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(54) Title: COMPOUNDS AND METHODS FOR TREATMENT OF HCV AND CONDITIONS ASSOCIATED WITH CD81 BINDING

(57) Abstract: The invention features compositions and methods that are useful for treating or preventing HCV infection and associated conditions. In addition, the invention provides methods for identifying compounds useful for treatment of HCV infection and associated conditions.

COMPOUNDS AND METHODS FOR TREATMENT OF HCV AND CONDITIONS ASSOCIATED WITH CD81 BINDING

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No. 60/970,951, filed September 8, 2007, the contents of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

Hepatitis C viral (HCV) infection is a common cause of chronic liver disease and a major public health problem.

Except for symptomatic control and replacement therapy, there is currently no effective treatment available for subjects having HCV infection; the current combination therapy with interferon α (IFN) and Ribavirin is only partially effective.

New compounds and methods for the treatment of HCV infection, and for generally for conditions associated with binding of proteins to CD81, would be beneficial.

SUMMARY OF THE INVENTION

The invention features compositions and methods that are useful for treating and/or preventing conditions associated with CD81 binding (including, without limitation, Hepatitis C viral (HCV) infection and conditions or symptoms related to HCV infection; multiple sclerosis; and malaria infection and conditions or symptoms related to malaria infection) and methods for identifying compounds useful for such treatment.

In one aspect, the invention provides a method of treating or preventing a condition associated with CD81 binding in a subject in need of such treatment. The method includes administering to the subject a compound capable of binding to a binding site in a CD81 protein, said binding site comprising one or more amino acids (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 amino acids) of CD81 selected from Cys157, Ser159, Ser160, Thr163, Ala164, Thr166, Thr167, Ile181, Asn184, Leu185 and

Asp189, under conditions such that the condition associated with CD81 binding is treated (or prevented). In certain embodiments, the condition associated with CD81 binding is selected from HCV infection, multiple sclerosis, and malaria. In certain embodiments, the condition associated with CD81 binding is HCV infection. In certain embodiments, compound is a compound selected from the compounds of Tables 1 and 2.

In another aspect, the invention provides a method of treating HCV infection in a subject in need of such treatment, the method comprising administering to the subject a compound capable of reducing the level of hepatitis C virus in the subject under conditions such that HCV infection is treated or ameliorated.

In a further aspect, the invention provides a method of treating a condition related to or associated with HCV infection in a subject in need of such treatment, the method comprising administering to the subject a compound capable of disrupting NS3 helicase or RNA-dependent RNA polymerase NS5B under conditions such that a condition related to or associated with HCV infection is treated or ameliorated.

In another aspect, the invention provides a method of inhibiting viral replication (e.g., HCV replication) in a cell, the method comprising contacting the cell with a compound capable of inhibiting HCV helicase or polymerase activity.

In yet another aspect, the invention provides a method of inhibiting HCV NS3 helicase in a cell, the method comprising contacting the cell with a compound capable of inhibiting HCV NS3 helicase activity under conditions such that HCV NS3 is partially or wholly inhibited.

In yet another aspect, the invention provides a method of inhibiting HCV NS5B RNA polymerase in a cell, the method comprising contacting the cell with a compound capable of inhibiting HCV NS5B RNA polymerase under conditions such that HCV NS5B RNA polymerase is partially or wholly inhibited.

In a still further aspect, the invention provides a method for treating a subject diagnosed as having HCV infection, the method comprising administering to the subject a pharmaceutically effective amount of a compound capable of inhibiting HCV helicase or polymerase activity in the subject.

In one aspect, the invention provides a method of treating HCV infection (or a condition associated with CD81) in a subject in need of such treatment, the method comprising administering to the subject a compound capable of blocking interaction between CD81 and a protein such as HCV E2 (e.g., viral entry inhibitors), thereby

treating HCV infection (or a condition associated with CD81), e.g., by disrupting or inhibiting interaction between CD81 and an endogenous or exogenous protein, e.g., thereby preventing entry of virus into a cell of the subject and/or preventing HCV infection in the subject and/or reducing the level of hepatitis C virus in the subject under conditions such that HCV infection (or the condition associated with CD81) is treated, ameliorated or prevented (e.g., entry of virus into a cell is inhibited or prevented and/or the level of hepatitis C virus in the subject is reduced).

In another aspect, the invention provides a pharmaceutical composition comprising a compound capable of inhibiting HCV helicase or polymerase activity, or a compound capable of blocking, inhibiting and/or reducing an interaction between CD81 and a protein (such as HCV E2), or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable vehicle.

In another aspect, the invention provides an oral dosage form comprising a compound capable of inhibiting HCV helicase or polymerase activity, or a compound capable of blocking, inhibiting and/or reducing an interaction between CD81 and a protein (such as HCV E2), or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable vehicle.

In a further aspect, the invention provides a kit for the treatment of HCV infection in a sample or subject, the kit comprising an effective amount of a compound capable of inhibiting HCV helicase or polymerase activity, and instructions for administering the compound capable of inhibiting HCV helicase or polymerase activity to a subject to treat HCV infection.

In a further aspect, the invention provides a kit for the treatment of a condition associated with CD81 binding (including, e.g., HCV) in a sample or subject, the kit comprising an effective amount of a compound capable of inhibiting an interaction between CD81 and a protein, and instructions for administering the compound capable of inhibiting an interaction between CD81 and a protein to a subject to treat a condition associated with CD81 binding.

In any of the above methods, pharmaceutical compositions, oral dosage forms, or kits of the invention, the compound can be a compound identified by computational screening, and/or can be a compound selected from the following: methyl 5-amino-1-(4-chloro-2-methyl-phenyl)triazole-4-carboxylate, 3-anilinophenol, 2-(4-oxochromen-3-yl)-1,3-thiazolidine-4-carboxylic acid, 2-benzothiophen-3-yl-7-methyl-8H-1,8-naphthyridin-4-one, 3-(5-oxo-1-phenyl-2-sulfanylidene-imidazolidin-4-yl)propanoic

acid, 3-(2-furylmethylideneamino)-2-methyl-quinazolin-4-one, 3-[(4S)-5-oxo-1-phenyl-2-sulfanylidene-imidazolidin-4-yl]propanamide, ethyl 4-[(2-methylphenyl)amino]-2-methylsulfanyl-pyrimidine-5-carboxylate, 2-Methoxy-5H-pyrido(3',2':5,6)(1,4)thiazino(2,3-b)quinoxaline, 3-phenyl-5-(2-methylpropyl)-2-sulfanylidene-imidazolidin-4-one, 3-chloro-4-methylphenylphosphinic acid, 4-(diethylamino)phenyl-phosphinic acid, Hydroxy(phenyl)methyl-phosphinic acid, 1-Amino-3-(methylthio)propyl-phosphinic acid, 2-amino-1-(4-methoxybenzyl)ethyl-phosphonic acid, 2,2,2-Trichloro-1-((hydroxy(oxido)amino)methyl)ethyl phenylcarbamate, 1-(3-Chlorophenoxy)-2,4-dinitrobenzene, Ethyl 3-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-5-methyl-2-oxotetrahydrofuran-3-carboxylate, 2-amino-7-methoxy-6,10-dihydro-5aH-pyrido[2,3-b]pyrimido[4,5-e]thiazin-4-ol, 2-(((1-carboxy-2-(1H-imidazol-4-yl)ethyl)amino)carbonyl)-benzoic acid, 1,1,3,4-tetrabromo-4-cyclohexylbutan-2-one, 2,3,4-Triphenyl-1,2,4-oxadiazolidin-5-one, N-methylbenzanilide, N-(triphenylmethyl) pyridin-2-amine, N-carbamoyl-2-(phenylmethyl)butanamide, 5-phenyl-[1,2,5]oxadiazolo[3,4-e]pyrimidin-7-amine, N-(2,6-dimethylphenyl)-1-(4-nitrophenyl)methanimine, NSC269216; or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the compound is methyl 5-amino-1-(4-chloro-2-methyl-phenyl)triazole-4-carboxylate, 3-anilinophenol, 2-(4-oxochromen-3-yl)-1,3-thiazolidine-4-carboxylic acid, 2-benzothiophen-3-yl-7-methyl-8H-1,8-naphthyridin-4-one, 3-(5-oxo-1-phenyl-2-sulfanylidene-imidazolidin-4-yl)propanoic acid, 3-(2-furylmethylideneamino)-2-methyl-quinazolin-4-one, 3-[(4S)-5-oxo-1-phenyl-2-sulfanylidene-imidazolidin-4-yl]propanamide, ethyl 4-[(2-methylphenyl)amino]-2-methylsulfanyl-pyrimidine-5-carboxylate, 2-Methoxy-5H-pyrido(3',2':5,6)(1,4)thiazino(2,3-b)quinoxaline, 3-phenyl-5-(2-methylpropyl)-2-sulfanylidene-imidazolidin-4-one, 3-chloro-4-methylphenylphosphinic acid, 4-(diethylamino)phenyl-phosphinic acid, Hydroxy(phenyl)methyl-phosphinic acid, 1-Amino-3-(methylthio)propyl-phosphinic acid, 2-amino-1-(4-methoxybenzyl)ethyl-phosphonic acid, 2,2,2-Trichloro-1-((hydroxy(oxido)amino)methyl)ethyl phenylcarbamate, 1-(3-Chlorophenoxy)-2,4-dinitrobenzene, Ethyl 3-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-5-methyl-2-oxotetrahydrofuran-3-carboxylate, 2-amino-7-methoxy-6,10-dihydro-5aH-pyrido[2,3-b]pyrimido[4,5-e]thiazin-4-ol, 2-(((1-carboxy-2-(1H-imidazol-4-yl)ethyl)amino)carbonyl)-benzoic acid; or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the compound is 1,1,3,4-tetrabromo-4-

cyclohexylbutan-2-one, 2,3,4-Triphenyl-1,2,4-oxadiazolidin-5-one, N-methylbenzanilide, N-(triphenylmethyl) pyridin-2-amine, N-carbamoyl-2-(phenylmethyl)butanamide, 5-phenyl-[1,2,5]oxadiazolo[3,4-e]pyrimidin-7-amine, N-(2,6-dimethylphenyl)-1-(4-nitrophenyl)methanimine, or NSC269216; or a pharmaceutically acceptable salt or solvate thereof.

Also provided are methods, including computational screening methods, for identifying compounds which can bind to an HCV replication enzyme, and compounds which can inhibit replication of HCV enzymes (e.g., HCV polymerase, HCV helicase, HCV protease). Also provided are methods, including computational screening methods, for identifying compounds which can bind to, or inhibit the binding of a protein to, CD81.

In one aspect, the invention provides a computer for producing a three-dimensional representation of a) a molecule or molecular complex, wherein said molecule or molecular complex comprises a binding site in the HCV NS3 or HCV NS5B enzyme; or

b) a three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than about 2.0 (more preferably not more than 1.5) angstroms, wherein said computer comprises: (i) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of structure coordinates of amino acid residues in the HCV NS3 or HCV NS5B protein; (ii) a working memory for storing instructions for processing said machine-readable data; (iii) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and (iv) a display coupled to said central-processing unit for displaying said three-dimensional representation.

In one aspect, the invention provides a computer for producing a three-dimensional representation of a) a molecule or molecular complex, wherein said molecule or molecular complex comprises a binding site in the CD81 protein which binds to proteins (including HCV E2 protein) including at least one of amino acids Cys157, Ser159, Ser160, Thr163, Ala164, Thr166, Thr167, Ile181, Asn184, Leu185 and Asp189; or

b) a three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of amino acids Cys157, Ser159, Ser160, Thr163, Ala164, Thr166, Thr167, Ile181, Asn184, Leu185 and Asp189 of CD81 of not more than about 2.0 (more preferably not more than 1.5) angstroms, wherein said computer comprises: (i) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of structure coordinates of one or more amino acid residues selected from Cys157, Ser159, Ser160, Thr163, Ala164, Thr166, Thr167, Ile181, Asn184, Leu185 and Asp189 of the human CD81 protein; (ii) a working memory for storing instructions for processing said machine-readable data; (iii) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and (iv) a display coupled to said central-processing unit for displaying said three-dimensional representation.

In another aspect, the invention provides a method for evaluating the potential of a chemical entity to associate with a) a molecule or molecular complex comprising a binding pocket defined by structure coordinates of HCV NS3 or HCV NS5B protein, or b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 2.0 (more preferably 1.5) angstroms,

the method comprising the steps of: i) employing computational means to perform a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex; and ii) analyzing the results of the fitting operation to quantify the association between the chemical entity and the binding pocket.

In another aspect, the invention provides a method for evaluating the potential of a chemical entity to bind with a) a molecule or molecular complex comprising a binding pocket defined by structure coordinates of one or more of amino acid residues Cys157, Ser159, Ser160, Thr163, Ala164, Thr166, Thr167, Ile181, Asn184, Leu185 and Asp189 of the CD81 protein, or b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 2.0 (more preferably 1.5) angstroms, the method comprising the steps of:

i) employing computational means to perform a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex; and

ii) analyzing the results of the fitting operation to quantify the association between the chemical entity and the binding pocket.

In another aspect, the invention provides a method for preventing HCV infection (or a condition associated with binding of a protein to CD81) in a subject, the method comprising administering to the subject an effective amount of a compound capable of disrupting binding of a protein with CD81 protein, such that a condition associated with CD81 binding (including HCV) is prevented in the subject. In certain embodiments, the compound is a compound capable of binding to CD81 at or about a binding pocket defined by structure coordinates of one or more of amino acid residues Cys157, Ser159, Ser160, Thr163, Ala164, Thr166, Thr167, Ile181, Asn184, Leu185 and Asp189 of the CD81 protein. In certain embodiments, the compound is a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a method of treating or preventing liver damage in a subject suffering from HCV infection, the method comprising administering to the subject a compound capable of inhibiting HCV helicase (e.g., NS3) or HCV polymerase (e.g., NS5B) in the subject under conditions such that liver damage in the subject is treated, ameliorated or prevented.

In another aspect, wherein the method further comprises the step of identifying the subject as suffering from HCV infection-related liver damage prior to the step of administering to the subject the compound capable of inhibiting HCV helicase or HCV polymerase. In certain embodiments, the method further comprises the step of determining the efficacy of administration to the subject of the compound capable of inhibiting HCV helicase or HCV polymerase. In certain embodiments, the step of determining the efficacy of administration to the subject of the compound comprises testing liver function of the subject before and after administration of the compound, and comparing the liver function determined before administration of the compound and after administration of the compound.

In another aspect, the invention provides a method of preserving liver function in a subject suffering from HCV infection, the method comprising administering to the subject a compound capable of inhibiting HCV helicase or HCV polymerase under conditions such that liver function in the subject is preserved.

In another aspect, the invention provides a packaged pharmaceutical formulation for the treatment or prevention of liver damage in a subject suffering from HCV infection, the packaged pharmaceutical formulation comprising: an effective amount of the amount of a compound capable of inhibiting HCV helicase or HCV polymerase; and

instructions for administering the compound capable of inhibiting HCV helicase or HCV polymerase to a subject suffering from HCV infection for the treatment or prevention of liver damage in the subject.

In another aspect, the invention provides a packaged pharmaceutical formulation for preserving liver function in a subject suffering from HCV infection, the packaged pharmaceutical formulation comprising: an effective amount of the amount of a compound capable of inhibiting HCV helicase or HCV polymerase; and instructions for administering the compound capable inhibiting HCV helicase or HCV polymerase to a subject suffering from HCV infection for the preservation of liver function in the subject.

Other aspects and embodiments of the invention are described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a scheme illustrating the computational docking approach used to identify compounds according to the invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

By "reduces" or "increases" is meant a negative or positive alteration, respectively, of at least 10%, 25%, 50%, 75%, or 100%.

The term "treating" or "treated" refers to administering a compound described herein to a subject with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect a disease or condition, the symptoms of the disease or condition or the predisposition toward the disease or condition.

The term "condition associated with CD81 binding in a subject" refers to a disease or condition in which the symptoms or progress of the disease or condition is associated with or related to binding of a protein (including either an endogenous protein or an exogenous protein (e.g., viral protein or a malarial protein)) to CD81 in a

subject. For example, a condition associated with CD81 binding in a subject can include HCV infection, malaria infection (see, e.g., Dijstra et al., Neurobiology of Disease, 31:413-421 (2008) or multiple sclerosis (MS) (see, e.g., Silvie et al., Cellular Microbiology 8(7):1134-1146 (2006)).

"An effective amount" refers to an amount of a compound, which confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). An effective amount of a compound described herein may range from about 1 mg/Kg to about 5000 mg/Kg body weight. Effective doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

Compounds of the Invention

It has been found that certain compounds are capable of binding to a binding site in the CD81 protein, said binding site comprising one or more amino acids of CD81 selected from Cys157, Ser159, Ser160, Thr163, Ala164, Thr166, Thr167, Ile181, Asn184, Leu185 and Asp189 of CD81, and thereby modulating the activity of CD81 and/or the ability of proteins (including, e.g., HCV proteins involved in viral entry into host cells, or malarial proteins SPECT-1 and/or SPECT-2) to bind to CD81. In certain embodiments, a compound of the invention can prevent, inhibit, or disrupt (e.g., reduce by at least 10%, 25%, 50%, 75%, or 100%) the binding of an endogenous or exogenous protein to CD81 (e.g., in a host cell).

Without wishing to be bound by theory, it is believed that compounds capable of binding to the binding site of CD81 may have one or more of the following structural features: (i) an aromatic ring, (ii) an oxygen atom(s) that likely interact with elements at the base of the structural pocket of CD81. For example, the oxygen atoms in active compounds may be capable of interaction with non-carbon atoms in Cys157, Ser159, Thr166 and Asn184 residues at the base of the structural pocket. As a further example, the aromatic ring in the active compounds may be capable of interaction with carbon atoms in Thr163, Thr166 and Thr167, Ile181 and Leu185.

Thus, in certain embodiments, a compound of this invention includes at least one aromatic ring (such as a phenyl ring, or a heteroaromatic ring such as a pyridyl ring, a triazole ring, a furanyl ring, a pyrimidinyl ring or an imidazolyl ring) or a fused aromatic ring system such as quinazolinyl, pyrido[2,3-b]pyrimido[4,5-e]thiazinyl. In

certain embodiments, a compound of this invention includes at least one oxygen atom, e.g., an oxygen atom(s) capable of interaction with non-carbon atoms in Cys157, Ser159, Thr166 and Asn184. In certain embodiments, the compound includes a carboxylic, phosphonic, or phosphinic acid or ester group.

It has further been found that certain compounds are capable of modulating (e.g., inhibiting) proteins that participate in the HCV viral replication cascade. Such compounds are sometimes referred to herein as "HCV polymerase", "HCV helicase" or "HCV inhibitor" compounds. In certain embodiments, a compound of the invention can bind to enzymes that are relevant in HCV replication, and thereby interfere with proliferation or replication of HCV.

In certain embodiments, a compound of the invention can prevent, inhibit, or disrupt (e.g., reduce by at least 10%, 25%, 50%, 75%, or 100%) the activity of HCV helicase or HCV polymerase.

In certain embodiments, a compound of the invention is a non-polymeric (e.g., small molecule) compound having a molecular weight less than about 1000 daltons, less than 800, less than 600, less than 500, less than 400, or less than about 300 daltons. In certain embodiments, an active compound can increase the amount (e.g., from or in a cell) of a stably-folded and/or physiologically active mutant protein by at least 10%, 15%, 20%, 25%, 50%, 75%, or 100% compared to an untreated control cell or protein.

Examples of compounds of the invention include the compounds of Table 1, Table 2 and Table 3, and pharmaceutically acceptable salts and solvates thereof.

As used herein, the term "pharmaceutically acceptable salt," is a salt formed from an acid and a basic group of one of the compounds of the invention (e.g., of Tables 1-3). Illustrative salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts.

The term "pharmaceutically acceptable salt" also refers to a salt prepared from a compound of the invention (e.g., of Tables 1-3) having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable

inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl, N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)- amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N, N,-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)-amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like. The term "pharmaceutically acceptable salt" also refers to a salt prepared from a compound disclosed herein, e.g., a compound of Tables 1-3, having a basic functional group, such as an amino functional group, and a pharmaceutically acceptable inorganic or organic acid. Suitable acids include, but are not limited to, hydrogen sulfate, citric acid, acetic acid, oxalic acid, hydrochloric acid, hydrogen bromide, hydrogen iodide, nitric acid, phosphoric acid, isonicotinic acid, lactic acid, salicylic acid, tartaric acid, ascorbic acid, succinic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucaronic acid, saccharic acid, formic acid, benzoic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, and *p*-toluenesulfonic acid.

Methods of the Invention

In certain aspects, the present invention features methods, compounds, and compositions useful for treating or preventing a condition associated with CD81 binding in a subject in need of such treatment.

In these aspects, the invention is generally based on the discovery that certain compounds can be used to inhibit the binding of proteins (such as HCV protease, or malarial proteins SPECT-1 and/or SPECT-2) to CD81. Without wishing to be bound by any particular theory, these compounds are believed to prevent entry of infectious particles into cells (in the case of HCV and malaria) or modulating cellular infiltration or immune response (in the case of multiple sclerosis (MS)).

In certain aspects, the method includes administering to the subject a compound capable of binding to a binding site in the CD81 protein, said binding site comprising one or more amino acids of CD81 selected from Cys157, Ser159, Ser160,

Thr163, Ala164, Thr166, Thr167, Ile181, Asn184, Leu185 and Asp189 of CD81, under conditions such that a condition associated with CD81 binding is treated. In certain embodiments, the condition associated with CD81 binding is selected from HCV infection, multiple sclerosis, and malaria. In certain embodiments, the condition associated with CD81 binding is HCV infection. In certain embodiments, the compound is a compound selected from the compounds of Tables 1 and 2.

The invention also features compositions and methods that are useful for inhibiting HCV helicase or HCV polymerase proteins *in vitro* or *in vivo* and for treatment of conditions associated with HCV infection.

This aspect of the invention is generally based on the discovery that certain compounds can be used to inhibit HCV helicase or HCV polymerase proteins in a cell, or inhibit the binding of HCV E2 to CD81. Without wishing to be bound by any particular theory, these compounds are believed to prevent viral replication (in the case of HCV helicase or HCV polymerase inhibitors) or prevent entry of HCV into cells (in the case of compounds capable of disrupting binding of, or interaction between, HCV E2 to CD81).

In one aspect, the invention provides a method of treating HCV infection, or a condition related HCV infection, in a subject in need of such treatment, the method comprising administering to the subject a compound capable of inhibiting HCV helicase or HCV polymerase in a subject under conditions such that the HCV infection, or a condition related to HCV infection, is treated or ameliorated.

Conditions related to HCV infection include conditions related to the presence and/or proliferation of HCV levels in a subject, and include, for example, liver damage, and liver diseases such as chronic hepatitis, cirrhosis, and liver cancer (e.g., hepatocellular carcinoma).

In a still further aspect, the invention provides a method for treating a subject diagnosed as having HCV infection (e.g., by diagnosis, identification of marker, etc.), the method comprising administering to the subject a pharmaceutically effective amount of a compound capable of inhibiting HCV helicase or HCV polymerase activity in the subject.

In another aspect, the invention provides a method for preventing HCV infection in a subject, the method comprising administering to the subject an effective amount of a compound capable of disrupting binding of HCV E2 protein with CD81 protein, such that HCV infection is prevented in the subject. In effect, administration

of a compound capable of disrupting binding of HCV E2 protein with CD81 protein prevents entry of HCV into cells, preventing (in whole or in part) the establishment of HCV infection. In this aspect, the compound can be administered until the HCV viral particles are cleared from subject's body, e.g., by the immune system. The administration of a compound in this way is analogous to "passive" vaccination in that infection is inhibited or prevented by administration of a compound which prevents establishment of infection (e.g., by inhibiting viral entry into a cell) but does not itself promote an immune response to the virus. In certain embodiments, the compound is a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a method for preventing malaria infection in a subject, the method comprising administering to the subject an effective amount of a compound capable of disrupting binding of a malarial protein (such as SPECT-1 and/or SPECT-2)with CD81 protein, such that HCV infection is prevented in the subject. In effect, administration of a compound capable of disrupting binding of HCV E2 protein with CD81 protein prevents entry of HCV into cells, preventing (in whole or in part) the establishment of HCV infection. In this aspect, the compound can be administered until the HCV viral particles are cleared from subject's body, e.g., by the immune system. The administration of a compound in this way is analogous to "passive" vaccination in that infection is inhibited or prevented by administration of a compound which prevents establishment of infection (e.g., by inhibiting viral entry into a cell) but does not itself promote an immune response to the virus. In certain embodiments, the compound is a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt thereof.

The compounds delineated herein can be used alone or in combination with one or more additional compounds to treat or prevent conditions associated with HCV infection, for example, cirrhosis or liver damage.

Pharmaceutical Compositions

The present invention features pharmaceutical preparations comprising compounds together with pharmaceutically acceptable carriers, where the compounds provide for the treatment, prevention or amelioration of HCV infection. Such preparations have both therapeutic and prophylactic applications. In one embodiment, a pharmaceutical composition includes compound capable of inhibiting HCV helicase

or HCV polymerase (e.g., a compound of Table 3) or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, a pharmaceutical composition includes compound capable of inhibiting an interaction between CD81 and a protein (such as HCV E2 protein) (e.g., a compound of Table 1 or Table 2) or a pharmaceutically acceptable salt or solvate thereof. Compounds of the invention may be administered as part of a pharmaceutical composition.

The compositions should be sterile and contain a therapeutically effective amount of the active compound in a unit of weight or volume suitable for administration to a subject. The compositions and combinations of the invention can be part of a pharmaceutical pack, where each of the compounds is present in individual dosage amounts.

The phrase "pharmaceutically acceptable" refers to those compound of the inventions of the present invention, compositions containing such compounds, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

In another aspect, the invention provides a pharmaceutical composition comprising a compound capable of inhibiting HCV helicase or HCV polymerase, or a pharmaceutically acceptable salt or solvate thereof, in a pharmaceutically acceptable vehicle.

In another aspect, the invention provides an oral dosage form comprising a compound capable of inhibiting an interaction between CD81 and a protein (such as HCV E2 protein) , or a pharmaceutically acceptable salt or solvate thereof, in a pharmaceutically acceptable vehicle.

In another aspect, the invention provides an oral dosage form comprising a compound capable of inhibiting HCV helicase or HCV polymerase, or a pharmaceutically acceptable salt or solvate thereof, in a pharmaceutically acceptable vehicle.

Pharmaceutical compositions of the invention to be used for prophylactic or therapeutic administration should be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 μm membranes), by gamma irradiation, or any other suitable means known to those skilled in the art. Therapeutic

compound compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle. These compositions ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution.

The compounds may be combined, optionally, with a pharmaceutically acceptable excipient. The term "pharmaceutically-acceptable excipient" as used herein means one or more compatible solid or liquid filler, diluents or encapsulating substances that are suitable for administration into a human. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate administration. The components of the pharmaceutical compositions also are capable of being co-mingled with the molecules of the present invention, and with each other, in a manner such that there is no interaction that would substantially impair the desired pharmaceutical efficacy.

Compounds of the present invention can be contained in a pharmaceutically acceptable excipient. The excipient preferably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetate, lactate, tartrate, and other organic acids or their salts; tris- hydroxymethylaminomethane (TRIS), bicarbonate, carbonate, and other organic bases and their salts; antioxidants, such as ascorbic acid; low molecular weight (for example, less than about ten residues) polypeptides, e.g., polyarginine, polylysine, polyglutamate and polyaspartate; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers, such as polyvinylpyrrolidone (PVP), polypropylene glycols (PPGs), and polyethylene glycols (PEGs); amino acids, such as glycine, glutamic acid, aspartic acid, histidine, lysine, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, sucrose, dextrins or sulfated carbohydrate derivatives, such as heparin, chondroitin sulfate or dextran sulfate; polyvalent metal ions, such as divalent metal ions including calcium ions, magnesium ions and manganese ions; chelating agents, such as ethylenediamine tetraacetic acid (EDTA); sugar alcohols, such as mannitol or sorbitol; counterions, such as sodium or ammonium; and/or nonionic surfactants, such as polysorbates or poloxamers. Other additives may be included, such as stabilizers, anti-microbials, inert gases, fluid and

nutrient replenishers (i.e., Ringer's dextrose), electrolyte replenishers, and the like, which can be present in conventional amounts.

The compositions, as described above, can be administered in effective amounts. The effective amount will depend upon the mode of administration, the particular condition being treated and the desired outcome. It may also depend upon the stage of the condition, the age and physical condition of the subject, the nature of concurrent therapy, if any, and like factors well known to the medical practitioner. For therapeutic applications, it is that amount sufficient to achieve a medically desirable result.

Generally, doses of the compounds of the present invention would be from about 0.01 mg/kg per day to about 1000 mg/kg per day, e.g., from about 0.1 mg/kg per day to about 100 mg/kg per day. It is expected that doses ranging from about 1 to about 1000 mg/kg will be suitable. Lower doses may be used with certain forms of administration, such as intravenous administration. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Multiple doses per day are contemplated to achieve appropriate systemic levels of a composition of the present invention.

A variety of administration routes are available. The methods of the invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. In one embodiment, a composition of the invention is administered orally. Oral administration may provide certain advantages, e.g., for treatment or prevention of liver damage, oral administration can provide a high concentration of the drug to hepatic circulation and thus to the liver. Other modes of administration include rectal, topical, intraocular, buccal, intravaginal, intracisternal, intracerebroventricular, intratracheal, nasal, transdermal, within/on implants, or parenteral routes. The term "parenteral" includes subcutaneous, intrathecal, intravenous, intramuscular, intraperitoneal, or infusion. Compositions comprising a composition of the invention can be added to a physiological fluid, such as to the intravitreal humor. For CNS administration, a variety of techniques are available for promoting transfer of the therapeutic across the blood brain barrier including disruption by surgery or injection, drugs which transiently open adhesion contact between the CNS vasculature

endothelial cells, and compounds that facilitate translocation through such cells. Oral administration can be preferred for prophylactic treatment because of the convenience to the patient as well as the dosing schedule. Oral administration is also beneficial because of the first passage effect on the liver, which may reduce the systemic side effects.

Pharmaceutical compositions of the invention can optionally further contain one or more additional proteins as desired, including plasma proteins, proteases, and other biological material, so long as it does not cause adverse effects upon administration to a subject. Suitable proteins or biological material may be obtained from human or mammalian plasma by any of the purification methods known and available to those skilled in the art; from supernatants, extracts, or lysates of recombinant tissue culture, viruses, yeast, bacteria, or the like that contain a gene that expresses a human or mammalian plasma protein which has been introduced according to standard recombinant DNA techniques; or from the fluids (e.g., blood, milk, lymph, urine or the like) or transgenic animals that contain a gene that expresses a human plasma protein which has been introduced according to standard transgenic techniques.

Pharmaceutical compositions of the invention can comprise one or more pH buffering compounds to maintain the pH of the formulation at a predetermined level that reflects physiological pH, such as in the range of about 5.0 to about 8.0. The pH buffering compound used in the aqueous liquid formulation can be an amino acid or mixture of amino acids, such as histidine or a mixture of amino acids such as histidine and glycine. Alternatively, the pH buffering compound is preferably an agent which maintains the pH of the formulation at a predetermined level, such as in the range of about 5.0 to about 8.0, and which does not chelate calcium ions. Illustrative examples of such pH buffering compounds include, but are not limited to, imidazole and acetate ions. The pH buffering compound may be present in any amount suitable to maintain the pH of the formulation at a predetermined level.

Pharmaceutical compositions of the invention can also contain one or more osmotic modulating agents, i.e., a compound that modulates the osmotic properties (e.g., tonicity, osmolality and/or osmotic pressure) of the formulation to a level that is acceptable to the blood stream and blood cells of recipient individuals. The osmotic modulating agent can be an agent that does not chelate calcium ions. The osmotic modulating agent can be any compound known or available to those skilled in the art

that modulates the osmotic properties of the formulation. One skilled in the art may empirically determine the suitability of a given osmotic modulating agent for use in the inventive formulation. Illustrative examples of suitable types of osmotic modulating agents include, but are not limited to: salts, such as sodium chloride and sodium acetate; sugars, such as sucrose, dextrose, and mannitol; amino acids, such as glycine; and mixtures of one or more of these agents and/or types of agents. The osmotic modulating agent(s) may be present in any concentration sufficient to modulate the osmotic properties of the formulation.

Pharmaceutical compositions of the invention can also be a non-aqueous liquid formulation. Any suitable non-aqueous liquid may be employed, provided that it provides stability to the active agents (s) contained therein. Preferably, the non-aqueous liquid is a hydrophilic liquid. Illustrative examples of suitable non-aqueous liquids include: glycerol; dimethyl sulfoxide (DMSO); polydimethylsiloxane (PMS); ethylene glycols, such as ethylene glycol, diethylene glycol, triethylene glycol, polyethylene glycol ("PEG") 200, PEG 300, and PEG 400; and propylene glycols, such as dipropylene glycol, tripropylene glycol, polypropylene glycol ("PPG") 425, PPG 725, PPG 1000, PPG 2000, PPG 3000 and PPG 4000.

Pharmaceutical compositions of the invention can also be a mixed aqueous/non-aqueous liquid formulation. Any suitable non-aqueous liquid formulation, such as those described above, can be employed along with any aqueous liquid formulation, such as those described above, provided that the mixed aqueous/non-aqueous liquid formulation provides stability to the compound contained therein. Preferably, the non- aqueous liquid in such a formulation is a hydrophilic liquid. Illustrative examples of suitable non-aqueous liquids include: glycerol; DMSO; PMS; ethylene glycols, such as PEG 200, PEG 300, and PEG 400; and propylene glycols, such as PPG 425, PPG 725, PPG 1000, PPG 2000, PPG 3000 and PPG 4000.

Suitable stable formulations can permit storage of the active agents in a frozen or an unfrozen liquid state. Stable liquid formulations can be stored at a temperature of at least -70°C, but can also be stored at higher temperatures of at least 0°C, or between about 0.1°C and about 42°C, depending on the properties of the composition. It is generally known to the skilled artisan that proteins and polypeptides are sensitive

to changes in pH, temperature, and a multiplicity of other factors that may affect therapeutic efficacy.

In certain embodiments a desirable route of administration can be by pulmonary aerosol. Techniques for preparing aerosol delivery systems containing polypeptides are well known to those of skill in the art. Generally, such systems should utilize components that will not significantly impair the biological properties of the antibodies, such as the paratope binding capacity (see, for example, Sciarra and Cutie, "Aerosols," in Remington's Pharmaceutical Sciences, 18th edition, 1990, pp 1694-1712; incorporated by reference). Those of skill in the art can readily modify the various parameters and conditions for producing polypeptide aerosols without resorting to undue experimentation.

Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of compositions of the invention, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer base systems such as polylactides (U.S. Pat. No. 3,773,919; European Patent No. 58,481), poly(lactide-glycolide), copolyoxalates, polycaprolactones, polyesteramides, polyorthoesters, polyhydroxybutyric acids, such as poly-D-(-)-3-hydroxybutyric acid (European Patent No. 133, 988), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, K.R. et al., Biopolymers 22: 547-556), poly (2-hydroxyethyl methacrylate) or ethylene vinyl acetate (Langer, R. et al., J. Biomed. Mater. Res. 15:267-277; Langer, R. Chem. Tech. 12:98-105), and polyanhydrides.

Other examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Delivery systems also include non-polymer systems that are: lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono- di- and tri-glycerides; hydrogel release systems such as biologically-derived bioresorbable hydrogel (i.e., chitin hydrogels or chitosan hydrogels); sylastic systems; peptide based systems; wax coatings; compressed tablets using conventional binders and excipients; partially fused implants; and the like. Specific examples include, but are not limited to: (a) erosional systems in which the agent is contained in a form within a matrix such as those described in U.S. Patent Nos. 4,452,775, 4,667,014, 4,748,034 and 5,239,660 and (b) diffusional systems in which an active component

permeates at a controlled rate from a polymer such as described in U.S. Patent Nos. 3,832,253, and 3,854,480.

Another type of delivery system that can be used with the methods and compositions of the invention is a colloidal dispersion system. Colloidal dispersion systems include lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Liposomes are artificial membrane vessels, which are useful as a delivery vector *in vivo* or *in vitro*. Large unilamellar vessels (LUV), which range in size from 0.2 - 4.0 μm, can encapsulate large macromolecules within the aqueous interior and be delivered to cells in a biologically active form (Fraley, R., and Papahadjopoulos, D., Trends Biochem. Sci. 6: 77-80).

Liposomes can be targeted to a particular tissue by coupling the liposome to a specific ligand such as a monoclonal antibody, sugar, glycolipid, or protein. Liposomes are commercially available from Gibco BRL, for example, as LIPOFECTIN™ and LIPOFECTACE™, which are formed of cationic lipids such as N-[1-(2, 3 dioleyloxy)-propyl]-N, N, N-trimethylammonium chloride (DOTMA) and dimethyl dioctadecylammonium bromide (DDAB). Methods for making liposomes are well known in the art and have been described in many publications, for example, in DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. (USA) 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88, 046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Liposomes also have been reviewed by Gregoriadis, G., Trends Biotechnol., 3: 235-241).

Another type of vehicle is a biocompatible microparticle or implant that is suitable for implantation into the mammalian recipient. Exemplary bioerodible implants that are useful in accordance with this method are described in PCT International application no. PCT/US/03307 (Publication No. WO 95/24929, entitled "Polymeric Gene Delivery System"). PCT/US/03307 describes biocompatible, preferably biodegradable polymeric matrices for containing an exogenous gene under the control of an appropriate promoter. The polymeric matrices can be used to achieve sustained release of the exogenous gene or gene product in the subject.

The polymeric matrix preferably is in the form of a microparticle such as a microsphere (wherein an agent is dispersed throughout a solid polymeric matrix) or a microcapsule (wherein an agent is stored in the core of a polymeric shell). Microcapsules of the foregoing polymers containing drugs are described in, for

example, U.S. Patent 5,075,109. Other forms of the polymeric matrix for containing an agent include films, coatings, gels, implants, and stents. The size and composition of the polymeric matrix device is selected to result in favorable release kinetics in the tissue into which the matrix is introduced. The size of the polymeric matrix further is selected according to the method of delivery that is to be used. Preferably, when an aerosol route is used the polymeric matrix and composition are encompassed in a surfactant vehicle. The polymeric matrix composition can be selected to have both favorable degradation rates and also to be formed of a material, which is a bioadhesive, to further increase the effectiveness of transfer. The matrix composition also can be selected not to degrade, but rather to release by diffusion over an extended period of time. The delivery system can also be a biocompatible microsphere that is suitable for local, site-specific delivery. Such microspheres are disclosed in Chickering, D.E., et al., Biotechnol. Bioeng., 52: 96-101; Mathiowitz, E., et al., Nature 386: 410-414.

Both non-biodegradable and biodegradable polymeric matrices can be used to deliver the compositions of the invention to the subject. Such polymers may be natural or synthetic polymers. The polymer is selected based on the period of time over which release is desired, generally in the order of a few hours to a year or longer. Typically, release over a period ranging from between a few hours and three to twelve months is most desirable. The polymer optionally is in the form of a hydrogel that can absorb up to about 90% of its weight in water and further, optionally is cross-linked with multivalent ions or other polymers.

Exemplary synthetic polymers which can be used to form the biodegradable delivery system include: polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, poly-vinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes and co-polymers thereof, alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, polymers of acrylic and methacrylic esters, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxy-propyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl cellulose, cellulose triacetate, cellulose sulphate sodium salt, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate),

poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), polyethylene, polypropylene, poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl alcohols), polyvinyl acetate, poly vinyl chloride, polystyrene, polyvinylpyrrolidone, and polymers of lactic acid and glycolic acid, polyanhydrides, poly(ortho)esters, poly(butic acid), poly(valeric acid), and poly(lactide-cocaprolactone), and natural polymers such as alginate and other polysaccharides including dextran and cellulose, collagen, chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), albumin and other hydrophilic proteins, zein and other prolamines and hydrophobic proteins, copolymers and mixtures thereof. In general, these materials degrade either by enzymatic hydrolysis or exposure to water *in vivo,* by surface or bulk erosion.

Nanoparticles are a colloidal carrier system that has been shown to improve the efficacy of the encapsulated drug by prolonging the serum half-life. Polyalkylcyanoacrylates (PACAs) nanoparticles are a polymer colloidal drug delivery system that is in clinical development, as described by Stella et al., J. Pharm. Sci., 2000. 89: p. 1452-1464; Brigger et al., Int. J. Pharm., 2001. 214: p. 37-42; Calvo et al., Pharm. Res., 2001. 18: p. 1157-1166; and Li et al., Biol. Pharm. Bull., 2001. 24: p. 662-665. Biodegradable poly (hydroxyl acids), such as the copolymers of poly (lactic acid) (PLA) and poly (lactic-co-glycolide) (PLGA) are being extensively used in biomedical applications and have received FDA approval for certain clinical applications. In addition, PEG-PLGA nanoparticles have many desirable carrier features including (i) that the agent to be encapsulated comprises a reasonably high weight fraction (loading) of the total carrier system; (ii) that the amount of agent used in the first step of the encapsulation process is incorporated into the final carrier (entrapment efficiency) at a reasonably high level; (iii) that the carrier have the ability to be freeze-dried and reconstituted in solution without aggregation; (iv) that the carrier be biodegradable; (v) that the carrier system be of small size; and (vi) that the carrier enhance the particles persistence.

Nanoparticles are synthesized using virtually any biodegradable shell known in the art. In one embodiment, a polymer, such as poly (lactic-acid) (PLA) or poly (lactic-co-glycolic acid) (PLGA) is used. Such polymers are biocompatible and

biodegradable, and are subject to modifications that desirably increase the photochemical efficacy and circulation lifetime of the nanoparticle. In one embodiment, the polymer is modified with a terminal carboxylic acid group (COOH) that increases the negative charge of the particle and thus limits the interaction with negatively charge nucleic acid aptamers. Nanoparticles are also modified with polyethylene glycol (PEG), which also increases the half-life and stability of the particles in circulation. Alternatively, the COOH group is converted to an N-hydroxysuccinimide (NHS) ester for covalent conjugation to amine-modified aptamers.

Biocompatible polymers useful in the composition and methods of the invention include, but are not limited to, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes and copolymers thereof, alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, polymers of acrylic and methacrylic esters, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxy-propyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetage phthalate, carboxylethyl cellulose, cellulose triacetate, cellulose sulphate sodium salt, poly(methyl methacrylate), poly(ethylmethacrylate), poly(butylmethacrylate), poly(isobutylmethacrylate), poly(hexylmethacrylate), poly(isodecylmethacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), polyethylene, polypropylene poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl alcohols), poly(vinyl acetate, poly vinyl chloride polystyrene, polyvinylpyrrolidone, polyhyaluronic acids, casein, gelatin, glutin, polyanhydrides, polyacrylic acid, alginate, chitosan, poly(methyl methacrylates), poly(ethyl methacrylates), poly(butylmethacrylate), poly(isobutylmethacrylate), poly(hexylmethacrylate), poly(isodecl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) and combinations of any of these. In one embodiment, the nanoparticles of the invention include PEG-PLGA polymers.

Compositions of the invention may also be delivered topically. For topical delivery, the compositions are provided in any pharmaceutically acceptable excipient that is approved for topical delivery.

Those of skill in the art will recognize that the best treatment regimens for using compounds of the present invention to treat, prevent or ameliorate HCV infection can be straightforwardly determined. This is not a question of experimentation, but rather one of optimization, which is routinely conducted in the medical arts. *In vivo* studies in nude mice often provide a starting point from which to begin to optimize the dosage and delivery regimes. The frequency of injection will initially be once a week, as has been done in some mice studies. However, this frequency might be optimally adjusted from one day to every two weeks to monthly, depending upon the results obtained from the initial clinical trials and the needs of a particular patient.

Human dosage amounts can initially be determined by extrapolating from the amount of compound used in mice, as a skilled artisan recognizes it is routine in the art to modify the dosage for humans compared to animal models. In certain embodiments it is envisioned that the dosage may vary from between about 1 mg compound/Kg body weight to about 2000 mg compound/Kg body weight; or from about 5 mg/Kg body weight to about 1000 mg/Kg body weight or from about 10 mg/Kg body weight to about 5000 mg/Kg body weight; or from about 50 mg/Kg body weight to about 200 mg/Kg body weight; or from about 100 mg/Kg body weight to about 1000 mg/Kg body weight; or from about 150 mg/Kg body weight to about 500 mg/Kg body weight. In other embodiments this dose may be about 0.1, 1, 5, 10, 25, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, 1200, 1250, 1300, 1350, 1400, 1450, 1500, 1600, 1700, 1800, 1900, 2000, 2500, 3000, 3500, 4000, 4500, or 5000 mg/Kg body weight. In other embodiments, it is envisaged that doses may be in the range of about 5 mg compound/Kg body to about 20 mg compound/Kg body. Of course, this dosage amount may be adjusted upward or downward, as is routinely done in such treatment protocols, depending on the results of the initial clinical trials and the needs of a particular patient.

SCREENING METHODS AND SYSTEMS

In another aspect, the invention provides a machine readable storage medium which comprises the structural coordinates of an HCV enzyme or protein (e.g., HCV helicase, HCV polymerase, HCV E2 protein) or the structural coordinates of a CD81 binding site identified herein, (e.g., a binding site of CD81 which includes at least one (more preferably at least 2, 3, 4, 5 or 6) amino acid(s) selected from Ser160,Thr163, Ala164, Thr167, Ile181, Leu185 and Asp189 of CD81. Such storage medium encoded with these data are capable of displaying a three-dimensional graphical representation of a molecule or molecular complex which comprises such binding pockets on a computer screen or similar viewing device.

The invention also provides methods for designing, evaluating and identifying compounds which bind to the aforementioned binding pockets. Such compounds are potential inhibitors of HCV helicase or HCV polymerase activity or inhibitors of an interaction between CD81 and HCV E2.

According to another aspect, the invention provides a computer for producing a) a three-dimensional representation of a molecule or molecular complex, wherein said molecule or molecular complex comprises a binding site of CD81 which includes one or more amino acids (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 amino acids) of CD81 selected from Cys157, Ser159, Ser160, Thr163, Ala164, Thr166, Thr167, Ile181, Asn184, Leu185 and Asp189 more preferably 2, 3, 4 or more amino acids); or

b) a three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than about 2.0 (more preferably not more than 1.5) angstroms, wherein said computer comprises:

(i) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of structure coordinates of one or more amino acids (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 amino acids) of CD81 selected from Cys157, Ser159, Ser160, Thr163, Ala164, Thr166, Thr167, Ile181, Asn184, Leu185 and Asp189 (more preferably 2, 3, 4 or more amino acids);

(ii) a working memory for storing instructions for processing said machine-readable data;

(iii) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

(iv) a display coupled to said central-processing unit for displaying said three-dimensional representation.

According to another aspect, the invention provides a computer for producing a) a three-dimensional representation of a molecule or molecular complex, wherein said molecule or molecular complex comprises a binding site of CD81 which includes one or more amino acids (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 amino acids) of CD81 selected from Cys157, Ser159, Ser160, Thr163, Ala164, Thr166, Thr167, Ile181, Asn184, Leu185 and Asp189 (more preferably 2, 3, 4 or more amino acids); or

b) a three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than about 2.0 (more preferably not more than 1.5) angstroms, wherein said computer comprises:

(i) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of structure coordinates of a binding site of HCV polymerase NS5B;

(ii) a working memory for storing instructions for processing said machine-readable data;

(iii) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

(iv) a display coupled to said central-processing unit for displaying said three-dimensional representation.

Thus, the computer produces a three-dimensional graphical structure of a molecule or a molecular complex which comprises a binding site.

In another embodiment, the invention provides a computer for producing a three-dimensional representation of a molecule or molecular complex defined by structure coordinates of all of the HCV enzyme amino acids or of CD81, or a three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square

deviation from the backbone atoms of said amino acids of not more than 2.0 (more preferably not more than 1.5) angstroms

In exemplary embodiments, the computer or computer system can include components which are conventional in the art, e.g., as disclosed in U.S. Patent No. 5,978,740 and/or 6,183,121 (incorporated herein by reference). For example, a computer system can includes a computer comprising a central processing unit ("CPU"), a working memory (which may be, e.g., RAM (random-access memory) or "core" memory), a mass storage memory (such as one or more disk drives or CD-ROM drives), one or more cathode-ray tube (CRT) or liquid crystal display (LCD) display terminals, one or more keyboards, one or more input lines, and one or more output lines, all of which are interconnected by a conventional system bus.

Machine-readable data of this invention may be inputted to the computer via the use of a modem or modems connected by a data line. Alternatively or additionally, the input hardware may include CD-ROM drives, disk drives or flash memory. In conjunction with a display terminal, a keyboard may also be used as an input device.

Output hardware coupled to the computer by output lines may similarly be implemented by conventional devices. By way of example, output hardware may include a CRT or LCD display terminal for displaying a graphical representation of a binding pocket of this invention using a program such as QUANTA or PYMOL. Output hardware might also include a printer, or a disk drive to store system output for later use.

In operation, the CPU coordinates the use of the various input and output devices, coordinates data accesses from the mass storage and accesses to and from working memory, and determines the sequence of data processing steps. A number of programs may be used to process the machine-readable data of this invention, including commercially-available software.

A magnetic storage medium for storing machine-readable data according to the invention can be conventional. A magnetic data storage medium can be encoded with a machine-readable data that can be carried out by a system such as the computer system described above. The medium can be a conventional floppy diskette or hard disk, having a suitable substrate which may be conventional, and a suitable coating , which may also be conventional, on one or both sides, containing magnetic domains whose polarity or orientation can be altered magnetically. The medium may also have

an opening (not shown) for receiving the spindle of a disk drive or other data storage device.

The magnetic domains of the medium are polarized or oriented so as to encode in manner which may be conventional, machine readable data such as that described herein, for execution by a system such as the computer system described herein.

An optically-readable data storage medium also can be encoded with machine-readable data, or a set of instructions, which can be carried out by a computer system. The medium can be a conventional compact disk read only memory (CD-ROM) or a rewritable medium such as a magneto-optical disk which is optically readable and magneto-optically writable.

In the case of CD-ROM, as is well known, a disk coating is reflective and is impressed with a plurality of pits to encode the machine-readable data. The arrangement of pits is read by reflecting laser light off the surface of the coating. A protective coating, which preferably is substantially transparent, is provided on top of the reflective coating.

In the case of a magneto-optical disk, as is well known, a data-recording coating has no pits, but has a plurality of magnetic domains whose polarity or orientation can be changed magnetically when heated above a certain temperature, as by a laser. The orientation of the domains can be read by measuring the polarization of laser light reflected from the coating. The arrangement of the domains encodes the data as described above.

Structure data, when used in conjunction with a computer programmed with software to translate those coordinates into the 3-dimensional structure of a molecule or molecular complex comprising a binding pocket may be used for a variety of purposes, such as drug discovery.

For example, the structure encoded by the data may be computationally evaluated for its ability to associate with chemical entities. Chemical entities that associate with a binding site of an HCV protein may inhibit HCV helicase or HCV polymerase, and are potential drug candidates. Alternatively, the structure encoded by the data may be displayed in a graphical three-dimensional representation on a computer screen. This allows visual inspection of the structure, as well as visual inspection of the structure's association with chemical entities.

Thus, according to another embodiment, the invention relates to a method for evaluating the potential of a chemical entity to associate with a) a molecule or

molecular complex comprising a binding pocket defined by structure coordinates of one or more amino acids (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 amino acids) of CD81 selected from Cys157, Ser159, Ser160, Thr163, Ala164, Thr166, Thr167, Ile181, Asn184, Leu185 and Asp189 (more preferably 2, 3, 4 or more amino acids), as described herein, or b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 2.0 (more preferably 1.5) angstroms.

This method comprises the steps of:

i) employing computational means to perform a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex; and

ii) analyzing the results of the fitting operation to quantify the association between the chemical entity and the binding pocket. This embodiment relates to evaluating the potential of a chemical entity to associate with or bind to a binding site of CD81.

Thus, according to another embodiment, the invention relates to a method for evaluating the potential of a chemical entity to associate with a) a molecule or molecular complex comprising a binding pocket defined by structure coordinates of at least one (more preferably 2, 3, 5, 10, 20, or 30) amino acids of HCV NS5B, as described herein, or b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 2.0 (more preferably 1.5) angstroms.

This method comprises the steps of:

i) employing computational means to perform a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex; and

ii) analyzing the results of the fitting operation to quantify the association between the chemical entity and the binding pocket. This embodiment relates to evaluating the potential of a chemical entity to associate with or bind to a binding site of HCV protein.

The term "chemical entity", as used herein, refers to chemical compounds, complexes of at least two chemical compounds, and fragments of such compounds or complexes.

In certain embodiments, the method evaluates the potential of a chemical entity to associate with a molecule or molecular complex defined by structure coordinates of all of the amino acids of HCV NS5B, as described herein, or a homologue of said molecule or molecular complex having a root mean square deviation from the backbone atoms of said amino acids of not more than 2.0 (more preferably not more than 1.5) angstroms.

In certain embodiments, the method evaluates the potential of a chemical entity to associate with a molecule or molecular complex defined by structure coordinates of all of the amino acids of CD81, as described herein, or a homologue of said molecule or molecular complex having a root mean square deviation from the backbone atoms of said amino acids of not more than 2.0 (more preferably not more than 1.5) angstroms.

In a further embodiment, the structural coordinates one of the binding pockets described herein can be utilized in a method for identifying a potential agonist or antagonist of a molecule comprising an HCV protein binding site. This method comprises the steps of:

a) using the atomic coordinates of all or a portion of HCV NS5B or CD81;

b) employing the three-dimensional structure to design or select the potential agonist or antagonist. The method further includes the optional steps of c) synthesizing the agonist or antagonist; and d) contacting the agonist or antagonist with the molecule to determine the ability of the potential agonist or antagonist to interact with the molecule.

In another embodiment, the invention provides a method for identifying a potential agonist or antagonist of HCV enzyme, the method comprising the steps of:

a) using the atomic coordinates of all or a portion of HCV NS5B or CD81;

b) employing the three-dimensional structure to design or select the potential agonist or antagonist.

The present inventors' elucidation of heretofore unknown binding sites of HCV proteins (or binding of a protein, such as an HCV protein, such as HCV E2, to CD81), provides the necessary information for designing new chemical entities and compounds that may interact with HCV proteins, in whole or in part, and may therefore modulate (e.g., inhibit) the activity of HCV proteins, or modulate the binding of a protein, including an HCV protein, to CD81.

The design of compounds that bind to binding sites according to this invention generally involves consideration of several factors. First, the entity must be capable of physically and structurally associating with parts or all of the binding site. Non-covalent molecular interactions important in this association include hydrogen bonding, van der Waals interactions, hydrophobic interactions and electrostatic interactions. Second, the entity must be able to assume a conformation that allows it to associate with the binding site(s) directly. Although certain portions of the entity will not directly participate in these associations, those portions of the entity may still influence the overall conformation of the molecule. This, in turn, may have a significant impact on potency. Such conformational requirements include the overall three-dimensional structure and orientation of the chemical entity in relation to all or a portion of the binding pocket, or the spacing between functional groups of an entity comprising several chemical entities that directly interact with the binding pocket or homologues thereof.

The potential inhibitory or binding effect of a chemical entity on a protein binding site may be analyzed prior to its actual synthesis and testing by the use of computer modeling techniques. If the theoretical structure of the given entity suggests insufficient interaction and association between it and the target binding pocket, testing of the entity is obviated. However, if computer modeling indicates a strong interaction, the molecule may then be synthesized and tested for its ability to bind to a binding site. This may be achieved, e.g., by testing the ability of the molecule to inhibit HCV enzyme activity (e.g., replication activity, viral entry, etc.), e.g., using assays described herein or known in the art. In this manner, synthesis of inoperative compounds may be avoided.

A potential inhibitor of an HCV enzyme binding site may be computationally evaluated by means of a series of steps in which chemical entities or fragments are screened and selected for their ability to associate with the HCV enzyme binding site.

One skilled in the art may use one of several methods to screen chemical entities or fragments for their ability to associate with an a binding site. This process may begin by visual inspection of, for example, a binding site on the computer screen based on the an protein structure coordinates described herein, or other coordinates which define a similar shape generated from the machine-readable storage medium. Selected fragments or chemical entities may then be positioned in a variety of orientations, or docked, within that binding site as defined supra. Docking may be

accomplished using software such as Quanta and DOCK, followed by energy minimization and molecular dynamics with standard molecular mechanics force fields, such as CHARMM and AMBER.

Specialized computer programs (e.g., as known in the art and/or commercially available and/or as described herein) may also assist in the process of selecting fragments or chemical entities.

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

Instead of proceeding to build an inhibitor of a binding pocket in a step-wise fashion one fragment or chemical entity at a time as described above, inhibitory or other binding compounds may be designed as a whole or "de novo" using either an empty binding site or optionally including some portion(s) of a known inhibitor(s). There are many de novo ligand design methods known in the art, some of which are commercially available (e.g., LeapFrog, available from Tripos Associates, St. Louis, Mo.).

Other molecular modeling techniques may also be employed in accordance with this invention (see, e.g., N. C. Cohen et al., "Molecular Modeling Software and Methods for Medicinal Chemistry, J. Med. Chem., 33, pp. 883-894 (1990); see also, M. A. Navia and M. A. Murcko, "The Use of Structural Information in Drug Design", Current Opinions in Structural Biology, 2, pp. 202-210 (1992); L. M. Balbes et al., "A Perspective of Modern Methods in Computer-Aided Drug Design", in Reviews in Computational Chemistry, Vol. 5, K. B. Lipkowitz and D. B. Boyd, Eds., VCH, New York, pp. 337-380 (1994); see also, W. C. Guida, "Software For Structure-Based Drug Design", Curr. Opin. Struct. Biology,, 4, pp. 777-781 (1994)).

Once a compound has been designed or selected, the efficiency with which that entity may bind to a binding pocket may be tested and optimized by computational evaluation.

Specific computer software is available in the art to evaluate compound deformation energy and electrostatic interactions. Examples of programs designed for such uses include: AMBER; QUANTA/CHARMM (Accelrys, Inc., Madison, WI) and the like. These programs may be implemented, for instance, using a

commercially-available graphics workstation. Other hardware systems and software packages will be known to those skilled in the art.

Another technique involves the *in silico* screening of virtual libraries of compounds, e.g., as described herein (see, e.g., Examples 1 and 2). Many thousands of compounds can be rapidly screened and the best virtual compounds can be selected for further screening (e.g., by synthesis and *in vitro* testing). Small molecule databases can be screened for chemical entities or compounds that can bind, in whole or in part, to a protein or enzyme binding site. In this screening, the quality of fit of such entities to the binding site may be judged either by shape complementarity or by estimated interaction energy.

Screening Assays

As discussed herein, useful compounds inhibit HCV enzymes and their activity or the binding of proteins to CD81. Any number of methods are available for carrying out screening assays to identify such compounds. In one approach, a HCV enzyme protein is expressed in a cell (e.g., a cell *in vitro* or *in vivo)*; the cell is contacted with a candidate compound; and the effect of the compound on the inhibition of HCV enzyme and functional activity is assayed using any method known in the art or described herein. Useful compounds decrease the amount of HCV enzyme or polymerization by at least 10%, 15%, or 20%, or preferably by 25%, 50%, or 75%; or most preferably by at least 100%, 200%, 300% or even 400%.

Test Compounds and Extracts

In general, compounds capable of inhibiting HCV proliferation in a cell are identified from large libraries of either natural product or synthetic (or semi-synthetic) extracts or chemical libraries according to methods known in the art. Those skilled in the field of drug discovery and development will understand that the precise source of test extracts or compounds is not critical to the screening procedure(s) of the invention. Accordingly, large numbers of chemical extracts or compounds can be screened using the methods described herein. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic- or animal-based extracts, fermentation broths, and synthetic compounds, as well as modification of existing compounds. Numerous methods are also available for generating random or directed synthesis (e.g., semi-synthesis or total synthesis) of any number of

chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, and nucleic acid-based compounds. Synthetic compound libraries are commercially available from Brandon Associates (Merrimack, N.H.) and Aldrich Chemical (Milwaukee, Wis.). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant, and animal extracts are commercially available from a number of sources, including Biotics (Sussex, UK), Xenova (Slough, UK), Harbor Branch Oceangraphics Institute (Ft. Pierce, Fla.), and PharmaMar, U.S.A. (Cambridge, Mass.). In addition, natural and synthetically produced libraries are produced, if desired, according to methods known in the art, e.g., by standard extraction and fractionation methods. Furthermore, if desired, any library or compound is readily modified using standard chemical, physical, or biochemical methods.

Combination Therapies

Compositions of the invention useful for the treatment of HCV inhibition (or conditions related to protein binding to CD81) can optionally be combined with additional therapies. For example, interferons (such as interferon-alpha, and nucleoside antimetabolite antiviral compounds such as ribavirin can be used in combination with a compound according to this invention.

Kits

The invention provides kits for the treatment or prevention of HCV infection or conditions associated with binding to CD81, or symptoms thereof.

In one embodiment, the kit includes a pharmaceutical pack comprising an effective amount of a compound of the invention for prevention or treatment of HCV infection. Preferably, the compositions are present in unit dosage form. In some embodiments, the kit comprises a sterile container which contains a therapeutic or prophylactic composition; such containers can be boxes, ampules, bottles, vials, tubes, bags, pouches, blister-packs, or other suitable container forms known in the art. Such containers can be made of plastic, glass, laminated paper, metal foil, or other materials suitable for holding medicaments. In certain embodiments, the kit further comprises a second compound for treatment of HCV infection, e.g., interferon-alfa or ribavirin.

If desired compositions of the invention or combinations thereof are provided together with instructions for administering them to a subject having or at risk of

developing HCV infection. The instructions will generally include information about the use of the compounds for the treatment or prevention of HCV infection. In other embodiments, the instructions include at least one of the following: description of the compound or combination of compounds; dosage schedule and administration for treatment of HCV infection or symptoms thereof; precautions; warnings; indications; counter-indications; overdosage information; adverse reactions; animal pharmacology; clinical studies; and/or references. The instructions may be printed directly on the container (when present), or as a label applied to the container, or as a separate sheet, pamphlet, card, or folder supplied in or with the container.

The following examples are provided to illustrate the invention, not to limit it.

EXAMPLES

Example 1. Identification of CD81 binding inhibitors

The crystal structure of CD81 provided the basis for selection of potential small molecule inhibitors.

RESEARCH DESIGN AND METHODS

Database Preparation

The National Cancer Institute/Developmental Therapeutics Program (NCI/DTP) maintains a repository of approximately 220,000 samples (the plated compound set) which are non-proprietary and offered to the extramural research community for the discovery and development of new agents for the treatment of cancer, AIDS, or opportunistic infections afflicting patients with cancer or AIDS (Monga and Sausville 2002). The three-dimensional coordinates for the NCI/DTP plated compound set was obtained in the MDL SD format and converted to the mol2 format by the DOCK utility program SDF2MOL2 (UCSF). Partial atomic charges, solvation energies and van der Waals parameters for the ligands were calculated using SYBDB (Tripos, Inc.) and added to the plated compound set mol2 file.

Molecular Docking

Docking calculations were performed with the October 15, 2002, development version of DOCK, v5.1.0 (Charifson et al. 1999; Ewing et al. 2001). The general features of DOCK include rigid orienting of ligands to receptor spheres, AMBER

energy scoring, GB/SA solvation scoring, contact scoring, internal non-bonded energy scoring, ligand flexibility and both rigid and torsional simplex minimization (Gschwend et al.; Good et al. 1995). Unlike previously distributed versions, this release incorporates automated matching, internal energy (used in flexible docking), scoring function hierarchy and new minimizer termination criteria.

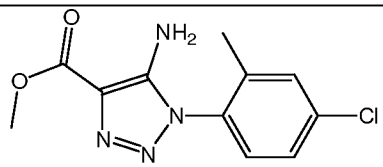
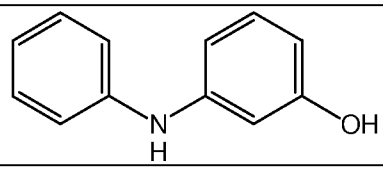
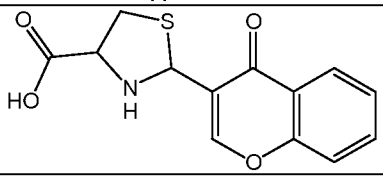
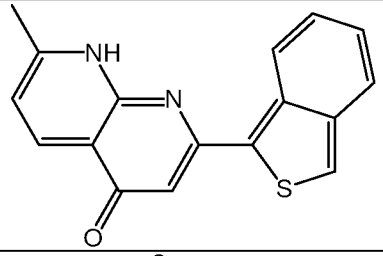
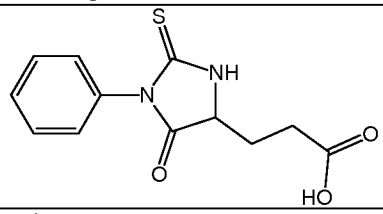
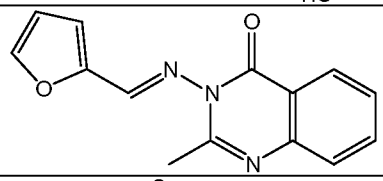
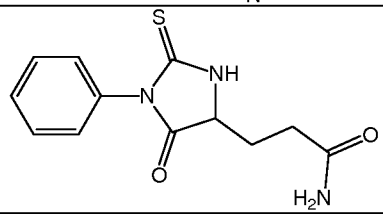
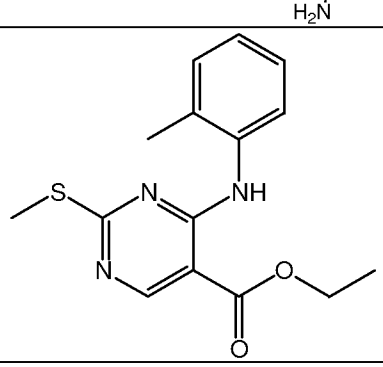
To identify molecules that would specifically interact with CD81, the crystal structure of the human form of CD81 was used (PDB code 1G8Q, accessed at http://www.rcsb.org/pdb/explore.do?structureId=1G8Q) (see Appendix A for the sequence/PDB file for 1G8Q, which is incorporated herein by reference), combined with information on the residues thought to bind HCV through mutagenesis data. The residues of interest included Ser160,Thr163, Ala164, Thr167, Ile181, Leu185 and Asp189. When these residues were mapped on to the CD81 structure, they appeared to form part of a structural pocket with characteristics favorable to small molecule binding. Approximately 20,000 druglike molecules (that follow the Lipinski rules) that are in the NCI/DTP repository of compounds were computational docked using a supercomputer. The top scoring molecules were obtained and tested for activity.

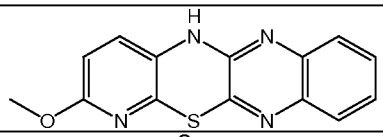
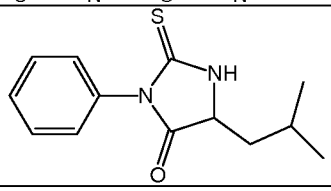
To prepare the site for docking, all water molecules were removed. Protonation of receptor residues was performed with Sybyl (Tripos, St. Louis, MO). The structure was explored using sets of spheres to describe potential binding pockets. The number of orientations per molecule was 100. Intermolecular AMBER energy scoring (vdw + columbic), contact scoring and bump filtering were implemented in DOCK5.1.0 (Gschwend et al.). SETOR (Evans 1993) and GRASP (Petrey and Honig 2003) were used to generate molecular graphic images.

The approach is generally illustrated in Figure 1.

Compounds identified using virtual screening are shown in Table 1.

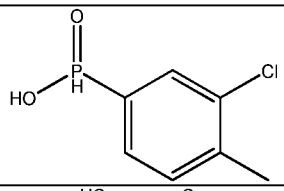
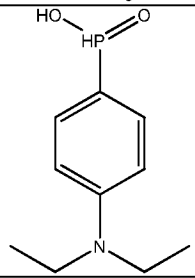
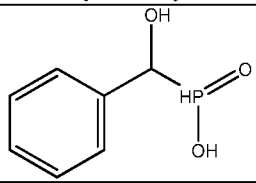
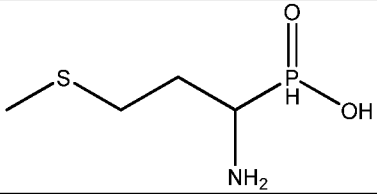
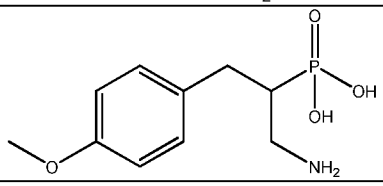
Table 1. CD81 binding inhibitors

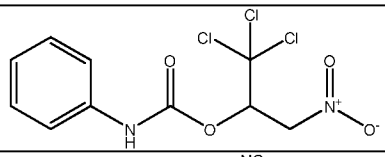
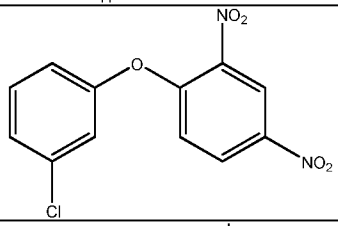
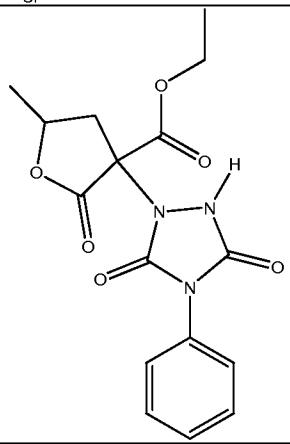
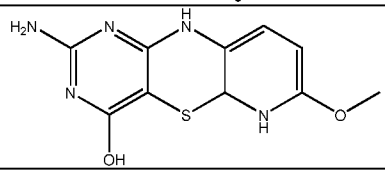
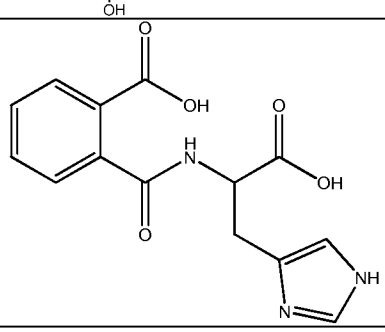
Compound Name	Structure	Energy Score
methyl 5-amino-1-(4-chloro-2-methyl-phenyl)triazole-4-carboxylate		-18.1
3-anilinophenol		-17.8
2-(4-oxochromen-3-yl)-1,3-thiazolidine-4-carboxylic acid		-17.6
2-benzothiophen-3-yl-7-methyl-8H-1,8-naphthyridin-4-one		-16.3
3-(5-oxo-1-phenyl-2-sulfanylidene-imidazolidin-4-yl)propanoic acid		-16.0
3-(2-furylmethylideneamino)-2-methyl-quinazolin-4-one		-15.7
3-[(4S)-5-oxo-1-phenyl-2-sulfanylidene-imidazolidin-4-yl]propanamide		-15.6
ethyl 4-[(2-methylphenyl)amino]-2-methylsulfanyl-pyrimidine-5-carboxylate		-15.0

2-Methoxy-5H-pyrido(3',2':5,6)(1,4)thiazino(2,3-b)quinoxaline		-15.0
3-phenyl-5-(2-methylpropyl)-2-sulfanylidene-imidazolidin-4-one		-15.0

An additional round of molecular docking using DOCK6, with improved scoring functions. This round of scoring resulted in identification of additional compounds; the top ten scoring molecules are shown in Table 2 (note that the energy scores in Table 2 are not directly comparable to the energy scores of Table 1).

Table 2. Additional CD81 binding inhibitors

Compound Name	Structure	Energy Score
3-chloro-4-methylphenylphosphinic acid		-96.3
4-(diethylamino)phenyl-phosphinic acid		-90.1
Hydroxy(phenyl)methyl-phosphinic acid		-88.6
1-Amino-3-(methylthio)propyl-phosphinic acid		-42.9
2-amino-1-(4-methoxybenzyl)ethyl-phosphonic acid		-39.4

2,2,2-Trichloro-1-((hydroxy(oxido)amino)methyl)ethyl phenylcarbamate		-35.4
1-(3-Chlorophenoxy)-2,4-dinitrobenzene		-35.3
Ethyl 3-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-5-methyl-2-oxotetrahydrofuran-3-carboxylate		-35.1
2-amino-7-methoxy-6,10-dihydro-5aH-pyrido[2,3-b]pyrimido[4,5-e]thiazin-4-ol		-35.1
2-(((1-carboxy-2-(1H-imidazol-4-yl)ethyl)amino)carbonyl)-benzoic acid		-34.9

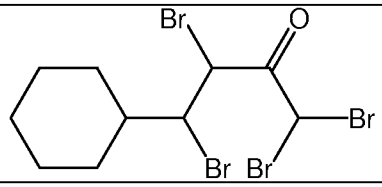
Example 2. Identification of HCV polymerase inhibitors

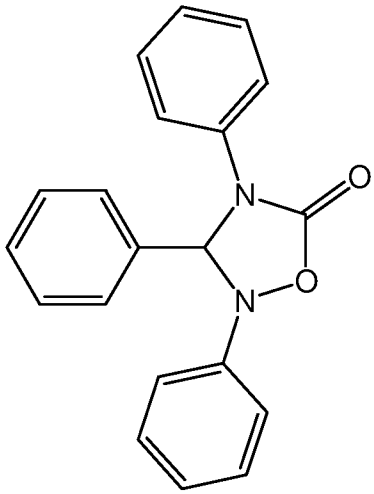
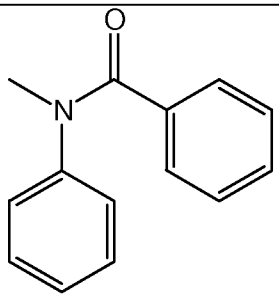
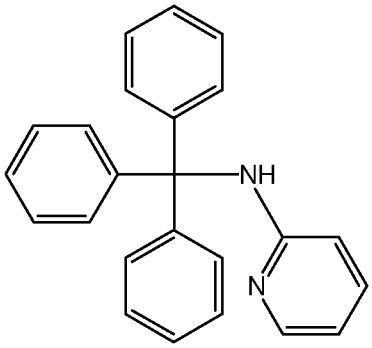
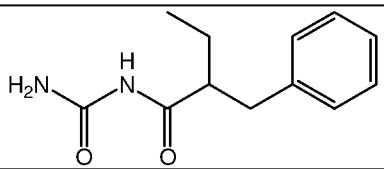
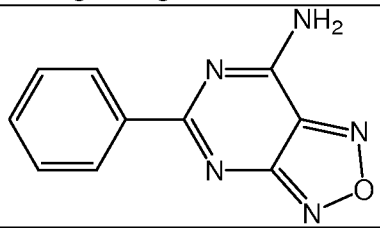
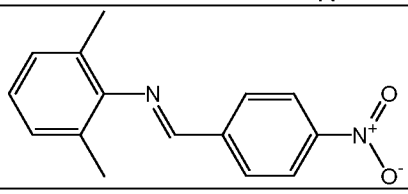
The crystal structure of NS5B provided the basis for selection of potential small molecule inhibitors HCV polymerase inhibitors. The coordinates for the crystal structure of NS5B (see, e.g., Love, R.A., et al., *J.Virol.* (2003) 77:7575-7581, incorporated herein by reference), were used in the molecular docking calculations. The atomic positions of the amino acid residues of the NS5B protein were used for the site selected for molecular docking, with the aim of inhibiting HCV polymerase

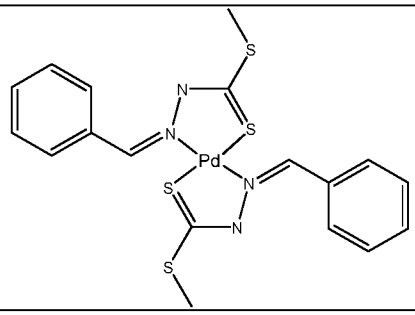
activity with small molecules. The site consists of residues in the crystal structure of PDB code 1OS5 (accessed at http://www.rcsb.org/pdb/explore.do?structureId=1OS5).

The location of the allosteric site on NS5B is approximately 35 Å from the active site in the "thumb" domain. The domain arrangement of NS5B and other polymerases has been referred to as the "fingers," "palm," and "thumb" of a right hand. Known small molecule inhibitors were previously characterized in an allosteric site near the second to last helix in the C-terminal region of the thumb subdomain. The characterized inhibitors were bound in a wedge manner to a largely hydrophobic pocket. Although this pocket is relatively shallow, the characterized inhibitors form hydrogen bonds, hydrophobic and van der Waals interactions with NS5B. We have utilized the chemical and geometric characteristics of this site on NS5B by conducting dynamic molecular docking simulations (DOCK, UCSF) of 140,000 small molecules (available through the NCI/DTP) interacting with this site (100 orientations for each compound) using the atomic coordinates provided by NS5B/inhibitor crystal structures. Through this preliminary study, we have identified several compounds that exhibit strong binding activity in this region (Table 3). One of the top compounds, N-methylbenzanilide ($C_{14}H_{13}NO$), showed inhibitory activity against HCV in replicon cell culture (see below). We then modeled this compound in the context of NS5B structure and found that this compound is located in the active site of NS5B.

Table 3. HCV polymerase inhibitors

Compound Name	Structure	Energy Score
1,1,3,4-tetrabromo-4-cyclohexylbutan-2-one		-10.3

2,3,4-Triphenyl-1,2,4-oxadiazolidin-5-one		-10.2
N-methylbenzanilide		-9.9
N-(triphenylmethyl) pyridin-2-amine		-9.5
N-carbamoyl-2-(phenylmethyl)butanamide		-9.4
5-phenyl-[1,2,5]oxadiazolo[3,4-e]pyrimidin-7-amine		-9.4
N-(2,6-dimethylphenyl)-1-(4-nitrophenyl)methanimine		-8.8

NSC269216 72871-91-1		-8.7

Example 3

We first tested five compounds (the top five compounds in Table 3) on HCV NS5B enzymatic activity *in vitro*. Among all the compounds tested, all of them showed inhibitory effect on NS5B activity (data not shown). To further test the effectiveness of these compounds on HCV RNA replication in a cell culture system, we incubated varying doses of the compounds with the GSB cell line, which contains a subgenomic replicon in Huh7 cells (Lohmann V. et al., , *Science* (1999) 285:110-3; Blight KJ, et al., *Science* (2000) 290:1972-4). Our previous studies have shown the feasibility of this cell culture system on evaluation of antiviral agents (see, e.g., Zhu H et al., *Hepatology* (2003) 37:1180-8). IFN-treated cells serve as a positive control (IFN exhibits dose-dependent, anti-HCV activity in GSB cells). The compounds were incubated with the cells for 48 hours. Two of the five compounds (N-methylbenzanilide and N-(triphenylmethyl) pyridin-2-amine) exhibited antiviral effect. The inhibitory effect is dose-dependent.

As discussed above, two compounds showed antiviral activity in cell culture. We next tested whether these two compounds have any toxicity on liver cells. We incubated the compounds with Huh7 cells and GSB cells for 48 hours. The cells were fixed and stained with DAPI and examined under a microscope. In this test, N-methylbenzanilide did not appear to cause cell apoptosis, while N-(triphenylmethyl) pyridin-2-amine induced up to 30% of the cells undergoing apoptosis. The data suggest that N-(triphenylmethyl) pyridin-2-amine is toxic at certain concentrations, and its antiviral effect could be due, at least in part, to cell toxicity. The apparent lack of cell toxicity of N-methylbenzanilide suggests that this compound could be an effective viral inhibitor.

Other Embodiments

From the foregoing description, it will be apparent that variations and modifications may be made to the invention described herein to adopt it to various usages and conditions. Such embodiments are also within the scope of the following claims.

All patents and publications mentioned in this specification are herein incorporated by reference to the same extent as if each independent patent and publication was specifically and individually indicated to be incorporated by reference.

From the above description, one skilled in the art can make various changes and modifications without departing from the spirit and scope of the invention. Thus, other embodiments are also within the scope of the following claims.

APPENDIX A

HEADER IMMUNE SYSTEM 20-NOV-00 1G8Q
TITLE CRYSTAL STRUCTURE OF HUMAN CD81 EXTRACELLULAR DOMAIN, A
TITLE 2 RECEPTOR FOR HEPATITIS C VIRUS
COMPND MOL_ID: 1;
COMPND 2 MOLECULE: CD81 ANTIGEN, EXTRACELLULAR DOMAIN;
COMPND 3 CHAIN: A, B;
COMPND 4 FRAGMENT: EXTRACELLULAR DOMAIN;
COMPND 5 SYNONYM: CD81, TARGET OF ANTIPROLIFERATIVE ANTIBODY 1, 26
COMPND 6 KDA CELL SURFACE PROTEIN TAPA-1;
COMPND 7 ENGINEERED: YES
SOURCE MOL_ID: 1;
SOURCE 2 ORGANISM_SCIENTIFIC: HOMO SAPIENS;
SOURCE 3 ORGANISM_COMMON: HUMAN;
SOURCE 4 EXPRESSION_SYSTEM: ESCHERICHIA COLI;
SOURCE 5 EXPRESSION_SYSTEM_COMMON: BACTERIA;
SOURCE 6 EXPRESSION_SYSTEM_VECTOR_TYPE: PLASMID;
SOURCE 7 EXPRESSION_SYSTEM_PLASMID: PEZZ18
KEYWDS ALPHA HELICAL
EXPDTA X-RAY DIFFRACTION
AUTHOR K.KITADOKORO,M.BOLOGNESI,D.BORDO,G.GRANDI,G.GALLI,
AUTHOR 2 R.PETRACCA,F.FALUGI
REVDAT 1 21-FEB-01 1G8Q 0
JRNL AUTH K.KITADOKORO,D.BORDO,G.GALLI,R.PETRACCA,F.FALUGI,
JRNL AUTH 2 S.ABRIGNANI,G.GRANDI,M.BOLOGNESI
JRNL TITL CD81 EXTRACELLULAR DOMAIN 3D STRUCTURE: INSIGHT
JRNL TITL 2 INTO THE TETRASPANIN SUPERFAMILY STRUCTURAL MOTIFS.
JRNL REF EMBO J. V. 20 12 2001
JRNL REFN ASTM EMJODG UK ISSN 0261-4189
REMARK 1
REMARK 2
REMARK 2 RESOLUTION. 1.60 ANGSTROMS.
REMARK 3
REMARK 3 REFINEMENT.
REMARK 3 PROGRAM : REFMAC
REMARK 3 AUTHORS : MURSHUDOV,VAGIN,DODSON
REMARK 3
REMARK 3 DATA USED IN REFINEMENT.

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REMARK   3   NUMBER OF REFLECTIONS            : 23143
REMARK   3
REMARK   3  FIT TO DATA USED IN REFINEMENT.
REMARK   3   CROSS-VALIDATION METHOD         : THROUGHOUT
REMARK   3   FREE R VALUE TEST SET SELECTION  : RANDOM
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REMARK   3   R VALUE           (WORKING SET) : 0.188
REMARK   3   FREE R VALUE                     : 0.238
REMARK   3   FREE R VALUE TEST SET SIZE   (%) : 4.800
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REMARK   3
REMARK   3  NUMBER OF NON-HYDROGEN ATOMS USED IN REFINEMENT.
REMARK   3   PROTEIN ATOMS            : 1356
REMARK   3   NUCLEIC ACID ATOMS       : 0
REMARK   3   HETEROGEN ATOMS          : 0
REMARK   3   SOLVENT ATOMS            : 194
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REMARK   3   FROM WILSON PLOT           (A**2) : 26.30
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REMARK   3    B13 (A**2) : NULL
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REMARK 100 THE RCSB ID CODE IS RCSB012373.
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REMARK 280 DIFFUSION, SITTING DROP, TEMPERATURE 298K
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REMARK 290 CRYSTALLOGRAPHIC SYMMETRY
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REMARK 290
REMARK 290 SYMOP SYMMETRY
REMARK 290 NNNMMM OPERATOR
REMARK 290 1555 X,Y,Z
REMARK 290 2555 -X,1/2+Y,-Z
REMARK 290
REMARK 290 WHERE NNN -> OPERATOR NUMBER
REMARK 290 MMM -> TRANSLATION VECTOR
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REMARK 350 GIVEN BELOW. BOTH NON-CRYSTALLOGRAPHIC AND
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REMARK 350 BIOMT3 1 0.000000 0.000000 1.000000 0.00000
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REMARK 465 IDENTIFIER; SSSEQ=SEQUENCE NUMBER; I=INSERTION CODE.)
REMARK 465
REMARK 465 M RES C SSSEQI
REMARK 465 ASP B 238
REMARK 465 ASP B 239
REMARK 465 ALA B 240
REMARK 465 ASN B 241
REMARK 470
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REMARK 470 I=INSERTION CODE):
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REMARK 470 SER B 279 CB OG
REMARK 500
REMARK 500 GEOMETRY AND STEREOCHEMISTRY
REMARK 500 SUBTOPIC: CLOSE CONTACTS IN SAME ASYMMETRIC UNIT

REMARK 500
REMARK 500 THE FOLLOWING ATOMS ARE IN CLOSE CONTACT.
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REMARK 500 ATM1 RES C SSEQI ATM2 RES C SSEQI
REMARK 500 OD2 ASP A 138 O HOH 118 1.91
REMARK 500 OD2 ASP A 155 O HOH 158 2.03
REMARK 500 O HIS A 202 O HOH 33 2.08
REMARK 500 NZ LYS B 271 O HOH 154 2.10
REMARK 500 O HOH 134 O HOH 168 2.12
REMARK 500 CG GLN B 229 O HOH 194 2.17
REMARK 500 O HOH 44 O HOH 134 2.19
REMARK 500
REMARK 500 GEOMETRY AND STEREOCHEMISTRY
REMARK 500 SUBTOPIC: CLOSE CONTACTS
REMARK 500
REMARK 500 THE FOLLOWING ATOMS THAT ARE RELATED BY CRYSTALLOGRAPHIC
REMARK 500 SYMMETRY ARE IN CLOSE CONTACT. AN ATOM LOCATED WITHIN 0.15
REMARK 500 ANGSTROMS OF A SYMMETRY RELATED ATOM IS ASSUMED TO BE ON
A
REMARK 500 SPECIAL POSITION AND IS, THEREFORE, LISTED IN REMARK 375
REMARK 500 INSTEAD OF REMARK 500. ATOMS WITH NON-BLANK ALTERNATE
REMARK 500 LOCATION INDICATORS ARE NOT INCLUDED IN THE CALCULATIONS.
REMARK 500
REMARK 500 DISTANCE CUTOFF:
REMARK 500 2.2 ANGSTROMS FOR CONTACTS NOT INVOLVING HYDROGEN ATOMS
REMARK 500 1.6 ANGSTROMS FOR CONTACTS INVOLVING HYDROGEN ATOMS
REMARK 500
REMARK 500 ATM1 RES C SSEQI ATM2 RES C SSEQI SSYMOP DISTANCE
REMARK 500 CZ PHE B 213 O HOH 173 1655 0.78
REMARK 500 OD1 ASP A 138 O HOH 180 2646 1.37
REMARK 500 CE1 PHE B 213 O HOH 173 1655 1.43
REMARK 500 CE2 PHE B 213 O HOH 173 1655 1.66
REMARK 500 C ILE B 282 O HOH 141 2556 1.83
REMARK 500 CG2 ILE B 282 O HOH 141 2556 1.87
REMARK 500 CE2 PHE B 213 O HOH 47 1655 2.15
REMARK 500 O HOH 82 O HOH 143 1455 2.15
REMARK 500 O ILE B 282 O HOH 141 2556 2.17
REMARK 500 CB ILE B 282 O HOH 141 2556 2.17
REMARK 500
REMARK 500 GEOMETRY AND STEREOCHEMISTRY

REMARK 500 SUBTOPIC: COVALENT BOND LENGTHS
REMARK 500
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REMARK 500 HAVE VALUES WHICH DEVIATE FROM EXPECTED VALUES BY MORE
REMARK 500 THAN 6*RMSD (M=MODEL NUMBER; RES=RESIDUE NAME; C=CHAIN
REMARK 500 IDENTIFIER; SSEQ=SEQUENCE NUMBER; I=INSERTION CODE).
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REMARK 500
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REMARK 500 ASP A 138 CB ASP A 138 CG 0.291
REMARK 500 SER B 277 C GLY B 278 N 0.352
REMARK 500
REMARK 500 GEOMETRY AND STEREOCHEMISTRY
REMARK 500 SUBTOPIC: COVALENT BOND ANGLES
REMARK 500
REMARK 500 THE STEREOCHEMICAL PARAMETERS OF THE FOLLOWING RESIDUES
REMARK 500 HAVE VALUES WHICH DEVIATE FROM EXPECTED VALUES BY MORE
REMARK 500 THAN 6*RMSD (M=MODEL NUMBER; RES=RESIDUE NAME; C=CHAIN
REMARK 500 IDENTIFIER; SSEQ=SEQUENCE NUMBER; I=INSERTION CODE).
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REMARK 500 STANDARD TABLE:
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REMARK 500
REMARK 500 M RES CSSEQI ATM1 ATM2 ATM3
REMARK 500 SER B 277 O - C - N ANGL. DEV. =-92.9 DEGREES
REMARK 525
REMARK 525 SOLVENT
REMARK 525 THE FOLLOWING SOLVENT MOLECULES LIE FARTHER THAN
EXPECTED
REMARK 525 FROM THE PROTEIN OR NUCLEIC ACID MOLECULE AND MAY BE
REMARK 525 ASSOCIATED WITH A SYMMETRY RELATED MOLECULE (M=MODEL
REMARK 525 NUMBER; RES=RESIDUE NAME; C=CHAIN IDENTIFIER;
SSEQ=SEQUENCE
REMARK 525 NUMBER; I=INSERTION CODE):

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REMARK 525
REMARK 525  M RES CSSEQI
REMARK 525    HOH   110       DISTANCE =  8.01 ANGSTROMS
REMARK 525    HOH   163       DISTANCE =  5.25 ANGSTROMS
REMARK 525    HOH   171       DISTANCE =  6.32 ANGSTROMS
REMARK 525    HOH   175       DISTANCE =  5.32 ANGSTROMS
DBREF  1G8Q A  113   202  UNP    P60033   CD81_HUMAN     113    202
DBREF  1G8Q B  213   302  UNP    P60033   CD81_HUMAN     113    202
SEQADV 1G8Q HIS A  202  UNP  P60033    LEU   202 CONFLICT
SEQADV 1G8Q HIS B  302  UNP  P60033    LEU   202 CONFLICT
SEQRES   1 A   90  PHE VAL ASN LYS ASP GLN ILE ALA LYS ASP VAL LYS GLN
SEQRES   2 A   90  PHE TYR ASP GLN ALA LEU GLN GLN ALA VAL VAL ASP ASP
SEQRES   3 A   90  ASP ALA ASN ASN ALA LYS ALA VAL VAL LYS THR PHE HIS
SEQRES   4 A   90  GLU THR LEU ASP CYS CYS GLY SER SER THR LEU THR ALA
SEQRES   5 A   90  LEU THR THR SER VAL LEU LYS ASN ASN LEU CYS PRO SER
SEQRES   6 A   90  GLY SER ASN ILE ILE SER ASN LEU PHE LYS GLU ASP CYS
SEQRES   7 A   90  HIS GLN LYS ILE ASP ASP LEU PHE SER GLY LYS HIS
SEQRES   1 B   90  PHE VAL ASN LYS ASP GLN ILE ALA LYS ASP VAL LYS GLN
SEQRES   2 B   90  PHE TYR ASP GLN ALA LEU GLN GLN ALA VAL VAL ASP ASP
SEQRES   3 B   90  ASP ALA ASN ASN ALA LYS ALA VAL VAL LYS THR PHE HIS
SEQRES   4 B   90  GLU THR LEU ASP CYS CYS GLY SER SER THR LEU THR ALA
SEQRES   5 B   90  LEU THR THR SER VAL LEU LYS ASN ASN LEU CYS PRO SER
SEQRES   6 B   90  GLY SER ASN ILE ILE SER ASN LEU PHE LYS GLU ASP CYS
SEQRES   7 B   90  HIS GLN LYS ILE ASP ASP LEU PHE SER GLY LYS HIS
FORMUL   3  HOH   *194(H2 O)
HELIX    1   1 ASN A  115  ASP A  137  1                                  23
HELIX    2   2 ALA A  140  ASP A  155  1                                  16
HELIX    3   3 LEU A  162  ALA A  164  5                                   3
HELIX    4   4 LEU A  165  ASN A  172  1                                   8
HELIX    5   5 ASN A  180  PHE A  186  1                                   7
HELIX    6   6 ASP A  189  GLY A  200  1                                  12
HELIX    7   7 ASN B  215  VAL B  236  1                                  22
HELIX    8   8 ASN B  242  ASP B  255  1                                  14
HELIX    9   9 LEU B  262  ASN B  272  1                                  11
HELIX   10  10 GLY B  278  ASN B  284  1                                   7
HELIX   11  11 ASP B  289  GLY B  300  1                                  12
SSBOND   1 CYS A  156    CYS A  190
SSBOND   2 CYS A  157    CYS A  175
SSBOND   3 CYS B  256    CYS B  290
SSBOND   4 CYS B  257    CYS B  275
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CRYST1  31.485  77.172  38.462  90.00 107.39  90.00 P 1 21 1     4
ORIGX1      1.000000  0.000000  0.000000        0.00000
ORIGX2      0.000000  1.000000  0.000000        0.00000
ORIGX3      0.000000  0.000000  1.000000        0.00000
SCALE1      0.031761 -0.000001  0.009946        0.00000
SCALE2      0.000000  0.012958  0.000000        0.00000
SCALE3      0.000000  0.000000  0.027245        0.00000
ATOM      1  N   PHE A 113      15.167  44.770  -2.797  1.00 39.24           N
ATOM      2  CA  PHE A 113      13.708  45.147  -2.958  1.00 34.94           C
ATOM      3  C   PHE A 113      13.024  44.596  -1.659  1.00 35.10           C
ATOM      4  O   PHE A 113      13.487  43.617  -1.121  1.00 35.93           O
ATOM      5  CB  PHE A 113      13.050  44.429  -4.084  1.00 35.75           C
ATOM      6  CG  PHE A 113      13.549  44.896  -5.455  1.00 34.69           C
ATOM      7  CD1 PHE A 113      13.430  46.212  -5.878  1.00 33.45           C
ATOM      8  CD2 PHE A 113      14.081  43.938  -6.285  1.00 31.71           C
ATOM      9  CE1 PHE A 113      13.797  46.605  -7.119  1.00 41.37           C
ATOM     10  CE2 PHE A 113      14.510  44.351  -7.562  1.00 34.14           C
ATOM     11  CZ  PHE A 113      14.380  45.642  -7.911  1.00 29.25           C
ATOM     12  N   VAL A 114      11.997  45.314  -1.304  1.00 30.58           N
ATOM     13  CA  VAL A 114      11.331  44.894  -0.015  1.00 29.62           C
ATOM     14  C   VAL A 114      10.546  43.656  -0.280  1.00 34.38           C
ATOM     15  O   VAL A 114       9.775  43.436  -1.243  1.00 39.07           O
ATOM     16  CB  VAL A 114      10.340  46.075   0.213  1.00 28.69           C
ATOM     17  CG1 VAL A 114       9.250  45.669   1.193  1.00 38.63           C
ATOM     18  CG2 VAL A 114      11.113  47.339   0.485  1.00 32.13           C
ATOM     19  N   ASN A 115      10.625  42.728   0.669  1.00 25.83           N
ATOM     20  CA  ASN A 115       9.993  41.447   0.619  1.00 26.00           C
ATOM     21  C   ASN A 115       9.027  41.300   1.849  1.00 29.46           C
ATOM     22  O   ASN A 115       9.603  40.949   2.880  1.00 29.57           O
ATOM     23  CB  ASN A 115      11.110  40.401   0.766  1.00 32.45           C
ATOM     24  CG  ASN A 115      10.691  38.989   0.428  1.00 37.56           C
ATOM     25  OD1 ASN A 115       9.537  38.605   0.619  1.00 37.64           O
ATOM     26  ND2 ASN A 115      11.677  38.219  -0.112  1.00 41.69           N
ATOM     27  N   LYS A 116       7.809  41.729   1.649  1.00 28.35           N
ATOM     28  CA  LYS A 116       6.882  41.668   2.805  1.00 31.24           C
ATOM     29  C   LYS A 116       6.730  40.323   3.475  1.00 29.73           C
ATOM     30  O   LYS A 116       6.713  40.228   4.699  1.00 27.86           O
ATOM     31  CB  LYS A 116       5.546  42.199   2.325  1.00 32.44           C
ATOM     32  CG  LYS A 116       4.449  42.271   3.367  1.00 42.56           C
ATOM     33  CD  LYS A 116       3.441  41.207   2.964  1.00 59.59           C
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ATOM   34  CE  LYS A 116      2.091  41.586   3.570  1.00 54.79       C
ATOM   35  NZ  LYS A 116      1.324  40.335   3.706  1.00 44.76       N
ATOM   36  N   ASP A 117      6.590  39.253   2.686  1.00 30.24       N
ATOM   37  CA  ASP A 117      6.532  37.911   3.325  1.00 30.86       C
ATOM   38  C   ASP A 117      7.808  37.647   4.074  1.00 31.67       C
ATOM   39  O   ASP A 117      7.619  37.085   5.190  1.00 29.62       O
ATOM   40  CB  ASP A 117      6.370  36.796   2.280  1.00 36.10       C
ATOM   41  CG  ASP A 117      5.042  36.832   1.557  1.00 42.66       C
ATOM   42  OD1 ASP A 117      4.957  36.194   0.452  1.00 44.88       O
ATOM   43  OD2 ASP A 117      4.130  37.497   2.098  1.00 46.14       O
ATOM   44  N   GLN A 118      9.018  37.973   3.673  1.00 27.21       N
ATOM   45  CA  GLN A 118     10.205  37.641   4.470  1.00 23.73       C
ATOM   46  C   GLN A 118     10.221  38.518   5.768  1.00 25.02       C
ATOM   47  O   GLN A 118     10.586  38.025   6.858  1.00 28.58       O
ATOM   48  CB  GLN A 118     11.519  37.791   3.721  1.00 33.27       C
ATOM   49  CG  GLN A 118     12.351  36.517   3.936  1.00 51.73       C
ATOM   50  CD  GLN A 118     11.848  35.378   3.072  1.00 60.56       C
ATOM   51  OE1 GLN A 118     11.324  34.393   3.608  1.00 68.76       O
ATOM   52  NE2 GLN A 118     11.942  35.430   1.742  1.00 56.06       N
ATOM   53  N   ILE A 119      9.860  39.753   5.560  1.00 25.35       N
ATOM   54  CA  ILE A 119      9.895  40.703   6.722  1.00 23.35       C
ATOM   55  C   ILE A 119      8.948  40.174   7.778  1.00 23.36       C
ATOM   56  O   ILE A 119      9.315  40.183   9.007  1.00 25.20       O
ATOM   57  CB  ILE A 119      9.497  42.128   6.252  1.00 28.02       C
ATOM   58  CG1 ILE A 119     10.556  42.719   5.326  1.00 29.50       C
ATOM   59  CG2 ILE A 119      9.264  43.026   7.517  1.00 23.83       C
ATOM   60  CD1 ILE A 119     10.195  44.036   4.621  1.00 30.12       C
ATOM   61  N   ALA A 120      7.709  39.796   7.396  1.00 24.29       N
ATOM   62  CA  ALA A 120      6.783  39.332   8.475  1.00 25.45       C
ATOM   63  C   ALA A 120      7.284  38.050   9.156  1.00 24.83       C
ATOM   64  O   ALA A 120      7.233  37.973  10.395  1.00 25.98       O
ATOM   65  CB  ALA A 120      5.371  38.968   7.933  1.00 29.86       C
ATOM   66  N   LYS A 121      7.884  37.147   8.322  1.00 25.79       N
ATOM   67  CA  LYS A 121      8.445  35.944   8.931  1.00 28.41       C
ATOM   68  C   LYS A 121      9.578  36.321   9.881  1.00 24.24       C
ATOM   69  O   LYS A 121      9.627  35.796  11.048  1.00 26.75       O
ATOM   70  CB  LYS A 121      8.938  35.059   7.745  1.00 32.64       C
ATOM   71  CG  LYS A 121     10.364  34.549   7.911  1.00 44.31       C
ATOM   72  CD  LYS A 121     11.287  35.259   6.938  1.00 69.09       C
ATOM   73  CE  LYS A 121     12.675  34.657   6.834  1.00 57.61       C
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ATOM   74 NZ  LYS A 121     13.589  35.621   6.165  1.00 50.39      N
ATOM   75 N   ASP A 122     10.373  37.294   9.564  1.00 23.37      N
ATOM   76 CA  ASP A 122     11.501  37.727  10.378  1.00 24.26      C
ATOM   77 C   ASP A 122     10.983  38.467  11.667  1.00 24.20      C
ATOM   78 O   ASP A 122     11.557  38.256  12.735  1.00 23.00      O
ATOM   79 CB  ASP A 122     12.558  38.595   9.757  1.00 22.89      C
ATOM   80 CG  ASP A 122     13.357  37.803   8.676  1.00 26.88      C
ATOM   81 OD1 ASP A 122     13.258  36.555   8.568  1.00 32.41      O
ATOM   82 OD2 ASP A 122     14.097  38.531   7.966  1.00 31.40      O
ATOM   83 N   VAL A 123     9.959  39.272  11.554  1.00 25.26      N
ATOM   84 CA  VAL A 123     9.366  39.889  12.760  1.00 22.33      C
ATOM   85 C   VAL A 123     8.835  38.836  13.703  1.00 20.29      C
ATOM   86 O   VAL A 123     9.011  38.893  14.920  1.00 22.67      O
ATOM   87 CB  VAL A 123     8.275  40.934  12.399  1.00 18.96      C
ATOM   88 CG1 VAL A 123     7.797  41.561  13.712  1.00 20.18      C
ATOM   89 CG2 VAL A 123     9.055  42.031  11.573  1.00 23.67      C
ATOM   90 N   LYS A 124     8.096  37.850  13.096  1.00 21.86      N
ATOM   91 CA  LYS A 124     7.557  36.770  14.029  1.00 24.09      C
ATOM   92 C   LYS A 124     8.717  36.046  14.718  1.00 25.15      C
ATOM   93 O   LYS A 124     8.683  35.781  15.934  1.00 24.94      O
ATOM   94 CB  LYS A 124     6.796  35.780  13.133  1.00 25.89      C
ATOM   95 CG  LYS A 124     5.506  36.417  12.615  1.00 25.29      C
ATOM   96 CD  LYS A 124     4.836  35.401  11.665  1.00 29.66      C
ATOM   97 CE  LYS A 124     3.760  36.151  10.867  1.00 33.26      C
ATOM   98 NZ  LYS A 124     3.127  35.134   9.944  1.00 31.77      N
ATOM   99 N   GLN A 125     9.820  35.785  14.057  1.00 22.36      N
ATOM  100 CA  GLN A 125     10.964  35.104  14.641  1.00 25.16      C
ATOM  101 C   GLN A 125     11.681  35.921  15.679  1.00 22.14      C
ATOM  102 O   GLN A 125     12.014  35.492  16.746  1.00 26.91      O
ATOM  103 CB  GLN A 125     11.945  34.652  13.543  1.00 29.01      C
ATOM  104 CG  GLN A 125     13.031  33.807  14.174  1.00 28.57      C
ATOM  105 CD  GLN A 125     12.622  32.700  15.114  1.00 54.17      C
ATOM  106 OE1 GLN A 125     11.511  32.150  15.215  1.00 49.09      O
ATOM  107 NE2 GLN A 125     13.581  32.238  15.938  1.00 56.90      N
ATOM  108 N   PHE A 126     11.883  37.250  15.397  1.00 21.36      N
ATOM  109 CA  PHE A 126     12.391  38.153  16.405  1.00 24.32      C
ATOM  110 C   PHE A 126     11.618  38.143  17.688  1.00 22.26      C
ATOM  111 O   PHE A 126     12.053  38.072  18.817  1.00 22.96      O
ATOM  112 CB  PHE A 126     12.368  39.573  15.870  1.00 20.57      C
ATOM  113 CG  PHE A 126     12.963  40.600  16.766  1.00 22.49      C
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ATOM   114  CD1 PHE A 126     14.371  40.653  16.807  1.00 24.90      C
ATOM   115  CD2 PHE A 126     12.179  41.436  17.582  1.00 24.61      C
ATOM   116  CE1 PHE A 126     14.990  41.590  17.635  1.00 28.22      C
ATOM   117  CE2 PHE A 126     12.843  42.365  18.366  1.00 21.62      C
ATOM   118  CZ  PHE A 126     14.187  42.409  18.445  1.00 27.52      C
ATOM   119  N   TYR A 127     10.253  38.186  17.529  1.00 20.08      N
ATOM   120  CA  TYR A 127      9.357  38.138  18.709  1.00 20.07      C
ATOM   121  C   TYR A 127      9.558  36.810  19.423  1.00 18.65      C
ATOM   122  O   TYR A 127      9.654  36.867  20.698  1.00 21.80      O
ATOM   123  CB  TYR A 127      7.862  38.220  18.163  1.00 24.10      C
ATOM   124  CG  TYR A 127      6.916  38.008  19.347  1.00 22.09      C
ATOM   125  CD1 TYR A 127      6.572  38.938  20.301  1.00 21.15      C
ATOM   126  CD2 TYR A 127      6.387  36.697  19.442  1.00 21.40      C
ATOM   127  CE1 TYR A 127      5.739  38.648  21.380  1.00 17.95      C
ATOM   128  CE2 TYR A 127      5.535  36.347  20.518  1.00 23.42      C
ATOM   129  CZ  TYR A 127      5.219  37.313  21.437  1.00 22.63      C
ATOM   130  OH  TYR A 127      4.375  36.938  22.472  1.00 22.57      O
ATOM   131  N   ASP A 128      9.601  35.711  18.665  1.00 23.53      N
ATOM   132  CA  ASP A 128      9.711  34.412  19.441  1.00 22.47      C
ATOM   133  C   ASP A 128     11.092  34.261  20.060  1.00 24.09      C
ATOM   134  O   ASP A 128     11.163  33.757  21.206  1.00 22.97      O
ATOM   135  CB  ASP A 128      9.677  33.281  18.369  1.00 26.18      C
ATOM   136  CG  ASP A 128      8.242  33.030  17.920  1.00 30.00      C
ATOM   137  OD1 ASP A 128      8.112  32.186  17.003  1.00 33.09      O
ATOM   138  OD2 ASP A 128      7.285  33.596  18.476  1.00 27.78      O
ATOM   139  N   GLN A 129     12.138  34.813  19.426  1.00 22.90      N
ATOM   140  CA  GLN A 129     13.445  34.792  20.155  1.00 22.90      C
ATOM   141  C   GLN A 129     13.295  35.635  21.407  1.00 22.52      C
ATOM   142  O   GLN A 129     13.817  35.218  22.484  1.00 24.95      O
ATOM   143  CB  GLN A 129     14.513  35.596  19.319  1.00 25.15      C
ATOM   144  CG  GLN A 129     14.765  34.861  18.052  1.00 25.16      C
ATOM   145  CD  GLN A 129     15.677  35.679  17.066  1.00 26.58      C
ATOM   146  OE1 GLN A 129     15.971  35.072  16.036  1.00 30.99      O
ATOM   147  NE2 GLN A 129     15.997  36.941  17.458  1.00 31.51      N
ATOM   148  N   ALA A 130     12.694  36.840  21.393  1.00 20.21      N
ATOM   149  CA  ALA A 130     12.613  37.548  22.651  1.00 19.29      C
ATOM   150  C   ALA A 130     11.817  36.889  23.683  1.00 22.30      C
ATOM   151  O   ALA A 130     12.037  36.954  24.923  1.00 23.00      O
ATOM   152  CB  ALA A 130     12.057  39.015  22.407  1.00 21.56      C
ATOM   153  N   LEU A 131     10.662  36.254  23.275  1.00 19.17      N
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ATOM   154  CA  LEU A 131      9.735  35.649  24.274  1.00 21.49      C
ATOM   155  C   LEU A 131     10.463  34.445  24.955  1.00 21.26      C
ATOM   156  O   LEU A 131     10.319  34.276  26.152  1.00 22.13      O
ATOM   157  CB  LEU A 131      8.491  35.143  23.506  1.00 21.78      C
ATOM   158  CG  LEU A 131      7.340  34.770  24.524  1.00 26.50      C
ATOM   159  CD1 LEU A 131      6.816  36.103  25.128  1.00 24.46      C
ATOM   160  CD2 LEU A 131      6.210  34.112  23.753  1.00 23.66      C
ATOM   161  N   GLN A 132     11.180  33.702  24.131  1.00 22.34      N
ATOM   162  CA  GLN A 132     11.877  32.528  24.718  1.00 23.45      C
ATOM   163  C   GLN A 132     12.919  32.988  25.683  1.00 22.56      C
ATOM   164  O   GLN A 132     13.005  32.390  26.763  1.00 23.72      O
ATOM   165  CB  GLN A 132     12.511  31.671  23.583  1.00 22.67      C
ATOM   166  CG  GLN A 132     11.360  30.974  22.801  1.00 23.87      C
ATOM   167  CD  GLN A 132     11.970  30.208  21.612  1.00 25.58      C
ATOM   168  OE1 GLN A 132     11.931  28.953  21.568  1.00 28.70      O
ATOM   169  NE2 GLN A 132     12.435  30.860  20.528  1.00 25.53      N
ATOM   170  N   GLN A 133     13.708  34.060  25.414  1.00 21.29      N
ATOM   171  CA  GLN A 133     14.731  34.499  26.352  1.00 21.06      C
ATOM   172  C   GLN A 133     14.083  35.143  27.568  1.00 22.06      C
ATOM   173  O   GLN A 133     14.476  34.990  28.747  1.00 24.74      O
ATOM   174  CB  GLN A 133     15.523  35.627  25.616  1.00 23.19      C
ATOM   175  CG  GLN A 133     16.684  36.003  26.552  1.00 25.93      C
ATOM   176  CD  GLN A 133     17.644  37.020  25.918  1.00 23.37      C
ATOM   177  OE1 GLN A 133     17.459  37.428  24.795  1.00 29.00      O
ATOM   178  NE2 GLN A 133     18.737  37.244  26.654  1.00 29.97      N
ATOM   179  N   ALA A 134     12.951  35.892  27.350  1.00 22.33      N
ATOM   180  CA  ALA A 134     12.278  36.527  28.484  1.00 24.62      C
ATOM   181  C   ALA A 134     11.792  35.644  29.628  1.00 23.96      C
ATOM   182  O   ALA A 134     11.707  35.941  30.837  1.00 28.27      O
ATOM   183  CB  ALA A 134     11.055  37.336  27.981  1.00 24.32      C
ATOM   184  N   VAL A 135     11.447  34.406  29.258  1.00 22.77      N
ATOM   185  CA  VAL A 135     10.919  33.424  30.211  1.00 21.49      C
ATOM   186  C   VAL A 135     12.053  32.697  30.814  1.00 25.43      C
ATOM   187  O   VAL A 135     11.880  32.230  31.966  1.00 31.77      O
ATOM   188  CB  VAL A 135      9.962  32.451  29.523  1.00 31.30      C
ATOM   189  CG1 VAL A 135      8.684  33.113  29.087  1.00 30.27      C
ATOM   190  CG2 VAL A 135     10.510  31.424  28.603  1.00 47.56      C
ATOM   191  N   VAL A 136     13.146  32.476  30.096  1.00 30.78      N
ATOM   192  CA  VAL A 136     14.200  31.646  30.772  1.00 29.87      C
ATOM   193  C   VAL A 136     15.227  32.424  31.468  1.00 31.70      C
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ATOM 194 O VAL A 136 16.091 31.916 32.217 1.00 35.77 O
ATOM 195 CB VAL A 136 14.689 30.731 29.658 1.00 31.34 C
ATOM 196 CG1 VAL A 136 15.644 31.431 28.729 1.00 28.41 C
ATOM 197 CG2 VAL A 136 15.185 29.397 30.181 1.00 33.24 C
ATOM 198 N ASP A 137 15.515 33.682 31.066 1.00 28.53 N
ATOM 199 CA ASP A 137 16.663 34.476 31.489 1.00 29.09 C
ATOM 200 C ASP A 137 16.141 35.528 32.452 1.00 36.48 C
ATOM 201 O ASP A 137 15.425 36.451 32.034 1.00 36.05 O
ATOM 202 CB ASP A 137 17.245 35.177 30.255 1.00 30.94 C
ATOM 203 CG ASP A 137 18.518 35.945 30.541 1.00 39.46 C
ATOM 204 OD1 ASP A 137 19.163 36.437 29.580 1.00 33.64 O
ATOM 205 OD2 ASP A 137 18.930 36.186 31.696 1.00 34.86 O
ATOM 206 N ASP A 138 16.497 35.446 33.720 1.00 42.16 N
ATOM 207 CA ASP A 138 16.037 36.353 34.714 1.00 45.68 C
ATOM 208 C ASP A 138 16.515 37.774 34.527 1.00 46.37 C
ATOM 209 O ASP A 138 15.704 38.564 34.947 1.00 45.11 O
ATOM 210 CB ASP A 138 16.249 35.931 36.174 1.00 58.56 C
ATOM 211 CG ASP A 138 14.551 35.422 36.525 0.00 27.18 C
ATOM 212 OD1 ASP A 138 14.174 34.275 36.165 0.00 27.18 O
ATOM 213 OD2 ASP A 138 13.773 36.235 37.082 0.00 27.18 O
ATOM 214 N ASP A 139 17.692 38.042 33.967 1.00 47.83 N
ATOM 215 CA ASP A 139 18.036 39.452 33.855 1.00 48.21 C
ATOM 216 C ASP A 139 17.981 39.832 32.377 1.00 44.90 C
ATOM 217 O ASP A 139 18.711 40.782 32.038 1.00 46.82 O
ATOM 218 CB ASP A 139 19.266 39.981 34.547 1.00 63.50 C
ATOM 219 CG ASP A 139 20.196 38.861 34.969 1.00 65.14 C
ATOM 220 OD1 ASP A 139 20.797 38.271 34.063 1.00 69.59 O
ATOM 221 OD2 ASP A 139 20.264 38.631 36.185 1.00 56.99 O
ATOM 222 N ALA A 140 17.141 39.123 31.588 1.00 35.51 N
ATOM 223 CA ALA A 140 17.128 39.654 30.167 1.00 33.37 C
ATOM 224 C ALA A 140 16.152 40.797 30.148 1.00 29.22 C
ATOM 225 O ALA A 140 14.961 40.676 29.731 1.00 28.56 O
ATOM 226 CB ALA A 140 16.553 38.540 29.289 1.00 30.39 C
ATOM 227 N ASN A 141 16.517 41.994 30.622 1.00 29.97 N
ATOM 228 CA ASN A 141 15.581 43.085 30.732 1.00 30.12 C
ATOM 229 C ASN A 141 15.221 43.641 29.300 1.00 24.22 C
ATOM 230 O ASN A 141 14.013 43.975 29.236 1.00 31.05 O
ATOM 231 CB ASN A 141 16.330 44.259 31.407 1.00 37.38 C
ATOM 232 CG ASN A 141 16.706 43.864 32.830 1.00 58.73 C
ATOM 233 OD1 ASN A 141 15.788 43.782 33.649 1.00 48.24 O

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ATOM   234  ND2 ASN A 141     18.008  43.643  33.006  1.00 57.88           N
ATOM   235  N   ASN A 142     16.216  43.572  28.421  1.00 32.80           N
ATOM   236  CA  ASN A 142     15.797  44.049  27.087  1.00 27.16           C
ATOM   237  C   ASN A 142     14.791  43.063  26.472  1.00 25.25           C
ATOM   238  O   ASN A 142     13.778  43.555  25.867  1.00 26.68           O
ATOM   239  CB  ASN A 142     16.939  44.271  26.146  1.00 32.32           C
ATOM   240  CG  ASN A 142     17.647  45.608  26.355  1.00 58.15           C
ATOM   241  OD1 ASN A 142     18.860  45.694  26.097  1.00 61.45           O
ATOM   242  ND2 ASN A 142     16.938  46.632  26.824  1.00 61.87           N
ATOM   243  N   ALA A 143     15.051  41.760  26.595  1.00 23.56           N
ATOM   244  CA  ALA A 143     14.043  40.852  25.997  1.00 25.35           C
ATOM   245  C   ALA A 143     12.672  40.992  26.542  1.00 24.18           C
ATOM   246  O   ALA A 143     11.602  40.992  25.893  1.00 22.84           O
ATOM   247  CB  ALA A 143     14.437  39.381  26.220  1.00 22.46           C
ATOM   248  N   LYS A 144     12.502  41.187  27.921  1.00 21.61           N
ATOM   249  CA  LYS A 144     11.244  41.402  28.521  1.00 20.65           C
ATOM   250  C   LYS A 144     10.671  42.724  28.035  1.00 19.70           C
ATOM   251  O   LYS A 144      9.482  42.704  27.781  1.00 24.51           O
ATOM   252  CB  LYS A 144     11.362  41.380  30.080  1.00 28.93           C
ATOM   253  CG  LYS A 144     11.844  39.995  30.576  1.00 26.32           C
ATOM   254  CD  LYS A 144     12.204  40.227  32.081  1.00 31.73           C
ATOM   255  CE  LYS A 144     13.013  39.015  32.563  1.00 48.57           C
ATOM   256  NZ  LYS A 144     12.006  37.966  32.970  1.00 44.07           N
ATOM   257  N   ALA A 145     11.519  43.763  27.883  1.00 22.86           N
ATOM   258  CA  ALA A 145     10.873  45.027  27.376  1.00 24.48           C
ATOM   259  C   ALA A 145     10.440  44.881  25.892  1.00 21.02           C
ATOM   260  O   ALA A 145      9.289  45.361  25.646  1.00 21.56           O
ATOM   261  CB  ALA A 145     11.954  46.092  27.435  1.00 24.03           C
ATOM   262  N   VAL A 146     11.195  44.081  25.205  1.00 22.42           N
ATOM   263  CA  VAL A 146     10.683  43.860  23.785  1.00 20.82           C
ATOM   264  C   VAL A 146      9.364  43.160  23.740  1.00 19.53           C
ATOM   265  O   VAL A 146      8.396  43.570  23.091  1.00 21.74           O
ATOM   266  CB  VAL A 146     11.726  43.079  22.969  1.00 22.25           C
ATOM   267  CG1 VAL A 146     11.106  42.475  21.692  1.00 23.53           C
ATOM   268  CG2 VAL A 146     12.889  44.018  22.740  1.00 22.40           C
ATOM   269  N   VAL A 147      9.239  42.070  24.565  1.00 19.41           N
ATOM   270  CA  VAL A 147      7.957  41.314  24.518  1.00 19.37           C
ATOM   271  C   VAL A 147      6.838  42.199  25.053  1.00 21.11           C
ATOM   272  O   VAL A 147      5.742  42.218  24.524  1.00 22.13           O
ATOM   273  CB  VAL A 147      8.261  40.138  25.599  1.00 23.01           C
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ATOM  274  CG1 VAL A 147      7.175  39.622  26.405  1.00 36.11      C
ATOM  275  CG2 VAL A 147      8.919  39.135  24.597  1.00 33.30      C
ATOM  276  N   LYS A 148      7.074  42.915  26.186  1.00 19.30      N
ATOM  277  CA  LYS A 148      5.965  43.779  26.680  1.00 21.11      C
ATOM  278  C   LYS A 148      5.557  44.921  25.703  1.00 20.10      C
ATOM  279  O   LYS A 148      4.356  45.113  25.577  1.00 23.49      O
ATOM  280  CB  LYS A 148      6.519  44.432  27.966  1.00 26.75      C
ATOM  281  CG  LYS A 148      6.576  43.380  29.078  1.00 28.35      C
ATOM  282  CD  LYS A 148      6.786  44.050  30.392  1.00 30.73      C
ATOM  283  CE  LYS A 148      7.984  44.914  30.530  1.00 48.22      C
ATOM  284  NZ  LYS A 148      8.157  45.443  31.942  1.00 46.26      N
ATOM  285  N   THR A 149      6.510  45.383  24.915  1.00 22.89      N
ATOM  286  CA  THR A 149      6.185  46.446  23.968  1.00 24.65      C
ATOM  287  C   THR A 149      5.451  45.863  22.786  1.00 21.98      C
ATOM  288  O   THR A 149      4.446  46.357  22.351  1.00 22.98      O
ATOM  289  CB  THR A 149      7.486  47.002  23.362  1.00 29.44      C
ATOM  290  OG1 THR A 149      8.176  47.740  24.406  1.00 27.47      O
ATOM  291  CG2 THR A 149      7.132  47.985  22.234  1.00 25.81      C
ATOM  292  N   PHE A 150      5.840  44.643  22.350  1.00 20.37      N
ATOM  293  CA  PHE A 150      5.029  43.981  21.297  1.00 20.95      C
ATOM  294  C   PHE A 150      3.639  43.743  21.813  1.00 21.53      C
ATOM  295  O   PHE A 150      2.635  43.979  21.168  1.00 22.27      O
ATOM  296  CB  PHE A 150      5.655  42.615  20.805  1.00 19.63      C
ATOM  297  CG  PHE A 150      6.573  42.857  19.630  1.00 19.52      C
ATOM  298  CD1 PHE A 150      7.777  43.521  19.819  1.00 23.32      C
ATOM  299  CD2 PHE A 150      6.215  42.274  18.434  1.00 22.00      C
ATOM  300  CE1 PHE A 150      8.645  43.659  18.717  1.00 24.62      C
ATOM  301  CE2 PHE A 150      7.101  42.466  17.310  1.00 25.97      C
ATOM  302  CZ  PHE A 150      8.286  43.138  17.494  1.00 26.51      C
ATOM  303  N   HIS A 151      3.490  43.159  23.064  1.00 19.53      N
ATOM  304  CA  HIS A 151      2.124  42.897  23.515  1.00 20.47      C
ATOM  305  C   HIS A 151      1.264  44.156  23.688  1.00 18.01      C
ATOM  306  O   HIS A 151      0.095  44.036  23.367  1.00 20.92      O
ATOM  307  CB  HIS A 151      2.332  42.200  24.888  1.00 20.82      C
ATOM  308  CG  HIS A 151      2.929  40.811  24.743  1.00 19.15      C
ATOM  309  ND1 HIS A 151      3.427  40.314  25.929  1.00 24.25      N
ATOM  310  CD2 HIS A 151      3.109  39.945  23.781  1.00 21.66      C
ATOM  311  CE1 HIS A 151      3.822  39.078  25.667  1.00 23.06      C
ATOM  312  NE2 HIS A 151      3.720  38.801  24.348  1.00 23.88      N
ATOM  313  N   GLU A 152      1.801  45.274  24.157  1.00 21.42      N
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ATOM   314  CA  GLU A 152      0.991  46.475  24.410  1.00 21.40      C
ATOM   315  C   GLU A 152      0.649  47.098  23.021  1.00 25.13      C
ATOM   316  O   GLU A 152     -0.536  47.381  22.669  1.00 26.67      O
ATOM   317  CB  GLU A 152      1.893  47.394  25.196  1.00 24.42      C
ATOM   318  CG  GLU A 152      1.128  48.749  25.464  1.00 34.65      C
ATOM   319  CD  GLU A 152      1.913  49.423  26.598  1.00 37.56      C
ATOM   320  OE1 GLU A 152      3.043  49.857  26.265  1.00 64.84      O
ATOM   321  OE2 GLU A 152      1.398  49.543  27.716  1.00 55.50      O
ATOM   322  N   THR A 153      1.681  47.044  22.171  1.00 22.11      N
ATOM   323  CA  THR A 153      1.552  47.629  20.833  1.00 23.71      C
ATOM   324  C   THR A 153      0.537  46.966  19.962  1.00 25.46      C
ATOM   325  O   THR A 153     -0.256  47.627  19.283  1.00 27.48      O
ATOM   326  CB  THR A 153      2.872  47.940  20.170  1.00 22.71      C
ATOM   327  OG1 THR A 153      3.720  48.793  20.993  1.00 25.38      O
ATOM   328  CG2 THR A 153      2.701  48.567  18.771  1.00 25.64      C
ATOM   329  N   LEU A 154      0.586  45.635  19.885  1.00 24.29      N
ATOM   330  CA  LEU A 154     -0.281  44.863  19.040  1.00 24.20      C
ATOM   331  C   LEU A 154     -1.521  44.276  19.702  1.00 25.11      C
ATOM   332  O   LEU A 154     -2.242  43.542  19.024  1.00 31.73      O
ATOM   333  CB  LEU A 154      0.471  43.693  18.386  1.00 23.92      C
ATOM   334  CG  LEU A 154      1.721  44.169  17.720  1.00 23.37      C
ATOM   335  CD1 LEU A 154      2.494  42.937  17.204  1.00 28.56      C
ATOM   336  CD2 LEU A 154      1.402  45.022  16.462  1.00 27.60      C
ATOM   337  N   ASP A 155     -1.645  44.486  20.999  1.00 23.85      N
ATOM   338  CA  ASP A 155     -2.803  43.999  21.759  1.00 26.72      C
ATOM   339  C   ASP A 155     -2.836  42.476  21.723  1.00 31.14      C
ATOM   340  O   ASP A 155     -3.738  41.901  21.132  1.00 30.16      O
ATOM   341  CB  ASP A 155     -4.086  44.605  21.165  1.00 29.88      C
ATOM   342  CG  ASP A 155     -5.284  44.202  22.046  1.00 62.82      C
ATOM   343  OD1 ASP A 155     -6.416  44.204  21.488  1.00 39.28      O
ATOM   344  OD2 ASP A 155     -5.071  43.903  23.251  1.00 34.83      O
ATOM   345  N   CYS A 156     -1.733  41.821  22.173  1.00 25.43      N
ATOM   346  CA  CYS A 156     -1.687  40.326  22.076  1.00 25.93      C
ATOM   347  C   CYS A 156     -0.778  39.856  23.222  1.00 26.10      C
ATOM   348  O   CYS A 156     -0.272  40.683  24.015  1.00 26.38      O
ATOM   349  CB  CYS A 156     -1.081  39.823  20.712  1.00 27.65      C
ATOM   350  SG  CYS A 156      0.624  40.431  20.467  1.00 24.42      S
ATOM   351  N   CYS A 157     -0.841  38.498  23.386  1.00 26.16      N
ATOM   352  CA  CYS A 157     -0.019  37.979  24.534  1.00 27.59      C
ATOM   353  C   CYS A 157      0.313  36.537  24.102  1.00 24.85      C
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ATOM   354  O   CYS A 157     -0.512  35.605  23.948  1.00 27.75           O
ATOM   355  CB  CYS A 157     -0.963  37.941  25.755  1.00 33.15           C
ATOM   356  SG  CYS A 157     -0.198  37.066  27.122  1.00 32.82           S
ATOM   357  N   GLY A 158      1.574  36.270  23.768  1.00 23.57           N
ATOM   358  CA  GLY A 158      1.986  34.979  23.277  1.00 23.42           C
ATOM   359  C   GLY A 158      1.869  34.744  21.807  1.00 25.49           C
ATOM   360  O   GLY A 158      1.349  35.496  20.998  1.00 31.29           O
ATOM   361  N   SER A 159      2.414  33.581  21.339  1.00 23.29           N
ATOM   362  CA  SER A 159      2.359  33.220  19.919  1.00 24.98           C
ATOM   363  C   SER A 159      1.881  31.744  19.739  1.00 29.71           C
ATOM   364  O   SER A 159      2.048  30.954  20.649  1.00 28.92           O
ATOM   365  CB  SER A 159      3.592  33.368  19.048  1.00 38.22           C
ATOM   366  OG  SER A 159      4.674  32.685  19.718  1.00 33.40           O
ATOM   367  N   SER A 160      1.533  31.533  18.480  1.00 29.16           N
ATOM   368  CA  SER A 160      1.006  30.167  18.156  1.00 31.53           C
ATOM   369  C   SER A 160      2.124  29.147  18.136  1.00 30.90           C
ATOM   370  O   SER A 160      1.872  27.967  18.164  1.00 41.00           O
ATOM   371  CB  SER A 160      0.219  30.309  16.840  1.00 29.50           C
ATOM   372  OG  SER A 160      0.984  30.787  15.768  1.00 39.90           O
ATOM   373  N   THR A 161      3.375  29.476  17.923  1.00 29.06           N
ATOM   374  CA  THR A 161      4.554  28.637  17.920  1.00 32.53           C
ATOM   375  C   THR A 161      4.973  28.367  19.379  1.00 28.69           C
ATOM   376  O   THR A 161      5.909  27.498  19.535  1.00 30.18           O
ATOM   377  CB  THR A 161      5.743  29.318  17.183  1.00 33.24           C
ATOM   378  OG1 THR A 161      5.878  30.621  17.769  1.00 30.51           O
ATOM   379  CG2 THR A 161      5.579  29.437  15.695  1.00 30.20           C
ATOM   380  N   LEU A 162      4.410  29.011  20.350  1.00 25.65           N
ATOM   381  CA  LEU A 162      4.843  28.891  21.737  1.00 27.51           C
ATOM   382  C   LEU A 162      3.727  28.800  22.731  1.00 26.68           C
ATOM   383  O   LEU A 162      3.784  29.279  23.870  1.00 25.46           O
ATOM   384  CB  LEU A 162      5.751  30.132  21.999  1.00 23.77           C
ATOM   385  CG  LEU A 162      7.083  30.158  21.261  1.00 24.78           C
ATOM   386  CD1 LEU A 162      7.772  31.517  21.579  1.00 24.05           C
ATOM   387  CD2 LEU A 162      8.035  29.027  21.780  1.00 25.38           C
ATOM   388  N   THR A 163      2.648  28.102  22.281  1.00 33.72           N
ATOM   389  CA  THR A 163      1.426  27.933  23.021  1.00 34.30           C
ATOM   390  C   THR A 163      1.605  27.355  24.405  1.00 32.24           C
ATOM   391  O   THR A 163      1.038  27.846  25.352  1.00 37.92           O
ATOM   392  CB  THR A 163      0.304  27.257  22.238  1.00 50.44           C
ATOM   393  OG1 THR A 163      0.579  25.851  22.212  1.00 41.17           O
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ATOM   394  CG2 THR A 163      0.359  27.673  20.762  1.00 37.36      C
ATOM   395  N   ALA A 164      2.575  26.400  24.460  1.00 32.95      N
ATOM   396  CA  ALA A 164      2.860  25.919  25.797  1.00 33.55      C
ATOM   397  C   ALA A 164      3.585  26.806  26.718  1.00 35.24      C
ATOM   398  O   ALA A 164      3.697  26.461  27.906  1.00 32.41      O
ATOM   399  CB  ALA A 164      3.315  24.481  25.766  1.00 39.49      C
ATOM   400  N   LEU A 165      4.091  27.987  26.277  1.00 33.05      N
ATOM   401  CA  LEU A 165      4.713  28.934  27.170  1.00 31.37      C
ATOM   402  C   LEU A 165      3.847  30.044  27.639  1.00 28.59      C
ATOM   403  O   LEU A 165      4.160  30.749  28.603  1.00 31.69      O
ATOM   404  CB  LEU A 165      5.792  29.699  26.290  1.00 28.17      C
ATOM   405  CG  LEU A 165      7.222  29.534  26.511  1.00 27.01      C
ATOM   406  CD1 LEU A 165      8.004  30.520  25.746  1.00 23.83      C
ATOM   407  CD2 LEU A 165      7.826  28.591  27.467  1.00 27.70      C
ATOM   408  N   THR A 166      2.561  30.087  27.075  1.00 31.94      N
ATOM   409  CA  THR A 166      1.689  31.171  27.588  1.00 40.87      C
ATOM   410  C   THR A 166      1.516  31.275  29.073  1.00 42.39      C
ATOM   411  O   THR A 166      1.563  32.362  29.701  1.00 38.40      O
ATOM   412  CB  THR A 166      0.448  31.306  26.680  1.00 36.13      C
ATOM   413  OG1 THR A 166      0.804  31.293  25.311  1.00 36.62      O
ATOM   414  CG2 THR A 166     -0.435  32.499  26.978  1.00 44.79      C
ATOM   415  N   THR A 167      1.399  30.168  29.837  1.00 42.15      N
ATOM   416  CA  THR A 167      1.302  30.193  31.270  1.00 40.32      C
ATOM   417  C   THR A 167      2.376  30.942  32.017  1.00 36.81      C
ATOM   418  O   THR A 167      2.358  31.776  32.931  1.00 37.99      O
ATOM   419  CB  THR A 167      1.201  28.762  31.883  1.00 61.23      C
ATOM   420  OG1 THR A 167      0.557  27.876  30.964  1.00 67.37      O
ATOM   421  CG2 THR A 167      0.376  28.868  33.146  1.00 53.56      C
ATOM   422  N   SER A 168      3.590  30.607  31.494  1.00 35.37      N
ATOM   423  CA  SER A 168      4.825  31.188  31.902  1.00 31.87      C
ATOM   424  C   SER A 168      4.873  32.668  31.486  1.00 30.23      C
ATOM   425  O   SER A 168      5.226  33.518  32.274  1.00 34.03      O
ATOM   426  CB  SER A 168      5.911  30.387  31.166  1.00 40.72      C
ATOM   427  OG  SER A 168      7.074  30.623  31.911  1.00 41.48      O
ATOM   428  N   VAL A 169      4.409  32.950  30.280  1.00 36.11      N
ATOM   429  CA  VAL A 169      4.454  34.354  29.866  1.00 26.69      C
ATOM   430  C   VAL A 169      3.607  35.222  30.816  1.00 32.76      C
ATOM   431  O   VAL A 169      3.926  36.296  31.349  1.00 36.23      O
ATOM   432  CB  VAL A 169      4.106  34.440  28.374  1.00 30.41      C
ATOM   433  CG1 VAL A 169      4.076  35.927  27.930  1.00 25.68      C
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ATOM   434  CG2 VAL A 169      5.156  33.698  27.574  1.00 33.52      C
ATOM   435  N   LEU A 170      2.443  34.712  31.170  1.00 35.41      N
ATOM   436  CA  LEU A 170      1.519  35.415  32.068  1.00 40.24      C
ATOM   437  C   LEU A 170      2.089  35.585  33.450  1.00 36.07      C
ATOM   438  O   LEU A 170      2.021  36.646  34.047  1.00 37.93      O
ATOM   439  CB  LEU A 170      0.287  34.558  32.121  1.00 34.96      C
ATOM   440  CG  LEU A 170     -0.755  34.811  31.021  1.00 38.88      C
ATOM   441  CD1 LEU A 170     -2.050  34.225  31.647  1.00 42.60      C
ATOM   442  CD2 LEU A 170     -1.038  36.249  30.722  1.00 45.47      C
ATOM   443  N   LYS A 171      2.675  34.477  33.945  1.00 40.34      N
ATOM   444  CA  LYS A 171      3.223  34.540  35.317  1.00 45.51      C
ATOM   445  C   LYS A 171      4.338  35.539  35.439  1.00 44.28      C
ATOM   446  O   LYS A 171      4.525  36.108  36.536  1.00 41.55      O
ATOM   447  CB  LYS A 171      3.821  33.166  35.694  1.00 69.69      C
ATOM   448  CG  LYS A 171      4.311  33.137  37.140  1.00 79.83      C
ATOM   449  CD  LYS A 171      3.175  32.835  38.111  1.00 95.86      C
ATOM   450  CE  LYS A 171      3.497  33.257  39.535  1.00 94.11      C
ATOM   451  NZ  LYS A 171      2.737  32.464  40.542  1.00 99.00      N
ATOM   452  N   ASN A 172      5.103  35.691  34.317  1.00 33.49      N
ATOM   453  CA  ASN A 172      6.157  36.717  34.392  1.00 32.00      C
ATOM   454  C   ASN A 172      5.665  38.134  34.144  1.00 32.19      C
ATOM   455  O   ASN A 172      6.466  39.064  33.993  1.00 34.93      O
ATOM   456  CB  ASN A 172      7.198  36.377  33.271  1.00 38.64      C
ATOM   457  CG  ASN A 172      8.169  35.294  33.642  1.00 47.08      C
ATOM   458  OD1 ASN A 172      9.214  35.622  34.197  1.00 50.53      O
ATOM   459  ND2 ASN A 172      7.916  34.038  33.334  1.00 37.12      N
ATOM   460  N   ASN A 173      4.355  38.407  34.211  1.00 31.88      N
ATOM   461  CA  ASN A 173      3.768  39.741  34.092  1.00 28.39      C
ATOM   462  C   ASN A 173      4.219  40.419  32.746  1.00 29.05      C
ATOM   463  O   ASN A 173      4.317  41.667  32.724  1.00 32.53      O
ATOM   464  CB  ASN A 173      4.000  40.649  35.250  1.00 36.22      C
ATOM   465  CG  ASN A 173      3.422  39.922  36.518  1.00 34.79      C
ATOM   466  OD1 ASN A 173      2.550  39.072  36.379  1.00 40.09      O
ATOM   467  ND2 ASN A 173      4.051  40.320  37.608  1.00 54.78      N
ATOM   468  N   LEU A 174      4.263  39.558  31.711  1.00 31.35      N
ATOM   469  CA  LEU A 174      4.666  40.153  30.400  1.00 26.80      C
ATOM   470  C   LEU A 174      3.456  40.549  29.567  1.00 30.61      C
ATOM   471  O   LEU A 174      3.735  41.127  28.467  1.00 26.30      O
ATOM   472  CB  LEU A 174      5.493  39.102  29.554  1.00 27.25      C
ATOM   473  CG  LEU A 174      6.789  38.710  30.323  1.00 29.12      C
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ATOM   474  CD1 LEU A 174      7.407  37.492  29.580  1.00 28.38           C
ATOM   475  CD2 LEU A 174      7.781  39.902  30.305  1.00 30.60           C
ATOM   476  N   CYS A 175      2.239  40.256  30.018  1.00 30.48           N
ATOM   477  CA  CYS A 175      1.099  40.710  29.225  1.00 30.38           C
ATOM   478  C   CYS A 175      0.355  41.866  29.885  1.00 31.31           C
ATOM   479  O   CYS A 175      0.399  41.963  31.124  1.00 28.50           O
ATOM   480  CB  CYS A 175      0.199  39.520  28.920  1.00 33.34           C
ATOM   481  SG  CYS A 175      1.156  38.385  27.801  1.00 34.59           S
ATOM   482  N   PRO A 176     -0.204  42.749  29.139  1.00 26.97           N
ATOM   483  CA  PRO A 176     -1.053  43.853  29.594  1.00 29.17           C
ATOM   484  C   PRO A 176     -2.084  43.390  30.647  1.00 27.85           C
ATOM   485  O   PRO A 176     -2.604  42.299  30.578  1.00 29.34           O
ATOM   486  CB  PRO A 176     -1.827  44.329  28.344  1.00 31.13           C
ATOM   487  CG  PRO A 176     -0.663  44.246  27.400  1.00 30.18           C
ATOM   488  CD  PRO A 176     -0.193  42.805  27.620  1.00 27.08           C
ATOM   489  N   SER A 177     -2.235  44.409  31.562  1.00 30.71           N
ATOM   490  CA  SER A 177     -3.167  44.149  32.688  1.00 34.85           C
ATOM   491  C   SER A 177     -4.474  43.650  32.148  1.00 38.23           C
ATOM   492  O   SER A 177     -4.906  44.246  31.131  1.00 44.22           O
ATOM   493  CB  SER A 177     -3.430  45.468  33.436  1.00 36.64           C
ATOM   494  OG  SER A 177     -2.230  46.130  33.766  1.00 47.00           O
ATOM   495  N   GLY A 178     -5.092  42.630  32.719  1.00 42.86           N
ATOM   496  CA  GLY A 178     -6.328  42.131  32.167  1.00 43.31           C
ATOM   497  C   GLY A 178     -6.163  40.767  31.552  1.00 49.40           C
ATOM   498  O   GLY A 178     -7.083  39.958  31.631  1.00 50.03           O
ATOM   499  N   SER A 179     -5.002  40.522  30.904  1.00 40.11           N
ATOM   500  CA  SER A 179     -4.740  39.228  30.344  1.00 38.50           C
ATOM   501  C   SER A 179     -4.702  38.131  31.408  1.00 42.66           C
ATOM   502  O   SER A 179     -4.184  38.293  32.525  1.00 38.05           O
ATOM   503  CB  SER A 179     -3.244  39.353  29.832  1.00 34.49           C
ATOM   504  OG  SER A 179     -3.426  40.086  28.568  1.00 45.66           O
ATOM   505  N   ASN A 180     -5.255  36.994  31.049  1.00 36.63           N
ATOM   506  CA  ASN A 180     -5.357  35.816  31.870  1.00 38.62           C
ATOM   507  C   ASN A 180     -5.683  34.707  30.858  1.00 39.82           C
ATOM   508  O   ASN A 180     -5.910  35.039  29.670  1.00 42.39           O
ATOM   509  CB  ASN A 180     -6.475  35.962  32.911  1.00 44.98           C
ATOM   510  CG  ASN A 180     -7.734  36.498  32.242  1.00 54.54           C
ATOM   511  OD1 ASN A 180     -7.928  37.720  32.228  1.00 48.38           O
ATOM   512  ND2 ASN A 180     -8.540  35.625  31.660  1.00 40.36           N
ATOM   513  N   ILE A 181     -5.536  33.473  31.246  1.00 40.38           N
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ATOM   514  CA  ILE A 181     -5.619  32.322  30.350  1.00 33.89           C
ATOM   515  C   ILE A 181     -6.927  32.320  29.578  1.00 39.65           C
ATOM   516  O   ILE A 181     -6.906  32.314  28.339  1.00 40.11           O
ATOM   517  CB  ILE A 181     -5.290  31.027  31.097  1.00 42.70           C
ATOM   518  CG1 ILE A 181     -5.682  29.801  30.268  1.00 36.84           C
ATOM   519  CG2 ILE A 181     -5.990  30.883  32.438  1.00 55.03           C
ATOM   520  CD1 ILE A 181     -5.037  28.508  30.724  1.00 68.03           C
ATOM   521  N   ILE A 182     -8.052  32.516  30.283  1.00 30.27           N
ATOM   522  CA  ILE A 182     -9.314  32.528  29.550  1.00 33.50           C
ATOM   523  C   ILE A 182     -9.455  33.647  28.558  1.00 32.77           C
ATOM   524  O   ILE A 182     -9.685  33.380  27.358  1.00 32.51           O
ATOM   525  CB  ILE A 182     -10.567  32.386  30.435  1.00 34.82           C
ATOM   526  CG1 ILE A 182     -10.600  30.970  31.022  1.00 33.43           C
ATOM   527  CG2 ILE A 182     -11.790  32.405  29.474  1.00 38.83           C
ATOM   528  CD1 ILE A 182     -11.987  30.860  31.646  1.00 40.57           C
ATOM   529  N   SER A 183     -9.278  34.894  28.997  1.00 32.05           N
ATOM   530  CA  SER A 183     -9.493  35.999  28.043  1.00 29.75           C
ATOM   531  C   SER A 183     -8.547  35.850  26.870  1.00 29.63           C
ATOM   532  O   SER A 183     -8.841  36.216  25.711  1.00 30.58           O
ATOM   533  CB  SER A 183     -9.198  37.356  28.688  1.00 40.54           C
ATOM   534  OG  SER A 183     -7.868  37.360  29.219  1.00 51.48           O
ATOM   535  N   ASN A 184     -7.323  35.333  27.167  1.00 29.71           N
ATOM   536  CA  ASN A 184     -6.380  35.237  26.066  1.00 29.17           C
ATOM   537  C   ASN A 184     -6.778  34.178  25.058  1.00 30.40           C
ATOM   538  O   ASN A 184     -6.425  34.318  23.902  1.00 30.51           O
ATOM   539  CB  ASN A 184     -4.964  35.149  26.618  1.00 33.28           C
ATOM   540  CG  ASN A 184     -3.919  35.618  25.611  1.00 40.11           C
ATOM   541  OD1 ASN A 184     -3.908  36.769  25.141  1.00 39.35           O
ATOM   542  ND2 ASN A 184     -3.047  34.682  25.259  1.00 37.40           N
ATOM   543  N   LEU A 185     -7.599  33.181  25.411  1.00 28.40           N
ATOM   544  CA  LEU A 185     -8.001  32.193  24.408  1.00 28.04           C
ATOM   545  C   LEU A 185     -8.978  32.805  23.402  1.00 25.68           C
ATOM   546  O   LEU A 185     -9.124  32.206  22.298  1.00 29.24           O
ATOM   547  CB  LEU A 185     -8.796  31.070  25.161  1.00 32.33           C
ATOM   548  CG  LEU A 185     -7.869  30.239  26.084  1.00 37.66           C
ATOM   549  CD1 LEU A 185     -8.768  29.246  26.840  1.00 38.27           C
ATOM   550  CD2 LEU A 185     -6.856  29.476  25.205  1.00 30.37           C
ATOM   551  N   PHE A 186     -9.573  33.938  23.697  1.00 24.99           N
ATOM   552  CA  PHE A 186     -10.529  34.513  22.702  1.00 29.36           C
ATOM   553  C   PHE A 186     -9.895  35.675  21.914  1.00 28.13           C
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ATOM   554  O   PHE A 186    -10.571  36.481  21.285  1.00 31.04       O
ATOM   555  CB  PHE A 186    -11.728  35.132  23.493  1.00 29.08       C
ATOM   556  CG  PHE A 186    -12.625  34.081  24.099  1.00 32.29       C
ATOM   557  CD1 PHE A 186    -12.436  33.599  25.337  1.00 30.56       C
ATOM   558  CD2 PHE A 186    -13.703  33.693  23.334  1.00 29.12       C
ATOM   559  CE1 PHE A 186    -13.292  32.589  25.881  1.00 34.73       C
ATOM   560  CE2 PHE A 186    -14.592  32.742  23.884  1.00 27.34       C
ATOM   561  CZ  PHE A 186    -14.365  32.198  25.091  1.00 30.52       C
ATOM   562  N   LYS A 187     -8.559  35.758  21.958  1.00 29.75       N
ATOM   563  CA  LYS A 187     -7.850  36.828  21.190  1.00 30.16       C
ATOM   564  C   LYS A 187     -6.870  36.196  20.212  1.00 27.54       C
ATOM   565  O   LYS A 187     -6.369  35.096  20.451  1.00 29.14       O
ATOM   566  CB  LYS A 187     -6.950  37.552  22.237  1.00 31.45       C
ATOM   567  CG  LYS A 187     -7.789  38.660  22.850  1.00 44.24       C
ATOM   568  CD  LYS A 187     -7.042  39.413  23.917  1.00 50.91       C
ATOM   569  CE  LYS A 187     -6.068  40.421  23.290  1.00 41.03       C
ATOM   570  NZ  LYS A 187     -5.788  41.434  24.348  1.00 42.16       N
ATOM   571  N   GLU A 188     -6.613  36.918  19.077  1.00 26.33       N
ATOM   572  CA  GLU A 188     -5.605  36.497  18.138  1.00 25.15       C
ATOM   573  C   GLU A 188     -4.173  36.621  18.820  1.00 20.95       C
ATOM   574  O   GLU A 188     -4.023  37.452  19.696  1.00 25.60       O
ATOM   575  CB  GLU A 188     -5.534  37.536  17.003  1.00 30.19       C
ATOM   576  CG  GLU A 188     -6.917  37.630  16.345  1.00 39.33       C
ATOM   577  CD  GLU A 188     -6.924  38.451  15.077  1.00 62.86       C
ATOM   578  OE1 GLU A 188     -6.644  39.671  15.116  1.00 57.85       O
ATOM   579  OE2 GLU A 188     -7.234  37.823  14.039  1.00 69.92       O
ATOM   580  N   ASP A 189     -3.388  35.694  18.396  1.00 25.72       N
ATOM   581  CA  ASP A 189     -2.034  35.624  18.977  1.00 22.36       C
ATOM   582  C   ASP A 189     -1.163  36.692  18.313  1.00 22.67       C
ATOM   583  O   ASP A 189     -1.535  37.333  17.268  1.00 23.90       O
ATOM   584  CB  ASP A 189     -1.384  34.229  18.800  1.00 28.19       C
ATOM   585  CG  ASP A 189     -0.828  34.102  17.432  1.00 23.97       C
ATOM   586  OD1 ASP A 189      0.444  33.906  17.301  1.00 27.23       O
ATOM   587  OD2 ASP A 189     -1.280  34.345  16.311  1.00 35.18       O
ATOM   588  N   CYS A 190      0.069  36.801  18.812  1.00 22.63       N
ATOM   589  CA  CYS A 190      0.962  37.863  18.218  1.00 21.85       C
ATOM   590  C   CYS A 190      1.355  37.538  16.787  1.00 21.58       C
ATOM   591  O   CYS A 190      1.567  38.595  16.082  1.00 24.53       O
ATOM   592  CB  CYS A 190      2.127  38.130  19.098  1.00 23.37       C
ATOM   593  SG  CYS A 190      1.734  38.715  20.750  1.00 27.18       S
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ATOM   594  N   HIS A 191      1.500  36.320  16.296  1.00 22.69           N
ATOM   595  CA  HIS A 191      1.879  36.206  14.899  1.00 21.61           C
ATOM   596  C   HIS A 191      0.835  36.792  14.024  1.00 21.85           C
ATOM   597  O   HIS A 191      1.141  37.323  12.894  1.00 24.99           O
ATOM   598  CB  HIS A 191      2.238  34.743  14.596  1.00 26.50           C
ATOM   599  CG  HIS A 191      3.562  34.373  15.239  1.00 27.06           C
ATOM   600  ND1 HIS A 191      4.111  33.174  14.859  1.00 29.05           N
ATOM   601  CD2 HIS A 191      4.375  34.972  16.080  1.00 27.99           C
ATOM   602  CE1 HIS A 191      5.281  33.116  15.522  1.00 25.16           C
ATOM   603  NE2 HIS A 191      5.435  34.101  16.356  1.00 26.21           N
ATOM   604  N   GLN A 192     -0.438  36.467  14.384  1.00 26.34           N
ATOM   605  CA  GLN A 192     -1.522  36.979  13.515  1.00 26.48           C
ATOM   606  C   GLN A 192     -1.503  38.492  13.540  1.00 26.16           C
ATOM   607  O   GLN A 192     -1.716  39.137  12.488  1.00 25.33           O
ATOM   608  CB  GLN A 192     -2.876  36.550  14.173  1.00 25.24           C
ATOM   609  CG  GLN A 192     -3.942  37.057  13.181  1.00 36.75           C
ATOM   610  CD  GLN A 192     -3.936  36.521  11.790  1.00 44.62           C
ATOM   611  OE1 GLN A 192     -4.135  35.362  11.492  1.00 47.15           O
ATOM   612  NE2 GLN A 192     -3.751  37.335  10.736  1.00 34.56           N
ATOM   613  N   LYS A 193     -1.329  39.160  14.690  1.00 23.16           N
ATOM   614  CA  LYS A 193     -1.206  40.598  14.776  1.00 21.55           C
ATOM   615  C   LYS A 193     -0.027  41.129  13.979  1.00 24.18           C
ATOM   616  O   LYS A 193     -0.184  42.211  13.368  1.00 25.04           O
ATOM   617  CB  LYS A 193     -1.175  41.147  16.231  1.00 21.00           C
ATOM   618  CG  LYS A 193     -2.470  40.784  16.893  1.00 22.09           C
ATOM   619  CD  LYS A 193     -3.691  41.485  16.251  1.00 28.55           C
ATOM   620  CE  LYS A 193     -4.974  41.632  17.082  1.00 41.86           C
ATOM   621  NZ  LYS A 193     -4.886  42.624  18.158  1.00 43.09           N
ATOM   622  N   ILE A 194      1.102  40.447  13.928  1.00 20.51           N
ATOM   623  CA  ILE A 194      2.216  40.881  13.064  1.00 22.80           C
ATOM   624  C   ILE A 194      1.766  40.844  11.636  1.00 22.89           C
ATOM   625  O   ILE A 194      1.949  41.793  10.875  1.00 23.90           O
ATOM   626  CB  ILE A 194      3.443  39.973  13.316  1.00 22.37           C
ATOM   627  CG1 ILE A 194      3.906  40.423  14.719  1.00 20.93           C
ATOM   628  CG2 ILE A 194      4.504  40.098  12.156  1.00 23.35           C
ATOM   629  CD1 ILE A 194      4.909  39.440  15.373  1.00 24.02           C
ATOM   630  N   ASP A 195      1.084  39.718  11.301  1.00 25.74           N
ATOM   631  CA  ASP A 195      0.668  39.648   9.871  1.00 28.30           C
ATOM   632  C   ASP A 195     -0.329  40.794   9.595  1.00 25.05           C
ATOM   633  O   ASP A 195     -0.251  41.449   8.523  1.00 28.16           O
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ATOM   634  CB  ASP A 195     -0.152  38.352   9.678  1.00 31.28       C
ATOM   635  CG  ASP A 195      0.718  37.210   9.174  1.00 46.09       C
ATOM   636  OD1 ASP A 195      0.316  36.027   9.312  1.00 41.35       O
ATOM   637  OD2 ASP A 195      1.760  37.572   8.669  1.00 40.30       O
ATOM   638  N   ASP A 196     -1.217  41.115  10.484  1.00 25.73       N
ATOM   639  CA  ASP A 196     -2.232  42.179  10.283  1.00 27.60       C
ATOM   640  C   ASP A 196     -1.509  43.501  10.052  1.00 30.61       C
ATOM   641  O   ASP A 196     -1.968  44.397   9.310  1.00 28.90       O
ATOM   642  CB  ASP A 196     -3.208  42.318  11.472  1.00 26.94       C
ATOM   643  CG  ASP A 196     -4.136  41.119  11.526  1.00 35.93       C
ATOM   644  OD1 ASP A 196     -4.177  40.397  10.506  1.00 37.15       O
ATOM   645  OD2 ASP A 196     -4.846  40.880  12.529  1.00 39.81       O
ATOM   646  N   LEU A 197     -0.453  43.756  10.837  1.00 26.22       N
ATOM   647  CA  LEU A 197      0.333  44.981  10.641  1.00 24.82       C
ATOM   648  C   LEU A 197      0.863  45.122   9.183  1.00 22.79       C
ATOM   649  O   LEU A 197      0.751  46.207   8.598  1.00 25.32       O
ATOM   650  CB  LEU A 197      1.463  45.077  11.611  1.00 23.28       C
ATOM   651  CG  LEU A 197      2.383  46.265  11.536  1.00 24.62       C
ATOM   652  CD1 LEU A 197      1.777  47.633  11.859  1.00 28.09       C
ATOM   653  CD2 LEU A 197      3.571  45.954  12.461  1.00 27.71       C
ATOM   654  N   PHE A 198      1.461  44.123   8.667  1.00 22.04       N
ATOM   655  CA  PHE A 198      2.079  44.191   7.292  1.00 26.13       C
ATOM   656  C   PHE A 198      1.059  44.049   6.211  1.00 28.05       C
ATOM   657  O   PHE A 198      1.400  44.535   5.131  1.00 29.34       O
ATOM   658  CB  PHE A 198      3.185  43.173   7.240  1.00 25.38       C
ATOM   659  CG  PHE A 198      4.410  43.555   8.033  1.00 24.43       C
ATOM   660  CD1 PHE A 198      4.580  43.022   9.308  1.00 28.24       C
ATOM   661  CD2 PHE A 198      5.301  44.487   7.607  1.00 25.92       C
ATOM   662  CE1 PHE A 198      5.663  43.425  10.067  1.00 26.65       C
ATOM   663  CE2 PHE A 198      6.381  44.911   8.320  1.00 26.61       C
ATOM   664  CZ  PHE A 198      6.589  44.372   9.590  1.00 24.33       C
ATOM   665  N   SER A 199     -0.174  43.659   6.579  1.00 29.98       N
ATOM   666  CA  SER A 199     -1.185  43.616   5.508  1.00 32.71       C
ATOM   667  C   SER A 199     -2.109  44.784   5.575  1.00 32.16       C
ATOM   668  O   SER A 199     -3.095  44.885   4.812  1.00 37.24       O
ATOM   669  CB  SER A 199     -1.922  42.255   5.637  1.00 35.46       C
ATOM   670  OG  SER A 199     -2.765  42.483   6.739  1.00 44.29       O
ATOM   671  N   GLY A 200     -1.941  45.713   6.499  1.00 26.22       N
ATOM   672  CA  GLY A 200     -2.716  46.906   6.625  1.00 29.91       C
ATOM   673  C   GLY A 200     -4.091  46.674   7.198  1.00 38.21       C
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ATOM   674  O   GLY A 200     -5.052  47.375   6.885  1.00 43.66       O
ATOM   675  N   LYS A 201     -4.190  45.788   8.172  1.00 35.17       N
ATOM   676  CA  LYS A 201     -5.461  45.573   8.888  1.00 39.35       C
ATOM   677  C   LYS A 201     -5.348  46.318  10.202  1.00 44.71       C
ATOM   678  O   LYS A 201     -5.971  47.376  10.413  1.00 49.67       O
ATOM   679  CB  LYS A 201     -5.747  44.086   9.136  1.00 40.21       C
ATOM   680  CG  LYS A 201     -5.604  43.404   7.780  1.00 43.04       C
ATOM   681  CD  LYS A 201     -6.339  42.071   7.665  1.00 54.53       C
ATOM   682  CE  LYS A 201     -6.446  41.874   6.136  1.00 55.98       C
ATOM   683  NZ  LYS A 201     -6.339  43.249   5.533  1.00 52.57       N
ATOM   684  N   HIS A 202     -4.651  45.701  11.114  1.00 41.23       N
ATOM   685  CA  HIS A 202     -4.434  46.283  12.438  1.00 47.90       C
ATOM   686  C   HIS A 202     -4.979  47.679  12.559  1.00 53.34       C
ATOM   687  O   HIS A 202     -6.090  47.898  13.099  1.00 53.27       O
ATOM   688  CB  HIS A 202     -2.885  46.285  12.654  1.00 38.96       C
ATOM   689  CG  HIS A 202     -2.577  45.518  13.899  1.00 56.54       C
ATOM   690  ND1 HIS A 202     -3.210  45.799  15.094  1.00 65.67       N
ATOM   691  CD2 HIS A 202     -1.741  44.480  14.102  1.00 31.29       C
ATOM   692  CE1 HIS A 202     -2.753  44.973  16.037  1.00 60.49       C
ATOM   693  NE2 HIS A 202     -1.871  44.167  15.449  1.00 75.99       N
TER    694      HIS A 202
ATOM   695  N   PHE B 213     20.058  33.920  13.960  0.00 39.06       N
ATOM   696  CA  PHE B 213     18.978  34.566  14.749  1.00 38.41       C
ATOM   697  C   PHE B 213     18.659  35.842  13.948  1.00 40.74       C
ATOM   698  O   PHE B 213     19.499  36.370  13.188  1.00 42.23       O
ATOM   699  CB  PHE B 213     19.717  35.136  16.091  0.00 34.83       C
ATOM   700  CG  PHE B 213     20.197  34.465  17.321  0.00 44.80       C
ATOM   701  CD1 PHE B 213     21.533  34.182  17.521  0.00 58.13       C
ATOM   702  CD2 PHE B 213     19.319  34.146  18.350  0.00 62.44       C
ATOM   703  CE1 PHE B 213     21.983  33.580  18.677  0.00 56.87       C
ATOM   704  CE2 PHE B 213     19.751  33.535  19.518  0.00 69.83       C
ATOM   705  CZ  PHE B 213     21.091  33.243  19.683  0.00 53.63       C
ATOM   706  N   VAL B 214     17.443  36.311  14.054  1.00 28.80       N
ATOM   707  CA  VAL B 214     17.119  37.603  13.402  1.00 28.19       C
ATOM   708  C   VAL B 214     17.743  38.629  14.254  1.00 28.65       C
ATOM   709  O   VAL B 214     17.539  38.806  15.455  1.00 28.65       O
ATOM   710  CB  VAL B 214     15.592  37.799  13.483  1.00 22.91       C
ATOM   711  CG1 VAL B 214     15.158  39.177  12.869  1.00 26.83       C
ATOM   712  CG2 VAL B 214     14.962  36.737  12.578  1.00 28.94       C
ATOM   713  N   ASN B 215     18.422  39.630  13.608  1.00 29.43       N
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ATOM   714  CA  ASN B 215     19.111  40.632  14.417  1.00 28.01        C
ATOM   715  C   ASN B 215     18.250  41.899  14.531  1.00 26.65        C
ATOM   716  O   ASN B 215     17.721  42.319  13.493  1.00 27.96        O
ATOM   717  CB  ASN B 215     20.425  40.910  13.648  1.00 33.11        C
ATOM   718  CG  ASN B 215     21.123  42.071  14.253  1.00 39.12        C
ATOM   719  OD1 ASN B 215     21.817  41.841  15.248  1.00 56.16        O
ATOM   720  ND2 ASN B 215     20.892  43.271  13.756  1.00 37.49        N
ATOM   721  N   LYS B 216     18.227  42.531  15.676  1.00 29.82        N
ATOM   722  CA  LYS B 216     17.431  43.700  15.908  1.00 29.12        C
ATOM   723  C   LYS B 216     17.562  44.847  14.904  1.00 34.06        C
ATOM   724  O   LYS B 216     16.653  45.383  14.266  1.00 33.52        O
ATOM   725  CB  LYS B 216     17.580  44.261  17.335  1.00 36.94        C
ATOM   726  CG  LYS B 216     17.289  45.709  17.513  1.00 54.25        C
ATOM   727  CD  LYS B 216     18.239  46.428  18.458  1.00 64.48        C
ATOM   728  CE  LYS B 216     17.962  47.933  18.361  1.00 38.71        C
ATOM   729  NZ  LYS B 216     18.156  48.577  19.701  1.00 58.40        N
ATOM   730  N   ASP B 217     18.816  45.213  14.659  1.00 30.48        N
ATOM   731  CA  ASP B 217     19.064  46.400  13.757  1.00 27.61        C
ATOM   732  C   ASP B 217     18.715  46.051  12.331  1.00 28.01        C
ATOM   733  O   ASP B 217     18.213  46.925  11.581  1.00 30.15        O
ATOM   734  CB  ASP B 217     20.621  46.565  13.847  1.00 36.86        C
ATOM   735  CG  ASP B 217     20.988  47.040  15.245  1.00 51.98        C
ATOM   736  OD1 ASP B 217     20.330  47.972  15.757  1.00 52.18        O
ATOM   737  OD2 ASP B 217     21.885  46.396  15.841  1.00 47.67        O
ATOM   738  N   GLN B 218     18.952  44.837  11.886  1.00 27.01        N
ATOM   739  CA  GLN B 218     18.651  44.360  10.561  1.00 26.84        C
ATOM   740  C   GLN B 218     17.114  44.418  10.338  1.00 27.29        C
ATOM   741  O   GLN B 218     16.690  44.973   9.344  1.00 23.91        O
ATOM   742  CB  GLN B 218     19.185  43.019  10.100  1.00 28.38        C
ATOM   743  CG  GLN B 218     18.864  42.617   8.674  1.00 28.89        C
ATOM   744  CD  GLN B 218     19.524  43.615   7.718  1.00 39.42        C
ATOM   745  OE1 GLN B 218     20.719  43.874   7.908  1.00 51.78        O
ATOM   746  NE2 GLN B 218     18.883  44.178   6.720  1.00 38.09        N
ATOM   747  N   ILE B 219     16.363  43.802  11.271  1.00 23.35        N
ATOM   748  CA  ILE B 219     14.913  43.779  11.028  1.00 22.53        C
ATOM   749  C   ILE B 219     14.358  45.188  11.119  1.00 23.20        C
ATOM   750  O   ILE B 219     13.419  45.540  10.380  1.00 24.75        O
ATOM   751  CB  ILE B 219     14.214  42.799  11.995  1.00 24.05        C
ATOM   752  CG1 ILE B 219     12.719  42.604  11.632  1.00 28.34        C
ATOM   753  CG2 ILE B 219     14.324  43.075  13.482  1.00 23.51        C
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ATOM   754  CD1 ILE B 219     12.584  42.167  10.195  1.00 28.70           C
ATOM   755  N   ALA B 220     14.867  46.026  11.971  1.00 21.26           N
ATOM   756  CA  ALA B 220     14.394  47.398  12.036  1.00 23.23           C
ATOM   757  C   ALA B 220     14.562  48.139  10.721  1.00 24.18           C
ATOM   758  O   ALA B 220     13.693  48.843  10.260  1.00 23.88           O
ATOM   759  CB  ALA B 220     14.924  48.143  13.203  1.00 28.83           C
ATOM   760  N   LYS B 221     15.777  47.919  10.174  1.00 26.11           N
ATOM   761  CA  LYS B 221     16.087  48.583   8.865  1.00 26.06           C
ATOM   762  C   LYS B 221     15.114  48.094   7.776  1.00 26.41           C
ATOM   763  O   LYS B 221     14.587  48.888   6.957  1.00 25.25           O
ATOM   764  CB  LYS B 221     17.522  48.113   8.524  1.00 23.76           C
ATOM   765  CG  LYS B 221     17.847  48.631   7.093  1.00 32.95           C
ATOM   766  CD  LYS B 221     19.345  48.559   6.864  1.00 54.82           C
ATOM   767  CE  LYS B 221     19.731  48.843   5.400  1.00 52.81           C
ATOM   768  NZ  LYS B 221     18.551  48.626   4.505  1.00 64.66           N
ATOM   769  N   ASP B 222     14.909  46.751   7.728  1.00 24.33           N
ATOM   770  CA  ASP B 222     13.993  46.174   6.769  1.00 22.83           C
ATOM   771  C   ASP B 222     12.591  46.755   6.856  1.00 24.06           C
ATOM   772  O   ASP B 222     11.822  46.980   5.901  1.00 25.49           O
ATOM   773  CB  ASP B 222     13.988  44.694   6.974  1.00 26.43           C
ATOM   774  CG  ASP B 222     15.290  43.940   6.667  1.00 38.66           C
ATOM   775  OD1 ASP B 222     16.186  44.549   6.004  1.00 35.31           O
ATOM   776  OD2 ASP B 222     15.440  42.767   7.105  1.00 31.82           O
ATOM   777  N   VAL B 223     12.132  46.913   8.186  1.00 22.14           N
ATOM   778  CA  VAL B 223     10.762  47.428   8.371  1.00 20.33           C
ATOM   779  C   VAL B 223     10.663  48.907   8.026  1.00 22.02           C
ATOM   780  O   VAL B 223      9.645  49.303   7.488  1.00 24.09           O
ATOM   781  CB  VAL B 223     10.359  47.221   9.914  1.00 20.11           C
ATOM   782  CG1 VAL B 223      8.923  47.827  10.101  1.00 20.89           C
ATOM   783  CG2 VAL B 223     10.266  45.704  10.015  1.00 22.50           C
ATOM   784  N   LYS B 224     11.692  49.718   8.317  1.00 24.63           N
ATOM   785  CA  LYS B 224     11.648  51.112   7.867  1.00 22.39           C
ATOM   786  C   LYS B 224     11.742  51.101   6.333  1.00 22.61           C
ATOM   787  O   LYS B 224     11.018  51.997   5.790  1.00 25.15           O
ATOM   788  CB  LYS B 224     12.866  51.847   8.429  1.00 23.88           C
ATOM   789  CG  LYS B 224     12.803  51.930   9.957  1.00 27.07           C
ATOM   790  CD  LYS B 224     14.039  52.838  10.291  1.00 30.44           C
ATOM   791  CE  LYS B 224     14.473  52.595  11.710  1.00 37.24           C
ATOM   792  NZ  LYS B 224     15.959  52.861  11.954  1.00 36.84           N
ATOM   793  N   GLN B 225     12.399  50.170   5.716  1.00 23.11           N
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ATOM   794  CA  GLN B 225     12.361  50.229   4.231  1.00 25.47      C
ATOM   795  C   GLN B 225     11.027  49.943   3.641  1.00 26.73      C
ATOM   796  O   GLN B 225     10.493  50.497   2.664  1.00 27.89      O
ATOM   797  CB  GLN B 225     13.411  49.249   3.687  1.00 31.78      C
ATOM   798  CG  GLN B 225     13.591  49.218   2.169  1.00 38.01      C
ATOM   799  CD  GLN B 225     14.593  48.122   1.787  1.00 52.24      C
ATOM   800  OE1 GLN B 225     14.887  47.110   2.466  1.00 39.10      O
ATOM   801  NE2 GLN B 225     15.161  48.357   0.596  1.00 52.36      N
ATOM   802  N   PHE B 226     10.293  48.963   4.237  1.00 26.05      N
ATOM   803  CA  PHE B 226      8.973  48.532   3.931  1.00 19.95      C
ATOM   804  C   PHE B 226      8.061  49.723   4.114  1.00 25.34      C
ATOM   805  O   PHE B 226      7.137  49.995   3.322  1.00 25.01      O
ATOM   806  CB  PHE B 226      8.520  47.335   4.808  1.00 23.99      C
ATOM   807  CG  PHE B 226      7.078  47.018   4.704  1.00 23.19      C
ATOM   808  CD1 PHE B 226      6.614  46.106   3.757  1.00 32.26      C
ATOM   809  CD2 PHE B 226      6.114  47.611   5.520  1.00 24.45      C
ATOM   810  CE1 PHE B 226      5.294  45.767   3.622  1.00 31.82      C
ATOM   811  CE2 PHE B 226      4.767  47.297   5.398  1.00 27.22      C
ATOM   812  CZ  PHE B 226      4.345  46.351   4.485  1.00 31.10      C
ATOM   813  N   TYR B 227      8.136  50.361   5.335  1.00 24.23      N
ATOM   814  CA  TYR B 227      7.277  51.568   5.520  1.00 23.29      C
ATOM   815  C   TYR B 227      7.515  52.651   4.467  1.00 21.71      C
ATOM   816  O   TYR B 227      6.536  53.214   3.929  1.00 27.93      O
ATOM   817  CB  TYR B 227      7.521  52.038   6.991  1.00 24.74      C
ATOM   818  CG  TYR B 227      6.901  53.409   7.209  1.00 23.08      C
ATOM   819  CD1 TYR B 227      5.522  53.556   7.483  1.00 23.12      C
ATOM   820  CD2 TYR B 227      7.590  54.577   7.181  1.00 23.26      C
ATOM   821  CE1 TYR B 227      4.877  54.744   7.637  1.00 21.74      C
ATOM   822  CE2 TYR B 227      6.971  55.810   7.347  1.00 26.24      C
ATOM   823  CZ  TYR B 227      5.622  55.906   7.534  1.00 23.27      C
ATOM   824  OH  TYR B 227      5.113  57.204   7.736  1.00 28.41      O
ATOM   825  N   ASP B 228      8.771  52.947   4.225  1.00 24.07      N
ATOM   826  CA  ASP B 228      9.112  54.010   3.219  1.00 26.13      C
ATOM   827  C   ASP B 228      8.530  53.681   1.848  1.00 25.40      C
ATOM   828  O   ASP B 228      7.948  54.619   1.256  1.00 28.30      O
ATOM   829  CB  ASP B 228     10.598  54.183   3.098  1.00 26.65      C
ATOM   830  CG  ASP B 228     11.283  54.732   4.341  1.00 27.40      C
ATOM   831  OD1 ASP B 228     10.503  55.158   5.247  1.00 28.45      O
ATOM   832  OD2 ASP B 228     12.550  54.757   4.381  1.00 31.87      O
ATOM   833  N   GLN B 229      8.547  52.455   1.467  1.00 27.81      N
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ATOM   834  CA  GLN B 229      7.973  52.053   0.189  1.00 31.66       C
ATOM   835  C   GLN B 229      6.486  52.170   0.149  1.00 30.19       C
ATOM   836  O   GLN B 229      5.831  52.682  -0.747  1.00 30.67       O
ATOM   837  CB  GLN B 229      8.476  50.634  -0.146  1.00 31.73       C
ATOM   838  CG  GLN B 229      7.591  50.067  -1.270  1.00 40.23       C
ATOM   839  CD  GLN B 229      8.057  48.688  -1.756  1.00 35.25       C
ATOM   840  OE1 GLN B 229      7.384  47.710  -1.522  1.00 55.87       O
ATOM   841  NE2 GLN B 229      9.225  48.775  -2.390  1.00 50.23       N
ATOM   842  N   ALA B 230      5.754  51.854   1.279  1.00 28.10       N
ATOM   843  CA  ALA B 230      4.290  52.029   1.307  1.00 24.10       C
ATOM   844  C   ALA B 230      3.931  53.498   1.278  1.00 27.94       C
ATOM   845  O   ALA B 230      2.888  53.958   0.745  1.00 31.55       O
ATOM   846  CB  ALA B 230      3.795  51.431   2.642  1.00 29.30       C
ATOM   847  N   LEU B 231      4.740  54.354   1.931  1.00 23.97       N
ATOM   848  CA  LEU B 231      4.442  55.785   1.967  1.00 26.83       C
ATOM   849  C   LEU B 231      4.529  56.323   0.503  1.00 28.89       C
ATOM   850  O   LEU B 231      3.647  57.118   0.180  1.00 32.83       O
ATOM   851  CB  LEU B 231      5.448  56.501   2.793  1.00 33.06       C
ATOM   852  CG  LEU B 231      5.286  57.827   3.481  1.00 34.95       C
ATOM   853  CD1 LEU B 231      4.017  57.819   4.373  1.00 37.01       C
ATOM   854  CD2 LEU B 231      6.460  57.952   4.470  1.00 30.54       C
ATOM   855  N   GLN B 232      5.592  55.891  -0.152  1.00 28.34       N
ATOM   856  CA  GLN B 232      5.808  56.306  -1.543  1.00 25.85       C
ATOM   857  C   GLN B 232      4.606  55.803  -2.297  1.00 32.51       C
ATOM   858  O   GLN B 232      3.984  56.532  -3.068  1.00 35.03       O
ATOM   859  CB  GLN B 232      7.146  55.923  -2.148  1.00 27.31       C
ATOM   860  CG  GLN B 232      7.040  56.328  -3.665  1.00 39.26       C
ATOM   861  CD  GLN B 232      7.200  57.837  -3.811  1.00 48.48       C
ATOM   862  OE1 GLN B 232      8.230  58.427  -3.464  1.00 48.35       O
ATOM   863  NE2 GLN B 232      6.175  58.514  -4.347  1.00 63.54       N
ATOM   864  N   GLN B 233      4.282  54.521  -2.251  1.00 30.22       N
ATOM   865  CA  GLN B 233      3.123  53.964  -2.883  1.00 31.30       C
ATOM   866  C   GLN B 233      1.804  54.580  -2.597  1.00 37.96       C
ATOM   867  O   GLN B 233      1.001  54.779  -3.493  1.00 32.91       O
ATOM   868  CB  GLN B 233      3.062  52.438  -2.817  1.00 35.74       C
ATOM   869  CG  GLN B 233      4.280  51.738  -3.376  1.00 48.14       C
ATOM   870  CD  GLN B 233      4.237  50.226  -3.100  1.00 60.95       C
ATOM   871  OE1 GLN B 233      3.335  49.679  -2.460  1.00 55.12       O
ATOM   872  NE2 GLN B 233      5.249  49.503  -3.591  1.00 53.03       N
ATOM   873  N   ALA B 234      1.478  54.933  -1.343  1.00 33.85       N
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ATOM   874  CA  ALA B 234      0.212  55.540  -0.966  1.00 30.65           C
ATOM   875  C   ALA B 234     -0.035  56.911  -1.609  1.00 37.42           C
ATOM   876  O   ALA B 234     -1.164  57.383  -1.543  1.00 40.95           O
ATOM   877  CB  ALA B 234      0.227  55.871   0.528  1.00 37.79           C
ATOM   878  N   VAL B 235      1.009  57.576  -1.999  1.00 34.25           N
ATOM   879  CA  VAL B 235      0.879  58.954  -2.490  1.00 46.72           C
ATOM   880  C   VAL B 235      0.344  58.994  -3.902  1.00 47.75           C
ATOM   881  O   VAL B 235     -0.480  59.829  -4.219  1.00 42.71           O
ATOM   882  CB  VAL B 235      2.243  59.671  -2.437  1.00 46.39           C
ATOM   883  CG1 VAL B 235      2.400  60.622  -3.584  1.00 55.69           C
ATOM   884  CG2 VAL B 235      2.511  60.147  -1.040  1.00 52.76           C
ATOM   885  N   VAL B 236      0.661  57.984  -4.673  1.00 55.00           N
ATOM   886  CA  VAL B 236      0.241  57.833  -6.051  1.00 63.72           C
ATOM   887  C   VAL B 236     -1.111  57.157  -6.210  1.00 65.71           C
ATOM   888  O   VAL B 236     -1.763  56.686  -5.285  1.00 67.29           O
ATOM   889  CB  VAL B 236      1.284  56.949  -6.776  1.00 64.32           C
ATOM   890  CG1 VAL B 236      2.592  56.862  -6.003  1.00 58.65           C
ATOM   891  CG2 VAL B 236      0.676  55.569  -6.973  1.00 55.88           C
ATOM   892  N   ASP B 237     -1.574  57.092  -7.452  1.00 69.34           N
ATOM   893  CA  ASP B 237     -2.819  56.471  -7.841  1.00 70.85           C
ATOM   894  C   ASP B 237     -3.935  56.519  -6.817  1.00 70.40           C
ATOM   895  O   ASP B 237     -3.875  57.426  -5.951  1.00 72.42           O
ATOM   896  CB  ASP B 237     -2.566  55.033  -8.302  1.00 74.85           C
ATOM   897  CG  ASP B 237     -2.566  54.902  -9.815  1.00 77.81           C
ATOM   898  OD1 ASP B 237     -2.807  55.913 -10.514  1.00 73.42           O
ATOM   899  OD2 ASP B 237     -2.333  53.766 -10.290  1.00 73.26           O
ATOM   900  N   ASN B 242     -3.210  48.670  -1.883  1.00 39.18           N
ATOM   901  CA  ASN B 242     -3.055  48.493  -0.438  1.00 44.04           C
ATOM   902  C   ASN B 242     -2.190  49.418   0.378  1.00 40.11           C
ATOM   903  O   ASN B 242     -2.350  49.368   1.631  1.00 39.92           O
ATOM   904  CB  ASN B 242     -2.785  47.028  -0.089  1.00 53.02           C
ATOM   905  CG  ASN B 242     -3.593  46.705   1.154  1.00 52.89           C
ATOM   906  OD1 ASN B 242     -4.816  46.659   1.117  1.00 74.32           O
ATOM   907  ND2 ASN B 242     -2.903  46.505   2.255  1.00 60.76           N
ATOM   908  N   ALA B 243     -1.374  50.266  -0.256  1.00 36.30           N
ATOM   909  CA  ALA B 243     -0.477  51.139   0.437  1.00 33.91           C
ATOM   910  C   ALA B 243     -1.149  52.151   1.352  1.00 37.82           C
ATOM   911  O   ALA B 243     -0.611  52.347   2.465  1.00 33.56           O
ATOM   912  CB  ALA B 243      0.520  51.837  -0.521  1.00 32.40           C
ATOM   913  N   LYS B 244     -2.321  52.706   0.984  1.00 31.44           N
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ATOM   914  CA  LYS B 244     -2.917  53.649   1.905  1.00 35.82           C
ATOM   915  C   LYS B 244     -3.226  52.940   3.220  1.00 30.55           C
ATOM   916  O   LYS B 244     -3.050  53.525   4.305  1.00 38.19           O
ATOM   917  CB  LYS B 244     -4.095  54.431   1.321  1.00 39.68           C
ATOM   918  CG  LYS B 244     -3.645  55.272   0.105  1.00 48.03           C
ATOM   919  CD  LYS B 244     -4.610  56.417  -0.160  1.00 61.93           C
ATOM   920  CE  LYS B 244     -4.235  57.325  -1.338  1.00 44.53           C
ATOM   921  NZ  LYS B 244     -3.769  56.503  -2.497  1.00 47.52           N
ATOM   922  N   ALA B 245     -3.860  51.781   3.154  1.00 36.14           N
ATOM   923  CA  ALA B 245     -4.192  51.049   4.369  1.00 35.51           C
ATOM   924  C   ALA B 245     -2.969  50.595   5.178  1.00 32.87           C
ATOM   925  O   ALA B 245     -3.057  50.755   6.423  1.00 30.07           O
ATOM   926  CB  ALA B 245     -5.204  49.939   4.220  1.00 37.71           C
ATOM   927  N   VAL B 246     -1.895  50.248   4.473  1.00 34.22           N
ATOM   928  CA  VAL B 246     -0.706  49.853   5.279  1.00 29.25           C
ATOM   929  C   VAL B 246     -0.168  51.056   5.995  1.00 30.43           C
ATOM   930  O   VAL B 246      0.202  51.090   7.187  1.00 29.85           O
ATOM   931  CB  VAL B 246      0.365  49.273   4.377  1.00 29.35           C
ATOM   932  CG1 VAL B 246      1.786  49.347   4.933  1.00 29.84           C
ATOM   933  CG2 VAL B 246      0.092  47.930   3.736  1.00 34.46           C
ATOM   934  N   VAL B 247     -0.089  52.213   5.275  1.00 28.21           N
ATOM   935  CA  VAL B 247      0.358  53.458   5.918  1.00 26.35           C
ATOM   936  C   VAL B 247     -0.534  53.835   7.097  1.00 28.87           C
ATOM   937  O   VAL B 247     -0.042  54.180   8.176  1.00 26.97           O
ATOM   938  CB  VAL B 247      0.296  54.642   4.861  1.00 32.02           C
ATOM   939  CG1 VAL B 247      0.476  55.967   5.598  1.00 28.64           C
ATOM   940  CG2 VAL B 247      1.542  54.413   3.985  1.00 38.44           C
ATOM   941  N   LYS B 248     -1.855  53.790   6.924  1.00 25.72           N
ATOM   942  CA  LYS B 248     -2.712  54.159   8.046  1.00 28.85           C
ATOM   943  C   LYS B 248     -2.550  53.215   9.244  1.00 27.54           C
ATOM   944  O   LYS B 248     -2.550  53.735  10.357  1.00 27.13           O
ATOM   945  CB  LYS B 248     -4.194  54.134   7.636  1.00 42.84           C
ATOM   946  CG  LYS B 248     -5.069  54.520   8.847  1.00 58.35           C
ATOM   947  CD  LYS B 248     -6.463  53.918   8.740  1.00 54.75           C
ATOM   948  CE  LYS B 248     -7.516  54.714   9.498  1.00 59.22           C
ATOM   949  NZ  LYS B 248     -7.758  56.018   8.804  1.00 69.89           N
ATOM   950  N   THR B 249     -2.355  51.944   8.971  1.00 28.19           N
ATOM   951  CA  THR B 249     -2.139  50.941  10.018  1.00 25.54           C
ATOM   952  C   THR B 249     -0.864  51.232  10.713  1.00 22.00           C
ATOM   953  O   THR B 249     -0.862  51.158  11.961  1.00 26.72           O
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ATOM 954 CB THR B 249 -2.072 49.561 9.309 1.00 32.90 C
ATOM 955 OG1 THR B 249 -3.456 49.249 8.998 1.00 34.27 O
ATOM 956 CG2 THR B 249 -1.701 48.502 10.386 1.00 28.18 C
ATOM 957 N PHE B 250 0.223 51.503 10.050 1.00 24.03 N
ATOM 958 CA PHE B 250 1.442 51.890 10.752 1.00 22.07 C
ATOM 959 C PHE B 250 1.256 53.105 11.616 1.00 24.13 C
ATOM 960 O PHE B 250 1.722 53.169 12.779 1.00 23.95 O
ATOM 961 CB PHE B 250 2.632 51.983 9.774 1.00 24.35 C
ATOM 962 CG PHE B 250 3.359 50.718 9.517 1.00 20.35 C
ATOM 963 CD1 PHE B 250 2.734 49.631 8.939 1.00 27.04 C
ATOM 964 CD2 PHE B 250 4.711 50.655 9.879 1.00 24.67 C
ATOM 965 CE1 PHE B 250 3.463 48.450 8.759 1.00 26.35 C
ATOM 966 CE2 PHE B 250 5.401 49.452 9.717 1.00 27.07 C
ATOM 967 CZ PHE B 250 4.813 48.395 9.092 1.00 25.85 C
ATOM 968 N HIS B 251 0.645 54.147 11.025 1.00 23.26 N
ATOM 969 CA HIS B 251 0.507 55.413 11.786 1.00 24.35 C
ATOM 970 C HIS B 251 -0.302 55.195 13.025 1.00 20.70 C
ATOM 971 O HIS B 251 0.069 55.679 14.076 1.00 27.98 O
ATOM 972 CB HIS B 251 -0.106 56.471 10.897 1.00 28.47 C
ATOM 973 CG HIS B 251 0.845 56.859 9.809 1.00 22.44 C
ATOM 974 ND1 HIS B 251 0.466 57.612 8.744 1.00 27.96 N
ATOM 975 CD2 HIS B 251 2.173 56.588 9.692 1.00 20.58 C
ATOM 976 CE1 HIS B 251 1.546 57.769 7.996 1.00 24.43 C
ATOM 977 NE2 HIS B 251 2.607 57.164 8.463 1.00 22.99 N
ATOM 978 N GLU B 252 -1.408 54.485 12.899 1.00 25.24 N
ATOM 979 CA GLU B 252 -2.283 54.273 14.078 1.00 28.83 C
ATOM 980 C GLU B 252 -1.656 53.316 15.065 1.00 24.84 C
ATOM 981 O GLU B 252 -1.715 53.637 16.291 1.00 28.08 O
ATOM 982 CB GLU B 252 -3.520 53.530 13.531 1.00 33.80 C
ATOM 983 CG GLU B 252 -4.529 54.586 13.053 1.00 51.18 C
ATOM 984 CD GLU B 252 -5.195 55.154 14.298 1.00 62.22 C
ATOM 985 OE1 GLU B 252 -5.078 54.441 15.318 1.00 75.33 O
ATOM 986 OE2 GLU B 252 -5.789 56.246 14.231 1.00 81.41 O
ATOM 987 N THR B 253 -0.940 52.278 14.602 1.00 24.38 N
ATOM 988 CA THR B 253 -0.335 51.348 15.543 1.00 25.28 C
ATOM 989 C THR B 253 0.815 51.947 16.284 1.00 26.73 C
ATOM 990 O THR B 253 0.983 51.668 17.495 1.00 26.95 O
ATOM 991 CB THR B 253 0.142 50.092 14.754 1.00 30.77 C
ATOM 992 OG1 THR B 253 -1.082 49.514 14.253 1.00 30.13 O
ATOM 993 CG2 THR B 253 0.636 49.050 15.765 1.00 29.29 C

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ATOM   994  N   LEU B 254     1.653  52.721  15.598  1.00 25.61           N
ATOM   995  CA  LEU B 254     2.892  53.219  16.200  1.00 26.00           C
ATOM   996  C   LEU B 254     2.783  54.632  16.714  1.00 22.88           C
ATOM   997  O   LEU B 254     3.697  55.128  17.327  1.00 30.40           O
ATOM   998  CB  LEU B 254     4.118  53.101  15.235  1.00 26.38           C
ATOM   999  CG  LEU B 254     4.366  51.789  14.516  1.00 28.75           C
ATOM  1000  CD1 LEU B 254     5.329  51.864  13.337  1.00 26.49           C
ATOM  1001  CD2 LEU B 254     4.772  50.720  15.562  1.00 31.20           C
ATOM  1002  N   ASP B 255     1.662  55.314  16.415  1.00 26.40           N
ATOM  1003  CA  ASP B 255     1.352  56.656  16.876  1.00 29.10           C
ATOM  1004  C   ASP B 255     2.396  57.628  16.358  1.00 26.00           C
ATOM  1005  O   ASP B 255     3.199  58.345  16.968  1.00 30.49           O
ATOM  1006  CB  ASP B 255     1.586  56.728  18.458  1.00 27.91           C
ATOM  1007  CG  ASP B 255     0.716  57.837  18.996  1.00 39.98           C
ATOM  1008  OD1 ASP B 255    -0.400  57.996  18.450  1.00 40.21           O
ATOM  1009  OD2 ASP B 255     1.140  58.490  19.981  1.00 52.19           O
ATOM  1010  N   CYS B 256     2.402  57.595  14.962  1.00 23.36           N
ATOM  1011  CA  CYS B 256     3.291  58.553  14.232  1.00 23.75           C
ATOM  1012  C   CYS B 256     2.652  58.844  12.864  1.00 23.79           C
ATOM  1013  O   CYS B 256     1.512  58.452  12.503  1.00 25.84           O
ATOM  1014  CB  CYS B 256     4.633  57.847  13.915  1.00 27.39           C
ATOM  1015  SG  CYS B 256     4.516  56.306  12.977  1.00 25.46           S
ATOM  1016  N   CYS B 257     3.398  59.728  12.150  1.00 23.91           N
ATOM  1017  CA  CYS B 257     2.877  60.183  10.857  1.00 23.10           C
ATOM  1018  C   CYS B 257     4.132  60.537  10.008  1.00 24.58           C
ATOM  1019  O   CYS B 257     4.858  61.478  10.306  1.00 35.32           O
ATOM  1020  CB  CYS B 257     1.990  61.433  11.086  1.00 24.93           C
ATOM  1021  SG  CYS B 257     1.462  62.126   9.522  1.00 38.86           S
ATOM  1022  N   GLY B 258     4.499  59.751   9.003  1.00 28.29           N
ATOM  1023  CA  GLY B 258     5.582  60.043   8.168  1.00 29.82           C
ATOM  1024  C   GLY B 258     6.985  59.918   8.772  1.00 28.11           C
ATOM  1025  O   GLY B 258     7.323  59.282   9.774  1.00 27.13           O
ATOM  1026  N   SER B 259     7.902  60.536   7.973  1.00 23.81           N
ATOM  1027  CA  SER B 259     9.313  60.368   8.266  1.00 24.67           C
ATOM  1028  C   SER B 259    10.025  61.698   8.103  1.00 23.57           C
ATOM  1029  O   SER B 259     9.876  62.252   6.979  1.00 25.69           O
ATOM  1030  CB  SER B 259     9.928  59.300   7.326  1.00 25.07           C
ATOM  1031  OG  SER B 259    11.349  59.212   7.646  1.00 25.11           O
ATOM  1032  N   SER B 260    10.983  62.038   8.915  1.00 23.52           N
ATOM  1033  CA  SER B 260    11.844  63.194   8.671  1.00 26.60           C
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ATOM  1034  C   SER B 260     12.687  63.035   7.368  1.00 30.13       C
ATOM  1035  O   SER B 260     13.078  64.065   6.854  1.00 31.35       O
ATOM  1036  CB  SER B 260     12.899  63.255   9.763  1.00 27.65       C
ATOM  1037  OG  SER B 260     12.181  63.575  10.970  1.00 28.41       O
ATOM  1038  N   THR B 261     12.891  61.835   6.872  1.00 26.25       N
ATOM  1039  CA  THR B 261     13.701  61.600   5.664  1.00 26.86       C
ATOM  1040  C   THR B 261     12.862  61.805   4.427  1.00 28.21       C
ATOM  1041  O   THR B 261     13.431  61.761   3.286  1.00 31.07       O
ATOM  1042  CB  THR B 261     14.262  60.145   5.670  1.00 34.63       C
ATOM  1043  OG1 THR B 261     13.250  59.130   5.650  1.00 27.58       O
ATOM  1044  CG2 THR B 261     15.182  59.966   6.845  1.00 32.42       C
ATOM  1045  N   LEU B 262     11.547  61.905   4.538  1.00 24.65       N
ATOM  1046  CA  LEU B 262     10.632  61.948   3.435  1.00 26.11       C
ATOM  1047  C   LEU B 262      9.613  63.054   3.649  1.00 23.05       C
ATOM  1048  O   LEU B 262      8.451  62.765   3.797  1.00 26.64       O
ATOM  1049  CB  LEU B 262      9.876  60.609   3.119  1.00 28.16       C
ATOM  1050  CG  LEU B 262     10.880  59.522   2.727  1.00 26.71       C
ATOM  1051  CD1 LEU B 262     10.363  58.132   2.880  1.00 30.36       C
ATOM  1052  CD2 LEU B 262     11.273  59.679   1.213  1.00 28.82       C
ATOM  1053  N   THR B 263     10.110  64.271   3.759  1.00 26.37       N
ATOM  1054  CA  THR B 263      9.166  65.383   4.052  1.00 28.15       C
ATOM  1055  C   THR B 263      8.031  65.640   3.112  1.00 26.08       C
ATOM  1056  O   THR B 263      6.867  65.841   3.488  1.00 29.18       O
ATOM  1057  CB  THR B 263      9.882  66.710   4.411  1.00 26.13       C
ATOM  1058  OG1 THR B 263     10.725  66.983   3.289  1.00 30.06       O
ATOM  1059  CG2 THR B 263     10.828  66.428   5.583  1.00 27.31       C
ATOM  1060  N   ALA B 264      8.320  65.541   1.756  1.00 26.65       N
ATOM  1061  CA  ALA B 264      7.200  65.689   0.854  1.00 28.62       C
ATOM  1062  C   ALA B 264      6.122  64.622   0.960  1.00 30.46       C
ATOM  1063  O   ALA B 264      4.913  64.883   0.824  1.00 27.48       O
ATOM  1064  CB  ALA B 264      7.792  65.648  -0.580  1.00 37.44       C
ATOM  1065  N   LEU B 265      6.572  63.328   1.103  1.00 26.43       N
ATOM  1066  CA  LEU B 265      5.525  62.299   1.258  1.00 24.79       C
ATOM  1067  C   LEU B 265      4.747  62.415   2.561  1.00 22.99       C
ATOM  1068  O   LEU B 265      3.551  62.173   2.557  1.00 27.18       O
ATOM  1069  CB  LEU B 265      6.174  60.876   1.277  1.00 28.63       C
ATOM  1070  CG  LEU B 265      6.906  60.624  -0.059  1.00 30.02       C
ATOM  1071  CD1 LEU B 265      7.551  59.278   0.106  1.00 33.74       C
ATOM  1072  CD2 LEU B 265      5.826  60.540  -1.141  1.00 29.11       C
ATOM  1073  N   THR B 266      5.455  63.026   3.541  1.00 25.60       N
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ATOM  1074  CA  THR B 266      4.714  63.275   4.809  1.00 21.94           C
ATOM  1075  C   THR B 266      3.646  64.393   4.568  1.00 22.37           C
ATOM  1076  O   THR B 266      2.563  64.267   5.086  1.00 28.65           O
ATOM  1077  CB  THR B 266      5.727  63.736   5.883  1.00 23.32           C
ATOM  1078  OG1 THR B 266      6.653  62.623   6.058  1.00 25.53           O
ATOM  1079  CG2 THR B 266      5.065  63.999   7.261  1.00 23.80           C
ATOM  1080  N   THR B 267      4.055  65.401   3.791  1.00 25.88           N
ATOM  1081  CA  THR B 267      3.009  66.434   3.520  1.00 25.86           C
ATOM  1082  C   THR B 267      1.809  65.737   2.864  1.00 28.07           C
ATOM  1083  O   THR B 267      0.684  65.971   3.201  1.00 29.20           O
ATOM  1084  CB  THR B 267      3.640  67.463   2.606  1.00 28.82           C
ATOM  1085  OG1 THR B 267      4.741  68.114   3.207  1.00 28.97           O
ATOM  1086  CG2 THR B 267      2.567  68.483   2.131  1.00 28.36           C
ATOM  1087  N   SER B 268      2.100  64.819   1.910  1.00 27.77           N
ATOM  1088  CA  SER B 268      0.980  64.132   1.240  1.00 25.14           C
ATOM  1089  C   SER B 268      0.085  63.350   2.124  1.00 30.63           C
ATOM  1090  O   SER B 268     -1.170  63.416   2.200  1.00 33.42           O
ATOM  1091  CB  SER B 268      1.584  63.597  -0.086  1.00 32.82           C
ATOM  1092  OG  SER B 268      0.590  62.714  -0.614  1.00 44.95           O
ATOM  1093  N   VAL B 269      0.740  62.576   3.063  1.00 27.41           N
ATOM  1094  CA  VAL B 269     -0.109  61.858   4.007  1.00 35.06           C
ATOM  1095  C   VAL B 269     -0.916  62.801   4.886  1.00 30.74           C
ATOM  1096  O   VAL B 269     -2.059  62.350   5.136  1.00 33.39           O
ATOM  1097  CB  VAL B 269      0.609  60.683   4.632  1.00 38.56           C
ATOM  1098  CG1 VAL B 269      0.874  59.618   3.566  1.00 46.61           C
ATOM  1099  CG2 VAL B 269      1.839  61.044   5.415  1.00 45.95           C
ATOM  1100  N   LEU B 270     -0.405  63.984   5.270  1.00 28.46           N
ATOM  1101  CA  LEU B 270     -1.300  64.824   6.093  1.00 30.42           C
ATOM  1102  C   LEU B 270     -2.391  65.379   5.191  1.00 33.09           C
ATOM  1103  O   LEU B 270     -3.505  65.541   5.686  1.00 49.14           O
ATOM  1104  CB  LEU B 270     -0.497  66.080   6.565  1.00 36.39           C
ATOM  1105  CG  LEU B 270      0.523  65.639   7.630  1.00 33.94           C
ATOM  1106  CD1 LEU B 270      1.528  66.779   7.853  1.00 42.38           C
ATOM  1107  CD2 LEU B 270     -0.242  65.417   8.913  1.00 35.66           C
ATOM  1108  N   LYS B 271     -2.124  65.639   3.953  1.00 33.63           N
ATOM  1109  CA  LYS B 271     -3.148  66.240   3.071  1.00 41.91           C
ATOM  1110  C   LYS B 271     -4.212  65.210   2.700  1.00 48.60           C
ATOM  1111  O   LYS B 271     -5.248  65.555   2.127  1.00 48.91           O
ATOM  1112  CB  LYS B 271     -2.480  66.753   1.809  1.00 32.24           C
ATOM  1113  CG  LYS B 271     -2.054  68.186   1.686  1.00 44.33           C
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ATOM  1114  CD  LYS B 271     -0.929  68.387   0.709  1.00 55.54      C
ATOM  1115  CE  LYS B 271     -1.200  69.070  -0.604  1.00 57.61      C
ATOM  1116  NZ  LYS B 271      0.002  69.089  -1.513  1.00 56.79      N
ATOM  1117  N   ASN B 272     -3.886  63.940   2.833  1.00 45.66      N
ATOM  1118  CA  ASN B 272     -4.790  62.838   2.477  1.00 41.76      C
ATOM  1119  C   ASN B 272     -5.354  62.111   3.684  1.00 42.61      C
ATOM  1120  O   ASN B 272     -5.852  60.978   3.608  1.00 42.97      O
ATOM  1121  CB  ASN B 272     -4.101  61.820   1.574  1.00 50.22      C
ATOM  1122  CG  ASN B 272     -3.727  62.434   0.234  1.00 49.65      C
ATOM  1123  OD1 ASN B 272     -2.921  61.846  -0.482  1.00 60.21      O
ATOM  1124  ND2 ASN B 272     -4.315  63.591  -0.035  1.00 51.81      N
ATOM  1125  N   ASN B 273     -5.360  62.721   4.869  1.00 41.71      N
ATOM  1126  CA  ASN B 273     -5.944  62.081   6.051  1.00 45.37      C
ATOM  1127  C   ASN B 273     -5.448  60.660   6.255  1.00 46.94      C
ATOM  1128  O   ASN B 273     -6.212  59.731   6.572  1.00 42.59      O
ATOM  1129  CB  ASN B 273     -7.440  62.261   6.197  1.00 55.99      C
ATOM  1130  CG  ASN B 273     -8.146  61.973   7.499  1.00 72.23      C
ATOM  1131  OD1 ASN B 273     -9.295  61.480   7.449  1.00 60.94      O
ATOM  1132  ND2 ASN B 273     -7.609  62.219   8.694  1.00 49.92      N
ATOM  1133  N   LEU B 274     -4.110  60.522   6.192  1.00 32.57      N
ATOM  1134  CA  LEU B 274     -3.513  59.186   6.422  1.00 37.62      C
ATOM  1135  C   LEU B 274     -2.797  59.240   7.778  1.00 34.70      C
ATOM  1136  O   LEU B 274     -2.223  58.226   8.190  1.00 40.32      O
ATOM  1137  CB  LEU B 274     -2.537  58.790   5.304  1.00 32.87      C
ATOM  1138  CG  LEU B 274     -3.131  58.533   3.903  1.00 36.48      C
ATOM  1139  CD1 LEU B 274     -2.191  58.031   2.850  1.00 36.11      C
ATOM  1140  CD2 LEU B 274     -4.255  57.495   3.999  1.00 44.60      C
ATOM  1141  N   CYS B 275     -3.000  60.318   8.517  1.00 34.07      N
ATOM  1142  CA  CYS B 275     -2.507  60.328   9.903  1.00 35.97      C
ATOM  1143  C   CYS B 275     -3.582  60.423  10.977  1.00 41.71      C
ATOM  1144  O   CYS B 275     -4.477  61.280  10.878  1.00 43.31      O
ATOM  1145  CB  CYS B 275     -1.450  61.425  10.009  1.00 37.23      C
ATOM  1146  SG  CYS B 275      0.034  60.839   8.984  1.00 40.12      S
ATOM  1147  N   PRO B 276     -3.355  59.744  12.093  1.00 42.17      N
ATOM  1148  CA  PRO B 276     -4.203  59.752  13.252  1.00 45.49      C
ATOM  1149  C   PRO B 276     -4.546  61.112  13.832  1.00 44.88      C
ATOM  1150  O   PRO B 276     -3.726  62.022  13.871  1.00 39.71      O
ATOM  1151  CB  PRO B 276     -3.414  58.959  14.292  1.00 41.06      C
ATOM  1152  CG  PRO B 276     -2.174  58.448  13.720  1.00 43.43      C
ATOM  1153  CD  PRO B 276     -2.217  58.798  12.266  1.00 47.75      C
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ATOM   1154  N   SER B 277     -5.782  61.285  14.330  1.00 49.29           N
ATOM   1155  CA  SER B 277     -6.089  62.561  14.975  1.00 54.22           C
ATOM   1156  C   SER B 277     -5.580  62.399  16.427  1.00 58.72           C
ATOM   1157  O   SER B 277     -4.853  63.241  16.939  1.00 60.37           O
ATOM   1158  CB  SER B 277     -7.584  62.855  14.999  1.00 64.24           C
ATOM   1159  OG  SER B 277     -7.855  63.410  16.288  1.00 58.29           O
ATOM   1160  N   GLY B 278     -4.040  62.942  16.826  0.00 72.91           N
ATOM   1161  CA  GLY B 278     -3.441  63.319  18.073  0.00 72.16           C
ATOM   1162  C   GLY B 278     -2.623  64.614  17.863  0.00 71.11           C
ATOM   1163  O   GLY B 278     -1.745  64.671  17.014  0.00 72.04           O
ATOM   1164  N   SER B 279     -2.952  65.657  18.662  0.00 67.96           N
ATOM   1165  CA  SER B 279     -2.265  66.962  18.645  0.00 66.01           C
ATOM   1166  C   SER B 279     -0.889  66.699  19.187  0.00 61.41           C
ATOM   1167  O   SER B 279      0.045  67.486  19.082  0.00 60.21           O
ATOM   1168  N   ASN B 280     -0.831  65.502  19.816  0.00 43.63           N
ATOM   1169  CA  ASN B 280      0.516  64.893  20.332  1.00 41.52           C
ATOM   1170  C   ASN B 280      1.095  64.425  18.979  1.00 39.21           C
ATOM   1171  O   ASN B 280      2.335  64.401  18.895  1.00 45.78           O
ATOM   1172  CB  ASN B 280      0.346  63.670  21.244  1.00 50.54           C
ATOM   1173  CG  ASN B 280      1.546  62.856  21.624  1.00 68.21           C
ATOM   1174  OD1 ASN B 280      2.207  63.064  22.646  1.00 65.20           O
ATOM   1175  ND2 ASN B 280      1.904  61.830  20.842  1.00 75.37           N
ATOM   1176  N   ILE B 281      0.249  64.007  18.025  1.00 36.82           N
ATOM   1177  CA  ILE B 281      0.892  63.548  16.792  1.00 40.92           C
ATOM   1178  C   ILE B 281      1.634  64.712  16.156  1.00 38.73           C
ATOM   1179  O   ILE B 281      2.803  64.571  15.783  1.00 38.63           O
ATOM   1180  CB  ILE B 281     -0.001  62.914  15.718  1.00 35.85           C
ATOM   1181  CG1 ILE B 281     -0.643  61.609  16.206  1.00 33.19           C
ATOM   1182  CG2 ILE B 281      0.956  62.467  14.587  1.00 50.96           C
ATOM   1183  CD1 ILE B 281      0.365  60.492  16.128  1.00 39.56           C
ATOM   1184  N   ILE B 282      0.919  65.849  16.022  1.00 29.27           N
ATOM   1185  CA  ILE B 282      1.457  66.992  15.332  1.00 29.07           C
ATOM   1186  C   ILE B 282      2.624  67.557  16.088  1.00 27.73           C
ATOM   1187  O   ILE B 282      3.614  67.974  15.466  1.00 27.37           O
ATOM   1188  CB  ILE B 282      0.322  68.011  15.054  1.00 29.28           C
ATOM   1189  CG1 ILE B 282     -0.876  67.390  14.361  1.00 37.40           C
ATOM   1190  CG2 ILE B 282      0.830  69.268  14.380  1.00 32.57           C
ATOM   1191  CD1 ILE B 282     -0.464  66.633  13.121  1.00 40.21           C
ATOM   1192  N   SER B 283      2.544  67.673  17.447  1.00 31.59           N
ATOM   1193  CA  SER B 283      3.643  68.243  18.178  1.00 27.76           C
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ATOM  1194  C   SER B 283      4.901  67.386  18.070  1.00 30.37           C
ATOM  1195  O   SER B 283      6.010  67.933  18.272  1.00 30.76           O
ATOM  1196  CB  SER B 283      3.232  68.496  19.653  1.00 36.68           C
ATOM  1197  OG  SER B 283      3.256  67.364  20.451  1.00 56.57           O
ATOM  1198  N   ASN B 284      4.770  66.101  17.790  1.00 26.37           N
ATOM  1199  CA  ASN B 284      5.992  65.274  17.629  1.00 27.78           C
ATOM  1200  C   ASN B 284      6.070  64.706  16.199  1.00 21.84           C
ATOM  1201  O   ASN B 284      6.748  63.711  15.987  1.00 27.17           O
ATOM  1202  CB  ASN B 284      5.744  64.004  18.525  1.00 29.03           C
ATOM  1203  CG  ASN B 284      5.951  64.593  19.959  1.00 37.00           C
ATOM  1204  OD1 ASN B 284      7.016  65.184  20.168  1.00 33.60           O
ATOM  1205  ND2 ASN B 284      4.924  64.444  20.727  1.00 40.16           N
ATOM  1206  N   LEU B 285      5.431  65.412  15.244  1.00 25.64           N
ATOM  1207  CA  LEU B 285      5.470  64.927  13.838  1.00 23.96           C
ATOM  1208  C   LEU B 285      6.819  64.397  13.395  1.00 29.62           C
ATOM  1209  O   LEU B 285      6.908  63.266  12.842  1.00 26.40           O
ATOM  1210  CB  LEU B 285      5.002  66.067  12.904  1.00 28.34           C
ATOM  1211  CG  LEU B 285      5.069  65.740  11.397  1.00 26.79           C
ATOM  1212  CD1 LEU B 285      4.109  64.561  11.188  1.00 27.83           C
ATOM  1213  CD2 LEU B 285      4.493  67.010  10.671  1.00 24.57           C
ATOM  1214  N   PHE B 286      7.897  65.203  13.548  1.00 25.76           N
ATOM  1215  CA  PHE B 286      9.219  64.787  13.175  1.00 22.99           C
ATOM  1216  C   PHE B 286     10.090  64.505  14.425  1.00 24.06           C
ATOM  1217  O   PHE B 286     11.150  63.937  14.218  1.00 28.06           O
ATOM  1218  CB  PHE B 286      9.895  65.849  12.282  1.00 23.00           C
ATOM  1219  CG  PHE B 286      9.193  65.968  10.935  1.00 20.76           C
ATOM  1220  CD1 PHE B 286      8.527  67.111  10.535  1.00 24.21           C
ATOM  1221  CD2 PHE B 286      9.104  64.906  10.059  1.00 24.16           C
ATOM  1222  CE1 PHE B 286      7.908  67.333   9.345  1.00 28.76           C
ATOM  1223  CE2 PHE B 286      8.483  65.070   8.834  1.00 26.34           C
ATOM  1224  CZ  PHE B 286      7.929  66.268   8.444  1.00 25.84           C
ATOM  1225  N   LYS B 287      9.630  64.973  15.581  1.00 25.94           N
ATOM  1226  CA  LYS B 287     10.497  64.672  16.748  1.00 28.87           C
ATOM  1227  C   LYS B 287     10.380  63.155  17.036  1.00 27.08           C
ATOM  1228  O   LYS B 287     11.384  62.698  17.635  1.00 32.05           O
ATOM  1229  CB  LYS B 287      9.988  65.355  18.011  1.00 30.07           C
ATOM  1230  CG  LYS B 287     10.028  66.861  17.818  1.00 39.43           C
ATOM  1231  CD  LYS B 287      9.570  67.558  19.107  1.00 38.49           C
ATOM  1232  CE  LYS B 287     10.244  67.044  20.346  1.00 45.19           C
ATOM  1233  NZ  LYS B 287      9.672  67.754  21.535  1.00 54.43           N
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ATOM  1234  N   GLU B 288     9.242  62.575  16.862  1.00 25.64      N
ATOM  1235  CA  GLU B 288     9.178  61.116  17.052  1.00 26.32      C
ATOM  1236  C   GLU B 288     8.413  60.476  15.877  1.00 24.61      C
ATOM  1237  O   GLU B 288     7.285  60.027  15.991  1.00 25.25      O
ATOM  1238  CB  GLU B 288     8.387  60.806  18.309  1.00 32.86      C
ATOM  1239  CG  GLU B 288     8.902  61.607  19.503  1.00 35.25      C
ATOM  1240  CD  GLU B 288     7.951  61.297  20.659  1.00 54.44      C
ATOM  1241  OE1 GLU B 288     7.664  62.114  21.548  1.00 57.99      O
ATOM  1242  OE2 GLU B 288     7.431  60.153  20.674  1.00 68.94      O
ATOM  1243  N   ASP B 289     9.128  60.422  14.758  1.00 27.23      N
ATOM  1244  CA  ASP B 289     8.555  59.981  13.522  1.00 24.79      C
ATOM  1245  C   ASP B 289     8.508  58.473  13.335  1.00 25.29      C
ATOM  1246  O   ASP B 289     8.887  57.768  14.308  1.00 24.41      O
ATOM  1247  CB  ASP B 289     9.360  60.708  12.422  1.00 25.83      C
ATOM  1248  CG  ASP B 289     10.692  60.129  12.073  1.00 27.56      C
ATOM  1249  OD1 ASP B 289     11.569  60.765  11.368  1.00 26.69      O
ATOM  1250  OD2 ASP B 289     11.066  58.996  12.481  1.00 26.79      O
ATOM  1251  N   CYS B 290     7.886  58.010  12.275  1.00 22.84      N
ATOM  1252  CA  CYS B 290     7.704  56.500  12.199  1.00 21.60      C
ATOM  1253  C   CYS B 290     9.037  55.805  12.161  1.00 23.32      C
ATOM  1254  O   CYS B 290     8.987  54.643  12.636  1.00 24.35      O
ATOM  1255  CB  CYS B 290     6.852  56.139  11.005  1.00 26.57      C
ATOM  1256  SG  CYS B 290     5.243  56.859  11.098  1.00 24.46      S
ATOM  1257  N   HIS B 291    10.201  56.313  11.700  1.00 22.17      N
ATOM  1258  CA  HIS B 291    11.434  55.536  11.831  1.00 19.85      C
ATOM  1259  C   HIS B 291    11.748  55.412  13.330  1.00 22.53      C
ATOM  1260  O   HIS B 291    12.291  54.353  13.749  1.00 25.72      O
ATOM  1261  CB  HIS B 291    12.580  56.283  11.067  1.00 25.25      C
ATOM  1262  CG  HIS B 291    12.309  56.139   9.600  1.00 23.27      C
ATOM  1263  ND1 HIS B 291    13.419  56.391   8.799  1.00 28.09      N
ATOM  1264  CD2 HIS B 291    11.299  55.759   8.803  1.00 26.35      C
ATOM  1265  CE1 HIS B 291    13.068  56.164   7.518  1.00 30.90      C
ATOM  1266  NE2 HIS B 291    11.827  55.756   7.487  1.00 25.80      N
ATOM  1267  N   GLN B 292    11.617  56.535  14.053  1.00 20.87      N
ATOM  1268  CA  GLN B 292    11.899  56.378  15.528  1.00 21.35      C
ATOM  1269  C   GLN B 292    10.971  55.416  16.173  1.00 22.91      C
ATOM  1270  O   GLN B 292    11.438  54.601  16.992  1.00 25.94      O
ATOM  1271  CB  GLN B 292    11.760  57.776  16.134  1.00 27.57      C
ATOM  1272  CG  GLN B 292    11.963  57.676  17.656  1.00 28.32      C
ATOM  1273  CD  GLN B 292    13.452  57.457  17.835  1.00 31.90      C
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ATOM  1274  OE1 GLN B 292      14.419  58.099  17.349  1.00 38.69           O
ATOM  1275  NE2 GLN B 292      13.881  56.477  18.651  1.00 35.17           N
ATOM  1276  N   LYS B 293       9.712  55.406  15.846  1.00 20.55           N
ATOM  1277  CA  LYS B 293       8.762  54.451  16.449  1.00 24.55           C
ATOM  1278  C   LYS B 293       9.085  53.009  16.085  1.00 25.63           C
ATOM  1279  O   LYS B 293       9.017  52.090  16.922  1.00 25.63           O
ATOM  1280  CB  LYS B 293       7.318  54.705  16.127  1.00 21.56           C
ATOM  1281  CG  LYS B 293       6.901  56.145  16.539  1.00 21.24           C
ATOM  1282  CD  LYS B 293       7.196  56.244  18.097  1.00 26.20           C
ATOM  1283  CE  LYS B 293       6.384  57.524  18.409  1.00 31.10           C
ATOM  1284  NZ  LYS B 293       6.423  57.726  19.903  1.00 43.02           N
ATOM  1285  N   ILE B 294       9.490  52.776  14.823  1.00 23.31           N
ATOM  1286  CA  ILE B 294       9.902  51.416  14.444  1.00 21.72           C
ATOM  1287  C   ILE B 294      11.119  50.970  15.201  1.00 21.93           C
ATOM  1288  O   ILE B 294      11.260  49.854  15.735  1.00 23.80           O
ATOM  1289  CB  ILE B 294      10.141  51.380  12.882  1.00 20.77           C
ATOM  1290  CG1 ILE B 294       8.820  51.436  12.192  1.00 23.01           C
ATOM  1291  CG2 ILE B 294      10.908  50.055  12.593  1.00 22.59           C
ATOM  1292  CD1 ILE B 294       9.017  51.734  10.679  1.00 22.74           C
ATOM  1293  N   ASP B 295      12.090  51.915  15.439  1.00 24.00           N
ATOM  1294  CA  ASP B 295      13.279  51.556  16.193  1.00 23.03           C
ATOM  1295  C   ASP B 295      12.810  51.238  17.660  1.00 22.93           C
ATOM  1296  O   ASP B 295      13.358  50.296  18.280  1.00 26.64           O
ATOM  1297  CB  ASP B 295      14.306  52.726  16.294  1.00 28.01           C
ATOM  1298  CG  ASP B 295      15.087  52.932  15.022  1.00 38.27           C
ATOM  1299  OD1 ASP B 295      15.208  51.983  14.218  1.00 33.40           O
ATOM  1300  OD2 ASP B 295      15.581  54.108  14.880  1.00 42.08           O
ATOM  1301  N   ASP B 296      11.920  52.041  18.191  1.00 23.66           N
ATOM  1302  CA  ASP B 296      11.461  51.902  19.576  1.00 23.31           C
ATOM  1303  C   ASP B 296      10.754  50.568  19.719  1.00 27.34           C
ATOM  1304  O   ASP B 296      10.846  49.917  20.781  1.00 29.90           O
ATOM  1305  CB  ASP B 296      10.523  53.024  20.023  1.00 27.92           C
ATOM  1306  CG  ASP B 296      11.243  54.375  20.115  1.00 29.10           C
ATOM  1307  OD1 ASP B 296      12.476  54.417  20.174  1.00 31.43           O
ATOM  1308  OD2 ASP B 296      10.435  55.308  20.207  1.00 39.50           O
ATOM  1309  N   LEU B 297       9.999  50.114  18.738  1.00 23.57           N
ATOM  1310  CA  LEU B 297       9.297  48.826  18.793  1.00 27.72           C
ATOM  1311  C   LEU B 297      10.306  47.716  18.989  1.00 22.65           C
ATOM  1312  O   LEU B 297      10.243  46.851  19.874  1.00 25.81           O
ATOM  1313  CB  LEU B 297       8.513  48.608  17.442  1.00 23.42           C
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ATOM  1314  CG  LEU B 297      7.866  47.205  17.399  1.00 25.90           C
ATOM  1315  CD1 LEU B 297      6.812  46.977  18.509  1.00 23.36           C
ATOM  1316  CD2 LEU B 297      7.211  47.055  16.051  1.00 30.35           C
ATOM  1317  N   PHE B 298     11.366  47.725  18.188  1.00 22.40           N
ATOM  1318  CA  PHE B 298     12.391  46.661  18.204  1.00 22.91           C
ATOM  1319  C   PHE B 298     13.335  46.770  19.381  1.00 22.01           C
ATOM  1320  O   PHE B 298     13.984  45.762  19.702  1.00 26.38           O
ATOM  1321  CB  PHE B 298     13.156  46.542  16.835  1.00 21.43           C
ATOM  1322  CG  PHE B 298     12.207  45.937  15.757  1.00 21.93           C
ATOM  1323  CD1 PHE B 298     11.605  46.773  14.838  1.00 23.82           C
ATOM  1324  CD2 PHE B 298     11.960  44.572  15.714  1.00 19.56           C
ATOM  1325  CE1 PHE B 298     10.708  46.295  13.908  1.00 23.51           C
ATOM  1326  CE2 PHE B 298     10.970  44.081  14.887  1.00 23.21           C
ATOM  1327  CZ  PHE B 298     10.370  44.951  13.968  1.00 22.84           C
ATOM  1328  N   SER B 299     13.467  47.943  19.995  1.00 25.99           N
ATOM  1329  CA  SER B 299     14.276  48.175  21.182  1.00 27.97           C
ATOM  1330  C   SER B 299     13.442  47.959  22.437  1.00 27.60           C
ATOM  1331  O   SER B 299     14.127  47.927  23.491  1.00 33.25           O
ATOM  1332  CB  SER B 299     14.675  49.724  21.230  1.00 27.83           C
ATOM  1333  OG  SER B 299     15.549  49.784  20.090  1.00 48.34           O
ATOM  1334  N   GLY B 300     12.122  47.850  22.391  1.00 25.83           N
ATOM  1335  CA  GLY B 300     11.403  47.602  23.639  1.00 26.72           C
ATOM  1336  C   GLY B 300     11.192  48.880  24.413  1.00 30.91           C
ATOM  1337  O   GLY B 300     11.025  48.835  25.657  1.00 31.51           O
ATOM  1338  N   LYS B 301     11.070  49.971  23.686  1.00 29.75           N
ATOM  1339  CA  LYS B 301     10.888  51.281  24.368  1.00 33.01           C
ATOM  1340  C   LYS B 301      9.712  52.045  23.807  1.00 34.70           C
ATOM  1341  O   LYS B 301      9.648  53.260  24.046  1.00 43.76           O
ATOM  1342  CB  LYS B 301     12.064  52.152  23.774  1.00 33.50           C
ATOM  1343  CG  LYS B 301     13.401  51.715  24.317  1.00 45.65           C
ATOM  1344  CD  LYS B 301     14.547  52.570  23.781  1.00 57.56           C
ATOM  1345  CE  LYS B 301     15.836  52.170  24.485  1.00 66.05           C
ATOM  1346  NZ  LYS B 301     15.703  50.863  25.187  1.00 63.08           N
ATOM  1347  N   HIS B 302      8.898  51.483  22.961  1.00 35.10           N
ATOM  1348  CA  HIS B 302      7.798  52.142  22.301  1.00 37.49           C
ATOM  1349  C   HIS B 302      6.747  52.604  23.289  1.00 40.04           C
ATOM  1350  O   HIS B 302      6.231  51.751  24.034  1.00 39.71           O
ATOM  1351  CB  HIS B 302      7.224  51.206  21.268  1.00 35.19           C
ATOM  1352  CG  HIS B 302      6.067  51.578  20.440  1.00 49.29           C
ATOM  1353  ND1 HIS B 302      5.681  50.761  19.395  1.00 47.23           N
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ATOM 1354 CD2 HIS B 302 5.217 52.623 20.430 1.00 63.81 C
ATOM 1355 CE1 HIS B 302 4.609 51.269 18.805 1.00 64.17 C
ATOM 1356 NE2 HIS B 302 4.315 52.414 19.413 1.00 68.77 N
ATOM 1357 OXT HIS B 302 6.454 53.826 23.197 1.00 53.33 O
TER 1358 HIS B 302
HETATM 1359 O HOH 1 -4.215 33.391 34.133 1.00 53.22 O
HETATM 1360 O HOH 2 18.838 49.534 11.779 1.00 44.39 O
HETATM 1361 O HOH 3 18.287 39.678 10.876 1.00 40.67 O
HETATM 1362 O HOH 4 8.917 33.059 11.916 1.00 39.17 O
HETATM 1363 O HOH 5 4.222 60.992 19.391 1.00 53.63 O
HETATM 1364 O HOH 6 14.649 53.645 5.675 1.00 47.99 O
HETATM 1365 O HOH 7 11.281 35.124 -0.410 1.00 43.81 O
HETATM 1366 O HOH 8 10.073 32.343 34.003 1.00 39.83 O
HETATM 1367 O HOH 9 15.435 57.496 13.875 1.00 47.64 O
HETATM 1368 O HOH 10 1.986 52.789 20.289 1.00 58.39 O
HETATM 1369 O HOH 11 4.975 60.743 16.901 1.00 39.41 O
HETATM 1370 O HOH 12 -3.385 52.917 -1.600 1.00 51.02 O
HETATM 1371 O HOH 13 -13.243 36.380 20.476 1.00 42.17 O
HETATM 1372 O HOH 14 0.264 32.024 34.744 1.00 47.18 O
HETATM 1373 O HOH 15 -6.609 45.944 14.783 1.00 70.97 O
HETATM 1374 O HOH 16 12.032 51.791 0.727 1.00 41.27 O
HETATM 1375 O HOH 17 14.999 64.979 4.406 1.00 48.65 O
HETATM 1376 O HOH 18 17.982 48.567 24.010 1.00 67.58 O
HETATM 1377 O HOH 19 18.188 40.205 24.486 1.00 48.05 O
HETATM 1378 O HOH 20 1.933 28.876 14.156 1.00 45.02 O
HETATM 1379 O HOH 21 3.796 66.937 -1.003 1.00 45.54 O
HETATM 1380 O HOH 22 -3.930 63.076 7.853 1.00 45.06 O
HETATM 1381 O HOH 23 19.377 45.063 31.421 1.00 63.88 O
HETATM 1382 O HOH 24 10.030 47.404 30.475 1.00 66.92 O
HETATM 1383 O HOH 25 13.644 53.484 2.115 1.00 43.24 O
HETATM 1384 O HOH 26 -5.065 60.214 -2.204 1.00 60.28 O
HETATM 1385 O HOH 27 6.822 67.425 21.500 1.00 54.16 O
HETATM 1386 O HOH 28 17.916 33.371 34.751 1.00 43.97 O
HETATM 1387 O HOH 29 17.128 43.746 3.192 1.00 82.65 O
HETATM 1388 O HOH 30 -6.266 67.668 0.459 1.00 46.23 O
HETATM 1389 O HOH 31 7.405 62.268 10.357 1.00 42.73 O
HETATM 1390 O HOH 32 15.581 43.945 1.401 1.00 57.25 O
HETATM 1391 O HOH 33 -7.910 47.795 12.095 1.00 45.59 O
HETATM 1392 O HOH 34 17.024 49.940 15.276 1.00 49.07 O
HETATM 1393 O HOH 35 8.499 65.007 22.461 1.00 47.51 O

HETATM	1394	O	HOH	36	-0.367	48.312	28.954	1.00 51.02	O
HETATM	1395	O	HOH	37	-1.643	35.106	10.278	1.00 51.80	O
HETATM	1396	O	HOH	38	8.875	32.312	14.589	1.00 44.92	O
HETATM	1397	O	HOH	39	14.591	53.421	26.734	1.00 54.47	O
HETATM	1398	O	HOH	40	-11.341	62.679	8.845	1.00 65.05	O
HETATM	1399	O	HOH	41	3.927	62.066	15.472	1.00 38.47	O
HETATM	1400	O	HOH	42	-7.281	41.736	19.860	1.00 52.54	O
HETATM	1401	O	HOH	43	-2.014	56.542	17.379	1.00 58.28	O
HETATM	1402	O	HOH	44	4.173	49.699	23.881	1.00 48.81	O
HETATM	1403	O	HOH	45	15.763	51.418	6.274	1.00 50.89	O
HETATM	1404	O	HOH	46	-5.015	40.116	20.052	1.00 38.76	O
HETATM	1405	O	HOH	47	-13.876	33.442	19.654	1.00 41.56	O
HETATM	1406	O	HOH	48	11.100	53.490	-1.243	1.00 51.95	O
HETATM	1407	O	HOH	49	14.296	48.222	26.202	1.00 46.15	O
HETATM	1408	O	HOH	50	12.094	58.957	-1.935	1.00 66.19	O
HETATM	1409	O	HOH	51	-0.363	33.562	11.861	1.00 47.15	O
HETATM	1410	O	HOH	52	16.748	63.226	4.115	1.00 49.17	O
HETATM	1411	O	HOH	53	16.029	41.422	23.111	1.00 41.73	O
HETATM	1412	O	HOH	54	-15.194	36.941	22.656	1.00 28.98	O
HETATM	1413	O	HOH	55	13.284	40.873	6.595	1.00 29.61	O
HETATM	1414	O	HOH	56	12.067	61.344	14.857	1.00 27.44	O
HETATM	1415	O	HOH	57	3.230	32.037	23.779	1.00 30.77	O
HETATM	1416	O	HOH	58	9.568	62.641	0.360	1.00 32.73	O
HETATM	1417	O	HOH	59	6.579	69.146	1.553	1.00 39.07	O
HETATM	1418	O	HOH	60	5.396	68.921	-0.875	1.00 43.11	O
HETATM	1419	O	HOH	61	-0.765	50.376	19.294	1.00 33.30	O
HETATM	1420	O	HOH	62	17.619	40.867	26.969	1.00 32.47	O
HETATM	1421	O	HOH	63	1.175	39.117	32.509	1.00 34.26	O
HETATM	1422	O	HOH	64	-3.108	37.232	22.171	1.00 33.78	O
HETATM	1423	O	HOH	65	14.036	57.095	4.198	1.00 33.08	O
HETATM	1424	O	HOH	66	15.991	40.644	9.396	1.00 31.36	O
HETATM	1425	O	HOH	67	5.370	35.591	5.654	1.00 34.91	O
HETATM	1426	O	HOH	68	-4.254	34.143	21.881	1.00 41.64	O
HETATM	1427	O	HOH	69	-10.321	38.410	25.612	1.00 36.21	O
HETATM	1428	O	HOH	70	-2.807	46.890	24.208	1.00 39.64	O
HETATM	1429	O	HOH	71	13.876	64.869	12.996	1.00 34.52	O
HETATM	1430	O	HOH	72	4.755	27.441	30.254	1.00 46.13	O
HETATM	1431	O	HOH	73	-15.942	32.065	20.573	1.00 39.55	O
HETATM	1432	O	HOH	74	5.416	34.430	8.102	1.00 40.39	O
HETATM	1433	O	HOH	75	-0.534	32.451	14.335	1.00 34.37	O

HETATM	1434	O	HOH	76	2.188	32.706	11.148	1.00 37.38	O
HETATM	1435	O	HOH	77	10.184	56.092	-0.224	1.00 39.79	O
HETATM	1436	O	HOH	78	5.731	48.343	1.193	1.00 36.56	O
HETATM	1437	O	HOH	79	-4.296	33.874	16.230	1.00 37.09	O
HETATM	1438	O	HOH	80	2.789	25.851	19.884	1.00 37.03	O
HETATM	1439	O	HOH	81	12.818	43.187	2.482	1.00 35.03	O
HETATM	1440	O	HOH	82	-7.902	39.359	18.484	1.00 41.93	O
HETATM	1441	O	HOH	83	16.109	44.634	21.227	1.00 32.29	O
HETATM	1442	O	HOH	84	11.052	65.001	0.599	1.00 38.18	O
HETATM	1443	O	HOH	85	12.818	45.671	3.492	1.00 33.67	O
HETATM	1444	O	HOH	86	15.127	60.190	1.698	1.00 45.84	O
HETATM	1445	O	HOH	87	-4.938	50.954	0.702	1.00 49.34	O
HETATM	1446	O	HOH	88	9.131	42.936	32.780	1.00 44.90	O
HETATM	1447	O	HOH	89	9.780	58.075	20.182	1.00 48.35	O
HETATM	1448	O	HOH	90	12.526	34.159	9.787	1.00 47.64	O
HETATM	1449	O	HOH	91	17.890	51.629	10.711	1.00 39.90	O
HETATM	1450	O	HOH	92	-3.389	39.620	8.151	1.00 45.53	O
HETATM	1451	O	HOH	93	6.934	42.923	-0.634	1.00 43.21	O
HETATM	1452	O	HOH	94	7.777	55.462	21.607	1.00 51.04	O
HETATM	1453	O	HOH	95	12.824	64.410	2.571	1.00 38.10	O
HETATM	1454	O	HOH	96	11.080	46.801	-5.487	1.00 44.36	O
HETATM	1455	O	HOH	97	13.258	59.480	9.903	1.00 36.96	O
HETATM	1456	O	HOH	98	14.870	39.034	19.574	1.00 41.18	O
HETATM	1457	O	HOH	99	-2.140	41.896	25.495	1.00 42.12	O
HETATM	1458	O	HOH	100	-3.695	31.825	24.645	1.00 41.51	O
HETATM	1459	O	HOH	101	5.856	33.181	1.065	1.00 44.58	O
HETATM	1460	O	HOH	102	23.450	39.517	35.251	1.00 58.45	O
HETATM	1461	O	HOH	103	17.607	63.014	7.448	1.00 51.52	O
HETATM	1462	O	HOH	104	19.084	43.155	28.944	1.00 41.89	O
HETATM	1463	O	HOH	105	19.569	41.448	18.016	1.00 45.55	O
HETATM	1464	O	HOH	106	6.282	39.156	-0.594	1.00 40.95	O
HETATM	1465	O	HOH	107	3.608	31.521	12.838	1.00 38.29	O
HETATM	1466	O	HOH	108	5.340	58.553	23.325	1.00 56.09	O
HETATM	1467	O	HOH	109	-0.098	26.492	16.742	1.00 51.50	O
HETATM	1468	O	HOH	110	17.107	48.579	-9.575	1.00 48.19	O
HETATM	1469	O	HOH	111	1.112	44.707	2.608	1.00 40.43	O
HETATM	1470	O	HOH	112	16.036	35.486	8.319	1.00 51.54	O
HETATM	1471	O	HOH	113	12.626	35.166	33.691	1.00 39.95	O
HETATM	1472	O	HOH	114	3.330	49.012	-0.102	1.00 54.48	O
HETATM	1473	O	HOH	115	20.022	39.070	22.895	1.00 55.71	O

HETATM	1474	O	HOH	116	10.117	47.515	34.607	1.00	55.47	O
HETATM	1475	O	HOH	117	10.802	41.433	-3.200	1.00	41.94	O
HETATM	1476	O	HOH	118	12.699	36.753	35.595	1.00	54.83	O
HETATM	1477	O	HOH	119	-0.799	31.347	21.947	1.00	46.24	O
HETATM	1478	O	HOH	120	3.962	25.054	22.563	1.00	45.46	O
HETATM	1479	O	HOH	121	13.790	59.142	13.294	1.00	41.19	O
HETATM	1480	O	HOH	122	4.266	55.549	20.922	1.00	47.14	O
HETATM	1481	O	HOH	123	-7.352	30.602	20.888	1.00	45.74	O
HETATM	1482	O	HOH	124	15.898	45.939	-5.495	1.00	49.10	O
HETATM	1483	O	HOH	125	-3.050	47.320	18.265	1.00	42.75	O
HETATM	1484	O	HOH	126	10.403	31.668	10.731	1.00	50.32	O
HETATM	1485	O	HOH	127	17.448	40.984	20.774	1.00	55.89	O
HETATM	1486	O	HOH	128	-6.202	32.811	19.196	1.00	61.25	O
HETATM	1487	O	HOH	129	16.550	45.787	-1.303	1.00	60.67	O
HETATM	1488	O	HOH	130	2.461	51.469	22.030	1.00	47.89	O
HETATM	1489	O	HOH	131	11.519	67.677	23.175	1.00	55.94	O
HETATM	1490	O	HOH	132	5.350	61.193	13.514	1.00	30.11	O
HETATM	1491	O	HOH	133	13.495	40.851	3.965	1.00	37.96	O
HETATM	1492	O	HOH	134	6.125	48.964	24.558	1.00	99.00	O
HETATM	1493	O	HOH	135	12.692	45.086	31.102	1.00	46.72	O
HETATM	1494	O	HOH	136	8.372	40.368	-2.803	1.00	47.67	O
HETATM	1495	O	HOH	137	-8.788	32.927	33.336	1.00	50.16	O
HETATM	1496	O	HOH	138	15.804	49.105	17.346	1.00	55.58	O
HETATM	1497	O	HOH	139	-15.741	39.473	21.927	1.00	60.70	O
HETATM	1498	O	HOH	140	-5.089	45.153	17.414	1.00	44.88	O
HETATM	1499	O	HOH	141	-13.400	30.643	20.791	1.00	50.50	O
HETATM	1500	O	HOH	142	-13.246	60.819	8.552	1.00	51.52	O
HETATM	1501	O	HOH	143	23.320	40.711	16.836	1.00	47.25	O
HETATM	1502	O	HOH	144	13.575	60.846	17.292	1.00	44.01	O
HETATM	1503	O	HOH	145	12.004	47.323	-3.094	1.00	48.02	O
HETATM	1504	O	HOH	146	10.599	61.322	-1.495	1.00	48.28	O
HETATM	1505	O	HOH	147	8.019	61.170	-4.066	1.00	53.49	O
HETATM	1506	O	HOH	148	-6.253	49.514	11.028	1.00	56.76	O
HETATM	1507	O	HOH	149	-9.451	40.692	26.921	1.00	44.83	O
HETATM	1508	O	HOH	150	19.204	50.228	21.178	1.00	59.13	O
HETATM	1509	O	HOH	151	2.582	26.513	15.245	1.00	51.39	O
HETATM	1510	O	HOH	152	4.026	46.486	-3.013	1.00	57.34	O
HETATM	1511	O	HOH	153	16.267	55.892	11.019	1.00	48.44	O
HETATM	1512	O	HOH	154	1.210	67.411	-1.165	1.00	48.04	O
HETATM	1513	O	HOH	155	2.360	46.499	0.941	1.00	66.58	O

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HETATM 1514  O   HOH   156      11.053  55.907  23.988  1.00 54.62           O
HETATM 1515  O   HOH   157      -4.436  30.868  22.082  1.00 60.65           O
HETATM 1516  O   HOH   158      -3.896  44.317  24.858  1.00 42.03           O
HETATM 1517  O   HOH   159      14.528  53.202  20.544  1.00 49.82           O
HETATM 1518  O   HOH   160      -3.587  31.389  19.616  1.00 66.25           O
HETATM 1519  O   HOH   161       6.792  25.487  17.573  1.00 50.39           O
HETATM 1520  O   HOH   162      10.764  30.263  35.419  1.00 36.82           O
HETATM 1521  O   HOH   163      21.353  50.293   9.049  1.00 55.17           O
HETATM 1522  O   HOH   164      -6.155  45.722   4.030  1.00 58.56           O
HETATM 1523  O   HOH   165      -1.643  33.968  22.162  1.00 32.78           O
HETATM 1524  O   HOH   166      20.572  39.489   9.475  1.00 54.99           O
HETATM 1525  O   HOH   167      16.138  59.711   9.718  1.00 50.63           O
HETATM 1526  O   HOH   168       7.237  50.386  25.663  1.00 46.62           O
HETATM 1527  O   HOH   169      23.376  32.725  15.317  1.00 57.83           O
HETATM 1528  O   HOH   170      -6.893  46.336  20.725  1.00 51.05           O
HETATM 1529  O   HOH   171      -8.757  52.883  -3.912  1.00 55.02           O
HETATM 1530  O   HOH   172      -2.827  48.125  26.461  1.00 67.86           O
HETATM 1531  O   HOH   173     -10.391  32.607  19.235  1.00 53.07           O
HETATM 1532  O   HOH   174      12.604  56.386  22.103  1.00 58.51           O
HETATM 1533  O   HOH   175      22.798  50.951   6.720  1.00 54.25           O
HETATM 1534  O   HOH   176       9.471  60.615  -6.502  1.00 60.38           O
HETATM 1535  O   HOH   177      15.724  60.671  14.619  1.00 61.18           O
HETATM 1536  O   HOH   178      22.143  45.991   8.636  1.00 64.81           O
HETATM 1537  O   HOH   179      14.368  57.230   1.558  1.00 52.29           O
HETATM 1538  O   HOH   180       6.260  72.265   1.689  1.00 58.15           O
HETATM 1539  O   HOH   181      -5.293  56.914  16.553  1.00 62.84           O
HETATM 1540  O   HOH   182      20.371  47.749  25.744  1.00 62.07           O
HETATM 1541  O   HOH   183      -0.726  65.989  -1.991  1.00 57.90           O
HETATM 1542  O   HOH   184       8.049  52.633  -3.838  1.00 56.88           O
HETATM 1543  O   HOH   185      22.895  31.309  13.193  1.00 61.69           O
HETATM 1544  O   HOH   186      21.848  46.891  18.577  1.00 64.50           O
HETATM 1545  O   HOH   187      12.606  56.305  -0.147  1.00 62.06           O
HETATM 1546  O   HOH   188       0.808  33.921   8.196  1.00 52.41           O
HETATM 1547  O   HOH   189      -4.938  46.394  29.675  1.00 61.58           O
HETATM 1548  O   HOH   190      -1.908  31.725  34.223  1.00 52.77           O
HETATM 1549  O   HOH   191      -1.212  41.160   2.846  1.00 55.54           O
HETATM 1550  O   HOH   192      22.586  44.657  11.116  1.00 62.81           O
HETATM 1551  O   HOH   193      -5.191  44.209  13.767  1.00 61.83           O
HETATM 1552  O   HOH   194       5.483  49.662  -0.942  1.00 53.72           O
CONECT  350  593
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CONECT  356  481
CONECT  481  356
CONECT  593  350
CONECT 1015 1256
CONECT 1021 1146
CONECT 1146 1021
CONECT 1256 1015
MASTER    286    0    0   11    0    0    0    6 1550    2    8   14
END
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What is claimed is:

1. A method of treating or preventing a condition associated with CD81 binding in a subject in need of such treatment, the method comprising administering to the subject a compound capable of binding to a binding site in a CD81 protein, said binding site comprising one or more amino acids of CD81 selected from Cys157, Ser159, Ser160, Thr163, Ala164, Thr166, Thr167, Ile181, Asn184, Leu185 and Asp189 of CD81, under conditions such that the condition associated with CD81 binding is treated or prevented.

2. The method of claim 1, wherein the condition associated with CD81 binding is selected from HCV infection, multiple sclerosis, and malaria.

3. The method of claim 1, wherein the condition associated with CD81 binding is HCV infection.

4. The method of claim 1, wherein the compound is a compound selected from the compounds of Tables 1 and 2.

5. A method of treating HCV infection in a subject in need of such treatment, the method comprising administering to the subject a compound of Table 1, Table 2 or Table 3 under conditions such that HCV infection is treated.

6. A method of inhibiting HCV helicase in a cell, the method comprising contacting the cell with a compound capable of inhibiting HCV helicase.

7. A method of inhibiting HCV polymerase in a cell, the method comprising contacting the cell with a compound of Table 3.

8. A method of inhibiting HCV infection in a cell, the method comprising contacting the cell with a compound of Table 1, Table 2 or Table 3.

9. An oral dosage form comprising a compound of Table 1, Table 2 or Table 3, or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable vehicle.

10. A method for treating a subject diagnosed as having HCV infection, the method comprising

administering to the subject a pharmaceutically effective amount of a compound of Table 1, Table 2 or Table 3, or a pharmaceutically acceptable salt thereof.

11. A kit for the treatment of HCV infection, the kit comprising

an effective amount of the amount of a compound of Table 1, Table 2 or Table 3 or a pharmaceutically acceptable salt thereof; and

instructions for administering the compound of Table 1, Table 2 or Table 3 or a pharmaceutically acceptable salt thereof to a subject to treat HCV infection.

12. A computer for producing a three-dimensional representation of

a) a molecule or molecular complex, wherein said molecule or molecular complex comprises a binding site defined by structure coordinates of amino acid residues of the NS5B protein; or

b) a three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than about 2.0 (more preferably not more than 1.5) angstroms, wherein said computer comprises:

(i) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of structure coordinates of amino acid residues of the NS5B protein;

(ii) a working memory for storing instructions for processing said machine-readable data;

(iii) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

(iv) a display coupled to said central-processing unit for displaying said three-dimensional representation.

13. A method for evaluating the potential of a chemical entity to associate with a) a molecule or molecular complex comprising a binding pocket defined by structure coordinates of amino acid residues of the NS5B protein, or b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 2.0 (more preferably 1.5) angstroms,

the method comprising the steps of:

i) employing computational means to perform a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex; and

ii) analyzing the results of the fitting operation to quantify the association between the chemical entity and the binding pocket.

14. A method of preserving liver function in a subject suffering from HCV infection, the method comprising administering to the subject a compound of Table 1 or Table 2 or a pharmaceutically acceptable salt thereof, under conditions such that liver function in the subject is preserved.

15. A packaged pharmaceutical formulation for the treatment or prevention of liver damage in a subject suffering from HCV infection, the packaged pharmaceutical formulation comprising:

an effective amount of the amount of a compound of Table 1, Table 2 or Table 3 or a pharmaceutically acceptable salt thereof; and

instructions for administering the compound of Table 1, Table 2 or Table 3 or a pharmaceutically acceptable salt thereof to a subject suffering from HCV infection for the treatment or prevention of liver damage in the subject.

16. A computer for producing a three-dimensional representation of

a) a molecule or molecular complex, wherein said molecule or molecular complex comprises a binding site in the CD81 protein which binds to HCV E2 protein; or

b) a three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of one or more amino acids Cys157, Ser159, Ser160, Thr163, Ala164, Thr166, Thr167, Ile181, Asn184, Leu185 and Asp189 of CD81 of not more than about 2.0 (more preferably not more than 1.5) angstroms,

wherein said computer comprises: (i) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of structure coordinates of one or more amino acid residues selected from Cys157, Ser159, Ser160, Thr163, Ala164, Thr166, Thr167, Ile181, Asn184, Leu185 and Asp189 of the human CD81 protein; (ii) a working memory for storing instructions for processing said machine-readable data; (iii) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and (iv) a display coupled to said central-processing unit for displaying said three-dimensional representation.

17. A method for evaluating the potential of a chemical entity to bind with a) a molecule or molecular complex comprising a binding pocket defined by structure coordinates of one or more of amino acid residues Ser160,Thr163, Ala164, Thr167, Ile181, Leu185 and Asp189 of the CD81 protein, or b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 2.0 (more preferably 1.5) angstroms,

the method comprising the steps of:

i) employing computational means to perform a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex; and

ii) analyzing the results of the fitting operation to quantify the association between the chemical entity and the binding pocket.

18. A method for preventing HCV infection in a subject, the method comprising administering to the subject an effective amount of a compound capable of disrupting binding of HCV E2 protein with CD81 protein, such that HCV infection is prevented in the subject.

19. The method of claim 18, wherein the compound is a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt thereof.

20. A method for treating or preventing a condition associated with CD81 binding in a subject in need of such treatment, the method comprising administering to the subject an effective amount of a compound capable of disrupting binding of a protein with CD81 protein, such that a condition associated with CD81 binding is treated or prevented in the subject.

21. The method of claim 20, wherein the compound is a compound of Table 1 or Table 2, or a pharmaceutically acceptable salt thereof.

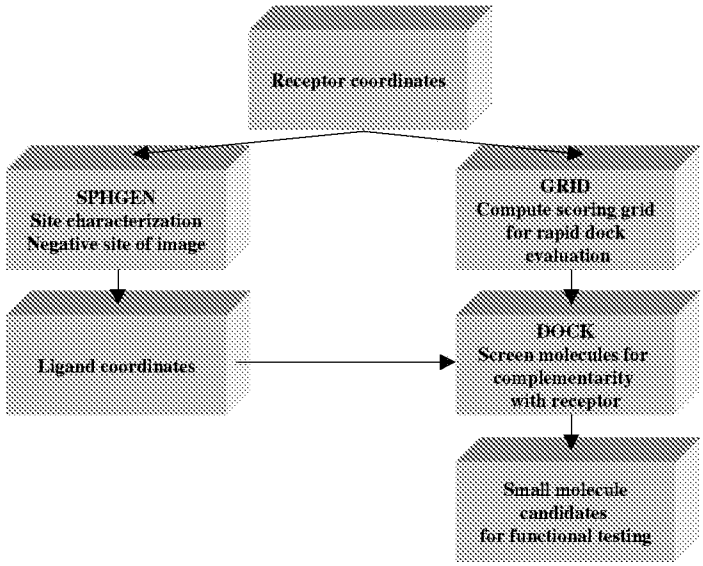

Figure 1. *In silico* molecular docking strategy