversely affect protein activity, a number of the newly generated MGLL mutants were analyzed using by enzyme assay and then compared to wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3). A small fluorescent substrate, 4-methyl coumarin butyrate (4MC-B) was used to compare the activity of the engineered mutants to the activity of wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3). The catalytic efficiency (k_{cat}/K_M) for the hydrolysis of the 4MC-B was similar

for wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) and all MGLL mutants tested (Table 2). A larger more aliphatic fluorescent substrate, Coumarin Arachidonate (C-A), structurally more closely related to the MGLL natural substrate, 2-AG, was used to compare the activity of wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) to TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S) (SEQ ID NO: 5). The catalytic efficiency for the hydrolysis of the C-A substrate was equivalent between wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) and TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S) (SEQ ID NO: 5), which confirmed that the mutations did not affect MGLL activity (Table 2).

[00212] The Michaelis-Menten parameters for the hydrolysis of 4-methylcoumarin butyrate (4MC-B) and coumarin arachidonate (C-A) substrate were determined using 4-5 nM of MGLL in 20 mM Pipes pH 7 and 150 mM NaCl at 37 °C. The change in fluorescence due to substrate hydrolysis was monitored using excitation/emission wavelengths of 335/440 in a Safire II instrument from Tecan. The hyperbolic rates versus substrate concentration curves for the hydrolysis of 4MC-B were fit to the Michaelis-Menten equation using Excel.

$$v = \frac{V_{max} * [S]}{K_M + [S]}$$

[00213] The solubility limit of coumarin arachidonate (C-A) substrate did not allow for the determination of K_M and k_{cat}. The apparent k_{cat}/K_M ratio for the hydrolysis of C-A was determined at $[S] << K_M$. The apparent K_M for C-A was estimated to be >30 μM. The k_{cat}/K_M values reported are the average from independent values determined from five substrate concentrations ranging from 700 to 40 nM.

Thermal stability

[00214] The Thermofluor® assay is a powerful tool to screen for small molecule inhibitors interacting with a protein's active site or allosteric site. The assay detects small changes in the intrinsic melting temperature of proteins based on binding of ligands. Compounds that interact preferentially with the native form of the protein will increase the T_m, the temperature at which half of the protein is unfolded (Pantoliano et al. 2001). The technique monitors changes in the fluorescent intensity of dyes such as 1-anilinonaphthalene-8-sulfonic acid (1,8-ANS). The fluorescent dyes are quenched in

aqueous environments but increase in fluorescence on binding to the hydrophobic core of denatured proteins.

[00215] Thermofluor® assays were conducted to characterize wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) and mut-MGLL (hMGLL 1-303 L169S, L176S) and evaluate if the MGLL mutants could be used for high-throughput screening using Thermofluor®. Three microliters of protein at a concentration of 0.05 mg/ml in 50 mM Pipes pH 7, 200 mM NaCl, 100 μM 1,8-ANS, and 0.001% Tween was added to pre-dispensed compound plates. Wells were overlaid with silicone oil (1 μL, Fluka, type DC 200) to prevent evaporation. Final compound concentrations varied from 150 to 0.15 μM. Assay plates were heated at a rate of 1°C/min for all experiments over a temperature range sufficient to measure protein unfolding. Fluorescence was measured by continuous illumination with UV light (Hamamatsu LC6) supplied via fiber optic and filtered through a custom band-pass filter (380-400 nm; >6 OD cutoff). Fluorescence emission was detected by measuring light intensity using a CCD camera (Sensys, Roper Scientific) filtered to detect emission at 500 ± 25 nm, resulting in simultaneous and independent readings of all 384 wells. One or more images were collected at each temperature, and the sum of the pixel intensity in a given area of the assay plate was recorded vs temperature, and fit to standard equations to yield the T_m.

[00216] The study using Thermofluor® showed that wt-MGLL (hMGLL 1-303) (SEQ ID NO: 3) had a very poor transition, characteristic for aggregated or unfolded proteins (Figure 5). TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S) (SEQ ID NO: 5), however, gave a strong transition with a T_m value of 56.7 °C, indicating that the engineered mutation produced a more soluble MGLL protein that was suitable for high-throughput screening.

Crystallization

[00217] All mutants were purified according to the procedure described above and submitted for crystallization trials. Purity greater than 95% as determine by SDS Page was achieved for all constructs. Combinations of high-throughput and manual crystallization screens were used. Several constructs generated crystals but only crystallization conditions containing detergent yielded crystals (data not shown). Apo

proteins generated crystals diffracting between 8.0 Å and 9.0 Å only, despite extensive optimization trials. Co-crystallization with methyl arachidonyl fluorophosphonate (MAFP) did not significantly improve diffraction.

[00218] Co-crystallization of TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S, K36A) (SEQ ID NO: 7) with Compound 1 generated crystals that diffracted to 2.3 Å, but with diffused scattering in one orientation. Further optimization experiments did not improve data quality with that complex. High quality diffraction was achieved by co-crystallization of TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S, K36A) (SEQ ID NO: 7) with Compound 2, a compound that was 10 fold more potent than Compound 1. Crystallization of the TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S, K36A) (SEQ ID NO: 7) and Compound 2 complex was achieved at 22°C with a hanging droplet containing 6 mg/ml protein solution combined with a modified well solution containing 8% polyethylene glycol monomethyl ether 5000 molecular weight (PEG MME 5K), 100mM Na Citrate pH 5.5 and 2% n-Octyl-Beta-D-Glucopyranoside (OBG), which was suspended over a well solution containing 6% PEG MME 5K, 100mM Na Citrate pH 5.5 and 2% OBG. Crystals, however, were not generated spontaneously. A seed solution generated from poor quality crystals obtained previously was used to seed crystallization droplets. The optimal volume ratios for obtaining good quality crystals were 1 ul protein solution, 0.5 ul modified well solution, and 0.2 ul diluted seed stock solution. Any increase in protein concentration resulted in heavy showers and stacked plate crystals despite adjustments in crystallization reagent concentration. Protein supplied at concentrations higher than 6 mg/ml and diluted to 6 mg/ml before crystallization trials also resulted in heavy crystal showers. Final resolution was 1.3 Å for the TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S, K36A) (SEQ ID NO: 7) and Compound 2 complex.

Structure Determination

[00219] Crystals were harvested, transferred to 16% PEG MME 5K, 100 mM Na-MES pH 6.0, 25% glycerol and flash frozen in liquid nitrogen. Datasets were collected on a Rigaku M007HF generator at 100K or at the ID19 beamline at IMCA-CAD at the Advanced Photon Source, Chicago. A summary of the data-collection statistics is in Table 3. The data was processed in the *HKL2000* suite (Otwinowski and Minor 1997) and the

structure was solved by molecular replacement using a modified structure of "*Non-haem bromoperoxidase BPO-A1*" (PDB ID 1A8Q) as search model in *PHASER* (McCoy et al. 2007). The initial rebuilding was performed using the default protocol in the AutoBuild Wizard in *PHENIX* (Adams et al. 2002; Adams et al. 2004; Terwilliger et al. 2008), refinement and automated water picking was carried out in *PHENIX.refine* (Adams et al. 2002; Adams et al. 2004; Terwilliger et al. 2008); *Coot* (Emsley and Cowtan 2004) was employed for model building, ligand placement and manual assignment of water molecules. Ligand restraints were generated in *PHENIX.elbow* (Adams et al. 2002; Adams et al. 2004) and the final model validated using tools implemented in *Coot*; Figures were generated in *PyMol* (DeLano 2002). Coordinates for the structure of the complex of TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S, K36A) (SEQ ID NO: 7) with Compound 2 are included as Table 5.

Overall Structure of MGLL

[00220] MGLL is part of the sub-family of lipid hydrolases, which in turn is part of a larger family of α/β-hydrolases with diverse catalytic functions. Members of this super-family include: ester hydrolases, lipid hydrolases, thioester hydrolases, peptide hydrolases, haloperoxidases, dehalogenases epoxide hydrolases and C-C bond breaking enzymes (Holmquist 2000). All of these enzymes share a common folding motif called the α/β-hydrolase fold (Ollis et al. 1992; Heikinheimo et al. 1999). This fold is characterized by eight β-sheets flanked on both sides by α-helices. β-sheet 2 is antiparallel to the other sheets and the first and last helix (α1 or αA and α6 or αF) are located on one side of the sheets, whereas the remainder of the helices are present on the opposite side. The α/β-hydrolase fold tolerates a vide variety of inserts without losing the core folding motif. These inserts serve to modify and regulate the catalytic activity of the respective proteins. They can occur in several locations, but are mostly located in a loop region between strand β6 and helix α6.

[00221] Herein is described the structure of the inhibitor bound form of human MGLL Isoform 2 (TEV cleaved mut-MGLL (hMGLL 1-303 L169S, L176S, K36A) (SEQ ID NO: 7) with Compound 2), which has been determined by molecular replacement to a resolution of 1.3 Å. The structure of MGLL conforms very closely to the canonical α/β-hydrolase fold. The structure is characterized by eight β-sheets, which form a partial β-

barrel adorned on both sides with eight α-helices. MGLL contains two additional helices (α4 ($\alpha D'_1$) and α5 (D'_2)), which are part of the cap-domain and are inserted in the protein sequence between sheet β6 and helix α6 (αD). Helices α1 (αA) and α8 (αF) are located on the concave side of the barrel and helices α2 (αB), α3 (αC), α6(D) and α7(E) are on the convex side. Both cap-domain helices are oriented in front of the molecule perpendicular to the plane of the β-barrel.

[00222] Interestingly the overall structure of this mammalian MGLL is closer to bacterial lipases than any mammalian lipase when the structure is compared to the latest release of the Protein Databank using the protein structure-matching tool (SSM) at the European Institute of Bioinformatics (EBI) (Boutselakis et al. 2003). The 3D-alignment produces several close hits against bacterial Bromoperoxidases, Chloroperoxidases and Arylesterases. The same hits were also produced by a PHI-blast search of the Protein Databank against the protein sequence alone. Since no similar 3D-hits were found against any diacylglycerol lipases or triacylglycerol lipases, it can be inferred that the structural requirements for cleavage of triacylglycerol and diacylglycerol esters are substantially different from those required for the cleavage of mono-glycerol esters. It appears as if these classes of proteins, even though they perform similar functions, represent a different branch on the evolutionary tree of lipases.

[00223] Superposition of several hits from the 3D-alignment (Chloroperoxidase L, PDBID:1A88; Bromoperoxidase A1, PDBID:1A8Q; *P. putida* Esterase, PDBID:1ZOI; Gamma Lactamase, PDBID:1HKH) shows that the α/β-hydroxylase core without the cap-domain superimposes very well (Table 4 and Figure 10). The largest differences are seen in the first 20 residues of the N-terminus of MGLL, for which there is no complement in the other proteins. Further differences are evident in helix α6 (D). In MGLL α6 continuously spans approximately 20 residues, whereas in the other structures it is partially unraveled and split into two pieces connected by a short loop.

MGLL Binding Pocket

[00224] Compound 2 is bound in an extended and closed binding pocket, which is located between helices α4, α6, α7 and α5. Even though the solvent accessible surface area of the compound (712$Å^2$) is fairly large, it is almost completely enclosed by the

protein. The protein accomplishes this by employing a so-called "cap-domain", "lid", or "flap", which regulates access to the binding site based on the membrane bound state of the protein. The cap-domain is compromised of residues from helices α4 to α5 (also referred to as $\alpha D'_1$ and $\alpha D'_2$ throughout the literature). The catalytic triad of MGLL consists of residues Ser122, Asp239, His269 and is located in the center of the binding pocket. The catalytic nucleophile Ser122 resides on a tight turn between strand β5 and helix α3, which is also commonly referred to as the "nucleophilic elbow". The structurally conserved network of hydrogen-bond donors, which comprises the nucleophilic elbow and the loop connecting α1 and β3 (Gly50, Ala51, Met123 and Gly124) is called the oxyanion hole and serves to stabilize the anionic transition state of the catalytic reaction. The amide carbonyl of Compound 2 points into the oxyanion hole and forms a critical hydrogen bond with the backbone amide nitrogen of Met123 adjacent to the catalytic Serine. The azetidine-piperazine-pyrazine part of the ligand projects into a narrow amphiphilic pocket and fills the available space almost completely. This portion of the ligand does not participate in hydrogen bond interactions with the protein, but one of the pyrazine nitrogens forms an H-bond to a water-network involving two buried water molecules and the side-chains of residues Glu53, Arg57 and His272. A face-to-face π-stacking interaction with of the pyrazine ring with Tyr194 provides further interaction energy.

[00225] The binding pocket on the benzoxazole-cyclohexane site of the ligand is less occluded than its counter part on the opposite site. The benzoxazole portion of the ligand is located in a hydrophobic environment constituted mainly from side chains of aliphatic residues. The cyclohexane portion projects into a more spacious void, and along with the benzoxazole, is the only part of the inhibitor, which is accessible by solvent in the protein bound state. These parts of the ligand form mostly van der Waals interactions with the protein. The cyclohexane part of the molecule is less well ordered than the remainder of the ligand. This can be explained by the fact that this region of the cap-domain (α4 and part of the loop connecting to α5) with which the inhibitor interacts, is displays significantly higher temperature factors as compared to the rest of the protein. The elevated temperature factors signify the inherent flexibility of this region, which probably

facilitates its displacement from the surface of the protein during ligand binding and release.

Enabling mutations

[00226] In order to obtain the MGLL structure several enabling mutations were required. Two mutations in the lid sub-domain (L169S and L176S) helped to increase solubility of the protein enough to prevent aggregation and to eliminate the need for detergents in protein purification. L169S is located at the C-terminal end of helix α4 ($\alpha D'_1$) and L176S on a loop connecting α4 to α5. Interestingly, the cap-domain in the engineered protein still contains quite a few surface exposed aliphatic residues, but the mutations are apparently sufficient to reverse the inherent lipophilic character of the protein enough to prevent aggregation in solution.

[00227] The K36A surface mutation was inspired by a series of reports indicating that the replacement of flexible residues with high conformational entropy present on the surface of proteins helps to promote crystallization under certain circumstances (Longenecker et al. 2001; Mateja et al. 2002). The K36A mutation is present on a loop connecting sheets β2 and β3. This loop interacts with the cap-domain of a neighboring symmetry related molecule between Val170 and Pro172. Analysis of this packing interaction reveals that the Lysine would have fit snugly into this packing interface, so the immediate reason necessitating its absence for crystallization is not obvious.

[00228] The mutation appears nevertheless to be beneficial, since this particular part of the cap-domain exhibits relatively high temperature factors and is less well ordered than other parts of the molecule. It is conceivable that this high dynamic mobility would cause the lid to clash into Lys36 in certain parts of the conformational pool. The K36A mutation would eliminate this potential for clashes and may thus contribute to the successful crystallization of the molecule.

TABLES

Table 1:

Engineered forms of MGLL

Cap Mutations	Purification yield mg/L
mut-MGLL (1-303) L169S, L176S	4.5
mut-MGLL (1-303) L167Q	2.3
mut-MGLL (1-303) L171Q	0.7
mut-MGLL (1-303) L174Q	0
mut-MGLL (1-303) L167Q, L171Q	5
mut-MGLL (1-303) L167Q, L174Q	7
mut-MGLL (1-303) L171Q, L174Q	1.5
mut-MGLL (1-303) L167Q, L171Q, L174Q	0
mut-MGLL (1-303) L169Q, L176Q	*N.D.
mut-MGLL (1-303) L169S	*N.D.
mut-MGLL (1-303) L176S	*N.D.
mut-MGLL (1-303) L162S	*N.D.
mut-MGLL (1-303) L162Q	*N.D.
mut-MGLL (1-303) L162R	*N.D.
mut-MGLL (1-303) L184S	*N.D.
mut-MGLL (1-303) L184Q	*N.D.
mut-MGLL (1-303) L184R	*N.D.
mut-MGLL (1-303) L169S	*N.D.
mut-MGLL (1-303) L169Q	*N.D.
mut-MGLL (1-303) L169R	*N.D.
mut-MGLL (1-303) L176S	*N.D.
mut-MGLL (1-303) L176Q	*N.D.
mut-MGLL (1-303) L176R	*N.D.
mut-MGLL (1-303) L167S	*N.D.
mut-MGLL (1-303) L167R	*N.D.
mut-MGLL (1-303) L171S	*N.D.
mut-MGLL (1-303) L171R	*N.D.
mut-MGLL (1-303) L174S	*N.D.
mut-MGLL (1-303) L174R	*N.D.

Cap Mutations + Surface Mutations	Purification yield mg/L
mut-MGLL (1-303) L169S, L176S, K36A	3.6
mut-MGLL (1-303) L169S, L176S, K160A	0.7
mut-MGLL (1-303) L169S, L176S, K165A	0.5
mut-MGLL (1-303) L169S, L176S, K226A	2.3
mut-MGLL (1-303) L169S, L176S, K36A, K226A	1.5
mut-MGLL (1-303) L169S, L176S, K36A, K188A	*N.D.
mut-MGLL (1-303) L169S, L176S, K36A, K206A	*N.D.
mut-MGLL (1-303) L169S, L176S, K36A, K269A	*N.D.
mut-MGLL (1-303) L169S, L176S, K188A	*N.D.
mut-MGLL (1-303) L169S, L176S, K206A	*N.D.
mut-MGLL (1-303) L169S, L176S, K259A	*N.D.

Cap Mutations + Truncations	Purification yield mg/L
mut-MGLL (9-303) L169S, L176S	2
mut-MGLL (9-297) L169S, L176S	1
mut-MGLL (1-292) L169S, L176S	0.5
mut-MGLL (19-303) L169S, L176S	0
mut-MGLL (19-297) L169S, L176S	0
mut-MGLL (19-292) L169S, L176S	0
mut-MGLL (26-303) L169S, L176S	0
mut-MGLL (26-297) L169S, L176S	0
mut-MGLL (26-292) L169S, L176S	0
mut-MGLL (33-303) L169S, L176S	0
mut-MGLL (33-297) L169S, L176S	0
mut-MGLL (33-292) L169S, L176S	0

*N.D. is Not Determined

Table 2:

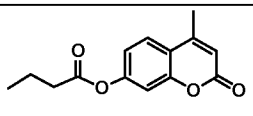
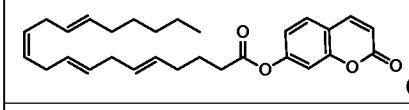
 4MC-B			
Construct	K_M (uM)	K_{cat} ($uM^{-1}min^{-1}$)	K_{cat}/K_M ($uM^{-1}min^{-1}$)
wt-MGLL.1-303	162	68	0.42
CAP MUTANTS			
Construct	K_M (uM)	K_{cat} ($uM^{-1}min^{-1}$)	K_{cat}/K_M ($uM^{-1}min^{-1}$)
mut-MGLL. 1-303, L169S, L176S	136	48	0.35
mut-MGLL 9-303, L169S, L176S	88	27	0.31
mut-MGLL 9-297, L169S, L176S	126	26	0.21
mut-MGLL 1-303, L171Q	105	51	0.48
mut-MGLL 1-303, L167Q, L171Q	84	59	0.71
mut-MGLL. 1-303, L167Q, L174Q	84	70	0.83
mut-MGLL 1-303, L171Q, L174Q	89	47	0.52
CAP + SURFACE MUTANTS			
Construct	K_M (uM)	K_{cat} ($uM^{-1}min^{-1}$)	K_{cat}/K_M ($uM^{-1}min^{-1}$)
mut-MGLL 1-303, L169S, L176S, K36A	124	51	0.41
mut-MGLL. 1-303, L169S, L176S, K160A	90	30	0.33
mut-MGLL. 1-303, L169S, L176S, K165A	137	27	0.2
mut-MGLL 1-303, L169S, L176S, K226A	110	38	0.35
mut-MGLL 1-303, L169S, L176S, K36A, K226A	123	30	0.25
 C-A			
Construct	K_{cat}/K_M ($uM^{-1}min^{-1}$		
wt-MGLL 1-303	0.09		
mut-MGLL 1-303, L169S, L176S	0.1		

Table 3:

	mut-MGLL complex with Compound 2
Data collection	
Wavelength (Å)	1.0
Resolution (Å)	1.3
Space group	$C222_1$
Unit cell parameters (Å)	a = 93.95, b = 128.45, c = 60.6
No. of reflections	336035
No. of unique reflections	79954
Redundancy	4.2 (1.8)
Completeness (%)	89.2 (53.3)
R_{merge}	6.2 (31.9)
I/σ(I)	19.0 (1.75)
Refinement	
No. of reflections	75577
No. of reflections in R_{free} set	1896
Total No. of non H atoms	2720
No. of protein atoms	2320
No. of ligand atoms	33
No. of solvent molecules	377
R-factor (%)	17.8
R_{free} (%)	20.6
R.M.S. Deviation from ideal geometry	
Bonds (Å)	0.006
Angles (°)	1.050
B-factors ($Å^2$)	
Protein	14.8
Ligand	10.2
Ramachandran Plot	
Preferred Regions (%)	96.6
Allowed regions (%)	3.0
Disallowed regions (%)	0.4

Table 4:

	Chloroperoxidase L	**Bromoperoxidase A1**	***P.fluorescens* Arylesterase**	**Gamma Lactamase**
Distance [Å]	1.23	1.27	1.29	1.44
No. of matching residues	168	165	175	173

Table 5:

```
CRYST1   93.947  128.145   60.602  90.00  90.00  90.00 C 2 2 21
SCALE1      0.010644 -0.000000 -0.000000        0.00000
SCALE2      0.000000  0.007804  0.000000        0.00000
SCALE3      0.000000  0.000000  0.016501        0.00000
ATOM      1  N   PRO A   7     -24.135  50.110  -0.751  1.00 38.62           N
ATOM      2  CA  PRO A   7     -24.819  48.812  -0.835  1.00 48.66           C
ATOM      3  C   PRO A   7     -23.834  47.683  -1.121  1.00 27.13           C
ATOM      4  CB  PRO A   7     -25.762  48.987  -2.031  1.00 56.71           C
ATOM      5  CG  PRO A   7     -25.901  50.460  -2.210  1.00 69.43           C
ATOM      6  CD  PRO A   7     -24.588  51.041  -1.797  1.00 66.62           C
ATOM      7  O   PRO A   7     -23.163  47.709  -2.152  1.00 27.37           O
ATOM      8  N   ARG A   8     -23.737  46.710  -0.219  1.00 19.22           N
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ATOM     12  CG  ARG A   8     -22.085  45.452   2.003  1.00 25.04           C
ATOM     13  CD  ARG A   8     -20.586  45.608   1.857  1.00 23.77           C
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ATOM     15  CZ  ARG A   8     -19.479  44.080   3.453  1.00 18.56           C
ATOM     16  NH1 ARG A   8     -19.744  44.894   4.472  1.00 16.20           N
ATOM     17  NH2 ARG A   8     -18.816  42.959   3.671  1.00 13.17           N
ATOM     18  O   ARG A   8     -24.639  44.451  -1.605  1.00 11.63           O
ATOM     19  N   ARG A   9     -22.589  44.386  -2.546  1.00 17.31           N
ATOM     20  CA  ARG A   9     -23.017  43.667  -3.747  1.00 15.23           C
ATOM     21  C   ARG A   9     -22.202  42.401  -3.960  1.00 12.13           C
ATOM     22  O   ARG A   9     -21.048  42.328  -3.554  1.00 15.48           O
ATOM     23  CB  ARG A   9     -22.851  44.558  -4.984  1.00 20.10           C
ATOM     24  CG  ARG A   9     -23.745  45.788  -5.019  1.00 21.95           C
ATOM     25  CD  ARG A   9     -23.339  46.711  -6.167  1.00 29.40           C
ATOM     26  NE  ARG A   9     -24.116  47.949  -6.182  1.00 31.93           N
ATOM     27  CZ  ARG A   9     -25.269  48.098  -6.824  1.00 41.04           C
ATOM     28  NH1 ARG A   9     -25.782  47.087  -7.507  1.00 25.69           N
ATOM     29  NH2 ARG A   9     -25.911  49.259  -6.786  1.00 35.67           N
ATOM     30  N   THR A  10     -22.815  41.422  -4.621  1.00 13.54           N
ATOM     31  CA  THR A  10     -22.103  40.220  -5.047  1.00 14.38           C
ATOM     32  C   THR A  10     -21.025  40.604  -6.058  1.00 21.65           C
ATOM     33  O   THR A  10     -21.064  41.705  -6.620  1.00 18.22           O
ATOM     34  CB  THR A  10     -23.056  39.216  -5.709  1.00 14.17           C
ATOM     35  OG1 THR A  10     -23.504  39.739  -6.972  1.00 14.78           O
ATOM     36  CG2 THR A  10     -24.260  38.949  -4.824  1.00 13.27           C
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ATOM     38  CA  PRO A  11     -19.002  39.977  -7.280  1.00 20.97           C
ATOM     39  C   PRO A  11     -19.595  40.202  -8.663  1.00 18.43           C
ATOM     40  O   PRO A  11     -18.911  40.714  -9.553  1.00 28.22           O
ATOM     41  CB  PRO A  11     -18.166  38.692  -7.261  1.00 23.08           C
ATOM     42  CG  PRO A  11     -18.376  38.133  -5.880  1.00 20.36           C
ATOM     43  CD  PRO A  11     -19.814  38.445  -5.561  1.00 18.78           C
ATOM     44  N   GLN A  12     -20.857  39.834  -8.837  1.00 16.57           N
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ATOM     46  C   GLN A  12     -22.422  41.311 -10.049  1.00 22.29           C
ATOM     47  O   GLN A  12     -23.222  41.573 -10.953  1.00 24.66           O
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ATOM     49  CG  GLN A  12     -21.571  37.496 -10.571  1.00 15.70           C
ATOM     50  CD  GLN A  12     -21.138  36.897  -9.229  1.00 17.63           C
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ATOM    118  C   PRO A  20     -29.035  35.204   1.093  1.00 10.92           C
ATOM    119  O   PRO A  20     -28.221  34.932   0.209  1.00 10.00           O
ATOM    120  CB  PRO A  20     -30.996  33.714   0.551  1.00 12.85           C
ATOM    121  CG  PRO A  20     -31.910  33.798  -0.652  1.00 12.45           C
ATOM    122  CD  PRO A  20     -31.355  34.929  -1.471  1.00 13.91           C
ATOM    123  N   HIS A  21     -28.659  35.564   2.315  1.00  9.52           N
ATOM    124  CA  HIS A  21     -27.255  35.688   2.652  1.00  8.77           C
ATOM    125  C   HIS A  21     -27.013  35.531   4.145  1.00  8.21           C
ATOM    126  O   HIS A  21     -27.963  35.527   4.940  1.00 11.76           O
ATOM    127  CB  HIS A  21     -26.707  37.044   2.193  1.00 12.50           C
ATOM    128  CG  HIS A  21     -27.346  38.212   2.880  1.00 12.08           C
ATOM    129  ND1 HIS A  21     -28.470  38.836   2.386  1.00 17.03           N
ATOM    130  CD2 HIS A  21     -27.033  38.852   4.032  1.00 18.83           C
ATOM    131  CE1 HIS A  21     -28.819  39.819   3.200  1.00 26.65           C
ATOM    132  NE2 HIS A  21     -27.966  39.847   4.206  1.00 21.10           N
ATOM    133  N   LEU A  22     -25.747  35.406   4.502  1.00  8.64           N
ATOM    134  CA  LEU A  22     -25.311  35.446   5.895  1.00  6.76           C
ATOM    135  C   LEU A  22     -23.982  36.170   5.920  1.00  9.47           C
ATOM    136  O   LEU A  22     -23.294  36.247   4.898  1.00 14.08           O
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ATOM    137  CB  LEU A  22     -25.178  34.038   6.483  1.00 13.24           C
ATOM    138  CG  LEU A  22     -24.073  33.100   6.000  1.00 15.59           C
ATOM    139  CD1 LEU A  22     -22.694  33.547   6.456  1.00 17.18           C
ATOM    140  CD2 LEU A  22     -24.349  31.688   6.516  1.00 20.78           C
ATOM    141  N   VAL A  23     -23.620  36.746   7.058  1.00  6.83           N
ATOM    142  CA  VAL A  23     -22.341  37.409   7.176  1.00  6.32           C
ATOM    143  C   VAL A  23     -21.464  36.555   8.079  1.00  6.79           C
ATOM    144  O   VAL A  23     -21.885  36.200   9.196  1.00  7.54           O
ATOM    145  CB  VAL A  23     -22.500  38.837   7.772  1.00  7.74           C
ATOM    146  CG1 VAL A  23     -21.163  39.562   7.798  1.00 10.24           C
ATOM    147  CG2 VAL A  23     -23.538  39.638   6.977  1.00  9.52           C
ATOM    148  N   ASN A  24     -20.288  36.172   7.603  1.00  6.28           N
ATOM    149  CA  ASN A  24     -19.422  35.309   8.392  1.00  7.25           C
ATOM    150  C   ASN A  24     -18.643  36.082   9.467  1.00  8.55           C
ATOM    151  O   ASN A  24     -18.799  37.308   9.611  1.00 10.11           O
ATOM    152  CB  ASN A  24     -18.509  34.447   7.496  1.00  6.73           C
ATOM    153  CG  ASN A  24     -17.357  35.219   6.885  1.00  8.40           C
ATOM    154  OD1 ASN A  24     -17.116  36.389   7.213  1.00  8.49           O
ATOM    155  ND2 ASN A  24     -16.601  34.553   6.007  1.00  8.52           N
ATOM    156  N   ALA A  25     -17.824  35.369  10.233  1.00  8.14           N
ATOM    157  CA  ALA A  25     -17.137  35.971  11.376  1.00  8.35           C
ATOM    158  C   ALA A  25     -16.101  37.007  10.966  1.00 11.92           C
ATOM    159  O   ALA A  25     -15.619  37.777  11.803  1.00 15.43           O
ATOM    160  CB  ALA A  25     -16.497  34.897  12.238  1.00 12.36           C
ATOM    161  N   ASP A  26     -15.737  37.019   9.687  1.00 10.81           N
ATOM    162  CA  ASP A  26     -14.794  37.998   9.162  1.00 11.24           C
ATOM    163  C   ASP A  26     -15.527  39.170   8.504  1.00  9.54           C
ATOM    164  O   ASP A  26     -14.896  40.025   7.867  1.00 15.54           O
ATOM    165  CB  ASP A  26     -13.840  37.328   8.166  1.00 11.66           C
ATOM    166  CG  ASP A  26     -12.891  36.357   8.840  1.00 22.26           C
ATOM    167  OD1 ASP A  26     -12.372  36.694   9.930  1.00 24.50           O
ATOM    168  OD2 ASP A  26     -12.657  35.258   8.288  1.00 19.65           O
ATOM    169  N   GLY A  27     -16.847  39.201   8.644  1.00  8.36           N
ATOM    170  CA  GLY A  27     -17.647  40.275   8.091  1.00 10.32           C
ATOM    171  C   GLY A  27     -17.901  40.175   6.598  1.00 12.61           C
ATOM    172  O   GLY A  27     -18.324  41.148   5.976  1.00 12.32           O
ATOM    173  N   GLN A  28     -17.661  38.998   6.021  1.00  9.34           N
ATOM    174  CA  GLN A  28     -17.881  38.776   4.588  1.00  8.07           C
ATOM    175  C   GLN A  28     -19.263  38.219   4.330  1.00  6.30           C
ATOM    176  O   GLN A  28     -19.725  37.332   5.051  1.00  8.36           O
ATOM    177  CB  GLN A  28     -16.833  37.810   4.037  1.00  9.11           C
ATOM    178  CG  GLN A  28     -15.413  38.318   4.197  1.00 10.98           C
ATOM    179  CD  GLN A  28     -14.370  37.258   3.910  1.00 11.09           C
ATOM    180  OE1 GLN A  28     -13.533  37.414   3.005  1.00 15.32           O
ATOM    181  NE2 GLN A  28     -14.409  36.177   4.668  1.00  8.14           N
ATOM    182  N   TYR A  29     -19.950  38.742   3.326  1.00  6.77           N
ATOM    183  CA  TYR A  29     -21.250  38.230   2.942  1.00  6.19           C
ATOM    184  C   TYR A  29     -21.135  36.937   2.139  1.00  6.61           C
ATOM    185  O   TYR A  29     -20.410  36.886   1.130  1.00  8.93           O
ATOM    186  CB  TYR A  29     -22.002  39.271   2.106  1.00  9.22           C
ATOM    187  CG  TYR A  29     -22.628  40.389   2.924  1.00  8.73           C
ATOM    188  CD1 TYR A  29     -21.838  41.288   3.634  1.00 10.30           C
ATOM    189  CD2 TYR A  29     -23.999  40.536   2.983  1.00 10.59           C
ATOM    190  CE1 TYR A  29     -22.413  42.307   4.381  1.00 11.19           C
ATOM    191  CE2 TYR A  29     -24.582  41.561   3.725  1.00 10.78           C
ATOM    192  CZ  TYR A  29     -23.773  42.435   4.413  1.00  8.82           C
ATOM    193  OH  TYR A  29     -24.344  43.451   5.158  1.00 12.21           O
ATOM    194  N   LEU A  30     -21.853  35.911   2.585  1.00  6.17           N
ATOM    195  CA  LEU A  30     -21.936  34.654   1.848  1.00  5.98           C
ATOM    196  C   LEU A  30     -23.334  34.514   1.280  1.00  7.23           C
ATOM    197  O   LEU A  30     -24.333  34.704   1.975  1.00  9.08           O
ATOM    198  CB  LEU A  30     -21.629  33.462   2.760  1.00  8.48           C
ATOM    199  CG  LEU A  30     -20.300  33.501   3.519  1.00  8.51           C
ATOM    200  CD1 LEU A  30     -20.093  32.171   4.263  1.00 11.37           C
ATOM    201  CD2 LEU A  30     -19.126  33.807   2.603  1.00 10.67           C
ATOM    202  N   PHE A  31     -23.418  34.168  -0.003  1.00  6.05           N
ATOM    203  CA  PHE A  31     -24.692  33.900  -0.642  1.00  6.03           C
ATOM    204  C   PHE A  31     -25.241  32.543  -0.202  1.00  6.46           C
ATOM    205  O   PHE A  31     -24.484  31.573  -0.167  1.00  6.52           O
ATOM    206  CB  PHE A  31     -24.508  33.934  -2.167  1.00  6.59           C
ATOM    207  CG  PHE A  31     -25.711  33.500  -2.921  1.00  7.69           C
ATOM    208  CD1 PHE A  31     -26.739  34.395  -3.200  1.00 10.06           C
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ATOM    209  CD2 PHE A  31     -25.835  32.185  -3.363  1.00  8.63           C
ATOM    210  CE1 PHE A  31     -27.869  33.984  -3.895  1.00 12.38           C
ATOM    211  CE2 PHE A  31     -26.955  31.778  -4.049  1.00 10.13           C
ATOM    212  CZ  PHE A  31     -27.974  32.674  -4.321  1.00 11.21           C
ATOM    213  N   CYS A  32     -26.527  32.483   0.110  1.00  5.60           N
ATOM    214  CA  CYS A  32     -27.173  31.252   0.594  1.00  5.42           C
ATOM    215  C   CYS A  32     -28.256  30.757  -0.343  1.00  7.15           C
ATOM    216  O   CYS A  32     -28.868  31.533  -1.082  1.00  7.80           O
ATOM    217  CB  CYS A  32     -27.782  31.476   1.982  1.00  7.97           C
ATOM    218  SG  CYS A  32     -26.589  31.940   3.264  1.00  9.76           S
ATOM    219  N   ARG A  33     -28.524  29.455  -0.263  1.00  6.41           N
ATOM    220  CA  ARG A  33     -29.521  28.801  -1.095  1.00  6.58           C
ATOM    221  C   ARG A  33     -30.301  27.808  -0.238  1.00  6.95           C
ATOM    222  O   ARG A  33     -29.699  27.074   0.576  1.00  9.26           O
ATOM    223  CB  ARG A  33     -28.790  28.056  -2.217  1.00 12.39           C
ATOM    224  CG  ARG A  33     -29.458  28.057  -3.570  1.00 21.52           C
ATOM    225  CD  ARG A  33     -28.543  27.396  -4.608  1.00 13.00           C
ATOM    226  NE  ARG A  33     -27.652  28.315  -5.317  1.00  9.53           N
ATOM    227  CZ  ARG A  33     -28.037  29.049  -6.361  1.00  8.94           C
ATOM    228  NH1 ARG A  33     -29.287  28.978  -6.788  1.00 13.78           N
ATOM    229  NH2 ARG A  33     -27.172  29.848  -6.972  1.00 10.48           N
ATOM    230  N   TYR A  34     -31.619  27.773  -0.405  1.00  8.28           N
ATOM    231  CA  TYR A  34     -32.485  26.905   0.388  1.00  9.23           C
ATOM    232  C   TYR A  34     -33.474  26.170  -0.498  1.00 12.77           C
ATOM    233  O   TYR A  34     -33.998  26.735  -1.466  1.00 12.90           O
ATOM    234  CB  TYR A  34     -33.270  27.722   1.427  1.00  9.73           C
ATOM    235  CG  TYR A  34     -32.366  28.475   2.366  1.00 10.63           C
ATOM    236  CD1 TYR A  34     -31.785  27.835   3.453  1.00 11.93           C
ATOM    237  CD2 TYR A  34     -32.066  29.820   2.157  1.00 10.99           C
ATOM    238  CE1 TYR A  34     -30.933  28.511   4.301  1.00 12.94           C
ATOM    239  CE2 TYR A  34     -31.212  30.505   3.005  1.00  9.78           C
ATOM    240  CZ  TYR A  34     -30.651  29.838   4.072  1.00 10.20           C
ATOM    241  OH  TYR A  34     -29.795  30.492   4.921  1.00 11.98           O
ATOM    242  N   TRP A  35     -33.742  24.916  -0.154  1.00 10.36           N
ATOM    243  CA  TRP A  35     -34.792  24.152  -0.817  1.00 10.15           C
ATOM    244  C   TRP A  35     -35.623  23.508   0.286  1.00 11.14           C
ATOM    245  O   TRP A  35     -35.197  22.524   0.909  1.00 11.77           O
ATOM    246  CB  TRP A  35     -34.206  23.065  -1.721  1.00 10.42           C
ATOM    247  CG  TRP A  35     -33.285  23.499  -2.831  1.00 12.61           C
ATOM    248  CD1 TRP A  35     -33.609  23.625  -4.160  1.00 13.17           C
ATOM    249  CD2 TRP A  35     -31.879  23.777  -2.736  1.00  9.72           C
ATOM    250  NE1 TRP A  35     -32.500  23.988  -4.884  1.00 13.29           N
ATOM    251  CE2 TRP A  35     -31.421  24.082  -4.041  1.00 11.08           C
ATOM    252  CE3 TRP A  35     -30.959  23.791  -1.677  1.00  9.17           C
ATOM    253  CZ2 TRP A  35     -30.091  24.403  -4.310  1.00 11.75           C
ATOM    254  CZ3 TRP A  35     -29.643  24.108  -1.943  1.00  9.91           C
ATOM    255  CH2 TRP A  35     -29.218  24.414  -3.254  1.00 12.71           C
ATOM    256  N   ALA A  36     -36.793  24.077   0.554  1.00 13.64           N
ATOM    257  CA  ALA A  36     -37.613  23.643   1.682  1.00 14.33           C
ATOM    258  C   ALA A  36     -38.871  22.927   1.209  1.00 17.02           C
ATOM    259  CB  ALA A  36     -37.990  24.850   2.559  1.00 16.53           C
ATOM    260  O   ALA A  36     -39.523  23.383   0.274  1.00 19.88           O
ATOM    261  N   PRO A  37     -39.221  21.807   1.859  1.00 14.84           N
ATOM    262  CA  PRO A  37     -40.460  21.101   1.510  1.00 20.24           C
ATOM    263  C   PRO A  37     -41.685  21.874   2.015  1.00 18.75           C
ATOM    264  O   PRO A  37     -41.540  22.811   2.801  1.00 20.85           O
ATOM    265  CB  PRO A  37     -40.315  19.769   2.257  1.00 19.92           C
ATOM    266  CG  PRO A  37     -39.457  20.111   3.431  1.00 20.70           C
ATOM    267  CD  PRO A  37     -38.444  21.075   2.875  1.00 14.82           C
ATOM    268  N   THR A  38     -42.872  21.479   1.572  1.00 25.39           N
ATOM    269  CA  THR A  38     -44.096  22.193   1.923  1.00 30.82           C
ATOM    270  C   THR A  38     -44.415  22.120   3.413  1.00 36.92           C
ATOM    271  O   THR A  38     -44.878  23.097   4.002  1.00 62.88           O
ATOM    272  CB  THR A  38     -45.298  21.661   1.127  1.00 40.57           C
ATOM    273  OG1 THR A  38     -45.516  20.283   1.455  1.00 75.45           O
ATOM    274  CG2 THR A  38     -45.039  21.786  -0.365  1.00 33.30           C
ATOM    275  N   GLY A  39     -44.169  20.963   4.019  1.00 26.40           N
ATOM    276  CA  GLY A  39     -44.489  20.769   5.423  1.00 34.27           C
ATOM    277  C   GLY A  39     -43.270  20.683   6.320  1.00 44.58           C
ATOM    278  O   GLY A  39     -42.160  21.033   5.914  1.00 35.00           O
ATOM    279  N   THR A  40     -43.481  20.224   7.550  1.00 28.10           N
ATOM    280  CA  THR A  40     -42.392  20.033   8.500  1.00 24.60           C
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ATOM    281  C   THR A  40     -41.346  19.088   7.915  1.00 26.04           C
ATOM    282  O   THR A  40     -41.672  17.976   7.501  1.00 22.08           O
ATOM    283  CB  THR A  40     -42.902  19.444   9.829  1.00 30.60           C
ATOM    284  OG1 THR A  40     -43.947  20.276  10.349  1.00 44.32           O
ATOM    285  CG2 THR A  40     -41.772  19.352  10.852  1.00 25.32           C
ATOM    286  N   PRO A  41     -40.083  19.532   7.871  1.00 20.06           N
ATOM    287  CA  PRO A  41     -39.027  18.659   7.350  1.00 14.83           C
ATOM    288  C   PRO A  41     -38.722  17.536   8.332  1.00 15.43           C
ATOM    289  O   PRO A  41     -38.907  17.706   9.542  1.00 18.25           O
ATOM    290  CB  PRO A  41     -37.807  19.590   7.246  1.00 15.58           C
ATOM    291  CG  PRO A  41     -38.331  20.986   7.462  1.00 21.18           C
ATOM    292  CD  PRO A  41     -39.568  20.847   8.283  1.00 20.08           C
ATOM    293  N   LYS A  42     -38.244  16.407   7.817  1.00 12.49           N
ATOM    294  CA  LYS A  42     -37.840  15.276   8.648  1.00 15.17           C
ATOM    295  C   LYS A  42     -36.405  15.425   9.127  1.00 13.51           C
ATOM    296  O   LYS A  42     -36.002  14.831  10.133  1.00 15.33           O
ATOM    297  CB  LYS A  42     -37.978  13.968   7.866  1.00 20.90           C
ATOM    298  CG  LYS A  42     -39.415  13.620   7.520  1.00 33.71           C
ATOM    299  CD  LYS A  42     -39.587  12.137   7.262  1.00 65.22           C
ATOM    300  CE  LYS A  42     -38.819  11.702   6.034  1.00 53.35           C
ATOM    301  NZ  LYS A  42     -39.110  10.284   5.687  1.00 78.02           N
ATOM    302  N   ALA A  43     -35.630  16.213   8.387  1.00 11.61           N
ATOM    303  CA  ALA A  43     -34.228  16.414   8.693  1.00  9.88           C
ATOM    304  C   ALA A  43     -33.707  17.595   7.880  1.00  7.84           C
ATOM    305  O   ALA A  43     -34.377  18.073   6.961  1.00  9.50           O
ATOM    306  CB  ALA A  43     -33.421  15.156   8.373  1.00 13.77           C
ATOM    307  N   LEU A  44     -32.517  18.047   8.250  1.00  8.06           N
ATOM    308  CA  LEU A  44     -31.815  19.114   7.551  1.00  7.73           C
ATOM    309  C   LEU A  44     -30.613  18.507   6.858  1.00  7.26           C
ATOM    310  O   LEU A  44     -30.001  17.577   7.379  1.00  8.67           O
ATOM    311  CB  LEU A  44     -31.312  20.154   8.560  1.00 10.75           C
ATOM    312  CG  LEU A  44     -32.320  20.734   9.558  1.00 14.46           C
ATOM    313  CD1 LEU A  44     -31.600  21.580  10.594  1.00 18.22           C
ATOM    314  CD2 LEU A  44     -33.367  21.546   8.837  1.00 14.89           C
ATOM    315  N   ILE A  45     -30.232  19.069   5.718  1.00  7.30           N
ATOM    316  CA  ILE A  45     -28.991  18.659   5.084  1.00  7.17           C
ATOM    317  C   ILE A  45     -28.270  19.843   4.445  1.00  6.26           C
ATOM    318  O   ILE A  45     -28.850  20.592   3.644  1.00  7.44           O
ATOM    319  CB  ILE A  45     -29.206  17.489   4.079  1.00  7.19           C
ATOM    320  CG1 ILE A  45     -27.868  16.995   3.511  1.00  7.97           C
ATOM    321  CG2 ILE A  45     -30.224  17.865   3.008  1.00  9.73           C
ATOM    322  CD1 ILE A  45     -27.975  15.599   2.857  1.00 11.27           C
ATOM    323  N   PHE A  46     -27.021  20.011   4.837  1.00  5.88           N
ATOM    324  CA  PHE A  46     -26.169  21.039   4.251  1.00  5.70           C
ATOM    325  C   PHE A  46     -25.371  20.481   3.084  1.00  5.52           C
ATOM    326  O   PHE A  46     -24.738  19.426   3.211  1.00  7.72           O
ATOM    327  CB  PHE A  46     -25.216  21.629   5.298  1.00  5.92           C
ATOM    328  CG  PHE A  46     -24.325  22.708   4.757  1.00  6.50           C
ATOM    329  CD1 PHE A  46     -23.082  22.413   4.216  1.00  7.76           C
ATOM    330  CD2 PHE A  46     -24.758  24.027   4.769  1.00  7.33           C
ATOM    331  CE1 PHE A  46     -22.267  23.423   3.693  1.00  7.27           C
ATOM    332  CE2 PHE A  46     -23.954  25.038   4.250  1.00  8.02           C
ATOM    333  CZ  PHE A  46     -22.715  24.742   3.711  1.00  8.11           C
ATOM    334  N   VAL A  47     -25.375  21.211   1.970  1.00  5.46           N
ATOM    335  CA  VAL A  47     -24.617  20.813   0.783  1.00  6.17           C
ATOM    336  C   VAL A  47     -23.379  21.693   0.648  1.00  7.61           C
ATOM    337  O   VAL A  47     -23.491  22.930   0.600  1.00  8.01           O
ATOM    338  CB  VAL A  47     -25.480  20.904  -0.495  1.00  9.99           C
ATOM    339  CG1 VAL A  47     -24.642  20.584  -1.753  1.00 10.76           C
ATOM    340  CG2 VAL A  47     -26.673  19.965  -0.389  1.00  9.71           C
ATOM    341  N   SER A  48     -22.210  21.053   0.604  1.00  5.98           N
ATOM    342  CA  SER A  48     -20.915  21.711   0.581  1.00  6.93           C
ATOM    343  C   SER A  48     -20.251  21.506  -0.791  1.00  7.30           C
ATOM    344  O   SER A  48     -19.782  20.401  -1.130  1.00  6.87           O
ATOM    345  CB  SER A  48     -20.035  21.111   1.688  1.00  8.37           C
ATOM    346  OG  SER A  48     -18.758  21.704   1.745  1.00  8.59           O
ATOM    347  N   HIS A  49     -20.194  22.579  -1.580  1.00  5.91           N
ATOM    348  CA  HIS A  49     -19.621  22.526  -2.923  1.00  5.97           C
ATOM    349  C   HIS A  49     -18.089  22.530  -2.893  1.00  5.83           C
ATOM    350  O   HIS A  49     -17.461  22.768  -1.861  1.00  5.76           O
ATOM    351  CB  HIS A  49     -20.161  23.674  -3.800  1.00  6.87           C
ATOM    352  CG  HIS A  49     -19.608  25.028  -3.457  1.00  4.44           C
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ATOM    353  ND1 HIS A  49     -18.365  25.450  -3.876  1.00  5.38           N
ATOM    354  CD2 HIS A  49     -20.152  26.072  -2.781  1.00  6.37           C
ATOM    355  CE1 HIS A  49     -18.151  26.685  -3.445  1.00  7.05           C
ATOM    356  NE2 HIS A  49     -19.224  27.087  -2.786  1.00  5.73           N
ATOM    357  N   GLY A  50     -17.475  22.238  -4.039  1.00  6.83           N
ATOM    358  CA  GLY A  50     -16.033  22.155  -4.121  1.00  6.75           C
ATOM    359  C   GLY A  50     -15.362  23.413  -4.651  1.00  6.47           C
ATOM    360  O   GLY A  50     -16.022  24.420  -4.955  1.00  6.59           O
ATOM    361  N   ALA A  51     -14.050  23.344  -4.781  1.00  5.98           N
ATOM    362  CA  ALA A  51     -13.268  24.487  -5.244  1.00  5.62           C
ATOM    363  C   ALA A  51     -13.654  24.862  -6.662  1.00  8.12           C
ATOM    364  O   ALA A  51     -13.866  23.984  -7.511  1.00  7.71           O
ATOM    365  CB  ALA A  51     -11.805  24.181  -5.188  1.00  8.37           C
ATOM    366  N   GLY A  52     -13.719  26.164  -6.927  1.00  6.60           N
ATOM    367  CA  GLY A  52     -13.966  26.656  -8.270  1.00  9.14           C
ATOM    368  C   GLY A  52     -15.413  26.649  -8.709  1.00  7.08           C
ATOM    369  O   GLY A  52     -15.730  27.192  -9.773  1.00  8.55           O
ATOM    370  N   GLU A  53     -16.302  26.044  -7.927  1.00  5.30           N
ATOM    371  CA  GLU A  53     -17.719  26.013  -8.276  1.00  6.20           C
ATOM    372  C   GLU A  53     -18.570  26.767  -7.242  1.00  5.56           C
ATOM    373  O   GLU A  53     -18.087  27.730  -6.635  1.00  6.90           O
ATOM    374  CB  GLU A  53     -18.233  24.582  -8.536  1.00  8.29           C
ATOM    375  CG  GLU A  53     -17.953  23.602  -7.388  1.00  6.83           C
ATOM    376  CD  GLU A  53     -18.750  22.300  -7.486  1.00 10.34           C
ATOM    377  OE1 GLU A  53     -19.440  22.076  -8.496  1.00 10.71           O
ATOM    378  OE2 GLU A  53     -18.712  21.494  -6.522  1.00  9.53           O
ATOM    379  N   HIS A  54     -19.811  26.356  -7.054  1.00  5.72           N
ATOM    380  CA  HIS A  54     -20.727  27.085  -6.173  1.00  6.19           C
ATOM    381  C   HIS A  54     -21.987  26.260  -5.929  1.00  5.74           C
ATOM    382  O   HIS A  54     -22.179  25.207  -6.563  1.00  7.20           O
ATOM    383  CB  HIS A  54     -21.089  28.443  -6.801  1.00  7.71           C
ATOM    384  CG  HIS A  54     -21.857  28.312  -8.079  1.00  6.04           C
ATOM    385  ND1 HIS A  54     -23.223  28.457  -8.149  1.00  7.69           N
ATOM    386  CD2 HIS A  54     -21.445  27.990  -9.332  1.00  6.29           C
ATOM    387  CE1 HIS A  54     -23.622  28.253  -9.395  1.00  8.02           C
ATOM    388  NE2 HIS A  54     -22.561  27.967 -10.129  1.00  7.68           N
ATOM    389  N   SER A  55     -22.869  26.749  -5.064  1.00  6.06           N
ATOM    390  CA  SER A  55     -24.028  25.992  -4.616  1.00  5.79           C
ATOM    391  C   SER A  55     -25.064  25.729  -5.710  1.00  6.93           C
ATOM    392  O   SER A  55     -25.864  24.794  -5.609  1.00  8.85           O
ATOM    393  CB  SER A  55     -24.697  26.711  -3.434  1.00  7.37           C
ATOM    394  OG  SER A  55     -25.185  27.981  -3.824  1.00  9.12           O
ATOM    395  N   GLY A  56     -25.093  26.577  -6.736  1.00  7.19           N
ATOM    396  CA  GLY A  56     -26.086  26.425  -7.789  1.00  9.39           C
ATOM    397  C   GLY A  56     -25.890  25.189  -8.663  1.00  8.15           C
ATOM    398  O   GLY A  56     -26.812  24.773  -9.367  1.00 11.61           O
ATOM    399  N   ARG A  57     -24.706  24.599  -8.591  1.00  7.21           N
ATOM    400  CA  ARG A  57     -24.409  23.405  -9.371  1.00  8.23           C
ATOM    401  C   ARG A  57     -25.023  22.147  -8.738  1.00 12.55           C
ATOM    402  O   ARG A  57     -24.861  21.049  -9.268  1.00 15.41           O
ATOM    403  CB  ARG A  57     -22.900  23.280  -9.594  1.00 11.50           C
ATOM    404  CG  ARG A  57     -22.300  24.548 -10.261  1.00 11.08           C
ATOM    405  CD  ARG A  57     -21.326  24.258 -11.403  1.00 14.23           C
ATOM    406  NE  ARG A  57     -21.863  23.251 -12.312  1.00 16.18           N
ATOM    407  CZ  ARG A  57     -22.803  23.478 -13.219  1.00 20.13           C
ATOM    408  NH1 ARG A  57     -23.305  24.698 -13.381  1.00 23.25           N
ATOM    409  NH2 ARG A  57     -23.241  22.477 -13.971  1.00 20.33           N
ATOM    410  N   TYR A  58     -25.759  22.318  -7.639  1.00  8.94           N
ATOM    411  CA  TYR A  58     -26.351  21.196  -6.889  1.00  8.78           C
ATOM    412  C   TYR A  58     -27.876  21.187  -6.952  1.00 10.23           C
ATOM    413  O   TYR A  58     -28.545  20.471  -6.201  1.00 10.07           O
ATOM    414  CB  TYR A  58     -25.808  21.182  -5.437  1.00 10.33           C
ATOM    415  CG  TYR A  58     -24.356  20.813  -5.471  1.00  7.86           C
ATOM    416  CD1 TYR A  58     -23.367  21.764  -5.755  1.00  8.45           C
ATOM    417  CD2 TYR A  58     -23.968  19.487  -5.324  1.00  9.90           C
ATOM    418  CE1 TYR A  58     -22.039  21.403  -5.859  1.00  8.11           C
ATOM    419  CE2 TYR A  58     -22.649  19.117  -5.413  1.00  8.69           C
ATOM    420  CZ  TYR A  58     -21.682  20.061  -5.696  1.00  9.51           C
ATOM    421  OH  TYR A  58     -20.374  19.682  -5.811  1.00 12.95           O
ATOM    422  N   GLU A  59     -28.429  21.975  -7.869  1.00  9.80           N
ATOM    423  CA  GLU A  59     -29.868  22.136  -7.978  1.00 11.59           C
ATOM    424  C   GLU A  59     -30.645  20.816  -8.039  1.00 10.87           C
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ATOM    425  O   GLU A  59     -31.608  20.616  -7.297  1.00 10.96           O
ATOM    426  CB  GLU A  59     -30.203  22.987  -9.208  1.00 13.77           C
ATOM    427  CG  GLU A  59     -31.654  23.394  -9.288  1.00 14.77           C
ATOM    428  CD  GLU A  59     -32.069  24.310  -8.144  1.00 16.52           C
ATOM    429  OE1 GLU A  59     -31.216  25.088  -7.671  1.00 20.67           O
ATOM    430  OE2 GLU A  59     -33.245  24.251  -7.728  1.00 25.13           O
ATOM    431  N   GLU A  60     -30.235  19.916  -8.930  1.00 10.53           N
ATOM    432  CA  GLU A  60     -30.993  18.683  -9.117  1.00 10.68           C
ATOM    433  C   GLU A  60     -30.896  17.758  -7.908  1.00  9.92           C
ATOM    434  O   GLU A  60     -31.894  17.181  -7.476  1.00 10.77           O
ATOM    435  CB  GLU A  60     -30.553  17.959 -10.391  1.00 14.50           C
ATOM    436  CG  GLU A  60     -30.925  18.708 -11.667  1.00 24.44           C
ATOM    437  CD  GLU A  60     -32.401  19.063 -11.722  1.00 89.95           C
ATOM    438  OE1 GLU A  60     -33.241  18.168 -11.485  1.00 55.36           O
ATOM    439  OE2 GLU A  60     -32.723  20.237 -12.003  1.00106.69           O
ATOM    440  N   LEU A  61     -29.694  17.608  -7.372  1.00  8.91           N
ATOM    441  CA ALEU A  61     -29.506  16.811  -6.161  0.50  9.95           C
ATOM    442  C   LEU A  61     -30.339  17.376  -5.013  1.00 10.94           C
ATOM    443  O   LEU A  61     -31.003  16.637  -4.278  1.00  9.90           O
ATOM    444  CB ALEU A  61     -28.031  16.777  -5.757  0.50 11.94           C
ATOM    445  CG ALEU A  61     -27.140  15.693  -6.367  0.50  9.56           C
ATOM    446  CD1ALEU A  61     -25.700  15.937  -5.975  0.50  8.30           C
ATOM    447  CD2ALEU A  61     -27.591  14.303  -5.926  0.50  9.49           C
ATOM    448  CA BLEU A  61     -29.513  16.807  -6.168  0.50  9.77           C
ATOM    449  CB BLEU A  61     -28.039  16.757  -5.782  0.50 12.63           C
ATOM    450  CG BLEU A  61     -27.659  15.622  -4.834  0.50 14.96           C
ATOM    451  CD1BLEU A  61     -28.276  14.307  -5.303  0.50 15.85           C
ATOM    452  CD2BLEU A  61     -26.151  15.511  -4.742  0.50 14.56           C
ATOM    453  N   ALA A  62     -30.303  18.694  -4.849  1.00  8.48           N
ATOM    454  CA  ALA A  62     -31.054  19.331  -3.778  1.00 10.11           C
ATOM    455  C   ALA A  62     -32.555  19.111  -3.938  1.00 13.13           C
ATOM    456  O   ALA A  62     -33.267  18.881  -2.955  1.00 10.27           O
ATOM    457  CB  ALA A  62     -30.732  20.826  -3.722  1.00 10.95           C
ATOM    458  N   ARG A  63     -33.052  19.194  -5.169  1.00  9.46           N
ATOM    459  CA  ARG A  63     -34.475  18.973  -5.402  1.00 13.75           C
ATOM    460  C   ARG A  63     -34.891  17.549  -5.042  1.00 11.63           C
ATOM    461  O   ARG A  63     -35.964  17.327  -4.481  1.00 12.65           O
ATOM    462  CB  ARG A  63     -34.846  19.301  -6.849  1.00 11.63           C
ATOM    463  CG  ARG A  63     -34.838  20.793  -7.131  1.00 15.77           C
ATOM    464  CD  ARG A  63     -35.202  21.085  -8.579  1.00 27.72           C
ATOM    465  NE  ARG A  63     -35.167  22.516  -8.871  1.00 33.09           N
ATOM    466  CZ  ARG A  63     -35.623  23.058  -9.995  1.00 84.41           C
ATOM    467  NH1 ARG A  63     -36.156  22.291 -10.937  1.00 43.78           N
ATOM    468  NH2 ARG A  63     -35.549  24.370 -10.175  1.00 46.62           N
ATOM    469  N   MET A  64     -34.035  16.584  -5.362  1.00 10.52           N
ATOM    470  CA AMET A  64     -34.299  15.192  -5.002  0.75 11.44           C
ATOM    471  C   MET A  64     -34.394  15.041  -3.485  1.00 11.99           C
ATOM    472  O   MET A  64     -35.315  14.410  -2.965  1.00 12.08           O
ATOM    473  CB AMET A  64     -33.212  14.277  -5.575  0.75 11.53           C
ATOM    474  CG AMET A  64     -33.399  12.800  -5.229  0.75 11.45           C
ATOM    475  SD AMET A  64     -32.651  12.319  -3.663  0.75 14.16           S
ATOM    476  CE AMET A  64     -30.923  12.298  -4.124  0.75 13.84           C
ATOM    477  CA BMET A  64     -34.318  15.202  -5.003  0.25 12.08           C
ATOM    478  CB BMET A  64     -33.259  14.270  -5.583  0.25 12.80           C
ATOM    479  CG BMET A  64     -33.680  12.815  -5.583  0.25 26.52           C
ATOM    480  SD BMET A  64     -32.270  11.723  -5.382  0.25 12.18           S
ATOM    481  CE BMET A  64     -31.712  12.205  -3.742  0.25  0.00           C
ATOM    482  N   LEU A  65     -33.437  15.628  -2.777  1.00  9.40           N
ATOM    483  CA  LEU A  65     -33.394  15.534  -1.319  1.00 10.14           C
ATOM    484  C   LEU A  65     -34.594  16.228  -0.671  1.00 10.86           C
ATOM    485  O   LEU A  65     -35.174  15.723   0.296  1.00 10.56           O
ATOM    486  CB  LEU A  65     -32.082  16.117  -0.793  1.00  8.51           C
ATOM    487  CG  LEU A  65     -30.836  15.282  -1.120  1.00 10.20           C
ATOM    488  CD1 LEU A  65     -29.562  16.095  -0.943  1.00 11.61           C
ATOM    489  CD2 LEU A  65     -30.803  14.004  -0.274  1.00 12.05           C
ATOM    490  N   MET A  66     -34.973  17.383  -1.209  1.00 11.05           N
ATOM    491  CA AMET A  66     -36.136  18.088  -0.703  0.50 11.92           C
ATOM    492  C   MET A  66     -37.395  17.241  -0.931  1.00 14.01           C
ATOM    493  O   MET A  66     -38.328  17.265  -0.120  1.00 14.48           O
ATOM    494  CB AMET A  66     -36.239  19.471  -1.354  0.50  7.66           C
ATOM    495  CG AMET A  66     -37.413  20.298  -0.867  0.50 16.42           C
ATOM    496  SD AMET A  66     -38.927  19.913  -1.763  0.50 19.91           S
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ATOM    497  CE AMET A  66     -38.623  20.747  -3.320  0.50 29.87           C
ATOM    498  CA BMET A  66     -36.151  18.103  -0.735  0.50 10.75           C
ATOM    499  CB BMET A  66     -36.301  19.432  -1.483  0.50 20.22           C
ATOM    500  CG BMET A  66     -37.520  20.250  -1.071  0.50 16.81           C
ATOM    501  SD BMET A  66     -37.739  21.751  -2.054  0.50 18.63           S
ATOM    502  CE BMET A  66     -38.028  21.070  -3.685  0.50 28.73           C
ATOM    503  N   GLY A  67     -37.404  16.473  -2.021  1.00 12.11           N
ATOM    504  CA  GLY A  67     -38.501  15.567  -2.320  1.00 18.68           C
ATOM    505  C   GLY A  67     -38.616  14.423  -1.324  1.00 13.55           C
ATOM    506  O   GLY A  67     -39.651  13.763  -1.249  1.00 17.32           O
ATOM    507  N   LEU A  68     -37.550  14.180  -0.570  1.00 14.11           N
ATOM    508  CA  LEU A  68     -37.555  13.207   0.520  1.00 15.51           C
ATOM    509  C   LEU A  68     -37.984  13.857   1.838  1.00 15.63           C
ATOM    510  O   LEU A  68     -37.854  13.257   2.911  1.00 17.55           O
ATOM    511  CB  LEU A  68     -36.164  12.605   0.693  1.00 14.48           C
ATOM    512  CG  LEU A  68     -35.579  11.827  -0.482  1.00 16.34           C
ATOM    513  CD1 LEU A  68     -34.187  11.326  -0.122  1.00 19.31           C
ATOM    514  CD2 LEU A  68     -36.495  10.672  -0.866  1.00 25.16           C
ATOM    515  N   ASP A  69     -38.477  15.090   1.742  1.00 15.49           N
ATOM    516  CA  ASP A  69     -38.936  15.859   2.903  1.00 13.48           C
ATOM    517  C   ASP A  69     -37.799  16.365   3.800  1.00 14.51           C
ATOM    518  O   ASP A  69     -37.982  16.554   5.007  1.00 15.76           O
ATOM    519  CB  ASP A  69     -39.958  15.059   3.724  1.00 18.23           C
ATOM    520  CG  ASP A  69     -40.801  15.939   4.622  1.00 52.91           C
ATOM    521  OD1 ASP A  69     -41.032  17.110   4.255  1.00 35.35           O
ATOM    522  OD2 ASP A  69     -41.236  15.461   5.690  1.00 43.13           O
ATOM    523  N   LEU A  70     -36.622  16.574   3.219  1.00 11.72           N
ATOM    524  CA  LEU A  70     -35.529  17.218   3.940  1.00 12.54           C
ATOM    525  C   LEU A  70     -35.487  18.700   3.571  1.00 11.28           C
ATOM    526  O   LEU A  70     -35.809  19.083   2.444  1.00 12.36           O
ATOM    527  CB  LEU A  70     -34.174  16.572   3.621  1.00 12.49           C
ATOM    528  CG  LEU A  70     -33.854  15.265   4.351  1.00 19.34           C
ATOM    529  CD1 LEU A  70     -34.549  14.111   3.654  1.00 21.20           C
ATOM    530  CD2 LEU A  70     -32.350  15.016   4.415  1.00 16.83           C
ATOM    531  N   LEU A  71     -35.100  19.533   4.530  1.00  9.16           N
ATOM    532  CA  LEU A  71     -34.777  20.916   4.226  1.00  9.27           C
ATOM    533  C   LEU A  71     -33.307  20.979   3.834  1.00  8.70           C
ATOM    534  O   LEU A  71     -32.415  20.689   4.639  1.00  8.84           O
ATOM    535  CB  LEU A  71     -35.051  21.799   5.440  1.00 10.92           C
ATOM    536  CG  LEU A  71     -35.014  23.311   5.176  1.00 14.41           C
ATOM    537  CD1 LEU A  71     -35.732  24.045   6.305  1.00 17.57           C
ATOM    538  CD2 LEU A  71     -33.592  23.831   5.014  1.00 17.60           C
ATOM    539  N   VAL A  72     -33.060  21.347   2.586  1.00  7.86           N
ATOM    540  CA  VAL A  72     -31.708  21.395   2.055  1.00  8.85           C
ATOM    541  C   VAL A  72     -31.214  22.828   2.109  1.00  8.92           C
ATOM    542  O   VAL A  72     -31.950  23.753   1.749  1.00  7.86           O
ATOM    543  CB  VAL A  72     -31.668  20.911   0.591  1.00  7.35           C
ATOM    544  CG1 VAL A  72     -30.227  20.797   0.097  1.00  9.49           C
ATOM    545  CG2 VAL A  72     -32.412  19.583   0.451  1.00  9.13           C
ATOM    546  N   PHE A  73     -29.986  23.021   2.561  1.00  6.35           N
ATOM    547  CA  PHE A  73     -29.439  24.374   2.612  1.00  6.13           C
ATOM    548  C   PHE A  73     -27.967  24.386   2.237  1.00  7.10           C
ATOM    549  O   PHE A  73     -27.275  23.372   2.342  1.00  6.36           O
ATOM    550  CB  PHE A  73     -29.728  25.081   3.959  1.00  6.94           C
ATOM    551  CG  PHE A  73     -29.071  24.458   5.160  1.00  7.16           C
ATOM    552  CD1 PHE A  73     -29.459  23.209   5.624  1.00  8.74           C
ATOM    553  CD2 PHE A  73     -28.101  25.156   5.873  1.00  9.73           C
ATOM    554  CE1 PHE A  73     -28.858  22.649   6.746  1.00 11.57           C
ATOM    555  CE2 PHE A  73     -27.503  24.609   7.010  1.00 11.39           C
ATOM    556  CZ  PHE A  73     -27.889  23.356   7.450  1.00 11.64           C
ATOM    557  N   ALA A  74     -27.487  25.535   1.771  1.00  5.58           N
ATOM    558  CA  ALA A  74     -26.122  25.665   1.312  1.00  6.13           C
ATOM    559  C   ALA A  74     -25.710  27.124   1.322  1.00  5.53           C
ATOM    560  O   ALA A  74     -26.562  28.008   1.381  1.00  5.91           O
ATOM    561  CB  ALA A  74     -25.996  25.112  -0.117  1.00  7.97           C
ATOM    562  N   HIS A  75     -24.418  27.365   1.229  1.00  5.08           N
ATOM    563  CA  HIS A  75     -23.942  28.683   0.855  1.00  4.98           C
ATOM    564  C   HIS A  75     -22.762  28.529  -0.070  1.00  6.30           C
ATOM    565  O   HIS A  75     -22.151  27.455  -0.160  1.00  6.97           O
ATOM    566  CB  HIS A  75     -23.603  29.556   2.073  1.00  5.32           C
ATOM    567  CG  HIS A  75     -22.565  28.985   2.985  1.00  6.21           C
ATOM    568  ND1 HIS A  75     -22.865  28.561   4.263  1.00  7.36           N
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ATOM    569  CD2 HIS A  75     -21.228  28.821   2.835  1.00  6.89           C
ATOM    570  CE1 HIS A  75     -21.758  28.146   4.854  1.00  6.18           C
ATOM    571  NE2 HIS A  75     -20.747  28.289   4.012  1.00  6.86           N
ATOM    572  N   ASP A  76     -22.428  29.608  -0.771  1.00  5.01           N
ATOM    573  CA  ASP A  76     -21.200  29.646  -1.548  1.00  5.14           C
ATOM    574  C   ASP A  76     -20.058  29.931  -0.589  1.00  5.33           C
ATOM    575  O   ASP A  76     -20.124  30.898   0.189  1.00  5.80           O
ATOM    576  CB  ASP A  76     -21.280  30.708  -2.658  1.00  6.05           C
ATOM    577  CG  ASP A  76     -22.301  30.360  -3.726  1.00  7.92           C
ATOM    578  OD1 ASP A  76     -22.795  29.212  -3.750  1.00  7.77           O
ATOM    579  OD2 ASP A  76     -22.637  31.243  -4.548  1.00  7.72           O
ATOM    580  N   HIS A  77     -19.043  29.077  -0.577  1.00  5.59           N
ATOM    581  CA  HIS A  77     -17.908  29.282   0.298  1.00  5.52           C
ATOM    582  C   HIS A  77     -17.261  30.624  -0.020  1.00  5.25           C
ATOM    583  O   HIS A  77     -17.368  31.144  -1.141  1.00  6.90           O
ATOM    584  CB  HIS A  77     -16.872  28.166   0.122  1.00  7.14           C
ATOM    585  CG  HIS A  77     -17.404  26.795   0.413  1.00  6.26           C
ATOM    586  ND1 HIS A  77     -17.922  26.440   1.641  1.00  8.66           N
ATOM    587  CD2 HIS A  77     -17.465  25.679  -0.357  1.00  7.29           C
ATOM    588  CE1 HIS A  77     -18.313  25.176   1.605  1.00  9.31           C
ATOM    589  NE2 HIS A  77     -18.035  24.689   0.407  1.00  9.66           N
ATOM    590  N   VAL A  78     -16.572  31.196   0.956  1.00  6.80           N
ATOM    591  CA AVAL A  78     -15.924  32.466   0.703  0.50  6.73           C
ATOM    592  C   VAL A  78     -15.026  32.332  -0.531  1.00  7.87           C
ATOM    593  CB AVAL A  78     -15.163  32.972   1.947  0.50 15.02           C
ATOM    594  CG1AVAL A  78     -13.972  32.076   2.248  0.50  3.02           C
ATOM    595  CG2AVAL A  78     -14.756  34.438   1.771  0.50  5.54           C
ATOM    596  O   VAL A  78     -14.417  31.286  -0.791  1.00  7.09           O
ATOM    597  CA BVAL A  78     -15.839  32.437   0.752  0.50 10.12           C
ATOM    598  CB BVAL A  78     -14.889  32.695   1.942  0.50  4.36           C
ATOM    599  CG1BVAL A  78     -13.801  33.684   1.564  0.50 10.71           C
ATOM    600  CG2BVAL A  78     -15.667  33.180   3.151  0.50 15.80           C
ATOM    601  N   GLY A  79     -15.002  33.392  -1.338  1.00  7.60           N
ATOM    602  CA  GLY A  79     -14.198  33.399  -2.552  1.00  8.95           C
ATOM    603  C   GLY A  79     -14.813  32.627  -3.704  1.00  5.87           C
ATOM    604  O   GLY A  79     -14.131  32.419  -4.721  1.00  8.58           O
ATOM    605  N   HIS A  80     -16.072  32.226  -3.569  1.00  4.89           N
ATOM    606  CA  HIS A  80     -16.745  31.427  -4.592  1.00  4.97           C
ATOM    607  C   HIS A  80     -18.108  31.959  -4.922  1.00  6.40           C
ATOM    608  O   HIS A  80     -18.766  32.612  -4.100  1.00  6.52           O
ATOM    609  CB  HIS A  80     -16.888  29.958  -4.138  1.00  5.51           C
ATOM    610  CG  HIS A  80     -15.581  29.255  -3.999  1.00  7.26           C
ATOM    611  ND1 HIS A  80     -15.113  28.348  -4.931  1.00  9.83           N
ATOM    612  CD2 HIS A  80     -14.609  29.374  -3.067  1.00  4.47           C
ATOM    613  CE1 HIS A  80     -13.918  27.921  -4.561  1.00  4.41           C
ATOM    614  NE2 HIS A  80     -13.591  28.527  -3.431  1.00 11.14           N
ATOM    615  N   GLY A  81     -18.558  31.659  -6.134  1.00  7.03           N
ATOM    616  CA  GLY A  81     -19.903  31.969  -6.550  1.00  7.68           C
ATOM    617  C   GLY A  81     -20.301  33.409  -6.297  1.00  7.61           C
ATOM    618  O   GLY A  81     -19.609  34.336  -6.722  1.00  8.19           O
ATOM    619  N   GLN A  82     -21.410  33.585  -5.595  1.00  7.12           N
ATOM    620  CA  GLN A  82     -21.947  34.916  -5.350  1.00  7.50           C
ATOM    621  C   GLN A  82     -21.557  35.462  -3.983  1.00  8.34           C
ATOM    622  O   GLN A  82     -22.111  36.478  -3.553  1.00  9.53           O
ATOM    623  CB  GLN A  82     -23.459  34.917  -5.510  1.00  7.66           C
ATOM    624  CG  GLN A  82     -23.918  34.420  -6.890  1.00  7.96           C
ATOM    625  CD  GLN A  82     -25.416  34.400  -7.029  1.00 11.20           C
ATOM    626  OE1 GLN A  82     -26.058  35.446  -7.145  1.00 12.46           O
ATOM    627  NE2 GLN A  82     -25.998  33.207  -7.017  1.00  9.37           N
ATOM    628  N   SER A  83     -20.630  34.787  -3.306  1.00  6.24           N
ATOM    629  CA  SER A  83     -20.130  35.262  -2.022  1.00  5.93           C
ATOM    630  C   SER A  83     -18.974  36.210  -2.224  1.00  7.64           C
ATOM    631  O   SER A  83     -18.346  36.241  -3.292  1.00  9.96           O
ATOM    632  CB  SER A  83     -19.670  34.088  -1.157  1.00  6.90           C
ATOM    633  OG  SER A  83     -20.781  33.296  -0.820  1.00  5.65           O
ATOM    634  N   GLU A  84     -18.684  36.989  -1.185  1.00  8.21           N
ATOM    635  CA  GLU A  84     -17.549  37.900  -1.200  1.00  8.55           C
ATOM    636  C   GLU A  84     -16.218  37.169  -1.054  1.00 10.87           C
ATOM    637  O   GLU A  84     -16.181  35.963  -0.796  1.00 10.07           O
ATOM    638  CB  GLU A  84     -17.701  38.956  -0.097  1.00  8.81           C
ATOM    639  CG  GLU A  84     -18.819  39.932  -0.371  1.00 10.32           C
ATOM    640  CD  GLU A  84     -18.897  41.045   0.662  1.00 14.70           C
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ATOM    641  OE1 GLU A  84     -18.584  40.792   1.844  1.00 12.02           O
ATOM    642  OE2 GLU A  84     -19.285  42.171   0.285  1.00 17.48           O
ATOM    643  N   GLY A  85     -15.123  37.909  -1.214  1.00 10.41           N
ATOM    644  CA  GLY A  85     -13.785  37.373  -1.061  1.00 11.16           C
ATOM    645  C   GLY A  85     -13.025  37.311  -2.371  1.00 12.67           C
ATOM    646  O   GLY A  85     -13.611  37.083  -3.428  1.00 12.70           O
ATOM    647  N   GLU A  86     -11.717  37.516  -2.307  1.00 12.86           N
ATOM    648  CA  GLU A  86     -10.900  37.312  -3.497  1.00 15.49           C
ATOM    649  C   GLU A  86     -11.139  35.894  -4.012  1.00 14.29           C
ATOM    650  O   GLU A  86     -11.252  34.955  -3.220  1.00 11.66           O
ATOM    651  CB  GLU A  86      -9.429  37.536  -3.177  1.00 16.36           C
ATOM    652  CG  GLU A  86      -9.114  38.976  -2.782  1.00 31.32           C
ATOM    653  CD  GLU A  86      -7.662  39.174  -2.392  1.00101.84           C
ATOM    654  OE1 GLU A  86      -6.862  38.229  -2.567  1.00 54.48           O
ATOM    655  OE2 GLU A  86      -7.321  40.277  -1.912  1.00 74.42           O
ATOM    656  N   ARG A  87     -11.240  35.739  -5.329  1.00 12.44           N
ATOM    657  CA  ARG A  87     -11.629  34.455  -5.910  1.00 11.77           C
ATOM    658  C   ARG A  87     -10.641  33.329  -5.596  1.00 10.94           C
ATOM    659  O   ARG A  87      -9.435  33.443  -5.846  1.00 11.69           O
ATOM    660  CB  ARG A  87     -11.803  34.562  -7.432  1.00 12.45           C
ATOM    661  CG  ARG A  87     -12.817  35.592  -7.926  1.00 17.92           C
ATOM    662  CD  ARG A  87     -14.243  35.195  -7.585  1.00 18.43           C
ATOM    663  NE  ARG A  87     -14.578  35.661  -6.249  1.00 11.89           N
ATOM    664  CZ  ARG A  87     -15.736  35.459  -5.638  1.00 12.44           C
ATOM    665  NH1 ARG A  87     -16.707  34.782  -6.235  1.00 13.57           N
ATOM    666  NH2 ARG A  87     -15.916  35.950  -4.414  1.00 13.60           N
ATOM    667  N   MET A  88     -11.172  32.232  -5.059  1.00  9.91           N
ATOM    668  CA  MET A  88     -10.380  31.028  -4.820  1.00 11.60           C
ATOM    669  C   MET A  88      -9.109  31.274  -4.009  1.00 12.66           C
ATOM    670  O   MET A  88      -8.019  30.791  -4.335  1.00 13.08           O
ATOM    671  CB  MET A  88     -10.068  30.294  -6.129  1.00 13.27           C
ATOM    672  CG  MET A  88     -11.227  29.455  -6.646  1.00 23.14           C
ATOM    673  SD  MET A  88     -10.720  28.240  -7.892  1.00 20.98           S
ATOM    674  CE  MET A  88      -9.588  27.226  -6.961  1.00 30.54           C
ATOM    675  N   VAL A  89      -9.285  32.044  -2.942  1.00  9.61           N
ATOM    676  CA AVAL A  89      -8.252  32.187  -1.938  0.50  8.87           C
ATOM    677  C   VAL A  89      -8.935  32.155  -0.579  1.00  8.58           C
ATOM    678  O   VAL A  89     -10.128  32.442  -0.452  1.00 10.43           O
ATOM    679  CB AVAL A  89      -7.439  33.484  -2.102  0.50 20.29           C
ATOM    680  CG1AVAL A  89      -6.728  33.502  -3.451  0.50 21.26           C
ATOM    681  CG2AVAL A  89      -8.335  34.689  -1.951  0.50 11.60           C
ATOM    682  CA BVAL A  89      -8.264  32.316  -1.942  0.50 15.07           C
ATOM    683  CB BVAL A  89      -7.752  33.771  -2.069  0.50 13.11           C
ATOM    684  CG1BVAL A  89      -7.120  34.254  -0.767  0.50 15.31           C
ATOM    685  CG2BVAL A  89      -6.786  33.900  -3.241  0.50 28.13           C
ATOM    686  N   VAL A  90      -8.184  31.737   0.427  1.00  9.08           N
ATOM    687  CA  VAL A  90      -8.738  31.651   1.774  1.00 11.86           C
ATOM    688  C   VAL A  90      -7.583  31.817   2.759  1.00 11.67           C
ATOM    689  O   VAL A  90      -6.506  31.267   2.556  1.00 10.65           O
ATOM    690  CB  VAL A  90      -9.530  30.322   1.992  1.00  9.75           C
ATOM    691  CG1 VAL A  90      -8.584  29.132   2.112  1.00 10.71           C
ATOM    692  CG2 VAL A  90     -10.449  30.428   3.209  1.00 12.69           C
ATOM    693  N   SER A  91      -7.793  32.610   3.807  1.00 11.86           N
ATOM    694  CA  SER A  91      -6.708  32.895   4.745  1.00 11.26           C
ATOM    695  C   SER A  91      -6.179  31.607   5.380  1.00 10.82           C
ATOM    696  O   SER A  91      -4.972  31.401   5.489  1.00 13.74           O
ATOM    697  CB  SER A  91      -7.170  33.884   5.817  1.00 14.65           C
ATOM    698  OG  SER A  91      -8.265  33.367   6.549  1.00 16.21           O
ATOM    699  N   ASP A  92      -7.105  30.743   5.789  1.00 10.07           N
ATOM    700  CA  ASP A  92      -6.784  29.407   6.285  1.00  9.45           C
ATOM    701  C   ASP A  92      -7.983  28.523   5.981  1.00  8.51           C
ATOM    702  O   ASP A  92      -9.130  28.967   6.055  1.00  8.70           O
ATOM    703  CB  ASP A  92      -6.516  29.407   7.795  1.00 12.63           C
ATOM    704  CG  ASP A  92      -6.132  28.016   8.322  1.00 12.62           C
ATOM    705  OD1 ASP A  92      -4.934  27.663   8.272  1.00 15.77           O
ATOM    706  OD2 ASP A  92      -7.030  27.276   8.782  1.00 13.34           O
ATOM    707  N   PHE A  93      -7.714  27.266   5.644  1.00  7.96           N
ATOM    708  CA  PHE A  93      -8.783  26.351   5.260  1.00  9.18           C
ATOM    709  C   PHE A  93      -9.900  26.284   6.304  1.00  7.89           C
ATOM    710  O   PHE A  93     -11.059  26.057   5.975  1.00  8.19           O
ATOM    711  CB  PHE A  93      -8.233  24.949   4.997  1.00  8.72           C
ATOM    712  CG  PHE A  93      -9.171  24.080   4.204  1.00  8.08           C
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ATOM    713  CD1 PHE A  93      -9.243  24.196   2.822  1.00  9.70           C
ATOM    714  CD2 PHE A  93      -9.994  23.163   4.834  1.00  9.05           C
ATOM    715  CE1 PHE A  93     -10.117  23.401   2.082  1.00  8.73           C
ATOM    716  CE2 PHE A  93     -10.870  22.363   4.105  1.00  9.40           C
ATOM    717  CZ  PHE A  93     -10.936  22.488   2.726  1.00  8.70           C
ATOM    718  N   HIS A  94      -9.546  26.468   7.572  1.00  7.76           N
ATOM    719  CA  HIS A  94     -10.545  26.363   8.621  1.00  9.12           C
ATOM    720  C   HIS A  94     -11.690  27.367   8.476  1.00  6.64           C
ATOM    721  O   HIS A  94     -12.782  27.138   8.982  1.00  8.47           O
ATOM    722  CB  HIS A  94      -9.922  26.487  10.014  1.00 10.83           C
ATOM    723  CG  HIS A  94     -10.891  26.175  11.107  1.00 12.48           C
ATOM    724  ND1 HIS A  94     -11.497  27.153  11.868  1.00 18.24           N
ATOM    725  CD2 HIS A  94     -11.407  24.996  11.526  1.00 14.58           C
ATOM    726  CE1 HIS A  94     -12.323  26.586  12.729  1.00 18.04           C
ATOM    727  NE2 HIS A  94     -12.289  25.278  12.541  1.00 20.93           N
ATOM    728  N   VAL A  95     -11.433  28.476   7.790  1.00  6.79           N
ATOM    729  CA  VAL A  95     -12.482  29.445   7.525  1.00  7.84           C
ATOM    730  C   VAL A  95     -13.713  28.751   6.923  1.00  5.99           C
ATOM    731  O   VAL A  95     -14.852  29.036   7.299  1.00  7.00           O
ATOM    732  CB  VAL A  95     -11.981  30.569   6.580  1.00  9.46           C
ATOM    733  CG1 VAL A  95     -13.146  31.338   5.972  1.00 10.88           C
ATOM    734  CG2 VAL A  95     -11.040  31.504   7.333  1.00 10.22           C
ATOM    735  N   PHE A  96     -13.482  27.834   5.976  1.00  5.97           N
ATOM    736  CA  PHE A  96     -14.606  27.148   5.328  1.00  6.34           C
ATOM    737  C   PHE A  96     -15.432  26.338   6.323  1.00  4.91           C
ATOM    738  O   PHE A  96     -16.661  26.310   6.262  1.00  6.56           O
ATOM    739  CB  PHE A  96     -14.124  26.191   4.231  1.00  7.50           C
ATOM    740  CG  PHE A  96     -13.463  26.855   3.057  1.00  6.47           C
ATOM    741  CD1 PHE A  96     -13.997  27.991   2.453  1.00  7.28           C
ATOM    742  CD2 PHE A  96     -12.332  26.286   2.512  1.00  7.30           C
ATOM    743  CE1 PHE A  96     -13.378  28.572   1.333  1.00  8.59           C
ATOM    744  CE2 PHE A  96     -11.707  26.847   1.388  1.00  8.91           C
ATOM    745  CZ  PHE A  96     -12.237  27.993   0.794  1.00  7.27           C
ATOM    746  N   VAL A  97     -14.732  25.648   7.228  1.00  6.11           N
ATOM    747  CA  VAL A  97     -15.375  24.815   8.242  1.00  6.27           C
ATOM    748  C   VAL A  97     -16.135  25.682   9.259  1.00  5.36           C
ATOM    749  O   VAL A  97     -17.277  25.403   9.594  1.00  6.07           O
ATOM    750  CB  VAL A  97     -14.312  23.943   8.952  1.00  7.37           C
ATOM    751  CG1 VAL A  97     -14.941  23.145  10.091  1.00 10.36           C
ATOM    752  CG2 VAL A  97     -13.620  23.008   7.943  1.00  9.21           C
ATOM    753  N   ARG A  98     -15.480  26.734   9.740  1.00  6.54           N
ATOM    754  CA  ARG A  98     -16.117  27.695  10.638  1.00  7.12           C
ATOM    755  C   ARG A  98     -17.430  28.221  10.051  1.00  5.89           C
ATOM    756  O   ARG A  98     -18.456  28.299  10.723  1.00  6.29           O
ATOM    757  CB  ARG A  98     -15.142  28.850  10.852  1.00  8.63           C
ATOM    758  CG  ARG A  98     -15.637  29.977  11.756  1.00 10.60           C
ATOM    759  CD  ARG A  98     -14.744  31.189  11.573  1.00 10.59           C
ATOM    760  NE  ARG A  98     -15.017  31.792  10.268  1.00 10.15           N
ATOM    761  CZ  ARG A  98     -14.335  32.796   9.731  1.00 10.10           C
ATOM    762  NH1 ARG A  98     -13.310  33.337  10.377  1.00 11.94           N
ATOM    763  NH2 ARG A  98     -14.697  33.265   8.543  1.00 10.42           N
ATOM    764  N   ASP A  99     -17.395  28.585   8.770  1.00  6.39           N
ATOM    765  CA  ASP A  99     -18.579  29.151   8.127  1.00  7.52           C
ATOM    766  C   ASP A  99     -19.709  28.118   7.947  1.00  4.77           C
ATOM    767  O   ASP A  99     -20.882  28.438   8.121  1.00  5.81           O
ATOM    768  CB  ASP A  99     -18.211  29.818   6.795  1.00  7.19           C
ATOM    769  CG  ASP A  99     -17.358  31.083   6.974  1.00  9.39           C
ATOM    770  OD1 ASP A  99     -17.061  31.490   8.129  1.00  9.24           O
ATOM    771  OD2 ASP A  99     -16.950  31.677   5.948  1.00  8.90           O
ATOM    772  N   VAL A 100     -19.349  26.875   7.611  1.00  5.99           N
ATOM    773  CA  VAL A 100     -20.360  25.815   7.575  1.00  5.66           C
ATOM    774  C   VAL A 100     -21.017  25.659   8.958  1.00  4.09           C
ATOM    775  O   VAL A 100     -22.228  25.583   9.061  1.00  6.12           O
ATOM    776  CB  VAL A 100     -19.783  24.457   7.079  1.00  5.14           C
ATOM    777  CG1 VAL A 100     -20.807  23.349   7.288  1.00  8.00           C
ATOM    778  CG2 VAL A 100     -19.404  24.560   5.599  1.00  8.22           C
ATOM    779  N   LEU A 101     -20.184  25.628  10.001  1.00  5.14           N
ATOM    780  CA  LEU A 101     -20.722  25.484  11.361  1.00  6.56           C
ATOM    781  C   LEU A 101     -21.636  26.651  11.768  1.00  6.23           C
ATOM    782  O   LEU A 101     -22.652  26.444  12.419  1.00  6.91           O
ATOM    783  CB  LEU A 101     -19.591  25.278  12.369  1.00  7.60           C
ATOM    784  CG  LEU A 101     -18.909  23.905  12.286  1.00  9.07           C
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ATOM    785  CD1 LEU A 101     -17.675  23.904  13.156  1.00 13.36           C
ATOM    786  CD2 LEU A 101     -19.878  22.797  12.691  1.00 12.74           C
ATOM    787  N   GLN A 102     -21.294  27.864  11.342  1.00  5.43           N
ATOM    788  CA  GLN A 102     -22.177  28.997  11.599  1.00  5.19           C
ATOM    789  C   GLN A 102     -23.543  28.772  10.970  1.00  6.32           C
ATOM    790  O   GLN A 102     -24.579  28.956  11.610  1.00  6.82           O
ATOM    791  CB  GLN A 102     -21.552  30.286  11.068  1.00  6.74           C
ATOM    792  CG  GLN A 102     -22.446  31.499  11.276  1.00  7.84           C
ATOM    793  CD  GLN A 102     -21.965  32.740  10.550  1.00  7.29           C
ATOM    794  OE1 GLN A 102     -20.883  32.767   9.977  1.00  9.47           O
ATOM    795  NE2 GLN A 102     -22.787  33.791  10.585  1.00  8.18           N
ATOM    796  N   HIS A 103     -23.552  28.370   9.699  1.00  5.94           N
ATOM    797  CA  HIS A 103     -24.801  28.171   9.002  1.00  6.08           C
ATOM    798  C   HIS A 103     -25.598  27.012   9.607  1.00  4.80           C
ATOM    799  O   HIS A 103     -26.801  27.111   9.797  1.00  6.26           O
ATOM    800  CB  HIS A 103     -24.531  27.925   7.515  1.00  6.90           C
ATOM    801  CG  HIS A 103     -25.677  28.278   6.631  1.00  7.96           C
ATOM    802  ND1 HIS A 103     -25.565  28.282   5.256  1.00  8.59           N
ATOM    803  CD2 HIS A 103     -26.945  28.655   6.910  1.00  6.64           C
ATOM    804  CE1 HIS A 103     -26.719  28.655   4.728  1.00  8.29           C
ATOM    805  NE2 HIS A 103     -27.581  28.872   5.708  1.00  9.02           N
ATOM    806  N   VAL A 104     -24.913  25.903   9.888  1.00  5.95           N
ATOM    807  CA  VAL A 104     -25.605  24.765  10.486  1.00  7.58           C
ATOM    808  C   VAL A 104     -26.224  25.153  11.843  1.00  5.80           C
ATOM    809  O   VAL A 104     -27.385  24.851  12.108  1.00  7.78           O
ATOM    810  CB  VAL A 104     -24.653  23.572  10.668  1.00  7.05           C
ATOM    811  CG1 VAL A 104     -25.302  22.506  11.558  1.00 10.12           C
ATOM    812  CG2 VAL A 104     -24.250  22.984   9.309  1.00  9.57           C
ATOM    813  N   ASP A 105     -25.434  25.831  12.676  1.00  6.23           N
ATOM    814  CA  ASP A 105     -25.933  26.244  13.994  1.00  6.14           C
ATOM    815  C   ASP A 105     -27.133  27.178  13.856  1.00  8.33           C
ATOM    816  O   ASP A 105     -28.112  27.052  14.592  1.00  8.56           O
ATOM    817  CB  ASP A 105     -24.839  26.905  14.843  1.00  7.42           C
ATOM    818  CG  ASP A 105     -23.776  25.920  15.336  1.00 13.92           C
ATOM    819  OD1 ASP A 105     -24.061  24.704  15.406  1.00 16.13           O
ATOM    820  OD2 ASP A 105     -22.648  26.361  15.663  1.00 13.33           O
ATOM    821  N   SER A 106     -27.082  28.111  12.903  1.00  7.27           N
ATOM    822  CA ASER A 106     -28.184  29.047  12.712  0.33  8.06           C
ATOM    823  C   SER A 106     -29.453  28.338  12.241  1.00  9.29           C
ATOM    824  O   SER A 106     -30.557  28.661  12.670  1.00 12.36           O
ATOM    825  CB ASER A 106     -27.791  30.152  11.727  0.33 12.36           C
ATOM    826  OG ASER A 106     -28.878  31.033  11.504  0.33 11.64           O
ATOM    827  CA BSER A 106     -28.189  29.044  12.739  0.33  7.72           C
ATOM    828  CB BSER A 106     -27.798  30.224  11.836  0.33  8.33           C
ATOM    829  OG BSER A 106     -27.502  29.800  10.519  0.33  9.09           O
ATOM    830  CA CSER A 106     -28.187  29.046  12.697  0.33  8.20           C
ATOM    831  CB CSER A 106     -27.805  30.112  11.671  0.33 14.56           C
ATOM    832  OG CSER A 106     -26.705  30.866  12.126  0.33 10.99           O
ATOM    833  N   MET A 107     -29.301  27.365  11.344  1.00  7.49           N
ATOM    834  CA AMET A 107     -30.442  26.604  10.845  0.50 10.61           C
ATOM    835  C   MET A 107     -31.031  25.708  11.936  1.00  6.77           C
ATOM    836  O   MET A 107     -32.255  25.615  12.087  1.00 11.21           O
ATOM    837  CB AMET A 107     -30.024  25.765   9.629  0.50 11.62           C
ATOM    838  CG AMET A 107     -31.142  24.962   8.981  0.50 11.62           C
ATOM    839  SD AMET A 107     -32.524  25.957   8.382  0.50 17.80           S
ATOM    840  CE AMET A 107     -31.659  27.299   7.589  0.50 16.49           C
ATOM    841  CA BMET A 107     -30.454  26.617  10.859  0.50  6.28           C
ATOM    842  CB BMET A 107     -30.076  25.798   9.625  0.50 11.75           C
ATOM    843  CG BMET A 107     -29.649  26.659   8.460  0.50 12.02           C
ATOM    844  SD BMET A 107     -30.974  27.746   7.914  0.50 26.78           S
ATOM    845  CE BMET A 107     -32.093  26.557   7.189  0.50 15.11           C
ATOM    846  N   GLN A 108     -30.154  25.044  12.688  1.00  9.49           N
ATOM    847  CA AGLN A 108     -30.611  24.118  13.720  0.50  9.57           C
ATOM    848  C   GLN A 108     -31.458  24.812  14.782  1.00 11.46           C
ATOM    849  O   GLN A 108     -32.441  24.243  15.262  1.00 12.43           O
ATOM    850  CB AGLN A 108     -29.439  23.367  14.357  0.50 12.58           C
ATOM    851  CG AGLN A 108     -28.938  22.209  13.504  0.50 12.65           C
ATOM    852  CD AGLN A 108     -28.137  21.196  14.294  0.50 68.54           C
ATOM    853  OE1AGLN A 108     -28.661  20.161  14.699  0.50 23.41           O
ATOM    854  NE2AGLN A 108     -26.864  21.489  14.521  0.50  7.83           N
ATOM    855  CA BGLN A 108     -30.589  24.119  13.737  0.50  8.69           C
ATOM    856  CB BGLN A 108     -29.391  23.463  14.430  0.50  9.25           C
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ATOM    857  CG BGLN A 108     -29.780  22.432  15.483  0.50 13.14           C
ATOM    858  CD BGLN A 108     -30.122  21.075  14.882  0.50 70.97           C
ATOM    859  OE1BGLN A 108     -29.236  20.263  14.616  0.50 17.19           O
ATOM    860  NE2BGLN A 108     -31.413  20.820  14.679  0.50  9.82           N
ATOM    861  N   LYS A 109     -31.099  26.046  15.133  1.00 10.35           N
ATOM    862  CA  LYS A 109     -31.860  26.757  16.166  1.00 12.18           C
ATOM    863  C   LYS A 109     -33.260  27.117  15.670  1.00 15.37           C
ATOM    864  O   LYS A 109     -34.181  27.259  16.477  1.00 15.02           O
ATOM    865  CB  LYS A 109     -31.119  28.010  16.647  1.00 12.62           C
ATOM    866  CG  LYS A 109     -31.207  29.149  15.643  1.00 24.20           C
ATOM    867  CD  LYS A 109     -30.473  30.401  16.074  1.00 26.44           C
ATOM    868  CE  LYS A 109     -30.940  31.602  15.256  1.00 17.15           C
ATOM    869  NZ  LYS A 109     -31.147  31.297  13.808  1.00 22.59           N
ATOM    870  N   ASP A 110     -33.420  27.265  14.352  1.00 11.64           N
ATOM    871  CA  ASP A 110     -34.731  27.502  13.748  1.00 14.09           C
ATOM    872  C   ASP A 110     -35.540  26.202  13.650  1.00 17.43           C
ATOM    873  O   ASP A 110     -36.768  26.227  13.596  1.00 16.72           O
ATOM    874  CB  ASP A 110     -34.603  28.125  12.349  1.00 16.62           C
ATOM    875  CG  ASP A 110     -33.858  29.459  12.349  1.00 35.51           C
ATOM    876  OD1 ASP A 110     -33.892  30.183  13.363  1.00 27.26           O
ATOM    877  OD2 ASP A 110     -33.242  29.795  11.314  1.00 33.71           O
ATOM    878  N   TYR A 111     -34.838  25.070  13.614  1.00 12.88           N
ATOM    879  CA  TYR A 111     -35.463  23.749  13.495  1.00 11.95           C
ATOM    880  C   TYR A 111     -34.929  22.816  14.570  1.00 14.36           C
ATOM    881  O   TYR A 111     -34.283  21.805  14.270  1.00 15.37           O
ATOM    882  CB  TYR A 111     -35.195  23.153  12.104  1.00 14.49           C
ATOM    883  CG  TYR A 111     -35.903  23.906  11.010  1.00 11.25           C
ATOM    884  CD1 TYR A 111     -35.303  24.996  10.389  1.00 11.70           C
ATOM    885  CD2 TYR A 111     -37.177  23.536  10.605  1.00 13.97           C
ATOM    886  CE1 TYR A 111     -35.964  25.702   9.397  1.00 12.73           C
ATOM    887  CE2 TYR A 111     -37.842  24.229   9.609  1.00 13.65           C
ATOM    888  CZ  TYR A 111     -37.234  25.306   9.013  1.00 13.00           C
ATOM    889  OH  TYR A 111     -37.903  25.994   8.027  1.00 17.94           O
ATOM    890  N   PRO A 112     -35.184  23.159  15.842  1.00 16.22           N
ATOM    891  CA  PRO A 112     -34.592  22.419  16.956  1.00 17.66           C
ATOM    892  C   PRO A 112     -35.069  20.974  16.951  1.00 18.24           C
ATOM    893  O   PRO A 112     -36.225  20.702  16.616  1.00 23.82           O
ATOM    894  CB  PRO A 112     -35.132  23.166  18.190  1.00 24.32           C
ATOM    895  CG  PRO A 112     -36.365  23.857  17.695  1.00 22.23           C
ATOM    896  CD  PRO A 112     -35.988  24.298  16.318  1.00 19.06           C
ATOM    897  N   GLY A 113     -34.176  20.058  17.295  1.00 21.11           N
ATOM    898  CA  GLY A 113     -34.537  18.657  17.369  1.00 27.87           C
ATOM    899  C   GLY A 113     -34.396  17.874  16.075  1.00 37.60           C
ATOM    900  O   GLY A 113     -34.388  16.645  16.105  1.00 26.73           O
ATOM    901  N   LEU A 114     -34.294  18.556  14.937  1.00 17.32           N
ATOM    902  CA  LEU A 114     -34.147  17.831  13.678  1.00 16.13           C
ATOM    903  C   LEU A 114     -32.712  17.349  13.481  1.00 14.38           C
ATOM    904  O   LEU A 114     -31.757  18.081  13.758  1.00 14.82           O
ATOM    905  CB  LEU A 114     -34.560  18.689  12.485  1.00 15.76           C
ATOM    906  CG  LEU A 114     -36.039  19.009  12.274  1.00 19.83           C
ATOM    907  CD1 LEU A 114     -36.244  19.522  10.860  1.00 22.33           C
ATOM    908  CD2 LEU A 114     -36.907  17.787  12.537  1.00 26.81           C
ATOM    909  N   PRO A 115     -32.559  16.110  12.993  1.00 14.51           N
ATOM    910  CA  PRO A 115     -31.241  15.578  12.631  1.00 14.94           C
ATOM    911  C   PRO A 115     -30.640  16.390  11.484  1.00  9.64           C
ATOM    912  O   PRO A 115     -31.386  16.881  10.636  1.00 12.08           O
ATOM    913  CB  PRO A 115     -31.554  14.159  12.140  1.00 16.54           C
ATOM    914  CG  PRO A 115     -32.911  13.846  12.664  1.00 25.57           C
ATOM    915  CD  PRO A 115     -33.640  15.148  12.735  1.00 14.61           C
ATOM    916  N   VAL A 116     -29.320  16.522  11.472  1.00  8.33           N
ATOM    917  CA AVAL A 116     -28.656  17.245  10.396  0.50  6.55           C
ATOM    918  C   VAL A 116     -27.608  16.371   9.703  1.00  9.54           C
ATOM    919  O   VAL A 116     -26.774  15.730  10.337  1.00  9.56           O
ATOM    920  CB AVAL A 116     -28.055  18.584  10.888  0.50 13.27           C
ATOM    921  CG1AVAL A 116     -27.021  18.342  11.977  0.50 10.54           C
ATOM    922  CG2AVAL A 116     -27.472  19.385   9.721  0.50  6.54           C
ATOM    923  CA BVAL A 116     -28.606  17.265  10.430  0.50 11.46           C
ATOM    924  CB BVAL A 116     -27.833  18.463  11.022  0.50  7.27           C
ATOM    925  CG1BVAL A 116     -26.972  19.144   9.954  0.50 10.48           C
ATOM    926  CG2BVAL A 116     -28.798  19.447  11.664  0.50 11.77           C
ATOM    927  N   PHE A 117     -27.694  16.350   8.377  1.00  8.25           N
ATOM    928  CA  PHE A 117     -26.766  15.613   7.523  1.00  6.73           C
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ATOM    929  C   PHE A 117     -25.872  16.596   6.781  1.00  7.65           C
ATOM    930  O   PHE A 117     -26.221  17.782   6.646  1.00  7.95           O
ATOM    931  CB  PHE A 117     -27.544  14.791   6.495  1.00  7.19           C
ATOM    932  CG  PHE A 117     -28.342  13.659   7.089  1.00  9.66           C
ATOM    933  CD1 PHE A 117     -29.578  13.888   7.675  1.00  9.86           C
ATOM    934  CD2 PHE A 117     -27.858  12.366   7.035  1.00 11.39           C
ATOM    935  CE1 PHE A 117     -30.315  12.846   8.221  1.00 11.17           C
ATOM    936  CE2 PHE A 117     -28.592  11.316   7.576  1.00 12.02           C
ATOM    937  CZ  PHE A 117     -29.810  11.552   8.167  1.00 12.26           C
ATOM    938  N   LEU A 118     -24.751  16.093   6.272  1.00  6.39           N
ATOM    939  CA  LEU A 118     -23.844  16.851   5.409  1.00  6.79           C
ATOM    940  C   LEU A 118     -23.696  16.104   4.084  1.00  9.58           C
ATOM    941  O   LEU A 118     -23.659  14.869   4.053  1.00 10.15           O
ATOM    942  CB  LEU A 118     -22.467  16.990   6.054  1.00  8.39           C
ATOM    943  CG  LEU A 118     -22.423  17.678   7.421  1.00  7.65           C
ATOM    944  CD1 LEU A 118     -21.069  17.514   8.065  1.00 12.05           C
ATOM    945  CD2 LEU A 118     -22.805  19.163   7.274  1.00 14.26           C
ATOM    946  N   LEU A 119     -23.606  16.848   2.989  1.00  6.75           N
ATOM    947  CA  LEU A 119     -23.262  16.262   1.695  1.00  6.84           C
ATOM    948  C   LEU A 119     -22.159  17.111   1.091  1.00  6.93           C
ATOM    949  O   LEU A 119     -22.288  18.341   1.039  1.00  9.68           O
ATOM    950  CB  LEU A 119     -24.478  16.235   0.780  1.00  9.51           C
ATOM    951  CG  LEU A 119     -24.279  15.572  -0.595  1.00  8.88           C
ATOM    952  CD1 LEU A 119     -25.576  14.929  -1.069  1.00 14.75           C
ATOM    953  CD2 LEU A 119     -23.738  16.566  -1.628  1.00 12.64           C
ATOM    954  N   GLY A 120     -21.076  16.486   0.640  1.00  5.97           N
ATOM    955  CA  GLY A 120     -19.986  17.265   0.088  1.00  6.20           C
ATOM    956  C   GLY A 120     -19.321  16.567  -1.078  1.00  7.47           C
ATOM    957  O   GLY A 120     -19.260  15.334  -1.112  1.00  8.48           O
ATOM    958  N   HIS A 121     -18.805  17.354  -2.013  1.00  4.99           N
ATOM    959  CA  HIS A 121     -18.051  16.840  -3.158  1.00  5.24           C
ATOM    960  C   HIS A 121     -16.656  17.442  -3.172  1.00  4.93           C
ATOM    961  O   HIS A 121     -16.494  18.663  -3.004  1.00  6.29           O
ATOM    962  CB  HIS A 121     -18.791  17.217  -4.456  1.00  6.08           C
ATOM    963  CG  HIS A 121     -17.985  17.032  -5.712  1.00  7.22           C
ATOM    964  ND1 HIS A 121     -17.405  15.831  -6.075  1.00  8.06           N
ATOM    965  CD2 HIS A 121     -17.688  17.906  -6.707  1.00  6.53           C
ATOM    966  CE1 HIS A 121     -16.785  15.977  -7.238  1.00  8.61           C
ATOM    967  NE2 HIS A 121     -16.941  17.227  -7.641  1.00  7.27           N
ATOM    968  N   SER A 122     -15.635  16.614  -3.358  1.00  5.44           N
ATOM    969  CA  SER A 122     -14.288  17.105  -3.623  1.00  6.10           C
ATOM    970  C   SER A 122     -13.779  17.939  -2.431  1.00  7.18           C
ATOM    971  O   SER A 122     -13.808  17.447  -1.292  1.00  6.60           O
ATOM    972  CB  SER A 122     -14.240  17.852  -4.976  1.00  7.68           C
ATOM    973  OG  SER A 122     -12.925  17.935  -5.480  1.00  8.60           O
ATOM    974  N   MET A 123     -13.298  19.163  -2.648  1.00  7.05           N
ATOM    975  CA  MET A 123     -12.930  20.012  -1.510  1.00  6.85           C
ATOM    976  C   MET A 123     -14.067  20.114  -0.498  1.00  5.95           C
ATOM    977  O   MET A 123     -13.825  20.180   0.715  1.00  6.61           O
ATOM    978  CB  MET A 123     -12.544  21.418  -1.969  1.00  6.44           C
ATOM    979  CG  MET A 123     -12.132  22.321  -0.808  1.00  6.74           C
ATOM    980  SD  MET A 123     -11.872  24.035  -1.346  1.00  9.51           S
ATOM    981  CE  MET A 123     -13.527  24.679  -1.392  1.00 11.77           C
ATOM    982  N   GLY A 124     -15.294  20.162  -0.991  1.00  5.76           N
ATOM    983  CA  GLY A 124     -16.465  20.242  -0.134  1.00  5.33           C
ATOM    984  C   GLY A 124     -16.644  19.005   0.733  1.00  6.28           C
ATOM    985  O   GLY A 124     -17.250  19.080   1.807  1.00  7.72           O
ATOM    986  N   GLY A 125     -16.131  17.871   0.258  1.00  6.88           N
ATOM    987  CA  GLY A 125     -16.123  16.647   1.048  1.00  6.32           C
ATOM    988  C   GLY A 125     -15.096  16.702   2.164  1.00  7.06           C
ATOM    989  O   GLY A 125     -15.362  16.219   3.275  1.00  8.26           O
ATOM    990  N   ALA A 126     -13.936  17.291   1.906  1.00  6.65           N
ATOM    991  CA  ALA A 126     -12.967  17.542   2.966  1.00  7.07           C
ATOM    992  C   ALA A 126     -13.560  18.468   4.027  1.00  8.51           C
ATOM    993  O   ALA A 126     -13.390  18.234   5.232  1.00  8.99           O
ATOM    994  CB  ALA A 126     -11.685  18.140   2.394  1.00  9.00           C
ATOM    995  N   ILE A 127     -14.256  19.510   3.587  1.00  5.80           N
ATOM    996  CA  ILE A 127     -14.899  20.425   4.512  1.00  5.81           C
ATOM    997  C   ILE A 127     -15.919  19.663   5.359  1.00  7.22           C
ATOM    998  O   ILE A 127     -15.978  19.846   6.586  1.00  8.40           O
ATOM    999  CB  ILE A 127     -15.560  21.585   3.757  1.00  5.20           C
ATOM   1000  CG1 ILE A 127     -14.479  22.471   3.125  1.00  6.80           C
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ATOM   1001  CG2 ILE A 127     -16.455  22.395   4.692  1.00  7.18           C
ATOM   1002  CD1 ILE A 127     -14.991  23.467   2.072  1.00  8.65           C
ATOM   1003  N   ALA A 128     -16.708  18.794   4.735  1.00  6.54           N
ATOM   1004  CA  ALA A 128     -17.685  17.983   5.472  1.00  6.61           C
ATOM   1005  C   ALA A 128     -17.014  17.098   6.525  1.00  6.98           C
ATOM   1006  O   ALA A 128     -17.470  17.038   7.676  1.00  8.44           O
ATOM   1007  CB  ALA A 128     -18.527  17.138   4.522  1.00  8.15           C
ATOM   1008  N   ILE A 129     -15.951  16.402   6.138  1.00  6.43           N
ATOM   1009  CA  ILE A 129     -15.234  15.541   7.073  1.00  8.20           C
ATOM   1010  C   ILE A 129     -14.742  16.355   8.274  1.00  7.24           C
ATOM   1011  O   ILE A 129     -14.921  15.943   9.432  1.00  9.40           O
ATOM   1012  CB  ILE A 129     -14.056  14.835   6.372  1.00  7.21           C
ATOM   1013  CG1 ILE A 129     -14.577  13.788   5.374  1.00  8.59           C
ATOM   1014  CG2 ILE A 129     -13.099  14.196   7.392  1.00  8.65           C
ATOM   1015  CD1 ILE A 129     -13.518  13.302   4.381  1.00  8.43           C
ATOM   1016  N   LEU A 130     -14.109  17.494   8.016  1.00  7.88           N
ATOM   1017  CA  LEU A 130     -13.564  18.322   9.090  1.00  7.26           C
ATOM   1018  C   LEU A 130     -14.648  18.930   9.968  1.00  8.38           C
ATOM   1019  O   LEU A 130     -14.440  19.099  11.175  1.00 11.78           O
ATOM   1020  CB  LEU A 130     -12.629  19.396   8.522  1.00  7.43           C
ATOM   1021  CG  LEU A 130     -11.379  18.824   7.851  1.00  7.20           C
ATOM   1022  CD1 LEU A 130     -10.588  19.932   7.164  1.00 11.26           C
ATOM   1023  CD2 LEU A 130     -10.499  18.088   8.856  1.00 11.11           C
ATOM   1024  N   THR A 131     -15.792  19.247   9.381  1.00  6.76           N
ATOM   1025  CA  THR A 131     -16.937  19.765  10.120  1.00  7.15           C
ATOM   1026  C   THR A 131     -17.469  18.709  11.090  1.00 10.49           C
ATOM   1027  O   THR A 131     -17.694  18.990  12.278  1.00 10.09           O
ATOM   1028  CB  THR A 131     -18.044  20.221   9.142  1.00  6.73           C
ATOM   1029  OG1 THR A 131     -17.544  21.303   8.342  1.00  9.73           O
ATOM   1030  CG2 THR A 131     -19.293  20.695   9.876  1.00  9.04           C
ATOM   1031  N   ALA A 132     -17.667  17.493  10.591  1.00  8.54           N
ATOM   1032  CA  ALA A 132     -18.145  16.401  11.429  1.00 10.74           C
ATOM   1033  C   ALA A 132     -17.152  16.098  12.545  1.00 13.98           C
ATOM   1034  O   ALA A 132     -17.559  15.799  13.674  1.00 17.35           O
ATOM   1035  CB  ALA A 132     -18.395  15.153  10.588  1.00 12.21           C
ATOM   1036  N   ALA A 133     -15.862  16.190  12.247  1.00 11.80           N
ATOM   1037  CA  ALA A 133     -14.836  15.861  13.228  1.00 13.45           C
ATOM   1038  C   ALA A 133     -14.746  16.916  14.325  1.00 17.15           C
ATOM   1039  O   ALA A 133     -14.327  16.619  15.451  1.00 19.66           O
ATOM   1040  CB  ALA A 133     -13.475  15.669  12.546  1.00 15.60           C
ATOM   1041  N   GLU A 134     -15.139  18.143  14.001  1.00 16.89           N
ATOM   1042  CA  GLU A 134     -15.107  19.240  14.961  1.00 17.80           C
ATOM   1043  C   GLU A 134     -16.272  19.188  15.952  1.00 21.56           C
ATOM   1044  O   GLU A 134     -16.207  19.805  17.023  1.00 21.34           O
ATOM   1045  CB  GLU A 134     -15.086  20.585  14.232  1.00 19.70           C
ATOM   1046  CG  GLU A 134     -15.042  21.779  15.166  1.00 31.66           C
ATOM   1047  CD  GLU A 134     -14.422  22.997  14.524  1.00 77.78           C
ATOM   1048  OE1 GLU A 134     -13.675  22.834  13.534  1.00 29.11           O
ATOM   1049  OE2 GLU A 134     -14.678  24.116  15.017  1.00 32.70           O
ATOM   1050  N   ARG A 135     -17.328  18.457  15.597  1.00 15.43           N
ATOM   1051  CA  ARG A 135     -18.489  18.264  16.470  1.00 14.20           C
ATOM   1052  C   ARG A 135     -18.795  16.777  16.633  1.00 15.41           C
ATOM   1053  O   ARG A 135     -19.804  16.274  16.129  1.00 16.46           O
ATOM   1054  CB  ARG A 135     -19.717  18.994  15.924  1.00 15.89           C
ATOM   1055  CG  ARG A 135     -19.520  20.485  15.716  1.00 19.46           C
ATOM   1056  CD  ARG A 135     -19.647  21.282  17.015  1.00 22.44           C
ATOM   1057  NE  ARG A 135     -19.498  22.713  16.762  1.00 17.05           N
ATOM   1058  CZ  ARG A 135     -20.503  23.518  16.428  1.00 13.79           C
ATOM   1059  NH1 ARG A 135     -21.738  23.043  16.315  1.00 15.86           N
ATOM   1060  NH2 ARG A 135     -20.264  24.802  16.195  1.00 15.95           N
ATOM   1061  N   PRO A 136     -17.921  16.062  17.353  1.00 20.51           N
ATOM   1062  CA  PRO A 136     -18.056  14.607  17.494  1.00 24.54           C
ATOM   1063  C   PRO A 136     -19.441  14.177  17.975  1.00 29.40           C
ATOM   1064  O   PRO A 136     -19.924  14.677  18.994  1.00 23.65           O
ATOM   1065  CB  PRO A 136     -16.966  14.262  18.554  1.00 27.33           C
ATOM   1066  CG  PRO A 136     -16.000  15.361  18.471  1.00 33.77           C
ATOM   1067  CD  PRO A 136     -16.774  16.596  18.109  1.00 22.45           C
ATOM   1068  N   GLY A 137     -20.063  13.257  17.244  1.00 19.62           N
ATOM   1069  CA  GLY A 137     -21.346  12.689  17.613  1.00 16.56           C
ATOM   1070  C   GLY A 137     -22.563  13.519  17.260  1.00 18.57           C
ATOM   1071  O   GLY A 137     -23.687  13.134  17.559  1.00 24.49           O
ATOM   1072  N   HIS A 138     -22.347  14.657  16.605  1.00 14.73           N
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ATOM   1073  CA  HIS A 138     -23.423  15.610  16.384  1.00 14.81           C
ATOM   1074  C   HIS A 138     -24.243  15.369  15.103  1.00 13.75           C
ATOM   1075  O   HIS A 138     -25.472  15.419  15.122  1.00 17.01           O
ATOM   1076  CB  HIS A 138     -22.853  17.027  16.385  1.00 17.64           C
ATOM   1077  CG  HIS A 138     -23.888  18.087  16.192  1.00 19.02           C
ATOM   1078  ND1 HIS A 138     -24.835  18.385  17.150  1.00 24.37           N
ATOM   1079  CD2 HIS A 138     -24.131  18.918  15.151  1.00 21.19           C
ATOM   1080  CE1 HIS A 138     -25.615  19.354  16.706  1.00 53.43           C
ATOM   1081  NE2 HIS A 138     -25.210  19.695  15.496  1.00 28.81           N
ATOM   1082  N   PHE A 139     -23.557  15.105  13.993  1.00 12.98           N
ATOM   1083  CA  PHE A 139     -24.235  14.934  12.708  1.00 12.74           C
ATOM   1084  C   PHE A 139     -24.824  13.537  12.536  1.00  8.88           C
ATOM   1085  O   PHE A 139     -24.244  12.555  13.007  1.00 12.86           O
ATOM   1086  CB  PHE A 139     -23.280  15.293  11.558  1.00 11.40           C
ATOM   1087  CG  PHE A 139     -22.933  16.751  11.522  1.00  8.97           C
ATOM   1088  CD1 PHE A 139     -23.765  17.647  10.875  1.00 10.65           C
ATOM   1089  CD2 PHE A 139     -21.807  17.228  12.169  1.00 10.08           C
ATOM   1090  CE1 PHE A 139     -23.456  19.002  10.856  1.00 11.55           C
ATOM   1091  CE2 PHE A 139     -21.501  18.580  12.162  1.00  9.46           C
ATOM   1092  CZ  PHE A 139     -22.330  19.464  11.501  1.00 11.90           C
ATOM   1093  N   ALA A 140     -25.969  13.462  11.872  1.00 10.10           N
ATOM   1094  CA  ALA A 140     -26.681  12.201  11.680  1.00 11.80           C
ATOM   1095  C   ALA A 140     -26.034  11.356  10.589  1.00 12.36           C
ATOM   1096  O   ALA A 140     -26.193  10.135  10.557  1.00 13.34           O
ATOM   1097  CB  ALA A 140     -28.128  12.459  11.333  1.00 12.22           C
ATOM   1098  N   GLY A 141     -25.327  12.009   9.675  1.00  9.31           N
ATOM   1099  CA  GLY A 141     -24.774  11.289   8.546  1.00  9.56           C
ATOM   1100  C   GLY A 141     -24.130  12.212   7.548  1.00 11.98           C
ATOM   1101  O   GLY A 141     -24.391  13.420   7.525  1.00 10.18           O
ATOM   1102  N   MET A 142     -23.292  11.614   6.711  1.00  8.32           N
ATOM   1103  CA AMET A 142     -22.502  12.331   5.725  0.70  8.58           C
ATOM   1104  C   MET A 142     -22.554  11.573   4.389  1.00  9.98           C
ATOM   1105  O   MET A 142     -22.320  10.356   4.367  1.00 10.51           O
ATOM   1106  CB AMET A 142     -21.067  12.360   6.237  0.70 25.98           C
ATOM   1107  CG AMET A 142     -20.126  13.326   5.579  0.70 16.80           C
ATOM   1108  SD AMET A 142     -18.699  13.543   6.679  0.70 15.44           S
ATOM   1109  CE AMET A 142     -18.032  11.891   6.773  0.70 13.72           C
ATOM   1110  CA BMET A 142     -22.589  12.353   5.680  0.30  8.38           C
ATOM   1111  CB BMET A 142     -21.163  12.652   6.104  0.30  4.61           C
ATOM   1112  CG BMET A 142     -21.010  13.930   6.885  0.30 26.62           C
ATOM   1113  SD BMET A 142     -19.322  14.124   7.459  0.30 21.03           S
ATOM   1114  CE BMET A 142     -18.407  13.324   6.145  0.30 22.67           C
ATOM   1115  N   VAL A 143     -22.825  12.281   3.299  1.00  7.01           N
ATOM   1116  CA  VAL A 143     -22.730  11.708   1.964  1.00  7.21           C
ATOM   1117  C   VAL A 143     -21.561  12.389   1.268  1.00  7.22           C
ATOM   1118  O   VAL A 143     -21.534  13.624   1.135  1.00  7.86           O
ATOM   1119  CB  VAL A 143     -24.017  11.957   1.159  1.00  8.34           C
ATOM   1120  CG1 VAL A 143     -23.839  11.460  -0.286  1.00 10.34           C
ATOM   1121  CG2 VAL A 143     -25.207  11.275   1.833  1.00 10.57           C
ATOM   1122  N   LEU A 144     -20.576  11.601   0.853  1.00  5.85           N
ATOM   1123  CA  LEU A 144     -19.357  12.139   0.276  1.00  6.51           C
ATOM   1124  C   LEU A 144     -19.222  11.661  -1.160  1.00  8.86           C
ATOM   1125  O   LEU A 144     -19.195  10.456  -1.439  1.00  7.94           O
ATOM   1126  CB  LEU A 144     -18.143  11.680   1.084  1.00  6.27           C
ATOM   1127  CG  LEU A 144     -18.117  12.083   2.559  1.00  9.97           C
ATOM   1128  CD1 LEU A 144     -16.959  11.359   3.232  1.00 11.52           C
ATOM   1129  CD2 LEU A 144     -17.983  13.615   2.693  1.00 11.05           C
ATOM   1130  N   ILE A 145     -19.179  12.618  -2.079  1.00  5.85           N
ATOM   1131  CA  ILE A 145     -18.973  12.315  -3.490  1.00  6.29           C
ATOM   1132  C   ILE A 145     -17.545  12.689  -3.844  1.00  6.81           C
ATOM   1133  O   ILE A 145     -17.194  13.876  -3.904  1.00  6.91           O
ATOM   1134  CB  ILE A 145     -19.957  13.103  -4.377  1.00  5.41           C
ATOM   1135  CG1 ILE A 145     -21.400  12.836  -3.954  1.00  9.22           C
ATOM   1136  CG2 ILE A 145     -19.742  12.726  -5.846  1.00  8.27           C
ATOM   1137  CD1 ILE A 145     -22.431  13.717  -4.651  1.00  9.95           C
ATOM   1138  N   SER A 146     -16.689  11.689  -4.034  1.00  6.84           N
ATOM   1139  CA  SER A 146     -15.301  11.934  -4.411  1.00  6.91           C
ATOM   1140  C   SER A 146     -14.655  12.966  -3.493  1.00  7.51           C
ATOM   1141  O   SER A 146     -14.114  13.975  -3.958  1.00  7.48           O
ATOM   1142  CB  SER A 146     -15.201  12.439  -5.857  1.00  8.55           C
ATOM   1143  OG  SER A 146     -16.035  11.684  -6.705  1.00 19.57           O
ATOM   1144  N   PRO A 147     -14.668  12.714  -2.178  1.00  7.19           N
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ATOM   1145  CA  PRO A 147     -14.114  13.708  -1.250  1.00  6.02           C
ATOM   1146  C   PRO A 147     -12.612  13.828  -1.423  1.00  8.82           C
ATOM   1147  O   PRO A 147     -11.933  12.854  -1.765  1.00  8.83           O
ATOM   1148  CB  PRO A 147     -14.431  13.108   0.123  1.00  7.28           C
ATOM   1149  CG  PRO A 147     -14.419  11.598  -0.149  1.00  7.97           C
ATOM   1150  CD  PRO A 147     -15.119  11.491  -1.486  1.00  7.21           C
ATOM   1151  N   LEU A 148     -12.077  15.017  -1.183  1.00  7.64           N
ATOM   1152  CA  LEU A 148     -10.643  15.212  -1.171  1.00  7.57           C
ATOM   1153  C   LEU A 148     -10.037  14.612   0.100  1.00 10.69           C
ATOM   1154  O   LEU A 148     -10.082  15.230   1.180  1.00 13.01           O
ATOM   1155  CB  LEU A 148     -10.308  16.702  -1.295  1.00 10.01           C
ATOM   1156  CG  LEU A 148      -8.831  17.084  -1.238  1.00 13.54           C
ATOM   1157  CD1 LEU A 148      -8.050  16.349  -2.318  1.00 18.01           C
ATOM   1158  CD2 LEU A 148      -8.660  18.592  -1.378  1.00 19.64           C
ATOM   1159  N   VAL A 149      -9.491  13.403  -0.029  1.00 10.28           N
ATOM   1160  CA  VAL A 149      -8.837  12.724   1.087  1.00  9.11           C
ATOM   1161  C   VAL A 149      -7.359  12.529   0.775  1.00 11.36           C
ATOM   1162  O   VAL A 149      -6.496  12.909   1.560  1.00 13.79           O
ATOM   1163  CB  VAL A 149      -9.514  11.374   1.410  1.00  7.75           C
ATOM   1164  CG1 VAL A 149      -8.733  10.636   2.512  1.00  9.82           C
ATOM   1165  CG2 VAL A 149     -10.957  11.592   1.816  1.00  8.89           C
ATOM   1166  N   LEU A 150      -7.069  11.934  -0.380  1.00 10.74           N
ATOM   1167  CA  LEU A 150      -5.705  11.867  -0.886  1.00 12.38           C
ATOM   1168  C   LEU A 150      -5.711  12.416  -2.295  1.00 13.20           C
ATOM   1169  O   LEU A 150      -6.533  12.017  -3.119  1.00 14.22           O
ATOM   1170  CB  LEU A 150      -5.185  10.428  -0.916  1.00 13.51           C
ATOM   1171  CG  LEU A 150      -4.880   9.789   0.439  1.00 17.14           C
ATOM   1172  CD1 LEU A 150      -3.807  10.577   1.181  1.00 19.78           C
ATOM   1173  CD2 LEU A 150      -4.453   8.333   0.248  1.00 21.23           C
ATOM   1174  N   ALA A 151      -4.803  13.338  -2.572  1.00 12.30           N
ATOM   1175  CA  ALA A 151      -4.701  13.879  -3.917  1.00 16.69           C
ATOM   1176  C   ALA A 151      -3.972  12.890  -4.819  1.00 15.92           C
ATOM   1177  O   ALA A 151      -3.240  12.021  -4.344  1.00 15.20           O
ATOM   1178  CB  ALA A 151      -3.981  15.220  -3.893  1.00 20.19           C
ATOM   1179  N   ASN A 152      -4.191  13.011  -6.120  1.00 14.44           N
ATOM   1180  CA  ASN A 152      -3.363  12.292  -7.071  1.00 13.52           C
ATOM   1181  C   ASN A 152      -1.896  12.543  -6.728  1.00 14.72           C
ATOM   1182  O   ASN A 152      -1.469  13.694  -6.634  1.00 15.93           O
ATOM   1183  CB  ASN A 152      -3.674  12.764  -8.487  1.00 19.76           C
ATOM   1184  CG  ASN A 152      -2.809  12.089  -9.524  1.00 18.69           C
ATOM   1185  OD1 ASN A 152      -1.632  12.417  -9.674  1.00 20.74           O
ATOM   1186  ND2 ASN A 152      -3.389  11.138 -10.251  1.00 23.13           N
ATOM   1187  N   PRO A 153      -1.122  11.467  -6.513  1.00 16.79           N
ATOM   1188  CA  PRO A 153       0.264  11.579  -6.041  1.00 17.04           C
ATOM   1189  C   PRO A 153       1.151  12.434  -6.946  1.00 16.59           C
ATOM   1190  O   PRO A 153       1.901  13.272  -6.445  1.00 17.20           O
ATOM   1191  CB  PRO A 153       0.749  10.125  -6.034  1.00 23.14           C
ATOM   1192  CG  PRO A 153      -0.491   9.322  -5.850  1.00 26.11           C
ATOM   1193  CD  PRO A 153      -1.570  10.065  -6.589  1.00 18.51           C
ATOM   1194  N   GLU A 154       1.072  12.222  -8.254  1.00 17.01           N
ATOM   1195  CA  GLU A 154       1.860  13.019  -9.191  1.00 17.94           C
ATOM   1196  C   GLU A 154       1.463  14.494  -9.151  1.00 16.34           C
ATOM   1197  O   GLU A 154       2.329  15.369  -9.141  1.00 16.77           O
ATOM   1198  CB  GLU A 154       1.754  12.464 -10.616  1.00 19.72           C
ATOM   1199  CG  GLU A 154       2.514  11.160 -10.810  1.00 56.06           C
ATOM   1200  CD  GLU A 154       2.713  10.806 -12.270  1.00 91.32           C
ATOM   1201  OE1 GLU A 154       2.125  11.488 -13.136  1.00 55.91           O
ATOM   1202  OE2 GLU A 154       3.462   9.845 -12.549  1.00 63.05           O
ATOM   1203  N   SER A 155       0.161  14.767  -9.124  1.00 14.06           N
ATOM   1204  CA  SER A 155      -0.333  16.141  -9.044  1.00 13.04           C
ATOM   1205  C   SER A 155       0.097  16.835  -7.752  1.00 13.20           C
ATOM   1206  O   SER A 155       0.483  18.007  -7.764  1.00 15.06           O
ATOM   1207  CB  SER A 155      -1.856  16.180  -9.150  1.00 19.70           C
ATOM   1208  OG  SER A 155      -2.293  15.617 -10.374  1.00 24.81           O
ATOM   1209  N   ALA A 156       0.018  16.113  -6.641  1.00 13.13           N
ATOM   1210  CA  ALA A 156       0.429  16.669  -5.357  1.00 14.25           C
ATOM   1211  C   ALA A 156       1.913  17.014  -5.368  1.00 14.95           C
ATOM   1212  O   ALA A 156       2.321  18.091  -4.916  1.00 13.46           O
ATOM   1213  CB  ALA A 156       0.118  15.696  -4.224  1.00 16.70           C
ATOM   1214  N   THR A 157       2.723  16.098  -5.890  1.00 13.19           N
ATOM   1215  CA  THR A 157       4.164  16.321  -5.953  1.00 12.51           C
ATOM   1216  C   THR A 157       4.494  17.494  -6.868  1.00 11.38           C
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ATOM   1217  O   THR A 157       5.311  18.351  -6.521  1.00 13.00           O
ATOM   1218  CB  THR A 157       4.897  15.066  -6.435  1.00 16.00           C
ATOM   1219  OG1 THR A 157       4.623  13.991  -5.527  1.00 20.31           O
ATOM   1220  CG2 THR A 157       6.400  15.307  -6.485  1.00 16.90           C
ATOM   1221  N   THR A 158       3.858  17.525  -8.036  1.00 11.66           N
ATOM   1222  CA  THR A 158       4.036  18.639  -8.965  1.00 12.58           C
ATOM   1223  C   THR A 158       3.720  19.944  -8.250  1.00 12.22           C
ATOM   1224  O   THR A 158       4.459  20.927  -8.360  1.00 11.34           O
ATOM   1225  CB  THR A 158       3.119  18.502 -10.194  1.00 13.07           C
ATOM   1226  OG1 THR A 158       3.539  17.373 -10.972  1.00 16.60           O
ATOM   1227  CG2 THR A 158       3.174  19.755 -11.065  1.00 12.95           C
ATOM   1228  N   PHE A 159       2.620  19.962  -7.506  1.00 10.44           N
ATOM   1229  CA  PHE A 159       2.245  21.202  -6.850  1.00 11.72           C
ATOM   1230  C   PHE A 159       3.243  21.604  -5.765  1.00  9.72           C
ATOM   1231  O   PHE A 159       3.589  22.777  -5.652  1.00 11.95           O
ATOM   1232  CB  PHE A 159       0.842  21.161  -6.256  1.00 10.51           C
ATOM   1233  CG  PHE A 159       0.509  22.417  -5.524  1.00 12.93           C
ATOM   1234  CD1 PHE A 159       0.146  23.552  -6.224  1.00 12.61           C
ATOM   1235  CD2 PHE A 159       0.658  22.492  -4.150  1.00 13.42           C
ATOM   1236  CE1 PHE A 159      -0.113  24.742  -5.566  1.00 15.13           C
ATOM   1237  CE2 PHE A 159       0.399  23.682  -3.479  1.00 12.40           C
ATOM   1238  CZ  PHE A 159       0.013  24.805  -4.189  1.00 11.69           C
ATOM   1239  N   LYS A 160       3.699  20.645  -4.969  1.00 11.04           N
ATOM   1240  CA  LYS A 160       4.644  20.969  -3.906  1.00 13.94           C
ATOM   1241  C   LYS A 160       5.937  21.531  -4.483  1.00 14.48           C
ATOM   1242  O   LYS A 160       6.520  22.463  -3.936  1.00 14.62           O
ATOM   1243  CB  LYS A 160       4.933  19.743  -3.041  1.00 14.06           C
ATOM   1244  CG  LYS A 160       3.750  19.302  -2.200  1.00 16.18           C
ATOM   1245  CD  LYS A 160       4.049  18.014  -1.454  1.00 19.05           C
ATOM   1246  CE  LYS A 160       2.930  17.694  -0.473  1.00 30.54           C
ATOM   1247  NZ  LYS A 160       3.310  16.609   0.472  1.00 58.66           N
ATOM   1248  N   VAL A 161       6.391  20.961  -5.591  1.00 13.06           N
ATOM   1249  CA  VAL A 161       7.601  21.457  -6.237  1.00 17.55           C
ATOM   1250  C   VAL A 161       7.391  22.878  -6.766  1.00 15.74           C
ATOM   1251  O   VAL A 161       8.248  23.749  -6.605  1.00 14.78           O
ATOM   1252  CB  VAL A 161       8.044  20.524  -7.372  1.00 14.83           C
ATOM   1253  CG1 VAL A 161       9.160  21.173  -8.186  1.00 19.24           C
ATOM   1254  CG2 VAL A 161       8.494  19.183  -6.797  1.00 18.97           C
ATOM   1255  N   LEU A 162       6.239  23.110  -7.380  1.00 11.62           N
ATOM   1256  CA  LEU A 162       5.875  24.434  -7.867  1.00 10.78           C
ATOM   1257  C   LEU A 162       5.815  25.443  -6.726  1.00 15.67           C
ATOM   1258  O   LEU A 162       6.360  26.543  -6.826  1.00 14.46           O
ATOM   1259  CB  LEU A 162       4.520  24.381  -8.572  1.00 14.81           C
ATOM   1260  CG  LEU A 162       3.973  25.727  -9.046  1.00 22.23           C
ATOM   1261  CD1 LEU A 162       4.800  26.249 -10.206  1.00 23.30           C
ATOM   1262  CD2 LEU A 162       2.507  25.604  -9.439  1.00 24.52           C
ATOM   1263  N   ALA A 163       5.148  25.070  -5.639  1.00 11.29           N
ATOM   1264  CA  ALA A 163       4.999  25.983  -4.509  1.00 14.76           C
ATOM   1265  C   ALA A 163       6.362  26.338  -3.922  1.00 14.91           C
ATOM   1266  O   ALA A 163       6.602  27.491  -3.560  1.00 16.78           O
ATOM   1267  CB  ALA A 163       4.086  25.382  -3.442  1.00 14.03           C
ATOM   1268  N   ALA A 164       7.250  25.351  -3.835  1.00 13.62           N
ATOM   1269  CA  ALA A 164       8.598  25.582  -3.322  1.00 18.16           C
ATOM   1270  C   ALA A 164       9.400  26.525  -4.226  1.00 23.79           C
ATOM   1271  O   ALA A 164      10.109  27.402  -3.732  1.00 18.76           O
ATOM   1272  CB  ALA A 164       9.331  24.262  -3.137  1.00 20.61           C
ATOM   1273  N   LYS A 165       9.297  26.339  -5.544  1.00 17.69           N
ATOM   1274  CA  LYS A 165       9.950  27.243  -6.494  1.00 23.27           C
ATOM   1275  C   LYS A 165       9.456  28.657  -6.279  1.00 23.11           C
ATOM   1276  O   LYS A 165      10.238  29.600  -6.157  1.00 33.57           O
ATOM   1277  CB  LYS A 165       9.604  26.885  -7.940  1.00 30.74           C
ATOM   1278  CG  LYS A 165      10.148  25.590  -8.486  1.00 58.56           C
ATOM   1279  CD  LYS A 165      10.057  25.660 -10.004  1.00 28.67           C
ATOM   1280  CE  LYS A 165       9.648  24.348 -10.632  1.00 63.54           C
ATOM   1281  NZ  LYS A 165       9.245  24.586 -12.048  1.00 25.56           N
ATOM   1282  N   VAL A 166       8.137  28.800  -6.273  1.00 19.68           N
ATOM   1283  CA  VAL A 166       7.504  30.102  -6.156  1.00 19.36           C
ATOM   1284  C   VAL A 166       7.910  30.804  -4.862  1.00 38.58           C
ATOM   1285  O   VAL A 166       8.095  32.019  -4.840  1.00 41.10           O
ATOM   1286  CB  VAL A 166       5.966  29.992  -6.274  1.00 23.38           C
ATOM   1287  CG1 VAL A 166       5.300  31.297  -5.869  1.00 33.39           C
ATOM   1288  CG2 VAL A 166       5.576  29.597  -7.698  1.00 19.99           C
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ATOM   1289  N   LEU A 167       8.069  30.031  -3.793  1.00 30.39           N
ATOM   1290  CA  LEU A 167       8.493  30.578  -2.504  1.00 29.35           C
ATOM   1291  C   LEU A 167      10.005  30.798  -2.400  1.00 37.42           C
ATOM   1292  O   LEU A 167      10.451  31.869  -1.989  1.00 45.82           O
ATOM   1293  CB  LEU A 167       8.033  29.670  -1.359  1.00 36.36           C
ATOM   1294  CG  LEU A 167       8.823  29.820  -0.053  1.00 72.40           C
ATOM   1295  CD1 LEU A 167       8.542  31.166   0.601  1.00 72.35           C
ATOM   1296  CD2 LEU A 167       8.525  28.677   0.910  1.00 57.03           C
ATOM   1297  N   ASN A 168      10.787  29.784  -2.765  1.00 27.55           N
ATOM   1298  CA  ASN A 168      12.237  29.810  -2.569  1.00 27.38           C
ATOM   1299  C   ASN A 168      13.020  30.567  -3.639  1.00 50.32           C
ATOM   1300  O   ASN A 168      14.246  30.674  -3.565  1.00 38.60           O
ATOM   1301  CB  ASN A 168      12.791  28.387  -2.456  1.00 31.18           C
ATOM   1302  CG  ASN A 168      12.355  27.689  -1.185  1.00 60.71           C
ATOM   1303  OD1 ASN A 168      12.552  26.483  -1.028  1.00 56.08           O
ATOM   1304  ND2 ASN A 168      11.759  28.443  -0.268  1.00 64.87           N
ATOM   1305  N   SER A 169      12.313  31.077  -4.639  1.00 23.88           N
ATOM   1306  CA  SER A 169      12.939  31.844  -5.708  1.00 29.73           C
ATOM   1307  C   SER A 169      12.086  33.057  -6.050  1.00 22.64           C
ATOM   1308  CB  SER A 169      13.123  30.976  -6.957  1.00 35.25           C
ATOM   1309  OG  SER A 169      13.964  29.866  -6.694  1.00 55.90           O
ATOM   1310  O   SER A 169      12.359  33.753  -7.029  1.00 27.12           O
ATOM   1311  N   VAL A 170      11.059  33.298  -5.237  1.00 20.95           N
ATOM   1312  CA  VAL A 170      10.077  34.351  -5.489  1.00 17.05           C
ATOM   1313  C   VAL A 170       9.765  34.510  -6.985  1.00 23.05           C
ATOM   1314  O   VAL A 170       9.865  35.603  -7.545  1.00 22.27           O
ATOM   1315  CB  VAL A 170      10.503  35.708  -4.858  1.00 23.73           C
ATOM   1316  CG1 VAL A 170      10.500  35.607  -3.335  1.00 22.54           C
ATOM   1317  CG2 VAL A 170      11.874  36.134  -5.362  1.00 28.79           C
ATOM   1318  N   LEU A 171       9.395  33.406  -7.632  1.00 19.61           N
ATOM   1319  CA  LEU A 171       8.996  33.451  -9.036  1.00 17.49           C
ATOM   1320  C   LEU A 171       7.615  34.085  -9.147  1.00 17.41           C
ATOM   1321  O   LEU A 171       6.686  33.667  -8.453  1.00 19.36           O
ATOM   1322  CB  LEU A 171       8.963  32.047  -9.636  1.00 18.63           C
ATOM   1323  CG  LEU A 171      10.282  31.276  -9.665  1.00 26.27           C
ATOM   1324  CD1 LEU A 171      10.099  29.942 -10.378  1.00 25.23           C
ATOM   1325  CD2 LEU A 171      11.364  32.100 -10.339  1.00 22.36           C
ATOM   1326  N   PRO A 172       7.471  35.094 -10.022  1.00 14.88           N
ATOM   1327  CA  PRO A 172       6.223  35.853 -10.159  1.00 14.86           C
ATOM   1328  C   PRO A 172       5.302  35.268 -11.227  1.00 19.81           C
ATOM   1329  O   PRO A 172       5.760  34.501 -12.068  1.00 19.14           O
ATOM   1330  CB  PRO A 172       6.715  37.221 -10.627  1.00 20.22           C
ATOM   1331  CG  PRO A 172       7.938  36.910 -11.435  1.00 18.21           C
ATOM   1332  CD  PRO A 172       8.543  35.636 -10.880  1.00 14.89           C
ATOM   1333  N   ASN A 173       4.024  35.633 -11.184  1.00 22.85           N
ATOM   1334  CA  ASN A 173       3.073  35.266 -12.235  1.00 29.29           C
ATOM   1335  C   ASN A 173       3.027  33.769 -12.528  1.00 31.64           C
ATOM   1336  O   ASN A 173       2.795  33.356 -13.665  1.00 39.41           O
ATOM   1337  CB  ASN A 173       3.386  36.033 -13.520  1.00 32.47           C
ATOM   1338  CG  ASN A 173       3.475  37.531 -13.296  1.00 85.40           C
ATOM   1339  OD1 ASN A 173       4.280  38.218 -13.926  1.00 59.68           O
ATOM   1340  ND2 ASN A 173       2.652  38.044 -12.388  1.00 49.78           N
ATOM   1341  N   LEU A 174       3.262  32.962 -11.499  1.00 20.60           N
ATOM   1342  CA  LEU A 174       3.201  31.512 -11.623  1.00 18.27           C
ATOM   1343  C   LEU A 174       2.155  30.946 -10.685  1.00 25.26           C
ATOM   1344  O   LEU A 174       2.226  31.128  -9.472  1.00 24.16           O
ATOM   1345  CB  LEU A 174       4.550  30.872 -11.296  1.00 24.24           C
ATOM   1346  CG  LEU A 174       5.479  30.472 -12.438  1.00 55.63           C
ATOM   1347  CD1 LEU A 174       6.625  29.655 -11.870  1.00 27.72           C
ATOM   1348  CD2 LEU A 174       4.722  29.681 -13.495  1.00 33.38           C
ATOM   1349  N   SER A 175       1.178  30.253 -11.247  1.00 19.56           N
ATOM   1350  CA  SER A 175       0.212  29.552 -10.427  1.00 21.54           C
ATOM   1351  C   SER A 175       0.218  28.100 -10.855  1.00 20.84           C
ATOM   1352  O   SER A 175       0.958  27.711 -11.761  1.00 18.86           O
ATOM   1353  CB  SER A 175      -1.182  30.157 -10.597  1.00 21.73           C
ATOM   1354  OG  SER A 175      -1.679  29.929 -11.903  1.00 27.11           O
ATOM   1355  N   SER A 176      -0.599  27.294 -10.192  1.00 16.51           N
ATOM   1356  CA  SER A 176      -0.839  25.940 -10.640  1.00 17.04           C
ATOM   1357  C   SER A 176      -1.830  26.028 -11.798  1.00 16.54           C
ATOM   1358  CB  SER A 176      -1.400  25.104  -9.485  1.00 17.23           C
ATOM   1359  OG  SER A 176      -1.399  23.728  -9.797  1.00 20.69           O
ATOM   1360  O   SER A 176      -2.331  27.110 -12.112  1.00 18.57           O
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ATOM   1361  N   GLY A 177      -2.104  24.904 -12.451  1.00 17.84           N
ATOM   1362  CA  GLY A 177      -3.036  24.906 -13.564  1.00 18.83           C
ATOM   1363  C   GLY A 177      -4.467  25.206 -13.144  1.00 14.12           C
ATOM   1364  O   GLY A 177      -4.815  25.120 -11.960  1.00 14.14           O
ATOM   1365  N   PRO A 178      -5.312  25.585 -14.105  1.00 13.09           N
ATOM   1366  CA  PRO A 178      -6.729  25.736 -13.773  1.00 11.60           C
ATOM   1367  C   PRO A 178      -7.390  24.370 -13.676  1.00 12.12           C
ATOM   1368  CB  PRO A 178      -7.290  26.513 -14.962  1.00 13.40           C
ATOM   1369  CG  PRO A 178      -6.386  26.154 -16.109  1.00 22.97           C
ATOM   1370  CD  PRO A 178      -5.029  25.841 -15.532  1.00 16.39           C
ATOM   1371  O   PRO A 178      -6.763  23.345 -13.972  1.00 14.28           O
ATOM   1372  N   ILE A 179      -8.640  24.359 -13.244  1.00 11.60           N
ATOM   1373  CA  ILE A 179      -9.404  23.126 -13.199  1.00 11.12           C
ATOM   1374  C   ILE A 179      -9.693  22.662 -14.633  1.00 13.21           C
ATOM   1375  O   ILE A 179     -10.218  23.434 -15.444  1.00 14.90           O
ATOM   1376  CB  ILE A 179     -10.707  23.357 -12.430  1.00 10.34           C
ATOM   1377  CG1 ILE A 179     -10.392  23.610 -10.955  1.00 14.08           C
ATOM   1378  CG2 ILE A 179     -11.661  22.179 -12.590  1.00 14.20           C
ATOM   1379  CD1 ILE A 179     -11.518  24.273 -10.208  1.00 12.85           C
ATOM   1380  N   ASP A 180      -9.324  21.421 -14.957  1.00 12.91           N
ATOM   1381  CA  ASP A 180      -9.567  20.876 -16.302  1.00 10.51           C
ATOM   1382  C   ASP A 180     -10.792  19.985 -16.253  1.00 10.15           C
ATOM   1383  O   ASP A 180     -10.707  18.794 -15.928  1.00 12.02           O
ATOM   1384  CB  ASP A 180      -8.352  20.098 -16.819  1.00 15.37           C
ATOM   1385  CG  ASP A 180      -8.568  19.517 -18.225  1.00 13.01           C
ATOM   1386  OD1 ASP A 180      -9.687  19.646 -18.779  1.00 13.99           O
ATOM   1387  OD2 ASP A 180      -7.603  18.924 -18.759  1.00 17.65           O
ATOM   1388  N   SER A 181     -11.938  20.570 -16.553  1.00 10.15           N
ATOM   1389  CA  SER A 181     -13.199  19.873 -16.436  1.00  8.88           C
ATOM   1390  C   SER A 181     -13.310  18.686 -17.396  1.00  8.77           C
ATOM   1391  O   SER A 181     -14.090  17.763 -17.151  1.00  9.07           O
ATOM   1392  CB  SER A 181     -14.345  20.842 -16.676  1.00  9.62           C
ATOM   1393  OG  SER A 181     -14.145  21.506 -17.921  1.00 11.79           O
ATOM   1394  N   SER A 182     -12.554  18.727 -18.494  1.00  8.53           N
ATOM   1395  CA  SER A 182     -12.675  17.689 -19.518  1.00  8.81           C
ATOM   1396  C   SER A 182     -12.171  16.328 -19.032  1.00  9.43           C
ATOM   1397  O   SER A 182     -12.534  15.295 -19.607  1.00 11.89           O
ATOM   1398  CB  SER A 182     -11.943  18.093 -20.807  1.00 10.60           C
ATOM   1399  OG  SER A 182     -10.552  17.939 -20.670  1.00 14.76           O
ATOM   1400  N   VAL A 183     -11.337  16.319 -17.996  1.00  8.40           N
ATOM   1401  CA  VAL A 183     -10.853  15.054 -17.451  1.00  9.30           C
ATOM   1402  C   VAL A 183     -11.542  14.715 -16.136  1.00  7.84           C
ATOM   1403  O   VAL A 183     -11.115  13.791 -15.443  1.00  9.46           O
ATOM   1404  CB  VAL A 183      -9.327  15.039 -17.257  1.00  9.77           C
ATOM   1405  CG1 VAL A 183      -8.625  15.275 -18.591  1.00 13.98           C
ATOM   1406  CG2 VAL A 183      -8.889  16.064 -16.216  1.00 12.72           C
ATOM   1407  N   LEU A 184     -12.597  15.457 -15.809  1.00  6.49           N
ATOM   1408  CA  LEU A 184     -13.291  15.282 -14.531  1.00  7.18           C
ATOM   1409  C   LEU A 184     -14.721  14.767 -14.699  1.00  8.94           C
ATOM   1410  O   LEU A 184     -15.369  14.390 -13.728  1.00  7.03           O
ATOM   1411  CB  LEU A 184     -13.225  16.574 -13.686  1.00  7.27           C
ATOM   1412  CG  LEU A 184     -11.797  17.033 -13.382  1.00  5.81           C
ATOM   1413  CD1 LEU A 184     -11.784  18.379 -12.656  1.00  8.64           C
ATOM   1414  CD2 LEU A 184     -11.033  15.993 -12.570  1.00  8.78           C
ATOM   1415  N   SER A 185     -15.217  14.731 -15.934  1.00  6.60           N
ATOM   1416  CA  SER A 185     -16.447  14.011 -16.253  1.00  8.04           C
ATOM   1417  C   SER A 185     -16.374  13.507 -17.684  1.00  9.06           C
ATOM   1418  O   SER A 185     -15.879  14.221 -18.562  1.00  9.74           O
ATOM   1419  CB  SER A 185     -17.690  14.892 -16.123  1.00  7.37           C
ATOM   1420  OG  SER A 185     -18.831  14.192 -16.585  1.00  7.90           O
ATOM   1421  N   ARG A 186     -16.913  12.318 -17.932  1.00  7.99           N
ATOM   1422  CA  ARG A 186     -16.986  11.784 -19.296  1.00  8.17           C
ATOM   1423  C   ARG A 186     -18.178  12.352 -20.056  1.00 11.97           C
ATOM   1424  O   ARG A 186     -18.309  12.136 -21.264  1.00 11.61           O
ATOM   1425  CB  ARG A 186     -17.057  10.250 -19.272  1.00 10.81           C
ATOM   1426  CG  ARG A 186     -15.777   9.591 -18.788  1.00 10.26           C
ATOM   1427  CD  ARG A 186     -15.960   8.081 -18.583  1.00 10.74           C
ATOM   1428  NE  ARG A 186     -17.037   7.816 -17.635  1.00 10.08           N
ATOM   1429  CZ  ARG A 186     -17.587   6.622 -17.426  1.00 13.38           C
ATOM   1430  NH1 ARG A 186     -17.149   5.566 -18.108  1.00 14.05           N
ATOM   1431  NH2 ARG A 186     -18.572   6.479 -16.551  1.00 12.05           N
ATOM   1432  N   ASN A 187     -19.062  13.055 -19.358  1.00  8.13           N
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ATOM   1433  CA  ASN A 187     -20.254  13.610 -19.978  1.00  8.18           C
ATOM   1434  C   ASN A 187     -19.929  14.967 -20.601  1.00 10.33           C
ATOM   1435  O   ASN A 187     -19.820  15.977 -19.899  1.00  9.28           O
ATOM   1436  CB  ASN A 187     -21.383  13.720 -18.943  1.00  7.71           C
ATOM   1437  CG  ASN A 187     -22.700  14.159 -19.548  1.00  8.65           C
ATOM   1438  OD1 ASN A 187     -22.731  14.989 -20.462  1.00 10.78           O
ATOM   1439  ND2 ASN A 187     -23.797  13.613 -19.046  1.00 11.01           N
ATOM   1440  N   LYS A 188     -19.750  14.982 -21.918  1.00 10.09           N
ATOM   1441  CA  LYS A 188     -19.290  16.182 -22.611  1.00 10.45           C
ATOM   1442  C   LYS A 188     -20.274  17.335 -22.497  1.00  8.22           C
ATOM   1443  O   LYS A 188     -19.854  18.498 -22.440  1.00 10.20           O
ATOM   1444  CB  LYS A 188     -18.984  15.865 -24.079  1.00 12.84           C
ATOM   1445  CG  LYS A 188     -17.682  15.087 -24.242  1.00 16.21           C
ATOM   1446  CD  LYS A 188     -17.316  14.886 -25.702  1.00 30.25           C
ATOM   1447  CE  LYS A 188     -17.788  13.538 -26.215  1.00 59.11           C
ATOM   1448  NZ  LYS A 188     -16.968  12.425 -25.656  1.00 62.44           N
ATOM   1449  N   THR A 189     -21.558  17.018 -22.461  1.00  8.16           N
ATOM   1450  CA  THR A 189     -22.590  18.029 -22.287  1.00  9.52           C
ATOM   1451  C   THR A 189     -22.440  18.716 -20.921  1.00 11.14           C
ATOM   1452  O   THR A 189     -22.499  19.947 -20.822  1.00 10.76           O
ATOM   1453  CB  THR A 189     -24.002  17.422 -22.419  1.00 11.47           C
ATOM   1454  OG1 THR A 189     -24.083  16.672 -23.641  1.00 21.86           O
ATOM   1455  CG2 THR A 189     -25.069  18.514 -22.442  1.00 15.48           C
ATOM   1456  N   GLU A 190     -22.243  17.917 -19.866  1.00  7.70           N
ATOM   1457  CA  GLU A 190     -22.042  18.473 -18.525  1.00  6.48           C
ATOM   1458  C   GLU A 190     -20.762  19.295 -18.456  1.00  6.09           C
ATOM   1459  O   GLU A 190     -20.723  20.327 -17.779  1.00  7.57           O
ATOM   1460  CB  GLU A 190     -22.047  17.360 -17.468  1.00  7.78           C
ATOM   1461  CG  GLU A 190     -23.387  16.671 -17.321  1.00 10.63           C
ATOM   1462  CD  GLU A 190     -24.469  17.574 -16.735  1.00 19.84           C
ATOM   1463  OE1 GLU A 190     -24.149  18.687 -16.262  1.00 14.70           O
ATOM   1464  OE2 GLU A 190     -25.650  17.164 -16.743  1.00 48.07           O
ATOM   1465  N   VAL A 191     -19.709  18.864 -19.139  1.00  6.34           N
ATOM   1466  CA  VAL A 191     -18.481  19.653 -19.206  1.00  7.23           C
ATOM   1467  C   VAL A 191     -18.752  21.037 -19.820  1.00  9.26           C
ATOM   1468  O   VAL A 191     -18.303  22.054 -19.289  1.00  8.62           O
ATOM   1469  CB  VAL A 191     -17.369  18.914 -19.990  1.00  7.21           C
ATOM   1470  CG1 VAL A 191     -16.176  19.816 -20.252  1.00 10.02           C
ATOM   1471  CG2 VAL A 191     -16.945  17.649 -19.229  1.00  9.40           C
ATOM   1472  N   ASP A 192     -19.496  21.067 -20.924  1.00  8.63           N
ATOM   1473  CA  ASP A 192     -19.794  22.326 -21.601  1.00  9.12           C
ATOM   1474  C   ASP A 192     -20.662  23.232 -20.723  1.00  7.92           C
ATOM   1475  O   ASP A 192     -20.481  24.456 -20.705  1.00  8.58           O
ATOM   1476  CB  ASP A 192     -20.505  22.061 -22.930  1.00  8.58           C
ATOM   1477  CG  ASP A 192     -19.550  21.589 -24.026  1.00 12.97           C
ATOM   1478  OD1 ASP A 192     -18.343  21.894 -23.950  1.00 19.09           O
ATOM   1479  OD2 ASP A 192     -20.020  20.912 -24.968  1.00 13.65           O
ATOM   1480  N   ILE A 193     -21.614  22.636 -20.014  1.00  6.50           N
ATOM   1481  CA  ILE A 193     -22.479  23.391 -19.111  1.00  6.64           C
ATOM   1482  C   ILE A 193     -21.658  24.019 -17.992  1.00  8.30           C
ATOM   1483  O   ILE A 193     -21.797  25.211 -17.684  1.00  9.16           O
ATOM   1484  CB  ILE A 193     -23.594  22.499 -18.555  1.00  6.90           C
ATOM   1485  CG1 ILE A 193     -24.608  22.219 -19.667  1.00  9.28           C
ATOM   1486  CG2 ILE A 193     -24.291  23.153 -17.355  1.00  9.32           C
ATOM   1487  CD1 ILE A 193     -25.635  21.164 -19.323  1.00 11.81           C
ATOM   1488  N   TYR A 194     -20.766  23.230 -17.403  1.00  6.21           N
ATOM   1489  CA  TYR A 194     -19.902  23.749 -16.359  1.00  6.09           C
ATOM   1490  C   TYR A 194     -19.037  24.896 -16.880  1.00  6.70           C
ATOM   1491  O   TYR A 194     -18.930  25.955 -16.238  1.00  7.31           O
ATOM   1492  CB  TYR A 194     -19.023  22.623 -15.814  1.00  6.50           C
ATOM   1493  CG  TYR A 194     -17.954  23.098 -14.861  1.00  6.88           C
ATOM   1494  CD1 TYR A 194     -18.239  23.297 -13.501  1.00  7.46           C
ATOM   1495  CD2 TYR A 194     -16.670  23.355 -15.305  1.00  6.99           C
ATOM   1496  CE1 TYR A 194     -17.254  23.734 -12.635  1.00  6.75           C
ATOM   1497  CE2 TYR A 194     -15.681  23.774 -14.445  1.00  8.92           C
ATOM   1498  CZ  TYR A 194     -15.981  23.965 -13.105  1.00  7.57           C
ATOM   1499  OH  TYR A 194     -14.961  24.384 -12.276  1.00 11.18           O
ATOM   1500  N   ASN A 195     -18.401  24.688 -18.028  1.00  6.89           N
ATOM   1501  CA  ASN A 195     -17.462  25.666 -18.552  1.00  8.53           C
ATOM   1502  C   ASN A 195     -18.103  27.032 -18.812  1.00  8.54           C
ATOM   1503  O   ASN A 195     -17.411  28.044 -18.744  1.00 10.97           O
ATOM   1504  CB  ASN A 195     -16.820  25.175 -19.856  1.00  8.26           C
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ATOM   1505  CG  ASN A 195     -15.794  24.074 -19.648  1.00 13.25           C
ATOM   1506  OD1 ASN A 195     -15.364  23.433 -20.610  1.00 14.63           O
ATOM   1507  ND2 ASN A 195     -15.385  23.861 -18.416  1.00  9.36           N
ATOM   1508  N   SER A 196     -19.388  27.069 -19.120  1.00  6.92           N
ATOM   1509  CA ASER A 196     -20.047  28.337 -19.432  0.35  8.60           C
ATOM   1510  C   SER A 196     -20.869  28.885 -18.264  1.00  8.11           C
ATOM   1511  O   SER A 196     -21.634  29.832 -18.424  1.00  8.53           O
ATOM   1512  CB ASER A 196     -20.917  28.198 -20.679  0.35 15.69           C
ATOM   1513  OG ASER A 196     -21.879  27.180 -20.503  0.35 10.54           O
ATOM   1514  CA BSER A 196     -20.047  28.337 -19.432  0.35  8.84           C
ATOM   1515  CB BSER A 196     -20.917  28.198 -20.679  0.35 15.69           C
ATOM   1516  OG BSER A 196     -21.878  27.179 -20.504  0.35 10.54           O
ATOM   1517  CA CSER A 196     -20.030  28.350 -19.424  0.30  7.88           C
ATOM   1518  CB CSER A 196     -20.829  28.311 -20.741  0.30 17.42           C
ATOM   1519  OG CSER A 196     -21.208  26.999 -21.123  0.30  5.94           O
ATOM   1520  N   ASP A 197     -20.712  28.283 -17.088  1.00  7.36           N
ATOM   1521  CA  ASP A 197     -21.378  28.788 -15.890  1.00  7.39           C
ATOM   1522  C   ASP A 197     -20.675  30.091 -15.452  1.00  5.11           C
ATOM   1523  O   ASP A 197     -19.472  30.105 -15.231  1.00  7.19           O
ATOM   1524  CB  ASP A 197     -21.307  27.710 -14.799  1.00  7.00           C
ATOM   1525  CG  ASP A 197     -22.001  28.111 -13.506  1.00 12.88           C
ATOM   1526  OD1 ASP A 197     -22.176  29.315 -13.216  1.00  9.53           O
ATOM   1527  OD2 ASP A 197     -22.354  27.193 -12.734  1.00  9.68           O
ATOM   1528  N   PRO A 198     -21.441  31.197 -15.362  1.00  7.84           N
ATOM   1529  CA  PRO A 198     -20.779  32.480 -15.077  1.00  8.09           C
ATOM   1530  C   PRO A 198     -20.238  32.580 -13.644  1.00  9.46           C
ATOM   1531  O   PRO A 198     -19.519  33.532 -13.335  1.00 12.16           O
ATOM   1532  CB  PRO A 198     -21.895  33.517 -15.282  1.00  8.81           C
ATOM   1533  CG  PRO A 198     -23.166  32.783 -15.271  1.00 12.52           C
ATOM   1534  CD  PRO A 198     -22.891  31.321 -15.544  1.00  8.16           C
ATOM   1535  N   LEU A 199     -20.561  31.604 -12.796  1.00  7.46           N
ATOM   1536  CA  LEU A 199     -20.220  31.683 -11.372  1.00 10.37           C
ATOM   1537  C   LEU A 199     -19.048  30.798 -10.951  1.00 12.05           C
ATOM   1538  O   LEU A 199     -18.687  30.775  -9.763  1.00 11.02           O
ATOM   1539  CB  LEU A 199     -21.451  31.367 -10.526  1.00  7.80           C
ATOM   1540  CG  LEU A 199     -22.611  32.350 -10.675  1.00 10.76           C
ATOM   1541  CD1 LEU A 199     -23.818  31.905  -9.861  1.00 11.32           C
ATOM   1542  CD2 LEU A 199     -22.164  33.760 -10.266  1.00 14.15           C
ATOM   1543  N   ILE A 200     -18.459  30.065 -11.895  1.00  8.07           N
ATOM   1544  CA  ILE A 200     -17.275  29.255 -11.599  1.00  6.42           C
ATOM   1545  C   ILE A 200     -16.006  30.084 -11.705  1.00  7.71           C
ATOM   1546  O   ILE A 200     -16.051  31.229 -12.184  1.00 12.31           O
ATOM   1547  CB  ILE A 200     -17.172  28.017 -12.531  1.00  7.22           C
ATOM   1548  CG1 ILE A 200     -16.906  28.441 -13.992  1.00 10.03           C
ATOM   1549  CG2 ILE A 200     -18.421  27.151 -12.401  1.00  8.89           C
ATOM   1550  CD1 ILE A 200     -16.361  27.315 -14.869  1.00 10.39           C
ATOM   1551  N   CYS A 201     -14.875  29.524 -11.293  1.00  7.95           N
ATOM   1552  CA  CYS A 201     -13.587  30.182 -11.468  1.00  9.49           C
ATOM   1553  C   CYS A 201     -12.723  29.352 -12.404  1.00 13.48           C
ATOM   1554  O   CYS A 201     -12.434  28.187 -12.106  1.00 13.84           O
ATOM   1555  CB  CYS A 201     -12.870  30.343 -10.125  1.00 12.53           C
ATOM   1556  SG  CYS A 201     -11.270  31.173 -10.289  1.00 17.94           S
ATOM   1557  N   ARG A 202     -12.303  29.959 -13.515  1.00 11.34           N
ATOM   1558  CA  ARG A 202     -11.533  29.264 -14.554  1.00 11.13           C
ATOM   1559  C   ARG A 202     -10.064  29.653 -14.550  1.00 12.74           C
ATOM   1560  O   ARG A 202      -9.317  29.269 -15.449  1.00 14.37           O
ATOM   1561  CB  ARG A 202     -12.123  29.558 -15.936  1.00 12.12           C
ATOM   1562  CG  ARG A 202     -13.617  29.317 -16.013  1.00 15.07           C
ATOM   1563  CD  ARG A 202     -14.121  29.443 -17.439  1.00 19.32           C
ATOM   1564  NE  ARG A 202     -13.749  28.272 -18.222  1.00 18.70           N
ATOM   1565  CZ  ARG A 202     -13.869  28.184 -19.543  1.00 26.00           C
ATOM   1566  NH1 ARG A 202     -14.349  29.207 -20.236  1.00 22.12           N
ATOM   1567  NH2 ARG A 202     -13.509  27.071 -20.166  1.00 19.47           N
ATOM   1568  N   ALA A 203      -9.646  30.408 -13.538  1.00 12.06           N
ATOM   1569  CA  ALA A 203      -8.263  30.859 -13.438  1.00 13.49           C
ATOM   1570  C   ALA A 203      -7.346  29.766 -12.897  1.00 12.80           C
ATOM   1571  O   ALA A 203      -7.812  28.796 -12.294  1.00 12.79           O
ATOM   1572  CB  ALA A 203      -8.180  32.109 -12.557  1.00 16.80           C
ATOM   1573  N   GLY A 204      -6.043  29.919 -13.104  1.00 12.71           N
ATOM   1574  CA  GLY A 204      -5.083  29.005 -12.518  1.00 13.49           C
ATOM   1575  C   GLY A 204      -5.213  29.001 -11.006  1.00 14.76           C
ATOM   1576  O   GLY A 204      -5.478  30.037 -10.395  1.00 14.87           O
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ATOM   1577  N   LEU A 205      -5.053  27.838 -10.394  1.00 12.15           N
ATOM   1578  CA ALEU A 205      -5.099  27.763  -8.938  0.50 12.52           C
ATOM   1579  C   LEU A 205      -3.877  28.430  -8.323  1.00 12.12           C
ATOM   1580  O   LEU A 205      -2.738  28.073  -8.617  1.00 14.37           O
ATOM   1581  CB ALEU A 205      -5.233  26.317  -8.455  0.50 21.10           C
ATOM   1582  CG ALEU A 205      -6.675  25.832  -8.280  0.50 22.60           C
ATOM   1583  CD1ALEU A 205      -7.347  25.614  -9.629  0.50 46.72           C
ATOM   1584  CD2ALEU A 205      -6.729  24.565  -7.437  0.50 21.86           C
ATOM   1585  CA BLEU A 205      -5.093  27.740  -8.941  0.50 14.43           C
ATOM   1586  CB BLEU A 205      -5.152  26.271  -8.524  0.50 15.12           C
ATOM   1587  CG BLEU A 205      -5.569  25.980  -7.083  0.50 25.82           C
ATOM   1588  CD1BLEU A 205      -6.333  24.666  -6.994  0.50 50.50           C
ATOM   1589  CD2BLEU A 205      -4.358  25.965  -6.180  0.50 39.57           C
ATOM   1590  N   LYS A 206      -4.119  29.419  -7.467  1.00 10.85           N
ATOM   1591  CA  LYS A 206      -3.027  30.161  -6.853  1.00 11.66           C
ATOM   1592  C   LYS A 206      -2.265  29.295  -5.866  1.00 12.14           C
ATOM   1593  O   LYS A 206      -2.852  28.446  -5.188  1.00 11.48           O
ATOM   1594  CB  LYS A 206      -3.563  31.409  -6.157  1.00 15.47           C
ATOM   1595  CG  LYS A 206      -4.079  32.451  -7.138  1.00 20.12           C
ATOM   1596  CD  LYS A 206      -4.787  33.588  -6.426  1.00 37.03           C
ATOM   1597  CE  LYS A 206      -5.080  34.727  -7.388  1.00 51.15           C
ATOM   1598  NZ  LYS A 206      -3.843  35.225  -8.052  1.00 92.27           N
ATOM   1599  N   VAL A 207      -0.959  29.503  -5.774  1.00 10.91           N
ATOM   1600  CA  VAL A 207      -0.145  28.709  -4.867  1.00 11.61           C
ATOM   1601  C   VAL A 207      -0.645  28.809  -3.421  1.00 12.70           C
ATOM   1602  O   VAL A 207      -0.680  27.816  -2.702  1.00 12.20           O
ATOM   1603  CB  VAL A 207       1.347  29.092  -4.957  1.00 13.57           C
ATOM   1604  CG1 VAL A 207       2.124  28.508  -3.785  1.00 16.27           C
ATOM   1605  CG2 VAL A 207       1.918  28.614  -6.280  1.00 15.13           C
ATOM   1606  N   CYS A 208      -1.043  30.001  -2.988  1.00 10.56           N
ATOM   1607  CA  CYS A 208      -1.537  30.138  -1.619  1.00 12.51           C
ATOM   1608  C   CYS A 208      -2.766  29.252  -1.368  1.00 12.06           C
ATOM   1609  O   CYS A 208      -2.927  28.698  -0.284  1.00 12.63           O
ATOM   1610  CB  CYS A 208      -1.844  31.602  -1.287  1.00 13.86           C
ATOM   1611  SG  CYS A 208      -3.147  32.334  -2.291  1.00 19.08           S
ATOM   1612  N   PHE A 209      -3.620  29.107  -2.378  1.00 10.09           N
ATOM   1613  CA  PHE A 209      -4.827  28.297  -2.226  1.00 10.18           C
ATOM   1614  C   PHE A 209      -4.474  26.817  -2.261  1.00  9.52           C
ATOM   1615  O   PHE A 209      -4.999  26.045  -1.466  1.00  9.70           O
ATOM   1616  CB  PHE A 209      -5.862  28.632  -3.298  1.00  8.96           C
ATOM   1617  CG  PHE A 209      -7.213  28.020  -3.047  1.00 10.85           C
ATOM   1618  CD1 PHE A 209      -7.979  28.421  -1.965  1.00 15.24           C
ATOM   1619  CD2 PHE A 209      -7.721  27.055  -3.904  1.00 11.35           C
ATOM   1620  CE1 PHE A 209      -9.230  27.863  -1.737  1.00 19.47           C
ATOM   1621  CE2 PHE A 209      -8.967  26.493  -3.680  1.00 13.97           C
ATOM   1622  CZ  PHE A 209      -9.722  26.901  -2.603  1.00 16.68           C
ATOM   1623  N   GLY A 210      -3.596  26.423  -3.179  1.00 10.17           N
ATOM   1624  CA  GLY A 210      -3.119  25.054  -3.215  1.00 10.27           C
ATOM   1625  C   GLY A 210      -2.529  24.619  -1.887  1.00  9.64           C
ATOM   1626  O   GLY A 210      -2.727  23.483  -1.453  1.00 10.94           O
ATOM   1627  N   ILE A 211      -1.798  25.525  -1.246  1.00  9.76           N
ATOM   1628  CA  ILE A 211      -1.219  25.237   0.060  1.00 10.73           C
ATOM   1629  C   ILE A 211      -2.334  24.946   1.064  1.00  9.63           C
ATOM   1630  O   ILE A 211      -2.225  24.023   1.872  1.00 11.27           O
ATOM   1631  CB  ILE A 211      -0.326  26.394   0.547  1.00 10.51           C
ATOM   1632  CG1 ILE A 211       0.968  26.424  -0.264  1.00 14.10           C
ATOM   1633  CG2 ILE A 211      -0.019  26.260   2.051  1.00 15.16           C
ATOM   1634  CD1 ILE A 211       1.777  27.688  -0.060  1.00 19.74           C
ATOM   1635  N   GLN A 212      -3.415  25.716   0.999  1.00  8.87           N
ATOM   1636  CA  GLN A 212      -4.550  25.457   1.887  1.00  9.46           C
ATOM   1637  C   GLN A 212      -5.228  24.114   1.579  1.00 10.55           C
ATOM   1638  O   GLN A 212      -5.725  23.448   2.492  1.00 10.09           O
ATOM   1639  CB  GLN A 212      -5.549  26.618   1.865  1.00  8.41           C
ATOM   1640  CG  GLN A 212      -4.979  27.899   2.496  1.00  9.42           C
ATOM   1641  CD  GLN A 212      -4.434  27.662   3.902  1.00 10.45           C
ATOM   1642  OE1 GLN A 212      -5.011  26.906   4.686  1.00 11.66           O
ATOM   1643  NE2 GLN A 212      -3.323  28.311   4.222  1.00 14.57           N
ATOM   1644  N   LEU A 213      -5.241  23.704   0.306  1.00  9.40           N
ATOM   1645  CA  LEU A 213      -5.764  22.378  -0.036  1.00 10.49           C
ATOM   1646  C   LEU A 213      -4.854  21.266   0.505  1.00  9.28           C
ATOM   1647  O   LEU A 213      -5.343  20.236   0.962  1.00 10.04           O
ATOM   1648  CB  LEU A 213      -5.973  22.236  -1.546  1.00  9.58           C
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ATOM   1649  CG  LEU A 213      -7.050  23.140  -2.143  1.00 10.05           C
ATOM   1650  CD1 LEU A 213      -7.097  22.976  -3.663  1.00 14.31           C
ATOM   1651  CD2 LEU A 213      -8.407  22.838  -1.528  1.00 14.79           C
ATOM   1652  N   LEU A 214      -3.541  21.477   0.478  1.00  9.43           N
ATOM   1653  CA  LEU A 214      -2.616  20.540   1.123  1.00 11.38           C
ATOM   1654  C   LEU A 214      -2.855  20.488   2.634  1.00 11.40           C
ATOM   1655  O   LEU A 214      -2.800  19.411   3.249  1.00 11.93           O
ATOM   1656  CB  LEU A 214      -1.157  20.914   0.856  1.00 12.30           C
ATOM   1657  CG  LEU A 214      -0.639  20.817  -0.582  1.00 17.43           C
ATOM   1658  CD1 LEU A 214       0.811  21.288  -0.643  1.00 17.60           C
ATOM   1659  CD2 LEU A 214      -0.764  19.397  -1.091  1.00 18.65           C
ATOM   1660  N   ASN A 215      -3.105  21.650   3.234  1.00 10.49           N
ATOM   1661  CA  ASN A 215      -3.460  21.701   4.651  1.00 11.90           C
ATOM   1662  C   ASN A 215      -4.717  20.879   4.909  1.00 10.86           C
ATOM   1663  O   ASN A 215      -4.788  20.130   5.884  1.00 12.49           O
ATOM   1664  CB  ASN A 215      -3.696  23.143   5.109  1.00  9.81           C
ATOM   1665  CG  ASN A 215      -2.413  23.943   5.231  1.00 13.81           C
ATOM   1666  OD1 ASN A 215      -1.309  23.393   5.195  1.00 15.52           O
ATOM   1667  ND2 ASN A 215      -2.556  25.257   5.381  1.00 15.57           N
ATOM   1668  N   ALA A 216      -5.709  21.009   4.031  1.00  9.70           N
ATOM   1669  CA  ALA A 216      -6.940  20.245   4.172  1.00 10.39           C
ATOM   1670  C   ALA A 216      -6.662  18.742   4.172  1.00 11.63           C
ATOM   1671  O   ALA A 216      -7.177  18.013   5.021  1.00 11.59           O
ATOM   1672  CB  ALA A 216      -7.942  20.617   3.078  1.00 11.90           C
ATOM   1673  N   VAL A 217      -5.856  18.282   3.217  1.00 11.05           N
ATOM   1674  CA  VAL A 217      -5.522  16.864   3.131  1.00 12.23           C
ATOM   1675  C   VAL A 217      -4.844  16.383   4.417  1.00 11.43           C
ATOM   1676  O   VAL A 217      -5.205  15.340   4.961  1.00 11.37           O
ATOM   1677  CB  VAL A 217      -4.642  16.575   1.898  1.00 12.66           C
ATOM   1678  CG1 VAL A 217      -4.053  15.157   1.955  1.00 15.90           C
ATOM   1679  CG2 VAL A 217      -5.449  16.780   0.618  1.00 13.74           C
ATOM   1680  N   SER A 218      -3.884  17.155   4.910  1.00 10.49           N
ATOM   1681  CA ASER A 218      -3.194  16.822   6.152  0.50 11.81           C
ATOM   1682  C   SER A 218      -4.174  16.752   7.322  1.00 12.18           C
ATOM   1683  O   SER A 218      -4.142  15.814   8.127  1.00 13.97           O
ATOM   1684  CB ASER A 218      -2.103  17.853   6.442  0.50 15.09           C
ATOM   1685  OG ASER A 218      -1.031  17.731   5.527  0.50 17.82           O
ATOM   1686  CA BSER A 218      -3.194  16.811   6.151  0.50 10.96           C
ATOM   1687  CB BSER A 218      -2.072  17.812   6.439  0.50 14.67           C
ATOM   1688  OG BSER A 218      -1.434  17.523   7.675  0.50 19.05           O
ATOM   1689  N   ARG A 219      -5.054  17.740   7.415  1.00  9.30           N
ATOM   1690  CA  ARG A 219      -6.019  17.783   8.511  1.00 11.05           C
ATOM   1691  C   ARG A 219      -7.045  16.657   8.422  1.00 10.10           C
ATOM   1692  O   ARG A 219      -7.451  16.091   9.439  1.00 10.71           O
ATOM   1693  CB  ARG A 219      -6.700  19.152   8.579  1.00 10.50           C
ATOM   1694  CG  ARG A 219      -5.708  20.260   8.925  1.00 10.95           C
ATOM   1695  CD  ARG A 219      -6.290  21.639   8.732  1.00 13.38           C
ATOM   1696  NE  ARG A 219      -5.238  22.651   8.755  1.00 13.54           N
ATOM   1697  CZ  ARG A 219      -5.455  23.955   8.635  1.00 12.88           C
ATOM   1698  NH1 ARG A 219      -6.690  24.413   8.499  1.00 12.45           N
ATOM   1699  NH2 ARG A 219      -4.427  24.797   8.662  1.00 14.24           N
ATOM   1700  N   VAL A 220      -7.466  16.320   7.206  1.00  9.48           N
ATOM   1701  CA  VAL A 220      -8.391  15.216   7.021  1.00 10.61           C
ATOM   1702  C   VAL A 220      -7.758  13.921   7.526  1.00 10.79           C
ATOM   1703  O   VAL A 220      -8.403  13.143   8.223  1.00 11.64           O
ATOM   1704  CB  VAL A 220      -8.834  15.084   5.547  1.00  9.99           C
ATOM   1705  CG1 VAL A 220      -9.476  13.727   5.296  1.00 10.95           C
ATOM   1706  CG2 VAL A 220      -9.802  16.210   5.190  1.00 11.57           C
ATOM   1707  N   GLU A 221      -6.489  13.706   7.198  1.00 13.35           N
ATOM   1708  CA  GLU A 221      -5.800  12.492   7.633  1.00 14.85           C
ATOM   1709  C   GLU A 221      -5.815  12.368   9.157  1.00 18.26           C
ATOM   1710  O   GLU A 221      -6.082  11.295   9.701  1.00 18.73           O
ATOM   1711  CB  GLU A 221      -4.362  12.481   7.115  1.00 18.69           C
ATOM   1712  CG  GLU A 221      -3.543  11.285   7.574  1.00 51.12           C
ATOM   1713  CD  GLU A 221      -2.103  11.354   7.102  1.00 92.75           C
ATOM   1714  OE1 GLU A 221      -1.704  12.403   6.551  1.00 79.10           O
ATOM   1715  OE2 GLU A 221      -1.369  10.358   7.283  1.00103.53           O
ATOM   1716  N   ARG A 222      -5.545  13.473   9.844  1.00 14.30           N
ATOM   1717  CA  ARG A 222      -5.568  13.479  11.305  1.00 15.32           C
ATOM   1718  C   ARG A 222      -6.967  13.282  11.865  1.00 13.43           C
ATOM   1719  O   ARG A 222      -7.139  12.698  12.936  1.00 19.93           O
ATOM   1720  CB  ARG A 222      -4.954  14.774  11.853  1.00 20.09           C
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ATOM   1721  CG  ARG A 222      -3.440  14.809  11.778  1.00 30.84           C
ATOM   1722  CD  ARG A 222      -2.868  16.013  12.513  1.00 36.59           C
ATOM   1723  NE  ARG A 222      -3.115  17.262  11.798  1.00 51.40           N
ATOM   1724  CZ  ARG A 222      -2.332  17.740  10.837  1.00 65.64           C
ATOM   1725  NH1 ARG A 222      -1.245  17.073  10.471  1.00 72.52           N
ATOM   1726  NH2 ARG A 222      -2.635  18.885  10.240  1.00 34.72           N
ATOM   1727  N   ALA A 223      -7.971  13.770  11.149  1.00 12.61           N
ATOM   1728  CA  ALA A 223      -9.345  13.670  11.607  1.00 14.25           C
ATOM   1729  C   ALA A 223      -9.941  12.264  11.444  1.00 14.35           C
ATOM   1730  O   ALA A 223     -10.856  11.894  12.178  1.00 17.85           O
ATOM   1731  CB  ALA A 223     -10.211  14.692  10.886  1.00 15.85           C
ATOM   1732  N   LEU A 224      -9.429  11.502  10.476  1.00 14.85           N
ATOM   1733  CA  LEU A 224     -10.055  10.231  10.085  1.00 19.59           C
ATOM   1734  C   LEU A 224     -10.274   9.268  11.252  1.00 18.08           C
ATOM   1735  O   LEU A 224     -11.392   8.799  11.455  1.00 21.08           O
ATOM   1736  CB  LEU A 224      -9.277   9.537   8.958  1.00 18.13           C
ATOM   1737  CG  LEU A 224      -9.303  10.188   7.572  1.00 21.40           C
ATOM   1738  CD1 LEU A 224      -8.687   9.260   6.531  1.00 28.66           C
ATOM   1739  CD2 LEU A 224     -10.712  10.584   7.173  1.00 23.13           C
ATOM   1740  N   PRO A 225      -9.213   8.985  12.031  1.00 23.78           N
ATOM   1741  CA  PRO A 225      -9.334   8.027  13.138  1.00 24.17           C
ATOM   1742  C   PRO A 225     -10.310   8.479  14.215  1.00 26.85           C
ATOM   1743  O   PRO A 225     -10.636   7.694  15.106  1.00 34.94           O
ATOM   1744  CB  PRO A 225      -7.915   7.974  13.713  1.00 28.13           C
ATOM   1745  CG  PRO A 225      -7.034   8.443  12.608  1.00 36.69           C
ATOM   1746  CD  PRO A 225      -7.833   9.477  11.884  1.00 20.63           C
ATOM   1747  N   LYS A 226     -10.771   9.723  14.130  1.00 25.36           N
ATOM   1748  CA  LYS A 226     -11.684  10.280  15.120  1.00 25.72           C
ATOM   1749  C   LYS A 226     -13.132  10.300  14.630  1.00 33.01           C
ATOM   1750  O   LYS A 226     -14.058  10.524  15.408  1.00 28.49           O
ATOM   1751  CB  LYS A 226     -11.248  11.700  15.486  1.00 44.44           C
ATOM   1752  CG  LYS A 226      -9.761  11.834  15.776  1.00 42.51           C
ATOM   1753  CD  LYS A 226      -9.371  13.289  15.988  1.00 69.34           C
ATOM   1754  CE  LYS A 226      -7.876  13.432  16.224  1.00 70.90           C
ATOM   1755  NZ  LYS A 226      -7.485  14.853  16.441  1.00 84.95           N
ATOM   1756  N   LEU A 227     -13.318  10.062  13.336  1.00 20.18           N
ATOM   1757  CA ALEU A 227     -14.637  10.116  12.716  0.50 15.98           C
ATOM   1758  C   LEU A 227     -15.525   8.981  13.183  1.00 13.40           C
ATOM   1759  O   LEU A 227     -15.109   7.818  13.166  1.00 17.01           O
ATOM   1760  CB ALEU A 227     -14.512  10.017  11.196  0.50 17.93           C
ATOM   1761  CG ALEU A 227     -14.149  11.259  10.394  0.50 13.32           C
ATOM   1762  CD1ALEU A 227     -14.050  10.874   8.923  0.50 13.43           C
ATOM   1763  CD2ALEU A 227     -15.179  12.355  10.601  0.50 15.66           C
ATOM   1764  CA BLEU A 227     -14.632  10.132  12.717  0.50 15.66           C
ATOM   1765  CB BLEU A 227     -14.470  10.100  11.192  0.50 18.07           C
ATOM   1766  CG BLEU A 227     -15.573  10.629  10.274  0.50 15.22           C
ATOM   1767  CD1BLEU A 227     -15.891  12.088  10.568  0.50 24.87           C
ATOM   1768  CD2BLEU A 227     -15.155  10.453   8.822  0.50 11.89           C
ATOM   1769  N   THR A 228     -16.746   9.311  13.596  1.00 10.05           N
ATOM   1770  CA  THR A 228     -17.727   8.299  13.997  1.00 12.36           C
ATOM   1771  C   THR A 228     -19.067   8.438  13.272  1.00 10.02           C
ATOM   1772  O   THR A 228     -19.946   7.580  13.400  1.00 10.20           O
ATOM   1773  CB  THR A 228     -17.994   8.324  15.523  1.00 15.46           C
ATOM   1774  OG1 THR A 228     -18.544   9.596  15.893  1.00 17.33           O
ATOM   1775  CG2 THR A 228     -16.710   8.077  16.300  1.00 16.53           C
ATOM   1776  N   VAL A 229     -19.231   9.526  12.518  1.00 10.47           N
ATOM   1777  CA  VAL A 229     -20.485   9.808  11.826  1.00  9.15           C
ATOM   1778  C   VAL A 229     -20.779   8.746  10.744  1.00  7.39           C
ATOM   1779  O   VAL A 229     -19.859   8.294  10.059  1.00  8.94           O
ATOM   1780  CB  VAL A 229     -20.438  11.233  11.185  1.00 11.08           C
ATOM   1781  CG1 VAL A 229     -19.367  11.300  10.106  1.00 13.13           C
ATOM   1782  CG2 VAL A 229     -21.788  11.640  10.626  1.00 12.72           C
ATOM   1783  N   PRO A 230     -22.041   8.320  10.620  1.00  7.45           N
ATOM   1784  CA  PRO A 230     -22.387   7.423   9.507  1.00  6.36           C
ATOM   1785  C   PRO A 230     -22.051   8.070   8.168  1.00  9.18           C
ATOM   1786  O   PRO A 230     -22.254   9.273   8.002  1.00 10.77           O
ATOM   1787  CB  PRO A 230     -23.898   7.272   9.630  1.00  9.15           C
ATOM   1788  CG  PRO A 230     -24.173   7.499  11.112  1.00  9.93           C
ATOM   1789  CD  PRO A 230     -23.181   8.547  11.527  1.00 10.30           C
ATOM   1790  N   PHE A 231     -21.543   7.296   7.211  1.00  6.79           N
ATOM   1791  CA  PHE A 231     -21.343   7.874   5.886  1.00  7.46           C
ATOM   1792  C   PHE A 231     -21.514   6.920   4.722  1.00  7.73           C
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ATOM   1793  O   PHE A 231     -21.356   5.690   4.853  1.00  7.65           O
ATOM   1794  CB  PHE A 231     -20.019   8.643   5.779  1.00  7.69           C
ATOM   1795  CG  PHE A 231     -18.787   7.796   5.905  1.00  7.77           C
ATOM   1796  CD1 PHE A 231     -18.230   7.177   4.784  1.00  9.21           C
ATOM   1797  CD2 PHE A 231     -18.145   7.656   7.125  1.00  8.70           C
ATOM   1798  CE1 PHE A 231     -17.076   6.414   4.892  1.00 10.86           C
ATOM   1799  CE2 PHE A 231     -16.986   6.901   7.243  1.00  9.68           C
ATOM   1800  CZ  PHE A 231     -16.446   6.274   6.122  1.00 10.56           C
ATOM   1801  N   LEU A 232     -21.861   7.532   3.590  1.00  7.02           N
ATOM   1802  CA  LEU A 232     -21.907   6.871   2.291  1.00  5.67           C
ATOM   1803  C   LEU A 232     -20.836   7.551   1.462  1.00  7.56           C
ATOM   1804  O   LEU A 232     -20.824   8.788   1.349  1.00  8.41           O
ATOM   1805  CB  LEU A 232     -23.257   7.105   1.638  1.00  7.44           C
ATOM   1806  CG  LEU A 232     -23.360   6.631   0.181  1.00  8.89           C
ATOM   1807  CD1 LEU A 232     -23.158   5.113   0.097  1.00  9.59           C
ATOM   1808  CD2 LEU A 232     -24.689   7.035  -0.430  1.00  9.38           C
ATOM   1809  N   LEU A 233     -19.937   6.755   0.893  1.00  5.98           N
ATOM   1810  CA  LEU A 233     -18.816   7.251   0.123  1.00  5.46           C
ATOM   1811  C   LEU A 233     -18.961   6.736  -1.311  1.00  6.46           C
ATOM   1812  O   LEU A 233     -19.020   5.524  -1.546  1.00  8.99           O
ATOM   1813  CB  LEU A 233     -17.536   6.719   0.749  1.00  6.96           C
ATOM   1814  CG  LEU A 233     -16.204   6.995   0.085  1.00 11.73           C
ATOM   1815  CD1 LEU A 233     -15.985   8.484  -0.098  1.00 11.86           C
ATOM   1816  CD2 LEU A 233     -15.087   6.376   0.926  1.00 11.71           C
ATOM   1817  N   LEU A 234     -19.047   7.664  -2.266  1.00  6.30           N
ATOM   1818  CA  LEU A 234     -19.146   7.328  -3.690  1.00  5.53           C
ATOM   1819  C   LEU A 234     -17.887   7.806  -4.387  1.00  6.67           C
ATOM   1820  O   LEU A 234     -17.482   8.964  -4.214  1.00  7.50           O
ATOM   1821  CB  LEU A 234     -20.366   8.015  -4.299  1.00  7.09           C
ATOM   1822  CG  LEU A 234     -21.692   7.778  -3.587  1.00  7.45           C
ATOM   1823  CD1 LEU A 234     -22.809   8.556  -4.278  1.00 12.21           C
ATOM   1824  CD2 LEU A 234     -22.056   6.295  -3.498  1.00 10.51           C
ATOM   1825  N   GLN A 235     -17.263   6.930  -5.172  1.00  6.02           N
ATOM   1826  CA  GLN A 235     -15.962   7.230  -5.746  1.00  6.69           C
ATOM   1827  C   GLN A 235     -15.826   6.601  -7.122  1.00  7.26           C
ATOM   1828  O   GLN A 235     -16.188   5.433  -7.310  1.00  9.83           O
ATOM   1829  CB  GLN A 235     -14.878   6.664  -4.823  1.00  8.10           C
ATOM   1830  CG  GLN A 235     -13.460   6.805  -5.331  1.00  8.78           C
ATOM   1831  CD  GLN A 235     -12.945   8.235  -5.263  1.00 14.60           C
ATOM   1832  OE1 GLN A 235     -13.229   8.969  -4.310  1.00 11.92           O
ATOM   1833  NE2 GLN A 235     -12.176   8.639  -6.273  1.00 14.30           N
ATOM   1834  N   GLY A 236     -15.324   7.367  -8.092  1.00  7.16           N
ATOM   1835  CA  GLY A 236     -15.027   6.814  -9.410  1.00  7.05           C
ATOM   1836  C   GLY A 236     -13.626   6.241  -9.448  1.00  7.13           C
ATOM   1837  O   GLY A 236     -12.698   6.781  -8.847  1.00  9.31           O
ATOM   1838  N   SER A 237     -13.451   5.143 -10.182  1.00  7.90           N
ATOM   1839  CA  SER A 237     -12.139   4.515 -10.244  1.00 10.56           C
ATOM   1840  C   SER A 237     -11.158   5.288 -11.122  1.00  8.69           C
ATOM   1841  O   SER A 237      -9.947   5.107 -11.016  1.00 12.81           O
ATOM   1842  CB  SER A 237     -12.244   3.065 -10.734  1.00 14.27           C
ATOM   1843  OG  SER A 237     -12.468   3.007 -12.137  1.00 14.14           O
ATOM   1844  N   ALA A 238     -11.676   6.132 -12.009  1.00  8.64           N
ATOM   1845  CA  ALA A 238     -10.806   6.884 -12.918  1.00 12.93           C
ATOM   1846  C   ALA A 238     -10.783   8.358 -12.539  1.00 12.31           C
ATOM   1847  O   ALA A 238     -10.740   9.239 -13.402  1.00 11.93           O
ATOM   1848  CB  ALA A 238     -11.257   6.704 -14.359  1.00 11.58           C
ATOM   1849  N   ASP A 239     -10.803   8.616 -11.238  1.00  9.91           N
ATOM   1850  CA  ASP A 239     -10.753   9.975 -10.703  1.00 11.61           C
ATOM   1851  C   ASP A 239      -9.331  10.528 -10.745  1.00 11.01           C
ATOM   1852  O   ASP A 239      -8.434  10.018 -10.070  1.00 12.82           O
ATOM   1853  CB  ASP A 239     -11.255   9.950  -9.260  1.00  9.49           C
ATOM   1854  CG  ASP A 239     -11.495  11.338  -8.701  1.00 10.07           C
ATOM   1855  OD1 ASP A 239     -10.756  12.276  -9.080  1.00  9.43           O
ATOM   1856  OD2 ASP A 239     -12.430  11.490  -7.888  1.00 10.75           O
ATOM   1857  N   ARG A 240      -9.131  11.573 -11.549  1.00 10.38           N
ATOM   1858  CA  ARG A 240      -7.807  12.154 -11.748  1.00 11.86           C
ATOM   1859  C   ARG A 240      -7.387  13.173 -10.695  1.00 13.94           C
ATOM   1860  O   ARG A 240      -6.243  13.631 -10.692  1.00 15.63           O
ATOM   1861  CB  ARG A 240      -7.736  12.819 -13.124  1.00 15.76           C
ATOM   1862  CG  ARG A 240      -7.703  11.848 -14.277  1.00 26.43           C
ATOM   1863  CD  ARG A 240      -6.677  12.317 -15.281  1.00 32.76           C
ATOM   1864  NE  ARG A 240      -6.988  11.882 -16.633  1.00 71.10           N
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ATOM   1865  CZ  ARG A 240      -6.466  12.441 -17.716  1.00 19.70           C
ATOM   1866  NH1 ARG A 240      -5.618  13.457 -17.587  1.00 26.60           N
ATOM   1867  NH2 ARG A 240      -6.798  11.989 -18.914  1.00 79.96           N
ATOM   1868  N   LEU A 241      -8.305  13.521  -9.803  1.00 10.36           N
ATOM   1869  CA  LEU A 241      -8.077  14.586  -8.841  1.00 12.06           C
ATOM   1870  C   LEU A 241      -8.030  14.068  -7.404  1.00 14.79           C
ATOM   1871  O   LEU A 241      -7.048  14.283  -6.685  1.00 17.27           O
ATOM   1872  CB  LEU A 241      -9.189  15.621  -8.995  1.00 12.48           C
ATOM   1873  CG  LEU A 241      -8.962  16.968  -8.329  1.00 17.56           C
ATOM   1874  CD1 LEU A 241      -7.606  17.547  -8.721  1.00 17.75           C
ATOM   1875  CD2 LEU A 241     -10.086  17.899  -8.744  1.00 14.80           C
ATOM   1876  N   CYS A 242      -9.103  13.402  -6.990  1.00 13.17           N
ATOM   1877  CA  CYS A 242      -9.172  12.777  -5.674  1.00 14.00           C
ATOM   1878  C   CYS A 242      -8.910  11.295  -5.861  1.00 12.30           C
ATOM   1879  O   CYS A 242      -9.775  10.554  -6.343  1.00 16.19           O
ATOM   1880  CB  CYS A 242     -10.531  13.035  -5.026  1.00 14.14           C
ATOM   1881  SG  CYS A 242     -10.791  14.786  -4.632  1.00 17.18           S
ATOM   1882  N   ASP A 243      -7.701  10.872  -5.514  1.00 14.74           N
ATOM   1883  CA  ASP A 243      -7.270   9.511  -5.787  1.00 15.90           C
ATOM   1884  C   ASP A 243      -8.125   8.489  -5.046  1.00 18.69           C
ATOM   1885  O   ASP A 243      -8.421   8.649  -3.860  1.00 14.40           O
ATOM   1886  CB  ASP A 243      -5.804   9.327  -5.418  1.00 17.66           C
ATOM   1887  CG  ASP A 243      -5.180   8.144  -6.122  1.00 49.96           C
ATOM   1888  OD1 ASP A 243      -4.757   8.299  -7.289  1.00 39.78           O
ATOM   1889  OD2 ASP A 243      -5.123   7.057  -5.512  1.00 25.88           O
ATOM   1890  N   SER A 244      -8.527   7.436  -5.748  1.00 15.66           N
ATOM   1891  CA  SER A 244      -9.378   6.416  -5.142  1.00 17.72           C
ATOM   1892  C   SER A 244      -8.736   5.808  -3.894  1.00 15.64           C
ATOM   1893  O   SER A 244      -9.435   5.302  -3.025  1.00 15.29           O
ATOM   1894  CB  SER A 244      -9.721   5.322  -6.155  1.00 17.74           C
ATOM   1895  OG  SER A 244      -8.542   4.671  -6.580  1.00 20.33           O
ATOM   1896  N   LYS A 245      -7.412   5.860  -3.800  1.00 14.32           N
ATOM   1897  CA  LYS A 245      -6.711   5.394  -2.606  1.00 12.72           C
ATOM   1898  C   LYS A 245      -7.198   6.097  -1.339  1.00 16.08           C
ATOM   1899  O   LYS A 245      -7.211   5.508  -0.255  1.00 15.31           O
ATOM   1900  CB  LYS A 245      -5.203   5.593  -2.754  1.00 18.83           C
ATOM   1901  CG  LYS A 245      -4.394   5.124  -1.557  1.00 44.09           C
ATOM   1902  CD  LYS A 245      -2.929   5.507  -1.692  1.00 75.26           C
ATOM   1903  CE  LYS A 245      -2.150   5.169  -0.430  1.00 60.92           C
ATOM   1904  NZ  LYS A 245      -0.732   5.618  -0.513  1.00 81.77           N
ATOM   1905  N   GLY A 246      -7.597   7.357  -1.475  1.00 12.05           N
ATOM   1906  CA  GLY A 246      -8.129   8.112  -0.354  1.00 11.97           C
ATOM   1907  C   GLY A 246      -9.462   7.569   0.115  1.00 12.09           C
ATOM   1908  O   GLY A 246      -9.752   7.562   1.312  1.00 11.82           O
ATOM   1909  N   ALA A 247     -10.288   7.118  -0.820  1.00 11.78           N
ATOM   1910  CA  ALA A 247     -11.562   6.515  -0.461  1.00 12.42           C
ATOM   1911  C   ALA A 247     -11.315   5.279   0.404  1.00 11.27           C
ATOM   1912  O   ALA A 247     -11.993   5.079   1.417  1.00 11.32           O
ATOM   1913  CB  ALA A 247     -12.369   6.151  -1.713  1.00 11.97           C
ATOM   1914  N   TYR A 248     -10.349   4.451   0.001  1.00 11.26           N
ATOM   1915  CA  TYR A 248     -10.022   3.256   0.776  1.00 12.36           C
ATOM   1916  C   TYR A 248      -9.458   3.631   2.155  1.00 12.09           C
ATOM   1917  O   TYR A 248      -9.752   2.971   3.152  1.00 11.59           O
ATOM   1918  CB  TYR A 248      -9.074   2.322   0.001  1.00 11.60           C
ATOM   1919  CG  TYR A 248      -9.652   1.861  -1.322  1.00 14.61           C
ATOM   1920  CD1 TYR A 248     -10.872   1.201  -1.371  1.00 13.55           C
ATOM   1921  CD2 TYR A 248      -8.985   2.092  -2.520  1.00 19.12           C
ATOM   1922  CE1 TYR A 248     -11.419   0.784  -2.571  1.00 18.03           C
ATOM   1923  CE2 TYR A 248      -9.528   1.677  -3.728  1.00 19.37           C
ATOM   1924  CZ  TYR A 248     -10.743   1.025  -3.742  1.00 16.03           C
ATOM   1925  OH  TYR A 248     -11.302   0.600  -4.929  1.00 19.87           O
ATOM   1926  N   LEU A 249      -8.673   4.703   2.215  1.00 11.41           N
ATOM   1927  CA  LEU A 249      -8.116   5.181   3.484  1.00 10.25           C
ATOM   1928  C   LEU A 249      -9.220   5.627   4.447  1.00 10.35           C
ATOM   1929  O   LEU A 249      -9.189   5.328   5.647  1.00 10.53           O
ATOM   1930  CB  LEU A 249      -7.150   6.339   3.226  1.00 13.46           C
ATOM   1931  CG  LEU A 249      -6.365   6.824   4.444  1.00 18.08           C
ATOM   1932  CD1 LEU A 249      -5.351   5.760   4.858  1.00 19.06           C
ATOM   1933  CD2 LEU A 249      -5.667   8.146   4.150  1.00 18.48           C
ATOM   1934  N   LEU A 250     -10.209   6.336   3.923  1.00  9.37           N
ATOM   1935  CA  LEU A 250     -11.329   6.757   4.724  1.00  9.21           C
ATOM   1936  C   LEU A 250     -12.080   5.543   5.271  1.00 12.66           C
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ATOM   1937  O   LEU A 250     -12.435   5.510   6.450  1.00 11.83           O
ATOM   1938  CB  LEU A 250     -12.235   7.661   3.897  1.00 13.06           C
ATOM   1939  CG  LEU A 250     -13.559   8.092   4.496  1.00 13.37           C
ATOM   1940  CD1 LEU A 250     -13.375   8.747   5.858  1.00 14.48           C
ATOM   1941  CD2 LEU A 250     -14.209   9.066   3.529  1.00 16.04           C
ATOM   1942  N   MET A 251     -12.304   4.531   4.431  1.00  9.91           N
ATOM   1943  CA  MET A 251     -12.998   3.327   4.888  1.00 10.56           C
ATOM   1944  C   MET A 251     -12.189   2.596   5.950  1.00 10.04           C
ATOM   1945  O   MET A 251     -12.759   1.991   6.860  1.00 13.87           O
ATOM   1946  CB  MET A 251     -13.284   2.381   3.719  1.00  9.50           C
ATOM   1947  CG  MET A 251     -14.342   2.899   2.762  1.00 13.01           C
ATOM   1948  SD  MET A 251     -15.992   3.057   3.473  1.00 11.08           S
ATOM   1949  CE  MET A 251     -16.458   1.331   3.656  1.00 12.29           C
ATOM   1950  N   GLU A 252     -10.872   2.640   5.835  1.00  8.28           N
ATOM   1951  CA  GLU A 252     -10.013   1.916   6.763  1.00 10.79           C
ATOM   1952  C   GLU A 252      -9.890   2.619   8.110  1.00 14.17           C
ATOM   1953  O   GLU A 252      -9.960   1.979   9.162  1.00 16.34           O
ATOM   1954  CB  GLU A 252      -8.620   1.717   6.171  1.00 14.04           C
ATOM   1955  CG  GLU A 252      -7.682   0.962   7.109  1.00 18.86           C
ATOM   1956  CD  GLU A 252      -6.248   0.940   6.620  1.00 88.82           C
ATOM   1957  OE1 GLU A 252      -5.970   1.541   5.561  1.00 68.03           O
ATOM   1958  OE2 GLU A 252      -5.398   0.324   7.297  1.00 99.02           O
ATOM   1959  N   LEU A 253      -9.701   3.933   8.082  1.00 11.41           N
ATOM   1960  CA  LEU A 253      -9.336   4.662   9.294  1.00 11.04           C
ATOM   1961  C   LEU A 253     -10.506   5.218  10.100  1.00 11.58           C
ATOM   1962  O   LEU A 253     -10.383   5.395  11.309  1.00 14.92           O
ATOM   1963  CB  LEU A 253      -8.355   5.785   8.958  1.00 14.04           C
ATOM   1964  CG  LEU A 253      -6.961   5.350   8.512  1.00 15.41           C
ATOM   1965  CD1 LEU A 253      -6.066   6.565   8.335  1.00 19.75           C
ATOM   1966  CD2 LEU A 253      -6.354   4.367   9.504  1.00 26.28           C
ATOM   1967  N   ALA A 254     -11.625   5.526   9.451  1.00  9.74           N
ATOM   1968  CA  ALA A 254     -12.783   6.055  10.171  1.00 10.79           C
ATOM   1969  C   ALA A 254     -13.301   5.031  11.184  1.00 12.72           C
ATOM   1970  O   ALA A 254     -13.301   3.828  10.913  1.00 13.12           O
ATOM   1971  CB  ALA A 254     -13.887   6.452   9.198  1.00 13.02           C
ATOM   1972  N   LYS A 255     -13.738   5.502  12.347  1.00 11.30           N
ATOM   1973  CA  LYS A 255     -14.265   4.593  13.360  1.00 13.33           C
ATOM   1974  C   LYS A 255     -15.774   4.394  13.233  1.00 14.71           C
ATOM   1975  O   LYS A 255     -16.377   3.634  13.992  1.00 16.28           O
ATOM   1976  CB  LYS A 255     -13.899   5.072  14.772  1.00 17.14           C
ATOM   1977  CG  LYS A 255     -12.399   5.098  15.036  1.00 23.75           C
ATOM   1978  CD  LYS A 255     -11.776   3.721  14.861  1.00 30.83           C
ATOM   1979  CE  LYS A 255     -10.267   3.744  15.092  1.00 45.25           C
ATOM   1980  NZ  LYS A 255      -9.509   4.223  13.898  1.00 43.77           N
ATOM   1981  N   SER A 256     -16.387   5.067  12.265  1.00 10.29           N
ATOM   1982  CA  SER A 256     -17.821   4.987  12.074  1.00  9.83           C
ATOM   1983  C   SER A 256     -18.307   3.548  12.017  1.00  9.52           C
ATOM   1984  O   SER A 256     -17.734   2.720  11.306  1.00 12.49           O
ATOM   1985  CB  SER A 256     -18.221   5.704  10.779  1.00 11.18           C
ATOM   1986  OG  SER A 256     -17.631   6.993  10.743  1.00 11.20           O
ATOM   1987  N   GLN A 257     -19.374   3.264  12.747  1.00  9.12           N
ATOM   1988  CA  GLN A 257     -20.003   1.942  12.704  1.00 12.22           C
ATOM   1989  C   GLN A 257     -20.865   1.739  11.464  1.00 13.06           C
ATOM   1990  O   GLN A 257     -21.242   0.613  11.143  1.00 14.98           O
ATOM   1991  CB  GLN A 257     -20.847   1.714  13.959  1.00 13.19           C
ATOM   1992  CG  GLN A 257     -20.018   1.658  15.238  1.00 16.99           C
ATOM   1993  CD  GLN A 257     -20.834   1.258  16.450  1.00 67.11           C
ATOM   1994  OE1 GLN A 257     -22.052   1.432  16.479  1.00 74.68           O
ATOM   1995  NE2 GLN A 257     -20.163   0.719  17.462  1.00 83.33           N
ATOM   1996  N   ASP A 258     -21.186   2.829  10.772  1.00  8.32           N
ATOM   1997  CA  ASP A 258     -22.065   2.767   9.614  1.00  9.96           C
ATOM   1998  C   ASP A 258     -21.342   3.413   8.433  1.00  9.10           C
ATOM   1999  O   ASP A 258     -21.434   4.625   8.226  1.00 10.80           O
ATOM   2000  CB  ASP A 258     -23.365   3.512   9.942  1.00  8.32           C
ATOM   2001  CG  ASP A 258     -24.395   3.468   8.825  1.00 11.84           C
ATOM   2002  OD1 ASP A 258     -24.184   2.773   7.806  1.00 11.26           O
ATOM   2003  OD2 ASP A 258     -25.450   4.120   8.973  1.00 13.37           O
ATOM   2004  N   LYS A 259     -20.599   2.614   7.677  1.00  6.95           N
ATOM   2005  CA  LYS A 259     -19.839   3.150   6.547  1.00  7.68           C
ATOM   2006  C   LYS A 259     -19.924   2.230   5.339  1.00  9.90           C
ATOM   2007  O   LYS A 259     -19.757   1.001   5.443  1.00 10.58           O
ATOM   2008  CB  LYS A 259     -18.389   3.463   6.914  1.00 12.50           C
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ATOM   2009  CG  LYS A 259     -17.667   2.376   7.675  1.00 10.44           C
ATOM   2010  CD  LYS A 259     -16.259   2.799   8.055  1.00 10.64           C
ATOM   2011  CE  LYS A 259     -15.610   1.749   8.959  1.00 11.27           C
ATOM   2012  NZ  LYS A 259     -14.164   1.975   9.132  1.00 11.78           N
ATOM   2013  N   THR A 260     -20.192   2.846   4.192  1.00  6.48           N
ATOM   2014  CA ATHR A 260     -20.426   2.128   2.937  0.70  5.21           C
ATOM   2015  C   THR A 260     -19.679   2.820   1.804  1.00  7.56           C
ATOM   2016  O   THR A 260     -19.699   4.058   1.710  1.00  8.70           O
ATOM   2017  CB ATHR A 260     -21.925   2.119   2.590  0.70  7.13           C
ATOM   2018  OG1ATHR A 260     -22.686   1.596   3.693  0.70  8.97           O
ATOM   2019  CG2ATHR A 260     -22.190   1.270   1.340  0.70  8.35           C
ATOM   2020  CA BTHR A 260     -20.360   2.105   2.955  0.30  8.55           C
ATOM   2021  CB BTHR A 260     -21.842   1.896   2.629  0.30 10.28           C
ATOM   2022  OG1BTHR A 260     -22.498   3.164   2.524  0.30 15.39           O
ATOM   2023  CG2BTHR A 260     -22.511   1.083   3.722  0.30 17.62           C
ATOM   2024  N   LEU A 261     -19.051   2.029   0.942  1.00  5.66           N
ATOM   2025  CA  LEU A 261     -18.343   2.540  -0.225  1.00  7.03           C
ATOM   2026  C   LEU A 261     -18.930   1.930  -1.486  1.00  8.11           C
ATOM   2027  O   LEU A 261     -19.079   0.710  -1.580  1.00  8.85           O
ATOM   2028  CB  LEU A 261     -16.878   2.162  -0.147  1.00  8.55           C
ATOM   2029  CG  LEU A 261     -16.055   2.355  -1.429  1.00  7.61           C
ATOM   2030  CD1 LEU A 261     -15.940   3.844  -1.802  1.00 10.12           C
ATOM   2031  CD2 LEU A 261     -14.679   1.753  -1.241  1.00  9.79           C
ATOM   2032  N   LYS A 262     -19.273   2.775  -2.459  1.00  5.57           N
ATOM   2033  CA  LYS A 262     -19.587   2.288  -3.810  1.00  7.37           C
ATOM   2034  C   LYS A 262     -18.569   2.856  -4.785  1.00  9.49           C
ATOM   2035  O   LYS A 262     -18.314   4.066  -4.798  1.00  9.23           O
ATOM   2036  CB  LYS A 262     -20.996   2.686  -4.224  1.00  9.44           C
ATOM   2037  CG  LYS A 262     -21.487   2.018  -5.527  1.00 14.01           C
ATOM   2038  CD  LYS A 262     -22.988   2.224  -5.735  1.00 17.20           C
ATOM   2039  CE  LYS A 262     -23.449   1.716  -7.104  1.00 18.72           C
ATOM   2040  NZ  LYS A 262     -23.405   0.223  -7.191  1.00 18.42           N
ATOM   2041  N   ILE A 263     -17.949   1.975  -5.567  1.00  7.42           N
ATOM   2042  CA AILE A 263     -16.971   2.372  -6.583  0.90  9.22           C
ATOM   2043  C   ILE A 263     -17.617   2.289  -7.953  1.00  7.84           C
ATOM   2044  O   ILE A 263     -18.215   1.266  -8.303  1.00  9.35           O
ATOM   2045  CB AILE A 263     -15.715   1.470  -6.574  0.90  9.09           C
ATOM   2046  CG1AILE A 263     -14.885   1.681  -5.301  0.90 11.72           C
ATOM   2047  CG2AILE A 263     -14.865   1.719  -7.834  0.90 11.99           C
ATOM   2048  CD1AILE A 263     -14.085   2.991  -5.280  0.90 11.94           C
ATOM   2049  CA BILE A 263     -16.994   2.399  -6.575  0.10 10.98           C
ATOM   2050  CB BILE A 263     -15.721   1.559  -6.521  0.10  6.66           C
ATOM   2051  CG1BILE A 263     -15.124   1.623  -5.119  0.10  7.98           C
ATOM   2052  CG2BILE A 263     -14.718   2.040  -7.561  0.10 17.27           C
ATOM   2053  CD1BILE A 263     -13.981   0.698  -4.927  0.10  3.99           C
ATOM   2054  N   TYR A 264     -17.498   3.363  -8.726  1.00  7.78           N
ATOM   2055  CA  TYR A 264     -18.012   3.401 -10.095  1.00  9.35           C
ATOM   2056  C   TYR A 264     -16.856   3.194 -11.063  1.00  8.73           C
ATOM   2057  O   TYR A 264     -16.002   4.063 -11.239  1.00  7.97           O
ATOM   2058  CB  TYR A 264     -18.727   4.723 -10.348  1.00  9.49           C
ATOM   2059  CG  TYR A 264     -20.043   4.815  -9.615  1.00  5.92           C
ATOM   2060  CD1 TYR A 264     -21.221   4.371 -10.195  1.00  9.53           C
ATOM   2061  CD2 TYR A 264     -20.108   5.343  -8.330  1.00 10.30           C
ATOM   2062  CE1 TYR A 264     -22.440   4.448  -9.525  1.00 10.75           C
ATOM   2063  CE2 TYR A 264     -21.316   5.425  -7.650  1.00  8.15           C
ATOM   2064  CZ  TYR A 264     -22.476   4.978  -8.241  1.00  8.75           C
ATOM   2065  OH  TYR A 264     -23.684   5.059  -7.585  1.00 10.60           O
ATOM   2066  N   GLU A 265     -16.811   2.008 -11.667  1.00  9.58           N
ATOM   2067  CA  GLU A 265     -15.690   1.611 -12.504  1.00 12.10           C
ATOM   2068  C   GLU A 265     -15.638   2.432 -13.796  1.00  8.46           C
ATOM   2069  O   GLU A 265     -16.606   2.477 -14.549  1.00 11.89           O
ATOM   2070  CB  GLU A 265     -15.789   0.114 -12.824  1.00 16.13           C
ATOM   2071  CG  GLU A 265     -14.547  -0.464 -13.462  1.00 17.85           C
ATOM   2072  CD  GLU A 265     -13.347  -0.469 -12.534  1.00 21.43           C
ATOM   2073  OE1 GLU A 265     -13.508  -0.218 -11.312  1.00 20.61           O
ATOM   2074  OE2 GLU A 265     -12.227  -0.726 -13.020  1.00 32.40           O
ATOM   2075  N   GLY A 266     -14.507   3.096 -14.005  1.00  9.44           N
ATOM   2076  CA  GLY A 266     -14.289   3.887 -15.205  1.00 11.21           C
ATOM   2077  C   GLY A 266     -14.797   5.313 -15.075  1.00 11.31           C
ATOM   2078  O   GLY A 266     -14.514   6.145 -15.936  1.00 10.95           O
ATOM   2079  N   ALA A 267     -15.548   5.598 -14.015  1.00  9.68           N
ATOM   2080  CA  ALA A 267     -16.150   6.920 -13.851  1.00 10.27           C
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ATOM   2081  C   ALA A 267     -15.114   7.942 -13.397  1.00  6.06           C
ATOM   2082  O   ALA A 267     -14.166   7.627 -12.691  1.00  7.71           O
ATOM   2083  CB  ALA A 267     -17.324   6.859 -12.875  1.00  9.22           C
ATOM   2084  N   TYR A 268     -15.291   9.176 -13.865  1.00  7.32           N
ATOM   2085  CA  TYR A 268     -14.391  10.267 -13.504  1.00  7.50           C
ATOM   2086  C   TYR A 268     -14.858  10.929 -12.194  1.00  9.01           C
ATOM   2087  O   TYR A 268     -15.804  10.481 -11.556  1.00 11.16           O
ATOM   2088  CB  TYR A 268     -14.357  11.317 -14.632  1.00  8.84           C
ATOM   2089  CG  TYR A 268     -13.629  10.892 -15.905  1.00  9.04           C
ATOM   2090  CD1 TYR A 268     -13.218   9.575 -16.106  1.00 12.36           C
ATOM   2091  CD2 TYR A 268     -13.385  11.812 -16.915  1.00 10.68           C
ATOM   2092  CE1 TYR A 268     -12.557   9.193 -17.278  1.00 13.18           C
ATOM   2093  CE2 TYR A 268     -12.736  11.442 -18.087  1.00 15.29           C
ATOM   2094  CZ  TYR A 268     -12.324  10.140 -18.259  1.00 14.67           C
ATOM   2095  OH  TYR A 268     -11.687   9.783 -19.436  1.00 17.75           O
ATOM   2096  N   HIS A 269     -14.191  12.013 -11.834  1.00  7.57           N
ATOM   2097  CA  HIS A 269     -14.368  12.696 -10.548  1.00  6.36           C
ATOM   2098  C   HIS A 269     -15.795  13.154 -10.224  1.00  7.22           C
ATOM   2099  O   HIS A 269     -16.295  12.928  -9.115  1.00  7.15           O
ATOM   2100  CB  HIS A 269     -13.421  13.898 -10.549  1.00  7.11           C
ATOM   2101  CG  HIS A 269     -13.401  14.689  -9.274  1.00  7.54           C
ATOM   2102  ND1 HIS A 269     -13.058  14.144  -8.053  1.00  9.09           N
ATOM   2103  CD2 HIS A 269     -13.599  16.012  -9.051  1.00  9.50           C
ATOM   2104  CE1 HIS A 269     -13.070  15.096  -7.130  1.00  8.18           C
ATOM   2105  NE2 HIS A 269     -13.393  16.237  -7.711  1.00 10.12           N
ATOM   2106  N   VAL A 270     -16.464  13.813 -11.161  1.00  6.45           N
ATOM   2107  CA  VAL A 270     -17.721  14.471 -10.832  1.00  6.65           C
ATOM   2108  C   VAL A 270     -18.897  13.531 -11.071  1.00  7.38           C
ATOM   2109  O   VAL A 270     -19.610  13.613 -12.081  1.00  6.78           O
ATOM   2110  CB  VAL A 270     -17.896  15.798 -11.602  1.00  5.79           C
ATOM   2111  CG1 VAL A 270     -19.038  16.584 -10.997  1.00  7.82           C
ATOM   2112  CG2 VAL A 270     -16.630  16.622 -11.516  1.00  7.71           C
ATOM   2113  N   LEU A 271     -19.103  12.637 -10.108  1.00  6.65           N
ATOM   2114  CA  LEU A 271     -20.053  11.534 -10.285  1.00  6.15           C
ATOM   2115  C   LEU A 271     -21.499  11.970 -10.477  1.00  5.91           C
ATOM   2116  O   LEU A 271     -22.285  11.283 -11.133  1.00  7.39           O
ATOM   2117  CB  LEU A 271     -19.957  10.556  -9.105  1.00  6.48           C
ATOM   2118  CG  LEU A 271     -18.615   9.871  -8.906  1.00  5.62           C
ATOM   2119  CD1 LEU A 271     -18.659   9.055  -7.613  1.00  9.62           C
ATOM   2120  CD2 LEU A 271     -18.321   8.957 -10.089  1.00  8.14           C
ATOM   2121  N   HIS A 272     -21.873  13.103  -9.886  1.00  5.74           N
ATOM   2122  CA  HIS A 272     -23.233  13.610 -10.006  1.00  5.90           C
ATOM   2123  C   HIS A 272     -23.448  14.420 -11.291  1.00  5.61           C
ATOM   2124  O   HIS A 272     -24.538  14.940 -11.511  1.00  8.27           O
ATOM   2125  CB  HIS A 272     -23.602  14.449  -8.773  1.00  6.29           C
ATOM   2126  CG  HIS A 272     -22.612  15.529  -8.463  1.00  8.33           C
ATOM   2127  ND1 HIS A 272     -21.309  15.262  -8.108  1.00  8.50           N
ATOM   2128  CD2 HIS A 272     -22.731  16.879  -8.481  1.00 11.04           C
ATOM   2129  CE1 HIS A 272     -20.669  16.402  -7.905  1.00 12.80           C
ATOM   2130  NE2 HIS A 272     -21.510  17.396  -8.128  1.00 11.63           N
ATOM   2131  N   LYS A 273     -22.403  14.505 -12.121  1.00  6.91           N
ATOM   2132  CA  LYS A 273     -22.487  15.162 -13.432  1.00  7.10           C
ATOM   2133  C   LYS A 273     -21.801  14.293 -14.470  1.00  7.81           C
ATOM   2134  O   LYS A 273     -21.114  14.800 -15.363  1.00  8.13           O
ATOM   2135  CB  LYS A 273     -21.778  16.519 -13.399  1.00  8.99           C
ATOM   2136  CG  LYS A 273     -22.307  17.505 -12.362  1.00  9.49           C
ATOM   2137  CD  LYS A 273     -23.666  18.011 -12.739  1.00  9.39           C
ATOM   2138  CE  LYS A 273     -24.085  19.150 -11.798  1.00 11.48           C
ATOM   2139  NZ  LYS A 273     -25.494  19.505 -12.017  1.00 16.06           N
ATOM   2140  N   GLU A 274     -21.948  12.978 -14.319  1.00  7.75           N
ATOM   2141  CA  GLU A 274     -21.254  12.023 -15.169  1.00  7.79           C
ATOM   2142  C   GLU A 274     -22.186  11.460 -16.249  1.00  7.03           C
ATOM   2143  O   GLU A 274     -23.236  12.024 -16.542  1.00  9.33           O
ATOM   2144  CB  GLU A 274     -20.654  10.908 -14.297  1.00 10.21           C
ATOM   2145  CG  GLU A 274     -19.145  10.870 -14.300  1.00  9.08           C
ATOM   2146  CD  GLU A 274     -18.598  10.004 -15.429  1.00  8.56           C
ATOM   2147  OE1 GLU A 274     -17.403  10.118 -15.749  1.00 10.56           O
ATOM   2148  OE2 GLU A 274     -19.388   9.210 -15.979  1.00 11.18           O
ATOM   2149  N   LEU A 275     -21.787  10.352 -16.869  1.00  8.50           N
ATOM   2150  CA  LEU A 275     -22.669   9.703 -17.836  1.00  9.61           C
ATOM   2151  C   LEU A 275     -23.985   9.365 -17.146  1.00 11.58           C
ATOM   2152  O   LEU A 275     -23.991   9.062 -15.954  1.00 10.17           O
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ATOM   2153  CB  LEU A 275     -22.016   8.439 -18.394  1.00  9.97           C
ATOM   2154  CG  LEU A 275     -20.737   8.703 -19.181  1.00 12.18           C
ATOM   2155  CD1 LEU A 275     -20.108   7.415 -19.713  1.00 14.42           C
ATOM   2156  CD2 LEU A 275     -21.026   9.667 -20.329  1.00 15.54           C
ATOM   2157  N   PRO A 276     -25.107   9.413 -17.881  1.00 11.73           N
ATOM   2158  CA  PRO A 276     -26.427   9.164 -17.288  1.00 14.10           C
ATOM   2159  C   PRO A 276     -26.511   7.906 -16.417  1.00 16.89           C
ATOM   2160  O   PRO A 276     -27.109   7.964 -15.336  1.00 17.36           O
ATOM   2161  CB  PRO A 276     -27.334   9.016 -18.512  1.00 16.90           C
ATOM   2162  CG  PRO A 276     -26.692   9.878 -19.538  1.00 21.28           C
ATOM   2163  CD  PRO A 276     -25.205   9.809 -19.300  1.00 13.96           C
ATOM   2164  N   GLU A 277     -25.939   6.792 -16.870  1.00 14.89           N
ATOM   2165  CA  GLU A 277     -25.994   5.547 -16.100  1.00 16.63           C
ATOM   2166  C   GLU A 277     -25.385   5.732 -14.712  1.00 16.38           C
ATOM   2167  O   GLU A 277     -25.934   5.261 -13.712  1.00 19.95           O
ATOM   2168  CB  GLU A 277     -25.286   4.408 -16.841  1.00 21.94           C
ATOM   2169  CG  GLU A 277     -26.111   3.796 -17.961  1.00 85.26           C
ATOM   2170  CD  GLU A 277     -25.461   2.565 -18.564  1.00121.84           C
ATOM   2171  OE1 GLU A 277     -24.359   2.187 -18.112  1.00109.89           O
ATOM   2172  OE2 GLU A 277     -26.055   1.973 -19.490  1.00104.17           O
ATOM   2173  N   VAL A 278     -24.252   6.421 -14.655  1.00 10.73           N
ATOM   2174  CA  VAL A 278     -23.595   6.693 -13.384  1.00  9.85           C
ATOM   2175  C   VAL A 278     -24.407   7.674 -12.541  1.00 11.95           C
ATOM   2176  O   VAL A 278     -24.734   7.391 -11.387  1.00 11.20           O
ATOM   2177  CB  VAL A 278     -22.169   7.242 -13.601  1.00  9.03           C
ATOM   2178  CG1 VAL A 278     -21.597   7.780 -12.299  1.00 12.15           C
ATOM   2179  CG2 VAL A 278     -21.269   6.158 -14.196  1.00 13.85           C
ATOM   2180  N   THR A 279     -24.757   8.814 -13.119  1.00  9.26           N
ATOM   2181  CA  THR A 279     -25.478   9.838 -12.372  1.00 10.05           C
ATOM   2182  C   THR A 279     -26.818   9.334 -11.848  1.00  9.97           C
ATOM   2183  O   THR A 279     -27.201   9.644 -10.721  1.00 10.35           O
ATOM   2184  CB  THR A 279     -25.640  11.119 -13.200  1.00 10.89           C
ATOM   2185  OG1 THR A 279     -24.336  11.655 -13.456  1.00 15.41           O
ATOM   2186  CG2 THR A 279     -26.464  12.144 -12.443  1.00 11.76           C
ATOM   2187  N   ASN A 280     -27.534   8.562 -12.660  1.00 10.65           N
ATOM   2188  CA  ASN A 280     -28.815   8.023 -12.224  1.00 11.97           C
ATOM   2189  C   ASN A 280     -28.632   7.108 -11.016  1.00  9.96           C
ATOM   2190  O   ASN A 280     -29.428   7.140 -10.067  1.00 10.76           O
ATOM   2191  CB  ASN A 280     -29.510   7.269 -13.360  1.00 11.47           C
ATOM   2192  CG  ASN A 280     -30.038   8.195 -14.441  1.00 21.55           C
ATOM   2193  OD1 ASN A 280     -30.206   9.391 -14.221  1.00 21.86           O
ATOM   2194  ND2 ASN A 280     -30.305   7.639 -15.617  1.00 25.48           N
ATOM   2195  N   SER A 281     -27.577   6.303 -11.056  1.00  9.62           N
ATOM   2196  CA  SER A 281     -27.240   5.423  -9.943  1.00  9.05           C
ATOM   2197  C   SER A 281     -26.862   6.227  -8.703  1.00 10.69           C
ATOM   2198  O   SER A 281     -27.311   5.922  -7.607  1.00 10.10           O
ATOM   2199  CB  SER A 281     -26.089   4.494 -10.331  1.00  9.22           C
ATOM   2200  OG  SER A 281     -25.601   3.798  -9.193  1.00 11.41           O
ATOM   2201  N   VAL A 282     -26.029   7.250  -8.878  1.00  8.01           N
ATOM   2202  CA  VAL A 282     -25.625   8.113  -7.769  1.00  9.36           C
ATOM   2203  C   VAL A 282     -26.851   8.703  -7.059  1.00  8.59           C
ATOM   2204  O   VAL A 282     -26.955   8.650  -5.827  1.00  8.36           O
ATOM   2205  CB  VAL A 282     -24.668   9.223  -8.262  1.00  8.18           C
ATOM   2206  CG1 VAL A 282     -24.550  10.343  -7.228  1.00  8.83           C
ATOM   2207  CG2 VAL A 282     -23.313   8.620  -8.597  1.00  9.21           C
ATOM   2208  N   PHE A 283     -27.787   9.254  -7.828  1.00  7.90           N
ATOM   2209  CA  PHE A 283     -29.005   9.804  -7.247  1.00  7.68           C
ATOM   2210  C   PHE A 283     -29.799   8.730  -6.507  1.00 10.02           C
ATOM   2211  O   PHE A 283     -30.290   8.961  -5.403  1.00 10.89           O
ATOM   2212  CB  PHE A 283     -29.881  10.463  -8.316  1.00  8.60           C
ATOM   2213  CG  PHE A 283     -29.534  11.907  -8.593  1.00  8.21           C
ATOM   2214  CD1 PHE A 283     -28.295  12.257  -9.084  1.00  9.31           C
ATOM   2215  CD2 PHE A 283     -30.478  12.907  -8.395  1.00  9.23           C
ATOM   2216  CE1 PHE A 283     -27.977  13.595  -9.350  1.00 10.77           C
ATOM   2217  CE2 PHE A 283     -30.172  14.238  -8.666  1.00 10.37           C
ATOM   2218  CZ  PHE A 283     -28.929  14.575  -9.137  1.00 10.84           C
ATOM   2219  N   HIS A 284     -29.932   7.556  -7.121  1.00  9.09           N
ATOM   2220  CA  HIS A 284     -30.675   6.463  -6.508  1.00  9.12           C
ATOM   2221  C   HIS A 284     -30.033   6.025  -5.189  1.00  9.99           C
ATOM   2222  O   HIS A 284     -30.737   5.828  -4.188  1.00  9.74           O
ATOM   2223  CB  HIS A 284     -30.765   5.290  -7.492  1.00 11.67           C
ATOM   2224  CG  HIS A 284     -31.431   4.069  -6.935  1.00 14.61           C
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ATOM   2225  ND1 HIS A 284     -32.760   4.046  -6.573  1.00 20.82           N
ATOM   2226  CD2 HIS A 284     -30.958   2.820  -6.717  1.00 21.94           C
ATOM   2227  CE1 HIS A 284     -33.074   2.837  -6.138  1.00 19.80           C
ATOM   2228  NE2 HIS A 284     -31.998   2.075  -6.216  1.00 23.11           N
ATOM   2229  N   GLU A 285     -28.713   5.876  -5.181  1.00  8.55           N
ATOM   2230  CA  GLU A 285     -28.016   5.410  -3.977  1.00  8.60           C
ATOM   2231  C   GLU A 285     -28.134   6.419  -2.836  1.00  9.27           C
ATOM   2232  O   GLU A 285     -28.337   6.043  -1.678  1.00 10.15           O
ATOM   2233  CB  GLU A 285     -26.548   5.102  -4.266  1.00 10.27           C
ATOM   2234  CG  GLU A 285     -26.341   3.975  -5.284  1.00 12.66           C
ATOM   2235  CD  GLU A 285     -26.784   2.615  -4.761  1.00 48.46           C
ATOM   2236  OE1 GLU A 285     -26.861   2.438  -3.526  1.00 24.33           O
ATOM   2237  OE2 GLU A 285     -27.051   1.714  -5.586  1.00 26.17           O
ATOM   2238  N   ILE A 286     -27.999   7.703  -3.158  1.00  8.06           N
ATOM   2239  CA  ILE A 286     -28.130   8.738  -2.137  1.00  7.60           C
ATOM   2240  C   ILE A 286     -29.561   8.758  -1.615  1.00  8.03           C
ATOM   2241  O   ILE A 286     -29.797   8.844  -0.404  1.00  9.29           O
ATOM   2242  CB  ILE A 286     -27.726  10.117  -2.697  1.00  7.44           C
ATOM   2243  CG1 ILE A 286     -26.225  10.131  -2.982  1.00  8.11           C
ATOM   2244  CG2 ILE A 286     -28.104  11.222  -1.702  1.00  9.25           C
ATOM   2245  CD1 ILE A 286     -25.730  11.355  -3.736  1.00  8.46           C
ATOM   2246  N   ASN A 287     -30.525   8.668  -2.524  1.00  7.56           N
ATOM   2247  CA  ASN A 287     -31.927   8.632  -2.145  1.00  9.10           C
ATOM   2248  C   ASN A 287     -32.196   7.506  -1.135  1.00  9.78           C
ATOM   2249  O   ASN A 287     -32.777   7.731  -0.068  1.00 10.92           O
ATOM   2250  CB  ASN A 287     -32.792   8.481  -3.408  1.00  9.77           C
ATOM   2251  CG  ASN A 287     -34.280   8.468  -3.121  1.00 16.23           C
ATOM   2252  OD1 ASN A 287     -34.738   7.846  -2.167  1.00 16.90           O
ATOM   2253  ND2 ASN A 287     -35.046   9.144  -3.968  1.00 17.83           N
ATOM   2254  N   MET A 288     -31.756   6.295  -1.457  1.00  9.68           N
ATOM   2255  CA AMET A 288     -32.008   5.164  -0.571  0.75 10.52           C
ATOM   2256  C   MET A 288     -31.283   5.304   0.765  1.00 10.26           C
ATOM   2257  O   MET A 288     -31.858   5.002   1.817  1.00 11.11           O
ATOM   2258  CB AMET A 288     -31.618   3.853  -1.246  0.75 13.43           C
ATOM   2259  CG AMET A 288     -32.543   3.452  -2.384  0.75 11.44           C
ATOM   2260  SD AMET A 288     -32.159   1.788  -2.967  0.75 19.23           S
ATOM   2261  CE AMET A 288     -30.435   1.981  -3.415  0.75 25.05           C
ATOM   2262  CA BMET A 288     -31.970   5.141  -0.586  0.25 13.65           C
ATOM   2263  CB BMET A 288     -31.454   3.872  -1.264  0.25 10.56           C
ATOM   2264  CG BMET A 288     -32.177   3.528  -2.550  0.25 11.01           C
ATOM   2265  SD BMET A 288     -33.911   3.126  -2.263  0.25 15.84           S
ATOM   2266  CE BMET A 288     -33.757   1.686  -1.209  0.25 35.78           C
ATOM   2267  N   TRP A 289     -30.041   5.768   0.732  1.00  8.12           N
ATOM   2268  CA  TRP A 289     -29.239   5.874   1.947  1.00  8.46           C
ATOM   2269  C   TRP A 289     -29.847   6.893   2.916  1.00 10.60           C
ATOM   2270  O   TRP A 289     -30.013   6.619   4.106  1.00 10.10           O
ATOM   2271  CB  TRP A 289     -27.809   6.262   1.588  1.00  8.04           C
ATOM   2272  CG  TRP A 289     -26.829   6.080   2.699  1.00  8.76           C
ATOM   2273  CD1 TRP A 289     -26.110   4.953   2.987  1.00  8.96           C
ATOM   2274  CD2 TRP A 289     -26.452   7.057   3.681  1.00  7.64           C
ATOM   2275  NE1 TRP A 289     -25.307   5.171   4.076  1.00  8.96           N
ATOM   2276  CE2 TRP A 289     -25.501   6.452   4.525  1.00  7.40           C
ATOM   2277  CE3 TRP A 289     -26.815   8.386   3.916  1.00  8.72           C
ATOM   2278  CZ2 TRP A 289     -24.912   7.130   5.594  1.00  8.56           C
ATOM   2279  CZ3 TRP A 289     -26.232   9.055   4.981  1.00  9.78           C
ATOM   2280  CH2 TRP A 289     -25.292   8.429   5.801  1.00  7.77           C
ATOM   2281  N   VAL A 290     -30.202   8.061   2.392  1.00  7.61           N
ATOM   2282  CA  VAL A 290     -30.822   9.098   3.210  1.00  8.87           C
ATOM   2283  C   VAL A 290     -32.228   8.697   3.658  1.00 11.01           C
ATOM   2284  O   VAL A 290     -32.591   8.898   4.821  1.00 12.42           O
ATOM   2285  CB  VAL A 290     -30.834  10.451   2.465  1.00 10.20           C
ATOM   2286  CG1 VAL A 290     -31.622  11.483   3.254  1.00 13.69           C
ATOM   2287  CG2 VAL A 290     -29.410  10.923   2.232  1.00 10.54           C
ATOM   2288  N   SER A 291     -33.018   8.122   2.757  1.00 11.05           N
ATOM   2289  CA  SER A 291     -34.362   7.653   3.105  1.00 12.68           C
ATOM   2290  C   SER A 291     -34.337   6.683   4.286  1.00 15.97           C
ATOM   2291  O   SER A 291     -35.128   6.805   5.226  1.00 16.56           O
ATOM   2292  CB  SER A 291     -35.013   6.968   1.903  1.00 14.10           C
ATOM   2293  OG  SER A 291     -35.461   7.922   0.957  1.00 20.61           O
ATOM   2294  N   GLN A 292     -33.428   5.717   4.236  1.00 13.80           N
ATOM   2295  CA  GLN A 292     -33.346   4.702   5.281  1.00 13.65           C
ATOM   2296  C   GLN A 292     -32.926   5.283   6.628  1.00 15.92           C
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ATOM   2297  O   GLN A 292     -33.192   4.697   7.676  1.00 19.93           O
ATOM   2298  CB  GLN A 292     -32.414   3.577   4.841  1.00 15.28           C
ATOM   2299  CG  GLN A 292     -33.016   2.750   3.714  1.00 31.36           C
ATOM   2300  CD  GLN A 292     -32.018   1.827   3.059  1.00 59.35           C
ATOM   2301  OE1 GLN A 292     -31.042   1.409   3.679  1.00 46.54           O
ATOM   2302  NE2 GLN A 292     -32.259   1.500   1.795  1.00 52.18           N
ATOM   2303  N   ARG A 293     -32.290   6.449   6.604  1.00 11.83           N
ATOM   2304  CA  ARG A 293     -31.758   7.049   7.818  1.00 11.03           C
ATOM   2305  C   ARG A 293     -32.577   8.254   8.293  1.00 10.89           C
ATOM   2306  O   ARG A 293     -32.172   8.968   9.215  1.00 14.96           O
ATOM   2307  CB  ARG A 293     -30.273   7.380   7.632  1.00  9.52           C
ATOM   2308  CG  ARG A 293     -29.406   6.126   7.665  1.00 10.01           C
ATOM   2309  CD  ARG A 293     -28.042   6.325   7.036  1.00 10.98           C
ATOM   2310  NE  ARG A 293     -27.297   5.065   7.004  1.00  9.60           N
ATOM   2311  CZ  ARG A 293     -27.508   4.099   6.111  1.00  9.62           C
ATOM   2312  NH1 ARG A 293     -28.431   4.249   5.166  1.00  9.87           N
ATOM   2313  NH2 ARG A 293     -26.789   2.987   6.171  1.00 11.78           N
ATOM   2314  N   THR A 294     -33.731   8.453   7.667  1.00 14.09           N
ATOM   2315  CA  THR A 294     -34.681   9.485   8.068  1.00 15.85           C
ATOM   2316  C   THR A 294     -36.072   8.869   8.199  1.00 22.42           C
ATOM   2317  O   THR A 294     -37.067   9.584   8.311  1.00 36.87           O
ATOM   2318  CB  THR A 294     -34.731  10.651   7.053  1.00 16.73           C
ATOM   2319  OG1 THR A 294     -35.000  10.137   5.743  1.00 18.85           O
ATOM   2320  CG2 THR A 294     -33.417  11.393   7.022  1.00 15.10           C
ATOM   2321  O01 INH I   1     -12.895  20.823  -4.999  1.00  7.09           O
ATOM   2322  C02 INH I   1     -12.391  20.703  -6.129  1.00  8.09           C
ATOM   2323  C03 INH I   1     -10.917  20.735  -6.329  1.00  7.66           C
ATOM   2324  C04 INH I   1     -10.371  21.511  -7.372  1.00  8.80           C
ATOM   2325  C05 INH I   1      -9.002  21.548  -7.621  1.00 11.29           C
ATOM   2326  C06 INH I   1      -8.161  20.785  -6.808  1.00  9.74           C
ATOM   2327  N07 INH I   1      -6.763  20.578  -6.783  1.00 12.42           N
ATOM   2328  C08 INH I   1      -6.533  19.727  -5.790  1.00 14.65           C
ATOM   2329  O09 INH I   1      -7.712  19.334  -5.112  1.00 13.07           O
ATOM   2330  C10 INH I   1      -8.755  19.997  -5.760  1.00  9.91           C
ATOM   2331  C11 INH I   1     -10.110  19.953  -5.499  1.00  7.61           C
ATOM   2332  C12 INH I   1      -5.241  19.125  -5.317  1.00 16.69           C
ATOM   2333  C13 INH I   1      -4.117  19.335  -6.328  1.00 15.09           C
ATOM   2334  C14 INH I   1      -2.767  18.863  -5.823  1.00 19.81           C
ATOM   2335  C15 INH I   1      -2.421  19.447  -4.476  1.00 19.20           C
ATOM   2336  C16 INH I   1      -3.512  19.142  -3.467  1.00 19.60           C
ATOM   2337  C17 INH I   1      -4.893  19.592  -3.914  1.00 17.98           C
ATOM   2338  N18 INH I   1     -13.235  20.690  -7.197  1.00  6.87           N
ATOM   2339  C19 INH I   1     -14.672  20.540  -7.283  1.00  6.93           C
ATOM   2340  C20 INH I   1     -14.471  19.893  -8.684  1.00  6.67           C
ATOM   2341  C21 INH I   1     -12.952  20.266  -8.587  1.00  8.77           C
ATOM   2342  N22 INH I   1     -15.178  20.424  -9.813  1.00  6.45           N
ATOM   2343  C23 INH I   1     -16.588  20.190  -9.789  1.00  5.98           C
ATOM   2344  C24 INH I   1     -17.328  20.733 -11.042  1.00  6.80           C
ATOM   2345  N25 INH I   1     -16.634  20.331 -12.248  1.00  7.33           N
ATOM   2346  C26 INH I   1     -15.203  20.541 -12.284  1.00 10.22           C
ATOM   2347  C27 INH I   1     -14.523  19.973 -11.038  1.00  7.33           C
ATOM   2348  C28 INH I   1     -17.296  19.725 -13.318  1.00  6.80           C
ATOM   2349  N29 INH I   1     -16.488  19.205 -14.329  1.00  7.30           N
ATOM   2350  C30 INH I   1     -17.138  18.618 -15.336  1.00  7.90           C
ATOM   2351  C31 INH I   1     -18.527  18.508 -15.408  1.00  7.42           C
ATOM   2352  C32 INH I   1     -19.257  19.048 -14.354  1.00  7.83           C
ATOM   2353  N33 INH I   1     -18.670  19.648 -13.307  1.00  6.45           N
HETATM 2354  O   HOH W   1     -17.954  27.691   4.082  1.00  7.52           O
HETATM 2355  O   HOH W   2     -16.687  30.118   3.647  1.00  7.58           O
HETATM 2356  O   HOH W   3     -16.903  29.964  -7.861  1.00  8.56           O
HETATM 2357  O   HOH W   4     -24.521  30.541  -6.460  1.00  8.76           O
HETATM 2358  O   HOH W   5     -18.264  32.412  10.389  1.00  8.02           O
HETATM 2359  O   HOH W   6     -23.247   3.675   5.398  1.00  9.13           O
HETATM 2360  O   HOH W   7     -15.105  23.282  -9.818  1.00 10.08           O
HETATM 2361  O   HOH W   8     -20.744   0.215  -8.443  1.00  9.73           O
HETATM 2362  O   HOH W   9     -11.897  30.578  -1.691  1.00 10.64           O
HETATM 2363  O   HOH W  10     -22.252  20.341 -15.373  1.00 11.45           O
HETATM 2364  O   HOH W  11     -27.187  18.469  -8.872  1.00 12.11           O
HETATM 2365  O   HOH W  12     -11.733  34.673  -0.588  1.00 12.31           O
HETATM 2366  O   HOH W  13     -11.423  12.123 -13.304  1.00 11.25           O
HETATM 2367  O   HOH W  14     -18.816  28.913  13.424  1.00 11.56           O
HETATM 2368  O   HOH W  15      -9.196  10.830  -2.094  1.00 12.11           O
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HETATM 2369  O   HOH W  16      -9.803  26.896 -12.434  1.00 12.21           O
HETATM 2370  O   HOH W  17     -21.490   5.488  12.067  1.00 12.81           O
HETATM 2371  O   HOH W  18     -32.761  29.987  -2.012  1.00 14.02           O
HETATM 2372  O   HOH W  19     -18.414  31.657  13.060  1.00 12.16           O
HETATM 2373  O   HOH W  20      -5.462  30.956  -0.225  1.00 13.69           O
HETATM 2374  O   HOH W  21     -11.248  35.923   1.786  1.00 14.53           O
HETATM 2375  O   HOH W  22     -30.857  31.479  -3.105  1.00 12.95           O
HETATM 2376  O   HOH W  23     -17.537  30.497 -17.209  1.00 13.52           O
HETATM 2377  O   HOH W  24     -27.943  15.491  13.891  1.00 15.19           O
HETATM 2378  O   HOH W  25      -6.754  29.942  -6.600  1.00 14.74           O
HETATM 2379  O   HOH W  26     -21.995  24.699  -0.661  1.00 15.81           O
HETATM 2380  O   HOH W  27     -24.620  37.557  -8.143  1.00 14.70           O
HETATM 2381  O   HOH W  28     -11.836  10.105  -2.131  1.00 13.84           O
HETATM 2382  O   HOH W  29      -6.977  17.152 -20.873  1.00 14.48           O
HETATM 2383  O   HOH W  30     -27.778  25.779  17.062  1.00 14.55           O
HETATM 2384  O   HOH W  31     -28.099  20.389 -10.972  1.00 15.25           O
HETATM 2385  O   HOH W  32     -26.572  16.678 -10.935  1.00 15.41           O
HETATM 2386  O   HOH W  33     -21.236  20.183  -9.116  1.00 14.32           O
HETATM 2387  O   HOH W  34     -21.239  28.606  14.850  1.00 15.96           O
HETATM 2388  O   HOH W  35     -24.773  29.548 -12.422  1.00 15.43           O
HETATM 2389  O   HOH W  36     -20.822  20.806 -11.819  1.00 14.61           O
HETATM 2390  O   HOH W  37      -9.275  15.936 -22.055  1.00 14.71           O
HETATM 2391  O   HOH W  38     -20.594  14.589  13.855  1.00 17.78           O
HETATM 2392  O   HOH W  39       5.208  15.094 -10.204  1.00 16.41           O
HETATM 2393  O   HOH W  40     -20.072   5.193  14.956  1.00 15.13           O
HETATM 2394  O   HOH W  41     -13.159  26.020 -13.404  1.00 16.62           O
HETATM 2395  O   HOH W  42     -26.282  23.518  16.511  1.00 20.84           O
HETATM 2396  O   HOH W  43     -10.302  34.220   3.868  1.00 18.17           O
HETATM 2397  O   HOH W  44      -1.928  29.772   2.061  1.00 15.99           O
HETATM 2398  O   HOH W  45      -2.744  28.535   7.126  1.00 19.79           O
HETATM 2399  O   HOH W  46      -5.515  17.879 -17.351  1.00 19.09           O
HETATM 2400  O   HOH W  47     -12.817   5.509 -17.997  1.00 18.20           O
HETATM 2401  O   HOH W  48     -14.357  31.242  -7.410  1.00 17.27           O
HETATM 2402  O   HOH W  49     -14.923  14.930 -21.033  1.00 17.02           O
HETATM 2403  O   HOH W  50      -9.458  23.156   9.139  1.00 21.87           O
HETATM 2404  O   HOH W  51       0.257  31.525  -7.428  1.00 18.65           O
HETATM 2405  O   HOH W  52     -25.578  20.460 -14.720  1.00 18.62           O
HETATM 2406  O   HOH W  53     -20.547  12.617 -23.501  1.00 20.46           O
HETATM 2407  O   HOH W  54     -23.950  26.787 -18.563  1.00 17.02           O
HETATM 2408  O   HOH W  55     -14.696   9.975  -8.189  1.00 19.62           O
HETATM 2409  O   HOH W  56     -25.051  13.877 -15.630  1.00 17.92           O
HETATM 2410  O   HOH W  57      -8.564   7.506  -8.708  1.00 18.44           O
HETATM 2411  O   HOH W  58     -26.198  31.102 -16.423  1.00 16.37           O
HETATM 2412  O   HOH W  59     -37.176  12.986  -4.281  1.00 21.18           O
HETATM 2413  O   HOH W  60      -0.408  19.850  -9.658  1.00 20.96           O
HETATM 2414  O   HOH W  61     -27.390   2.115  -8.137  1.00 20.41           O
HETATM 2415  O   HOH W  62     -18.345   0.114  10.794  1.00 19.73           O
HETATM 2416  O   HOH W  63      -7.560  17.472  11.844  1.00 20.82           O
HETATM 2417  O   HOH W  64     -10.060  27.021 -17.033  1.00 19.15           O
HETATM 2418  O   HOH W  65     -11.889  25.550 -15.567  1.00 17.58           O
HETATM 2419  O   HOH W  66      -0.270  32.535  -4.292  1.00 23.13           O
HETATM 2420  O   HOH W  67      -2.409  13.621  -0.840  1.00 20.38           O
HETATM 2421  O   HOH W  68     -26.262  31.478 -13.675  1.00 20.59           O
HETATM 2422  O   HOH W  69     -28.229   3.738 -13.695  1.00 21.62           O
HETATM 2423  O   HOH W  70     -31.712  27.290  -6.129  1.00 18.31           O
HETATM 2424  O   HOH W  71      -6.300  21.250 -19.853  1.00 16.05           O
HETATM 2425  O   HOH W  72     -28.617   2.134   3.116  1.00 24.09           O
HETATM 2426  O   HOH W  73      -6.265  12.778 -21.032  1.00 20.88           O
HETATM 2427  O   HOH W  74      -5.345  21.003  -9.170  1.00 20.95           O
HETATM 2428  O   HOH W  75     -13.672  40.032   1.481  1.00 20.82           O
HETATM 2429  O   HOH W  76       3.970  33.284  -8.733  1.00 21.52           O
HETATM 2430  O   HOH W  77     -27.601   3.453  -1.085  1.00 19.94           O
HETATM 2431  O   HOH W  78     -16.463  32.339  14.904  1.00 20.41           O
HETATM 2432  O   HOH W  79     -30.731  36.819   4.054  1.00 22.74           O
HETATM 2433  O   HOH W  80     -10.846   1.831  -7.270  1.00 21.37           O
HETATM 2434  O   HOH W  81     -27.313  22.838 -11.310  1.00 24.03           O
HETATM 2435  O   HOH W  82     -15.217  31.789 -19.315  1.00 23.88           O
HETATM 2436  O   HOH W  83     -33.912  16.169  -9.052  1.00 22.87           O
HETATM 2437  O   HOH W  84     -20.209  -1.679  12.463  1.00 21.35           O
HETATM 2438  O   HOH W  85      -5.913  10.247  -9.105  1.00 22.32           O
HETATM 2439  O   HOH W  86      -0.959  17.408   2.354  1.00 20.98           O
HETATM 2440  O   HOH W  87     -10.503  38.192   0.316  1.00 24.62           O
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HETATM 2441  O   HOH W  88     -32.112   7.871 -10.243  1.00 21.94           O
HETATM 2442  O   HOH W  89     -13.180  25.290 -17.756  1.00 19.54           O
HETATM 2443  O   HOH W  90      -7.804  19.778 -13.041  1.00 24.06           O
HETATM 2444  O   HOH W  91     -33.427  27.311  -4.139  1.00 23.94           O
HETATM 2445  O   HOH W  92     -12.229  34.941   5.552  1.00 22.55           O
HETATM 2446  O   HOH W  93     -40.268  22.945   5.322  1.00 24.66           O
HETATM 2447  O   HOH W  94     -11.361  -0.276   9.385  1.00 24.33           O
HETATM 2448  O   HOH W  95      -5.594  12.673   4.154  1.00 21.98           O
HETATM 2449  O   HOH W  96     -30.277   8.393  11.189  1.00 23.95           O
HETATM 2450  O   HOH W  97      -3.885  31.646   2.132  1.00 23.08           O
HETATM 2451  O   HOH W  98     -15.349  37.712 -10.155  1.00 22.78           O
HETATM 2452  O   HOH W  99     -27.793   8.032  10.121  1.00 21.52           O
HETATM 2453  O   HOH W 100       1.726  25.595 -13.323  1.00 24.61           O
HETATM 2454  O   HOH W 101      -4.022  23.204 -10.234  1.00 23.85           O
HETATM 2455  O   HOH W 102      -0.283  27.133   5.706  1.00 27.07           O
HETATM 2456  O   HOH W 103     -17.612  12.195  13.686  1.00 22.47           O
HETATM 2457  O   HOH W 104     -20.617  38.511  11.379  1.00 22.85           O
HETATM 2458  O   HOH W 105     -12.949  21.628 -20.519  1.00 22.65           O
HETATM 2459  O   HOH W 106      -8.950  13.120 -21.827  1.00 24.72           O
HETATM 2460  O   HOH W 107     -24.860   6.230 -19.460  1.00 22.27           O
HETATM 2461  O   HOH W 108     -19.286  25.663 -23.124  1.00 24.09           O
HETATM 2462  O   HOH W 109      -4.483  32.563 -11.039  1.00 27.41           O
HETATM 2463  O   HOH W 110     -29.993  33.249   4.804  1.00 24.16           O
HETATM 2464  O   HOH W 111      12.207  32.873   0.335  1.00 25.14           O
HETATM 2465  O   HOH W 112     -34.084  27.205  19.146  1.00 21.94           O
HETATM 2466  O   HOH W 113     -26.787   5.452  10.766  1.00 22.13           O
HETATM 2467  O   HOH W 114       1.550  16.445 -12.673  1.00 29.27           O
HETATM 2468  O   HOH W 115       0.773  22.236  -9.903  1.00 21.44           O
HETATM 2469  O   HOH W 116     -15.044  17.209 -22.620  1.00 21.87           O
HETATM 2470  O   HOH W 117     -25.901  32.220   9.915  1.00 21.85           O
HETATM 2471  O   HOH W 118     -15.258  40.579  -2.244  1.00 27.72           O
HETATM 2472  O   HOH W 119      -7.794  30.680  -9.041  1.00 23.66           O
HETATM 2473  O   HOH W 120     -18.635  35.461 -11.584  1.00 24.31           O
HETATM 2474  O   HOH W 121     -26.081  16.654 -25.505  1.00 22.43           O
HETATM 2475  O   HOH W 122      -9.221   9.291 -15.768  1.00 27.18           O
HETATM 2476  O   HOH W 123     -28.859  32.651  -7.827  1.00 31.44           O
HETATM 2477  O   HOH W 124      -1.147  11.892  -2.485  1.00 25.34           O
HETATM 2478  O   HOH W 125     -16.717  23.990 -23.206  1.00 22.72           O
HETATM 2479  O   HOH W 126     -16.904  27.933  15.146  1.00 28.48           O
HETATM 2480  O   HOH W 127     -24.881  -0.157  -9.675  1.00 30.44           O
HETATM 2481  O   HOH W 128     -12.528  32.808 -13.738  1.00 23.97           O
HETATM 2482  O   HOH W 129     -31.526  33.432  -4.910  1.00 29.01           O
HETATM 2483  O   HOH W 130     -10.048  37.820  -7.038  1.00 29.37           O
HETATM 2484  O   HOH W 131     -11.867  19.403  12.228  1.00 29.42           O
HETATM 2485  O   HOH W 132     -37.133  10.668   3.881  1.00 30.27           O
HETATM 2486  O   HOH W 133     -19.747   3.815 -16.456  1.00 27.29           O
HETATM 2487  O   HOH W 134      -7.880  35.404  -6.844  1.00 24.86           O
HETATM 2488  O   HOH W 135      -8.998   3.716  -9.036  1.00 28.14           O
HETATM 2489  O   HOH W 136      -2.967  12.137   4.048  1.00 26.40           O
HETATM 2490  O   HOH W 137     -17.049  39.326 -11.678  1.00 25.80           O
HETATM 2491  O   HOH W 138     -10.257  -2.109 -12.040  1.00 29.56           O
HETATM 2492  O   HOH W 139     -26.119  34.050 -13.125  1.00 25.74           O
HETATM 2493  O   HOH W 140     -16.994  38.359  14.121  1.00 32.67           O
HETATM 2494  O   HOH W 141     -10.346  37.403 -10.034  1.00 28.07           O
HETATM 2495  O   HOH W 142       6.226  22.804  -1.176  1.00 26.21           O
HETATM 2496  O   HOH W 143      -7.855  32.548   9.121  1.00 31.08           O
HETATM 2497  O   HOH W 144     -38.520  18.008  -5.332  1.00 28.74           O
HETATM 2498  O   HOH W 145       0.863  30.021 -14.155  1.00 25.22           O
HETATM 2499  O   HOH W 146     -14.539  12.832 -22.506  1.00 34.74           O
HETATM 2500  O   HOH W 147      -9.685  35.266   7.783  1.00 39.75           O
HETATM 2501  O   HOH W 148      -4.940  15.663  -7.095  1.00 28.86           O
HETATM 2502  O   HOH W 149     -19.875  12.007  14.866  1.00 29.93           O
HETATM 2503  O   HOH W 150     -25.128  -0.534  -5.095  1.00 28.37           O
HETATM 2504  O   HOH W 151      -1.385  12.790   1.731  1.00 27.27           O
HETATM 2505  O   HOH W 152     -28.589  35.688  -8.140  1.00 29.37           O
HETATM 2506  O   HOH W 153     -39.946  16.242  11.666  1.00 27.63           O
HETATM 2507  O   HOH W 154     -12.005  32.563  12.899  1.00 28.89           O
HETATM 2508  O   HOH W 155     -32.382  11.270  10.718  1.00 27.03           O
HETATM 2509  O   HOH W 156      -6.547  26.498  11.420  1.00 26.38           O
HETATM 2510  O   HOH W 157     -15.098   4.994 -20.108  1.00 30.09           O
HETATM 2511  O   HOH W 158     -40.304  25.037   6.932  1.00 29.28           O
HETATM 2512  O   HOH W 159     -19.654  42.452 -11.933  1.00 28.67           O
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HETATM 2513  O   HOH W 160       7.165  33.655 -14.239  1.00 29.40           O
HETATM 2514  O   HOH W 161     -29.918   4.810 -15.685  1.00 30.16           O
HETATM 2515  O   HOH W 162      10.935  23.184  -6.110  1.00 32.43           O
HETATM 2516  O   HOH W 163     -26.145   2.186   1.054  1.00 36.44           O
HETATM 2517  O   HOH W 164     -34.339   6.200  -6.038  1.00 31.60           O
HETATM 2518  O   HOH W 165      -7.577  23.852  11.873  1.00 37.15           O
HETATM 2519  O   HOH W 166     -28.374  17.766  15.757  1.00 33.08           O
HETATM 2520  O   HOH W 167      -8.878  30.353  10.450  1.00 33.65           O
HETATM 2521  O   HOH W 168     -39.240  24.455  13.603  1.00 32.18           O
HETATM 2522  O   HOH W 169      -5.259  32.467 -14.521  1.00 30.28           O
HETATM 2523  O   HOH W 170     -19.002  44.014  -6.429  1.00 36.88           O
HETATM 2524  O   HOH W 171     -41.472  23.045  -1.746  1.00 34.68           O
HETATM 2525  O   HOH W 172     -41.240  17.380  -0.287  1.00 30.69           O
HETATM 2526  O   HOH W 173     -18.871  43.325  -2.077  1.00 32.89           O
HETATM 2527  O   HOH W 174     -15.823  41.421   2.253  1.00 29.64           O
HETATM 2528  O   HOH W 175      -7.050  21.485 -11.124  1.00 32.96           O
HETATM 2529  O   HOH W 176     -37.741  26.386  -1.056  1.00 29.25           O
HETATM 2530  O   HOH W 177     -37.633  14.168  12.267  1.00 41.58           O
HETATM 2531  O   HOH W 178     -36.152  30.566  14.397  1.00 32.08           O
HETATM 2532  O   HOH W 179     -16.547  10.926 -22.860  1.00 29.03           O
HETATM 2533  O   HOH W 180     -41.727  23.706   9.092  1.00 33.88           O
HETATM 2534  O   HOH W 181       6.999  23.263 -12.013  1.00 36.81           O
HETATM 2535  O   HOH W 182     -17.044   8.041 -22.415  1.00 38.12           O
HETATM 2536  O   HOH W 183     -35.338  12.042  10.329  1.00 31.94           O
HETATM 2537  O   HOH W 184       2.050  23.137 -12.328  1.00 30.75           O
HETATM 2538  O   HOH W 185     -19.726  45.933  -2.467  1.00 38.74           O
HETATM 2539  O   HOH W 186      -0.301   9.788  -9.818  1.00 33.75           O
HETATM 2540  O   HOH W 187      -5.231  11.780  14.591  1.00 34.83           O
HETATM 2541  O   HOH W 188     -14.916  41.932   5.514  1.00 41.07           O
HETATM 2542  O   HOH W 189     -42.696  19.572  -0.424  1.00 32.59           O
HETATM 2543  O   HOH W 190      -0.895  14.955   4.198  1.00 36.30           O
HETATM 2544  O   HOH W 191     -18.995   3.659 -13.597  1.00 34.12           O
HETATM 2545  O   HOH W 192     -37.998  28.389  15.014  1.00 31.37           O
HETATM 2546  O   HOH W 193     -30.890  10.641  13.026  1.00 32.22           O
HETATM 2547  O   HOH W 194     -11.626  11.766 -21.687  1.00 36.98           O
HETATM 2548  O   HOH W 195     -14.658  39.550  -8.121  1.00 38.81           O
HETATM 2549  O   HOH W 196     -29.019  13.051  14.830  1.00 36.98           O
HETATM 2550  O   HOH W 197      -4.504  18.598 -10.348  1.00 38.67           O
HETATM 2551  O   HOH W 198      -0.549  14.853 -12.387  1.00 44.66           O
HETATM 2552  O   HOH W 199      -4.956  22.211 -15.525  1.00 36.99           O
HETATM 2553  O   HOH W 200      -4.889  15.947 -10.022  1.00 35.93           O
HETATM 2554  O   HOH W 201     -23.924  21.128 -22.907  1.00 33.50           O
HETATM 2555  O   HOH W 202     -15.047  33.244 -10.368  1.00 35.92           O
HETATM 2556  O   HOH W 203     -38.527  11.133  10.261  1.00 37.83           O
HETATM 2557  O   HOH W 204      -9.009  31.981 -16.860  1.00 31.39           O
HETATM 2558  O   HOH W 205     -38.191  21.671  15.013  1.00 36.15           O
HETATM 2559  O   HOH W 206     -18.868  10.333 -23.932  1.00 46.13           O
HETATM 2560  O   HOH W 207     -35.132  25.919  -6.614  1.00 52.07           O
HETATM 2561  O   HOH W 208     -27.841  21.763 -15.855  1.00 41.85           O
HETATM 2562  O   HOH W 209     -34.644  43.404  -1.444  1.00 38.81           O
HETATM 2563  O   HOH W 210     -30.201   3.894 -11.360  1.00 37.63           O
HETATM 2564  O   HOH W 211     -22.748  49.399  -4.251  1.00 36.11           O
HETATM 2565  O   HOH W 212      -1.483  14.264   8.431  1.00 41.49           O
HETATM 2566  O   HOH W 213     -23.051  11.708 -21.920  1.00 36.32           O
HETATM 2567  O   HOH W 214       1.620  18.299   2.516  1.00 40.18           O
HETATM 2568  O   HOH W 215     -24.103  43.355 -12.751  1.00 37.49           O
HETATM 2569  O   HOH W 216     -26.738   0.134  -2.192  1.00 40.25           O
HETATM 2570  O   HOH W 217      11.242  21.332  -4.106  1.00 38.90           O
HETATM 2571  O   HOH W 218     -14.341  33.661  14.752  1.00 43.39           O
HETATM 2572  O   HOH W 219     -42.307  15.549   8.867  1.00 48.18           O
HETATM 2573  O   HOH W 220     -36.432  28.737  -0.897  1.00 39.64           O
HETATM 2574  O   HOH W 221     -25.417  28.494 -16.695  1.00 29.40           O
HETATM 2575  O   HOH W 222     -19.511  43.409   6.951  1.00 28.17           O
HETATM 2576  O   HOH W 223     -10.123  16.512 -24.639  1.00 31.70           O
HETATM 2577  O   HOH W 224     -25.245  45.166 -11.086  1.00 29.38           O
HETATM 2578  O   HOH W 225     -23.616  45.957   4.604  1.00 46.22           O
HETATM 2579  O   HOH W 226      -4.587  19.737 -15.634  1.00 37.60           O
HETATM 2580  O   HOH W 227     -24.137   7.274 -21.752  1.00 39.86           O
HETATM 2581  O   HOH W 228     -12.824  13.338  18.692  1.00 35.98           O
HETATM 2582  O   HOH W 229      -0.643  15.774  -0.049  1.00 38.98           O
HETATM 2583  O   HOH W 230     -19.204  39.608  13.339  1.00 44.88           O
HETATM 2584  O   HOH W 231     -40.196  18.266  13.870  1.00 39.93           O
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HETATM 2585  O   HOH W 232     -18.669  36.100  15.012  1.00 40.93           O
HETATM 2586  O   HOH W 233     -29.410  26.628  -9.566  1.00 40.47           O
HETATM 2587  O   HOH W 234     -30.809  34.598  -7.203  1.00 42.41           O
HETATM 2588  O   HOH W 235     -22.479  15.485  19.837  1.00 46.47           O
HETATM 2589  O   HOH W 236     -22.471   4.871  16.342  1.00 44.82           O
HETATM 2590  O   HOH W 237     -34.347  29.636  -4.151  1.00 41.68           O
HETATM 2591  O   HOH W 238     -36.466  16.190  -8.418  1.00 38.78           O
HETATM 2592  O   HOH W 239     -17.832  41.337  -3.943  1.00 40.59           O
HETATM 2593  O   HOH W 240      -5.599   3.373   1.035  1.00 37.39           O
HETATM 2594  O   HOH W 241     -31.315  43.021   6.641  1.00 44.12           O
HETATM 2595  O   HOH W 242      -0.730   9.262  -1.771  1.00 40.88           O
HETATM 2596  O   HOH W 243       4.759  11.224  -6.950  1.00 47.42           O
HETATM 2597  O   HOH W 244     -10.999   3.648 -16.952  1.00 46.46           O
HETATM 2598  O   HOH W 245      -5.652  21.836  12.464  1.00 42.81           O
HETATM 2599  O   HOH W 246     -14.550  10.917  18.018  1.00 41.09           O
HETATM 2600  O   HOH W 247      -4.947   4.565  -7.195  1.00 46.09           O
HETATM 2601  O   HOH W 248     -24.134  51.667  -5.997  1.00 46.36           O
HETATM 2602  O   HOH W 249     -37.327  13.552  -6.997  1.00 53.05           O
HETATM 2603  O   HOH W 250       0.506  22.694   3.267  1.00 47.90           O
HETATM 2604  O   HOH W 251     -13.591  16.310 -24.807  1.00 50.85           O
HETATM 2605  O   HOH W 252      -9.018   7.158 -17.757  1.00 46.53           O
HETATM 2606  O   HOH W 253     -26.754  28.420 -10.600  1.00 29.06           O
HETATM 2607  O   HOH W 254     -18.410  44.305   9.205  1.00 29.63           O
HETATM 2608  O   HOH W 255     -32.584  10.434 -11.160  1.00 41.22           O
HETATM 2609  O   HOH W 256     -16.091   1.690  16.162  1.00 36.96           O
HETATM 2610  O   HOH W 257      -4.505   9.349  11.016  1.00 39.86           O
HETATM 2611  O   HOH W 258     -40.947  18.159  -3.757  1.00 43.42           O
HETATM 2612  O   HOH W 259       0.000  24.141 -15.150  1.00 38.32           O
HETATM 2613  O   HOH W 260     -44.582  24.137   6.565  1.00 51.92           O
HETATM 2614  O   HOH W 261     -35.232  13.693  -8.515  1.00 55.39           O
HETATM 2615  O   HOH W 262     -29.872  45.235   6.694  1.00 17.67           O
HETATM 2616  O   HOH W 263     -27.113  45.109  -0.458  1.00 22.65           O
HETATM 2617  O   HOH W 264     -25.323  47.035   2.382  1.00 28.79           O
HETATM 2618  O   HOH W 265       0.000  26.981 -15.150  1.00 32.82           O
HETATM 2619  O   HOH W 266     -18.156  20.703 -27.017  1.00 35.61           O
HETATM 2620  O   HOH W 267     -37.722  10.433  -4.365  1.00 45.06           O
HETATM 2621  O   HOH W 268     -16.805  35.390  -9.635  1.00 40.40           O
HETATM 2622  O   HOH W 269     -16.918  18.529 -26.281  1.00 39.96           O
HETATM 2623  O   HOH W 270     -13.491  38.406  -6.271  1.00 39.29           O
HETATM 2624  O   HOH W 271      -8.148  20.081  11.966  1.00 44.03           O
HETATM 2625  O   HOH W 272      -6.821   1.644   3.126  1.00 40.41           O
HETATM 2626  O   HOH W 273     -18.313   5.740 -22.619  1.00 47.63           O
HETATM 2627  O   HOH W 274     -13.103   2.644 -18.422  1.00 45.18           O
HETATM 2628  O   HOH W 275      -0.862  26.991   8.197  1.00 49.93           O
HETATM 2629  O   HOH W 276     -12.480  35.715  13.919  1.00 48.53           O
HETATM 2630  O   HOH W 277      -6.665   2.991  -5.698  1.00 47.86           O
HETATM 2631  O   HOH W 278      -6.235  34.850 -10.896  1.00 49.10           O
HETATM 2632  O   HOH W 279     -15.224  26.534  14.107  1.00 34.50           O
HETATM 2633  O   HOH W 280     -26.785  17.717 -14.048  1.00 32.29           O
HETATM 2634  O   HOH W 281     -10.359   3.127 -14.054  1.00 35.76           O
HETATM 2635  O   HOH W 282      -9.964  34.823 -10.668  1.00 36.66           O
HETATM 2636  O   HOH W 283     -10.871  37.987   5.889  1.00 39.81           O
HETATM 2637  O   HOH W 284     -26.828  12.543 -16.696  1.00 39.23           O
HETATM 2638  O   HOH W 285     -28.134  16.073 -12.715  1.00 39.10           O
HETATM 2639  O   HOH W 286      -8.308  33.139  -8.609  1.00 41.47           O
HETATM 2640  O   HOH W 287       4.685  22.519 -12.295  1.00 43.15           O
HETATM 2641  O   HOH W 288      -6.455  17.658 -13.209  1.00 43.22           O
HETATM 2642  O   HOH W 289     -29.264   4.527  11.185  1.00 38.52           O
HETATM 2643  O   HOH W 290       1.948  31.540 -15.946  1.00 42.96           O
HETATM 2644  O   HOH W 291     -28.001  47.360  -9.030  1.00 42.25           O
HETATM 2645  O   HOH W 292     -21.578   9.488  15.696  1.00 48.22           O
HETATM 2646  O   HOH W 293     -36.209  19.343 -11.413  1.00 43.75           O
HETATM 2647  O   HOH W 294       0.319  29.212   4.405  1.00 42.45           O
HETATM 2648  O   HOH W 295     -43.593  18.340   3.119  1.00 44.30           O
HETATM 2649  O   HOH W 296      -8.690   9.796 -18.360  1.00 48.63           O
HETATM 2650  O   HOH W 297     -13.183  20.728 -23.025  1.00 42.14           O
HETATM 2651  O   HOH W 298     -28.554  16.113 -23.692  1.00 44.64           O
HETATM 2652  O   HOH W 299     -11.671  39.418  10.822  1.00 44.26           O
HETATM 2653  O   HOH W 300      -7.956   4.305 -13.456  1.00 46.03           O
HETATM 2654  O   HOH W 301     -39.821  23.326  16.353  1.00 43.78           O
HETATM 2655  O   HOH W 302     -13.526  31.064  14.928  1.00 53.12           O
HETATM 2656  O   HOH W 303     -17.878  33.786  16.873  1.00 50.15           O
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HETATM	2657	O	HOH W	304	-33.678	7.362	-8.182	1.00	49.39	O
HETATM	2658	O	HOH W	305	-11.597	39.294	-8.859	1.00	53.94	O
HETATM	2659	O	HOH W	306	2.882	29.239	3.191	1.00	45.89	O
HETATM	2660	O	HOH W	307	-38.649	20.156	-7.082	1.00	49.36	O
HETATM	2661	O	HOH W	308	-40.591	26.658	0.275	1.00	43.29	O
HETATM	2662	O	HOH W	309	-6.537	4.311	13.825	1.00	47.40	O
HETATM	2663	O	HOH W	310	-5.558	35.013	-13.517	1.00	48.80	O
HETATM	2664	O	HOH W	311	-28.826	11.425	-15.322	1.00	49.38	O
HETATM	2665	O	HOH W	312	-38.320	28.225	17.606	1.00	55.51	O
HETATM	2666	O	HOH W	313	-23.593	4.828	13.752	1.00	27.36	O
HETATM	2667	O	HOH W	314	-23.921	26.545	-16.243	1.00	34.27	O
HETATM	2668	O	HOH W	315	-22.322	11.653	14.462	1.00	34.83	O
HETATM	2669	O	HOH W	316	-12.651	34.045	-11.232	1.00	31.40	O
HETATM	2670	O	HOH W	317	-11.298	29.991	11.215	1.00	37.94	O
HETATM	2671	O	HOH W	318	-22.524	14.427	-23.824	1.00	34.38	O
HETATM	2672	O	HOH W	319	-17.894	26.130	16.911	1.00	40.42	O
HETATM	2673	O	HOH W	320	-30.095	30.303	9.084	1.00	43.47	O
HETATM	2674	O	HOH W	321	-13.730	28.546	14.642	1.00	45.76	O
HETATM	2675	O	HOH W	322	0.192	20.485	4.996	1.00	42.15	O
HETATM	2676	O	HOH W	323	8.773	19.721	-2.795	1.00	41.00	O
HETATM	2677	O	HOH W	324	-24.325	35.749	-12.402	1.00	41.84	O
HETATM	2678	O	HOH W	325	-24.805	13.589	-22.690	1.00	42.74	O
HETATM	2679	O	HOH W	326	-16.673	23.836	17.169	1.00	42.32	O
HETATM	2680	O	HOH W	327	-26.618	15.414	-14.762	1.00	52.87	O
HETATM	2681	O	HOH W	328	-17.876	41.703	11.298	1.00	40.21	O
HETATM	2682	O	HOH W	329	2.710	12.479	-3.493	1.00	41.71	O
HETATM	2683	O	HOH W	330	-40.522	22.831	11.667	1.00	40.68	O
HETATM	2684	O	HOH W	331	-5.318	8.894	-11.975	1.00	45.24	O
HETATM	2685	O	HOH W	332	6.465	34.844	-5.820	1.00	41.37	O
HETATM	2686	O	HOH W	333	-7.294	7.847	-13.196	1.00	46.21	O
HETATM	2687	O	HOH W	334	-27.575	-1.555	-9.482	1.00	43.31	O
HETATM	2688	O	HOH W	335	-16.302	44.157	6.300	1.00	50.65	O
HETATM	2689	O	HOH W	336	7.324	25.112	-0.042	1.00	46.30	O
HETATM	2690	O	HOH W	337	-25.386	14.745	-27.433	1.00	48.90	O
HETATM	2691	O	HOH W	338	-11.898	7.106	-19.877	1.00	48.25	O
HETATM	2692	O	HOH W	339	-6.543	5.813	-9.614	1.00	50.85	O
HETATM	2693	O	HOH W	340	-24.469	1.696	-2.733	1.00	49.67	O
HETATM	2694	O	HOH W	341	-25.761	37.027	-10.672	1.00	43.85	O
HETATM	2695	O	HOH W	342	-37.486	7.329	-1.731	1.00	48.83	O
HETATM	2696	O	HOH W	343	-17.291	4.085	16.803	1.00	48.72	O
HETATM	2697	O	HOH W	344	-14.036	26.435	-22.926	1.00	43.49	O
HETATM	2698	O	HOH W	345	0.692	30.664	2.086	1.00	53.06	O
HETATM	2699	O	HOH W	346	-41.805	14.047	-3.004	1.00	45.34	O
HETATM	2700	O	HOH W	347	-5.313	18.738	12.526	1.00	56.10	O
HETATM	2701	O	HOH W	348	-15.979	2.222	-18.286	1.00	52.97	O
HETATM	2702	O	HOH W	349	12.845	27.550	2.215	1.00	51.89	O
HETATM	2703	O	HOH W	350	-24.703	2.114	13.280	1.00	52.54	O
HETATM	2704	O	HOH W	351	-13.629	8.385	17.755	1.00	53.31	O
HETATM	2705	O	HOH W	352	0.600	10.756	1.065	1.00	52.20	O
HETATM	2706	O	HOH W	353	-6.584	3.294	-8.664	1.00	58.25	O
HETATM	2707	O	HOH W	354	-19.526	1.509	-15.069	1.00	58.64	O
HETATM	2708	O	HOH W	355	-37.744	8.976	-6.842	1.00	49.38	O
HETATM	2709	O	HOH W	356	11.571	31.022	2.199	1.00	49.80	O
HETATM	2710	O	HOH W	357	-5.947	36.986	-4.732	1.00	50.31	O
HETATM	2711	O	HOH W	358	-15.405	41.052	11.474	1.00	51.49	O
HETATM	2712	O	HOH W	359	-12.833	40.449	-4.727	1.00	51.48	O
HETATM	2713	O	HOH W	360	-5.438	1.935	-3.550	1.00	50.92	O
HETATM	2714	O	HOH W	361	-10.249	0.894	-12.528	1.00	59.44	O
HETATM	2715	O	HOH W	362	-31.963	40.849	5.308	1.00	56.17	O
HETATM	2716	O	HOH W	363	-20.396	19.502	-28.110	1.00	57.97	O
HETATM	2717	O	HOH W	364	-38.545	15.892	-6.873	1.00	53.86	O
HETATM	2718	O	HOH W	365	-8.651	36.740	4.818	1.00	56.42	O
HETATM	2719	O	HOH W	366	-16.900	45.179	-0.086	1.00	57.28	O
HETATM	2720	O	HOH W	367	-15.600	42.705	-0.411	1.00	53.55	O
HETATM	2721	O	HOH W	368	-1.122	22.193	-13.088	1.00	50.00	O
HETATM	2722	O	HOH W	369	-3.015	2.725	5.944	1.00	49.17	O
HETATM	2723	O	HOH W	370	-32.840	41.664	3.046	1.00	55.05	O
HETATM	2724	O	HOH W	371	-31.332	6.082	11.720	1.00	55.05	O
HETATM	2725	O	HOH W	372	-5.263	32.737	9.359	1.00	53.35	O
HETATM	2726	O	HOH W	373	-17.185	11.511	17.118	1.00	55.25	O
HETATM	2727	O	HOH W	374	-9.075	41.015	-9.468	1.00	55.28	O
HETATM	2728	O	HOH W	375	-2.683	7.946	9.076	1.00	55.07	O

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HETATM 2729  O   HOH W 376       7.720  16.995  -3.341  1.00 52.87           O
HETATM 2730  O   HOH W 377      -4.253  13.777 -12.953  1.00 51.97           O
END
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What is claimed is:

1. A composition comprising a form of monoacylglycerol lipase (MGLL), or a fragment, or structural motif, or derivative thereof, wherein one or more hydrophobic residues of the cap-domain is mutated to improve solubility.

2. A composition comprising the form of MGLL of Claim 1, wherein said one or more hydrophobic residues of the cap-domain is a Leucine.

3. A composition comprising the form of MGLL Claim 1, wherein said one or more hydrophobic residues of the cap-domain is selected from the group consisting of Leucine 162, Leucine 167, Leucine 169, Leucine 171, Leucine174, Leucine 176, and Leucine 184, wherein said amino acid numbering is based on the reference sequence for human MGLL Isoform 2 (SEQ ID NO: 1).

4. A composition comprising the form of MGLL of Claim 1, wherein said one or more hydrophobic residues of the cap-domain is mutated to Serine, Glutamine, or Arginine.

5. A composition comprising the form of MGLL as in any of the preceding claims, further comprising a Lysine mutated to an Alanine.

6. A composition comprising the form of MGLL of Claim 1, wherein said one or more hydrophobic residues is a Lysine residue selected from the group consisting of: Lysine 36, Lysine 160, Lysine 165, Lysine 188, Lysine 206, Lysine 226, Lysine 259 and Lysine 269, wherein said amino acid numbering is based on the reference sequence for human MGLL Isoform 2 (SEQ ID NO: 1).

7. A method of identifying an agent that binds to the form of MGLL of Claim1, comprising the steps of:

a. contacting the form of MGLL with the agent;

b. determining whether the agent binds to the form of MGLL;

c. thereby identifying an agent that binds to the form of MGLL.

8. The method of claim 7, wherein the form of MGLL has an amino acid sequence selected from the group consisting of: SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7.

9. The method of claim 7, wherein the binding is determined by measuring the thermal stability of the form of MGLL.

10. A method of identifying an agent that inhibits the activity of the form of MGLL of Claim1, comprising the steps of:

a. contacting the form of MGLL with the agent;

b. measuring the biological activity of the form of MGLL in the presence of the agent;

c. measuring the biological activity of the form of MGLL in the absence of the agent; and,

d. comparing the biological activity measured in step (b) with the biological activity measured in step (c); thereby identifying an agent that inhibits the biological activity of the form of MGLL, when the biological activity measured in step (b) is less than the biological activity measured in step (c).

11. The method of claim 10, wherein the form of MGLL has an amino acid sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7.

12. The method of claim 10, wherein the biological activity is measured with an enzyme assay.

Figure 1:

A. SEQ ID NO: 1

```
   1 mpeessprrt pqsipyqdlp hlvnadgqyl fcrywkptgt pkalifvshg agehsgryee
  61 larmlmglldl lvfahdhvgh gqsegermvv sdfhvfvrdv lqhvdsmqkd ypglpvfllg
 121 hsmggaiail taaerpghfa gmvlisplvl anpesattfk vlaakvlnlv lpnlslgpid
 181 ssvlsrnkte vdiynsdpli craglkvcfg iqllnavsrv eralpkltvp flllqgsadr
 241 lcdskgayll melaksqdkt lkiyegayhv lhkelpevtn svfheinmwv sqrtatagta
 301 spp
```

B. SEQ ID NO: 2

```
   1 METGPEDPSS mpeessprrt pqsipyqdlp hlvnadgqyl fcrywkptgt pkalifvshg
  61 agehsgryee larmlmglldl lvfahdhvgh gqsegermvv sdfhvfvrdv lqhvdsmqkd
 121 ypglpvfllg hsmggaiail taaerpghfa gmvlisplvl anpesattfk vlaakvlnlv
 181 lpnlslgpid ssvlsrnkte vdiynsdpli craglkvcfg iqllnavsrv eralpkltvp
 241 flllqgsadr lcdskgayll melaksqdkt lkiyegayhv lhkelpevtn svfheinmwv
 301 sqrtatagta spp
```

C.

```
Identities = 303/303 (100%), Positives = 303/303 (100%), Gaps = 0/303 (0%)

Iso 2  1    MPEESSPRRTPQSIPYQDLPHLVNADGQYLFCRYWKPTGTPKALIFVSHGAGEHSGRYEE  60
            MPEESSPRRTPQSIPYQDLPHLVNADGQYLFCRYWKPTGTPKALIFVSHGAGEHSGRYEE
Iso 1  11   MPEESSPRRTPQSIPYQDLPHLVNADGQYLFCRYWKPTGTPKALIFVSHGAGEHSGRYEE  70

Iso 2  61   LARMLMGLLDLLVFAHDHVGHGQSEGERMVVSDFHVFVRDVLQHVDSMQKDYPGLPVFLLG  120
            LARMLMGLLDLLVFAHDHVGHGQSEGERMVVSDFHVFVRDVLQHVDSMQKDYPGLPVFLLG
Iso 1  71   LARMLMGLLDLLVFAHDHVGHGQSEGERMVVSDFHVFVRDVLQHVDSMQKDYPGLPVFLLG  130

Iso 2  121  HSMGGAIAILTAAERPGHFAGMVLISPLVLANPESATTFKVLAAKVLNLVLPNLSLGPID  180
            HSMGGAIAILTAAERPGHFAGMVLISPLVLANPESATTFKVLAAKVLNLVLPNLSLGPID
Iso 1  131  HSMGGAIAILTAAERPGHFAGMVLISPLVLANPESATTFKVLAAKVLNLVLPNLSLGPID  190

Iso 2  181  SSVLSRNKTEVDIYNSDPLICRAGLKVCFGIQLLNAVSRVERALPKLTVPFLLLQGSADR  240
            SSVLSRNKTEVDIYNSDPLICRAGLKVCFGIQLLNAVSRVERALPKLTVPFLLLQGSADR
Iso 1  191  SSVLSRNKTEVDIYNSDPLICRAGLKVCFGIQLLNAVSRVERALPKLTVPFLLLQGSADR  250

Iso 2  241  LCDSKGAYLLMELAKSQDKTLKIYEGAYHVLHKELPEVTNSVFHEINMWVSQRTATAGTA  300
            LCDSKGAYLLMELAKSQDKTLKIYEGAYHVLHKELPEVTNSVFHEINMWVSQRTATAGTA
Iso 1  251  LCDSKGAYLLMELAKSQDKTLKIYEGAYHVLHKELPEVTNSVFHEINMWVSQRTATAGTA  310

Iso 2  301  SPP  303
            SPP
                          Iso 1  311  SPP  313
```

Figure 2:

A.

```
hMGLL iso2  MPEESSPRRTPQSIPYQDLPHLVNADGQYLFCRYWKPTGTPKALIFVSHGAGEHSGRYEE  (60)
RsbQ        ---------------AGHMTSILSRN-------HVKVKGSGKASIMFAPGFGQDQSVWNA  (26)
                           ***********        ::::    :::::     ******

hMGLL iso2  LARMLMGLDLLVFAHDHVGHGQSEGERMVVSDFHVFVRDVLQHVDSMQKDYPGLPVFLLG (120)
RsbQ        VAPAFE-EDHRIILFDYVGSGHSDLRAYDLNRYQTLDG-YAQDVLDVCEALDLKETVFVG  (84)
            ******    ::::          ******  ******** *******          :::::

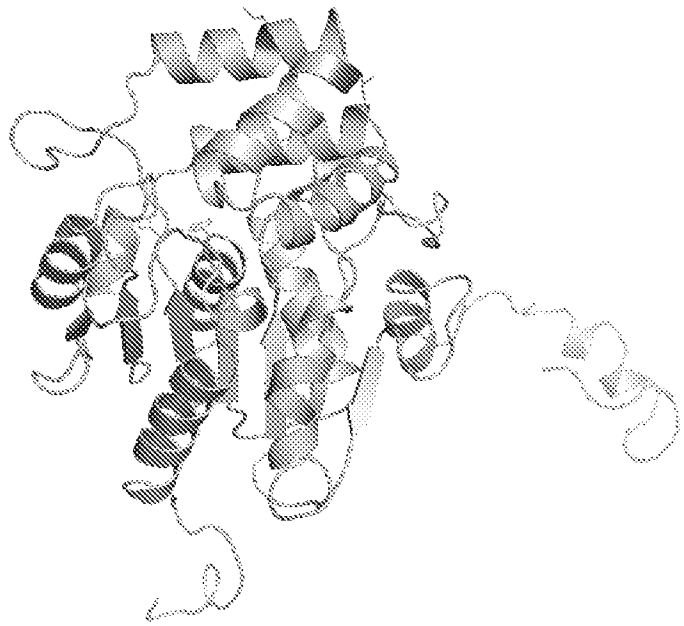
hMGLL iso2  HSMGGAIAILTAAERPGHFAGMVLISP---LVLANPESATTFKVLAAKVLNFVLPNLSL (176)
RsbQ        HSVGALIGMIASIRRPELFSHLVMVGPSPCYLNDPPEYYGGFEEEQLLGLLEMMEKNYI (143)
            :***************   :::::::        ::    :: ******************

hMGLL iso2  GPIDSSVLSRNK---TEVDIYNSDPLICRAGLKVCFGIQLLNAVSRVERALPKLTVPFLL (233)
RsbQ        GWATVFAATVLNQPDRPEIKEELESRFCSTDPVIARQFAKAAFFSDHREDISKVTVPSLI (203)
            **************   *************   **************  ********   :::

hMGLL iso2  LQGSADRL-CDSKGAYLLMELAKSQDKTLKIYEGAYHVLHKELPEVTNSVFHEINMWVSQ (292)
RsbQ        LQCADDIIAPATVGKYMHQHLPYS---SLKQMEARGHCPHMSHPDETIQLIGDYLKAHV- (269)
            ::::     ************      :::::::::  **********************

hMGLL iso2  RTATAGTASPP (303)
RsbQ        -----------
```

B.



C.

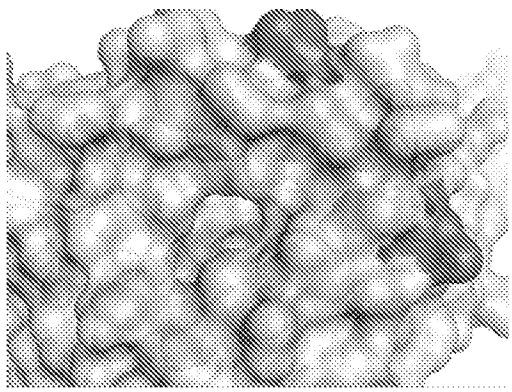


Figure 3:

A.

SEQ ID NO: 3, wt-MGLL (hMGLL 1-303)

TEV Cleavage Site

MVDhhhhhhE**nlyfqg**MPEESSPRRTPQSIPYQDLPHLVNADGQYLFCRYWKPTGTPKALIFVSHGAGEHSG
RYEELARMLMGLDLLVFAHDHVGHGQSEGERMVVSDFHVFVRDVLQHVDSMQKDYPGLPVFLLGHSMGGAIA
ILTAAERPGHFAGMVLISPLVLANPESATTFKVLAAKVLNLVLPNLSLGPIDSSVLSRNKTEVDIYNSDPLI
CRAGLKVCFGIQLLNAVSRVERALPKLTVPFLLLQGSADRLCDSKGAYLLMELAKSQDKTLKIYEGAYHVLH
KELPEVTNSVFHEINMWVSQRTATAGTASPP

B.

SEQ ID NO: 4, mut-MGLL (hMGLL 1-303 **L169S, L176S**)

TEV Cleavage Site

MVDhhhhhhE**nlyfqg**MPEESSPRRTPQSIPYQDLPHLVNADGQYLFCRYWKPTGTPKALIFVSHGAGEHSG
RYEELARMLMGLDLLVFAHDHVGHGQSEGERMVVSDFHVFVRDVLQHVDSMQKDYPGLPVFLLGHSMGGAIA
ILTAAERPGHFAGMVLISPLVLANPESATTFKVLAAKVLN**s**VLPNLS**s**GPIDSSVLSRNKTEVDIYNSDPLI
CRAGLKVCFGIQLLNAVSRVERALPKLTVPFLLLQGSADRLCDSKGAYLLMELAKSQDKTLKIYEGAYHVLH
KELPEVTNSVFHEINMWVSQRTATAGTASPP

C.

SEQ ID NO: 5, TEV Cleaved mut-MGLL (hMGLL 1-303 **L169S, L176S**)

gMPEESSPRRTPQSIPYQDLPHLVNADGQYLFCRYWKPTGTPKALIFVSHGAGEHSGRYEELARMLMGLDLL
VFAHDHVGHGQSEGERMVVSDFHVFVRDVLQHVDSMQKDYPGLPVFLLGHSMGGAIAILTAAERPGHFAGMV
LISPLVLANPESATTFKVLAAKVLN**s**VLPNLS**s**GPIDSSVLSRNKTEVDIYNSDPLICRAGLKVCFGIQLLN
AVSRVERALPKLTVPFLLLQGSADRLCDSKGAYLLMELAKSQDKTLKIYEGAYHVLHKELPEVTNSVFHEIN
MWVSQRTATAGTASPP

D.

SEQ ID NO: 6, mut-MGLL (hMGLL 1-303 **L169S, L176S, K36A**)

TEV Cleavage Site

MVDhhhhhhE**nlyfqg**MPEESSPRRTPQSIPYQDLPHLVNADGQYLFCRYW**a**PTGTPKALIFVSHGAGEHSG
RYEELARMLMGLDLLVFAHDHVGHGQSEGERMVVSDFHVFVRDVLQHVDSMQKDYPGLPVFLLGHSMGGAIA
ILTAAERPGHFAGMVLISPLVLANPESATTFKVLAAKVLN**s**VLPNLS**s**GPIDSSVLSRNKTEVDIYNSDPLI
CRAGLKVCFGIQLLNAVSRVERALPKLTVPFLLLQGSADRLCDSKGAYLLMELAKSQDKTLKIYEGAYHVLH
KELPEVTNSVFHEINMWVSQRTATAGTASPP

E.

SEQ ID NO: 7, TEV Cleaved mut-MGLL (hMGLL 1-303 **L169S, L176S, K36A**)

gMPEESSPRRTPQSIPYQDLPHLVNADGQYLFCRYW**a**PTGTPKALIFVSHGAGEHSGRYEELARMLMGLDLL
VFAHDHVGHGQSEGERMVVSDFHVFVRDVLQHVDSMQKDYPGLPVFLLGHSMGGAIAILTAAERPGHFAGMV
LISPLVLANPESATTFKVLAAKVLN**s**VLPNLS**s**GPIDSSVLSRNKTEVDIYNSDPLICRAGLKVCFGIQLLN
AVSRVERALPKLTVPFLLLQGSADRLCDSKGAYLLMELAKSQDKTLKIYEGAYHVLHKELPEVTNSVFHEIN
MWVSQRTATAGTASPP

Figure 4:

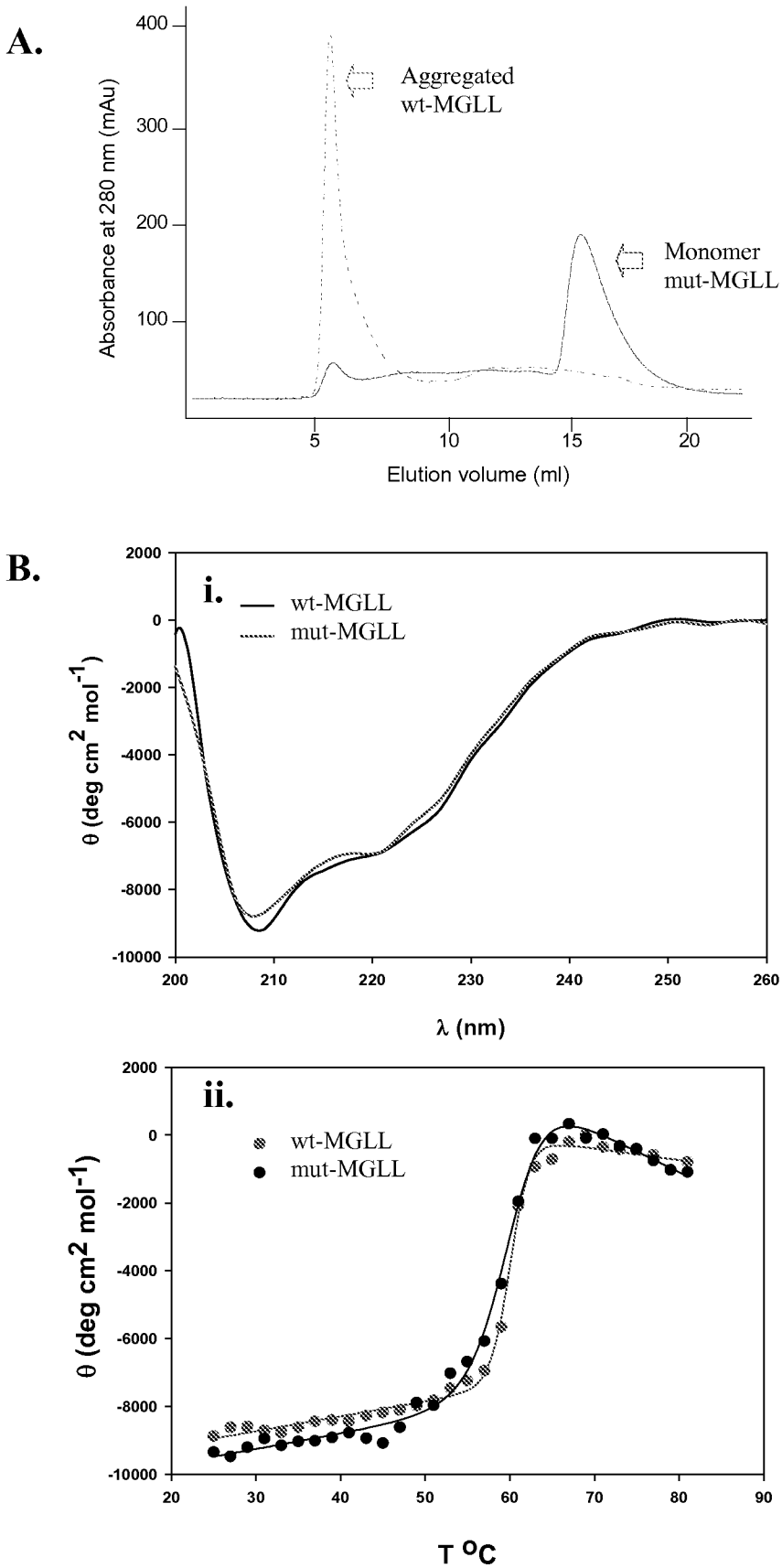

A.
Absorbance at 280 nm (mAu)
400
300
200
100
Aggregated
wt-MGLL
Monomer
mut-MGLL
5
10
15
20
Elution volume (ml)
B.
i.
wt-MGLL
mut-MGLL
θ (deg cm 2 mol-1)
2000
0
-2000
-4000
-6000
-8000
-10000
200
210
220
230
240
250
260
λ (nm)
ii.
wt-MGLL
mut-MGLL
θ (deg cm2 mol-1)
2000
0
-2000
-4000
-6000
-8000
-10000
20
30
40
50
60
70
80
90
T °C

Figure 5:

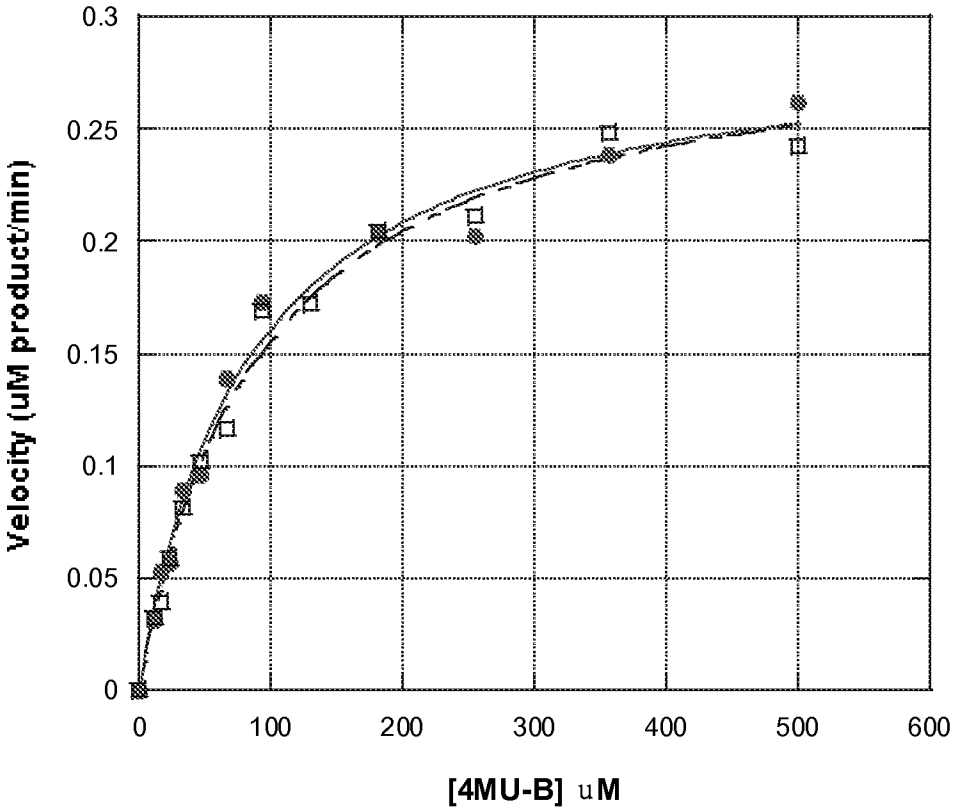

0.3
0.25
0.2
0.15
0.1
0.05
0
Velocity (uM product/min)
0
100
200
300
400
500
600
[4MU-B] uM

Figure 6:

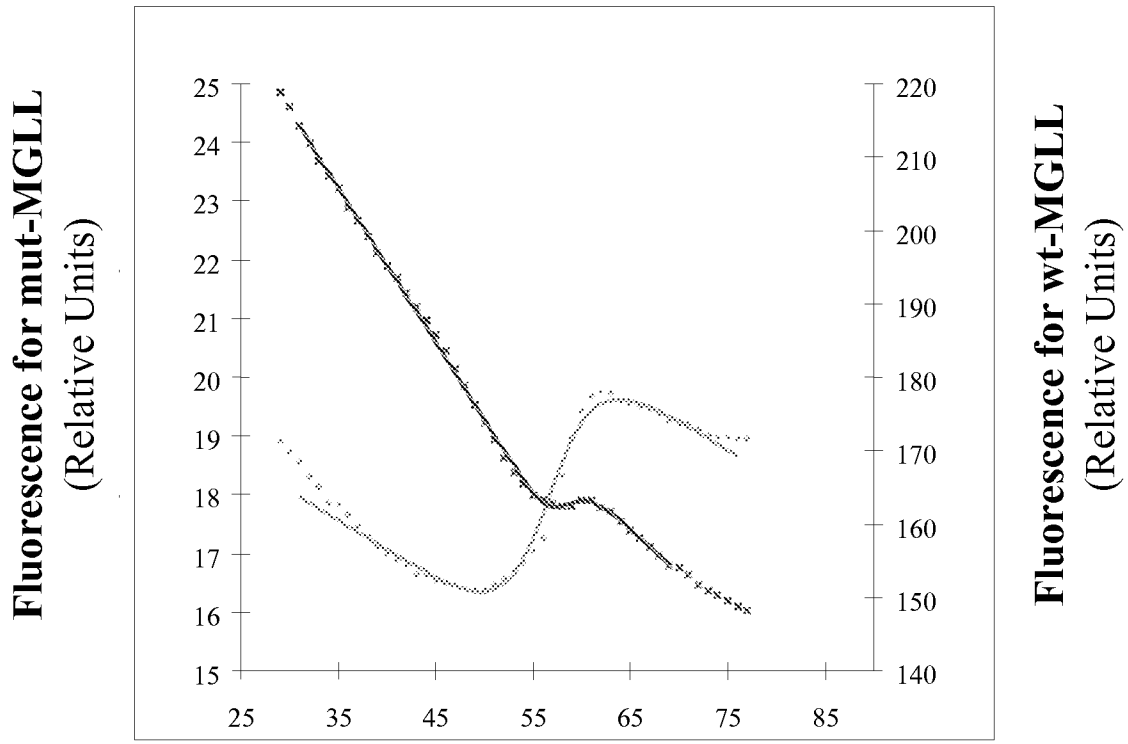
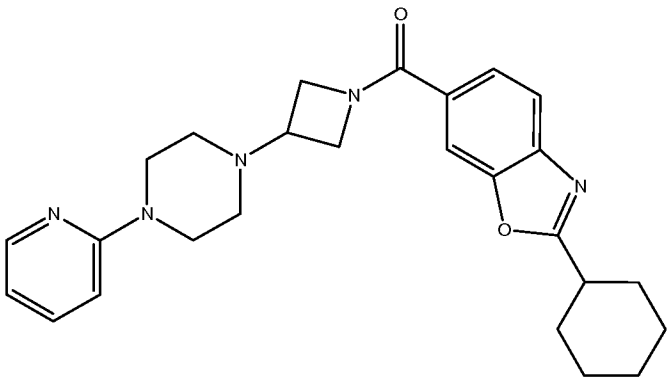

Fluorescence for mut-MGLL
(Relative Units)
25
24
23
22
21
20
19
18
17
16
15
220
210
200
190
180
170
160
150
140
25
35
45
55
65
75
85
Fluorescence for wt-MGLL
(Relative Units)

Figure 7:

A. Compound 1:



B. Compound 2:

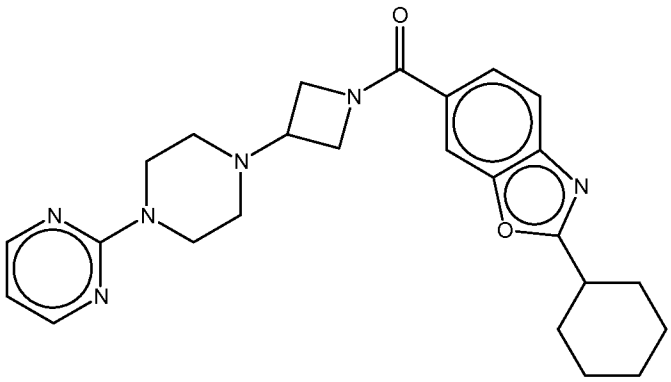


Figure 8:

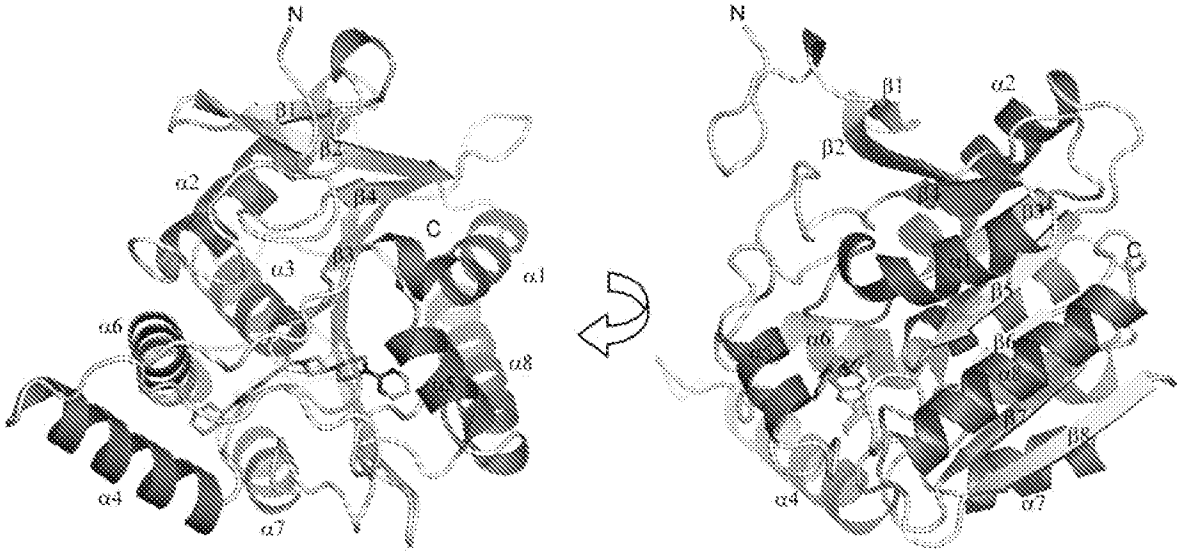


Figure 9:

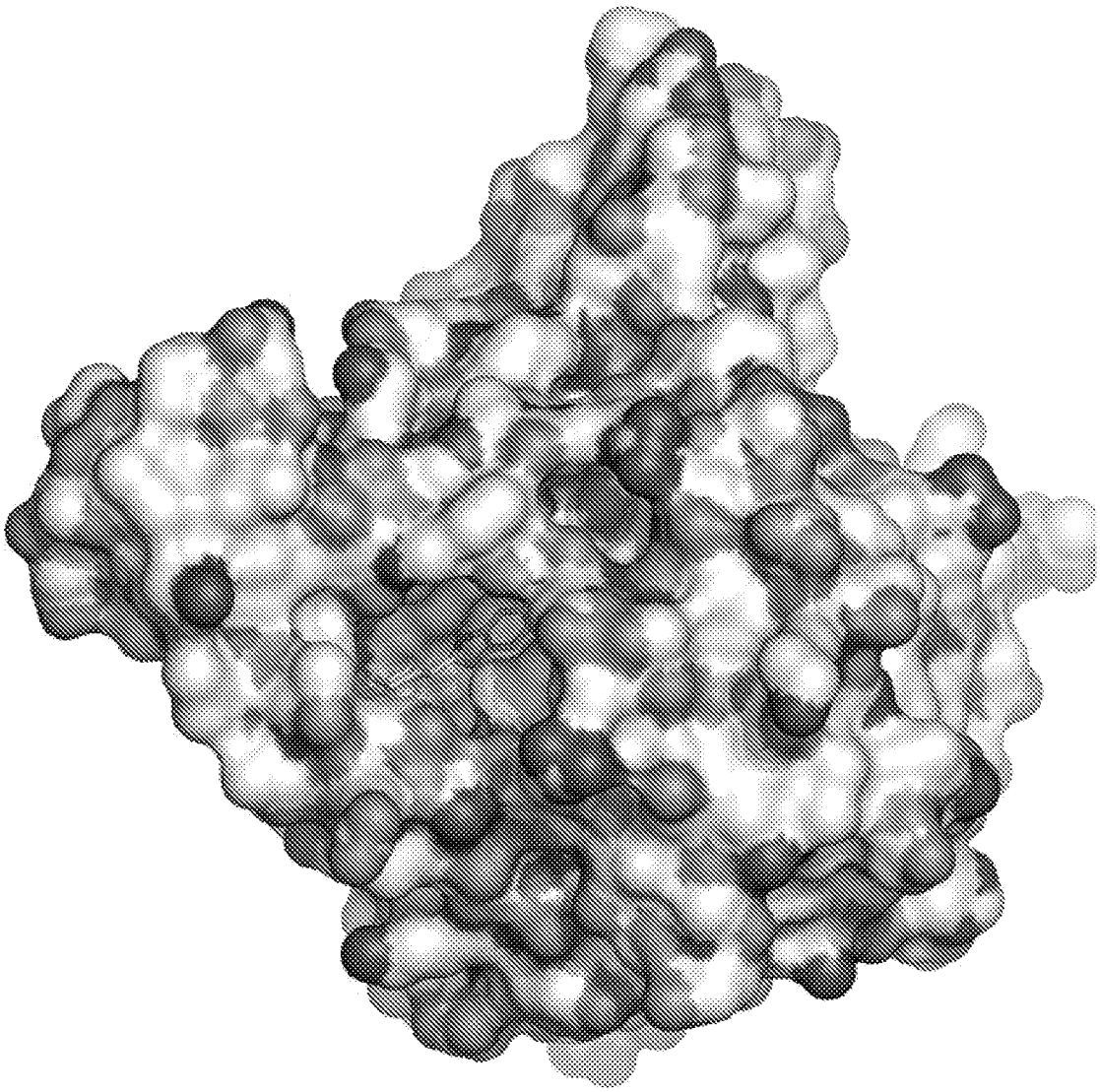


Figure 10:

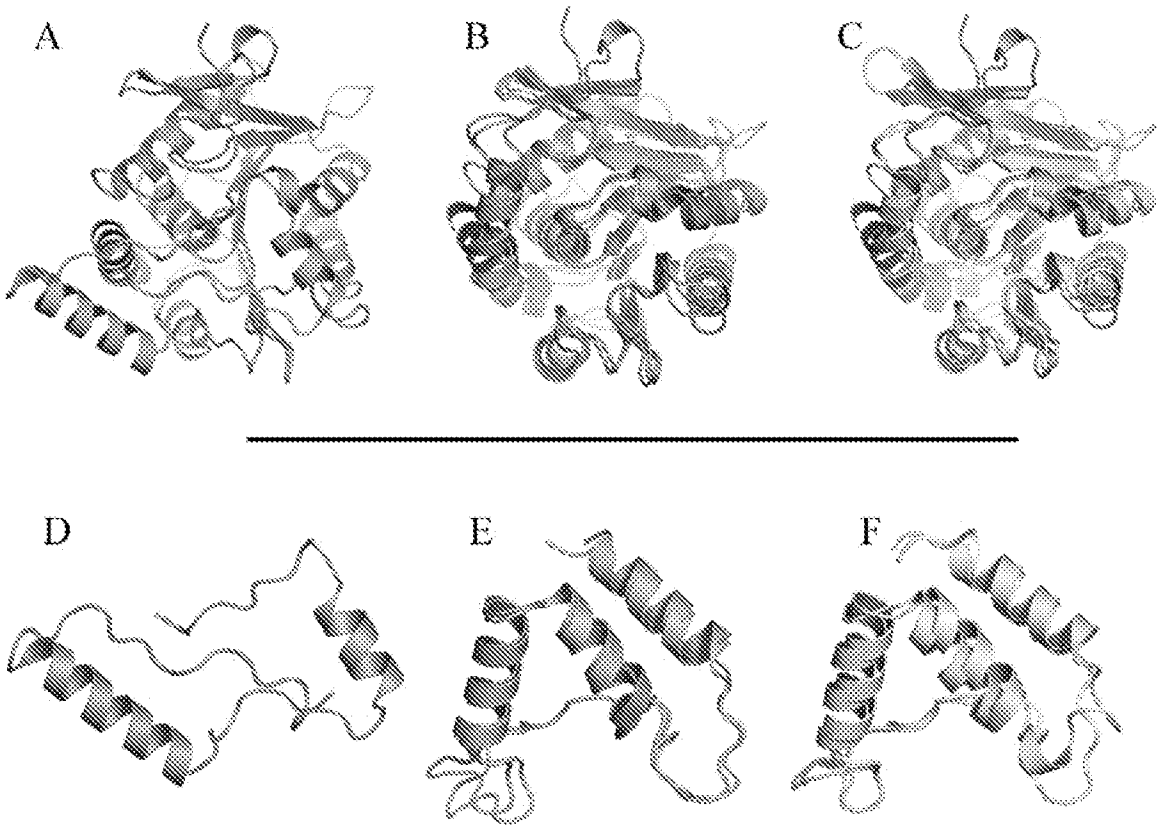
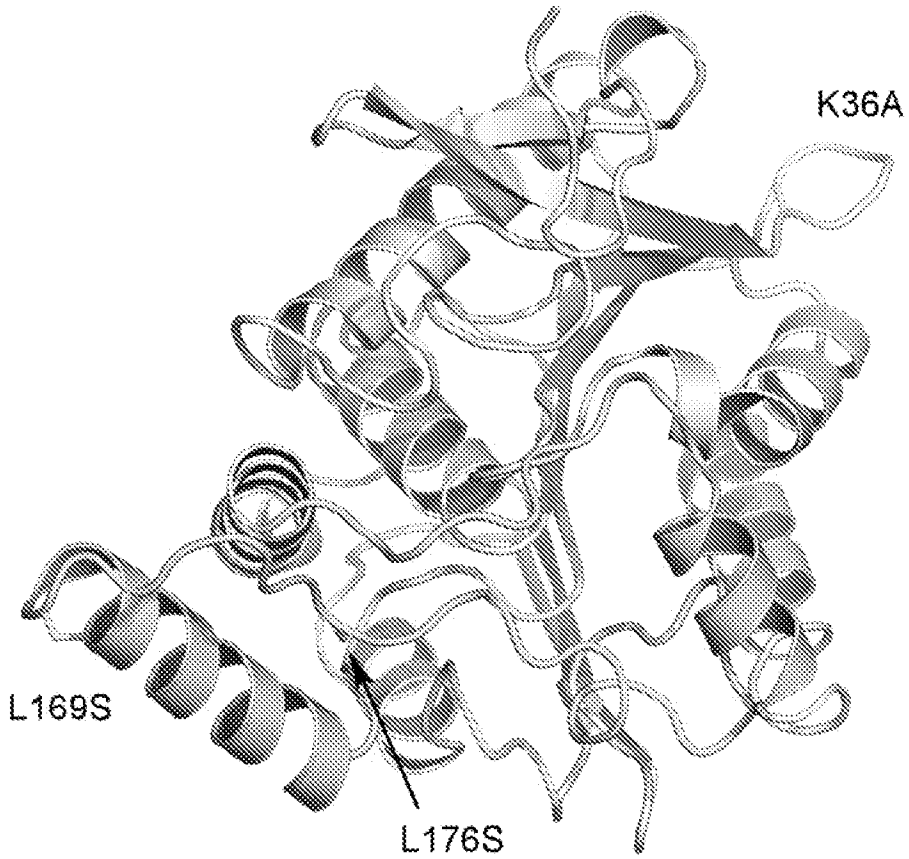


Figure 11:



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/041646

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N9/18 C12Q1/44

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N C12Q

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VANDEVOORDE SÉVERINE ET AL: "Focus on the three key enzymes hydrolysing endocannabinoids as new drug targets." CURRENT PHARMACEUTICAL DESIGN, vol. 11, no. 20, 2005, pages 2647-2668, XP002537175 ISSN: 1381-6128 page 2656, right-hand column, line 6 - page 2657, right-hand column, paragraph 1 page 2663, left-hand column, line 28 - line 33	

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[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2009	03/08/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Mandl, Birgit

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DINH T P ET AL: "Brain monoglyceride lipase participating in endocannabinoid inactivation." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 99, no. 16, 6 August 2002 (2002-08-06), pages 10819-10824, XP002537180 ISSN: 0027-8424 cited in the application the whole document figure 1	
A	SAARIO SUSANNA M ET AL: "Therapeutic potential of endocannabinoid-hydrolysing enzyme inhibitors." BASIC & CLINICAL PHARMACOLOGY & TOXICOLOGY, vol. 101, no. 5, November 2007 (2007-11), pages 287-293, XP002537178 ISSN: 1742-7835 page 288, right-hand column, paragraph 2 page 290, left-hand column, last paragraph page 290, right-hand column, last paragraph	
A	LONGENECKER K L ET AL: "Protein crystallization by rational mutagenesis of surface residues: Lys to Ala mutations promote crystallization of RhoGDI." ACTA CRYSTALLOGRAPHICA. SECTION D, BIOLOGICAL CRYSTALLOGRAPHY, vol. 57, no. Pt 5, May 2001 (2001-05), pages 679-688, XP002537176 ISSN: 0907-4449 cited in the application abstract page 687, left-hand column, last paragraph - right-hand column, paragraph 2	
A	PANTOLIANO M W ET AL: "HIGH-DENSITY MINIATURIZED THERMAL SHIFT ASSAYS AS A GENERAL STRATEGY FOR DRUG DISCOVERY" JOURNAL OF BIOMOLECULAR SCREENING, vol. 6, no. 6, 1 January 2001 (2001-01-01), pages 424-440, XP008066622 ISSN: 1087-0571 cited in the application the whole document	

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/041646

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	ZVONOK NIKOLAI ET AL: "Full mass spectrometric characterization of human monoacylglycerol lipase generated by large-scale expression and single-step purification." JOURNAL OF PROTEOME RESEARCH, vol. 7, no. 5, 2 May 2008 (2008-05-02), pages 2158-2164, XP002537177 ISSN: 1535-3893 abstract	
P,A	WANG YUREN ET AL: "A fluorescence-based assay for monoacylglycerol lipase compatible with inhibitor screening." ASSAY AND DRUG DEVELOPMENT TECHNOLOGIES, vol. 6, no. 3, June 2008 (2008-06), page: 387-393, XP002537179 ISSN: 1540-658X abstract page 392, right-hand column, paragraph 4	