[DESCRIPTION]

[Title of Invention]

PPARδ ACTIVATOR

[Technical Field]

[0001]

The present invention relates to a peroxisome proliferator-activated receptor δ (PPARδ) activator.

Priority is claimed on Japanese Patent Application No. 2018-199523 filed in Japan on October 23, 2018, the content of which is incorporated herein by reference.

[Background Art]

[0002]

PPAR is a member of the nuclear hormone receptor superfamily, and is a ligand-activated transcriptional factor. In mammals, PPAR has family members of α, γ and δ. PPARα binds free fatty acids as its endogenous ligands and regulates the expression of various genes regulating lipolysis and is therefore regarded as a target of drug for treatment of hyperlipidemia. PPARγ binds long-chain fatty acids, eicosanoids and their related chemicals like as its endogenous ligands to promote adipocyte differentiation, and is therefore regarded as a target substance for thiazolidine, which is an insulin resistance-improving medicine. PPARδ is widely expressed in various tissues, but the endogenous ligands and its physiological functions have been remained largely unknown, therefore PPARδ can be classified an orphan receptor (see, for example, PTL 1). PPARδ is composed of an N-terminal domain with ligand-independent transcriptional activation ability, a zinc finger domain with a DNA binding ability, and a ligand binding domain (LBD) having a ligand-dependent transcriptional activation ability. The amino acid sequence of LBD of PPARδ has 70% homology (sequence identity) with LBD of PPARα

and 68% homology (sequence identity) with LBD of PPARγ (see, for example, NPL 2).

[0003]

In recent years, PPARδ has been reported to be an important transcriptional regulator of lipid catabolism, transport, accumulation, etc. (see, for example, NPL 3), attracting keen attention as a new molecular target of therapeutic agents for metabolic disorders and the like. For example, it has been reported that ingestion of a PPARδ agonist enhances an exercise-induced effect such as exercise endurance, and that the PPARδ agonist serves as an exercise performance-enhancing medicine (see, for example, PTL 1 and NPL 4). Further, by using the AMPK (5'AMP-activated protein kinase) agonist and the PPARδ agonist in combination, the exercise effect on the subject is further improved (see, for example, PTL 2 and NPL 4). In addition, it has been reported that administration of PPARδ agonist suppresses lipid-induced endoplasmic reticulum (ER) stress, which plays an important role in the development of cardiomyopathy (see, for example, NPL 5), and that a hepatic protective effect and an antifibrotic effect can be obtained in hepatic fibrosis induced by carbon tetrachloride administration (see, for example, NPL 6).

[0004]

Examples of the PPARδ agonists include a phenoxyacetic acid derivative represented by GW501516 (CAS No.: 317318-70-0). The basic skeleton of the phenoxyacetic acid derivative is a chemical structure, in which a long-chain hydrophobic group such as a non-polar hydrocarbon is bonded to a carboxyl group (-COOH). From the results of structural analysis of a complex of PPARδ and a phenoxyacetic acid derivative that acts as a PPARδ agonist, it has been found that the ligand-binding pocket of PPARδ is a Y-shaped pocket consisting of three tunnel-shaped cavities called arms I, II and III (arm I, arm II and arm III) (see, for example, NPL 7 and NPL 8). As the PPARδ

agonist, a medicine having a skeleton in which a hydrophobic group is branched, such as GW2331 (CAS No.: 190844-95-2), has also been developed.

[0005]

On the other hand, metformin is a biguanide-based medicine widely used as an oral antidiabetic medicine. It is known that metformin enhances sugar uptake in skeletal muscle and fatty acid β-oxidation in the liver by activating AMPK (see, for example, NPL 9). In addition, it has also been reported that metformin suppresses mitochondrial glycerophosphate dehydrogenase in the liver to suppress gluconeogenesis and lower blood glucose (see, for example, NPL 10).

[Citation List]

[Patent Literature]

[0006]

[PTL 1] Published Japanese Translation No. 2010-514804 of the PCT International Publication

[PTL 2] Published Japanese Translation No. 2011-507970 of the PCT International Publication

[Non-Patent Literature]

[0007]

[NPL 1] Evans et al., Nature Medicine 2004, vol. 10 (4), p. 355-361

[NPL 2] Willson et al., Journal of Medicinal Chemistry, 2000, vol. 43(4), p. 527-550

[NPL 3] Barish et al., The Journal of Clinical Investigation, 2006, vol.116 (3), p. 590-597

[NPL 4] Narkar et al., Cell, 2008, vol. 134 (3), p. 405-415

[NPL 5] Palomer et al, International Journal of Cardiology, 2014, Vol. 174, P. 110-118

[NPL 6] Iwaisako et al., Proceedings of the National Academy of Sciences of the United States of America, 2012, vol. 109 (21), p. E1369-E1376

[NPL 7] Xu et al., Molecular Cell, 1999, vol. 3(3), p. 397-403

[NPL 8] Wu et al, Proceedings of the National Academy of Sciences of the United States of America, 2017, Vol. 114(13), P. E2563-E2570

[NPL 9] Zhou et al., Journal of Clinical Investigation, 2001, vol. 108(8), p. 1167-1174

[NPL 10] Madiraju et al., Nature, 2014, vol. 510(7506), p. 542-546

[NPL 11] Eikawa et al., Proceedings of the National Academy of Sciences of the United States of America, 2015, vol. 112(6), p. 1809-1814

[NPL 12] Sugden et al., Pharmacological Research, 2009, vol. 60, p. 141–150

[Summary of Invention]

[Technical Problem]

[0008]

A main object of the present invention is to provide a PPARδ activator containing a novel PPARδ agonist as an active ingredient, and an exercise tolerance-improving agent containing the PPARδ agonist as an active ingredient.

[Solution to problem]

[0009]

The present inventors have conducted intensive studies, and as a result, discovered that metformin is a PPARδ agonist and activates the transcriptional activity of PPARδ. Furthermore, from the results of the co-crystal structure analysis of metformin and ligand-binding domain (LBD) of human PPARδ (hPPARδ), it was found that metformin binds to the ligand binding pocket of PPARδ. In this binding mode, the two amino groups of the biguanide skeleton of metformin interact with and bind to the amino acid residues near the entrance of the ligand-binding pocket. As a result, the LBD of PPARδ changes its structure into an active conformation, thereby completing the present invention.

[0010]

That is, the PPARδ activators and the exercise tolerance-improving agents according to the present invention are as following [1] to [8].

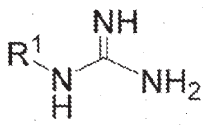
[1] A PPARδ activator comprising a guanidine derivative or a biguanidine derivative as an active ingredient, wherein the PPARδ activator activates transcriptional activity of PPARδ (peroxisome proliferator-activated receptor δ).

[2] The PPARδ activator according to [1], wherein the guanidine derivative and the biguanidine derivative are capable of fitting within a ligand binding pocket of PPARδ, in a state where a guanidino group or a biguanidino group forms a hydrogen bond with amino acid residues of the 413th histidine, 287th histidine, 253rd threonine and the 437th tyrosine of human PPARδ that constitute an interior surface of the ligand binding pocket.

[3] The PPARδ activator according to [1] or [2], wherein the guanidine derivative is a compound represented by the following general formula (1) (excluding the biguanidine derivative),

[0011]

[Chemical formula 1]



(1)

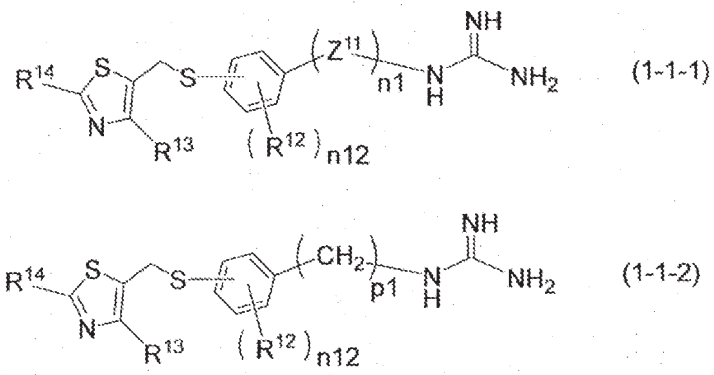
[in formula (1), R^1 represents a monovalent organic group].

[0012]

[4] The PPARδ activator according to [3], wherein the guanidine derivative is a compound represented by any one of the following general formulas (1-1-1) to (1-1-4),

[0013]

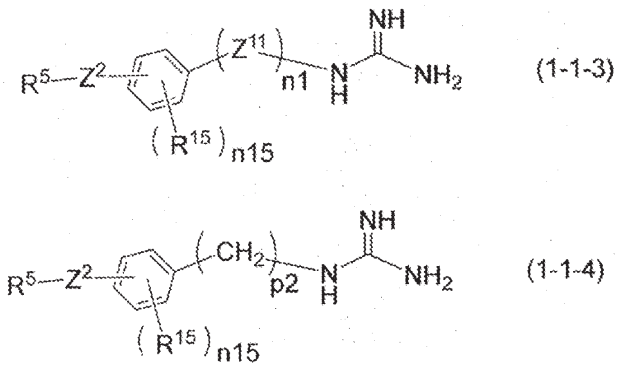
[Chemical formula 2]



[in formulas (1-1-1) and (1-1-2), Z^{11} represents an oxygen atom or a sulfur atom, n1 represents 0 or 1, R^{12} represents an aliphatic hydrocarbon group having 1 to 6 carbon atoms, n12 represents an integer of 0 to 2, R^{13} represents a hydrogen atom or an aliphatic hydrocarbon group having 1 to 6 carbon atoms, R^{14} represents an optionally substituted aromatic hydrocarbon group, and p1 represents an integer of 1 or more],

[0014]

[Chemical formula 3]



[in formulas (1-1-3) and (1-1-4), Z^{11} represents an oxygen atom or a sulfur atom, n1 represents 0 or 1, R^{15} represents an aliphatic hydrocarbon group having 1 to 6 carbon atoms or an alkoxy group having 1 to 6 carbon atoms, n15 represents an integer of 0 to 2,

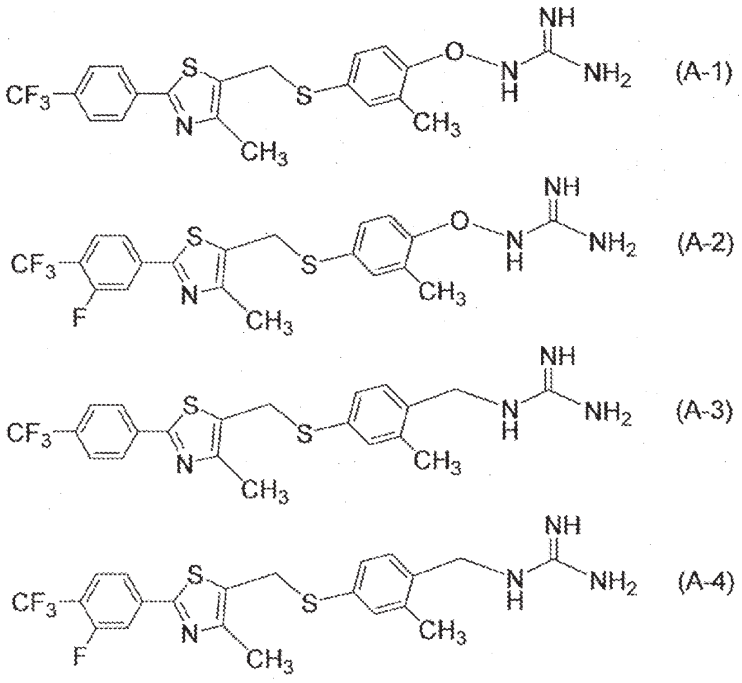
Z^2 represents a divalent linking group, R^5 represents an optionally substituted aromatic hydrocarbon group or an optionally substituted cyclic hydrocarbon group, p2 represents an integer of 1 or more].

[0015]

[5] The PPARδ activator according to [1], wherein the guanidine derivative is a compound represented by any of the following formulas (A-1) to (A-4), (B-1) to (B-3),

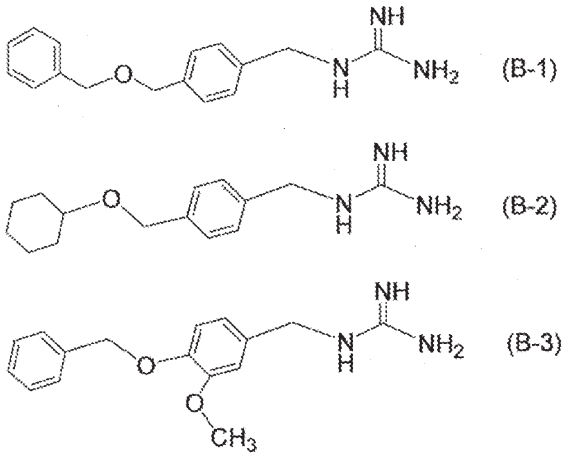
[0016]

[Chemical formula 4]



[0017]

[Chemical formula 5]

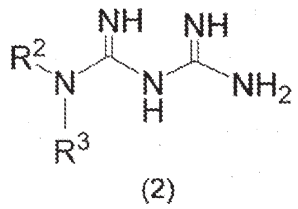


[0018]

[6] The PPARδ activator according to any one of [1] to [3], wherein the biguanidine derivative is a compound represented by the following general formula (2),

[0019]

[Chemical formula 6]



(2)

[in formula (2), R^2 and R^3 independently represent a hydrogen atom or a monovalent organic group, when both R^2 and R^3 are monovalent organic groups, they may be linked to form a ring structure].

[0020]

[7] The PPARδ activator according to [1], wherein at least one selected from the group consisting of metformin, phenformin and buformin is included as an active ingredient.

[8] An exercise tolerance-improving agent comprising the PPARδ activator defined in any

one of [1] to [7] as the active ingredient.

[Advantageous Effects of Invention]

[0021]

The PPARδ activators according to the present invention can activate the transcriptional activity of PPARδ and can affect various physiological actions transcriptionally regulated by PPARδ. Therefore, the PPARδ activators are useful as an active ingredient of an exercise tolerance-improving agent, and can be expected to be useful as an active ingredient of a pharmaceutical composition for treating or preventing metabolic disorders and the like.

[Brief Description of Drawings]

[0022]

FIG. 1 is an amino acid sequence of the hPPARδ ligand binding pocket. In the sequence, the amino acid residues with a black circle at the top indicate the amino acid residues constituting the interior surface of the hPPARδ ligand binding pocket, and the amino acid residues surrounded by a square are the amino acid residues forming hydrogen bonds with the guanidino group in the guanidine derivative.

FIG. 2 is a diagram schematically showing the structure of a conjugate of hPPARδ and a compound in which R^1 is an organic group branched in the arrow direction among the guanidine derivatives represented by the general formula (1).

FIG. 3 is a schematic diagram of the reaction of metformin immobilization on COOH FG beads in Example 1.

FIG. 4 is a silver-stained image of two-dimensional electrophoresis of eluates isolated from Met-beads (right figure) and NC-beads (left figure) in the affinity purification experiments using Met-beads in Example 1.

FIG. 5 is a diagram showing the amino acid sequence of PPARδ and the amino

acid sequence of the peptide identified by TOF-MS in Example 1.

FIG. 6 is a diagram showing the results of Western blotting of eluates affinity-purified by Met-beads from purified Myc-hPPARδ protein and a mouse liver extract in Example 1. An anti-PPARδ antibody was used in this Western blotting experiment.

FIG. 7 is a diagram showing a bond dissociation curve between the metformin immobilized on a biosensor and serially diluted purified Myc-hPPARδ in Example 1.

FIG. 8 shows the total length of the PPARδ used in Example 1 and a schematic view of each mutant.

FIG. 9 shows the quantitative results of the relative amount (relative amount where Myc-tagged protein in cell extract is 100%) obtained from the cell extracts of cells overexpressing each of Myc-hPPARδ, Myc-ΔN-term, and Myc-ΔLBD by using Met-beads in Example 1.

FIG. 10A is a schematic diagram showing the mechanism by which the PPARδ complex (hPPARδ, PGC1α, RXRα) transcriptionally activates PPRE (PPAR-response element), and the relationship between the PPARδ complex and metformin.

FIG. 10B is a diagram showing the results of a luciferase assay using PPRE×2-tk-luciferase in cells treated with metformin or GW501516 in Example 2.

FIG. 11 is a diagram showing the measurement results of the amount of PGC1α co-purifed along with Myc-hPPARδ by an anti-Myc antibody (PGC1α amount relative to Myc-hPPARδ amount in immunoprecipitate: [PGC1α amount]/[Myc-hPPARδ amount]). Immunoprecipitation was carried out on the extracts of cells overexpressing, RXRα, and PGC1α treated with metformin, GW501516, or DMSO in Example 2.

FIG. 12 is a diagram showing the measurement results of the relative expression level of the target genes of PPARδ (the expression level of DMSO-treated cells is set as 1) in C2C12 cells on day 6 of skeletal muscle differentiation induced by low concentration-

serum. Cells were treated with metformin, GW501516, or DMSO in Example 3.

FIG. 13 is a diagram showing the results of chromatin immunoprecipitation using an anti-FLAG antibody on C2C12-Flag-tagged PPARδ expressing cells treated with metformin, GW501516, or DMSO on day 6 of skeletal muscle differentiation induced by low concentration-serum in Example 3.

FIG. 14 is a diagram showing the results of measuring the mitochondrial activity of C2C12 cells in the presence of metformin or GW501516 in Example 4.

FIG. 15 is a photomicrograph of the complex crystal (A) of PPARδ-LBD and metformin and the complex crystal (B) of PPARδ-LBD and phenformin in Example 5.

FIG. 16 is a diagram showing the structure of a complex crystal of PPARδ-LBD and metformin in Example 5.

FIG. 17 is a diagram showing a metformin molecule in a ligand-binding pocket of PPARδ-LBD in a complex crystal of PPARδ-LBD and metformin in Example 5.

FIG. 18 is a diagram comparing the structures of metformin bound to PPARδ-LBD and phenformin in Example 5.

FIG. 19 is a diagram showing the measurement results of the number of shocks (NOS) in each elapsed time from the start of training in each group in Example 6. FIG. 19A shows the results of the control group (“cont” in the figure) and the metformin administration group (“met” in the figure), and FIG. 19B shows the results of the training group (“cont + train” in the figure) and the results of the training + metformin administration group (“met + train” in the figure).

FIG. 20 is a diagram showing the interaction between the guanidino group of metformin and the amino acid residue on the interior surface of the PPARδ ligand binding pocket in the structure of the complex crystal of PPARδ and metformin in Example 7.

FIG. 21 is a diagram showing the calculation results of the interaction energy of

metformin, GW0742, or GW501516 with seven amino acid residues (Tyr437, Leu433, Met417, His287, Thr253, Grn250, Ph246) in the hPPARδ ligand binding pocket in Example 7.

FIG. 22 is a diagram showing the results of a luciferase assay using PPRE × 2-tk-luciferase in the cells treated with compound (A-4) in Example 9.

FIG. 23A is a diagram showing the measurement results of the relative expression level of the angptl4 gene in the cells treated with compound (A-4) or GW0742 in Example 10.

FIG. 23B is a diagram showing the measurement results of the relative expression level of the pdk4 gene in the cells treated with compound (A-4) or GW0742 in Example 10.

FIG. 23C is a diagram showing the measurement results of the relative expression level of the cpt1a gene in the cells treated with compound (A-4) or GW0742 in Example 10.

[Description of Embodiments]

[0023]

PPARδ is composed of an N-terminal domain having ligand-independent transcriptional activation ability, a zinc finger domain as a DNA binding region, and a ligand binding domain (LBD) having a ligand-dependent transcriptional activation ability. The LBD composed of twelve α-helices and three β-sheets, and the 3rd to 8th α-helices form a ligand binding pocket. FIG. 1 shows the amino acid sequence of the ligand binding pocket of hPPARδ. In the amino acid sequence shown in Figure 1, the following 33 amino acid residues constitute the interior surface of the ligand binding pocket: Asn191, Met192, Ile213, Leu219, Glu223, Trp228, Val245, Phe246, Arg248, Cys249, Gln250, Thr252, Thr253, Glu255, Thr256, Glu259, His287, Ile290, Phe291, Leu294,

Ile297, Leu303, Val305, Ala306, Asn307, Val312, Phe316, Leu317, Ile327, Ile328, His413, Met417, Leu433, Tyr437.

[0024]

From the structural study of the complex of hPPARδ and GW501516, the following was clarified. A phenoxyacetic acid derivative such as GW501516 specifically binds its carboxyl group to an amino acid residue at the entrance (arm I) of the ligand binding pocket of PPARδ by forming a plurality of hydrogen bonds. This binding causes the 12th α-helix (helix-12) of PPARδ to tilt-down to cover the ligand binding pocket, and the remaining hydrophobic groups fit into the non-polar pocket. The tilt-down helix-12 serves as a lid for the ligand-binding pocket, thereby activating the transcriptional activity of PPARδ (NPL 7 and 8).

[0025]

The PPARδ activators according to the present invention are medicines that activate the transcriptional activity of PPARδ, and contain guanidine derivatives or biguanidine derivatives as active ingredients. The guanidine derivative means a compound having a guanidino group. The biguanidine derivatives mean compounds having a biguanidino group. The active ingredient of the PPARδ activator according to the present invention may be guanidine derivatives having a biguanidino group or biguanidine derivatives having a guanidino group.

[0026]

The PPARδ activators according to the present invention fit within a ligand binding pocket and forms a plurality of hydrogen bonds by amino acid residues at the entrance (arm I) of the ligand binding pocket of PPARδ and a guanidino group or a biguanidino group, thereby tilting-down the helix-12 to cover the ligand binding pocket. The PPARδ activators according to the present invention can achieve the structural change

(tilting-down and immobilization of helix-12) necessary for activating the transcriptional activity of PPARδ by the guanidino group or biguanidino group.

[0027]

Specifically, the guanidino group or biguanidino group of the PPARδ activators according to the present invention forms hydrogen-bonds with the amino acid residues corresponding to each of the 413th histidine (His413), 287th histidine (His287), 253rd threonine (Thr253), and the 437th tyrosine (Tyr437) of the hPPARδ, among the amino acid residues constituting the interior surface of the ligand binding pocket of PPARδ. Due to these hydrogen bonds, the PPARδ activators according to the present invention are placed at the entrance of the ligand binding pocket of PPARδ. As a result, the helix-12 is tilted down and fixed while covering the ligand binding pocket, thereby the PPARδ is activated.

[0028]

The guanidino group or biguanidino group of the PPARδ activators according to the present invention also interacts with the amino acid residues corresponding to each of the 246th phenylalanine (Phe246), the 417th methionine (Met417), the 433rd leucine (Leu433) and the 250th glutamine (Gln250) of the hPPARδ, among the amino acid residues constituting the interior surface of the ligand binding pocket of PPARδ. The interaction between the guanidino or biguanidino group with the entrance (arm I) of the ligand binding pocket of PPARδ is more stable than the phenoxyacetic acid derivatives that bind though the carboxyl group, and the helix-12 is efficiently tilted down and fixed. Therefore, it can be expected that the activating action of PPARδ is stronger than that of the phenoxyacetic acid derivative.

[0029]

The guanidine derivatives as an active ingredient of the PPARδ activator

according to the present invention, are not particularly limited as long as they are compounds capable of fitting within the ligand binding pocket of PPARδ in a state where the guanidino group forms hydrogen bonds with His413, His287, Thr253 and Tyr437 of the hPPARδ. Similarly, the biguanidine derivatives as active ingredients of the PPARδ activator according to the present invention, are not particularly limited as long as they are compounds capable of fitting within the ligand binding pocket of PPARδ in a state where the biguanidino group forms hydrogen bonds with His413, His287, Thr253 and Tyr437 of the hPPARδ.

[0030]

The phrase "the compound fits within the ligand binding pocket" means that the compound may occupy the entire pocket or occupy only a part of the pocket as long as it is contained inside the ligand binding pocket. The active ingredients of the PPARδ activator according to the present invention may be a compound that occupies only a part or all of arm I of PPARδ, or may be a compound that occupies only a part or all of arm I and arm II of PPARδ, or may be a compound that occupies only a part or all of arm I and arm III of PPARδ. Further, it may also be compounds having a branched structure that occupies a part or all of arm I and arm II of PPARδ, and a part or all of arm III.

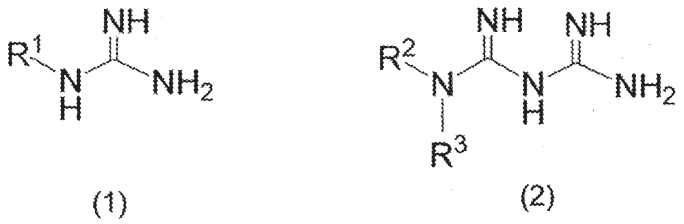
[0031]

Examples of the guanidine derivatives as the active ingredient of the PPARδ activator according to the present invention include compounds represented by the following general formula (1) (except for the biguanidine derivative) (hereinafter, referred to as "compound (1)"). Examples of the biguanidine derivatives as the active ingredient of the PPARδ activator according to the present invention include compounds represented by the following general formula (2) (hereinafter, referred to as “compound (2)”). In the general formula (1), R^1 represents a monovalent organic group. In the general formula

(2), R^2 and R^3 independently represent a hydrogen atom or a monovalent organic group. Among the compounds (2), the compound in which R^2 and R^3 are both hydrogen atoms is metformin.

[0032]

[Chemical formula 7]



(1) (2)

[0033]

The monovalent organic groups of R^1, R^2 and R^3 are not particularly limited as long as they are organic groups having a size and shape that allow the entire compound to fit within the ligand binding pocket of PPARδ in a state where the guanidino groups or the biguanidino groups form hydrogen bonds with the amino acid residues corresponding to His413, His287, Thr253 and Tyr437 of the hPPARδ. For example, the monovalent organic group may be an acidic group or a basic group. Further, it may be a hydrophilic group or a hydrophobic group.

[0034]

The monovalent organic group may be linear, may be branched, or may have a cyclic structure. FIG. 2 is a diagram schematically showing the structure of a conjugate of PPARδ and a compound in which R^1 is a branched-chain organic group branched in the arrow direction among compounds (1). This branched organic group extends to each of arm II and arm III.

[0035]

Examples of the monovalent organic group include -(Z^1)-R^4 (wherein, Z^1 represents a single bond, oxygen atom, sulfur atom, -NH-, -N=CH-, -CO-, -CO-O-, -O-CO-, -CO-NH-, or -NH-CO-; R^4 represents an aliphatic hydrocarbon group, an aromatic hydrocarbon group, or a heterocyclic group), a carboxyl group, nitro group, cyanide group, hydroxy group, amino group and the like.

[0036]

When R^4 is an aliphatic hydrocarbon group, the aliphatic hydrocarbon group is not particularly limited, and examples thereof include saturated or unsaturated hydrocarbon groups having 1 to 20 carbon atoms. The monovalent aliphatic hydrocarbon group may be a chain hydrocarbon group or a cyclic hydrocarbon group. Specific examples of the monovalent chain hydrocarbon group include a methyl group, ethyl group, propyl group, isopropyl group, n-butyl group, t-butyl group, n-pentyl group, isopentyl group, neopentyl group, tert-pentyl group, n-hexyl group, isohexyl group, 2-ethylhexyl group, n-heptyl group, n-octyl group, n-nonyl group, n-decyl group and the like. Examples of the monovalent cyclic hydrocarbon group include a group obtained by removing one hydrogen atom from an alicyclic compound such as a cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, adamantane dicyclopentadiene and the like. These aliphatic hydrocarbon groups may have one or more substituents. Examples of the substituent include a halogen atom (fluorine atom, chlorine atom, bromine atom, iodine atom), trifluoromethyl group, carboxy group, nitro group, cyano group, hydroxy group, amino group, ketone group, alkoxy group, aromatic hydrocarbon group, heterocyclic group, multi-ring linking group and the like. Examples of the aromatic hydrocarbon group and the heterocyclic group include the same groups as those exemplified as R^4 later. Examples of the multi-ring linking group include those similar to the multi-ring linking group exemplified as the monovalent organic group later.

Specific examples of the alkoxy group include a methoxy group, ethoxy group. propyloxy group, isopropyloxy group, n-butoxy group, t-butoxy group, n-pentyloxy group, isopentyloxy group, neopentyloxy group, tert-pentyloxy group, n-hexyloxy group, isohexyloxy group and the like. When the aliphatic hydrocarbon group has an aromatic hydrocarbon group, a heterocyclic group, or a multi-ring linking group as a substituent, the aliphatic hydrocarbon group preferably has 1 to 6 carbon atoms.

[0037]

When R4 is an aromatic hydrocarbon group, the aromatic hydrocarbon group is not particularly limited, and examples thereof include a group obtained by removing one hydrogen atom from an aromatic cyclic compound such as a benzene, naphthalene, anthracene, phenanthrene or the like. These aromatic hydrocarbon groups may have one or more substituents. Examples of the substituent include a halogen atom, trifluoromethyl group, carboxy group, nitro group, cyano group, hydroxy group, amino group, ketone group, alkoxy group, aliphatic hydrocarbon group and the like. Examples of the aliphatic hydrocarbon group include the same groups as those exemplified as R^4 above. Examples of the alkoxy group include the same groups as those exemplified as the substituent of the aliphatic hydrocarbon group above.

[0038]

When R^4 is a heterocyclic group, the heterocyclic group is not particularly limited, and examples thereof include a group obtained by removing one hydrogen atom from a heterocyclic compound such as 5-membered heterocyclic compounds such as a pyrrolidine, pyrrole, imidazole, pyrazole, imidazoline, triazole, tetrazole, oxazole, thiazole, tetrahydrofuran, furan, dioxolane, tetrahydrothiophene, thiophene or the like; 6-membered heterocyclic compounds such as a piperidine, pyridine, pyrimidine, pyrazine, pyridazine, morpholine, thiazine, oxane, pyririum ion, dioxane, thiane, thiapyran or the

like; condensed heterocyclic compounds such as an indol, isoindole, benzimidazole, purine, benzotriazole, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline, pteridine, chromium, isochromen, xanthene, carbazole, benzo-C-cinnoline or the like; or the like. These heterocyclic groups may have one or more substituents. Examples of the substituent include a halogen atom, trifluoromethyl group, carboxy group, nitro group, cyano group, hydroxy group, amino group, ketone group, alkoxy group, aliphatic hydrocarbon group and the like. Examples of the aliphatic hydrocarbon group include the same groups as those exemplified as R^4 above. Examples of the alkoxy group include the same groups as those exemplified as the substituent of the aliphatic hydrocarbon group above.

[0039]

The monovalent organic group may be a group in which two or more rings are linked by a single bond or a divalent linking group (multi-ring linking group). The rings are not particularly limited, and may be an alicyclic compound, an aromatic cyclic compound, or a heterocyclic compound. Further, the rings to be linked may be the same or different. Specifically, the same alicyclic compound, aromatic cyclic compound, or heterocyclic compound as described above can be used.

[0040]

Examples of the divalent linking group linking the rings in the multi-ring linking group include a divalent chain aliphatic hydrocarbon group, -O-, -S-, -NH-, -N = CH-, -CO-, and groups in which two or more of these are bonded. The divalent chain aliphatic hydrocarbon group may be linear or branched. Further, it may be a divalent aliphatic hydrocarbon group consisting only of saturated bonds, or it may be a divalent aliphatic hydrocarbon group having one or more unsaturated bonds. As the divalent chain aliphatic hydrocarbon group, an alkylene group having 1 to 10 carbon atoms, an

alkenylene group and the like can be used.

[0041]

Examples of the group in which two or more of a divalent chain aliphatic hydrocarbon group, -O-, -S-, -NH-, -N = CH- and -CO-are bonded include -CO-O-, -O-CO-, -CO-NH-, -NH-CO-, $-(CH_2)_n-O-(CH_2)_m-$, $-(CH_2)_n-S-(CH_2)_m-$ (wherein, n and m are each independently an integer of 0 or more satisfying $n+m \geqq 1$, and $-(CH_2)_0-$ represents a single bond), and the like.

[0042]

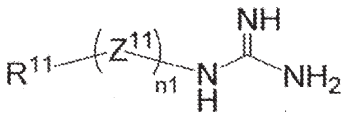
In the general formula (2), when both R^2 and R^3 are monovalent organic groups, they may be linked together to form a ring structure. The ring formed by linking R^2 and R^3 may be an alicyclic compound, an aromatic ring compound, or a heterocyclic compound. Examples of the alicyclic compound, the aromatic ring compound, and the heterocyclic compound include the same groups as those exemplified as R^4 above. Furthermore, these cyclic compounds may have substituents. Examples of the substituent include the same groups as those exemplified as the monovalent organic groups for R^1, R^2 and R^3.

[0043]

Examples of compound (1) include a compound represented by the following general formula (1-1) (compound (1-1)) and the like.

[0044]

[Chemical formula 8]



(1-1)

[0045]

In the general formula (1-1), Z^{11} represents an oxygen atom or a sulfur atom, and n1 represents 0 or 1.

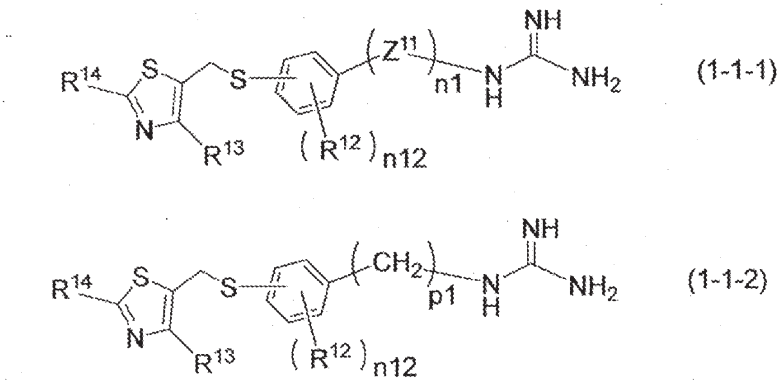
In the general formula (1-1), R^{11} represents an optionally substituted aliphatic hydrocarbon group having 1 to 6 carbon atoms, an optionally substituted aromatic hydrocarbon group, or an optionally substituted multi-ring linking group. Examples of the optionally substituted aliphatic hydrocarbon group having 1 to 6 carbon atoms and the optionally substituted aromatic hydrocarbon group include the same groups as those exemplified as R^4 above. Examples of the optionally substituted multi-ring linking group include the same groups as those exemplified as the monovalent organic group.

[0046]

Examples of compound (1-1) include a compound represented by the following general formula (1-1 -1) (compound (1-1 -1)) and a compound represented by the general formula (1-1-2) (compound (1-1-2)).

[0047]

[Chemical formula 9]



[0048]

In the general formula (1-1-1), Z^{11} and n1 are as defined in the general formula (1-1).

In the general formula (1-1-2), p1 is an integer of 1 or more, preferably an integer of 1 to 6, more preferably an integer of 1 to 3, and particularly preferably 1.

[0049]

In the general formula (1-1-1) and the general formula (1-1-2), n12 represents an integer of 0 to 2.

In the general formula (1-1-1) and the general formula (1-1-2), R^{12} represents an aliphatic hydrocarbon group having 1 to 6 carbon atoms. Examples of the aliphatic hydrocarbon group include the same groups as those exemplified as R^4 above.

In the general formula (1-1-1) and the general formula (1-1-2), R^{13} represents a hydrogen atom or an aliphatic hydrocarbon group having 1 to 6 carbon atoms. Examples of the aliphatic hydrocarbon group include the same groups as those exemplified as R4 above.

In the general formula (1-1-1) and the general formula (1-1-2), R^{14} represents an optionally substituted aromatic hydrocarbon group. Examples of the aromatic hydrocarbon group include the same groups as those exemplified as R^4 above.

[0050]

Compound (1-1-1) is preferably a compound in which Z^{11} is an oxygen atom or a sulfur atom, n1 is 1, n12 is 0 or 1, R^{12} is a methyl group, ethyl group, a propyl group, isopropyl group, n-butyl group, t-butyl group, n-pentyl, iso-pentyl, neopentyl group, tert-pentyl, n-hexyl or isohexyl group, R^{13} is a hydrogen atom, methyl group, ethyl group, propyl group, isopropyl group, n-butyl group, t-butyl group, n-pentyl, iso-pentyl group, neopentyl group, tert-pentyl, n-hexyl or isohexyl group, and R^{14} is an optionally substituted phenyl group. Among the compounds, a compound in which Z^{11} is an oxygen atom or a sulfur atom, n1 is 1, n12 is 0 or 1, R^{12} is a methyl group, ethyl group, propyl group, isopropyl group, n-butyl group or t-butyl group, R^{13} is a hydrogen atom,

methyl group, ethyl group, propyl group, isopropyl group, n-butyl group or t-butyl group, and R^{14} is an unsubstituted phenyl group or a phenyl group having one or two substituents selected from the group consisting of a halogen atom, trifluoromethyl group, and methyl group is preferable, and a compound in which Z^{11} is an oxygen atom or a sulfur atom, n1 is 1, n12 is 0 or 1, R^{12} is a methyl group, R^{13} is a hydrogen atom or a methyl group, and R^{14} is an unsubstituted phenyl group or a phenyl group having one or two substituents selected from the group consisting of a halogen atom, trifluoromethyl group, and methyl group is more preferable.

[0051]

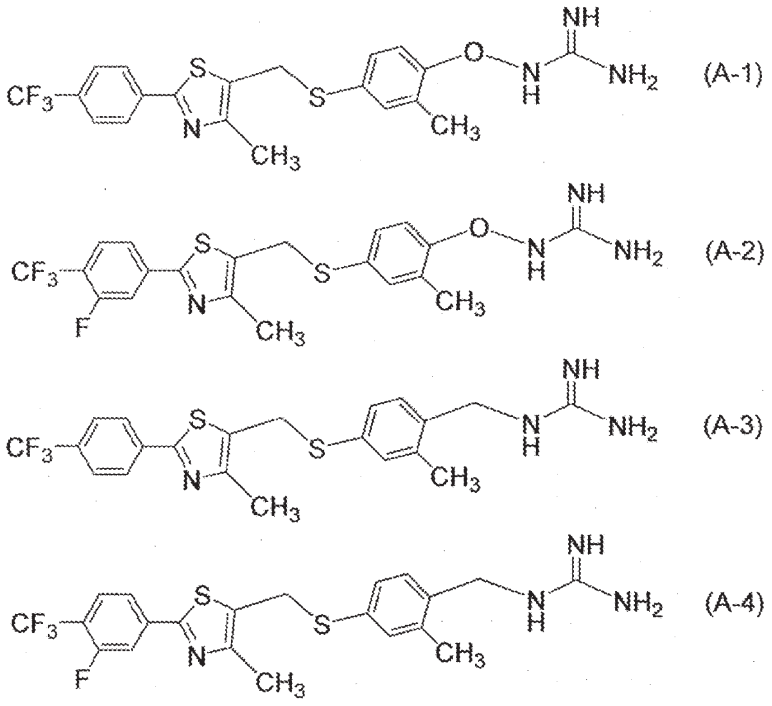
Compound (1-1-2) is preferably a compound in which p1 is 1, n12 is 0 or 1, R^{12} is a methyl group, ethyl group, propyl group, isopropyl group, n-butyl group, t-butyl group, n-pentyl group, iso-pentyl group, neopentyl group, tert-pentyl group, n-hexyl group or an isohexyl group, R^{13} is a hydrogen atom, methyl group, ethyl group, propyl group, isopropyl group, n-butyl group, t-butyl group, n-pentyl group, iso pentyl group, neopentyl group, tert-pentyl group, n-hexyl group or an isohexyl group, and R^{14} is an optionally substituted phenyl group. Among the compounds, a compound in which p1 is 1, n12 is 0 or 1, R^{12} is a methyl group, ethyl group, propyl group, isopropyl group, n-butyl group or a t-butyl group, R^{13} is a hydrogen atom, methyl group, ethyl group, propyl group, isopropyl group, n-butyl group or a t-butyl group, and R^{14} is an unsubstituted phenyl group or a phenyl group having one or two substituents selected from the group consisting of a halogen atom, trifluoromethyl group and a methyl group is preferable, and a compound in which p1 is 1, n12 is 0 or 1, R^{12} is a methyl group, R^{13} is a hydrogen atom or a methyl group, and R^{14} is an unsubstituted phenyl group or a phenyl group having one or two substituents selected from the group consisting of a halogen atom, trifluoromethyl group and a methyl group is more preferable.

[0052]

Examples of compound (1-1-1) include compounds represented by the following formulas (A-1) to (A-2). Examples of compound (1-1-2) include the compounds represented by the following formulas (A-3) to (A-4).

[0053]

[Chemical formula 10]

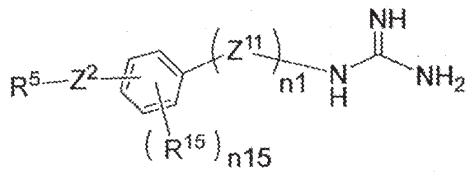


[0054]

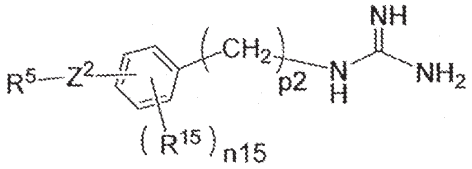
Examples of compound (1-1) include a compound represented by the following general formula (1-1-3) (compound (1-1-3)) and a compound represented by the following general formula (1-1-4) (compounds (1-1-4)).

[0055]

[Chemical formula 11]



(1-1-3)



(1-1-4)

[0056]

In the general formula (1-1-3), Z^{11} and n1 are as defined in the general formula (1-1).

In the general formula (1-1-4), p2 is an integer of 1 or more, preferably an integer of 1 to 6, more preferably an integer of 1 to 3, and particularly preferably 1.

[0057]

In the general formula (1-1-3) and the general formula (1-1-4), n15 represents an integer of 0 to 2.

In the general formula (1-1-3) and the general formula (1-1-4), R^{15} represents an aliphatic hydrocarbon group or an alkoxy group having 1 to 6 carbon atoms. Examples of the aliphatic hydrocarbon group include the same groups as those exemplified as R^4 above. Examples of the alkoxy group include the same groups as those exemplified as the substituent of the aliphatic hydrocarbon group above.

[0058]

In the general formula (1-1-3) and the general formula (1-1-4), Z^2 is a divalent linking group. Examples of the divalent linking group include the same groups as those exemplified as the divalent linking group linking the rings in the multi-ring linking group. Compound (1-1-3) and compound (1-1-4) are preferably a compound in which Z^2 is -

$(CH_2)_2$-, -$(CH_2)_3$-, -O-CH_2-, -CH_2-O-, -CH_2-O-CH_2-, -S-CH_2-, -CH_2-S-, -CH_2-S-CH_2-, -NH-CH_2-, -CH_2-NH, or -CH_2-NH-CH_2 -.

[0059]

In the general formula (1-1-3) and the general formula (1-1-4), R^5 is an optionally substituted aromatic hydrocarbon group or an optionally substituted cyclic hydrocarbon group. Examples of the optionally substituted aromatic hydrocarbon group include the same groups as those exemplified as R^4 above. Examples of the optionally substituted multi-ring linking group include the same groups as those exemplified as the monovalent organic group. Compound (1-1-3) and compound (1-1-4) are preferably a compound in which R^5 is an optionally substituted phenyl group or an optionally substituted cyclohexyl group.

[0060]

Compound (1-1-3) is preferably a compound in which Z^{11} is an oxygen atom or a sulfur atom, n1 is 1, n15 is 0 or 1, R^{15} is a methyl group, ethyl group, propyl group, isopropyl group, methoxy group, ethoxy group or a propyl group, Z^2 is -$(CH_2)_2$-, -$(CH_2)_3$-, -O-CH_2-, -CH_2-O-, -CH_2-O-CH_2-, -S-CH_2-, -CH_2-S-, -CH_2-S-CH_2-, -NH-CH_2-, -CH_2-NH-, or -CH_2-NH-CH_2-, and R^5 is an optionally substituted phenyl group or an optionally substituted cyclohexyl group; and more preferably a compound in which Z^{11} is an oxygen atom or a sulfur atom, n1 is 1, n15 is 0 or 1, R^{15} is a methyl group, ethyl group, propyl group, isopropyl group, methoxy group, ethoxy group or a propyl group, Z^2 is -$(CH_2)_2$-, -$(CH_2)_3$-, -O-CH_2-, -CH_2-O-, -CH_2-O-CH_2-, -S-CH_2-, -CH_2-S-, or -CH_2-S-CH_2-, and R^5 is an unsubstituted cyclohexyl group, an unsubstituted phenyl group or a phenyl group having one or two substituents selected from the group consisting of a halogen atom, trifluoromethyl group and a methyl group. Compound (1-1-3) is particularly preferably a compound in which Z^{11} is a sulfur atom, n1 is 1, n15 is 0 or 1, R^{15} is a methyl group or a

methoxy group, and Z^2 is -CH-O_2-, -CH_2-O- or -CH_2-O-CH_2-, and R^5 is an unsubstituted cyclohexyl group or an unsubstituted phenyl group.

[0061]

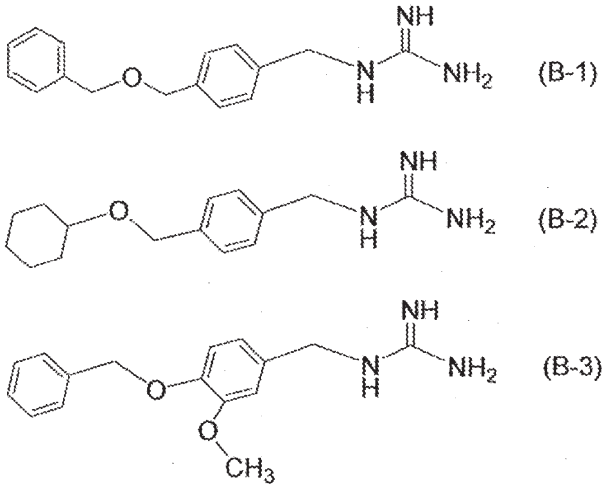
Compound (1-1-4) is preferably a compound in which p2 is 1, n15 is 0 or 1, R^{15} is a methyl group, ethyl group, propyl group, isopropyl group, methoxy group, ethoxy group or a propyl group, Z^2 is -$(CH_2)_2$-, -$(CH_2)_3$-, -O-CH_2-, -CH_2-O-, -CH_2-O-CH_2-, -S-CH_2-, -CH_2-S-, -CH_2-S-CH_2-, -NH-CH_2-, -CH_2-NH-, or -CH_2-NH-CH_2-, and R^5 is an optionally substituted phenyl group or an optionally substituted cyclohexyl group; and more preferably a compound in which p2 is 1, n15 is 0 or 1, R^{15} is a methyl group, ethyl group, propyl group, isopropyl group, methoxy group, ethoxy group or a propyl group, Z^2 is -$(CH_2)_2$-, -$(CH_2)_3$-, -O-CH_2-, -CH_2-O-, -CH_2-O-CH_2-, -S-CH_2-, -CH_2-S-, or -CH_2-S-CH_2-, and R^5 is an unsubstituted cyclohexyl group, an unsubstituted phenyl group or a phenyl group having one or two substituents selected from the group consisting of a halogen atom, trifluoromethyl group and a methyl group. Compound (1-1-3) is particularly preferably a compound in which p2 is 1, n15 is 0 or 1, R^{15} is a methyl group or a methoxy group, and Z^2 is -CH-O_2-, -CH_2-O- or -CH_2-O-CH_2-, and R^5 is an unsubstituted cyclohexyl group or an unsubstituted phenyl group.

[0062]

Examples of compound (1-1-4) include N-({4-[(benzyloxy) methyl] phenyl} methyl) guanidine hydrobromide (PubChem CID: 51131487) (hereinafter, referred to as compound (B-1).)), N-({3-[(cyclohexyloxy) methyl] phenyl} methyl) guanidine hydrogen iodide (PubChem CID: 53598567) (hereinafter, referred to as compound (B-2)), and N-{[4-(benzyl) oxy)-3-methoxyphenyl] methyl} guanidine hydrogen iodide (PubChem CID: 16261695) (hereinafter, referred to as compound (B-3)) and the like.

[0063]

[Chemical formula 12]

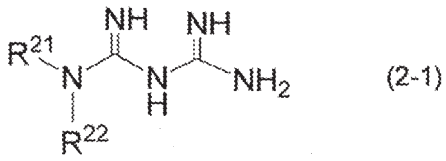


[0064]

Examples of compound (2) include a compound represented by the following general formula (2-1) (compound (2-1)).

[0065]

[Chemical formula 13]



[0066]

In the general formula (2-1), R^{21} and R^{22} independently represent a hydrogen atom or an optionally substituted aliphatic hydrocarbon group having 1 to 6 carbon atoms. Examples of the aliphatic hydrocarbon group include the same groups as those exemplified as R^4 above.

[0067]

Examples of compound (2-1) include a metformin, buformin, phenformin and the like.

[0068]

The results of crystal structure analysis of the ligand binding pocket of PPARδ have been published (NPL 7 or 8). Therefore, whether or not compound (1) or compound (2) has a size and shape that can be fitted within the ligand binding pocket of PPARδ, can be determined by using the structural data of the ligand binding pocket of PPARδ. For example, the shape of the ligand binding pocket of hPPARδ is a three-dimensional structure drawn by incorporating the data of Tables 1 to 63 of Example 5 below into the molecular graphics software PyMOL (https://www.pymol.org). That is, a compound having at least one of a guanidino group and a biguanidino group and having a shape that can be included inside the three-dimensional structure can be used as the active ingredient of the PPARδ activator according to the present invention.

[0069]

By introducing the PPARδ activators according to the present invention into cells expressing PPARδ, the transcriptional activity of PPARδ in the cells can be activated. The cells to be treated with the PPARδ activator according to the present invention may be cells existing in a living body or cells in culture. When the cells to be treated are in a culture vessel, the PPARδ activator can be incorporated into the cells by endocytosis by culturing the cells in a medium containing the PPARδ activator. In addition, the PPARδ activators may also be introduced into the cells by a known introduction method such as a lipofection method, calcium phosphate precipitation method, lithium acetate method, electroporation method or the like.

[0070]

When the cells to be treated with the PPARδ activator are in a living body of an

animal, the administration route for the PPARδ activators to the animal is not particularly limited. Examples of the administration route of the PPARδ activators according to the present invention include oral administration, intravenous administration, intraperitoneal administration, enema administration and the like.

[0071]

The animal to be administered with the PPARδ activators according to the present invention is not particularly limited, and may be a human or a non-human animal. The non-human animal is preferably a domestic animal or an experimental animal such as cows, pigs, horses, sheep, goats, monkeys, dogs, cats, rabbits, mice, rats, hamsters, guinea pigs or the like.

[0072]

The PPARδ activators according to the present invention can be formulated into an oral solid agent such as powders, granules, capsules, tablets, chewable agents, sustained-release agents or the like, an oral liquid agent such as solutions, syrups or the like, injections, enema agents, sprays, patches, ointments, and the like. The formulation can be carried out by a conventional method by blending excipients, binders, lubricants, disintegrants, fluidizers, solvents, solubilizers, buffers, suspension agents, emulsifiers, isotonic agents, stabilizers, preservatives, antioxidants, flavoring agents, colorants or the like as necessary for the formulation.

[0073]

The dose of the PPARδ activator according to the present invention is not limited as long as it is sufficient to make the transcriptional activity of PPARδ in the administered cells stronger than that before administration, and can be appropriately determined in consideration of the species, sex, age, body weight, usage (administration route, dosage form, number of administrations per day, etc.) of the animal to be treated. For example,

the daily dose of the active ingredient for an adult (assuming a body weight of 60 kg) is preferably 0.01 mg to 10 g, more preferably 1 mg to 5 mg, and even more preferably 100 mg to 1 g in terms of the active ingredient of the PPARδ activator (guanidine derivative or guanidine derivative). Such a dose can be administered once or in several divided doses.

[0074]

The PPARδ activators according to the present invention is suitable as an active ingredient of a pharmaceutical composition that can be expected to have therapeutic effects for treating or preventing various diseases by activating the transcriptional activity of PPARδ. Examples of the disease include various metabolic disorders such as diabetes, obesity or the like, diseases caused by ER stress such as cardiomyopathy or the like, liver fibrosis, and the like.

[0075]

The PPARδ activators according to the present invention, like other PPARδ agonists, is useful as an active ingredient of an exercise tolerance-improving agent. Improving exercise tolerance by activating PPARδ means improving exercise tolerance, suppressing fatigue during exercise, increasing the amount of possible exercise, and increasing the effect of a certain amount of exercise. By taking the exercise tolerance-improving agent, it is possible to perform exercise with the same load for a longer period of time than when not taking the exercise tolerance-improving agent, and the effect of the exercise can be enhanced. As a result, lifestyle-related diseases such as obesity, diabetes or the like are expected to improve. In addition, enhancing the exercise effect can be expected to lead to health promotion. The exercise tolerance-improving agents containing the PPARδ activator according to the present invention preferably also contains AMPK or is preferably used in combination with AMPK.

[0076]

As the PPARδ activity increases, so does the mitochondrial activity. Therefore, the PPARδ activators according to the present invention are preferable as an active ingredient of a pharmaceutical composition that can be expected to have a therapeutic effect for treating or preventing various diseases by improving mitochondrial activity. For example, when the mitochondrial activity is improved, immune cells are also activated. Therefore, the PPARδ activators according to the present invention are effective as an immunostimulatory agent and can be used as an active ingredient of a pharmaceutical composition for immunotherapy. Further, similarly to metformin (NPL 11), the PPARδ activators according to the present invention are also effective for use in combination with a cancer immunotherapeutic agent such as an immune checkpoint inhibitor.

[Example]

[0077]

Next, the present invention will be described in more detail with reference to the Examples and the like, but the present invention is not limited to these Examples.

[0078]

[Example 1]

A target molecule of metformin in vivo was searched for by an affinity purification method using FG beads (registered trademark), on which metformin was immobilized. A cell extract of human liver cancer-derived cell line HepG2 cells was used to search for a target of metformin.

[0079]

<Met-Bead production>

FG beads on which metformin was immobilized (hereinafter, referred to as "Met-beads") were prepared. The method of immobilization followed a protocol provided by

the manufacturer of COOH FG beads. Specifically, first, an N-hydroxysuccinimide (NHS) compound was formed by dehydrating and condensing the linker-terminal carboxylic acid of COOH FG beads (manufactured by Tamagawa Seiki Co., Ltd.) equilibrated with N, N'-dimethylformamide and NHS. Next, metformin was added to the obtained NHS compound, the NH_2 group of metformin was reacted with the NHS ester, and the COOH group of COOH FG beads and the NH_2 group of metformin were immobilized by amide bonding. FIG. 3 is a schematic diagram of the immobilization reaction of metformin on COOH FG beads. Unbound linker group on the FG beads was masked with aminoethanol. The masked Met-beads were washed and then suspended in 50 volume% methanol-water for use in subsequent experiments.

[0080]

As a control group, metformin non-immobilized beads (hereinafter, referred to as "NC-beads") obtained by masking COOH FG beads with aminoethanol, followed by washing and suspending in 50 volume% methanol-water, were used in the subsequent experiments.

[0081]

<Affinity purification using Met-beads>

The prepared Met-beads were suspended in KCl buffer (100 mM KCl, 0.126 g/mL glycerol, 20 mM HEPES (pH 7.9), 1 mM $MgCl_2$, 200 μM $CaCl_2$, 0.2 mM EDTA, 0.1% NP-40), and then magnetically separated and the supernatant was discarded. Next, a washing process of adding 200 μL of KCl buffer to the Met-beads, dispersing the beads with an ultrasonic disperser, followed by discarding the supernatant by magnetic separation, was repeated 3 times.

[0082]

The cell extract of the human liver cancer-derived cell line HepG2 cells was

diluted with the KCl buffer so that the protein concentration was adjusted to 3 mg/mL, and the obtained diluted solution was centrifuged (15k rpm/4°C/30 minutes). The insoluble fraction was removed by separating the supernatant. The washed Met-beads were added to 400 μL of the supernatant to disperse, and the resulting mixture was allowed to react by inversion and stirring with a rotator at 4°C for 4 hours. After the reaction, the supernatant was discarded by magnetic separation, and a washing process of adding 200 μL of KCl buffer to the recovered Met-beads, dispersing the beads with an ultrasonic disperser, followed by discarding the supernatant by magnetic separation, was repeated 4 times. 40 μL of 2D sample buffer (60 mM Tris-HCl (pH 8.8), 7M Urea, 2M Thiourea, 1% CHAPS, 1% Triton X-100, 1×protease inhibitor, 10 mM DTT, 1×BPB) was added to the washed Met-beads, and the resulting mixture was stirred and allowed to stand at room temperature for 10 minutes. Then, 4 μL of an aqueous acrylamide solution (71 mg/mL) was added to suspend, the resulting mixture was allowed to stand at room temperature for 10 minutes, and then magnetically separated to recover the supernatant. The recovered supernatant was subjected to two-dimensional electrophoresis using an agar gel (PI: pH3-10, e-PAGE, manufactured by ATTO CORPORATION), and the gel after electrophoresis was stained with silver to detect the proteins eluted from the Met-beads. Similar experiments were performed on the NC-beads which were non-immobilized with metformin, and the gels after silver staining were compared to visually confirm spots specific to the Met-beads. FIG. 4 shows a silver-stained image of the gel after two-dimensional electrophoresis of the supernatant eluted from the Met-beads (right figure) and the supernatant eluted from the NC-beads (left figure).

[0083].

In the silver-stained image of the supernatant eluted from the Met-beads, two specific spots (indicated by arrowheads in Fig. 4), which were not found in the silver-

stained image of the supernatant eluted from the NC-beads, were observed. The gels of these two spots were cut out and collected, and analyzed by TOF-MS (time-of-flight mass spectrometry). As a result, the proteins in both spots were identified as PPARδ (peroxisome proliferator-activated receptor δ). FIG. 5 shows the amino acid sequence of hPPARδ (SEQ ID NO: 1) and the amino acid sequence of the peptide identified by TOF-MS. In FIG. 5, the underlined region is the peptide identified by TOF-MS. The peptides identified by TOF-MS covered 26% of the total length of hPPARδ.

[0084]

<Metformin and PPARδ binding experiment by immunoprecipitation method>

The binding between PPARδ and metformin was confirmed by co-immunoprecipitation. Affinity-precipitation using the Met-beads was performed on the Myc-hPPARδ that was purified by immunoprecipitation using an anti-Myc antibody (sc-40, manufactured by Santa Cruz Bitechnology, Inc.) from an extract of human embryonic kidney-derived cell line HEK293 overexpressing cell Myc-tagged PPARδ (Myc-hPPARδ) and from a mouse liver extract.

[0085]

Specifically, first, the Met-beads were added to each of the purified Myc-hPPARδ and the mouse liver extract, the resulting mixtures were inverted and stirred, and then the Met-beads were recovered by magnetic separation. Western blotting was performed on the protein eluted from the recovered Met-beads using an anti-PPARδ antibody (sc-74517, manufactured by Santa Cruz Biotechnology, Inc.) that recognizes endogenous PPARδ. The result of Western blotting is shown in FIG. 6. As a result, it was confirmed that both the over-expressed Myc-hPPARδ and the endogenous PPARδ in the mouse liver extract bind to metformin.

[0086]

<Verification of binding between metformin and PPARα>

PPARδ is a member of the nuclear receptor superfamily, with PPARα and PPARγ as the other two family members. Affinity purification was performed using the Met-beads and HepG2 cell extract to verify the binding to endogenous PPARα. As a result, the binding between metformin and PPARα was not detected.

[0087]

<Verification of binding between metformin and AMPK>

Metformin is known to regulate the enhancement of sugar uptake in skeletal muscle and fatty acid β-oxidation in the liver by activating AMPK (5'AMP-activated protein kinase). Therefore, affinity purification was performed using the Met-beads and HepG2 cell extract to verify the binding between endogenous AMPK and metformin. As a result, the binding between metformin and AMPK was not detected.

[0088]

<Measurement of affinity between metformin and PPARδ>

The affinity between metformin and PPARδ was measured using an intermolecular interaction-measuring device (product name: BLItz (registered trademark), manufactured by Pall ForteBio Corp.). The intermolecular interaction between metformin and Myc-hPPARδ was measured using the metformin-immobilized biosensor and the purified Myc-hPPARδ. Immobilization of metformin on the biosensor of the intermolecular interaction-measuring device was performed through the NH_2 group of metformin. The concentration of Myc-PPARδ was diluted in 6 steps, and the average intermolecular interaction calculated from each concentration was calculated by global fitting. FIG. 7 shows the association/dissociation curve between the metformin immobilized on a biosensor and the serially diluted purified Myc-hPPARδ. In the figure, the vertical axis is the distance (nm) of the Myc-hPPARδ protein from the sensor tip on

which metformin was immobilized, and is an index of the amount of the Myc-hPPARδ protein bound to the sensor tip. As a result, the binding association rate constant (ka) was calculated to be 3.40×10^{4} $M^{-1}S^{-1}$, the dissociation rate constant (kd) was calculated to be 1.03×10^{-6} S^{-1}, the dissociation constant (KD) was calculated to be 3.30×10^{-10} M, and it was confirmed that PPARδ strongly binds to metformin.

[0089]

<Identification of binding site of metformin in PPARδ>

In order to determine the binding site of metformin in PPARδ, a mutant lacking the N-term domain of PPARδ (ΔN-term: mutant lacking an amino acid region from the 1st amino acid to 70th amino acid) and a mutant having up to the third α-helix of LBD, hence completely lacking the ligand binding pocket (ΔLBD: mutant lacking an amino acid region from the 237th amino acid to the 441st amino acid) were prepared. FIG. 8 shows a schematic diagram of the total length of PPARδ and the structure of each mutant.

[0090]

Similar to the PPARδ-overexpressing cells that strongly express Myc-hPPARδ, ΔN-term-overexpressing cells that strongly express Myc-tagged ΔN-term (Myc-ΔN-term), and ΔLBD-overexpressing cells that strongly express Myc-tagged ΔLBD (Myc-ΔLBD) were prepared using HEK293 cells. The Met-beads were reacted with each of the cell extracts (Lysate) of these overexpressed cells, and affinity purification was performed. The protein eluted from the recovered Met-beads was subjected to Western blotting using an anti-Myc antibody to quantify the amount of immunoprecipitation. The quantitative results are shown in FIG. 9. As a result, when the amount of Myc-tagged protein in the cell extract was set as 100%, the relative amount (relative immunoprecipitation amount) (%) of the Myc-tagged protein bound to the Met-beads was about 58% for Myc-hPPARδ, about 34% for Myc-ΔN-term, and 0% for Myc-ΔLBD (bands were not confirmed in the

Western blotting). From these results, it was found that metformin binds to LBD of PPARδ.

[0091]

[Example 2]

PPARδ forms a heterodimer with the nuclear receptor RXR (Retinoid X receptor) in the nucleus, binds to the transcriptional activator PGC1α (peroxisome proliferative activated receptor gamma coactivator-1) in the presence of a ligand for PPARδ, and serves as a positive transcriptional regulator. Therefore, a luciferase assay was performed to verify the effect of metformin on the transcriptional regulation of PPARδ.

[0092]

<Luciferase assay using PPRE×2-tk-luciferase>

In order to investigate the transcriptional activation of PPARδ by metformin, human PPARδ was overexpressed in human embryonic kidney-derived cultured cell line HEK293 cells together with RXRα and PGC1α. A luciferase assay was performed using a thymidine kinase promoter (tk)/luciferase gene reporter plasmid having two DNA sequences (PPAR-Response Elements) to which the PPARδ/RXRα complex binds as a reporter. As a positive control for PPARδ activation, GW501516 (manufactured by GlaxoSmithKline plc.), which is an agonist of PPARδ, was used. The ratio (Relative Light Unit; RLU) of the amount of luminescence of a reaction solution to the amount of luminescence of a reaction solution to which an equal amount of DMSO was added (control) was defined as a relative activity value.

[0093]

The results of the luciferase assay are shown in FIG. 10B. In the presence of the PPARδ complex (hPPARδ, PGC1α, RXRα), metformin was able to activate the transcription in a concentration-dependent manner through PPRE (PPAR-Response

Element, PPAR response sequence that also has a PPARδ binding sequence) (FIGS. 10A and 10B). Moreover, this activation ability was about the same as that of GW501516. From these results, it was confirmed that metformin activates the transcription by hPPARδ.

[0094]

<Measurement of PPARδ/PGC1α transcription complex formation by co-immunoprecipitation method>

It is known that transcriptional activation by an agonist of PPARδ is caused by binding the agonist to the ligand binding pocket of PPARδ and inducing the formation of a transcriptional complex with PGC1α, which is a transcriptional co-activator. The agonist binds to the ligand binding pocket of PPARδ. Therefore, the amount of the PPARδ/PGC1α transcription complex of the cells treated with metformin or GW501516 was quantified. As a control, DMSO (dimethyl sulfoxide) treatment was performed.

[0095]

First, overexpressed cells that strongly express Myc-hPPARδ, RXRα, and PGC1α were prepared using HEK293 cells. The overexpressed cells were treated with metformin, GW501516, or DMSO, and then a cell extract was prepared. Immunoprecipitation was performed on the obtained cell extract using an anti-Myc antibody, and Western blotting was performed on the obtained immunoprecipitates using an anti-PGC1α antibody (ab54481, manufactured by Abcam), thereby measuring the relative amount of co-precipitated PGC1α (amount of PGC1α relative to amount of Myc-hPPARδ in the immunoprecipitate (IPed): [amount of PGC1α in the immunoprecipitate]/[amount of Myc-hPPARδ in the immunoprecipitate]). The results are shown in FIG. 11. In metformin-treated cells and GW501516-treated cells, an increase in the amount of co-precipitated PGC1α was observed as compared with DMSO-

treated cells. This result showed that metformin binds to the ligand binding pocket of PPARδ and induces the formation of a transcription complex with PGC1α.

[0096]

[Example 3]

The effect of metformin on the transcriptional activation by PPARδ in muscle differentiation was investigated.

[0097]

<qPCR analysis of target gene of PPARδ>

Mouse skeletal muscle-derived myoblast cell line C2C12 cells were stimulated by low-serum concentration to induce muscle differentiation and further treated with 100 μM metformin, 1 μM GW501516, or DMSO on day 6 of differentiation. The expression of the target genes of PPARδ was analyzed by qPCR in the treated cells. As the target genes, four genes, namely, the angptl4 gene, pdk4 gene, pin gene, and the ucp3 gene were measured.

[0098]

FIG. 12 shows the measurement results of the relative expression level when the expression level of the DMSO-treated cells was set as 1. As a result, although the target gene induction efficiency by GW501516 treatment was inferior, metformin was able to induce the expression of the target genes of PPARδ.

[0099]

<Measurement of effect of metformin on recruitment of PPARδ to PPRE>

Investigation of whether the transcription factor PPARδ was recruited to the promoter of the target genes by metformin treatment was carried out.

First, C2C12-PPARδ cells, in which FLAG-tagged PPARδ (FLAG-PPARδ) was constitutively over-expressed in C2C12 cells were prepared. C2C12-PPARδ cells were

stimulated by low-serum concentration to induce muscle differentiation and treated with 100 μM metformin, 1 μM GW501516, or DMSO on day 6 of differentiation. The treated cells were subjected to chromatin immunoprecipitation (Conventional ChIP) using an antibody that recognizes the FLAG tag.

[0100]

FIG. 13 shows the measurement results of the relative values of the DNA amounts of the Angptl4 gene, Pdk4 gene, Plin2 gene, and the Ucp3 gene in the chromatin immunoprecipitation (ratio of chromatin amount obtained in each IP to input chromatin amount, the amount of DNA in the IgG control was set as 1). As a result, it was shown that PPARδ was recruited in the vicinity of PPRE (the PPAR response regions) on the promoters of the Angptl4 gene, Pdk4 gene, Plin2 gene, and the Ucp3 gene by metformin treatment or GW501516 treatment, as in the results observed in gene expression.

[0101]

[Example 4]

PPARδ is known to induce the expression of lipid metabolism-related genes and enhance β-oxidation of fatty acids, especially in skeletal muscle. The PPARδ agonist is expected to have an effect of increasing mitochondrial activity. Therefore, investigation of the effect of metformin on metabolism, especially mitochondrial activity was carried out. Specifically, using C2C12 cells, the oxygen consumption rate (OCR: Oxygen Consumption Rate) of the cells was measured by a cell metabolism-measuring device (extracellular flux analyzer manufactured by Agilemt Technologies Inc.).

[0102]

In this metabolic measurement, four inhibitors were used to force changes in intracellular metabolism (Fig. 14). First, oligomycin, which inhibits Complex V of the electron transport chain, was added. Oligomycin inhibited ATP production and reduced

OCR. Next, the uncoupling agent FCCP (Carbonyl cyanide-p-trifluoromethoxyphenylhydrazone) was added. FCCP forcibly discharges hydrogen ions in the mitochondrial membrane to the outside of the membrane to eliminate the proton concentration gradient. Since a proton concentration gradient is required to produce ATP, the TCA cycle and electron transport chain are maximally activated when the gradient is forcibly eliminated by FCCP. This makes it possible to measure the maximum respiration rate of cells. It is known that OCR at this time is further increased in cells in which fatty acid oxidation is enhanced. Finally, rotenone and antimycin were added. Rotenone inhibits the electron transport chain complex I, and antimycin inhibits complex III. With the addition of these inhibitors, the electron transport chain was completely stopped and the OCR of the cells became almost zero.

[0103]

C2C12 cells were treated with solvent (DMSO), 100 μM metformin, or 10 μM GW501516 for 24 hours, inhibitors were added in the above order, and OCR was measured. The measurement result of OCR is shown in FIG. 14. As a result, the base OCR (pmol/min) before the inhibitor treatment did not change in either the metformin treatment or the GW501516 treatment. After FCCP addition, an increase in OCR was observed in metformin-treated cells and GW501516-treated cells as compared to DMSO-treated cells (FIG. 14, arrow). This indicates that metformin also increased mitochondrial metabolic activity (respiratory activity) in the same manner as GW501516.

[0104]

[Example 5]

A series of conventionally developed synthetic agonists of PPARδ (GW agonists) represented by GW501516 are phenoxyacetic acid derivatives and have a basic skeleton of a chemical structure in which a long-chain hydrophobic group such as a non-polar

hydrocarbon is bonded to a carboxyl group (-COOH). In contrast, metformin is a biguanide-based medicine having no chemical structural similarity to conventional GW medicines. Metformin does not have either the carboxyl group or the long-chain hydrophobic group that are essential for the specific binding of the ligand-binding pocket of GW medicines and PPARδ. In addition, the physical characteristics of the conventional GW agonists are characterized by being acidic and non-polar, whereas metformin is basic and water-soluble. In addition, the molecular size of the conventional GW agonists corresponds to the size of the ligand binding pocket of PPARδ, but metformin is significantly smaller. For example, the molecular weights of the typical synthetic agonists GW501516 and GW2331 are 453.5 and 490.3, respectively, while metformin is 169.2, which is about one-third. Thus, metformin has no commonality with any conventional medicine targeting PPARδ, and it is not possible to predict how it binds to PPARδ from conventional agonists with known complex structures. Therefore, a crystal of a complex of PPARδ LBD and metformin was prepared, and the three-dimensional structure of the complex was determined by X-ray crystallography.

[0105]

<Production of LBD polypeptide of PPARδ>

The crystal structure of the complex of the polypeptide (PPARδ-LBD) from the 170th glutamine to the 441st tyrosine (carboxyl terminal, C-terminal) of the amino acid sequence of PPARδ and metformin was analyzed.

PPARδ-LBD was prepared as follows. First, it was expressed in Escherichia coli as a His × 6-tagged polypeptide, and then lysed to separate an insoluble fraction. The separated insoluble fraction was solubilized with a solubilizing solution (20 mM Tris-Cl (pH 7.5), 2 M urea, 2 mM DTT, 500 mM NaCl, 0.5% Tween 20) and then centrifuged (25,000 rpm, 45 minutes) to separate the supernatant. The obtained supernatant was

dialyzed to remove urea and Tween20, purified using a Ni-affinity column (Ni-NTA Agarose, manufactured by QIAGEN, Beverly Inc.), and then the His × 6 tag was cleaved with HRV3C. The cleaved polypeptide was concentrated with Amicon (Amicon Ultra tube cutoff molecular weight 10,000, manufactured by Merck Millipore), and purified with an equilibrated Superdex 75 pg gel filtration column (manufactured by GE Healthcare) using a development solution (20 mM TrisCl (pH 7.5), 500 mM NaCl, 0.5 mM Tris (2-carboxyl) phosphate (TCEP)). Fractions containing PPARδ-LBD were concentrated to 10 mg/mL with amicon to prepare crystallization samples. The purified samples were confirmed to be PPARδ-LBD by mass spectrometry (MALDI-TOF MS, manufactured by Bruker Daltonics Inc.), and were instantly frozen in liquid nitrogen and stored at a low temperature of -80°C.

[0106]

<Crystal preparation>

The complex crystal of PPARδ-LBD and metformin was prepared by a hanging drop type vapor diffusion equilibrium method. Metformin aqueous solution prepared by dissolving metformin hydrochloride (manufactured by LKT Laboratories, Inc.) in purified distilled water to 100 mM was mixed with a purified PPARδ-LBD sample to prepare a sample solution for crystallization (PPARδ-LBD concentration: 0.3 mM, PPARδ-LBD : metformin = 1:10 (molar ratio)). For crystallization, 1 μL of the sample solution for crystallization and a reservoir solution (40 mM bis-tris-propylene (pH 6.8), 10 mM DTT, 2.5% EDTA (1,2-propanediol, 1 mM propylenediaminetetraacetic acid), 0.5% HBDG (detergent n-Heptyl-β-D-thioglucoside)), 200 μM KCl, 4% PEG8K) were mixed and vapor equilibrated against the reservoir solution at a temperature of 20°C to obtain crystals in about 4 days.

[0107]

A photomicrograph of the obtained complex crystal of metformin-bound PPARδ-LBD is shown in FIG. 15 (A). In the figure, the scale bar is 100 μm. The crystal had a unit lattice constant of 49.34 Å for a; 57.88 Å for b; 59.16 Å for c; 98.07° for α; 90.08° for β; 107.02° for γ, and belonged to the triclinic space group P1. The crystals were flash frozen in liquid nitrogen using 30% glycerol as an antifreeze.

[0108]

<Acquisition of three-dimensional structural coordinates>

X-ray intensity data was collected using a MX300HE detector at the beamline BL41XU of the large radiation facility SPring-8 at a temperature of 100 K°C. The collected X-ray intensity data was subjected to various corrections and the like with software for X-ray diffraction data processing (DENZO/SCALPACK, HKL2000 program) to obtain an X-ray intensity data set (resolution: 2.00 Å) for structural analysis. The structural analysis was based on the published structure (PDB code 5U3Q) of PPARδ-LBD registered in the RCSB Protein Data Bank (Rutgers, UCSD), and the initial phase was determined by the molecular substitution method using a program (PHASER). The structural model was modified and reconstructed using a molecular graphics program (COOT) and refined by a program (PHENIX). By repeating these model modifications and refinements, an atomic model of a complex of 18.4% of R-factor and 21.4% of Free R-factor was obtained.

[0109]

For the complex of PPARδ-LBD and phenformin, the same experiment as that for metformin was carried out, and crystals (the unit lattice constant was 49.21 Å for a; 57.64 Å for b; 107.82 Å for c; 98.02° for α; 90.03° for β; 107.08° for γ, and belonged to the triclinic space group P1) of almost the same type as the complex of PPARδ-LBD and metformin were obtained. A photomicrograph of the obtained crystal is shown in FIG.

15 (B). In the figure, the scale bar is 100 μm.

Furthermore, structural analysis was carried out using the PPARδ-LBD structure in the metformin complex. As a result, an atomic model of a complex having a resolution of 2.29 Å, 19.3% of R-factor, and 22.0% of Free R-factor was obtained.

[0110]

<Three-dimensional structural data of complex crystal of PPARδ-LBD and metformin>

The structure of the complex crystal of PPARδ-LBD and metformin is shown in FIG. 16. Two molecules of PPARδ-LBD (molecule A and Molecule B in the figure) having almost the same structure were present in the crystal, and metformin was bound to a ligand-binding pocket in each domain. The surfactant HBDG used for crystallization was bound to the molecular surface of each PPARδ-LBD.

[0111]

The structure of PPARδ-LBD in the complex crystal was composed of fifteen α-helices H1-H12, H2', H2", H3' and three β-strands S1, S2, S3, and the three β-strands formed one antiparallel β-sheet (Fig. 16). There was a cavity (ligand binding pocket) in the center of the molecule to which a Y-shaped ligand could bind. This overall structure was almost the same as the basic structure of PPARδ-LBD reported so far (NPL 7 and 8). It was also similar to the structure of LBD of PPARα and LBD of PPARγ.

[0112]

FIG. 17 shows the metformin molecule in the ligand binding pocket in the complex crystal. In the figure, the broken line indicates the hydrogen bond, and the attached numerical value indicates the distance. H3, H4, H11 and the like represent α-helices that form ligand binding pockets. This ligand-binding pocket was Y-shaped and had three tunnel-like cavities called arms I, II, and III. The metformin molecule was bound to arm I formed from the α-helices H3, H4, H11, and H12, and the two amino

groups of the biguanide skeleton of metformin were immobilized by forming direct hydrogen bonds with residues of each α-helix, Thr253 (α-helix H3), His287 (α-helix H4), His413 (α-helix H11) and Tyr437 (α-helix H12). A peptide region (Leu429-Med441) called the AF-2 fragment (activation function-2 segment), which is essential for PPAR activation, was bound to the LBD by forming α-helix H12 so as to cover the ligand-binding pocket. This means that the LBD of PPARδ bound to metformin has an active conformation. Since the formation of this α-helix H12 was induced by the direct interaction with metformin described above, it corresponds well to metformin being an agonist of PPARδ.

[0113]

In addition to the polar interactions such as hydrogen bonds mentioned above, by fitting metformin within the narrow space at the tip of arm I, all the atoms were in contact with the atoms of PPARδ-LBD in addition to the hydrogen bond, and the bond was stabilized. The biguanide skeleton of metformin was in non-polar contact with Leu433, Phe246, and Met417. The two methyl groups of metformin were in non-polar contact with Thr253, Ph291, Cys249 and Ile327. Metformin is a small molecule and is not large enough to fill all the ligand binding pockets of PPARδ-LBD. The tips of the two methyl groups of metformin were connected to the cavities of arm II and arm III, but these arms remained empty.

[0114]

The above interaction characteristics were also observed in the structure of the complex of phenformin and PPARδ-LBD. FIG. 18 is a diagram in which the structure of the complex crystal of metformin and PPARδ-LBD and the structure of the complex crystal of phenformin and PPARδ-LBD are superimposed. In the figure, the broken line indicates the hydrogen bond, and the attached numerical value indicates the distance.

H3, H4, H11, and H12 indicate α-helices that form ligand-binding pockets. The biguanide skeleton of phenformin overlapped well with the biguanide skeleton of metformin, and phenformin also formed hydrogen bonds similar to the four hydrogen bonds of metformin. The phenyl group of phenformin protruded into the large space behind the hydrophobic ligand-binding pocket, but there was no close non-polar contact with PPARδ.

[0115]

The shape of the ligand binding pocket of hPPARδ can be drawn by incorporating the data of Tables 1 to 63 into the molecular graphics software PyMOL.

[0116]

[Table 1]

ATOM	1	N	VAL	A	172	-76.185	38.759	23.431	1.00 52.70	N
ATOM	2	CA	VAL	A	172	-77.335	39.035	22.492	1.00 50.01	C
ATOM	3	C	VAL	A	172	-78.505	39.589	23.289	1.00 50.21	C
ATOM	4	O	VAL	A	172	-79.014	40.651	22.934	1.00 46.42	O
ATOM	5	CB	VAL	A	172	-77.751	37.772	21.675	1.00 59.23	C
ATOM	6	CG1	VAL	A	172	-79.149	37.894	21.007	1.00 56.55	C
ATOM	7	CG2	VAL	A	172	-76.677	37.483	20.631	1.00 61.76	C
ATOM	8	N	ALA	A	173	-78.916	38.880	24.351	1.00 42.75	N
ATOM	9	CA	ALA	A	173	-80.048	39.296	25.221	1.00 44.81	C
ATOM	10	C	ALA	A	173	-80.006	40.762	25.699	1.00 49.28	C
ATOM	11	O	ALA	A	173	-81.047	41.447	25.653	1.00 43.42	O
ATOM	12	CB	ALA	A	173	-80.197	38.379	26.433	1.00 44.28	C
ATOM	13	N	ASP	A	174	-78.834	41.202	26.186	1.00 40.11	N
ATOM	14	CA	ASP	A	174	-78.687	42.529	26.733	1.00 42.61	C
ATOM	15	C	ASP	A	174	-78.667	43.604	25.625	1.00 31.66	C
ATOM	16	O	ASP	A	174	-79.182	44.676	25.837	1.00 32.54	O
ATOM	17	CB	ASP	A	174	-77.467	42.622	27.621	1.00 48.17	C
ATOM	18	CG	ASP	A	174	-77.573	41.709	28.833	1.00 51.88	C
ATOM	19	OD1	ASP	A	174	-78.571	41.792	29.570	1.00 58.12	O
ATOM	20	OD2	ASP	A	174	-76.667	40.885	29.031	1.00 54.26	O1-
ATOM	21	N	LEU	A	175	-78.102	43.295	24.479	1.00 29.50	N
ATOM	22	CA	LEU	A	175	-78.105	44.220	23.355	1.00 35.50	C
ATOM	23	C	LEU	A	175	-79.527	44.345	22.747	1.00 33.52	C
ATOM	24	O	LEU	A	175	-79.900	45.381	22.183	1.00 25.39	O
ATOM	25	CB	LEU	A	175	-77.110	43.795	22.290	1.00 35.60	C
ATOM	26	CG	LEU	A	175	-75.606	43.968	22.595	1.00 39.37	C
ATOM	27	CD1	LEU	A	175	-74.788	43.137	21.631	1.00 36.52	C
ATOM	28	CD2	LEU	A	175	-75.140	45.403	22.529	1.00 40.09	C
ATOM	29	N	LYS	A	176	-80.272	43.253	22.793	1.00 30.78	N
ATOM	30	CA	LYS	A	176	-81.667	43.264	22.342	1.00 30.46	C
ATOM	31	C	LYS	A	176	-82.485	44.083	23.317	1.00 24.09	C
ATOM	32	O	LYS	A	176	-83.309	44.931	22.903	1.00 28.28	O
ATOM	33	CB	LYS	A	176	-82.187	41.821	22.156	1.00 32.44	C
ATOM	34	CG	LYS	A	176	-83.358	41.701	21.224	1.00 46.17	C
ATOM	35	CD	LYS	A	176	-83.949	40.281	21.175	1.00 48.50	C

[0117]

[Table 2]

ATOM	36	CE	LYS	A	176	-85.386	40.271	21.683	1.00 53.08	C
ATOM	37	NZ	LYS	A	176	-85.892	38.878	21.847	1.00 55.95	N1+
ATOM	38	N	ALA	A	177	-82.295	43.889	24.604	1.00 20.61	N
ATOM	39	CA	ALA	A	177	-82.997	44.685	25.563	1.00 24.27	C
ATOM	40	C	ALA	A	177	-82.707	46.175	25.514	1.00 23.29	C
ATOM	41	O	ALA	A	177	-83.559	46.976	25.845	1.00 24.10	O
ATOM	42	CB	ALA	A	177	-82.779	44.202	27.003	1.00 26.55	C
ATOM	43	N	PHE	A	178	-81.454	46.530	25.294	1.00 28.53	N
ATOM	44	CA	PHE	A	178	-81.050	47.934	25.261	1.00 27.37	C
ATOM	45	C	PHE	A	178	-81.719	48.583	24.054	1.00 24.62	C
ATOM	46	O	PHE	A	178	-82.253	49.682	24.168	1.00 25.13	O
ATOM	47	CB	PHE	A	178	-79.509	48.020	25.140	1.00 27.11	C
ATOM	48	CG	PHE	A	178	-78.961	49.415	25.227	1.00 26.79	C
ATOM	49	CD1	PHE	A	178	-78.863	50.205	24.085	1.00 26.67	C
ATOM	50	CD2	PHE	A	178	-78.513	49.932	26.436	1.00 28.08	C
ATOM	51	CE1	PHE	A	178	-78.334	51.526	24.127	1.00 26.61	C
ATOM	52	CE2	PHE	A	178	-78.010	51.241	26.496	1.00 29.20	C
ATOM	53	CZ	PHE	A	178	-77.887	52.025	25.339	1.00 27.65	C
ATOM	54	N	SER	A	179	-81.587	47.940	22.897	1.00 24.32	N
ATOM	55	CA	SER	A	179	-82.240	48.400	21.691	1.00 25.78	C
ATOM	56	C	SER	A	179	-83.748	48.636	21.790	1.00 26.17	C
ATOM	57	O	SER	A	179	-84.258	49.609	21.227	1.00 28.31	O
ATOM	58	CB	SER	A	179	-82.027	47.458	20.554	1.00 25.46	C
ATOM	59	OG	SER	A	179	-80.652	47.358	20.287	1.00 27.99	O
ATOM	60	N	LYS	A	180	-84.446	47.677	22.370	1.00 26.41	N
ATOM	61	CA	LYS	A	180	-85.881	47.773	22.647	1.00 26.93	C
ATOM	62	C	LYS	A	180	-86.184	48.894	23.598	1.00 26.62	C
ATOM	63	O	LYS	A	180	-87.176	49.597	23.425	1.00 22.77	O
ATOM	64	CB	LYS	A	180	-86.401	46.433	23.233	1.00 28.63	C
ATOM	65	CG	LYS	A	180	-87.914	46.349	23.412	1.00 31.99	C
ATOM	66	CD	LYS	A	180	-88.584	46.557	22.076	1.00 38.19	C
ATOM	67	CE	LYS	A	180	-88.228	45.451	21.094	1.00 40.17	C
ATOM	68	NZ	LYS	A	180	-88.587	44.089	21.621	1.00 45.48	N1+
ATOM	69	N	HIS	A	181	-85.324	49.108	24.606	1.00 23.61	N
ATOM	70	CA	HIS	A	181	-85.570	50.177	25.502	1.00 24.20	C

[0118]

[Table 3]

ATOM	71	C	HIS A 181	-85.507	51.590	24.810	1.00	21.61	C
ATOM	72	O	HIS A 181	-86.349	52.440	24.987	1.00	20.60	O
ATOM	73	CB	HIS A 181	-84.564	50.083	26.652	1.00	27.72	C
ATOM	74	CG	HIS A 181	-84.624	51.236	27.574	1.00	29.34	C
ATOM	75	CD2	HIS A 181	-83.963	52.421	27.566	1.00	30.58	C
ATOM	76	ND1	HIS A 181	-85.508	51.290	28.626	1.00	33.01	N
ATOM	77	CE1	HIS A 181	-85.343	52.428	29.274	1.00	34.58	C
ATOM	78	NE2	HIS A 181	-84.425	53.142	28.647	1.00	32.87	N
ATOM	79	N	ILE A 182	-84.510	51.778	23.978	1.00	24.67	N
ATOM	80	CA	ILE A 182	-84.369	52.999	23.222	1.00	26.38	C
ATOM	81	C	ILE A 182	-85.564	53.147	22.227	1.00	22.03	C
ATOM	82	O	ILE A 182	-86.101	54.243	22.039	1.00	23.94	O
ATOM	83	CB	ILE A 182	-82.992	53.011	22.516	1.00	24.35	C
ATOM	84	CG1	ILE A 182	-81.797	53.039	23.528	1.00	25.44	C
ATOM	85	CG2	ILE A 182	-82.858	54.181	21.579	1.00	22.74	C
ATOM	86	CD1	ILE A 182	-81.825	54.167	24.530	1.00	29.44	C
ATOM	87	N	TYR A 183	-85.969	52.059	21.615	1.00	23.11	N
ATOM	88	CA	TYR A 183	-87.124	52.120	20.632	1.00	25.83	C
ATOM	89	C	TYR A 183	-88.388	52.482	21.376	1.00	25.20	C
ATOM	90	O	TYR A 183	-89.053	53.417	20.978	1.00	24.99	O
ATOM	91	CB	TYR A 183	-87.265	50.826	19.881	1.00	25.77	C
ATOM	92	CG	TYR A 183	-88.375	50.749	18.873	1.00	27.56	C
ATOM	93	CD1	TYR A 183	-88.736	51.833	18.117	1.00	25.51	C
ATOM	94	CD2	TYR A 183	-89.016	49.548	18.656	1.00	29.78	C
ATOM	95	CE1	TYR A 183	-89.729	51.750	17.163	1.00	29.45	C
ATOM	96	CE2	TYR A 183	-90.031	49.433	17.712	1.00	33.07	C
ATOM	97	CZ	TYR A 183	-90.388	50.545	16.966	1.00	32.67	C
ATOM	98	OH	TYR A 183	-91.405	50.438	16.055	1.00	32.23	O
ATOM	99	N	ASN A 184	-88.610	51.884	22.558	1.00	26.33	N
ATOM	100	CA	ASN A 184	-89.697	52.319	23.413	1.00	25.07	C
ATOM	101	C	ASN A 184	-89.716	53.770	23.731	1.00	27.45	C
ATOM	102	O	ASN A 184	-90.805	54.394	23.663	1.00	26.57	O
ATOM	103	CB	ASN A 184	-89.769	51.559	24.744	1.00	28.54	C
ATOM	104	CG	ASN A 184	-90.248	50.151	24.562	1.00	33.01	C
ATOM	105	ND2	ASN A 184	-89.860	49.296	25.498	1.00	35.70	N

[0119]

[Table 4]

ATOM	106	OD1	ASN	A	184	-90.869	49.798	23.531	1.00 32.82	O
ATOM	107	N	ALA	A	185	-88.559	54.309	24.134	1.00 25.16	N
ATOM	108	CA	ALA	A	185	-88.461	55.727	24.489	1.00 24.60	C
ATOM	109	C	ALA	A	185	-88.822	56.613	23.283	1.00 21.27	C
ATOM	110	O	ALA	A	185	-89.439	57.648	23.440	1.00 23.34	O
ATOM	111	CB	ALA	A	185	-87.071	56.086	24.982	1.00 27.11	C
ATOM	112	N	TYR	A	186	-88.327	56.237	22.112	1.00 22.27	N
ATOM	113	CA	TYR	A	186	-88.597	56.943	20.889	1.00 21.03	C
ATOM	114	C	TYR	A	186	-90.119	57.000	20.635	1.00 24.36	C
ATOM	115	O	TYR	A	186	-90.715	58.061	20.386	1.00 23.47	O
ATOM	116	CB	TYR	A	186	-87.867	56.270	19.779	1.00 21.85	C
ATOM	117	CG	TYR	A	186	-88.076	56.707	18.346	1.00 22.41	C
ATOM	118	CD1	TYR	A	186	-89.070	56.126	17.589	1.00 26.35	C
ATOM	119	CD2	TYR	A	186	-87.187	57.548	17.704	1.00 24.76	C
ATOM	120	CE1	TYR	A	186	-89.241	56.422	16.230	1.00 28.94	C
ATOM	121	CE2	TYR	A	186	-87.333	57.847	16.344	1.00 26.27	C
ATOM	122	CZ	TYR	A	186	-88.389	57.297	15.623	1.00 28.95	C
ATOM	123	OH	TYR	A	186	-88.556	57.498	14.260	1.00 28.54	O
ATOM	124	N	LEU	A	187	-90.745	55.859	20.734	1.00 25.86	N
ATOM	125	CA	LEU	A	187	-92.198	55.777	20.565	1.00 25.87	C
ATOM	126	C	LEU	A	187	-92.983	56.530	21.571	1.00 26.59	C
ATOM	127	O	LEU	A	187	-94.066	57.036	21.241	1.00 26.00	O
ATOM	128	CB	LEU	A	187	-92.689	54.326	20.516	1.00 24.38	C
ATOM	129	CG	LEU	A	187	-92.192	53.544	19.352	1.00 22.73	C
ATOM	130	CD1	LEU	A	187	-92.515	52.061	19.564	1.00 27.08	C
ATOM	131	CD2	LEU	A	187	-92.786	54.020	18.054	1.00 26.39	C
ATOM	132	N	LYS	A	188	-92.461	56.646	22.784	1.00 24.71	N
ATOM	133	CA	LYS	A	188	-93.120	57.426	23.769	1.00 30.26	C
ATOM	134	C	LYS	A	188	-92.996	58.925	23.536	1.00 31.07	C
ATOM	135	O	LYS	A	188	-93.787	59.690	24.091	1.00 33.85	O
ATOM	136	CB	LYS	A	188	-92.590	57.124	25.197	1.00 34.62	C
ATOM	137	CG	LYS	A	188	-93.579	56.325	26.004	1.00 38.65	C
ATOM	138	CD	LYS	A	188	-93.032	55.886	27.367	1.00 41.52	C
ATOM	139	CE	LYS	A	188	-93.446	54.445	27.638	1.00 45.53	C
ATOM	140	NZ	LYS	A	188	-92.983	54.006	28.975	1.00 49.87	N1+

[0120]

[Table 5]

ATOM	141	N	ASN A 189	-91.974	59.378	22.809	1.00	26.38	N
ATOM	142	CA	ASN A 189	-91.663	60.818	22.804	1.00	25.85	C
ATOM	143	C	ASN A 189	-91.933	61.497	21.494	1.00	26.44	C
ATOM	144	O	ASN A 189	-92.064	62.694	21.479	1.00	29.96	O
ATOM	145	CB	ASN A 189	-90.206	61.007	23.244	1.00	26.95	C
ATOM	146	CG	ASN A 189	-90.054	60.856	24.742	1.00	28.25	C
ATOM	147	ND2	ASN A 189	-89.518	59.749	25.204	1.00	26.96	N
ATOM	148	OD1	ASN A 189	-90.485	61.721	25.462	1.00	24.74	O
ATOM	149	N	PHE A 190	-91.959	60.767	20.387	1.00	24.89	N
ATOM	150	CA	PHE A 190	-92.113	61.397	19.069	1.00	28.46	C
ATOM	151	C	PHE A 190	-93.489	61.145	18.488	1.00	33.62	C
ATOM	152	O	PHE A 190	-93.987	60.031	18.564	1.00	36.21	O
ATOM	153	CB	PHE A 190	-90.991	60.998	18.112	1.00	25.42	C
ATOM	154	CG	PHE A 190	-89.666	61.313	18.676	1.00	27.59	C
ATOM	155	CD1	PHE A 190	-89.340	62.651	18.939	1.00	28.25	C
ATOM	156	CD2	PHE A 190	-88.786	60.308	19.065	1.00	24.59	C
ATOM	157	CE1	PHE A 190	-88.137	63.003	19.541	1.00	28.57	C
ATOM	158	CE2	PHE A 190	-87.559	60.662	19.656	1.00	28.38	C
ATOM	159	CZ	PHE A 190	-87.258	62.004	19.916	1.00	28.52	C
ATOM	160	N	ASN A 191	-94.100	62.197	17.939	1.00	35.72	N
ATOM	161	CA	ASN A 191	-95.480	62.070	17.499	1.00	44.39	C
ATOM	162	C	ASN A 191	-95.609	61.499	16.099	1.00	39.01	C
ATOM	163	O	ASN A 191	-96.577	60.866	15.814	1.00	48.11	O
ATOM	164	CB	ASN A 191	-96.261	63.378	17.626	1.00	54.13	C
ATOM	165	CG	ASN A 191	-97.708	63.124	18.050	1.00	65.01	C
ATOM	166	ND2	ASN A 191	-98.173	63.868	19.049	1.00	70.35	N
ATOM	167	OD1	ASN A 191	-98.388	62.237	17.510	1.00	70.56	O
ATOM	168	N	MET A 192	-94.640	61.677	15.242	1.00	33.14	N
ATOM	169	CA	MET A 192	-94.737	61.141	13.882	1.00	35.43	C
ATOM	170	C	MET A 192	-93.640	60.107	13.682	1.00	34.11	C
ATOM	171	O	MET A 192	-92.504	60.438	13.788	1.00	38.98	O
ATOM	172	CB	MET A 192	-94.523	62.310	12.939	1.00	35.95	C
ATOM	173	CG	MET A 192	-94.571	61.990	11.451	1.00	39.68	C
ATOM	174	SD	MET A 192	-96.067	61.093	11.033	1.00	43.83	S
ATOM	175	CE	MET A 192	-97.212	62.454	11.103	1.00	42.08	C

[0121]

[Table 6]

ATOM	176	N	THR	A	193	-93.969	58.863	13.425	1.00	29.64	N
ATOM	177	CA	THR	A	193	-92.972	57.856	13.147	1.00	29.54	C
ATOM	178	C	THR	A	193	-92.826	57.686	11.660	1.00	32.16	C
ATOM	179	O	THR	A	193	-93.731	58.066	10.878	1.00	30.21	O
ATOM	180	CB	THR	A	193	-93.392	56.545	13.751	1.00	28.89	C
ATOM	181	CG2	THR	A	193	-93.542	56.732	15.265	1.00	29.71	C
ATOM	182	OG1	THR	A	193	-94.644	56.151	13.196	1.00	27.83	O
ATOM	183	N	LYS	A	194	-91.709	57.112	11.279	1.00	25.68	N
ATOM	184	CA	LYS	A	194	-91.463	56.815	9.919	1.00	29.45	C
ATOM	185	C	LYS	A	194	-92.523	55.844	9.368	1.00	33.65	C
ATOM	186	O	LYS	A	194	-92.911	55.942	8.200	1.00	29.84	O
ATOM	187	CB	LYS	A	194	-90.084	56.188	9.751	1.00	27.21	C
ATOM	188	CG	LYS	A	194	-89.759	56.048	8.311	1.00	25.95	C
ATOM	189	CD	LYS	A	194	-88.290	55.769	8.013	1.00	27.58	C
ATOM	190	CE	LYS	A	194	-88.063	55.739	6.522	1.00	25.56	C
ATOM	191	NZ	LYS	A	194	-86.718	55.308	6.129	1.00	26.53	N1+
ATOM	192	N	LYS	A	195	-92.939	54.905	10.206	1.00	31.19	N
ATOM	193	CA	LYS	A	195	-93.996	53.954	9.846	1.00	35.70	C
ATOM	194	C	LYS	A	195	-95.294	54.660	9.475	1.00	32.58	C
ATOM	195	O	LYS	A	195	-95.896	54.369	8.424	1.00	29.06	O
ATOM	196	CB	LYS	A	195	-94.258	52.976	10.998	1.00	36.70	C
ATOM	197	CG	LYS	A	195	-95.420	52.028	10.740	1.00	45.84	C
ATOM	198	CD	LYS	A	195	-95.641	51.070	11.901	1.00	48.59	C
ATOM	199	CE	LYS	A	195	-94.658	49.924	11.848	1.00	60.77	C
ATOM	200	NZ	LYS	A	195	-95.288	48.672	12.385	1.00	69.98	N1+
ATOM	201	N	LYS	A	196	-95.702	55.583	10.319	1.00	32.50	N
ATOM	202	CA	LYS	A	196	-96.904	56.377	10.038	1.00	34.50	C
ATOM	203	C	LYS	A	196	-96.677	57.229	8.772	1.00	34.61	C
ATOM	204	O	LYS	A	196	-97.494	57.165	7.864	1.00	30.35	O
ATOM	205	CB	LYS	A	196	-97.300	57.258	11.213	1.00	40.01	C
ATOM	206	CG	LYS	A	196	-98.443	58.194	10.860	1.00	48.30	C
ATOM	207	CD	LYS	A	196	-99.127	58.814	12.059	1.00	50.20	C
ATOM	208	CE	LYS	A	196	-100.177	57.888	12.664	1.00	56.16	C
ATOM	209	NZ	LYS	A	196	-101.237	58.717	13.308	1.00	61.35	N1+
ATOM	210	N	ALA	A	197	-95.570	57.985	8.702	1.00	25.18	N

[0122]

[Table 7]

ATOM	211	CA	ALA	A	197	-95.312	58.847	7.547	1.00 29.66	C
ATOM	212	C	ALA	A	197	-95.347	58.115	6.211	1.00 32.31	C
ATOM	213	O	ALA	A	197	-95.981	58.621	5.231	1.00 31.92	O
ATOM	214	CB	ALA	A	197	-94.009	59.581	7.710	1.00 32.70	C
ATOM	215	N	ARG	A	198	-94.713	56.941	6.154	1.00 31.55	N
ATOM	216	CA	ARG	A	198	-94.635	56.151	4.923	1.00 36.68	C
ATOM	217	C	ARG	A	198	-95.992	55.615	4.513	1.00 40.95	C
ATOM	218	O	ARG	A	198	-96.284	55.571	3.319	1.00 40.04	O
ATOM	219	CB	ARG	A	198	-93.666	54.982	5.017	1.00 40.12	C
ATOM	220	CG	ARG	A	198	-92.196	55.397	5.078	1.00 47.18	C
ATOM	221	CD	ARG	A	198	-91.670	56.059	3.783	1.00 57.47	C
ATOM	222	NE	ARG	A	198	-91.036	57.334	4.140	1.00 68.80	N
ATOM	223	CZ	ARG	A	198	-90.732	58.335	3.313	1.00 68.29	C
ATOM	224	NH1	ARG	A	198	-90.952	58.264	2.003	1.00 69.84	N1+
ATOM	225	NH2	ARG	A	198	-90.191	59.431	3.822	1.00 63.73	N
ATOM	226	N	SER	A	199	-96.818	55.216	5.479	1.00 37.94	N
ATOM	227	CA	SER	A	199	-98.134	54.718	5.132	1.00 42.22	C
ATOM	228	C	SER	A	199	-99.048	55.847	4.579	1.00 47.84	C
ATOM	229	O	SER	A	199	-99.856	55.607	3.652	1.00 49.67	O
ATOM	230	CB	SER	A	199	-98.778	54.057	6.319	1.00 41.34	C
ATOM	231	OG	SER	A	199	-99.263	55.088	7.142	1.00 53.26	O
ATOM	232	N	ILE	A	200	-98.916	57.059	5.133	1.00 42.42	N
ATOM	233	CA	ILE	A	200	-99.624	58.240	4.600	1.00 39.98	C
ATOM	234	C	ILE	A	200	-99.047	58.587	3.241	1.00 40.57	C
ATOM	235	O	ILE	A	200	-99.790	58.795	2.319	1.00 47.87	O
ATOM	236	CB	ILE	A	200	-99.476	59.454	5.506	1.00 34.95	C
ATOM	237	CG1	ILE	A	200	-100.161	59.193	6.831	1.00 37.25	C
ATOM	238	CG2	ILE	A	200	-100.062	60.720	4.862	1.00 36.32	C
ATOM	239	CD1	ILE	A	200	-99.742	60.182	7.903	1.00 37.05	C
ATOM	240	N	LEU	A	201	-97.727	58.636	3.114	1.00 38.24	N
ATOM	241	CA	LEU	A	201	-97.064	59.066	1.864	1.00 39.20	C
ATOM	242	C	LEU	A	201	-97.270	58.151	0.675	1.00 50.00	C
ATOM	243	O	LEU	A	201	-97.123	58.604	-0.464	1.00 55.84	O
ATOM	244	CB	LEU	A	201	-95.536	59.283	2.038	1.00 35.38	C
ATOM	245	CG	LEU	A	201	-95.097	60.600	2.704	1.00 37.94	C

[0123]

[Table 8]

ATOM	246	CD1	LEU A 201	-93.635	60.616	3.159	1.00	36.58	C
ATOM	247	CD2	LEU A 201	-95.377	61.804	1.797	1.00	40.74	C
ATOM	248	N	THR A 202	-97.561	56.871	0.920	1.00	51.78	N
ATOM	249	CA	THR A 202	-97.797	55.910	-0.149	1.00	54.02	C
ATOM	250	C	THR A 202	-99.267	55.481	-0.295	1.00	55.85	C
ATOM	251	O	THR A 202	-99.544	54.582	-1.066	1.00	51.84	O
ATOM	252	CB	THR A 202	-96.931	54.650	0.040	1.00	50.12	C
ATOM	253	CG2	THR A 202	-95.472	54.994	0.007	1.00	51.23	C
ATOM	254	OG1	THR A 202	-97.278	54.018	1.281	1.00	47.02	O
ATOM	255	N	GLY A 203	-100.190	56.085	0.454	1.00	59.43	N
ATOM	256	CA	GLY A 203	-101.616	55.902	0.209	1.00	64.43	C
ATOM	257	C	GLY A 203	-102.318	54.911	1.118	1.00	67.48	C
ATOM	258	O	GLY A 203	-103.543	54.878	1.149	1.00	74.08	O
ATOM	259	N	LYS A 204	-101.553	54.108	1.853	1.00	69.89	N
ATOM	260	CA	LYS A 204	-102.098	53.112	2.773	1.00	66.42	C
ATOM	261	C	LYS A 204	-102.657	53.794	4.027	1.00	74.34	C
ATOM	262	O	LYS A 204	-103.770	53.498	4.466	1.00	84.31	O
ATOM	263	CB	LYS A 204	-100.999	52.118	3.153	1.00	56.83	C
TER	264		LYS A 204						
ATOM	265	N	ALA A 209	-106.293	61.454	1.202	1.00	55.53	N
ATOM	266	CA	ALA A 209	-105.038	62.090	0.830	1.00	54.52	C
ATOM	267	C	ALA A 209	-104.730	63.270	1.774	1.00	54.60	C
ATOM	268	O	ALA A 209	-105.668	63.879	2.320	1.00	53.35	O
ATOM	269	CB	ALA A 209	-105.092	62.568	-0.604	1.00	51.75	C
ATOM	270	N	PRO A 210	-103.421	63.601	1.978	1.00	48.56	N
ATOM	271	CA	PRO A 210	-103.097	64.868	2.681	1.00	40.74	C
ATOM	272	C	PRO A 210	-103.422	66.082	1.785	1.00	33.37	C
ATOM	273	O	PRO A 210	-103.268	66.021	0.596	1.00	31.34	O
ATOM	274	CB	PRO A 210	-101.566	64.760	2.915	1.00	40.59	C
ATOM	275	CG	PRO A 210	-101.259	63.307	2.695	1.00	44.72	C
ATOM	276	CD	PRO A 210	-102.175	62.925	1.560	1.00	44.48	C
ATOM	277	N	PHE A 211	-103.832	67.175	2.376	1.00	32.36	N
ATOM	278	CA	PHE A 211	-104.097	68.420	1.635	1.00	33.25	C
ATOM	279	C	PHE A 211	-102.803	68.977	1.101	1.00	32.20	C
ATOM	280	O	PHE A 211	-101.881	69.176	1.870	1.00	31.71	O

[0124]

[Table 9]

ATOM	281	CB	PHE A 211	-104.716	69.440	2.595	1.00	32.28	C
ATOM	282	CG	PHE A 211	-105.018	70.763	1.941	1.00	37.76	C
ATOM	283	CD1	PHE A 211	-105.996	70.851	0.938	1.00	38.37	C
ATOM	284	CD2	PHE A 211	-104.278	71.905	2.253	1.00	37.26	C
ATOM	285	CE1	PHE A 211	-106.278	72.059	0.321	1.00	38.29	C
ATOM	286	CE2	PHE A 211	-104.558	73.114	1.632	1.00	37.21	C
ATOM	287	CZ	PHE A 211	-105.579	73.205	0.689	1.00	35.97	C
ATOM	288	N	VAL A 212	-102.731	69.267	-0.195	1.00	33.46	N
ATOM	289	CA	VAL A 212	-101.490	69.702	-0.822	1.00	32.40	C
ATOM	290	C	VAL A 212	-101.333	71.250	-0.788	1.00	32.85	C
ATOM	291	O	VAL A 212	-102.205	72.005	-1.239	1.00	31.47	O
ATOM	292	CB	VAL A 212	-101.361	69.147	-2.267	1.00	34.62	C
ATOM	293	CG1	VAL A 212	-100.081	69.657	-2.906	1.00	37.02	C
ATOM	294	CG2	VAL A 212	-101.352	67.650	-2.280	1.00	37.32	C
ATOM	295	N	ILE A 213	-100.206	71.703	-0.259	1.00	28.76	N
ATOM	296	CA	ILE A 213	-99.851	73.094	-0.168	1.00	28.25	C
ATOM	297	C	ILE A 213	-98.799	73.363	-1.237	1.00	30.12	C
ATOM	298	O	ILE A 213	-97.661	72.906	-1.127	1.00	27.80	O
ATOM	299	CB	ILE A 213	-99.293	73.430	1.210	1.00	27.64	C
ATOM	300	CG1	ILE A 213	-100.384	73.300	2.253	1.00	31.93	C
ATOM	301	CG2	ILE A 213	-98.777	74.851	1.290	1.00	28.09	C
ATOM	302	CD1	ILE A 213	-99.769	73.030	3.628	1.00	35.50	C
ATOM	303	N	HIS A 214	-99.177	74.128	-2.253	1.00	26.14	N
ATOM	304	CA	HIS A 214	-98.297	74.401	-3.353	1.00	31.25	C
ATOM	305	C	HIS A 214	-98.249	75.866	-3.781	1.00	30.04	C
ATOM	306	O	HIS A 214	-97.569	76.202	-4.735	1.00	33.51	O
ATOM	307	CB	HIS A 214	-98.630	73.466	-4.542	1.00	31.14	C
ATOM	308	CG	HIS A 214	-100.037	73.559	-5.012	1.00	37.86	C
ATOM	309	CD2	HIS A 214	-100.872	72.640	-5.533	1.00	42.12	C
ATOM	310	ND1	HIS A 214	-100.742	74.738	-4.989	1.00	43.19	N
ATOM	311	CE1	HIS A 214	-101.952	74.540	-5.447	1.00	38.08	C
ATOM	312	NE2	HIS A 214	-102.073	73.267	-5.749	1.00	39.03	N
ATOM	313	N	ASP A 215	-98.958	76.736	-3.081	1.00	29.01	N
ATOM	314	CA	ASP A 215	-99.014	78.156	-3.387	1.00	29.06	C
ATOM	315	C	ASP A 215	-99.573	78.935	-2.191	1.00	27.03	C

[0125]

[Table 10]

ATOM	316	O	ASP A 215	-99.911	78.345	-1.164	1.00 25.52		O
ATOM	317	CB	ASP A 215	-99.858	78.384	-4.653	1.00 31.06		C
ATOM	318	CG	ASP A 215	-101.351	78.135	-4.444	1.00 36.19		C
ATOM	319	OD1	ASP A 215	-101.803	77.450	-3.520	1.00 35.10		O
ATOM	320	OD2	ASP A 215	-102.117	78.632	-5.291	1.00 44.50		O1-
ATOM	321	N	ILE A 216	-99.598	80.243	-2.333	1.00 26.54		N
ATOM	322	CA	ILE A 216	-100.082	81.140	-1.310	1.00 28.71		C
ATOM	323	C	ILE A 216	-101.464	80.833	-0.850	1.00 29.59		C
ATOM	324	O	ILE A 216	-101.742	80.776	0.352	1.00 27.49		O
ATOM	325	CB	ILE A 216	-99.957	82.645	-1.714	1.00 33.33		C
ATOM	326	CG1	ILE A 216	-100.482	83.559	-0.587	1.00 34.01		C
ATOM	327	CG2	ILE A 216	-100.744	83.041	-2.984	1.00 35.34		C
ATOM	328	CD1	ILE A 216	-99.969	84.996	-0.741	1.00 39.78		C
ATOM	329	N	GLU A 217	-102.361	80.626	-1.796	1.00 28.92		N
ATOM	330	CA	GLU A 217	-103.750	80.381	-1.456	1.00 31.25		C
ATOM	331	C	GLU A 217	-103.926	79.093	-0.662	1.00 28.15		C
ATOM	332	O	GLU A 217	-104.615	79.086	0.344	1.00 29.20		O
ATOM	333	CB	GLU A 217	-104.599	80.367	-2.742	1.00 35.18		C
ATOM	334	CG	GLU A 217	-106.058	80.016	-2.482	1.00 47.47		C
ATOM	335	CD	GLU A 217	-106.948	80.155	-3.732	1.00 57.20		C
ATOM	336	OE1	GLU A 217	-108.039	79.550	-3.715	1.00 70.21		O
ATOM	337	OE2	GLU A 217	-106.581	80.878	-4.698	1.00 58.40		O1-
ATOM	338	N	THR A 218	-103.329	77.998	-1.110	1.00 26.55		N
ATOM	339	CA	THR A 218	-103.449	76.745	-0.398	1.00 25.93		C
ATOM	340	C	THR A 218	-102.689	76.826	0.970	1.00 27.70		C
ATOM	341	O	THR A 218	-103.139	76.271	1.945	1.00 26.11		O
ATOM	342	CB	THR A 218	-102.958	75.536	-1.214	1.00 27.44		C
ATOM	343	CG2	THR A 218	-103.834	75.360	-2.518	1.00 32.83		C
ATOM	344	OG1	THR A 218	-101.567	75.667	-1.522	1.00 24.38		O
ATOM	345	N	LEU A 219	-101.619	77.605	1.041	1.00 26.88		N
ATOM	346	CA	LEU A 219	-100.909	77.798	2.329	1.00 28.99		C
ATOM	347	C	LEU A 219	-101.810	78.453	3.366	1.00 28.45		C
ATOM	348	O	LEU A 219	-101.833	78.029	4.526	1.00 27.21		O
ATOM	349	CB	LEU A 219	-99.670	78.668	2.140	1.00 26.14		C
ATOM	350	CG	LEU A 219	-98.844	79.045	3.403	1.00 27.90		C

[0126]

[Table 11]

ATOM	351	CD1	LEU	A	219	-98.059	77.854	3.974	1.00 28.82	C
ATOM	352	CD2	LEU	A	219	-97.849	80.127	3.039	1.00 25.88	C
ATOM	353	N	TRP	A	220	-102.483	79.544	2.969	1.00 26.01	N
ATOM	354	CA	TRP	A	220	-103.385	80.225	3.882	1.00 27.72	C
ATOM	355	C	TRP	A	220	-104.581	79.350	4.254	1.00 30.97	C
ATOM	356	O	TRP	A	220	-104.984	79.286	5.430	1.00 28.16	O
ATOM	357	CB	TRP	A	220	-103.865	81.591	3.332	1.00 27.25	C
ATOM	358	CG	TRP	A	220	-103.464	82.718	4.139	1.00 25.20	C
ATOM	359	CD1	TRP	A	220	-104.249	83.772	4.520	1.00 27.15	C
ATOM	360	CD2	TRP	A	220	-102.148	82.964	4.694	1.00 24.07	C
ATOM	361	CE2	TRP	A	220	-102.213	84.206	5.382	1.00 24.73	C
ATOM	362	CE3	TRP	A	220	-100.926	82.284	4.642	1.00 22.88	C
ATOM	363	NE1	TRP	A	220	-103.502	84.669	5.267	1.00 25.61	N
ATOM	364	CZ2	TRP	A	220	-101.095	84.772	6.039	1.00 24.36	C
ATOM	365	CZ3	TRP	A	220	-99.826	82.822	5.354	1.00 24.87	C
ATOM	366	CH2	TRP	A	220	-99.914	84.081	5.987	1.00 24.01	C
ATOM	367	N	GLN	A	221	-105.085	78.631	3.270	1.00 31.28	N
ATOM	368	CA	GLN	A	221	-106.223	77.726	3.469	1.00 35.33	C
ATOM	369	C	GLN	A	221	-105.943	76.582	4.450	1.00 32.72	C
ATOM	370	O	GLN	A	221	-106.837	76.150	5.182	1.00 32.09	O
ATOM	371	CB	GLN	A	221	-106.592	77.221	2.103	1.00 40.68	C
ATOM	372	CG	GLN	A	221	-107.866	76.499	1.946	1.00 49.08	C
ATOM	373	CD	GLN	A	221	-108.041	76.052	0.484	1.00 55.49	C
ATOM	374	NE2	GLN	A	221	-109.051	75.214	0.269	1.00 61.19	N
ATOM	375	OE1	GLN	A	221	-107.248	76.417	-0.431	1.00 47.72	O
ATOM	376	N	ALA	A	222	-104.705	76.096	4.478	1.00 31.67	N
ATOM	377	CA	ALA	A	222	-104.353	75.014	5.390	1.00 31.76	C
ATOM	378	C	ALA	A	222	-104.401	75.464	6.871	1.00 33.22	C
ATOM	379	O	ALA	A	222	-104.444	74.631	7.757	1.00 37.17	O
ATOM	380	CB	ALA	A	222	-102.984	74.459	5.058	1.00 32.29	C
ATOM	381	N	GLU	A	223	-104.385	76.765	7.164	1.00 30.55	N
ATOM	382	CA	GLU	A	223	-104.313	77.185	8.585	1.00 28.25	C
ATOM	383	C	GLU	A	223	-105.737	77.197	9.173	1.00 30.28	C
ATOM	384	O	GLU	A	223	-106.596	77.924	8.681	1.00 31.72	O
ATOM	385	CB	GLU	A	223	-103.704	78.582	8.679	1.00 32.89	C

[0127]

[Table 12]

ATOM	386	CG	GLU	A	223	-102.186	78.675	8.474	1.00	38.82	C
ATOM	387	CD	GLU	A	223	-101.356	77.917	9.542	1.00	39.25	C
ATOM	388	OE1	GLU	A	223	-101.881	77.591	10.664	1.00	42.27	O
ATOM	389	OE2	GLU	A	223	-100.161	77.644	9.244	1.00	41.46	O1-
ATOM	390	N	LYS	A	224	-105.975	76.438	10.227	1.00	30.44	N
ATOM	391	CA	LYS	A	224	-107.327	76.273	10.784	1.00	32.21	C
ATOM	392	C	LYS	A	224	-107.403	76.659	12.267	1.00	29.82	C
ATOM	393	O	LYS	A	224	-108.402	76.411	12.919	1.00	27.58	O
ATOM	394	CB	LYS	A	224	-107.753	74.831	10.579	1.00	43.59	C
ATOM	395	CG	LYS	A	224	-107.842	74.447	9.084	1.00	44.22	C
ATOM	396	CD	LYS	A	224	-108.768	73.274	8.865	1.00	54.69	C
ATOM	397	CE	LYS	A	224	-110.055	73.717	8.205	1.00	61.58	C
ATOM	398	NZ	LYS	A	224	-109.791	74.233	6.826	1.00	61.34	N1+
ATOM	399	N	GLY	A	225	-106.411	77.369	12.771	1.00	28.25	N
ATOM	400	CA	GLY	A	225	-106.477	77.807	14.165	1.00	30.48	C
ATOM	401	C	GLY	A	225	-107.680	78.702	14.401	1.00	28.06	C
ATOM	402	O	GLY	A	225	-108.175	79.389	13.500	1.00	25.43	O
ATOM	403	N	LEU	A	226	-108.183	78.678	15.633	1.00	30.00	N
ATOM	404	CA	LEU	A	226	-109.372	79.429	15.954	1.00	28.45	C
ATOM	405	C	LEU	A	226	-109.153	80.958	16.023	1.00	25.19	C
ATOM	406	O	LEU	A	226	-109.975	81.699	15.561	1.00	26.61	O
ATOM	407	CB	LEU	A	226	-110.037	78.883	17.220	1.00	31.57	C
ATOM	408	CG	LEU	A	226	-110.466	77.405	17.202	1.00	32.24	C
ATOM	409	CD1	LEU	A	226	-110.867	77.008	18.645	1.00	35.09	C
ATOM	410	CD2	LEU	A	226	-111.654	77.197	16.252	1.00	36.04	C
ATOM	411	N	VAL	A	227	-108.037	81.427	16.565	1.00	23.49	N
ATOM	412	CA	VAL	A	227	-107.781	82.837	16.586	1.00	25.44	C
ATOM	413	C	VAL	A	227	-107.507	83.303	15.105	1.00	25.27	C
ATOM	414	O	VAL	A	227	-107.988	84.344	14.646	1.00	26.27	O
ATOM	415	CB	VAL	A	227	-106.661	83.145	17.568	1.00	27.09	C
ATOM	416	CG1	VAL	A	227	-106.369	84.618	17.523	1.00	27.54	C
ATOM	417	CG2	VAL	A	227	-107.098	82.781	18.983	1.00	26.25	C
ATOM	418	N	TRP	A	228	-106.697	82.539	14.418	1.00	23.62	N
ATOM	419	CA	TRP	A	228	-106.385	82.794	13.014	1.00	26.38	C
ATOM	420	C	TRP	A	228	-107.653	83.023	12.212	1.00	23.20	C

[0128]

[Table 13]

ATOM	421	O	TRP	A	228	-107.776	84.060	11.527	1.00 26.18	O
ATOM	422	CB	TRP	A	228	-105.622	81.599	12.444	1.00 25.18	C
ATOM	423	CG	TRP	A	228	-105.316	81.692	10.961	1.00 23.48	C
ATOM	424	CD1	TRP	A	228	-106.172	81.470	9.929	1.00 25.70	C
ATOM	425	CD2	TRP	A	228	-104.060	81.988	10.387	1.00 23.62	C
ATOM	426	CE2	TRP	A	228	-104.224	81.941	8.974	1.00 25.23	C
ATOM	427	CE3	TRP	A	228	-102.813	82.301	10.912	1.00 23.99	C
ATOM	428	NE1	TRP	A	228	-105.534	81.654	8.730	1.00 24.36	N
ATOM	429	CZ2	TRP	A	228	-103.179	82.164	8.096	1.00 25.75	C
ATOM	430	CZ3	TRP	A	228	-101.766	82.511	10.041	1.00 27.72	C
ATOM	431	CH2	TRP	A	228	-101.966	82.477	8.645	1.00 29.61	C
ATOM	432	N	LYS	A	229	-108.610	82.111	12.348	1.00 28.40	N
ATOM	433	CA	LYS	A	229	-109.904	82.239	11.613	1.00 27.35	C
ATOM	434	C	LYS	A	229	-110.716	83.486	11.916	1.00 27.34	C
ATOM	435	O	LYS	A	229	-111.341	84.042	11.021	1.00 24.15	O
ATOM	436	CB	LYS	A	229	-110.739	80.955	11.719	1.00 34.49	C
ATOM	437	CG	LYS	A	229	-110.199	79.862	10.814	1.00 42.23	C
ATOM	438	CD	LYS	A	229	-110.501	80.213	9.335	1.00 50.98	C
ATOM	439	CE	LYS	A	229	-109.668	79.455	8.298	1.00 51.88	C
ATOM	440	NZ	LYS	A	229	-109.962	78.008	8.382	1.00 55.83	N1+
ATOM	441	N	GLN	A	230	-110.646	83.988	13.163	1.00 22.13	N
ATOM	442	CA	GLN	A	230	-111.308	85.169	13.499	1.00 23.23	C
ATOM	443	C	GLN	A	230	-110.559	86.376	12.914	1.00 26.53	C
ATOM	444	O	GLN	A	230	-111.172	87.342	12.530	1.00 28.96	O
ATOM	445	CB	GLN	A	230	-111.530	85.244	15.041	1.00 28.25	C
ATOM	446	CG	GLN	A	230	-112.576	86.265	15.474	1.00 31.72	C
ATOM	447	CD	GLN	A	230	-112.625	86.472	17.007	1.00 33.18	C
ATOM	448	NE2	GLN	A	230	-113.091	87.665	17.433	1.00 29.89	N
ATOM	449	OE1	GLN	A	230	-112.288	85.555	17.776	1.00 31.36	O
ATOM	450	N	LEU	A	231	-109.245	86.284	12.742	1.00 25.55	N
ATOM	451	CA	LEU	A	231	-108.451	87.359	12.171	1.00 23.69	C
ATOM	452	C	LEU	A	231	-108.307	87.445	10.627	1.00 28.39	C
ATOM	453	O	LEU	A	231	-108.149	88.537	10.062	1.00 27.36	O
ATOM	454	CB	LEU	A	231	-107.033	87.265	12.748	1.00 23.92	C
ATOM	455	CG	LEU	A	231	-107.009	87.610	14.255	1.00 23.15	C

[0129]

[Table 14]

ATOM	456	CD1	LEU	A	231	-105.611	87.391	14.789	1.00 24.33	C
ATOM	457	CD2	LEU	A	231	-107.454	89.041	14.526	1.00 26.45	C
ATOM	458	N	VAL	A	232	-108.246	86.293	10.001	1.00 27.90	N
ATOM	459	CA	VAL	A	232	-107.851	86.215	8.615	1.00 31.48	C
ATOM	460	C	VAL	A	232	-108.803	87.040	7.747	1.00 33.91	C
ATOM	461	O	VAL	A	232	-110.005	86.973	7.957	1.00 30.37	O
ATOM	462	CB	VAL	A	232	-107.714	84.773	8.150	1.00 27.87	C
ATOM	463	CG1	VAL	A	232	-109.030	84.025	8.160	1.00 29.47	C
ATOM	464	CG2	VAL	A	232	-107.050	84.696	6.783	1.00 30.88	C
ATOM	465	N	ASN	A	233	-108.221	87.833	6.838	1.00 35.16	N
ATOM	466	CA	ASN	A	233	-108.945	88.690	5.860	1.00 37.19	C
ATOM	467	C	ASN	A	233	-108.160	88.790	4.536	1.00 36.25	C
ATOM	468	O	ASN	A	233	-107.350	89.715	4.316	1.00 42.41	O
ATOM	469	CB	ASN	A	233	-109.134	90.071	6.479	1.00 45.16	C
ATOM	470	CG	ASN	A	233	-109.772	91.051	5.526	1.00 51.93	C
ATOM	471	ND2	ASN	A	233	-109.249	92.287	5.479	1.00 56.58	N
ATOM	472	OD1	ASN	A	233	-110.706	90.693	4.819	1.00 50.78	O
ATOM	473	N	GLY	A	234	-108.364	87.818	3.668	1.00 33.18	N
ATOM	474	CA	GLY	A	234	-107.680	87.803	2.378	1.00 36.80	C
ATOM	475	C	GLY	A	234	-106.224	87.294	2.444	1.00 39.73	C
ATOM	476	O	GLY	A	234	-105.660	87.016	3.510	1.00 35.01	O
ATOM	477	N	LEU	A	235	-105.620	87.199	1.274	1.00 34.38	N
ATOM	478	CA	LEU	A	235	-104.260	86.704	1.114	1.00 30.03	C
ATOM	479	C	LEU	A	235	-103.306	87.700	1.654	1.00 31.66	C
ATOM	480	O	LEU	A	235	-103.575	88.894	1.638	1.00 33.19	O
ATOM	481	CB	LEU	A	235	-103.970	86.477	-0.365	1.00 33.48	C
ATOM	482	CG	LEU	A	235	-104.871	85.423	-0.998	1.00 36.37	C
ATOM	483	CD1	LEU	A	235	-104.533	85.326	-2.508	1.00 40.42	C
ATOM	484	CD2	LEU	A	235	-104.764	84.087	-0.280	1.00 36.84	C
ATOM	485	N	PRO	A	236	-102.191	87.243	2.194	1.00 28.44	N
ATOM	486	CA	PRO	A	236	-101.250	88.187	2.765	1.00 29.55	C
ATOM	487	C	PRO	A	236	-100.332	88.751	1.654	1.00 33.40	C
ATOM	488	O	PRO	A	236	-100.176	88.109	0.614	1.00 27.71	O
ATOM	489	CB	PRO	A	236	-100.406	87.271	3.642	1.00 29.57	C
ATOM	490	CG	PRO	A	236	-100.374	85.996	2.917	1.00 26.53	C

[0130]

[Table 15]

ATOM	491	CD	PRO	A	236	-101.769	85.853	2.402	1.00	31.12	C
ATOM	492	N	PRO	A	237	-99.623	89.839	1.947	1.00	37.59	N
ATOM	493	CA	PRO	A	237	-98.528	90.215	1.033	1.00	39.69	C
ATOM	494	C	PRO	A	237	-97.493	89.095	0.834	1.00	44.89	C
ATOM	495	O	PRO	A	237	-97.217	88.309	1.770	1.00	37.55	O
ATOM	496	CB	PRO	A	237	-97.898	91.457	1.709	1.00	42.96	C
ATOM	497	CG	PRO	A	237	-98.639	91.688	2.995	1.00	42.18	C
ATOM	498	CD	PRO	A	237	-99.841	90.810	3.042	1.00	38.98	C
ATOM	499	N	TYR	A	238	-96.930	89.015	-0.372	1.00	40.75	N
ATOM	500	CA	TYR	A	238	-95.859	88.071	-0.668	1.00	40.80	C
ATOM	501	C	TYR	A	238	-94.695	88.111	0.344	1.00	33.52	C
ATOM	502	O	TYR	A	238	-94.179	87.083	0.659	1.00	32.36	O
ATOM	503	CB	TYR	A	238	-95.272	88.274	-2.094	1.00	46.05	C
ATOM	504	CG	TYR	A	238	-94.080	87.365	-2.470	1.00	51.13	C
ATOM	505	CD1	TYR	A	238	-94.268	86.008	-2.812	1.00	55.84	C
ATOM	506	CD2	TYR	A	238	-92.749	87.880	-2.494	1.00	59.32	C
ATOM	507	CE1	TYR	A	238	-93.177	85.192	-3.137	1.00	56.49	C
ATOM	508	CE2	TYR	A	238	-91.638	87.077	-2.829	1.00	61.40	C
ATOM	509	CZ	TYR	A	238	-91.844	85.736	-3.153	1.00	65.15	C
ATOM	510	OH	TYR	A	238	-90.727	84.948	-3.480	1.00	63.19	O
ATOM	511	N	LYS	A	239	-94.263	89.284	0.764	1.00	31.44	N
ATOM	512	CA	LYS	A	239	-93.214	89.435	1.780	1.00	32.68	C
ATOM	513	C	LYS	A	239	-93.479	88.548	3.006	1.00	30.12	C
ATOM	514	O	LYS	A	239	-92.579	87.958	3.561	1.00	29.08	O
ATOM	515	CB	LYS	A	239	-93.170	90.916	2.113	1.00	41.84	C
ATOM	516	CG	LYS	A	239	-92.178	91.459	3.105	1.00	48.30	C
ATOM	517	CD	LYS	A	239	-92.088	92.986	2.936	1.00	51.72	C
ATOM	518	CE	LYS	A	239	-91.803	93.740	4.221	1.00	55.22	C
ATOM	519	NZ	LYS	A	239	-92.859	93.440	5.244	1.00	55.94	N1+
ATOM	520	N	GLU	A	240	-94.737	88.390	3.368	1.00	26.04	N
ATOM	521	CA	GLU	A	240	-95.117	87.664	4.570	1.00	27.60	C
ATOM	522	C	GLU	A	240	-94.995	86.168	4.421	1.00	29.20	C
ATOM	523	O	GLU	A	240	-94.785	85.484	5.420	1.00	23.45	O
ATOM	524	CB	GLU	A	240	-96.527	88.036	5.030	1.00	25.48	C
ATOM	525	CG	GLU	A	240	-97.052	87.235	6.239	1.00	27.90	C

[0131]

[Table 16]

ATOM	526	CD	GLU	A	240	-98.372	87.776	6.836	1.00 29.26	C
ATOM	527	OE1	GLU	A	240	-98.778	88.875	6.510	1.00 31.53	O
ATOM	528	OE2	GLU	A	240	-99.053	87.054	7.558	1.00 32.36	O1-
ATOM	529	N	ILE	A	241	-95.168	85.635	3.203	1.00 25.20	N
ATOM	530	CA	ILE	A	241	-95.136	84.194	3.027	1.00 29.06	C
ATOM	531	C	ILE	A	241	-93.857	83.564	3.538	1.00 24.96	C
ATOM	532	O	ILE	A	241	-93.894	82.530	4.174	1.00 24.40	O
ATOM	533	CB	ILE	A	241	-95.339	83.840	1.521	1.00 36.65	C
ATOM	534	CG1	ILE	A	241	-96.739	84.273	1.041	1.00 42.81	C
ATOM	535	CG2	ILE	A	241	-95.166	82.377	1.263	1.00 39.69	C
ATOM	536	CD1	ILE	A	241	-97.869	83.936	2.003	1.00 46.32	C
ATOM	537	N	SER	A	242	-92.717	84.147	3.205	1.00 26.29	N
ATOM	538	CA	SER	A	242	-91.438	83.579	3.592	1.00 26.86	C
ATOM	539	C	SER	A	242	-91.229	83.569	5.094	1.00 25.88	C
ATOM	540	O	SER	A	242	-90.669	82.611	5.663	1.00 23.72	O
ATOM	541	CB	SER	A	242	-90.279	84.346	2.952	1.00 29.75	C
ATOM	542	OG	SER	A	242	-90.254	84.036	1.578	1.00 34.97	O
ATOM	543	N	VAL	A	243	-91.635	84.653	5.725	1.00 22.47	N
ATOM	544	CA	VAL	A	243	-91.489	84.745	7.171	1.00 24.78	C
ATOM	545	C	VAL	A	243	-92.425	83.761	7.834	1.00 24.92	C
ATOM	546	O	VAL	A	243	-92.061	83.141	8.857	1.00 24.19	O
ATOM	547	CB	VAL	A	243	-91.808	86.144	7.696	1.00 26.22	C
ATOM	548	CG1	VAL	A	243	-91.725	86.160	9.205	1.00 28.40	C
ATOM	549	CG2	VAL	A	243	-90.894	87.156	7.038	1.00 29.51	C
ATOM	550	N	HIS	A	244	-93.624	83.616	7.264	1.00 21.78	N
ATOM	551	CA	HIS	A	244	-94.631	82.676	7.764	1.00 21.33	C
ATOM	552	C	HIS	A	244	-94.086	81.259	7.755	1.00 21.60	C
ATOM	553	O	HIS	A	244	-94.242	80.500	8.726	1.00 21.80	O
ATOM	554	CB	HIS	A	244	-95.921	82.745	6.911	1.00 20.84	C
ATOM	555	CG	HIS	A	244	-96.969	81.778	7.330	1.00 21.23	C
ATOM	556	CD2	HIS	A	244	-97.973	81.896	8.242	1.00 22.30	C
ATOM	557	ND1	HIS	A	244	-97.051	80.489	6.838	1.00 26.16	N
ATOM	558	CE1	HIS	A	244	-98.068	79.863	7.420	1.00 25.54	C
ATOM	559	NE2	HIS	A	244	-98.623	80.681	8.289	1.00 24.70	N
ATOM	560	N	VAL	A	245	-93.458	80.861	6.653	1.00 21.27	N

[0132]

[Table 17]

ATOM	561	CA	VAL A 245	-92.901	79.506	6.559	1.00	20.74	C
ATOM	562	C	VAL A 245	-91.775	79.348	7.527	1.00	19.82	C
ATOM	563	O	VAL A 245	-91.657	78.299	8.178	1.00	21.82	O
ATOM	564	CB	VAL A 245	-92.439	79.172	5.125	1.00	23.52	C
ATOM	565	CG1	VAL A 245	-91.772	77.835	5.109	1.00	24.69	C
ATOM	566	CG2	VAL A 245	-93.621	79.122	4.191	1.00	25.48	C
ATOM	567	N	PHE A 246	-90.983	80.396	7.685	1.00	20.67	N
ATOM	568	CA	PHE A 246	-89.858	80.378	8.608	1.00	22.33	C
ATOM	569	C	PHE A 246	-90.310	80.194	10.049	1.00	23.48	C
ATOM	570	O	PHE A 246	-89.739	79.380	10.839	1.00	20.99	O
ATOM	571	CB	PHE A 246	-89.054	81.701	8.524	1.00	23.13	C
ATOM	572	CG	PHE A 246	-87.771	81.715	9.327	1.00	24.64	C
ATOM	573	CD1	PHE A 246	-86.838	80.682	9.214	1.00	25.20	C
ATOM	574	CD2	PHE A 246	-87.454	82.790	10.135	1.00	27.56	C
ATOM	575	CE1	PHE A 246	-85.631	80.750	9.914	1.00	29.06	C
ATOM	576	CE2	PHE A 246	-86.251	82.847	10.841	1.00	28.22	C
ATOM	577	CZ	PHE A 246	-85.356	81.823	10.764	1.00	26.60	C
ATOM	578	N	TYR A 247	-91.366	80.907	10.360	1.00	23.58	N
ATOM	579	CA	TYR A 247	-92.075	80.744	11.687	1.00	23.11	C
ATOM	580	C	TYR A 247	-92.576	79.331	11.937	1.00	23.49	C
ATOM	581	O	TYR A 247	-92.460	78.803	13.086	1.00	20.33	O
ATOM	582	CB	TYR A 247	-93.236	81.739	11.835	1.00	23.83	C
ATOM	583	CG	TYR A 247	-94.094	81.552	13.083	1.00	24.06	C
ATOM	584	CD1	TYR A 247	-93.611	81.908	14.330	1.00	25.10	C
ATOM	585	CD2	TYR A 247	-95.364	80.997	12.994	1.00	29.89	C
ATOM	586	CE1	TYR A 247	-94.383	81.692	15.473	1.00	24.45	C
ATOM	587	CE2	TYR A 247	-96.141	80.783	14.135	1.00	28.98	C
ATOM	588	CZ	TYR A 247	-95.622	81.159	15.354	1.00	27.55	C
ATOM	589	OH	TYR A 247	-96.383	81.002	16.474	1.00	30.95	O
ATOM	590	N	ARG A 248	-93.197	78.743	10.927	1.00	20.10	N
ATOM	591	CA	ARG A 248	-93.674	77.348	11.074	1.00	23.57	C
ATOM	592	C	ARG A 248	-92.524	76.328	11.238	1.00	23.70	C
ATOM	593	O	ARG A 248	-92.692	75.403	12.038	1.00	24.41	O
ATOM	594	CB	ARG A 248	-94.537	76.897	9.907	1.00	26.30	C
ATOM	595	CG	ARG A 248	-95.919	77.522	9.857	1.00	32.93	C

[0133]

[Table 18]

ATOM	596	CD	ARG A 248	-97.095	76.574	10.166	1.00	47.80	C
ATOM	597	NE	ARG A 248	-98.235	77.430	10.576	1.00	53.35	N
ATOM	598	CZ	ARG A 248	-98.489	77.878	11.821	1.00	58.22	C
ATOM	599	NH1	ARG A 248	-97.759	77.472	12.881	1.00	59.96	N1+
ATOM	600	NH2	ARG A 248	-99.518	78.731	12.021	1.00	52.67	N
ATOM	601	N	CYS A 249	-91.401	76.508	10.502	1.00	21.92	N
ATOM	602	CA	CYS A 249	-90.154	75.797	10.809	1.00	24.49	C
ATOM	603	C	CYS A 249	-89.676	75.856	12.274	1.00	23.26	C
ATOM	604	O	CYS A 249	-89.389	74.818	12.898	1.00	19.87	O
ATOM	605	CB	CYS A 249	-89.027	76.301	9.913	1.00	24.21	C
ATOM	606	SG	CYS A 249	-89.353	75.925	8.148	1.00	31.53	S
ATOM	607	N	GLN A 250	-89.604	77.056	12.799	1.00	21.07	N
ATOM	608	CA	GLN A 250	-89.245	77.255	14.213	1.00	24.78	C
ATOM	609	C	GLN A 250	-90.230	76.542	15.167	1.00	25.50	C
ATOM	610	O	GLN A 250	-89.794	75.912	16.104	1.00	24.08	O
ATOM	611	CB	GLN A 250	-89.205	78.726	14.544	1.00	24.55	C
ATOM	612	CG	GLN A 250	-88.047	79.484	13.934	1.00	26.53	C
ATOM	613	CD	GLN A 250	-87.925	80.855	14.528	1.00	28.68	C
ATOM	614	NE2	GLN A 250	-87.750	81.844	13.684	1.00	28.49	N
ATOM	615	OE1	GLN A 250	-87.953	81.016	15.767	1.00	28.35	O
ATOM	616	N	CYS A 251	-91.550	76.640	14.930	1.00	25.99	N
ATOM	617	CA	CYS A 251	-92.559	75.993	15.833	1.00	26.11	C
ATOM	618	C	CYS A 251	-92.270	74.482	15.874	1.00	25.63	C
ATOM	619	O	CYS A 251	-92.275	73.888	16.923	1.00	25.19	O
ATOM	620	CB	CYS A 251	-93.994	76.233	15.319	1.00	29.43	C
ATOM	621	SG	CYS A 251	-94.481	77.978	15.469	1.00	34.43	S
ATOM	622	N	THR A 252	-91.979	73.874	14.727	1.00	23.31	N
ATOM	623	CA	THR A 252	-91.750	72.473	14.672	1.00	24.92	C
ATOM	624	C	THR A 252	-90.428	72.029	15.308	1.00	25.51	C
ATOM	625	O	THR A 252	-90.401	71.018	16.019	1.00	25.21	O
ATOM	626	CB	THR A 252	-91.634	72.044	13.218	1.00	30.78	C
ATOM	627	CG2	THR A 252	-91.499	70.507	13.083	1.00	28.82	C
ATOM	628	OG1	THR A 252	-92.811	72.498	12.576	1.00	38.00	O
ATOM	629	N	THR A 253	-89.347	72.774	15.060	1.00	23.95	N
ATOM	630	CA	THR A 253	-88.046	72.441	15.656	1.00	24.48	C

[0134]

[Table 19]

ATOM	631	C	THR	A	253	-88.086	72.666	17.181	1.00	24.75	C
ATOM	632	O	THR	A	253	-87.534	71.853	17.940	1.00	24.55	O
ATOM	633	CB	THR	A	253	-86.820	73.151	14.980	1.00	28.62	C
ATOM	634	CG2	THR	A	253	-86.800	72.915	13.548	1.00	29.89	C
ATOM	635	OG1	THR	A	253	-86.870	74.547	15.222	1.00	29.20	O
ATOM	636	N	VAL	A	254	-88.755	73.723	17.645	1.00	22.78	N
ATOM	637	CA	VAL	A	254	-88.919	73.948	19.118	1.00	25.70	C
ATOM	638	C	VAL	A	254	-89.613	72.727	19.793	1.00	26.72	C
ATOM	639	O	VAL	A	254	-89.096	72.150	20.810	1.00	25.27	O
ATOM	640	CB	VAL	A	254	-89.708	75.250	19.376	1.00	27.37	C
ATOM	641	CG1	VAL	A	254	-90.315	75.319	20.805	1.00	29.63	C
ATOM	642	CG2	VAL	A	254	-88.820	76.431	19.047	1.00	25.01	C
ATOM	643	N	GLU	A	255	-90.723	72.281	19.204	1.00	29.93	N
ATOM	644	CA	GLU	A	255	-91.460	71.180	19.779	1.00	32.48	C
ATOM	645	C	GLU	A	255	-90.592	69.876	19.738	1.00	28.29	C
ATOM	646	O	GLU	A	255	-90.632	69.093	20.660	1.00	28.79	O
ATOM	647	CB	GLU	A	255	-92.817	70.959	19.078	1.00	38.57	C
ATOM	648	CG	GLU	A	255	-93.470	69.575	19.331	1.00	46.15	C
ATOM	649	CD	GLU	A	255	-93.851	69.184	20.795	1.00	54.90	C
ATOM	650	OE1	GLU	A	255	-93.224	69.606	21.829	1.00	52.64	O
ATOM	651	OE2	GLU	A	255	-94.822	68.375	20.922	1.00	62.08	O1-
ATOM	652	N	THR	A	256	-89.850	69.651	18.668	1.00	26.33	N
ATOM	653	CA	THR	A	256	-88.992	68.486	18.605	1.00	27.86	C
ATOM	654	C	THR	A	256	-87.810	68.521	19.540	1.00	25.69	C
ATOM	655	O	THR	A	256	-87.359	67.474	20.028	1.00	21.71	O
ATOM	656	CB	THR	A	256	-88.462	68.263	17.208	1.00	26.98	C
ATOM	657	CG2	THR	A	256	-87.836	66.890	17.081	1.00	26.68	C
ATOM	658	OG1	THR	A	256	-89.568	68.396	16.339	1.00	26.38	O
ATOM	659	N	VAL	A	257	-87.257	69.692	19.716	1.00	20.54	N
ATOM	660	CA	VAL	A	257	-86.212	69.861	20.718	1.00	22.72	C
ATOM	661	C	VAL	A	257	-86.696	69.451	22.107	1.00	24.68	C
ATOM	662	O	VAL	A	257	-85.966	68.767	22.866	1.00	22.82	O
ATOM	663	CB	VAL	A	257	-85.678	71.329	20.734	1.00	21.52	C
ATOM	664	CG1	VAL	A	257	-84.841	71.640	21.961	1.00	22.71	C
ATOM	665	CG2	VAL	A	257	-84.870	71.630	19.450	1.00	22.77	C

[0135]

[Table 20]

ATOM	666	N	ARG A 258	-87.922	69.867	22.455	1.00	23.96	N
ATOM	667	CA	ARG A 258	-88.506	69.491	23.762	1.00	27.75	C
ATOM	668	C	ARG A 258	-88.687	67.984	23.876	1.00	25.70	C
ATOM	669	O	ARG A 258	-88.484	67.379	24.939	1.00	19.96	O
ATOM	670	CB	ARG A 258	-89.827	70.215	24.006	1.00	29.54	C
ATOM	671	CG	ARG A 258	-89.598	71.694	24.303	1.00	36.50	C
ATOM	672	CD	ARG A 258	-90.907	72.457	24.122	1.00	42.37	C
ATOM	673	NE	ARG A 258	-90.762	73.853	24.447	1.00	45.82	N
ATOM	674	CZ	ARG A 258	-91.566	74.824	24.040	1.00	44.79	C
ATOM	675	NH1	ARG A 258	-92.605	74.570	23.234	1.00	49.04	N1+
ATOM	676	NH2	ARG A 258	-91.297	76.058	24.441	1.00	39.28	N
ATOM	677	N	GLU A 259	-89.059	67.369	22.758	1.00	22.49	N
ATOM	678	CA	GLU A 259	-89.266	65.934	22.723	1.00	23.47	C
ATOM	679	C	GLU A 259	-87.945	65.165	22.850	1.00	23.30	C
ATOM	680	O	GLU A 259	-87.900	64.162	23.516	1.00	21.31	O
ATOM	681	CB	GLU A 259	-89.944	65.554	21.413	1.00	23.94	C
ATOM	682	CG	GLU A 259	-91.415	65.918	21.391	1.00	28.57	C
ATOM	683	CD	GLU A 259	-92.009	65.642	19.990	1.00	31.69	C
ATOM	684	OE1	GLU A 259	-91.236	65.458	18.994	1.00	33.72	O
ATOM	685	OE2	GLU A 259	-93.247	65.550	19.930	1.00	39.03	O1-
ATOM	686	N	LEU A 260	-86.927	65.610	22.114	1.00	20.99	N
ATOM	687	CA	LEU A 260	-85.543	65.124	22.241	1.00	22.23	C
ATOM	688	C	LEU A 260	-84.964	65.185	23.644	1.00	19.81	C
ATOM	689	O	LEU A 260	-84.330	64.230	24.085	1.00	21.52	O
ATOM	690	CB	LEU A 260	-84.655	65.866	21.244	1.00	20.41	C
ATOM	691	CG	LEU A 260	-84.813	65.354	19.789	1.00	21.07	C
ATOM	692	CD1	LEU A 260	-84.187	66.403	18.867	1.00	21.47	C
ATOM	693	CD2	LEU A 260	-84.180	63.987	19.597	1.00	22.68	C
ATOM	694	N	THR A 261	-85.197	66.291	24.303	1.00	20.33	N
ATOM	695	CA	THR A 261	-84.839	66.484	25.703	1.00	23.03	C
ATOM	696	C	THR A 261	-85.505	65.411	26.581	1.00	27.17	C
ATOM	697	O	THR A 261	-84.793	64.774	27.404	1.00	28.62	O
ATOM	698	CB	THR A 261	-85.184	67.888	26.172	1.00	22.70	C
ATOM	699	CG2	THR A 261	-84.713	68.139	27.590	1.00	27.27	C
ATOM	700	OG1	THR A 261	-84.555	68.867	25.346	1.00	23.21	O

[0136]

[Table 21]

ATOM	701	N	GLU A 262	-86.813	65.129	26.366	1.00	26.54	N
ATOM	702	CA	GLU A 262	-87.505	64.117	27.142	1.00	28.98	C
ATOM	703	C	GLU A 262	-86.952	62.764	26.755	1.00	25.16	C
ATOM	704	O	GLU A 262	-86.681	61.935	27.616	1.00	25.51	O
ATOM	705	CB	GLU A 262	-89.065	64.096	26.996	1.00	29.46	C
ATOM	706	CG	GLU A 262	-89.804	65.206	27.688	1.00	37.91	C
ATOM	707	CD	GLU A 262	-89.393	65.458	29.156	1.00	38.92	C
ATOM	708	OE1	GLU A 262	-89.343	64.509	29.907	1.00	46.37	O
ATOM	709	OE2	GLU A 262	-89.117	66.616	29.537	1.00	41.43	O1-
ATOM	710	N	PHE A 263	-86.753	62.537	25.471	1.00	22.12	N
ATOM	711	CA	PHE A 263	-86.199	61.274	25.021	1.00	22.19	C
ATOM	712	C	PHE A 263	-84.832	60.945	25.683	1.00	21.53	C
ATOM	713	O	PHE A 263	-84.511	59.736	26.031	1.00	21.92	O
ATOM	714	CB	PHE A 263	-86.126	61.290	23.465	1.00	20.77	C
ATOM	715	CG	PHE A 263	-85.332	60.189	22.847	1.00	22.53	C
ATOM	716	CD1	PHE A 263	-85.879	58.886	22.695	1.00	23.74	C
ATOM	717	CD2	PHE A 263	-84.037	60.443	22.322	1.00	21.36	C
ATOM	718	CE1	PHE A 263	-85.157	57.855	22.082	1.00	23.16	C
ATOM	719	CE2	PHE A 263	-83.323	59.420	21.713	1.00	22.52	C
ATOM	720	CZ	PHE A 263	-83.872	58.113	21.590	1.00	23.87	C
ATOM	721	N	ALA A 264	-84.013	61.973	25.761	1.00	20.57	N
ATOM	722	CA	ALA A 264	-82.630	61.832	26.257	1.00	20.84	C
ATOM	723	C	ALA A 264	-82.643	61.333	27.684	1.00	22.31	C
ATOM	724	O	ALA A 264	-81.772	60.590	28.063	1.00	23.76	O
ATOM	725	CB	ALA A 264	-81.857	63.111	26.183	1.00	19.54	C
ATOM	726	N	LYS A 265	-83.656	61.698	28.448	1.00	25.83	N
ATOM	727	CA	LYS A 265	-83.764	61.250	29.843	1.00	26.84	C
ATOM	728	C	LYS A 265	-83.900	59.725	29.954	1.00	27.47	C
ATOM	729	O	LYS A 265	-83.539	59.154	30.995	1.00	23.98	O
ATOM	730	CB	LYS A 265	-84.939	61.903	30.514	1.00	29.97	C
ATOM	731	CG	LYS A 265	-84.858	63.418	30.681	1.00	31.35	C
ATOM	732	CD	LYS A 265	-86.149	63.869	31.323	1.00	33.74	C
ATOM	733	CE	LYS A 265	-86.202	65.355	31.504	1.00	35.36	C
ATOM	734	NZ	LYS A 265	-87.484	65.759	32.106	1.00	37.19	N1+
ATOM	735	N	SER A 266	-84.391	59.074	28.906	1.00	23.06	N

[0137]

[Table 22]

ATOM	736	CA	SER A 266	-84.514	57.605	28.866	1.00	23.53	C
ATOM	737	C	SER A 266	-83.317	56.846	28.324	1.00	22.93	C
ATOM	738	O	SER A 266	-83.305	55.613	28.389	1.00	23.34	O
ATOM	739	CB	SER A 266	-85.783	57.165	28.097	1.00	23.51	C
ATOM	740	OG	SER A 266	-86.917	57.659	28.781	1.00	27.04	O
ATOM	741	N	ILE A 267	-82.292	57.558	27.839	1.00	21.32	N
ATOM	742	CA	ILE A 267	-81.043	56.965	27.365	1.00	20.33	C
ATOM	743	C	ILE A 267	-80.297	56.593	28.641	1.00	24.01	C
ATOM	744	O	ILE A 267	-80.084	57.462	29.493	1.00	26.38	O
ATOM	745	CB	ILE A 267	-80.212	57.907	26.560	1.00	21.56	C
ATOM	746	CG1	ILE A 267	-80.948	58.246	25.253	1.00	24.08	C
ATOM	747	CG2	ILE A 267	-78.852	57.273	26.220	1.00	24.45	C
ATOM	748	CD1	ILE A 267	-80.390	59.479	24.606	1.00	23.72	C
ATOM	749	N	PRO A 268	-80.036	55.298	28.835	1.00	27.46	N
ATOM	750	CA	PRO A 268	-79.385	54.876	30.078	1.00	27.50	C
ATOM	751	C	PRO A 268	-78.088	55.633	30.323	1.00	26.85	C
ATOM	752	O	PRO A 268	-77.247	55.797	29.403	1.00	24.54	O
ATOM	753	CB	PRO A 268	-79.095	53.375	29.833	1.00	31.30	C
ATOM	754	CG	PRO A 268	-80.077	52.961	28.765	1.00	31.63	C
ATOM	755	CD	PRO A 268	-80.177	54.180	27.875	1.00	27.41	C
ATOM	756	N	SER A 269	-77.965	56.117	31.552	1.00	25.73	N
ATOM	757	CA	SER A 269	-76.825	56.875	32.071	1.00	26.29	C
ATOM	758	C	SER A 269	-76.777	58.364	31.676	1.00	26.88	C
ATOM	759	O	SER A 269	-75.985	59.116	32.270	1.00	22.24	O
ATOM	760	CB	SER A 269	-75.481	56.213	31.806	1.00	27.32	C
ATOM	761	OG	SER A 269	-75.460	54.962	32.435	1.00	38.88	O
ATOM	762	N	PHE A 270	-77.598	58.807	30.708	1.00	25.22	N
ATOM	763	CA	PHE A 270	-77.627	60.232	30.358	1.00	23.82	C
ATOM	764	C	PHE A 270	-77.924	61.093	31.588	1.00	23.99	C
ATOM	765	O	PHE A 270	-77.283	62.106	31.804	1.00	25.71	O
ATOM	766	CB	PHE A 270	-78.728	60.481	29.313	1.00	22.96	C
ATOM	767	CG	PHE A 270	-78.826	61.896	28.883	1.00	23.60	C
ATOM	768	CD1	PHE A 270	-77.966	62.384	27.883	1.00	22.76	C
ATOM	769	CD2	PHE A 270	-79.740	62.747	29.436	1.00	22.64	C
ATOM	770	CE1	PHE A 270	-78.058	63.692	27.451	1.00	20.70	C

[0138]

[Table 23]

ATOM	771	CE2	PHE	A	270	-79.819	64.070	29.014	1.00 22.58	C
ATOM	772	CZ	PHE	A	270	-78.955	64.542	28.023	1.00 20.60	C
ATOM	773	N	SER	A	271	-78.915	60.709	32.370	1.00 24.16	N
ATOM	774	CA	SER	A	271	-79.327	61.473	33.554	1.00 25.56	C
ATOM	775	C	SER	A	271	-78.318	61.460	34.729	1.00 25.23	C
ATOM	776	O	SER	A	271	-78.500	62.205	35.657	1.00 29.47	O
ATOM	777	CB	SER	A	271	-80.715	61.092	34.035	1.00 28.81	C
ATOM	778	OG	SER	A	271	-81.690	61.513	33.082	1.00 30.33	O
ATOM	779	N	SER	A	272	-77.281	60.663	34.638	1.00 26.56	N
ATOM	780	CA	SER	A	272	-76.201	60.569	35.617	1.00 30.69	C
ATOM	781	C	SER	A	272	-75.068	61.522	35.254	1.00 29.88	C
ATOM	782	O	SER	A	272	-74.169	61.744	36.060	1.00 24.66	O
ATOM	783	CB	SER	A	272	-75.664	59.122	35.651	1.00 28.77	C
ATOM	784	OG	SER	A	272	-74.755	58.874	34.546	1.00 36.04	O
ATOM	785	N	LEU	A	273	-75.079	62.028	34.020	1.00 25.71	N
ATOM	786	CA	LEU	A	273	-74.093	63.022	33.600	1.00 23.88	C
ATOM	787	C	LEU	A	273	-74.290	64.287	34.410	1.00 22.51	C
ATOM	788	O	LEU	A	273	-75.405	64.625	34.845	1.00 21.40	O
ATOM	789	CB	LEU	A	273	-74.228	63.396	32.106	1.00 23.37	C
ATOM	790	CG	LEU	A	273	-73.929	62.206	31.217	1.00 22.94	C
ATOM	791	CD1	LEU	A	273	-74.238	62.437	29.793	1.00 22.67	C
ATOM	792	CD2	LEU	A	273	-72.517	61.683	31.326	1.00 24.37	C
ATOM	793	N	PHE	A	274	-73.230	65.066	34.492	1.00 22.37	N
ATOM	794	CA	PHE	A	274	-73.401	66.466	34.990	1.00 25.17	C
ATOM	795	C	PHE	A	274	-74.501	67.196	34.207	1.00 27.10	C
ATOM	796	O	PHE	A	274	-74.594	67.075	32.968	1.00 21.50	O
ATOM	797	CB	PHE	A	274	-72.116	67.275	34.821	1.00 25.49	C
ATOM	798	CG	PHE	A	274	-70.909	66.724	35.528	1.00 25.96	C
ATOM	799	CD1	PHE	A	274	-71.003	66.250	36.845	1.00 27.77	C
ATOM	800	CD2	PHE	A	274	-69.647	66.782	34.914	1.00 26.44	C
ATOM	801	CE1	PHE	A	274	-69.867	65.841	37.534	1.00 29.91	C
ATOM	802	CE2	PHE	A	274	-68.517	66.364	35.586	1.00 27.25	C
ATOM	803	CZ	PHE	A	274	-68.628	65.903	36.899	1.00 27.19	C
ATOM	804	N	LEU	A	275	-75.243	68.047	34.882	1.00 22.79	N
ATOM	805	CA	LEU	A	275	-76.327	68.756	34.217	1.00 29.42	C

[0139]

[Table 24]

ATOM	806	C	LEU A 275	-75.856	69.660	33.071	1.00	25.86	C
ATOM	807	O	LEU A 275	-76.477	69.695	31.995	1.00	23.37	O
ATOM	808	CB	LEU A 275	-77.172	69.489	35.259	1.00	29.04	C
ATOM	809	CG	LEU A 275	-78.586	69.904	34.953	1.00	35.87	C
ATOM	810	CD1	LEU A 275	-79.414	68.750	34.373	1.00	36.71	C
ATOM	811	CD2	LEU A 275	-79.206	70.471	36.233	1.00	38.69	C
ATOM	812	N	ASN A 276	-74.689	70.294	33.268	1.00	26.58	N
ATOM	813	CA	ASN A 276	-74.067	71.089	32.242	1.00	25.96	C
ATOM	814	C	ASN A 276	-73.762	70.286	31.001	1.00	25.09	C
ATOM	815	O	ASN A 276	-73.963	70.787	29.858	1.00	21.28	O
ATOM	816	CB	ASN A 276	-72.766	71.760	32.718	1.00	33.65	C
ATOM	817	CG	ASN A 276	-73.011	72.964	33.626	1.00	41.49	C
ATOM	818	ND2	ASN A 276	-73.911	73.875	33.229	1.00	45.31	N
ATOM	819	OD1	ASN A 276	-72.363	73.081	34.682	1.00	56.87	O
ATOM	820	N	ASP A 277	-73.259	69.054	31.202	1.00	24.56	N
ATOM	821	CA	ASP A 277	-73.019	68.141	30.106	1.00	22.03	C
ATOM	822	C	ASP A 277	-74.276	67.709	29.404	1.00	22.69	C
ATOM	823	O	ASP A 277	-74.296	67.688	28.161	1.00	22.50	O
ATOM	824	CB	ASP A 277	-72.188	66.961	30.534	1.00	23.66	C
ATOM	825	CG	ASP A 277	-70.706	67.348	30.737	1.00	26.98	C
ATOM	826	OD1	ASP A 277	-70.264	68.503	30.342	1.00	25.55	O
ATOM	827	OD2	ASP A 277	-70.002	66.507	31.325	1.00	28.60	O1-
ATOM	828	N	GLN A 278	-75.324	67.384	30.166	1.00	21.69	N
ATOM	829	CA	GLN A 278	-76.596	67.085	29.544	1.00	22.92	C
ATOM	830	C	GLN A 278	-77.060	68.214	28.641	1.00	20.19	C
ATOM	831	O	GLN A 278	-77.434	67.979	27.465	1.00	18.26	O
ATOM	832	CB	GLN A 278	-77.673	66.714	30.560	1.00	25.99	C
ATOM	833	CG	GLN A 278	-77.374	65.494	31.445	1.00	26.28	C
ATOM	834	CD	GLN A 278	-78.435	65.308	32.519	1.00	29.01	C
ATOM	835	NE2	GLN A 278	-77.985	65.071	33.764	1.00	28.55	N
ATOM	836	OE1	GLN A 278	-79.634	65.443	32.254	1.00	23.66	O
ATOM	837	N	VAL A 279	-76.987	69.428	29.165	1.00	19.32	N
ATOM	838	CA	VAL A 279	-77.348	70.619	28.389	1.00	21.18	C
ATOM	839	C	VAL A 279	-76.511	70.805	27.117	1.00	21.38	C
ATOM	840	O	VAL A 279	-77.046	71.051	26.020	1.00	18.26	O

[0140]

[Table 25]

ATOM	841	CB	VAL A 279	-77.356	71.878	29.268	1.00	22.27	C
ATOM	842	CG1	VAL A 279	-77.634	73.150	28.422	1.00	23.34	C
ATOM	843	CG2	VAL A 279	-78.428	71.737	30.305	1.00	23.49	C
ATOM	844	N	THR A 280	-75.205	70.633	27.252	1.00	20.48	N
ATOM	845	CA	THR A 280	-74.315	70.757	26.122	1.00	20.50	C
ATOM	846	C	THR A 280	-74.589	69.754	25.006	1.00	20.85	C
ATOM	847	O	THR A 280	-74.563	70.104	23.817	1.00	18.46	O
ATOM	848	CB	THR A 280	-72.876	70.622	26.620	1.00	22.81	C
ATOM	849	CG2	THR A 280	-71.895	70.624	25.503	1.00	22.64	C
ATOM	850	OG1	THR A 280	-72.570	71.725	27.464	1.00	24.03	O
ATOM	851	N	LEU A 281	-74.792	68.471	25.406	1.00	21.37	N
ATOM	852	CA	LEU A 281	-75.085	67.455	24.473	1.00	21.63	C
ATOM	853	C	LEU A 281	-76.391	67.796	23.680	1.00	20.72	C
ATOM	854	O	LEU A 281	-76.447	67.645	22.430	1.00	20.46	O
ATOM	855	CB	LEU A 281	-75.147	66.097	25.178	1.00	21.96	C
ATOM	856	CG	LEU A 281	-73.837	65.487	25.736	1.00	20.61	C
ATOM	857	CD1	LEU A 281	-74.183	64.215	26.498	1.00	23.72	C
ATOM	858	CD2	LEU A 281	-72.877	65.208	24.559	1.00	21.50	C
ATOM	859	N	LEU A 282	-77.426	68.223	24.370	1.00	18.08	N
ATOM	860	CA	LEU A 282	-78.655	68.515	23.698	1.00	19.48	C
ATOM	861	C	LEU A 282	-78.453	69.787	22.777	1.00	22.33	C
ATOM	862	O	LEU A 282	-78.831	69.790	21.563	1.00	22.17	O
ATOM	863	CB	LEU A 282	-79.800	68.691	24.694	1.00	20.45	C
ATOM	864	CG	LEU A 282	-80.209	67.338	25.257	1.00	20.38	C
ATOM	865	CD1	LEU A 282	-80.939	67.520	26.547	1.00	20.70	C
ATOM	866	CD2	LEU A 282	-81.114	66.618	24.275	1.00	20.57	C
ATOM	867	N	LYS A 283	-77.843	70.824	23.333	1.00	22.22	N
ATOM	868	CA	LYS A 283	-77.566	72.061	22.544	1.00	23.13	C
ATOM	869	C	LYS A 283	-76.886	71.757	21.148	1.00	23.10	C
ATOM	870	O	LYS A 283	-77.382	72.293	20.120	1.00	20.83	O
ATOM	871	CB	LYS A 283	-76.740	73.034	23.368	1.00	26.13	C
ATOM	872	CG	LYS A 283	-76.298	74.328	22.662	1.00	34.37	C
ATOM	873	CD	LYS A 283	-75.236	75.038	23.529	1.00	37.83	C
ATOM	874	CE	LYS A 283	-74.649	76.271	22.868	1.00	36.06	C
ATOM	875	NZ	LYS A 283	-75.623	77.395	22.874	1.00	37.04	N1+

[0141]

[Table 26]

ATOM	876	N	TYR A 284	-75.844	70.879	21.103	1.00	21.05	N
ATOM	877	CA	TYR A 284	-75.096	70.637	19.874	1.00	25.09	C
ATOM	878	C	TYR A 284	-75.639	69.437	19.089	1.00	25.96	C
ATOM	879	O	TYR A 284	-75.240	69.230	17.975	1.00	27.41	O
ATOM	880	CB	TYR A 284	-73.592	70.442	20.141	1.00	28.51	C
ATOM	881	CG	TYR A 284	-72.908	71.712	20.518	1.00	26.70	C
ATOM	882	CD1	TYR A 284	-72.463	72.598	19.529	1.00	29.90	C
ATOM	883	CD2	TYR A 284	-72.642	72.012	21.845	1.00	28.97	C
ATOM	884	CE1	TYR A 284	-71.833	73.808	19.892	1.00	31.05	C
ATOM	885	CE2	TYR A 284	-72.053	73.216	22.224	1.00	30.46	C
ATOM	886	CZ	TYR A 284	-71.641	74.121	21.249	1.00	31.92	C
ATOM	887	OH	TYR A 284	-71.035	75.327	21.678	1.00	34.89	O
ATOM	888	N	GLY A 285	-76.510	68.654	19.711	1.00	21.57	N
ATOM	889	CA	GLY A 285	-77.076	67.439	19.141	1.00	23.64	C
ATOM	890	C	GLY A 285	-78.475	67.503	18.543	1.00	22.01	C
ATOM	891	O	GLY A 285	-78.808	66.715	17.624	1.00	19.61	O
ATOM	892	N	VAL A 286	-79.297	68.418	19.041	1.00	20.76	N
ATOM	893	CA	VAL A 286	-80.749	68.322	18.712	1.00	20.62	C
ATOM	894	C	VAL A 286	-80.991	68.575	17.196	1.00	21.05	C
ATOM	895	O	VAL A 286	-81.785	67.872	16.624	1.00	21.59	O
ATOM	896	CB	VAL A 286	-81.697	69.157	19.613	1.00	18.67	C
ATOM	897	CG1	VAL A 286	-81.732	68.623	21.006	1.00	19.98	C
ATOM	898	CG2	VAL A 286	-81.293	70.657	19.617	1.00	17.89	C
ATOM	899	N	HIS A 287	-80.291	69.500	16.577	1.00	22.17	N
ATOM	900	CA	HIS A 287	-80.506	69.758	15.130	1.00	22.28	C
ATOM	901	C	HIS A 287	-80.044	68.646	14.217	1.00	22.53	C
ATOM	902	O	HIS A 287	-80.619	68.397	13.169	1.00	21.99	O
ATOM	903	CB	HIS A 287	-79.898	71.111	14.729	1.00	21.60	C
ATOM	904	CG	HIS A 287	-80.740	72.268	15.161	1.00	24.88	C
ATOM	905	CD2	HIS A 287	-81.795	72.866	14.543	1.00	27.99	C
ATOM	906	ND1	HIS A 287	-80.665	72.818	16.439	1.00	24.88	N
ATOM	907	CE1	HIS A 287	-81.623	73.741	16.555	1.00	29.36	C
ATOM	908	NE2	HIS A 287	-82.317	73.796	15.418	1.00	28.46	N
ATOM	909	N	GLU A 288	-78.940	68.015	14.607	1.00	24.77	N
ATOM	910	CA	GLU A 288	-78.441	66.873	13.908	1.00	22.59	C

[0142]

[Table 27]

ATOM	911	C	GLU A 288	-79.506	65.813	13.935	1.00	22.49	C
ATOM	912	O	GLU A 288	-79.880	65.249	12.900	1.00	21.29	O
ATOM	913	CB	GLU A 288	-77.122	66.343	14.515	1.00	21.63	C
ATOM	914	CG	GLU A 288	-75.918	67.172	14.195	1.00	24.38	C
ATOM	915	CD	GLU A 288	-74.594	66.727	14.884	1.00	27.68	C
ATOM	916	OE1	GLU A 288	-74.492	65.594	15.409	1.00	28.03	O
ATOM	917	OE2	GLU A 288	-73.580	67.480	14.835	1.00	28.04	O1-
ATOM	918	N	ALA A 289	-80.014	65.549	15.113	1.00	18.55	N
ATOM	919	CA	ALA A 289	-81.140	64.581	15.253	1.00	19.95	C
ATOM	920	C	ALA A 289	-82.401	65.009	14.515	1.00	22.31	C
ATOM	921	O	ALA A 289	-83.072	64.168	13.901	1.00	21.85	O
ATOM	922	CB	ALA A 289	-81.503	64.365	16.699	1.00	22.63	C
ATOM	923	N	ILE A 290	-82.716	66.297	14.549	1.00	20.91	N
ATOM	924	CA	ILE A 290	-83.903	66.799	13.850	1.00	20.12	C
ATOM	925	C	ILE A 290	-83.793	66.595	12.341	1.00	22.56	C
ATOM	926	O	ILE A 290	-84.753	66.166	11.713	1.00	21.26	O
ATOM	927	CB	ILE A 290	-84.144	68.303	14.158	1.00	23.07	C
ATOM	928	CG1	ILE A 290	-84.720	68.450	15.567	1.00	22.75	C
ATOM	929	CG2	ILE A 290	-85.131	68.982	13.167	1.00	23.95	C
ATOM	930	CD1	ILE A 290	-84.627	69.858	16.117	1.00	24.42	C
ATOM	931	N	PHE A 291	-82.633	66.866	11.747	1.00	20.57	N
ATOM	932	CA	PHE A 291	-82.505	66.682	10.294	1.00	24.21	C
ATOM	933	C	PHE A 291	-82.431	65.224	9.817	1.00	25.75	C
ATOM	934	O	PHE A 291	-82.874	64.929	8.718	1.00	26.46	O
ATOM	935	CB	PHE A 291	-81.349	67.512	9.763	1.00	25.80	C
ATOM	936	CG	PHE A 291	-81.517	69.000	10.004	1.00	25.84	C
ATOM	937	CD1	PHE A 291	-82.728	69.607	9.857	1.00	26.62	C
ATOM	938	CD2	PHE A 291	-80.426	69.769	10.341	1.00	27.31	C
ATOM	939	CE1	PHE A 291	-82.851	70.956	10.090	1.00	28.64	C
ATOM	940	CE2	PHE A 291	-80.540	71.108	10.543	1.00	27.00	C
ATOM	941	CZ	PHE A 291	-81.754	71.712	10.424	1.00	26.04	C
ATOM	942	N	ALA A 292	-81.923	64.330	10.670	1.00	23.64	N
ATOM	943	CA	ALA A 292	-82.073	62.888	10.509	1.00	24.86	C
ATOM	944	C	ALA A 292	-83.565	62.466	10.571	1.00	26.48	C
ATOM	945	O	ALA A 292	-83.983	61.686	9.739	1.00	28.30	O

[0143]

[Table 28]

ATOM	946	CB	ALA	A	292	-81.279	62.094	11.585	1.00	24.78	C
ATOM	947	N	MET	A	293	-84.325	62.908	11.589	1.00	24.92	N
ATOM	948	CA	MET	A	293	-85.750	62.557	11.677	1.00	27.27	C
ATOM	949	C	MET	A	293	-86.592	63.172	10.570	1.00	26.44	C
ATOM	950	O	MET	A	293	-87.622	62.627	10.245	1.00	23.73	O
ATOM	951	CB	MET	A	293	-86.368	62.933	13.026	1.00	26.34	C
ATOM	952	CG	MET	A	293	-85.779	62.100	14.155	1.00	31.69	C
ATOM	953	SD	MET	A	293	-86.557	62.458	15.764	1.00	35.94	S
ATOM	954	CE	MET	A	293	-85.874	64.039	16.016	1.00	29.17	C
ATOM	955	N	LEU	A	294	-86.115	64.260	9.968	1.00	25.39	N
ATOM	956	CA	LEU	A	294	-86.838	64.967	8.906	1.00	27.32	C
ATOM	957	C	LEU	A	294	-87.003	64.080	7.686	1.00	27.45	C
ATOM	958	O	LEU	A	294	-88.034	64.124	7.003	1.00	25.25	O
ATOM	959	CB	LEU	A	294	-86.092	66.216	8.473	1.00	28.19	C
ATOM	960	CG	LEU	A	294	-86.629	66.971	7.267	1.00	31.75	C
ATOM	961	CD1	LEU	A	294	-88.020	67.474	7.553	1.00	35.67	C
ATOM	962	CD2	LEU	A	294	-85.712	68.169	6.990	1.00	33.60	C
ATOM	963	N	ALA	A	295	-85.988	63.278	7.416	1.00	25.31	N
ATOM	964	CA	ALA	A	295	-86.087	62.292	6.327	1.00	28.44	C
ATOM	965	C	ALA	A	295	-87.312	61.393	6.393	1.00	25.92	C
ATOM	966	O	ALA	A	295	-87.972	61.081	5.359	1.00	24.71	O
ATOM	967	CB	ALA	A	295	-84.809	61.508	6.189	1.00	29.31	C
ATOM	968	N	SER	A	296	-87.714	61.049	7.604	1.00	25.75	N
ATOM	969	CA	SER	A	296	-88.881	60.182	7.766	1.00	24.04	C
ATOM	970	C	SER	A	296	-90.151	60.770	7.067	1.00	24.95	C
ATOM	971	O	SER	A	296	-91.048	60.024	6.801	1.00	26.54	O
ATOM	972	CB	SER	A	296	-89.223	60.027	9.261	1.00	24.71	C
ATOM	973	OG	SER	A	296	-88.188	59.322	9.952	1.00	24.58	O
ATOM	974	N	ILE	A	297	-90.284	62.108	7.019	1.00	25.84	N
ATOM	975	CA	ILE	A	297	-91.469	62.765	6.505	1.00	26.52	C
ATOM	976	C	ILE	A	297	-91.314	63.374	5.113	1.00	26.15	C
ATOM	977	O	ILE	A	297	-92.266	64.037	4.655	1.00	26.39	O
ATOM	978	CB	ILE	A	297	-92.065	63.816	7.482	1.00	24.20	C
ATOM	979	CG1	ILE	A	297	-91.076	64.901	7.838	1.00	27.94	C
ATOM	980	CG2	ILE	A	297	-92.558	63.111	8.714	1.00	25.71	C

[0144]

[Table 29]

ATOM	981	CD1	ILE	A	297	-91.709	66.192	8.340	1.00 29.46	C
ATOM	982	N	VAL	A	298	-90.172	63.124	4.451	1.00 24.11	N
ATOM	983	CA	VAL	A	298	-89.777	63.778	3.216	1.00 27.33	C
ATOM	984	C	VAL	A	298	-89.801	62.746	2.100	1.00 29.01	C
ATOM	985	O	VAL	A	298	-89.520	61.595	2.346	1.00 28.72	O
ATOM	986	CB	VAL	A	298	-88.376	64.445	3.346	1.00 29.27	C
ATOM	987	CG1	VAL	A	298	-87.790	64.899	2.023	1.00 33.75	C
ATOM	988	CG2	VAL	A	298	-88.460	65.673	4.229	1.00 28.97	C
ATOM	989	N	ASN	A	299	-90.243	63.139	0.906	1.00 28.92	N
ATOM	990	CA	ASN	A	299	-89.891	62.397	-0.304	1.00 30.58	C
ATOM	991	C	ASN	A	299	-89.312	63.426	-1.298	1.00 32.51	C
ATOM	992	O	ASN	A	299	-89.147	64.637	-0.931	1.00 28.01	O
ATOM	993	CB	ASN	A	299	-91.055	61.502	-0.793	1.00 31.13	C
ATOM	994	CG	ASN	A	299	-92.219	62.274	-1.323	1.00 28.40	C
ATOM	995	ND2	ASN	A	299	-93.344	61.639	-1.365	1.00 29.96	N
ATOM	996	OD1	ASN	A	299	-92.104	63.451	-1.703	1.00 34.32	O
ATOM	997	N	LYS	A	300	-88.958	63.016	-2.534	1.00 30.47	N
ATOM	998	CA	LYS	A	300	-88.235	63.969	-3.401	1.00 29.89	C
ATOM	999	C	LYS	A	300	-89.132	65.188	-3.780	1.00 27.63	C
ATOM	1000	O	LYS	A	300	-88.667	66.223	-4.250	1.00 29.06	O
ATOM	1001	CB	LYS	A	300	-87.687	63.285	-4.659	1.00 35.59	C
ATOM	1002	CG	LYS	A	300	-88.750	62.747	-5.570	1.00 38.65	C
ATOM	1003	CD	LYS	A	300	-88.136	61.929	-6.702	1.00 47.73	C
ATOM	1004	CE	LYS	A	300	-89.131	60.885	-7.220	1.00 49.64	C
ATOM	1005	NZ	LYS	A	300	-90.300	61.555	-7.835	1.00 52.34	N1+
ATOM	1006	N	ASP	A	301	-90.426	65.020	-3.614	1.00 26.61	N
ATOM	1007	CA	ASP	A	301	-91.418	66.023	-4.043	1.00 29.63	C
ATOM	1008	C	ASP	A	301	-91.893	66.959	-2.921	1.00 26.96	C
ATOM	1009	O	ASP	A	301	-92.591	67.908	-3.200	1.00 26.32	O
ATOM	1010	CB	ASP	A	301	-92.607	65.278	-4.599	1.00 33.60	C
ATOM	1011	CG	ASP	A	301	-92.250	64.519	-5.914	1.00 40.31	C
ATOM	1012	OD1	ASP	A	301	-91.302	64.917	-6.630	1.00 43.22	O
ATOM	1013	OD2	ASP	A	301	-92.898	63.500	-6.195	1.00 44.23	O1-
ATOM	1014	N	GLY	A	302	-91.551	66.693	-1.650	1.00 27.44	N
ATOM	1015	CA	GLY	A	302	-92.019	67.536	-0.541	1.00 25.67	C

[0145]

[Table 30]

ATOM	1016	C	GLY	A	302	-92.089	66.826	0.805	1.00	26.48	C
ATOM	1017	O	GLY	A	302	-91.515	65.719	0.977	1.00	24.94	O
ATOM	1018	N	LEU	A	303	-92.810	67.417	1.739	1.00	25.81	N
ATOM	1019	CA	LEU	A	303	-92.871	66.824	3.099	1.00	28.72	C
ATOM	1020	C	LEU	A	303	-94.223	66.934	3.779	1.00	25.52	C
ATOM	1021	O	LEU	A	303	-94.978	67.846	3.489	1.00	26.54	O
ATOM	1022	CB	LEU	A	303	-91.809	67.489	4.000	1.00	33.05	C
ATOM	1023	CG	LEU	A	303	-92.083	68.931	4.503	1.00	37.71	C
ATOM	1024	CD1	LEU	A	303	-91.452	69.106	5.871	1.00	46.52	C
ATOM	1025	CD2	LEU	A	303	-91.519	69.933	3.526	1.00	48.79	C
ATOM	1026	N	LEU	A	304	-94.522	65.987	4.659	1.00	25.67	N
ATOM	1027	CA	LEU	A	304	-95.691	65.985	5.501	1.00	26.69	C
ATOM	1028	C	LEU	A	304	-95.648	67.075	6.544	1.00	27.32	C
ATOM	1029	O	LEU	A	304	-94.589	67.349	7.110	1.00	28.79	O
ATOM	1030	CB	LEU	A	304	-95.835	64.672	6.232	1.00	27.60	C
ATOM	1031	CG	LEU	A	304	-96.280	63.556	5.390	1.00	30.36	C
ATOM	1032	CD1	LEU	A	304	-96.254	62.264	6.221	1.00	32.11	C
ATOM	1033	CD2	LEU	A	304	-97.653	63.833	4.726	1.00	31.15	C
ATOM	1034	N	VAL	A	305	-96.789	67.715	6.735	1.00	27.58	N
ATOM	1035	CA	VAL	A	305	-96.998	68.713	7.785	1.00	29.03	C
ATOM	1036	C	VAL	A	305	-98.285	68.401	8.501	1.00	30.86	C
ATOM	1037	O	VAL	A	305	-99.098	67.531	8.047	1.00	29.76	O
ATOM	1038	CB	VAL	A	305	-97.000	70.180	7.242	1.00	33.39	C
ATOM	1039	CG1	VAL	A	305	-95.640	70.512	6.669	1.00	32.65	C
ATOM	1040	CG2	VAL	A	305	-98.081	70.395	6.179	1.00	34.76	C
ATOM	1041	N	ALA	A	306	-98.447	69.080	9.645	1.00	34.51	N
ATOM	1042	CA	ALA	A	306	-99.693	69.059	10.454	1.00	39.54	C
ATOM	1043	C	ALA	A	306	-100.179	67.667	10.754	1.00	37.23	C
ATOM	1044	O	ALA	A	306	-101.317	67.311	10.429	1.00	37.16	O
ATOM	1045	CB	ALA	A	306	-100.814	69.886	9.795	1.00	41.57	C
ATOM	1046	N	ASN	A	307	-99.257	66.893	11.335	1.00	38.88	N
ATOM	1047	CA	ASN	A	307	-99.435	65.496	11.687	1.00	36.18	C
ATOM	1048	C	ASN	A	307	-99.849	64.610	10.518	1.00	38.54	C
ATOM	1049	O	ASN	A	307	-100.667	63.732	10.677	1.00	43.99	O
ATOM	1050	CB	ASN	A	307	-100.383	65.376	12.900	1.00	44.83	C

[0146]

[Table 31]

ATOM	1051	CG	ASN A 307	-100.159	64.078	13.703	1.00	46.49	C
ATOM	1052	ND2	ASN A 307	-101.237	63.360	13.959	1.00	48.74	N
ATOM	1053	OD1	ASN A 307	-99.023	63.722	14.068	1.00	55.10	O
ATOM	1054	N	GLY A 308	-99.262	64.829	9.336	1.00	35.63	N
ATOM	1055	CA	GLY A 308	-99.594	64.057	8.150	1.00	36.15	C
ATOM	1056	C	GLY A 308	-100.887	64.454	7.450	1.00	35.26	C
ATOM	1057	O	GLY A 308	-101.201	63.863	6.439	1.00	38.21	O
ATOM	1058	N	SER A 309	-101.585	65.493	7.931	1.00	40.95	N
ATOM	1059	CA	SER A 309	-102.782	66.010	7.249	1.00	40.17	C
ATOM	1060	C	SER A 309	-102.482	66.930	6.082	1.00	39.05	C
ATOM	1061	O	SER A 309	-103.366	67.111	5.266	1.00	35.55	O
ATOM	1062	CB	SER A 309	-103.725	66.731	8.224	1.00	41.20	C
ATOM	1063	OG	SER A 309	-103.202	67.970	8.672	1.00	40.95	O
ATOM	1064	N	GLY A 310	-101.256	67.488	5.987	1.00	35.81	N
ATOM	1065	CA	GLY A 310	-100.831	68.262	4.794	1.00	34.10	C
ATOM	1066	C	GLY A 310	-99.499	67.840	4.189	1.00	34.17	C
ATOM	1067	O	GLY A 310	-98.680	67.191	4.847	1.00	29.87	O
ATOM	1068	N	PHE A 311	-99.308	68.195	2.926	1.00	27.08	N
ATOM	1069	CA	PHE A 311	-98.099	67.932	2.202	1.00	26.72	C
ATOM	1070	C	PHE A 311	-97.691	69.220	1.554	1.00	27.50	C
ATOM	1071	O	PHE A 311	-98.437	69.744	0.699	1.00	27.00	O
ATOM	1072	CB	PHE A 311	-98.338	66.847	1.152	1.00	25.30	C
ATOM	1073	CG	PHE A 311	-97.123	66.411	0.434	1.00	25.91	C
ATOM	1074	CD1	PHE A 311	-96.312	65.407	0.938	1.00	25.46	C
ATOM	1075	CD2	PHE A 311	-96.774	66.998	-0.776	1.00	28.41	C
ATOM	1076	CE1	PHE A 311	-95.201	64.985	0.270	1.00	25.30	C
ATOM	1077	CE2	PHE A 311	-95.636	66.584	-1.448	1.00	29.01	C
ATOM	1078	CZ	PHE A 311	-94.880	65.555	-0.956	1.00	26.16	C
ATOM	1079	N	VAL A 312	-96.503	69.719	1.889	1.00	25.15	N
ATOM	1080	CA	VAL A 312	-95.995	70.918	1.233	1.00	28.02	C
ATOM	1081	C	VAL A 312	-95.008	70.530	0.156	1.00	26.25	C
ATOM	1082	O	VAL A 312	-94.114	69.693	0.415	1.00	23.84	O
ATOM	1083	CB	VAL A 312	-95.369	71.910	2.194	1.00	28.36	C
ATOM	1084	CG1	VAL A 312	-94.076	71.395	2.725	1.00	36.63	C
ATOM	1085	CG2	VAL A 312	-95.097	73.226	1.466	1.00	28.30	C

[0147]

[Table 32]

ATOM	1086	N	THR	A	313	-95.158	71.105	-1.060	1.00 25.88	N
ATOM	1087	CA	THR	A	313	-94.270	70.720	-2.188	1.00 23.69	C
ATOM	1088	C	THR	A	313	-92.909	71.349	-2.054	1.00 24.56	C
ATOM	1089	O	THR	A	313	-92.736	72.543	-1.657	1.00 22.77	O
ATOM	1090	CB	THR	A	313	-94.863	71.029	-3.616	1.00 24.89	C
ATOM	1091	CG2	THR	A	313	-96.202	70.500	-3.730	1.00 28.58	C
ATOM	1092	OG1	THR	A	313	-94.983	72.422	-3.797	1.00 25.05	O
ATOM	1093	N	ARG	A	314	-91.913	70.551	-2.414	1.00 26.93	N
ATOM	1094	CA	ARG	A	314	-90.532	71.028	-2.567	1.00 26.40	C
ATOM	1095	C	ARG	A	314	-90.474	72.222	-3.518	1.00 27.49	C
ATOM	1096	O	ARG	A	314	-89.771	73.198	-3.257	1.00 24.83	O
ATOM	1097	CB	ARG	A	314	-89.646	69.922	-3.125	1.00 30.47	C
ATOM	1098	CG	ARG	A	314	-88.165	70.234	-3.051	1.00 31.22	C
ATOM	1099	CD	ARG	A	314	-87.436	68.980	-3.396	1.00 32.57	C
ATOM	1100	NE	ARG	A	314	-86.003	69.098	-3.282	1.00 31.11	N
ATOM	1101	CZ	ARG	A	314	-85.178	68.093	-3.478	1.00 30.25	C
ATOM	1102	NH1	ARG	A	314	-85.660	66.901	-3.813	1.00 29.81	N1+
ATOM	1103	NH2	ARG	A	314	-83.874	68.270	-3.351	1.00 32.89	N
ATOM	1104	N	GLU	A	315	-91.250	72.177	-4.611	1.00 26.96	N
ATOM	1105	CA	GLU	A	315	-91.214	73.294	-5.527	1.00 27.20	C
ATOM	1106	C	GLU	A	315	-91.684	74.602	-4.864	1.00 24.24	C
ATOM	1107	O	GLU	A	315	-91.045	75.647	-5.012	1.00 28.17	O
ATOM	1108	CB	GLU	A	315	-92.019	72.995	-6.825	1.00 32.10	C
ATOM	1109	CG	GLU	A	315	-91.911	74.121	-7.834	1.00 34.65	C
ATOM	1110	CD	GLU	A	315	-92.958	74.111	-8.954	1.00 44.98	C
ATOM	1111	OE1	GLU	A	315	-93.171	75.216	-9.516	1.00 48.23	O
ATOM	1112	OE2	GLU	A	315	-93.544	73.060	-9.286	1.00 41.82	O1-
ATOM	1113	N	PHE	A	316	-92.804	74.560	-4.172	1.00 26.94	N
ATOM	1114	CA	PHE	A	316	-93.266	75.690	-3.366	1.00 25.64	C
ATOM	1115	C	PHE	A	316	-92.219	76.239	-2.352	1.00 26.19	C
ATOM	1116	O	PHE	A	316	-92.005	77.437	-2.251	1.00 27.22	O
ATOM	1117	CB	PHE	A	316	-94.593	75.376	-2.676	1.00 25.72	C
ATOM	1118	CG	PHE	A	316	-95.077	76.494	-1.828	1.00 28.23	C
ATOM	1119	CD1	PHE	A	316	-95.518	77.713	-2.414	1.00 30.04	C
ATOM	1120	CD2	PHE	A	316	-94.947	76.422	-0.438	1.00 28.46	C

[0148]

[Table 33]

ATOM	1121	CE1	PHE	A	316	-95.902	78.776	-1.589	1.00 29.08	C
ATOM	1122	CE2	PHE	A	316	-95.325	77.487	0.369	1.00 29.30	C
ATOM	1123	CZ	PHE	A	316	-95.841	78.626	-0.187	1.00 27.55	C
ATOM	1124	N	LEU	A	317	-91.552	75.372	-1.637	1.00 27.97	N
ATOM	1125	CA	LEU	A	317	-90.489	75.800	-0.745	1.00 29.76	C
ATOM	1126	C	LEU	A	317	-89.286	76.473	-1.468	1.00 32.56	C
ATOM	1127	O	LEU	A	317	-88.729	77.484	-0.955	1.00 33.64	O
ATOM	1128	CB	LEU	A	317	-90.064	74.591	0.099	1.00 29.57	C
ATOM	1129	CG	LEU	A	317	-91.143	74.037	1.025	1.00 26.60	C
ATOM	1130	CD1	LEU	A	317	-90.628	72.854	1.787	1.00 30.32	C
ATOM	1131	CD2	LEU	A	317	-91.571	75.132	1.973	1.00 27.32	C
ATOM	1132	N	ARG	A	318	-88.944	75.996	-2.675	1.00 28.99	N
ATOM	1133	CA	ARG	A	318	-87.932	76.668	-3.554	1.00 30.66	C
ATOM	1134	C	ARG	A	318	-88.374	77.986	-4.118	1.00 29.76	C
ATOM	1135	O	ARG	A	318	-87.553	78.688	-4.669	1.00 30.33	O
ATOM	1136	CB	ARG	A	318	-87.548	75.803	-4.787	1.00 31.20	C
ATOM	1137	CG	ARG	A	318	-86.840	74.518	-4.448	1.00 32.86	C
ATOM	1138	CD	ARG	A	318	-86.870	73.537	-5.594	1.00 38.04	C
ATOM	1139	NE	ARG	A	318	-85.870	72.509	-5.351	1.00 40.73	N
ATOM	1140	CZ	ARG	A	318	-85.633	71.482	-6.161	1.00 43.75	C
ATOM	1141	NH1	ARG	A	318	-86.274	71.382	-7.316	1.00 50.04	N1+
ATOM	1142	NH2	ARG	A	318	-84.718	70.586	-5.839	1.00 39.06	N
ATOM	1143	N	SER	A	319	-89.666	78.298	-4.063	1.00 30.15	N
ATOM	1144	CA	SER	A	319	-90.189	79.598	-4.540	1.00 29.62	C
ATOM	1145	C	SER	A	319	-90.018	80.688	-3.467	1.00 31.07	C
ATOM	1146	O	SER	A	319	-90.237	81.861	-3.717	1.00 31.84	O
ATOM	1147	CB	SER	A	319	-91.680	79.499	-4.893	1.00 30.60	C
ATOM	1148	OG	SER	A	319	-92.537	79.518	-3.712	1.00 33.57	O
ATOM	1149	N	LEU	A	320	-89.613	80.328	-2.269	1.00 30.91	N
ATOM	1150	CA	LEU	A	320	-89.473	81.357	-1.199	1.00 30.30	C
ATOM	1151	C	LEU	A	320	-88.311	82.315	-1.462	1.00 30.25	C
ATOM	1152	O	LEU	A	320	-87.407	82.007	-2.194	1.00 30.75	O
ATOM	1153	CB	LEU	A	320	-89.318	80.670	0.157	1.00 32.70	C
ATOM	1154	CG	LEU	A	320	-90.498	79.747	0.489	1.00 33.74	C
ATOM	1155	CD1	LEU	A	320	-90.253	79.051	1.816	1.00 37.75	C

[0149]

[Table 34]

ATOM	1156	CD2	LEU	A	320	-91.841	80.461	0.517	1.00 35.95	C
ATOM	1157	N	ARG	A	321	-88.279	83.476	-0.850	1.00 34.72	N
ATOM	1158	CA	ARG	A	321	-87.131	84.319	-1.126	1.00 39.89	C
ATOM	1159	C	ARG	A	321	-85.852	83.746	-0.512	1.00 38.94	C
ATOM	1160	O	ARG	A	321	-85.886	82.870	0.382	1.00 38.76	O
ATOM	1161	CB	ARG	A	321	-87.406	85.786	-0.857	1.00 44.97	C
ATOM	1162	CG	ARG	A	321	-87.454	86.221	0.560	1.00 51.89	C
ATOM	1163	CD	ARG	A	321	-87.847	87.703	0.600	1.00 52.73	C
ATOM	1164	NE	ARG	A	321	-88.101	88.029	1.988	1.00 61.32	N
ATOM	1165	CZ	ARG	A	321	-87.164	88.291	2.905	1.00 58.38	C
ATOM	1166	NH1	ARG	A	321	-85.875	88.337	2.587	1.00 55.74	N1+
ATOM	1167	NH2	ARG	A	321	-87.544	88.523	4.159	1.00 63.74	N
ATOM	1168	N	LYS	A	322	-84.735	84.234	-1.037	1.00 37.36	N
ATOM	1169	CA	LYS	A	322	-83.456	83.546	-1.095	1.00 43.64	C
ATOM	1170	C	LYS	A	322	-82.946	83.029	0.220	1.00 44.96	C
ATOM	1171	O	LYS	A	322	-82.555	81.840	0.293	1.00 49.36	O
ATOM	1172	CB	LYS	A	322	-82.370	84.407	-1.742	1.00 47.65	C
ATOM	1173	CG	LYS	A	322	-81.089	83.647	-2.117	1.00 54.93	C
ATOM	1174	CD	LYS	A	322	-80.150	84.451	-3.041	1.00 57.30	C
ATOM	1175	CE	LYS	A	322	-78.682	84.138	-2.786	1.00 62.36	C
ATOM	1176	NZ	LYS	A	322	-78.390	82.672	-2.909	1.00 63.93	N1+
ATOM	1177	N	PRO	A	323	-82.946	83.874	1.268	1.00 39.25	N
ATOM	1178	CA	PRO	A	323	-82.337	83.257	2.431	1.00 35.75	C
ATOM	1179	C	PRO	A	323	-83.086	81.977	2.862	1.00 33.66	C
ATOM	1180	O	PRO	A	323	-82.445	80.981	3.250	1.00 36.45	O
ATOM	1181	CB	PRO	A	323	-82.349	84.357	3.487	1.00 41.07	C
ATOM	1182	CG	PRO	A	323	-82.934	85.566	2.809	1.00 41.49	C
ATOM	1183	CD	PRO	A	323	-83.571	85.171	1.530	1.00 39.84	C
ATOM	1184	N	PHE	A	324	-84.414	81.983	2.741	1.00 30.84	N
ATOM	1185	CA	PHE	A	324	-85.269	80.904	3.255	1.00 32.81	C
ATOM	1186	C	PHE	A	324	-85.244	79.687	2.309	1.00 34.96	C
ATOM	1187	O	PHE	A	324	-84.997	78.564	2.749	1.00 31.26	O
ATOM	1188	CB	PHE	A	324	-86.662	81.433	3.524	1.00 29.38	C
ATOM	1189	CG	PHE	A	324	-86.655	82.614	4.459	1.00 28.03	C
ATOM	1190	CD1	PHE	A	324	-86.329	82.456	5.789	1.00 31.40	C

[0150]

[Table 35]

ATOM	1191	CD2	PHE	A	324	-86.891	83.894	3.985	1.00 27.91	C
ATOM	1192	CE1	PHE	A	324	-86.281	83.580	6.632	1.00 29.78	C
ATOM	1193	CE2	PHE	A	324	-86.842	84.989	4.789	1.00 31.67	C
ATOM	1194	CZ	PHE	A	324	-86.533	84.851	6.129	1.00 30.12	C
ATOM	1195	N	SER	A	325	-85.375	79.909	1.006	1.00 34.91	N
ATOM	1196	CA	SER	A	325	-85.151	78.776	0.054	1.00 35.71	C
ATOM	1197	C	SER	A	325	-83.806	78.107	0.270	1.00 34.34	C
ATOM	1198	O	SER	A	325	-83.716	76.867	0.251	1.00 35.46	O
ATOM	1199	CB	SER	A	325	-85.293	79.241	-1.398	1.00 38.23	C
ATOM	1200	OG	SER	A	325	-84.467	80.397	-1.605	1.00 38.78	O
ATOM	1201	N	ASP	A	326	-82.760	78.895	0.526	1.00 33.95	N
ATOM	1202	CA	ASP	A	326	-81.391	78.332	0.648	1.00 35.77	C
ATOM	1203	C	ASP	A	326	-81.186	77.525	1.920	1.00 35.75	C
ATOM	1204	O	ASP	A	326	-80.344	76.645	1.993	1.00 34.49	O
ATOM	1205	CB	ASP	A	326	-80.310	79.424	0.589	1.00 36.49	C
ATOM	1206	CG	ASP	A	326	-80.116	80.010	-0.839	1.00 45.20	C
ATOM	1207	OD1	ASP	A	326	-80.609	79.447	-1.847	1.00 44.51	O
ATOM	1208	OD2	ASP	A	326	-79.457	81.070	-0.922	1.00 51.56	O1-
ATOM	1209	N	ILE	A	327	-81.917	77.853	2.963	1.00 35.65	N
ATOM	1210	CA	ILE	A	327	-81.743	77.140	4.207	1.00 32.20	C
ATOM	1211	C	ILE	A	327	-82.533	75.797	4.186	1.00 32.61	C
ATOM	1212	O	ILE	A	327	-82.168	74.827	4.850	1.00 30.41	O
ATOM	1213	CB	ILE	A	327	-82.098	78.098	5.364	1.00 36.21	C
ATOM	1214	CG1	ILE	A	327	-81.299	77.726	6.594	1.00 38.79	C
ATOM	1215	CG2	ILE	A	327	-83.599	78.139	5.625	1.00 36.14	C
ATOM	1216	CD1	ILE	A	327	-81.490	78.705	7.707	1.00 44.53	C
ATOM	1217	N	ILE	A	328	-83.563	75.727	3.353	1.00 27.73	N
ATOM	1218	CA	ILE	A	328	-84.440	74.559	3.260	1.00 28.93	C
ATOM	1219	C	ILE	A	328	-83.884	73.450	2.333	1.00 32.14	C
ATOM	1220	O	ILE	A	328	-83.926	72.263	2.708	1.00 26.34	O
ATOM	1221	CB	ILE	A	328	-85.867	74.998	2.817	1.00 31.22	C
ATOM	1222	CG1	ILE	A	328	-86.567	75.730	4.005	1.00 33.04	C
ATOM	1223	CG2	ILE	A	328	-86.707	73.801	2.353	1.00 31.79	C
ATOM	1224	CD1	ILE	A	328	-87.856	76.463	3.628	1.00 31.93	C
ATOM	1225	N	GLU	A	329	-83.427	73.839	1.150	1.00 27.80	N

[0151]

[Table 36]

ATOM	1226	CA	GLU A 329	-83.094	72.864	0.076	1.00	34.00	C
ATOM	1227	C	GLU A 329	-82.006	71.824	0.486	1.00	31.52	C
ATOM	1228	O	GLU A 329	-82.184	70.666	0.254	1.00	27.83	O
ATOM	1229	CB	GLU A 329	-82.723	73.634	-1.209	1.00	37.62	C
ATOM	1230	CG	GLU A 329	-82.535	72.864	-2.526	1.00	42.96	C
ATOM	1231	CD	GLU A 329	-83.600	71.816	-2.877	1.00	45.48	C
ATOM	1232	OE1	GLU A 329	-84.786	71.843	-2.476	1.00	46.26	O
ATOM	1233	OE2	GLU A 329	-83.227	70.877	-3.584	1.00	48.60	O1-
ATOM	1234	N	PRO A 330	-80.935	72.235	1.179	1.00	30.91	N
ATOM	1235	CA	PRO A 330	-79.948	71.258	1.598	1.00	32.27	C
ATOM	1236	C	PRO A 330	-80.460	70.148	2.536	1.00	31.83	C
ATOM	1237	O	PRO A 330	-79.871	69.015	2.537	1.00	30.14	O
ATOM	1238	CB	PRO A 330	-78.685	72.094	2.281	1.00	34.82	C
ATOM	1239	CG	PRO A 330	-79.112	73.467	1.818	1.00	32.89	C
ATOM	1240	CD	PRO A 330	-80.489	73.610	1.406	1.00	32.19	C
ATOM	1241	N	LYS A 331	-81.563	70.417	3.245	1.00	30.14	N
ATOM	1242	CA	LYS A 331	-82.186	69.397	4.125	1.00	29.88	C
ATOM	1243	C	LYS A 331	-82.899	68.348	3.297	1.00	33.54	C
ATOM	1244	O	LYS A 331	-82.809	67.148	3.658	1.00	26.34	O
ATOM	1245	CB	LYS A 331	-83.107	70.018	5.128	1.00	30.19	C
ATOM	1246	CG	LYS A 331	-82.384	70.639	6.299	1.00	30.43	C
ATOM	1247	CD	LYS A 331	-81.524	71.811	5.891	1.00	34.10	C
ATOM	1248	CE	LYS A 331	-80.955	72.559	7.090	1.00	29.44	C
ATOM	1249	NZ	LYS A 331	-80.286	73.798	6.676	1.00	27.39	N1+
ATOM	1250	N	PHE A 332	-83.556	68.773	2.195	1.00	27.68	N
ATOM	1251	CA	PHE A 332	-84.119	67.815	1.261	1.00	29.60	C
ATOM	1252	C	PHE A 332	-83.042	66.992	0.631	1.00	29.15	C
ATOM	1253	O	PHE A 332	-83.220	65.789	0.494	1.00	31.95	O
ATOM	1254	CB	PHE A 332	-84.907	68.472	0.116	1.00	34.27	C
ATOM	1255	CG	PHE A 332	-86.319	68.791	0.452	1.00	33.67	C
ATOM	1256	CD1	PHE A 332	-87.327	67.835	0.274	1.00	36.80	C
ATOM	1257	CD2	PHE A 332	-86.658	70.046	0.919	1.00	36.26	C
ATOM	1258	CE1	PHE A 332	-88.642	68.118	0.619	1.00	33.33	C
ATOM	1259	CE2	PHE A 332	-87.983	70.346	1.209	1.00	35.96	C
ATOM	1260	CZ	PHE A 332	-88.960	69.380	1.073	1.00	35.56	C

[0152]

[Table 37]

ATOM	1261	N	GLU	A	333	-81.955	67.614	0.178	1.00 30.84	N
ATOM	1262	CA	GLU	A	333	-80.906	66.836	-0.496	1.00 33.91	C
ATOM	1263	C	GLU	A	333	-80.378	65.765	0.474	1.00 32.01	C
ATOM	1264	O	GLU	A	333	-80.221	64.638	0.098	1.00 30.20	O
ATOM	1265	CB	GLU	A	333	-79.751	67.708	-1.015	1.00 39.71	C
ATOM	1266	CG	GLU	A	333	-79.906	68.234	-2.451	1.00 47.09	C
ATOM	1267	CD	GLU	A	333	-79.504	69.720	-2.661	1.00 57.66	C
ATOM	1268	OE1	GLU	A	333	-80.004	70.330	-3.648	1.00 59.77	O
ATOM	1269	OE2	GLU	A	333	-78.715	70.307	-1.857	1.00 65.31	O1-
ATOM	1270	N	PHE	A	334	-80.123	66.128	1.728	1.00 27.07	N
ATOM	1271	CA	PHE	A	334	-79.680	65.172	2.718	1.00 23.94	C
ATOM	1272	C	PHE	A	334	-80.680	64.069	2.916	1.00 26.86	C
ATOM	1273	O	PHE	A	334	-80.331	62.864	2.899	1.00 25.41	O
ATOM	1274	CB	PHE	A	334	-79.435	65.863	4.099	1.00 24.87	C
ATOM	1275	CG	PHE	A	334	-79.056	64.872	5.167	1.00 26.47	C
ATOM	1276	CD1	PHE	A	334	-77.747	64.423	5.281	1.00 28.80	C
ATOM	1277	CD2	PHE	A	334	-80.034	64.250	5.934	1.00 29.25	C
ATOM	1278	CE1	PHE	A	334	-77.397	63.455	6.230	1.00 30.11	C
ATOM	1279	CE2	PHE	A	334	-79.702	63.210	6.850	1.00 28.11	C
ATOM	1280	CZ	PHE	A	334	-78.373	62.868	7.023	1.00 29.58	C
ATOM	1281	N	ALA	A	335	-81.939	64.478	3.156	1.00 25.83	N
ATOM	1282	CA	ALA	A	335	-82.978	63.563	3.460	1.00 27.40	C
ATOM	1283	C	ALA	A	335	-83.240	62.532	2.354	1.00 28.95	C
ATOM	1284	O	ALA	A	335	-83.369	61.315	2.622	1.00 28.87	O
ATOM	1285	CB	ALA	A	335	-84.237	64.330	3.791	1.00 32.76	C
ATOM	1286	N	VAL	A	336	-83.282	62.963	1.102	1.00 30.25	N
ATOM	1287	CA	VAL	A	336	-83.492	61.968	0.020	1.00 30.76	C
ATOM	1288	C	VAL	A	336	-82.391	60.918	-0.046	1.00 32.47	C
ATOM	1289	O	VAL	A	336	-82.671	59.749	-0.287	1.00 36.43	O
ATOM	1290	CB	VAL	A	336	-83.720	62.651	-1.365	1.00 33.20	C
ATOM	1291	CG1	VAL	A	336	-83.961	61.614	-2.436	1.00 35.94	C
ATOM	1292	CG2	VAL	A	336	-84.994	63.444	-1.309	1.00 34.36	C
ATOM	1293	N	LYS	A	337	-81.149	61.298	0.207	1.00 32.94	N
ATOM	1294	CA	LYS	A	337	-80.064	60.296	0.262	1.00 34.09	C
ATOM	1295	C	LYS	A	337	-80.073	59.414	1.482	1.00 33.35	C

[0153]

[Table 38]

ATOM	1296	O	LYS	A	337	-79.733	58.220	1.404	1.00	31.09	O
ATOM	1297	CB	LYS	A	337	-78.703	60.942	0.073	1.00	39.33	C
ATOM	1298	CG	LYS	A	337	-78.524	61.469	-1.368	1.00	41.68	C
ATOM	1299	CD	LYS	A	337	-77.126	61.996	-1.628	1.00	47.73	C
ATOM	1300	CE	LYS	A	337	-76.908	63.377	-1.025	1.00	57.47	C
ATOM	1301	NZ	LYS	A	337	-75.490	63.826	-1.218	1.00	63.57	N1+
ATOM	1302	N	PHE	A	338	-80.490	59.977	2.606	1.00	28.72	N
ATOM	1303	CA	PHE	A	338	-80.582	59.205	3.850	1.00	29.56	C
ATOM	1304	C	PHE	A	338	-81.675	58.142	3.725	1.00	26.33	C
ATOM	1305	O	PHE	A	338	-81.496	56.982	4.196	1.00	24.28	O
ATOM	1306	CB	PHE	A	338	-80.893	60.157	4.987	1.00	27.25	C
ATOM	1307	CG	PHE	A	338	-80.789	59.572	6.335	1.00	23.40	C
ATOM	1308	CD1	PHE	A	338	-79.559	59.451	6.957	1.00	24.14	C
ATOM	1309	CD2	PHE	A	338	-81.949	59.208	7.024	1.00	23.49	C
ATOM	1310	CE1	PHE	A	338	-79.432	58.998	8.295	1.00	25.03	C
ATOM	1311	CE2	PHE	A	338	-81.843	58.722	8.335	1.00	26.26	C
ATOM	1312	CZ	PHE	A	338	-80.565	58.572	8.962	1.00	23.60	C
ATOM	1313	N	ASN	A	339	-82.796	58.534	3.089	1.00	25.99	N
ATOM	1314	CA	ASN	A	339	-83.865	57.625	2.868	1.00	27.86	C
ATOM	1315	C	ASN	A	339	-83.469	56.390	2.032	1.00	28.78	C
ATOM	1316	O	ASN	A	339	-84.102	55.363	2.224	1.00	27.74	O
ATOM	1317	CB	ASN	A	339	-85.121	58.245	2.289	1.00	28.67	C
ATOM	1318	CG	ASN	A	339	-85.923	58.984	3.332	1.00	32.98	C
ATOM	1319	ND2	ASN	A	339	-86.794	59.910	2.856	1.00	30.47	N
ATOM	1320	OD1	ASN	A	339	-85.790	58.714	4.557	1.00	29.32	O
ATOM	1321	N	ALA	A	340	-82.403	56.471	1.234	1.00	29.95	N
ATOM	1322	CA	ALA	A	340	-81.920	55.301	0.450	1.00	32.57	C
ATOM	1323	C	ALA	A	340	-81.323	54.196	1.338	1.00	33.57	C
ATOM	1324	O	ALA	A	340	-81.206	53.056	0.908	1.00	35.97	O
ATOM	1325	CB	ALA	A	340	-80.949	55.747	-0.625	1.00	35.62	C
ATOM	1326	N	LEU	A	341	-81.050	54.506	2.610	1.00	29.03	N
ATOM	1327	CA	LEU	A	341	-80.643	53.525	3.566	1.00	29.20	C
ATOM	1328	C	LEU	A	341	-81.782	52.663	4.076	1.00	29.94	C
ATOM	1329	O	LEU	A	341	-81.492	51.612	4.559	1.00	34.09	O
ATOM	1330	CB	LEU	A	341	-79.922	54.183	4.756	1.00	29.54	C

[0154]

[Table 39]

ATOM	1331	CG	LEU	A	341	-78.657	54.963	4.438	1.00	30.55	C
ATOM	1332	CD1	LEU	A	341	-77.949	55.324	5.726	1.00	32.49	C
ATOM	1333	CD2	LEU	A	341	-77.699	54.202	3.505	1.00	34.94	C
ATOM	1334	N	GLU	A	342	-83.045	53.110	4.007	1.00	28.01	N
ATOM	1335	CA	GLU	A	342	-84.188	52.297	4.329	1.00	29.20	C
ATOM	1336	C	GLU	A	342	-84.170	51.939	5.797	1.00	30.98	C
ATOM	1337	O	GLU	A	342	-84.538	50.837	6.168	1.00	27.93	O
ATOM	1338	CB	GLU	A	342	-84.271	51.020	3.422	1.00	33.67	C
ATOM	1339	CG	GLU	A	342	-84.436	51.396	1.951	1.00	40.93	C
ATOM	1340	CD	GLU	A	342	-84.641	50.210	0.996	1.00	51.71	C
ATOM	1341	OE1	GLU	A	342	-85.155	50.443	-0.127	1.00	59.40	O
ATOM	1342	OE2	GLU	A	342	-84.304	49.050	1.343	1.00	63.85	O1-
ATOM	1343	N	LEU	A	343	-83.720	52.858	6.671	1.00	25.57	N
ATOM	1344	CA	LEU	A	343	-83.886	52.596	8.061	1.00	25.55	C
ATOM	1345	C	LEU	A	343	-85.344	52.538	8.436	1.00	27.74	C
ATOM	1346	O	LEU	A	343	-86.157	53.182	7.841	1.00	28.31	O
ATOM	1347	CB	LEU	A	343	-83.220	53.709	8.903	1.00	28.96	C
ATOM	1348	CG	LEU	A	343	-81.727	53.983	8.696	1.00	31.46	C
ATOM	1349	CD1	LEU	A	343	-81.209	54.885	9.856	1.00	33.37	C
ATOM	1350	CD2	LEU	A	343	-80.941	52.709	8.626	1.00	34.61	C
ATOM	1351	N	ASP	A	344	-85.637	51.821	9.513	1.00	29.04	N
ATOM	1352	CA	ASP	A	344	-86.914	51.879	10.183	1.00	28.97	C
ATOM	1353	C	ASP	A	344	-86.795	52.599	11.538	1.00	28.57	C
ATOM	1354	O	ASP	A	344	-85.724	53.074	11.935	1.00	26.79	O
ATOM	1355	CB	ASP	A	344	-87.534	50.437	10.314	1.00	31.24	C
ATOM	1356	CG	ASP	A	344	-86.814	49.528	11.308	1.00	35.96	C
ATOM	1357	OD1	ASP	A	344	-86.302	49.977	12.382	1.00	36.16	O
ATOM	1358	OD2	ASP	A	344	-86.792	48.293	11.031	1.00	39.22	O1-
ATOM	1359	N	ASP	A	345	-87.918	52.728	12.213	1.00	25.19	N
ATOM	1360	CA	ASP	A	345	-87.985	53.504	13.466	1.00	25.66	C
ATOM	1361	C	ASP	A	345	-87.069	52.911	14.571	1.00	26.11	C
ATOM	1362	O	ASP	A	345	-86.457	53.688	15.373	1.00	23.67	O
ATOM	1363	CB	ASP	A	345	-89.404	53.610	13.932	1.00	26.03	C
ATOM	1364	CG	ASP	A	345	-90.233	54.534	13.040	1.00	28.95	C
ATOM	1365	OD1	ASP	A	345	-89.933	55.771	12.961	1.00	28.73	O

[0155]

[Table 40]

ATOM	1366	OD2	ASP	A	345	-91.164	54.006	12.412	1.00 29.19	O1-
ATOM	1367	N	SER	A	346	-86.934	51.572	14.589	1.00 22.04	N
ATOM	1368	CA	SER	A	346	-86.156	50.947	15.601	1.00 24.46	C
ATOM	1369	C	SER	A	346	-84.683	51.316	15.433	1.00 24.51	C
ATOM	1370	O	SER	A	346	-83.931	51.458	16.447	1.00 26.04	O
ATOM	1371	CB	SER	A	346	-86.340	49.372	15.630	1.00 22.35	C
ATOM	1372	OG	SER	A	346	-85.962	48.762	14.413	1.00 26.81	O
ATOM	1373	N	ASP	A	347	-84.262	51.361	14.189	1.00 23.65	N
ATOM	1374	CA	ASP	A	347	-82.915	51.787	13.808	1.00 25.55	C
ATOM	1375	C	ASP	A	347	-82.708	53.241	14.146	1.00 25.43	C
ATOM	1376	O	ASP	A	347	-81.659	53.605	14.673	1.00 23.57	O
ATOM	1377	CB	ASP	A	347	-82.668	51.659	12.315	1.00 24.52	C
ATOM	1378	CG	ASP	A	347	-82.962	50.244	11.744	1.00 29.96	C
ATOM	1379	OD1	ASP	A	347	-82.716	49.211	12.390	1.00 26.87	O
ATOM	1380	OD2	ASP	A	347	-83.366	50.185	10.554	1.00 32.36	O1-
ATOM	1381	N	LEU	A	348	-83.666	54.082	13.744	1.00 22.88	N
ATOM	1382	CA	LEU	A	348	-83.526	55.533	13.919	1.00 23.14	C
ATOM	1383	C	LEU	A	348	-83.418	55.906	15.392	1.00 23.29	C
ATOM	1384	O	LEU	A	348	-82.708	56.817	15.750	1.00 20.74	O
ATOM	1385	CB	LEU	A	348	-84.733	56.249	13.298	1.00 26.01	C
ATOM	1386	CG	LEU	A	348	-84.830	56.220	11.764	1.00 27.73	C
ATOM	1387	CD1	LEU	A	348	-86.220	56.657	11.283	1.00 28.83	C
ATOM	1388	CD2	LEU	A	348	-83.781	57.196	11.227	1.00 35.38	C
ATOM	1389	N	ALA	A	349	-84.130	55.171	16.228	1.00 21.48	N
ATOM	1390	CA	ALA	A	349	-84.161	55.444	17.644	1.00 22.55	C
ATOM	1391	C	ALA	A	349	-82.699	55.339	18.229	1.00 21.78	C
ATOM	1392	O	ALA	A	349	-82.229	56.231	18.918	1.00 22.46	O
ATOM	1393	CB	ALA	A	349	-85.111	54.498	18.315	1.00 22.51	C
ATOM	1394	N	LEU	A	350	-81.998	54.263	17.905	1.00 21.46	N
ATOM	1395	CA	LEU	A	350	-80.629	54.098	18.309	1.00 24.29	C
ATOM	1396	C	LEU	A	350	-79.702	55.144	17.615	1.00 25.71	C
ATOM	1397	O	LEU	A	350	-78.792	55.659	18.232	1.00 21.47	O
ATOM	1398	CB	LEU	A	350	-80.105	52.719	17.939	1.00 24.44	C
ATOM	1399	CG	LEU	A	350	-80.666	51.672	18.856	1.00 24.44	C
ATOM	1400	CD1	LEU	A	350	-80.655	50.318	18.218	1.00 27.61	C

[0156]

[Table 41]

ATOM	1401	CD2	LEU	A	350	-79.946	51.679	20.177	1.00 25.21	C
ATOM	1402	N	PHE	A	351	-79.910	55.393	16.337	1.00 23.65	N
ATOM	1403	CA	PHE	A	351	-79.095	56.396	15.645	1.00 23.35	C
ATOM	1404	C	PHE	A	351	-79.224	57.773	16.332	1.00 23.86	C
ATOM	1405	O	PHE	A	351	-78.223	58.435	16.512	1.00 24.52	O
ATOM	1406	CB	PHE	A	351	-79.614	56.536	14.235	1.00 24.24	C
ATOM	1407	CG	PHE	A	351	-78.802	57.412	13.357	1.00 24.31	C
ATOM	1408	CD1	PHE	A	351	-77.522	57.049	13.022	1.00 26.61	C
ATOM	1409	CD2	PHE	A	351	-79.298	58.609	12.871	1.00 26.91	C
ATOM	1410	CE1	PHE	A	351	-76.758	57.849	12.196	1.00 26.41	C
ATOM	1411	CE2	PHE	A	351	-78.558	59.379	12.001	1.00 26.41	C
ATOM	1412	CZ	PHE	A	351	-77.296	59.009	11.659	1.00 26.29	C
ATOM	1413	N	ILE	A	352	-80.443	58.217	16.645	1.00 21.10	N
ATOM	1414	CA	ILE	A	352	-80.605	59.502	17.327	1.00 24.83	C
ATOM	1415	C	ILE	A	352	-79.978	59.557	18.723	1.00 21.55	C
ATOM	1416	O	ILE	A	352	-79.393	60.572	19.084	1.00 19.85	O
ATOM	1417	CB	ILE	A	352	-82.016	60.100	17.265	1.00 29.03	C
ATOM	1418	CG1	ILE	A	352	-83.005	59.379	18.095	1.00 36.21	C
ATOM	1419	CG2	ILE	A	352	-82.504	60.161	15.776	1.00 31.79	C
ATOM	1420	CD1	ILE	A	352	-84.390	59.985	17.963	1.00 39.03	C
ATOM	1421	N	ALA	A	353	-80.101	58.457	19.469	1.00 20.01	N
ATOM	1422	CA	ALA	A	353	-79.389	58.293	20.747	1.00 21.50	C
ATOM	1423	C	ALA	A	353	-77.869	58.496	20.609	1.00 20.07	C
ATOM	1424	O	ALA	A	353	-77.246	59.208	21.417	1.00 20.35	O
ATOM	1425	CB	ALA	A	353	-79.734	56.946	21.369	1.00 20.22	C
ATOM	1426	N	ALA	A	354	-77.280	57.918	19.568	1.00 21.05	N
ATOM	1427	CA	ALA	A	354	-75.823	58.049	19.310	1.00 21.54	C
ATOM	1428	C	ALA	A	354	-75.410	59.462	18.908	1.00 24.20	C
ATOM	1429	O	ALA	A	354	-74.270	59.896	19.229	1.00 25.28	O
ATOM	1430	CB	ALA	A	354	-75.366	57.100	18.228	1.00 22.04	C
ATOM	1431	N	ILE	A	355	-76.270	60.154	18.163	1.00 19.97	N
ATOM	1432	CA	ILE	A	355	-76.071	61.606	17.879	1.00 21.04	C
ATOM	1433	C	ILE	A	355	-75.988	62.473	19.125	1.00 20.36	C
ATOM	1434	O	ILE	A	355	-75.034	63.215	19.267	1.00 21.97	O
ATOM	1435	CB	ILE	A	355	-77.165	62.107	16.889	1.00 19.44	C

[0157]

[Table 42]

ATOM	1436	CG1	ILE	A	355	-76.841	61.537	15.500	1.00 20.75	C
ATOM	1437	CG2	ILE	A	355	-77.214	63.634	16.782	1.00 22.87	C
ATOM	1438	CD1	ILE	A	355	-77.870	61.812	14.475	1.00 22.49	C
ATOM	1439	N	ILE	A	356	-76.949	62.321	20.016	1.00 18.50	N
ATOM	1440	CA	ILE	A	356	-77.011	63.045	21.264	1.00 21.24	C
ATOM	1441	C	ILE	A	356	-75.793	62.759	22.182	1.00 21.61	C
ATOM	1442	O	ILE	A	356	-75.284	63.651	22.860	1.00 22.74	O
ATOM	1443	CB	ILE	A	356	-78.298	62.779	22.026	1.00 22.53	C
ATOM	1444	CG1	ILE	A	356	-79.474	63.255	21.207	1.00 26.44	C
ATOM	1445	CG2	ILE	A	356	-78.400	63.637	23.310	1.00 26.07	C
ATOM	1446	CD1	ILE	A	356	-80.834	62.868	21.784	1.00 28.83	C
ATOM	1447	N	LEU	A	357	-75.361	61.509	22.268	1.00 23.38	N
ATOM	1448	CA	LEU	A	357	-74.235	61.135	23.122	1.00 23.00	C
ATOM	1449	C	LEU	A	357	-72.830	61.320	22.432	1.00 25.58	C
ATOM	1450	O	LEU	A	357	-71.901	60.605	22.667	1.00 28.10	O
ATOM	1451	CB	LEU	A	357	-74.431	59.726	23.674	1.00 22.36	C
ATOM	1452	CG	LEU	A	357	-75.231	59.567	24.936	1.00 24.42	C
ATOM	1453	CD1	LEU	A	357	-74.475	60.212	26.130	1.00 27.78	C
ATOM	1454	CD2	LEU	A	357	-76.610	60.180	24.796	1.00 28.11	C
ATOM	1455	N	CYS	A	358	-72.664	62.386	21.663	1.00 30.54	N
ATOM	1456	CA	CYS	A	358	-71.441	62.672	20.980	1.00 29.56	C
ATOM	1457	C	CYS	A	358	-70.370	63.242	21.932	1.00 30.58	C
ATOM	1458	O	CYS	A	358	-70.540	64.268	22.580	1.00 28.86	O
ATOM	1459	CB	CYS	A	358	-71.771	63.636	19.880	1.00 36.65	C
ATOM	1460	SG	CYS	A	358	-70.315	64.123	19.048	1.00 40.83	S
ATOM	1461	N	GLY	A	359	-69.236	62.554	22.022	1.00 29.82	N
ATOM	1462	CA	GLY	A	359	-68.175	62.973	22.913	1.00 28.68	C
ATOM	1463	C	GLY	A	359	-67.345	64.150	22.501	1.00 27.86	C
ATOM	1464	O	GLY	A	359	-66.635	64.692	23.326	1.00 26.90	O
ATOM	1465	N	ASP	A	360	-67.462	64.635	21.275	1.00 28.26	N
ATOM	1466	CA	ASP	A	360	-66.650	65.781	20.943	1.00 33.38	C
ATOM	1467	C	ASP	A	360	-67.365	67.138	20.821	1.00 32.73	C
ATOM	1468	O	ASP	A	360	-66.950	67.996	20.051	1.00 36.71	O
ATOM	1469	CB	ASP	A	360	-65.722	65.483	19.795	1.00 43.49	C
ATOM	1470	CG	ASP	A	360	-66.387	65.509	18.508	1.00 50.36	C

[0158]

[Table 43]

ATOM	1471	OD1	ASP	A	360	-67.548	65.068	18.536	1.00 46.79	O
ATOM	1472	OD2	ASP	A	360	-65.732	65.968	17.502	1.00 59.28	O1-
ATOM	1473	N	ARG	A	361	-68.375	67.359	21.646	1.00 29.07	N
ATOM	1474	CA	ARG	A	361	-69.056	68.660	21.633	1.00 25.70	C
ATOM	1475	C	ARG	A	361	-68.204	69.687	22.382	1.00 25.12	C
ATOM	1476	O	ARG	A	361	-67.634	69.371	23.416	1.00 26.08	O
ATOM	1477	CB	ARG	A	361	-70.434	68.538	22.286	1.00 23.66	C
ATOM	1478	CG	ARG	A	361	-71.375	67.460	21.695	1.00 24.32	C
ATOM	1479	CD	ARG	A	361	-71.536	67.626	20.192	1.00 23.61	C
ATOM	1480	NE	ARG	A	361	-72.640	66.855	19.664	1.00 23.03	N
ATOM	1481	CZ	ARG	A	361	-72.930	66.740	18.357	1.00 25.65	C
ATOM	1482	NH1	ARG	A	361	-72.234	67.367	17.427	1.00 23.62	N1+
ATOM	1483	NH2	ARG	A	361	-73.956	65.994	17.990	1.00 26.41	N
ATOM	1484	N	PRO	A	362	-68.169	70.925	21.904	1.00 26.30	N
ATOM	1485	CA	PRO	A	362	-67.454	71.943	22.606	1.00 25.70	C
ATOM	1486	C	PRO	A	362	-67.926	72.155	24.036	1.00 25.10	C
ATOM	1487	O	PRO	A	362	-69.088	72.307	24.278	1.00 25.35	O
ATOM	1488	CB	PRO	A	362	-67.727	73.239	21.794	1.00 27.18	C
ATOM	1489	CG	PRO	A	362	-68.181	72.784	20.444	1.00 26.84	C
ATOM	1490	CD	PRO	A	362	-68.723	71.386	20.611	1.00 25.25	C
ATOM	1491	N	GLY	A	363	-67.012	72.146	24.986	1.00 24.11	N
ATOM	1492	CA	GLY	A	363	-67.379	72.537	26.369	1.00 24.36	C
ATOM	1493	C	GLY	A	363	-67.838	71.398	27.239	1.00 23.85	C
ATOM	1494	O	GLY	A	363	-68.159	71.633	28.392	1.00 26.14	O
ATOM	1495	N	LEU	A	364	-67.887	70.185	26.674	1.00 24.65	N
ATOM	1496	CA	LEU	A	364	-68.207	68.956	27.377	1.00 23.42	C
ATOM	1497	C	LEU	A	364	-67.102	68.663	28.380	1.00 23.38	C
ATOM	1498	O	LEU	A	364	-65.913	68.657	28.031	1.00 23.52	O
ATOM	1499	CB	LEU	A	364	-68.359	67.799	26.403	1.00 27.51	C
ATOM	1500	CG	LEU	A	364	-69.153	66.569	26.815	1.00 31.79	C
ATOM	1501	CD1	LEU	A	364	-70.600	66.975	27.150	1.00 29.07	C
ATOM	1502	CD2	LEU	A	364	-69.126	65.552	25.652	1.00 33.09	C
ATOM	1503	N	MET	A	365	-67.508	68.494	29.633	1.00 23.03	N
ATOM	1504	CA	MET	A	365	-66.560	68.245	30.745	1.00 22.95	C
ATOM	1505	C	MET	A	365	-66.144	66.761	30.857	1.00 22.88	C

[0159]

[Table 44]

ATOM	1506	O	MET	A	365	-64.970	66.414	30.699	1.00 22.23	O
ATOM	1507	CB	MET	A	365	-67.161	68.756	32.074	1.00 22.80	C
ATOM	1508	CG	MET	A	365	-67.306	70.282	32.122	1.00 25.16	C
ATOM	1509	SD	MET	A	365	-65.681	71.146	32.093	1.00 26.95	S
ATOM	1510	CE	MET	A	365	-65.685	71.755	30.366	1.00 31.57	C
ATOM	1511	N	ASN	A	366	-67.079	65.886	31.145	1.00 21.97	N
ATOM	1512	CA	ASN	A	366	-66.672	64.480	31.383	1.00 23.05	C
ATOM	1513	C	ASN	A	366	-66.784	63.668	30.040	1.00 23.58	C
ATOM	1514	O	ASN	A	366	-67.741	62.922	29.795	1.00 23.77	O
ATOM	1515	CB	ASN	A	366	-67.499	63.916	32.507	1.00 22.41	C
ATOM	1516	CG	ASN	A	366	-66.996	62.556	32.991	1.00 25.52	C
ATOM	1517	ND2	ASN	A	366	-67.666	62.001	34.020	1.00 28.47	N
ATOM	1518	OD1	ASN	A	366	-66.080	61.993	32.427	1.00 25.40	O
ATOM	1519	N	VAL	A	367	-65.781	63.856	29.216	1.00 21.67	N
ATOM	1520	CA	VAL	A	367	-65.688	63.263	27.860	1.00 22.09	C
ATOM	1521	C	VAL	A	367	-65.621	61.724	27.960	1.00 23.24	C
ATOM	1522	O	VAL	A	367	-66.350	61.047	27.269	1.00 23.85	O
ATOM	1523	CB	VAL	A	367	-64.501	63.879	27.126	1.00 23.86	C
ATOM	1524	CG1	VAL	A	367	-64.253	63.219	25.765	1.00 26.29	C
ATOM	1525	CG2	VAL	A	367	-64.833	65.357	26.853	1.00 27.28	C
ATOM	1526	N	PRO	A	368	-64.795	61.176	28.857	1.00 26.69	N
ATOM	1527	CA	PRO	A	368	-64.708	59.698	28.895	1.00 25.75	C
ATOM	1528	C	PRO	A	368	-66.062	59.004	29.188	1.00 24.91	C
ATOM	1529	O	PRO	A	368	-66.386	57.959	28.627	1.00 27.21	O
ATOM	1530	CB	PRO	A	368	-63.646	59.433	30.026	1.00 27.92	C
ATOM	1531	CG	PRO	A	368	-62.850	60.723	30.112	1.00 27.86	C
ATOM	1532	CD	PRO	A	368	-63.858	61.828	29.823	1.00 27.07	C
ATOM	1533	N	ARG	A	369	-66.829	59.558	30.101	1.00 24.48	N
ATOM	1534	CA	ARG	A	369	-68.110	59.014	30.423	1.00 24.27	C
ATOM	1535	C	ARG	A	369	-69.101	59.119	29.249	1.00 22.94	C
ATOM	1536	O	ARG	A	369	-69.774	58.165	28.967	1.00 23.90	O
ATOM	1537	CB	ARG	A	369	-68.708	59.645	31.660	1.00 25.39	C
ATOM	1538	CG	ARG	A	369	-69.898	58.924	32.175	1.00 33.11	C
ATOM	1539	CD	ARG	A	369	-70.260	59.332	33.620	1.00 39.02	C
ATOM	1540	NE	ARG	A	369	-71.500	58.634	34.020	1.00 42.90	N

[0160]

[Table 45]

ATOM	1541	CZ	ARG A 369	-71.590	57.326	34.265	1.00	46.73	C
ATOM	1542	NH1	ARG A 369	-70.515	56.558	34.198	1.00	47.69	N1+
ATOM	1543	NH2	ARG A 369	-72.770	56.775	34.572	1.00	46.26	N
ATOM	1544	N	VAL A 370	-69.165	60.237	28.589	1.00	21.98	N
ATOM	1545	CA	VAL A 370	-70.026	60.366	27.419	1.00	22.26	C
ATOM	1546	C	VAL A 370	-69.581	59.416	26.320	1.00	21.72	C
ATOM	1547	O	VAL A 370	-70.412	58.787	25.703	1.00	23.73	O
ATOM	1548	CB	VAL A 370	-70.010	61.815	26.910	1.00	21.33	C
ATOM	1549	CG1	VAL A 370	-70.721	61.960	25.575	1.00	21.99	C
ATOM	1550	CG2	VAL A 370	-70.615	62.706	27.951	1.00	20.86	C
ATOM	1551	N	GLU A 371	-68.280	59.299	26.065	1.00	21.47	N
ATOM	1552	CA	GLU A 371	-67.778	58.353	25.054	1.00	23.96	C
ATOM	1553	C	GLU A 371	-68.132	56.881	25.396	1.00	24.41	C
ATOM	1554	O	GLU A 371	-68.518	56.126	24.480	1.00	21.17	O
ATOM	1555	CB	GLU A 371	-66.260	58.475	24.817	1.00	24.96	C
ATOM	1556	CG	GLU A 371	-65.978	59.812	24.166	1.00	32.81	C
ATOM	1557	CD	GLU A 371	-64.566	59.971	23.628	1.00	39.02	C
ATOM	1558	OE1	GLU A 371	-63.689	59.252	24.167	1.00	40.72	O
ATOM	1559	OE2	GLU A 371	-64.367	60.841	22.711	1.00	46.45	O1-
ATOM	1560	N	ALA A 372	-68.067	56.521	26.669	1.00	23.17	N
ATOM	1561	CA	ALA A 372	-68.470	55.168	27.121	1.00	25.96	C
ATOM	1562	C	ALA A 372	-69.985	54.858	26.948	1.00	27.50	C
ATOM	1563	O	ALA A 372	-70.382	53.729	26.543	1.00	24.51	O
ATOM	1564	CB	ALA A 372	-68.038	54.906	28.548	1.00	26.90	C
ATOM	1565	N	ILE A 373	-70.828	55.850	27.210	1.00	23.63	N
ATOM	1566	CA	ILE A 373	-72.262	55.689	26.943	1.00	22.73	C
ATOM	1567	C	ILE A 373	-72.473	55.621	25.396	1.00	24.64	C
ATOM	1568	O	ILE A 373	-73.173	54.749	24.918	1.00	23.01	O
ATOM	1569	CB	ILE A 373	-73.039	56.819	27.540	1.00	22.89	C
ATOM	1570	CG1	ILE A 373	-72.850	56.840	29.066	1.00	25.00	C
ATOM	1571	CG2	ILE A 373	-74.515	56.806	27.147	1.00	22.76	C
ATOM	1572	CD1	ILE A 373	-73.288	58.149	29.652	1.00	25.70	C
ATOM	1573	N	GLN A 374	-71.817	56.488	24.625	1.00	22.07	N
ATOM	1574	CA	GLN A 374	-71.956	56.435	23.142	1.00	23.40	C
ATOM	1575	C	GLN A 374	-71.552	55.082	22.558	1.00	22.83	C

[0161]

[Table 46]

ATOM	1576	O	GLN	A	374	-72.215	54.525	21.693	1.00 22.36	O
ATOM	1577	CB	GLN	A	374	-71.233	57.551	22.412	1.00 23.14	C
ATOM	1578	CG	GLN	A	374	-71.749	57.654	20.938	1.00 23.59	C
ATOM	1579	CD	GLN	A	374	-70.908	58.520	20.053	1.00 26.27	C
ATOM	1580	NE2	GLN	A	374	-71.540	59.443	19.261	1.00 22.90	N
ATOM	1581	OE1	GLN	A	374	-69.696	58.399	20.094	1.00 25.56	O
ATOM	1582	N	ASP	A	375	-70.477	54.533	23.075	1.00 25.96	N
ATOM	1583	CA	ASP	A	375	-70.011	53.219	22.648	1.00 24.82	C
ATOM	1584	C	ASP	A	375	-71.028	52.137	22.875	1.00 25.19	C
ATOM	1585	O	ASP	A	375	-71.224	51.324	21.976	1.00 25.31	O
ATOM	1586	CB	ASP	A	375	-68.719	52.845	23.394	1.00 28.10	C
ATOM	1587	CG	ASP	A	375	-67.537	53.667	22.980	1.00 29.79	C
ATOM	1588	OD1	ASP	A	375	-67.590	54.233	21.882	1.00 32.18	O
ATOM	1589	OD2	ASP	A	375	-66.522	53.690	23.727	1.00 33.07	O1-
ATOM	1590	N	THR	A	376	-71.639	52.092	24.075	1.00 23.06	N
ATOM	1591	CA	THR	A	376	-72.751	51.169	24.336	1.00 24.01	C
ATOM	1592	C	THR	A	376	-73.927	51.281	23.342	1.00 24.51	C
ATOM	1593	O	THR	A	376	-74.398	50.312	22.856	1.00 22.48	O
ATOM	1594	CB	THR	A	376	-73.319	51.420	25.708	1.00 28.77	C
ATOM	1595	CG2	THR	A	376	-74.453	50.453	26.017	1.00 27.76	C
ATOM	1596	OG1	THR	A	376	-72.273	51.265	26.669	1.00 32.71	O
ATOM	1597	N	ILE	A	377	-74.366	52.510	23.044	1.00 23.15	N
ATOM	1598	CA	ILE	A	377	-75.373	52.768	22.047	1.00 22.26	C
ATOM	1599	C	ILE	A	377	-74.935	52.286	20.662	1.00 21.93	C
ATOM	1600	O	ILE	A	377	-75.688	51.607	19.964	1.00 22.09	O
ATOM	1601	CB	ILE	A	377	-75.676	54.280	21.954	1.00 23.90	C
ATOM	1602	CG1	ILE	A	377	-76.197	54.815	23.307	1.00 24.70	C
ATOM	1603	CG2	ILE	A	377	-76.692	54.543	20.864	1.00 25.87	C
ATOM	1604	CD1	ILE	A	377	-76.264	56.331	23.373	1.00 26.10	C
ATOM	1605	N	LEU	A	378	-73.712	52.619	20.281	1.00 22.56	N
ATOM	1606	CA	LEU	A	378	-73.210	52.194	19.002	1.00 24.21	C
ATOM	1607	C	LEU	A	378	-73.055	50.672	18.857	1.00 24.14	C
ATOM	1608	O	LEU	A	378	-73.281	50.136	17.796	1.00 22.82	O
ATOM	1609	CB	LEU	A	378	-71.914	52.893	18.683	1.00 29.61	C
ATOM	1610	CG	LEU	A	378	-72.061	54.354	18.311	1.00 29.65	C

[0162]

[Table 47]

ATOM	1611	CD1	LEU	A	378	-70.680	55.054	18.063	1.00 32.08	C
ATOM	1612	CD2	LEU	A	378	-72.946	54.465	17.087	1.00 32.66	C
ATOM	1613	N	ARG	A	379	-72.646	49.984	19.907	1.00 25.21	N
ATOM	1614	CA	ARG	A	379	-72.591	48.484	19.883	1.00 25.30	C
ATOM	1615	C	ARG	A	379	-74.007	47.901	19.699	1.00 26.76	C
ATOM	1616	O	ARG	A	379	-74.195	46.888	18.960	1.00 27.40	O
ATOM	1617	CB	ARG	A	379	-71.877	47.941	21.131	1.00 27.61	C
ATOM	1618	CG	ARG	A	379	-70.377	48.349	21.083	1.00 27.10	C
ATOM	1619	CD	ARG	A	379	-69.395	47.763	22.099	1.00 33.04	C
ATOM	1620	NE	ARG	A	379	-69.356	48.394	23.346	1.00 35.36	N
ATOM	1621	CZ	ARG	A	379	-68.411	49.150	23.920	1.00 32.49	C
ATOM	1622	NH1	ARG	A	379	-67.193	49.476	23.463	1.00 34.96	N1+
ATOM	1623	NH2	ARG	A	379	-68.777	49.617	25.060	1.00 32.64	N
ATOM	1624	N	ALA	A	380	-74.977	48.532	20.352	1.00 24.60	N
ATOM	1625	CA	ALA	A	380	-76.383	48.132	20.183	1.00 23.29	C
ATOM	1626	C	ALA	A	380	-76.880	48.407	18.790	1.00 24.65	C
ATOM	1627	O	ALA	A	380	-77.542	47.537	18.223	1.00 24.36	O
ATOM	1628	CB	ALA	A	380	-77.269	48.757	21.197	1.00 22.00	C
ATOM	1629	N	LEU	A	381	-76.558	49.571	18.248	1.00 23.87	N
ATOM	1630	CA	LEU	A	381	-76.915	49.888	16.866	1.00 25.43	C
ATOM	1631	C	LEU	A	381	-76.324	48.885	15.883	1.00 28.15	C
ATOM	1632	O	LEU	A	381	-76.995	48.413	14.977	1.00 27.26	O
ATOM	1633	CB	LEU	A	381	-76.481	51.294	16.512	1.00 26.61	C
ATOM	1634	CG	LEU	A	381	-76.660	51.771	15.082	1.00 26.84	C
ATOM	1635	CD1	LEU	A	381	-78.122	51.687	14.713	1.00 27.00	C
ATOM	1636	CD2	LEU	A	381	-76.190	53.210	14.983	1.00 30.28	C
ATOM	1637	N	GLU	A	382	-75.026	48.645	16.000	1.00 31.12	N
ATOM	1638	CA	GLU	A	382	-74.364	47.669	15.133	1.00 30.35	C
ATOM	1639	C	GLU	A	382	-75.028	46.289	15.191	1.00 29.03	C
ATOM	1640	O	GLU	A	382	-75.232	45.669	14.160	1.00 31.24	O
ATOM	1641	CB	GLU	A	382	-72.851	47.583	15.464	1.00 33.36	C
ATOM	1642	CG	GLU	A	382	-72.126	46.427	14.819	1.00 39.35	C
ATOM	1643	CD	GLU	A	382	-70.620	46.465	15.101	1.00 45.14	C
ATOM	1644	OE1	GLU	A	382	-70.168	46.336	16.287	1.00 48.21	O
ATOM	1645	OE2	GLU	A	382	-69.906	46.647	14.114	1.00 56.89	O1-

[0163]

[Table 48]

ATOM	1646	N	PHE	A	383	-75.364	45.836	16.378	1.00 27.04	N
ATOM	1647	CA	PHE	A	383	-76.008	44.560	16.565	1.00 31.77	C
ATOM	1648	C	PHE	A	383	-77.452	44.538	16.012	1.00 32.97	C
ATOM	1649	O	PHE	A	383	-77.863	43.594	15.328	1.00 27.70	O
ATOM	1650	CB	PHE	A	383	-76.078	44.218	18.036	1.00 31.21	C
ATOM	1651	CG	PHE	A	383	-77.033	43.106	18.310	1.00 39.96	C
ATOM	1652	CD1	PHE	A	383	-76.664	41.781	18.031	1.00 40.89	C
ATOM	1653	CD2	PHE	A	383	-78.325	43.376	18.788	1.00 39.47	C
ATOM	1654	CE1	PHE	A	383	-77.579	40.758	18.251	1.00 46.44	C
ATOM	1655	CE2	PHE	A	383	-79.237	42.360	18.993	1.00 41.69	C
ATOM	1656	CZ	PHE	A	383	-78.857	41.051	18.736	1.00 46.86	C
ATOM	1657	N	HIS	A	384	-78.188	45.609	16.317	1.00 30.88	N
ATOM	1658	CA	HIS	A	384	-79.553	45.814	15.842	1.00 32.42	C
ATOM	1659	C	HIS	A	384	-79.672	45.825	14.321	1.00 29.76	C
ATOM	1660	O	HIS	A	384	-80.626	45.246	13.809	1.00 34.18	O
ATOM	1661	CB	HIS	A	384	-80.151	47.089	16.400	1.00 31.32	C
ATOM	1662	CG	HIS	A	384	-81.590	47.247	16.086	1.00 34.28	C
ATOM	1663	CD2	HIS	A	384	-82.219	48.045	15.183	1.00 33.92	C
ATOM	1664	ND1	HIS	A	384	-82.575	46.527	16.726	1.00 32.34	N
ATOM	1665	CE1	HIS	A	384	-83.756	46.871	16.224	1.00 33.77	C
ATOM	1666	NE2	HIS	A	384	-83.566	47.785	15.286	1.00 34.10	N
ATOM	1667	N	LEU	A	385	-78.753	46.488	13.635	1.00 27.91	N
ATOM	1668	CA	LEU	A	385	-78.803	46.635	12.186	1.00 31.02	C
ATOM	1669	C	LEU	A	385	-78.566	45.309	11.473	1.00 40.36	C
ATOM	1670	O	LEU	A	385	-79.283	44.953	10.517	1.00 39.50	O
ATOM	1671	CB	LEU	A	385	-77.757	47.604	11.709	1.00 30.41	C
ATOM	1672	CG	LEU	A	385	-78.016	49.104	11.921	1.00 31.38	C
ATOM	1673	CD1	LEU	A	385	-76.734	49.827	11.543	1.00 30.60	C
ATOM	1674	CD2	LEU	A	385	-79.200	49.639	11.091	1.00 29.78	C
ATOM	1675	N	GLN	A	386	-77.542	44.606	11.937	1.00 43.61	N
ATOM	1676	CA	GLN	A	386	-77.183	43.282	11.408	1.00 55.03	C
ATOM	1677	C	GLN	A	386	-78.395	42.374	11.603	1.00 45.90	C
ATOM	1678	O	GLN	A	386	-78.865	41.754	10.639	1.00 52.92	O
ATOM	1679	CB	GLN	A	386	-75.871	42.744	12.079	1.00 54.20	C
ATOM	1680	CG	GLN	A	386	-75.213	41.553	11.390	1.00 63.42	C

[0164]

[Table 49]

ATOM	1681	CD	GLN	A	386	-76.038	40.284	11.555	1.00	70.69	C
ATOM	1682	NE2	GLN	A	386	-76.317	39.594	10.448	1.00	69.88	N
ATOM	1683	OE1	GLN	A	386	-76.462	39.960	12.665	1.00	76.95	O
ATOM	1684	N	ALA	A	387	-78.952	42.373	12.809	1.00	42.99	N
ATOM	1685	CA	ALA	A	387	-80.151	41.569	13.122	1.00	44.81	C
ATOM	1686	C	ALA	A	387	-81.277	41.916	12.162	1.00	47.01	C
ATOM	1687	O	ALA	A	387	-81.801	41.074	11.436	1.00	54.11	O
ATOM	1688	CB	ALA	A	387	-80.602	41.803	14.570	1.00	41.95	C
ATOM	1689	N	ASN	A	388	-81.582	43.197	12.114	1.00	48.33	N
ATOM	1690	CA	ASN	A	388	-82.710	43.718	11.376	1.00	44.38	C
ATOM	1691	C	ASN	A	388	-82.557	43.793	9.805	1.00	40.56	C
ATOM	1692	O	ASN	A	388	-83.560	43.707	9.103	1.00	44.07	O
ATOM	1693	CB	ASN	A	388	-83.049	45.100	12.025	1.00	46.83	C
ATOM	1694	CG	ASN	A	388	-84.420	45.668	11.600	1.00	56.78	C
ATOM	1695	ND2	ASN	A	388	-84.589	47.009	11.776	1.00	43.52	N
ATOM	1696	OD1	ASN	A	388	-85.323	44.917	11.127	1.00	50.08	O
ATOM	1697	N	HIS	A	389	-81.342	43.998	9.273	1.00	36.28	N
ATOM	1698	CA	HIS	A	389	-81.080	44.195	7.826	1.00	36.61	C
ATOM	1699	C	HIS	A	389	-79.933	43.232	7.438	1.00	43.24	C
ATOM	1700	O	HIS	A	389	-78.866	43.693	7.037	1.00	39.40	O
ATOM	1701	CB	HIS	A	389	-80.584	45.637	7.477	1.00	41.48	C
ATOM	1702	CG	HIS	A	389	-81.486	46.758	7.920	1.00	42.12	C
ATOM	1703	CD2	HIS	A	389	-81.666	47.330	9.132	1.00	41.68	C
ATOM	1704	ND1	HIS	A	389	-82.335	47.415	7.061	1.00	49.03	N
ATOM	1705	CE1	HIS	A	389	-82.991	48.356	7.722	1.00	52.40	C
ATOM	1706	NE2	HIS	A	389	-82.625	48.305	8.989	1.00	43.14	N
ATOM	1707	N	PRO	A	390	-80.128	41.887	7.549	1.00	49.76	N
ATOM	1708	CA	PRO	A	390	-78.923	41.035	7.366	1.00	50.61	C
ATOM	1709	C	PRO	A	390	-78.281	41.183	5.965	1.00	49.25	C
ATOM	1710	O	PRO	A	390	-77.064	41.210	5.828	1.00	50.40	O
ATOM	1711	CB	PRO	A	390	-79.415	39.588	7.674	1.00	49.35	C
ATOM	1712	CG	PRO	A	390	-80.861	39.666	7.893	1.00	51.85	C
ATOM	1713	CD	PRO	A	390	-81.274	41.114	8.077	1.00	53.39	C
ATOM	1714	N	ASP	A	391	-79.098	41.436	4.965	1.00	52.37	N
ATOM	1715	CA	ASP	A	391	-78.592	41.599	3.623	1.00	57.91	C

[0165]

[Table 50]

ATOM	1716	C	ASP	A	391	-77.830	42.908	3.369	1.00	61.02	C
ATOM	1717	O	ASP	A	391	-77.303	43.061	2.256	1.00	53.48	O
ATOM	1718	CB	ASP	A	391	-79.753	41.496	2.629	1.00	60.11	C
ATOM	1719	CG	ASP	A	391	-80.583	40.253	2.840	1.00	60.88	C
ATOM	1720	OD1	ASP	A	391	-80.012	39.180	3.120	1.00	65.09	O
ATOM	1721	OD2	ASP	A	391	-81.813	40.362	2.749	1.00	69.00	O1-
ATOM	1722	N	ALA	A	392	-77.767	43.834	4.344	1.00	53.30	N
ATOM	1723	CA	ALA	A	392	-77.197	45.187	4.106	1.00	54.52	C
ATOM	1724	C	ALA	A	392	-75.796	45.310	4.721	1.00	58.71	C
ATOM	1725	O	ALA	A	392	-75.588	45.671	5.930	1.00	48.19	O
ATOM	1726	CB	ALA	A	392	-78.142	46.262	4.642	1.00	54.46	C
ATOM	1727	N	GLN	A	393	-74.808	44.949	3.918	1.00	60.15	N
ATOM	1728	CA	GLN	A	393	-73.426	45.011	4.422	1.00	71.87	C
ATOM	1729	C	GLN	A	393	-73.008	46.475	4.326	1.00	69.85	C
ATOM	1730	O	GLN	A	393	-73.469	47.230	3.442	1.00	72.69	O
ATOM	1731	CB	GLN	A	393	-72.441	44.055	3.699	1.00	73.80	C
ATOM	1732	CG	GLN	A	393	-71.089	43.858	4.414	1.00	76.08	C
ATOM	1733	CD	GLN	A	393	-71.200	43.125	5.752	1.00	81.05	C
ATOM	1734	NE2	GLN	A	393	-70.926	43.833	6.841	1.00	74.51	N
ATOM	1735	OE1	GLN	A	393	-71.518	41.934	5.796	1.00	87.90	O
ATOM	1736	N	TYR	A	394	-72.163	46.868	5.266	1.00	60.68	N
ATOM	1737	CA	TYR	A	394	-71.626	48.201	5.328	1.00	58.14	C
ATOM	1738	C	TYR	A	394	-72.698	49.233	5.756	1.00	46.03	C
ATOM	1739	O	TYR	A	394	-72.455	50.436	5.590	1.00	43.17	O
ATOM	1740	CB	TYR	A	394	-70.965	48.628	3.970	1.00	69.18	C
ATOM	1741	CG	TYR	A	394	-69.910	47.684	3.402	1.00	77.03	C
ATOM	1742	CD1	TYR	A	394	-70.267	46.549	2.666	1.00	82.29	C
ATOM	1743	CD2	TYR	A	394	-68.551	47.954	3.564	1.00	87.23	C
ATOM	1744	CE1	TYR	A	394	-69.314	45.691	2.145	1.00	84.59	C
ATOM	1745	CE2	TYR	A	394	-67.585	47.104	3.037	1.00	94.30	C
ATOM	1746	CZ	TYR	A	394	-67.977	45.975	2.329	1.00	92.67	C
ATOM	1747	OH	TYR	A	394	-67.032	45.128	1.807	1.00	102.03	O
ATOM	1748	N	LEU	A	395	-73.857	48.798	6.282	1.00	38.11	N
ATOM	1749	CA	LEU	A	395	-74.900	49.738	6.645	1.00	35.94	C
ATOM	1750	C	LEU	A	395	-74.387	50.554	7.861	1.00	31.05	C

[0166]

[Table 51]

ATOM	1751	O	LEU	A	395	-74.544	51.750	7.892	1.00	29.03	O
ATOM	1752	CB	LEU	A	395	-76.267	49.038	6.865	1.00	35.47	C
ATOM	1753	CG	LEU	A	395	-77.471	49.905	7.289	1.00	35.99	C
ATOM	1754	CD1	LEU	A	395	-77.721	51.043	6.300	1.00	38.61	C
ATOM	1755	CD2	LEU	A	395	-78.733	49.066	7.407	1.00	33.86	C
ATOM	1756	N	PHE	A	396	-73.696	49.909	8.790	1.00	29.46	N
ATOM	1757	CA	PHE	A	396	-73.213	50.578	10.005	1.00	30.43	C
ATOM	1758	C	PHE	A	396	-72.160	51.670	9.689	1.00	34.51	C
ATOM	1759	O	PHE	A	396	-72.368	52.815	10.073	1.00	32.82	O
ATOM	1760	CB	PHE	A	396	-72.728	49.564	10.982	1.00	30.07	C
ATOM	1761	CG	PHE	A	396	-72.214	50.125	12.233	1.00	29.62	C
ATOM	1762	CD1	PHE	A	396	-73.070	50.683	13.154	1.00	29.80	C
ATOM	1763	CD2	PHE	A	396	-70.864	50.093	12.502	1.00	29.69	C
ATOM	1764	CE1	PHE	A	396	-72.568	51.247	14.335	1.00	31.86	C
ATOM	1765	CE2	PHE	A	396	-70.362	50.634	13.683	1.00	33.55	C
ATOM	1766	CZ	PHE	A	396	-71.226	51.185	14.621	1.00	31.57	C
ATOM	1767	N	PRO	A	397	-71.115	51.359	8.883	1.00	36.63	N
ATOM	1768	CA	PRO	A	397	-70.219	52.470	8.497	1.00	34.78	C
ATOM	1769	C	PRO	A	397	-70.848	53.557	7.663	1.00	28.84	C
ATOM	1770	O	PRO	A	397	-70.445	54.675	7.798	1.00	30.67	O
ATOM	1771	CB	PRO	A	397	-69.087	51.796	7.723	1.00	39.59	C
ATOM	1772	CG	PRO	A	397	-69.530	50.383	7.508	1.00	41.58	C
ATOM	1773	CD	PRO	A	397	-70.510	50.042	8.589	1.00	35.62	C
ATOM	1774	N	LYS	A	398	-71.780	53.250	6.780	1.00	30.76	N
ATOM	1775	CA	LYS	A	398	-72.474	54.289	6.014	1.00	34.97	C
ATOM	1776	C	LYS	A	398	-73.254	55.233	6.938	1.00	33.02	C
ATOM	1777	O	LYS	A	398	-73.292	56.431	6.727	1.00	32.65	O
ATOM	1778	CB	LYS	A	398	-73.473	53.685	5.051	1.00	37.65	C
ATOM	1779	CG	LYS	A	398	-72.873	53.014	3.844	1.00	40.10	C
ATOM	1780	CD	LYS	A	398	-73.997	52.351	3.075	1.00	46.51	C
ATOM	1781	CE	LYS	A	398	-73.532	51.798	1.755	1.00	53.01	C
ATOM	1782	NZ	LYS	A	398	-74.562	50.826	1.280	1.00	56.91	N1+
ATOM	1783	N	LEU	A	399	-73.839	54.668	7.971	1.00	32.88	N
ATOM	1784	CA	LEU	A	399	-74.566	55.457	8.954	1.00	37.65	C
ATOM	1785	C	LEU	A	399	-73.625	56.305	9.828	1.00	36.37	C

[0167]

[Table 52]

ATOM	1786	O	LEU	A	399	-73.969	57.454	10.164	1.00 32.54	O
ATOM	1787	CB	LEU	A	399	-75.462	54.561	9.839	1.00 40.16	C
ATOM	1788	CG	LEU	A	399	-76.932	54.332	9.481	1.00 40.74	C
ATOM	1789	CD1	LEU	A	399	-77.578	53.483	10.567	1.00 40.82	C
ATOM	1790	CD2	LEU	A	399	-77.705	55.644	9.381	1.00 40.84	C
ATOM	1791	N	LEU	A	400	-72.441	55.757	10.166	1.00 35.29	N
ATOM	1792	CA	LEU	A	400	-71.371	56.528	10.810	1.00 33.69	C
ATOM	1793	C	LEU	A	400	-70.948	57.732	9.956	1.00 32.60	C
ATOM	1794	O	LEU	A	400	-70.721	58.820	10.496	1.00 29.48	O
ATOM	1795	CB	LEU	A	400	-70.166	55.626	11.146	1.00 38.44	C
ATOM	1796	CG	LEU	A	400	-70.322	54.633	12.320	1.00 39.28	C
ATOM	1797	CD1	LEU	A	400	-68.963	54.045	12.677	1.00 41.77	C
ATOM	1798	CD2	LEU	A	400	-70.903	55.269	13.561	1.00 40.93	C
ATOM	1799	N	GLN	A	401	-70.891	57.565	8.634	1.00 28.99	N
ATOM	1800	CA	GLN	A	401	-70.632	58.683	7.756	1.00 28.21	C
ATOM	1801	C	GLN	A	401	-71.802	59.721	7.742	1.00 28.34	C
ATOM	1802	O	GLN	A	401	-71.539	60.949	7.658	1.00 29.06	O
ATOM	1803	CB	GLN	A	401	-70.324	58.183	6.329	1.00 33.09	C
ATOM	1804	CG	GLN	A	401	-69.962	59.231	5.286	1.00 33.74	C
ATOM	1805	CD	GLN	A	401	-68.758	60.048	5.688	1.00 36.66	C
ATOM	1806	NE2	GLN	A	401	-68.888	61.388	5.659	1.00 31.14	N
ATOM	1807	OE1	GLN	A	401	-67.733	59.488	6.068	1.00 39.63	O
ATOM	1808	N	LYS	A	402	-73.070	59.264	7.797	1.00 25.96	N
ATOM	1809	CA	LYS	A	402	-74.209	60.199	7.909	1.00 25.95	C
ATOM	1810	C	LYS	A	402	-74.077	61.033	9.154	1.00 23.94	C
ATOM	1811	O	LYS	A	402	-74.447	62.187	9.128	1.00 26.38	O
ATOM	1812	CB	LYS	A	402	-75.552	59.490	7.934	1.00 28.50	C
ATOM	1813	CG	LYS	A	402	-75.879	58.714	6.657	1.00 26.31	C
ATOM	1814	CD	LYS	A	402	-75.772	59.517	5.388	1.00 28.54	C
ATOM	1815	CE	LYS	A	402	-76.303	58.718	4.190	1.00 27.64	C
ATOM	1816	NZ	LYS	A	402	-76.102	59.461	2.930	1.00 29.00	N1+
ATOM	1817	N	MET	A	403	-73.544	60.488	10.232	1.00 23.90	N
ATOM	1818	CA	MET	A	403	-73.350	61.299	11.454	1.00 30.10	C
ATOM	1819	C	MET	A	403	-72.378	62.437	11.180	1.00 28.49	C
ATOM	1820	O	MET	A	403	-72.597	63.543	11.639	1.00 28.00	O

[0168]

[Table 53]

ATOM	1821	CB	MET	A	403	-72.844	60.472	12.638	1.00	28.20	C
ATOM	1822	CG	MET	A	403	-73.860	59.483	13.161	1.00	31.77	C
ATOM	1823	SD	MET	A	403	-73.214	58.354	14.434	1.00	35.49	S
ATOM	1824	CE	MET	A	403	-73.028	59.555	15.771	1.00	31.96	C
ATOM	1825	N	ALA	A	404	-71.301	62.157	10.453	1.00	27.71	N
ATOM	1826	CA	ALA	A	404	-70.361	63.232	10.058	1.00	27.46	C
ATOM	1827	C	ALA	A	404	-71.032	64.242	9.088	1.00	25.78	C
ATOM	1828	O	ALA	A	404	-70.881	65.480	9.243	1.00	24.01	O
ATOM	1829	CB	ALA	A	404	-69.091	62.624	9.437	1.00	28.74	C
ATOM	1830	N	ASP	A	405	-71.760	63.728	8.080	1.00	27.41	N
ATOM	1831	CA	ASP	A	405	-72.509	64.591	7.159	1.00	28.82	C
ATOM	1832	C	ASP	A	405	-73.501	65.493	7.913	1.00	27.63	C
ATOM	1833	O	ASP	A	405	-73.618	66.675	7.576	1.00	23.81	O
ATOM	1834	CB	ASP	A	405	-73.290	63.818	6.102	1.00	30.66	C
ATOM	1835	CG	ASP	A	405	-72.432	62.877	5.308	1.00	34.80	C
ATOM	1836	OD1	ASP	A	405	-71.214	63.111	5.266	1.00	35.46	O
ATOM	1837	OD2	ASP	A	405	-72.998	61.904	4.729	1.00	36.84	O1-
ATOM	1838	N	LEU	A	406	-74.197	64.936	8.913	1.00	24.47	N
ATOM	1839	CA	LEU	A	406	-75.100	65.752	9.726	1.00	26.31	C
ATOM	1840	C	LEU	A	406	-74.418	66.918	10.481	1.00	27.81	C
ATOM	1841	O	LEU	A	406	-74.951	68.060	10.530	1.00	25.13	O
ATOM	1842	CB	LEU	A	406	-75.882	64.901	10.737	1.00	26.02	C
ATOM	1843	CG	LEU	A	406	-77.054	64.187	10.067	1.00	25.97	C
ATOM	1844	CD1	LEU	A	406	-77.586	63.066	10.943	1.00	27.40	C
ATOM	1845	CD2	LEU	A	406	-78.173	65.203	9.749	1.00	28.95	C
ATOM	1846	N	ARG	A	407	-73.284	66.625	11.096	1.00	28.99	N
ATOM	1847	CA	ARG	A	407	-72.489	67.682	11.750	1.00	31.04	C
ATOM	1848	C	ARG	A	407	-72.159	68.857	10.827	1.00	30.99	C
ATOM	1849	O	ARG	A	407	-72.317	70.029	11.207	1.00	27.68	O
ATOM	1850	CB	ARG	A	407	-71.190	67.134	12.303	1.00	34.80	C
ATOM	1851	CG	ARG	A	407	-70.461	68.197	13.129	1.00	43.33	C
ATOM	1852	CD	ARG	A	407	-69.122	67.691	13.542	1.00	51.25	C
ATOM	1853	NE	ARG	A	407	-69.321	66.561	14.439	1.00	57.12	N
ATOM	1854	CZ	ARG	A	407	-68.864	66.458	15.682	1.00	59.61	C
ATOM	1855	NH1	ARG	A	407	-68.124	67.403	16.249	1.00	64.83	N1+

[0169]

[Table 54]

ATOM	1856	NH2	ARG	A	407	-69.141	65.347	16.356	1.00 66.29	N
ATOM	1857	N	GLN	A	408	-71.786	68.527	9.588	1.00 31.95	N
ATOM	1858	CA	GLN	A	408	-71.521	69.528	8.578	1.00 33.21	C
ATOM	1859	C	GLN	A	408	-72.785	70.287	8.165	1.00 30.84	C
ATOM	1860	O	GLN	A	408	-72.720	71.491	8.021	1.00 28.93	O
ATOM	1861	CB	GLN	A	408	-70.844	68.919	7.329	1.00 31.28	C
ATOM	1862	CG	GLN	A	408	-70.323	69.898	6.269	1.00 39.38	C
ATOM	1863	CD	GLN	A	408	-69.468	71.054	6.819	1.00 48.21	C
ATOM	1864	NE2	GLN	A	408	-69.571	72.230	6.176	1.00 52.23	N
ATOM	1865	OE1	GLN	A	408	-68.721	70.902	7.792	1.00 54.34	O
ATOM	1866	N	LEU	A	409	-73.869	69.565	7.889	1.00 26.13	N
ATOM	1867	CA	LEU	A	409	-75.142	70.190	7.625	1.00 27.05	C
ATOM	1868	C	LEU	A	409	-75.568	71.182	8.693	1.00 24.72	C
ATOM	1869	O	LEU	A	409	-76.069	72.279	8.359	1.00 24.70	O
ATOM	1870	CB	LEU	A	409	-76.246	69.138	7.451	1.00 29.77	C
ATOM	1871	CG	LEU	A	409	-77.575	69.537	6.833	1.00 29.39	C
ATOM	1872	CD1	LEU	A	409	-77.431	69.753	5.317	1.00 31.31	C
ATOM	1873	CD2	LEU	A	409	-78.652	68.478	7.150	1.00 30.11	C
ATOM	1874	N	VAL	A	410	-75.394	70.812	9.964	1.00 22.17	N
ATOM	1875	CA	VAL	A	410	-75.784	71.666	11.009	1.00 22.63	C
ATOM	1876	C	VAL	A	410	-74.872	72.886	11.176	1.00 29.03	C
ATOM	1877	O	VAL	A	410	-75.337	74.043	11.498	1.00 24.83	O
ATOM	1878	CB	VAL	A	410	-75.967	70.878	12.348	1.00 24.73	C
ATOM	1879	CG1	VAL	A	410	-76.122	71.823	13.542	1.00 25.10	C
ATOM	1880	CG2	VAL	A	410	-77.207	69.957	12.230	1.00 23.96	C
ATOM	1881	N	THR	A	411	-73.577	72.668	10.993	1.00 28.16	N
ATOM	1882	CA	THR	A	411	-72.654	73.789	10.950	1.00 29.59	C
ATOM	1883	C	THR	A	411	-73.014	74.791	9.875	1.00 27.22	C
ATOM	1884	O	THR	A	411	-73.030	75.987	10.117	1.00 30.48	O
ATOM	1885	CB	THR	A	411	-71.186	73.265	10.750	1.00 32.40	C
ATOM	1886	CG2	THR	A	411	-70.210	74.386	10.803	1.00 30.16	C
ATOM	1887	OG1	THR	A	411	-70.894	72.374	11.832	1.00 33.61	O
ATOM	1888	N	GLU	A	412	-73.337	74.323	8.686	1.00 26.93	N
ATOM	1889	CA	GLU	A	412	-73.772	75.236	7.631	1.00 30.29	C
ATOM	1890	C	GLU	A	412	-75.121	75.933	8.006	1.00 31.12	C

[0170]

[Table 55]

ATOM	1891	O	GLU	A	412	-75.300	77.150	7.885	1.00 30.51	O
ATOM	1892	CB	GLU	A	412	-73.861	74.455	6.317	1.00 33.75	C
ATOM	1893	CG	GLU	A	412	-72.457	74.039	5.822	1.00 40.20	C
ATOM	1894	CD	GLU	A	412	-72.465	73.001	4.698	1.00 47.08	C
ATOM	1895	OE1	GLU	A	412	-73.554	72.617	4.233	1.00 54.41	O
ATOM	1896	OE2	GLU	A	412	-71.365	72.546	4.285	1.00 49.65	O1-
ATOM	1897	N	HIS	A	413	-76.047	75.148	8.528	1.00 29.49	N
ATOM	1898	CA	HIS	A	413	-77.315	75.699	8.977	1.00 26.39	C
ATOM	1899	C	HIS	A	413	-77.109	76.805	9.993	1.00 25.11	C
ATOM	1900	O	HIS	A	413	-77.722	77.876	9.860	1.00 26.38	O
ATOM	1901	CB	HIS	A	413	-78.188	74.580	9.560	1.00 23.12	C
ATOM	1902	CG	HIS	A	413	-79.522	75.046	9.984	1.00 23.11	C
ATOM	1903	CD2	HIS	A	413	-80.026	75.273	11.221	1.00 21.55	C
ATOM	1904	ND1	HIS	A	413	-80.532	75.312	9.089	1.00 24.68	N
ATOM	1905	CE1	HIS	A	413	-81.586	75.745	9.763	1.00 26.14	C
ATOM	1906	NE2	HIS	A	413	-81.315	75.686	11.064	1.00 22.15	N
ATOM	1907	N	ALA	A	414	-76.242	76.571	10.967	1.00 26.07	N
ATOM	1908	CA	ALA	A	414	-76.002	77.519	12.049	1.00 28.84	C
ATOM	1909	C	ALA	A	414	-75.500	78.868	11.514	1.00 35.11	C
ATOM	1910	O	ALA	A	414	-75.861	79.953	12.016	1.00 32.56	O
ATOM	1911	CB	ALA	A	414	-75.030	76.929	13.067	1.00 29.01	C
ATOM	1912	N	GLN	A	415	-74.678	78.794	10.483	1.00 36.20	N
ATOM	1913	CA	GLN	A	415	-74.135	79.967	9.872	1.00 37.44	C
ATOM	1914	C	GLN	A	415	-75.207	80.700	9.101	1.00 33.89	C
ATOM	1915	O	GLN	A	415	-75.237	81.917	9.156	1.00 31.76	O
ATOM	1916	CB	GLN	A	415	-72.961	79.619	8.942	1.00 42.32	C
ATOM	1917	CG	GLN	A	415	-71.739	79.097	9.696	1.00 48.89	C
ATOM	1918	CD	GLN	A	415	-70.750	78.337	8.794	1.00 53.99	C
ATOM	1919	NE2	GLN	A	415	-69.698	77.808	9.413	1.00 53.75	N
ATOM	1920	OE1	GLN	A	415	-70.929	78.224	7.568	1.00 52.41	O
ATOM	1921	N	MET	A	416	-76.017	79.984	8.320	1.00 33.05	N
ATOM	1922	CA	MET	A	416	-77.150	80.589	7.624	1.00 34.79	C
ATOM	1923	C	MET	A	416	-78.164	81.280	8.596	1.00 34.33	C
ATOM	1924	O	MET	A	416	-78.642	82.392	8.313	1.00 30.58	O
ATOM	1925	CB	MET	A	416	-77.845	79.572	6.747	1.00 32.26	C

[0171]

[Table 56]

ATOM	1926	CG	MET	A	416	-77.055	79.242	5.502	1.00	40.07	C
ATOM	1927	SD	MET	A	416	-77.961	78.233	4.300	1.00	43.33	S
ATOM	1928	CE	MET	A	416	-77.903	76.610	5.083	1.00	44.36	C
ATOM	1929	N	MET	A	417	-78.450	80.622	9.731	1.00	35.67	N
ATOM	1930	CA	MET	A	417	-79.346	81.182	10.760	1.00	35.07	C
ATOM	1931	C	MET	A	417	-78.753	82.490	11.291	1.00	40.63	C
ATOM	1932	O	MET	A	417	-79.468	83.481	11.416	1.00	32.87	O
ATOM	1933	CB	MET	A	417	-79.635	80.196	11.909	1.00	30.27	C
ATOM	1934	CG	MET	A	417	-80.411	78.925	11.468	1.00	29.12	C
ATOM	1935	SD	MET	A	417	-82.097	79.317	10.974	1.00	27.51	S
ATOM	1936	CE	MET	A	417	-82.697	79.803	12.592	1.00	26.14	C
ATOM	1937	N	GLN	A	418	-77.453	82.501	11.554	1.00	40.22	N
ATOM	1938	CA	GLN	A	418	-76.812	83.728	12.067	1.00	46.89	C
ATOM	1939	C	GLN	A	418	-76.914	84.889	11.083	1.00	40.56	C
ATOM	1940	O	GLN	A	418	-77.210	85.995	11.502	1.00	38.88	O
ATOM	1941	CB	GLN	A	418	-75.360	83.513	12.493	1.00	51.33	C
ATOM	1942	CG	GLN	A	418	-74.894	84.615	13.454	1.00	64.12	C
ATOM	1943	CD	GLN	A	418	-75.706	84.655	14.761	1.00	75.41	C
ATOM	1944	NE2	GLN	A	418	-75.754	83.512	15.479	1.00	70.14	N
ATOM	1945	OE1	GLN	A	418	-76.304	85.695	15.106	1.00	82.82	O
ATOM	1946	N	ARG	A	419	-76.759	84.623	9.787	1.00	37.57	N
ATOM	1947	CA	ARG	A	419	-77.018	85.608	8.785	1.00	39.41	C
ATOM	1948	C	ARG	A	419	-78.448	86.137	8.731	1.00	42.52	C
ATOM	1949	O	ARG	A	419	-78.655	87.349	8.509	1.00	40.64	O
ATOM	1950	CB	ARG	A	419	-76.605	85.094	7.406	1.00	49.15	C
ATOM	1951	CG	ARG	A	419	-75.085	85.231	7.162	1.00	63.02	C
ATOM	1952	CD	ARG	A	419	-74.635	85.012	5.704	1.00	68.99	C
ATOM	1953	NE	ARG	A	419	-75.476	85.695	4.694	1.00	77.28	N
ATOM	1954	CZ	ARG	A	419	-75.563	87.019	4.484	1.00	74.70	C
ATOM	1955	NH1	ARG	A	419	-74.881	87.905	5.217	1.00	80.67	N1+
ATOM	1956	NH2	ARG	A	419	-76.366	87.471	3.525	1.00	75.19	N
ATOM	1957	N	ILE	A	420	-79.434	85.244	8.893	1.00	37.33	N
ATOM	1958	CA	ILE	A	420	-80.842	85.642	8.903	1.00	35.66	C
ATOM	1959	C	ILE	A	420	-81.054	86.502	10.131	1.00	36.93	C
ATOM	1960	O	ILE	A	420	-81.709	87.557	10.052	1.00	36.22	O

[0172]

[Table 57]

ATOM	1961	CB	ILE	A	420	-81.817	84.419	8.864	1.00	36.90	C
ATOM	1962	CG1	ILE	A	420	-81.766	83.780	7.454	1.00	35.07	C
ATOM	1963	CG2	ILE	A	420	-83.271	84.828	9.183	1.00	36.40	C
ATOM	1964	CD1	ILE	A	420	-82.362	82.379	7.393	1.00	38.25	C
ATOM	1965	N	LYS	A	421	-80.500	86.084	11.257	1.00	39.35	N
ATOM	1966	CA	LYS	A	421	-80.686	86.883	12.457	1.00	47.01	C
ATOM	1967	C	LYS	A	421	-80.216	88.337	12.251	1.00	50.25	C
ATOM	1968	O	LYS	A	421	-80.980	89.261	12.521	1.00	48.27	O
ATOM	1969	CB	LYS	A	421	-80.004	86.250	13.646	1.00	53.66	C
ATOM	1970	CG	LYS	A	421	-80.390	86.947	14.932	1.00	58.38	C
ATOM	1971	CD	LYS	A	421	-80.467	86.006	16.116	1.00	60.16	C
ATOM	1972	CE	LYS	A	421	-80.092	86.751	17.394	1.00	65.92	C
ATOM	1973	NZ	LYS	A	421	-78.606	86.913	17.398	1.00	65.71	N1+
ATOM	1974	N	LYS	A	422	-79.024	88.544	11.676	1.00	53.97	N
ATOM	1975	CA	LYS	A	422	-78.508	89.921	11.459	1.00	56.84	C
ATOM	1976	C	LYS	A	422	-79.177	90.701	10.334	1.00	49.14	C
ATOM	1977	O	LYS	A	422	-79.312	91.903	10.452	1.00	48.85	O
ATOM	1978	CB	LYS	A	422	-76.969	89.965	11.349	1.00	57.20	C
ATOM	1979	CG	LYS	A	422	-76.376	89.343	12.601	1.00	67.73	C
ATOM	1980	CD	LYS	A	422	-74.963	89.745	12.960	1.00	72.93	C
ATOM	1981	CE	LYS	A	422	-74.532	88.920	14.175	1.00	72.23	C
ATOM	1982	NZ	LYS	A	422	-73.070	88.994	14.433	1.00	76.51	N1+
ATOM	1983	N	THR	A	423	-79.635	90.046	9.281	1.00	41.52	N
ATOM	1984	CA	THR	A	423	-80.119	90.778	8.131	1.00	38.98	C
ATOM	1985	C	THR	A	423	-81.668	90.835	7.934	1.00	41.51	C
ATOM	1986	O	THR	A	423	-82.165	91.703	7.203	1.00	44.20	O
ATOM	1987	CB	THR	A	423	-79.503	90.197	6.860	1.00	43.81	C
ATOM	1988	CG2	THR	A	423	-77.959	90.314	6.900	1.00	44.09	C
ATOM	1989	OG1	THR	A	423	-79.886	88.814	6.752	1.00	46.10	O
ATOM	1990	N	GLU	A	424	-82.420	89.900	8.507	1.00	37.39	N
ATOM	1991	CA	GLU	A	424	-83.872	89.821	8.284	1.00	37.32	C
ATOM	1992	C	GLU	A	424	-84.493	90.382	9.554	1.00	38.93	C
ATOM	1993	O	GLU	A	424	-84.763	89.637	10.487	1.00	35.52	O
ATOM	1994	CB	GLU	A	424	-84.304	88.367	8.089	1.00	38.32	C
ATOM	1995	CG	GLU	A	424	-83.875	87.720	6.807	1.00	36.39	C

[0173]

[Table 58]

ATOM	1996	CD	GLU	A	424	-84.428	88.447	5.617	1.00	42.27	C
ATOM	1997	OE1	GLU	A	424	-85.530	89.054	5.688	1.00	44.21	O
ATOM	1998	OE2	GLU	A	424	-83.755	88.429	4.584	1.00	42.57	O1-
ATOM	1999	N	THR	A	425	-84.735	91.692	9.557	1.00	33.28	N
ATOM	2000	CA	THR	A	425	-85.046	92.404	10.771	1.00	36.06	C
ATOM	2001	C	THR	A	425	-86.535	92.273	11.058	1.00	33.78	C
ATOM	2002	O	THR	A	425	-86.962	92.617	12.140	1.00	35.79	O
ATOM	2003	CB	THR	A	425	-84.693	93.888	10.667	1.00	36.18	C
ATOM	2004	CG2	THR	A	425	-83.180	94.077	10.557	1.00	45.18	C
ATOM	2005	OG1	THR	A	425	-85.263	94.412	9.484	1.00	40.54	O
ATOM	2006	N	GLU	A	426	-87.308	91.740	10.111	1.00	28.03	N
ATOM	2007	CA	GLU	A	426	-88.702	91.358	10.401	1.00	28.81	C
ATOM	2008	C	GLU	A	426	-88.887	89.927	10.908	1.00	26.50	C
ATOM	2009	O	GLU	A	426	-90.049	89.498	11.134	1.00	27.64	O
ATOM	2010	CB	GLU	A	426	-89.590	91.676	9.178	1.00	31.39	C
ATOM	2011	CG	GLU	A	426	-89.490	93.134	8.729	1.00	37.17	C
ATOM	2012	CD	GLU	A	426	-90.436	93.456	7.573	1.00	41.18	C
ATOM	2013	OE1	GLU	A	426	-91.004	92.520	6.968	1.00	43.10	O
ATOM	2014	OE2	GLU	A	426	-90.593	94.641	7.289	1.00	48.02	O1-
ATOM	2015	N	THR	A	427	-87.789	89.211	11.198	1.00	24.14	N
ATOM	2016	CA	THR	A	427	-87.833	87.855	11.789	1.00	25.42	C
ATOM	2017	C	THR	A	427	-87.072	87.891	13.119	1.00	27.29	C
ATOM	2018	O	THR	A	427	-86.379	88.852	13.372	1.00	25.89	O
ATOM	2019	CB	THR	A	427	-87.213	86.806	10.872	1.00	28.91	C
ATOM	2020	CG2	THR	A	427	-87.688	86.976	9.496	1.00	27.62	C
ATOM	2021	OG1	THR	A	427	-85.779	86.911	10.853	1.00	32.19	O
ATOM	2022	N	SER	A	428	-87.350	86.932	13.984	1.00	23.04	N
ATOM	2023	CA	SER	A	428	-86.653	86.655	15.246	1.00	24.42	C
ATOM	2024	C	SER	A	428	-86.608	85.144	15.357	1.00	25.83	C
ATOM	2025	O	SER	A	428	-87.149	84.387	14.451	1.00	24.95	O
ATOM	2026	CB	SER	A	428	-87.386	87.236	16.455	1.00	25.64	C
ATOM	2027	OG	SER	A	428	-87.487	88.641	16.271	1.00	33.94	O
ATOM	2028	N	LEU	A	429	-85.989	84.713	16.445	1.00	25.40	N
ATOM	2029	CA	LEU	A	429	-86.058	83.357	16.904	1.00	27.19	C
ATOM	2030	C	LEU	A	429	-86.785	83.184	18.183	1.00	28.22	C

[0174]

[Table 59]

ATOM	2031	O	LEU	A	429	-86.598	83.980	19.109	1.00	24.64	O
ATOM	2032	CB	LEU	A	429	-84.623	82.866	17.131	1.00	30.15	C
ATOM	2033	CG	LEU	A	429	-83.726	82.738	15.906	1.00	34.00	C
ATOM	2034	CD1	LEU	A	429	-82.352	82.206	16.315	1.00	37.07	C
ATOM	2035	CD2	LEU	A	429	-84.371	81.744	14.985	1.00	33.70	C
ATOM	2036	N	HIS	A	430	-87.474	82.032	18.293	1.00	25.38	N
ATOM	2037	CA	HIS	A	430	-88.078	81.564	19.523	1.00	25.37	C
ATOM	2038	C	HIS	A	430	-86.980	81.514	20.600	1.00	24.20	C
ATOM	2039	O	HIS	A	430	-85.832	81.192	20.289	1.00	24.18	O
ATOM	2040	CB	HIS	A	430	-88.690	80.175	19.316	1.00	25.72	C
ATOM	2041	CG	HIS	A	430	-89.483	79.668	20.470	1.00	26.51	C
ATOM	2042	CD2	HIS	A	430	-90.822	79.599	20.670	1.00	31.13	C
ATOM	2043	ND1	HIS	A	430	-88.898	79.140	21.608	1.00	24.62	N
ATOM	2044	CE1	HIS	A	430	-89.825	78.789	22.472	1.00	28.44	C
ATOM	2045	NE2	HIS	A	430	-91.012	79.072	21.942	1.00	30.35	N
ATOM	2046	N	PRO	A	431	-87.316	81.822	21.852	1.00	24.22	N
ATOM	2047	CA	PRO	A	431	-86.234	81.861	22.871	1.00	26.27	C
ATOM	2048	C	PRO	A	431	-85.456	80.546	23.072	1.00	24.41	C
ATOM	2049	O	PRO	A	431	-84.279	80.571	23.389	1.00	24.67	O
ATOM	2050	CB	PRO	A	431	-86.953	82.253	24.184	1.00	28.01	C
ATOM	2051	CG	PRO	A	431	-88.387	82.417	23.844	1.00	30.68	C
ATOM	2052	CD	PRO	A	431	-88.625	82.247	22.383	1.00	26.76	C
ATOM	2053	N	LEU	A	432	-86.122	79.389	22.943	1.00	24.66	N
ATOM	2054	CA	LEU	A	432	-85.424	78.157	23.006	1.00	24.56	C
ATOM	2055	C	LEU	A	432	-84.352	78.015	21.919	1.00	26.38	C
ATOM	2056	O	LEU	A	432	-83.231	77.514	22.186	1.00	24.65	O
ATOM	2057	CB	LEU	A	432	-86.395	76.988	22.951	1.00	26.50	C
ATOM	2058	CG	LEU	A	432	-85.756	75.588	22.999	1.00	30.72	C
ATOM	2059	CD1	LEU	A	432	-84.950	75.447	24.293	1.00	30.92	C
ATOM	2060	CD2	LEU	A	432	-86.847	74.513	22.889	1.00	33.22	C
ATOM	2061	N	LEU	A	433	-84.705	78.404	20.682	1.00	23.00	N
ATOM	2062	CA	LEU	A	433	-83.713	78.388	19.597	1.00	23.15	C
ATOM	2063	C	LEU	A	433	-82.637	79.414	19.830	1.00	24.87	C
ATOM	2064	O	LEU	A	433	-81.473	79.173	19.541	1.00	23.68	O
ATOM	2065	CB	LEU	A	433	-84.396	78.595	18.221	1.00	23.49	C

[0175]

[Table 60]

ATOM	2066	CG	LEU	A	433	-85.464	77.588	17.854	1.00 22.17	C
ATOM	2067	CD1	LEU	A	433	-86.067	77.876	16.457	1.00 25.22	C
ATOM	2068	CD2	LEU	A	433	-84.916	76.155	17.851	1.00 24.45	C
ATOM	2069	N	GLN	A	434	-83.013	80.573	20.372	1.00 27.89	N
ATOM	2070	CA	GLN	A	434	-82.031	81.542	20.744	1.00 30.08	C
ATOM	2071	C	GLN	A	434	-80.977	80.942	21.626	1.00 31.49	C
ATOM	2072	O	GLN	A	434	-79.800	81.173	21.411	1.00 27.37	O
ATOM	2073	CB	GLN	A	434	-82.648	82.731	21.472	1.00 35.38	C
ATOM	2074	CG	GLN	A	434	-83.253	83.747	20.529	1.00 43.02	C
ATOM	2075	CD	GLN	A	434	-83.772	84.985	21.253	1.00 45.98	C
ATOM	2076	NE2	GLN	A	434	-84.840	85.550	20.753	1.00 37.28	N
ATOM	2077	OE1	GLN	A	434	-83.205	85.419	22.238	1.00 52.64	O
ATOM	2078	N	GLU	A	435	-81.424	80.218	22.644	1.00 30.28	N
ATOM	2079	CA	GLU	A	435	-80.540	79.620	23.629	1.00 33.08	C
ATOM	2080	C	GLU	A	435	-79.659	78.568	22.944	1.00 29.56	C
ATOM	2081	O	GLU	A	435	-78.475	78.487	23.218	1.00 31.31	O
ATOM	2082	CB	GLU	A	435	-81.375	78.991	24.792	1.00 32.24	C
ATOM	2083	CG	GLU	A	435	-80.552	78.283	25.851	1.00 37.81	C
ATOM	2084	CD	GLU	A	435	-81.439	77.735	26.964	1.00 39.56	C
ATOM	2085	OE1	GLU	A	435	-82.154	78.550	27.599	1.00 33.75	O
ATOM	2086	OE2	GLU	A	435	-81.478	76.482	27.161	1.00 37.57	O1-
ATOM	2087	N	ILE	A	436	-80.221	77.763	22.054	1.00 27.00	N
ATOM	2088	CA	ILE	A	436	-79.421	76.759	21.383	1.00 28.05	C
ATOM	2089	C	ILE	A	436	-78.345	77.415	20.476	1.00 28.60	C
ATOM	2090	O	ILE	A	436	-77.173	77.000	20.504	1.00 28.23	O
ATOM	2091	CB	ILE	A	436	-80.308	75.755	20.610	1.00 29.27	C
ATOM	2092	CG1	ILE	A	436	-81.154	74.945	21.616	1.00 29.22	C
ATOM	2093	CG2	ILE	A	436	-79.510	74.905	19.624	1.00 26.42	C
ATOM	2094	CD1	ILE	A	436	-82.322	74.256	20.982	1.00 32.89	C
ATOM	2095	N	TYR	A	437	-78.719	78.424	19.689	1.00 28.08	N
ATOM	2096	CA	TYR	A	437	-77.777	79.039	18.763	1.00 29.60	C
ATOM	2097	C	TYR	A	437	-76.717	79.960	19.410	1.00 33.35	C
ATOM	2098	O	TYR	A	437	-75.689	80.254	18.821	1.00 36.32	O
ATOM	2099	CB	TYR	A	437	-78.521	79.786	17.623	1.00 31.05	C
ATOM	2100	CG	TYR	A	437	-79.132	78.814	16.679	1.00 29.90	C

[0176]

[Table 61]

```
ATOM   2101  CD1 TYR A 437     -78.312  77.953  15.952  1.00 30.45           C
ATOM   2102  CD2 TYR A 437     -80.519  78.674  16.550  1.00 33.02           C
ATOM   2103  CE1 TYR A 437     -78.835  76.957  15.136  1.00 31.07           C
ATOM   2104  CE2 TYR A 437     -81.040  77.728  15.673  1.00 32.36           C
ATOM   2105  CZ  TYR A 437     -80.174  76.885  14.959  1.00 33.29           C
ATOM   2106  OH  TYR A 437     -80.617  75.894  14.108  1.00 30.56           O
ATOM   2107  N   LYS A 438     -77.000  80.453  20.600  1.00 37.60           N
ATOM   2108  CA  LYS A 438     -76.123  81.401  21.251  1.00 39.75           C
ATOM   2109  C   LYS A 438     -74.796  80.720  21.465  1.00 38.00           C
ATOM   2110  O   LYS A 438     -74.729  79.623  22.071  1.00 38.03           O
ATOM   2111  CB  LYS A 438     -76.718  81.793  22.612  1.00 42.46           C
ATOM   2112  CG  LYS A 438     -76.254  83.122  23.159  1.00 51.86           C
ATOM   2113  CD  LYS A 438     -77.234  83.525  24.268  1.00 58.95           C
ATOM   2114  CE  LYS A 438     -76.733  84.712  25.064  1.00 65.81           C
ATOM   2115  NZ  LYS A 438     -75.394  84.406  25.647  1.00 62.26           N1+
ATOM   2116  N   ASP A 439     -73.742  81.365  21.029  1.00 44.04           N
ATOM   2117  CA  ASP A 439     -72.388  80.934  21.395  1.00 49.58           C
ATOM   2118  C   ASP A 439     -72.078  79.534  20.870  1.00 55.28           C
ATOM   2119  O   ASP A 439     -71.323  78.795  21.499  1.00 64.49           O
ATOM   2120  CB  ASP A 439     -72.187  80.982  22.951  1.00 49.50           C
ATOM   2121  CG  ASP A 439     -72.214  82.378  23.502  1.00 51.51           C
ATOM   2122  OD1 ASP A 439     -71.786  83.305  22.792  1.00 54.56           O
ATOM   2123  OD2 ASP A 439     -72.655  82.568  24.654  1.00 55.70           O1-
ATOM   2124  N   MET A 440     -72.638  79.198  19.708  1.00 56.46           N
ATOM   2125  CA  MET A 440     -72.558  77.857  19.135  1.00 59.32           C
ATOM   2126  C   MET A 440     -71.533  77.799  17.991  1.00 60.65           C
ATOM   2127  O   MET A 440     -70.714  78.708  17.818  1.00 75.07           O
ATOM   2128  CB  MET A 440     -73.951  77.429  18.628  1.00 54.21           C
ATOM   2129  CG  MET A 440     -73.981  75.993  18.131  1.00 57.89           C
ATOM   2130  SD  MET A 440     -75.366  75.444  17.097  1.00 44.85           S
ATOM   2131  CE  MET A 440     -76.330  74.727  18.421  1.00 46.57           C
TER    2132      MET A 440
HETATM 2133  C01 MF8 C 181     -85.170  73.923  10.756  1.00 52.79      A    C
HETATM 2134  N02 MF8 C 181     -85.289  75.323  10.348  1.00 42.65      A    N
HETATM 2135  C03 MF8 C 181     -85.285  75.440   8.852  1.00 40.00      A    C
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[0177]

[Table 62]

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HETATM 2136  C04 MF8 C 181     -85.397  76.452  11.325  1.00 34.99      A    C
HETATM 2137  N05 MF8 C 181     -85.502  77.620  10.870  1.00 55.93      A    N
HETATM 2138  N06 MF8 C 181     -85.440  76.490  12.785  1.00 35.76      A    N
HETATM 2139  C07 MF8 C 181     -84.265  76.024  13.505  1.00 28.27      A    C
HETATM 2140  N08 MF8 C 181     -83.041  76.223  13.080  1.00 28.33      A    N
HETATM 2141  N09 MF8 C 181     -84.537  75.301  14.632  1.00 23.77      A    N
HETATM 2142  C01 LIG E   2     -94.683  67.061  -9.236  1.00 65.08      A    C
HETATM 2143  C02 LIG E   2     -95.038  68.145  -8.216  1.00 68.98      A    C
HETATM 2144  C03 LIG E   2     -94.468  67.851  -6.824  1.00 72.22      A    C
HETATM 2145  C04 LIG E   2     -95.527  67.671  -5.740  1.00 74.19      A    C
HETATM 2146  C05 LIG E   2     -96.313  66.354  -5.786  1.00 72.54      A    C
HETATM 2147  C06 LIG E   2     -97.830  66.572  -5.923  1.00 76.99      A    C
HETATM 2148  C07 LIG E   2     -98.580  66.325  -4.598  1.00 76.58      A    C
HETATM 2149  O08 LIG E   2     -98.974  64.973  -4.421  1.00 82.85      A    O
HETATM 2150  C09 LIG E   2     -98.344  64.301  -3.373  1.00 82.20      A    C
HETATM 2151  O10 LIG E   2     -97.243  63.407  -3.921  1.00 89.30      A    O
HETATM 2152  C11 LIG E   2     -96.605  62.459  -2.968  1.00 79.70      A    C
HETATM 2153  C12 LIG E   2     -95.845  61.429  -3.751  1.00 76.49      A    C
HETATM 2154  O13 LIG E   2     -94.981  62.130  -4.602  1.00 76.49      A    O
HETATM 2155  C14 LIG E   2     -97.626  61.796  -2.015  1.00 77.56      A    C
HETATM 2156  O15 LIG E   2     -96.896  61.145  -0.986  1.00 92.84      A    O
HETATM 2157  C16 LIG E   2     -98.445  62.865  -1.374  1.00 69.52      A    C
HETATM 2158  O17 LIG E   2     -99.200  62.390  -0.206  1.00 62.74      A    O
HETATM 2159  C18 LIG E   2     -99.279  63.567  -2.369  1.00 68.74      A    C
HETATM 2160  O19 LIG E   2    -100.097  64.494  -1.626  1.00 68.99      A    O
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[0178]

[Table 63]

```
CONECT 2133 2134
CONECT 2134 2133 2135 2136
CONECT 2135 2134
CONECT 2136 2134 2137 2138
CONECT 2137 2136
CONECT 2138 2136 2139
CONECT 2139 2138 2140 2141
CONECT 2140 2139
CONECT 2141 2139
CONECT 2142 2143
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CONECT 2145 2144 2146
CONECT 2146 2145 2147
CONECT 2147 2146 2148
CONECT 2148 2147 2149
CONECT 2149 2148 2150
CONECT 2150 2149 2151 2159
CONECT 2151 2150 2152
CONECT 2152 2151 2153 2155
CONECT 2153 2152 2154
CONECT 2154 2153
CONECT 2155 2152 2156 2157
CONECT 2156 2155
CONECT 2157 2155 2158 2159
CONECT 2158 2157
CONECT 2159 2150 2157 2160
CONECT 2160 2159
END
```

[0179]

[Example 6]

A final exercise tolerance test was performed in mice to verify whether metformin could improve exercise tolerance.

[0180]

Metformin was administered by intraperitoneal injection of metformin/PBS

solution (solution of metformin dissolved in PBS) so that the dose of metformin per body weight of mice was 25 mg/kg. For the metformin-non-administered group, an equal volume of PBS was intraperitoneally administered instead of the metformin/PBS solution.

[0181]

The training for the final exercise tolerance test, in which the speed at start was 15 m/min and increased by 1 m/min every 10 minutes, and the running time after the speed reached 20 m/min was 10 minutes (1 hour in total), was performed 5 times a week for a total of 4 weeks using a treadmill device. Metformin administration was performed at 10 pm each time, and the training was performed by a protocol starting 12 hours later (10 am).

[0182]

First, twenty 10-week-old male C57BL/6 mice were divided into 4 groups (5 mice per group). Among these 4 groups, for one group, neither training nor metformin administration was performed (hereinafter, referred to as "control group"), for another group, only training was performed without metformin administration (hereinafter, referred to as "training group"), for another group, only metformin administration was performed without training (hereinafter, referred to as "metformin administration group"), and for the remaining group, both metformin administration and training were performed (hereinafter, referred to as "training + metformin administration group"). In addition, in order to average the motivation for exercise and exercise preference of individual mice in each group, the first exercise tolerance test was performed after training acclimatization to rank the mice, and the mice were divided into 4 groups so that the test results were even. Furthermore, in the test after the training period, the exercise tolerance was evaluated in such a manner that the running time was set as the time until the number of electrode contacts during the test reached 50 (number of shocks: NOS50), the speed at the start was

set as 15 m/min and increased by 1 m/min every 10 minutes, and when the speed reached the maximum speed of 30 m/min, the running at the maximum speed was performed until NOS50 was reached.

[0183]

FIG. 19 shows the measurement results of the number of shocks (NOS) in each elapsed time from the start of training in each group. FIG. 19A shows the results of the control group ("cont" in the figure) and the metformin administration group ("met" in the figure), and FIG. 19B shows the results of the training group ("cont + train" in the figure) and the results of the training + metformin administration group ("met + train" in the figure). As shown in FIG. 19 (A), the metformin administration group did not show an improvement in exercise tolerance as compared with the control group, and showed a slight decreasing tendency. On the other hand, as shown in FIG. 19 (B), the training + metformin administration group showed higher exercise tolerance than the training group. From these results, it was found that metformin alone does improve exercise tolerance, but the combination of metformin administration and training improves exercise tolerance.

[0184]

[Example 7]

A new PPARδ activator was searched for using the structure data of the co-crystal of metformin/PPARδ.

[0185]

Specifically, guanidine derivatives or biguanidine derivatives capable of fitting within the ligand binding pocket similar to metformin were searched for by performing a docking mode analysis between metformin and PPARδ based on the structure data of the co-crystal of metformin/PPARδ and performing a docking mode prediction calculation considering the solvent effects for known guanidine derivatives and biguanidine

derivatives. In the prediction, the binding free energy was calculated based on the thermodynamic cycle, and the accuracy was improved by using a trajectory of molecular dynamics calculation (MM-PBSA: Molecular Mechanic/Poisson Boltzmann Surface Area, MM-GBSA: Molecular Mechanic/Generalized Born Surface Area).

[0186]

As shown in FIG. 20, the guanidino group of metformin interacts with and binds to an amino acid residue in the ligand binding pocket of hPPARδ (Tyr437, Leu433, Met417, His287, Thr253, Grn250, Ph246 are shown in the figure). His413 is not shown because it is located in front of the drawing. In addition, as a result of calculation of molecular dynamics, it was found that the guanidino group of metformin can interact with amino acid residues more than the amino acid residues shown in FIG. 2 depending on the solvent conditions and the like. The energy of interaction with each amino acid was calculated and the results of comparison with GW501516 and GW0742 (CAS No.: 317318-84-6) among the GW medicines which are known as PPARδ synthetic agonists are shown in FIG. 21. As shown in FIG. 21, similar to GW agonists, metformin can bind to the seven amino acid residues in the ligand binding pocket of hPPARδ with the illustrated binding energy. In particular, the binding energies with Met417 and Ph246 were apparently higher in metformin than in GW agonists. This indicates that metformin is more stably immobilized at the entrance of the ligand-binding pocket, has higher tilting-down activity of helix-12, and has higher activity as an agonist than GW agonists.

[0187].

By the docking mode analysis, compounds having a guanidino group or a biguanidino group at the molecular end were selected in which the entire molecule entered into the ligand binding pocket of hPPARδ in a state where the guanidino group and the like form hydrogen bonds with His413, His287, Thr253 and Tyr437 of hPPARδ. The

selected compounds are candidate compounds for the PPARδ activator.

[0188]

[Example 8]

Among the compounds (1-1-4), the effects of compound (B-1), compound (B-2), and compound (B-3) on the transcriptional regulation of PPARδ were investigated. The effects on the transcriptional activity of PPARδ were measured by performing a luciferase assay on the cells treated with 10 μM of each compound dissolved in DMSO.

[0189]

Specifically, CV1 cells, which are cultured cells derived from African green monkey kidneys, were seeded on a 24-well plate (1 × 105 cells/well) and cultured until they became 70% confluent. DMEM containing 10% fetal bovine serum and 1% antibiotic was used as the culture medium. After reaching the desired cell density, the entire medium was removed, and a mixture obtained by mixing 2 μL of MH2004 (plasmid encoding a firefly luciferase gene having a Gal4 activation sequence upstream: 100 ng/μL), 1 μL of pRL-CMV (plasmid encoding the *Renilla reniformis* luciferase gene directly under the CMV promoter: 100 ng/μL), 2 μL of GAL4-Ppard (plasmid encoding Gal4-DNA binding region fused with PPARδ gene: 100 ng/μL) and 1.5 μL of PEI (polyethylenimine: manufactured by Invitrogen) with 45 μL culture medium "Opti-MEM" (registered trademark) (manufactured by Thermo Fisher Scientific) was added to each well, and the cells were cultured for about 36 hours. Then, the entire medium was replaced with a medium containing a test substance to be examined for the transcriptional activation ability of PPARδ such as metformin, and then cultured for 12 hours.

[0190]

Then, the collected cells were lysed in a cell lysis buffer, suspended with a luminescent substrate (firefly luciferin), and the luminescence of the suspension was

measured with a luminometer. In addition, the remaining suspension was mixed with Renilla luciferin and the amount of luminescence was measured with a luminometer. The result of the amount of light emitted by Renilla luciferin was used as the intrinsic control of gene transfer. Finally, the amount of luminescence of firefly luciferin was calculated as a light emission intensity (RLU) by dividing by the amount of luminescence of Renilla luciferin.

[0191]

The results of the luciferase assay (n = 3) are shown in Table 64. The relative emission intensity of the reaction solution treated with each compound was determined as the transcriptional activation ability of PPARδ in each compound treatment, where the light emission intensity of the reaction solution to which an equal amount of DMSO was added (control) was defined as 1. The relative emission intensities were all 1.1 or more in the reaction solutions to which the compounds were added, and the transcriptional activity of PPARδ was increased. From this result, it was found that these compounds can be PPARδ activators.

[0192]

[Table 64]

	Light emission intensity (RLU)		Relative emission intensity	
Compound	Average	SD	Average	SD
No addition	223550	-	1.00	-
B-1	250467	6573	1.12	0.03
B-2	265600	1652	1.19	0.01
B-3	457033	10308	2.04	0.05

[0193]

[Example 9]

Among the compounds (1-1-2), compound (A-4) (1-{4-[({2-[3-fluoro-4-(trifluoromethyl) phenyl] 4-methylthiazole-5-yl} methyl) thio] -2-methylbenzyl} guanidine) was synthesized and its effect on the transcriptional regulation of PPARδ was

investigated.

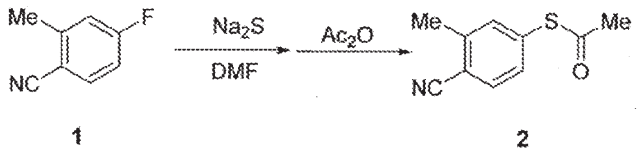
[0194]

<Synthesis of compound (A-4)>

(1) Synthesis of S-(4-cyano-3-methylphenyl) ethanethioate

[0195]

[Chemical formula 14]



1 2

[0196]

Na_2S (5.08 g, 65.1 mmol) was added at once to a solution obtained by dissolving 4-fluoro-2-methylbenzonitrile (CAS No.: 147754-12-9, Compound 1) (8 g, 59.2 mmol) in DMF (9 mL) at room temperature and in a nitrogen atmosphere. The reaction mixture was stirred overnight. The resulting mixture was cooled to 0°C, acetic anhydride (9 mL) was added dropwise, and the mixture was then stirred at room temperature for 1 hour. Subsequently, ethyl acetate (100 mL) and water (30 mL) were added to the mixture. The entire amount was layer-separated, and the organic layer was washed with saturated brine (30 mL×2) and then dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (silica gel, eluted with 3% to 40% ethyl acetate in hexane) to obtain the above compound (1.4 g, 12.4% yield) as a brown oil.

[0197]

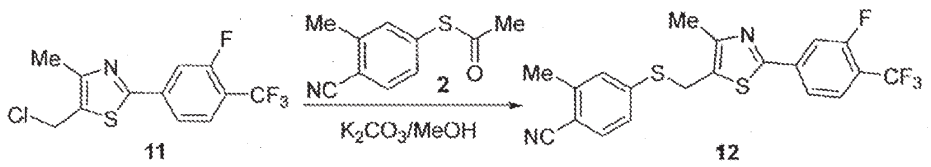
^1H NMR (400MHz, $CDCl_3$) δ 7.62 (d, J = 8.0Hz, 1H), 7.39 (s, 1H), 7.33 (dd, J = 8.0, 1.1Hz, 1H), 2.56 (s, 3H), 2.45 (s, 3H).

[0198]

(2) Synthesis of 4-[({2-[3-fluoro-4-(trifluoromethyl) phenyl]-4-methylthiazole-5-yl} methyl) thio]-2-methylbenzonitrile

[0199]

[Chemical formula 15]



[0200]

A mixture of 5-(chloromethyl)-2-[3-fluoro-4- (trifluoromethyl) phenyl]-4-methylthiazole (CAS No. 317319-33-8, US Patent Publication 2003/0203947A1, Compound 11) (2.23 g, 7.22 mmol), S-(4-cyano-3-methylphenyl) ethanethioate (Compound 2) (1.38 g, 7.22 mmol) and a solution obtained by dissolving potassium carbonate (1.22 g, 8.66 mmol) in methanol (20 mL) was stirred at room temperature for 1 hour. The resulting mixture was filtered under vacuum and the filter cake was collected and dissolved in dichloromethane (200 mL). The obtained organic matter was washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the above compound (1.8 g, yield 59.1%) as a white solid.

[0201]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 13.8, 9.8 Hz, 2H), 7.67-7.61 (m, 1H), 7.51 (d, J = 8.1Hz, 1H), 7.22 (s, 1H), 7.17 (d, J = 8.2Hz, 1H), 4.32 (s, 2H), 2.51 (s, 3H), 2.43 (s, 3H).

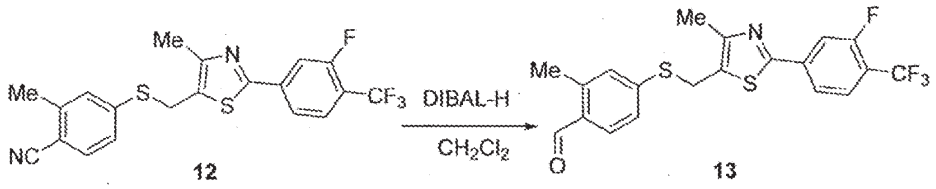
MS-ESI (m/z) 423.1 $[M + H]^+$.

[0202]

(3) Synthesis of 4-[({2-[3-fluoro-4-(trifluoromethyl) phenyl]-4-methylthiazole-5-yl} methyl) thio]-2-methylbenzaldehyde

[0203]

[Chemical formula 16]



[0204]

DIBAL-H (1.5 M toluene solution, 4.69 mL, 7.04 mmol) was added dropwise to a solution obtained by dissolving 4-[({2-[3-fluoro-4-(trifluoromethyl) phenyl]-4-methylthiazole-5-yl} methyl) thio]-2-methylbenzonitrile (Compound 12) (1.98 g, 4.69 mmol) in dichloromethane (20 mL) at 0°C. The obtained reaction mixture was stirred at 0°C for 1 hour and then quenched with 10% hydrochloric acid (34 mL). The resulting mixture was vigorously stirred for 30 minutes. The resulting mixture was then treated with 20% sodium potassium tartrate (34 mL) and the resulting mixture was vigorously stirred for an additional 30 minutes. The reaction mixture was basified to pH 9 with 15% sodium hydroxide and then extracted with dichloromethane (60 mL×3). All the obtained organic layers were combined, washed with brine (40 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluted with 2% to 10% ethyl acetate in hexane) to obtain the above compound (1.28 g, yield 64.0%) as a pale yellow solid.

[0205]

^{1}H NMR (400MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.72 (dd, J = 15.8, 7.6Hz, 3H), 7.63 (t, J =

7.6Hz, 1H), 7.24 (s, 1H), 7.16 (s, 1H), 4.35 (s, 2H), 2.64 (s, 3H), 2.45 (s, 3H).

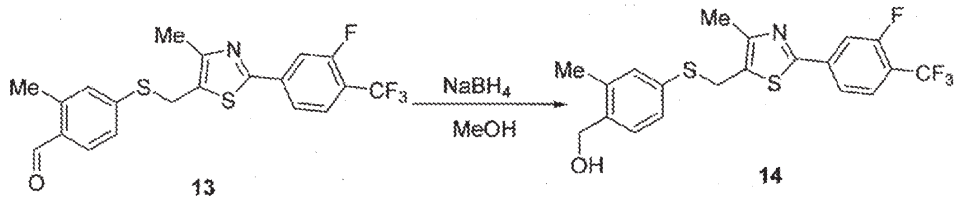
MS-ESI (m/z) 426.1 $[M + H]^+$.

[0206]

(4) Synthesis of {4-[({2-[3-fluoro-4-(trifluoromethyl) phenyl]-4-methylthiazole-5-yl} methyl} thio)-2-methylphenyl} methanol

[0207]

[Chemical formula 17]



[0208]

Sodium borohydride ($NaBH_4$) (295 mg, 7.76 mmol) was added in small portions to a solution obtained by dissolving 4-[({2-[3-fluoro-4- (trifluoromethyl) phenyl]-4-methylthiazole-5-yl} methyl) thio}-2-methylbenzaldehyde (Compound 13) (1.5 g, 3.53 mmol) in methanol (15 mL) at 0°C. The resulting mixture was stirred at 0°C for 30 minutes. An aqueous ammonium chloride solution (20 mL) was added to the mixture, and the mixture was extracted with ethyl acetate (60 mL×2). The organic layers were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the above compound (1.45 g, 96.0% yield) as a pale yellow solid.

[0209]

^1H NMR (400 MHz, $CDCl_3$) δ 7.75-7.67 (m, 2H), 7.65-7.59 (m, 1H), 7.30 (d, J = 7.7 Hz, 1H), 7.19 (d, J = 8.5Hz, 2H), 4.68 (d, J = 5.4Hz, 2H), 4.21 (s, 2H), 2.30 (s, 6H).

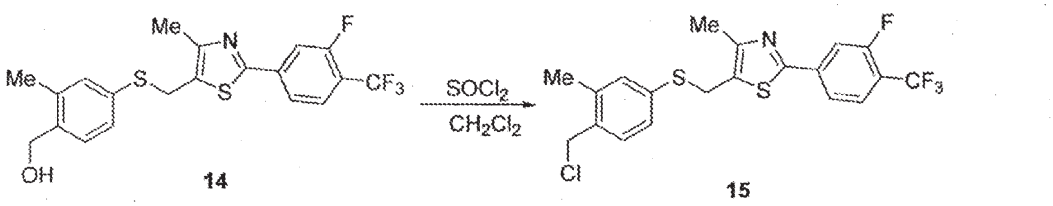
MS-ESI (m/z) 428.1 $[M + H]^+$.

[0210]

(5) Synthesis of 5-({[4-(chloromethyl)-3-methylphenyl] thio] methyl}-2-[3-fluoro-4-(trifluoromethyl) phenyl]-4-methylthiazole

[0211]

[Chemical formula 18]



[0212]

DMF (1 drop) and thionyl chloride (0.37 mL, 5.09 mmol) were added dropwise to a solution obtained by dissolving {4-[({2-[3-fluoro-4-(trifluoromethyl) phenyl]-4-methylthiazole-5-yl} methyl) thio]-2-methylphenyl} methanol (Compound 14) (1.45 g, 3.39 mmol) in dichloromethane (14 mL) at 0°C. The resulting mixture was stirred at 0°C for 1 hour. Water (10 mL) was added to the mixture and then the organic layer was separated. The recovered organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the above compound (1.47 g, 97.0% yield) as a yellow solid.

[0213]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.67 (m, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.19–7.12 (m, 2H), 4.57 (s, 2H), 4.23 (s, 2H), 2.38 (s, 3H), 2.32 (s, 3H)).

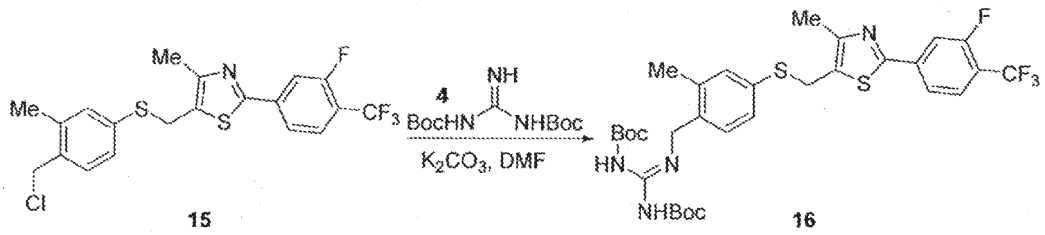
MS-ESI (m/z) 446.0 $[M + H]^+$.

[0214]

(6) Synthesis of 1,3-di-Boc-2-{4-[({2-[3-fluoro-4-(trifluoromethyl) phenyl]-4-methylthiazole-5-yl] methyl} thio)-2-methyl benzyl] guanidine

[0215]

[Chemical formula 19]



[0216]

A mixture containing 5-({[4-(chloromethyl)-3-methylphenyl) thio] methyl}-2-[3-fluoro-4-(trifluoromethyl) phenyl]-4-methylthiazole (Compound 15) (1.47 g, 3.3 mmol), 1,3-bis (tert-butoxycarbonyl) guanidine (CAS No. 154476-57-0, Compound 4) (1.28 g, 4.95 mmoL) and potassium carbonate (685 mg, 4.95 mmol) dissolved in DMF (15 mL) was heated at 75°C for 1 hour in a nitrogen atmosphere. The mixture was then diluted with water (60 mL). The entire amount was extracted with ethyl acetate (60 mL×3). All of the recovered organic layers were combined, washed with brine (30 mL×2), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluted with 1% to 10% ethyl acetate in hexane) to obtain the above compound (1.6 g, yield 73%) as a pale green solid.

[0217]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 9.35 (s, 1H), 7.70 (t, J = 10.1 Hz, 2H), 7.62 (t, J) = 7.5Hz, 1H), 7.14-7.16 (m, 2H), 6.90 (d, J = 7.8Hz, 1H), 5.12 (s, 2H), 4.19 (s, 2H), 2.30 (s, 3H), 2.25 (s, 3H), 1.46 (s, 9H), 1.22 (s, 9H).

MS-ESI (m/z) 669.3 $[M + H]^+$.

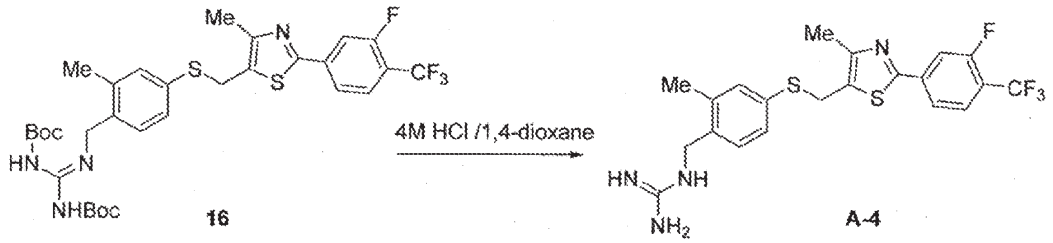
[0218]

(7) Synthesis of 1-{4-[({2-[3-fluoro-4-(trifluoromethyl) phenyl] 4-methylthiazole-5-yl}

methyl) thio]-2-methylbenzyl} guanidine

[0219]

[Chemical formula 20]



[0220]

A mixture of a solution obtained by dissolving 1,3-di-Boc-2-{4-[({2-[3-fluoro-4-(trifluoromethyl) phenyl]-4-methylthiazole-5-yl} methyl) thio]-2-methyl benzyl} guanidine (Compound 16) (800 mg, 1.2 mmol) in 1,4-dioxane (8 mL) with HCl/1,4-dioxane (4.0M, 3.0 mL) was stirred at 50°C for 2 hours. Next, the solvent was removed under reduced pressure, the residue was dissolved in methanol (6 mL), and the pH was adjusted to 8 to 9 with an aqueous sodium carbonate solution. Water (15 mL) was added to the obtained mixture, and the mixture was vacuum filtered. The resulting filter cake was washed with water (10 mL) and dried in high vacuum to obtain the above compound (A-4) (350 mg, 62% yield) as a white solid.

[0221]

^{1}H NMR (300 MHz, DMSO-d6): δ 7.92-7.84 (m, 3H), 7.55-7.00 (m, 5H), 4.48 (s, 2H), 4.20 (S, 2H), 2.31 (s, 3H), 2.22 (s, 3H).

MS-ESI (m/z) 469.2 $[M + H]^+$.

[0222]

The effect of the obtained compound (A-4) on PPARδ activity was investigated. Specifically, a luciferase assay was carried out in the same manner as in Example 8 except

that compound (A-4) dissolved in DMSO (0.1%) was added to the reaction system as a test substance (n=3). The measurement result of the relative transcriptional activation ability obtained by the luciferase assay is shown in FIG. 22. As a result, it was observed that the transcriptional activity of PPARδ tended to increase depending on the amount of compound (A-4) added. However, when the addition amount was 50 μM or more, the cells died and it was impossible to measure the transcription activity of PPARδ. From these results, it was found that compound (A-4) can be used as a PPARδ activator.

[0223]

[Example 10]

The effect of compound (A-4) on the expression of the gene whose expression is induced by PPARδ was investigated. Specifically, compound (A-4) was added to mouse skeletal muscle-derived myoblast cell line C2C12 cells, and the expression levels of the angptl4, pdk4 and the cpt1a genes, whose expression is induced by PPARδ (NPL 12), were measured. In addition, the Hprt gene was used as an endogenous control, and GW0742 was used as a positive control for PPARδ activation.

[0224]

First, C2C12 cells were seeded on a 24-well plate (1×10^5 cells/well) and cultured until 80-90% confluent. DMEM containing 10% bovine serum and 1% antibiotic was used as the culture medium. After culturing for 36 hours, when the target cell density was reached, the entire medium was replaced with a serum-free DMEM medium containing each concentration of compound (A-4), and the cells were cultured for 16 hours (n = 3). After culturing, the medium was discarded, a trizol reagent (manufactured by Invitrogen) for RNA extraction was directly added to each well to lyse the cells, and then the total RNA was extracted by ethanol precipitation. Using the obtained total RNA as a template, cDNA was synthesized using the reverse transcriptase "Superscript"

(manufactured by Biorad).

[0225]

Quantitative PCR was performed using the obtained cDNA as a template. The cDNA of the template, the primer that amplifies each gene to be measured, and the polymerase mix "ssoFast EvaGreen Supermix" (manufactured by Biorad) for quantitative PCR were mixed. Analysis was performed using a real-time PCR detection system "CFX connect (registered trademark)" (manufactured by Biorad).

From the obtained gene expression data, the expression level of each gene was divided by the expression level of the endogenous control gene to calculate the relative expression level.

[0226]

The results are shown in FIGS. 23A-C. As a result, in the cells to which 10 μM of compound (A-4) was added, the expression levels of the angptl4 gene, pdk4 gene, and the cpt1a gene were increased, as in the cells to which the GW0742 was added. From the results, it was confirmed that compound (A-4) has an ability to activate the transcriptional activity of PPARδ.

[CLAIMS]

[Claim 1]

A PPARδ activator comprising a guanidine derivative or a biguanidine derivative as an active ingredient, wherein

the PPARδ activator activates transcriptional activity of PPARδ (peroxisome proliferator-activated receptor δ).

[Claim 2]

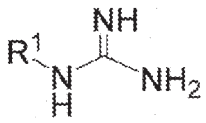
The PPARδ activator according to Claim 1, wherein

The guanidine derivative and the biguanidine derivative are capable of fitting within a ligand binding pocket of PPARδ, in a state where a guanidino group or a biguanidino group form a hydrogen bond with amino acid residues corresponding to each of the 413th histidine, 287th histidine, 253rd threonine and the 437th tyrosine of human PPARδ, among amino acid residues constituting an interior surface of the ligand binding pocket.

[Claim 3]

The PPARδ activator according to Claim 1 or 2, wherein

the guanidine derivative is a compound represented by the following general formula (1) (excluding the biguanidine derivative),



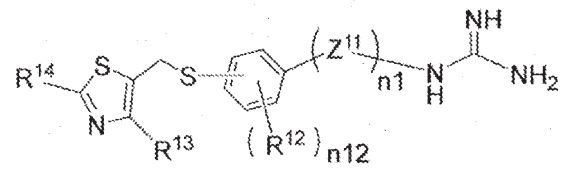
(1)

[in formula (1), R^1 represents a monovalent organic group].

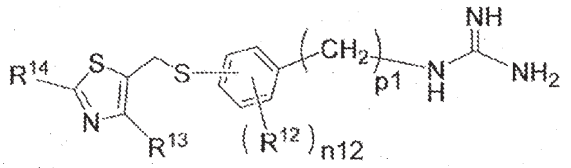
[Claim 4]

The PPARδ activator according to Claim 3, wherein

the guanidine derivative is a compound represented by any one of the following general formulas (1-1-1) to (1-1-4),

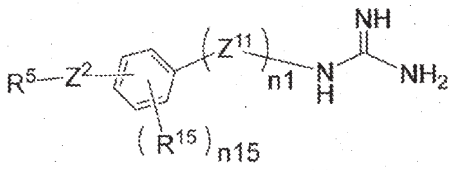


(1-1-1)

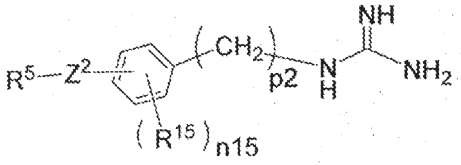


(1-1-2)

[in formulas (1-1-1) and (1-1-2), Z^{11} represents an oxygen atom or a sulfur atom, n1 represents 0 or 1, R^{12} represents an aliphatic hydrocarbon group having 1 to 6 carbon atoms, n12 represents an integer of 0 to 2, R^{13} represents a hydrogen atom or an aliphatic hydrocarbon group having 1 to 6 carbon atoms, R^{14} represents an optionally substituted aromatic hydrocarbon group, and p1 represents an integer of 1 or more],



(1-1-3)



(1-1-4)

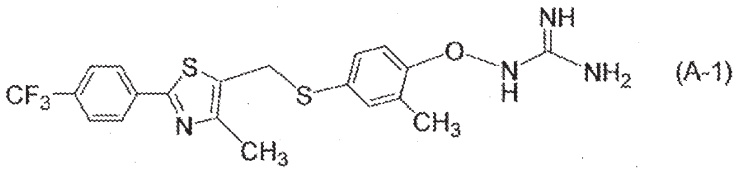
[in formulas (1-1-3) and (1-1-4), Z^{11} represents an oxygen atom or a sulfur atom, n1 represents 0 or 1, R^{15} represents an aliphatic hydrocarbon group having 1 to 6 carbon atoms or an alkoxy group having 1 to 6 carbon atoms, n15 represents an integer of 0 to 2, Z^2 represents a divalent linking group, R^5 represents an optionally substituted aromatic

hydrocarbon group or an optionally substituted cyclic hydrocarbon group, p2 represents an integer of 1 or more].

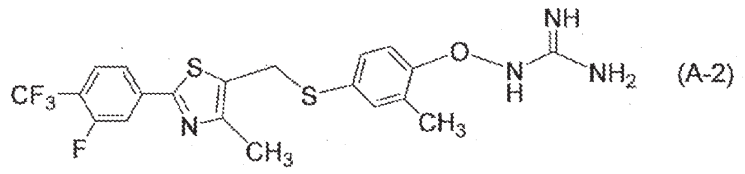
[Claim 5]

The PPARδ activator according to Claim 1, wherein

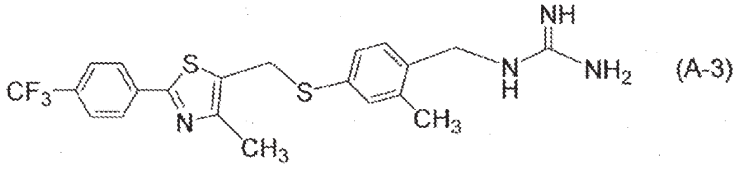
the guanidine derivative is a compound represented by any of the following formulas (A-1) to (A-4), (B-1) to (B-3),



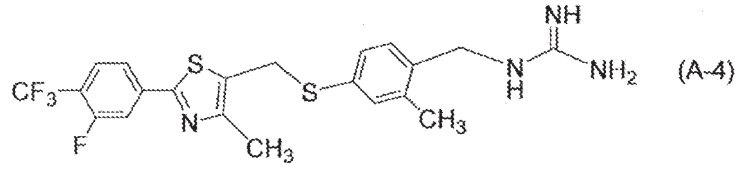
(A-1)



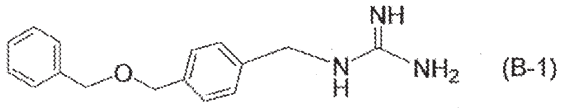
(A-2)



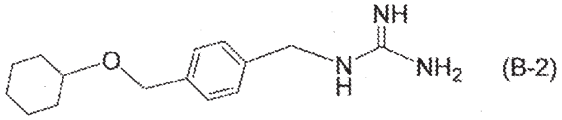
(A-3)



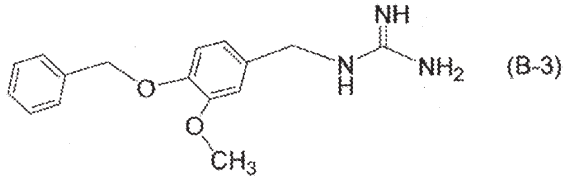
(A-4)



(B-1)



(B-2)

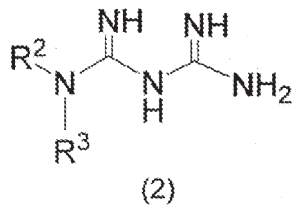


(B-3)

[Claim 6]

The PPARδ activator according to any one of Claims 1 to 3, wherein

the biguanidine derivative is a compound represented by the following general formula (2),



(2)

[in formula (2), R^2 and R^3 independently represent a hydrogen atom or a monovalent organic group, when both R^2 and R^3 are monovalent organic groups, they may be linked to form a ring structure].

[Claim 7]

The PPARδ activator according to Claim 1, wherein

at least one selected from the group consisting of metformin, phenformin and buformin is included as the active ingredient.

[Claim 8]

An exercise tolerance-improving agent comprising the PPARδ activator defined in any one of Claims 1 to 7 as an active ingredient.